6.09 PEMBROLIZUMAB, Solution concentration for I.V. infusion, 100 mg in 4 mL, Keytruda®, Merck Sharp & Dohme (Australia) Pty Ltd

1 Purpose of submission

1.1 The submission requested Section 100 (Efficient Funding of Chemotherapy), Authority Required listing for pembrolizumab for the first line treatment of mismatch repair deficient (dMMR) metastatic (Stage IV) colorectal cancer (mCRC).

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus standard of care (SoC).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with Stage IV (metastatic) colorectal cancer, with mismatch repair deficient (dMMR) tumours who have not previously received systemic therapy for metastatic colorectal cancer
Intervention	Pembrolizumab 200 mg Q3W for up to 35 cycles
Comparator	Standard of care (SoC). Various regimens that are complex but the following were identified as representative of all comparators: FOLFOX (represents other chemotherapy regimens including FOLFIRI and XELOX); cetuximab + FOLFOX (representing EGFR antibodies + chemotherapy) bevacizumab + FOLFOX (representing bevacizumab + chemotherapy)
Outcomes	Objective response rate (ORR), Progression Free Survival and Overall Survival.
Clinical claim	In patients with Stage IV (metastatic) mismatch repair deficient (dMMR) colorectal cancer pembrolizumab is more effective than standard chemotherapy, cetuximab + chemotherapy or bevacizumab + chemotherapy at improving survival, progression free survival, safety and quality of life

Source: Table 1.1.1, p5 of the submission.
FOLFOX = folinic acid (leucovorin) "FOL", Fluorouracil (5-FU) "F", and Oxaliplatin (Eloxatin) "OX"; FOLFIRI = folinic acid, fluorouracil and irinotecan; EGFR = Epidermal growth factor receptor; Q3W = every 3 weeks; XELOX=capecitabine (XEL) and oxaliplatin (OX).

2 Background

Registration status

2.1 **TGA status at time of PBAC consideration**: registered.

2.2 Pembrolizumab was approved by the TGA on 4 December 2020 for the first-line treatment of patients with unresectable or metastatic colorectal cancer (CRC) that is MSI-H or dMMR as determined by a validated test.

2.3 Other dMMR indications:

- CRC – Adult and paediatric patients for the treatment of unresectable or metastatic, MSI-H or dMMR CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan (provisional approval pathway).
- Non-CRC indications - Adult and paediatric patients for the treatment of unresectable or metastatic, MSI-H/dMMR solid tumours that have progressed following prior treatment and when there are no satisfactory alternative treatment options (provisional approval pathway).

2.4 Non-dMMR indications: Pembrolizumab is also approved for various lines of treatment and subsets of patients with melanoma, non-small cell lung cancer, head and neck squamous cell carcinoma, Hodgkin lymphoma, primary mediastinal B cell lymphoma, urothelial carcinoma, endometrial carcinoma and renal cell carcinoma.

2.5 The recommended dose of pembrolizumab monotherapy to treat adults with dMMR CRC is a 200 mg injection every 3 weeks (Q3W) for up to 24 months in the absence of disease progression. This was the pembrolizumab dosing regimen used in the key KN177 trial.

Previous PBAC consideration

2.6 This is the first consideration of pembrolizumab for the first line treatment of mCRC.

2.7 At the March 2019 PBAC Meeting, the PBAC considered a submission to list pembrolizumab for dMMR locally advanced (unresectable) or mCRC in patients who had failed at least one prior therapy (Pembrolizumab Public Summary Document (PSD), March 2019 PBAC meeting). The evidence was based on a naïve indirect comparison between Study KN164 (a single-arm pembrolizumab study in heavily pre-treated MSI-H/dMMR mCRC patients) and 16 SoC comparator studies on 'all comers' (i.e. irrespective of MMR status). The PBAC decided not to recommend pembrolizumab as a second-line treatment for the proposed indication as the limited evidence provided suggested that the benefit of pembrolizumab was modest in dMMR mCRC. The PBAC also 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 (Paragraph 7.1, Pembrolizumab PSD, March 2019 PBAC meeting).

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, restriction, manner of administration, form	Maximum amount (units)	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
PEMBROLIZUMAB Injection, 100 mg, 1 vial	200 mg	6 Initial 6 Continuing	Published: $8,135.78 (public) $8,289.11 (private) Effective: $[redacted] (public) $[redacted] (private)	Keytruda®, Merck Sharp & Dohme (Australia) Pty Ltd

Category / Program	Section 100 – Efficient Funding of Chemotherapy - Public/Private hospitals
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	~~Stage IV (metastatic)~~ colorectal cancer
Severity:	*Metastatic*
PBS Indication:	~~Stage IV~~ metastatic ~~dMMR~~ colorectal cancer
Treatment phase:	Initial treatment
Restriction:	☒Authority Required – Streamed line [New existing code]
Clinical criteria:	Patient must not have previously been treated for this condition in the metastatic setting, AND Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for colorectal cancer AND Patient must have a WHO performance status of 0 or 1, AND Patient must have deficient mismatch repair (dMMR) colorectal cancer, as determined by immunohistochemistry test
Treatment criteria:	The treatment must not exceed a total of 7 doses under this restriction.
Administrative Advice:	In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later
Category / Program	Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	~~Stage IV (metastatic)~~ colorectal cancer
Severity:	*metastatic*
PBS Indication:	~~Stage IV~~ metastatic ~~dMMR~~ colorectal cancer
Treatment phase:	Continuing treatment
Restriction:	Authority Required – Streamed line [New existing code]
Clinical criteria:	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.
Treatment criteria:	The treatment must not exceed a total of 35 cycles or up to 24 months of treatment under this restriction
Category / Program	Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	~~Stage IV (metastatic)~~ colorectal cancer
Severity:	*metastatic*
PBS Indication:	~~Stage IV~~metastatic ~~dMMR~~ colorectal cancer
Treatment phase:	Initial treatment – Grandfather patients
Restriction:	☒Authority Required - Streamlined

Clinical criteria:	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date] **AND** Patient must not have received prior PBS funded treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for colorectal cancer **AND** Patient must not have had been treated for this condition in the metastatic setting prior to initiating non-PBS subsidised treatment with this drug for this condition, **AND** Patient must have stable or responding disease, AND Patient must have a WHO performance status of 0 or 1, **AND** Patient must have deficient mismatch repair (dMMR) colorectal cancer, as determined by immunohistochemistry test
Treatment criteria	The treatment must not exceed a total of 35 cycles or up to 24 months of treatment under this restriction
Administrative Advice:	In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later. A patient may only qualify for PBS-subsidised treatment under this restriction once. Following completion of the initial PBS subsidised course, further applications for treatment will be assessed under the continuing treatment restriction.

Source: pp18-19 of the submission

3.2 The submission requested a special pricing arrangement (SPA). The proposed effective and published ex-manufacturer price per 100 mg vial of pembrolizumab is $[redacted] and $4,025.00, respectively. The pre-PBAC response reduced the effective ex-manufacturer price to $[redacted] per 100 mg vial.

3.3 The submission requested a restriction critiera to allow grandfathering of approximately 50 patients on cost share programs or paying privately and patients on patient familiarisation programs to access PBS-subisided pembrolizumab.

3.4 The submission stated that as noted by the MSAC Executive, MMR testing in CRC is routine in Australia and reimbursed under a general MBS item number for IHC staining, and therefore the sponsor was not required to lodge an integrated co-dependent submission (Application 1452, MSAC Executive minutes March 3 2017).

3.5 The requested restriction is for mCRC that is dMMR only whereas the approved TGA indication (as in the key KN177 trial) is for mCRC that is either MSI-H or dMMR. The submission argued that MSI testing and IHC are considered complementary, and loss of MMR protein expression, by IHC, has been shown to be highly concordant with DNA-based MSI testing, with good sensitivity (see 4. Population and disease for further details).

3.6 In the key KN177 trial, there was no specific test or assay used (to represent the "evidentiary" test) to determine dMMR/MSI-H status for the purposes of inclusion in the trial. Diagnosis was determined using different "local standard-of-care tests". Some Australian sites were included in the KN177 trial.

3.7 The proposed PBS indication specified only metastatic disease (similar to the inclusion criteria of the key KN177 trial) whereas the TGA indication included patients with unresectable advanced non-metastatic disease. The ESC considered it may be reasonable to allow access to pembrolizumab for patients with unresectable disease, and noted it was likely to result in an increase in the number of patients of less than 10%.

3.8 The PBAC considered an Authority Required (telephone) listing would be appropriate for all treatment phases to limit use outside of the TGA indication (i.e., in the second-line setting).

3.9 The PBAC noted flow on changes would be required to the restriction criteria for panitumumab, cetuximab and bevacizumab to allow treatment of patients after progression on pembrolizumab.

4 Population and disease

4.1 Approximately 20% of people with CRC have metastatic disease at the time of initial diagnosis. The 5-year relative survival rate of Australians diagnosed with registry derived (RD) stage IV colorectal cancer is around 13%[1]. 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[2]. dMMR tumours have significant gene upregulation of immune checkpoint proteins, including PD-L1, enabling them to survive the immune response.

4.2 The rate of dMMR in mCRC is uncertain (6.9% from the Australian Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) registry[3] and as low as 3.5% from a reference[4] cited in the 2019 PSD for pembrolizumab (Paragraph 4.1, Pembrolizumab PSD, March 2019 PBAC meeting). The ESC previously expressed concern that, with a lower prevalence of dMMR, there would be a higher risk of false positive results which may lead to futile therapy with pembrolizumab and deprivation of effective first line SoC therapies (paragraph 4.1, pembrolizumab PSD, March 2019 PBAC meeting). However, as dMMR testing in the key KN177 trial was done using heterogeneous, local standard-of-care testing and included Australian sites, it seems reasonable to accept that the IHC performance of dMMR testing in the trial is applicable to Australian

[1]Australian Institute of Health and Welfare 2018. Colorectal and other digestive-tract cancers. Cancer series no. 114. Cat. no. CAN 117. Canberra: AIHW.

[2] 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.

[3] Wong HJ, J; et al. Impact of mismatch repair deficiency on treatment and outcomes in advanced colorectal cancer. Melbourne, Australia: The Walter and Eliza Hall Institute for Medical Research, 2017.

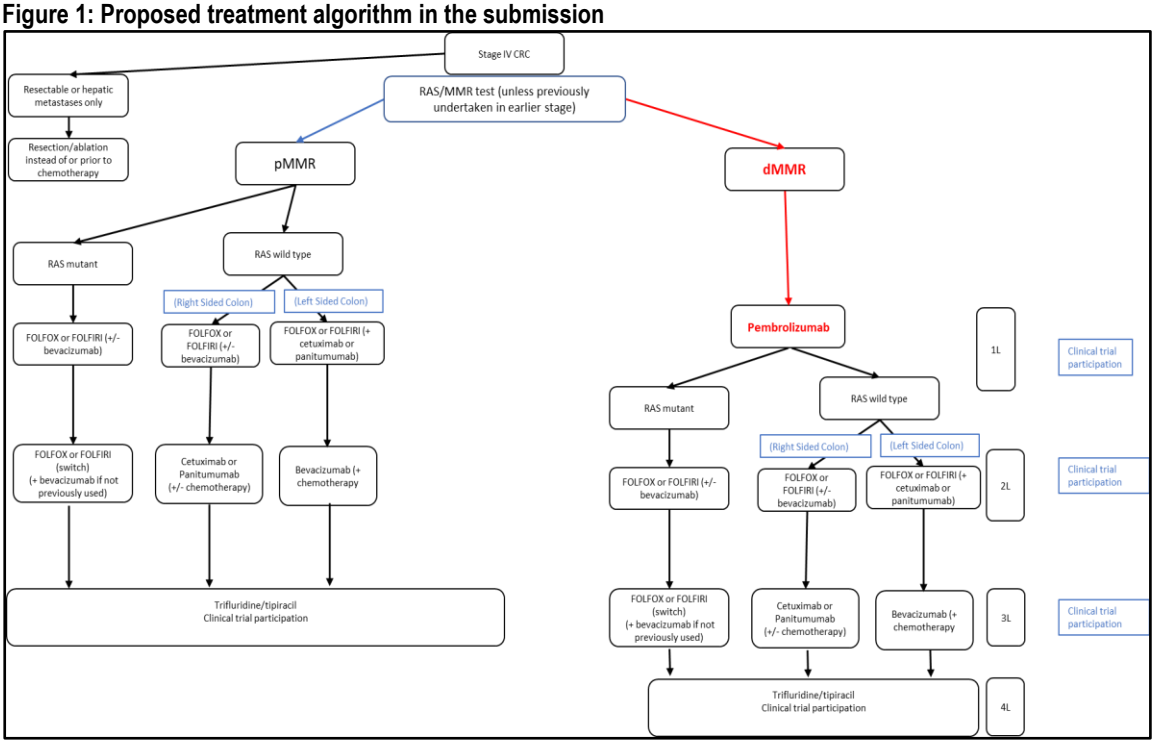
[4] Venderbosch S, Nagtegaal ID, Maughan TS, Smith CG, Cheadle JP, Fisher D, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN and FOCUS studies. Clinical Cancer Research. 2014:clincanres. 0332.2014.

practice. As such, false positive results would be expected to occur to a similar extent in Australia as in the trial, and there is therefore no need to adjust the extent of effectiveness of pembrolizumab to account for false positive results.

