

6.05 CABOZANTINIB, Tablet 20 mg, Tablet 40 mg, Cabometyx®, Ipsen Pty Ltd

1 Purpose of submission

- 1.1 The Category 2 submission requested a Section 85 Authority Required (STREAMLINED) listing for cabozantinib (CBZ from herein) and a Section 100 (Efficient Funding of Chemotherapy (EFC) Authority Required (STREAMLINED) listing for nivolumab (NIVO from herein) for the first-line treatment of advanced (Stage IV) clear cell variant renal cell carcinoma in patients who are classified as intermediate or poor risk according to the International Metastatic renal cell cancer Database Consortium (IMDC) prognostic criteria.
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus pembrolizumab in combination with lenvatinib (PEM+LEN from herein). The key components of the clinical issue addressed by the submission are summarised below.

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

Component	Description
Population	Patients with previously untreated advanced (Stage IV) clear cell variant renal cell carcinoma who are classified as intermediate or poor risk according to the IMDC prognostic criteria.
Intervention	Cabozantinib 40 mg orally once daily plus nivolumab at either 240 mg IV every 2 weeks or 480 mg IV every 4 weeks (up to 24 months) until progression or unacceptable toxicity.
Comparator	<ul style="list-style-type: none"> - Primary comparator: pembrolizumab 200 mg IV every 3 weeks (7 cycles) plus lenvatinib 20 mg orally once daily followed by pembrolizumab 400 mg IV every 6 weeks plus lenvatinib 20 mg orally once daily until progression or unacceptable toxicity^a - Secondary comparator: nivolumab 3 mg/kg IV plus ipilimumab 1 mg/kg IV every 3 weeks for 4 doses followed by nivolumab 480 mg IV fixed dose every 4 weeks until progression or unacceptable toxicity.
Outcomes	Progression-free survival (PFS), Objective response rate (ORR), Overall survival (OS) and safety
Clinical claim	<ul style="list-style-type: none"> - Cabozantinib plus nivolumab is non-inferior in terms of effectiveness (at improving PFS, ORR and OS) and safety compared to pembrolizumab plus lenvatinib. - Cabozantinib plus nivolumab is non-inferior in terms of effectiveness (at improving PFS, ORR and OS) and is different, but comparable, in terms of safety to nivolumab plus ipilimumab

Source: Table 1-2, p13 of the submission.

IMDC = International Metastatic renal cell cancer Database Consortium

^a Pembrolizumab treatment is for a maximum of 24 months

2 Background

Registration status

- 2.1 CBZ was registered with the Therapeutic Goods Administration (TGA) in October 2021 for the following relevant indication: in combination with NIVO for the first-line

treatment of advanced renal cell carcinoma (aRCC). CBZ is also indicated as monotherapy for the treatment of aRCC in (i) treatment-naïve adults with intermediate or poor risk, and (ii) adults following prior treatment with vascular endothelial growth factor targeted therapy.

- 2.2 NIVO is TGA registered for the same relevant indication: in combination with CBZ for the first-line treatment of patients with advanced renal cell carcinoma. In addition it is indicated in combination with ipilimumab (IPI) for the first-line treatment of patients with advanced renal cell carcinoma, and as monotherapy for the treatment of patients with clear cell aRCC after prior anti-angiogenic therapy.

Previous PBAC consideration

- 2.3 CBZ is currently PBS listed for patients with clear cell aRCC (i) as monotherapy in the first-line treatment setting (intermediate or poor IMDC survival risk score), or (ii) as monotherapy for patients with progressive disease following treatment with a tyrosine kinase inhibitor (TKI), irrespective of current IMDC survival risk score. A request to amend this listing to allow treatment in patients with non-clear cell advanced RCC was considered at the March 2024 PBAC meeting.
- 2.4 NIVO is currently PBS listed for patients with clear cell aRCC (i) in combination with IPI in the first-line treatment setting for patients with intermediate or poor risk IMDC survival risk score, or (ii) as monotherapy for patients with progressive disease or intolerance following treatment with a TKI.

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

3 Requested listing

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

Name, Restriction, Manner of administration and form	Max. qty packs	Max. qty units	No. of Rpts	Dispensed Price for Max. Qty	Available brands
Initial Treatment					
CABOZANTINIB					
Cabozantinib, 40 mg tablet, 30	1	30	2	Published price:	Cabometyx® Ipsern Pty Ltd
Cabozantinib, 20 mg tablet, 30	1	30	2	\$9,962.13	
Continuing Treatment					
CABOZANTINIB					
Cabozantinib, 40 mg tablet, 30	1	30	5	Published price:	Cabometyx® Ipsern Pty Ltd
Cabozantinib, 20 mg tablet, 30	1	30	5	\$9,962.13	

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Requested restriction. Cabozantinib - Initial Treatment

Category / Program: General Schedule/Section 85
Restriction type: Authority Required (STREAMLINED)
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment Phase: Initial treatment <i>in combination with nivolumab</i>
Clinical criteria:
Patient must have a prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score at treatment initiation with this drug and nivolumab of either (i) 1 to 2 (intermediate risk); or (ii) 3 to 6 (poor risk) documented in the patient's medical records.
AND
Clinical criteria:
Patient must have a WHO performance status of 2 or less.
AND
Clinical criteria:
The condition must be untreated <i>not have been previously treated</i>
Treatment criteria:
Patient must be undergoing combination therapy consisting of (i) cabozantinib and (ii) nivolumab
OR
Treatment criteria:
Patient must be undergoing monotherapy with this drug due to a contraindication/intolerance to the other drug in the combination mentioned above, requiring temporary/permanent discontinuation; document the details in the patient's medical records.

Source: Table 1-12, pp31-32 of the submission.

Requested restriction. Cabozantinib - Continuing Treatment

Category / Program: General Schedule/Section 85
Restriction type: Authority Required (STREAMLINED)
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment Phase: Continuing treatment <i>in combination with nivolumab</i>
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria:
Patient must not have developed disease progression while receiving treatment with this drug for this condition.
Treatment criteria:
Patient must be undergoing combination therapy consisting of (i) cabozantinib and (ii) nivolumab.
OR
Patient must be undergoing monotherapy with this drug due to a contraindication/intolerance to the other drug in the combination mentioned above, requiring temporary/permanent discontinuation, document the details in the patient's medical records.
OR
Patient must be undergoing monotherapy with this drug after completing an equivalent of 24 cumulative months of nivolumab treatment, measured from the first administered dose.
Treatment criteria:
In a patient who has experienced an intolerance to nivolumab, details of intolerance must be documented in the patient's medical record.

Source: Table 1-13, p32 of the submission.

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Name, Restriction, Manner of administration and form	Max. amount	No. of Rpts	Dispensed Price for Max. Amount	Available brands
Initial Treatment				
NIVOLUMAB Nivolumab 40mg/4mL injection 4mL Nivolumab 100mg/10mL injection 10mL	480 mg 480 mg	5/44 5/44	Published price \$7,191.12 (Public) \$7,333.85 (Private)	Opdivo® Bristol-Myers Squibb
Continuing Treatment				
NIVOLUMAB Nivolumab 40mg/4mL injection 4mL Nivolumab 100mg/10mL injection 10mL	480 mg 480 mg	5/11 5/11	Published price \$9,558.60 (Public) \$9,734.47 (Private)	Opdivo® Bristol-Myers Squibb

Requested restriction. Nivolumab - Initial Treatment

Category / Program: Chemotherapy items for Public/Private Hospital use
Restriction type: Authority Required (STREAMLINED)
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment Phase: Initial treatment <i>in combination with cabozantinib</i>
Clinical criteria:
Patient must have a prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score at treatment initiation with this drug of either (i) 1 to 2 (intermediate risk), or (ii) 3 to 6 (poor risk) IMDC classification score documented in the patient's medical records.
AND
Clinical criteria:
The condition must be untreated not <i>not have been previously treated.</i>
AND
Clinical criteria:
Patient must have a WHO performance status of 2 or less.
Treatment criteria:
Patient must be undergoing combination therapy consisting of (i) cabozantinib and (ii) nivolumab.
OR
Patient must be undergoing monotherapy with this drug due to a contraindication/intolerance to the other drug in the combination mentioned above, requiring temporary/permanent discontinuation, document the details in the patient's medical records.
AND
Treatment criteria:
Patient must be undergoing treatment with this drug administered once every 2 weeks - prescribe up to 44 5 repeat prescriptions.
OR
Patient must be undergoing treatment with this drug administered once every 4 weeks - prescribe up to 5 2 repeat prescriptions.

Source: Table 1-14, p33 of the submission.

Requested restriction. Nivolumab - Continuing Treatment

Category / Program: Chemotherapy items for Public/Private Hospital use
Restriction type: Authority Required (STREAMLINED)
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment Phase: Continuing treatment <i>in combination with cabozantinib</i>

Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria:
Patient must not have developed disease progression while receiving treatment with this drug for this condition.
Treatment criteria:
Patient must be undergoing combination therapy consisting of (i) cabozantinib and (ii) nivolumab.
OR
Patient must be undergoing monotherapy with this drug due to a contraindication/intolerance to the other drug in the combination mentioned above, requiring temporary/permanent discontinuation, document the details in the patient's medical records.
AND
Treatment criteria:
Patient must be undergoing treatment with this drug administered once every 2 weeks - prescribe up to 11 repeat prescriptions.
OR
Patient must be undergoing treatment with this drug administered once every 4 weeks - prescribe up to 5 repeat prescriptions.
AND
Treatment criteria:
Patient must not be undergoing continuing PBS-subsidised treatment where this benefit is extending treatment beyond 24 cumulative months from the first administered dose, once in a lifetime.

Source: Table 1-15, pp33-34 of the submission.

- 3.2 The sponsor requested a special pricing arrangement (SPA). The sponsor noted the effective price of the comparator was not known, so all calculations in the submission were based on published prices.
- 3.3 The proposed wording of the requested restrictions for the combination use of CBZ and NIVO was consistent with the existing PBS listings for the combination use of PEM and LEN, which is the primary comparator for this submission.
- 3.4 The Secretariat suggested that the maximum number of repeats for initial therapy for NIVO should be 5 (based on fortnightly dosing) to align with the 3 months of initial treatment requested for CBZ, and for continuing therapy with NIVO should be 11 (based on fortnightly dosing) to align with the 6 months of continuing treatment requested for CBZ.
- 3.5 The Pre-PBAC Response proposed an amendment to the current restriction wording for sunitinib (SUN) and pazopanib (PAZ) to align the post-progression options with PEM+LEN, where subsequent treatment with SUN and PAZ is not precluded (Pre-PBAC Response). The request was to change the wording from “(i) cabozantinib” to “(i) cabozantinib monotherapy.” The PBAC recommended that the current wording of the SUN and PAZ restriction (i.e., (i) cabozantinib) should be maintained as use of CBZ in the first-line setting (either in combination or as monotherapy) should preclude use of another first-line TKI (i.e., SUN and PAZ). Additionally, the PBAC considered use of LEN

in the first-line setting should also preclude subsequent use of SUN and PAZ and that the restrictions for SUN and PAZ should reflect this.

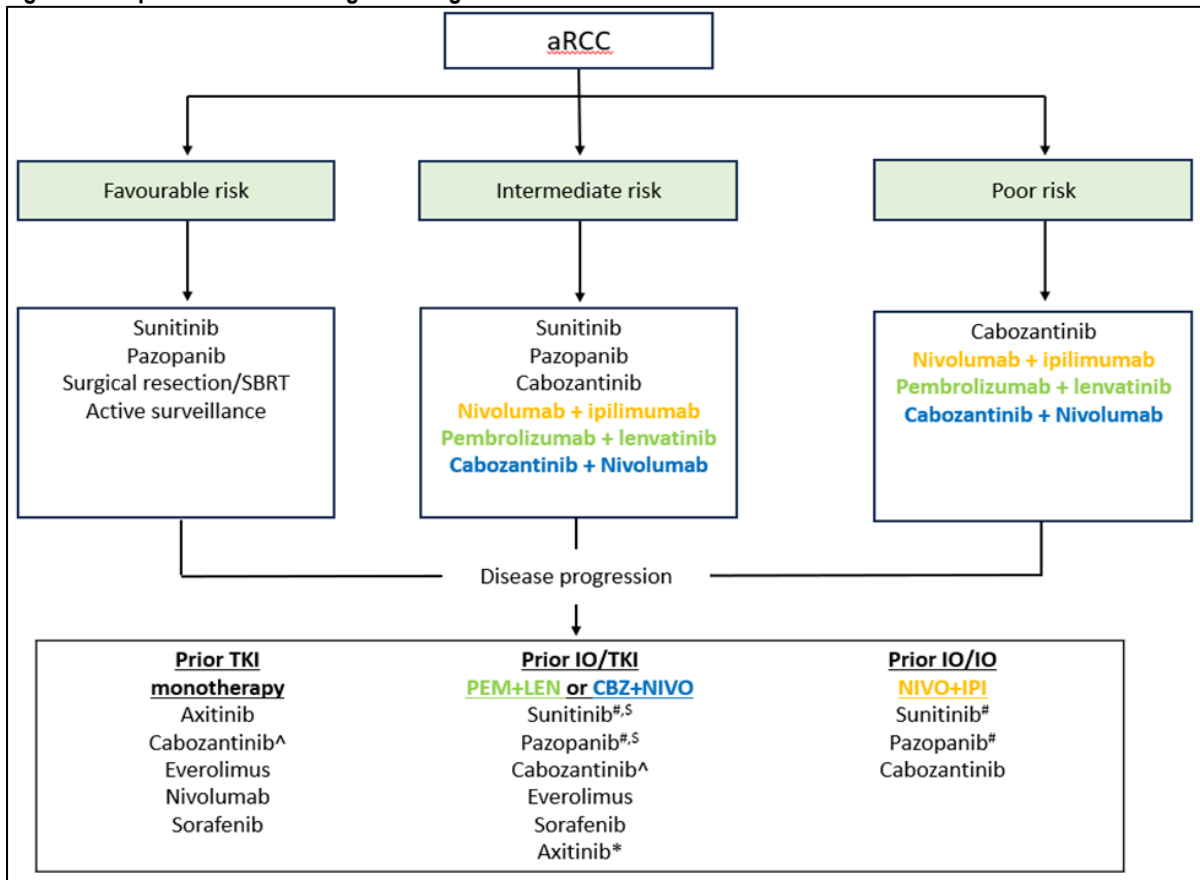
For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Kidney cancer was the seventh most-diagnosed cancer in Australia in 2018 and was likely to remain so in 2022¹. An estimated 4,552 new cases of kidney cancer (3,081 males and 1,471 females) were diagnosed in 2022. The incidence rate for kidney cancer increases with age and is highest for those aged 70–74 years. In terms of mortality, it is estimated that there were 912 deaths (618 males and 294 females) in 2022. Approximately 85-90% of kidney cancers are RCC and, of these, 70% are clear cell variant.
- 4.2 CBZ is an oral inhibitor of a broad range of tyrosine kinase receptors associated with angiogenesis, pathological bone remodelling, drug resistance, and metastatic progression of cancer. NIVO is a fully human immunoglobulin G4 monoclonal antibody that binds to the programmed death-1 (PD-1) receptor and blocks its interaction with the ligands PD-L1 and PD-L2.
- 4.3 The submission proposed the combination therapy of CBZ+NIVO for patients with previously untreated clear cell aRCC who are classified as intermediate or poor risk according to the IMDC prognostic criteria and have a WHO performance status of 2 or less. The submission's proposed place in therapy for CBZ+NIVO is presented in Figure 1.

