

CADTH

pCODR PAN-CANADIAN
ONCOLOGY DRUG REVIEW

**pan-Canadian Oncology Drug Review
Stakeholder Feedback on a pCODR Expert Review
Committee Initial Recommendation
(Manufacturer)**

Lenvatinib (Lenvima) for Renal Cell Carcinoma

January 4, 2019

Feedback on pERC Initial Recommendation

Name of the Drug:	Lenvatinib (LENVIMA®) in combination with everolimus
Indication: 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.	
Eligible Stakeholder Role in Review:	Manufacturer
Organization Providing Feedback	Eisai Limited

3.1 Comments on the Initial Recommendation

- a) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

_____ Agrees _____ agrees in part X disagree

After careful review of the pERC recommendation and summary of deliberations, Eisai strongly disagrees with the pERC initial recommendation that Lenvatinib in combination with everolimus (LEN+EVE) not be reimbursed. Our disagreement is centered around three overarching points: (1) pERC has neglected the advice of pCODR's Clinical Guidance Report (CGR), (2) pERC's perception of the increased risk of a false positive result with the HOPE-205 trial is incorrect and is strongly refuted by the statistical analyses contained within this response and (3) pERC has disregarded the review conducted by Health Canada (HC) and other global regulatory agencies, where a determination of the robust efficacy and safety of LEN+EVE was repeatedly confirmed.

- (1) Eisai believes that pERC did not fully appreciate the robustness of the HOPE-205 study and supporting analyses, making a recommendation that is counter to its expert clinical guidance panel (CGP). The CGP concluded in the CGR, **“that there is a net overall clinical benefit to LEN+EVE compared with everolimus monotherapy for the second-line...that demonstrated a clinically meaningful and statistically significant benefit in response rate, PFS and OS for LEN+EVE compared with everolimus. Based on previous experience with TKIs, the acceptable toxicity of LEN+EVE and the high unmet need for these patients, ECOG performance status of 2 or the presence of brain metastases should not exclude patients from LEN+EVE treatment.”**¹ The CGR also noted that LEN+EVE 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.”**¹
- (2) A key issue identified by pERC was the increased risk of a false-positive result in the HOPE-205 trial with the pre-specified alpha of 0.15 and power of 70%. The increased risk of a false-positive in this dataset has been mischaracterized by pERC. The false positive risk (FPR) of a trial can be estimated based on the obtained p-value from a RCT, and a presumed prior probability of a true effect.² Assuming a prior probability of effect of 50% (which is considered an appropriate cut-off for prior probability), **the estimated FPR for the PFS outcome in the HOPE-205 trial based on the obtained p-value of 0.0005 is only 1.1%.**³ Therefore, the 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 LEN+EVE in the HOPE-205 trial.
- (3) The question of the net clinical benefit of LEN+EVE has already been validated locally and globally by several regulatory and HTA agencies including HC⁴, FDA⁵, and the EMA⁶, which has led to reimbursement through NICE (England)⁷, G-BA (Germany)⁸, NVMO (Netherlands)⁹, Austria¹⁰, and Israel¹¹. As part of the submission to HC, HOPE-205 was evaluated to assess the appropriateness and robustness of the statistical analyses and efficacy results using the same stringent standards applied for phase III pivotal trials. The evaluation focused on the potential bias of the investigator assessment of PFS and the lack of adjustment for multiplicity in the primary analyses. 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 statistically significant (P=0.0005).**¹² An independent biostatistical consult (at the request of the HC reviewer) arrived at the same conclusion, noting the overall study design and statistical analysis plan were appropriate. Based on the review, HC concluded that, “Results showed that the combination (Lenvatinib 18 mg with everolimus 5 mg) significantly prolonged investigator-assessed PFS compared to everolimus monotherapy (10 mg). The results from [the key secondary endpoints of OS and ORR] were consistent with the PFS benefit. **Although**

the efficacy results stemmed from a Phase 2 trial conducted in a small number of patients, the PFS and ORR gains are robust for the second-line setting and are clinically meaningful...Lenvatinib in combination with everolimus has demonstrated clinically significant benefits in patients with advanced RCC who have received one prior VEGFR-targeted therapy. The overall benefits of Lenvatinib in combination with everolimus are considered to outweigh the risks.¹³ As outlined in the clinical overview module, the robust improvement in PFS was supported by sensitivity and exploratory analyses.¹² As a result, HC granted a NOC for the combination therapy, **without any requirements for post-approval commitment studies. This combination was the first treatment to receive a full NOC from HC based on phase 2 data in over 7 years.**^{14,15}

3.2 Comments Related to Eligible Stakeholder Provided Information

Support conversion to Final Recommendation. Recommendation does not require reconsideration by pERC.

