

6.02 CABOZANTINIB, Tablet 20 mg, 40 mg, and 60 mg, Cabometyx[®], Ipsen Pty Ltd

1 Purpose of Application

- 1.1 The submission requested a Section 85, Authority Required (Streamlined), listing of cabozantinib as first-line treatment of Stage IV clear cell variant renal cell carcinoma (RCC) in patients meeting the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria for intermediate to poor risk disease.
- 1.2 The submission presented a cost-utility analysis (CUA), on the basis that cabozantinib was superior to sunitinib in terms of efficacy, with a different safety profile. This used clinical evidence from a randomised controlled trial comparing cabozantinib with sunitinib (CABOSUN).
- 1.3 The submission also presented a cost-minimisation analysis (CMA), on the basis that cabozantinib 60 mg orally per day was non-inferior to nivolumab and ipilimumab (NIVO+IPI) in terms of efficacy and may be superior with respect to safety. An indirect comparison of cabozantinib with NIVO+IPI, using sunitinib as the common reference, was presented.
- 1.4 The key components of the clinical issues addressed by the submission are shown in Table 1.

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

Component	Description
Population	Patients with previously untreated mRCC, ECOG status of 0-2 and intermediate to poor risk classification by IMDC criteria.
Intervention	Cabozantinib 60 mg orally once daily (QD) until disease progression or unacceptable toxicity.
Comparator	<u>Main comparator</u> : Sunitinib 50 mg orally once daily (QD) for the first 4 weeks of consecutive 6-week cycles, until disease progression or unacceptable toxicity. <u>Near market comparator</u> : Nivolumab 3 mg/kg with ipilimumab 1 mg/kg intravenously every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg alone every 2 weeks, for as long as clinical benefit is observed or until treatment is no longer tolerated.
Outcomes	Progression free survival (PFS); objective response rate (ORR); and overall survival (OS).
Clinical claim	In adults with previously untreated mRCC, ECOG status of 0-2 and intermediate to poor risk classification by IMDC criteria, cabozantinib provides: <ul style="list-style-type: none"> • Significantly superior PFS and ORR compared to sunitinib with a trend towards improved OS, and different but broadly comparable safety; • Superior PFS, and non-inferior ORR and OS compared to nivolumab + ipilimumab, with a potentially more tolerable safety profile.

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium Criteria; kg = kilogram; mg = milligram; mRCC = metastatic renal cell carcinoma; PFS = progression free survival; ORR = objective response rate.

Source: Table 1-1, p.18 of the submission.

2 Requested listing

- 2.1 The details of the proposed listing are summarised in Table 2. The submission proposed that a special pricing arrangement (SPA) apply, consistent with the existing

PBS listing of cabozantinib for treatment of stage IV clear cell variant RCC following prior treatment with a tyrosine kinase inhibitor (TKI). The submission did not provide any further details for the SPA. The proposed effective DPMQ for cabozantinib was \$ [REDACTED] with a published DPMQ of \$9,951.04 per 30 tablets for all three strengths (60 mg, 40 mg and 20 mg).

Table 2: Details of the proposed listing

Name, restriction, manner of administration, form	Max quantity (packs)	Max quantity (units)	Number of repeats	Dispensed price for max quantity (DPMQ)		Proprietary name and manufacturer
				Published Price	Effective Price*	
CABOZANTINIB						
Cabozantinib, 60 mg tablet, 30	1	30	2 (initial phase)	\$9,951.04	\$ [REDACTED]	Cabometryx® Ipsen Pty Ltd
Cabozantinib, 40 mg tablet, 30	1	30	5 (continuing phase)	\$9,951.04	\$ [REDACTED]	
Cabozantinib, 20 mg tablet, 30	1	30		\$9,951.04	\$ [REDACTED]	

Abbreviations: mg = milligram; DPMQ = dispensed price per maximum quantity.

Source: Table 1.3, p.34 of the submission; PB11a form.

Note: * Calculated based on an effective AEMP price of \$ [REDACTED] provided in PB11a from key documents of the submission.

2.2 The submission proposed restrictions for initiating and continuing treatment with cabozantinib on the PBS. These are provided in Table 3 and Table 4.

Table 3: Proposed PBS listing – treatment initiation

Category / program	Section 85 - General Schedule
Prescriber type	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	Monthly
Severity:	Stage IV
Condition:	Clear cell variant renal cell carcinoma (RCC)
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Initial treatment
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must meet the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate or poor risk group criteria; AND Patient must have a WHO performance status of 2 or less; AND The treatment must be the sole PBS-subsidised tyrosine kinase inhibitor therapy for this condition. Patients who have progressive disease on pazopanib or sunitinib are not eligible to receive PBS-subsidised cabozantinib under this restriction.
Prescriber Instructions:	Patients who have developed intolerance to sunitinib or pazopanib of a severity necessitating permanent treatment withdrawal are eligible to receive PBS-subsidised cabozantinib. Patients who have progressive disease with pazopanib or sunitinib are no longer eligible for PBS-subsidised cabozantinib under this restriction.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium Criteria; PBS = Pharmaceutical Benefits Scheme; RCC = renal cell carcinoma; WHO = World Health Organisation
Source: Table 1.5, p.37 of the submission.

Table 4: Proposed PBS listing – treatment continuation

Category / program	Section 85 - General Schedule
Prescriber type	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	Monthly
Severity:	Stage IV
Condition:	Clear cell variant renal cell carcinoma (RCC)
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Continuing treatment beyond 3 months
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have received an initial authority prescription for this drug for this condition; AND Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST); AND The treatment must be the sole PBS-subsidised tyrosine kinase inhibitor therapy for this condition.
Prescriber Instructions	A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug. Patients who have developed progressive disease on pazopanib or sunitinib are not eligible to receive PBS-subsidised cabozantinib under this PBS restriction.
Administrative Advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.
Definitions	RECIST is defined as follows: Complete response (CR) is disappearance of all target lesions. Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions. Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions. Stable disease (SD) is small changes that do not meet above criteria.

Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium Criteria; PBS = Pharmaceutical Benefits Scheme; RCC = renal cell carcinoma; RECIST = response evaluation criteria in solid tumors; WHO = World Health Organisation
Source: Table 1.5, p.37 of the submission.

2.3 The indication approved by the TGA is broader (advanced RCC may include more patients than those with stage IV) than the proposed PBS listing.

- 2.4 The submission requested listing in patients who are previously untreated, however the proposed restriction did not limit use to this setting (i.e. to limit use to the requested population, the restriction should include the clinical criterion “The condition must not have previously been treated”). As such, the proposed restriction would allow use in patients who have previously received NIVO+IPI. No evidence was presented for such use, which would be outside the TGA-registered indications, which are for:
- the treatment of advanced renal cell carcinoma (RCC) in treatment-naïve adults with intermediate or poor risk; and
 - the treatment of advanced renal cell carcinoma (RCC) in adults following prior treatment with vascular endothelial growth factor targeted therapy.
- 2.5 The proposed listing allows for the use of cabozantinib in patients who have developed an intolerance to sunitinib or pazopanib. The ESC considered that, although there was no evidence presented for patients intolerant to sunitinib and pazopanib, it would be appropriate to include this criteria consistent with the existing listings for sunitinib and pazopanib.
- 2.6 The sunitinib listing currently includes the clinical criterion “Patients who have developed progressive disease on pazopanib are not eligible to receive PBS-subsidised sunitinib” and pazopanib listing includes the clinical criterion “patients who have progressive disease on sunitinib are not eligible to receive PBS-subsidised pazopanib”. The PBAC considered that if cabozantinib is PBS listed the restrictions for pazopanib and sunitinib should similarly be amended to exclude use in patients who have progressive disease on cabozantinib.
- 2.7 The submission proposed that both initial and continuing therapy restrictions would be Section 85 (General Schedule) Authority Required (STREAMLINED) items. This is consistent with the existing second line listing for cabozantinib, but differs from the current restrictions for sunitinib and pazopanib, for which initiation is an ‘Authority Required’ item. The restriction for nivolumab + ipilimumab in RCC is at the streamlined level for both induction (combination) and continuing treatment. The submission argued that Australian clinicians are now experienced with prescribing the various targeted therapies for RCC and the scope for use outside the approved restrictions would be minimal.

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

3 Background

Registration status

- 3.1 In October 2018, the TGA Delegate approved registration of cabozantinib for the treatment of advanced RCC in treatment-naïve adults with intermediate or poor risk. The TGA Clinical Evaluation Report was not provided with the submission.

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

4 Population and disease

- 4.1 RCC is a type of cancer originating from the lining of renal tubules of the kidney. It is the most common form of kidney cancer accounting for 80-90% of all cases. Kidney cancer is more frequently reported in males than in females. It has been estimated that the incidence of kidney cancer was 3,617 new cases in 2018 representing 2.6% of all new cancer cases, with 1,069 deaths associated with this tumour type (Cancer Australia 2018).
- 4.2 The submission proposed that cabozantinib be used as a first-line treatment for IMDC intermediate to poor risk patients with Stage IV clear cell variant RCC. This was based on the action of cabozantinib inhibiting certain tyrosine kinases (such as MET and AXL) in this disease.
- 4.3 NIVO+IPI was also PBS-listed in this setting on 1 March 2019. The PBAC noted that the US National Comprehensive Cancer Network (NCCN) preferred regimens for first-line treatment of intermediate to poor risk RCC are (i) NIVO+IPI (Category 1, based on high-level evidence) and (ii) cabozantinib (Category 2A, based on lower-level evidence).
- 4.4 The pre-PBAC response stated that, with NIVO+IPI now available for the first-line treatment of intermediate to poor risk patients, the patients most likely to receive cabozantinib would be those for whom immunotherapy is deemed inappropriate (e.g. older patients or those with an underlying immunological disorder).
- 4.5 The submission included a treatment algorithm in which cabozantinib was proposed as an alternative to NIVO+IPI in the first line treatment of patients who are at intermediate to poor risk, and sunitinib or pazopanib are first-line treatments for patients at favourable to intermediate risk. In the proposed treatment algorithm, subsequent treatments included everolimus, sorafenib, cabozantinib, axitinib and nivolumab. However, the proposed algorithm did not take into account that the restrictions for these 'subsequent treatments' require patients to have received prior TKI therapy. In its recommendation for the listing of NIVO+IPI, the PBAC recommended an amendment to the PBS restrictions applied to axitinib, cabozantinib, sorafenib, everolimus, and nivolumab monotherapy to remove the requirement for the prior TKI therapy to have been in the first-line setting (NIVO+IPI PSD November 2018, paragraphs 2.10 and 6.5). Essentially, this means that patients are able to receive these therapies (everolimus, sorafenib, cabozantinib and axitinib) either:
- in the second-line setting following first-line TKI (sunitinib or pazopanib); or
 - in the third-line setting following a second-line TKI (sunitinib or pazopanib) and first-line NIVO+IPI.
- 4.6 The PBAC noted that with the recent PBS listing of NIVO+IPI in first line RCC the current clinical place for cabozantinib (under the existing listing), for many patients, is in the third-line setting after NIVO+IPI followed by second-line sunitinib or pazopanib. The pre-PBAC response noted that patients with poor risk status who progress on NIVO+IPI are not eligible for treatment with subsequent sunitinib or pazopanib under the

current restrictions (as sunitinib and pazopanib are PBS-listed in patients with favourable to intermediate risk only); thus poor risk patients are only eligible for treatment with 'later-line' TKIs (such as cabozantinib) if they have received prior sunitinib or pazopanib despite being outside the restriction criteria. The PBAC noted that the requirement for cabozantinib, under the existing restriction, to be used post-TKI was based on the evidence presented in that submission, the METEOR trial, which enrolled patients who had received prior (VEGFR-targeted) TKI therapy.

