Australian Government

Department of Health

Application Form

Pembrolizumab (MK-3475) in Mismatch Repair Deficient (dMMR) Stage IV Solid tumours other than colorectal cancer

(Version 0.1)

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires in order to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

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Version Control

Document History

Version Number	Date Changed	Author	Reason for Change
0.1	8 April 2016	Bianca Ledbrook	Final for Publication
0.2	12 April 2016	Sean McCandless	Document made WCAG 2.0 compliant

Document Approval

Version Number	Date Changed	Author	Reason for Change
1.0	12 April 2016	Bianca Ledbrook	Document released for publication

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details *(where relevant)*: Corporation name: ABN: Business trading name:	 **Merck Sharp & Dohme (Australia) Pty Limited** **Redacted** **Redacted**
Primary contact name:	**Redacted**
Primary contact numbers: Business: Mobile: Email:	 **Redacted** **Redacted** **Redacted**
Alternative contact name:	**Redacted**
Alternative contact numbers: Business: Mobile: Email:	 **Redacted** **Redacted** **Redacted**

2. (a) Are you a lobbyist acting on behalf of an Applicant?

Yes:	
No:	**X**

(b) If yes, are you listed on the Register of Lobbyists?

Yes	
No:	x

PART 2 – BACKGROUND

In May 2017, the FDA granted accelerated approval for pembrolizumab for the treatment of adult and paediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) cancer or mismatch repair deficient (dMMR)

- solid tumours that have progressed following prior treatment and who have no satisfactory alternative treatment options,
- or colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan.

This is the first tumour agnostic approval granted by the FDA. MSD (Australia) would now like to commence the reimbursement process for this patient population. Earlier this year, advice to MSD from the MSAC Executive confirmed that use of pembrolizumab in dMMR colorectal cancer (CRC) would not require a co-dependent submission (See 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 colorectal cancer which could be used as a benchmark against which subsequent proposals for tumour testing in other tumour types could be assessed. MSD understand that the benchmarking exercise will commence in July 2017 and would like to be involved in this process.

This application is for MMR testing in solid tumours other than colorectal cancer for access to pembrolizumab. As this is the first tumour agnostic co-dependent technology application in Australia, MSD 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 MMR testing by tumour type; similarly overall survival (OS) comparisons for pembrolizumab + test vs SOC for each individual tumour location will not be possible. Hence the purpose of this application is to commence dialogue with the Department about a reasonable approach to reimbursement for pembrolizumab in patients with solid tumours which exhibit dMMR.

In addition MSD is aware that dMMR testing is frequently done in other cancers such as endometrial cancer (EC) and in circumstances where there is a suspicion of Lynch syndrome such as lynch-syndrome associated cancers in patients aged less than 50 years[1] . Thus, MSD would like PASC to consider whether a co-dependent technology application is required for endometrial cancer and any other cancers where dMMR testing is already undertaken.

Test

In normal cells, the DNA mismatch repair (MMR) system recognises and repairs genetic mismatches generated during DNA replication. A deficient MMR (dMMR) system results in the persistence of DNA mismatches in microsatellites that may then be incorporated into the genetic code as mutations. Four key MMR proteins (MLH1, MSH2, MSH6 and PMS2) are involved, and loss of one or more of the four key proteins defines the genomic characteristic of dMMR.

A dMMR system can be hereditary (ie Lynch syndrome) or sporadic in nature. The phenotype described by dMMR has been most widely studied in colorectal cancer (CRC), where it is associated with longer overall survival, and a reduced response to chemotherapy. However, it has been identified in more than 30 separate tumour sub-types, including endometrial, ovarian, gastric, small bowel, ampullary, cholangiocarcinoma and pancreatic cancers. Analysis of 12,019 cancers across 32 types found dMMR in 11 tumour types, and in 4% of stage IV cancers (Le 2017).

Tumours that have a dMMR system develop microsatellite instability (MSI) (expansion or reduction in the length of repetitive sequences in tumour DNA compared with normal DNA) and thus exhibit the MSI-high (MSI-H) phenotype. Although tumours can be tested for either dMMR or MSI-high, in Australia the dMMR test is routinely done for colorectal cancer, as it is inexpensive and already reimbursed using existing immunohistochemical item numbers.

