Phase IB study of the mTOR inhibitor ridaforolimus with capecitabine


PURPOSE: Synergistic/additive cytotoxicity in tumor models and widespread applicability of fluoropyrimidines in solid tumors prompted the study of the combination of the mammalian target of rapamycin (mTOR) inhibitor, non-prodrug rapamycin analog ridaforolimus, with capecitabine. PATIENTS AND METHODS: Thirty-two adult patients were treated. Intravenous ridaforolimus was given once weekly for 3 weeks and capecitabine was given from days 1 to 14 every 4 weeks. Ridaforolimus was given at 25, 37.5, 50, or 75 mg with capecitabine at 1,650 mg/m(2) or 1,800 mg/m(2) divided into two daily doses. Pharmacokinetics of both drugs were determined during cycles 1 and 2. Pharmacodynamic studies in peripheral blood mononuclear cells (PBMCs) and wound tissue of the skin characterized pathways associated with the metabolism or disposition of fluoropyrimidines and mTOR and ERK signaling.

RESULTS: Two recommended doses (RDs) were defined: 75 mg ridaforolimus/1,650 mg/m(2) capecitabine and 50 mg ridaforolimus/1,800 mg/m(2) capecitabine. Dose-limiting toxicities were stomatitis and skin rash. One patient achieved a partial response lasting 10 months and 10 of 29 evaluable patients had stable disease for >= 6 months. The only pharmacokinetic interaction was a ridaforolimus-induced increase in plasma exposure to fluorouracil. PBMC data suggested that prolonged exposure to capecitabine reduced the ridaforolimus inhibition of mTOR. Ridaforolimus influenced the metabolism of fluoropyrimidines and inhibited dihydropyrimidine dehydrogenase, behavior similar to that of rapamycin. Inhibition of the target thymidylate synthase by capecitabine was unaffected. mTOR and ERK signaling was inhibited in proliferating endothelial cells and was more pronounced at the RD with the larger amount of ridaforolimus. CONCLUSION: Good tolerability, feasibility of prolonged treatment, antitumor activity, and favorable pharmacologic profile support further investigation of this combination.

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