- 4.7 The PBAC noted clinical evidence is available for other first-line combination regimens showing survival benefit over sunitinib, such as axitinib + pembrolizumab¹ and others demonstrating PFS benefit over sunitinib, such as axitinib + avelumab² and bevacizumab + atezolizumab³ along with other regimens currently being studied.

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

5 Comparator

- 5.1 The submission nominated sunitinib as the main comparator on the basis that it was the market leader in the first-line treatment of patients with Stage IV RCC who are capable of receiving systemic first-line treatment (at the time the submission was made). The submission further argued that sunitinib was the first PBS-listed targeted therapy for the treatment of Stage IV, clear cell variant RCC, with pazopanib listed on a non-inferiority basis to sunitinib in the first-line setting. Pazopanib, as an alternative first-line therapy, remains a relevant comparator but given that pazopanib was listed on a non-inferiority basis with sunitinib, the submission's approach to the presentation of the evidence was reasonable. The implications of using pazopanib as a comparator in the economic evaluation were tested in sensitivity analyses by the evaluator. The ESC agreed with the evaluator that sunitinib was a reasonable comparator and that it was reasonable as a proxy for pazopanib in terms of the clinical evidence presented.
- 5.2 Sunitinib is listed on the PBS for use in RCC patients of favourable to intermediate risk (but not in patients at poor risk), while the proposed restriction for cabozantinib is for patients at intermediate to poor risk. The PBAC has previously acknowledged that sunitinib (and pazopanib) are used in clinical practice in patients who are at poor risk and accepted sunitinib as the appropriate comparator in its consideration of NIVO+IPI (Nivolumab plus ipilimumab PSD July 2018 PBAC).
- 5.3 The submission noted the potential for NIVO+IPI to become available for use in the proposed indication, and thus proposed that regimen as a near market comparator. The evaluation considered that this was appropriate as NIVO+IPI was recommended

¹ Rini, B.i., Plimack, E.R., Stus, V. et al Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal Cell Carcinoma. NEJM February 16 2019.

² Motzer, R.J., Penkov, K., Haanen, J. et al Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. NEJM February 16 2019.

³ Motzer, R.J., Powles, T., Atkins, M.B. et al. IMmotion151: A Randomized Phase III Study of Atezolizumab Plus Bevacizumab vs Sunitinib in Untreated Metastatic Renal Cell Carcinoma (mRCC). Journal of Clinical Oncology 2018 36:6_suppl, 578-578.

in the first-line setting at the November 2018 PBAC meeting.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the clinical place for cabozantinib and the clinical need for effective first line treatments for patients who are not suitable for NIVO+IPI or who do not tolerate treatment with NIVO+IPI. The clinician addressed questions from the PBAC regarding the availability of trial data for newer combination therapies in first-line RCC, and stated that regardless of the availability of other immunotherapies, there will always be a proportion of patients who are not suitable for these treatments.
- 6.2 The clinician stated that cabozantinib has superior efficacy to sunitinib and noted that some patients do not receive subsequent lines of treatment after progression (e.g. because they become too unwell for further treatment) and therefore the clinician considered that it is desirable to have the most effective treatment available in the first-line setting.
- 6.3 The clinician also addressed questions from the PBAC regarding the availability of clinical data for cabozantinib therapy following first line NIVO+IPI, noting that there is currently no prospective data for any TKIs in this setting, only retrospective studies.

Consumer comments

- 6.4 The Medical Oncology Group of Australia (MOGA) expressed its support for the cabozantinib submission, on the basis of the PFS benefit shown in the CABOSUN trial, noting MOGA considered it a high priority for PBS listing. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for cabozantinib, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)^[4], based on a comparison with sunitinib. MOGA noted that the score was not upgraded to 4 since CABOSUN was a randomised phase 2 study, in which the Quality of Life (QoL) benefit seen was based on a post-hoc analysis.
- 6.5 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.6 The submission was based on a Phase II, head-to-head, randomised, open-label trial comparing cabozantinib to sunitinib (CABOSUN), in previously untreated patients with advanced or metastatic clear cell variant RCC, with IDMC intermediate to poor risk disease (n = 157).

⁴ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017

- 6.7 To construct the indirect treatment comparison (ITC) against NIVO+IPI, the submission identified one trial, CheckMate214 (N=1,096) which is a Phase 3, randomised, open-label, active-controlled trial of patients with previously untreated Stage IV clear cell variant RCC. A subset of the population who had poor or intermediate risk in the trial (n=847) was used for the ITC.
- 6.8 Details of the trials presented in the submission are provided in Table 5.

Table 5: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
<p>CABOSUN (NCT01835158 (A031203/CABOSUN)</p>	<p>Clinical study report (CSR).</p> <p>Choueiri, T. K., Halabi, S., Sanford, B. et al. 2016. "PR CABOZantinib versus SUNitinib (CABOSUN) as initial targeted therapy for patients with metastatic renal cell carcinoma (mRCC) of poor and intermediate risk groups: results from ALLIANCE A031203/CABOSUN trial."</p> <p>Choueiri TK, Halabi S, Sanford BL et al. 2017. "Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203/CABOSUN CABOSUN Trial</p> <p>Choueiri, T. K., Hessel, C., Halabi, S. et al. 2018. "Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203/CABOSUN CABOSUN randomised trial): progression-free survival by independent review and overall survival update."</p>	<p>31 July 2017</p> <p>Annals of oncology. Conference: 41st European Society for Medical Oncology Congress, ESMO 2016. Denmark. 27 (no pagination)</p> <p>J Clin Oncol 35 (6): 591-597</p> <p>European J Cancer 94:115-125.</p>
<p>CheckMate214 (NCT02231749)</p>	<p>Motzer RJ, Tannir NM, McDermott DF et al. 2018. "Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma."</p> <p>Hammers, H., Sternberg, C., McDermott, D. F. et al. 2014. "A phase 3, randomised, open label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in patients with previously untreated metastatic renal cell carcinoma."</p> <p>Hammers, H. J., Plimack, E. R., Sternberg, C. et al. 2015. "CheckMate 214: A phase III, randomised, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in patients with previously untreated metastatic renal cell carcinoma."</p> <p>Rexer, H. 2015. "[Therapy of untreated local advanced or metastatic renal cell carcinoma. Phase III, randomised, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in patients with previously untreated, local advanced or metastatic renal cell carcinoma (CheckMate 214 - AN 36/15 of the AUO)]."</p> <p>Therapie des unbehandelten lokal fortgeschrittenen oder metastasierten Nierenzellkarzinoms. Randomisierte offene Phase-III-Studie von Nivolumab kombiniert mit Ipilimumab- vs. Sunitinib-Monotherapie bei Patienten mit unbehandeltem, lokal fortgeschrittenem oder metastasiertem Nierenzellkarzinom</p>	<p>N Engl J Med 378 (14):1277-1290</p> <p>BJU International 114 (SUPPL. 4):9</p> <p>Journal of Clinical Oncology 33 (15 SUPPL. 1).</p> <p>CheckMate 214 - AN 36/15 of the AUO)"</p> <p>CheckMate 214 - AN36/15 der AUO). 54 (10):1443-5</p>

Source: Table 2.2, p.44-45 of the submission.

6.9 The key features of the randomised trials CABOSUN and CheckMate214 are summarised in Table 6.

Table 6: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Cabozantinib vs sunitinib						
CABOSUN	157	R, OL 25 months	High risk for performance bias; up-to moderate for remaining criteria.	Previously untreated patients with advanced or metastatic clear cell RCC, having intermediate to poor risk classification by IDMC criteria	PFS, OS, ORR, AEs	PFS, OS, AEs
NIVO+IPI vs sunitinib						
CheckMate214	1,096	R, OL, MC 25.2 months	High risk for performance bias; up-to moderate for remaining criteria.	Previously untreated Stage IV clear cell variant RCC who have intermediate to poor prognostic risk	PFS, OS, ORR, AEs, EQ-5D	Not used

Abbreviations: AEs = adverse events; EQ-5D = EuroQol five-dimensions; MC = multi-centre; NIVO+IPI = nivolumab + ipilimumab; OL= open label; ORR = objective response rate; OS = overall survival; PFS = progression free survival; R = randomised.

Source: compiled during the evaluation based on Sections 2.3 and 2.4 of the submission.

- 6.10 CABOSUN enrolled a relatively small number of patients. The trial was open label, and the evaluation of the primary endpoint (PFS) using RECIST v1.1 criteria was undertaken by the investigators, with subsequent retrospective review by an Independent Radiographical Committee (IRC). The PFS results assessed by the IRC were more favourable to cabozantinib than by the (Alliance) investigator assessment.
- 6.11 Analyses of PFS were performed based on two different sets of censoring rules: “Alliance” (the original study investigators) rules and FDA-recommended rules (applied retrospectively, using IRC). The application of the FDA-recommended censoring rules for PFS reduced the number of events available for analysis, and so an additional 5 months of follow-up data were used (data-cut of 15 September versus 11 April 2016). However, even with the extended data-cut, the assessment of PFS using the FDA-recommended censoring rules (and IRC assessment) was based on a smaller number of events (n=92; 59%) compared to the Alliance analysis using investigator assessment of PFS (n=123; 78%).
- 6.12 There was also an imbalance of missing data for PFS assessment between cabozantinib and sunitinib. Based on FDA censoring rules, there were 8 (11%) instances of missing data for sunitinib (due to no baseline and post-baseline ATAs (adequate tumour assessments), or no post-baseline ATAs) compared to only 1 (1%) for cabozantinib. The date of randomisation was assigned as the date of outcome for these missing data. There were 5 (6%) instances of missing data from patients who had ≥ 2 missed ATAs prior to events. These missing data occurred only in cabozantinib. The date of outcome was assigned as the date of their most recent ATA prior to the missing/inadequate assessments for these missing data. The balance of censoring would thus appear to favour cabozantinib for assessment of PFS. However, the submission did not report the number of progression events in each arm according to

the (Alliance) investigator definition of events. Therefore, it is not possible to assess how the investigator definition may have impacted on the assessment of PFS relative to the use of the FDA definition. The Pre-Sub-Committee (PSCR) stated that sensitivity analyses were conducted on IRC-assessed PFS to evaluate the impact of potentially informative censoring. The results (p7) showed that the application of the FDA censoring rules likely favoured cabozantinib but had limited impact on the HR for PFS (varied from 0.48 (95% CI: 0.31, 0.74) to 0.53 (95% CI: 0.35, 0.81) using the most conservative censoring).

