TRATAMIENTO ANTINEOPLÁSICO EN HEMATOLOGÍA: MUCHO QUE APRENDER, MUCHO QUE RECORDAR

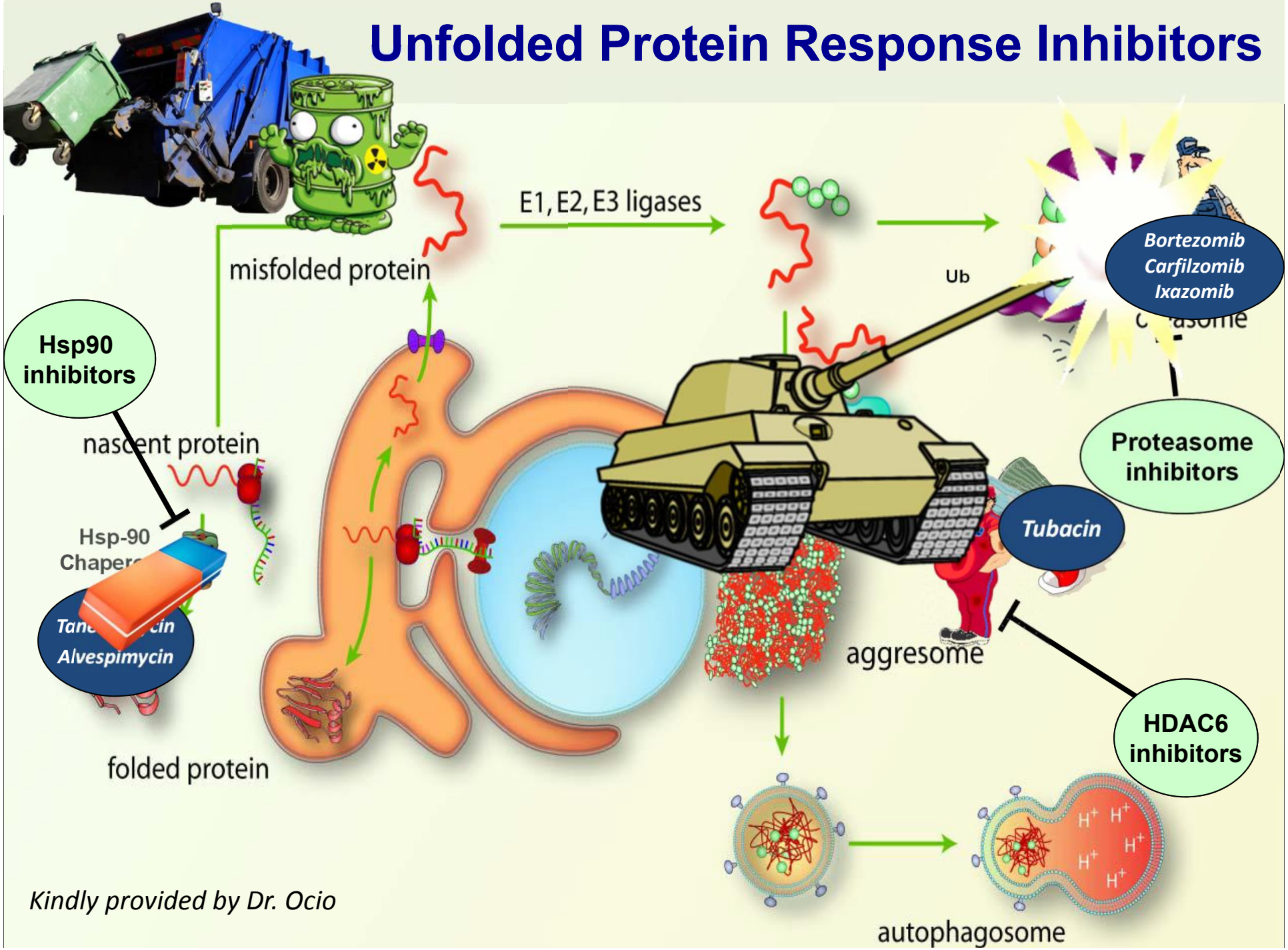
AGENTES FRENTE A NUEVAS DIANAS TERAPEÚTICAS

