

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

1 Purpose of submission

- 1.1 The Category 2 submission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing of pembrolizumab, in combination with lenvatinib (PEM+LEN) for the first-line treatment of advanced (Stage IV) clear cell variant renal cell carcinoma (aRCC) in patients who are classified as intermediate or poor risk according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic criteria.
- 1.2 Lenvatinib is not listed on the PBS for the requested indication. The intervention presented in the submission is the combination of pembrolizumab plus lenvatinib (PEM+LEN).
- 1.3 Listing was requested on the basis of a cost-minimisation approach versus nivolumab in combination with ipilimumab (NIVO+IPI). The key components addressed by the submission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with previously untreated advanced (Stage IV) clear cell variant RCC who are classified as intermediate or poor risk according to the IMDC prognostic criteria.
Intervention	Pembrolizumab 200 mg IV every 3 weeks (7 cycles) plus lenvatinib 20 mg orally once daily followed by pembrolizumab 400 mg IV every 6 weeks ^a plus lenvatinib 20 mg orally once daily until progression.
Comparator	Nivolumab 3 mg/kg IV plus ipilimumab 1 mg/kg IV every 3 weeks for 4 doses followed by nivolumab 480 mg IV fixed dose every 4 weeks until progression.
Outcomes	PFS, OS, ORR and Safety
Clinical claim	Pembrolizumab plus lenvatinib is more effective than nivolumab plus ipilimumab at improving PFS and ORR, has comparable effectiveness in terms of OS, and is different, but comparable, in terms of safety.

Source: Table 1.1-2, p16 of the submission.

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, IV = intravenous, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, RCC = renal cell carcinoma.

^a Pembrolizumab treatment is capped at equivalent to 35 cycles at 200 mg.

2 Background

Registration status

- 2.1 The submission was made under the TGA/PBAC Parallel Process. Although at the time of evaluation for PBAC consideration, no TGA documents were available, the Clinical Evaluation Report was available prior to the ESC meeting. The Delegate's Overview was available for the March 2022 PBAC meeting.

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2.2 The Delegate’s Overview stated that the delegate proposed to approve pembrolizumab for the following indication: KEYTRUDA® (pembrolizumab), in combination with lenvatinib, is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma.

2.3 Pembrolizumab, in combination with lenvatinib, was approved by the FDA on 10 August 2021 for the first-line treatment of adult patients with aRCC.

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

3 Requested listing

3.1 The submission presented separate proposed listings for pembrolizumab and lenvatinib for initial and continuing therapy, and for use in grandfathered patients. The proposed restrictions for grandfathered patients have been excluded for brevity.

Name, Restriction, Manner of administration and form	Max. Qty.	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
PEMBROLIZUMAB 100 mg injection, 1 vial	200 mg	6	\$7,881.87 (private)	KEYTRUDA®
	200 mg	6	\$7,733.78 (public)	Merck Sharp & Dohme
	400 mg	3	\$15,636.43 (private)	(Australia) Pty Ltd
	400 mg	3	\$15,381.28 (public)	

Category/Program:	Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
PBS indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Initial treatment
Restriction:	Authority Streamlined
Clinical criteria:	<p>Patient must have a current prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score of either: (i) 1 to 2 (intermediate risk), (ii) 3 to 6 (poor risk), documented in the patient’s medical records at the time of prescribing.</p> <p>AND</p> <p>The condition must not have previously been treated</p> <p>AND</p> <p>Patient must have a WHO performance status of 2 or less</p> <p>AND</p> <p>The treatment must be in combination with PBS-subsidised lenvatinib for this indication, unless an intolerance to lenvatinib requires a temporary or permanent dose reduction or discontinuation of lenvatinib</p> <p>AND</p> <p>The treatment must not exceed a total of 7 doses under this restriction.</p>
Treatment phase:	Continuing treatment
Episodicity:	3 weekly treatment
Restriction:	Authority Streamlined

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Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not have developed disease progression while being treated with this drug for this condition AND The treatment must be in combination with PBS-subsidised lenvatinib for this indication, unless an intolerance to lenvatinib requires a temporary or permanent dose reduction or discontinuation of lenvatinib The treatment must not exceed a total of 35 cycles of pembrolizumab treatment in a lifetime. Patients with stable or responding disease may continue to receive lenvatinib alone after cessation of pembrolizumab.</p>
Treatment phase:	Continuing treatment
Episodicity:	6 weekly treatment
Restriction:	Authority Streamlined
Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not have developed disease progression while being treated with this drug for this condition AND The treatment must be in combination with PBS-subsidised lenvatinib for this indication, unless an intolerance to lenvatinib requires a temporary or permanent dose reduction or discontinuation of lenvatinib. The treatment must not exceed a total of 18 cycles of pembrolizumab (if using Q6W) or up to a maximum of 24 months treatment in a lifetime (if using a combination of Q3W and Q6W). Patients with stable or responding disease may continue to receive lenvatinib alone after cessation of pembrolizumab.</p>

Name, Restriction, Manner of administration and form	Max. Qty. (packs)	Max. Qty. (packs)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
LENVATINIB 4 mg, 30 capsules 10 mg, 30 capsules	2	60	2	\$6,471.22	LENVIMA ® Eisai Australia Pty Ltd

Category/Program:	General Schedule – Section 85
PBS indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Initial treatment
Restriction:	Authority Streamlined
Clinical criteria:	<p>Patient must have a current prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score of either: (i) 1 to 2 (intermediate risk), (ii) 3 to 6 (poor risk), documented in the patient’s medical records at the time of prescribing. AND The condition must not have previously been treated AND Patient must have a WHO performance status of 2 or less AND The treatment must be in combination with PBS-subsidised pembrolizumab for this indication, unless an intolerance to pembrolizumab requires a temporary or permanent dose reduction or discontinuation of pembrolizumab.</p>
Treatment phase:	Continuing treatment
Restriction:	Authority Streamlined
Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition AND</p>

	Patient must not have developed disease progression while being treated with this drug for this condition AND The treatment is prescribed in combination with PBS subsidised pembrolizumab for this indication, unless the patient has completed the equivalent of 35 Q3W cycles of pembrolizumab or develops an intolerance to pembrolizumab and requires a temporary or permanent discontinuation of pembrolizumab.
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- 3.1 The submission stated that the effective prices of PEM+LEN would need to be calculated based on the results of the cost-minimisation approach using the effective prices of nivolumab and ipilimumab which were not known by the sponsor.
- 3.2 The requested PBS listings of pembrolizumab and lenvatinib restrict use to aRCC patients who are classified as intermediate to poor risk according to the IMDC criteria. This is narrower than the proposed TGA indication, which allows use in all patients with aRCC. The ESC considered there would be a small risk of leakage to the favourable risk group.
- 3.3 The proposed wording of the requested restrictions is broader than the inclusion criteria for the KN 581 trial in that the restriction allows use in patients with a WHO performance status of 2 or less, while the trial required patients to have a WHO performance status of 1 or less. However, the ESC noted this was consistent with the existing listing for NIVO+IPI and the March 2021 recommendation for avelumab in combination with axitinib (AVE+AXI) and considered it was reasonable.
- 3.4 Overall, the proposed restrictions for PEM+LEN were consistent with the existing PBS listings for NIVO+IPI and the March 2021 recommendation for AVE+AXI.

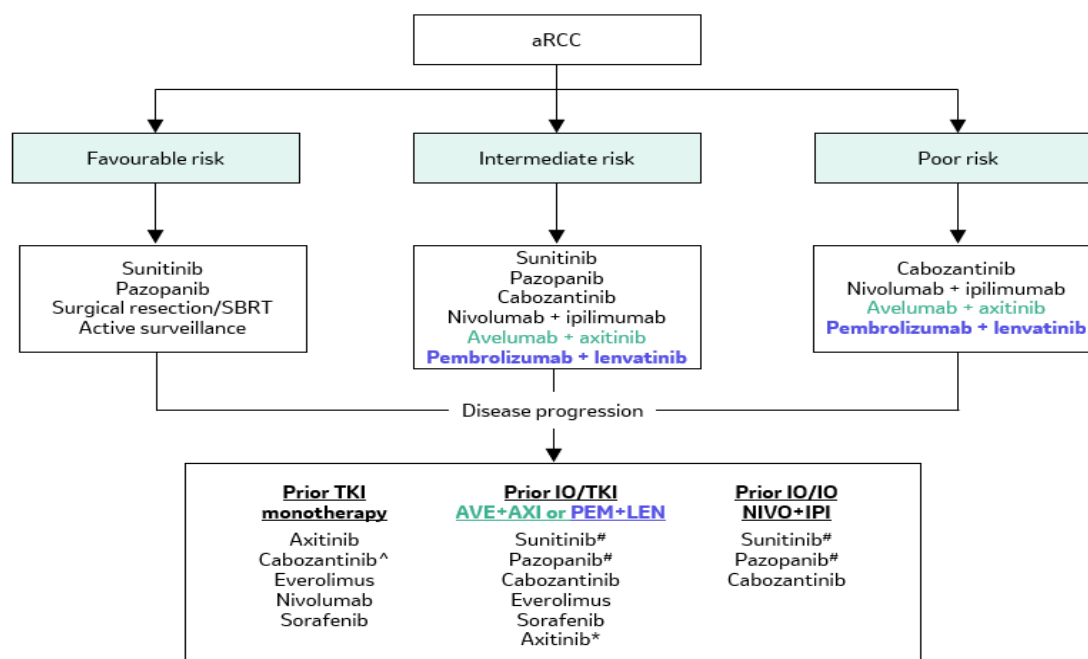
For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Approximately, 90% of kidney cancers are RCC, and the most common histological subtype is the clear cell variant which accounts for 70-80% of RCC cases. Since more than 50% of patients with RCC are asymptomatic, diagnosis often occurs incidentally and approximately 25-30% of newly diagnosed RCC are advanced (Stage IV). An additional 25% of patients initially diagnosed at an early stage will relapse and require treatment in the advanced setting.
- 4.2 Pembrolizumab is an anti-PD-1 humanised monoclonal antibody (mAb) that releases the natural break on the immune system by blocking the interaction between the PD-1 receptor expressed on T cells and its 2 ligands, PD-L1 and PD-L2. Lenvatinib is a multiple-receptor tyrosine kinase (RTK) inhibitor that selectively inhibits VEGF receptors in addition to other proangiogenic and oncogenic pathway-related RTKs.
- 4.3 The submission proposed PEM+LEN as a first-line treatment option for patients with intermediate or poor risk aRCC. The submission's proposed place in therapy for

PEM+LEN in aRCC is presented in Figure 1. The ESC considered that the proposed place in therapy was reasonable.

Figure 1: Proposed clinical management algorithms for patients with aRCC



Source: Figure 1.2-2, p24 of the submission.

aRCC = advanced renal cell carcinoma, AVI+AXE = avelumab + axitinib, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, IO = immune-oncology, NIVO+IPI = nivolumab + ipilimumab, PEM+LEN = pembrolizumab + lenvatinib, SBRT = stereotactic body radiotherapy, TKI = Tyrosine kinase inhibitor.

Note: Risk is defined as per the IMDC criteria.

Note: Green text indicates a near market comparator.

[^] Only if cabozantinib has not been used in the first-line setting.

[#] Only for patients classified as intermediate risk according to the IMDC criteria.

^{*} Only if PEM+LEN has been used in the first-line setting.

4.4 Current clinical practice guidelines from the European Association of Urology, the European Society for Medical Oncology and the National Comprehensive Cancer Network recommend immunotherapy (IO)/tyrosine kinase inhibitor (TKI) combinations including PEM+LEN, pembrolizumab in combination with axitinib (PEM+AXI), and nivolumab in combination with cabozantinib (CaboNivo) as preferred options in all risk groups (i.e., favourable, intermediate and poor risk). Therefore, there is a small risk of use of PEM+LEN outside the proposed restriction in the favourable risk group. There is also a risk that pembrolizumab will be used with TKIs other than lenvatinib (e.g., axitinib) if listed in this indication.

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

5 Comparator

- 5.1 The submission nominated NIVO+IPI as the main comparator. The main argument provided in support of this nomination was that NIVO+IPI is the only immunotherapy containing regimen currently listed on the PBS for this indication. The ESC considered that the nomination of NIVO+IPI as the main comparator was reasonable as AVE+AXI, which like PEM+LEN is an IO/TKI combination therapy, was not yet listed on the PBS.
- 5.2 The submission identified the combination of AVE+AXI and CaboNivo as near market comparators. AVE+AXI was recommended at the March 2021 PBAC meeting but was not PBS listed at the time of evaluation. CaboNivo has not previously been considered by the PBAC.
- 5.3 The submission did not consider PEM+AXI to be a near market comparator. The submission stated that it was not able to submit PEM+AXI for reimbursement in Australia “due to challenges of intercompany working and a lack of a formal alliance with the sponsor of axitinib”.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item and presented a clinician statement outlining that, in the clinician’s expert view, approximately 75% of Australian patients with intermediate or poor risk metastatic RCC would receive NIVO+IPI and 25% would be treated with VEGF TKI monotherapy. The clinician stated that TKI monotherapy would be used for patients who have a contraindication to immunotherapy or in those where the potential toxicity of NIVO+IPI was perceived as too great. The clinician estimated that approximately 50% of the TKI monotherapy population would be offered PEM+LEN if it was available on the PBS as the incidence of fatal toxicity and severe immune related toxicity (hepatitis, colitis) are lower with PEM+LEN than with NIVO+IPI.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (2) and an organisation (1) via the Consumer Comments facility on the PBS website. One of the health professionals described the difficulties associated with the NIVO+IPI regimen including adverse events and the uncertainties in identifying whether patients are responding to treatment. The comment described the need for alternate therapies and stated that the more predictable response to PEM+LEN early in treatment makes it easier for clinicians to determine whether a patient is benefiting. The other health professional also described the more predictable response to PEM+LEN compared to NIVO+IPI. The PBAC noted that this advice received was supportive of the evidence

provided in the submission.

- 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 “high priority for PBS listing” on the basis of the KN 581 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for PEM+LEN, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹, based on a comparison with sunitinib.

Clinical trials

- 6.4 The submission stated that there were no direct head-to-head trials of PEM+LEN compared with NIVO+IPI for the first-line treatment of patients with aRCC. Therefore, the submission presented an indirect treatment comparison (ITC), using the Bucher method, of PEM+LEN and NIVO+IPI with sunitinib as the common reference based on two randomised controlled trials (RCTs): KEYNOTE 581 (KN 581) which compared PEM+LEN with sunitinib, and CheckMate 214 (CM 214) which compared NIVO+IPI with sunitinib in previously untreated aRCC.
- 6.5 Details of the trials presented in the submission are provided in the Table 2.

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

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Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
KN 581	<p>A Multicentre, Open-label, Randomised, Phase III Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Renal Cell Carcinoma (CLEAR).</p> <p>Motzer R, Alekseev B, Rha S et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma.</p> <p>Motzer R, Porta C, Eto M et al. Phase 3 trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) or everolimus (EVE) versus sunitinib (SUN) monotherapy as a first-line treatment for patients with advanced renal cell carcinoma (RCC) (CLEAR study).</p>	<p>Aug 2020</p> <p><i>New England Journal of Medicine</i> 2021; 384(14):1289-1300.</p> <p><i>Journal of Clinical Oncology</i> 2021; 39(6_suppl): 269-269</p>
CM 214	<p>Motzer R, Tannir N, McDermott D et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma.</p> <p>Motzer R, Rini B, McDermott D et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial.</p> <p>Albiges L, Tannir N, Burotto M et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial.</p> <p>Wan X, Zhang Y, Tan C et al. First-line Nivolumab Plus Ipilimumab vs Sunitinib for Metastatic Renal Cell Carcinoma.</p> <p>Cakar E, May J, Malcolm B et al. PCN421 STABILITY OF LIFETIME OVERALL SURVIVAL ESTIMATES OF NIVOLUMAB+IPILIMUMAB IN FIRST-LINE ADVANCED/METASTATIC INTERMEDIATE- OR POOR-RISK RENAL CELL CARCINOMA.</p> <p>Cella D, Escudier B, Ivanescu C. et al. Quality of life in previously untreated patients with advanced renal cell carcinoma (aRCC) in CheckMate 214: Updated results.</p> <p>Cella D, Escudier B, Saggi S et al. 714P Time to deterioration in quality of life in previously untreated patients with advanced renal cell carcinoma (aRCC) in CheckMate 214.</p> <p>Cella, D, Choueiri T, Blum S et al. Patient-reported outcomes of patients with advanced renal cell carcinoma (aRCC) treated with first-line nivolumab plus cabozantinib versus sunitinib: The CheckMate 9ER trial.</p> <p>Escudier B, Tannir N, McDermott D et al. CheckMate 214: Efficacy and safety of nivolumab + ipilimumab (N+I) v sunitinib (S) for treatment-naïve advanced or metastatic renal cell carcinoma (mRCC), including IMDC risk and PD-L1 expression subgroups.</p> <p>Escudier B, Motzer R, Tannir N et al. Efficacy of Nivolumab plus Ipilimumab According to Number of IMDC Risk Factors in CheckMate 214.</p> <p>Grünwald V, Choueiri T, Rini B et al. Association between depth of response and overall survival: Exploratory analysis in patients with previously untreated advanced renal cell carcinoma (aRCC) in CheckMate 214.</p> <p>McDermott D, Rini B, Motzer R et al. Treatment-free interval (TFI) following discontinuation of first-line nivolumab plus ipilimumab (N+I) or sunitinib (S) in patients (Pts) with advanced renal cell carcinoma (aRCC): CheckMate 214 analysis.</p>	<p><i>New England Journal of Medicine</i> 2018; 378(14): 1277-1290</p> <p><i>The Lancet Oncology</i> 2019; 20(10): 1370-1385.</p> <p><i>ESMO Open</i> 2020; 5(6): p.e001079.</p> <p><i>JAMA Oncology</i> 2019; 5(4): p.491.</p> <p><i>Value in Health</i> 2019; 22: S517-S518.</p> <p><i>Annals of Oncology</i> 2019; 30: v383-v384.</p> <p><i>Annals of Oncology</i> 2020; 31: S562.</p> <p><i>Journal of Clinical Oncology</i> 2021; 39(6_suppl): 285-285.</p> <p><i>Annals of Oncology</i> 2017; 28:v621-v622.</p> <p><i>European Urology</i> 2020; 77(4): 449-453.</p> <p><i>Annals of Oncology</i> 2019; 30: v382-v383.</p> <p><i>Annals of Oncology</i> 2018; 29: viii309.</p>

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Trial ID	Protocol title/ Publication title	Publication citation
	Rini B, Tannir N, Escudier B et al. Characterization of response to nivolumab plus ipilimumab (N+I) or sunitinib (S) in patients (Pts) with previously untreated advanced renal cell carcinoma (arcc): Checkmate 214.	<i>Annals of Oncology</i> 2018; 29: viii309-viii310.
	Tannir N, Hammers H, Amin A et al. Characterization of the benefit-risk profile of nivolumab + ipilimumab (N+I) v sunitinib (S) for treatment-naïve advanced renal cell carcinoma (arCC; CheckMate 214).	<i>Journal of Clinical Oncology</i> 2018; 36(6_suppl): 686-686.
	Tannir N, McDermott D, Escudier B et al. Overall survival and independent review of response in CheckMate 214 with 42-month follow-up: First-line nivolumab + ipilimumab (N+I) versus sunitinib (S) in patients (pts) with advanced renal cell carcinoma (arCC).	<i>Journal of Clinical Oncology</i> 2020; 38(6_suppl): 609-609.

Source: Table 2.2-1, pp47-49 of the submission.

6.6 The key features of the KN 581 and CM 214 trials are summarised in Table 3.

Table 3: Key features of the included evidence - indirect comparison

Trial	N	Design/duration	Risk of bias	Patient population	Outcome(s)
PEM+LEN vs. sunitinib					
KN 581	712	R, MC, MN, OL 26 months ^a	Low	Previously untreated patients with aRCC	OS, PFS, ORR
NIVO+IPI vs. sunitinib					
CM 214 ^b	1,096	R, MC, MN, OL 25.2 months ^c	Moderate to high ^d	Previously untreated patients with aRCC	OS, PFS, ORR

Source: Table 2.3-3, pp55-56, Table 2.3-4, p5, Table 2.4-5, pp67-68, and Table 2.6-16, p112 of the submission.

aRCC = advanced renal cell carcinoma, AVE+AXI = avelumab + axitinib, MC = multi-centre, MN = multi-national, NIVO+IPI = nivolumab + ipilimumab, OL = open label, ORR = objective response rate, OS = overall survival, PEM+LEN = pembrolizumab + lenvatinib, PFS = progression-free survival, R = randomised

^a Data cut-off: 28 August 2020

^b The results of CM 214 have previously been considered by the PBAC in the July 2018 consideration of NIVO+IPI and March 2020 consideration of AVE+AXI for the first-line treatment of patients with intermediate to poor risk aRCC.

^c Data cut-off: 7 August 2017

^d The PBAC has previously considered that the overall risk of bias in CheckMate 214 was high for PFS due to patients being able to receive subsequent treatment prior to progression; and moderate to unclear for OS (Table 3, NIVO+IPI PSD, July 2018).

6.7 The full analysis set (FAS) of KN 581 and the intention to treat (ITT) population of CM 214 included patients regardless of IMDC prognostic risk. Given the requested PBS population was for patients with intermediate or poor prognostic risk, the submission presented a post-hoc analysis of KN 581 by IMDC prognostic risk to conduct the ITC and inform the economic analysis. The ESC noted that the PSCR provided baseline characteristics for the intermediate or poor prognostic risk subgroup and its complement and that the subgroups were similar to the ITT population.

6.8 For KN 581, results were based on the Interim Analysis 3 (IA3) in the Clinical Study Report (data cut off: 28 August 2020). An Overall Survival Update (OSU; data cut off: 31 March 2021) was also presented in the submission for KN 581.

6.9 For CM 214, results were based on one interim analysis (data cut-off: 7 August 2017). The extended follow-up data for NIVO+IPI for CM 214 was based on publications by Motzer et al., 2019 (data cut off: 6 August 2018) and Albiges et al., 2020 (data cut off: 25 February 2020). The results from the extended follow-up for NIVO+IPI may not be

comparable with the KN 581 IA3 results due to protocol amendments to CM 214 that allowed patients in the sunitinib arm to cross over to NIVO+IPI pre-progression. Patients were eligible to cross-over from the sunitinib arm to the NIVO+IPI arm if they were of intermediate or poor risk prior to initial randomisation, and patients were not required to have progressed to cross-over (Motzer et al, 2019, Supplement). Cross over from sunitinib to PEM+LEN was not permitted in KN 581 protocol.

- 6.10 The ESC noted that the eligibility criteria were largely similar for KN 581 and CM 214. However, there were key differences between the trials that may affect transitivity:
- CM 214 had a higher proportion of poor risk patients according to IMDC when compared to KN 581 (16% compared with 11%). This may favour NIVO+IPI since subgroup analyses in CM 214 and KN 581 showed that patients with poor risk have improved OS (CM 214) and PFS (KN 581) compared to the overall study population.
 - CM 214 had a lower proportion of patients with a PD-L1 score of > 1% compared with KN 581 (22% compared with 32%). The direction of bias is unclear. Subgroup analyses in KN 581 showed no impact for PD-L1 status on PFS; however, subgroup analyses in CM 214 showed that median PFS was longer with NIVO+IPI among patients with 1% or greater PD-L1 compared with patients with less than 1% PD-L1 expression (22.8 months compared with 11 months).
 - CM 214 had a lower proportion of patients with > 2 metastatic disease sites (68% compared with 78%). The direction of bias is unclear. Subgroup analyses in KN 581 showed improved PFS in patients with > 2 metastatic disease sites compared to the overall study population, but no subgroup analyses of this factor were reported in CM 214.
- 6.11 The impact of these differences on the comparative effectiveness of the two combinations was not presented in the submission.

Comparative effectiveness

Overall Survival

- 6.12 A summary of primary OS results across KN 581 (median follow-up of 26 months) and CM 214 (median follow-up of 25.2 months) is provided in Table 4.

Table 4: Results of overall survival across KN 581 and CM 214

	KN 581 ^a				CM 214 ^b			
	FAS		Intermediate/poor		ITT		Intermediate/poor	
	PEM+LEN N = 355	Sunitinib N = 357	PEM+LEN N = 243	Sunitinib N = 229	NIVO+IPI N = 550	Sunitinib N = 546	NIVO+IPI N = 425	Sunitinib N = 422
Events, n (%)	80 (22.5)	101 (28.3)	66 (27.2)	85 (37.1)	161 ^c (29.3)	204 ^c (37.4)	140 (32.9)	188 (44.5)
Median, months (95% CI)	NE (33.6, NE)	NE (NE, NE)	NR (32.4, NE)	NR (30.7, NE)	NE	32.9	NE (28.2, NE)	26.0 (22.1, NE)
HR (95% CI)	0.66 (0.49, 0.88)		0.58 (0.42, 0.80)		0.68^d (0.49, 0.95)		0.63^d (0.44, 0.89)	
p-value	0.005		<0.001		< 0.001		< 0.001	

Source: Table 2.6-1, p89, Table 2.6-2, p91, Table 2.6-7, p97 of the submission; Table 5 p14 NIVO+IPI PSD; Table 14.2.2.2.2.1.2, p591, Figure 6, p109 of KN 581 CSR.

CI = confidence interval, FAS = full analysis set, HR = hazard ratio, IA3 = interim analysis 3, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, ITT = intention to treat, NE = not estimable, NIVO+IPI = nivolumab + ipilimumab, NR = not reported, PEM+LEN = pembrolizumab + lenvatinib

^a Data cut off for IA3 was 28 August 2020

^b Data cut off was 7 August 2017

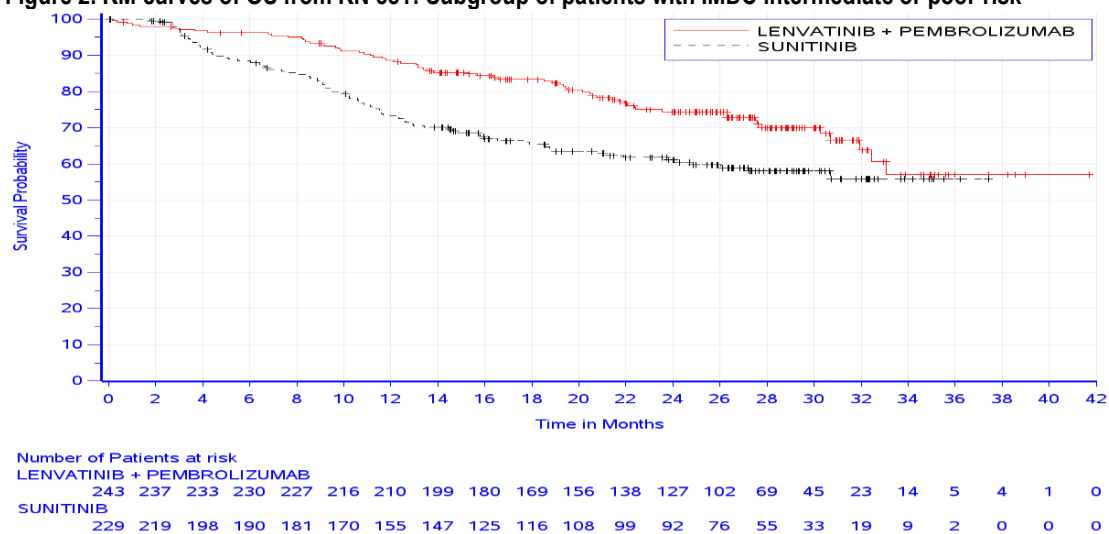
^c The submission obtained the calculation by adding the number of patient deaths in the favourable and the intermediate to poor IMDC risk groups.

^d CheckMate 214 presented the HR 99.8% CI at primary analysis.

Bold indicates statistical significance.

6.13 The Kaplan Meier curves for OS in KN 581 and CM 214 are presented in Figure 2 and Figure 3, respectively.

Figure 2. KM curves of OS from KN 581: Subgroup of patients with IMDC intermediate or poor risk

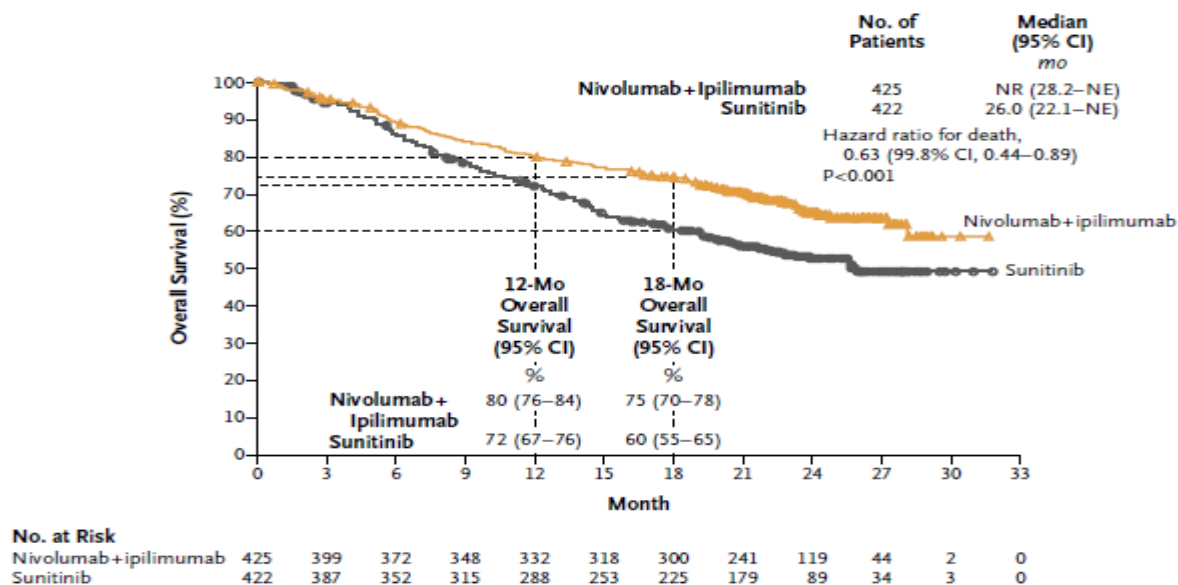


Source: Figure 2.6-1, p90 of the submission.

Data cut-off date: 28 August 2020

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, KM = Kaplan Meier, OS = overall survival

Figure 3. KM curves of OS from CM 214: Subgroup of patients with IMDC intermediate or poor risk



Source: Figure 2.6-3, p92 of the submission.

Data cut-off date: 7 August 2017

CI = confidence interval, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, KM = Kaplan Meier, mo = months, NE = not estimable, NR = not reported, OS = overall survival

- 6.14 In intermediate to poor risk patients, PEM+LEN was associated with a statistically significant improvement in OS compared with sunitinib; however, the median OS had not been reached in either of the treatment arms at IA3 (median follow-up of 26 months). At similar durations of follow-up (median follow-up of 25.2 months), NIVO+IPI was associated with a statistically significant improvement in OS compared with sunitinib; however, median OS had not been reached in the NIVO+IPI arm. The ESC noted that the OS data for both the trials, but particularly KN 581, were immature at the time of the data-cut off and may not accurately reflect the long-term survival benefits. The comparison of extended data may be confounded by the differences in subsequent therapies.
- 6.15 At the OSU data cut-off (31 March 2021) for patients with intermediate to poor risk in KN 581, the median OS was 43.0 months in PEM+LEN arm compared with 34.5 months in the sunitinib arm, with a HR of 0.62 (95% CI: 0.46, 0.83).
- 6.16 Updated data from an extended four-year follow-up of CM 214 showed that OS remained superior in the NIVO+IPI arm when compared to sunitinib, with an HR of 0.65 (95% CI: 0.54, 0.78) in intermediate to poor risk patients. Median OS was 48.1 months in the NIVO+IPI arm and 26.6 months in the sunitinib arm.
- 6.17 Notably, in the extended follow-up, the median OS for patients in the sunitinib arm was longer in KN 581 than CM 214 (34.5 months compared with 26.6 months), which may indicate that patients randomised to the sunitinib arm in KN 581 had a better

prognosis for survival than those in CM 214. This could be also a result of the different subsequent anticancer treatments used.

Progression-Free Survival

6.18 A summary of the primary PFS results across KN 581 (median follow-up of 26 months) and CM 214 (median follow-up of 25.2 months) is provided in Table 5.

Table 5: Results of progression free survival across KN 581 and CM 214

	KN 581 ^a				CM 214 ^b			
	FAS		Intermediate/poor		ITT		Intermediate/poor	
	PEM+LEN N = 355	Sunitinib N = 357	PEM+LEN N = 243	Sunitinib N = 229	NIVO+IPI N = 550	Sunitinib N = 546	NIVO+IPI N = 425	Sunitinib N = 422
Events, n (%)	160 (45.1)	205 (57.4)	115 (47.3)	136 (59.4)	296 (53.8)	271 (49.6)	219 (52)	225 (53)
Median, months (95% CI)	23.9 (20.8,27.7)	9.2 (6.0, 11.0)	22.1 (16.6,27.6)	5.9 (5.6, 7.5)	12.4 (9.9, 16.5)	12.3 (9.8, 15.2)	11.6 (8.7, 15.5)	8.4 (7.0, 10.8)
Difference, months	14.7		16.2		0.1		3.2	
HR (95% CI)	0.39 (0.32, 0.49)		0.36 (0.28, 0.47)		0.98 ^c (0.79, 1.23)		0.82 ^c (0.64, 1.05)	
p-value	<0.0001		<0.001		0.85		0.03	

Source: Table 2.6-3, p93, Table 2.6-7, p97 of the submission; Table 5, p14 of NIVO+IPI PSD; Table 14.2.1.3.3.2, p550, Figure 6, p109 of CSR.

CI = confidence interval, FAS = full analysis set, HR = hazard ratio, IA3 = interim analysis 3, ITT = intention to treat, NIVO+IPI = nivolumab + ipilimumab, PEM+LEN = pembrolizumab + lenvatinib

^a Data cut off for IA3 was 28 August 2020

^b Data cut off was 7 August 2017

^c CheckMate 214 presented the HR of 99.1% CI at primary analysis; pre-specified threshold of p=0.009.

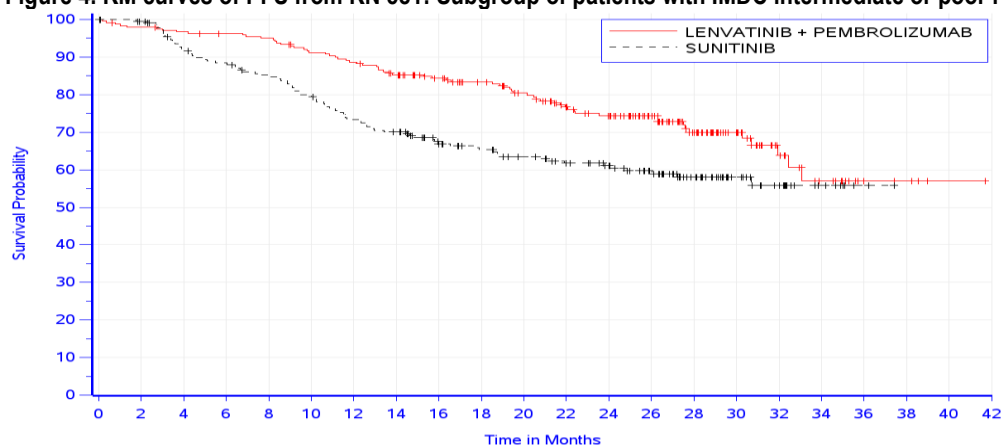
Bold indicates statistical significance.

6.19 In intermediate to poor risk patients, PEM+LEN was associated with a statistically significant improvement in PFS compared to sunitinib with an absolute difference of 16.2 months in median PFS, demonstrating a 64% reduction in the risk of disease progression or death compared with sunitinib. In CM 214, NIVO+IPI demonstrated an improvement in PFS compared with sunitinib among patients with intermediate to poor risk; however, the difference (3.2 months) did not reach statistical significance.

6.20 The median PFS in the sunitinib arm of KN 581 was shorter than the sunitinib arm of CM 214 (5.9 months compared with 8.4 months), which may indicate that patients in CM 214 had a better prognosis for a response to sunitinib than those in KN 581. The submission stated that this difference might relate to the ability of the patients in CM 214 to receive subsequent anticancer therapy before progression; however, the proportion of patients this affected was not reported in the submission or publications for CM 214. In the July 2018 consideration of NIVO+IPI, the PBAC and ESC considered that the ability to receive subsequent treatment prior to progression resulted in a “high risk of bias for the PFS results” (paragraph 6.12, NIVO+IPI, public summary document (PSD), July 2018).

6.21 The Kaplan Meier curves for PFS in KN 581 and CM 214 are presented in Figure 4 and Figure 5, respectively.

Figure 4. KM curves of PFS from KN 581: Subgroup of patients with IMDC intermediate or poor risk



Number of Patients at risk

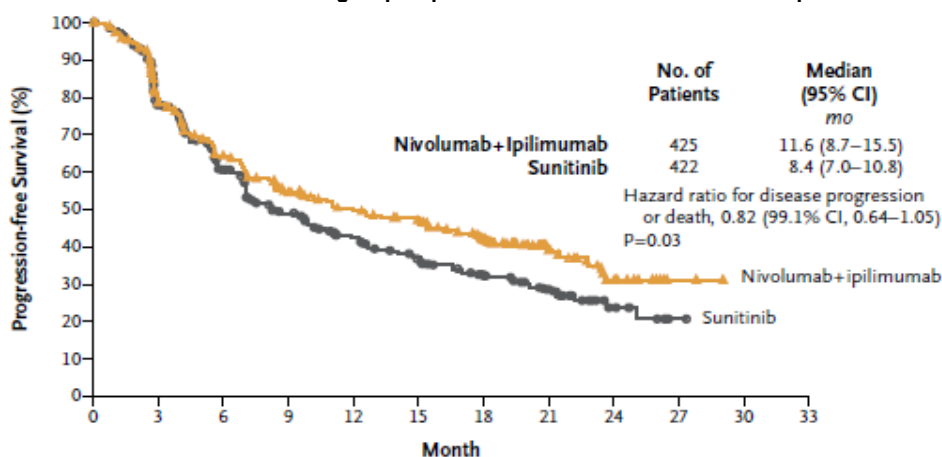
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42
LENVATINIB + PEMBROLIZUMAB	243	237	233	230	227	216	210	199	180	169	156	138	127	102	69	45	23	14	5	4	1	0
SUNITINIB	229	219	198	190	181	170	155	147	125	116	108	99	92	76	55	33	19	9	2	0	0	0

Source: Figure 2.6-4, p93 of the submission.

Data cut-off date: 28 August 2020

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, KM = Kaplan Meier, PFS = progression free survival

Figure 5. KM curves of PFS from CM 214: Subgroup of patients with IMDC intermediate or poor risk



No. at Risk

Time (Months)	0	3	6	9	12	15	18	21	24	27	30	33
Nivolumab+ipilimumab	425	304	233	187	163	149	118	46	17	3	0	0
Sunitinib	422	282	191	139	107	86	57	33	11	1	0	0

Source: Figure 2.6-5, p95 of the submission.

Data cut-off date: 7 August 2017

CI = confidence interval, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, KM = Kaplan Meier, mo = months, NE = not estimable, NR = not reported, PFS = progression free survival

6.22 In the extended four-year follow-up of CM 214, PFS outcomes favoured NIVO+IPI and remained consistent with the previous results for both ITT population (HR 0.89; 95% CI 0.76, 1.05) and intermediate to poor risk patients (HR 0.74; 95% CI 0.62, 0.88).

Objective Response Rate

6.23 A summary of the ORR results across KN 581 and CM 214 is provided in Table 6.

Table 6. Results of objective response rate across KN 581 and CM 214

	KN 581 ^a				CM 214 ^b			
	FAS		Intermediate/poor		ITT		Intermediate/poor	
	PEM+LEN N = 355	SUN N = 357	PEM+LEN N = 243	SUN N = 229	NIVO+IPI N = 550	SUN N = 546	NIVO+IPI N = 425	SUN N = 422
ORR, n (%)	252 (71.0)	129 (36.1)	176 (72.4)	66 (28.8)	215 (39.1)	175 (32.1)	177 (41.6)	112 (26.5)
p-value	NR		NR		0.02		NR	
% difference (95% CI)	34.9 (27.4, 42.4)		43.6 (35.5, 51.7)		7.0 (1.4, 12.7)		15.1 (8.8, 21.4)	

Source: Table 2.6-5 p96 of the submission; Table 5, p14 NIVO+IPI PSD; Table 14.2.2.1.4 p581 of CSR.

CI = confidence interval, FAS = full analysis set, IA3 = interim analysis 3, ITT = intention to treat, NIVO+IPI = nivolumab + ipilimumab, NR = not reported, ORR = objective response rate, PEM+LEN = pembrolizumab + lenvatinib

^a Data cut off for IA3 was 28 August 2020

^b Data cut off was 7 August 2017

6.24 In KN 581, the ORR was higher in the PEM+LEN arm compared with the sunitinib arm in both ITT and intermediate/poor risk patients. In CM 214, the ORR was higher in the NIVO+IPI arm compared with sunitinib in both ITT and intermediate/poor risk patients.

Patient-reported outcomes

6.25 The submission presented FKSI-DRS, EORTC QLQ-30, and EQ-5D-3L to estimate health-related quality of life for PEM+LEN compared with sunitinib in the intention to treat population (not in intermediate to poor risk).

6.26 Although not statistically significant, the least mean squares for FKSI-DRS, EORTC QLQ-30, and EQ-5D-3L were slightly higher in the PEM+LEN arm when compared to the sunitinib arm in KN 581 trial. The submission stated that the timing of HRQoL assessment for participants in the sunitinib arm may have biased the analysis in favour of sunitinib given that they coincided with the end of the sunitinib two-week off treatment period. This may not be reasonable as adverse events may happen anytime during treatments and not necessarily at the time of drug administration.

6.27 In the intermediate to poor risk group in CM 214, the mean change in FKSI-19 from baseline was greater in the NIVO+IPI group than in the sunitinib group at each assessment during the first 6 months of the trial.

Indirect Treatment Comparison

6.28 The results of the main ITC are summarised in Table 7.

Table 7: Results of OS and PFS indirect comparison of PEM+LEN and NIVO+IPI for IMDC risk intermediate or poor subgroups

Trial	Outcome	PEM+LEN	Sunitinib	Absolute difference	HR (95% CI)
KN 581 IA3 ^a	OS event, n/N (%)	66/243 (27.2%)	85/229 (37.1%)	-	-
	Median OS, months (95% CI)	NR (32.4, NE)	NR (30.7, NE)	NE	0.58 (0.42, 0.80)
	PFS event, n/N (%)	115/243 (47.3%)	136/299 (59.4%)		
	Median PFS, months (95% CI)	22.1 (16.6, 27.6)	5.9 (5.6, 7.5)	16.2	0.36 (0.28, 0.47)
		NIVO+IPI			
CheckMate 214 ^b	OS event, n/N (%)	141/425 (33.2%)	187/422 (44.3%)	-	-
	Median OS, months (95% CI)	NR (28.2, NE)	26.0 (22.1, NE)	NE	0.63 (0.44, 0.90)
	PFS event, n/N (%)	219/425 (51.5%)	225/422 (53.3%)	-	
	Median PFS, months (95% CI)	11.6 (8.7, 15.5)	8.4 (7.0, 10.8)	3.2	0.82 (0.64, 1.05)
PEM+LEN versus NIVO+IPI for OS					0.92 (0.62, 1.36)
PEM+LEN versus NIVO+IPI for PFS					0.44 (0.32; 0.61)

Source: Table 2.6-13, p105, Table 2.6-14, p109 of the submission.

CI = confidence interval, FAS = full analysis set, HR = hazard ratio, IA3 = interim analysis 3, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, ITT = intention to treat, NE = not estimable, NIVO+IPI = nivolumab + ipilimumab, NR = not reported, OS = overall survival, PEM+LEN = pembrolizumab + lenvatinib, PFS = progression free survival

^a Data cut off for IA3 was 28 August 2020

^b Data cut off was 7 August 2017

Bold indicates statistically significant results.

- 6.29 The indirect comparison showed no statistically significant difference in OS between PEM+LEN and NIVO+IPI (HR = 0.92; 95% CI: 0.62, 1.36). The submission did not provide a non-inferiority margin. The PSCR noted that AVE+AXI was recommended despite the submission not specifying a non-inferiority margin. The ITC showed that PEM+LEN was associated with a statistically significant improvement in PFS compared with NIVO+IPI (HR = 0.44; 95% CI: 0.32, 0.61). The evaluation considered that the results of the indirect comparison may not be reliable due to the transitivity issues resulting from the differences between the two trials.
- 6.30 The submission presented a matching-adjusted indirect comparison (MAIC) to adjust for differences in baseline characteristics between trials. Individual participants from the trial with available individual patient-level data (KN 581) were re-weighted to match the mean baseline characteristics reported for the trial with only aggregate data (CM 214). The MAIC was anchored using sunitinib as a common comparator, which was reasonable.
- 6.31 The common effect modifiers identified by the submission were age, bone metastasis and liver metastasis. However, the basis for the selection of these effect modifiers was not clear. Furthermore, the submission did not demonstrate that there was a sufficient imbalance in these effect modifiers to result in a material bias in observed relative treatment effect. Notably, the submission did not adjust for important confounding factors such as IMDC risk group and PD-L1 expression status, which were identified as key differences between the KN 581 and CM 214 and included in

subgroup analyses within the respective key publications. The PSCR argued that IMDC risk group was a prognostic factor, not an effect modifier, and stated that the status of PD-L1 expression as an effect modifier was uncertain for immunotherapies in RCC.

- 6.32 The key results of the MAIC were:
- There was no significant difference in the OS between PEM+LEN and NIVO+IPI, with HR of 0.92 (95% CI: 0.62, 1.37).
 - PEM+LEN was associated with a statistically significant improvement in PFS compared with NIVO+IPI, with a HR of 0.44 (95% CI: 0.32, 0.60).
- 6.33 The ESC noted that the MAIC estimates for OS and PFS were similar to the ITC estimates, which may suggest that the effect modifiers included were not relevant.
- 6.34 Although the submission did not conduct a pairwise comparison or a network meta-analysis to compare PEM+LEN with other immune-TKI combinations, a summary of the key efficacy outcomes of first-line combinations for aRCC treatment was presented - see Table 8.

Table 8: Summary of key efficacy outcomes for the first-line combination therapies (intermediate-poor risk sub-population)

	KN 581	CM 214	JAVELIN	CM 9ER ^a	KN 426 ^a
Therapy vs sunitinib	PEM+LEN	NIVO+IPI	AVE+AXI	NIVO+CABO	PEM+AXI
Median duration of follow-up for OS	26 months	25 months	28 months ^b	18.1 months	12 months
Median OS, months	NR vs NR	NR vs 26.0	40.0 vs 29.5	NR vs NR	91.4% vs 76.7% ^c
OS HR (95% CI)	0.58 (0.42, 0.80)	0.63 (0.44, 0.89)	0.79 (0.64, 0.98)	NE	0.53 (0.35, 0.82)
Median PFS, months	22.1 vs 5.9	11.6 vs 8.4	11.1 vs 8.2	17.7 vs 8.5	14.5 vs 9.5
PFS HR (95% CI)	0.36 (0.28, 0.47)	0.82 (0.64, 1.05)	0.66 (0.55, 0.79)	NE	0.70 (0.54, 0.91)

Source: Table 2.6-17, p113 of the submission.

AVE = avelumab, AXI = avatinib, CABO = cabozantinib, IPI = ipilimumab, LEN = lenvatinib, NE = not estimable, NIVO = nivolumab, NR = not reached, OS = overall survival, PEM = pembrolizumab, PFS = progression-free survival.

^a Estimates reported for intermediate risk sub-population.

^b Minimum follow-up reported instead of median follow-up.

^c 12 month survival rate reported instead of median OS

- 6.35 The point estimate of the HR for PFS was lower for AVE+AXI versus sunitinib (JAVELIN) than NIVO+IPI versus sunitinib (CM 214). As such, the submission's claim of superior PFS may be diminished if AVE+AXI were to be used as the comparator.
- 6.36 Median PFS was consistent for intermediate to poor risk patients randomised to sunitinib across all the trials, except for KN 581 in which the PFS was shorter (5.9 months). The PSCR stated that review of the baseline characteristics for the intermediate or poor risk subgroups noted no additional imbalances that would explain the difference in median PFS in the sunitinib arm of KN 581.
- 6.37 The ESC, noting the shorter PFS in the sunitinib arm of KN 581, considered that the trial populations potentially differed.

Comparative harms

6.38 The submission presented safety data for PEM+LEN and NIVO+IPI based on the KN 581 and CM 214 trials, respectively. The adverse event summary is shown in Table 9.

Table 9: Adverse event summary (ASAT population)

	KN 581 ^a		CM 214 ^b	
	PEM+LEN (n=352)	Sunitinib (n=340)	NIVO+IPI (n=547)	Sunitinib (n=535)
Median duration of treatment, months (range)	17.0 (0.1 to 39.1)	7.8 (0.1 to 37.0)	7.9 (6.5,8.4) ^c	7.8 (6.4,8.5) ^c
TRAEs, %				
Any grade	96.9	92.1	93	97
Grade 3-5	71.6	58.8	47.2 ^d	63.4 ^d
Any serious TRAE	33.8	15.0	-	-
Any fatal TRAE	1.1	0.3	1.5	0.75
Led to dose reduction of lenvatinib or sunitinib	67.3	49.7	NA	-
Led to discontinuation	31.3	10.0	22	12
Lenvatinib	18.5	NA	NA	NA
Pembrolizumab	25.0	NA	NA	NA
PEM+LEN	9.7	NA	NA	NA

Source: KN 581 Clinical Study Report, Table 14.3.1.2.2, p649; Motzer et al. 2018, Table 3, p1286 and p1277

ASAT = all subjects as treated, CI = confidence interval, NIVO+IPI = nivolumab + ipilimumab, NA = not applicable, PEM+LEN = pembrolizumab + lenvatinib, TRAE = treatment-related adverse event

^a Data cut-off: 20 August 2020

^b Data cut-off: 7 August 2017

^c Median duration of treatment, months (95% CI)

^d Grade 3 or 4 TRAEs and TRAE deaths (which refers to Grade 5 adverse events)

6.39 Key adverse events in the All Subjects as Treated (ASaT) population, which included all randomised patients who had received at least one dose of study medication, are summarised in Table 10.

Table 10: Summary of key adverse events (≥Grade 3) in the trials

KN 581	PEM+LEN n with event/N (%)	Sunitinib n with event/N (%)
Hypertension	89/352 (25.3%)	61/340 (17.9%)
Diarrhoea	29/352 (8.2%)	15/340 (4.4%)
Proteinuria	26/352 (7.4%)	10/340 (2.9%)
Decrease appetite	12/352 (3.4%)	5/340 (1.5%)
Fatigue	11/352 (3.1%)	13/340 (3.8%)
Study drug related death	4/352 (1.1%)	1/340 (0.3%)
CM 214	NIVO+IPI n with event/N (%)	Sunitinib n with event/N (%)
Lipase increased	56/547 (10.2%)	35/535 (6.5%)
Fatigue	23/547 (4.2%)	49/535 (9.2%)
Diarrhoea	21/547 (3.8%)	28/535 (5.2%)
Hypertension	4/547 (0.7%)	85/535 (15.8%)
Study drug related death	8/547 (1.5%)	4/535 (0.75%)

Source: Table 2.5-8 p82, Table 2.5-11 p84 of the submission; Table 14.3.1.4.1, pp1097-1125 of KN 581 CSR.

NIVO+IPI = nivolumab + ipilimumab, PEM+LEN = pembrolizumab + lenvatinib, TRAE = treatment-related adverse event

^a Grade 3 or 4 TRAEs and TRAE deaths

- 6.40 The safety profiles of PEM+LEN and NIVO+IPI are different. The proportion of patients who experienced any adverse event (AEs) was similar between KN 581 and CM 214 (97% compared with 93%); however, more patients had Grade ≥3 treatment-related AEs with PEM+LEN compared with NIVO+IPI (71.6% compared with 47.2%).
- 6.41 The most common AEs of Grade ≥3 reported for PEM+LEN in the KN 581 trial were hypertension (25.3%), diarrhoea (8.2%), proteinuria (7.4%), decreased appetite (3.4%), and fatigue (3.1%). The most common AEs of Grade ≥3 reported for NIVO+IPI in the CM 214 trial were increased lipase (10.2%), fatigue (4.2%), and diarrhoea (3.8%). The ESC noted that PEM+LEN was associated with higher rates of Grade ≥ 3 diarrhoea than NIVO+IPI (8.2% versus 3.8%).
- 6.42 The submission did not conduct an indirect comparison for the safety outcomes to support the claim of safety outcomes being comparable.

Benefits/harms

- 6.43 A summary of the benefits and harms was not presented given the claim of non-inferiority.

Clinical claim

- 6.44 The submission described PEM+LEN as non-inferior on the basis of OS and superior on the basis of PFS and ORR compared to NIVO+IPI. The evaluation and the ESC considered that the key issues were:
- There were transitivity issues between the KN 581 (PEM+LEN) and CM 214 (NIVO+IPI) trials used in the indirect comparison including differences in the proportion of poor risk patients, status of PD-L1 expression, and subsequent treatments. The MAIC did not adjust for these factors.

- Although the results of the ITC for PFS statistically favoured PEM+LEN, the ESC considered that PFS was not a reliable measure of the clinical effectiveness of immunotherapies as tumour responses can occur after conventional RECIST-defined progressive disease (paragraph 6.37, AVE+AXI PSD, March 2020).
 - In addition, it was unclear why median PFS in the sunitinib arm of KN 581 (5.9 months) was lower than in CM 214 (8.4 months). The submission stated that this difference might relate to the ability of the patients in CM 214 to receive subsequent anticancer therapy before progression; however, the proportion of patients this affected was not reported in the submission or publications for CM 214.
- 6.45 Overall, the PBAC considered that PEM+LEN was likely non-inferior to NIV+IPI in terms of OS, but that the claims of superior PFS and ORR were not supported.
- 6.46 The submission described PEM+LEN as comparable in terms of safety compared to NIVO+IPI. The key issues were:
- PEM+LEN and NIVO+IPI have distinct AE profiles.
 - The submission did not present an indirect comparison of AEs associated with PEM+LEN and NIVO+IPI.
- 6.47 Overall, the PBAC considered that PEM+LEN has a different, yet non-inferior, safety profile compared to NIVO+IPI.

Economic analysis

- 6.48 The submission presented a cost-minimisation approach (CMA) based on a MAIC comparing PEM+LEN (KN 581) with NIVO+IPI (CM 214) for the patients with intermediate or poor risk aRCC.
- 6.49 The submission did not calculate the cost minimised price based on equi-effective doses; rather, the submission presented a partitioned survival model to estimate the time on treatment and incremental costs between PEM+LEN and NIVO+IPI.
- 6.50 The submission made the following assumptions in the CMA base case:
- Both treatments were assumed to have the same duration of OS based on the non-inferiority claim of PEM+LEN compared with NIVO+IPI.
 - Time on treatment (ToT) would be longer for PEM+LEN compared with NIVO+IPI i.e. mean ToT of █ months for pembrolizumab (and █ months for lenvatinib) versus █ months for nivolumab (and █ months for ipilimumab).
 - There were differences between the two combinations in terms of dosing, administration and AEs.
- 6.51 The submission stated that the “CMA quantifies the differences in ToT between these therapies and uses this information to calculate the costs of each therapy”. The net cost per patient was calculated by extrapolating the ToT curves for pembrolizumab (truncated at 2 years) and lenvatinib. ToT for NIVO+IPI was estimated using the

lenvatinib ToT curve with the HR for PFS (derived from the MAIC presented in the clinical section) applied. The ESC considered that the underlying assumptions, as applied in the base case, though not well supported (see paragraph 6.44), were potentially conservative in terms of calculating vial/unit prices for PEM+LEN given the longer treatment duration for PEM+LEN.

6.52 The key components of the model are summarised in the Table 11.

Table 11: Key components and assumptions of the model

Component	Summary
Treatments	PEM+LEN versus NIVO+IPI
Methods used to generate results	Partitioned survival model
Health states	Pre-progression, Progressed, and Death
Median duration of follow-up	26.6 months (based on KN 581 trial)
Time Horizon	7.5 years
Extrapolation method	Parametric distribution with best relative fit according to AIC and BIC were used to extrapolate the PEM+LEN KM function curves (OS, PFS and ToT) from the median follow-up time over the time horizon.
Best fitting parametric functions ^a	OS: Gompertz PFS: Exponential ToT (Pembrolizumab): Generalised Gamma ToT (Lenvatinib): Gompertz
HR of treatment effect ^b	OS: 1.0 PFS: 0.46 ToT: 0.46

Source: Table 3.4-6, p136 of the submission.

AIC = Akaike's Information Criteria, BIC = Bayesian Information Criteria, HR = hazard ratio, KM = Kaplan Meier, MAIC = matching-adjusted indirect comparison; NIVO+IPI = nivolumab + ipilimumab, OS = overall survival, PEM+LEN = pembrolizumab + lenvatinib, PFS = progression-free survival, ToT= time on treatment.

^a Based on most plausible and best relative fit according to average AIC and BIC

^b Submission stated that 0.46 was based on the hazard ratio estimated from MAIC of PEM+LEN and NIVO+IPI. The MAIC resulted in a HR = 0.44 in PFS between the two combinations

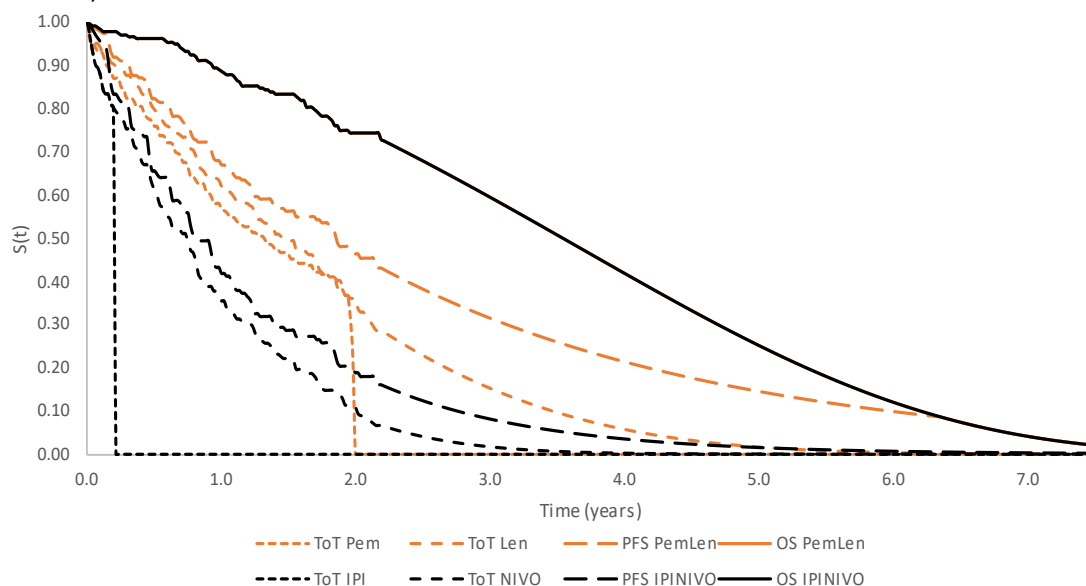
6.53 The Gompertz distribution was applied to the lenvatinib ToT arm from a median duration of follow-up of 26.6 months. The Gompertz distribution had the best statistical fit according to Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC). Other distributions were tested in the sensitivity analyses.

6.54 To estimate ToT for the NIVO+IPI arm, a HR of 0.46 was applied to the ToT function for lenvatinib based on the HR for PFS derived from the MAIC. The ESC considered that this might not have been appropriate as PFS is a poor proxy for ToT in immunotherapy. The PBAC previously considered that “PFS is a surrogate outcome and extrapolation of PFS may not be a reliable basis upon which to estimate treatment exposure” (paragraph 6.43, AVE+AXI PSD, March 2020). Furthermore, the submission used a HR of 0.46 to generate PFS and ToT curves for NIVO+IPI; however, the MAIC showed a HR of 0.44 in PFS between the two combinations. The pre-PBAC response stated that given the uncertainty introduced by using the PFS HR from the MAIC to estimate the relative ToT from PEM+LEN versus NIVO+IPI, it may be reasonable to set ToT for both arms to parity (i.e. HR = 1). The pre-PBAC response further stated this would be consistent with the CMA used in the AVE+AXI submission; however, the PBAC noted

that one of the reasons this was accepted was because “the assumption was likely to be conservative in this case” (paragraph 6.40, avelumab PSD, March 2021). The ESC and PBAC have previously stated that cost-minimisation on the basis of the total drug cost that achieves the same OS outcomes may be a more reasonable approach (paragraph 7.9, alectinib PSD, July 2017).

- 6.55 To generate the OS curves for NIVO+IPI arm, a HR of 1 was applied to the PEM+LEN arm. To generate PFS for the NIVO+IPI arm, a HR of 0.46 was applied to the PEM+LEN arm based on the results of the MAIC. The assumption of proportional hazards was not justified in the submission. Although the following issues were either conservative or had no effect on the net cost per patient in the submission base case, the ESC noted that:
- (i) the relative treatment effect beyond the duration of KN 581 (median follow-up of 26.6 months) was uncertain given that median OS had not been reached at the data cut-offs used (while later data-cuts were available these may be confounded by the differences in subsequent therapies);
 - (ii) on visual inspection, the extrapolation of PFS for PEM+LEN appeared to be overestimated with its curve crossing the OS curve at year six which was clinically implausible; and
 - (iii) the use of the MAIC HR to generate the PFS curve for the NIVO+IPI arm in the CMA may have underestimated PFS compared with that observed in the NIVO+IPI arm of CM 214. Updated data from an extended four-year follow-up showed that PFS rates for NIVO+IPI for poor to intermediate risk patients were 36.4% at Year 2 and 32.7% at Year 4. This was different from the PFS probabilities generated by the CMA model, which were approximately 18.8% at Year 2 and 3.5% at Year 4.
- 6.56 Figure 6 summarises the KM curves for PEM+LEN and NIVO+IPI used in the modelled CMA.

Figure 6: OS, PFS and ToT curves used in the modelled CMA



Source: Pembrolizumab CMIN RCC_final.xlsx, worksheet 'Results & Settings' of the submission.

CMA = cost minimisation approach, IPI = ipilimumab, LEN = lenvatinib, NIVO = nivolumab, PEM = pembrolizumab, PFS = progression free survival, OS = overall survival, ToT = time on treatment

Note: The OS curve for PEM+LEN is not visible as it is situated underneath the NIVO+IPI OS curve as they are assumed to be identical. Per trial protocol, participants were required to cease treatment with pembrolizumab after 35 cycles (approximately 2 years).

- 6.57 The submission stated that there were differences in the mode and frequency of administration between PEM+LEN and NIVO+IPI, and there would be costs associated with the IV administration of pembrolizumab, nivolumab, and ipilimumab (lenvatinib is administered orally). The submission also acknowledged that PEM+LEN and NIVO+IPI have different safety profiles which will generate different costs to the healthcare system. These costs were included in the CMA base case.
- 6.58 Dosing of NIVO + IPI in the initial phase (the first four doses) is weight-based. The submission assumed that the weight of an average patient was 79.4 kg. This was consistent with the average weight of patient in KN 581.
- 6.59 The published prices, treatment regimens and relative dose intensities (RDIs) applied for PEM+LEN and NIVO+IPI are presented in Table 12.

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Table 12: Published prices, treatment regimens, durations, RDIs and average number of vials/tablets applied in the CMA

	Published AEMP	Treatment regimen assumed in CMA	RDI	DoT, cycles (RDI applied)	DoT, weeks (RDI applied)	Average # vials/tablets ^c
PEM	\$3,823.75 per 100 mg vial	Initial: 200 mg IV on Day 1 of a 21-day cycle for 7-cycles Continuing: 400 mg IV on Day 1 of a 42-day cycle (max 14 cycles ^d)	█	Initial: █	Initial: █	Initial: █ vials
				Continuing: █	Continuing: █	Continuing: █ vials
LEN	\$3,155 per 30 × 10 mg tablets	Oral 20 mg per day	█	█	█	█ tablets (█ packs)
IPI	\$5,625.92 per 50 mg vial	1.0 mg/kg (assumed mean = 100 mg) IV on Day 1 of a 21-day cycle (max 4 cycles)				█ vials
NIVO	\$2,076.75 per 100 mg vial	Initial: 3 mg/kg (assumed mean = 240 mg) IV on Day 1 of a 21-day cycle for 4-cycles Continuing: 480 mg IV on Day 1 of a 28-day cycle	█	Initial: █	Initial: █	Initial: █ vials
				Continuing: █	Continuing: █	Continuing: █ vials

Source: Table 3.4-3, pp132-133 of the submission.

AEMP = approved ex-manufacturer price, CMA = cost minimisation approach, DoT = duration of treatment, IPI = ipilimumab, IV = intravenous, LEN = lenvatinib, NIVO = nivolumab, PEM = pembrolizumab, RDI = relative dose intensity

Average weight of patient was assumed to be 79.4 kg by the submission.

^a Pembrolizumab regimen – product information; RDI - KN-581

^b Lenvatinib regimen – product information; RDI - KN-581

^c Average number of vials = (Treatment duration (cycle with RDI applied)*mg required per cycle)/ mg per vial. Average number of tablets = (Treatment duration (cycle with RDI applied)*7*mg required per cycle)/ mg per tablet.

^d Pembrolizumab treatment is capped at equivalent to 35 cycles at 200 mg every three weeks.

- 6.60 The submission applied relative dose intensities (RDI) of █% and █% to PEM+LEN, respectively, based on KN 581. However, a relative dose intensity of 1 was applied to the NIVO+IPI arm, which favoured PEM+LEN (i.e. resulted in a higher price for PEM+LEN).
- 6.61 The CMA applied a pembrolizumab dose regimen of 200 mg every three weeks for seven cycles, then 400 mg every six weeks thereafter up to a maximum of 14 cycles (consistent with the requested restriction), while the Product Information for pembrolizumab states that the recommended dose of pembrolizumab is either: 200 mg every 3 weeks; or 400 mg every 6 weeks. The proportion of patients who would use each dose regimen was unclear, but the assumption that patients would be more likely to use the more frequent dosing at the start of treatment was likely reasonable.
- 6.62 The CMA assumed that all patients would cease pembrolizumab after approximately 2 years, consistent with the proposed restriction and the key trial (KN 581); however, this assumption may not be conservative given there may be a risk that some patients will use pembrolizumab for longer durations noting a Streamlined Authority was requested (e.g. the model estimates that around 10% of patients are still continuing on nivolumab at 2 years).
- 6.63 The submission stated that it did not request a price increase for the claimed superiority in PFS and the potential improvement in health-related quality of life or

the possible reduction in the costs of subsequent treatment resulting from a longer PFS duration. The submission suggested that if recommended by the PBAC, the Commonwealth would substitute the published prices (AEMP) used in the analysis with effective prices for each product in the CMA and then calculate the total cost of the PEM+LEN treatment that would result in a nil cost to the health care system of Australia. Once the total cost for PEM+LEN treatment is calculated, the sponsor of pembrolizumab and the sponsor of lenvatinib would work with the Department of Health to achieve the appropriate total costs of pembrolizumab and lenvatinib.

6.64 The results of the cost-minimisation approach are presented in Table 13.

Table 13: Results of the cost-minimisation approach (based on published AEMPs)

	PEM+LEN			NIVO+IPI			Increment
	PEM	LEN	Total	NIVO	IPI	Total	
Drugs	\$	\$	\$	\$	\$	\$	\$
Administration							
Adverse events		\$190			\$30		\$160
Total cost		\$			\$		\$

Source: Table 3.4-1, p131 of the submission.

AEMP = approved ex-manufacturer price, IPI = ipilimumab, LEN = lenvatinib, NIVO = nivolumab, PEM = pembrolizumab

6.65 Based on published prices, the total cost per treatment course per patient for PEM+LEN was \$|. The corresponding cost for NIVO+IPI was \$|, resulting in an incremental cost of \$|.

6.66 In order to result in an incremental cost of \$0 for the CMA, the total cost for PEM+LEN would need to be \$|. Of this, | would be administration costs and \$190 would be related to adverse events. Hence, the total drug cost for PEM+LEN would be \$| (based on published prices). The ESC considered that the unit prices of pembrolizumab and lenvatinib should be calculated such that the CMA, as calculated in Table 13, results in an incremental cost of \$0.

6.67 The submission did not apply discounting to the estimated effects or costs, this was tested in sensitivity analyses.

6.68 Sensitivity analyses calculated as a part of the evaluation as are presented in Table 14. The sensitivity analyses were based on a scenario in which the incremental cost of treatment with PEM+LEN is set to \$0.

Table 14: Sensitivity analyses (using submission base case)

	Total cost of treatment		% change from base case with \$0 incremental cost
	PEM+LEN	NIVO+IPI	
Base case (published AEMPs)	\$	\$	-
Base case with \$0 incremental cost in CMA (published AEMPs)	\$		-
Sensitivity analyses: all with incremental costs set to \$0 in CMA (published AEMPs)			
ToT for lenvatinib extrapolation (base case = Gompertz):			
Exponential distribution (2 nd best fit)	\$		1.0%
Weibull	\$		1.5%
Generalised gamma	\$		-0.7%
HR applied to NIVO/IPI ToT arm (base case = 0.46)			
0.44 (as per MAIC)	\$		-3.0%
0.61 (upper 95% CI of MAIC; NIVO ToT = 13.8 months)	\$		21.0%
1.00 (i.e. ToT in both arms is equal)	\$		67.8%
RDI for NIVO = ■■■, RDI for IPI = ■■■ ^a (base case = 1.00)	\$		-0.5%
Vial sharing (base case = no vial sharing)	\$		-6.1%
Time horizon (base case = 7.5 years)			
3 years	\$		-0.7%
1 year ^b	\$		-23.7%
Discount rate of 5% for effects and costs (base case = 0%)	\$		-3.0%

Source: Pembrolizumab CMIN RCC_final.xlsx, worksheet 'Results & Settings'.

AEMP = approved ex-manufacturer price, CMA = cost minimisation approach, HR = hazard ratio, IPI = ipilimumab, LEN = lenvatinib, MAIC = matching-adjusted indirect comparison, NIVO = nivolumab, HR = hazard ratio, PEM = pembrolizumab, RDI = relative dose intensity, ToT = time on treatment.

^a Equal to RDI for pembrolizumab in KN 581

^b While not clinically plausible, this analysis was conducted to test the sensitivity of the model to the extrapolation

6.64 Should the PBAC accept the clinical claim of overall non-inferior effectiveness and safety, the cost-minimisation approach must establish that the cost per patient for treatment with PEM+LEN would be no more than the cost per patient of NIVO+IPI. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.

Scenario Analysis 1

6.65 The submission presented a scenario analysis (SA1) in which the cost of subsequent treatments were also considered. In SA1, the submission assumed that PEM+LEN has a superior duration of PFS compared to NIVO+IPI, and patients treated with NIVO+IPI will spend longer in the progressed health state than those in the PEM+LEN arm (2.4 years versus 1.1 years). As a result, patients treated with NIVO+IPI will receive subsequent therapies for a longer duration than those treated with PEM+LEN. Subsequent therapies included in SA1 were pazopanib, sunitinib, cabozantinib and axitinib.

6.66 The results of the CMA with subsequent treatment costs (SA1) are presented in Table 15 (based on published prices).

Table 15: Results of the cost-minimisation approach with subsequent treatment costs (SA1, based on published AEMPs)

	PEM+LEN			NIVO+IPI			Increment
	PEM	LEN	Total	NIVO	IPI	Total	
Drugs	\$	\$	\$	\$	\$	\$	\$
Subsequent treatments							
Administration							
Adverse events		\$190			\$30		\$160
Total cost		\$			\$		\$

Source: Table 3.4-2, pp131-132 of the submission.

AEMP = approved ex-manufacturer price, IPI = ipilimumab, LEN = lenvatinib, NIVO = nivolumab, PEM = pembrolizumab

6.67 The total cost per treatment course per patient for PEM+LEN, including subsequent treatments, was \$ compared with \$ for NIVO+IPI. PEM+LEN had a lower cost of subsequent therapies, given that the submission assumed that patients receive subsequent therapies for a shorter duration than in the NIVO+IPI arm. The ESC noted the uncertainty in the relative effectiveness in PFS as well as the uncertainty in subsequent treatment utilisation. Under SA1, and assuming nil incremental cost, the ESC noted that the proposed cost of PEM+LEN would increase from \$ to \$ compared to the base case (difference: \$).

Drug cost/patient/course

6.68 A summary of the drug cost per patient for PEM+LEN and NIVO+IPI is provided in Table 16. The cost/patient/course for PEM+LEN was estimated to be \$ (based on the CMA provided in the submission). This was calculated using published prices of pembrolizumab, lenvatinib, nivolumab, and ipilimumab.

Table 16: Drug cost per patient for PEM+LEN and NIVO+IPI using published prices

	PEM+LEN				NIVO+IPI			
		Trial dose/ duration ^a	Model	Financial estimates		Trial dose/ duration	Model	Financial estimates
Dose regimen	PEM	200 mg Q3W	Initial: 200 mg Q3W (7 cycles) Maintenance: 400 mg Q6W	Initial: 200 mg Q3W (7 cycles) Maintenance: 400 mg Q6W	NIVO	Initial: 3 mg/kg Q3W (4 cycles) Maintenance: 3 mg/kg Q2W	Initial: 240 mg Q3W (4 cycles) Maintenance: 480 mg Q4W	Initial: 240 mg Q3W (4 cycles) Maintenance: 480 mg Q4W
	LEN	20 mg OD	20 mg OD	20 mg OD	IPI	1 mg/kg Q3W (4 cycles)	100 mg Q3W (4 cycles)	100 mg Q3W (4 cycles)
Mean dose	PEM	20.7 doses ^b	Initial: 200 mg Q3W (7 cycles) Maintenance: 400 mg Q6W	Initial: 200 mg Q3W (7 cycles) Maintenance: 400 mg Q6W	NIVO	NR	Initial: 240 mg Q3W (4 cycles) Maintenance: 480 mg Q4W	Initial: 240 mg Q3W (4 cycles) Maintenance: 480 mg Q4W
	LEN	14.1 mg ^b	20 mg OD	20 mg OD	IPI	NR	100 mg Q3W (4 cycles)	100 mg Q3W (4 cycles)
Mean duration ^c	PEM	17.29 months ^b	■ months (no RDI)	■ months (no RDI)	NIVO	7.9 months	■ months	■ months
	LEN	(RDI applied)	■ months (no RDI)	■ months (no RDI)	IPI		■ months	■ months
Cost/ patient/ course ^{d,e}	PEM	\$ ^f	\$	\$	NIVO	\$ ^h	\$	\$
	LEN	\$ ^g	\$	\$	IPI	\$	\$	\$
	Σ	\$	\$	\$	Σ	\$	\$	\$

Source: Table 2.4-4, p64 of the submission, Table 4.2-4, p 143 of the submission, Table 4.3-1, p 148 of the submission; Table 18, p132, Table 19, p133 of the KN 581 CSR.

IPI = ipilimumab, LEN = lenvatinib, NIVO = nivolumab, NR = not reported, OD = once daily, PEM = pembrolizumab, Q2W = every 2 weeks, Q3W = every 3 weeks, Q4W = every 4 weeks, Q6W = every 6 weeks, RDI = relative dose intensity

Average RCC patient weight is assumed to be 79.4 kg

^a RDI was not applied in calculating cost in the trial dose and duration estimate.

^b Estimates for mean dose and mean duration in the trial were derived from KN 581 CSR.

^c Time on treatment was converted to months for comparison

^d Cost/patient/course calculated as: Time on treatment (cycle)*cost per weighted mg*dosage (mg)

^e RDI of ■ and ■ was applied to PEM and LEN, respectively, to calculate cost/patient/course in the economic model

^f Calculation = (74.92/3) weeks*38.24*200 mg (rounding applied)

^g Calculation = (74.92*7) days*10.52*20 mg

^h Calculation = (4)weeks*20.77*240 mg + (34.23-4)/2 weeks*20.77*240 mg

ⁱ Calculation = (4)weeks*112.52*80 mg

Estimated PBS usage & financial implications

6.69 This submission was not considered by DUSC.

6.70 The submission applied an epidemiological approach to estimate the financial impact of PEM+LEN as first line therapy for patients with aRCC with intermediate or poor risk disease according to the IMDC criteria. The sponsor argued that an epidemiological approach was used due to the complexities of the regimens which involved tablets and intravenous agents using weight based and flat dosing at different intervals and for different treatment periods. The ESC considered that the use of an epidemiological approach was reasonable. The submission also argued that NIVO+IPI was under-utilised given that only 44% of patients were initiated on NIVO+IPI, despite 87% of patients being eligible (based on Tran et al. (Cabozantinib, PSD, PBAC Meeting March

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2020); however, this is higher than the proportion of patients in clinical trials (e.g., 77% in CM 214) and in the Australian retrospective study by Day et al (73%).

6.71 Key inputs for financial estimates are presented in Table 17.

Table 17: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incident patients with kidney cancer	█ ¹ in year 1 increasing to █ ² in year 6, based on linear projection of AIHW 2021 Cancer data in Australia.	-
Proportion with RCC	90%, based on unreferenced number on the Cancer Council NSW website explaining RCC to patients	Could be an overestimate. DUSC June 2014 review for pazopanib and sunitinib estimated 85%.
Proportion with clear cell variant	80%, based on an unreferenced number from the National Cancer Institute website explaining RCC to patients	Did not appear to be well substantiated
Proportion metastatic at diagnosis	30%, based on Gupta et al, 2008.	This is was likely overestimated. DUSC June 2014 review for pazopanib and sunitinib estimated 25%.
Earlier stage disease (Stage I-III) 5 years prior	70%, based on Gupta et al, 2008.	-
Recurrence rate	25%, based on Expert Advice and Cabozantinib PSD, March 2020	Likely overestimated as patients who relapse from Stage III do not automatically become Stage IV. Could result in double counting given the uncertainty regarding the proportion of patients who are metastatic at diagnosis.
Proportion of patients who meet IMDC intermediate or poor risk criteria	87%, based on Tran et al. (Cabozantinib PSD March 2020). Updated to 77%, based on CM 214, in the PSCR.	Patients were included regardless of WHO performance status.
Uptake rate	50%, assumed by the submission	Not justified in the submission and inappropriately remains fixed over the 6 years of estimates.
Growth rate	2-3%	Forecasted equation from AIHW data 2007 – 2021.
Growth rate	128 persons per year (2-3%) per forecasted equation from AIHW data 2007 – 2021.	-
MBS costs	\$112.40	This is consistent with administration costs applied in the model

Source: Table 4.2-1 p139, Table 4.2-2 p141, Table 4.2-3 p142, Table 4.2-5 p143, Table 4.2-7 p145, Table 4.2-8 p145, Table 4.2-9 p145 of the submission.

AIHW = Australian Institute of Health and Welfare, DUSC = Drug Utilisation Sub-Committee, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, MBS = Medicare benefits schedule, PSCR = pre-Sub-Committee-Response, PSD = public summary document, RCC = renal cell carcinoma, WHO = World Health Organisation

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

- 6.72 The submission appeared to overestimate the number of treated patients by:
- using AIHW projections instead of PBS sample data.
 - using a higher proportion of patients with IMDC intermediate to poor risk compared with the proportions in clinical trials (87% in the submission compared with 77% in CM 214). The PSCR updated the proportion of patients with IMDC intermediate to poor risk to 77% to align with CM 214. The ESC noted that the proportion remained higher than the estimated proportion of Australian intermediate to poor risk patients (73%, Day et al, 2015).
 - assuming that 30% of RCC patients would be metastatic at diagnosis. The submission stated this was based on Gupta et al 2008, which stated “25–30% of patients present with metastatic disease at time of diagnosis” in its Introduction section, quoting a range of sources that were published from 1996 to 2005. It was unclear whether this estimate was reliable and applicable to current practice.
 - adding in a prevalent pool of patients who were diagnosed five years prior with Stage I-III (i.e. incident patients 5 years prior) who have progressed to Stage IV. This was likely an overestimate as patients who relapse from Stage III do not automatically become Stage IV. Further, this could lead to double counting given the uncertainty regarding the proportion of patients who are metastatic at diagnosis.
 - including all patients regardless of their performance status, despite the requested listing requiring patients to have a WHO performance status of 2 or less. The submission stated that this was part of the consideration of intermediate or poor risk status.
- 6.73 The estimated use and financial implications associated with the use of PEM+LEN are summarised in Table 18. The PSCR provided financial estimates which corrected for an error in the grandfather patient calculations and updated the proportion of intermediate to poor risk patients.

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Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Patients treated	1	1	1	1	1	1
PEM+LEN prescriptions dispensed ^a	2	2	2	2	2	2
PEM prescriptions dispensed ^a	3	3	3	3	3	3
LEN prescriptions dispensed ^a	3	3	3	3	3	3
Estimated financial implications of PEM+LEN						
Cost to PBS/RPBS less co-payments (\$)	4	4	4	4	4	4
Estimated financial implications for NIVO+IPI						
Cost to PBS/RPBS less co-payments (-\$)	5	5	5	5	5	5
Net financial implications						
Net cost to PBS/RPBS (\$)	6	9	7	7	7	7
Net cost to MBS (\$)	7	7	7	7	7	7
Net cost to PBS/RPBS/MBS (\$)	6	9	7	7	7	7
PSCR updated financial estimates						
Patients treated	1	1	1	1	1	1
Cost to PBS/RPBS of PEM+LEN (\$)	4	4	4	4	4	4
Cost to PBS/RPBS of NIVO+IPI (\$)	7	10	10	10	5	5
Net cost to PBS/RPBS (\$)	6	9	9	9	9	9
Net financial implications with nil financial impact in CMA (and using PSCR revised financials)						
Net cost to PBS/RPBS (\$)	8	8	8	8	8	8

Source: Source: KN581_1L aRCC_Budget Impact Mode.xlsx, worksheet '3b. Impact - proposed (pub)'; worksheet '4b. Impact - affected (pub)'; worksheet '5. Impact - net'

CMA = cost minimisation approach, LEN = lenvatinib, NIVO+IPI = nivolumab + ipilimumab, MBS = Medicare Benefits Schedule, PBS = Pharmaceutical Benefits Scheme, PEM = pembrolizumab, PSCR = pre-Sub-Committee Response, RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Assuming [redacted] scripts per patient for PEM and [redacted] scripts per patient for LEN per cycle as estimated by the submission.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 10,000 to < 20,000

³ 5,000 to < 10,000

⁴ \$100 million to < \$200 million

⁵ \$80 million to < \$90 million

⁶ \$30 million to < \$40 million

⁷ \$60 million to < \$70 million

⁸ \$0 to < \$10 million

⁹ \$50 million to < \$60 million

¹⁰ \$70 million to < \$80 million

6.74 The total cost to the PBS/RPBS of listing PEM+LEN, using the revised estimates provided in the PSCR, was estimated to be \$30 million to < \$40 million in Year 1, \$50 million to < \$60 million in Year 6 and total \$300 million to < \$400 million over the first 6 years of listing (based on the CMA using published prices).

- 6.75 Although the financial implications as presented in the submission resulted in a cost to Government, the submission stated that “once the effective prices are known, the net cost to government should be minimal, with a cost saving in year one reflecting the front loading of IPI costs. This will be offset in Year 2 due to a longer duration of treatment for PEM+LEN than NIVO+IPI. By Year 3 these effects should have washed through with minimal cost to the PBS/RPBS”.
- 6.76 The ESC noted that using the drug costs derived from Table 14 with a nil incremental cost (1% reduction to the published prices of PEM+LEN, i.e. an AEMP of \$1 per 100 mg vial of pembrolizumab and \$1 for lenvatinib 10 mg pack of 30 tablets) and the revised PSCR model results in a net saving over the first six years of listing (with a net cost saving in Year 1 and a net cost saving in Year 6).

Quality Use of Medicines

- 6.77 The submission presented a discussion on quality use of medicines. The submission stated that:
- Educational materials will be targeted at physicians, nurses, pharmacists and patients.
 - Face to face workshop sessions aligned to major oncology clinician and nurse conferences including peer-to-peer discussions of real case studies.
 - Information and support for patients, carers and health care professionals will be provided through the sponsors phone based medical information service.

Financial Management – Risk Sharing Arrangements

- 6.78 The sponsor noted the March 2021 PBAC recommendation for AVE+AXI and the PBAC’s advice that AVE+AXI should join the RSA for NIVO+IPI for the same indication with no changes to patient caps (paragraph 7.10, AVE+AXI PSD, March 2021).
- 6.79 The submission argued that utilisation below the current caps should not result in a lowering of the caps in the RSA, stating that the advantages of PEM+LEN will drive uptake and meet the unmet patient need. Without a patient cap, there is a risk of leakage to patients in the favourable risk group and to subsequent treatment lines.
- 6.80 The ESC considered that an increase to the RSA caps would only be appropriate if the PBAC considered the availability of PEM+LEN would lead to an increase in the number of patients compared to that used to estimate the NIVO+IPI (and, if listed, AVE+AXI) expenditure caps.
- 6.81 The pre-PBAC response argued that the introduction of PEM+LEN to the PBS will result in more patients being treated with an immunotherapy combination compared with the current utilisation of NIVO+IPI. The pre-PBAC response estimated that, based on the information provided in the clinician statement (see paragraph 6.1), 25% of intermediate or poor risk patients currently receive TKI monotherapy due to contraindications to immunotherapy or the potential for toxicity with NIVO+IPI and

that 50% of these patients would instead use PEM+LEN if it were available on the PBS. The pre-PBAC response therefore requested that the existing NIVO+IPI expenditure caps be increased by $\frac{1}{2} \left(\frac{1}{2} \times \frac{1}{2} \right) \frac{1}{2}$ to accommodate all eligible patients who would receive combination immunotherapy.

- 6.82 The pre-PBAC response also argued that rebate levels over the subsidisation caps should be set at $\frac{1}{2}$.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of pembrolizumab for use in combination with lenvatinib (PEM+LEN) for the treatment of advanced (Stage IV) clear cell variant renal cell carcinoma (aRCC) in patients who are classified as intermediate or poor risk, on the basis that it should be available only under special arrangements under Section 100 (Efficient Funding of Chemotherapy). The PBAC was satisfied that PEM+LEN was likely non-inferior to the nominated comparator, nivolumab plus ipilimumab (NIVO+IPI) in terms of overall survival (OS) and has a different, yet non-inferior, safety profile. The PBAC recommended listing on a cost-minimisation basis compared to NIVO+IPI, taking into account the likely duration of treatment for each therapy. The PBAC advised that PEM+LEN should join the existing risk sharing arrangement (RSA).
- 7.2 The PBAC noted and welcomed the input from individuals, health professionals and organisations via the Consumer Comments facility. The PBAC noted that the comments described the more predictable response observed with PEM+LEN over NIVO+IPI and that PEM+LEN provides an alternate therapy for patients who have a contraindication to NIVO+IPI or in whom the potential for toxicity is too great.
- 7.3 The PBAC considered that the proposed place in therapy for PEM+LEN as a treatment for patients with intermediate to poor risk aRCC was appropriate. The PBAC noted that the proposed TGA indication and current clinical guidelines recommended PEM+LEN as a preferred option in all risk groups (i.e. favourable, intermediate and poor), and considered there is a small risk of use outside the proposed restriction in patients with favourable risk disease.
- 7.4 The PBAC considered that the nominated comparator of NIVO+IPI was appropriate.
- 7.5 The PBAC noted that the submission presented an indirect treatment comparison (ITC) comparing PEM+LEN (KN 581 trial) and NIVO+IPI (CM214 trial) in patients with previously untreated aRCC using sunitinib as the common comparator. The PBAC considered there were some key differences across the trials that may have affected their transitivity (see paragraph 6.10). The PBAC also considered that the OS data for both the trials, particularly KN 581, were immature at the time of the data-cut off used in the ITC, but acknowledged that any comparison using the extended data may be confounded by the differences in subsequent therapies.

- 7.6 The PBAC noted that the ITC demonstrated that PEM+LEN was likely non-inferior to NIVO+IPI in terms of OS (HR = 0.92; 95% CI: 0.62, 1.36). The PBAC did not consider that the claim of superior PFS was supported (HR = 0.44; 95% CI: 0.32, 0.61) because PFS may not be a reliable measure of the clinical effectiveness of immunotherapies as tumour responses can occur after conventional RECIST-defined progressive disease.
- 7.7 The PBAC noted the results of the matching-adjusted indirect comparison (MAIC) for PFS (HR = 0.44; 95% CI: 0.32, 0.60) and OS (HR = 0.92; 95% CI: 0.62, 1.37) were similar to the ITC comparison estimates.
- 7.8 In terms of safety, the PBAC noted that although the profiles of PEM+LEN and NIVO+IPI are different, the proportion of patients experiencing any adverse event was similar between the KN 581 (97%) and CM 214 (93%) trials. The PBAC noted that PEM+LEN had more Grade \geq 3 treatment-related adverse events compared to NIVO+IPI (72% versus 47%). Based on the results of the naïve side-by-side comparison, the PBAC considered that PEM+LEN had a different, yet non-inferior safety profile compared to NIVO+IPI.
- 7.9 The PBAC noted that although the submission presented a cost minimisation approach based on the results of the MAIC, it did not calculate the cost minimised price based on equi-effective doses; rather, the submission presented a partitioned survival model to estimate the time on treatment (ToT) and incremental costs between PEM+LEN and NIVO+IPI.
- 7.10 The PBAC noted that to estimate ToT for the NIVO+IPI arm, a HR of 0.46 was applied to the ToT function for lenvatinib based on the HR for PFS derived from the MAIC. The PBAC noted that the HR of 0.46 applied differed from that calculated in the MAIC (PFS HR = 0.44) but considered that the difference was minimal. The PBAC recalled that it had previously considered that PFS was a poor proxy for ToT in immunotherapy and that PFS is a surrogate outcome and extrapolation of PFS may not be a reliable basis upon which to estimate treatment exposure (paragraph 6.43, avelumab PSD, March 2020). The PBAC noted that the pre-PBAC response stated that given the uncertainty introduced by using the PFS HR from the MAIC to estimate the relative ToT from PEM+LEN versus NIVO+IPI, it may be reasonable to set ToT for both arms to parity (i.e. HR = 1). The PBAC considered that increasing the HR to 1.00 was not adequately justified in the pre-PBAC response. However, the PBAC also considered that use of a HR of 0.46 may be overly conservative given the aforementioned issues with using PFS as a surrogate for ToT. In the absence of further information, the PBAC considered that it may be reasonable for the CMA to apply a HR higher than 0.46 and advised that the application of the upper limit of the confidence interval from the submission's MAIC (HR = 0.61) would be reasonable. This resulted in equi-effective ToTs (and, in brackets, the doses using the regimens and RDIs as per Table 12) of:

$$\left| \text{months at } \left| \frac{\%}{100} \right| \text{ dose intensity (} \left| \frac{\text{mg}}{\text{m}^2} \right| \text{) PEM} + \left| \text{months at } \left| \frac{\%}{100} \right| \text{ dose intensity (} \left| \frac{\text{mg}}{\text{m}^2} \right| \text{) LEN} =$$

| months (| mg) NIVO + | months (| mg) IPI, both at |% dose intensity.

- 7.11 The PBAC noted that the CMA should result in the cost of PEM+LEN being no more than the cost of NIVO+IPI, based on the effective approved ex-manufacturer prices and accounting for differences in the mode and frequency of administration between PEM+LEN and NIVO+IPI and the differences in the safety profiles (i.e. as calculated in Table 13 with an incremental cost of \$0, and using a ToT HR = 0.61).
- 7.12 The PBAC considered that there would be higher uptake of PEM+LEN as compared to NIVO+IPI due to contraindications to NIVO+IPI and the potential for toxicity with NIVO+IPI. The PBAC advised that PEM+LEN should join the existing risk sharing arrangement (RSA). The PBAC noted the pre-PBAC response's request for an increase to the expenditure caps. The PBAC agreed that there may be increased utilisation due to uptake in patients who are ineligible for NIVO+IPI. However, the PBAC considered that any amendment to the existing caps should take into account how current utilisation under the RCC RSA is tracking and advised that the RSA should be reviewed 12 months after the PBS listing of PEM+LEN.
- 7.13 The PBAC noted that the proposed restrictions for PEM+LEN were generally consistent with the existing PBS listings for NIVO+IPI. The PBAC advised that flow-on changes would be required to the current LEN listing to allow its use in aRCC. The PBAC advised that flow-on changes would also be required to the current NIVO restrictions to align the clinical criteria with respect to wording around the prognostic IMCD scores and that the IMDC score needs to be documented in the medical records. The PBAC advised that grandfather listings for both PEM and LEN be in place for a period of 12 months to transition approximately 50 patients from clinical trials and compassionate access programs to PBS-subsidised use.
- 7.14 The proposed restrictions for pembrolizumab were based on an initial dose of 200 mg every three weeks for seven cycles, then choice of either continuation of the three-weekly regimen or 400 mg every six weeks thereafter up to a maximum of 2 years treatment. However, the Product Information for pembrolizumab states that the recommended dose of pembrolizumab is either: 200 mg every 3 weeks; or 400 mg every 6 weeks (i.e. no requirement to initiate on the more frequent dosing regimen). The PBAC considered the restriction proposed by the sponsor was reasonable as patients would likely be initiated on the more frequent dosing regimen while being monitored for response or toxicity.
- 7.15 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because PEM+LEN is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over NIVO+IPI, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by *the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 7.16 The PBAC noted that this submission is not eligible for an Independent Review as it

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received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Amend existing pembrolizumab listings as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Amount	No. of Rpts	Available brands
PEMBROLIZUMAB				
pembrolizumab 100 mg/4 mL injections, 4 mL vial	New (public) New (private)	200 mg	6	Keytruda

Initial supply

Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
(for internal Dept. use)	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Type <input checked="" type="checkbox"/> Authority Required – Streamlined [new]
	Episodicity: 3 weekly treatment
	Severity: Advanced (Stage IV)
	Condition: Clear cell variant renal cell carcinoma (RCC)
	Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
	Treatment Phase: Initial treatment
	Clinical criteria:
	Patient must have a current prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score of either: (i) 1 to 2 (intermediate risk), (ii) 3 to 6 (poor risk), documented in the patient's medical records at the time of prescribing
	AND
	Clinical criteria:
	The condition must not have previously been treated
	AND
	Clinical criteria:
	Patient must have a WHO performance status of 2 or less
	AND
	Clinical criteria:
	The treatment must be in combination with PBS-subsidised lenvatinib for this indication condition, unless an intolerance to lenvatinib requires a temporary or permanent dose reduction or discontinuation of lenvatinib
	AND
	Clinical criteria:
	The treatment must not exceed a total of 7 doses of 200 mg every 3 weeks under this restriction for initial therapy with this drug for this condition
	Prescriber Instruction: Document any IMDC risk score in the patient's medical records.
	Prescribing Instruction: In a patient who has experienced an intolerance to lenvatinib, details of intolerance must be documents in the patient's medical record.

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	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
	<p>Administrative Advice: A prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk score can be calculated here: https://www.mdcalc.com/imdc-international-metastatic-renal-cell-carcinoma.</p> <p>One point is assigned for each of:</p> <ul style="list-style-type: none"> (i) a time of diagnosis to systemic therapy of less than 1 year (ii) a Karnofsky Performance Status of less than 80% (iii) a haemoglobin less than the lower limit of normal (iv) a corrected calcium level greater than the upper limit of normal (v) a neutrophil count greater than the upper limit of normal (vi) a platelet count greater than the upper limit of normal <p>Stated normal reference ranges may vary depending on the laboratory providing the measurement. 'Normal' here refers to the individual laboratory's stated normal reference range.</p> <p>Favourable IMDC risk is a score of 0. Intermediate IMDC risk is a score of 1 to 2. Poor IMDC risk is a score of 3 to 6.</p> <p>The Department of Health is not the webmaster of the website mentioned above. If the website link mentioned above is no longer functioning, notify the Department via email to: pbs@health.gov.au</p>

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Amount	No. of Rpts	Available brands
PEMBROLIZUMAB				
pembrolizumab 100 mg/4 mL injections, 4 mL vial	New (public) New (private)	200 mg	6	Keytruda
pembrolizumab 100 mg/4 mL injections, 4 mL vial	New (public) New (private)	400 mg	3	Keytruda

Grandfather supply

Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
(for internal Dept. use)	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Type <input checked="" type="checkbox"/> Authority Required – Streamlined [new]
	Episodicity: 3 weekly treatment
	Severity: Advanced (Stage IV)
	Condition: Clear cell variant renal cell carcinoma (RCC)
	Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
	Treatment Phase: Transitioning from non-PBS to PBS subsidised treatment – 'Grandfather' treatment
	Clinical criteria:
	Patient must have had a prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score of either: (i) 1 to 2 (intermediate risk), (ii) 3 to 6 (poor risk), documented in the patient's medical records at the time of prior to initiating non-PBS-subsidised treatment with pembrolizumab this drug and lenvatinib for this condition
	AND
	Clinical criteria:
	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date]

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	AND
	Clinical criteria:
	Patient must have had a WHO performance status of 2 or less prior to initiating non-PBS-subsidised treatment with pembrolizumab this drug and lenvatinib for this condition
	AND
	Clinical criteria:
	The condition must not have previously been treated prior to initiating non-PBS-subsidised treatment with pembrolizumab this drug and lenvatinib for this condition
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be in combination with PBS-subsidised lenvatinib for this indication condition, unless an intolerance to lenvatinib requires a temporary or permanent dose reduction or discontinuation of lenvatinib
	AND
	Clinical criteria:
	The treatment must not exceed a total of 7 doses of 200 mg every 3 weeks for initial therapy with this drug for this condition
	AND
	Clinical criteria:
	The treatment must not exceed a total of 28 doses in a lifetime at a dose of 200 mg every 3 weeks for continuing therapy for this condition, OR The treatment must not exceed a total of 14 doses in a lifetime at a dose of 400 mg every 6 weeks for continuing therapy for this condition, OR The treatment must not exceed a total of 24 months of treatment in a lifetime when a combined dose regimen of 200 mg every 3 weeks and 400 mg every 6 weeks is used for continuing therapy for this condition
	Prescribing instruction: 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.
	Prescribing Instruction: Document any IMDC risk score assessment in the patient's medical records.
	Prescribing Instruction: In a patient who has experienced an intolerance to lenvatinib, details of intolerance must be documented in the patient's medical record.
	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: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
	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: A prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk score can be calculated here: https://www.mdcalc.com/imdc-international-metastatic-ccc-database-consortium-risk-model-metastatic-renal-cell-carcinoma . One point is assigned for each of: (i) a time of diagnosis to systemic therapy of less than 1 year (ii) a Karnofsky Performance Status of less than 80% (iii) a haemoglobin less than the lower limit of normal (iv) a corrected calcium level greater than the upper limit of normal (v) a neutrophil count greater than the upper limit of normal (vi) a platelet count greater than the upper limit of normal

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<p>Stated normal reference ranges may vary depending on the laboratory providing the measurement. 'Normal' here refers to the individual laboratory's stated normal reference range.</p> <p>Favourable IMDC risk is a score of 0. Intermediate IMDC risk is a score of 1 to 2. Poor IMDC risk is a score of 3 to 6.</p> <p>The Department of Health is not the webmaster of the website mentioned above. If the website link mentioned above is no longer functioning, notify the Department via email to: pbs@health.gov.au</p>

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Amount	No. of Rpts	Available brands
PEMBROLIZUMAB				
pembrolizumab 100 mg/4 mL injections, 4 mL vial	New (public) New (private)	200 mg	6	Keytruda
pembrolizumab 100 mg/4 mL injections, 4 mL vial	New (public) New (private)	400 mg	3	Keytruda

Continuing supply

<p>Concept ID</p> <p>(for internal Dept. use)</p>	<p>Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals</p>
	<p>Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners</p>
	<p>Restriction Type</p> <p><input checked="" type="checkbox"/> Authority Required – Streamlined [new]</p>
	<p>Episodicity: 3 weekly treatment</p>
	<p>Severity: Advanced (Stage IV)</p>
	<p>Condition: Clear cell variant renal cell carcinoma (RCC)</p>
	<p>Indication: Stage IV clear cell variant renal cell carcinoma (RCC)</p>
	<p>Treatment Phase: Continuing treatment</p>
	<p>Clinical criteria:</p> <p>Patient must have previously received PBS-subsidised treatment with this drug for this condition</p>
	<p>AND</p>
	<p>Clinical criteria:</p> <p>Patient must not have developed disease progression while being treated with this drug for this condition</p>
	<p>AND</p>
	<p>Clinical criteria:</p> <p>The treatment must be in combination with PBS-subsidised lenvatinib for this indication condition, unless an intolerance to lenvatinib requires a temporary or permanent dose reduction or discontinuation of lenvatinib</p>
	<p>Clinical criteria:</p> <p>The treatment must not exceed a total of 28 cycles doses of pembrolizumab treatment in a lifetime at a dose of 200 mg every 3 weeks for continuing therapy for this condition, Patients with stable or responding disease may continue to receive lenvatinib alone after cessation of pembrolizumab. OR</p> <p>The treatment must not exceed a total of 14 doses in a lifetime at a dose of 400 mg every 6 weeks for continuing therapy for this condition, OR</p> <p>The treatment must not exceed a total of 24 months of treatment in a lifetime when a combined dose regimen of 200 mg every 3 weeks and 400 mg every 6 weeks is used for continuing therapy for this condition</p>
	<p>Prescriber Instructions:</p> <p><i>In a patient who has experienced an intolerance to lenvatinib, details of intolerance must be documented in the patient's medical record</i></p>
<p>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</p>	
<p>Administrative Advice: No increase in the maximum quantity or number of units may be authorised.</p>	

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Administrative Advice: No increase in the maximum number of repeats may be authorised
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8.2 Flow on changes are required to allow the use of lenvatinib in the treatment of aRCC. Amend existing lenvatinib listings as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Quantity (packs)	Max. Amount (units)	No. of Rpts	Available brands
LENVATINIB					
lenvatinib capsules 4 mg, 30	New	2	60	2	Lenvima
lenvatinib capsules 10 mg, 30	New	2	60	2	

Initial supply

Concept ID	Category / Program: General Schedule – Section 85
(for internal Dept. use)	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Type <input checked="" type="checkbox"/> Authority Required – Streamlined [new]
	Episodicity: Daily
	Severity: Advanced (Stage IV)
	Condition: Clear cell variant renal cell carcinoma (RCC)
	Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
	Treatment Phase: Initial treatment
	Clinical criteria:
	Patient must have a current prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score of either: (i) 1 to 2 (intermediate risk), (ii) 3 to 6 (poor risk), documented in the patient's medical records at the time of prescribing.
	AND
	Clinical criteria:
	The condition must not have previously been treated
	AND
	Clinical criteria:
	Patient must have a WHO performance status of 2 or less
	AND
	Clinical criteria:
	The treatment must be in combination with PBS-subsidised pembrolizumab for this indication <i>condition</i> , unless an intolerance to pembrolizumab requires a temporary or permanent dose reduction or discontinuation of pembrolizumab
	Prescribing Instruction: <i>Document any IMDC risk score assessment in the patient's medical records.</i>
	Prescribing Instruction: <i>In a patient who has experienced an intolerance to pembrolizumab, details of intolerance must be documented in the patient's medical record.</i>
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised. <i>[Remove this for the 4 mg strength]</i>
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice: A prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk score can be calculated here: https://www.mdcalc.com/imdc-international-metastatic-rcc-database-consortium-risk-model-metastatic-renal-cell-carcinoma . One point is assigned for each of: (i) a time of diagnosis to systemic therapy of less than 1 year (ii) a Karnofsky Performance Status of less than 80%

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	<p>(iii) a haemoglobin less than the lower limit of normal (iv) a corrected calcium level greater than the upper limit of normal (v) a neutrophil count greater than the upper limit of normal (vi) a platelet count greater than the upper limit of normal</p> <p>Stated normal reference ranges may vary depending on the laboratory providing the measurement. 'Normal' here refers to the individual laboratory's stated normal reference range.</p> <p>Favourable IMDC risk is a score of 0. Intermediate IMDC risk is a score of 1 to 2. Poor IMDC risk is a score of 3 to 6.</p> <p>The Department of Health is not the webmaster of the website mentioned above. If the website link mentioned above is no longer functioning, notify the Department via email to: pbs@health.gov.au</p>
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Grandfather supply

Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID	Category / Program: General Schedule – Section 85
(for internal Dept. use)	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Type <input checked="" type="checkbox"/> Authority Required – Streamlined [new]
	Episodicity: Daily
	Severity: Advanced (Stage IV)
	Condition: Clear cell variant renal cell carcinoma (RCC)
	Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
	Treatment Phase: Transitioning from non-PBS to PBS subsidised treatment – 'Grandfather' treatment
	Clinical criteria:
	Patient must have had a prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score of either: (i) 1 to 2 (intermediate risk), (ii) 3 to 6 (poor risk), documented in the patient's medical records <i>documented in the patient's medical records at the time of initiating non-PBS-subsidised treatment with lenvatinib this drug and pembrolizumab for this condition</i>
	AND
	Clinical criteria:
	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date]
	AND
	Clinical criteria:
	Patient must have had a WHO performance status of 2 or less prior to initiating non-PBS-subsidised treatment with lenvatinib <i>this drug and pembrolizumab for this condition</i>
	AND
	Clinical criteria:
	The condition must not have previously been treated prior to initiating non-PBS-subsidised treatment with lenvatinib <i>this drug and pembrolizumab for this condition</i>
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be in combination with PBS-subsidised pembrolizumab for this indication <i>condition</i> , unless an intolerance to pembrolizumab requires a temporary or permanent dose reduction or discontinuation of pembrolizumab
	Prescribing Instruction: 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.
	Prescribing Instruction: <i>Document any IMDC risk score assessment in the patient's medical records.</i>

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	Prescribing Instruction: <i>In a patient who has experienced an intolerance to pembrolizumab, details of intolerance must be documented in the patient's medical record.</i>
	Administrative Advice: <i>This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.</i>
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised. <i>[Remove this for the 4 mg strength]</i>
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	<p>Administrative Advice: A prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk score can be calculated here: https://www.mdcalc.com/imdc-international-metastatic-rcc-database-consortium-risk-model-metastatic-renal-cell-carcinoma.</p> <p>One point is assigned for each of:</p> <ul style="list-style-type: none"> (i) a time of diagnosis to systemic therapy of less than 1 year (ii) a Karnofsky Performance Status of less than 80% (iii) a haemoglobin less than the lower limit of normal (iv) a corrected calcium level greater than the upper limit of normal (v) a neutrophil count greater than the upper limit of normal (vi) a platelet count greater than the upper limit of normal <p>Stated normal reference ranges may vary depending on the laboratory providing the measurement. 'Normal' here refers to the individual laboratory's stated normal reference range.</p> <p>Favourable IMDC risk is a score of 0. Intermediate IMDC risk is a score of 1 to 2. Poor IMDC risk is a score of 3 to 6.</p> <p>The Department of Health is not the webmaster of the website mentioned above. If the website link mentioned above is no longer functioning, notify the Department via email to: pbs@health.gov.au</p>

Continuing supply

	Category / Program: General Schedule – Section 85
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Type <input checked="" type="checkbox"/> Authority Required – Streamlined [new]
	Episodicity: Daily
	Severity: Advanced (Stage IV)
	Condition: Clear cell variant renal cell carcinoma (RCC)
	Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
	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 developed disease progression while being treated with this drug for this condition
	AND
	Clinical criteria: The treatment is prescribed must be in combination with PBS subsidised pembrolizumab for this indication condition, unless the patient (i) has completed the equivalent a total of 35 Q3W cycles of pembrolizumab doses of pembrolizumab in a lifetime at a dose of 200 mg every 3 weeks for continuing therapy, (ii) has completed a total of 18 doses of pembrolizumab in a lifetime at a dose of 400 mg every 6 weeks for continuing therapy, (iii) has exceeded a total of 24 months of pembrolizumab treatment in a lifetime when a combined dose regimen of 200 mg every 3 weeks and 400 mg every 6 weeks is used for continuing therapy, (iv) or develops an intolerance to pembrolizumab and requires a temporary or permanent discontinuation of pembrolizumab.

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	Prescribing Instruction: <i>In a patient who has experienced an intolerance to pembrolizumab, details of intolerance must be documented in the patient's medical record.</i>
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised. <i>[Remove this for the 4 mg strength]</i>
	Administrative Advice: No increase in the maximum number of repeats may be authorised

8.3 Flow on changes are also required to the existing listing for nivolumab in aRCC. Amend existing nivolumab listings as follows:

Medicinal Product: Nivolumab	
Indication: Stage IV clear cell variant renal cell carcinoma (RCC) [7597]	Treatment Phase: Induction treatment
Affected PBS item codes: 11627Y and 11636K	Affected Restriction Summary Number: 8609

	Clinical criteria: The condition must be classified as intermediate to poor risk according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC).
	Clinical criteria: <i>Patient must have a current prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score of either: (i) 1 to 2 (intermediate risk), (ii) 3 to 6 (poor risk) at the time of prescribing.</i>
	Prescribing Instruction: <i>Document any IMDC risk score assessment in the patient's medical records.</i>

This restriction 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 welcomes the positive recommendation made by the PBAC and the acknowledged benefit that reimbursed access will bring to those patients who currently lack an effective IO/TKI treatment.

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MSD will work closely with the Department of Health to ensure that this combination therapy is made available to Australian patients as soon as possible.