Organ Biomarker Responses in Patients With Light Chain Amyloidosis Treated With NEOD001 Are Independent of Previous Hematologic Responses

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  - Amgen
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  - Prothena
  - Takeda

Background

- Existing PCD therapies reduce LC production but do not address resident amyloid
  - ~75% of patients do not achieve organ response and have persistent organ dysfunction[1-6] – major unmet need
  - Safe and well-tolerated therapies are needed to improve organ function
- NEOD001 is an investigational antibody that specifically targets AL amyloid
- NEOD001 may neutralize soluble toxic aggregates and induce clearance of insoluble deposited fibrils through phagocytosis
- Final data (ASH2016, Gertz, #644 at 7:15 AM) demonstrated safety and organ response

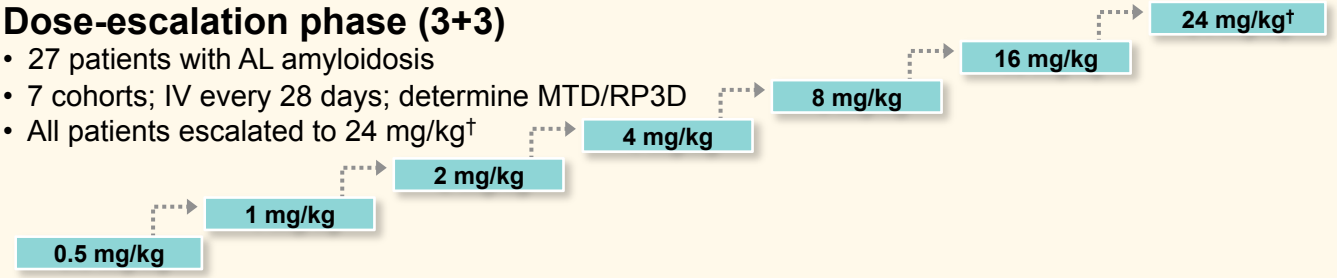
AL, amyloid light chain; LC, light chain; PCD, plasma-cell–directed.

1. Palladini G et al. *Blood*. 2015;126. Abstract 190. 2. Palladini G et al. *Blood*. 2015;126:612-615. 3. Comenzo RL et al. *Leukemia*. 2012;2317-2325.
4. Palladini G et al. *Haematologica*. 2013;98:433-436. 5. Dispenzieri A et al. *Blood*. 2012;119:4397-4504. 6. Reece DE et al. *Blood*. 2011;118:865-873.
7. Gertz MA et al. *J Clin Oncol*. 2016:34:1097-1103.

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

- **All patients previously received PCD treatment and had <u>persistent organ dysfunction</u>**

Dose-escalation phase (3+3)
- 27 patients with AL amyloidosis
- 7 cohorts; IV every 28 days; determine MTD/RP3D
- All patients escalated to 24 mg/kg†



Expansion Cohorts

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

Primary objectives
- Evaluate the safety and tolerability of NEOD001
- 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)**

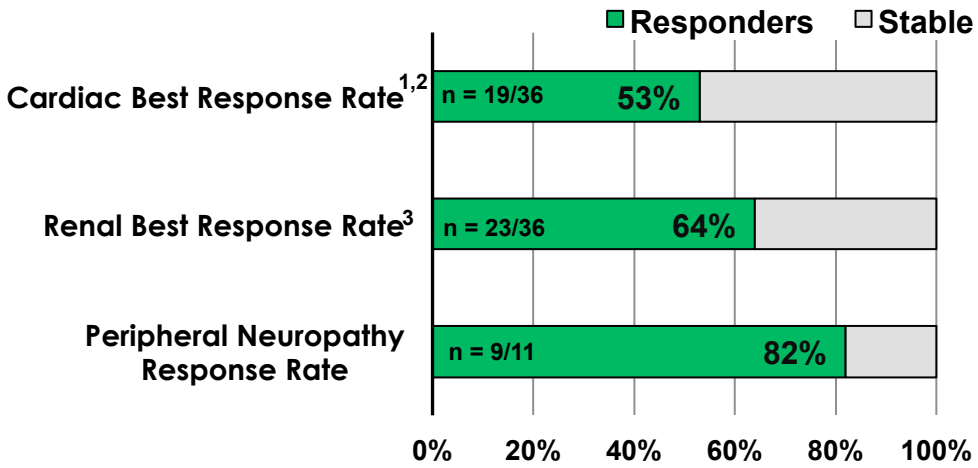
† Maximum of 2500 mg per dose permitted – 24 mg/kg selected based on patient body weight.

IV, intravenous; MTD, maximum tolerated dose; PC, plasma-cell–directed; PK, pharmacokinetics; RP3D, recommended phase 3 dose.

Phase 1/2 Study: Summary of NEOD001 Safety, Tolerability, and Organ Responses

SAFETY AND TOLERABILITY

- NEOD001 was safe and well tolerated
  - –No dose-limiting toxicities
  - –No treatment-related discontinuations or SAEs
  - –No anti-drug antibodies detected
  - –1 treatment-emergent patient death (not related)
- Treatment duration (every 28 days): mean, 12.8 months (range, 2-35)
- Total number of infusions: 994 (N = 69 patients)

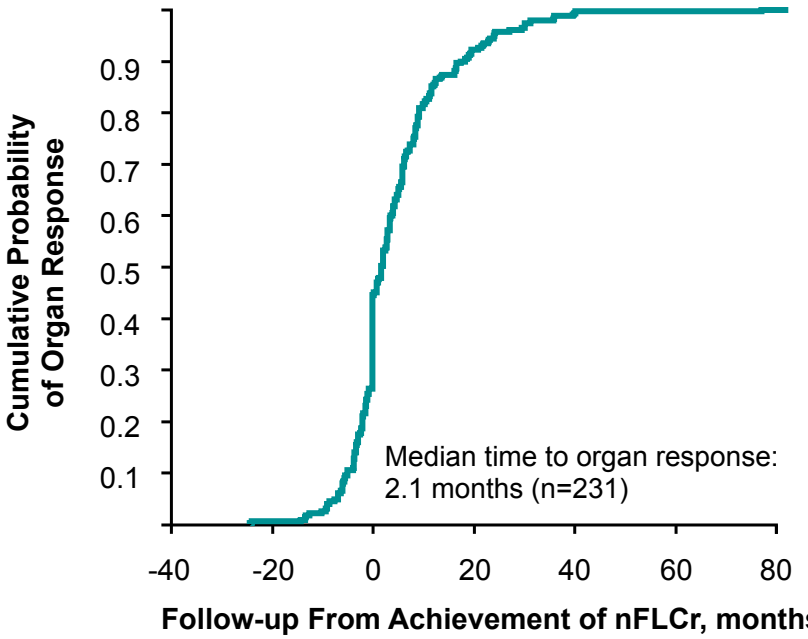


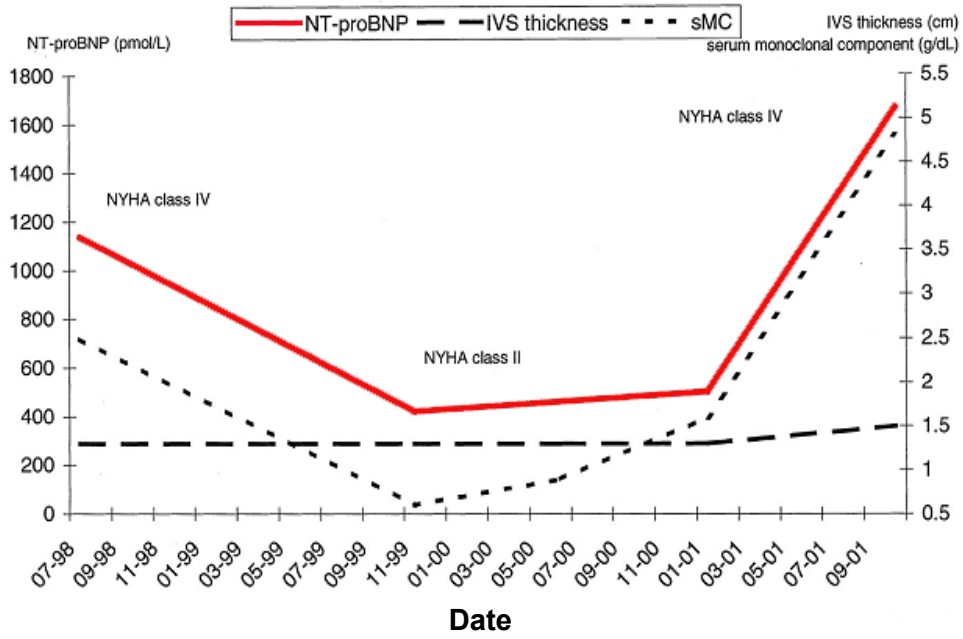
Key question for subanalysis:
Are NEOD001 organ responses related to previous PCD?

SAEs, serious adverse events.

1. Comenzo R et al. *Leukemia.* 2012;26:2317-2325. 2. Palladini G et al. *J Clin Oncol.* 2012;30:4541-4549. 3. Palladini G et al. *Blood.* 2014;124:2325-2332.

Background: If Organ Response Occurs After Hematologic Response (HR), It Is Generally Rapid





- **FLC reduction is paralleled by simultaneous NT-proBNP reduction and clinical improvement**

FLC, free light chain; IVS, interventricular septum; nFLCr, normal ratio of involved and uninvolved free light chains; NYHA, New York Heart Association; sMC, serum monoclonal component.

Modified with permission from Kaufman GP et al. *Am J Hematol.* 2015;90:181-186.

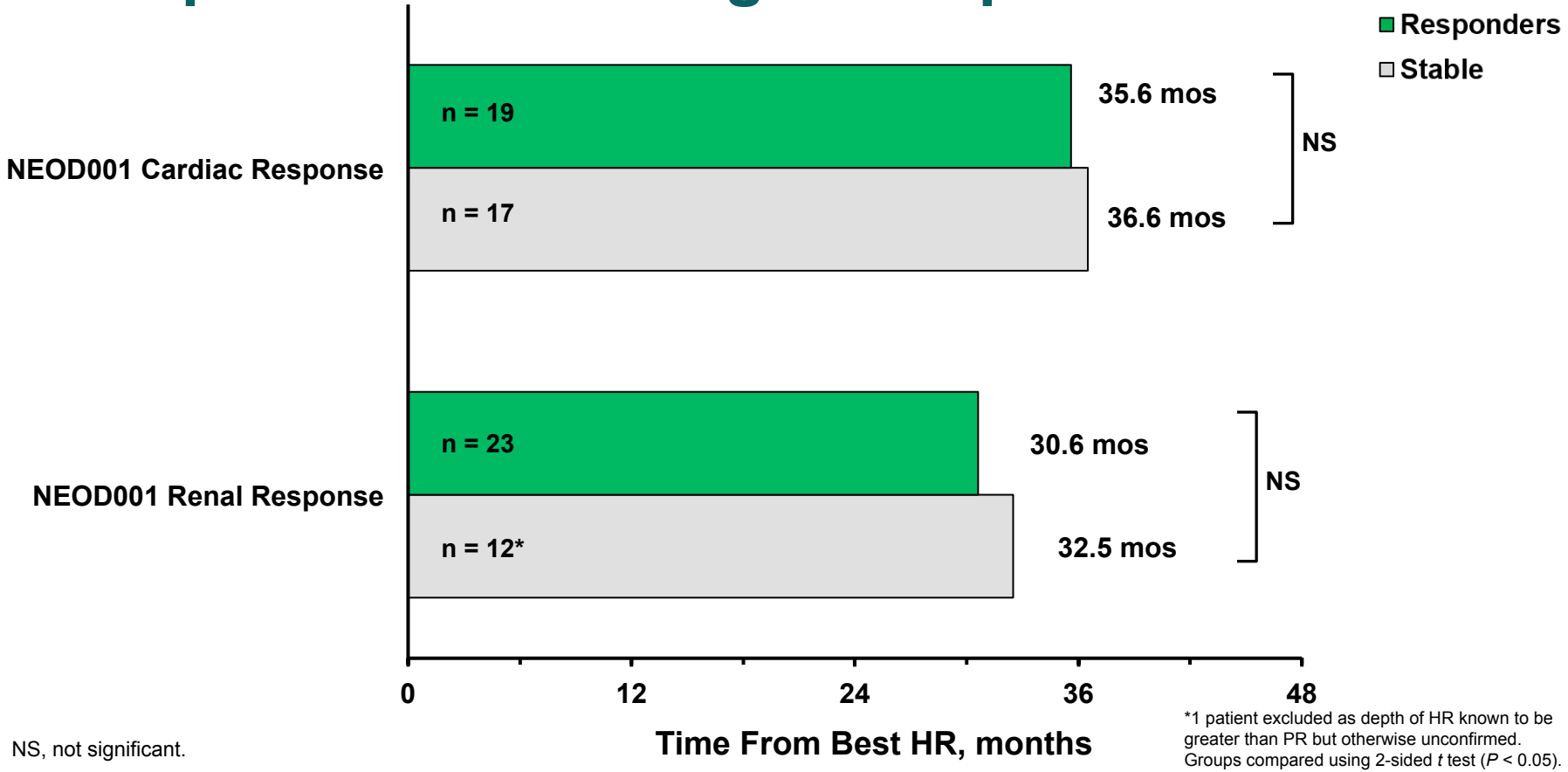
Modified with permission from Palladini G et al. *Circulation* 2003;107:2440-2445.

Phase 1/2 Patients Were Heavily Pretreated, and Most Experienced Significant Duration Since Last PCD Treatment

	All Patients (N = 69)
Median age, years (range)	61 (38-82)
Sex, n (% male)	42 (61)
Median time since initial diagnosis, years (range)	2.9 (0.4-16.0)
No. previous PCD regimens per patient, n (%)	
1	22 (32)
2	16 (23)
≥3	31 (45)
Median time since last PCD treatment, months (range)	5.8 (0.6-85.8)

For full characteristics, see Gertz et al (ASH2016, #644, 7:15 AM)

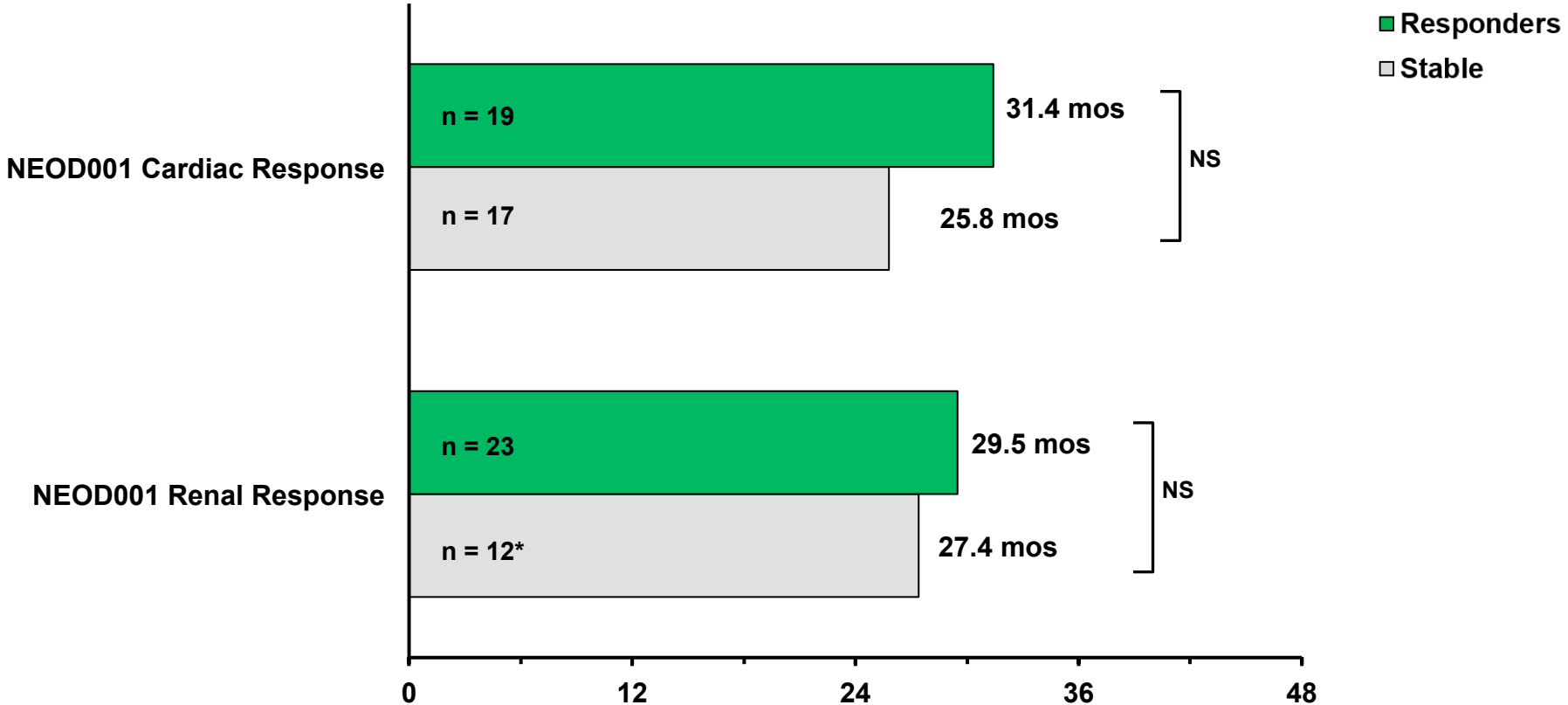
Time From Patients' Best HR to PCD Therapy Did Not Impact NEOD001 Organ Response



NS, not significant.

*1 patient excluded as depth of HR known to be greater than PR but otherwise unconfirmed. Groups compared using 2-sided *t* test ($P < 0.05$).

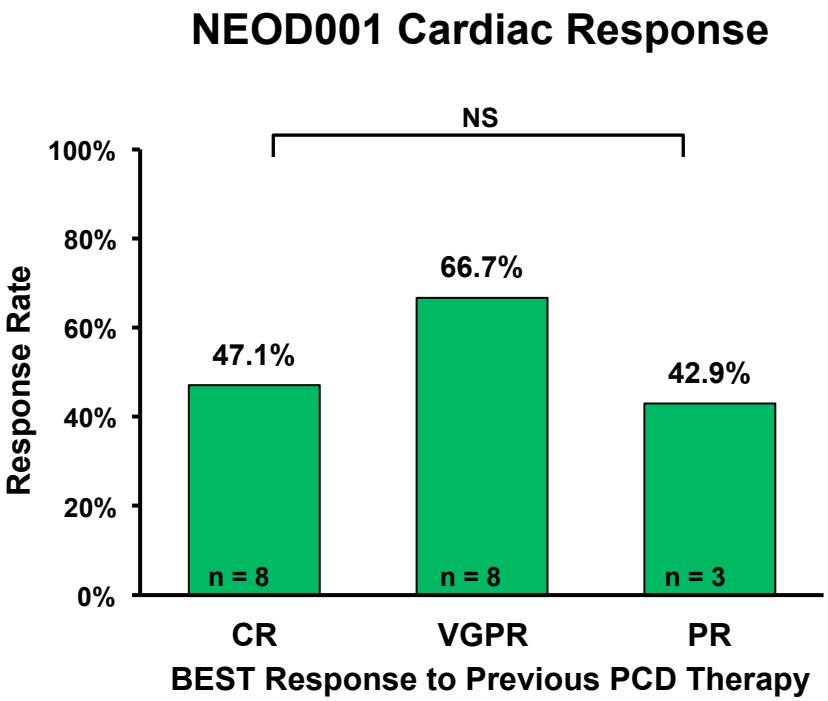
Time From Patients' Last HR to PCD Therapy Did Not Impact NEOD001 Organ Responses

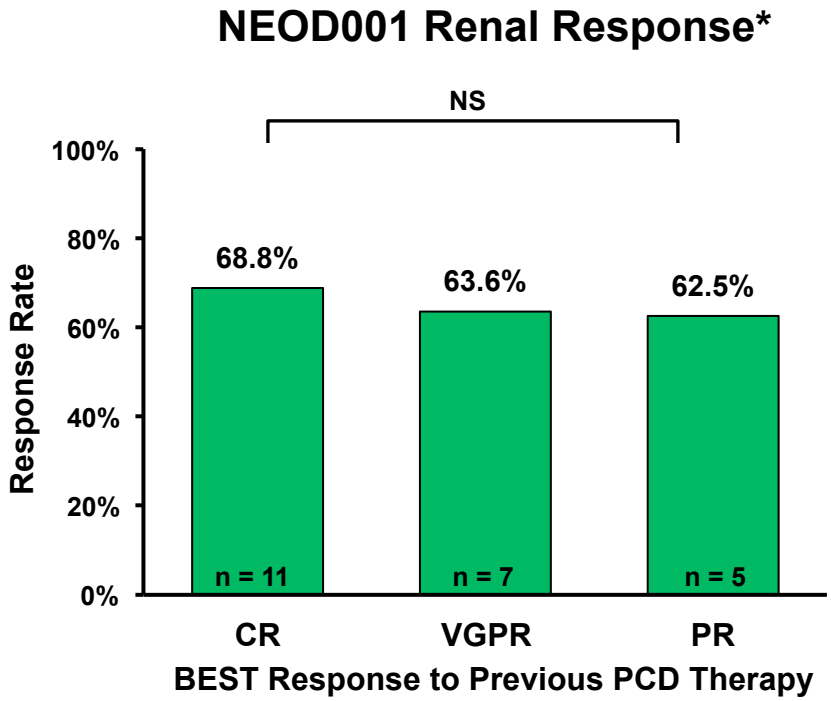


HR, hematologic response; NS, not significant

* 1 patient excluded as depth of HR known to be > PR but otherwise unconfirmed.
Groups compared using 2-sided t-test, $p<0.05$

Depth of Patients' Best HR Did Not Impact NEOD001 Organ Response

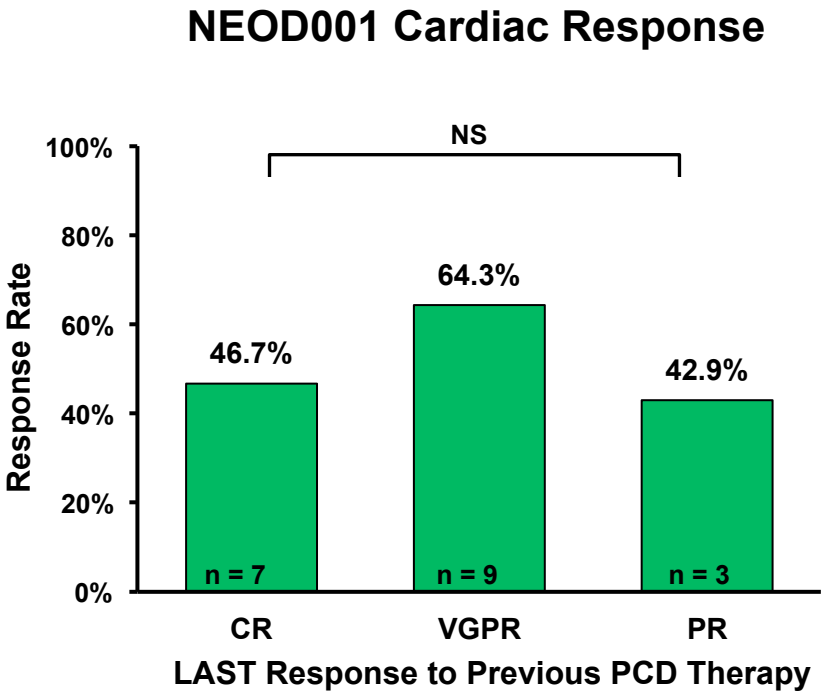


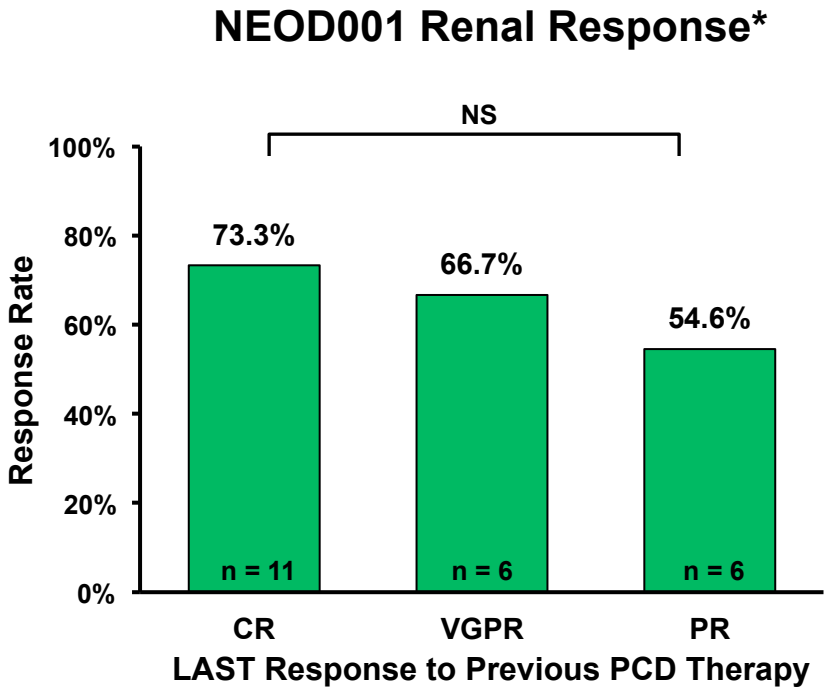


NS, not significant, Responder vs Stable for each category

*1 patient excluded as depth of HR known to be greater than PR but otherwise unconfirmed. Groups compared using 2-sided Fisher exact test ($P < 0.05$).

Depth of Patients' Last HR Did Not Impact NEOD001 Organ Response





NS, not significant, Responder vs Stable for each category

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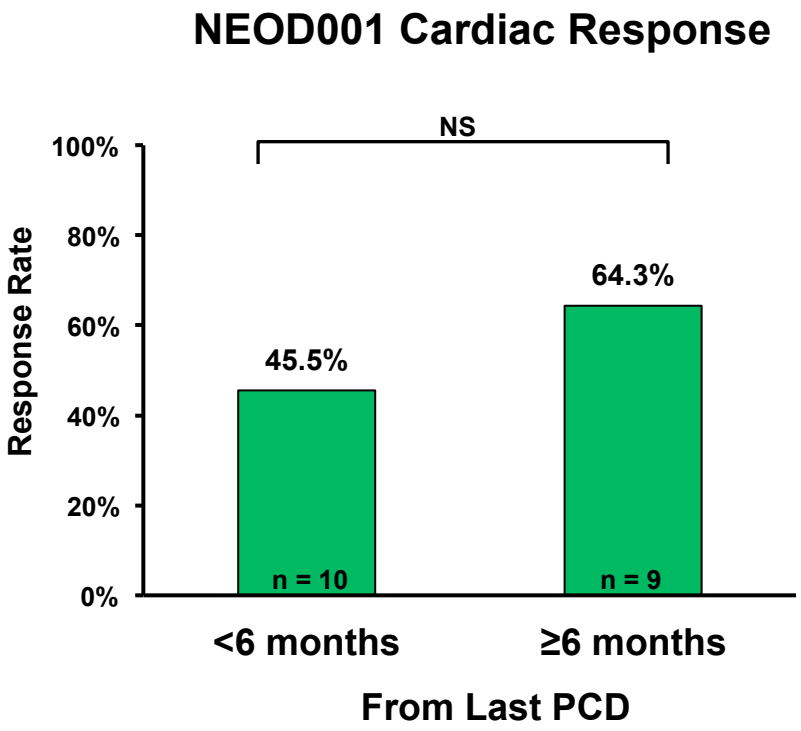
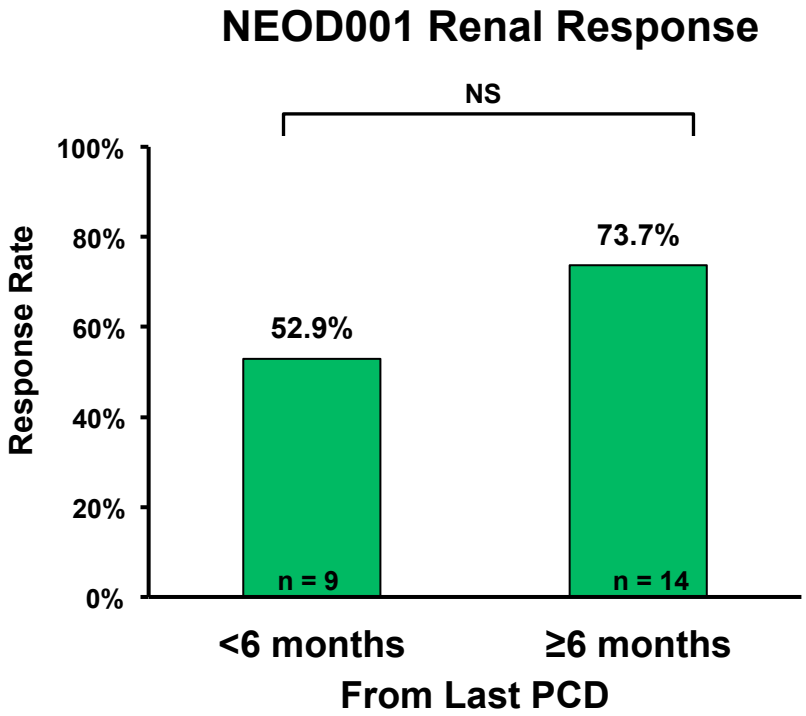
NEOD001 Organ Response Was Similar in Patients With Durations <6 vs ≥6 Months Since Last PCD Therapy

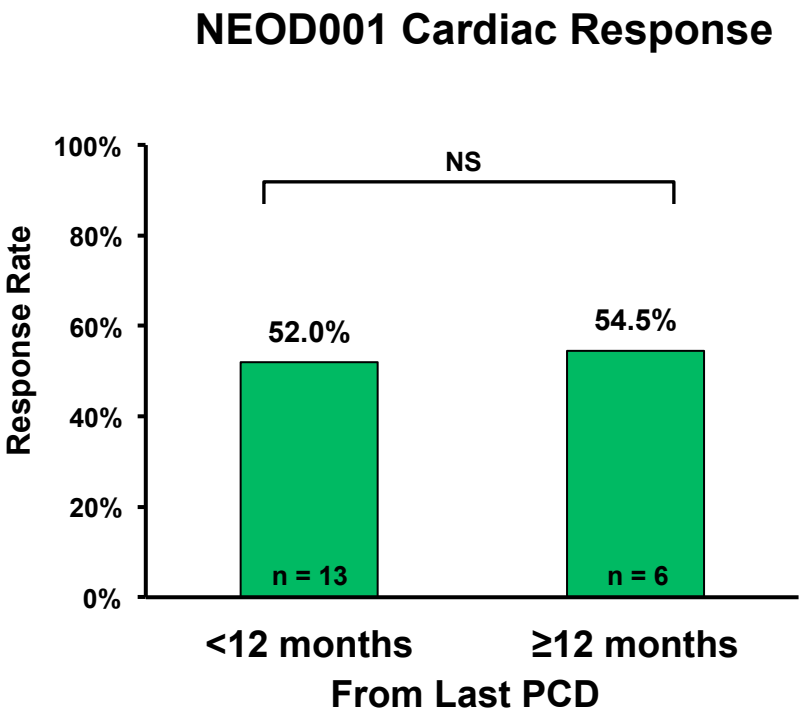


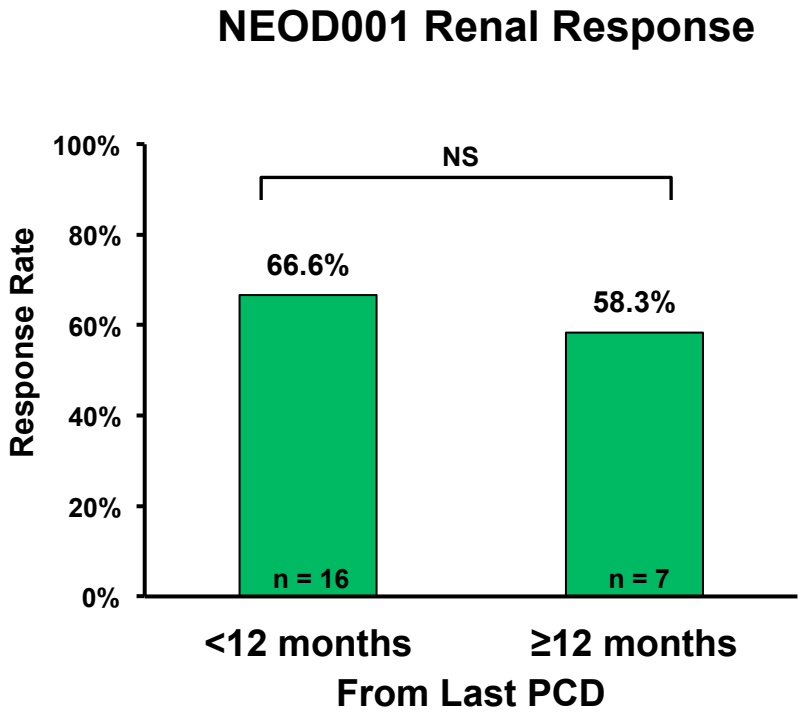


NS, not significant, Responder vs Stable for each category

Groups compared using 2-sided Fisher exact test ($P < 0.05$).

NEOD001 Organ Response Was Similar in Patients With Durations <12 vs ≥12 Months Since Last PCD Therapy

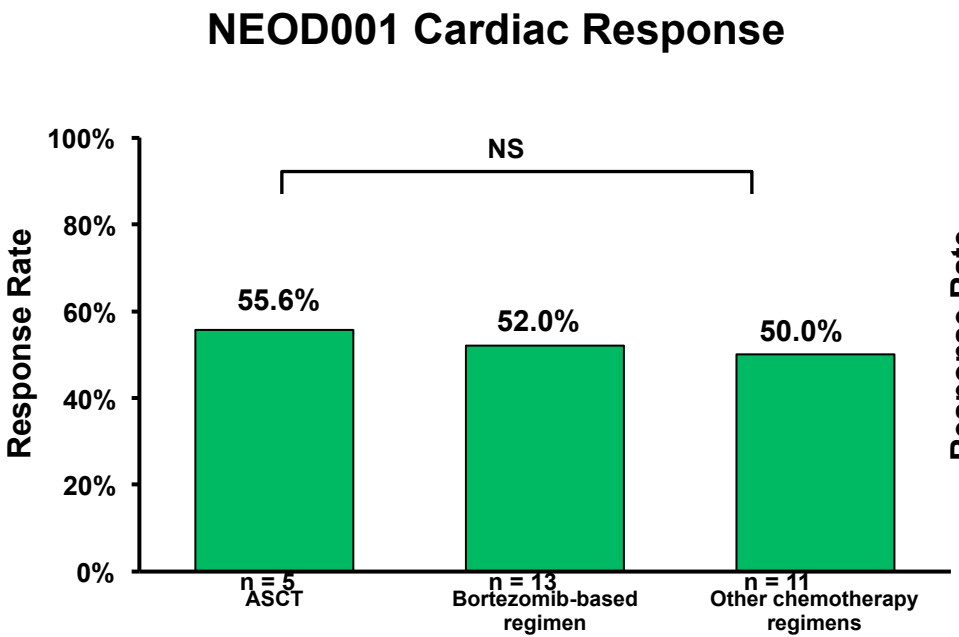


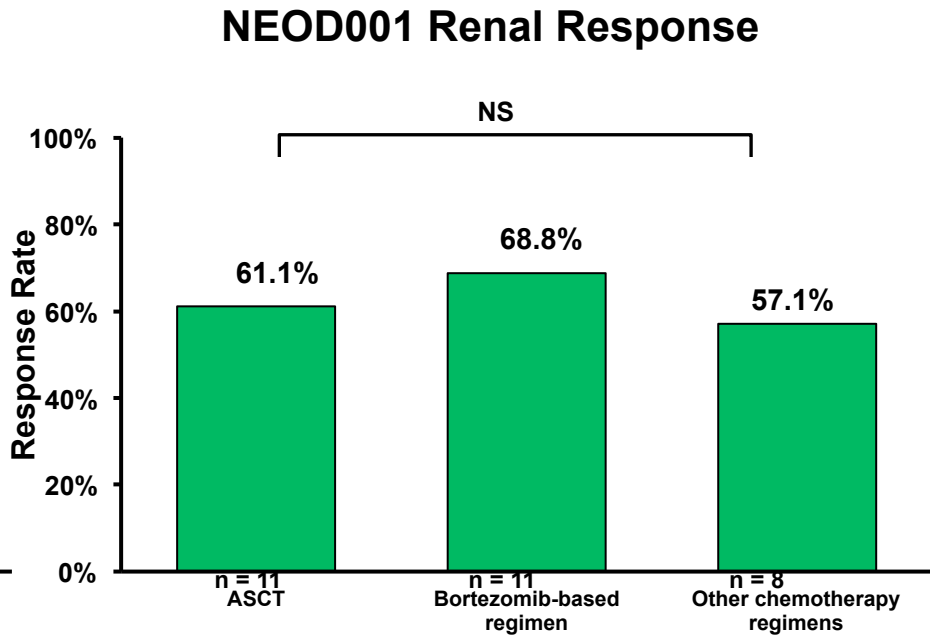


NS, not significant, Responder vs Stable for each category

Groups compared using 2-sided Fisher exact test ($P < 0.05$).

Type of Previous PCD Therapy Did Not Impact Organ Response to NEOD001





NS, not significant, Responder vs Stable for each category

ASCT, autologous stem cell transplantation; NS, not significant.

Groups compared using 2-sided Fisher exact test ($P < 0.05$).

Conclusions From Subanalyses

NEOD001 organ responses are not related to

- ***Time*** since best or last HR
- ***Depth*** of best or last HR
- ***Time*** since last PCD therapy
- ***Type*** of last PCD therapy

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)

Phase 2b

THE PRONTO AMYLOIDOSIS STUDY

Patients must have previously received ≥1 therapy (≥6 months before study start) with partial hematologic response or better, confirmed AL amyloidosis diagnosis, and persistent cardiac dysfunction

Phase 3

THE VITAL AMYLOIDOSIS STUDY

Patients must be treatment naive and have a confirmed diagnosis of AL amyloidosis with cardiac involvement

Acknowledgments

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