¹ <https://www.canceraustralia.gov.au/cancer-types/kidney-cancer/statistics>

Figure 1. Proposed clinical management algorithm



Source: Figure 1-5, p23 of the submission. Source: PEM+LEN PSD, March 2022 PBAC Meeting.

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

Note: Risk is defined as per the IMDC criteria.

Note: Green text indicates a primary comparator.

Note: Orange text indicates a relevant secondary comparator.

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

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

[§] Only if CAB+NIV not used in the first-line setting.

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

4.4 While the proposed restriction for CBZ+NIVO is similar to those for PEM+LEN and NIVO+IPI, it is narrower than current clinical practice recommendations for clear cell aRCC. For example, the National Comprehensive Cancer Network (NCCN) guidelines include CBZ+NIVO and PEM+LEN as preferred treatment options for clear cell aRCC, regardless of IMDC prognostic risk profile (with NIVO+IPI the preferred regimen for intermediate/ poor risk patients only). The ESC noted that the following criterion from the IMDC risk profile: ‘Time from diagnosis to treatment <1 year’ means that a decision to initiate systemic treatment automatically shifts a patient into the intermediate risk group. The ESC expressed some concern that with more treatments becoming available, this could lead to more patients being deemed intermediate risk.

- 4.5 CBZ+NIVO is also included in the NCCN guidelines as an “other recommended regimen” for non-clear cell aRCC.

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

5 Comparator

- 5.1 The submission nominated PEM+LEN as the main comparator, with NIVO+IPI as the secondary comparator. Although NIVO+IPI was the market leader at the time of the submission, the submission stated that CBZ+NIVO was most likely to replace PEM+LEN given that both combinations are immunotherapy plus tyrosine kinase inhibitor (IO+TKI). The submission noted PEM+LEN was recommended on the basis of a CMA versus NIVO+IPI.
- 5.2 The ESC considered the primary and secondary comparators nominated by the submission were appropriate. The ESC noted CBZ+NIVO was more likely to replace PEM+LEN as the clinical decision to use an IO+TKI or NIVO+IPI is different (as discussed in paragraph 6.39).
- 5.3 The submission did not consider avelumab plus axitinib (AVE+AXI) and PEM plus axitinib (PEM+AXI) to be near-term comparators for the following reasons, which were reasonable:
- AVE+AXI was approved by the TGA and recommended by the PBAC in March 2021 (on the basis of a CMA versus NIVO+IPI) but is not yet listed in the PBS.
 - PEM+AXI has not been submitted to the PBAC by the sponsor of PEM due to the challenges of intercompany working and a lack of a formal alliance with the sponsor of AXI (Para 5.2 and 5.3, PEM Public Summary Document (PSD), March 2022 PBAC Meeting).
- 5.4 In the context of the CMA taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is satisfied, it must make a statement to this effect. Alternative therapies include PEM+LEN, NIVO+IPI and AVE+ AXI (should the last combination be listed on the PBS).

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 two organisations via the Consumer Comments facility on the PBS website. Rare Cancers Australia (RCA) expressed its support for a listing for CBZ+NIVO in aRCC because it provides an alternative combination therapy option. The Medical Oncology Group of Australia (MOGA) also expressed its support for the use of CBZ (in combination with NIVO) for the first-line treatment of aRCC on the basis of the CheckMate-9ER trial, noting that other treatment options are available. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for CBZ of 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement),² based on a comparison with SUN.

Clinical trials

6.3 No head-to-head randomised trials comparing CBZ+NIVO to PEM+LEN or NIVO+IPI were available. The submission was based on three randomised trials to inform anchored Bucher indirect treatment comparisons (ITCs), with SUN as the common comparator:

- The CheckMate 9ER trial (CBZ+NIVO vs SUN);
- The CLEAR trial (PEM+LEN vs SUN); and
- The CheckMate214 trial (NIVO+IPI vs SUN).

6.4 A claim of non-inferiority was made based on progression-free survival (PFS), objective response rate (ORR), overall survival (OS) and safety.

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

Table 2. Trials and main publications presented in the submission.

Trial ID	Protocol title/ Publication title	Publication citation
Indirect randomised trials		
CheckMate 9ER	Primary analysis (median 18.1 months) Choueiri, T. K., Powles, T., Burotto, M., et al. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma.	The New England Journal of Medicine 2021; 384(9), 829-841.
NCT03141177	Extended follow-up 1 (median 23.5 months) Motzer, R. J., T. K. Choueiri, T. Powles, et al. (2021). Nivolumab + cabozantinib (NIVO+CABO) versus sunitinib (SUN) for advanced renal cell carcinoma (aRCC): outcomes by sarcomatoid histology and updated trial results with extended follow-up of CheckMate 9ER. Motzer, R. J., T. K. Choueiri, T. Powles, et al. (2021). Nivolumab plus cabozantinib versus sunitinib for advanced renal cell carcinoma: outcomes by sarcomatoid histology and updated trial results with extended follow-up of CheckMate 9ER. [^]	Journal of Clinical Oncology 39(6 SUPPL). Genitourinary Cancers Symposium; February 11–13, 2021: Abstract 308

² Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017.

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Trial ID	Protocol title/ Publication title	Publication citation
	Phase 3 CheckMate-9ER Trial of Cabozantinib in Combination with nivolumab as a First-line Treatment for Patients with Advanced Renal Cell Carcinoma Shows Consistent Efficacy Benefits Across Subgroups. [^]	ASCO 2021 Press Release ³
	Extended follow-up 2 (median 32.9 months) Motzer, R. J., Powles, T., Burotto, M., et al. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomised, phase 3 trial.	The Lancet Oncology 2022; 23(7), 888-898.
	Extended follow-up 3 (median 44 months) Burotto, M., Powles, T., Escudier, B., et al. Nivolumab plus cabozantinib vs sunitinib for first-line treatment of advanced renal cell carcinoma (aRCC): 3-year follow-up from the phase 3 CheckMate 9ER trial.	Journal of Clinical Oncology 2023; 41(6_suppl), 603-603.
CLEAR/ KeyNote 581	Primary analysis (median 26.6 months) Motzer, R., Alekseev, B., Rha, S.Y., et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma.	The New England Journal of Medicine 2021; 384(14), 1289-1300.
NCT0281186 1	Extended follow-up 1 (median 33.7 months) Choueiri, T. K., Eto, M., Motzer, R. et al. Lenvatinib plus pembrolizumab versus sunitinib as first-line treatment of patients with advanced renal cell carcinoma (CLEAR): extended follow-up from the phase 3, randomised, open-label study.	The Lancet Oncology 2023; 24(3), 228-238.
	Extended follow-up 2 (median 49.8 months) Motzer, R. J., Porta, C., Eto, M., et al. Phase 3 trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) or everolimus (EVE) versus sunitinib (SUN) monotherapy as a first-line treatment for patients (pts) with advanced renal cell carcinoma (RCC) (CLEAR study).	Journal of Clinical Oncology 2021; 39(6_suppl), 269-269.
CheckMate 214	Primary analysis (median 25.2 months) Motzer, R.J., Tannir, N., McDermott, D., et al. Nivolumab combined with ipilimumab versus sunitinib in previously untreated advanced or metastatic renal cell carcinoma.	N Engl J Med 2018; 378:1277-1290
NCT0223174 9	Extended follow-up 1 (median 32.4 months) Motzer, R.J., Rini, B.I., McDermott, D.F., et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial.	The Lancet Oncology 2019; 20(10), 1370-1385.
	Extended follow-up 2 (median 55 months) Albiges, L., Tannir, N. M., Burotto, M., et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial.	ESMO Open 2020; 5(6), e001079-e001079.
	Extended follow-up 3 (median 67.7 months) Motzer, R.J., McDermott, D.F., Escudier, B., et al. Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma	Cancer. 2022 Jun 1;128(11):2085-2097.

Source: Table 2-5, pp 46-51 and Table 2-21, p81 of the submission

Note: Abstracts/ posters and publications not used to generate the clinical evidence have been excluded from this table.

[^] Publications identified during the evaluation

³ <https://www.urotoday.com/conference-highlights/asco-2021/asco-2021-press-releases/129923-phase-3-checkmate-9er-trial-of-cabozantinib-in-combination-with-nivolumab-as-a-first-line-treatment-for-patients-with-advanced-renal-cell-carcinoma-shows-consistent-efficacy-benefits-across-subgroups.html>

6.6 The key features of the three randomised trials used to perform the Bucher ITCs are summarised in Table 3.

Table 3. Key features of the included evidence

Trial	N	Design/	Duration Median FU in months	Risk of bias	Patient population	Outcomes
CBZ+NIVO vs. SUN						
CheckMate 9ER	CBZ+NIVO: 323	MC, R, OL	Primary analysis: 18.1 Extended FU 1: 23.5 Extended FU 2: 32.9 Extended FU 3: 44	Low to Moderate	Untreated clear cell aRCC	PFS, OS, ORR, HRQoL, AEs, SAEs, TEAEs
	SUN: 328					
PEM+LEN vs. SUN						
CLEAR	PEM+LEN: 355	MC, R, OL	Primary analysis: 26.6 Extended FU 1: 33.7 Extended FU 2: 49.8	Low to Moderate ^a	Untreated clear cell aRCC	PFS, OS, ORR, HRQoL, AEs, SAEs, TEAEs
	SUN: 357					
NIVO+IPI vs. SUN						
CheckMate 214	NIVO+IPI: 550	MC, R, OL	Primary analysis: 25.2 Extended FU 1: 32.4 Extended FU 2: 55 Extended FU 3: 67.7	Moderate to high ^b	Untreated clear cell aRCC	PFS, OS, ORR, HRQoL, AEs, SAEs, TEAEs
	SUN: 546					

Source: Table 2-11, pp 66-67; Table 2-12 pp 67-68; Table 2-13, pp 69-70; Table 2-14, pp 70-72; Table 2-15, pp 73-75; Table 2-21, p81; Table 2-22, p82; Table 2-25, pp 87-92; Table 2-26, pp 94-95; Table 2-65, pp 148, Figure 2-8, p62 of submission.

CBZ+NIVO = cabozantinib plus nivolumab; SUN= sunitinib; PEM+LEN = pembrolizumab plus Lenvatinib; NIVO+IPI = nivolumab plus ipilimumab; MC = multi-centre; R = randomised; OL = open label; FU = follow-up; aRCC= advanced renal cell carcinoma; PFS = progression-free survival; OS = overall survival; ORR = objective response rate; HRQoL= Health-Related Quality of Life; AEs =adverse events; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events; TRAEs = treatment-related treatment-emergent adverse event; N = number in the intention-to-treat population.

^a The PBAC has previously considered that the overall risk of bias in CLEAR was low overall (Table 3, PEM+LEN PSD, March 2022). During this evaluation, the risk was updated from low to low-to-moderate due to a high risk of performance bias and a moderate risk of detection bias (which was rated low in the PEM+LEN submission)

^b The PBAC has previously considered that the overall risk of bias in CheckMate 214 was high for PFS due to patients being able to receive subsequent treatment prior to progression; and moderate to unclear for OS (Table 3, NIVO+IPI PSD, July 2018). In the PEM+LEN submission, the overall risk was rated to moderate and high (Table 3, PEM+LEN PSD, March 2022).

6.7 The risk of bias was low-to-moderate overall for the CheckMate 9ER trial, low-to-moderate overall for the CLEAR trial, and moderate-to-high overall for the CheckMate 214 trial. In all three trials, the risk of performance bias was rated high because they were open-label, while the risk of selection, attrition and reporting bias was rated low. Due to the subjective nature of the measurement of safety and quality of life outcomes, these are likely to be at a higher risk of detection bias than objective efficacy outcomes including OS, and PFS/ORR where the outcome is determined via blinded, independent assessment.

6.8 The submission stated that the eligibility criteria for the three trials were comparable. In March 2022 the ESC noted that the eligibility criteria for the CLEAR and CheckMate 214 trials were largely similar (Para 6.10, PEM+LEN PSD, March 2022 PBAC meeting).

6.9 To align the trial population with the requested listing population, the submission provided subgroup analyses for the intermediate and poor IMDC risk subgroups.

Broadly, the participant characteristics in the intermediate and poor IMDC risk subgroups matched the intention-to-treat (ITT) characteristics of their respective trials. No major differences in patient characteristics were noted within or across the CheckMate 9ER and CheckMate 214 trials. The submission did not present patient characteristics of the intermediate and poor IMDC risk subgroups for the CLEAR trial. However, it is noted that for the PEM+LEN submission, the Pre Sub Committee Response (PSCR) provided baseline characteristics for the intermediate and poor IMDC risk subgroups, showing that the subgroups were similar to the ITT population (Para 6.7, PEM+LEN PSD, March 2022 PBAC meeting).

- 6.10 As per the November 2017 protocol amendment in the CheckMate 214 trial, after the primary endpoint had been met, participants were eligible to crossover from SUN to the NIVO+IPI arm if they were at intermediate or poor IMDC risk prior to initial randomisation, and participants were not required to have progressed prior to crossover. Crossover of participants was not permitted in the CheckMate 9ER and CLEAR trials, but subsequent anticancer medications were allowed in the extended follow-up. In the March 2022 meeting, the PBAC acknowledged that any comparisons between PEM+LEN (CLEAR trial) and NIVO+IPI (CheckMate 214 trial) using extended data may be confounded by the differences in subsequent therapies (Para 7.5, PEM+LEN PSD, March 2022 PBAC meeting). For the current submission, a similar issue would arise for the ITC of CBZ+NIVO vs NIVO+IPI if extended data were used for the CheckMate 214 trial. However, the base case for the ITC used the 25.2 - months median follow-up (FU), which was the primary analysis data cut for NIVO+IPI.
- 6.11 For the CheckMate 9ER trial, the results were based on the 23.5-month median FU (data cut off: September 2020). For the CLEAR trial, the results were based on the 26.6-month median FU (data cut off: August 2020). For the CheckMate 214 trial, the results were based on the 25.2-month median FU (data cut off: August 2017). A sensitivity analysis used a later timepoint for each trial (32.9 months for CheckMate 9ER, 33.7 months for CLEAR and 32.4 months for CheckMate 214).
- 6.12 The submission did not state a minimum clinically important difference for any outcome. The submission did not present a non-inferiority margin for any of the outcomes on the basis that AVE+AXI and PEM+LEN were both recommended for listing on a cost-minimisation basis without the nomination of a non-inferiority margin.

Comparative effectiveness

Overall Survival

- 6.13 A summary of the OS results for the CheckMate 9ER, CLEAR, and CheckMate 214 trials for the ITT population and IMDC risk subgroups are presented in Table 4 and Table 5.

