Lisaftoclax (APG-2575), a Novel BCL-2 Inhibitor, in Combination with Azacitidine in Treatment of Patients with Myelodysplastic Syndrome (MDS)

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INTRODUCTION

- Hypomethylating agents (HMAs) remain the standard of care in MDS. In the event of HMA failure/resistance, new therapeutic options are needed.
- Preclinical data have shown that novel, BCL-2 inhibitor lisaftoclax synergistically induces apoptosis in MDS/acute myeloid leukemia cell lines/derived xenograft models when combined with an HMA (data on file; Pharmacology report: APG-2575-PH-SZ-09 [July 2019]; *In vivo* report: APG-2575-PH-SZ-10, [June 2019]). Lisaftoclax is a compound under study as an investigational drug and not yet approved in the United States.
- Lisaftoclax combined with an HMA has the potential to effect deeper and more durable responses in MDS.[1]

OBJECTIVES

- In this open-label, multicenter, phase 1b/2 study, we evaluated the safety and efficacy of lisaftoclax in combination with azacitidine for patients with higher risk MDS.

METHODS

- Patients with higher-risk MDS (IPSS-R score > 3.5; bone marrow blasts > 5%), including those with treatment-naïve (TN) or relapsed or refractory (R/R) disease, were enrolled.
- Lisaftoclax at an assigned dose (400, 600, or 800 mg) was administered orally once daily from Day 1 to 14 and combined with azacitidine (75 mg/m^2/day) on Day 1 to 7 in repeated 28-day cycles.
- Patients continued treatment until disease progression, unacceptable toxicity, or withdrawal of consent.
- A daily lisaftoclax ramp-up schedule was used before the first cycle to prevent tumor lysis syndrome (TLS).
- Overall responses were evaluated in accordance with the 2006 International Working Group (IWG) criteria by investigators, as well as the 2023 IWG criteria for the 600-mg TN MDS cohort.
- Efficacy assessments were performed at the end of Cycle 1 and subsequent even-numbered cycles (Day 22 ~ Day 28).

RESULTS

- As of July 1, 2024, 49 patients were enrolled, including 8 with R/R and 41 with TN higher-risk MDS.
- Median duration of treatment for TN and R/R MDS was 4.5 (0.5-12.1) and 3.2 (1.2-9.4) months, respectively.

Table 1. Baseline characteristics

	N = 49
Median age, yr (range)	66 (22-83)
Male, n (%)	27 (55.1)
MDS diagnosis at enrollment, n (%)	
Chemo-R/R	8 (16.3)
Chemo-naïve	41 (83.7)
IPSS-R prognostic score, n (%)	
Intermediate	12 (24.5)
High	24 (49.0)
Very high	13 (26.5)
Common mutations, n (%)[a]	
TET2	11 (28.2)
TP53	9 (23.1)
ASXL1	10 (25.6)
RUNX1	10 (25.6)
Baseline cytopenia grade ≥ 3, %	
Anemia	70.8
Neutropenia	54.2
Thrombocytopenia	45.8

[a]39 patients with genetic mutational profile data. IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; R/R, relapsed/refractory; TN, treatment naïve.

SAFETY

- Common grade ≥ 3 hematologic treatment-related adverse events (TRAEs) included leukopenia (71.4%), neutropenia (65.3%), thrombocytopenia (61.2%), anemia (20.4%), and febrile neutropenia (12.2%).
- Grade ≥ 3 infections were reported in 46.9% of patients, of which 26.5% were treatment related.
- Treatment-emergent and treatment-related serious adverse events were reported in 34.7% and 28.6% of patients, respectively.
- Lisaftoclax dose reduction due to TRAEs occurred in 3 (6.1%) patients, including 2 with neutropenia and 1 with thrombocytopenia.
- Treatment delays between cycles due to adverse events occurred in 11 (22.4%) patients, with a median (range) delay of 12 (1-63) days.
- Neither 60-day mortality nor TLS was reported.

