AML-596

Matching-Adjusted Indirect Comparison of Olutasidenib and Ivosidenib in Isocitrate Dehydrogenase 1-mutated Relapsed/Refractory Acute Myeloid Leukemia

Justin M. Watts[1]; Brian A. Jonas[2]; Eunice S. Wang[3]; Florence R. Wilson[4]; Julie Park[4]; Shannon Cope[4]; Aaron Sheppard[5]; Stéphane de Botton[6]; Jorge E. Cortes[7]

[1]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; [2]University of California Davis School of Medicine, Sacramento, CA, USA; [3]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [4]Precision AQ, Vancouver, BC, Canada; [5]Rigel Pharmaceuticals, Inc., South San Francisco, CA, USA; [6]Institut Gustave Roussy, Villejuif, France; [7]Georgia Cancer Center, Augusta University, Augusta, GA, USA

Introduction

- Olutasidenib and ivosidenib are allosteric type II inhibitors of isocitrate dehydrogenase 1 (IDH1)
- The therapies have different molecular structures and IDH1 binding characteristics and kinetics, with olutasidenib demonstrating greater specificity by selectively inhibiting mutant but not wild-type IDH1[1-3]
- Olutasidenib and ivosidenib are approved by the US Food and Administration (FDA)[4,5] and recommended in the National Comprehensive Care Network Guidelines®[6] for treatment of *IDH1*-mutated (*mIDH1*) relapsed/refractory (R/R) acute myeloid leukemia (R/R AML) based on the results of single-arm trials[7,8]

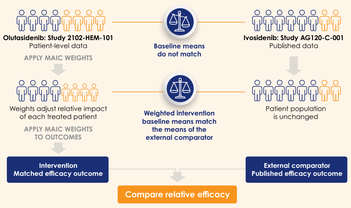
Objective

In the absence of a head-to-head trial, a matching-adjusted indirect comparison (MAIC) was performed to estimate the relative treatment effects of these therapies in m*IDH1* R/R AML

Methods

- The MAIC used registrational data for olutasidenib (Study 2102-HEM-101[4,7]; N=147; Jun 18, 2021 data cutoff [DCO]; individual patient-level data) and ivosidenib (Study AG120-C-001[5,8]; N=174; Nov 10, 2017 DCO; study-level data for revised FDA R/R AML population)
- Kaplan–Meier (KM) curves for overall survival (OS) were reconstructed for Study AG120-C-001 of ivosidenib
- A logistic propensity score model was used to estimate weights based on the first moment for Study 2102-HEM-101 patients to match those in Study AG120-C-001 (**Figure 1**)
- The model applied 8 clinically validated pre-defined covariates: (1) number of prior systemic therapies, (2) age, (3) prior stem cell transplant (SCT), (4) AML type, (5) relapse type, (6) cytogenetic risk, (7) Eastern Cooperative Oncology Group performance status, and (8) m*IDH1* type
- Analyzed outcomes included complete remission (CR), CR+CR with partial hematological recovery (CRh), duration of CR (DoCR), duration of CR+CRh, and OS
- A simulated treatment comparison (STC) was performed as a sensitivity analysis to validate the MAIC for CR and CR+CRh

Figure 1. Methods for MAIC of Olutasidenib vs. Ivosidenib



MAIC, matching-adjusted indirect comparison.

Results

- Patient characteristics were well balanced after matching; Study 2102-HEM-101 effective sample size (ESS) was 73.03 (**Table 1**)
- Naïve and MAIC-adjusted rates of CR and CR+CRh were comparable for olutasidenib vs. ivosidenib; point estimates favored olutasidenib for CR (**Table 2**; **Figure 2**)
- Naïve and adjusted differences in median DoCR were not statistically significant but favored olutasidenib vs. ivosidenib (**Table 2**; **Figure 3**)
- In the MAIC, olutasidenib had a significantly longer median duration of CR+CRh than ivosidenib (difference: 9.84 months) (**Table 2**; **Figure 3**)
- Naïve comparison suggested significantly better OS with olutasidenib than ivosidenib; the MAIC point estimate also favored olutasidenib (**Figure 4**). Results of naïve and adjusted restricted mean survival time (RMST) analyses showed similar trends (**Table 2**).
- STC results for response rates were consistent with the MAIC

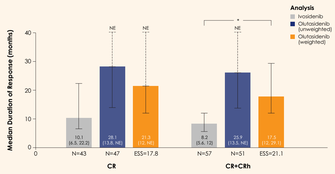
Results

Table 1. Patient Characteristics Before and After Weighting

Patient characteristics	Observed Olutasidenib Study 2102-HEM-101 N=147	Observed Ivosidenib Study AG120-C-001 N=174	MAIC-adjusted Olutasidenib Study 2102-HEM-101 ESS=73.03
ESS reduction (% of original sample size)	N/A	N/A	50.3
Number of prior systemic therapies			
1	32.7	41.6	41.6
2	67.3	58.4	58.4
Age categories			
<65 years	25.2	36.2	36.2
≥65 years	74.8	63.8	63.8
Prior SCT for AML			
Yes	11.6	23.0	23.0
No	88.4	77.0	77.0
AML type			
De novo	66.0	67.0	67.0
sAML with MDS	26.5	16.2	16.2
sAML without MDS	7.5	16.8	16.8
Relapse type			
Primary refractory	31.3	36.8	36.8
Refractory relapse	13.6	25.9	25.9
Untreated relapse	55.1	37.3	37.3
Cytogenetic risk			
Favorable	4.1	0.0	0.0
Intermediate/Poor	89.8	86.8	86.8
Unknown	6.1	13.2	13.2
ECOG Performance Status			
0	31.3	20.7	20.7
1	52.8	55.8	55.8
≥2	15.9	23.5	23.5
IDH1 mutation type			
R132C	57.8	58.6	58.6
R132H	23.8	24.7	24.7
R132L, G, or S	18.4	16.7	16.7

AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; IDH1, isocitrate dehydrogenase 1; MDS, myelodysplastic syndromes; sAML, secondary acute myeloid leukemia; SCT, stem cell transplant.

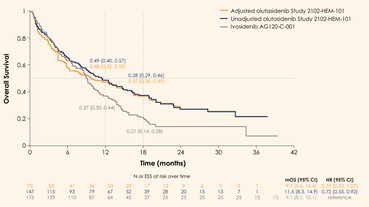
Figure 3. MAIC of Median Duration of Response Outcomes for Olutasidenib vs. Ivosidenib



*Statistically significant difference of 9.84 months (95% CI 3.24, 22.28).

CI, confidence interval; CR, complete remission; CRh, CR with partial hematological recovery; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; NE, non-estimable.

Figure 4. Overall Survival for Olutasidenib vs. Ivosidenib: Naïve and MAIC-Adjusted[a]



[a]MAIC based on FDA original cohort in Study AG120-C-001.

CI, confidence interval; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; mOS, median overall survival.

Table 2. Naïve, Unanchored MAIC, and STC Results for Olutasidenib vs. Ivosidenib

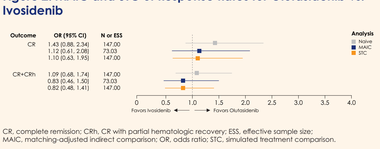
	Olutasidenib Absolute Effects (95% CI)				Ivosidenib Absolute Effects (95% CI)		Olutasidenib vs. Ivosidenib Relative Treatment Effects (95% CI)		
Outcome	**Observed**	**N**	**Adjusted**	**ESS**	**Observed**	**N**	**Naïve**	**MAIC**	**STC**
CR	32%	147	27%	73.03	25%	174	OR 1.43 (0.88, 2.34)	OR 1.12 (0.61, 2.08)	OR 1.10 (0.63, 1.95)
CR+CRh	35%	147	29%	73.03	33%	174	OR 1.09 (0.68, 1.74)	OR 0.83 (0.46, 1.50)	OR 0.82 (0.48, 1.41)
DoCR, median, months	28.1 (13.8, NE)	47	21.3 (12.0, NE)	17.76	10.1 (6.5, 22.2)	43	—[b]	Diff. medians: 11.18 (-4.30, 22.72)[b]	—
Duration of CR+CRh, median, months	25.9 (13.5, NE)	51	17.5 (12.0, 29.1)	21.06	8.2 (5.6, 12.0)	57	—[b]	**Diff. medians: 9.84 (3.24, 22.28)**	—
OS, median, months	11.5 (8.3, 14.9)	147	9.7 (5.6, 16.4)	73.03	9.0 (7.4, 10.2)	173[c]	**HR 0.72 (0.55, 0.92)**	HR 0.75 (0.53, 1.07)	—
OS, RMST, months[a]	16.16 (13.77, 18.55)	147	15.62 (12.09, 19.15)	73.03	12.23 (10.56, 13.90)	173[c]	**Difference: 3.93 (1.02, 6.84)**	Difference: 3.39 (-0.51, 7.29)	—

Darker-shaded boxes indicate point estimates in favor of olutasidenib. Bolded values indicate statistical significance. Double Dashes indicate analysis not performed.

[a]The upper limit of unweighted olutasidenib data was not reached, so it was not feasible to generate reliable bootstrap samples for calculation of median duration of remission. [b]Based on the original FDA R/R AML cohort in Study AG120-C-001 (N=173) given lack of KM curves in the revised R/R AML population. [c]RMST is a measure of average survival from time 0 to a specified time point and can be estimated as the area under the survival curve up to that point; RMST was calculated up to 37.8 months (maximum OS time in Study 2102-HEM-101).

AML, acute myeloid leukemia; CI, confidence interval; CR, complete remission; CRh, CR with partial hematologic recovery; DoCR, duration of CR; HR, hazard ratio; KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparison; NE, non-estimable; OR, odds ratio; OS, overall survival; RMST, restricted mean survival time; R/R, relapsed/refractory; STC, simulated treatment comparison.

Figure 2. MAIC and STC of Response Rates for Olutasidenib vs. Ivosidenib



CR, complete remission; CRh, CR with partial hematologic recovery; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; OR, odds ratio; STC, simulated treatment comparison.

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Conclusions

Results of this MAIC suggest that while naive and adjusted response rates were comparable for ivosidenib and olutasidenib, olutasidenib provided a longer duration of CR+CRh, with potential benefits for CR, DoCR, and OS

- Findings were consistent in MAIC and STC sensitivity analyses
- The results rely on publicly available data for ivosidenib and assumption of no unmeasured confounders, which reflect limitations of the methodology