

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

Peter Paschka¹, Hervé Dombret², Xavier Thomas³, Christian Recher⁴, Sylvain Chantepie⁵, Pau Montesinos^{6,7}, Evelyn Acuña-Cruz⁷, Paresh Vyas⁸, Karl-Anton Kreuzer⁹, Michael Heuser¹⁰, Klaus H Metzeler¹¹, Michael Dennis¹², Bruno Quesnel¹³, Mathilde Hunault-Berger¹⁴, Mohamad Mohty¹⁵, Arnaud Pigneux¹⁶, Stéphane de Botton¹⁷, Daniela Weber¹, Konstanze Döhner¹, Gary Milkovich¹⁸, John Reitan¹⁸, Sarah C MacDonald¹⁹, Deborah Casso²⁰, Michael Storm²¹, Hua Liu²¹, Stephanie M Kapsalis²¹, Eyal C Attar²¹, Thomas Winkler²¹, Hartmut Döhner¹

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

BACKGROUND

Ivosidenib (IVO) monotherapy was approved by the US FDA for the treatment of acute myeloid leukemia (AML) with a susceptible *IDH1* mutation as detected by an FDA-approved test in adults with newly diagnosed AML who are ≥ 75 years of age or who have comorbidities that preclude the use of intensive induction chemotherapy and in adults with relapsed or refractory (R/R) AML, based on the results of the open-label AG120-C-001 (ClinicalTrials.gov NCT02074839) study

OBJECTIVES

To evaluate the comparative benefit of IVO, matched patient analyses were conducted using data on m*IDH1* R/R AML patients from the AML Study Group (AMLSG) database (NCT01252485) and a real-world chart review study (RWD) from France, Germany, the UK, and Spain

METHODS

IVO trial patients (N = 159)

- Patients enrolled in Arm 1+ of Study AG120-C-001 (phase 1, multicenter, open-label trial) with an *IDH1* mutation, R/R AML, whose starting dose was 500 mg once daily, and met all of the following key eligibility criteria:
 - Patients who relapsed after transplantation
 - Patients in second or later relapse
 - Patients who were refractory to initial induction or reinduction treatment, or
 - Patients who relapsed within 1 year of initial treatment, excluding patients with favorable-risk status

Historical controls: AMLSG patients (N = 127)

- Adult R/R AML patients with documented *IDH1* mutations for whom data were collected as part of an AMLSG study or clinical registry

Historical controls: RWD patients (N = 148)

- A retrospective, multi-center, chart-review study of adult patients with R/R AML who had a mutation in *IDH1*, were treated with at least one anti-leukemic agent for R/R AML, and did not receive prior treatment with an *IDH1* inhibitor

Statistical analysis

- Baseline was defined as the date of first dose of IVO, date of first dose of the most recent AML therapy received, and date of most recent documented relapsed or refractory AML for the AG120-C-001 study, RWD, and AMLSG, respectively
- Four propensity score-based matching/weighting methods were used
- A literature review and data availability led to the inclusion of 8 baseline prognostic factors for estimation of propensity score: prior hematopoietic stem cell transplantation (HSCT), age, number of prior regimens for AML, nature of AML, cytogenetic risk, primary refractory status, relapse-free survival (RFS) after the first induction chemotherapy, and prior induction chemotherapy. Eastern Cooperative Oncology Group (ECOG) performance status was also included in sensitivity analyses
- Balance between populations was assessed pre- and post-match via comparison of (weighted) standardized differences for each covariate
- Time-to-event data were summarized via Kaplan-Meier estimators with 95% CIs
- Cox regression analysis, using the key prognostic factors as covariates, was applied to estimate hazard ratios (HRs) of overall survival (OS), and the corresponding 95% CI was estimated using the sandwich estimator

Analysis sets

- All Arm 1+ patients from the AG120-C-001 study were compared to the entirety of the combined historical control dataset in the base case
- Additional analyses were conducted comparing IVO patients who were, by eligibility criteria, not candidates for intensive salvage therapies (IC), to the subset of RWD patients who received non-intensive salvage therapies (non-IC) as their last therapy

RESULTS: Ivosidenib vs all historical controls (AMLSG + RWD)

Baseline characteristics

- Standardized differences were reduced in all of the matching/weighting methods compared to the cohort prior to matching (Table 1)

Table 1. Baseline disease characteristics and standardized differences between IVO and HC cohorts before and after matching

Prognostic factor	Prior to match population characteristics		[Weighted] ^a standardized differences				
	IVO (n = 159)	HC (n = 275)	Prior to match	Optimal full matched sample	Optimal 1:1 matched sample	Greedy nearest neighbor matched sample	IPTW weighted sample
			(n = 159 IVO and 275 HC)	(n = 152 IVO and 225 HC)	(n = 157 IVO and 157 HC)	(n = 117 IVO and 117 HC)	(n = 157 IVO and 238 HC)
Prior HSCT, n (%)	43 (27.0)	49 (17.8)	0.223	-0.069	0.058	-0.059	0.052
Age, mean (SD)	64.3 (13.51)	57.5 (13.59)	0.501	0.024	0.228	0.012	-0.007
Number of prior regimens ^b , n (%)							
< 2	73 (45.9)	167 (60.7)	-0.300	0.061	0.013	0.000	-0.015
≥ 2	86 (54.1)	108 (39.3)	0.300	-0.061	-0.013	0.000	0.015
Nature of AML, n (%)							
De novo	110 (69.2)	229 (83.3)	-0.336	-0.083	-0.220	0.040	0.048
Secondary	49 (30.8)	45 (16.4)	0.345	0.083	0.220	-0.040	-0.048
Cytogenetic risk status, n (%)							
Intermediate	103 (64.8)	208 (75.6)	-0.239	0.021	-0.137	-0.092	0.029
Poor	56 (35.2)	52 (18.9)	0.373	-0.021	0.137	0.092	-0.029
Primary refractory, n (%)	64 (40.3)	88 (32.0)	0.172	0.028	0.092	0.089	0.054
RFS after the first induction chemotherapy ^c , mean (SD)	5.9 (12.19)	7.9 (19.69)	-0.121	0.051	-0.086	-0.071	-0.036
Prior induction chemotherapy, n (%)	118 (74.2)	258 (93.8)	-0.555	-0.065	-0.393	-0.025	0.052

^aWeighted standardized differences are presented for optimal full matching and IPTW methods

^bNumber of prior regimens is determined by medical review

^cRFS from the first induction chemotherapy is defined as time from the date of first CR/CRi/CRp/MLFS from the first induction chemotherapy to the date of first relapse

HC = historical control; IPTW = inverse probability of treatment weighting

RESULTS: Ivosidenib vs non-IC RWD

Table 3. Baseline disease characteristics and standardized differences between IVO and the non-IC RWD cohort before and after matching

Prognostic factor	Prior to match population characteristics		[Weighted] ^a standardized differences			
	RWD (n = 65)	IVO (n = 155 IVO and 64 RWD)	Optimal full matched sample	Optimal 1:1 matched sample	Greedy nearest neighbor matched sample	IPTW weighted sample
			(n = 155 IVO and 64 RWD)	(n = 65 IVO and 65 RWD)	(n = 59 IVO and 59 RWD)	(n = 157 IVO and 65 RWD)
Prior HSCT, n (%)	12 (18.5)	0.015	0.114	0.043	0.046	
Age, mean (SD)	65.6 (13.1)	0.026	0.030	0.081	0.023	
Number of prior regimens ^b , n (%)						
< 2	34 (52.3)	0.039	0.062	0.034	0.036	
≥ 2	31 (47.7)	-0.039	-0.062	-0.034	-0.036	
Nature of AML, n (%)						
De novo	45 (69.2)	0.176	0.098	0.000	0.053	
Secondary	20 (30.8)	-0.176	-0.098	0.000	-0.053	
Cytogenetic risk status, n (%)						
Intermediate	42 (64.6)	0.186	0.000	0.072	0.032	
Poor	23 (35.4)	-0.186	0.000	-0.072	-0.032	
Primary refractory, n (%)	18 (27.7)	0.066	0.000	0.108	0.012	
RFS after the first induction chemotherapy ^c , mean (SD)	10.1 (23.4)	0.088	0.139	0.022	0.006	
Prior induction chemotherapy, n (%)	51 (78.5)	0.045	0.038	0.129	0.003	

