

## 6.06 PEMBROLIZUMAB, SOLUTION CONCENTRATE FOR I.V. INFUSION 100 MG IN 4 ML, KEYTRUDA<sup>®</sup>, MERCK SHARP & DOHME (AUSTRALIA) PTY LTD

### 1 Purpose of Application

- 1.1 The submission requested a Section 100 (Efficient Funding of Chemotherapy), Streamlined listing for pembrolizumab for the treatment of locally advanced (unresectable) or Stage IV (metastatic) colorectal cancer (mCRC) with deficient mismatch repair (dMMR), hereafter referred to as dMMR mCRC. Pembrolizumab has not been considered by the PBAC for this indication previously.
- 1.2 The requested listing was based on a cost-utility analysis of pembrolizumab compared with standard of care (SOC), represented by FOLFIRI (folinic acid, 5-fluorouracil and irinotecan), FOLFIRI with bevacizumab, or FOLFIRI with cetuximab. The key components of the clinical issue addressed by the submission are summarised below.

**Table 1: Key components of the clinical issue addressed in the submission**

Component	Description
Population	Patients with locally advanced unresectable, or Stage IV (metastatic) colorectal cancer (mCRC), with mismatch repair deficient (dMMR) tumours and who have received at least one prior therapy, i.e. second-line and beyond.
Intervention	Pembrolizumab 200 mg every three weeks (Q3W) for up to 35 cycles.
Comparator	Standard of care (SOC). The following therapies were identified as the main comparators in the submission: <ul style="list-style-type: none"> <li>FOLFIRI (representing other chemotherapy regimens including FOLFOX and XELOX)</li> <li>Cetuximab + FOLFIRI (representing EGFR antibodies + chemotherapy)</li> <li>Bevacizumab + FOLFIRI (representing bevacizumab + chemotherapy).</li> </ul>
Outcomes	Objective response rate (ORR), progression-free survival (PFS) and overall survival (OS).
Clinical claim	In patients with locally advanced unresectable, or Stage IV (metastatic) mismatch repair deficient (dMMR) colorectal cancer, who have failed at least one prior therapy; pembrolizumab is more effective than standard chemotherapy, cetuximab + chemotherapy or bevacizumab + chemotherapy at improving survival.

FOLFIRI = Leucovorin calcium (folinic acid), 5-fluorouracil, irinotecan; FOLFOX = Leucovorin calcium (folinic acid), 5-fluorouracil, oxaliplatin; EGFR = epidermal growth factor receptor; XELOX = oxaliplatin + capecitabine.

Source: Table 1.1-1, p3 of the main submission.

## 2 Requested listing

### Essential elements of the requested listing

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
PEMBROLIZUMAB			Published:	KEYTRUDA®
<u>Initial treatment</u> 100 mg/4 mL injection, 1 x 4 mL vial	200 mg	5	\$9,024.44 (Public) \$9,188.54 (Private)	Merck Sharp & Dohme Pty Ltd
<u>Continuing treatment</u> 100 mg/4 mL injection, 1 x 4 mL vial	200 mg	6	Effective: \$ [REDACTED] (Public) \$ [REDACTED] (Private)	

<b>Category / Program:</b>	Section 100 - Efficient funding of Chemotherapy
<b>Prescriber type</b>	Medical Practitioners
<b>Severity:</b>	Locally advanced (unresectable) or metastatic (Stage IV)
<b>Condition:</b>	Locally advanced (unresectable), or Stage IV (metastatic) dMMR colorectal cancer
<b>PBS Indication:</b>	Locally advanced (unresectable) or Stage IV (metastatic) dMMR colorectal cancer in patients who have failed at least one prior therapy.
<b>Treatment phase:</b>	Initial treatment
<b>Restriction Level/Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	Locally advanced (unresectable) or metastatic (Stage IV) mismatch repair deficient (dMMR) colorectal carcinoma AND Patient must have failed at least one prior standard chemotherapy (with or without an EGFR or VEGF antibody) AND Patient must not have received prior PBS-subsidised treatment with a PD-1 inhibitor for this condition AND The treatment must be the sole PBS-subsidised therapy for this condition.
<b>Prescriber instructions</b>	The treatment must not exceed a total of 35 cycles in a lifetime.
<b>Administrative Advice</b>	No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. Special Pricing Arrangements apply

<b>Treatment phase:</b>	Continuing treatment
<b>Restriction Level/Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not have progressive disease while receiving PBS-subsidised treatment with this drug for this condition.
<b>Prescriber instructions</b>	The treatment must not exceed a total of 35 cycles in a lifetime.
<b>Administrative Advice</b>	No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. Special Pricing Arrangements apply

<b>Treatment phase:</b>	Grandfathering
<b>Restriction Level/Method:</b>	<input checked="" type="checkbox"/> Streamlined

<b>Clinical criteria:</b>	Patient must have received non-PBS-subsidised treatment with a programmed cell death 1 (PD-1) inhibitor for this condition prior to [insert listing date] AND Patient must not have developed disease progression while receiving treatment with a PD-1 inhibitor for this condition AND The treatment must be the sole PBS-subsidised therapy for this condition AND The treatment must not exceed a total of 35 cycles in a lifetime.
<b>Prescriber Instructions</b>	A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
<b>Administrative Advice</b>	No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. Special Pricing Arrangements apply

Source: pp12-16, Section 1.4 of the main submission.

- 2.1 During the evaluation, it was advised that the proposed target population in the submission had changed from mCRC with dMMR or microsatellite instability high (MSI-H) status to dMMR mCRC only, as MSI-H testing is not currently reimbursed under a Medicare Benefits Schedule (MBS) item number. Unlike MSI-H testing, dMMR testing in CRC is routine clinical practice in Australia (to identify patients with Lynch syndrome). For a dMMR mCRC target population, the Medical Services Advisory Committee (MSAC) Executive has previously advised the applicant that a codependent submission would not be required, as the MMR test is currently reimbursed under a general MBS item number for immunohistochemical (IHC) staining (MSAC Executive minutes 1452, March 3 2017). The Secretariat noted that the MSAC was considering the comparability of MSI-H and dMMR testing. Current literature (Jin et al, 2018<sup>a</sup>) suggests that colorectal tumours that have dMMR status are biologically similar to those with MSI-H status.
- 2.2 The submission proposed a Special Pricing Arrangement (SPA). The submission noted that the effective approved ex-manufacturer price (AEMP) per 100 mg pembrolizumab vial of \$ [REDACTED] was based on the economic evaluation. The submission stated that “If positively recommended, the Sponsor will work with the Department to develop a Deed to ensure the appropriate effective price is paid by the government”.
- 2.3 The PBAC noted that the requested restriction, as a second-line therapy, did not align with the recommendations made by the first Clinical Evaluation Report for the TGA. This recommended that pembrolizumab be used in patients who “have exhausted all subsequent effective or suitable treatment options” (see paragraphs 3.3 and 3.4 below). The PBAC advised that the place in therapy and proposed PBS restriction should align with this recommended indication.

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<sup>a</sup> Jin Z, Sanhueza C, Johnson B, et al. Outcome of mismatch repair-deficient metastatic colorectal cancer: The Mayo Clinic experience. *The Oncologist*. 2018;23:1083-1091.

- 2.4 A STREAMLINED authority was requested, aligning with the restrictions for cetuximab, bevacizumab and panitumumab in the same line of therapy. The PBAC advised that the restriction level should be Authority Required (Written), with the clinician providing evidence of dMMR status.
- 2.5 The submission proposed a grandfathering listing for patients who have already initiated pembrolizumab treatment before the PBS listing. The submission estimated that 59 patients would be eligible for grandfathering.
- 2.6 The requested PBS restriction states that a patient must have failed at least one prior standard chemotherapy (with or without an epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF) antibody). Thus, the requested restriction includes second- and later-line treatment. The KN164 study provided limited evidence for treatment with pembrolizumab in the second-line setting as the majority of patients (90.2%) had failed at least two prior lines of therapy at study baseline. Approximately 44% and 23% of patients had progressed on at least three and at least four prior lines of therapy, respectively.
- 2.7 Consistent with the view of the ESC, the PBAC advised that an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 may need to be specified in the requested restriction to: 1) reflect the KN164 study population, and 2) address the safety concern that patients with a poor PS may be more likely to have adverse outcomes from the immune mediated AEs associated with PD-1/PD-L1 inhibitors.

