PROF. QIU LI (Orcid ID : 0000-0002-5158-3838)

Article type : Original Articles

Editor : Helena Cortez-Pinto

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

Weiting Liao[1,2*], Jiaxing Huang[1,2*], David Hutton[3], Guiqi Zhu[4], Qiuji Wu[1,2], Feng Wen[1,2], Liangliang Bai[1,2], Qiu Li[1,2†]

1. Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu 610041 , China.

2. West China Biomedical Big Data Center, Sichuan University, Chengdu 610041, China

3. Department of Health Management and Policy, University of Michigan, Ann Arbor, Ann Arbor 48109, America

4. Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai 200032, China

*These authors contributed equally to the manuscript.

CORRESPONDING AUTHOR:

Dr Qiu Li†, Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, No. 37, GuoXue Xiang, Chengdu 610041, China. Tel: +86-28-85423262; Fax: +86-28-85423609; E-mail: fbqiu9@163.com

WORD COUNT: 3925

NUMBER OF FIGURES AND TABLES: 6

ABBREVIATIONS: Hepatocellular carcinoma, HCC; United States, US; United Kingdom, UK; Quality-adjusted life years; QALYs; Incremental cost-effectiveness ratio, ICER; Adverse events, AE; Average wholesale price, AWP; Willingness-to-pay, WTP; PFS, progression-free survival; OS, overall survival; Progression-free, PF; Progression disease, PD.

CONFLICT OF INTEREST: NONE

FINANCIAL SUPPORT: National Natural Science Foundation of China (General Program: 81572988) and Science & Technology Department of Sichuan Province Funding Project (No.2016FZ0108, 18ZDYF1981).

TRIAL REGISTRATION NUMBER: NO NEED FOR THIS MANUSCRIPT.

ACKNOWLEDGEMENT: NONE.

SUMMARY

From a payers' perspective, second-line cabozantinib at current price for

advanced HCC is more than the commonly accepted willingness-to-pay threshold in the US, UK, and China.

To be cost-effective, the price of cabozantinib would likely require a decrease of 80-85% in the US, UK, and China.

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 aim to investigate the cost-effectiveness of cabozantinib for sorafenib-resistant HCC from the payers' perspectives of the United States(US), United Kingdom (UK), and China.

METHODS: We developed Markov models to simulate the patients pretreated 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 were acquired from the Red Book, the British National Formulary, West China hospital and reported literatures. 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 US, $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 versus best supportive care of $833,497/QALY in the US, $304,177/QALY in the UK, and $156,437/QALY in China. The model was most sensitive to assumptions about transitions to progression with both cabozantinib and best supportive care, the utility associated with being progession-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 perspectives in the US, UK, or China. Substantial discounts are necessary to meet conventional cost-effectiveness thresholds.

KEYWORDS: Hepatocellular carcinoma; Cost-effective; Second-line therapy; Cabozantinib; Incremental cost-effectiveness ratio; Markov model

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 United States (US) and Europe.[3] Sorafenib was the first systemic regimen to be approved for patients with advanced HCC.[4] For those who have pretreated 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 3 CELESTIAL trial[7] has compared the efficacy of cabozantinib versus placebo

in the second-line setting. Median overall survival was 10.2 months in the cabozantinib group versus 8.0 months in the placebo group and median progression-free survival was 5.2 months in the cabozantinib group versus 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 diarrhea (10%). Cabozantinib was approved by the European Commission on November 15, 2018[8] and the US Food and Drug Administration on January 14, 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 perspectives in the US, United Kingdom (UK) and China.

METHODS

STUDY DESIGN

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

DECISION MODEL

A Markov model using TreeAge Pro 2011 (TreeAge Software, Williamstown, MA) was conducted to simulate patients with sorafenib-resistant HCC receiving either cabozantinib or best supportive care. Patients start progression-free status, then move 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 uses a one-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.

