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.

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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): AstraZeneca Australia Pty Ltd
Corporation name: AstraZeneca Australia Pty Ltd
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 in recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) to determine eligibility for durvalumab monotherapy or durvalumab/tremelimumab combination therapy (co-dependent).

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 6 of the Application Form)

SCCHN is a form of cancer arising from the squamous cells of various structures including the mouth, tongue, pharynx, larynx and oesophagus. It is associated with smoking, alcohol consumption and poor oral health. In recent years, human papilloma virus (HPV) has also been identified as a cause of SCCHN. HPV-related cases are steadily increasing in prevalence. Patients with HPV-related SCCHN tend to be younger and have a better prognosis than those whose cancers have other causes.

SCCHN can be disfiguring, particularly in advanced disease. Surgery and radiotherapy offer the best options for treatment, but surgery can be complicated because of the location of the tumours, and may require partial neck dissection which can leave significant scarring. In the case of recurrent tumours, multiple surgeries and radiotherapies can be contraindicated. Because of this, medical treatments are sometimes the preferred option in recurrent or metastatic SCCHN.

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)

By expressing programmed cell death ligand-1 (PD-L1) on its surface, a tumour cell can evade detection and destruction by the body's innate immune system. PD-L1 expression exists on a spectrum ranging from not detectable to (theoretically) 100% expression. A PD-L1 test involves taking a biopsy of the tumour and performing an immunohistochemical (IHC) assay to detect the percentage of PD-L1 expression within a tumour, measured as a total proportion score (TPS).

This application requests MBS listing of PD-L1 testing to direct treatment to either monotherapy with the PD-L1 inhibitor durvalumab, or combination therapy with durvalumab and tremelimumab, a CTLA-4 inhibitor, in patients with unresectable recurrent or metastatic SCCHN. Although trials are ongoing, it is expected that patients with a higher (≥25%) PD-L1 expression rate will benefit from monotherapy, while those with a lower (<25%) expression rate will benefit more from combination therapy. Co-dependent PBAC/MSAC submissions are expected to follow this application.

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)

Although MBS item codes for IHC testing already exist, none are specific to PD-L1 testing for the purposes of directing durvalumab and tremelimumab therapy. At the time of writing, the Sponsor is not aware of any other applications to the MSAC for an MBS item code covering PD-L1 testing for the purposes of directing PD-L1 inhibitor therapy for recurrent or metastatic SCCHN. Should such an MBS item code be generated before this application is approved, that MBS item code may need to be amended to include access to 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):

Not currently applicable.

(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, as a co-dependent submission, public funding for PBS access to durvalumab monotherapy or durvalumab/tremelimumab combination therapy is being sought for this indication.

(g) If yes, please advise:

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):

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

It is expected that two PBAC/MSAC co-dependent submissions will follow this application (pending the outcome of ongoing clinical trials). The first will seek MBS reimbursement of PD-L1 testing plus PBS reimbursement of durvalumab ± tremelimumab for metastatic or recurrent unresectable SCCHN that has progressed on or shortly after treatment with platinum-based chemotherapy (second-line treatment). The second submission will request PBS/MBS listing of PD-L1 testing and durvalumab ± tremelimumab for first-line treatment of unresectable recurrent or metastatic SCCHN. The two submissions will be submitted separately and will be based on different data sets.

However, because the timing of these planned submissions will be very close (currently expected to be one PBAC/MSAC cycle apart), this application requests MBS listing for PD-L1 testing of patients who present with unresectable recurrent or metastatic disease to inform PD-L1 expression rate for treatment with durvalumab ± tremelimumab in either the first-line or second-line settings (Figure 2). This will enable timely treatment of patients in the first-line setting and avoid MSAC evaluation duplication.

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

PBS listing will be sought for two pharmaceutical agents: durvalumab and tremelimumab. Durvalumab may be used as monotherapy or in combination with tremelimumab. Tremelimumab will only be used in combination with durvalumab.

Trade name: Redacted
Generic name: durvalumab

Trade name: Redacted
Generic name: 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):
Trade name of prostheses:
Clinical name of prostheses:
Other device components delivered as part of the service:

(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):

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.
Multi-use consumables: Instrumentation/software, such as the Ventana BenchMark ULTRA IHC automated slide stainer.

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 (MEDI4736); CTLA-4 antagonist 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 will be conducted as part of two co-dependent submissions 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 Roche/Ventana SP263 PD-L1 IHC assay is registered in Australia as a Class II diagnostic, but is not yet registered as a Class III diagnostic. An application to the TGA requesting Class III registration of the assay is planned. Details of the timing for this application are provided in the response to Question 17.

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

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

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

Estimated date of submission to TGA:
Redacted

Proposed indication(s), if applicable:
Redacted

Proposed purpose(s), if applicable:
Redacted

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.	Non-randomised Phase I/II study	Development of a programmed cell death ligand-1 immunohistochemical assay validated for analysis of non-small cell lung cancer and head and neck squamous cell carcinoma. (Study 1108) Clinicaltrials.gov identifier: NCT01693562	Study 1108 is a multicentre, open-label, first-in-human study in which durvalumab 10 mg/kg q2w treatment for up to one year was selected for the Phase II dose expansion phase to assess safety, tolerability and efficacy. PD-L1 expression was determined at baseline with PD-L1 high cut-off ≥25% in tumour tissue using the SP263 assay optimised on the BenchMark ULTRA platform (Ventana Medical Systems Inc).	Rebelatto MC et al. Diagnostic Pathology 2016; 11:95. DOI 10.1186/s13000-016-0545-8. Link to publication here. This publication presents the results of the validation study of the assay using samples from Study 1108.	2016

