



Australian Government
Department of Health

Application 1508:

Pembrolizumab (MK-3475) in mismatch repair deficient Stage IV solid tumours, other than colorectal cancer

PICO Confirmation

(To guide a new application to MSAC)

(Version 2.0)

Background information

Recently, the US Food and Drug Administration (FDA) granted accelerated approval for pembrolizumab in adult and paediatric patients with locally advanced or metastatic solid tumours that are mismatch-repair deficient (dMMR) or microsatellite instability-high (MSI-H). who have progressed after prior treatment and who have no satisfactory alternative treatment options. This is the first ‘tumour-agnostic’ or pan-tumour approval granted by the FDA.

Earlier this year, the Medical Services Advisory Committee (MSAC) Executive advised the applicant that use of pembrolizumab in dMMR colorectal cancer (CRC) would not require a co-dependent submission as the test is already used in routine clinical practice. Additionally, the test is currently reimbursed under a general Medicare Benefits Schedule (MBS) item number for immunohistochemical (IHC) staining (MSAC Executive minutes 1452, March 3 2017). The advice also indicated that the Department would work with an assessment group to obtain a position paper evaluating dMMR testing for CRC, which could be used as a benchmark against which subsequent proposals for tumour testing in other tumour types could be assessed. The applicant understands that the benchmarking exercise will commence in July 2017 and would like to be involved in this process.

As this is the first pan-tumour co-dependent technology application in Australia, the purpose of this application is to commence dialogue with the Department about a reasonable approach for the assessment of the effectiveness of pembrolizumab in patients with solid dMMR tumours.

The applicant would like to highlight that it needs to be viewed differently than a traditional co-dependent technology application, particularly as the submission will be based on data from single arm studies in over 15 different tumour types. For instance:

- It will not be feasible to establish analytical validity, clinical validity and clinical utility of dMMR testing by tumour type. *However, it is important to show that testing in the different tumour types is feasible (i.e. that the surrounding tissue does not interfere with testing and that the expression level in that tumour type is sufficient for detection) by comparison to a gold standard or via a well-established quality assurance program (QAP).*
- Overall survival comparisons for pembrolizumab plus test versus standard of care for each individual tumour location will not be possible. *In this case, it will be necessary to provide strong biological plausibility. However, some comparative data will be required. Perhaps an indirect comparison with the pembrolizumab arm of the CRC trials (if the same line of treatment).*

In addition, the applicant is aware that dMMR testing is frequently done in other cancers such as endometrial cancer and in circumstances where there is a suspicion of Lynch syndrome such as lynch-syndrome associated cancers in patients aged less than 50 years. Thus, the applicant would like the PICO Advisory Sub-committee to consider whether a co-dependent technology application is required for endometrial cancer and any other cancers where dMMR testing is already undertaken.

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 evidence is available, direct effectiveness of the intervention can be determined using the following PICO criteria.

Component	Description
Patients	Patients diagnosed with Stage IV unresectable or metastatic solid tumours other than colorectal cancer (CRC) who have progressed following first-line treatment and have not already been tested for mismatch repair (MMR) deficiency (dMMR)
Prior tests	Routine histology, cytology and immunohistochemical (IHC) tests to confirm diagnosis and stage of tumour
Interventions	a. IHC dMMR testing using antibodies directed against the four MMR proteins to detect a deficiency for eligibility for treatment with pembrolizumab on progression after first-line treatment for unresectable or metastatic disease, and standard of care in those who are MMR proficient b. No IHC dMMR testing plus pembrolizumab
Comparators	No IHC dMMR testing plus standard of care second-line treatment options No IHC dMMR testing plus palliative care if no second-line treatment options are available
Outcomes	Safety: harms from testing (including rates of re-biopsy required for testing); treatment-associated adverse events and tolerability Effectiveness: Critical outcomes ^a : Overall survival, progression-free survival, overall response rate; Important outcomes ^a : Quality of life Cost-effectiveness: 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 Total Australian Government healthcare costs
Direct research question	What is the safety, effectiveness, and cost-effectiveness of IHC dMMR testing for determining access to pembrolizumab in patients with unresectable or metastatic solid tumours other than CRC who have progressed following first-line treatment, compared with no testing and standard of care second-line treatment options?