Inhibidores de proteasomas

Ramón García-Sanz

FEHH

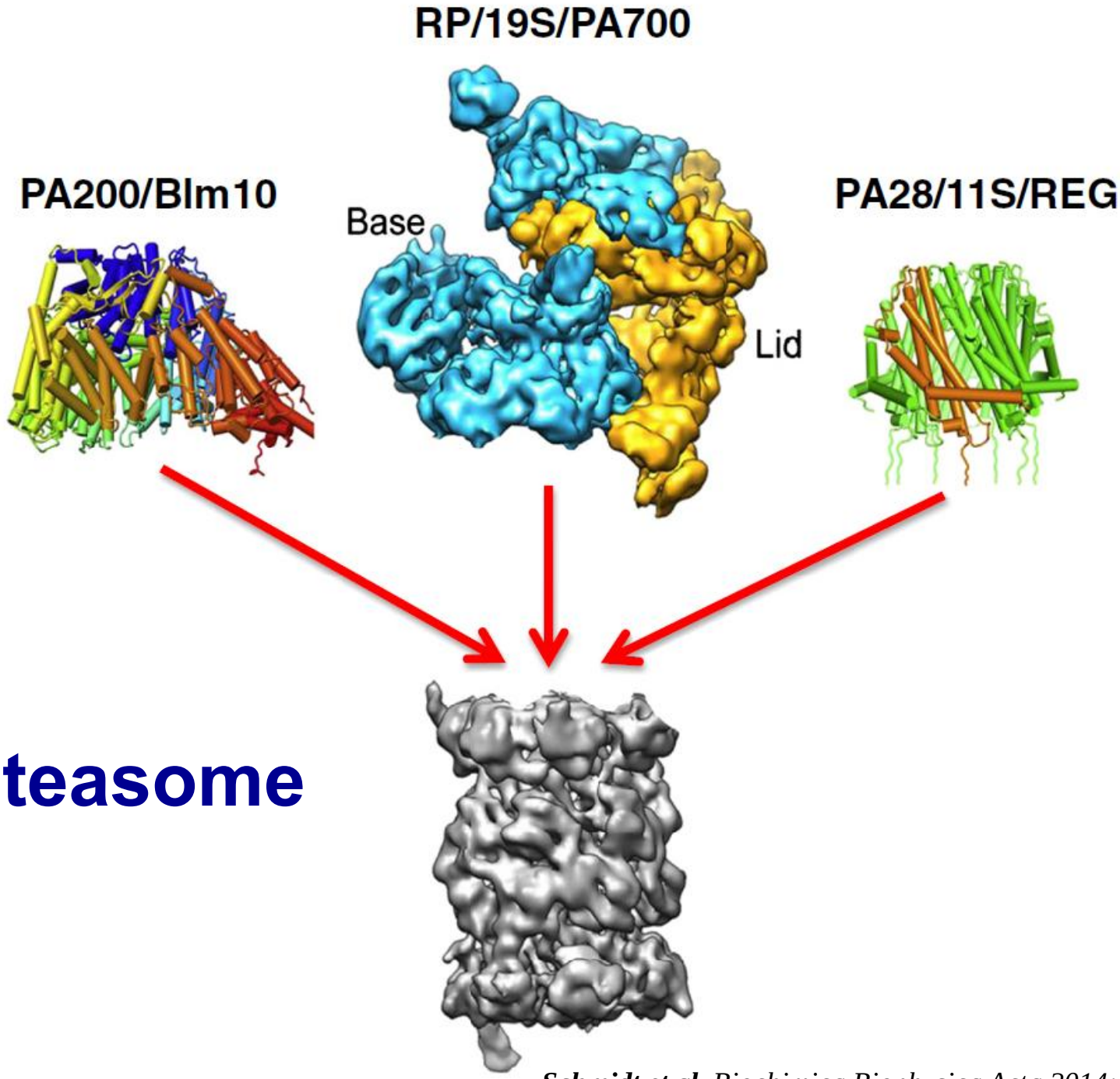
Unfolded Protein Response Inhibitors



Kindly provided by Dr. Ocio

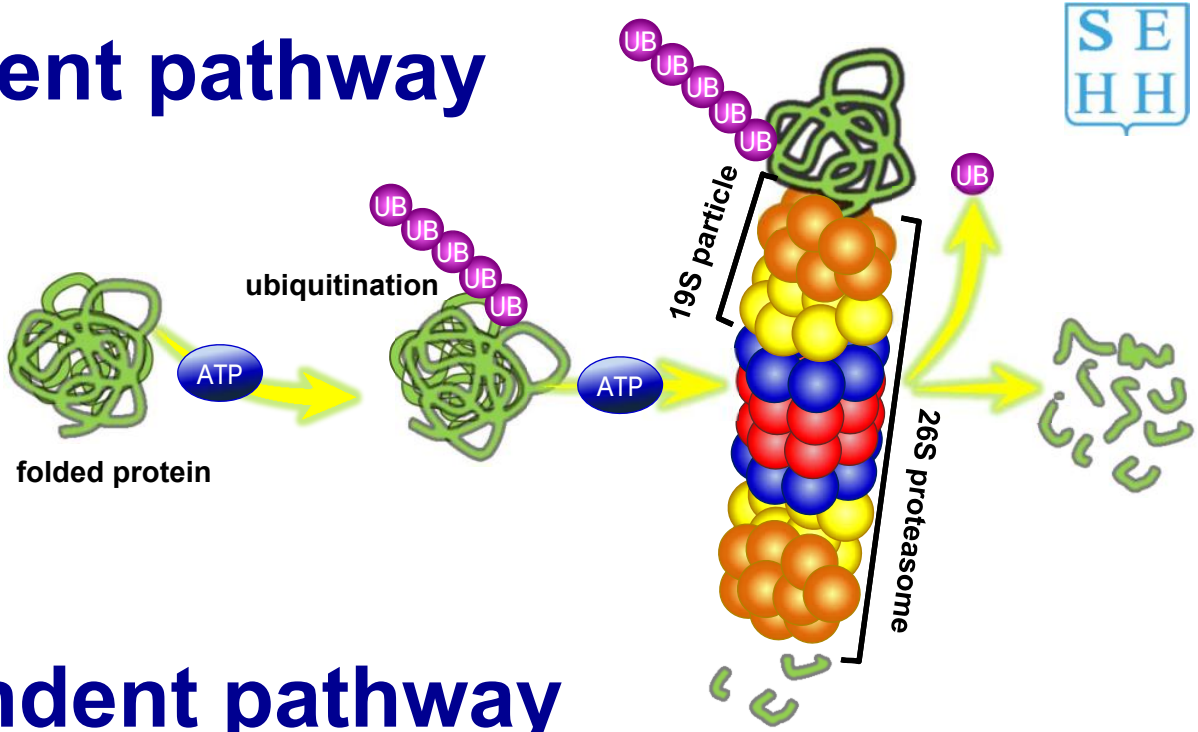
Proteasome inhibitors

Proteasome

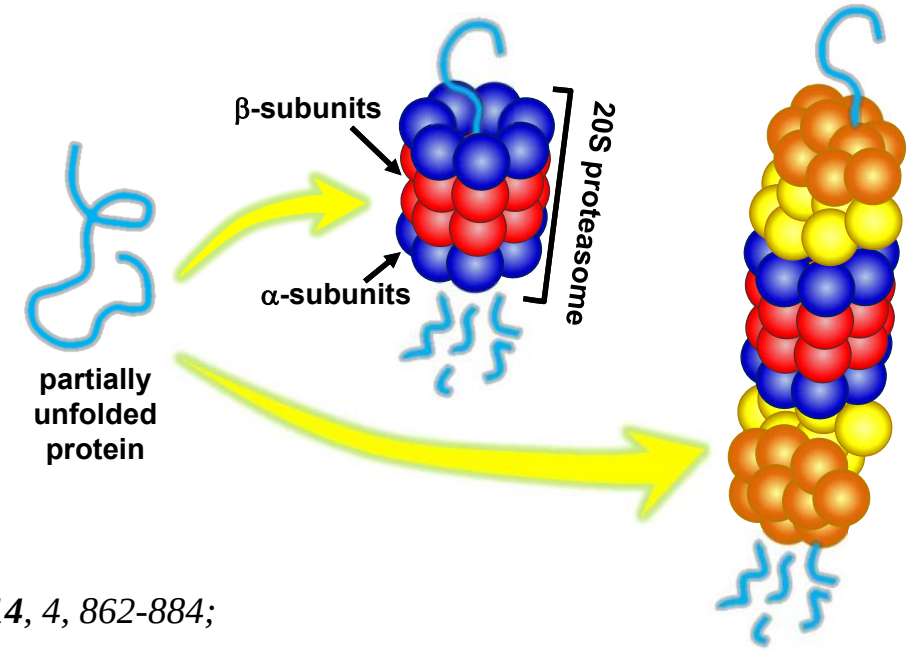


Schmidt et al, *Biochimica Biophysica Acta 2014; 1843:13–25*

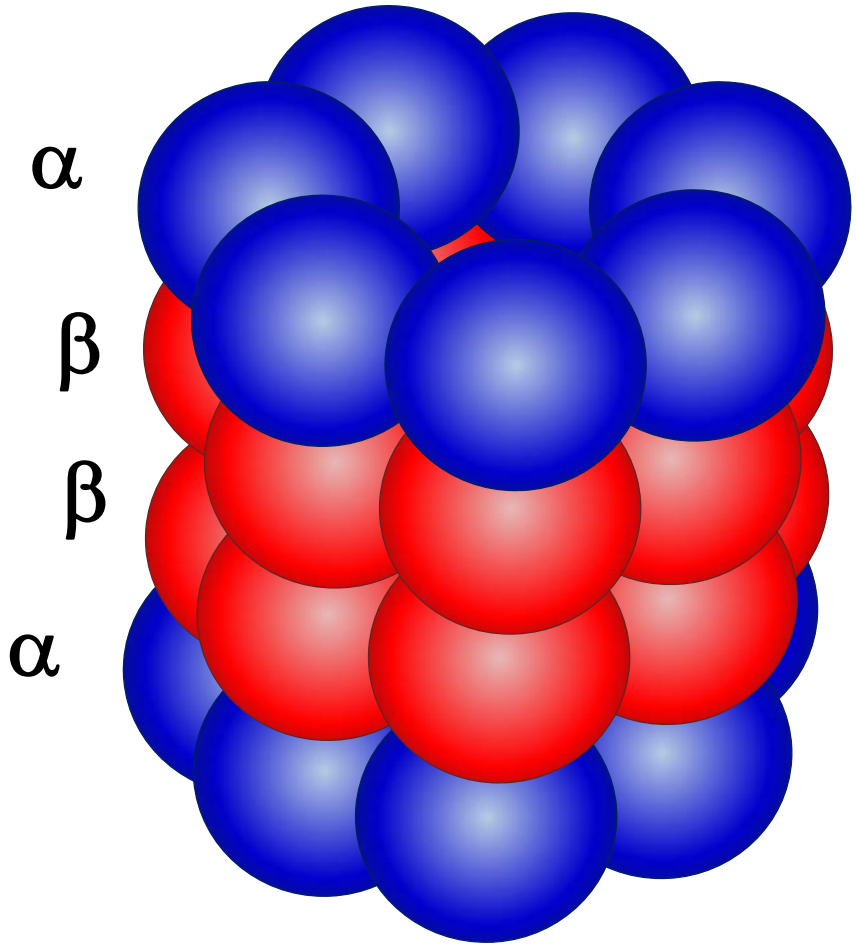
Ubiquitin dependent pathway



Ubiquitin independent pathway



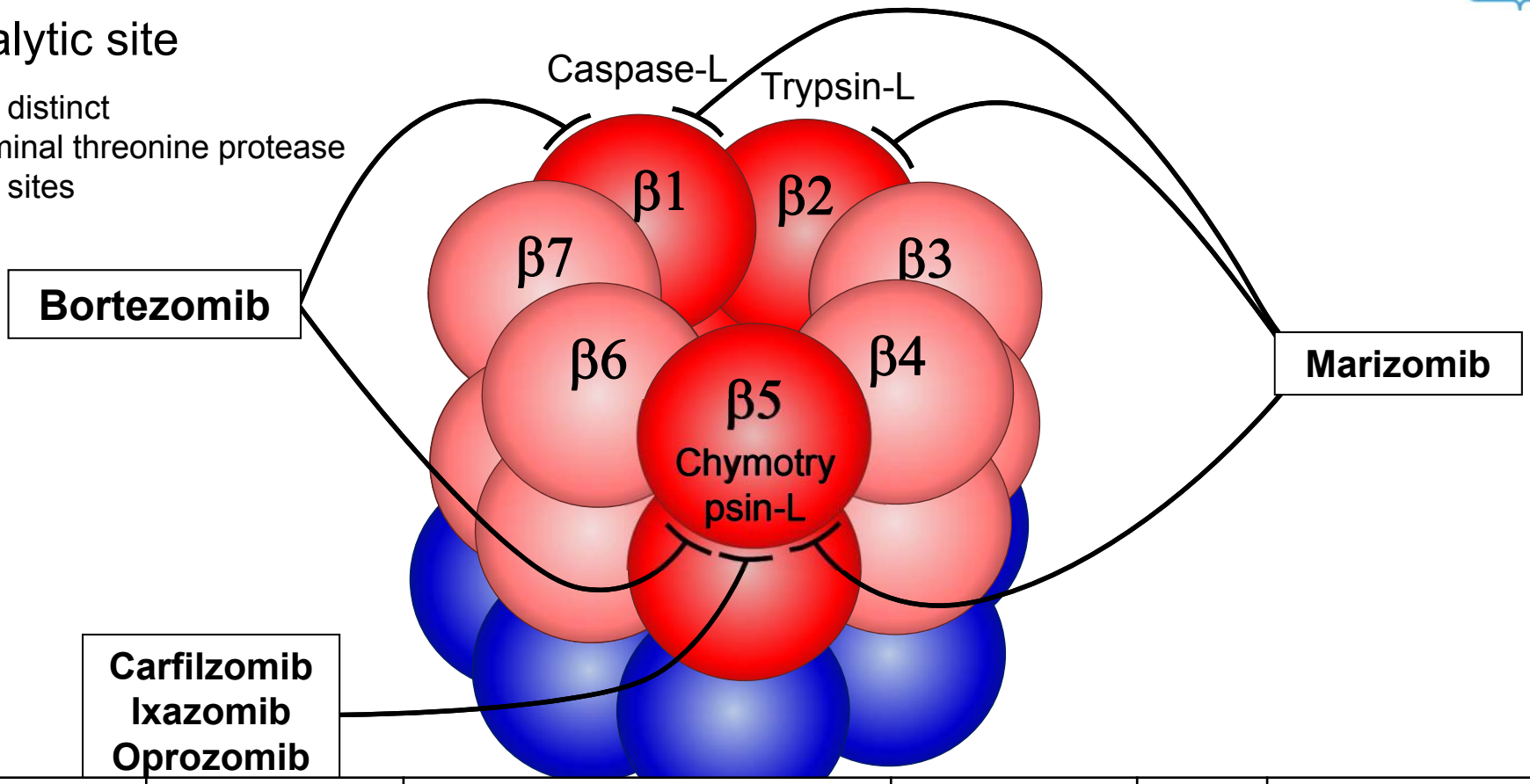
Ben-Nissan & Sharon. *Biomolecules* ***2014****, 4, 862-884;*


α
β
β
α

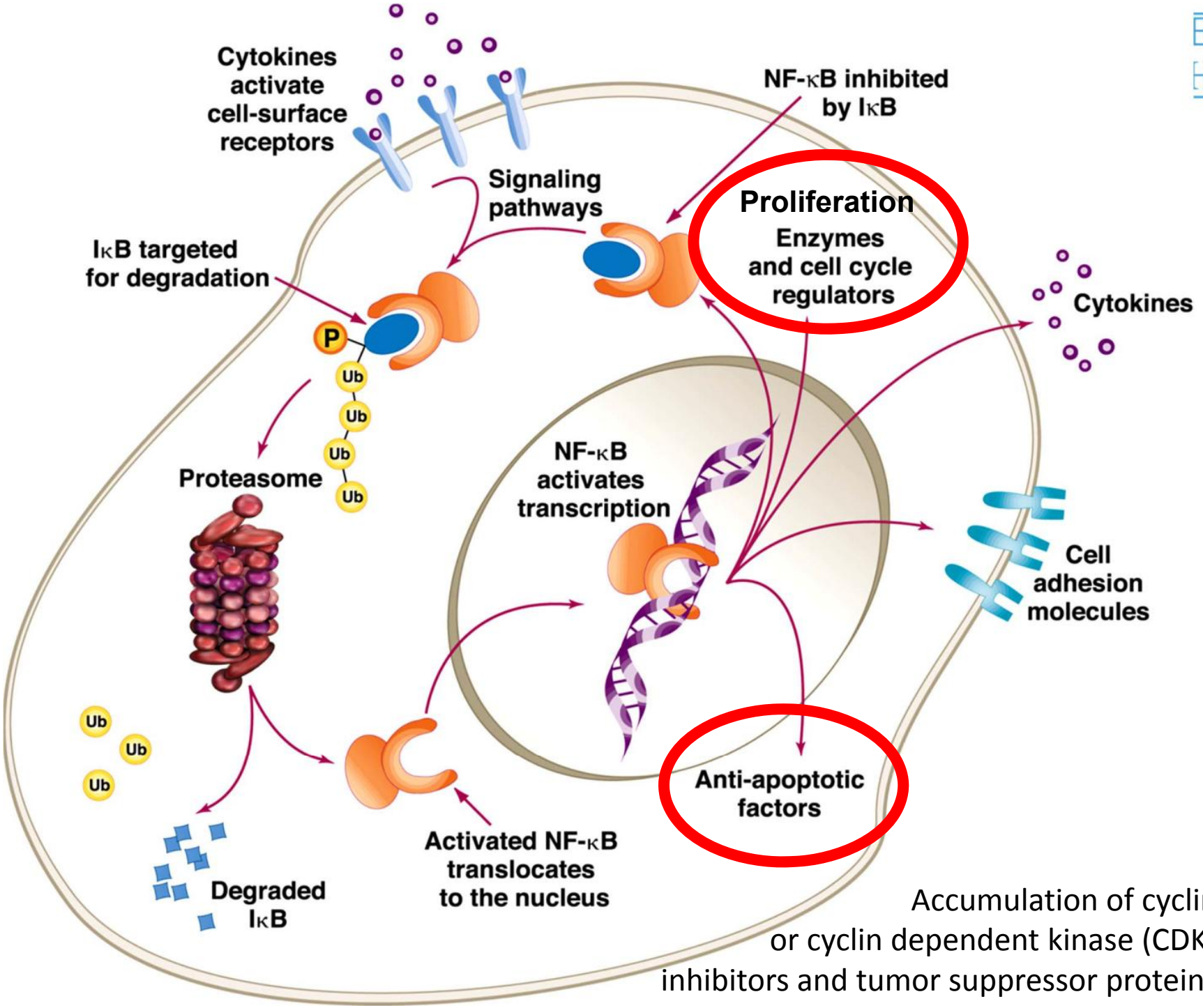
β-subunit ring of the proteasome

Catalytic site

Three distinct
N-terminal threonine protease
active sites



	Type	Catalytic inhibition			Reversibility	PO/IV	Dosing (days/cycle)
		Chymotryp.	Casp.	Tryp.			
Bortezomib	Boronic	X	X		Reversible	IV	1, 4, 8, 11
Carfilzomib	Epoxiketone	X			Irreversible	IV	1-2, 8-9, 15-16
Marizomib	Salinospora	X	X	X	Reversible	IV/PO	1, 8, 15
Ixazomib		X			Reversible	IV/PO	1, 8, 15
Oprozomib	Epoxiketone	X			Irreversible	IV/PO	1-2, 8-9, 15-16