	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
2.	Non-randomised Phase I/II study	Updated safety and efficacy of durvalumab (MEDI4736), an anti -PD-L1 antibody, in patients from a head and neck squamous cell carcinoma cell carcinoma (HNSCC) expansion cohort (Study 1108) Clinicaltrials.gov identifier: NCT01693562	Study 1108 is a multicentre, open-label, first-in-human study in which durvalumab 10 mg/kg q2w treatment for up to one year was selected for the Phase II dose expansion phase to assess safety, tolerability and efficacy. PD-L1 expression was determined at baseline with PD-L1 high cut-off ≥25% in tumour tissue using the SP263 assay optimised on the BenchMark ULTRA platform (Ventana Medical Systems Inc).	Segal MH et al. Annals of Oncology 2016; 27(6): 328–350. DOI: 10.1093/annonc/mdw376 Link to publication here This publication presents updated safety and efficacy results for the SCCHN cohort of study 1108. Further results for this cohort will be available in early 2018.	2016
3.	Concordance study	A comparative study of PD-L1 diagnostic assays in squamous cell carcinoma of the head and neck (SCCHN)	Tumour biopsy samples from stage I–IV SCCHN pts, obtained from a commercial source and including HPV positive and HPV negative, were assessed using 3 PD-L1 diagnostic assays.	Link to abstract here.	2016

	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
4.	Comparison of the analytical performance and clinical comparability of four PD-L1 immunohistochemical assays available for use with different PD-1/PD-L1 immune checkpoint inhibitors.	BLUEPRINT Study	The BLUEPRINT Programmed Death Ligand 1 (PD-L1) Immunohistochemistry (IHC) Assay Comparison Project is an industrial-academic collaborative partnership to provide information on the analytical and clinical comparability of four PD-L1 IHC assays (antibody clones 22C3, 28-8, SP142, and SP263), as used in the NSCLC clinical trials of the immune checkpoint inhibitors pembrolizumab, nivolumab, atezolizumab and durvalumab .	Hirsch F et al. PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project. *J. Thoracic Oncol.* 2017 12(2): p.208–222. Link to publication here Conference abstracts/presentations: Fred R. Hirsch (chair), Reena Philip, Steven D. Averbuch, Kenneth Emancipator, Abigail McElhinny, John Longshore, Dave Stanforth, Jill Walker, and J. Andy Williams. The Blueprint Project: Harmonizing Companion Diagnostics Across a Class of Targeted Therapies. American Association for Cancer Research Annual Meeting 2016 April 19. Link to presentation here	April 2016

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
Early-phase studies					
1.	Non-randomised trial	A Phase I Study to Evaluate the Safety, Tolerability and Efficacy of MEDI4736 (Durvalumab) With Tremelimumab in Head and Neck Cancer (Study 11) Clinicaltrials.gov identifier: NCT02262741	A multicentre, open-label, dose-exploration and dose-expansion study to evaluate the safety, tolerability, antitumor activity, pharmacokinetics, pharmacodynamics, and immunogenicity of MEDI4736 in combination with tremelimumab in subjects with recurrent/metastatic squamous cell carcinoma of the head and neck. A total of 139 patients are expected to be enrolled in the study.	Siu LL et al. J Clin Oncol 2015; 33(15 Suppl):Abstract TPS3090. Link to abstract here	Q4 2017
First-line treatment					
2.	Randomised controlled trial	A Phase III Randomized, Open-label, Multi-center, Global Study of MEDI4736 Alone or in combination with Tremelimumab versus Standard of Care in the Treatment of First-line Recurrent or Metastatic Squamous Cell Head and Neck Cancer Patients (KESTREL) Clinicaltrials.gov identifier: NCT02551159	A randomised, open-label, multi-centre, three-arm, global Phase III study to determine the efficacy and safety of durvalumab + tremelimumab combination or durvalumab monotherapy versus standard of care (EXTREME regimen) in the treatment of patients with SCCHN who have not received prior systemic chemotherapy for recurrent or metastatic disease. A total of 823 patients are expected to be enrolled in the study.	Link to details here	Q4 2017
Second-line treatment					

	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
3.	Non-randomised trial	A Phase II, Multi-Center, Single-Arm, Global Study of MEDI4736 Monotherapy in Patients With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN) (HAWK) Clinicaltrials.gov identifier: NCT02207530	A Phase II, multi-centre, single-arm, global study to determine the efficacy and safety of durvalumab monotherapy in patients with recurrent or metastatic PD-L1-positive squamous cell carcinoma of the head and neck (SCCHN). This study is active but not recruiting. A total of 112 patients are expected to enrol in the trial.	Link to details here	Q2 2017
4.	Randomised trial	A Phase II, Randomized, Open-Label, Multi-Center, Global Study of MEDI4736 Monotherapy, Tremelimumab Monotherapy, and MEDI4736 in Combination With Tremelimumab in Patients With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN) (CONDOR) Clinicaltrials.gov identifier: NCT02319044	The purpose of this open-label study is to determine the efficacy and safety of investigational medical products (durvalumab monotherapy, tremelimumab monotherapy, and durvalumab + tremelimumab combination therapy) in the treatment of patients with PD-L1-negative recurrent or metastatic carcinoma of the head and neck who have progressed during or after treatment with a platinum containing regimen for recurrent/metastatic disease. This study is active but not recruiting. A total of 240 patients are expected to enrol in the trial.	Link to details here	Q2 2017

	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
5.	Randomised controlled trial	A Phase III Randomized, Open-Label, Multi-Center, Global Study of MEDI4736 Monotherapy and MEDI4736 in Combination With Tremelimumab Versus Standard of Care Therapy in Patients With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN) (EAGLE) Clinicaltrials.gov identifier: NCT02369874	A randomised, open-label, multi-centre, global, Phase III study to determine the efficacy and safety of durvalumab + tremelimumab combination therapy and durvalumab monotherapy versus standard of care therapy in patients with recurrent or metastatic PD-L1-positive or -negative squamous cell carcinoma of the head and neck (SCCHN). This study is still recruiting patients. A total of 720 patients are expected to be enrolled in the study.	Link to details here	Q1 2018

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):

Royal College of Pathologists Australasia (RCPA).

