First-in-Human Phase I/II Study of NEOD001 in Patients With Light Chain Amyloidosis and Persistent Organ Dysfunction

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ABSTRACT

Purpose

Light chain (AL) amyloidosis is caused by the accumulation of misfolded proteins, which induces the dysfunction of vital organs. NEOD001 is a monoclonal antibody targeting these misfolded proteins. We report interim data from a phase I/II dose-escalation/expansion study of NEOD001 in patients with AL amyloidosis and persistent organ dysfunction (NCT01707264).

Patients and Methods

Patients who had completed at least one previous anti-plasma cell-directed therapy, had partial hematologic response or better, and had persistent organ dysfunction received NEOD001 intravenously every 28 days. Dose levels of 0.5, 1, 2, 4, 8, 16, and 24 mg/kg were evaluated (3 + 3 study design). Primary objectives were to determine the maximum tolerated dose and the recommended dose for future studies and to evaluate safety/tolerability. Secondary and exploratory objectives included pharmacokinetics, immunogenicity, and organ responses on the basis of published consensus criteria.

Results

Twenty-seven patients were enrolled in seven cohorts (dose-escalation component). No drug-related serious adverse events (AEs), discontinuations because of drug-related AEs, dose-limiting toxicities, or antidrug antibodies were reported. The most frequent AEs were fatigue, upper respiratory tract infection, cough, and dyspnea. Recommended dosing was 24 mg/kg. Pharmacokinetics support intravenous dosing every 28 days. Of 14 cardiac-evaluable patients, eight (57%) met the criteria for cardiac response and six (43%) had stable disease. Of 15 renal-evaluable patients, nine (60%) met the criteria for renal response and six (40%) had stable disease.

Conclusion

Monthly infusions of NEOD001 were safe and well tolerated. Recommended future dosing was 24 mg/kg. Organ response rates compared favorably with those reported previously for chemotherapy. A phase II expansion is ongoing. A global phase III study (NCT02312206) has been initiated. Antibody therapy targeting misfolded proteins is a potential new therapy for the management of AL amyloidosis.

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INTRODUCTION

Systemic amyloidoses are a group of diseases characterized by the accumulation of abnormal, misfolded protein (amyloid) in tissues and organs.¹ In immunoglobulin light chain (AL) amyloidosis, the most common form of systemic amyloidosis,¹ the amyloidogenic protein is a misfolded light chain or light chain fragment produced by clonal plasma cells.^{1,2} Amyloid aggregates can affect multiple organs, including

the heart (approximately 70% of patients), kidneys (70%), liver (17%), soft tissue (17%), nervous system (15%), and gastrointestinal tract (10%).³⁻⁵ Amyloid accumulation progressively affects organ structure and function,² but diagnosis is often delayed because subtle symptoms at onset mimic those of common conditions.² For patients with cardiac amyloidosis, the extent of cardiac involvement is a major outcome determinant; most deaths are attributed to cardiac involvement, and survival is poor with advanced involvement.^{1,2,6}

No therapies for AL amyloidosis have received regulatory approval, and optimal treatment regimens remain undefined.^{7,8} Options include high-dose chemotherapy with autologous stem cell transplant, alkylating agents, steroids, proteasome inhibitors, and immunomodulatory drugs.^{2,4,7,8} These treatments reduce the production of immunoglobulin light chain precursor proteins by targeting the plasma cells that synthesize them, but they do not directly address the soluble aggregates or the deposited amyloid.^{2,4,7,8} Although plasma cell-directed therapies may induce hematologic responses that result in organ improvement, the improvement achieved is highly variable and often incomplete.^{2,3,8} A critical unmet need in patients with AL amyloidosis is a therapy that directly targets soluble aggregates and amyloid protein deposits to improve organ function.

NEOD001, a humanized form of murine monoclonal antibody 2A4, binds to an epitope unique to the misfolded light chain protein. The cryptic light chain epitope is thought to be exposed during misfolding and aggregation but is not available in light chain's native conformation or in fully formed immunoglobulin.⁹ Accordingly, 2A4 was shown to immunoreact with both soluble and insoluble light chain aggregates derived from samples from patients with AL while sparing normally folded light chain. In vivo, 2A4 promoted AL amyloid clearance in a mouse amyloidoma model by engaging phagocytes.⁹ Therefore, NEOD001 is hypothesized to directly target and clear light chain amyloid deposited in affected organs of patients with AL, with the potential to restore organ function. We report interim results from the dose-escalation component of an ongoing, first-in-human, phase I/II dose-escalation/expansion study of NEOD001 in patients with AL amyloidosis and persistent organ dysfunction.

