

## CLINICAL TRIALS AND OBSERVATIONS

## A phase 2 trial of pomalidomide and dexamethasone rescue treatment in patients with AL amyloidosis

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## Key Points

- PDex can be a rescue regimen for patients with AL amyloidosis previously exposed to alkylators, proteasome inhibitors, and lenalidomide.
- Responses to PDex are frequent, rapid, and improve survival.

Immunomodulatory drugs are active agents in light-chain (AL) amyloidosis. However, previous studies could not show a survival advantage for patients with AL amyloidosis responding to salvage treatment with pomalidomide. In this phase 2 trial, we assessed the safety and efficacy of pomalidomide and dexamethasone (PDex) in patients with AL amyloidosis who were previously exposed to bortezomib, alkylators, and other immunomodulatory drugs. Twenty-eight patients were enrolled. Three patients received pomalidomide 2 mg/d with no dose-limiting toxicity. The remaining patients received 4 mg/d. Pomalidomide was administered continuously and dexamethasone was given once per week at a dose of 20 or 40 mg. Fifteen patients experienced grade 3 to 4 adverse events; the most common were fluid retention and infection. Hematologic response was observed in 68% of patients (very good partial response or complete response in 29%), as well as improved survival. Median time to response was 1 month. PDex is a rapidly active regimen and improves survival in responding, heavily pretreated patients with AL amyloidosis. This trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) as #NCT01510613. (*Blood*. 2017;129(15):2120-2123)

## Introduction

A rapid and profound reduction of amyloid-forming circulating free light chains (FLCs) is the key to improving the outcome of patients with light-chain (AL) amyloidosis.<sup>1</sup> Thalidomide and lenalidomide are effective, particularly in relapsed/refractory patients.<sup>2-5</sup> The immunomodulatory agent pomalidomide is active in patients with relapsed/refractory multiple myeloma, including those who failed to respond to prior treatment with lenalidomide and bortezomib.<sup>6</sup> Most patients with AL amyloidosis are currently treated upfront with combinations of alkylating agents and bortezomib.<sup>1</sup> Although these regimens are highly effective, there is a need for active rescue options in patients who fail to respond.<sup>7,8</sup> Two independent trials showed efficacy of pomalidomide in AL amyloidosis; hematologic response occurred in 48% to 50% of patients.<sup>9,10</sup> However, these studies could not show an impact of response on survival. We designed the present phase 2 trial to assess the efficacy, safety, and impact on survival of the combination of pomalidomide and dexamethasone (PDex) in patients with AL amyloidosis treated upfront with bortezomib and an alkylating agent.

patients who could not be treated with alkylators and/or bortezomib due to contraindications were also eligible); difference between amyloidogenic (involved) and uninvolved FLCs (dFLC) > 50 mg/L; and adequate renal (estimated glomerular filtration rate  $\geq$  30 mL/min) and cardiac (New York Heart Association Class < IV) function. The primary end point was hematologic response at 3 months by intent-to-treat according to current criteria.<sup>11</sup> Secondary end points were rate and severity of adverse events, quality of hematologic response, organ response according to validated criteria,<sup>11,12</sup> and survival. A 3 + 3 dose-escalation design was used (detailed in the supplemental Material, available on the *Blood* Web site). Pomalidomide was administered continuously in 28-day cycles, and dexamethasone was given once per week at a dose of 40 mg (20 mg in cases of severe fluid retention and/or repetitive ventricular arrhythmia) until disease progression or unacceptable toxicity. Prophylactic cotrimoxazole, omeprazole, and aspirin were administered. Criteria for disease progression and statistical methods are reported in the supplemental Material. The study was approved by the Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo Review Board, and all patients gave written informed consent.