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

Not applicable.

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

Rare Cancers Australia (RCA) is the consumer group most representative of those with SCCHN.

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

There is no 'gold standard' PD-L1 assay accepted at present. A comparison of the evidentiary standard (the test method used in the AstraZeneca trials) with alternative PD-L1 testing methods will be conducted in the co-dependent submissions that will follow 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): Redacted

Email address: Redacted

Name of expert 2: Redacted

Telephone number(s): Redacted

Email address: Redacted

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:

Head and neck cancers are among the most commonly diagnosed cancers in Australia, ranked fifth in males, eleventh in females, and eighth overall (AIHW 2017). Most head and neck cancers arise from the squamous cells. Squamous cell carcinomas of the head and neck (SCCHN), as they are collectively known, are observed in the mucosa of the mouth, nose, larynx, pharynx, lips, salivary glands and associated structures.

In Western countries, SCCHN is most closely associated with cigarette smoking, alcohol consumption and poor oral health. In other countries, risk factors also include using snuff, chewing betel nut and smoking bidis (Sanderson and Ironside 2002). Recently, human papilloma virus (HPV) has been implicated in an increasing number of cases of SCCHN (Economopoulou et al 2016). Patients with HPV-related SCCHN tend to be younger and have a better prognosis than those whose cancers have other causes.

The symptoms of head and neck cancers may include a lump or a sore that does not heal, a sore throat that does not go away, difficulty in swallowing, and a change or hoarseness in the voice. Site-specific symptoms include a white or red patch on the gums, the tongue, or the lining of the mouth; a swelling of the jaw; difficulty speaking or breathing; headaches; ear pain; and difficulty hearing.

Treatment of Stage I or II tumours may be curative. Left untreated, the tumours continue to grow and progress (Deschler et al 2014). Due to the location of the tumours, they can cause significant physical and functional impairment that can impact the patient's health and quality of life. Survival rates fall as the tumours grow and metastasise (Sanderson and Ironside 2002; Tinhofer et al 2016).

Although surgery and radiotherapy are the mainstay of treatment (Deschler et al 2014), the size and location of tumours may make surgery difficult and risky in some cases, especially as the disease progresses. Further, resections can be disfiguring. In advanced cases, surgery may not be possible. In recurrent cases, multiple surgeries or radiotherapies may be contraindicated because of the increased risks associated with scar tissue arising from operating in the same location. When the disease has recurred or progressed to metastatic disease, treatment options are limited and are generally palliative.

References

Australian Institute of Health and Welfare 2017. Cancer in Australia 2017. Cancer series no.101. Cat. no. CAN 100. Canberra: AIHW.

Deschler DG, Moore MG, Smith RV, eds. Quick Reference Guide to TNM Staging of Head and Neck Cancer and Neck Dissection Classification, 4th ed. Alexandria, VA: American Academy of Otolaryngology–Head and Neck Surgery Foundation, 2014.

Economopoulou P et al. The emerging role of immunotherapy in head and neck squamous cell carcinoma (HNSCC): anti-tumor immunity and clinical applications. Ann Transl Med 2016; 4(9): 173. DOI: 10.21037/atm.2016.03.34.

Sanderson RJ and Ironside JAD. Squamous cell carcinomas of the head and neck. BMJ 2002; 325: 822–827.

Tinhofer I et al. The rationale for including immune checkpoint inhibition into multimodal primary treatment concepts of head and neck cancer. Cancers of the Head & Neck 2016; 1:8. DOI 10.1186/s41199-016-0009-6.

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:

It is proposed that PD-L1 testing be reimbursed for patients with unresectable recurrent or metastatic SCCHN, to allow PBS access to durvalumab monotherapy or durvalumab/tremelimumab combination therapy either as first-line therapy or as second-line therapy for those whose disease has progressed while on or shortly after receiving platinum chemotherapy. Although studies are ongoing, it is expected that PD-L1 testing will determine the most appropriate clinical pathway for individual patients.

The Sponsor anticipates that patients with a high PD-L1 expression rate (those with a PD-L1 rate ≥25%) are likely to respond well to monotherapy with the PD-L1 inhibitor durvalumab; patients whose tumours express a lower PD-L1 expression rate (a PD-L1 rate <25%) are expected to respond better to durvalumab/tremelimumab combination therapy. Therefore, rather than PD-L1 testing being used to exclude patients with lower PD-L1 expression rates from treatment, PD-L1 testing will likely inform which therapeutic pathway (mono- or combination therapy) is most appropriate for individual patients.

The test itself involves analysing tissue collected from a biopsy of the tumour to determine the rate of PD-L1 expression on the tumour cell surface. The biopsy will be collected predominantly by a medical oncologist. The testing will be undertaken by an anatomical pathologist, most likely alongside other histopathology tests.

An immunohistochemical (IHC) assay forms the basis of PD-L1 testing. IHC testing is a common practice in Australian pathology laboratories.

