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Cost-effectiveness analysis of cabozantinib as second-line therapy in advanced hepatocellular carcinoma

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Abstract

Background: In the CELESTIAL trial for patients with advanced hepatocellular carcinoma (HCC), cabozantinib showed improved survival compared with placebo but comes at a price. We aimed to investigate the cost-effectiveness of cabozantinib for sorafenib-resistant HCC from the payer's perspective of the USA, UK and China.

Methods: We developed Markov models to simulate the patients pre-treated with first-line sorafenib following the CELESTIAL trial. Quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratio (ICER) were calculated for the treatment with cabozantinib or best supportive care. The list price for drugs was acquired from the Red Book, the British National Formulary, West China hospital and reported literature. Adverse events, utilities weights, and transition likelihood between states were sourced from the published randomized phase III trial. A willing-to-pay threshold was set $150 000/QALY in the USA, $70 671/QALY (£50 000/QALY) in the UK and $26 481/QALY (3x GDP per capita) in China. Deterministic and probabilistic sensitivity analyses were developed to test the models' uncertainty.

Results: In the base case, treatment with cabozantinib increased effectiveness by 0.13 QALYs, resulting in an ICER vs best supportive care of $833 497/QALY in the USA, $304 177/QALY in the UK and $156 437/QALY in China. The models were most sensitive to assumptions about transitions to progression with both cabozantinib and best supportive care, the utility associated with being progression free. These results were robust across a range of scenarios and sensitivity analyses, including deterministic and probabilistic analyses.

Conclusions: Cabozantinib at its current cost would not be a cost-effective treatment option for patients with sorafenib-resistant HCC from the payer's perspective in the USA, UK or China. Substantial discounts are necessary to meet conventional cost-effectiveness thresholds.

KEYWORDS
cabozantinib, cost-effective, hepatocellular carcinoma, incremental cost-effectiveness ratio, Markov model, second-line therapy

Abbreviations: AE, adverse events; AWP, average wholesale price; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; PD, progression disease; PF, progression free; QALYs, quality-adjusted life-years; WTP, willingness-to-pay.

Weiting Liao and Jiaxing Huang contributed equally to the manuscript.

1 | INTRODUCTION

The global burden of hepatocellular carcinoma (HCC) is an escalating public health concern,[1] with the highest incidence rates of HCC in China[2] and recently increasing incidence in the USA and Europe.[3] Sorafenib was the first systemic regimen to be approved for patients with advanced HCC.[4] For those who have pre-treated with sorafenib, overall survival in the placebo group is approximately 8 months.[5]

Cabozantinib (CABOMETYX®, Exelixis, Inc) is a multikinase inhibitor targeting c-MET but also VEGFRs, AXL, RET, KIT and FLT3.[6] The phase III CELESTIAL trial[7] has compared the efficacy of cabozantinib vs placebo in the second-line setting. Median overall survival was 10.2 months in the cabozantinib group vs 8.0 months in the placebo group and median progression-free survival was 5.2 months in the cabozantinib group vs 1.9 months in the placebo group. Most common grade 3 or 4 adverse events (AE) observed in the cabozantinib group include hand–foot syndrome (17%), hypertension (16%), increased aspartate aminotransferase level (12%), fatigue (10%) and diarrhoea (10%). Cabozantinib was approved by the European Commission on 15 November 2018[8] and the US Food and Drug Administration on 14 January 2019,[9] for patients with HCC who have been previously treated with sorafenib.

Several drugs failed to demonstrate an improved survival in patients with sorafenib-resistant HCC compared with placebo,[10-13] with an unmet need required for valid salvage therapy after first-line sorafenib.[14] However, expensive prices potentially limit accessibility of innovative anticancer drugs to the public. Identifying the value of cabozantinb for patients with HCC may allow an understanding of the appropriate price(s) at which it could be appropriately utilized in several international settings. We performed a cost-effectiveness analysis of cabozantinib compared with best supportive care for patients with advanced sorafenib-resistant HCC from the payer's perspective in the USA, UK and China.

