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Management of Myeloma at Relapse

A. Keith Stewart

Scottsdale, Arizona

Rochester, Minnesota

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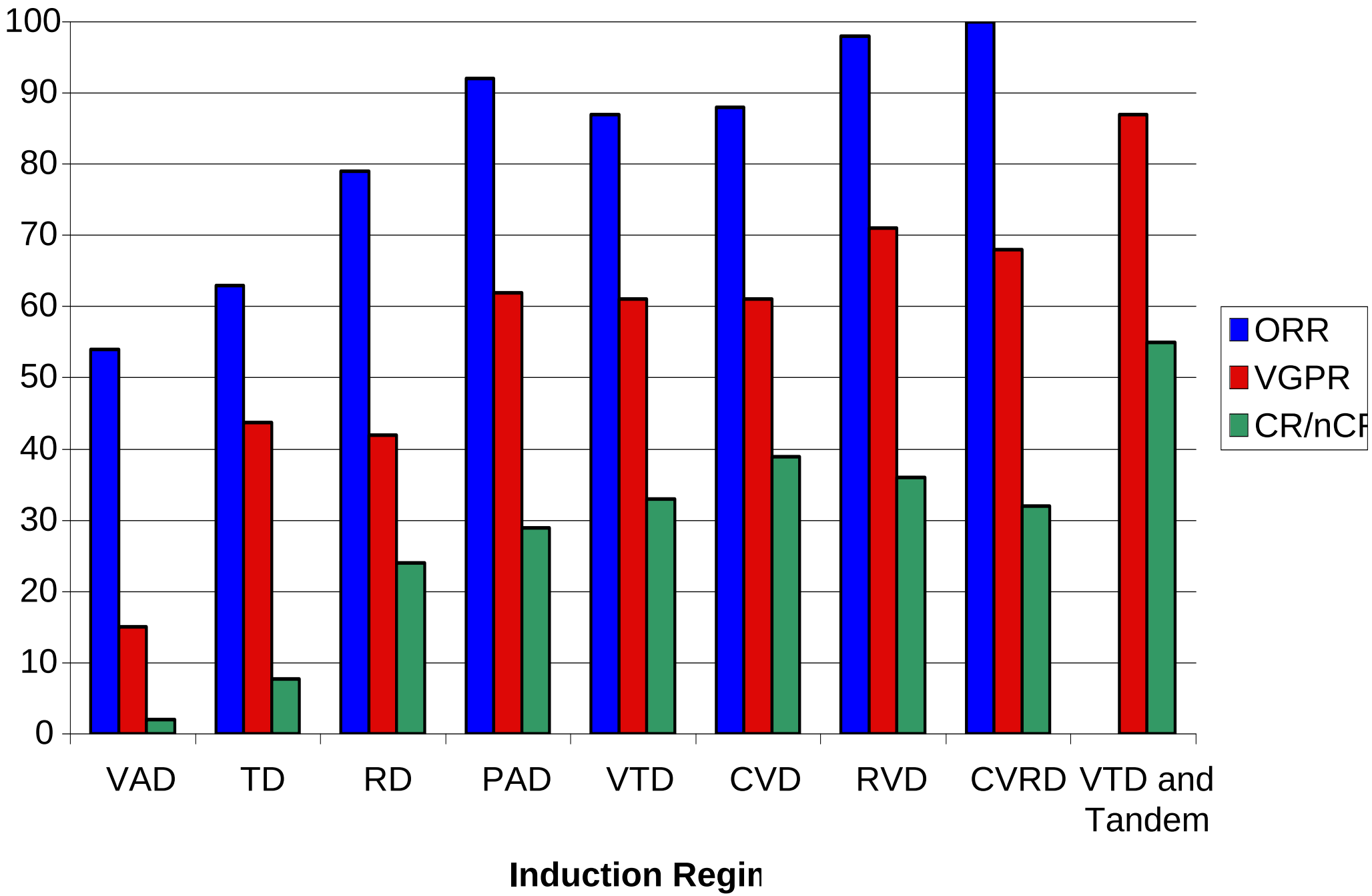
100
90
80
70
60
50
40
30
20
10
0
VAD
TD
RD
PAD
VTD
CVD
RVD
CVRD
VTD and Tandem
ORR
VGPR
CR/nCR
Induction Regin

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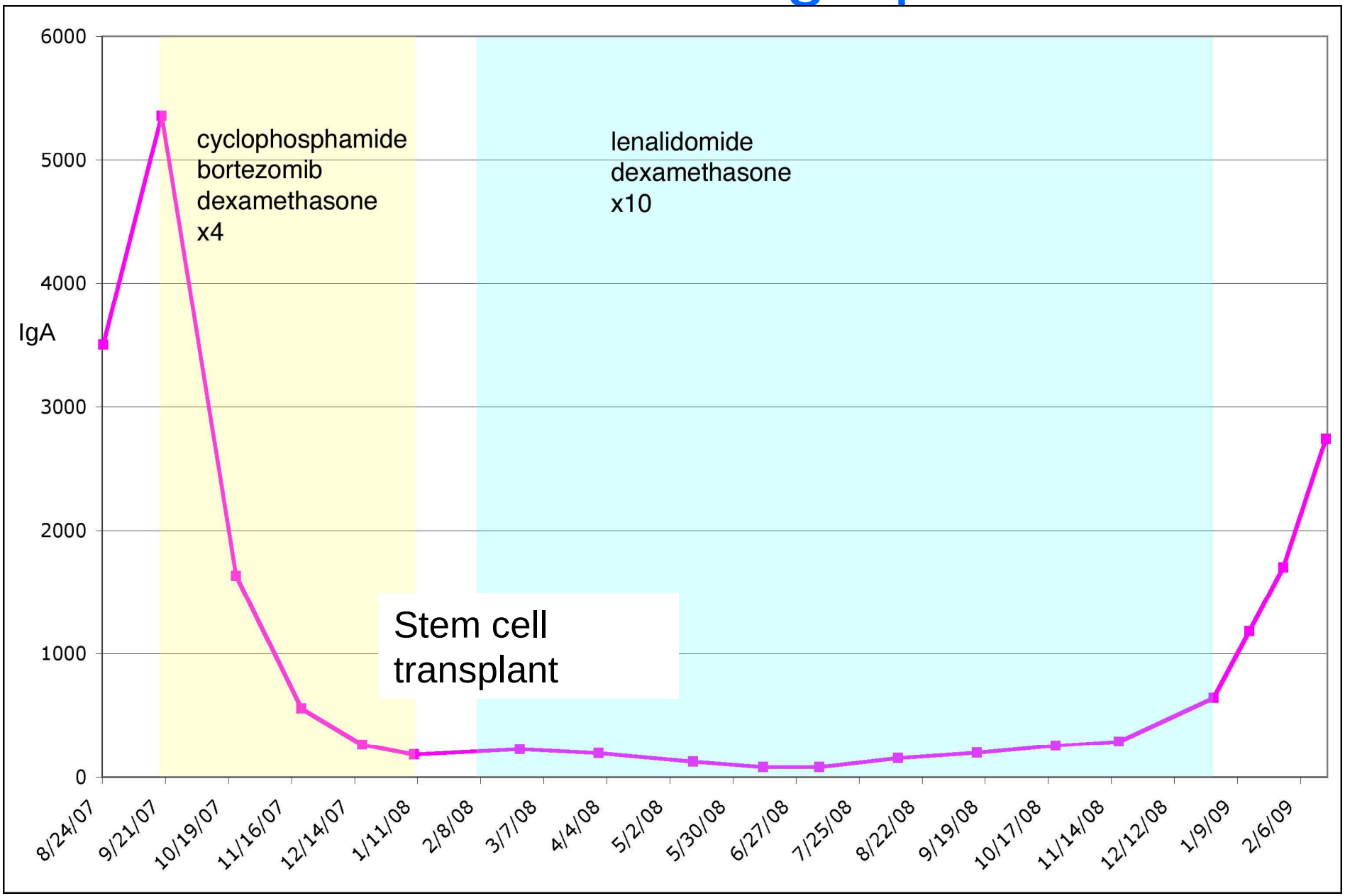
Clinical course graphic



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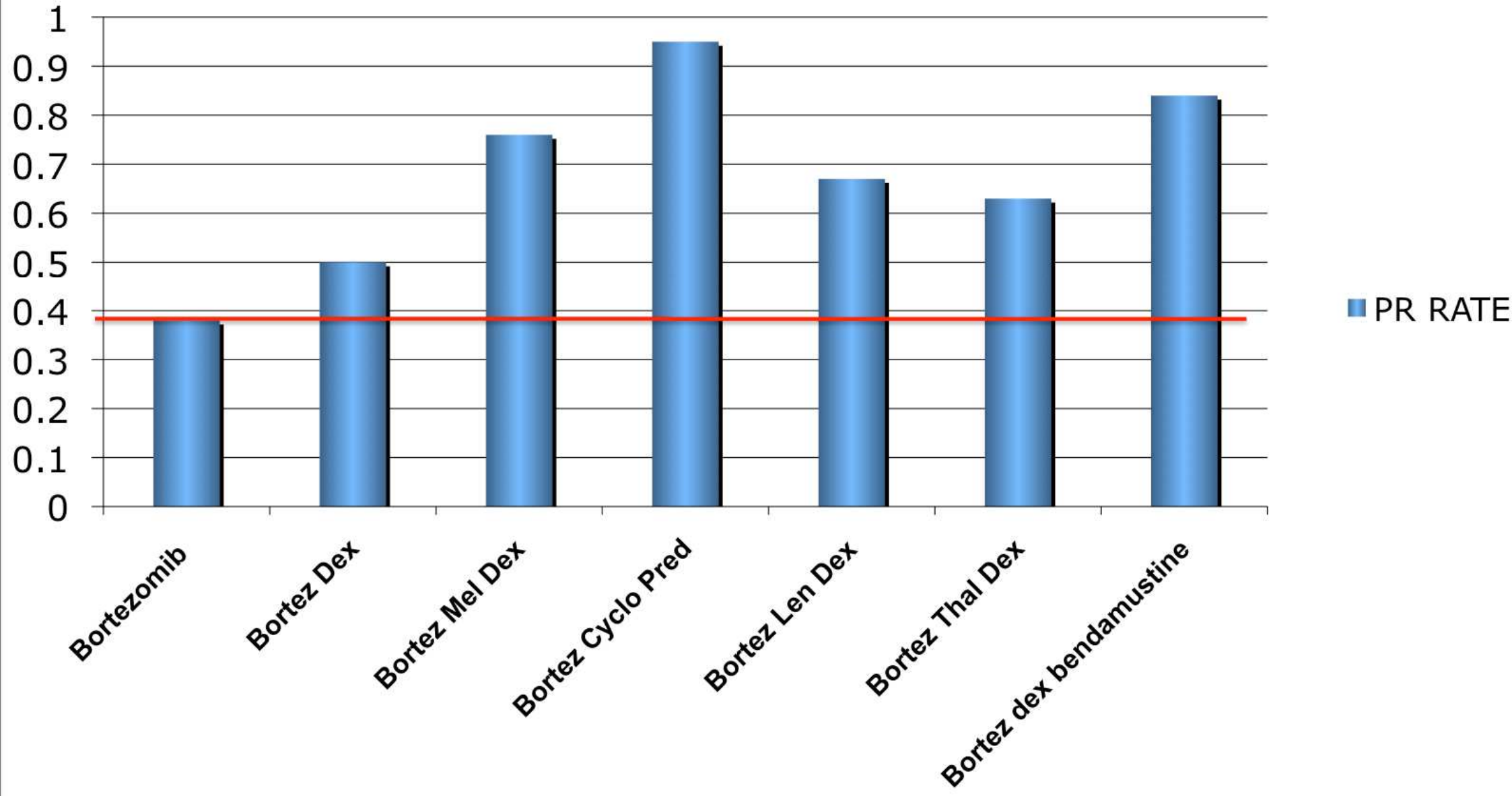
Approach to Treatment at Relapse Must Be Individualized