4.3 Current first-line SoC therapy for advanced CRC is not specific to patients whose disease has been identified to be dMMR (or MSI-H). The submission noted that in Australia, first- and second-line SoC for mCRC usually consists of a fluoropyrimidine-based chemotherapy regimen (usually leucovorin and fluorouracil) plus oxaliplatin (e.g., FOLFOX) or irinotecan (e.g. FOLFIRI). Monoclonal antibodies are generally added to these regimens (e.g., an anti- VEGF pathway drug (such as bevacizumab) or if RAS wild-type, an EGFR antibody (such as cetuximab or panitumumab)).

4.4 The management algorithm for the intended use of pembrolizumab is presented in the figure below.

Figure 1: Proposed treatment algorithm in the submission



Source: Figure 1.2.2, p13 of the submission.
CRC=colorectal cancer; RAS= rat sarcoma; pMMR=proficient mismatch repair; dMMR=efficient mismatch repair; FOLFOX = folinic acid (leucovorin) "FOL", Fluorouracil (5-FU) "F", and Oxaliplatin (Eloxatin) "OX"; FOLFIRI = folinic acid, fluorouracil and irinotecan; 1L=first line.

4.5 The submission described the impact of listing pembrolizumab as first line therapy for dMMR mCRC as displacement of current comparators by "just one line". However, the current PBS listings for cetuximab and bevacizumab preclude use in patients who have been treated with pembrolizumab. The current TGA indication for use of cetuximab in mCRC would also preclude use of cetuximab with a FOLXOX-based regimen, post progression on first line pembrolizumab. The ESC noted the current PBS restriction

criteria for EGFR and VEGF inhibitors would need to be amended to allow for prior treatment with pembrolizumab in patients with dMMR mCRC.

4.6 In the intended clinical management algorithm, Stage IV CRC patients are required to have an IHC test (if not previously tested) to determine MMR status in order to be able to access pembrolizumab. Patients who are determined to be dMMR would be eligible for treatment with pembrolizumab for a maximum of 35 cycles at a dose of 200mg Q3W.

5 Comparator

5.1 The submission nominated SoC as the main comparator. There is no specific regimen recommended for the first line treatment of dMMR mCRC. The submission noted that SoC is complex in terms of the different available agents and their regimens. The choice of agent in the first line setting is determined by the patients' RAS status, performance status and organ function.

5.2 The three main chemotherapy regimens used in Australia are 1) leucovorin calcium (folinic acid), 5-fluorouracil (5FU) and oxaliplatin (FOLFOX), 2) leucovorin calcium (folinic acid), 5FU and irinotecan hydrochloride (FOLFIRI), and 3) capecitabine plus oxaliplatin (XELOX or CAPOX).

5.3 Patients who are RAS wild type can also receive an EGFR antibody (cetuximab or panitumumab) or a VEGF antibody (bevacizumab) in combination with one of the chemotherapy regimens described above. Patient who are RAS mutant can receive a VEGF antibody (bevacizumab) in combination with one of the chemotherapy regimens described above.

5.4 The submission argued that since FOLFOX and FOLFIRI are most commonly used (as per guidelines), and since neither regimen is superior (or cheaper), FOLFOX was chosen as being representative of all chemotherapy regimens.

5.5 Similarly, as cetuximab is the most commonly used EGFR antibody (Colorectal DUSC review, February 2018) and is similar in price and efficacy to panitumumab, cetuximab + FOLFOX was selected as a comparator to represent EGFR antibody + chemotherapy.

5.6 Bevacizumab + FOLFOX was nominated in the submission as another main comparator.

5.7 The key KN177 trial compared pembrolizumab monotherapy with mFOLFOX6 or FOLFIRI, +/- cetuximab or bevacizumab in an MSI-H/dMMR mCRC population. Thus the nominated comparators are "therapy subsets" of the SoC arm in KN177. There was limited evidence from the KN177 trial to inform on the comparative effectiveness of pembrolizumab compared with cetuximab. Only 10% of patients received a cetuximab-based regimen as part of the SoC arm in KN177 (see further below). The ESC noted dMMR disease is more likely to be right sided and a higher proportion of dMMR disease have a BRAF mutation compared to an all-comer mCRC population. This is reflected in the patient population in KN177 (67% right sided primary, 35% BRAF

mutation in evaluable patients). The ESC noted EGFR inhibitors are generally utilised first line for patients with RAS/BRAF wild type and left sided CRC primary disease. The ESC considered the proportion of patients receiving an EGFR inhibitor (cetuximab) in KN177 was consistent with the proportion expected in clinical practice.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the poor prognosis for patients with metastatic CRC and outlined their positive experience with pembrolizumab which improves survival and qualify of life.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (2), individuals (9) and organisations (4) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with pembrolizumab compared to chemotherapy, including improved survival, less toxicity and better qualify of life. A number of comments raise concerns regarding the affordability of pembrolizumab if it is not included on the PBS. Many of the consumer comments highlight the high clinical need for additional treatments for mCRC. One health care professional was also in support of a tumour agnostic listing for rare and less common cancers.

6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the pembrolizumab submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the Keynote 177 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pembrolizumab, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[5], based on a comparison with chemotherapy plus targeted therapy.

Clinical trials

6.4 The submission was based on one open-label, randomised (1:1), active-controlled trial comparing pembrolizumab 200mg Q3W to first-line SoC (fluorouracil-based chemotherapy + oxaliplatin or irinotecan with or without bevacizumab or cetuximab) in treatment naïve patients with MSI-H/dMMR mCRC (Trial KN177). An MSI or MMR tumour status was determined in local laboratory sites using PCR/IHC. The co-primary endpoint of the trial was progression-free survival (PFS) by RECIST v1.1 as assessed by a blinded independent review committee (BIRC) and overall survival (OS).

6.5 A total of 307 patients were randomised and 296 received treatment (153 patients received pembrolizumab and 143 patients received SoC). Of 154 allocated subjects in

[5] Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017

the SoC arm, 143 received per-protocol chemotherapy. As an approximate proportion of allocated SoC subjects: 11 (7%) received mFOLFOX, 64 (42%) received mFOLFOX + bevacizumab, 5 (3%) received mFOLFOX + cetuximab, 16 (10%) received FOLFIRI, 36 (23%) received FOLFIRI + bevacizumab, and 11 (7%) received FOLFIRI + cetuximab. The majority of SoC subjects received a bevacizumab-based chemotherapy regimen (70%: bevacizumab plus either mFOLFOX or FOLFIRI), and 10% received a cetuximab-based regimen (cetuximab plus either mFOLFOX or FOLFIRI).

6.6 Details of the KN177 trial are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
KEYNOTE-177 (KN177)	Clinical Study Report A Phase III Study of Pembrolizumab (MK-3475) vs. Chemotherapy in Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Stage IV Colorectal Carcinoma (KEYNOTE-177). ClinicalTrials.gov Identifier: NCT02563002	19-MAY-2020
	André T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, Smith D, Garcia-Carbonero R, Benavides M, Gibbs P, de la Fouchardiere C, Rivera F, Elez E, Bendell J, Le DT, Yoshino T, Van Cutsem E, Yang P, Farooqui MZH, Marinello P, Diaz LA Jr; KEYNOTE-177 Investigators. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer.	*New England Journal of Medicine* 2020 Dec 3; 383(23):2207-2218.
	Andre, T et al. Pembrolizumab versus chemotherapy for microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer: The phase 3 KEYNOTE-177 Study. American Society of Clinical Oncology (ASCO). DOI: 10.1200/JCO.2020.38.18_suppl.LBA4	*Journal of Clinical Oncology* 2016; 38 (18)

Source: Table 2.2.1, p25 of the submission. Full trial results were published post-submission date

6.7 The key features of the direct randomised trial are summarised in the table below.

Table 3: Key features of the evidence (KN177 trial)

N	Design/duration	Risk of bias	Patient population	Primary Outcome(s)	Use in modelled evaluation
307	R, OL Median follow-up: ~28 months Median duration of exposure: Pembro 11.1 months; SoC 5.7 months	Low for PFS High for OS due to treatment switching which is likely to favour SoC if OS was unadjusted for switching.	Treatment naïve dMMR mCRC	PFS and OS	Used (adjusted for treatment switching)

Source: Section 2.3 of the submission.
dMMR = mismatch repair deficient; mCRC = metastatic colorectal cancer; OL = open label; OS = overall survival; PFS = progression-free survival; R = randomised; Pembro = pembrolizumab; SoC = standard of care.

6.8 There was treatment switching from the SoC arm to the pembrolizumab arm and to other PD-1/PD-L1 inhibitor therapies post progression (approximately 60% of the 154 patients in the SoC arm). Given that these immune checkpoint inhibitors are not currently reimbursed on the PBS for use in this population, there is the potential for confounding of OS that may have favoured the SoC treatment arm. Analyses to adjust OS for treatment switching were presented in the submission.

Comparative effectiveness

6.9 The median duration of exposure was 11.1 months and 5.7 months in the pembrolizumab and SoC arms, respectively. The median duration of follow up was approximately 28 months.

6.10 The results for the final PFS analysis and planned interim OS analysis at IA2 are summarised in the table and Kaplan-Meier figures below.

Table 4: KN177 - PFS and OS efficacy results

	Pembrolizumab (n= 153)	**SOC (n=154)**
PFS per BICR		
Events, n (%)	82 (53.6)	113 (73.4)
Median PFS, months (95% CI)	16.5 (5.4, 32.4)	8.2 (6.1, 10.2)
Stratified HR[a]	**0.60 (0.45, 0.80)**	
p-value[b]	**0.0002**	
PFS rate at 12 months (95% CI)	55.3 (47.0, 62.9)	37.3 (29.0, 45.5)
PFS rate at 18 months (95% CI)	49.1 (40.7, 57.0)	26.7 (19.2, 34.7)
PFS rate at 24 months (95% CI)	48.3 (39.9, 56.2)	18.6 (12.1, 26.3)
OS		
Events, n (%)	56 (36.6)	69 (44.8)
Median OS, months (95% CI)	NR (NR, NR)	34.8 (26.3, NR)
Stratified HR[a]	0.77 (0.54, 1.09)	
p-value[c]	0.0694	
OS rate at 12 months (95% CI)	77.8 (70.3, 83.6)	74.0 (66.2, 80.3)
OS rate at 18 months (95% CI)	71.2 (63.4, 77.7)	65.9 (57.7, 72.9)
OS rate at 24 months (95% CI)	68.0 (59.9, 74.7)	59.8 (51.5, 67.2)

Source: Table 4, p12 of Delegate's overview for pembrolizumab (MSD PM-2020-03165-1-4).

Database Cutoff Date: 19FEB2020. Median duration of follow up across both treatment groups was 27.6 months.

Bolded results are statistically significant.

