## Abstract: P560

# Title: IMPACT OF TP53 MUTATIONS IN PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML) DURING ORAL AZACITIDINE MAINTENANCE THERAPY: OUTCOMES FROM THE QUAZAR AML-001 TRIAL

**Abstract Type: Poster Presentation**

**Topic: Acute myeloid leukemia - Clinical**

**Background:**

*TP53* mutant (mut) AML is a poor-risk entity, present in ~20% of older patients (pts) and associated with poor survival (OS <9 months, mo). Only a small fraction of pts are successfully bridged to allogeneic stem cell transplant (SCT), thus alternative post-remission strategies are needed. Among pts with *TP53*mut MDS-EB or AML achieving CR after intensive chemotherapy (IC), 73% have persistent *TP53*mut in remission (Grob, *Blood* 2022). In the QUAZAR trial (NCT01757535), Oral azacitidine (Oral-AZA) significantly prolonged OS and RFS vs placebo (PBO) as maintenance therapy in pts with AML in first remission after IC who were ineligible for SCT (Wei, *NEJM* 2020). The impact of post-remission Oral-AZA maintenance on the natural history of disease course of pts with persistent *TP53*mut after IC or AML is not known.

**Aims:**

To characterize 1) *TP53*mut prevalence post IC, 2) flow MRD status and response to Oral-AZA maintenance therapy, 3) clinical outcomes according to post-remission *TP53*mut status, 4) changes in clonal architecture from baseline (BL) to relapse after Oral-AZA vs PBO.

**Methods:**

Among pts who consented to biomarker analyses, targeted NGS (37 myeloid genes) was performed on bone marrow DNA. *TP53* sequencing covered all coding regions (exons 1-11). Mean NGS coverage was 13K reads and median minimal detectable variant allele frequency (VAF) was 0.12% (range: 0.04–0.30). RFS and OS were estimated by Kaplan–Meier methods.

**Results:**

In the NGS cohort (n=310), median RFS (mRFS) for Oral-AZA vs PBO was 10.2 vs 4.7 mo, respectively (P=0.0005). At study BL, 221/310 pts (71.3%) had detectable mutations, with *TP53*mut identified in 48 pts (15%). In remission pts, the median *TP53*mut VAF was 0.8% and 46% had VAF >2%. Multihit *TP53* abnormalities were present in 15 (31%) cases. Pts with *TP53*mut were more commonly male, had adverse cytogenetic risk and secondary AML and/or AML with myelodysplasia-related changes.

