Aim: Ponatinib is an oral multi-targeted TKI with potent preclinical activity against mutant oncoproteins KIT and PDGFRα, including a broad range of clinically-relevant primary (especially KIT exon 11) and secondary (including KIT exon 17) resistance mutants. This in vitro activity suggests it may be effective in GIST pts with failure of primary (especially KIT exon 11) and secondary (including KIT exon 17) resistance mutant oncoproteins KIT and PDGFRα.

Methods: This phase 2 single arm trial evaluated efficacy and safety of ponatinib at 45 mg qd in advanced GIST pts after failure of prior TKI therapies. Pts were enrolled in Cohorts based on the presence (A) or absence (B) of KIT exon 11 mutations. Primary end point: clinical benefit rate (CRR=CR+PR+SD at 16 wks) by modified RECIST 1.1 in Cohort A. Secondary end points: CRR in Cohort B and total; ORR, PFS, OS, safety/tolerability in each cohort and total. New pt enrollment was held due to safety observations in other ponatinib trials; enrollment criteria are being revised to include only pts with failure of all 3 GIST-approved TKI.

Results: From Jun to Oct 2013, 35 pts were enrolled (Cohorts A: 24, B: 11). Median age: 58 yrs; 46% had 2 prior approved TKIs, 46% had 3 prior approved TKIs. 74% pts had ≥4 prior cancer regimens. Median time since diagnosis: 6 yrs. Median follow-up as of Apr 7 2014: Cohorts A: 7 mos, B: 4 mos. 14 pts on study, 21 discontinued: 10 PD, 7 AE, 4 other. Cohort A CRR: 50% (11/22 pts); ORR: 9% (2/22); Best Response: 2 PR and 14 SD. All 5 Cohort A pts with matched PET scans (BL v. C1) had decreased FDG uptake in active lesions, 3 remain on study with SD or better. Cohort B CRR: 27% (3/11); ORR: 0%. Most common (≥30%) treatment-emergent AE (TEAE): rash (57%), fatigue (49%), myalgia (46%), dry skin (43%), headache (43%), constipation (40%), abdominal pain (37%), hypertension (34%) and increased serum alkaline phosphatase (31%). Serious TEAE (22 pts): abdominal pain (11%), nausea (6%), vomiting (6%), and fatigue (6%). One pt had myocardial ischemia and 1 pt had right ventricular dysfunction. There was 1 death (pneumonia) that was possibly ponatinib-related.

Conclusions: Initial analysis of this ongoing trial suggests that ponatinib has clinical activity in advanced GIST pts after failure of prior TKI therapies.

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