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 US,[21] $91 in the UK,[20] $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 5mg daily for hypertension, Eucerin cream for hand-foot syndrome, and atropine/diphenoxylate and loperamide for diarrhea.[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 for the utilities of 0.76 for progression-free and 0.68 for progression.[27, 28]

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 probability cabozantinib treatment would be cost-effective at various thresholds of willingness-to-pay (WTP) per QALY.

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 versus 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 US, $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 a table in the supplement.[36]

RESULTS

BASE-CASE

The base-case results are 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 US, $40,135 compared to $531 in the UK, $20,848 compared to $481 in China. The ICER of cabozantinib versus best supportive care was $833,497/QALY in the US, $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.

SENSITIVITY ANALYSES

All one-way sensitivity analyses are described in tornado diagrams. (Fig 3) Our cost-effectiveness model was 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 US, $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 US, $93,613 per QALY gained in the UK, $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. (Fig 4)

DISCUSSION

Our study is the first cost-effectiveness analysis of cabozantinib in sorafenib-resistant HCC. From a payers' perspective, second-line cabozantinib at current prices for advanced HCC is not cost-effective in the US, 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 US, UK, and China.

The CELESTIAL[7] study showed the highest increase in progression-free survival (3.3 months) and overall survival (2.2 months) versus 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 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 -6,742 GBP and additional QALY of 0.18. However, the authors didn't 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 were accepted for regulatory approval by FDA. The cost-effectiveness of a proposed treatment is not a legislative mandate in the United States. The FDA does not consider potential costs when making regulatory decisions on marketing applications.[40,41] Based on thirty 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 health-care 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 health care systems.[47] Drugs may appear more affordable in high-income countries (UK, etc.) than in the US and

middle-income countries (China,etc.).[48] Limited transparency and absent federal control over American drug prices has led to the highest drug costs worldwide.[49] On May 11, 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 health care 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 US, $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.

REFERENCE

1. Bosch FX, Ribes J, Díaz M, Cléries R. Primary liver cancer: worldwide incidence and trends. Gastroenterology 2004; 127(5 Suppl 1):S5-S16.
2. Sayiner M, Golabi P, Younossi ZM. Disease Burden of Hepatocellular Carcinoma: A Global Perspective. Dig Dis Sci 2019; 64(4):910-917.
3. West J, Wood H, Logan RF, Quinn M, Aithal GP. Trends in the incidence of primary liver and biliary tract cancers in England and Wales 1971-2001. Br J Cancer 2006; 94(11):1751-8.
4. Raoul JL, Kudo M, Finn RS, Edeline J, Reig M, Galle PR. Systemic therapy for intermediate and advanced hepatocellular carcinoma: Sorafenib and beyond. Cancer Treat Rev 2018; 68:16-24.
5. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017; 389(10064):56-66.
6. Yakes FM, Chen J, Tan J, et al. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Mol Cancer Ther 2011; 10(12):2298-308.
7. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med 2018; 379(1):54-63.
8. Ipsen Pharma. Cabometyx flm-coated tablets: EU summary of product characteristics. 2019. https://www.ema.europa.eu. Accessed 4 Feb 2019.
9. Exelixis Inc. Cabometyx® (cabozantinib) tablets for oral use: US prescribing information. 2019. https://cabometyx.com/resou rces. Accessed 15 Jan 2019.