^a Outcomes ranked as recommended by GRADE

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 Stage IV solid tumours other than colorectal cancer (CRC) 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 Stage IV unresectable or metastatic solid tumours other than CRC 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 pembrolizumab 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 pembrolizumab
Reference standard	Polymerase chain reaction-based microsatellite instability-high testing

Component	Description
Comparator	<p>Diagnostic accuracy: Methylation specific multiple ligation-dependent probe amplification to detect hyper-methylation of the <i>MLH1</i> gene promoter</p> <p>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</p>
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^a: Overall survival, progression-free survival, overall response rate; Important outcomes^a: 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 pembrolizumab in patients with unresectable or metastatic solid tumours other than CRC 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 unresectable or metastatic solid tumours other than CRC 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 pembrolizumab lead to better health outcomes in patients with dMMR unresectable or metastatic solid tumours other than CRC 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 pembrolizumab 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

2. PICO or PPICO rationale for therapeutic and investigative medical services only

2.1 Population

The proposed testing population are those patients diagnosed with unresectable or metastatic solid tumours other than colorectal cancer (CRC) 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 pembrolizumab, 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 cancer spectrum of non-CRC tumours that occur in Lynch syndrome families from three different sources.

Table 1 Location and proportion of non-CRC tumours 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%
Stomach	15%	18%	10%
Urinary tract	12%	6%	8%
Biliary tract	-	10%	1%
Small bowel	8%	2%	5%
Breast	8%	-	9%
Ovary	6%	9%	9%
Pancreas	6%	-	1%
Brain	5%	3%	4%
Lung	-	5%	4%
Renal	-	-	4%
Breast	-	6%	9%
Prostate	5%	-	2%

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). The lifetime risks for patients with Lynch syndrome developing ovarian cancer is 8% (95%CI 2, 39), 0.7% (95%CI 0.08, 4.4) for stomach cancer, 1.9% (95%CI 0.3, 5.3) for urinary tract cancer, 0.6% (95%CI 0.1, 1.3) for small bowel cancer, and 0.6% (95%CI 0.07, 2.5) for biliary tract cancer. Thus, Lynch syndrome patients would account for only a small proportion of patients with solid tumours. The prevalence of MSI-H due to dMMR mutations among different solid tumour types, and their prevalence in Australia, is listed in **Error! Reference source not found.**

Table 2 Prevalence of the most common sporadic cancer cases in Australia, proportion that are Stage IV, and MSI-H prevalence per tumour type

Carcinoma	Proportion of all cancers	Number of patients that are Stage IV	Proportion of all (Stage IV) cancers that are MSI-H
Breast cancer	26.5%	2,521	(1%)
Prostate cancer	24.5%	2,678	12% (4%)
Colorectal cancer	12.3%	3,784	15% (4%)
Melanoma	10.6%	1,352	(11–77%)
Lung cancer	9.0%	7,495	(1%)
Endometrial cancer	4.1%	295	33% (17%)
Renal cell carcinoma	2.6%	835	(1–4%)
Thyroid cancer	2.6%	123	(23%)
Head and neck cancer	2.5%	1,007	(1–3%)
Pancreatic cancer	2.4%	2,408	(1–4%)
Ovarian cancer	2.3%	811	(10–11%)
Gastric cancer	1.7%	1,007	15% (7.5%)
Cervical cancer	1.5%	221	(5–9%)
Glioma	1.5%	1,278	(0–33%)
Oesophageal cancer	1.2%	1,179	(5–10%)

Source: Scarpa, Cataldo & Salvatore (2016); Appendix to the application; Cancer in Australia 2017, Australian Institute of Health and Welfare. Available from URL <<https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2017/data>>. Accessed 11 September 2017

Le et al. (2017) tested 12,019 tumours using a next-generation sequencing (NGS) approach and found that dMMR mutations were found in 75% (24/32) of tumour subtypes. They also reported that between 17% and 2% of tumours of the endometrium, stomach, small intestine, colon and rectum, cervix, prostate, bile duct, and liver, as well as neuroendocrine tumours, uterine sarcomas, and thyroid carcinomas, had dMMR. Additionally, across tumour types, 10% of stage I-III cancers and 5% of stage IV cancers had dMMR. The applicant estimated that approximately 4% of Australian pan-tumour patients would be confirmed with dMMR and be eligible for treatment with pembrolizumab.

