MSAC Application 1549

PD-L1 immunohistochemistry testing for access to pembrolizumab in combination with chemotherapy for first line treatment of triple negative breast cancer

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.

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: MSD (Australia) Pty Limited
ABN: 14 000 173 508
Business trading name: N/A

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?

N/A

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?

N/A

(c) Have you engaged a consultant on your behalf?

N/A

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

MSD has previously submitted two co-dependent applications for MBS funding of PD-L1 testing in non-small cell lung cancer (NSCLC) [Applications 1414, 1440, 1440.1]; and head and neck squamous cell carcinoma (HNSCC) [Applications 1522, 1522.1]. Application 1440.1 was supported by MSAC and a PD-L1 test in patients with NSCLC is now included on the MBS (Item 72184). Furthermore, HNSCC was also recently considered at the November 2021 meeting where MSAC supported amending MBS item 72814 for PD-L1 immunohistochemistry (IHC) testing to include patients with recurrent or metastatic HNSCC to identify those with a CPS≥20 who may be eligible for pembrolizumab monotherapy.

We understand that PASC and MSAC have extensive experience reviewing PD-L1 tests to determine eligibility for treatment with various PD-(L)1 inhibitors across a range of tumours. Furthermore, the specific scoring system (Combined Positive Score, CPS) used in this application is identical to the scoring system used in HNSCC, which was recently reviewed by both committees. We hope to incorporate some learnings from that previous submission into the co-dependent submission for PD-L1 testing and pembrolizumab in Triple Negative Breast Cancer (TNBC), to ensure that the significant unmet clinical need can be addresses as soon as possible.

4. Application title

PD-L1 (Programmed Death 1 Ligand) immunohistochemistry (IHC) testing for access to pembrolizumab in combination with chemotherapy for Triple Negative Breast Cancer (TNBC)

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)

Patients included within this application will have previously untreated locally recurrent inoperable or metastatic triple negative breast cancer (R/M TNBC) that is PD-L1 positive as determined by Combined Positive Score (CPS).

TNBC refers to breast cancer that does not present with the three most common types of receptors known to fuel breast cancer growth: estrogen (ER), progesterone (PR), and the human epidermal growth factor receptor 2 (HER2) gene. TNBC comprises approximately 15% of all breast cancers and it tends to be more aggressive than other breast cancer sub-types with a poor prognosis and is more likely to affect premenopausal women.

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 testing has already been listed for NSCLC (MBS item 72184) and an amendment to the existing item number to include head and neck squamous cell carcinoma (HNSCC) has been supported by MSAC (1522.1 Final MSAC PSD). It is suggested that this item number will also be amended to include TNBC patients.

It is proposed that IHC testing be used for the evaluation of Programmed Cell Death- Ligand 1 (PD-L1) expression to determine eligibility for treatment with pembrolizumab in combination with chemotherapy in patients with R/M TNBC. Tissue obtained through core or excisional biopsy at diagnosis of R/M TNBC will be used for IHC testing of PD-L1 expression (CPS≥10). The testing would be done by a pathologist alongside other immunohistochemical tests which are done routinely, and it is proposed that the test is a pathologist determinable test.

If newly obtained tissue is unavailable, then archival tissue can be used. This is consistent with the study protocol for KN-355. Based on the Information for Use (IFU) for PD-L1 IHC 22C3 pharmDx assay, the archival tissue should be <5 years old.

Based on the results of KEYNOTE-355 (KN-355), the clinically relevant cut-point for PD-L1 expression in R/M TNBC is CPS≥10. CPS is the number of PD-L1 staining cells divided by the total number of viable

tumour cells, multiplied by 100. Distinction of viable tumour cells, lymphocytes, and macrophages is essential for accurate denominator estimation. CPS is defined as follows:

$$\text{CPS} = \frac{\text{\# PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# of viable tumor cells}} \times 100$$

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)

(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:

MBS item 72814

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

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

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

☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group
☐ A new item that is proposing a way of clinically delivering a service that is new to the MBS
☐ A new item for a specific single consultation item
☐ A new item for a global consultation item(s)

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

☐ Yes
☒ No

(g) If yes, please advise:

N/A

8. What is the type of medical service/technology?

☐ 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)*:

☐ To be used as a screening tool in asymptomatic populations
☐ Assists in establishing a diagnosis in symptomatic patients
☐ Provides information about prognosis
☒ Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
☐ Monitors a patient over time to assess treatment response and guide subsequent treatment decisions
☐ 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):

N/A

(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

MSD intends to lodge an integrated co-dependent application for pembrolizumab in combination with chemotherapy for the treatment of R/M TNBC patients who are PD-L1 positive **REDACTED**.

Pembrolizumab (KEYTRUDA) is currently PBS listed for use in advanced malignant melanoma, adjuvant melanoma, relapsed/refractory Hodgkin's Lymphoma, 1L non-small cell lung cancer, 1L metastatic urothelial cancer, primary mediastinal B-cell lymphoma and 1L metastatic mismatch repair deficient colorectal cancer. At the time of this application, pembrolizumab is under consideration for head and neck squamous cell carcinoma, oesophageal carcinoma, renal cell carcinoma and endometrial cancer.