10. Llovet JM, Decaens T, Raoul JL, et al. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. J Clin Oncol 2013; 31(28):3509-16.
11. Rimassa L, Assenat E, Peck-Radosavljevic M, et al. Tivantinib for second-line treatment of MET-high, advanced hepatocellular carcinoma (METIV-HCC): a final analysis of a phase 3, randomised, placebo-controlled study. Lancet Oncol 2018; 19(5):682-693.
12. Zhu AX, Kudo M, Assenat E, et al. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. JAMA 2014; 312(1):57-67.
13. Zhu AX, Park JO, Ryoo BY, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 2015; 16(7):859-70.
14. Kim JH, Kim BJ, Jang HJ, Lee J. Molecular targeted agents as second-line treatment for hepatocellular carcinoma: a meta-analysis and review. Oncotarget 2017; 8(60):102321-102327.
15. Kobayashi M, Kudo M, Izumi N, 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.
16. Shlomai A, Leshno M, Goldstein DA. Regorafenib treatment for patients with hepatocellular carcinoma who progressed on sorafenib-A cost-effectiveness analysis. PLoS One 2018; 13(11): e0207132.
17. Rognoni C, Ciani O, Sommariva S, Tarricone R. Real-World Data for the Evaluation of Transarterial Radioembolization versus Sorafenib in Hepatocellular Carcinoma: A Cost-Effectiveness Analysis. Value Health 2017; 20(3): 336-44.
18. Parikh ND, Singal AG, Hutton DW. Cost effectiveness of regorafenib as second-line therapy for patients with advanced hepatocellular carcinoma. Cancer 2017; 123(19):3725-3731.
19. [IBM. RED BOOK Online®/ Micromedex [database online]. 2018. http://www.micromedexsolutions.com. Accessed December 10, 2018.
20. Meng J, Lister J, Vataire AL, et al. Cost-effectiveness comparison of cabozantinib with everolimus, axitinib, and nivolumab in the treatment of

advanced renal cell carcinoma following the failure of prior therapy in England. Clinicoecon Outcomes Res 2018; 10:243-250.

21. Cadier B, Bulsei J, Nahon P, et al. Early detection and curative treatment of hepatocellular carcinoma: A cost-effectiveness analysis in France and in the United States. Hepatology 2017; 65(4):1237-1248.
22. Stafylas P, Kourlaba G, Hatzikou M, et al. Economic evaluation of a single-pill triple antihypertensive therapy with valsartan, amlodipine, and hydrochlorothiazide against its dual components. Cost Eff Resour Alloc 2015; 13:10.
23. British National Formulary. 2018. https://www.nice.org.uk/bnf-bnfc-uk-only. Accessed December 20, 2018.
24. Zhang P, Yang Y, Wen F, et al. Cost-effectiveness analysis of antiviral therapy in patients with advanced hepatitis B virus-related hepatocellular carcinoma treated with sorafenib. J Gastroenterol Hepatol 2016; 31(12):1978-1985.
25. Wu B, Zhang Q, Sun J. Cost-effectiveness of nivolumab plus ipilimumab as first-line therapy in advanced renal-cell carcinoma. J Immunother Cancer 2018; 6(1):124.
26. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001; 33(5):337-43.
27. Qin S, Kruger E, Tan SC, et al. Cost-effectiveness analysis of FOLFOX4 and sorafenib for the treatment of advanced hepatocellular carcinoma in China. Cost Eff Resour Alloc 2018; 16:29.
28. Leung HW, Liu CF, Chan AL. Cost-effectiveness of sorafenib versus SBRT for unresectable advanced hepatocellular carcinoma. Radiat Oncol 2016; 11:69.
29. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics 2000; 17(5):479-500.
30. Acevedo JR, Fero KE, Wilson B, et al. Cost-Effectiveness Analysis of Elective Neck Dissection in Patients With Clinically Node-Negative Oral Cavity Cancer. J Clin Oncol 2016; 34(32):3886-3891.
31. Drummond M, Sculpher MJ, Torrance GW et al. (2005) Methods for the economic evaluation of health care programmes, 3rd edn. Oxford University Press, Oxford.
32. Gold MR, Russell LB, Seigel JE, Weinstein MC. (1996) Cost-effectiveness in health and medicine. Oxford University Press, New York.

33. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness-the curious resilience of the $50,000-per-QALY threshold. N Engl J Med 2014; 371(9):796-7.
34. Bertranou E, Bodnar C, Dansk V. Cost-effectiveness of osimertinib in the UK for advanced EGFR-T790M non-small cell lung cancer. J Med Econ 2018; 21(2):113-121.
35. Liao W, Huang J, Hutton D, Li Q. Cost-effectiveness analysis of first-line pembrolizumab treatment for PD-L1 positive, non-small cell lung cancer in China. J Med Econ 2019; 22(4):344-349.
36. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ (Clinical research ed.), 2013. 346: p. f1049.
37. Kudo M. Cabozantinib as a Second-Line Agent in Advanced Hepatocellular Carcinoma. Liver Cancer, 2018. 7(2): p. 123-133.
38. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet (London, England), 2017. 389(10064): p. 56-66.
39. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet (London, England), 2017. 389(10088): p. 2492-2502.
40. Niraula S, Nugent Z. New Cancer Drug Approvals From the Perspective of a Universal Healthcare System: Analyses of the Pan-Canadian Oncology Drug Review Recommendations. J Natl Compr Canc Netw, 2018. 16(12): p. 1460-1466.
41. McKee AE, Farrell AT, Pazdur R, Woodcock J. The role of the U.S. Food and Drug Administration review process: clinical trial endpoints in oncology. The oncologist, 2010. 15(Suppl 1): p. 13-8.
42. Oren O. Cost-Effectiveness Analyses of FDA-Approved Drugs for Cancer Indications, 2015-2017. Blood, 2018. 132(Suppl 1): p. 5833-5833.
43. Vivot A, Jacot J, Zeitoun JD, Ravaud P, Crequit P, Porcher R. Clinical benefit, price and approval characteristics of FDA-approved new drugs for treating advanced solid cancer, 2000-2015. Annals of oncology : official

journal of the European Society for Medical Oncology, 2017. 28(5): p. 1111-1116.

44. McKenna C, Soares M, Claxton K, et al. Unifying Research and Reimbursement Decisions: Case Studies Demonstrating the Sequence of Assessment and Judgments Required. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research, 2015. 18(6): p. 865-75
45. Mamiya H, Tahara RK, Tolaney SM, Choudhry NK, Najafzadeh M. Cost-effectiveness of palbociclib in hormone receptor-positive advanced breast cancer. Ann Oncol 2017; 28(8):1825-1831.
46. Wolford JE, Bai J, Eskander RH, et al. Evaluating the cost-effectiveness of current FDA-approved PARP inhibitors for the treatment of recurrent ovarian cancer. Journal of Clinical Oncology, 2017. 35(15_suppl): p. 5516-5516.
47. Gyawali B. Low-value practices in oncology contributing to financial toxicity. Ecancermedicalscience, 2017. 11: p. 727
48. Goldstein DA, Clark J, Tu Y, et al. A global comparison of the cost of patented cancer drugs in relation to global differences in wealth. Oncotarget 2017; 8(42):71548-71555.
49. Prasad V, De Jesús K, Mailankody S. The high price of anticancer drugs: origins, implications, barriers, solutions. Nat Rev Clin Oncol 2017; 14(6):381-390.
50. Burki TK. A new strategy to reduce US drug prices. Lancet Oncol 2018; pii: S1470-2045(18)30374-7.
51. Goldstein DA, Sarfaty M. Cancer Drug Pricing and Reimbursement: Lessons for the United States From Around the World. Oncologist 2016; 21(8):907-9.
52. Wan XM, Peng LB, Ma JA, Li YJ. Economic evaluation of nivolumab as a second-line treatment for advanced renal cell carcinoma from US and Chinese perspectives. Cancer 2017; 123(14):2634-2641.
53. What's cost-effective in cancer care? Cancer Discov 2011; 1(6):Of1-2.
54. Vogler S, Vitry A, Babar ZU. Cancer drugs in 16 European countries, Australia, and New Zealand: a cross-country price comparison study. Lancet Oncol 2016; 17(1):39-47.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

FUNDING

National Natural Science Foundation of China (General Program: 81572988) and Science & Technology Department of Sichuan Province Funding Project (No.2016FZ0108, 18ZDYF1981).

FIGURE LEGENDS

Table 1. Input parameters and ranges.

Table 2. Cost-effectiveness results.

Fig 1. Model structure.

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

Fig 3.Tornado diagrams.