- Tempo of disease
- Previous toxicities and response
- Time of previous remission
- Pragmatic concerns (access, geography, age, preference)

To sequence or to combine existing approved drugs ?

Increasing Response Rates With Combination Therapy

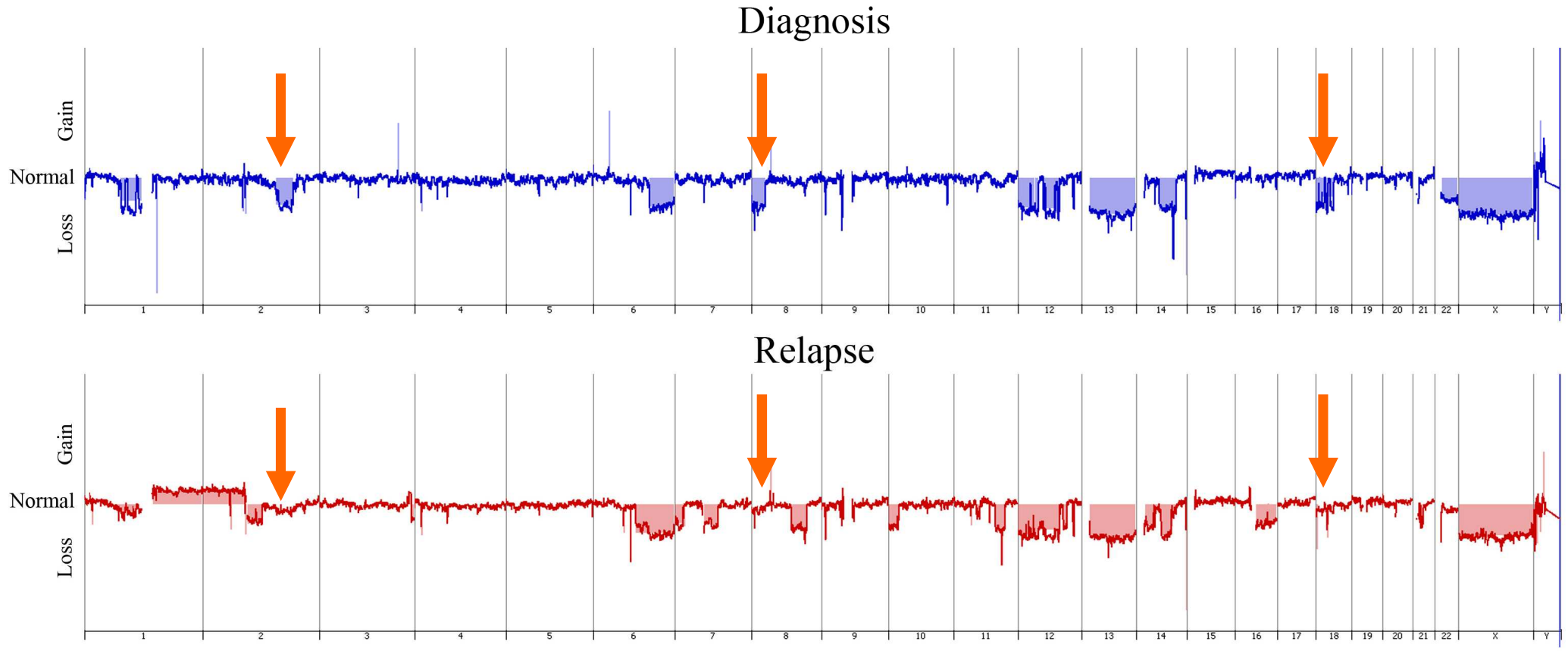


Treatment at Relapse

In general combinations outperform sequencing in randomized trials (faster response, higher overall response rates, improved progression free and /or overall survival)

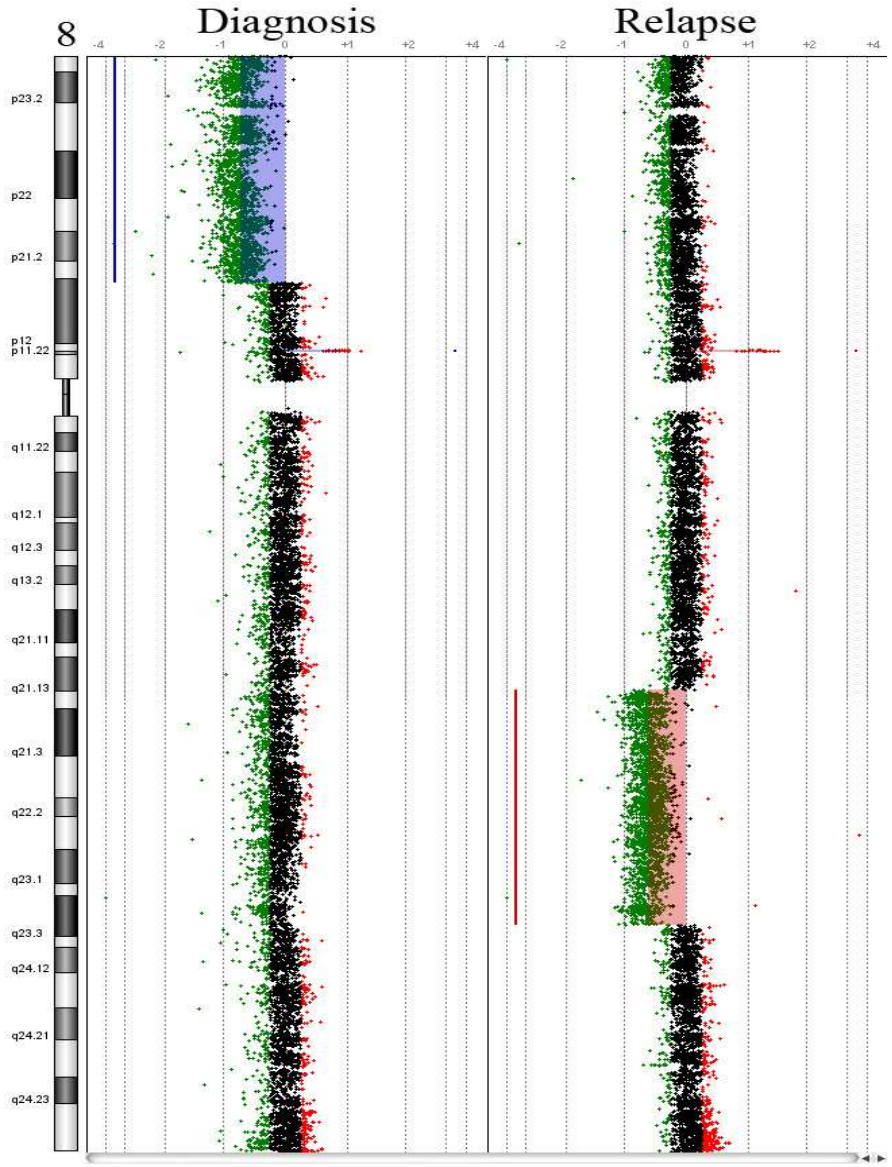
- MPV versus MP
- MPT versus MP
- RD versus D
- MPR versus MP
- VTD versus TD

Whole Genome Comparison of Diagnostic and Relapse Samples



2,733 ~9% of all genes potentially changed at relapse

Unique Genomes are Present in the Two Samples



Conclusions

1. **In general combinations outperform sequencing in randomized trials (faster response, higher overall response rates, improved survival)**

2. **In high risk disease multiple genomic clones**

In rapidly relapsing, symptomatic or high genetic risk patients favor combination therapy.

In indolent relapse, elderly and particularly in low genetic risk disease more conservative therapy sequencing otherwise reasonable.

What about New Drugs ?

