First-in-human open-label study of lisaftoclax (APG-2575), a novel BCL-2 inhibitor, in patients (pts) with relapsed/refractory chronic lymphocytic leukemia (R/R CLL) and other hematologic malignancies (HMs)

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INTRODUCTION

- Many B-cell malignancies evade apoptosis by overexpressing BCL-2 proteins.[1]
- The BCL-2 inhibitor venetoclax is active in certain HMs but can increase the risk of tumor lysis syndrome (TLS), requiring a 5-week dose ramp-up for pts with CLL. Cases of severe neutropenia with venetoclax treatment have also been reported.[2-4]
- Lisaftoclax is a novel molecule, with a potent BCL-2 inhibitory and unique pharmacokinetic (PK) profile, to enhance efficacy and minimize toxicities.[5,6]

METHODS

- This first-in-human global phase 1 dose escalation and expansion study assessed the safety, PK, pharmacodynamics, efficacy, and maximum tolerated dose (MTD) or recommended phase 2 dose of lisaftoclax in pts with R/R CLL and other HMs.
- Lisaftoclax was orally administered once daily in 28-day cycles until disease progression or unacceptable toxicity.
- In TLS intermediate/high-risk groups, defined per expert TLS panel criteria,[7] the daily dose ramp-up was initiated at 20 mg on day 1 (D1), followed by 50 mg on D2, 100 mg on D3, 200 mg on D4, 400 mg on D5 (for the target dose of 400 mg, D5 was also Cycle 1 day 1 [C1D1]), and increased by 200 mg each subsequent day.

Table 1. Daily ramp-up dosing schedule

Day	Lisaftoclax dose, mg	Duration of ramp-up period, day
1	20	0
2	50	1
3	100	2
4	200	3
5	400	4
6	600	5
7	800	6
8	1,000	7
9	1,200	8

RESULTS

- As of October 22, 2022, 52 pts were enrolled and treated with lisaftoclax at doses ranging from 20 to 1,200 mg. Pts received a median (range) of 2 (1-13) prior lines of treatment and had diagnoses of R/R CLL or small lymphocytic lymphoma (SLL; n = 23), non-Hodgkin lymphoma (NHL; n = 14), multiple myeloma (MM; n = 11), and either acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), hairy-cell leukemia (HCL), or Castleman disease (CD; n = 1 each).
- Of the 52 pts, 17 (32.7%) remained on treatment and 35 discontinued treatment (because of progressive disease [PD; n = 23]; physician decision or pt withdrawal, mainly because of lack of response [n = 5 each]; and adverse events [AEs; n = 2]) and were switched to other therapies.
- The median (range) treatment duration was 7 (1-43) cycles.

Table 2. Baseline demographics of pts with CLL/SLL (N = 23)

Characteristic	No.
Median (range) age, yr	67 (48-83)
Diagnosis, no. (%)	
CLL	22 (95.7)
SLL	1 (4.3)
Rai stage, no. (%)	
I-II	12 (52.2)
III-IV	11 (47.8)
IPI risk group, no. (%)	
Low	6 (26.1)
Intermediate	8 (34.8)
High	8 (34.8)
Very high	1 (4.3)
Prognostic features, no. (%)	
Del(17p)/*TP53* mutation	3 (13.0)
Del(11q)	2 (8.7)
Del(13q)	9 (39.1)
Trisomy 12	2 (8.7)
CD38$^+$	3 (13.0)
Unmutated IgVH	10 (43.5)
Complex cytogenetics[a]	3 (13.0)
No. of prior therapies, median (range)	2 (1-3)
Prior therapies, no. (%)	
Fludarabine/chemo-based	9 (39.1)
CD20 antibody-based	22 (95.7)
BTKi	10 (43.5)
Bulky adenopathy[b], no. (%)	6 (26.1)

[a]Complex cytogenetics is defined as ≥ 3 unrelated chromosome abnormalities. [b]Bulky adenopathy is defined as any single lymph node mass measuring > 5 cm in any single dimension. BTKi, Bruton tyrosine kinase inhibitor; IPI, International Prognostic Index.

- Lisaftoclax was well tolerated, with no DLTs at doses of up to 1,200 mg. MTD was not reached. No laboratory or clinical TLS was reported.