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

Trade name: KEYTRUDA
Generic name: pembrolizumab

12. If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

N/A

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

Single use consumables: The PD-L1 test comes as part of a kit (PD-L1 22C3 PharmDxkit). The kit is designed for 50 single use tests on the Dako ASL 48 platform. The 22C3 antibody concentrate is also available for use on alternate platforms (e.g. Ventana)

Multi-use consumables: Nil

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

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

Type of therapeutic good: The PD-L1 test is a class III in vitro diagnostic test which uses IHC (CT1056 Immunohistology cell marker IVDs)
Manufacturer's name: Dako Pty Ltd/Agilent
Sponsor's name: Agilent Technologies Australia Pty Ltd

(b) Has it been listed on the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)? If the therapeutic good has been listed on the ARTG, please state the ARTG identification numbers, TGA-approved indication(s), and TGA-approved purpose(s).

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(c) If a medical device is involved, has the medical device been classified by TGA as a Class III OR Active Implantable Medical Device (AIMD) under the TGA regulatory scheme for devices?

☒ Class III
☐ AIMD
☐ N/A

(d) Is the therapeutic good classified by TGA for Research Use Only (RUO)?

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15. (a) <u>If not listed on the ARTG</u>, 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 the therapeutic good is <u>not ARTG listed</u>, is the therapeutic good in the process of being considered by TGA?

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

(c) If the therapeutic good is NOT in the process of being considered by TGA, is an application to TGA being prepared?

☒ Yes (please provide details below)
☐ No

Estimated date of submission to TGA:

The ARTG entry 282596 includes the following indications:

- Companion Diagnostic (CDx) claims for NSCLC, Urothelial Carcinoma
- Analytical claim for Melanoma

On October 29, 2020, Agilent submitted application DV-2020-IVA-30161-1/Submission ID DA-2020-0930-1 to the TGA for inclusion of PD-L1 IHC 22C3 pharmDx into the ARTG as a Class 3 in vitro diagnostic (IVD) CDx as per the new TGA CDx IVD regulations (effective Feb 2020).

The proposed instructions for use (IFU) of the PD-L1 IHC 22C3 pharmDx under review include NSCLC, melanoma, and the addition of an intended use for PD-L1 testing as an aid in identifying HNSCC patients for treatment with pembrolizumab. That submission remains under review with the TGA.

Upon approval of the IFU currently under review, and when a new ARTG number is issued for this PD-L1 IHC 22C3 pharmDx submission under the new CDx regulations, Agilent will submit an application for the addition of an intended use for PD-L1 testing for patients with TNBC.

Proposed indication(s), if applicable: As above.

Proposed purpose(s), if applicable: For in vitro diagnostic use.

PD-L1 IHC 22C3 pharmDx is a qualitative immunohistochemical assay using monoclonal mouse anti-PD-L1, Clone 22C3 intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), and melanoma tissues using EnVision FLEX visualization system on Autostainer Link 48.

PART 4 – SUMMARY OF EVIDENCE

16. Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement', please do not attach full text articles; just provide a summary.

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	**Single Arm Trial**	**Pembrolizumab in Patients with advanced triple-negative breast cancer: Phase 1b KEYNOTE-012 Study**	A phase 1b trial of single-agent pembrolizumab was conducted for patients with advanced PD-L1-positive TNBC. Among the 27 patients who had received chemotherapy for both early and advanced disease, pembrolizumab demonstrated an ORR of 18.5%. This study supported further development of pembrolizumab for treatment of mTNBC.	https://ascopubs.org/doi/10.1200/JCO.2015.64.8931?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed	2 May 2016
2.	**Single Arm Trial**	**Pembrolizumab monotherapy for previously treated metastatic triple-negative breast cancer: cohort A of the phase II KEYNOTE-086 study**	A phase 2 single-arm trial of pembrolizumab for previously treated metastatic triple-negative breast cancer was conducted. 105 patients had PD-L-positive tumours. ORR was 5.7% in the PD-L1-positive populations, demonstrating pembrolizumab's durable antitumour activity in patients with previously treated mTNBC.	https://www.annalsofoncology.org/article/S0923-7534(19)31075-0/fulltext	1 March 2019

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
3.	**Randomised, open-label trial**	**Pembrolizumab versus investigator-choice chemotherapy for metastatic triple-negative breast cancer (KEYNOTE-119): a randomised, open-label, phase 3 trial**	A randomised, open-label phase 3 trial was conducted on patients who had metastatic triple-negative breast cancer who had completed previous systemic treatment. While pembrolizumab did not significantly improve overall survival in patients, it informed a combinatorial approach for the treatment of patients with mTNBC.	https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(20)30754-3/fulltext	1 April 2021
4.	**Randomised clinical trial**	**Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial**	A randomised, placebo-controlled phase 3 trial (N=847) was completed for untreated locally recurrent inoperable or mTNBC. A total of 566 participants received pembrolizumab-chemotherapy combination, and 281 received chemotherapy plus placebo. Among participants in the CPS≥10 subpopulation, median progression-free survival was 9.7 months, as opposed to 5.6 months with placebo-chemotherapy.	https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32531-9/fulltext	5 December 2020

17. Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application). Do not attach full text articles; this is just a summary.