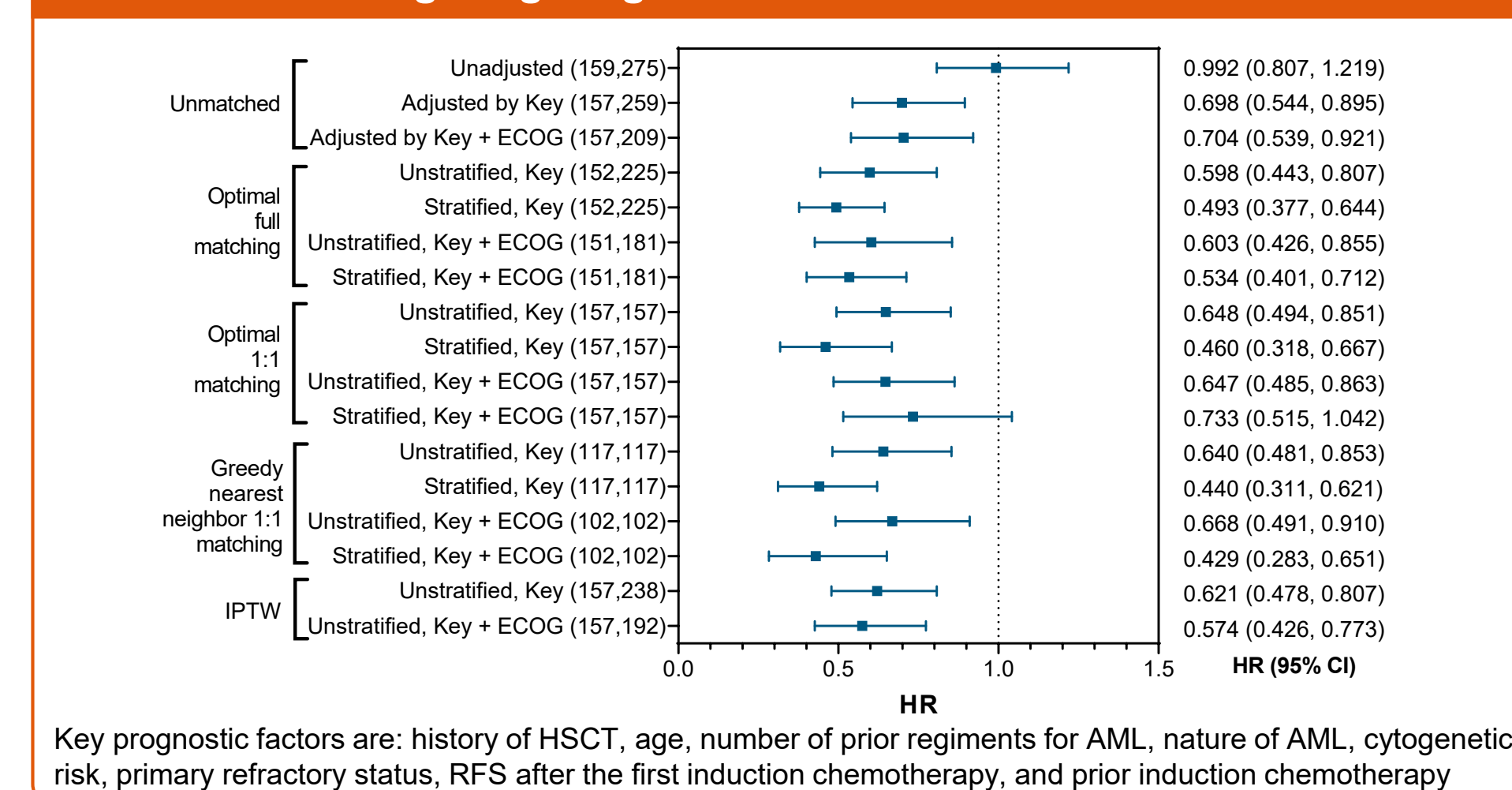
Overall survival

- Before matching/weighting, IVO patients had numerically longer OS than historical controls (median, 8.8 vs 5.4 months; Table 2), despite a higher proportion of patients with adverse prognostic factors (Table 1)
- In matched/weighted analyses, IVO patients had longer survival than historical controls, with HRs ranging from 0.43–0.73 and non-overlapping 95% CIs (Table 2, Figure 1)

Table 2. Median overall survival by matching method

Analysis cohorts	Median OS, months (95% CI)	
	IVO	Historical control
Prior to match	8.8 (6.8, 10.2)	5.4 (4.4, 6.7)
Optimal full matched sample	8.9 (6.7, 10.2)	4.1 (2.6, 6.1)
Optimal 1:1 matched sample	8.8 (6.8, 10.2)	4.5 (3.6, 6.1)
Greedy nearest neighbor matched sample	9.0 (6.7, 10.4)	3.6 (2.7, 4.8)
IPTW weighted sample	9.3 (8.1, 12.5)	4.4 (3.4, 5.3)

Figure 1. Forest plot of HRs with different propensity score matching/weighting methods



Key prognostic factors are: history of HSCT, age, number of prior regimens for AML, nature of AML, cytogenetic risk, primary refractory status, RFS after the first induction chemotherapy, and prior induction chemotherapy

RESULTS: Ivosidenib vs non-IC RWD (CONTINUED)

Figure 2. Kaplan-Meier curve of OS in IVO patients vs non-IC RWD patients after applying IPTW adjustment

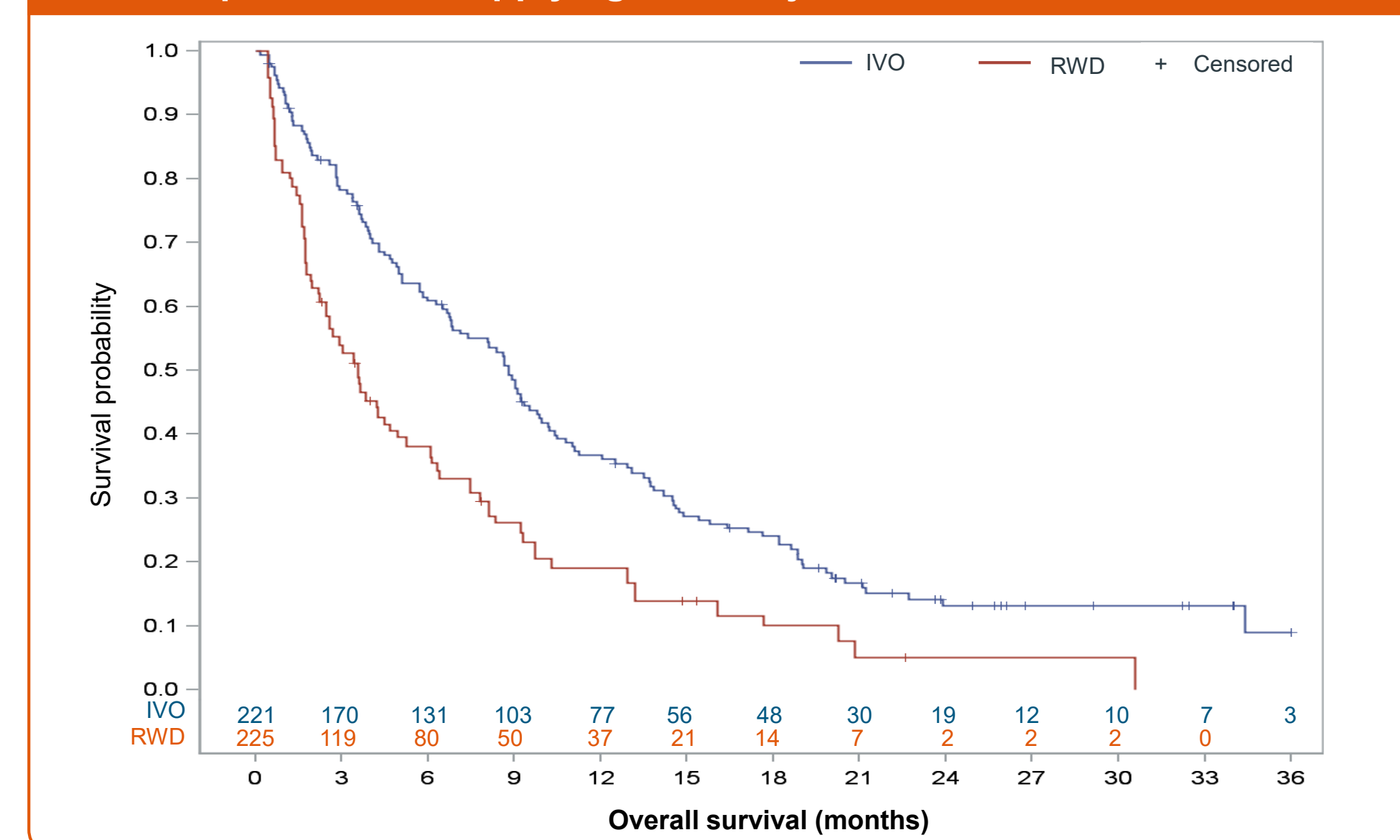
