developmental therapeutics

460P PHASE I CLINICAL TRIAL OF DS-7423, AN ORAL PI3K/MTOR DUAL INHIBITOR, IN JAPANESE PATIENTS WITH ADVANCED SOLID TUMORS

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Aim: Activation of the PI3K/Akt/mTOR pathway promotes tumor growth. DS-7423 is a novel inhibitor of PI3K/mTOR and has demonstrated anticancer activity in several types of human tumor xenograft models.

Methods: This phase I dose-escalation study used the modified continuous reassessment method following escalation with overdose control. The study was conducted in Japanese subjects with advanced solid tumors. Oral DS-7423 was administered once-daily (QD) starting at dose of 4 mg. Pharmacokinetics (PK) and pharmacodynamics (PD) samples were collected from Day1 to Day29. Primary objectives were to assess the safety and PK profiles, and to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D). Blood samples and archived tumor specimens were used for biomarker analysis. All subjects provided written informed consent.

Results: A total of 26 subjects were enrolled (13 male and 13 female; age range 40-73 years), and received treatment at doses of 4mg QD (n = 3), 8 mg QD (n = 3), 16 mg QD (n = 3), 32 mg QD (n = 3), 56 mg QD (n = 3), 96 mg QD (n = 3), 160 mg QD (n = 3) and 240 mg QD (n = 5). A DLT was observed in 1 subject in the 240 mg QD cohort (Gr 4 hyperglycemia). Three additional subjects were recruited at this same dose. The MTD was not reached yet. Common adverse events were anorexia, diarrhea, nausea and rash. No objective response was observed, and 10 out of 26 patients showed stable disease (SD). Four subjects (2 thymic cancer, 1 thymoma and 1 carcinoid) showed SD over 4 months with tumor shrinkage. FDG-PET demonstrated that the 18F-FDG uptake in tumors was strongly inhibited with treatment with the higher doses of DS-7423. PK data indicated serum DS-7423 concentration was dose-proportional.

Conclusions: DS-7423, a novel inhibitor of PI3K/mTOR, is tolerated and shows evidence of anticancer activity and disease stabilization. Although the MTD was not reached in these Japanese subjects, 240 mg QD will be selected as the global RP2D, as in the US FIH study. Clinical, PK/PD and exploratory biomarker data will be presented upon availability.

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