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):

Currently, patients with unresectable recurrent or metastatic disease do not undergo PD-L1 testing and are provided with palliative chemotherapy-based regimens as both a first- and second line of treatment. Which treatment or combination of treatments they receive will depend on their general state of health, and what they have previously been given. A broader discussion of the current treatment algorithm is provided in the response to question 41. A discussion of the anticipated changes to the current treatment algorithm following MBS funding of PD-L1 testing and PBS reimbursement of durvalumab ± tremelimumab is provided in the response to question 43.

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

PD-L1 testing

The rate of PD-L1 gene expression can be assessed by immunohistochemical (IHC) testing using antibodies that bind specifically to the PD-L1 protein. Tumour biopsy material is sectioned and dried before the IHC staining process. The IHC staining must be conducted, interpreted and reported by a professional anatomical pathologist. The test results can then be used to inform the treatment pathway for the individual patient.

The Roche/Ventana SP263 PD-L1 IHC assay is used in EAGLE and KESTREL, the pivotal Phase III SCCHN studies.

The co-dependent submission will include data comparing the KESTREL and EAGLE trial–based PD-L1 testing method and other PD-L1 testing methods available in Australia.

Durvalumab

Durvalumab (MEDI4736) is a human monoclonal antibody (mAb) of the IgG1 kappa subclass that specifically binds human programmed cell death ligand-1 (PD-L1).

PD-L1 is a member of the B7 family of transmembrane proteins, which delivers inhibitory signals to T lymphocytes. Through the expression of PD-L1 on its surface, a tumour cell can evade detection and destruction by the body's innate immune system by binding to the programmed cell death-1 (PD-1) receptor expressed on T-cells, thereby repressing the anti-tumour T-cell response. Durvalumab prevents PD-L1 from interacting with the PD-1 receptor, thus relieving PD-L1's immunosuppressive effects and enhancing the cytotoxic activity of anti-tumour T-cells.

Tremelimumab

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

Durvalumab/tremelimumab

Targeting both the PD-1/PD-L1 and CTLA-4 pathways are thought to have additive or synergistic activity because the mechanisms of action of the PD-1/PD-L1 and CTLA-4 pathways are non-redundant: whereas PD-1 contributes to T-cell exhaustion in peripheral tissues, CTLA-4 intervenes at an earlier stage of T-cell activation (Pardoll 2012). In addition, CTLA-4 antagonists have been shown to upregulate PD-1 and vice versa, further strengthening the rationale for combination therapy.

References

Lin Y-M et al. (2015) High PD-L1 expression correlates with metastasis and poor prognosis in oral squamous cell carcinoma. PLoS ONE 10(11): e0142656. doi:10.1371/journal.pone.0142656

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?

Redacted.

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?

Inclusion of PD-L1 testing on the MBS to determine eligibility for PBS access to durvalumab monotherapy or durvalumab/tremelimumab combination therapy would involve a new approach to the management of patients with recurrent or metastatic SCCHN. In this application, it is proposed that PD-L1 testing be used to determine whether durvalumab monotherapy or durvalumab/tremelimumab combination therapy would be the more beneficial treatment, based on whether the patient's tumour expresses a high (≥25%) or low (<25%) rate of PD-L1, respectively.

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):

The Sponsor proposes that only patients with recurrent or metastatic SCCHN be tested for PD-L1 expression. It is expected in the substantial majority of cases that patients will require only one PD-L1 test to guide treatment choice. In a very small number of cases where there is insufficient tissue available, a second biopsy to obtain more tissue may be required. IHC testing generally requires only a very small amount of tissue; consequently, this circumstance is likely to be rare.

The Sponsor does not expect that patients treated with first-line immunotherapy will be retreated with immunotherapy in the second-line setting; therefore, patients will only require one test for PD-L1 expression, prior to initiation of durvalumab ± tremelimumab in either the first-line or second-line setting.

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:

Not applicable.

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

Patients with head and neck cancer are seen by a multi-disciplinary team, which may include medical oncologists, radiation oncologists and maxillofacial surgeons. It is likely that medical oncologists will order PD-L1 testing and undertake the biopsy in the majority of cases. Qualified, trained anatomical pathologists will undertake the assay and report on the results.

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

Not applicable. The assay must be conducted and interpreted by a suitably qualified, trained anatomical pathologist.

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

Specialists, predominantly medical oncologists, may order the test and perform the biopsy. Appropriately trained anatomical pathologists will undertake the assay.

PD-L1 testing in the unresectable recurrent or metastatic SCCHN setting is proposed as pathologist determinable so that the pathologist can promptly report these additional results to medical oncologists and the most appropriate treatment for the patient can be selected without delays associated with additional test requests.

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 anatomical pathologists who have been trained to conduct IHC testing specifically for PD-L1 following Australian National Association of Testing Authorities (NATA) accreditation. A quality assurance (QA) programme conducted by the Royal College of Pathologists of Australasia (RCPA) would also help to ensure consistency of results.

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

(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

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 appropriate comparator for the purposes of this application is no PD-L1 test and the subsequent continuation of a chemotherapy-based treatment regimen, the current standard of care. PD-L1 testing is not currently listed on the MBS for any indication, including SCCHN. In the absence of the test, access to durvalumab and tremelimumab combination therapy would be denied to patients. In this case, patients would be relegated to the current standard of care. Alternatively, without testing, patients could be receive untargeted treated with durvalumab or durvalumab/tremelimumab combination therapy.

There are three applications being reviewed by the MSAC relating to PD-L1 testing (applications 1414, 1440 and 1457). None of these applications relate to SCCHN.

