Letter to the Editor

Molecular Cancer Therapeutics

Sorafenib Inhibits ABCG2 and Overcomes Irinotecan Resistance—Response

Céline Gongora

We are aware that sorafenib binds to plasma proteins. At steady state, when sorafenib is orally administered at 800 mg/d, accumulation ratios are 5.7 to 6.4, indicating that it has a good distribution range. Of note, 90% of sorafenib is bound to the plasma proteins (1), but the large distribution volume indicates that this binding does not affect the body distribution. Moreover, binding to plasmatic proteins is not predictive at all of the tissue distribution of a given drug; rather, the affinity of this binding could be an issue. Furthermore, the recent publication by Villarroel and colleagues states that "the binding of sorafenib in plasma is concentration-independent, indicating a low-affinity, and nonspecific and nonsaturable process" (2), showing that the sorafenib affinity for plasmatic proteins is lower than its affinity for cell membranes [sorafenib displays a high lipophilicity (log P = 3.8)]. Pharmacokinetic studies are performed using total (bound + unbound) drug concentrations as a variable further strengthening that it is not the free concentration in plasma but the total concentration of the drug that is a better representative of the drug effect. Thus, levels of plasmatic proteins are not predictive for pharmacodynamic effects of tyrosine kinase inhibitors and there is no reason to argue that our preclinical observations are not relevant for subsequent clinical trials.

We have conducted a phase I/II trial, precisely based on our preclinical results showing that combination induced significantly better responses *in vivo* as compared with each drug alone, with some complete tumor regression in mice. The aim of this trial was to assess the feasibility and efficacy of the irinotecan–sorafenib combination (180 mg/m^2 and 400 mg twice a day) in patients with Kras mutated metastatic colorectal cancer who had progressed after irinotecan-based chemotherapy. The results are now accepted in the *British Journal of Cancer* (3) and were presented at the American Society of Clinical Oncology (4). Disease control rate of 65% with a median progression-free survival and overall survival of 3.7 months and 8 months, respectively, further confirmed the potential synergy between sorafenib and irinotecan.

We believe that the arbitrary nature of the last comment made by the author is seriously deleterious for the field. The results of our phase I/II clinical trial are the most compelling evidence that, conversely to what is stated, our lines of research (that took into account accumulating evidence in both cell lines and animal models) did not end in failure and will certainly contribute to the improvement of treatments for patients with metastatic colon cancer or colorectal cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received December 19, 2013; accepted December 27, 2013; published online March 10, 2014.

Author's Affiliation: IRCM INSERM U896, Montpellier, France

Corresponding Author: Céline Gongora, IRCM INSERM U896, 208, rue des Apothicaires, 34298 Montpellier, France. Phone: 33-4-6761-3745; Fax: 33-4-6761-3787; E-mail: celine.gongora@inserm.fr

doi: 10.1158/1535-7163.MCT-13-1026

References

1. Di Gion P, Kanefendt F, Lindauer A, Scheffler M, Doroshyenko O, Fuhr U, et al. Clinical pharmacokinetics of tyrosine kinase inhibitors: focus on pyrimidines, pyridines, and pyrroles. Clin Pharmacokinet 2011;50:551–603.
2. Villarroel MC, Pratz KW, Xu L, Wright JJ, Smith BD, Rudek MA. Plasma protein binding of sorafenib, a multi kinase inhibitor: *in vitro* and in cancer patients. Invest New Drugs 2012;30:2096–102.
3. Samalin E, Bouché O, Thézenas S, Francois E, Adenis A, Bennouna J, et al. Sorafenib and irinotecan (NEXIRI) as second- or later-line treatment for patients with metastatic colorectal cancer and KRAS-mutated tumours: a multicentre Phase I/II trial. Br J Cancer. Epub 2014 Jan 9.
4. Ychou M, Bouche O, Thezenas S, Francois E, Adenis A, Bennouna J, et al. Final results of a multicenter phase II trial assessing sorafenib (S) in combination with irinotecan (i) as second- or later-line treatment in metastatic colorectal cancer (mCRC) patients (pts) with KRAS-mutated tumors (mt; NEXIRI). J Clin Oncol 2011;29:15s (suppl; abstr e14002).

Molecular Cancer Therapeutics

Sorafenib Inhibits ABCG2 and Overcomes Irinotecan Resistance—Response

Céline Gongora

Mol Cancer Ther 2014;13:764.