	Type of study design	Title of research	Short description of research	Website link to research	Date
1.	**Randomised, double-blind**	**Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial**	Interim results from KN-355 are outlined in the table above. Results from the final analysis were presented at the San Antonio Breast Cancer Symposium (SABSC) 2021. In patients with CPS≥10, pembrolizumab was associated with a statistically significant benefit in terms of overall survival, with median OS of 23.0 months in the pembrolizumab-chemotherapy arm versus 16.1 months in the chemotherapy-only arm (HR: 0.73, 95% CI 0.55-0.95; p=0.0093).	https://oncologypro.esmo.org/meeting-resources/esmo-congress/keynote-355-final-results-from-a-randomized-double-blind-phase-iii-study-of-first-line-pembrolizumab-chemotherapy-vs-placebo-chemotherapy-for	19 September 2021 Peer reviewed publication expected in 2022.
2	**Concordance Study**	Analytical Comparison of a PD-L1 22C3 Antibody Laboratory-Developed Test Protocol on the Benchmark XT and PD-L1 IHC 22C3 pharmDx: Pan-Tumor and Triple-Negative Breast Cancer Samples	A study to compare PD-L1 22C3 antibody–based LDT on the BenchMark XT platform with the gold standard PD-L1 IHC 22C3 pharmDx, alone or together in a pan-tumor analysis, in patients with CC, ESCC, HNSCC, TNBC, or UC	Currently available as a poster and can be provided if needed.	Presented at SITC November 2021

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

18. **List all appropriate professional bodies/organisations representing the health professionals who provide the service. For MBS-related applications ONLY, please attach a brief 'Statement of Clinical Relevance' from the most relevant college/society.**

    Royal College of Pathologists Australasia.

    The statement of clinical relevance is not applicable. As MSAC has recommended PD-L1 testing in relation to pembrolizumab access for NSCLC and HNSCC, the clinical relevance of the test has been determined.

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

    As above.

20. **List the consumer organisations relevant to the proposed medical service (noting there is NO NEED to attach a support letter at the 'Application Lodgement' stage of the MSAC process):**

    Breast Cancer Network Australia (BCNA)

21. **List the relevant sponsor(s) and / or manufacturer(s) who produce <u>similar</u> products relevant to the proposed medical service:**

    Roche Products Pty Ltd (Ventana PD-L1 (SP142) assay)

22. **Nominate two experts who could be approached about the proposed medical service, and the current clinical management of the condition:**

    Name of expert 1: REDACTED

    Telephone number(s): REDACTED

    Email address: REDACTED

    Justification of expertise: REDACTED

    Name of expert 2: REDACTED

    Telephone number(s): REDACTED

    Email address: REDACTED

    Justification of expertise: 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

23. 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):

TNBC refers to breast cancer that does not present with the three most common types of receptors known to fuel breast cancer growth: estrogen (ER), progesterone (PR), and the human epidermal growth factor receptor 2 (HER2) gene. TNBC comprises approximately 15%[1] of all breast cancers and it tends to be more aggressive than other breast cancer sub-types with a poor prognosis and is more likely to affect premenopausal women. Additionally, there is an association of TNBC with BRCA1/2 mutations.[1] The majority of breast cancer patients that carry the BRCA1 mutation exhibit the triple negative phenotype.[1]

The main treatments for advanced breast cancer are surgery, chemotherapy and radiation therapy. Therapeutic options for TNBC are limited to non-targeted therapies due to a lack of an identified molecular target, which makes treatment of TNBC challenging. Taxanes, cyclophosphamide and anthracyclines are the preferred option in the neoadjuvant and adjuvant settings, but resistance develops rapidly upon disease recurrence.[2] This translates into decreased overall survival for TNBC patients compared to other breast cancer subtypes, making TNBC an area of high unmet clinical need.[2]

Breast cancer is the second most commonly diagnosed cancer in Australia and the most commonly diagnosed cancer in females, with 20,030 patients diagnosed in 2021.[3] It accounts for approximately 13% of all new cancers in Australia and 6% of cancer deaths. Overall survival of breast cancer has increased over the last thirty years, with 2013-2017 data showing a five-year overall survival rate of 92% (2013-2017).[3] However, TNBC can be more aggressive, difficult-to-treat and is often diagnosed at a more advanced disease stage, leading to poorer prognosis compared with breast cancer as a whole.

