

## 6.06 LENVATINIB, Capsule 4 mg (as mesilate), Capsule 10 mg (as mesilate) Lenvima<sup>®</sup>, Eisai Australia Pty Ltd.

### 1 Purpose of application

- 1.1 The submission requested a Section 85, Authority Required (Streamlined), listing of lenvatinib for use in combination with everolimus for treatment of patients with stage IV clear cell variant renal cell carcinoma (RCC). This submission had not been considered by the PBAC previously.
- 1.2 The submission presented a cost-utility analysis, where the combination therapy of lenvatinib 18 mg orally per day and everolimus 5 mg orally per day was claimed to be superior in terms of effectiveness against everolimus 10 mg orally per day. Clinical evidence comparing the combination treatment with nivolumab, and secondary comparisons with axitinib and cabozantinib, were also presented. 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 Stage IV clear cell variant renal cell carcinoma.
Intervention	Lenvatinib 18 mg and everolimus 5 mg orally, once daily.
Comparator	Everolimus 10 mg orally, once daily, was nominated as the primary comparator upon which the clinical and cost-effectiveness data presented were based. A secondary indirect comparison with nivolumab, and supplementary comparisons with axitinib and cabozantinib, for clinical effectiveness were also presented.
Outcomes	Progression free survival (PFS); Overall Survival (OS).
Clinical claim	In the primary comparison, the combination of lenvatinib and everolimus was claimed to be superior to everolimus monotherapy in terms of effectiveness and inferior in terms of safety. The overall safety profile was claimed to be acceptable in consideration of the improvements in PFS and OS. In the secondary comparison, the combination of lenvatinib and everolimus was claimed to be superior to nivolumab in terms of effectiveness for the outcome of PFS and non-inferior in terms of OS. The combination was inferior in terms of safety. In the supplementary naïve comparison with axitinib, the submission claimed that lenvatinib/everolimus was superior in clinical effectiveness when compared to axitinib, with a different safety profile. In the supplementary indirect comparison with cabozantinib, the submission claimed that lenvatinib/everolimus was non-inferior in clinical effectiveness when compared to cabozantinib, with a different safety profile.

### 2 Requested listing

- 2.1 The proposed PBS listings for lenvatinib (initial and continuing treatment) are presented below.

Public Summary Document – November 2017 PBAC Meeting

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Lenvatinib, 10 mg, capsule	1	30	2 (initial phase) 5 (continuing phase)	\$3,302.88 (published) \$ [REDACTED] (effective)	Lenvima®  Eisai Australia Pty Ltd
Lenvatinib, 4 mg, capsule	2	60	4 (initial phase) 10 (continuing phase)	\$6,605.76 (published) \$ [REDACTED] (effective)	

Category / Program:	Section 85 – General Schedule
Condition	Clear cell variant renal cell carcinoma (RCC)
PBS indication	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Initial treatment
Restriction:	Authority required (STREAMLINED)
Clinical criteria:	<ul style="list-style-type: none"> <li>• The treatment must be used in combination with everolimus at a maximum everolimus dose of 5 mg daily</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>• Patient must have progressive disease according to the Response Evaluation Criteria in Solid Tumours (RECIST) following first-line treatment with a tyrosine kinase inhibitor</li> </ul> <p>OR</p> <ul style="list-style-type: none"> <li>• Patient must have developed intolerance to a tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>• Patient must have a WHO performance status of 2 or less</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>• Patients who have developed progressive disease with lenvatinib are no longer eligible for PBS-subsidised lenvatinib</li> </ul>

Category / Program	Section 85 – General Schedule
Condition:	Clear cell variant renal cell carcinoma (RCC)
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Continuing treatment
Restriction:	Authority required (STREAMLINED)
Clinical criteria:	<ul style="list-style-type: none"> <li>• Patient must have previously been issued with an authority prescription for this drug for this condition</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>• The treatment must be used in combination with everolimus at a maximum everolimus dose of 5 mg daily</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>• Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST)</li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li>• Patients who have developed progressive disease with lenvatinib are no longer eligible for PBS-subsidised lenvatinib</li> </ul>

2.2 The intent of this listing, and in accordance with the clinical evidence presented in the submission, was that the lenvatinib/everolimus combination would be used as a second line therapy following treatment with a first line tyrosine kinase inhibitor (TKI).

- 2.3 The restriction allows for treatment to continue until disease progression. The median duration of time to disease progression in the key clinical trial was reported at 14.6 months. The mean time to disease progression was not reported, but is likely to be higher. The corresponding median duration of therapy in the trial was significantly lower at 7.6 months. This implies that there were significant treatment discontinuations and interruptions during therapy in the trial. The impact of such discontinuations and interruptions on the likely duration of therapy for the PBS population is unknown.
- 2.4 Lenvatinib is currently listed on the PBS as a treatment for locally advanced or metastatic radioactive iodine refractory differentiated thyroid cancer. The current PBS listing for lenvatinib is based on a special pricing arrangement (SPA). The submission proposed that the same SPA would also apply to its listing for RCC. The relevant prices are shown in the requested listing above.

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

### **3 Background**

#### **Registration status**

- 3.1 TGA status at the time of PBAC consideration: The submission was lodged under the TGA/PBAC parallel process. TGA documentation supplied with the submission included the clinical evaluator's report (Round 2). On 26 July 2017, the Delegate approved the registration of the product for the new indication.
- 3.2 The TGA approved indication for lenvatinib is for its use in combination with everolimus for the treatment of adult patients with advanced RCC whose disease has progressed following **one** prior vascular endothelial growth factor targeted therapy.
- 3.3 The PBAC noted that the proposed PBS restriction would permit use of lenvatinib at second and subsequent lines of tyrosine kinase inhibitor therapy.

*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 80–95% of all cases. Kidney cancer is more frequently reported in males than in females. In 2013, there were 2,256 cases of kidney cancer in males and 1,256 cases in females. Most RCC patients are diagnosed with advanced disease, and this is often resistant to systemic therapy.
- 4.2 First line treatment options for advanced RCC include the currently PBS listed tyrosine kinase inhibitors (TKIs), sunitinib and pazopanib. Following disease progression with these agents, currently listed PBS items for second line therapy include nivolumab, everolimus, axitinib and sorafenib. At present there are no validated predictive biomarkers to guide treatment selection.
- 4.3 Most recently, in March 2017, the PBAC recommended the listing of nivolumab as a treatment option for patients with advanced RCC in a second line setting, as a

potential alternative to the currently available drugs. The PBAC considered that, for some patients, nivolumab provided a significant improvement in efficacy and a reduction in toxicity over everolimus, which was the nominated comparator (paragraph 7.1, nivolumab PSD, March 2017). In November 2014, the PBAC recommended listing axitinib in a second line setting for the treatment of patients with stage IV clear cell variant RCC, on a cost-minimisation basis with everolimus (paragraph 7.1, axitinib PSD, November 2014).

- 4.4 The PBAC noted that the submission proposes use of lenvatinib/everolimus in a second line setting, whereas the sponsors clinical Advisory Board advised that use would likely be third line. The PBAC considered that concerns regarding the magnitude of clinical benefit and the toxicity profile of lenvatinib/everolimus, when compared with both everolimus and nivolumab, meant that its clinical place in therapy was unclear given the treatments currently available.