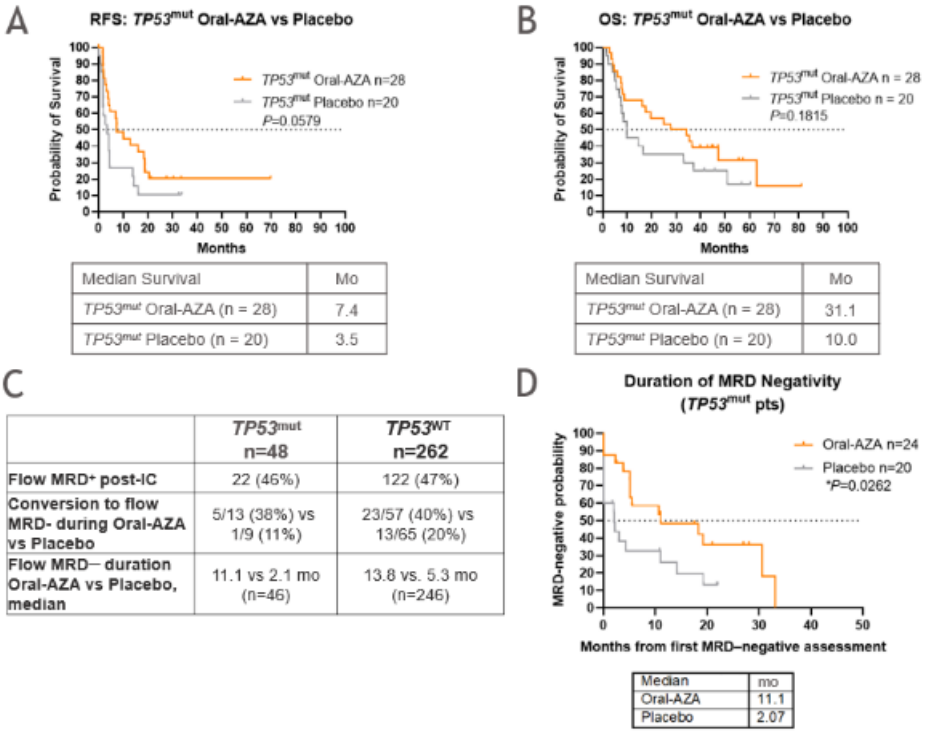
In the PBO arm, there was a trend for shorter RFS (median 3.5 vs 4.9 mo) and OS (median 10.0 vs 15.2 mo) with *TP53*mut vs wt pts. Among pts with *TP53*mut detected at BL, mRFS was 7.4 vs 3.5 mo (*P*=0.06 and mOS 31.1 vs 10.0 mo (*P*=0.18) in the Oral-AZA vs PBO arms, respectively (Figure). Flow MRD+ disease (≥0.1%) at BL was similar between pts with *TP53*mut (46%) and *TP53*wt (47%). More pts on Oral-AZA converted from MRD+ to MRD− status than those on PBO (38% vs 11%). Importantly, pts with *TP53*mut at BL remained flow MRD− significantly longer with Oral-AZA (11.1 mo vs PBO 2.1 mo, *P*=0.03) (Figure).

At relapse, *TP53* variants were detected at the same frequency (25%) in both Oral-AZA and PBO arms, with no evidence for greater selection of *TP53* variants upon exposure to Oral-AZA. Longitudinal analyses showed a ≥2-fold increase in the *TP53*mut VAF at relapse in 18/55 (33%) and 16/42 (38%) pts in the Oral-AZA and PBO arms, respectively. At relapse, ≥50% reduction in *TP53*mut VAF was observed in 7/55 (13%) and 2/42 (5%) pts in the Oral-AZA and PBO arms, respectively. Beyond *TP53*mut, the mutational landscape at relapse was similar between treatment arms.

**Summary/Conclusion:** In the post-remission setting after IC, *TP53*mut detection was associated with a trend

for inferior survival, with the caveat that some of these variants could be pre-leukemic or related to clonal hematopoiesis. Among pts with *TP53*mut detected in remission, Oral-AZA was more effective than PBO at clearing flow MRD+ disease, sustaining MRD– remission and nominally prolonging RFS. These preliminary findings warrant further validation.

**Figure. In the QUAZAR-AML-001 study, (A) RFS, (B) OS among patients with *TP53*mut detected at baseline receiving Oral-AZA or placebo. (C) Flow MRD detected at baseline according to *TP53*mut status and response to therapy. (D) Flow MRD remission duration in baseline *TP53*mut patients according to treatment arm.**




| Median Survival | Mo |
|---|---|
| *TP53*mut Oral-AZA (n = 28) | 7.4 |
| *TP53*mut Placebo (n = 20) | 3.5 |

| Median Survival | Mo |
|---|---|
| *TP53*mut Oral-AZA (n = 28) | 31.1 |
| *TP53*mut Placebo (n = 20) | 10.0 |

| | *TP53*mut n=48 | *TP53*WT n=262 |
|---|---|---|
| Flow MRD+ post-IC | 22 (46%) | 122 (47%) |
| Conversion to flow MRD- during Oral-AZA vs Placebo | 5/13 (38%) vs 1/9 (11%) | 23/57 (40%) vs 13/65 (20%) |
| Flow MRD– duration Oral-AZA vs Placebo, median | 11.1 vs 2.1 mo (n=46) | 13.8 vs. 5.3 mo (n=246) |

| Median | mo |
|---|---|
| Oral-AZA | 11.1 |
| Placebo | 2.07 |

**Keywords:** Maintenance, TP53, Acute myeloid leukemia, Azacitidine