New IMiD Therapy

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IMiDs

	Thalidomide + dex	Lenalidomide + dex
Newly diagnosed MM	60-75%	70-90%
Relapsed MM	45-55%	60%

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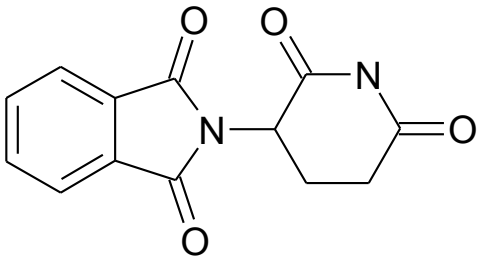
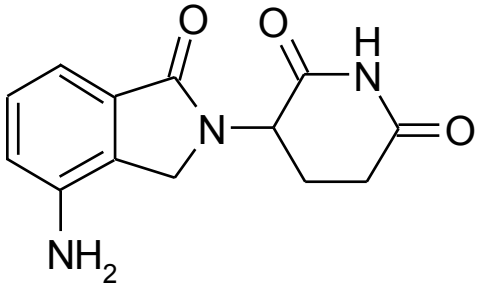
Molecular Structure of Thalidomide, Lenalidomide and Pomalidomide



Thalidomide

100-200 mg/d

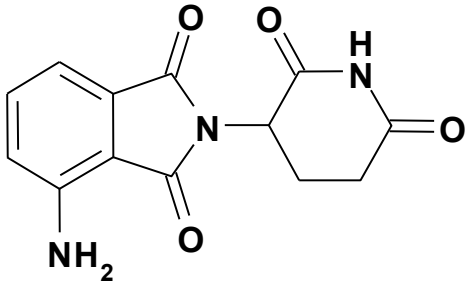
Neuropathy
Constipation
Sedation
DVT



Lenalidomide

15-25 mg/d

Myelosuppression
Skin rash
DVT



Pomalidomide

1-4 mg/d

Structurally similar, but functionally different both qualitatively and quantitatively

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In vitro Pharmacology

	Thalidomide	Pomalidomide
Anti-angiogenic activity (human explant model)	++++	++++
Anti-inflammatory activity against monocytes	+	+++++
T cell/NK cell costimulation	+	+++++
T regulatory cell inhibition	-	+++++
Antibody-dependent Cellular Cytotoxicity (ADCC)	-	++++

+ = potency factor of 10

Teo ST, et al. Drug Discovery Today. 2005;10:107-14.

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Phase I trials for Pomalidomide

	N	Dose	MTD	ORR
Schey	24	1-10 mg	2 mg	54%
Streetly	20	1-10* mg QOD	5 mg QOD	50%

* Nine patients also received dexamethasone

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Phase II Trial of Pomalidomide + Dexamethasone in Relapsed MM

Study Goals:

- **To assess the response rate and duration of remission with Pom/dex in patients with relapsed or refractory myeloma.**
- **To assess the toxicity, overall survival and progression free survival of Pom/dex in this patient population.**

Study design

- Phase II trial, 60 patients
- A confirmed response is defined to be a CR, PR or VGPR as assessed by the International Myeloma Working Group Uniform Response criteria.

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Eligibility

- Previously treated, relapsed multiple myeloma.
- > 1 and ≤ 3 prior regimens.
- Measurable disease (one of the following) :
  - Serum M-spike ≥1.0 g/dL
  - 24-hour Urine M-spike >200 mg
  - Serum immunoglobulin FLC ≥ 10 mg/dL with abnormal FLC ratio
  - Measurable soft tissue plasmacytoma, not previously radiated
  - > 30% plasma cells in bone marrow
- Age ≥ 18 years.
- ANC ≥ 1000/µL and PLT ≥ 75,000/µL
- Creatinine ≤ 2.5 mg/dL
- ECOG PS 0, 1, or 2.

