pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Lenvatinib (Lenvima) for Renal Cell Carcinoma

January 4, 2019

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding lenvatinib (Lenvima) in combination with everolimus for advanced or metastatic renal cell carcinoma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding lenvatinib (Lenvima) in combination with everolimus for advanced or metastatic renal cell carcinoma (RCC) conducted by the Endocrine Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on lenvatinib (Lenvima) in combination with everolimus for advanced or metastatic RCC, a summary of submitted Provincial Advisory Group Input on lenvatinib (Lenvima) in combination with everolimus for advanced or metastatic RCC, and a summary of submitted Registered Clinician Input on lenvatinib (Lenvima) in combination with everolimus for advanced or metastatic RCC, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The purpose of this review is to evaluate the efficacy and safety of lenvatinib (Lenvima) in combination with everolimus compared with everolimus monotherapy in adult patients with predominant clear cell advanced or metastatic renal cell carcinoma (RCC) who have been treated with one prior vascular endothelial growth factor (VEGF)-targeted agent.

Lenvatinib is a multiple receptor tyrosine kinase inhibitor that selectively inhibits the kinase activities of VEGF and fibroblast growth factor (FGF) receptors. Lenvatinib has the following pCODR reimbursement criteria: lenvatinib in combination with everolimus for the treatment of patients with advanced or metastatic, clear-cell RCC following one prior VEGF-targeted therapy. Health Canada has issued marketing authorisation for lenvatinib in combination with everolimus for the treatment of patients with advanced RCC following one prior VEGF-targeted therapy. Note that the Health Canada indication differs slightly from the reimbursement criteria, in that it does not specify ‘metastatic, clear-cell’ in its indication.

The recommended daily dose of Lenvatinib is 18 mg (one 10 mg capsules and two 4 mg capsules) in combination with 5 mg everolimus orally taken once daily. The daily dose is to be modified as needed according to the dose/toxicity management plan. Treatment should continue as long as there is clinical benefit.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one randomized-controlled trial (RCT). The results of the HOPE-205 trial (N=153) will be presented below:

HOPE-205

HOPE-205 was a multicentre, open-label phase 1b/phase 2 RCT comparing (in a 1:1:1 ratio) lenvatinib + everolimus (arm A) with lenvatinib monotherapy (arm B) and everolimus monotherapy (arm C) in adult patients with histologically or cytologically confirmed predominant clear cell advanced or metastatic renal cell carcinoma (RCC) who had been treated with one prior vascular endothelial growth factor (VEGF)-targeted agent.

Dose escalation was performed, during the Phase 1b part (n=20) of the study, to determine the maximum tolerated dose (MTD) of lenvatinib in combination with everolimus. This pCODR review will only present the efficacy results from the phase II design of the trial. Further, this review will report efficacy and safety results of arms A and C only, as single agent lenvatinib (arm B) is currently not a treatment option in Canada for 2nd line advanced or metastatic RCC and is therefore beyond the scope of this review.

The primary outcome in the trial was investigator-assessed progression-free survival (PFS), defined as the time from randomization to the first documentation of disease progression or death. Secondary outcomes included: objective response rate (ORR), overall survival (OS), disease control rate (DCR), durable stable disease, clinical benefit rate (CBR), and safety.[1,2]

The median age of the study population was 61 years, ranging from 37 to 79 years between the three study arms. The majority of study participants were 65 years of age or younger (65%), white (97%), and male (73%).[1,2] Overall, the baseline demographic and disease characteristics were well balanced between the study arms, except for number of metastases: 35% of patients in the lenvatinib + everolimus arm had only one metastasis, when compared with 10% of patients in the everolimus arm. On the other hand, a higher proportion of patients in the everolimus arm had three or more metastasis (60% vs. 35% in the lenvatinib + everolimus arm).[1,3] All patients received one previous VEGF-targeted therapy, with the most frequent agent being sunitinib (71% and 56% in the lenvatinib + everolimus and everolimus arms, respectively) and pazopanib (18% and 26% in the lenvatinib + everolimus and everolimus arms, respectively). The proportion of patients who underwent previous radiotherapy was 12 % in the lenvatinib + everolimus arm and 22% in the everolimus arm.[1,3]

Efficacy

The key efficacy outcomes of the HOPE-205 trial are presented in Table 1.1.

As of the 13-Jun-2014 data cut-off (primary analyses), after a median follow-up of 24.2 months for the lenvatinib + everolimus arm and 25 months for the everolimus arm: the median PFS was 14.6 months (95% CI 5.9, 20.1) in the lenvatinib + everolimus arm and 5.5 months (95% CI 3.5, 7.1) in the everolimus arm (Stratified HR= 0.401, 95% CI 0.239, 0.675; p=0.0005).[1,3] PFS benefit with lenvatinib + everolimus was consistent across subgroups categorized by the baseline patients characteristics.[3] ORR was significantly higher in the lenvatinib + everolimus arm (43.1%; 95% CI 29.3, 57.8) than in the everolimus arm (6.0%; 95% CI 1.3, 16.5; p<0.0001).[2,3] The median time to response was similar between the lenvatinib + everolimus (8.2 weeks) and everolimus (8.0 weeks) arms.[3] The median duration of response was higher by 4.5 months with lenvatinib + everolimus (13.0 months; 95% CI 3.7, not estimable) than with everolimus monotherapy (8.5 months; 95% CI 7.5, 9.4).[2]

At the time of the latest updated OS analysis (31-Jul-2015 data cut-off), 63% of patients in the lenvatinib + everolimus arm and 74% of those in the everolimus arm had died, with a median OS of 25.5 months (95% CI 16.4, 32.1) for the lenvatinib + everolimus arm and 15.4 months (95% CI 11.8, 20.6.6) for the everolimus arm (stratified HR = 0.59; 95% CI 0.36, 0.96; p=0.06).[2,3]

Harms

All patients in the trial reported at least one treatment emergent adverse event (TEAE). The most common TEAEs of any grade were in the lenvatinib plus everolimus arm were diarrhoea, fatigue

and asthenia. Grade 3 or 4 TEAEs occurred in 71% of patients in the lenvatinib + everolimus arm and 50% of those in the everolimus arm. The most common grade 3 TEAEs were diarrhoea (20% with lenvatinib + everolimus vs. 2% with everolimus), hypertension (14% with lenvatinib + everolimus vs. 2% with everolimus), fatigue (14% with lenvatinib + everolimus vs. 0% with everolimus), anaemia (8% with lenvatinib + everolimus vs. 12% with everolimus), hypertriglyceridemia (8% with either lenvatinib + everolimus or everolimus), and vomiting (8% with lenvatinib + everolimus vs. 0% with everolimus).[1] The incidence of grade 3 or worst serious AEs was 45% in the lenvatinib + everolimus arm and 38% in the everolimus arm.[1]

Twenty four percent of patients in the lenvatinib + everolimus arm and 12% in the everolimus arm discontinued study treatment due to adverse events.[1] One patient in the lenvatinib + everolimus arm and two patients in the everolimus arm died due to AEs.[1]

Table 1.1: Highlights of Key Outcomes in the HOPE-205 trial

	HOPE-205		
Primary Outcome	**Lenvatinib + everolimus (N=51)**	**lenvatinib (N=52)**	**everolimus (N=50)**
PFS (by Investigator)†			
Events (%)	26 (51)	38 (73)	37 (74)
Median, months (95% CI)	14.6 (5.9, 20.1)	7.4 (5.6, 10.2)	5.5 (3.5, 7.1)
HR (95% CI) vs. everolimus	0.40 (0.24, 0.68)		
p-value	0.0005		
PFS rate [%] (95% CI)			
at 9 months	56.7 (40.7, 96.9)	45.6 (31.1, 59.0)	33.4 (19.6, 47.8)
at 12months	50.9 (34.8, 64.9)	34.2 (21.0, 47.8)	21.2 (9.9, 35.5)
PFS (by Independent Radiological Review)			
Median, months (95% CI)	12.8 (7.4, 17.5)	NR	5.6 (3.6, 9.3)
HR (95% CI) vs. everolimus	0.45 (0.26, 0.79)		
p-value	p=0.003		
Key Secondary Outcomes			
OS			
Primary analysis†			
Median, months (95% CI)	25.5 (20.8, 25.5)	18.4 (13.3, NE)	17.5 (11.8, NE)
HR (95% CI) vs. everolimus	0.55 (0.30, 1.01)		
p-value	0.06		
Updated analysis‡			
Median, months (95% CI)	25.5 (16.4, NE)	19.1 (13.6, 26.2)	15.4 (11.8, 19.6)
HR (95% CI) vs. everolimus	0.51 (0.30, 0.88)		
p-value	0.02		
Final analysis††			
median, months (95% CI)	25.5 (16.4, 32.1)	19.1 (13.6, 26.2)	15.4 (11.8, 20.6)
HR (95% CI) vs. everolimus	0.59 (0.36, 0.96)		
p-value	0.06		
ORR† (CR + PR), n (%)	22 (43)	14 (29)	3 (6)
RR (95% CI) vs. everolimus	7.2 (2.3, 22.5)		
p-value	<0.0001		
Duration of objective response†, months			
median (95% CI)	13.0 (3.7, NE)	7.5 (3.8, NE)	8.5 (7.5, 9.4)
HrQoL			
		Not Available	

Safety Outcomes†**, n (%)**	**lenvatinib + everolimus (N=51)**	**lenvatinib (N=52)**	**everolimus (N=50)**
TEAEs any grade	50 (99)	49 (94)	48 (96)
Grade ≥3 TEAEs	36 (71)	41 (79)	25 (50)
Grade ≥3 SAEs	23 (45)	23 (44)	19 (38)
WDAE	12 (24)	13 (25)	6 (12)
TEADs leading to death	1 (2)	NR	2 (4)

CI = confidence interval, **CR** = complete remission; **HR** = hazard ratio, **HRQoL** = health-related quality of life, **NE** = not estimable; **NR** = not reported; ORR = objective response rate; **PR** = partial remission; **RR** = rate ratio; **SAE** = serious adverse event; **SD** = standard deviation, **TEAE** = treatment-emergent adverse event, **WDAE** = withdrawal due to adverse event

† Primary analysis data cut-off date: 13-Jun-2014

‡ Updated OS analysis data cut-off date: 10-Dec-2014

†† Final OS analysis data cut-off date: 31-Jul-2015

Limitations

The key limitations of the HOPE 205 trial are as follows:

- HOPE-205 has an open-label design which could potentially increase the risk of performance and detection biases, as both physician/ outcome assessors and patients are aware of the treatment status.
- Disease progression was determined using RECIST (version 1.1) criteria by the investigator. This could result in performance and information biases. As per request by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), the manufacturer conducted a post-hoc independent blinded radiological review for PFS.[2]
- The sample size calculation for the phase 2 part the trial, used a type II error of 0.30 (70% power), and a one-sided significance level of 0.15. By using a one-sided alpha of 15% the calculated sample size was less than if a smaller alpha had been selected (e.g., a one-sided alpha of 10% or two-sided alpha of 5%). It is possible that the HR and statistical significance observed in this small cohort of patients may represent a sample of outliers in the population and not represent the treatment effect expected in the full population. As such, it is possible that the observed treatment effect may be a false positive result or that the true treatment effect may be smaller than what was reported in this study.

  In their feedback on the initial recommendation, the submitter noted that the perceived increased risk of a false positive result given the actual data from HOPE-205 is extremely low and well within the accepted confidence intervals, confirming the efficacy of lenvatinib in combination with everolimus in the HOPE-205 trial. Furthermore, the submitter also provided feedback that a Bonferroni correction was applied to adjust for multiplicity in the primary outcome to maintain the type 1 error rate at 0.05. In response to the submitter's feedback the pCODR Methods Team acknowledges that a statistical significance for PFS was concluded based on a significance level of 0.05 (2-sided) and that by applying a Bonferroni correction to adjust for multiple comparisons of the PFS results, there was no increased risk of a type 1 error for the primary outcome. However, the results of the secondary endpoints and subgroup analyses of PFS were still at risk of type 1 error because of the lack of multiplicity adjustment. Further, there is a distinction between the type 1 error rate and a general risk of a false positive finding, the latter of which relates to the limitation of the study design. By using a one-sided alpha of 15% the calculated sample size was less than if a smaller alpha had been selected (e.g., a one-sided alpha of 10% or two-sided alpha of 5%). It is possible that the HR and statistical significance observed in this small cohort of patients may represent a sample of outliers in the population and not represent the treatment effect expected in the full population. As such, it is possible that the observed treatment effect may be a false positive result or that the true treatment effect may be smaller than what was reported in this study. Therefore, while there was no increased risk of type 1 error rate in the primary outcome, this phase II trial could be more likely to produce a false positive result than trials of larger sample size. Therefore the pCODR Methods team agreed to revise the bullet point above to:

  - The sample size calculation for the phase 2 part the trial, used a type II error of 0.30 (70% power), and a one-sided significance level of 0.15. By using a one-sided alpha of 15% the calculated sample size was less than if a smaller alpha had been selected (e.g., a one-sided alpha of 10% or two-sided alpha of 5%). It is possible that the HR and statistical significance observed in this small cohort of patients may represent a sample of outliers in the population and not represent the treatment effect expected in the full population. As such, it is possible that the observed treatment effect

may be a false positive result or that the true treatment effect may be smaller than what was reported in this study.

In addition feedback from registered clinicians was received noting that this trial was: 1) randomized and reasonably powered, 2) chose a primary outcome measure (PFS) that is commonly used as a primary outcome in larger phase III cancer trials, and 3) that the credibility of the control arm was confirmed by the ORR (6%) and PFS (5.5 months) with everolimus, which are very similar to the outcome of the everolimus control arm in the Checkmate-025 study (ORR 5% and PFS 4.4 months). In response to point (1) above, the pCODR Methods Lead noted the statistical power of a trial (i.e., ability of the study to detect a difference between the study arms when such a difference exists) is determined by several factors, including the expected magnitude of the effect, number of events (in studies with a time-to-event variable as the primary outcome), and the study design. Conventionally, large values of power are desirable (at least 80%) in clinical trials. However, to increase power, a larger sample size is required and this might not be feasible in all oncology trials. Therefore, using a power of 70% (used in the HOPE 205 trial) in a phase II trial could be considered as reasonable. Importantly, because the study has already found a statistically significant difference in the primary endpoint, this level of power should not be concerning.

In response to the second point (2) raised by the registered clinicians above, the pCODR Clinical Guidance Panel (CGP) reiterated that PFS has been suggested as a surrogate for OS in several studies. In addition, PFS in itself is an important clinical endpoint and therefore PFS represents an appropriate endpoint for randomized clinical trials in RCC. As in other tumor types such as breast cancer, PFS has been accepted as an appropriate endpoint for randomized trials across the modern RCC literature. Most randomized trials in the modern era of RCC were designed with PFS as a sole primary endpoint with very few exceptions (Checkmate 025; Checkmate 214; ARCC trials). The pCODR Methods Team agreed that PFS is a commonly-used primary outcome in oncology trials because this endpoint can be evaluated with relatively shorter follow up times, requires smaller sample size (due to greater number of events), and is not usually affected by subsequent treatments. However, as mentioned above, it is important to note that the primary objective of phase 2 (randomized or non-randomized) trials is to document the safety outcomes and investigate if the estimate of effect for a new drug is large enough to use it in confirmatory phase 3 trials.

In response to the third point (3) raised by the registered clinicians above, the CGP reiterated that the positive results in the lenvatinib/everolimus trial cannot be attributed to a suboptimal performing standard arm. The outcomes in the everolimus arm of the lenvatinib/everolimus trial are very comparable to the outcomes data of everolimus in the general RCC literature and also very comparable to the outcomes seen with everolimus in the Checkmate 025 and METEOR phase III randomized trials.

- HOPE-205 was not powered to detect a statistically significant OS benefit.
- No adjustments were made for multiplicity introduced by analysing multiple secondary endpoints or subgroup analyses of PFS. Therefore, p-values in these analyses are considered nominal. Multiple testing can increase the probability of type 1 error and, therefore, lead to false positive conclusions.

  In their feedback on the initial recommendation, the submitter noted that HOPE 205 was evaluated by Health Canada to assess the appropriateness and robustness of the statistical analyses, noting that the overall study design and statistical analysis plan were appropriate. The submitter reported that the Health Canada review specifically focused on

the potential biases of: 1) the lack of adjustment for multiplicity in the primary analyses and 2) the investigator assessment of PFS (please see this point addressed beneath the next bullet point). In addressing the first point (1) from above, the submitter suggested that when applying the most conservative Bonferroni adjustment (each of the 2 hypotheses tested at a 2-sided alpha level of 0.025), the results remain statically significant (P=0.0005). For the response by the pCODR Methods Team, to the submitter's feedback please refer to the pCODR Methods Team response to page 5 above regarding submitter's feedback on an increased risk of a false positive result.

- Subgroup analyses in the HOPE-205 trial should be considered exploratory, as the study was not designed to detect any differences between the subgroups. In their feedback on the initial recommendation, the submitter reported that the Health Canada review specifically focused on the potential bias of the investigator assessment of PFS. It was suggested that the results of key secondary endpoints of OS and ORR were consistent with the PFS. Further, the improvement in PFS was supported by sensitivity and exploratory analyses. In response to the submitter's feedback the pCODR Methods Team agrees that the results of the exploratory subgroup and sensitivity analyses, conducted to test the robustness of PFS results, and showed similar estimates to those obtained in the primary analysis; reiterating that the outcome results in each subgroup should be considered exploratory and hypothesis-generating, because of lack of adjustment for multiplicity and the exploratory nature of the analysis.
- Patient-reported quality of life outcomes have not been measured in the HOPE-205 trial. Therefore, the direction and degree to which the study treatments could impact patients' quality of life are unknown.
- HOPE-205 compared the effect of lenvatinib + everolimus with that of everolimus monotherapy. Other comparators that are potentially relevant to this review were not assessed in this trial (i.e., nivolumab and axitinib). Of note, the submitter provided an indirect treatment comparison (ITC) report that included other comparators (i.e., nivolumab, axitinib and cabozantinib (see section 7 for more details).[4] Please note that cabozantinib was not regarded as relevant comparator at the time of this pCODR review, as it is not publicly funded in any participating jurisdictions and is currently under review with pCODR.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, while current therapies are relatively tolerable among patients, patients reported that there was still a need for drug options that were less toxic. Most commonly reported side effects experienced by patients in this submission by KCC as a result of previously used therapies were fatigue and a lack of energy, diarrhea, loss of appetite, and hand-foot syndrome. While the majority of patients stated that these side effects were tolerable a significant proportion (27%) indicated that the toxicity was difficult to tolerate. KCC emphasized that the following factors were important for patients when assessing the value of a new drug: treatment choice, patient preferences and the availability of treatment alternatives within the same line of therapy, in case of treatment intolerance. Further KCC highlighted the need for new effective 2nd line treatment alternatives to afford patients the opportunity to halt disease progression, to control drug resistance, and overcome dug resistance mechanisms. By incorporating more choices for drug treatments, patients and physicians can implement treatment plans that are tailored to the individual and enable the best possible outcomes and quality of life for patients. In regards to lenvatinib and everolimus, 14 patients across Canada reported having experience with this combination of drugs. These patients gained access to lenvatinib and everolimus through various means, for example, through insurance, clinical trial, and access programs. The majority of patients considered lenvatinib and everolimus to be a very effective therapy against their kidney cancer affording them a high quality of life with side effects that are well tolerable. From a list of 13 side effects reported by patients as a result of taking the lenvatinib combination, cough was reported as being most difficult to tolerate followed by hand-foot syndrome, loss of appetite, diarrhea, fatigue/loss of energy , and nosebleeds. Most patients agreed that the benefits of the lenvatinib combination outweighed the experience of the side effects.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Comparison to nivolumab or axitinib
- Place in therapy and sequencing with currently available treatments and upcoming treatments

Economic factors:

- Drug wastage, if dose adjustments require different tablet strength

Please see below for more details.

Registered Clinician Input

Two clinician groups provided input. The clinician groups reported that lenvatinib in combination with everolimus would meet a current unmet need in the metastatic renal cell carcinoma (mRCC) space. The clinician groups outlined efficacy results in Study 205, noting that

progression-free survival was prolonged with lenvatinib plus everolimus compared to everolimus alone (14.6 versus 5.5 months). Improved overall survival of 10 months for everolimus plus lenvatinib compared to everolimus alone and an improved objective response rate (43% versus 6%) was also mentioned. The clinician groups made note of a consistent safety profile of the combination therapy compared to each agent individually, and indicated that toxicities would be manageable. In addition, one clinician group noted that the ability of the drug combination to target both the receptor tyrosine kinase and mTOR pathway is advantageous. In terms of sequencing, the clinician groups were not certain as to where in the treatment pathway the drug combination fits; one clinician group provided a reference to a figure that outlines treatments in second-line and beyond for metastatic kidney cancer. In the other clinician input, it was suggested that lenvatinib plus everolimus would either be given before or after nivolumab. Companion diagnostic testing is not required for the new drug.

Summary of Supplemental Questions

Critical appraisal of an indirect treatment comparison comparing the efficacy and safety of anti-cancer therapies in the second line treatment of advanced or metastatic renal cell carcinoma (RCC).

Given the absence of head-to-head trials, the submitter provided an indirect treatment comparisons (ITC) that included indirect comparisons of lenvatinib + everolimus with cabozantinib and nivolumab as well as a direct comparison of lenvatinib + everolimus with everolimus monotherapy. Please note that cabozantinib was not regarded as relevant comparator at the time of this pCODR review, as it is not publicly funded in any participating jurisdictions and is currently under review with pCODR.

The efficacy of lenvatinib + everolimus was compared with everolimus, cabozantinib, and nivolumab through an indirect treatment comparison using parametric fractional polynomial that does not rely on the proportional hazard assumption. The submitted indirect treatment comparison included three trials comparing lenvatinib + everolimus (HOPE-205),[1] nivolumab (CHECKMATE-025),[5] and cabozantinib (METEOR)[6] with everolimus monotherapy as the common comparator.

Point estimates of effect resulting from the ITC suggested that lenvatinib + everolimus could be superior to everolimus monotherapy, cabozantinib, and nivolumab in terms of PFS and OS (HRs < 1) in patients with advanced or metastatic RCC, 2 – 8 month after initiation of treatment. However, the credible intervals overlapped (i.e., statistical non-significance) and the results were limited by the lack of close loops in the network, limited number of studies for each treatment comparison (one study per comparison), and lack of indirect comparisons for safety data and other efficacy outcomes (including quality of life). Therefore, the relative efficacy of lenvatinib + everolimus over nivolumab and cabozantinib remained uncertain in patients with advanced or metastatic RCC who failed on prior VEGF inhibitors.

In their feedback on the initial recommendation, the submitter noted that the ITC was appropriate for decision making and performed based on the best available evidence and well-accepted methods, including appropriate handling (through fractional polynomials) of survival data that did not support the proportional hazard assumption. The submitter further suggested, that overlapping confidence intervals ["confidence intervals' as per original submitter's feedback, however, this should be corrected to be 'credible intervals'] are a common finding in ITCs and therefore not a limitation and patient characteristics across trials were generally similar, suggesting a low risk of is due to between trial heterogeneity in the ITC results. Furthermore, the submitter suggested that the CGP had made the following statement in support of the ITC: *"Overall, the company's network analyses criteria and assumption were appropriate for the comparison in question. Within*

this network analysis, lenvatinib in combination with everolimus compared favourable to the other second line therapies." In response to the submitter's feedback the pCODR Methods Team noted that overlapping credible intervals, where reported, indicate a lack of statistical significance between the comparators of interest. In the CGR, the overlapping credible intervals were not listed as a methodological limitation of the ITC. Rather, they were highlighted as a point to consider when interpreting the ITC results. The Methods Team agreed that the submitted ITC was conducted based on "best available evidence" and "well-accepted methods". In the CGR, potential limitations of the available evidence were brought into end-users' attention, with no specific concerns regarding the appropriateness of ITC methods (design and analysis). The CGP used the information in sections 6 and 7 of CGR to issue the statement cited in the Submitter's feedback (i.e., *"overall, the company's network analysis criteria and assumptions were appropriate for the comparison in question.")* However, this specific statement does not imply that the available evidence was sufficiently conclusive.