Table 4. OS results across CheckMate 9ER, CLEAR and CheckMate214 in ITT population

	CheckMate 9ER		CLEAR		CheckMate 214	
	CBZ + NIVO N=323	SUN N=328	PEM + LEN N=355	SUN N=357	NIVO + IPI N=550	SUN N=546
Median follow up	23.5 months		26.6 months		25.2 months	
Events, n (%)	Not reported	Not reported	80 (22.5)	101 (28.3)	161 (29.3) ^a	204 (37.4) ^a
Median, months (95% CI)	NR (NE)	29.5 (28.4-NE)	NR (33.6-NE)	NR (NE)	NR	32.9
HR (95% CI)	0.66 (0.50-0.87)		0.66 (0.49-0.88)		0.68 (0.49-0.95)^b	

Source: Table 2-31, pp102-103, Table 2-36, p111, Table 2-40, p115 of the submission

CBZ+NIVO = cabozantinib plus nivolumab; SUN = sunitinib; PEM+LEN = pembrolizumab plus lenvatinib; NIVO+IPI = nivolumab plus ipilimumab; NE = not estimable; NR = not reached, HR = hazard ratio; N = participants in group.

Bold indicates statistically significant results

^a As reported (%) in PEM+LEN PSD (Table 4, p11, March 2022 PBAC Meeting).

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

Table 5. OS results across CheckMate 9ER, CLEAR and CheckMate 214 in intermediate and poor IMDC risk subgroups

	CheckMate 9ER		CLEAR		CheckMate 214	
	CBZ + NIVO	SUN	PEM + LEN	SUN	NIVO + IPI	SUN
Median follow up	23.5 months		26.6 months		25.2 months	
Intermediate risk	N=188	N=188	N=210	N=192	N=314	N=317
Events, n (%)	Not reported	Not reported	56 (27) ^a	60 (31) ^a	87 (28) ^a	121 (38) ^a
Median, months (95% CI)	NR	NR	NE	NE	NE	NE
HR (95% CI)	0.74 (0.50-1.08)		0.72 (0.50-1.05)		0.66 (0.50-0.87)^b	
Poor risk	N=61	N=68	N=33	N=37	N=102	N=97
Events, n (%)	Not reported	Not reported	10 (30) ^a	25 (68) ^a	52 (51) ^a	66 (68) ^a
Median, months (95% CI)	NE	11.2 (not reported)	NE	NE	NE	NE
HR (95% CI)	0.45 (0.27-0.76)		0.30 (0.14-0.64)		0.57 (0.39-0.82)^b	

Source: Table 2-56, pp137-138, Table 2-59, pp141-142, Table 2-63, p146 of the submission

CBZ+NIVO = cabozantinib plus nivolumab; SUN = sunitinib; PEM+LEN = pembrolizumab plus lenvatinib; NIVO+IPI = nivolumab plus ipilimumab; NE = not estimable; NR = not reached, HR = hazard ratio; N = participants in group.

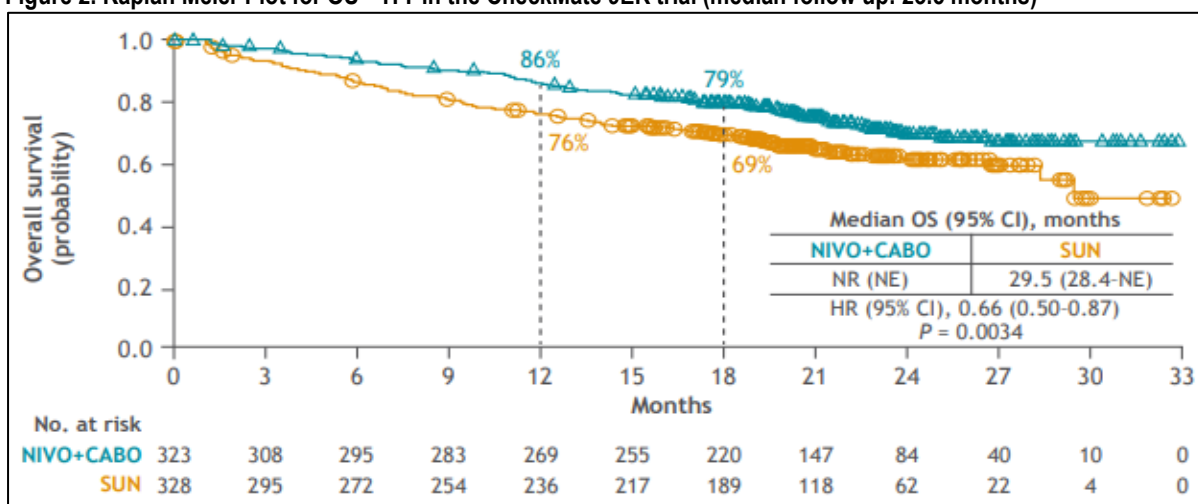
Bold indicates statistically significant results

^a Percentage calculated during evaluation.

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

6.14 The Kaplan Meier (KM) curves for OS from the CheckMate 9ER and CLEAR trials are presented in Figure 2 and Figure 3, respectively.

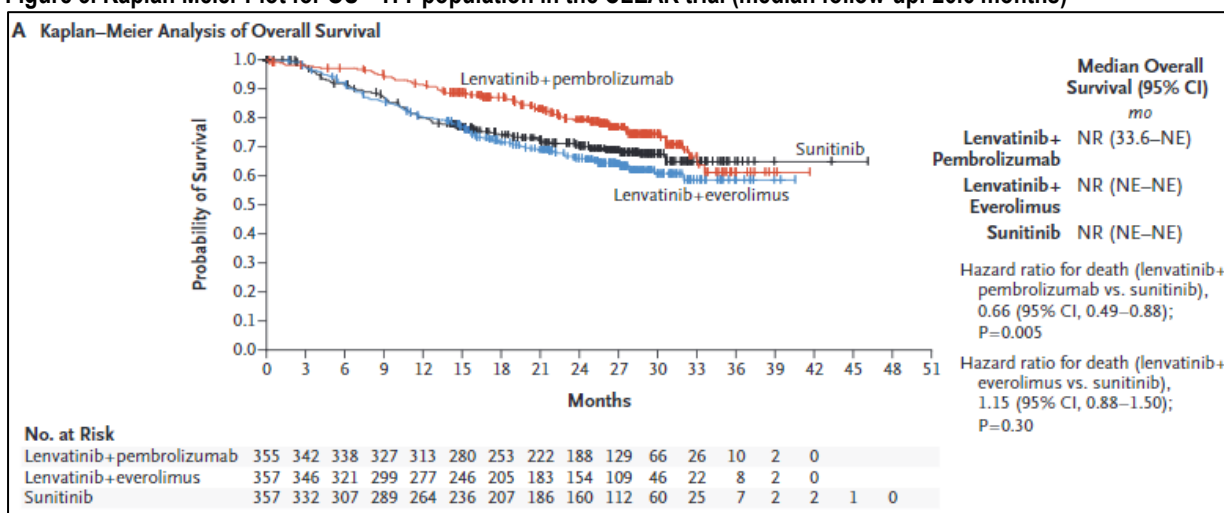
Figure 2. Kaplan Meier Plot for OS – ITT in the CheckMate 9ER trial (median follow up: 23.5 months)



Source: Figure 2-17, p104 of the submission

NIVO+CAB = cabozantinib plus nivolumab; SUN = sunitinib; OS = overall survival; ITT = intent to treat; HR = hazard ratio; CI = confidence interval; NE = Not estimable

Figure 3. Kaplan Meier Plot for OS – ITT population in the CLEAR trial (median follow-up: 26.6 months)



Source: Figure 2-24, p112 of the submission

ITT = intent to treat; HR = hazard ratio; CI = confidence interval; NR = not reached; NE = Not estimable

6.15 For CheckMate 9ER (23.5-month median FU), the median OS in the ITT population was 29.6 months (95% CI: 28.4-NE) in the SUN arm but was not reached in the CBZ+NIVO arm. CBZ+NIVO was associated with a statistically significant improvement in OS compared with SUN: HR 0.66 (95% CI 0.50-0.87). At 44 months median FU, the median OS in the CBZ + NIVO arm was 49.5 months vs 35.5 months in the SUN arm: HR 0.70 (95% CI 0.56-0.87).

6.16 At 23.5 months median FU, CBZ+NIVO did not show a significant difference to SUN for OS in the intermediate IMDC risk subgroup: HR 0.74 (95% CI 0.50-1.08). However, in the poor IMDC risk subgroup, CBZ+NIVO showed a significant difference to SUN for OS: HR 0.45 (95% CI 0.27-0.76). At 44 months median FU, the median OS in the

intermediate risk group was 49.5 months in the CBZ + NIVO arm vs 36.2 months in the SUN arm [HR 0.75 (95% CI 0.56-1.00)]. The median OS in the poor risk group was 34.8 months in the CBZ + NIVO arm vs 10.5 months in the SUN arm: HR 0.46 (95% CI 0.30-0.72).

- 6.17 For the CLEAR trial at 26.6-month median FU, PEM+LEN was associated with a statistically significant improvement in OS compared with SUN: HR 0.66 (95% CI 0.49-0.88) in the ITT population. PEM+LEN did not show a significant difference in OS compared to SUN in the intermediate IMDC risk subgroup: HR 0.72 (95% CI 0.50-1.05). In the poor IMDC risk subgroup, PEM+LEN showed a significant difference for OS: HR 0.30 (95% CI 0.14-0.64).
- 6.18 For CheckMate 214 at the 25.2-month median FU, NIVO+IPI was associated with a statistically significant improvement in OS compared with SUN: HR 0.68 (95% CI 0.49-0.95) in the ITT population. In the intermediate risk IMDC subgroup, the NIVO+IPI treatment arm showed a significant difference to the SUN treatment arm for OS: HR 0.66 (95% CI 0.50-0.87), while in the poor IMDC risk subgroup, the NIVO+IPI treatment arm showed a significant difference to the SUN treatment arm for OS: HR 0.57 (95% CI 0.39-0.82).

Progression-Free Survival

- 6.19 A summary of the PFS results for the CheckMate 9ER, CLEAR, and CheckMate 214 trials for the ITT and intermediate and poor IMDC risk subgroups is presented in Table 6 and Table 7. In the CheckMate 214 trial, the PFS results of the intermediate and poor IMDC risk subgroups were aggregated.

Table 6. PFS results across CheckMate 9ER, CLEAR and CheckMate214 in ITT population

	CheckMate 9ER		CLEAR		CheckMate 214	
	CBZ + NIVO N=323	SUN N=328	PEM + LEN N=355	SUN N=357	NIVO + IPI N=550	SUN N=546
Median follow up	23.5 months		26.6 months		25.2 months	
Events, n (%)	NR	NR	160 (47)	205 (57)	NR	NR
Median, months (95% CI)	17.0 (12.6,19.4)	8.3 (6.9,9.7)	23.9 (20.8,27.7)	9.2 (6.0,11.0)	12.4 (9.9,16.5)	12.3 (9.8,15.2)
HR (95% CI)	0.52 (0.43,0.64)		0.39 (0.32,0.49)		0.98 (0.79, 1.23)	

Source: Table 2-27, pp 97-98; Table 2-34, p110; Table 2-39, p114 of the submission

CBZ+NIVO = cabozantinib plus nivolumab; SUN = sunitinib; PEM+LEN = pembrolizumab plus lenvatinib; NIVO+IPI = nivolumab plus ipilimumab; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITT = intention-to-treat; PFS = progression free survival; HR = hazard ratio; NR = not reported; n = number of participants reporting data; N = participants in group; FU = follow-up.

* CheckMate 214 did not report separate results for intermediate and poor risk, only the pooled results of the intermediate/poor risk.

HR<1 denotes better outcomes for CBZ+NIVO, PEM+LEN and NIVO+IPI and worse for SUN

Bold indicates statistically significant results

Table 7. PFS results across CheckMate 9ER, CLEAR and CheckMate 214 in intermediate and poor IMDC risk subgroups

	CheckMate 9ER		CLEAR		CheckMate 214*	
	CBZ + NIVO	SUN	PEM + LEN	SUN	NIVO + IPI	SUN
Median follow up	23.5 months		26.6 months		25.2 months	
Intermediate risk	N=188	N=188	N=210	N=192	NR	NR
Events, n (%)	NR	NR	97 (46) ^a	110 (57) ^a	NR	NR
Median, months (95% CI)	17.5 (11.3,19.4)	8.5 (7.0,9.8)	NR	NR	NR	NR
HR (95% CI)	0.58 (0.45, 0.76)		0.39 (0.29, 0.52)		NR	
Poor risk	N=61	N=68	N=33	N=37	NR	NR
Events, n (%)	NR	NR	18 (55) ^a	26 (70) ^a	NR	NR
Median, months (95% CI)	9.9 (5.9,17.7)	4.2 (2.9,5.6)	NR	NR	NR	NR
HR (95% CI)	0.36 (0.23, 0.56)		0.28 (0.13, 0.60)		NR	
Intermediate and poor risk (combined)	NR	NR	NR	NR	N=425	N=422
Events, n (%)	NR	NR	NR	NR	NR	NR
Median, months (95% CI)	NR	NR	NR	NR	11.6 (8.7,15.5)	8.4 (7.0,10.8)
HR (95% CI)	NR		NR		0.82 (0.64, 1.05)	

Source: Table 2-55, pp136-137; Table 2-58, p141; Table 2-61, p144 of the submission

CBZ+NIVO = cabozantinib plus nivolumab; SUN = sunitinib; PEM+LEN = pembrolizumab plus lenvatinib; NIVO+IPI = nivolumab plus ipilimumab; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; PFS = progression free survival; HR = hazard ratio; NR = not reported; n = number of participants reporting data; N = participants in group; FU = follow-up.

* CheckMate 214 did not report separate results for intermediate and poor risk, only the pooled results of the intermediate/poor risk.

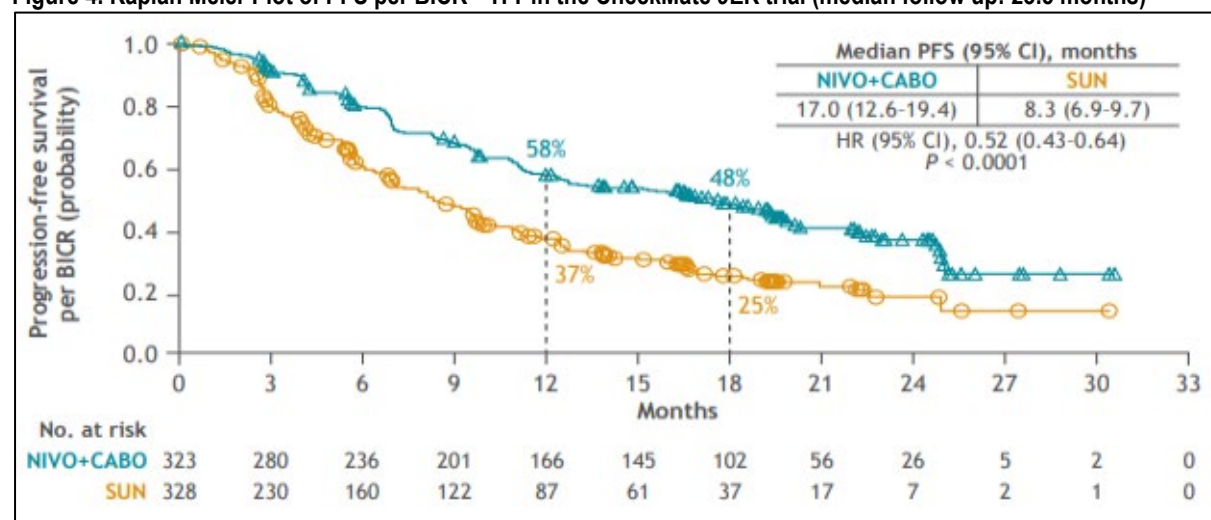
HR<1 denotes better outcomes for CBZ+NIVO, PEM+LEN and NIVO+IPI and worse for SUN

Bold indicates statistically significant results

^a Values calculated during the evaluation

6.20 The KM curves for PFS for the CheckMate 9ER trial and the CLEAR trial are presented in Figure 4 and Figure 5, respectively.

