



Australian Government

Department of Health

MSAC Application 1674

Dostarlimab in mismatch repair deficient recurrent or advanced endometrial 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 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.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on 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):

Corporation name: GlaxoSmithKline

ABN: **REDACTED**

Business trading name: **REDACTED**

Primary contact name: REDACTED

Primary contact numbers

Business: NA

Mobile: **REDACTED**

Email: **REDACTED**

Alternative contact name: REDACTED

Alternative contact numbers

Business: NA

Mobile: **REDACTED**

Email: **REDACTED**

2. (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

BACKGROUND

Endometrial cancer (EC) is a malignancy of the endometrium, the inner lining of the uterus (uterine corpus).

Because most endometrial cancers are symptomatic, the majority are diagnosed early (~80% at stage I) when the cancer is still confined to the uterus. Early diagnosis is associated with a good prognosis: 70% of localised cases (confined to the primary site; also referred to as stage I) can be cured with surgery, and their 5-year survival rate is 95%. Despite a good prognosis, patients diagnosed with localised disease are at risk of recurrence. Patients diagnosed with advanced disease, while only representing approximately 9% of cases at diagnosis, have a poor prognosis, with 5-year survival rates as low as 17%. Second-line (2L) treatment for recurrent or advanced endometrial cancer is an area of unmet medical need.

The DNA mismatch repair (MMR) system is a mechanism utilised to restore DNA integrity after mismatch errors have occurred. In normal tissue, the MMR system recognises and repairs base mismatches that occur during DNA replication. This process is controlled by 4 genes, including MLH1, MSH2, MSH6, and PMS2. Inactivation in any one of these genes results in deficiency of the MMR system. This deficiency of MMR (dMMR) function can be a result of hereditary gene mutation (as in Lynch syndrome), spontaneous mutation of the MMR gene in tumours, or methylation of the MMR gene, both seen in sporadic dMMR endometrial cancer.

Comprehensive genomic and transcriptomic analysis of endometrial cancers have defined a subgroup of tumours that present with a high frequency of somatic mutations that are attributable to defects in mismatch repair. Endometrial cancer has the highest rate of dMMR/MSI-H across all cancer types. A subgroup of endometrial cancers present with defects in MMR are considered microsatellite instability - high (MSI-H). A common and established method to categorize tumours and to test for the presence of the MSI-H phenotype is by assessing the expression of the four MMR proteins using an immunohistochemistry (IHC) assay. Loss of expression of at least 1 MMR protein in this assay will result in the tumour being called dMMR with a phenotype of MSI-H.

Several systematic literature reviews have shown that the current chemotherapies used do not offer better or worse treatment outcomes, including overall survival (OS), progression-free survival (PFS), disease-free survival (DFS), recurrence, and tumour response, in endometrial cancer patients with this specific subset of tumour. As such, the prognostic value of dMMR/MSI-H remains unclear based on the current literature findings.

dMMR or MSI-H endometrial tumours have an elevated mutation burden leading to the expression of unique tumour antigens, or neoantigens, infiltration of T-cell lymphocytes, and overexpression of PD-L1 in the tumour and microenvironment. dMMR/MSI-H status is predictive of clinical benefit from PD-1 inhibitors that block PD-1's interaction with its ligands, restoring cytotoxic T-cell activity and freeing the T-cell to kill the tumour cell.

Dostarlimab is a humanised, monoclonal antibody of the immunoglobulin G4 isotype that binds to PD-1, resulting in inhibition of binding to PD-L1 and PD-L2. This results in the release of inhibition of PD-1 pathway-mediated immune responses. GSK intend to register dostarlimab for use as monotherapy for the treatment of adult patients with recurrent or advanced dMMR/MSI-H endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen utilising results from the GARNET study.

The GARNET study of dostarlimab was the largest prospective evaluation to date of an anti-PD-1/L1 agent as monotherapy in patients with advanced or recurrent endometrial cancer who had progressed on or after prior platinum-based therapy.

Dostarlimab demonstrated a durable response in the dMMR/MSI-H cohort with an overall response rate (ORR) of 44.7% (median duration of response [DOR] was not reached) and a disease control rate (DCR) of 57.3%.

Dostarlimab was generally well tolerated with a manageable adverse events profile; the most common treatment-emergent adverse events (TEAEs) observed in GARNET were diarrhoea, asthenia, fatigue and nausea, and the occurrence of serious TEAEs (\geq Grade 3) was low (11.5%) with a low discontinuation rate (**REDACTED**). No deaths were associated with dostarlimab.

GSK notes that dMMR testing in endometrial cancer for treatment with an anti-PD-/L1 agent has been considered as part of another application to MSAC (Application 1508) which has a ratified PICO. GSK believes this PICO could be adjusted to be limited to endometrial cancer and provides it as an attachment for reference.

3. Application title

Dostarlimab in mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer

4. 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 with recurrent or advanced endometrial cancer which are mismatch repair deficient (dMMR) who have progressed following prior treatment.

5. 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)

Immunohistochemistry (IHC) test for identification of Mismatch Repair Deficiency (dMMR) for access to dostarlimab in patients with recurrent or advanced endometrial cancer.

6. (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 # 72847 – IHC testing for MMR is already performed in most pathology centres under this MBS item number. This item could be amended for testing for eligibility for dostarlimab.

(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):

(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

(g) If yes, please advise:

PBS funding will be sought for dostarlimab treatment of patients with endometrial cancer which are mismatch repair deficient (dMMR) who have progressed following prior treatment.

7. 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

8. 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

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

- Pharmaceutical / Biological
 Prosthesis or device
 No

10. (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):

(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

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

Trade name: Not determined as yet
Generic name: Dostarlimab

11. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Protheses List?

N/A

(b) If yes, please provide the following information (where relevant):

N/A

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Protheses List Advisory Committee (PLAC)?

N/A

(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?

N/A

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

N/A

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

N/A

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

GSK is proposing that clinicians use the same dMMR antibody clones that they use for endometrial cancer and colorectal cancer. Examples of clones that are used in Australia include:

- MLH1- ES05 (Dako)
- MSH2- G219-1129 (Ventana)
- MSH6 – 44 (BD Biosciences)
- PMS2 – EPR3947 (Ventana)

GSK is not planning to commercialise a new dMMR test. Hence the remainder of part 3 has not been completed.