There is a paucity of Australian survival data specific to TNBC. However, the US National Cancer Institute (NCI) Surveillance, Epidemiology, and End Result Program (SEER) database reports a similar five-year overall survival rate of 90.3% for all breast cancers, irrespective of stage at diagnosis.[4] For TNBC, the corresponding figure is 76.9% across all stages, 65.4% if regional disease is present at diagnosis and only 12.2% for distant/metastatic disease, compared with 30-45% five-year overall survival for female breast cancer patients with other subtypes who were diagnosed with distant/metastatic disease.[4]

24. Specify the characteristics of patients with (or suspected of having) the medical condition, who would be eligible for the proposed medical service/technology (including details on how a patient would be investigated, managed and referred within the Australian health care system, in the lead up to being eligible for the service):

[1] Bcna.org.au. 2022. *Triple negative early breast cancer | Breast Cancer Network Australia | TCNM*. [online] Available at: <https://www.bcna.org.au/understanding-breast-cancer/what-is-breast-cancer/triple-negative-early-breast-cancer/> [Accessed 21 February 2022].

[2] Breastcancer.org. 2022. *Triple-Negative Breast Cancer: Overview, Treatment, and More*. [online] Available at: <https://www.breastcancer.org/symptoms/types/triple-negative> [Accessed 21 February 2022].

[3] <https://www.canceraustralia.gov.au/cancer-types/breast-cancer/statistics>

[4] National Cancer Institute. 2022 *Cancer Stat Facts: Female Breast Cancer Subtypes*. [online] Available at: <https://seer.cancer.gov/statfacts/html/breast-subtypes.html> [Accessed 8 March 2022].

The Cancer Council Victoria and Department of Health Victoria's *Optimal care pathway for people with breast cancer, Second Edition*[5] (see Attachment 1), provides detailed information on how breast cancer patients are investigated, referred and managed. To summarise:

- At least one-third of breast cancers are found in apparently asymptomatic women through routine breast cancer screening (BreastScreen Australia)
- Women who experience symptoms are likely to present to their general practitioner
- Initial investigations include:
    - Medical history and clinical breast examination
    - Imaging – mammography and/or ultrasound
    - Non-excision biopsy
- Patients with a positive result on any component above would be referred for specialist surgical assessment and/or further investigation.
- Diagnostic work-up is undertaken under the guidance of a specialist. This includes:
    - appropriate breast imaging tests including bilateral mammography and ultrasound
    - ultrasound of the axilla (including fine-needle aspiration of nodes if the axillary ultrasound is abnormal)
    - breast core biopsy, if not already undertaken (which allows determination of breast cancer receptor profiles [ER, PR, HER2]).
- Regardless of breast cancer subtype, patients would then be staged, performance status would be determined, and treatment planning would occur.

With respect to TNBC, patients with early-stage disease may be referred for neoadjuvant chemotherapy. It should be noted that PD-L1 testing is not relevant in this stage of disease and would not be undertaken, however, tissue may be obtained and archived. The expectation is that archived tissue would not be used for PD-L1 testing if the patient experiences recurrence unless a new tissue biopsy is not available.

It is proposed that TNBC patients would have access to PD-L1 testing via the MBS upon diagnosis of locally recurrent inoperable or metastatic disease to inform eligibility for pembrolizumab in the first-line setting.

PART 6b – INFORMATION ABOUT THE INTERVENTION

25. Describe the key components and clinical steps involved in delivering the proposed medical service/technology:

As IHC testing is a common procedure, it is proposed that PD-L1 IHC testing be carried out in any pathology laboratory holding the appropriate accreditation to claim pathology services through the MBS. While kits are available, they can only be performed on the Dako/Agilent platform. Antibodies can be validated on alternate platforms and MSD has previously developed protocols for this validation process.

The testing would be performed by a pathologist, and it is proposed that the test is a pathologist determinable test. The test would enable identification of those patients most likely to benefit from first line treatment with pembrolizumab in combination with clinician's choice of chemotherapy.

The PD-L1 assay used during the pembrolizumab TNBC clinical development program is known as the PD-L1 IHC 22C3 pharmDx Market Ready Assay (developed by Dako/Agilent). The PD-L1 IHC 22C3 pharmDx Market Ready Assay was used to determine PD-L1 expression in tumour tissue in order to explore the relationship between tumour PD-L1 expression and response to treatment with pembrolizumab. Furthermore, the CPS method has been validated by MSD for predicting response to pembrolizumab in R/M TNBC.

[5] Cancer Council Victoria and Department of Health Victoria 2021, Optimal care pathway for people with breast cancer, 2nd edn, Cancer Council Victoria, Melbourne.

Pembrolizumab is a highly selective humanised monoclonal antibody that targets the programmed death ligand-1 (PD-L1) receptor to potentiate an immune response. PD-L1 expression in R/M TNBC biopsies can be assessed using IHC testing with antibodies that bind specifically to the PD-L1 protein.

The therapeutically important cut-point for CPS has been shown to differ by tumour and is still being prospectively validated across different cancers in the Pembrolizumab clinical trial program. In R/M TNBC, the Phase 3 trial (KN-355) demonstrated that the addition of pembrolizumab to chemotherapy was associated with improved PFS and OS in patients with CPS $\geq$10.

