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

Peter Paschka, MD,[1*] Hervé Dombret, MD,[2] Xavier Thomas, MD, PhD,[3] Christian Recher, MD, PhD,[4] Sylvain Chantepie, MD,[5] Pau Montesinos, MD, PhD,[6,7] Evelyn Acuña-Cruz, MD,[7] Paresh Vyas, MRCP FRCP FRCPath,[8] Karl-Anton Kreuzer, MD,[9] Michael Heuser, MD,[10] Klaus H. Metzeler, MD,[11] Michael Dennis, MD,[12] Bruno Quesnel, MD, PhD,[13] Mathilde Hunault-Berger, MD, PhD,[14] Mohamad Mohty, MD, PhD,[15] Arnaud Pigneux, MD, PhD,[16] Stéphane de Botton, MCU-PH,[17] Daniela Weber, MSc,[1] Konstanze Döhner, MD,[1] Gary Milkovich, PharmD,[18] John Reitan, PharmD,[18] Sarah C. MacDonald, SD,[19] Deborah Casso, MPH,[20] Michael Storm, MSc,[21] Hua Liu, PhD,[21] Stephanie M. Kapsalis, OTR,[21] Eyal C. Attar, MD,[21] Thomas Winkler, MD,[21] Hartmut Döhner, MD[1]

[1]Ulm University Hospital Ulm, Germany; [2]Hôpital Saint-Louis, Paris, France; [3]Centre Hospitalier Lyon-Sud, Pierre-Benite, France; [4]IUCT-Oncopole, Centre Hospitalier Universitaire de Toulouse, Toulouse, France; [5]Institut d'Hématologie de Basse-Normandie, Centre Hospitalier Universitaire de Caen, Caen, France; [6]CIBERONC, Instituto Carlos III, Madrid, Spain; [7]Hospital Universitario y Politécnico La Fe, Valencia, Spain; [8]University of Oxford, Oxford, United Kingdom; [9]Uniklinik Köln, Köln, Germany; [10]Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany; [11]Department of Medicine III, University Hospital, LMU Munich, Munich, Germany; [12]The Christie NHS Foundation Trust, Manchester, United Kingdom; [13]Centre Hospitalier Régional Universitaire de Lille, Lille, France; [14]CRCINA Centre Hospitalier Universitaire d'Angers, Angers, France; [15]Sorbonne University, Hôpital Saint-Antoine, Paris, France; [16]CHU Bordeaux, Université de Bordeaux, Bordeaux, France; [17]Institut Gustave Roussy, Villejuif, France; [18]RJM Group, LLC, Washington, DC, United States; [19]IQVIA, Kirkland, QC, Canada; [20]IQVIA, Seattle, WA, United States; [21]Agios Pharmaceuticals, Inc., Cambridge, MA, United States

**Current address: Klinikum Ludwigshafen, Ludwigshafen am Rhein, Germany*

This study was funded by Agios Pharmaceuticals, Inc.

Background

Background

- IVO is an oral, targeted inhibitor of m*IDH1* approved by the FDA for the treatment of m*IDH1* 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 therapies[1]
  - 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]

AML = acute myeloid leukemia; AMLSG = AML Study Group; CI = confidence interval; IC = intensive chemotherapy; FDA = Food and Drug Administration; HR = hazard ratio; IPTW = inverse probability of treatment weighting method; IVO = ivosidenib; mo = months; m*IDH1* = mutant isocitrate dehydrogenase 1; ND = newly diagnosed; OS = overall survival; R/R = relapsed/refractory; RWD = real-world chart review study

1. Paschka P et al. *2020 EHA Annual Meeting*: Poster EP540. **2.** DiNardo CD et al. *N Engl J Med* 2018;378:2386–98. **3.** Roboz GJ et al. *J Clin Oncol* 2014;32:1919–26. **4.** Nanah R et al. *Am J Hematol* 2017;92:866–71.