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Patient Characteristics

	N=60
Age, median (range)	65.5 (35-88)
Gender, male	36 (60%)
ISS Stage	
Stage I	12 (28%)
Stage II	17 (40%)
Stage III	14 (32%)
β-2 M	3.5 (1.5-14.0)
PC Labeling Index, %	0.7 (0.0-9.6)
Baseline neuropathy	
Grade 1	24 (40%)
Grade 2	3 (5%)

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Prior treatments

	Total (N=60)
Diagnosis to On Study, median (months, range)	44 (9.1-192.5)
No. Prior Chemotherapies	
1	17 (28%)
2	22 (37%)
3	21 (35%)
Transplant, yes	39 (65%)
Previous IMiD use, yes	36 (60%)
- Lenalidomide	21 (35%)
- Thalidomide	28 (47%)
Bortezomib	20 (33%)

Study treatment

- **Starting Dose:**
  - **Pomalidomide - 2mg p.o. daily days 1-28**
  - **Dexamethasone - 40mg p.o. days 1, 8, 15 & 22**
  - **Aspirin - 325mg p.o. days 1-28**
- **G-CSF was not permitted**
- **Patients allowed to increase to 4 mg/day if no grade 3/4 toxicity and if NR or progressing**

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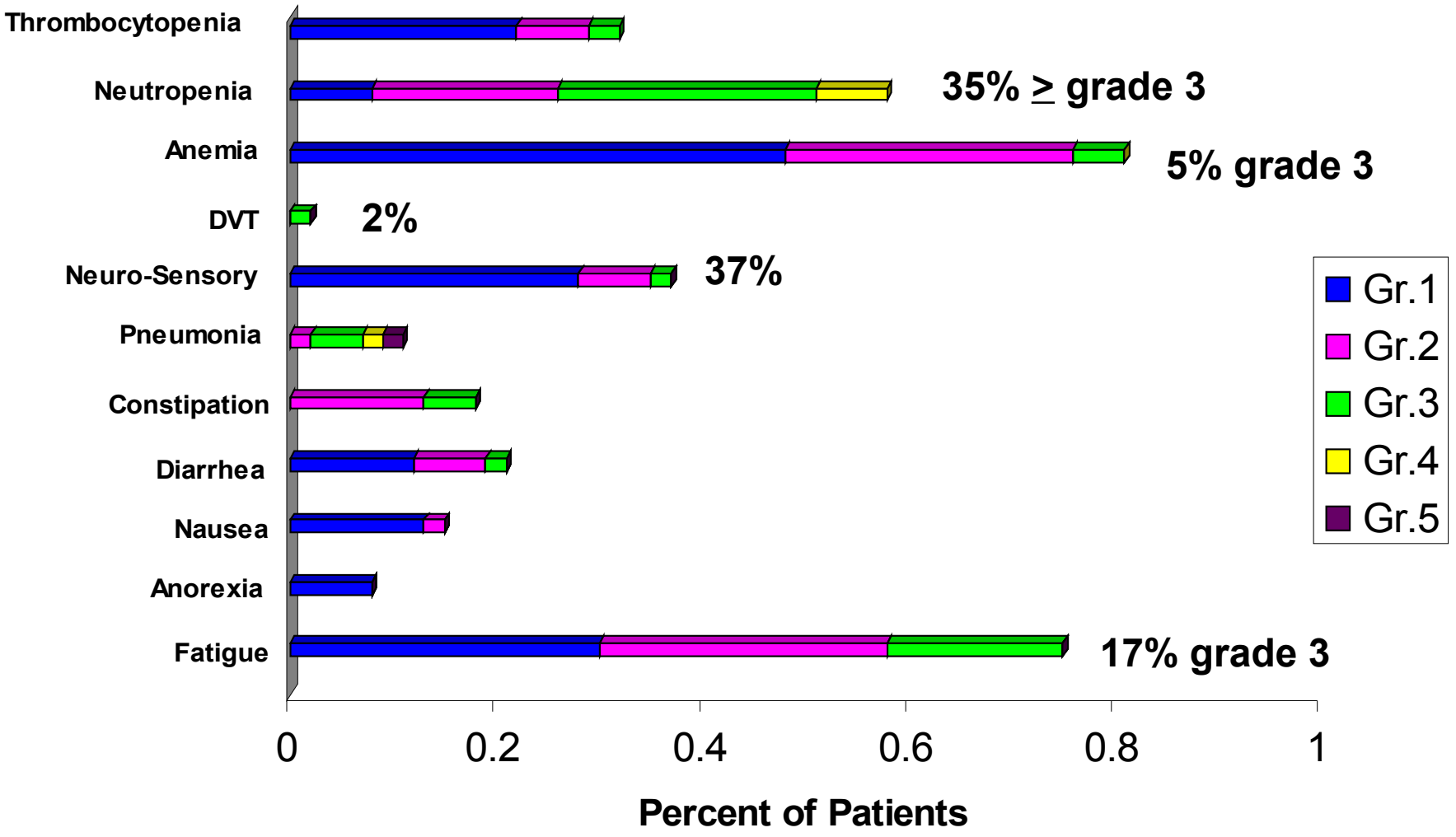
Toxicity