RESULTS

Table 3. Selected treatment-emergent AE (TEAEs)[a], N = 52

TEAE, no. (%)	Any grade[b] (≥ 15%)	Grade 3/4
Diarrhea	25 (48.1)	1 (1.9)
Fatigue	18 (34.6)	1 (1.9)
Nausea	16 (30.8)	2 (3.8)
Anemia	15 (28.8)	5 (9.6)
Thrombocytopenia	15 (28.8)	7 (13.5)
Neutropenia	14 (26.9)	11 (21.2)
Constipation	13 (25.0)	1 (1.9)
Vomiting	12 (23.1)	-
Headache	11 (21.2)	2 (3.8)
Peripheral edema	9 (17.3)	2 (3.8)
Hypokalemia	9 (17.3)	1 (1.9)
Arthralgia	8 (15.4)	-

[a]Highest-frequency AEs. [b]A pt with > 1 AE is counted once.

- Of 22 evaluable pts with R/R CLL/SLL, objective response rate (ORR) was 63.6% (95% CI [41-83]), with a median (range) time to response of 2 (2-8) cycles.
- Among 28 evaluable pts without CLL/SLL, clinical benefit was observed in 14 (50.0%).

Table 4. Treatment responses in malignancy subgroups

		Non-CLL/SLL					
	CLL/SLL	NHL[a]	MM	Myeloid malignancy[b]	HCL	CD	Overall response
Population, no.	23	14	11	2	1	1	29
Evaluable	22	13	11	2	1	1	28
Median (range) treatment, cycles	15 (6-43)	4 (1-40)	3 (1-31)	2 (2-2)	4 (4-4)	11 (11-11)	7 (1-43)
Best response[c], no. (%)							
PR	14 (63.6)	0	1[e] (9.1)	0	0	0	1 (3.6)
MR	0	1[d] (7.7)	1[f] (9.1)	0	0	0	2 (7.1)
SD	8 (36.4)	7 (53.8)	2 (18.2)	0	1 (100.0)	1 (100.0)	11 (39.3)
PD	0	5 (38.5)	7 (63.6)	2 (100.0)	0	0	14 (50.0)
ORR	14 (63.6)	0	1 (9.1)	0	0	0	1 (3.6)
CBR, no. (%)	-	8 (61.5)	4 (36.4)	0	1 (100.0)	1 (100.0)	14 (50.0)

Median (range) number of prior regimens in pts without CLL/SLL: 3 (1-13). [a]NHL includes WM/LPL (n = 5), FL (n = 5), MCL (n = 1), and DLBCL (n = 3; including one pt who was not evaluable for efficacy). [b]Myeloid malignancy includes AML (n = 1) and MDS (n = 1). [c]Certain percentages do not sum to 100 because of rounding. [d]One pt with WM achieved MR after 18 cycles of treatment and maintains MR. [e]One pt with MM achieved a PR after 2 cycles of treatment and discontinued because of disease progression at the end of C6. [f]One pt with MM carrying t(11;14) achieved MR after 2 cycles of treatment and maintained MR at the end of treatment (C9). CBR, clinical benefit rate; DLBCL, diffuse large B-cell lymphoma; LPL, lymphoplasmacytic lymphoma; MCL, mantle-cell lymphoma; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; WM, Waldenström macroglobulinemia.

RESULTS

- The PK profile showed that exposures increased with lisaftoclax doses from 20 to 1,200 mg.
- Lisaftoclax had a plasma elimination half-life ($t_{1/2}$) of approximately 3 to 5 hours and a median time to maximum concentration (t_{max}) of 3 to 6 hours.
- No significant accumulation was observed after multiple oral daily dosing, with an accumulation ratio of approximately 1.
- BH3 profiling showed that lisaftoclax rapidly induced changes in BCL-2 complex and triggered cytochrome c release in CLL/SLL pt samples, which were consistent with rapid clinical reductions in absolute lymphocyte counts.

CONCLUSIONS

- Lisaftoclax was well tolerated at doses of up to 1,200 mg/day.
- No TLS was observed, even with the daily ramp-up schedule.
- There were no significant new or unmanageable safety findings.
- The ORR in pts with R/R CLL/SLL was 63.6%.
- BCL-2 inhibitor lisaftoclax offers a potential treatment alternative for pts with R/R CLL/SLL and other HMs, with a daily ramp-up schedule that may be more pt "user friendly" and a favorable preliminary safety profile.

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