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

## **5 Comparator**

- 5.1 The nominated main comparator in the submission was everolimus monotherapy at a dose of 10 mg orally per day. The submission argued that this is the currently listed PBS treatment that would most likely be replaced in the event of a PBS listing for lenvatinib/everolimus combination therapy.
- 5.2 The submission acknowledged that nivolumab, once PBS listed, would be likely to become the standard of care in the second line setting for these patients given that the available clinical guidelines describe it as a Category 1 preferred treatment. It expected a "rapid and substantial uptake [of nivolumab] in the near future". However, it took the view that there still needed to be an oral treatment option available for some patients as an alternative to nivolumab, which is infused intravenously every two weeks. This could be because of a lack of access to an infusion administration facility, because of patient preference for an oral therapy (lenvatinib + everolimus), or because of contraindication to nivolumab. The submission provided an indirect comparison of the clinical evidence from the lenvatinib/everolimus trial with the nivolumab trial, where everolimus monotherapy was a common comparator to both. Evidence from the nivolumab trial was not used in the economic evaluation, and an economic evaluation incorporating nivolumab was not presented. The pre-PBAC response (p1) argued that everolimus is a more appropriate comparator, because nivolumab has a different mode of administration, and is in a different treatment class to both lenvatinib and everolimus.
- 5.3 The ESC noted that given the same mechanism of action (TKI inhibition), mode of administration (oral), and feedback from the sponsors' clinical advisors that axitinib is used for second line therapy, axitinib may be a more appropriate comparator than everolimus and possibly nivolumab. The submission included a supplementary naïve comparison against axitinib. In the pre-PBAC response (p1) the sponsor disagreed that axitinib would be a more appropriate comparator. The sponsor noted that the TGA-approved indication and the proposed PBS restriction require use in combination with everolimus. Hence, the sponsor argues that the nomination of

everolimus as a comparator provides a basis for establishing the additive clinical benefit and cost-effectiveness of the combination of lenvatinib/everolimus compared with everolimus.

- 5.4 Cabozantinib is a new orally active TKI that is not yet TGA approved, but has been approved by the FDA and EMA as a second line treatment option in RCC, and is a recommended treatment option for patients with RCC in clinical management guidelines (Category 1, preferred). An application for listing of cabozantinib on the PBS for clear cell variant RCC in the second line (post-TKI) is scheduled for consideration by the PBAC at its meeting on 15<sup>th</sup> December 2017. It could thus represent a plausible comparator for lenvatinib/everolimus. The submission included an indirect comparison of the lenvatinib/everolimus combination with cabozantinib formed using everolimus as the common comparator.
- 5.5 The PBAC noted that the introduction of nivolumab as second line therapy had already led to the displacement of axitinib in the second line setting, and that the latter had displaced everolimus. The PBAC reiterated that the clinical place in therapy of lenvatinib/everolimus was unclear, given the treatments currently available. Hence, the PBAC considered the appropriate comparator for lenvatinib/everolimus was uncertain.

*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 that no consumer comments were received for this item.

### ***Clinical trials***

- 6.3 The submission was based on a single Phase II open-label trial that compared the combination of lenvatinib plus everolimus with everolimus monotherapy in patients with metastatic RCC whose disease had progressed after first line therapy. This was referred to as Study 205. This trial included a third randomised arm where patients were allocated to receive lenvatinib monotherapy in a dose higher than that used in the combination arm. The sponsor has not sought to have monotherapy authorised in its regulatory approvals with the EMA, FDA or TGA; and has not sought to have it PBS listed. Accordingly, lenvatinib monotherapy was not discussed by the PBAC.
- 6.4 A secondary, indirect comparison of nivolumab and lenvatinib/everolimus was presented using the clinical evidence from Study 205 and data from the nivolumab trial CheckMate 025. Both of these trials had everolimus 10 mg per day as the common comparator. Data from the CheckMate 025 trial formed the basis of the clinical evidence provided to the PBAC in its consideration and subsequent recommendation to list nivolumab on the PBS (nivolumab public summary document, July 2016).

- 6.5 The submission included a supplementary comparison of lenvatinib/everolimus with axitinib. Data for axitinib were sourced from the AXIS trial which compared axitinib with sorafenib. The PBAC noted that on the basis of these data, it was not possible to form an indirect comparison of lenvatinib/everolimus with axitinib via a common reference (such as everolimus).
- 6.6 Details of the trials presented in the submission, including the supplementary comparator, are provided in Table 2.

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
Study 205 (lenvatinib and everolimus versus everolimus)	CSR: An Open-Label, Multicenter Phase 1b/2 Study of E7080 Alone, and in Combination with Everolimus in Subjects With Unresectable Advanced or Metastatic Renal Cell Carcinoma Following One Prior VEGF-Targeted Treatment.	October 2015
	Motzer, RJ et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: A randomised, phase 2, open-label, multicentre trial.	The Lancet Oncology (2015) 16, 1473-1482.
	Motzer, RJ et al. Independent assessment of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma.	The Lancet Oncology (2016) 17.1: e4-e5.
	Hutson, TE., et al. Subgroup analyses and updated overall survival from the phase 2 trial of lenvatinib (LEN), everolimus (EVE), and LEN+ EVE in metastatic renal cell carcinoma (mRCC)	American Society for Clinical Oncology Annual Meeting (2016).
	Motzer, RJ et al Randomized phase II, three-arm trial of lenvatinib (LEN), everolimus (EVE), and LEN+ EVE in patients (pts) with metastatic renal cell carcinoma (mRCC).	Journal of clinical oncology (2015), 33, Conference Start: 2015 May 29 Conference End: 2015 Jun 2
CheckMate 025 (nivolumab versus everolimus)	Motzer, RJ et al. Nivolumab versus everolimus in advanced renal-cell carcinoma (primary publication).	New England Journal of Medicine (2015), 373, 1803-1813
AXIS (axitinib versus sorafenib)	Rini, B et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised Phase III trial (primary publication).	Lancet (2011), 378(9807), 1931-1939.

Source: Table 2-5, pages 47 and 48 of submission; Appendix 1 of the submission.  
Abbreviations: CSR, clinical study report.

- 6.7 The key features of the randomised trial are summarised in Table 3.

Table 3: Key features of the included direct evidence

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>Study 205 (lenvatinib and everolimus versus everolimus)</b>						
Study 205	101	R, OL, MC Median duration of follow up 18.5 mths for lenvatinib and 17.8 mths for everolimus.	High due to non-blinded nature of study, and investigator assessment of benefit.	Advanced/metastatic RCC following one prior VEGF-targeted treatment	OS, PFS (primary), overall response, objective response rate, duration of response, time to response. Rate and nature adverse events	OS PFS Adverse events
<b>CheckMate 025 (nivolumab versus everolimus)</b>						
Motzer et al 2015	821	Phase III, R, OL, MC	Moderate (due to open-label design, and potential for early termination to influence magnitude of treatment effect).	RCC progressed following first line treatment	OS, PFS (RECIST-defined), EQ-5D, Safety and tolerability	Not used
<b>AXIS (axitinib versus sorafenib)</b>						
AXIS	723	Phase III, R, OL, MC	Moderate (due to potential for open-label design to influence magnitude of treatment effect).	RCC after failure of one prior systemic 1 <sup>st</sup> -line therapy	PFS, OS, safety	Not used

Source: compiled during the evaluation, data from Table 2-3 page 49, Table 2-16 page 63 and Table 2-18 page 65 of the submission. Paragraph 6.6, nivolumab PSD, March 2017. Appendix 1 of the submission.

Abbreviations: R, randomised; OL, open-label; MC, multi-centre; mths, months; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor; OS, overall survival; PFS, progression-free survival.

- 6.8 Study 205, a small-scale Phase II trial, was assessed as having a high risk of bias. The trial was open-label, and the reporting of the primary endpoint (PFS) using RECIST v1.1 criteria was undertaken by the investigators.
- 6.9 The PBAC noted that of the 235 patients assessed for eligibility in Study 205, 82 (35%) were deemed ineligible.
- 6.10 At the time of the primary efficacy assessment for PFS in June 2014, only 26 patients (51%) in the lenvatinib/everolimus arm and 37 patients (74%) in the everolimus monotherapy arm had disease progression. This results in some uncertainty in the interpretation of the magnitude of the reported PFS gain. Evidence reported in the submission for PFS related to the primary efficacy assessment by the investigators, together with the blinded independent radiologist review that had been requested by

regulatory agencies. The PBAC noted the results of the blinded assessment were less favourable for lenvatinib/everolimus than those from the primary assessment.