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Neutropenia

- Overall, 21 (35%) patients experience grade 3/4 neutropenia.
- All patients first experienced the neutropenia in cycle 1-3.
- No new patients experienced grade 3/4 neutropenia in cycle 4 or later.

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Treatment Administration

No. of Cycles Administered	399

Pomalidomide

 # Patients with Reductions — **11 (18%)**

- **Neutropenia**
- **Neuropathy**

Dexamethasone

 # Patients with Reductions — **24 (40%)**

- **Edema**
- **Hyperglycemia**
- **Confusion/Mood Alteration**
- **Muscle Weakness**

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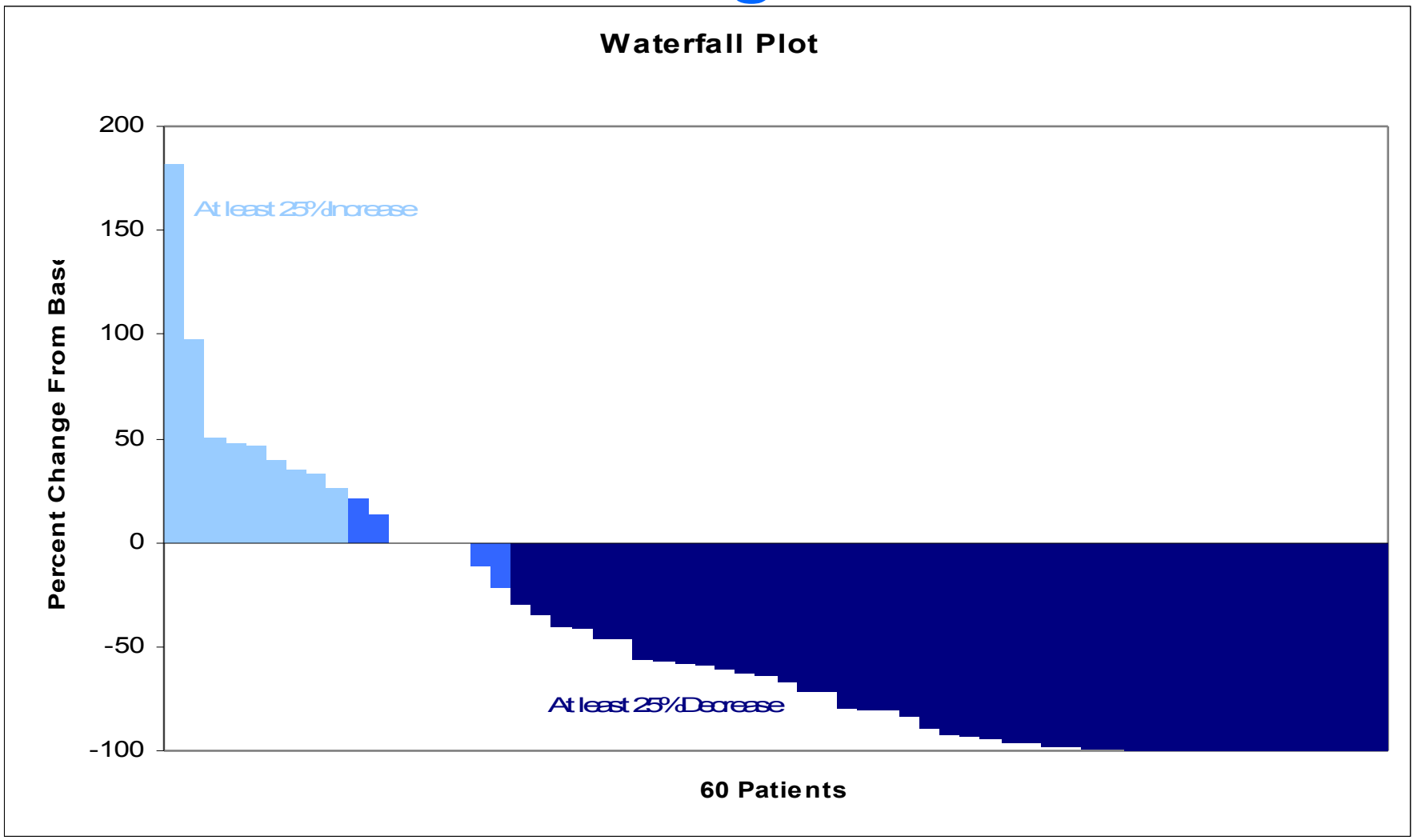
Measurable parameter as maximum % change from baseline



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Best Responses

Confirmed Response	IMWG* response criteria N= 60
CR	3 (5%)
VGPR	17 (28%)
PR	18 (30%)
SD	18 (30%)
PD	3 (5%)
NE	1 (2%)

CR +VGPR 33%

ORR 63%

Median follow-up 7 months

Kyle and Rajkumar Leukemia. January 2009

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Dose Escalation

- Escalation to 4 mg/day permitted if NR or if progressing if no grade 3/4 toxicity
- 4 patients escalated the dose to 4 mg/d
  - 1 VGPR
  - 2 SD
  - 1 Prog

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Responses in patients treated with other novel agents

	Previously treated	Refractory	≥PR in refractory patients
Bortezomib	20 (33%)	10	6 (60%)
Lenalidomide	21 (35%)	20	8 (40%)
Thalidomide	28 (47%)	16	6 (37%)

Refractory defined as progressing on therapy regardless of previous response

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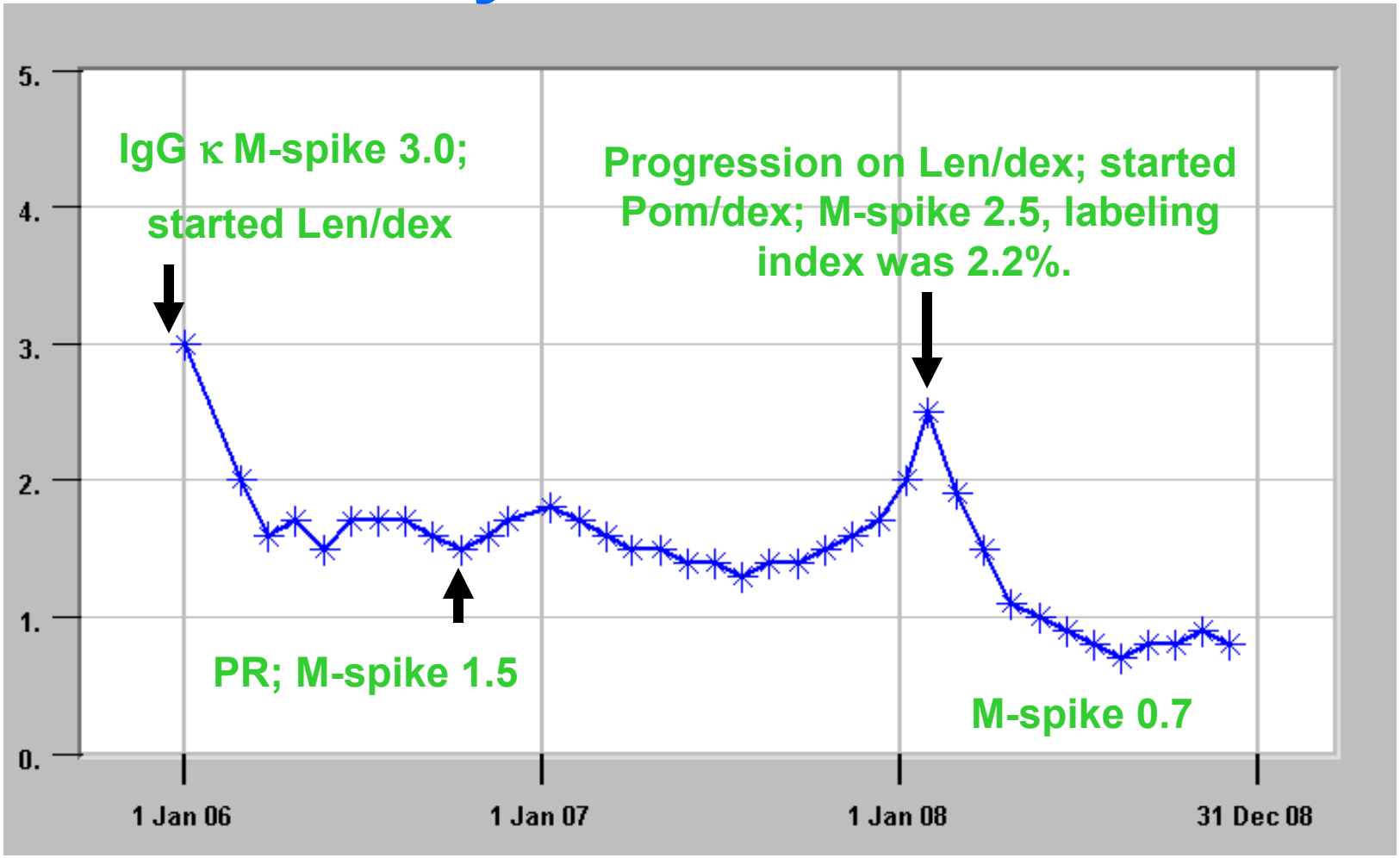
Patient 1, Lenalidomide refractory 69 year old male



Patients refractory to both Bortezomib and Lenalidomide

- 5 patients refractory to both Bortez and lenalidomide
  - 2 SD
  - 3 ≥ PR

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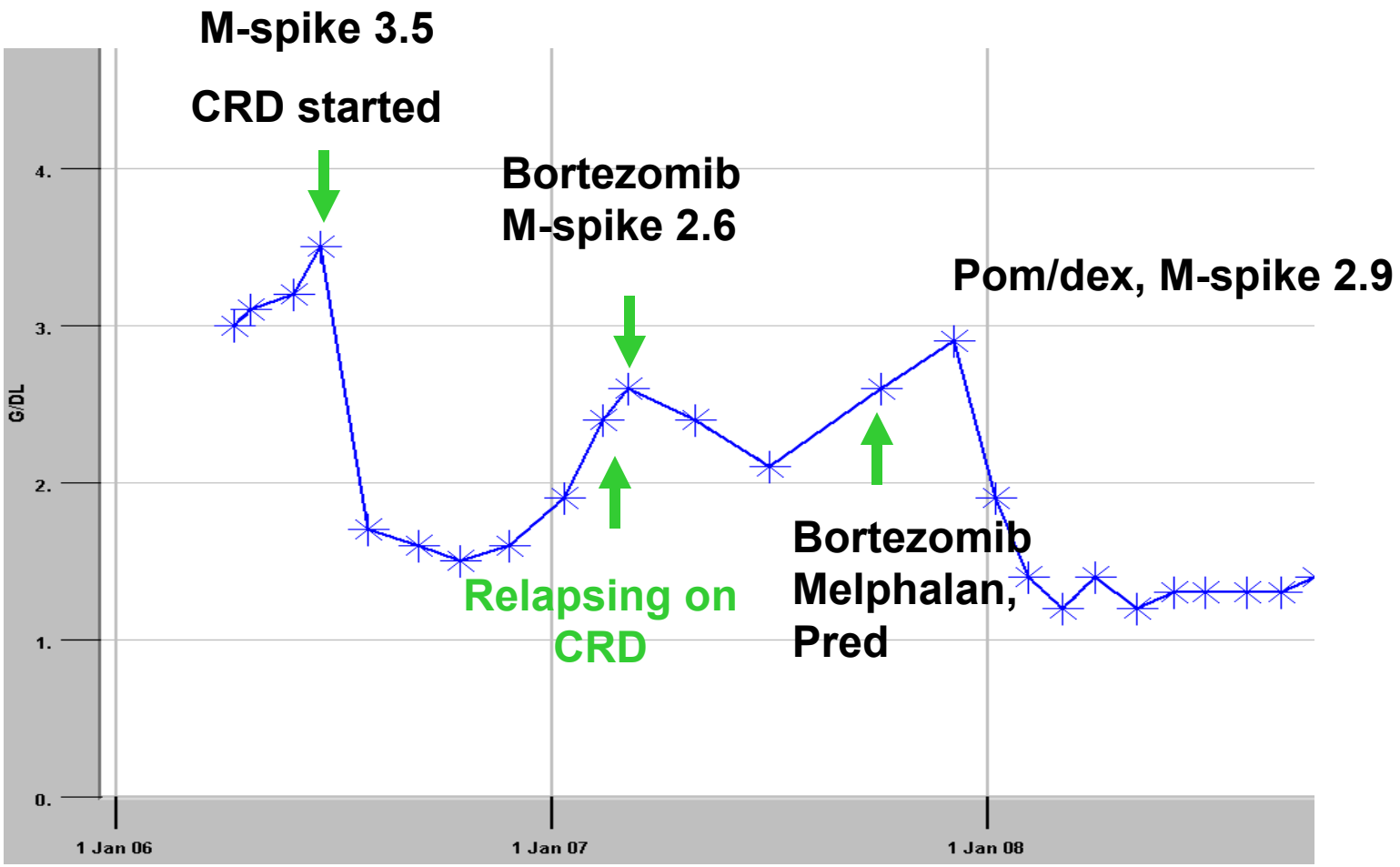
Patient 2, 67 year old female



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Follow-up

Continuation of treatment	Total
Currently Receiving Treatment	34 (57%)
Reason for Ending Treatment	
Disease Progression	19 (73%)
Died on Study	2 (8%)
Other - MD Discretion	5 (19%)
Deaths (2 on-study; 2 off)	**4**
Disease Progression	2
Unrelated (valvular heart disease)	1
Neutropenic sepsis	1

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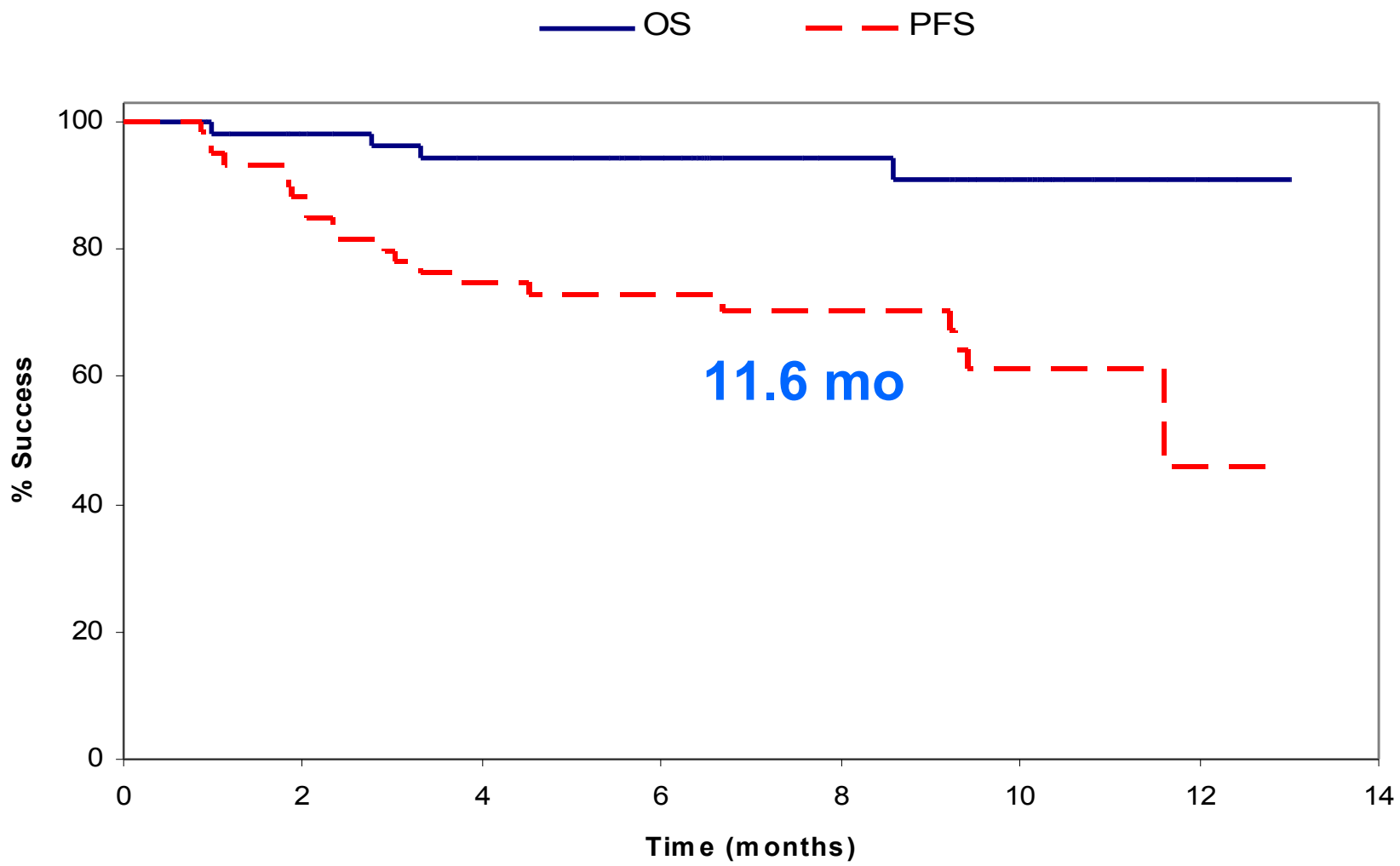
Overall and Progression free Survival



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Other Novel Agents for Relapsed Myeloma

	Regimen	Dex dose/cycle	DVT	ORR
Dimopoulos	Thal/dex	480 mg	7%	55%
Anagnostopoulos	Thal/dex	480 mg	8%	47%
Weber	Len/dex	480 mg	14%	61%
Dimopoulos	Len/dex	480 mg	11%	60%
Palumbo	VMPT	-	0	67%
Current Study	Pom/Dex	160 mg	2%	63%

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Conclusions

- The combination of Pom/dex is highly active in relapsed/refractory MM.
- Toxicity in our trial has been manageable and consists primarily of myelosuppression with neutropenia.
- Future directions include phase II trials
  - Pom/dex for lenalidomide- and bortezomib –refractory patients
  - trials using combination therapy

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Thanks for inviting me

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