VIEWPOINTS

Exciting Progress in Acute Myeloid Leukemia Management

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QuANTUM-First: Clinically meaningful improvement in overall survival with quizartinib in patients with newly diagnosed *FLT3*-ITD-positive AML

Of the many genetic mutations associated with acute myeloid leukemia (AML), alterations in the *FLT3* gene are the most common.[1] Patients with a mutation in *FLT3* often have a poor prognosis, high relapse rates and inferior overall survival (OS).[2] Therefore, its encoded protein, the class II receptor tyrosine kinase, is a prime therapeutic target. Quizartinib is a highly potent, selective, second-generation inhibitor of class II receptor tyrosine kinases[3] and has shown signs of clinical efficacy and a manageable safety profile.[4-6] The QuANTUM-First study is the first randomized trial investigating the efficacy and safety of quizartinib in patients with relapsed/refractory (R/R) AML who are *FLT3*-internal tandem duplication positive (ITD+) and less than 75 years old with up to 3 years of continuation therapy.[7] The primary endpoint of this double-blind, placebo (PBO)-controlled phase III trial was OS; key secondary endpoints included safety, event-free survival (EFS) and complete response (CR).

Newly diagnosed patients (n=539) between the age of 18 and 75 years and ≥3% *FLT3*-ITD allelic frequency were randomized 1:1 to either the treatment arm or the control arm. Patients in the treatment arm (n=268) were initially put on 2 cycles of standard induction therapy of cytarabine 200 mg/m^2/day for 7 days, daunorubicin 60 mg/m^2/day or idarubicin 12 mg/m^2/day for 3 days and quizartinib (40 mg, once daily, 8–21 days). Following this, 4 cycles of consolidation therapy began with high-dose cytarabine (HiDAC) and quizartinib (40 mg, once daily), with or without allogeneic hematopoietic stem cell transplant (allo-HCT). The study protocol ended with a continuation stage, where quizartinib (60 mg, once daily) was administered for up to 36 cycles. Patients in the control arm (n=271) received an oral placebo instead of quizartinib with the same treatment over the course of the study. Of the 265 treated patients in the treatment arm, 116 patients entered the continuation phase of single-agent quizartinib, with the remainder of patients discontinuing for reasons such as death (n=133) and withdrawal of consent (n=13). In the control arm, 92 of 268 patients entered the

continuation phase, where they received a single-agent placebo. The primary reasons for discontinuation in this group were death (n=158) and the withdrawal of consent (n=9).

Gender distribution between the two arms was comparable, although there were more female than male participants which is rare for clinical trials of this nature. The proportion of patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 1 was similar in the two treatment arms (quizartinib: 50.0% vs placebo: 50.2%). In the quizartinib group, 73.5% of patients had an intermediate cytogenetic risk, which was similar to the placebo group, with 71.2%. Over half of the patients in each group harbored a mutation in the *NPM1* gene (53.0% vs 51.7%). Furthermore, the *FLT3*-ITD/total *FLT3* allele burden was >25% to ≤50% in 53.4% of quizartinib-treated patients and 50.9% in placebo-treated patients.

Regarding the primary endpoint, the median OS was longer in the quizartinib group versus the placebo group (31.9 months vs 15.1 months; HR: 0.776 [95% CI: 0.615–0.979]; p=0.0324).[7] In addition, OS in patients achieving CR was investigated in a post hoc analysis, which compared patients on whether they received allo-HCT. This analysis showed that the difference between the two treatment arms could not be equalized by using allo-HCT, the inclusion of which greatly prolonged the OS in patients with CR compared with patients who did not receive allo-HCT (HR: 0.591 [95% CI: 0.330–1.059] vs HR: 0.607 [95% CI: 0.387–0.954], respectively). Furthermore, the duration of CR is a major consideration, given that the median CR was 38.6 months in the quizartinib group versus 12.4 months in the placebo group. A higher proportion of patients achieved a CR with incomplete hematologic recovery (CRi) in the quizartinib group compared with placebo (16.8% vs 9.6%). An additional post hoc analysis showed that the rate of relapse after 24 months in patients who achieved CR was higher in the placebo group compared with the quizartinib group, further supporting the effectiveness of the test drug (43.3% vs 31.2%).

In conclusion, quizartinib showed a clinically meaningful improvement in OS when combined with standard induction and consolidation therapy which continued for up to 3 years in patients aged 18–75 years with newly diagnosed *FLT3*-ITD+ AML. This OS improvement was robust and long-lasting. No new safety signals were reported with quizartinib combined with intensive chemotherapy and as continuation monotherapy. The data showcased in this study have the potential to change the standard of care for the treatment of this patient population.

