



Australian Government

Department of Health

Ratified PICO Confirmation

Application 1674:

**Testing for mismatch repair deficiency
(dMMR) in endometrial cancer to help
determine eligibility for PBS-subsidised
dostarlimab**

Table 1 PICO for IHC dMMR and dostarlimab in recurrent or advanced endometrial cancer: PICO Set 1

Component	Description
Population	<u>Test</u> : Patients with endometrial cancer. <u>Drug</u> : Patients whose tumours are mismatch repair deficient (dMMR) and whose recurrent or advanced endometrial cancer has progressed following first-line treatment.
Prior tests	Definitive diagnosis of endometrial cancer is based on biopsy. Imaging is conducted at diagnosis and to identify metastases.
Intervention	<u>Test</u> : Immunohistochemical (IHC) examination of tissue from either a surgical resection or biopsy from a patient diagnosed with endometrial cancer, by immunoperoxidase (IPX) or other labelled antibody techniques using four antibodies to the four mismatch repair proteins (MLH1, MSH2, MSH6 and PMS2). <u>Drug</u> : Dostarlimab for patients whose tumours are dMMR and whose recurrent or advanced endometrial cancer has progressed following first-line treatment.
Comparators	<u>Test</u> : No IHC dMMR testing. <u>Drug</u> : Specified standard of care second-line treatment.
Reference standard	Polymerase chain reaction-based microsatellite instability (PCR-based MSI) testing.
Clinical utility standard	IHC dMMR testing as described in the GARNET study, including information on: <ul style="list-style-type: none"> • When was testing conducted (e.g., initial diagnosis, disease recurrence)? • What sample was tested (i.e., tissue blocks or cytology)? • What was the sample source (e.g., primary site or metastases)? • When was testing conducted with respect to when the sample was collected (i.e., fresh or archival tissue)? • What dMMR antibody clones were used? • What test platform was used? • How were ambiguous results managed (e.g., was subclonal loss of MMR protein expression deemed dMMR or MMR proficient)?
Outcomes	Safety : Harm related to testing procedure; adverse events related to dostarlimab. Diagnostic performance : Sensitivity, specificity, assessment of extent of and implications of discordances between Australian IHC testing and clinical utility standard, test-retest reliability, evidence of stability of proteins in archival tissue, evidence of stability in MMR status over time, test failure rate. Clinical validity : Positive and negative predictive values, positive and negative likelihood ratios. Prognosis : Prognostic effect of dMMR. Clinical utility : % change in management plan (e.g., changes in treatment). Therapeutic effectiveness : Critical outcomes ^a : Overall survival, progression-free survival, overall response rate; Important outcomes ^a : Quality of life. Predictive validity : Dostarlimab treatment effect modification by MMR status. Cost-effectiveness : Cost, cost per quality adjusted life year. Financial implications : Number of patients tested; number of patients treated.
Assessment questions	What is the safety, effectiveness, and cost-effectiveness of IHC dMMR testing and dostarlimab treatment versus no testing and standard care in patients with recurrent or advanced endometrial cancer?

dMMR = mismatch repair deficient; IHC = immunohistochemistry; MMR = mismatch repair; MSI = microsatellite instability; PCR = polymerase chain reaction

^a Outcomes ranked as recommended by GRADE

Purpose of application

The codependent application requested:

- Medicare Benefits Schedule (MBS) listing of immunohistochemistry (IHC) testing for identification of mismatch repair deficiency (dMMR) for the determination of patient eligibility for treatment with dostarlimab; and
- Pharmaceutical Benefits Scheme (PBS) Authority Required listing of dostarlimab for the treatment of patients with dMMR recurrent or advanced endometrial cancer.

PICO criteria

Population

The testing population proposed for PASC consideration comprised patients diagnosed with endometrial cancer who have not already been tested for mismatch repair deficiency (dMMR). Patients would receive immunohistochemical (IHC) dMMR testing using antibodies directed against the four mismatch repair proteins to help determine eligibility for treatment with dostarlimab for those patients who subsequently progress following first-line treatment of recurrent or advanced disease.

The proposed testing population in the application was patients diagnosed with recurrent or advanced endometrial cancer who have progressed following prior treatment (p.13 in the application). The terms 'Stage IV', 'recurrent or advanced', and 'unresectable or metastatic' are used interchangeably in the application. The term 'recurrent or advanced' is applied throughout the draft PICO confirmation. The applicant should advise whether 'recurrent or advanced' is appropriate, or another definition is preferred, preferably with reference to the proposed PBS restriction for dostarlimab. It is expected that this will be based on the main clinical study nominated to support the application, Cohort A1 of the GARNET study. Eligible patients had dMMR endometrial cancer which had progressed on or after platinum doublet therapy for recurrent or advanced (Stage \geq IIIB) disease. Patients were required to have received no more than 2 lines of anticancer therapy.

Endometrial cancer 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 (Colombo et al., 2016). Approximately 13% of patients diagnosed with localised disease experience disease recurrence (Fung-Kee-Fung et al., 2006) and an additional 10-15% of cases have advanced disease at diagnosis (Behbakht et al., 1994, Tobias et al., 2020). Patients with advanced disease have a poor prognosis, with a 17.5% (16.8% - 18.3%) 5-year survival rate¹.

The mismatch repair (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

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https://seer.cancer.gov/explorer/application.html?site=58&data_type=4&graph_type=6&compareBy=race&chk_race_1=1&hdn_s_ex=3&age_range=1&stage=106&advopt_precision=1&advopt_show_ci=on&advopt_display=2 [accessed 29-Jun-2021]

microsatellites, which results in a genetic instability (Buecher et al., 2013, Dudley et al., 2016). Microsatellite instability (MSI) arises from either a germline (hereditary) variant in one copy of any of the four genes that encode the MMR proteins (Lynch syndrome) or from a sporadic somatic variant, usually hyper-methylation of the MLH1 promoter (Dudley et al., 2016).