[1] Mascarenhas L et al. 2015 for link see section 4; http://www.lynchsyndrome.org.au/the-facts/getting-tested/

Medicine

The PD-1 pathway is a key suppressor of the cytotoxic immune response. In 2015, Le *et al* reported the results of a small phase 2 study (KEYNOTE-16) that investigated the clinical activity of pembrolizumab, a programmed death receptor-1 (PD-1)-blocking antibody, in 41 patients with metastatic disease across 3 cohorts: dMMR CRC, MMR-proficient CRC and dMMR cancers of other types. All patients were refractory to previous treatments. A post-hoc comparison of the cohorts with dMMR or MMR–proficient CRC showed hazard ratios for disease progression or death (HR=0.10; 95% CI 0.03, 0.37; P<0.001) and for death (HR=0.22; 95% CI 0.05, 1.00; P=0.05) that favoured patients with dMMR CRC. The data from this small trial supported the hypothesis that dMMR tumours are more responsive to PD-1 blockade than MMR–proficient tumours. The mutational loads were significantly higher in the dMMR tumours, and correlated with improved efficacy. Further to this, the KEYNOTE 016 trial expanded enrolment to 86 patients with dMMR, with the recently published results consistent with the earlier findings in the smaller cohort (Le 2017). Patients with dMMR tumours other than CRC demonstrated similarly positive results to those with dMMR CRC (ORR 54% and 52% respectively). To further investigate the efficacy of pembrolizumab in patients whose tumours are dMMR, MSD has initiated KEYNOTE 158, Cohort K (ID: NCT02628067), a trial of pembrolizumab in patients with a range of advanced solid tumours that exhibit dMMR/MSI-H, that have progressed on standard of care. This trial is ongoing, with preliminary results presented by Diaz *et al* 2017.

PART 2 - INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

Pembrolizumab (MK-3475) in Mismatch Repair Deficient (dMMR) unresectable or metastatic solid tumours other than colorectal cancer

4. Provide a succinct description of the medical condition relevant to the proposed service *(no more than 150 words – further information will be requested in Part 6 of the Application Form)*

Patients with unresectable or metastatic solid tumours other than colorectal cancer which are mismatch repair deficient (dMMR) who have progressed following prior treatment

5. Provide a succinct description of the proposed medical service *(no more than 150 words – further information will be requested in Part 6 of the Application Form)*

The proposed medical service is an ImmunoHistoChemistry (IHC) test for identification of dMMR for access to pembrolizumab in patients with metastatic or unresectable solid tumours other than colorectal cancers.

6. (a) Is this a request for MBS funding?

Yes:	**X**
No:	

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

Amendment to existing MBS item(s):	**X**
New MBS item(s):	

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

As IHC testing for MMR is already routinely performed in most pathology centres under item 72847 (4-6 antibodies), this item could be augmented for testing for eligibility for pembrolizumab.

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

i.	An amendment to the way the service is clinically delivered under the existing item(s)	
ii.	An amendment to the patient population under the existing item(s)	X
iii.	An amendment to the schedule fee of the existing item(s)	
iv.	An amendment to the time and complexity of an existing item(s)	
v.	Access to an existing item(s) by a different health practitioner group	
vi.	Minor amendments to the item descriptor that does not affect how the service is delivered	
vii.	An amendment to an existing specific single consultation item	
viii.	An amendment to an existing global consultation item(s)	
ix.	Other (please describe below)	

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

i.	A new item which also seeks to allow access to the MBS for a specific health practitioner group	
ii.	A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)	
iii.	A new item for a specific single consultation item	
iv.	A new item for a global consultation item(s)	

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

Yes:	**X**
No:	

(g) If yes, please advise:

PBS funding will be sought for pembrolizumab treatment of patients with solid tumours which are mismatch repair deficient (dMMR) who have progressed following prior treatment

7. What is the type of service:

Therapeutic medical service	
Investigative medical service	
Single consultation medical service	
Global consultation medical service	
Allied health service	
Co-dependent technology	**X**
Hybrid health technology	

8. For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:

i	To be used as a screening tool in asymptomatic populations	
ii.	Assists in establishing a diagnosis in symptomatic patients	
iii.	Provides information about prognosis	
iv.	Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy	**X**
v.	Monitors a patient over time to assess treatment response and guide subsequent treatment decisions	

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

Pharmaceutical / Biological	**X**
Prosthesis or device	
No	

10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

Yes	
No	**X**

(b) If yes, please list the relevant PBS item code(s)?

