OLUTASIDENIB FOR THE TREATMENT OF m*IDH1* ACUTE MYELOID LEUKEMIA IN PATIENTS RELAPSED OR REFRACTORY TO HEMATOPOIETIC STEM CELL TRANSPLANT, PRIOR mIDH1 INHIBITOR, OR VENETOCLAX

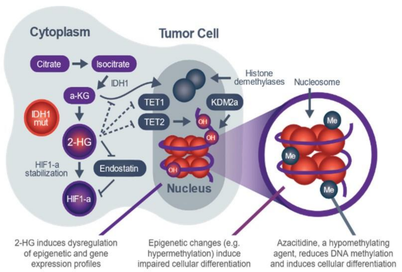
Amber Thomassen[1], Jorge Cortes[2], Joseph G. Jurcic[3], Maria R. Baer[4], William Blum[5], P. Brent Ferrell[6], Brian A. Jonas[7], Alice S. Mims[8], Shyam A. Patel[9], Gary J. Schiller[10], Jay Yang[11], Justin M. Watts[12]

[1]Dept of Medical Affairs, Rigel Pharmaceuticals, Inc., South San Francisco, CA; [2]Georgia Cancer Center, Georgia Cancer Center Augusta University, Augusta, GA; [3]Columbia University Medical Center, New York, NY; [4]Department of Medicine, University of Maryland School of Medicine, Baltimore, MD; [5]Winship Cancer Institute of Emory University, Atlanta, GA; [6]Department of Medicine, Vanderbilt University Medical Center Nashville, TN; [7]Department of Internal Medicine, Division of Malignant Hematology/Cellular Therapy and Transplantation, University of California Davis School of Medicine, Sacramento, CA; [8]Division of Hematology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH; [9]Department of Medicine – Division of Hematology/Oncology, UMass Chan Medical School, Worcester, MA; [10]Hematological Malignancy/Stem Cell Transplant Program, David Geffen School of Medicine, UCLA, Los Angeles, CA; [11]Department of Oncology, Karmanos Cancer Institute/ Wayne State University, Detroit, MI; [12]Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL

INTRODUCTION

- Olutasidenib is a potent, selective, oral, small-molecule inhibitor of mutant isocitrate dehydrogenase 1 (mIDH1) (**Figure 1**)
- Olutasidenib is approved in the for the treatment of relapsed/refractory (R/R) AML based on the pivotal cohort of a registrational Phase 1/2 trial (NCT02719574)[1-4]
- The trial demonstrated[2]:
  - CR/CRh of 35%
  - Duration of response of 25.9 months
  - Overall response rate of 48%

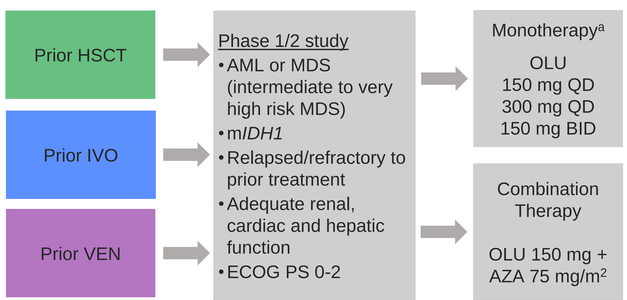
Figure 1. mIDH1 Disease Mechanism[5]



METHODS

- The Phase 1/2, open-label, multi-center study enrolled 335 patients with confirmed m*IDH1* AML or intermediate, high-, or very high-risk myelodysplastic syndromes/neoplasms (MDS) who were newly diagnosed, R/R to prior therapy, or in a maintenance therapy cohort
- We conducted subgroup analyses in patients previously treated with hematopoietic stem cell transplant (HSCT), ivosidenib (IVO) or and/or venetoclax (VEN) to better understand the response to olutasidenib in these poor-prognosis subgroups of m*IDH1* AML
- This analysis included patients from the 2 cohorts in phase 1 and 6 of 8 cohorts in phase 2; no newly diagnosed patients were included in this analysis
- Patients received olutasidenib 150mg QD, 300mg QD or 150mg BID monotherapy or the combination of olutasidenib 150mg BID plus azacitidine 75 mg/m^2 (AZA) (**Figure 2**)
- Endpoints were based on response by modified IWG criteria 2003: Rate of complete remission (CR) plus CR with partial hematologic recovery (CRh)

Figure 2. Source of Patients for Subgroup Analysis



[a]Olutasidenib 150 mg QD was received by a subgroup of patients (n=3) in a fed state.
Olutasidenib was per os over continuous 28-day cycles. Azacitidine was IV or SC on days 1-7 of each 28-day cycle.
AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HSCT, hematopoietic stem cell transplant; m*IDH1*, mutated isocitrate dehydrogenase 1; IV, intravenous; IVO, ivosidenib; MDS, myelodysplastic syndrome; OLU, olutasidenib; QD, once daily; SC, subcutaneous; VEN, venetoclax.

