QUIZARTINIB WITH DECITABINE AND VENETOCLAX (TRIPLET) IS ACTIVE IN PATIENTS WITH FLT3-ITD MUTATED ACUTE MYELOID LEUKEMIA - A PHASE I/II STUDY

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Background

Quizartinib (QUIZ), a potent 2nd generation FLT3 inhibitor (FLT3i) demonstrated synergy with venetoclax (VEN) in AML cell lines and PDX models (Mali Haematologica 2020).

Aims

To evaluate the safety and efficacy of Decitabine (DAC) + VEN + QUIZ triplet in patients (pts) with newly diagnosed (ineligible for intensive induction chemotherapy) or relapsed/refractory (R/R; up to 5 prior chemotherapies) FLT3 ITD mutated AML.

Methods

All pts received 10 days of DAC (20 mg/m2) in Cycle 1. Pts underwent day 14 bone marrow (BM) biopsy, and VEN (400 mg/day starting from day1) was put on hold in pts with BM blasts ≤ 5% or aplasia. Those with day14 BM blast >5% continued VEN for 21 days during cycle 1. In subsequent cycles, DAC was reduced to 5 days. QUIZ (30 or 40 mg/day) was administered daily continuously.

Results

Overall 28 pts were enrolled and evaluable at the time of this report. Of 23 pts with R/R AML (median 3 prior Rx, 78% with ≥1 prior FLT3i including prior gilteritinib in 70%, and 39% had a prior alloSCT), 78% achieved CRc (3 CR, 15 CRi) with 6/16 and 5/18 responders achieving FLT3-PCR and multicolor flow cytometry negativity, respectively. The CRc rates were 75% and 72% in pts who received prior gilteritinib and prior HMA+VEN, respectively. 60-day mortality rate was 5%. Of 5 pts with newly diagnosed AML (median age 69), all achieved CRc (2 CR, 3 CRi) with 4/5 and 2/4 responders achieving FLT3-PCR and MFC negativity, respectively. 60-day mortality in frontline was 0.

