TPS7068

Phase III Randomized Study of Crenolanib versus Midostaurin Administered Following Induction Chemotherapy and Consolidation Therapy in Newly Diagnosed Subjects with FLT3-mutated Acute Myeloid Leukemia

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Abstract

Background

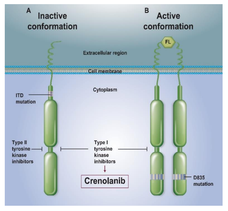
Despite the approval of multi-targeted protein kinase inhibitor midostaurin for use in combination with chemotherapy which improves 5-year survival in newly diagnosed (NDx) acute myeloid leukemia (AML) associated with *FLT3* mutations; the cumulative incidence of relapse in *FLT3* mutant AML remains high, with progression often characterized by secondary *FLT3-TKD* mutations. Crenolanib is a potent pan-*FLT3* inhibitor that has shown promising efficacy and tolerability in combination with chemotherapy in Phase 1/2 trials for AML patients with *FLT3-ITD* or *-TKD* mutations. This is the first globally initiated, randomized Phase 3 trial comparing the efficacy of two *FLT3*-TKIs, crenolanib and midostaurin, combined with intensive chemotherapy in NDx *FLT3*-mutated AML patients.

Methods

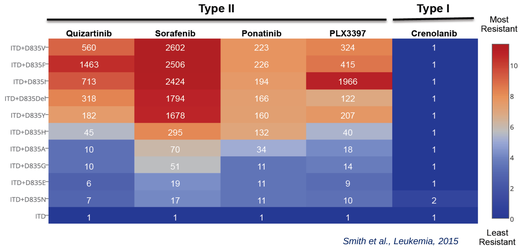
This Phase 3, randomized, multi-center trial (NCT03258931) will be conducted at multiple sites worldwide, with a target enrollment of 510 subjects. Patient inclusion was modified to match the midostaurin RATIFY criteria to enroll NDx *FLT3*-mutated AML (18 – 60 yo), who are eligible for intensive chemotherapy; with the addition of any *FLT3-ITD* and/or *-TKD* mutations being eligible. All subjects will receive TKI treatment and will be randomized in a 1:1 ratio to receive either crenolanib (arm A) or the active-control, midostaurin (arm B). All patients will be treated with 7+3 (100 mg/m^2 IV cytarabine; 90 mg/m^2 IV daunorubicin) and can initiate treatment while awaiting *FLT3* results prior to randomization. Consolidation could include chemotherapy (3000 mg/m^2 IV HiDAC) for up to 4 cycles and/or Allo-HSCT, depending on patient condition. During induction and consolidation patients on arm A will take crenolanib (100 mg TID) from d9 until 72h prior to the next cycle, and patients on arm B will take midostaurin (50 mg BID) on d8 to d21 of each cycle. Following consolidation or HSCT, patients may receive up to 13 cycles of *FLT3*-TKI maintenance. Maintenance efficacy will be evaluated using single-cell sequencing of longitudinally acquired samples to assess MRD over the course of treatment. Primary endpoint is event-free survival. Interim analyses will occur at approximately 178 and 267 events, and primary analysis at 356 events. Enrollment is underway as of January 31, 2019.

Background

- Mutations in FLT3 are found in approximately one-third of AML patients and are associated with a poor prognosis
- While FLT3 inhibitors have provided clinical benefit, combination of targeted agents with chemotherapy may provide patients the best chance at achieving durable, long-term remissions
- Crenolanib is a FLT3 inhibitor with activity against novel variant FLT3 mutations[1]
- Crenolanib has shown preliminary efficacy in combination with chemotherapy in Phase II studies[2]