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

Yes (please provide PBAC submission item number below)	
No	**X**

Redacted

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

Trade name	**KEYTRUDA**
Generic name	**Pembrolizumab**

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

NOT APPLICABLE

Yes	
No	

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

Billing code(s)	
Trade name of prostheses	
Clinical name of prostheses	
Other device components delivered as part of the service	

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

NOT APPLICABLE

Yes	
No	

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

NOT APPLICABLE

Yes	
No	

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

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

Single use consumables	**Not Applicable**
Multi-use consumables	**Not Applicable**

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

MSD is proposing that clinicians use the same dMMR antibody clones that they use for colorectal cancer for other solid tumours. Examples of clones that are used in Australia include:

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

MSD is not planning to conmmercialise a new dMMR test. Hence the sponsor has not completed the remainder of Part 3.

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

Type of therapeutic good	**N/A**
Manufacturer's name	
Sponsor's name	

(b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

Class III	
AIMD	
N/A	

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

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

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

Yes (please provide details below)	
No	

ARTG listing, registration or inclusion number:	
TGA approved indication(s), if applicable:	
TGA approved purpose(s), if applicable:	

15. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

Yes (please provide details below)	
No	

Date of submission to TGA	
Estimated date by which TGA approval can be expected	
TGA Application ID	
TGA approved indication(s), if applicable	
TGA approved purpose(s), if applicable	

16. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

Yes (please provide details below)	
No	

Estimated date of submission to TGA	
Proposed indication(s), if applicable	
Proposed purpose(s), if applicable	

PART 4 – SUMMARY OF EVIDENCE

17. Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only). ***Please do not attach full text articles, this is just intended to be a summary.***

MSD would like to highlight that this section focusses on evidence for solid tumours other than colorectal cancer.

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
1	Single-arm (Phase II)	Le DT et al. Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade (KEYNOTE-16). Science; 372(26):2509-20. NCT01876511 – expanded	**Design**: Phase 2 study in patients with metastatic solid tumours with MMR deficiency **Intervention**: Pembrolizumab **Population:** dMMR solid tumours (12 types) = 86 patients (CRC=40; non-CRC=46) **Results:** Objective response rate in non-CRC tumours was 54%, with complete response in 28%. Responses durable; median progression-free survival was 18.1 months and overall survival not yet reached. 2 year OS: 57%. **Long term follow up ongoing**	https://doi.org/10.1126/science.aan6733	8 Jun 2017
2	Single-arm (Phase II)	Le DT et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency (KEYNOTE-16). NEJM; 372(26):2509-20. NCT01876511 – initial	**Design**: Phase II study in patients with metastatic carcinoma +/- MMR deficiency. **Intervention**: Pembrolizumab **Population:** MMR-deficient CRC=11 patients, MMR-proficient CRC=21 patients and non-CRC = 9 patients. **Results:** Objective response and progression-free survival rates were 40% and 78%, respectively, for MMR-deficient CRC and 0% and 11% for MMR-proficient CRC.	http://www.nejm.org/doi/full/10.1056/NEJMoa1500596	25 Jun 2015

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
3	Single-arm (Phase II)	Diaz et al. Pembrolizumab Therapy for Microsatellite Instability High (MSI-H) Colorectal Cancer (CRC) and Non-CRC. ASCO Annual Meeting 2017; June 2-6, 2017; Chicago Illinois. Poster KN164. (KEYNOTE 158) NCT02628067	**Design:** Phase II study in patients with metastatic carcinoma, MSI-H non CRC, after SOC **Intervention:** Pembrolizumab **Population:** n= 77 patients at interim analysis **Results**: ORR 38%. Median DOR not reached over median follow-up of 6.1 months. Median OS not reached, 6 months survival 73%. for non-CRC. **Study ongoing, final reporting August 2023.**	http://abstracts.asco.org/199/AbstView_199_191363.html	2 June 2017 (interim results)
4	Retrospective analysis of 2 x single arm Phase Ib studies.	Ayers M, et al. Association Between Microsatellite Instability and Clinical Response Across Tumor Types in the Phase 1b KEYNOTE-012 and KEYNOTE-028 Studies of Pembrolizumab in PD-L1 Expressing Advanced Solid Tumors. [Poster 61] Presented at the 31st Annual Meeting of The Society for immunotherapy of Cancer (SITC) November 11-13, 2016 National Harbor, MD USA.	**Design**: Retrospective analysis of patients in Phase 1b studies in patients with advanced solid tumours expressing PD-L1 to assess association between MSI-H status and response to pembrolizumab. **Intervention**: Pembrolizumab **Population:** n=310 with MSI status and response data **Results:** MSI-H status identified in 3% overall. ORR was 70% in MSI-H vs. 12% in non-MSI-H, 1-sided p=0.0001.	//www.eventscribe.com/2016/SITC/	November 2016
5	Clinical guidelines	Various	A number of Guidelines provide recommendations for dMMR testing. Overall, strong recommendations exist for CRC, endometrial, and ovarian cancers, with additional recommendations where red flag criteria for Lynch Syndrome is met. See Appendix for specific advice.	www.rcpa.edu.au www.nccn.edu.au www.cancer.org.au/ocp	

