DEVELOPMENTAL THERAPEUTICS-EXPERIMENTAL THERAPEUTICS

A phase I study of recombinant human arginase I (rhArgI) for patients with advanced hepatocellular carcinoma.

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Abstract

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Background: Patients (pts) with advanced hepatocellular carcinoma (HCC) have a poor prognosis. Pre-clinical data suggest that HCC cells are auxotrophic for arginine through the lack of expression of argininosuccinate synthetase. Recombinant human arginase I (rhArgI) is a novel compound which can achieve near total depletion of plasma arginine. A phase Ia/Ib, open-label, dose-escalation study was conducted to determine the safety, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor activity of rhArgI in patients with advanced HCC.

Methods: Eligibility criteria included unresectable and/or metastatic HCC with at least 1 target lesion, Karnofsky performance status (KPS) 80% or above, Child-Pugh A or B, and adequate organ function. Weekly doses of rhArgI were escalated from 500 U/kg to 3800 U/kg in a 3 + 3 design. Response was measured by computed tomography according to RECIST criteria.

Results: 15 patients enrolled at weekly doses of 500 U/kg (3 pts), 1000 (3), 1600 (3), 2500 (6). The median age was 56 years (33-74); M/F =4:1; KPS 80/90/100 = 13%/47%/40%; 86% hepatitis B carriers; 27% with prior systemic therapy, 20% with prior TACE and 40% had prior surgery. Most common AEs were: diarrhea (14%); nausea (7%) and abdominal pain (7%). Liver function derangement was presented in 14% of enrolled patients. DLT was Gr 3 prolonged elevation of bilirubin in 2 patients at 2500 U/kg. MTD was determined to be 1600 U/kg. Median duration on study was 10 weeks overall. PK and PD studies indicated that RhArgI was efficacious in inducing arginine depletion in a dose-dependent manner and adequate arginine depletion as defined by arginine level <8mM throughout treatment period, is achieved in 1,600 – 2,500 U/kg. Eight pts were evaluable for tumor response and best response was SD > 8 weeks in 4 pts (50%). The median time-to-progression was 2.8 months and the median overall survival was 5.1 months.

Conclusions: RhArgI has favorable safety profile with preliminary evidence of antitumor activity in treating patients with advanced HCC. It emerges as one of the potential promising therapeutic targets for patients with advanced HCC.