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Cost-effectiveness of lenvatinib compared to sorafenib for the first-line treatment of advanced hepatocellular carcinoma in Australia

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Abstract

Background and Objective

In the REFLECT trial, lenvatinib showed superior clinical benefits to sorafenib in terms of progression-free survival and was non-inferior for overall survival in the treatment of advanced hepatocellular carcinoma (HCC). We assessed the cost-effectiveness of lenvatinib compared with sorafenib for patients with advanced HCC in Australia.

Method

A partitioned-survival model was built to perform a cost-effectiveness analysis comparing lenvatinib and sorafenib from an Australian health system perspective. Survival curves were obtained from the REFLECT trial and fitted with parametric survival functions for extrapolation purposes beyond the trial follow-up. Cost and quality-adjusted life-years (QALYs) were accrued over the 10-year time horizon of the model. Deterministic and probability sensitivity analysis (PSA) were carried out to verify the validity of the model.

Results

Lenvatinib incurred higher costs ($96,325) and superior health outcomes (QALYs: 1.205), while sorafenib had lower costs ($92,394) and inferior health outcomes (QALYs: 1.086). Thus, lenvatinib yielded an incremental cost-utility ratio of A$33,028/QALY gained. Further, the results of the PSA found that the probability of lenvatinib to be cost-effective at a willingness-to-pay threshold of A$50,000/QALY was 64%.

Conclusion

Our study found that, at current-prices, lenvatinib is a cost-effective treatment option for the first-line treatment of patients with advanced HCC.

Word count: 199

Key words: Lenvatinib, Sorafenib, hepatocellular carcinoma, cost-effectiveness analysis

Short running title: Cost-Effectiveness of Lenvatinib for Hepatocellular carcinoma in Australia.

Key points for the decision-makers

- There is no previously published economic evaluation for lenvatinib in treating advanced HCC in Australia.
- Lenvatinib was associated with both higher costs and greater benefits (i.e. QALYs and LYs) compared with sorafenib.
- Our study indicated that, based on current prices, lenvatinib is cost-effective compared with sorafenib at WTP threshold of A$50,000. However, any unilateral reduction in the price of sorafenib would reduce the cost-effectiveness of Lenvatinib.

1 Introduction

Globally, liver cancer is one of the main reasons for cancer-associated mortality [1]. The majority of liver cancers are diagnosed as hepatocellular carcinoma (HCC) that accounts for almost 75% of all cases of liver cancers [1]. Over the past several decades, the incidence of HCC in Australia has significantly increased from 1.38 per 100,000 in 1982 to 4.96 per 100,000 in 2014 with an average upsurge of 4.46% on an annual basis [2]. Chronic viral hepatitis (types B & C), aflatoxin exposure, and alcohol consumption remain as the primary risk factors for HCC [3].

Systemic therapies are the mainstay treatment strategy for patients with advanced HCC who are not suitable for surgical resection. Sorafenib, a multikinase inhibitor, was the only systemic treatment option in advanced HCC according to international treatment guidelines following the results reported a decade ago [4]. Lenvatinib, also a multikinase inhibitor, has recently been approved for first-line treatment of advanced HCC in Australia by the Therapeutic Goods Administration [5], based on the results of the pivotal multicentre, randomized, phase 3, noninferiority trial (-REFLECT) [6]. Previously, lenvatinib was approved for the treatment of advanced renal cell carcinoma and metastatic, radioactive iodine refractory, differentiated thyroid cancer [5]. In the REFLECT trial, the median survival time for lenvatinib of 13·6 months (95% CI 12·1–14·9) was non-inferior to sorafenib (12·3 months, 10·4–13·9; hazard ratio 0·92, 95% CI 0·79–1·06), satisfying the non-inferiority criteria [6], Lenvatinib also showed a statistically significant gain of 3.7 months in median progression free survival and 5.2 months in median time to progression [6]. Treatment-related adverse events of grade 3 or higher were similar across the lenvatinib and sorafenib arms (episodes per patient-year 3·2 *vs.* 3·3) [6].

The availability of lenvatinib as an alternative therapeutic option for treatment-naïve advanced HCC patients in Australia is a potentially practice-changing opportunity for clinicians. In many countries including Australia, the decision to prescribe a new medicine are often based on a cost-effectiveness analysis. Many health technology assessment bodies in countries including the United Kingdom and Canada have recommended the use of lenvatinib for HCC in routine practice based on its demonstrated cost-effectiveness and value for money [7, 8]. However, in Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing of lenvatinib for HCC based on a cost-minimisation analysis [9]. As a result, there is a lack of information on the cost-effectiveness of lenvatinib for HCC treatment in the Australian setting. and how it would be impacted due to availability of a cheaper generic brand of sorafenib in the future. Therefore, the aim of this study was to estimate the cost-effectiveness of lenvatinib in first-line treatment of patients with advanced HCC in Australia compared with sorafenib. This information will assist clinicians and decision makers when evaluating the cost-effectiveness of incorporating lenvatinib in advanced HCC treatments.