- 6.13 Within CheckMate214, more patients received subsequent systemic therapies following sunitinib than NIVO+IPI (54% versus 39%). The PBAC previously suggested that this difference may arise because clinicians may persist with a period of observation off all treatment to determine if a patient responds or continues to respond to NIVO+IPI, while in patients treated with sunitinib clinicians are more likely to start a new treatment immediately after cessation of sunitinib (6.14 nivolumab plus ipilimumab PSD July 2018).
- 6.14 In CABOSUN, the proportion of patients receiving any systemic non-radiation anti-cancer therapy following cabozantinib and sunitinib was similar (57% versus 58%). However, there was an imbalance in the patients receiving everolimus (8% and 19% in the cabozantinib and sunitinib arms, respectively) and bevacizumab (0% and 6%) across the arms. Although treatment beyond progression was expressly prohibited in CABOSUN, 13% of patients in the sunitinib arm continued treatment after progression compared to 1% in the cabozantinib arm.

Comparative effectiveness

6.15 The results for PFS from both CABOSUN and CheckMate214 are presented in Table 7. Cabozantinib was associated with a statistically significant increase in PFS compared with sunitinib for both the investigator and IRC assessment. The ESC and PBAC noted that there was a substantial difference between the IRC and investigator assessed PFS results.

Table 7: Results of progression-free survival across trials

	Intervention		Sunitinib		Difference in median, mths	p value ^a	HR (95% CI)
	n/N with event (%)	Median mths (95% CI)	n/N with event (%)	Median mths (95% CI)			
CABOSUN (IRC assessed-September 2016 data-cut-off, FDA censoring rules)	43/79 (54)	8.6 (6.8, 14.0)	49/78 (63)	5.3 (3.0, 8.2)	3.3	0.0008	0.48 (0.31, 0.74)
CABOSUN (investigator assessed-April 2016 data cut-off, Alliance censoring rules)	NR ^b	8.2 (6.2, 8.8)	NR ^b	5.6 (3.4, 8.1)	2.6	0.012	0.66 (0.46, 0.95)
CheckMate214	NR	11.6 (8.7, 15.5)	NR	8.4 (7.0, 10.8)	3.2	0.03 ^c	0.82 (0.64, 1.05) ^d

Abbreviations: CI= confidence interval; HR= hazard ratio; IRC = Independent Radiographical Committee; mths = months; n = number of participants with event; N = total participants in group; NR = not reported; PFS = progression free survival;

Sources: Table 2.11, p.92; Table 2.12, p.93; and Table 2.28, p.114 of the submission.

Notes: ^a Log-rank p-value (stratified)

^b Total PFS events were 123. There is an explanation in the CSR as to why events were not available per treatment group – the study was conducted by a National Cancer Institute Alliance and the CSR states that “Exelixis did not participate in the conduct of the trial and did not have access to study data until after the top-line analyses of the study primary endpoint were performed by the Alliance in May of 2016.”

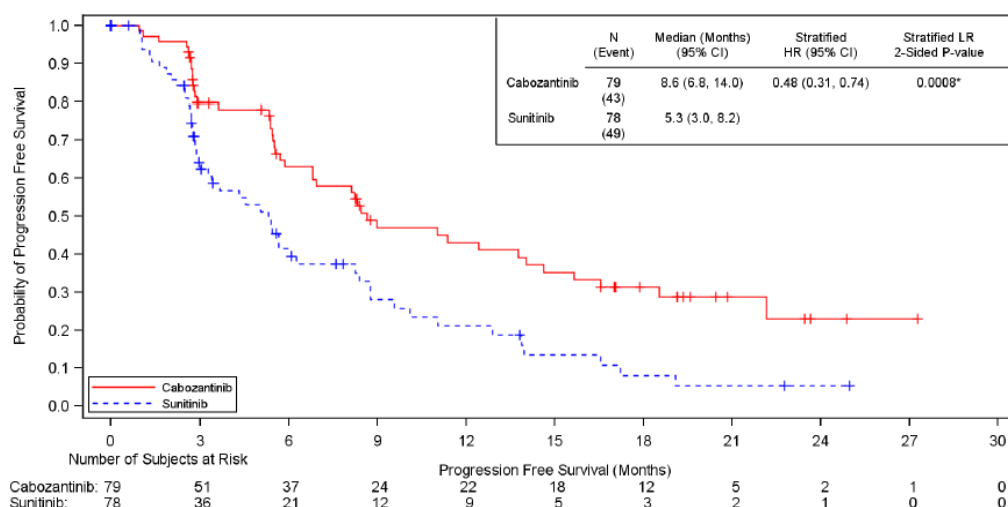
^c The between-group difference did not meet the prespecified threshold (P = 0.009) for statistical significance.

^d 99.1% CI

Statistical differences noted in bold.

6.16 The IRC assessed PFS was used, rather than the investigator assessed outcomes, in the economic evaluation. These data indicated a PFS advantage for cabozantinib with a HR of 0.48 (95% CI: 0.31, 0.74) which had a point estimate that was lower than the results from the investigator assessment at 0.66 (95% CI: 0.46, 0.95). The KM plot of PFS in CABOSUN based on the IRC assessment is shown in Figure 1. The KM plot of PFS based on the investigator assessment was not available.

Figure 1: KM plot of PFS in CABOSUN (IRC-determined/FDA-recommended censoring rules; ITT population)



Source: Figure 2-14, p.94 of the submission.

6.17 In CABOSUN, the treatment effect for cabozantinib compared with sunitinib was not statistically significant in terms of OS for either the earlier data cut-off of September 2016 (HR=0.74; 95% CI: 0.47, 1.14) or the more recent data cut-off of July 2017 (HR=0.80; 95% CI: 0.53, 1.21), as outlined in Table 8.

6.18 For the comparison of cabozantinib versus sunitinib, the ESC noted that the hazard ratio for overall survival was not statistically significant and the difference in OS compared with sunitinib appeared to be decreasing with additional follow-up. The ESC considered that the data did not support a difference in OS between cabozantinib and sunitinib.

Table 8: Results of overall survival across trials

	Intervention		Sunitinib		Difference in median, mths	p value ^a	HR (95% CI)
	n with event (%)	Median mths (95% CI)	n with event (%)	Median mths (95% CI)			
CABOSUN (September 2016 cut-off)	38 (48)	30.3 (14.6, NE)	45 (58)	21.0 (16.3, 27.0)	9.3	0.1700	0.74 (0.47, 1.14)
CABOSUN (July 2017 cut-off)	43 (54)	26.6 (14.6, NE)	47 (60)	21.2 (16.3, 27.4)	5.4	0.29	0.80 (0.53, 1.21)
CheckMate214	140 (32.9)	NR (28.2, NE)	188 (44.5)	26.0 (22.1, NE)	NE	<0.001	0.63 (0.44, 0.89)^b

Abbreviations: CI= confidence interval; HR= hazard ratio; n = number of participants with event; N = total participants in group; NE = not estimable; PFS = progression free survival;

Sources: Table 2.20, p.103; Figure 2.16, p.104 & p 103; and Table 2.29, p.115 of the submission.

^a Log-rank p-value (stratified)

^b 99.8% CI

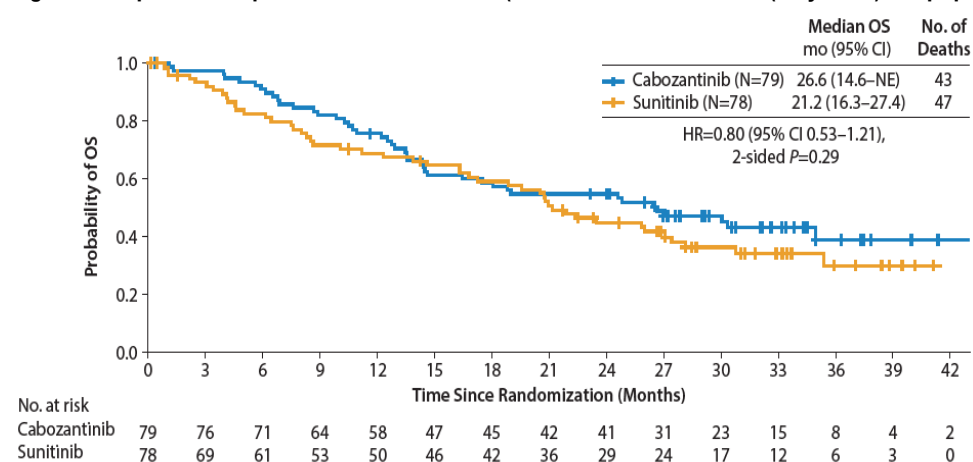
Statistical differences noted in bold.

6.19 The OS outcome from the September 2016 data cut-off for CABOSUN was used in both the clinical and economic sections of the submission (being slightly numerically better than the results from the July 2017 cut-off). The KM plots of OS in CABOSUN from both data-cuts are shown in Figures 2 and 3. The use of September 2016 data cut-off was

not justified and was inconsistent with the use of PFS outcomes that were derived from the most recent data cut-off.

