On behalf of the American Association for the Study of Liver Diseases (AASLD) Consensus Panel for Clinical Trials in Hepatocellular Carcinoma (HCC), we appreciate the interest of Di Maio et al. in our article. The authors have inquired about two relevant methodological issues that merit further clarification.

First, Di Maio et al., question the recommendation that all new drugs should first be tested in patients with well-preserved liver function (Child–Pugh–Turcotte class A) and only subsequently extended to patients with more impaired liver function. Their principal concern is the generalizability of a study conducted only in patients with well-preserved liver function to the general population of patients with HCC, which includes patients with advanced liver disease. The AASLD consensus panel considered that the main goal of a clinical trial for patients with HCC is to determine whether the drug has
anticancer efficacy (1). Efficacy is defined in phase 3 studies as overall survival advantage compared with the standard of care. The study of patients with advanced liver failure is confounded by altered drug pharmacokinetics and potential hepatotoxicity. More important, though, is the natural progression of the underlying liver disease, which by itself can lead to impaired survival. These confounding issues cloud and confuse interpretation of the data regarding the agent’s antineoplastic efficacy. For example, efficacious drugs might be discarded because the inclusion of patients with advanced liver failure will jeopardize the capacity of the study to capture true outcome benefits. In fact, deaths due to liver failure are expected in 20%–30% of Child–Pugh–Turcotte B patients at 2 years (2). Thus, the consensus panel recommended that new agents be tested in only patients with Child–Pugh–Turcotte A liver disease to more rigorously determine if the drug does or does not alter the natural history of the underlying cancer. Although phase 3 trials could be performed with stratification of patients by Child–Pugh–Turcotte status (A vs B), such studies would be relatively large and would require careful delineation of the drug’s pharmacokinetics and toxicity in the Child–Pugh–Turcotte B patient population prior to the study design. In addition, stratification does not prevent competing risks for the primary endpoint. Thus, the consensus panel considered that proving efficacy in HCC patients with advanced liver failure is a second-generation question that would be more appropriately examined after a drug has initially proven its antineoplastic efficacy.

Di Maio et al., also note that the consensus panel recommended randomized phase 2 trials. We agree that multiple references, in addition to the 1994 reference by Simon that we cited, more completely define the phase 2 randomized controlled trial. The precise details of such a study and the magnitude of statistical difference were not meant to be proscribed by the consensus panel; instead, we advocated for the more expansive use of randomized phase 2 trials. This trial design should help to expedite the evaluation of novel molecular therapies for HCC.

We appreciate Di Maio et al., acknowledging the importance of having a common frame posed by the consensus panel report that will help standardize and promote studies for the treatment of an otherwise devastating but inadequately studied disease.

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References

Notes
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