Triplet therapy shows activity in heavily pretreated older/unfit patients with *FLT3*-ITD AML

FLT3-ITD mutations are observed in 20–30% of all patients with AML.[8] These mutations are associated with an increased likelihood of relapse as well as a poor OS; this is especially evident in older/unfit patients with newly diagnosed *FLT3*-mutated AML.[9] Quizartinib has shown a clinical benefit in OS and response rates in patients with R/R *FLT3*-mutated AML.[10] In this context, the primary objective of this phase I/II study was to establish the recommended phase II dose (RP2D) of quizartinib (QUIZ) in combination with decitabine (DAC) and venetoclax (VEN) in patients with newly diagnosed *FLT3*-ITD mutated AML or high-risk myelodysplastic syndrome (MDS) or R/R *FLT3*-mutated AML unfit for intensive chemotherapy.[11] Key secondary objectives included the complete remission rate (CRc), CR with incomplete recovery (CRi), minimal residue disease (MRD) rate and the OS. All patients started with an induction therapy of DAC (20 mg/m^2 for 10 days) in Cycle 1. Patients then underwent bone marrow (BM) biopsy after 14 days, and VEN (400 mg/day starting from day 1) was put on hold in patients with BM blasts ≤5% or aplasia. Those with BM blast >5% at day 14 continued VEN treatment for 21 days during cycle 1. In subsequent cycles, DAC was reduced to 5 days. QUIZ (30–40 mg/day) was administered daily. Of the 35 patients enrolled, 28 had R/R for *FLT3*-ITD AML, 23 of whom achieved CRc (3 CR, 15 CRi).

The dose-limiting toxicity (DLT) of quizartinib was 40 mg when in combination with decitabine and venetoclax. Following these results, the trial investigators decided on the RP2D of 30 mg. On day 14, BM blasts count of ≤5% was seen in 46% (n=13) of patients with R/R *FLT3*-ITD AML and in 100% (n=7) of patients in the frontline setting, demonstrating the effectiveness of the triplet combination. In a subgroup analysis of patients previously treated with gilteritinib, 80% of patients with R/R *FLT3*-ITD AML showed complete remission. Regarding tolerability, myelosuppression is a concern for clinicians. When quizartinib therapy was continued beyond 28 days, the median time to neutropenia was longer in patients compared with those who discontinued quizartinib at Day 28 (51 days vs 26 days). Regarding OS, there was a 1-year OS rate of 32% in responders in the R/R cohort. Overall, in this phase I/II study, quizartinib showed activity in heavily pretreated patients as well as patients previously treated with an FLT3 inhibitor, with a CRc rate of 82%, a median OS of 6.9 months and a 1-year OS rate of 25%.

"InDACtion" versus "3+7" trial: Possibility of substituting intensive chemotherapy with 10-day decitabine in AML patients aged >60 years

In the phase III study of the European Organization for Research and Treatment of Cancer (EORTC) Leukemia Group, CELG, GIMEMA and German MDS study group, 10-day decitabine was compared with conventional chemotherapy ("3+7") followed by allografting in AML patients with age >60 years.[12] This open-label trial enrolled patients who were newly diagnosed with AML, were eligible for intensive chemotherapy (IC) and had a World Health Organization (WHO) PS of 0–2. Patients were randomized 1:1 to receive either IC or a 10-day treatment regimen of decitabine in cycle 1, followed by 10- or 5-day regimens in subsequent cycles. IC treatment included daunorubicin (60 mg/m^2 for 3 days) and cytarabine (200 mg/m^2 for 7 days), followed by 1–3 additional chemotherapy cycles. Both groups progressed, if possible, to allografting, decitabine maintenance was an alternative to allografting in the decitabine treatment arm. The primary endpoint of this trial was OS and the key secondary endpoints included CR/CRi, progression-free survival (PFS), disease-free survival (DFS), transplantation rate and safety.

The median age of patients in the decitabine group and the IC group was 67 years and 68 years, respectively.[12] Within each group, the majority of patients had an ECOG PS score of 0 (50% vs 52%). Nearly half of the patients within each group had a normal karyotype (53% vs 45%). In the IC arm, marginally better CR/CRi results were seen in slightly younger patients (age: 60–64) compared with the decitabine arm, as well as in patients with favorable cytogenetics. In general, however, the results in terms of CR were uniform between the two groups. The OS was not significantly different between the decitabine and IC groups (HR: 1.04 [95% CI: 0.86–1.26]; p=0.68). The median OS was comparable, with 15 months in the decitabine group and 18 months in the IC group; this OS trend was similar in the allo-HSCT patients. The major difference between the two groups recorded in this trial concerned tolerability. Grade 3–5 treatment-emergent adverse events (TEAEs) were more prominent in the IC group compared with the decitabine group. The incidence of grade 5 TEAEs after HSCT was comparable in both treatment arms (25% vs 22%). In conclusion, 10-day decitabine and IC, followed by an allogeneic BM transplant, had a similar OS rate across the subgroups in this trial. Despite a slightly lower CRc compared with the IC group, the decitabine group had a better tolerability rate and health economics profile. These results suggest that 10-day decitabine may, in some patients, be a viable management strategy in place of the 3+7 intensive chemotherapy.

Conflict of interest

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Author contributions

The author has created and approved the final manuscript.

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