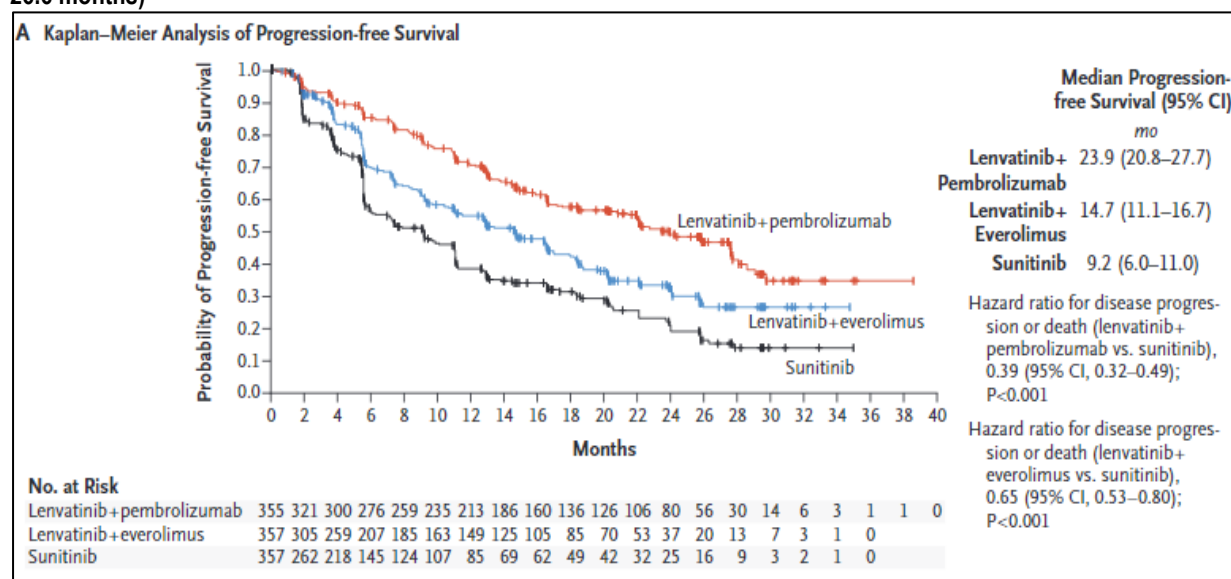
Figure 4. Kaplan Meier Plot of PFS per BICR – ITT in the CheckMate 9ER trial (median follow up: 23.5 months)



Source: Figure 2-10, p98 of the submission

BICR = blinded independent committee for review; ITT = intent to treat; NIVO+CABO = cabozantinib plus nivolumab; SUN = sunitinib; HR = hazard ratio; CI = confidence interval; PFS = progression free survival.

Figure 5. Kaplan Meier plot of PFS per independent committee review – ITT in the CLEAR trial (median follow-up: 26.6 months)



Source: Figure 2-23, p110 of the submission

ITT = intent to treat; HR = hazard ratio; CI = confidence interval.

- 6.21 For the CheckMate 9ER trial, with 23.5-month median FU, the median PFS in the ITT group was 17.0 months (95% CI 12.6-19.4) for the CBZ+NIVO treatment arm and 8.3 months (95% CI 6.9-9.7) for the SUN treatment arm. At this timepoint, CBZ+NIVO did show a significant difference to SUN for PFS: HR 0.52 (95% CI 0.43-0.64). At 44 months median FU, the median PFS in the CBZ + NIVO arm was 16.6 months vs 8.4 months in the SUN arm: HR 0.59 (95% CI 0.49-0.71).
- 6.22 For the CheckMate 9ER trial with 23.5-month median FU, the median PFS for the intermediate IMDC risk group was 17.5 months (95% CI 11.3-19.4) in the CBZ+NIVO treatment arm and 8.5 months (95% CI 7.0-9.8) in the SUN treatment arm. In the poor IMDC risk subgroup, the median PFS was 9.9 months (95% CI 5.9-17.7) in the CBZ+NIVO treatment arm and 4.2 months (95% CI 2.9-5.6) in the SUN treatment arm. CBZ+NIVO showed a PFS benefit in both the intermediate IMDC risk subgroup (HR 0.58, 95% CI 0.45-0.76) and the poor IMDC risk subgroup (HR 0.36, 95% CI 0.23-0.56). At 44 months median FU, the median PFS in the intermediate risk group was 16.6 months in the CBZ + NIVO arm vs 8.7 months in the SUN arm: HR 0.63 (95% CI 0.49-0.80). The median PFS in the poor risk group was 9.9 months in the CBZ + NIVO arm vs 4.2 months in the SUN arm: HR 0.37 (95% CI 0.24-0.57).
- 6.23 For the CLEAR trial, the median PFS for the ITT group at the 26.6-month median FU was 23.9 months (95% CI 20.8-27.7) in the PEM+LEN treatment arm and 9.2 months (95% CI 6.0-11.0) in the SUN treatment arm. At this timepoint, PEM+LEN showed a significant difference to SUN for PFS in the ITT group: HR 0.39 (95% CI 0.32-0.49).
- 6.24 For the CLEAR trial, the median PFS for both the intermediate and poor IMDC risk subgroups at the 26.6-month median FU was not reported in either treatment arm. At

this timepoint PEM+LEN showed a significant difference to SUN for PFS in the intermediate IMDC risk subgroup (HR 0.39; 95% CI 0.29-0.52) and the poor IMDC risk subgroup (HR 0.28; 95% CI 0.13-0.60).

- 6.25 For the CheckMate 214 trial, the median PFS for the ITT group at the 25.2-month median FU was 12.4 months (95% CI 9.9-16.5) in the NIVO+IPI treatment arm and 12.3 months (95% CI 9.8-15.2) in the SUN treatment arm. At this timepoint, NIVO+IPI did not show a significant difference to SUN for PFS in the ITT group: HR 0.98 (95% CI 0.79-1.23).
- 6.26 In the CheckMate 214 trial, PFS results for the intermediate and poor IMDC risk subgroups were only reported as an aggregated group across all timepoints. At the 25.2-month median FU, in the aggregated intermediate and poor IMDC risk subgroup, the NIVO+IPI treatment arm did not show a significant difference to the SUN treatment arm for survival: HR 0.82 (95% CI 0.64-1.05).

Objective Response Rate

- 6.27 Table 8 and Table 9 summarise the results for the ORR across the CheckMate 9ER, CLEAR, and Checkmate 214 trials in the ITT population and the intermediate and poor IMDC risk subgroups.

Table 8. ORR results across CheckMate 9ER, CLEAR and CheckMate214 in ITT group

	CheckMate 9ER		CLEAR		CheckMate 214	
	CBZ + NIVO N=323	SUN N=328	PEM + LEN N=355	SUN N=357	NIVO + IPI N=550	SUN N=546
Median follow up	23.5 months		26.6 months		25.2 months	
ORR (%)	177 ^a (54.8)	93 ^a (28.4)	252 ^a (71.0)	129 ^a (36.1)	215 ^a (39)	175 ^a (32)
Difference in % (95% CI)	26.4 (NR) ^a		34.9 (NR) ^a		7 (NR) ^a	
OR (95% CI)	3.2 (2.3-4.4)		4.35 (3.16-5.97)		1.36 (1.06-1.74)	

Source: Table 2-57, pp138-140; Table 2-60, p143; Table 2-64, p147 of the submission

CBZ+NIVO = cabozantinib plus nivolumab; SUN = sunitinib; PEM+LEN = pembrolizumab plus lenvatinib; NIVO+IPI = nivolumab plus ipilimumab; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITT = intention-to-treat; ORR= objective response rate, OR= odds ratio; NR= reached; NE = not estimable; n = number of participants reporting data; N = participants in group; DOR= duration of response; FU = follow-up.

^a Values calculated during the evaluation

Table 9. ORR results across CheckMate 9ER, CLEAR and CheckMate214 in intermediate and poor IMDC groups

	CheckMate 9ER		CLEAR		CheckMate 214	
	CBZ + NIVO N=323	SUN N=328	PEM + LEN N=355	SUN N=357	NIVO + IPI N=550	SUN N=546
Median follow up	23.5 months		26.6 months		25.2 months	
Intermediate risk	N=188	N=188	N=210	N=192	NR	NR
ORR (%)	107 (55.9)	54 (28.7)	153 (72.9)	61 (31.8)	NR	NR
Difference in % (95% CI)	28.2 (NR)		41.1 (32.2-50.0)		NR	
OR (95% CI)	3.28 (2.14-5.03)		6.01 (3.88-9.32)		NR	
Poor risk	N=61	N=68	N=33	N=37	NR	NR
ORR (%)	23 (37.7)	7 (10.3)	23 (69.7)	5 (13.5)	NR	NR
Difference in % (95% CI)	27.4 (NR)		56.2 (37.0-75.3)		NR	
OR (95% CI)	5.27 (2.06-13.48)		11.19 (3.37-37.15)		NR	
Intermediate and poor risk^a	NR	NR	N=243	N=229	N=425	N=422
ORR (%)	NR	NR	176 (72.4)	66 (28.8)	177 (42)	112 (27)
Difference in % (95% CI)	NR		43.6 (35.5-51.7)		15 (NR) ^b	
OR (95% CI)	NR		6.60 (4.39-9.90)		1.98 (1.31- 3.14)^b	

Source: Table 2-57, pp138-140; Table 2-60, p143; Table 2-64, p147; Table 2-75, p156; Table 2-76, p157 of the submission
 CBZ+NIVO = cabozantinib plus nivolumab; SUN = sunitinib; PEM+LEN = pembrolizumab plus lenvatinib; NIVO+IPI = nivolumab plus ipilimumab; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITT = intention-to-treat; ORR= objective response rate, OR= odds ratio; NR= not reached; NE = not estimable; n = number of participants reporting data; N = participants in group; DOR= duration of response; FU = follow-up.

^a CheckMate 214 did not report separate results for the intermediate and poor risk groups, only pooled results of the intermediate/poor risk group

Bold indicates statistically significant results.

^b Calculated during the evaluation.

- 6.28 In the CheckMate 9ER trial, the ORR was higher in the CBZ+NIVO arm compared with the SUN arm for the ITT, intermediate and poor risk populations.
- 6.29 In the CLEAR trial, the ORR was higher in the PEM+LEN arm compared with the SUN arm for the ITT, intermediate, poor and intermediate/poor risk populations.
- 6.30 In the CheckMate 214 trial, the ORR was higher in the NIVO+IPI arm compared with the SUN arm in the intermediate/poor risk population.

Indirect Treatment Comparison

- 6.31 An anchored ITC using the Bucher method was conducted between CBZ+NIVO and PEM+LEN, and between CBZ+NIVO and NIVO+IPI, using SUN as a common reference.
- 6.32 The ITC analyses presented by the submission were conducted for the data from CheckMate 9ER trial (CBZ+NIVO vs SUN) at the 23.5-month median FU, the CLEAR trial (PEM+LEN vs SUN) at the 26.6-month median FU, and the CheckMate 214 trial (NIVO+IPI vs SUN) at the 25.2-month median FU. These timepoints were deemed the most comparable, as they occurred before crossover was allowed in the CheckMate 214 trial. This approach reduces transitivity issues that would occur for comparisons of data-cuts subsequent to the permitted crossover for participants in the NIVO+IPI treatment group of the CheckMate 214 trial. These timepoints are consistent with those in the comparative analyses for individual trial data.

- 6.33 The submission noted that there was a slightly higher proportion of participants in the poor IMDC risk subgroup in the CheckMate 9ER trial compared to the other two trials, which may bias efficacy results in the ITT population in favour of CBZ+NIVO. Additional heterogeneity issues were noted during the evaluation that might potentially increase uncertainty in the ITCs. However, the direction of potential impacts differed across the different sources of heterogeneity, so may not systematically bias against or in favour of one treatment option.
- 6.34 Table 10 presents the results of anchored Bucher ITCs for OS, PFS and ORR in the ITT population and the intermediate and poor IMDC risk subgroups. It is noted that the PBAC has previously considered the intermediate and poor IMDC risk subgroups combined for the ITCs in the AVE+AXI submission and in the PEM+LEN submission. However, this submission presented the ITC analyses separately for the intermediate IMDC risk subgroup and the poor IMDC risk subgroup.
- 6.35 The submission did not provide a non-inferiority margin. The submission noted that in both the PEM+LEN and AVE+AXI submissions, no non-inferiority margins were specified.

Table 10. Results of Bucher ITC of OS and PFS of CBZ+NIVO versus PEM+LEN and NIVO+IPI in the ITT population and the intermediate or poor IMDC risk subgroups

Outcome	Population	Indirect estimate CBZ+NIVO vs. PEM+LEN via SUN	Indirect estimate CBZ+NIVO vs. NIVO+IPI via SUN
OS, [HR (95% CI)]	ITT	1.00 (0.67-1.50)	0.97 (0.63-1.49)
	Poor	1.50 (0.60-3.76)	0.79 (0.42-1.49)
	Intermediate	1.03 (0.60-1.75)	1.12 (0.70-1.80)
PFS, [HR (95% CI)]	ITT	1.33 (1.00-1.78)	0.53 (0.39-0.71)
	Poor	1.29 (0.53-3.11)	NR
	Intermediate	1.49 (1.00-2.20)	NR
ORR, [OR (95% CI)]	ITT	0.74 (0.47-1.16)	2.35 (1.56-3.54)
	Poor	0.47 ^a (0.10-2.16)	NR
	Intermediate	0.55 (0.30-1.01)	NR

Source: Table 2-66 p151; Table 2-67, p152; Table 2-68, pp152-153; Table 2-71, p154; Table 2-72, p154-155; Table 2-75, p156-157 of the submission; Attachment 4 – Bucher ITCs Final ‘ORR (ICR)’

CBZ+NIVO = cabozantinib plus nivolumab; NIVO+IPI = nivolumab plus ipilimumab; PEM+LEN = pembrolizumab plus lenvatinib; PFS = progression free survival; OR = odds ratio; OS = overall survival; PFS = progression free survival; ORR = objective response rate; HR = hazard ratio; CI = confidence interval; NR = not reached; RE = risk estimate.

Bold indicates statistically significant results.

