Efficacy of a Type I FLT3 Inhibitor, Crenolanib, with Idarubicin and High-Dose Ara-C in Multiply Relapsed/Refractory FLT3 Mutant AML

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Abstract
Crenolanib is a novel, type I and pan-FLT3 inhibitor with in vitro activity against FLT3-ITD and FLT3-TKD mutant kinase domain (TKD) mutations. Crenolanib has a half-life of 6-7 h and does not accumulate after chronic dosing. As a single agent, an overall response rate (ORR) of 33% (95% CI: 0.25-0.42) has been reported among patients (pts) with multiply relapsed/refractory (RR) AML with FLT3 mutations despite sixty-five percent of the patients having prior exposure to FLT3 inhibitors. We report data from the first 13 pts with RR FLT3+ AML treated with salvage idarubicin and high-dose ara-C (HiDAC) followed by crenolanib. In 2016, the protocol was amended to allow a maximum of 3 prior therapies in June 2016. In the dose-finding cohort, crenolanib was administered at 572 mg/m2/d for 4 d or for 3 d if >60 y), followed by crenolanib at the same dose received during induction. Patients could then continue on maintenance with crenolanib. Post-SCT crenolanib maintenance therapy was not allowed. Results: To date, all 3 dose escalation cohorts have been completed, which included 13 pts (11 males, 2 females) with a median age of 51 yrs (range 19-73). Six/13 pts had prior exposure to FLT3 inhibitors and 6-7h half-life with no accumulation after chronic dosing. Crenolanib does not circulate at detectable levels, allowing for hematologic cell count recovery. Key Eligibility

• FLT3 activating mutations w/ no restriction on FLT3 burden

• Bone marrow aspiration with blasts ≥ 50%

• Activating point mutations: E6201 (KIAA1549), ITD

• Activation loop mutations: Y842 (ITD), D835V/Y/H/R (ITD + TKD)

• 6-7h half-life with no accumulation after chronic dosing

• Adequate hepatic and renal function required

Table 1. Patient Characteristics Event Name % of Patients (Max Grade) n=15

Cough 12 67% 0 0

Neutropeniaa 11 61% 0 0

Diarthea 10 56% 0 0

Anemia 9 44% 0 0

Hypertension 8 44% 0 0

Fatigue 7 39% 0 0

Tachycardia 7 39% 0 0

Chills 7 39% 0 0

Alkaline phosphatase increased 7 39% 0 0

Blood alkaline phosphatase increased 7 39% 0 0

Blood bilirubin increased 7 39% 0 0

Edema peripheral 6 33% 0 0

Headache 6 33% 0 0

Dyspnea 6 33% 0 0

Constitution 4 22% 0 0

Cohort 3: 10 mg TID 0 0

Cohort 2: 5 Pts treated at 80 mg TID, no DLTs seen

Cohort 1: 10 mg TID in 3 of 5 pts; 1 Pt (20%) had decreased platelet count seen at day 5 of TID, therefore dose was decreased to 7 mg TID for the subsequent chemotherapy regimen

Conclusion/Current Status

- Full dose of crenolanib (100 mg TID) can be safely combined with idarubicin and high dose ara-C in multiply relapsed/refractory FLT3 mutant AML

- High overall response rate was seen in patients who had relapsed after no more than 2 previous therapies

- This trial has been expanded to allow combination of full dose crenolanib with other standard salvage chemotherapies, including MEC (mitoxantrone, etoposide, cytarabine) and FLA(G)-HiDAC (fludarabine, cytarabine, etoposide w/ or w/o G-CSF).

Table 5. Summary of CR/CRi Patients

Table 3. TEAEs Reported in ≥ 5 Patients

Table 4. Overall Survival

Table 6. Response by FLT3 Mutations