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

At the time of lodging this application, PD-L1 testing is listed on the MBS for use in 1L NSCLC and and MSAC has supported an amendment to this MBS item to include patients with HNSCC. The PD-L1 22C3 pharmDx assay Market Ready Assay will be made commercially available in Australia. The PD-L1 22C3 pharmDx assay Market Ready Assay, including any applicable registered trademark, is TGA registered. The 22C3 antibody is also available for use on other platforms.

27. 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?

N/A

28. 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):

Accessibility
Patients with suspected advanced breast cancer undergo imaging and core biopsy as part of standard diagnostic work-up. Tissue biopsy allows determination of breast cancer receptor profiles (ER, PR, HER2).

It is proposed that PD-L1 expression testing with the 22C3 antibody would be carried out on the tissue sample when a patient with advanced disease is found to have the TNBC subtype. As IHC testing does not require a large volume of tissue, tissue availability should not limit access to PD-L1 testing.

Frequency
It is proposed that one PD-L1 test be performed once for each patient as part of the diagnostic biopsy, once the TNBC subtype has been confirmed. There is no known role for PD-L1 testing in ongoing monitoring of a patient's response to pembrolizumab treatment. Accordingly, repeat PD-L1 testing will not be required.

Sample consideration
As mentioned previously, in KN-355, PD-L1 status was tested using newly or recently obtained tissue samples in the majority of patients. However, archival tissue samples obtained before the diagnosis of R/M TNBC were considered adequate if neither a recently nor newly obtained biopsy from a locally recurrent inoperable or metastatic site were available.

MSAC previously considered that genuine TNBC would not change in PD-L1 status over time to the same extent as in lung cancer (Public Summary Document, Application No. 1570). MSAC also considered that a repeat biopsy would be impractical for many patients. Therefore, MSAC advised the PBAC that "the most prudent and practical balance would be to specify the 'most recent sample' for PD-L1 testing, which could be archival if necessary".

The co-dependent application will explore information on other relevant sample considerations as needed (pending available data).

Testing Considerations
IHC testing is a well-established technique in all major pathology labs. Laboratories already have the platform infrastructure and reagents to perform PD-L1 IHC testing.

It is acknowledged that there are differences between PD-L1 antibody assays for immune cell staining. Consequently, it is important that the antibody being used to assess PD-L1 status is aligned to the drug being considered. In this instance, the 22C3 antibody and CPS≥10 cut point should be used to determine eligibility for pembrolizumab.

29. 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:

Patients with suspected advanced breast cancer already undergo a core biopsy as part of their standard diagnostic work-up (to determine breast cancer receptor profiles – ER, PR, HER2). As outlined above, IHC testing does not require a large volume of tissue. As such, it is anticipated that PD-L1 testing would be undertaken on the same biopsied tissue sample and no additional healthcare resources would be required beyond the proposed service.

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

A certified pathologist would be responsible for conducting the test and reporting the results. Consistent with the introduction of diagnostic tests associated with access to other targeted therapies, pathologist training and quality assurance programs are underway to educate reporting pathologists to understand the scoring of CPS for TNBC samples.

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

A certified pathologist would be responsible for conducting the test and reporting the results. Specialists including (e.g. oncologists) will provide a referral for PD-L1 testing.

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

As IHC testing is a common procedure, it is proposed that PD-L1 IHC testing be carried out in any pathology laboratory holding the appropriate accreditation to claim pathology services through the MBS.

33. 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:

A certified pathologist would be responsible for conducting the test and reporting the results. Consistent with introduction of diagnostic tests associated with access to other targeted therapies, pathologist training and quality assurance programs would be developed with respect to delivery of diagnostic tests for access to treatments targeting the PD-1 pathway on the PBS.

The RCPA QAP are providing Technical modules for PD-L1 IHC for NSCLC, HNSCC, and TNBC in 2022. It is expected that this will be expanded to cover additional indications as required. In addition, MSD facilitates one day peer-to-peer workshops for Australian pathologists, with a training effectiveness performed with those who participate. This results in pathologists having greater experience in performing the test and applying the scoring methods.

34. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered

Laboratory

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

N/A

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

☒ Yes
☐ No

<u>PART 6c – INFORMATION ABOUT THE COMPARATOR(S)</u>

36. 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 is no PD-L1 testing and the current standard of care (monotherapy or combination chemotherapy regimens containing anthracycline, taxanes, capecitabine, gemcitabine or carboplatin).

37. 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

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

☒ In addition to (i.e. it is an add-on service)
☐ Instead of (i.e. it is a replacement or alternative)

