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Comparison of Ivosidenib- and Venetoclax-Based Treatment Sequencing and Outcomes in Patients With mIDH1 Acute Myeloid Leukemia: A Real-World Study

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AIM

To identify optimal ivosidenib (IVO)- and venetoclax (VEN)-based treatment sequences by characterizing and comparing real-world outcomes among patients receiving IVO then VEN (IVO→VEN) vs VEN then IVO (VEN→IVO)

CONCLUSIONS

- In real-world practice, IVO was associated with longer treatment duration, improved transfusion independence (TI), and lower acute care utilization compared with VEN, regardless of treatment sequence
- The magnitude of these benefits over VEN was more pronounced when IVO was used as index versus subsequent therapy, suggesting a sequencing-dependent modulation of treatment effect
- These findings support earlier integration of IVO within treatment sequencing to enhance treatment durability while reducing acute care burden in patients with mutant isocitrate dehydrogenase 1 (mIDH1) acute myeloid leukemia (AML)

LIMITATIONS

This study has several limitations inherent to retrospective analyses of real-world data, particularly those based on administrative claims. Claims data are collected for billing rather than clinical purposes and therefore may lack important clinical details such as disease severity, molecular subtype confirmation, and performance status. As such, identification of AML diagnoses and treatments relies on the accurate coding of procedures and diagnoses. Additionally, because *IDH1* mutation status is not captured in claims data, IVO use was considered a proxy for mIDH1 status in this study.

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INTRODUCTION

- IVO and VEN are approved therapies for the treatment of mIDH1 AML and target mIDH1 and B-cell lymphoma 2 protein, respectively[1–4]
- In the setting of susceptible *IDH1* mutation, IVO is approved as monotherapy or combined with azacitidine for patients with newly diagnosed AML who are aged ≥75 years or who have comorbidities that preclude intensive induction chemotherapy, and for the treatment of adults with relapsed/refractory AML[2]
- Real-world evidence guiding the optimal sequencing of IVO- and VEN-based regimens across lines of therapy in mIDH1 AML remains limited

METHODS

Treatment Cohorts

- This retrospective cohort study used the Komodo Research Dataset, which includes longitudinal medical and pharmacy claims data from >150 payers for >330 million patients from the USA
- Eligible patients were adults (≥18 years old) newly diagnosed with AML between Jan 2018 and Jun 2025 and with ≥180 days of continuous medical and pharmacy insurance coverage prior to AML diagnosis, a prescription of VEN or IVO on or after index diagnosis date between Jul 2018 and Jun 2025, no AML treatment in the 180-day lookback period, no prior leukemias, no stem cell transplantation (SCT) prior to initiating VEN or IVO, and confirmation that patients received VEN/IVO sequentially, with two cohorts defined: IVO→VEN and VEN→IVO
- The first occurrence of either agent was designated as the index treatment (received during the 'index phase') and the treatment immediately following as the subsequent treatment (received during the 'subsequent phase')
- Patients were followed up from index AML diagnosis until the earliest of end of insurance coverage or end of data availability in the database

Outcomes

- Outcomes evaluated in both phases included treatment patterns (duration of treatment [DOT], time to next treatment [TTNT]), transfusion outcomes (eg, TI, defined as ≥8 weeks without transfusion), AML-related healthcare resource utilization (eg, frequency and rate of hospitalizations), safety (hematologic adverse events), and SCT rates

Statistical Analysis

- Analyses were conducted for both treatment sequences during index and subsequent phases, irrespective of treatment line
- Categorical variables were compared using chi-squared or Fisher's exact tests, and continuous variables were compared using t-tests or Mann–Whitney U tests, as appropriate
- Time-to-event outcomes, including TTNT, were analyzed using Kaplan–Meier methods

PLAIN LANGUAGE SUMMARY

Why Was This Study Done?

- People with AML and changes (mutations) in the *IDH1* gene can be treated with medicines such as IVO (which targets the mutated enzyme) and VEN
- It is not known which medicine works best when given first
- This study looked at whether the order of these treatments affects how long people are able to stay on treatment

What Did the Study Look at?

- This study looked back at information from health insurance records that track treatments and healthcare use
- Information was included from 130 adults diagnosed with mutated *IDH1* AML in the USA who received both treatments, either:
  - VEN first, then IVO (VEN→IVO); or
  - IVO first, then VEN (IVO→VEN)

What Were the Results?