HR>1 denotes worse outcomes for CBZ+NIVO; HR<1 denotes better outcomes for CBZ+NIVO

^a Corrected during the evaluation

- 6.36 The ITC showed no statistically significant difference in OS between CBZ+NIVO and PEM+LEN, or between CBZ+NIVO and NIVO+IPI for the ITT population and the intermediate and poor IMDC risk subgroups.
- 6.37 The ITC showed no statistically significant difference in PFS between CBZ+NIVO and PEM+LEN for the poor IMDC risk subgroup. However, there was a statistically significant difference in PFS in the ITT population and the intermediate IMDC risk subgroup in favour of PEM+LEN: HRs of 1.33 (1.00-1.78) and 1.49 (95% CI 1.00-2.20), respectively. The PSCR noted that the PBAC has previously stated that “PFS may not

be a reliable measure of the clinical effectiveness of immunotherapies as tumour responses can occur after conventional RECIST-defined progressive disease" (Para 7.6, PEM+LEN PSD, March 2022 PBAC Meeting,)."

- 6.38 The ITC showed no statistically significant difference in ORR between CBZ+NIVO and PEM+LEN for the ITT population and the intermediate and poor IMDC risk subgroups.
- 6.39 The ITC showed a statistically significant difference in PFS and ORR between CBZ+NIVO and NIVO+IPI in favour of CBZ+NIVO for the ITT population (HR 0.53; 95% CI 0.39-0.71 and OR 2.35; 95% CI 1.56-3.54, respectively). The ESC considered that these differences were expected given the different approach to care for patients treated with NIVO+IPI. The ESC considered that an IO+TKI is generally used for patients in whom rapid tumour response is indicated (e.g. bulky, symptomatic disease), while NIVO+IPI is used to control disease long-term.
- 6.40 It was noted that the submission also presented the ITC sensitivity analyses using a second time point of 32.9-month median FU for the CheckMate 9ER trial, 33.7-month median FU for the CLEAR trial and 32.4-month median FU for the Checkmate 214 trial. The results of the sensitivity analyses were consistent with those of the primary ITC analyses. The PBAC noted the OS HR in the intermediate risk subgroup using a longer duration of follow-up was 1.03 (95% CI 0.65-1.62) and for the poor risk subgroup was 1.26 (95% CI 0.55-2.85).

Comparative harms

- 6.41 A summary of treatment-related adverse events (TRAEs) from the CheckMate 9ER, CLEAR, and CheckMate 214 trials for the All Subjects as Treated (ASaT) population is presented in Table 11.

Table 11. Adverse event summary (ASaT population)

CheckMate 9ER (23.5 months median follow-up)	CBZ+NIVO n with event/N (%)	SUN n with event/N (%)
Treatment related (any grade) AE	310/320 (96.9%)*	298/320 (93.1%)*
Treatment related (\geq Grade 3) AE ^a	199/320 (62.2%)	168/320 (52.5%)
- Hypertension ^a	37/320 (11.6%)	39/320 (12.2%)
- Diarrhoea ^a	21/320 (6.6%)	14/320 (4.4%)
- Palmar-plantar erythrodysesthesia syndrome ^a	24/320 (7.5%)	26/320 (8.1%)
- Decrease appetite ^a	4/320 (1.3%)	2/320 (0.6%)
- Fatigue ^a	8/320 (2.5%)	14/320 (4.4%)
- Hypothyroidism ^a	1/320 (0.3%)	1/320 (0.3%)
Study drug related death*	1/320 (0.3%)*	2/320 (0.6%)*
Discontinuation due to treatment related AE ^a	75/320 (23.4%)	29/320 (9.1%)
CLEAR (26.6 months median follow-up)	PEM+LEN n with event/N (%)	SUN n with event/N (%)
Treatment related (any grade) AE	341/352 (96.9%)	313/340 (92.1%)
Treatment related (\geq Grade 3) AE	252/352 (71.6%)	200/340 (58.8%)
- Hypertension	89/352 (25.3%)	61/340 (17.9%)
- Diarrhoea	29/352 (8.2%)	15/340 (4.4%)
- Proteinuria	26/352 (7.4%)	10/340 (2.9%)
- Palmar-plantar erythrodysesthesia syndrome	14/352 (4.0%)	11/340 (3.2%)
- Decrease appetite	12/352 (3.4%)	5/340 (1.5%)
- Fatigue	11/352 (3.1%)	13/340 (3.8%)
- Hypothyroidism	4/352 (1.1%)	0/340 (0%)
Study drug related death	4/352 (1.1%)	1/340 (0.3%)
Discontinuation due to treatment related AE ^a	115/352 (37.2%)	49/340 (14.4%)
CheckMate 214 (25.2 months median follow-up)	NIVO+IPI n with event/N (%)	SUN n with event/N (%)
Treatment related (any grade) AE	509/547 (93%)	521/535 (97%)
Treatment related (\geq Grade 3) AE	250/547 (46%)	335/535 (63%)
- Lipase increased	56/547 (10.2%)	35/535 (6.5%)
- Fatigue	23/547 (4.2%)	49/535 (9.2%)
- Diarrhoea	21/547 (3.8%)	28/535 (5.2%)
- Hypertension	4/547 (0.7%)	85/535 (15.8%)
Study drug related death	8/547 (1.5%)	4/535 (0.75%)
Discontinuation due to treatment related AE	118/547 (22%)	63/535 (12%)

Source: Table 2-50, p127; Table 2-51, pp128-129; Figure 2-25, p123 of the submission.

ASaT = all subjects as treated; CBZ+NIVO = cabozantinib plus nivolumab; SUN = sunitinib; PEM+LEN = pembrolizumab plus lenvatinib; NIVO+IPI = nivolumab plus ipilimumab; AE = adverse event; n = number of participants reporting data; N = total participants in group.

* Unable to be locate or verify these data from the submission.

^a Calculations undertaken during the evaluation.

- 6.42 The safety profiles of CBZ+NIVO and PEM+LEN appear similar; however, they are different from those of NIVO+IPI. The frequency of \geq Grade 3 TRAEs were 62.2% and 71.6% for CBZ+NIVO and PEM+LEN, respectively, which are higher than that of NIVO+IPI (46%).
- 6.43 The submission noted that due to the different safety profile of NIVO+IPI, for specific TRAEs, the ITCs were conducted between CBZ+NIVO and PEM+LEN only. These include hypothyroidism, hypertension, diarrhoea, fatigue, and palmar-plantar erythrodysesthesia. The selection of these TRAEs was based on (i) the highest rates of

≥ Grade 3 TRAEs and/or all-grade TRAEs; and (ii) those that are considered on-target or common TRAEs for vascular endothelial growth factor (VEGF) inhibitors.

- 6.44 The safety results of TRAEs in the ITC in the ASaT populations for the CheckMate 9ER trial 23.5-month median FU (CBZ+LEN vs SUN), the CLEAR 26.6 months median FU (PEM+LEN vs SUN) and the CheckMate 214 25.2-month median FU (NIVO+IPI vs SUN) are presented in Table 12.

Table 12. Results of TRAEs indirect treatment comparison in the ASaT population of CBZ+LEN, PEM+LEN and NIVO+IPI

Trial	Outcome	CBZ+NIVO n with event/N (%)	SUN n with event/N (%)	Adjusted Difference (%) ^a	OR (95%-CI)
CheckMate 9ER (23.5 months median FU)	T-R deaths	1/320 (0.3%)	2/320 (0.6%)	-0.3%	0.50 (0.04-5.52)
	T-R AEs (any grade)	310/320 (96.9%)	298/320 (93.1%)	3.8%	2.29 (1.07-4.91)
	T-R AEs (≥Grade 3)	199/320 (62.2%)	168/320 (52.5%)	9.7%	1.49 (1.09-2.04)
	Discontinuation due to T-R AE	75/320 (23.4%)	29/320 (9.1%) ^d	14.3%	3.07 (1.94-4.87)
CLEAR (26.6 months median FU) ^a	Outcome	PEM+LEN n with event/N (%)	SUN n with event/N (%)	Adjusted Difference (%)^a	OR (95%-CI)^a
	T-R deaths	4/352 (1.1%)	1/340 (0.3%)	0.8%	3.90 (0.43-35.04)
	T-R AEs (all-grade)	341/352 (96.9%)	313/352 (92.1%)	4.8%	2.67 (1.30-5.48)
	T-R AEs (≥Grade 3)	252/352 (71.6%)	200/340 (58.8%)	12.8%	1.76 (1.29-2.42)
	Discontinuation due to T-R AE	115/352 (37.2%)	49/340 (14.4%)	22.8%	2.88 (1.98-4.20)
ITC odds ratio: CBZ+NIVO vs. PEM+LEN for T-R deaths (95% CI)					0.13 (0.00-3.32)
ITC odds ratio: CBZ+NIVO vs. PEM+LEN for T-R AEs (all-grade) (95% CI)					0.86 (0.30-2.44)
ITC odds ratio: CBZ+NIVO vs. PEM+LEN for T-R AEs (≥Grade 3) (95% CI)					0.84 (0.54-1.32)
ITC odds ratio: CBZ+NIVO vs. PEM+LEN for T-R AEs Discontinuation due to T-R AE (95% CI)					1.07 (0.59-1.932)
CheckMate 214 (25.2- month median FU)	Outcome	NIVO+IPI n with event/N (%)	SUN n with event/N (%)	Adjusted Difference (%)	OR (95%-CI)
	T-R deaths	8/547 (1.5%)	4/535 (0.7%)	0.8%	1.97 (0.59-6.58)
	T-R AEs (all-grade)	509/547 (93.1%)	521/535 (97.4%)	-4.3%	0.36 (0.19-0.67)
	T-R AEs (≥Grade 3)	250/547 (45.7%)	335/535 (62.6%)	-16.9%	0.50 (0.39-0.64)
Discontinuation due to T-R AE	118/547 (21.6%)	63/535 (11.8%)	9.8%	2.06 (1.48-2.87)	
ITC odds ratio: CBZ+NIVO vs. NIVO+IPI for T-R deaths (95% CI)					0.25 (0.02-3.73)
ITC odds ratio: CBZ+NIVO vs. NIVO+IPI for T-R AEs (all-grade) (95% CI)					6.36 (2.37-17.06)
ITC odds ratio: CBZ+NIVO vs. NIVO+IPI for T-R AEs (≥Grade 3) (95% CI)					2.96 (1.99-4.41)
ITC odds ratio: CBZ+NIVO vs. NIVO+IPI for T-R AEs Discontinuation due to T-R AE (95% CI)					1.49 (0.84-2.63)

Source: Table 2-77, p157; Table 2-79, p158-159; Table 2-81, p159-160; Table 2-83, p160 of the submission; Table S4, Motzer et al (2021) CBZ+NIVO = cabozantinib plus nivolumab; NIVO+IPI = nivolumab plus ipilimumab; PEM+LEN = pembrolizumab plus lenvatinib; SUN = sunitinib; CI = confidence interval; HR = hazard ratio; OR = odds ratio; n= number of participants reporting data; N = total participants in group; T-R = treatment-related; AE = adverse event, FU = follow-up; TRAE = treatment related adverse event.

Bold font indicates statistically significant results.

^a Calculated during the evaluation.

6.45 For all-grade TRAEs and Grade 3-4 TRAEs, respectively, the ITC results showed a statistically significant difference between CBZ+NIVO and NIVO+IPI, in favour of NIVO+IPI: ORs 6.36 (95% CI 2.37-17.06) for all grade TRAEs and 2.96 (95% CI 1.99-4.41) for Grade 3-4 TRAEs.

6.46 The ITC safety results of the specific TRAEs in the ASaT population for CBZ+NIVO (data from CheckMate 9ER 23.5-month median FU) and for PEM+LEN (data from CLEAR 26.6-month median FU) are presented in Table 13.

Table 13. Results of specific TRAEs indirect treatment comparison in the ASaT population of CBZ+NIVO and PEM+LEN

Trial	Outcome	CBZ+NIVO n with event/N (%)	SUN n with event/N (%)	Adjusted Difference (%) ^a	OR (95%-CI)
CheckMate 9ER (23.5 months median FU)	Hypertension	100/320 (31.3%)	107/320 (33.4%)	2.1%	0.90 (0.65-1.26)
	Hypothyroidism	112/320 (35.0%)	94/320 (29.4%)	5.6%	1.29 (0.93-1.81)
	Diarrhoea	187/320 (58.4%)	143/320 (44.7%)	13.7%	1.74 (1.27-2.38)
	Fatigue	86/320 (26.9%)	101/320 (31.6%)	4.7%	0.80 (0.57-1.12)
	PPE	122/320 (38.1%)	132/320 (41.3%)	3.2%	0.88 (0.64-1.20)
CLEAR (26.6 months median FU) ^a	Outcome	PEM+LEN n with event/N (%)	SUN n with event/N (%)	Adjusted Difference (%)	OR (95%-CI)
	Hypertension	184/352 (52.3%)	133/340 (39.1%)	13.2%	1.70 (1.26-2.31)
	Hypothyroidism	150 (42.6%)	79/340 (23.2%)	19.4%	2.45 (1.77-3.41)
	Diarrhoea	192 (54.5%)	151/340 (44.4%)	10.1%	1.50 (1.11-2.03)
	Fatigue	113 (32.1%)	109/340 (32.1%)	0%	1.00 (0.73-1.38)
PPE	99/352 (28.1%)	122/340 (35.9%)	7.8%	0.70 (0.51-0.96)	
ITC odds ratio: CBZ+NIVO vs PEM+LEN for hypertension (95% CI)					0.53 (0.34-0.83)
ITC odds ratio: CBZ+NIVO vs PEM+LEN for hypothyroidism (95% CI)					0.53 (0.33-0.84)
ITC odds ratio: CBZ+NIVO vs PEM+LEN for diarrhoea (95% CI)					1.16 (0.75-1.79)
ITC odds ratio: CBZ+NIVO vs PEM+LEN for fatigue (95% CI)					0.80 (0.50-1.27)
ITC odds ratio: CBZ+NIVO vs PEM+LEN for palmar-plantar erythrodysesthesia (95% CI)					1.26 (0.80-1.97)

Source: Table 2-84, p161; Table 2-85, p161-162; Table 2-86, p162; Table 2-87, p162; Table 2-88, p163; of the submission; Table S4, Motzer et al (2021)

CBZ+NIVO = cabozantinib plus nivolumab; PEM+LEN = pembrolizumab plus lenvatinib; SUN = sunitinib; PPE = palmar-plantar erythrodysesthesia; OR = odds ratio; n = number of participants reporting data; N = total participants in group; FU = follow-up; CI = confidence interval; ITC = indirect treatment comparison; TRAE = treatment-related adverse event.

Bold font indicates statistically significant results.

^a Calculated during the evaluation

6.47 For specific TRAEs, the ITC showed statistically significant ORs in favour of CBZ+NIVO for hypertension and hypothyroidism: 0.53 (95% CI: 0.34-0.83) and 0.53 (95% CI: 0.33-0.84), respectively. However, it is noted that most hypothyroidism TRAEs were Grade 1-2. There were no statistically significant differences in diarrhoea, fatigue, or palmar-plantar erythrodysesthesia between CBZ+NIVO and PEM+LEN.

Benefits/harms

6.48 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

6.49 The submission described CBZ+NIVO as non-inferior in terms of effectiveness and safety compared to PEM+LEN in patients with clear cell aRCC classified as intermediate or poor risk according to the IMDC prognostic criteria.