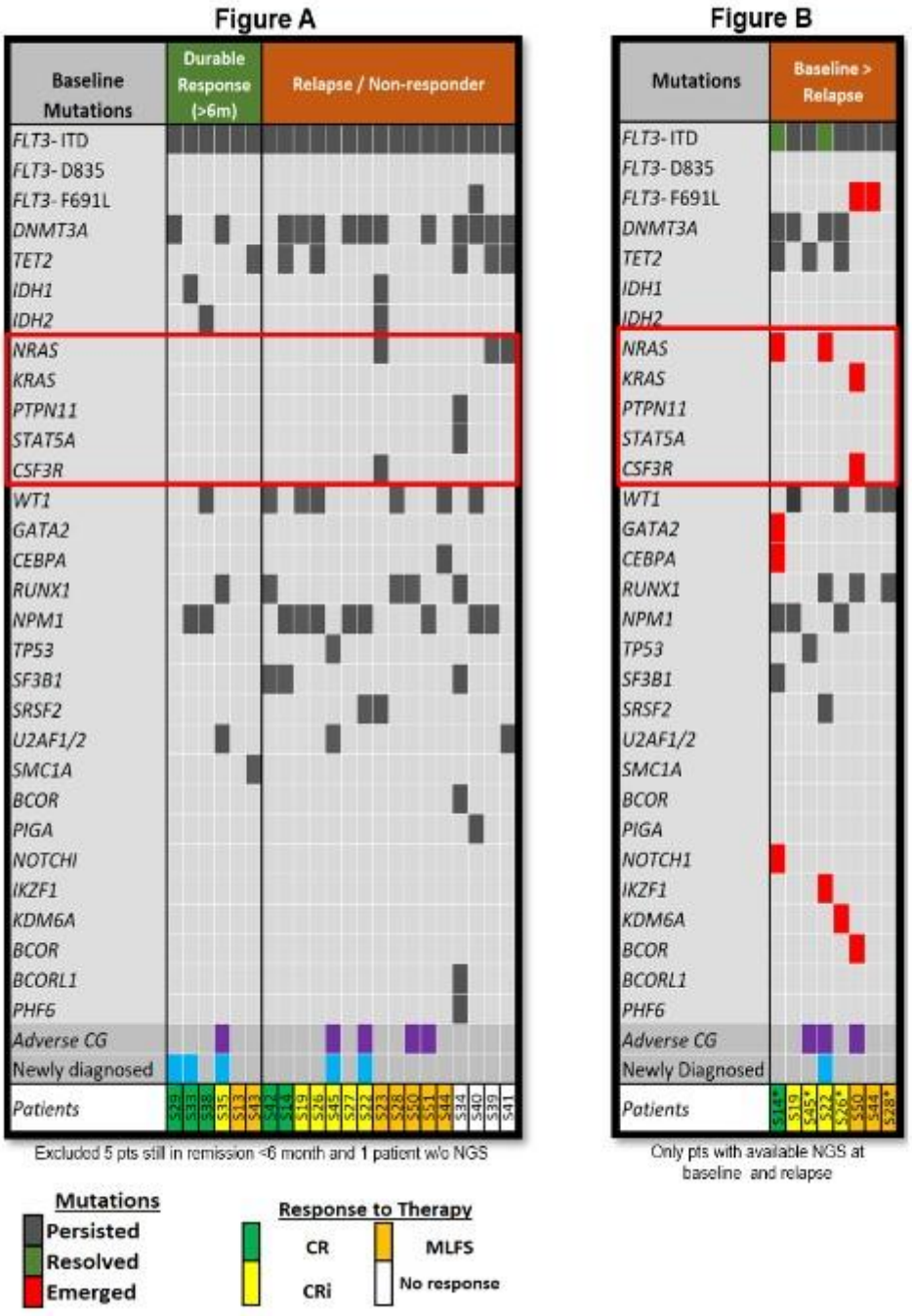
RAS/MAPK mutations appear to drive both primary and secondary resistance. Pts with underlying RAS/MAPK mutations had the lowest response rates, at 40% compared to 94% in those without**.** None of the six pts who achieved a durable remission (> 6months) had RAS/MAPK mutations at baseline (**Figure A**). 4 of 16 (25%) of pts who relapsed (< 6 months of remission) or were refractory to this triplet regimen had baseline RAS/MAPK mutations. We

had pre- and post-treatment NGS data from 8 pts who had a response but then relapsed (**Figure B**). Emergent RAS/MAPK mutations were noted in 37% of relapses (3/8), while emergent FLT3 F691L gatekeeper mutations was noted in 25% of relapses (2/8). Interestingly, there were no emergent FLT3 TKD mutations.

No pts developed a dose limiting toxicity (DLT) with 30 mg/day quizartinib, however with the 40mg/day quizartinib 2 pts developed hematologic DLT (grade 4 neutropenia with a <5% cellular bone marrow lasting ≥42 days). Hence, quizartinib 30 mg/day dose was determined to be the recommended phase 2 dose for the triplet. Most common Grade 3/4 non-hematologic toxicities included lung infections (42%) and neutropenic fever (30%). No QTcF prolongations >480 msec were noted.

With a median follow-up (f/u) of 13 months, the median OS was 7.6 months in R/R cohort. Median OS in prior Gilt exposed pts was 6.3 months and ≥1 prior FLT3i exposed pts was 6.3 months. 8/18 R/R pts (including 5/8 prior Gilt exposed pts) underwent ASCT with a median OS of 19 vs 8 months in pts who underwent ASCT versus not (p=0.26). Of the 5 frontline responding pts median OS was 14.5, 2 were alive in CR, 1 died in CR1 post-ASCT, 2 died due to progressive disease at the last f/u.

RAS/MAPK mutations drive primary and secondary resistance



Conclusion

DAC + VEN + QUIZ is active in R/R FLT3-ITD mutated AML pts, with CRc rates of 78% and the median OS of 7.6 months. The high response rate was maintained in prior Gilteritinib exposed pts. Interestingly, RAS/MAPK mutations but not emergent TKD mutations were associated with primary and secondary resistance to the triplet. Accrual continues and updated clinical, NGS and mass cytometry (CyTOF) data will be presented.