*For more detail on PBAC's view, see Section 7 PBAC outcome.*

### **3 Background**

#### ***Registration status***

- 3.1 Pembrolizumab is currently under review by the TGA via the provisional approval pathway and the submission was made under the TGA/PBAC Parallel Process. The requested TGA indication is:

“Use as monotherapy for the treatment of patients with advanced MSI-H or dMMR cancer who have received prior therapy.”
- 3.2 The requested TGA indication did not specify tumour type, whereas the requested PBS restriction was for locally advanced (unresectable) or metastatic Stage IV CRC.
- 3.3 The first round Clinical Evaluation Report for the TGA found that there was insufficient evidence to support registration of pembrolizumab for the proposed indications, and that the available evidence for treatment of MSI-H/dMMR colorectal and non-colorectal pan-tumour subtypes remained unclear.
- 3.4 This Clinical Evaluation Report recommended two alternate indications:

“For the treatment of adult patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), Stage IV colorectal cancer with no evidence of brain metastases and who have

progressed following prior standard treatment which included a fluoropyrimidine, oxaliplatin, and irinotecan, and who have exhausted all subsequent effective or suitable treatment options.”

OR

“For the treatment of adult patients who have exhausted all effective or suitable treatment options and who have unresectable or metastatic, MSI-H or dMMR:

- Solid tumours that have progressed following prior standard treatments; or
- Stage IV colorectal cancer who have progressed following prior standard treatments which included a fluoropyrimidine, oxaliplatin, and irinotecan.

Patients with a history of brain metastases are not eligible for pembrolizumab.”

- 3.5 The pre-PBAC response indicated a willingness to develop a PBS restriction that aligned with the TGA proposed wording.
- 3.6 Although the submission stated that the Delegate’s overview would be made available prior to the PBAC meeting in March 2019, the PBAC noted that this had not happened, and that the TGA evaluation plan indicated the following due dates: Delegate’s overview on 7 May 2019, the Advisory Committee on Medicines (ACM) outcomes on 28 June 2019, and the Decision letter in July 2019.
- 3.7 Other TGA-approved indications include previously untreated metastatic non-small cell lung cancer (NSCLC) patients with tumours that are programmed cell death ligand 1 (PD-L1) tumour proportion score (TPS)  $\geq 50\%$  (as determined by a validated test), advanced NSCLC (PD-L1  $\geq 1\%$  TPS) pre-treated with platinum-containing chemotherapy, unresectable or metastatic melanoma in adults, recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy, monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin Lymphoma (cHL) following autologous stem cell transplant or at least two prior therapies, and locally advanced or metastatic urothelial carcinoma who have received platinum containing chemotherapy or are not eligible for cisplatin-containing therapy.

### ***Previous PBAC considerations***

- 3.8 This is the first PBAC consideration of pembrolizumab for the proposed indication. Pembrolizumab is currently listed on the PBS for unresectable Stage III or Stage IV malignant melanoma and for relapsed or refractory Hodgkin lymphoma, regardless of PD-L1 expression, and for previously untreated Stage IV (metastatic) non-small cell lung cancer (NSCLC) which must have a PD-L1 TPS of at least 50%.

*For more detail on PBAC’s view, see Section 7 PBAC outcome.*

## 4 Population and disease

- 4.1 Approximately 20% of people with CRC have metastatic disease at the time of initial diagnosis. Patients diagnosed with CRC have about an 8% chance of surviving for five years. The MMR system is mainly composed of four proteins interacting together to recognize any deoxyribonucleic acid (DNA) mismatches during replication. 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<sup>b</sup>. dMMR tumours have significant gene upregulation of immune checkpoint proteins, including PD-L1, enabling them to survive the immune response. In mCRC, the prevalence of dMMR is low (3.5%)<sup>c</sup>. The ESC expressed concern that, with this low prevalence of dMMR if tested at this stage of CRC, there would be a higher risk of false positive test results, and thus potentially futile therapy.

## 5 Comparator

- 5.1 The submission nominated three main comparators:
- 1) chemotherapy, represented by FOLFIRI, as it was representative of all the chemotherapy regimens (FOLFOX and FOLFIRI are most commonly used and neither one is superior to, nor cheaper than, the other);
  - 2) cetuximab + chemotherapy as cetuximab was the most commonly used EGFR antibody and is similar in price and efficacy to panitumumab; and
  - 3) bevacizumab + chemotherapy as bevacizumab is a VEGF antibody that is only PBS reimbursed in second-line RAS wild type patients who have failed prior EGFR therapy.
- 5.2 The submission stated that the choice of chemotherapy agent in the second-line setting is determined by the patients' RAS status, prior therapy, performance status (PS) and organ function. Patients who are RAS wildtype may receive an EGFR antibody (cetuximab or panitumumab) or a VEGF antibody (bevacizumab) in combination with chemotherapy.
- 5.3 The submission did not nominate trifluridine with tipiracil as a relevant comparator. This combination was recommended by the PBAC in July 2018 for the treatment of mCRC patients who have been treated previously or are not considered suitable for current available therapies involving fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapies, or anti-VEGF or anti-EGFR agents (Trifluridine with tipiracil Public Summary Document (PSD), July 2018).

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<sup>b</sup> Dudley JC, Lin M-T, Le DT, Eshleman JR. Microsatellite instability as a biomarker for PD-1 blockade. *Clinical Cancer Research*. 2016;22(4):813-20.

<sup>c</sup> Venderbosch S, Nagtegaal ID, Maughan TS, Smith CG, Cheadle JP, Fisher D, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN and FOCUS studies. *Clinical Cancer Research*. 2014;clincanres. 0332.2014.

- 5.4 Although not currently TGA registered or PBS reimbursed, the submission nominated nivolumab or nivolumab + ipilimumab as near-market comparators. This was based on a study of nivolumab ± ipilimumab in dMMR mCRC patients who have progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
- 5.5 The PBAC, noting the Clinical Evaluation Report for the TGA, considered that as the appropriate place in therapy for pembrolizumab was as a last-line treatment option, the comparators nominated in the submission were inappropriate. The PBAC advised that best supportive care (BSC) or trifluridine with tipiracil would be more appropriate comparators in a last line therapy population.

*For more detail on PBAC's view, see Section 7 PBAC outcome.*

## 6 Consideration of the evidence

### **Sponsor hearing**

- 6.1 There was no hearing for this item.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from individuals (10) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with pembrolizumab in general, including improved survival.
- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the pembrolizumab submission, categorising it as one of the therapies of “high priority for PBS listing” on the basis of the Keynote 164 study. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pembrolizumab, which was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>d</sup>.

### **Clinical trials**

- 6.4 The clinical evidence provided in the submission consisted of a naïve indirect comparison between:
- Study KN164: a single-arm study of pembrolizumab (200 mg administered every three weeks) in heavily pre-treated MSI-H/dMMR Stage IV mCRC patients (N = 61). Objective response rate (ORR), which was a summation of complete response and partial response, was the primary outcome. OS data were immature; and
  - Single arms from 16 comparator studies (nine studies of bevacizumab + chemotherapy, five studies of chemotherapy (FOLFIRI), one study of cetuximab + chemotherapy, and one study of the near-market comparators, nivolumab ±

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<sup>d</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017.

ipilimumab). All main comparator studies were conducted on ‘all comers’ (i.e. irrespective of MMR status).

- 6.5 None of the evidence from the comparator studies was used in the economic evaluation.
- 6.6 Details of the studies included in the submission are provided in the table below.