- 6.11 In the reporting of OS benefits from a later data cut-off (July 2015), 63% of patients in the lenvatinib/everolimus arm and 74% of patients in the everolimus monotherapy arm had died. The economic evaluation used OS and PFS data from this later trial cut-off (median duration of follow up 32 months) with the PFS values being less favourable than those reported in the initial assessments of clinical efficacy. The pre-PBAC response (p3) states that as of the latest data cut for Study 205 (15<sup>th</sup> April 2016) 80% of patients in the lenvatinib/everolimus arm and 75% of patients in the everolimus arm had died. The sponsor stated that the OS data reported is highly consistent with OS data used in the economic evaluation of lenvatinib/everolimus.
- 6.12 The submission relied on the first data cut-off from Study 205 to estimate the mean daily doses of treatment administered in each treatment arm and to estimate the duration of therapy and time to progression. At the first data cut-off 13 patients in the lenvatinib/everolimus arm (25.5%) and 3 patients in the everolimus monotherapy arm (6%) remained on treatment. This led to an under-estimate of the duration of therapy which was used in the financial estimates. The impact on the estimated mean dose administered was unknown.
- 6.13 A significant number of patients in both arms of Study 205 had prematurely discontinued therapy prior to the development of disease progression. Of these, adverse events led 9 patients (17.6%) in the lenvatinib/everolimus arm and 5 patients (10%) in the everolimus monotherapy arm to discontinue prematurely. Four patients (7.9%) in the lenvatinib/everolimus arm and 1 patient (2%) in the everolimus arm chose to withdraw from the trial. The applicability to the proposed PBS population of trial based estimates of exposure is uncertain, due to potential differences in the pattern of discontinuation. In particular, trial patients may be younger and have an improved performance status than PBS patients, which may impact on treatment exposure in practice.
- 6.14 Some issues with the CheckMate 025 trial for nivolumab have previously been identified by the PBAC. The pre-specified boundary for significance was crossed at the first interim analysis of OS, and the trial was terminated early to allow the everolimus treated patients to receive nivolumab. The outcomes reported from the first database lock are not confounded by crossover. Similar to Study 205, significant numbers of patients were continuing on treatment at the time of the database lock (16.3% for nivolumab and 6.8% for everolimus) potentially leading to the duration of therapy being underestimated. Unlike Study 205, patients in the CheckMate 025 trial were able to continue receiving treatment beyond progression if they were assessed by the investigators as still deriving clinical benefit and tolerating treatment (6.6-6.8, PSD, nivolumab July 2016). The current submission claimed that the ability to continue treatment beyond progression may have biased the results of CheckMate 025 in favour of nivolumab, since investigators would be more inclined to continue with nivolumab therapy and less inclined to continue with everolimus.
- 6.15 AXIS was used as the basis of the evidence considered by the PBAC for the listing of axitinib in RCC (Axitinib PSD, November 2014). This trial did not include everolimus

and therefore cannot be used to form an indirect comparison with lenvatinib/everolimus. In addition, patients treated with axitinib in AXIS who progressed were able to receive sorafenib at progression, potentially biasing any comparative analysis formed between lenvatinib/everolimus and axitinib using those data.

### ***Comparative effectiveness***

- 6.16 The key outcomes of PFS and OS from Study 205, CheckMate 025 and AXIS are presented in the following paragraphs. The results of the indirect comparison of lenvatinib/everolimus with nivolumab between the interventions using the common comparator are presented in 6.24. An indirect comparison with axitinib could not be formed due to the absence of a common reference.
- 6.17 PFS data are shown in Table 4. To address potential bias from the open-label design of Study 205, at the request of regulatory agencies, a separate analysis of PFS was undertaken by blinded independent radiologic review, and these data are also shown. The PBAC noted this review showed a reduction in the duration of PFS reported for lenvatinib/everolimus over what had been reported in the primary analysis. The difference in PFS for lenvatinib/everolimus combination compared with everolimus monotherapy was statistically significant, whereas the difference in PFS for nivolumab compared with everolimus monotherapy was not statistically significant. The PBAC noted that the use of RECIST based assessment of progression is known to underestimate the extent of benefit with respect to the use of immunotherapies. Accordingly, the PBAC considered that a comparison of RECIST based PFS from Study 205 with that from CheckMate 025 was biased in favour of lenvatinib/everolimus and was not a reasonable basis for the assessment of comparative benefit. While the results for AXIS indicate axitinib achieved superior PFS when compared with sorafenib, the PBAC considered the absence of a common comparator means it is difficult to draw any conclusions from this result for the comparison of axitinib with lenvatinib/everolimus.

**Table 4: Results of progression-free survival across trials**

Trial ID	Intervention <sup>a</sup>		Comparator <sup>b</sup>		Difference in Median, months	P-value	HR (95% CI)
	n/N with event (%)	Median, months (95% CI)	n/N with event (%)	Median, months (95% CI)			
Study 205 (investigator assessed)	26/51 (51%)	14.6 (5.9, 20.1)	37/50 (74%)	5.5 (3.5, 7.1)	9.1	0.0005	0.40 (0.24, 0.68)
Study 205: BIRR assessed	24/51 (47%)	12.8 (7.4, 17.5)	29/50 <sup>c</sup> (58%)	5.5 (3.6, 9.3)	7.3	0.0029	0.45 (0.27, 0.79)
CheckMate 025	318/410 (78%)	4.6 (3.7, 5.4)	322/411 (78%)	4.4 (3.7, 5.5)	0.2	0.11	0.88 (0.75, 1.03)
AXIS	NR	8.3 (6.7, 9.2)	NR	5.7 (4.7, 6.5)	2.6	<0.0001	0.67 (0.55, 0.78)

Source: Table 2-22 and table 2-23, pages 74-75 of submission; Table 10, Appendix 1 of the Submission.

Notes: Study 205: Data cut=13<sup>th</sup> June 2014, Length of follow-up=18.5 months (median); CheckMate 025: Data cut=June 2015, Length of follow-up=14 months (minimum).

<sup>a</sup> Intervention in Study 205 was lenvatinib/everolimus; intervention in CheckMate025 was nivolumab; intervention in AXIS was axitinib 5 mg b.d.

<sup>b</sup> Comparator in Study 205 and CheckMate025 was everolimus 10 mg; comparator in AXIS was sorafenib 400 mg b.d.

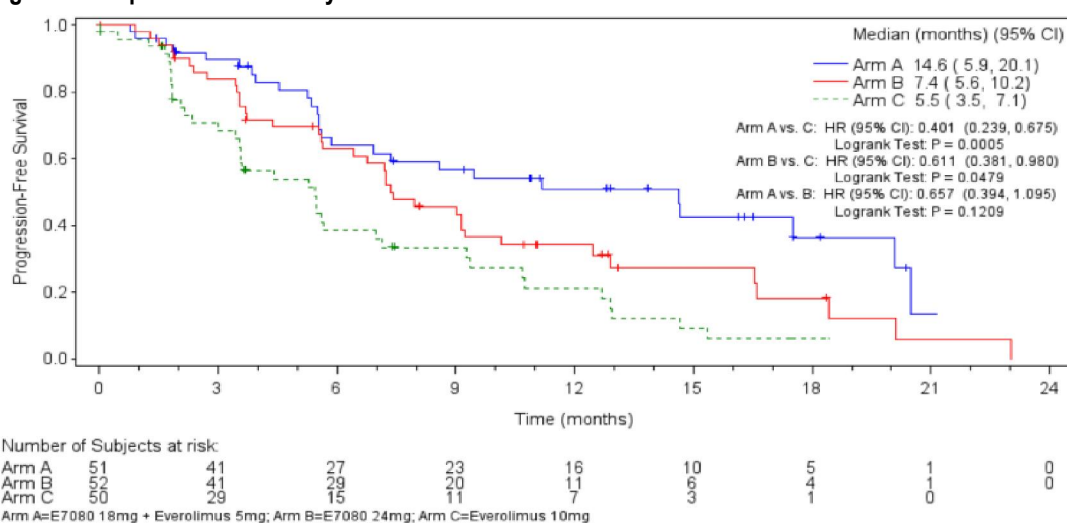
<sup>c</sup> the submission had a typographical error in that this number (50) was written as 58.

Abbreviations: CI, confidence interval; BIRR, blinded independent radiologist review; HR, hazard ratio; NR, not reported.

6.18 PFS data from the later July 2015 cut-off in Study 205 were used in the economic analysis. These data indicated a numerically less favourable PFS advantage with a HR of 0.5 (95% CI: 0.26, 0.79). Median PFS was not reported for this cut-off.