Objective and study populations

Objective

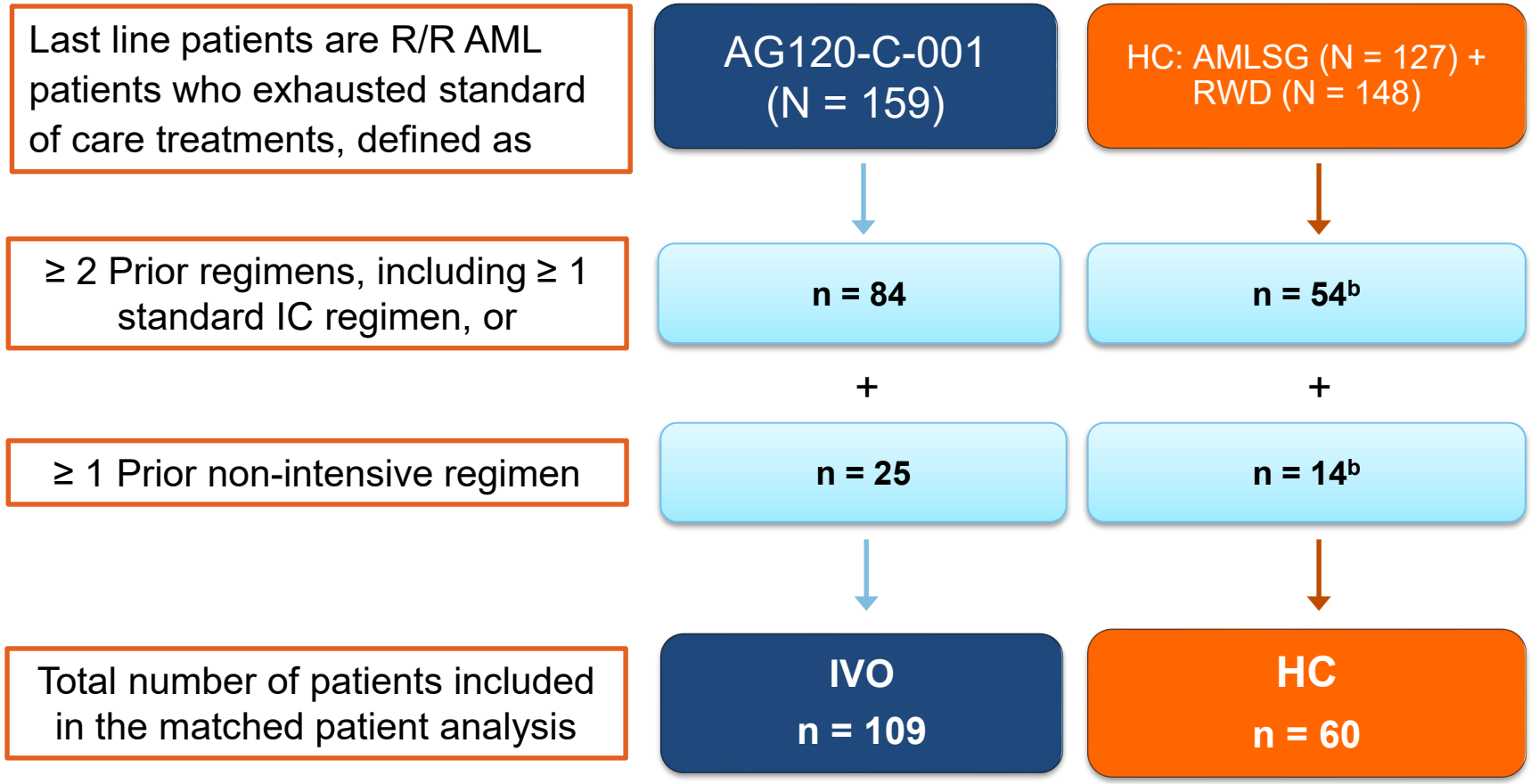
- The aim of this analysis was to investigate the benefit of IVO monotherapy in patients who exhausted standard of care treatment options

- **Study populations**

R/R AML patients with *IDH1* mutation		
AG120-C-001 (N = 159)	**AMLSG Registry (N = 127)**	**RWD (N = 148)**
• 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	• German AML study group or clinical registry • No treatment with m*IDH1* inhibitor • ≥ 1 standard IC regimen between 1998 and 2012	• 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*IDH1* inhibitor

AML = acute myeloid leukemia; AMLSG = AML Study Group; IC = intensive chemotherapy; IPTW = inverse probability of treatment weighting; IVO = ivosidenib; m*IDH1* = mutant isocitrate dehydrogenase 1; R/R = relapsed/refractory; RWD = real-world chart review study; yr = year.

Identification of patients in the last line setting[a]



[a]A medical review of prior therapies was conducted to identify AG120-C-001 and HC patients who met the criteria for last line treatment. [b]Eight patients were not considered for this analysis due to favorable baseline cytogenic 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] < 2 ≥ 2	23 (21.1) 86 (78.9)	12 (20.0) 48 (80.0)	0.027 –0.027	–0.249 0.249	**–0.028** **0.028**
Nature of AML *De novo* Secondary	77 (70.6) 32 (29.4)	45 (75.0) 15 (25.0)	–0.098 0.098	0.057 –0.057	**0.012** **–0.012**
Cytogenetic risk status[b] Intermediate Poor	68 (62.4) 41 (37.6)	44 (73.3) 16 (26.7)	–0.236 0.236	–0.003 0.003	**0.021** **–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

[a]Determined by medical review. [b]Determined 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.