- People who received IVO first stayed on treatment longer and had fewer blood transfusions and hospital stays than those who had VEN first

What Might These Findings Mean for Patients?

- When appropriate, starting treatment with IVO may help people stay on treatment longer
- Using IVO first might also reduce the need for blood transfusions and hospital care

RESULTS

Baseline Characteristics

- Of 219,863 patients diagnosed with AML between Jan 1, 2018, and Jun 30, 2025, 130 met the study eligibility criteria, of whom 25 received IVO→VEN and 105 received VEN→IVO. Median age was 68 and 71 years, respectively (**Table 1**)
- Median follow-up was 22 and 18 months for IVO→VEN and VEN→IVO, respectively

Table 1: Baseline Patient Characteristics

Characteristic	IVO→VEN (n=25)	VEN→IVO (n=105)
Sex, n (%)		
Female	12 (48.0)	55 (52.4)
Unknown	0 (0.0)	2 (1.9)
Age at index diagnosis		
Median (IQR), years	68 (57–73)	71 (63–76)
Type of insurance, n (%)		
Commercial	5 (20.0)	34 (32.4)
Medicaid	4 (16.0)	6 (5.7)
Medicare	16 (64.0)	65 (61.9)
Region, n (%)		
Midwest	6 (24.0)	18 (17.1)
Northwest	9 (36.0)	37 (35.2)
West	4 (16.0)	20 (19.0)
South	6 (24.0)	30 (28.6)
Available follow-up from index diagnosis		
Median (IQR), months	22 (19–31)	18 (11–28)
Charlson Comorbidity Index, n (%)		
0	12 (48.0)	50 (47.6)
1–2	8 (32.0)	32 (30.5)
≥3	5 (20.0)	23 (21.9)

IQR, interquartile range; IVO, ivosidenib; n, number of patients; VEN, venetoclax

Treatment Duration

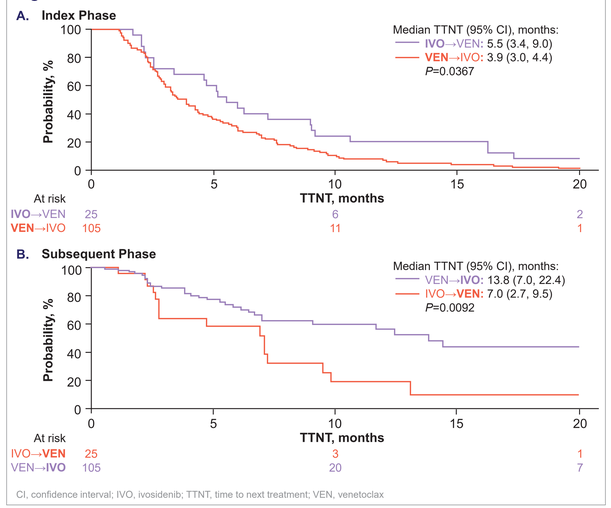
- During the index phase, IVO treatment was associated with significantly longer DOT and TTNT than VEN treatment; in the subsequent phase, IVO treatment was associated with numerically longer DOT and significantly longer TTNT than VEN treatment (**Table 2** and **Figure 1**)

Table 2: Treatment Duration

DOT	Index phase			Subsequent phase		
	*IVO→VEN	*VEN→IVO	*P* value	VEN→*IVO	IVO→*VEN	*P* value
Median (IQR)	4.7 (2.5–9.1)	3.0 (2.1–5.2)	0.0285	3.8 (2.1–5.7)	2.8 (2.6–4.7)	0.7840
Mean (SD)	6.9 (5.7)	4.2 (3.7)	0.0328	6.0 (8.5)	4.0 (2.6)	0.0398

*Indicates IVO or VEN treatment phase. DOT, duration of treatment; IQR, interquartile range; IVO, ivosidenib; SD, standard deviation; VEN, venetoclax

Figure 1: Time to Next Treatment



CI, confidence interval; IVO, ivosidenib; TTNT, time to next treatment; VEN, venetoclax

Blood Transfusions

- In the index phase, IVO was associated with higher rates of TI than VEN treatment (52.0% vs 25.7%; *P*=0.0155); a similar trend was observed in the subsequent phase (statistical significance not reached). Additional blood transfusion outcomes are described in **Table 3**