Do not support conversion to Final Recommendation. Recommendation should be reconsidered by pERC.

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer Provided information
2	Summary of pERC Deliberations	Par 1, Line 2	Given the availability of other treatments following progression on a VEGF-targeted therapy, pERC was uncertain whether lenvatinib in combination with everolimus addresses an unmet need
<p><u>The CGR report states that limited treatment options exist for patients who have failed 1st line therapies and even though axitinib and nivolumab are available there is still “an urgent need for better and additional treatment options in RCC.”</u>¹ Input from the two clinician groups, Kidney Cancer Canada, and the CGR consistently state that LEN+EVE addresses a clear unmet need.¹ Clinicians felt 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, notably the FGFR pathway for RCC. Increased levels of FGF in the plasma have correlated with high tumour grade and stage, metastatic spreading, and poor prognosis in kidney cancer patients.¹⁶⁻¹⁸ LEN+EVE was noted to have unique advantages over current therapies due to its synergistic effects and unique targeting of both the receptor tyrosine kinase, VEGFR and FGFR, as well as the mTOR pathways resulting in more durable responses.¹</p>			
3	Summary of pERC Deliberations	Par 2, Line 18	pERC was unsure whether about whether the results observed in this phase II trial will translate into positive phase III trials or real world clinical practice
<p>HOPE-205 was granted breakthrough designation status and a priority review by the FDA and accelerated review by the EMA.^{5,6} <u>The FDA, EMA and other regulators were confident that HOPE-205 demonstrated clinically significant anti-tumour activity and did not require Eisai to conduct a follow up confirmatory phase III trial.</u>¹⁹ The suggestion by pERC that a phase III trial should be conducted strictly for the purposes of HTA or reimbursement when it's not required by regulators is an unrealistic expectation that unnecessarily impedes patient access to a therapy deemed to have a favourable benefit-risk profile by regulators around the world. pERC also questioned whether the trial results were generalizable to real world clinical practice. HOPE-205 was a study that scored patient risk-groups by both the MSKCC and IMDC models. When accounting for either risk-scoring models, patients were predominantly intermediate- or poor-risk ($\geq 75\%$), while the minority were favourable-risk ($\leq 25\%$) after progressing on a first-line VEGFR TKI.²⁰ This is highly representative of the typical Canadian metastatic RCC patient who is seen for second-line treatment in clinic.²¹ Additionally, baseline characteristics in HOPE-205 are reflective of the Canadian patient presenting for second-line treatment and beyond with respect to the majority receiving prior nephrectomy, and common sites of metastasis with lung being the most common, followed by lymph nodes for locally advanced disease, and then bone and liver.²² Lastly, the majority of patients in HOPE-205 had received sunitinib as their first-line VEGFR TKI, with pazopanib being the second most commonly received upfront agent, which reflects Canadian practice as they are the two reimbursed agents in this setting.^{22,23}</p>			
4	Summary of pERC	Par 1, Line 6	...given the limitations in the underlying data, overlapping credible intervals [...], limitations arising from the lack of