**Table 2: Studies and associated key reports presented in the submission**

Study ID	Protocol title/ Publication title	Publication citation
<b>Proposed medicine: pembrolizumab</b>		
KN164	<p>Clinical Study Report P164V02MK3475: A Phase II Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects With Previously Treated Locally Advanced Unresectable or Metastatic (Stage IV) Mismatched Repair Deficient or Microsatellite Instability-High Colorectal Carcinoma (KEYNOTE-164).</p> <p>Dung T. Le, Petr Kavan, Tae Won Kim, et al. KEYNOTE-164: Pembrolizumab for patients with advanced microsatellite instability high (MSI-H) colorectal cancer.</p> <p>Dung T. Le, Takayuki Yoshino, Dirk Jäger, et al. KEYNOTE-164: Phase II study of pembrolizumab (MK-3475) for patients with previously treated, microsatellite instability-high advanced colorectal carcinoma.</p> <p>Diaz L, A, Marabelle A, Delord JP, et al. Pembrolizumab therapy for microsatellite instability high (MSI-H) colorectal cancer (CRC) and non –CRC. [abstract]</p> <p>Diaz L, Marabelle A, Kim TW, et al. Efficacy of pembrolizumab in phase 2 KEYNOTE -164 and KEYNOTE- 158 studies of microsatellite instability high cancers.</p>	<p>April 2018</p> <p>Journal of Clinical Oncology 2018; 36:15_suppl, 3514</p> <p>Journal of Clinical Oncology 2016; 34:4_suppl, TPS787-</p> <p>Journal of Clinical Oncology 2017; (Suppl 15): Abstract no. 3071.</p> <p>Annals of Oncology 2017; 28 (Suppl 5): 128-9:386P</p>
<b>Comparator: chemotherapy (FOLFIRI)</b>		
DaVINCI	Clarke SJ, Yip S, Brown C, van Hazel GA, et al on behalf of the Australasian Gastro - Intestinal Trials Group. Single-agent irinotecan or 5-fluorouracil and leucovorin (FOLFIRI) as second-line chemotherapy for advanced colorectal cancer; results of a randomised phase II study (DaVINCI) and meta-analysis.	European Journal of Cancer 2011;47(12):1826–36.
GERCOR	Tournigand C, Andre T, Achille E, et al. FOLFIRI Followed by FOLFOX6 or the Reverse Sequence in Advanced Colorectal Cancer: A Randomized GERCOR Study.	Journal of Clinical Oncology 2004; 22(2), 229-237.
FLIGHT 2	Hirata K, Nagata N, Kato T, et al. Prospective phase II trial of second-line FOLFIRI in patients with advanced colorectal cancer including analysis of UGT1A1 polymorphisms: FLIGHT 2 study.	Anticancer research 2014; 34 (1),195-201.
VELOUR	Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen.	Journal of Clinical Oncology 2012; 1;30(28):3499-506.
Sanoff 2018	Sanoff K, Goldberg M, Ivanova A, et al. Multicenter, randomized, double-blind phase 2 trial of FOLFIRI with regorafenib or placebo as second-line therapy for metastatic colorectal cancer.	Cancer 2018; 124(15), 3118-3126.
<b>Comparator: cetuximab + chemotherapy</b>		
CAPRI-GOIM	Ciardello F, Normanno N, Martinelli E, et al. Cetuximab continuation after first progression in metastatic colorectal cancer (CAPRI-GOIM): a randomized phase II trial of FOLFOX plus cetuximab versus FOLFOX.	Annals of Oncology 2016; 27, (6),1055–61.
<b>Comparator: bevacizumab + chemotherapy</b>		
Tournigand	Bendell C, Johanna C, Christophe T, et al. Axitinib or Bevacizumab Plus FOLFIRI or Modified FOLFOX-6 After Failure of First-Line Therapy for Metastatic Colorectal Cancer: A Randomized Phase II Study.	Clinical Colorectal Cancer 2013 12 (4):239-47.

Study ID	Protocol title/ Publication title	Publication citation
Eagle	Iwamoto S, Takahashi T, Tamagawa H, et al. FOLFIRI plus bevacizumab as second-line therapy in patients with metastatic colorectal cancer after first-line bevacizumab plus oxaliplatin-based therapy: the randomized phase III EAGLE study.	Annals of Oncology 2015; 26:1427–33.
AXEPT	Xu RH, Muro K, Morita S, et al. Modified XELIRI (capecitabine plus irinotecan) versus FOLFIRI (leucovorin, fluorouracil, and irinotecan), both either with or without bevacizumab, as second-line therapy for metastatic colorectal cancer (AXEPT).	Lancet Oncology 2018; 19(5):660-71.
WJOG 6210G (6210G)	Shitara K, Yonesaka T, Denda K, et al. Randomized study of FOLFIRI plus either panitumumab or bevacizumab for wild-type KRAS colorectal cancer-WJOG 6210G.	Cancer Science 2016 107 (12):1843-50.
Horizon 1	Cunningham D, Wong P, D'Haens G, et al. Cediranib with mFOLFOX6 vs bevacizumab with mFOLFOX6 in previously treated metastatic colorectal cancer.	British Journal of Cancer 2013; 108: 493–502.
M10-300	O'Neil H, C Cainap, E Van Cutsem, et al. Randomized phase II open-label study of mFOLFOX6 in combination with linifanib or bevacizumab for metastatic colorectal cancer.	Clinical Colorectal Cancer 2014; 13 (3):156-163.e2.
E3200	Giantonio J, Paul J, Catalano J, et al. Bevacizumab in Combination With Oxaliplatin, Fluorouracil, and Leucovorin (FOLFOX4) for Previously Treated Metastatic Colorectal Cancer: Results From the Eastern Cooperative Oncology Group Study E3200.	Journal of Clinical Oncology 2007; 25 (12):1539-44.
ML18147	Bennouna J, Sastre D, Arnold P, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial.	Lancet Oncology 2013; 14 (1):29-37.
Cao 2015	Cao R, Zhang S, Ma D, Hu L. A multicenter randomized phase II clinical study of bevacizumab plus irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) compared with FOLFIRI alone as second-line treatment for Chinese patients with metastatic colorectal cancer.	Medical Oncology 2015; 32:325.
<b>Near market comparator: nivolumab ± ipilimumab</b>		
CH142	Overman MJ, McDermott R, Leach S, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study.	Lancet Oncology 2017; 18 (9):1182-91.

Source: Table 2.2-1, pp22-27 of the submission.

6.7 There is an ongoing randomised controlled trial (KN177) assessing the comparative efficacy and safety of pembrolizumab relative to SOC<sup>e</sup> in treatment-naïve Stage IV MSI-H or dMMR CRC patients. The primary endpoints are progression-free survival (PFS) and overall survival (OS). For the current evaluation, it was acknowledged that the KN177 trial is being conducted in a different treatment setting (first-line) to that proposed in the submission (second-line and beyond). However, in the absence of RCT evidence in the later-line treatment setting, any forthcoming results from KN177 would be important to establishing the comparative effect of pembrolizumab compared to chemotherapy in Stage IV MSI-H/dMMR mCRC. The estimated study completion date is September 2019 (ClinicalTrials.gov Identifier: NCT02563002). The

<sup>e</sup> mFOLFOX6 (modified FOLFOX6), or mFOLFOX6 + bevacizumab, or mFOLFOX6 + cetuximab or FOLFIRI, or FOLFIRI + bevacizumab, or FOLFIRI + cetuximab

Pre-Sub-Committee Response (PSCR) stated that the preliminary data from KN177 was not yet available.