180 drugs reported in preclinical studies

~ 30 - 40 in trials

3 with known significant single agent activity

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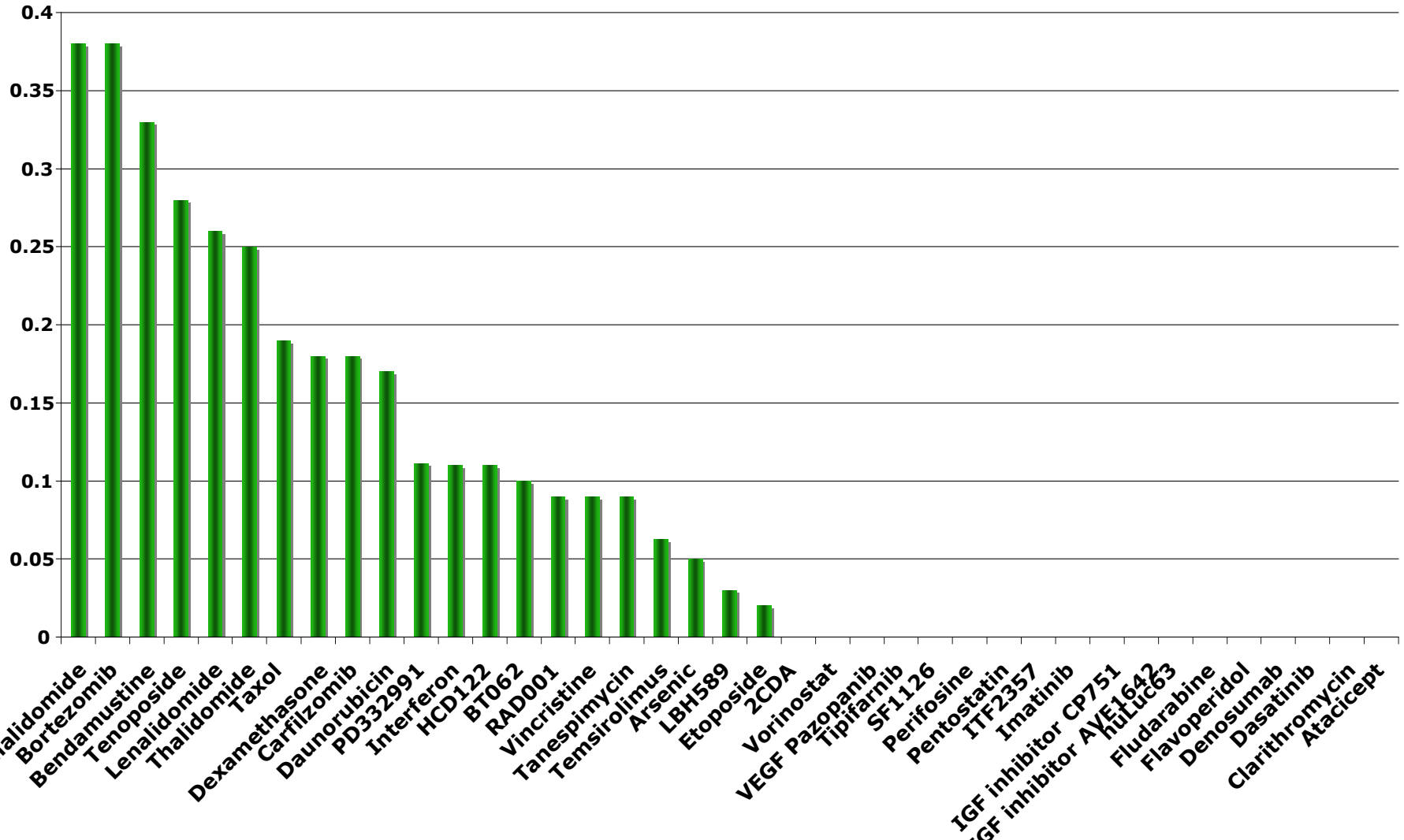
Single Agent Activity (>PR) 39 Drugs in Multiple M



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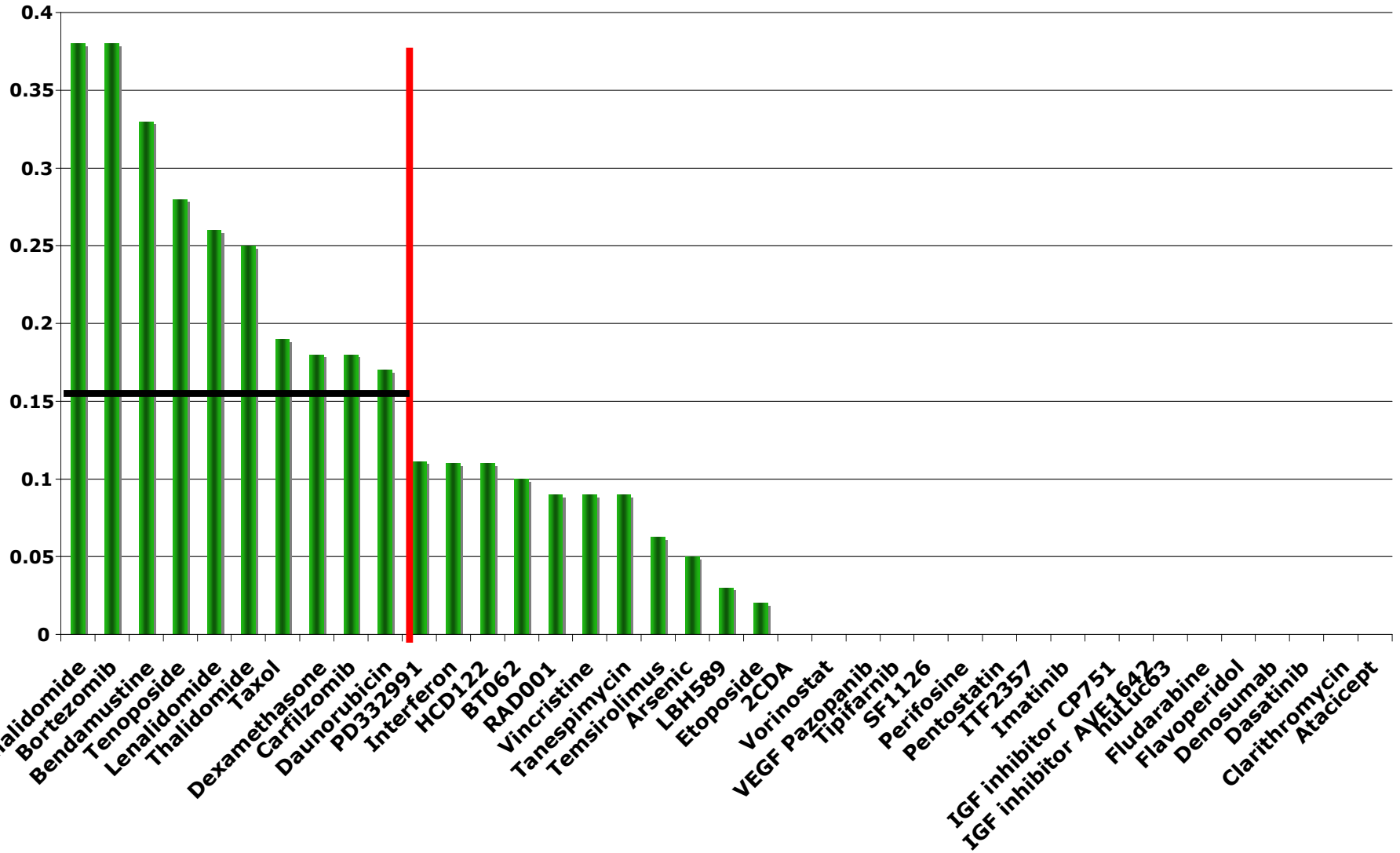
Single Agent Activity (>PR) 39 Drugs in Multiple M



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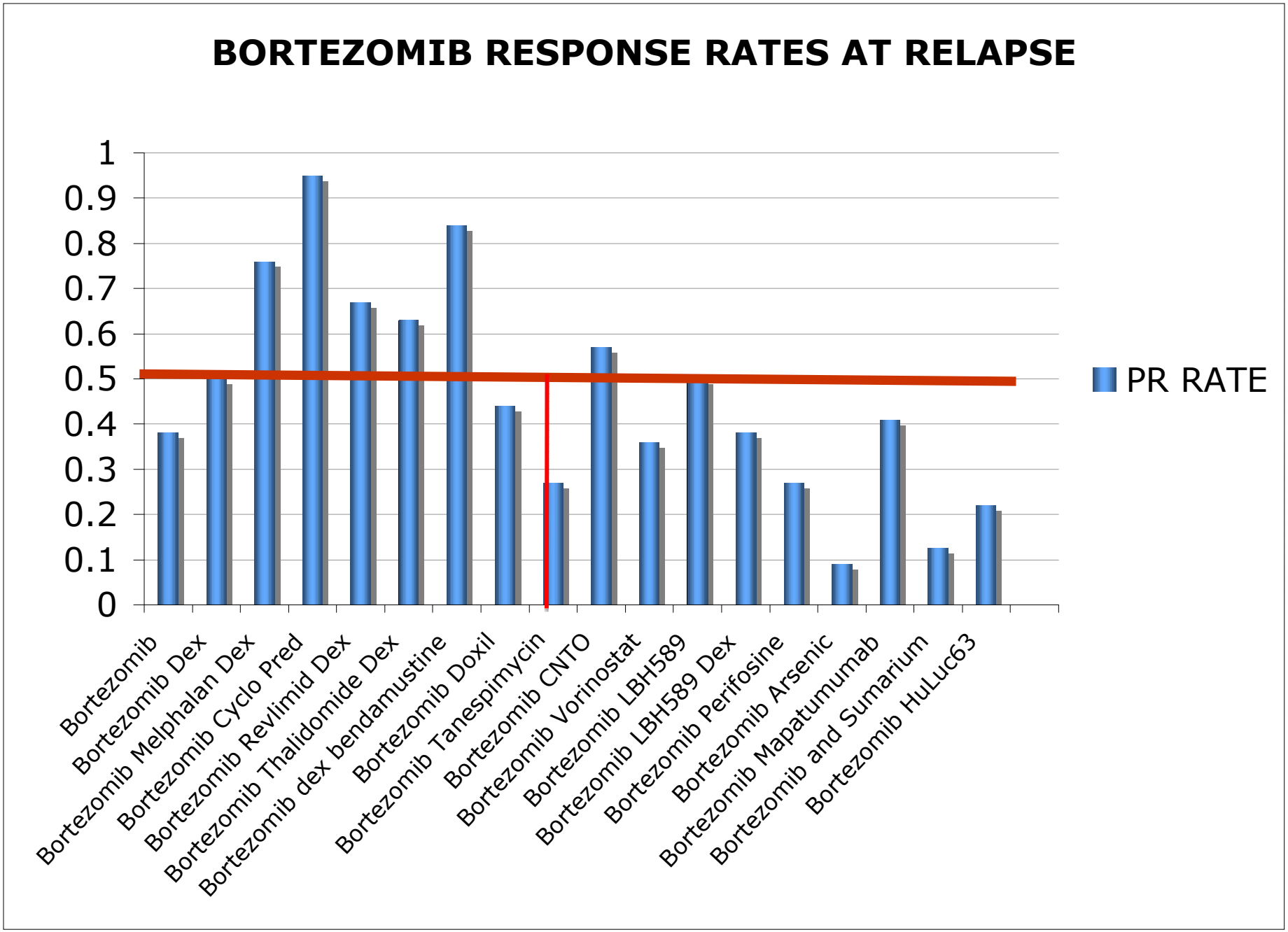
BORTEZOMIB RESPONSE RATES AT RELAPSE
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
PR RATE
Bortezomib
Bortezomib Dex
Bortezomib Melphalan Dex
Bortezomib Cyclo Pred
Bortezomib Revlimid Dex
Bortezomib Thalidomide Dex
Bortezomib dex bendamustine
Bortezomib Doxil
Bortezomib Tanespimycin
Bortezomib CNTO
Bortezomib Vorinostat
Bortezomib LBH589
Bortezomib LBH589 Dex
Bortezomib Perifosine
Bortezomib Arsenic
Bortezomib Mapatumumab
Bortezomib and Sumarium
Bortezomib HuLuc63

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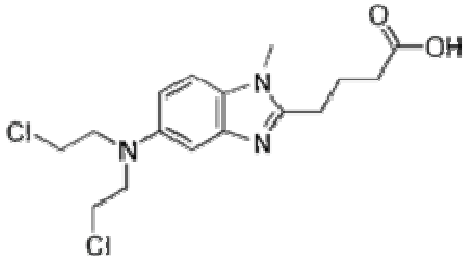
Bendamustine



The efficacy and toxicity of bendamustine in recurrent multiple myeloma after high-dose chemotherapy.

