Phase 1b/2 study of lisaftoclax (APG-2575) combined with azacitidine in patients with newly diagnosed (ND) or prior venetoclax–exposed myeloid malignancies

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Introduction

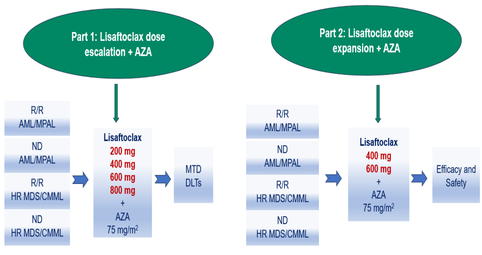
- Acute myeloid leukemia (AML), mixed phenotype acute leukemia (MPAL), chronic myelomonocytic leukemia (CMML) and myelodysplastic syndromes (MDS) are myeloid hematologic malignancies with poor prognoses.
- Venetoclax combined with azacitidine (AZA) or decitabine is approved to treat patients with ND AML who are elderly or cannot tolerate intensive chemotherapy. However, most patients experience resistance or intolerance.
- Additional therapies are needed to treat patients with ND or prior venetoclax-exposed myeloid malignancies. It is unknown whether other novel BCL-2 inhibitor(s) can overcome venetoclax resistance.
- Lisaftoclax (APG-2575), a novel, orally active small molecule BCL-2 inhibitor, has shown enhanced treatment responses when combined with AZA in preclinical and clinical studies.[1,2]

Objectives

- This phase 1b/2 study was designed to explore the safety, efficacy, and pharmacokinetic (PK) profile of lisaftoclax combined with AZA in patients with ND or previously venetoclax-exposed myeloid malignancies, including ND or relapsed/refractory (R/R) AML, MPAL, CMML, or higher-risk (HR) MDS.
- Primary end points for phase 1 were to determine safety and tolerability, including the DLT and MTD/RP2D, of lisaftoclax combined with AZA.
- The primary end point for phase 2 was to assess the efficacy of lisaftoclax combined with AZA in AML/MPAL, CMML, and HR MDS in different cohorts.
- Potential pharmacodynamic and predictive biomarkers associated with the combination therapy were concurrently explored.

Methods

Figure 1. Study design



Summary

- Lisaftoclax combined with AZA led to a high response rate and was well tolerated in patients with HR-MDS and AML, with few dose modifications and low infection rates, supporting further clinical development of this regimen in these populations.
- Lisaftoclax combined with AZA provides a promising treatment option for patients with HR-MDS or AML.

Discussion

- Lisaftoclax has shown potential to overcome venetoclax resistance in AML and MDS.
- GLORA-4, a global, multicenter, double-blind, randomized phase 3 study of lisaftoclax combined with AZA in ND HR-MDS, is ongoing (NCT06641414).
- GLORA-3, a global, multicenter, double-blind, randomized phase 3 study of lisaftoclax in combination with AZA in elderly/unfit ND AML, is also ongoing (NCT06389292).

References

1. Zhai Y et al. *Clin Cancer Res* 2023;29:183-196.
2. Wang H et al. *Blood* 2023;142(suppl 1):2925.

Acknowledgments

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Results

- As of April 21, 2025, 103 patients were treated with lisaftoclax combined with AZA. Of them, 27 with R/R AML/MPAL and 1 with ND AML (evolved from MDS) were R/R to prior venetoclax exposure.

Table 1. Baseline characteristics

	R/R AML/MPAL (n = 56)	ND AML/MPAL (n = 7)*	R/R MDS/CMML (n = 25)	ND MDS/CMML (n = 15)
Median age, yr (range)	67.0 (23-88)	72.0 (67-81)	73.0 (61-89)	74.0 (33-82)
Male sex, n (%)	33 (58.9)	3 (42.9)	14 (56.0)	14 (56.0)
No. prior therapies, median (range)	2 (1-8)	2 (1-3)	1 (1-2)	0
Prior venetoclax, n (%)				
Relapsed	9 (16.1)	1 (14.3)	0	0
Refractory	18 (32.1)	0 (0.0)	0	0
Prior HMAs, n (%)	32 (57.1)	2 (28.6)	23 (92.0)	0
Azacitidine	23 (41.1)	2 (28.6)	11 (44.0)	0
Decitabine	14 (25.0)	1 (14.3)	8 (32.0)	0
Azacitidine + decitabine	5 (8.9)	1 (14.3)	4 (16.0)	0
Prior allogeneic HCT, n (%)	9 (16.1)	1 (14.3)	2 (8.0)	0
No. of treatment cycles, median (range)	2.0 (1-13)	4.0 (0-11)	3.0 (1-11)	5.0 (1-18)