6.19 The Kaplan-Meier (KM) plot of PFS in Study 205 (based on the earlier cut-off of June 2014) is shown in Figure 1.

**Figure 1: KM plot of PFS in Study 205**



Source: Figure 2-7, page 76 of submission.

Note: Arm B in this figure relates to a third arm in Study 205 (lenvatinib 24 mg orally per day as monotherapy) which has not been discussed in this Commentary.

6.20 OS from the primary efficacy data cut-off for Study 205 and CheckMate 025, and the naïve comparison from AXIS is shown in Table 5.

**Table 5: Results of overall survival across trials**

Trial ID	Intervention <sup>a</sup>		Comparator <sup>b</sup>		Difference in Median, months	P-value	Hazard ratio (95% CI)
	n/N with event (%)	Median, months (95% CI)	n/N with event (%)	Median, months (95% CI)			
Study 205	19/51 (37%)	25.5 (20.8, 25.5)	26/50 (52%)	17.5 (11.8, NE)	8.0	0.062	0.55 (0.30, 1.01)
CheckMate 025	183/410 (45%)	25.0 (21.8, NE)	215/411 (52%)	19.6 (17.6, 23.1)	5.4	0.002	0.73 (98.5% CI: 0.57, 0.93)
AXIS	211/359 (59%)	20.1 (16.7, 23.4)	214/355 (60%)	19.2 (17.5, 22.3)	0.9	0.3744	0.97 (0.80, 1.17)

Source: Table 2-20, page 70 of submission; Table 12, Appendix 1 of the Submission...

Notes: Study 205: Data cut=13th June 2014, Length of follow-up=18.5 months (median); CheckMate 025: Data cut=June 2015, Length of follow-up=14 months (minimum)

<sup>a</sup> Intervention in Study 205 was lenvatinib/everolimus; intervention in CheckMate025 was nivolumab; intervention in AXIS was axitinib 5 mg b.d.

<sup>b</sup> Comparator in Study 205 and CheckMate025 was everolimus 10 mg; comparator in AXIS was sorafenib 400 mg b.d.

Abbreviations: CI, confidence interval; HR, hazard ratio; n number; NE, not evaluable

6.21 The median OS gain of 8 months in the lenvatinib/everolimus arm over everolimus monotherapy was not statistically significant in the primary efficacy analysis. At this time (13th June 2014 cut-off), only 37% of patients in the lenvatinib/everolimus arm and 52% of patients in the everolimus monotherapy arm had died.

6.22 Additional evidence for OS based on later data cut-offs is shown in Table 6. These data indicate that the numerical survival gains reported from the primary efficacy analysis were maintained, although the differences between the interventions at each of the cut-offs were not all statistically significant. The pre-PBAC response (p3) argued that across all time points the median OS reported for patients treated with lenvatinib/everolimus was at least 8 months longer than for patients with everolimus, with improvements of [REDACTED] months reported with more mature data. The PBAC considered that the magnitude of the reported OS gain was uncertain and possibly due to chance, noted the trial was a randomised phase 2 design with only 153 patients in 3 arms powered for PFS, and that the trial was not powered to detect differences in OS. Data from the latest cut-off were used in the economic evaluation.

**Table 6: Results of additional overall survival data from Study 205**

Data cut	Lenvatinib/everolimus		Everolimus 10 mg		Difference in Median, months	P-value	HR (95% CI)
	n/N with event (%)	Median, months (95% CI)	n/N with event (%)	Median, months (95% CI)			
13 <sup>th</sup> June 2014	19/51 (37%)	25.5 (20.8, 25.5)	26/50 (52%)	17.5 (11.8, NE)	8.0	0.062	0.55 (0.30, 1.01)
10 <sup>th</sup> December 2014	24/51 (47%)	25.5 (16.4, NE)	33/50 (66%)	15.4 (11.8, 19.6)	10.1	0.024	0.51 (0.30, 0.88)
31 <sup>st</sup> July 2015	██████	██████	██████	██████	██████	██████	██████

Source: Table 2-21, page 71 of submission.

Notes: Study 205: Data cut=13<sup>th</sup> June 2014, Length of follow-up=18.5 months (median). Data cut = 10<sup>th</sup> December 2014, length of follow up = 24.2 months (median). Data cut = 31<sup>st</sup> July 2015, length of follow up = ██████ months (median)

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not evaluable

6.23 The KM plot of OS in Study 205 (based on the latest cut-off of July 2015) is shown in Figure 2 below.

**Figure 2: KM plot of OS in Study 205 (July 2015 cut-off)**



6.24 The results of the indirect comparison between lenvatinib/everolimus and nivolumab are summarised in Table 7 below. The submission claimed that the results of this indirect comparison indicated a significantly reduced risk of progression associated with the lenvatinib/everolimus combination compared with nivolumab. The PBAC disagreed with this conclusion, noting that such a comparison was biased against nivolumab given that the use of RECIST based assessments of progression are considered to underestimate the impact of immunotherapies on disease progression.

The OS difference for lenvatinib/everolimus versus nivolumab in the indirect comparison was not statistically significant. The significance of these results is uncertain given the within trial uncertainty as to the significance of the estimates of OS gain in Study 205. The PBAC also noted that while the median survival estimates for lenvatinib/everolimus and nivolumab were of a similar magnitude, those of the common reference, everolimus, differed being more than 2 months higher in CheckMate 025.

**Table 7: Summary results of the indirect treatment comparison of lenvatinib/everolimus with nivolumab**

	Intervention <sup>a</sup>		Everolimus		HR (95% CI)	Indirect comparison: HR (95%CI)
	n/N with event (%)	Median mths (95% CI)	n/N with event (%)	Median mths (95% CI)		
<b>Progression free survival</b>						
Study 205	26/51 (51%)	14.6 (5.9, 20.1)	37/50 (74%)	5.5 (3.5, 7.1)	0.4 (0.24, 0.68)	■
CheckMate 025	318/410 (78%)	4.6 (3.7, 5.4)	322/411 (78%)	4.4 (3.7, 5.5)	0.88 (0.75, 1.03)	
<b>Overall survival</b>						
Study 205	19/51 (37%)	25.5 (20.8, 25.5)	26/50 (52%) <sup>b</sup>	17.5 (11.8, NE)	0.55 (0.3, 1.01)	■
CheckMate 025	183/410 (45%)	25.0 (21.8, NE)	215/411 (52%)	19.6 (17.6, 23.1)	0.73 (98.5% CI 0.57, 0.93)	

Source: Table 2-35, page 95 of submission.

Notes: <sup>a</sup> In Study 205, intervention is lenvatinib/everolimus. In CheckMate 025 intervention is nivolumab.

<sup>b</sup> This is incorrectly written in submission as 183/410 (45%).

Abbreviations: CI, confidence interval; HR, hazard ratio; n number.

6.25 The PBAC considered the overall applicability of evidence from Study 205 to the intended Australian population to be uncertain. In the clinical trial, the mean age of participants enrolling in the trial was 60.3 years. The mean age of Australians diagnosed with kidney cancer is 63.7 years<sup>1</sup>. Applying the 3.8 year lag time between first diagnosis and treatment with second line therapy as seen in Study 205 would suggest that the mean age of patients commencing therapy with second line agents would be 67.5 years. A pre-specified sub-group analysis of the primary efficacy endpoint in Study 205 (PFS) was undertaken in the subgroups age ≤ 65 years and > 65 years. The results of that analysis indicated that the median duration of PFS was reduced to ■ months in patients > 65 years (HR ■, 95% CI: ■, p=■), versus 9.1 months in the full analysis set (HR 0.4, 95% CI: 0.24, 0.68; p=0.0005), and ■ months in the patients ≤ 65 years (HR ■, 95% CI: ■; p=■). The submission noted that this subgroup analysis was exploratory in nature only and that Study 205 was not designed or powered to detect a difference in treatment efficacy by age. The PBAC noted the caveats associated with the conduct of such a subgroup analysis. Nonetheless it felt that the results indicated that the efficacy of lenvatinib/everolimus may be diminished in Australian clinical practice relative to Study 205 on the basis that patients are likely to be older at the time of receiving

<sup>1</sup> Cancer in Australia 2017. Australian Institute for Health and Welfare.

second and subsequent lines of treatment for RCC than they were in the study. This would have implications for the comparative efficacy and cost-effectiveness of lenvatinib/everolimus in clinical practice.