For the purposes of the planned co-dependent PBAC/MSAC applications in first-line and second-line SCCHN, an active drug comparator may also be used, particularly for assessing the efficacy and safety of durvalumab monotherapy. Both nivolumab and pembrolizumab have been evaluated for use in second-line treatment of SCCHN, and pembrolizumab has been registered for use in Australia for SCCHN in the second-line setting (on the basis of early-phase trial data; Phase III trial results are pending). Both of these agents are also being evaluated for first-line treatment of SCCHN. Should either or both of these agents become reimbursed before durvalumab, an indirect comparison with durvalumab will be presented in the co-dependent submissions.

Both the EAGLE and KESTREL trials pre-specified that patients be stratified by a PD-L1 rate of <25% or ≥25%. However, if the relevant comparators include other PD-1/PD-L1 inhibitors, post-hoc analyses of the data at other PD-L1 rates will be undertaken to allow an indirect comparison to be made.

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

Not applicable.

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):

Error! Reference source not found. shows the current clinical treatment algorithm for SCCHN. It should be noted that the therapy chosen for an individual patient will depend on several factors, including the stage of the disease; the patient's age and general state of physical and mental health; and performance status.

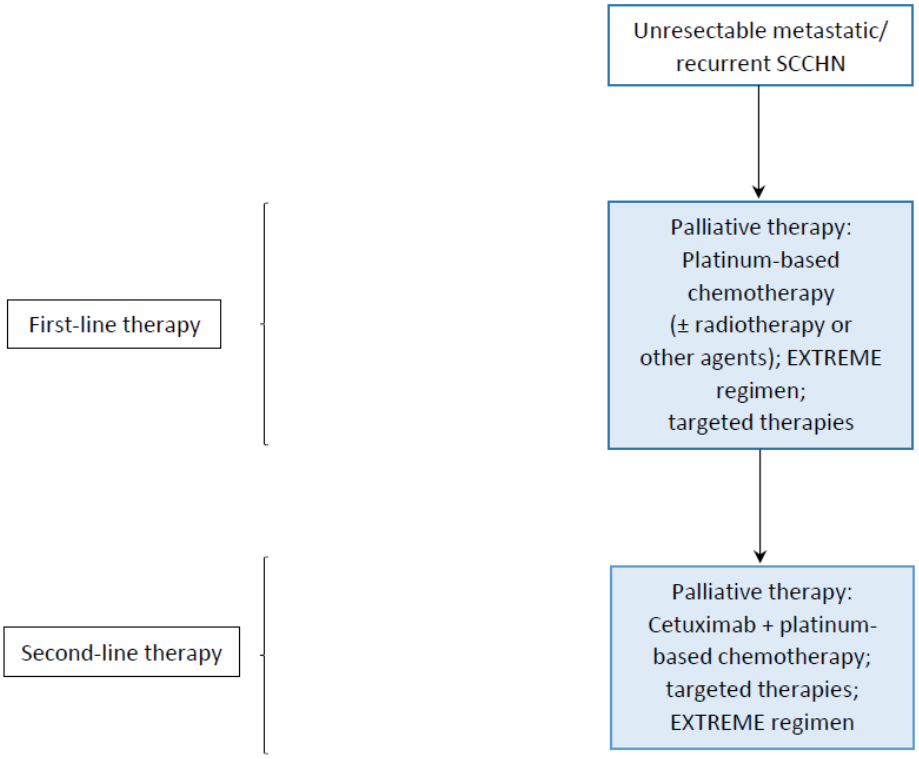

Figure 1. Current clinical treatment algorithm for unresectable recurrent or metastatic squamous-cell carcinoma of the head and neck (SCCHN) in the absence of PD-L1 testing

As shown in **Error! Reference source not found.**, first-line treatment for unresectable metastatic or recurrent SCCHN comprises chemotherapy in combination with other agents or radiotherapy. A variety of drugs may be used in the first-line setting and the treatment regimen chosen will reflect the patient's general health and prognosis (Deschler et al 2014). Currently available therapies, while offering some survival benefit to patients, are palliative and the incremental increase in life expectancy is low.

When the disease progresses, effective treatment options are limited and are, again, palliative. Previously-treated patients with unresectable tumours may receive one or more agents, including platinum-based chemotherapy in combination with cetuximab; cisplatin/carboplatin in combination with cetuximab and 5-fluoruracil (the EXTREME regimen; Vermorken et al 2008); or other therapies such as taxanes, methotrexate, pemetrexed, capecitabine, or vinorelbine.

These treatments are associated with significant toxicity. Further, while some regimens have demonstrated some improvement in survival (Vermorken et al 2008), response rates vary and the duration of the survival benefit remains relatively short (Deschler et al 2014; Tinhofer et al 2016). There is a compelling need for more effective therapies for patients with SCCHN who are not eligible for surgical resection.

References

Deschler DG, Moore MG, Smith RV, eds. Quick Reference Guide to TNM Staging of Head and Neck Cancer and Neck Dissection Classification, 4th ed. Alexandria, VA: American Academy of Otolaryngology–Head and Neck Surgery Foundation, 2014.

Tinhofer I et al. The rationale for including immune checkpoint inhibition into multimodal primary treatment concepts of head and neck cancer. Cancers of the Head & Neck 2016; 1:8. DOI 10.1186/s41199-016-0009-6.

Vermorken JB et al. Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer. N Engl J Med 2008; 359(11): 1116–1127.

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

☒ Yes
☐ No

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

The proposed medical service (PD-L1 testing) will be used instead of the comparator (no testing). The proposed treatments, durvalumab monotherapy or durvalumab/tremelimumab combination therapy, would be used instead of chemotherapy-based regimens, the currently available standard of care.

It is expected that PD-L1 testing and subsequent treatment with durvalumab ± tremelimumab will become the new standard of care over time; therefore, the majority of patients will receive PD-L1 testing as a normal part of their treatment regimen.