The application approximated the number of patients meeting the criteria for IHC dMMR testing (i.e. patients who have unresectable or metastatic tumours and have progressed after first-line treatment) to be 17,766, an annual incidence of 76.8 per 100,000 persons. This was derived from the cancer mortality statistics for Australia, estimated for 2017. Of these patients, between 0% and 80% across the different tumour sub-types currently proceed to second-line treatment of metastatic disease. However, patients with melanoma, lung cancer, or renal cell carcinoma were not included in these estimates. It was noted

that pembrolizumab has a Pharmaceutical Benefits Scheme (PBS) listing for melanoma. In addition, PD-1 inhibitors are expected to be available in the near future for patients with non-small cell lung cancer (NSCLC), or renal cell carcinoma, independent of MMR status.

MSAC should consider excluding patients who already have access to treatment with pembrolizumab from IHC dMMR testing in this pan-tumour application. Assuming PBS listing for NSCLC with $\geq 50\%$ tumour cells expressing PD-L1 does occur, only NSCLC patients with PD-L1 expression levels below 50% may benefit from IHC dMMR testing as an alternative pathway to pembrolizumab treatment. However, the requirement to test these patients would depend on the relationship between dMMR and PD-L1 expression levels in NSCLC. If all dMMR NSCLC tumours express high levels of PD-L1 ($\geq 50\%$), there would be no need for additional dMMR testing of this population.

The applicant estimated that approximately 4% of patients would be confirmed with dMMR and be eligible for treatment with pembrolizumab.

Further details about the number of patients with different types of solid tumours, with varying proportions of patients with IHC dMMR tumours should be provided to enable the number needed-to-test and the relative cost-effectiveness can be determined.

MSAC may wish to consider different testing approaches for different tumour types. Tumours with relatively high proportions of dMMR mutations could be tested at diagnosis, as suggested by the applicant. However, if cost-effectiveness becomes an issue, testing of tumours less likely to have dMMR mutations, especially those with $\leq 1\%$ probability, could be limited to patients who meet certain criteria, such as a suspicion of Lynch syndrome, presence of tumour-infiltrating lymphocytes, or the lack of alternative treatment options. MSAC could also consider the use of additional tests to confirm dMMR status and reduce the number of false-positive patients receiving inappropriate treatment.

Biological plausibility

Tumours with dMMR commonly have increased numbers of tumour infiltrating lymphocytes than MMR-proficient tumours (Drescher, Sharma & Lynch 2010). This is most likely due to the increased mutation rate leading to an increased tumour mutation burden (TMB); repetitive sequences found in many genes are vulnerable to frame-shift mutations due to the loss of MMR functions. These mutations often lead to the expression of frame-shift peptides that may be displayed on the cell surface. These peptides would be recognised as foreign by the immune system (Drescher, Sharma & Lynch 2010). Tumours with dMMR are associated with a good prognosis, and the presence of this immune response may partially explain their better clinical outcome (Buecher et al. 2013).

Llosa et al. (2015) found that dMMR tumours had significant gene upregulation of immune checkpoint proteins, including PD-L1, enabling them to survive the immune response. Rosenbaum et al. (2016) was able to detect PD-L1 expression by IHC (using the anti-PD-L1 monoclonal antibody E1L3N) in 12/54 (22%) CRC dMMR tumours (primary and metastatic), and found that PD-L1 positivity was associated with a lower survival within this dMMR CRC patient cohort. As the role of immune checkpoint proteins is the same in all cells, regardless of origin, immune checkpoint inhibitors, such as the PD-1 inhibitor pembrolizumab, may provide a clinical benefit in treating all dMMR tumours.

It should be noted that there are other known (and as-yet unknown) genetic mutations that lead to tumours with an increased TMB who will likely respond to immune checkpoint inhibitors. NGS panels are currently being used in the research setting to identify these tumours. Rizvi et al. (2018) found that the

TMB was significantly greater in patients with a durable clinical benefit from immune checkpoint inhibitors than in those with no durable benefit (p=0.006). They also found that TMB and PD-L1 expression were independent variables, and a composite of these two variables was better able to identify patients who were more likely to benefit from immune checkpoint inhibitor therapy than either biomarker alone. PASC has recommended that this issue be considered in the submission.

