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Clinical Activity in a Phase 1 Study of BLU-285, a Potent, Highly-Selective inhibitor of KIT D816V in Advanced Systemic Mastocytosis (AdvSM)

Background: The KIT D816V mutant is a key oncogenic driver found in ~90% of AdvSM, a group of poor prognosis mast cell (MC) neoplasms comprising, aggressive systemic mastocytosis (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL). The only currently approved agent to treat AdvSM is midostaurin, a multikinase inhibitor with a broad inhibitory spectrum that includes KIT D816V (IC50: 2.8 nM). In contrast, BLU-285 was designed as a highly potent (IC50: 0.27 nM) and highly specific oral inhibitor of KIT activation loop mutants including D816V. We report results from an ongoing phase 1 study (NCT02561988) in AdvSm with primary objectives to define the MTD, recommended dose for part 2 (RP2D), and safety profile of BLU-285 and secondary objectives to assess the pharmacokinetics (PK) and preliminary anti-neoplastic activity of BLU-285.

Methods: Adult patients (pts) with AdvSM or refractory hematologic neoplasms per WHO diagnostic criteria were eligible. BLU-285 was administered once daily on a 4-week cycle following a 3+3 escalation (Part 1)/dose expansion (Part 2) design. Serial monitoring on therapy included adverse events (AEs) per CTCAE, PK, biomarkers (blood/bone marrow (BM) D816V mutant allele fraction (allele-specific PCR); co-occurring somatic mutations (Illumina TruSight panel) and MC burden measures (serum tryptase, BM MC content, splenomegaly [CT or MRI]).

Results: At a 14-JUL-2017 cutoff, 30 pts (15 ASM; 9 SM-AHN; 3 MCL; 3 other D816V-mutant hematologic neoplasms) have been treated with BLU-285 in 7 cohorts at doses of 30 to 400 mg daily. 24 pts had KIT D816V mutation, 2 pts had KIT D816Y mutation, 1 pt had KIT polymorphism M541L and 3 pts had no detectable KIT alteration. 24 pts had ≥ 1 co-occurring mutation(s) in BM, most frequently *TET2* (17), *DNMT3A* (9), *ASXL1* (7), *SRSF2* (6), and *GATA2* (6). 21 pts (70%) had received prior anti-neoplastic therapy including cladribine (5), imatinib (4), interferon-α (4), midostaurin (4), 5-azacitidine (3). The median number of prior anti-neoplastic therapies for all pts was 1 (range 0-3).

BLU-285 demonstrated significant clinical activity across all dose levels, with rapid and durable reductions in MC burden and D816V mutant allele fraction relative to baseline (Table 1).

10 of 12 pts showed marked reductions of urticarial pigmentosa lesions. Improvements in malabsorption (n = 30, median (range) weight gain 5 (-3.7 to 16.3) kg; serum albumin increase 0.5 (-0.3 to 1.7) mg/dL) were also observed. Reductions in MC burden and D816V mutant allele fraction were durable with 28/30 pts remaining on therapy (7 1 year) and occurred regardless of AdvSM subtype, prior therapy, concomitant mutations, and performance status. Importantly, marked reductions in MC burden were noted in 2 MCL pts that had progressed on midostaurin and 2 ASM pts intolerant to midostaurin and all remain on therapy at 5, 12, 7, and 14 months, respectively. BLU-285 is rapidly absorbed (T_{max} 2-4 h), and half-life is ~25 h supporting once daily dosing. Mean steady-state AUC and C_{max} at 300 mg are above the maximally efficacious exposure in KIT D816-mutant xenograft models.

BLU-285 was well tolerated with most AEs being CTCAE grade 1 or 2. The most common AEs were periorbital edema (43%), anemia, diarrhea, fatigue, peripheral edema (27% each), headache (23%), thrombocytopenia, and nausea (20% each). Grade 3 treatment related AEs occurring in 2 pts included neutropenia (13%), anemia, and periorbital edema (7% each). 2 pts discontinued BLU-285 (1 PD AML; 1 pt with no detectable KIT mutation withdrew consent); no pts discontinued therapy due to drug-related AEs. 1 DLT (grade 3 alkaline phosphatase elevation) was observed at 60 mg, but an MTD was not reached. Based on safety profile, PK, and anti-tumor activity, 300 mg was selected as the RP2D. Part 2 is now enrolling. We will report additional results including response per IWG-MRT-ECNM criteria at the time of the meeting.

Conclusion: BLU-285, a potent, highly-selective inhibitor of KIT D816V and other activation loop mutants is well tolerated at the 300 mg RP2D and demonstrates considerable clinical activity in all AdvSM subtypes, including pts who have failed midostaurin and other anti-neoplastic therapies. These encouraging phase 1 data validate selective targeting of KIT D816V and warrant further clinical testing of BLU-285 in SM.

Table 1:

Measure	# Evaluable Patients (N)	Median (range) at baseline	Median (range) at best response	# with > 50% (> 35% for spleen volume) reduction n (%)
Serum tryptase (ug/L)	30	124 (14 - 1414)	11 (3 - 251)	28 (93%)
BM MC burden (%)	23	20 (2 - 95)	5 (0 – 60)	17 (74%)
Spleen volume (mL)	24	1014 (295 – 3069)	505 (143 – 1757)	13 (54%)
Blood/BM D816V allele burden (%)	23	4.5 (0.1 - 47)	1.1 (BLQ – 41)	15 (63%)