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FLT3

Randomized phase IIb study of two doses of quizartinib in patients with relapsed or refractory acute myeloid leukemia

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Jorge Cortes from MD Anderson Cancer Center (MDACC), Houston, TX, and colleagues reported data from a randomized phase IIb study (NCT01565668), which is assessing the safety and efficacy of two quizartinib (an oral, highly potent and selective FLT3 inhibitor) dosing regimens in patients with relapsed /refractory (R/R) *FLT3*-internal tandem duplication (*FLT3-ITD*)-mutated acute myeloid leukemia (AML) who previously underwent hematopoietic stem cell transplantation (HSCT) or received one second-line salvage therapy. The results of the study were reported in Blood in June 2018.[1]

In previous clinical studies, quizartinib has demonstrated promising clinical activity in patients with R/R AML, however, QT interval corrected by Fridericia's formula (QTcF) was a dose-limiting toxicity. The main objective of this phase IIb study was to determine whether different doses of quizartinib would have the same clinical activity while improving the safety in patients with R/R *FLT3*-mutated AML. Between May 2012 and March 2015, 76 patients (median age = 55 years, range 19–77) were enrolled and randomized to receive either 30 mg/day (n = 38) or 60 mg/day (n = 38) quizartinib.

The primary endpoints of the study were composite complete remission (CRc) rate and the incidence of grade ≥ 2 QTcF.

Key findings:

Efficacy

- CRc rate
  - All patients: 47.4% (50/76)
  - 30 mg arm: 47.4 (18/38)
  - 60 mg arm: 47.4 (18/36)
- Median duration of CRc in the 30- and 60 mg arms: 4.2 (95% CI, 2.1–9.7) vs 9.1 (95% CI, 4.1–22.3) weeks, respectively
- Median overall survival (OS) in the 30- and 60 mg arms were 20.9 (95% CI, 17.7–25.3) and 27.3 (95% CI, 17.3–34.9) weeks, respectively
- Twelve patients (32%) in the 30 mg arm and 16 patients (42%) in the 60 mg arm were bridged to HSCT
- Twenty-three patients (61%) in the 30 mg arm were escalated to 60 mg/day quizartinib
- Five patients (14%) in the 60 mg arm were escalated to 90 mg/day quizartinib

Safety

- Grade ≥ 2 QTcF (>480 msec) prolongation occurred in 11% and 17% of patients in the 30- and 60 mg arm, respectively

- Grade 3 QTcF prolongation (>500 msec) occurred in 5% and 3% of patients in the 30- and 60 mg arm, respectively
- Most common treatment-related treatment-emergent adverse events (TR-TEASs) include anemia (20%), febrile neutropenia (11%), nausea (16%), diarrhea (11%) and fatigue (12%)
    - Four patients discontinued treatment due to TR-TEASs, all of whom in the 30 mg arm

In summary, the findings of this randomized phase IIb study demonstrated encouraging anti-leukemic activity and an improved safety profile particularly in terms of QTcF prolongation, according to the researchers. Moreover, compared to quizartinib at 30 mg/day, quizartinib at 60-mg/day was associated with higher CRc rate, OS, and more patients were bridged to transplant in this arm. Key limitations of this study include the trial design and the small sample size.

The researchers concluded that the benefit-risk profile of quizartinib in R/R *FLT3-ITD*-mutated AML warrants further evaluation of the 60-mg once daily dose which is currently being investigated in the phase III randomized QuANTUM-R study (NCT02039726). The phase III study is assessing the efficacy and safety of quizartinib (60 mg, with a 30 mg lead-in for 15 days) *versus* salvage chemotherapy in patients with R/R *FLT3-ITD*-mut AML. Data from this study presented at the 23rd Congress of the European Hematology Association, Stockholm, Sweden, demonstrated that quizartinib significantly prolongs OS in R/R *FLT3-ITD* AML patients compared to salvage chemotherapy. More results from this study were reported here.[2]

References

1. Cortes J. *et al*. Phase 2b study of two dosing regimens of quizartinib monotherapy in FLT3-ITD mutated, relapsed or refractory AML. Blood. 2018 Jun 6. DOI: 10.1182/blood-2018-01-821629. [Epub ahead of print].
2. Cortes J. *et al*. Quizartinib significantly prolongs overall survival in patients with FLT3-internal tandem duplication–mutated (MUT) relapsed/refractory AML in the phase 3, randomized, controlled QuANTUM-R trial. Abstract LB2600. 23rd Congress of the European Hematology Association; 2018 June 14–17, Stockholm, SE.