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Clinical activity of BLU-285 in advanced gastrointestinal stromal tumor (GIST)

Background: Oncogenic mutations in KIT or PDGFRα drive > 85% of GIST. However, primary and acquired mutations in the activation loop of PDGFRα and KIT are not effectively treated by approved therapies. A phase 1 study (NCT02508532) was initiated in advanced GIST to assess the safety, PK and clinical activity of BLU-285, a potent, highly-selective oral inhibitor that targets KIT Exon 17 and PDGFRα D842 activation loop mutants.

Methods: Adult patients (pts) with unresectable GIST, who had received ≥2 kinase inhibitors including imatinib or who had a primary PDGFRα D842 mutation regardless of prior therapy, were given BLU-285 once daily on a 4-week cycle following a 3+3 escalation design, which allowed additional accrual to dose levels demonstrated to be safe. Adverse events (AEs) per CTCAE v4.03, PK and plasma/tumor mutant DNA levels were assessed. Response was determined by RECIST 1.1 every 8 weeks.

Results: At a 01JAN17 cutoff, 40 pts (21 PDGFRa/19 KIT) have been treated with BLU-285 at doses of 30-600 mg. Median number of prior kinase inhibitor regimens was 4.5 (2-12) KIT/2.5 (0-4) PDGFRα. RECIST 1.1 responses were seen across all dose levels for PDGFRα GIST and at higher dose levels for KIT GIST. Of 17 PDGFRα D842V pts with ≥1 radiographic assessment, 7 had confirmed PR (ORR 41%) and 10 had SD. Of 11 evaluable KIT pts treated at doses ≥ 135 mg, 2 had PR (1 confirmed; ORR 18%) and 5 SD. BLU-285 is rapidly absorbed (Tmax 2-8 h), exposure increases linearly with dose, and half-life is > 24 h supporting QD dosing. Most AEs were grade 1 or 2, most commonly nausea (48%), fatigue (45%), peripheral edema, periorbital edema, vomiting (30% each), diarrhea (25%), anemia, dizziness, and lacrimation (23% each). There were no grade 4 or 5 BLU-285-related AEs, dose limiting toxicities, or discontinuations. 29 pts (all 21 PDGFRα pts) remain on treatment (duration 1-14 mo). Updated results including MTD, ct-DNA and central radiographic assessments will be presented.

Conclusions: Precision targeted therapy with BLU-285 demonstrates important clinical activity in pts with both PDGFRα- and KIT-mutant GIST that is resistant to available therapies.