CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic 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 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Eisai Limited** compared lenvatinib in combination with everolimus to nivolumab, everolimus, axitinib and sorafenib for the treatment of patients with advanced or metastatic, clear-cell renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

Table 1. Submitted Economic Model

Patient Population Modelled	Patient population modeled aligns with patients in the HOPE-205 trial. 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 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.
Type of Analysis	*CUA & CEA*
Type of Model	*Partitioned survival model*
Comparator	*Nivolumab* *Everolimus* *Axitinib* *Sorafenib* *The pCODR Clinical Guidance Panel (CGP), registered clinicians and PAG did not consider sorafenib as an appropriate comparator as it is funded in second line following cytokine based treatment and not VEGF targeted therapy and is very rarely used as Cytokine based treatment has fallen out of use.*
Year of costs	*2017*
Time Horizon	*20 years* *Monthly cycle*
Discount rate	*1.5% for both costs and outcomes*
Perspective	*Government (third-party payer)*
Cost of lenvatinib plus everolimus*	*Lenvatinib:* *At the recommended dose of 18 mg once daily (1 X 10mg, 2 X 4mg capsules), lenvatinib costs:* • *$8.14 per mg or $732.86 per unit (5-day blister card)* • *$146.57 per day* *Everolimus:* *At the recommended dose of 5 mg once daily (one 5 mg tablet), everolimus costs:* • *$202.65 per day*

	Lenvatinib plus everolimus cost: • *$8,896.00 per 28-day drug cycle.*
Cost of everolimus monotherapy*	*Everolimus monotherapy:* *At the recommended dose of 10 mg once daily (two 5 mg tablets), everolimus costs:* • *$5,704.00 per 28-day cycle*
Cost of axitinib*	*Axitinib costs:* • *$97.13 per 5 mg tablet* *At the recommended dose of 5 mg twice daily, axitinib costs:* • *$194.26 per day* • *$5,469.00 per 28-day cycle*
Cost of nivolumab*	*Nivolumab costs:* • *$1,955.56 per 100 mg vial* *At the recommended dose of 3 mg/kg every 2 weeks, nivolumab costs:* • *$5,866.68per day* • *$11,842.00 per 28-day cycle*
Model Structure	*Patients transition between the three health states of: pre-progression, post-progression and death. Patients first enter in pre-progression. A patient's health state at any time point is derived from parametric curves obtained from the fractional polynomial network meta-analysis.*
Key Data Sources	*HOPE 205* [1] *(phase 2 trial) to compare lenvatinib plus everolimus with everolimus monotherapy in terms of efficacy and adverse events.* *Indirect treatment comparison through a fractional polynomial network meta-analysis to derive progression free survival (PFS) and overall survival (OS) associated with other comparators (Nivolumab and cabozantinib). Cabozantinib was not considered to be an appropriate 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.* *It was assumed that axitinib has same efficacy as everolimus. The CGP agreed that this is a reasonable assumption.* *Utility data based on AXIS*[4] *Resource utilization and costs taken from various sources.*
** Drug costs in this table are based on costing information provided by the submitter, Eisai Limited, and used in the economic model.*	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison of lenvatinib plus everolimus to everolimus, axitinib and nivolumab is appropriate.

- Relevant issues identified included:
  - *The CGP considered that there is a net overall clinical benefit when comparing lenvatinib plus everolimus to everolimus monotherapy.*
  - *The HOPE-205 trial[1] (phase 2) demonstrated a clinically meaningful and statistically significant benefit in response rate, progression free survival (PFS) and overall survival (OS) for lenvatinib plus everolimus compared with everolimus.*
  - *The acceptable toxicity of lenvatinib plus everolimus.*
  - *The current standard of care for patients with advanced or metastatic, clear-cell RCC who have had one prior VEGF-targeted therapy includes nivolumab, which is the most commonly used therapy, axitinib or everolimus.*
  - *There is an urgent need for more effective and additional treatment options in RCC.*

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered the unmet need for patients with advanced or metastatic renal cell carcinoma. The treatments included in this cost-effectiveness analysis were considered relevant in current clinical practice. Lenvatinib plus everolimus represents a novel therapy that could meet the needs of patients with renal cell carcinoma in the 2nd line setting. Lenvatinib plus everolimus showed favourable PFS, OS and objective response rates compared with everolimus monotherapy. Lenvatinib plus everolimus has a safety profile that is familiar and manageable.