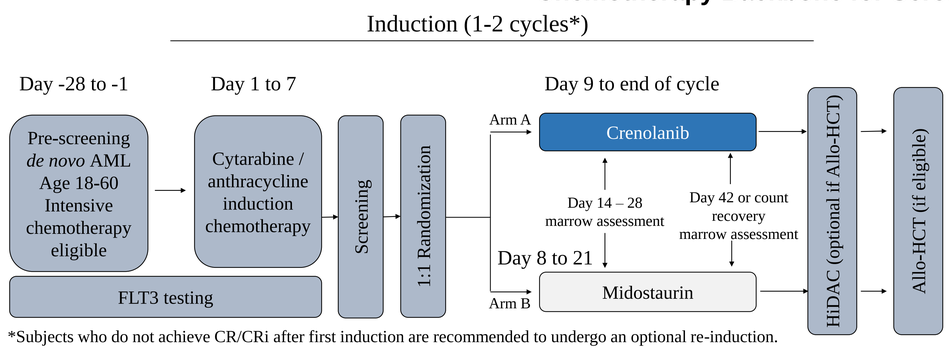
Fathi AT Blood. 2013;122(22):3547-8



Smith et al., Leukemia, 2015

Treatment Schema for Induction, Consolidation, and Maintenance

Chemotherapy Backbone for Screening and Induction

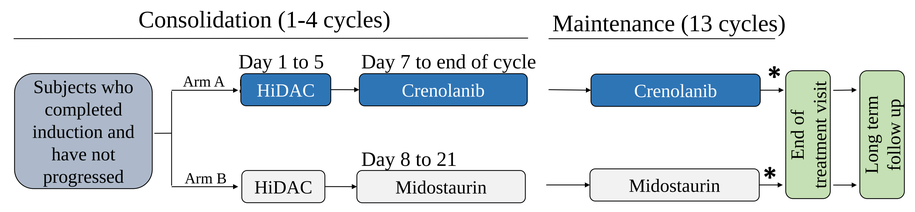


*Subjects who do not achieve CR/CRi after first induction are recommended to undergo an optional re-induction.

Cytarabine and Daunorubicin Regimen, Dose, and Schedule		
Days	**Agents**	**Dose**
D 1-7	Cytarabine	100 mg/m^2 IV continuous infusion over 24 hours
D 1-3	Daunorubicin	90 mg/m^2 IV

TKI Regimen, Dose, and Schedule			
Arm	**Days**	**Agents**	**Dose**
Arm A	Day 9 until 72 hours prior to next cycle	Crenolanib	100 mg TID p.o.
Arm B	Days 8 to 21	Midostaurin	50 mg BID p.o.

HiDAC Consolidation, Crenolanib Maintenance, and Follow-up

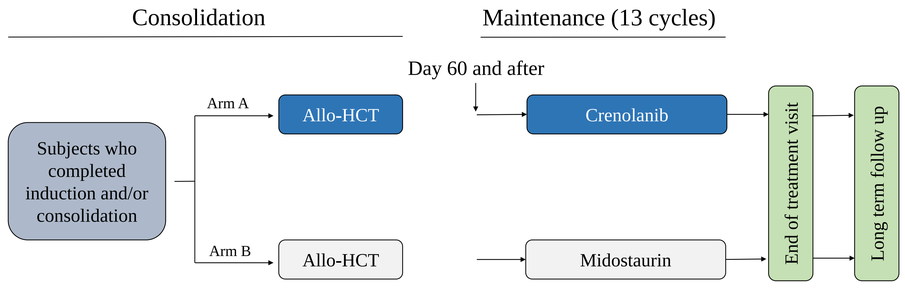


*Eligible patients may proceed to Allo-HCT after HiDAC consolidation

HiDAC Regimen, Dose, and Schedule		
Days	**Agents**	**Dose**
Days 1, 3, and 5	Cytarabine	3000 mg/m^2 IV over 3 hrs BID

TKI Regimen, Dose, and Schedule			
Arm	**Days**	**Agents**	**Dose**
Arm A	Day 7 until 72 hours prior to next cycle	Crenolanib	100 mg TID p.o.
Arm B	Days 8 to 21	Midostaurin	50 mg BID p.o.

Allo-HCT Consolidation, Crenolanib Maintenance, and Follow-up



- Subjects who are eligible should proceed to Allo-HCT, either directly after induction therapy or after HiDAC consolidation therapy

TKI Regimen, Dose, and Schedule			
Arm	**Days**	**Agents**	**Dose**
Arm A	Day 60+ to end of cycle	Crenolanib	100 mg BID p.o.
Arm B	Day 60+ to end of cycle	Midostaurin	50 mg BID p.o.

Key Eligibility

Important Inclusion Criteria

- Newly diagnosed acute myeloid leukemia
- A broad range of FLT3 mutations, including:
  - FLT3-ITD
  - FLT3-TKD (e.g. D835)
  - Other FLT3 activating mutations
- Adequate hepatic and renal function required
- Age ≥ 18 years and ≤ 60 years
- ECOG performance status 0-3
- Eligible for intensive cytarabine/daunorubicin (7 + 3) chemotherapy

Important Exclusion Criteria

- AML secondary to prior chemotherapy or radiation therapy
- AML secondary to prior myelodysplastic syndrome, or myeloproliferative neoplasms, including chronic myelomonocytic leukemia

Study Objectives

Primary Endpoints:

- Event-free Survival (EFS)

Secondary Efficacy Endpoints:

- Overall Survival (OS)
- Relapse-free Survival (RFS)

References

1. Tyner. J. et al., Functional genomic landscape of acute myeloid leukaemia. Nature, 2018. 562: 526-531.
2. Walter R.B. et al. Addition of crenolanib to standard induction and consolidation therapy improves long term outcomes in newly diagnosed FLT3-mutant AML patients ≤ 60 years old
3. Fathi A.T., Emergence of crenolanib for FLT3-mutant AML. Blood, 2013. 122(22):3547-3548
4. C.C. Smith et al. FLT3 D835 mutations confer differential resistance to type II FLT3 inhibitors. Leukemia, 2015. 29(12); 2390-92

Please contact info@arogpharma.com or visit https://clinicaltrials.gov if you would like more information about this trial or if you have a patient who may be interested in participating.