Oral azacitidine in patients with acute myeloid leukemia in first remission after intensive chemotherapy: long-term overall survival results from the phase 3 QUAZAR AML-001 trial

Poster Number AML-457

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Introduction

- Standard intensive chemotherapy (IC) regimens for acute myeloid leukemia (AML) induce complete remission (CR) in 60%–80% of patients (pts) aged ≤ 60 years and in 40%–60% of pts aged > 60 years[1]
- Most pts who attain CR during IC will eventually experience disease relapse[2-4]
  - AML relapse is the primary obstacle to long-term (LT) overall survival (OS)[5]
- Oral azacitidine (Oral-AZA [CC-486]) is a hypomethylating agent with a distinct pharmacokinetic/pharmacodynamic profile from that of injectable AZA[6,7]
  - Oral dosing allows for extended drug exposure to prolong therapeutic activity of AZA
- The randomized, placebo (PBO)-controlled, phase 3 QUAZAR AML-001 trial assessed Oral-AZA as maintenance treatment (Tx) for pts with AML in CR or CR with incomplete blood count recovery (CRi) after IC who were not eligible for hematopoietic stem cell transplant (HSCT)
- The QUAZAR AML-001 study was unblinded in August 2019 (data cut-off 15-Jul 2019)
- At a median follow-up of 41.2 months, Oral-AZA significantly prolonged OS vs PBO ($P < 0.001$)[8]
  - The tails of the OS curves began to converge after ~48 months
  - 125/472 pts (26.5%) were still alive in survival follow-up at the primary cut-off
- After unblinding, 39 pts receiving Oral-AZA entered an extension phase and continued Tx
- Here, we assess longer-term OS using a data cut-off of September 2020, providing > 1 additional year of survival follow-up

Methods

- Study design and key eligibility criteria are presented in **Figure 1**
- Within 4 months of achieving first CR/CRi with IC (induction ± consolidation), eligible pts were randomized 1:1 to Oral-AZA 300 mg or PBO once-daily for 14 days per 28-day Tx cycle
- After trial unblinding, pts in the Oral-AZA arm could continue to receive Tx in an extension phase while they continued to benefit; pts in the PBO arm discontinued Tx and were followed for OS
- Kaplan-Meier (KM) estimated OS was calculated from the time of randomization until death, withdrawal of consent, or loss to follow-up, and compared between Tx arms by log-rank test

Results

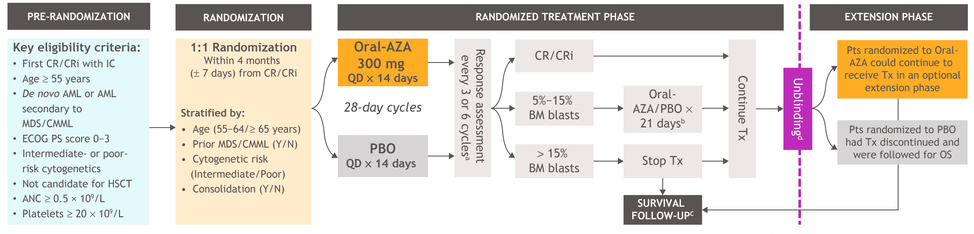
Updated disposition and survival

- Pt disposition at the updated follow-up in September 2020 is shown in **Figure 2**
  - 54 pts (22.7%) in the Oral-AZA arm were alive in survival follow-up, including 31 pts (13.0%) still receiving Oral-AZA in the extension phase
  - 35 pts (15.0%) in the PBO arm remained alive and in survival follow-up
- At a median follow-up of 51.7 months, median OS in each arm remained unchanged from the primary cut-off date: 24.7 vs 14.8 months with Oral-AZA vs PBO, respectively ($P = 0.0008$) (**Figure 3**)
- The KM OS curves for Oral-AZA and PBO showed greater separation with additional follow-up, and the 2 curves did not touch or cross at any time
- KM estimated 3-year survival rates were 37.4% vs 27.9% in the Oral-AZA and PBO arms, respectively (Δ +9.5% [95% CI 0.9%, 18.1%])

Profiling LT survivors

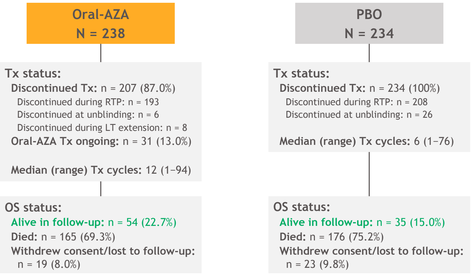
- To determine whether LT OS was influenced by pt-related factors, baseline (BL) characteristics were compared between pt subgroups defined by survival duration:
  - **LT Survivors:** pts alive in survival follow-up for ≥ 3 years from randomization
  - **Non-LT Survivors:** pts who died or were censored for OS before 3 years from randomization
- The LT Survivors cohort comprised 140 pts (29.7%) in the Oral-AZA (n = 83) and PBO (n = 57) arms
- BL characteristics between the LT and Non-LT Survivors cohorts are shown for Oral-AZA in **Figure 4** and for PBO in **Figure 5**
  - Compared with the Non-LT cohort, LT Survivors were more likely to have intermediate-risk cytogenetics and *NPM1* mutations at AML diagnosis, and less likely to have measurable residual disease (MRD) by multiparameter flow cytometry at screening (post-IC)
- The overall rate of MRD response (ie, conversion from MRD-positive [MRD+] at BL to MRD-negative [MRD−] on study) was significantly higher in the LT Survivors cohort than in the Non-LT Survivors group ($P < 0.0001$)

Figure 1. QUAZAR AML-001 study design and key eligibility criteria



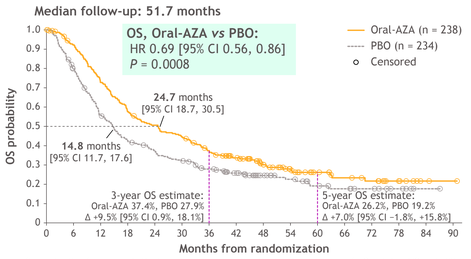
[a]BM aspirates were collected every 3 cycles through cycle 24, at cycle 30 and cycle 36, and as clinically indicated thereafter. [b]Pts who developed 5–15% blasts on study could receive a 21-day dosing regimen of their assigned Tx at the discretion of the treating investigator. [c]Pts were followed until death, withdrawal of consent, study termination, or loss to follow-up. [d]Unblinding occurred after the July 2019 data cut.
ANC, absolute neutrophil count; BM, bone marrow; CMML, chronic myelomonocytic leukaemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IWG, International Working Group; *MDS*, myelodysplastic syndromes; QD, once-daily.

Figure 2. Patient disposition at the updated data cut-off (September 2020)



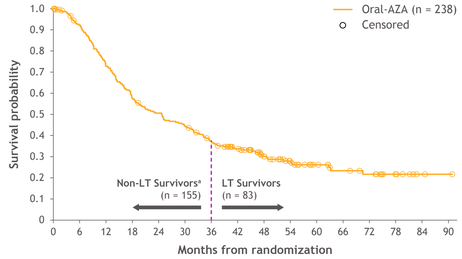
RTP, randomized treatment phase.

Figure 3. OS at the updated data cut-off (September 2020)



OS was defined as the time from randomization to death by any cause. KM estimated OS was compared for Oral-AZA vs PBO by stratified log-rank test. HRs and 95% CIs were generated using a stratified Cox proportional hazards model.
HR, hazard ratio.

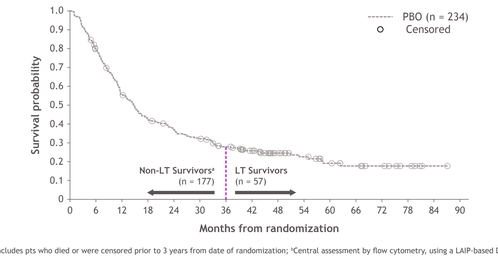
Figure 4. Baseline characteristics for LT Survivors vs Non-LT Survivors randomized to Oral-AZA



Parameter	Oral-AZA N = 238	
	LT Survivors (n = 83)	Non-LT Survivors[a] (n = 155)
Age, median (range), years	67 (55–80)	69 (55–86)
NCCN cytogenetic risk at Dx, %		
Intermediate	94	81
Poor	6	19
NPM1[mut] at AML Dx, %	45	19
Response after induction, %		
CR	80	78
CRi	20	22
Received consolidation, %		
Yes	77	79
1 cycle	42	48
2 cycles	33	28
3 cycles	2	3
No	23	21
MRD+ at randomization,[b] %	35 (n = 29)	48 (n = 74)
Became MRD− on study, % (n/N)	76 (22/29)	22 (16/74)
	Total: 37 (38/103)	

[a]Includes pts who died or were censored prior to 3 years from date of randomization; [b]Central assessment by flow cytometry, using a LAIP-based DfN approach and ≥ 0.1% *MRD* positivity threshold.
DfN, different-from-normal; Dx, diagnosis; LAIP, leukemia-associated immunophenotype; [mut], mutation; NCCN, National Comprehensive Cancer Network.

Figure 5. Baseline characteristics for LT Survivors vs Non-LT Survivors randomized to PBO



Parameter	PBO N = 234	
	LT Survivors (n = 57)	Non-LT Survivors[a] (n = 177)
Age, median (range), years	67 (55–79)	69 (55–82)
NCCN cytogenetic risk at Dx, %		
Intermediate	96	84
Poor	5	16
NPM1[mut] at AML Dx, %	46	26
Response after induction, %		
CR	84	84
CRi	16	16
Received consolidation, %		
Yes	88	80
1 cycle	39	45
2 cycles	42	30
3 cycles	7	5
No	12	20
MRD+ at randomization,[b] %	30 (n = 17)	56 (n = 99)
Became MRD− on study, % (n/N)	71 (12/17)	10 (10/99)
	Total: 19 (22/116)	

[a]Includes pts who died or were censored prior to 3 years from date of randomization; [b]Central assessment by flow cytometry, using a LAIP-based DfN approach and ≥ 0.1% *MRD* positivity threshold.

Conclusions

- The primary OS analysis of the QUAZAR AML-001 study was subject to extensive censoring (> 25% pts remained alive at that data cut-off)
- With > 1 additional year of survival follow-up, median OS remained unchanged in both Tx arms, but the tails of the Oral-AZA and PBO OS curves showed greater separation at later time points than in the primary analysis
- LT survival (> 3 years) in both arms was associated with intermediate cytogenetic risk and *NPM1* mutation at AML diagnosis
- MRD response (conversion from MRD+ at BL to MRD− on study) was also associated with LT survival
  - MRD response on study was ~2 times more frequent with Oral-AZA vs PBO (37% vs 19%)[9]
- These updated data indicate Oral-AZA maintenance therapy provides a sustained, LT OS benefit in older pts with AML in first remission

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