S131 SURVIVAL OUTCOMES FROM THE QUAZAR AML-001 TRIAL WITH ORAL AZACITIDINE FOR PATIENTS WITH ACUTE MYELOID LEUKEMIA IN REMISSION BY DISEASE SUBTYPE, CYTOGENETIC RISK, AND NPM1 MUTATION STATUS AT DIAGNOSIS

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Background:

Oral azacitidine (Oral-AZA; CC-486) is approved in the US for adult patients (pts) with acute myeloid leukemia (AML) who have achieved first complete remission (CR) or CR with incomplete blood count recovery (CRi) after intensive chemotherapy and are ineligible for intensive curative therapy. In the phase 3 QUAZAR trial, Oral-AZA significantly improved overall survival (OS) vs placebo (PBO) (median [med] 24.7 vs 14.8 months [mo], respectively; P<0.001). It has not been elucidated which subgroups of pts may derive greater benefit from Oral-AZA maintenance treatment (Tx) based on prognostic features or mutational profile.

Aims:

Investigate the relationship between Oral-AZA and survival in post hoc analyses based on cytogenetic risk classification, AML subtype (de novo or secondary), and NPM1/FLT3 status at diagnosis (Dx).

Methods:

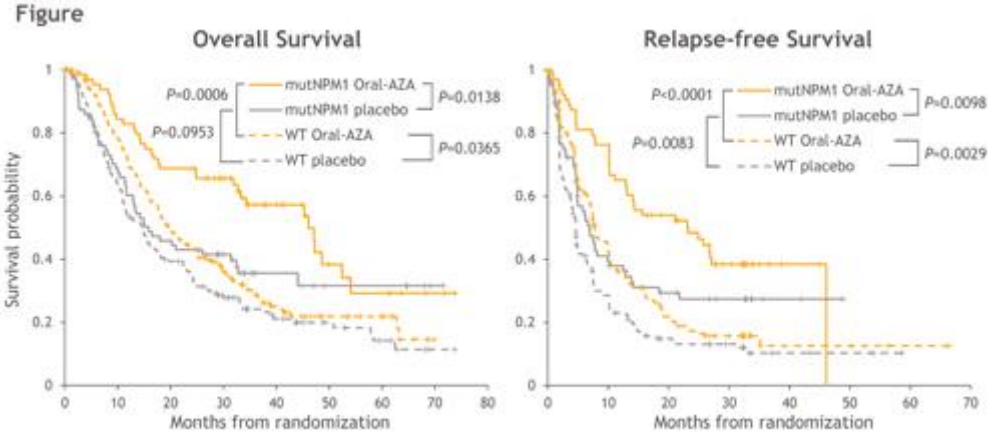
Cytogenetic risk classification of intermediate- (int) and poor-risk pts was based on the 2012 NCCN Guidelines; pts with favorable risk were excluded. Pts were randomized 1:1 to Oral-AZA 300 mg or PBO within 4 mo of achieving first CR/CRi. Mutant (mut) or wild-type (WT) NPM1/FLT3-ITD status was determined at Dx. OS and relapse-free survival (RFS) were estimated using Kaplan-Meier methods. Cox Proportional Hazard Regression was used to obtain hazard ratios (HR; P values, Log-rank test). Measurable residual disease (MRD) analysis used a cutoff of ≥0.1% (P values, Fisher's exact test).

Results:

Of 472 randomized pts, 90.9% had de novo AML, and Oral-AZA provided a significant increase in med OS vs PBO (23.2 vs 14.6 mo; HR 0.73; P=0.0068) and RFS (10.2 vs 4.9 mo; HR 0.66; P=0.0002). For the underpowered pt group with secondary AML (n=43), there was a trend for increased OS with Oral-AZA vs PBO (28.2 vs 15.7 mo; HR 0.58; P=0.11) and significantly increased RFS (4.7 vs 2.4 mo; HR 0.47; P=0.0118). 86% of pts had int-risk cytogenetics, and within this population, OS was significantly increased with Oral-AZA vs PBO (25.4 vs 15.9 mo; HR 0.73; P=0.0093), as was RFS (11.0 vs 5.8 mo; HR 0.66; P=0.0004). The poor-risk cohort (14%; n=66), though underpowered, showed a trend for

increased OS with Oral-AZA vs PBO (13.9 vs. 7.4 mo; HR 0.61; P=0.06), and RFS was similar (Oral-AZA 4.6 mo, PBO 3.7 mo; HR 0.63; P=0.08). Overall, 29.2% of pts had mutNPM1 at Dx (137/469), 9.8% (n=48) were FLT3-ITD positive, and 6% (n=30) had co-mutated NPM1/FLT3-ITD. In the PBO arm, mutNPM1 status vs WT was prognostically favorable for RFS (6.9 vs 4.6 mo; HR 0.64; P=0.0083) with a trend in increased OS (15.9 vs 14.6 mo; HR 0.75; P=0.10). Comparing treatment arms, the med OS for pts with mutNPM1 was considerably longer in the Oral-AZA arm vs PBO (46.1 vs 15.9 mo; HR 0.57; P=0.0138), and med RFS was significantly prolonged (23.2 vs 6.9 mo; HR 0.55; P=0.0098) (Figure). A larger fraction of pts with mutNPM1 were MRD– (61.7%) than were MRD+ (38.4%) at screening (P=0.0178). For pts with WT NPM1 (Oral-AZA n=170; PBO n=162), Tx with Oral-AZA significantly increased OS (19.6 vs 14.6 mo; HR 0.77; P=0.0365) and RFS (7.7 vs 4.6 mo; HR 0.69; P=0.0029). Pts with WT NPM1 were evenly distributed between MRD– (49.2%) and MRD+ (50.8%) status at screening.

Figure



AZA, azacitidine; mut, mutated; NPM1, Nucleophosmin 1.

Conclusion:

Oral-AZA considerably improved survival for pts with de novo AML and int-risk cytogenetics. Additionally, pts with mutNPM1 in the Oral-AZA arm derived an extended OS benefit of more than 2.5 years vs PBO, whereas OS for all pts in QUAZAR AML-001 was lengthened by 9.9 months with Oral-AZA vs PBO. This suggests that mutNPM1 status is both prognostically favorable in general and independently predictive of increased OS with Oral-AZA.

Keyword(s): AML, Azacitidine, Maintenance, Mutation