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):

Figure 2 summarises the ways in which the treatment algorithm for patients with recurrent or metastatic SCCHN are likely to change with the MBS listing of PD-L1 testing and PBS listing of durvalumab and tremelimumab for this indication. The boxes in darker blue indicate the proposed changes to the current treatment algorithm (**Error! Reference source not found.**, reproduced below for convenience).

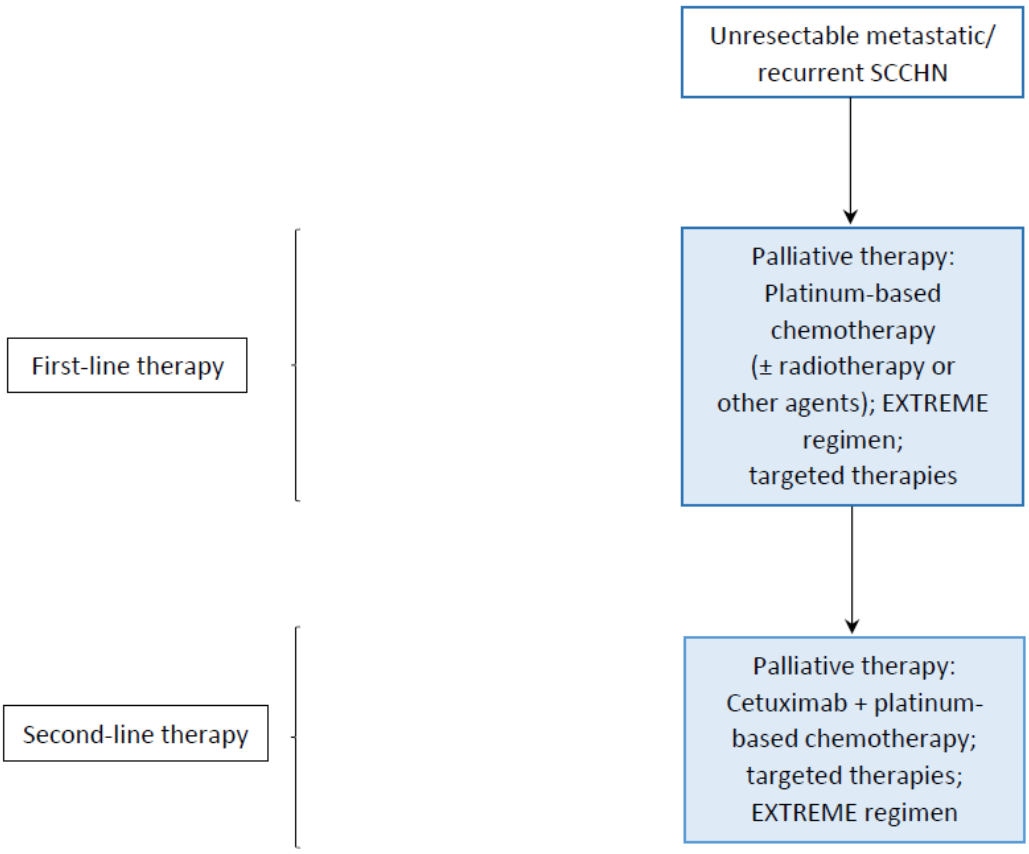

Figure 1. Current clinical treatment algorithm for unresectable recurrent or metastatic squamous-cell carcinoma of the head and neck (SCCHN) in the absence of PD-L1 testing

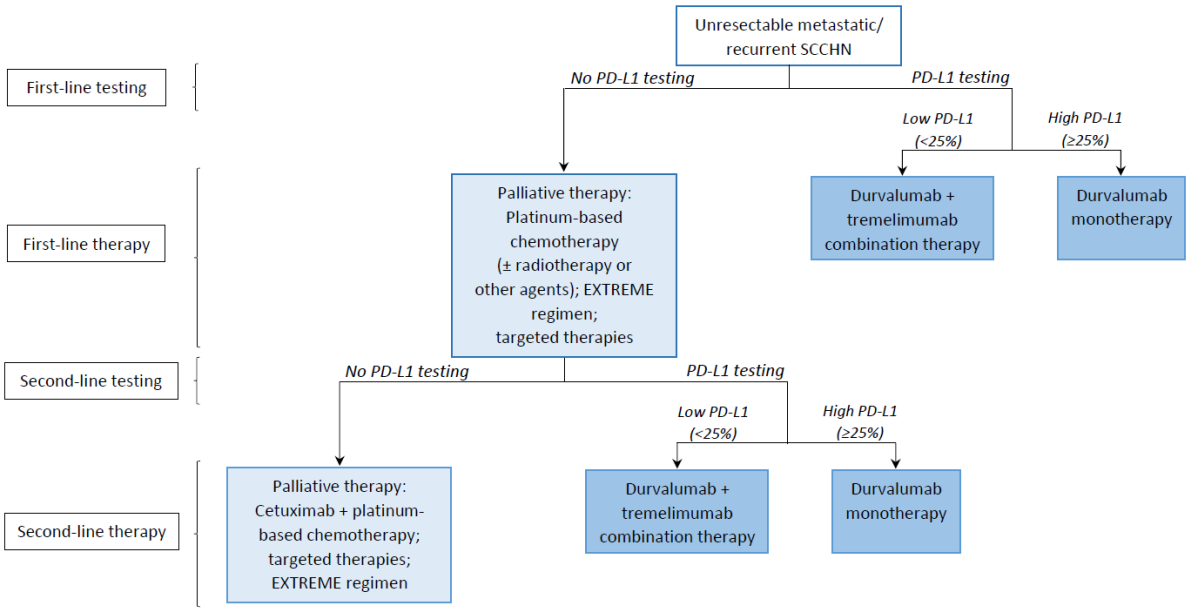

Figure 2. Proposed clinical treatment algorithm for unresectable recurrent or metastatic squamous-cell carcinoma of the head and neck (SCCHN) with PD-L1 testing

It is proposed that patients whose disease has recurred or metastasised receive a PD-L1 test to determine eligibility for durvalumab ± tremelimumab in either the first-line or second-line setting, according to PBS restriction criteria. Patients with a high PD-L1 expression rate (≥25%) are expected to benefit from durvalumab monotherapy, while it is anticipated that those with a low rate (<25%) will benefit most from durvalumab and tremelimumab combination therapy. The Sponsor does not expect that patients treated with first-line immunotherapy will be retreated with immunotherapy in the second-line setting; therefore, it is expected that patients will only require one test for PD-L1 expression.