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
6	Diagnostic accuracy	Ward R et al. Routine testing for mismatch repair deficiency in sporadic colorectal cancer is justified. J Pathol. 2005 ;207(4):377-84.	**Design:** Prospective cohort study on a consecutive series of fresh tissue samples at one Australian institution **Aim:** To examine the accuracy of IHC staining (**MLH1 and MSH2 only**) in the identification of dMMR CRC in routine clinical practice. **Results:** Sensitivity was 83% and Specificity was 98%.	http://www.ncbi.nlm.nih.gov/pubmed/16175654	Dec 2005
7	Diagnostic Accuracy	Lindor NM et al. Immunohistochemistry Versus Microsatellite Instability Testing in Phenotyping Colorectal Tumors. J Clin Oncol 2002; 20: 1043-8.	**Design:** Colorectal cancers from 1,144 patients at 3 centres were assessed. **Aim**: To compare microsatellite instability (MSI) testing with immunohistochemical (IHC) detection of hMLH1 and hMSH2 in colorectal cancer. **Results:** Sensitivity was 92.3% and specificity was 100% for DNA mismatch repair defects.	http://www.ncbi.nlm.nih.gov/pubmed/11844828	Feb 2002
8	Literature review of Diagnostic Accuracy Studies	Shia J. Immunohistochemistry versus Microsatellite Instability Testing For Screening Colorectal Cancer Patients at Risk For Hereditary Nonpolyposis Colorectal Cancer Syndrome. J Mol Diagn 2008, 10:293–300.	**Design:** A review of the literature, including studies that conducted IHC on MLH1, MSH2, PMS2 and MSH6 proteins. **Aim**: To identify studies that report on the utility of IHC testing for dMMR. **Results:** Including PMS2 and MSH6 proteins in IHC MMR testing has improved its sensitivity to 94%.	http://www.ncbi.nlm.nih.gov/pubmed/18556767	July 2008
9	Pathologist Survey	Mascarenhas L et al. A survey of the current provision of screening tumours for mismatch repair deficiency in Australia: An Inherited Cancer Connect Partnership initiative. COSA 42nd Annual Scientific Meeting 2015 Nov, Hobart, Australia	**Design:** Heads of RCPA accredited laboratories in Australia were surveyed. **Aim:** To survey the current availability of screening for CRC and endometrial cancer (EC) tumour dMMR. **Results:** The response rate was 76%, with 78% of laboratories conducting MMR IHC testing. 54% are routinely screening all CRC, and 26% are screening all endometrial cancer specimens for MMR.	http://cosa-2015.m.asnevents.com.au/schedule/session/7496/abstract/29440	Nov 2015

