Phase I trial of the oral smoothened inhibitor sonidegib in combination with paclitaxel in patients with advanced solid tumors

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Purpose To establish a recommended phase II dose (RP2D) for the oral smoothened inhibitor sonidegib in combination with paclitaxel; secondary objectives include evaluation of safety, tolerability, markers of Hedgehog (Hh) signaling and preliminary antitumor activity. Methods Patients with advanced solid tumors were enrolled in cohorts of escalating sonidegib dose levels (400mg, 600mg and 800mg orally, once daily on days 1-28) in combination with paclitaxel 80 mg/m2 on days 1, 8 and 15 in 4-weekly cycles. Dose-limiting toxicities (DLTs) were assessed using CTCAE v4. Once the RP2D was defined, patients with advanced ovarian carcinoma were treated at this dose level in an expansion phase. Biomarkers of Hh signaling were assessed by immunohistochemistry in archival tissue and antitumor activity evaluated using RECIST 1.1. Results 18 patients were treated: 3 at 400 mg, 3 at 600 mg and 12 at 800 mg sonidegib. Only one patient treated at 800 mg presented a DLT (prolonged neutropenia resulting in failure to receive 75% of the planned sonidegib dose). However, 4 of 12 patients treated at 800 mg had their sonidegib dose reduced for toxicity after cycle 1. Hh biomarker (SHH, Patched, SMO and GLI1) staining did not correlate with clinical activity. Best response was partial response in 3 patients (2 ovarian, 1 breast cancer) and stable disease >4 cycles in 3 patients (2 ovarian, 1 anal cancer). Conclusions The combination of sonidegib and paclitaxel is tolerable and evidence of antitumor activity was identified. The RP2D of sonidegib was 800 mg in combination with paclitaxel 80mg/m2.

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