Lynch syndrome is caused by a pathogenic germline variant in one of the MMR genes or the EPCAM gene (MSAC 2020). The cumulative lifetime risk (at 70 years of age) of having endometrial cancer ranges between 19-71% for an individual with Lynch syndrome (Barrow et al., 2009). Lynch syndrome patients only account for a small proportion of patients with endometrial cancer. A systematic review of 53 studies of patients with endometrial cancer suggests the prevalence of Lynch syndrome in endometrial cancer is approximately 3% (Ryan et al., 2019).

The application estimated that endometrial cancer accounted for 2.1% of all cancers in Australia, 890 patients in Australia have recurrent or advanced endometrial cancer, and 33% of these would be dMMR tumours (Table 2, Attachment 3 of the application form). Part 6a of the application form stated that approximately 25% of endometrial cancers are dMMR and could be treated with dostarlimab. The prevalence of dMMR in recurrent or advanced endometrial cancer should be clarified in the assessment report.

Utilisation

The application estimated that the number of patients meeting the criteria for IHC dMMR testing (i.e., patients who have recurrent or advanced endometrial cancer who have progressed following first-line treatment and have not already been tested for dMMR) to be 175 (p18). This was derived from the AIHW cancer statistics that stated there were 3,115 cases of uterine cancer in 2019, of which 92% (2,866) were endometrial. Approximately 13% of endometrial cancers recur and 18% are diagnosed as advanced or metastatic, meaning REDACTED have recurrent or advanced endometrial cancer. The proportion of patients diagnosed with advanced endometrial cancer was not justified in the application and could not be verified.

The application assumed that 70% of patients with recurrent or advanced endometrial cancer REDACTED would receive first-line treatment and of these, 40% (~250) would receive second-line treatment (p18). The application stated that 30% of patients receiving second-line treatment (75) would have had previous IHC testing (i.e., testing at diagnosis), leaving 175 patients eligible for IHC testing (p18). This means REDACTED would be eligible for treatment with dostarlimab in Year 1.

The application stated that approximately 30% of patients with recurrent or advanced endometrial cancer receiving second-line treatment will already have had IHC dMMR testing (p18). The source of this estimate was not provided in the application.

At the pre-PASC teleconference, the applicant reported clinician feedback that IHC dMMR testing is often conducted at diagnosis (i.e., more frequently than 30%) for the purposes of private access to pembrolizumab or to ascertain clinical trial eligibility.

Potential advantages of conducting IHC dMMR testing early include using fresh tissue, efficiencies associated with a reflex test on confirmation of endometrial cancer, private access to pembrolizumab, access to clinical trials, and potential future benefits when more becomes known about the prognostic value of the dMMR biomarker in endometrial cancer. Potential disadvantages of conducting IHC dMMR

testing early include testing many patients when only a small proportion will subsequently progress to be considered for dostarlimab (increasing the cost of testing per person treated with dostarlimab), the currently limited prognostic value of the dMMR biomarker, and the need to assess the applicability of the clinical evidence given differences with the GARNET study, which primarily tested archival tissue. The option of testing after failure of first-line therapy for recurrent or advanced disease is difficult to support as the turnaround time for requesting, conducting and reporting the test would delay the start of second-line treatment.

PASC advised that the appropriate test population was patients with endometrial cancer, at initial diagnosis.

PASC acknowledged the consultation feedback and the view of the applicant that most, if not all, patients with endometrial cancer currently have an IHC dMMR test performed at initial diagnosis. A small number of patients not tested at initial diagnosis may require an IHC dMMR test prior to second line treatment of recurrent or advanced disease.

PASC advised that the appropriate treatment population was patients whose tumours are mismatch repair deficient (dMMR) and whose recurrent or advanced endometrial cancer has progressed following first-line treatment.

Biological plausibility

Approximately 20 to 40% of endometrial cancer cases are dMMR (Reijnen et al., 2019). The prognostic or predictive value of MMR status is not clear from the summary of evidence presented in the application form. A survival analysis of 728 Australian endometrial cancer patients found overall and cancer-specific survival did not differ by MMR status (Nagle et al., 2018). A study by Llosa et al. (2015) identified that dMMR/MSI colorectal cancers have a high mutation burden leading to the expression of unique tumour antigens, or neoantigens, infiltration of T-cell lymphocytes, and overexpression of five immune checkpoints (PD-1, PD-L1, CTLA-4, LAG-3 and IDO) in the tumour and microenvironment.

The immune system targets neoantigens to trigger an antitumor immune response (Yarchoan et al., 2017, Riaz et al., 2016) via several immunological processes such as antigen-presenting dendritic cells, helper and cytotoxic T-cell activation, and human leukocyte antigen (HLA) presentation. The overactive immune system also has the propensity to induce detrimental inflammation and autoimmunity. Several immune checkpoints prevent the immune system from attacking cells indiscriminately. However, in malignant settings, the immune checkpoints can be manipulated by the tumour cells to mediate immune tolerance and subsequent malignancy progression. Inhibiting the immune checkpoints promises to halt or reverse disease progression.

Based on the study by Llosa et al. (2015), Dudley et al. (2016) proposed a relationship between dMMR/MSI-high (MSI-H) status and immunological response. In the absence of functional MMR, frameshift mutations occur, resulting in proteins that contain a mutation associated neoantigen. Upregulation of immune checkpoint proteins, including PD-1 and PD-L1, inhibit the T-cell response and enable the tumour cells to survive (Dudley et al., 2016). Llosa et al. (2015) predicted that due to the differential expression of immune-inhibitory ligands, receptors, and metabolic enzymes, dMMR/MSI-H tumours would respond better to checkpoint blockade with anti-PD-1 or anti-PD-L1 agents.

An analysis of the biological plausibility for the use of IHC dMMR testing to identify endometrial tumours susceptible to immune checkpoint inhibitors, such as dostarlimab, should be provided in the assessment

report. Furthermore, evidence of dMMR being an effect modifier for treatment with dostarlimab, above and beyond its prognostic effect, should be provided.

Rationale

The summary of evidence presented in the application to support IHC dMMR testing for patients with advanced or recurrent endometrial cancer focused on identifying patients likely to respond to dostarlimab based on the dMMR biomarker.

