Current Status of Pomalidomide in Myeloma

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Disclosures

- **Funding for clinical trials from Celgene**

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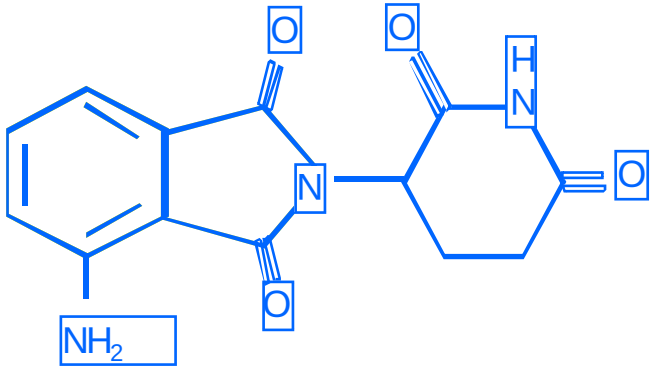
Background

- **Pomalidomide (POM) is a novel IMiD(R) immunomodulatory compound**
- **Although a chemical analog of thalidomide and lenalidomide, POM has distinctively different clinical efficacy and side effects**



Pomalidomide

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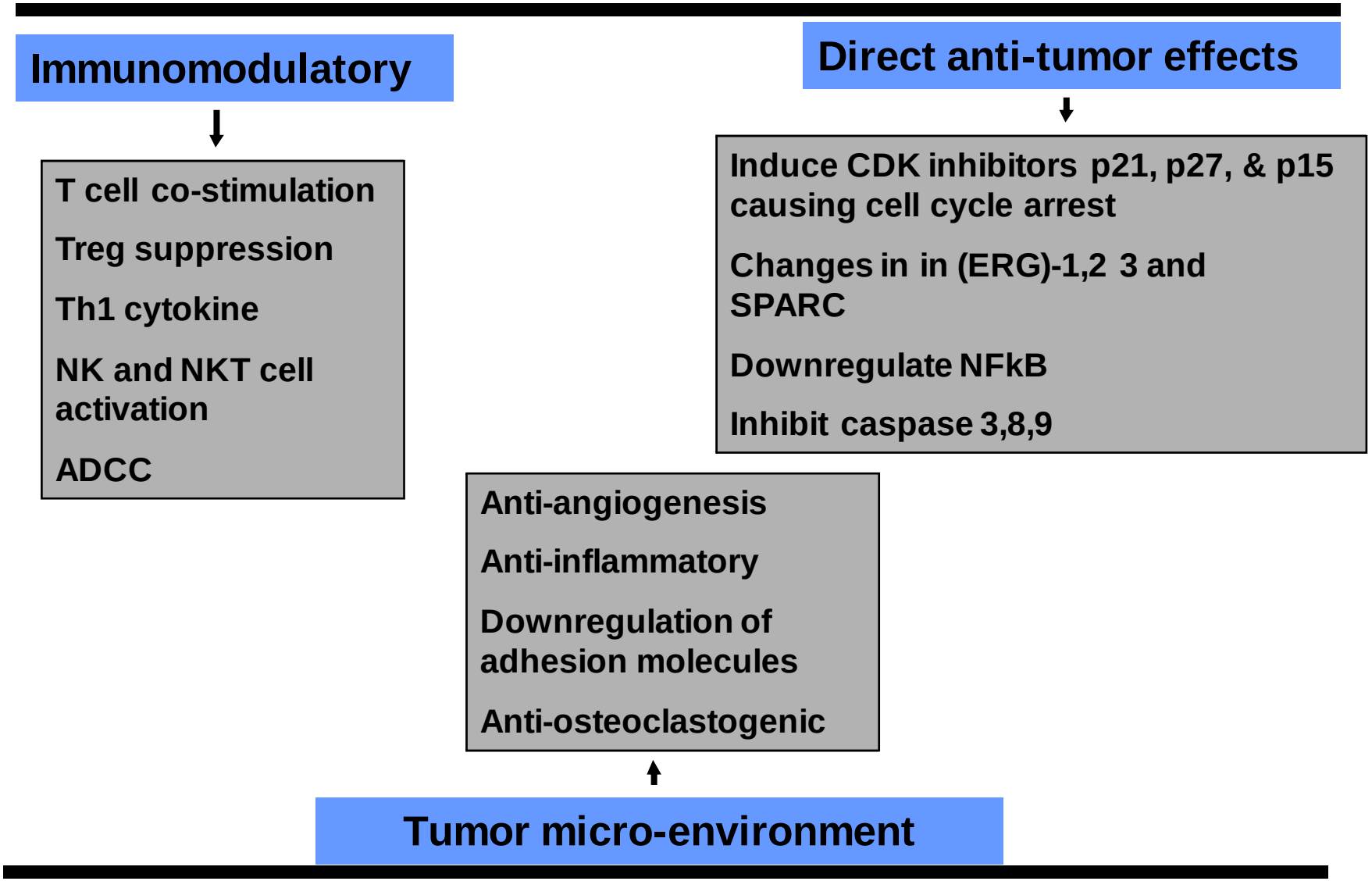
Proposed Mechanisms of Pom



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Phase I trials for Pomalidomide in relapsed myeloma

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

- Nine patients also received dexamethasone
- Accrued before novel agents routinely available