In a relatively short time after they become available in the second-line setting, it is likely that durvalumab monotherapy and durvalumab/tremelimumab combination therapy will become part of the standard of care in the first-line setting. Therefore, the requirement for PD-L1 testing prior to initiation of first-line therapy will increase. Patients who receive the test to determine eligibility for treatment in the first-line setting are not expected to be eligible for immunotherapy re-treatment and thus will not require a repeat test for determination of treatment in the second-line setting.

The introduction of PD-L1 testing to the MBS is therefore expected to replace no PD-L1 testing, while the addition of durvalumab monotherapy and durvalumab/tremelimumab combination therapy to the PBS will replace chemotherapy-based regimens, the current standard of care.

As discussed in question 39, it is possible that either nivolumab or pembrolizumab will be reimbursed for SCCHN before durvalumab ± tremelimumab. Should this happen, it is likely that either or both of these agents will become part of the standard of care in SCCHN. In this case, nivolumab and/or pembrolizumab would take the place of palliative platinum-based chemotherapy regimens in the treatment algorithms.

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):

Trials are ongoing, but it is anticipated that the clinical claims that will be made in the co-dependent PBAC/MSAC submission for durvalumab and tremelimumab will be as follows.

1. PD-L1 testing followed by durvalumab monotherapy for patients with a PD-L1 expression rate ≥25% results in superior efficacy compared with no testing and treatment with chemotherapy-based regimens, the current standard of care.
2. PD-L1 testing followed by durvalumab/tremelimumab combination therapy for patients with a PD-L1 expression rate <25% results in superior efficacy compared with durvalumab monotherapy and with chemotherapy-based regimens, the current standard of care.

PD-L1 testing is not currently listed on the MBS. The appropriate comparator for the purposes of this application is no testing. Without testing, it is not possible to determine the PD-L1 status of a tumour, resulting in either denial of access to durvalumab monotherapy or durvalumab/tremelimumab combination therapy, or untargeted treatment of all patients with these medicines.

In patients with SCCHN, PD-L1 expression is a prognostic marker; higher PD-L1 expression has been shown to predict a poorer prognosis (Lin et al 2015). Early-phase research of durvalumab monotherapy indicates that there is a difference in treatment response based on PD-L1 expression rate in patients with solid tumours across several indications, including those with SCCHN and NSCLC (Antonia et al 2016; Rizvi et al 2015; Segal et al 2016). Further, the mechanism of action of the two drugs suggest that durvalumab monotherapy is likely to be most effective in patients with a higher PD-L1 expression rate, while the addition of tremelimumab may have an additive or synergistic effect to durvalumab monotherapy, thereby improving response rates in those with a lower PD-L1 expression rate.

The key clinical trials on which the co-dependent submission will be based divide patients into those with ≥25% PD-L1 expression and those with <25% PD-L1 expression. It is expected that PD-L1 testing will help to determine the most appropriate clinical pathway for individual patients. By determining that a patient has a high PD-L1 expression rate (those with a PD-L1 rate ≥25%), it will be possible to determine whether the patient is likely to respond well to the PD-L1 inhibitor durvalumab in comparison with the current standard of care, while identifying those with a lower PD-L1 expression rate (a PD-L1 rate ≥25%) will allow access to combination durvalumab and tremelimumab therapy, which is likely to produce a better response in these patients than durvalumab monotherapy or standard of care alone, but may cause greater toxicity than durvalumab monotherapy.

References

Antonia SJ et al. Safety and clinical activity of durvalumab (MEDI4736), an anti-PD-L1 antibody, in treatment-naïve patients with advanced non–small-cell lung cancer. J Clin Oncol 2016; 34(Suppl; abstr 9029).

Lin Y-M et al. (2015) High PD-L1 expression correlates with metastasis and poor prognosis in oral squamous cell carcinoma. PLoS ONE 10(11): e0142656. doi:10.1371/journal.pone.0142656

Rizvi NA et al. Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand 1 (PD-L1) antibody, in patients with non–small cell lung cancer (NSCLC). J Clin Oncol 2015; 33 (Suppl: 8032).

Segal MH et al. Updated safety and efficacy of durvalumab (MEDI4736), an anti -PD-L1 antibody, in patients from a head and neck squamous cell carcinoma cell carcinoma (HNSCC) expansion cohort. Ann Oncol 2016; 27(6): 328–350.

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

☒ Superiority
☐ Non-inferiority

As described previously, it is expected that durvalumab monotherapy will result in improved efficacy compared with the current standard of care in patients with a higher PD-L1 expression rate, while durvalumab/tremelimumab combination therapy will improve efficacy outcomes in patients with a lower PD-L1 expression rate compared with both durvalumab monotherapy and the current standard of care.

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

Adverse events relating to tolerability and toxicity.