The summary of evidence presented in the application to support dostarlimab as second-line treatment for recurrent or advanced endometrial cancer included one open-label, single-group, multicohort phase I study evaluating the safety and efficacy of dostarlimab monotherapy (GARNET). The GARNET study was conducted in two parts: Part 1 was a dose-escalation study to evaluate weight-based dosing of dostarlimab, Part 2A evaluated non-weight based fixed doses of dostarlimab in patients with advanced solid tumours, and Part 2B enrolled patients into five expansion cohorts based on tumour type and MMR status (Oaknin 2020). Part 2B, Cohort A1 includes participants with dMMR/MSI-H recurrent or advanced endometrial cancer who have progressed on or after platinum doublet therapy. The other four cohorts in Part 2B are MMR proficient endometrial cancer, non-small cell lung cancer, dMMR/MSI-H non-endometrial solid tumours, and high-grade serous, endometrioid, or clear cell ovarian, fallopian tube, or primary peritoneal cancer without a known *BRCA* mutation².

Oaknin et al. (2020) presents the interim analysis of 71 patients with dMMR/MSI-H recurrent or advanced endometrial cancer who have progressed on or after platinum doublet therapy (GARNET Part 2B, Cohort A1).

Other MSAC applications (1414, 1440, 1445, 1453, 1457, 1486, 1505, 1506, 1520, 1522, 1570) have requested IHC PD-L1 testing, not IHC dMMR testing, to determine access to other PD-(L)1 inhibitors (pembrolizumab, durvalumab, and atezolizumab). A discussion of why the dMMR biomarker is preferred to PD-L1 in endometrial cancer should be included in the assessment report.

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

The initial work-up for patients who present with symptoms of endometrial cancer includes a pelvic examination and imaging. Definitive histological diagnosis is based on biopsy. 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. 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.

² <https://www.clinicaltrials.gov/ct2/show/NCT02715284?term=dostarlimab%2C+garnet&draw=2&rank=1> [accessed 29-Jun-21]

Intervention

Test

The proposed intervention to be assessed is IHC dMMR 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. Examples of dMMR antibody clones used in Australia are: MLH1 -ES05 (DAKO), MSH2 – G219-1129 (Ventana), MSH6 – 44 (BD Biosciences), PMS2 – EPR3947 (Ventana) (Part 3 of the application form). Concordance between antibody clones used in Australia and the clinical utility standard clones should be discussed in the assessment report.

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. NATA-accredited laboratories are required to validate IHC testing on any tissue they use (i.e. fresh or FFPE); however, it is known that archival tissue is not optimal (ISO, 2018). The National Pathology Accreditation Advisory Council requires that blocks of tissue embedded in wax or other permanent embedding medium to be kept for minimum 10 years (NPAAC, 2018).

Even though IHC antibody staining requires four individual “tests”, the result of the four sections is 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 tumours 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 pathogenic MSH2 germline variant, and loss of expression of MLH1/PMS2 may result either from a pathogenic *MLH1* germline variant 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 thus would be potentially eligible for treatment with dostarlimab.

Potential advantages of IHC dMMR testing, compared with polymerase chain reaction (PCR) -based MSI testing, include its lower cost, widespread use in Australia, and only requiring one tumour tissue sample (rather than matched tumour/normal tissue samples) (Scott, 2020). In addition, IHC dMMR testing is able to identify the candidate protein affected, which is not possible in PCR-based MSI testing (Scott, 2020). Potential disadvantages of IHC dMMR testing include subclonal loss (tumour heterogeneity) and variation in tissue fixation (Scott, 2020, Stelloo et al., 2017). Rare cases of MSI-H cannot be detected by IHC. Apparent intact expression of all four proteins by IHC cannot entirely exclude MSI-H and Lynch syndrome as missense variants can lead to a non-functional protein with retained antigenicity (Buecher et al., 2013, Stelloo et al., 2017). There is also a potential need for confirmatory MSI testing for tumours identified as dMMR by IHC.³

³ The GARNET study did not conduct confirmatory MSI testing for patients identified as dMMR by IHC.

The application stated that patients are expected to receive one IHC dMMR test throughout the course of their disease as endometrial tumours do not change their MMR status over time (p27). Evidence to support the stability of MMR status over time should be provided with the assessment report.

The IHC test is a Class 2 in vitro diagnostic and must be performed in an accredited laboratory by a certified pathologist. A survey provided with the application indicated that 95% of Australian pathology laboratories can conduct IHC dMMR testing (80% survey response rate). If found to be dMMR, treatment with dostarlimab would be managed by medical oncologists.

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

PASC advised that a specific MBS item for IHC dMMR testing is not required.

The application did not address whether:

- confirmatory MSI testing should be conducted for tumours that are dMMR on IHC; and
- MSI testing should be proposed as a second-tier test for non-informative IHC (e.g., cases with subclonal loss); and
- confirmatory MSI testing should be conducted for tumours that are MMR proficient on IHC but may harbour somatic variants not detectable by IHC.

PASC confirmed the test intervention is IHC testing for identification of dMMR for the determination of patient eligibility for treatment with dostarlimab. The treatment intervention is dostarlimab for patients with dMMR recurrent or advanced endometrial cancer.

PASC considered that additional testing with PCR-based MSI may be required for ambiguous or inconclusive IHC dMMR results (~6% of tests).

Rationale

The Royal College of Pathologists of Australasia Structured Reporting Protocol for endometrial cancer recommends that IHC dMMR testing be performed on all patients with endometrioid differentiation if resources are available (RCPA, 2019). However, the Protocol notes that IHC dMMR testing guidelines for endometrial cancer have not been standardised.

A survey of Australian pathology laboratories provided with the application indicated that 12% of laboratories conducted universal dMMR screening of endometrial tumours, 37% screened at clinician request, 27% screened 'red flag' cases, 15% screened both at clinician request and 'red flag' cases (9% unknown) (Mascarenhas et al., 2018). 'Red flag' cases were suggestive of genetic predisposition to endometrial cancer, such as family history, diagnosis at a young age, histopathological and molecular features. The proportion of endometrial cancer patients screened at diagnosis was not discussed as part of the survey.

