blood advances



TO THE EDITOR:

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

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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-naive 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 $\geq$50 mg/L, $\geq$1 organ (renal, cardiac, gastrointestinal, and/or nervous system/soft tissue) involved, and Eastern Cooperative Oncology Group performance status $\leq$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 $\geq$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).

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**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 stage**[11] | | |
| I | 12 (55) | 7 (50) |
| II | 9 (41) | 7 (50) |
| III | 1 (5) | 0 (0) |
| Evaluable for renal response‡ | 12 (55) | 6 (43) |
| 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 IxaCyD 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 IxaCyD 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 IxaCyD 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

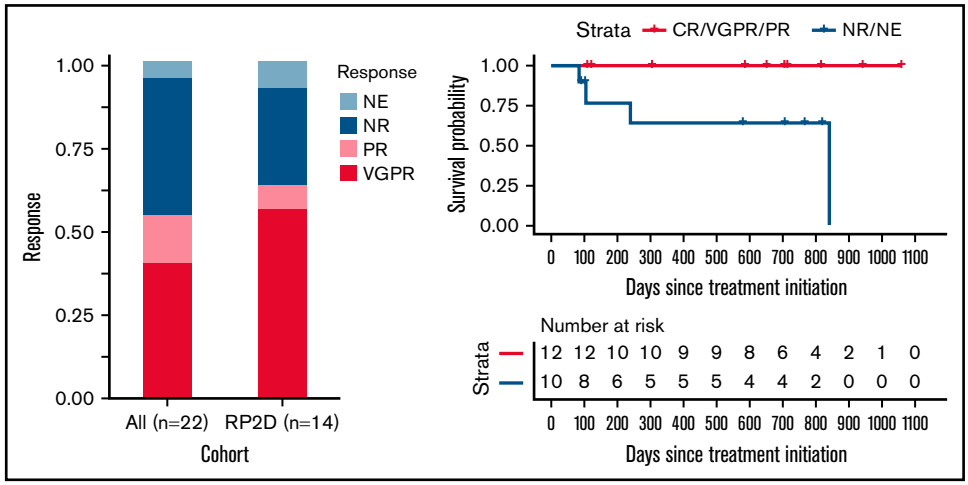


**Figure 1. Best response and survival data.** (A) Best hematologic response. Among the ITT population (n = 22), 9 patients had VGPR, and 3 had PR. Of the 14 patients treated at RP2D (DL3), the overall hematologic response rate (CR/VGPR/PR) was 64%, with 8 achieving VGPR and 1 PR. (B) OS by best hematologic response. All patients achieving hematologic response (≥PR) are alive, and there was a statically significant difference between the groups ($P$ = .011). DL3, dose level 3; IIT, 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 (≥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.

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