6.8 The key features of the included studies are summarised in the table below.

**Table 3: Key features of the included clinical evidence – naïve indirect comparisons**

Studies	N	Design/duration	Risk of bias <sup>2</sup>	Patient population	Outcomes	Use in modelled evaluation
<b>Pembrolizumab</b>						
KN164	N = 61	<b>Single-arm study;</b> 200 mg Q3W; Median follow-up: 13.2 months	HIGH	dMMR or MSI-H Stage IV CRC; 90% had failed 2 prior treatment lines	Primary: objective response; Secondary: duration of response, PFS, OS <sup>1</sup> , safety	USED  PFS OS HR OS:PFS HR ToT:PFS
<b>Main comparators</b>						
<b>5 x chemotherapy studies</b>	Range: N = 44 to N = 614	4 of 5 studies were single arms extracted from randomised trials used for naïve comparisons; Median follow-up ranged from 22.3 months to 48.0 months.	HIGH	Locally advanced or mCRC. All patients regardless of dMMR/MSI-H status. 3 of 5 studies had 100% of patients had failed only 1 prior line. Unclear for 2 of 5 studies.	Primary outcome varied: ORR, OS, PFS, safety	NOT USED
<b>1 x cetuximab + chemotherapy study</b>	N = 74	Single-arm study extracted from a randomised trial used for naïve comparisons; Median follow-up 35.3 months	HIGH	Locally advanced or mCRC. All patients regardless of dMMR/MSI-H status. 100% of patients had failed only 1 prior line.	ORR, OS, PFS, safety	NOT USED
<b>9 x bevacizumab + chemotherapy studies</b>	Range: N = 35 to N = 407	Single-arm studies extracted from randomised trials used for naïve comparisons; Bevacizumab doses ranged from 5 mg/kg to 10 mg/kg across studies; Median follow-up ranged from 9.6 months to 28 months.	HIGH	Locally advanced or mCRC 7 of 9 enrolled mCRC. All patients regardless of dMMR/MSI-H status. 7 of 9 studies had 100% of patients had failed only 1 prior line. Not reported for remaining studies.	Primary outcome varied: OS, PFS, ORR, safety	NOT USED
<b>1 x near term comparator study (nivolumab ± ipilimumab)</b>	N = 74	Single-arm study used for naïve comparisons; Median follow-up Nivolumab: 12 months; Nivolumab + ipilimumab 13.4 months.	HIGH	dMMR or MSI-H Stage IV CRC. 15% in nivolumab arm failed only 1 prior line. 33% in nivolumab + ipilimumab had failed only 1 prior therapy.	Primary: ORR; Secondary: duration of response, OS, PFS, safety	NOT USED

<sup>1</sup> OS immature.

<sup>2</sup> Risk of bias for naïve comparisons is high regardless of risk of bias in individual studies.

ORR = overall/objective response rate; OS = overall survival; PFS = progression-free survival; ToT = time on treatment.

Source: Sections 2.2 to 2.6 of the submission. Risk of bias assessed during the evaluation.

- 6.9 The key study, KN164, provided limited data on the effectiveness and safety of pembrolizumab as a second-line therapy, as only 10% of patients had received one prior line of therapy for recurrent or metastatic disease at baseline. The ESC noted that the majority of patients in KN164 (90.2%) had failed at least two prior lines of therapy, with approximately 44% and 23% of patients progressing after three and four prior lines, respectively.
- 6.10 The effect of dMMR status on the efficacy of pembrolizumab could not be quantified as the submission did not provide any comparative data on its effectiveness in patients with and without dMMR mCRC. In addition, the populations of the comparator studies included all patients, irrespective of their dMMR status. The PSCR stated that a preliminary study (Keynote 016) reported that patients with MSI-H colorectal tumours had a 40% response rate with pembrolizumab monotherapy, whereas no patients with microsatellite stable disease achieved a response. The PSCR contended that, as there was more than 90% concordance in testing for MSI-H and dMMR tumours, it was likely and biologically plausible that the treatment effect of pembrolizumab should be very similar in both dMMR and MSI-H colorectal tumours. The ESC noted that current literature (Jin et al, 2018) suggests that colorectal tumours that have dMMR status are biologically similar to those with MSI-H status.
- 6.11 The ESC noted that there was extensive heterogeneity among the comparator studies in terms of baseline demographic and disease characteristics, treatment dosing regimens, durations of follow-up and treatment outcomes.

### **Comparative effectiveness**

- 6.12 Detailed results from study KN164 are presented in Table 4 and Figure 1 below.

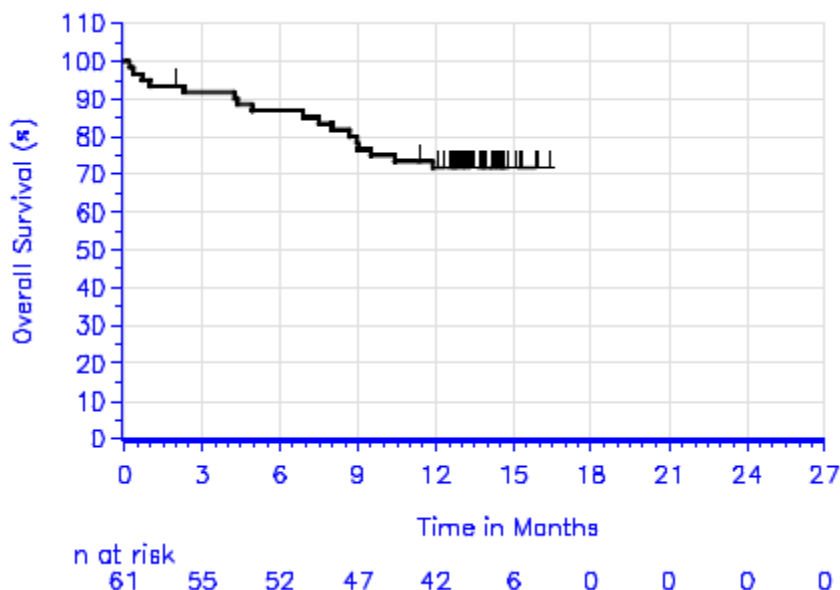
**Table 4: Results from KN164 (median duration of follow up = 13.2 months)**

<b>Outcome</b>	<b>Result</b>
Partial response (PR); n/N, %, (95% CI)	17/61; 27.9% (17.1, 40.8)
Complete response (CR); n/N, %, (95% CI)	0
Objective response (PR + CR); n/N, %, (95% CI)	17/61; 27.9% (17.1, 40.8)
Progressive disease (PD); n/N, %, (95% CI)	28/61; 45.9% (33.1, 59.2)
Mean time to response (i.e. to PR); months (SD)	4.4 months (2.8)
Median PFS; months (95% CI)	2.3 months (2.1, 8.1)
Median ToT; days (range)	273 (1, 477)
Median OS; months (95% CI)	Not reached
Deaths; n/N (%)	17/61 (27.9%)

CI = confidence interval; OS = overall survival; PFS = progression-free survival; SD = standard deviation; ToT = time on treatment.

Source: Table 2.5-1, p50 and Table 2.5-6, p54 of the submission; Table 14.2-13, p141 and Table 14.2-16, p144 of the CSR.

Figure 1: Kaplan-Meier plot of overall survival in KN164



Source: Figure 2.5-1, p56 of the submission.

- 6.13 The primary outcome of study KN164 was ORR, which was the summation of complete response and partial response. At a median duration of follow up of 13.2 months, no patients had achieved a complete response and 27.9% had achieved a partial response. Approximately 46% of patients had progressed.
- 6.14 OS data were immature as the median OS had not been reached. OS rates at six and 12 months were 86.8% and 71.7%, respectively, by Kaplan-Meier estimation.
- 6.15 As there were no direct comparative data, the submission presented naïve indirect comparisons between pembrolizumab and the three nominated comparators. The submission argued that the comparisons were biased against pembrolizumab as:
- the KN164 population comprised 90.2% of participants who had progressed from second-line chemotherapy whereas the majority of the comparator studies enrolled patients who had progressed on only one previous line of therapy; and
  - pembrolizumab was investigated in a MSI-H/dMMR population, whereas the majority of the comparator studies were in an all-comers population. Acknowledging the conflicting evidence around the impact of MSI-H or dMMR status on patient survival, the submission noted that a survival analysis of Australian patients found that microsatellite instability was associated with poorer survival compared to micro-satellite stable tumours.
- 6.16 Table 5 summarises the naïve indirect comparison between pembrolizumab and chemotherapy.

**Table 5: Naïve indirect comparison of effectiveness: pembrolizumab vs. chemotherapy**

	ORR, % (95% CI)	Median PFS, months (95% CI)	Median OS, months (95% CI)
<b>Pembrolizumab</b>			
KN164	27.9% (17.1, 40.8)	2.3 (2.1, 8.1)	NR
<b>Chemotherapy</b>			
GERCOR	4% (0, 9)	2.5 (2.1, 3.3)	21.5 (16.9, 25.2)
VELOUR	11.1%	4.7	12.1 (11.1, 13.1)
Sanoff 2018	21% (11, 33)	5.3 (4.1, 6.0)	11.3 (8.9, 15.8)
FLIGHT 2	12% (4.5, 24.3)	5.8 (4.2, 7.3)	17.8 (12.6, 22.5)
DaVINCI	11.4% (3.7, 24.6)	6.2 (8.1, 19.3)	15.4 (8.1, 19.3)

CI = confidence interval; NR = not reached; ORR = objective/overall response rate; OS = overall survival; PFS = progression-free survival.  
Source: Table 2.6-3, p80 of the submission

6.17 The ORR of 28% in KN164 was somewhat higher than that observed in the chemotherapy studies which ranged from 4% in GERCOR to 21% in Sanoff 2018. Compared to a median PFS of 2.3 months in KN164, the median PFS varied in the chemotherapy studies, ranging from 2.5 months in GERCOR to 6.2 months in DaVINCI, although the 95% confidence intervals overlapped. Median OS was not reached in KN164, but ranged from 12.1 months in VELOUR to 21.5 months in GERCOR.