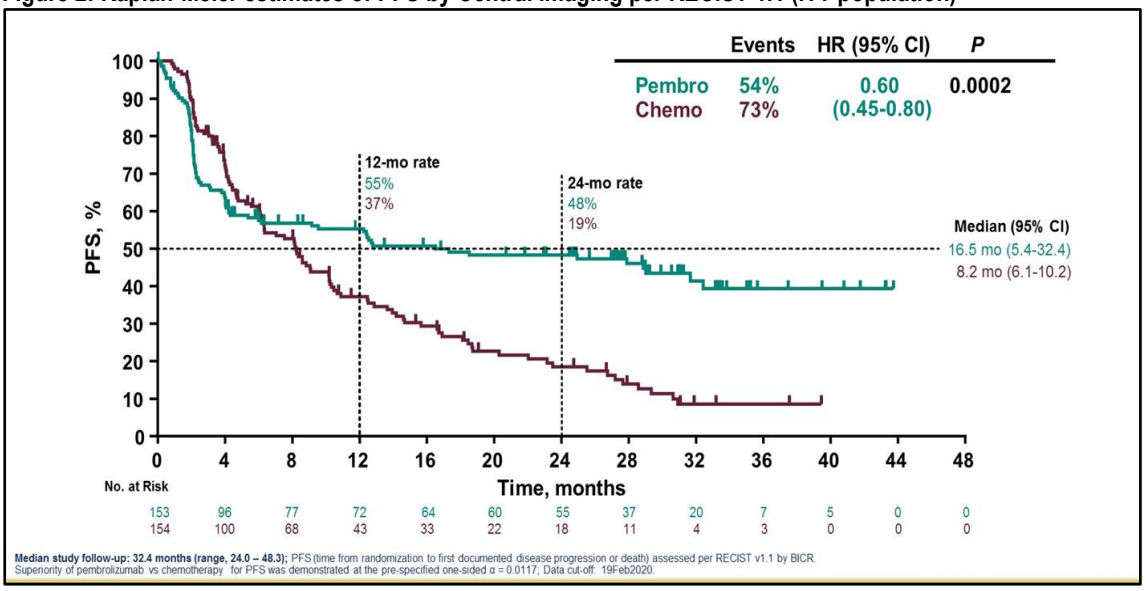
BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; n=number; NR=not reached; OS=overall survival; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumours Version 1.1; SOC=standard of care.

[a] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.

[b] One-sided p-value based on log-rank test; pre-specified significance boundary = 0.0117

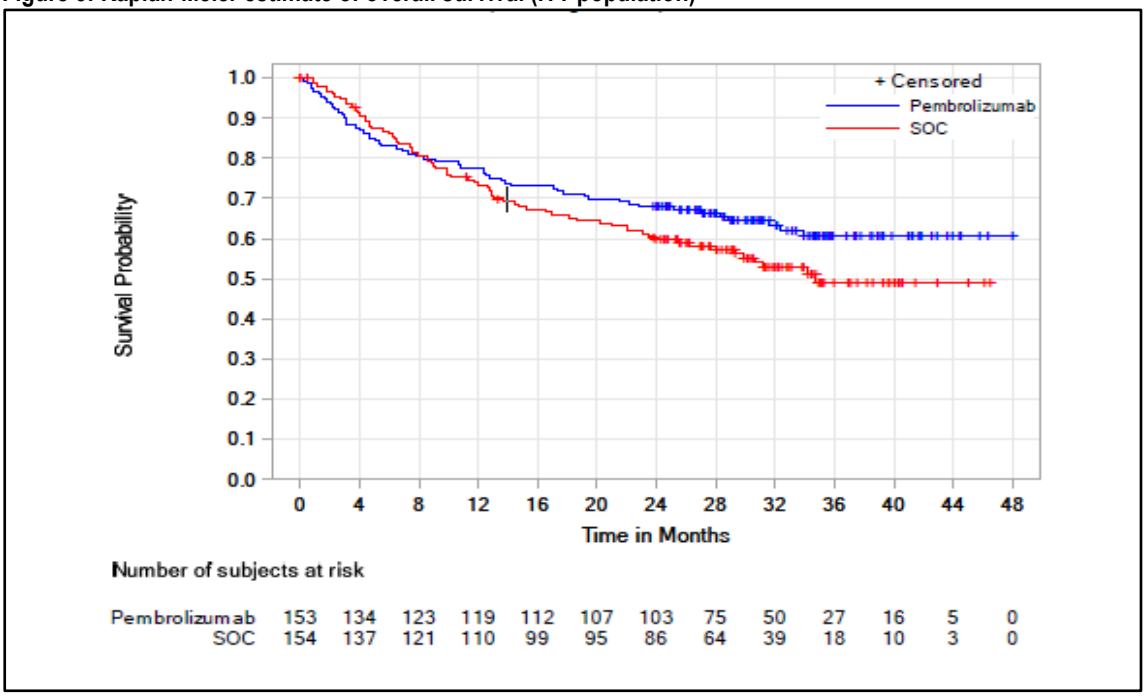
[c] One-sided p-value based on log-rank test; pre-specified significance boundary = 0.0053

Figure 2: Kaplan-Meier estimates of PFS by Central Imaging per RECIST 1.1 (ITT population)



Source: Figure 2.5.1, p50 of the submission.
Note: the median duration of follow-up of 32.4 months is inconsistent with that provided in the CSR for the February 2020 cut-off date.
PFS=progression-free survival; ITT=Intention to treat; HR=hazard ratio; PEMBRO=pembrolizumab; Chemo=chemotherapy; mo=months; RECIST 1.1=Response Evaluation Criteria in Solid Tumours Version 1.1

Figure 3: Kaplan-Meier estimate of overall survival (ITT population)



Source: Figure 2.5.3, p53 of the submission.
ITT=Intention to treat; SoC=standard of care; mo=months. Data cut-off=19 February 2020

6.11 The HR is difficult to interpret as the Kaplan-Meier curves indicated the constant proportional hazards (PH) assumption did not apply. Notwithstanding this issue, the HR suggested there was a 40% reduction of the hazard of progression or death

associated with pembrolizumab over SoC which was statistically significant (HR= 0.60, 95% CI: 0.45, 0.80; p=0.0002). The median duration of PFS for pembrolizumab was approximately two fold that observed for SoC (16.5 months versus 8.2 month). The PFS rates were higher for the pembrolizumab arm versus the SoC arm at the 18 - month (49.1% versus 26.7%) and 24 - month (48.3% versus 18.6%) time points.

6.12 The Delegate's Overview presented an exploratory restricted mean "survival" time (RMST) analysis for PFS that was performed by the FDA, as supportive information to account for the non-PH effect associated with immunotherapies. The PFS RMST estimates are summarised in the table below.

Table 5: Exploratory RMST estimates of progression free survival (KN177)

	Pembrolizumab (n=153)		**SoC (n=154)**		**Difference (95% CI) pembrolizumab vs SoC**
	#of events	RMST (95% CI)	#of events	RMST (95% CI)	
6 months	64	4.4 (4.1, 4.7)	57	4.8 (4.6, 5.1)	-0.5 (00.9, 0.0)
9 months	65	6.1 (5.5, 6.6)	75	6.4 (5.9, 6.9)	-0.3 (-1.1, 0.4)
12 months	67	7.8 (7.0, 8.5)	85	7.6 (6.9, 8.3)	0.1 (-0.9, 1.2)
18 months	75	10.8 (9.6, 12.0)	97	9.5 (8.4, 10.6)	1.3 (-0.3, 2.9)
24 months	76	13.7 (12.0, 15.4)	105	10.8 (9.4, 12.2)	2.9 (0.7, 5.1)

Source: Table 5 of the Delegate's overview for pembrolizumab MSD PM-2020-03165-1-4.
CI=confidence interval; RMST= restricted mean survival time; SOC=standard of care. Database cut-off date: 19FEB2020

6.13 At the 24 month truncated time point, the additional average PFS time associated with pembrolizumab over SoC was approximately 3 months.

6.14 The OS data remain immature at 66% of the planned events. Only 41% of patients across both arms of the key KN177 trial had died at the time of the interim analysis and the median OS had not been reached in the pembrolizumab arm. A final analysis of OS is planned at 190 events or 12 months after IA2 (final analysis according to the submission expected early in 2021).

6.15 Recognising the limitations of the HR as the PH assumption was violated, the immature OS data indicated a 23% reduction in the hazard of death associated with pembrolizumab which was not statistically significant (HR= 0.77, 95% CI: 0.54, 1.09; p=0.0694). The p-value boundary criterion (0.0053) was not met. The OS rates were higher for the pembrolizumab arm versus the SoC arm at the 18 - month (71.2% versus 65.9%) and 24 - month (68.0% versus 59.8%) time points.

6.16 The ESC noted the pembrolizumab and SoC KM curves crossed around the 8 month time point before which there was an apparent increased hazard of death associated with pembrolizumab, but noted the absolute patient numbers were small.

6.17 The TGA Delegate noted the following:

- Immunotherapies are associated with excess early mortality when compared to chemotherapy in a number of settings, including KEYNOTE-177;

- The Delegate intends to make a condition of registration the submission of the mature OS analysis from KEYNOTE-177 when available, including consideration of whether there is early crossover of the K-M curves for the two arms, and any possible associations for who may be at higher risk of early mortality with immunotherapy compared to chemotherapy.

6.18 The OS results from the adjustment methods presented in the submission are summarised in the table below.

Table 6: KN177 - Adjustment of OS for treatment switching from SoC to pembrolizumab or other PD-1/PD-L1 inhibitors.

Analysis method (KN177): Switching to pembrolizumab or other Anti-PD1/PD-L1	Hazard ratio [95% CI]	Median OS[a] , months (95% CI)	
		Pembrolizumab	SoC
ITT (Unadjusted)	0.77 [0.54, 1.09]	NR (NR, NR)	34.8 (26.3, NR)
RPSFT (without recensoring)[b]	0.68 [0.40, 1.14]	NR (NR, NR)	28.0 (23.2, NR)
RPSFT (with recensoring)	0.72 [0.47, 1.11]	NR (NR, NR)	NR (20.2, NR)
Simplified two-stage (without recensoring)	0.59 [0.30, 1.19]	NR (NR, NR)	23.5 (16.6, NR)
Simplified two-stage (with recensoring)	0.89 [0.76, 1.04]	NR (NR, NR)	NR (NR, NR)
IPCW[c]	0.59 [0.32, 1.24]	NR (NR, NR)	15.2 (15.2, 34.2)

Source: Attachments 10, 11, 12 and 13 accompanying the submission.

NR = not reached; CI = confidence interval; IPCW = inverse probability of censoring weighting method; ITT = intention-to-treat; OS = overall survival; RPSFT = rank-preserving structural failure time method; SoC = standard of care

[a] From product-limit (Kaplan-Meier) method

[b] Considered as the primary analysis in the submission.

[c] Second phase of the IPCW approach (i.e. logistic model to estimate the stabilized weights), as pre-specified in the SAP are slightly different from those used in the analyses presented in the CSR. Specifically, the following additional covariates; site of primary tumour (right, left, other), metastases location (hepatic, other) and tumour size (continuous), were, after the CSR was finalised, identified as possible confounders and were added in the second stage of the IPCW approach presented in this report

6.19 The submission selected the rank-preserving structural failure time method (RPSFTM) adjusted result, without recensoring, as the base case in the economic evaluation.

6.20 In the RPSFTM, a key assumption is the common treatment effect. That is, the effect of pembrolizumab or anti PD1/PD-L1 therapy after chemotherapy is equivalent to that of pembrolizumab at randomisation. This may not represent a valid assumption when patients who switch only receive the experimental treatment when their disease has progressed. The key issue is if patients who switch on to pembrolizumab part way through the KN177 trial receive a different treatment effect, compared to patients originally randomised to pembrolizumab, the RPSFTM estimate received by patients in the pembrolizumab group will be biased. As the primary reason for treatment switching to pembrolizumab was disease progression, at which time the capacity for a patient to benefit may be substantially reduced compared to preprogression, the evaluation considered the clinical plausibility of this assumption had not been established.

6.21 The HR (95% CI) results varied slightly depending on whether recensoring was (0.72 (0.47, 1.11)) or was not (0.68 (0.40, 1.14)) applied. In the economic evaluation, the

submission selected the RPSFT approach (without recensoring) for the base case. Recensoring mitigates informative censoring but however may lead to loss of information.

6.22 For the inverse probability of censoring weighting (IPCW) method, a fundamental assumption is that there are no unmeasured confounders that determined switching and the ESC considered the plausibility of this assumption was uncertain. The IPCW method 1) involves censoring when patients switch to other treatments and may thus be prone to bias if this proportion is very high, and 2) the presence of any time-dependent confounding, could have occurred between the time of treatment discontinuation and the time of treatment switching. Approximately two thirds of the patients switched over within 83 days after disease progression, with a median time from disease progression until switching of 37 days.

6.23 The two-stage model relies on the assumption of no time-dependent confounding between disease progression and switch-over. The submission argued that although it took a slightly longer time for some patients to switch-over (refer to paragraph 6.21), the bias was likely to be small. This is highly uncertain as the time between progression and switching is a crucial factor that may affect the validity of the results. An acceleration factor was used to adjust the survival time of the 91 patients who switched from the SoC arm to pembrolizumab monotherapy or other anti-PD1/PD-L1 therapies. The ESC considered the point estimate of the resulting estimated acceleration factor 4.047 (1.967, 8.327) appears very high and imprecise with a wide confidence interval. The survival period after treatment switch was reduced by approximately 75.3% as compared to the unadjusted observed data.

