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pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Lenvatinib (Lenvima) for Hepatocellular Carcinoma

July 24, 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

On December 19, 2018, Lenvatinib received NOC for the following new indication: for the first-line treatment of adult patients with advance, unresectable Hepatocellular Carcinoma (HCC) with no prior systemic therapy for disease.

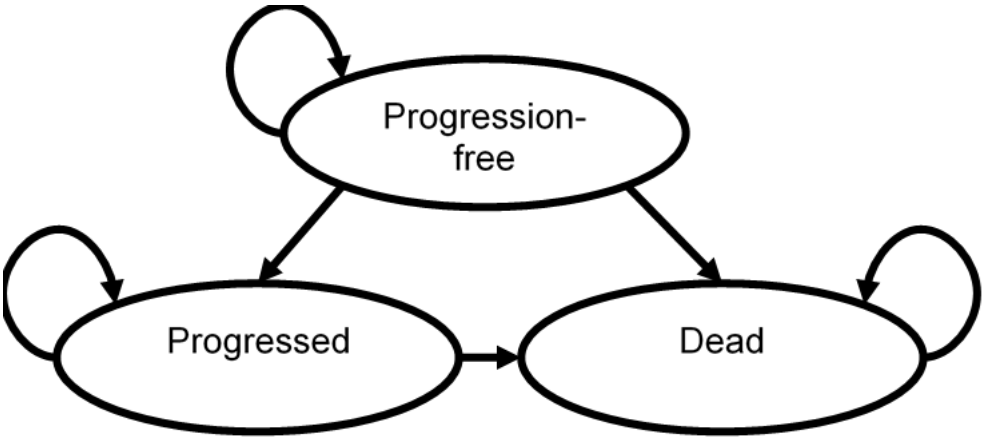
1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Eisai Limited** compared Lenvatinib versus Sorafenib for the first-line treatment of adult patients with unresectable HCC.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	**Eisai Limited** is requesting Lenvatinib for the first-line treatment of adult patients with advanced, unresectable HCC with no prior systemic therapy for disease. This aligns with the patient population that the economic model is built on.
Type of Analysis	*CEA, CUA*
Type of Model	*Partitioned-survival model*
Comparator	Sorafenib
Year of costs	*Not explicitly stated; presumably 2018*
Time Horizon	*10 years*
Perspective	*Health payer and societal*
Cost of lenvatinib	Lenvatinib costs $8.1429 per mg. At the recommended dose of 8mg per day (<60Kg bodyweight) or 12mg per day (>60kg bodyweight), lenvatinib costs: 12 mg daily-dose • $97.7145 per day $2,736.01 per 28-day course 8 mg daily-dose (2x4 mg) • $65.1430 per day $1,824.01 per 28-day course
Cost of Sorafenib * *Price Source:* Ontario Ministry of Health and Long-Term Care (MoHLTC) Exceptional Access Program (EAP) Formulary	Sorafenib listed costs $46.4689 per 200mg tablet. At the recommended dose of 400mg twice daily, sorafenib costs: • $185.84 per day • $5,203.52 per 28-day course
Model Structure	*The analysis uses a partitioned survival model (PSM) with Progression-free, Progressed, and Death health states, over a time horizon of 10 years.* *Data informing overall survival (OS), progression-free survival (PFS), time to discontinuation (TTD), adverse events (AEs) (Grade 3+), and health state utilities were derived from the REFLECT trial.* *Figure 1*
Key Data Sources	*REFLECT trial data*

Figure 1. Model structure



1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. Relevant issues identified included:

Sorafenib is an appropriate standard of care arm for first line advanced HCC since it is the only therapy approved in this setting.

The REFLECT trial clearly demonstrated the non-inferiority of lenvatinib to sorafenib for OS, the primary endpoint of the study, median OS 13.6 vs. 12.3 months for lenvatinib vs. sorafenib, HR 0·92, 95% CI 0·79–1·06). However, superiority could not be shown. At the end of study treatment, patients randomized to sorafenib were eligible for potential second-line trials specifically requiring enrollment of sorafenib failures and/or sorafenib-intolerant patients, while lenvatinib patients would probably be ineligible for such trials. A higher proportion of subjects received post-study treatment with investigational anticancer drugs in the sorafenib arm (9.5%) vs lenvatinib (3.1%). These factors might favour the sorafenib arm, but no definitive conclusions can be made. Subgroup analyses for OS revealed that the effect of lenvatinib and sorafenib on OS was generally consistent across subgroups.