PATIENTS AND METHODS

Study Design

This is an ongoing, phase I/II, open-label study of NEOD001 in patients with AL amyloidosis and persistent organ dysfunction (ClinicalTrials.gov NCT01707264; EudraCT 2012-002683-27). There are two components: (1) dose escalation to assess the safety/tolerability and to determine the maximum tolerated dose (MTD) and recommended dose of NEOD001 for future studies and (2) expansion to assess the safety, preliminary efficacy, and pharmacokinetics (PK) of NEOD001 administered at the recommended future dose. In the absence of confirmed organ dysfunction, unacceptable treatment-related toxicity, or withdrawal of consent, patients may receive NEOD001 for ≤ 1 year at the investigator's discretion and for more than 1 year with the additional agreement of the sponsor. The study was conducted according to International Committee on Harmonization Good Clinical Practice guidelines. All patients provided informed consent.

Patients

Eligible patients were aged ≥ 18 years and had diagnoses of AL amyloidosis and ongoing organ involvement, Eastern Cooperative Oncology Group performance status of 0 to 2, at least one previous plasma cell-directed therapy, and at least partial hematologic response to previous therapy. Patients in the dose-escalation component had to meet predefined definitions of systemic organ involvement (online only Appendix). Exclusion criteria included N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration of more than 5,000 pg/mL, life expectancy of less than 3 months, and symptomatic multiple myeloma. Patients who required plasma cell-directed therapy were excluded.

Treatments and Assessments

The dose-escalation component followed a standard 3 + 3 design, with cohorts of three to six patients enrolled at each dose level. NEOD001 was administered intravenously once every 28 days. The starting dose was 0.5 mg/kg and, once deemed safe and well tolerated, this was increased to 1, 2, 4, 8, 16, and 24 mg/kg. Dose escalation was to proceed to 30 mg/kg (or an absolute maximum of 2,500 mg, whichever was lower). However, a dose of 24 mg/kg was selected for cohort 7 (the highest dose level studied). On the basis of body weights (cohorts 1 to 6), a significant number of patients would have reached the absolute maximum dose of 2,500 mg with doses greater than 24 mg/kg. The selection of 24 mg/kg as the cohort 7 dose allowed a greater number of patients to be dosed on an mg/kg basis rather than at the absolute maximum dose of 2,500 mg. Patients enrolled at the original 1 and 24 mg/kg dose levels were expanded from 3 to 6 patients to assess safety and PK (six patients per dose level). Each patient participated in only one dose-level cohort, but the dosage could be increased to 24 mg/kg at the discretion of the investigator once 24 mg/kg was selected as the recommended dose for future study (if the patient had received NEOD001 at a lower dose for at least three infusions without experiencing dose-limiting toxicities [DLTs]).

The primary objectives of the dose-escalation component were to determine the MTD and the recommended dose for future studies and to evaluate the safety and tolerability of intravenous NEOD001 administered every 28 days. Secondary objectives included evaluation of the PK and immunogenicity of NEOD001. Assessment of hematologic and organ responses and correlation of changes in serum biomarkers of organ function with NEOD001 exposure levels were exploratory end points. MTD was defined as the highest dose level at which no more than one of six patients experienced a DLT during the first month of therapy (Appendix). The recommended future dose was based on toxicities and on biologic, pharmacologic, and clinical activities noted, up to the maximum dose level tested (if MTD was not reached at the maximum dose level).

Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. Cardiac response was assessed using previously described criteria¹⁰ (Appendix). Renal response was assessed using the Palladini et al⁵ criteria (Appendix).

Blood samples for PK analysis were obtained for months 1 and 3 before the start of an infusion (baseline) and immediately after infusion, at 0.5, 1, 2, and 4 hours and at 1, 8, and 15 days after infusion.

Statistical Analyses

Demographic and baseline characteristics were summarized using descriptive statistics. Safety was assessed through summaries of AEs, changes in laboratory test values, and vital signs. Serum antidrug antibody titers were correlated with PK values and clinical toxicity. Individual and mean serum NEOD001 concentrations at each sampling time were summarized by dose level. PK parameters were calculated from serum NEOD001 concentrations using noncompartmental techniques, and exploratory assessments for dose proportionality were performed. Hematologic and organ (heart, kidney, liver) response assessment data were listed for all patients by assigned dose, and rates were calculated by assigned dose. Hematologic response was monitored according to the standard of care. For a specific organ, the corresponding response rate was assessed only in patients who had had involvement of that organ at screening.