## Study design

Key eligibility criteria included the following: prior treatment with alkylating agents (melphalan or cyclophosphamide) and bortezomib (relapsed/refractory

## Results and discussion

Between June 2012 and November 2013, 28 patients were enrolled. Their clinical characteristics are reported in Table 1. Median time from

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**Table 1. Patient characteristics**

Characteristic	No. (%) or median (range)
Male sex	16 (57)
Age, y	64 (41-80)
<b>Organ involvement</b>	
Heart	22 (79)
Kidney	11 (39)
Soft tissues	5 (18)
Peripheral nervous system	4 (14)
Liver	1 (4)
<b>Performance status (ECOG)</b>	
0	2 (7)
1	11 (39)
2	14 (50)
3	1 (4)
<b>Cardiac stage*</b>	
I	6 (21)
II	14 (50)
IIIa	6 (21)
IIIb	2 (8)
NYHA class III	11 (39)
<b>Renal stage†</b>	
I	20 (71)
II	8 (29)
III	0 (0)
Bone marrow plasma cell infiltrate, %	12 (4-34)
dFLC, mg/L	153 (75-2972)
dFLC > 180 mg/L	12 (43)
Previous treatment lines	2 (1-7)
<b>Previous treatment</b>	
Bortezomib	27 (96)
Melphalan‡	21 (75)
Cyclophosphamide	19 (68)
Lenalidomide	7 (25)
Thalidomide	4 (14)
Ixazomib	4 (14)
Bendamustine	3 (11)

All of the patients were refractory to the last line of treatment administered before PDex.

ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal proatriuretic peptide type B; NYHA, New York Heart Association.

\*Cardiac stage is defined by NT-proBNP (cutoff, 332 ng/L) and cardiac troponin I (cutoff, 0.1 ng/mL); stage I, II, and III patients have none, 1, or 2 markers greater than the cutoff, respectively. In stage IIIb patients, NT-proBNP is > 8500 ng/L.

†Renal stage is defined by eGFR (cutoff, 50 mL/min per 1.73 m<sup>2</sup>) and proteinuria (cutoff, 5 g/24 h); stage I patients have both eGFR greater than and proteinuria less than the cutoff, stage II have either eGFR less than or proteinuria greater than the cutoff, and stage III patients have both eGFR less than and proteinuria greater than the cutoff.

‡Six patients (21%) underwent autologous stem cell transplantation.

diagnosis was 16 months. In the dose-escalation phase, 3 patients received pomalidomide 2 mg/d, and the following 3 patients received 4 mg/d. No dose-limiting toxicity was observed. The maximum tolerated dose was 4 mg/d, and was administered to the subsequent 22 patients. A total of 227 cycles were delivered. The median number of cycles per patient was 6 (range, 1-30). Dexamethasone was started at 20 mg/wk in 12 patients (43%).

### Toxicity

Thirty-one grade 3 to 4 adverse events were recorded (supplemental Table 1) in 15 patients (54%); the most common were fluid retention (25%), infection (25%), atrial fibrillation (7%), and deep vein thrombosis (7%). The most common grade 1 to 2 adverse events were fever (15 patients; 54%), neutropenia (12 patients; 43%), skin rash

(4 patients; 14%), and worsening peripheral neuropathy (2 patients; 7%). The pomalidomide dose was reduced in 9 patients (32%), and dexamethasone was reduced in 10 patients (36%). Dose reductions were not associated with clinical, biochemical, and echographic markers of heart involvement. Treatment was discontinued as a result of disease progression in 14 patients (50%), adverse events in 8 patients (29%), patient choice in 3 patients (11%), and achievement of durable complete response in 1 patient (4%). Two patients are receiving treatment after 28 and 30 cycles, having achieved a very good partial response (VGPR) and partial response (PR), respectively.