S. Knop et al. Hematologica 9:1287, 2005

Patients (n = 31) relapse post transplant

Dose Escalation to MTD 100mg/m2 days 1, 2 of 28 day cycle

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Bendamustine in Relapsed Myeloma

- **ORR 55%**
- **PR rate 12 of 31 (38%)**
- **Median Duration of response 8 months**
- **Toxicities mild nausea, emesis, neutropenia, no neuropathy**

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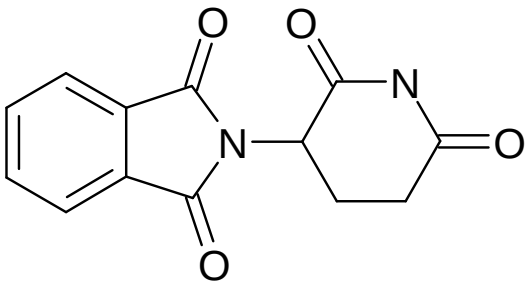
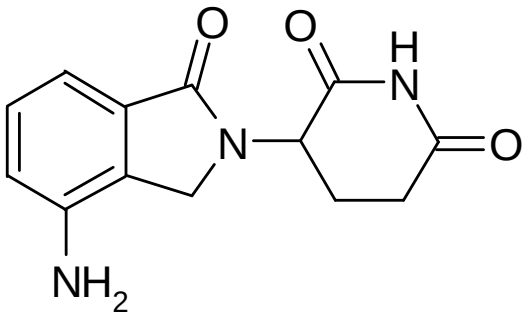
Molecular Structure of Thalidomide, Lenalidomide and Pomalidomide



Thalidomide

100-200 mg/d

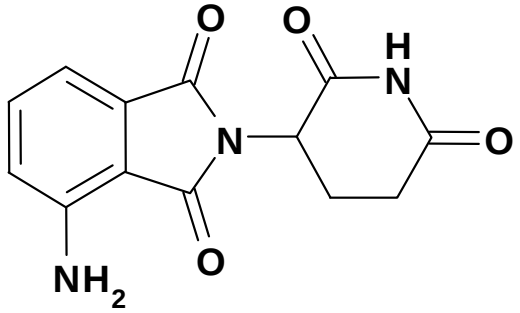
Neuropathy
Constipation
Sedation
DVT



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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Pomalidomide (CC4047) plus low-dose dexamethasone (Pom/Dex) is highly effective therapy in relapsed multiple myeloma

MQ Lacy, S Hayman, M Gertz, J Allred, S Mandrekar, A Dispenzieri, S Zeldenrust, S Kumar, P Greipp, J Lust, S Russell, F Buadi, R Kyle, PL Bergsagel, R Fonseca, V Roy, J Mikhael, AK Stewart, and SV Rajkumar

Mayo Clinic

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

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Study design & treatment

- **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.**
- **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**

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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%)

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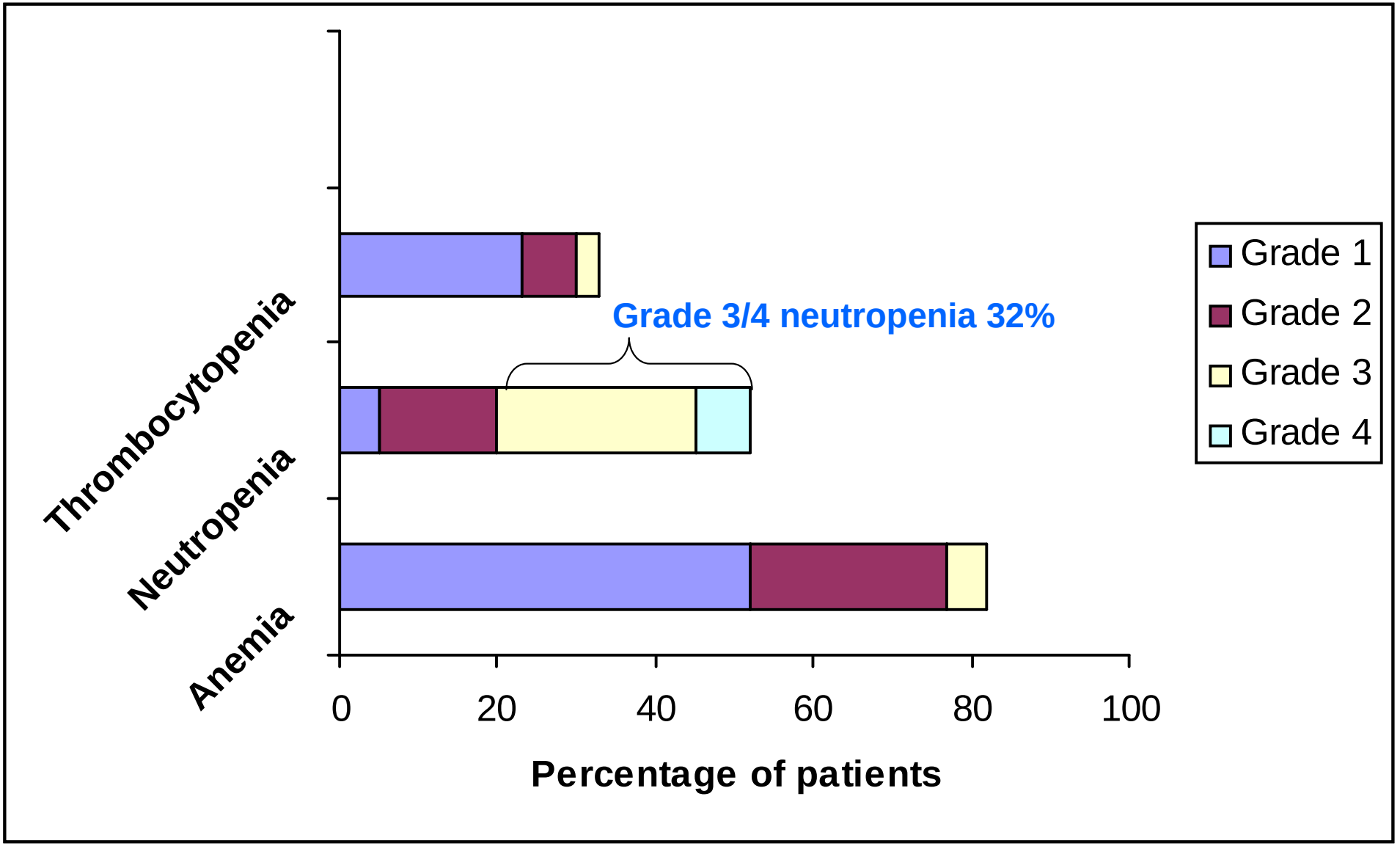
Hematologic Toxicity



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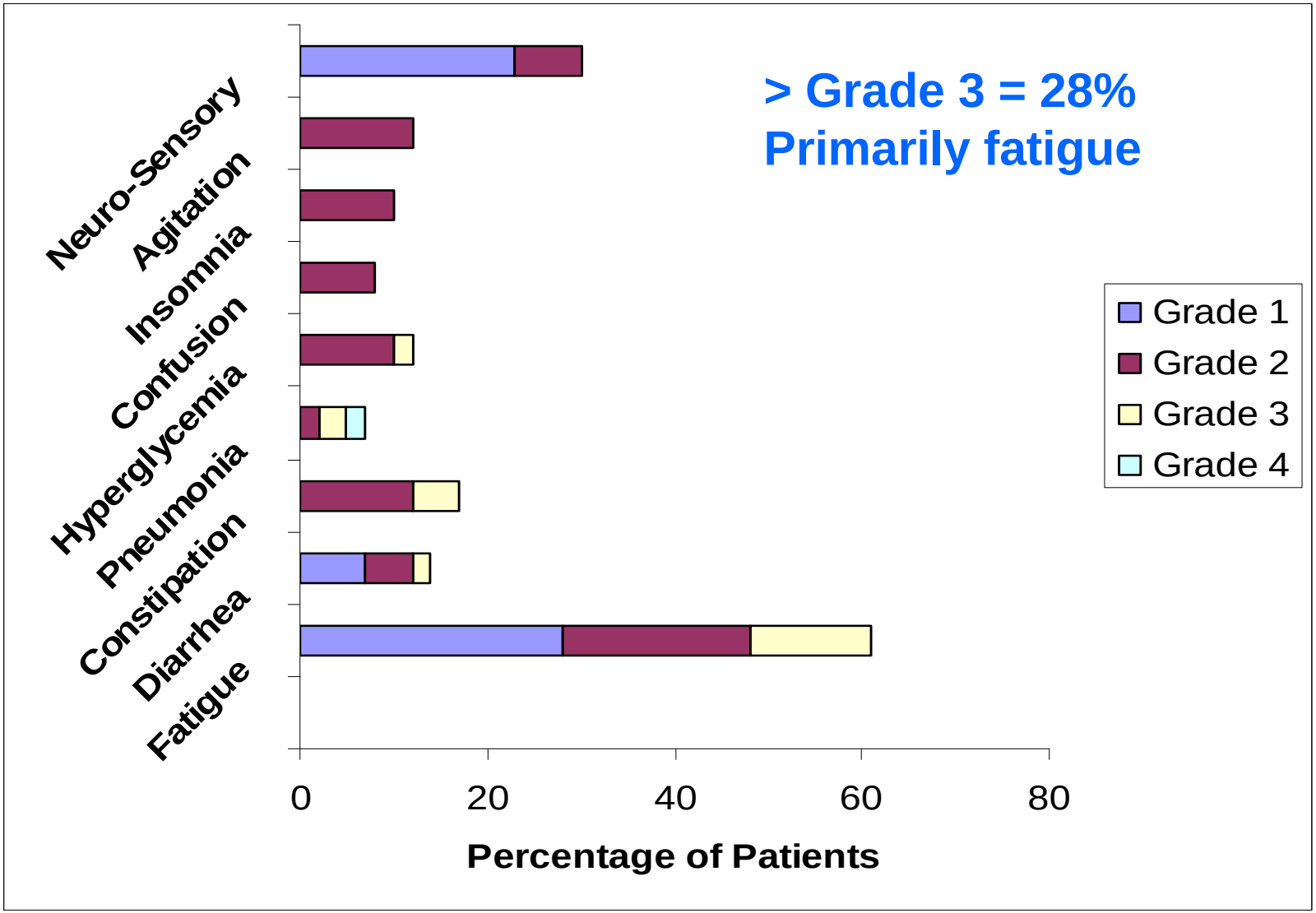
Non-Hematologic Toxicity