- 6.26 The PBAC noted that Study 205 only enrolled patients with an ECOG performance status of  $\leq 1$ . It is unknown whether this criterion biased the recruitment in favour of younger patients, and it is also unknown whether lenvatinib/everolimus would be equally efficacious and safe in patients with a performance status of  $>1$  and  $<2$  as it is in patients with a performance status of  $<1$ . Based on the proposed PBS listing, patients with a performance status of  $\leq 2$  would be eligible for treatment. In light of the toxicity of lenvatinib/everolimus, the ESC was concerned by the proposed inclusion of patients with poorer performance status, who may be more susceptible to toxicity. The PBAC considered that in practice toxicity concerns would likely restrict use to patients with a performance status  $\leq 1$ .

### ***Comparative harms***

- 6.27 A summary of the adverse events reported in Study 205 and CheckMate 025 is provided in Table 8. In Study 205, the occurrence of adverse events was higher in the lenvatinib/everolimus group compared with everolimus monotherapy. This included serious adverse events and adverse events leading to treatment discontinuation, dose delay or dose reduction. One patient in the lenvatinib/everolimus arm had an adverse event resulting in death compared with two patients in the everolimus monotherapy group.
- 6.28 Adverse event rates associated with everolimus monotherapy were broadly similar in both trials, while nivolumab administered in CheckMate 025 had a lower rate of events (any grade, or serious adverse events) than either the lenvatinib/everolimus combination or everolimus monotherapy.

**Table 8: Adverse events by category in Study 205 and CheckMate 025**

Trial ID	Intervention <sup>a</sup> n/N with event (%)	Everolimus (10 mg) n/N with event (%)	Relative risk (95% CI)
<b>Any AE</b>			
Study 205	51/51 (100%)	50/50 (100%)	██████████
CheckMate 025	319/406 (79%)	349/397 (88%) <sup>b</sup>	██████████
<b>Any SAE (≥ Grade 3)</b>			
Study 205	28/51 (55%)	21/50 (42%)	██████████
CheckMate 025	76/406 (19%)	145/397 (37%)	██████████
<b>AE leading to discontinuation of treatment</b>			
Study 205	12/51 (24%)	6/50 (12%)	██████████
CheckMate 025	31/406 (8%)	52/397 (13%)	██████████
<b>AE leading to dose delay</b>			
Study 205	35/51 (69%)	25/50 (50%)	██████████
CheckMate 025	207/406 (51%)	266/397 (66%)	██████████
<b>AE leading to dose reduction</b>			
Study 205	34/51 (67%)	8/50 (16%)	██████████
CheckMate 025	Not permitted	102/397 (26%)	█
<b>AE resulting in death</b>			
Study 205	1/51 (2%)	2/50 (4%)	██████████
CheckMate 025	0	2/397 (0.5%)	██████████

Source: Table 2-27, page 82 of submission.

Notes: <sup>a</sup> Study 205 intervention: lenvatinib/everolimus; CheckMate 025 intervention: nivolumab; <sup>b</sup> Reported as 249 events in submission.

Abbreviations: AE, adverse event; SAE, serious adverse event

6.29 A summary of the most frequently reported adverse events is presented in Table 9. In all cases these adverse events occurred more frequently for the lenvatinib/everolimus arm than for everolimus monotherapy or for nivolumab.

**Table 9: Treatment-emergent adverse events reported in at least 10% of patients in Study 205 and CheckMate 025**

Preferred term, n (%)	Study 205		CheckMate 025	
	Lenvatinib 18 mg + Everolimus 5 mg (N=51)	Everolimus 10 mg (N=50)	Nivolumab (N=406)	Everolimus (N=397)
Diarrhoea	43 (84%)	17 (34%)	50 (12%)	84 (21%)
Decreased appetite	26 (51%)	9 (18%)	48 (12%)	82 (21%)
Fatigue	24 (47%)	16 (32%)	134 (33%)	134 (34%)
Vomiting	23 (45%)	5 (10%)	-	-
Nausea	21 (41%)	8 (16%)	57 (14%)	66 (17%)
Hypertension	21 (41%)	5 (10%)	-	-

Source: Table 2-29, page 85-86 of submission.

6.30 The PBAC noted that serious adverse events of Grade 3 or 4 occurring more frequently in the combination arm included diarrhoea (19.2% vs 2%); fatigue/asthenia (9.8% vs 0%); vomiting (7.8% vs 0%); nausea (5.9% vs 0%) and hypertension (13.7% vs 2%). The PBAC considered that the toxicity associated with the combination of lenvatinib/everolimus was not insignificant, particularly in the context of its use in a Phase II study (which typically enrolls healthier patients than would be treated in clinical practice). There is thus the potential for greater toxicity to occur in clinical practice, resulting in poorer quality of life and increased health care use, or for there to be more dose reductions/interruptions due to associated toxicity events, than occurred in Study 205.

6.31 The naïve comparison of safety for lenvatinib/everolimus with axitinib presented in the submission concluded that the two therapies had a different safety profile. This comparison was largely uninformative given the absence of a common reference. Moreover, the PBAC considered that axitinib is generally a well tolerated therapy which would favour it instead of lenvatinib/everolimus in any comparison of safety.

### Benefits and harms

6.32 A summary of the comparative benefits and harms for the lenvatinib/everolimus combination versus everolimus monotherapy is presented in Table 10.

Table 10: Summary of comparative benefits and harms for lenvatinib/everolimus versus everolimus monotherapy

Benefits					
Progression free survival (median duration of follow up 18.5 months)					
Event	Lenvatinib/ everolimus	Everolimus	Absolute Difference	HR (95% CI)	
Progressed, n (%)	26/51 (51%)	37/50 (74%)			
Investigator assessed PFS median months (95% CI)	14.6 (5.9, 20.1)	5.5 (3.5, 7.1)	9.1	0.40 (0.24, 0.68) p=0.0005	
Overall survival (median duration of follow up ██████████)					
Deaths, n (%)	32/51 (63%)	37/50 (74%)			
OS median months (95% CI)	██████████	██████████	████	██████████	
Harms (median duration of follow up 18.5 months)					
Adverse event	Lenvatinib/ everolimus (n=51)	Everolimus (n=50)	Events/100 patients*		RD % (95% CI)
			Lenvatinib/ everolimus	Everolimus	
Diarrhoea	43	17	84	34	50.3 (33.8, 66.8)
Decreased appetite	26	9	51	18	33.0 (15.6, 50.3)
Fatigue	24	16	47	32	15.1 (-3.8, 33.9)
Vomiting	23	5	45	10	35.1 (19.1, 51.1)
Nausea	21	8	41	16	25.2 (8.3, 42.1)
Hypertension	21	5	41	10	31.2 (15.3, 47.0)

Source: Compiled during the evaluation/using tables 2-21, page 71, 2-23, page 75, 2-29, page 85  
Abbreviations: CI, confidence interval; n, number; RD, risk difference; RR, risk ratio

6.33 On the basis of the direct evidence presented by the submission, the comparison of lenvatinib/everolimus and everolimus indicated that:

- Of all patients treated with lenvatinib/everolimus, half would progress within 14.6 months of commencing treatment, whereas the corresponding period for everolimus would be 5.5 months.
- It is not possible to state the potential benefit associated with survival because the estimates of the survival advantage were not statistically significant.
- For every 100 patients treated with lenvatinib/everolimus in comparison to everolimus monotherapy over 18.5 months:
  - 50 more patients will experience diarrhoea
  - 33 more patients will have a decreased appetite
  - 35 more patients will experience vomiting
  - 25 more patients will experience nausea
  - 31 more patients will experience hypertension.

6.34 A summary of the comparative benefits for the lenvatinib/everolimus combination versus nivolumab generated through the indirect comparison is presented in Table 11.

