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LETTER TO THE EDITOR

Atezolizumab plus bevacizumab versus sorafenib as first-line treatment for unresectable hepatocellular carcinoma: a cost-effectiveness analysis

Dear Editor,

Liver cancer is the third leading cause of cancer deaths worldwide and accounted for 8.9% of all neoplasms, as shown by the Global Burden of Disease Study 2017 [1]. Hepatocellular carcinoma (HCC) comprises 75%-85% of liver cancers [2]. The abysmal statistic is partly contributed by the fact that only 30%-40% of all patients are diagnosed at early stages that are amenable to potentially curative treatments [3]. For over a decade, the availability of new agents, such as lenvatinib- and sorafenib-based targeted therapy, has significantly improved the outcome of patients with advanced HCC, prolonging the median overall survival (OS) from 4-8 months to 10-15 months [4, 5]. However, the therapeutic options for advanced HCC are still limited, and the prognosis is poor.

The IMbrave150 study demonstrated the efficacy and safety of atezolizumab plus bevacizumab versus sorafenib in advanced metastatic or unresectable HCC [6]. The results indicated that atezolizumab plus bevacizumab achieved notably favorable progression-free survival (PFS) and OS compared with sorafenib. The rate of grade 3 or higher adverse events (AEs) was comparable between the atezolizumab plus bevacizumab group and the sorafenib group (56.5% vs. 55.1%). Thus, the combination of atezolizumab and bevacizumab seemed to be an attractive alternative first-line treatment for advanced HCC. However, considering cost-effectiveness is crucial in medical decisions for physicians and policy decision-makers to reasonably allocate limited health resources. To reduce the price of medicines, the Chinese government adopted a process of centralized strategic price negotiation with pharmaceutical companies underpinned by health technology assessment evidence [7]. Herein, by adopting an economic modeling approach (Supplementary Materials and Methods), we report the cost-effectiveness of atezolizumab plus bevacizumab as first-line therapy for advanced HCC from the Chinese health sector perspective.

In the base-case analysis, atezolizumab plus bevacizumab treatment gained a marginal 0.811 quality-adjusted life-year (QALY) and 1.297 overall life years with an augmented cost of $49,994 as compared with sorafenib, which led to an ICER of $61,613/QALY. The incremental net health benefit (INHB) and incremental monetary benefit (INMB) were -0.810 QALY and $-24,980 at the threshold of $30,828/QALY (three times the per capita gross domestic product of China in 2019) (Table 1).

By varying the HRs of OS, the subgroup analysis showed that atezolizumab plus bevacizumab demonstrated a trend of achieving negative INHBs and less than 50% probability of being cost-effective in all subgroups at the threshold of $30,828/QALY, except in female patients (Supplementary Figure S3). The INHBs in the subgroups varied from -1.66 (range: -2.10 to 0.18; probability of being cost-effective: 8.0%) in patients with Barcelona Clinic liver cancer stage B to 0.08 (range: -1.31 to 1.46; probability of being cost-effective: 52.7%) in female patients. The subgroup analysis by varying the HRs of PFS showed that atezolizumab plus bevacizumab had a 0% probability of being cost-effectiveness in all subgroups (Supplementary Figure S4).

The model outputs were sensitive to the following parameters: body weight, the costs of atezolizumab and bevacizumab, and the HR of OS between atezolizumab plus bevacizumab and sorafenib. The remainder sensitive variables, such as the cost and utility related to AEs, had moderate or minor impacts (Supplementary Figure S5). However, no parameter adjustments could lead to an ICER lower than $30,828/QALY. The cost-effectiveness acceptability curve showed a nearly 0.1% probability of atezolizumab plus bevacizumab and 99.9% probability of sorafenib being a cost-effective strategy at the threshold of

Abbreviations: AE, adverse event; CI, confidence interval; HCC, Hepatocellular carcinoma; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; INMB, incremental monetary benefit; LY, life-year; OS, overall survival; PD, progressed disease; PFD, progression-free disease; PFS, progression-free survival; WTP, willingness-to-pay; QALY, quality-adjusted life-year

TABLE 1 Health and monetary benefits of atezolizumab plus bevacizumab over sorafenib as first-line treatment for unresectable hepatocellular carcinoma in base-case analysis

Strategy	Cost ($)	Progression-free LYs	Overall LYs	QALYs	ICER ($/QALY)*	INHB (QALY)*	INMB ($/)*
Sorafenib	15,178	0.548	1.736	1.173	NA	NA	NA
Atezolizumab plus bevacizumab	65,172	0.938	3.033	1.984	61,613	−0.810	−24,980

*Comparing with sorafenib strategy.

Abbreviations: NA, not applicable; LY, life-year; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; INMB, incremental monetary benefit.

$30,828 per additional QALY gained (Supplementary Figure S6 and S7).

While oncologists and patients were interested in the clinical benefit of atezolizumab plus bevacizumab in the IMbrave150 trial [6] owing to the high mortality of advanced HCC, the high prices of these anticancer agents can be a barrier in clinical practice. Health policymakers and payers should assess the health value of the agent to ensure that patients can access the drug and that the drug is sustainable for both national healthcare and reimbursement systems as well as pharmaceutical companies [8]. This study addressed the emergent need for a health-economic evaluation of atezolizumab plus bevacizumab. Based on the results of the IMbrave150 trial [6], our analysis demonstrated that atezolizumab plus bevacizumab for advanced HCC was unfavorable when the willingness-to-pay threshold was lower than $30,828/QALY. This result is generally robust as shown by the one-way probabilistic sensitivity analyses. At a threshold of $30,828/QALY, most of the subgroups were not favored to atezolizumab plus bevacizumab because of its trend of gaining negative incremental net health benefits compared to sorafenib. The ability of atezolizumab plus bevacizumab to prevent disease-related death was the main impact factor on model outcomes. One-way sensitivity analyses showed that the HR for OS was the most sensitive parameter, suggesting that the atezolizumab plus bevacizumab regimen might be more attractive in patients with a favorable prognosis, such as female patients and those with HCC caused by hepatitis B or C infection, than in those with a poor prognosis. However, in those with poor prognoses, such as the patients with Barcelona Clinic stage B liver cancer and those with non-viral HCC, atezolizumab plus bevacizumab treatment might not be cost-effective. The costs of bevacizumab, sorafenib, and atezolizumab were also found to be important influential factors on model outcomes. When the cost of either bevacizumab or atezolizumab decreased, the ICER of atezolizumab plus bevacizumab over sorafenib would be improved.

PD-1 blockade alone or in combination with other regimens is becoming popular in advanced HCC [9]. However, the economic data of immune checkpoint inhibitors for advanced HCC are in dearth. The present study simultaneously evaluated the economic outcomes of atezolizumab plus bevacizumab treatment for unresectable HCC by synthesizing the latest data through an economic modeling approach. In addition, we examined the economic data of 22 subgroups prespecified by the IMbrave150 study [6], which could be helpful to tailor a decision for physicians, patients, and policymakers.

The main weakness is that we did not include other agents as the first-line treatment, such as pembrolizumab and nivolumab, which have shown favorable health benefits in patients with advanced HCC in the second-line setting [9]. Another limitation is that health outcomes beyond the follow-up time in the IMbrave150 trial [6] were fitted to the reported PFS and OS data by using the parametric distributions, which might lead to uncertainty in the final results although the predicted and observed data were well matched.

In conclusion, our findings suggest that atezolizumab plus bevacizumab is unlikely to be a cost-effective first-line option for Chinese patients with unresectable HCC. The economic outcomes could be improved by tailoring the treatment based on individual patient factors, such as sex. The cost of atezolizumab plus bevacizumab should be reduced by more than 50% for achieving an economic benefit.

DISCLAIMER

DECLARATION OF PERSONAL INTERESTS

None of the authors have any conflict of interest to declare.

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AUTHORS' CONTRIBUTIONS

YL and BW were involved in the design of the study, collected the data, and performed the economic analysis. BW wrote the first draft of the manuscript, which was critically revised by YL.

DATA SHARING STATEMENT

No additional data are available.

ETHICS APPROVAL

This study was based on a literature review and modelling techniques; this study did not require approval by an institutional research ethics board.

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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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