Olutasidenib (FT-2102) Induces Durable Complete Remissions in Patients with Relapsed/Refractory mIDH1 Acute Myeloid Leukemia. Results from a Phase 2 Pivotal Clinical Trial

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INTRODUCTION

- A mutation in isocitrate dehydrogenase 1 (mIDH1) is present in 7-14% of patients with acute myeloid leukemia (AML).[1]
- Inhibition of mIDH1 in tumor cells can restore normal cellular differentiation and provide therapeutic benefit in mIDH1-cancers.[2]
- Inhibitors of mIDH1 have demonstrated efficacy in both newly diagnosed and relapsed/refractory (R/R) AML.[3,4]
- Olutasidenib is a potent, selective, oral, small-molecule inhibitor of mIDH1.[5,6]
- Olutasidenib previously demonstrated a manageable tolerability profile and clinical activity in mIDH1 AML patients in the completed Phase 1 portion of an open-label, multi-center, Phase 1/2 trial.[2]
- We report herein results from the pivotal Phase 2 cohort of the Phase 1/2 trial in patients with R/R mIDH1 AML.

METHODS

- Study 2102-HEM-101 (NCT02719574) is an open-label, multi-center, Phase 1/2 trial.
- Patients received olutasidenib 150 mg BID monotherapy in continuous 28-day cycles.
- The Primary Endpoint was rate of Complete Remission (CR) + Complete Remission with partial hematologic recovery (CRh) (modified IWG criteria 2003).
- Secondary Endpoints included Overall Response Rate (ORR); Duration of CR+CRh; Duration of Overall Response (DOR); Rate of Transfusion Independence (TI), including red blood cells (RBC) and/or platelets; and Overall Survival (OS).

Patients

- 153 patients with mIDH1 R/R AML were enrolled and received at least one dose of olutasidenib (150 mg BID).
- The Efficacy Evaluable (EE) Set comprised 147 patients with centrally confirmed mIDH1 who received the first dose of olutasidenib ≥6 months prior to the data cut-off date (18 June 2021). Six patients in the Safety Set were not included in the EE Set due to lack of centrally confirmed mIDH1.

RESULTS

Disposition

Patient Disposition as of Data Cut-off	
Safety Set, n	153
Efficacy Evaluable Set, n	147
Treatment ongoing, n (%)	21 (14)
Discontinued from treatment, n (%)	132 (86)
Primary reason for discontinuation, n (%)	
Disease progression	62 (41)
Adverse event	26 (17)
HSCT	15 (10)
Death	14 (9)
Other*	15 (10)

*Includes investigator decision 7 (5%); permanent withdrawal of consent 5 (3%); patient decision, lack of response, and patient non-compliance / protocol violation each 1 (1%).

Patient Characteristics

Patient Characteristics in the EE Set (N=147)	
Men, n (%)	74 (50)
Median age (range)	71.0 years (32-87)
AML type, n (%)	
Primary de novo / Secondary	97 (66) / 50 (34)
Cytogenetics, n (%)*	
Favorable	6 (4)
Intermediate	107 (73)
Poor	25 (17)
Unknown	9 (6)
Prior therapy outcomes, n (%)	
Refractory / Relapsed**	51 (35) / 96 (65)
Median no. of prior treatments (range)	2.0 (1-7)
Prior Induction Therapy***	143 (97)
Prior HSCT, n (%)	17 (12)

*Data were not collected on which classification system of cytogenetic risk was used (either NCCN or ELN guidelines). **70% patients had remission duration ≤12 months. ***Data were not collected on the on the specific induction regimen used.

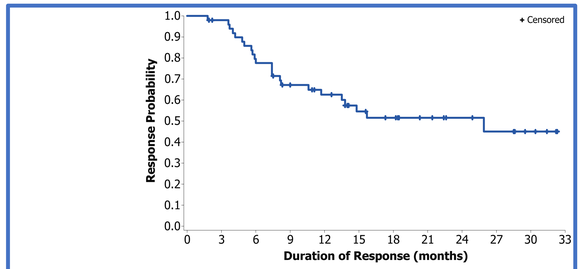
Response

	Response Rate, n (%)	Median Time to Response (Range), Months
CR	47 (32)	2.8 (0.9-7.4)
CRh	4 (3)	N/A
CR+CRh	51 (35)	1.9 (0.9-5.6)
Other Responders		
CRi	15 (10)	N/A
PR / MLFS*	3 (2) / 2 (1)	N/A
ORR, n (%)	71 (48)	1.9 (0.9-10.2)
Non-Responders	52 (35)	N/A

*CRi = CR with incomplete recovery. MLFS = morphologic leukemia-free state; PR = partial remission.

Duration of Response

- In the primary efficacy evaluation, the CR+CRh rate was 51/147 (35%) (95% CI, 27.0-43.0), with most responses a CR 47/147 (32%) (95% CI, 24.5-40.2).
- Median duration of CR+CRh was 25.9 months (95% CI, 13.5-NE) and median duration of CR was 28.1 months (95% CI, 13.8-NE).