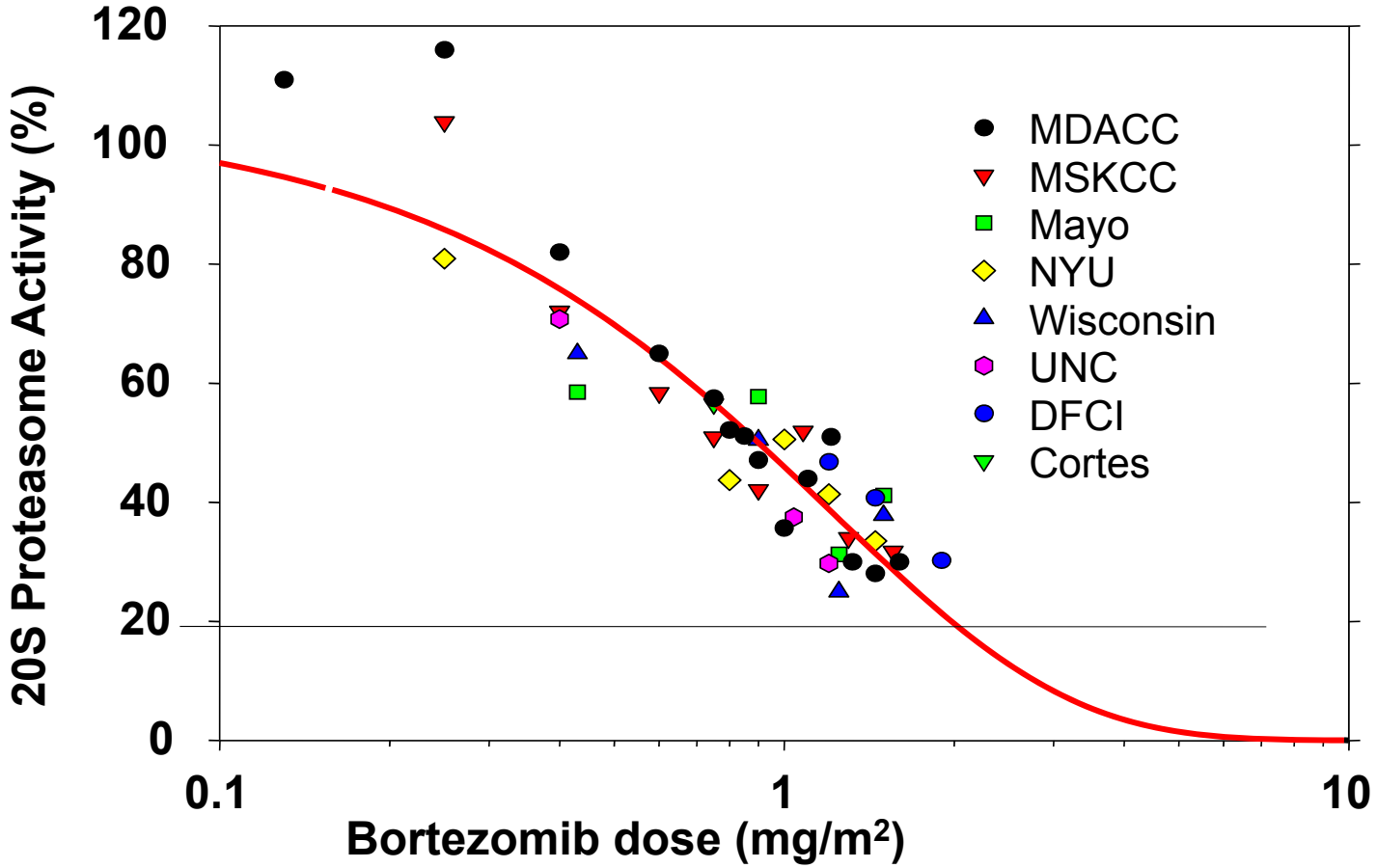


Accumulation of cyclin
or cyclin dependent kinase (CDK)
inhibitors and tumor suppressor proteins

Proteasome inhibitors

Inhibition of Proteasome Activity

Ex Vivo Proteasome Activity: 1-Hour Post Treatment



Nix D. Presented at ASCO 2001. Abstract 339.

Phase I trial of bortezomib in advanced hematological malignancies

- **Advanced, previously treated haematologic malignancies (n=27)**
  - ECOG PS 0, 1, 2: 6/16/5
  - Multiple myeloma (MM) (n=11), NHL (n=10)
  - Median prior chemo: 3 regimens (1-12)

- **Treatment schedule**
  - Bortezomib 0.40 mg/m^2 → 1.38 mg/m^2 IVP twice weekly × 4 weeks, followed by 2 weeks rest

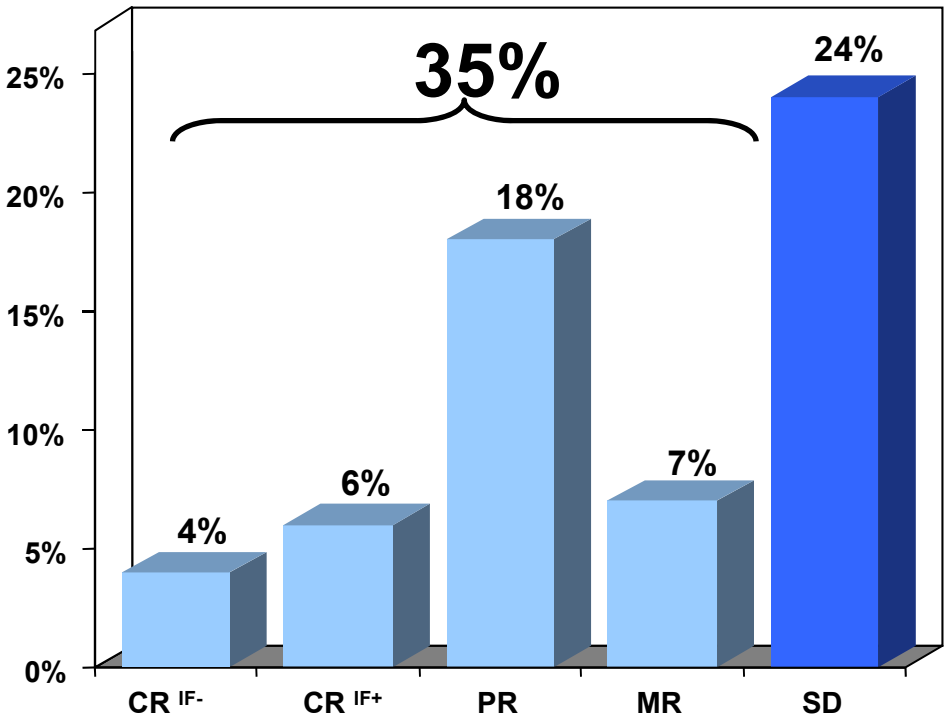
- **Activity observed**
  - 1 CR in patient with MM
  - 8 other patients with MM experienced either minor response or SD
  - PR observed in mantle cell (n=1) and follicular NHL (n=1)

Orlowski RZ et al. J Clin Oncol. 2002;20:4420-27

Bortezomib Clinical Trials

Trial		Summary	Result	Ref
Phase II	CREST	Clinical response and efficacy study of bortezomib in the treatment of refractory myeloma in MM patients 54 patients with relapsed myeloma following 1 line of therapy at 1.0mg/m^2 or 1.3mg/m^2	33% ORR in patients treated with 1.0mg/m^2 of bortezomib 50% ORR in patients treated with 1.3mg/m of bortezomib	Jagannath 2003 Jagannath 2008
	SUMMIT	Study of uncontrolled myeloma management with proteasome inhibition therapy 202 patients with relapsed refractory myeloma	35% ORR with single agent bortezomib 50% ORR with addition of dexamethasone	Richardson 2003
Phase III	APEX	The Assessment of Proteasome inhibition for EXtending remissions compared bortezomib with high dose dexamethasone 669 patients with MM relapsed after one or more prior therapies	38% ORR of bortezomib alone 8% dexamethasone alone Trial was terminated early and dexamethasone arm joined the bortezomib arm	Richardson 2005 Richardson 2007
	VISTA	Velcade as initial standard therapy in multiple myeloma melphalan and prednisone (MP) with or without bortezomib were compared in 682 newly diagnosed MM patients not candidates for autologous stem cell transplantation	30% ORR with combination of bortezomib and MP 4% ORR without bortezomib addition to MP	San Miguel 2003 Mateos 2008
Phase I/II	PINNACLE	Study of 155 relapsed mantle cell lymphoma patients who had at least one prior therapy for use of bortezomib as front line therapy	32% ORR with single agent bortezomib	Fisher 2006 Goy 2009
	VERTICAL	Velcade in combination with bendamustine and rituximab 73 subjects with relapsed or refractory follicular lymphoma	88% ORR with combination of bortezomib	Fowler 2011

SUMMIT – Response Rates Bortezomib Alone

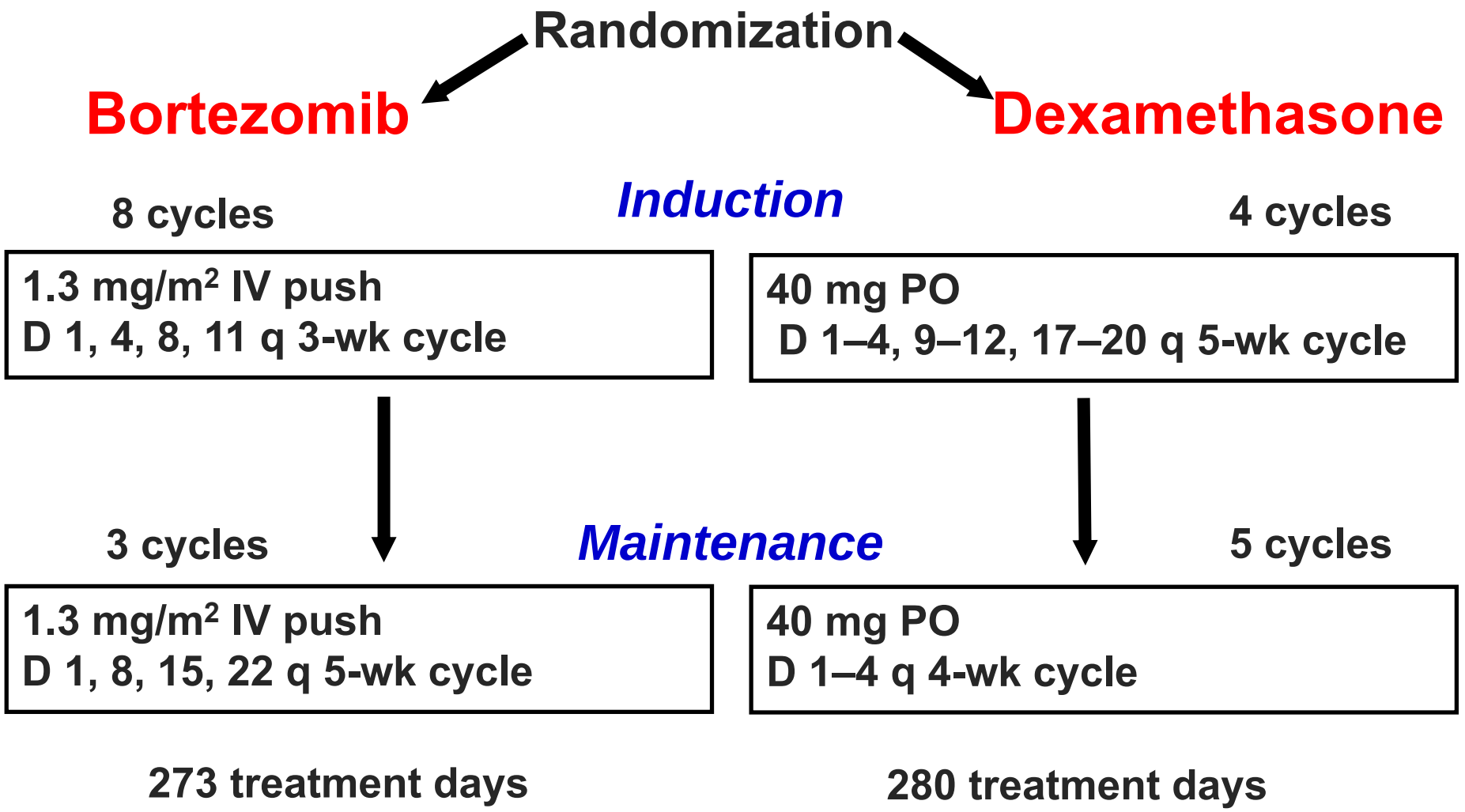


- 35% overall response (CR+PR+MR)
- 27% CR+PR
- 24% stable disease
- 59% of patients SD or better

Of 202 Patients, 193 were evaluable for response and duration of response by an Independent Review Committee. All response data based on stringent Bladé criteria: CR as defined by Bladé required disappearance of M protein by immunofixation; bone marrow <5% plasma cells; no new bone disease; no plasmacytomas; and confirmation 6 weeks apart.