6.18 Table 6 summarises the naïve indirect comparison between pembrolizumab and cetuximab + chemotherapy.

**Table 6: Naïve indirect comparison of effectiveness: pembrolizumab vs. cetuximab + chemotherapy**

	ORR, % (95% CI)	Median PFS, months (95% CI)	Median OS, months (95% CI)
<b>Pembrolizumab</b>			
KN164	27.9% (17.1, 40.8)	2.3 (2.1, 8.1)	NR
<b>Cetuximab + chemotherapy</b>			
CAPRI-GOIM	21.6% (11.0, 32.2)	6.4 (5.5, 8.2)	17.6 (14.1, 21.1)

CI = confidence interval; NR = not reached; ORR = objective/overall response rate; OS = overall survival; PFS = progression-free survival.  
Source: Table 2.6-2, p77 of the submission.

6.19 ORR was higher in KN164 (27.9%) compared to the CAPRI-GOIM study (21.6%). The sponsor noted that all patients in the CAPRI-GOIM trial had progressed on one previous line of therapy compared to 10% of patients in KN164. Median OS was not reached for pembrolizumab in KN164 whereas the median OS for cetuximab + chemotherapy was 17.6 months. The point estimate of the median PFS was lower in the KN164 study (2.3 months; 95% CI: 2.1, 8.1) compared that in the CAPRI-GOIM study 6.4 months (95% CI: 5.5, 8.2), although the 95% confidence intervals overlapped.

6.20 Table 7 summarises the naïve indirect comparison between pembrolizumab and bevacizumab + chemotherapy.

**Table 7: Naïve indirect comparison of effectiveness: pembrolizumab vs. bevacizumab plus chemotherapy**

	<b>ORR, % (95% CI)</b>	<b>Median PFS, months (95% CI)</b>	<b>Median OS, months (95% CI)</b>
<b>Pembrolizumab</b>			
KN164	27.9% (17.1, 40.8)	2.3 (2.1, 8.1)	NR
<b>Bevacizumab plus chemotherapy</b>			
Tournigand_A/B <sup>1</sup>	23.5%/ 20%	6.9/ 6.4	15.7/ 14.1
EAGLEA/B <sup>2</sup>	11%/ 11%	6.1 (5.3, 7.0)/ 6.4 (5.6, 7.4)	16.3 (14.1, 21.2)/ 17.0 (14.6, 19.1)
AXEPT	19%	7.2 (6.6, 8.5)	15.4 (13.0, 17.7)
6210G	5.7% (1.2, 15.7)	5.9	13.4
Cao 2015	47.7%	8.5 (5.8, 10.5)	15.2 (11.8, 19.4)
Horizon 1	27.3%	7.8	19.6
M10300	34.7% (21.7, 49.6)	9 (6.7, NR)	16.5 (13, NR)
E3200	22.7%	7.3 (5.8, NR)	12.9
ML18147	5.0%	5.7 (5.2, 6.2)	11.2 (10.4, 12.2)

<sup>1</sup> Tournigand had two treatment arms: Bevacizumab with neither FOLFIRI or with FOLFOX. As the results are similar between treatment arms and used in the context of a naïve comparison, both results have been summarised together.

<sup>2</sup> EAGLE had two treatment arms: FOLFIRI with either 5 mg/kg or 10 mg/kg bevacizumab. As the results are similar between arms and used in the context of a naïve comparison, both results are summarised together.

CI = confidence interval; NR = not reached; ORR = objective/overall response rate; OS = overall survival; PFS = progression-free survival. Source: Table 2.6.1, p72 of the submission.

- 6.21 Compared to an ORR of 28% in KN164, the ORR in the comparator studies ranged from 5% in ML18147 to 47.7% in Cao 2015. The median PFS of 2.3 months in KN164, was less than the median PFS in the comparator studies which ranged from 5.7 months in ML18147 to 9 months in M10300. The median OS was not reached in KN164 and ranged from 11.2 months in ML18147 to 19.6 months in Horizon 1.
- 6.22 The ESC considered that the results of the three naïve indirect comparisons were highly uncertain. There were no common comparators which did not permit quantitative assessment, and, as noted above, there was extensive heterogeneity among the main comparator studies in terms of baseline demographic and disease characteristics (e.g. the comparator studies were conducted in patients irrespective of dMMR status), treatment dosing regimens, durations of follow-up, and treatment outcomes. This resulted in substantial heterogeneity between the efficacy results and prevented any meaningful conclusions regarding the magnitude of comparative effectiveness of pembrolizumab.
- 6.23 In addition, there were no comparative data for the proposed dMMR mCRC population (KN164 did not provide a sub-group analysis and the comparator studies were conducted on all patients regardless of their dMMR status).
- 6.24 Table 8 summarises the naïve indirect comparison between pembrolizumab and the near-market comparators, nivolumab and nivolumab plus ipilimumab.

**Table 8: Naïve indirect comparison of effectiveness: pembrolizumab vs. nivolumab or nivolumab + ipilimumab**

		ORR, % (95% CI)	Median PFS, months (95% CI)	Median OS, months (95% CI)
<b>Pembrolizumab</b>				
KN164		27.9% (17.1, 40.8)	2.3 (2.1, 8.1)	NR
<b>Near-market comparators</b>				
CH142	Nivolumab	32% (22, 44)	14.3 (4.3, NR)	NR
	Nivolumab + ipilimumab	55% (45.2, 63.8)	NR	NR

CI = confidence interval; NR = not reached; ORR = objective/overall response rate; OS = overall survival; PFS = progression-free survival.  
Source: Table 2.6-4, p83 of the submission.

- 6.25 The submission noted that nivolumab ± ipilimumab therapies are not currently reimbursed in the Australian market for the proposed indication. In addition, comparisons are likely to be confounded by differences between the study populations: the KN164 study enrolled a larger proportion of patients who had progressed on second-line therapy than the CH142 study.
- 6.26 The proportion of patients who had progressed after two prior lines of therapy at baseline was 46% in KN164 compared to 30% and 36% in the nivolumab and nivolumab + ipilimumab arms of CH142, respectively. However, the proportion of patients who had progressed after three lines of therapy appeared to be higher in the nivolumab arm (54%) than the single pembrolizumab arm in KN164 (44%); the proportion of nivolumab + ipilimumab patients who had progressed after three lines of therapy was 40%. The proportion of patients who had progressed after only one prior line of therapy was higher in CH142 (15% for the nivolumab arm and 33% for the nivolumab + ipilimumab arm) compared to KN164 (10%). Mutation status (KRAS and BRAF) varied across the trials and between the arms of CH142. The differing underlying tumour biology may have affected prognoses, which might confound treatment effects in either direction.
- 6.27 The ORR for pembrolizumab (28%) was lower than that observed in CH142 for both the nivolumab and nivolumab + ipilimumab arms (32% and 55%, respectively). The median PFS in CH142 was substantially longer for patients in the nivolumab arm (14.3 months), and not reached for patients in the nivolumab + ipilimumab arm, compared to pembrolizumab (2.3 months) in KN164. Median OS was not reached in either study. The differences in results may have been due to the heterogeneous factors discussed above or other unknown confounders.

### **Comparative harms**

- 6.28 Pembrolizumab vs. bevacizumab + chemotherapy: The incidence of Grade ≥ 3 adverse events (AEs) in KN164 (59%) appeared lower compared to that observed in the bevacizumab + chemotherapy studies which ranged from 61.3% (Cao 2015) to 84.8% (Horizon 1). There was a lower rate of serious AEs in KN164 (47.5%) compared to the M10300 (31.1%) and Horizon 1 (43.9%) studies. However, the rate of serious AEs in Tournigand (14.3%) was much lower than that in KN164. Clinical heterogeneity and limited drug-related AE data reported for the bevacizumab + chemotherapy studies made the naïve comparison difficult to interpret.

