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 Program), Authority Required (Streamlined) listing for pembrolizumab for the adjuvant treatment of patients with renal cell carcinoma (RCC) with clear cell component who are at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions (M1 no evidence of disease [NED]).

1.2 Listing was requested on the basis of a cost-effectiveness analysis *versus* surveillance. The key components of the clinical issue are summarised in Table 1.

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

Component	Description
Population	Adjuvant treatment of patients with RCC with clear cell component who are at intermediate-high[a] or high risk of recurrence[b] following nephrectomy, or following nephrectomy and resection of metastatic lesions (M1 NED)[c], where the risk categories were based on pathological tumour-node-metastasis staging, Fuhrman grade and presence of sarcomatoid features.
Intervention	Pembrolizumab 200 mg IV, every 3 weeks (maximum 17 cycles)
Comparator	Surveillance[d]
Outcomes	Primary outcome: DFS per investigator review Secondary outcomes: OS, DRSS, EFS [e]
Clinical claim	In patients who have undergone nephrectomy and have intermediate-high, high risk or M1 NED RCC with clear cell component, pembrolizumab is superior with respect to DFS and OS and has an inferior but manageable safety profile when compared to surveillance[d].

Source: Table 1.1-1, p3 of the submission.
DFS = disease-free survival; DRSS = disease recurrence-specific survival; EFS = event-free survival; IV = intravenous; M1 NED = M1 no evidence of disease; OS = overall survival; RCC = renal cell carcinoma
[a] Intermediate-high risk is defined as pT2 with Grade 4 or sarcomatoid features; or pT3, any grade without nodal involvement (N0) or distant metastases (M0).
[b] High-risk is defined as pT4, any grade N0 and M0; or any pT, any grade, nodal involvement and M0
[c] M1 NED is defined as patients that present with not only the primary kidney tumour but also solid, isolated, soft tissue metastases that can be completely resected at the time or within 12 months of nephrectomy
[d] The comparator nominated in the submission was surveillance, and placebo was used as a proxy for surveillance in the clinical trial KN564.
[e] Other important secondary outcomes include safety and health-related quality of life measures.

2 Background

Registration status

2.1 Pembrolizumab was approved by the TGA on 6th October 2022 for the following indication: KEYTRUDA® (pembrolizumab), as monotherapy, is indicated for the

adjuvant treatment of patients with RCC with a clear cell component who are at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions.

2.2 The relevant TGA application was reviewed under the collaborative arrangements of the United States (US) Food and Drug Administration (FDA) Project Orbis initiative, based on the clinical data from the key trial KEYNOTE-564 (herein referred to as KN564) at the data cutoff (DCO) date for the pre-specified interim analysis 1 (IA1) (14th December 2020) and the updated analysis (DCO: 14th June 2021) with additional 6 months follow up after IA1 on request of the FDA.

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics.

MEDICINAL PRODUCT Form	**Dispensed Price Max Amt**	**Max. Amount**	**№.of Rpts**
Pembrolizumab Solution concentration for I.V. infusion	Published prices: $7,889.36 (private)[a] $7,737.63 (public)[a] Effective prices: $[redacted] (private)[a] $[redacted] (public)[a]	200 mg	7
Pembrolizumab Solution concentration for I.V. infusion	Published prices: $15,643.92 (private)[a] $15,385.13 (public)[a] Effective prices: $[redacted] (private)[a] $[redacted] (public)[a]	400 mg	3
Available brands			
Keytruda® (pembrolizumab 100 mg in 4mL solution concentration for I.V. infusion, 1 vial)			

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED)
Severity: Intermediate or high risk of recurrence
Condition: Clear cell variant renal cell carcinoma (RCC)
Indication: Intermediate or high risk of recurrence clear cell variant renal cell carcinoma (RCC)
Treatment Phase: Initial treatment
Clinical criteria:
Patient must have: (i) pT2 with Grade 4 or sarcomatoid features OR (ii) pT3, with any grade without nodal involvement (N0) or distant metastases (M0) OR (iii) pT4, any grade N0 and M0 OR (iv) any pT, any grade with nodal involvement and M0 OR (v) metastatic disease and has undergone complete resection of primary and metastatic lesions.
AND
Clinical criteria:
The treatment must be in addition to complete surgical resection
AND

Clinical criteria:
The treatment must commence within 12 weeks of complete resection
AND
Clinical criteria:
Patient must have a WHO performance status of 1 or less
AND
Clinical criteria:
Patient must not have previously been treated with systemic therapy for this condition, *prior to commencing treatment with this drug for this condition*
AND
Clinical Criteria:
The treatment must be the sole PBS-subsidised *anti-cancer* therapy for this condition.
Treatment Criteria:
Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS-subsidised adjuvant therapy.
Administrative Advice: No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Administrative Advice Applications for authorisation under this restriction may be made in real-time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333

Source: Table 1.4-1, p16 and Table on pp17-18 of the submission.

[a] The dispensed prices have been updated using the Efficient Funding for Chemotherapy mark-ups and fees as of July 2024.

MEDICINAL PRODUCT Form	Dispensed Price Max Amt	Max. Amount	№.of Rpts
Pembrolizumab Solution concentration for I.V. infusion	Published prices: $7,889.36 (private)[a] $7,737.63 (public)[a] Effective prices: $[redacted] (private)[a] $[redacted] (public)[a]	200 mg	8
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Available brands			
Keytruda® (pembrolizumab 100 mg in 4mL solution concentration for I.V. infusion, 1 vial)			

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED)
Severity: Intermediate or high risk of recurrence
Condition: Clear cell variant renal cell carcinoma (RCC)
Indication: Intermediate or high risk of recurrence 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 experienced disease recurrence while being treated with this drug for this condition
AND
Clinical Criteria:
The treatment must be the sole PBS-subsidised *anti-cancer* therapy for this condition.
Treatment Criteria:
Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS-subsidised adjuvant therapy.
Administrative Advice: No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Administrative Advice Applications for authorisation under this restriction may be made in real-time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333

Source: Table 1.4-1, p16 and Table on pp17-18 of the submission.

[a] The dispensed prices have been updated using the Efficient Funding for Chemotherapy mark-ups and fees as of July 2024.

3.2 The submission requested a special pricing arrangement (SPA). The proposed effective and published ex-manufacturer prices per 100 mg vial of pembrolizumab are $ and $3,823.75, respectively. The pre-PBAC response reduced the effective ex-manufacturer price per 100 mg vial to $.

3.3 The recommended dose regimen of pembrolizumab as adjuvant therapy for RCC is pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) or 400 mg IV every 6 weeks (Q6W), administered for up to 1 year or until disease recurrence or unacceptable toxicity. The original script plus repeats will provide approximately 6 months of treatment for both initial treatment and continuing treatment. This is consistent with programmed cell death (ligand) 1 (PD-(L)1) inhibitors listed on the PBS in the adjuvant setting for other indications, such as triple negative breast cancer (TNBC) and melanoma. After confirmation of no disease recurrence or toxicity, a patient would be eligible to receive the remaining 6-month supply via a continuing treatment script (plus repeats) to complete their 12-month treatment course. The ESC advised that limiting treatment to 12 months was appropriate and consistent with the trial.

3.4 The submission requested two restrictions – one for initial treatment and one for continuing treatment. The PBAC considered it would be appropriate to have a single listing, similar to the current listing for early triple negative breast cancer. The submission noted that these proposed restrictions have been written in a manner that enables grandfathered patients to access PBS therapy. However, the initial listing PBS restriction proposed in the submission specifies that the "patient must not have previously been treated with systemic therapy for this condition" which would preclude grandfathered patients having access to PBS-subsidised treatment. The Secretariat has suggested revised wording to enable grandfathered patients to transition to PBS subsidised treatment.

3.5 The proposed PBS restrictions are in line with the TGA-approved indication for the treatment of RCC in the adjuvant setting. The definitions of intermediate-high risk, high risk and M1 NED specified in the proposed PBS listing are based on the patient

selection criteria in the KN564 trial and are appropriate. Other clinical criteria in the PBS restrictions, such as Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 or 1), the duration between complete surgical resection and initiation of pembrolizumab therapy (≤ 12 weeks), and prior treatment history (treatment-naïve), are also consistent with the eligibility criteria in the KN564 trial. The ESC considered the descriptions of risk featured in the clinical criteria were appropriate and would minimise risk of use outside the restriction. Patients with pre-existing brain or bone metastatic lesions were excluded from the trial; however, according to the proposed PBS restriction, this patient group would still be eligible for pembrolizumab adjuvant therapy if their metastatic lesions were completely resected. The PBAC considered this would apply to a small population and the restriction was appropriate.

3.6 The submission noted that, to be consistent with the once-in-a-lifetime rule for PD-(L)1 inhibitors in treatment of other tumour indications, the PBAC may wish to consider flow-on restriction changes to the current listings of pembrolizumab + lenvatinib and nivolumab + ipilimumab for the treatment of Stage IV RCC, to prevent sequential use of PD-(L)1 agents. The ESC agreed this would be appropriate. The key trial did not provide efficacy data in patients randomised to the pembrolizumab arm who were treated with a PD-(L) inhibitor following metastatic recurrence.

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

4 Population and disease

4.1 The number of new cases of kidney cancer diagnosed and the age-standardised incidence rate have increased over time. Kidney cancer was the 7th most commonly diagnosed cancer in Australia in 2019. According to the Australian Institute of Health and Welfare (AIHW) Cancer data[1], there were 4,061 new cases of kidney cancer diagnosed in Australia in 2019, with an aged-standardised incidence rate of 13.8 cases per 100,000 persons. In 2021, there were 993 deaths (653 males and 340 females) from kidney cancer in Australia, using the National Mortality Database.

4.2 RCC comprises approximately 90% of all kidney cancers. The most common histological subtype of RCC is clear cell carcinoma (80%-90%). Typical clinical manifestations associated with RCC include flank pain, abdominal mass, and haematuria. However, there has been a shift towards tumours being diagnosed incidentally[2].

4.3 In 2015-2019, 81.7% of patients diagnosed with kidney cancer survived 5 years after diagnosis after adjusting for general mortality[1]. Prognosis is dependent upon tumour size, grade, local extent, regional nodal involvement, and metastatic disease at

[1] Australian Institute of Health and Welfare. Cancer in Australia. Canberra: Australian Institute of Health and Welfare, Australian Government. 2023; Available from: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/about. [Accessed 22 July 2024].

[2] Arora RD, Limaiem F. Renal clear cell cancer. StatPearls. 2023; Available from: https://www.ncbi.nlm.nih.gov/books/NBK563230/. [Accessed 22 July 2024].

presentation. Five-year survival was 93% for localised disease, 74% for regional disease and 17% for distant metastatic disease, based on the Surveillance, Epidemiology, and End Results (SEER) database[3]. There are different ways to categorise recurrence risk. The risk categories for recurrence used in the key trial and in the proposed PBS restrictions were based on the American Joint Committee on Cancer (AJCC 2017) Tumour, Node, Metastasis (TNM)[4] staging, Fuhrman grade and the presence of sarcomatoid features:

- Intermediate-high risk is defined as: 1) pT2 with Grade 4 or sarcomatoid features; or 2) pT3, any grade without nodal involvement (N0) or distant metastases (M0).
- High-risk is defined as: 1) pT4, any grade N0 and M0; or 2) any pT, any grade, nodal involvement and M0.
- M1 NED is defined as patients that present with not only the primary kidney tumour but also solid, isolated, soft tissue metastases that can be completely resected at the time or within 12 months of nephrectomy.

4.4 Surgical resection, including partial nephrectomy and radical nephrectomy, remains the standard of care for localised RCC. If metastatic lesions are resectable, radical nephrectomy plus metastasectomy (removal of metastatic tumour) can be considered.

4.5 Adjuvant pembrolizumab for patients with intermediate-high or high risk RCC has been recommended by international clinical management guidelines, including National Comprehensive Cancer Network guidelines (version 1.2025), European Association of Urology guidelines (2024), and European Society for Medical Oncology guidelines (2024)[5]. Recommendations were based on the evidence from KN-564. All guidelines specify that the risk of recurrence should be defined as per the trial.

4.6 Pembrolizumab is a selective, humanised monoclonal antibody of the immunoglobulin G4 which binds to the PD-1 receptor on T-cells. It acts as an immunomodulating agent by blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is proposed to be used as adjuvant therapy following complete

[3] American Cancer Society. Survival rates for kidney cancer. Cancer.org. 2024; Available from: https://www.cancer.org/cancer/types/kidney-cancer/detection-diagnosis-staging/survival-rates.html. [Accessed 22 July 2024].

[4] According to the eighth edition of the AJCC (2017) Tumour, Node, Metastasis (TNM) staging system, tumours limited to the kidney are classified as T1 (<7cm) or T2 (7-10cm) based on size, T3 tumours extend into the renal vein or perinephric tissues but not beyond the Gerota fascia, and T4 tumours extend beyond the Gerota fascia, including direct extension into the ipsilateral adrenal gland. Nodal and distant metastases are classified as absent (N0 or M0) or present (N1 and M1).

[5] Powles T, Albiges L, Bex A, *et al*. Renal cell carcinoma: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol. 2024;35(8):692-706.
Ljungberg B, Albiges L, *et al*. EAU guidelines on renal cell carcinoma. Presented at the EAU Annual Congress Paris 2024. Available from: https://uroweb.org/guidelines.
Motzer R, Jonasch E, *et al*. NCCN Guidelines for Kidney Cancer. Version 1.2025. 2024: Available from: https://www.nccn.org/.

resection of the primary tumour (and metastatic lesions) of RCC in patients with a risk of disease recurrence.

5 Comparator

5.1 The submission nominated surveillance as the comparator. Surveillance is the current standard of care as there is no systemic therapy listed on the PBS as adjuvant therapy for RCC. Overall, the ESC considered the nomination of surveillance as the main comparator is appropriate.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The PBAC noted and welcomed the input from individuals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from individuals noted the importance of having equitable access to effective treatments. The comments from Rare Cancers Australia described the impact RCC has on the quality of life and overall well-being of patients and their carers and noted the significant financial burden paying for treatments can have.

6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the pembrolizumab submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the KN564 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pembrolizumab, which was a Grade A. This is the highest grade on a scale from A to C, where A and B represent the grades with substantial improvement for new approaches to adjuvant therapy or new potentially curative therapies.[6]

Clinical trials

6.4 The submission was based on one head-to-head, double blind, randomised trial (KN564) comparing pembrolizumab (200 mg every 3 weeks [Q3W]) (N=496) with placebo (N=498) in patients with clear cell RCC who were at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions. Randomisation was stratified by metastasis status (M0 *vs*. M1 NED

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

by investigator assessment). The M0 group was further stratified by ECOG PS (0 *vs*. 1) and geographic region (US *vs*. non-US).