2 | METHODS

2.1 | Study design

We followed the CELESTIAL protocol to model the treatments. Cabozantinib patients took a 60-mg tablet of cabozantinib orally once per day until disease progression. The other group was assumed to receive best supportive care, which cabozantinib patients also received after progression. Computed tomography was assessed at baseline and every 8 weeks after randomization in the cabozantinib group.

2.2 | Decision model

A Markov model using TreeAge Pro 2011 (TreeAge Software) was conducted to simulate patients with sorafenib-resistant HCC receiving either cabozantinib or best supportive care. Patients started progression-free status, then moved to progression disease or death (Figure 1). This type of model has been used frequently to evaluate the cost-effectiveness of therapies for advanced liver cancer.[15-18] The model used a 1-month cycle length extending over a 10-year time horizon. Monthly transition probabilities between health states were calibrated to best fit the Kaplan–Meier progression-free and overall survival curves from the CELESTIAL trial (Figure 2). The resulting curves were validated by clinical experts from West China Hospital.

2.3 | Cost and utility estimate

Only direct medical costs were considered, including costs for cabozantinib, computed tomography and management of grade 3-4 AEs (Table 1). The US cost of cabozantinib using the average wholesale price (AWP) in the Red Book[19] was $10.93 per mg, the UK cost was $4.04 per mg[20] and the Hong Kong list price was $2.06 per mg. Monthly costs for computed tomography were $448 in the USA,[21] $91 in the UK[20] and $85 in China (Table 1). The trial identified AEs in both the cabozantinib and placebo arms. Costs for managing grade 3-4 AEs weighted by frequency were calculated based on the use of amlodipine 5 mg daily for hypertension, Eucerin cream for hand–foot syndrome and atropine/diphenoxylate and loperamide for diarrhoea.[18] These costs were sourced from published literature,[22] the Red Book,[19] the British National Formulary[23] and Chinese national drug prices.[24] All costs were converted to 2017 US dollars at exchange rate of 1USD = 0.7075GBP and 1USD = 6.8RMB.[25] EQ-5D index scores[26] were used with the utilities of 0.76 for progression free and 0.68 for progression.[27,28]

2.4 | Sensitivity analyses

Deterministic one-way analyses were developed to identify the influence of input parameters. If confidence intervals on parameters were not available, we used a wide range of ±30% of the base-case values (Table 1). In probabilistic sensitivity analyses, we ran 10 000 iterations of the model varying all the parameters based on the sampling distributions. Costs were assigned gamma distributions, and utility values, probabilities or proportions were assigned beta distributions,[29] assuming the standard deviation of 20% from mean values.[30] Cost-effectiveness acceptability curves were generated to present the probabilities when cabozantinib treatment would be cost-effective at various thresholds of willingness-to-pay (WTP) per QALY.

2.5 | Statistical analyses

All costs and health outcomes were discounted at 3% per year.[31] We included half-cycle corrections. Effectiveness was expressed in quality-adjusted life-years (QALYs), calculated by multiplying the time spent in a given state by the utility weight associated with that state.[32] Cost-effectiveness of one treatment vs another was measured with an incremental cost-effectiveness ratio (ICER) which is expressed as the incremental cost per QALY gained. We investigated the probability of cabozantinib being cost-effective at 100%, 50%, 30%, 20%, 15% and 10% of the current drug price in three countries

based on a WTP threshold of $150 000/QALY in the USA, $70 671/QALY (£50 000/QALY) in the UK and $26 481/QALY (3x GDP per capita) in China.[33-35] The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist is included as Table S1 in the supplement.[36]

3 | RESULTS

3.1 | Base case

The base-case results are shown in Table 2. Treatment with cabozantinib yielded 0.61 QALYs compared to 0.48 QALYs with best supportive care. Treatment with cabozantinib costs $111 726 compared to $3205 with best supportive care in the USA, $40 135 compared to $531 in the UK and $20 848 compared to $481 in China. The ICER of cabozantinib vs best supportive care was $833 497/QALY in the USA, $304 177/QALY in the UK and $156 437/QALY in China, higher than the conventional WTP thresholds, indicating that cabozantinib at its current price is unlikely a cost-effective treatment for second-line HCC.