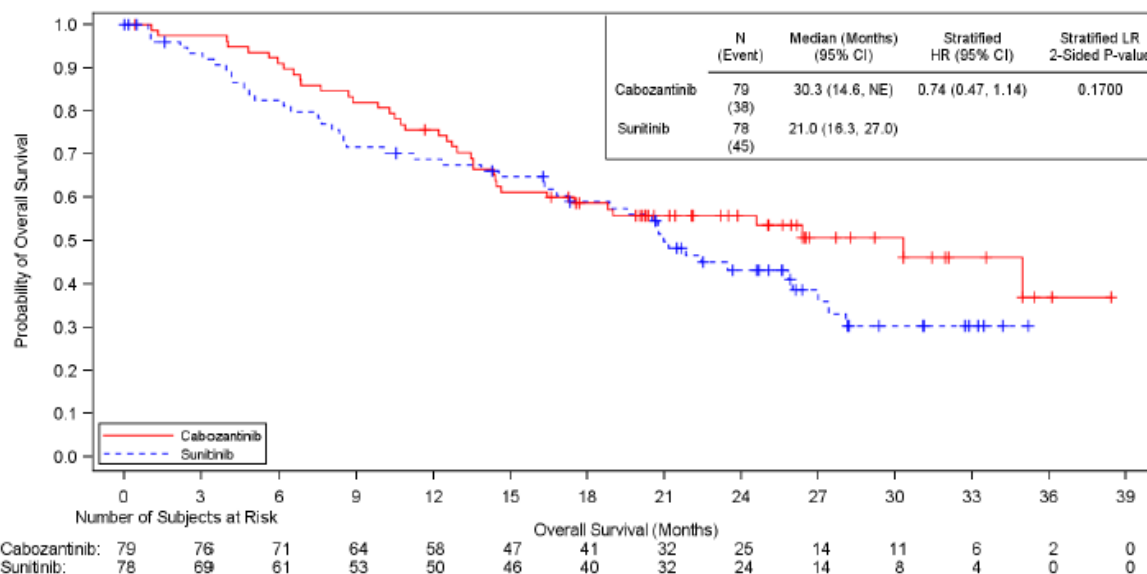
- 6.20 The OS results could be confounded from subsequent anticancer treatments utilised by a high proportion of patients in both groups, together with the imbalance in types of treatments received in the respective study groups within CABOSUN. The direction of bias is uncertain given the lack of details provided on outcomes following subsequent treatments.

Figure 2: Kaplan-Meier plot of OS in CABOSUN (more recent data cut-off (July 2017)/ITT population)



Source: Figure 2-16, p.104 of the submission.

Figure 3: Kaplan-Meier plot of OS in CABOSUN (late data cut-off (September 2016)/ITT population) – used in economic model



Source: Figure 4, p.101 of the CSR.

- 6.21 Both CABOSUN and CheckMate214 reported higher ORR for their investigational therapies compared with sunitinib with differences of 11.3% for cabozantinib (95% CI: 0.4, 22.2; stratified 2-sided p-value = 0.0406) and 15% for NIVO+IPI (CI not reported), respectively.

- 6.22 The PBAC noted that no QoL data were collected in the CABOSUN trial. The PBAC noted a quality-adjusted time without symptoms of disease or toxicity of treatment (Q-TWiST) analysis was presented in the submission. This was a post-hoc analysis based on time without grade 3-4 AEs or progression. However, the PBAC considered that these data were not informative as it was a post-hoc analysis of time without grade 3-4 AEs or progression, which failed to incorporate data regarding the presence or absence of symptoms of disease.

Indirect treatment comparison

- 6.23 For the ITC, the evaluation and the ESC considered that the transitivity assumption may not hold due to differences in the patient populations and treatment practices. CABOSUN included patients with ECOG performance status (PS) of 0-2; 20 (13%) patients in CABOSUN had an ECOG score of 2. In contrast, CheckMate214 included only patients with a Karnofsky PS of at least 70%, equating to 0-1 on the ECOG scale. Thus, it is likely that patients in CABOSUN had a poorer performance status which might bias against cabozantinib. The PSCR noted that the median PFS in the sunitinib arm of CABOSUN was consistent with median PFS reported in a real world setting for patients with intermediate to poor prognosis (5.6 months, Ko JJ, 2014). There were differences in treatment duration for sunitinib (median of 3.1 months for CABOSUN compared with 6.4 months in CheckMate214, albeit including the favourable risk group in the latter), and subsequent treatments after disease progression. It is unknown if the shorter duration of therapy biased against cabozantinib, or reflected the poorer performance status of patients in the CABOSUN study.
- 6.24 In addition, comparison of the primary outcomes (RECIST-assessed PFS) was confounded in that the use of that outcome is considered to be biased against immunotherapies. In its consideration of the previous submission for cabozantinib (in the post-TKI treatment setting), the PBAC considered that “As tumour responses to immunotherapies can occur after conventional RECIST-defined progressive disease (i.e. the tumour flare effect), RECIST-defined PFS is not a reliable measure of the clinical effectiveness of nivolumab” (Paragraph 6.12, Cabozantinib PSD December 2017). Thus, a comparison of primary outcomes based on RECIST defined PFS would bias against NIVO+IPI. The ESC agreed with the evaluator that the indirect comparison based on PFS was biased in favour of cabozantinib due to the potential tumour flare effect for NIVO+IPI and the ESC considered that OS is a more meaningful outcome for the comparison of cabozantinib with NIVO+IPI.
- 6.25 The results of the ITC between cabozantinib and NIVO+IPI are summarised in Table 9. These results showed a statistically significant treatment effect for cabozantinib compared with NIVO+IPI for PFS, but it was not statistically significant for OS. The results with respect to PFS are not meaningful given: the uncertainty within CABOSUN; that PFS may not be an accurate measure of benefit for NIVO+IPI; and the issues of transitivity between CABOSUN and CheckMate214. The transitivity concerns are highlighted by the differences in median PFS between the sunitinib arms of the two studies (i.e. the median PFS with sunitinib was 5.3 months in CABOSUN but 8.4 months in CheckMate214). There was insufficient evidence to conclude that there was a

statistically significant difference between cabozantinib and NIVO+IPI in ORR. The PSCR stated that the “key issues of transitivity in the ITC largely are due to subtle differences in the comparability of the patient populations and treatment practices” and that some of the differences might bias against cabozantinib. Overall, the PSCR contended that despite differences in the patient populations, the comparison remains informative as to the likely comparative clinical effect. The ESC agreed with the evaluator that the indirect comparison was difficult to interpret due to transitivity issues between the trials. The ESC noted that it appeared that OS for cabozantinib may be inferior to NIVO+IPI and considered that this would be consistent with the results of trials of immunotherapies compared with other tyrosine kinase inhibitors (TKIs) that have found superior OS with immunotherapies versus TKIs.

Table 9: Results of the indirect comparison for PFS, OS, and ORR

PFS		Proposed medicine n/N (%)	Common reference n/N (%)	Absolute difference	HR (95% CI)	
CABOSUN	Progressed	43 (54)	49 (63)		-	
	Median months PFS	8.6 (6.8, 14.0)	5.3 (3.0, 8.2)	3.3	0.48 (0.31, 0.74) P=0.0008	
CheckMate214	Progressed	NR	NR	NE	-	
	Median months PFS	11.6 (8.7, 15.5)	8.4 (7.0, 10.8)	3.2	0.82* (0.64, 1.05) P=0.03**	
Indirect estimate of relative treatment effect					0.585 (0.355, 0.966)	
OS		Proposed medicine n/N (%)	Common reference n/N (%)	Absolute difference	HR (95% CI)	
CABOSUN	Death	38/79 (48.1)	45/78 (57.7)		-	
	Median months OS	30.3 (14.6, NE)	21.0 (16.3, 27.0)	9.3	0.74 (0.47, 1.14) P=0.17	
CheckMate214	Death	140/425 (32.9)	188/422 (44.6)		-	
	Median months OS	NR (28.2, NE)	26.0 (22.1, NE)	NE	0.63 (0.44–0.89)*** P<0.001	
Indirect estimate of relative treatment effect					1.13 (0.80, 1.56)	
ORR		Proposed medicine n/N (%)	Common reference n/N (%)	Absolute difference	OR (95% CI)	RR (95% CI)
CABOSUN		16/79 (20.0)	7/78 (9.0)	11%	2.5760 (0.9955, 6.6658)	2.2568 (0.9828, 5.1821)
CheckMate214		177/425 (42.0)	112/422 (27.0)	15%	1.9754 (1.4787, 2.6391)	1.5692 (1.2917, 1.9063)
Indirect estimate of relative treatment effect					1.304 (0.483, 3.523)	1.438 (0.612, 3.377)

Abbreviations: CI= confidence interval; HR= hazard ratio; n = number of participants with event; N = total participants in group; NE = not estimable; NR = not reported; PFS = progression free survival; OR = odd ratio; ORR = objective response rate; OS = overall survival; RR = relative risk

Source: Table 2.43, p.145; Table 2.44, p.146; Table 2.45, p.146 of the submission; and developed for the Commentary

Notes: * 99.1% CI for CheckMate214

** The between-group difference did not meet the prespecified threshold (P = 0.009) for statistical significance.

*** 99.8% CI for CheckMate214

Statistical differences noted in bold.

6.26 There are unlikely to be sufficient differences between CABOSUN and the Australian treatment setting that would result in a difference in the treatment effect. The trial included several medicines for post-progression treatment that are not available for RCC on the PBS. The direction of the potential bias is unclear. The ESC considered that, in general, the clinical trial data are applicable to the proposed PBS population, however the subsequent treatments used in CABOSUN do not necessarily reflect those likely to be used in practice. The ESC considered that patients treated with a TKI in first line treatment of RCC are likely to be treated with immunotherapy on progression.

Comparative harms

- 6.27 A summary of the key adverse events reported in CABOSUN is provided in Table 10. The occurrence of overall adverse events (AEs) was similar in the cabozantinib arm compared to sunitinib. AEs of potential clinical importance were diarrhoea, hypertension and hypothyroidism (higher in cabozantinib), and decreased neutrophil count (higher in sunitinib), although all occurrences of these AEs were Grade 1-2. The ESC considered that decreased neutrophil counts, in the absence of febrile neutropenia, were unlikely to have a significant clinical impact on patients.

Table 10: Summary of key adverse events in CABOSUN

n (%)	Cabozantinib n (%) N=78	Sunitinib n (%) N=72	RD (95% CI)
Any AEs	75 (96)	71 (99)	-0.02 (-0.08, 0.03)
Grade 3-4	53 (68)	47 (65)	0.03 (-0.12, 0.18)
SAEs	38 (49)	37 (51)	-0.02 (-0.19, 0.13)
Discontinuation due to AEs/Complications	16 (21)	16 (22)	-0.02 (-0.15, 0.11)
Any grade			
Solicited AEs			
Diarrhoea	57 (73)	39 (54)	0.19 (0.04, 0.34)
Hypertension	52 (67)	32 (44)	0.22 (0.06, 0.38)
Reduced neutrophil count	12 (15)	25 (35)	-0.19 (-0.33, -0.06)
Unsolicited AEs reported in >15% patients in either treatment arm			
Hypothyroidism	18 (23)	4 (5.6)	0.18 (0.06, 0.29)

Abbreviations: AEs = adverse events; CI = confidence interval; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk; SAEs = serious adverse events

Source: Compiled during the evaluation based on Table 2.34, p.124; Table 2.36, p.126; Table 2.37, p.128-129 of the submission.