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

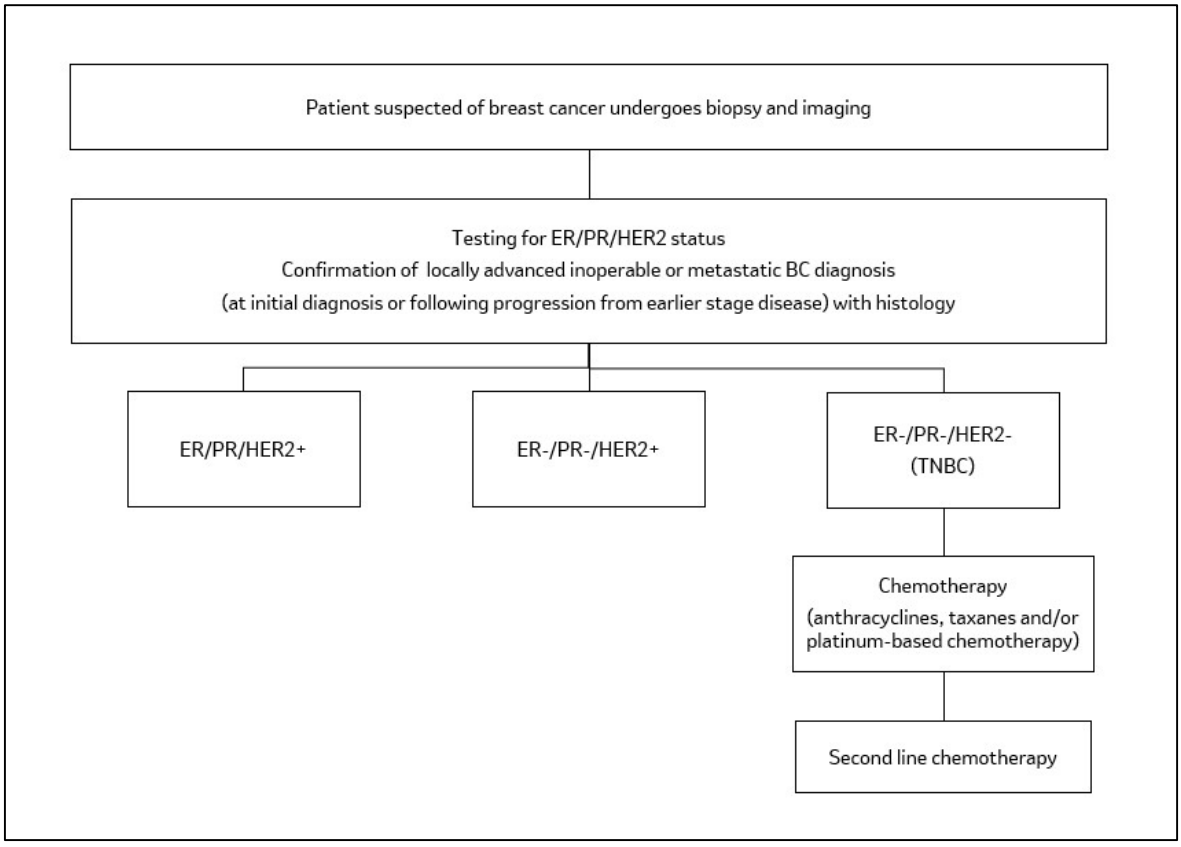
PART 6c CONTINUED – INFORMATION ABOUT ALGORITHMS (CLINICAL MANAGEMENT PATHWAYS)

39. Define and summarise the CURRENT clinical management pathway (algorithm) that patients follow when they receive the COMPARATOR service (i.e. the landscape before the proposed service is introduced). An easy-to-follow flowchart is preferred, depicting the current clinical management pathway), but dot-points would be acceptable. Please include health care resources used in the current landscape (e.g. pharmaceuticals, diagnostics and investigative services, etc.).

Patients presenting to their healthcare provider (e.g. GP, ED) with symptoms of breast cancer (including breast discomfort, inverted nipple, lumps, or nipple discharge) or following identification of a mass via BreastScreen Australia (e.g., mammogram) will have further investigations undertaken (refer to Q24 for more information).

A core biopsy is one component of the standard diagnostic work-up, which allows breast cancer receptor profiles (ER, PR, HER2) to be determined. Following determination of breast cancer sub-type and staging, treatment planning will take place. As outlined in Figure 1, the majority of patients with R/M TNBC, are currently treated with either monotherapy or combination chemotherapy regimens containing anthracycline, taxanes, capecitabine, gemcitabine or carboplatin. However, resistance develops rapidly upon disease recurrence. Thus, more effective treatments are needed.

Figure 1: Current clinical management algorithm



40. Define and summarise the PROPOSED clinical management pathway (algorithm) that patients would follow <u>after</u> the proposed service/technology is introduced, including variation in health care resources.

