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# Adjuvant sorafenib for liver cancer: wrong stage, wrong dose

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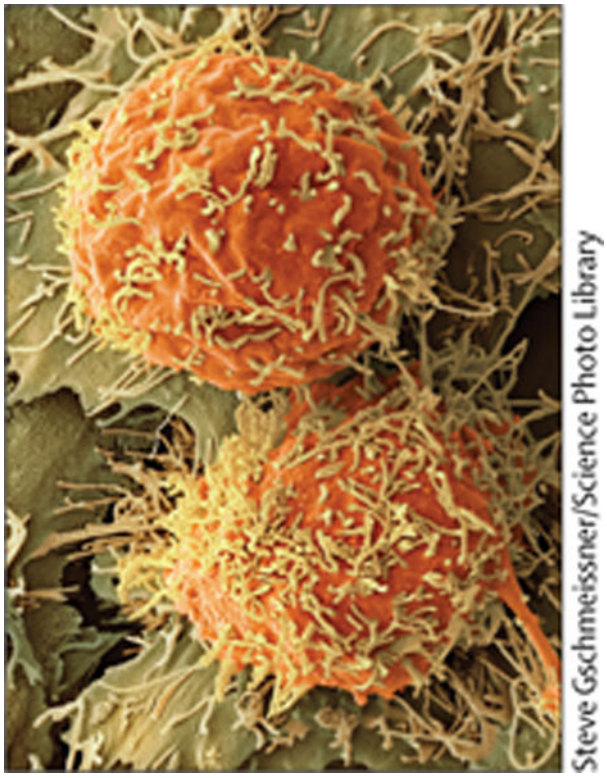
In this issue of *The Lancet Oncology*, Jordi Bruix and colleagues report the results of STORM, a multinational, randomised phase 3 trial of adjuvant sorafenib versus placebo in patients with hepatocellular carcinoma at high risk of recurrence after curative resection or ablation.[1] In the STORM trial, 1114 patients were randomly assigned to receive either 400 mg sorafenib or matching placebo twice a day for up to 4 years. The researchers noted no significant difference in the primary endpoint of centrally-adjudicated recurrence-free survival (RFS) between groups, with median RFS of 33·4 months for patients given sorafenib and 33·8 months for those patients given placebo (HR 0·940, 95% CI 0·780–1·134; one-sided p=0·26). Likewise, there was no significant difference in overall survival. The investigators appropriately concluded that adjuvant sorafenib does not prolong RFS after surgery or ablation for patients with hepatocellular carcinoma.



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The STORM trial joins a growing list of negative adjuvant studies of anti-angiogenic treatments across cancer types, including bevacizumab in breast, colon, and lung cancers,[2–4] and sunitinib and sorafenib in renal cell carcinoma.[5] Collectively, these negative trials underscore the importance of developing mechanistic preclinical models for studying adjuvant treatments, as well as reinforcing a recurring lesson in oncology: antitumour activity against established or advanced tumours is not necessarily associated with efficacy in the adjuvant setting against micrometastatic disease.[6]

The high biological heterogeneity across hepatocellular carcinoma presents an additional challenge. Certain clinical or biological subsets of patients might be more likely to respond to sorafenib, and an unselected adjuvant population could obscure a signal of efficacy within a subset. However, without established predictive biomarkers of sorafenib response in advanced disease, a biomarker-enriched adjuvant population cannot be defined.

The findings from the STORM trial are especially relevant because studies of sorafenib as an adjuvant strategy in combination with transarterial chemoembolisation, transarterial radioembolisation, or liver transplantation are still in progress. The absence of RFS improvement from sorafenib after surgery or ablation in the STORM trial is consistent with existing findings from randomised trials that have not shown a survival benefit from adjuvant sorafenib after transarterial chemoembolisation.[7,8] The STORM data reinforce the notion that the use of sorafenib in combination with or as an adjuvant to liver-directed treatments remains investigational, and should be undertaken under the auspices of a clinical trial or in cases with a known residual or recurrent tumour. We look to the ongoing trials, ECOG 1208 (NCT01004978) and TACE-2 (NCT01324076), for additional clarity on the role of sorafenib when used as an adjuvant to transarterial chemoembolisation in a population with intermediate-stage hepatocellular carcinoma.

Despite the negative outcome, the STORM trial offers an extremely important vantage on the dosing and tolerability of sorafenib in a fit, Child-Pugh A population eligible for resection or ablation. In advanced disease cohorts receiving first-line treatment with sorafenib,[9,10] high incidences of dose modification and treatment discontinuation are a recurring theme for treatment groups, but attribution of toxic effects can be confounded by symptoms of progressive hepatocellular carcinoma and cirrhosis, as shown by the high number of toxic effects recorded in the placebo groups of these studies. The STORM trial provides definitive evidence for drug-related intolerability and toxic effects for adjuvant sorafenib in patients with hepatocellular carcinoma at its labelled dose of 400 mg twice a day. In STORM, the median duration of treatment was only 12·5 months for the sorafenib group versus 22·2 months for the placebo group, and 24% of patients discontinued sorafenib due to toxic effects compared with only 7% in the placebo group. Almost 90% of patients required dose modification in the sorafenib group compared with less than 40% for the placebo group, resulting in a much lower mean daily dose of sorafenib than placebo (577·7 mg *vs* 777·9 mg).

The disparity in dose modification and treatment discontinuation between patients given sorafenib and placebo in the STORM trial calls into question the optimum starting dose of sorafenib in patients with hepatocellular carcinoma, a population with varying degrees of

liver dysfunction in most patients. In the ASSURE study, a randomised phase 3 trial of adjuvant sorafenib in patients with resected renal cell carcinoma at high risk of recurrence, investigators also noted high incidences of dose modification and treatment discontinuation of 26% due to intolerability, leading to a mid-study protocol amendment lowering the starting dose of sorafenib to 400 mg once a day with allowance of intra-patient dose escalation if well-tolerated.[5] With this amendment, discontinuation fell to 14%. Findings of the CALGB 60301 study showed that hepatic or renal dysfunction can significantly affect the tolerability of sorafenib,[14] suggesting that subclinical organ dysfunction might have contributed to the high number of toxic effects and intolerability as seen in the STORM and ASSURE studies. Supporting a lower starting dose with an individualised dose-escalation model, pharmacodynamic activity of sorafenib has been recorded with a dose of 400 mg per day,[15] and pharmacokinetic analyses indicate high degrees of intra-and inter-patient variability.[11,12]

In conclusion, the STORM trial is a reminder that there remains no established role for sorafenib as adjuvant therapy for patients with hepatocellular carcinoma after liver-directed therapy. Sorafenib at the approved starting dose was intolerable in the fit, adjuvant population of the STORM study. We should reassess the optimum starting dose of sorafenib to avoid these liabilities of delay and discontinuation for future trials and patients, across disease stages.

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