- 6.29 Pembrolizumab vs. cetuximab + chemotherapy: For this comparison, the submission noted that AE reporting varied across the studies, and that for the cetuximab + chemotherapy study, diarrhoea was one of the most frequently reported Grade  $\geq 3$  non-haematological AE. Although all grade diarrhoea was frequently reported in KN164 (34.4%), there were no reports of a Grade  $> 3$  diarrhoea AE.
- 6.30 Pembrolizumab vs. chemotherapy: The submission presented a similar discussion to that for pembrolizumab vs. cetuximab + chemotherapy.
- 6.31 Pembrolizumab vs. near term comparators (nivolumab  $\pm$  ipilimumab): Compared to nivolumab monotherapy, pembrolizumab was associated with fewer drug-related AEs (57.4% vs 70%) and, drug related Grade  $\geq 3$  AEs (14.8% vs 20%). The most frequently reported Grade  $> 3$  AEs for nivolumab monotherapy were increased lipase (8%) and amylase (2%) levels. The corresponding rates in KN164 were 4.9% and 1.6%, respectively. There were fewer drug-related discontinuations on pembrolizumab compared to nivolumab (1.6% vs 7%). Although more patients died on nivolumab (5% vs 1.6%), there were no drug-related deaths on either treatment. Compared to nivolumab +ipilimumab, pembrolizumab was associated with fewer drug-related AEs, drug-related Grade  $\geq 3$  AEs, drug-related serious AEs and drug-related discontinuations.

### **Benefits/harms**

- 6.32 The naïve indirect comparison presented in the submission did not allow for a quantitative comparison of the benefits and harms of pembrolizumab compared with the nominated comparators. Accordingly, a benefits/harms table has not been presented.

### **Clinical claim**

- 6.33 The submission described pembrolizumab as superior in terms of effectiveness compared with SOC and “better” in terms of safety compared to SOC for the treatment of dMMR mCRC in patients who have failed a previous line of therapy.
- 6.34 The clinical evidence presented did not support the therapeutic conclusion as:
- No direct comparative data were presented. The key clinical evidence for pembrolizumab was from a small single-arm study (KN164) of 61 patients.
  - The primary analysis of effectiveness was objective response rate (ORR). This was a summation of patients who had achieved a complete response and a partial response. At a median follow up of 13.2 months, no patients in KN164 had achieved a complete response and 27.9% had achieved a partial response. 45.9% of patients had progressed.
  - The study population did not match the proposed PBS population, which was for patients who have failed at least one prior therapy. KN164 provided limited evidence for pembrolizumab as a second-line therapy, with approximately 10% of the study population having received only one prior line of therapy at baseline;

90% had failed two or more previous lines of therapy. The results of the naïve indirect comparisons between the pembrolizumab and the comparator studies were highly uncertain. The lack of a common comparator meant that there could be no quantitative assessment of the comparative benefits and harms of pembrolizumab. In addition, there was extensive heterogeneity among the comparator studies in terms of baseline demographic and disease characteristics, treatment dosing regimens administered, durations of follow-up, and treatment outcomes. There were no data provided from KN164 specifically for dMMR patients as MSI-H status (as determined by PCR) was an optional inclusion criterion for enrolment into KN164; however, testing for MSI-H is not routine clinical practice in Australia. It was unclear whether the results observed in KN164 would be replicated in practice where patient selection would be based principally on dMMR status.

- 6.35 The PBAC considered that the claim of superior comparative effectiveness was not supported by the indirect comparisons.
- 6.36 The PBAC considered that the claim of superior comparative safety was not supported by the indirect comparisons.

### ***Economic analysis***

- 6.37 The submission presented an economic evaluation based on a comparison of a non-randomised study (KN164 for the pembrolizumab arm) and a subset of registry data (for the comparator arm). The type of economic evaluation presented was a cost-utility analysis.
- 6.38 The submission nominated a mixed comparator of FOLFIRI ± bevacizumab or cetuximab. The submission assumed that 65% of patients would receive FOLFIRI monotherapy, 25% FOLFIRI + cetuximab and 10% FOLFIRI + bevacizumab. For ease of reference, this was referred to as the standard of care (SOC) arm.
- 6.39 A summary of the model structure and rationale is presented in Table 9.

**Table 9: Summary of model structure and rationale**

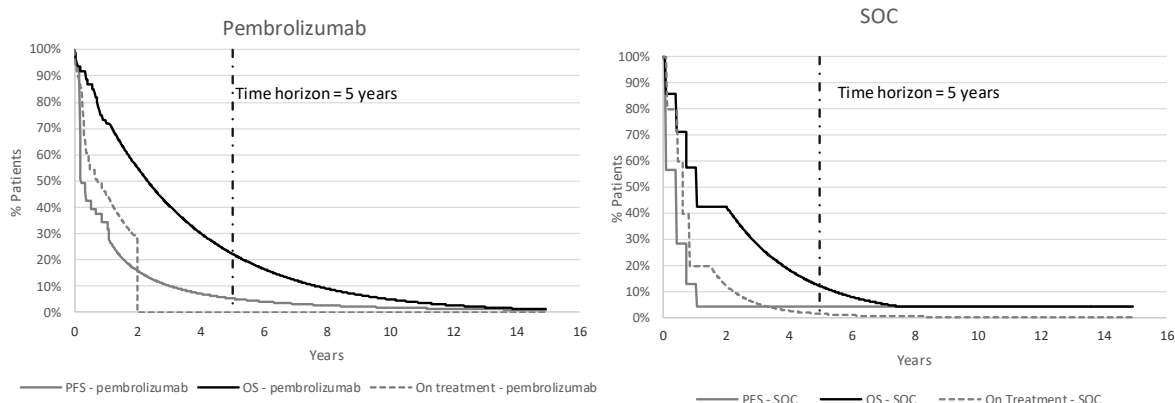
Component	Description
Type of analysis	Cost-utility analysis
Outcomes	Cost per quality adjusted life year (QALY) gained Cost per life year (LY) gained
Time horizon	Five years in the base case, with a range of 0-15 years for sensitivity analysis. Median follow-up of 57 weeks in KN164.
Method used to generate results	Partitioned survival analysis
Health states	Pre-progression Post-progression Dead
Cycle length	One week (7 days)
Transition probabilities	Partitioned survival analysis. Based on analyses of progression-free and overall survival and time on treatment, with KN164 providing evidence for pembrolizumab, and results from the Australian Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) registry informing the 'standard of care' comparator.
Software	Microsoft Excel 2016 (Excel 2010 compatible)

Source: Table 3.1-1, p93 of the submission.

- 6.40 The modelled treatment effect did not reflect the clinical evidence presented in the clinical evaluation. While the pembrolizumab arm was informed by KN164, the submission used data from a small subset of patients from the Australian Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) registry (n=7 from a pool of 2,312 patients) to inform OS and time on treatment (ToT) estimates in the SOC arm. The PSCR stated that the small number of patients in the registry who aligned with the proposed PBS population reflected the rarity of this subgroup of patients. The ESC considered that, given the very small sample size, any resultant estimates were highly unreliable and therefore, the subsequent economic evaluation was also unreliable. The ESC also noted that the estimated patient population in the financial estimates was much larger, at approximately 150 patients per year.
- 6.41 Patients included in the TRACC subgroup analyses were limited to Stage IV patients with dMMR, who had received at least two lines of therapy, and had not received immunotherapies. The ESC noted the seven TRACC patients were more highly treated than the proposed PBS population, who would have received at least one line of prior therapy.
- 6.42 The submission did not adequately address issues regarding the transitivity of the seven patients from the TRACC database with those in KN164, nor possible sources of bias in the resulting naïve indirect comparison:
- The submission did not provide baseline characteristics or treatment details for the seven TRACC patients. It was therefore unclear whether there were transitivity issues associated with differences in baseline characteristics or differences in prior or subsequent treatments. The PSCR stated that specific characteristics of the seven patients included in the analysis were not made available from the registry; and