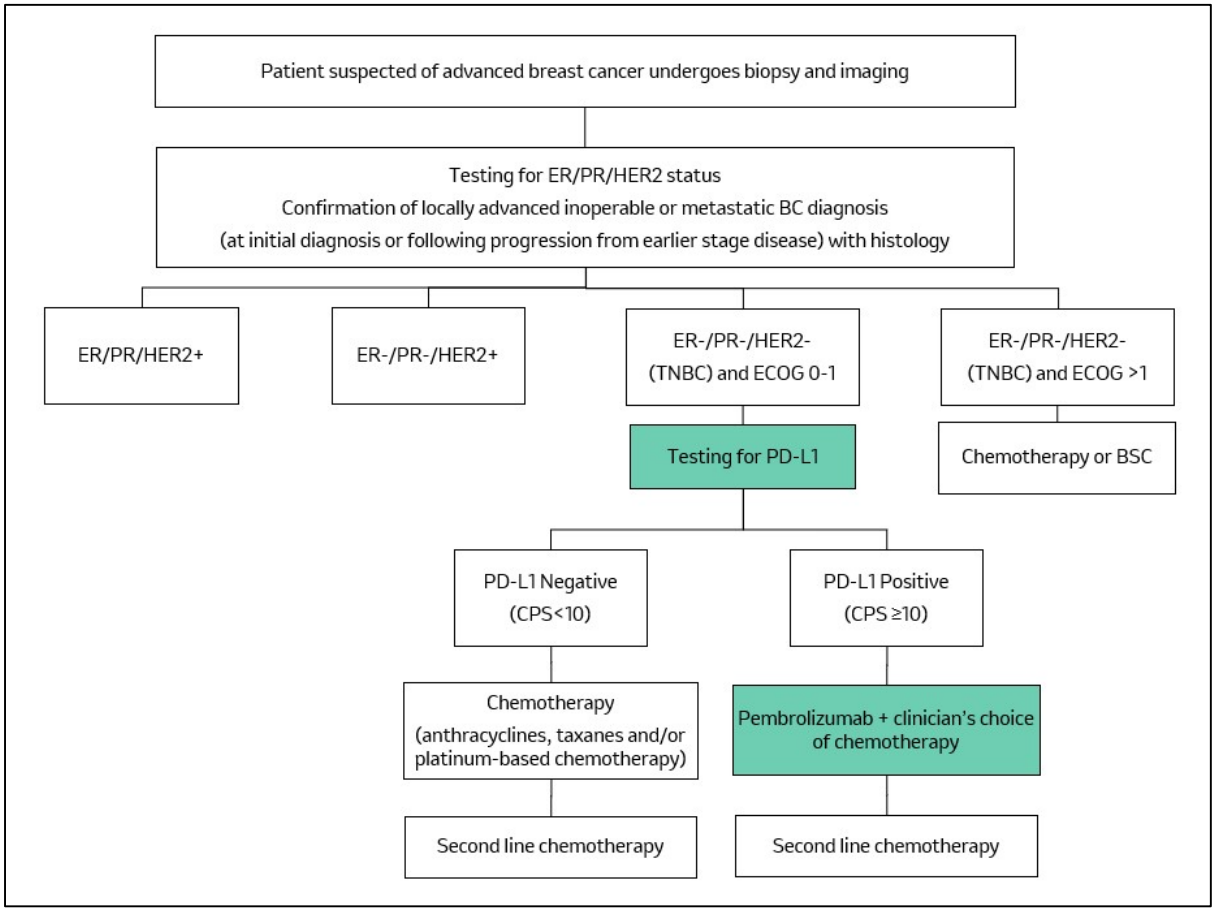
As shown in Figure 2, in the proposed clinical management algorithm, R/M TNBC patients who are ECOG stage 0 or 1 would be eligible for PD-L1 testing.

There are currently no biomarker tests reimbursed by MSAC for this purpose (i.e. access to Pembrolizumab) in this setting and therefore the proposed test will replace no test plus standard of care.

It is expected that PD-L1 testing and subsequent treatment with pembrolizumab will become the new standard of care over time; therefore, the majority of patients will receive PD-L1 testing as a routine part of their diagnostic work-up.

Patients who have a CPS≥10 would be considered for treatment with pembrolizumab in combination with chemotherapy by their oncologist for first-line therapy. As outlined previously, it is anticipated testing would occur on newly or recently obtained tissue for the majority of patients (i.e. the same tissue used for IHC testing of ER/PR/HER2 status). MSAC has previously advised that PD-L1 should be undertaken on the most recent sample, which could be archival if necessary (see Q28).

Figure 2: Proposed clinical management algorithm



<u>PART 6d – INFORMATION ABOUT CLINICAL OUTCOMES</u>

41. 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 testing followed by treatment with pembrolizumab plus chemotherapy is associated with superior outcomes compared to no testing and the current standard of care for patients with R/M TNBC.

Hence, the clinical claim is driven by three factors:

1. Acceptable safety and analytical performance of PD-L1 test. (To be assessed by MSAC.)
2. Superior effectiveness with acceptable safety of treating PD-L1 positive patients with pembrolizumab relative to standard of care without testing. (To be assessed by PBAC).
3. Clinical utility of the test + drug combination (To be assessed by MSAC/PBAC).

Clinical efficacy and utility claims plus safety outcomes will be based on KN-355.

The co-dependent submission will present efficacy and safety data for patients with PD-L1 expression CPS≥10 and the complement (CPS<10). 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 (CPS ≥10), it will be possible to determine whether the patient is likely to respond well to pembrolizumab in comparison with the current standard of care.

42. Please state what the overall clinical claim is:

☒ Superiority
☐ Non-inferiority

43. List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

Clinical Effectiveness Outcomes

- Primary endpoints: Progression free survival (PFS) and Overall Survival (OS) with PD-L1 positive tumours who have a CPS ≥10.
- Secondary endpoints: Objective Response Rate (ORR), Duration of Response (DOR) and Disease Control Rate (DCR) in patients with PD-L1 positive tumours who have a CPS ≥10.

