NEOD001 Demonstrates Cardiac, Renal and Neuropathy Responses in Patients with Light Chain Amyloidosis and Persistent Organ Dysfunction: Results from the Dose-Escalation and Expansion Phases of a Phase 1/2 Study

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Background

- AL amyloidosis is caused by an accumulation of misfolded proteins (amyloid) resulting in vital organ (e.g. heart and kidney) dysfunction
- Existing therapies reduce LC production
  - DO NOT address resident amyloid
  - ~75% of patients do not achieve organ response and have persistent organ dysfunction[1-5]
- Safe and well-tolerated therapies are needed to improve organ function
- NEOD001 is an investigational antibody designed to specifically target AL amyloid
- We report data from the dose-escalation phase and expansion cohorts of the phase 1/2 study of NEOD001 in previously treated patients with AL amyloidosis and persistent organ dysfunction (NCT01707264)

AL, amyloid light chain; LC, light chain.

1. Palladini et al, *Blood*, 2015. 2. Palladini et al, *Blood*, 2015. 3. Comenzo et al, *Leukemia*. 2012. 3. Palladini et al, *Haematologica*, 2013. 4. Dispenzieri et al, *Blood*. 2012. 5. Reece et al, *Blood*, 2011.

NEOD001 Is Hypothesised to Neutralise Soluble Amyloid and to Clear Insoluble Amyloid

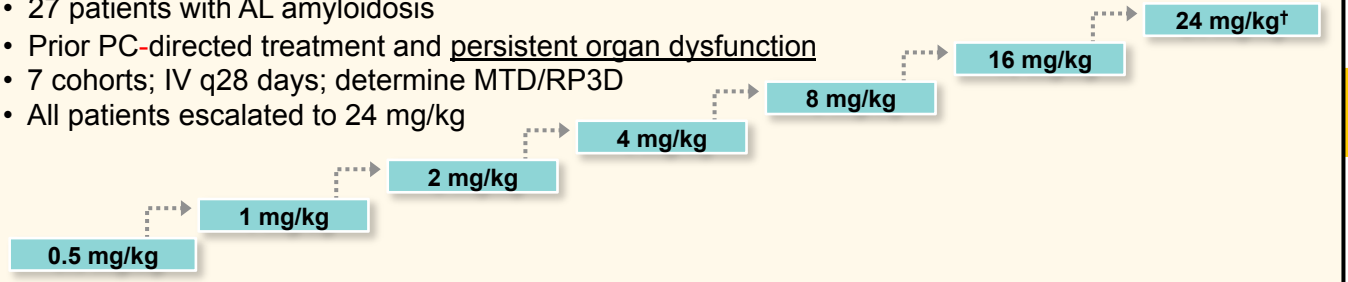
- Plasma cells overproduce LCs that misfold, aggregate and become toxic amyloid
- NEOD001 may neutralise and disaggregate circulating soluble amyloid and clear insoluble amyloid[1]

1. Zago W et al. *Amyloid*. 2016; in press.

NEOD001 Phase 1/2 Trial (N = 69) Design

Dose-escalation phase (3+3)

- 27 patients with AL amyloidosis
- Prior PC-directed treatment and persistent organ dysfunction
- 7 cohorts; IV q28 days; determine MTD/RP3D
- All patients escalated to 24 mg/kg



Expansion Cohorts

Additional 42 previously treated patients with **cardiac**, **renal** and/or **peripheral neuropathy** involvement

†Maximum of 2,500 mg per dose permitted – 24 mg/kg selected based on patient body weight

Primary objectives

- Evaluate the safety and tolerability of NEOD001 (NCT01707264)
- Determine MTD or recommended dose for future clinical study of NEOD001

Secondary objectives

- Evaluate the serum PK of NEOD001
- Assess the immunogenicity of NEOD001
- Evaluate organ response (cardiac, renal, peripheral neuropathy)

IV, intravenous; MTD, maximum tolerated dose; PC, plasma cell; PK, pharmacokinetics; q28d, every 28 days; RP3D, recommended phase 3 dose.

Ongoing NEOD001 Phase 1/2 Study Design: Expansion Cohorts

- Enrolled 42 additional previously treated patients with AL amyloidosis and prospectively defined organ involvement
- 24.0 mg/kg; IV q28 days

Cardiac cohort n = 15	Renal cohort n = 16	Peripheral neuropathy cohort n = 11
• **Key inclusion**: Cardiac involvement as defined by elevated **NT-proBNP of ≥650 pg/ml** in the absence of renal failure	• **Key inclusion**: Renal involvement as defined by **proteinuria >0.5 g/day in a 24-hour urine collection**	• **Key inclusion**: Positive sural nerve biopsy or evidence of typical sensorimotor peripheral neuropathy due to AL amyloidosis
• **Secondary endpoint**: NT-proBNP best response	• **Secondary endpoint:** Proteinuria best response	• **Secondary endpoint**: NIS-LL (baseline to month 10)

Key exclusion
NT-proBNP level **>7,000 pg/ml**

NIS-LL, Neuropathy Impairment Score−Lower Limb; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Patient Characteristics

	All Patients (N = 69)
Median age, years (range)	60 (38-81)
Gender (% male)	42 (61)
Median time since initial diagnosis, years (range)	2.8 (0.4-12.8)
Median previous regimens, n (range)	2 (1-8)
Number (%) prior PCD regimens per patient	
1	25 (36)
2	13 (19)
≥3	31 (45)
No. organ systems involved, n (%)	
1	22 (32)
2	29 (42)
≥3	18 (26)
Median months since last PCD treatment, n (range)	6.5 (0.6-85.8)
Median NT-proBNP (pg/ml) at baseline, n (range)	
Total cardiac evaluable [n = 36]	1,507 (651-5,620)

PCD, plasma cell−directed.

Data current as of 9 May 2016

Safety and Dosing Summary

- NEOD001 was safe and well tolerated
  - No dose-limiting toxicities
  - No discontinuations due to NEOD001
  - No anti-drug antibodies detected
  - No treatment-related SAEs
  - One patient death (not related)
- Treatment duration (q28 days): mean, 13.2 months (range, 3-35)
- Total number of infusions: 913 (N = 69 patients)

SAEs, serious adverse events.

Treatment-Emergent Adverse Events (≥10%) Regardless of Relationship to NEOD001

Most Common TEAEs (preferred terms)	Total Patients (N = 69)	
	Total AEs, N (%)	≥Grade 3, n (%)
Fatigue	23 (33.3)	1 (1.4)
Upper respiratory tract infection	18 (26.1)	0
Nausea	17 (24.6)	0
Diarrhoea	16 (23.2)	0
Oedema	13 (18.8)	0
Anaemia	12 (17.4)	1 (1.4)
Dizziness	12 (17.4)	0
Increased blood creatinine	10 (14.5)	0
Cough	10 (14.5)	0
Constipation	9 (13.0)	0
Headache	9 (13.0)	0
Dyspnoea	8 (11.6)	0
Rash	8 (11.6)	0
Vomiting	8 (11.6)	0
Peripheral oedema	7 (10.1)	0
Pain in extremity	7 (10.1)	0

AEs, adverse events; TEAEs, treatment-emergent adverse events.

Cardiac Functional Biomarker Responses

NEOD001: Cardiac Biomarker Response

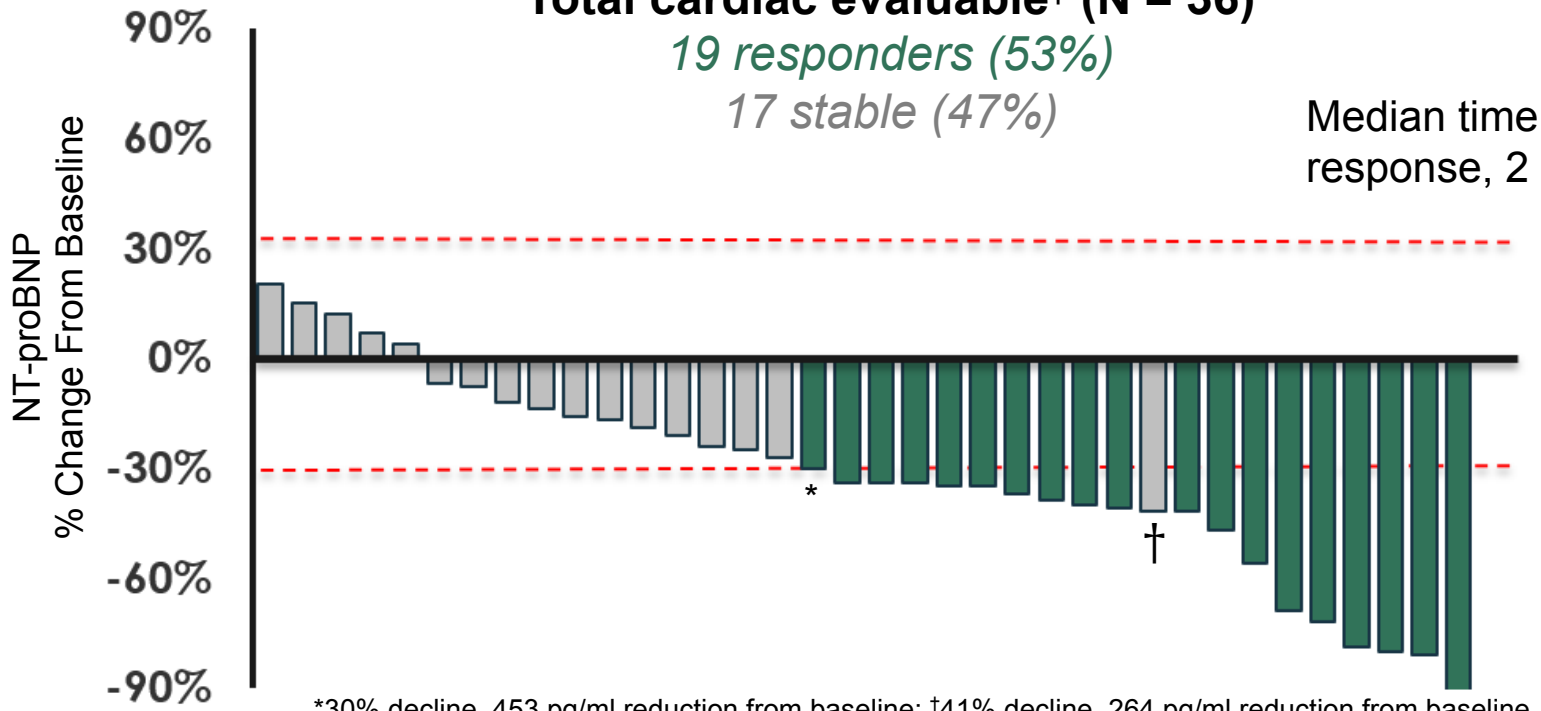
Best Response Analysis

Total cardiac evaluable† (N = 36)

19 responders (53%)

17 stable (47%)

Median time to initial response, 2 months



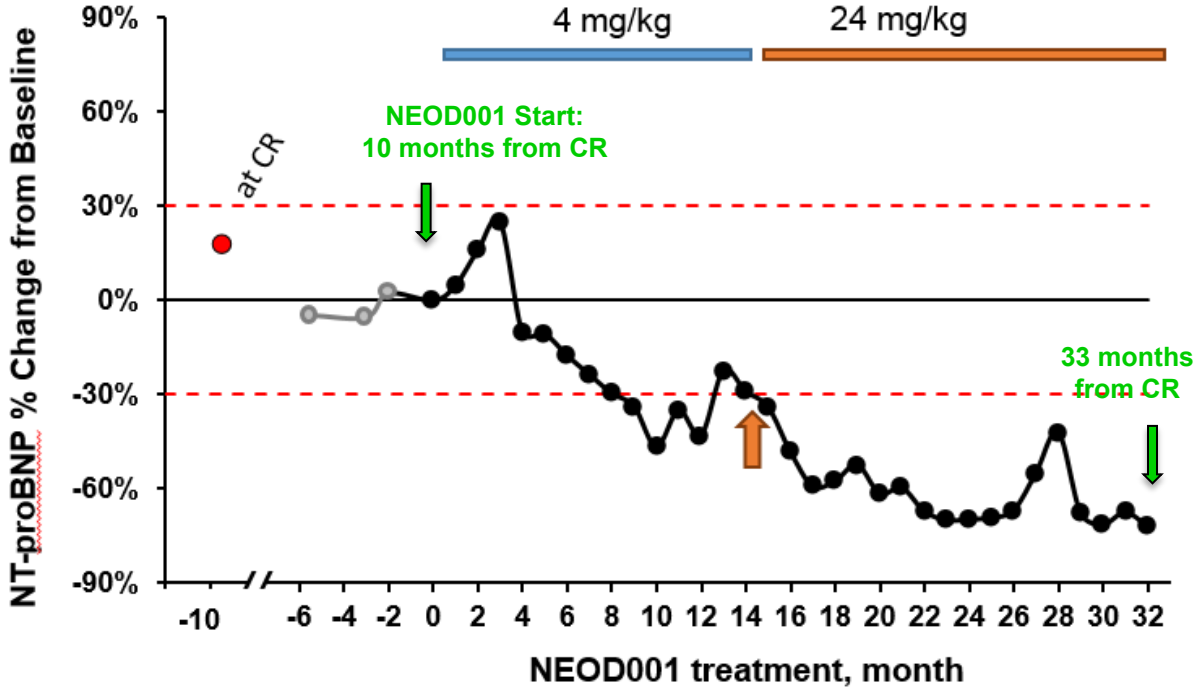
*30% decline, 453 pg/ml reduction from baseline; †41% decline, 264 pg/ml reduction from baseline

†Evaluable patients had baseline NT-proBNP ≥650 pg/ml without progressive renal dysfunction

- **Response:** >30% and >300 pg/ml decrease in NT-proBNP
- **Progression:** >30% and >300 pg/ml increase in NT-proBNP
- **Stable disease:** neither response nor progression

Comenzo R et al, *Leukemia,* 2012. Palladini et al, *J Clin Oncol,* 2012.

NEOD001 Cardiac Responses Continue to Improve for 32 Months



46-Year-Old Man

Previous treatment: CyBorD
Baseline NT-proBNP: 3312 pg/ml

Best NT-proBNP: 996 pg/ml (-70%)

Safety: 1 grade 3 SAE (chest pain), not related; no dose interruptions

Clinical outcome:
progressive functional improvement, edema significantly improved with reduction in diuretic needs

ASCT, autologous stem cell transplantation; CR, complete response; HDM, high-dose melphalan.

Renal Functional Biomarker Responses

NEOD001: Renal Biomarker Response

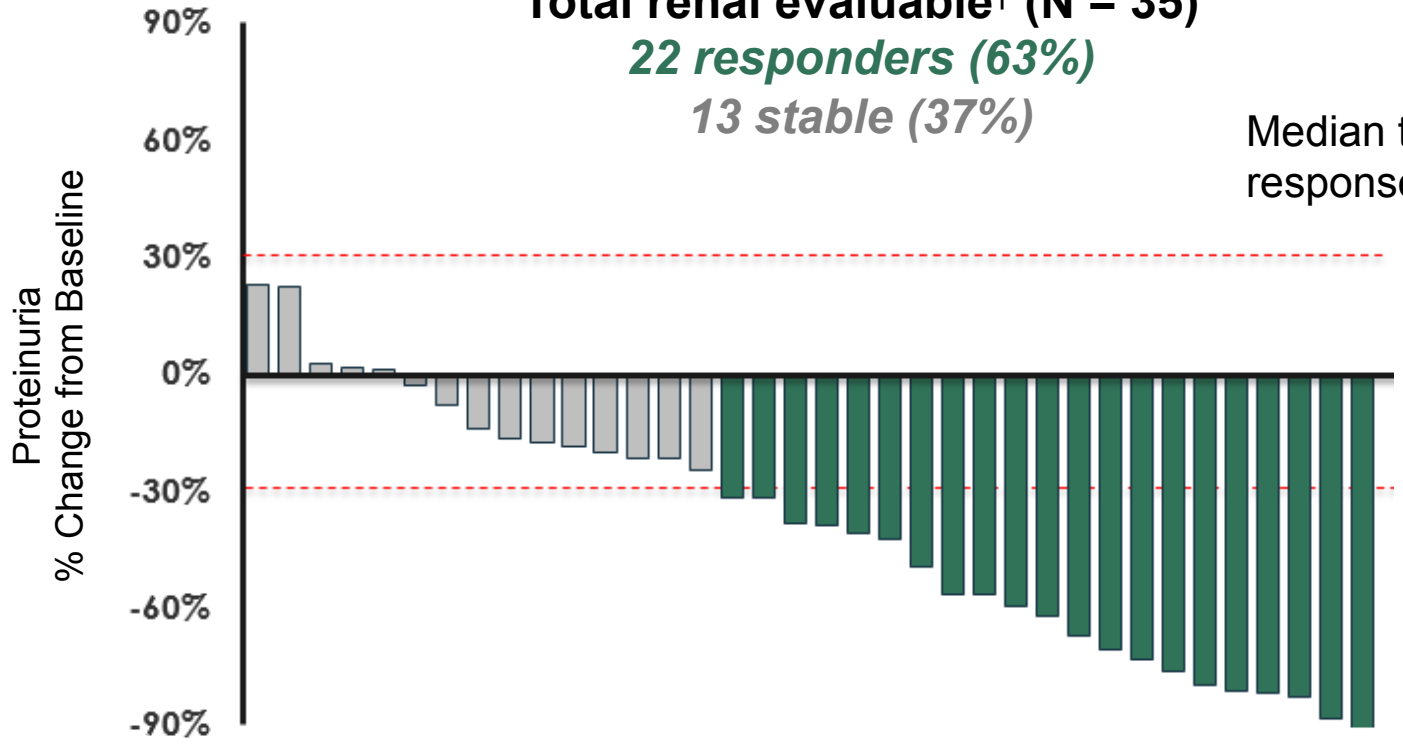
Best Response Analysis

Total renal evaluable† (N = 35)

22 responders (63%)

13 stable (37%)

Median time to initial response, 4 months



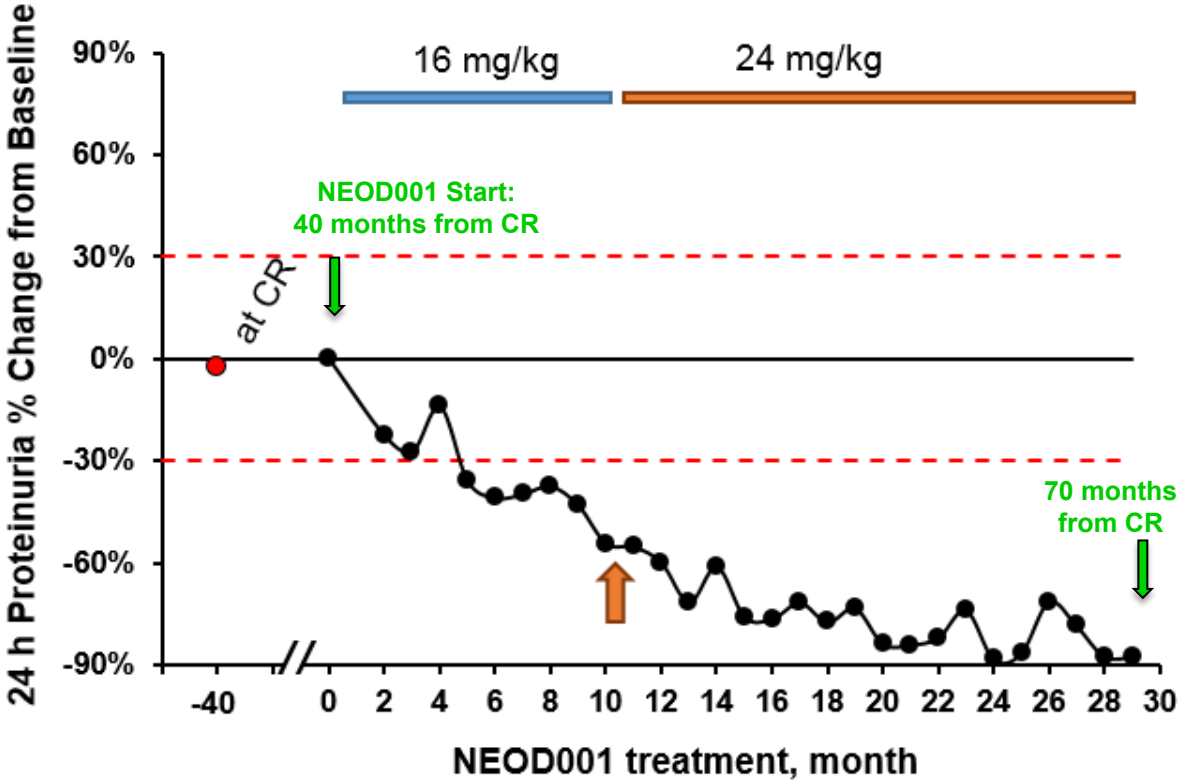
†Evaluable patients had baseline proteinuria ≥0.5 g/24 hours

- **Response:** >30% decrease in proteinuria or a decrease to <0.5 g/24 hours in the absence of renal progression
- **Progression:** >25% worsening in eGFR
- **Stable disease:** neither response nor progression

eGFR, estimated glomerular filtration rate.

Palladini et al, *Blood,* 2014.

NEOD001 Renal Responses Continue to Improve for 29 Months



60-Year-Old Man

Previous treatment: LDex then Bor-LDex then HDM/ ASCT

Baseline proteinuria (24 hours): 5,129 mg/d

Best proteinuria (24 hours): 819 mg/d (-84%)

Safety: No SAEs; no grade ≥3 AEs; no dose interruptions

Clinical outcome: progressive functional improvement, edema completely resolved, patient no longer has fatigue

ASCT, autologous stem cell transplantation; CR, complete response; HDM, high-dose melphalan.

Peripheral Neuropathy Responses

NEOD001 Treatment in Patients with AL Amyloidosis and Peripheral Neuropathy: Improvement at Month 10†

	NEOD001	
	Median	Mean
n	11	11
Baseline NIS-LL*	20.0	28.1
Point difference at month 10†	-7.0	-9.5
% Change	-23%	-35%

- Median time since last plasma cell therapy 18 months
- No patient received bortezomib ≤13 months prior to NEOD001

*Patients in the peripheral neuropathy cohort had significant peripheral neuropathy at baseline.
†After 9 months of treatment.

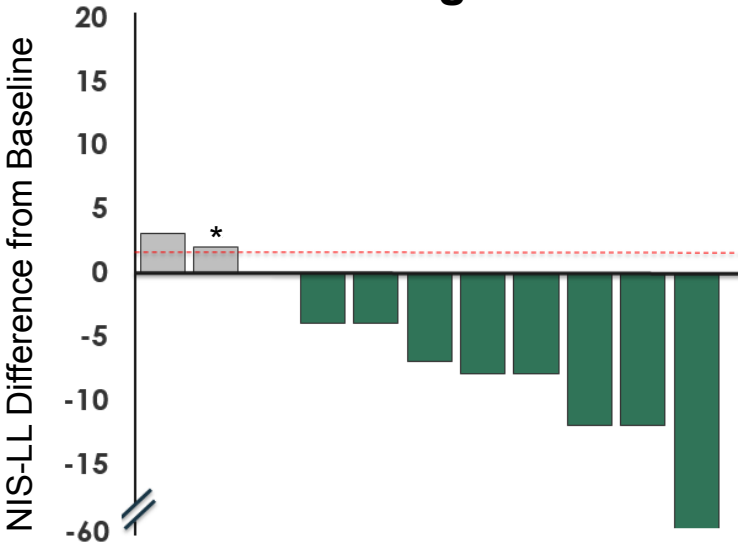
NEOD001: Neuropathy Response at Month 10 (NIS-LL)

Peripheral Neuropathy Expansion Cohort (N = 11)

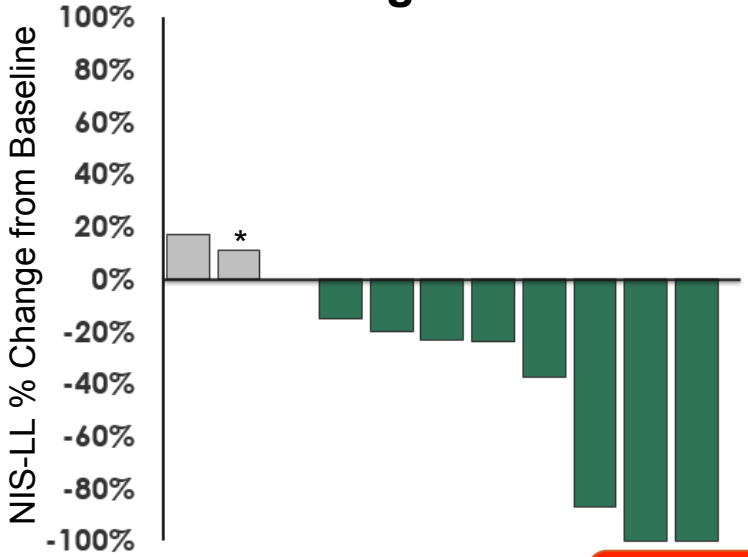
9 responders (82%)

2 progressors (18%)

Point Change in NIS-LL



% Change in NIS-LL

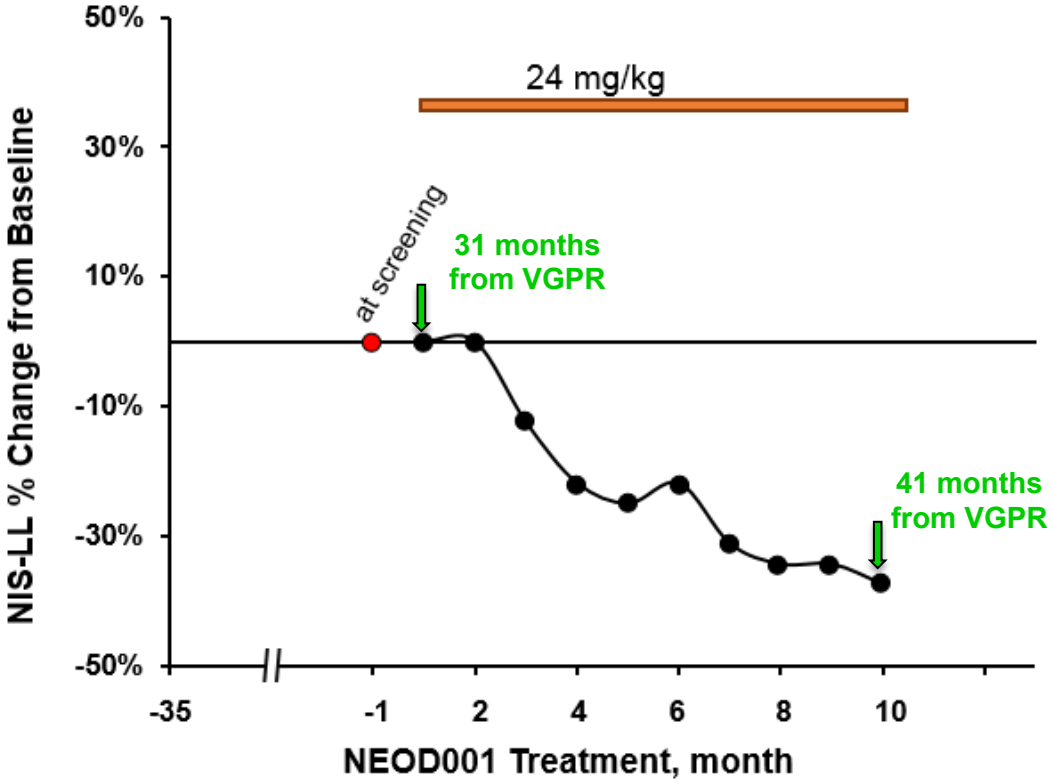


Complete resolution

*Patient discontinued at month 4.

Neuropathy responders: <2-point increase in NIS-LL from baseline; response criteria established in patients with diabetic nephropathy and in use in clinical trials for diabetic neuropathy and TTR polyneuropathy.

NEOD001 Peripheral Neuropathy Response Continues to Improve



70-Year-Old Man

Previous treatment: HDM/ ASCT then CyBorD

Achieved VGPR 31 months prior to NEOD001

Baseline NIS-LL: 32 (wheelchair bound)

NIS-LL at month 10: 20 (-38%)

Safety:
No SAEs; no grade ≥3 AEs; no dose interruptions

Clinical outcome:
Muscle strength increased; improvement in mobility; improvement in edema

NEOD001 Organ Responses Not Related to Prior Plasma Cell-Directed Therapy

- Not related to **depth** of best or last hematological response
- Not related to **time** since best or last hematological response
- Not related to time since last chemotherapy

Conclusions

- NEOD001 was safe and well tolerated
- Encouraging results have now been observed across three organ systems
  - Cardiac (n = 36; 53%) and renal (n = 35; 63%) best response rates are better than those previously reported for patients treated with plasma cell–directed therapies
  - Improvement in peripheral neuropathy (median NIS-LL decrease of 23%; n = 11) was seen for the first time in patients with AL amyloidosis leading to a response rate of 82%
- Ongoing studies:
  - Global phase 2b PRONTO study – previously treated patients with persistent cardiac dysfunction (NCT02632786)
  - Global phase 3 VITAL study – patients with newly diagnosed AL amyloidosis with cardiac involvement (NCT02312206)
- The organ response rates from the expansion patients were consistent with the overall study population, providing further confidence in the ongoing NEOD001 clinical program

Acknowledgements

- We thank the patients and their families who participated in these studies

These slides will be available for later download at ir.prothena.com/events.cfm