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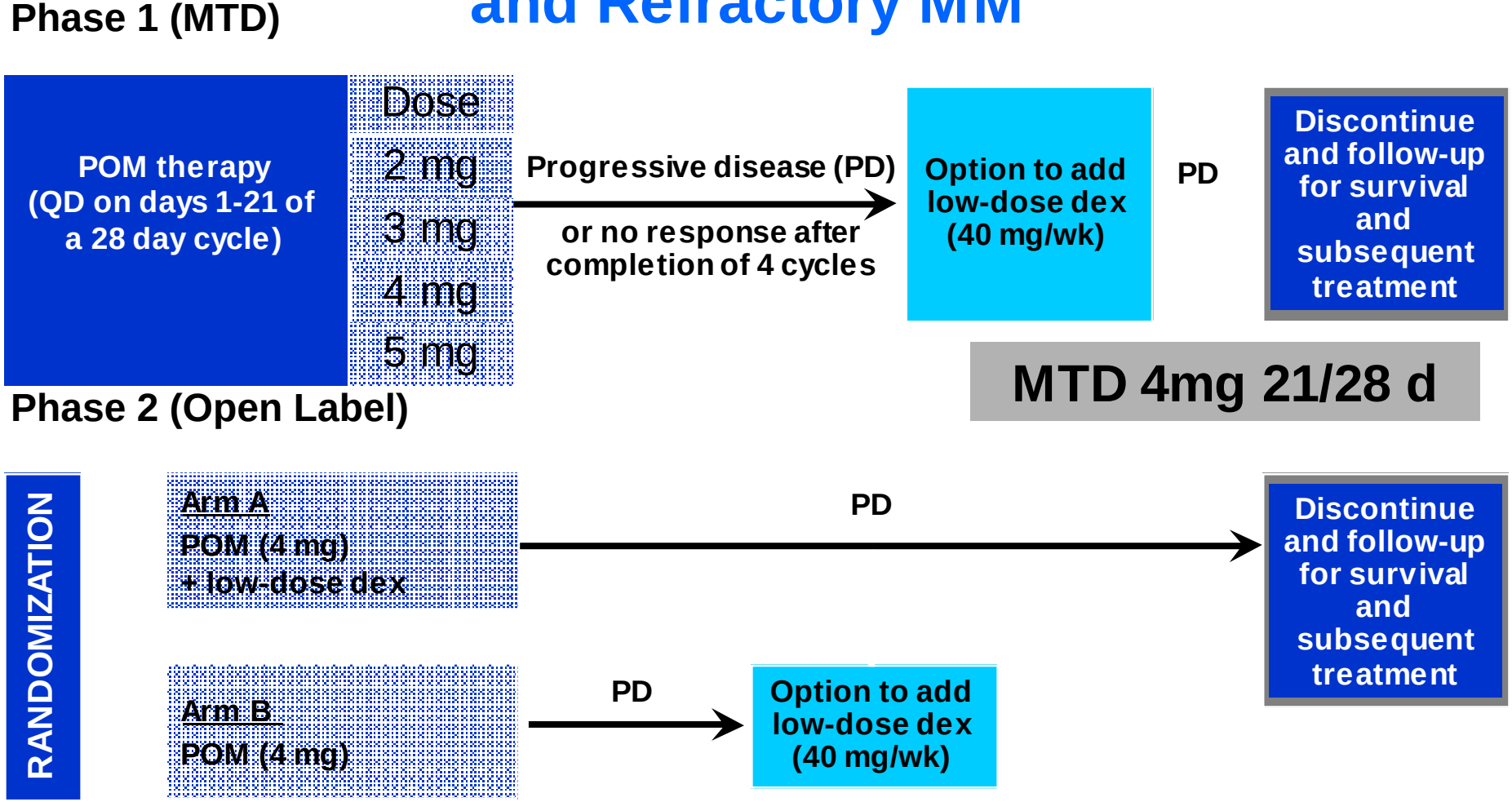
MM-002: POM ± Low-Dose Dex in Relapsed and Refractory MM



Concomitant Medications: anti-coagulants, G-CSF use after Cycle 1, erythroid growth factors, bisphosphonates, transfusions with platelet, RBCs as clinically indicated .

Richardson, P. G., et al. (2010) ASH Abstract 864.

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MM-002: Phase 2 Preliminary Results
Best Response (Aggregated Data)

N = 120	EBMT n (%)	IMWG n (%)
≥PR	**30 (25)**	**33 (28)**
CR	1 (1)	1 (1)
VGPR	N/A	6 (5)
PR	29 (24)	26 (22)
MR	16 (13)	N/A
SD	64 (53)	76 (63)
PD	10 (8)	11 (9)

CR: complete response; VGPR: very good partial response; PR: partial response; MR: minimal response; SD: stable disease; progressive disease

Richardson, P. G., et al. (2010) ASH Abstract 864.

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MM-002: Phase 2 Preliminary Results
Safety (Aggregated Data)

Grade 3/4 Events of Clinical Importance	Total (N = 120) %
Hematologic	
Neutropenia	42
Thrombocytopenia	22
Anemia	20
Febrile neutropenia	5
Non-Hematologic	
Infections	31
Fatigue	12
Renal failure	7
Cardiac disorders[a]	4
DVT	1
Peripheral neuropathy	0

a. Cardiac disorders include: atrial fibrillation, myocardial ischemia, CHF

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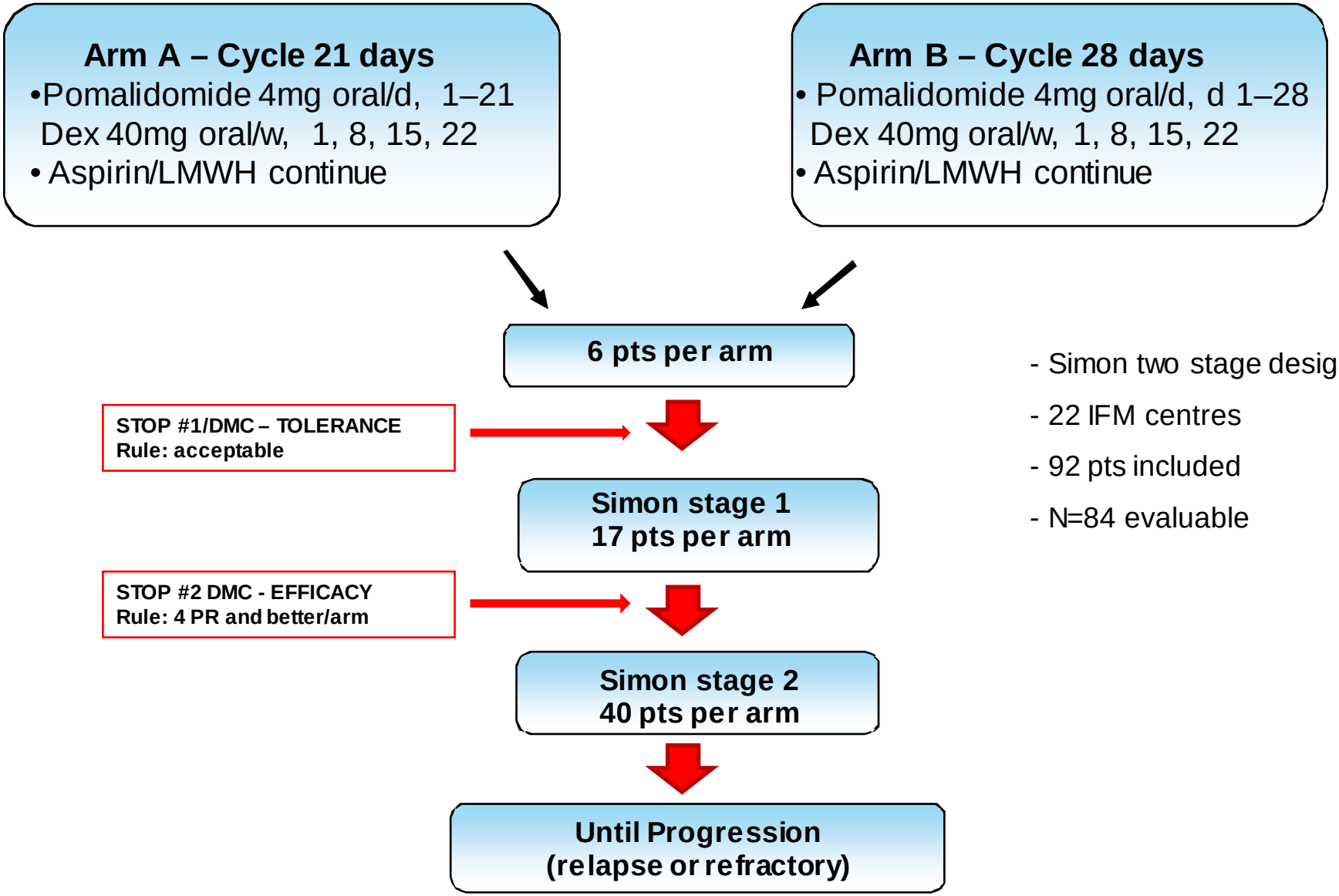
Phase 2 Study of 2 Modalities of Pomalidomide (CC4047) Plus Low-Dose Dexamethasone as Therapy for Relapsed Multiple Myeloma. IFM 2009-02