Summary of patient input relevant to the economic analysis
Overall the following factors were important for patients when assessing the value of a new drug for advanced or metastatic RCC: treatment choice, patient preferences and the availability of treatment alternatives within the same line of therapy, in case of treatment intolerance. Further the need for new effective 2nd line treatment alternatives was highlighted to afford patients the opportunity to halt disease progression, to control drug resistance, and overcome drug resistance mechanisms. It was stated that 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. The majority of patients who had experience with lenvatinib and everolimus reported their treatment to be a very effective therapy against their kidney cancer affording them a high quality of life with side effects that are well tolerable. Adverse events, quality of life and effectiveness were considered in the economic model.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for lenvatinib plus everolimus which are relevant to the economic analysis:

- Currently funded treatments in second-line in the Canadian setting for advanced or metastatic RCC include nivolumab, axitinib, and everolimus. It should be noted that nivolumab and axitinib are currently the most relevant comparators.
- Additional resources may be required to monitor and treat adverse events. Increased resource use in the lenvatinib and everolimus arm was not examined as the CGP confirmed that even though there may be more adverse events with the lenvatinib combination than with everolimus monotherapy, the resources to monitor and treat adverse events would be similar.

- There is a potential for dose adjustments for both lenvatinib and everolimus, which may result in drug wastage if dose adjustments are made prior to finishing the tablets dispensed, due to the dispensing through blister packs. Wastage was included in this model by rounding up the dose to the next strength available, which seemed reasonable.

These factors have been considered in the economic analysis.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Reanalysis Estimates, lenvatinib plus everolimus versus everolimus

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ΔE (LY)	0.86	0.55	Not estimable
Progression-free	0.56	0.64	
Post-progression	0.30	-0.09	
ΔE (QALY)	0.56	0.38	Not estimable
Progression-free	0.38	0.43	
Post-progression	0.18	-0.05	
ΔC ($)	$71,102	$69,710	Not estimable
ICER estimate ($/QALY)	$126,667	$185,802	

Table 3. Submitted and EGP Reanalysis Estimates, lenvatinib plus everolimus versus axitinib

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ΔE (LY)	0.80	0.54	Not estimable
Progression-free	0.55	0.63	
Post-progression	0.24	-0.09	
ΔE (QALY)	0.52	0.36	Not estimable
Progression-free	0.38	0.43	
Post-progression	0.15	-0.06	
ΔC ($)	$73,507	$68,586	Not estimable
ICER estimate ($/QALY)	$140,084	$184,055	

Table 4. Submitted and EGP Reanalysis Estimates, lenvatinib plus everolimus versus nivolumab

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ΔE (LY)	0.49	0.26	Not estimable
Progression-free	0.43	0.48	
Post-progression	0.06	-0.22	
ΔE (QALY)	0.32	0.20	Not estimable
Progression-free	0.29	0.33	
Post-progression	0.04	-0.13	
ΔC ($)	-$62,622	-$52,409	Not estimable
ICER estimate ($/QALY)	Dominant*	Dominant*	
* Lenvatinib plus everolimus costs less and is more effective than nivolumab.			

The main assumptions and limitations with the submitted economic evaluation were:

- **Time horizon:** The time horizon in the submitted base case was 20 years. OS was extrapolated beyond the time horizon of the clinical trial. In the economic model, few patients were predicted to be alive at 10 years.
- **Duration of treatment effect:** In the submitted base case, the submitter assumed that the duration of treatment effect would continue indefinitely over the entire time horizon. In reality, it is unlikely that any benefit from treatment would extend indefinitely once a patient progresses on that treatment.
- **Use of fractional polynomials for modeling survival:** Indirect treatment comparisons synthesize evidence by estimating the relative treatment effect between comparators in the absence of head-to-head data. In the submitted base case, the submitter fitted fractional polynomials instead of using hazard ratios to estimate treatment effect as the proportional hazards assumption did not hold.
  Though this method was appropriate given that the proportional hazards did not hold, fitting curves for fractional polynomials relies on an average fit across the network. This could mean that the selected curve would fit one treatment well, and another treatment less well. In the case of OS, the best fitting curve (according to fit statistics) visually fit lenvatinib + everolimus better than nivolumab. The result is that OS predictions may be underestimated for nivolumab, thus impacting the incremental QALYs.
  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. Among other points, the submitter suggested that the EGP agreed that the fractional polynomials methodology was appropriate. In response to the submitter's feedback the EGP agreed that given the proportional hazards assumption did not hold, the fractional polynomials method was appropriate to use. However, this does not negate the fact, that the EGP identified limitations resulting from the use of the fractional polynomials in this economic model. The EGP re-iterated that fitting curves for fractional polynomials relies on an average fit across the network. This could mean that the selected curve would fit one treatment well, and another treatment less well. In the case of OS, the best fitting curve (according to fit statistics) visually fit lenvatinib + everolimus better than nivolumab. The result is that OS predictions may be underestimated for nivolumab, thus impacting the incremental QALYs.
- **Distributions for PSA:** In the probabilistic sensitivity analysis, the submitter assumed a 20% distribution around efficacy inputs. This 20% is an arbitrary assumption of uncertainty and does not reflect uncertainty of the results due to parameter uncertainty. The use of 95% credible intervals, standard errors, minimum or maximum values would have been a better choice. The submitter did not acknowledge this limitation.
  Given the lack of statistical significance in the efficacy data as observed by overlapping credible intervals, the lack of an appropriate exploration around the uncertainty of the efficacy is a major limitation.
  In their feedback on the Initial Recommendation, the submitter acknowledged that the 20% distribution around the OS and PFS curves in the economic model was set arbitrarily. As a consequence, the submitter provided a revised analysis to pCODR to more appropriately account for the uncertainty of efficacy inputs by incorporating the uncertainty estimated in the fractional polynomial indirect treatment comparison through 95% credible intervals fitted within the Bayesian network meta-analysis (NMA). The 95% credible intervals are calculated based on the inputs in the NMA and are not arbitrarily chosen. Furthermore, the submitter suggested that revised results based on the incorporation of these 95% credible intervals would enable the estimation of the currently undefined upper bound ICER. The EGP agrees with the submitter that the revised

analysis more appropriately captures the uncertainty around the efficacy inputs as evidenced by the Figures 9a and 9b below. However, the 95% credible intervals further highlight the uncertainty with the data from the NMA, demonstrating that the intervals extend beyond the "+/- 20%" originally submitted. Despite the provision of a revised model with improved handling of uncertainty around effectiveness, the EGP reiterated that there is still a high level of underlying uncertainty in the data, due to the lack of statistical significance in the efficacy data as observed by overlapping credible intervals. Therefore, the EGP agreed that no change is required in the original EGP's best case reanalyses.

1.4 Detailed Highlights of the EGP Reanalysis

Despite the limitations above, the EGP modified two assumptions which were considered essential: time horizon and duration of treatment effect. This hypothetical lower bound with these two assumptions incorporated does not negate the uncertainty around effectiveness nor does it explore the uncertainty around the effectiveness.

Hypothetical lower bound

- Time horizon of 10 years: The time horizon in the submitted base case was 20 years. OS was extrapolated beyond the time horizon of the clinical trial. In the economic model, few patients were predicted to be alive at 10 years. In consultation with the CGP and in order to maintain consistency with other pCODR reviews, the time horizon was shortened from 20 years to 10 years.
- Duration of treatment effect limited to 60 months: In the submitted base case, the submitter assumed that the duration of treatment effect would continue indefinitely over the entire time horizon (240 months). In reality, it is unlikely that any benefit from treatment would extend indefinitely once a patient progresses on that treatment. Given the reliance on indirect treatment comparison data, the EGP elected to set all treatment effects to the equivalent of everolimus at 60 months (unless the treatment effect was originally lower than that of everolimus, in which case, the treatment effect remains unchanged). This acknowledges the within trial treatment effect of each intervention, but does not assume an indefinite duration of treatment effect.

Table 5. Hypothetical lower bound EGP Reanalysis Estimates: 10-year time horizon & duration of treatment effect truncated at 60 months

Description	Costs	QALYs	Incremental cost per QALY gained (ICER)	
			versus everolimus	Sequential ICER*
EGP Reanalyses - probabilistic				
Cost-utility analysis				
Everolimus	$78,216	1.23		
Axitinib	$79,340	1.23	$441,641	$441,641
Len+Everolimus	$147,926	1.61	$185,802	$184,055
Nivolumab	$200,335	1.41	$670,975	Dominated**

*Sequential ICERs are calculated versus the last non-dominated treatment.
**Nivolumab costs more and is less effective than lenvatinib plus everolimus.