- The measurements of OS and ToT were not comparable. For KN164 these outcomes were measured from time of enrolment; whereas in the TRACC database, OS was measured from diagnosis of mCRC and ToT was the time on first-line therapy. The PSCR stated that the OS data was adjusted by 21 weeks to account for the misalignment in the measurement of OS.
- 6.43 The following applicability issues were not addressed in the submission:
- Although the requested listing was for patients who have been previously treated (i.e. second-line and beyond), the vast majority of patients in KN164 were receiving third-line (45.9%) or a later-line (4L+; 44.3%) therapy and all TRACC patients had received two or more prior therapies; and
  - The submission provided some general comments about the patient population included in the TRACC database, of which the seven patients were a subset. However, the applicability of the seven TRACC patients to the proposed PBS population was uncertain.
- 6.44 As PFS was not recorded in the TRACC database, the submission used two methods to estimate PFS in the SOC arm. In the base case, PFS was determined by applying the ratio of hazards (OS:PFS) from KN164 to the OS from TRACC. An alternative approach in the submission was to apply the ratio of hazards of ToT:PFS from KN164 to the TRACC ToT data. The validity of these approaches was uncertain as:
- Log-cumulative hazard plots revealed that the proportional hazards assumption appeared to have been violated for both the OS:PFS and the ToT:PFS ratio of hazards;
  - OS for the seven TRACC patients was determined from the time of diagnosis of mCRC, adjusted by 21 weeks, rather than at the commencement of second- and later-line therapies; and
  - ToT for the seven TRACC patients was measured only in the first-line treatment setting (not in the more relevant later-line setting as per the proposed PBS population).
- 6.45 In addition, for the first two years of both methods of estimating PFS in the economic model, the ToT curves were above the PFS curves for both the pembrolizumab and SOC arms. This is demonstrated for the base case economic model in Figure 2 below.

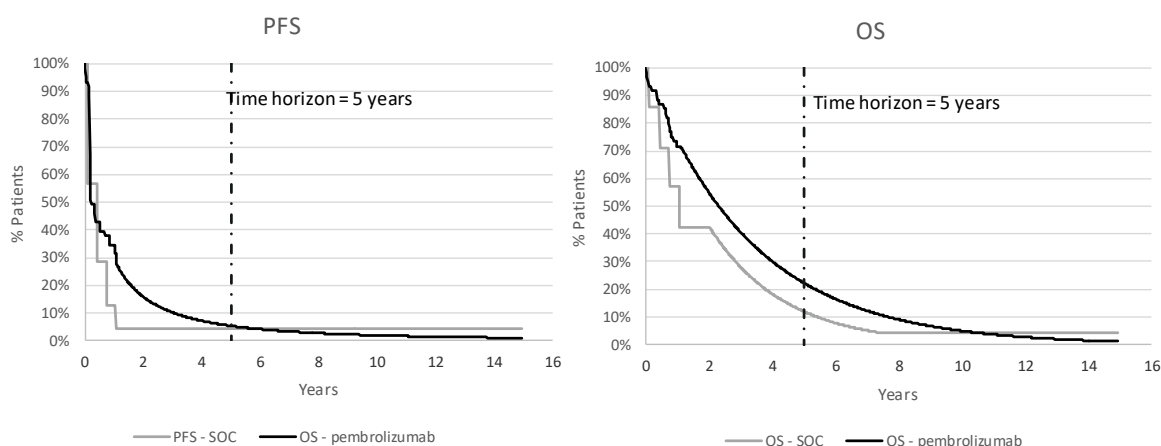
Figure 2: Modelled PFS, OS and ToT curves (base case)



OS = overall survival; PFS = progression-free survival; SOC = standard of care; ToT = time on treatment.  
 Source: Compiled during the evaluation based on information presented in 'Att 6.xlsx'.

- 6.46 No justification was provided for modelling a longer ToT duration compared to PFS. The PSCR provided an analysis in which the ToT was equal to PFS in both arms; this resulted in an ICER of \$45,000/QALY to \$75,000/QALY.
- 6.47 OS estimates in the pembrolizumab arm were based on immature data, as median OS in KN164 had not been reached. Trial-based data were used to inform the OS curve to a median follow-up of 57 weeks, after which an extrapolation using the exponential model was applied.
- 6.48 Figure 3 provides a comparison of the PFS and OS curves for pembrolizumab and SOC. The ESC, noting that the PFS curves cross at approximately six years and the OS curves at approximately 11 years, were concerned about the plausibility of these extrapolations.

Figure 3: PFS and OS curves for the pembrolizumab and SOC arms



OS = overall survival; PFS = progression-free survival; SOC = standard of care.  
 Source: Compiled during the evaluation based on information presented in 'Traces' worksheet of 'Att 6.xlsx'.

- 6.49 The model sourced utilities from the published literature. The evaluation considered that the pre-progression utility value used (0.765) was unlikely to be applicable to the patient population in KN164, the seven TRACC registry patients, or the proposed PBS

population as it was based on a population of patients at baseline, before receiving a second-line therapy, not whilst receiving treatment. Patients in KN164, of which 10% of patients were receiving second-line therapy and 90% receiving third- or later-line treatment, would likely have a lower pre-progression utility.

- 6.50 Treatment costs associated with SOC were based on the time on first-line treatment for the seven patients from the TRACC registry. The evaluation considered that this data source was inappropriate as it would likely overestimate the time on treatment in the SOC arm as it does not relate to patients receiving the nominated comparators (FOLFIRI ± bevacizumab or cetuximab) in a second- or later-line setting. An overestimation of treatment costs in the SOC arm would bias the results in favour of pembrolizumab.
- 6.51 The results of the economic model are provided in the table below. The PSCR provided an updated ICER, which corrected for errors in the pricing of pembrolizumab and SOC.

**Table 10: Results of the economic evaluation**

Component	SOC	Pembrolizumab	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	1.8139	2.4218	0.6079
QALY	1.1825	1.6132	0.4307
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Incremental cost/extra QALY gained – PSCR*			\$ [REDACTED]

LY = life year, LYG = life year gained; PSCR = pre-Sub-Committee response; QALY = quality-adjusted life year; SOC = standard of care.  
 \* PSCR amendments included correcting the methodology used to calculate the dispensed price for pembrolizumab and applying the methodology to the SOC arm.

Source: 'Control' worksheet of 'Att 6.xlsx' and p3 of the PSCR.

- 6.52 The ESC considered that the results of the economic evaluation were unreliable due to the very small size of the subgroup used to inform the SOC arm (seven patients), issues with the structure of the modelled treatment effect, extrapolation issues and transitivity issues.

**Drug cost/patient/course: \$ [REDACTED]**

- 6.53 The cost of treatment with pembrolizumab for the average patient is \$ [REDACTED], including patient co-payments, based on an ex-manufacturer price of \$ [REDACTED]/100 mg vial and 200 mg fixed dosing every three weeks for a maximum of 35 cycles (2 years). This cost excludes \$ [REDACTED] in drug administration costs.
- 6.54 The cost of treatment with SOC for the average patient is \$48,138, based on published ex-manufacturer prices and treatment in accordance with published protocols until disease progression. This does not include costs associated with administration<sup>f</sup>. As

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<sup>f</sup> Administration costs were incorrectly calculated by the submission and were not corrected during the evaluation. Correcting for the error in the calculation of administration costs was unlikely to be useful given the uncertainty relating to the duration of therapies, and estimation of the size of the eligible patient population. Costs associated with these MBS items were not provided in the main body of the submission.

noted above, time on treatment for the SOC was based on time on first-line treatment for a small number of patients in the TRACC database (n=7) and was not related to time on second- or later-line treatments.

