Addition of Crenolanib to Standard Induction and Consolidation Therapy Improves Long-Term Outcomes in Newly Diagnosed FLT3-Mutant AML Patients ≤ 60 Years Old


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Background: The multi-ikinase inhibitor midostaurin was recently approved in combination with chemotherapy for a survival benefit (5-year OS 60%) in patients with adverse risk FLT3-ITD and FLT3-TKD mutations who were intolerant to HCT. We have shown that the selective FLT3 tyrosine kinase inhibitor (TKI) crenolanib is potent and specific for FLT3ITD and FLT3-TKD mutations, would further improve patient outcomes when combined with chemotherapy. We have now reported an analysis of patients treated with crenolanib combined with chemotherapy similar to the population studied in the RATIFY trial, and to be studied in a phase III trial of chemotherapy combined with crenolanib or midostaurin in newly diagnosed FLT3-mutant AML (NCT03289337).

Aims: To assess the outcomes of a subgroup of newly diagnosed FLT3-mutant AML patients treated with crenolanib and standard chemotherapy to be targeted in a pivotal phase II trial comparing crenolanib with midostaurin.

Methods: Twenty-seven of 29 consecutive patients ≤ 60 years old enrolled in a phase II study of crenolanib combined with chemotherapy in newly diagnosed FLT3-mutant AML (NCT02283177) were included in this analysis. Two patients were excluded due to 1) prior treatment for a myeloproliferative disorder and 2) pre-existing liver cirrhosis. Patients received 7+3 induction with cytarabine 100 mg/m² for 7 days and either 1000 mg/m² idarubicin 12 mg/m² (n=16) or idarubicin 12 mg/m² (n=11) for 3 days. Crenolanib 100 mg TID was administered continuously starting 24 hours after chemotherapy until 72 hours prior to the next chemotherapy cycle.

Consolidation consisted of up to four cycles of high-dose cytarabine (HDAC): 3 g/m² for < 60 years and 1.5 g/m² for ≥ 60 years every 12 days, starting 24 hours after the final HDAC dose in each cycle. Eligible patients proceeded to allotransplantation hematopoietic stem cell transplant (HSCT). Maintenance crenolanib at 100 mg TID was started after HDAC or 30-90 days after HSCT for a maximum of 12 cycles.

Results: Patients included in the analysis were generally older (median 51 vs. 47 years for RATIFY) and most patients (86%) had FLT3-ITD mutations. Six patients had concurrent NPM1 and DNMT3A mutations, a combination associated with poor prognosis. Only 4 (15%) patients had more favorable FLT3-TKD mutations compared with 23% in the RATIFY study. As of February 2018, 22/27 (81%) patients are alive with a median follow-up of 20.8 months. Median overall survival (OS), event-free survival (EFS), and cumulative incidence of relapse (CIR) have not been reached. Fourteen patients received HSCT of which 11 are still alive without evidence of disease. Seventeen patients completed maintenance with crenolanib after HSCT. Only one of these seven patients has relapsed and the other six are alive free of disease. Of the 14 patients who completed chemotherapy without HSCT, 13 (93%) patients achieved a complete remission (CR). Of the 4 patients who received crenolanib maintenance, 3 (75%) patients achieved CR with crenolanib maintenance. Fourteen patients received HSCT of which 11 are still alive without evidence of disease. Overall, only 3 (13%) patients have relapsed, none of whom received > 1 week of crenolanib maintenance.

Conclusions: Patients treated with crenolanib + standard chemotherapy can be safely combined with cytarabine/daunorubicin or cytarabine/idarubicin induction chemotherapy. Only 3 patients have relapsed, none of whom received > 1 week of crenolanib maintenance.