2 Method

2.1 Interventions

Two interventions were compared for the analysis: lenvatinib and sorafenib. Patients received oral lenvatinib 12 mg/day (for bodyweight ⩾60 kg) or 8 mg/day (for bodyweight <60 kg) or sorafenib 400 mg twice-daily in each 28-day cycle. Interruption, modification, and discontinuation to the treatment dose was allowed for patients who experienced drug-related toxicity. Given no drugs are PBS listed for second-line treatment, patients only received ongoing care in the post-progression phase.

2.2 Population, Time horizon, Cycle Length and Perspective

The modelled population is assumed to be of equivalent characteristics to the patients enrolled in the REFLECT trial. Briefly, 954 treatment-naïve patients with advanced HCC from 20 countries were randomised to receive either lenvatinib or sorafenib. The enrolled patients had: one or more measurable target lesions based on mRECIST criteria,, Barcelona Clinic Liver Cancer stage B or C categorization; Child-Pugh class A; and Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0 or 1. Patients were excluded if they had 50% or more liver occupation or had received previous systemic treatment for HCC.

Patient baseline characteristics were similar in both treatment groups. The median age was 62 years (range: 20-88 years) and 84% of patients were male [6]. The median trial follow-up was 27·7 months in the lenvatinib group and 27·2 months in the sorafenib group.

A 10-year time horizon for the economic model was deemed suitable to capture all the health and economic consequences associated with the disease. This was supported by published Australian data, indicating that less than 15% of patients with HCC remain alive at 10 years from the date of diagnosis [10]. Further, it is important to note that the previous modelled economic evaluation of sorafenib in advanced HCC patients for the Australian population used a time horizon of 10 years and was accepted by the PBAC [11]. Alternative time horizons (5 and 15 years) were tested in sensitivity analyses. The cycle length was kept to one month to coincide with 28-day treatment cycle in the REFLECT trial. The model implemented the half-cycle correction using the Simpson 1/3 rule [12] and a 5% discount rate for costs, quality-adjusted life years (QALYs) and life years (LYs) in accordance with the PBAC guidelines [13] As the Pharmaceutical Benefits Scheme (PBS) in Australia is publicly funded a health system perspective was adopted [13].

2.3 Model structure

A cohort-based Partitioned Survival Model (PSM) was developed to estimate the long-term health and economic outcomes. The PSM approach is intuitive, easy to implement, and has been used widely in the advanced cancer setting. The PSM model constructed here comprised of three health states: Progression-free (PF), Progressed Disease (PD), and Dead (Figure 1). This structure is well-suited to model the cost-effectiveness of late-line treatments for cancer and has also been previously used for manufacturer submissions to the National Institute for Health and Care Excellence (NICE) in the United Kingdom and the PBAC in Australia [14, 15]. The modelled health states reflect the primary- (overall survival, OS) and secondary-endpoints (progression free survival, PFS) of the REFLECT trial [6]. All patients initiated in the PF health state and then either transitioned to PD, or , dDead, or remained in PF after each cycle. Once patients moved to PD state, they could either remain there or move to the Dead state at each cycle. The transition model estimated the likelihood of being in each of the three health states at the end of each month. Survival estimates from the PFS curve included the

probability that a patient was in PF health state. The survival estimates from the OS curve reflected the probability of the patient being dead or alive at any given point in time. Finally, the difference between the OS and the PFS curves gave the transition probability for the patient to move to a PD health state. The proportion of patients in each health state was estimated by parametric modelling of OS and PFS data from the lenvatinib and sorafenib arms of REFLECT trial. The model was built in Microsoft Excel® (Microsoft Corp., Redmond, WA, USA).