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.*

**** If the publication is a follow-up to an initial publication, please advise.*

18. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

	Type of study design*	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)**	Website link to research (if available)	Date***
			Primary Evidence		
1	Single arm, multi-cohort phase 2 study in patients with advanced solid tumours with MMR deficiency	KEYNOTE 016 NCT01876511	**Intervention**: Pembrolizumab **Population:** Cohort C: Patients with any advanced solid tumour, with the exception of colorectal cancer, which is Microsatellite Instability - High (MSI-H) who have received at least one prior therapy. **Estimated enrolment for all cohorts:** 171 (Cohorts A-C) **Study stage:** Recruiting; interim results Le 2017	https://clinicaltrials.gov/ct2/show/record/NCT01876511	**Estimated completion date:** August 2020; interim analysis may be available prior to this date.
2	Single arm, multi-cohort phase 2 study in patients with advanced solid tumours with MMR deficiency	KEYNOTE 158 NCT02628067	**Intervention**: Pembrolizumab **Population:** Cohort K: Patients with any advanced solid tumour, with the exception of colorectal cancer, which is Microsatellite Instability - High (MSI-H) who have received at least one prior therapy **Estimated enrolment:** 1350 (cohorts A-K) **Study stage:** Recruiting; interim results Diaz 2017	https://clinicaltrials.gov/ct2/show/record/NCT02628067	**Estimated completion date:** August 2023; interim analysis may be available prior to this date.

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*

****Date of when results will be made available (to the best of your knowledge)*

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

19. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a letter of support for each group nominated).

Royal College of Pathologists

(IHC testing of MMR is already undertaken under MBS item #72847, so we have not requested a letter of support to comment on the service or the fee. Please refer to "COLORECTAL CANCER STRUCTURED REPORTING PROTOCOL" for the College's specific recommendations on dMMR IHC testing [items CG4.01-CG4.02])

MSD has approached the RCPA and not received a response. MSD recommends that PASC approach them directly.

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

Medical Oncology Group of Australia (MOGA)

MOGA has sent a letter directly to Andrew Wilson, chair of PASC

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

Given the tumour-agnostic nature of this submission, a number of other associations will be impacted such as Ovarian Cancer Australia, PanCARE, Lynch Syndrome Australia and Rare Cancers Australia.

A letter from Rare Cancers is provided with this application.

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

MSD is not aligning with any specific manufacturer for this application. Therefore, the current manufacturers would be used for the IHC MMR test.

23. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):

Name of expert 1	**Redacted**
Telephone number(s)	**Redacted**
Email address	**Redacted**
Justification of expertise	**Redacted**

Name of expert 2	**Redacted**
Telephone number(s)	**Redacted**
Email address	**Redacted**
Justification of expertise	**Redacted**

Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.

PART 6 – POPULATION (AND PRIOR TESTS), INDICATION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

24. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality.

As outlined in Background, in normal cells, the DNA mismatch repair (MMR) system recognises and repairs genetic mismatches generated during DNA replication. A deficient MMR (dMMR) system results in the persistence of DNA mismatches in microsatellites that may then be incorporated into the genetic code as mutations. Four key MMR proteins (MLH1, MSH2, MSH6 and PMS2) are involved, and loss of one or more of the four key proteins defines the genomic characteristic of dMMR.

The patient cohort who would undergo testing for dMMR comprise those with unresectable or metastatic solid tumours other than colorectal cancer that have progressed following prior treatment, and who have no satisfactory alternative treatment options.

Therefore, the medical condition is: previously treated unresectable or metastatic carcinoma other than colorectal cancer, exhibiting dMMR.

25. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service.

The proposed patient population includes patients diagnosed with unresectable or metastatic solid tumours other than colorectal cancer that have progressed following prior treatment and who have no satisfactory alternative treatment options.

The median age of this patient population is expected to be approximately 70 years but could range from 20 to 100+. Patients with hereditary dMMR (Lynch Syndrome) are likely to be younger, given their higher risk of developing certain cancers before 50 years of age. The male to female ratio is roughly 1:1. Due to the age of the cohort, various age-related comorbidities are likely to be present (Cancer in Australia, AIHW 2017).

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

Although the treatment pathways differ according to the tumour sub-type, however there are some commonalities. Patients who present with symptoms of carcinoma of any sub-type will receive further investigations. Other patients may be identified through screening procedures, such as mammograms in breast cancer. To identify metastases, computerised tomography (CT) scans, magnetic resonance imaging (MRI) scans, positron emission tomography (PET) scans, ultrasounds, and X-rays may also be undertaken. Once diagnosed, many patients undergo surgery, with tissue from the resection tested by pathologists. In some tumour sub-types, this testing includes IHC for dMMR. If resected tissue is not available, biopsy tissue can also be used. Biopsy material has been shown to be as reliable as resection specimen material in detecting a dMMR.

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

26. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point).

