LISAFTOCLAX (APG-2575) COMBINED WITH NOVEL THERAPEUTIC REGIMENS IN PATIENTS WITH RELAPSED OR REFRACTORY (R/R) MULTIPLE MYELOMA (MM) OR IMMUNOGLOBULIN LIGHT-CHAIN (AL) AMYLOIDOSIS

S. AILAWADHI,[1] A. CHANAN-KHAN,[1] J. KHOURI,[2] C.K. YANNAKOU,[3] Z. CHEN,[4] Y. WANG,[4] H. GUO,[5] H. WANG,[4] M. LI,[6] M. AHMAD,[6] D. YANG,[4,6,7] and Y. ZHAI[4-6*]

[1]Mayo Clinic, Jacksonville, FL, United States; [2]Cleveland Clinic, Cleveland, OH, United States; [3]Epworth HealthCare, Melbourne, Australia; [4]Ascentage Pharma (Suzhou) Co., Ltd., Suzhou, China; [5]Guangzhou Healthquest Pharma Co., Ltd., Guangzhou, China; [6]Ascentage Pharma Group Inc., Rockville, MD, United States; [7]Department of Experimental Research, State Key Laboratory of Oncology in South China Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China. *Correspondence to: yzhai@ascentage.com

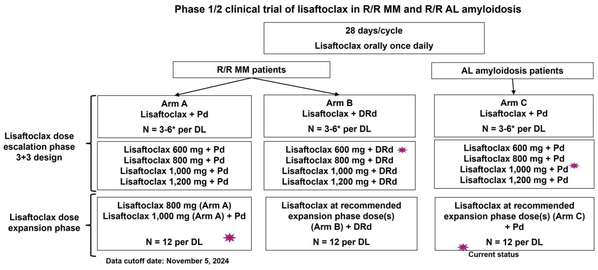
Poster number: MM-718

Introduction

- Lisaftoclax, a novel, investigational BCL-2 inhibitor, effectively inhibited cell proliferation in multiple myeloma (MM) cell lines [being more effective in a subset carrying t(11;14) translocation] and induced apoptosis in primary cells derived from patients with MM.
- Lisaftoclax was well tolerated at higher doses in a phase 1 trial and has shown greater sensitivity than venetoclax in certain preclinical data, suggesting that lisaftoclax may be a promising BCL-2 inhibitor for R/R MM.
- The aim of this study was to explore the safety and efficacy of lisaftoclax combined with pomalidomide and dexamethasone (Pd) or daratumumab, lenalidomide, and dexamethasone (DRd) in patients with R/R MM or AL amyloidosis.

Methods

Figure 1. Study design



Primary Objectives: Assess safety, tolerability, DLT, MTD, and RP2/3D of lisaftoclax with Pd in R/R MM and AL amyloidosis, and DRd in R/R MM.

Secondary Objectives: Evaluate efficacy of lisaftoclax with Pd or DRd in R/R MM (ORR, sCR, CR, VGPR, PR, PFS, OS, DoR, TTR). Evaluate efficacy of lisaftoclax with Pd in AL amyloidosis (hematologic: ORR, sCR, amyloid CR, VGPR, PR, DoR, TTR, PFS, OS; organ: heart, kidney, liver, neuropathy, GI). Determine PK profile of lisaftoclax with Pd (Arms A, C) and DRd (Arm B).

- Dexamethasone: 40 mg for patients aged ≤ 75 years and 20 mg for patients > 75 years on Days 1, 8, 15, and 22.
- Pomalidomide, daratumumab, and lenalidomide were administered according to manufacturer labelling.

Results

Table 1. Patient characteristics (R/R MM and AL Amyloidosis)

