

TO THE EDITOR:

Phase 1/2 study of ixazomib with cyclophosphamide and dexamethasone in newly diagnosed AL amyloidosis

Cara A. Rosenbaum,¹ Umut Özbek,² Larysa Sanchez,² Jonathan Lagdameo,² Alex Abrahams,² Hani Hassoun,^{1,3} Oscar Lahoud,^{1,3} Ruben Niesvizky,^{1,*} Heather J. Landau,^{1,3} and Keren Osman^{2,*}

¹Weill Cornell Medicine, New York, NY; ²Icahn School of Medicine at Mt. Sinai and the Mount Sinai Hospital, New York, NY; and ³Memorial Sloan-Kettering Cancer Center, New York, NY

Immunoglobulin light chain (AL) amyloidosis is a rare clonal plasma cell disorder producing misfolded immunoglobulin light chains that deposit as fibrils in tissues and organs, leading to multiorgan dysfunction.^{1,2} Historically, high-dose melphalan and autologous hematopoietic cell transplantation resulted in the best long-term outcomes for patients with AL amyloidosis, but many are ineligible for intensive therapy owing to their advanced organ disease and poor performance status. Bortezomib, a first-in-class proteasome inhibitor, emerged as standard induction therapy based on promising results in the relapsed setting and rapid and deep responses to bortezomib combined with cyclophosphamide or melphalan and corticosteroids.³⁻⁷

Ixazomib is an oral proteasome inhibitor with a favorable toxicity profile and known activity against amyloidogenic plasma cells.⁸ The current trial was designed to investigate the combination of ixazomib (Ixa), cyclophosphamide (Cy), and dexamethasone (D) before the recent US Food and Drug Administration approval of daratumumab with bortezomib, cyclophosphamide, and dexamethasone in 2021.⁹ This study indicates that IxaCyD is a safe and effective all-oral induction regimen for treatment-naïve patients with AL amyloidosis.

This multicenter phase 1/2 trial (NCT03236792) had the primary objectives of establishing a recommended phase 2 dose (RP2D) and determining the best hematologic response to 6 cycles of IxaCyD in patients with newly diagnosed AL amyloidosis. Secondary endpoints included event-free survival (EFS), overall survival (OS), and organ response rates. Eligible patients had untreated, biopsy-proven AL amyloidosis with a difference in the involved and uninvolved free light chains ≥ 50 mg/L, ≥ 1 organ (renal, cardiac, gastrointestinal, and/or nervous system/soft tissue) involved, and Eastern Cooperative Oncology Group performance status ≤ 2 . Patients were excluded for New York Heart Association class III/IV heart failure, cardiac stage IIIb, hemodialysis-dependent renal failure, and/or painful grade ≥ 2 peripheral neuropathy. Patients gave written informed consent as approved by Institutional Review Boards.

In phase 1, patients received escalating doses of Ixa and Cy, with D 20 mg orally, on days 1, 8, and 15 every 28 days. A standard 3 + 3 dose-escalation design was used, with dose-limiting toxicities assessed according to NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) v4.03. The highest tolerated dose was expanded and designated the RP2D. Phase 2 enrolled patients at the RP2D. Hematologic response and organ response, when evaluable, were assessed according to standard criteria.^{10,11} The dose levels (DLs) were: DL-1 (Ixa, 3 mg/Cy, 300 mg/D, 20 mg), DL1 (Ixa, 3 mg/Cy, 400 mg/D, 20 mg), DL2 (Ixa, 4 mg/Cy, 400 mg/D, 20 mg), and DL3 (Ixa, 4 mg/Cy, 500 mg/D, 20 mg). Treatment was discontinued for unsatisfactory response, toxicity, hematologic or organ progression, or completing 6 cycles of IxaCyD. EFS (hematologic progression, next treatment, or death) and OS were estimated by the Kaplan-Meier method. Differences between groups were compared using the log-rank test. The duration of follow-up was calculated by the reverse Kaplan-Meier estimate of OS. All analyses were performed using R statistical package v4.0.3 (R Core Team 2020).

Submitted 11 April 2022; accepted 28 June 2022; prepublished online on *Blood Advances* First Edition 20 July 2022; final version published online 23 September 2022. DOI 10.1182/bloodadvances.2022007826.

*R.N. and K.O. contributed equally to this study.

Contact the corresponding author for data sharing: keren.osman@mountsinai.org.

© 2022 by The American Society of Hematology. Licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0), permitting only noncommercial, nonderivative use with attribution. All other rights reserved.

