

# The Sorafenib for Hepatocellular Carcinoma (HCC) in Adjuvant Setting: The End of the Story was Already Written?

**Abbreviations:** HCC, hepatocellular carcinoma; ASCO, American Society of Clinical Oncology

## Editorial

Although early diagnosis of hepatocellular carcinoma (HCC) can improve survival, the outcome after treatment with curative intent can be hampered by early recurrence (30%-40%) or secondary primary tumor (60-70%).<sup>1</sup> Recurrence after resection may reach 50% and 80% of cases at 2 and 5 years respectively,<sup>2</sup> with a 5-year survival of 50%<sup>3</sup> even in the case of early stage without portal venous invasion or satellite nodules.<sup>4</sup> Recurrences compromising dramatically shorten overall survival,<sup>5</sup> preventing or delaying relapse after curative treatment has become a major challenge. Recently, Bruix et al.,<sup>6</sup> communicated, on behalf of all investigators, the results of the STORM (NCT00692770) trial at the ASCO (American Society of Clinical Oncology) 2014 meeting. This international randomized placebo-controlled phase III trial investigated for 4-years adjuvant sorafenib or placebo in patients with HCC treated either by resection

or local ablation. The hypothesis of the study was that sorafenib could reduce tumor recurrence and therefore improve the overall survival. The primary and secondary endpoints of the trial were the recurrence-free survival and overall survival and safety, respectively.<sup>6</sup> The trial enrolled the largest cohort of patients with HCC treated in this setting. Overall, 1,114 patients were equitably randomized to take either sorafenib or placebo. The study did not meet its primary and secondary endpoints since no differences were observed regarding recurrence-free survival (33.4 vs 33.8 months; HR=0.94; 95% CI: 0.78-1.13, p=0.26), time to recurrence (38.6 vs 35.8 months; HR=0.89, 95% CI: 0.73-1.08) and overall survival (not reached vs not reached, HR=0.99, 95% CI: 0.76-1.30, p=0.48). In this trial, a higher rate of sorafenib discontinuation due to drug-adverse events was observed compared to placebo (24% vs 7%).<sup>6</sup>

Therefore, the primary and secondary endpoints of the trial were not achieved and these negative results were somehow not surprising. First, previous experiences with adjuvant therapies in HCC were disappointing. Before the era of sorafenib, transarterial chemotherapy, systemic chemotherapy, retinoids, adjuvant interferon, adoptive immunotherapy, and intra-arterial radioactive lipiodol<sup>1</sup> have been explored as adjuvant therapies in clinical trials aiming reducing relapse. The overall benefit was almost anecdotal not allowing the adoption of any adjuvant treatment in routine practice. Second, the sorafenib, an oral multi-kinases inhibitor, showed evident clinical benefit in patients with advanced HCC.<sup>7,8</sup> For the first time in the history of systemic treatment for HCC, this compound improved by 44% the overall survival of patients with advanced HCC.<sup>8</sup> The sorafenib had a double antiangiogenic and antiproliferative activity by targeting vascular endothelial growth factor receptor 2/3, platelet derived growth factor receptor beta tyrosine kinases and Raf/MEK/ERK signaling. In the advanced setting, the angiogenesis was florid and the antitumoral effect of sorafenib was probably maximal.

However it is unclear if this antiangiogenic and antiproliferative effect could be achieved sufficiently in earlier stage and the appropriate timing to blockade the angiogenesis is not so clear. Expectations in preventing HCC recurrence using targeted therapies may appear as a real challenge since several signaling inhibitors have recently failed showing benefit when used in adjuvant setting in other cancers.<sup>9</sup> Third, The STORM trial is a well conducted and designed prospective and statically powerful trial. Biases of selection were avoided and patients were stratified according to the risk of recurrence. However the median time duration of sorafenib was obsolete (12.5 months) compared to the 4 years planned and the mean daily dose (578 mg) was lower to the recommended 800 mg daily. Therefore, the duration of the treatment initially proposed for the trial appears to be so long. The poor tolerability of sorafenib may be a barrier for treatment maintaining and exposure. In this trial, about quarter of patients discontinued sorafenib due to drug-related side effects. This rate was lower than observed in the SHARP trial which reached 38% of patients.<sup>7</sup> However, in case of advanced HCC, patients were more symptomatic and are more fragile because of the disease and the underlying liver cirrhosis. Moreover, consent withdraw rate was significantly higher in the sorafenib group compared to placebo group (17% vs 6%). This rate is perturbing in a prospective and international clinical trial. Comparatively, less than 10 % of patients treated in the phase III clinical trial testing sorafenib in advanced HCC, withdraw their consent.<sup>7</sup> This finding could be explained in a part by the fact that patients, who received curative intent treatment, feel less the need for further treatment as long as they consider themselves definitely cured. In contrast, patients who were managed with advanced disease; they feel the need to receive even heavy therapy and were more likely to put up with related-drug side effects. Finally, the economic feature could be stressed. The sorafenib was an expensive therapy and the cost-effectiveness of such 4-years adjuvant was not studied.

Volume 1 Issue 3 - 2014

Mohamed Bouattour

Department of Hepatology, Beaujon University Hospital, France

**Correspondence:** Mohamed Bouattour, Department of Hepatology, Beaujon University Hospital, Public Assistance-Hospitals of Paris, 100 BLD the General Leclerc 92110 Clichy, France, Tel +33-1-40-87-55-25, Fax +33-1-47-39-61-78, Email mohamed.bouattour@bjn.aphp.fr

Received: August 11, 2014 | Published: August 12, 2014

Thus, sorafenib is added to the list of therapies and approaches that failed showing any benefit in adjuvant setting. The end of the great story was almost written in advance.

## Acknowledgments

None.

## Conflicts of interest

Author declares that there is no conflict of interest.

## References

1. Schwartz JD, Schwartz M, Mandeli J, et al. Neoadjuvant and adjuvant therapy for resectable hepatocellular carcinoma: review of the randomised clinical trials. *Lancet Oncol.* 2002;3(10):593–603.
2. Imamura H, Matsuyama Y, Tanaka E, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol.* 2003;38(2):200–207.
3. Belghiti J, Kianmanesh R. Surgical treatment for hepatocellular carcinoma. *HPB (Oxford).* 2005;7(1):42–49.
4. Adachi E, Maeda T, Matsumata T, et al. Risk factors for intrahepatic recurrence in human small hepatocellular carcinoma. *Gastroenterology.* 1995;108(3):768–775.
5. Rougier P, Mitry E, Barbare JC, et al. Hepatocellular carcinoma (HCC): an update. *Semin Oncol.* 2007;34(2Suppl 1):S12–S20.
6. Bruix J, Takayama T, Mazzaferro V, et al. STORM: A phase III randomized, double-blind, placebo-controlled trial of adjuvant sorafenib after resection or ablation to prevent recurrence of hepatocellular carcinoma (HCC). *J Clin Oncol.* 2014;32:5s.
7. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008;359(4):378–390.
8. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol.* 2009;10(1):25–34.
9. Allegra CJ, Yothers G, O'Connell MJ, et al. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. *J Clin Oncol.* 2011;29(1):11–16.