R/R MM (N = 41)	400 (n=3)	600 (n=4)	800 (n=15)	1,000 (n=13)	1,200 (n=6)	Total (N=41)
Age, yr						
Mean (SD)	57.7 (8.50)	72.0 (11.46)	72.5 (7.77)	69.8 (10.69)	70.8 (8.70)	70.2 (9.62)
Median (range)	58.0 (49-66)	72.0 (58-86)	73.0 (56-87)	66.0 (56-90)	70.0 (61-81)	71.0 (49-90)
Sex, n (%)						
Female	0 (0.0)	3 (75.0)	5 (33.3)	7 (53.8)	2 (33.3)	17 (41.5)
Male	3 (100.0)	1 (25.0)	10 (66.7)	6 (46.2)	4 (66.7)	24 (58.5)
No. of prior systemic therapies						
Mean (SD)[a]	4.3 (4.93)	5.8 (2.50)	4.9 (2.72)	4.2 (4.62)	3.3 (1.63)	4.5 (3.38)
Median (range)	2.0 (1-10)	5.5 (3-9)	5.0 (2-10)	3.0 (1-19)	3.0 (1-6)	3.0 (1-19)
Time from diagnosis to first dose, yr						
Mean (SD)	2.7 (1.84)	9.1 (3.73)	8.2 (2.85)	6.3 (4.96)	11.7 (11.45)	7.8 (5.75)
Median (range)	3.0 (1-4)	9.6 (4-13)	9.4 (3-13)	4.7 (1-17)	5.5 (2-29)	6.2 (1-29)
t(11;14), n (%)	2 (66.7)	0 (0.0)	1 (6.7)	1 (7.7)	0 (0.0)	4 (9.8)

AL Amyloidosis (N = 10)	400 (n=1)	600 (n=4)	800 (n=3)	1,000 (n=2)	Overall (N=10)
Age, yr					
Mean (SD)	24.0 (0.00)	67.0 (5.48)	69.0 (11.27)	59.0 (0.00)	61.7 (15.10)
Median (range)	24.0 (24-24)	67.5 (60-73)	63.0 (62-82)	59.0 (59-59)	62.5 (24-82)
Sex, n (%)					
Female	0 (0.0)	1 (25.0)	1 (33.3)	1 (50.0)	3 (30.0)
Male	1 (100.0)	3 (75.0)	2 (66.7)	1 (50.0)	7 (70.0)
No. of prior systemic therapies					
Mean (SD)	2.0 (0.00)	2.0 (0.00)	2.0 (1.00)	2.0 (0.00)	2.0 (0.47)
Median (range)	2.0 (2-2)	2.0 (2-2)	2.0 (1-3)	2.0 (2-2)	2.0 (1-3)

[a]Patients were heavily treated with current MM therapies. Abbreviations: AL, amyloid light-chain; MM, multiple myeloma; Pd, pomalidomide and dexamethasone; R/R, relapsed/refractory.

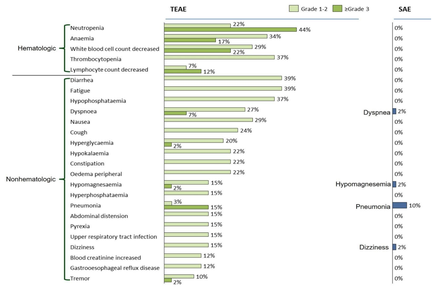


Figure 2. Profile of 41 safety-assessed R/R MM patients

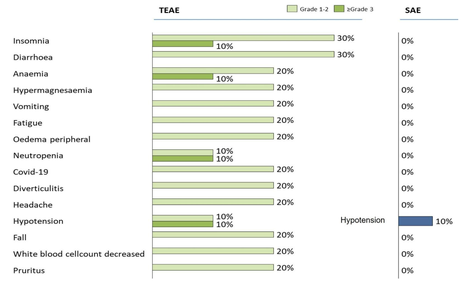


Figure 3. Profile of 10 safety-assessed AL amyloidosis patients

Table 2. Hematologic responses (R/R MM and AL Amyloidosis)

R/R MM (N = 36)	400 (n=3)	600 (n=4)	800 (n=14)	1,000 (n=9)	1,200 (n=6)	Total (N=36)
Best overall response, n (%)						
CR	0 (0.0)	0 (0.0)	1 (7.1)	1 (11.1)	1 (16.7)	3 (8.3)
VGPR	1 (33.3)	1 (25.0)	2 (14.3)	2 (22.2)	2 (33.3)	8 (22.2)
PR	0 (0.0)	2 (50.0)	5 (35.7)	5 (55.6)	0 (0.0)	12 (33.3)
MR	0 (0.0)	0 (0.0)	3 (21.4)	0 (0.0)	0 (0.0)	3 (8.3)
SD	2 (66.7)	1 (25.0)	2 (14.3)	1 (11.1)	3 (50.0)	9 (25.0)
PD	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	1 (2.8)
VGPR or better	1 (33.3)	1 (25.0)	3 (21.4)	3 (33.3)	3 (50.0)	11 (30.6)
95% CI	(0.8-90.6)	(0.6-80.6)	(4.7-50.8)	(7.5-70.1)	(11.8-88.2)	(16.3-48.1)
ORR (PR or better)	1 (33.3)	3 (75.0)	8 (57.1)	8 (88.9)	3 (50.0)	23 (63.9)
95% CI	(0.8-90.6)	(19.4-99.4)	(28.9-82.3)	(51.8-99.7)	(11.8-88.2)	(46.2-79.2)

