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POSTER ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Clonal Dynamics of Gene Mutations during Oral Azacitidine Maintenance Therapy in Patients with Acute Myeloid Leukemia (AML): Outcomes from the QUAZAR AML-001 Trial

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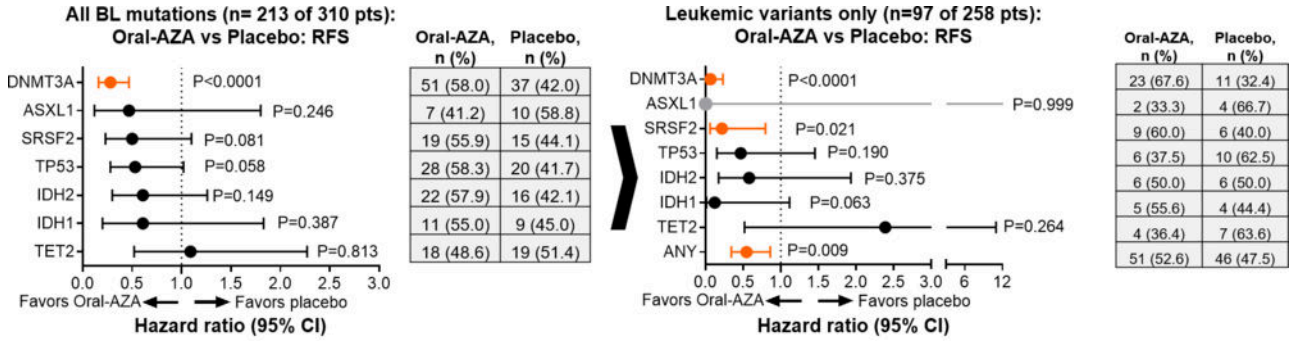
Background: Acute myeloid leukemia (AML) is a genetically heterogeneous disease and despite some patients (pts) achieving remission with frontline intensive chemotherapy (IC), most eventually relapse. In the QUAZAR trial (NCT01757535), oral azacitidine (Oral-AZA) prolonged overall survival and relapse-free survival (RFS) vs placebo (PBO) in older pts with AML in remission post IC (Wei et al, *N Engl J Med* 2020). Here, we studied the molecular landscape and clonal dynamics of pts treated with Oral-AZA/PBO in the QUAZAR study. The mutational landscape for older patients with AML in remission after IC may be confounded by persistence of pre-leukemic (PL) or age-related clonal hematopoietic (CH) variants. The implications of these residual mutations on disease relapse and treatment (Tx) outcome are largely unknown.
Aims: 1) characterize the mutational landscape from remission bone marrow at baseline (BL) prior to Oral-AZA maintenance (i.e., in remission post-IC); 2) determine the fate of variants over time and at relapse in the Oral-AZA vs PBO arms; 3) examine associations between mutational landscape and relapse risk between Tx arms.
Methods: In QUAZAR, 472 pts (≥55 years) with AML with intermediate- or poor-risk cytogenetics in remission after IC (BL) were randomized 1:1 to Oral-AZA or PBO. Among pts who consented to biomarker analyses (n=310), targeted NGS (37 myeloid genes) was performed on bone marrow DNA at BL (Oral-AZA/PBO: n=165/145), cycle 6 (n=107/79) and relapse (n=83/77). Mean NGS coverage was 13K reads and median minimal detectable variant allele frequency (VAF) was 0.12% (range: 0.02-2.79). Clonal variants were categorized by the longitudinal association between VAF and blast percentage (slope of leukemic variants >0.1; PL/CHIP <0.1). RFS was computed from time of randomization to relapse (≥5% BM blasts) or death, estimated by Kaplan-Meier methods. Hazard ratios (HR) and 95% confidence intervals (CI) were obtained from Cox regression models. Nominal *P* values were derived from log-rank tests.

Results: In the NGS cohort (n=310), median RFS (mRFS) for Oral-AZA vs PBO was 10.2 vs 4.7 months (mo), respectively. At BL, prior to maintenance Tx, 221 (71.3%) had detectable mutations, the most frequently occurring mutations (>5% of pts) were in *DNMT3A* (28.4%), *TP53* (15.5%), *IDH2* (12.3%), *TET2* (11.9%), *SRSF2* (11.0%), *IDH1* (6.1%) and *ASXL1* (5.5%).
At BL, 110/310 (35.5%) pts had VAF >5%, potentially representing persistence of PL/CH variants in remission. Comparative analysis of all gene variants at BL and relapse revealed that some VAFs increased with blast frequency, while other variants remained largely static. Applying a variant classification algorithm, 97/258 pts had potential leukemic variants detected at BL. These involved *DNMT3A* (16.1%), *SRSF2* (7.1%), *TP53* (7.1%) and *IDH2* (5.7%). PL/CH variants included *DNMT3A* (17.5%), *TP53* (8%), *IDH2* (5.7%) or *TET2* (5.7%). *TP53* was detected in 19.4% PL/CH variants (mean VAF 1.7%; range 0.2-13.4).
Notably, when analyses were limited to potential leukemic variants at BL (<5% VAF), their presence was correlated with worse RFS (PBO: mRFS for 0, 1 or 2+ mutations was 6.1, 4.7 or 1.9 mo, respectively). The presence of ≥2 leukemic mutations was associated with shorter RFS only in PBO arm (mRFS vs <2 mutations: 1.9 vs 5.7 mo, *P*=0.02; Oral-AZA: 10.2 vs 10.2 mo). RFS favored Oral-AZA in pts with low mutational burden at BL (<2 mutations: mRFS 10.2 vs 5.7 mo [*P*=0.003]; n=145 vs 122 [PBO]), and in a small subset of pts with higher mutational burden (≥2 mutations: mRFS 10.2 vs 1.9 mo [*P*=0.008]; n=14 vs 13 [PBO]). Oral-AZA prolonged RFS vs PBO in pts across most mutational subtypes, when assessed for mutations that were deemed potentially leukemic (Figure).
At relapse, the frequency of mutations, hotspots variants and co-mutations were comparable between Tx arms. Mutation-based pathway analysis indicated *Ras* pathway genes were enriched at relapse in PBO (28.6%) vs Oral-AZA arm (14.5%, *P*=0.03).
Summary: In pts with AML in remission post IC, *post-hoc* analyses showed that Oral-AZA improved RFS vs PBO regardless of the mutational landscape at baseline. The spectrum of mutations at relapse was similar between Tx arms, suggesting that Oral-AZA maintenance prolongs remission without altering mutational heterogeneity.