RESULTS

Patient Characteristics

Twenty-seven patients enrolled at seven clinical sites were included in the dose-escalation component of this study, comprising seven dose cohorts: 0.5 mg/kg ($n = 3$), 1 mg/kg ($n = 6$), 2 mg/kg ($n = 3$), 4 mg/kg ($n = 3$), 8 mg/kg ($n = 3$), 16 mg/kg ($n = 3$), and 24 mg/kg

(n = 6). Patient characteristics are summarized in Table 1; 18 patients (66.7%) were male, and the median time since initial diagnosis was 2.5 years. All patients had received previous systemic therapy; 10 of 27 (37%) received two to three and five of 27 (18.5%) received at least three previous plasma cell-directed therapies. Twenty-one (77.8%) had previously received bortezomib. The best hematologic response across all previous systemic therapies was complete response (CR), very good partial response (VGPR), and partial response (PR) in 14 patients (51.9%), seven patients (25.9%), and three patients (11.1%), respectively. The best hematologic response to the most recent systemic treatment was CR, VGPR, and PR in 12 patients (44.4%), five patients (18.5%), and four patients (14.8%), respectively.

All patients were escalated to 24 mg/kg as of December 2, 2014. As of the February 28, 2015, data cutoff date, 11 of the 27 enrolled patients had discontinued the dose-escalation phase of the study. Discontinuations were either protocol required (organ progression in four patients [one each in the 0.5, 2, 4, and 8 mg/kg dose cohorts] and hematologic progression in one patient [0.5 mg/kg cohort]) or nonprotocol required/voluntary (patient decision in five cases [two in the 1 mg/kg cohort and one each in the 2, 16, and 24 mg/kg cohorts] and one patient death [24 mg/kg cohort]). Travel was a contributing factor in most voluntary discontinuations. Three patients who withdrew from the study did not complete the 30-day follow-up period (one was lost to follow-up [1 mg/kg cohort], one died [24 mg/kg cohort], and one returned to local oncologist to receive chemotherapy [24 mg/kg cohort]); all remaining patients who withdrew completed the 30-day follow-up period.

Dosing

The median number of 28-day treatment periods entered for the overall population in the dose-escalation phase of the study was 12 (range, four to 24). The total number of infusions administered was 327.

Safety

NEOD001 was well tolerated. All patients reported at least one treatment-emergent AE (TEAE); the most commonly reported of any severity were fatigue (10 patients; 37.0%), upper respiratory tract infection (seven patients; 25.9%), cough (five patients; 18.5%), dyspnea (five patients; 18.5%), anemia (four patients; 14.8%), increased blood creatinine (four patients; 14.8%), headache (four patients; 14.8%), and peripheral edema (four patients; 14.8%), as shown in Table 2. AEs did not seem to be infusion related (did not appear shortly after infusion and were not correlated with treatment duration).

In an analysis of TEAEs occurring in $\geq 5\%$ of patients (all NEOD001 doses), the occurrence of grade 3 and 4 events was limited to two cases of grade 3 hyponatremia and one case each of diverticulitis and pneumonia, which were not related to NEOD001. Twelve patients (44.4%) reported TEAEs related to the study drug. No TEAEs of grade 3 or higher and no serious TEAEs were related to the study drug. One patient in the 24 mg/kg dose group died. This patient had an NT-proBNP value of 3,958 pg/mL before the first NEOD001 infusion and received 10 months of NEOD001 before death. Serial NT-proBNP values were 4,053 (infusion 2),