6.5 Details of the trial presented in the submission are provided in Table 2.

Table 2: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
KEYNOTE-564 (KN564)	A Phase 3, randomised, double-blind, placebo-controlled clinical trial of pembrolizumab (MK-3475) as monotherapy in the adjuvant treatment of renal cell carcinoma post nephrectomy (KEYNOTE-564). Clinical study report (CSR). Interim analysis 1.	December 2020
	A Phase 3, randomised, double-blind, placebo-controlled clinical trial of pembrolizumab (MK-3475) as monotherapy in the adjuvant treatment of renal cell carcinoma post nephrectomy (KEYNOTE-564). Clinical study report (CSR). Interim analysis 3.	September 2023
	Choueiri TK, Tomczak P, Park SH, *et al.* Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma.	*New England Journal of Medicine* 2021; 385(8):683-694
	Choueiri TK, Tomczak P, Park SH, *et al*. Overall survival with adjuvant pembrolizumab in renal-cell carcinoma.	*New England Journal of Medicine* 2024; 390(15):1359-1371
	Choueiri TK, Tomczak P, Park SH, *et al*. Patient-reported outcomes in KEYNOTE-564: adjuvant pembrolizumab *versus* placebo for renal cell carcinoma.	*Oncologist* 2024; *29*(2):142-150
	Powles T, Tomczak P, Park SH, *et al*. Pembrolizumab *versus* placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial.	*The Lancet Oncology* 2022; 23(9):1133-1144
	Choueiri TK, Tomczak P, Park SH, *et al*. Adjuvant pembrolizumab (pembro) for renal cell carcinoma (RCC) across UCLA Integrated Staging System (UISS) risk groups and disease stage: subgroup analyses from the KEYNOTE-564 study. Abstract.	*Journal of Clinical Oncology* 2023; 41(6_suppl):679-679
	Park SH, Chang YH, Lee JL, *et al*. Phase 3 study of pembrolizumab vs placebo as adjuvant therapy for patients with renal cell carcinoma (RCC): KEYNOTE-564 Asia subset. Abstract.	*Asia-Pacific Journal of Clinical Oncology* 2021; 17(S7):38-71.

Source: Table 2.2-1, p22 of the submission.

6.6 The key features of the direct randomised trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Pembrolizumab *versus* placebo						
KN564	994	R, DB 55.8 months[a]	Low	Patients with clear cell RCC who were at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions	DFS by investigator assessment, OS, safety, DRSS, EFS by BICR, HRQoL	HRQoL[b]

Source: Table 2.3-3, p26 and Table 2.3-4, p27 of the submission.

BICR = blinded independent central review; DB = double blind; DF = disease-free; DFS = disease-free survival; DM = distant DRSS = disease recurrence-specific survival; EFS = event-free survival; HRQoL = health-related quality of life; OS = overall survival; R = randomised; RCC = renal cell carcinoma

[a] Pooled median follow-up at data cutoff of interim analysis 3 (15th September 2023).

[b] DFS and OS curves from the trial were not directly used in the economic model. Instead, survival analyses of individual patient-level data were used to model transitions from DF to LR, DM and dead and to model transitions after LR and DM.

6.7 KN564 has a double-blind study design. However, it is possible that there were characteristic adverse events (AEs) associated with pembrolizumab which may have alerted investigators (and possibly patients) to guess the treatment allocation. This could affect those subjective assessments reported or measured by investigators and/or patients, such as disease-free survival (DFS) by investigator assessment and health-related quality of life (HRQoL) outcomes. However, overall risk of bias in the key trial was considered generally low.

6.8 The submission provided results of the primary endpoint, *i.e.* DFS by investigator assessment, and the key secondary outcome of overall survival (OS) at the pre-specified IA1 (data cutoff [DCO] 14th December 2020) and IA3 (DCO 15th September 2023). The trial data with a longer duration of follow-up, i.e. IA3 is presented below.

6.9 Table 4 presents a summary of subsequent anti-cancer treatments reported for the pembrolizumab and placebo arms in the KN564 trial. The proportion of patients by type of subsequent therapy was based on the number of patients randomised.

Table 4: Subsequent anti-cancer therapies in the KN564 trial (ITT population)

	Pembrolizumab (N=496)	Placebo (N=498)	Total (N=994)
Participants who had any subsequent anti-cancer therapy for RCC, n (%)	132 (26.6)	172 (34.2)	304 (30.6)
Subsequent radiation, n (%)	32 (6.5)	34 (6.8)	66 (6.6)
Subsequent surgery	36 (7.3)	50 (10.0)	86 (8.7)
Subsequent drug therapy	105 (21.2)	145 (29.1)	250 (25.2)
PD-1/PD-L1 inhibitors[a]	43 (8.7)	101 (20.3)	144 (14.5)
VEGF/VEGFR targeted therapies[b]	97 (19.6)	123 (24.7)	220 (22.1)
Others[c]	32 (6.5)	60 (12.0)	92 (9.3)

Source: Table 2.4-6, p34 of the submission; Table 10-6, p65 of the KN564 clinical study report of interim analysis 3 (report date: December 2023).

ITT = intention-to-treat; PD-1/PD-L1 = programmed cell death 1/programmed cell death ligand 1; RCC = renal cell carcinoma; VEGF/VEGFR = vascular endothelial growth factor/vascular endothelial growth factor receptor

Note: The total number of participants in the subcategories under any subsequent anticancer drug therapy can exceed the total number of participants with any subsequent anticancer drug therapy because a participant can have multiple types of subsequent anticancer drug therapy.

[a] Included pembrolizumab, avelumab, nivolumab, atezolizumab and durvalumab.

[b] Included axitinib, pazopanib, sunitinib, sorafenib, cabozantinib, lenvatinib, tivozanib, and bevacizumab.

[c] Included all other anticancer drugs than "anti PD1/PD-L1 therapies" and "VEGF/VEGFR targeted therapies".

6.10 Among all randomised participants, subsequent anti-cancer therapy was received by 26.6% of patients in the pembrolizumab arm and 34.2% of patients in the placebo arm. The most common form of subsequent anti-cancer therapy was drug therapy (21.2% in the pembrolizumab arm and 29.1% patients in the placebo arm). Subsequent therapy with a PD-(L)1 inhibitor was received by 8.7% and 20.2% of patients in the pembrolizumab and placebo arms, respectively. In the trial, 161 patients in the pembrolizumab arm and 210 patients in the placebo arm experienced disease recurrence. Using these disease recurrence events as the denominator, the proportion of patients who subsequently received PD-(L)1 inhibitors, post recurrence, was 26.7% (43/161) in the pembrolizumab arm and 48.1% (101/210) in the placebo arm. The ESC

noted that as subsequent PD-(L)1 inhibitor use would not be permitted under the proposed restriction, the sequential use of PD-(L)1 inhibitors, as was observed in the pembrolizumab arm of KN564, may not reflect Australian clinical practice. It was also noted that use of PD-(L)1 inhibitors as subsequent therapy in less than 50% of patients with disease recurrence in the placebo arm is lower than expected in the Australian setting. Therefore, the survival benefit in the placebo arm may have been underestimated (favouring pembrolizumab). The overall impact of subsequent anti-cancer treatments in KN564 on the OS results remains unclear from the available data.

Comparative effectiveness

6.11 Results of the primary endpoint in KN564, *i.e.* DFS by investigator assessment, at IA3 are presented in Table 5. The corresponding Kaplan-Meier (KM) curves are presented in Figure 1. DFS was defined as time from randomisation to the first documented local recurrence, or occurrence of distant metastasis(es), or death due to any cause, whichever occurs first.

Table 5: Results of DFS based on investigator assessment at IA3 in the KN564 trial (ITT population)

	Pembrolizumab (N=496)	**Placebo (N=498)**
Number of events (%)	174 (35.1)	224 (45.0)
Death	13 (2.6)	14 (2.8)
Documented progression	161 (32.5)	210 (42.2)
Kaplan-Meier estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (54.9, NR)
[Q1, Q3]	[30.0, NR]	[13.8, NR]
Person-months	19,815.3	18,255.4
Event rate/100 person-months	0.9	1.2
HR (95% CI)[b] (pembrolizumab *vs.* placebo)	0.72 (0.59, 0.87)	
P-value[c]	0.0005	
DFS rate, % (95% CI)		
At Month 12	85.5 (82.0, 88.4)	76.1 (72.0, 79.6)
At Month 24	78.2 (74.2, 81.6)	67.2 (62.8, 71.1)
At Month 36	72.4 (68.1, 76.2)	62.9 (58.5, 67.0)
At Month 48	64.9 (60.3, 69.1)	56.6 (52.0, 60.9)

Source: Table 2.5-1, p38 of the submission; Table 11-1, p71 of the KN564 clinical study report of interim analysis 3 (report date: December 2023)

CI = confidence interval; DFS = disease-free survival; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; IA3 = interim analysis 3; ITT = intention-to-treat; M1 NED = M1 no evidence of disease; NR = not reached

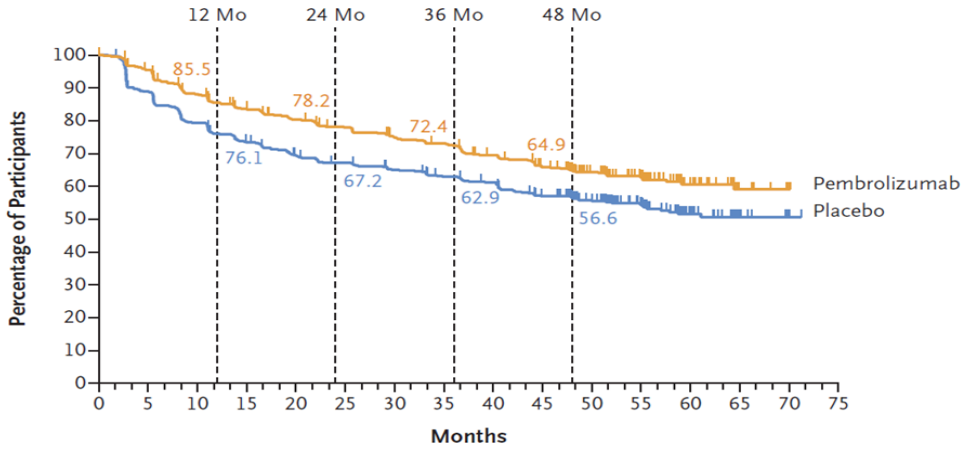
Data cutoff date: 15th September 2023

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1), US participant (Yes versus No) within M0 group by investigator.

[c] One-sided p-value based on log-rank test stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1), US participant (Yes versus No) within M0 group by investigator.

Figure 1: Kaplan-Meier estimates of DFS by investigator assessment at IA3 in the KN564 trial (ITT population)



No. at Risk

Pembrolizumab	496	458	416	388	370	355	337	327	307	284	221	160	65	19	5	0
Placebo	498	438	390	357	333	320	307	292	282	254	210	139	62	16	2	0

Source: Figure 2.5-1, p39 of the submission.
DFS = disease-free survival; IA3 = interim analysis 3; ITT = intention-to-treat
Data cutoff date: 15th September 2023

6.12 At the IA3 DCO (September 2023), the median follow-up duration for the ITT population was 56.2 months in the pembrolizumab arm and 55.3 months in the pembrolizumab arm, respectively.

6.13 A total of 174 (35.1%) in the pembrolizumab group and 224 (45.0%) in the placebo group experienced recurrent disease or death. The difference between pembrolizumab and placebo was driven by events of disease recurrence (161 [32.5%] versus 210 [42.2%]).

6.14 Pembrolizumab adjuvant therapy was associated with a 28% reduction in the hazard of DFS events, compared with placebo (hazard ratio [HR]: 0.72; 95% confidence interval [CI]: 0.59, 0.87). Median DFS was not reached in either arm. The KM curves for DFS separated early at approximately 3 months, *i.e.* time of the first post-randomisation tumour assessment, and remained separated over time in favour of pembrolizumab. The DFS rate at Month 48 was 64.9% in the pembrolizumab arm and 56.6% in the placebo arm.

6.15 Results of the key secondary outcomes of OS are summarised in Table 6, with corresponding OS curves presented in Figure 2.

Table 6: Results of OS at IA3 in the KN564 trial (ITT population)

	Pembrolizumab (N=496)	Placebo (N=498)
Number of events (%)	55 (11.1)	86 (17.3)
Kaplan-Meier estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[NR, NR]	[NR, NR]
Person-months	27,086.3	26,397.2
Event rate/100 person-months	0.2	0.3
HR (95% CI)[b] (pembrolizumab *vs.* placebo)	0.62 (0.44, 0.87)	
P-value[c]	0.0024	
OS rate, % (95% CI)		
At Month 12	98.6 (97.0, 99.3)	98.0 (96.3, 98.9)
At Month 24	96.3 (94.2, 97.7)	93.9 (91.4, 95.7)
At Month 36	93.9 (91.4, 95.7)	89.5 (86.4, 91.9)
At Month 48	91.2 (88.3, 93.4)	86.0 (82.6, 88.8)

Source: Table 2.5-2, p41 of the submission; Table 11-3, p76 of the KN564 clinical study report of interim analysis 3 (report date: December 2023)

CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; IA3 = interim analysis 3; ITT = intention-to-treat; M1 NED = M1 no evidence of disease; NR = not reached; OS = overall survival

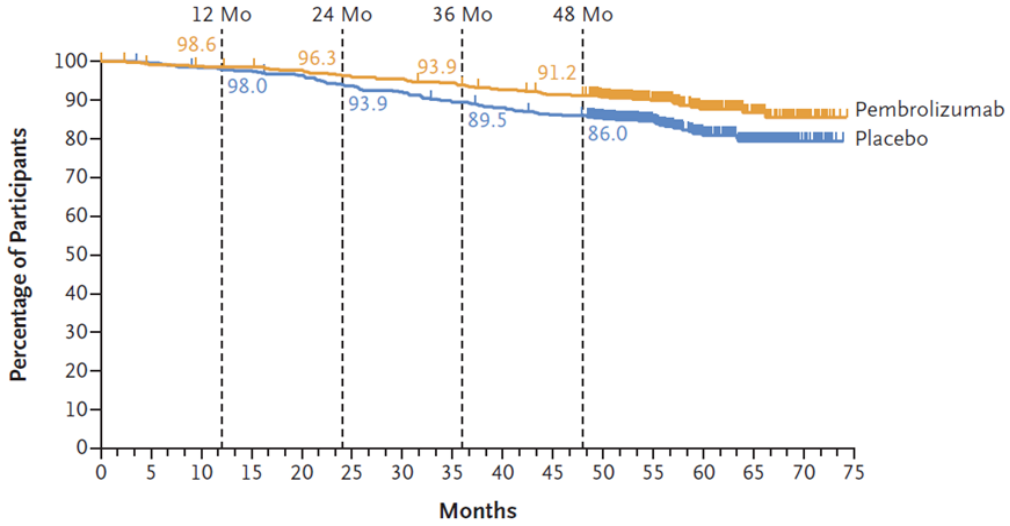
Data cutoff date: 15th September 2023

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1), US participant (Yes versus No) within M0 group by investigator.

[c] One-sided p-value based on log-rank test stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1), US participant (Yes versus No) within M0 group by investigator.

Figure 2: Kaplan-Meier estimates of OS at IA3 in the KN564 trial (ITT population)



Source: Figure 2.5-2, p42 of the submission.

IA3 = interim analysis 3; ITT = intention-to-treat; OS = overall survival

Data cutoff date: 15th September 2023

6.16 By the IA3 DCO, a total of 141 OS events were observed in the ITT population, with 55 (11.1%) events in the pembrolizumab group and 86 (17.3%) events in the placebo group. The Pre-Sub-Committee Response (PSCR) argued this analysis was conducted

after 141 OS events had occurred (representing 71% of the total 200 OS events planned for the final analysis), and as such a 71% information fraction is considered as reasonably mature for OS data. The median OS was not reached in either treatment group. Pembrolizumab showed an improvement in OS, associated with a 38% reduction in the hazard of death events in the pembrolizumab group compared to the placebo group (HR: 0.62; 95% CI: 0.44, 0.87). The OS KM curves of the two treatment arms separated at approximately 15 months and remained separated throughout the trial observation period in favour of pembrolizumab over placebo. The OS rate at Month 48 was 91.2% in the pembrolizumab group and 86.0% in placebo.