	Deliberations		closed loops in the network, the limited number of studies for each treatment comparison [...], and lack of indirect comparisons for safety data and other efficacy outcomes [...], the comparative effectiveness of LEN+EVE versus nivolumab remained uncertain.
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Both NICE and the CGP conducted a critical appraisal of the indirect treatment comparison (ITC) and have stated that the ITC was appropriate for decision making.^{1,7} The ITC was performed based on the best available evidence and well-accepted methods, including appropriate handling (through fractional polynomials [FP]) of survival data that did not support the proportional hazards assumption.²⁴ The EGP also agreed that the FP methodology was appropriate.²⁵ As per the CGP report, the expert reviewers had conducted a critical appraisal of the ITC using the recommendations made by the ISPOR Task Force on ITCs.¹ Based on the ISPOR checklist, the submitted ITC fulfilled nearly every criteria. Overlapping confidence intervals are cited as a limitation, however this is a common finding in ITCs. Patient characteristics across trials were generally similar, suggesting a low risk of bias due to between-trial heterogeneity in the ITC results. In fact, HOPE-205 enrolled patients with more severe disease on average, as measured by performance status and MSKCC risk, therefore any bias may have been against LEN+EVE.¹ Finally, after its assessment, the CGP stated “overall, the company's network analysis criteria and assumptions were appropriate for the comparison in question. Within this network analysis, LEN+EVE compared favorably to the other second line therapies.”¹

4	Summary of pERC deliberations	Par 1, Line 11	In addition, pERC noted that axitinib was not included in the submitted ITC due to concerns with transitivity (different eligibility criteria).
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The assumption that axitinib and everolimus perform similarly is supported by NICE recommendations made for nivolumab²⁶, cabozantinib²⁷, and LEN+EVE⁷, and by the pCODR CGP¹. In the NICE assessment of the ITC submitted for nivolumab, NICE concluded “that axitinib and everolimus were likely to have similar effectiveness and that it was appropriate to use a hazard ratio of 1 for overall survival and progression-free survival in the model.”²⁶ Additionally, the CGP re-iterated this point, stating “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.”²⁸⁻³⁰ Hence, while axitinib wasn’t included directly in the ITC, pERC should note the assumption made is consistent with recommendations made in the past, and that the assumption of axitinib performing similarly to everolimus provides an avenue to indirectly compare LEN+EVE to axitinib.

9	Economic Evaluation	Par 3, Line 6	...the inability of the economic model to account for the resulting uncertainty in the parameter estimates [...] the clinical effectiveness estimates could not be used to inform credible [ICER] estimates.
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Given that this was identified as a “major limitation” in the EGR, Eisai is disappointed that a request to address this limitation was not made by the EGP during the review process (via the Checkpoint Meeting or through an additional information request) in order to assist in the calculation of a hypothetical upper bound ICER. **To address this concern, Eisai has updated the model so that the uncertainty around the OS and PFS survival curves for LEN+EVE, everolimus, axitinib, and nivolumab can be captured (using the ITC without sorafenib). This is consistent with the recommendation made by the EGP:** “The use of 95% credible intervals, standard errors, minimum or maximum values would have been a better choice. [...] the lack of an appropriate exploration around the uncertainty of the efficacy is a major limitation.”²⁵ There is no formal guidance on the approach to be taken to incorporate FP analyses probabilistically into health economic modeling. After exploring multiple options, it was determined that the uncertainty would be best captured within the formulae for calculating the best-fit FP curves. For OS, the two parameters for the best-fit first order FP are sampled from a multivariate normal distribution based on the mean and standard deviation from the ITC and taking into account their correlations using Cholesky decomposition. A similar approach is taken for PFS using the three parameters for the best-fit second order FP. When also incorporating the changes noted by the EGP for the hypothetical lower bound ICER (time horizon of 10 years, duration of treatment effect truncated at 60 months), the **sequential analysis results remain**

Comparator	Costs	QALYs	ICER	
			vs EVE	Sequential
EVE	77,891	1.19		
AXI	77,906	1.18	Dominated	Dominated
LEN+EVE	146,565	1.52	202,706	202,706
NIV	200,629	1.38	617,980	Dominated

consistent with the Eisai submitted base case (see table on right), where LEN+EVE is more effective than

AXI or EVE at increased cost, and dominates NIV.

These estimates may form the basis of the currently undefined upper bound ICER. As such, Eisai requests that this information be considered in a revision of the EGR prior to the pERC reconsideration meeting (as per Section B7.5.3 of the pCODR Procedures); a copy of the updated model, as well as an accompanying report detailing the updates is provided separately.

Based on the evidence presented, Eisai respectfully requests pERC reconsiders their initial recommendation and in turn, make a positive funding recommendation for Lenvatinib in combination with everolimus for the treatment of patients with advanced or metastatic, clear-cell RCC following one prior VEGF-targeted therapy.

References

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