AMLGlobalPortal

FLT3, NPM1

ASH 2017 | Impact of NPM1/FLT3-ITD genotype on the clinical outcomes of patients treated in the phase III RATIFY study

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The phase randomized III RATIFY trial (NCT00651261) assessed the effect of midostaurin, a multi-targeted tyrosine kinase inhibitor, in combination with standard induction and consolidation chemotherapy in Fms-Like Tyrosine Kinase 3 (*FLT3*)-mutated Acute Myeloid Leukemia (AML) patients. In this study, 717 *FLT3* mutated AML patients 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 newly diagnosed *FLT3*-mutated AML patients.[1] More results of this study were reported on the AML Global Portal (AGP) in July 2017.

At the 59th American Society of Hematology (ASH) Annual Meeting, Atlanta, GA, Konstanze Döhner, MD, from the University Hospital of Ulm, Ulm, Germany, presented data from a post-hoc analysis, which aimed to evaluate the clinical impact in a post-hoc analysis of Nucleophosmin 1 (*NPM1*)/ *FLT3*- Internal Tandem Duplication (*FLT3-ITD*) genotypes as defined by the 2017 European LeukemiaNet (ELN) recommendations, in patients treated within the phase III randomized RATIFY trial (NCT00651261). The post-hoc analysis also aimed to evaluate the potential impact of midostaurin in distinct *NPM1*/*FLT3-ITD* genotypes.[2]

In this post-hoc analysis, 428 patients (median age = 47 years) of 717 patients enrolled in the RATIFY study with biomarker analysis were categorized into one of the four ELN *NPM1*/*FLT3* subgroup including $NPM1^{mut}$/$FLT3\text{-}ITD^{low}$ (n = 85), $NPM1^{mut}$/$FLT3\text{-}ITD^{high}$ (n = 159), $NPM1^{wt}$/$FLT3\text{-}ITD^{low}$ (n = 75) and $NPM1^{wt}$/$FLT3\text{-}ITD^{high}$ (n = 109). The median follow-up time was 59 months (range, 42–81)

Key findings:

- Median OS in patients in the $NPM1^{mut}$/$FLT3\text{-}ITD^{low}$, $NPM1^{mut}$/$FLT3\text{-}ITD^{high}$, $NPM1^{wt}$/$FLT3\text{-}ITD^{low}$, and $NPM1^{wt}$/$FLT3\text{-}ITD^{high}$ group; not reached *vs* 27 *vs* 20 *vs* 17 months respectively, $P = 0.001$
- Median Event Free Survival (EFS) in patients in the $NPM1^{mut}$/$FLT3\text{-}ITD^{low}$, $NPM1^{mut}$/$FLT3\text{-}ITD^{high}$, $NPM1^{wt}$/$FLT3\text{-}ITD^{low}$, and $NPM1^{wt}$/$FLT3\text{-}ITD^{high}$ group; 16 *vs* 8 *vs* 4 *vs* 4 months respectively, $P = 0.001$
- Median OS in patients in the $NPM1^{wt}$/$FLT3\text{-}ITD^{high}$ treated with midostaurin or placebo; 26 *vs* 14 months respectively, $P = 0.025$
- Median EFS in patients in the $NPM1^{wt}$/$FLT3\text{-}ITD^{high}$ treated with midostaurin or placebo; 8 *vs* 3 months respectively, $P = 0.016$
- Analysis censored at allo-HCT

- Median OS was significantly better in the midostaurin arm compared to placebo in patients with *NPM1*^{mut}/*FLT3-ITD*^{low} (*P* = 0.038) and *NPM1*^{mut}/*FLT3-ITD*^{high} (*P* = 0.032) genotype
- Median OS was not significantly different between the midostaurin and the placebo arm in patients with *NPM1*^{wt}/*FLT3-ITD*^{high} genotype
- Median EFS in patients in the *NPM1*^{wt}/*FLT3-ITD*^{high} treated with midostaurin or placebo; 8 *vs* 3 months respectively, *P* = 0.016

- Significant independent prognostic factors for OS include *NPM1*/*FLT3-ITD* genotype (*P* < 0.001), treatment arm with midostaurin in favor to placebo (*P* = 0.011), white blood cell count (*P* = 0.028) and allo-HCT (*P* < 0.001)

Konstanze Döhner concluded by noting that the findings of this post-hoc analysis suggests a "high prognostic value of the *NPM1*/*FLT3-ITD* genotypes" which provides support for the 2017 ELN risk stratification that includes *FLT3-ITD* allelic burden.

Furthermore, an advantageous effect for midostaurin was more prominent in patients with *NPM1*^{wt}/*FLT3-ITD*^{high} genotype although these patients might not benefit from allo-HCT.

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; 277(5): 454–464. DOI: 10.1056/NEJMoa1614359. Epub 2017 Jun 23.
2. Döhner K. *et al*. Prognostic Impact of NPM1/FLT3-ITD genotypes from Randomized Patients with Acute Myeloid Leukemia (AML) Treated within the International Ratify Study Oral Abstract #467; 59th ASH Annual Meeting and Exposition, Atlanta, GA.