The tornado diagrams show the one-way sensitivity analyses within the appropriate range for each variable. PF, progression-free; PD, progression disease.

Fig 4. Probabilistic sensitivity analysis.

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).

SUPPLEMENTARY MATERIAL

Supplementary table. CHEERS checklist.

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		
Diarrhea	0.10 (0.07-0.13)	[7]
Decreased appetite	0.06 (0.042-0.078)	[7]
Palmar–plantarerythrodysesthesia	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		
Diarrhea	0.02 (0.01-0.03)	[7]
Decreased appetite	<0.01 (0-0.01)	[7]
Palmar–plantarerythrodysesthesia	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, $		
United States	10.93 (7.65-14.21)	Red Book
United Kingdom	4.04 (2.83-5.25)	[20]
China	2.06 (1.44-2.68)	Hong Kong list price
Computed tomography imaging, per cycle, $		
United States	448 (313.6-582.4)	[21]
United Kingdom	91.16 (63.81-118.51)	[20]
China	84.56 (59.19-109.93)	West China Hospital
Cost of managing adverse events, per event, $		
Diarrhea		
United States	1183.7 (828.59-1538.81)	Red Book
United Kingdom	22.45 (15.72-29.19)	British National Formulary
China	12.79 (8.95-16.63)	West China Hospital
Palmar-plantarerythrodysesthesia		
United States	8.31 (5.82-10.80）	Local estimate
United Kingdom	13.41 (9.39-17.43)	Local estimate
China	3.57 (2.50-4.64)	Local estimate
Hypertension		
United States	2.39 (1.67-3.11）	Red Book
United Kingdom	0.92 (0.64-1.20)	British National Formulary
China	2.13 (1.49-2.80)	West China Hospital

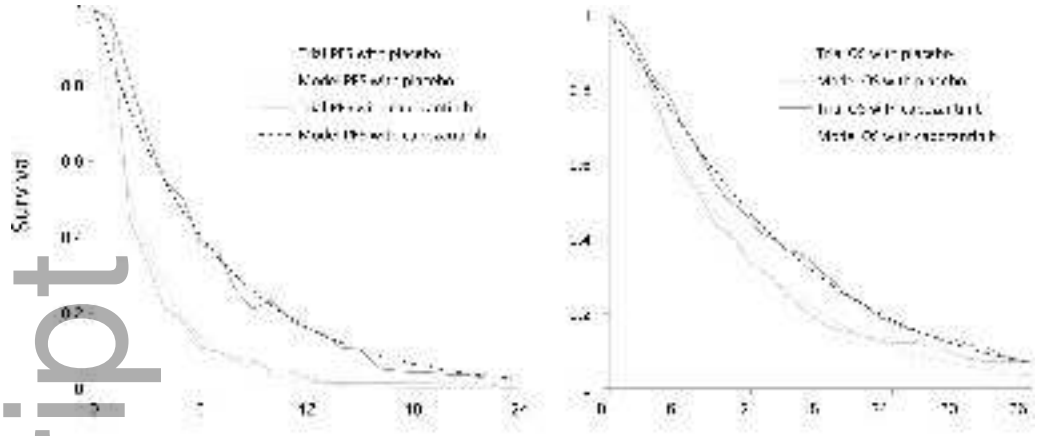
Utilities		
HCC progression free	0.76 (0.532 to 0.988)	[27,28]
HCC progressed	0.68 (0.476 to 0.884)	[27,28]
Discount rate, %	3 (0-5)	[31]

Table 2. Cost-effectiveness results.

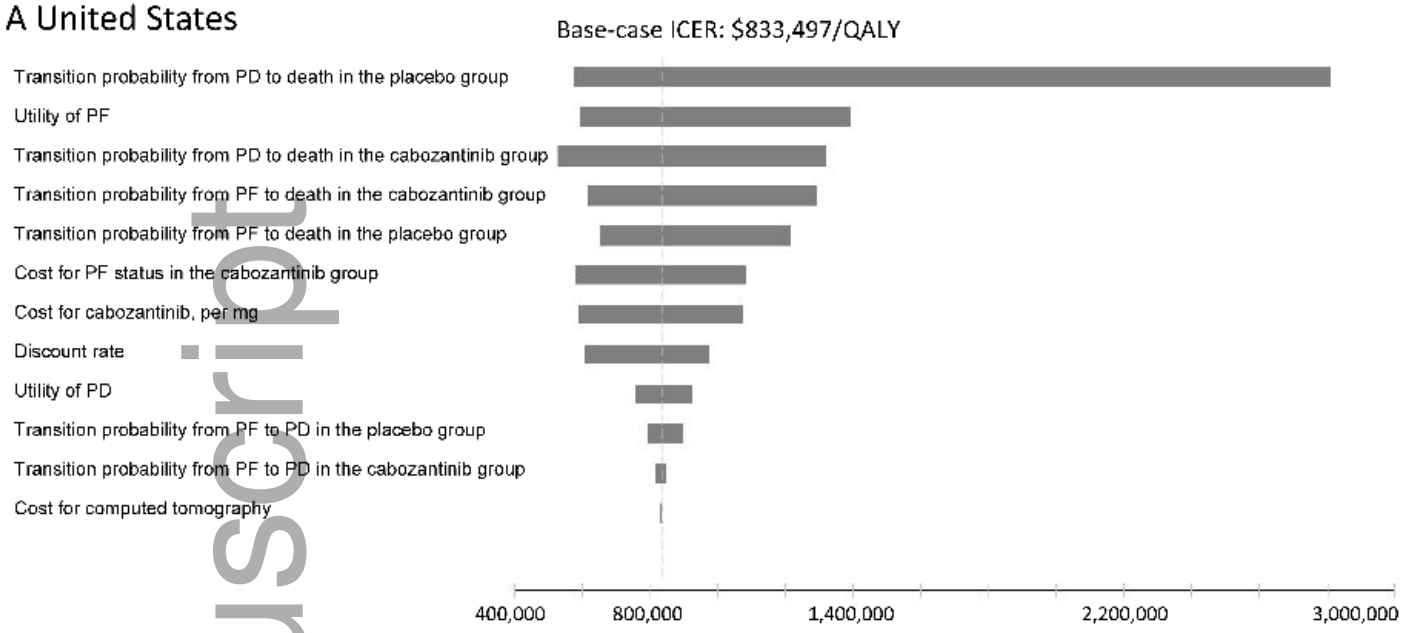
Cabozantinib price	Incremental Cost, $	Increnmental Benefits, QALYs	ICER, $/QALY	Comments
United States				
Full cost (Base-case)	108,521	0.13	833,497	Not cost-effective
50% cost	55,535	0.13	426,532	Not cost-effective
30% cost	34,340	0.13	263,747	Not cost-effective
20% cost	23,742	0.13	182,354	Not cost-effective
15% cost	18,444	0.13	141,657	Cost-effective
10% cost	13,145	0.13	100,961	Cost-effective
United Kingdom				
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

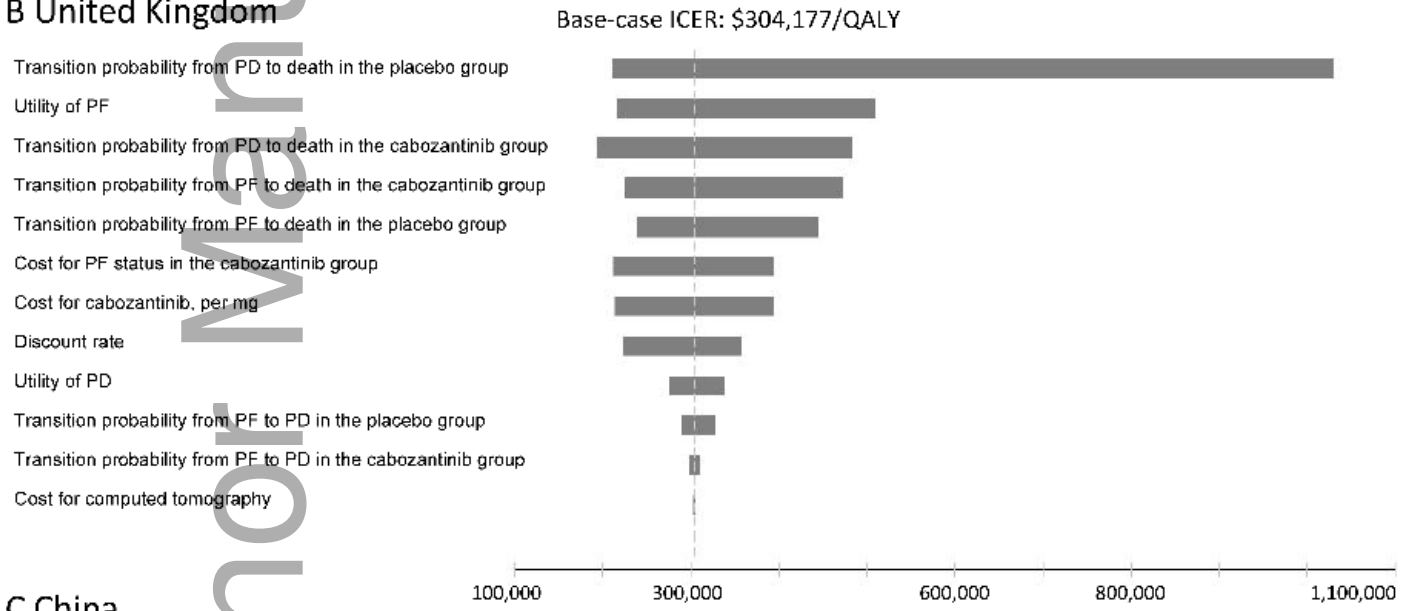
QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

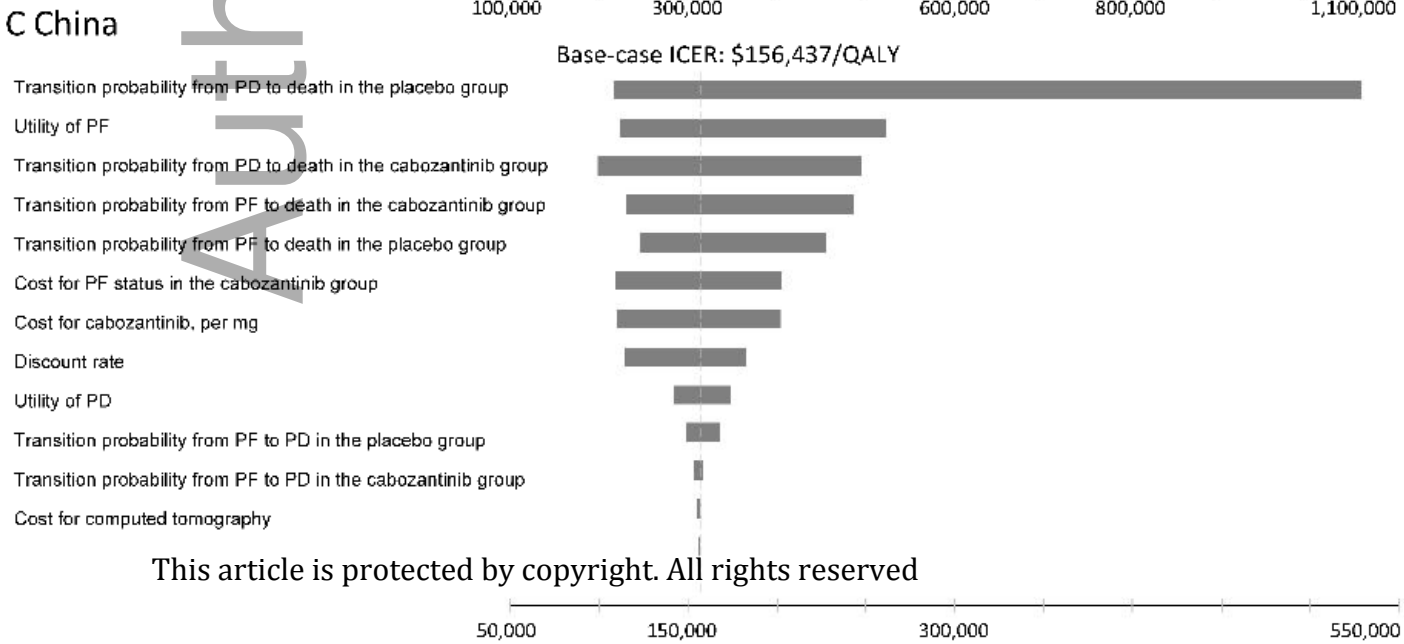
liv_14257_f1.tif

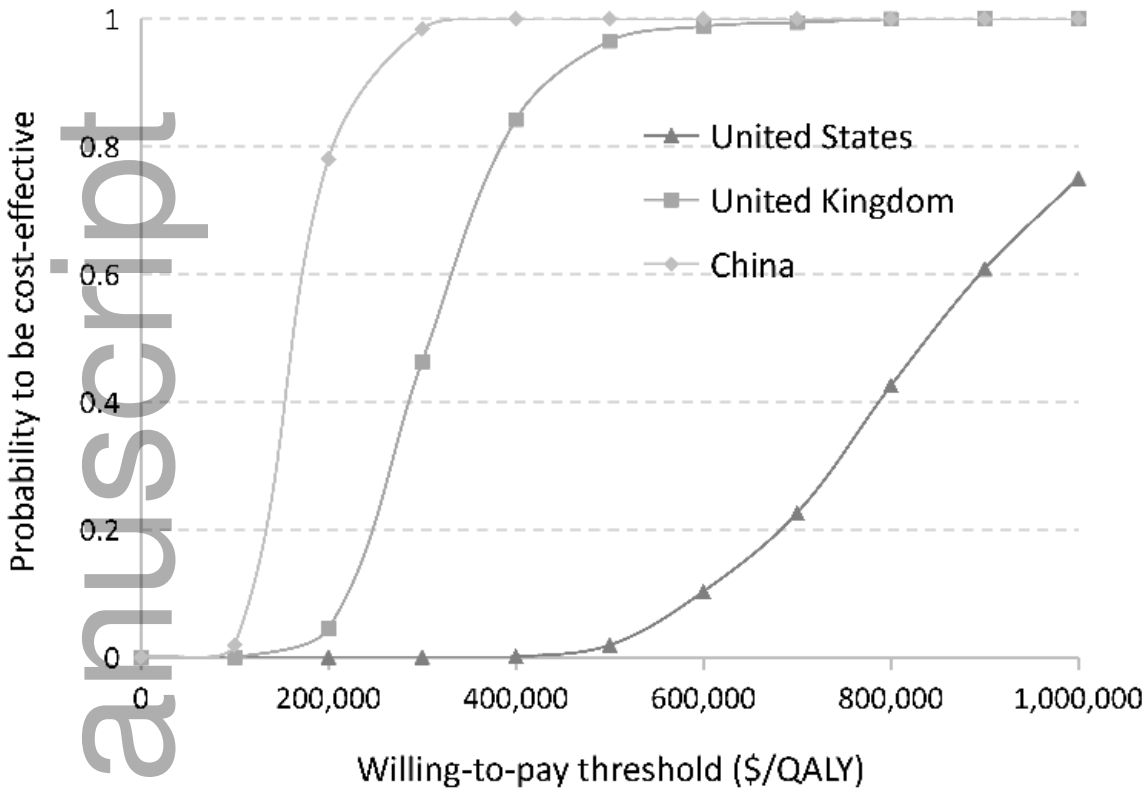


liv_14257_f2.tif









liv_14257_f4.tif