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). The applicant for MSAC Application 1508 reported that IHC dMMR testing is already routinely undertaken in Australian laboratories and is increasingly routine for endometrial cancer. Although the routine testing of

colorectal tumours and endometrial tumours for those under the age of 50 and 60 years, 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, and instead indicated that this level of screening does not occur 'routinely'. A recent audit of Lynch syndrome testing and referral practices in Australian hospitals found that tumour testing approaches differed between hospitals, with up to 19% of patients undergoing colorectal cancer resections not tested for dMMR using IHC or MSI (Steinberg et al., Submitted for publication). If dMMR testing is not universal practice in colorectal cancer it may not be reasonable to assume a high uptake of dMMR IHC testing in endometrial cancer.

Drug

The proposed test is to determine the eligibility for dostarlimab in those who have a dMMR tumour and for current standard of care second-line treatment in those whose tumours are MMR-proficient. Dostarlimab is not registered for use in Australia. A submission for this indication was made to the TGA in January 2021.

The application appropriately proposed no IHC dMMR testing plus dostarlimab administered to all patients as an alternative intervention scenario to clarify the benefit of testing (p24).

Comparators

The comparator for IHC dMMR testing proposed in the draft PICO was no IHC dMMR testing. The proposed comparator for dostarlimab was specified standard of care second-line treatment.

PASC advised that the comparator for the test is the 'current testing regimen', which may or may not include IHC dMMR, for reasons other than treatment (e.g., familial cancer risk).

PASC noted that there may be a small increase in IHC testing corresponding to the number of patients not currently tested at diagnosis but are subsequently considered for second-line treatment with dostarlimab.

PASC noted the comparator for drug treatment.

Rationale

The European Society for Medical Oncology guidelines for endometrial cancer note that most patients with recurrent or advanced endometrial cancer will be candidates for systemic palliative therapy (Colombo et al., 2016). Patients could receive hormonal treatment or chemotherapy, with treatment choice guided by the patient's histopathological and clinical features.

The application indicated that second-line treatment options included hormone treatment (medroxyprogesterone) if hormone receptor positive or monotherapy with taxol, doxorubicin or epirubicin (p25). REDACTED. EviQ provides medroxyprogesterone, doxorubicin + cisplatin, and carboplatin + paclitaxel treatment protocols for recurrent or metastatic endometrial cancer⁴. The UK data does not appear to align with Australian treatment protocols, as outlined by EviQ. Additional

⁴ <https://www.eviq.org.au/medical-oncology/gynaecological/endometrial> [accessed 20-Jun-21]

information regarding standard second-line treatment for recurrent or advanced endometrial cancer in Australia should be provided in the assessment report.

Reference standard

The application stated that IHC is the appropriate standard for establishing dMMR in endometrial cancer (p16) and that 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 (p25). Nevertheless, some data on the accuracy of the test in endometrial cancer should be provided in the assessment report to demonstrate testing equivalence. Data on the extent of discordances comparing dMMR testing using IHC to MSI testing using PCR and next generation sequencing (NGS) may be available from the GARNET study.

An ESMO review of MSI and dMMR biomarkers concluded that molecular testing of polyA microsatellites provides direct proof of dMMR in a given cancer and IHC is an efficient indirect test when a molecular laboratory is unavailable (Scarpa et al., 2016). PCR-based MSI testing is performed on DNA from fresh, frozen, or paraffin-embedded tissue and compares microsatellite markers from matched tumour/normal tissue samples (Scarpa et al., 2016, Scott, 2020). A range of biomarker panels may be used and a MSI phenotype is typically defined by the presence of ≥ 2 unstable markers out of a core panel of 5, or $\geq 30\%$ of unstable markers when a larger panel is used (Dudley et al., 2016, Morona et al., January 2020).

The application reported concordance rates of 94% between IHC and MSI PCR based on a study by Stelloo (2017) and noted that most instances of discordances being due to low MSI but absent MSH6 or PMS2 protein (p25). Stelloo et al. (2017) reported that ambiguous cases (n=41, 6%) included 18 cases of subclonal loss of MMR protein expression, 20 microsatellite stable or MSI-low cases with dMMR and 3 MSI-high cases with retained MMR protein expression.

The MSAC discussion paper for pan-tumour applications indicated that methylation specific multiple ligation-dependent probe amplification (MS-MLPA) testing of the *MLH1* promoter and MSI testing were the relevant reference standards for IHC dMMR in most non-colorectal (non-CRC) tumours, given their sporadic nature (Morona et al., January 2020). *MLH1* promoter hypermethylation tests are often used to exclude somatic *MLH1* loss, suggesting a low likelihood of Lynch syndrome. MS-MLPA assays can also be used to detect sporadic cases of dMMR by hyper-methylation of multiple *MMR* genes, including *MLH1*, *MSH2*, *MLH3*, *MPS2*, and *MSH6* (Morona et al., January 2020), and to resolve discordance between IHC and MSI (Stelloo et al., 2017). NGS of the *MMR* genes is used for the diagnosis of Lynch syndrome (Morona et al., January 2020), to resolve discordance between IHC and MSI (Stelloo et al., 2017), and in the research setting to assess determinants of tumour response to immune checkpoint inhibitors (Rizvi et al., 2018, Le et al., 2015).

A review of studies evaluating the impact of MMR/MSI status on patient prognosis identified eight studies; of these, three studies determined MMR/MSI status based on a combination of PCR-based MSI and IHC for dMMR, three used PCR-based MSI alone, and two used IHC for dMMR alone (Kurnit et al., 2019).

A review of immune checkpoint inhibitors in recurrent and advanced endometrial cancer identified nine studies that selected patients based on biomarkers; of these, one study selected patients based on the

PD-L1 biomarker, two selected patients based on MSI or MMR status, two selected on MSI status alone, two selected on MMR status alone, and two were unselected (Gomez-Raposo et al., 2021).

In its consideration of Application 1452 (pembrolizumab in dMMR Stage IV CRC) the MSAC Executive advised that MSI testing is the gold standard to determine dMMR in metastatic CRC (MSAC, January 2017).

