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Abstract

A phase I study with tumor molecular pharmacodynamic (MPD) evaluation of dose and schedule of the oral mTOR-inhibitor Everolimus (RAD001) in patients (pts) with advanced solid tumors

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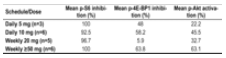
Background: Everolimus (E), an oral derivative of rapamycin, inhibits mTOR, a protein kinase downstream of PI3K and Akt, involved in the regulation of cell growth, proliferation and survival. In preclinical models, the administration of E is associated with reduction of mTOR downstream phosphorylated(p)-S6 (p-S6) and p-4E-BP1, and occasionally with increase in upstream p-Akt. This study explores safety, PK and MPD changes in tumor at different doses and schedules of E to define the recommended dose for further development. **Methods**: Pts with advanced solid tumors were treated in successive cohorts of E: weekly 20, 50 and 70 mg or daily 5 and 10 mg. Dose escalation depended on dose limiting toxicity (DLT) rate during the first 4-week period. Pre- and on-treatment steady-state (24hr post-dose and, for the weekly schedule, 5 days post-dose) tumor biopsies were obtained from each pt. Tumor tissue was evaluated by immunohistochemistry (IHC) for p-S6, p-4E-BP1 and p-Akt expression by a pathologist blinded for the biopsy sequence. **Results:** 33 pts have been treated with 6–8 pts in each cohort. Grade 3 DLT occurred in 5 pts comprising stomatitis (1 pt at 10 mg daily, 2 at 70 mg weekly), neutropenia and hyperglycemia (1 pt each at 70 mg weekly). There were one partial response (colon cancer) and 2 stabilizations of >4 months (renal cell and breast cancer). MPD studies (see table) demonstrated an almost complete inhibition of p-S6 at all doses and schedules (p=0.001). Preliminary results suggest a dose-related decrease in p-4E-BP1 and increase in p-Akt expression with maximal effect at 10 mg daily and ≥50 mg weekly. **Conclusions:** This phase I study shows that E, at the doses and schedules studied, results in intratumoral inhibition of mTOR signaling. Based on the toxicity profile and the MPD findings, a dosage of 10 mg daily can be recommended for further phase II-III development with E as a single agent.



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Author Disclosure

Employment or Leadership	Consultant or Advisory Role	Stock Ownership	Honoraria	Research Funding	Expert Testimony	Other Remuneration
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