Table 1. Baseline patient characteristics

Characteristic	Phase 1/2 Population (n = 22)	RP2D Population (n = 14)
Age (y), median (range)	65 (45-80)	66.5 (60-80)
Sex		
Male	14 (64)	9 (64)
Race		
White	16 (73)	10 (71)
ECOG performance status		
0	7 (32)	5 (36)
1	12 (54)	6 (43)
2	3 (14)	3 (21)
Median time from diagnosis, d	21	17
Monoclonal light chain and IgH isotype		
λ	19 (86)	12 (86)
λ light chain only	8 (36)	6 (43)
IgG λ	5 (23)	4 (29)
IgA λ	3 (14)	1 (7)
IgM λ	2 (9)	0 (0)
IgD λ	1 (4.5)	1 (7)
κ	3 (14)	2 (14)
κ light chain only	2 (9)	1 (7)
IgG κ	1 (4.5)	1 (7)
dFLC (mg/L), median (range)	27.8 (5.7-114.8)	25.5 (5.7-114.8)
Organ involvement at screening, median (range)	2 (1-3)	2 (1-2)
Multiorgan involvement (≥2 organs)	17 (77)	9 (64)
Involved organ*		
Cardiac	18 (82)	10 (71)
Renal	8 (36)	4 (29)
GI (nonhepatic)	4 (18)	4 (29)
GI (hepatic)	1 (5)	0 (0)
Mayo 2004/EU cardiac stage^{12,13}		
I	6 (27)	5 (36)
II	9 (41)	5 (36)
IIIa	6 (27)	4 (29)
Missing data	1 (6)	0 (0)
Evaluable for cardiac response†	15 (68)	9 (64)
NYHA class		
I	12 (55)	9 (64)
II	9 (41)	5 (36)
Missing data	1 (5)	0 (0)
NT-proBNP (pg/mL), median (range)	1521 (56-7621)	1625 (56-7621)
Renal stage¹¹		
I	12 (55)	7 (50)
II	9 (41)	7 (50)
III	1 (5)	0 (0)
Evaluable for renal response‡	12 (55)	6 (43)

Table 1. (continued)

Characteristic	Phase 1/2 Population (n = 22)	RP2D Population (n = 14)
Median baseline eGFR	17	9
>50 mL/min per 1.73 m ²	13 (76)	6 (67)
≤50 mL/min per 1.73 m ²	4 (24)	3 (33)
24-h urine protein (mg/24h), median (range)	1209 (0-15884)	433 (0-15884)

dFLC, difference in the involved and uninvolved free light chains; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; NYHA, New York Heart Association. Data are n (%) unless noted.

*n (%) includes all patients with ≥1 organ involved.

†Based on the Palladini 2012 response criteria (ie, baseline NT-proBNP ≥650 ng/L required for cardiac response determination).¹⁰

‡Includes patients who met the International Society of Amyloidosis (ISA) 2005 criteria for renal involvement (ie, proteinuria >0.5 g per 24 hours, predominantly albumin).¹⁴ Renal response based on the Palladini 2014 renal response criteria.¹¹

Between June 2017 and October 2020, 24 patients were enrolled. The first patient in phase 1 experienced cardiopulmonary arrest at DL1, requiring 3 patients to be enrolled at DL-1. In the absence of toxicity, dose-escalation continued with DL1, DL2, and DL3 accruing 3, 3, and 6 patients, respectively. DL3 was determined as the RP2D. Eight additional patients were enrolled at the RP2D in phase 2. Two patients with cardiac stage IIIb disease at screening were excluded from the analysis. Patient characteristics are reported in Table 1, including the total intention to treat (ITT) (n = 22) and RP2D (n = 14) populations.

Figure 1A shows the best hematologic response. By ITT, the overall hematologic response rate was 55% (12 of 22), including 9 very good partial responses (VGPRs) and 3 partial responses (PRs). No complete responses (CRs) were observed during study treatment, although 1 patient in VGPR converted to CR off therapy at the 3-month follow-up. Among patients treated at RP2D, the hematologic response rate was 64% (9 of 14), including 8 VGPRs and 1 PR. The median number of IxαCyD cycles was 2.5, and the median times to the first and best hematologic responses were 35 and 45 days, respectively.

Among the 14 patients treated at the RP2D, 6 completed all planned cycles of IxαCyD and achieved sustained VGPR. Two additional patients achieved VGPR but were taken off the study by treating physicians for lack of CR after 1 and 4 cycles, respectively. Four patients who had <PR at the RP2D discontinued IxαCyD to start alternative therapy. One patient treated at the RP2D who achieved PR as the best response had progressive disease on treatment. One patient treated at the RP2D experienced cardiac complications and was taken off the study after cycle 1; hematologic response is not available, although the patient is included in both efficacy and safety analyses. Of the 8 patients in the RP2D cohort who did not complete 6 planned cycles, the median duration of time on treatment was 3 months, and the overall hematologic response rate was 38% (2 VGPRs and 1 PR).