- 6.50 The evaluation considered the clinical claim that CBZ+NIVO is non-inferior to PEM+LEN in terms of effectiveness was uncertain because:
- The ITC analyses comparing CBZ+NIVO vs PEM+LEN resulted in estimates with wide confidence intervals. A claim of non-inferiority may be uncertain in the absence of a nominated non-inferiority margin; however, the submission noted that the PBAC previously accepted non-inferiority for PEM+LEN for this indication without a margin (PEM+LEN, March 2022 PBAC Meeting).
 - For OS, the point estimates were approximately 1 for the ITT population and the intermediate risk subgroup (HR 1.00; 95% CI 0.67-1.50 and HR 1.03; 95% CI 0.60-1.75, respectively). For the poor risk subgroup, the point estimate favoured PEM+LEN, however the 95% CI was wide (HR 1.50; 95% CI 0.60-3.76). For PFS, the HRs for the ITC favoured PEM+LEN for the three comparisons, and the difference was nominally statistically significant for the ITT population and poor risk subgroup. However, the ESC noted the PBAC has previously stated that PFS may not be a reliable measure of the clinical effectiveness of immunotherapies (as discussed in paragraph 6.37).
- 6.51 The ESC agreed with the evaluation that there were some uncertainties regarding the clinical claim that CBZ+NIVO is non-inferior to PEM+LEN in terms of effectiveness but considered that, overall, it was reasonable. The ESC considered the clinical claim that CBZ+NIVO is non-inferior to PEM+LEN in terms of safety was reasonable and adequately supported by the ITC results.
- 6.52 For the secondary comparator, the submission described CBZ+NIVO as non-inferior in terms of effectiveness and having a different but non-inferior safety profile compared to NIVO+IPI.
- 6.53 The ESC considered the clinical claim that CBZ+NIVO is non-inferior to NIVO+IPI in terms of effectiveness was reasonable.
- 6.54 The ESC considered the clinical claim that CBZ+NIVO has a different safety profile from NIVO+IPI was reasonable; the claim that CBZ+NIVO is non-inferior to NIVO+IPI in terms of safety was not supported. The ESC noted the ITC result showed a statistically significant difference favouring NIVO+IPI for any-grade TRAEs and Grade 3-4 TRAEs.
- 6.55 The PBAC considered that the claims of non-inferior comparative effectiveness against PEM+LEN and NIVO+IPI were reasonable.
- 6.56 The PBAC considered that the claim of non-inferior comparative safety against PEM+LEN was reasonable.
- 6.57 The PBAC noted CBZ+NIVO was associated with more any-grade TRAEs and more \geq Grade 3 TRAEs than NIVO+IPI. The PBAC noted that although the safety profile of CBZ+NIVO and NIVO+IPI is different, the proportion of patients experiencing any adverse event was similar in CheckMate 9ER (97%) and CheckMate 214 (93%).

Consistent with its consideration of PEM+LEN, the PBAC considered that CBZ+NIVO had a different safety profile compared to NIVO+IPI.

Economic analysis

- 6.58 The submission presented a cost-minimisation approach (CMA) based on the claim of non-inferiority for the effectiveness and safety of CBZ+NIVO compared with PEM+LEN in patients with clear cell aRCC with an intermediate or poor IMDC risk status.
- 6.59 The submission presented a CMA using the published Approved Ex-Manufacturer Price (AEMP) for PEM+LEN because the confidential net pricing arrangements for this combination were not available. The submission noted that the CMA presented is a framework that allows for the estimation of the total cost of treatment with CBZ+NIVO such that it is not more expensive than PEM+LEN once the effective prices are applied.
- 6.60 A summary of the key inputs and rationale of the CMA is presented in Table 14.

Table 14: Summary of key inputs and rationale of the CMA

Component	Claim or assumption
Therapeutic claim: effectiveness	CBZ+NIVO is non-inferior in terms of effectiveness (at improving PFS, ORR and OS) compared to PEM+LEN.
Therapeutic claim: safety	CBZ+NIVO is non-inferior in terms of safety compared to PEM+LEN.
Evidence base	Bucher Indirect Treatment Comparison of randomised trials
Equi-effective doses	<p>CBZ+NIVO:</p> <ul style="list-style-type: none"> - NIVO Initial: 240 mg IV on Day 1 of a 14-day cycle for 4 cycles - NIVO Continuing: 480 mg IV on Day 1 of a 28-day cycle (up to 2 years, including initial and continuing) - CBZ: Oral 40 mg per day; RDI is 73.88% (=29.55 mg/40 mg) <p>PEM+LEN:</p> <ul style="list-style-type: none"> - PEM Initial: 200 mg IV on Day 1 of a 21-day cycle for 7 cycles. - PEM Continuing: 400 mg IV on Day 1 of a 42-day cycle (max 14 cycles) - LEN: Oral 20 mg per day; RDI is 70.50% (=14.1 mg / 20 mg) <p>RDI was assumed to be 100% for NIVO and PEM.</p>
Duration of treatment	21.75 months applied for both arms. Estimated DoT was based on the extrapolation of data from the CheckMate 9ER 23.5 months median FU using a Weibull distribution, which has the best relative fit according to AIC and BIC.
Direct medicine costs ^a	Equivalent cost per patient per course (equivalent duration of treatment), including cost offsets relating to administration and adverse events.
Other costs or cost offsets ^a	<p>Cost offsets relating to administration and adverse events.</p> <p>Administration costs:</p> <ul style="list-style-type: none"> - IV administration (MBS item 13950) - Specialist visits (MBS item 116): the submission incorrectly used the fee of \$48.05. The fee for item 116 should be \$84.35. <p>Costs associated with treatment related adverse events: two most frequently occurring TRAEs, hypertension and hypothyroidism, were included:</p> <ul style="list-style-type: none"> - Patients with hypertension are assumed to be treated with an angiotensin II receptor blocker (telmisartan 40mg) for the treatment duration. The drug cost (\$142) was sourced from PBS. - Patients with hypothyroidism are assumed to be treated with levothyroxine (100mcg/day) for the duration of their treatment. The drug cost (\$240) was sourced from PBS. <p>. There were small discrepancies in the percentage of TRAEs for PEM+LEN arm presented in the clinical evaluation (hypertension = 52.3% and hypothyroidism = 42.6%) and the CMA (hypertension = 55% and hypothyroidism = 47%). This was corrected during the evaluation using the values presented in the clinical evaluation.</p>

Source: Table 3-1, p173 of the submission; Table 3-7, p180 of the submission.

AIC = Akaike's Information Criteria; BIC = Bayesian Information Criteria; CBZ+NIVO = cabozantinib plus nivolumab; PEM+LEN = pembrolizumab plus lenvatinib; PFS = progression-free survival; OS = overall survival; ORR = objective response rate; TRAE = treatment related adverse events.

^a During the evaluation, the published prices for relevant agents and MBS fees were checked and updated, and the base case CMA in the submission was revised to reflect these updated prices.

6.61 The CMA considered drug costs (CBZ, NIVO, PEM and LEN), specialist visits (for continuing treatment), drug administration costs (IV infusion for NIVO and PEM), and costs associated with the management of adverse events (hypertension and hypothyroidism).

6.62 The submission presented the following assumptions for the CMA:

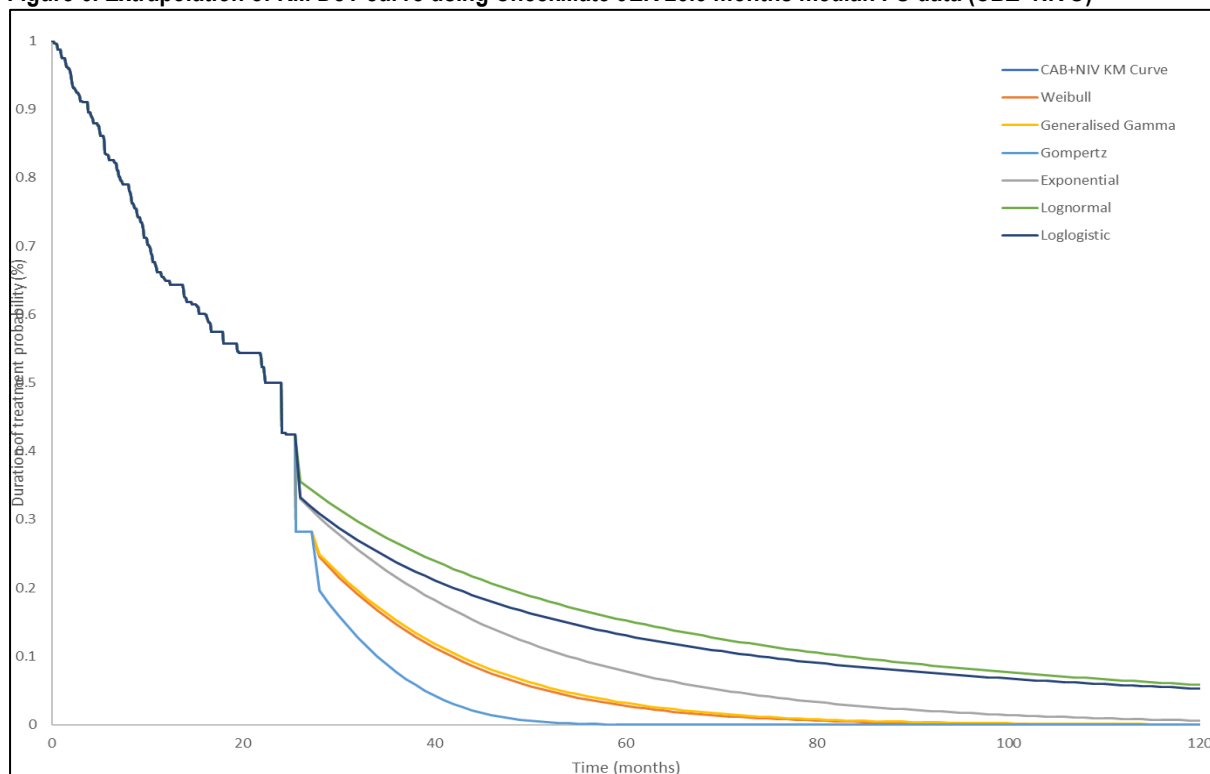
- The durations of treatment (DoT) for CBZ+NIVO and PEM+LEN are the same.

- There are differences in administration between CBZ+NIVO and PEM+LEN that are expected to impact the total cost of treatment.
- There are differences in the proportion of patients who experienced the TRAEs of hypertension and hypothyroidism. It was assumed that patients only required one course of treatment for each TRAE for the entire DoT. The evaluation noted that the majority of TRAEs were Grade 1-2 which might not require treatment. The ESC considered treatment is unlikely to be sought for Grade 1 hypertension or hypothyroidism. The ESC considered Grade 2 hypertension may lead to intervention, but grade 2 hypothyroidism by definition means treatment is indicated.

6.63 To calculate the mean DoT for the CMA, the submission presented the following steps:

- Extrapolation of the DoT KM data of CBZ+NIVO from CheckMate 9ER using a series of distributions. The Weibull distribution was selected as the final model using AIC and BIC statistics.
- Calculation of the DoT using the extrapolated KM data using the Weibull distribution over a 7.5-year period, which resulted in an estimated DoT of 21.75 months (which was applied to both CBZ+NIVO and PEM+LEN).

Figure 6. Extrapolation of KM DoT curve using CheckMate 9ER 23.5 months median FU data (CBZ+NIVO)



Source: Figure 3-2, p 178 of the Submission.

6.64 The equi-effective doses in the submission were estimated as:

- NIVO 240 mg IV on Day 1 of a 14-day cycle for 4 cycles (initial) and a continuing dose 480 mg IV on Day 1 of a 28-day cycle (up to 2 years) plus 29.55 mg⁴ per day of CBZ (oral) over 21.75 months.
 - PEM 200 mg IV on Day 1 of a 21-day cycle for 7 cycles and a continuing dose 400 mg IV on Day 1 of a 42-day cycle (max 14 cycles) plus LEN (oral) 14.10 mg⁵ per day over 21.75 months.
- 6.65 The submission stated that the estimates of equi-effective doses were sourced from trial-based data for CBZ+NIVO, while PEM+LEN was sourced from the PSD (March 2022). Relative dose intensity (RDI) was calculated from the trial and recommended doses and applied for CBZ and LEN but not for NIVO and PEM.
- 6.66 The evaluation noted that the submission did not present the DoT estimates for CBZ and NIVO separately, and the DoT estimation did not account for the 24-month maximum treatment time for NIVO.
- 6.67 The PSCR stated that the DoT for CBZ+NIVO should align with the DoT accepted by the PBAC for PEM+LEN in their March 2022 consideration of PEM+LEN, which is Committee-in-Confidence. The ESC noted the PEM+LEN CMA applied different treatment durations for PEM and LEN and accounted for the 24 month maximum treatment duration for PEM. The ESC considered it would be reasonable to assume the same treatment duration for CBZ as was accepted for LEN and the same treatment duration for NIVO as was accepted for PEM by the PBAC in its March 2022 consideration of PEM + LEN. This was noted and accepted in the Pre-PBAC Response.
- 6.68 The published AEMPs for CBZ+NIVO and PEM+LEN used in the CMA are presented in Table 15. The submission noted that the final estimated effective prices can be adjusted according to the DoTs recommended for PEM+ LEN.

⁴ 40 mg per day x 73.88% RDI

⁵ 20mg per day x 70.50% RDI

Table 15. List prices and treatment regimens for index treatments applied in in the CMA

Description	List price (AEMP, published)	Treatment regimen	RDI	DoT (cycles)	DoT (weeks. RDI applied)	Average number of vials/packs, RDI applied
Cabozantinib	\$9,800.00 per 30 x 40 mg tablets	Oral 40 mg per day	73.88% ^g	21.75	N/A	16.30 ^a
Nivolumab	\$1,972.91 per 100 mg vial	Initial: 240 mg IV on d1 of a 14d cycle for 4 cycles	N/A	4.00	8	9.6 ^b
		Continuing: 480 mg IV on d1 of a 28d cycle		21.56	86.25	103.50 ^c
Pembrolizumab	\$3,823.75 per 100 mg vial	Initial: 200 mg IV d1 21d cycle for 7 cycles	N/A	7.00	21.00	14.00 ^d
		Continuing: 400 mg IV d1 of a 42d cycle (maximum 14 cycles)		12.21	73.25	48.83 ^e
Lenvatinib	\$2,000.00 ^h per 30 x 10 mg tablets	Oral 20 mg per day	70.50% ^g	21.75	N/A	31.11 ^{f, h}

Source: Table 3-6, p179 of the submission

AEMP = Approved Ex-manufacturer price; CMA = Cost minimisation analysis; RDI = Relative dose intensity; DoT = Duration of Treatment; N/A = Not applicable; IV = intravenous.

