A PHASE IB/2 TRIAL OF AN ALL ORAL "TRIPLET" REGIMEN FOR IDH-MUTATED MYELOID MALIGNANCIES: DECITABINE/CEDAZURIDINE AND VENETOCLAX IN COMBINATION WITH IVOSIDENIB/ENASIDENIB

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INTRODUCTION

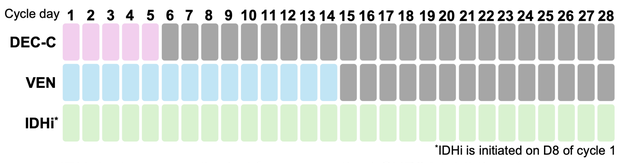
- Isocitrate dehydrogenase (IDH) mutations occur in ~20% of patients with acute myeloid leukemia (AML)[1]
- Long-term follow up of the VIALE-A trial demonstrated a median overall survival (mOS) of 10.2 and 27.5 months for IDH1 and IDH2 mutations, respectively, with composite complete remission (CRc) rates of 66.7% and 86%[2]
- Targeted mutant IDH inhibitors (IDHi), such as ivosidenib (IVO) and enasidenib (ENA), are approved as single agents, or IVO in combination with SQ or IV azacitidine (AZA)[3-5]
- Decitabine/cedazuridine (ASTX727; DEC-C) is an oral formulation of decitabine with equivalent drug exposure to IV decitabine
- Approved "singlet" and "doublet" IDHi regimens are effective, but not curative, with eventual relapse over time

AIM

In this Phase Ib/2 clinical trial, we explored the safety and efficacy of an **all oral** triplet regimen of DEC-C + venetoclax (VEN) + either IVO or ENA (for *IDH1* or *IDH2* mutant disease, respectively. (NCT04774393)

METHODS

- **Key Inclusion Criteria:**
  - Adults ≥ 18 years with adequate organ function
  - *IDH1* or *IDH2* mutation
  - Newly diagnosed (ND) AML ineligible for intensive chemotherapy
  - Relapsed/refractory (R/R) AML
  - High-risk MDS or MPN with ≥ 10% blasts
  - **Prior hypomethylating agent (HMA), VEN, and/or IDHi therapy was allowable**
- **Treatment Schedule:**



*IDHi is initiated on D8 of cycle 1

  - VEN dosing was adjusted for concomitant CYP3A inhibitors (e.g. posaconazole, voriconazole)
  - Dosing attenuation of DEC-C and/or VEN was permitted once in remission at the discretion of the treating physician and study PI
- **Primary Outcomes:**
  - Safety
  - Composite CR within five cycles: CRc = CR + CRi +CRh
- **Secondary Outcomes:**
  - Overall survival (OS) and Duration of Remission (DOR) censored at SCT
  - Measurable residual disease (MRD) measured by multiparameter flow cytometry (10^{-4}) sensitivity

RESULTS

Table 1. Patient Characteristics

Variable	All[1] (n=105)	ND[1] (n=62)	R/R[1] (n=43)
Age	71 (41, 87)	71 (58, 87)	68 (41, 86)
Male Sex	59 (56%)	35 (56%)	24 (56%)
IDH inhibitor	-	-	-
Ivosidenib	47 (45%)	28 (45%)	19 (44%)
Enasidenib	58 (55%)	34 (55%)	24 (56%)
Prior Therapy	-	-	-
Prior HMA	-	-	29 (67%)
Prior VEN	-	-	28 (65%)
Prior IDHi	-	-	13 (30%)
HMA-VEN-IDHi naive	-	-	8 (19%)
AML Type	-	-	-
De Novo	70 (67%)	37 (60%)	33 (77%)
Secondary	28 (27%)	20 (32%)	8 (19%)
tsAML[2]	22 (21%)	16 (26%)	6 (14%)
Therapy-related	7 (7%)	5 (8%)	2 (5%)
ELN 2022	-	-	-
Favorable	12 (12%)	8 (13%)	4 (9%)
Intermediate	7 (7%)	3 (5%)	4 (9%)
Adverse	85 (82%)	50 (82%)	35 (81%)
***K/NRAS* mutation**	13 (12%)	11 (18%)	2 (5%)
***FLT3-ITD* mutation**	2 (2%)	2 (3%)	0 (0%)
***NPM1* mutation**	17 (16%)	12 (19%)	5 (12%)
***TP53* mutation**	20 (19%)	6 (10%)	14 (33%)
SCT	21 (20%)	13 (21%)	8 (19%)
On protocol[3]	35 (55%)	29 (64%)	6 (32%)

[1] Median (Range); n (%)
[2] Therapy-related secondary AML to an antecedent hematologic disorder
[3] Of responding patients who did not undergo SCT

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RESULTS (CONT.)

