

# Phase 2 Trial of Lenalidomide, Cyclophosphamide, And Dexamethasone (RCd) For Newly Diagnosed Myeloma

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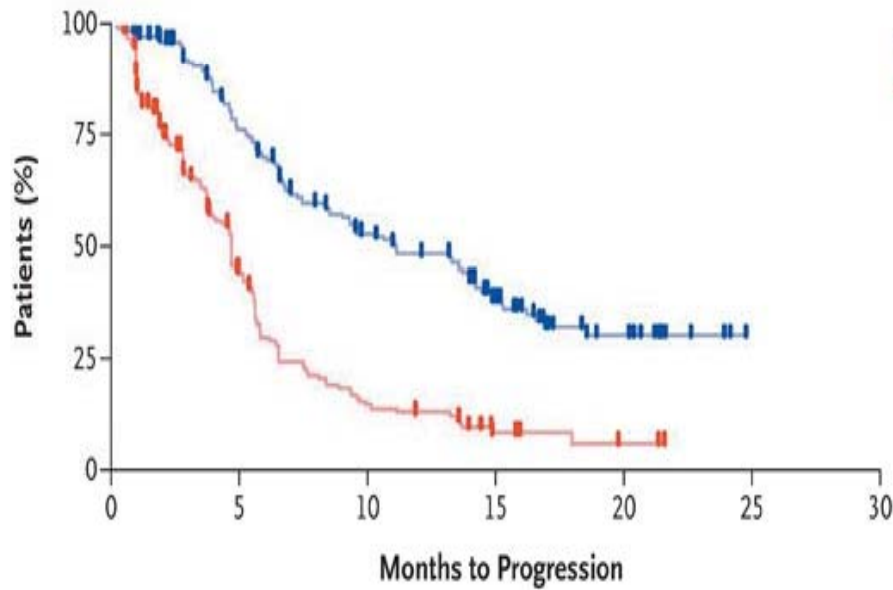
## Disclosures for Shaji Kumar, M.D.

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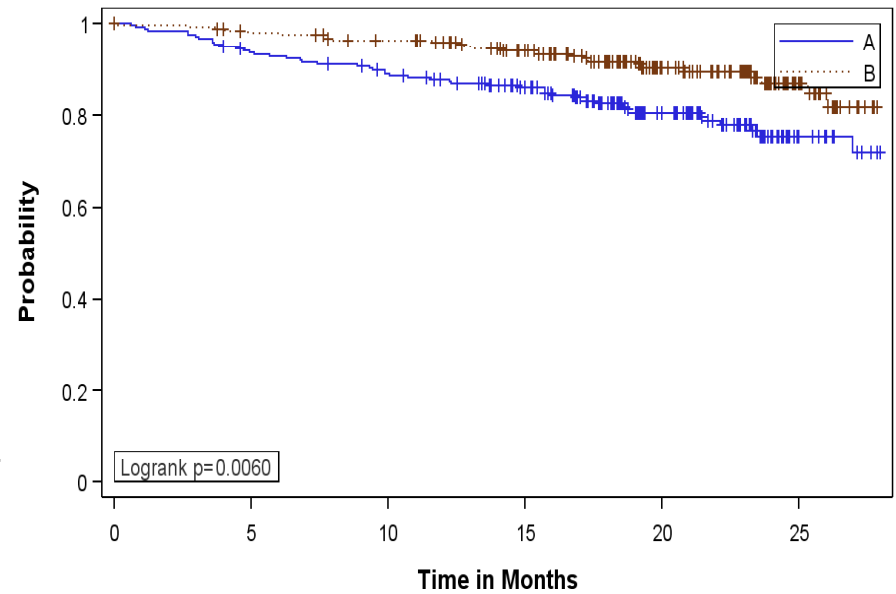
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<b>Employee</b>	<b>No relevant conflicts of interest to declare</b>
<b>Consultant</b>	<b>No relevant conflicts of interest to declare</b>
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<b>Scientific Advisory Board</b>	<b>No relevant conflicts of interest to declare</b>

Presentation includes discussion of the following off-label use of a drug or medical device:  
Lenalidomide, Cyclophosphamide and dexamethasone combination for untreated myeloma

# Lenalidomide

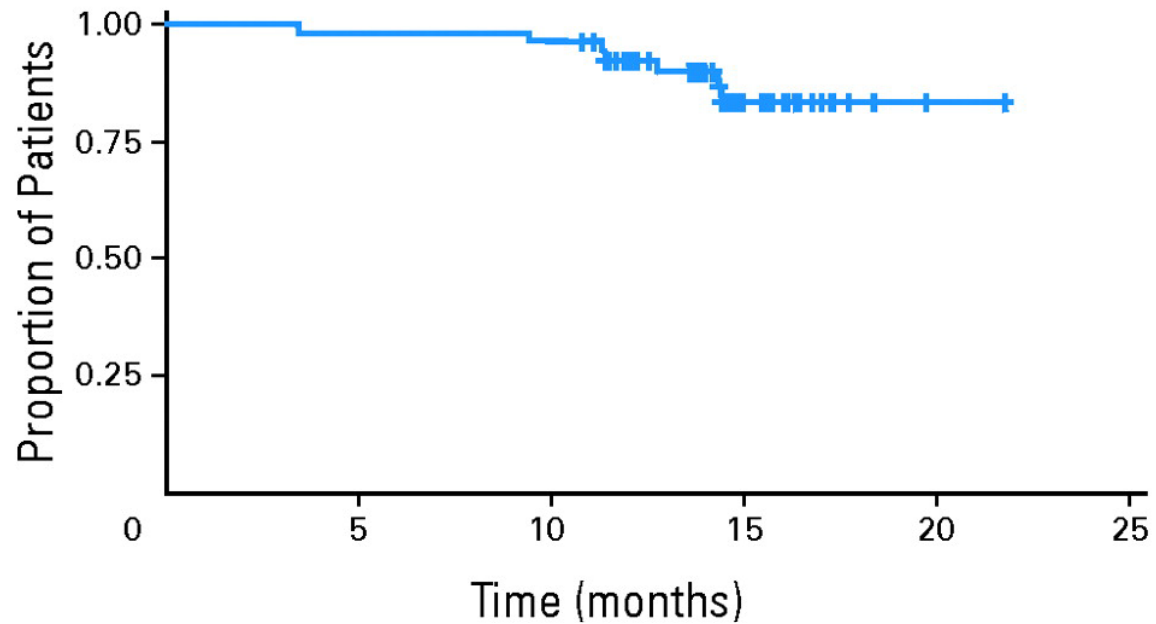


Weber et al.; Dimopoulos et al. NEJM 357 (21): 2007



Rajkumar et al. ASCO 2008

# Alkylator combinations

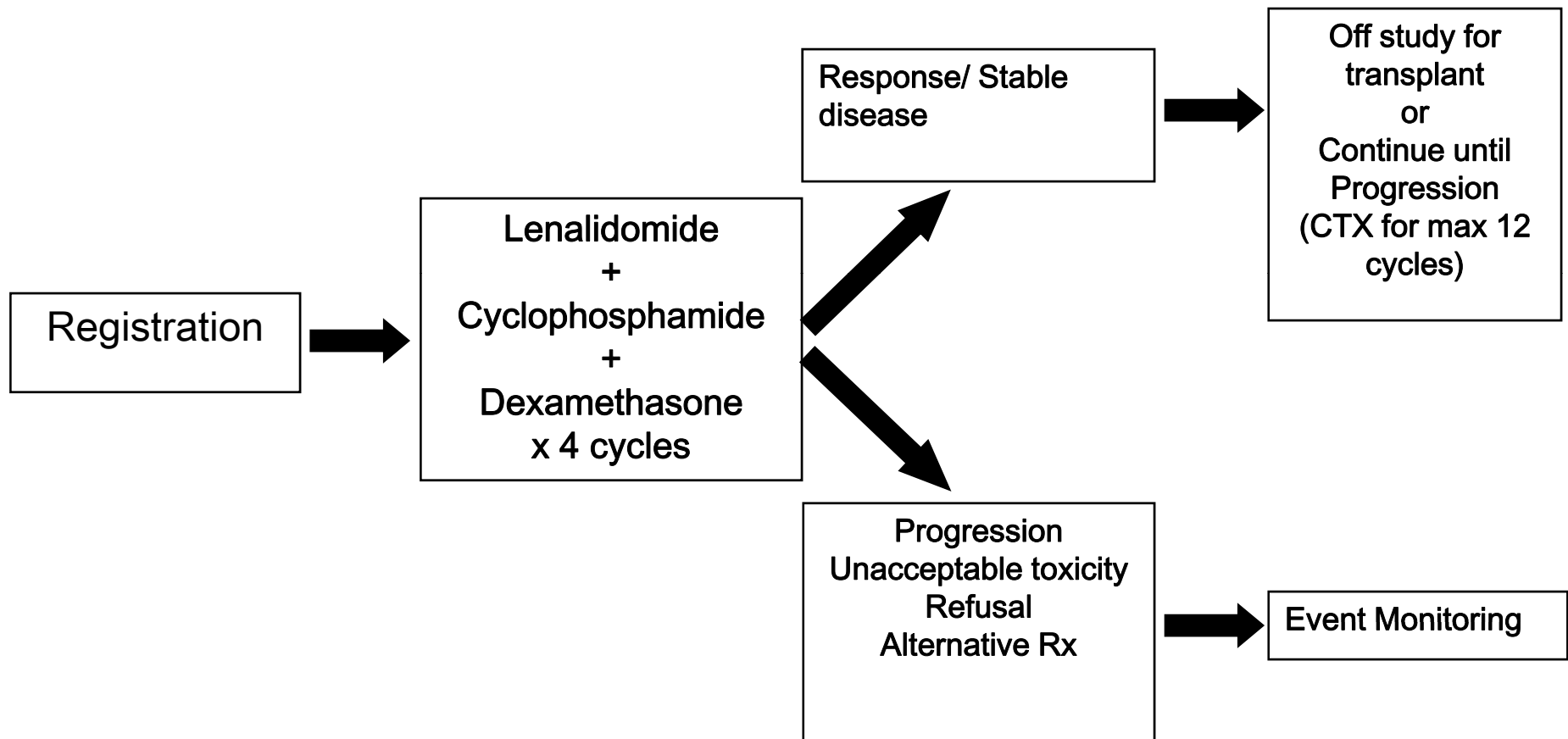


**Event-free survival for 53 patients treated with melphalan, prednisone, and lenalidomide (MPR).**

# Rationale

The study was designed to examine the activity and tolerability of adding cyclophosphamide to lenalidomide-low dose dex

# Study Design



Primary endpoint: Response at 4 cycles

Enrollment: 33 patients (Cohort 1), 20 patients (Cohort 2)

# Objectives

- **Primary: To assess the response rate in patients with untreated myeloma**
- **Secondary:**
  - **To assess the toxicity, overall survival and progression free survival**
  - **To determine the effect on CD34 stem cell collection and time to engraftment in patients going to SCT.**

# Entry Criteria

- Previously untreated symptomatic myeloma.
- Measurable or evaluable disease:
  - Serum M-protein  $\geq 1.0$  g or  $>200$  mg M protein in 24hr urine
  - Serum FLC  $\geq 10$  mg/dL AND abnormal FLC ratio.
  - Bone marrow plasmacytosis  $\geq 30\%$
- The following laboratory values obtained  $\leq 21$  days prior to registration:
  - ANC  $\geq 1500/\mu\text{L}$ , PLT  $\geq 75,000/\mu\text{L}$ , Hemoglobin  $\geq 8.0$
  - Creatinine  $\leq 2.5$  mg/dL
- ECOG performance status 0, 1, or 2

# Treatment protocol

Drug	Dose		Days (28 day cycle)	Duration
Lenalidomide	25 mg	25 mg	Days 1-21	4 cycles (or until disease progression).  Cyclophosphamide discontinued after 12 cycles.
Cyclophosphamide	300 mg/m <sup>2</sup>	300 mg	Days 1, 8, 15	
Dexamethasone	40 mg	40 mg	Days 1, 8, 15, 22	

Cohort 2

All patients received Aspirin or full anticoagulation

# Enrollment

- **34 patients enrolled in cohort 1**
- **19 patients enrolled in cohort 2**
- **Median Age: 64 years (range; 37-82)**
- **Males: 27 (51%)**

# Baseline characteristics

	<b>Cohort 1 (N=34)</b>	<b>Cohort 2 (N=19)</b>	<b>Total (N=53)</b>
<b>ISS Stage</b>			
Stage I	11 (34%)	7 (37%)	18 (35%)
Stage II	12 (38%)	7 (37%)	19 (37%)
Stage III	9 (28%)	5 (26%)	14 (28%)
	<b><i>Median (Range)</i></b>	<b><i>Median (Range)</i></b>	<b><i>Median (Range)</i></b>
Serum M-Protein, g/dL	3.0 (0.0-6.6)	3.1 (0.1-6.1)	3.1 (0.0-6.6)
Urine M-protein, mg/24 hrs	112.5 (0.0-9639.0)	88.5 (0.0-4721.0)	88.5 (0.0-9639.0)
Involved FLC, mg/dL	30.6 (0.1-1760.0)	46.7 (4.4-407.0)	34.6 (0.1-1760.0)
Calcium, mg/dL	9.6 (8.7-11.4)	9.4 (8.5-10.7)	9.6 (8.5-11.4)
Creatinine, mg/dL	1.0 (0.6-2.1)	0.9 (0.6-1.6)	1.0 (0.6-2.1)
BM Labeling Index, %	0.7 (0.0-4.2)	1.0 (0.0-3.8)	0.7 (0.0-4.2)

## Response within 4 cycles

	<b>Confirmed responses (n=53)</b>	<b>Len-Dex (n=34)</b>
<b>VGPR/ CR</b>	<b>13 (25%)</b>	
<b>PR</b>	<b>28 (53%)</b>	
<b><i>ORR</i></b>	<b><i>41 (78%)</i></b>	
<b>&lt; PR</b>	<b>12 (23%)</b>	

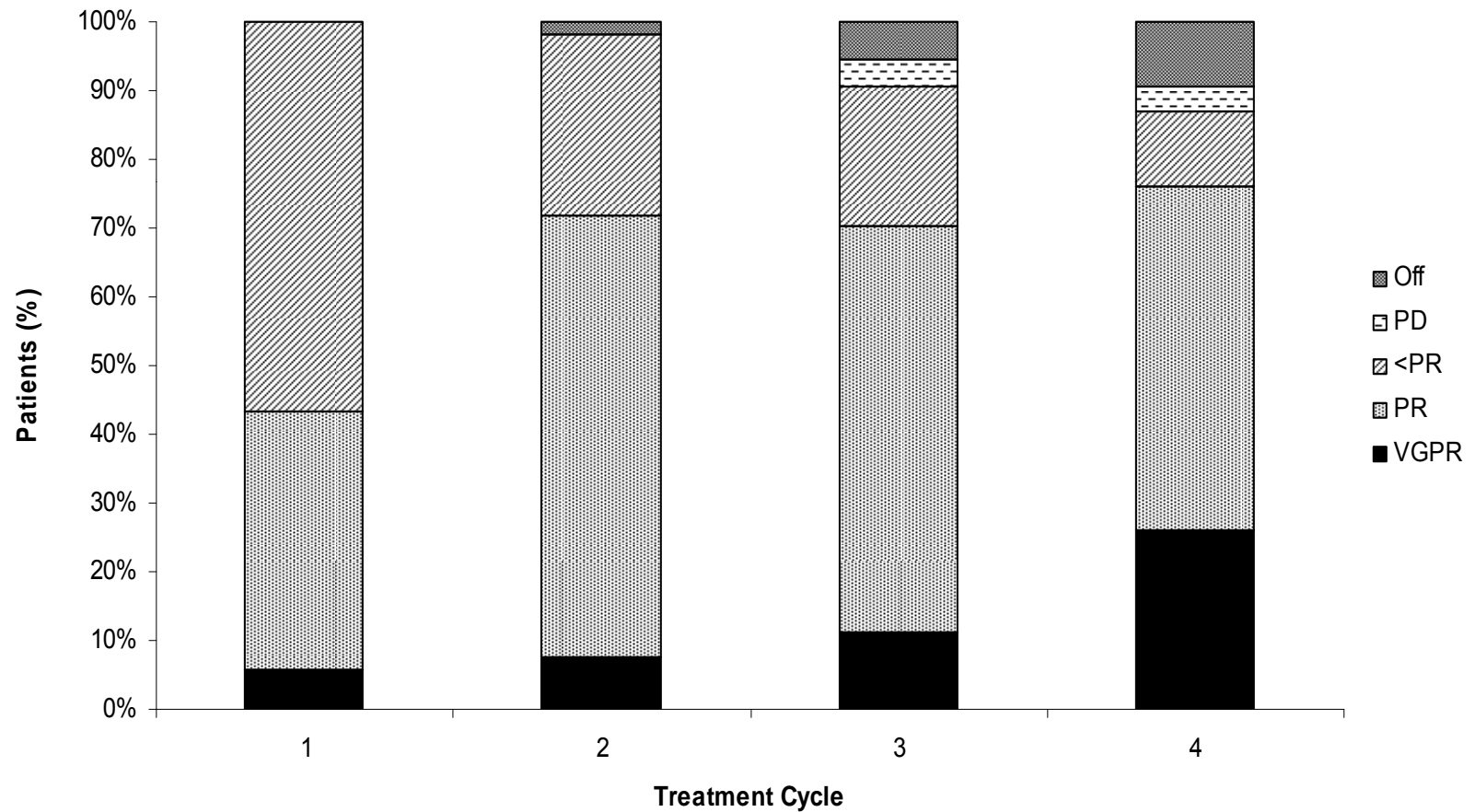
## Response within 4 cycles

- **Six patients (11%) went off study < 4 cycles (5 cohort 1, 1 cohort 2)**
  - **Two patients had progression**
  - **One developed interstitial nephritis**
  - **Two due to multiple AEs (one pt with poorly controlled DM, one with previously undetected AL amyloidosis)**
  - **One patient went on to alternative treatment**

## All Responses (4 cycles)

	Cohort 1 (n=34)	Cohort 2 (n=19)
<b>VGPR/ CR</b>	<b>9 (26%)</b>	<b>5 (26%)</b>
<b>PR</b>	<b>17 (50%)</b>	<b>11 (58%)</b>
<b><i>ORR</i></b>	<b>26 (76%)</b>	<b>16 (84%)</b>
<b>&lt; PR</b>	<b>8 (24%)</b>	<b>3 (16%)</b>

# Dynamics of response



## Best Response (All cycles)

	<b>Confirmed responses (n=53)</b>
<b>VGPR/ CR</b>	<b>17 (32%)</b>
<b>PR</b>	<b>28 (53%)</b>
<b>&lt; PR</b>	<b>8 (15%)</b>

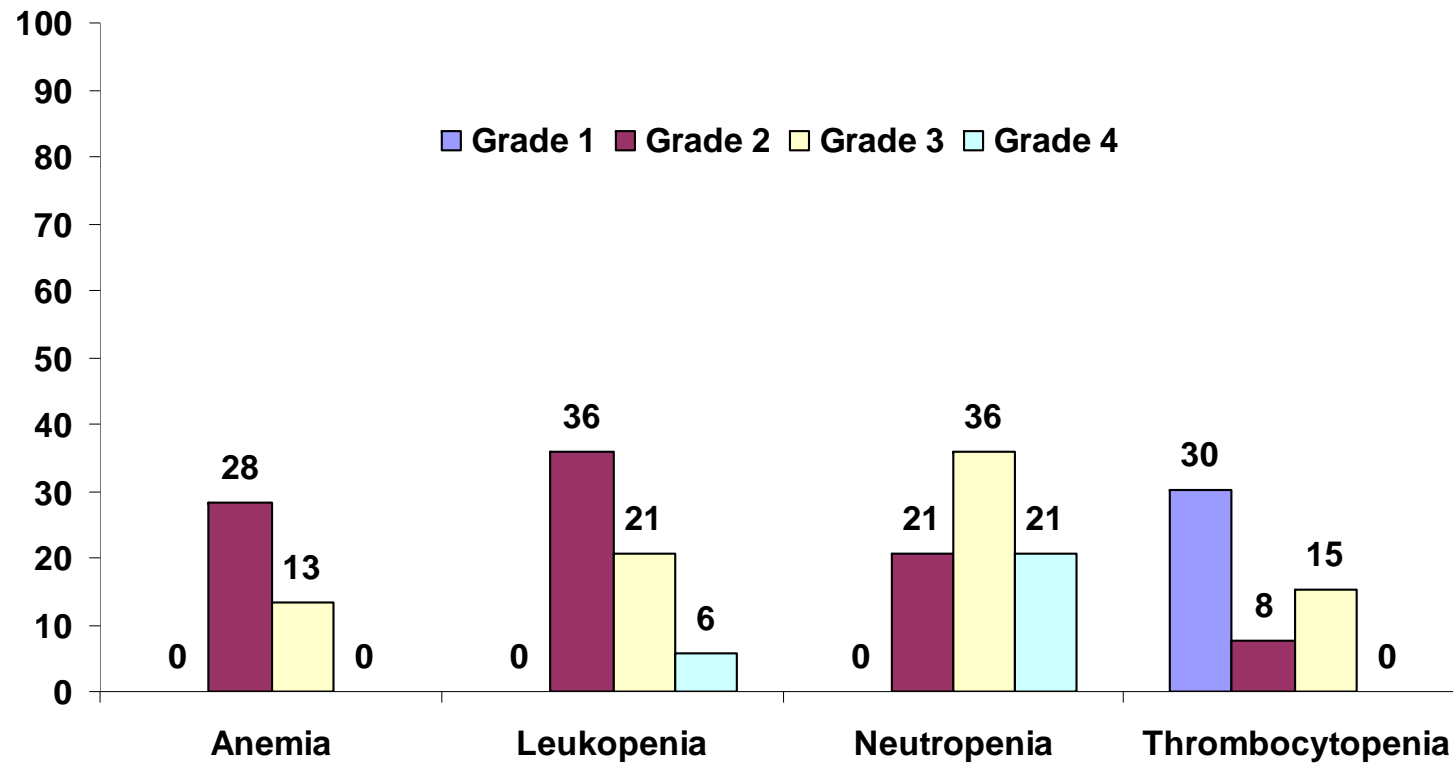


**85%**

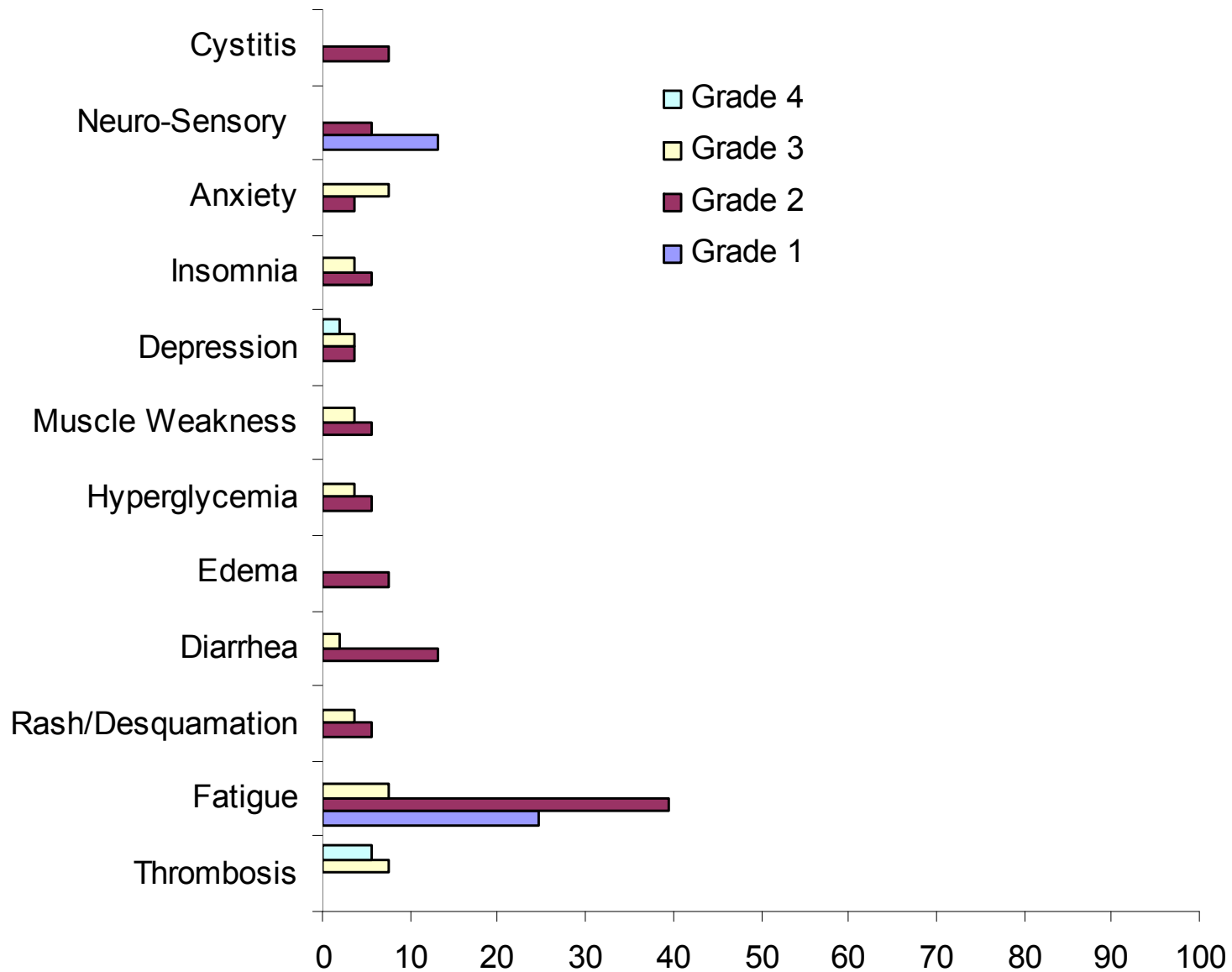
## Best Response (All cycles)

	Cohort 1 (n=34)	Cohort 2 (n=19)
<b>VGPR/ CR</b>	<b>12 (35%)</b>	<b>5 (26%)</b>
<b>PR</b>	<b>17 (50%)</b>	<b>11 (58%)</b>
<b>&lt; PR</b>	<b>5 (15%)</b>	<b>3 (16%)</b>
<b><i>Total cycles</i></b>	<b>291 (1-26)</b>	<b>106 (1-8)</b>

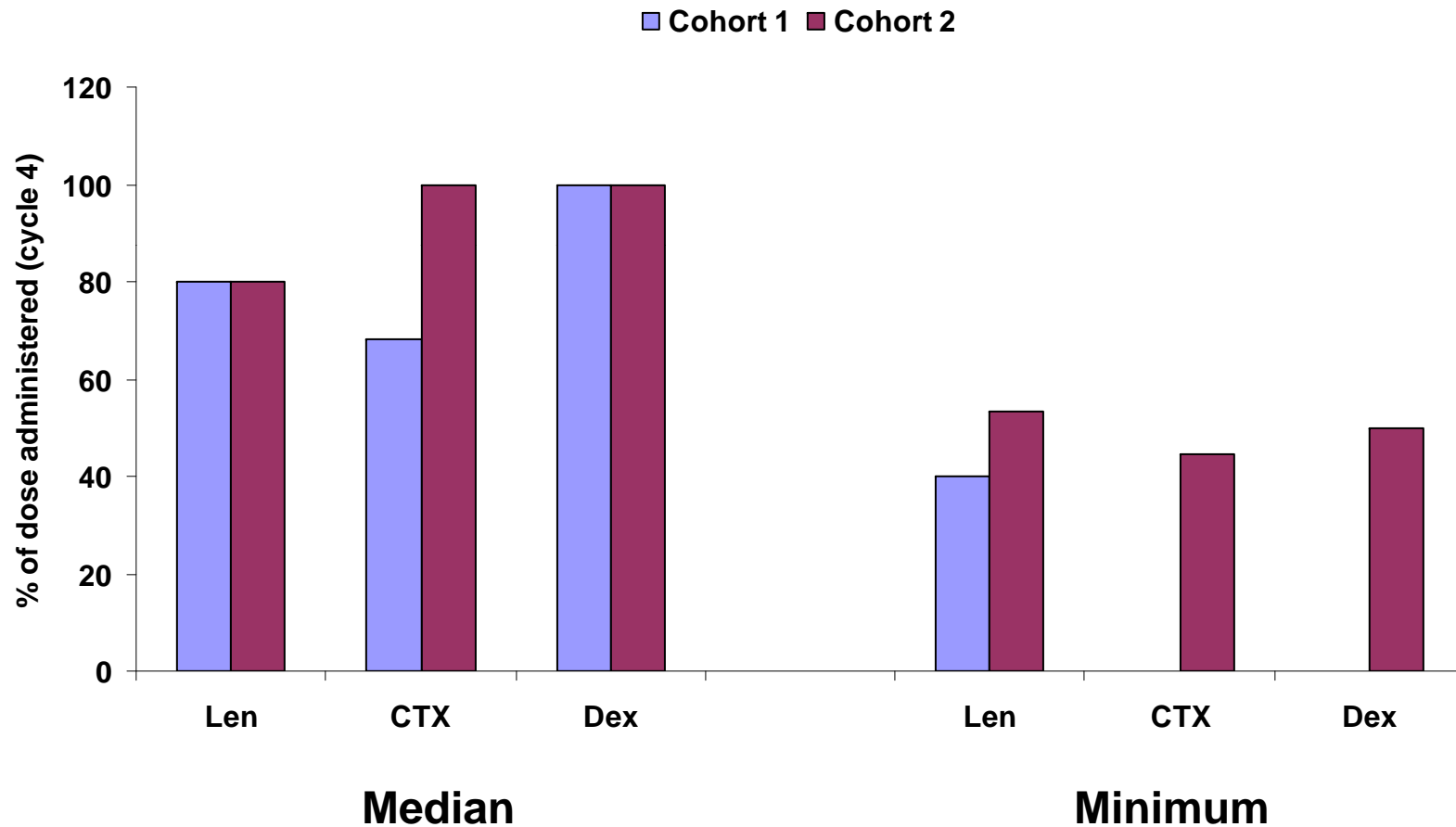
# Hematologic AEs



# Non-Hematologic AE



# Drug delivered during cycle 4



## Follow up

- **21 (40%) continue on study**
- **32 patients have discontinued study treatment**
  - **Completed study per protocol (20)**
  - **Disease progression (6)**
  - **Adverse event (3)**
  - **Alternate treatment (3).**
- **The median number of cycles per patient is 4 (range: 1 – 25)**

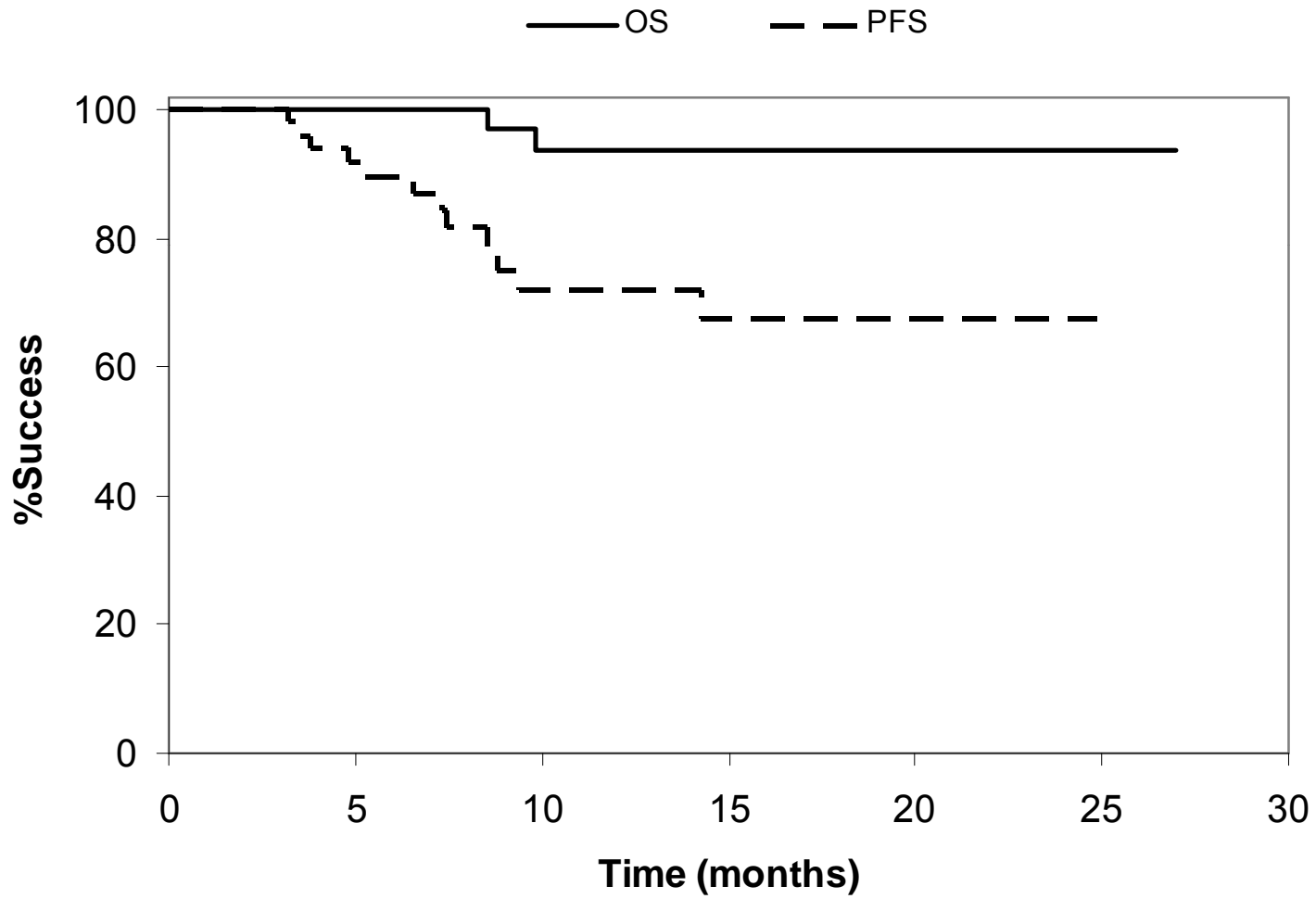
## Follow up

- **Median time on study was 4.9 (1.6 - 25.8) months**
- **Eleven patients have progressed**
- **Two patients have died**
- **Median follow up 12.3 months (2.8-15.2 months)**

# Response duration

- **11 patients had disease progression:**
  - **5 on study (one after a PR, two after VGPR)**
  - **5 after off study after completing 4 cycles**
  - **1 after off study for adverse event**

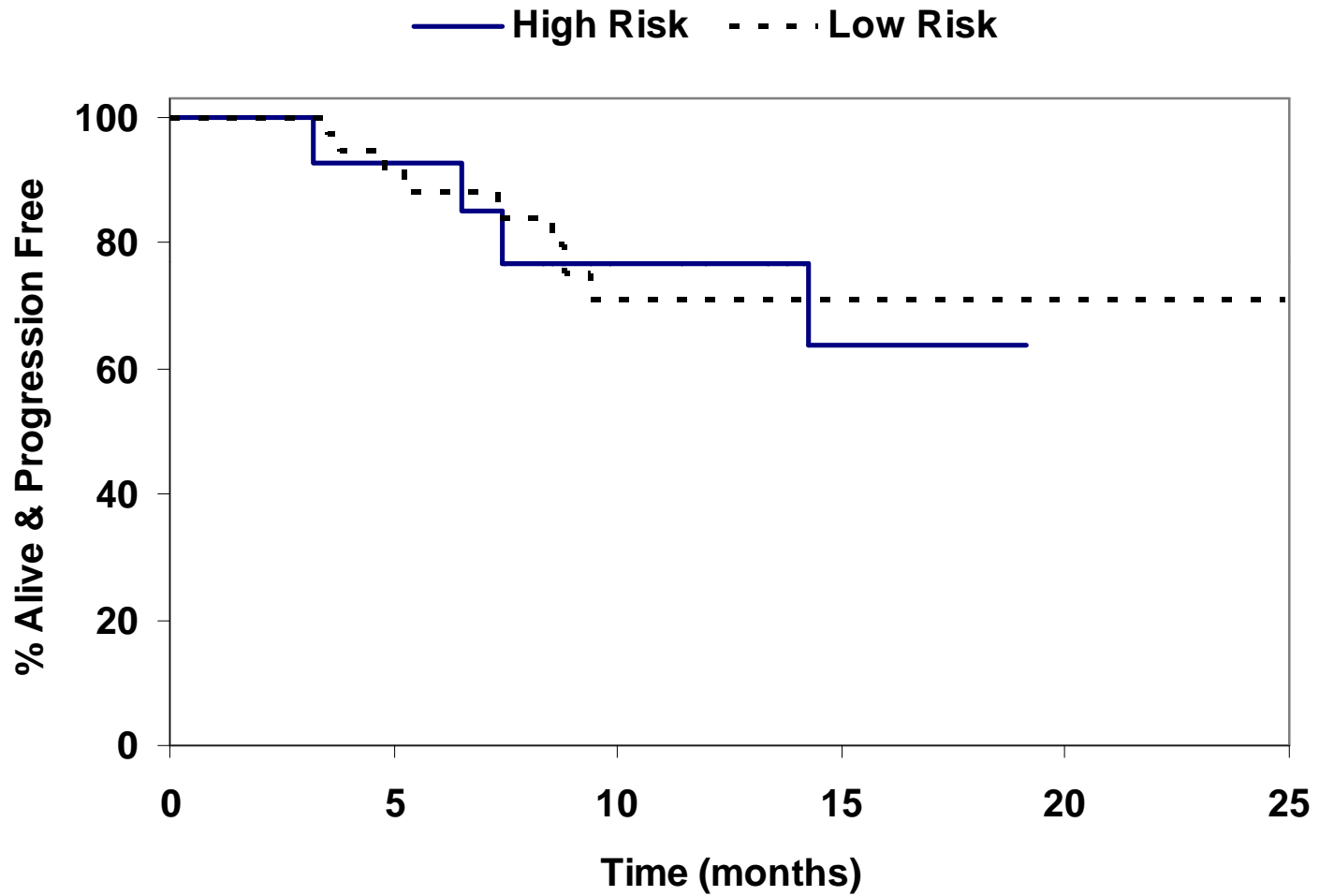
# Survival



## High Risk Myeloma

- **14 patients (26%) considered HR**
- **Best overall response was 93% (including 8 VGPR/CR; 57%)**
- **For standard risk best ORR was 82%, including 8 VGPR/CR; 21%)**

# High Risk Myeloma



## Stem cell collection/ SCT

- Thirty patients went to stem cell collection
- 8 patients failed first attempt
  - 3 salvaged with AMD3100
  - 1 salvaged with CTX
  - 4 did not reattempt
- Median collection 7.0 million CD34 cells/Kg
- 11 (21%) have since gone to ASCT

# Conclusions and Future directions

- Active regimen
- Lower dose of cyclophosphamide (300 mg weekly) more appropriate dose
- Future trials need to compare this regimen with other combinations

# Acknowledgements

## Our Patients

### Members of Myeloma, Amyloid, Dysproteinemia group

- Leif Bergsagel, MD
- Francis K Buadi, MD
- David Dingli, MD
- Angela Dispenzieri, MD
- Rafael Fonseca, MD
- Morie A. Gertz, MD
- Philip R. Greipp, MD
- Suzanne Hayman, MD
- Shaji Kumar, MD
- Robert A. Kyle, MD
- Martha Q. Lacy, MD
- John A. Lust, MD, PhD
- Keith Stewart, MD
- S. V. Rajkumar, MD
- Craig Reeder, MD
- Vivek Roy, MD
- Steve Russell, MD, PhD
- Thomas E. Witzig, MD
- Steve Zeldenrust, MD, PhD

### Hematology Clinical Trials Staff

- Tammy S. McCarty
- Carol S. Schimek
- Deb Schott
- Jacob Allred
- Megan Campbell

# Dose modifications

<b>Dose Level</b>	<b>Lenalidomide (Days 1 – 21)</b>	<b>Cyclophosphamide (Days 1, 8, and 15)</b>		<b>Dexamethasone (Once weekly)</b>
<b>Start</b>	<b>25 mg</b>	<b>300 mg/m<sup>2</sup></b>	<b>300 mg</b>	<b>40 mg</b>
<b>-1</b>	<b>20 mg</b>	<b>200 mg/m<sup>2</sup></b>	<b>200 mg</b>	<b>30 mg</b>
<b>-2</b>	<b>15 mg</b>	<b>100 mg/m<sup>2</sup></b>	<b>100 mg</b>	<b>20 mg</b>
<b>-3</b>	<b>10 mg</b>	<b>100 mg/m<sup>2</sup> (Day 1)</b>	<b>100 mg (Day 1)</b>	<b>10 mg</b>
<b>-4</b>	<b>5 mg</b>			

Cohort 2