Tumours with an increased TMB or hyper-mutated tumours can have either MSI-H or microsatellite stable phenotypes. In contrast to the MSI-H phenotype seen with MMR mutations, mutations in the delta and epsilon subunits of the DNA polymerase (POLD1 and POLE) have hyper-mutated but microsatellite stable cancer phenotypes (Briggs & Tomlinson 2013). Other gene mutations that lead to the MSI-H phenotype include BRCA1/2, especially BRCA2 (Strickland et al. 2016). EGFR and NRTK mutations have also been strongly associated with the MSI-H phenotype in CRC (Gokare, Lulla & El-Deiry 2017). In contrast, NSCLC patients with an EGFR mutation rarely experienced a durable clinical benefit when treated with an immune checkpoint inhibitor; however, the expression of an MSI-H phenotype by these tumours was not investigated (Rizvi et al. 2018). Thus, the expression of a TMB and/or MSI-H phenotype may vary among tumour types for some genetic markers. Nevertheless, these MSI-H tumours will not be identified by IHC dMMR testing but are likely to respond to immune checkpoint inhibitors. PASC has recommended that this issue be considered in the submission. Would MSI-H testing, rather than IHC dMMR testing, identify a broader population that may benefit from pembrolizumab treatment?

A more detailed analysis of the biological plausibility for the use of IHC dMMR testing to identify tumours susceptible to immune checkpoint inhibitors, such as the PD-1 inhibitor pembrolizumab, should be provided in the report. Furthermore, evidence of dMMR being an effect modifier for treatment with pembrolizumab, above and beyond its prognostic effect should be provided.

Rationale

Four studies reporting on single-arm trials treating patients who had non-CRC dMMR tumours with pembrolizumab were listed in the summary of evidence. One study did not provide separate clinical outcomes for CRC and non-CRC patients. Two of the studies included only 30 non-CRC dMMR patients, and the fourth is a conference abstract that could not be accessed. Thus, there is little evidence for the effectiveness of pembrolizumab in treating non-CRC dMMR tumours.

As dMMR is a strong prognostic marker in earlier stages of CRC disease, its role as a treatment effect modifier for non-CRC solid tumours must be clearly demonstrated in order to interpret the results of single arm trials enrolling these patients. In addition, PASC requires that the prognostic effect of MMR status in non-CRC patients treated with standard of care be clarified in order to interpret the results of these single arm trials.

It is noted in the application that this is the first pan-tumour co-dependent technology application in Australia. The applicant also noted that the submission would be based on data from single arm studies in over 15 different tumour types. Therefore, the applicant wished to highlight that it needs to be viewed differently to a traditional co-dependent technology application, as it will not be feasible to establish analytical validity, clinical validity and clinical utility of dMMR testing by tumour type. Similarly, overall survival comparisons for pembrolizumab plus test versus standard of care for each individual tumour location will not be possible. Hence, the applicant has stated that the purpose of this application is to commence dialogue with the Department, about a reasonable approach for reimbursement for pembrolizumab in patients with solid tumours that exhibit dMMR.

If the sensitivity and specificity of the IHC dMMR test compared to the reference standard is reported in the literature, then clinical validity, in particular the positive predictive value (PPV) and negative predictive value (NPV) can be determined using the estimated prevalence rate of each tumour type. The PPV will provide valuable information about the ratio of false-positives compared to true positives that would be treated by pembrolizumab, and the NPV will provide similar information about the proportion of patients with false-negative results receiving standard of care instead of pembrolizumab.

This information is especially of interest when the prevalence is very low. Using breast cancer and a test specificity of 95% as an example, the PPV would be 16%. This means that only one out of every six positive test results would be true positive. The specificity indicates a 5% false positive rate; therefore, five out of every 100 people who are truly negative will have a false-positive result. The prevalence of dMMR for breast cancer is very low at 1%, thus one out of every 100 people tested would be truly positive and the other 99 would be truly negative. As outlined above, we would expect five (5%) of these 99 true-negative patients to have a false-positive result. This means that six out of the 100 breast cancer patients would be eligible for treatment with pembrolizumab, but only one will truly benefit. In the case of breast cancer, the five false-positive patients have forgone potentially beneficial second-line treatments.

PASC noted that the role of pathologist triage in selecting appropriate cases for testing has not been considered in this application. Pathologist review could decrease the number of patients needing testing. Tumours with a dMMR genotype often exhibit characteristic microscopic appearances. PASC suggested that the addition of a confirmatory test, such as MSI-H testing, to be considered for all dMMR test-positive patients who have “low true positivity” tumour types. This would have both cost and clinical effectiveness implications.

2.2 Prior tests

Routine histology, cytology and IHC tests to confirm diagnosis and stage of disease.

2.3 Intervention

The intervention to be assessed is IHC dMMR testing plus pembrolizumab 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 pembrolizumab 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).* PASC also noted that, 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 pembrolizumab. 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. *Evidence of the stability of these proteins in FFPE tissue blocks should be provided if archival tissue is likely to be retrieved for 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 pembrolizumab at diagnosis of or progression to stage IV disease.

