A phase 1 safety study of SBP-101, a polyamine metabolic inhibitor, for pancreatic ductal adenocarcinoma (PDA).

Abstract:

Background: SBP-101 (diethyl dihydroxyhomospermine), a polyamine (PA) analogue of spermine, inhibited growth in 6 human PDA cell lines and 3 murine xenograft tumor models. A Phase 1 dose escalation study assessed the safety, tolerability and pharmacokinetics (PK) of SBP-101 in previously treated patients with locally advanced or metastatic PDA.

Methods: In a modified 3x3 dose escalation scheme, daily subcutaneous injections of SBP-101 were dosed at 0.05, 0.1, 0.2, 0.4 or 0.8 mg/kg, Monday-Friday for 3 weeks, followed by 5 weeks of observation (1 cycle), for 1 or 2 cycles. Safety and tolerability were evaluated by clinical and laboratory assessments. PK was evaluated on Days 1 and 18 of cycle 1. Efficacy was assessed by RECIST criteria and overall survival.

Results: Twenty-nine patients were enrolled in 5 cohorts: (1: N = 3; 2: N = 5; 3: N = 4; 4: N = 7; 5: N = 10). Twenty-six had ≥2 prior chemotherapy regimens. Drug-related toxicity in cohorts 1-4 was minimal, although one patient in cohort 4 developed focal pancreatitis at 2.3 months. Most common adverse events (AEs) were abdominal pain, constipation, decreased appetite, dehydration, diarrhea, fatigue, nausea, and vomiting. Most were grades 1 or 2 or considered unlikely or not related. No drug-related bone marrow suppression or peripheral neuropathy was seen at any dose. No DLTs occurred in cohorts 1-4. Three patients in cohort 5 developed serious adverse events considered dose limiting toxicities: bacterial sepsis with metabolic acidosis (N = 1), hepatic and renal failure with elevated lipase (N = 1) and superior mesenteric vein thrombosis with metabolic acidosis (N = 1). Plasma $C_{max}$ and $AUC_{0-\infty}$ increased linearly with dose. Stable disease occurred in 2 patients each in cohorts 3 and 4, and in 4 patients in cohort 5. Median survival in cohort 3 was 5.9 months.

Conclusions: SBP-101 was well tolerated in this study at dose levels 1-4; 0.8 mg/kg exceeded the maximum tolerated dose (MTD). Best tumor response and survival occurred with 0.2 mg/kg/day. The low incidence of AEs below the MTD and absence of bone marrow toxicity or peripheral neuropathy suggest the potential for SBP-101 as an addition to front line treatment for PDA and justify a combination study. Clinical trial information: NCT02657330