

Ivosidenib improves overall survival relative to standard therapies in relapsed or refractory mutant *IDH1* AML: results from matched comparisons to historical controls

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Background

Background

- IVO is an oral, targeted inhibitor of *mIDH1* approved by the FDA for the treatment of *mIDH1* R/R AML, and in adults with ND AML ≥ 75 years of age or patients ineligible for IC, based on the results of the single-arm, AG120-C-001 (NCT02074839) study
- A propensity score matching analysis was performed to compare the IVO treatment group with patients from a historical control group (HC; AMLSG registry [NCT01252485] + RWD) treated with available therapies¹
 - Consistent benefit of IVO monotherapy was observed regardless of propensity score methods applied with HRs ranging from 0.43–0.73 and non-overlapping 95% CIs
 - After applying the IPTW method, IVO monotherapy prolonged median overall survival (IVO, 9.3 mo; HC, 4.4 mo) with non-overlapping 95% CIs and HR (95% CI) of 0.621 (0.478, 0.807, IPTW method)
- For R/R AML patients who have exhausted standard of care treatment options, published studies indicate a lack of effective treatments (OS, 2–4 mo)^{2–4}

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Objective and study populations

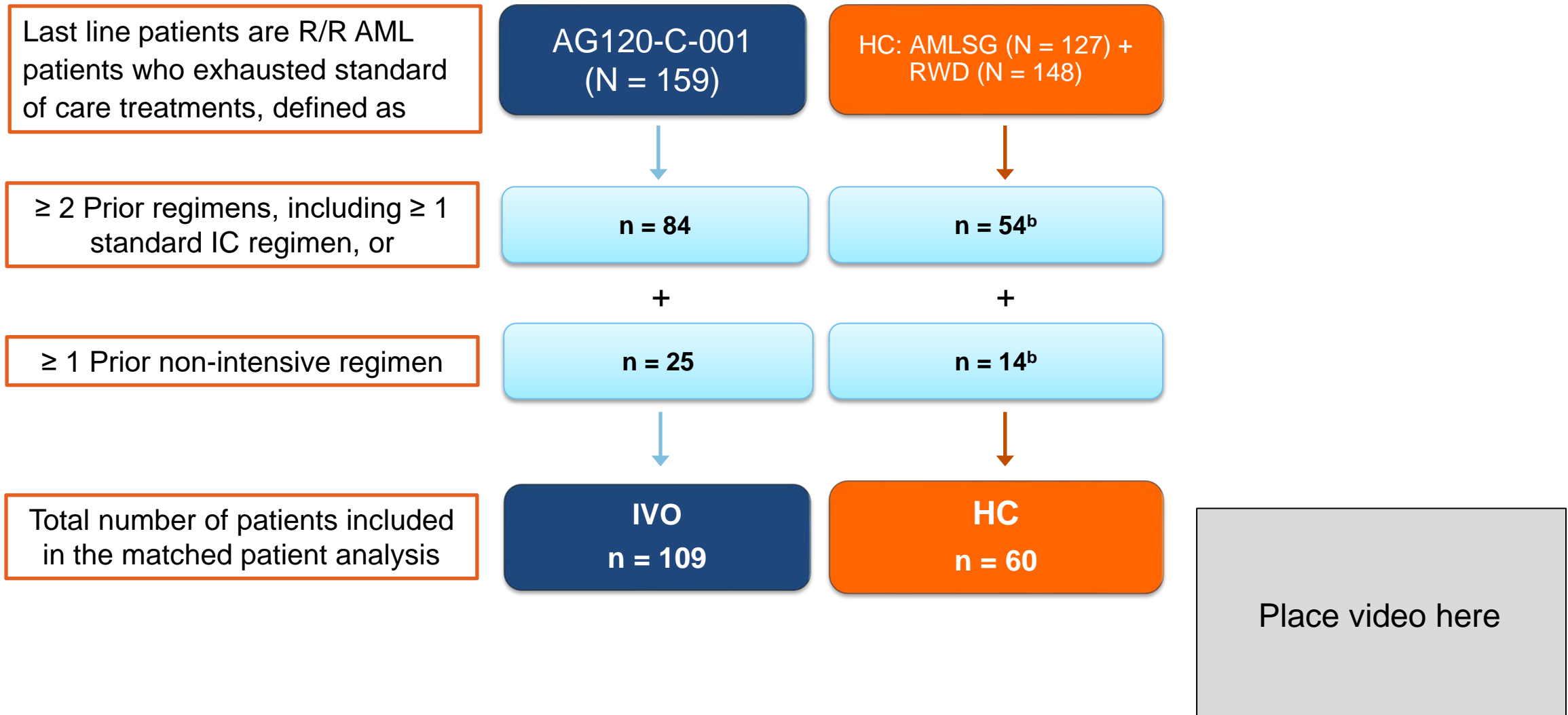
Objective

- The aim of this analysis was to investigate the benefit of IVO monotherapy in patients who exhausted standard of care treatment options
- **Study populations**