Richardson et al N. E. J. M. 2003, 348:2609

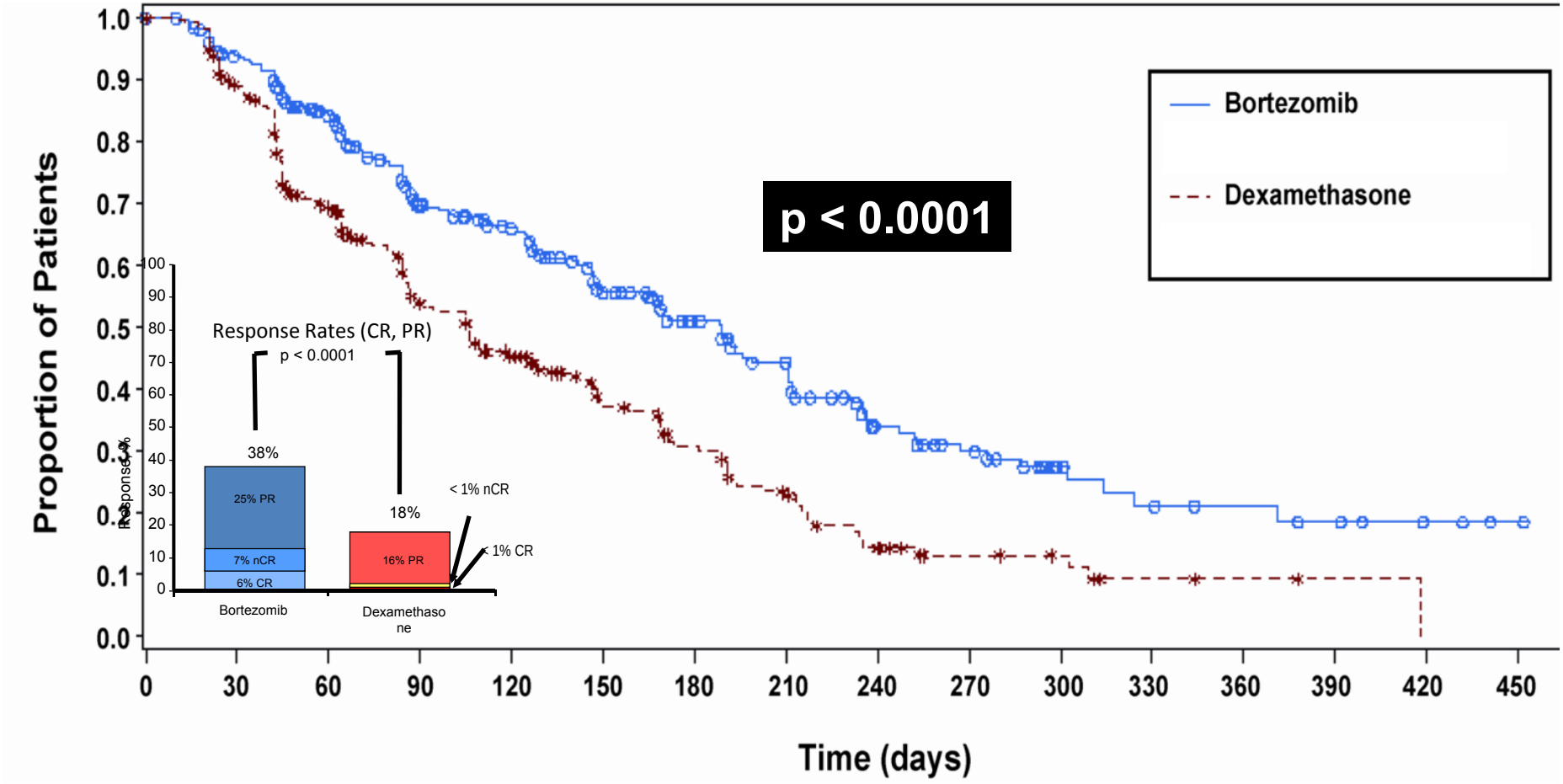
APEX: Treatment Plan



Richardson et al, *N Engl J Med. 2005;352:2487-98.*

Time to Progression (N = 669)

78% improvement in median TTP with Bortezomib

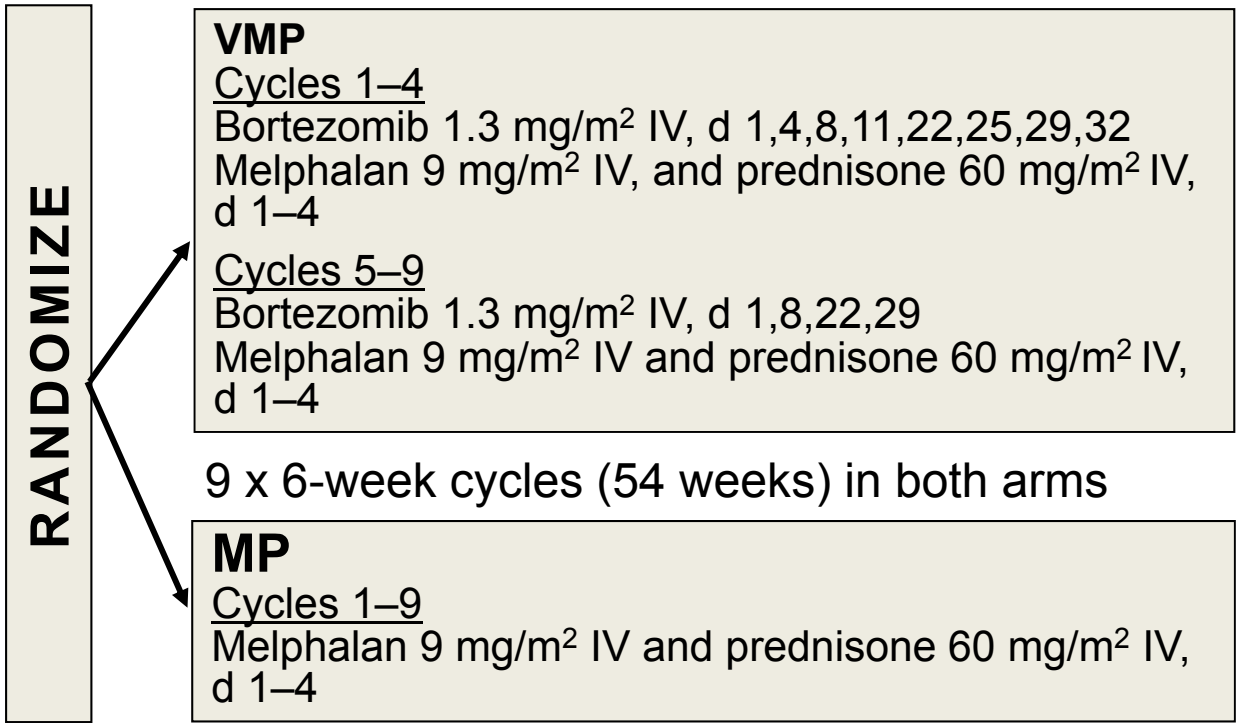


Median TTP: Bortezomib 6.2 mos
Dexamethasone 3.5 mos

Richardson et al, *N Engl J Med. 2005;352:2487-98.*

VISTA: VELCADE as Initial Standard Therapy in multiple myeloma: Assessment with melphalan and prednisone

- Randomized, international, phase III trial of VMP vs MP in previously untreated MM patients who were not candidates for HDT-ASCT
- Patients: Symptomatic multiple myeloma/end organ damage with measurable disease
  - ≥ 65 years or < 65 years and not transplant-eligible; KPS ≥ 60



- Primary end point: TTP
- Secondary end points: CR rate, ORR, time to response, DOR, time to next therapy, OS, PFS, QoL (PRO)

- Stratification: β_2-microglobulin, albumin, region

***San Miguel et al**, N Engl J Med. 2008; 359:906-17*

Bortezomib+MP (VMP) vs MP: Efficacy data

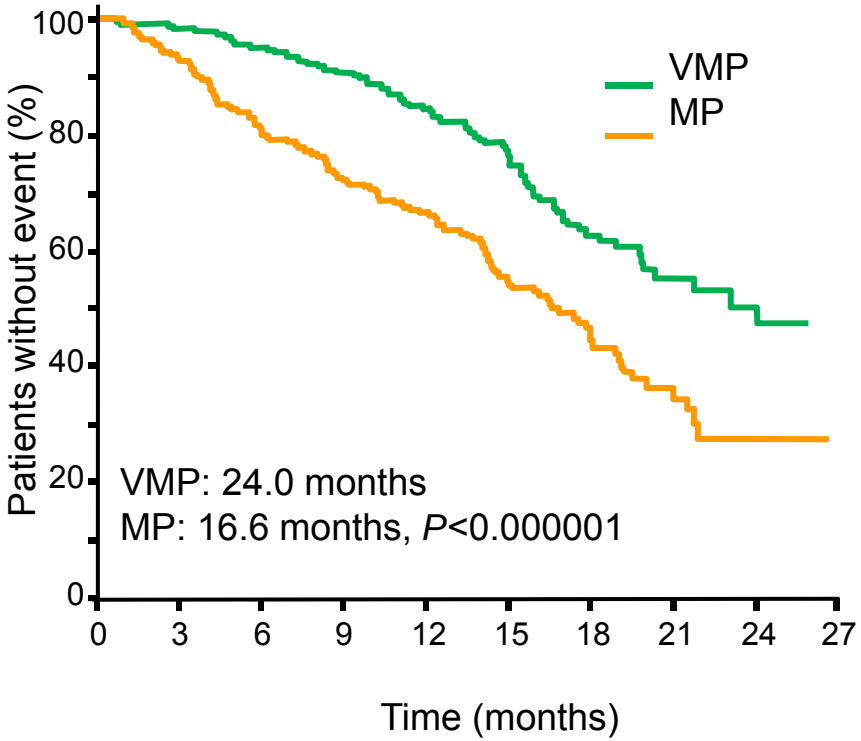
(682 patients)