> Grade 3 = 28%
Primarily fatigue

1 death due to pneumonia

while neutropenic

No DVT/PE

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Best Response

Median follow-up
7 months

Response	N =60
CR	3 (5%)
VGPR	17 (28%)
PR	18 (30%)
SD	15 (25%)
PD	6 (10%)
NE	1 (2%)

ORR 63%

CR +VGPR
33%

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Responses in patients refractory to other novel agents

Refractory to	N	CR	VGPR	PR	SD	PD	RR*
Bortezomib	10	1 (10%)	2 (20%)	3 (30%)	4 (40%)	0	6 (60%)
Lenalidomide	20	0	1 (5%)	7 (35%)	9 (45%)	3 (15%)	8 (40%)
Thalidomide	16	0	2 (12.5%)	4 (25%)	6 (37.5%)	4 (25%)	6 (37.5%)

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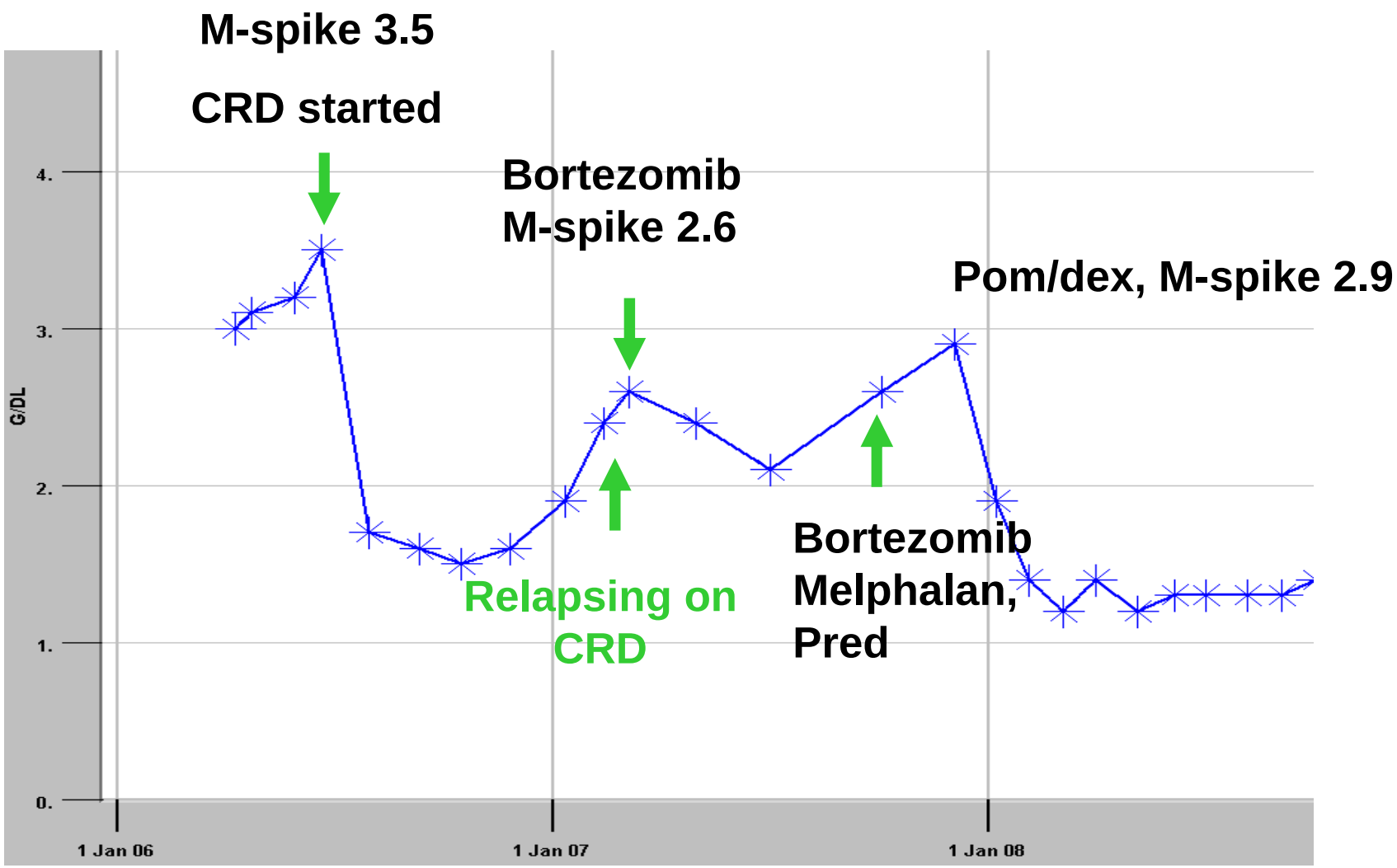
Patient 2, 67 year old female



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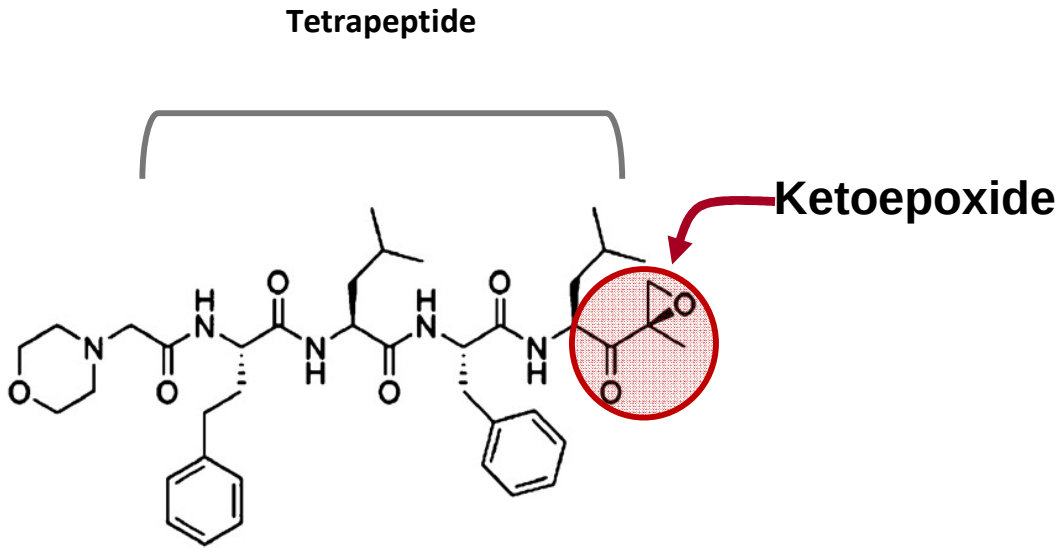
Conclusions

- **The combination of pomalidomide and low dose dexamethasone is highly active in the treatment of relapsed/refractory multiple myeloma.**
- **Toxicity has been manageable and consists primarily of myelosuppression with neutropenia.**
- **Future directions include phase II trial of pomalidomide and dexamethasone for lenalidomide-refractory and bortezomib – refractory patients**

Carfilzomib:

Carfilzomib is a new, selective and irreversible proteasome inhibitor with pre-clinical anti-tumor activity.

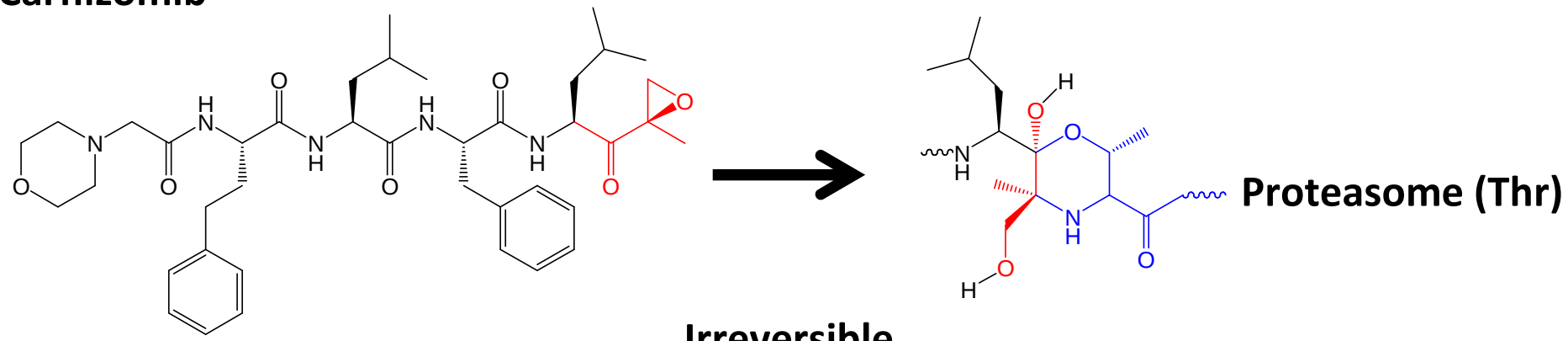
Responses seen in Phase I Myeloma trials.