- Simon two stage design
- 22 IFM centres
- 92 pts included
- N=84 evaluable

Leleu, X., et al. (2010). ASH Abstract 859.

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Phase 2 Study of 2 Modalities of Pomalidomide (CC4047) Plus Low-Dose Dexamethasone as Therapy for Relapsed Multiple Myeloma. IFM 2009-02

Arm	A N=43	B N=41
Number of cycle, median	**5**	**5**
ORR (PR and better), N(%)	**18 (42)**	**16 (39)**
sCR	**0**	**0**
CR	**1 (2)**	**0**
VGPR	**3 (7)**	**2 (5)**
PR	**14 (32.5)**	**14 (34)**
Stable disease, N(%)	**20 (46.5)**	**21 (51)**
Progression, N(%)	**5 (12)**	**4 (10)**
Median, days (range)		
Time to first response	**54.5 (25-259)**	**28 (24-252)**
Time to best response	**56 (25-259)**	**48 (28-252)**
Duration of response	**119 (28-280)**	**126 (28-280)**

Leleu, X., et al. (2010). ASH Abstract 859.

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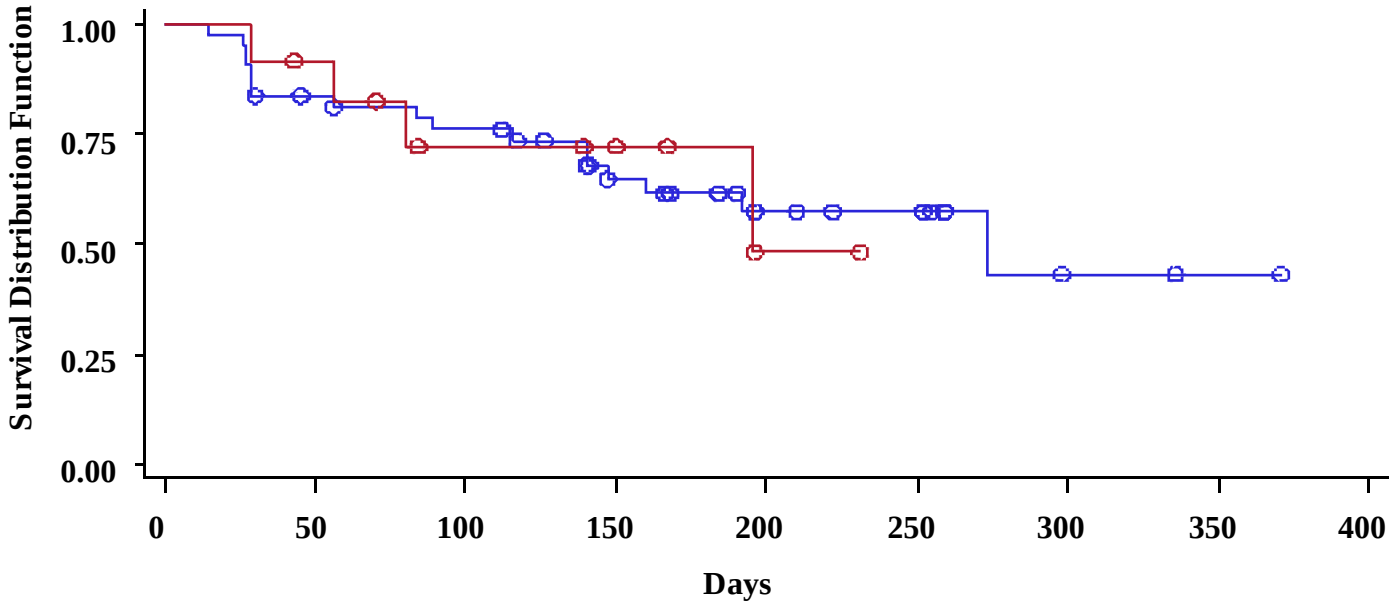
PFS according to Presence of del17p or t(4;14)



Arm	Del17p	t(4;14)	Total
A, (N)	5	0	5
B, (N)	4	3	7

	Del17p or t(4;14)	O/N	Median, days
	No	17/43	273 (147-)
	Yes	4/12	195 (56-)

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Hematological Adverse Events (≥ grade 3)

Arm	A N = 43	B N = 41
Grade 3 and more, N	**122**	**141**
% / All AE	**23.5**	**26.5**
% / All AE ≥grade 3	**66**	**76**
Hb<= 8 g/dL, N (%)	**21 (11)**	**26 (14)**
PNn<= 1 x10^9/L, N (%)	**62 (34)**	**62 (33.5)**
Plat<= 50 x10^9/L, N (%)	**34 (18)**	**39 (21)**
Support (at least once per patient), N (%)		
EPO	**14 (32.5)**	**14 (34)**
G-CSF	**13 (30)**	**18 (44)**
Red cell transfusion	**12 (28)**	**14 (34)**
Platelet transfusion	**7 (16)**	**7 (17)**

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Non Hematological Adverse Events (≥ grade 3)