6.17 Subgroup analyses of DFS and OS were conducted by age (<65 years *vs.* ≥65 years), sex (female *vs*. males), race (white *vs*. other), performance status (0 *vs.* 1), PD-L1 status (combined positive score [CPS] <1 *vs*. ≥1), geographic region (US *vs*. non-US), metastatic staging by investigator (M0 *vs*. M1 NED), disease risk category (M0 intermediate-high *vs.* M0 high *vs.* M1 NED), and sarcomatoid features (present *vs*. absent). The DFS and OS HRs numerically favoured pembrolizumab over placebo across all subgroups, except for the OS result in the female subgroup (HR: 1.08 [0.57, 2.04] *vs.* 0.50 [0.33, 0.75] in the male subgroup). Any interpretation of the subgroup results should consider the exploratory nature of the analyses. In addition, in the KN564 trial, randomisation was not stratified by gender, and it is unknown whether patient baseline characteristics were balanced across the treatment arms in each subgroup.

6.18 Results of other secondary outcomes provided supportive evidence showing improvements in patients receiving pembrolizumab in terms of:

- Disease recurrence-specific survival 1 (DRSS1, time from randomisation to the first documented local recurrence of RCC): cumulative incidence at Month 48: 4.7% *vs.* 8.0%.
- Disease recurrence-specific survival 2 (DRSS2, time from randomisation to the first documented local recurrence with visceral lesion or occurrence of distant metastasis(es) with visceral lesion, whichever occurs first): cumulative incidence at Month 48: 30.1% *vs.* 37.6%.
- Event-free survival (EFS) assessed by BICR (time from randomisation to the first documented local recurrence or occurrence of distant metastasis(es) among participants, which by BICR were considered M0/M1 NED; or disease progression among participants, which by BICR were considered to have M1, or death due to any cause, whichever occurs first): HR: 0.77 (95% CI: 0.63, 0.95).

6.19 In the KN564 trial, HRQoL was assessed using European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) global health status/quality of life (QoL) and functional scales, Functional Assessment of Cancer Therapy - Kidney Symptom Index Disease-Related Symptoms (FKSI-DRS), and EuroQol 5-Dimensions 5-Level Questionnaire (EQ-5D-5L) visual analogue scale (VAS). For all these measures, the compliance rates were above 90% at baseline and around

80% at Week 52 in both treatment arms. Results showed no clinically meaningful mean change from baseline in both the pembrolizumab and placebo groups at Week 52, with generally overlapping 95%CIs, which suggests no meaningful difference between treatment groups.

6.20 Agents such as pembrolizumab may be associated with serious toxicities such as pneumonitis and colitis. The onset of these symptoms may be highly variable, and such events may occur beyond the 1-year duration of therapy. In the KN564 trial, the HRQoL data were scarcely collected 30 days after discontinuation of study drug (annually during post-treatment follow-up until disease recurrence or initiation of new anti-cancer treatment); and the full impact of pembrolizumab treatment-related toxicity may not have been fully captured. Furthermore, whilst EORTC QLQ-C30 and EQ-5D-5L have become widely used HRQoL measurement tools, they have limitations in capturing immune mediated adverse reactions associated with immune checkpoint inhibitors, but do include questions relating to AEs associated with cytotoxic chemotherapy (not a comparator in the KN564 trial), such as nausea and vomiting. Overall, the HRQoL data were not reflective of the increased risk of drug related toxicity associated with pembrolizumab (refer to safety section below).

Comparative harms

6.21 Table 7 summarises the results of safety outcomes for the KN564 trial at the IA3 DCO. The median duration of treatment was 11.1 months in both treatment arms. Participants were followed for 30 days after the last dose of study treatment for AEs and events of clinical interest; serious adverse events (SAEs) were collected up to 90 days after the last dose of study treatment or for 30 days following cessation of treatment if the participant initiated new anti-cancer therapy, whichever came first.

Table 7: Adverse event summary at IA3 in the KN564 trial (all participants as treated population)

Category	Pembrolizumab N=488 n (%)	Placebo N=496 n (%)	RD (95% CI)[a]	RR (95% CI)[a]
All cause				
AEs (any grade)	470 (96.3)	453 (91.3)	0.05 (0.02, 0.08)	1.05 (1.02, 1.09)
Grade 3-5 AEs	156 (32.0)	88 (17.7)	0.14 (0.09, 0.20)	1.80 (1.43, 2.27)
SAEs (any grade)	101 (20.7)	57 (11.5)	0.09 (0.05, 0.14)	1.80 (1.33, 2.43)
Death	2 (0.4)	1 (0.2)	0.00 (0.00, 0.01)	2.03 (0.18, 22.35)
Discontinuation of study treatment due to AEs	103 (21.1)	11 (2.2)	0.19 (0.15, 0.23)	9.52 (5.18, 17.50)
Discontinuation of study treatment due to SAEs	49 (10.0)	5 (1.0)	0.09 (0.06, 0.12)	9.96 (4.00, 24.79)
Study drug related				
AEs (any grade)	386 (79.1)	263 (53.0)	0.26 (0.20, 0.32)	1.49 (1.36, 1.64)
Grade 3-5 AEs	91 (18.6)	6 (1.2)	0.17 (0.14, 0.21)	15.42 (6.81, 34.88)
SAEs (any grade)	59 (12.1)	1 (0.2)	0.12 (0.09, 0.15)	59.97 (8.34, 431.12)
Death	0 (0.0)	0 (0.0)	0.00 (0.00, 0.00)	Not calculable
Discontinuation of study treatment due to AEs	89 (18.2)	4 (0.8)	0.17 (0.14, 0.21)	22.61 (8.37, 61.10)
Discontinuation of study treatment due to SAEs	38 (7.8)	0 (0.0)	0.08 (0.05, 0.10)	Not calculable

Source: Table 2.5-11, p54 of the submission

AEs = adverse events; CI = confidence interval; IA3 = interim analysis 3; RD = risk difference; RR = relative risk; SAEs = serious adverse events

Data cutoff date: 15th September 2023

[a] RDs, RRs and their 95% CIs were calculated during the evaluation, using Stata 15.

6.22 AEs were reported in more than 90% of the participants who received at least one dose of study drug in both the pembrolizumab and placebo arms (96.3% *vs*. 91.3%). The proportions of patients who had all-cause and drug-related Grade ≥3 AEs, SAEs and AEs leading to discontinuation of study treatment were, as expected, consistently much higher in patients receiving pembrolizumab than those in the placebo group.

6.23 A total of three deaths due to AEs were reported, two (0.4%) in the pembrolizumab arm (preferred term: pneumonia and multiple organ dysfunction syndrome) and one (0.2%) in the placebo arm (preferred term: haemorrhage intracranial). None of these fatal AEs were considered treatment related by the investigator who was blinded to treatment allocation.

6.24 The most frequently reported drug-related AEs in the pembrolizumab group included fatigue (20.3%), pruritus (18.6%), hypothyroidism (17.4%), diarrhoea (15.8%), and rash (15.0%). Most of these events were Grade 1 or 2 AEs. The most common drug-related Grade ≥3 AEs were increased alanine aminotransferase (1.8%), diarrhoea (1.6%), adrenal insufficiency (1.2%), increased aspartate aminotransferase (1.2%), colitis (1.0%), diabetic ketoacidosis (1.0%) and Type 1 diabetes mellitus (1.0%).

6.25 AEs of special interest (AEOSIs) were reported in 36.5% of participants in the pembrolizumab group and 7.3% in the placebo group. Grade 3 AEOSIs were experienced by 8.2% of participants in the pembrolizumab group *versus* 0.6% in the placebo group, and Grade 4 AEOSIs by 1.2% of participants in the pembrolizumab

group *versus* 0.0% in the placebo group. No participants died due to an AEOSI. The frequency of each Grade ≥3 AEOSI was ≤1% in patients receiving pembrolizumab, with exceptions of type 1 diabetes mellitus (2.0%), severe skin reactions (1.6%), and adrenal insufficiency (1.2%).

6.26 Overall, no new safety issues were identified for pembrolizumab, based on the safety data from KN564 trial. The safety profile of pembrolizumab monotherapy was consistent with previously documented safety data. Most of the events observed in the trial were Grade 1 or 2 AEs and were manageable.

Benefits/harms

6.27 A summary of the comparative benefits and harms for pembrolizumab *versus* placebo is presented in Table 8.

Table 8: Summary of the comparative benefits and harms for pembrolizumab *versus* placebo (proxy for surveillance)[a]

Benefits				
	Pembrolizumab N=496	**Placebo N=498**	**Absolute difference**	**HR (95% CI) p-value**
DFS (ITT population)				
Recurrence or death, n (%)	174 (35.1)	224 (45.0)	–	0.72 (0.59, 0.87) p=0.0005
Median DFS, months (95% CI)	NR	NR	–	
DFS rate at Month 12, % (95% CI)	85.5 (82.0, 88.4)	76.1 (72.0, 79.6)	9.4	
DFS rate at Month 24, % (95% CI)	78.2 (74.2, 81.6)	67.2 (62.8, 71.1)	11	
DFS rate at Month 36, % (95% CI)	72.4 (68.1, 76.2)	62.9 (58.5, 67.0)	9.5	
DFS rate at Month 48, % (95% CI)	64.9 (60.3, 69.1)	56.6 (52.0, 60.9)	8.3	
OS				
Death, n (%)	55 (11.1)	86 (17.3)	–	0.62 (0.44, 0.87) p=0.0024
Median OS, months (95% CI)	NR	NR	–	
Alive at Month 12, % (95% CI)	98.6 (97.0, 99.3)	98.0 (96.3, 98.9)	0.6	
Alive at Month 24, % (95% CI)	96.3 (94.2, 97.7)	93.9 (91.4, 95.7)	2.4	
Alive at Month 36, % (95% CI)	93.9 (91.4, 95.7)	89.5 (86.4, 91.9)	4.4	
Alive at Month 48, % (95% CI)	91.2 (88.3, 93.4)	86.0 (82.6, 88.8)	5.2	

Harms (all participants as treated population)						
Event	**Pembrolizumab n/N**	**Placebo n/N**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				Pembrolizumab	**Placebo**	
Grade 3-5 AEs	156/488	88/496	1.8 (1.4, 2.3)	32.0	17.7	0.14 (0.09, 0.20)
Grade 3-5 AEOSIs	46/488	3/496	15.6 (4.9, 49.8)	9.4	0.6	0.09 (0.06, 0.12)

Source: Table 2.5-1, p38, Table 2.5-2, p41, Table 2.5-11, p54, and Table 2.5-18, p60 of the submission

AEs = adverse events; AEOSIs = adverse events of special interests; CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; ITT = intention-to-treat; NR = not reached; OS = overall survival

Notes: Data cutoff date: 15th September 2023. Median duration of follow-up: 56.2 months for pembrolizumab and 55.3 months for placebo. The median duration of treatment was 11.1 months in both treatment arms.

HR for DFS and OS were for pembrolizumab *versus* placebo. HR <1 favours pembrolizumab over placebo. Risk ratios (RR) and risk differences (RD) in safety outcomes were for pembrolizumab *versus* placebo. RRs > 1 and RDs > 0 favour placebo over pembrolizumab.

6.28 On the basis of the direct evidence presented by the submission, for every 100 RCC patients treated with adjuvant pembrolizumab in comparison with placebo (median follow-up: 56.2 months for pembrolizumab and 55.3 months for placebo):

- Approximately 8 additional patients will remain free of disease recurrence or death at 4 years.
- Approximately 5 additional patients will remain alive at 4 years.
- Approximately 14 additional patients will experience Grade 3-5 AEs.
- Approximately 9 additional patients will experience Grade 3-5 immune-mediated AEs or infusion-related reactions.

Clinical claim

6.29 The submission described pembrolizumab as superior in terms of effectiveness and inferior but manageable in terms of safety compared with placebo (as proxy for surveillance) in patients with RCC at intermediate-high risk or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions.

6.30 The ESC agreed with the evaluation that the therapeutic conclusion of superior efficacy is supported by the evidence presented. Results from the KN564 trial showed that pembrolizumab was associated with a 28% reduction in the hazard of a DFS event by investigator assessment (HR: 0.72; 95% CI: 0.59, 0.87) and a 38% reduction in the hazard of death (HR: 0.62; 95% CI: 0.44, 0.87), compared with placebo, indicating clinically meaningful and statistically significant improvements in DFS and OS for patients in the pembrolizumab arm compared with patients in the placebo arm. The superior efficacy was also supported by other secondary outcomes, such as DRSS by investigator assessment and EFS by BICR. The following are areas of concern about, and limitations of, the KN564 data as presented:

- The OS data remained immature at the most recent DCO of IA3. During a median follow-up of around 56 months, 11.1% and 17.3% of events had occurred in the pembrolizumab and placebo arms, respectively. It is unknown whether the treatment effect from pembrolizumab as observed during the trial period would be maintained over time. The ESC considered the hazard ratio was promising, but given the nature of RCC it is not surprising the median OS following adjuvant treatment has not been reached after 56 months follow-up. The ESC considered it remained unclear whether the separation in the OS curves was driven by preventing or delaying disease progression.
- The extent of use of subsequent therapy with PD-1/PD-L1 inhibitors in the pembrolizumab and in the placebo arm of the KN564 trial would not reflect clinical practice. Thus, the applicability of the trial OS results to the Australian setting is uncertain.

6.31 The ESC considered the therapeutic claim of inferior but manageable safety of pembrolizumab compared with placebo (proxy for surveillance) was reasonable.

6.32 The PBAC considered that the claim of superior comparative effectiveness and inferior comparative safety compared with placebo (as proxy for surveillance) was reasonable.

Economic analysis

6.33 The submission presented a stepped economic evaluation that compared adjuvant treatment with pembrolizumab to active surveillance based on the KN564 placebo-controlled randomised trial. The type of economic evaluation presented was a cost-utility analysis.

6.34 Table 9 summarises the key components of the economic evaluation.

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

Component	Summary
Treatments	Adjuvant pembrolizumab vs surveillance.
Time horizon	30 years in the model base case vs 55.8 months median follow-up in the KN564 trial.
Outcomes	QALYs and LYs gained.
Methods used to generate results	Markov cohort model.
Health states	Four health states: DF, LR, DM and Dead.
Cycle length	1 week, with half-cycle correction on modelled costs and outcomes, except adjuvant treatment cost (and administration) and those related to AEs.
Transition probabilities and extrapolation	A multistate parametric modelling approach was used to derive and extrapolate DF transition probabilities from KN564 (Sept 2023 data cut off). Models were fitted separately across trial arms, and separately for each transition, accounting for competing risks. The functions used to estimate the cause-specific hazards were: log-normal functions for LR and DM, respectively; and exponential functions for death. The base case assumed no waning of the treatment effect over time, and that patients in the DF health state remained at-risk of recurrence throughout the model time horizon. Exponential models were fitted to KN564 data (accounting for competing risks, where relevant) to estimate transitions after recurrence. All rates applied a benefit for adjuvant pembrolizumab continuing after recurrence, which does not appear justified based on the supporting data. 94.9% of LYs (undiscounted) were gained in the extrapolated period
Health related quality of life	EQ-5D-5L data from the KN564 trial using Australian-based preferences. Regression models were used that included independent variables to estimate the impact of different states of health on utility values (e.g. no AEs, LR, DM). Health state utility was not assumed to vary by treatment arm: DF, 0.942; LR, 0.927; and DM, 0.895. Utility values were not adjusted for age. Disutility of Grade 3+ AEs in KN564 estimated from the regression model was -0.0516. This estimate was applied to the average duration of Grade 3+ AE (from the trial across model arms) and incidence (varied across model arms). It was unclear how representative the trial data were of the disutility of Grade 3+ AEs that occurred and resolved between PRO assessment.
Subsequent treatment costs	A one-off cost applied on transition into the DM health state to account for 1L and LL treatment of metastatic disease. Patients treated with adjuvant pembrolizumab were not assumed to be eligible for PD-(L)1 retreatment. The distribution of treatments received was based on PBS item statistics in advanced RCC. 1L PFS was used to approximate ToT, unless maximum durations applied. PFS of sunitinib [c] was used as a reference from which PFS for other 1L PFS estimates were derived using published HRs [d, e] for PFS.