13. (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:

N/A

- (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

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

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

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

- Yes (if yes, please provide details below)
 No

ARTG listing, registration or inclusion number: 343608, 343607, 324144, 287144, 283317, 279628, 269420, 240833, 239099, 216549, 248292, 224218, 175635, 262536, 183436, 229929, 240833, 224829, 224373, 214553, 212747, 208140, 178442

TGA approved purpose(s), if applicable: To be used in histology and cytology to provide information about the presence and localisation of specific proteins and antigens present in histological tissue sections, cytological smears and fluids.

(Please note that all of the above registered tests have approval to be used for IHC testing of tissue section proteins. As GSK is not pairing with a specific test manufacturer, we have left the response to this question broad to accommodate different laboratory practices. However, this does not necessarily mean that all of these tests will be used in practice.)

15. 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?

N/A

16. 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?

N/A

PART 4 – SUMMARY OF EVIDENCE

17. 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	Short description of research	Website link to journal article or research (if available)	Date of publication
1.	Review	A review of the current testing methodologies for the detection of mismatch repair deficiency in tumours	A summary of the key issues underlying the science, evidence and uncertainties regarding the use of microsatellite instability (MSI) testing and immunohistochemical analysis for the detection cancers of mismatch repair deficiency (dMMR) in the Australian setting.	link to MSAC Review paper	January 2020
2.	Single arm (Phase I)	Clinical activity and safety of the anti-programmed death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced mismatch repair-deficient endometrial cancer. A non-randomized phase 1 clinical trial. GARNET (NCT02715284)	Part 2B: Cohort A1 Design: Phase I Intervention: Dostarlimab (TSR-042), MSI testing was undertaken by IHC Population: participants with mismatch repair deficient microsatellite instability high (dMMR) endometrial cancer who have progressed on or after platinum doublet therapy. Participants have received no more than 2 lines of anti-cancer therapy for recurrent or advanced (Stage \geq IIIB) disease.	<i>JAMA Oncol.</i> 2020;6(11):1766-1772. doi: 10.1001/jamaoncol.2020.4515 link	October 1, 2020

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research (if available)	Date of publication
	Clinical guidelines	Various	A number of Guidelines provide recommendations for dMMR testing. Overall, strong recommendations exist for CRC, endometrial, and ovarian cancers, with additional recommendations where red flag criteria for Lynch Syndrome is met. See Appendix for specific advice.	www.rcpa.edu.au NCCN Guidelines	
	Analysis of endometrial cancers using IHC and MSI methods.	Stelloo E, Jansen A, Osse E, et al. Practical guidance for mismatch repair deficiency testing in endometrial cancer.	The aim of this study was to define the optimal approach for MMR-deficiency testing and to clarify discrepancies between microsatellite instability (MSI) analysis and immunohistochemical (IHC) analysis of MMR protein expression. Found that MSI and IHC analysis are highly concordant and an IHC approach is sufficient for determining MMR-deficiency in endometrial cancer.	Ann Oncol. 2017;28(1):96-102. doi: 10.1093/annonc/mdw542	1 January 2017
	Comment on Stelloo et al 2017	Powell 2017. Immunohistochemistry to determine mismatch repair-deficiency in endometrial cancer: the appropriate standard.	Comment on the research by Stelloo. States that IHC is the appropriate standard for establishing mismatch repair in endometrial cancer. Also states that MMR status has not consistently been shown to have a prognostic or predictive value for patients with endometrial cancer	Annals of Oncology 2017;28(1): 9-10.	1 January 2017

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research (if available)	Date of publication
	Prospective, single centre cohort study	Mismatch repair deficiency identifies patients with high-intermediate-risk (HIR) endometrioid endometrial cancer at the highest risk of recurrence: A prognostic biomarker.	Assessment of the correlation between mismatch repair (MMR) status, disease recurrence patterns, and recurrence-free survival (RFS) in patients with high-intermediate-risk (HIR) endometrioid endometrial cancer (EEC).	Backes et al 2019 https://doi.org/10.1002/cncr.31901	
	Retrospective, multicentre cohort study.	Mismatch repair deficiency as a predictor of adjuvant radiotherapy response in endometrioid endometrial carcinoma.	Investigation of the predictive value of MMR status in terms of survival benefit after adjuvant radiotherapy in patients with stage1B/II, grade 3 endometrial cancer. The study demonstrated the predictive ability of MMR IHC to identify women who likely have increased benefit from radiotherapy.	Kommoss et al 2019 https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.5586	2019
	Retrospective, multi-centre cohort study	Mismatch repair deficiency and aberrations in the Notch and Hedgehog pathways are of prognostic value in patients with endometrial cancer.	Show that MMRd was associated with significant better survival but not with decreased risk for relapse.	Polychronidou et al 2018 https://doi.org/10.1371/journal.pone.0208221	2018

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research (if available)	Date of publication
	Retrospective multicentre cohort study	Mismatch repair deficiency as a predictive marker for response to adjuvant radiotherapy in endometrial cancer.	<p>Radiotherapy improved survival in patients with MMR-deficient EC.</p> <p>Patients with MMR-proficient ECs did not experience improved survival after radiotherapy.</p> <p>MMR status could be used to select patients that benefit most from adjuvant radiotherapy.</p>	<p>Reijnen et al 2019</p> <p>https://www.sciencedirect.com/science/article/pii/S0090825819302707</p>	2019
	Retrospective single centre cohort study.	Lack of association between deficient mismatch repair expression and outcome in endometrial carcinomas of the endometrioid type.	<p>Deficient mismatch repair is not associated with outcome in endometrioid carcinomas.</p> <p>Mismatch repair deficiency is not associated with outcome in FIGO stage subgroups.</p> <p>MMR deficiency does not seem to be a good prognostic marker in endometrioid type endometrial carcinomas.</p>	<p>Ruiz et al 2014</p> <p>https://www.sciencedirect.com/science/article/pii/S0090825814009147</p>	2014
	Retrospective multicentre cohort study	Endometrial cancer risk and survival by tumor MMR status	<p>Assessment of the association between tumor MMR status and the risk of developing EC and survival following a diagnosis of EC. Risk of EC was not associated with MMR status. Overall survival did not differ by tumor MMR status. Suggest that patients with somatic MMRd have poorer EC-specific survival.</p>	<p>Nagle et al 2018</p> <p>https://doi.org/10.3802/jgo.2018.29.e39</p>	2018