Arm	A N = 43	B N = 41
Grade 3 and more, N (% / All AE)	**63 (12)**	**54 (9)**
Neuropathy, N	**0**	**0**
DVT (with DVT prophylaxis)	**0**	**0**
Anorexia	**0**	**1**
Asthénia	**4**	**2**
Bronchitis	**1**	**1**
Cramps	**0**	**2**
Diarrhea	**0**	**2**
Generalized pain	**1**	**1**
Chest pain	**1**	**1**
Dyspnea	**1**	**0**
Fever	**1**	**0**
Hyperglycemia with diabetis	**1**	**0**
Hypokaliemia	**1**	**0**
Hypotension orthostatic	**1**	**0**
Lombalgia	**0**	**1**
Pneumonia	**1**	**1**
Caugh	**1**	**0**
Other	**48**	**42**

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Mayo Myeloma Pomalidomide Trials, 225 patients

Cohort	Group	Dose mg/day	N	Accrual dates
1	Relapsed < 4 prior reg	2	60	Nov 2007 - Aug 2008
2	Len refractory	2	34	Nov 2008 - April 2009
3	Bortez/Len refractory	2	35	May 2009 - Nov 2009
4	Bortez/Len refractory	4	35	Nov 2009 - April 2010
5	Len refractory <4 prior reg	4	61	May 2010 – Nov 2010

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Patient Characteristics

	2mg Relapsed <4 Reg N=60	2mg Len Refrac-tory N=34	2mg Bortez/ Len Refrac-tory N=35	4mg Bortez/ Len Refrac-tory N=35	4mg Len Refrac-tory <4 Reg N=61	Total N=225
Median Age (years)	66	62	62	61	65	63
Months from Diagnosis to On-study (Months)	46	62	57	72	37	53
mSMART High Risk	32%	42%	56%	60%	25%	39%

High risk defined as deletion17p, t(4;14), or t(14;16) by FISH or deletion 13 by conventional cytogeneticsor PCLI $\geq$3%

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Prior therapies

	2mg Relapsed <4 Reg N=60	2mg Len Refrac-tory N=34	2mg Bortez/ Len Refrac-tory N=35	4mg Bortez/ Len Refrac-tory N=35	4mg Len Refrac-tory <4 Reg N=61	Total N=225
# of Prior Therapy Median (range)	2 (1-3)	4 (1-14)	6 (3-9)	6 (2-11)	2 (1-5)	3 (1-14)
<u>Prior Therapy</u>						
Previous ImiDs	60%	100%	100%	100%	100%	89%
Thalidomide	47%	38%	63%	76%	21%	53%
Lenalidomide	35%	100%	100%	100%	98%	82%
Bortezomib	33%	59%	100%	100%	48%	62%
Transplant	65%	68%	77%	80%	77%	73%

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Follow-up

	2mg Relapsed <4 Reg N=60	2mg Len Refrac-tory N=34	2mg Bortez/Len Refractory N=35	4mg Bortez/Len Refractory N=35	4mg Len Refrac-tory <4 Reg N=61	Total N=225
Accrual Period	11/07-08/08	11/08-4/09	5/09-11/09	11/09-4/10	5/10-11/10	
Progression Free	33%	21%	26%	31%	61%	37%
Alive	80%	62%	54%	57%	93%	73%
Months of Follow-up for Alive Patients						
Median (Range)	29 (1-36)	22 (5-25)	15 (1-20)	9 (1-12)	6 (1-10)	10 (1-36)
Cycles Administered						
Median (Range)	12 (1-38)	5 (1-25)	6 (1-19)	3 (1-12)	5 (0-10)	6 (0-38)
Currently Receiving Treatment	25 %	12%	11%	9%	46%	24%
Off Rx for Prog.	82%	87%	84%	69%	67%	78%

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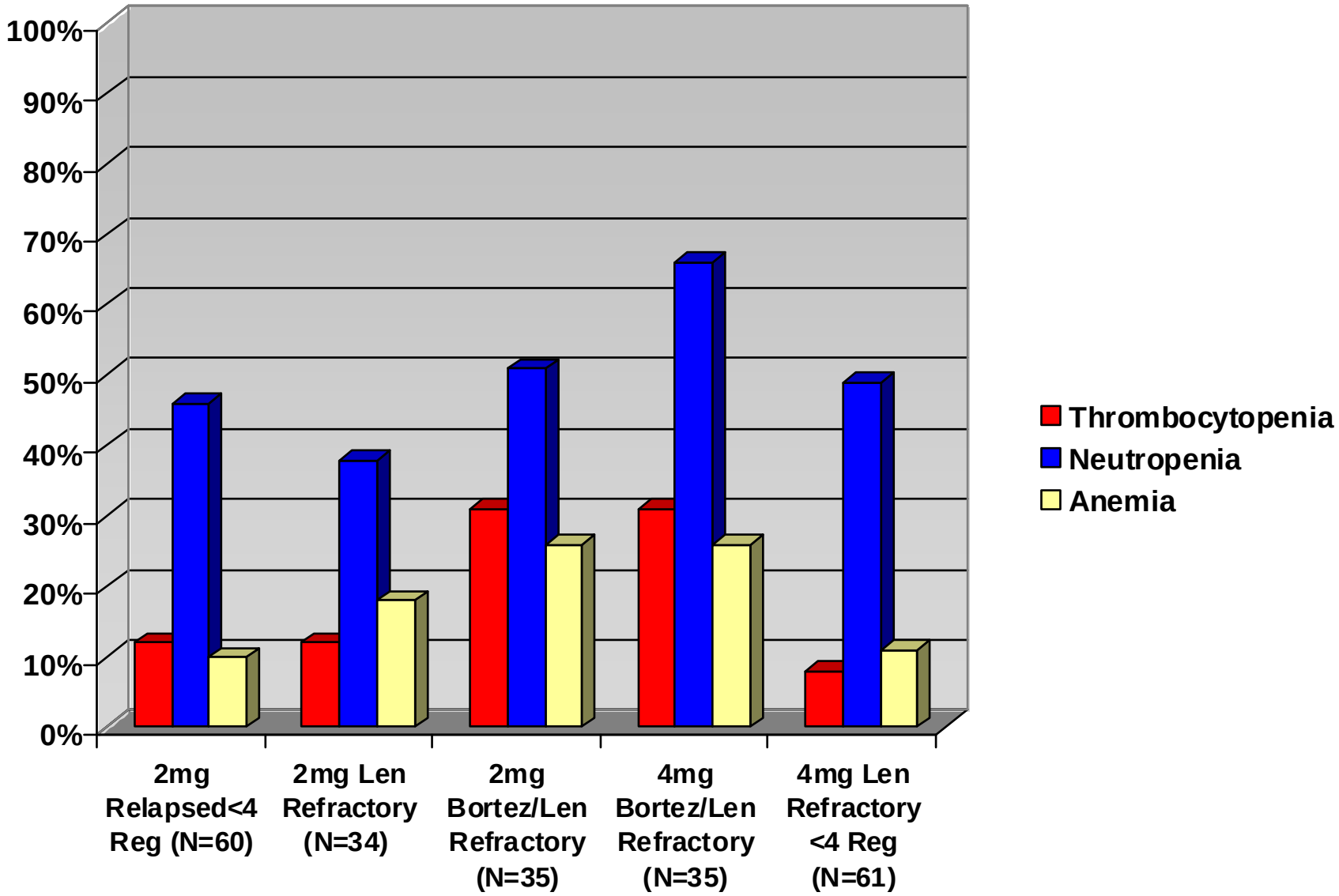
Hematologic Adverse Events, ≥ grade3