RESULTS

- Of 335 patients in the Phase 1/2 olutasidenib study, 31 had prior HSCT, 9 had prior IVO and 20 had prior VEN. Median ages were 60, 72 and 74, respectively (**Table 1**)

Table 1. Demographics and Baseline Characteristics

	Post-HSCT	Post-IVO	Post-VEN
N	31	9	20
Study Treatment, n **Monotherapy** **Combination therapy**	 22 9	 4 5	 16 4
Median Age, years (range)	60 (40-73)	72 (61-83)	74 (65-83)
Sex, n **Female** **Male**	 14 17	 4 5	 5 15
AML Type, n **Primary** **Secondary**	 22 8 (1 MDS)	 8 1	 10 10
Duration of AML, months, median (range)	17.3 (0-144)	17.9 (9.1-85.7)	22.1 (1.2-85.7)
Status[a], n **Refractory** **Relapsed-Refractory** **Relapsed ≤12 months** **Relapsed >12 months** **CR/CRi**	 3 1 8 17 2[b] / 0	 1 0 6 2 0	 6 0 10 2 0 / 2[b]
***IDH1* Mutation, n** **R132C** **R132H** **R132L/G/S**	 17 12 2	 5 4 0	 13 4 3
Cytogenetic Risk, n **Poor** **Intermediate** **Favorable** **Unknown**	 5 23 1 2	 1 7 0 1	 6 12 1 1
Bone Marrow Blasts, % median (range)	58 (1-98)	83 (5-90)	23 (1-95)
Prior Treatment Regimens, median (range)	4 (2-7)	4 (2-6)	2 (1-6)

[a]Relapsed or refractory (or CR/CRi) status following the last treatment prior to receiving olutasidenib.
[b]Maintenance cohort.
AML, acute myeloid leukemia; CR, complete remission; CRi, CR with incomplete recovery; HSCT, hematopoietic stem cell transplant; IDH, isocitrate dehydrogenase; IVO, ivosidenib; VEN, venetoclax.

Post-HSCT Olutasidenib

- Six (19%) of the 31 patients in the post-HSCT group had a CR to olutasidenib therapy (including the 1 patient with MDS), and 3 (10%) patients had a CR with incomplete count recovery (CRi) resulting in a 29% composite complete remission (CRc) rate (**Table 2**)
- One patient had a morphologic leukemia-free status, resulting in a 32% overall response rate (ORR). Half the responders received monotherapy, and half received a combination of olutasidenib and azacitidine. Two patients were enrolled in the monotherapy maintenance cohort while in CR to prior HSCT; one of these patients maintained a CR for 13 months before progressing, and the other progressed and discontinued due to a new central nervous system disease (**Table 2**)
- For the 10 patients with overall response, the median duration of response was 7.1 months (range 1-23.4+). At data cutoff, 2 patients were ongoing responders, 3 patients proceeded to a second HSCT, and 3 to donor lymphocyte infusion (DLI) (**Table 2**)

Table 2. Response, Duration of Response, and Disposition

	Post-HSCT	Post-IVO	Post-VEN
N	31	9	20
Status, n (%) **CR** **CRh** **CRi**	 6[a,b] (19) 0 3 (10)	 2[c] (22) 0 0	 6[d,e] (30) 1 (5) 2 (10)
CRc, n (%)	9 (29)	2 (22)	9 (45)
MLFS or PR	1 MLFS (<1%)	0	0
ORR, n (%)	10 (32)	2 (22)	9 (45)
DOR, months, median (range)	7.1 (1-23.4+)	5.6 (3.1 > HSCT)	NR (4.8-28.5+)
Disposition	2 Ongoing 3 HSCT + 3 DLI 12 Progression 4 AE 4 Death 1 Patient decision 1 Physician decision 1 Other	1 HSCT 4 Progression 1 AE 2 Physician decision 1 Other	5 Ongoing 6 Progression 5 AE 2 Patient decision 2 Physician decision