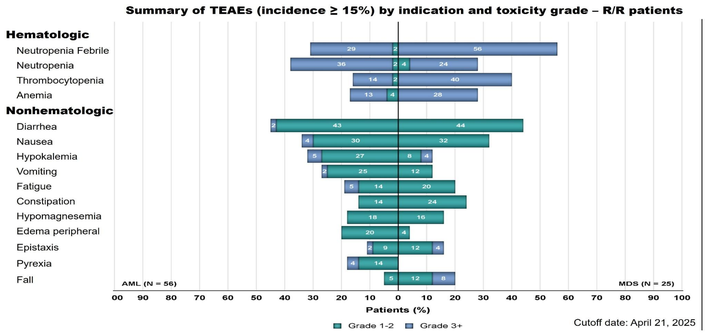
*In the ND AML/MPAL cohort, two patients with MDS had previously received treatment, but MDS had evolved to AML.

Table 2. Patient disposition

	R/R AML/ MPAL (n = 56)	ND AML/ MPAL (n = 7)*	R/R MDS/CMML (n = 25)	ND MDS/CMML (n = 15)
Median follow-up, mo. (range)	3.7 (0-17)	5.2 (0-10)	3.9 (0-13)	6.5 (1-20)
Death within 30 days after first dose#, n (%)	3 (5.4)	0	1 (4.0)	0
Treatment discontinuation, n (%)				
Yes	49 (87.5)	6 (85.7)	21 (84.0)	11 (73.3)
No	7 (12.5)	1 (14.3)	4 (16.0)	4 (26.7)
Reason for discontinuation of treatment, n (%)				
Disease progression	25 (44.6)	3 (42.9)	9 (36.0)	5 (33.3)
Patient withdrew	3 (5.4)	1 (14.3)	1 (4.0)	0
Investigator decision	1 (1.8)	0	0	0
Changed treatment after remission	0	0	4 (16.0)	0
Unacceptable adverse event(s)	6 (10.7)	0	4 (16.0)	1 (6.7)
Transplantation	4 (7.1)	0	0	2 (13.3)
Treatment failure	7 (12.5)	1 (14.3)	1 (4.0)	3 (20)
Death*	3 (5.4)	1 (14.3)	2 (8.0)	0

#3 patients with R/R AML/MPAL and 1 with HR-MDS died within 30 days: 2 R/R AML/MPAL died of progressive disease (PD), 1 patient with R/R AML/MPAL died because of TEAEs, 1 R/R HR-MDS died from PD. *One patient with R/R HR-MDS died because of neutropenic sepsis, possibly related to underlying disease and lisaftoclax + AZA based on the investigator's evaluation; others died because of disease progression.

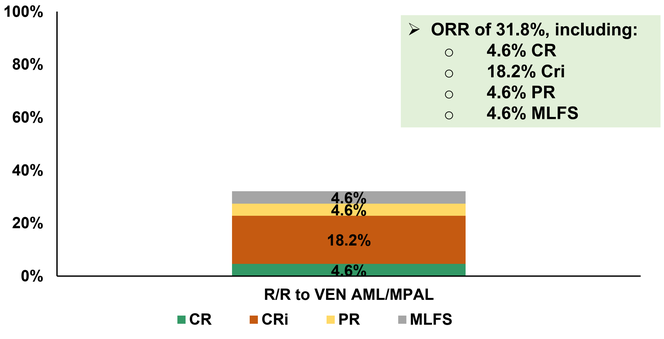
Figure 2. Safety



Summary of treatment-emergent adverse events (TEAEs) in R/R AML/MPAL and R/R MDS/CMML:

- Serious AEs occurred in 39 (69.6%) patients with AML/MPAL and 15 (60.0%) with MDS/CMML.
- Febrile neutropenia was reported in 17 (30.4%) patients with AML/MPAL and 5 (20.0%) with MDS/CMML; infections were reported in 21 (37.5%) patients with AML/MPAL and 6 (24.0%) with MDS/CMML.

Figure 3. Efficacy, N = 22



CR, complete response; Cri, complete response with incomplete hematologic recovery; PR, partial response; MLFS, morphologic leukemia-free state.

- Overall response rates (ORRs) were 83.3% and 43.2% in ND and R/R AML/MPAL, and 80% and 50% in ND and R/R MDS/CMML, respectively.
- Among 22 evaluable patients who were confirmed R/R to prior venetoclax treatment (21 R/R AML, 1 ND AML evolved from HR-MDS), lisaftoclax combined with AZA induced measurable responses, as shown in Figure 3.