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FLT3

ASH 2018 | Clinical impact of insertion site in *FLT3-ITD*-mutated acute myeloid leukemia – analysis from the phase III RATIFY trial

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The randomized phase III RATIFY trial (NCT00651261) assessed the effect of midostaurin, a multi-targeted tyrosine kinase inhibitor, in combination with standard induction and consolidation chemotherapy in patients with fms-like tyrosine kinase 3 (*FLT3*)-mutated acute myeloid leukemia (AML). In this study, 717 patients with *FLT3*-mutated AML were randomly assigned to receive either placebo or midostaurin 50 mg orally twice daily on days 8–21 of each cycle of induction and consolidation chemotherapy followed by continuous daily midostaurin for up to 12 cycles. Published data from this study showed that midostaurin in combination with standard induction and consolidation therapy prolonged the overall survival (OS) of patients with newly diagnosed *FLT3*-mutated AML.[1]

At the 60th American Society of Hematology Annual Meeting & Exposition, Frank G. Rücker from the University Hospital of Ulm, Ulm, Germany, presented data from an analysis, which aimed to assess the number and structure of internal tandem duplication (ITD) insertion sites, and its prognostic impact in patients treated in the phase III RATIFY study. The study also aimed to evaluate the predictive impact of *FLT3-ITD* insertion sites for response to treatment with midostaurin.

Next-generation sequencing (NGS) was performed in 452 of 555 *FLT3-ITD* positive patients enrolled in the RATIFY trial.

Key findings:

- Nine-hundred and eight high confidence *FLT3-ITDs* were observed in 452 patients
- According to the 4 functional groups, 70.8% of ITDs were located within the juxtamembrane domain (JMD), 17.1% of ITDs within the hinge region, 23.2% of ITDs within the beta1-sheet, and 5.9% of ITDs within the 3´of beta1-sheet
    - Fifty-four percent of patients (242/452) exhibited more than one ITD
- Correlation of ITD insertion site with $NPM1^{mut}$ revealed a significantly lower incidence of $NPM1^{mut}$ in patients with insertion located within the hinge region (47.2% *vs* 60.7%; *P* = 0.02) and 3´of beta1-sheet (34.1% *vs* 59.6%; *P* = 0.002)
- $NPM1^{mut}$ were significantly more frequent in patients with insertions affecting JMD: 60.9% *vs* 48.8%, *P* = 0.03
- Complete remission (CR) achieved within 60 days: 54.9% (248/452)
    - Significant variables for achievement of CR include number of ITDs (unfavorable; OR = 0.72, *P* = 0.0043) and concurrent *NPM1* mutation (favorable; OR = 2.69, *P* < 0.0001)
- Median follow-up for survival: 60.6 months
    - Median event-free survival (EFS) and OS were 3.9 months and 24.4 months, respectively

    - Patients exhibiting insertion exclusively in the beta1-sheet had a significantly inferior OS (*P* = 0.014) compared to patients with beta1-sheet plus other insertions and patients with other insertion sites
- Patients with sole beta1-sheet insertions might not derive benefit from treatment with midostaurin

The speaker concluded by stating that "in this large cohort of 452 *FLT3-ITD* mutated AML treated within the RATIFY trial, the negative prognostic impact of the beta1-sheet insertion site of *FLT3-ITD* could be confirmed."

References

1. Stone R.M. *et al*. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 Mutation. N Engl J Med. 2017 Aug 3; 377(5): 454–464. DOI: 10.1056/NEJMoa1614359. Epub 2017 Jun 23.
2. Rücker. F. G. *et al*. Prognostic impact of insertion site in acute myeloid leukemia (AML) with FLT3 internal tandem duplication: results from the Ratify study (Alliance 10603). 2018 Dec 2; Oral Abstract #435: 60th ASH Annual Meeting and Exposition, San Diego, CA.