PASC noted the MSAC Executive advice for Application 1452 and the MSAC discussion paper on pan-tumour biomarker testing which considered reference standards for IHC dMMR testing in colorectal and endometrial cancer.

PASC advised that PCR-based MSI testing was the appropriate reference standard for this application.

Clinical utility standard

The application did not state a clinical utility standard for establishing IHC dMMR in endometrial cancer.

The clinical utility standard is defined as the test and method of interpretation used to allocate patients to alternative options in the key clinical studies generating direct evidence of health outcome gains (MSAC, 2021). The description of the test should explicitly state the test reagents, test platform, biospecimen type and preparation, what is tested, and a definition of the test threshold result that differentiates between different clinical management actions (MSAC, 2021).

At the pre-PASC teleconference the applicant indicated that the clinical utility standard would be IHC dMMR testing as conducted in the GARNET study. Subsequent communication received from the applicant indicated that IHC dMMR was performed by local laboratories when available, otherwise central. The use of local IHC dMMR results, which was agnostic to the choice of assay and performed in an accredited laboratory, reflect real-world patient selection given that IHC dMMR test is already well-established based on current clinical practice guidelines.

In the GARNET study, for patients with local IHC dMMR results, tumour samples were submitted to a central IHC laboratory for quality to be checked and cleared prior to study treatment initiation⁵. For participants without local MMR results (patients with local PCR or NGS test results), MMR testing was conducted by the central IHC laboratory on archival tumour tissue that is formalin-fixed and paraffin-embedded⁶. For patients who did not have archival tissue, a new biopsy was required to be performed to obtain a tissue sample prior to study treatment initiation. The preliminary results from Cohort A1 reported in the GARNET study protocol (p35) showed that all responders were dMMR by IHC. There was a subgroup of patients, initially identified as dMMR/MSI-H by IHC who could not be confirmed by central NGS testing. Consequently, to ensure that all responders to dostarlimab were categorized by their appropriate cohort: Cohorts A1, the trial Sponsor decided to define dMMR/MSI-H according to the IHC test.

For entry into Part 2B (including Cohort A1 – dMMR endometrial cancer) of the GARNET study, patients without archival tissue were required to undergo a new biopsy from a tumour lesion (primary or metastatic). New biopsy from liver, brain, lung/mediastinum, pancreas, or from endoscopic procedures

⁵ <https://www.clinicaltrials.gov/ct2/show/NCT02715284?term=dostarlimab%2C+garnet&draw=2&rank=1> [accessed 6-Jul-21]

⁶ <https://www.clinicaltrials.gov/ct2/show/NCT02715284?term=dostarlimab%2C+garnet&draw=2&rank=1> [accessed 29-Jun-21]

extending beyond the oesophagus, stomach or bowel were excluded for safety reasons (p49, GARNET study protocol).

To define the clinical utility standard as part of the PICO confirmation, the applicant should provide the following information:

- When was testing conducted (e.g., initial diagnosis, disease recurrence)?
- What was tested (i.e., tissue blocks or cytology)?
- What was the sample source (e.g., primary site or metastases)?
- When was testing conducted with respect to when the sample was collected (i.e., fresh or archival tissue)?
- What dMMR antibody clones were used?
- What test platform was used?
- How ambiguous results were managed (e.g., was subclonal loss of MMR protein expression deemed dMMR or MMR proficient)?

If the central laboratory clearance process involved re-testing tissue samples with a particular assay to confirm eligibility for dostarlimab treatment, that assay would form part of the clinical utility standard. The assessment report should examine the concordance between central IHC and local PCR and NGS, and, discuss the implications of discordances.

Noting that the choice of clones for IHC dMMR testing was up to the local pathology laboratory at each study site in the GARNET study, PASC considered the circumstances of IHC dMMR testing in this study are applicable to Australian practice.

Outcomes

The evidence base for the drug consisted of a single-arm phase I study (GARNET) in which patients with endometrial cancer were treated with dostarlimab.

The GARNET study does not provide direct evidence for a codependent technology as defined by the PBAC Guidelines below⁷:

- 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 biomarker 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.

The application reported that, as patients with MMR-proficient tumours were not included in the study, any potential benefit generated from an indirect comparison in patients with dMMR tumours cannot be

⁷ See section 2d of the 'Guidelines for preparing a submission to the PBAC' for Product Type 4 – Codependent technologies for further details

confirmed (p25). However, Cohort A2 of the GARNET study includes patients with MMR proficient endometrial cancer treated with dostarlimab; some comparative data based on biomarker status may be available.

Linked evidence

Patient relevant

<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 compared to the reference standard(s), implications of discordances between Australian IHC methodologies and clinical utility standard (incorrect diagnosis of dMMR or MMR proficient), test-retest reliability, evidence of stability of proteins in archival tissue, evidence of stability in MMR status over time, test failure rate (unsatisfactory or uninterpretable results).
<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).
<i>Therapeutic effectiveness</i>	Critical outcomes: overall survival (OS), progression-free survival (PFS), overall response rate (ORR); Important outcomes: quality of life (QoL).
<i>Predictive validity</i>	Dostarlimab treatment effect modification by MMR status.

Healthcare system

<i>Cost-effectiveness</i>	Cost, incremental cost per life year gained, incremental cost per quality adjusted life year, cost of testing per patient treated with dostarlimab.
<i>Financial implications</i>	Number and cost of patients tested, number and cost of patients tested per dMMR result, number and cost 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 help determine eligibility of patients with endometrial cancer for dostarlimab.

PASC confirmed the proposed outcomes for this application.

PASC noted that limited outcome data is available in the GARNET study.

Rationale

As a codependent technology, any treatment effect modification and/or prognostic effect operating in the relationship between IHC dMMR testing and dostarlimab would need to be explained.

Assessment framework (for investigative technologies)

An initial assessment framework linking IHC dMMR testing to relevant health outcomes is presented in Figure 1.