Disclosures Lopes De Menezes: *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company, Patents & Royalties: Patents filed/pending. **Guerrero:** *Bristol Myers Squibb:* Current Employment. **Amzallag:** *BMS:* Current Employment, Current equity holder in publicly-traded company. **See:** *Bristol Myers Squibb:* Current Employment, Other: Consultant. **Risueno:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company, Patents & Royalties: named in patents. **Kyriakopoulos:** *Bristol Myers Squibb:* Current Employment. **Suragani:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Beach:** *Bristol Myers Squibb:* Ended employment in the past 24 months. **Prebet:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Voso:** *Novartis:* Research Funding; *Jazz:* Other: Advisory Board; *Celgene/BMS:* Other: Advisory Board; *Astra Zeneca:* Speakers Bureau; *Novartis:* Speakers Bureau; *Abbvie:* Speakers Bureau; *Jazz:* Speakers Bureau; *Celgene/BMS:* Research Funding, Speakers Bureau; *Syros:* Other: Advisory Board; *Astellas:* Speakers Bureau. **Schuh:** *Abbvie:* Honoraria, Research Funding; *Agios:* Honoraria, Research Funding; *Glycomimetics:* Research Funding; *Pfizer:* Consultancy, Honoraria; *Kite/Gilead:* Research Funding; *Servier:* Honoraria, Research Funding; *Bristol Myers Squibb:* Honoraria, Research Funding; *Astellas:* Honoraria, Research Funding; *Amgen:* Honoraria, Research Funding; *Teva:* Consultancy, Honoraria. **Roboz:** *Amgen:* Consultancy; *Argenx:* Consultancy; *Jasper pharmaceuticals:* Consultancy; *Jazz Pharmaceuticals:* Consultancy; *Novartis:* Consultancy; *Molecular Partners:* Consultancy; *Takeda:* Consultancy; *Roche:* Consultancy; *Pfizer:* Consultancy; *Astra Zeneca:* Consultancy; *Celgene/Bristol Myers Squibb:* Consultancy; *Blueprint Medicines:* Consultancy; *Ellipsis Pharma:* Consultancy; *Bluebird Bio:* Consultancy; *Daiichi Sankyo:* Consultancy; *Glaxo Smith Kline:* Consultancy; *Janssen:* Consultancy, Research Funding; *Syndax:* Consultancy; *Abbvie:* Consultancy. **Döhner:** *Bristol Myers Squibb:* Consultancy, Honoraria, Research Funding; *Berlin-Chemie:* Consultancy, Honoraria; *Amgen:* Consultancy, Honoraria, Research Funding; *Astellas:* Consultancy, Honoraria, Research Funding; *AstraZeneca:* Consultancy, Honoraria; *Agios:* Consultancy, Honoraria, Research Funding; *Abbvie:* Consultancy, Honoraria, Research Funding; *Celgene:* Consultancy, Honoraria, Research Funding; *Daiichi Sankyo:* Consultancy, Honoraria; *Stemline:* Consultancy, Honoraria; *Gilead:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *Servier:* Consultancy, Honoraria; *Jazz Pharmaceuticals:* Consultancy, Honoraria, Research Funding; *Novartis:* Consultancy, Honoraria, Research Funding; *Pfizer:* Research Funding; *Syndax:* Honoraria; *Kronos-Bio:* Research Funding. **Wei:** *Abbvie:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Servier:* Consultancy, Honoraria, Patents & Royalties: MCL1 use, Research Funding, Speakers Bureau; *Roche:* Consultancy, Honoraria; *Beigene:* Consultancy, Honoraria; *BMS:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Gilead:* Consultancy, Honoraria; *Pfizer:* Consultancy, Honoraria; *Astra Zeneca:* Consultancy, Honoraria, Research Funding; *Amgen:* Consultancy, Honoraria, Research Funding; *Shoreline:* Consultancy; *Astellas:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Research Funding; *Syndax:* Research Funding; *Walter and Eliza Hall Institute of Medical Research:* Patents & Royalties; *Aculeus:* Consultancy; *Jazz:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria, Research Funding, Speakers Bureau. **Gandhi:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company.



* Orange indicates significance; ASXL1 (undetermined; right Figure)

Figure 1

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