ORR: VMP 71%, MP 35%,

CR: VMP 30%, MP 4%

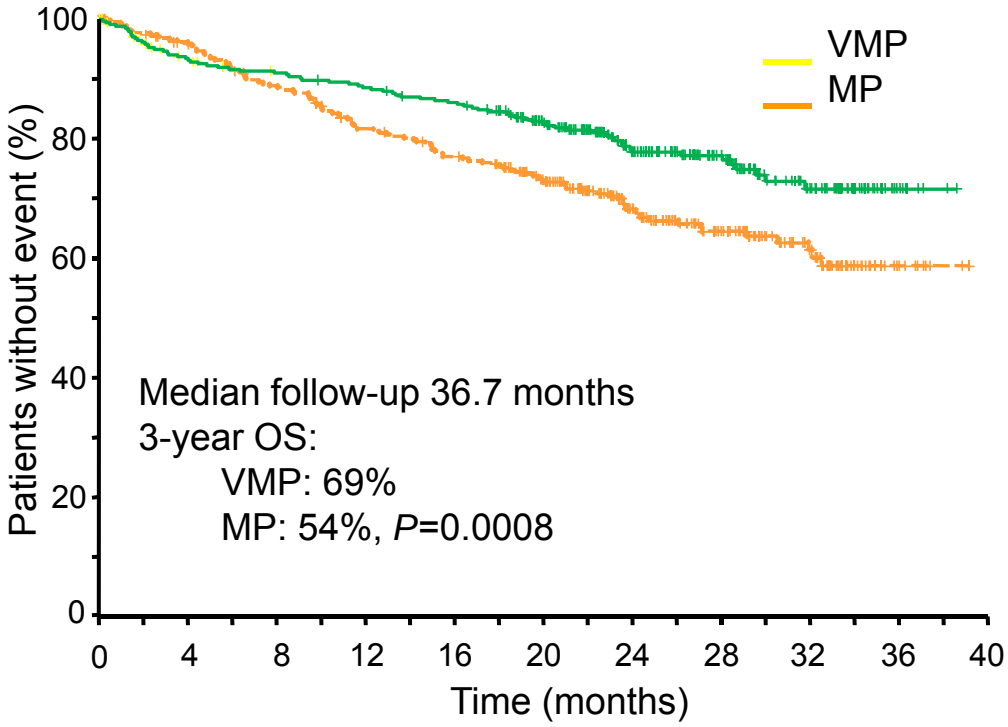
Time to progression

52% reduced risk of progression on VMP



Overall survival

~36% reduced risk of death on VMP

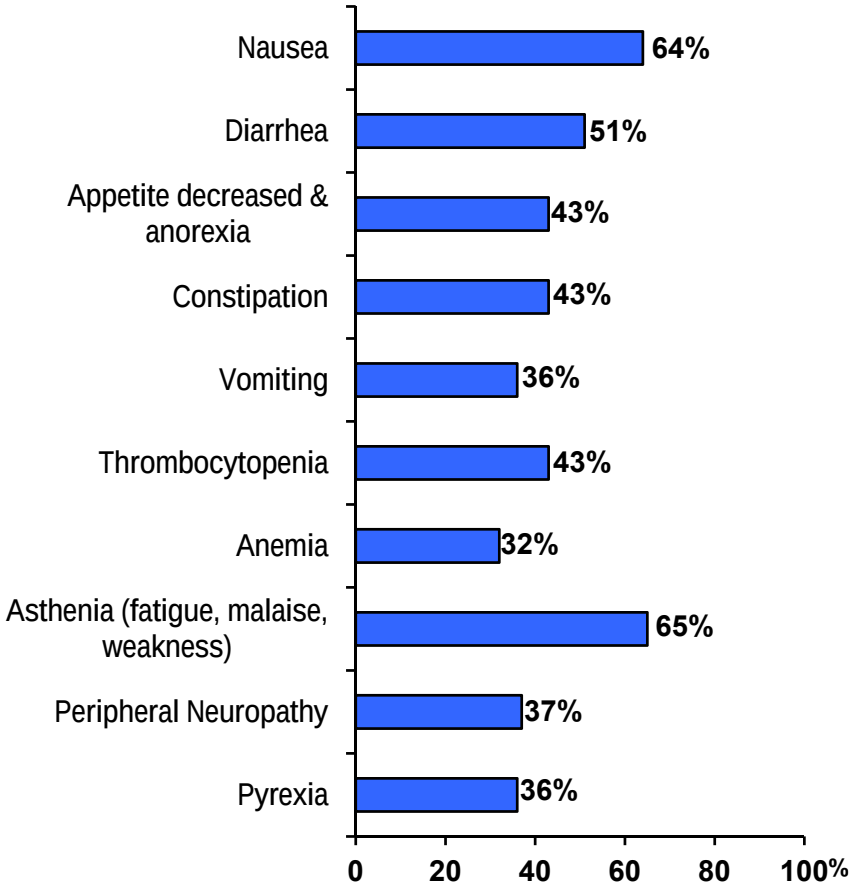


San Miguel et al. *N Engl J Med 2008;359:906–917 , Updated by* ***Mateos*** *et al JCO 2010*

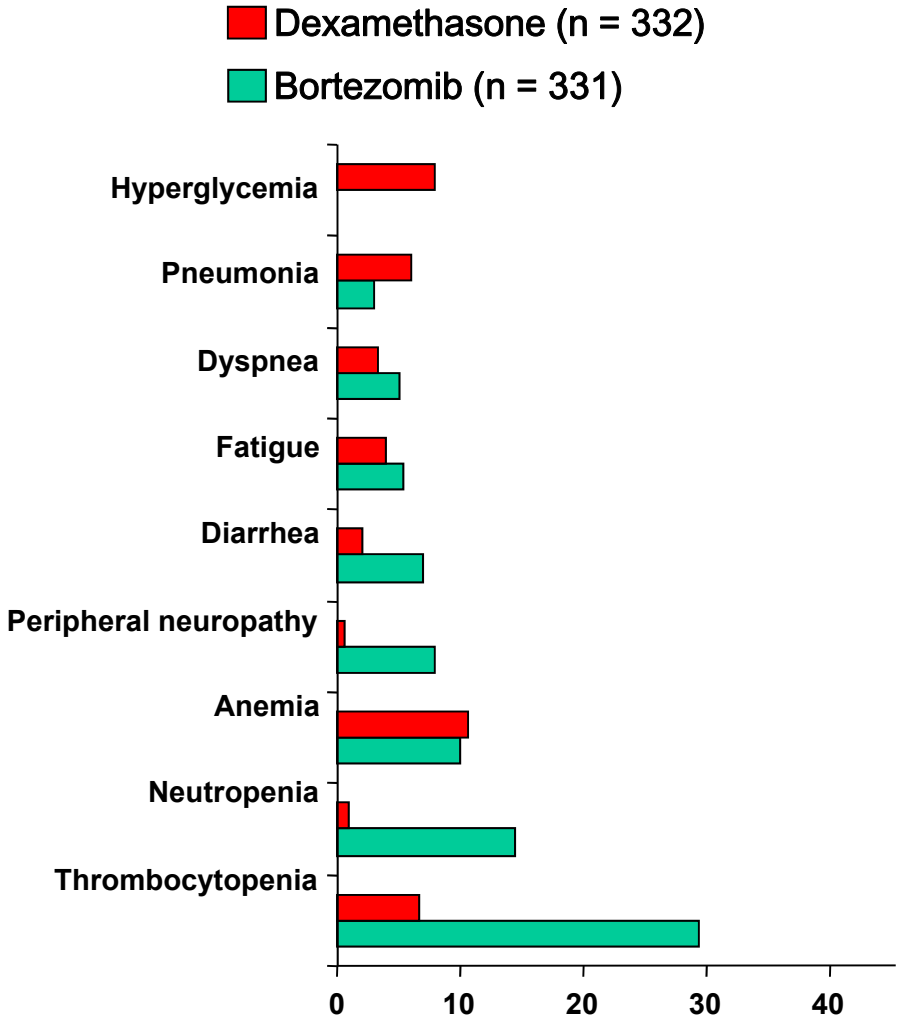
Bortezomib safety

combined data from
SUMMIT and CREST

On-Study adverse events (≥30% overall) at 1.3 mg/m² dose (n=228)



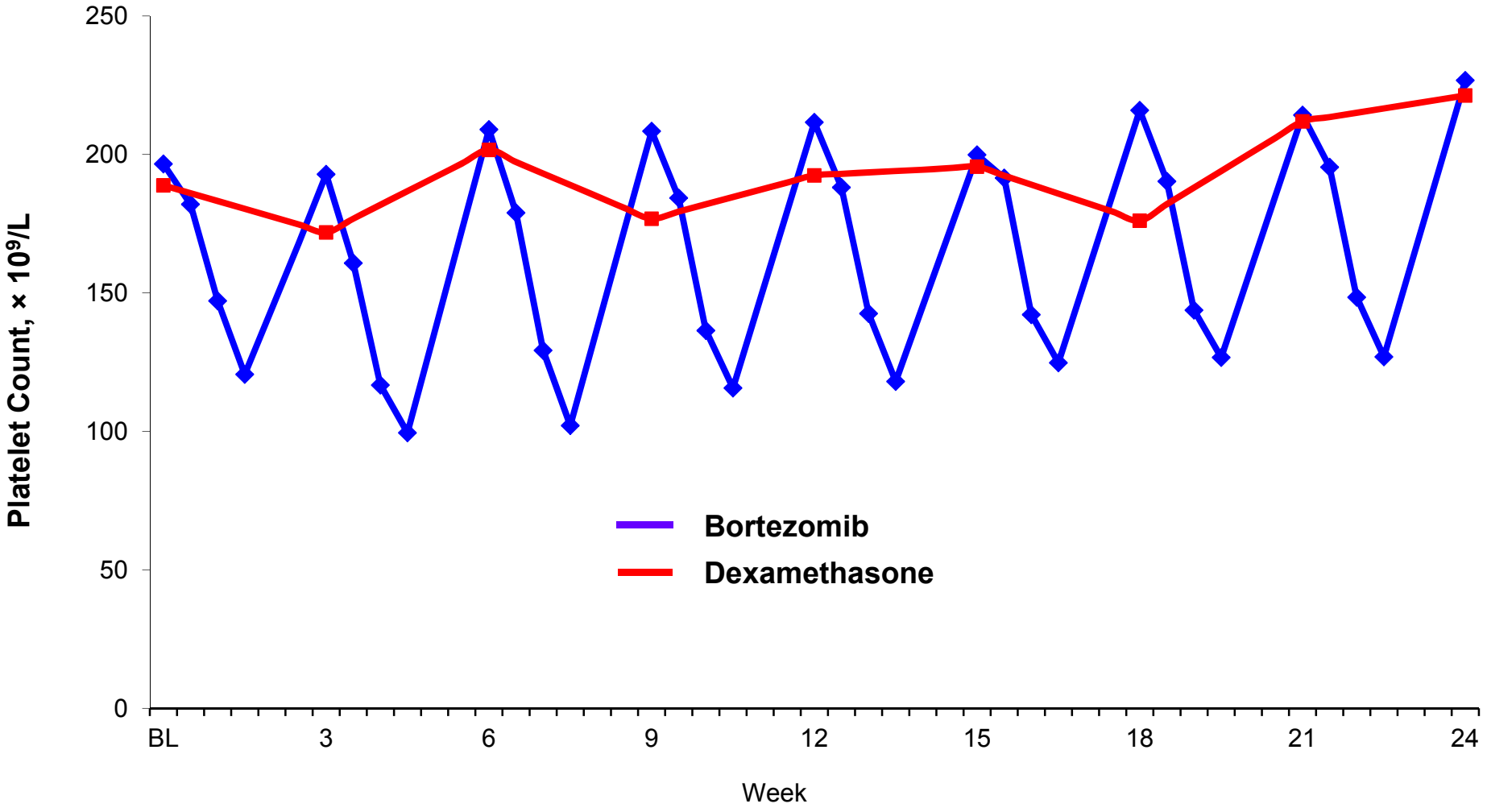
APEX Trial
Treatment-Emergent ≥ G3 AEs Reported by ≥ 5% of Pts Receiving Bortezomib or Dex



* AEs reported for all events, drug related or not. † National Cancer Institute Common Toxicity Criteria (NCI CTC, Version 2.0).