Among the 12 and 15 patients from the phase 1/2 ITT population evaluable for renal and cardiac responses, respectively, 5 (42%) renal and 4 (27%) cardiac responses were achieved at 6 months. Of the 6 and 9 RP2D patients evaluable for renal and cardiac

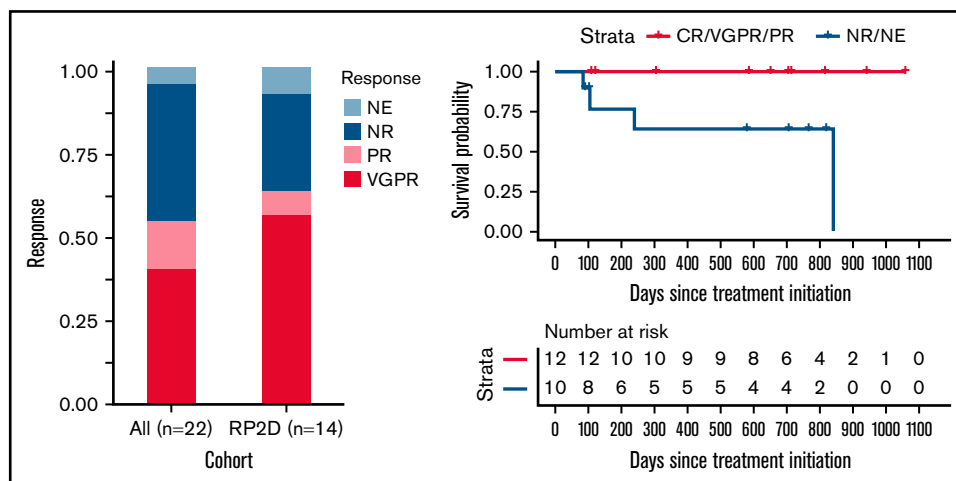


Figure 1. Best response and survival data. (A) Best hematologic response. Among the ITT population (n = 22), 9 patients had VGPR, and 3 had PR. Of the 14 patients treated at RP2D (DL3), the overall hematologic response rate (CR/VGPR/PR) was 64%, with 8 achieving VGPR and 1 PR. (B) OS by best hematologic response. All patients achieving hematologic response (\geq PR) are alive, and there was a statically significant difference between the groups ($P = .011$). DL3, dose level 3; ITT, intention to treat; NE, not evaluable; NR, no response; PR, partial response; VGPR, very good partial response.

responses, respectively, 3 (50%) renal and 2 (22%) cardiac responses were achieved at 6 months. Among all evaluable patients, 9 had cardiac progression, 67% (6 of 9) of whom had never achieved a hematologic response. Renal progression occurred in a single patient.

With a median follow up of 23 months, EFS and OS for all patients were 53.4% (95% confidence interval [CI], 23.3%, 1) and 56.5% (95% CI, 24.8%, 1), respectively. All patients who achieved a hematologic response (\geq PR) remained alive and had significantly improved OS compared with nonresponders ($P = .011$) (Figure 1B).

IxaCyD was well tolerated, and no patient discontinued treatment because of treatment-related adverse events (AEs). In the ITT population, 9 of 22 patients (41%) experienced grade 3/4 AEs, including hyponatremia (n = 2), lower extremity edema (n = 1), weakness (n = 1), anemia (n = 2), and lymphocytopenia (n = 2). Nine grade 3/4 serious AEs occurred, including hyponatremia (n = 2) and cellulitis, sinusitis, weakness, syncope, dehydration, diarrhea, and heart failure exacerbation (n = 1 each). One patient died on treatment (DL1) because of cardiopulmonary arrest not related to treatment. Fourteen patients did not complete all planned cycles of treatment owing to hematologic progression (n = 1), organ progression/complications because of organ disease (n = 3), lack of optimal response/change of therapy (n = 9), and lost to follow-up (n = 1).

In summary, this phase 1/2 trial demonstrates the safety and efficacy of the oral IxaCyD regimen in newly diagnosed AL amyloidosis. An overall hematologic response rate of 55% was observed in the phase 1/2 ITT population. At the RP2D (Ixa, 4 mg/Cy, 500 mg/D, 20 mg), 64% of patients achieved a hematologic response, including 57% who rapidly achieved VGPR in a median of 1.5 cycles. This hematologic response led to renal responses in 50% of evaluable RP2D patients at 6 months, but cardiac responses in only 22% of evaluable RP2D patients at 6 months.