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research (if available)	Date of publication
	Retrospective single centre cohort study	Clinicopathologic implications of DNA mismatch repair status in endometrial carcinomas.	Investigated the clinicopathologic significance of deficient MMR and Lynch syndrome presumed by MMR analyses in unselected endometrial carcinomas. Clinicopathologic variables and prognosis were compared according to MMR status and sporadic/PLS classification. Deficient MMR showed only trends towards favorable overall survival (OS) compared with intact MMR	Shikama et al 2016 https://doi.org/10.1016/j.ygyno.2015.11.032	2016
	Pathologist Survey	Mascarenhas L et al. Current mismatch repair deficiency tumor testing practices and capabilities: A survey of Australian pathology providers	Design: RCPA accredited laboratories in Australia were surveyed. Aim: To survey the current availability of screening for CRC and endometrial cancer (EC) tumour dMMR. Results: The response rate was 80%, with 95% of laboratories conducting MMR IHC testing. 37% are screening endometrial cancer specimens for MMR on clinician request, 27% on 'red flag' and 12% are screening all.	Asia-Pac J Clin Oncol 2018; 14:417-25. DOI: 10.1111/ajco.13076	7 October 2018

18. 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.

None identified

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

- 19. 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

(IHC testing of MMR is already undertaken under MBS item #72847, so we have not requested a letter of support to comment on the service or the fee. Please refer to “ENDOMETRIAL CANCER STRUCTURED REPORTING PROTOCOL” for the College’s specific recommendations on dMMR IHC testing [items G4.01-G4.02])

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

Medical Oncology Group of Australia (MOGA)

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

There are no associations specifically supporting patients with endometrial cancer but some that generally support patients with cancer including Cancer Australia and Cancer Council.

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

Not applicable – GSK is not aligning with a specific manufacturer of IHC tests.

- 23. 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**

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), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

24. 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:

Endometrial cancer is the sixth most common type of malignancy diagnosed in women globally and the second most common gynaecological cancer. Because most endometrial cancers are symptomatic, the majority are diagnosed early (~80% at stage 1) when the cancer is still confined to the uterus. Early diagnosis is associated with good prognosis: 70% of localised cases can be cured with surgery and their 5-year survival rate is 95%. Despite a good prognosis, patients diagnosed with local disease are at risk of recurrence.

Despite treatment, an estimated 13-15% of patients with endometrial cancer will experience disease recurrence. Advanced or recurrent disease is life-threatening and incurable, with a 5-year survival rate of ~20%. For those that relapse on or after first-line platinum-based therapy, median life expectancy is less than 1 year. Approximately 25% of endometrial cancers are dMMR and could be treated with dostarlimab.

The most common symptom associated with endometrial cancer is abnormal vaginal bleeding present in approximately 90% patients. This includes a change in menstrual cycles, bleeding between menstrual cycles, or bleeding after menopause. Additionally, non-bloody abnormal vaginal discharge may be a sign of endometrial cancer. In advanced stages of endometrial cancer, other symptoms may be present, including pelvic pain during urination or intercourse, the presence of a mass, or unintentional weight loss.

25. 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:

The proposed patient population includes patients diagnosed with advanced or recurrent endometrial cancer that have progressed following prior treatment.

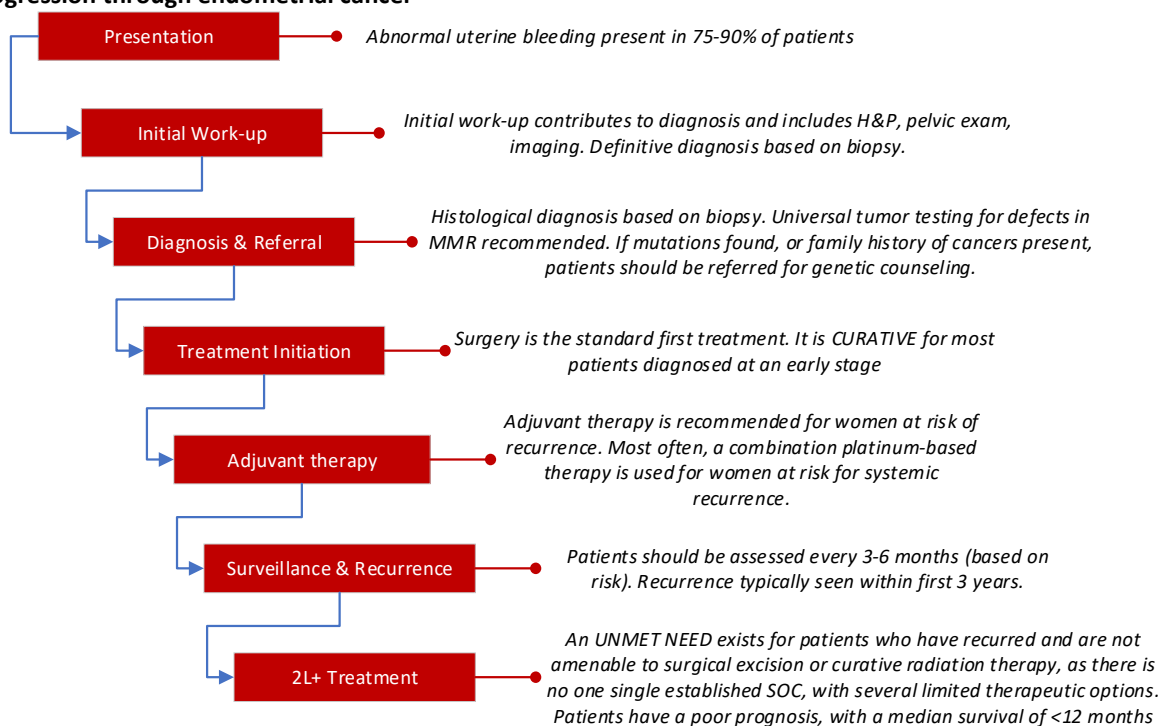
The median age at diagnosis of endometrial cancer is 63 years old from 15 to 100+. Patients with hereditary dMMR (Lynch Syndrome) are likely to be younger, given their higher risk of developing certain cancers before 50 years of age (Colombo et al 2016).