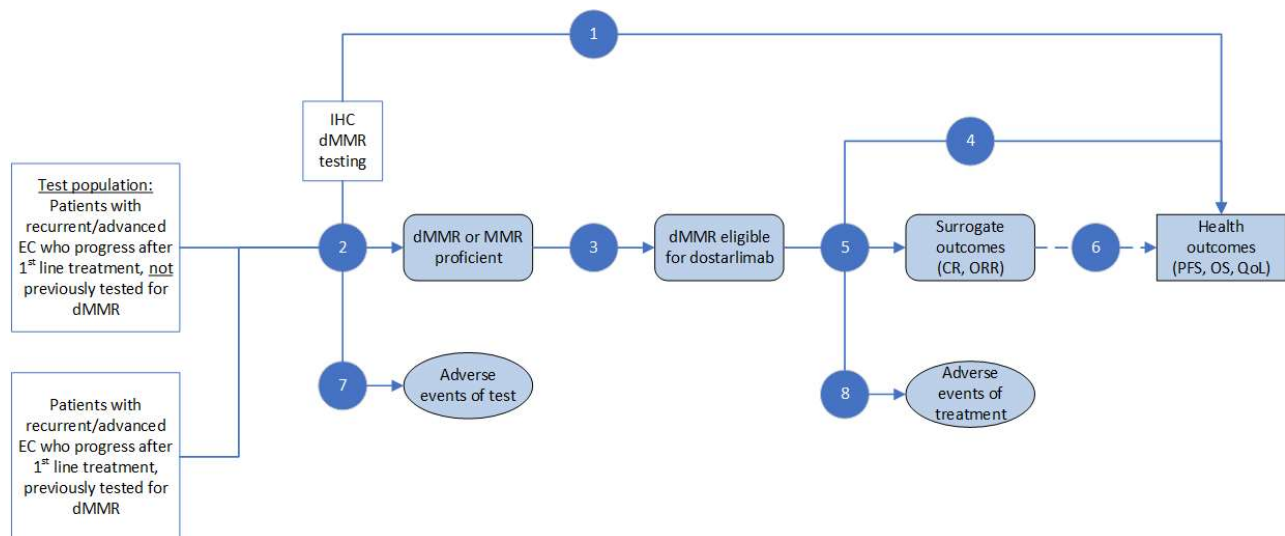


Figure 1 Assessment framework showing the links from the test population to health outcomes

CR = complete response; dMMR = mismatch repair deficient; IHC = immunohistochemistry; MMR = mismatch repair; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; QoL = quality of life.

1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: association of intermediate outcomes with health outcomes; 7: adverse events due to testing; 8: adverse events due to treatment

Assessment questions for a claim of superiority:

1. Does the use of IHC dMMR in place of no testing result in the claimed superior health outcomes?
2. Test accuracy
 - a. Versus PCR-based MSI as a reference standard: How does the information from IHC dMMR testing differ from PCR-based MSI testing? What are the implications of discordances between the findings from IHC dMMR and PCR-based MSI testing?
 - b. Versus IHC dMMR in the GARNET study as the clinical utility standard: What are the implications of discordances between the findings from Australian IHC assays and the clinical utility standard?
3. Does the availability of new information (MMR status) from IHC dMMR testing lead to a change in management of the patient?
4. Do the differences in the management derived from IHC dMMR testing (dostarlimab treatment for patients with dMMR recurrent or advanced endometrial cancer) result in the claimed superior health outcomes (PFS, OS, QoL)?
5. Do the differences in the management derived from IHC dMMR testing (dostarlimab treatment for patients with dMMR recurrent or advanced endometrial cancer) result in the claimed superior surrogate outcomes (complete response, ORR)?

6. Is the observed change in surrogate outcomes (complete response, ORR) associated with a concomitant change in the claimed health outcomes (PFS, OS, QoL), and how strong is the association?
7. What are the adverse events associated with IHC dMMR testing compared to a no testing strategy?
8. What are the adverse events associated with dostarlimab treatment for patients with dMMR recurrent and advanced endometrial cancer? What are the adverse events associated with standard care treatment for patients recurrent and advanced endometrial cancer?

PASC confirmed the proposed assessment framework for an overall outcome claim of clinical superiority would apply for an assessment of the test.

Clinical management algorithms

Current clinical management algorithm (comparator)

The current management algorithm for endometrial cancer described in the Application form is shown in Figure 2. IHC dMMR testing is included as part of the initial work-up for some patients, including those with suspected Lynch syndrome. There are currently no targeted treatment options available to patients with dMMR recurrent or advanced endometrial cancer.

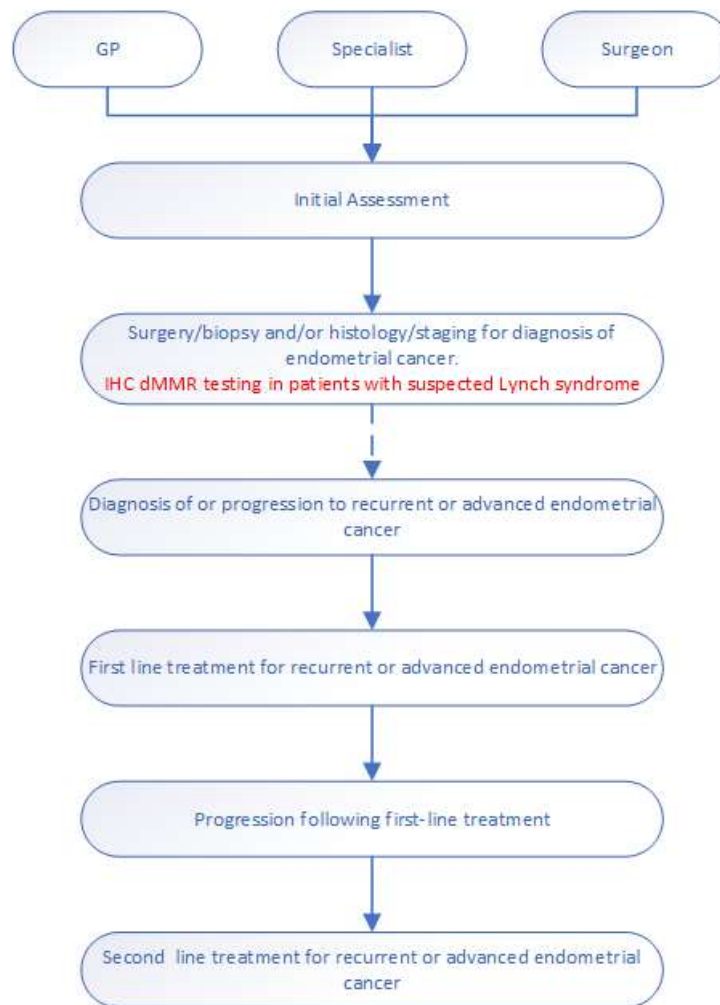


Figure 2 Current clinical management algorithm for the treatment of patients with endometrial cancer

Source: Attachment 1 of the application form. Terminology updated to 'recurrent or advanced endometrial cancer' by the assessment group

dMMR = DNA mismatch repair system deficient; GP = general practitioner; IHC = immunohistochemistry.