In addition, the submitter noted that an ITC between lenvatinib in combination with everolimus with axitinib is appropriate, as the assumption that axitinib and everolimus perform similarly is supported by NICE and the CGP. In response to the submitter's feedback the pCODR Methods Team confirmed that the ITC reported in the CGR (updated network that excludes sorafenib as an irrelevant comparator) does not include axitinib due to lack of evidence. The CGP confirmed that the assumption of equal effect sizes for axitinib and everolimus sounded clinically reasonable. However, the validity of an ITC is based on several fundamental methodological assumptions; without including the trial of axitinib in the ITC, these assumptions cannot be fully and directly explored, thus leaving uncertain the relative effectiveness of lenvatinib in combination with everolimus with axitinib.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 1.2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 1.2: Assessment of generalizability of evidence for lenvatinib (Lenvima) in combination with everolimus for advanced or metastatic renal cell carcinoma

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from the HOPE Trial</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Population</td><td>Histological Subtype</td><td>HOPE trial eligibility criteria required that patients have histological or cytological confirmed predominant clear cell advanced or metastatic RCC).</td><td>Do the trial results apply to patients with non-clear cell histology?
Why (why not)?</td><td>Currently, patients with non-clear cell carcinoma are treated according to clear cell cancer guidelines and it is expected that lenvatinib/ everolimus will have activity in non-clear cell RCC. Lenvatinib/ everolimus should therefore be made available to patients with non-clear cell histology (for more details see section 2.2).</td></tr>
<tr><td></td><td>ECOG Performance Status</td><td>The HOPE trial limited eligibility to patients with an ECOG performance status of 0-1. Patients with an ECOG of 2 or greater were excluded.
<table>
<tr><th>ECOG PS</th><th>LEN + EVE (n=51)</th><th>LEN (n=52)</th><th>EVE (n=50)</th></tr>
<tr><td>0</td><td>27 (53%)</td><td>29 (56%)</td><td>28 (56%)</td></tr>
<tr><td>1</td><td>24 (47%)</td><td>23 (44%)</td><td>22 (44%)</td></tr>
</table></td><td>Do the trial results (efficacy and toxicity) apply to patients with an ECOG PS of 2 or greater?
Why (why not)?</td><td>As with other targeted agents, lenvatinib/ everolimus has an acceptable and manageable toxicity profile, which will safely allow treatment for patients with performance status 0-2. This is consistent with current clinical practice where patients with performance status 2 are treated with tyrosine kinase inhibitors such as sunitinib and have shown a good benefit although these patients were initially excluded from the pivotal studies.</td></tr>
<tr><td></td><td>Brain metastases</td><td>The HOPE trial excluded patients with untreated or unstable brain metastases</td><td>Do the trial results apply to patients with brain metastases?</td><td>In clinical practice, patients with brain metastases are treated the same way as patients without brain metastases. Therefore patients with brain metastases should</td></tr>
</table>

Domain	Factor	Evidence from the HOPE Trial	Generalizability Question	CGP Assessment of Generalizability
				not be excluded from treatment with lenvatinib/everolimus.
Intervention	Treatment Intent	The treatment intent in the trial was palliative since cure is exceedingly rare with targeted agents.	Are the results of the treatment generalizable to an alternative treatment intent? (i.e., if the trial is palliative in intent, could the therapy also be used in the adjuvant setting or vice versa?)	Since the HOPE trial was a trial in metastatic patients the results cannot be generalized to the adjuvant situation. None of the adjuvant trials with targeted agents has yet demonstrated a benefit.
	Line of therapy	HOPE trial eligibility criteria required that patients had one prior VEGF-targeted treatment. Patients had to have a disease progression during or within 9 months of stopping VEGF-targeted therapy.	Do the trial results apply to patients who have previously been treated with more than one VEGF inhibitor? Why (why not)?	Since the HOPE trial included only patients with one prior VEGF-targeted therapy, no trial based conclusion can be drawn for patients pretreated with more than 1 prior VEGF-targeted therapy. However, looking at the general evidence and real world data, it appears that TKIs are active even after more than one prior, different TKI. Everolimus has previously demonstrated activity even in patients with more than 1 prior TKI (RECORD-1 study).
Comparator	Everolimus	The comparator in the HOPE trial was everolimus was administered orally, 5 mg/day once daily (28-day cycles) until disease progression, unacceptable toxic effects, or withdrawal of consent. Currently funded treatments in second line treatment of advanced or metastatic renal cell carcinoma include axitinib, everolimus and nivolumab. (Nivolumab takes 70% of the market share).	Are the findings of the HOPE trial generalizable to patients who may receive axitinib or nivolumab instead of everolimus?	The assumption that axitinib performs similarly to everolimus is justified by the available phase III[6,9] evidence as well as the available real world evidence for axitinib and everolimus. Overall, the

Domain	Factor	Evidence from the HOPE Trial	Generalizability Question	CGP Assessment of Generalizability
		The submitter provided an ITC that included indirect comparisons of lenvatinib + everolimus with cabozantinib and nivolumab as well as a direct comparison of lenvatinib + everolimus combination with everolimus monotherapy. The submitter assumed that axitinib has the same efficacy as everolimus. Please refer to the Method lead ITC assessment section 7 for more information.		company's network analysis criteria and assumptions were appropriate for decision-making. Overall, the company's network analysis criteria and assumptions were appropriate for the comparison in question. Within this network analysis, lenvatinib/everolimus compared favorably to the other second line therapies. However, the 95% credible intervals crossed 1 indicating these differences were not statistically significant. These results have to be interpreted with caution due to the methodological limitations of the indirect treatment comparison (see section 7 for more details).
Outcomes	Appropriateness of Primary and Secondary Outcomes	• Primary outcome: investigator-assessed progression free survival (PFS) • Secondary outcomes: objective response rate (ORR), overall survival (OS), disease control rate (DCR), durable stable disease, clinical benefit rate (CBR), and safety.	Were the primary and secondary outcomes appropriate for the trial design?	PFS has served as the primary endpoint in the majority of randomized second line studies. Several studies suggest that PFS maybe a surrogate for OS in first and second line setting although the correlation has not yet been firmly established. Yes, secondary endpoints were appropriate and are in line with the endpoints of other prospective

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from the HOPE Trial</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td></td><td></td><td>randomized studies.</td></tr>
<tr><td>Setting</td><td>Countries participating in the Trial</td><td>The trial was conducted at 37 centres in five countries (Czech Republic, Poland, Spain, UK, and USA).</td><td>Is there any known difference in the practice pattern between the countries that the trial was conducted in and Canada? Differences in the patterns of care might impact the clinical outcomes or the resources used to achieve the outcomes.</td><td>Since the trial was conducted in Western Europe and the US the results are fully applicable to the Canadian landscape.</td></tr>
<tr><td></td><td>Supportive medications, procedures, or care</td><td>All study participants received at least one concomitant medication.
<table><tr><th></th><th>LEN + EVE (n=51)</th><th>LEN (n=52)</th><th>EVE (n=5</th></tr><tr><td>Anti-hypertensive agents</td><td>82%</td><td>87%</td><td>60%</td></tr><tr><td>Lopereamide</td><td>59%</td><td>46%</td><td>12%</td></tr><tr><td>Thyroid preparations</td><td>53%</td><td>62%</td><td>20%</td></tr></table></td><td>Are the results of the trial generalizable to a setting where different supportive medications, procedures, or care are used?</td><td>The concomitant medication used in the HOPE trial are standard medications which are very frequently used to manage side effects of TKI and mTOR inhibitors in clinical practice.</td></tr>
<tr><td colspan="5">ECOG = Eastern Cooperative Oncology Group; ITC = Indirect treatment comparison; mTOR = mammalian target of rapamycin; TKI = Tyrosine Kinase Inhibitors; RCC = renal cell carcinoma; VEGF = vascular endothelial growth factor.</td></tr>
</table>

1.2.4 Interpretation

Burden of Illness and Need

The management of metastatic renal cell carcinoma has undergone tremendous change in the past 5-8 years.[7] An increasing understanding of the disease biology has translated into the development of various new therapeutic approaches. Targeted agents such as the small molecule tyrosine kinase inhibitors: sunitinib, pazopanib, axitinib and sorafenib; the mTOR inhibitors: everolimus and temsirolimus; and the monoclonal antibody bevacizumab have shown significant activity in the treatment of this disease.[8-13] More recently, the immunotherapy agent Nivolumab, a PD-1 inhibitor was introduced.[5] Immunotherapy combinations for example the combination of Nivolumab and Ipilumumab are currently explored and Nivolumab/Ipilimumab has received approval for patients with intermediate or poor risk metastatic RCC. A second generation TKI, cabozantinib, a new VEGFR, c-met and AXL inhibitor, has just been granted market access for the treatment of adult patients with advanced renal cell carcinoma (RCC) who have received prior vascular endothelial growth factor (VEGF)-targeted therapy.[6,14]

Sunitinib and Pazopanib are the most commonly used first-line treatment options. Everolimus, axitinib and nivolumab are the available standard second-line options in Canada. Everolimus and Axitinib were both approved based on a modest progression-free survival benefit (PFS), while Nivolumab was approved based on an overall survival (OS) benefit. For everolimus PFS was 4.9 versus 1.9 months for placebo in a large randomized phase III trial (RECORD 1 trial); while for axitinib progression-free survival was 4.8 versus 3.4 months for sorafenib in patients who had failed prior sunitinib therapy (AXIS trial).[9,15,16] Nivolumab demonstrated an improved OS of 25 months vs. 19.6 months for everolimus (p,0.001) in a randomized phase III study.[5]

At this time, no predictive biomarkers exist which would allow the rationale selection of therapy for individual patients. Long-term survival and cure are still rare for patients with metastatic RCC, particularly in the second-line setting, where response rates are only in the range of 15-25%.

Thus, there still is an unmet need in metastatic RCC for novel therapies which are associated with increased efficacy and in particular increased overall survival.

Effectiveness:

Hope-205 was a randomized phase Ib/II trial comparing lenvatinib/everolimus to lenvatinib monotherapy and everolimus monotherapy.[1] As one of the two standard second-line treatment options available in Canada at the time of conduct of the trial, Everolimus represents an appropriate comparator for this clinical scenario.

Main inclusion criteria were comparable to the inclusion criteria of other randomized trials in this setting, namely the everolimus versus placebo (RECORD-1) and axitinib versus sorafenib trial (AXIS) and included clear cell or clear cell component, good performance status, absence of brain metastases and 1 prior line of TKI therapy among others.

Patient characteristics were well balanced between the 3 groups and are consistent with the characteristics of a real life patient population.

Approximately 75 percent of patients in each treatment group had intermediate or poor disease according to IMDC criteria. The vast majority (80-90%) of patients were pretreated with either sunitinib or pazopanib.

In addition, the majority of patients had been recruited in North America or Western Europe which makes the results fully applicable to a Canadian patient population.

It is important to note that the primary endpoint of this study was investigator assessed PFS. Secondary endpoints included safety and tolerability, OS and response rate.

The combination of lenvatinib plus everolimus significantly prolonged PFS compared with single-agent everolimus (HR 0·40, 95% CI 0·24–0·68; p=0·0005). Median PFS was 14·6 months (95% CI 5·9–20·1) for lenvatinib plus everolimus and 5·5 months (95% CI 3·5–7·1) for single-agent everolimus.

Objective responses were achieved by 22 (43%) of 51 patients allocated lenvatinib plus everolimus compared with 3 (6%) of 50 who received single-agent everolimus (rate ratio [RR] 7·2, 95% CI 2·3–22·5; p<0·0001). This is the highest objective response rate ever reported in the second-line setting, although complete responses were extremely rare.

The efficacy of everolimus in this trial compares favorably with the results published in the literature making it very unlikely that the superiority of lenvatinib/everolimus was caused by suboptimal activity of single agent everolimus.

The median overall survival was 25·5 months [95% CI 16·4–NE] vs 15·4 months [11·8–19·6] (HR 0·51, 95% CI 0·30–0·88; p=0·024) for the combination of lenvatinib/everolimus and single agent everolimus, respectively. The OS reported for the combination of lenvatinib/everolimus is among the highest ever reported in the second line setting.

In their feedback on the initial recommendation, registered clinicians noted that the overall magnitude of superiority in ORR and PFS demonstrated in the HOPE-205 trial clearly favors lenvatinib in combination with everolimus over everolimus alone. In addition, the submitter reiterated the CGP's statement that lenvatinib in combination with everolimus demonstrated the "highest [ORR] ever reported in the second line setting and that "OS […] is among the highest ever reported in the second line setting." In response to the registered clinicians' and the submitter's feedback the CGP provided additional details on the activity of lenvatinib in combination with everolimus in comparison to other currently used and upcoming agents (see Table 1.3. below).

Table 1.3: Comparison of randomized trials in the second line setting after failure of first-line TKI therapy:

Treatment	Study type/ Primary endpoint	Comparator	ORR	PFS	OS
Axitinib (AXIS trial)	Phase III PFS	Sorafenib	12% vs. 8%	4.8 vs. 3.4 months	15.2 vs. 16.5 months
Nivolumab (Checkmate 025 trial)	Phase III OS	Everolimus	25% vs. 5%	4.6 vs. 4.4 months	25.0 vs. 19.6 months
Cabozantinib (METEOR trial)	Phase III PFS	Everolimus	21% vs. 3%	7.4 vs. 3.8 months	21.4 vs 16.5 months
Lenvatinib/Everolimus	Phase II PFS	Everolimus	43% vs. 6%	14.6 vs. 5.5 months	25.5 vs. 15.4 months

The CGP further noted that, as seen in Table 1.3, all relevant comparators were tested in randomized phase III studies. The comparator arms of all trials, including the lenvatinib/everolimus study, are comparable with regards to type of standard arm as well as with regards to efficacy outcomes for the standard arm. The response rate as well as PFS in the randomized phase II lenvatinib/everolimus study stands out as the highest ever reported in a second-line randomized study in metastatic RCC and were considerably and substantially higher than the ones reported from the other phase III trials. Response rate as well as PFS are important endpoints clinically but also for the patients since response and/or lack of progression are usually associated with improved quality of life. There are several studies suggesting that PFS is a surrogate and reasonable predictor for OS. Although lenvatinib in combination with everolimus study was not powered for an overall survival comparison, the reported overall survival of 25.5 months is among the highest ever reported in a second line study.

Overall, the CGP noted that, with the limitations of a randomized phase II study in mind, PFS and ORR for lenvatinib/everolimus are the best and OS among the best ever reported in the second line setting for metastatic RCC. It therefore appears to have all the important characteristics of a treatment option with great potential.

In addition, feedback from registered clinicians stated that the extremely high ORR seen with lenvatinib in iodine-refractory thyroid cancer (65% compared to 12% with sorafenib) suggests

lenvatinib has unique activity for a TKI and that this is unlikely to be a chance phenomenon. In response to the registered clinicians' feedback the CGP cautioned about comparing response rates between RCC and thyroid cancer. Response to TKIs depends significantly on tumor biology and tumor driving relevant pathways and inhibition profile of the TKI. Since the underlying tumor biology between thyroid and kidney cancer is very different, comparisons are questionable.

Safety:

The toxicity profile for lenvatinib/everolimus is consistent with the toxicity profile of other targeted agents used in RCC and included the expected toxicities for a combination of a VEGFR-TKI and an mTOR inhibitor. Grade 3 or worse serious adverse events occurred in more patients taking lenvatinib plus everolimus (45%) than in patients taking everolimus alone (38%). The incidence of grade 3 or 4 TEAEs were higher in the lenvatinib + everolimus arm at 71% (36/51), compared with 50% (25/50) in the everolimus arm. In addition, a larger proportion of patients had dose interruptions of lenvatinib (80.4%) or everolimus (76.5%) in the lenvatinib plus everolimus group compared with the everolimus alone group (54.0%), mainly because of adverse events. However, toxicity was overall acceptable and manageable.

Several issues have been raised with respect to the HOPE-205 study.

HOPE 205 was a randomized phase II trial and included a limited number of patients (around 100 patients across the lenvatinib plus everolimus and the everolimus alone groups). Small sample sizes undermine the internal and external validity of a study. When sample sizes are small, the risk that observed effects will be due to chance is higher. The trial investigators were willing to accept the risk of false-positive result of 15%. The clinical standard is to accept a type I error risk of no greater than 5%, as seen in phase III trials. In this trial the primary outcome was tested at a 2-sided alpha of 5%. This risk is especially concerning in this trial, given the one-sided alpha level of 0.15 that was used in the sample size calculation, meaning the risk of a false-positive result (i.e., Type I error) that the trial investigators were willing to accept was 15%.

While these shortcomings may increase the uncertainty regarding the extent of clinical benefit from lenvatinib/everolimus, the overall magnitude of superiority in response rate, PFS and OS clearly favors the combination of lenvatinib/everolimus over everolimus alone.

Due to the lack of head-to-head trials comparing lenvatinib/everolimus with axitinib, nivolumab or cabozantinib, the company compared the treatments indirectly using an indirect treatment comparison. Axitinib and Nivolumab are the correct comparators for the second-line situation, since cabozantinib has not been publicly funded in any participating jurisdictions and is currently under review with pCODR. The assumption that axitinib performs similarly to everolimus is justified by the available phase III evidence as well as the available real world evidence for axitinib and everolimus.[9,10,16] Overall, the company's network analysis criteria and assumptions were appropriate for the comparison in question. Within this network analysis, lenvatinib/everolimus compared favorably to the other second line therapies. However, the 95% credible intervals crossed 1 indicating these differences were not statistically significant. These results have to be interpreted with caution due to the methodological limitations of the indirect treatment comparison.

Several issues have been raised regarding the generalization and applicability of these results to certain patient populations:

The current study was limited to patients with clear cell carcinoma or tumors with clear cell components but excluded patients with non-clear cell RCC. Non-clear cell RCC is rare and patients with non-clear cell renal cell carcinoma represent a particularly difficult group. As well, there are

a number of patients labelled as non-clear cell carcinoma who in fact harbor clear cell components and thus should be eligible. Non-clear cell renal cell carcinoma includes a variety of histologically and genetically distinct subtypes with papillary, chromophobe, oncocytoma and collecting duct subtypes probably the most common ones. Due to the heterogeneity and small patient numbers larger studies are extremely difficult to complete. Today, most of these patients are treated according to clear cell cancer guidelines with targeted agents despite the lack of large randomized studies. Due to the distinct differences between clear cell and non-clear cell RCC, the results of HOPE 205 are not generalizable to non-clear cell RCC. However, given the mechanism of action of lenvatinib/everolimus as well as the results of other targeted agents in non-clear cell RCC, lenvatinib/everolimus should be made available to patients with non-clear cell histology.

Patients with performance status 2 or 3 represent a particular problem since almost all randomized RCC studies to date have excluded these patients. However, performance status should not be a criterion to exclude patients from lenvatinib/everolimus therapy. Real world data with other targeted agents such as sunitinib have shown a good benefit for TKIs even in patients with performance status 2 although these patients were initially excluded from the pivotal studies. There is no biologic reason why patients with performance status > 1 should respond differently to lenvatinib/everolimus. Given the toxicity of lenvatinib/everolimus we would caution its use in very poor performance status, ECOG > 2 patients.

Hope 205 permitted 1 prior TKI therapy as well as prior immunotherapy although only a small proportion of patients actually received both, a prior TKI and checkpoint inhibitor immunotherapy (2% and 4% in the lenvatinib/everolimus and everolimus arm, respectively). However, given the available data of other targeted agents and the completely different mechanism of action of lenvatinib/everolimus there is no reason why patients pretreated with 1 prior TKI and immunotherapy should not respond to lenvatinib/everolimus.

As with every randomized study in metastatic RCC in the targeted therapy era, patients with brain metastases were excluded from the study. The reasons for the exclusion are two-fold. Patients with brain metastases carry a worse prognosis and have a higher risk of bleeding in these metastases if not properly treated e.g. with radiation. While brain metastases are a negative prognostic factor and these patients do worse than patients without brain metastases, real world data with TKIs and mTOR inhibitors have demonstrated a benefit even for these patients. Today in clinical practice, patients with brain metastases are treated in the same way as patients without brain metastases. Therefore patients with brain metastases should not be excluded from treatment with lenvatinib/everolimus.

The results of this trial are not generalizable to the first-line situation. Randomized trials in the first-line setting are currently ongoing and will determine the value of lenvatinib/everolimus in the first-line setting.

PAG Clinical Scenario Question

Several questions have been raised regarding the applicability of these results to certain clinical scenarios:

1) For patients who do not tolerate the lenvatinib plus everolimus combination, PAG is seeking guidance on whether treatment with single agent lenvatinib or single agent everolimus is appropriate?
    a. If patients don't tolerate lenvatinib/everolimus they should be switched to one of the other options, e.g. nivolumab (or cabozantinib).
2) PAG is seeking guidance on the place in therapy for lenvatinib plus everolimus and which

patient population would benefit most from the combination and which patient population would be best suited for treatment with other available therapies.

   a. Ideally lenvatinib/everolimus should be approved for second or third line therapy after 1 prior TKI or after TKI and immunotherapy.

3) PAG noted that nivolumab is funded for patients previously treated with tyrosine kinase inhibitors and is not funded for patients previously treated with mTOR inhibitors (e.g. everolimus). Currently, everolimus is not funded for patients previously treated with nivolumab. PAG is seeking information on the benefits of using lenvatinib plus everolimus in patients who have progressed on nivolumab and of using nivolumab in patients who have progressed on lenvatinib plus everolimus.

   a. See response to questions 2. Lenvatinib/everolimus should be categorized under "TKI based" therapy and therefore be accepted as a "TKI treatment".

1.3 Conclusions

The Clinical Guidance Panel concluded that there ***is a net overall clinical benefit*** to lenvatinib in combination with everolimus compared with everolimus monotherapy for the second-line (after 1 prior VEGF-targeted therapy) treatment of advanced and metastatic RCC based on one randomized controlled phase Ib/II trial (HOPE-205) that demonstrated a clinically meaningful and statistically significant benefit in response rate, PFS and OS for lenvatinib/everolimus compared with everolimus. Based on previous experience with TKIs, the acceptable toxicity of lenvatinib/everolimus and the high unmet need for these patients, ECOG performance status of 2 or the presence of brain metastases should not exclude patients from lenvatinib/everolimus treatment.

In their feedback on the initial recommendation, the registered clinicians suggested that their clinical experience with the drug combination is supportive of the Clinical Guidance Panel's conclusion in that in their experience with lenvatinib in combination with everolimus in real-world clinical practice, patients respond very well to this treatment. In response to the registered clinicians' feedback, the CGP noted that clinical expert opinion of different kidney cancer specialists, who have experience with the regimen, consistently suggests that lenvatinib in combination with everolimus is a very active regimen with a tolerable and acceptable toxicity profile. It appears, therefore, that the regimen performs well in daily clinical practice.

In making this recommendation, the Clinical Guidance Panel considered:

- While significant advances have been achieved in recent years in the treatment of metastatic kidney cancer, it remains an incurable disease. Approximately one quarter of patients with RCC presents with metastases at diagnosis and at least one half of all patients will eventually develop advanced disease.
- Limited treatment options exist for patients with metastatic RCC who have failed first-line therapy. Axitinib and nivolumab are the only funded drugs available. These drugs have different toxicity profiles and are associated with a number of substantial side effects, including hypertension, fatigue, diarrhea, hand-foot syndrome or autoimmune syndromes, all of which can greatly impact a patient's quality of life, optimal administration of therapy and subsequent outcomes. Hence there is an urgent need for better and additional treatment options in RCC.

In their feedback on the initial recommendation, the submitter and registered clinicians suggested that there is an urgent need for better and additional treatment options in RCC. Specifically, it was noted that while existing approved therapies have led to improved patient outcomes, durable responses are still infrequent and there remains an unmet need for more active therapies that

target primary resistance mechanisms to antiangiogenic therapy, including FGFR and mTOR synergistic inhibition, which area major tumour escape mechanisms in RCC. Treatment options for patients who cannot receive nivolumab due to contraindication such as solid organ transplant or severe autoimmune disease are limited to everolimus, a much less effective drug. These patients deserve more effective treatments with manageable adverse events. In response to the submitter's and registered clinicians' feedback, the CGP reiterated that there is still an unmet need for further second/third-line treatment options. While nivolumab and axitinib are currently available and cabozantinib is going through the regulatory process at the present time, all of these agents have distinct advantages and disadvantages. Cabozantinib has not yet received a positive recommendation or funding. Lenvatinib in combination with everolimus could therefore add benefit in this portfolio. For example, given the high response rate, particularly patients with an urgent need for a tumor response (e.g. significant clinical symptoms due to disease burden or size/location) or patients with very rapidly progressing disease, who require rapid tumor control, could be excellent candidates for a combination regimen with a high response rate. Current treatment options for patients with contraindications to nivolumab are very limited (axitinib and everolimus) and lenvatinib in combination with everolimus represents an additional active option which appears superior. Although most of these exceptional patient groups are small, lenvatinib/everolimus would allow clinicians to further refine patient selection for the most appropriate treatment. Furthermore, the CGP agreed that lenvatinib is a VEGFR and FGFR inhibitor. FGFR is a known escape mechanism for VEGFR inhibitors and therefore has theoretical advantages over other second/third line agents, in particular in patients with FGF driven tumors. However, since it is currently unclear how many and which tumors utilize the FGF pathway as an escape route it is impossible to estimate the impact of this aspect.

