A Phase II Study of Azacitidine and Venetoclax as Maintenance Therapy in Patients with Acute Myeloid Leukemia

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Abstract

CONTEXT: Patients with acute myeloid leukemia (AML) experience high relapse rates. Oral azacitidine (CC-486) prolongs relapse-free survival (RFS) and overall survival (OS) in SCT-ineligible patients. The addition of venetoclax (VEN) may enhance the efficacy of azacitidine (AZA) within a maintenance regimen.
OBJECTIVE: Establish the efficacy and tolerability of maintenance AZA plus VEN in AML.
DESIGN: This is a phase 2, single-center, single-arm study ongoing since 9/2019. Current median follow-up time is 15.1 months.
PATIENTS: AML patients ≥ 18 years in first remission (CR1) after induction and 1+ consolidation cycles not immediately eligible for SCT were eligible. High and low-intensity induction regimens were permitted. Patients in CR2 and beyond were eligible if minimal residual disease (MRD)-positive.
INTERVENTIONS: AZA 50 mg/m^2 IV/SQ x 5 days and VEN 400mg x 14 days (or 7 days at the discretion of the treating physician in patients at high risk of cytopenias/infections) were administered in 28-day cycles, up to 24 cycles.
MAIN OUTCOME MEASURES: RFS (enrollment to death/relapse), OS, and safety/tolerability. Patients who later became eligible for SCT were censored at the time of SCT.
RESULTS: 34 patients with a median age of 53.5 years (19-82) have been enrolled (25 after intensive induction, 9 after low-intensity induction). 13 (38%) received 14 days of venetoclax and 21 (62%) received 7 days. The median number of cycles given was 10 (1-24). To date, 9 patients (26%) have relapsed and 7 (21%) have died (all following relapse or SCT). The median RFS was not reached (NR) (1-yr 68.4%) and median OS was NR (1-yr 88.3%). 8 patients (24%) went off protocol for SCT. Median RFS stratified by ELN 2017 was NR (1-yr 84.6%), NR (1-yr 70%), and 4 months (1-yr 22.9%) in ELN favorable, intermediate, and adverse, respectively. 2/7 (29%) of the MRD(+) patients became MRD(-) on maintenance. The most common grade 3/4 adverse events were infections (26%, including 6% neutropenic fever), thrombocytopenia (21%), and neutropenia (18%).
CONCLUSIONS: AZA plus VEN is tolerable and yields encouraging RFS in AML patients not immediately eligible for SCT.

Background

- AML has a high rate of complete remission (CR) with modern therapies but **relapse remains common**.
- **Maintenance therapy:**
  - Consists of prolonged administration of easily tolerable agents.
  - Goal is to delay or prevent relapse.
- **QUAZAR AML-001**
  - **Phase III RCT** demonstrated improved RFS and OS with oral AZA (CC-486) in AML in CR1 after intensive chemotherapy.
  - Proof of concept for maintenance in AML
- **Venetoclax**
  - **BCL2 inhibitor** that is synergistic with AZA and highly effective in AML.
  - May enhance the activity of AZA within a maintenance regimen.

Objective

- Evaluate the efficacy and safety/tolerability of **AZA plus VEN** as **maintenance therapy** in AML following both **intensive and low-intensity induction regimens.**

Study Design and Interventions

- Phase II single-center, single-arm trial

Key inclusion criteria
- AML ≥ age 18
- In first CR/CRi, not immediately eligible for SCT:
  - **COHORT 1**: s/p **intensive** induction + at least 1 consolidation
  - **COHORT 2:** s/p **low-int** induction + at least 2 consolidations
- **CR2 and beyond** with positive measurable residual disease (MRD)
- PS ≤ 3
- Adequate hepatic/renal function
- Adequate marrow reserve (ANC > 0.5 x 10^9/L, PLT ≥ 30 x 10^9/L)

Key exclusion criteria
- APL/FAB M3/t(15;17)
- AML with t(9;22)
- Active CNS involvement
- History of extramedullary AML

Azacitidine
50 mg/m^2 IV/SQ on D1-5

Venetoclax
400 mg PO*
on D1-7 or D1-14†

28-day cycles
Up to 24 cycles

Until relapse or unacceptable toxicity

Off protocol if became SCT-eligible (censored at SCT)

*200 mg if on isavuconazonium, 100 mg on voriconazole, 70 mg on posaconazole
† Default duration 14 days. Could be reduced to 7 days at the discretion of the treating physician in patients at risk for cytopenias/toxicity

Primary objective: Relapse-free survival (RFS), defined as enrollment to relapse/death
Key secondary objectives: Overall survival (OS), safety/toxicity, MRD clearance