2.4 Model input parameters

2.4.1 Modelling PFS and OS

PFS and OS data were sourced from the REFLECT trial as it was the only head-to-head RCT that evaluated the efficacy and safety of first-line lenvatinib and sorafenib in advanced HCC [6]. As the REFLECT trial had a median follow-up of 27.7 months, it was essential to extrapolate the observed PFS and OS beyond the duration of the trial. We digitized the published PFS and OS Kaplan-Meier (KM) curve from the REFLECT trial using a validated graphical digitiser (WebPlotDigitizer; https://automeris.io/WebPlotDigitizer/). Using the digitised KM data points and the number at risk at each time point, we generated the individual-patient data (IPD) using the methods reported in Wei et al [16]. The generated IPD were then used to fit parametric survival models. We compared the median PFS, OS and hazard ratio from our reconstructed IPD with REFLECT trial published outcome and found it to be similar (Supplementary Table 1). The standard parametric survival functions (exponential, Weibull, log-normal, log-logistic, generalised gamma and gompertz) were fitted to the simulated IPD for extrapolation to a longer time duration. The parametric survival extrapolation was performed as per the NICE Decision Support Unit (DSU) guidance [17]. Briefly, a three-step method was applied: (1) proportional hazard (PH) assumption testing by visual inspection of log-cumulative hazard plot and Schoenfeld residual test; (2) based on the step 1 results, we then fitted the same or independent parametric survival function(s) on the reconstructed IPD; and 3) finally, the most appropriate fit was selected based on a visual check, and the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) goodness-of-fit statistics. To further evaluate the external validity of survival extrapolation, we performed a naïve comparison with the published Australian HCC survival data [13, 2]. Parametric survival analysis was performed in Stata/SE for windows version 13.1.

The visual inspection of the hazard plots showed that the lines crossed at the start and merged towards the end of the study. This indicated a deviation from the PH assumption (supplementary Figure 1-2). Since the PH assumption was violated, a separate parametric survival for each treatment arm was deemed suitable. Subsequently, log-normal and log-logistic distributions were chosen as preferred survival distributions for PFS and OS in lenvatinib and sorafenib, respectively (supplementary Table 2). A generalised gamma distribution resulted in clinically implausible higher PFS for sorafenib than lenvatinib and therefore was not considered for extrapolation purposes. Model fit statistics of each parametric survival distribution and visual inspection of the fitted curves are provided in the supplementary Table 3 and supplementary Figures 3-5.

2.4.2 Costs

All the costs were obtained from published sources and have been reported to values in the year 2020. The detailed resource use and unit costs are shown in Table 1. The cost of lenvatinib and sorafenib for the treatment of advanced HCC was based on the PBS drug pricing website The KM curve for time to treatment failure was based on the REFLECT trial without any

extrapolation as the data was complete. The mean treatment duration was 9.8 months for lenvatinib and 7.8 months for sorafenib. The drug costs were based on the mean dose intensity in the REFLECT trial. The mean lenvatinib and sorafenib dose intensity was 88% and 83% of the recommended dose respectively [6]. As observed in the REFLECT trial, the body weight distribution for lenvatinib was: 32% of patients weighing less than 60 kilograms and 68% patients weighing more than 60 kilograms. This information was then used to derive the mean dose per day *i.e.* 9.43 milligrams for lenvatinib accounting for the dose intensity. More details on the derivation of cost of full treatment cycles is provided in Supplementary Table 8. As there is a risk of drug wastage due to dose modifications post dispensing, a scenario analysis for 100% dose intensity was conducted. No cost of administration was included as both drugs can be self-administered orally. Disease management costs were based on a physician survey of resource use submitted by the manufacturer in the lenvatinib submission for NICE UK [7] and included physician visits, laboratory tests, hospitalization, and post-hospital follow-up care. The incidence of adverse events (AEs) was taken from the REFLECT trial [6]. The costs associated with AEs are presented in Supplementary Table 4. The economic model included a one-off end-of-life (EOL) cost to dead patients [7]. As EOL care is a portion of palliative care, there is a risk that there may be some double counting for all components of end of life care costs, given that each of these aspects of resource use is costed in the PD health state. As such, a scenario analysis was conducted excluding the end-of-life cost.

2.4.3 Utilities

The utility values were sourced from the lenvatinib submission for the NICE UK ([7]. Specifically, the submission estimated utility values from the IPD of the pivotal trial using the European Quality-of-Life 5-Dimension Questionnaire, three level (EQ-5D-3L) and with the United Kingdom's value set [7]. In the REFLECT trial, EQ-5D-3L was administered at the start of trial, on first day of each subsequent treatment cycle, and at the off-treatment visit. The mean utility values were derived using a mixed effects linear regression model adjusting for prior treatment, age, sex, geographical location, and baseline EQ-5D [7]. The utility estimates for progression-free and progressed disease were 0.745 (95% CI 0.73-0.76) and 0.678 (95% CI 0.655 - 0.701), respectively. The disutility associated with the incidence of AEs as observed in the REFLECT trial and were informed based on the literature (presented in Supplementary Table 5) [18-20].

2.5 Base-case analysis

Incremental cost-utility ratios (ICUR) were calculated by dividing the difference in costs by the difference in outcomes (QALYs) between lenvatinib versus sorafenib. The ICUR provided a ratio of extra cost for extra unit of QALY.

2.6 Sensitivity analyses

We conducted one-way deterministic sensitivity analyses by varying individual parameters within the 95% confidence intervals wherever available otherwise assumed variance of $\pm$30% in absence of precise estimate. Parameter uncertainty was investigated through a probabilistic sensitivity analysis (PSA), in which parameter were assigned an appropriate distribution. The PSA was performed using a second-order Monte Carlo simulation with 5,000 iterations. The model convergence and stability were assessed by running the model until the 95% confidence

interval of the incremental net monetary benefit (INMB) does not include zero. The PSA model convergence was evaluated using the tool provided by the Hatswell *et al* [21]. For correlated parameters, a joint distribution was assigned. For example, the two parameters in the loglogistic survival function fitted to OS were assigned a multivariate-normal distribution. The results of the PSA are reported as the cost-effectiveness plane (CEP) and cost-effectiveness acceptability curve (CEAC).

Multiple scenario-based sensitivity analyses were also performed. One such analysis explored the price discounting of sorafenib range from 25% to 30% anticipating availability of a generic brand due to patent expiration of sorafenib. Other scenario analyses considered application of other plausible parametric functions for the extrapolation of either OS or PFS for both drugs and excluding the cost of EOL care.

3 Results

3.1 Base-case

In PSM over time horizon of 10 years, we found that advanced HCC patients treated with lenvatinib incurred higher costs ($96,325) and superior health outcomes (LYs: 1.705 & QALYs: 1.205), while patients who were treated sorafenib had lower costs ($92,394) and inferior health outcomes (LYs: 1.572 & QALYs: 1.086). Thus, lenvatinib yielded an incremental cost-utility ratio (ICUR) of A$33,028/QALY gained. It is noted that the benefit associated with lenvatinib was primarily dependant on the prolongation of PFS. Accordingly, the costs in the PF heath state were much higher with lenvatinib compared with sorafenib (Table 2).

3.2 Sensitivity analysis

The results of the one-way sensitivity analyses are shown in the Figure 2. The most sensitive parameters with the greatest influence on the ICUR were the constant hazard terms for the selected base-case PFS distribution for lenvatinib followed by the PD state costs. As shown in Table 3, all scenario analyses, except the discounted price of sorafenib, found lenvatinib to be a cost-effective treatment option at a willingness-to-pay threshold of $50,000 per QALY.

3.2.1 Probabilistic Sensitivity Analyses

The probabilistic sensitivity analysis including the parameter distribution of 5000 iterations found that the mean ICUR of $33,899 (95% CI $32,693 to $35,106) closely matched with the base-case results. With 5000 simulations, the 95% CI of INMB was $1,775 to $2,072 and the PSA model provided sufficiently stable results. The probability that lenvatinib was cost-effective at a threshold of $50,000 per QALY was 64%. (Figure 3).

4 Discussion

The main findings of the economic evaluation indicate that lenvatinib could be a cost-effective therapeutic option compared to sorafenib among treatment-naïve patients with advanced HCC. Although the clinical benefits in terms of overall survival were non-inferior in the REFLECT trial, the higher PFS duration lead to higher QALYs gained with lenvatinib. The cost of the progression-free health state and drug therapy were higher for lenvatinib owing to prolonged PFS and longer treatment duration. However, this was nullified by lower cost in the progressed-

disease health state with lenvatinib than in sorafenib. Overall, lenvatinib is likely to be a cost-effective treatment option compared to sorafenib at an often-quoted WTP of $50,000/QALY due to gains in PFS.

Previous model-based studies, conducted in Japan and Canada, reported lenvatinib to be a cost-saving (lower cost and higher benefit) rather than as a cost-effective treatment strategy among advanced HCC patients [22, 23]. The minor discrepancy in findings is because in both studies the price of lenvatinib was almost half the price of sorafenib and savings in drug therapy cost were the main cost driver of their model. In Australia, both lenvatinib and sorafenib have a special pricing agreement in place with the government. During the PBAC submission in November 2019, on a positive recommendation, the manufacturer agreed to set the price of lenvatinib based on the cost-minimising price resulted from applying the estimated dose relativity between lenvatinib and sorafenib to the actual effective price for sorafenib [14]. Therefore, we used the cost-minimised drug prices in our model which was similar to published real-world monthly cost of sorafenib ($4,321) in Australia [24].

A brief comparison between the current model-based study and existing studies can be found in Supplementary Table 9. When compared to previous modelling approach in the same indication PSM approach was used in lenvatinib submission for NICE UK [20] and in the cost-effectiveness analysis of lenvatinib in Japan [23], However, the health economic model for the Canadian study was based on a Markov state transition model [22]. In our study, we have chosen a using PSM approach as opposed to Markov state-transition model. The PSM approach assumes independence in the progression-free survival (PFS), and overall survival (OS) curves and usually predicts outcomes well for the within-trial period compared with a Markov model approach [14]. The main limitation of PSM approach is that the dependency between OS and PFS might not be reflected in the long-term extrapolation if the underlying trial data is immature [14]. However, this was not an issue in the REFLECT trial as the PFS and OS data in the lenvatinib arm were relatively complete:; 73.01% had disease progression and 73.43% had died during the trial period [6]. Consequently, the strengths of the PSM approach were considered to outweigh its limitations in this case.

The selection of post-progression therapy among patients who progressed following first-line treatment was different. Kim et al considered regorafenib as the second-line treatment for patients who progressed after lenvatinib or sorafenib [22]. The European Society of Medical Oncology (ESMO) treatment guidelines for HCC recommends several drugs for second-line treatment such as regorafenib, cabozantinib, ramucirumab, nivolumab, and pembrolizumab [4]. Given none of these drugs are publicly funded in Australia, we assumed no chemotherapy after first-line treatment with either lenvatinib or sorafenib. The lack of second-line chemotherapy in our economic model is unlikely to provide biased cost-effectiveness estimate as the REFLECT trial found no significant difference in overall survival [6]. Kobayashi et al extrapolated the survival data from the alpha fetoprotein-adjusted sub-group having statistically significant OS [23]. We utilised the survival curves reported for the intention-to-treat population from the REFLECT trial as it may be considered more representative of a real-world population. Kobayashi et al used a price of lenvatinib and sorafenib as indicated for renal cell carcinoma and thyroid cancer respectively rather than using the HCC indication specific prices as in our model [23].

In the absence of long-term cost-effectiveness, our study results could aid decision-making by clinicians, researchers and policymakers locally. It is worth noting that a generic brand of sorafenib may soon become available in the market due its patent expiration in the year 2020-21 [25]. According to the PBS, a 25% statutory price reduction is applied to the first generic brand introduced in the market [11]. Our scenario analysis revealed that lenvatinib would not be cost-effective if the sorafenib price was reduced by 25% or more. Consequently, it is recommended that the funding decision for lenvatinib is reviewed should the price of sorafenib be reduced.

4.1 Limitations

The study has some limitations. In the absence of IPD, the economic model was built using the pseudo-IPD recreated from the published study [6]. However, the model validation results (Supplementary Table 7) provided sufficient confidence that the survival outcomes in our PSM model was congruent with the REFLECT trial. Parametric survival functions allowed the extrapolation of outcomes beyond the trial follow-up but not without uncertainty regarding its clinical plausibility. The results of the scenario analysis reconfirmed that the base-case results were not sensitive to the choice of parametric survival distributions implemented. The health utility for PF and PD were derived from the EQ-5D-3L data collected in the REFLECT trial using the UK tariffs. We believe that these utility values were the best available estimates for our study given a large proportion of Australians are of European heritage. and previous research has demonstrated that utilities derived from the UK value sets are comparable to the Australian value set [26]. Immunotherapy such as atezolizumab in combination with bevacizumab has been recently approved by USFDA for first-line treatment for advanced HCC patients [27, 4], we have not appraised these drugs due to paucity of head-to-head trials and the fact that they are yet to be available in Australia.

5 Conclusion

The availability of lenvatinib for HCC patients in Australia provides a first-time opportunity for clinicians with an alternative treatment option in more than 10 years. Our analysis concurs with the body of evidence demonstrating that, at current prices, lenvatinib is cost-effective in treating patients with advanced HCC patients compared with sorafenib. The results support the PBAC's decision to extend the reimbursement for this drug via the PBS as an alternate treatment option to sorafenib in treatment of patients with HCC.

Declarations

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Informed Consent: Not applicable

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Availability of data and material: The authors declare that all input data to parameterize the decision analytic model are available within the article and the ESM. The model can be re-built entirely based on the detailed description of the model structure in the "Method" section and information provided.

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