In terms of presentation, patients with hereditary dMMR may initially be referred to a familial cancer clinical after a discussion of family history with their doctor and would then undergo dMMR testing. Additional family members may be offered predictive testing to find out whether they too have Lynch syndrome (i.e. the same genetic mutation). If the result is positive, a surveillance plan will be drawn up to ensure any tumour is detected early.

Patients who present with symptoms of endometrial cancer will receive further investigations. To identify metastases, computerised tomography (CT) scans, magnetic resonance imaging (MRI) scans, positron emission tomography (PET) scans, ultrasounds, and X-rays may also be undertaken. Once diagnosed, many patients undergo surgery, with tissue from the resection tested by pathologists. This testing can include IHC for dMMR. If resected tissue is not available, biopsy tissue can also be used. Biopsy material has been shown to be as reliable as resection specimen material in detecting a dMMR.

This treatment pathway is part of standard care in Australia, so the current management is not expected to change up to the point of referral for the service.

Progression through endometrial cancer



26. 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):

Patients receive an initial diagnosis work-up. Tissue would be obtained from scoping procedures or surgical resection if patients have received surgery and sent to the pathology laboratory for histology/staging and molecular testing. For some patients, MMR testing will be completed as part of this process.

For the remaining patients whose tumours are not already tested for dMMR, it is proposed that MMR testing is undertaken once the patients has progressed following prior treatment and thus become eligible for treatment with dostarlimab.

Please refer to attachment 1 and 2 for the current and proposed clinical algorithms, respectively.

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

The IHC method used antibodies directed against each MMR protein to detect the expression of the proteins in the tumour cells. Tests are performed on formalin-fixed paraffin-embedded tumour tissue to identify one of four MMR proteins (MLH1, MSH2, MSH6 and PMS2). Protein expression is scored positive if at least one cancer cell nucleus shows staining, negative if none of the tumour cells show staining with positive internal control, and not applicable if neither tumour nor stromal cells show protein expression.

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

No

29. 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

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

Patients are expected to receive one test throughout the course of their disease. Testing must be performed in an accredited laboratory by a certified pathologist.

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

A biopsy or surgical resection is required to obtain tissue for the IHC test. These procedures are part of standard management of endometrial cancer, so they would not be an additional burden to patients.

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

Pathologists will be responsible for delivering the MMR IHC test. If found to be dMMR, treatment with dostarlimab would be managed by medical oncologists.

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

N/A

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

Medical oncologists would request the MMR IHC test for the purposes of dostarlimab treatment, for the proportion of patients for whom MMR testing was not previously undertaken as part of routine care.

35. 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:

IHC testing is a well-established technique in all major pathology labs. Most laboratories already perform the MMR IHC test, either routinely or based on clinician request. Testing must be performed in an accredited laboratory by a certified pathologist. Laboratories should adhere to the Royal College of Pathologists of Australasia Structured Reporting Protocols.

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

- Inpatient private hospital (admitted patient)
- Inpatient public hospital (admitted patient)
- Private outpatient clinic
- Public outpatient clinic
- Emergency Department
- Private consulting rooms - GP
- Private consulting rooms – specialist
- Private consulting rooms – other health practitioner (nurse or allied health)
- Private day surgery clinic (admitted patient)
- Private day surgery clinic (non-admitted patient)
- Public day surgery clinic (admitted patient)
- Public day surgery clinic (non-admitted patient)
- 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:

N/A

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

- Yes
- No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

- 38. 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 comparators are:

1. **Diagnostic accuracy** – IHC is the appropriate standard for establish mismatch repair in endometrial cancer, given the frequency of MSH6 and PMS2 mutations as a cause of dMMR in endometrial cancer and Lynch syndrome (MSAC 2020). This supports that no comparison is necessary.
2. **Therapeutic effectiveness:** no ICH dMMR testing plus standard of care second-line treatment options.

For comparison 2, therapeutic effectiveness of current clinical practice (IHC testing in some 2L EC patients + SoC in all patients) to the proposed clinical practice (IHC testing in all 2L EC patients with dMMR patients treated with dostarlimab and all remaining patients receiving standard of care).

Real world data has been collected in the UK for outcomes from 2nd-line treatment which could be used as a comparator. **REDACTED**

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

- Yes (please list all relevant MBS item numbers below)
 No

MBS Item # 72847

- 40. Define and summarise the current clinical management pathway/s 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):**

Patients will undergo a single event of dMMR testing, either at the time of initial diagnostic work-up or on development of recurrent endometrial cancer.

Response rates in the setting of progression after first-line platinum-containing regimens are poor, and there is no standard of care. In general, use of chemotherapy in this setting is limited by low response rates and is associated with high rates of toxicity, such as cytopenias and neuropathies. Re-administering carboplatin and paclitaxel may be appropriate in patients if there has been a substantial amount of time since the initial administration, usually greater than 6 months; alternatively, various single-agent or combination chemotherapies may be used. Examples of agents used as single or combination therapies include cisplatin, carboplatin, paclitaxel, doxorubicin, liposomal doxorubicin, ifosfamide, or topotecan. The most common treatment is doxorubicin.

- 41. (a) Will the proposed medical service 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 instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:**

42. 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):

If patients are found to be dMMR, they would receive treatment with dostarlimab (500 mg IV every 3 weeks for the first 4 cycles followed by 1000mg every 6 weeks thereafter for up to 2 years). All other patients would continue to receive standard management.

It is hypothesised that treatment with dostarlimab will delay disease progression and mortality and may have a superior safety profile. Therefore, healthcare resource utilisation in the following areas could potentially be reduced:

- Adverse event related treatment;
- Ongoing disease management resource utilisation;
- Post-progression therapy; and
- Palliative care costs.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

43. 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):

Testing in all patients + dostarlimab administered to dMMR patients and standard of care administered to the remainder provides superior effectiveness and safety when compared to no testing and standard of care administered to all patients.