Table 1. Patient and Disease Characteristics in the Dose-Escalation Phase

Characteristic	Value
Total patients, No.	27
Median age (range), years	60 (38-80)
Male, No. (%)	18 (66.7)
Race, No. (%)	
White	23 (85.2)
Black or African American	1 (3.7)
Asian	1 (3.7)
Unknown	2 (7.4)
Time since initial diagnosis, median (range), years	2.46 (0.7-12.9)
Physician-determined organs involved at baseline (by physical evaluation), No. (%)	
1	9 (33.3)
2	9 (33.3)
≥ 3	9 (33.3)
Physician-determined organ involvement at baseline (by physical evaluation), No. (%)	
Renal	19 (70.4)
Cardiac	18 (66.7)
Hepatic	3 (11.1)
Peripheral nervous system	3 (11.1)
Gastrointestinal	6 (22.2)
Autonomic nervous system	1 (3.7)
Soft tissue/lymphatic	4 (14.8)
Other involvement	2 (7.4)
Baseline NT-proBNP, median (lower Q, upper Q), pg/mL	
All patients (n = 27)	651 (160, 1,129)
Evaluable patients (n = 14)	1,102.5 (866.75, 2,250.75)
Responders (n = 8)	1,768.5 (1,089, 2,456)
Baseline proteinuria, median (lower Q, upper Q), mg/24 hours	
All patients (n = 23)*	3,134 (163, 6,112.5)
Evaluable patients (n = 14)	5,189.5 (3,354.5, 6,749)
Responders (n = 9)	4,834 (3,002, 6,049)
Previous plasma cell-directed treatments, No. (%)	
Chemotherapy, alkylating agent	23 (85.2)
Proteasome inhibitor	21 (77.8)
IMiD	4 (14.8)
Steroid	21 (77.8)
Autologous transplantation	8 (29.6)
Other	4 (14.8)
No. previous plasma cell-directed treatments, median (range)	2 (1-7)
Best hematologic response across all previous plasma cell-directed treatments, No. (%)	
Complete response	14 (51.9)
VGPR	7 (25.9)
Partial response	3 (11.1)
No response	0
Progressive disease	0
Unknown	3 (11.1)
Not assessed	0
Best hematologic response to most recent plasma cell-directed treatments, No. (%)	
Complete response	12 (44.4)
VGPR	5 (18.5)
Partial response	4 (14.8)
No response	2 (7.4)
Progressive disease	0
Unknown	3 (11.1)
Not assessed	1 (3.7)

Abbreviations: IMiD, immunomodulatory drug; NT-proBNP, N-terminal pro-brain natriuretic peptide; Q, quartile; VGPR, very good partial response.

*Baseline was not assessable in four patients because baseline levels were below the level of assay quantitation (n = 3) or because of an inability to collect the urine sample (n = 1).

Table 2. TEAEs Occurring in $\geq 5\%$ of Patients (all doses of NEOD001)

AEs (Preferred Term) ($\geq 5\%$ Total Incidence)	All Patients (N = 27)	
	Total AEs	Grade 3 or Higher AEs
Fatigue	10 (37.0)	0
Upper respiratory tract infection	7 (25.9)	0
Cough	5 (18.5)	0
Dyspnea	5 (18.5)	0
Headache	4 (14.8)	0
Anemia	4 (14.8)	0
Peripheral edema	4 (14.8)	0
Increased blood creatinine	4 (14.8)	0
Diarrhea	3 (11.1)	0
Edema	3 (11.1)	0
Nausea	3 (11.1)	0
Hyponatremia	3 (11.1)	2 (7.4)
Infusion site reaction	2 (7.4)	0
Dyspnea exertional	2 (7.4)	0
Oropharyngeal pain	2 (7.4)	0
Productive cough	2 (7.4)	0
Upper airway cough syndrome	2 (7.4)	0
Wheezing	2 (7.4)	0
Diverticulitis	2 (7.4)	1 (3.7)
Pneumonia	2 (7.4)	1 (3.7)
Arthralgia	2 (7.4)	0
Back pain	2 (7.4)	0
Dizziness	2 (7.4)	0
Thrombocytopenia	2 (7.4)	0
Depression	2 (7.4)	0
Insomnia	2 (7.4)	0

NOTE. Ten patients (37.0%) reported a TEAE of grade 3 or higher, which included colitis, gastroenteritis, syncope, hypertriglyceridemia, fall, hypertension, noncardiac chest pain, diverticulitis, pneumonia, disseminated herpes zoster, and large diffuse B-cell lymphoma (grade 3 AE in one patient [3.7%] each), hyponatremia (grade 3 AE in two patients [7.4%]), intracardiac thrombus and spleen rupture (grade 4 AE in one patient [3.7%] each), and death (grade 5 in one patient [3.7%]).

Abbreviation: AE, adverse event; TEAE, treatment-emergent adverse event.