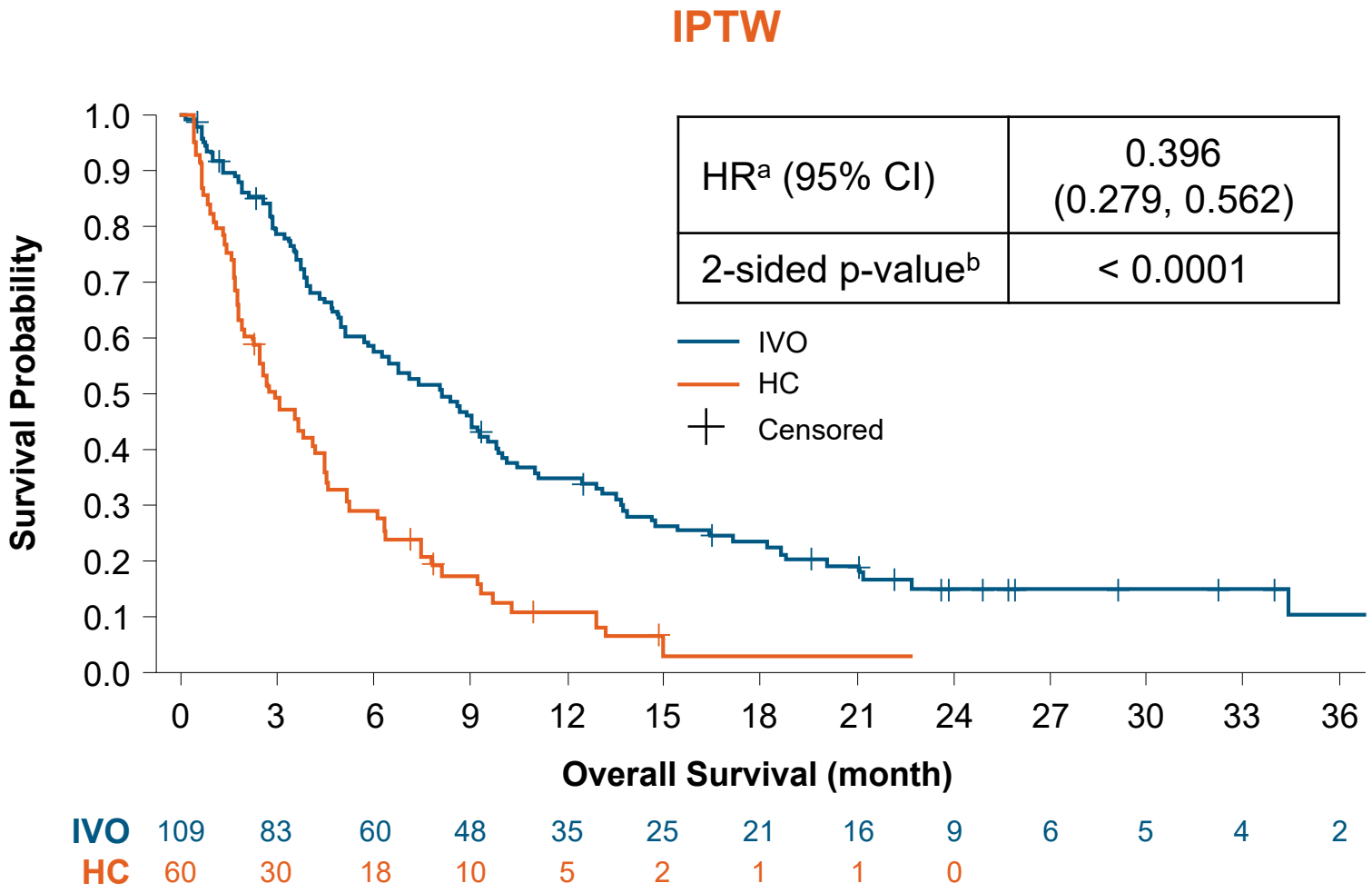
IVO monotherapy demonstrates a significant overall survival advantage

	Unmatched		IPTW		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

[a]Cox 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.
[b]P-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



- 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

[a]Cox 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. [b]P-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

AML = acute myeloid leukemia; IVO = ivosidenib; R/R = relapsed/refractory