^a Adjusts for 365.25/12 days in month to calculate # of packs required; $RDI * DoT(cycles) * (365.25/12) / 30 \text{ tablets/pack}$

^b 4 cycles at 2.4 x 100mg vials/cycle

^c 21.56 cycles @ 4.8 x 100mg vials/cycle

^d 7 cycles @ 2 x 100mg vials/cycle

^e 12.21 cycles @ 4 x 100mg vials/cycle

^f Adjusts for 365.25/12 days in month to calculate # of packs required, 30 tablets 10mg per pack is equivalent to 15 days of treatment (20mg per day); $RDI * DoT(cycles) * (365.25/12) / 30 \text{ tablets/pack} * 2 \text{ packs}$

^g For LEN and CBZ, the RDI was estimated as the mean dose in the trial divided by the recommended dose; $73.88\% = 29.55\text{mg}/40\text{mg}$ (CBZ) and $70.5\% = 14.1\text{mg}/20\text{mg}$ (LEN).

^h Updated published AEMP (LEN) and calculation during the evaluation: \$2,000 instead of \$2,500 per 30 x 10 mg tablets.

6.69 The submission used the estimated DoT to calculate the number of packs / vials for each agent and the administration cost, including specialist visits (MBS item 116) and IV administration costs for PEM and NIVO (MBS item 13950 = \$118.90). The submission used the incorrect fee (\$48.05) for MBS item 116; the fee for item 116 should be \$84.35. The calculation implied that a specialist visit would be required in each IV administration (for PEM or NIVO). The PBAC considered it was appropriate to only include the cost of IV infusion for immunotherapy administration and advised the cost for specialist visits should be removed from both treatment arms in the CMA.

6.70 The CMA assumed costs associated with TRAEs happened once during treatment. Two specific TRAEs were included – hypertension and hypothyroidism. The submission included any-grade TRAEs for both hypertension and hypothyroidism. This might not be reasonable because in practice, treatment might not be sought for Grade 1-2 events. The incidence of \geq Grade 3 events was above 10% for hypertension yet approximately 1% or less for hypothyroidism (see Table 11 above). The evaluation noted the impact on the CMA result was small.

6.71 The results of the CMA are presented in Table 16.

Table 16. Results of the cost-minimisation approach (DoT = 21.75 months in both arms)

Description	CBZ+NIVO			PEM+LEN			Increment
	CBZ	NIVO	Total	PEM	LEN	Total	
Updated base case during the evaluation							
Medicine costs ^a	\$159,761	\$223,136	\$382,897	\$240,259	\$62,229	\$302,488	\$80,409
Administration ^a		\$5,196			\$3,904		\$1,291
Adverse Events ^a		\$142			\$227		-\$85
Total costs		\$388,235			\$306,620^a		\$81,615

Source: Table 3.8, p181 of the submission and CBZ_NIVO Section 3 workbook – CMA

CBZ+NIVO = cabozantinib plus nivolumab; PEM+LEN = pembrolizumab plus lenvatinib; DoT = duration of treatment.

Notes: There was minor inconsistency between the numbers reported in the submission document and the excel file. The submission base case here is sourced from Table 3-8 of the submission.

^a Updated base case during the evaluation includes: (1) updated published price for LEN, (2) corrected MBS fee for item 116, treatment management, and (3) % of treatment related adverse events for PEM+LEN arm.

6.72 Based on the updated base case, the total cost per treatment course per patient for CBZ+NIVO was \$388,235. The corresponding cost for PEM+LEN was \$306,620, resulting in an incremental cost of \$81,615. In order to result in an incremental cost of \$0 for the CMA, the total cost for CBZ+NIVO would need to be \$306,620. Of this, \$5,196 would be administration costs and \$142 would be related to adverse events. Hence, the total drug cost for CBZ+NIVO would be \$301,282 (based on published prices).

6.73 The CMA must establish that the cost per patient for treatment with CBZ+NIVO would be no more than the cost per patient for PEM+LEN. Where the cost per patient calculation is uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe. In this case, the PBAC should consider the following parameter: duration of treatment. If in practice the treatment duration for CBZ+NIVO is longer than for PEM+LEN, the cost per patient for CBZ+NIVO will be higher than for PEM+LEN.

Drug cost/patient/course

6.74 The drug cost per patient for CBZ+NIVO and PEM+LEN based on published AEMP is presented in Table 17.

Table 17: Drug cost per patient treatment course for proposed and comparator drugs based on published AEMP

Description	CBZ+NIVO CMA and financial estimates	PEM+LEN CMA and financial estimates
Mean dose	CBZ 29.55mg per day (RDI adjusted) + NIVO 240mg per 14-day cycle (initial) + NIVO 480mg per 28-day cycle (continuing)	PEM 200mg per 21-day cycle (initial) + PEM 400mg per 42-day cycle (continuing) + LEN 14.10mg per day (RDI adjusted)
Mean duration (months)	21.75 ^a	21.75 ^a
Cost/patient/ month ^b	CBZ \$7,345.33 + NIVO \$10,259.13 = \$17,604.46	PEM \$11,046.39 + LEN \$3,096.15 = \$13,907.51
Cost/patient/ course ^b	\$382,897	\$302,488

Source: Calculated during the evaluation

CBZ+NIVO = cabozantinib plus nivolumab; PEM+LEN = pembrolizumab plus lenvatinib; CMA = cost minimisation analysis; DoT = duration of treatment; AEMP = approved ex-manufacturer price.

^a Duration of treatment assumed in the submission.

^b Calculations conducted during the evaluation.

Estimated PBS usage & financial implications

- 6.75 This submission was not considered by DUSC.
- 6.76 The submission used a market share approach to estimate utilisation and financial impact of CBZ+NIVO. The submission assumed that the market share of CBZ+NIVO, if listed on the PBS, will come from PEM+LEN, as these two combinations are both IO+TKIs, making them the closest substitutes.
- 6.77 The key inputs for financial estimates are presented in Table 18.

Table 18: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Script volume (total) for PEM and LEN in 2024	PEM: █████ ¹ (public + private hospitals) LEN 4mg: █████ ² LEN 10mg: █████ ¹	The submission estimated the script volumes by annualising the volume of services for the most recent months of available data (May – August 2023). The submission assumed that the IO+TKI market would grow to account for 50% of the first-line ccRCC market, based on estimated average number of treatment initiations for NIVO+IPI vs PEM+LEN for the period May – August 2023.
Growth rate of the IO+TKI market	14% per annum	The submission noted that prior to the PBS listing of PEM+LEN, the NIVO+IPI market grew at an average rate of 14% each year, based on the prior 24-month period. The 14% growth rate was applied to the IO+TKI market because the submission assumed that the growth of the PEM+LEN market would reflect what was observed in the NIVO+IPI market prior to the availability of PEM+LEN.
Percentage of PEM+LEN market share that CBZ+NIVO expects to replace	2025: 25% 2026+: 50%	The submission noted that 50% was derived from advice received from an advisory board of Australian prescribers.
Substitution rate for scripts	1 script PEM= 1.5 scripts NIVO 1 script LEN 4 mg= 1 CBZ 20mg 1 script LEN 10 mg= 2 CBZ 20 mg= 1 CBZ 40 mg	These ratios were calculated from the dosage frequency.
Scripts dispensed: CBZ 20mg x 2 (continuing)	Yr 1: █████ ² , increasing to Yr 6: █████ ²	The scripts for CBZ 20mg and 40mg were estimated separately from the script conversions of LEN 4mg and 10mg.
Scripts dispensed: CBZ 40mg (initial and continuing)	Yr 1: █████ ² , increasing to Yr 6: █████ ¹	
Scripts dispensed: NIVO	Yr 1: █████ ² , increasing to Yr 6: █████ ¹	
Costs		
Cabozantinib	CBZ 40mg or 20mg (x2) continuing, daily - AEMP = \$9,800 (per 30x40mg tablets) - DPMQ = \$9,962.13	
Nivolumab	NIVO 40mg/4mL, 100mg/10mL Initial 240mg IV, 14-day cycle for 4 cycles - AEMP= \$1,972.91 per 100mg vial (or \$4,734.98 for 240mg) - DPMQ Public= \$9,558.60 - DPMQ Private= \$9,734.47 NIVO 40mg/4mL, 100mg/10mL Continuing 480mg IV, 28-day cycle - AEMP= \$1972.91 per 100mg vial (or \$9,469.98 for 480mg) - DPMQ Public= \$9,558.60 - DPMQ Private= \$9,734.47	The submission did not provide a separate calculation for initial and continuing. This will affect the financial estimates because of the dosage difference between initial and continuing.

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Parameter	Value applied and source	Comment
Pembrolizumab	PEM 100mg/4mL injection Initial 200mg IV, 14-day cycle for 4 cycles - AEMP= \$3,823.75 per 100mg vial (or 7,647.50 for 200mg) - DPMQ Public= \$15,383.62 - DPMQ Private= \$15,641.03 PEM 100mg/4mL injection Initial (400mg IV, 42-day cycle) - AEMP= \$3,823.75 per 100mg vial (or 15,295.00 for 400mg) - DPMQ Public = \$15,383.62 - DPMQ Private = \$15,641.03	The submission did not provide a separate calculation for initial and continuing. This will affect the financial estimates because of the dosage difference between initial and continuing.
Lenvatinib	LEN 20mg daily (10 mg x 2) - AEMP = \$2,000 ^a (per 30 x 10mg capsules) - DPMQ = \$4,162.13 ^a	
Patient co-payment	PBS: \$19.30 RPBS: \$7.07	
MBS costs	\$118.90 Parenteral administration of antineoplastic agents (MBS item 13950)	This is consistent with the administration costs in the CMA.

Source: Compiled during the evaluation using Section 4 – Workbook – CBZ_NIVO.

AEMP = Approved Ex-manufacturer Price; CBZ = cabozantinib; DPMQ = Dispensed Price for Maximum Quantity; LEN = lenvatinib; MBS = Medicare benefits schedule; NIVO = nivolumab; PEM = pembrolizumab; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; IO = immunotherapy; TKI = tyrosine kinase inhibitor; ccRCC = clear cell advanced renal cell carcinoma; AEs = adverse events; CMA = cost minimisation analysis

^a Updated prices for LEN during the evaluation.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

6.78 The submission stated that estimation of script numbers reflects the forecast growth in the IO+TKI market. That is, within 3 years of the availability of PEM+LEN, the IO+TKI market would grow to approximately 50% of the overall immunotherapy-based combination market for first-line treatment of clear cell aRCC, which is in line with prescribing trends internationally. Data analysis of the processed prescription claims for May-August 2023 data for PEM+LEN was also presented to support the 50% IO+TKI market share estimate.

6.79 To estimate the script volumes for CBZ and NIVO, the following steps were conducted:

- Estimate the script volumes for individual agents in the current IO+TKI market that CBZ+NIVO would replace from the market data. The first year of estimated script replacement was 2024. The submission presented script volumes for PEM and LEN for May-August 2023. However, there was no discussion of the forecasting method used to estimate the script volume in 2024. Since the PEM+LEN market share grew rapidly during this 4-month period and might not yet have stabilised, the number of scripts might be under-estimated.

- Apply a growth rate of 14% to the estimated script volumes for PEM and LEN in 2024 and then for 2025-2030 (6 years). The submission neither presented the data source nor the forecasting method used to estimate the 14% growth rate.
- Calculate the script volumes that represent the PEM+LEN market share that CBZ+NIVO would replace, using a replacement rate of 25% in 2025 and 50% from 2026. While this assumption is uncertain, it should not affect the overall financial estimate if the effective price for CBZ+NIVO is set to achieve \$0 incremental cost in the CMA.
- Convert the script volumes of PEM to NIVO at the ratio of 1 PEM script = 1.5 NIVO scripts, as PEM is administered every 3 weeks or every 6 weeks whereas NIVO is administered every 2 weeks or every 4 weeks. This means NIVO requires 1.5 times the scripts in comparison to PEM.
- Convert the script volumes of LEN to CBZ at two different ratios, for two different LEN scripts (4 mg and 10 mg). The rationale was that the ratio of LEN 4 mg to LEN 10 mg services to August 2023 was approximately 1:4; the submission therefore assumed that 80% of LEN 10mg patients will be on the full dose and CBZ 40 mg represents the appropriate alternative. Twenty per cent of LEN 10 mg patients are then assumed to be on a reduced dose that requires use of the 10 mg presentation as part of the required dose (10 mg, 14 mg or 18 mg), which would be substituted with CBZ 20 mg. An additional assumption was that a small percentage of patients on LEN will exclusively be on LEN 4 mg tablets to make the dosage of 4 mg, 8 mg, 12 mg and 16 mg. The submission then allocated 20% for the conversion of LEN to CBZ 20 mg to avoid double-counting.

6.80 The estimated use and financial implications are presented in Table 19.

Table 19. Estimated use and financial implications

		Calculation	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
A	Annual growth rate	14%						
Estimated scripts for PEM+LEN – without CBZ+NIVO listing (PBS + RPBS)								
B	PEM 100mg/4mL injection	Estimated scripts 2024	1	1	1	1	1	1
	LEN capsule 4mg	x	2	2	2	2	2	2
	LEN capsule 10mg	(1+A)^(year)	1	1	1	1	1	1
C	Market share of PEM+LEN to be replaced		25%	50%	50%	50%	50%	50%
Estimated scripts for PEM+LEN to be replaced by CBZ+NIVO (PBS + RPBS)								
D	PEM 100mg/4mL injection	B x C	2	1	1	1	1	1
	LEN capsule 4mg		2	2	2	2	2	2
	LEN capsule 10mg		2	2	2	1	1	1
Estimated scripts for CBZ+NIVO from PEM+LEN script volume								
E	CBZ tablet 20mg	From LEN 4mg, 1:1 + From LEN 10mg, 1:2	2	2	2	2	2	2
F	CBZ tablet 40mg	From LEN 10mg, 1:1	2	2	2	2	2	1
G	NIVO 40mg/4mL, 100mg/10mL injection	From PEM 100mg/4mL, 1:1.5	2	1	1	1	1	1
H	PBS/RPBS cost of listing CBZ+NIVO (less co-payment)	E, F and G @ respective CBZ and NIVO prices	\$ ³	\$ ⁴	\$ ⁴	4	\$ ⁵	\$ ⁵
I	PBS/RPBS cost of PEM+LEN (less co-payment)	D @ respective PEM and LEN prices	\$ ³	\$ ⁴	\$ ⁴	\$ ⁴	\$ ⁴	\$ ⁴
J	Net cost to PBS/RPBS	H-I	\$ ³	\$ ³	\$ ³	\$ ³	\$ ³	\$ ³
K	Net change to the MBS (due change in IV administration cost)		\$ ³	\$ ³	\$ ³	\$ ³	\$ ³	\$ ³
L	Net implications for the health budget ^a	J+K	\$ ³	\$ ³	\$ ³	\$ ³	\$ ³	\$ ³

Source: Excel workbook, 2e Scripts – market and 3a. Scripts proposed

CBZ = cabozantinib; NIVO = nivolumab; PEM = pembrolizumab; LEN = lenvatinib; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Calculated during evaluation: sum of '5. Impact – net' cells C24: H24 and '7. Net changes - MBS' cells F26:K26.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

³ \$0 to < \$10 million⁴ \$10 million to < \$20 million⁵ \$20 million to < \$30 million

6.81 Based on the published prices for all medicines, the listing of CBZ+NIVO as a first-line treatment of patients with clear cell aRCC with an intermediate or poor IMDC

prognostic risk is expected to result in a cost increase to the health budget of \$0 to < \$10 million in Year 1 of listing, increasing to \$0 to < \$10 million in Year 6.

- 6.82 The submission noted that while these financial implications result in an incremental net cost to the health budget, the calculation was based on the published prices for all agents. Once the effective prices of other drugs are known the listing is expected to be cost-neutral to the health budget, consistent with the claim of non-inferiority and the cost-minimisation approach presented.
- 6.83 If listed, CBZ+NIVO would be the third combination treatment option for the target population, and it is not expected to add to market growth.
- 6.84 Two sources of uncertainty were noted in the submission: market share of CBZ+NIVO and market growth of the IO+TKI market. The submission stated the impact of a different market share was expected to be negligible given the same cost per patient is requested and the overall RCC market is not assumed to grow due to the listing of CBZ + NIVO.

Financial Management – Risk Sharing Arrangements

- 6.85 The submission noted that a Risk Sharing Arrangement exists for combination therapies in first-line aRCC (including NIVO+IPI and PEM+LEN). The submission stated that it is assumed that if recommended, CBZ+NIVO would be incorporated within this existing Deed and provide certainty around Government expenditure. Since the listing of CBZ+NIVO is not expected to increase the market, the ESC considered it would be reasonable that there is no change in the existing caps. The Pre-PBAC response noted the PBAC's previous conclusion that the RCC RSA should be reviewed 12 months after the listing of PEM+LEN (PSD, March 2022 PBAC meeting, paragraph 7.12) and requested that any future change to funding caps for PEM+LEN arising from the review be applied to CBZ+NIVO.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of cabozantinib for use in combination with nivolumab (CBZ+NIVO) for the treatment of advanced (Stage IV) clear cell variant renal cell carcinoma (aRCC) in patients who are classified as intermediate or poor risk using the **IIIIII** (IMDC) survival risk classification score. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of CBZ+NIVO would be acceptable if it were cost-minimised against PEM+LEN. The PBAC considered a cost minimisation approach (CMA) was reasonable, assuming the same treatment duration and relative dose intensity (RDI) for CBZ as was accepted for lenvatinib (LEN) and the same treatment duration and RDI for NIVO as was accepted for pembrolizumab (PEM) by the PBAC in its March 2022 consideration of PEM+LEN. The PBAC advised that CBZ+NIVO should join the existing Risk Sharing Arrangement

- (RSA) with PEM+LEN and other aRCC treatments with no increase in expenditure caps.
- 7.2 The PBAC noted and welcomed the input from organisations via the Consumer Comments facility. The PBAC noted that the comments stated the availability of CBZ+NIVO would provide an alternate combination therapy for patients.
 - 7.3 The PBAC considered that the proposed place in therapy for CBZ+NIVO as a treatment for patients with intermediate to poor risk aRCC was appropriate and its listing on the PBS would provide an additional combination immunotherapy (IO) + tyrosine kinase inhibitor (TKI) treatment option. The PBAC agreed with the ESC that the clinical decision to use an IO+TKI or NIVO+IPI may be different (see paragraph 6.39).
 - 7.4 The PBAC considered that the nominated primary comparator of PEM+LEN was appropriate and nivolumab plus ipilimumab (NIVO+IPI) was a reasonable secondary comparator.
 - 7.5 The PBAC noted the clinical evidence for CBZ+NIVO was from a randomised, open-label trial (CheckMate 9ER, n=651) comparing CBZ+NIVO to sunitinib (SUN) in patients with previously untreated clear-cell aRCC. The PBAC noted that, overall, treatment with CBZ+NIVO resulted in a statistically significant improvement in progression free survival (PFS) and overall survival (OS) compared to SUN for the subgroups of patients with intermediate or poor risk disease.
 - 7.6 The PBAC noted that the submission presented an anchored Bucher indirect treatment comparison (ITC) comparing CBZ+NIVO and PEM+LEN (CLEAR trial) in patients with previously untreated aRCC using SUN as the common comparator.
 - 7.7 The PBAC noted that the Bucher ITC demonstrated that CBZ+NIVO was likely non-inferior to PEM+LEN in terms of OS in the poor (HR 1.50; 95% CI 0.60-3.76) and intermediate (HR 1.03; 95% CI 0.60-1.75) IMDC risk groups. The PBAC noted the wide confidence intervals and considered this resulted in some uncertainty in the relative effectiveness, especially for the poor risk group. However, the PBAC considered that, given the same mechanism of action of the components, on balance, the claim of non-inferior comparative effectiveness versus PEM+LEN was reasonable.
 - 7.8 The PBAC noted that the Bucher ITC demonstrated there was no statistically significant difference between CBZ+NIVO and PEM+LEN for any grade TRAEs (OR 0.86; 95% CI 0.30-2.44) and Grade ≥ 3 TRAEs (OR 0.84; 95% CI 0.54-1.32). The PBAC considered that CBZ+NIVO had a non-inferior safety profile compared to PEM+LEN.
 - 7.9 The PBAC noted that although it was reasonable to present a CMA (given the non-inferiority claim), the submission did not calculate the cost minimised price based on appropriately estimated equi-effective doses, with a single treatment duration applied to both components of CBZ+NIVO that did not account for the 24-month maximum treatment time for NIVO. This single treatment duration was also applied to both components of PEM+LEN. The PBAC advised that in order to estimate the equi-effective doses, the duration of treatment and RDI for CBZ and NIVO should be aligned

- with those used for LEN and PEM in the March 2022 PBAC consideration of PEM+LEN.
- 7.10 The PBAC noted that the CMA should result in the cost of CBZ+NIVO being no more than the cost of PEM+LEN, based on the effective ex-manufacturer prices and accounting for differences in the mode and frequency of administration between CBZ+NIVO and PEM+LEN and the differences in the safety profiles (i.e. as calculated in Table 14, with an incremental cost of \$0). The PBAC advised the cost for specialist visits should be removed from both treatment arms in the CMA.
- 7.11 The PBAC considered that NIVO+IPI was an alternative therapy to CBZ+NIVO and PEM+LEN, and that CBZ+NIVO does not provide a significant improvement in efficacy and/or reduction in toxicity over NIVO+IPI. The PBAC advised that the cost of CBZ+NIVO should also therefore not be higher than the cost of NIVO+IPI.
- 7.12 The PBAC noted there were some uncertainty regarding the market growth of the IO+TKI market but considered that the availability of CBZ+NIVO would not add to the market growth. The PBAC considered that, at the same cost per patient as PEM+LEN, CBZ+NIVO would be cost-neutral to the PBS/RPBS. The PBAC advised that CBZ+NIVO should join the existing RSA with PEM+LEN and other aRCC treatments with no increase in expenditure caps.
- 7.13 The PBAC advised the following changes to the restriction criteria proposed in Section 3 would be reasonable:
- Amend the number of repeats as discussed in paragraph 3.4.
 - The treatment criterion in the initial treatment restrictions for CBZ and NIVO “Patient must be undergoing monotherapy with this drug due to a contraindication/intolerance to the other drug in the combination mentioned above, requiring temporary/permanent discontinuation; document the details in the patient's medical records” could be removed as patients should initiate treatment with both agents. The PBAC noted this change should also flow on to the PEM+LEN restriction criteria.
 - The treatment criterion in the continuing treatment restrictions for CBZ and NIVO “Patient must be undergoing monotherapy with this drug due to an ~~contraindication~~/intolerance to the other drug in the combination mentioned above, requiring temporary/permanent discontinuation; document the details in the patient's medical records” should be amended as indicated with strikethrough. The PBAC considered a patient contraindicated to either CBZ or NIVO would not have been able to initiate treatment with this combination. The PBAC noted this change should also flow on to the PEM+LEN restriction criteria.
- 7.14 The PBAC considered that it was appropriate to amend the restriction criteria for sunitinib and pazopanib to preclude prior treatment with LEN as discussed in paragraph 3.5.

- 7.15 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because CBZ+NIVO is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over PEM+LEN, or not expected to address a high and urgent unmet clinical need given the presence of alternative therapies, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines - Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 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 medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
CABOZANTINIB					
Cabozantinib, 40 mg tablet, 30	NEW	1	30	2	cabometryx
Cabozantinib, 20 mg tablet, 30	NEW	1	30	2	cabometryx
Restriction Summary [new] / Treatment of Concept: [new]					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new]					
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					
<p>Administrative Advice: A prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk score can be calculated here: https://www.mdcalc.com/imdc-international-metastatic-renal-cell-carcinoma-consortium-risk-model-metastatic-renal-cell-carcinoma.</p> <p>One point is assigned for each of: (i) a time of diagnosis to systemic therapy of less than 1 year (ii) a Karnofsky Performance Status of less than 80% (iii) a haemoglobin less than the lower limit of normal (iv) a corrected calcium level greater than the upper limit of normal (v) a neutrophil count greater than the upper limit of normal (vi) a platelet count greater than the upper limit of normal</p> <p>Stated normal reference ranges may vary depending on the laboratory providing the measurement. 'Normal' here refers to the individual laboratory's stated normal reference range.</p> <p>Favourable IMDC risk is a score of 0.</p>					

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	Intermediate IMDC risk is a score of 1 to 2. Poor IMDC risk is a score of 3 to 6. Document any IMDC risk score assessment in the patient's medical records.
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	Severity: Stage IV
	Condition: Clear cell variant renal cell carcinoma (RCC)
	Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
	Treatment Phase: Initial treatment in combination with nivolumab
	Clinical criteria:
	Patient must have a prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score at treatment initiation with this drug and nivolumab of either: (i) 1 to 2 (intermediate risk), (ii) 3 to 6 (poor risk); document the IMDC risk classification score in the patient's medical records,
	AND
	Clinical criteria:
	The condition must not have been previously treated
	AND
	Clinical criteria:
	Patient must have a WHO performance status of 2 or less
	Treatment criteria:
	Patient must be undergoing combination therapy consisting of: (i) cabozantinib, (ii) nivolumab

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
CABOZANTINIB					
Cabozantinib, 20 mg tablet, 30	NEW	1	30	5	cabometyx
Cabozantinib, 40 mg tablet, 30	NEW	1	30	5	cabometyx

Restriction Summary [new] / Treatment of Concept: [new]

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new]
	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: Stage IV
	Condition: Clear cell variant renal cell carcinoma (RCC)
	Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
	Treatment Phase: Continuing treatment in combination with nivolumab
	Clinical criteria:

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	Patient must have previously received PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	Patient must not have developed disease progression while receiving treatment with this drug for this condition
	Treatment criteria:
	Patient must be undergoing combination therapy consisting of: (i) cabozantinib, (ii) nivolumab; OR
	Patient must be undergoing monotherapy with this drug due to an intolerance to the other drug in the combination mentioned above, requiring temporary/permanent discontinuation; document the details in the patient's medical records; OR
	Patient must be undergoing monotherapy with this drug after completing an equivalent of 24 cumulative months of nivolumab treatment, measured from the first administered dose

8.2 Add new listing for nivolumab for use in combination with cabozantinib:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. amount	No. of Rpts	Available brands
NIVOLUMAB				
Nivolumab 40 mg/mL injection 4mL	NEW	480 mg	5	opdivo
Nivolumab 100 mg/mL injection 10mL	NEW	480 mg	5	opdivo

Restriction Summary [new] / Treatment of Concept: [new]

	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new]
	Administrative Advice: No increase in the maximum number of repeats may be authorised
	Administrative Advice: Special pricing arrangements apply
	<p>Administrative Advice: A prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk score can be calculated here: https://www.mdcalc.com/imdc-international-metastatic-ccc-database-consortium-risk-model-metastatic-renal-cell-carcinoma.</p> <p>One point is assigned for each of: (i) a time of diagnosis to systemic therapy of less than 1 year (ii) a Karnofsky Performance Status of less than 80% (iii) a haemoglobin less than the lower limit of normal (iv) a corrected calcium level greater than the upper limit of normal (v) a neutrophil count greater than the upper limit of normal (vi) a platelet count greater than the upper limit of normal</p> <p>Stated normal reference ranges may vary depending on the laboratory providing the measurement. 'Normal' here refers to the individual laboratory's stated normal reference range.</p> <p>Favourable IMDC risk is a score of 0. Intermediate IMDC risk is a score of 1 to 2. Poor IMDC risk is a score of 3 to 6.</p>

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	Document any IMDC risk score assessment in the patient's medical records.
	Severity: Stage IV
	Condition: Clear cell variant renal cell carcinoma (RCC)
	Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
	Treatment Phase: Initial treatment in combination with cabozantinib
	Clinical criteria:
	Patient must have a prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score at treatment initiation with this drug and nivolumab of either: (i) 1 to 2 (intermediate risk), (ii) 3 to 6 (poor risk); document the IMDC risk classification score in the patient's medical records,
	AND
	Clinical criteria:
	The condition must not have been previously treated
	AND
	Clinical criteria:
	Patient must have a WHO performance status of 2 or less
	Treatment criteria:
	Patient must be undergoing combination therapy consisting of: (i) cabozantinib, (ii) nivolumab
	AND
	Treatment criteria:
	Patient must be undergoing treatment with this drug administered once every 2 weeks - prescribe up to 5 repeat prescriptions; OR
	Patient must be undergoing treatment with this drug administered once every 4 weeks - prescribe up to 2 repeat prescriptions.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. amount	No. of Rpts	Available brands
NIVOLUMAB				
Nivolumab 40 mg/mL injection 4mL	NEW	480 mg	11	opdivo
Nivolumab 100 mg/mL injection 10mL	NEW	480 mg	11	opdivo
Restriction Summary [new] / Treatment of Concept: [new]				
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners			
	Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new]			
	Administrative Advice: No increase in the maximum number of repeats may be authorised			
	Administrative Advice: Special pricing arrangements apply			
	Severity: Stage IV			
	Condition: Clear cell variant renal cell carcinoma (RCC)			
	Indication: Stage IV clear cell variant renal cell carcinoma (RCC)			

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	Treatment Phase: Continuing treatment in combination with cabozantinib
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	Patient must not have developed disease progression while receiving treatment with this drug for this condition
	Treatment criteria:
	Patient must be undergoing combination therapy consisting of: (i) cabozantinib, (ii) nivolumab; OR
	Patient must be undergoing monotherapy with this drug, due to an intolerance to the other drug in the combination mentioned above, requiring temporary/permanent discontinuation; document the details in the patient's medical records.
	AND
	Treatment criteria:
	Patient must be undergoing treatment with this drug administered once every 2 weeks - prescribe up to 11 repeat prescriptions; OR
	Patient must be undergoing treatment with this drug administered once every 4 weeks - prescribe up to 5 repeat prescriptions.
	AND
	Treatment criteria
	Patient must not be undergoing continuing PBS-subsidised treatment where this benefit is extending treatment beyond 24 cumulative months from the first administered dose, once in a lifetime.

- 8.3 Flow on changes for sunitinib (PBS item codes: 10504W, 9417P, 9418Q, 9419R, 9420T, 9421W, 9422X) and pazopanib (PBS item codes: 11252F, 11261Q, 2029T, 2030W, 2201W, 2232L). Amend prescribing instruction:

	Prescribing instructions: PBS-subsidy does not apply to a patient who has progressive disease whilst on, or, who has recurrent disease following treatment with any of: (i) cabozantinib, (ii) lenvatinib, (iii) pazopanib, (iv) sunitinib.
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This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.