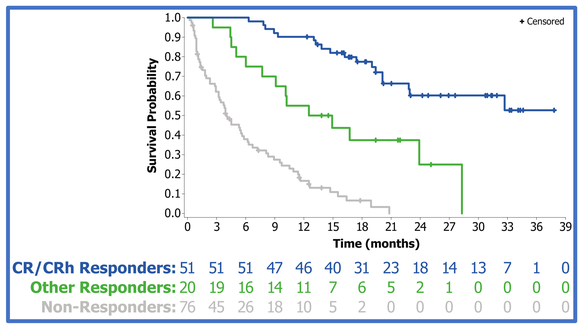


- Median DOR was 11.7 months (95% CI, 6.9-25.9).
- Response rates were similar for 12 pts who had received prior venetoclax: the CR+CRh rate was 33% (n=4; 95% CI, 9.9-65.1) and the CR rate was 25% (n=3; 95% CI, 5.5-57.2).

Overall Survival

- Median overall survival (OS) was 11.6 months (95% CI, 8.9-15.5) in the overall population of 153 patients.
- Estimated 18-month survival of patients with a CR+CRh was 78%.

Median OS (95% CI) by Response Category	
CR+CRh Responders	Not Reached (22.8-NR)
Other Responders	13.7 months (6.0-NR)
Non-Responders	4.0 months (3.2-5.8)



Transfusion Independence

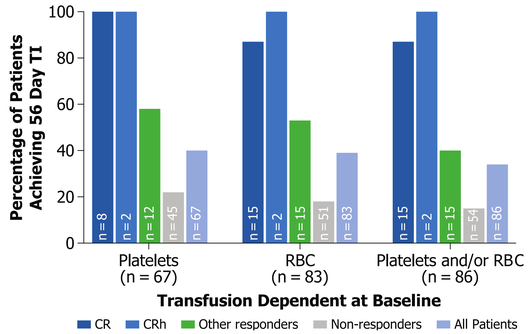
- Among 86 patients who were platelet and/or RBC transfusion dependent at baseline, a 56-day TI was achieved in 29 (34%), across all response groups.
- Higher rates of TI were observed among transfusion dependent patients at baseline who achieved CR+CRh than for Other Responders.

Stem Cell Transplant

- In total, 16 (11%) patients were able to proceed to HSCT following Olutasidenib treatment (includes 1 patient who discontinued for an AE prior to HSCT).
- Of 15 patients who discontinued Olutasidenib to receive HSCT, 11 were in CR/CRh, 3 in CRi and 1 had SD.

Safety

Treatment-Related TEAEs (N=153)		
Adverse Events, n (%)	All Grades (>5%)	Grade 3 or 4 (>2%)
Patients with any AE	111 (73)	59 (39)
Nausea	35 (23)	0 (0)
Differentiation syndrome	22 (14)	13 (8)
Leukocytosis	20 (13)	7 (5)
ALT increased	13 (8)	4 (3)
Constipation	12 (8)	0 (0)
Fatigue	11 (7)	1 (1)
Vomiting	11 (7)	0 (0)
Anemia	9 (6)	7 (5)
AST increased	9 (6)	3 (2)
Thrombocytopenia	8 (5)	6 (4)
Neutropenia	8 (5)	8 (5)
GGT increased	8 (5)	7 (5)
Hepatic enzyme increased	6 (4)	5 (3)



- Differentiation syndrome (DS) occurred in 22 (14%) patients, with Grade ≥3 events in 14 (9%) and 1 fatal case; most cases resolved with treatment interruption, dexamethasone and/or supportive care.
- Hepatic AEs occurred in 38 (25%) patients, with Grade 3 events in 19 (12%) and Grade 4 events in 4 (3%); Grade 3/4 events (>1%) were increases in laboratory liver function parameters. Hepatic AEs were manageable with dose modifications and concomitant medications.
- QTc prolongation occurred in 12 (8%) patients with 1 (1%) Grade 3 event. None led to discontinuation.
- TEAEs leading to treatment discontinuation occurred in 48 (31%) patients including (>1%) disease progression (14%), and DS, febrile neutropenia, and pneumonia (2% each).
- Deaths were reported in 48 (31%) patients, with the majority related to progression of AML or its complications. Events leading to death in >1 patient were disease progression (14%), pneumonia (2%), and pneumonia fungal, cerebral hemorrhage, respiratory failure, sepsis, and other (1% each).

CONCLUSIONS

- Olutasidenib induced durable remissions and transfusion independence with a well-characterized and manageable side-effect profile.
- Some patients were able to proceed to HSCT.
- The observed activity is clinically meaningful and represents a therapeutic advance in the treatment of this molecularly defined, poor-prognosis patient population with R/R mIDH1 AML.

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