The applicant indicated that IHC dMMR testing for access to pembrolizumab should be requested by the treating clinician. 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 pembrolizumab would be managed by medical oncologists.

The IHC dMMR test is a simple, fast and inexpensive and many patients diagnosed with endometrial or ovarian 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. The applicant estimated that the maximum number of patients who would be considered for IHC dMMR testing in 2017 is 18,872. The applicant plans to refine the patient numbers for use in the submission.

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. *MSAC may wish to consider whether a specific item number for IHC dMMR testing will help determine how many IHC dMMR tests are performed for determining access to immune checkpoint inhibitors.*

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).

The sponsor 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, 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'.

Lynch Syndrome Australia advocated for all tumours and unresectable tumours to be tested for dMMR. They predicted that should pathology testing become mandatory for all cancers, this would lead to identifying tens of thousands of Australians with Lynch syndrome who are currently undiagnosed.

Lynch Syndrome Australia also commented that in their experience, clinicians misinterpret the 'negative result' of an MMR test (i.e., indicating loss of staining in proteins) as a positive result requiring no further

action, whereas that ‘negative result’ indicates dMMR. This suggests that appropriate training of pathologists would be required, along with the implementation of a QAP for dMMR IHC testing.

2.4 Comparator

The comparator is no testing plus standard of care second-line treatment administered to all patients. Standard of care second-line treatment will differ according to the tumour types, and in some cases there will be no viable treatment options. The second-line treatment options for the most common non-CRC tumour types that do not have access to pembrolizumab 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 pembrolizumab treatment

Carcinoma	Predicted number of dMMR Stage IV patients	Second-line treatment options
Endocrine receptor-positive breast cancer	11 out of 2,123	Various combinations of anti-HER-2 therapy, chemotherapy and endocrine therapy
Triple negative breast cancer	7 out of 398	Monotherapy with taxane, capecitabine, eribulin, gemcitabine, or vinorelbine
Prostate cancer	107 out of 2,678	Abiraterone plus prednisone, or enzalutamide
Small cell lung cancer	11 (15% of 75) out of 1,124	Topotecan or CAV (cyclophosphamide, adriamycin and vincristine)
NSCLC: 28% excluding PD-L1 positive (i.e. TPS \geq 50%)	64 (85% of 75) – 18 = 46 out of 6,371	Monotherapy with docetaxel or pemetrexed, third-line therapy with erlotinib
Endometrial cancer	50 out of 295	Hormonal treatment (Provera) if ER-positive or monotherapy with taxol, doxorubicin or epirubicin
Renal cell carcinoma	33 out of 835	Monotherapy with everolimus, axitinib or sorafenib
Thyroid cancer	28 out of 123	No SOC
Head and neck cancer	30 out of 1,007	Monotherapy with methotrexate or taxane
Pancreatic cancer	96 out of 2,408	Combination therapy of MM-398 irinotecan plus 5-FU, folinic acid
Ovarian cancer	89 out of 811	If previous response to platinum agents was good (at least 6 months previous), re-treatment with a taxane plus carboplatin or cisplatin. For platinum-resistant disease use single agent therapy
Gastric cancer	76 out of 1,007	Oxaliplatin +/- 5-FU (FOLFOX) or irinotecan +/- 5-FU (FOLFIRI) or taxane monotherapy (paclitaxel, docetaxel)
Cervical cancer	20 out of 221	No SOC. Try monotherapy with taxol, gemcitabine or xeloda
Oesophageal cancer	118 out of 1,179	Best supportive care or palliative monotherapy

Source: Appendix to the application; ESMO guidelines available from URL: <<http://www.esmo.org/Guidelines>>, accessed 26 October 2017

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

For some cancer types, such as endocrine receptor-positive breast cancer and NSCLC with <50% of tumour cells expressing PD-L1, there are several viable second-line and subsequent-line treatment options. Thus, there is a broad range of comparators to pembrolizumab in second-line treatment. Comparisons cannot be made to all available treatment options, but the comparator should include the most common chemotherapy agents used to treat the largest proportions of dMMR pan-tumour patients. *The applicant has discussed with MSAC the use of the best and worst case scenarios.*

For both endocrine receptor-positive breast cancer and TPS <50% NSCLC, a large number of patients would have been tested to treat very few patients. It may be beneficial to delay dMMR testing for these

patients until no satisfactory alternative treatment options remain. This will reduce the number of tests that need to be conducted and still provide dMMR-positive patients access to pembrolizumab.