- The economic evaluation provided a scenario analysis to adjust for this imbalance in post-progression treatments, considering that all patients who received post-progression therapy in the REFLECT trial will receive Regorafenib. The CGP and EGP considered this appropriate. The EGP considered it in his reanalyses.

The open-label nature of the trial does not affect the primary endpoint of OS, which is the most relevant and unbiased measure of efficacy. There were baseline imbalances between the Lenvatinib and Sorafenib treatment arms regarding the proportion of patients with post-progression treatments, proportion of patients with alpha-fetoprotein (AFP) levels ≥200 ng/mL, and in the etiology of HCC [hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol]. The CGP agreed that these imbalances are unlikely to affect the activity of lenvatinib.

- The economic evaluation provided base-case and scenario analyses adjusting for these imbalances via multivariable parametric models. These caused little variation of the results of this economic evaluation.

Treatment-emergent adverse events of grade 3 or higher occurred at similar rates in the lenvatinib and sorafenib arms (episodes per patient-year 3.2 vs 3.3). The most common

treatment-emergent adverse events among patients who received lenvatinib were hypertension, diarrhoea, decreased appetite, and decreased weight. In the sorafenib arm, the most common treatment-emergent adverse events were palmar-plantar erythrodysaesthesia (hand-foot syndrome), diarrhoea, hypertension, and decreased appetite. Fatal adverse events due to treatment occurred in 11 (2%) lenvatinib treated patients and four (1%) in the sorafenib group. The toxicity of lenvatinib was overall manageable, by dose interruptions and dose reductions. The CGP agreed that hypertension can be managed with antihypertensive medications and usually does not cause symptoms. In contrast, hand-foot syndrome can affect daily activities.

- The economic evaluation included the base-case analysis assuming that utility values in the lenvatinib and sorafenib arms are equal in both groups, to the mean values in the full REFLECT population. The EGP considered this assumption a conservative approach, and no additional re-analysis was performed.

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to lenvatinib in the treatment of advanced HCC compared with sorafenib. Lenvatinib improved clinically relevant secondary endpoints such as progression free survival and response rate compared to sorafenib, with no significant difference in quality of life summary scores. There is an expanding number of second line options for HCC, which could have potentially affected overall survival in this trial. There is no scientific rationale to suggest that the efficacy of second line HCC treatments would be influenced by the first line therapy.

Summary of registered clinician input relevant to the economic analysis

One joint input from six registered clinicians at the BC Cancer Agency was provided for the pCODR review of lenvatinib for the first line treatment of adult patients with unresectable hepatocellular carcinoma (HCC). A summary of the input is provided below.

According to the clinician input, sorafenib is currently the standard first line therapy for HCC. The clinicians believe that lenvatinib would be an appropriate and preferable first-line therapy owing to its milder side effect profile. Sorafenib toxicity manifests more frequently as hand-foot syndrome, a relatively impactful disorder, whereas lenvatinib more readily elevates the risk of hypertension, which is easier to manage. Clinicians deemed that regorafenib, cabozantinib, and possibly sorafenib, would be suitable next-line therapies after lenvatinib. They believed that both lenvatinib and sorafenib should be available as first-line options for HCC to allow drug switching due to tolerance issues.

- The economic evaluation took into account the quality of life as estimated in REFLECT trial. Same utility values were considered for sorafenib and lenvatinib. Also, a scenario analysis was provided to account for unbalance between groups regarding the post-progression treatments. This assumed that all patients who received post-progression therapy in the REFLECT trial will receive Regorafenib.

Summary of patient input relevant to the economic analysis

The following patient advocacy groups provided input on Lenvatinib for hepatocellular carcinoma (HCC), and their input is summarized below: Canadian Cancer Survivor Network (CCSN) and Canadian Liver Foundation (CLF).