Table 2. Summary of Clinical Outcomes

	ND		R/R	
	IVO (n=28)	ENA (n=34)	IVO (n=19)	ENA (n=24)
2-year OS	64%	63%	30%	35%
2-year DOR	59%	54%	30%	22%
CRc[1]	24 (86)	30 (91)	10 (54)	15 (65)
MRD (-) CR[2]	20 (74)	28 (85)	7 (37)	7 (30)
30-day mortality	0 (0)	1 (3)	0 (0)	1 (4)

[1] Within 5 cycles of treatment
[2] By multiparameter flow cytometry (sensitivity 10^{-4})

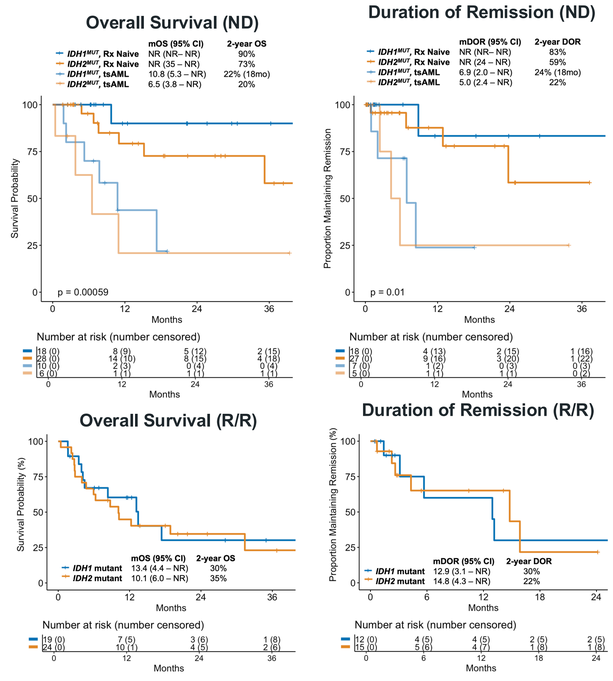


Figure 1. Overall survival (OS) and Duration of remission (DOR) receiving an all oral IDH inhibitor triplet therapy. From May 2021 – February 2024, 105 patients [62 newly diagnosed (ND), 43 relapsed/refractory (R/R)] were enrolled with a median follow up of 19.1 months. Survival curves were constructed using the Kaplan Meier method and separated by those who were *IDH1* (blue) or *IDH2* (yellow) mutated. For ND patients, outcomes were separated by treatment naïve patients (dark line) versus tsAML (light line).

Table 3. Non-Hematologic Adverse Events

Event[1]	All Grades	≥Grade 3
All	55 (52)	31 (30)
Infections	46 (44)	30 (29)
All (non-infectious)	18 (17)	6 (6)
Hyperbilirubinemia	8 (8)	3 (3)
Transaminitis	5 (5)	1 (1)
Rash / pruritus	3 (3)	-
QTc prolongation	3 (3)	-
Diarrhea	2 (2)	-
Differentiation syndrome	2 (2)	2 (2)
Fatigue	2 (2)	-
Myalgia / arthralgias	2 (2)	-
Acute kidney injury	1 (1)	-
Electrolyte abnormality	1 (1)	-
Stomatitis	1 (1)	-
Weakness	1 (1)	-

[1]At least possibly related while on protocol, n (%)

CONCLUSIONS

- Oral DEC-C + VEN + IVO/ENA demonstrated a CRc rate of 87% and 60% in patients with newly diagnosed and relapse/refractory IDH mutant myeloid neoplasms, respectively
- This triplet regimen was well tolerated, with no new safety signals and low early mortality
- This "total oral" regimen may be particularly appealing to patients and providers, minimizing the burden of frequent appointments related to infusions or injections

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