3.2 | Sensitivity analyses

All one-way sensitivity analyses are described in tornado diagrams. (Figure 3) Our cost-effectiveness models were most sensitive to assumptions about the transition probability from PD to death in the placebo group and in the cabozantinib group, and the utility of the PF health state. The assumption that decreased the ICER of cabozantinib the most was the probability of death from PD in the cabozantinib group. If that were much lower (0.0581 per month), then the ICER dropped to $530 243 per QALY in the USA, $192 783 per QALY in the UK and $99 391 per QALY in China.

When the cost of cabozantinib was reduced by 70%, it still cost $263 747 per QALY gained in the USA, $93 613 per QALY gained in the UK, and $49 070 per QALY gained in China. Cabozantinib became cost-effective in the three countries after its price is reduced by 80%-85%. (Table 2) The cost-effectiveness acceptability curves showed that the probabilities for cabozantinib to be cost-effective were 0% at a WTP of $150 000, $70 671 and $26 481 per QALY gained in three countries at its current price (Figure 4).

4 | DISCUSSION

Our study is the first cost-effectiveness analysis of cabozantinib in sorafenib-resistant HCC based on several international settings. From the payer's perspective, second-line cabozantinib at current prices for advanced HCC is not cost-effective in the USA, UK and China. The current price is beyond the value it provides according to current thresholds for cost-effectiveness. To be cost-effective, the price of cabozantinib would likely require a decrease of 80%-85% in the USA, UK and China.

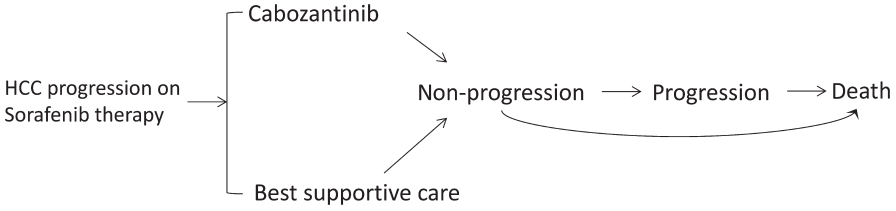

FIGURE 1 Model structure

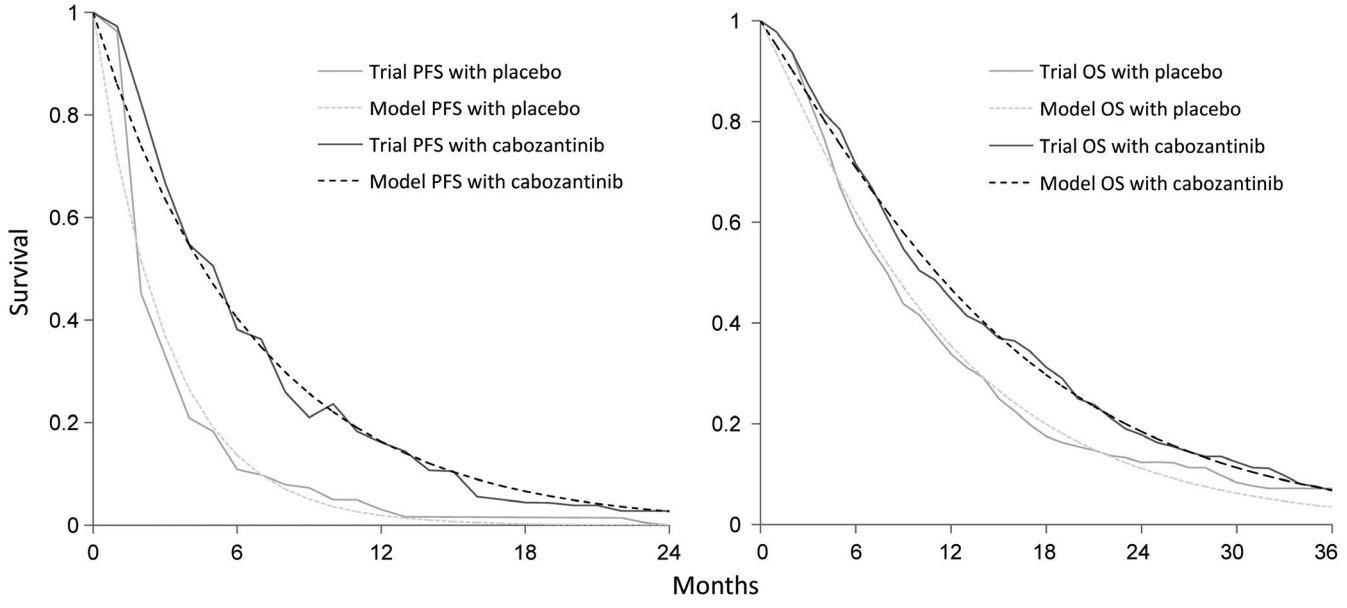

FIGURE 2 Kaplan–Meier survival for the cabozantinib and placebo arms in CELESTIAL trial and modelled curves. PFS, progression-free survival; OS, overall survival

TABLE 1 Input parameters and ranges

Parameter	Value (ranges)	Reference
Outcome, month		
Cabozantinib		
Median overall survival	10.2 (9.1-12.0)	[7]
Median progression-free survival	5.2 (4.0-5.5)	[7]
Median time to progression	5.2 (4.0-5.5)	[7]
Best supportive care		
Median overall survival	8.0 (6.8-9.4)	[7]
Median progression-free survival	1.9 (1.9-1.9)	[7]
Median time to progression	1.9 (1.9-1.9)	[7]
Transition probability		
Cabozantinib		
Progression free to progression	0.091 (0.0637-0.1183)	[7]
Progression free to death	0.054 (0.0378-0.0702)	[7]
Progression to death	0.083 (0.0581-0.1079)	[7]
Best supportive care		
Progression free to progression	0.218 (0.1526-0.2834)	[7]
Progression free to death	0.082 (0.0574-0.1066)	[7]
Progression to death	0.093 (0.0651-0.1209)	[7]
Proportion of patients with grade 3-4 adverse events		
Cabozantinib		
Diarrhoea	0.10 (0.07-0.13)	[7]
Decreased appetite	0.06 (0.042-0.078)	[7]
Palmar–plantar erythrodysesthesia	0.17 (0.119-0.221)	[7]
Hypertension	0.16 (0.112-0.208)	[7]
Abdominal pain	0.01 (0-0.02)	[7]
Fatigue	0.10 (0.07-0.13)	[7]
Best supportive care		
Diarrhoea	0.02 (0.01-0.03)	[7]
Decreased appetite	<0.01 (0-0.01)	[7]
Palmar–plantar erythrodysesthesia	0	[7]
Hypertension	0.02 (0.01-0.03)	[7]
Abdominal pain	0.04 (0.03-0.05)	[7]
Fatigue	0.04 (0.03-0.05)	[7]
Cabozantinib per mg, $		
USA	10.93 (7.65-14.21)	Red Book
UK	4.04 (2.83-5.25)	[20]
China	2.06 (1.44-2.68)	Hong Kong list price
Computed tomography imaging, per cycle, $		
USA	448 (313.6-582.4)	[21]
UK	91.16 (63.81-118.51)	[20]
China	84.56 (59.19-109.93)	West China Hospital
Cost of managing adverse events, per event, $		
Diarrhoea		
USA	1183.7 (828.59-1538.81)	Red Book
UK	22.45 (15.72-29.19)	British National Formulary

(Continues)

TABLE 1 (Continued)

Parameter	Value (ranges)	Reference
China	12.79 (8.95-16.63)	West China Hospital
Palmar-plantar erythrodysesthesia		
USA	8.31 (5.82-10.80)	Local estimate
UK	13.41 (9.39-17.43)	Local estimate
China	3.57 (2.50-4.64)	Local estimate
Hypertension		
USA	2.39 (1.67-3.11)	Red Book
UK	0.92 (0.64-1.20)	British National Formulary
China	2.13 (1.49-2.80)	West China Hospital
Utilities		
HCC progression free	0.76 (0.532 to 0.988)	[27,28]
HCC progressed	0.68 (0.476 to 0.884)	[27,28]
Discount rate, %	3 (0-5)	[31]

TABLE 2 Cost-effectiveness results

Cabozantinib price	Incremental cost, $	Incremental benefits, QALYs	ICER, $/QALY	Comments
USA				
Full cost (Base case)	108 521	0.13	833 497	Not cost-effective
50% cost	55 535	0.13	426 532	Not cost-effective
30% cost	34 340	0.13	263 747	Not cost-effective
20% cost	23 742	0.13	182 354	Not cost-effective
15% cost	18 444	0.13	141 657	Cost-effective
10% cost	13 145	0.13	100 961	Cost-effective
UK				
Full cost (Base case)	39 604	0.13	304 177	Not cost-effective
50% cost	20 021	0.13	153 775	Not cost-effective
30% cost	12 188	0.13	93 613	Not cost-effective
20% cost	8272	0.13	63 533	Cost-effective
15% cost	6314	0.13	48 493	Cost-effective
10% cost	4355	0.13	33 452	Cost-effective
China				
Full cost (Base case)	20 368	0.13	156 437	Not cost-effective
50% cost	10 383	0.13	79 747	Not cost-effective
30% cost	6389	0.13	49 070	Not cost-effective
20% cost	4392	0.13	33 732	Not cost-effective
15% cost	3393	0.13	26 063	Cost-effective
10% cost	2395	0.13	18 394	Cost-effective

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

The CELESTIAL[7] study showed the highest increase in progression-free survival (3.3 months) and overall survival (2.2 months) vs placebo when compared with other second-line therapy options. As Kudo M mentioned,[37] the sample size of 470 patients in CELESTIAL was fairly larger than that of other second-line trials (379 patients in RESORCE,[38] 214 patients in CheckMate 040 expansion cohort[39]) and thus had power to detect small differences as significant. Cabozantinib as well as immunotherapy proved to have statistically

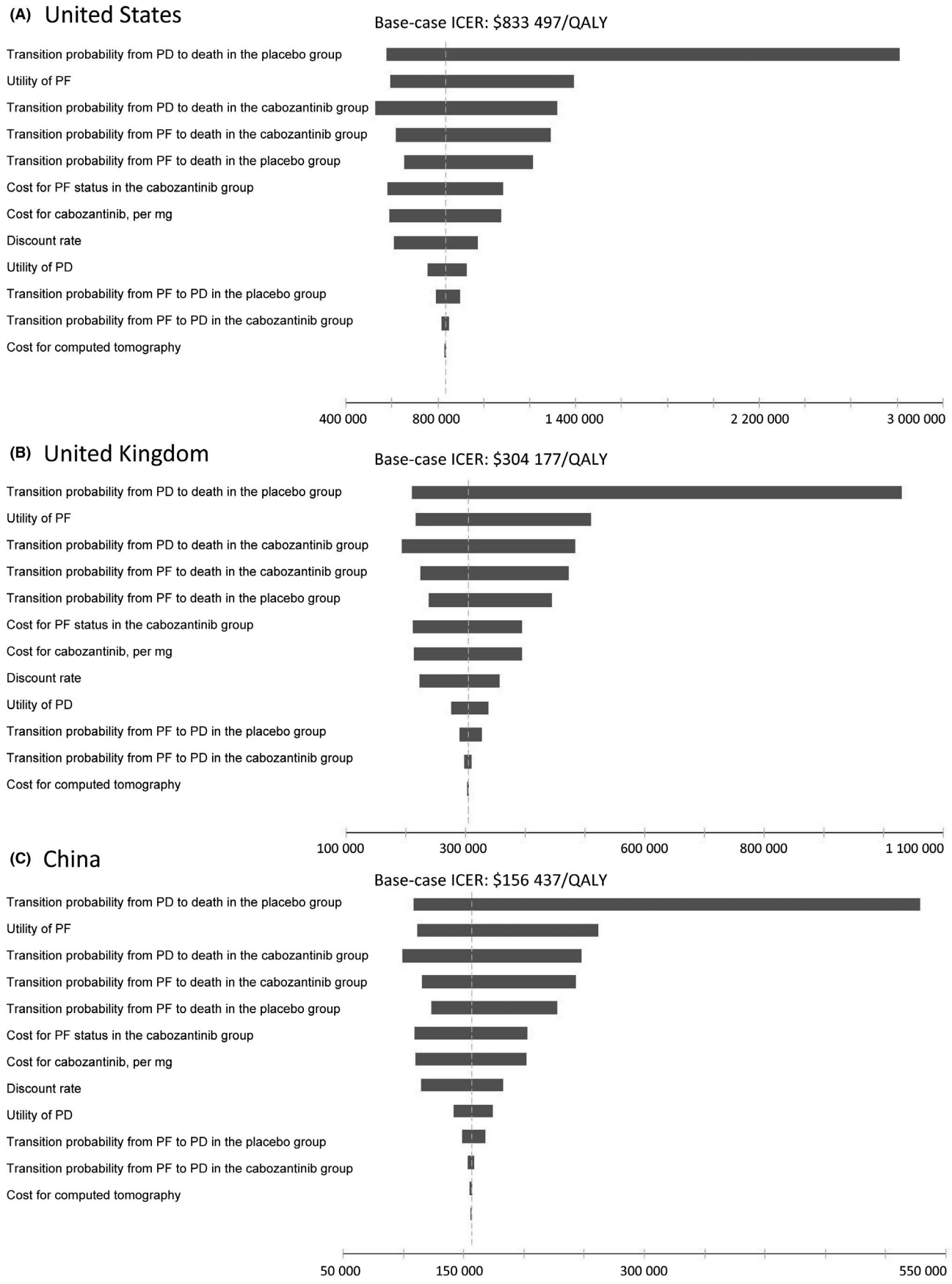

FIGURE 3 Tornado diagrams. The tornado diagrams show the one-way sensitivity analyses within the appropriate range for each variable in the setting of the USA, UK, or China respectively. PD, progression disease; PF, progression free

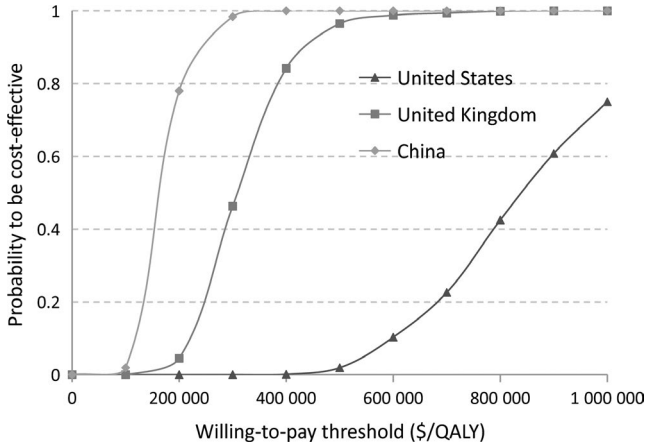

FIGURE 4 Cost-effectiveness acceptability curves. The curve indicates the probability (y-axis) when cabozantinib become cost-effective compared with best supportive care given the willing-to-pay threshold (x-axis)

significant improvements as second-line options. However, with a limited few months of survival benefit for treating advanced HCC, it is important to weigh the trade-offs between costs and clinical benefits for these promising therapies.

A previous cost-effectiveness analysis about cabozantinib in England for patients with advanced renal cell carcinoma after failure of prior therapy[20] showed that cabozantinib cost an average of 84 136 GBP per patient and offered 1.78 QALYs, resulting in an ICER of 98 967 and 137 450 GBP/QALY compared with axitinib and everolimus respectively. Compared with nivolumab, cabozantinib was less costly and more effective, with incremental cost of −6742 GBP and additional QALY of 0.18. However, the authors did not compare cabozantinib with best supportive care directly, instead using other expensive drugs as the control groups. If the price of the comparison is high, it may make cabozantinib appear more cost-effective. Furthermore, high-cost comparative medications may be inaccessible to large portions of the population and may not be realistic alternatives.

Over the past decades, direct evidence of clinical benefit regarding objective response rate, surrogate or combination endpoints was accepted for regulatory approval by FDA. The cost-effectiveness of a proposed treatment is not a legislative mandate in the USA. The FDA does not consider potential costs when making regulatory decisions on marketing applications.[40,41] Based on 30 drugs approved for cancer indications in 2015-2017, gaps persist as to their financial harm compared with the related clinical benefit, although they are being routinely applied in a large-scale fashion.[42] This scenario is not rare in oncology, especially for orphan drugs,[43] like cabozantinib. Use of the innovative drugs confirmed to be effective in randomized phase III clinical trials may lead to an inefficient use of resources, whereas rejection of these new innovative drugs may risk failing to offer access to a valuable intervention,[44] igniting an ethical problem. So even for those approved anti-cancer compounds, affordability is a pivotal factor determining their net value.

In the current healthcare reform environment, cost-effectiveness analysis focused on newly approved agents can help evaluate the overall balance between the clinical and economic repercussions. This study is another example of a remarkably effective cancer drug that will not be cost-effective unless the drug price is discounted significantly.[45,46] Financial toxicity of cancer medicine remains a well-recognized problem resulting in patient bankruptcy and even poor prognosis, whether in high-income countries or countries with public healthcare systems.[47] Drugs may appear more affordable in high-income countries (UK) than in the USA and middle-income countries (China).[48] Limited transparency and absent federal control over American drug prices have led to the highest drug costs worldwide.[49] On 11 May 2018, the US administration released American Patients First for the purpose of cutting drug prices and decreasing out-of-pocket payments.[50] In the UK, the National Institute for Health and Care Excellence legislate maximum pricing, as do Canada and other European countries.[51] Chinese state council issued the 13th 5-year plan in January 2017 for deepening medical and healthcare system reform, highlighting the important role of economic evaluation in multilateral negotiations.[52] Therefore, our findings are expected to inform policy regulators when making coverage decisions.

Our cost-effectiveness study has several limitations. Firstly, this model reflected patients' outcomes from the CELESTIAL trial, but patients eligible for randomized clinical trials are usually highly selected and may not be representative of real-world practice.[53] Secondly, we conducted our study according to official, published list prices and do not include discounts, which are often not reported. Lower prices might be achieved in subsequent reimbursement negotiations,[54] so we calculated the 50%-off, 70%-off, 80%-off, 85%-off, 90%-off price of cabozantinib mimicking possible scenarios of lower discounted prices. Thirdly, costs may vary from different sources and in different settings, so we used a wide range of ±30% of costs in sensitivity analysis and confirmed the cost-effectiveness results. Fourthly, patients who experience major toxicity could have a lower utility score than those who do not. Fifthly, we did not include the specific costs associated with complications related to cirrhosis in both the cabozantinib and best-supportive care arms, and thus may underestimate the total costs. Future prospective studies with more detailed data on complications of cirrhosis and causes of death may be valuable. Finally, it may be the case that a specific subsets of patients exists that have a more robust response to cabozantinib than what was seen in the CELESTIAL trial. If those patients exist and could be identified, the cost-effectiveness of cabozantinib could improve.

Cabozantinib treatment for sorafenib-resistant HCC yields high incremental costs and additional 0.13 QALYs. From the payer's perspective, we found an ICER of $833 497 per QALY in the USA, $304 177 per QALY in the UK and $156 437 per QALY in China. These are far higher than conventional cost-effectiveness thresholds at the current price. A significant price reduction is essential for cabozantinib to be financially viable for private payers.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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