Mechanism of Binding

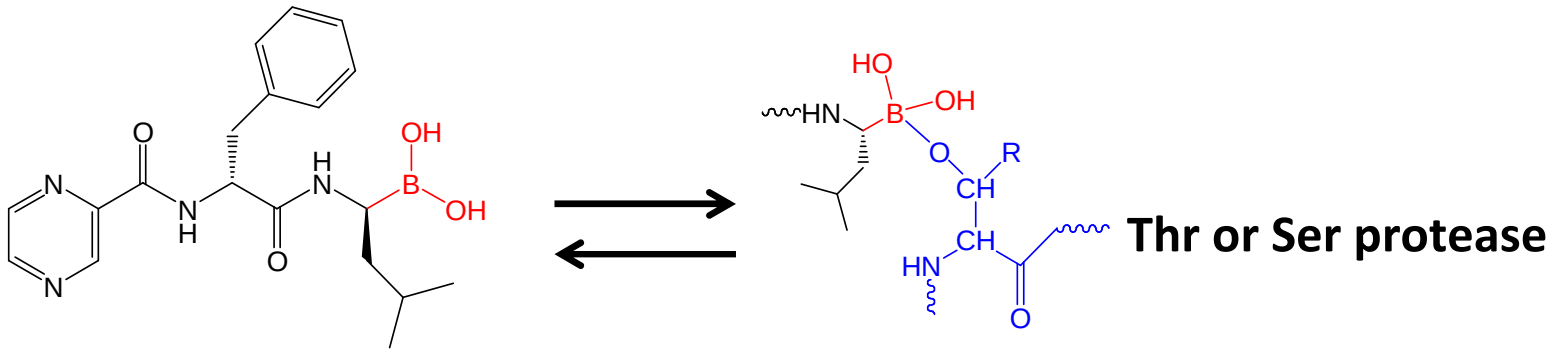
Selectivity and prolonged inhibition

Carfilzomib



Irreversible

Bortezomib



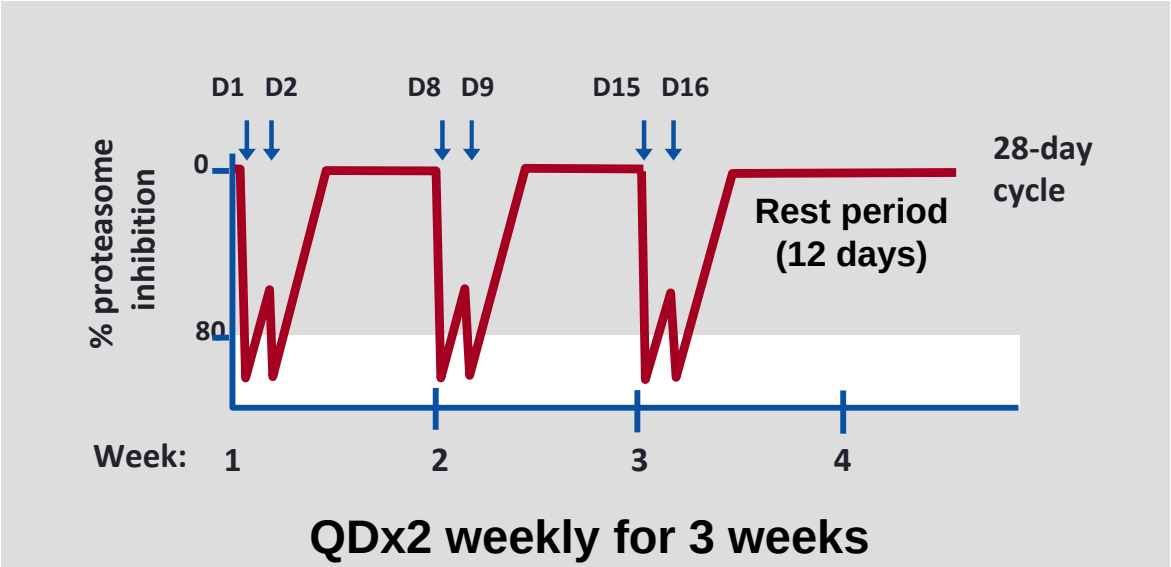
Slowly reversible

PX-171-004 Carfilzomib Phase 2 Study Design

Population: Multiple Myeloma, relapsed after 1-3 prior therapies

CFZ administration: 20 mg/m^2 IV bolus; maximum 12 cycles

Premedication: Hydration, Dexamethasone 4 mg during Cycle 1



Primary endpoint: Overall response rate (ORR = CR + VGPR + PR)*

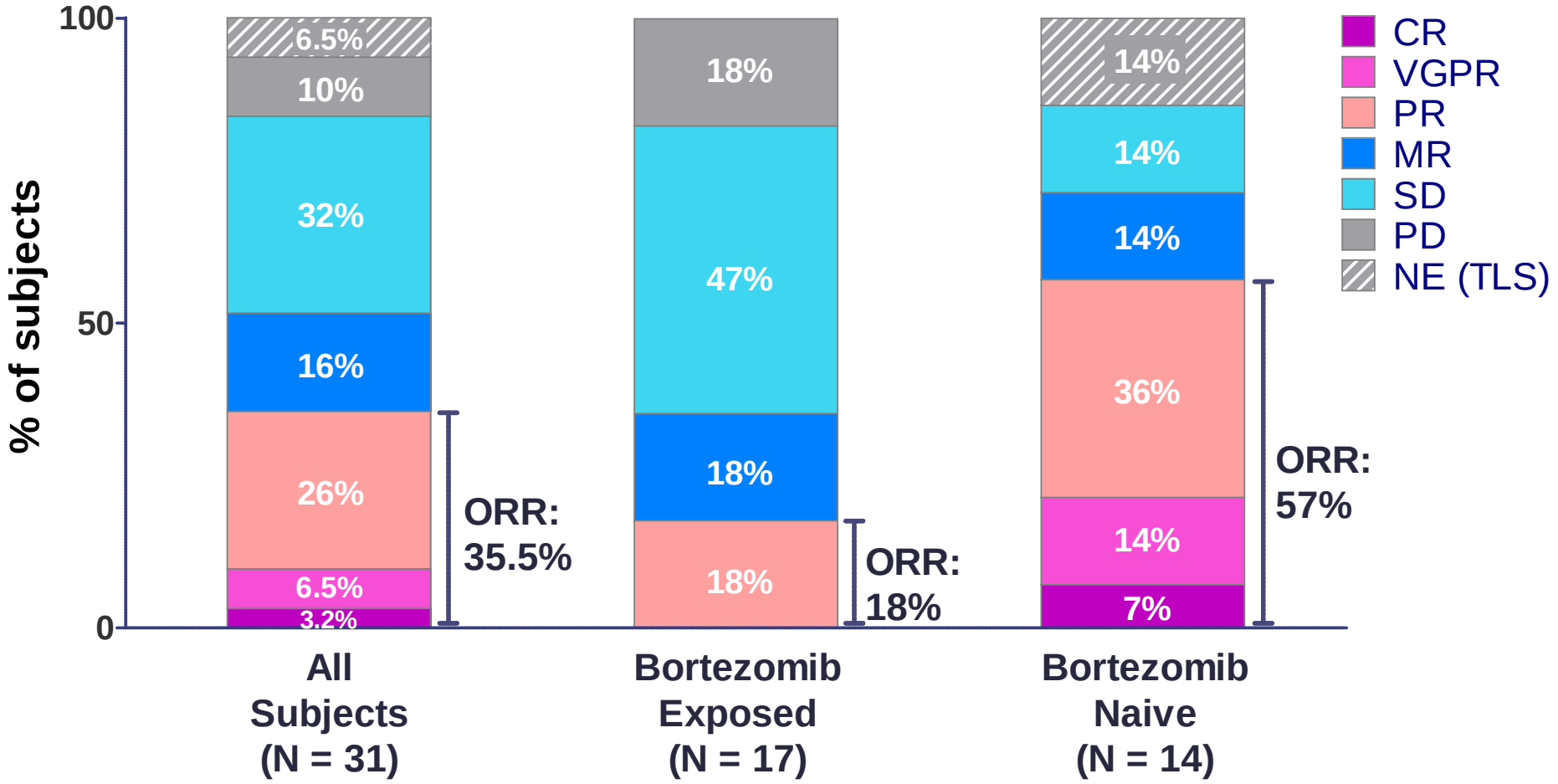
Secondary endpoints: DOR, PFS, TTP, OS, Safety

*IMWG response criteria

Baseline Characteristics (N=31)

	BTZ-Naïve (N=14) N (%)	BTZ-Exposed (N=17) N (%)
Peripheral Neuropathy		
Prior History	9 (64)	14 (82)
Grade 1/2 Neuropathy at baseline	4 (29)	6 (35)
Prior Bortezomib Therapy		
Single Agent	-	3 (18)
In Combination	-	14 (82)
Other Prior Therapies		
Corticosteroid	16 (94)	14 (100)
Lenalidomide *OR* Thalidomide	13 (93)	12 (71)
Lenalidomide *AND* Thalidomide	3 (21)	4 (24)
Alkylator	16 (94)	13 (93)
Anthracycline	1 (7)	8 (47)
Stem Cell Transplant	15 (88)	12 (86)

