Combining a dual mTOR/PI3K inhibitor and the multikinase inhibitor sorafenib inhibits progression of renal cell carcinoma.

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Objective: Molecular targeted therapies for metastatic renal cell carcinoma (RCC), including mammalian target of rapamycin (mTOR) inhibitors and small-molecule multikinase inhibitors, have produced promising clinical effects. However, most patients acquire resistance over time. Here, we evaluated the effect of the novel dual PI3K/mTOR inhibitor NVP-BEZ235, applied alone, or with the multikinase inhibitor sorafenib, on RCC cell proliferation in vitro, and tumor formation in vivo. Methods: RCC cell lines 786-0 and Caki-1 were treated with various concentrations of NVP-BEZ235 or sorafenib, and tumor cell proliferation and apoptosis were investigated in vitro. Moreover, treatment efficacy of NVP-BEZ235 alone, or in combination with sorafenib, was evaluated on RCC subcutaneous xenograft models in athymic nude mice. Results: NVP-BEZ235 or sorafenib reduced cell proliferation and increased cell apoptosis in vitro, and reduced tumor xenograft growth in vivo. Combination of both drugs in vitro resulted in significant RCC growth inhibition and increased apoptosis compared to monotherapy. This synergistic effect was also observed on tumor progression in vivo. Conclusions: The simultaneous use of NVP-BEZ235 and sorafenib presented a distinct combinatorial benefit and thus may provide a treatment strategy in RCC.