Table 11: Summary of comparative benefits and harms for lenvatinib/everolimus versus nivolumab

Progression free survival						
	Intervention <sup>a</sup>		Everolimus			Indirect comparison: HR (95%CI)
	n/N with event (%)	Median months (95% CI)	n/N with event (%)	Median months (95% CI)	HR (95% CI)	
Study 205	26/51 (51%)	14.6 (5.9, 20.1)	37/50 (74%)	5.5 (3.5, 7.1)	0.40 (0.24, 0.68)	[REDACTED]
CheckMate 025	318/410 (78%)	4.6 (3.7, 5.4)	322/411 (78%)	4.4 (3.7, 5.5)	0.88 (0.75, 1.03)	
Overall survival						
Study 205	19/51 (37%)	25.5 (20.8, 25.5)	26/50 (52%)	17.5 (11.8, NE)	0.55 (0.3, 1.01)	[REDACTED]
CheckMate 025	183/410 (45%)	25.0 (21.8, NE)	215/411 (52%)	19.6 (17.6, 23.1)	0.73 (98.5% CI 0.57, 0.93)	
Harms						
	Intervention n/N (%)	Everolimus n/N (%)	Odds Ratio (95% CI)	Relative Risk (95% CI)	Risk Difference (95% CI)	
At least one treatment grade 3 or 4 AE						
Study 205	32/51 (62.7%)	21/50 (42.0%)	[REDACTED]	[REDACTED]	[REDACTED]	
CheckMate 025	76/406 (18.7%)	145/397 (36.5%)	[REDACTED]	[REDACTED]	[REDACTED]	
Lenvatinib plus everolimus vs nivolumab			[REDACTED]	[REDACTED]	[REDACTED]	
Discontinuation due to AE						
Study 205	12/51 (23.5%)	6/50 (12.0%)	[REDACTED]	[REDACTED]	[REDACTED]	
CheckMate 025 <sup>b</sup>	31/406 (7.6%)	52/397 (13.1%)	[REDACTED]	[REDACTED]	[REDACTED]	
Lenvatinib plus everolimus vs nivolumab			[REDACTED]	[REDACTED]	[REDACTED]	

Source: Table 2-35, page 95 of submission, and Table 3.5.2, page 19 of Attachment 2 indirect treatment comparison report supplied with the submission.

Notes: <sup>a</sup> In Study 205, intervention is lenvatinib/everolimus. In CheckMate 025 intervention is nivolumab.

<sup>b</sup> CHECKMATE-025 reported discontinuation due to treatment-related AE.

Abbreviations: AE, adverse event; CI, confidence interval; HR, hazard ratio; NE, not evaluable; n/N, number;

6.35 On the basis of the indirect evidence presented by the submission, the comparison of lenvatinib/everolimus and nivolumab indicated that:

- The difficulty with interpretation of RECIST based PFS in the context of immunotherapies makes the potential benefit associated with PFS uncertain.
- There was no evidence of a difference in OS between lenvatinib/everolimus and nivolumab.
- For every 100 patients treated with lenvatinib/everolimus compared with nivolumab with a median follow up of 18 months, approximately 39 more patients would have an adverse event of Grade 3 or 4, and approximately 17 more patients would discontinue treatment due to an adverse event.

### **Interpretation of clinical evidence**

- 6.36 The submission claimed that lenvatinib/everolimus therapy when compared with everolimus monotherapy was superior in terms of effectiveness for both the outcomes of OS and PFS, although inferior in terms of safety. It was claimed that the overall safety profile of the lenvatinib/everolimus combination was acceptable taking into account the improvements in the key efficacy outcomes.
- 6.37 The PBAC considered that these claims are not strongly supported for the following reasons:
- There were relatively few patients (small sample size) enrolled in the key clinical trial, and the open-label design with investigator assessed outcomes for PFS resulted in a high degree of bias.
  - The difference between the trial based assessment of PFS and the independent review creates some uncertainty in the magnitude of PFS gain.
  - There was no statistically significant difference in OS between lenvatinib/everolimus and everolimus monotherapy at the initial and latest data cut-offs. Moreover, the trial was not powered to detect a difference in OS.
  - Adverse events were more common in the lenvatinib/everolimus group, as were dose delays, dose reductions and discontinuations. As a Phase II study, which generally enrolls patients of a better performance status, it may be expected that Study 205 would demonstrate a higher benefit to harm ratio than that expected in clinical practice.
- 6.38 For the comparison of lenvatinib/everolimus with nivolumab, it was claimed that:
- Lenvatinib/everolimus was superior in terms of effectiveness for the outcome of PFS compared with nivolumab.
  - Lenvatinib/everolimus was non-inferior in terms of effectiveness for the outcome of OS compared with nivolumab.
  - Lenvatinib/everolimus was inferior in terms of safety compared with nivolumab.
- 6.39 The PBAC did not agree with the claim in the submission that lenvatinib/everolimus was superior to nivolumab in relation to RECIST defined PFS, given that the use of this outcome measure may not be reliably associated with delay in disease progression with immunotherapies. The PBAC considered that there was high uncertainty regarding differences from nivolumab in relation to OS, noting the small size of Study 205. The claim that lenvatinib/everolimus is inferior to nivolumab in terms of safety was well supported.
- 6.40 In a supplementary comparison, the submission claimed that lenvatinib/everolimus was superior in clinical effectiveness (PFS and OS) when compared to axitinib. The PBAC considered that this claim was not supported by the naïve comparison that lacked a common reference and formal indirect comparison. In the absence of any studies comparing axitinib with everolimus (see axitinib PSD, November 2014), any claim of superiority or non-inferiority between lenvatinib/everolimus and axitinib would rely on acceptance of (a) the transitivity of Study 205 and AXIS, or (b) sorafenib being non-inferior to everolimus. Sorafenib (400 mg b.d.) was recommended for

listing for the treatment of RCC on a cost-minimisation basis against everolimus 10 mg (PBAC Therapeutic Relativity Sheets). Similarly, axitinib 5 mg b.d. was recommended for listing on the basis of a cost-minimisation analysis with everolimus 10 mg (axitinib PSD, November 2014). For consistency therefore, acceptance of a claim of superiority of lenvatinib/everolimus to everolimus would thus suggest that any comparison formed against axitinib would necessarily also need to show superiority.

- 6.41 The PBAC considered on balance that the claim of superior comparative effectiveness versus everolimus was not adequately supported by the data.
- 6.42 The PBAC considered that the claim of inferior comparative safety versus everolimus was reasonable.

### ***Economic analysis***

- 6.43 The submission presented a cost-utility analysis to demonstrate the cost-effectiveness of the lenvatinib/everolimus combination compared with everolimus monotherapy. An overview of the model structure is presented in Table 12.
- 6.44 The ESC considered that given the suggested place in therapy of lenvatinib/everolimus, nivolumab or axitinib would be more appropriate comparators. The submission did not contain an economic evaluation comparing the lenvatinib/everolimus combination with either of these therapies. However, the ESC noted that the Pre-Sub-Committee Response (PSCR) (p1) included a brief analysis which suggested that lenvatinib/everolimus dominated nivolumab in terms of the costs and outcomes of therapy (when restricted to OS). This analysis was again included in the pre-PBAC response (p2), as the sponsor argued that a robust economic evaluation of lenvatinib/everolimus versus nivolumab was not possible due to the confidentiality of critical data inputs required for the model. The PBAC noted that the analysis was not evaluated, and considered that inadequate data were presented upon which to draw conclusions about this comparison. Any such conclusions would more reliably depend on an assessment of all the comparative costs and outcomes of nivolumab compared with lenvatinib/everolimus. The PBAC noted that the pre-PBAC response (p2) argued an economic evaluation of lenvatinib/everolimus against axitinib would lead to a significant increase in uncertainty compared to the comparison with everolimus due to the lack of a common reference.
- 6.45 Presentation of a cost-utility analysis for the lenvatinib/everolimus combination relative to everolimus monotherapy rested on the assumption of a difference in one or all of OS, PFS, or quality of life in favour of lenvatinib/everolimus. The submission did not demonstrate an unequivocal difference in OS in favour of lenvatinib/everolimus, and the trial did not measure health related quality of life (HRQoL) data for that treatment combination.