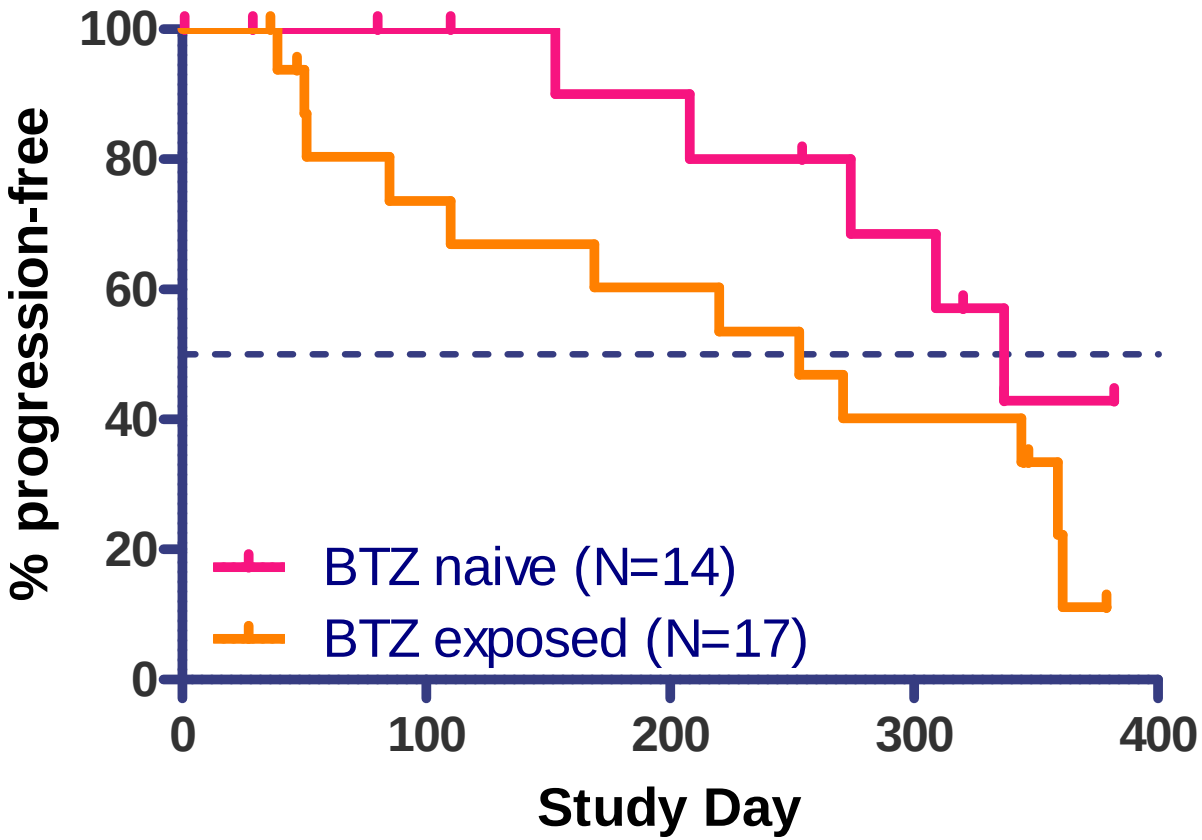
Single Agent Anti-tumor Activity



≥ MR 71% for BTZ-Naïve

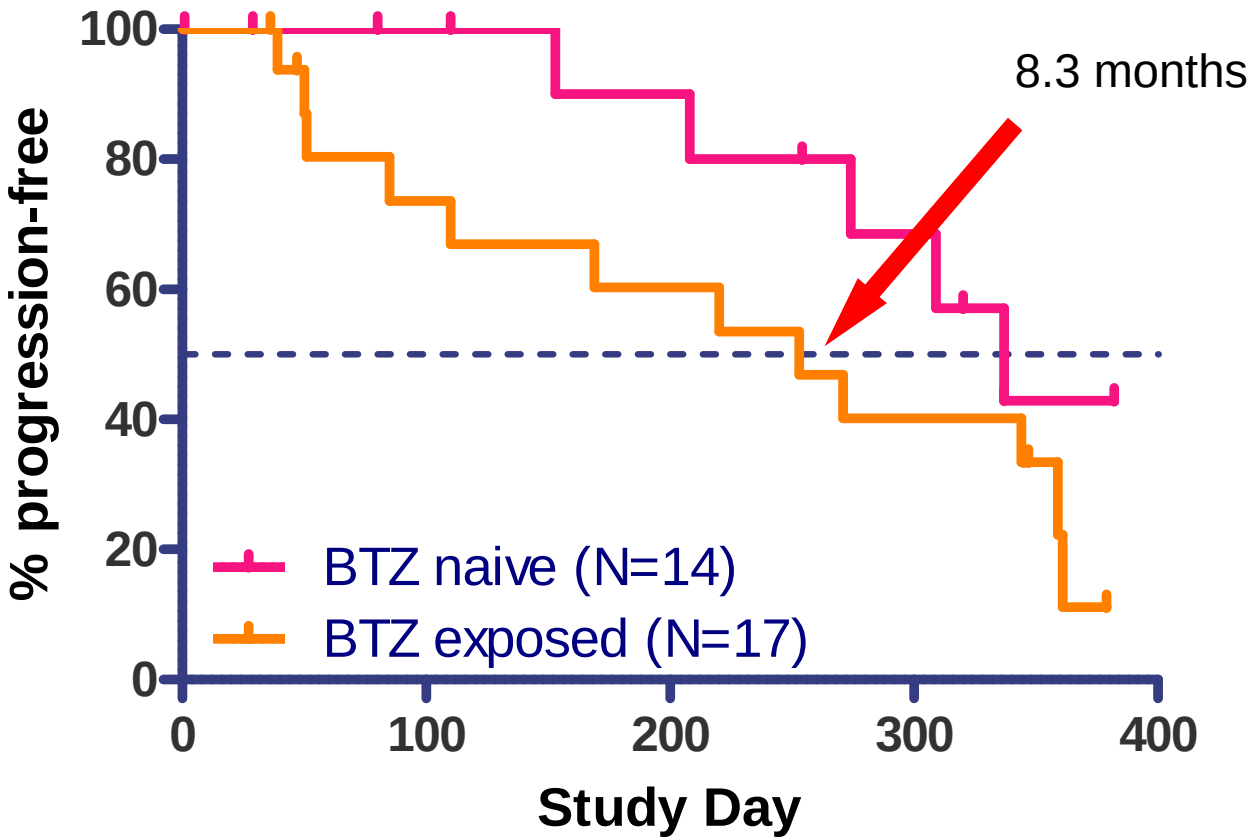
≥ MR 36% for BTZ-Exposed

PX-171-004: Time To Progression



	BTZ naïve (N=14)	BTZ exposed (N=17)
Time to Progression (median)	11.1 months	8.3 months
Median follow up	10.8 months	12.5 months

PX-171-004: Time To Progression



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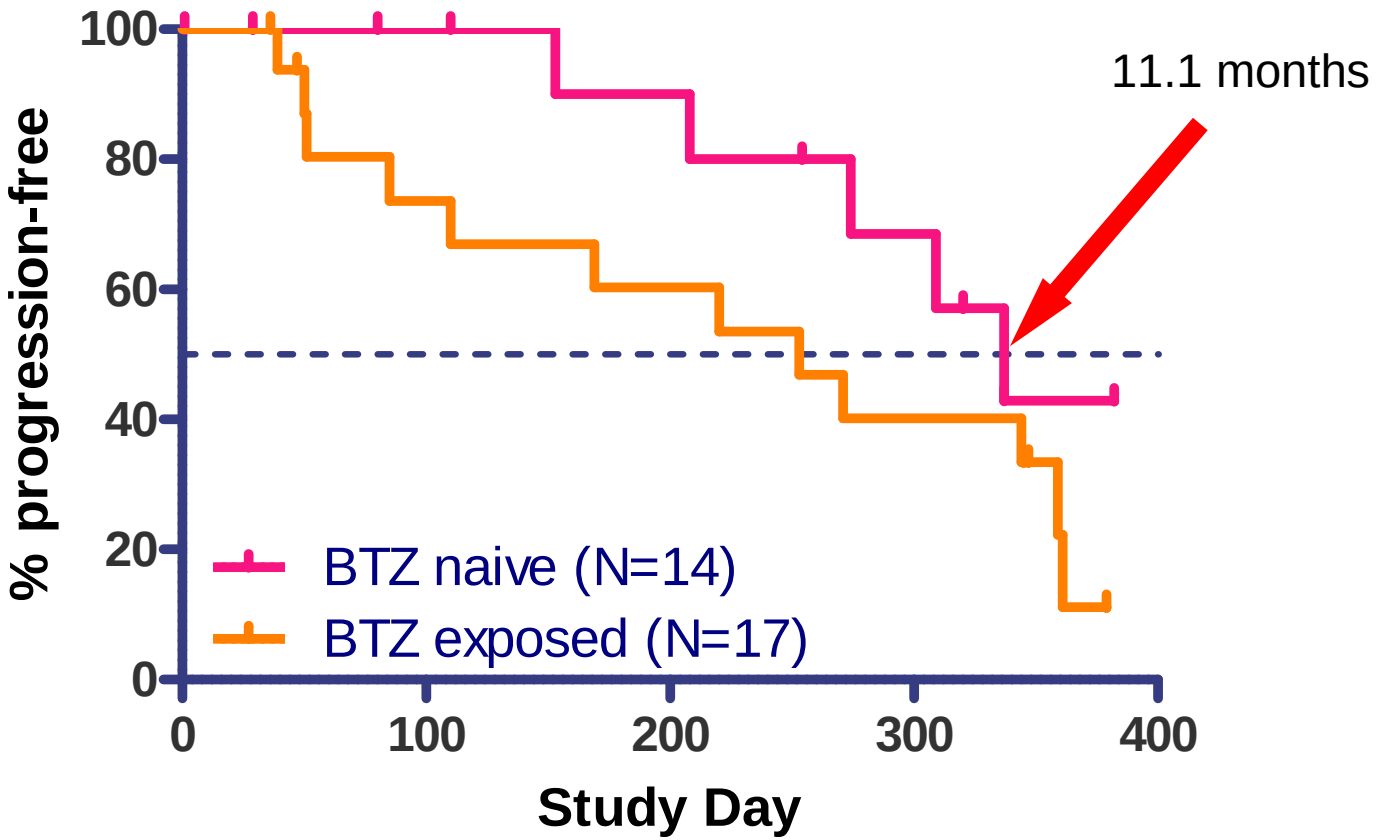
PX-171-004: Time To Progression