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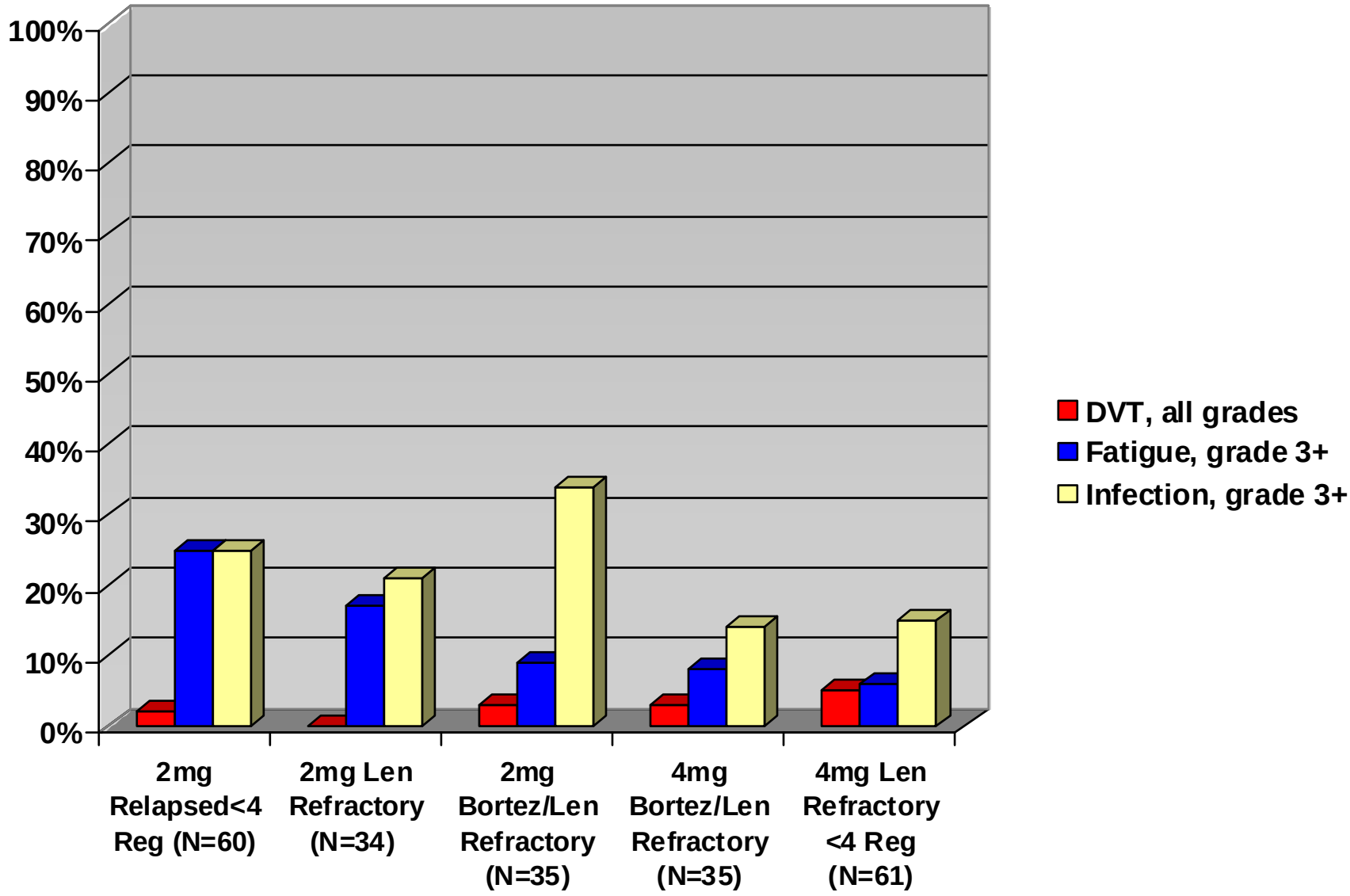
Non-Hematologic Adverse Events



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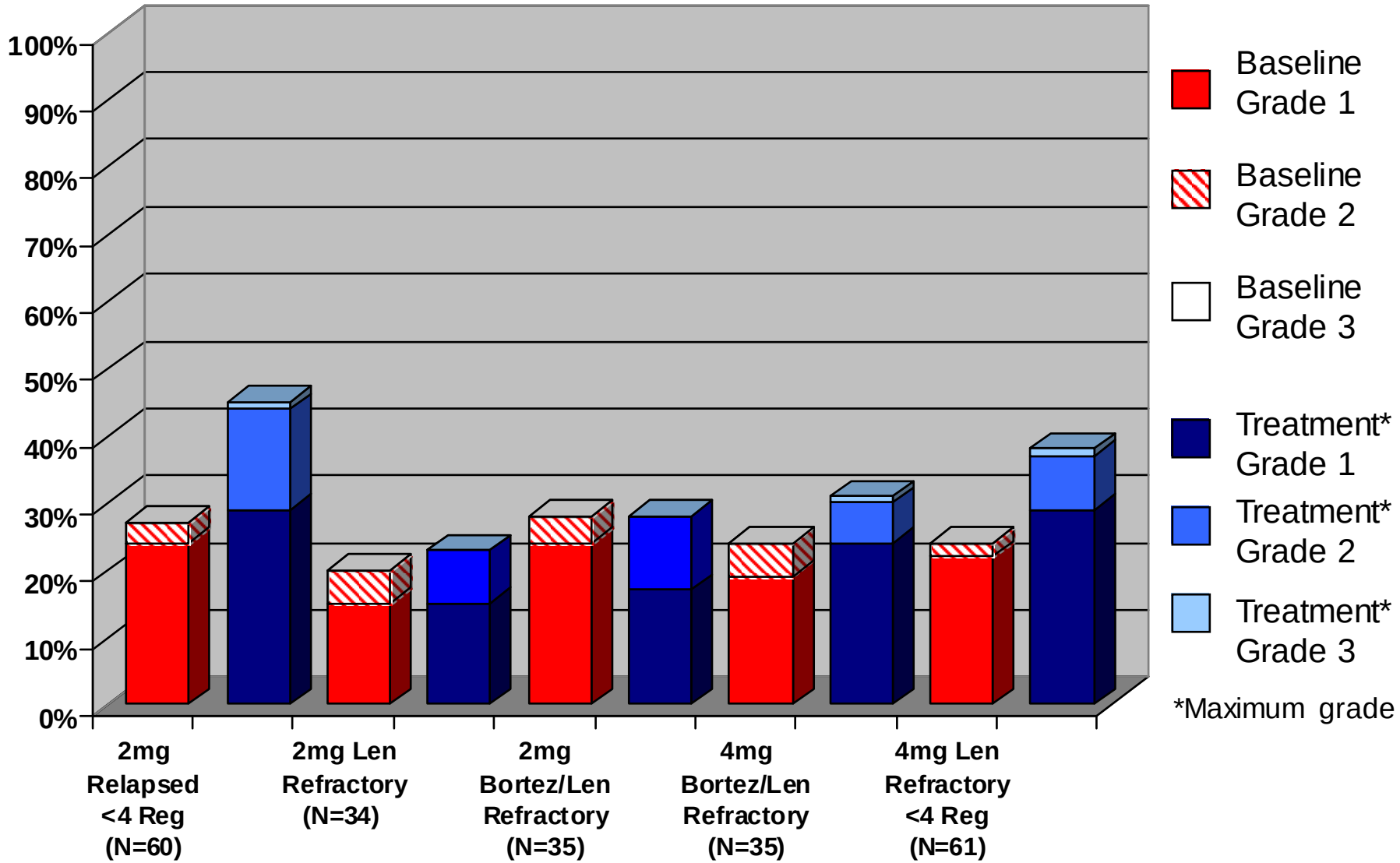
Neuropathy