[a]One CR patient with prior HSCT was in a maintenance cohort and entered with a CR to prior HSCT.
[b]Response in post-HSCT patients by regimen: 3 CR, 1 CRi and 1 MLFS were in patients receiving combination therapy; all other responders received monotherapy.
[c]Both CR patients with prior IVO received combination therapy.
[d]Two CR patients with prior VEN were in a maintenance cohort, and both entered with a CRi to prior HSCT.
[e]Response in post-VEN patients by regimen: one CR was in a patient on combination; all other responders received monotherapy.
AE, adverse event; CR, complete remission; CRh, CR with partial hematologic recovery; CRc, composite CR; CRi, CR with incomplete recovery; DLI, donor lymphocyte infusion; DOR, duration of response; HSCT, hematopoietic stem cell transplant; IVO, ivosidenib; MLFS, morphologic leukemia-free state; NR, not reached; ORR, overall response rate; PR, partial remission; VEN, venetoclax.

Table 3. Grade 3/4 Adverse Events (AE)

	Post-HSCT	Post-IVO	Post-VEN
N	31	9	20
No. Patients With Any Grade AE	31	9	20
Grade 3/4 AE, patients, n	28	7	17
Common Grade 3/4 AE, n (%)			
RBC count decreased	7 (25)	0	6 (35)
Febrile neutropenia	8 (29)	5 (71)	5 (29)
Neutrophil count decreased	5 (18)	0	4 (24)
Pneumonia	5 (18)	1 (14)	4 (24)
White blood cell count decreased	7 (25)	1 (14)	3 (18)
Platelet count decreased	7 (25)	2 (29)	3 (18)
Hypokalemia	2 (7)	3 (43)	0

Adverse events were consistent with the prescribing information and those reported in patients undergoing treatment for AML.
Death occurred in 14 patients in the post-HSCT group, due to disease progression in 6 patients, pneumonia in 3 patients, and in one patient each: cerebral hemorrhage, enterococcal sepsis, hemorrhagic stroke, respiratory failure, and septic shock. Death occurred in 4 patients in the post-IVO group, due to disease progression in 3 patients and enterococcal bacteremia in 1. Death occurred in 3 patients in the post-VEN group, due to COVID-19, enterococcal bacteremia, and disease progression.
HSCT, hematopoietic stem cell transplant; IVO, ivosidenib; VEN, venetoclax.

Post-IVO Olutasidenib

- In the post-IVO group (n=9), 2 patients (22%) achieved a CR; both CRc and ORR were 22% (**Table 2**)
- Both responders had received olutasidenib in combination with azacitidine
- One responder proceeded to HSCT after 3.1 months, and one responded for 5.6 months and then progressed

Post-VEN Olutasidenib

- Response rates in the post-VEN group (n=20) included CR in 6 patients (30%), CRh in 1 (5%), and CRi in 2 (10%) resulting in a CRc of 9 (45%) and an ORR of 45% (**Table 2**)
- One responder received combination olutasidenib and azacitidine
- Two patients in the monotherapy maintenance cohort were CRi to prior treatment; both improved their response to a CR
- Median duration of response was ongoing at 28.5 months

CONCLUSIONS

- This descriptive analysis suggests that olutasidenib alone or in combination with azacitidine may induce complete remissions in patients with m*IDH1* AML or MDS that is R/R to prior therapy with venetoclax, ivosidenib or HSCT
- Although only a small number of patients receiving maintenance therapy were included in this analysis, the data show that maintenance of a CR and even improvement of response from CRi to CR is possible with olutasidenib
- Olutasidenib offers a valuable treatment option for patients with m*IDH1* AML who are refractory or relapsed to prior therapy where there are limited treatment options and a very poor prognosis

REFERENCES

1. Rezlidhia® (olutasidenib) tablets, for oral use [prescribing information]. San Francisco, CA: Rigel Pharmaceuticals, Inc.; 2022.
2. Watts, et al. Lancet Hematol. 2023;10(1):346-e58.
3. de Botton S, et al. *Blood Adv.* 2023;7(13):3117-27.
4. de Botton, et al. *Blood.* 2021; 138(supplement 1):2351.
5. Cortes J, et al. *Blood.* 2019; 134(supplement 1):674.

For more information, please contact: Jorge.cortes@augusta.edu

Presented at the International Congress on Hematologic Malignancies, Miami, FL, February 29-March 3, 2023, and the American Society of Hematology Annual Meeting • San Diego, California, USA • December 9-12, 2023