In some cases, such as oesophageal, cervical and thyroid cancers, there is no truly viable second-line treatment and for these patients, treatment of dMMR tumours with pembrolizumab will provide an additional treatment option, prior to palliative care. Although the exact nature of palliative care may differ for different tumour types, a comparison in the absence of an active comparative treatment should be possible.

However, as only data from single arm studies enrolling patients with MSI-H will be available, any comparisons (even with palliative care) will need to be indirect.

The comparator to the IHC dMMR test is methylation specific multiple ligation-dependent probe amplification (MS-MLPA). Most cases of dMMR in solid tumours of diverse origins are likely to be sporadic, which is caused by epigenetic inactivation (hyper-methylation) of MLH-1 gene promoter; this can be assessed by MS-MLPA, which requires only small quantities of short fragments of DNA, making it suitable for use with FFPE DNA. This test can be used to detect methylation in the promoter of several MMR genes, including MLH1, MSH2, MLH3, PMS2, MSH3, MSH6, and MGMT.

The clinical utility of other tests that could determine eligibility for pembrolizumab, such as PD-L1 testing, in tumour types with low dMMR prevalence rates should also be considered. For example, a study by Mills et al. (2017) reported that 12% of breast cancers tested (32% of triple-negative breast cancers) expressed PD-L1 while dMMR was found in only 1 case out of 285 samples (giving a 0.4% prevalence rate). The dMMR case was also PD-L1 positive, indicating that the PD-L1 test was sufficient to detect all patients likely to benefit from pembrolizumab in this study.

Rationale

The applicant claims that 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 pembrolizumab could be assumed given the routine nature of the test, especially if the test is subject to a quality assurance program. Nevertheless, some data on the accuracy of the test in solid tumour types other than CRC should be provided to demonstrate testing equivalence across different tumour types. However, the clinical validity and clinical utility of IHC dMMR testing with respect to pembrolizumab therapy has not been validated in these patients.

Reference standard

The applicant has nominated polymerase chain reaction (PCR)-based MSI-H testing as the reference standard. On 3 March 2017, the MSAC Executive met via teleconference to discuss MSAC application 1452 – dMMR IHC testing of CRC for access to pembrolizumab, and agreed that MSI-H testing would be an accepted reference standard.

PCR amplification of specific microsatellite markers, usually by multiplex PCR, can be performed on fresh, frozen or FFPE tumour material (Buecher et al. 2013). An MSI-H phenotype is defined by the presence of at least two unstable markers (identified as having insertions or deletions) among five (or $\geq 30\%$ of

unstable markers if a larger panel is used). All other tumours, with 0–30% unstable markers, are considered to be microsatellite stable owing to their clinical, histological and outcome similarities.

It should be noted that 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 mutations can lead to a non-functional protein with retained antigenicity (Buecher et al. 2013).

2.5 Outcomes

Evidence summary provided in application

The evidence base identified by the Applicant consists of four single-arm phase II trials in which patients with non-CRC dMMR tumours were treated with pembrolizumab. (Redacted sentence)

Thus, there will be no direct comparative data available. Additionally, as patients with MMR-proficient tumours are not being included in these trials, 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 non-CRC 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 pembrolizumab
<i>Therapeutic effectiveness</i>	(ranked as recommended by GRADE) Critical outcomes: overall survival, progression-free survival, overall response rate; Important outcomes: quality of life

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

<i>Predictive validity</i>	Treatment effect modification
<u>Healthcare system</u>	
<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 pembrolizumab

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 solid tumours to pembrolizumab.

PASC noted that it would be impractical to establish analytical validity, clinical validity and clinical utility for each different tumour type. PASC confirmed that the diagnostic accuracy of IHC dMMR testing in non- CRC (sensitivity/specificity/PPV/NPV) is to be compared with MSI-H testing.

Rationale

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

3. Current clinical management algorithm for identified population

The current management of solid tumours (shown in Figure 1) includes IHC dMMR testing as part of the initial work-up for patients with some tumour types and those at high risk. The treatment options are generalised, as they would vary with tumour type. However, current treatment options available to patients with dMMR stage IV cancer do not include any targeted treatment options.