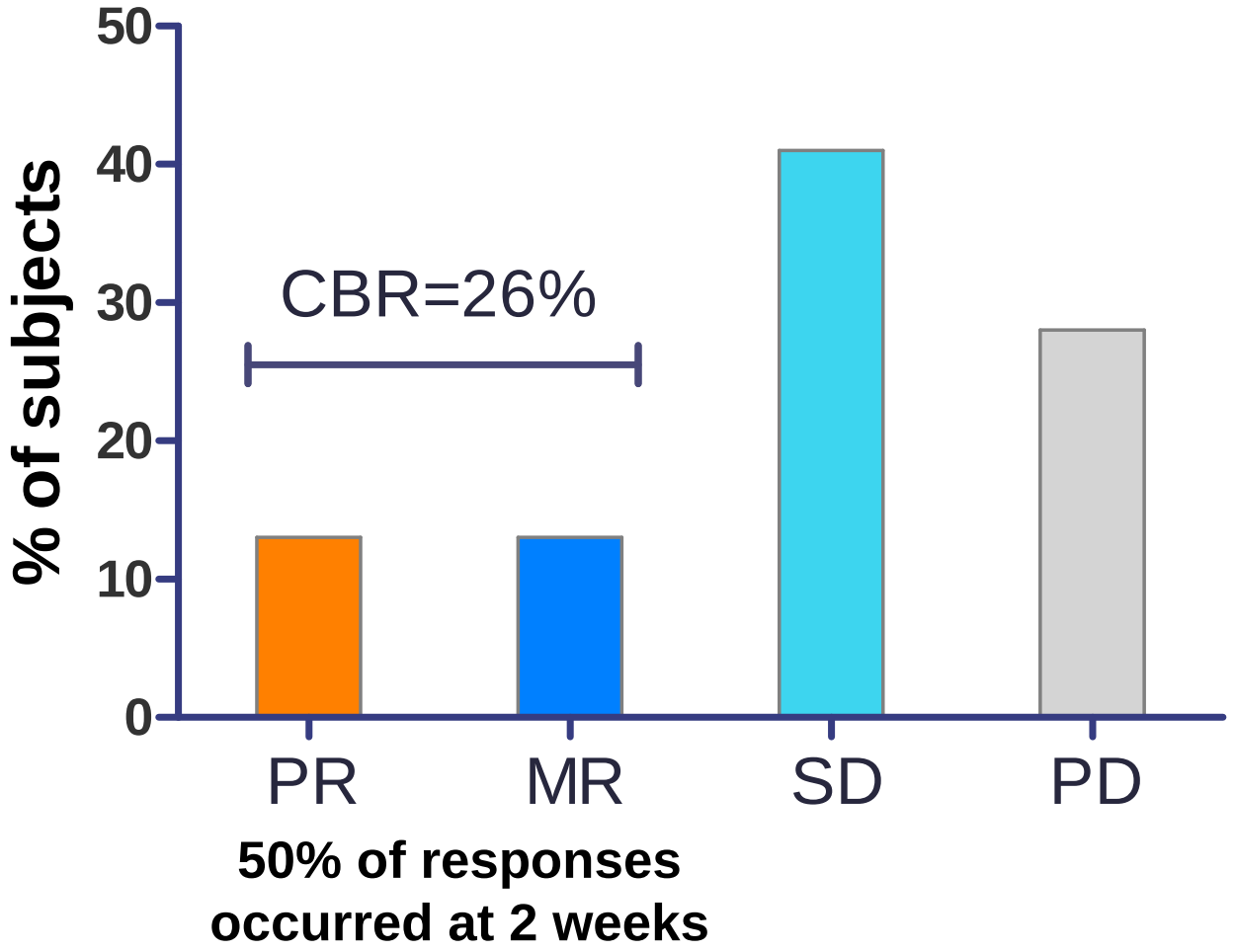


	BTZ naïve (N=14)	BTZ exposed (N=17)
Time to Progression (median)	11.1 months	8.3 months
Median follow up	10.8 months	12.5 months

PX-171-003: Response Summary (N=39)

Seven subjects excluded from response analysis:

- Serum free light chain only (4)
- Received < 1 cycle of therapy (2)
- No baseline value (1)



50% of responses occurred at 2 weeks

Most Common Non-Hematologic AEs (N=31)

Adverse Event*, [1]	Overall n (%)	≥ Grade 3 n (%)
Fatigue	23 (74.2)	0
Nausea	20 (64.5)	0
Vomiting	13 (41.9)	0
ALT increased	12 (38.7)	0
URI	12 (38.7)	1 (3.2)
Dyspnea	11 (35.5)	3 (9.7)
Headache	11 (35.5)	0
AST increased	10 (32.3)	0
Diarrhea	10 (32.3)	0
Hypoesthesia	10 (32.3)	0
Hypophosphatemia	9 (29.0)	1 (3.2)
Cough	9 (29.0)	0
Pyrexia	9 (29.0)	0
Increased creatinine	8 (25.8)	1 (3.2)
Hypomagnesemia	8 (25.8)	0
Insomnia	8 (25.8)	0
Non-Neuropathic Extremity Pain	8 (25.8)	0

*All AEs reported in >25% patients

[1]Includes both related and non-related

Data through March 2009

Increased Creatinine: Reversible and Non cumulative

Adverse Event*, [1]	Overall n (%)	≥ Grade 3 n (%)
Fatigue	23 (74.2)	0
Nausea	20 (64.5)	0
Vomiting	13 (41.9)	0
ALT increased	12 (38.7)	0
URI	12 (38.7)	1 (3.2)
Dyspnea	11 (35.5)	3 (9.7)
Headache	11 (35.5)	0
AST increased	10 (32.3)	0
Diarrhea	10 (32.3)	0
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Insomnia	8 (25.8)	0
Non-Neuropathic Extremity Pain	8 (25.8)	0

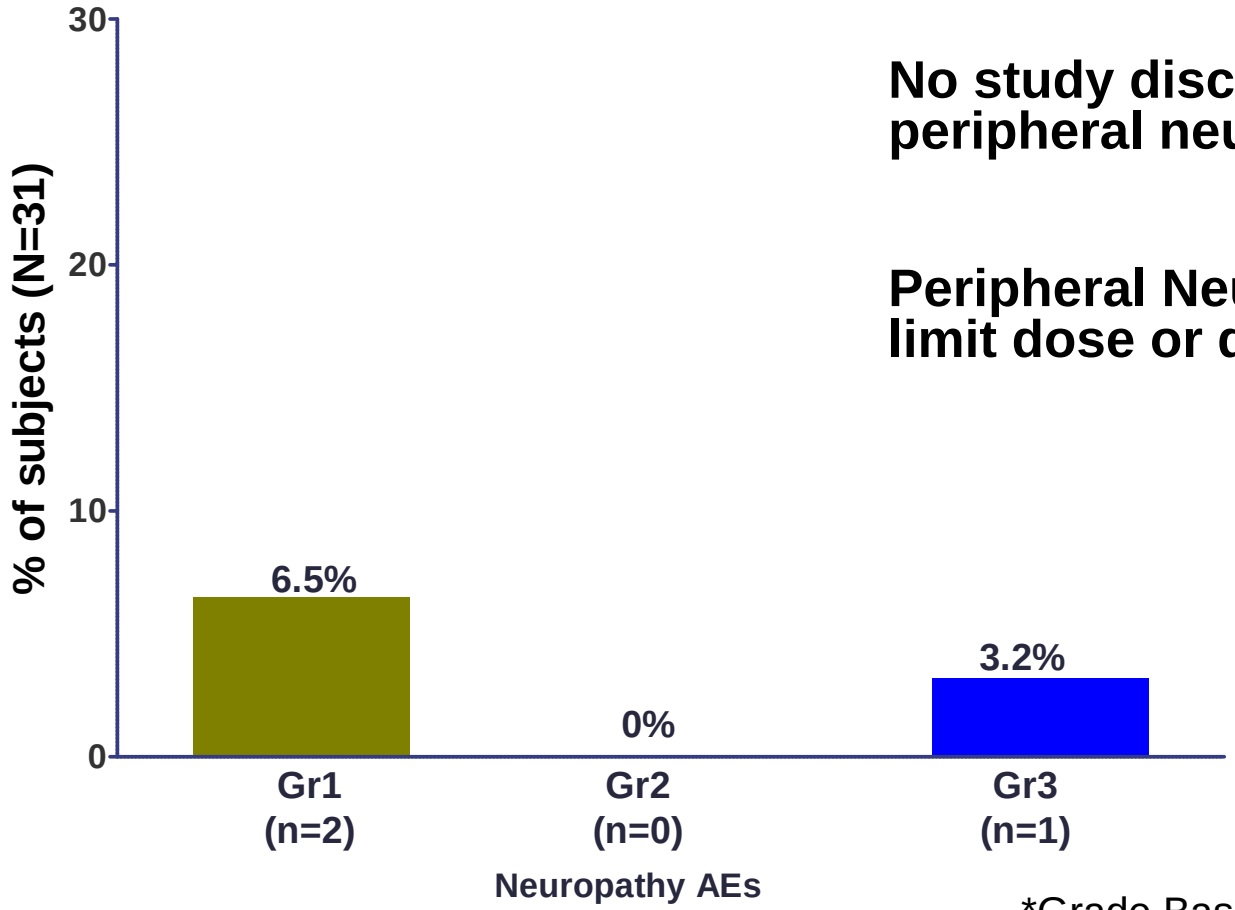
*All AEs reported in >25% patients

[1]Includes both related and non-related

Data through March 2009

Low Rate of Treatment Emergent Peripheral Neuropathy

- **73% had a prior history of drug or disease related neuropathy**
- **32% had Grade 1/2 neuropathy at baseline***



No study discontinuations for peripheral neuropathy

Peripheral Neuropathy does not limit dose or duration of therapy

*Grade Based on physical assessment at screening (NCI-CTC scale)

Data through March 2009

Carfilzomib Conclusions: Ph 2 Relapsed MM

- **Single agent carfilzomib is highly active in relapsed patients**
  - **57% response rate in BTZ-naïve patients**
  - **26% CBR in Refractory disease**
- **CFZ achieves durable disease control with continued dosing**
  - **Median TTP 11.1 mos in BTZ-naïve patients**
  - **Median TTP 8.3 mos in BTZ-exposed patients**
- **Few ≥ grade 3 Aes**
- **Peripheral neuropathy is not a treatment-limiting toxicity with CFZ**

Carfilzomib: Future Directions

- **Dose escalation to 27 mg/m^2**
- **Combination with Lenalidomide and Dexamethasone**
- **Registrational Development**
  - **single arm monotherapy Phase 2 in refractory pts completed**
  - **Randomized Phase 3 lenalidomide/dexamethasone +/- CFZ planned for 2010**

Many drugs in trials – some current examples

AUY922

TAK901 / MLN8237

NPI-052 / CEP070 / MLN9708

TKI258 / MFGR1877S

PD0332991

Vorinostat

Tanespimycin

Perifosine

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Conclusions

- At relapse suggest combination therapy in rapid relapsing, symptomatic or high genetic risk patient
- More conservative therapy otherwise reasonable
- Three new active drugs with many more being tested in clinical trials