Triplet Therapy with Decitabine, Venetoclax, and Quizartinib for FLT3-ITD Mutated AML: A Phase I/II Study

M. YILMAZ[1], M. MUFTUOGLU[1], N. SHORT[1], S. LOGHAVI[1], T. KADIA[1], C. DINARDO[1], G. BORTHAKUR[1], N. PEMMARAJU[1], Y. ALVARADO[1], A. MAITI[1], M. KONOPLEVA[2], L. MASAROVA[1], G. MONTALBAN[1], C. JURISPRUDENCIA[1], A. PIKE[1], K. PATEL[1], G. TANG[1], J. MATTHEWS[1], S. KORNBLAU[1], E. JABBOUR[1], G. GARCIA-MANERO[1], K. TAKAHASHI[1], F. RAVANDI[1], M. ANDREEFF[1], H. KANTARJIAN[1], N. DAVER[1]

[1] MD Anderson Cancer Center, Houston, Texas, USA [2] Albert Einstein College of Medicine, Bronx, New York, USA

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Introduction

The addition of FLT3 inhibitors to intensive chemotherapy has improved outcomes in younger adults; however, older or unfit patients with newly diagnosed FLT3-ITD mutated AML continue to experience poor outcomes. In this group, treatment with hypomethylating agents combined with venetoclax or a FLT3 inhibitor yields a median overall survival of 8–12 months. Given the well-established preclinical synergy between quizartinib and venetoclax, and the favorable clinical signal seen with quizartinib plus a hypomethylating agent, we designed this clinical trial.

Methods

This was a phase 1/2 trial design that enrolled both newly diagnosed and relapsed/refractory FLT3-ITD mutated AML patients. The phase 1 portion was conducted to determine the recommended phase 2 dose (RP2D) and schedule of quizartinib when combined with decitabine and venetoclax, while the phase 2 portion evaluated the efficacy and safety of the triplet regimen in these patient populations.

Results

Patient Characteristics	Newly Diagnosed Cohort (N=30)	Relapsed Refractory Cohort (N=46)
Age, years		
Median	70 (62-85)	58 (19-86)
≥75 years, No. (%)	11 (37)	5 (11)
Diagnosis, AML, No. (%)		
De novo	18 (60)	34 (74)
Secondary	8 (27)	9 (20)
Therapy related	4 (13)	3 (6)
Bone marrow blasts %, median	67 (20-96)	52 (6-92)
Karyotype, No. (%)		
Diploid	19 (63)	18 (40)
Other	7 (24)	14 (30)
Adverse	4 (13)	14 (30)
FLT3 mutation type, No. (%)		
ITD	28 (93)	45 (98)
TKD	0	0
ITD + TKD	2 (7)	1 (2)
No. of prior therapies, median	-	3 (1-5)
Any prior FLT3 inhibitor, No.	-	39 (85)
Prior Gilteritinib, No.	-	35 (76)
Prior HMA + venetoclax, No.	-	27 (59)
HMA + venetoclax + FLT3i	-	24 (52)
Prior bone marrow transplant	-	17 (37)

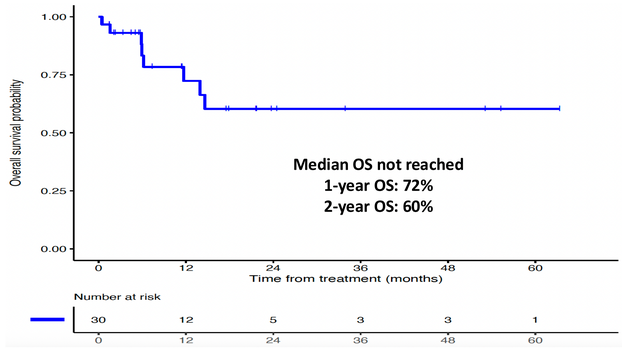
Phase 1 Results

A total of 11 patients were treated in the phase 1 portion of the study—nine received quizartinib at 26.5 mg/day and two received 35.4 mg/day. No DLTs were observed at the 26.5 mg/day dose level. However, both patients treated at the 35.4 mg/day dose experienced hematologic DLTs (grade 4 neutropenia). Based on these findings, 26.5 mg/day was established as the MTD and selected as the recommended phase 2 dose.

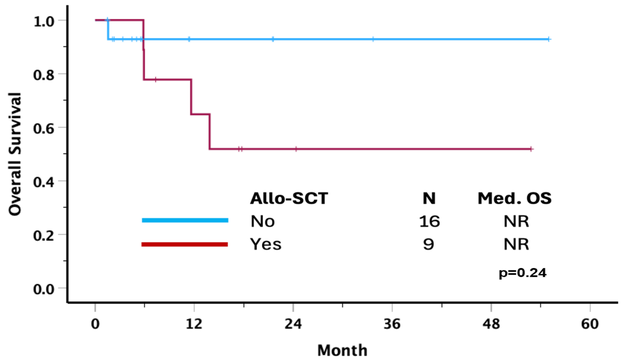
Hematologic and MRD responses

Response*, N (%)	Newly Diagnosed Cohort (N=30)	Relapsed Refractory Cohort (N=46)
Hematologic Response		
mCRc	28 (94)	28 (61)
CR	21 (70)	5 (10)
CRi	7 (24)	8 (18)
MLFS	0	15 (33)
No response	1 (3)	17 (37)
Induction death	1 (3)	1 (2)
MRD Response, EOC1, N (%)		
Flow cytometry negative	14/24 (58)	3/25 (12)
FLT3 PCR negative	11/18 (61)	7/25 (28)
MRD Response, best, N (%)		
Flow cytometry negative	18/26 (69)	7/26 (27)
FLT3 PCR negative	18/21 (86)	10/26 (38)
Bridge to bone marrow transplant	9 (30)	17 (37)

Overall Survival in Frontline Cohort



Impact of allo-SCT in CR1 on OS (Frontline Cohort) – Landmark analysis



In relapsed and refractory cohort, the median OS was 6.3 months. The 30-day mortality rate was 4%. Patients without prior exposure to a hypomethylating agent plus venetoclax had significantly improved OS compared to those previously treated (8.7 vs. 4.6 months; p = 0.02)

Infections were the most common grade ≥3 non-hematological adverse events, occurring more frequently in the relapsed/refractory cohort, with pneumonia (83%) and febrile neutropenia (57%) being notably higher compared to the frontline cohort.

Summary

The triplet combination of quizartinib, decitabine, and venetoclax resulted in high CR/CRi rates, deep molecular MRD responses, and encouraging OS in newly diagnosed patients with *FLT3*-ITD mutated AML.