Clinical effectiveness outcomes

Test outcomes

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

Sensitivity

Specificity

Positive predictive value (PPV)

Negative predictive value (NPV)

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 PDL-1 positive (≥25%) and PD-L1 negative (<25%) result detected

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 PDL-1 positive (≥25%) and PD-L1 negative (<25%) result detected

Number of patients tested per case of PD-L1 positive (≥25%) treated with durvalumab and PD-L1 negative (<25%) treated with durvalumab/tremelimumab

Cost of testing per case of PDL-1 positive (≥25%) and PD-L1 negative (<25%) result detected

Cost of testing per case of PD-L1 positive (≥25%) treated with durvalumab and PD-L1 negative (<25%) treated with durvalumab/tremelimumab

Drug outcomes

Second-line therapy

Primary outcome: Overall survival

Secondary outcomes: Progression-free survival, overall response rate, duration of response, disease control rate, the proportion of patients alive and progression-free at 6 and 12 months, and overall survival at 12, 18 and 24 months.

First-line therapy

Primary outcomes: Overall survival and progression-free survival

Secondary outcomes: Overall response rate, duration of response, second progression, proportion alive and progression-free at 12 months, overall survival at 24 months, quality of life.

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

Table 1 summarises the number of PD-L1 tests that are expected to be given in a year.

Few data are readily available identifying the number of patients with unresectable SCCHN whose disease recurs or metastasises. Given that treatment for SCCHN post-recurrence or metastasis is largely palliative and survival is usually 7–10 months (Vermorken et al 2008), it is assumed that all patients whose disease recurs or metastasises will eventually die from the condition within 12 months. Therefore, the mortality rate for the condition is a reasonable proxy for the annual number of patients whose disease will recur or metastasise, and therefore also as a proxy for the number of PD-L1 tests that will be required (assuming 100% uptake of the test). Using this methodology, the Sponsor estimates that around 892 PD-L1 tests will be undertaken in the first year of MBS listing in this indication.

As discussed previously, patients are unlikely to receive immunotherapy in both the first- and second-line settings; therefore, testing is only likely to occur once prior to initial immunotherapy treatment. When durvalumab and tremelimumab are PBS listed, it is expected that immunotherapy with these drugs will become the standard of care for patients with SCCHN and that these treatments will increasingly take place in the first-line setting, when recurrence or metastasis is first diagnosed. Therefore, the number of PD-L1 tests to determine eligibility for second-line treatment will reduce over time as patients are increasingly treated in the first-line setting. A more thorough estimation of the expected number of tests will be provided in the PBAC/MSAC co-dependent submissions.

Table 1. Estimated number of patients requiring PD-L1 testing to direct the treatment of SCCHN

A	Australian population 2017	24,781,121
B	Incidence rate of SCCHN	17.2/100,000
C	Proportion with squamous cell origin	90%
D	**Number of new cases** *(A x B x C)*	**3,836**
E	Mortality rate	4/100,000
F	**Number of recurrent or metastatic cases** (using mortality as a proxy measure) *(A x C x E)*	**892**

References

ABS Australian population projections. Publication 3222.0 Series B. Available at http://www.abs.gov.au/ausstats/abs@.nsf/mf/3222.0. Accessed 28 March 2017.

Australian Institute of Health and Welfare (AIHW) 2017. Australian Cancer Incidence and Mortality (ACIM) books. ACIM Book for Head and Neck Including Lip. Canberra: AIHW. Available at http://www.aihw.gov.au/acim-books. Accessed 28 March 2017.

Vermorken JB et al. Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer. N Engl J Med 2008; 359(11): 1116–1127.

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

The test would be conducted only once per patient, to establish eligibility for PBS access to durvalumab and tremelimumab for the treatment of recurrent or metastatic squamous cell cancer of the head and neck. Those who receive the test to determine eligibility for treatment in the first-line setting are not expected to be retreated with immunotherapy and therefore will not require a repeat test for determination of treatment in the second-line setting.

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

The test would be given once only, to establish eligibility for PBS access to durvalumab and tremelimumab for the treatment of recurrent or metastatic squamous cell cancer of the head and neck. There is no evidence indicating that repeated PD-L1 testing has a role to play in ongoing management of these patients.

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

As outlined in Question 47, the projected number of SCCHN patients eligible for PD-L1 testing has been estimated at approximately 892 to determine eligibility for either first- or second-line treatment. Because it is proposed that, with few exceptions, patients will only require one PD-L1 test, the projected number of patients who will use the proposed service (PD-L1 testing) in the first year would also be approximately 892 patients.

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.

It is not expected that there will be significant constraints in supply and demand of PD-L1 testing over the first 3 years of listing. There are no anticipated constraints in the supply of commercial PD-L1 testing kits for SCCHN. It is also anticipated in-house PD-L1 test methods will be developed over the one- to three-year timeframe, particularly at major hospital pathology laboratories with research capabilities. Over this time, MBS listing of PD-L1 testing may be sought for other indications or tumour types to determine access to PBS treatments.

To reduce the risk of leakage to other populations, it is proposed that the MBS restriction should specify PD-L1 testing of tumour tissue from patients with a diagnosis of unresectable recurrent or metastatic SCCHN.

PART 8 – COST INFORMATION

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

The final cost for the test has yet to be determined. It is expected that the fee will be consistent with other, similar assays already covered on the MBS.

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 and 4 hours to perform, depending on the instrumentation used and the 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 a new tissue sample from a patient diagnosed with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) to determine whether the requirements relating to PD-L1 expression for access to durvalumab monotherapy or durvalumab/tremelimumab combination therapy 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?

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

☐ Yes
☐ No

(b) If no, provide areas of concern:

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

☐ Yes
☐ No

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

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: