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# Multi-kinase inhibition in ovarian cancer

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Commmentary to: Koshiyama M, Matsumura N, Baba T, Yamaguchi K, Yoshioka Y, Konishi I. Two cases of recurrent ovarian clear cell carcinoma treated with sorafenib. Cancer Biol Ther 2014; 15:22-5; PMID:24096267; http://dx.doi.org/10.4161/cbt.26608

**Sorafenib (Nexavar) is a multi-kinase inhibitor that was developed as an inhibitor of RAF-1, in the ERK1/2 pathway, but which was subsequently shown to inhibit class III tyrosine kinase receptors.[1] More recently regorafenib (Stivarga) has been developed, which is a further fluorinated version of sorafenib with greater bioavailability and similar inhibitory properties against RAF-1/class III RTKs.[2] Some of the anti-tumor effects of sorafenib have been ascribed to anti-angiogenic actions of this agent on endothelial associated kinases such as VEGFR2. Other effects of sorafenib clearly have to be due to its effects on the inherent biology of the tumor cells themselves. For example, through various mechanisms sorafenib has been shown in the laboratory and the clinic to suppress expression of the protective protein MCL-1.[3] Sorafenib has also been linked to inhibition of STAT3, NFκB, and activation of the death receptor CD95.[4] Sorafenib is routinely dosed daily (400 mg BID) and 7 d after the start of dosing has a $C_{max}$ of ~21 μM with a nadir at 12 h of ~10 μM, and is a highly protein bound based on in vitro assays.[5] Despite this in vitro binding data sorafenib has profound in vivo effects on tumor cells in renal carcinoma and hepatocellular carcinoma patients; cells which are not per se addicted to high activity oncogene signals that are targets of sorafenib/regorafenib. Thus the precise stable bioavailable level of sorafenib/regorafenib in patient plasma is not known.**

In the manuscript by Koshiyama et al., the authors noted that not only does clear cell ovarian carcinoma morphologically appear similar to renal carcinoma, but that the ovarian clear cells also have a similar gene expression profile to kidney cancer cells.[6] Based on these facts, the authors determined in two recurrent chemoresistant patients whether the renal carcinoma therapeutic sorafenib could impact on disease progression in clear cell ovarian carcinoma, as judged by progression-free survival for at least 6 mo. In the first patient, who had progressed on multiple other therapies, sorafenib at a 200 mg BID resulted in disease stabilization for over 6 mo. Following sorafenib therapy, the tumor began to re-grow. In the second patient a larger and more advanced tumor was diagnosed. The patient received multiple high dose chemotherapy regimens followed by surgery. The tumor recurred in the neck lymph nodes and chemoradiation was performed. Again, sorafenib monotherapy stabilized the disease for many months. Withdrawal of sorafenib resulted again in the rapid growth of the tumor. In general agreement with the results of this manuscript, the GOG recently reported that although sorafenib was largely ineffective in the serous subtype of ovarian cancer one of two ovarian cancer patients who did respond in their study was a clear cell patient.[7]

The molecular reasons why clear cell ovarian cancer cells, but not serous cells, are sensitive to sorafenib at present remains unclear. The authors noted that renal cancer and clear cell ovarian cancer both express HIF1α, though that may only be a secondary target; nevertheless this transcription factor can act to increase expression of multiple growth factor receptors and promote angiogenesis. The molecular actions of sorafenib are pleiotropic including inhibition of the ERK1/2 pathway but also inhibition of tyrosine kinases.

Chemo-resistant clear cell cancer overexpresses c-Met and are believed to originate in part from endometriosis and are driven in part by the cytokine IL-6.[8] As clear cell tumors also overexpress VEGFR2 it is possible that combinations of sorafenib, c-Met inhibitors, and JAK inhibitors could be used in this disease.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.


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