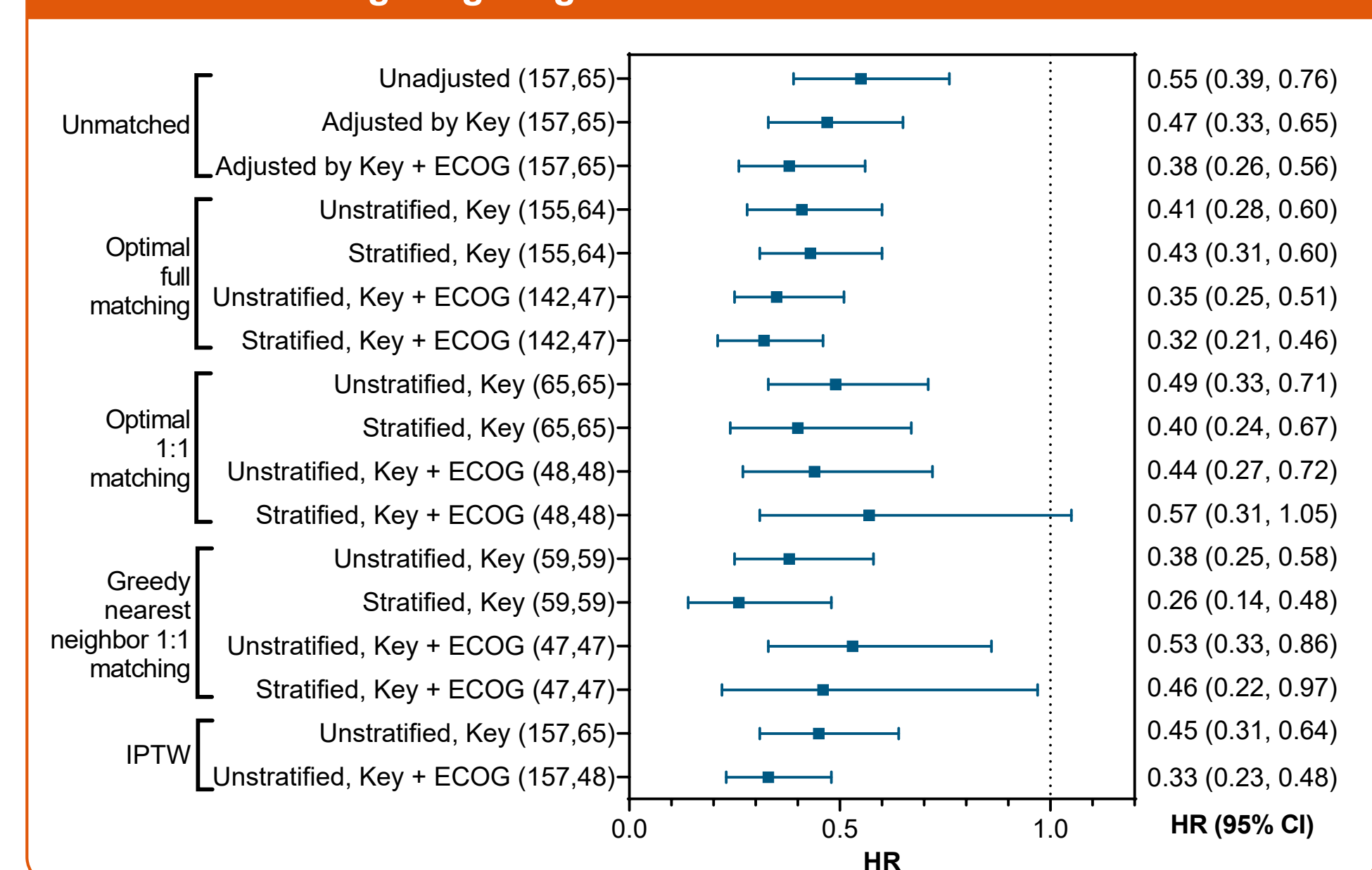


Figure 3. Forest plot of HRs with different propensity score matching/weighting methods in the non-IC cohort



CONCLUSION

- IVO monotherapy prolonged survival in patients with m*IDH1* R/R AML when compared to historical control patients treated with standard therapies in this analysis
- The survival benefit was more pronounced when compared to patients treated with non-intensive therapies

Disclosures

Agius Pharmaceuticals, Inc. provided funding for this study.