6.24 The ESC considered the point estimate of the HR from the 2 stage model with recensoring (0.89 (0.76, 1.04)) also does not appear plausible given that the reduction in hazard of death (11%) is much less than that estimated from the unadjusted ITT analysis (23%).

6.25 Overall response rate (ORR) at IA2 was not formally tested for significance, per the pre-specified testing strategy[6]. The ORR per RECIST 1.1 was higher 43.8% (95% CI: 35.8, 52.0) versus 33.1% (95% CI: 25.8, 41.1); more participants achieved a complete response (CR) in the pembrolizumab group than in the SoC group (11.0% vs 4.0%).

6.26 For those who responded, median time to response was similar (2.2 months vs 2.1 months); median response duration was not reached in the pembrolizumab group (range: 2.3+ to 41.4+ months) and was 10.6 months in the SOC group (range: 2.8 to 37.5+ months).

[6] Based on the KN177 protocol-specified multiplicity strategy, if ORR was not significant at IA1, ORR at IA1 could be tested following a statistically significant PFS or OS hypothesis test at IA2 or FA. Because PFS was statistically significant at IA2, ORR at IA1 was formally tested and statistical significance was not demonstrated, as the p-value of 0.0582 for ORR at IA1 was above the p-value boundary of 0.000125

6.27 For patient reported outcomes (PRO) (exploratory endpoints), patients in the pembrolizumab treatment arm showed a least-squares (LS) mean improvement in the EQ-5D visual analogue scale (VAS) score by 4.5 points (95% CI 1.16, 7.83), while those in the SoC arm showed a decline from baseline in their VAS score of -2.88 (95% CI -6.46, 0.69). The difference in LS means between the two treatment arms was 7.38 points (95% CI 2.82, 11. 93), which the submission noted was statistically significant (p=0.0016) and clinically meaningful.

Comparative harms

6.28 The safety results are summarised below.

Table 7: Overall adverse events in KN177 (safety population)

Subjects in population	Pembrolizumab (n=153)		Standard of care (n=143)	
	n	(%)	n	(%)
With one or more adverse events	149	(97.4)	142	(99.3)
With drug-related[a] adverse events	122	(79.7)	141	(98.6)
With toxicity grade 3-5 adverse events	86	(56.2)	111	(77.6)
With toxicity grade 3-5 drug-related adverse events	33	(21.6)	94	(65.7)
With serious adverse events	62	(40.5)	75	(52.4)
With serious drug-related adverse events	25	(16.3)	41	(28.7)
Who died[b]	6	(3.9)	7	(4.9)
Who died due to a drug-related adverse event	0	(0.0)	1	(0.7)
Who discontinued[c] drug due to an adverse event	21	(13.7)	17	(11.9)
Who discontinued[c] drug due to a drug-related adverse event	15	(9.8)	8	(5.6)
Who discontinued[c] drug due to a serious adverse event	12	(7.8)	13	(9.1)
Who discontinued[c] drug due to a serious drug-related adverse event	7	(4.6)	5	(3.5)
Grade 3 or 4 adverse events of special interest	14	(9.1)	3	(2.1)

Source: Table 12.1, p91 of the CSR

Median durations of treatment in pembrolizumab and SoC arms were 11.1 months and 5.7 months, respectively.

Grades are based on NCI CTCAE version 4.03.

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

Database Cutoff Date: 19FEB2020.

[a] Determined by the investigator to be related to the drug.

b Pembrolizumab arm: one event each of abdominal sepsis, death, diarrhoea, duodenal perforation, failure to thrive, pseudobulbar palsy. SoC arm: one event each of aortic dissection, aspiration, cardiac arrest, cholangitis, intestinal perforation, pulmonary embolism, upper gastrointestinal haemorrhage.

[c] All study medications withdrawn

6.29 For drug related AEs >10% in any treatment arm:

- events that were reported at least 5% more frequently in the pembrolizumab treated arm than in the SoC arm were upper abdominal pain, pruritus, aspartate aminotransferase increased, arthralgia, nasopharyngitis, and hypothyroidism.
- AEs that were reported at least 5% more frequently in the SoC arm than in the pembrolizumab arm were diarrhoea, fatigue, nausea, decreased appetite, vomiting, anaemia, constipation, asthenia, hypokalaemia, alopecia, stomatitis, dyspepsia, weight decreased, mucosal inflammation, peripheral sensory

neuropathy, neutropenia, epistaxis, peripheral neuropathy, palmar-plantar erythrodysaesthesia, and white blood cell (WBC) decreased.

6.30 Greater than Grade 2 adverse events of special interest (AEOSI) for the pembrolizumab arm versus the SoC arm included Grades 3 and 4 colitis (3.3% versus 0%), Grade 3 autoimmune/immune mediated hepatitis (2.6% versus 0%), and one Grade 3 event each, only in the pembrolizumab arm (0.7% versus 0%), for the following: adrenocortical insufficiency, pancreatitis, and Type 1 diabetes. (0.7% versus 0%).

6.31 AEs resulted in the deaths of 6 patients in the pembrolizumab arm and 7 patients in the SoC arm. In the SOC arm three fatal events consistent with the known risks of VEGF inhibition (duodenal perforation, cardiac arrest, and aortic dissection) occurred in patients whose SOC regimen included bevacizumab.

6.32 A lower proportion of participants in the pembrolizumab group experienced an AE resulting in treatment interruption than in the SoC group (37.9% vs 69.2%). Similarly, a lower proportion of participants in the pembrolizumab group experienced a drug-related AE resulting in treatment interruption than in the SOC arm (22.9% vs 58.7%).

6.33 Overall, the observed AEs are consistent with the different established toxicity profiles of pembrolizumab (and immune check point inhibitors in general) and of chemotherapy.

Benefits/harms

6.34 A summary of the comparative benefits and harms for pembrolizumab compared with SoC is presented in the table below.

Table 8: Summary of comparative benefits and harms

	Pembrolizumab (n= 153)	SoC (n=154)
Median duration of follow up across both arms: 28 months.		
Median duration of exposure.	11.1 months	5.7 months
BENEFITS		
PFS by blinded independent review		
Events, n (event rate per 100 patients, %)	82 (53.6)	113 (73.4)
Median PFS duration, months (95% CI)	16.5 (5.4, 32.4)	8.2 (6.1, 10.2)
Difference between pembrolizumab and SoC	8.3 months	
Stratified HR[a] (95% CI); p-value[b]	**0.60 (0.45, 0.80); 0.0002**	
PFS rate at 18 months (95% CI)	49.1 (40.7, 57.0)	26.7 (19.2, 34.7)
Difference between pembrolizumab and SoC	22.4%	
PFS rate at 24 months (95% CI)	48.3 (39.9, 56.2)	18.6 (12.1, 26.3)
Difference between pembrolizumab and SoC	29.7%	
OS not adjusted for treatment switching (immature data at 66% of the planned events)		
Events, n (event rate per 100 patients, %)	56 (36.6)	69 (44.8)
Median OS, months (95% CI)	NR (NR, NR)	34.8 (26.3, NR)
Stratified HR[a]	0.77 (0.54, 1.09)	
p-value[c]	0.0694	
OS rate at 24 months (95% CI)	68.0 (59.9, 74.7)	59.8 (51.5, 67.2)
Difference between pembrolizumab and SoC	8.2%	
HARMS (event rate per 100 patients)		
With toxicity Grade 3-5 drug-related AEs, n (%)	33 (21.6)	94 (65.7)
Difference between pembrolizumab and SoC[d]	-44.1%	
With serious drug-related AEs, n (%)	25 (16.3)	41 (28.7)
Difference between pembrolizumab and SoC	-12.4%	
With Grade 3-4 AEOSI, n (%)	14 (9.1%)	3 (2.1%)
Difference between pembrolizumab and SoC	-7.0%	

Source: For benefits, Table 4, p12 of Delegate's overview for pembrolizumab (MSD PM-2020-03165-1-4); For harms, Table 12.1, p91 of the CSR, and Table 14.3-46, p319 of the KN177 CSR.

Database Cut-off Date: 19FEB2020. Median duration of follow up across both treatment groups was 27.6 months.

Bolded results are statistically significant.

CI=confidence interval; HR=hazard ratio; n=number; NR=not reached; OS=overall survival; PFS=progression-free survival; SoC=standard of care; AEs = adverse events; AEOSI = adverse events of special interest.

[a] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.

[b] One-sided p-value based on log-rank test; pre-specified significance boundary = 0.0117

[c] One-sided p-value based on log-rank test; pre-specified significance boundary = 0.0053

[d] Number of patients in SoC arm who received treatment was 143.

6.35 On the basis of direct evidence from KN177 presented by the submission, for every 100 patients treated with pembrolizumab (median duration of exposure 11.1 months) in comparison with SoC (median duration of exposure 5.7 months), over a median duration of follow up of approximately 28 months:

- Approximately 30 additional patients will remain progression-free after 24 months. OS benefit was not significant although the data remain immature and

are potentially biased against pembrolizumab due to SoC patients switching over to pembrolizumab or other anti-PD-1/PD-L1 therapies.

- 44 less patients will experience a Grade 3-5 drug-related AE, 12 less patients will experience a serious drug-related AE. However, 7 additional patients will experience a Grade 3-4 AEOSI. These would primarily include colitis and immune mediated hepatitis.

Clinical claim

6.36 The submission described pembrolizumab monotherapy, administered until progression or for a maximum of 35 cycles (200 mg Q3W), as superior compared with mFOLFOX6 or FOLFIRI chemotherapy regimens (with or without bevacizumab, cetuximab or panitumumab), in terms of both effectiveness and safety.

6.37 For PFS, the benefit associated with pembrolizumab appeared clinically meaningful. This provides patients with metastatic disease a chemotherapy free regimen in the first line setting. The magnitude of the OS benefit associated with pembrolizumab is uncertain due to treatment switching and because only about 40% of patients had died at the time of analysis. OS results adjusted for treatment switching varied according to the methods of adjustment used. The ESC noted that dMMR mCRC is associated with an upregulated immune microenvironment and considered the PFS benefit observed with pembrolizumab was likely to correlate with an OS survival benefit.

6.38 There were some early excess progressive disease and deaths which is not an observation unique to pembrolizumab or to the KN177 trial. This observation is common to PD-1/PD-L1 inhibitor monotherapy across several different indications. The ESC considered that determining which patients would respond to SoC better than to pembrolizumab in the first line setting cannot be established from the available KN177 data.

6.39 The PBAC considered the claim that pembrolizumab was superior to standard of care in terms of effectiveness and safety was reasonable.

Economic analysis

6.40 The submission presented a modelled economic evaluation, based on the direct randomised trial KN177. The type of economic evaluation presented was a cost-effectiveness analysis and a cost-utility analysis, measuring outcomes in terms of life-years (LYs) gained and quality-adjusted life years (QALYs) gained, respectively. The key components of the economic evaluation are summarised below.

Table 9: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Pembrolizumab *vs.* SoC (represented by a mix of FOLFOX or FOLFIRI ± bevacizumab or cetuximab)
Time horizon	10 years in the model base case vs. median follow-up of 27.2-28.4 months in KN177
Outcomes	LYs gained and QALYs gained
Methods used to generate results	Cohort analysis of partitioned survival (i.e. area under the curve)
Health states	Three heath states: PFS, PD and death. The proportion of patients in each health state was determined on the basis of the PFS and OS curves.
Cycle length	1 week
Allocation to health states	The Kaplan-Meier estimates for PFS and OS were derived from KN177, with crossover adjustment using a RPSFT (without recensoring) method. The trial-based survival estimates were used up until 20 weeks for PFS and 52 weeks for OS in both treatment arms.
Extrapolation method	Parametric functions were fitted to the trial data to extrapolate respective survival curves to the model time horizon of 10 years. In the base case, an independent exponential function was chosen for both PFS and OS extrapolation in both treatment arms. The selection was based on goodness of fit and clinical plausibility. 97% of the incremental QALYs and 48% of incremental costs were generated beyond 1 year (i.e. the extrapolation time point for OS).
Health related quality of life	EQ-5D scores from KN177 were used to derive utility estimates based on an Australian scoring algorithm PFS health state utility: 0.855 for pembrolizumab and 0.815 for SoC PD health state utility: 0.751 for both arms AE-related disutility was also applied to the economic model.