R/R AML patients with <i>IDH1</i> mutation		
AG120-C-001 (N = 159)	AMLSG Registry (N = 127)	RWD (N = 148)
<ul style="list-style-type: none">• Treated with IVO 500 mg• Relapsed after transplantation• ≥ 2 Relapses• Refractory to initial induction or reinduction treatment• Relapsed ≤ 1 yr of initial treatment, excluding patients with favorable risk status	<ul style="list-style-type: none">• German AML study group or clinical registry• No treatment with m<i>IDH1</i> inhibitor• ≥ 1 standard IC regimen between 1998 and 2012	<ul style="list-style-type: none">• Retrospective chart review study from France, Germany, UK, and Spain• ≥ 18 years at time of R/R diagnosis• ≥ 1 anti-leukemic agent for R/R AML• No treatment with m<i>IDH1</i> inhibitor

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Identification of patients in the last line setting^a



^aA medical review of prior therapies was conducted to identify AG120-C-001 and HC patients who met the criteria for last line treatment. ^bEight patients were not considered for this analysis due to favorable baseline cytogenetic risk (n = 5) and missing prognostic factors (n = 3).

AML = acute myeloid leukemia; AMLSG = AML Study Group; HC = historical control; IC = intensive chemotherapy; IVO = ivosidenib; R/R = relapsed/refractory; RWD = real-world chart review study

Matched patient analysis using propensity score method

– key prognostic factors

Key prognostic factors, n (%)	IVO (N = 109)	HC (N = 60)	Standardized differences	Weighted standardized differences	
				Optimal full matching	IPTW
Prior HSCT	31 (28.4)	16 (26.7)	0.040	0.038	0.016
Age, yr, mean (SD)	64.1 (14.0)	61.8 (13.1)	0.167	-0.121	-0.012
Number of prior regimens ^a	23 (21.1)	12 (20.0)	0.027	-0.249	-0.028
	86 (78.9)	48 (80.0)	-0.027	0.249	0.028
Nature of AML	77 (70.6)	45 (75.0)	-0.098	0.057	0.012
	32 (29.4)	15 (25.0)	0.098	-0.057	-0.012
Cytogenetic risk status ^b	68 (62.4)	44 (73.3)	-0.236	-0.003	0.021
	41 (37.6)	16 (26.7)	0.236	0.003	-0.021
Primary refractory	36 (33.0)	14 (23.3)	0.217	-0.010	-0.018

Two approaches, optimal full matching and IPTW, were applied

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^aDetermined by medical review. ^bDetermined using NCCN 2015 cytogenetic group. AML = acute myeloid leukemia; HC = historical control; HSCT = hematopoietic stem cell transplant; IPTW = inverse probability of treatment weighting method; IVO = ivosidenib; NCCN = National Comprehensive Cancer Network; SD = standard deviation; yr = year.

IVO monotherapy demonstrates a significant overall survival advantage

	Unmatched		IPTW matching		Optimal full matching	
	IVO	HC	IVO	HC	IVO	HC
OS ^a , median (95% CI)	8.1 (5.7, 9.5)	3.0 (1.9, 4.5)	8.1 (5.7, 9.8)	2.9 (1.9, 4.5)	8.1 (5.1, 9.5)	2.6 (1.8, 4.1)
Hazard ratio ^a (95% CI)	0.417 (0.292, 0.593)		0.396 (0.279, 0.562)		0.438 (0.306, 0.627)	
P-value ^b	< 0.0001		< 0.0001		0.003	

A significant OS benefit was observed for IVO monotherapy in the unmatched population and independent of propensity score method