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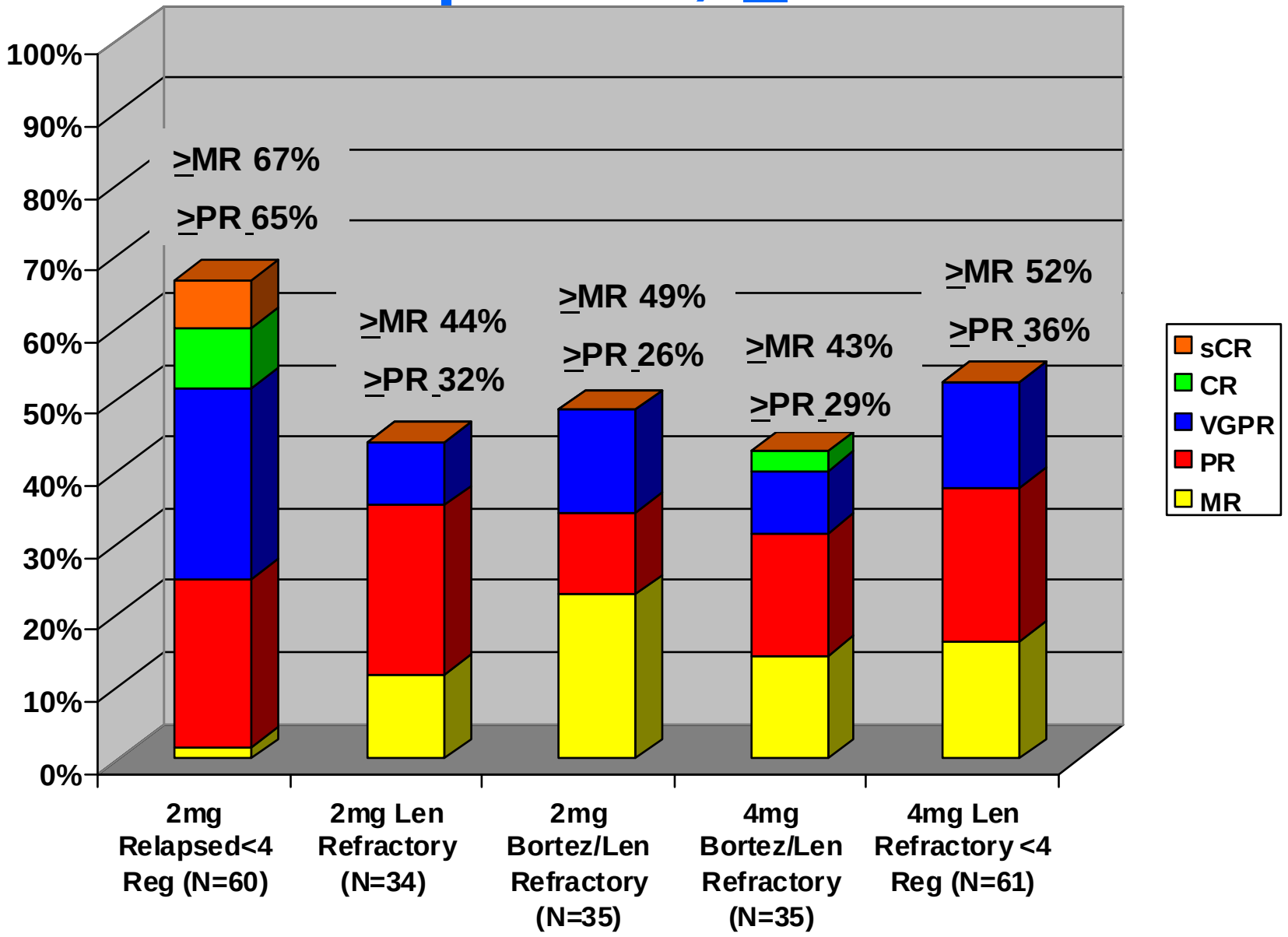
Responses, ≥ MR