Source: Adapted from Table 3.1–1, p67 of the submission.

1L = first-line; AE = adverse event; DF = disease-free; DM = distant metastases; EQ-5D-5L = EuroQol 5-Dimensions 5-Level Questionnaire; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; LL = later-line; LR = locoregional recurrence; LY = life year; PD-(L)1 = programmed cell death (ligand) 1; PFS = progression-free survival; PRO = patient-reported outcome; QALY = quality-adjusted life year; RCC = renal cell carcinoma; ToT = time-on-treatment

[a] Kidney Cancer Australian Registry and Biobank [KRAB Registry]. Victorian Cohort of Nephrectomy for early-stage Renal Cell Carcinoma. 2023.

[b] Redwood L, Currow D, Kochovska S, Thomas SJ. Australian population norms for health-related quality of life measured using the EQ-5D-5L, and relationships with sociodemographic characteristics. *Qual Life Res*. 2024 Mar;33(3):721-33.

[c] Rini BI, Plimack ER, Stus V, Waddell T, Gafanov R, Pouliot F, et al. Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma (ccRCC): Results from 42-month follow-up of KEYNOTE-426. Journal of Clinical Oncology. 2021;39(15_suppl):4500.
[d] Riaz IB, He H, Ryu AJ, Siddiqi R, Naqvi SAA, Yao Y, et al. A Living, Interactive Systematic Review and Network Meta-analysis of First-line Treatment of Metastatic Renal Cell Carcinoma. *Eur Urol*. 2021 Dec;80(6):712-23.
[e] Motzer R, Alekseev B, Rha SY, Porta C, Eto M, Powles T, et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. *N Engl J Med*. 2021 Apr 8;384(14):1289-300.

6.35 The submission adopted a Markov model that included four health states: Disease-Free (DF); Locoregional Recurrence (LR); Distant Metastasis (DM); and Dead. All patients enter the model in the DF health state and receive active surveillance. Patients in the intervention arm also receive adjuvant treatment with pembrolizumab for up to one year.

6.36 The time horizon nominated in the base case analysis was 30 years. The submission stated that this was consistent with previous submissions presented to the PBAC in the adjuvant setting (abemaciclib, November 2023 PBAC meeting). In this context, the PBAC previously considered that a time horizon of 20 years would be reasonable, though a 30-year time horizon was accepted following changes that yielded more reasonable extrapolations, including a waning of the treatment effect and increase in age at model entry (Table 2, paragraph 7.10, abemaciclib Public Summary Document (PSD), November 2023 PBAC meeting). Given the age (median 65.5 years) and distribution of sex (70% male) in the population expected to be treated[7], the ESC considered a reduced time horizon was appropriate (combined with plausible extrapolations that project small proportions of patients remaining alive at that time point). The pre-PBAC response proposed a respecified base case model with a 25 year time horizon.

6.37 The average age of patients in KN564 was 58.4 years (median: 60 years). Patients in Australian clinical practice appear likely to be older (median 65.5 years)[7] than those enrolled in the trial and the modelled population. While this may not impact the relative effect of pembrolizumab treatment, increased background mortality will reduce the extent of benefit (i.e. absolute life-years gained) achieved from treatment. The ESC considered the model age should have been matched to the Australian population. The pre-PBAC response proposed a respecified base case model with a starting age of 63.8 years.

6.38 The transition probabilities used in the model were all derived from the KN564 trial, with adjustment for background mortality, where relevant. A multistate parametric modelling approach was used to estimate each transition from the DF health state (i.e. to LR, DM or to Dead). Transitions to Dead were informed by very small patient numbers: 13/496 (2.6%) in the pembrolizumab, and 14/498 (2.8%) in the placebo arm of KN564. Differences across model arms based on such data are therefore highly uncertain, and it would have been more appropriate to use a pooled estimate.

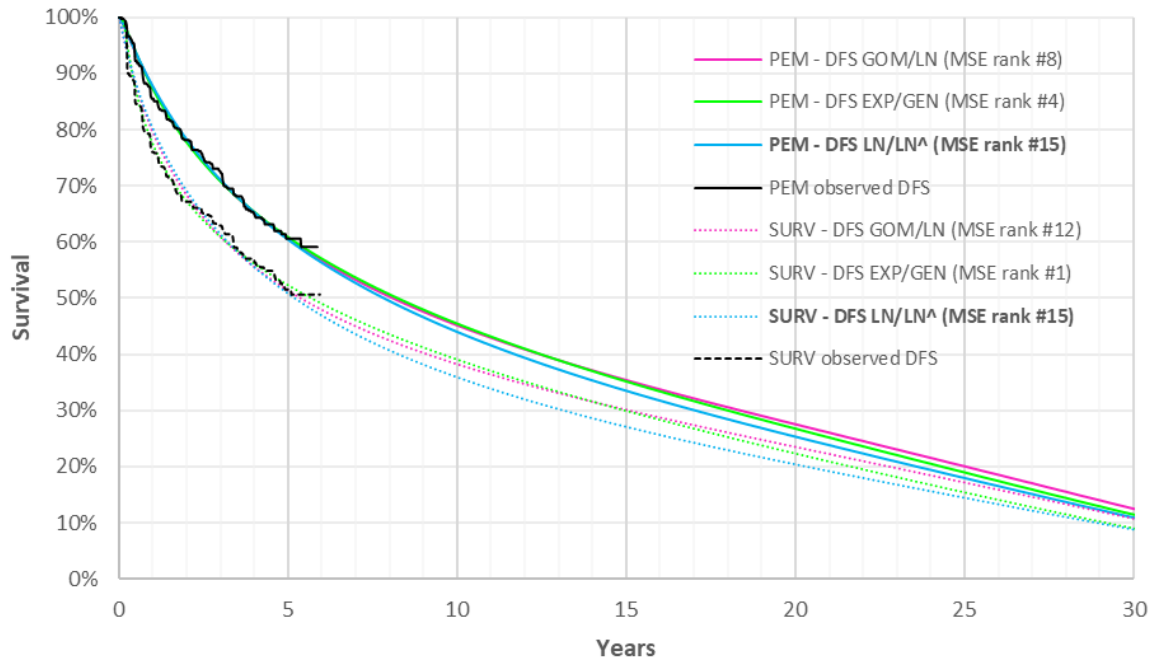
[7] Kidney Cancer Australian Registry and Biobank [KRAB Registry]. Victorian Cohort of Nephrectomy for early-stage Renal Cell Carcinoma. 2023.

Assuming the same rate of death across model arms had a moderate impact on the ICER (6–7% increase, see Table 15).

6.39 Standard parametric models were fitted separately across treatment arms to estimate the transitions to LR and DM. Due to the small number of deaths observed, the submission fitted only exponential distributions for the transitions to death. Given the multistate modelling approach where the outcome of interest (e.g. DFS) was determined by a combination of survival models (e.g. cumulative incidence of each LR, DM and death), parametric model selection considered all possible combinations for each of the separate survival models. Statistical fit was assessed by mean squared error. This was reasonable as the Akaike information criterion is not suitable when modelling competing risks.[8] The submission chose log-normal functions to model transitions to LR and DM in the base case. This was not well justified as this combination did not have the best statistical fit in either treatment arm, and other combinations were observed to fit the DFS data better (exponential/generalised gamma and Gompertz/log-normal). The ICER was sensitive to parametric model selection. A comparison of the composite to observed DFS for model combinations with the best statistical fit is presented in Figure 3. The pre-PBAC response proposed a respecified base case model with Gompertz/ log-normal extrapolation.

[8] Williams C, Lewsey JD, Briggs AH, Mackay DF. Cost-effectiveness Analysis in R Using a Multi-state Modeling Survival Analysis Framework: A Tutorial. *Med Decis Making*. 2017 May;37(4):340-52.

Figure 3: Comparison of observed versus composite modelled DFS



Difference in DFS between model arms

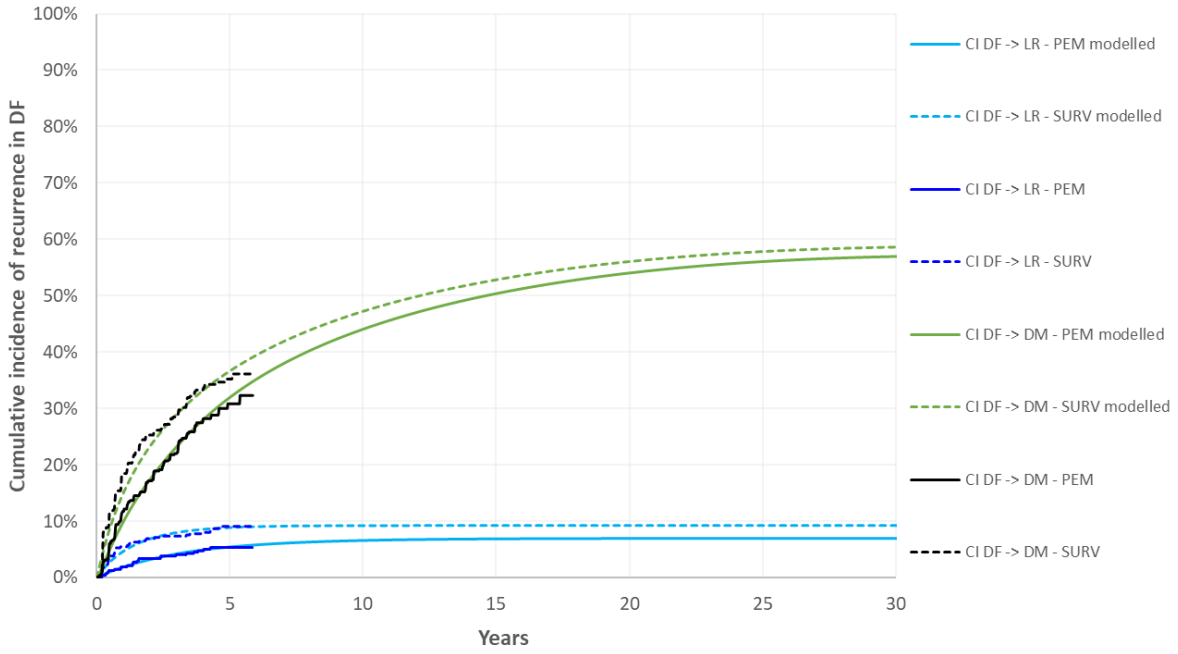
LN/LN^	0.0%	9.6%	8.1%	6.4%	4.9%	3.5%	2.1%
EXP/GG	0.0%	8.6%	6.4%	5.2%	4.4%	3.6%	2.4%
GOM/LN	0.0%	9.2%	6.9%	5.3%	4.0%	2.9%	1.8%

Source: Constructed during the evaluation from the 'Effectiveness' worksheet of the 'Attachment 5 CUA (1).xlsm' workbook included in the submission.
DF = disease-free; DFS = disease-free survival; DM = distant metastasis; GG = generalised gamma; GOM = Gompertz; LN = log-normal; LR = locoregional recurrence; PEM = pembrolizumab; SURV = surveillance.
Note: Composite extrapolations were based on parametric model selection for the transition from DF → LR and parametric model selection for the transition from DF → DM. 'PEM – DFS GOM/LN' can be interpreted as the composite DFS curve using a Gompertz model to fit the DF → LR data, and a log-normal model to fit the DF → DM data.
^ Denotes combination of parametric models chosen in the base case

6.40 No further adjustments, aside from background mortality, were made to the transitions from the DF health state. The base case analysis therefore assumed that the effect of adjuvant pembrolizumab treatment (which is given for one year) persists throughout the model time horizon. No data were provided to support persistence of the effect beyond that observed in the KN564 trial. The PBAC noted a moderate increase in the ICER was observed when treatment waning was assumed from 2 to 4 years (consistent with CADTH consideration as presented in the evaluation) was incorporated (see Table 15), although noted trial data with a longer follow-up was now available. The ESC considered it reasonable that the OS curves remain separated over the observed period in the trial based on a delay in recurrence, however, the separation should not increase, and the curves should converge at some point. The base case also assumed that patients in the DF health state would remain at-risk of LR and DM throughout the model time horizon. The risk of recurrence – in either model arm – would likely decrease over time. As shown in Figure 4, while the modelled cumulative incidence of LR appeared to plateau from 10 years, the modelled

cumulative incidence of DM suggested that, while reducing, the risk of a distant recurrence persisted beyond 10 years. Clinical experts consulted by CADTH[9] noted that very few patients (< 1%) present with distant recurrence 10 years after surgery, and on this basis, excluded transitions to LR and DM after 10 years to represent the possibility of cure. The PBAC noted excluding transitions to LR and DM after 10 years had a small impact on the ICER (see Table 15).

Figure 4: Observed versus modelled cumulative incidence of recurrence over time



Source: Constructed during the evaluation from the 'Trace_AdjReg1' and 'Trace_AdjReg2' worksheets of the 'Attachment 5 CUA (1).xlsm' workbook included in the submission.
CI = cumulative incidence; DF = disease-free; DM = distant metastasis; LR = locoregional recurrence; PEM = pembrolizumab; SURV = surveillance.

6.41 To inform the transitions from the LR health state, the submission used data from KN564 in patients who experienced LR as their DFS failure event. Exponential parametric functions were fitted to time from LR until DM or Death, respectively, with censoring as required. The exponential rates applied for each transition are presented in Table 10. The data – in particular following adjuvant pembrolizumab – are based on small numbers of patients at-risk and small numbers of events. These are unlikely to provide a reliable basis upon which to determine transition probabilities, particularly differences across treatment arms. The ICER was sensitive to differences applied between model arms for these transitions. Furthermore, the rate of death estimated for the surveillance arm may be implausibly high given it was 4x higher than that

[9] Canadian Agency for Drugs and Technologies in Health [CADTH]. CADTH Reimbursement Recommendation Pembrolizumab (Keytruda) Canadian Agency for Drugs and Technologies in Health; 2023 [cited 2024 July]; Available from: https://www.cadth.ca/pembrolizumab-4.

applied following pembrolizumab, and similar to rates estimated for the transition from DM to Dead (Table 11).

Table 10: Modelled exponential rates for transitions from the LR health state

	Exponential rate (se)	
	KN564 Pembrolizumab	KN564 Surveillance
LR → DM	0.00145 (0.00059)	0.00185 (0.00056)
LR → Dead	0.00048 (0.00034)	0.00202 (0.00058)

Source: Table 3.4–2, p79 of the submission and the 'Effectiveness' worksheet of the 'Attachment 5 CUA (1).xlsm' workbook included in the submission.
DF = disease-free; DM = distant metastases; LR = locoregional recurrence; se = standard error.

6.42 A similar approach was used to estimate the transition to Dead in the DM health state, where data from KN564 in patients who experienced DM either as their DFS failure event or who first experienced LR and experienced DM as a subsequent recurrence event was used. The exponential rate applied in the pembrolizumab arm was lower than that following surveillance (Table 11). The observed data did not appear to be dissimilar across trial arms, and are unlikely to support differences across model arms in the rates applied. It may be more appropriate to use a pooled estimate. The ICER was sensitive to the application of the same rate applied across model arms.

6.43 As the submission assumed that patients treated with adjuvant pembrolizumab would not be eligible for PD-(L)1 therapies in the advanced setting, it does not seem reasonable to apply a lower rate of death from DM following adjuvant pembrolizumab, despite the subsequent, more effective, PD-(L)1 treatments being modelled only in the comparator arm. However, the data from KN564 reflect some PD-(L)1 rechallenge after adjuvant pembrolizumab. If re-treatment with PD-(L)1 inhibitors is associated with a survival benefit, the results from KN564 may overestimate survival in the pembrolizumab arm following distant recurrence. An alternate approach was included in the model using external data sources to derive alternate exponential rates of death. While this approach estimated a higher rate of death in DM following adjuvant pembrolizumab (which may be more consistent with first-line treatments expected in practice), a number of issues were noted which would likely affect the reliability of the estimates applied.

Table 11: Modelled exponential rates for transitions from the DM health state

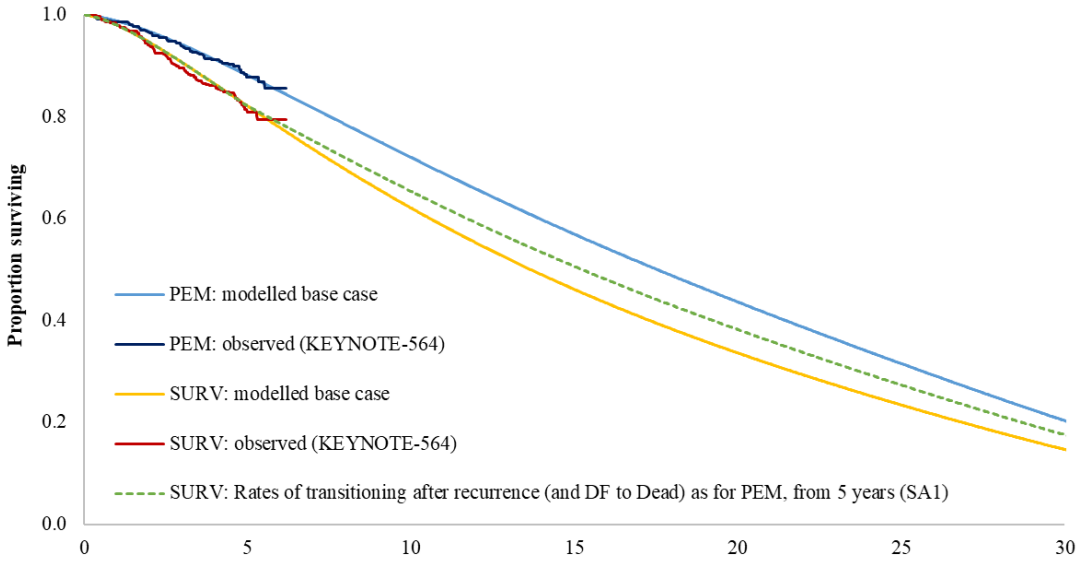
	Exponential rate (se) of death from DM to death	
	Pembrolizumab	Surveillance
KN564	0.00212 (0.0003)	0.00242 (0.0003)
External data	0.00338 (NA)	0.00281 (NA)

Source: Table 3.4–3, p79 of the submission and the 'Effectiveness' worksheet of the 'Attachment 5 CUA (1).xlsm' workbook included in the submission.
DM = distant metastases; NA = not available; se = standard error.

6.44 To validate the operation of the model, the submission presented a comparison of observed OS data from KN564, to composite modelled estimates used in the base case analysis, extrapolated over the time horizon (Figure 5). Landmark analyses show that the OS curves continue to diverge until approximately Year 15. The ESC considered it was not reasonable to assume that the benefit of pembrolizumab continues to increase until such time. The ESC advised it may be appropriate to maintain the

submission's approach to extrapolation until 5 years, and to assume no difference in rates after recurrence (or DF to Dead) across model arms after that. The ESC noted this resulted in a difference in OS of 6.7% at 10 years (rather than 9.9%) (Figure 5). The ESC noted the ICER using this approach increased from $25,000 to < $35,000per QALY to $45,000 to < $55,000per QALY. However, the ESC noted that with this approach a difference in survival was still maintained out to 30 years, which it considered optimistic. The pre-PBAC response proposed a respecified base case model that assumed no difference in rates after recurrence (or DF to Dead) across model arms after 5 years.

.Figure 5: Composite modelled OS over the time horizon, base case and sensitivity analysis varying transition probabilities after recurrence



	Difference in OS						
BC	0.0%	6.0%	9.9%	10.8%	10.0%	8.1%	5.7%
SA1	0.0%	6.0%	6.7%	6.3%	5.4%	4.2%	2.8%

Source: Constructed for ESC advice using economic model spreadsheet
BC = base case; DF = Disease-free; PEM = pembrolizumab; SA1 = sensitivity analysis #1 (no difference in transitions DF to death, LR to DM, LR to death, DM to death across model arms after 5 years);SURV: surveillance

6.45 All health state utility values used were sourced from the KN564 trial. Patient-reported outcomes were assessed in (treatment) cycles 1, 5, 9, 13, and 17, as well as at discontinuation, 30-days following the last dose (i.e. safety visit), and annually during post-treatment follow-up until disease recurrence or initiation of a new anticancer treatment. Therefore, the LR and DM values reported from the trial are not likely to be representative of the utility in those health states. Despite this, the ICER is not sensitive to the utility values applied in the LR or DM health states. To estimate the utility in the DF health state, a regression model was used, fitted to observations from patients who were disease-free (n = 972, obs = 5,600), with independent variables for an absence of any AE during the patient-visit, or presence of Grade 1–2 AEs. The DF utility applied in the base case (0.942) was calculated from the sum of the intercept

(0.8906) and the parameter for the absence of any AE (0.0516). The utility applied was noted to be substantially higher than the utility reported in a representative sample of the general Australian population (n = 9,958) measured using the EQ-5D-5L (0.86).[10] This may not be reasonable. The ESC considered the utilities from KN564 using UK preferences provided a more reasonable estimate of utilities (DF=0.868, LR=0.839, DM=0.798, AEs=-0.0642). The ESC noted that with the use of these utilities, the ICER increased from $35,000 to < $45,000 per QALY to $35,000 to < $45,000 per QALY. The pre-PBAC response proposed a respecified base case model that applied the utilities using the UK preferences.

6.46 The submission assumed patients in the intervention arm of the model would receive 200 mg pembrolizumab every third model cycle up to a maximum of 17 administrations (approx. one year). The proportion of patients remaining on treatment was informed by the pembrolizumab time-on-treatment (ToT) curve from KN564, truncated at week 51. The submission applied a relative dose intensity (RDI) (98.9%) on the weighted dispensed price for the maximum amount (DPMA) per dose of pembrolizumab. The RDI applied could not be verified from the CSRs included in the submission. Compliance in the trial was measured as a comparison of the total volume infused, relative to that prepared (p56, KN564 protocol). The PI states that the product is for single use in one patient only and that any residue should be discarded. Thus, reduced compliance may result in wastage, rather than reduced costs. A sensitivity analysis conducted during the evaluation observed that the ICER was not sensitive to this change.

6.47 A one-off cost was applied on transition into the DM health state to account for first- and later-line treatment of metastatic disease, including administration where relevant. Treatments received varied by whether pembrolizumab was available in the adjuvant setting. First-line treatment costs were derived from PFS estimates reported in external studies, unless maximum treatment durations apply. This resulted in substantially longer treatment durations than those considered previously by the PBAC (Table 12). The cost of first-line and later line treatment applied is presented in Table 12. It does not seem reasonable that first-line treatments applied after adjuvant pembrolizumab were more costly than those after surveillance. This was driven by the use (and therefore cost) of cabozantinib, which was substantially longer than the average duration previously accepted by the PBAC (33.4 months vs 12.6 months). The PSCR stated the sponsor is amenable to applying treatment durations of first-line treatments in the metastatic setting based on estimates previously accepted by the PBAC. The pre-PBAC response proposed a respecified base case model that applied treatment durations previously accepted by the PBAC.

[10] Redwood L, Currow D, Kochovska S, Thomas SJ. Australian population norms for health-related quality of life measured using the EQ-5D-5L, and relationships with sociodemographic characteristics. *Qual Life Res*. 2024 Mar;33(3):721-33.

Table 12: Duration of first-line treatments in the advanced RCC setting (based on assumed effective prices)

Treatment	Exponential rate of treatment discontinuation [a]	Derivation	Cost per course [b]	PEM [c]	SURV [d]
Sunitinib	0.0144	Median PFS [e] of 11.1 months, approx. equal to mean PFS 16.0 months [f] or 69.6 weeks. Mean duration in PBAC PSDs: 6.3 months [g]	$[redacted] $[redacted]	14.2%	0.0%
Pazopanib	0.0151	PFS HR 1.05 vs sunitinib [h], mean PFS 66.3 weeks (15.3 months) Mean duration in PBAC PSDs: NA	$[redacted] $[redacted] [i]	22.6%	0.0%
Cabozantinib	0.0069	PFS HR 0.48 vs sunitinib [h], mean PFS 145.1 weeks (33.4 months) Mean duration in PBAC PSDs: 12.6 months [g]	$[redacted] $[redacted]	63.2%	0.0%
NIVO+IPI [j]	0.0128	PFS HR 0.89 vs sunitinib [h], mean PFS 78.2 weeks (18.0 months) Mean duration in PBAC PSDs: 16.4 months [k]	$[redacted] $[redacted]	0.0%	78.7%
PEM+LEN [l]	0.0056	PFS HR 0.39 vs sunitinib [m], mean PFS 178.5 weeks (41.1 months) Mean duration in PBAC PSDs: 21.8 months [n]	$[redacted] $[redacted]	0.0%	21.4%
Average 1L treatment cost				$[redacted]	$[redacted]
Average 1L treatment cost, based on durations reported in PBAC PSDs				$[redacted]	$[redacted]
Average LL treatment cost (B)				$[redacted]	$[redacted]
Total cost applied				$[redacted]	$[redacted]
Pre-PBAC response					
Average 1L treatment cost, based on durations reported in PBAC PSDs + reduction in subsequent PD-L(1) use in comparator arm to [redacted]% (A)				$[redacted]	$[redacted]
Total cost applied (A + B)				$[redacted]3	$[redacted]
PBAC analysis					
Average 1L treatment cost, based on durations reported in PBAC PSDs + reduction in subsequent PD-L(1) use in comparator arm to [redacted]% with remaining [redacted]% using sunitinib, pazopanib and cabozantinib with relative use as for the pembrolizumab arm				$[redacted]	$[redacted]

Source: 'Tx Duration' and 'Market Shares' worksheets of the 'Attachment 5 CUA (1).xlsm' workbook included in the submission.
1L = first-line; HR = hazard ratio; LL = later line; NA = not available; NIVO+IPI = nivolumab and ipilimumab; PEM = pembrolizumab; PEM+LEN = pembrolizumab and lenvatinib; PFS = progression-free survival; RCC = renal cell carcinoma; SURV = surveillance

[a] Calculated as 1 / mean PFS (in weeks)

[b] Discounted cost per course, including administration. For pembrolizumab, the effective DPMA was used. For all other medicines where special pricing arrangements exist, discounts on the published prices to approximate effective prices were assumed: pazopanib ([redacted]% discount), cabozantinib ([redacted]% discount), nivolumab ([redacted]% discount), ipilimumab ([redacted]% discount) and lenvatinib (effective DMPQ $[redacted]).

[c] Distribution of TKI use was based on PBS use of pazopanib, sunitinib and cabozantinib in advanced RCC, 2023.

[d] Distribution of PD-(L)1 use was based on PBS use of NIVO+IPI and PEM+LEN in advanced RCC, 2023

[e] Rini BI, Plimack ER, Stus V, Waddell T, Gafanov R, Pouliot F, et al. Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma (ccRCC): Results from 42-month follow-up of KEYNOTE-426. Journal of Clinical Oncology. 2021;39(15_suppl):4500.

[f] Mean PFS = Median PFS / LN(2)

[g] Paragraph 6.53, cabozantinib Public Summary Document (PSD), March 2019 PBAC meeting.

[h] Riaz IB, He H, Ryu AJ, Siddiqi R, Naqvi SAA, Yao Y, et al. A Living, Interactive Systematic Review and Network Meta-analysis of First-line Treatment of Metastatic Renal Cell Carcinoma. Eur Urol. 2021 Dec;80(6):712-23.

[i] Assuming the same duration of treatment as for sunitinib.

[j] Ipilimumab treatment was capped at 12 weeks.

[k] Paragraph 6.72, nivolumab and ipilimumab PSD, July 2018 reports 33.6 doses of nivolumab per patient. Assuming four doses are over the first 12 weeks, the remaining 29.6 doses are given Q2W (59.2 weeks) – so total treatment time of 71.2 weeks (16.4 months).

[l] Pembrolizumab treatment was capped at 104 weeks duration.

[m] Motzer R, Alekseev B, Rha SY, Porta C, Eto M, Powles T, et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. N Engl J Med. 2021 Apr 8;384(14):1289-300.

[n] Table 14, cabozantinib PSD, March 2024 PBAC meeting.

6.48 The submission assumed that patients who received pembrolizumab in the adjuvant setting would not be eligible for PD-(L)1 rechallenge in the advanced setting. This differed to the KN564 trial, where 27% of patients that recurred received a PD-(L)1 inhibitor (paragraph 6.10). While it may be reasonable to exclude these costs in the analysis, outcomes were not adjusted accordingly. In the comparator arm of the model, 100% of patients are assumed to receive first-line treatment with PD-(L)1 therapy. Subsequent PD-(L)1 use in the placebo arm of KN564 was <50% in patients who had experienced a recurrence (paragraph 6.10). The ESC considered it was not reasonable to assume the cost in all patients, where the outcomes modelled reflect use in fewer patients. The ESC noted the model overestimated the cost and underestimated the benefit of subsequent PD-(L)1 inhibitors in the surveillance arm. The ESC also noted the assumptions regarding the use (and cost) of other treatments (i.e., targeted therapies) in the first-line and later line treatment settings may not be consistent with the outcomes observed in the KN564 trial (noting not all patients with recurrence received subsequent drug therapy, see Table 4). The pre-PBAC response proposed a respecified economic model that assumed 75% of patients who recurred in the comparator arm receive PD-(L)1 inhibitors. The PBAC noted in KN564 approximately 50% of patients in the comparator arm received PD-(L)1 inhibitors, however the cost ($) is similar to that in the respecified economic model if it is assumed the remaining 50% of patients receive targeted therapies ($) (Table 12).

6.49 A summary of the key model drivers is presented in Table 13.

Table 13: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1]/QALY gained
Exponential rate of death in DM	Treatment-specific estimates derived from exponential models fitted to KN564 data from patients who experienced DM either as their first DFS failure event or following an earlier LR (PEM: 0.00212; SURV: 0.00242). The observed data do not appear to be dissimilar across model arms, and are unlikely to support differences across model arms in the rates applied. A pooled estimate from the trial may be more appropriate.	High, favours pembrolizumab Assuming a rate of 0.00212 applied across model arms increased the ICER to $[redacted][2]/QALY gained.
Duration of cabozantinib in first-line advanced RCC	33.4 months, derived using PFS HR 0.48 vs sunitinib [a], using sunitinib median PFS of 11.1 months [b] (mean PFS approximated: 16.0 months) [c] as a reference. The average duration of cabozantinib in this setting previously reported was 12.6 months (paragraph 6.53, cabozantinib PSD, March 2019 PBAC meeting)	High, favours surveillance Use of average duration considered previously by the PBAC reduced the ICER to $[redacted][3]/QALY gained.
Exponential rate of death in LR	Treatment-specific estimates derived from exponential models fitted to KN564 data from patients who experienced LR as their DFS failure event (PEM 0.00048; SURV 0.00202). The trial data were unlikely to provide a reliable basis on which to determine transition probabilities, let alone differences across treatment arms.	High, favours pembrolizumab Assuming a rate of 0.00048 applied across model arms increased the ICER to $[redacted][2]/QALY gained.
Time horizon	30 years, consistent with previous submissions presented to the PBAC in the adjuvant setting (abemaciclib, November 2023 PBAC meeting). This time-horizon was accepted following changes that yielded more reasonable extrapolations, including a waning of the treatment effect and increase in age at model entry (Table 2, paragraph 7.10, abemaciclib PSD, November 2023 PBAC meeting).	Moderate, favours pembrolizumab Using a 20-year time horizon increases the ICER to $[redacted][2]/QALY gained. Using a 25-year time horizon increases the ICER to $[redacted][1]/QALY gained
Age at model entry	58.4 years, based on mean age in KN564 (median age: 60.0 years). Patients in Australian clinical practice are likely older than those enrolled in the trial (median: 65.5 years) [d]	Moderate, favours pembrolizumab Increasing the starting age to 65.5 years increased the ICER to $[redacted][2]/QALY gained. An increase to 63.8 years, [e] increased the ICER to $[redacted][1]/QALY gained.
Treatment waning	No treatment waning was assumed in the base case, on the basis that these treatments offer the potential for durable response and long-term survival, particularly in the early stage setting with curative intent. No data were provided to support persistence of the effect beyond that observed in the KN564 trial.	Moderate, favours pembrolizumab Assuming waning of the treatment effect from Year 2–4 increased the ICER to $[redacted][2]/QALY gained
DF parametric model selection	Log-normal models were each selected to estimate transitions from DF to LR and DM. Statistical fit of the composite DFS curve derived from this combination of models was not the best fit relative to observed DFS.	Moderate, favours pembrolizumab Using the combination of exponential and generalised gamma models to estimate transitions to LR and DM, respectively, increased the ICER to $[redacted][2]/QALY gained.
DF health state utility	0.942, based on a regression model fitted to KN564 data. The utility applied was noted to be substantially higher than utility reported in a representative sample of the general Australian population (0.86). [f]	Moderate, favours pembrolizumab Applying UK tariffs increased the ICER to $[redacted][2]/ QALY.

Source: Constructed during the evaluation.

DF = disease-free; DFS = disease-free survival; DM = distant metastases; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; LR = locoregional recurrence; PEM = pembrolizumab; PFS = progression-free survival; QALY = quality-adjusted life year; RCC = renal cell carcinoma; SURV = surveillance

[a] Riaz IB, He H, Ryu AJ, Siddiqi R, Naqvi SAA, Yao Y, et al. A Living, Interactive Systematic Review and Network Meta-analysis of First-line Treatment of Metastatic Renal Cell Carcinoma. *Eur Urol*. 2021 Dec;80(6):712-23.

[b] Rini BI, Plimack ER, Stus V, Waddell T, Gafanov R, Pouliot F, et al. Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma (ccRCC): Results from 42-month follow-up of KEYNOTE-426. *Journal of Clinical Oncology*. 2021;39(15_suppl):4500.
[c] calculated assuming mean PFS = median PFS / LN(2)
[d] Kidney Cancer Australian Registry and Biobank [KRAB Registry]. Victorian Cohort of Nephrectomy for early-stage Renal Cell Carcinoma. 2023.
[e] Assuming the ratio observed between mean (58.4 years) and median (60.0 years) age in KN564 applies in practice
[f] Redwood L, Currow D, Kochovska S, Thomas SJ. Australian population norms for health-related quality of life measured using the EQ-5D-5L, and relationships with sociodemographic characteristics. *Qual Life Res*. 2024 Mar;33(3):721-33.
The redacted values correspond to the following ranges:
1 $25,000 to < $35,000
2 $35,000 to < $45,000
3 $5,000 to < $15,000

6.50 The results of the stepped economic evaluation is presented in

6.51 Table 14. These results were based on assumed effective prices of treatments in the advanced setting.

Table 14: Results of the stepped economic evaluation

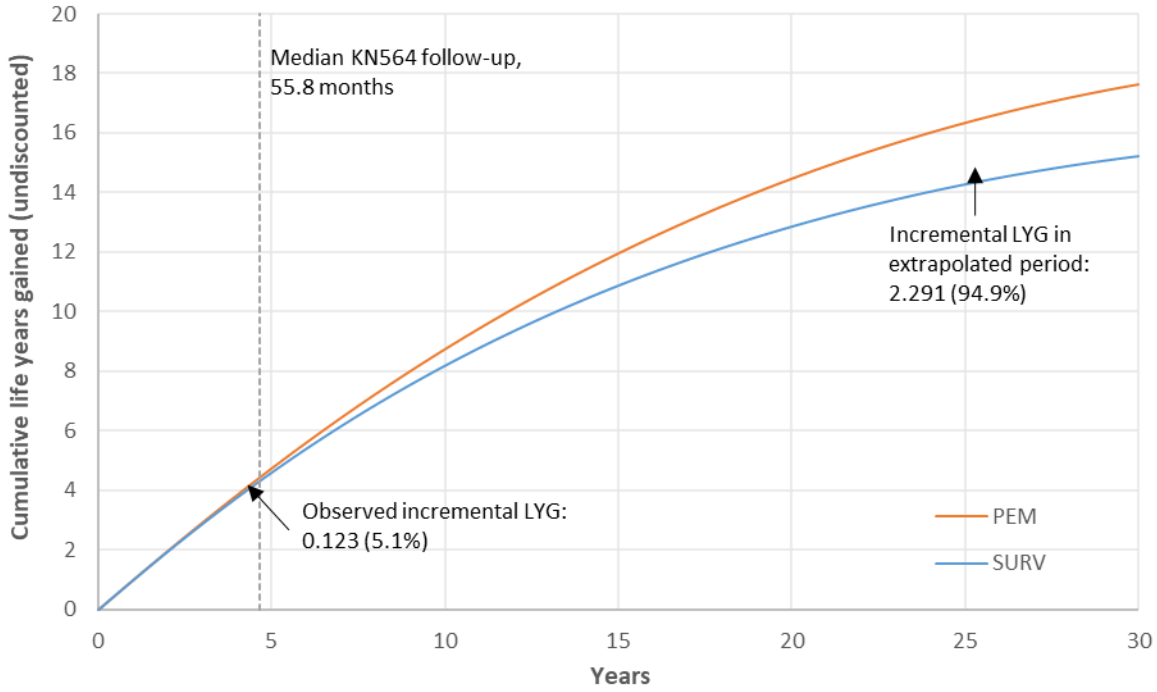
Step and component	Pembrolizumab	Surveillance	Increment
Step 1: trial-based costs and outcomes			
Costs	$	$35,231	$
Recurrence [a]	32.4%	41.8%	–9.4%
Any DM (from DF or LR)	28.3%	35.0%	–6.7%
LY[b]	3.5969	3.5181	0.0788
Incremental cost/extra LY gained[b]			$ [1]
Incremental cost/recurrence avoided			$ [1]
Incremental cost/distant recurrence avoided			$ [2]
Step 2: time horizon extended to 30 years			
Costs	$	$55,257	$
LY	11.0937	9.9017	1.1920
Incremental cost/extra LY gained			$ [3]
Step 3: incorporation of medical resource costs			
Costs	$	$69,215	$
LY	11.0937	9.9017	1.1920
Incremental cost/extra LY gained			$ [3]
Step 4: utility weights applied			
Costs	$	$69,215	$
QALYs	10.3016	9.1833	1.1183
Incremental cost/extra QALY gained (base case)			**$** [3]

Source: Table 3.8–2, p107 of the submission.
DF = disease-free; LR = locoregional recurrence; LY = life year; QALY = quality-adjusted life year
[a] Recurrence estimates as generated in the economic model using a time horizon set to 4 years. Slight differences were noted to the reported trial estimates in Table 5.
[b] Estimates were revised during the evaluation due to an error resulting from the number of years the different disease management costs were applied. When the time horizon was set to 4 years, in the final model cycle included in the analysis, health state membership in the DF state doubles (and so the number of patients in the model, in that cycle, exceeds 1).
The redacted values correspond to the following ranges:
1 $355,000 to < $455,000
2 $455,000 to < $555,000
3 $25,000 to < $35,000

6.52 The step that had the largest impact on the results was extending the time horizon to 30 years. The ESC noted the majority (~95%) of the incremental LYs gained are in the extrapolated period (Figure 6). The model extrapolations assume no waning of the treatment effect over time, and after recurrence, assumes lower rates of further

events following adjuvant pembrolizumab than surveillance, which was unlikely to be supported by the data presented. The average undiscounted QALY gain per treated patient was 2.25.

Figure 6: Cumulative life years gained over the time horizon of the model (undiscounted)



Source: Constructed during the evaluation from the 'Attachment 5 CUA (1).xlsm' workbook included in the submission.
LYG = life years gained; PEM = pembrolizumab; SURV: surveillance

6.53 The results of key sensitivity analyses are summarised in Table 15. The analyses were sensitive to changes in rates of events following recurrence, first-line treatment durations costed and assumptions around starting age, treatment waning and model time horizon.

Table 15: Results of key sensitivity analyses

	Incremental cost ($)	Incremental QALY	ICER	% change
Base case	[redacted]	**1.1183**	[redacted][1]	**–**
Discount rate (base case: 5%)				
• 0%	[redacted]	2.2516	[redacted][2]	–[redacted]%
• 3.50%	[redacted]	1.3572	[redacted][1]	–[redacted]%
Starting age (base case: 58.4 years)				
• 63.8 years [a]	[redacted]	0.9625	[redacted][3]	[redacted]%
• 65.5 years	[redacted]	0.8913	[redacted][3]	[redacted]%
Treatment waning (base case: none)				
• From 2 to 4 years	[redacted]	1.0002	[redacted][3]	[redacted]%
• No difference in effect after 4 years	[redacted]	1.0415	[redacted][3]	[redacted]%
Implementation of cure (base case: none)				
• Both arms: from 10 years	[redacted]	1.1117	[redacted][1]	–[redacted]%
Time horizon (base case: 30 years)				
• 20 years	[redacted]	0.8879	[redacted][3]	[redacted]%
• 25 years	[redacted]	1.0323	[redacted][1]	[redacted]%
Transition probabilities (base case: difference in rates after recurrence and DF to Dead across model arms throughout model time horizon)				
• No difference in rates after recurrence (or DF to Dead) across model arms after 5 years	[redacted]	0.7567	[redacted][4]	[redacted]%
DF to Dead exponential rates (base case: PEM 0.00014; SURV: 0.00018)				
• Both arms: 0.00014	[redacted]	1.0457	[redacted][1]	[redacted]%
• Both arms: 0.00018	[redacted]	1.0313	[redacted][1]	[redacted]%
• Both arms: Background mortality only	[redacted]	1.0558	[redacted][1]	[redacted]%
DF extrapolation (base case: DF to LR log-normal; DF to DM log-normal)				
• to LR Gompertz; to DM log-normal	[redacted]	1.0266	[redacted][3]	[redacted]%
• to LR exponential; to DM generalised gamma	[redacted]	1.0915	[redacted][3]	[redacted]%
LR to DM exponential rates (base case: PEM 0.00145; SURV 0.00185)				
• Both arms: 0.00145	[redacted]	1.1129	[redacted][1]	[redacted]%
• Both arms: 0.00185	[redacted]	1.0940	[redacted][1]	[redacted]%
LR to Dead exponential rates (base case: PEM 0.00048; SURV 0.00202)				
• Both arms: 0.00048	[redacted]	0.8315	[redacted][3]	[redacted]%
• Both arms: 0.00202	[redacted]	0.8982	[redacted][3]	[redacted]%
• Both arms: 0.00014 (i.e. DF to Dead rate, PEM arm)	[redacted]	0.8102	[redacted][3]	[redacted]%
• Both arms: 0.00018 (i.e. DF to Dead rate, SURV arm)	[redacted]	0.8122	[redacted][3]	[redacted]%
DM to Dead exponential rates (base case: KN564 PEM: 0.00212; SURV: 0.00242)				
• Both arms: 0.00212	[redacted]	0.8822	[redacted][3]	[redacted]%
• Both arms: 0.00242	[redacted]	0.9043	[redacted][3]	[redacted]%
DF health state utility (base case: 0.942, no age adjustment)				
• 0.86	[redacted]	1.0248	[redacted][3]	[redacted]%
• UK (DF: 0.868, LR: 0.839, DM: 0.798, AEs: –0.0642)	[redacted]	1.0276	[redacted][3]	[redacted]%
First-line advanced treatment duration (base case: derived estimates of PFS)				
• Average durations reported in previous PSDs, all	[redacted]	1.1183	[redacted][2]	–[redacted]%

Source: Table 3.9–1, p110 of the submission.

DF = disease-free; DM = distant metastases; ICER = incremental cost-effectiveness ratio; LR = locoregional recurrence; PEM = pembrolizumab; PFS = progression-free survival; QALY = quality-adjusted life year; SURV = surveillance

[a] Assuming the ratio observed between mean (58.4 years) and median (60.0 years) age in KN564 applies in practice

The redacted values correspond to the following ranges:

1 $25,000 to < $35,000

2$15,000 to < $25,000

3 $35,000 to < $45,000
4 $45,000 to < $55,000

6.54 The ESC noted a multivariate analysis that assumed a higher average starting age (63.8 years as proposed by the evaluation) and applied the submission's approach to extrapolation until 5 years and assumed no difference in rates of recurrence (or DF to Dead) after that (see paragraph 6.44) increased the ICER from $25,000 to < $35,000 per QALY to $45,000 to < $55,000 per QALY. The ESC noted reducing the time horizon from 30 years to 25 year or 20 years further increased the ICER to $55,000 to < $75,000 per QALY and $55,000 to < $75,000 per QALY, respectively. The ESC noted a number of additional outstanding issues that would likely further impact on the ICER, including:

- Utilities, as discussed in paragraph 6.45.
- Functions used to extrapolate transition to LR and DM, as discussed in paragraph 6.39.
- Treatment waning, as discussed in paragraph 6.52.
- Inclusion of costs and benefits of subsequent treatments, as discussed in paragraph 6.48.

6.55 The pre-PBAC response proposed a respecified base case model incorporating the following:

- reduction in model time horizon to 25 years;
- increasing patient age to 63.8 years;
- using previously accepted treatment durations for subsequent treatments;
- incorporating a Gompertz/log-normal extrapolation for transitions from the DF health state to the LR and DM health states;
- assuming no difference for the pembrolizumab and comparator arms in rates of transition from recurrence (or DF) to Dead after 5 years[11];
- applying UK values to utilities;
- reduction in subsequent PD-L(1) inhibitor use in comparator arm to 75%; and
- reduced EMP per 100 mg vial.

The resulting ICER is presented in Table 16 with additional sensitivity analyses also presented.

[11] DF to dead, LR to dead, DM to dead, LR to DM

Table 16: Results of respecified base case economic model presented in the pre-PBAC response and additional PBAC analyses

	Incremental cost ($)	Incremental QALY	ICER
Base case - EMP $ per 100 mg vial		1.1183	[1]
Respecified base case - EMP $ per 100 mg vial		0.5740*	[2]
Respecified base case - EMP $ per 100 mg vial (A)		0.5740	[1]
A + 20 year time horizon		0.5251	[3]
A + subsequent therapy costs in both arms equal (based on that for surveillance arm)		0.5740	[4]
A + subsequent therapy costs in both arms equal (based on that for pembrolizumab arm)		0.5740	[2]
A + first line subsequent therapy cost only (PBAC preferred scenario)		0.5740	[2]
A + first line subsequent therapy cost only + 20 year time horizon		0.5251	[2]

EMP = ex-manufacturer price; ICER – incremental cost effectiveness ratio; QALY = quality adjusted life year.

* Undiscounted QALY gain = 0.9804

The redacted values correspond to the following ranges:

1 $25,000 to < $35,000

2 $45,000 to < $55,000

3 $35,000 to < $45,000

4 $55,000 to < $75,000

Drug cost course

6.56 The per patient cost of pembrolizumab based on use in the KN564 trial, in the economic model and in the financial estimates model are presented in Table 17. As pembrolizumab treatment in KN564 was complete, the modelled cost per course estimated was similar to that based on the trial. The modelled ToT curve (despite truncated) estimated a slightly higher use, although a lower cost per course was estimated, due to the application of the RDI to the weighted DPMA. The cost per course applied in the financial estimates was lower again. Due to the approach used to estimate the number of scripts, the submission estimated 13.1 scripts, which was then adjusted for RDI.

Table 17: Drug cost per patient for pembrolizumab

	Trial dose and duration	Model	Financial estimates
Mean dose	197.8 mg	200 mg	200 mg
No. scripts	13.5	13.5	13.0 [b]
Cost/patient/script	$ [c]	$ [d]	$ [c]
Cost/patient/course	$	$	$

Source: Constructed during the evaluation from Table –8, p68 of the KN564 CSR IA3 DCO Sept 2023 and the 'Attachment 5 CUA (1).xlsm' and 'Attachment 6 UCM (1)'.xlsx' workbooks included in the submission.

[a] The comparator nominated in the submission was surveillance. Therefore, comparator costs are not included in the table.

[b] Modelled ToT

[c] Weighted DPMA

[d] Weighted DPMA, adjusted for RDI (98.9%)

Estimated PBS usage & financial implications

6.57 This submission was not considered by DUSC. An epidemiological approach was used to estimate the financial implications of pembrolizumab for the adjuvant treatment of intermediate-high to high risk RCC.

6.58 The key inputs in the financial analysis are summarised in Table 18.

Table 18: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incidence of kidney cancer	5,004 in Year 1 (2025), increasing to 5,783 in Year 6 (2030), based on AIHW (2023) [a] Cancer incidence projections	
Proportion with RCC	90.0% (Cancer Council Victoria 2023) [b]	These were consistent with advice provided by DUSC (paragraph 6.54, cabozantinib PSD, March 2024 PBAC meeting)
Proportion of RCC that is clear cell	80.0% (Arora and Limaiem 2023) [c]	
Distribution of stage at diagnosis	25.0% assumed to be Stage IV at diagnosis (Gupta 2008) [d]	DUSC considered that 30% of incident kidney cancer cases would be Stage IV at diagnosis (paragraph 6.54, cabozantinib PSD, March 2024 PBAC meeting)
Proportion of Stage I–III who have at intermediate-high to high risk following nephrectomy	26.4%, assuming 94.3% of patients would receive curative nephrectomy (Ta 2013) [e], of whom 28.0% would meet the risk criteria for adjuvant pembrolizumab (KRAB registry 2023) [f]	Some applicability concerns were noted due to the age of the data cited in Ta (2013) [e], which was based on surgeries performed in 2009.
Proportion of Stage IV with no residual disease	6.2%, derived assuming 44.0% of patients would receive nephrectomy (KRAB registry 2023) [g], and that of these 14.0% would have a complete resection (Alt 2011) [h].	The estimate for complete resection has uncertain applicability to current clinical practice and may depend on the location (and number) of metastases and clinical practice. The PSCR increased the proportion of patients with a complete resection from 14% to 20% based on recent publications.
Proportion with no residual disease	88.7% (Powles 2022) [i]	The application of this estimate to patients with Stage IV disease who have complete resection may constitute double-counting.
Proportion with ECOG PS 0–1	95.0% (Karam 2024) [j]	
Uptake rate in incident patients	90.0% (Assumption)	A high rate of uptake would be expected due to the lack of options in the adjuvant RCC setting
Compliance	98.9% (KN564)	The RDI applied could not be verified
Scripts dispensed per incident patient	13.0 based on the proportion of patient-years on treatment (39.3 weeks, 75.6%) multiplied by the scripts per patient-year on treatment, adjusted for compliance (17.3 × 98.9%)	This was lower than mean (complete) estimates reported in KN564 (13.5) (Table 10–8 of the KN564 CSR IA3 DCO Sept 2023).
Grandfathered patients	[redacted][1] (Assumption). Grandfathered patients were assumed to use 50% of the scripts in incident patients	These patients were appropriately removed from the estimated prevalent patients in the PSCR.
Pembrolizumab	$[redacted], estimated weighted proposed effective DPMA, assuming 35% public based on PBS statistics for items 11627Y, 11636K, 11626X and 11642R	
Chemotherapy administration	$95.12 (MBS item 13950, assuming 80%)	

Source: Constructed during the evaluation from Section 4 of the submission.
DPMA = dispensed price for the max. amount; ECOG PS = European Cooperative Oncology Group performance status; IV = intravenous; RCC = renal cell carcinoma; RDI = relative dose intensity
[a] Australian Institute of Health and Welfare. Cancer in Australia. Canberra: Australian Institute of Health and Welfare, Australian Government; 2023 [22 July 2024]; Available from: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/about.
[b] Cancer Council Victoria. Kidney cancer statistics and trends. 2024; Available from: https://www.cancervic.org.au/cancer-information/statistics/kidney-cancer.html.
[c] Arora RD, Limaiem F. Renal Clear Cell Cancer. StatPearls [Internet]: StatPearls Publishing; 2023.

[d] Gupta K, Miller JD, Li JZ, Russell MW, Charbonneau C. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. *Cancer Treat Rev*. 2008 May;34(3):193-205.
[e] Ta AD, Bolton DM, Dimech MK, White V, Davis ID, Coory M, et al. Contemporary management of renal cell carcinoma (RCC) in Victoria: implications for longer term outcomes and costs. *BJU Int*. 2013 Nov;112 Suppl 2:36-43.
[f] Kidney Cancer Australian Registry and Biobank [KRAB Registry]. Victorian Cohort of Nephrectomy for early-stage Renal Cell Carcinoma. 2023.
[g] Kidney Cancer Australian Registry and Biobank [KRAB Registry]. Metastatic Renal Cell Carcinoma Cohort. 2023.
[h] Alt AL, Boorjian SA, Lohse CM, Costello BA, Leibovich BC, Blute ML. Survival after complete surgical resection of multiple metastases from renal cell carcinoma. *Cancer*. 2011 Jul 1;117(13):2873-82.
[i] Powles T, Tomczak P, Park SH, Venugopal B, Ferguson T, Symeonides SN, et al. Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2022 Sep;23(9):1133-44.
[j] Karam JA, Bhattacharya R, Ogbomo A, Gautam S, Yu R, Sundaram M, et al. Real-world study on the characteristics, post-nephrectomy journey, and outcomes of patients with early-stage renal cell carcinoma based on risk groups. *Cancer Med*. 2024 Jun;13(11):e7247.
The redacted values correspond to the following ranges:
1 <500

6.59 The submission's estimates for the number of patients treated and financial impact of pembrolizumab over the first six years of listing is presented in Table 19.

Table 19: Estimated use and financial implications

		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
A	Incidence of kidney cancer	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
B	No. with RCC (A × 90.0%)	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]1	[redacted]1
C	No. with ccRCC (B × 80.0%)	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
D	No. with non-metastatic disease at diagnosis (C × 75.0%)	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
E	No. Stage I-III patients who receive upfront curative nephrectomy (D × 94.3%)	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
F	No. intermediate-high/high risk ccRCC (E × 28.0%)	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
G	No. with metastatic disease at diagnosis (C × 25.0%)	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
H	No. who receive nephrectomy for metastatic disease (G × 44.0%)	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
I	No. with complete resection of metastatic disease (H × 14.0%)	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
J	No. patients eligible (F + I)	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
K	No. grandfathered patients	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
L	No. incident patients (J – K)	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
M	No. with no residual disease (L × 88.7%)	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
N	No. with ECOG PS 0–1 (M × 95.0%) **Incident patients eligible for pembrolizumab**	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
O	No. who uptake treatment (N × 90.0%)	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
P	No. scripts in incident patients (O × 12.96)[a]	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Q	No. scripts in grandfathered patients (K × 6.48)[b]	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
R	**Total no. scripts** (P + Q)	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
	Cost to the PBS/RPBS, less copayments ($[redacted] per script)	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4
	Net financial implications						
	Net cost to PBS/RPBS	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4
	Net cost to MBS	[redacted]5	[redacted]5	[redacted]5	[redacted]5	[redacted]5	[redacted]5
	Revised financials provided in PSCR						
	No. who uptake treatment	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
	Cost to the PBS/RPBS, less copayments ($[redacted] per script)	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4

Source: Constructed during the evaluation from Table 4.2–1, p119; Table 4.2–3, p120; Table 4.3–5 and Table 4.3–6, p123; and Table 4.6–3, p125 of the submission and 'Attachment 6 UCM (1)'.xlsx'.

ECOG PS = European Cooperative Oncology Group performance status; RCC = renal cell carcinoma; ccRCC = clear cell renal cell carcinoma

[a] Average time-on-treatment assumed was 39.3 weeks, equivalent to 75.6% of a patient-year on treatment, multiplied by the number of scripts per patient-year on treatment (52 weeks × 0.3333 scripts per week; 17.33), adjusted for compliance (98.9%).

[b] Grandfathered patients were assumed to use half the number of scripts of incident patients.

The redacted values correspond to the following ranges:

1 5,000 to < 10,000

2 500 to < 5,000

3< 500

4 $20 million to < $30 million
5 $0 to < $10 million

6.60 The total cost to the PBS/RPBS of listing pembrolizumab was estimated to be $20 million to < $30 million in Year 6, and a total of $100 million to < $200 million in the first 6 years of listing. The PSCR provided revised financials (increased proportion of patients with M1 NED disease from 14% to 20% and inclusion of < 500 prevalent patients in Year 1) which resulted in a total to the PBS/ RPBS in year 1 of $20 million to < $30 million and $100 million to < $200 million in the first 6 years of listing.

6.61 AIHW projections were used to estimate the incidence of kidney cancer each year over the projected period. Of incident cases, 90.0% were assumed to have RCC, with most of these cases (80.0%) being clear cell RCC; 25% of patients were assumed to be diagnosed with Stage IV disease. These estimates were generally consistent with advice recently provided by DUSC (paragraph 6.54, cabozantinib PSD [nccRCC], March 2024 PBAC meeting).

6.62 Of incident cases diagnosed with Stage I–III disease, only those with intermediate-high and high risk of recurrence after nephrectomy would be eligible for adjuvant pembrolizumab. The submission assumed that 94.3% of patients would receive curative nephrectomy, based on a retrospective review[12] of Victorian patients diagnosed and treated for RCC in 2009. It would be expected that most patients with early-stage disease would receive surgery, though given the age of the data cited, there is some uncertainty as to the applicability of the source used (and whether this reflects use following the availability of robotic-assistance). The proportion of patients who met the proposed criteria for intermediate-high to high risk was based on an analysis of consecutive patients in the KRAB registry[7] who had undergone curative-intent nephrectomy between 2016–2022 in Victoria (101/356, 28.4%).

6.63 Of incident cases diagnosed with Stage IV disease, only those who had undergone complete resection of primary and metastatic lesions would be eligible for adjuvant pembrolizumab. The submission considered that 44.0% of patients would undergo nephrectomy, based on an analysis of the KRAB registry in consecutive patients diagnosed with Stage IV RCC, 2007–2023 (120/271, 44.3%)[13]. Complete resection was assumed in 14.0% of patients, based on a retrospective review[14] of patients who underwent radical nephrectomy 1976–2006 and who were diagnosed with multiple metastases either at the time of or after nephrectomy in the US. The ability to achieve complete resection may depend on a number of factors, including location and number of metastases. Limited detail was provided in Alt (2011)[14] to discern whether the distribution of metastases' location was similar to what would be expected in

[12] Ta AD, Bolton DM, Dimech MK, White V, Davis ID, Coory M, et al. Contemporary management of renal cell carcinoma (RCC) in Victoria: implications for longer term outcomes and costs. *BJU Int*. 2013 Nov;112 Suppl 2:36-43.
[13] Kidney Cancer Australian Registry and Biobank [KRAB Registry]. Metastatic Renal Cell Carcinoma Cohort. 2023.
[14] Alt AL, Boorjian SA, Lohse CM, Costello BA, Leibovich BC, Blute ML. Survival after complete surgical resection of multiple metastases from renal cell carcinoma. *Cancer*. 2011 Jul 1;117(13):2873-82.

practice. Further, the evaluation considered it is unknown to what extent the availability of pembrolizumab in the adjuvant setting may change uptake of surgery, or attempts at complete resection in patients with Stage IV disease at diagnosis. However, of patients estimated to be eligible for treatment, those who had Stage IV at diagnosis (approx. 7%) was similar to the proportion of patients with M1 NED in KN564 (57/994, 5.7%). The PSCR increased the proportion of patients with a complete resection of metastatic disease from 14% to 20% based on recent publications[15][16]. The PSCR stated that recent publications have reported M1 NED epidemiology of ~10% and, based on this, considered it reasonable that the proportion of M1 NED patients in Australia be higher than observed in KN564 (5.7%). The PSCR stated it would be amenable to increasing the proportion of patients who undergo complete resection from 14% to 20%, which equates to the M1 NED population accounting for 10% of the total high-risk criteria. The ESC considered it was unlikely the availability of pembrolizumab would change the uptake of surgery The ESC considered the proportion of patients with complete resection of M1 NED disease in Australia remained uncertain.

6.64 The submission has not considered use in patients with prevalent RCC who experience a recurrence and have complete resection of their lesions. This use is not precluded by the wording of the proposed PBS restriction. The PSCR proposed inclusion of an additional < 500 treated patients in Year 1 to account for prevalent patients[17]. The PBAC agreed with the ESC that there would be only a very small number of prevalent patients and considered an estimate of < 500 would be more reasonable.

6.65 The submission further restricted the number of eligible patients to those with no residual disease and good performance status. No residual disease was estimated in 88.7% of patients and was based on the proportion of patients screened for KN564 who were excluded due to presence of residual disease (156/1406, 11.1%). This estimate was applied to both patients diagnosed with Stage I–III and Stage IV disease. The submission did not consider whether the application of this estimate to patients with Stage IV disease who have complete resection would constitute double-counting e.g., if their residual disease were defined by metastases that were subsequently completely resected.

6.66 The average number of scripts applied per incident patient was 12.96. This was derived from the average ToT estimated in the economic model (39.3 weeks, equivalent to 75.6% of a patient-year on treatment), multiplied by the number of

[15] El Zarif T, et al. First-line Systemic Therapy Following Adjuvant Immunotherapy in Renal Cell Carcinoma: An International Multicenter Study. Eur Urol. 2024 Aug 14: S0302-2838(24)02499-0

[16] Bencina G, et al. Recurrence patterns following nephrectomy for renal cell carcinoma in a Danish nationwide cohort. BJUI Compass. 2024 Jun 10;5(8):791-798

[17] Calculated as 5 year prevalence (10,000 to < 20,000) x 72% with ccRCC x 57% with Stage T1 x 92% with nephrectomy x 8.4% with recurrence x 28% who are intermediate or high risk = < 500. (< 500 – < 500 GF) x 75% eligibility/ uptake = < 500

scripts per patient-year on treatment (17.33)[18], adjusted for compliance (98.9%). The submission stated that the RDI was sourced from the KN564 trial. This could not be verified.

6.67 The submission estimated that there would be <500 patients grandfathered on to the PBS. Grandfathered patients were assumed to receive on average half the number of scripts an incident patient would use.

6.68 The submission included no changes in use and financial impact of other medicines, due to the listing of pembrolizumab. The ESC noted this was not appropriate and should have been included in the submission. The submission recognised, however, that listing may impact the use of therapies to treat advanced RCC, but did not include these in the financial estimates, given the projections to six years only. Impact on existing RSAs is discussed below ('Financial Management – Risk Sharing Arrangements').

Quality Use of Medicines

6.69 The sponsor proposed a number of activities intended to promote safe and effective use of pembrolizumab in clinical practice. These included the development of materials and educational activities to provide updated information to physicians, nurses, pharmacists and patients on the identification and management of treatment-related AEs (in particular immune-related AEs).

Financial Management – Risk Sharing Arrangements

6.70 The sponsor acknowledged that if pembrolizumab receives a positive recommendation, renegotiation of the existing metastatic RCC deeds will need to be considered to factor the increased number of patients who are cured. Additionally, the evaluation noted there will be reduced use of PD-(L)1 in the first line setting if patients are treated in the adjuvant setting as treatment with PD-(L)1 inhibitors is currently limited to once per lifetime. The expected reduction in PD-(L)1 treatment in the first-line advanced RCC setting was estimated during the evaluation based on the incidence of DM in the absence of adjuvant pembrolizumab and uptake of PD-(L)1 therapies for DM as estimated in the submission's economic model (Table 20).

[18] 52 weeks × 0.3333 scripts per week

Table 20: Estimated reduction in patients treated with PD-(L)1 in the first-line advanced RCC setting, due to the listing of adjuvant pembrolizumab

	Years following adjuvant treatment					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
Cumulative incidence of DM (from either DF or LR) predicted in SURV arm of the economic model provided in the submission	15.1%	23.9%	30.2%	35.0%	38.9%	42.1%
Annual incidence of DM [a]	15.1%	8.8%	6.3%	4.8%	3.9%	3.2%
	Years following listing					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
No. patients treated with adj. pembrolizumab each year [b]	1	1	1	1	1	1
No. with DM in absence of adj. pembrolizumab						
- First year following surgery (15.1%) - Second year following surgery (8.8%) - Third year following surgery (6.3%) - Fourth year following surgery (4.8%) - Fifth year following surgery (3.9%) - Sixth year following surgery (3.2%)	2	2 2	2 2 2	2 2 2 2	2 2 2 2 2	2 2 2 2 2 2
Total no. patients with DM	2	2	2	2	2	2
No. who would have been treated with PD-(L)1 in the advanced RCC setting (100.0%)	2	2	2	2	2	2

Source: Constructed during the evaluation from the 'Attachment 5 CUA (1).xlsm' and 'Attachment 6 UCM (1)'.xlsx' workbooks included in the submission.
DF = disease-free; DM = distant metastasis; LR = locoregional recurrence; PD-(L)1 = programmed cell death (ligand) 1; SURV = surveillance.
[a] Cumulative incidence in Year T + 1 – cumulative incidence in Year T
[b] Row K + Row O, Table 22
The redacted values correspond to the following ranges:
1 500 to < 5,000
2< 500

6.71 The pre-PBAC response provided revised financial estimates, including cost offsets, based on:

- revised patient numbers included in the PSCR (increase in M1 NED patients to 20% as described in paragraph 6.63 and addition of < 500 prevalent patients as described in paragraph 6.64) and the revised pembrolizumab price included in the pre-PBAC response;
- the cumulative incidence of DM in the surveillance arm of the respecified base case model (14.9% in Year 1, to 39.4% in Year 6);
- 75% of patients would have otherwise received PD-(L)1 inhibitors in the absence of adjuvant pembrolizumab;
- a market share of 72% for NIVO + IPI and 28% for PEM + LEN (based on script data from July 23 to July 24);
- treatment durations for NIVO (10.80 + 48.54 weeks); IPI (9.89 + 0 weeks); PEM (18.67 + 44.11 weeks) and LEN (12 + 48.63 weeks); and

- the effective prices of NIVO, IPI, PEM and LEN (based on previous pricing negotiations).

Table 21: Revised net cost to government, accounting for cost offsets in the metastatic setting

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Treated patients	[redacted][1](+ [redacted] [2]GF)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Base Case	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Offset patients	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]
Cost Offsets	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Net cost	[redacted][3]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]

Source: pre-PBAC response Attachment UCM (PES-ESC Accepted Changes).xlsx provided with pre-PBC response

The redacted values correspond to the following ranges:
1 500 to < 5,000
2 < 500
3 $20 million to < $30 million
4 net cost saving
5 $10 million to < $20 million

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 the adjuvant treatment of patients with renal cell carcinoma (RCC) with clear cell component who are at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions. The PBAC considered that pembrolizumab provided a meaningful improvement in disease free survival and overall survival compared with surveillance. The PBAC advised the subsequent therapies included in the economic model presented in the pre-PBAC response should be revised and a price reduction would be required for pembrolizumab to be considered cost effective in the adjuvant treatment setting. The PBAC considered the financial estimates should account for reduced use in the later line treatment setting. The PBAC considered the expenditure for listing pembrolizumab (accounting for reduced later line use) should be included in the current risk sharing arrangement in place for RCC.

7.2 The PBAC considered there was a clinical need for an adjuvant treatment for patients at high risk of recurrence following nephrectomy and noted the consumer comments were supportive of listing pembrolizumab.

7.3 The PBAC advised that the following changes to the proposed restriction criteria are appropriate:

- A single restriction criteria allowing for up to 12 months of treatment for patients treated with 200 mg every 3 weeks or 400 mg every 6 weeks.
- The amendments as proposed by the Secretariat in paragraph 3.1.

- The addition of flow on changes to pembrolizumab and nivolumab in the metastatic treatment setting to restrict limit use of PD-(L)1 inhibitors to once in a life time.

7.4 The PBAC noted the submission nominated surveillance as the comparator and considered this was reasonable.

7.5 The PBAC is satisfied that pembrolizumab provides, for some patients, a significant improvement in efficacy over surveillance.

7.6 The PBAC noted the submission was based on one head-to-head, double blind, randomised trial (KN564) comparing pembrolizumab (200 mg every 3 weeks [Q3W]) (N=496) with placebo (as a proxy for surveillance) (N=498) in patients with clear cell RCC who were at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions. The PBAC noted the primary outcome of KN564 was disease free survival (DFS) defined as randomisation to the first documented local recurrence, or occurrence of distant metastasis(es), or death due to any cause, whichever occurs first. After a median follow up of 55.8 months, 35.1% of patients in the pembrolizumab arm and 45.0% of patients in the placebo arm had experienced a DFS event with most events in both treatment arms metastatic events. The hazard ratio (HR) for DFS was 0.72 (95% CI: 0.59, 0.87). The PBAC noted that, based on immature data (141/994 events across both treatment arms), the HR for overall survival (OS) was 0.62 (95% CI: 0.44, 0.87). The PBAC considered the claim of superior comparative effectiveness was supported by the evidence presented.

7.7 The PBAC noted that the proportion of patients in the KN564 study who subsequently received PD-(L)1 inhibitors, post recurrence, was 26.7% (43/161) in the pembrolizumab arm and 48.1% (101/210) in the placebo arm. The PBAC noted that patients in the Australian treatment setting would not generally receive PD-(L)1 inhibitors after pembrolizumab as retreatment is not subsidised. The PBAC noted the use of PD-(L)1 inhibitors in the placebo arm was lower than would be expected. The PBAC considered this resulted in some uncertainty regarding the magnitude of clinical benefit that would be observed in the Australian treatment setting.

7.8 The PBAC noted pembrolizumab was associated with more Grade 3 – 5 adverse events (AEs) than placebo (32.0% vs 17.7%) and a higher rate of discontinuation due to AEs (21.1% vs 2.2%). The PBAC considered the claim of inferior but manageable comparable safety was reasonable.

7.9 The submission presented a cost utility analysis to determine the cost-effectiveness of pembrolizumab in the adjuvant setting. The PBAC noted that ESC considered the economic model presented in the submission to be unreliable for decision making, and that the modelled outcomes (average of 2.25 undiscounted [1.12 discounted] QALYs gained per patient treated, Table 14, paragraph 6.52) appeared substantially overestimated in the context of the observed clinical trial results (treatment of 100 patients resulting in 8 additional patients remaining free of disease recurrence or

death at 4 years, paragraph 6.28), as this resulted in 28 [2.25/0.08] QALYs gained for each recurrence or death avoided.

7.10 The PBAC noted that the pre-PBAC response presented a revised economic model that reduced the time horizon to 25 years, increased the starting age to 63.8 years, used functions that better fitted the trial data for the transitions from the disease free (DF) to recurrence (LR and DM) health states, removed differences across the pembrolizumab and surveillance arms after 5 years for transitions to the dead health state from the DF, LR and DM health states, applied a more reasonable estimate of utilities, reduced the duration of subsequent therapies to be consistent with those previously accepted and reduced the percent of patients in the surveillance arm receiving PD-(L)1 inhibitors following a relapse event from 100% to 75%. The PBAC noted the QALYs gained with the revised model were reduced substantially from 2.25 to 0.98 undiscounted (1.12 to 0.57, discounted, Table 16). The PBAC noted although this gain better reflects that expected based on the outcomes observed in KN564, uncertainty remains regarding the magnitude of clinical benefit that would be observed in the Australian treatment setting (see paragraph 7.7). In that context, the PBAC considered an analysis using a 20 year time horizon to also be informative.

7.11 The PBAC noted the ICER was sensitive to the higher cost assumed for treating a recurrence event in the surveillance arm of the model compared to the pembrolizumab arm $75,000 to < $95,000 versus $45,000 to < $55,000, see Table 12). The PBAC noted that the additional cost in the surveillance arm was due to the use of PD-(L)1 inhibitors rather than sunitinib, pazopanib and cabozantinib as first line regimens in the advanced setting, and the flow on effects to the treatments used as later line regimens in the advanced setting. The economic model in the pre-PBAC response assumed 75% of patients in the surveillance arm received PD-(L)1 inhibitors with no cost assigned for the remaining 25%. The PBAC considered that for the economic model the use should better reflect that observed in KN564, and hence that 50% of patients receive PD-(L)1 inhibitors with the remaining 50% receiving targeted therapies (sunitinib, pazopanib and cabozantinib). The PBAC noted that this resulted in a very similar first line treatment cost as proposed in the pre-PBAC response ($ versus $, Table 12). The PBAC considered the assumed differences across the arms in the treatments received, and hence costs, for the later line regimens may not reflect the outcomes modelled (paragraph 6.48) and were inadequately supported.

7.12 The PBAC noted the ICER for the revised model as presented in the pre-PBAC response was $25,000 to < $35,000 per QALY gained (based on a vial price of $ per 100 mg vial as proposed in the pre-PBAC response). The PBAC noted accounting only for the cost of the first line regimens in the advanced setting increased the ICER to $45,000 to < $55,000 per QALY gained. The PBAC considered pembrolizumab would be cost-effective in the adjuvant treatment setting if the ICER for this scenario was less than $25,000 to < $35,000 per QALY gained. The PBAC noted that reducing the model time horizon from 25 years to 20 years would increase the ICER by approximately 9% (Table

16), but in the context of the available clinical evidence considered it reasonable for the base case analysis to use a 25 year time horizon.

7.13 The PBAC noted the submission took an epidemiological approach to estimating the utilisation and financial implications of listing pembrolizumab for the adjuvant treatment of RCC. The PBAC noted the PSCR provided revised utilisation estimates which it considered would be reasonable with a reduction in prevalent patients (as per paragraph 6.64). The PBAC noted the submission did not include any changes in use and financial impact of other medicines due to the listing of pembrolizumab and considered this was not appropriate. However, the pre-PBAC response provided an estimate of cost offsets due to the reduction in use of pembrolizumab, nivolumab, ipilimumab and lenvatinib in the metastatic treatment setting. The PBAC considered the approach was reasonable, noting the net financial cost needs to be revised to include the cost-effective price of adjuvant pembrolizumab (as per paragraph 7.11).

7.14 The PBAC considered it would be appropriate for pembrolizumab to be included in the existing RSA in place for RCC (which includes nivolumab, ipilimumab, pembrolizumab and lenvatinib) with expenditure caps adjusted to account for the net cost of listing pembrolizumab for adjuvant treatment (accounting for cost offsets in the later line treatment setting).

7.15 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for pembrolizumab:

a) The treatment is not expected to provide a substantial improvement in efficacy over surveillance in terms of DFS and OS

b) The treatment is not expected to address a high and urgent unmet clinical need as there are currently PD-(L)1 inhibitors listed on the PBS for treatment of RCC; and

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT Form	PBS item code	Max. amount	№.of Repeats

PEMBROLIZUMAB injection	New (Public) New (Private)	400 mg	7
Available brands			
Keytruda® (pembrolizumab 100 mg/4 ml injection, 4 ml vial)			

Restriction Summary [new3] / Treatment of Concept: [new3A]	
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (STREAMLINED)
	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: Special Pricing Arrangements apply.
	Severity: Intermediate or high risk of recurrence
	Condition: Clear cell renal cell carcinoma (RCC)
	Indication: Intermediate or high risk of recurrence clear cell renal cell carcinoma (RCC)
	Treatment Phase: [blank]
	Clinical criteria:
	Patient must have: (i) pT2 with Grade 4 or sarcomatoid features OR (ii) pT3, with any grade without nodal involvement (N0) or distant metastases (M0) OR (iii) pT4, any grade N0 and M0 OR (iv) any pT, any grade with nodal involvement and M0 OR (v) metastatic disease and has undergone complete resection of primary and metastatic lesions.
	AND
	Clinical criteria:
	The treatment must be in addition to complete surgical resection
	AND
	Clinical criteria:
	The treatment must commence within 12 weeks of complete resection
	AND
	Clinical criteria:
	Patient must have a WHO performance status of 1 or less
	AND
	Clinical criteria:
	Patient must not have previously been treated with systemic therapy for this condition, prior to commencing treatment with this drug for this condition
	AND
	Clinical Criteria:
	The treatment must be the sole PBS-subsidised anti-cancer therapy for this condition.
	Treatment Criteria:
	Patient must not receive more than 12 months of combined PBS-subsidised and non-PBS-subsidised adjuvant therapy.
	AND
	Treatment Criteria:
	Patient must be undergoing treatment with this drug administered once every 3 weeks - prescribe up to 7 repeat prescriptions; or
	Patient must be undergoing treatment with this drug administered once every 6 weeks - prescribe up to 3 repeat prescriptions

8.2 Amend the following restrictions to restrict limit use of PD-(L)1 inhibitors to once in a life time. The following criteria will be added to the listings of Nivolumab (item codes: 11627Y, 11636K) and Pembrolizumab (item codes: 13254N, 13267G):

	Clinical criteria:
	Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition

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

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.