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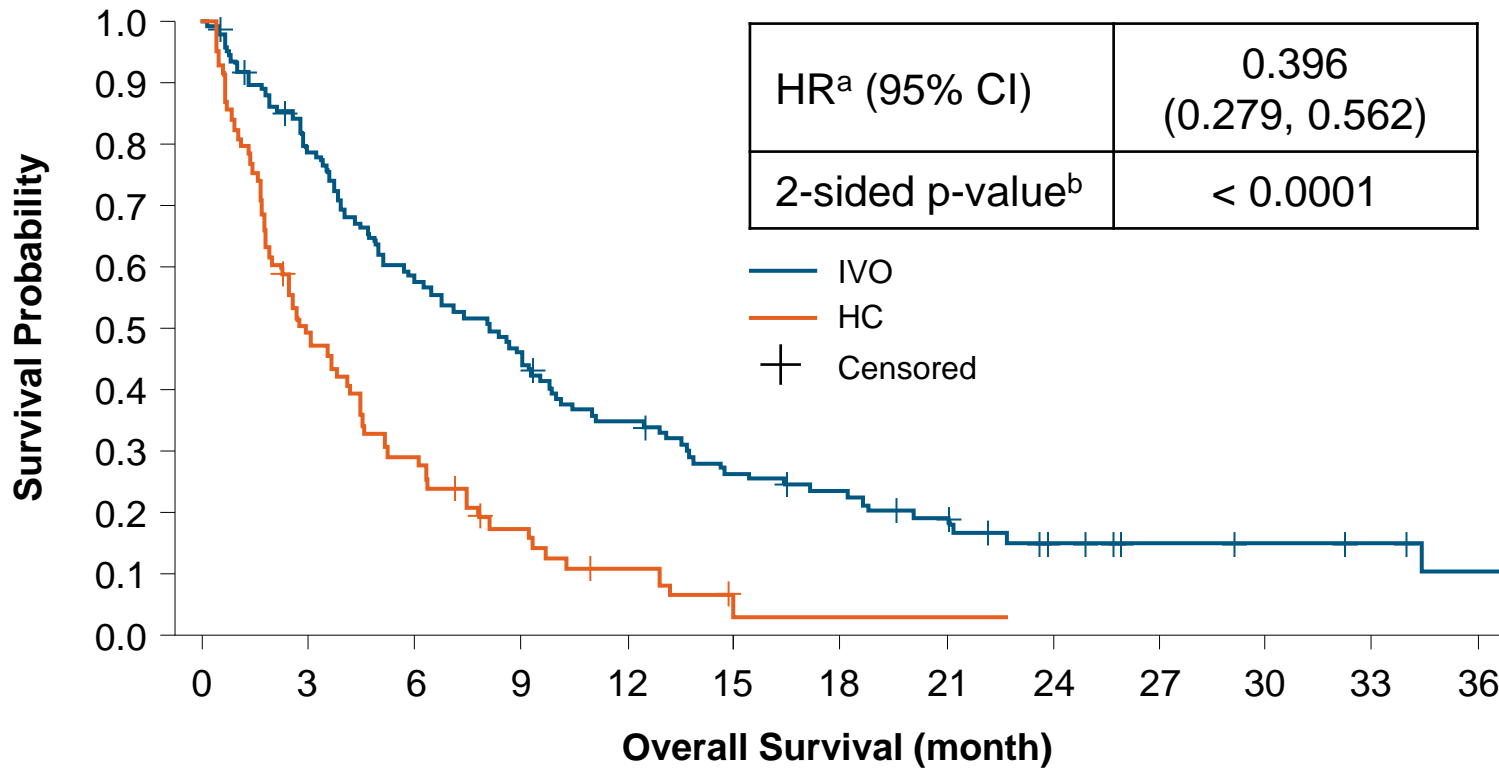
^aCox regression analysis, using the key prognostic factors as covariates, was applied to estimate HR of OS, and the corresponding 95% CI was estimated using the sandwich estimator.

^bP-value based on 2-sided log-rank test.

CI = confidence interval; HC = historical control; HR = hazard ratio; IPTW = inverse probability of treatment weighting method; IVO = ivosidenib; OS = overall survival

Kaplan–Meier curves demonstrate significant OS benefit for IVO

IPTW matching



- Clear separation of the IVO and HC KM curves demonstrates that patients in the last line setting benefit from IVO treatment
- KM curves were comparable for unmatched and optimal full matching

IVO	109	83	60	48	35	25	21	16	9	6	5	4	2
HC	60	30	18	10	5	2	1	1	0				

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^aCox regression analysis, using the key prognostic factors as covariates, was applied to estimate HR and the corresponding 95% CI was estimated using the sandwich estimator. ^bP-value based on 2-sided log-rank test. CI = confidence interval; HC = historical control; HR = hazard ratio; IPTW = inverse probability of treatment weighting method; IVO = ivosidenib; KM = Kaplan-Meier; OS = overall survival

Conclusions

- In the R/R AML last line setting, the benefit of IVO monotherapy was observed when not applying propensity score matching/weighting compared with standard of care therapies in historical controls
- A consistent benefit of IVO monotherapy was observed after applying different propensity score matching/weighting methods
- Compared to historical controls, an increased benefit of IVO monotherapy was observed in the full population and this analysis demonstrated that the benefit of IVO is even more compelling in the last line setting