Furthermore, it was suggested by the registered clinicians that there is no reason why patients pretreated with one prior TKI and immunotherapy should not respond to lenvatinib in combination with everolimus, which therefore could be beneficial as a third line therapy after TKI and immunotherapy. Having three lines of therapy available for patients, is extremely important in this setting as some patients will not respond to existing available therapies. In response to this feedback the CGP agreed that three lines of therapy are beneficial for patients and are certainly associated with improved outcomes, noting that most patients in Canada have already access to three lines of therapy. The CGP further reiterated that, since a small portion of patients in the lenvatinib/everolimus study was also pretreated with immunotherapy, which represents a fast growing patient population, there is no reason why patients pretreated with one prior TKI and immunotherapy should not respond to lenvatinib in combination with everolimus.

In addition, feedback from registered clinicians suggested that lenvatinib's unique dosing possibilities ultimately afford physicians a powerful novel therapy for RCC patients to address existing unmet need. In response to this feedback the CGP noted that while dosing flexibility is important and good with lenvatinib in combination with everolimus, other drugs also have some dosing flexibility, in particularly axitinib. Nivolumab has the least dosing flexibility but is usually very well tolerated and dose changes are rarely necessary nor performed.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Endocrine Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Kidney cancer accounts for approximately 3% of all cancers in Canada. In 2017, there were 6600 new cases and 1,900 kidney cancer deaths.[17] About 90% of kidney cancers are renal cell cancers (RCC), which are genetically and histologically distinctly different from carcinomas arising from the renal pelvis, which are known as urothelial carcinomas (UC). About 80% of all RCCs are of clear-cell histology, whereas 20% are classified as non-clear cell cancers and include papillary, and chromophobe subtypes amongst others. At presentation 75% of patients with RCC will have localized disease (confined to the kidney/extensive growth in the area of the kidney but no distant metastases), while about 25% are already metastatic. Of the patients diagnosed with localized disease, 30-50% of patients will eventually relapse and metastasize. The most important prognostic factor for outcome is tumour stage. Survival rates in localized stages range from 70-90% for smaller tumours (stages I and II) but drop significantly to 50-60% for patients with more extensive tumours (stage III). Patients with metastatic disease are rarely cured.[18]

Advanced or metastatic RCC is considered refractory to both conventional cytotoxic chemotherapy and conventional radiation therapy. Historically, older immunotherapy approaches like cytokines such as interferon or interleukin were the treatment of choice in the metastatic setting although only a small group of patients derived meaningful benefit and toxicity was a treatment limiting issue. In the era of immunotherapy, median overall survival across all metastatic patients was in the range of 12-14 months.[19,20] Several key prognostic factors have been identified in patients with metastatic disease that can divide metastatic patients into favourable, intermediate or poor risk groups. The most commonly used classification for mRCC in the era of targeted agents and modern immunotherapy is the IMDC (International Metastatic Renal Cell Carcinoma Database Consortium) criteria which has come into regular use for the purposes of clinical trials.[23] This classification is based on 6 clinical factors including white blood count, platelet count, hemoglobin level, time from diagnosis to treatment, calcium level and performance status.

Advances in our understanding of RCC biology and the development of new therapeutic agents (targeted therapies / antiangiogenic agents / Immunotherapy), in particular for the clear-cell subtype of RCC, have resulted in the availability of a number of new treatment options for patients with metastatic RCC.[24] This includes targeted anti-angiogenic agents as well as immunotherapy agents such as programmed-death-receptor-1 (PD-1) inhibitors.

Clear-cell carcinomas are characterized by the presence of inactivating mutations in the von-Hippel-Lindau gene. Loss of functional VHL protein results in the activation of pro-angiogenic and growth factor pathways which drive tumor progression and metastases. Elucidation of the VHL/HIF pathway has led to the successful evaluation and regulatory approval of agents targeting the VEGF and mTOR pathways which today are considered a standard of care for the treatment of kidney cancer. Targeted therapies have a distinct mechanism of action, fundamentally different from classic chemotherapy and also have a different toxicity profile.

Over the past few years, the RCC treatment landscape has changed significantly and continues to evolve rapidly. While targeted anti-angiogenic therapies are active in clear cell RCC, the vast majority of tumours eventually become treatment refractory through different, as yet poorly understood, mechanisms. Cure is still a rare outcome for metastatic RCC patients. A number of resistance and escape pathways have been described in including the c-met and FGF pathway. Therefore, agents which block the VEGF and FGF or c-met pathway maybe active in VEGF blockade refractory RCC.[25,26]

2.2 Accepted Clinical Practice

Surgery with complete removal of the tumour remains the mainstay of therapy in localized or locally advanced disease.[27] There is currently no role for neoadjuvant therapy. Studies evaluating the use of adjuvant therapy have shown mixed results. But, on the basis of the recent S-TRAC study evaluating adjuvant sunitinib in high risk RCC patients, which showed a disease-free survival benefit, despite excess toxicity, the FDA has approved adjuvant sunitinib in high risk patients.

In the setting of metastatic disease, until the introduction of targeted therapies, immunotherapy (cytokines) with low dose interferon-α, low dose interleukin-2 or high dose interleukin-2 represented the standard of care. Although these agents were helpful for a small subset of patients, the majority of patients derived no benefit or the clinical benefit was very modest and achieved at the expense of significant toxicity. Targeted therapies and now modern immunotherapy have replaced older immunotherapy as standard treatment for patients with metastatic disease.

There are currently three different classes of agents in routine clinical use in Canada for the treatment of metastatic clear-cell RCC: small molecule tyrosine kinase inhibitors (TKIs) such as sunitinib, pazopanib; inhibitors of mTOR (mammalian target of rapamycin) such as temsirolimus or everolimus; and the monoclonal PD-1 antibody nivolumab. While TKIs and m-TOR inhibitors interfere with the VEGF pathway and cell signalling, nivolumab activates the immune system by blocking PD-1.

Current treatment landscape:

Sunitinib and pazopanib, both small molecule tyrosine kinase inhibitors of the vascular-endothelial-growth-factor receptor are considered the standard treatment options in the first-line setting.[11,12]

Second Line

After failure of first-line TKI therapy, everolimus, an oral mTOR inhibitor and axitinib, a VEGFR-TKI have both been evaluated and were approved based on a PFS benefit.[9,16] In the RECORD1 trial in patients failing at least one prior line of TKI therapy Everolimus showed a significant PFS benefit over placebo (4.9 vs.1.9 months; HR 0.32).[22] In the AXIS study, in a similar population, Axitinib showed a PFS benefit over sorafenib with a median PFS of 6.7 vs 4.7 months (HR 0.67) in the overall group and 4.8 vs 3.4 months (HR 0.74) in sunitinib pretreated patients. Neither of these studies demonstrated a clear overall survival benefit.

Nivolumab is a novel fully human IgG4 programmed death 1 (PD-1) immune checkpoint inhibitor that was tested against Everolimus in a large open-label phase III study (Checkmate 025) of 821 mRCC patients failing one or two lines of prior TKI therapy. The median overall survival was 25.0 months (95% confidence interval [CI], 21.8 to not estimable) with nivolumab and 19.6 months (95% CI, 17.6 to 23.1) with everolimus. The confirmed response rates were 21.5% versus 3.9%; median durations of response were 23.0 versus 13.7 months.[5]

In their feedback on the initial recommendation, the registered clinicians and the patient advocacy group noted that there are few head-to-head comparisons between currently approved drugs in the 2nd line setting and given the historically limited patient population available for 2nd and 3rd line treatment in metastatic RCC, phase III trials are not always feasible. In response to the feedback the CGP noted that although it is challenging to perform randomized trials in the second and third line setting of metastatic RCC, at least 5-6 randomized trials have been successfully performed. An additional challenge is the constantly changing therapeutic landscape in first and second line RCC due to the introduction of novel therapies.

Although now approved in second line, there is still a majority of patients that will not respond to Nivolumab, or will respond and subsequently progress, for whom there are no curative options, underscoring the need for new treatment strategies.

One strategy is to combine agents with no or only partial cross resistance. Lenvatinib/ Everolimus are a combination of a VEGFR/FGFR TKI and the mTOR inhibitor everolimus. Lenvatinib not only blocks the VEGF pathway but also the FGF pathway which is a mechanism of resistance to VEGF inhibitors which forms the rationale to administer lenvatinib after failure of a previous VEGFR-TKI.

2.3 Evidence-Based Considerations for a Funding Population

The currently available evidence supports the use of lenvatinib in combination with everolimus monotherapy or patients with the following criteria:

- Metastatic or advanced, inoperable renal cell carcinoma
- Clear cell histology or clear cell component
- Failure of one prior line of TKI therapy ± a line of immunotherapy.

Currently, no clinically useful and reliable biomarkers exist for the prediction of response and/or benefit.

2.4 Other Patient Populations in Whom the Drug May Be Used

Patients with non-clear cell renal cell carcinoma represent a particularly difficult group. Non-clear cell renal cell carcinoma includes papillary, collecting duct, chromophobe and a number of other kidney cancer subtypes. Due to the heterogeneity and small patient numbers larger studies are extremely difficult to complete. Today, most of these patients are treated according to clear cell cancer guidelines despite the lack of large randomized studies.

Patients after complete resection of their primary tumor and no metastases (adjuvant treatment of localized RCC) have a certain risk of recurrence depending on their disease stage. No adjuvant therapy is yet approved in Canada and standard of care remains observation after complete resection of the local tumor.

A number of active drugs are now available for the treatment of metastatic RCC for patients who have failed several lines of therapy including several TKIs.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group input on lenvatinib for renal cell carcinoma was submitted by Kidney Cancer Canada (KCC). Input provided by KCC is summarized below.

KCC obtained patient and caregiver information through the use of online surveys and follow-up telephone interviews. Surveys contained free-form commentary, scoring options and limited closed questions. An interview guide was used during the live telephone interviews.

Through the online surveys, conducted between June 8, 2018 and June 19, 2018, KCC was able to obtain information from a total of 168 patients and caregivers (150 and 18 out of 168 completed English and French versions, respectively). The majority of the surveys were completed in Canada (n=160, 95%) representing nine provinces and one territory. There were also responses from the US (n=5, 3%), France (n=2, 1%) and Australia (n=1, 1%). A total of 69 respondents (41%) were individuals living with cancer, 69 respondents (41%) were survivors of kidney cancer, and 30 (18%) were caregivers. There were 14 respondents who indicated having experience with lenvatinib and everolimus to treat their kidney cancer from five provinces across Canada (Alberta n=1, Ontario n=8, New Brunswick n=2, Nova Scotia n=1, and Quebec n=2).

From a patient's perspective, the most commonly reported side effects experienced as a result of previously used therapies were fatigue and a lack of energy, diarrhea, loss of appetite, and hand-foot syndrome. While the majority of patients stated that these side effects were tolerable a significant proportion (27%) indicated that the toxicity was difficult to tolerate. KCC emphasized that the following factors were important for patients when assessing the value of a new drug: treatment choice, patient preferences and the availability of treatment alternatives within the same line of therapy, in case of treatment intolerance. Further KCC highlighted the need for new effective 2nd line treatment alternatives to afford patients the opportunity to halt disease progression, to control drug resistance, and overcome dug resistance mechanisms. By incorporating more choices for drug treatments, patients and physicians can implement treatment plans that are tailored to the individual and enable the best possible outcomes and quality of life for patients. In regards to lenvatinib and everolimus, 14 patients across Canada reported having experience with this combination of drugs. These patients gained access to lenvatinib and everolimus through various means, for example, through insurance, clinical trial, and access programs. The majority of patients considered lenvatinib and everolimus to be a very effective therapy against their kidney cancer affording them a high quality of life with side effects that are well tolerable. From a list of 13 side effects reported by patients as a result of taking the lenvatinib combination, cough was reported as being most difficult to tolerate followed by hand-foot syndrome, loss of appetite, diarrhea, fatigue/loss of energy, and nosebleeds. Most patients agreed that the benefits of the lenvatinib combination outweighed the experience of the side effects.

Please see below for a summary of specific input received from KCC. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that were reported have also been reproduced according to the submission and have not been corrected.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Kidney Cell Carcinoma

KCC noted that kidney cancer is the sixth and eleventh most common cancer among men and women, respectively. Estimated by the Canadian Cancer Society (CCS) in 2017, 6,600 new cases of kidney cancer were diagnosed in Canada, approximately 25% of which were estimated to be diagnosed with stage IV kidney cancer. According to CCS, there is currently no known cure for

metastatic renal cell carcinoma (mRCC); patients with renal cell carcinoma localized to the kidney can often be cured, unlike patients with mRCC for whom the 5-year survival rate is less than 10%. However, KCC mentioned that there have been significant improvements in survival for patients with kidney cancer over the last decade due to new innovative treatments and improved access to treatments.

3.1.2 Patients' Experiences with Current Therapy for Kidney Cell Carcinoma

KCC highlighted that a main challenge for patients with mRCC, as well as for their physicians, is that complete response to treatment with a single agent is rare and eventual resistance to first line treatment is almost certain. While sequential treatment with existing second-line therapies have shown some effects in dealing with this drug resistance, over 75% of patients do not respond to second-line therapies. Therefore, KCC urged for improved treatment options with greater effects.

KCC asked respondents to report treatments, other than lenvatinib and everolimus, they had previously used; 80 survey respondents responded to this question with the majority of patients having used sunitinib (74%), followed by nivolumab (29%), and axitinib (25%; Table 1). Seventy-eight individuals reported on the side effects experienced from previously used therapies; side effects reported by over half of respondents were fatigue/lack of energy (79%), diarrhea (67%), and loss of appetite (53%). Other side effects are reported in Table 2.

When asked to rate the side effects of their previously used treatments on a scale from 1 to 5 where 1 is "completely intolerable" and 5 is "very tolerable", 79 patients responded. While 29% of patient respondents rated their side effects as easy to tolerate (4 or 5 on the scale) the majority of patients rated their side effects as tolerable (3 on the scale) and 27% of patients indicated that they find current treatments difficult to tolerate (1 or 2 on the scale). The weighted average of responses was 3.08 out of 5 (Table 3A). When asked to rate how important it was for respondents to be able to make treatment choices together with their physicians based on known side effects, on a scale from 1 to 5 (where 1 is "not important" and 5 is "very important") 72 patients responded. The majority of patient respondents felt very strongly about consideration of side effects associated with their treatment options, with 49 out of 72 (68%) patients choosing the "very important" (rating of 5) option. The weighted average of responses was 4.15 out of 5 (Table 3B).

KCC emphasized that the following factors were important when assessing the value of a new drug: treatment choice, patient preferences and the availability of treatment alternatives within the same line of therapy, in case of treatment intolerance.

Table 1: Previously Used Therapies by Respondents from the KCC Survey

Treatment	N (%)*
Sunitinib	59 (74)
Nivolumab	23 (29)
Axitinib	20 (25)
Everolimus	17 (21)
Pazopanib	12 (15)
Cabozantinib	9 (11)
HD-IL2	7 (9)
Sorafenib	5 (6)

Treatment	N (%)*
Temsorolimus	1 (1)
Other	23 (29)
*Total sample size: 80	

Table 2: Side Effects Experienced from Previously Used Therapies

Side effect	N (%)
Fatigue/lack of energy	62 (79)
Diarrhea	52 (67)
Loss of appetite	41 (53)
Hand-foot syndrome	35 (45)
Skin problems*	31 (40)
Nausea/vomiting	29 (37)
Pain	24 (31)
Shortness of breath	22 (28)
Bleeding	12 (15)
Fever	7 (9)
Other[1]	21 (31)
*including itching (pruritus) and rash [1] including mouth sores, coughing, insomnia	

Table 3: Perceptions of the survey participants about the side effects

A.

In general, how would you rate the side effects of these treatments? N=79					
1 (completely intolerable)	**2**	**3**	**4**	**5 (very tolerable)**	**Weighted Average (WA)**
3 (4%)	18 (23%)	32 (41%)	17 (22%)	8 (10%)	**3.08**

B.

How important it was for you and your physician to be able to make a choice of drug(s) based upon each different drug's known side effects? N=72					
1 (not important)	**2**	**3**	**4**	**5 (very important)**	**Weighted Average (WA)**
2 (3%)	4 (6%)	12 (17%)	5 (7%)	49 (68%)	**4.15**

3.1.3 Improved Outcomes

Acknowledging the positive impacts of new therapies on patient outcomes within the last 12 years, KCC indicated a need for therapies that do more to improve the outlook of patients

with advanced disease, effective predictive and prognostic biomarkers to better guide treatments and detect diseases at earlier stages, and more effective therapies with manageable side effects that escape resistance mechanisms to antiangiogenic therapy. While second-line therapies are available to help address drug resistance to antiangiogenic treatments, KCC urged that patients are requiring more effective options that offer better long-term control of the disease. KCC suggests that clinical trial data show that lenvatinib and everolimus seems to be effective in overcoming VEGF-targeted therapy resistance, possible because it targets multiple mechanisms of angiogenesis.

KCC indicated that immunotherapies are available to patients as an available treatment option, but that patients faced the risk of severe, and potentially life-threatening side effects or required hospitalization. KCC urged that, should patients find immunotherapy an unsuitable therapy, another option should be made available to them.

Using a scale from 1 (not important) to 5 (extremely important), respondents in KCC's survey were asked to rate the importance of having an improved physical condition, such as a decrease in the size of/stabilization of their tumours, reducing pain or improved breathing, overall improvement in their quality of life, or a chance for long-term stability or reduction of disease when considering taking a new therapy to combat their kidney cancer. In all cases, the majority of respondents indicated that each of those aspects of treatment considerations were extremely important, with weighted averages of 4.65, 4.68, and 4.81 out of 5 for an improved physical condition, an overall improvement in quality of life, and a chance for long-term stability or reduction of disease, respectively.

KCC emphasized that access to new effective 2nd line treatment alternatives is critical to afford patients the opportunity to halt disease progression, to control drug resistance, and overcome dug resistance mechanisms. KCC further noted, that more choice in this setting enables patients and oncologists to individualize treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible outcomes and quality of life for patient.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Experiences with Lenvatinib and Everolimus

Overall, 14 patients from across Canada reported having experience with the combination of lenvatinib and everolimus for the treatment of RCC. Five patients reported gaining access to lenvatinib and everolimus through a clinical trial (four in Canada, and one outside of Canada), five patients reported accessing lenvatinib and everolimus through a manufacturer-sponsored access program, and one patient explained that their *"private insurance pays for the everolimus and the drug company pays for the lenvatinib"*.

Patients were asked to rate the overall effectiveness of lenvatinib and everolimus on a scale from 1 (not effective) to 5 (extremely effective). Out of nine patients, five reported that lenvatinib and everolimus was extremely effective; the weighted average rating was 4.22 out of 5. No patients rated lenvatinib and everolimus as not effective (a score of 1). When rating the quality of life while on the combination of lenvatinib and everolimus on a scale of 1 (low/seriously impacted) to 5 (high/normal living), seven patients indicated a high quality of life (rating of 4 or 5); the weighted average of the responses was 3.78 out of 5. Patients were also asked to rate the tolerability of lenvatinib and everolimus on a scale from 1 (completely intolerable) to 5 (very tolerable). Out of ten patients, most (n=6) reported a score of either 3 or 4; the weighted average of scores was 3.1 out of 5 (Table 4).

Table 4: Patient Reported Experiences with Lenvatinib and Everolimus

How would you rate lenvatinib and everolimus in its effectiveness in controlling your kidney cancer?						
1 not effective	**2**	**3**	**4**	**5 extremely effective**	**Total**	**Weighted Average**
n=0	n=1	n=1	n=2	n=5	9	**4.22**
How would you rate your quality of life (QoL) while taking lenvatinib and everolimus?						
1 Low QOL	**2**	**3**	**4**	**5 High QOL**	**Total**	**Weighted Average**
n=1	n=1	n=0	n=4	n=3	9	**3.78**
How would you rate the side effects of lenvatinib and everolimus?						
1 Completely interoperable	**2**	**3**	**4**	**5 Very tolerable**	**Total**	**Weighted Average**
n=1	n=2	n=3	n=3	n=1	10	**3.1**

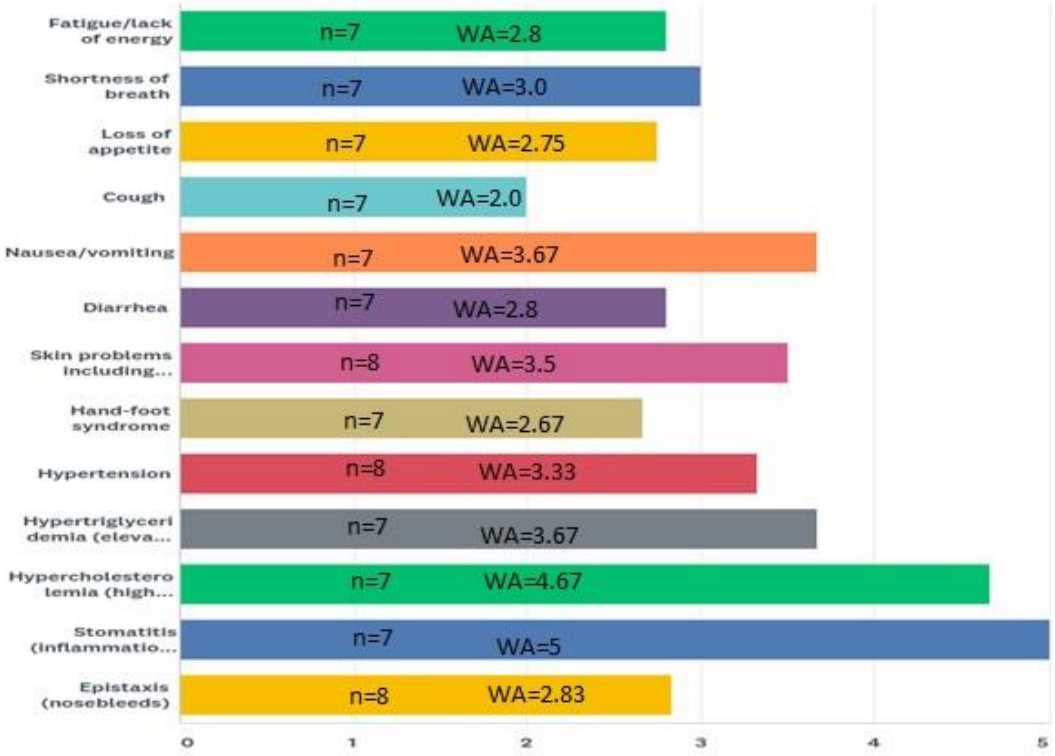
QoL = quality of life

A list of side effects experienced as a result of lenvatinib and everolimus are provided in Figure 1, in addition to their rated tolerability on a scale from 1 (completely intolerable) to 5 (very tolerable). Aside from cough, hand-foot syndrome, loss of appetite, diarrhea, fatigue/loss of energy, and epistaxis (nosebleeds) all reported side effects had a weighted average score of at least 3.

- When asked by KCC to report on side effects that were particularly difficult to tolerate the following quotes were provided by KCC from four patients: *"High protein counts in my urine has caused my oncologist to stop Lenvatinib twice (for one week each time) and reduce dose. I started at 18mg, dropped to 14mg and just dropped to 10mg."*
- *"High blood pressure, edema and significant proteinuria."*
- *"Insomnia, loss of appetite, fatigue."*
- *"Vomissements à cause de l'everolimus."*

Among nine patients who experienced side effects from lenvatinib and everolimus, seven patients reported that the benefits outweighed the experience of the side effects; the remaining two patients were waiting for results of an upcoming CT scan and did not comment on tolerability of their experienced of side effects.

Figure 1: Side Effects Experienced due to Lenvatinib and Everolimus & Their Rated Tolerability



3.3 Additional Information

Between June 15, 2018 and June 20, 2018 KCC conducted three telephone interviews with patients who had experience with lenvatinib and everolimus. All three patients were male. Two patients were between 50 and 65 years of age, while information regarding age was not provided for the third patient. All three patients had a nephrectomy, and previous treatments for these three patients included sunitinib and potentially pazopanib (it is still unclear whether one patient actually received pazopanib as he was part of a blinded trial comparing pazopanib to placebo). After being given lenvatinib and everolimus, all three males experienced tumour shrinkage; between these three patients, tumour shrinkage was reported to be between 12% to over 30% in some areas.

KCC included information regarding side effects from one of the three patients interviewed; one patient reported mouth sores and cankers as side effects due to lenvatinib and everolimus; however, he mentioned that these side effects are now well managed, and that he was able to spend his time continuing his recreational pursuits, living normally and maintaining a good quality of life. He also mentioned that he was seeing results which made him and his wife and family "very happy". While taking lenvatinib and everolimus another patient reported experiencing serious insomnia which resulted in fatigue and loss of appetite. However, according to KCC the patient insisted that the insomnia was a result of anxiety associated with kidney cancer instead of lenvatinib and everolimus. This patient reported a significant positive change to his quality of life as a result of treatment on lenvatinib and everolimus, allowing him to remain physically and socially active; for example, he stated:

"*…on the treadmill for half hour and many days walking the full length of Humber River. I move at a moderate pace and can clean house now. A few weeks ago not possible*." This patient also stated, "*This treatment has been a great success in shrinking my tumors. Great success! I don't know how my life would be now if I didn't have access to this treatment*."

