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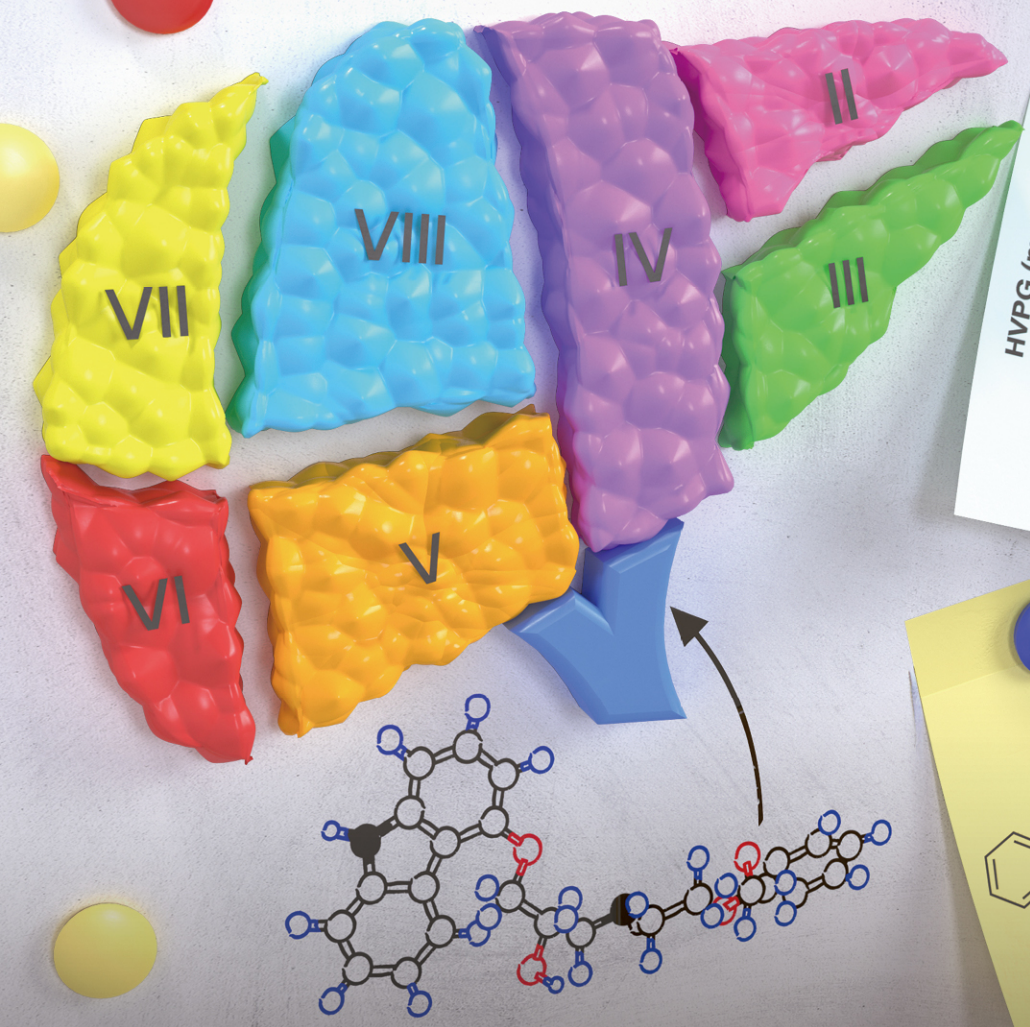

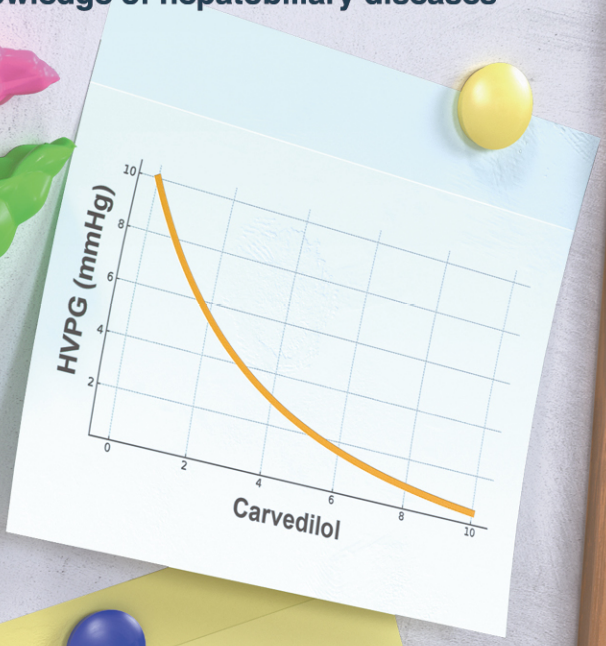

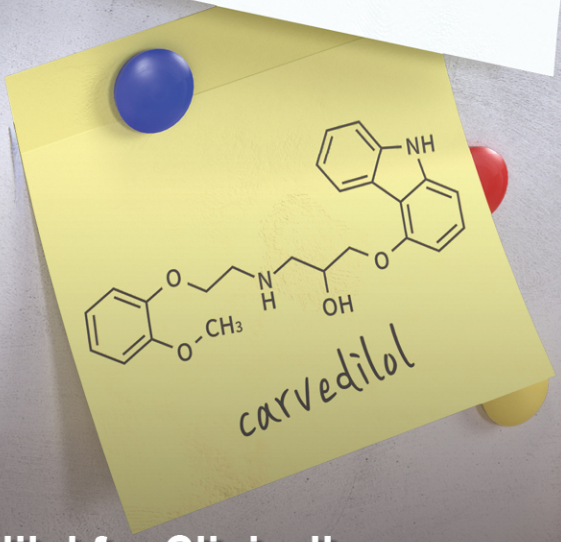

Non-invasive Model guiding Carvedilol for Clinically Significant Portal HTN

Intrapatient variability of tacrolimus on CKD in LT
HCV self-testing and disease burden reduction
MASLD and microbiota
Bariatric surgery for metabolic cirrhosis

KASL

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Correspondence

Correspondence to letter to the editor on "Sorafenib vs. lenvatinib in advanced hepatocellular carcinoma after atezolizumab/bevacizumab failure: a real-world study"

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Keywords: Sorafenib; Lenvatinib; Hepatocellular carcinoma

Dear Editor,

We are so grateful to receive the interesting letter from Professor Yi-Sheng Jhang on our publication.[1] We would like to discuss in depth the three points that Professor Jhang pointed out.

First, we agree with the idea that it needs to be explored whether different types of tyrosine kinase inhibitors (TKIs) have different treatment effects in hepatocellular carcinoma (HCC) patients with macrovascular invasion (MVI) with various grades or extrahepatic metastasis (EHM) with different sites. Of note, in the REFLECT (a randomized phase 3) trial comparing the efficacy of lenvatinib to sorafenib, patients with ≥50% liver occupation or tumor invasion of main portal vein were excluded.[2] However, later studies proved that lenvatinib was also effective in patients having the opposite traits of large tumor burden.[3] In our study, among 58 patients with MVI at the start of 2nd line treatment (lenvatinib 17 [52.1%], and sorafenib 41 [47.7%])[4] 36 patients had tumor invasion in main portal vein invasion (Vp4 invasion presence; lenvatinib 10 [25%], and sorafenib 26 [30.2%], $P>0.05$).[4] However, MVI invasion presence in our study was not associated with the survival outcome as documented on Table 4. The *P*-values were 0.33 for overall survival (OS) and 0.59 for progression-free survival (PFS). In contrast, Vp4 influenced OS significantly (*P*-value: 0.02) but had no significant impact on PFS (*P*-value: 0.27). As for EHM, the sites of metastases (lung, bone, peritoneum, or

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others) influenced PFS significantly (*P*-value: 0.04) but had no significant impact on OS (*P*-value: 0.04). Although these factors merit consideration due to their potential impact on survival outcomes, our cohorts demonstrated no statistically significant difference in these factors between the lenvatinib and sorafenib groups, both before and after propensity score matching (PSM). Future research is necessitated to determine which TKI to use, or to provide the personalized treatment (i.e., combination with other treatment modalities such as radiation) for each patient depending on the degree of MVI and EHM distribution at the start of 2nd line treatment.

Second, we fully understand the weakness of propensity score matching. To conduct this study, we went through countless steps together with a professional statistician to secure an appropriate number of matched cohorts while adjusting important covariates comparing more than 40 pairs of matched cohorts. Therefore, future studies with enlarged patient numbers are anticipated to expect the better matched PS cohort. However, we do not think that the number of previous atezolizumab plus bevacizumab (ATE+BEV) treatment cycles at the current time point have affected the survival outcomes, as we performed several subgroup analyses on the survival outcomes according to the number of treatment cycles (≤3 vs. >3, ≤2 vs. >2, ≤6 vs. >6) in both lenvatinib and sorafenib groups and found out that any of the classifications did not differentiate the outcomes. However, research about predicting the durability of ATE+BEV and the resistance to ATE+BEV should be continuously explored to optimize the subsequent treatment plan.

Lastly, various blood- and tissue- based biomarkers are under active investigation in patients with advanced HCC undergoing ATE+BEV treatment.[5] Based on molecular profiling, determining whether lenvatinib or sorafenib is more beneficial after ATE+BEV failure in advanced HCC depends on the molecular characteristics of the tumor. Lenvatinib inhibits VEGFR1–3, PDGFR, FGFR1–4, and RET, while sorafenib targets VEGFR1–3, PDGFR, RAF kinase, and the KIT receptor.[6] Importantly, lenvatinib is the only agent of the two that inhibits FGFR1–4, which may make it a more suitable option for patients whose tumor profiling reveals alterations in the FGFR pathway. This provides a rationale for considering lenvatinib in cases where FGFR signaling plays a role in tumor growth and progression. However, identifying these molecular characteristics requires tissue sampling, which was not feasible in all cases in our study. Despite this limitation, molecular profiling remains an important factor for guiding personalized treatment decisions in the future. Blood-based blood markers include alpha-feto protein, protein induced by vitamin K antagonist-II (PIVKA-II), C-reactive protein, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio, prognostic nutritional index, serum IL-6, or PD-1 expressions on granulocytes. Tissue-based blood markers include PD-L1 expression, immune cell infiltrations, and ATE-BEV response signature within tumor tissues. We have already published the predictive role of NLR and IL-6 in for the prognosis of patients receiving ATE+BEV treatment.[2,7] Baseline high PIVKA-II and NLR were prognostic for overall survival and progression free survival,[7] whereas high baseline IL-6 levels was associated with poor clinical outcomes and impaired T-cell function in patients with HCC during ATE+BEV treatment.[2] Finding biomarkers in patients receiving ATE+BEV (immunotherapy based) treatments will help navigating the 2nd or higher line-customized treatment for individual patients with HCC.

Authors' contributions

Young Eun Chon, Dong Yun Kim: drafting of the manuscript.

Hong Jae Chon, Do Young Kim: critical review and final approval of the manuscript.

Conflicts of Interest

The authors have no conflicts to disclose.

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Abbreviations:

ATE+BEV, atezolizumab plus bevacizumab; EHM, extrahepatic metastasis; HCC, hepatocellular carcinoma; MVI, macrovascular invasion; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PFS, progression-free survival; PIVKA-II, protein induced by vitamin K antagonist-II; PSM, propensity score matching; TKI, tyrosine kinase inhibitor

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