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

- Superiority
 Non-inferiority

45. 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:

- Serious adverse events (any untoward medical occurrence that results in death, is life-threatening, result in persistent or significant disability or incapacity, result in or prolongs hospitalisation, is a congenital anomaly/birth defect, or other important medical event)
- Adverse events
- Toxicities
- Safety of the MMR IHC test (including rates of re-biopsy required for testing)

Clinical Effectiveness Outcomes:

- progression free survival (PFS) according to RECIST 1.1
- Objective response rate (ORR) according to RECIST 1.1
- Overall survival (OS)
- Patient reported quality of life outcomes

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

There were 3115 cases of uterine cancer, of which 92% would be endometrial cancer, diagnosed in Australia in 2019 (AIHW Cancer in Australia). Approximately 13% of endometrial cancers recur and 18% are diagnosed as advanced or metastatic. Of these approximately 70% will receive 1L treatment which, on recurrence approximately 40% will receive 2L treatment. This results in approximately 250 cases of EC treated 2L. Approximately 30% of these cases will have previous IHC testing.

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

Patients would require only 1 test through the course of their disease.

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

The proposed medical service should only be required in year 1 (if the patient has not previously had a test or previous results are not available)

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

A proportion of patients will already have undergone testing for dMMR as part of routine clinical practice and already occurs relatively frequently in endometrial cancer. Approximately 30% of cases will have had prior IHC testing since all suspected Lynch syndrome cases should be tested.

Thus 75 recurrent endometrial cancer cases will have had prior testing, leaving 175 cases requiring additional IHC tests.

50. 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:

IHC MMR testing is routinely undertaken in Australian laboratories. It is not envisaged the small increase in tests necessary to identify patients with recurrent endometrial cancer will stretch the capabilities of these laboratories. It is also unlikely that there will be leakage to other populations where the benefit of testing is limited to identifying recurrent endometrial cancer which will benefit from treatment with dostarlimab.

PART 8 – COST INFORMATION

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

The MMR IHC is currently billed to MBS item 72847 (IHC with 4-6 antibodies). The Medicare fee of \$89.40 is not expected to change.

For patients who already incur an MBS item for IHC testing, expanding the testing to include the 4 MMR proteins may result in a change in the distribution of utilisation of item numbers, with a shift towards item numbers 72849 (7-10 antibodies) and 72850 (11+ antibodies).

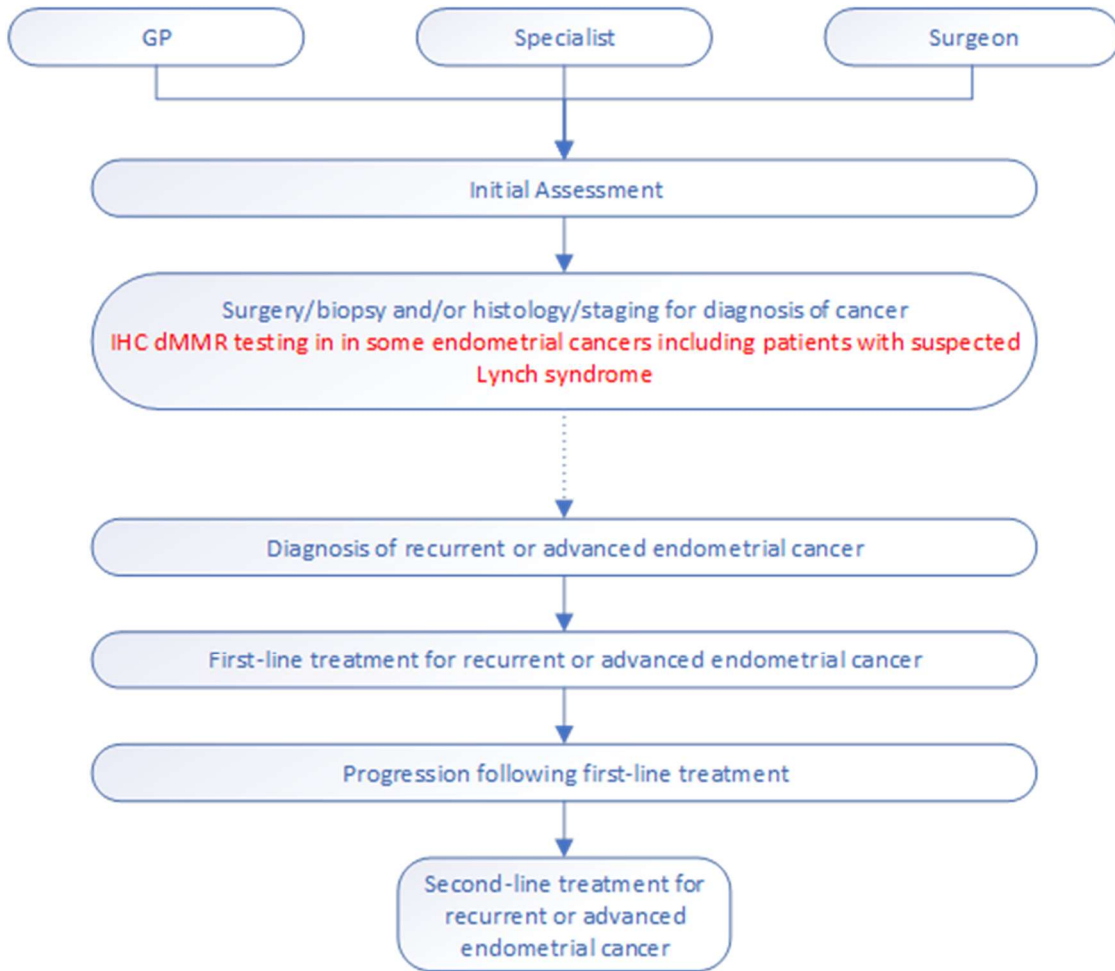
52. Specify how long the proposed medical service typically takes to perform:

Based on the time reported in previous applications for dMMR testing, a typical IHC MMR test takes 10 minutes to perform with results available within 24 hours.