The final patient described himself as being in “very rough shape” before taking lenvatinib and everolimus. According to KCC, this patient was reported to have returned to his previous vigour and resumed his social and recreational activities. It should be mentioned that he was awaiting another set of scans at the time of his interviews; he was confident that, after having failed two previous therapies, the results of the scan were going to be positive.

Among the three patients interviewed by KCC, all report positive experiences taking the combination treatment of lenvatinib and everolimus. All patients reported reduction and tumour size, and a return to relatively normal living and good quality of life.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of lenvatinib in combination with everolimus monotherapy for advanced or metastatic renal cell carcinoma (RCC).

Clinical factors:

- Comparison to nivolumab or axitinib
- Place in therapy and sequencing with currently available treatments and upcoming treatments

Economic factors:

- Drug wastage, if dose adjustments require different tablet strength

Please see below for more details.

4.1 Currently Funded Treatments

Currently funded treatments in second line treatment of advanced or metastatic renal cell carcinoma include axitinib, everolimus and nivolumab. PAG noted at the time of the trial starting, everolimus would have been the appropriate comparator. However, axitinib and nivolumab would be the more appropriate comparator now. Thus, information comparing lenvatinib to axitinib or nivolumab would be helpful for implementation, if lenvatinib plus everolimus is recommended.

PAG noted that there is an ongoing review on nivolumab plus ipilimumab for renal cell carcinoma.

4.2 Eligible Patient Population

PAG is seeking clarity on the patients eligible for treatment with lenvatinib plus everolimus. The trial only included patients with clear cell histology and PAG is seeking guidance on whether the trial results can be generalized to include patients with non-clear cell histology. In addition, PAG is seeking guidance on the use of lenvatinib plus everolimus in patients previously treated with more than one VEGF inhibitor.

PAG is seeking confirmation that lenvatinib plus everolimus would be a treatment option for patients with good performance status.

As the trial excluded patients with untreated or unstable CNS metastases, PAG identified that patients with brain metastasis would not be eligible for lenvatinib plus everolimus.

4.3 Implementation Factors

Additional resources may be required to monitor and treat adverse events as there is a relatively high incidence grade 3 to 4 adverse events. PAG identified that potential dose adjustments for both lenvatinib and everolimus may result in drug wastage, if dose

adjustments are made prior to finishing the tablets dispensed.

For patients who do not tolerate the lenvatinib plus everolimus combination, PAG is seeking guidance on whether treatment with single agent lenvatinib or single agent everolimus is appropriate.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the place in therapy for lenvatinib plus everolimus and which patient population would benefit most from the combination and which patient population would be best suited for treatment with other available therapies.

PAG noted that nivolumab is funded for patients previously treated with tyrosine kinase inhibitors and is not funded for patients previously treated with mTOR inhibitors (e.g. everolimus). Currently, everolimus is not funded for patients previously treated with nivolumab. PAG is seeking information on the benefits of using lenvatinib plus everolimus in patients who have progressed on nivolumab and of using nivolumab in patients who have progressed on lenvatinib plus everolimus.

4.5 Companion Diagnostic Testing

None

4.6 Additional Information

None

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician groups provided input. The clinician groups reported that lenvatinib in combination with everolimus would meet a current unmet need in the metastatic renal cell carcinoma (mRCC) space. The clinician groups outlined efficacy results in Study 205, noting that progression-free survival was prolonged with lenvatinib plus everolimus compared to everolimus alone (14.6 versus 5.5 months). Improved overall survival of 10 months for everolimus plus lenvatinib compared to everolimus alone and an improved objective response rate (43% versus 6%) was also mentioned. The clinician groups made note of a consistent safety profile of the combination therapy compared to each agent individually, and indicated that toxicities would be manageable. In addition, one clinician group noted that the ability of the drug combination to target both the receptor tyrosine kinase and mTOR pathway is advantageous. In terms of sequencing, the clinician groups were not certain as to where in the treatment pathway the drug combination fits; one clinician group provided a reference to a figure that outlines treatments in second-line and beyond for metastatic kidney cancer. In the other clinician input, it was suggested that lenvatinib plus everolimus would either be given before or after nivolumab. Companion diagnostic testing is not required for the new drug.

Please see below for details from the clinician group inputs. Quotes are reproduced as they appeared in the original input, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification.

5.1 Current Treatment(s) for Advanced or Metastatic Renal Cell Carcinoma

The clinician groups reported that the current standards of care following first line are: nivolumab or axitinib.

In one clinician input submission, it was reported that the currently approved and available second-line and third-line are: nivolumab, everolimus, and several tyrosine kinase inhibitors (TKI) including axitinib, sorafenib and sunitinib. It was noted that although a number of treatments are available, there are limitations and contraindications associated with some of them. It was also noted that drug efficacy research is evolving, such that historical comparators are being displaced by newer treatments with improved efficacy or tolerability.

The current treatments and their role in renal cell carcinoma were described individually by a group of clinicians and summarized below.

Available/Approved treatments in the 2nd line:

Nivolumab, an immune checkpoint inhibitor, was described as demonstrating improved overall survival compared to everolimus alone in patients with previously treated mRCC, however, the objective response rate was 25%, suggesting the majority of patients will not respond to this therapy. As well, it was noted that some patients have contraindications to nivolumab (i.e. some patients were excluded in the CheckMate 025 Study), and that nivolumab has different side effects than traditional therapy, which include immune-mediated reactions that may be life-threatening. It was stated: "*An additional treatment selection consideration is that because there are no currently-approved, funded 3rd line treatments in Canada for patients who progress after being treated in the 2nd line with publicly funded nivolumab, the selection of 2nd line nivolumab carries the significant risk to patients of having no further treatment options being publicly funded.*"

For axitinib, clinicians noted a past pCODR review in which the Kidney Cancer Research Network of Canada (KCRNC) responded to a Request for Advice from pCODR - it was shown that axitinib had a

statistically better time to treatment failure than everolimus in the second line but with similar overall survival outcomes. This evidence supported use of axitinib in patients post first line VEGFR-TKI regardless of intolerance or contraindication to everolimus.

Everolimus, an oral mTOR inhibitor, is funded for patients previously treated with a TKI, for second-line use in mRCC after progression on first-line VEGF TKI treatment. It was stated: "*everolimus was found to be inferior to the experimental arm in two large, randomized, phase 3 clinical trials (Nivolumab in CHECKMATE 025 and cabozantinib in METEOR), where the majority of patients were studied in the 2nd-line setting. Given these results, everolimus is likely not the optimal single-agent of choice for patients post-initial VEGFR TKI therapy.*"

Sunitinib and sorafenib are both available in the second line after previous treatment with cytokine-based treatment. It was stated: "*Cytokines such as interleukin-2 (IL-2) and interferon-a (IFN) have had historic utility in the treatment of mRCC; however, in the context of contemporary options (ie VEGF-TKIs) with improved efficacy and less toxicity, current use has generally fallen out of favor and high-dose IL-2 is offered only to a small percentage of patients in few centers. Therefore, the use of sunitinib and sorafenib in the 2nd line is an exceedingly rare clinical scenario."*

Available/Approved treatments in the 3rd line:

Third line options that were noted were nivolumab and everolimus. Nivolumab is funded for treatment of patients with advanced or metastatic RCC with disease progression after at least one prior anti-angiogenic systemic treatment and who have good performance status. Everolimus is available for treatment of patients with advanced or metastatic RCC with disease progression after at least one prior anti-angiogenic systemic treatment and who have good performance status. It was noted that single-agent everolimus is not an ideal option in patients with previously treated mRCC.

5.2 Eligible Patient Population

The clinicians providing input indicated that the population in the funding request meets the needs in the clinical practice setting. It was reported by clinicians that based on available clinical trials, only 50% of patients who receive first line therapy go on to receive second line treatment. It was suggested that it would be reasonable to assume that a portion of patients eligible for public drug coverage requiring second line treatment would be prescribed lenvatinib in combination with everolimus.

5.3 Relevance to Clinical Practice

It was indicated by clinicians that there is an unmet need in this space. Clinicians felt that while existing approved therapies have led to improved patient outcomes, durable responses are still infrequent and therefore there remains an unmet need for more active therapies that target resistance mechanisms to antiangiogenic therapy. Clinicians added that lenvatinib in combination with everolimus is a novel therapy that can meet the current need. It was reported that there are no current treatment options after nivolumab, and that lenvatinib has shown to be superior to axitinib. To add to this, it was reported that lenvatinib has shown improvements in overall survival (OS) compared to axitinib, but there is no current OS comparison to nivolumab. Clinicians reported that lenvatinib has more toxicities than nivolumab, but has demonstrated a superior response rate. As well, clinicians noted that lenvatinib in combination with everolimus also demonstrated superior PFS compared to everolimus alone.

To elaborate, clinicians reported on some of the trial results. It was stated: "l*envatinib in combination with everolimus significantly prolongs progression-free survival versus everolimus alone (14.6 versus 5.5 months). Further, 43% of patients assigned lenvatinib plus everolimus achieved an objective response compared with 6% of those assigned everolimus alone. More*

importantly, there is a clinically meaningful overall survival benefit in patients treated with lenvatinib plus everolimus compared to everolimus alone of an additional 10 months." I

It was also reported that the safety data from Study 205 showed that adverse events related to lenvatinib plus everolimus were consistent with known effects of each individual agent. In addition, clinicians felt that these effects are manageable with supportive care of pharmacological interventions.

Furthermore, clinicians felt that the synergistic effect of targeting both the receptor tyrosine kinase and mTOR pathways is advantageous over current therapies that target one pathway. It was also noted that the lenvatinib plus everolimus combination is an oral therapy and therefore patients may find it preferable over non-oral agents such as nivolumab, which requires intravenous transfusions.

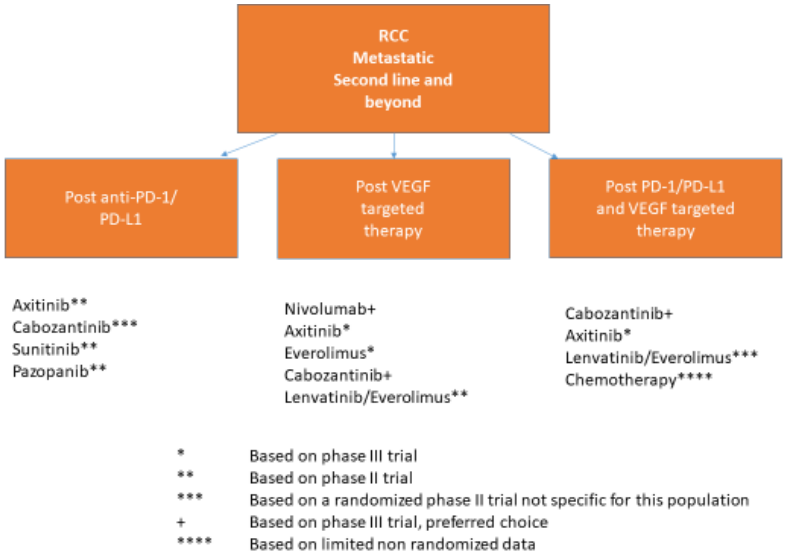
5.4 Sequencing and Priority of Treatments with New Drug Under Review

In one clinician input submission, it was reported that lenvatinib in combination with everolimus would either be given before or after nivolumab.

In the other clinician input submission, it was reported that the treatment algorithm for advanced RCC is dynamic, and because there are few head-to-head trials with second line treatments, the optimal for advanced RCC beyond first-line VEGF TKIs is relatively undefined.

One clinician group included the diagram below from "*Management of advanced kidney cancer: Canadian Kidney Cancer Forum (CKCF) consensus update 2018*" to provide some context as to how lenvatinib plus everolimus could be sequenced with current therapies.

Figure 1: Treatments in the Second line and Beyond for Patients with Metastatic Kidney Cancer



5.5 Companion Diagnostic Testing

Not required.

5.6 Additional Information

One clinician group noted that they recognize that there are very few head-to-head comparisons between currently approved drugs in the second line, and given the relatively small patient population requiring second line and third line treatment, very few head-to-head trials are to be expected.

This clinician group also highlighted specific pCODR submissions that are currently under review or expected (in different settings – first line, second line), and noted that along with these treatments, there are other combination agents in ongoing clinical trials that may also emerge as viable treatments for renal cell carcinoma.

It was also mentioned that Health Technology Assessment committees may encounter some uncertainty in the clinical data for some of these treatments, and that the (relatively) rapid adoption of new treatments may also result in lack of clarity as to the optimal sequencing of these new agents. However, it was expressed that KCRNC is uniquely positioned to provide real world evidence on survival, toxicities, cost-effectiveness, and drug utilization through use of the Canadian Kidney Cancer information system (CKCis), and that KCRNC is prepared to work with the pan Canadian Pharmaceutical Alliance and pCODR to support evidence-building on an ongoing basis for new and existing drugs approved for use in Canada for mRCC.

6 SYSTEMATIC REVIEW

6.1 Objectives

The objective of this review is to evaluate the efficacy and safety of lenvatinib in combination with everolimus for the treatment of patients with advanced or metastatic renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF) targeted therapy.

Note: The following Supplemental issue, most relevant to the pCODR review and to the Provincial Advisory Group, was identified while developing the review protocol and is outlined in section 7:

> Issue 1: Critical appraisal of a indirect treatment comparison comparing the efficacy and safety of anti-cancer therapies in the second line treatment of advanced or metastatic RCC.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the pCODR Clinical Guidance Panel (CGP) and the pCODR Methods Team. Studies will be chosen for inclusion in the review based on the criteria in Table 6.1. The literature search strategy and detailed methodology used by the pCODR Methods Team has been provided in Appendix A.

Table 6.1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of Lenvatinab plus everolimus for RCC will be included.	Adult patients with histologically verified advanced or metastatic RCC who progressed on one prior VEGF targeted therapy (second-line setting). <u>Subgroups:</u> – Age (≤65 years vs. >65 years) – Sex (male vs. female) – Baseline ECOG performance status (0 vs.1) – Corrected serum calcium level (≥10 mg/dL vs. <10 mg/dL) – Baseline hemoglobin level (≤ 13 or 11.5 [female] vs. >13 or 11.5 [female])	lenvatinib (18 mg/day) plus everolimus (5 mg/day)	everolimus (10 mg/day) Nivolumab Axitinib	Efficacy <u>Primary</u>: • PFS <u>Secondary</u> • OS • ORR • Disease control rate • Durable stable disease Safety • AEs • SAEs • WDAE Patient-reported outcomes/ QoL

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
	– Baseline hypertension status (Yes vs No)			

AE = adverse events; **ECOG** = Eastern Cooperative Oncology Group; **ORR** = objective response rate; **OS**= overall survival; **QoL**=health-related quality of life; **RCC** = renal cell carcinoma; **RCT**=randomized controlled trial; **SAE**=serious adverse events**; VEGF** = vascular endothelial growth factor**;** **WDAE**=withdrawal due to adverse events

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

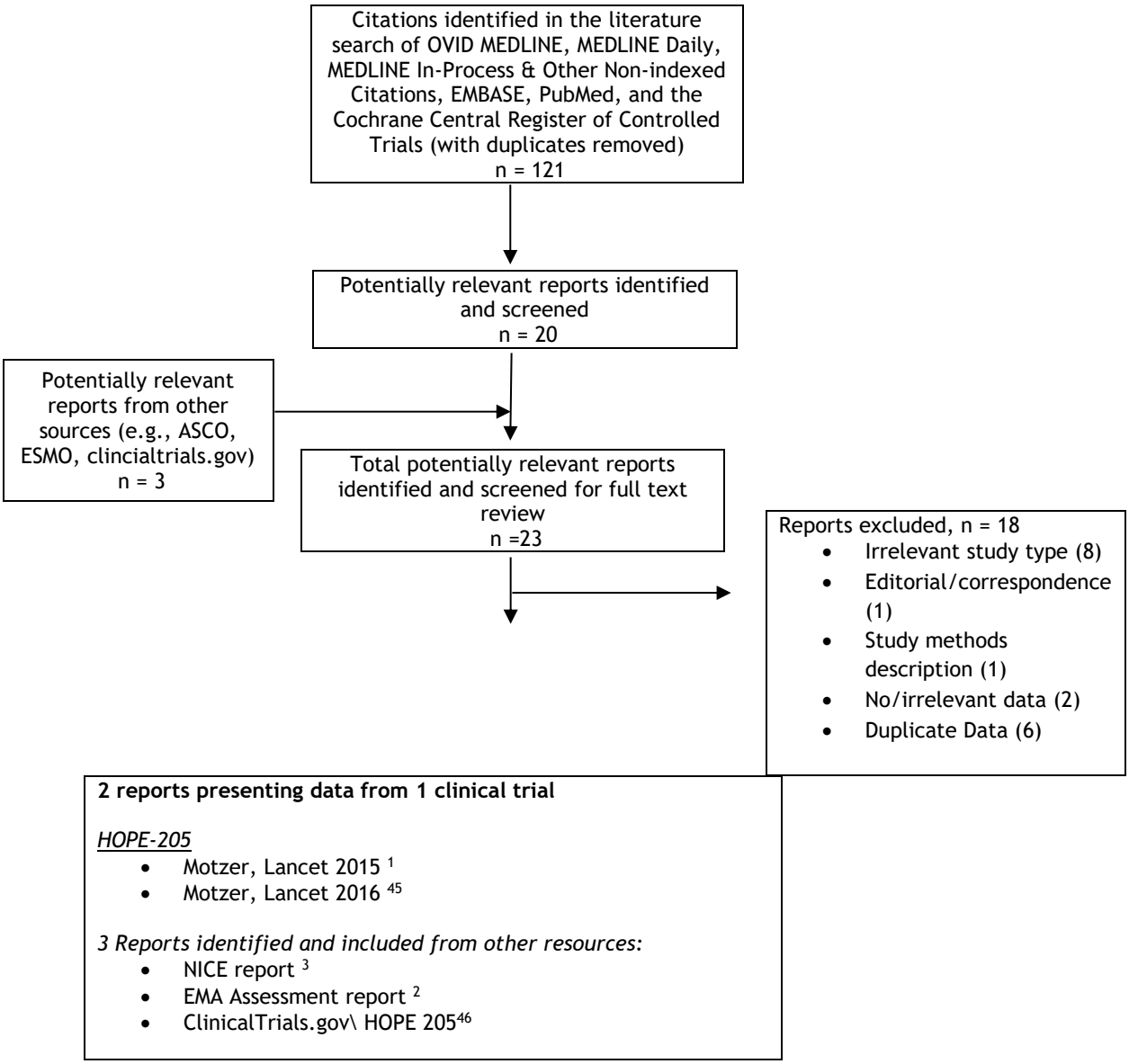
6.3 Results

6.3.1 Literature Search Results

Of the 20 potentially relevant citations identified, five citations, reporting data from one clinical trial, were included in the pCODR systematic review, and 18 studies were excluded. Studies were excluded because they were irrelevant study types[28-35], did not describe study designs,[36] or did not report data on outcomes and/or subgroups of interest,[37]. Comments or editorials,[38] as well as conference abstracts and journal articles reporting duplicate data from the included full articles[39-44] were also excluded. Figure 6.1 illustrates the PRISMA flow Diagram for the study selection process.

Figure 6.1. Sample PRISMA Flow Diagram for Inclusion and Exclusion of studies

Figure 6.1: PRISMA Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the HOPE 205 study were also obtained through requests to the Submitter by pCODR[4]

6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

One randomized trial met the selection criteria of this review. HOPE-205 was a multicentre, open-label phase 1b/phase 2 randomised controlled trial (RCT) comparing (in a 1:1:1 ratio) the combination of lenvatinib and everolimus with lenvatinib monotherapy and everolimus monotherapy in patients with advanced or metastatic RCC. Relevant information on trial characteristics is summarized in Table 6.2.

Table 6.2: Summary of Trial Characteristics of the Included Study

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: HOPE-205 [1] NCT01136733 [46] Characteristics: Phase 2, multicentre, open label, randomized (1:1:1 ratio) trial N randomized = 153 N treated = 153 Number of centres and number of countries: 37 centres in five countries (Czech Republic, Poland, Spain, UK, and USA) Patient Enrolment Dates: 16-Mar-2012 to 19-Jun-2013 Data cut-off: Final Analysis Date Primary analysis: 13-Jun-2014 Post-hoc updated analyses for OS: 1st analysis: 10-Dec-2014 2nd analysis: 31-Jul-2015 Funding: Eisai Inc.	<u>Key Inclusion Criteria:</u> • ≥ 18 years of age • Histological or cytological confirmed clear cell RCC • Documented evidence of unresectable advanced or metastatic RCC • ECOG PS of 0 or 1 • One prior VEGF-targeted treatment • Disease progression (according to RECIST 1.1) during or 9 months after stopping VEGF-targeted agent. • Key Exclusion Criteria: • Brain metastasis • Prior exposure to lenvatinib or rapamycin (mTOR) inhibitor • History of any anti-cancer treatment within 21 days, or any investigational agent within 30 days, prior to the first dose of study drug	<u>Arm 1</u> lenvatinib (orally, 18mg /day) + everolimus (orally, 5 mg/day) <u>Arm 2</u> lenvatinib (orally, 24mg /day) <u>Arm 3</u> everolimus (orally, 10 mg/day) Duration of treatment (all three arms): Once daily (28-day cycles) until disease progression, unacceptable toxic effects, or withdrawal of consent	Efficacy <u>Primary</u>: • PFS (investigator-assessed) <u>Secondary</u> • OS • ORR • DCR • Durable SD • Clinical benefit rate Safety • AEs • SAEs • WDAE
CBR = clinical benefit rate; **DCR** = Disease control rate; **ECOG** = Eastern Cooperative Oncology Group; mTOR = mammalian target of rapamycin; **ORR** = objective response rate; **OS** = overall survival; **PFS** = progression-free survival; **RCC** = renal cell carcinoma; **RECIST** = Response Evaluation Criteria in Solid Tumors **SD** = stable disease; **UK** = United Kingdom; **USA** = United States of America; **VEGF** = vascular endothelial growth factor			

Table 6.3: Select quality characteristics of the included study of lenvatinib plus everolimus in patients with advanced or metastatic RCC

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
HOPE-205	lenvatinib + everolimus combination therapy vs. Lenvatinib monotherapy vs. everolimus monotherapy	PFS	150	153	interactive voice response system (allocation ratio 1:1:1)	Yes	None	Yes	Yes	No	Yes

a) Trials

HOPE-205 was a multicentre, open-label phase 1b/phase 2 randomised controlled trial (RCT). During Phase 1b, dose escalation was performed to determine the maximum tolerated dose of lenvatinib in combination with everolimus. The phase 2 part of the study compared the combination of lenvatinib and everolimus (arm A) with lenvatinib monotherapy (arm B) and everolimus monotherapy (arm C) in patients with advanced or metastatic RCC. This pCODR review will report efficacy and safety results for arms A and C only, as single agent lenvatinib (arm B) is currently not a treatment option in Canada for 2nd line advanced or metastatic RCC and is therefore beyond the scope of this review. The trial was conducted at 37 centres in five countries.[1]

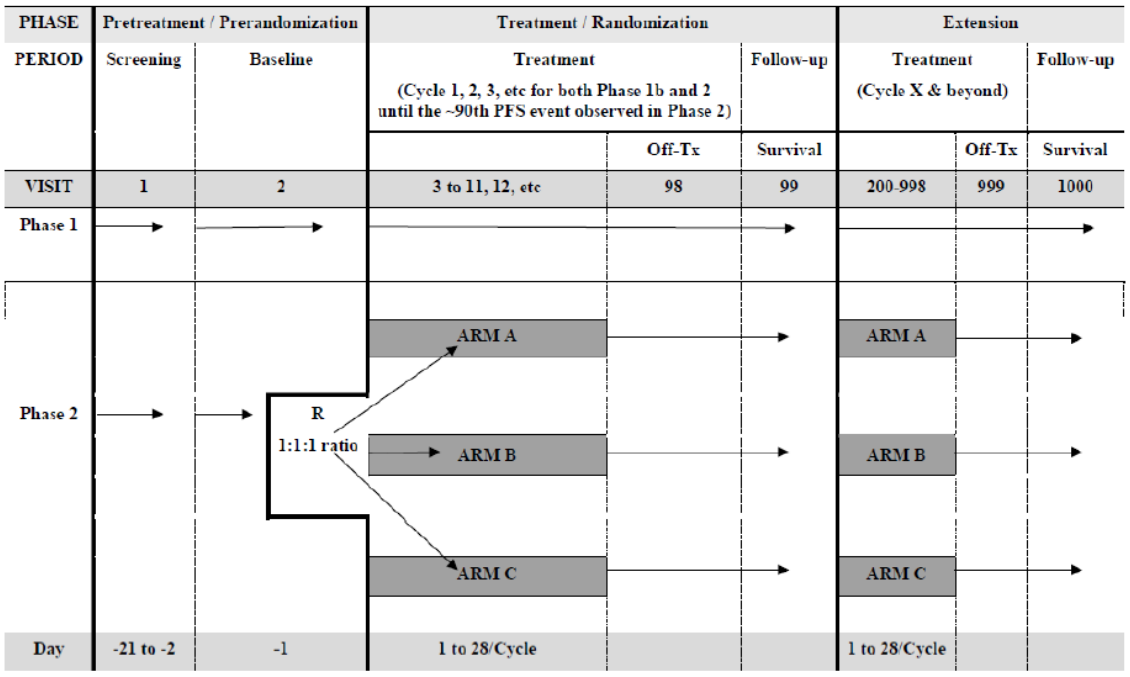
Trial design

The HOPE-205 study design is illustrated in Figure 6.2. As shown, phase 1b part of the study comprised a Pre-treatment Phase, a Treatment Phase, and an Extension Phase. The Phase 2 study consisted of a Pre-randomization Phase, a Randomization phase, and an Extension Phase.