2,688 (infusion 3), 2,687 (infusion 4), 2,514 (infusion 5), 2,958 (infusion 6), 2,969 (infusion 7), 3,514 (infusion 8), 1,660 (infusion 9), and 2,769 (infusion 10). The investigators at all study sites agreed that this death was not related to the study drug. No patients required dose reductions because of a TEAE, but five patients (18.5%) required interruption of study dosing because of TEAEs unrelated to the study drug. No DLTs were observed among the NEOD001 doses examined (up to 24 mg/kg), and no antidrug antibodies or hypersensitivity reactions were observed.

Cardiac and Renal Responses

Cardiac and renal responses were exploratory end points (assessed on day 1 before each infusion). Change from baseline in cardiac-evaluable patients (baseline NT-proBNP ≥ 650 pg/mL; $n = 14$) is presented in Figure 1 as a waterfall plot of best response analysis. Among cardiac-evaluable patients, eight (57%) met the criteria for cardiac response and six (43%) had stable disease. In cardiac responders, the median (lower quartile [Q], upper Q) NT-proBNP decreased from 1,768.5 (1,089, 2,456) pg/mL at baseline to 1,054 (349, 1,416) pg/mL at the best response assessment. The mean decrease from baseline was -890 pg/mL, which represented a 48% reduction and was statistically significant ($P < .008$) using the Wilcoxon matched-pairs signed rank test. The NT-proBNP decline

Fig 1. Best response analysis of percentage change in NT-proBNP from baseline in cardiac-evaluable patients (baseline NT-proBNP ≥ 650 pg/mL). Responders are identified with gold bars (cardiac response was defined as $> 30\%$ and 300 pg/mL decrease in NT-proBNP, and cardiac progression was defined as $> 30\%$ and 300 pg/mL increase in NT-proBNP in patients without progressive renal dysfunction and with baseline NT-proBNP ≥ 650 pg/mL). Patients with stable disease are identified with blue bars (stable disease was defined as neither response nor progression). NT-proBNP, N-terminal pro-brain natriuretic peptide.

for responders correlated significantly with the increased number of NEOD001 infusions ($r = -0.45$; $P < .0001$). New York Heart Association class improved from II to I in two cardiac responder patients (vs one nonresponder), worsened in one responder, and did not change in the remainder (four vs 15 nonresponders).

Change from baseline in proteinuria for renal-evaluable patients (baseline proteinuria ≥ 0.5 g/24 hours; $n = 15$) is presented in Figure 2 as a best response analysis. Note that baseline was not assessable in four patients because baseline levels were below the level of assay quantitation ($n = 3$) or because of an inability to collect the urine sample ($n = 1$). Among renal-evaluable patients, nine (60%) met the criteria for renal response and six (40%) had stable disease. In the nine responders, the median (lower Q, upper Q) proteinuria value decreased from 4,834 (3,002, 6,049) mg/24 hours at baseline to 1,647 (544, 2,783) mg/24 hours at the best response assessment. The mean decrease from baseline was $-2,647$ mg/24 hours, which represented a 62% decrease and was statistically significant ($P < .004$) using the Wilcoxon matched-pairs signed rank test. Albumin was unchanged or marginally reduced (3.4% to 4.5%) in most (seven of nine) renal responders (final measurement) compared with the baseline value. In two responders, serum albumin increased but remained below 4.0 g/dL (final assessment). Pretreatment estimated glomerular filtration rate was in the normal range in seven patients. In the two patients with a reduced screening estimated glomerular filtration rate, final measurements were increased by 7.7% in one patient and reduced by 12.8% in the other, compared with baseline.

The median (range) number of previous therapies was one (one to three) among cardiac responders and three (one to four) among renal responders. Two patients had both cardiac and renal responses. Of the remaining responders, six and seven patients had renal or cardiac responses, respectively (12 patients had

Fig 2. Best response analysis of percentage change in proteinuria from baseline in renal-evaluable patients (baseline proteinuria ≥ 0.5 g/24 h). Responders are identified with gold bars (renal response was defined as a $\geq 30\%$ decrease in proteinuria or a decrease in proteinuria to < 0.5 g/24 h in the absence of renal progression, defined as $> 25\%$ worsening in estimated glomerular filtration rate, for patients with baseline proteinuria ≥ 0.5 g/24 h). Patients with stable disease are identified with blue bars (stable disease was defined as neither response nor progression).

neither cardiac nor renal response). Durations of time at first NEOD001 treatment since best previous hematologic response and last hematologic response for cardiac and renal responders and nonresponders are presented in Table 3. Among responders, the best hematologic response for cardiac amyloidosis was CR 3, VGPR 5, and PR 0. For renal amyloidosis the best hematologic response was CR 4, VGPR 2, and PR 3.

Pharmacokinetics

Mean serum NEOD001 concentration-time profiles (months 1 and 3) are shown in Figure 3. No nonlinear accumulation of NEOD001 was observed over the dosing range. The terminal elimination half-life of NEOD001 in serum was approximately 13 to 16 days. The PK of NEOD001 is consistent with dosing by intravenous infusion every 28 days across the dose range.

DISCUSSION

In this first-in-human, dose-escalation, phase I/II study, NEOD001 was safe and well tolerated. No DLTs were observed at doses up to 24 mg/kg every 28 days. No drug-related serious AEs or hypersensitivity reactions were reported, and no antidrug antibodies were detected. The most frequent AEs were fatigue, upper respiratory tract infection, cough, and dyspnea, with the vast majority mild or moderate (grade 1/2). Monthly intravenous infusion of 24 mg/kg was identified as the recommended future dose. The ongoing expansion component of this study will enroll approximately 40 additional patients with AL amyloidosis and persistent organ dysfunction. The PK profile of NEOD001 was consistent with the expected behavior of a monoclonal antibody,¹¹ with a mean terminal elimination half-life of approximately 13 to 16 days and no unexpected drug accumulation, which supports dosing once every 28 days.

AL amyloidosis remains an incurable disease associated with significant morbidity and mortality.^{6,12} Although there are no approved therapies for this disease, current options include antimyeloma-based treatments that target the plasma cells producing light chains.^{7,8} However, these therapies do not address the soluble and/or accumulated light chains deposited in organs or the poor outcomes that result from this accumulation.^{6,7}

Because prognosis is determined largely by cardiac involvement and a significant number of patients die as a result of cardiac dysfunction without experiencing sufficient benefit from hematologic treatment,^{12,13} responses must translate into improved cardiac function. In AL amyloidosis patients, validated cardiac response criteria have enhanced patient care. NT-proBNP has been validated as a cardiac biomarker, and decreasing NT-proBNP levels predict lower mortality rates.¹⁰ NT-proBNP can also be used for early assessment of cardiac response, allowing treatment modification.⁵ In this study, monthly infusions of NEOD001 resulted in clinically meaningful reductions in NT-proBNP. Among cardiac-evaluable patients, eight (57%) had a response and six (43%) had stable disease according to consensus criteria.¹⁰ These results compare favorably with historical data sets. In a previous systematic study of 377 treatment-naïve patients with AL amyloidosis

Table 3. Time at First Administration of NEOD001 Since Best and Last Previous Hematologic Response

Response Time	Cardiac		Renal	
	Responders (n = 8)	Nonresponders (n = 6)	Responders (n = 6)*	Nonresponders (n = 5)†
Time at first treatment of NEOD001 since best previous hematologic response, months				
Median	8.53	6.18	3.9	4.2
Mean	24.17	10.39	26.6	25.5
Range	2.2-127.9	1.2-23.8	1.2-127.9	1.5-89.8
Time at first treatment of NEOD001 since last previous hematologic response, months				
Median	7.43	3.47	3.9	4.2
Mean	9.9	8.69	10.9	14
Range	2.2-20.63	1.2-27.2	1.17-40.3	1.5-32.4

*Data for previous plasma cell-directed therapy not reported in three patients.

†Data for previous plasma cell-directed therapy not reported in one patient.

Fig 3. Mean serum NEOD001 concentration-time profiles at infusions 1 and 3.

and baseline NT-proBNP ≥ 650 pg/mL, 100 (26.5%) had cardiac response, 108 (28.7%) had stable disease, and 169 (44.8%) had progressive disease^{10,14} after plasma cell-targeted treatment.

On the basis of consensus renal criteria,⁵ nine renal-evaluable patients (60%) had a response and six (40%) had stable disease. These results compare favorably with organ response rates reported after intervention with standard of care in plasma cell-directed treatments.^{3,6,15-21} A study of treatment-naïve patients with AL amyloidosis with renal involvement evaluated 3 months after plasma cell-directed therapy demonstrated renal responses for 47 patients (23.3%), stable disease for 89 patients (44.1%), and progressive disease for 66 patients (32.7%). Evaluations at 6 months included renal response for 115 patients (24.4%), stable disease for 171 patients (36.2%), and progression for 186 patients (39.4%).

It should be noted that patients had at least partial hematologic response to previous plasma cell-directed therapy during which organ responses may be expected. A delayed organ response to previous chemotherapy could have confounded the interpretation of organ responses to NEOD001. It seems unlikely that this can adequately explain the data described herein. Patients enrolled were required to demonstrate organ dysfunction despite previous plasma cell-directed therapies, and no decline was observed in NT-proBNP before the administration of NEOD001 in those patients with multiple baseline assessments (Appendix Table A1, online only). There did not seem to be any discernible relationship between time since or degree of previous hematologic response (no differences in NEOD001 responders vs non-responders) that could explain the NEOD001 responses. Finally, the observed rates of change in this study compared favorably with those reported in published data, although these intent-to-treat analyses included patients who died early as a result of amyloidosis-related factors or who did not respond to chemotherapy. The design of this study effectively removed such patients from the denominator, which may be expected to affect observed organ response rates.²² On the basis of the positive results reported herein, a global phase III trial (NCT02312206) has been initiated.

Patients with amyloidosis treated with an anti-serum amyloid P component experienced an acute-phase response.²³ Serum amyloid P plays a role in regulating inflammation and setting the threshold for immune cell activation.^{24,25} NEOD001 specifically targets the toxic amyloidogenic light chain. It should be noted that none of the patients treated with NEOD001 experienced an acute-phase response.

NEOD001 is safe and well tolerated in patients with AL amyloidosis and persistent organ dysfunction and has a PK profile supporting dosing once every 28 days. The phase II expansion component is ongoing at the recommended dose of 24 mg/kg every 28 days. Exploratory analyses suggest promising organ response rates using published consensus criteria. Antibody therapy targeting misfolded light chains may represent a new therapeutic platform for the management of AL amyloidosis.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

First-in-Human Phase I/II Study of NEOD001 in Patients With Light Chain Amyloidosis and Persistent Organ Dysfunction

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Appendix

Previously determined definitions of systemic organ involvement for patients in the dose-escalation component: Cardiac involvement (mean left ventricular wall thickness of > 12 mm in the absence of other cardiac causes or elevated N-terminal pro-brain natriuretic peptide [NT-proBNP; > 332 ng/L] in the absence of renal failure or atrial fibrillation) or renal involvement (proteinuria [predominantly albumin] > 0.5 g/day in a 24-hour urine collection)

Definition of DLT: Any of the following regardless of relationship to NEOD001, unless clearly related to the underlying disease, and regardless of occurrence in the 28 days following NEOD001 administration: grade ≥ 3 nonhematologic toxicity that has not responded to supportive therapy; grade ≥ 3 neutropenia or thrombocytopenia; other grade ≥ 4 hematologic toxicity; and any clinically significant occurrence thought to pose undue safety risk for patients

Definition of cardiac response: Cardiac response was defined as a $> 30\%$ and > 300 pg/mL NT-proBNP decrease, and cardiac progression was defined as an increase of the same magnitude. Of note, patients with progressively worsening renal function (defined as worsening of creatinine or creatinine clearance $> 25\%$ over baseline) could not be scored for NT-proBNP progression. Stable cardiac response was defined in patients who were not NT-proBNP responders or progressors. In addition, a decrease in the New York Heart Association (NYHA) class of two or greater was considered a response for patients with baseline NYHA class 3 or 4.

Definition of renal response: Renal response was defined as a $\geq 30\%$ decrease (or < 0.5 g/day) of 24-hour urine protein, where urine protein must be greater than 0.5 g/day before treatment and eGFR must not worsen by 25% over baseline

Table A1. NT-proBNP Did Not Decline Before NEOD001 Administration

Multiple Baseline NT-proBNP Measurements Before NEOD001 Treatment	n	NT-proBNP, pg/mL
Mean of all patients before NEOD001 treatment		
Measurement 1	10	1,468
Measurement 2	10	1,611
Difference		+143
Mean of cardiac responders before NEOD001 treatment		
Measurement 1	4	2,249
Measurement 2	4	2,365
Difference		+116
Abbreviation: NT-proBNP, N-terminal pro-brain natriuretic peptide.		