### ***Estimated PBS usage & financial implications***

- 6.55 This submission was considered by DUSC.
- 6.56 The submission used an epidemiological approach to estimate the size of the eligible patient population. DUSC considered the estimates presented in the submission to be overestimated. The main issues were:
- Although DUSC considered that the estimate of treated patients was likely to be reasonable, the number of treatments per patient was unlikely to be 17 or 18.
  - The risk of bias in the assumptions derived from expert opinion presented in the submission was unclear. There was a lack of detail provided in the submission for the clinician surveys that were conducted, including information about the questions asked, the method used, and whether the experts had any conflicts of interest.
  - The prevalent pool should represent patients who were diagnosed with Stage I to III disease, who progress to Stage IV each year. DUSC considered it would have been more appropriate to use a 5-year prevalent pool and estimate the number of patients in this pool who progress to Stage IV disease.
  - The rate of dMMR was uncertain, but DUSC considered that the submission's estimate of 4% may be reasonable.
  - Uncertainty around the treatment uptake rate and estimate of the proportion of patients who had first-line treatment, however DUSC considered that these assumptions were reasonable.
- 6.57 The submission assumed that if listed, the uptake of pembrolizumab would increase from 50% in Year 1 to 80% in Year 6.
- 6.58 In addition, the magnitude of the cost offsets remained uncertain. The submission used the SOC ToT curve from the economic model to estimate the average duration of therapy for the nominated comparators (FOLFIRI ± cetuximab or bevacizumab). As noted previously, this was estimated as the time on first-line therapy from a sample of seven patients from the TRACC registry.
- 6.59 The estimated use and financial implications are summarised in the table below.

**Table 42: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use of pembrolizumab</b>						
Number of patients treated						
Number of prescriptions						
<b>Estimated financial implications of pembrolizumab</b>						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Co-payments	\$	\$	\$	\$	\$	\$
Cost to PBS/RPBS less co-payments	\$	\$	\$	\$	\$	\$
<b>Estimated financial implications for FOLFIRI ± cetuximab or bevacizumab</b>						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Co-payments	\$	\$	\$	\$	\$	\$
Cost to PBS/RPBS less co-payments	\$	\$	\$	\$	\$	\$
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$

Source: compiled during the evaluation based on information presented in 'Att 13.xlsx'.

The redacted table shows that at Year 6, the estimate number of patients was less than 10,000 and the net cost to the PBS would be less than \$10 million.

### Quality Use of Medicines

6.60 The submission detailed a number of activities relating to the quality use of medicines, including the development and provision of education materials and education programs. The submission also highlighted that the sponsor provides a 1800 medical information service to respond to questions from patients, carers and health care professionals about all of their medicines.

For more detail on PBAC's view, see Section 7 PBAC outcome.

## 7 PBAC Outcome

7.1 The PBAC decided not to recommend pembrolizumab as a second-line treatment for locally advanced (unresectable) or Stage IV (metastatic) colorectal cancer (mCRC) with deficient mismatch repair (dMMR). The PBAC considered that the limited evidence provided suggested that the benefit of pembrolizumab was modest in dMMR mCRC. The PBAC considered that insufficient evidence was provided in the submission to evaluate the comparative efficacy and safety of pembrolizumab in either the second-line setting or a last-line setting. In addition, the PBAC considered that the economic evaluation was unreliable and the cost-effectiveness estimates were therefore highly uncertain.

7.2 The PBAC noted the consumer comments received in support of a PBS listing.

7.3 The PBAC considered that the proposed place in therapy, as a second-line treatment option, was incorrect. The PBAC, noting the Clinical Evaluation Report for the TGA and that 90.2% of patients in the key study KN164, had failed at least two lines of prior treatment, advised that it would have been more appropriate to position pembrolizumab as a last-line treatment option. The PBAC also advised that an Eastern

Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 would need to be specified in the eligibility criteria for an initial therapy restriction, and that the restriction level should be Authority Required (Written), with the clinician providing evidence of dMMR status.

- 7.4 The PBAC noted that the submission nominated three comparators to represent standard of care (SOC) second-line treatments, chemotherapy (represented by FOLFIRI), chemotherapy plus cetuximab and chemotherapy plus bevacizumab. The PBAC advised that best supportive care or possibly trifluridine with tipiracil would be more appropriate comparators in a last-line setting. The PBAC noted that the submission appropriately nominated nivolumab with/without ipilimumab as a near market comparator.
- 7.5 The PBAC noted that, as there was no direct randomised controlled trial, the primary clinical evaluation in the submission was based on naïve indirect comparisons between the results of the key pembrolizumab study, KN164, and those of the SOC comparator studies.
- 7.6 The PBAC noted that the KN164 study was a small (N = 61), single-arm, Phase II study with a high risk of bias. The PBAC noted that objective response rate (ORR) was the primary outcome, the data were still immature as median overall survival (OS) had not been reached at a median follow-up of 13.2 months. The PBAC noted that the European Society for Medical Oncology Magnitude of Clinical Benefit Scale to a grade of 2 (out of a maximum of 5, where 4 and 5 represent the grades with substantial improvement), which was considered modest. The PBAC also noted that there was extensive heterogeneity among the 16 comparator studies in terms of baseline demographics and disease characteristics, treatment dosing regimens, durations of follow-up and treatment outcomes.
- 7.7 The PBAC considered that the efficacy and safety results of the indirect comparisons were difficult to interpret and highly uncertain as there were no common comparators, the study population from KN164 did not match the proposed PBS population in terms of number of prior therapies (the study population was much more highly treated) and the significant heterogeneity and transitivity issues between the studies.
- 7.8 The PBAC considered that the claim that pembrolizumab was superior to SOC in terms of efficacy was not supported by the indirect comparisons.
- 7.9 The PBAC considered that the claim that pembrolizumab was superior to SOC in terms of safety was not supported by the indirect comparisons.
- 7.10 The PBAC noted that the OS and time on treatment (ToT) curves for the SOC arm in the economic model were informed, not by the clinical studies of SOC contributing to the primary indirect comparisons presented in the submission, but by a subgroup of seven patients from the Australian Treatment of Advanced Colorectal Cancer (TRACC) registry. Although these patients were more relevant to a comparison for a potentially

more suitable PBS listing of pembrolizumab in terms of two key characteristics (they were confirmed to be dMMR and they also more closely represented a last-line population having received at least two prior lines of therapy), the PBAC concluded overall that this alternative source of evidence did not form a sufficient basis for an informative clinical comparison with pembrolizumab. The PBAC agreed with the concerns of the ESC and considered that given the very small sample size in particular, the resultant estimates and the subsequent economic evaluation were unreliable.

- 7.11 The PBAC considered that there were a number of additional issues with the cost-utility analysis presented, including, but not limited to:
- As no baseline characteristics were presented for the seven TRACC registry patients, the PBAC noted that it was not possible to identify or address transitivity or applicability issues or possible sources of bias in the resulting alternative indirect comparison;
  - PFS was not recorded by the TRACC registry. The PBAC considered that the methods used to estimate PFS in the SOC arm of both the base case and the alternative method yielded results which were highly uncertain. In particular, the implication of these methods was that time on treatment exceeded time to progression, which favoured pembrolizumab because of the greater prolongation of time on treatment for SOC resulted in greater cost offsets;
  - Time on treatment for the seven TRACC patients was measured only in the first-line treatment setting, not in the second-line setting as per the proposed PBS population, which potentially overestimated SOC treatment costs;
  - OS estimates in the pembrolizumab arm were based on immature data; and
  - The PFS and OS extrapolations raised issues of plausibility because the pembrolizumab arm crossed the SOC arm at approximately six and 11 years, respectively.
- 7.12 The PBAC noted that the base case incremental cost-effectiveness ratio (ICER) of \$45,000/QALY to \$75,000/QALY, in addition to being unreliable, was high and did not reflect the high uncertainty in and across the compared sources of data. The PBAC advised that any future economic analysis should model the cost-effectiveness of pembrolizumab as a last-line therapy, and that a three-year time horizon would be more appropriate given the considerable uncertainty associated with the extrapolations.
- 7.13 The PBAC noted that the DUSC considered that the utilisation estimates presented in the submission were likely to be overestimated. The PBAC considered that the financial implications based on the estimates presented in the submission were not informative as the proposed place in therapy was not correct.
- 7.14 The PBAC advised that any future submission should be a major submission and address the issues raised regarding the proposed place in therapy, the eligible

population proposed for listing, the appropriate comparator, the immature clinical data, the basis of the clinical comparisons, the economic modelling approach, and the financial estimates.

7.15 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## **9 Sponsor's Comment**

Colorectal cancer is one of the leading causes of death in Australian males and females and MSI-H/dMMR tumours are rare and there is a high unmet need. MSD will continue to work towards collecting data to ensure funded access to dMMR CRC patients in the near future, who currently have limited or no long term hope.