Source: Table 3.1-1, p88 and information provided in Section 3.1, pp88-90 of the submission.
AE = adverse event; EQ-5D = EuroQol - 5 dimensions; LYs = life years; OS = overall survival; PD = progressive disease; PFS = progression-free survival; QALYs = quality-adjusted life years; RPSFT = rank-preserving structural failure time; SoC = standard of care

6.41 To address the applicability issue raised from the high rate of treatment switching from first-line SoC to pembrolizumab or other anti-PD-1/PD-L1 therapies upon disease progression in KN177 (59.1% of the randomised patients), adjustment for treatment switching was performed to estimate the OS for dMMR mCRC patients treated with first-line SoC if they do not crossover to anti-PD-1/PD-L1 therapies. The submission selected a RPSFT (without recensoring) approach in the base case, on the basis that it visually produced the most plausible adjusted OS curve and resulted in the most conservative estimate of the treatment effect of pembrolizumab, in comparison with simplified two-stage (without recensoring) and IPCW approaches (HR for OS: 0.68 vs. 0.59). The evaluation noted that the HR for OS from the RPSFT with recensoring method was less favourable to pembrolizumab than that from the RPSFT without recensoring approach as used in the base case (OS HR: 0.72 vs. 0.68) and matched most closely to the predicted OS HR based on the Kok (2020) model[7] (0.72 vs. 0.71). The evaluation considered the incremental cost-effectiveness ratio (ICER) result based on the RPSFT with recensoring approach would be informative to assess the cost-effectiveness of pembrolizumab in dMMR mCRC patients. The Pre-Sub-Committee

[7] Kok PS, Cho D, et al. Validation of progression-free survival rate at 6 months and objective response for estimating overall survival in immune checkpoint inhibitor trials: a systematic review and meta-analysis. *JAMA network open*. 2020;3(9):e2011809

Response (PSCR) reported an ICER of $55,000 to <$75,000/QALY gained applying the RPSFT with recensoring (compared to a corrected baseline ICER of $55,000 to <$75,000/ QALY).

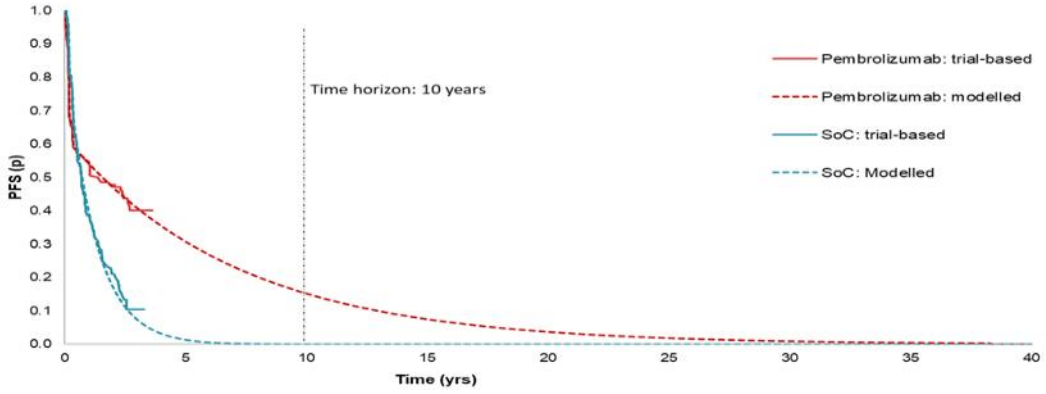
6.42 The ESC noted that the alternative treatment switching adjustment methods (RPSFT, IPCW and the two-stage approach) should be assessed with respect to the validity of the assumptions associated with each method and to the validity of the statistical analysis involved in the application of each method.

6.43 The ESC considered the RPSFT approach (without recensoring) appeared to perform best from a statistical perspective and appeared to be the most appropriate treatment switching adjustment approach, despite some concerns regarding the common treatment effect assumption (paragraph 6.20). The ESC considered pembrolizumab may be less effective as second line therapy due to increased burden of disease. This consideration may inform the interpretation of the ICERs based on the ITT and the RPSFT analyses, i.e. the expected ICER is between these two ICERs, but likely closer to the RPSFT ICER than the ITT ICER.

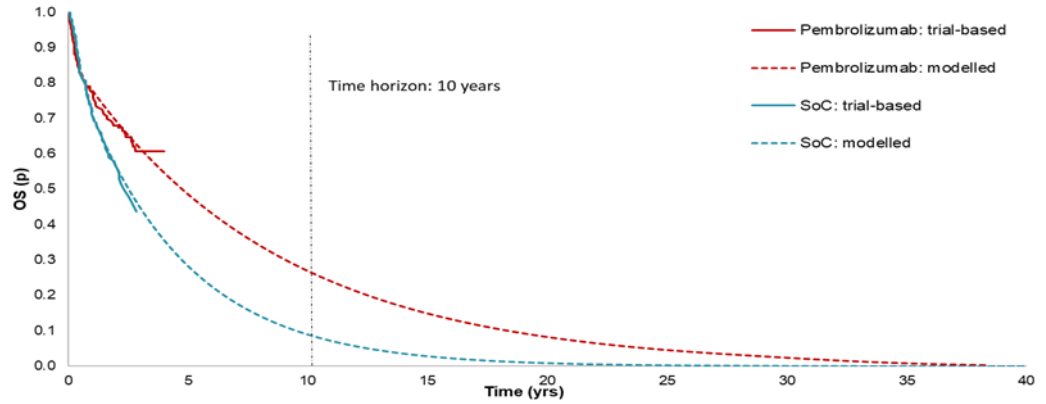
6.44 The submission used a 10-year time horizon in the base case economic evaluation. The PBAC has previously accepted a time horizon from 5 years to 10 years for assessment of first-line therapies in mCRC patients, dependent on the availability of long-term trial data (Bevacizumab PSD, March 2008 PBAC meeting; Panitumumab PSD, July 2014 PBAC meeting). In KN177, a substantial number of patients were censored from Year 2 and the ITT OS curves of the two treatment arms remained flat after Year 3. The trial data did not provide a reliable basis for a long-term extrapolation. The submission modelled greater survival estimates for patients in the pembrolizumab arm than those in the comparator SoC arm for more than 30 years after discontinuation of pembrolizumab therapy at the maximum treatment duration (Figure 4). The evaluation considered the implied ongoing treatment benefits associated with pembrolizumab over SoC was not well justified and appeared unrealistic. The evaluation considered the use of an extended model time horizon in combination with possibly optimistic extrapolations added uncertainty to the cost-effectiveness estimates.

6.45 The PSCR stated the use of a 10-year time horizon is conservative as the data suggests a 20-year time horizon may be justified. The ESC considered a 10 year survival of around 25% in the pembrolizumab arm, as predicted in the base case model, was uncertain as the data are too immature. The ESC considered additional follow up OS data from KN177 (due the first half of 2021) may further inform the extrapolation of OS and the reasonableness of 25% survival at 10 years. The PBAC agreed with the pre-PBAC response that more mature OS data may not alleviate these concerns due to the high rate of cross over in the SoC treatment arm. The PBAC considered that, given the immaturity of the clinical data, to mitigate the uncertainty associated with a 10 year time horizon, the economic model should be based on a 7.5 year time horizon.

Figure 4: Comparison of the trial-based and modelled PFS and OS survival curves [a]



(A) PFS



(B) OS

Source: Figure constructed during the evaluation, based on the "Section 3 Workbook_dMMR_CRC_PBAC_NOV20" workbook
OS = overall survival; PFS = progression-free survival; SoC = standard of care
[a] The Kaplan Meier OS curve for SoC has been adjusted for crossover using the rank-preserving structural failure time method (without recensoring).

6.46 The health state utility values applied to the economic model was based on the EQ-5D data from KN177, using an Australian scoring algorithm[8]. The evaluation considered the quality of life data from the trial, which were collected at scheduled visits during treatment up until 1 year or end of treatment, whichever came first, and at the 30-day post-treatment discontinuation visit, may not represent the overall utility weights for patients in the PFS and progressive disease (PD) health states. In addition, the EQ-5D results were subject to performance bias (due to the open-label study design). Overall, the evaluation considered the trial-based health state utility values used in the economic model (PFS state: 0.855 for pembrolizumab, 0.815 for SoC; PD state: 0.751 in both treatment arms) were likely overestimates. The ESC noted the open label trial design which may lead to performance bias and considered the use of treatment-specific utilities in the PFS state may not be reasonable. The pre-PBAC response stated

[8] Viney R, Norman R, *et al*. Time trade-off derived EQ-5D weights for Australia. *Value Health*. 2011;14(6):928-36.

the treatment-specific utilities were derived from the clinical trial and were clinically appropriate. The pre-PBAC response stated that despite the open label nature of the trial it is not unexpected that pembrolizumab would be better tolerated than and preferred to chemotherapy regimens and the adverse event rates and profiles demonstrate toxicity differences that would be noted by patients even if the study treatment was blinded. The PBAC considered that the treatment-specific utilities used in the model remained uncertain due in part being derived from the open label trial design, but were overall acceptable in the context of a statistical difference in quality of life seen in the trial (paragraph 6.27).

6.47 The treatment costs were calculated on the basis of the proposed effective price for pembrolizumab and the PBS-listed prices for SoC medicines. The submission noted that the PBAC has recently recommended the listing of a biosimilar brand of bevacizumab and anticipated that the listing of this biosimilar would have occurred by the listing date of pembrolizumab for the proposed indication. A statutory 25% price reduction was applied to bevacizumab in the financial analysis, but not in the submission's economic analysis. The ESC considered that, given the uncertain timing of its implementation, it was not appropriate to include the statutory price reduction for bevacizumab in the economic or the financial modelling.

6.48 In the economic model, the proportions of patients who would receive subsequent therapy with bevacizumab and cetuximab after disease progression were assumed to be 17.6% and 2.9%, respectively, in the pembrolizumab arm and 68.1% and 0%, respectively, in the SoC arm. These were estimated on the basis of data from KN177, after adjustment for the use of pembrolizumab and other PD-1/PD-L1 inhibitors post-progression in the SoC group. The current PBS restriction only allows limited use of bevacizumab in the second-line setting in RAS wild-type mCRC patients following first-line anti-EGFR therapy (cetuximab or panitumumab); whilst later-line cetuximab and panitumumab can only be used after failure of first-line chemotherapy. Therefore, if pembrolizumab is listed, patients won't be eligible for bevacizumab or cetuximab in a later-line setting after failure to first-line pembrolizumab; and the high proportion of patients receiving later-line bevacizumab (68.1%) following the restricted use of first-line cetuximab in the SoC arm (10.3%) as assumed in the model did not reflect Australian clinical practice. The PBAC considered the restriction criteria for bevacizumab, cetuximab and panitumumab should be revised to allow use in dMMR mCRC patients who have previously received pembrolizumab.

Table 10: Key drivers of the model

Description	Method/Value	Impact (base case: $[redacted][1]/QALY)
Comparative treatment effect	The OS estimates in the SoC arm were adjusted using a RPSFT (without recensoring) approach.	Moderate to high, uncertain Use of ITT results without crossover adjustment increased the ICER to $[redacted][2]/QALY. .
Time horizon	10 years.	Moderate, dependent on acceptance of fitted extrapolation curves.
Extrapolation	The submission modelled sustained survival benefits associated with pembrolizumab for more than 30 years after discontinuation of treatment.	Moderate to high, favours pembrolizumab Assuming the survival curves of the two treatment arms converged from Year 5 to Year 10 for both PFS and OS, the ICER increased to $[redacted][2].

Source: Table compiled during the evaluation, based on Section 3.9 of the submission and the sensitivity analyses performed during the evaluation.

ICER = incremental cost-effectiveness ratio; IPCW = inverse probability of censoring weighting; ITT = intention-to-treat; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; RPSFT = rank-preserving structural failure time; SoC = standard of care

The redacted values correspond to the following ranges:

[1]$55,000 to <$75,000/QALY gained

[2]$75,000 to <$95,000/QALY gained

6.49 Results of the economic evaluation are summarised in the table below.

Table 11: Results of the stepped economic evaluation

Step and component	Pembrolizumab	SoC	Increment
Step 1: KN177 trial-based (time horizon of 4 years)			
Costs	$	$28,633	$
LYs	2.612	2.383	0.229
QALYs	2.128	1.827	0.301
Incremental cost/extra LY gained			$ [1]
Incremental cost/extra QALY gained			$ [2]
Step 2: Translation of circumstances of use: adjust for SoC crossover and update SoC dosing[a]			
Costs	$	$30,325	$
LYs	2.612	2.238	0.374
QALYs	2.128	1.718	0.410
Incremental cost/extra LY gained			$ [2]
Incremental cost/extra QALY gained			$ [2]
Step 3: Transform resource use to non-drug costs (administration, AEs, and health state costs)			
Costs	$	$60,715	$
LYs	2.612	2.238	0.374
QALYs	2.128	1.718	0.410
Incremental cost/extra LY gained			$ [2]
Incremental cost/extra QALY gained			$ [2]
Step 4: Extrapolation of PFS and OS to a 10-year time horizon			
Costs *Revised [b]*	$ *$*	$60,715 *$57,853*	$ *$*
LYs	4.315	3.092	1.223
QALYs	3.516	2.362	1.154
Incremental cost/extra LY gained *Revised [b]*			$ [3] *$* [3]
Incremental cost/extra QALY gained *Revised [b]*			**$** [3] **$** [3]

Source: Table 3.8-2, pp148 of the submission.

AEs = adverse events; LYs = life years; OS = overall survival; PFS = progression-free survival; QALYs = quality-adjusted life years; SoC = standard of care

[a] The dosing of leucovorin changed from 400 mg/m^2 every 2 weeks in the clinical trial to 50 mg every 2 weeks as per eviQ guidelines

[b] In italics are results revised after correcting the submission's errors in calculation of the treatment costs of SoC therapies and updating the MBS cost for administration of chemotherapy (MBS item 13950). *The PSCR accepted the corrected base case ICER of $* [3].

The redacted values correspond to the following ranges:

[1] *$255,000 to <$355,000/QALY gained*

[2] *$155,000 to <$255,000/QALY gained*

[3] *$55,000 to <$75,000/QALY gained*

6.50 The incremental QALYs increased steadily over the time horizon. In contrast, the incremental costs were high during the first 2 years, corresponding to the maximum treatment duration for pembrolizumab. Thereafter, the difference in cumulative costs between the two treatment arms remained fairly stable until the end of the time horizon. About 97% of the incremental QALYs and 48% of the incremental costs were generated beyond 1 year (i.e. the extrapolation time point for OS).

6.51 The results of the key sensitivity analyses are summarised below.

Table 12: Key sensitivity analyses

Variables and assumptions	Incremental costs	Incremental QALYs	ICER	% change
Base case	**$[redacted]**	**1.154**	**$[redacted]** [1]	**–**
Survival curves (base case: adjustment for SoC crossover using the RPFST (without recensoring) method)				
ITT, no adjustment	$[redacted]	0.869	$[redacted] [2]	+30.0%
IPCW	$[redacted]	1.610	$[redacted] [3]	-25.8%
Two-stage (without recensoring)	$[redacted]	1.521	$[redacted] [4]	-22.0%
Parametric distribution for OS extrapolation (base case: exponential for both arms)				
Weibull for both arms	$[redacted]	1.554	$[redacted] [4]	-23.5%
Gompertz for both arms	$[redacted]	1.809	$[redacted] [3]	-33.0%
Log-logistic for both arms	$[redacted]	1.381	$[redacted] [4]	-15.0%
Lognormal for both arms	$[redacted]	1.305	$[redacted] [4]	-10.5%
Generalised gamma for both arms	$[redacted]	1.413	$[redacted] [4]	-16.7%
Exponential for pembrolizumab and lognormal for SoC [a]	*$[redacted]*	*0.892*	*$[redacted]* [2]	*+26.8%*
Convergence of the survival curves of the two treatment arms (base case: no)				
Pembrolizumab PFS and OS curves converging linearly towards respective SoC curves from Year 3 (i.e. Week 156) to Year 10 [a]	$[redacted]	0.892	$[redacted] [2]	+28.7%
Pembrolizumab PFS and OS curves converging linearly towards respective SoC curves from Year 5 (i.e. Week 260) to Year 10 [a]	$[redacted]	0.933	$[redacted] [1]	+23.3%
Cost of bevacizumab (ex-manufacture price of $303.94 per 100 mg vial and $1,215.75 per 400 mg vial)				
Expected statutory price reduction of 25% [a]	$[redacted]	1.154	$[redacted] [1]	+7.0%
Time horizon (base case: 10 years)				
7.5 years	$[redacted]	0.890	$[redacted] [2]	+26.9%
20 years	$[redacted]	1.661	$[redacted] [3]	-27.6%
Proportion of patients receiving no first-line SoC therapies (base case: 0%)				
7.1% as in KN177 [a]	$[redacted]	1.154	$[redacted] [1]	+2.3%
Proportion of patients receiving subsequent therapy in the SoC arm (base case: 83.2%)				
53.7%, same as the pembrolizumab arm [a, b]	$[redacted]	1.154	$[redacted] [1]	+6.4%
Multivariate analysis[b]				

Parametric distribution for OS extrapolation (base case: exponential for both arms): Exponential for pembrolizumab and lognormal for SoC Proportion of patients receiving no first-line SoC therapies (base case: 0%): 7.1% as in KN177 Proportion of patients receiving subsequent therapy in the SoC arm (base case: 83.2%): 53.7% Health state utility value for PFS (base case: 0.855 for pembrolizumab and 0.815 for SoC): No treatment difference (0.815 for both arms)	$[redacted]	0.777	$[redacted][5]	+57%

Source: Table 3.9-1, pp151-153 of the submission

ICER = incremental cost-effectiveness ratio; IPCW = inverse probability of censoring weighting; ITT = intention-to-treat; OS = overall survival; PFS = progression-free survival; QALYs = quality-adjusted life years; RPSFT = rank-preserving structural failure time; SoC = standard of care

[a] Additional sensitivity analyses performed during the evaluation.

[b] using the model correcting the submission's errors in calculation of the treatment costs of SoC therapies

The redacted values correspond to the following ranges:

[1]$55,000 to <$75,000/QALY gained

[2]$75,000 to <$95,000/QALY gained

[3]$35,000 to <$45,000/QALY gained

[4]$45,000 to <$55,000/QALY gained

[5]$95,000 to < $115,000/QALY gained

6.52 As commented previously, the comparative effectiveness of pembrolizumab relative to SoC, if treatment switching from SoC to pembrolizumab or other PD-1/PD-L1 inhibitors did not occur, was the major economic uncertainty. An ICER of $75,000 to <$95,000/QALY was estimated for a model without crossover adjustment, i.e. using ITT results of OS for SoC in KN177. The evaluation considered this should be interpreted with caution as the costs of subsequent treatment with pembrolizumab and other anti-PD-1/PD-L1 therapies following first-line SoC, were not included in this analysis, and if included would decrease the ICER.

6.53 The submission's assumption of ongoing treatment effect of pembrolizumab has not been well justified. During the evaluation, exploratory analyses were performed to examine the impact of the change in the extrapolation of OS benefits of pembrolizumab on the result of the model. If, for both PFS and OS, the survival curves for pembrolizumab and SoC started to converge from Year 3, i.e. 1 year after the discontinuation of pembrolizumab at its maximum treatment duration, and the complete convergence of the survival estimates of the two treatment arms occurred by the end of 10-year model time horizon, the ICER would increase to $75,000 to <$95,000/QALY. Assuming a later time point for commencement of convergence (i.e. 5 years) resulted in an ICER of $55,000 to <$75,000/QALY.

6.54 Model time horizon was also an important parameter which affected the economic evaluation result. The ICER would increase to $75,000 to <$95,000/QALY for a 7.5-year horizon and decrease to $35,000 to <$45,000/QALY for a 20-year time horizon.

6.55 In the base case, an exponential distribution was chosen to extrapolate OS in both arms, as this parametric function appeared to reasonably fit the trial-based Kaplan-

Meier OS estimates and provided the most conservative estimate of pembrolizumab OS. The ESC considered that use the exponential function to extrapolate OS for pembrolizumab was reasonable. The ESC considered that, given the immaturity of the clinical data, the most conservative estimate of the relative treatment effect of pembrolizumab versus SoC was based on an exponential extrapolation for pembrolizumab and a lognormal extrapolation for SoC.

6.56 Given the shape of the hazard function, the ESC noted that flexible parametric survival models may provide additional and potentially more realistic extrapolation curves (informed by a recent paper comparing standard and flexible parametric models)[9]. The ESC considered that, given the recommendation to consider the ITT and RPSFT ICERs (paragraph 6.41), it may be informative to see the extrapolation curves (including the flexible parametric models) for the ITT analysis and the associated ICERs to inform the selection of the base case ITT analysis.

6.57 In KN177, eleven (7.1%) patients randomised to the SoC group did not receive SoC chemotherapy. The economic model assumed 100% patients in the comparator arm would be treated with active first-line therapy and adjusted the trial-based proportion of patients receiving each SoC regimen and, thus, the treatment costs, without corresponding adjustment for health outcomes. The ESC noted that when it was assumed 7.1% of BSC patient did not receive treatment, consistent with KN177, the ICER increased to $55,000 to <$75,000/QALY.

6.58 In the economic model, the patients who received second-line immunotherapy in the trial were redistributed to receive chemotherapy, with the total proportion of patients on active second-line therapy remaining unchanged from the trial data (53.7% in the pembrolizumab arm and 83.2% in the SoC arm). The ESC noted a majority of the SoC patients who received second-line therapy were treated with immunotherapy. The ESC considered that, in the absence of immunotherapy being available as a second-line treatment, the proportion of SoC patients treated with second-line therapy may be lower. The ESC noted that when it was assumed 53.7% of SoC received second-line treatment the ICER increased to $55,000 to <$75,000/QALY.

6.59 The ESC noted a multivariate analysis applying (i) exponential extrapolation of OS in the pembrolizumab arm (ii) the proportion of SoC patients that received no first line therapy as 7.1% (iii) the proportion of SoC patients receiving subsequent therapy as 53.7% and (iv) no difference in utilities for the PFS health state increased the ICER to $95,000 to < $115,000/QALY gained[10]. The pre-PBAC response accepted the ESC proposed changes (i) to (iii) but did not accept change (iv) (paragraph 6.46). The pre-PBAC noted this resulted in an ICER of $75,000 to <$95,000 per QALY and proposed a

[9] Gray J, Sullivan T, Latimer NR et al. Extrapolation of survival curves using standard parametric models and flexible parametric spline models: comparisons in large registry cohorts with advanced cancer. Medical Decision Making 2021; 41(2), 179-193.

[10] Includes correction to SoC costs

23% reduction in the effective pembrolizumab price (to $[redacted] per 100 mg vial) to reduce the ICER to less than $55,000 to <$75,000 per QALY.

6.60 Other variables, including time point of extrapolation, method of PFS extrapolation, health state utilities, costs for disease monitoring/management, for treatment of AEs and for curative surgery, and discounting rate, did not have major impacts on the estimate for the cost-effectiveness of pembrolizumab versus SoC in the proposed target population.

Drug cost/patient/course

6.61 The per patient drug costs for first-line pembrolizumab (using the price proposed in the submission) and SoC therapies for treatment of dMMR mCRC are presented in the table below. The drug cost for pembrolizumab was estimated to be $[redacted], using the trial-based time-on-treatment (ToT) curve from KN177 (mean: 13.4 months) and a relative dosing intensity of 96.5% (to take into account missing doses). The drug cost for SoC therapies was estimated to be $29,561, based on the modelled time-on-treatment (ToT) curve and a relative dosing intensity of 88.6%.

Table 13: Drug cost per patient for proposed (using the price proposed in the submission) and comparator drugs (undiscounted, published prices for SoC agents)

	Pembrolizumab			SoC		
	Trial dose and duration	**Model**	**Financial estimates**	**Trial dose and duration**	**Model**	**Financial estimates**
Mean dose	200 mg Q3W	200 mg Q3W	200 mg Q3W	mFOLFOX or FOLFORI ± BEV or CET [a]	mFOLFOX or FOLFORI ± BEV or CET [b]	mFOLFOX ± BEV or CET [c]
Mean duration	13.3 months	13.4 months	13.3 months	8.3 months	8.8 months	8.0 months
Cost/patient/month	$[redacted] [d]	$[redacted] [d]	$[redacted] [e]	$3,133 [f]	$3,331 [f]	$4,152 [e]
Cost/patient/ course	$[redacted]	$[redacted]	$[redacted]	$26,077 [g]	$29,561 [h]	$33,227

Source: Table 2.4-3, p36, Table 2.4-3, pp36-37 of the submission; Table 10-6, p54 of the KN177 clinical study report
QW = every week; Q2W = every 2 weeks; Q3W = every 3 weeks; SoC = standard of care

[a] SoC regimens used in the clinical trial:

- mFOLFOX (in 7.1% patients): oxaliplatin: 85 mg/m^2 Q2W + leucovorin 400 mg/m^2 (or levoleucovorin 200mg/m^2) Q2W + 5-FU 400 mg/ m^2 then 5-FU 1200 mg/m^2/day x 2 days Q2W
- mFOLFOX+BEV (in 41.6% patients): mFOLFOX regimen as above + bevacizumab 5 mg/kg Q2W
- mFOLFOX+CET (in 3.2% patients): mFOLFOX regimen as above + cetuximab 400 mg/m^2 up front, followed by 250mg/m^2 QW
- FOLFIRI: irinotecan (in 10.4% patients): 180 mg/m^2 Q2W + leucovorin 400 mg/m^2 (or levoleucovorin 200mg/m^2) Q2W + 5-FU 400 mg/ m^2 then 5-FU 1200 mg/m^2/day x 2 days Q2W
- FOLFIRI+BEV (in 23.4% patients): FOLFIRI regimen as above + bevacizumab 5 mg/kg Q2W
- FOLFIRI+CET (in 7.1% patients): FOLFIRI regimen as above + cetuximab 400 mg/m^2 up front, followed by 250mg/m^2 QW
- No treatment (in 7.1% patients)

[b] SoC regimens in the economic model:

- mFOLFOX (in 9.1% patients): oxaliplatin: 85 mg/m^2 Q2W + leucovorin 50mg Q2W + 5-FU 400 mg/ m^2 then 5-FU 1200 mg/m^2/day x 2 days Q2W
- mFOLFOX+BEV (in 43.5% patients): mFOLFOX regimen as above + bevacizumab 5 mg/kg Q2W
- mFOLFOX+CET (in 3.2% patients): mFOLFOX regimen as above + cetuximab 500 mg/m^2 Q2W (revised according to the eviQ guidelines (https://www.eviq.org.au/medical-oncology/colorectal/metastatic/1756-colorectal-metastatic-folfox6-modified-flu, access 24 November 2020)
- FOLFIRI: irinotecan (in 11.0% patients): 180 mg/m^2 Q2W + leucovorin 50 mg Q2W + 5-FU 400 mg/ m^2 then 5-FU 1200 mg/m^2/day x 2 days Q2W
- FOLFIRI+BEV (in 26.0% patients): FOLFIRI regimen as above + bevacizumab 5 mg/kg Q2W
- FOLFIRI+CET (in 7.1% patients): FOLFIRI regimen as above + cetuximab 400 mg/m^2 up front, followed by 250mg/m^2 QW

[c] SoC regimens in the financial analysis:

- mFOLFOX (in 23.9% patients): oxaliplatin: 85 mg/m^2 Q2W + leucovorin 50mg Q2W + 5-FU 400 mg/ m^2 then 5-FU 1200 mg/m^2/day x 2 days Q2W
- mFOLFOX+BEV (in 57.4% patients): mFOLFOX regimen as above + bevacizumab 5 mg/kg Q2W
- mFOLFOX+CET (in 18.9% patients): mFOLFOX regimen as above + cetuximab 400 mg/m^2 up front, followed by 250mg/m^2 QW

[d] To account for missed doses, a trial-based relative dosing intensity of 96.5% was applied for pembrolizumab.

[e] Relative dosing intensity for pembrolizumab therapy and for SoC therapies was not taken into account in the financial analysis.

[f] After correcting the submission's errors in calculation of the treatment costs of SoC therapies. To account for missed doses, a trial-based relative dosing intensity of 88.6% was applied for SoC therapies.

[g] Including an additional drug cost of $707 for the first cycle of cetuximab, in combination with mFOLFOX or FOLFIRI (a total of 10.4% patients)

[h] Including an additional drug cost of $707 for the first cycle of cetuximab, in combination with FOLFIRI (7.1% patients)

Estimated PBS usage & financial implications

6.62 This submission was not considered by DUSC. The financial analysis took an epidemiological approach to estimate the financial impact of the proposed listing of pembrolizumab as first-line treatment for dMMR mCRC. The key inputs in the financial analysis are summarised in the table below.

Table 14: Key inputs for financial estimates

Data	Value applied	Source and comment
Incident patients	[redacted][1] in Year 2015, to [redacted][1] in Year 2021 (Year 1), to [redacted][1] in Year 2026	AIHW incidence of CRC in 2007 to 2019, extrapolated from linear regression.
Disease stage at diagnosis	24.3% Stage II, 23.6% Stage III, 20% Stage IV	NCCI, previous 2nd-line dMMR CRC submission.
% progressing from Stages II/III to Stage IV after 5 years	27.5%	An Australian population-based analysis (Luo et al 2017) Updated to 18.54% in pre-PBAC response (paragraph 6.66)
% progressing from Stage II/III to IV after 5 years and alive	77.5%	An Australian population-based analysis (Luo et al 2017)
Prevalent patients	[redacted][1] in 2020, to [redacted][1] in 2021, to [redacted][1] in Year 2026	AIHW prevalence of CRC in 2007, 2009, 2012 and 2015, extrapolated from linear regression.
1-year survival rate	49.3%	NCCI. The NCCI reported 1-year survival in 2011 in patients with Stage IV disease at diagnosis regardless of their treatment.
dMMR prevalence	6.9%	TRACC registry.
% with performance status 0-1	89.9%	TRACC registry.
Grandfathered patients	50 in Year 1	Submission's assumption. The submission's assumption that the treatment duration of PBS-subsidised pembrolizumab therapy in the grandfathered patients would be the same as that for the incidence/prevalent patients and the ESC considered this was not appropriate.
Uptake rate	95% in incident patients and 41% in prevalent patients	Assumption. The model calculated a total of 94 prevalent patients. 50 of these were assumed to be accounted for in the grandfather patient numbers. Of the remaining 44 prevalent patients, it was assumed 39 would be treated with pembrolizumab. The PBAC agreed with the ESC that it would be reasonable to assume approximately half of the remaining prevalent

Data	Value applied	Source and comment
		patients would be suitable for first line pembrolizumab. Updated in pre-PBAC response.
Pembrolizumab treatment duration	19.2 x 3-week cycles	Time-on treatment curve from KN177.
Uptake rate of SoC	85% of patients likely to receive pembrolizumab	Assumption, based on previous PBAC consideration on later-line dMMR CRC submission and DUSC mCRC review (2018).
Distribution of SoC therapies	23.9% mFOLFOX 57.4% mFOLFOX+BEV 18.9% mFOLFOX+CET	DUSC mCRC review (2018). The ESC considered that the use of mFOLFOX+BEV would be higher and the use of mFOLFOX + CET would be lower due to the biology of dMMR mCRC. 10% use of mFOLFOX+CET, consistent with KN177, would be a more reasonable estimate. Updated in pre-PBAC response.
Treatment duration of SoC	17.4 x 2-week cycles	KN177. The treatment duration used in the financial analysis was shorter than the modelled treatment duration used in the economic evaluation (19.2 cycles).
IV administration cost: <1 hour 1-6 hours Pump infuser	 $67.10 (MBS item 13915) $101.00 (MBS item 13918) $101.00 (MBS item 13939)	MBS. These chemotherapy administration items have been replaced by the MBS item 13950 ($111.40). Updated in pre-PBAC response

Source: Table compiled during the evaluation, based on information provided in Sections 4.1-4.5, pp154-171 of the submission
AIHW = Australian Institute of Health and Welfare; BEV = bevacizumab; CET = cetuximab; mCRC = metastatic colorectal cancer; dMMR = mismatch repair deficiency; DUSC = Drug Utilisation Sub-Committee; NCCI = National Cancer Control Indicator; TRACC = (Australian) Treatment of Recurrent and Advanced Colorectal Cancer
The redacted values correspond to the following ranges:
[1]10,000 to <20,000

6.63 The predicted use of pembrolizumab and financial implications associated with the proposed listing are summarised in the table below.

Table 15: Estimated use and financial implications (as provided in submission, using published price for cetuximab)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed[a]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of pembrolizumab						
Cost to PBS/RPBS less copayments	$[redacted][3]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Estimated financial implications for FOLFOX, with or without bevacizumab or cetuximab						
Cost to PBS/RPBS less copayments	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]
Net financial implications						
Net cost to PBS/RPBS	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Net cost to MBS	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]
Net cost to PBS/RPBS/MBS	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]

Source: Table 4.2-2, p159, Table 4.2-4, p161, Table 4.3-6, p164, Table 4.4-7, p171, Table 4.5-1, p171, Table 4.6-3, p173 of the submission.
[a] Assuming 19.23 prescriptions per patient per year.
The redacted values correspond to the following ranges:
[1]*<500*
[2]*5,000 to <10,000*
[3]*$40 million to <$50 million*
[4]*$30 million to <$40 million*
[5]*$10 million to <$20 million*
[6]*$20 million to <$30 million*
[7]*net cost saving*

6.64 The submission estimated that the total cost to the PBS/RPBS/MBS of listing pembrolizumab would be $20 million to <$30 million in Year 6, with a total of $100 million to <$200 million in the first 6 years of listing (based on the price proposed in the submission).

6.65 The average treatment duration of pembrolizumab was 57.7 weeks. The submission calculated the number of pembrolizumab prescriptions per year of listing by multiplying the number of patients likely to be treated per year by the number of prescriptions (administrations) per patient per course (i.e. 19.23), by assuming that all pembrolizumab prescriptions would be dispensed in the first treatment year. The PSCR clarified the financial model appropriately accounted for this by converting any treatment beyond one year into an equivalent number of patients that are moved and costed into the second year in addition to the incident patients in that year. The PBAC noted the clarification provided in the PSCR and noted the Department will confirm the financial model is appropriately accounting for the duration of treatment.

6.66 The financial analysis estimated the number of patients progressing from an earlier stage of CRC to Stage IV disease, based on an Australian population-based analysis

(Luo et al 2017)[11]. The weighted 5-year disease progression rate reported in this study (27.5%) was applied to the total incident population of Stage II and Stage III CRC patients who were diagnosed 5 years prior to each of the post listing years of pembrolizumab. The evaluation considered the application of the 5-year disease progression rate across Stages I-III from the study to the estimated incident patients diagnosed with Stages II-III disease in the Australian setting was not appropriate and the use of lower progression rate has underestimated the eligible mCRC population for pembrolizumab. The PSCR addressed this by applying a rate of 37.08% (rather than 27.5%) to the incident Stage II and III CRC patients who were diagnosed in the previous 5 years and provided revised financial estimates accounting for the higher patient numbers. However, the ESC noted that both rates (27.5% applied in the base case, and 37.08% applied in the PSCR) do not account for the reduced risk of progression from Stage II disease to metastatic disease in dMMR patients (which may be up to 50% lower compared to pMMR patients) which may lead to an overestimation of progressing patients[12]. The pre-PBAC response acknowledged the concerns raised by the ESC and reduced the rate applied to 18.54% (50% x 37.08%).

6.67 Prevalent patients and grandfathered patients were considered in the first year of listing. The prevalent population who are eligible for pembrolizumab was determined on the basis of Stage IV dMMR patients who were diagnosed in the previous year and still alive. The AIHW prevalent data as used in the financial analysis relates to the point prevalence as at a specific date, and does not include prevalent patients over the whole calendar year. The ESC considered the submission's assumption of identical treatment duration of pembrolizumab in the grandfathered patients and in the incident/prevalent patients was not reasonable, as the grandfathered patients should have received some cycles of pembrolizumab treatment prior to commencement of PBS-subsidised therapy. The pre-PBAC response stated an appropriate duration of treatment for grandfathered patients would be finalised with the Department of Health upon receipt of a recommendation to list. The PBAC was of the view that in accordance with the average treatment duration, it was likely that a significant part of treatment would have elapsed at time of listing for grandfathered patients, only half the course should be accounted for in the financial estimates.

6.68 The prevalence of dMMR used in the financial analysis was sourced from the Australian TRACC registry[13] (6.9%). The previous submission of pembrolizumab as later-line therapy for treatment of dMMR mCRC assumed a prevalence of 4% based on expert opinion. The PSCR stated that previous estimates of the proportion of dMMR in mCRC varied but was mostly taken from older studies and were not

[11] Luo Q, O'Connell DL, Kahn C, Yu XQ. Colorectal cancer metastatic disease progression in Australia: A population-based analysis. *Cancer epidemiology*. 2017;49:92-100.

[12] Sargent D, Marsoni S, Monges G et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluoroural-based adjuvant therapy in colon caner. J Clin Oncol. 2010 Jul 10; 28(20): 3219–3226.

[13] Wong HJ, J; et al. Impact of mismatch repair deficiency on treatment and outcomes in advanced colorectal cancer. Melbourne, Australia: The Walter and Eliza Hall Institute for Medical Research, 2017.

conducted in Australia. The PSCR stated that over the last decade, testing has become routine, and as a result, it is plausible for the proportion of dMMR patients to increase. Therefore, the sponsor maintains that the 6.9% prevalence of dMMR mCRC from the TRACC registry is the most accurate, objective estimate available. The ESC noted 6.9% was based on Australian registry data and considered it may be reasonable.

6.69 The pre-PBAC response provided revised financials with the following changes:

- Reduced progression rate for Stage II patients to 18.54% (paragraph 6.66);
- Removed the statutory price reduction for bevacizumab (paragraph 6.47);
- Assumed 50% of remaining prevalent patients would be suitable for first line pembrolizumab (Table 14);
- Assumed 10% of mFOLFOX used would be in combination with cetuximab (Table 14);
- Utilised MBS Item 13950 for administration costs (Table 14) and
- Using the revised AEMP ($[redacted] per 100 mg vial).

The financial estimates provided in the pre-PBAC response estimated the total net cost to the PBS/RPBS/MBS of listing pembrolizumab would be $10 million to <$20 million in Year 6, with a total of $100 million to <$200 million in the first 6 years of listing. These estimates have not been evaluated.

6.70 Uncertainty remained regarding the change in the SoC costs to the PBS/RPBS, as the financial analysis did not consider the cost implications relating to the change in use of subsequent SoC therapies as a result of listing of first-line pembrolizumab.

Quality Use of Medicines

6.71 The submission detailed a number of activities relating to the quality use of medicines, including the development of education materials, education programs and a 1800 medical information telephone service to respond to questions from patients, careers and health care professionals about all of their medicines.

Financial Management – Risk Sharing Arrangements

6.72 The submission stated that the sponsor is willing to enter into a Risk-Sharing Arrangement (RSA) with the Commonwealth. For the purpose of the RSA, the sponsor agrees to reimburse the Commonwealth with a proportion of the treatment costs of pembrolizumab, should use exceed the subsidisation cap in that year. Following a positive recommendation, the submission stated that the sponsor is committed to working with the Commonwealth to finalise the specific parameters for inclusion in the RSA including the rebate proportion to be paid.

7 PBAC outcome

7.1 The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital) Authority Required (Telephone) listing of pembrolizumab for the first line treatment of unresectable or metastatic (Stage IV) mismatch repair deficient (dMMR) colorectal cancer (mCRC). The PBAC considered a revision to the time horizon of the economic model was required to account for the uncertain gain in overall survival, and that with the revised model pembrolizumab would be cost effective with an ICER closer to what was presented as the base case in the submission. The PBAC considered a risk share arrangement was required to manage the uncertainty associated with the overall cost to the PBS.

7.2 The PBAC is satisfied that pembrolizumab provides, for some patients, a significant improvement in efficacy over standard of care, represented in the submission by a FOLFOX chemotherapy regimen with or without cetuximab or bevacizumab.

7.3 The PBAC noted the consumer comments received for this submission which highlighted the high clinical need for additional treatments for mCRC that improve survival and qualify of life.

7.4 The submission requested listing in patients with metastatic dMMR CRC. The PBAC noted the TGA indication included patients with unresectable disease and considered there was also a clinical need for additional treatments in these patients. The PBAC considered the clinical data in metastatic patients was also relevant to patients with unresectable disease and it was appropriate to allow PBS- subsidised access for this small group of patients.

7.5 The PBAC noted the submission was based on one open-label, randomised, active-controlled trial (n=307) comparing pembrolizumab 200 mg every 3 weeks to FOLFOX with or without cetuximab or bevacizumab in treatment naïve patients with MSI-H/dMMR mCRC. The PBAC noted the median PFS in the pembrolizumab treatment arm was 16.5 months compared to 8.2 months in the standard care arm [HR 0.60 (95%CI: 0.45, 0.80)]. The PBAC noted that the currently available OS data did not demonstrate a statistically significant OS benefit for pembrolizumab [HR 0.77 (95%CI: 0.54, 1.09)]. The PBAC noted the OS data is immature (eventsin 41% of patients) and median OS had not been reached in the pembrolizumab arm. The PBAC noted the OS results were likely confounded by the substantial cross over from the SoC treatment arm to immunotherapy (approximately 60% of all patients randomised). The PBAC noted the OS rates at the 18 month and 24 month time points numerically favoured pembrolizumab (paragraph 6.11). Overall, the PBAC agreed with the ESC that the PFS benefit observed with pembrolizumab in dMMR mCRC is likely to correlate with an OS benefit (paragraph 6.37), although the magnitude of the benefit is uncertain.

7.6 The PBAC noted the final analysis of OS was expected early in 2021, however considered that more mature clinical data may not reduce the uncertainty with respect to the magniture of benefit due to the extent of cross over. The PBAC noted

ESC considered that of the methods used to adjust for cross-over, the RPFST approach (without recensoring) was most appropriate (paragraph 6.43) and that the likely extent of benefit was greater than predicted by the ITT analysis, although possibly less than predicted by the RPSFT analysis.

7.7 The PBAC considered the claim of superior safety compared to SoC to be reasonable. The PBAC noted the adverse events observed for pembrolizumab were consistent with its established safety profile and no new safety signals were observed.

7.8 The PBAC noted the submission presented a cost-utility analysis to estimate the cost-effectiveness of pembrolizumab with a base case ICER of $55,000 to <$75,000 /QALY. With the revised assumptions provided in the pre-PBAC response the ICER increased to $75,000 to <$95,000/QALY (paragraph 6.59). The PBAC considered that, in addition to the changes outlined in paragraph 6.59, a time horizon of 7.5 years for the economic model was appropriate given the immaturity of the data and the uncertainty introduced through use of the RPSFT analysis (paragraph 6.45). The PBAC noted the ICER with a time horizon of 7.5 years and applying the effective price proposed in the pre-PBAC response (AEMP $[redacted] per 100 mg vial) was $55,000 to <$75,000 per QALY. The PBAC considered pembrolizumab would be cost effective with an ICER closer to what was presented for the base case in the submission.

7.9 The PBAC considered the changes made to the financial estimates in the pre-PBAC response (as outlined in paragraph 6.69) were appropriate. The PBAC considered the treatment duration for the < 500 grandfather patients should be less than 57.7 weeks to account for treatment already received prior to accessing PBS-subsidised treatment, and that it would be reasonable to only account for half the treatment duration for these patients in the financial estimates. The PBAC considered including access for unresectable patients would increase the number of patients to be treated with pembrolizumab by less than 10% and these should be added to the financial estimates.

7.10 The PBAC considered a risk sharing arrangement with expenditure caps based on revised financial estimates (as outlined in paragraph 7.9) would be required to manage overall and uncertain costs to the PBS. The PBAC noted the Sponsor is willing to reimburse the Commonwealth a considerable proportion of the pembrolizumab treatment costs above any expenditure cap and considered a rebate of at least [redacted]% would be required.

7.11 The PBAC considered a grandfather restriction was appropriate to allow the estimated < 500 patients being treated with non-PBS subsidised pembrolizumab to transition to PBS-subsidised treatment. The PBAC recommended that the grandfathering listing could be removed after 12 months.

7.12 The PBAC advised the following changes to the pembrolizumab restriction criteria were appropriate:

- amend all treatment phases (initial, continuing and grandfather) to Authority Required using immediate/real time assessment via telephone/online (paragraph 3.8).
- change the clinical criteria *"The treatment must not exceed a total of 35 cycles or up to 24 months of treatment under this restriction"* in the continuing treatment phase restriction to *"The treatment must not exceed a total of 35 cycles or up to 24 months of treatment in a lifetime for this condition".*
- include administration advice "*No increase in the maximum quantity or number of units may be authorised*" and "*No increase in the maximum number of repeats may be authorised*".

7.13 The PBAC advised flow-on changes were required to the restriction criteria for cetuximab, panitumumab and bevacizumab to allow use after progression on pembrolizumab (paragraphs 3.9 and 6.48).

7.14 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for pembrolizumab:

a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over SoC;
b) The treatment is not expected to address a high and urgent unmet clinical need because other subsidised therapies are available;
c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended.

8 Recommended listing

8.1 Add new listing:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Amount	№.of Rpts	Available brands
PEMBROLIZUMAB				
pembrolizumab injection, 100mg/4ml, 4mL vial	NEW (public) NEW (private)	200mg	6	Keytruda
Restriction Summary [new] / Treatment of Concept: [new]				
	Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospitals code)			
	Prescriber type: ☒Medical Practitioners			
	Restriction Type ☒Authority Required – immediate/real time assessment by Services Australia			
	Episodicity: (blank)			
	Severity: unresectable or metastatic			
	Condition: deficient mismatch repair colorectal cancer			
	Indication: Unresectable or metastatic deficient mismatch repair (dMMR) colorectal cancer			
	Treatment Phase: Initial treatment			
	Clinical criteria:			
	Patient must be untreated for this PBS indication (i.e untreated for each of: (i) unresectable disease, (ii) metastatic disease)			
	AND			
	Clinical criteria:			
	Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for colorectal cancer			
	AND			
	Clinical criteria:			
	Patient must have a WHO performance status of 0 or 1			
	AND			
	Clinical criteria:			
	Patient must have deficient mismatch repair (dMMR) colorectal cancer, as determined by immunohistochemistry test			
	AND			
	Clinical criteria:			
	The treatment must not exceed a total of 7 doses under this restriction			
	Administrative Advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later			
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.			
	Administrative Advice: No increase in the maximum number of repeats may be authorised			
	Administrative Advice Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333			
Restriction Summary [new] / Treatment of Concept: [new]				

	Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospitals code)
	Prescriber type: ☒Medical Practitioners
	Restriction Type ☒Authority Required – immediate/real time assessment by Services Australia
	Indication: Unresectable or metastatic deficient mismatch repair (dMMR) colorectal cancer
	Treatment Phase: Transitioning from non-PBS to PBS subsided treatment – 'Grandfather' treatment
	Clinical criteria:
	Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date]
	AND
	Clinical criteria:
	Patient must not have received prior PBS funded treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for colorectal cancer
	AND
	Clinical criteria:
	Patient must have been untreated for this indication (i.e untreated for each of: (i) unresectable disease, (ii) metastatic disease), prior to initiating treatment with this drug
	AND
	Clinical criteria:
	Patient must have stable or responding disease,
	AND
	Clinical criteria:
	Patient must have a WHO performance status of 0 or 1
	AND
	Clinical criteria:
	Patient must have deficient mismatch repair (dMMR) colorectal cancer, as determined by immunohistochemistry test
	AND
	Clinical criteria:
	The treatment must not exceed a total of 35 cycles or up to 24 months of treatment in a lifetime for this condition
	Prescribing Instructions: 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.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
	Administrative Advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333
Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospitals code)

	Prescriber type: ☒Medical Practitioners
	Restriction Type ☒Authority Required – immediate/real time assessment by Services Australia
	Indication: Unresectable or metastatic deficient mismatch repair (dMMR) colorectal cancer
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must not have progressive disease while receiving PBS-subsidised treatment with this drug for this condition.
	AND
	Clinical criteria:
	The treatment must not exceed a total of 35 cycles or up to 24 months of treatment in a lifetime for this condition
	Administrative Advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333

8.2 Flow on changes to cetuximab, panitumumab and bevacizumab to allow use after pembrolizumab for dMMR CRC patients. Restrictions to be finalised.

These restrictions may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

MSD is pleased that Australian colorectal cancer patients with deficient mismatch repair (dMMR) will be among the first in the world to receive reimbursed access to

Keytruda. For these patients, Keytruda not only improves survival, but also provides significant quality of life advantages over the current standard of care.

We are working with the Department of Health to ensure that listing on the PBS occurs as soon as possible. Importantly, this positive outcome for patients was only possible due to a first-time PBAC recommendation.