In Reply: Neoadjuvant TKI Study in Early- and Intermediate Stage Hepatocellular Carcinoma

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Letter to the Editor

In Reply: Neoadjuvant TKI Study in Early- and Intermediate Stage Hepatocellular Carcinoma

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We appreciate the letter by Rizzo et al,[1] in which they acknowledged the important pharmacodynamic information obtained from our neoadjuvant phase II study of dovitinib prior to local/locoregional therapy in early- and intermediate-stage hepatocellular carcinoma (HCC).[2]

Although we agree that the observed rate of clinical benefit needs to be confirmed in a larger cohort, the safety of this novel treatment approach in an often frail patient population with limited cirrhotic liver metabolic capacity was a concern to us.[3] We therefore designed a study with limited patient numbers in which we integrated a comprehensive panel of read-out methods to gain mechanistic insights in the effects of dovitinib in patients with HCC. The results may support the transition from early-stage research in small patient populations to larger studies plus future research of multi-receptor tyrosine kinase inhibitors (TKIs).

We share the authors' concern regarding underlying liver cirrhosis, particularly because subsequent locoregional treatments may result in loss of functional liver tissue. The authors also highlighted the risks of hepatotropic viral infections.[4] We are aware that TKIs next to their anti-angiogenesis activity have also been shown to affect immune cell activity,[5,6] and that dovitinib may exert similar immunomodulatory effects. In our cohort, 46% patients had HBV/HCV-associated HCC. All patients were closely monitored during the study period and follow-up, and hepatotropic virus activation was not observed in any patients.

We respectfully disagree with the comment of Rizzo et al. that the composition of the patient population ranging from BCLC 0 to B could have led to dilution of the effect of dovitinib and bias. Obviously, treatment response may differ between patients with different stages, but we consider dilution and bias not the appropriate terminology. As HCC, similar to other cancers, displays marked heterogeneity within the same stage of disease and between different clinical disease stages, this could also argue in favor of testing a somewhat broader BCLC stage population to evaluate tolerability and pick-up early signs of efficacy, which is the goal of any explorative phase II trial. Although data on TKI activity in early-stage HCC are scarce and need to be formally proven, it is unlikely that drugs proven to be effective in advanced stages are ineffective in the neoadjuvant setting, especially for HCC where upregulation of actionable targets VEGFR2, PDGFRβ, and FGFR1 has been shown not to differ significantly between BCLC stages A,

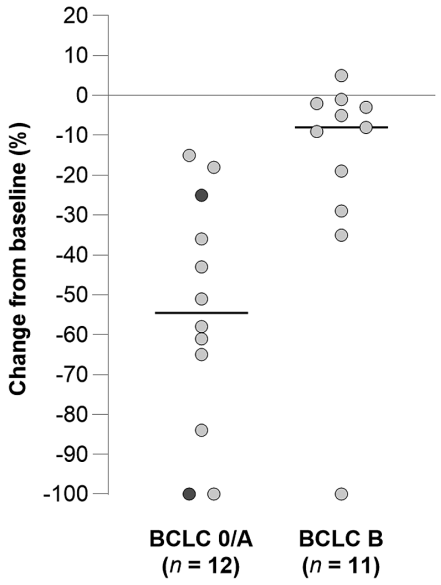

Figure 1. Median mRECIST response in 12 (very) early-stage HCC was higher than in 11 intermediate-stage HCC (−45% vs. −8%; $P = .0028$). The 2 very early (BCLC stage 0) patients are depicted in dark grey.

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B, and C.[7] Also, in our study, no statistically significant difference in plasma levels of pharmacodynamic VEGFR-pathway markers VEGF-A, VEGF-C, VEGF-D, PlGF, sVEGFR1, or sTIE2 were observed between patients with BCLC 0/A and BCLC B HCC. Furthermore, despite the very short treatment period, dovitinib induced mRECIST responses in both the BCLC 0/A group (9/12, 75%) and BCLC B group (2/11, 18%; Fig. 1). Absolute tumor shrinkage ≥1.5 cm was achieved in 9/12 BCLC 0/A and 4/11 BCLC B patients, whereas successful downstaging of 4/11 BCLC B patients allowed them to proceed to liver transplantation. Notwithstanding the small size of our study, the abovementioned data support efficacy of dovitinib in BCLC 0/A-B patients, though the efficacy may differ between groups.

We agree that evaluation of TKI bioactivity alone or in combination with other anticancer agents in early- and intermediate-stage HCC remains an important research aim. Currently ongoing trials evaluating TKIs, immune checkpoint inhibitors or combinations in neoadjuvant setting testify to the interest to further develop neoadjuvant treatment as an important treatment strategy to advance the HCC field.

Conflict of Interest

The authors indicated no financial relationships.

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