### Response

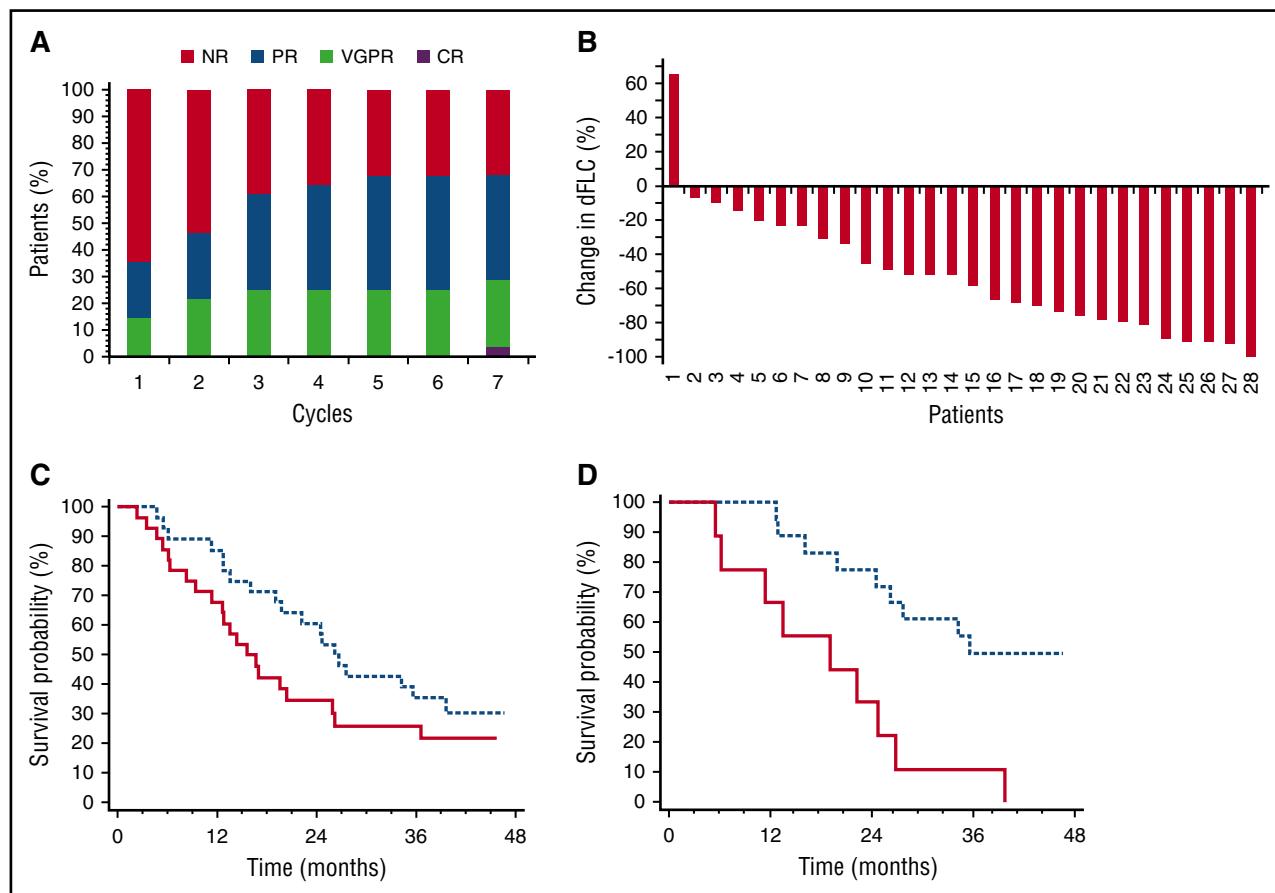
After cycle 3, 17 patients (61%) achieved hematologic responses; PR was achieved in 10 patients (36%) and VGPR in 7 patients (25%). Hematologic response rate and quality improved during treatment (Figure 1A). The best responses were achieved by cycle 7 in 19 subjects (68%; 95% confidence interval, 49% to 83%), and included complete response in 1 patient (4%), VGPR in 7 patients (25%), and PR in 11 patients (39%). With a single exception, treatment resulted in a dFLC decrease in patients who did not meet response criteria (Figure 1B). Hematologic responses were seen in 6 of 7 patients (86%) who received prior lenalidomide, and in 3 of 4 subjects (75%) who were exposed to ixazomib. Treatment was associated with a median 116% increase of N-terminal proatriuretic peptide type B, and this prevented the assessment of cardiac response. A renal response was observed in 2 of 12 evaluable patients (17%), one who achieved VGPR and one who achieved PR.