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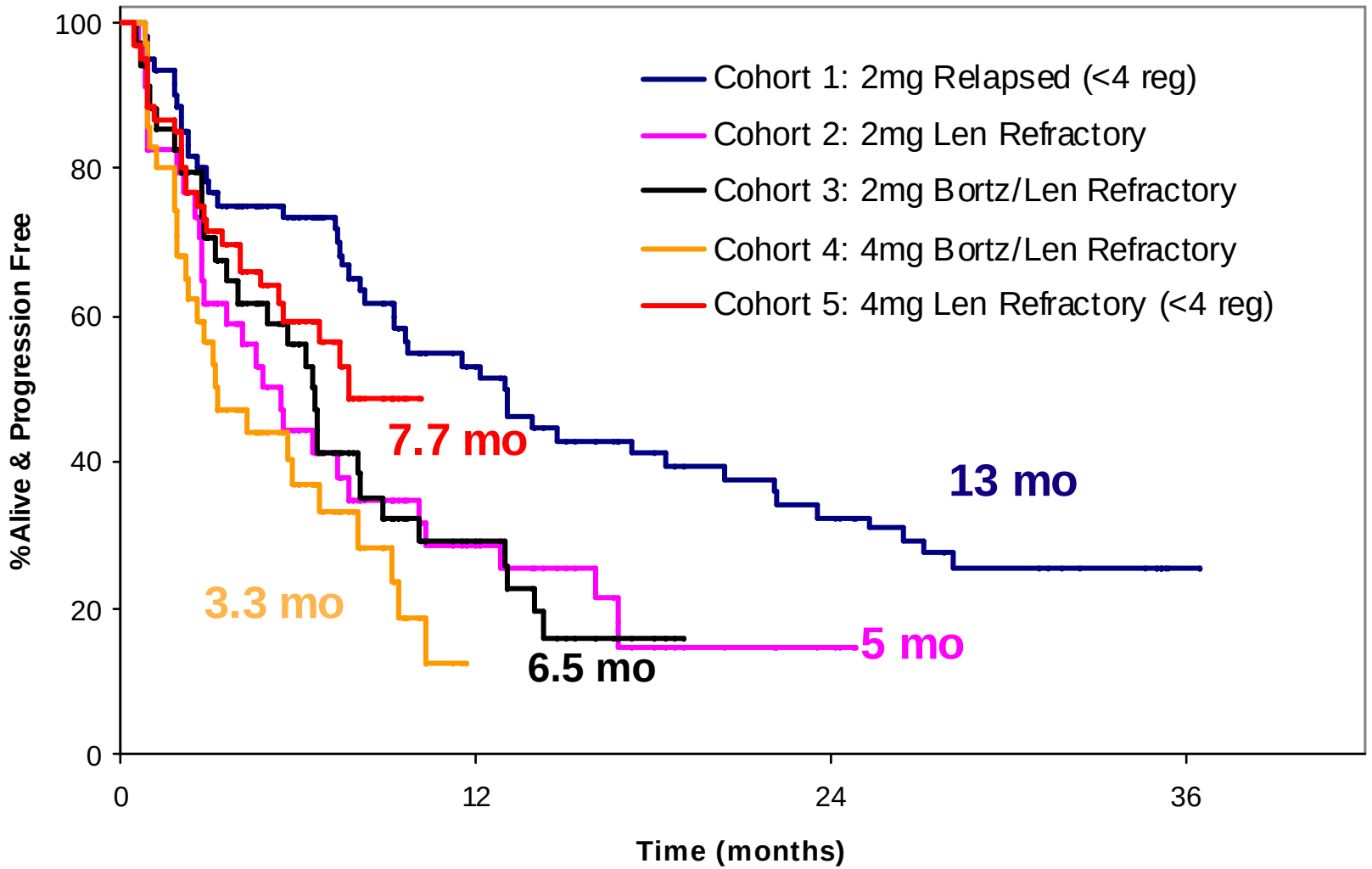
Progression Free Survival



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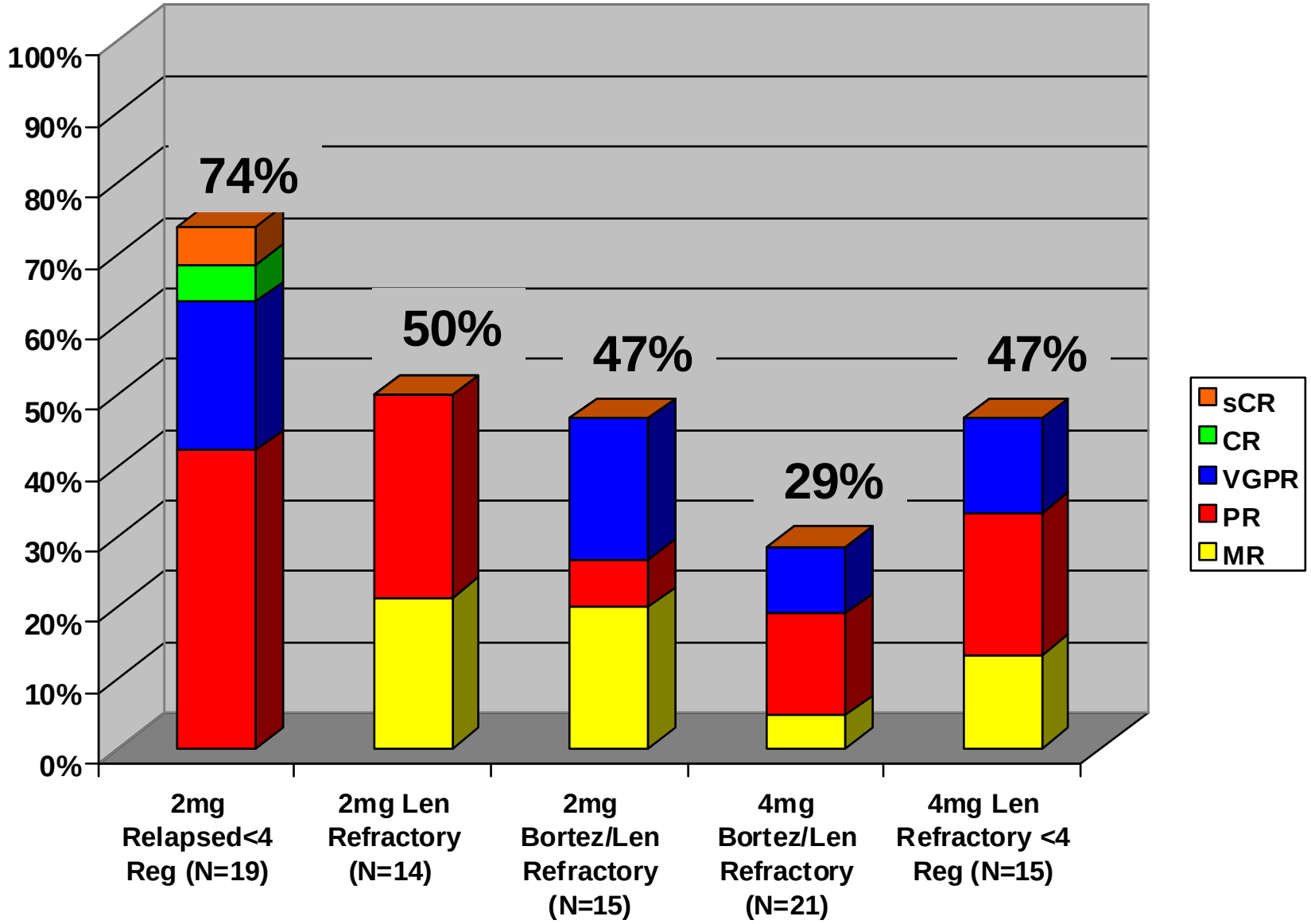
Responses in high risk (mSMART) patients



