Brivanib for Hepatocellular Carcinoma Trials: Selection Bias From Barcelona Clinic Liver Cancer Stage?

TO THE EDITOR: Nowadays, the position of sorafenib in the treatment of advanced hepatocellular carcinoma (HCC) is frequently challenged by other molecular targeted agents. However, regardless of whether they are considered as first-line or second-line treatment options, all completed phase III randomized controlled trials (RCTs) report negative results. Similarly, two phase III RCTs (Comparison of Brivanib and Best Supportive Care to Placebo + Best Supportive Care in Subjects With Advanced Hepatocellular Cancer Who Have Failed or Are Intolerant to Sorafenib Treatment [BRISK-PS] and A Randomized, Double-Blind, Multi-Center Phase III Study of Brivanib Versus Sorafenib As First-Line Treatment in Patients With Advanced Hepatocellular Carcinoma [BRISK-FL]) that were recently published in *Journal of Clinical Oncology* have shown the failure of brivanib for the treatment of advanced HCC.^{1,2} Apart from the reasons for the trial failure that were postulated in the two reports, we would like to express some additional issues of concern about the impact of baseline characteristics of the Barcelona Clinic Liver Cancer (BCLC) stage and Child-Pugh class on the trial results.

According to the BCLC staging system for HCC that was adopted by current practice guidelines of the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver/European Organisation for Research and Treatment of Cancer, sorafenib is recommended as the standard treatment option for BCLC stage C.^{3,4} Thus, it seems rational that the target population of trials comparing the efficacy of sorafenib with other molecular targeted therapies would be patients with BCLC stage C disease. As we looked more closely at the data from the two trials, approximately 20% of included patients did not have BCLC stage C disease. More specifically, in the BRISK-PS trial, 13% of patients (52 of 395) had BCLC stage A or B disease (12% and 15% in the brivanib and placebo groups, respectively),¹ and in the BRISK-FL trial, 23% of patients (259 of 1,152) had BCLC stage A or B disease (22% and 23% in the sorafenib and brivanib groups, respectively).² Indeed, these patients should be indicated for surgery, radiofrequency ablation, or transarterial chemoembolization. Additionally, given that the patients with BCLC

stage A or B had a better prognosis, it was difficult to achieve the significant difference in overall survival between the two groups.

However, as described in the BRISK-FL trial protocol, all included patients should have met the criterion of Child-Pugh class A liver function. On the contrary, 8% of patients (93 of 1,155) had Child-Pugh class B (8% and 8% in the sorafenib and brivanib groups, respectively). Whether or not such a deviation from the study protocol potentially affects the results of this trial was not explained by the investigators.

Undoubtedly, previous trial designs can greatly influence the results of future RCTs.⁵ By summarizing the lessons from these trial failures, we should be able to further refine the selection of the target population.

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G.H. has participated in a randomized, double-blind, multicenter phase III study of brivanib versus placebo as adjuvant therapy to trans-arterial chemoembolization in patients with unresectable hepatocellular carcinoma (BRISK-TA trial, CA182-037).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Reply to X. Qi et al

We appreciate the opportunity to respond to the letter from Qi et al¹ concerning our recent articles on brivanib in hepatocellular carcinoma (HCC).^{2,3} Qi et al have concerns about the fact that patients included in these trials were not Barcelona Clinic Liver Cancer (BCLC) stage C or Child-Pugh class A in all cases and that this might have biased the outcome results. We acknowledge that approximately 90% of patients in the Comparison of Brivanib and

Best Supportive Care to Placebo + Best Supportive Care in Subjects With Advanced Hepatocellular Cancer Who Have Failed or Are Intolerant to Sorafenib Treatment (BRISK-PS)² and 80% of patients in A Randomized, Double-Blind, Multi-Center Phase III Study of Brivanib Versus Sorafenib As First-Line Treatment in Patients With Advanced Hepatocellular Carcinoma (BRISK-FL)³ had BCLC stage C disease. Similarly, approximately 90% of patients belonged to Child-Pugh class A in both studies. Nonetheless, we believe that this patient distribution was reasonable for such trials and had no impact on the outcome results for several reasons.

First, in both studies, BCLC staging and Child-Pugh class were balanced between the brivanib and placebo arms² and between the brivanib and sorafenib arms.³ The fact that the characteristics of the patients were similar ensured a correct comparison between the target populations, thus preventing any significant bias in the trials. Second, the proportion of patients with BCLC A and B disease included in first-line therapy (23%) was similar to the populations previously described in the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial (18%)⁴ and other phase III studies. Similarly, patients with Child-Pugh class B liver function accounted for 5% of the SHARP population and 8% of the population in the brivanib trials.^{2,3} It is possible that these Child-Pugh class B patients reflect differences in analytic values that may have occurred between screening and trial entry or because of true protocol violations. Third, the studies were mostly designed according to previously published recommendations.⁵

It is important to clarify why patients at BCLC stages other than C are included in trials that target first-line (patients with advanced HCC) and second-line treatment (patients with advanced HCC who do not respond to sorafenib treatment or who are intolerant to sorafenib). The concept of treatment stage migration has been thoroughly described in guidelines of HCC research and management.⁶ In brief, it relies on the concept that a proportion of patients in each stage do not fulfill all of the criteria for the treatment allocation. In those cases, it is advised to offer the patient the next most suitable option within the same stage or the next prognostic stage. For instance, patients with BCLC stage A disease who do not respond to local ablation should be offered chemoembolization. Similarly, patients with BCLC stage B disease who do not respond to chemoembolization—at least two cycles of treatment—should be offered sorafenib, as reported in the SHARP trial.⁴ For example, a patient presenting with a single intrahepatic lesion (not suitable for resection or ablation) who is treated with multiple rounds of transarterial chemoembolization may show regrowth of the lesion or nonresponse, and therefore, may receive sorafenib even if the lesion is confined to the liver, is smaller in size, and has no vascular invasion. Obviously, this patient may or may not respond to systemic therapy, so it is quite possible that, in the instance of nonresponse to transarterial chemoembolization and sorafenib, the patient would be eligible for second-line systemic therapy and could have BCLC stage A or B disease. This has been the case in our trial as well. However, we are positive that the reasons for not achieving the primary end points of these trials were more related to the antitumoral potency of the drug rather than to a bias in trial design associated with BCLC or Child-Pugh stage.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Needs Assessments in Reducing Distress Among Patients With Cancer

TO THE EDITOR: We thank Carlson for her thoughtful appraisal and discussion¹ of our trial² evaluating the cost-effectiveness of the distress thermometer and problem list (DT&PL) in addressing psy-

chological distress among patients with cancer and would like to take this opportunity to respond.

We agree with some of the conclusions that Carlson¹ draws; in particular, the need for clear referral pathways for patients who need additional psychological or social support and the importance of initial and ongoing training and support for health care staff performing the needs assessment. In our trial, a consultant clinical psychologist