PASC advised that the current clinical management algorithm in the draft PICO is inconsistent with current clinical practice where most, if not all, patients receive IHC dMMR testing at initial diagnosis.

Proposed clinical management algorithm (intervention)

The clinical management algorithm proposed in the application (Figure 3) reflects that IHC dMMR testing is included as part of the initial work-up for some patients. 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. Patients with a dMMR tumour would be eligible for dostarlimab and those who are MMR proficient would receive standard of care second-line treatments.

It was proposed that IHC dMMR testing would only be required once as these tumours do not change their MMR status (in both familial and sporadic variants) and heterogeneity is not considered an issue.

The application stated that IHC dMMR testing following failure of first-line therapy 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 (p26). A sample retrieval fee would apply to the proportion of archived samples used for IHC dMMR testing of recurrent or advanced endometrial cancer.

There may be flow-on issues, including cost implications, arising from a positive IHC dMMR test result. Patients may need confirmatory MSI testing, or MSI testing as a second-tier test for non-informative IHC results. Patients not previously considered at-risk of Lynch syndrome due to a lack of family history with CRC might be identified. These patients might need genetic testing to establish a diagnosis of Lynch syndrome. If Lynch syndrome is diagnosed, genetic counselling would also be required. Testing of relatives might also occur, along with increased surveillance (e.g., colonoscopies) and preventative treatments (e.g., hysterectomies).

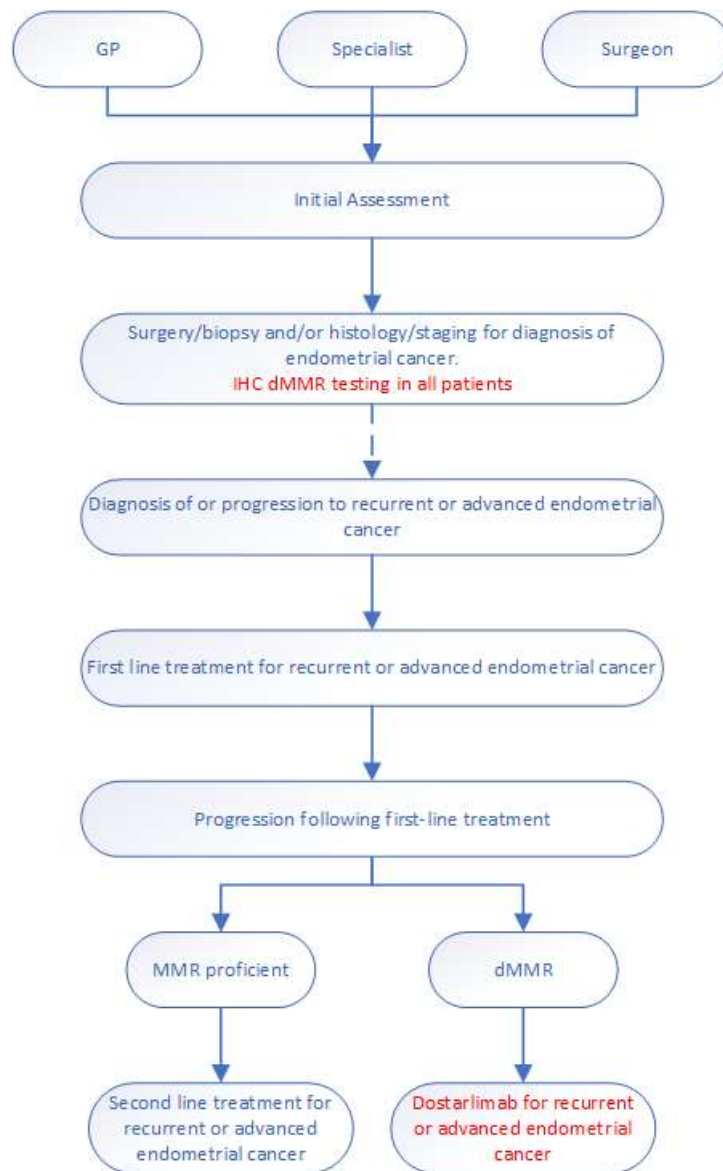


Figure 3 Proposed clinical management algorithm for the treatment of patients with endometrial cancer

Source: Attachment 2 of the application form. Terminology updated to 'recurrent or advanced endometrial cancer' by the assessment group and 'early' IHC dMMR testing implemented, where all patients are tested at diagnosis.

dMMR = DNA mismatch repair system deficient; GP = general practitioner; IHC = immunohistochemistry, MMR = DNA mismatch repair system.

PASC advised that the proposed clinical management algorithm in the draft PICO is already current practice. PASC noted that for the small number of patients who are not currently tested at diagnosis, IHC dMMR testing may occur if they are subsequently considered for second-line treatment with dostarlimab.

Proposed economic evaluation

The applicant predicts a claim of superior effectiveness and safety for the IHC test / dostarlimab combination when compared to no testing and standard care administered to all patients. The preliminary supporting evidence presented in the application is from a cohort of dMMR endometrial cancer patients in a single-arm phase I study.

PASC advised that the test comparator for the economic evaluation should be changed to 'current testing regimen'.