Safety Outcomes

- Primary endpoint: Percentage of Participants Who Experience an Adverse Event (AE)
- Percentage of Participants Who Discontinue Study Drug Due to an AE

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

EVALUATION VIA REPORTED INCIDENCE		
Estimated no. of persons diagnosed (incident) with breast cancer (includes all stages) (2021)	20,030	Cancer Australia. 2022. *Breast cancer in Australia statistics.* Available at: <https://www.canceraustralia.gov.au/cancer-types/breast-cancer/statistics> [Accessed 9 March 2022].
Percentage of cases diagnosed with Stage IV (metastatic)	~8% (4.6-10.1%)	AIHW. 2022. Breast cancer in Australia: an overview. Data tables: Chapter 2 Incidence of breast cancer. Available at: <https://www.aihw.gov.au/getmedia/3d93914e-6e3a-44f6-b13c-c7805b1d62b4/14225-chapter2_incidence.xls.aspx>. [Accessed 9 March 2022].
Total incident Stage IV (metastatic) patient population	~1,602 *(=20,030 x 8%)*	Calculated
Proportion patient population that is Triple Negative	~15%	Breast Cancer Network Australia. 2022. Triple negative early breast cancer. Available at: <https://www.bcna.org.au/understanding-breast-cancer/what-is-breast-cancer/triple-negative-early-breast-cancer>. [Accessed 22 February 2022].
1L metastatic (stage IV) TNBC	~240 *(=1,602 x 15%)*	Calculated

^ AIHW data indicates that 4.6% of breast cancer patients are diagnosed at Stage IV. This would increase to 10.1% if all cases where stage at diagnosis are unknown were assumed to be Stage IV. Given the aggressive nature of TNBC and the fact that many patients are younger and would not be part of population screening, it may be reasonable to assume that a higher proportion of TNBC patients may be diagnosed at Stage IV.

45. Estimate the number of times the proposed medical service/technology would be delivered to a patient per year:

Per the KN-355 protocol, one PD-L1 test would be performed following a diagnosis of R/M TNBC. The test would be undertaken prior to commencement of pembrolizumab in combination with chemotherapy to enable identification of those patients most likely to benefit from treatment. There is currently no known role for PD-L1 testing in monitoring a patient's response to pembrolizumab treatment, hence repeat testing is not required.

46. How many years would the proposed medical service/technology be required for the patient?
It is presumed that only one PD-L1 test is required per patient through the course of disease.

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

As presented in Item 44, the estimated number of new patients who will utilise the PD-L1 test is approximately 240 in the first year. Since the PD-L1 test is a one-off test, which will only be performed at diagnosis of locally recurrent inoperable or metastatic TNBC, the estimated number of patients who will be tested in the forthcoming years will include incident patients only.

48. Estimate the anticipated uptake of the proposed medical service/technology 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.

Currently, the majority of patients who are diagnosed with R/M TNBC will receive monotherapy or combination chemotherapy with anthracycline, taxanes, capecitabine, gemcitabine or carboplatin.

Based on the results of KN-355, pembrolizumab plus chemotherapy will become the new standard of care for first line R/M TNBC. Given the poor prognosis of R/M TNBC (12.2% five-year survival for patients diagnosed with Stage IV disease)[6], the uptake of the PD-L1 testing is assumed to be 100%. As such, it is anticipated that around 750 services would be conducted over the next three years.

Only those patients with expression of PD-L1 (CPS≥10) are eligible for pembrolizumab. Therefore, the addition of pembrolizumab to chemotherapy will be restricted to those who have high PD-L1 expression in tumour tissues. The risk of leakage for PD-L1 testing is minimal, as testing would be restricted to only those patients who would eventually be eligible for pembrolizumab.

[6] National Cancer Institute. 2022 Cancer Stat Facts: Female Breast Cancer Subtypes. [online] Available at: <https://seer.cancer.gov/statfacts/html/breast-subtypes.html> [Accessed 8 March 2022].

PART 8 – COST INFORMATION

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

The final fee request will be contingent on decisions made by Dako/Agilent. MSD anticipates that the fee for the proposed service would be consistent with other immunohistochemical tests currently available on the MBS.

50. Specify how long the proposed medical service/technology typically takes to perform:

The IHC service testing for PD-L1 expression can take between 2.5-4 hours depending on instrumentation and protocol used.

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

Category 6 – Pathology Services
Immunohistochemical examination by immunoperoxidase or other labelled antibody techniques using the programmed cell death ligand 1 (PD-L1) antibody of tumour material from a patient diagnosed with non-small cell lung cancer, recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx or locally recurrent unresectable ***or locally recurrent inoperable or metastatic triple negative breast cancer*** Fee: To be determined Benefit: To be determined

52. If public funding is sought through an alternative (non-MBS) funding arrangement, please draft a service description to define the population and usage characteristics that defines eligibility for the service/technology.

N/A