**Table 12: Summary of model structure and rationale**

Component	Description
Type of analysis	Cost-utility analysis
Outcomes	Quality adjusted life years (QALYs) Life years Progression-free life years
Time horizon	Lifetime (base case), scenario analyses of 5 years, 10 years and trial based (with extrapolation).
Discount rate	5%
Methods used to generate results	Partitioned survival model
Health states	Pre-progression: Patients enter the model in this health state and receive treatment with either lenvatinib/everolimus or everolimus monotherapy until disease progression.  Post-progression: Patients transition from the 'Pre-progression' health state into this health state upon disease progression.  Dead: This is an absorbing health state. Patients can enter this state from either the 'Pre-progression' or 'Post-progression' health states.
Cycle length	1 month (30.43 days), with half cycle correction.
Transition probabilities	The transitioning of patients is based on PFS and OS data reported in Study 205, up to data cut off, and extrapolated survival data thereafter.
Software	Microsoft Excel 2016

Source: Table 3-1, page 112 of submission.

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

**Table 13: Key drivers of the model**

Description	Method/Value	Impact
HR for OS	0.59 in base case.	High, favoured lenvatinib/everolimus.
HR for PFS	0.5 in base case.	Moderate, favoured lenvatinib/everolimus.
Mean daily dose of lenvatinib/everolimus	14 mg (taking into account impact of wastage).	High, would favour lenvatinib/everolimus if a higher mean dose in the trial had been observed (see 6.40 below).
Time horizon	An extrapolated (8.2 years) lifetime horizon was applied.	Moderate, a time horizon greater than the trial horizon or greater than 5 years previously preferred by the PBAC favoured lenvatinib/everolimus.
Treatment duration	7.6 months, the duration of treatment in Study 205.	Moderate, using duration of therapy rather than time to progression favoured lenvatinib/everolimus.
Extrapolation method	Extrapolation (KM and tail) used Weibull for OS and log-logistic for PFS.	Moderate, favoured lenvatinib/everolimus. Extrapolation with shortest tail (Gompertz) increased the ICER.
Utilities	█ for pre-progression and █ for progression, derived from literature and disutility applied for AEs.	Moderate, favoured lenvatinib/everolimus. A decrease in pre-progression utility value increased the ICER.

Source: compiled during the evaluation, reference section 3.8-3.9 of submission.

Abbreviations: AE, adverse event; CI, confidence interval; HR, hazard ratio; KM, Kaplan Meier; OS, overall survival; PFS, progression free survival.

6.47 The ESC noted that the model applied wastage to drug use when estimating resource use and costs. However, the method used applied wastage to the estimated mean doses of lenvatinib and everolimus from Study 205. It was unclear if the mean dose already incorporated wastage as may have occurred in the trial; applying wastage to

that mean dose for the purposes of the model may thus have overestimated the extent of wastage, which is likely to have favoured lenvatinib/everolimus.

6.48 The ESC also noted that lenvatinib is flat priced across the 10 mg and 4 mg strengths. This has the perverse effect that a dose of 18 mg per day (achieved with 1 x 10 mg and 2 x 4 mg capsules) costs 50% more than 20 mg per day (2 x 10 mg capsules).

6.49 An overview of the results of the economic evaluation, taking into account each of the time horizons assessed is provided in Table 14. The submission's within trial analysis inappropriately included a period of extrapolation. Excluding the extrapolated data reduced the ICER for the within trial analysis from \$75,000/QALY - \$105,000/QALY to \$75,000/QALY - \$105,000/QALY.

**Table 14: Results of the economic evaluation**

Steps	Lenvatinib/ everolimus arm costs	Everolimus monotherapy arm costs	Incremental costs	Lenvatinib/ everolimus QALYs gained	Everolimus monotherapy QALYs gained	Incremental QALYs	Incremental cost- effectiveness ratio (\$/QALY)
Trial Horizon	██████	██████	██████	1.24	0.99	0.25	██████
Extrapolated survival data: 5-year time horizon	██████	██████	██████	1.40	1.09	0.31	██████
Extrapolated survival data: Lifetime time horizon	██████	██████	██████	1.43	1.10	0.33	██████

Source: Table 3-25, page 158 of submission.

6.50 The ICER was sensitive to the time horizon applied in the economic model, reducing from \$75,000/QALY - \$105,000/QALY in the trial based horizon to \$45,000/QALY - \$75,000/QALY in the extrapolated lifetime horizon of 8.2 years. Previously, the PBAC has considered that a time horizon of five years is appropriate in the context of second line therapies for RCC (paragraph 7.9, nivolumab PSD, July 2016). With a 5-year time horizon the ICER is \$75,000/QALY - \$105,000/QALY. The ESC considered that the reduction in the time horizon to five years had a moderate effect on the ICER. The PBAC reaffirmed its previous advice that it considers a 5-year time horizon appropriate.

6.51 Sensitivity analyses indicated that the ICER was most sensitive to the estimate of OS improvement with the combination. A 20% increase in the base case HR estimate (from 0.59 to 0.7) increased the ICER from \$45,000/QALY - \$75,000/QALY to \$105,000/QALY - \$200,000/QALY. The economic model provided a series of prespecified sensitivity analyses and for the testing of the impact of some model inputs. However, for the comparison of lenvatinib with everolimus, it relied on the results of prespecified extrapolations for OS and PFS, variations in which could not be tested. This meant that the impact on the ICER of varying OS within the full range of the 95% confidence limit (0.36, 0.96) could not be tested in sensitivity analyses.

- 6.52 The model was also sensitive to the adopted method of treatment costing per cycle. The submission had used an approach of estimating the cost of treatment per cycle, which was based on the mean daily dose administered in the trial and the requested prices. Given that patients continued on study treatment after the data cut-off from which the mean dose had been calculated, and given that some patients had prematurely discontinued from the trial, it was uncertain whether the mean dose reported from the trial was a reliable estimate of what might be observed in practice. The submission did however include a sensitivity analysis which increased the treatment cost per cycle by 20%. This increased the ICER from \$45,000/QALY - \$75,000/QALY to \$75,000/QALY - \$105,000/QALY.
- 6.53 Sensitivity analyses undertaken with extrapolations that appended the shortest tails to the KM curves (Gompertz) for both the PFS and OS outcomes also had a moderate impact on the ICER. With this distribution, the ICER increased from \$45,000/QALY - \$75,000/QALY to \$75,000/QALY - \$105,000/QALY.
- 6.54 In the economic model, the cost of treatment per cycle was estimated based on the published DPMQ for everolimus. The impact of applying the costs of the everolimus, based on the effective DPMQ, was assessed during the evaluation.
- 6.55 The PBAC considered the base case ICER to be high and uncertain at the effective requested price.

**Drug cost/patient/course \$ [REDACTED]**

- 6.56 The submission provided an estimate of the average total treatment cost per patient per course of lenvatinib/everolimus of \$ [REDACTED]. This estimate was derived from the economic model that followed patients and their discounted costs through the lifetime of the disease on a per cycle basis.
- 6.57 Assuming a mean treatment dose per patient per day of 14 mg, a mean duration of treatment of [REDACTED] days (page 101 of Study 205 CSR), and the cost of \$ [REDACTED] per day that was estimated in the submission provided a similar cost per patient per course of \$ [REDACTED].
- 6.58 The mean time to progression of disease (when therapy would stop) was assessed in a sensitivity analysis as an alternative way of estimating the intervention costs per patient. In the clinical trial, median time to progression<sup>2</sup> was 14.6 months, and adopting this approach would increase the cost per patient per course to \$ [REDACTED]. This estimate is also uncertain, as it can reasonably be expected that treatment interruptions and delays will occur during treatment with the combination.

**Estimated PBS usage & financial implications**

- 6.59 This submission was not considered by DUSC.
- 6.60 The submission described an epidemiological approach used for the estimation of the total number of patients likely to be diagnosed with advanced clear cell RCC each year, and pharmaco-epidemiological data and expert opinion were used to estimate

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<sup>2</sup> Mean time to progression was not reported.

the proportion of these patients likely to be treated with first and second line agents. The estimated use and financial implications for the PBS/RPBS over the first six years of listing are summarised in Table 15. Analysis of 2016 PBS data of items processed for second line therapy in RCC indicated that the numbers presented may have been over-estimated.