1. Millennium Pharmaceuticals, Inc., 2003.

Mean Platelet Count During Treatment



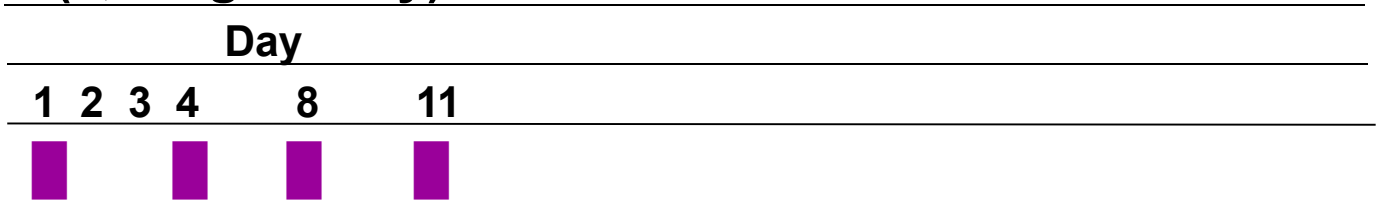
- **Bortezomib arm: platelet counts measured on D1, 4, 8, 11 of each 21d cycle**
- **Dexamethasone arm: platelet counts measured every 3 wks**

Peripheral Neuropathy (PNP)

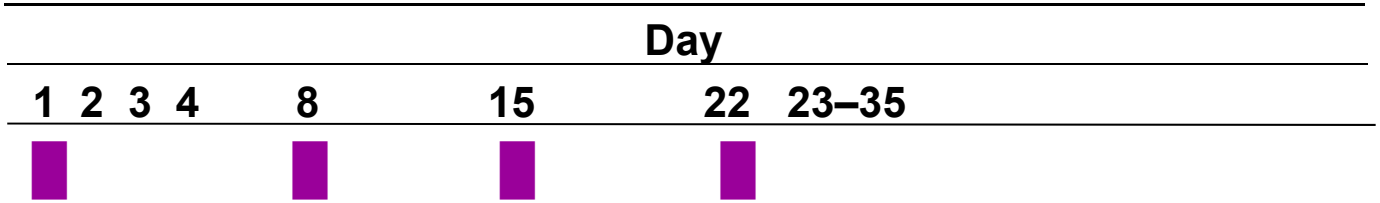
- 69% of 310 pts on Bortezomib reported symptoms of PNP at baseline (FACT/GOG-Ntx score >0)
- PNP reported in:
  - Bortezomib 36% (≥ Grade 3 = 8%)
  - Dex 9% (≥ Grade 3 < 1%)
- Baseline FACT/GOG-Ntx score directly correlated with development of ≥ Grade 3 PNP
- PNP ≥ Grade 2 improved or resolved in 51% of pts
  - Median time to improvement or resolution from first onset = 107 d (~ 3.5 mos)

Bortezomib: Treatment schedule

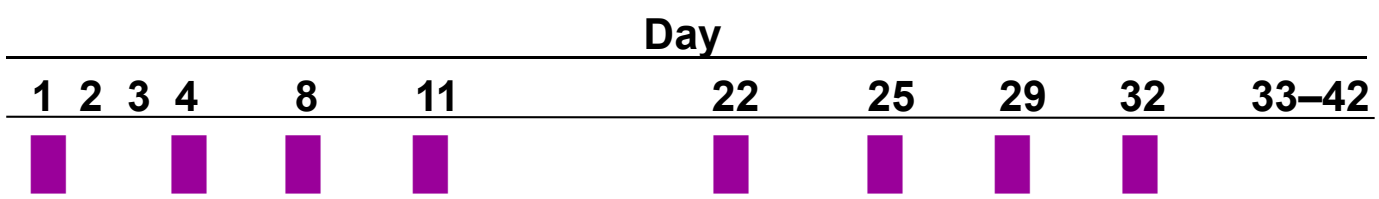
- Three week cycles (1,3 mg/m²/day)



- Five week cycles (1,3 mg/m²/day) (1,6 mg/m²/day)



- Six week cycles (1,3 mg/m²/day)



IV *vs.* SC

Bortezomib combinations

- VT
- VD_{ex}
- VD_{ox}

- VTD
- VRD
- PAD
- DVd
- VMP
- VCD

- VATD
- VRTD
- VMTP

- VTD-PACE
- VRD-PACE

Bortezomib in NHL

II) 155 relapsed or refractory mantle cell lymphoma (MCL) patients treated with bortezomib monotherapy: overall response rate (ORR) of 32% [PINNACLE study, FDA approval for MCL]	Fisher 2006 Goy 2009.
II) Bortezomib and gemcitabine combination for relapsed or refractory: ORR 60%	Kouroukis 2011
II) VERTICAL trial: relapsed/refractory follicular lymphoma (n=73) bortezomib + bendamustine+ rituximab: ORR of 88% (CR, 53%)	Fowler 2011
I/II) Bortezomib + R-CHOP • DLBCL (n=40): ORR, 100%, CR/uCR 86% • MCL (n=36): ORR 91%, CR/uCR 72%.	Ruan 2011

Bortezomib in WM

	Authors	n	Courses	Assot	MR	HQR
Treated	Dimopoulos, Haematologica 05	10	6	No	60%	0%
	Chen et al., JCO 07	27	6	No	44%	0%
	Treon et al., CCR 07	27	6	No	48%	0%
	Ghobrial et al, JCO 10	37	6	R	87%	5%
Untreated	Treon et al., JCO 2009*	23	6	RD	96%	22%
	Dimopoulos, Blood 2013*	59	6	RD	85%	10%

**PNP 69%, G2 39%, G3 30%; **45% PNP any grade; only 7% G3*

Conclusions

Bortezomib demonstrated high efficacy in 1st and ≥2nd line MM

Bortezomib is safe: thrombocytopenia and PNP concerns

Bortezomib can be used in combination with other drugs in MM

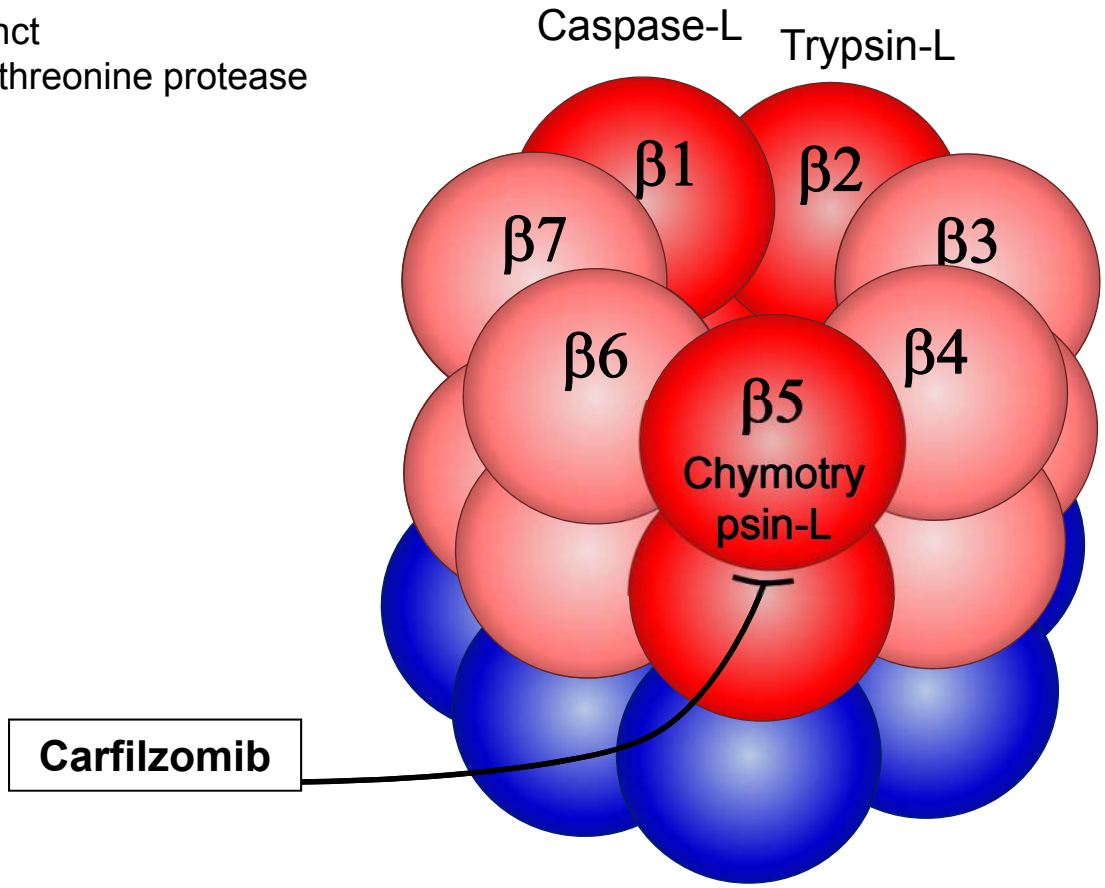
Boretozmib can be useful in other Hematological malignancies: WM, Amyloidosis, MCL DLBCL, FL

Proteasome inhibitors

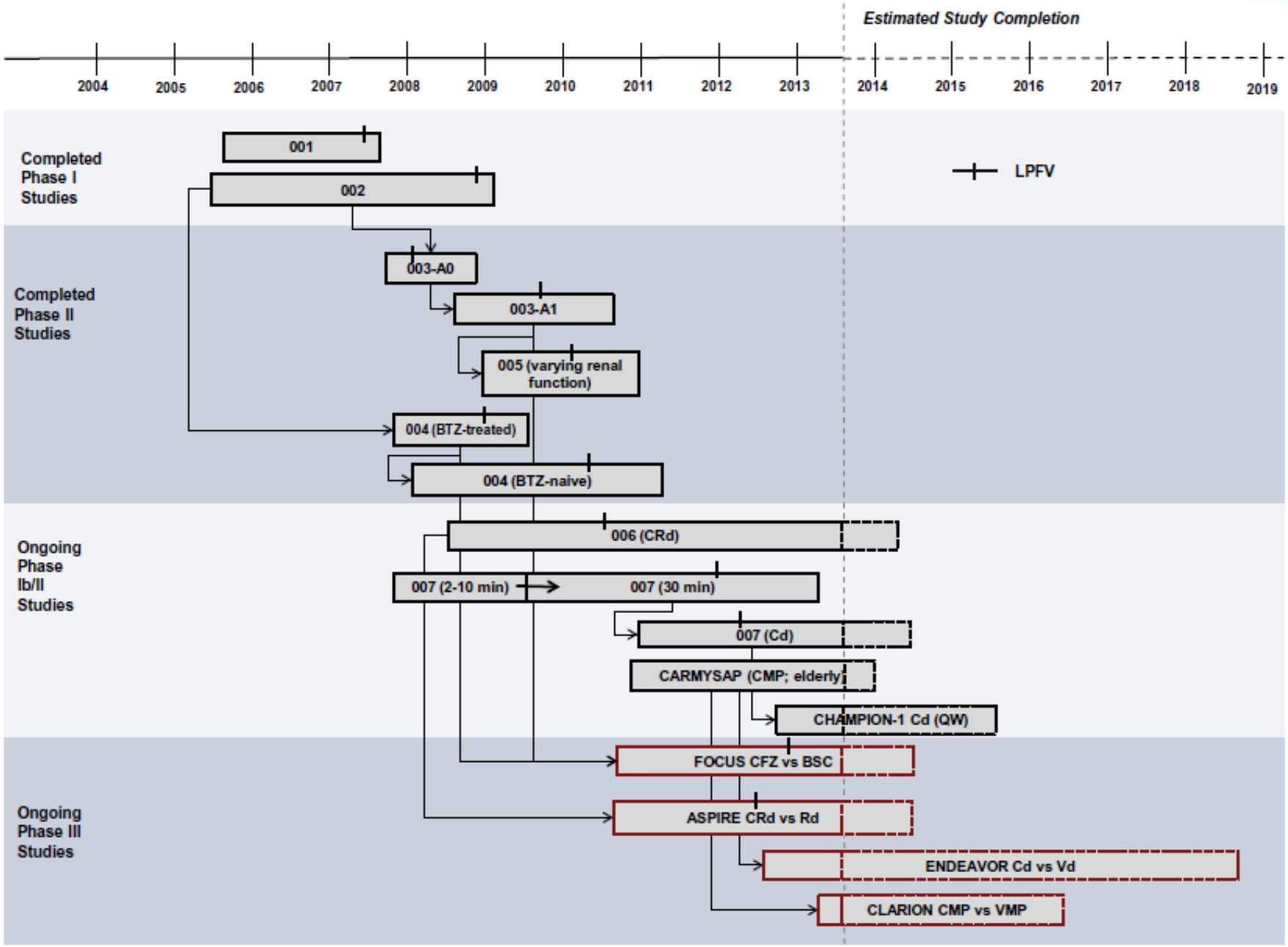
β-subunit ring of the proteasome

Catalytic site

Three distinct
N-terminal threonine protease
active sites



Carfilzomib completed and ongoing studies



Carfilzomib Efficacy Summary

- Pivotal 003A1 Study (N = 266)
  - Patients with high unmet medical need
    - Actively progressing, multiply relapsed, and refractory myeloma
  - Objective, durable, and clinically meaningful benefit
    - ORR 22.9%, median DOR of 7.8 months
      - ORR by IRC and investigator highly concordant
    - CBR 35.7%, median DOCBR of 8.3 months
    - Consistent benefit in clinically important subgroups
  - Benefit replicated in supportive Phase 2 myeloma trials

