We read with great interest the study by Llovet and colleagues (1), who reported on plasma biomarkers in a phase III trial of sorafenib for advanced hepatocellular carcinoma (HCC; ref. 2). One of the main scopes of this correlative study was to identify predictive markers of survival and response to sorafenib. Within a panel of 10 candidate biomarkers that were analyzed in both the placebo and the sorafenib arm of the trial (2), the authors tested the interaction between sorafenib treatment and each biomarker at baseline. However, the test did not allow for the detection of any biomarker whose baseline concentrations could predict the benefit deriving from sorafenib over placebo. Not included in the aforementioned panel, the authors also reported on a statistically significant prognostic value of the baseline levels of another biomarker, namely α-fetoprotein (AFP). Nevertheless, an interaction between treatment and AFP levels to address the potential predictive strength of this biomarker was not reported, thereby leaving the question of whether assessment of baseline AFP might help in selecting patients who are candidates for sorafenib.

In addition, recent studies (3–5) have introduced the concept of “AFP response,” which refers to a decline in serum AFP levels from baseline as a surrogate marker of outcome during treatment for advanced HCC. Among these studies, 2 focused on patients that were treated with sorafenib (4, 5), whereas a 3rd report considered metronomic chemotherapy in combination with various antiangiogenic agents, including sorafenib (3). Despite differing timings adopted for the appraisal of AFP response, results of these investigations indicate a substantial agreement in that they show that AFP responders experience longer time to progression (5), progression-free survival (3, 4), and overall survival, compared with patients classified as AFP nonresponders.

On the other hand, a flaw inherent to these studies is the nonrandomized design that prevents any effort to differentiate the causal effect of AFP response on sorafenib efficacy from a multitude of other possibly confounding factors. At present, clinical or molecular biomarkers to identify who responds to sorafenib are virtually absent, whereas mounting evidence supports a possible role for AFP response. In this respect, we anticipate that, as opposed to the cohort studies mentioned above (3–5), the phase III SHARP trial (2) should provide the appropriate context in which to explore AFP response as a surrogate marker of outcome in HCC patients receiving sorafenib.

Disclosure of Potential Conflicts of Interest
A. Santoro has participated in advisory activities for Bayer HealthCare Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

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Nicola Personeni, Lorenza Rimassa and Armando Santoro

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