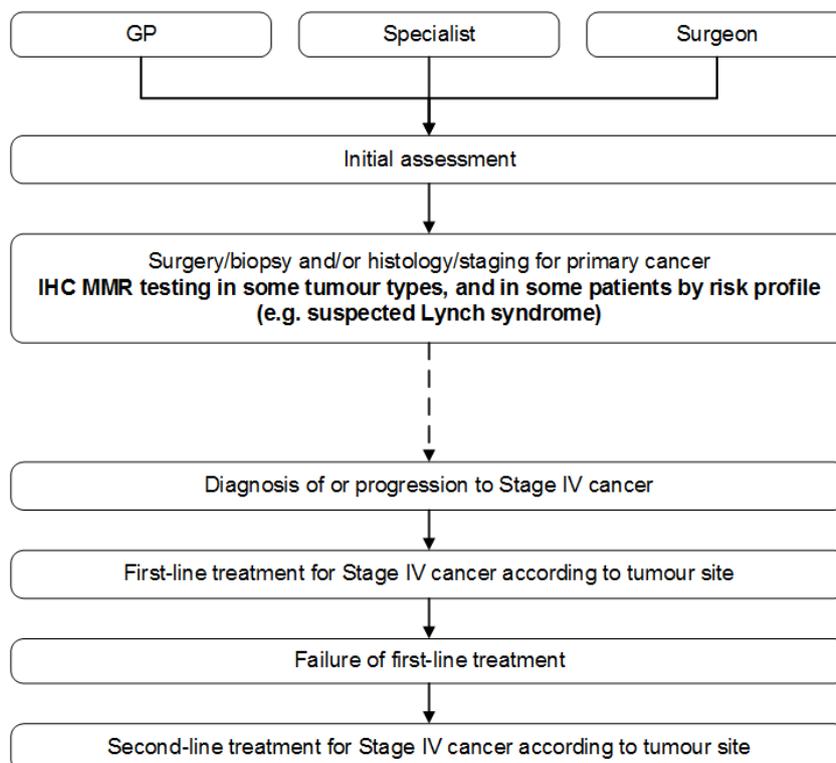


Figure 1 Current clinical algorithm for the treatment of patients with solid tumours

GP = general practitioner; IHC = immunohistochemistry; MMR = mismatch repair

4. Proposed clinical management algorithm for identified population

The clinical management algorithm that was proposed by the applicant (Figure 2) indicates that some patients with certain tumour types or risk factors 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 Stage IV would be tested for access to pembrolizumab 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 pembrolizumab and those who are MMR proficient would receive standard of care second-line treatments.

It is proposed that 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.*

However, the introduction of IHC dMMR testing for non-CRC tumours may result in testing outside the proposed parameters. In order to fully diagnose a case, the pathologist or clinician may wish to perform the IHC dMMR test at earlier stages of disease using the current MBS item number 72847. This could possibly be discouraged by appropriate education of both clinicians and pathologists. PASC noted that this issue would need to be considered in the submission.

MSAC may also wish to consider issues, including cost implications, arising from a positive IHC dMMR test result. Whereas BRAF IHC testing is an effective triage for Lynch syndrome in CRC, it may not be effective for non-CRC solid tumours due to its low prevalence rate in some tumour types. Thus, patients may need MS-MLPA or MMR gene sequencing to determine the presence or absence of Lynch syndrome. If Lynch syndrome is diagnosed, genetic counselling will also be required.