As noted previously, patients received an initial diagnostic work up relevant to the specific tumour type. Tissue would be obtained from scoping procedures (or surgical resection if patients have received surgery), and sent to the pathology laboratory for histology/staging and molecular testing. For some patients such as those with endometrial cancer, MMR testing is likely to be already undertaken, as part of this process.

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

Please refer to Attachment 1 for the current clinical algorithm and proposed algorithm.

Please note that alternative proposed testing algorithms will be explored during the submission process for patients who are not currently tested for dMMR.

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

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

The majority of dMMR cancers show loss of expression of both MMR proteins in a heterodimer (either MLH1/PMS2 or MSH2/MSH6) in the cancer cells, with preserved expression of the other heterodimer. In sporadic dMMR cancers, loss of MLH1/PMS2 expression is characteristic, whereas in Lynch syndrome (i.e. hereditary dMMR) either heterodimer may be lost.

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

No.

29. **If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?**

N/A

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

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

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

A biopsy or surgical resection is required to obtain tissue for the IHC test. These procedures are currently part of standard management for the majority of patients with solid tumours, so they would not present an additional burden to patients or the health system.

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

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

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

No

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

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

35. If applicable, advise what type of training or qualifications would be required to perform the proposed service as well as any accreditation requirements to support service delivery.

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

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

Inpatient private hospital	
Inpatient public hospital	
Outpatient clinic	
Emergency Department	
Consulting rooms	
Day surgery centre	
Residential aged care facility	
Patient's home	
Laboratory	**X**
Other – please specify	

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

N/A

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

Yes	**X**
No (please specify below)	

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

38. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service).

Ordinarily, this submission would require the following comparisons to be made:

1) **No testing + Standard of care administered to all patients**
2) **No testing + Pembrolizumab administered to all patients**

With regard to comparison 1), given the multitude of comparators and treatment settings, MSD would like to seek feedback from PASC on a practical and pragmatic way of making this comparison, in light of the single arm nature of the studies, number of comparators / settings, etc

With regard to comparison 2), as dMMR testing is routinely done in Australia for CRC[2] and other cancer types such as endometrial, it is already accepted as having adequate analytical validity, clinical validity and clinical utility. Therefore, for the purposes of this application, MSD proposes to assess the effectiveness and cost effectiveness of the test through a qualitative assessment rather than through the standard comparison of "Testing + pembrolizumab vs No testing + pembrolizumab administered to all patients"

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

Yes (please provide all relevant MBS numbers below)	
No	**X**

[2] Schofield et al, 2014 https://www.ncbi.nlm.nih.gov/pubmed/24474394;

40. Define and summarise the current clinical management pathways that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards including health care resources).

Patients will undergo a single event of dMMR testing, at the time of initial diagnostic workup. **A summary of the current treatment of patients with unresectable or metastatic disease of various tumour sub-types, which has progressed following prior treatment (ie 2L treatment) is provided in the Appendix. Broadly, the 2L treatment for metastatic disease is systemic chemotherapy, commonly in combinations. For some tumour types, immunotherapies are recommended (see Q.46). The choice of treatment is also dependent on prior treatment, and the ability of the patient to tolerate treatment. Standard of care 2L treatment for metastatic disease is not well established for rare cancers.** **In addition to drug and drug administration cost, healthcare resources associated with treatment may include the management of drug-related toxicities, on-going disease management costs.** **Please refer to Attachment 1 for the current clinical algorithm and proposed clinical algorithm.**

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

Yes	
No	**X**

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

42. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service including variation in health care resources (Refer to Question 39 as baseline).

If patients are found to be dMMR, they would receive treatment with pembrolizumab (200 mg IV every 3 weeks). All other patients would continue to receive standard management.

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

- **Adverse event related treatment;**
- **Ongoing disease management resource utilisation;**
- **Post-progression/2L therapy; and**
- **Palliative care costs.**

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

43. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms).