From a patient perspective, patients rated their most important symptoms or problems to control for HCC as fatigue (60%), pain (60%), weight loss and/or lack of appetite (40%), not

sleeping/restless (20%) and living with uncertainty (20%). Other factors influencing quality of life included appetite loss, weight loss, diarrhea, skin disorder and alopecia.

Patient respondents noted that lenvatinib generally maintained or improved their quality of life. The most common side effects with lenvatinib are diarrhea, nausea, hypertension.

Patients value an additional treatment option in the first-line setting for improving and managing their HCC symptoms and increasing survival.

- The economic evaluation took into account the quality of life as estimated in REFLECT trial.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis

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

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

Clinical factors:

- Priority of lenvatinib relative to sorafenib and sequencing with regorafenib

Response:

- The CGP considered lenvatinib and sorafenib similar in term of efficacy and adverse event profiles;
- The CGP considered that there is an expanding number of second line options for HCC, which could have potentially affected overall survival in this trial. Second line trials have inclusion criteria that mandate prior treatment with sorafenib. The efficacy of second line HCC treatments such as cabozantinib and regorafenib after lenvatinib are unknown, and further data may be available through observational trials. There is no scientific rationale to suggest that the efficacy of second line HCC treatments would be influenced by the first line therapy.

Economic factors:

- Weight-based dosing may lead to dosing errors

Although packaging according to dose may improve patient adherence, PAG identified that potential dose adjustments for lenvatinib may result in drug wastage as well as patient confusion, if dose adjustments are made prior to finishing the capsules dispensed. The economic model allows for modifications to dose intensity to account for wastage.

PAG noted that lenvatinib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home, and no chemotherapy chair time would be required. PAG identified the oral route of administration is an enabler to implementation.

Regorafenib for treatment of HCC after sorafenib recently received a conditional reimbursement recommendation conditional on the cost-effectiveness being improved to an acceptable level. At this time, no provinces are currently funding regorafenib. PAG is seeking guidance on second-line treatments following lenvatinib, particularly given regorafenib is indicated after sorafenib and

that the REFLECT trial is a non-inferiority trial between lenvatinib and sorafenib. The economic model includes the use of regorafenib as a subsequent line of treatment.

1.3 Submitted and EGP Reanalysis Estimates

The main economic evaluation was conducted using results of the REFLECT trial, an international, multicentre, randomized, open-label, head-to-head, Phase III study comparing Lenvatinib to Sorafenib for the first-line treatment of unresectable HCC.

Overall, the submitted model is appropriate, and considered several sensitivity analyses. One-way sensitivity analyses and PSA were described and conducted by the Submitter to evaluate important elements and assumptions used in the model. In general, the assumptions made in the model and related input variables caused little variation of the results of this economic evaluation. Specifically, all the scenarios results align with the base-case results, namely, that lenvatinib dominates sorafenib. The EGP considered the model structure appropriate and agreed with most of the choices made in the base-case. The EGP re-analyses re-confirm the submitter results.

Table 2. Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis
ΔE (LY)	0.22	0.30
Progression-free	NA	NA
Post-progression	NA	NA
ΔE (QALY)	0.17	0.22
Progression-free	0.26	NA
Post-progression	-0.09	NA
ΔC ($)	-$5,064	-$9.946
ICER estimate ($/QALY)	Dominant	Dominant

*** The submitted model did not allow conducting probabilistic re-analyses for the EGP selected parameters. Only pre-defined values were used by the probabilistic analysis. The submitted probabilistic results were very similar to the deterministic results.**

The main assumptions and limitations with the submitted economic evaluation were:
Imbalance in baseline covariates:

- Due to the open-label nature of the REFLECT trial, there were baseline imbalances between the Lenvatinib and Sorafenib treatment arms regarding the proportion of patients with AFP levels ≥200 ng/mL, and in the etiology of HCC (hepatitis B virus [HBV], hepatitis C virus [HCV], alcohol). Covariate analyses were performed to evaluate baseline factors that may have impacted OS in the overall study population, including AFP and HCC etiology. The submitted model included an adjustment for baselines covariates, considered in the base-case analysis.

Post progression treatments:

- In addition, there were imbalances in post-progression treatments received during the trial period. In the REFLECT trial, treatment after disease progression was allowed in both the lenvatinib and sorafenib arms. In the lenvatinib arm, patients could switch to sorafenib but were not eligible for trials using second-line treatment. In the sorafenib arm, patients could continue sorafenib and were eligible for trials using second-line treatments such as cabozantinib or regorafenib. As such, 51% of patients in the sorafenib group had post-progression treatment compared with only 43% in the lenvatinib group. It was noted that longer overall survival may be expected for people having post-progression treatment, so the overall survival results may favor patients in the sorafenib group. The EGP noted that more

patients having post-progression treatment in the sorafenib arm may affect the OS benefits observed between lenvatinib and sorafenib. In the base-case analysis the model included use of sorafenib and regorafenib, in post recurrence state, as observed in the REFLECT trial.

- The submitted model included an adjustment for post-progression treatments considered in a scenario analysis. In addition, an alternative scenario assumed that all patients who received post-progression therapy in the REFLECT trial (33% in the lenvatinib group and 39% in the sorafenib group) will receive regorafenib. This assumption was made in order to adjust for the extended OS that might be present in patients receiving post-progression treatments, and to balance their impact in both groups, lenvatinib and sorafenib. The EGP considered this appropriate and considered it in the EGP base-case estimates. This has an impact on both differences in costs and outcomes, that favoured Lenvatinib. This assumption aligns with the CGP comments on an unknown efficacy of second line HCC treatments such as cabozantinib and regorafenib after lenvatinib, and that further data may be available through observational trials. The CGP noted that there is no scientific rationale to suggest that the efficacy of second line HCC treatments would be influenced by the first line therapy.

Utilities:

- EQ-5D-3L data were collected in the REFLECT clinical trial. Patients completed the questionnaire at the Baseline visit, on Day 1 of each subsequent treatment cycle, and at the Off-Treatment visit. These were analysed to generate mean utility values at baseline, in the progression-free health state and in the progressed health state Additional analyses were conducted based on the Lenvatinib and Sorafenib arms of REFLECT separately to determine the adjusted mean utility value at baseline and in the progression-free and progressed health states, controlling for prior treatment, age, sex, geographical region, baseline EQ-5D and baseline ECOG-PS; adjustment was performed using a linear mixed model. These were similar between the Lenvatinib and Sorafenib arms, with a small numerical difference in favour of Lenvatinib. The Submitter base-case analysis assumed that utility values in the Lenvatinib and Sorafenib arms are equal to the mean values in the full REFLECT population.

- *The submitted model did not allow alterations related to the utilities specific to each treatment group.* The CGP suggested that lenvatinib might have a better toxicity profile than sorafenib. As such, the EGP considered this assumption (equal utility values in both groups) a conservative approach, and no additional re-analysis was performed.

Time Horizon

- In order to perform extrapolation over the 10-year time horizon, a three-stage process was followed by the Submitter: i) Assessment of the proportional hazards (PH) assumption; ii) Identification of prognostic factors upon which to base adjustment; iii) Estimation of parametric survival models to allow prediction of event rates.
    - First, the validity of the PH assumption between treatments was assessed using visual inspection of the log-cumulative hazard plots, and PH global test (Schoenfeld residual test). The PH assumption was demonstrated for OS, but not for PFS. As such, the submitted model was based on independent parametric models for each arm. These were adjusted for baseline covariates imbalanced between the Lenvatinib and Sorafenib arms.
    - Six parametric models were investigated: Weibull, exponential, log-logistic, log-normal, gamma and Gompertz, to find the best fit of the patient-level data from REFLECT trial.
    - The most appropriate distribution was selected based on (a) assessment of the statistical goodness of fit (measured using the Akaike Information Criteria [AIC] and Bayesian Information Criteria [BIC]) and (b) consistency with previous findings of extrapolation methods in advanced HCC.

- The EGP considered this appropriate, and no additional re-analysis was performed. (i.e., the survival models used by the Submitter were used in all EGP analysis.)

Dose intensity:

- Dose intensity was calculated to be 87.5% and 83.0% of the planned starting dose for Lenvatinib (7.0 mg for the 8.0 mg planned dose and 10.5 mg for the 12.0 mg planned dose) and Sorafenib (663.8 mg relative to an 800.0 mg planned dose), respectively. These were observed in the REFLECT trial. PAG identified that potential dose adjustments for lenvatinib may result in drug wastage as well as patient confusion, if dose adjustments are made prior to finishing the capsules dispensed.
- The EGP conducted a re-analysis in order to evaluate the impact of a dose intensity of 100% for both lenvatinib and sorafenib. This assumption accounts for a drug wastage, which is likely to occur, if the dose adjustments were made prior to finishing the capsules dispensed.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the submitted economic model:

- Dose intensity set to 100% for both lenvatinib and sorafenib;
- Costs in post-progression state assumed that all patients who received post-progression therapy in the REFLECT trial will receive Regorafenib.

Table 3: Detailed Description of EGP Reanalysis*

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Baseline (Submitter's base case)	-$5,064	0.17	0.22	dominant	--
EGP's re-analysis estimates					
Parameter 1: dose intensity of 100%	-$7,342	0.17	0.22	dominant	
Parameter 2: adjusted for post-progression treatment costs	-$7,001	0.22	0.30	dominant	
EGP Best case estimate of above 1 and 2 parameters	-$9,946	0.22	0.30	dominant	

* The submitted model did not allow conducting probabilistic re-analyses for the EGP selected parameters. Only pre-defined values were used by the probabilistic analysis. The submitted probabilistic results were very similar to the deterministic results.

Given that the cost of sorafenib is likely lower than what is used in the economic model (based on lower drug prices that have been negotiated by jurisdictions), the EGP considered several analyses reducing the cost of sorafenib by 25%, 50% and 75%. At a 75% cost reduction, lenvatinib would had an ICER of $79,414/QALY (Table 4).

Table 4: EGP reanalyses for sorafenib price reduction of 25%, 50% and 75%:

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Baseline (Submitter's base case)	-$5,064	0.17	0.22	dominant	--
Sorafenib Price reduction of 25%	$1,193	0.17	0.22	$6,913	--
Sorafenib Price reduction of 50%	$7,450	0.17	0.22	$43,163	--
Sorafenib Price reduction of 75%	$13,707	0.17	0.22	$79,414	--

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include: number of patients eligible to be treated with lenvatinib, the extent of market expansion, the frequency of progression monitoring in clinical practice, and the dose intensity.

Key limitations of the BIA model include the extent of market share and the dose intensity used to calculate the drugs costs. These parameters were able to be modified and explored by the EGP.

Finally, it is expected that the negotiated price of sorafenib to be lower that the listed price. The EGP conducted a re-analysis considering a price reduction of 25%, 50% and 75%.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for lenvatinib when compared to sorafenib is:

- dominant
- The extra cost of sorafenib is -$9,946. This corresponds to a 100% dose intensity for both treatments and adjustment for post-progression therapies. This dose intensity assumption accounts for drug wastage, which is likely to occur, if the dose adjustments were made prior to finishing the capsules dispensed.
- The extra clinical effect of lenvatinib is 0.22 QALYs. This corresponds to the scenario in which all patients who received post-progression therapy in the REFLECT trial will receive regorafenib.

Overall conclusions of the submitted model:

Overall, the submitted model is appropriate, and considered several sensitivity analyses. One-way sensitivity analyses and PSA were described and conducted by the Submitter to evaluate important elements and assumptions used in the model. In general, the assumptions made in the model and related input variables caused little variation of the results of this economic evaluation. Specifically, the results from all scenarios align with the base-case results, namely, that lenvatinib dominates sorafenib.

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 Genitourinary 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 (Lenvima) for HCC. A full assessment of the clinical evidence of lenvatinib (Lenvima) for hepatocellular 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).

Guidance Report. Note that no revisions were made 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 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.

References

1. Kobayashi M, Kudo M, Izumi N, Kaneko S, Azuma M, Copher R, et al. Cost-effectiveness analysis of lenvatinib treatment for patients with unresectable hepatocellular carcinoma (uHCC) compared with sorafenib in Japan. J Gastroenterol. 2019;54(6):558-70.