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/m² IV cytarabine; 90 mg/m² IV daunorubicin) and can initiate treatment while awaiting FLT3 results prior to randomization. Consolidation could include chemotherapy (3000 mg/m² 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.

Abstract

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.

Important Inclusion Criteria

- Newly diagnosed acute myeloid leukemia
- A broad range of FLT3 mutations, including:
  - FLT3-ITD
  - FLT3-TKD (e.g. DB35)
- 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

References

2. Walter R.B. et al. Addition of crenolanib to standard induction and consolidation chemotherapy improves long term outcomes in newly diagnosed FLT3-mutant AML patients ≤ 60 years old

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.