Upper bound not estimable

- Unable to explore uncertainty around efficacy: As identified previously, the indirect treatment comparison provided by the submitter did not demonstrate a statistically significant difference in PFS or OS. The economic model does not reflect this

uncertainty well. The EGP elected to not place an upper bound on any of the comparisons included in the sequential analysis in order to reflect this uncertainty. It is therefore difficult to conclude with any certainty if there is a benefit in survival of lenvatinib plus everolimus and the magnitude of this benefit. In the absence of being able to quantify this uncertainty, the EGP placed no upper bound on its estimate. By not placing an upper bound, the EGP acknowledges that it is unclear how high the ICER can go.

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include:

- treatment duration for nivolumab. Decreasing the treatment duration of nivolumab to 5.5 months (submitted base case: 7 months) increases the total three-year budget impact of lenvatinib in combination with everolimus by about 4.5% (rendering the treatment-funded scenario more expensive and eliminating any savings). Increasing the treatment duration of nivolumab to 16 months (submitted base case: 7 months) decreases the total three-year budget impact of lenvatinib in combination with everolimus by about 29% (rendering the treatment-funded scenario cheaper and increasing savings).
- drug plan eligible patients. Increasing the proportion of patients eligible to receive lenvatinib in combination with everolimus through publicly funded drug plans from 49% to 95%, decreases the total three-year budget impact of lenvatinib in combination with everolimus by about 0.5% (rendering the treatment-funded scenario cheaper and increasing savings).

A key limitation of the BIA model is the inclusion of those under 18 in the population estimates. The funding request is limited to adults.

1.6 Conclusions

In absence of head-to-head direct evidence, it is difficult to draw firm conclusions around the treatment effect of lenvatinib versus axitinib and nivolumab. The provided indirect treatment results did not conclude that PFS or OS were significantly different, as evidenced by overlapping 95% credible intervals. The impact on the uncertainty of the efficacy as provided through the indirect treatment comparison is unknown due to the inappropriate methodology of incorporating parameter uncertainty in the economic model. The extent of this uncertainty around the assumptions of efficacy for both PFS and OS, are therefore difficult to quantify, and potentially have a large impact on the ICER. The EGP acknowledges that the results of the HOPE 205[1] trial of lenvatinib plus everolimus versus everolimus demonstrated statistically significant PFS benefit (OS was not found to be statistically significant).

Table 6. Hypothetical lower bound **EGP Reanalysis Estimates: 10-year time horizon & duration of treatment effect truncated at 60 months - probabilistic**

Description	Costs	QALYs	Incremental cost per QALY gained (ICER)	
			versus everolimus	Sequential ICER*
EGP Reanalyses - probabilistic				
Cost-utility analysis				
Everolimus	$78,216	1.23		
Axitinib	$79,340	1.23	$441,641	$441,641
Len+Everolimus	$147,926	1.61	$185,802	$184,055
Nivolumab	$200,335	1.41	$670,975	Dominated**

*Sequential ICERs are calculated versus the last non-dominated treatment.
**Nivolumab costs more and is less effective than lenvatinib plus everolimus.

Upper bound: not estimable

Overall conclusions of the submitted model:

- *It is difficult to ascertain how much of the effectiveness difference is real in the absence of head-to-head clinical trials, given differences in the design of clinical trials included in the indirect treatment comparison.*
- *The parameter uncertainty around effectiveness was not incorporated appropriately in the model.*
- *Nivolumab, though more costly, does provide a better quality of life which was not reflected in this economic model as treatment-specific utilities were not incorporated.*
- *If you believe that lenvatinib plus everolimus has similar efficacy to nivolumab, the ICER is difficult to estimate given a small magnitude of incremental effectiveness.*

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Endocrine Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of lenvatinib and everolimus for advanced or metastatic renal cell carcinoma. A full assessment of the clinical evidence of lenvatinib and everolimus for advanced or metastatic renal cell carcinoma is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR 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 Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

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

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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