- The Pre-treatment/Pre-randomization phase included a screening period during which informed consent was obtained and the eligibility criteria and disease characteristics were assessed.
- The Treatment/Randomization phase consisted of 4-week (28 day) treatment cycles, and a follow up period. The Treatment/Randomization phase ended at the 13-Jun-2014 data cut-off date for the primary efficacy analysis. The follow-up period began immediately after the completion of treatment and continued until patients died or withdrew consent. Radiographic tumour assessments were performed by the investigators using RECIST criteria (version 1.1) in the Pre-randomization phase, and then every 8 weeks from randomization until disease progression or initiation of a new anti-cancer therapy. Patients who were receiving study medication at the time of the data cut-off continued to receive the same treatment during the Extension Phase. Patients who discontinued the study treatment without a progression event continued to undergo tumour assessments every 8 weeks until documentation of disease progression or start of another anticancer therapy.
- The Extension phase also consisted of 4-week treatment cycles and a follow up period. Patients received the same study treatment that they were receiving at the end of the Treatment/Randomization phase. The study treatment was continued until disease progression, development of unacceptable toxicities, or withdrawal of consent. During the follow-up period patients who discontinued study treatment were followed up for survival every 12 weeks until

death occurred or the patient withdrew consent. Patients who discontinued study treatment without disease progression underwent tumor assessments, at the investigator's discretion.[1,2]

Figure 6.2: HOPE-205 study design



Source:[EMA Assessment Report; Figure 5, page 75/162][2]

Randomization and treatment concealment

Patients were randomized in a 1:1:1 ratio to receive lenvatinib (18 mg/day) plus everolimus (5 mg/day), or lenvatinib (24 mg/day), or everolimus (10 mg/day). Randomization was performed by an interactive voice response system (Parexel Informatics, NJ, USA) using a Pocock and Simon dynamic balancing procedure.[1]

The randomization was stratified by the following factors:

- Haemoglobin (men ≤13 g/dL vs. >13 g/dL; women ≤11.5 g/dL vs. >11.5 g/dL) and corrected serum calcium (≥10 mg/dL vs. <10 mg/dL) levels.[1].

The study was open label and neither patients nor the investigators were blinded to the study interventions.[1]

Study endpoints and disease assessment

The primary outcome in the trial was investigator-assessed progression free survival (PFS), defined as the time from randomization to the first documentation of disease progression or death. Kaplan-Meier (K-M) estimates were used to estimate the median PFS. Median PFS for each arm was presented with 2-sided 95% CIs. Three-month, 6-month, 9-month and 1-year PFS rates were estimated from K-M curves and corresponding 95% CIs were calculated using the Greenwood formula. HRs between treatment groups and corresponding 95% CIs were estimated using a stratified Cox regression model, stratified by hemoglobin level (≤13 g/dL vs >13 g/dL for males and ≤11.5 g/dL vs >11.5 g/dL for females) and corrected serum calcium (≥10 mg/dL vs <10 mg/dL with treatment as a factor.[2,3] The stratified log-rank test (at a two-sided significance level (α) of 0.05) was used to compare PFS between treatment arms, taking into account the aforementioned strata.[2,3] A post-hoc independent blinded radiological review of PFS was also performed as per

request by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[2] Subgroup analyses of PFS were performed using the unstratified Cox proportional hazard model. The subgroup analyses adjusted for treatment and subgroup as factors and treatment-by-subgroup as an interaction term in the model.[2,3] No multiplicity adjustment was planned a priori.[3]

Secondary outcomes included:

- overall survival (OS), defined as the time from randomization to the date of death due to any cause;
- objective response rate (ORR), defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR) as determined by the investigator using RECIST 1.1;
- disease control rate (DCR), defined as the proportion of subjects who had BOR of CR or PR or stable disease (SD), with a minimum duration from randomization to SD ≥7 weeks;
- durable stable disease, defined as the proportion of subjects with duration of SD ≥23 weeks;
- clinical benefit rate (CBR), defined as the proportion of subjects who had BOR of CR or PR or durable SD; and
- safety.[1,2]

The median OS and the cumulative probabilities of OS at 12 months, 18 months, and 24 months were calculated using K-M estimates for each treatment arm. Patients lost to follow-up or alive at data cut-off were censored at the date they were last known to be alive.[3] ORR, DCR, CBR, and durable SD rate were calculated with exact 95% CIs using the method of Clopper and Pearson. Ad-hoc analyses were performed to estimate the crude rate ratio of each treatment comparison and to compute P values using the two-sided Fisher's exact test.[1,3]

Sample size calculation and statistical analysis

The trial was designed to have 70% power to detect a hazard ratio (HR) of 0.67 for PFS at a one-sided significance level (α) of 0.15. Based on the primary comparison of lenvatinib + everolimus (or lenvatinib monotherapy) versus everolimus monotherapy, the median PFS was assumed to be 5 months in the everolimus arm and 7.5 months for each, the lenvatinib + everolimus and the lenvatinib arm. The primary analysis was planned after 90 progression events or deaths were observed in 150 randomized patients. In addition, 60 progression events or deaths were needed to be observed in either both the lenvatinib monotherapy arm and everolimus monotherapy arm, or both the lenvatinib + everolimus arm and the everolimus monotherapy arm.[1] The trial was not powered to detect a significance difference in OS between the study arms.[1]The primary analysis was performed in June 2014. No interim analyses were planned for HOPE-205.[3] A sensitivity analysis to the primary analysis was pre-planned, adjusting for ECOG PS (0 vs. 1) as a factor in the stratified Cox regression model. However, after the database lock, a post-hoc sensitivity analysis was performed with ECOG PS (0 vs 1) as an additional stratum in the stratified Cox regression model.[2]

The first version of the study protocol was issued on 19-Apr-2010 and the protocol was amended five times. Four protocol amendments were issued before the data cut-off date for the primary analysis (i.e., 13-Jun-2014). Amendment 05 was implemented after the data cut-off date.[2] The final statistical analysis plan for HOPE-205 was issued on 20-May-2014 and included more technical details regarding the original planned analyses in the protocol.[2]

During the conduct of HOPE-205, nine major protocol deviations were reported for a total of nine (5.9%) patients, including two patients in the lenvatinib + everolimus arm, three patients in the lenvatinib monotherapy arm, and four patients in the everolimus monotherapy arm. These major protocol deviations were related to one histologically unconfirmed predominant clear cell RCC in the everolimus arm; one dispensing error (a patient in the everolimus arm received10mg/day

lenvatinib for one cycle); and lack of brains scans in seven patients (2, 2, and 3 patients in the lenvatinib + everolimus, lenvatinib, and everolimus arms, respectively).[2] No sensitivity analyses were performed to test the robustness of the primary analysis results.[2]

b) Populations

Eligibility criteria

To be eligible for enrollment in the study patients had to be 18 years of age or older; have documented unresectable or advanced RCC; have a histological or cytological confirmation of predominant clear cell carcinoma; have been treated with one prior VEGF-targeted agent (e.g., sunitinib, sorafenib, pazopanib, bevacizumab, axitinib, vatalanib, AV951/tivozanib); and have a radiographic evidence of disease progression according to modified Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) during or within 9 months of stopping VEGF-targeted therapy. The inclusion criteria also required a minimum of one measurable lesion according to RECIST criteria, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate renal, bone marrow, blood coagulation, liver, and cardiac function.[1,46]

Patients with untreated or unstable metastasis of the central nervous system (CNS), and those with a history of treatment with lenvatinib or mammalian target of rapamycin (mTOR) inhibitor were considered to be ineligible for inclusion in the trial. Patients who had been treated with any anti-cancer treatment within 21 days or any investigational agent within 30 days prior to the first dose of study drug, those who had had a major surgery within three weeks prior to the first dose of study drug, and those who had discontinued prior tyrosine kinase inhibitor due to toxicity were also excluded from the study.[1,46]

Baseline characteristics of the study population

In the phase 2 part of the HOPE-205 trial, a total of 153 patients were enrolled, and randomized to receive lenvatinib + everolimus combination therapy (n=51), lenvatinib monotherapy (n=52), or everolimus monotherapy (n=50).[1] Study participants were recruited in 37 centres in Czech Republic, Poland, Spain, the United Kingdom, and the United States.[1]

Demographic characteristics of the study population are summarized in Table 6.4. The median age was 61 years, ranging from 37 to 79 years between the three study arms. The majority of study participants were 65 years of age or younger (65%), white (97%), and male (73%).[1,2] Overall, the baseline demographic and disease characteristics were well balanced between the study arms, except for number of metastases: 35% of patients in the lenvatinib + everolimus arm had one metastasis, when compared with 17% of patients in the lenvatinib arm and 10% in the everolimus arm. On the other hand, a higher percentage of patients in the everolimus arm had three or more metastasis (60% vs. 54% in the lenvatinib and 35% in the lenvatinib + everolimus arms).[1,3]

The types, frequencies, and duration of prior treatments received by the participants are summarized in Table 6.5. All patients received one previous VEGF-targeted therapy, with the most frequent agent being sunitinib (71% and 56% in the lenvatinib + everolimus and everolimus arms, respectively) and pazopanib (18% and 26% in the lenvatinib + everolimus and everolimus arms, respectively).The duration of previous VEGF therapies was slightly higher in the lenvatinib + everolimus arm (9.8 month; 95% CI 2.0, 66.2) than that in the everolimus arm (8.9; 95% CI 1.6, 57.8). The proportion of patients who underwent previous radiotherapy was 12 % in the lenvatinib + everolimus arm and 21% in the lenvatinib arm.[1] A small portion of patients had received prior treatment with checkpoint inhibitors (anti-PD1)[2] (2% and 4% in the lenvatinib/everolimus and everolimus arm, respectively).[1]

Table 6.4: Baseline characteristics of the study population in the HOPE-205 trial

Baseline characteristic	Lenvatinib + everolimus (n=51)	Single-arm lenvatinib (n=52)	Single-arm everolimus (n=50)
Age (years)	61 (44–79)	64 (41–79)	59 (37–77)
Sex			
Men	35 (69%)	39 (75%)	38 (76%)
Women	16 (31%)	13 (25%)	12 (24%)
ECOG Performance status			
0	27 (53%)	29 (56%)	28 (56%)
1	24 (47%)	23 (44%)	22 (44%)
MSKCC risk group			
Favourable	12 (24%)	11 (21%)	12 (24%)
Intermediate	19 (37%)	18 (35%)	19 (38%)
Poor	20 (39%)	23 (44%)	19 (38%)
Heng risk group*			
Favourable	8 (16%)	7 (14%)	9 (18%)
Intermediate	32 (64%)	33 (64%)	29 (58%)
Poor	10 (20%)	12 (23%)	12 (24%)
Haemoglobin, n (%)			
≤130 g/L (men) or ≤115 g/L (women)	33 (65%)	36 (69%)	31 (62%)
>130 g/L (men) or >115 g/L (women)	18 (35%)	16 (31%)	19 (38%)
Corrected serum calcium, n (%)			
≥2 · 5 mmol/L	6 (12%)	8 (15%)	8 (16%)
<2 · 5 mmol/L	45 (88%)	44 (85%)	42 (84%)
Number of metastases			
1	18 (35%)	9 (17%)	5 (10%)
2	15 (29%)	15 (29%)	15 (30%)
≥3	18 (35%)	28 (54%)	30 (60%)
Sites of metastasis			
Bone	12 (24%)	13 (25%)	16 (32%)
Liver	10 (20%)	14 (27%)	13 (26%)
Lung	27 (53%)	35 (67%)	35 (70%)
Lymph nodes	25 (49%)	31 (60%)	33 (66%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan Kettering Cancer Center

Data are number of patients (%), or median (range). * One patient in the lenvatinib plus everolimus group was excluded because of missing baseline laboratory values.

Source: [NICE Committee Papers; Figure 20, page 49/199][3]

Table 6.5: Summary of previous cancer treatments in the HOPE-205 trial

Baseline characteristic	Lenvatinib + everolimus (n=51)	Single-arm lenvatinib (n=52)	Single-arm everolimus (n=50)
Previous nephrectomy†	44 (86%)	43 (83%)	48 (96%)
Previous VEGF-targeted therapy‡			
Axitinib	1 (2%)	2 (4%)	0
Bevacizumab	0	1 (2%)	4 (8%)
Pazopanib	9 (18%)	13 (25%)	13 (26%)
Sorafenib	1 (2%)	0	2 (4%)
Sunitinib	36 (71%)	35 (67%)	28 (56%)
Tivozanib	3 (6%)	1 (2%)	2 (4%)
Other	1 (2%)	0	1 (2%)
Duration of previous VEGF-targeted therapy (months)	9.8 (2.0–66.2)	14.5 (0.7–81.8)	8.9 (1.6–57.8)
Best response for previous VEGF-targeted therapy			
Complete response	1 (2%)	0	0
Partial response	14 (28%)	10 (19%)	10 (20%)
Stable disease	20 (39%)	28 (54%)	21 (42%)
Progressive disease	7 (14%)	10 (19%)	15 (30%)
Not evaluated or unknown	9 (18%)	4 (8%)	4 (8%)
Previous checkpoint inhibitor therapy	1 (2%)	2 (4%)	2 (4%)
Previous interferon therapy	4 (8%)	3 (6%)	7 (14%)
Previous radiotherapy	6 (12%)	11 (21%)	11 (22%)

Abbreviations: VEGF, Vascular endothelial growth factor

† One patient in the lenvatinib group had two nephrectomy procedures (partial and left radical) but was only counted once. ‡ All patients had one previous VEGF-targeted therapy.

Source: [NICE Committee Papers; Figure 21, page 50/199][3]

c) Interventions

Treatment Dosing Schedule

Study treatments were administered orally once daily in 28-days continuous cycles as follows:

- lenvatinib + everolimus arm: lenvatinib at 18 mg/day (one 10 mg capsule and two 4 mg capsules); plus everolimus at 5 mg/day (one 5 mg tablet), at the same time;
- lenvatinib monotherapy arm: lenvatinib at 24 mg/day (two 10 mg capsules and one 4 mg capsule); and
- everolimus monotherapy arm : everolimus at 10 mg/day (two 5 mg tablets).[1]

Patients were to remain on study treatment until disease progression, withdrawal of consent, or the development of unacceptable toxicity.[1] Median duration of lenvatinib exposure was 7.6 months (range 0.7 to 22.6) for patients in the lenvatinib + everolimus arm.[1]

Dose delays, reductions or modifications

For patients who experienced treatment-related severe and/or intolerable AEs in the everolimus monotherapy arm, dose alterations (temporary dose interruptions and no dose reduction below 5 mg) were permitted in accordance with prescribing information.[2,3] Everolimus dose reductions were required in one patient (out of 51; 2%) assigned to lenvatinib + everolimus (from 5 mg daily), and 13/50 (26%) patients assigned to everolimus monotherapy (from 10 mg daily). The median daily dose of everolimus was 4.7 mg/day (94% of the intended dose) per patient assigned to

lenvatinib + everolimus, and 9.7 mg/day (97% of the intended dose) per patient assigned to everolimus monotherapy.[1]

To manage treatment-related toxicities in the lenvatinib + everolimus arm, dose reduction and interruption were allowed in accordance with protocol pre-specified dose adjustment instructions, as follows:

- Stepwise dose reductions from 18 mg/day to 14 mg/day, 10 mg/day, and 8 mg/day. For everolimus-related toxicities in this arm (based on the investigator's discretion), dose reduction of everolimus to 5 mg was allowed every other day. Dose re-escalation was not permitted. [2,3]

Lenvatinib dose reductions were reported in 36/51 (71%) patients assigned to lenvatinib + everolimus.[1] Forty-nine percent (25/51) of the patients in the lenvatinib + everolimus arm had their first dose reduction within the first three cycles of treatment.[1] The median daily dose of lenvatinib was 13·6 mg/day (75% of the intended dose) per patient assigned lenvatinib + everolimus.[1]

Concomitant and subsequent interventions

All patients received at least one concomitant medication. Concomitant antihypertensive medications were taken by higher percentages of patients in the lenvatinib + everolimus (82%) arm than in the everolimus arm (60%). The most common antihypertensive medication was reported to be amlodipine (49% in the lenvatinib + everolimus, and 28%in the everolimus arm). Loperamide, an anti-propulsive agent for diarrhea, was used in 59% of patients in the lenvatinib + everolimus arm and 12% of those in the everolimus arm. Thyroid Preparations were used in 53% of patients in the lenvatinib + everolimus arm and 20% of those in the everolimus arm.[2]

A total of 47 patients (19 in the lenvatinib + everolimus, 16 in the lenvatinib arm, and 12 in the everolimus arm) discontinued study treatment for a reason other than disease progression. Eighteen of these 47 patients received subsequent anticancer therapy.[2] Table 6.6 summarizes the type and time to first received subsequent therapies in the HOPE-205 trial. As the table shows, the median duration of time to initiation of a subsequent anticancer therapy was higher with everolimus monotherapy (36 days) than with lenvatinib + everolimus (29 days).[2]

Table 6.6: Subsequent anticancer therapy in the HOPE-205 trial

	Lenvatinib 18 mg + Everolimus 5 mg	Lenvatinib 24 mg	Everolimus 10 mg
Subjects who discontinued treatment for a reason other than PD, n (%)[a]	19 (37.3%)	16 (30.8%)	12 (24.0%)
Subjects who took anticancer therapy after treatment discontinuation, n (%)[a]	7 (36.8)	6 (37.5)	5 (41.7)
Type of subsequent anticancer treatment received			
mTOR Inhibitor:	4 (21.1)	2 (12.5)	1 (8.3)
Everolimus	4 (21.1)	2 (12.5)	1 (8.3)
VEGF Inhibitor:	2 (10.5)	2 (12.5)	3 (25.0)
Axitinib	2 (10.5)	0	2 (16.7)
Bevacizumab	0	1 (6.3)	0
Cabozantinib	0	1 (6.3)	0
Sunitinib	0	0	1 (8.3)
Monoclonal Antibody[b]	1 (5.3)	2 (12.5)	0
Cytokine:	0	0	1 (8.3)
Interferon	0	0	1 (8.3)
Duration to start of subsequent therapy (days)[c]			
Number of subjects	7	6	5
Mean (SD)	56.1 (58.5)	54.2 (27.4)	68.0 (71.2)
Median	29	47	36
Q1, Q3	22, 91	34, 76	13, 135
Min, Max	16, 176	25, 96	2, 154

AE = adverse event, max = maximum, min = minimum, mTOR = mammalian target of rapamycin, PD = progressive disease, Q1 = first quartile, Q3 = third quartile, SD = standard deviation, VEGF = vascular endothelial growth factor. a: Denominator includes all subjects who discontinued treatment for non-PD reasons.b: Name of monoclonal antibody was not specified.c: Duration from end of treatment = date of first dose of new therapy - date of last dose of study drug + 1.

Source: [EMA Assessment Report; Table 27, page 85/162][2]

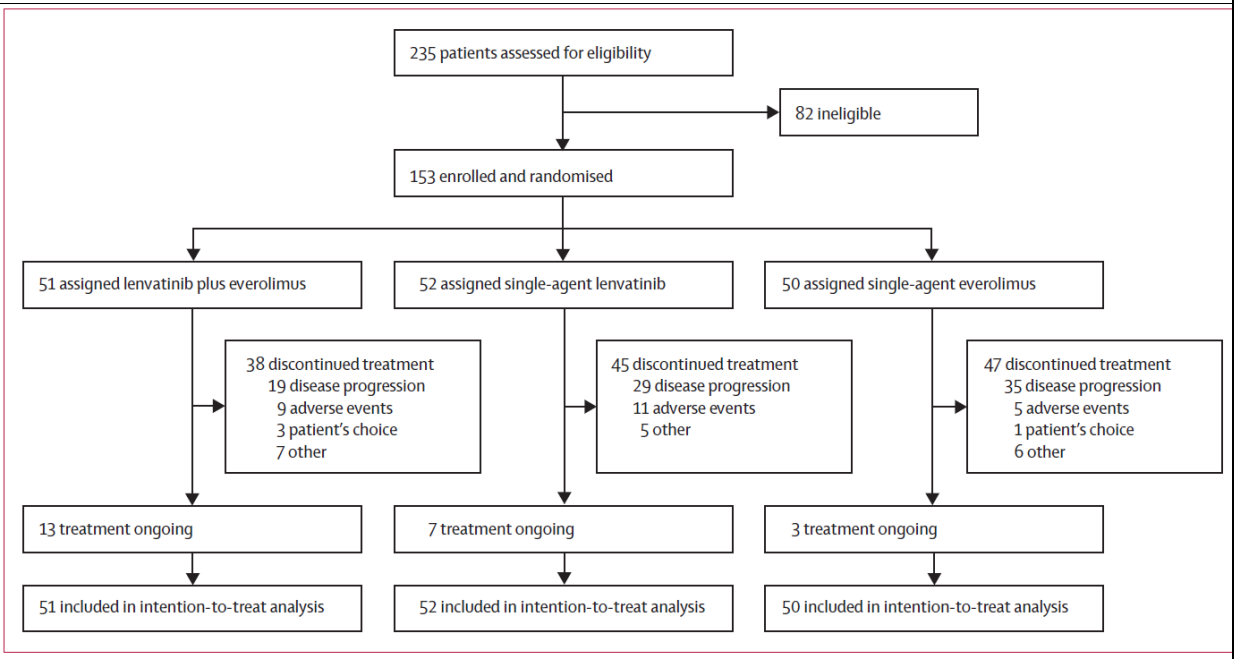
d) Patient Disposition

The patient disposition flow diagram for the HOPE-205 phase 2 trial is provided in Figure 6.3.

During the time period between 16-Mar-2012 and 19-Jun-2013, 235 patients were screened for eligibility; of whom 82 patients (35%) patients failed screening, and the remaining 153 patients were randomized to one of the three study arms: lenvatinib + everolimus combination therapy(n=51), lenvatinib monotherapy (n=52), and everolimus monotherapy (n=50).[1] Of the 82 screening failures, 63 patients failed to meet entry criteria, two patients were lost to follow-up, one patient withdraw consent, and 16 were considered to be ineligible for other reasons.[2] All randomised patients received the assigned treatment and were included in the intention-to-treat (ITT) analyses.

As of the 13-Jun-2014 data cut-off date, 23 patients were still receiving the assigned treatment; and a total of 130 patients had discontinued treatment (38 (74.5%) patients on lenvatinib + everolimus, 45 (86.5%) patients on lenvatinib monotherapy, and 47 (94%) patients on everolimus monotherapy). Disease progression was the most common reason for discontinuation (19 patients in the lenvatinib + everolimus arm, 29 in the lenvatinib arm and 35 in the everolimus arm), followed by AEs (nine patients in the lenvatinib + everolimus arm, 11 in the lenvatinib arm and five in the everolimus arm).[1]

Figure 6.3: Patient disposition flow diagram in HOPE-205 (phase 2)



Reprinted from Lancet Oncology, Vol 16 /issue 15, Motzer, R.J., Hutson, T.E. Glen, H. et al., Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial, pages 1473-1482, Copyright 2015, with permission from **Elsevier.**

e) Limitations/Sources of Bias

The following steps were taken in the HOPE-205 phase 2 trial to minimize potential biases:

- Randomization was performed through an interactive voice and web response system to conceal the treatment allocation sequence.
- The randomization was stratified based on two known prognostic factors (i.e., hemoglobin level and corrected serum calcium) to minimize potential imbalances between the study groups that might lead to biased results. The treatment arms were well-balanced for patient characteristics and prognostic factors.
- Data analysis included an ITT analysis. All patients received the intervention to which they were randomised and there were no unexpected imbalances in drop-outs between the three treatment arms which suggested a lack of systematic difference among those who dropped out and those who remained in the study.

Limitations

- HOPE-205 was an open-label trial; i.e., patients, care providers, and outcome assessors were not blind to treatment allocation. This could potentially increase the risk of performance and detection biases, as both physician/ outcome assessors and patients are aware of the treatment status.
- Disease progression was determined using RECIST (version 1.1) criteria by the investigator. It is unclear if the investigator's assessment of the imaging scans could result in performance and information biases. For PFS, the primary study outcome, a post-hoc

independent blinded radiological review was performed as per request by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA).[2]

- The sample size calculation for the phase 2 part the trial, used a type II error of 0.30 (70% power), and a one-sided significance level of 0.15. By using a one-sided alpha of 15% the calculated sample size was less than if a smaller alpha had been selected (e.g., a one-sided alpha of 10% or two-sided alpha of 5%). It is possible that the HR and statistical significance observed in this small cohort of patients may represent a sample of outliers in the population and not represent the treatment effect expected in the full population. As such, it is possible that the observed treatment effect may be a false positive result or that the true treatment effect may be smaller than what was reported in this study.

  In their feedback on the initial recommendation, the submitter noted that the perceived increased risk of a false positive result given the actual data from HOPE-205 is extremely low and well within the accepted confidence intervals, confirming the efficacy of lenvatinib in combination with everolimus in the HOPE-205 trial. The submitter also provided feedback that a Bonferroni correction was applied to adjust for multiplicity in the primary outcome to maintain the type 1 error rate at 0.05. The pCODR Methods Team agreed that PFS was statistically significant based on a significance level of 0.05 (2-sided) and that by applying a Bonferroni correction to adjust for multiple comparisons of the PFS results, there was no increased risk of a type 1 error for the primary outcome. However, the results of the secondary endpoints and subgroup analyses of PFS were still at risk of type 1 error because of the lack of multiplicity adjustment. Further, there is a distinction between the type 1 error rate and a general risk of a false positive finding, the latter of which relates to the limitation of the study design. By using a one-sided alpha of 15% the calculated sample size was less than if a smaller alpha had been selected (e.g., a one-sided alpha of 10% or two-sided alpha of 5%). It is possible that the HR and statistical significance observed in this small cohort of patients may represent a sample of outliers in the population and not represent the treatment effect expected in the full population. As such, it is possible that the observed treatment effect may be a false positive result or that the true treatment effect may be smaller than what was reported in this study. Therefore, while there was no increased risk of type 1 error rate in the primary outcome, this phase II trial could be more likely to produce a false positive result than trials of larger sample size. Therefore the pCODR Methods team agreed to revise the bullet point above to:

    - The sample size calculation for the phase 2 part the trial, used a type II error of 0.30 (70% power), and a one-sided significance level of 0.15. By using a one-sided alpha of 15% the calculated sample size was less than if a smaller alpha had been selected (e.g., a one-sided alpha of 10% or two-sided alpha of 5%). It is possible that the HR and statistical significance observed in this small cohort of patients may represent a sample of outliers in the population and not represent the treatment effect expected in the full population. As such, it is possible that the observed treatment effect may be a false positive result or that the true treatment effect may be smaller than what was reported in this study.

  In addition feedback from registered clinicians was received noting that this trial was: (1) randomized and reasonably powered, (2) chose a primary outcome measure (PFS) that is commonly used as a primary outcome in larger phase III cancer trials, and (3) that the credibility of the control arm was confirmed by the ORR (6%) and PFS (5.5 months) with everolimus, which are very similar to the outcome of the everolimus control arm in the Checkmate-025 study (ORR 5% and PFS 4.4 months). In response to point (1) above, the pCODR Methods Lead noted the statistical power of a trial (i.e., ability of the study to detect a difference between the study arms when such a difference exists) is determined by several factors, including the expected magnitude of the effect, number of events (in

studies with a time-to-event variable as the primary outcome), and the study design. Conventionally, large values of power are desirable (at least 80%) in clinical trials. However, to increase power, a larger sample size is required and this might not be feasible in all oncology trials. Therefore, using a power of 70% (used in the HOPE 205 trial) in a phase II trial could be considered as reasonable. Importantly, because the study has already found a statistically significant difference in the primary endpoint, this level of power should not be concerning.

In response to the second point (2) raised by the registered clinicians above, the CGP reiterated that PFS has been suggested as a surrogate for OS in several studies. In addition, PFS in itself is an important clinical endpoint and therefore PFS represents an appropriate endpoint for randomized clinical trials in RCC. As in other tumor types such as breast cancer, PFS has been accepted as an appropriate endpoint for randomized trials across the modern RCC literature. Most randomized trials in the modern era of RCC were designed with PFS as a sole primary endpoint with very few exceptions (Checkmate 025; Checkmate 214; ARCC trials). The pCODR Methods Team agreed that PFS is a commonly-used primary outcome in oncology trials because this endpoint can be evaluated with relatively shorter follow up times, requires smaller sample size (due to greater number of events), and is not usually affected by subsequent treatments. However, as mentioned above, it is important to note that the primary objective of phase 2 (randomized or non-randomized) trials is to document the safety outcomes and investigate if the estimate of effect for a new drug is large enough to use it in confirmatory phase 3 trials.

In response to the third point (3) raised by the registered clinicians above, the CGP reiterated that the positive results in the lenvatinib/everolimus trial cannot be attributed to a suboptimal performing standard arm. The outcomes in the everolimus arm of the lenvatinib/everolimus trial are very comparable to the outcomes data of everolimus in the general RCC literature and also very comparable to the outcomes seen with everolimus in the Checkmate 025 and METEOR phase III randomized trials.

- HOPE-205 was not powered to detect a statistically significant OS benefit.
- No adjustments were made for multiplicity introduced by analysing multiple secondary endpoints or subgroup analyses of PFS. Therefore, p-values in these analyses are considered nominal. Multiple testing can increase the probability of type 1 error and, therefore, lead to false positive conclusions.

- In their feedback on the initial recommendation, the submitter noted that HOPE 205 was evaluated by Health Canada to assess the appropriateness and robustness of the statistical analyses, noting that the overall study design and statistical analysis plan were appropriate. The submitter reported that the Health Canada review specifically focused on the potential biases of: 1) the lack of adjustment for multiplicity in the primary analyses and 2) the investigator assessment of PFS (please see this point addressed beneath the next bullet point). In addressing the first point (1) from above, the submitter suggested that when applying the most conservative Bonferroni adjustment (each of the 2 hypotheses tested at a 2-sided alpha level of 0.025), the results remain statically significant (P=0.0005). For the response by the pCODR Method's Team to the submitter's feedback please see the pCODR Methods team response on page 50, regarding the submitter's feedback on an increased risk of a false positive results.
- Overall, the baseline demographic and disease characteristics were well balanced between the study arms; however, higher proportion of patients in the everolimus arm had three or more metastasis (60% vs. 35% in the lenvatinib + everolimus arm).[1,3]

- Although the subgroup analyses were pre-specified, subgroup analyses in the HOPE-205 trial should be considered exploratory considering the fact that the study was not designed to detect differences in the specific subgroups.

  In their feedback on the initial recommendation, the submitter reported that the Health Canada review specifically focused on the potential bias of the investigator assessment of PFS. It was suggested that the results of key secondary endpoints of OS and ORR were consistent with the PFS. Further, the improvement in PFS was supported by sensitivity and exploratory analyses. In response to the submitter's feedback the pCODR Methods Team agrees that the results of the exploratory subgroup and sensitivity analyses, conducted to test the robustness of PFS results, and showed similar estimates to those obtained in the primary analysis; reiterating that the outcome results in each subgroup should be considered exploratory and hypothesis-generating, because of lack of adjustment for multiplicity and the exploratory nature of the analysis.
- Patient-reported quality of life outcomes have not been measured in the HOPE-205 trial. Therefore, the direction and degree to which the study treatments could impact patients' quality of life are unknown.
- HOPE-205 compared the effect of lenvatinib + everolimus with that of everolimus monotherapy. Other comparators that are potentially relevant to this review were not assessed in this trial (i.e., nivolumab and axitinib). Of note, the submitter provided an indirect treatment comparison (ITC) report that included other comparators (i.e., nivolumab, axitinib and cabozantinib (see section 7 for more details).[4] Please note that cabozantinib was not regarded as relevant comparator at the time of this pCODR review, as it is not publicly funded in any participating jurisdictions and is currently under review with pCODR.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy analyses were performed in 153 study participants: 51 on lenvatinib + everolimus, 52 on lenvatinib monotherapy, and 50 on everolimus monotherapy), using an ITT approach.[1] HOPE-205 aimed at comparing the efficacy outcomes for: 1) lenvatinib + everolimus versus everolimus monotherapy; and 2) lenvatinib monotherapy versus everolimus monotherapy, in patients with unresectable advanced or metastatic RCC whose disease progressed following one prior VEGF-targeted treatment. However, because lenvatinib monotherapy is not licensed in Canada for the treatment of advanced RCC, this section will focus on the comparison of lenvatinib + everolimus with everolimus monotherapy, with the doses used in the trial.

The pre-planned 13-Jun-2014 data cut-off date was used for the primary analysis, which represents a median PFS follow-up duration of 13.9 months for lenvatinib + everolimus and 17.5 months for everolimus monotherapy. At the data cut-off date, the median duration of follow up for OS was 18.5 months for lenvatinib + everolimus and 16.5 months for everolimus monotherapy.[1,3]

The journal article published by Motzer et al (Lancet 2015)[1] includes data from the pre-planned data cut-off, and an updated analysis data cut-off for OS that was performed on 10-Dec-2014, after a median follow-up of 24.2 months for lenvatinib + everolimus and 25.0 months for everolimus monotherapy.[1,3] A second updated analysis of OS was performed on 31-Jul-2015, as per request by EMA, to reduce uncertainties around OS data. [1,3]

Progression-Free Survival (PFS)

PFS was the primary outcome in the HOPE-205 trial. For regulatory purposes, a post-hoc independent, blinded review was performed to support the primary analysis of PFS data.[1,2]

As of 13-Jun-2014 data cut-off, 26/51 (51%) patients treated with lenvatinib + everolimus had disease progression (as assessed by the investigator) or died, as compared with 37/50 (74%) patients treated with everolimus.[3] The median PFS was 14.6 months (95% CI 5.9, 20.1) for the lenvatinib + everolimus arm and 5.5 months (95% CI 3.5, 7.1) in the everolimus arm (Table 6.7A).[3] The Kaplan-Meier curves are presented in Figure 6.4. Combination therapy with lenvatinib + everolimus was associated with a statistically longer PFS as compared to everolimus alone (Stratified HR= 0.401, 95% CI 0.239, 0.675; p=0.0005).[1,3]

The independent imaging review also demonstrated an improvement in median PFS favoring the lenvatinib + everolimus arm (12.8 months with lenvatinib + everolimus versus 5.6 months with everolimus alone; Table 6.7B), with an estimated HR of 0.449 (95% CI 0.257, 0.785; p=0.0029).[1,3]

Additional sensitivity analyses (with ECOG performance score as an additional stratum in the stratified Cox regression model) were also performed to test the robustness of PFS and showed similar estimates.[2,3]

Table 6.7: Progression-Free Survival in the HOPE-205 trial

A. Assessment by the Investigator

	Lenvatinib + everolimus (n=51)	Single-arm lenvatinib (n=52)	Single-arm everolimus (n=50)
Events (n)	26 (51%)	38 (73%)	37 (74%9
PFS (months) Median (95% CI)	14.6 (5.9, 20.1)	7.4 (5.6, 10.2)	5.5 (3.5, 7.1)
Stratified Hazard Ratio (95% CI)			
Primary endpoints: vs single-arm everolimus	0.40 (0.24, 0.68)	0.61 (0.38, 0.98)	
Secondary endpoint: vs single-arm lenvatinib	0.66 (0.39, 1.10)		
P value based on stratified log-rank test			
Primary endpoints: vs single-arm everolimus	0.0005	0.0479	
Secondary endpoint: vs single-arm lenvatinib	0.1209		
Progression-free survival rate (%) (95% CI)			
At 9 months	56.7 (40.7, 69.9)	45.6 (31.1, 59.0)	33.4 (19.6, 47.8)
At 12 months	50.9 (34.8, 64.9)	34.2 (21.0, 47.8)	21.2 (9.9, 35.5)

Abbreviations: CI, Confidence interval; PFS, Progression-free survival

B. Independent Assessment

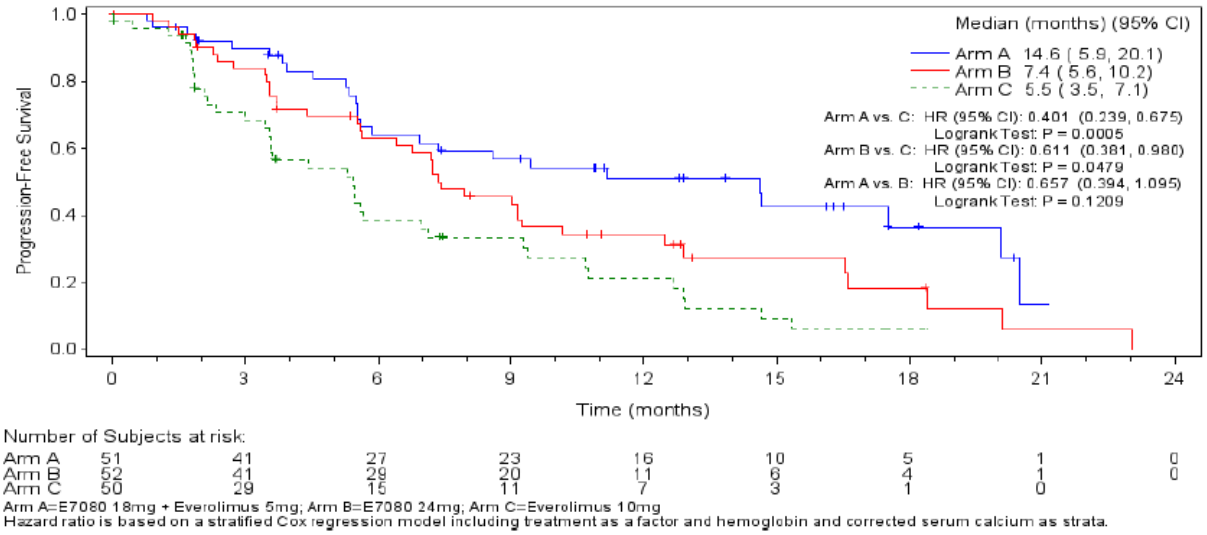
	Lenvatinib + everolimus (n=51)	Single-arm everolimus (n=50)
PFS (months) Median (95% CI)	12.8 (7.4, 17.5)	5.6 (3.6, 9.3)
Hazard Ratio (95% CI)	0.45 (0.26, 0.79) p=0.003	

Abbreviations: CI, Confidence interval; PFS, Progression-free survival

Source: [NICE Committee Papers; Figure 23 page 53/199 and Figure25 page 45/199][3]

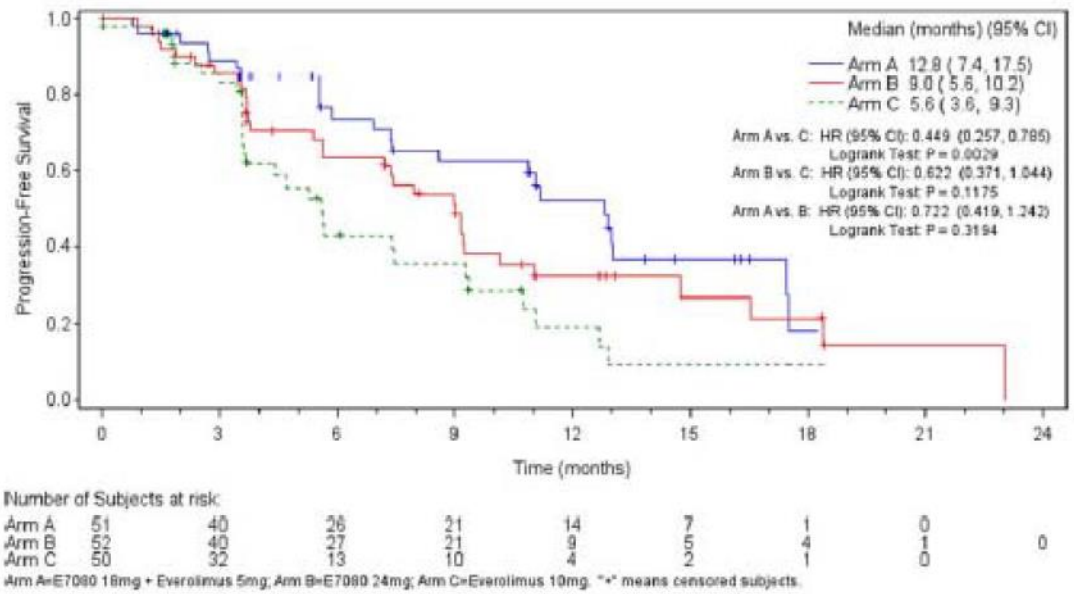
Figure 6.4: Kaplan-Meier curves of progression-free survival (as assessed by the investigator)

A. Assessment by the Investigator



Arm A=E7080 18mg + Everolimus 5mg; Arm B=E7080 24mg; Arm C=Everolimus 10mg
Hazard ratio is based on a stratified Cox regression model including treatment as a factor and hemoglobin and corrected serum calcium as strata.

B. Independent Assessment

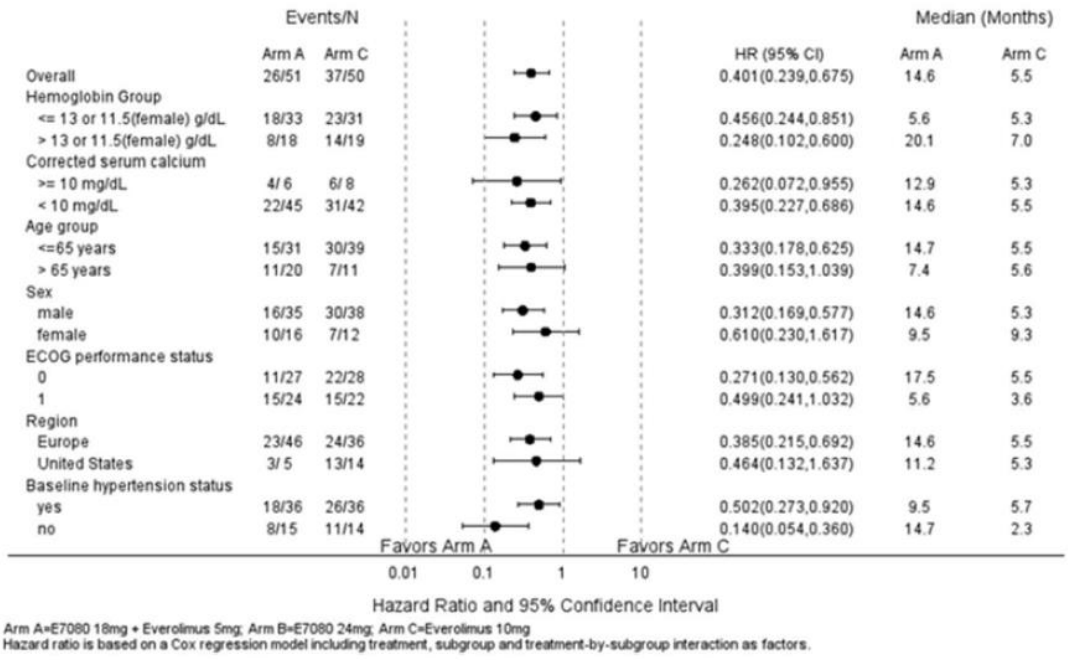


Source: [NICE Committee Papers; Figure 24 page 54/199 and Figure26 page 55/199][3]

Subgroup analyses of PFS:

The results of pre-planned subgroup analyses are demonstrated in Figure 6.5. As the figure shows, the PFS benefit with lenvatinib + everolimus was consistent across all subgroups. However, these subgroup analyses should be considered exploratory as the study was not designed to detect differences between the subgroups.

Figure 6.5: Subgroup analyses of PFS in the HOPE-205 trial (lenvatinib + everolimus vs. everolimus)



Source: [NICE Committee Papers, Figure 34, page 65/199][3]

Overall Survival (OS)

OS was a secondary outcome in the HOPE-205 trial, defined as the time from randomization to the date of death due to any cause.[1] A summary of the pre-planned (13-Jun-2014) and two ad-hoc updated (10-Dec-2014 and 31-Jul-2015) OS analyses are presented in Table 6.8 and the Kaplan-Meier curves are shown in Figure 6.6.

At the date of the latest updated OS analysis (31-Jul-2015), 32/51 (62.7%) patients in the lenvatinib + everolimus arm and 37/50 (74.0%) patients in the everolimus arm had died, with a median OS of 25.5 months (95% CI 16.4, 32.1) for the lenvatinib + everolimus arm and 15.4 months (95% CI 11.8, 20.6) for the everolimus arm (stratified HR = 0.59; 95% CI 0.36, 0.96; p=0.06).[2,3]

Table 6.8: Overall Survival Analyses in the HOPE-205 trial

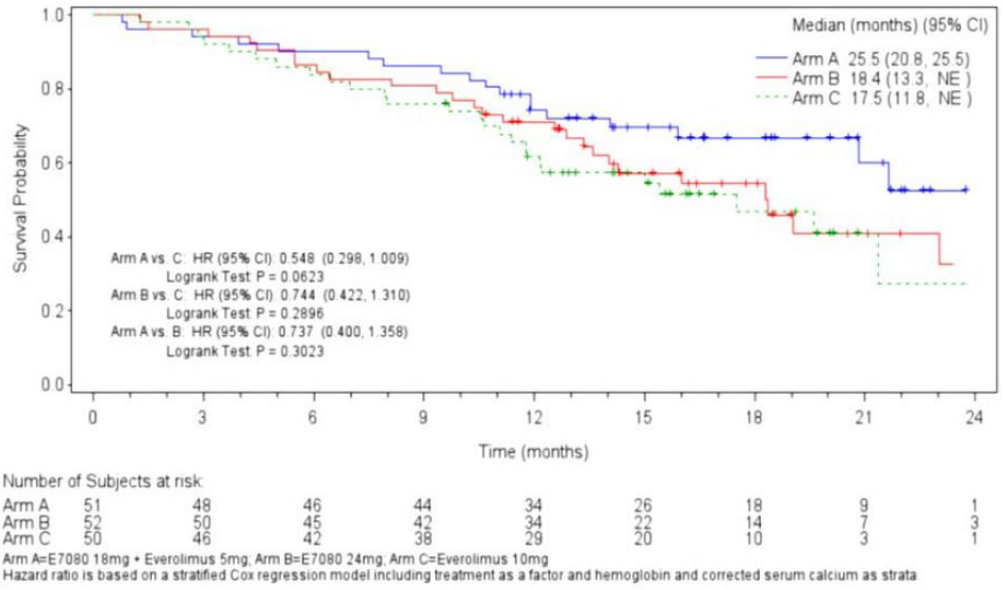
	Lenvatinib 18 mg + everolimus 5 mg (N=51)	Lenvatinib 24 mg (N=52)	everolimus 10 mg (N=50)
Primary Analysis (June 13, 2014)			
Median (months) (95% CI)	25.5 (20.8, 25.5)	18.4 (13.3, NE)	17.5 (11.8, NE)
HR (95% CI) vs everolimus	0.55 (0.30, 1.01)	0.74 (0.42, 1.31)	N/A
P-value vs everolimus	0.06	0.29	N/A
Updated Analysis (December 10, 2014)			
Median (months) (95% CI)	25.5 (16.4, NE)	19.1 (13.6, 26.2)	15.4 (11.8, 19.6)
HR (95% CI) vs everolimus	0.51 (0.30, 0.88)	0.68 (0.41, 1.14)	N/A
P-value vs everolimus	0.02	0.12	N/A
Final Update (July 31, 2015)			
Median (months) (95% CI)	25.5 (16.4, 32.1)	19.1 (13.6, 26.2)	15.4 (11.8, 20.6)
HR (95% CI) vs everolimus	0.59 (0.36, 0.96)	0.75 (0.47, 1.20)	N/A
P-value vs everolimus	0.06	0.13	N/A

Abbreviations: CI, Confidence Interval; HR, Hazard Ratio; NE, Not estimable.

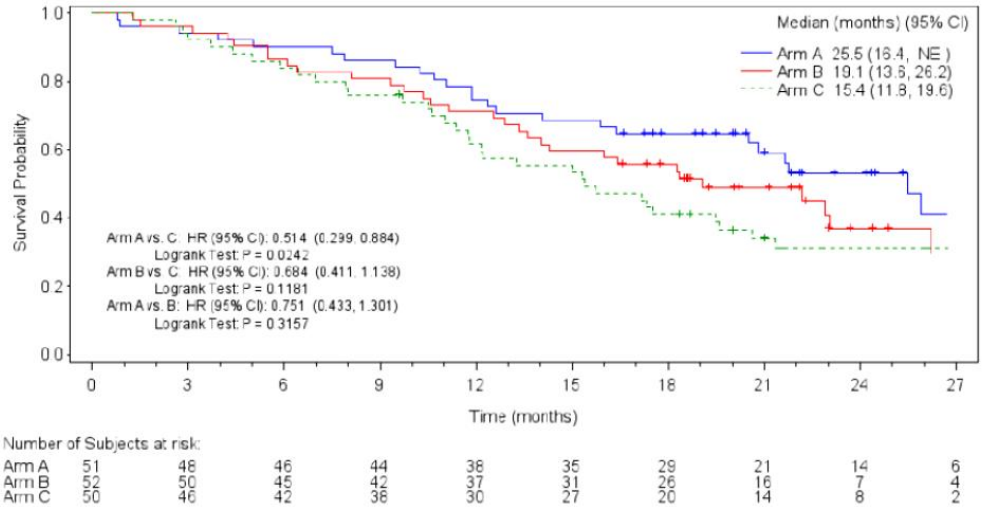
Source:[Eisai submission information; LENVIMA_Clinical Summary.pdf, page 27, Table 10][4]

Figure 6.6: Kaplan-Meier estimate of updated overall survival, by treatment group

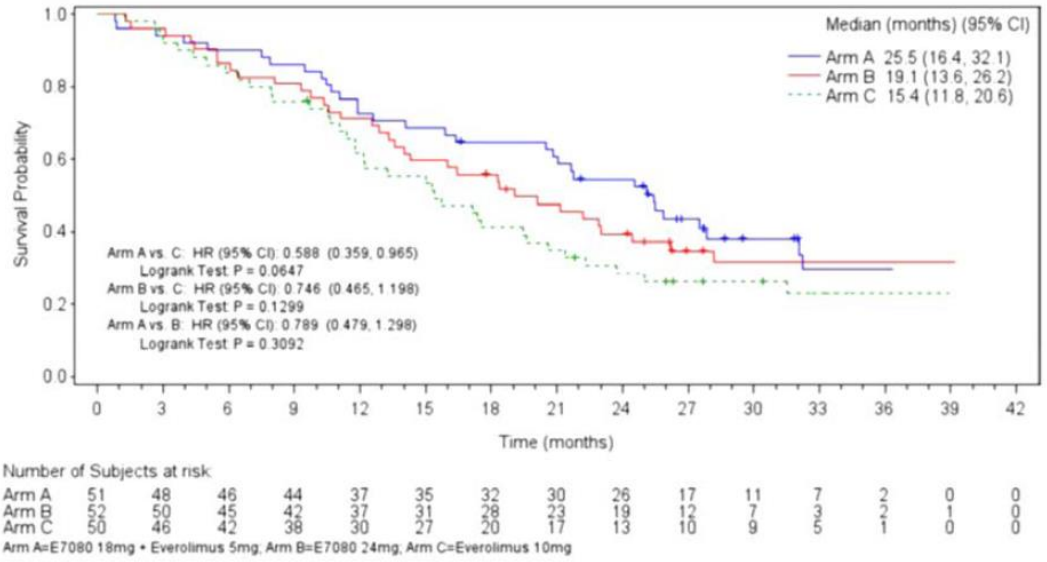
A. Pre-planned analysis (13-Jun-2014)



B. First updated analysis (10-Dec-2014)



C. Second updated analysis (13-Jul-2015)



Source:[EMA Assessment Report; page 88-89/162][2]

Tumour Response Outcomes

ORR, DCR, CBR, and durable SD rate were secondary outcomes in the HOPE-205 trial.[1] The results of analyses for the tumour response variables are summarized in Table 6.9.

Objective Response Rate (ORR)

As of the 13-Jun-2014 data cut-off date, a tumor response was reported in 22 patients in the lenvatinib + everolimus arm (one patient with a CR and 21 patients with a PR) versus three patients in the everolimus arm (zero patient with a CR and three patients with a PR).[3] ORR (CR + PR) was higher in the lenvatinib + everolimus arm (43.1%; 95% CI 29.3, 57.8) than that in the everolimus arm (6.0%; 95% CI 1.3, 16.5). The difference between the two arms was statistically significant (rate ratio [RR] = 7.2; 95% CI: 2.3, 22.5; p<0.0001; Table 6.9).[2,3]

The median time to response was similar between the lenvatinib + everolimus and everolimus arms (8.2 weeks with lenvatinib + everolimus and 8.0 weeks with everolimus).[3] The median duration of response was reported to be 13.0 months (95% CI 3.7, not estimable) in the lenvatinib + everolimus arm and 8.5 months (95% CI 7.5, 9.4) in the everolimus arm (Table 6.9).[2]

Disease Control Rate (DCR)

As of the 13-Jun-2014 data cut-off date, DCR was 84.3% for the lenvatinib + everolimus arm and 68.0% for the everolimus arm (Table 6.9).[2,3]

Durable Stable Disease

In the HOPE-205 trial, fewer patients in the lenvatinib + everolimus arm (21/51; 42.2%) were reported to have a stable disease than in the everolimus arm (31/50; 62.0%). Accordingly, the proportion of patients with a durable SD (≥ 23weeks) was lower in the lenvatinib + everolimus arm (25.5%) than in the everolimus arm (36.0%; Table 6.9).[3]

Clinical benefit rate (CBR)

CBR was a secondary outcome, defined as the proportion of subjects who had BOR of CR or PR or durable SD.[1,3] As of the 13-Jun-2014 data cut-off date, CBR was 68.6% (35/51 patients) for the lenvatinib + everolimus arm and 42.0% (21/50 patients) for the everolimus arm (Table 6.9).[2,3]

Table 6.9: Summary of ORR, DCR, CBR and durable stable disease rate- Investigator Assessment

	Lenvatinib 18 mg + Everolimus 5 mg (N=51)	Lenvatinib 24 mg (N=52)	Everolimus 10 mg (N=50)
Objective Response Rate (CR + PR), n (%)	22 (43.1)	14 (26.9)	3 (6.0)
95% CI of objective response rate[c]	(29.3, 57.8)	(15.6, 41.0)	(1.3, 16.5)
Rate Ratio, P Valued			
Lenvatinib 18 mg + Everolimus 5 mg vs. Everolimus 10 mg	7.2 (2.3, 22.5), P<0.0001		
Lenvatinib 24 mg vs. Everolimus 10 mg		4.5 (1.4, 14.7), P=0.0067	
Lenvatinib 18 mg + Everolimus 5 mg vs. lenvatinib 24 mg	1.6 (0.9, 2.8), P=0.1007		
Duration of Objective Response (months)e			
Median (95% CI)	13.0 (3.7, NE)	7.5 (3.8, NE)	8.5 (7.5, 9.4)
1st Quartile, 3rd Quartile	3.7, NE	6.3, 12.9	7.5, 9.4
Disease Control Rate (CR + PR + SD ≥7 weeks), n (%)	43 (84.3)	41 (78.8)	34 (68.0)
95% CI of disease control rate[c]	(71.4, 93.0)	(65.3, 88.9)	(53.3, 80.5)
Durable Stable Disease Rate (SD ≥23 weeks), n (%)	13 (25.5)	20 (38.5)	18 (36.0)
95% CI of durable stable disease rate[c]	(14.3, 39.6)	(25.3, 53.0)	(22.9, 50.8)
Clinical Benefit Rate (CR + PR + durable SD), n (%)	35 (68.6)	34 (65.4)	21 (42.0)
95% CI of clinical benefit rate[c]	(54.1, 80.9)	(50.9, 78.0)	(28.2, 56.8)

Data cut-off date = 13 Jun 2014. Percentages are based on the total number of subjects in the Full Analysis Set within relevant treatment group.
CI = confidence interval, CSR = clinical study report, FAS = full analysis dataset, NE = not estimable.
a: Not Evaluable indicates best overall response of Not Evaluable or SD shorter than 7 weeks postrandomization.
b: Not Assessable includes early deaths and subjects with progression who discontinued treatment or were censored prior to tumour assessment scans. All of these subjects were counted as failures.
c: 95% CI was constructed using the method of Clopper and Pearson.
d: Analyses performed after database lock. Rate ratio is based on the normal approximation and P value is based on the 2 sided Fisher's exact P value.

e: Point estimates are based on Kaplan-Meier method and 95% CIs are based on the Greenwood formula. f: After database lock, it was discovered that 1 of the 14 subjects (10222003) did not have a PR
Source:[EMA Assessment Report; page 90/162][2]

Quality of Life

Quality of life outcomes were not measured in the HOPE-205 trial.

Harms Outcomes

The analyses of the safety outcomes in the HOPE-205 trial included data from the Safety Analysis Set (i.e., patients who received at least one dose of study medication and had at least one post-baseline safety evaluation). All patients in the trial had at least one treatment emergent adverse event (TEAE). A summary of TEAEs is shown in Table 6.10.

As the table shows, the most common TEAEs of any grade were in the lenvatinib plus everolimus arm: diarrhoea (85% with lenvatinib + everolimus and 34% with everolimus) and fatigue or asthenia (59% with lenvatinib + everolimus and 38% with everolimus). The incidence of grade 3 or 4 TEAEs were higher in the lenvatinib + everolimus arm at 71% (36/51), compared with 50% (25/50) in the everolimus arm. This higher incidence in the lenvatinib + everolimus group was mainly driven by grade 3 TEAEs. The most common grade 3 TEAEs were diarrhoea (20% with lenvatinib + everolimus vs. 2% with everolimus), hypertension (14% with lenvatinib + everolimus vs. 2% with everolimus), fatigue (14% with lenvatinib + everolimus vs. 0% with everolimus), anaemia (8% with lenvatinib + everolimus vs. 12% with everolimus), hypertriglyceridemia (8% with either lenvatinib + everolimus or everolimus), and vomiting (8% with lenvatinib + everolimus vs. 0% with everolimus).[1] Seven (14%) patients receiving lenvatinib + everolimus were reported to have grade 4 TEAEs, as compared with four (8%) patients in the everolimus arm.[1] Grade 3 or worst serious AEs occurred more frequently in patients assigned to lenvatinib + everolimus (23/51; 45%) than those assigned to everolimus (19/50; 38%).[1]

Overall, 12/51 (24%) patients in the lenvatinib + everolimus arm, and 6/50 (12%) of those in the everolimus arm discontinued study treatment due to adverse events.[1] One patient in the lenvatinib + everolimus arm died due to cerebral haemorrhage that was judged by the investigators to be related to the study drug; and two patients assigned to receive everolimus died due to acute respiratory failure and sepsis (neither of which were judged to be treatment-related).[1]

Table 6.10: Treatment emergent adverse events reported in the HOPE-205 trial

	Lenvatinib plus everolimus (n=51)			Lenvatinib (n=52)			Everolimus (n=50)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade
Any TEAE	14 (28%)	29 (57%)	7 (14%)	8 (15%)	38 (73%)	3 (6%)	23 (46%)	21 (42%)	4 (8
Diarrhoea	33 (65%)	10 (20%)	0	31 (60%)	6 (12%)	0	16 (32%)	1 (2%)	0
Decreased appetite	23 (45%)	3 (6%)	0	28 (54%)	2 (4%)	0	9 (18%)	0	0
Fatigue or asthenia	23 (45%)	7 (14%)	0	22 (42%)	4 (8%)	0	18 (36%)	0	1 (2
Vomiting	19 (37%)	3 (8%)	0	18 (35%)	2 (4%)	0	5 (10%)	0	0
Nausea	18 (35%)	3 (6%)	0	28 (54%)	4 (8%)	0	8 (16%)	0	0
Cough	19 (37%)	0	0	8 (15%)	1 (2%)	0	15 (30%)	0	0
Hypercholesterolaemia	16 (31%)	1 (2%)	0	5 (10%)	0	1 (2%)	8 (16%)	0	0
Decreased weight	15 (29%)	1 (2%)	0	22 (42%)	3 (6%)	0	4 (8%)	0	0
Stomatitis	15 (29%)	0	0	12 (23%)	1 (2%)	0	20 (40%)	1 (2%)	0
Hypertriglyceridaemia	14 (27%)	4 (8%)	0	5 (10%)	2 (4%)	0	8 (16%)	4 (8%)	0
Hypertension	14 (27%)	7 (14%)	0	16 (31%)	9 (17%)	0	4 (8%)	1 (2%)	0
Peripheral oedema	14 (27%)	0	0	8 (15%)	0	0	9 (18%)	0	0
Upper abdominal or abdominal pain	13 (26%)	2 (4%)	0	14 (27%)	2 (4%)	0	5 (10%)	0	0
Hypothyroidism	12 (24%)	0	0	18 (35%)	1 (2%)	0	1 (2%)	0	0
Arthralgia	12 (24%)	0	0	13 (25%)	0	0	7 (14%)	0	0
Dyspnoea	11 (22%)	0	1 (2%)	10 (19%)	1 (2%)	0	7 (14%)	4 (8%)	0
Dysphonia	10 (20%)	0	0	19 (37%)	0	0	2 (4%)	0	0
Pyrexia	10 (20%)	1 (2%)	0	5 (10%)	0	0	4 (8%)	1 (2%)	0
Epistaxis	9 (18%)	0	0	4 (8%)	0	0	11 (22%)	0	0
Proteinuria	9 (18%)	2 (4%)	0	6 (12%)	10 (19%)	0	6 (12%)	1 (2%)	0
Rash	9 (18%)	0	0	9 (17%)	0	0	11 (22%)	0	0
Hyperglycaemia	8 (16%)	0	0	3 (6%)	0	0	6 (12%)	4 (8%)	1 (2
Back pain	8 (16%)	2 (4%)	0	11 (21%)	0	0	7 (14%)	0	0
Headache	8 (16%)	1 (2%)	0	11 (21%)	2 (4%)	0	4 (8%)	1 (2%)	0
Insomnia	8 (16%)	1 (2%)	0	7 (14%)	0	0	1 (2%)	0	0
Increased blood thyroid-stimulating hormone	7 (14%)	0	0	2 (4%)	0	0	1 (2%)	0	0
Musculoskeletal chest pain	7 (14%)	1 (2%)	0	5 (10%)	1 (2%)	0	2 (4%)	0	0
Constipation	6 (12%)	0	0	19 (37%)	0	0	9 (18%)	0	0
Dyspepsia	6 (12%)	0	0	5 (10%)	1 (2%)	0	5 (10%)	0	0
Nasopharyngitis	6 (12%)	0	0	3 (6%)	0	0	6 (12%)	0	0
Oral pain	6 (12%)	0	0	5 (10%)	0	0	1 (2%)	0	0
Pruritus	6 (12%)	0	0	3 (6%)	0	0	7 (14%)	0	0
Dry skin	5 (10%)	0	0	3 (6%)	0	0	3 (6%)	0	0
Mouth ulceration	5 (10%)	0	0	0	0	0	4 (8%)	1 (2%)	0
Musculoskeletal pain	5 (10%)	0	0	6 (12%)	1 (2%)	0	1 (2%)	0	0
Pain in extremity	5 (10%)	0	0	5 (10%)	1 (2%)	0	3 (6%)	0	0
Toothache	5 (10%)	0	0	3 (6%)	0	0	1 (2%)	0	0
Anaemia	4 (8%)	4 (8%)	0	3 (6%)	1 (2%)	0	7 (14%)	6 (12%)	0
Palmar-plantar erythrodysesthesia syndrome	4 (8%)	0	0	8 (15%)	0	0	2 (4%)	0	0
Lethargy	3 (6%)	0	0	7 (14%)	0	0	2 (4%)	0	0
Myalgia	3 (6%)	0	0	6 (12%)	1 (2%)	0	1 (2%)	0	0
Upper-respiratory-tract infection	3 (6%)	0	0	7 (14%)	0	0	5 (10%)	0	0
Dry mouth	2 (4%)	0	0	6 (12%)	0	0	3 (6%)	0	0
Exertional dyspnoea	2 (4%)	0	0	1 (2%)	0	0	5 (10%)	0	0
Lower-respiratory-tract infection	1 (2%)	0	0	0	4 (8%)	0	5 (10%)	1 (2%)	0

TEAEs (grade 1–2) with a frequency of 10% or higher in any treatment group are presented. Patients are counted only once and are categorised by the highest TEAE grade reported. TEAEs leading to deat cerebral haemorrhage (lenvatinib plus everolimus, one [2%]; judged probably related to study drug by the clinical investigator); myocardial infarction (single-agent lenvatinib, one [2%]; judged probably to study drug by the clinical investigator); intracranial haemorrhage (single-agent lenvatinib, one [2%]; judged unrelated to study drug); sepsis (single-agent lenvatinib, one [2%]; single-agent everolimu [2%]; both judged unrelated to study drug); and acute respiratory failure (single-agent everolimus, one [2%]; judged unrelated to study drug). TEAE=treatment-emergent adverse event.

Reprinted from Lancet Oncology, Vol 16 /issue 15, Motzer, R.J., Hutson, T.E. Glen, H. et al., Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial, pages 1473-1482, Copyright 2015, with permission from Elsevier.

6.4 Ongoing Trials

No ongoing trial were identified as being relevant to this review.

7 SUPPLEMENTAL QUESTIONS

The following supplemental issue was identified during development of the review protocol as relevant to the pCODR review of lenvatinib in combination with everolimus for advanced or metastatic renal cell carcinoma (RCC):

- Critical appraisal of an indirect treatment comparison comparing the efficacy and safety of anti-cancer therapies in the second line treatment of advanced or metastatic renal cell carcinoma.

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical Appraisal of an Indirect Treatment Comparison

Comparing the efficacy and safety of anti-cancer therapies in the second line treatment of advanced renal cell carcinoma

Given the absence of head-to-head trials against other currently funded therapies in Canada, the submitter provided an indirect treatment comparisons (ITC) report comparing the efficacy of therapies in the second line treatment of advanced renal cell carcinoma (RCC). The 'original' ITC report submitted to pCODR included a network of clinical trials based on all potential comparisons; i.e., indirect comparison of lenvatinib + everolimus versus cabozantinib, nivolumab, placebo and sorafenib and the direct comparison of lenvatinib + everolimus with everolimus. However, because sorafenib was not considered to be a relevant comparator, pCODR asked the submitter to provide a 'revised' ITC without sorafenib.

Review of the submitted ITC

7.1.1 Objectives of ITC

The objective of the submitter-provided ITC was to indirectly compare the effect of lenvatinib + everolimus on PFS and OS relative to other second line treatments for patients with advanced or metastatic RCC specifically everolimus, nivolumab, and cabozantinib, using fractional polynomials.[4]

7.1.2 Methods

Literature search and study selection

The submitter conducted a systematic review to identify eligible studies for the ITC. As the details of the systematic review methodology were not provided by the submitter for the 'revised ITC, the pCODR Methods team used the description of the systematic review methodology from the literature search protocol that was published by the National Institute for Health and Care Excellence (NICE) as part of their Single Technology Appraisal on lenvatinib + everolimus for previously treated advanced RCC (2017).[3] According to the NICE report, the literature search was conducted in Embase, MEDLINE, the Cochrane library, MEDLINE In-process and Other Non-indexed Citations (PubMed). Grey literature sources were also searched for additional information. Studies were eligible for inclusion if they were randomised controlled trials (RCT), systematic reviews, or meta-analysis that included adult patients with advanced/metastatic RCC. The searches were limited to articles published in English language. Details of the inclusion and exclusion criteria are presented in Table 7.1.[3] As can be seen in the table, the systematic search included all second-

line treatments for patients with advanced/metastatic RCC; however, studies relevant to the comparisons of interest were selected for the purpose of the ITC.

It was stated in the NICE report that a quality assessment was performed for all the studies included in the ITC; however, no details were provided in the available reports.

Table 7.1: Eligibility criteria used in the manufacturer's systematic review

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Advanced/metastatic renal cell carcinoma terms	Not in Advanced/metastatic RCC
Intervention / Comparators	▪ Lenvatinib ▪ Cabozantinib ▪ Nivolumab ▪ Temsirolimus ▪ Everolimus ▪ Pazopanib ▪ Sunitinib ▪ Sorafenib ▪ Bevacizumab ▪ Axitinib	Not second line a/mRCC treatment after one prior anti-VEGF therapy Surgical /Radiotherapy /Diagnostic intervention
Outcomes	▪ Progression free Survival ▪ Overall survival ▪ Response Rate ▪ Adverse events ▪ Quality of life	
Study design	Randomised controlled trials Systematic reviews Meta-analysis	Experimental or non-human studies Not a randomised trial or meta-analysis/systematic review Subgroup analyses/ abstracts/ publications of already identified trial with no additional information provided
Language restrictions	English	Non-English language

Abbreviations: a/m RCC, Advanced /metastatic Renal cell carcinoma; RCC, Renal cell carcinoma; VEGF, Vascular endothelial growth factor

Source: [NICE Committee Papers; Figure 12 page 37/199][3]

ITC methodology

The efficacy of Lenvatinib + everolimus was compared with everolimus, cabozantinib, and nivolumab through an indirect treatment comparison using parametric fractional polynomial survival functions as described by Jansen (2011).[47] This method does not rely on the proportional hazard assumption and allows a wide family of survival functions to be modelled including Weibull and Gompertz. Only fixed effects models were considered due to the sparseness of the network.[3,4]

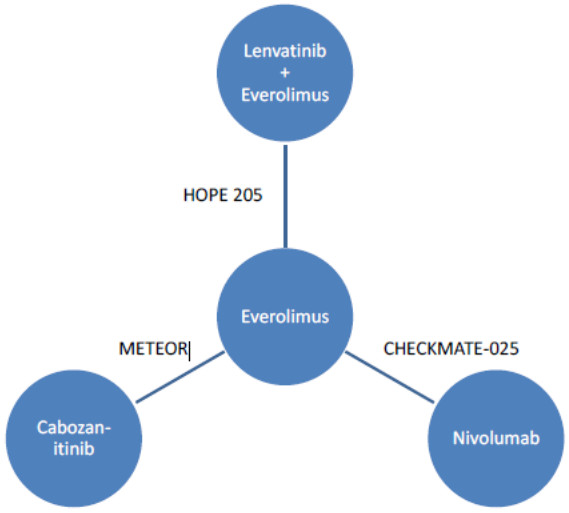
Baseline demographic and disease characteristics for the studies included in the ITC are presented in Table 7.2. This table which has been taken from the 'original' ITC provided by the submitter includes two additional placebo-controlled trials (i.e., RECORD-1 and TARGET) which are not relevant to this submission. The ITC results provided in this section will focus on three trials: HOPE-205, METEOR, and CHECKMATE-025 (Figure 7.1). As shown in the table, the trial populations were relatively similar between the studies; however, on average, patients in the HOPE-205 trial had more severe disease as measured by performance status and Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification. In addition, there were differences between trials relating to the use of prior therapy. Patients in the HOPE-205 trial were required to have one prior VEGF therapy, patients in the METEOR, and CHECKMATE-025 trials were required to have received one or more prior VEGF therapies.[4]

Table 7.2: Characteristics of the trials included in the ITC

	HOPE 205	CHECKMATE-025	METEOR	RECORD-1	TARGET
Study treatments	LEN+EVE vs EVE	NIV vs EVE	CAB vs EVE	PBO vs EVE	PBO vs SOR
Age (years), median	61 vs 59	62 vs 62	63 vs 62	60 vs 61	59 vs 58
Male, %	69 vs 76	77 vs 74	77 vs 73	76 vs 78	75 vs 70
Performance status, %	ECOG 0: 53 vs 56	Karnofsky 90-100: 68 vs 65	ECOG 0: 68 vs 66	Karnofsky 90-100: 68 vs 63	ECOG 0: 46 vs 49
Favourable MSKCC risk, %	24 vs 24	35 vs 36	45 vs 46	28 vs 29	51 vs 52
Prior VEGF therapy					
1	100%	72%	71%	74%	Not permitted
≥2	Not permitted	28%	29%	26%	Not permitted
Cytokines as only prior systemic therapy	NA	NA	NA	NA	82%
Prior radiotherapy	17%	Not reported	33%	30%	25%
Prior nephrectomy	48%	88%	85%	97%	93%
Control patients crossover to investigational treatment	Not permitted	Not permitted	Not permitted	80%	48%
Continued study treatment after progression	Not permitted	Not reported	Treatment continued while a clinical benefit was observed	Not permitted	Patients who responded could continue sorafenib

Source: [Eisai submission information; FP NMA 16 April 2018, page 7, Table 2.1.1][4]

Figure 7.1: Network of trials included in the fractional polynomial indirect treatment comparison



a/mRCC, advanced/metastatic renal cell carcinoma; ITC, indirect treatment comparison.