### Survival

The median follow-up of living patients is 44 months. Overall, 19 patients (68%) died and 23 (82%) experienced hematologic progression according to the protocol criteria. There were no deaths in the first 100 days. Median overall and progression-free survival were 26 and 16 months, respectively (Figure 1C). Hematologic response significantly improved overall survival (Figure 1D; median 36 vs 19 months in a 6-month landmark analysis;  $P = .001$ ). Patients with high concentrations of cardiac troponin I (best cutoff > 0.04 ng/mL) and N-terminal proatriuretic peptide type B (best cutoff > 1300 ng/L) at the time of treatment initiation had shorter overall survival (median 20 months vs not reached with both biomarkers;  $P = .016$  and  $P < .001$ , respectively). Hematologic progression predicted overall survival (median of 25 months in patients who progressed, no deaths observed in nonprogressing patients;  $P = .013$ ).

### Conclusion

The PDex combination was highly effective, with a 68% response rate, in patients who had been extensively exposed to currently available chemotherapy agents, including alkylators, first- and second-generation proteasome inhibitors, and other immunomodulatory drugs. The hematologic response rate observed in the present study (68%) compares favorably with that reported by the Mayo Clinic (48%)<sup>9</sup> and Boston University (50%)<sup>10</sup> groups, although with an overlap in confidence intervals due to small numbers. This might be a result of the greater proportion of patients initially exposed to full doses of pomalidomide and dexamethasone. However, dose reductions were frequent in our study, and lower pomalidomide doses could be better tolerated in fragile patients with AL amyloidosis. Moreover, the proportion of patients in the Mayo Clinic, Boston University, and present studies who had undergone previous transplantation (48%, 59%, and 21%, respectively) and patients exposed to proteasome



**Figure 1. Patient responses and outcomes.** (A) Hematologic response by treatment cycle. (B) Percent change in the dFLC at best response. Median dFLC change during therapy was  $-55\%$  (interquartile range,  $-31\%$  to  $-78\%$ ). (C) Patient survival. Median progression-free survival (solid line) was 16 months and median overall survival (dotted line) was 26 months. (D) Overall survival according to hematologic response. Nineteen patients were responders (dotted line) and 9 were nonresponders (solid line). Median survival was 19 vs 36 months ( $P = .001$ ). This is a 6-month landmark analysis. CR, complete response; NR, no response.

inhibitors (42%, 78%, and 100%, respectively) also differed, and these differences may have affected responses to pomalidomide. Importantly, responses were rapid and were achieved after a single cycle in 53% of responders. Unlike in previous studies, the longer follow-up of the present trial, and possibly differences in prior treatment exposure and in the availability of newer rescue agents, allowed demonstration of a survival benefit for responders even in heavily pretreated patients, indicating the need to actively pursue hematologic responses in this setting.

Toxicity was manageable and the maximum tolerated dose was 4 mg/d, in agreement with the Boston University data.<sup>10</sup> The rate of thromboembolic events (2 of 28 patients; 7%), although comparable with Mayo Clinic data,<sup>9</sup> was higher than that reported in multiple myeloma (1% to 3%)<sup>13</sup> and in the Boston University study (among 27 patients, no thromboembolic events were reported).<sup>10</sup>

In our study, the severity of cardiac dysfunction remained a powerful prognostic determinant, indicating the need to improve on the problem of organ damage that persists after chemotherapy.<sup>14</sup> Importantly, hematologic progression, defined with criteria (reported in the supplemental Material) compatible with the current revised response categories, predicts overall survival in AL amyloidosis. This observation and the availability of newer effective drugs such as daratumumab<sup>15</sup> support early treatment of hematologic relapses in patients who have been exposed to several lines of therapy. The validation of hematologic progression criteria in larger studies is warranted.

The present study shows that PDex is an effective treatment in relapsed/refractory AL amyloidosis. The high rate of rapid responses

suggests that pomalidomide can have a role in combination with other agents in upfront treatment.

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## Authorship

Contribution: G.P. designed the study, evaluated patients, collected data, analyzed data, wrote the manuscript, and gave final approval; G.M. designed the study, evaluated patients, critically reviewed the manuscript, and gave final approval; P.M. evaluated patients, collected data, analyzed data, critically reviewed the manuscript, and gave final approval; M.B., F.R., A.F., and S.P. evaluated patients, collected data, critically reviewed the manuscript, and gave final approval.

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