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# Lenvatinib Versus Sorafenib as First-Line Treatment of Unresectable Hepatocellular Carcinoma: A Cost–Utility Analysis

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*Disclosures of potential conflicts of interest may be found at the end of this article.*

**Key Words.** Lenvatinib • Unresectable hepatocellular carcinoma • Cost-effectiveness analysis

## Abstract

***Background.*** In a global, phase III, open-label, noninferiority trial (REFLECT), lenvatinib demonstrated noninferiority to sorafenib in overall survival and a statistically significant increase in progression-free survival in patients with unresectable hepatocellular carcinoma (HCC). Recently, lenvatinib became the first agent in more than 10 years to receive approval as first-line therapy for unresectable HCC, along with the previously approved sorafenib. The objective of this study was to determine the comparative cost-effectiveness of lenvatinib and sorafenib as a first-line therapy of unresectable HCC.

***Materials and Methods.*** A state-transition model of unresectable HCC was developed in the form of a cost–utility analysis. The model time horizon was 5 years; the efficacy of the model was informed by the REFLECT trial, and costs and utilities were obtained from published literature. Probabilistic sensitivity analyses and subgroup analyses were performed to test the robustness of the model.

***Results.*** Lenvatinib dominated sorafenib in the base case analysis. A probabilistic sensitivity analysis indicated that lenvatinib remains a cost-saving measure in 64.87% of the simulations. However, if the cost of sorafenib was reduced by 57%, lenvatinib would no longer be the dominant strategy.

***Conclusion.*** Lenvatinib offered a similar clinical effectiveness at a lower cost than sorafenib, suggesting that lenvatinib would be a cost-saving alternative in treating unresectable HCC. However, lenvatinib may fail to remain cost-saving if a significantly cheaper generic sorafenib becomes available. ***The Oncologist*** 2020;25:e512–e519

**Implications for Practice:** This analysis suggests an actionable clinical policy that will achieve cost saving. This cost–utility analysis showed that lenvatinib had a similar clinical effectiveness at a lower cost than sorafenib, indicating that lenvatinib may be a cost-saving measure in patients with unresectable HCC, in which $23,719 could be saved per patient. The introduction of a new therapeutic option for the first time in 10 years in Canada provides an important opportunity for clinicians, researchers, and health care decision-makers to explore potential modifications in recommendations and practice guidelines.

## Introduction

Hepatocellular carcinoma (HCC) is the most prevalent type of primary liver cancer, which is predicted to be the sixth most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths worldwide [1]. It is estimated that 70%–90% of patients with HCC have chronic liver disease and cirrhosis, which limits the feasibility of surgical procedures in advanced cases [2, 3]. Until recently, the only Food and Drug Administration (FDA)- and Health Canada–approved first-line systemic treatment available for unresectable HCC was sorafenib [2].

Lenvatinib, an oral multiple receptor tyrosine kinase inhibitor, has recently received FDA and Health Canada approval as a standalone first-line therapy for unresectable HCC based on a global, randomized, phase III, noninferiority trial named REFLECT [2–4]. Lenvatinib has previously received approval for differentiated thyroid cancer and advanced renal cell carcinoma in combination with everolimus [5]. Lenvatinib was found to be noninferior to, although not superior to, sorafenib for the primary outcome of overall survival (OS) [2]. Additionally, lenvatinib showed a statistically significant improvement in the secondary outcome of progression-free survival (PFS) time, with a median improvement in PFS of 5.2 months [2]. Lastly, the quality of life based on European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)

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C30 and EORTC QLQ-HCC18 questionnaires suggests that time to clinically meaningful deterioration of role functioning, pain, diarrhea, nutrition, and body image were observed earlier in patients treated with sorafenib than in those treated with lenvatinib [2].