Results

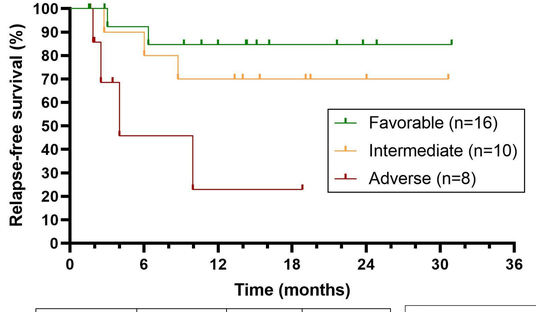
Cycle Information	All (n=34)
Cycle 1 VEN duration, n (%)	
7 days	21 (62)
14 days	13 (38)
C2 dose reduction to 7 days	2 (15)
Median cycles given [range]	10 [1-24]
Median follow-up time (months)	15.1
Off protocol for SCT, n (%)	8 (24)

Table 1: Baseline Patient Characteristics

	All (n=34)	Intensive (n=25)	Low-int (n=9)
Age	53.5 [19-82]	47 [19-70]	69 [60-82]
Male	17 (50)	10 (40)	7 (78)
Response			
CR	31 (91)	22 (88)	9 (100)
CRi	3 (9)	3 (12)	0 (0)
CR1	31 (91)	23 (92)	8 (89)
ELN risk			
Favorable	16 (47)	13 (52)	3 (33)
Intermediate	10 (29)	7 (28)	3 (33)
Adverse	8 (24)	5 (20)	3 (33)
Karyotype			
t(8;21)	2 (6)	2 (8)	0 (0)
inv(16)	4 (12)	4 (16)	0 (0)
Diploid	20 (59)	15 (60)	5 (56)
Other Int	3 (9)	2 (8)	1 (11)
-5/del(5q)	3 (9)	2 (8)	1 (11)
-7/del(7q)	4 (12)	2 (8)	2 (22)
-17/del(17p)	2 (6)	0 (0)	2 (22)
Complex	4 (12)	3 (12)	1 (11)
MRD status			
Positive	7 (21)	4 (16)	3 (33)
Negative	26 (76)	20 (80)	6 (66)
NA	1 (3)	1 (4)	0 (0)
Prior therapies	1 [1-3]	1 [1-3]	1 [1-2]
Prior VEN	19 (56)	14 (56)	5 (56)

Data displayed as n(%) or median [range]

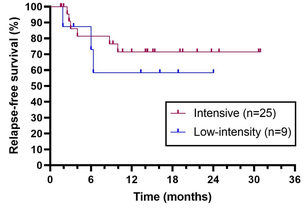
RFS by ELN 2017 (censored for SCT)



	Median RFS	12-month	P (log-rank)
Favorable	NR	84.6%	0.0172
Intermediate	NR	70%	
Adverse	4 months	22.9%	

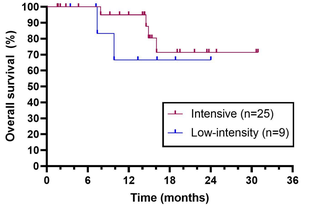
ELN favorable:
4/16 CBF-AML
5/16 *IDH1/2*-mutated
12/16 *NPM1*-mutated

RFS by Induction Intensity (censored for SCT)



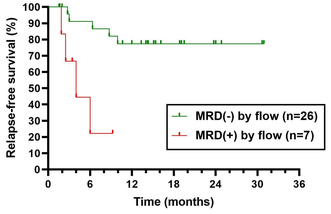
	Median RFS	12-month	P (log-rank)
Intensive	NR	71.5%	0.5101
Low-intensity	NR	58.3%	

OS by Induction Intensity (censored for SCT)



	Median OS	12-month	P (log-rank)
Intensive	NR	95%	0.4767
Low-intensity	NR	66.7%	

RFS by MRD status (censored for SCT)



	Median RFS	6-month	P (log-rank)
MRD(-)	NR	86.5%	0.0012
MRD(+)	4 months	22.2%	

Adverse Events

Most common grade 3/4 AEs

Adverse Event	# Occurrences
Thrombocytopenia	7
Neutropenia	6
Infections, other	4
Lung Infection	3
Febrile Neutropenia	2
Hypotension	2

Most common grade 1/2 AEs

Adverse Event	# Occurrences
Fatigue	6
Headache	6
Nausea	6
ALT increased	4
Arthralgia	4
Diarrhea	4
Hypercalcemia	4
Hyperuricemia	4

All deaths (7) occurred after relapse of AML (6) or going off protocol for SCT (1)

Conclusions

- Azacitidine plus venetoclax is **safe** and demonstrates **promising efficacy** in **non-adverse risk AML** patients not immediately eligible for SCT (after both intensive and low-intensity induction).
- Relapse remains common in ELN adverse and MRD-positive cases.
- Overall, our results support further study of venetoclax-based maintenance regimens in AML, including fully oral regimens (NCT04102020, NCT05010772).