Second-line Therapies in Hepatocellular Carcinoma: Emergence of Resistance to Sorafenib

Augusto Villanueva\textsuperscript{1,2} and Josep M. Llovet\textsuperscript{1,2,3,4}

Second-line therapies are needed for patients with advanced hepatocellular carcinoma who progress after sorafenib. Positive signals seen with brivanib in phase II studies, reported herein, have yet to be confirmed in phase III trials. Identification of the molecular mechanisms driving sorafenib resistance should guide drug development strategies in this setting. \textit{Clin Cancer Res}; 18(7); 1824–6. ©2012 AACR.

In this issue of \textit{Clinical Cancer Research}, Finn and colleagues (1) report the results of the first clinical trial evaluating a molecular-targeted agent, brivanib, in second-line treatment for patients with advanced hepatocellular carcinoma (HCC) who progressed after receiving sorafenib.

The landscape of systemic therapy of HCC has significantly changed in the past 5 years. Following the approval of sorafenib after its survival benefits were shown in patients with advanced HCC in the landmark SHARP trial (2), a number of molecular agents have entered different phases of clinical development, covering the whole spectrum of the disease. Currently, more than 250 ongoing clinical trials are assessing molecular-targeting agents in the adjuvant setting after resection or ablation, in combination with loco-regional therapies, as first-line treatment in combination (or competition) with sorafenib, or as second-line therapy after progression on sorafenib (3). However, only a subset (approximately 10 clinical trials) represent phase III studies designed to proceed to regulatory approval. Drugs tested include agents that block EGF receptor (EGFR; erlotinib), mTOR (everolimus) and VEGF receptor (VEGFR), platelet-derived growth factor receptor, and fibroblast growth factor receptor (FGFR; brivanib; Fig. 1). As described below, other multikinase inhibitors, such as sunitinib, recently failed to meet the end point.

In their study, Finn and colleagues (1) evaluated brivanib in 48 patients with advanced HCC as a second-line option after progression and/or intolerance to sorafenib, using a single-arm, phase II design. Results include a median survival of 9.7 months, similar to what was reported for this agent as first-line treatment, 10 months (4). The disease control rate was 70\% (10\% objective response; 60\% stable disease) as assessed by modified Response Evaluation Criteria in Solid Tumors (5). The toxicity profile of brivanib was different from that of sorafenib, with significantly less hand–foot syndrome and higher rates of arterial hypertension and fatigue. Similarly to sorafenib, brivanib did not induce liver dysfunction in enrolled patients with well-preserved liver function (90\% were Child-Pugh A class). A phase III randomized trial comparing brivanib versus placebo as second-line treatment in approximately 400 patients is ongoing. Just recently, a press release from Bristol-Myers Squibb, the manufacturer of brivanib, revealed that in the phase III trial, brivanib [sic] “did not meet the primary endpoint of improving overall survival versus placebo.” Until a full report of the phase III results is released, the exact response and overall survival rates are not fully known. Data on subgroup analyses could also highlight patients with a better response profile, which could be confirmed in future prospective studies.

Assuming that the median survival for brivanib-treated patients is similar in both phase II and III studies, the main question is the following: What should be the expected median survival of the control arm in second line that prevented a positive result in the phase III setting? This figure has not yet been reported, and expected outcomes derived from patients surviving after sorafenib failure based on the SHARP trial (natural history of 4–6 months), might have been underestimated. One can speculate that a selection bias with enrichment of patients with indolent HCC, those patients with good Eastern Cooperative Oncology Group status after sorafenib failure, might have contributed to these conflicting findings. In addition, the treatment migration effect, by which patients are currently receiving sorafenib at the intermediate stage after failure of chemoembolization, might also play a role (6). In any case, the results of the phase III study further emphasize the importance of the recommendation of conducting randomized phase II
studies to accurately capture signals of efficacy and provide reliable assumptions for trial design (7). Two phase III trials in the second-line setting are still ongoing, testing either everolimus (mTOR inhibitor) or ramucirumab (VEGFR2 monoclonal antibody); these trials will be informative. The negative result reported here adds to the recent failure of sunitinib as a first-line treatment (6) and further highlights the complexity of advancing the field of systemic treatment for patients with advanced HCC.

In 2003, the U.S. Food and Drug Administration approved the first molecular-targeted agent for a solid tumor (the EGFR inhibitor gefitinib in lung cancer). The development of this new family of drugs has dominated translational research in oncology during the past decade. Previous results of imatinib in chronic myeloid leukemia set high expectations for targeted therapies for solid tumors (8). Imatinib was able to induce remarkable clinical remissions by blocking the activity of the BCR–ABL fusion protein, the known molecular substrate of the disease. As a conceptual consequence, the rationale behind molecular therapies was not to target the molecular aberrations present in tumors, but to preferentially antagonize alterations implicated in tumor progression (“oncogene addiction”). Some recent successes using this approach include vemurafenib in BRAF-mutated melanomas (9) or crizotinib in lung tumors with ALK rearrangements (10). Unfortunately, the distinction between driver and passenger events in solid tumors is only beginning to be translated into clinical medicine. To date, potential drivers of oncogenic addiction have not been explored in the HCC clinical setting, either because of a lack of reliable biomarkers or because of a marginal interest in expensive explorations of small niches of patients with good responses.

The high molecular heterogeneity in HCC favors deregulation of multiple drivers, increasing the odds that a drug with a wider kinase blockade spectrum may be effective; such is the case of sorafenib. Our limited understanding of the mechanism of action of sorafenib in advanced HCC, however, makes it even more difficult to determine the possible resistance mechanisms. Preclinical models suggested that phenotypic resistance to VEGFR inhibition could induce activation of VEGF-independent angiogenic signals, by members of the FGF family (11). In addition, genomic and functional studies indicated that FGF19 could act as an oncogenic driver in HCC (12, 13). Together, these data provided sufficient rationale to test FGFR inhibition in patients with sorafenib-resistant HCC.

Increased understanding of the final results of the phase III trial will determine the role of brivanib as second-line therapy. However, it seems clear that mechanisms of resistance to...
sorafenib include both FGFR-dependent and -independent pathways. In the past 2 years, 2 studies testing molecular therapies did not reach the primary endpoint in first- and second-line settings for HCC. Several drugs with new targets are under evaluation in phase II and III trials (3). All of these agents need to balance efficacy with the true bottleneck of trial success in cirrhotic patients, which is toxicity. In fact, safety profiles were among the main issues jeopardizing trial success in 1 of the 2 cases in which results did not meet the primary endpoint (i.e., sunitinib). This finding suggests that the management and trial design of HCC may be unique in oncology. Alternatively, other backup strategies in drug development have to be taken into account; this requires a better understanding of the molecular pathogenesis of disease progression and resistance to sorafenib (Fig. 1). The development of targets based on their ability to behave as oncogenic addiction loops and the implementation of clinical trials designed to enrich populations, based on molecular biomarkers of these events, should move the field forward. The success of trial enrichment based on molecular biomarkers in other solid tumors encourages these types of approaches (12, 13).

Disclosure of Potential Conflicts of Interest
J.M. Llovet has received research support from Bayer Pharmaceuticals and Bristol-Myers Squibb and has consultancy agreements with Bayer Pharmaceuticals, Bristol-Myers Squibb, Imclone, and Biocompatibles. No potential conflicts of interest were disclosed by the other author.

Received January 31, 2012; accepted February 9, 2012; published Online-First February 21, 2012.

References