Pembrolizumab + testing administered to all patients provides superior effectiveness and safety when compared to:

1) No testing + Standard of care administered to all patients
2) No testing + Pembrolizumab administered to all patients

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

Superiority	**X**
Non-inferiority	

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

Safety Outcomes
• Serious adverse events (defined as events that result in death; are life threatening; result in persistent or significant disability/incapacity; result in or prolongs an existing inpatient hospitalization; are a congenital anomaly/birth defect; or other important medical event).
• Adverse events
• Toxicities
• Safety of the MMR IHC test (including rates of re-biopsy required for testing)
Clinical Effectiveness Outcomes

• Diagnostic Accuracy of MMR IHC test (Sensitivity, Specificity, Positive predictive value, Negative Predictive Value). As diagnostic accuracy has been determined in CRC, this submission will explore qualitatively whether this is expected to be any different in non-CRC tumours.
• Progression Free Survival (PFS) per RECIST 1.1
• Overall Response Rate (ORR) per RECIST 1.1
• Overall Survival
• Patient Reported Outcomes

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

The patient cohort who have not already been tested for MMR and hence would undergo testing for dMMR comprise those with unresectable or metastatic solid tumours that have progressed following prior treatment, and who have no satisfactory alternative treatment options. Patients with CRC or melanoma are not included in these estimates. Pembrolizumab has a PBS listing for melanoma, and previous advice to the sponsor is that use of pembrolizumab in CRC would not be considered co-dependent. In addition, PD-1 inhibitors are expected to be available in the near future for patients with lung cancer, or renal cell carcinoma, independent of MMR status, and these patients are also excluded from the estimates.

An approximation of the upper end of patients meeting these criteria has been derived from the cancer mortality statistics for Australia; in 2017, this number is projected to be 18,872 (see Appendix). This equates to an annual incidence of 76.8 per 100,000.

Not all patients at this stage of disease / treatment course will be considered for further treatment, Expert opinion notes between 0% and 80% across the different tumour sub-types currently proceed to 2L treatment of metastatic disease; some are too unwell for further treatment.

Patient numbers will be refined for the submission, work is ongoing to explore the use of other data sources to identify the eligible patient pool.

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

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

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

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

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

A proportion of patients will already have undergone testing for dMMR as part of routine clinical care. Currently, universal testing is recommended for colorectal cancer and endometrial cancer, with many others tested where red flag criteria exists such as certain cancers in those aged <50 years. As above, the upper estimate of patients who would be considered for testing is 18,872 in 2017. Of these, it is expected that those with endometrial (~1%) or ovarian cancer (~3%) will have previously had MMR IHC tests performed at earlier stages of disease. Therefore, the upper estimate of additional patients utilising the services is 17,766.

The frequency of dMMR differs across tumour sub-types. Approximately 4% of patients (Le 2017) would be confirmed with dMMR and be eligible for treatment with pembrolizumab (n=755, based on upper estimates as above).

Patient numbers will be refined for use in the submission; work is ongoing to explore the use of other data sources to identify the eligible patient pool.

50. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service.

IHC MMR testing is already routinely undertaken in Australian laboratories, with 78% of all reporting IHC MMR capability. Of these, 54% of laboratories perform MMR testing of all CRC as routine practice, For EC, the corresponding rate is 26% (Mascarenhas, 2015). The remainder of locations test CRC and EC on red flag criteria +/- clinician request. Uptake at these locations is expected to increase to allow for testing of unresectable or metastatic tumours of other types.

While uptake would increase in these laboratories, they are already performing MMR IHC testing and therefore have existing resources and referral arrangements in place.

MMR IHC results are used for other clinical-decision making purposes in some tumour sub-types, so many patients will have had testing performed at earlier stages of disease. Furthermore, some centres are already practising universal testing for some tumour sub-types. Leakage to populations outside the proposed group is unlikely.

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

PART 8 – COST INFORMATION

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

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

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

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

Based on pathologist feedback, a typical IHC MMR test typically takes 10 minutes to perform. Results are available within a 24 hour timeframe.

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

The wording of the current MBS item 72847 is sufficient to define eligibility for dMMR testing.

PART 9 – FEEDBACK

The Department is interested in your feedback.

54. How long did it take to complete the Application Form?

The application and related background research took several weeks to complete.

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

Yes	
No	**X**

(b) If no, provide areas of concern.

It was often unclear if the question was relating to the medical service or the pharmaceutical product.

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

Yes	
No	**X**

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

It would be useful if the guidelines' descriptions could articulate the requirements for co-dependent submissions. **For items Part 4, the required extent of the literature review/summary was unclear. We have provided a high level summary here but intend to submit a more in-depth analysis in the full application.**

57. (a) Is there any information that the Department should consider in the future relating to the questions within the Application Form that is not contained in the Application Form?

Yes	
No	**X**

(b) If yes, please advise:
