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Editorial

# The Position of Multikinase Inhibitors in the Era of Immune-Checkpoint Inhibitors for Hepatocellular Carcinoma

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**See "Sorafenib for 9,923 Patients with Hepatocellular Carcinoma: An Analysis from National Health Insurance Claim Data in South Korea" by Sojung Han, et al. on page 116, Vol. 18, No. 1, 2024**

Hepatocellular carcinoma (HCC) ranks as the sixth most prevalent cancer globally and is the fourth leading cause of cancer-related mortality. Initially, for approximately a decade, sorafenib, an established multikinase inhibitor, stood as the sole standard therapy demonstrating a proven survival benefit over a placebo in the first-line treatment of advanced-stage HCC. However, the emergence of a novel regimen i.e. lenvatinib as another type of multikinase inhibitor, provided an alternative first-line option compared to sorafenib.[1] And then, the introduction of immune-checkpoint inhibitors in the first-line setting for advanced-stage HCC has clearly become the breakthrough in the treatment landscape. The pivotal IMBrave150 trial was the first study to reveal that combining immune-checkpoint inhibitor and anti-vascular endothelial growth factor monoclonal antibodies, specifically atezolizumab plus bevacizumab regimen (Ate/Bev), resulted in an unprecedentedly high objective response rate (29.8% vs 11.3%) and overall survival (19.2 months vs 13.4 months) compared to sorafenib.[2-4] Hence, presently, international guidelines recommend Ate/Bev regimen as a 1st-line option.[2-4] This paradigm shift has prompted a re-evaluation of the position of multikinase inhibitors like sorafenib in managing advanced-stage HCC.[1,4]

In this issue of *Gut and liver*, Han *et al.*[5] performed a comprehensive analysis of real-life data, titled "Sorafenib for 9,923 patients with hepatocellular carcinoma: an analysis from National Health Insurance Claim Data in South Korea," which revealed that the treatment efficacies of sorafenib aligns with the outcomes observed in previous clinical trials. Their findings also suggest that employing appropriate subsequent therapies after sorafenib should potentially extend patient survival. This retrospective cohort study included all patients receiving sorafenib between July 1, 2008, and December 31, 2014, in the Republic of Korea. Notably, this study is unique as it is the first and only one which demonstrated real-world practices with sorafenib in HCC patients based on so called "big data" from the Korean National Health Insurance, covering around 99% of the population in the Republic of Korea. In particular, the choice of post-sorafenib treatment is crucial for determining patient survival. In one Italian study,[6] post-sorafenib survival was independently affected by performance status, prothrombin time, extrahepatic tumor spread, macrovascular invasion, and the reason for discontinuation. So, assuming preserved liver function and acceptable performance status, subsequent treatments following sorafenib could enhance patient survival. In line with this notion, the median overall survival for patients (n=2,591) undergoing post-sorafenib treatment was 14.5 months, significantly longer compared to the 4.6 months observed in patients (n=7,332) receiving only supportive care in the study by Han *et al.*[5] Remarkably, the longest median overall survival of 22.8 months was noted in 90 patients undergoing transarterial chemoembolization, followed by radiation therapy and even subsequent conventional cytotoxic chemotherapy. These results are particularly noteworthy, given that regorafenib, a treatment option with proven survival benefits in the context of progression after sorafenib, was not available in the Republic of Korea during the study period

from July 2008 to December 2014. Overall, these findings underscore the importance of establishing robust subsequent treatments for eligible patients, taking into consideration their performance status and liver function.

However, with the recommendation of Ate/Bev regimen as the first-line treatment for advanced-stage HCC, there exists a knowledge gap concerning the selection of a second-line regimen following disease progression.[7] This gap arises due to a lack of high-level evidence guiding the optimal choice and sequence of management. Up to the present time, most trials demonstrating positive results for second-line regimens have been conducted in the post-sorafenib setting. This is primarily because sorafenib remained the sole option and the "standard of care" for approximately a decade. As more than half of patients treated with Ate/Bev regimen unfortunately experience disease progression during their final disease course, the need for subsequent studies to identify second-line regimens in the near future should be underscored.

Considering the current landscape of immune-checkpoint inhibitors for advanced-stage HCC, it is imperative to reassess the position of multikinase inhibitors like sorafenib or lenvatinib.[8] Firstly, Yoo *et al.*[9] conducted a multinational, multicenter retrospective cohort study to examine the clinical outcomes of multikinase inhibitors as a second-line regimen following progression on Ate/Bev regimen. Among 49 patients in the study, 59.2% utilized sorafenib, 38.8% used lenvatinib, and 1% used cabozantinib as subsequent therapy. The results showed a median progression-free survival of 3.4 months (95% confidence interval, 1.8 to 4.9) and an overall survival of 14.7 months (95% confidence interval, 8.1 to 21.2). Secondly, the combination of multikinase inhibitors with immune-checkpoint inhibitors emerges as a potential option. In a study with a limited sample size, the use of nivolumab plus sorafenib demonstrated improved overall survival compared to sorafenib alone.[10] Likewise, there had been similar kinds of clinical trials based upon lenvatinib.[1] To determine optimal solutions for advanced-stage HCC, it is also essential to assess the efficacy and safety of various combinations based upon multikinase inhibitors plus immune-checkpoint inhibitors.

In conclusion, there is a crucial need to reassess the position of multikinase inhibitors in the context of managing advanced-stage HCC in the era of immune-checkpoint inhibitors. Given the current lack of a well-established second-line regimen following disease progression on Ate/Bev regimen, the utilization of multikinase inhibitors, either alone or in combination with other modalities such as immune-checkpoint inhibitors or loco-regional treatments, holds promise for potentially extending both patient survival and improving their quality of life.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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