Source[Eisai submission information; FP NMA 22 May 2017, page 8, Figure 2.1.1][4]

A summary of PFS and OS data sources included in the ITC are provided in Table 7.3.

Table 7.3: Sources of data used in the submitter's fractional polynomial network meta-analysis

Trial	PFS			OS		
	Median PFS (95% CI)	HR (95% CI)	KM source	Median OS (95% CI)	HR (95% CI)	KM source
HOPE 205	Investigator, all randomised; 31 Jul 2015			All randomised; 31 Jul 2015		
	NA	NA	IPD	L+E: 25.5 (16.4, 32.1) E: 15.4 (11.8, 20.6)	0.59 (0.36, 0.96)	IPD
CHECKMATE-025	Investigator, all randomised; June 2015			All randomised; June 2015		
	N: 4.6 (3.7, 5.4)[8] E: 4.4 (3.7, 5.5)[8]	0.88 (0.75, 1.03)[8]	Figure 2B[8]	N: 25.0 (21.8, ne)[8] E: 19.6 (17.6, 23.1)[8]	0.73 (0.57, 0.93)[a8]	Figure 1[8]
METEOR	IRR, all randomised; 22 May 2015			All randomised; 31 Dec 2015		
	C: 7.4 (6.6, 9.1)[4] E: 3.9 (3.7, 5.1)[4]	0.51 (0.41, 0.62)[4]	Figure 4[4]	C: 21.4 (18.7, ne)[4] E: 16.5 (14.7, 18.8)[4]	0.66 (0.53, 0.83)[4]	Figure 2[4]

C, cabozantinib; CI, confidence interval; E, everolimus; HR, hazard ratio; IPD, individual patient data; IRR, independent response review; ITC, indirect treatment comparison; KM, Kaplan-Meier; L, lenvatinib; N, nivolumab; NA, not available; ne, not estimable; OS, overall survival; PFS, progression-free survival.
Notes: a 98.5% CI
Source: HOPE 205 IPD provided in response B1 (PFS) and Company Submission (OS); CHECKMATE-025 Motzer et al (2015)[8]; METEOR Choueiri et al. (2016)[4].

Source: [Eisai submission information; FP NMA 22 May 2017, page 18, Table 3.1.1][4]

Survival data was digitally extracted from the relevant Kaplan-Meier curves (progression-free survival [PFS] and overall survival [OS]) for CHECKMATE-025 and METEOR trials; individual patient data (IPD) was used from the HOPE-205 trial.[3]

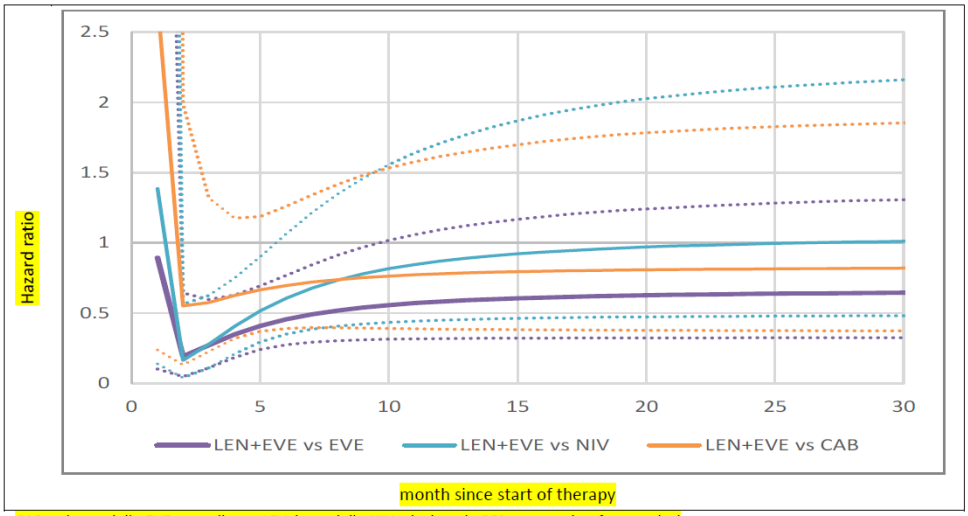
The proportional hazards assumption was violated for PFS in the CHECKMATE-025 and METEOR trials. The test for proportional hazards for PFS was not statistically significant for HOPE-205; however, the authors of the ITC report believed that the test was underpowered due to the sample size. They also noted that the diagnostic plots were similar to the other studies. The proportional hazard assumptions held for OS within the HOPE-205 and METEOR trials, but not for CHECKMATE-025.[4]

7.1.3 Findings

Progression-free survival (PFS)

The 'best' model fit for PFS was a second order fractional polynomial model (P1=-2, P2=-2). The hazard ratios (HR) over time for PFS resulting from this model showed that lenvatinib + everolimus was superior (HR < 1) to everolimus monotherapy, cabozantinib, and nivolumab from after the first two months of receiving treatment; however, the 95% credible intervals crossed 1 indicating these differences were not statistically significant. Similarly, the survival curves showed that PFS was higher for lenvatinib + everolimus than the other treatments after the first two months, but the credible intervals overlapped indicating a lack of statically significant difference between the treatments in terms of PFS. [4]

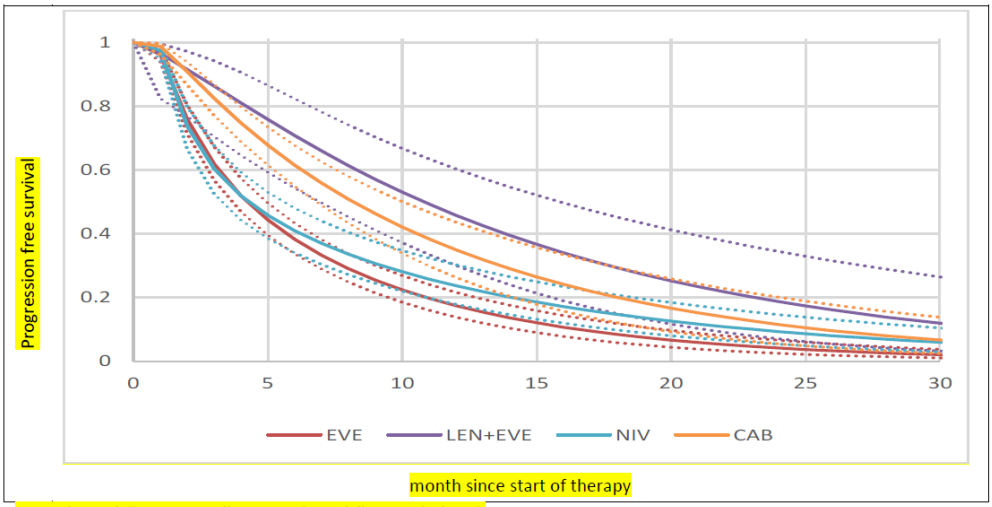
Figure 7.2: Hazard ratio over time estimated from the best-fitting fixed-effects second-order fractional polynomial model (P1=-2, P2=-2) for progression-free survival



CAB, cabozantinib; EVE, everolimus; LEV, lenvatinib; NIV, nivolumab; PFS, progression-free survival
Notes: Solid line is median and dotted lines 95% credible intervals. Hazard ratios based on average estimates for everolimus over the three studies (μ_0, μ_1, μ_2) per Jansen 2011.

Source: [Eisai submission information; FP NMA 22 May 2017, page 13, Figure 2.3.2][4]

Figure 7.3: Progression-free survival over time estimated from the best fitting fixed-effects second-order fractional polynomial model (P1=-2, P2=-2)



CAB, cabozantinib; EVE, everolimus; LEV, lenvatinib; NIV, nivolumab
Notes: Solid line is median and dotted lines 95% credible intervals.

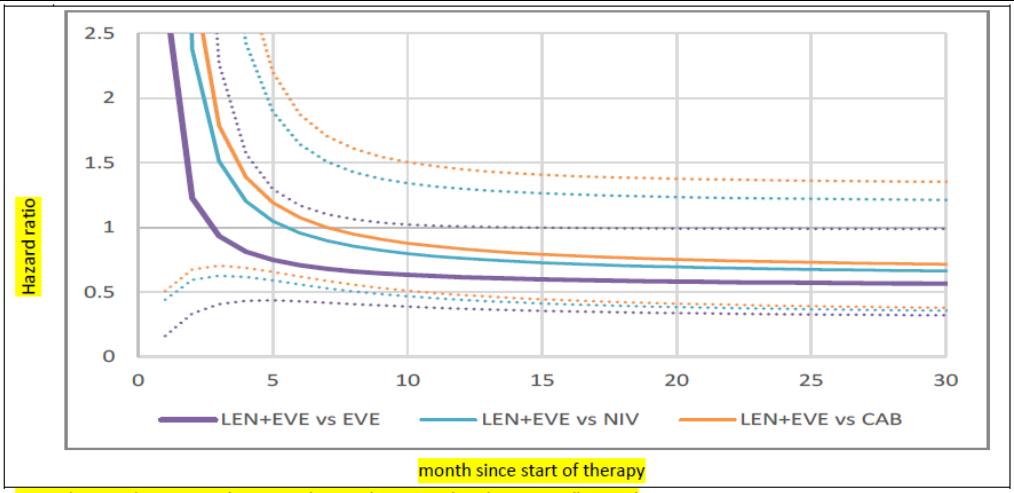
Source: [Eisai submission information; FP NMA 22 May 2017, page 13, Figure 2.3.3][4]

Overall survival (OS)

The 'best' model fit for OS was a first order fractional polynomial model (P1=-1). Although this model did not fit well to individual treatments, it was on average the best fit for the network. The HRs over time for OS resulting from this model showed that lenvatinib + everolimus was superior

(HR < 1) to everolimus monotherapy, cabozantinib, and nivolumab after approximately two (everolimus) to eight (cabozantinib) months of starting treatment; however, the 95% credible intervals crossed 1 indicating these differences were not statistically significant. The survival curves further illustrated a higher OS for lenvatinib + everolimus versus everolimus from around 8 months; and higher OS rates for lenvatinib + everolimus versus cabozantinib and nivolumab from around 20 months. The overlapping credible intervals, however, indicated a lack of statically significant difference between the treatments in terms of OS. [4]

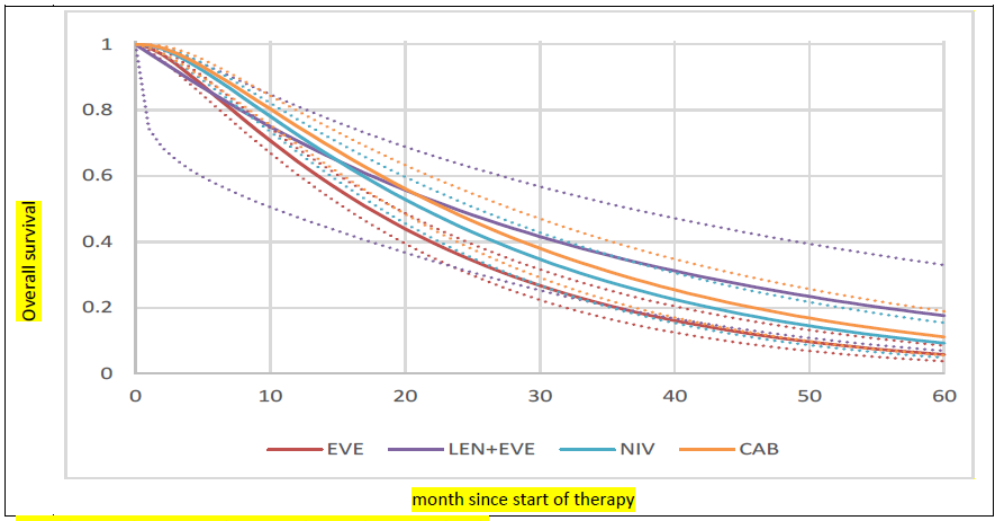
Figure 7.4: Hazard ratio over time estimated from the best-fitting fixed-effects first-order fractional polynomial model (P1=-1) for overall survival



CAB, cabozantinib; EVE, everolimus; LEV, lenvatinib; NIV, nivolumab; OS, overall survival
Notes: Solid line is median and dotted lines 95% credible intervals. Hazard ratios based on average estimates for everolimus over the three studies (μ_0, μ_1) per Jansen 2011.

Source: [Eisai submission information; FP NMA 22 May 2017, page 17, Figure 2.4.2][4]

Figure 7.5: Overall survival over time estimated from the best fitting fixed-effects first-order fractional polynomial model (P1=-1)



CAB, cabozantinib; EVE, everolimus; LEV, lenvatinib; NIV, nivolumab
Notes: Solid line is median and dotted lines 95% credible intervals.

Source: [Eisai submission information; FP NMA 22 May 2017, page 17, Figure 2.4.3][4]

7.1.4 Summary

Critical Appraisal of the ITC

The quality of the ITC provided by the submitter[4] was assessed according to the recommendations made by the ISPOR Task Force on Indirect Treatment Comparisons.[48] Details of the critical appraisal are presented in Table 7.4.

Table 7.4: Adapted ISPOR questionnaire to assess the credibility of an indirect treatment comparison or network meta-analysis†

ISPOR Questions	Details and Comments
1. Is the population relevant?	**Yes.** The study populations of the included trials in the NMA matched the review indication, which was to evaluate the efficacy and safety of lenvatinib + everolimus in patients with advanced or metastatic RCC who have received previous anti-VEGF-targeted therapy.
2. Are any critical interventions missing?	**Yes, in part.** Axitinib, a potentially relevant comparator that was identified by the pCODR CGP, was not in the submitted ITC due to concerns with transitivity (different eligibility criteria). For the purpose of the economic evaluation, the submitter assumed axitinib and everolimus monotherapy have similar efficacy, based on expert opinion.
3. Are any relevant outcomes missing?	**Yes.** The following outcomes were assessed: OS and PFS. Other relevant outcomes such as ORR, quality of life, and safety results were excluded from the submitted NMA.
4. Is the context (e.g., settings and circumstances) applicable to your population?	**Yes**. The settings of the included trials were similar, and applicable to the Canadian population.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Yes.** The submitter conducted a systematic review to identify eligible studies for the ITC. A summary of the systematic literature review process that was used in the ITC was published by NICE as part of their Single Technology Appraisal on lenvatinib + everolimus for previously treated advanced RCC (2017).[3]
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**No.** There were no closed loops in the ITC.
7. Is it apparent that poor quality studies were included thereby leading to bias?	**Unclear.** It was stated in the NICE report that a quality assessment was performed for all the studies included in the ITC; however, no details were provided in any of the available reports.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	**No.** There was no selective reporting of outcomes in the included trials.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Yes, in part.** The submitter provided a qualitative assessment of heterogeneity, with no statistical testing of the significance of the differences.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	**Yes.** It was noted in the submitter's ITC report that there were differences in the baseline prognostic factors such as disease severity and the use of prior therapies. Patients in the HOPE-205 trial had more severe disease and required to have one prior VEGF-targeted therapy; whereas, patients in the METEOR, and CHECKMATE-025 trials were to have received one or more prior VEGF-targeted therapies.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	**Yes**. A fractional polynomial NMA model was used.

Table 7.4: Adapted ISPOR questionnaire to assess the credibility of an indirect treatment comparison or network meta-analysis†	
ISPOR Questions	**Details and Comments**
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	**Not applicable.** There was no closed loop.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	**Not applicable.** There was no closed loop.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	**Yes, in part.** As the proportional hazards assumption did not hold within all trials in the network (the assumption was violated for PFS in the CHECKMATE-025 and METEOR trials, and for OS in the CHECKMATE-025 trial), it was concluded that an NMA based on fractional polynomials (which does not rely on proportional hazards) was a more suitable method than that based on HRs.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	**Yes.** The author stated that only fixed effects models were considered due to the sparseness of the network.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Not applicable.**
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**No.**
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	**Yes.** The network is presented in Figure 7.1.
19. Are the individual study results reported?	**Yes.** The submitter provided the baseline characteristics of the trials and the HRs of the outcomes used in the NMA.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	**No**. no closed loops were included in the NMA.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	**Yes**. Measures of uncertainty (95% credible intervals) were provided, where applicable.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**No.**
23. Is the impact of important patient characteristics on treatment effects reported?	**No.**
24. Are the conclusions fair and balanced?	Not clear. Point estimates of effect resulting from the ITC suggested that lenvatinib + everolimus could be superior to everolimus monotherapy, cabozantinib, and nivolumab in terms of PFS and OS (HRs < 1). However, these results should be interpreted with caution due to the overlapping credible intervals and the limitations that arise from the lack of close loops in the network, limited number of studies for each treatment comparison (one study per comparison), and lack of indirect comparisons for safety data and other efficacy outcomes (objective response rate, etc.).
25. Were there any potential conflicts of interest?	**Not reported.**
26. If yes, were steps taken to address these?	**Not reported.**

Table 7.4: Adapted ISPOR questionnaire to assess the credibility of an indirect treatment comparison or network meta-analysis†	
ISPOR Questions	**Details and Comments**
HR = hazard ratio; ISPOR = International Society For Pharmacoeconomics and Outcomes Research; ITC = indirect treatment comparisons; NICE = the National Institute for Health and Care Excellence (United Kingdom); NMA = network meta-analysis; PFS = progression-free survival; ORR = objective response rate; OS = overall survival; VEGF = vascular endothelial growth factor † Adapted from Jansen, Value Health. 2014;17(2):157-73[48]	

Conclusion

The submitter provided a network meta-analysis with three trials that used everolimus monotherapy as the common comparator: HOPE-205,[1] CHECKMATE-025,[5] and METEOR.[6] This network of trials permitted indirect comparisons of lenvatinib + everolimus with cabozantinib and nivolumab as well as a direct comparison of lenvatinib + everolimus combination with everolimus monotherapy. The indirect comparisons were performed using a NMA with parametric fractional polynomial survival functions which do not rely on the proportional hazard assumption.

Although the point estimates of effect resulting from the ITC (HR < 1) suggested that lenvatinib + everolimus could be superior to everolimus monotherapy, cabozantinib, and nivolumab in terms of PFS and OS, these results should be interpreted with caution due to the overlapping credible intervals (i.e., statistical non-significance) and the limitations that arise from the lack of close loops in the network, limited number of studies for each treatment comparison (one study per comparison), and lack of indirect comparisons for safety data and other efficacy outcomes (e.g., objective response rate, quality of life). Therefore, the relative efficacy of lenvatinib + everolimus over nivolumab and cabozantinib remains uncertain in patients with advanced or metastatic RCC who failed on prior VEGF inhibitors. Furthermore, because the submitted ITC assumed a similar efficacy for axitinib and everolimus (based on expert opinion), no conclusions can be made on the relative efficacy of lenvatinib + everolimus compared to axitinib.

In their feedback on the initial recommendation, the submitter noted that the ITC was appropriate for decision making and performed based on the best available evidence and well-accepted methods, including appropriate handling (through fractional polynomials) of survival data that did not support the proportional hazard assumption. The submitter further suggested, that overlapping confidence intervals ["confidence intervals' as per original submitter's feedback, however, this should be corrected to be 'credible intervals'] are a common finding in ITCs and therefore not a limitation and patient characteristics across trials were generally similar, suggesting a low risk of is due to between trial heterogeneity in the ITC results. Furthermore, the submitter suggested that the CGP had made the following statement in support of the ITC: *"Overall, the company's network analyses criteria and assumption were appropriate for the comparison in question. Within this network analysis, lenvatinib in combination with everolimus compared favourable to the other second line therapies."* In response to the submitter's feedback the pCODR Methods Team noted that overlapping credible intervals, where reported, indicate a lack of statistical significance between the comparators of interest. In the CGR, the overlapping credible intervals were not listed as a methodological limitation of the ITC. Rather, they were highlighted as a point to consider when interpreting the ITC results. The Methods Team agreed that the submitted ITC was conducted based on "best available evidence" and "well-accepted methods". In the CGR, potential limitations of the available evidence were brought into end-users' attention, with no specific concerns regarding the appropriateness of ITC methods (design and analysis). The CGP used the information in sections 6 and 7 of CGR to issue the statement cited in the Submitter's feedback (i.e., *"overall, the company's network analysis criteria and assumptions were appropriate for the comparison in question.")* However, this specific statement does not imply that the available evidence was sufficiently conclusive.

In addition, the submitter noted that an ITC between lenvatinib in combination with everolimus with axitinib is appropriate, as the assumption that axitinib and everolimus perform similarly is supported by NICE and the CGP. In response to the submitter's feedback the pCODR Methods Team confirmed that the ITC reported in the CGR (updated network that excludes sorafenib as an irrelevant comparator) does not include axitinib due to lack of evidence. The CGP confirmed that the assumption of equal effect sizes for axitinib and everolimus sounded clinically reasonable. However, the validity of an ITC is based on several fundamental methodological assumptions; without including the trial of axitinib in the ITC, these assumptions cannot be fully and directly explored, thus leaving uncertain the relative effectiveness of lenvatinib in combination with everolimus with axitinib.

8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Method Team did not identify other relevant literature proving supporting information for this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Endocrine Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on lenvatinib in combination with everolimus for advanced or metastatic renal cell carcinoma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Endocrine Clinical Guidance Panel is comprised of three medical oncologist. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** May 2018**, Embase** 1974 to 2018 June 14**, Ovid MEDLINE(R) ALL** 1946 to June 14, 2018

#	Searches	Results
1	(lenvima* or lenvatinib* or kisplyx* or E 7080 or E7080 or ER-203492-00 or ER203492-00 or EE83865G2 or 3J78384F61).ti,ab,ot,kf,kw,hw,rn,nm.	1568
2	everolimus/	28191
3	(everolimus* or afinitor* or affinitor* or certican* or votubia* or disperz* or advacan* or xience* or evertor* or zortress or HSDB 8255 or HSDB8255 or RAD or "RAD 001" or RAD001 or RAD001a or SDZ-RAD or 9HW64Q8G6G).ti,ab,ot,kf,kw,hw,rn,nm.	65809
4	2 or 3	65811
5	1 and 4	385
6	5 use cctr	24
7	5 use medall	50
8	*lenvatinib/	361
9	(lenvima* or lenvatinib* or kisplyx* or E 7080 or E7080 or ER-203492-00 or ER203492-00).ti,ab,kw,dq.	1031
10	8 or 9	1044
11	*everolimus/	8139
12	(everolimus* or afinitor* or affinitor* or certican* or votubia* or disperz* or advacan* or xience* or evertor* or zortress or HSDB 8255 or HSDB8255 or RAD or "RAD 001" or RAD001 or RAD001a or SDZ-RAD).ti,ab,kw,dq.	47625
13	11 or 12	48004
14	10 and 13	163
15	14 use oemezd	93
16	conference abstract.pt.	3075889
17	15 and 16	36
18	limit 17 to english language	36
19	limit 18 to yr="2013 -Current"	33

20	15 not 16	57
21	6 or 7 or 20	131
22	limit 21 to english language	123
23	remove duplicates from 22	74
24	19 or 23	107

2. **Literature search via PubMed**
   A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#7	Search **#5 AND #6**	0
#6	Search **publisher[sb]**	514191
#5	Search **#1 AND #4**	50
#4	Search **#2 OR #3**	16159
#3	Search **everolimus*[tiab] OR afinitor*[tiab] OR certican*[tiab] OR votubia* OR disperz*[tiab] OR advacan*[tiab] OR xience*[tiab] OR evertor*[tiab] OR zortress[tiab] OR HSDB 8255[tiab] OR HSDB8255[tiab] OR RAD[tiab] OR RAD 001[tiab] OR RAD001[tiab] OR SDZ-RAD[tiab]**	15629
#2	Search **Everolimus[MeSH]**	3854
#1	Search **lenvima[tiab] OR lenvatinib[tiab] OR E 7080[tiab] OR E7080[tiab] OR ER-203492-00[tiab] OR ER203492-00[tiab]**	290

3. Cochrane Central Register of Controlled Trials (Central)
   Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

U.S. NIH ClinicalTrials. gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Lenvima (lenvatinib) and Afinitor (everolimus), advanced renal cell carcinoma (aRCC)

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Lenvima (lenvatinib) and Afinitor (everolimus), advanced renal cell carcinoma (aRCC)

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Oncology (ESMO)

http://oncologypro.esmo.org/Meeting-Resources

Search: Lenvima (lenvatinib) and Afinitor (everolimus), advanced renal cell carcinoma (aRCC) – last 5 years

Detailed Methodology

The literature search was performed by the pCODR Methods Team using the search strategy above.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (May 2018) via OVID and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Lenvima (lenvatinib) and Afinitor (everolimus).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of September 28, 2018.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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