Table 3: Blood Transfusions

Transfusion outcome	Index phase			Subsequent phase		
	*IVO→VEN	*VEN→IVO	*P* value	VEN→*IVO	IVO→*VEN	*P* value
≥1 transfusion,† n (%)	12 (48.0)	78 (74.3)	0.0155	69 (65.7)	18 (72.0)	0.6407
Number of transfusions PPPM†	0.6	1.1	<0.0001	1.0	1.3	0.0059

*Indicates IVO or VEN treatment phase. †Red blood cell or platelet transfusion during treatment. IVO, ivosidenib; n, number of patients; PPPM, per person per month; VEN, venetoclax

Healthcare Resource Utilization

- Patients who received IVO during the index phase had significantly fewer AML-related inpatient stays than those who received VEN during the index phase (**Table 4**)

Table 4: AML-Related HCRU Outcomes

HCRU outcome	Index phase			Subsequent phase		
	*IVO→VEN	*VEN→IVO	*P* value	VEN→*IVO	IVO→*VEN	*P* value
Hospital stay						
Patients with ≥1 hospitalization, n (%)	10 (40.0)	63 (60.0)	0.0776	42 (40.0)	17 (68.0)	0.0142
Number of inpatient stays PPPM, mean (SE)	0.3 (0.2)	1.4 (0.1)	<0.0001	1.0 (0.1)	1.1 (0.1)	0.2077
Length of stay, days, mean (SE)	14.5 (0.3)	3.8 (0.1)	<0.0001	2.4 (0.1)	2.7 (0.1)	0.5368
ICU						
Patients with ≥1 ICU stay, n (%)	0.0 (0.0)	5 (4.8)	NE	6 (5.7)	1 (4.0)	>0.9999
Number of ICU admissions PPPM, mean (SE)	0.0 (0.0)	0.4 (0.4)	NE	0.5 (0.3)	0.2 (1.0)	0.1943
Length of stay, days, mean (SE)	0.0 (0.0)	3.2 (0.4)	NE	3.2 (0.3)	1.0 (0.9)	0.2823
ED						
Patients with ≥1 ED visit, n (%)	2 (8.0)	26 (24.8)	0.1019	15 (14.3)	5 (20.0)	0.5381
Number of ED visits PPPM, mean (SE)	0.4 (0.5)	0.2 (0.2)	0.4081	0.2 (0.2)	0.4 (0.4)	0.4068

*Indicates IVO or VEN treatment phase. ED, emergency department; HCRU, healthcare resource utilization; ICU, intensive care unit; IVO, ivosidenib; n, number of patients; NE, not estimable; PPPM, per person per month; SE, standard error; VEN, venetoclax

Safety

- Hematologic adverse events were consistently numerically less frequent during IVO treatment phases than during VEN treatment phases for both sequences (**Table 5**)

Table 5: Safety Outcomes

Safety outcome	3 months post-index phase					3 months post-subsequent phase				
	*IVO→VEN		*VEN→IVO		*P* value	VEN→*IVO		IVO→*VEN		*P* value
	n (%)	Mean days to AE	n (%)	Mean days to AE		n (%)	Mean days to AE	n (%)	Mean days to AE	
Any AE	21 (84.0)	4.9	95 (90.5)	9.6	0.4701	84 (80.0)	12.7	24 (96.0)	18.3	0.0736
Neutropenia	4 (16.0)	38.3	21 (20.0)	21.1	0.7826	18 (17.1)	17.0	7 (28.0)	33.1	0.2590
Febrile neutropenia	11 (44.0)	23.5	53 (50.5)	18.0	0.6581	37 (35.2)	22.7	11 (44.0)	22.0	0.4907
Thrombo-cytopenia	9 (36.0)	18.6	52 (49.5)	15.0	0.2685	42 (40.0)	19.2	13 (52.0)	17.9	0.3679
Anemia	11 (44.0)	21.0	57 (54.3)	21.2	0.3811	42 (40.0)	22.8	13 (52.0)	27.4	0.3679

*Indicates IVO or VEN treatment phase. AE, adverse event; IVO, ivosidenib; n, number of patients; VEN, venetoclax

Stem Cell Transplantation

- The proportion of patients proceeding to SCT was similar: 24.0% and 19.0% for the IVO→VEN cohort and the VEN→IVO cohort, respectively (*P*=0.5840)

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