The introduction of a new therapeutic option for the first time in 10 years in Canada provides an important opportunity for clinicians, researchers, and health care decision-makers to explore potential modifications in recommendations and practice guidelines. Currently, sorafenib is funded in most provinces in Canada for unresectable HCC through provincial special authorization programs [6–15]. Conversely, most provinces fund lenvatinib for recurrent or metastatic differentiated thyroid cancer, but no province provides funding for unresectable HCC [6–15]. In order to be able to make informed decisions on funding structures in Canada, it is important for decision-makers to assess the comparative cost-effectiveness of the two agents. In Japan, a cost-effectiveness study comparing lenvatinib and sorafenib has recently been published [16]. However, despite the availability of the Japanese results, this study provides additional and important analyses for Canadian decision-makers as our model is more representative of Canadian medical practices for HCC and offers more robust results represented by extensive sensitivity analyses.

## Materials and Methods

### Study Design

A state-transition model of unresectable HCC was developed to perform a cost–utility analysis of treatment with lenvatinib compared with sorafenib. The analyses were performed following the guidelines for economic evaluation by the Canadian Agency for Drugs and Technologies in Health (CADTH) [17]. The input data were primarily derived from the REFLECT trial and supplemented by other published literature [2]. Effectiveness was measured in quality-adjusted life years (QALYs), and cost was measured in Canadian dollars. Incremental cost-effectiveness ratio (ICER) of lenvatinib compared with sorafenib was the primary outcome of interest. The ICER values, which were calculated by dividing the difference in cost by the difference in effectiveness, were evaluated at discounted prices of sorafenib to account for the potential introduction of a generic sorafenib. The perspective of the analysis was that of a Canadian health care system with the costs adjusted for inflation to 2018 Canadian dollars. The model time horizon of 5 years was chosen to incorporate the results of the REFLECT trial and provide a time scale that is amenable for policy-makers. Additionally, the typical survival time for patients with unresectable HCC is approximately 1 year [18]. Therefore, the model time horizon of 5 years is sufficiently long enough to capture all the consequences of the disease. All health outcomes and costs were discounted at 1.5% annually, as per the CADTH guidelines [17]. The cycle length of the model was 1 month to reflect the length of the treatment cycles and to account for the rapid disease progression and poor prognosis of patients with unresectable HCC.

### Cohort

The study cohort in our model followed the reported characteristics of patients enrolled in the REFLECT trial, in which 954 patients with unresectable HCC from 154 sites in 20 countries throughout the Asia-Pacific, Europe, and North America were randomly assigned to receive either lenvatinib or sorafenib [2]. The patients had one or more measurable target lesions based on mRECIST, Barcelona Clinic Liver Cancer stage B or C categorization, Child-Pugh class A, and Eastern Cooperative Oncology Group performance status score of 0 or 1 [2]. Patients were excluded if they had 50% or higher liver occupation or had received previous systemic therapy for HCC [2].

### Strategies

Two treatment strategies were considered for the analysis: sorafenib and lenvatinib. In the sorafenib arm, all patients received a starting dose of sorafenib 400 mg orally twice daily in 28-day cycles [2]. In the REFLECT trial, modifications to the dosage regimen due to toxicities were implemented according to prescribing information specific to each region the patients were from [2]. However, in our model, all patients were assumed to have received a total daily dose of 800 mg. We did not allow patients to discontinue sorafenib or lenvatinib as a result of toxicity, as the percentage of patients who transitioned in the REFLECT trial was not available. Hence, it was not feasible to accurately implement the transition in our model without compromising the validity. As such, an assumption of all patients staying on the initial drug was made. At the recommended dose of 400 mg twice daily, the daily cost of sorafenib is $195.60, and $5,476.62 for a 28-day cycle [19].

In the lenvatinib arm, all patients of the REFLECT trial received a starting dose of lenvatinib 8 mg/day (for bodyweight <60 kg) or 12 mg/day (for bodyweight ≥60 kg) in 28-day cycles [2]. In the REFLECT trial, dose reductions to 8 mg/day, 4 mg/day, or 4 mg every other day were permitted following lenvatinib-related toxicity [2]. However, in our model, all patients were assumed to have received a total daily dose of 12 mg/day. At the study dose of 12 mg/day, the daily cost of lenvatinib is $97.68 and $2,735.04 for a 28-day cycle [20].

### Decision Model

A state-transition model was implemented in our analysis using TreeAge Pro 2019 decision analysis software [21]. Three health states were implemented to represent the disease progression from a state of unresectable HCC: progression-free disease (PFD), progressive disease (PD), and death (Fig. 1). All patients were assumed to be in the PFD state at the beginning of therapy. As the model progressed through each cycle, patients transitioned to PD state and then to death, or directly to death from PFD state. Transition from PFD to PD followed the PFS curve and transition to death followed the OS curve from the REFLECT trial (Fig. 1) [2].

### Model Inputs

#### *Efficacy*

All state-transition probabilities were obtained from the REFLECT trial [2]. Because the trial had a median duration of follow-up of only 27.7 months, transition probabilities were extrapolated to 60 months using R. The OS and PFS curves

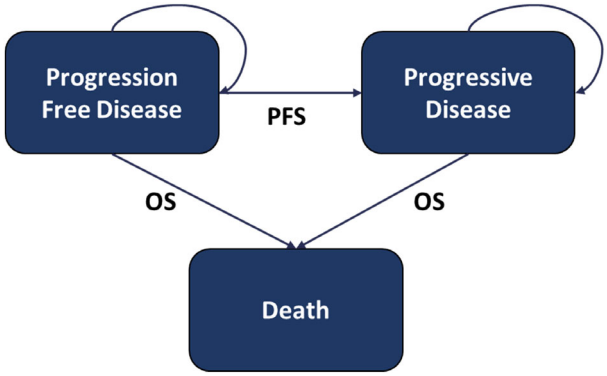


**Figure 1.** Health states and progression of unresectable hepatocellular carcinoma. All patients were assumed to be in the progression-free disease state at the start of the model. Patients moved to the progressive disease state and then to death, or they could move directly to death from progression-free disease. The OS and PFS curves determine the transition probabilities between the health states. Abbreviations: OS, overall survival; PFS, progression-free survival

from the REFLECT trial were digitized using the software WebPlotDigitizer Version 4.1 [22]. The transition probabilities were then projected using Weibull, log-logistic, lognormal, and gamma distributions by implementing an algorithm described in the Guyot study (supplemental online Fig. 1) [23]. Based on the Akaike information criterion and Bayesian information criterion, it was determined that log-logistic and lognormal distributions were preferred for lenvatinib and sorafenib, respectively. Thus, a mixed distribution of log-logistic for lenvatinib and lognormal for sorafenib was implemented to project transition probabilities (supplemental online Fig. 2).

### *Adverse Events*

Clinically relevant treatment-emergent adverse events of grade ≥3 from the REFLECT trial were included in the model to reflect the costs and disutilities associated with the adverse events (supplemental online Table 1). For the sensitivity analysis, the incidence was increased by 25% for the upper limit and the lower limit was set at 0%. Some key adverse events included hypertension, palmar-plantar erythrodysesthesia, diarrhea, and fatigue [2]. Hypertension was the most prevalent adverse event of grades ≥3 at 23% and 14% for lenvatinib and sorafenib, respectively [2].

### *Costs*

The costs of lenvatinib and sorafenib were obtained from published literature and the pan-Canadian Oncology Drug Review reports (Table 1) [19, 20, 24]. Based on the post-study anticancer therapy data during survival follow-up from the REFLECT trial, 32.6% and 38.7% of patients who progressed despite lenvatinib and sorafenib, respectively, were assumed to have received regorafenib as the second-line therapy [2]. The cost of regorafenib was calculated at $217.86 per day and was charged as a one-time cost to these patients who progressed after the first-line therapy [25]. It was charged for a mean duration of 5.9 months, as per the RESOURCE trial, for a 3-week regimen followed by 1-week drug-free period at a dose of 160 mg/day for a one-time charge of $26,992.85 [25].

Baseline health state costs associated with HCC included costs of outpatient visits, emergency room visits, acute inpatient care, home care, continuing care, and long-term care, which were obtained from a population-based retrospective cohort study using Ontario Cancer Registry linked administrative data (Table 1) [24]. The costs of care were adjusted based on whether the patient was in a PFD state or PD state (Table 1). The costs applied to the PD state represented costs associated with palliative care for patients who progressed despite first-line treatment. Costs and disutilities associated with each medication were also obtained from published literature [2, 24]. Drug-related adverse effect costs and disutilities were charged as a one-time cost where each patient was allowed to acquire multiple adverse events.

### *Utilities*

Utility values associated with treatment-emergent adverse events were obtained from published literature (Table 2) [26, 27]. There were limitations in the data availability of some of the drug-induced adverse events, as indicated in Table 2. As such, the model assumed that there were no disutilities associated with hypertension, decreased appetite, decreased weight, proteinuria, decreased platelet count, elevated aspartate aminotransferase, and increased blood bilirubin. Baseline health state utilities of patients with unresectable HCC were obtained from published literature [28]. The health state utility values subtracted by the disutility values associated with adverse events, together with the time associated with the health states, were used in calculating the QALY [29].

## Economic Assumptions

All costs and effects were discounted at a rate of 1.5% annually, as per the CADTH guidelines [17]. We imposed a willingness-to-pay (WTP) threshold of $0 per QALY for cost-saving but also analyzed the results at a threshold of $50,000 per QALY, a threshold that is considered to be reasonable for funding in Canada [30]. All international currencies used to measure the cost of adverse event treatment were converted to Canadian dollars for that particular year using the purchasing power parities [31]. Costs were then adjusted to 2018 Canadian dollars using the consumer price index from Statistics Canada [32].

## Analytic Strategy

For the base case analysis, average cost and effectiveness values of the probabilistic sensitivity analysis (PSA) were used to calculate the ICER rather than doing a deterministic sensitivity analysis (DSA). This follows the CADTH guideline, which recommends such practice because of the ability to account for underlying uncertainties regarding the costs and outcomes of the parameters [17]. The PSA was performed using a Monte Carlo simulation for 10,000 replications to determine the probability that lenvatinib will be cost-saving or cost-effective compared with sorafenib at multiple WTP thresholds. Key parameters that were considered included transition probabilities, costs and disutilities associated with treatment adverse events, health state utilities, and costs of study drugs. PSA was performed at

**Table 1.** Costs of treatment-emergent adverse events, treatment costs, and health-state costs

| Cost category | Cost | Lower limit | Upper limit | Source |
|---|---|---|---|---|
| Adverse events | | | | |
| Hand-foot syndrome[a] | 16.10 | 12.08 | 20.13 | Tam et al. [38] |
| Diarrhea[a] | 5,136.65 | 3,852.49 | 6,420.81 | Tam et al. [38] |
| Hypertension | 3,100.67 | 2,668.99 | 3,557.34 | Wong et al. [39] |
| Decreased appetite[b] | 145.88 | 113.16 | 178.56 | Thein et al. [24] |
| Decreased weight[b] | 145.88 | 113.16 | 178.56 | Thein et al. [24] |
| Fatigue[a] | 6,058.68 | 4,544.01 | 7,755.11 | Tam et al. [38] |
| Proteinuria[b] | 145.88 | 113.16 | 178.56 | Thein et al. [24] |
| Nausea/vomiting | 5,296.46 | 3,972.35 | 6,620.58 | Tam et al. [38] |
| Decreased platelet count | 8,324.16 | 7,141.01 | 9,682.35 | Wong et al. [39] |
| Elevated AST[a] | 6,772.29 | 5,079.22 | 8,465.36 | Rashid et al. [40] |
| Increased blood bilirubin[a] | 1,088.41 | 816.31 | 1,360.51 | Rashid et al. [40] |
| Other costs | | | | |
| Sorafenib[a,c] | 5,476.62 | 4,107.47 | 6,845.78 | pCODR [19] |
| Lenvatinib[a,d] | 2,735.04 | 2,051.28 | 3,418.80 | pCODR [20] |
| Regorafenib[a,e] | 26,992.85 | 20,244.64 | 33,741.06 | pCODR [25] |
| PFD health-state (≤12 months)[f] | 8,118.83 | — | — | Thein et al. [24] |
| PFD health-state (>12 months)[f] | 1,319.38 | — | — | Thein et al. [24] |
| PD health-state[f] | 11,681.57 | 9,164.07 | 14,382.29 | Thein et al. [24] |

All costs are shown in 2018 Canadian dollars.
[a]Upper and lower limits are set at ±25% of the baseline cost.
[b]Cost represents a one-time 1-day outpatient visit.
[c]Monthly cost of sorafenib 800 mg/day.
[d]Monthly cost of lenvatinib 12 mg/day.
[e]One-time drug cost charged at 160 mg/day for 5.9 months per RESOURCE trial.
[f]Baseline health-state cost includes outpatient visits, emergency room visits, acute inpatient care, home care, continuing care, and long-term care.
Abbreviations: —, no data; AST, aspartate aminotransferase; pCODR, pan-Canadian Oncology Drug Review; PD, progressive disease; PFD, progression-free disease.

**Table 2.** Disutility values of treatment-emergent adverse events and health-state utility values

| Utility category | QALY | Lower limit | Upper limit | Source |
|---|---|---|---|---|
| Adverse events | | | | |
| Hand-foot syndrome | −0.116 | −0.139 | −0.093 | Lloyd et al. [27] |
| Diarrhea | −0.050 | −0.096 | −0.019 | Pignata et al. [26] |
| Hypertension[a] | 0 | 0 | 0 | |
| Decreased appetite[a] | 0 | 0 | 0 | |
| Decreased weight[a] | 0 | 0 | 0 | |
| Fatigue | −0.070 | −0.114 | −0.036 | Pignata et al. [26] |
| Proteinuria[a] | 0 | 0 | 0 | |
| Nausea/vomiting | −0.050 | −0.096 | −0.019 | Pignata et al. [26] |
| Decreased platelet count[a] | 0 | 0 | 0 | |
| Elevated AST[a] | 0 | 0 | 0 | |
| Increased blood bilirubin[a] | 0 | 0 | 0 | |
| Health states | | | | |
| PFD | 0.760 | 0.546 | 1.014 | Leung et al. [28] |
| PD | 0.680 | 0.476 | 0.806 | Leung et al. [28] |

[a]Based on modeling assumptions
Abbreviations: AST, aspartate aminotransferase; PD, progressive disease; PFD, progression-free disease; QALY, quality-adjusted life year.

**Table 3.** Base case analysis

| Treatment | Cost | ΔCost | QALY | ΔQALY | ICER | WTP: $0 | WTP: $50K |
|---|---|---|---|---|---|---|---|
| Lenvatinib | 195,275.43 | N/A | 1.153 | N/A | N/A | N/A | N/A |
| Sorafenib (full price) | 218,994.77 | −23,719.34 | 1.021 | 0.132 | Dominated | 64.87% | 76.12% |
| Sorafenib (20% discount) | 210,653.52 | −15,378.09 | 1.021 | 0.132 | Dominated | 57.02% | 69.48% |
| Sorafenib (40% discount) | 202,312.28 | −7,036.85 | 1.021 | 0.132 | Dominated | 45.74% | 59.29% |
| Sorafenib (60% discount) | 193,971.03 | 1,304.40 | 1.021 | 0.132 | 9,881.82 | 30.72% | 42.62% |
| Sorafenib (80% discount) | 185,629.78 | 9,645.65 | 1.021 | 0.132 | 73,073.11 | 18.93% | 26.24% |
| Sorafenib (90% discount) | 181,459.16 | 13,816.27 | 1.021 | 0.132 | 104,668.71 | 13.95% | 19.74% |

All costs are shown in 2018 Canadian dollars.
Abbreviations: ICER, incremental cost-effectiveness ratio; N/A, not applicable; QALY, quality-adjusted life year; WTP, willingness-to-pay.

**Table 4.** Subgroup analysis

| Subgroup | OS HR (95% CI) | Average cost | ΔCost | QALY | ΔQALY | ICER | WTP: $0 | WTP: $50K |
|---|---|---|---|---|---|---|---|---|
| Overall | 0.916 (0.789–1.064) | $195,275.43 | −$23,719.34 | 1.153 | 0.132 | −$179,691.97 | 64.87% | 76.12% |
| ECOG PS (0, ≥1) | 0.923 (0.795–1.071) | $192,061.16 | −$26,568.35 | 1.140 | 0.118 | −$225,155.51 | 66.39% | 75.66% |
| Body weight (<60 kg, ≥60 kg) | 0.923 (0.796–1.071) | $192,606.75 | −$26,094.65 | 1.141 | 0.120 | −$217,455.42 | 66.03% | 75.45% |
| Age (<65, ≥65 to <75, ≥75) | 0.919 (0.791–1.067) | $193,595.95 | −$25,307.74 | 1.146 | 0.124 | −$204,094.68 | 65.57% | 75.64% |
| BCLC staging (stage B, stage C) | 0.918 (0.791–1.067) | $194,825.94 | −$24,253.84 | 1.153 | 0.130 | −$186,568.00 | 65.16% | 75.77% |
| Sex (male, female) | 0.916 (0.789–1.064) | $194,694.02 | −$23,635.26 | 1.150 | 0.132 | −$179,055.00 | 64.48% | 75.86% |
| Extrahepatic spread (yes, no) | 0.915 (0.788–1.062) | $195,588.37 | −$23,683.94 | 1.156 | 0.133 | −$178,074.74 | 64.90% | 75.93% |
| Underlying cirrhosis (yes, no) | 0.916 (0.789–1.063) | $195,034.65 | −$23,526.97 | 1.154 | 0.133 | −$176,894.51 | 64.97% | 76.14% |
| Region (Asia-Pacific, Western) | 0.915 (0.789–1.062) | $195,718.98 | −$23,262.68 | 1.155 | 0.134 | −$173,602.09 | 65.62% | 77.03% |
| Antiviral therapy for HBV or HCV (yes, no) | 0.912 (0.785–1.059) | $196,136.66 | −$22,398.93 | 1.161 | 0.139 | −$161,143.38 | 65.99% | 77.22% |
| Macroscopic portal vein invasion (yes, no) | 0.910 (0.784–1.057) | $196,939.59 | −$21,620.44 | 1.162 | 0.142 | −$152,256.62 | 64.88% | 76.27% |
| Macroscopic portal vein invasion, extrahepatic spread, or both (yes, no) | 0.908 (0.783–1.054) | $197,977.99 | −$21,162.18 | 1.169 | 0.144 | −$146,959.58 | 65.21% | 77.13% |
| Prior procedure (yes, no) | 0.902 (0.777–1.048) | $200,164.04 | −$18,897.51 | 1.178 | 0.156 | −$121,137.88 | 63.88% | 76.91% |
| No. of disease sites at baseline (1, 2, ≥3) | 0.878 (0.755–1.020) | $209,206.66 | −$9,812.93 | 1.223 | 0.200 | −$49,064.65 | 59.13% | 76.01% |
| AFP at baseline (<200 ng/mL, ≥200 ng/mL) | 0.856 (0.736–0.995) | $217,439.65 | −$1,897.26 | 1.260 | 0.238 | −$7,971.68 | 51.90% | 71.83% |
| Etiology (HBV, HCV, alcohol) | 0.855 (0.721–1.013) | $217,352.78 | −$1,332.00 | 1.261 | 0.240 | −$5,550.00 | 49.17% | 67.55% |

Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year; WTP, willingness-to-pay.

discounted sorafenib prices to evaluate the impact of a potential generic sorafenib on the study outcomes.

We performed further analyses using the subgroup hazard ratios (HRs) for OS provided in the REFLECT trial to assess in which subgroup lenvatinib would be more likely to be cost-saving. HR-adjusted OS and the original OS curves were used to reconstruct the new OS curve for lenvatinib and to calculate the ICER values for each subgroup.

## Validation

In order to validate our model, Kaplan-Meier survival curves for OS and PFS were plotted for both medications. The model

was inspected visually by overlaying and comparing the OS and PFS curves from the model and the original trial (supplemental online Fig. 2).

## Results

### Base Case Analysis

In our base case analysis, we compared lenvatinib with sorafenib. Rather than doing a DSA for the base case analysis, we performed a PSA and calculated the ICER value, which improves the reliability of the results compared with the DSA. Lenvatinib had a mean cost of $195,275.43 and mean effectiveness of 1.153 QALY, whereas sorafenib had a mean cost of $218,994.77 and mean effectiveness of 1.021 QALY. The incremental cost was −$23,719.34 and the incremental effectiveness was 0.132 QALY, making lenvatinib a cost-saving measure (Table 3).

### Probability Sensitivity Analysis

In the PSA, uncertainties were assessed in all parameters except for the costs of the medications. At full drug prices, lenvatinib was cost-saving in 64.87% of the simulations and cost-effective 76.12% of the time at a WTP of $50,000. Supplemental online Figure 3 illustrates the results of the PSA in an incremental cost-effectiveness scatterplot.

The ICER was also evaluated at discounted prices of sorafenib to reflect the impact of a cheaper generic sorafenib on the study outcome. Although it is difficult to speculate what the generic price would be, our analysis found that lenvatinib will no longer be cost-saving if the price of sorafenib was decreased by 57%. Additionally, lenvatinib would fail to remain cost-effective at WTPs of $50,000 and $100,000 if the price of sorafenib was decreased by more than 73% and 89%, respectively. Meaning, the financial benefit of lenvatinib will be less likely if a genericized sorafenib is priced significantly lower than the original drug. However, even when sorafenib price was discounted by 90%, lenvatinib was still cost-saving in 13.95% of the simulations and cost-effective 19.74% of the time at a WTP of $50,000 (Table 3).

### Subgroup Analysis

We analyzed the ICER for all subgroups included in the REFLECT trial by using the subgroup HR for OS. Overall, there were few variations in the ICER values between subgroups except for when the subgroups were stratified by baseline α-fetoprotein (AFP) value, number of disease sites at baseline, or the etiology (Table 4). In all subgroups, lenvatinib was cost-saving in at least 49% of the simulations and cost-effective at a WTP of $50,000 in at least 67% of the simulations.

## Discussion

The results of our study suggest that lenvatinib could be a cost-saving measure compared with sorafenib in patients with unresectable HCC as lenvatinib was found to have a greater effectiveness at a lower cost. Although lenvatinib did not increase the OS compared with sorafenib, the increase in PFS time led to higher QALYs for lenvatinib. Because first-line therapies were discontinued once patients' disease advanced despite therapy, the lenvatinib arm resulted in a longer duration of therapy. However, the significant difference in drug cost minimized lenvatinib from being penalized from longer use owing to its greater effectiveness. Lenvatinib dominating sorafenib is likely driven largely by the increased PFS and significant reduction in drug price of lenvatinib.

Similar conclusions were presented in an economic evaluation of lenvatinib and sorafenib in unresectable HCC in Japan by Kobayashi et al. in which lenvatinib dominated sorafenib [16]. Although our study looked to answer a similar question as the Japanese study, our models differed in several ways. First, the choices of second-line therapy for patients who progressed despite first-line treatment were different. Kobayashi et al. included transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC), in addition to regorafenib, as options for postprogression therapy, whereas our model only considered regorafenib as the second-line option [16]. Although locoregional therapies such as TACE and HAIC are often used in patients with HCC, they are more often used for patients who are diagnosed earlier on in the disease progression and as part of a strategy to bridge patients for other curative therapies and are not routinely performed for patients with unresectable HCC for postprogression therapy [33]. This is consistent with the recommendations by the National Comprehensive Cancer Network (NCCN) which recommends other systemic therapies for patients who progressed after lenvatinib, sorafenib, or systemic chemotherapy [33]. Although NCCN lists multiple second-line options such as regorafenib, cabozantinib, ramucirumab, nivolumab, and pembrolizumab, regorafenib is most commonly used in Canada as a result of funding structure [33]. Therefore, our model considered regorafenib exclusively as the second-line therapy to better reflect common practices. Second, the Kobayashi study used the AFP-adjusted population of the REFLECT trial for their base case analysis because this was the only subgroup that provided statistically significant OS HR [16]. In our study, we performed the base case analysis using the overall population because this would allow for an analysis that is more reflective of the general population.

The National Institute for Health and Care Excellence in the U.K. also announced a favorable decision on the use of lenvatinib for unresectable HCC. The committee recommended lenvatinib as an option for unresectable HCC owing to its clinical efficacy and because the cost-effectiveness estimates compared with sorafenib were within an acceptable range [34]. CADTH, the national Canadian organization providing recommendations to health care decision-makers, is currently reviewing the manufacturer's submission.

It is important to consider the fact that a generic version of sorafenib may become available in the near future as a result of an expiring patent protection [35]. In India, owing to a compulsory license granted by the government, a generic sorafenib is already available at less than 5% of the original price [37]. In anticipation of a potential generic sorafenib, it is important for decision-makers to consider the timing of sorafenib patent expiration and what the genericized price will be when proposing a funding recommendation for lenvatinib.

### Limitations

A number of limitations exist in our study. First, we assumed that all patients who received second-line therapy after

progression were given regorafenib. Although regorafenib is a clinically logical second-line therapy, and in agreement with international guidelines, we assumed that all patients received regorafenib for 5.9 months, as per the RESOURCE trial [36]. However, we did account for the variability in the duration of second-line therapy in the sensitivity analysis and determined that it did not significantly influence the results.

Second, our model used extrapolated OS and PFS curves based on the REFLECT trial. Although the extrapolated data were visually validated to be comparable to the trial data, there are always uncertainties surrounding extrapolation, particularly when projecting beyond the trial observation time period.

Third, the input values for the costs and utilities associated with treatment-emergent adverse events were not derived specifically from patients with HCC who were on lenvatinib or sorafenib. Rather, the values were obtained from published economic burden studies looking generally at anticancer adverse events. However, costs and utilities associated with the baseline health state, which are the most important, were obtained directly from a recent study that looked specifically at patients with HCC [24]. Additionally, the prevalence of treatment-emergent adverse events was comparable between the two drugs in that it did not have a significant impact on the overall outcome of the study.

## Conclusion

Having a cost-saving alternative is particularly important for a health care system that is facing an immense amount of economic pressure. Our cost–utility analysis showed that lenvatinib had a greater effectiveness at a lower cost than sorafenib, indicating that lenvatinib may be a cost-saving measure in patients with unresectable HCC, in which $23,719 could be saved per patient. However, it is important to consider that lenvatinib may fail to be cost-effective at a WTP of $50,000, and would most certainly not be cost-saving, if a significantly cheaper generic sorafenib becomes available. Nonetheless, at the current prices of lenvatinib and sorafenib, our model, which was robust to sensitivity analyses, indicates that lenvatinib dominates sorafenib.

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## Disclosures

**William W.L. Wong:** Canadian Liver Foundation (RF). The other authors indicated no financial relationships.

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