**Table 15: Estimated use and financial implications for PBS/RPBS**

	Year 1 2018	Year 2 2019	Year 3 2020	Year 4 2021	Year 5 2022	Year 6 2023
<b>Estimated extent of use</b>						
Number of patients treated	■	■	■	■	■	■
Number of scripts dispensed <sup>a b</sup>	■	■	■	■	■	■
<b>Estimated financial implications of lenvatinib/everolimus therapy</b>						
Cost to PBS/RPBS	■	■	■	■	■	■
Co-payments	■	■	■	■	■	■
Cost to PBS/RPBS less co-payments	■	■	■	■	■	■
<b>Estimated financial implications for everolimus 10 mg tablets (offset)</b>						
Cost to PBS/RPBS <sup>c</sup>	■	■	■	■	■	■
Co-payments <sup>c</sup>	■	■	■	■	■	■
Cost to PBS/RPBS less co-payments <sup>c</sup>	■	■	■	■	■	■
<b>Net financial implications to PBS/RPBS</b>						
Net cost to PBS/RPBS <sup>c</sup>	■	■	■	■	■	■

Source: developed for the commentary, using data from tables 4-5, 4-9, 4-12, 4-13, 4-17 and 4-19, pages 176-184 of submission.

Notes: <sup>a</sup> Each script is assumed to require the dispensing of 30 lenvatinib 4 mg capsules, 30 lenvatinib 10 mg capsules and 30 everolimus 5 mg tablets.

<sup>b</sup> There was a typographical error in Table 4-9 of submission with the figure ■ repeated for each of the years.

<sup>c</sup> These values were corrected during the evaluation as alternative estimate of everolimus PBS utilisation shown in an attachment were used in calculation but not used in the submission.

Abbreviations: PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

6.61 At year 6, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than \$10 million per annum.

6.62 This cost is based on the published price for everolimus. The net cost to Government using the everolimus effective price was assessed during the evaluation.

6.63 The submission made a claim that there was no additional or reduced use of MBS items anticipated with the PBS listing of lenvatinib as a treatment for RCC. This claim is not reasonable. In the economic model direct medical costs associated with oncologist examinations, CT scans, GP visits and blood tests were applied on a per cycle basis in both treatment arms. On the basis of assumed longer survival, these costs would therefore be greater for lenvatinib/everolimus than for everolimus monotherapy.

6.64 A significant contributor to uncertainty in the financial estimates was the manner in which duration of therapy was estimated. The derived estimates took into account the mean dose of drug administered in the trial and the median reported duration of therapy. The mean duration of treatment reported in the trial was longer than the

median (■■■ days versus 235 days) and it is likely that the mean time to progression would be longer than the median. Consequently the approach taken in the submission may have underestimated the financial impact.

### **Risk Sharing Arrangement**

6.65 The PBAC noted the PSCR (p4) proposed a risk sharing arrangement (RSA) to mitigate the financial risk to Government from uncertainty due to the dosing and the duration of treatment with lenvatinib/everolimus in clinical practice. The proposed RSA contained caps on expenditure beyond which an agreed percentage of expenditure on lenvatinib would be rebated.

*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 lenvatinib for advanced RCC on the basis that the clinical need and the clinical place in therapy were not adequately established. In addition, the PBAC considered that the magnitude of the clinical benefit was uncertain due to the small sample size of the key clinical trial (Study 205). The PBAC considered the cost-effectiveness of lenvatinib was unable to be established, as the clinical place in therapy and hence the appropriate comparator for the evaluation, were uncertain.
- 7.2 The PBAC noted that there are many established therapies for advanced RCC with two first line and four second line therapy options currently PBS listed. The PBAC considered that concerns regarding the magnitude of clinical benefit and the toxicity profile of lenvatinib/everolimus when compared with two existing treatments (everolimus and nivolumab) meant that its clinical place in therapy was unclear.
- 7.3 The PBAC noted that Study 205 only enrolled patients with an ECOG performance status  $\leq 1$ , while the proposed PBS restriction would allow access to treatment for those with a poorer ECOG performance status of  $\leq 2$ . The PBAC considered that in practice lenvatinib/everolimus toxicity concerns would likely restrict use to patients with a performance status of  $\leq 1$ .
- 7.4 The PBAC noted that the submission nominated everolimus as the main and nivolumab as a secondary comparator with axitinib and cabozantinib as supplementary comparators. The PBAC reiterated that the clinical place in therapy of lenvatinib/everolimus was unclear given the treatments currently available. The PBAC considered that until the clinical place in therapy is established an appropriate comparator for lenvatinib/everolimus cannot be determined.
- 7.5 The PBAC noted the submission claimed superior efficacy for lenvatinib/everolimus over everolimus monotherapy in terms of PFS and OS. The PBAC considered these claims were not well supported by the data, as Study 205 was a small phase II trial which was subject to bias due to its open-label design and use of investigator assessment for progression. The PBAC considered some uncertainty in the magnitude of PFS gain remains, given the difference between the trial based assessment and the

independent review. In addition, the PBAC did not accept the claim of superior effectiveness for the outcome of OS. The PBAC was concerned that the magnitude of the reported OS gain was uncertain and noted the trial was not powered to detect such a difference.

- 7.6 The PBAC was concerned regarding the generalisability of the Study 205 results to the intended Australian population. The PBAC considered that the trial represented a selected patient population who are likely to be younger with a better clinical status (ECOG 0–1) than patients who would be eligible for PBS subsidised treatment.
- 7.7 The PBAC noted the submission claimed the results of an indirect comparison indicated a significantly reduced risk of progression associated with lenvatinib/everolimus over nivolumab. The PBAC disagreed with this claim, noting that such a comparison was biased against nivolumab given that the use of RECIST based assessments of progression are considered to underestimate the impact of immunotherapies on disease progression. The PBAC noted the OS difference for this comparison was not statistically significant.
- 7.8 The PBAC considered the naïve comparison with axitinib provided in the submission was uninformative, due to the lack of a common reference and differences across the clinical trials included in the comparison.
- 7.9 The PBAC accepted the data showed lenvatinib/everolimus was inferior in safety in the comparisons with both everolimus and nivolumab. The PBAC considered that the toxicity associated with the combination of lenvatinib plus everolimus was not insignificant, with serious adverse events of Grade 3 or 4 occurring more frequently in patients receiving this treatment regimen.
- 7.10 The PBAC considered that it was unclear as to whether the clinical positioning for lenvatinib/everolimus would be the same as that of everolimus. As a result, the PBAC considered the cost-utility analysis presented against everolimus may not be informative. In addition, the PBAC considered the resulting ICER to be high and uncertain at the requested effective price for lenvatinib and using the current effective price for everolimus. The PBAC noted that sensitivity analyses indicated that the ICER was most sensitive to the estimate of OS improvement with lenvatinib/everolimus. The PBAC also noted the ICER was sensitive to the time horizon. The PBAC advised that, consistent with the Committee's previous preference for a 5-year time horizon with second line treatment of metastatic RCC (paragraph 7.9, nivolumab PSD, July 2016), the model should be restricted to a 5-year time horizon. The PBAC considered that, given the uncertainty in the magnitude of PFS and OS gains, the assumptions around these outcomes should be more conservative.
- 7.11 The PBAC considered that an economic evaluation against nivolumab or axitinib would be more informative. The PBAC noted a limited economic analysis compared with nivolumab was provided in the PSCR (p1) and again in the pre-PBAC response (p2), but considered the data presented were insufficient to draw conclusions.
- 7.12 The PBAC considered the financial estimates uncertain, although noted that partial protection would be provided by the proposal of a risk-share agreement.

7.13 The PBAC proposed that any future submission should clearly establish the clinical need and clinical place of lenvatinib/everolimus in the context of its clinical benefit and toxicity profile and in relation to established therapies for advanced RCC.

7.14 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.