Siegel et al, Blood. 2012; 120:2817-25

Common Hematologic AEs ≥ 20% Study 003A1

CS-5

AEs Regardless of Relationship	N = 266 %			
	All Grades	Grade 3	Grade 4	Grade 5
Anemia	46	22	2	0
Thrombocytopenia	39	17	12	0
Lymphopenia	23	18	2	0

- 1 patient discontinued
- Clinical sequelae of cytopenias
  - Bleeding (≥ Grade 2) and thrombocytopenia 2%
  - Zoster reactivation 2%
  - Febrile neutropenia 0.8%

Common Non-Hematologic AEs ≥ 20% Study 003A1

CS-6

N = 266

%

AEs Regardless of Relationship	All Grades	Grade 3	Grade 4	Grade 5
Fatigue	49	8	0	0
Nausea	45	2	0	0
Dyspnea	34	3	0	0.4
Diarrhea	32	0.4	0.4	0
Pyrexia	31	2	0	0
Headache	28	2	0	0
Upper respiratory tract infection	27	5	0	0
Blood creatinine increased	25	3	0	0
Cough	24	0.4	0	0
Back pain	24	5	0	0
Peripheral Edema	23	0.4	0	0
Vomiting	22	0.8	0	0
Constipation	21	0	0	0

Peripheral Neuropathy AEs 003A1

CS-7

N = 266

%

AE Regardless of Relationship	All Grades	Grade 3	Grade 4	Grade 5
Peripheral Neuropathy	12	1	0	0

- Baseline neuropathy: 77%
- No patient discontinued
- Consistent with selectivity of carfilzomib proteasome inhibition*

*Arastu-Kapur, 2011.

Serious Adverse Events ≥ 2%

SAEs Regardless of Relationship	003A1 N = 266 %	Phase 2 MM Population N = 526 %
Any Event	47.4	44.9
Pneumonia	8.6	9.9
Disease progression	6.0	5.9
Acute renal failure	3.4	4.2
Congestive cardiac failure	3.0	3.4
Pyrexia	3.0	3.4
Pathological fracture	3.0	2.1
Hypercalcemia	2.3	2.1
Spinal cord compression	2.3	1.3

Current Press Releases

ONYX PHARMACEUTICALS
An Amgen subsidiary

S E
H H

Amgen Announces Phase 3 ASPIRE Trial of Kyprolis in Patients with Relapsed Multiple Myeloma Met Primary Endpoint

THOUSAND OAKS, Calif. and SOUTH SAN FRANCISCO, Calif. . — Aug 04, 2014

Kyprolis Helped Patients Live 8.7 Months Longer Without Their Disease Worsening

Results to Form Basis of Regulatory Filings Beginning in 1H 2015

Amgen (NASDAQ:AMGN) and its subsidiary, Onyx Pharmaceuticals, Inc., today announced that a planned interim analysis demonstrated that the Phase 3 clinical trial ASPIRE (C**A**rfilzomib, Lenalidomide, and Dexametha**S**one versus Lenalidomide and Dexamethasone for the treatment of **P**at**I**ents with **R**elapsed Multiple My**E**loma) met its primary endpoint of progression-free survival (PFS). Patients treated with Kyprolis® (carfilzomib) for Injection in combination with Revlimid® (lenalidomide) and low-dose dexamethasone (KRd) lived significantly longer without their disease worsening (median 26.3 months) compared to patients treated with Revlimid and low-dose dexamethasone (Rd) (median 17.6 months) (HR=0.690, 95 percent CI, 0.570, 0.834, p<0.0001). While the data for overall survival, a secondary endpoint, are not yet mature, the analysis showed a trend in favor of KRd that did not reach statistical significance.

The safety profile observed in this study is consistent with the current U.S. Kyprolis label, including the rate of cardiac

Amgen Announces Top-Line Results From Phase 3 Focus Trial Of Kyprolis® In Patients With Relapsed And Advanced Refractory Multiple Myeloma

August 14, 2014

THOUSAND OAKS, Calif. and SOUTH SAN FRANCISCO, Calif., Aug. 13, 2014 /PRNewswire/ -- Amgen (NASDAQ:AMGN) and its subsidiary, Onyx Pharmaceuticals, Inc., today announced that the Phase 3 clinical trial FOCUS (CarFilzOmib for AdvanCed Refractory MUltiple Myeloma European Study) did not meet its primary endpoint of improving overall survival (OS) (HR=0.975, 95 percent CI, 0.760, 1.249). The 315-patient, open-label study evaluated single-agent Kyprolis® (carfilzomib) for Injection compared to an active control regimen of low-dose dexamethasone, or equivalent corticosteroids, plus optional cyclophosphamide in patients with relapsed and advanced refractory multiple myeloma. Nearly all patients in the control arm received cyclophosphamide. Patients were heavily pretreated and had received a median of five therapeutic regimens prior to study entry.

Treatment discontinuation due to adverse events and on-study deaths were

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenström's macroglobulinemia

Steven P. Treon,[1,2] Christina K. Tripsas,[1] Kirsten Meid,[1] Sandra Kanan,[1] Patricia Sheehy,[1] Stacey Chuma,[1] Lian Xu,[1] Yang Cao,[1] Guang Yang,[1] Xia Liu,[1] Christopher J. Patterson,[1] Diane Warren,[1] Zachary R. Hunter,[1] Barry Turnbull,[3] Irene M. Ghobrial,[1,2] and Jorge J. Castillo[1,2]

[1]Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA; [2]Harvard Medical School, Boston, MA; and [3]BioBridges Inc., Newton, MA

Key Points

- Carfilzomib, rituximab, and dexamethasone (CaRD) produce overall and CR/VGPR responses in 87% and 36% of frontline WM patients, respectively.
- CaRD activity was not impacted by MYD88 and CXCR4 mutations and represents a neuropathy-sparing option for treating WM patients.

Bortezomib frequently produces severe treatment-related peripheral neuropathy (PN) in Waldenström's macroglobulinemia (WM). Carfilzomib is a neuropathy-sparing proteasome inhibitor. We examined carfilzomib, rituximab, and dexamethasone (CaRD) in symptomatic WM patients naïve to bortezomib and rituximab. Protocol therapy consisted of intravenous carfilzomib, 20 mg/m2 (cycle 1) and 36 mg/m^2 (cycles 2-6), with intravenous dexamethasone, 20 mg, on days 1, 2, 8, and 9, and rituximab, 375 mg/m^2, on days 2 and 9 every 21 days. Maintenance therapy followed 8 weeks later with intravenous carfilzomib, 36 mg/m^2, and intravenous dexamethasone, 20 mg, on days 1 and 2, and rituximab, 375 mg/m^2, on day 2 every 8 weeks for 8 cycles. Overall response rate was 87.1% (1 complete response, 10 very good partial responses, 10 partial responses, and 6 minimal responses) and was not impacted by MYD88^{L265P} or CXCR4^{WHIM} mutation status. With a median follow-up of 15.4 months, 20 patients remain progression free. Grade ≥2 toxicities included asymptomatic hyperlipasemia (41.9%), reversible neutropenia (12.9%), and cardiomyopathy in 1 patient (3.2%) with multiple risk factors, and PN in 1 patient (3.2%) which was grade 2. Declines in serum IgA and IgG were common. CaRD offers a neuropathy-sparing approach for proteasome inhibitor-based therapy in WM. This trial is registered at www.clinicaltrials.gov as #NCT01470196. (*Blood*. 2014;124(4):503-510)

Response Evaluation

	n = 31
Best overall response rate,* n (%)	25 (81.0%)
CR	1 (3.2%)
VGPR	8 (25.8%)
Partial response	12 (38.7%)
Minor response (MR)	4 (12.9%)

* Using criteria adapted from the Third International Workshop on WM

- Median follow-up = 8 cycles
- Median time to response (for MR or better) = 2.1 months
- 22 patients remain on study, including 20 currently on maintenance therapy

Treon SP et al. *Proc ASH* 2013;Abstract 757 (abstract only).

Adverse Events (AEs) and Treatment Discontinuation

Grade >2 AEs	n = 31
Asymptomatic lipase elevation	12.9%
Hyperglycemia (dexamethasone-related)	6.5%
Reversible neutropenia	9.7%
Cardiomyopathy	3.2%
Peripheral neuropathy	0%

- **Treatment discontinuation occurred for the following reasons:**
  - Nonresponse (n = 8)
  - Cardiomyopathy in a patient with multiple cardiac risk factors (n = 1)
  - Progressive disease (n = 1)

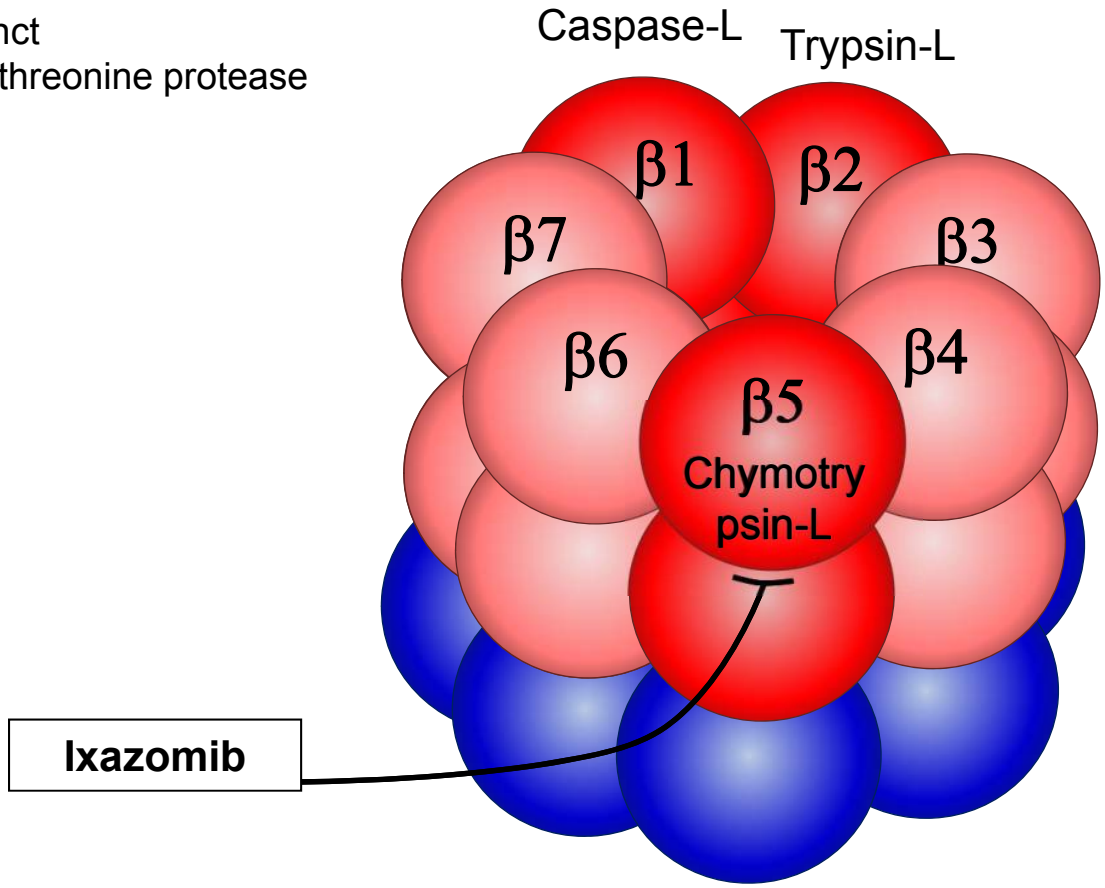
Treon SP et al. *Proc ASH* 2013;Abstract 757 (abstract only).