Note: Statistical differences noted in bold. The evaluators estimated risk difference (RD and 95% CI) for each types of AEs. AEs that were considered 'expected' per the protocol and presence/ absence and severity were referred as solicited while other AEs were collected as unsolicited events (the CSR p.9).

- 6.28 A summary for safety between cabozantinib and NIVO+IPI was based on a naïve comparison of the evidence. There was no difference in terms of the number of patients with at least one AE between cabozantinib and NIVO+IPI. Of all AEs identified from the trials, 11 specific types of AEs were reported (Table 11), among which the incidence of 10 (except for hypothyroidism) was higher with cabozantinib than NIVO+IPI.

Table 11: Summary of key adverse events between CABOSUN and CheckMate214

AEs	CABOSUN		CheckMate214	
	Cabozantinib	Sunitinib	NIVO+IPI	Sunitinib
	N=78	N=72	N=547	N=535
Any AE	75 (96)	71 (99)	509 (93)	521 (97)
Grade 3-4 AEs	53 (68)	47 (65)	357 (65)	407 (76)
Diarrhoea	57 (73)	39 (54)	145 (27)	278 (52)
Hypertension	52 (67)	32 (44)	12 (2)	216 (40)
Fatigue	50 (64)	49 (68)	202 (37)	264 (49)
Palmar-Plantar erythrodysesthesia	33 (42)	23 (32)	5 (<1)	231 (43)
Dysgeusia	32 (41)	21 (29)	31 (6)	179 (33)
Stomatitis	29 (37)	21 (29)	23 (4)	149 (28)
Nausea	24 (31)	26 (36)	109 (20)	202 (38)
Anaemia	23 (29)	32 (44)	34 (6)	83 (16)
Dyspepsia	18 (23)	12 (17)	15 (3)	96 (18)
Vomiting	18 (23)	16 (22)	59 (11)	110 (21)
Hypothyroidism	17 (22)	4 (5.6)	85 (16)	134 (25)

Abbreviations: AE = adverse event; CI = confidence interval; N = total participants in group; NIVO+IPI = nivolumab + ipilimumab
Source: Tables 2.46 p.147, 2.36 p.126 of the submission, Table 6 NIVO+IPI Public Summary Document, July 2018.

Benefits/harms

6.29 A summary of the comparative benefits and harms for cabozantinib versus sunitinib is presented in Table 12.

Table 12: Summary of comparative benefits and harms for cabozantinib versus sunitinib

Benefits					
Progression free survival (median duration of follow up 25 months)					
Event	Cabozantinib	Sunitinib	Absolute Difference		HR (95% CI)
Progressed, n (%)	40/79 (54)	43/78 (63)			0.48 (0.31, 0.74) P=0.0008
% not progressed at 12 months (95% CI)	43.1 (NR)	21.1 (NR)	22.0		
% not progressed at 18 months (95% CI)	31.4 (NR)	8.0 (NR)	23.4		
Overall survival (median duration of follow up 28.9 months)					
Deaths, n (%)	38 (48)	45 (58)			0.74 (0.47, 1.14) P=0.17
% Alive at 12 months (95% CI)	75.6 (NR)	68.9 (NR)	6.7		
% Alive at 24 months (95% CI)	55.8 (NR)	43.3 (NR)	12.5		
Harms (median duration of follow up 25 months)					
Potentially clinically relevant adverse events (any grade)	Cabozantinib (N=78)	Sunitinib (N=72)	Events/100 patients		RD % (95% CI)
			Cabozantinib	Sunitinib	
Diarrhoea	57	39	73	54	0.19 (0.04, 0.34)
Hypertension	52	32	67	44	0.22 (0.06, 0.38)
Hypothyroidism	18	4	23	5.6	0.18 (0.06, 0.29)
Neutrophil count decreased	12	25	15	35	-0.19 (-0.33, -0.06)

Abbreviations: n=number; CI, confidence interval; NR=not reported; RD = risk difference; RR = risk ratio

Source: Compiled during the evaluation using Table 2.12, p.93; Table 2.20, p.103; Table 2.34, p.124; Table 2.37, p.128-129.

Note: Statistical differences noted in bold. Progression was defined by IRC assessment.

- 6.30 On the basis of the direct evidence presented by the submission, for every 100 patients treated with cabozantinib in comparison with sunitinib:
- Approximately 22 additional patients will be progression-free at 12 months.
 - Approximately 19 additional patients will experience diarrhoea.
 - Approximately 22 additional patients will experience hypertension (high blood pressure).
 - Approximately 18 additional patients will experience hypothyroidism (an underactive thyroid gland).
 - Approximately 19 fewer patients will experience a decreased neutrophil count (low white blood cell count).

Clinical claim

Cabozantinib versus sunitinib

- 6.31 The submission described cabozantinib as superior in PFS and ORR, with a trend towards improved OS, and different but broadly comparable safety relative to sunitinib. The evaluation considered that the claim for the PFS and ORR treatment effects presented in the submission was adequately supported by the evidence presented. However, the magnitude of the PFS gain remains uncertain given the small number of patients enrolled in the trial, the high number of unevaluable events and issues of potential bias. The claim for OS was not supported. There was no statistically significant difference with respect to OS, potentially due to being underpowered for this endpoint and differences in subsequent treatments between study arms. The ESC considered that there was reasonable evidence of an improvement in PFS and ORR compared with sunitinib, though the magnitude of improvement was uncertain given the small number of patients enrolled in the trial (CABOSUN), and potential biases in the censoring of events for PFS. The ESC considered that a difference in OS was not supported by the evidence presented. The ESC noted that additional data cuts indicated that the difference in OS appeared to be decreasing with additional follow-up and considered that the data did not support a difference in OS between cabozantinib and sunitinib. The ESC considered that given the uncertain magnitude of PFS benefit for cabozantinib over sunitinib and the lack of OS benefit, a cost-minimisation analysis versus sunitinib and pazopanib may be a more appropriate approach. The Pre-PBAC response argued that this would not be an appropriate approach because there was a statistically significant PFS benefit for cabozantinib in the CABOSUN trial and QoL advantage demonstrated in the QTWiST analysis.
- 6.32 The evaluation considered that the claim of different but broadly comparable safety might be justifiable but is uncertain based on the small number of patients. The ESC noted that there were slight differences in the types of adverse events experienced with cabozantinib and sunitinib but considered that overall their safety profiles, and rates of adverse events, appear to be broadly similar.

- 6.33 The PBAC considered that the claim of superior PFS was supported, however the magnitude of the PFS benefit was uncertain and likely overestimated in the trial data presented. The PBAC considered that the claim for a trend towards improved OS was not supported by the evidence presented.
- 6.34 The PBAC considered that the claim of non-inferior comparative safety to sunitinib appeared reasonable, though the data were limited due to the small number of patients enrolled in the trial.

Cabozantinib versus NIVO+IPI

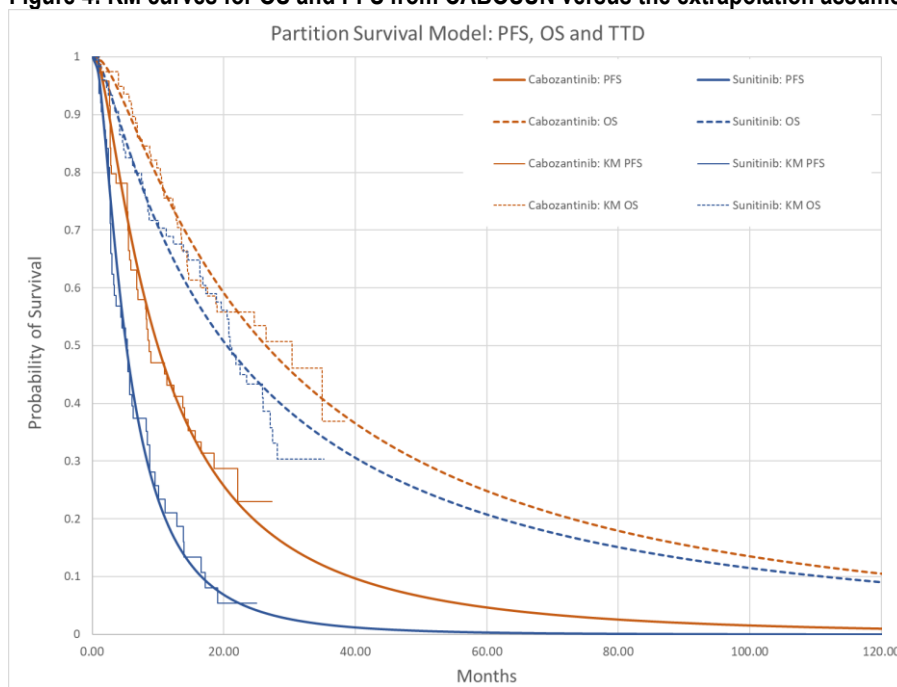
- 6.35 The submission described cabozantinib as superior in PFS, and non-inferior in ORR and OS compared to NIVO+IPI, with a potentially more tolerable safety profile. The evaluation considered that this claim was not adequately supported by the evidence presented. The evidence from the ITC indicated a superior PFS treatment effect for cabozantinib compared with NIVO+IPI. Notably, PFS may not be an appropriate assessment of benefit for immunotherapies (due to pseudo-progression), favouring cabozantinib in the comparison with NIVO+IPI. Moreover, there were transitivity issues between the studies as evidenced by the difference in magnitude of the results for the common reference, sunitinib. The ESC considered that the comparison with NIVO+IPI was not informative given the transitivity issues between trials and because RECIST-assessed PFS is not an appropriate outcome for comparisons with NIVO+IPI.
- 6.36 The evaluation and ESC considered that the claim that cabozantinib has a more tolerable safety profile than NIVO+IPI was not supported by the evidence. The ESC noted that immunotherapy is associated with severe toxicity in a proportion of patients whereas TKIs tend to be associated with less severe events but these events are experienced by nearly all patients.
- 6.37 The PBAC considered that the claim of superior comparative effectiveness in terms of PFS and the claim of non-inferior comparative effectiveness in terms of ORR and OS compared with NIVO+IPI were not adequately supported by the data.
- 6.38 The PBAC considered that the claim of superior safety compared to NIVO+IPI was not adequately supported by the data.

Economic analysis

- 6.39 The submission presented a CUA comparing cabozantinib with sunitinib, as outlined in Table 13. The ESC considered that given the uncertain magnitude of PFS benefit for cabozantinib over sunitinib and the lack of OS benefit, a cost-minimisation analysis versus sunitinib and pazopanib may be a more appropriate approach.
- 6.40 Extrapolation of outcomes was based on a small number of patients with limited follow-up time (within CABOSUN), leading to uncertain estimates. Extrapolation functions were applied independently for cabozantinib and sunitinib; this was not supported by some of the tests of proportional hazards (PH) provided by the submission (e.g. empirical tests suggested that PH held for PFS, OS and TTD, however, the results between Schoenfeld residuals test and log-log plots were inconsistent).

6.41 The chosen parametric distributions used to extrapolate the outcomes were not sufficiently justified. The choice of distribution was based on AIC and BIC criteria. It is unclear from the submission whether clinical plausibility was used to justify the appropriateness of different distributions. In particular, the choice of distribution for OS was uncertain; the choice of log-normal distribution was likely to provide an overly optimistic result for OS (i.e. potentially underestimate mortality rate). Moreover, the model applied extrapolated data for the entirety of the time-horizon (10 years), did not include the directly observed KM data and assumed an ongoing treatment effect. A shorter time horizon and/or applying convergence for OS would have been more appropriate. The ESC also noted that the modelled OS did not reliably reflect the Kaplan-Meier OS curve from the CABOSUN trial (per the figure below).

Figure 4: KM curves for OS and PFS from CABOSUN versus the extrapolation assumed in the model



Source: '3A. Control panel' worksheet, 'Attachment 7 – Section 3 – Economic model.xls'

6.42 The ESC noted that the utilities used in the model were taken from a study that appeared to have a healthier population than the likely PBS population as it included a significant proportion of patients with favourable risk and recruited only patients with ECOG status 0 or 1 (Motzer, 2007). The ESC considered that the utility values appear to be higher than would be expected for this population.

Table 13: Key components of the economic evaluation

Component	Description
Type(s) of analysis	Cost-utility analysis.
Outcomes	Cost per quality adjusted life years gained and cost per life year gained.
Time horizon	10 years
Method(s) used to generate results	Partitioned survival model.
Health states	Stable disease, progressive disease, death.
Cycle length	Four weeks (28 days), half cycle corrected.
Health state movements	Based on survival curves for PFS and OS from the CABOSUN trial (individual patient data). Time to treatment discontinuation estimates applied for a costing-based scenario analysis.
Quality of life	Based on estimates from the literatures: Utility values of progression free of 0.77 and post-progression of 0.72 from 'Sunitinib NICE STA'; and disutility value of -0.04 from 'METEOR study'.
Resource utilisation	Based on the available literature, review of published economic models.
Post-progression disease costs	Subsequent therapies, based on subsequent therapies as reported in the CABOSUN trial. These may not reflect the therapies available in the second-line setting for RCC.
Software	Microsoft Excel 2010

Abbreviations: PFS = progression-free survival; OS = overall survival; STA = single technology appraisal

Source: Table 3.2, p. 159 of the submission

6.43 A summary of the model results is presented in Table 14, with the key drivers summarised in Table 15. The estimates in Table 14 are based on the cabozantinib effective prices and the submission's assumed effective prices for sunitinib and nivolumab.

Table 14: Results of the economic evaluation (assumed effective prices – as per submission) ^a

	Cabozantinib	Sunitinib	Incremental
Life Years			0.37
QALYs			0.30
Pre-progression drug costs	\$	\$	\$
Post-progression drug costs	\$	\$	-\$
Other costs	\$	\$	\$
Total Costs	\$	\$	\$
ICER (cost per LYG)			\$
ICER (cost per QALY gained)			\$

Abbreviations: ICER= incremental cost effectiveness ratio; LYG = life years gained; QALYs= quality adjusted life years.

Source: Table 3.41, p.217 of the submission.

^a Note: this base case was replicated in the economic model presented in the submission by copying cells C37-C44 of the "3A. Control Panel" worksheet into cells C28-C35 of the same worksheet.

Table 15: Key drivers of the model – as per submission’s estimates

Description	Method/Value	Impact (Base case: \$45,000 - \$75,000/QALY)
Time horizon	10 years	Moderate, favours cabozantinib (\$45,000 - \$75,000/QALY at 7 years)
Treatment effects	Treatment effects for both PFS and OS continued beyond 25 months of trial period for up to 10 years	High, favours cabozantinib (\$45,000 - \$75,000/QALY with convergence between 30 months and 7.5 years)
Second-line treatment	Second-line treatments in the model were assumed to be the same as used in CABOSUN	High, favours of cabozantinib (\$75,000 - \$105,000 PBS medicines only)
Average weight of patients	89.7 kg as in CABOSUN	Moderate, favours of cabozantinib (\$45,000 - \$75,000/QALY at 80 kgs)
Extrapolation	Log-normal was used for PFS and OS in cabozantinib and sunitinib	High – bias depends on functional form (Weibull \$45,000 - \$75,000/QALY, generalised gamma \$15,000 - \$\$=45,000/QALY)

Abbreviations: OS=overall survival; PBS=Pharmaceutical Benefits Scheme; PFS=progression free survival.

Source: compiled during the evaluation

- 6.44 The model was sensitive to the assumption of a difference in the treatment effect over the entire model time-horizon. Assuming an ongoing treatment effect for the 10-year time-horizon was uncertain given that data were only available from CABOSUN for up to a median follow-up of 25 and 28.9 months for PFS and OS respectively. The PSCR noted that a 10 year time horizon was chosen to be consistent with the economic model used to inform the PBAC approval of sunitinib, however the PBAC considered that the estimate of OS over the 10 year time horizon in the sunitinib model was uncertain and noted that a shortened time horizon would make the ICER less favourable (Sunitinib PSD, March 2008 p5). The ESC considered that the use of a 10 year time-horizon in the model magnified the uncertainty around post-progression treatment costs and benefits. The ESC noted that a re-specified analysis with convergence of OS, PFS and TTD beginning at 30 months, with convergence at 7.5 years, resulted in an ICER of \$45,000 - \$75,000/QALY .
- 6.45 The model results were also sensitive to the types of second-line treatments included in the analysis; including only medicines that are PBS listed for second-line treatment for Stage IV RCC increased the ICER to \$75,000 - \$105,000/QALY (44% relative to base-case). The PSCR contested that while not funded by the PBS the treatments excluded in this scenario are available for patients and can be funded by the patient. The ESC considered that, while it was appropriate to include subsequent treatment costs for patients likely to receive subsequent therapies, it was not appropriate for the cost of non-PBS subsidised therapies to be included in the model. (For example, the model included subsequent therapy costs for bevacizumab of \$██████ per cycle, which was significantly higher than the cost assumed for any PBS-subsidised therapies.) Assuming the same cost per cycle of subsequent treatments in both arms and

convergence of the OS, PFS and TTD curves between 30 months and 7.5 years resulted in an ICER of \$105,000 - \$200,000/ QALY. The Pre-PBAC response argued that patients in the sunitinib arm would be eligible for treatment with nivolumab or cabozantinib post-progression, whereas patients in the cabozantinib arm would only be eligible for nivolumab and therefore it was reasonable for post-progression costs to be higher for the sunitinib arm.

- 6.46 The ESC noted that the model was very sensitive to the post-progression costs applied, and the duration over which they were applied. The ESC considered that there was a high degree of uncertainty around the post-progression costs which appear to be over-estimated due to: inclusion of sunitinib use post-progression in 21% of sunitinib patients; inclusion of drugs not listed on the PBS; and the assumption that patients who receive subsequent therapies continue to be treated until death (i.e. patients who received a subsequent therapy in the CABOSUN trial (which were 63% of patients in the cabozantinib arm and 67% in the sunitinib arm) were assumed to continue receiving subsequent therapies for every cycle that they remained in the post-progression health state). This resulted in a high total cost for post-progression therapies (of \$ [REDACTED] and \$ [REDACTED] per patient in the cabozantinib and sunitinib arms, respectively, see Table 14). Costs were higher in the sunitinib arm because patients were in the post-progression health state for longer, and a higher cost per cycle was estimated (largely due to the higher use of non-PBS subsidised therapies such as bevacizumab in the sunitinib arm).
- 6.47 The model was also sensitive to the average weight of patients (ICER = \$45,000 - \$75,000/QALY if 80 kg) as this was relevant to dosing (and therefore cost) for some second line treatments. The pre-PBAC response noted that the weight used in the economic model (89.7kg) was based on the mean weight of patients randomised into the CABOSUN trial.
- 6.48 As outlined in the Public Summary Document for pazopanib from March 2012, pazopanib has a lower effective price than sunitinib. Pazopanib was also a relevant comparator; the ICER/QALY increased when a 50%:50% split of use of sunitinib and pazopanib was used.

Table 16: Key results of sensitivity analyses from the submission

	Base case value	Variation tested	ICER (\$/QALY)	%Change in ICER
Sensitivity analyses presented by submission – assumed effective prices				
			\$ [REDACTED]	Reference
Time horizon	10 years	7 years	\$ [REDACTED]	14%
Parametric functions:				
PFS, OS & TTD: Independent curves	Log-normal	Weibull	\$ [REDACTED]	21%
PFS, OS & TTD: Independent curves	Log-normal	Generalised gamma	\$ [REDACTED]	-28%
PFS, OS & TTD: Joint curves	Independently estimated	Jointly estimated (proportional hazards)	\$ [REDACTED]	20%
OS Difference				
Modelled based on cabozantinib	Ind. curves based on CABOSUN	Cabozantinib OS applied to both groups	Dominant	

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	Base case value	Variation tested	ICER (\$/QALY)	%Change in ICER
Modelled based on sunitinib	Ind. curves based on CABOSUN	Sunitinib OS applied to both groups	\$ [REDACTED]	-29%
Modelled based on Ruis Morales (2016)	Ind. curves based on CABOSUN	Modelled based on Ruis Morales (2016)	\$ [REDACTED]	-81%
Utilities estimates	Sunitinib NICE STA	Health states: Swinburn et al (2010)	\$ [REDACTED]	-30%
	Sunitinib NICE STA	Health states: Hoyle et al (2010)	\$ [REDACTED]	12%
	Sunitinib NICE STA	Health states: Castello et al (2009)	\$ [REDACTED]	-14%
Sensitivity analyses developed or updated by Commentary				
Average weight of patients	89.7 kg	80 kg	\$ [REDACTED]	11%
Additional sensitivity analyses considered by ESC				
Convergence at 7.5 years	No convergence, time horizon 10 years	Convergence of OS, PFS and TTD beginning at 30 months, convergence at 7.5 years, time horizon 7.5 years	\$ [REDACTED]	19%
Subsequent treatment and convergence	No convergence, time horizon 10 years, different costs of subsequent treatment between arms	Same costs of subsequent treatment per cycle between arms ^a AND convergence at 7.5 years as above	\$ [REDACTED]	134%
Revised base case	As above +average weight 89.7 kg	As above + average weight 80 kg	\$ [REDACTED]	136%

Abbreviations: 2L = second line treatment; DPMQ=dispensed price per maximum quantity; ICER= incremental cost effectiveness ratio; PBS=Pharmaceutical Benefits Scheme; PFS = progression free survival; QALY= quality adjusted life years; OS = overall survival; TTD = time to treatment discontinuation.

Source: Compiled during the evaluation.

Note: Results using the jointly estimated Gompertz survival function need to be considered with caution, as there appears to have been an error in the empirical estimation of this function.

^a The cost per cycle of subsequent treatment in the cabozantinib arm was applied in sunitinib arm. Note: the cost per cycle was assumed to be the same, but the total cost of subsequent therapies remained higher in the sunitinib arm as: patients spent longer in the post-progression health state in the sunitinib arm; and a higher proportion of patients were assumed to receive subsequent therapies with sunitinib (67% vs 62% with cabozantinib).

6.49 The ESC noted a multivariate sensitivity analysis using: i) a time horizon of 7.5 years; ii) convergence of OS, PFS and TTD beginning at 30 months, with convergence at 7.5 years iii) average patient weight of 80 kg ; iv) the same costs (per cycle) of subsequent treatment between cabozantinib and sunitinib arms. This analysis increased the ICER to \$105,000 - \$200,000/QALY using the prices applied in the submission. The ESC considered that this respecified analysis provided a more reasonable estimate of the ICER than the base case in the submission and could be considered the respecified base case if the claim of superior comparative effectiveness is accepted.

6.50 The ESC noted that when the OS difference was removed and the cabozantinib survival curve was applied to both arms, the ICER became dominant (more effective and less costly). This was because subsequent therapy costs in the sunitinib arm were significantly increased due to the longer duration of time spent in the post-progression

health state. The ESC considered that if the post-progression costs were applied in a more appropriate way (e.g. include only appropriate, PBS-listed post-progression treatments), the model would likely be sensitive to the assumed difference in OS, despite the CABOSUN trial finding no statistically significant difference in OS.

Cost-minimisation analysis versus NIVO+IPI

- 6.51 The submission presented a CMA comparing cabozantinib with NIVO+IPI. Overall, the ESC and the PBAC considered that differences in the study designs, sample size and analysis methods, the lack of comparability of the primary outcome measures (that RECIST based PFS is less informative in the context of immunotherapies), and the absence of an OS benefit for cabozantinib, mean that the non-inferiority claim was not supported and thus the basis for a CMA was uncertain.
- 6.52 The treatment duration and mean dose used by the submission in the CMA were derived from CABOSUN for cabozantinib (49.4 mg daily) and CheckMate214 for NIVO+IPI. The mean dose for NIVO+IPI used in CheckMate214 was calculated based on the average weight of patients at 89.7 kg derived from CABOSUN (1 mg/kg ipilimumab, 3 mg/kg of nivolumab). The submission's calculation of dose relativities was based on the same OS outcomes observed with median treatment durations of 6.5 months for cabozantinib and 7.9 months for NIVO+IPI (rather than mean treatment duration). The average weight of patients used in the submission might be higher than the average weight of Australian patients. The treatment duration for sunitinib in CABOSUN was relatively short (approximately half that for CheckMate214). These differences introduced biases against NIVO+IPI, which the submission tested in scenario analyses where it doubled the duration of therapy for cabozantinib (to reflect the same duration relativity observed between the sunitinib dose groups in CABOSUN and CheckMate214).

Drug cost/patient/course \$ [REDACTED]

- 6.53 The average time on treatment estimated from the model was 12.6 months for cabozantinib and 6.3 months for sunitinib. Based on the submission's estimates, the drug cost/patient/course for cabozantinib was estimated to be \$ [REDACTED] compared to \$22,169 for sunitinib (using the submission's assumed effective prices).
- 6.54 At a median treatment duration of cabozantinib of 6.5 months and NIVO+IPI of 7.9 months, which are the equi-effective treatment durations proposed by the submission, the submission estimated the total cost of cabozantinib at \$ [REDACTED] and NIVO+IPI at \$128,424 (cost saving by \$ [REDACTED]). These estimates were based on published prices.

Estimated PBS usage & financial implications

- 6.55 This submission was not considered by DUSC. The submission presented the expected financial impact associated with the listing of cabozantinib based on a market share approach. The submission presented two scenarios in which i) cabozantinib will substitute sunitinib and pazopanib; and ii) both cabozantinib and NIVO+IPI will substitute for sunitinib and pazopanib (what the submission termed a 'dual listing'

hereafter referred as ‘simultaneous listing’). Published DPMQ prices used in the estimates were \$5,152.07 for nivolumab (240 mg) and \$12,085.42 for ipilimumab (80 mg).

6.56 The estimated use for cabozantinib as a first-line therapy, including its substitution for sunitinib and pazopanib, is presented in Table 17. The estimates as applied in the situation of the simultaneous listing are presented in Table 18.

Table 17: Estimated use and financial implications (cabozantinib listing only) based on published prices

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated*						
Number of scripts dispensed ^a						
Estimated financial implications of cabozantinib						
Cost to PBS/RPBS	\$41,867,836	\$51,664,169	\$54,247,378	\$56,959,746	\$59,807,734	\$62,798,120
Copayments	-\$69,978	-\$86,352	-\$90,669	-\$95,203	-\$99,963	-\$104,961
Cost to PBS/RPBS less co-payments	\$41,797,858	\$51,577,818	\$54,156,708	\$56,864,544	\$59,707,771	\$62,693,160
Estimated financial implications for sunitinib/pazopanib						
Cost to PBS/RPBS	-\$12,575,654	-\$16,215,807	-\$16,226,922	-\$16,222,598	-\$16,201,745	-\$16,163,210
Co-payments	\$47,573	\$58,174	\$58,214	\$58,198	\$58,124	\$57,985
Cost to PBS/RPBS less co-payments	-\$12,528,081	-\$16,157,633	-\$16,168,708	-\$16,164,400	-\$16,143,622	-\$16,105,224
Net financial implications						
Net cost to PBS/RPBS	\$29,269,778	\$35,420,184	\$37,988,001	\$40,700,144	\$43,564,150	\$46,587,935
Net cost to MBS	\$61,465	\$78,914	\$99,471	\$121,388	\$144,739	\$169,604
Net cost to PBS/RPBS/MBS	\$29,331,243	\$35,499,098	\$38,087,472	\$40,821,532	\$43,708,889	\$46,757,539

Source: Compiled during the evaluation using Table 4.8, p.237; Table 4.12, p.241; Table 4.17, p.244, and attachment 8 worksheet 4b. Displaced-PUB of the submission.

Note: * The evaluators estimated this number by dividing the total number of scripts for cabozantinib per year by the average number of script/patient/year (assumed 12.17 by the submission).

Table 18: Estimated use and financial implications (simultaneous listing) based on published prices

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated*	■	■	■	■	■	■
Number of scripts dispensed*	■	■	■	■	■	■
Estimated financial implications of cabozantinib						
Cost to PBS/RPBS	\$32,419,785	\$34,040,774	\$35,742,813	\$37,529,953	\$39,406,451	\$41,376,774
Co-payments	-\$54,186	-\$56,896	-\$59,741	-\$62,728	-\$65,864	-\$69,157
Cost to PBS/RPBS less copayments	\$32,365,598	\$33,983,878	\$35,683,072	\$37,467,226	\$39,340,587	\$41,307,616
Estimated financial implications for reduced use of sunitinib/pazopanib and new listing of NIVO+IPI**						
Cost to PBS/RPBS	\$22,745,682	\$23,450,100	\$25,422,281	\$27,509,065	\$29,716,501	\$32,050,949
Co-payments	\$42,658	\$47,603	\$52,852	\$58,421	\$64,327	\$70,588
Cost to PBS/RPBS less co-payments	\$22,703,024	\$23,402,497	\$25,369,429	\$27,450,643	\$29,652,174	\$31,980,361
Net financial implications of listing cabozantinib and NIVO+IPI						
Net cost to PBS/RPBS	\$55,068,623	\$57,386,375	\$61,052,501	\$64,917,869	\$68,992,761	\$73,287,977
Net cost to MBS	\$826,246	\$883,843	\$944,647	\$1,008,822	\$1,076,546	\$1,148,001
Net cost to PBS/RPBS/MBS	\$55,894,869	\$58,270,218	\$61,997,148	\$65,926,691	\$70,069,307	\$74,435,978

Source: Compiled during the evaluation using Table 4.9, p.238; Table 4.13, p.242; Table 4.18, p.245 and attachment 8 worksheet 4b. Displaced-PUB of the submission.

Note: * The evaluators estimated this number by dividing the total number of scripts for cabozantinib per year by the average number of script/patient/year (assumed 12.17 by the submission).

** The increased cost (i.e. negative reduction) in this scenario relates to increased utilisation of NIVO+IPI associated with the simultaneous listing. While the submission assumed a reduction in use of sunitinib/pazopanib which would be associated with a cost-saving, the increased cost of NIVO+IPI would result in an overall increase in costs.

- 6.57 The current utilisation of sunitinib and pazopanib reflects use in patients with favourable and intermediate-risk. The utilisation of cabozantinib will overlap with the current use for intermediate-risk patients only. This approach effectively assumed that the current utilisation of sunitinib/pazopanib in favourable-risk patients reflects the potential use of cabozantinib in poor-risk patients. Patients with poor-risk are likely to have a shorter duration of treatment compared to those with favourable-risk. The proportion of patients with intermediate and poor-risk, which was estimated at 87.5% (which will be eligible for the proposed medicine), was also likely to be overestimated relative to what has been reported in the literature. Therefore, it is likely that the utilisation of cabozantinib has been overestimated.
- 6.58 The submission applied 5% market growth for a new intervention and 10% growth due to the superiority of cabozantinib. These were not justified and were likely to overestimate the utilisation.
- 6.59 The submission did not address the potential changes in use of other PBS listed treatments subsequent to the first-line setting (e.g. second and third-line) in RCC patients. This included the impact on current use of cabozantinib in the post-TKI setting that may arise from its use in the first-line setting. Moreover, the submission did not address the potential for increased use of other medicines (in subsequent lines of therapy) that would be affected by availability of a first-line treatment for patients with poor risk.

- 6.60 The submission also assumed that a simultaneous listing may occur for cabozantinib relative to NIVO+IPI, and that in the event of such a listing the two would take market share away from sunitinib and pazopanib. However, NIVO+IPI received a positive recommendation at the November 2018 PBAC meeting (PBAC November 2018 outcomes document) and was listed on 1 March 2019. Further, the clinical evidence (in Section 2) suggest that NIVO+IPI would be more likely to be the preferred new entrant (and hence capture the bulk of the first-line market).
- 6.61 The submission requested flat pricing across the three strengths of cabozantinib. As part of its previous consideration of cabozantinib (in the post-TKI treatment setting), the PBAC considered that patients may receive prescriptions of varying strengths to assist with dose titration, and this may impact the overall cost of cabozantinib to the PBS (Cabozantinib PSD December 2017).

Quality Use of Medicines

- 6.62 No information related to the quality use of medicines was presented in the submission.

Financial Management – Risk Sharing Arrangements

- 6.63 There was no Risk Sharing Arrangement (RSA) proposed in the submission. However, Section 1 of the submission mentioned that “Moreover, a risk-sharing arrangement is also expected to apply, which would limit the risk of both inappropriate prescribing and resulting cost overruns for the health budget.” The Pre-PBAC response requested that any RSA be based on the financial implications model submitted by the sponsor.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of cabozantinib for the first line treatment of stage IV clear cell variant RCC. The PBAC considered that, for the comparison of cabozantinib versus sunitinib, the magnitude of the clinical benefit in terms of PFS was uncertain due to the small sample size and high risk of bias in the clinical trial, and the PBAC noted there was no demonstrated benefit in OS or safety. The PBAC considered that the revised ICER for cabozantinib versus sunitinib, based on the PBAC’s preferred assumptions, was high. The PBAC considered that, for the comparison against NIVO+IPI, cabozantinib may be inferior to NIVO+IPI based on the clinical evidence presented.
- 7.2 The PBAC considered that with the recent PBS listing of NIVO+IPI for the first line treatment of RCC, intermediate to poor risk patients have access to a highly effective immunotherapy treatment in the first line setting. The PBAC agreed with the pre-PBAC response that, with NIVO+IPI now available, the patients most likely to receive cabozantinib under the requested listing would be those for whom immunotherapy is deemed inappropriate.
- 7.3 The PBAC considered that there may be a clinical role for cabozantinib in the second-

line setting following NIVO+IPI. The PBAC noted that, under the existing listing, cabozantinib can only be used in patients who have had prior treatment with a TKI. Thus, the listing of NIVO+IPI has moved the clinical place of cabozantinib (under the existing listing) for most patients from second line (after prior treatment with a TKI) to third line (after treatment with NIVO+IPI followed by a TKI). The PBAC noted that no evidence was presented for use of cabozantinib following NIVO+IPI, and the advice of the clinician at the consumer hearing was that there are no prospective trials of cabozantinib in this setting. The PBAC noted that, similarly, there is limited prospective evidence for sunitinib or pazopanib post-immunotherapy.

- 7.4 The submission nominated sunitinib as the main comparator and the PBAC considered that sunitinib and pazopanib are the appropriate main comparators. The PBAC considered that sunitinib was a reasonable proxy for pazopanib in terms of the clinical evidence presented. The submission nominated NIVO+IPI as a near-market comparator. The PBAC noted that NIVO+IPI was PBS listed on 1 March 2019 and considered that the comparison against NIVO+IPI was informative, but that sunitinib and pazopanib were more relevant comparators given cabozantinib would most likely be used in patients for whom immunotherapy is deemed inappropriate.
- 7.5 The PBAC noted that the evidence for cabozantinib was based on a relatively small (n=157) Phase II open-label trial comparing cabozantinib to sunitinib in patients with previously untreated, stage IV clear cell variant RCC who are at intermediate to poor risk (CABOSUN). The PBAC noted that the CABOSUN trial showed a statistically significant improvement in PFS for cabozantinib, but considered the magnitude was uncertain and likely overestimated as the trial had a high risk of bias due to the open-label design and imbalances in missing data, with substantial differences in the investigator-assessed and IRC analyses of PFS.
- 7.6 The PBAC noted that the CABOSUN trial showed a numerical improvement in OS for cabozantinib versus sunitinib but the difference was not statistically significant and appeared to be decreasing with additional follow-up. The PBAC considered that the submission's claim that there was a trend towards improved OS was not supported by the evidence presented
- 7.7 The PBAC noted that the safety data from the CABOSUN trial indicated that diarrhoea, hypertension and hypothyroidism were more common for patients treated with cabozantinib compared to sunitinib, however the safety data were based on a small number of patients. Overall the PBAC considered that from the evidence presented, cabozantinib and sunitinib appear to have broadly comparable overall safety profiles.
- 7.8 The PBAC noted that the submission also presented an indirect comparison with NIVO+IPI based on the subset of patients with intermediate to poor risk prognosis from the CheckMate214 trial of NIVO+IPI versus sunitinib. The PBAC considered that the indirect comparison with NIVO+IPI in terms of PFS was not reliable due to: uncertainty in PFS outcomes from CABOSUN (as outlined in Paragraph 7.5); transitivity issues between the trials (due to differences in patient populations and treatment practices); and because PFS may not be an accurate measure of benefit for NIVO+IPI

due to the potential tumour flare effect for immunotherapies. The PBAC agreed with the ESC that OS is a more meaningful outcome for the comparison of cabozantinib with NIVO+IPI and considered that it appeared that cabozantinib may be inferior to NIVO+IPI in terms of OS. Overall, the PBAC considered that cabozantinib may be inferior to NIVO+IPI in terms of comparative efficacy.

- 7.9 The submission described cabozantinib as having a potentially more tolerable safety profile than NIVO+IPI. The PBAC agreed with the ESC that the evidence presented did not support this claim and considered that immunotherapy is typically associated with severe toxicity in a proportion of patients whereas TKIs tend to be associated with less severe events, but these events are experienced by nearly all patients.
- 7.10 The PBAC noted that the evaluation and ESC had identified a number of issues regarding the cost-utility analysis versus sunitinib including: the extrapolation of outcomes was based on a small number of patients with limited follow-up time leading to uncertain outcomes; the extrapolation assumed an on-going treatment effect over the time horizon of the model; the chosen parametric distributions were not sufficiently justified; the modelled OS did not reliably reflect the KM OS curve from the CABOSUN trial; and the utility values appeared higher than would be expected for this population.
- 7.11 The PBAC noted that the model was sensitive to the post-progression treatments included and the duration over which the costs of these were applied. The PBAC considered that the post-progression costs were over-estimated, particularly in the sunitinib arm, due to the inclusion of non PBS-listed drugs and the assumption that patients who receive subsequent therapies continue to be treated until death (i.e. patients who received a subsequent therapy in the CABOSUN trial were assumed to continue receiving subsequent therapies continuously until they died). The PBAC considered that these assumptions were not reasonable.
- 7.12 The PBAC noted that the ESC had proposed a re-specified base case using: (i) a time horizon of 7.5 years; (ii) convergence of OS, PFS and TTD beginning at 30 months, with convergence at 7.5 years; (iii) average patient weight of 80 kg; and (iv) the same costs (per cycle) of subsequent treatment in the cabozantinib and sunitinib arms. The PBAC considered that this was more appropriate than the submission's base case, and noted that this analysis increased the ICER to \$105,000 - \$200,000/QALY using the prices applied in the submission. In addition to these four changes, the PBAC considered that a revised base case would also need to amend the assumption that patients who receive subsequent therapies continue to be treated until death (i.e. subsequent therapy costs, where relevant, should not be applied every cycle that a patient remains alive post-progression).
- 7.13 The PBAC considered that the revised base case ICER (i.e. revised using the assumptions in Paragraph 7.12 above) was very high and the cost for cabozantinib would need to be reduced substantially to bring the ICER into an acceptable range. Even with these changes, the model would still include optimistic assumptions such as the inclusion of a PFS benefit that was likely overestimated in the trial and the use of

sunitinib costs for the comparator arm, while pazopanib was also a relevant comparator.

- 7.14 The PBAC noted that the cost per course of treatment for cabozantinib was estimated to be \$ [REDACTED], compared with \$22,169 for sunitinib. The PBAC noted that some of this difference was because treatment is until progression and the submission assumed that cabozantinib will be used for a longer duration due to the estimated increase in PFS. However, the PBAC considered that the difference in treatment durations is difficult to quantify given the uncertain magnitude of PFS benefit.
- 7.15 The PBAC considered that the basis for conducting a cost-minimisation analysis versus NIVO+IPI was not adequately supported by the clinical evidence presented. The PBAC recalled that the recommendation for NIVO+IPI was based on evidence from a large trial (CheckMate214) that provided reasonable certainty of an OS advantage for NIVO+IPI versus sunitinib, whereas there was low confidence in the CABOSUN trial and no demonstrated survival advantage for cabozantinib over sunitinib.
- 7.16 The PBAC considered that the estimated financial impact of listing cabozantinib was likely to be overestimated because it was based on the current utilisation of sunitinib and pazopanib in patients with favourable to intermediate risk status, who are likely to have a longer treatment duration than patients with intermediate to poor risk status, and because the estimates assumed additional market growth. The PBAC also considered that the assumed uptake rates are unlikely to be realised due to the listing of NIVO+IPI, which would be the preferred first line treatment for most patients.
- 7.17 The PBAC considered that any resubmission would need to be a major submission. The PBAC considered that, given the uncertain and likely small increase in PFS versus sunitinib, an alternative approach could be a CMA versus sunitinib. A resubmission would also need to address the issues raised in Section 6 regarding the financial estimates.
- 7.18 The PBAC considered there may also be a clinical role for cabozantinib in the second-line setting following NIVO+IPI (i.e. removing the requirement in the existing listing for use to be post-TKI) but noted that no evidence was presented for use of cabozantinib in this setting. Given the small and uncertain PFS benefit and the absence of a demonstrated OS benefit or improvement in QoL for cabozantinib versus sunitinib in the first-line setting, the PBAC considered that any future submission requesting use in a broader setting (e.g. a “line agnostic” listing) would need to be based on conservative assumptions. In settings where there is no RCT evidence of superiority, the PBAC considered that a higher cost for cabozantinib versus sunitinib may be difficult to justify. The PBAC noted that this may result in a weighted price, reflecting the different levels of evidence and benefits in the different settings.
- 7.19 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

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

9 Sponsor's Comment

The sponsor had no comment.