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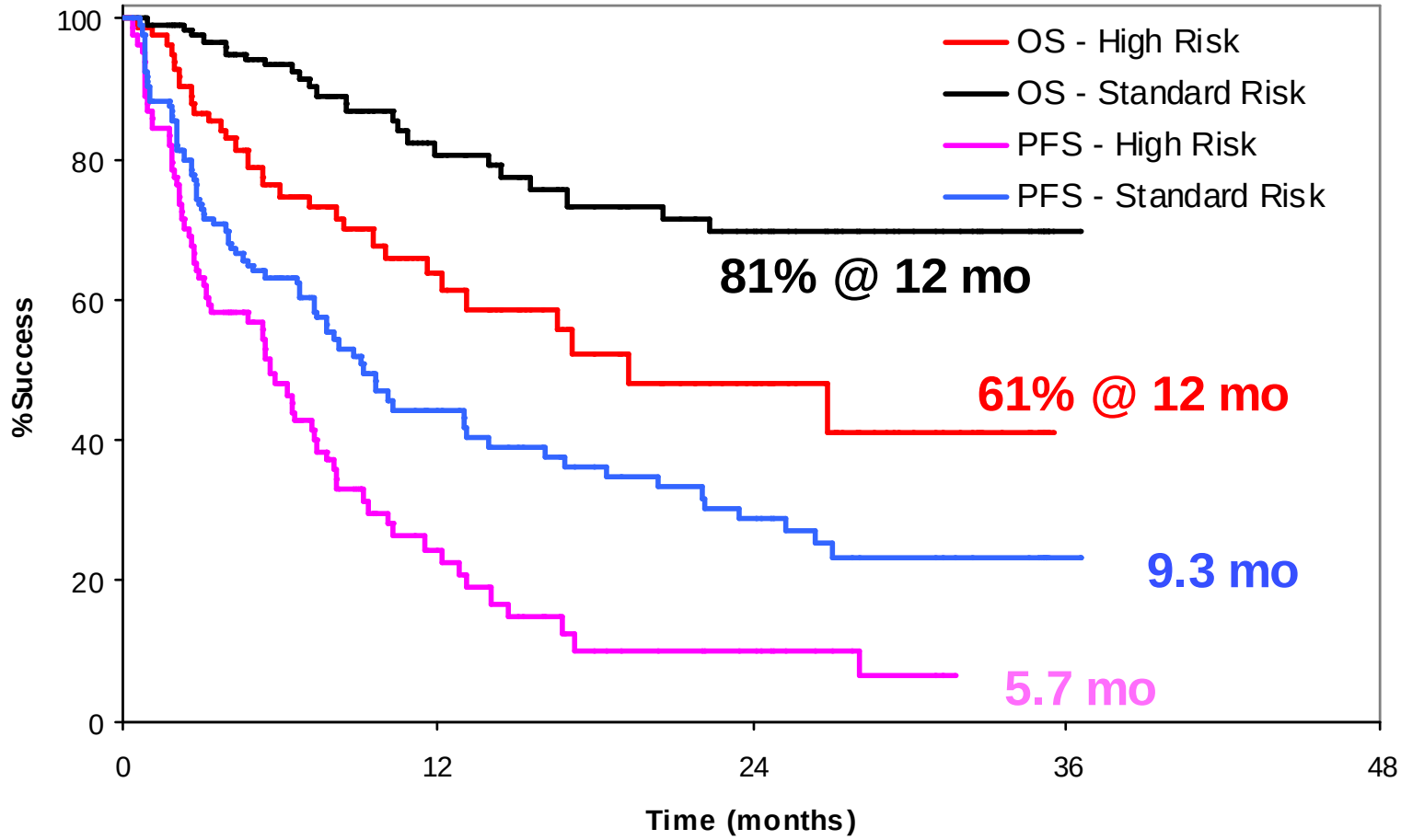
Overall and PFS in high risk vs standard risk



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Patient Outcomes

	2mg Relapsed <4 Reg N=60	2mg Len Refrac-tory N=34	2mg Bortez/Len Refractory N=35	4mg Bortez/Len Refractory N=35	4mg Len Refrac-tory <4 Reg N=61
Duration of response	21 mo (95%CI:11.2-NR)	9 mo (95%CI: 2 -NR)	NR	3 mo (95%CI:1-NR)	NR
Median Overall Survival	NR	27 mo (95%CI: 11-27)	17 mo (95%CI:10-NR)	NR	NR
6 Months OS	95% (95%CI:89-100)	85% (95%CI: 74-98)	76% (95%: 63-92)	67% (95%CI: 52-85)	94% (95%CI: 86-100)
Median Progression Free Survival	13 mo (95%CI:8-20.4)	5mo (95%CI : 2.7-10)	6.5mo (95%CI: 3-9)	3.3mo (95%CI: 1.9-7)	7.7 mo (95%CI: 5.4-NR)

NR: Not Reached; Mo: Months; CI: Confidence Interval

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Pom/dex for EMD

- EMD present in 13 of first 174 (7.5%) enrolled
- Response to Pom/dex 31% (2 CR and 2 PR)

Detweiler Short, *Leukemia*, 2011

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Response Rates with Pom/Dex According to Number of Prior Regimens

	# Prior regimens, median	N	Schema	Doses	≥ PR
Relapsed < 4 Reg	2	60	28/28	2 mg	63%
Len Refractory <4 Reg*	2	61	28/28	4mg	36%
Leleu	4	43	21/28	4 mg	42%
	4	41	28/28	4mg	39%
Len Refractory	4	34	28/28	2 mg	32%
Richardson Phase II	5	120	21/28	4 mg	25%
Richardson Phase I	6	38	21/28	4 mg MTD	25%
Bortez/Len	6	35	28/28	2 mg	26%
Refractory	6	35		4mg	28%

*Median Follow-up: 6 months

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Conclusions

- Pom/dex has remarkable activity in relapsed myeloma including heavily pre-treated population who are refractory to lenalidomide and bortezomib
- Responses are rapid with median time to response 1 - 2 month
- Toxicity is manageable at both dose levels and consists primarily of neutropenia
- No evidence for dose response within the tested dose schedules; ORR is similar between the 2 mg and 4 mg dose levels
- Effective in high risk patients
- Further studies ongoing to see if starting dose 4 mg for 21 of 28 days produces same response rates with less toxicity
- Pomalidomide combinations should be explored.

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Thanks for inviting me

Myeloma group at Mayo

- **Rochester**
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