Based on this claim, the appropriate type of economic evaluation would be a cost-utility analysis (Table 2). Since comparative evidence of IHC dMMR testing and dostarlimab treatment in dMMR and MMR-proficient patients is not included in the preliminary supporting evidence, additional evidence will be required in the assessment report to substantiate this claim (e.g., Cohort A2 of the GARNET study).

PASC noted that the preliminary supporting evidence presented in the application is from a cohort of dMMR endometrial cancer patients in a single-arm phase I study.

PASC advised that the appropriate type of economic evaluation would be a cost effectiveness analysis or cost utility analysis.

A preliminary search conducted during the PICO development identified one cost-effectiveness analysis comparing treatment with pembrolizumab to pegylated liposomal doxorubicin and bevacizumab in patients with recurrent endometrial cancer who have failed first-line treatment, stratified by MSI status (MSI-H and non-MSI-H) (Barrington et al., 2019). An application has been made to NICE to appraise the clinical and cost effectiveness of dostarlimab for previously treated recurrent or advanced MSI-H/dMMR endometrial cancer (GID-TA10670), with the first committee meeting scheduled for 2nd November 2021⁸.

⁸ <https://www.nice.org.uk/guidance/indevelopment/gid-ta10670/documents> [accessed 7-Jul-2021]

Table 2 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain ^a	Noninferior ^b	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain ^a	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior ^b	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

^a 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

^b An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

Proposal for public funding

The application proposed that MBS item 72847 be amended to determine eligibility for dostarlimab in patients with recurrent or advanced endometrial cancer (p3). However, Part 8 of the application form stated that the current wording of MBS item 72847 was adequate to define eligibility for dMMR testing. A submission for dostarlimab as monotherapy for adult patients with recurrent or advanced dMMR/MSI-H endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen was made to the TGA in January 2021.

IHC dMMR testing is already routinely performed in most pathology centres under item 72847 (4-6 antibodies). Based on the time reported in previous applications for dMMR testing, a typical IHC dMMR test takes 10 minutes to perform with results available within 24 hours (Part 8 of the application form). Item 72847 is not specific to MMR testing or endometrial cancer and is used for testing other antibody biomarkers in other diseases.

The application noted that 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 items, with a shift towards items 72849 (7-10 antibodies) and 72850 (11+ antibodies) (p19).

MSAC application 1452 (pembrolizumab in dMMR Stage IV CRC) proposed amending MBS item 72847 to facilitate access to PD-1 inhibitor treatment (pembrolizumab). The Ratified PICO for Application 1452 noted that if the current descriptor for MBS item 72847 were amended, the changes would restrict IHC dMMR testing to determining access to pembrolizumab for colorectal cancer, excluding the current usage for diagnostic, prognostic, and/or predictive purposes. It would also exclude reimbursement for other antibody tests conducted under this item.

The existing descriptor for MBS item 72847 and possible descriptions for a new MBS item are presented below. The proposed item descriptor for recurrent and advanced endometrial cancer to determine dostarlimab eligibility is based on the item proposed for IHC dMMR testing in Stage IV solid tumours other than colorectal cancer (MSAC Application 1508). The proposed fee is consistent with the current fee for MBS item 72847.

PASC advised that a new MBS item is not required for this application.

PASC advised that no change to MBS item 72847 is required to help determine access to PBS-subsidised dostarlimab.

Existing MBS item
Category 6 – Pathology Services
MBS item 72847 Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 4-6 antibodies (Item is subject to rule 13)
Fee: \$89.40
Proposed new MBS item (option 1: all endometrial cancer)
Category 6 – Pathology Services
MBS item XXXXX Immunohistochemical examination of biopsy material from a patient diagnosed with endometrial cancer, by immunoperoxidase or other labelled antibody techniques using four antibodies to the four mismatch repair proteins (MLH1, MSH2, MSH6 and PMS2). (Item is subject to rule 13)
Fee: \$89.40
Proposed new MBS item (option 2: recurrent and advanced endometrial cancer, to determine dostarlimab eligibility)
Category 6 – Pathology Services
MBS item XXXXX Immunohistochemical examination of biopsy material from a patient diagnosed with recurrent or advanced endometrial cancer by immunoperoxidase or other labelled antibody techniques using four antibodies to the four mismatch repair proteins (MLH1, MSH2, MSH6 and PMS2) to determine if the requirements relating to mismatch repair deficiency status for access to dostarlimab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. (Item is subject to rule 13)
Fee: \$89.40

Summary of public consultation input

The Department received seven responses to the targeted consultation, including from the Australia New Zealand Gynaecological Oncology Group (ANZGOG), the National Pathology Accreditation Advisory Council (NPAAC) and five medical specialists.

The responses were in agreement that immunohistochemistry (IHC) MMR testing in endometrial cancer is routine clinical practice in Australia and that patients with MMR deficient tumours would likely benefit from immunotherapy.

ANZGOG considers it important that MMR testing occur independent to any single drug therapy due to its range in terms of informing treatment planning, prognosis, and genetic status of patients.

NPAAC advised that an external quality assurance program is under development in Australia for release in 2022.

The individual responses were in agreement that MMR testing of endometrial cancers informs patients and clinicians with regards to potential germline testing and clinical prognosis. Some individual responses further stated that MMR testing may guide treatment in the future.

PASC noted the consultation feedback provided in the draft PICO. PASC noted that the consultation feedback considered that dMMR IHC testing was routinely performed.

PASC acknowledged additional feedback provided prior to the PASC meeting:

- *The Royal College of Pathologists of Australasia in principle supports this application.*
- *The Australian Genetic Cancer Medicine Centre supported this application and suggested multi-use panels to guide treatment.*
- *Cancer Australia supported this application.*

PASC acknowledged National Pathology Accreditation Advisory Council advice that an external quality assurance program for IHC testing is under development in Australia for release in 2022.

Next steps

Having accepted advice from multiple sources that IHC dMMR testing (whether funded by the MBS or otherwise) is already routine clinical and pathology practice in the management of endometrial cancer, PASC considered that this application should no longer be managed as a codependent submission given that the basis for requiring a codependent submission was not met. Noting that this matter had previously been considered by the MSAC Executive, PASC referred its consideration to the MSAC Executive for further advice.

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