SAFETY

Table 2. Adverse events

Preferred term	TEAEs (Any grade; >10% incidence)	TEAEs (Grade ≥ 3)	TRAEs (Any grade)	TRAEs (Grade ≥ 3)
Population, n (%)	49	49	49	49
Any adverse event	48 (98.0)	45 (91.8)	47 (95.9)	43 (87.8)
Leukopenia	39 (79.6)	37 (75.5)	37 (75.5)	35 (71.4)
Anemia	22 (44.9)	12 (24.5)	19 (38.8)	10 (20.4)
Febrile neutropenia	9 (18.4)	9 (18.4)	6 (12.2)	6 (12.2)
Neutropenia	35 (71.4)	34 (69.4)	33 (67.3)	32 (65.3)
Thrombocytopenia	35 (71.4)	32 (65.3)	33 (67.3)	30 (61.2)
Blood creatinine increased	10 (20.4)	0	7 (14.3)	0
LDH increased	8 (16.3)	0	6 (12.2)	0
Weight decreased	7 (14.3)	0	2 (4.1)	0
Nausea	28 (57.1)	0	28 (57.1)	0
Vomiting	28 (57.1)	0	27 (55.1)	0
Diarrhea	23 (46.9)	1 (2.0)	20 (40.8)	1 (2.0)
Constipation	20 (40.8)	1 (2.0)	14 (28.6)	1 (2.0)
Abdominal pain	6 (12.2)	0	5 (10.2)	0
Hypokalemia	21 (42.9)	5 (10.2)	13 (26.5)	3 (6.1)
Decreased appetite	16 (32.7)	0	12 (24.5)	0
Hypoalbuminemia	11 (22.4)	0	2 (4.1)	0
Hyponatremia	10 (20.4)	1 (2.0)	3 (6.1)	1 (2.0)
Hypocalcemia	8 (16.3)	1 (2.0)	4 (8.2)	1 (2.0)
Hypertriglyceridemia	6 (12.2)	0	3 (6.1)	0
Hyperuricemia	6 (12.2)	0	2 (4.1)	0
Pneumonia	13 (26.5)	12 (24.5)	8 (16.3)	8 (16.3)
Upper respiratory tract infection	9 (18.4)	4 (8.2)	5 (10.2)	3 (6.1)
Pyrexia	18 (36.7)	1 (2.0)	11 (22.4)	0
Cough	11 (22.4)	0	3 (6.1)	0
Hepatic function abnormal	5 (10.2)	0	5 (10.2)	0

LDH, lactate dehydrogenase; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

EFFICACY

In 23 patients with TN MDS treated with lisaftoclax 600 mg combined with azacitidine:

- Overall response (ORR) and complete remission (CR) rates were 73.9% and 30.4%, respectively, per 2006 IWG criteria.
- The composite CR rate was 69.6% (CR [52.2%] + CR with limited count recovery [17.4%]) per IWG 2023 criteria.
- Median (range) time to CR was 2.8 (1.1-8.7) months.
- Median progression-free survival was not reached (95% CI, 7.1-NR).

EFFICACY

Table 3. Efficacy

	TN MDS Dose, mg				R/R MDS Dose, mg		
	400	600	800	Total	600	800	Total
Evaluable, n	16	23	1	40	5	3	8
Response, n (%)							
ORR[a]	13 (81.3)	17 (73.9)	1 (100.0)	31 (77.5)	4 (80.0)	2 (66.7)	6 (75.0)
CR	3 (18.8)	7 (30.4)	0	10 (25.0)	1 (20.0)	0	1 (12.5)
mCR	10 (62.5)	10 (43.5)	1 (100.0)	21 (52.5)	3 (60.0)	2 (66.7)	5 (62.5)
SD	2 (12.5)	5 (21.7)	0	7 (17.5)	1 (20.0)	0	1 (12.5)
PD	1 (6.3)	1 (4.3)	0	2 (5.0)	0	1 (33.3)	1 (12.5)

[a]ORR = CR + mCR; mCR, morphologic complete remission; PD, progressive disease; SD, stable disease.

CONCLUSIONS

- In patients with higher-risk TN or R/R MDS, lisaftoclax combined with azacitidine showed encouraging activity and was well tolerated.
- The clinical data support further clinical development of this combination in patients with higher-risk MDS.
- A randomized, double-blind, phase 3 registration study (NCT06641414; GLORA-4) will further assess the survival benefits of lisaftoclax combined with azacitidine in patients with newly diagnosed high-risk MDS patients.

REFERENCE

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