All patients who achieved a hematologic response are alive. Patients with suboptimal responses to IxaCyD received second-line therapy with daratumumab-based regimens (data not shown). The FDA

approval of daratumumab in the upfront setting has changed the treatment paradigm for AL amyloidosis. Given the rate of hematologic VGPR and renal responses observed with this all-oral combination, the potential for use as a backbone with the addition of a CD38 monoclonal antibody in a frailer patient population should be investigated.

Acknowledgments: Suzanne Lentzsch was instrumental in helping with the concept for this trial and the preliminary design. Editorial support was provided by Hannah Rice.

This study was supported in part by a grant from Takeda Pharmaceutical and by Memorial Sloan-Kettering Cancer Center Core Grant (P30 CA008748).

Contribution: K.O., H.L., and U.Ö. designed the study; K.O., H.J.L., L.S., H.H., O.L., R.N., and C.A.R. evaluated patients and collected data; K.O., H.J.L., L.S., and C.A.R. analyzed data and wrote the manuscript; J.L. and A.A. collected data; U.Ö. carried out statistical and bioinformatics analyses; and all the authors reviewed, commented, edited, and approved the final version of this manuscript.

Conflict-of-interest disclosure: H.J.L. has participated on the advisory board for Takeda, Sanofi, Janssen, Karyopharm, Pfizer, Celgene/BMS, and Caelum Biosciences and has received research support from Takeda. C.A.R. has participated on the advisory board for Takeda, Janssen, GlaxoSmithKline, Oncopptides, and Akcea and has received research support from Janssen, Karyopharm, GlaxoSmithKline, and Amgen. K.O. has served on the advisory board for Kite Therapeutics and has received research support from Takeda. O.L. served on advisory boards for MorphoSys Inc. U.Ö. is currently employed by Eli Lilly and Company. The remaining authors declare no competing financial interests.

ORCID profile: H.L., 0000-0002-3152-1189.

Correspondence: Keren Osman, Ichan School of Medicine at Mt. Sinai and the Mount Sinai Hospital, One Gustave L. Levy Place, Box 1410, New York, NY 10029; e-mail: keren.osman@mountsinai.org.

References

1. Merlini G, Seldin DC, Gertz MA. Amyloidosis: pathogenesis and new therapeutic options. *J Clin Oncol*. 2011;29(14):1924-1933.
2. Wisniewski B, Wechalekar A. Confirming the diagnosis of amyloidosis. *Acta Haematol*. 2020;143(4):312-321.
3. Reece DE, Sanchorawala V, Hegenbart U, et al; VELCADE CAN2007 Study Group. Weekly and twice-weekly bortezomib in patients with systemic AL amyloidosis: results of a phase 1 dose-escalation study. *Blood*. 2009;114(8):1489-1497.
4. Reece DE, Hegenbart U, Sanchorawala V, et al. Long-term follow-up from a phase 1/2 study of single-agent bortezomib in relapsed systemic AL amyloidosis. *Blood*. 2014;124(16):2498-2506.
5. Venner CP, Lane T, Foard D, et al. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. *Blood*. 2012;119(19):4387-4390.
6. Mikhael JR, Schuster SR, Jimenez-Zepeda VH, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. *Blood*. 2012;119(19):4391-4394.
7. Palladini G, Milani P, Foli A, et al. Melphalan and dexamethasone with or without bortezomib in newly diagnosed AL amyloidosis: a matched case-control study on 174 patients. *Leukemia*. 2014;28(12):2311-2316.
8. Sanchorawala V, Palladini G, Kukreti V, et al. A phase 1/2 study of the oral proteasome inhibitor ixazomib in relapsed or refractory AL amyloidosis [published correction appears in *Blood*. 2020;135:1071]. *Blood*. 2017;130(5):597-605.
9. Palladini G, Kastiris E, Maurer MS, et al. Daratumumab plus CyBorD for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA. *Blood*. 2020;136(1):71-80.
10. Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. *J Clin Oncol*. 2012;30(36):4541-4549.
11. Palladini G, Hegenbart U, Milani P, et al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. *Blood*. 2014;124(15):2325-2332.
12. Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. *J Clin Oncol*. 2004;22(18):3751-3757.
13. Wechalekar AD, Schonland SO, Kastiris E, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. *Blood*. 2013;121(17):3420-3427.
14. Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. *Am J Hematol*. 2005;79(4):319-328.