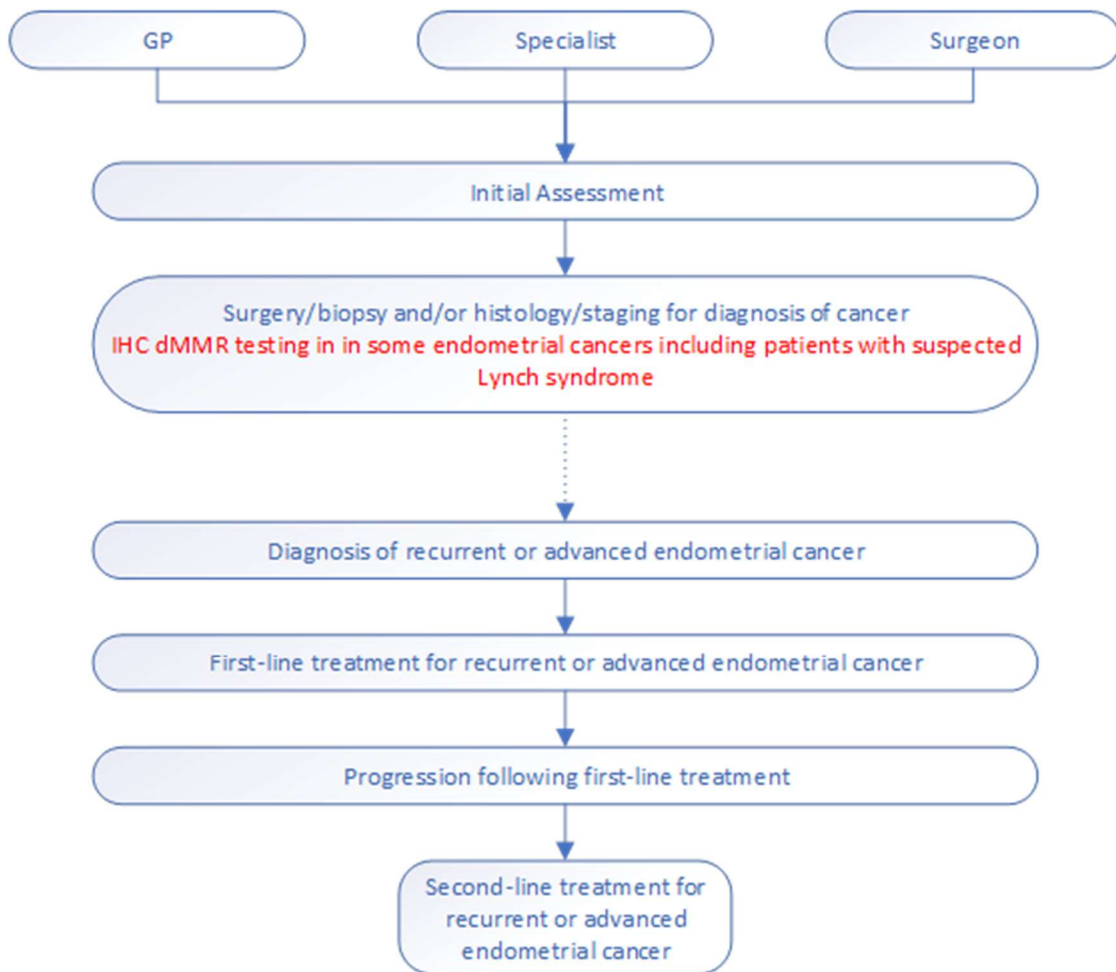
53. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

The current wording of item 72847 is adequate to define eligibility for dMMR testing.

ATTACHMENT 1 – Current clinical management flowchart



ATTACHMENT 2 – Proposed clinical management flowchart



ATTACHMENT 3 – Proposed PICO

DOSTARLIMAB – Co-dependent MSAC/PBAC submission

A PICO has been created for the pembrolizumab submission and is available here: [1508 Ratified PICO accessible \(1\)](#). The pembrolizumab PICO informs much of this document. A position paper evaluating dMMR testing has since been created by MSAC as attached. [C:\Users\mh48146\OneDrive - GSK\Documents\Dostarlimab\MSAC Review paper - detection of mismatch repair deficiencies.pdf](#).

The MSAC review paper identifies that dMMR detection by IHC is well-established and validated in endometrial cancer conducted in many endometrial cancers, and that IHC testing is recommended to be performed on all endometrial specimens which might indicate Lynch syndrome, that IHC is the appropriate standard for establishing dMMR in endometrial cancer, and there is no consensus on dMMR for prognostic utility.

This document has been created utilising information available through the above 2 papers.

1. Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

If direct effectiveness of the intervention cannot be determined, a linked approach may be used. A summary of the PICO criteria to address these are provided below.

Component	Description
Patients	<u>Testing population:</u> Patients with recurrent or advanced endometrial cancer who have progressed following first-line treatment and have not already been tested for mismatch repair (MMR) deficiency (dMMR) <u>Treatment population:</u> Patients with recurrent or advanced endometrial cancer who have progressed following first-line treatment
Prior tests	Routine histology, cytology and immunohistochemical (IHC) tests to confirm diagnosis and stage of tumour
Intervention	IHC dMMR testing using antibodies directed against the four MMR proteins to detect a deficiency for eligibility for treatment with dostarlimab on progression after first-line treatment for unresectable or metastatic disease, and standard of care in those who are MMR proficient No IHC dMMR testing plus dostarlimab
Reference standard	MSAC position paper suggests that IHC is the appropriate standard for establishing mismatch repair in endometrial cancer, given the frequency of MSH6 and PMS2 mutations as a cause of dMMR endometrial cancer and Lynch syndrome).
Comparator	Diagnostic accuracy: Methylation specific multiple ligation-dependent probe amplification to detect hyper-methylation of the <i>MLH1</i> gene promoter Therapeutic effectiveness: no IHC dMMR testing plus standard of care second-line treatment options, or palliative care if no second-line treatment options are available.

Component	Description
Outcomes	<p>Safety: harm related to testing procedure, harm due to false-positive or false-negative test result</p> <p>Diagnostic performance: Sensitivity and specificity (analytical validity), concordance, test-retest reliability</p> <p>Clinical validity: positive and negative predictive values, positive and negative likelihood ratios.</p> <p>Prognosis: prognostic effect of biomarker</p> <p>Clinical utility: % change in management plan (e.g. changes in treatment)</p> <p>Therapeutic effectiveness: Critical outcomes: Overall survival, progression-free survival, overall response rate; Important outcomes: Quality of life</p> <p>Predictive validity: treatment effect modification</p> <p>Cost-effectiveness: Cost, cost per quality adjusted life year</p>
Linked evidence research questions	<p>Are there any safety issues associated with IHC dMMR testing?</p> <p>What is the diagnostic accuracy of IHC dMMR testing compared with the reference standard for determining access to dostarlimab in patients with unresectable or metastatic endometrial cancer who have progressed following first-line treatment?</p> <p>Will the extra information generated as a result of IHC dMMR testing be of additional prognostic value in patients with endometrial cancer who have progressed following first-line treatment?</p> <p>Is there a change in management in patients in whom dMMR is diagnosed?</p> <p>Does treatment with dostarlimab lead to better health outcomes in patients with dMMR unresectable or metastatic endometrial cancer compared with standard of care second-line treatment options?</p> <p>Is MMR status a treatment effect modifier?</p> <p>Is IHC dMMR testing plus triage to dostarlimab or standard of care cost-effectiveness compared with no IHC dMMR testing plus standard of care for all?</p>

^a Outcomes ranked as recommended by GRADE

Population

The proposed testing population are those patients diagnosed with unresectable or metastatic endometrial cancer who have progressed following first-line treatment, and have not already been tested for mismatch repair (MMR) deficiency (dMMR). Patients would receive immunohistochemical (IHC) dMMR testing using antibodies directed against the four mismatch repair proteins to determine eligibility for treatment with dostarlimab, on progression to unresectable or metastatic disease.

The MMR system is mainly composed of four proteins (MLH1, MSH2, MSH6 and PMS2) interacting together to recognize DNA mismatches that may occur during DNA replication and excising them (Buecher et al. 2013). Microsatellites are short tandem DNA repeat sequences of 1–6 bases distributed throughout the coding and non-coding regions of the genome and are especially prone to replication errors that are normally repaired by the MMR system. A dMMR results in a cancer with a 10- to 100-fold increase in the mutation rate and leads to the accumulation of frameshift mutations in microsatellites, which results in a genetic instability (Buecher et al. 2013; Dudley et al. 2016). Microsatellite instability (MSI) arises from either a germline (hereditary) mutation in one copy of any of the four genes that encode the MMR proteins (Lynch syndrome), or from sporadic somatic hyper-methylation of the *MLH1* promoter (Dudley et al. 2016). Homozygous or compound heterozygous mutation in these genes leads to childhood cancer syndromes, such as Turcot syndrome. Turcot syndrome is clinically characterized by the early occurrence of primary brain and colorectal tumours (Scarpa, Cataldo & Salvatore 2016).

Solid dMMR tumours occur in many different parts of the body. Tumours likely to be included would include those associated with Lynch syndrome. Table 1 summarises the proportion of endometrial cancer occur in Lynch syndrome families from three different sources.

Table 1 Proportion of endometrial cancers in Lynch syndrome

Reference and population	Vasen et al. (1990) 24 Dutch Lynch syndrome families	Aarnio et al. (1995) 90 Finnish Lynch syndrome families	Barrow et al. (2009) 90 English Lynch syndrome families
Tumour location			
Endometrium	24%	33%	30%

However, only approximately 2% of endometrial cancers, the second most common cancer associated with Lynch syndrome, occur in patients with Lynch syndrome. These patients have a 35% (95%CI 17, 60) lifetime risk of developing endometrial cancer (Bonadona et al. 2011). Thus, Lynch syndrome patients account for only a small proportion of patients with endometrial cancer. The prevalence of dMMR mutations in endometrial cancer, and their prevalence in Australia, is listed in **Error! Reference source not found.**

Table 2 Prevalence endometrial cancer cases in Australia, proportion that are advanced and recurrent, and dMMR prevalence

Carcinoma	Proportion of all cancers (men and women)	Number of patients have advanced or recurrent EC	Proportion of all cancers that are dMMR
Endometrial cancer	2.1%	890	33%

Source: Scarpa, Cataldo & Salvatore (2016); Cancer in Australia 2019, Australian Institute of Health and Welfare. Available from URL <https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2019/data>.

Intervention

The intervention to be assessed is IHC dMMR testing plus dostarlimab in those who have a dMMR tumour and standard of care second-line treatment in those whose tumours are MMR-proficient.

An alternative intervention would be no IHC dMMR testing plus dostarlimab administered to all patients. This may be of use in clarifying the benefit of the testing component. (*Note this is an alternative intervention, not an alternative comparator*). *In the absence of this comparison, it would be difficult to demonstrate clinical utility of MMR IHC testing.*

IHC dMMR testing uses antibodies directed against each MMR protein (MLH1, MSH2, MSH6 and PMS2) and IHC staining to detect the expression of these proteins in the tumour cells to determine eligibility for treatment with dostarlimab. The test uses four formalin-fixed paraffin-embedded (FFPE) tumour tissue sections (one for each antibody) from either a surgical resection or a biopsy (if unresectable). The sample would be obtained as part of normal diagnostic work-up, and patients are unlikely to require a new biopsy for the specific purpose of IHC dMMR testing.

Even though IHC antibody staining requires four individual “tests”, the result of the four sections are combined to provide an overall picture and a single test result. The proteins form heterodimers (either MLH1/PMS2 or MSH2/MSH6), as the loss of one protein usually affects the expression of its partner; most dMMR CRCs show loss of expression of both proteins in the affected heterodimer. Loss of protein expression should be complete, with the absence of nuclear staining of all cancer cells and unequivocal positive staining of the nuclei of surrounding non-cancer cells and tumour-infiltrating lymphocytes. The loss of expression of MSH2/MSH6 is highly suggestive of a MSH2 germline mutation, and loss of expression of MLH1/PMS2 may result either from a MLH1 germline mutation or from acquired somatic hyper-methylation of the MLH1 gene promoter. Patients whose tumours showed a lack of expression of any of these proteins would be classed as dMMR and would be eligible for treatment with dostarlimab after progression following first-line treatment.

Patients are expected to receive one test throughout the course of their disease. The test is a Class II in vitro diagnostic test and must be performed in an accredited laboratory by a certified pathologist. It should be noted that most laboratories are already able to perform the IHC dMMR test. If found to be dMMR, treatment with dostarlimab would be managed by medical oncologists.

The IHC dMMR test is a simple, fast and inexpensive and many patients diagnosed with endometrial cancer, as well as those aged <50 years with Lynch syndrome-associated tumours, already receive IHC dMMR testing as part of their diagnostic work-up at initial diagnosis.

IHC dMMR testing is claimed using MBS item number 72847. This item is for general IHC testing with 4-6 antibodies and is not limited to either anti-MMR antibodies or a specific patient population.

Rationale

Currently, universal IHC dMMR testing is recommended for CRC and endometrial cancer, with many others tested where red flag criteria exists such as certain cancers in those aged <50 years.

Feedback received from Ovarian Cancer Australia for the Targeted Consultation Survey on MSAC Application 1508 indicated that histotype-specific Lynch syndrome screening in ovarian cancers, specifically endometrioid and clear cell carcinomas, independently of the patient’s age is advocated by the Austrian Organisation for Gynaecological Oncology (Zeimet et al. 2017).

IHC dMMR testing is already routinely undertaken in Australian laboratories, and is increasingly routine for endometrial cancer. Although the routine testing of endometrial tumours for those under the age of 50 and 60, respectively, is considered best practice, feedback received from Lynch Syndrome Australia on the Targeted Consultation Survey on MSAC Application 1508 reported that this is not the experience of Australians with Lynch syndrome. They indicated that this level of screening does not occur ‘routinely’.

Comparator

The comparator is no testing plus standard of care second-line treatment administered to all patients. The second-line treatment options for endometrial cancers that do not have access to dostarlimab are listed in Table 3.

Table 3 Second-line treatment options for the most common non-CRC solid tumour types in Australia that do not currently have access to dostarlimab treatment

Carcinoma	Predicted number of dMMR advanced and metastatic patients	Second-line treatment options
Endometrial cancer	75 out of 890	Hormonal treatment if endometrioid or monotherapy with taxol, doxorubicin or epirubicin

Source: ESMO guidelines available from URL: <<http://www.esmo.org/Guidelines>>

ER = endocrine receptor; HER-2 = human epidermal growth factor receptor 2; NSCLC = non-small cell lung cancer; SOC = standard of care

As only data from a single arm study enrolling patients with dMMR will be available, any comparisons will need to be indirect.

Rationale

As IHC dMMR testing is routinely done in Australia for CRC and other cancer types such as endometrial, it is already accepted as having adequate analytical validity, clinical validity and clinical utility.

Reasonable analytical validity in determining dMMR and eligibility for dostarlimab could be assumed given the routine nature of the test, especially if the test is subject to a quality assurance program.

Reference standard

Stelloo et al (2017) reported concordance rates of 94% between IHC and MSI PCR, with most instances of discordances being due to low MSI but absent MSH6 or PMS2 protein (also reported elsewhere for these 2 proteins). This suggests that IHC is the appropriate standard for establishing mismatch repair in endometrial cancer, given the frequency of MSH6 and PMS2 mutations as a cause of dMMR endometrial cancer and Lynch syndrome (Powell, 2017) [MSAC 2020].

Outcomes

The evidence base consists of a single-arm phase II trial in which patients with endometrial cancer were treated with dostarlimab.

Thus, there will be no direct comparative data available. Additionally, as patients with MMR-proficient tumours are not being included in the trial, any potential benefit generated from an indirect comparison in patients with dMMR tumours cannot be confirmed.

These trials do not provide direct evidence for a co-dependent technology as defined below¹;

- Level 1 direct evidence: Double-randomised controlled trial (randomised to test and to drug)
- Level 2 direct evidence: Single-randomised controlled trial (randomised to test plus drug versus no test plus usual care)
- Level 3 direct evidence: Prospective biomarker stratified randomised controlled trial of drug (population with and without biomarker randomised to drug or usual care)
- Level 4 direct evidence: Retrospective bio-marker stratified randomised controlled trial of drug (randomised to drug or usual care and then biomarker status determined)

Thus, a linked evidence approach will need to be undertaken.

Linked Evidence

Patient-relevant outcomes

<i>Safety</i>	Harms from testing (including rates of re-biopsy required for testing), treatment-associated adverse events and tolerability
<i>Diagnostic performance</i>	Sensitivity and specificity (analytical validity), concordance, test-retest reliability
<i>Clinical validity</i>	Positive and negative predictive values, positive and negative likelihood ratios
<i>Prognosis</i>	Prognostic effect of dMMR in endometrial cancer patients treated with standard of care
<i>Clinical utility</i>	Percent change in management plan (e.g. changes in treatment as a result of IHC dMMR testing). It should be noted that some patients are already tested and there may be no change in management outcomes to assess other than access to dostarlimab
<i>Therapeutic effectiveness</i>	Critical outcomes: overall survival, progression-free survival, overall response rate; Important outcomes: quality of life
<i>Predictive validity</i>	Treatment effect modification

Healthcare system

<i>Cost-effectiveness</i>	Cost, cost per life year gained, cost per quality adjusted life year or disability adjusted life year, incremental cost-effectiveness ratio, cost per case identified
<i>Financial implications</i>	Number of patients tested, number of patients tested per dMMR result, number of patients tested per dMMR result treated with dostarlimab

Most pathology laboratories already conduct IHC dMMR testing. However, there will be an increase in the number of tests conducted to determine access of patients with endometrial cancer to dostarlimab.

Rationale

As a co-dependent technology, any treatment effect modification and/or prognostic effect operating in the relationship between IHC dMMR testing and dostarlimab needs to be elucidated.

Proposed clinical management algorithm for identified population

The clinical management algorithm indicates that patients with endometrial cancer will receive IHC dMMR testing as part of the initial clinical work-up at diagnosis. This enables clinicians to use this information for diagnostic and/or prognostic/predictive purposes in early stages of disease. Patients who were not tested at diagnosis and progress to recurrent or advanced endometrial cancer would be tested for access to dostarlimab following failure of first-line therapy. This test would be performed using archival tumour tissue and patients would experience a small delay in commencement of treatment due to the requirement for block retrieval prior to testing. Patients with a dMMR tumour would be eligible for dostarlimab and those who are MMR proficient would receive standard of care second-line treatments.

¹ See section 2d of the 'Guidelines for preparing a submission to the PBAC' for Product Type 4 – Co-dependent technologies for further details

IHC dMMR testing would only be required once as these tumours do not change their MMR status (in both familial and sporadic mutations) and heterogeneity is not considered an issue. Therefore, a re-biopsy for the purpose of IHC dMMR testing would most likely not be required.

Proposed clinical algorithm for the treatment of patients with dMMR and MMR-proficient endometrial cancer.