AL Amyloidosis (N = 9)					
Parameter	400 (n = 1)	600 (n = 4)	800 (n = 2)	1,000 (n = 2)	Overall (N = 9)
Best overall response, n (%)					
sCR	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (11.1)
Unconfirmed sCR	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (11.1)
VGPR	0 (0.0)	2 (50.0)	2 (100.0)	2 (100.0)	6 (66.7)
SD	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
VGPR or better	0 (0.0)	4 (100.0)	2 (100.0)	2 (100.0)	8 (88.9)
95% CI	(0.0-97.5)	(39.8-100.0)	(15.8-100.0)	(15.8-100.0)	(51.8-99.7)
ORR (PR or better)	0 (0.0)	4 (100.0)	2 (100.0)	2 (100.0)	8 (88.9)
95% CI	(0.0-97.5)	(39.8-100.0)	(15.8-100.0)	(15.8-100.0)	(51.8-99.7)

Abbreviations: CI, confidence interval; CR, complete response; MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed or refractory; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response. Note: Because AL amyloidosis incidence is low, the current lisaftoclax dose of 1,000 mg was determined at the dose-escalation stage.

Table 3. Progression-free survival (PFS) in R/R MM

	Lisaftoclax dose (mg) combined with Pd					
	400 (n = 3)	600 (n = 4)	800 (n = 14)	1,000 (n = 9)	1,200 (n = 6)	Total (N = 36)
No. of patients with an event, n (%)	0 (0.0)	4 (100.0)	11 (78.6)	4 (44.4)	4 (66.7)	23 (63.9)
No. of patients censored, n (%)	3 (100.0)	0 (0.0)	3 (21.4)	5 (55.6)	2 (33.3)	13 (36.1)
PFS, mo.						
25th percentile (95% CI)	NE (NE-NE)	3.7 (2.2-7.7)	3.7 (1.4-7.4)	2.8 (1.2-15.2)	2.6 (2.5-10.2)	3.7 (2.2-6.7)
Median (95% CI)	NE (NE-NE)	6.5 (2.2-17.4)	7.4 (3.0-12.9)	11.1 (1.2-15.2)	7.0 (2.5-NE)	9.7 (4.7-12.9)
75th percentile (95% CI)	NE (NE-NE)	12.5 (2.2-17.4)	12.9 (7.4-13.7)	15.2 (11.1-15.2)	NE (2.6-NE)	13.7 (10.2-NE)

*Median follow-up: 9.2 months. Abbreviations: CI, confidence interval; mo., months; NE, not estimable; no., number.

Summary

- In heavily pretreated R/R MM, lisaftoclax combined with Pd achieved an ORR of 63.9% and extended duration of-responses, even in disease refractory to anti-CD38 monoclonal antibodies.
- For R/R AL amyloidosis, lisaftoclax could accelerate the time to hematologic responses, particularly to ≥VGPR.
- Lisaftoclax plus Pd or DRd demonstrated a manageable safety profile at doses up to 1,200 mg in R/R MM and AL amyloidosis, potentially promoting longer treatment duration, regardless of t(11;14) translocation status.
- Enrollment is ongoing to confirm the safety and efficacy of lisaftoclax in combination with Pd and to explore an optimal dosage for R/R MM.

References

1. Van de Donk NWCJ, Pawlyn C, Yong KL. Multiple myeloma. *Lancet* 2021;397:410–427.
2. Staron A, et al. Marked progress in AL amyloidosis survival: a 40-year longitudinal natural history study. *Blood Cancer J* 2021;11:139.
3. Palladini G, Milani P. Diagnosis and treatment of AL amyloidosis. *Drugs* 2023;83:203-216.

Acknowledgments

- The authors thank the co-investigators of the clinical trial and the patients, families, and caregivers who are participating. This study was sponsored by Ascentage Pharma Group Corp Ltd. (Hong Kong).
- Ashutosh K. Pathak, MD, PhD, MBA, FRCP (Edin.), Stephen W. Gutkin, Ndiya Drew, PhD, and Paul O. Fletcher, PhD, with Ascentage Pharma Group Inc., provided editorial support.