Proteasome inhibitors

β-subunit ring of the proteasome

Catalytic site

Three distinct
N-terminal threonine protease
active sites



Oral therapy for multiple myeloma: ixazomib arriving soon

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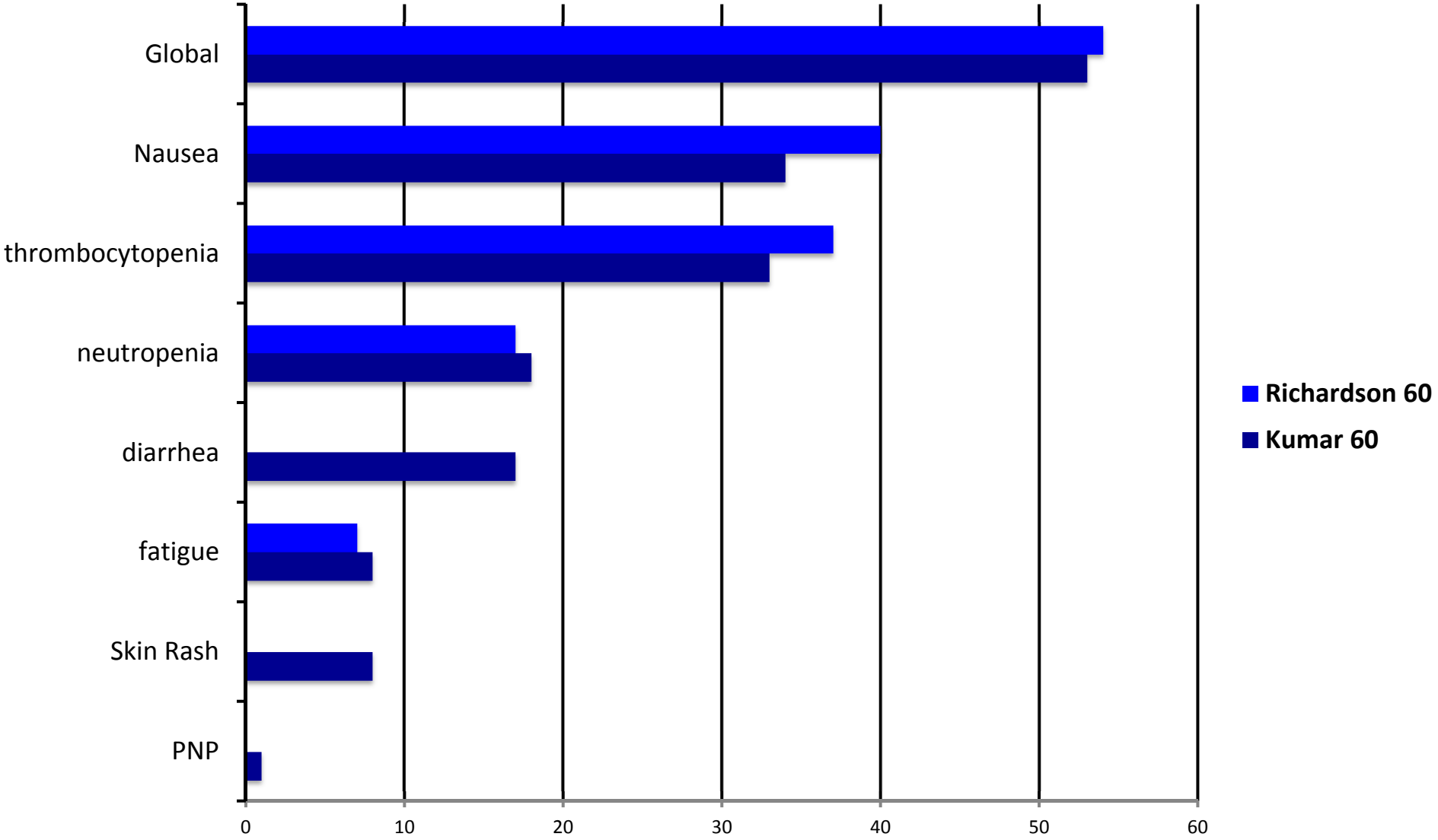
In this issue of *Blood*, Kumar et al and Richardson et al report the results of 2 phase 1 trials that investigated 2 different administration schedules of ixazomib in patients with relapsed/refractory multiple myeloma (MM): weekly and biweekly dosing.[1,2] Kumar et al determined that the maximum tolerated dose (MTD) of single-agent oral ixazomib given weekly for 3 of 4 weeks was 2.97 mg/m^2.[1] Detailed pharmacokinetic analyses showed that after multiple dosing, the terminal half-life was long (3.6–11.3 days), supporting once-weekly dosing. In the trial by Richardson et al, the MTD of single-agent, oral ixazomib, given on days 1, 4, 8, 11 of a 21-day cycle was found to be 2 mg/m^2.[2]

Two proteasome inhibitors (PI), bortezomib and carfilzomib, are currently approved for the treatment of myeloma; ixazomib is expected to be the first oral PI available in the near future.

Proteasome inhibition has emerged as an important therapeutic strategy in MM.[3] Bortezomib was the first-in-class PI to be introduced into the clinic.[4] It is a dipeptidyl boronic acid–based specific, reversible PI that targets the chymotrypsin- and caspase-like active sites of the 20S proteasome, with minimal effect on trypsin-like activity. By inhibiting the proteasome, bortezomib acts through multiple mechanisms, suppressing tumor survival, and arresting tumor growth, spread, and angiogenesis. Since the publication of the first phase 1 trials of bortezomib 12 years ago, this drug has contributed substantially to the observed improvement in survival in MM patients over the last decade.[4] First approved as an intravenous (IV) single agent in the relapsed setting, bortezomib is now predominantly used in combination regimens and is an integral part of front-line therapy. The standard twice-weekly schedule may be replaced by weekly infusion, especially when bortezomib is used as part of combination regimens. Additionally, a new route of bortezomib administration, subcutaneous (SC) infusion, was recently approved.[5] The most common bortezomib-associated toxicities are gastrointestinal symptoms, anemia, thrombocytopenia, fatigue, and peripheral neuropathy (PN). Neurotoxicity remains the most cumbersome adverse effect; however, it can be managed and limited with dose modification, weekly dosing, and by SC administration.

Carfilzomib is an irreversible PI that belongs to the epoxyketone class and is structurally and mechanistically distinct from bortezomib.[4] This second-in-class PI demonstrates potent and sustained inhibition of the chymotrypsin-like activity of the proteasome with a greater selectivity for the chymotrypsin-like protease compared with bortezomib and lower affinity for the trypsin- and caspase-like proteases. Single-agent IV carfilzomib has produced robust and durable responses in clinical trials, and it has been approved in the United States for the treatment of relapsed and refractory MM.[6] Due to its favorable safety profile, carfilzomib is an attractive agent for use in combination strategies. Ongoing pivotal randomized phase 3 studies are exploring the efficacy and safety of carfilzomib combinations in patients

Ixazomib: secondary effects



Kumar *et al Blood. 2014;124:1047;* ***Richardson*** *et al Blood. 2014;124:1038.*

Ixazomib: Efficay

	Kumar (wk)		Richardson (Bwk)	
Evaluable	50	%	55	%
CR	0	0%	1	2%
VGPR	1	2%	1	2%
PR	9	18%	6	11%
MR	1	2%	1	2%
SD	7	30%	33	60%
PD	25	50%	13	24%

Kumar *et al Blood. 2014;124:1047; Richardson et al Blood. 2014;124:1038.*

PI: Conclusions

Proteasome inhibitors are efficient in MM, and probably in NHL, WM, Amyloidosis, in first and 2nd line

PI are safe: thrombocytopenia, viral reactivation, PNP, and rare cardiopulmonary secondary effects

They can be used in combination with other drugs in several subsets

They are mostly available as IV compounds, but SC is also possible and ORAL formulations are coming

Unfolded Protein Response Inhibitors

Tanespimycin
Alvespimycin

misfolded protein

E1, E2, E3 ligases

Ub

proteasome

Hsp90 inhibitors

nascent protein

Hsp-90 Chaperone

folded protein

HDAC6

aggresome

Novel proteasome inhibitors

NPI-0052
Carfilzomib
AB1010

HDAC6 inhibitors

Tubacin

autophagosome

Several mechanisms have been proposed to explain these observed effects, such as:

- down regulation of NFκB and other anti-apoptotic proteins
- activation of the tumor suppressor protein p53
- modulation of cell cycle proteins and other pro-apoptotic factors.

Ixazomib: some ongoing studies

29: 61 cases R/R MM: 18% PR, Grade 3–4 thrombocytopenia and neutropenia occurred in 33% and 18% of patients, respectively. Thrombocytopenia was typically transient and cyclical, and only 8% of patients required platelet transfusions. Nonhematologic adverse events mainly included diarrhea (17%), nausea (7%), and vomiting (5%). Only 2% of patients experienced grade 3 peripheral neuropathy, and 12% discontinued therapy due to adverse events.

30: orally on days 1, 4, 8, and 11 . N=60. Grade 3 thrombocytopenia and neutropenia were reported in 37% and 17% of patients, respectively; skin disorders in 8%. 13% of patients discontinued

31. 5.5 mg days 1, 8, 15 every 28 days (+dexa 20 mg in 50%). N=33. Grade PNP. At 4 cycles PR in 16%, increasing to 34% after addition of dexa. With a median follow-up of 7 months, overall survival (OS) at 6 months was 96%.

Newly diagnosed, ixazomib on days 1, 8, and 15, lenalidomide 25 mg on days 1–21, and dexamethasone 40 mg on days 1, 8, 15, and 22 for up to 12 28-day cycles. Then, maintenance with ixazomib, same schedule every 28 days until progression. N=50: ORR 96%. G3–4 neutropenia and thrombocytopenia in 9% & 6% of patients. At least PR was documented in 94% of patients (CR 19%, VGPR 30%, PR 45%), and response improved after eight cycles when CR was documented in 32% of patients (88% of them MRD FCM-)

Carfilzomib completed and ongoing studies

Key ongoing studies of carfilzomib in MM that were informed by the results of phase I/II trials.

	PX-171-006	PX-171-007	CARMYSAP	ASPIRE	FOCUS	ENDEAVOR	CLARION	CHAMPION-1
Phase	Ib/II	Ib/II	I/II	III	III	III	III	I/II
Registration number	NCT00603447	NCT00531284	NCT01279694	NCT01080391	NCT01302392	NCT01568866	NCT01818752	NCT01677858
Age, y	⩾18	⩾18	>65	⩾18	⩾18	⩾18	⩾18	⩾18
Diagnosis	Relapsed or progressive MM	Relapsed and/or refractory MM[a]	Newly diagnosed, transplant-ineligible MM	Relapsed MM	Relapsed and refractory MM	Relapsed MM	Newly diagnosed, transplant-ineligible MM	Relapsed or refractory MM
Number of prior anti-MM therapies	1–3	⩾2	0	1–3	⩾3	1–3	0	1–3
ECOG PS	0–2	0–2	0–2	0–2	0–2	0–2	0–2	0 or 1
Hematologic parameters	ANC ⩾ 1000/mm^3, Hb ⩾ 8.0 g/dL, platelets ⩾ 50,000/mm^3	ANC ⩾ 1000/mm^3, platelets ