Phase-1 Study of PF-114 Mesylate in CML Failing Prior Tyrosine Kinase-Inhibitor Therapy

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Abstract

Background: PF-114 mesylate is a 4th-generation oral tyrosine kinase-inhibitor (TKI) active against wild-type and mutated *BCRABL1* isoforms including those with a *BCRABL1*^{T315I}. We present data from a phase-1 study in subjects with chronic or accelerated phase chronic myeloid leukaemia (CML) failing ≥2 TKIs or who have *BCRABL1*^{T315I} (NCT02885766).

Methods: 3+3 dose-escalation design to determine maximum tolerated dose (MTD) followed by expanded cohorts for doses ≤MTD. The primary objective was to determine the MTD and identify dose-limiting toxicities (DLTs) during cycle 1 (28 days). Secondary objectives included safety and anti-CML activity based on hematological, cytogenetic, and molecular criteria. Adverse events (AEs) were assessed and graded using NCI-CTCAE v4.03.

Results: 51 subjects were enrolled as of June 26, 2018. Daily doses were 50 mg (n=3), 100 mg (n=3), 200 mg (n=9), 300 mg (n=11), 400 mg (n=12), 500 mg (n=3), 600 mg (n=6), 750 mg (n=4) given on a continuous QD schedule. Median age was 50 years (range, 29-82 years). Median interval from diagnosis to study-entry was 10 years (range, 0-23 years). Subjects had baseline ECOG performance scores <2. 13 subjects were reported to have *BCRABL1*^{T315I}. Subjects were heavily pre-treated: 25 had received ≥3 prior TKIs; 5 subjects with *BCRABL1*^{T315I} received 1 prior TKI. 600 mg was identified as the MTD with 1 of 6 subjects experiencing a DLT at this dose (Gr 3 psoriasis-like skin lesion). Similar grade-3 skin lesions were also identified at the dose of 750 mg in 2 subjects and at 400 mg in 1 subject. Therapy is ongoing in 23 subjects at doses 200, 300 and 400 mg with median duration of exposure of 5 (range, 1-21), 3 (range, 1-12) and 4 (range, 1-19) cycles. Other subjects discontinued because of progression (n=16), AEs (n=6) or other reasons (n=6). The most common of non-hematologic toxicity was skin toxicity, which was common at doses of ≥400 mg. Grade-3 skin toxicity occurred in 3 subjects on daily dose 750 mg, 4 subjects on dose 600 mg, 1 patient on dose 500 mg and 3 subjects on dose 400 mg. Skin lesions resolved rapidly upon drug discontinuation and topical therapy. No other drug related non-hematologic grade-3 toxicities except a single case of grade-3 hepatitis on dose 400 mg were observed. No deterioration of ankle-brachial index or vascular occlusive events were observed. A complete hematologic response was achieved in 8 of 19 evaluable subjects including 3 of 8 with *BCRABL1*^{T315I}. Major cytogenetic response was achieved in 6 of 21 evaluable subjects including 3 of 7 with *BCRABL1*^{T315I}. Major molecular response was achieved in 2 of 18 subjects completing ≥13 cycles. Most cytogenetic and molecular responses were achieved at doses 200 and 300 mg which were well-tolerated and will be considered for the phase-2 study.

Conclusion: MTD of PF-114 is 600 mg with skin toxicity as the DLT. The best safety/efficacy ratio was seen at doses of 20 300 mg which are being studied in expanded cohorts and soon in a phase-2 study.

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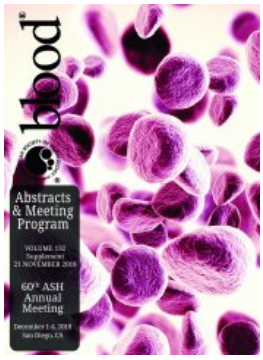

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