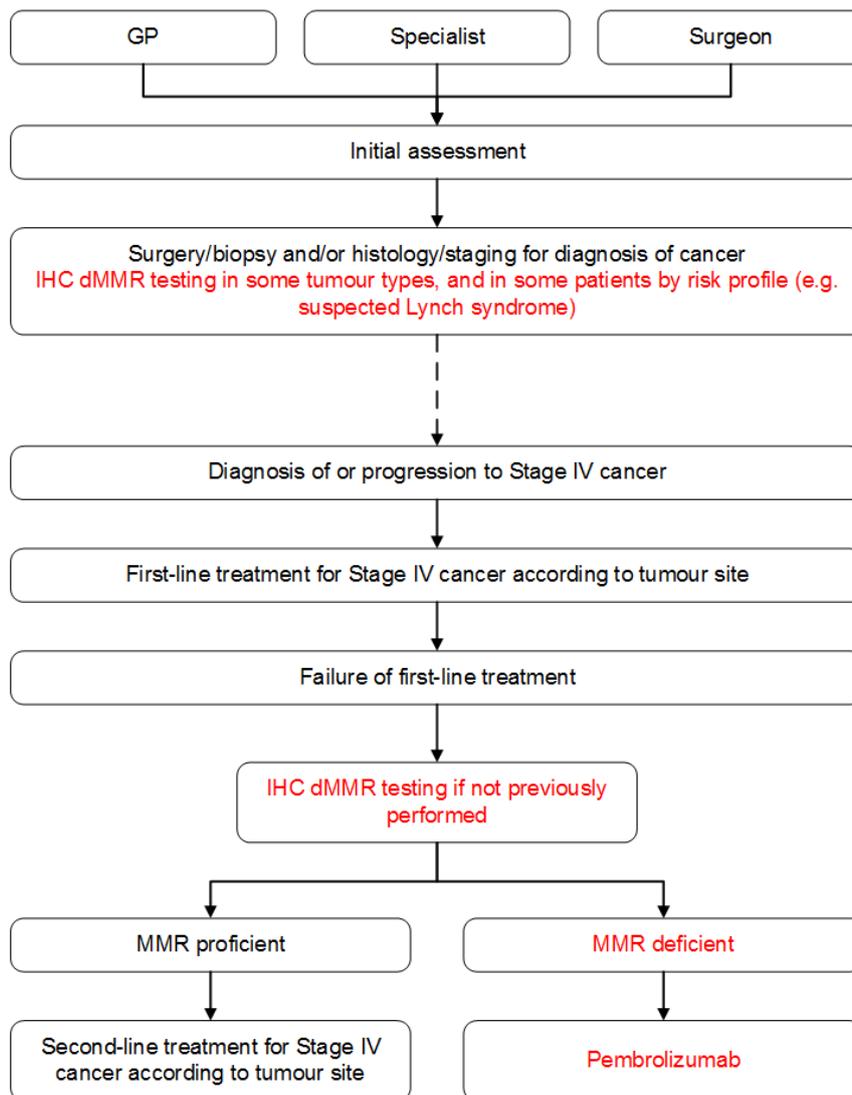


Figure 2 Proposed clinical algorithm for the treatment of patients with dMMR and MMR-proficient solid tumours
 GP = general practitioner; IHC = immunohistochemistry; MMR = mismatch repair

5. Proposed economic evaluation

The applicant predicts a claim of superiority in patients with dMMR tumours treated with pembrolizumab relative to standard of care. *PASC noted that this claim would only be supported by data from single arm trials only enrolling dMMR patients.*

On the basis of this claim, the appropriate type of economic evaluation would be a cost-utility analysis. However, comparative evidence of IHC dMMR testing or pembrolizumab treatment in both dMMR and MMR-proficient populations is not included in the preliminary supporting evidence identified in Part 4 of the Application Form. Additional evidence will need to be presented in order to substantiate these claims.

A cost-utility analysis would need underpinning evidence relating to:

- Pembrolizumab efficacy in dMMR versus MMR-proficient patients and preferably versus current standard of care.*
- Clinical utility of IHC dMMR testing to identify likely pembrolizumab responders separate to the prognostic value of being dMMR or MMR-proficient.*

PASC noted that issues arising when a dMMR tumour is detected – the proposed test could generate additional costs associated with the exclusion/diagnosis of Lynch syndrome (MLH1 methylation study/MMR gene sequencing) and genetic counselling – need to be considered in the submission. Most patients will have sporadic MSI-H/dMMR tumours, but BRAF IHC triage for sporadic cases outside the CRC setting is ineffective.

6. Proposed item descriptor

IHC dMMR testing is already routinely performed in most pathology centres under item 72847 (4-6 antibodies). Based on pathologist feedback, a typical IHC dMMR test typically takes 10 minutes to perform and results are available within 24 hours.

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).

MSAC will wish to consider creating a new item number for IHC dMMR testing of solid tumours in order to best ascertain item utilisation data. Should CRC be included or excluded from the item descriptor?

Retrieval of block is not funded for pathology services, PASC queried whether the item should be in the Genetics sections to allow use of retrieval item by pathologists.

Category 6 – Pathology Services	
MBS item number 72847	Group: P5 - TISSUE PATHOLOGY
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)	
MBS Fee: \$89.40 Benefit: 75% = \$67.05 85% = \$76.00	
Proposed MBS item number	Group: P5 - TISSUE PATHOLOGY
Immunohistochemical examination of biopsy material from a patient diagnosed with an unresectable or metastatic solid tumour who has progressed following first-line treatment, 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 pembrolizumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.	
(Item is subject to rule 13)	
MBS Fee: \$89.40 Benefit: 75% = \$67.05 85% = \$76.00	

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