

S131 A RANDOMISED ASSESSMENT OF THE SEQUENTIAL ADDITION OF THE KINASE INHIBITOR QUIZARTINIB TO INTENSIVE CHEMOTHERAPY IN OLDER ACUTE MYELOID LEUKAEMIA (AML) PATIENTS: RESULTS FROM THE NCRI AML18 TRIAL

Topic: Novel combinations in the treatment of AML

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Background:

The benefit of adding tyrosine kinase (TK) inhibition to intensive chemotherapy (IC) has not been demonstrated in patients aged >60yrs with newly diagnosed AML. Quizartinib (Quiz) is a class III receptor TKI with potent activity against FLT3 and clinical activity in relapsed/refractory FLT3-ITD+ AML. We have previously demonstrated that Quiz can be safely given sequentially after IC in older AML patients (Burnett et al, Blood 2013; 122:622).

Aims:

To assess whether the addition of Quiz following IC and as maintenance, improves survival in older AML patients.

Methods:

The NCRI AML18 Trial assessed several therapeutic questions in older patients with AML or high-risk MDS (>10% blasts). Following recovery from course 1, comprising daunorubicin 60mg/m² d1, 3, 5, AraC 100mg/m² bd d1-10 with 1 or 2 doses of gemtuzumab ozogamicin, patients were randomised (1:1) to receive Quiz or not irrespective of FLT3 status; those allocated Quiz were additionally randomised (1:1) between short and long therapy. Patients in both groups received Quiz 40mg/day for 14 days immediately following chemotherapy cycles 2 (DA or FLAG-Ida) and 3 (DA, mini-FLAG-Ida or IDAC) and for an additional 28 days following recovery from the final course. Long Quiz patients received 12 additional 28-day cycles of maintenance (including post allogeneic HSCT). Following interim advice from the IDMC in Jun 2019, the Quiz randomisations were restricted to FLT3-mutated patients (ITD and TKD).

Results:

Between Nov 2014 and Apr 2022, 464 patients were randomised to Quiz (n=233, long 116, short 117) or not (n=231). Median age was 68 yrs (51 - 79), AML remission status at time of randomisation was CR 68% (317), CRi 9% (40), flow MRD+ 43% (174), MRD- 57% (234), MRD unknown in 56 pts. 96 patients (22%) had FLT3-ITD mutation, 23 (5%) FLT3-TKD mutation, 2 (<1%) had both ITD and TKD and 314 (73%) were FLT3 wild type (WT). All characteristics, including FLT3 mutation type, allelic burden and NPM1 co-mutation, were balanced between arms. Median follow-up was 54 months. No difference was seen in median OS between Quiz and no Quiz patients (29 vs 29 months [HR = 1.035 (0.822-1.303); P = 0.768]) (Fig 1a) or between short and long Quiz (27 vs 30 months). There was a non-significant trend towards improved OS in FLT3-mutated patients allocated Quiz (33 vs 26 months; HR 0.69 (0.43 - 1.12); P = 0.123) (Fig 1b) and no difference between short and long Quiz. No

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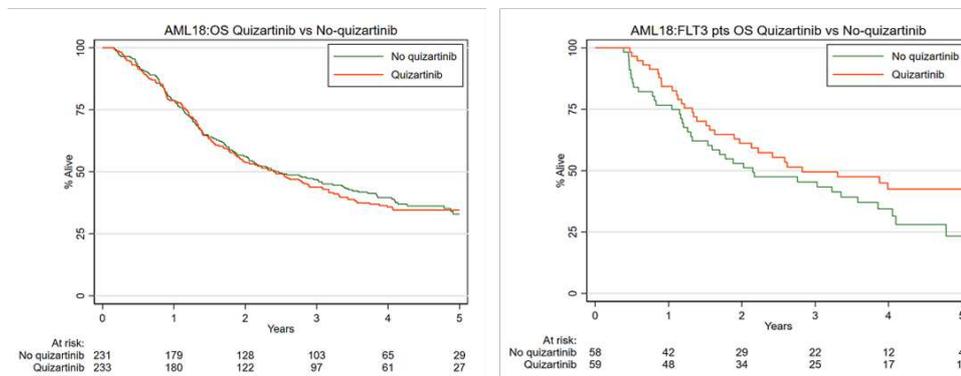
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differences were observed in median RFS between Quiz or not across the whole study population (18 vs 19 months; HR = 1.07 (0.86 – 1.34); P = 0.550) or in *FLT3*-mutated patients (21 vs 13 months; HR = 0.77 (0.49 – 1.21); P = 0.254). Allogeneic HSCT was performed in 36% (168) patients (53% [89] Quiz [26% (46) short, 27% (43) long] and 47% (79) no Quiz) and, after censoring for SCT, no significant differential effect of Quiz on OS was observed in either the whole population [HR = 0.99 (0.75 – 1.30); P = 0.916] or *FLT3*-mutated cohort [HR = 0.58 (0.32 – 1.04); P = 0.067]. Minimal difference in toxicity was seen; rates of grade ≥ 3 adverse events and supportive care requirements were similar with no difference in time to neutrophil or platelet recovery.

Summary/Conclusion:

In older AML patients, the sequential addition of Quiz to IC was well-tolerated but did not lead to improved survival. Although not powered to assess benefit, a sub-group analysis of *FLT3*-mutated patients showed a non-significant trend to survival benefit consistent with the results of the QuANTUM-First trial (Erba et al, EHA,2022).

Figure 1: Overall Survival Quizartinib vs not in (1a) whole population and (1b) *FLT3*^{mut} AML



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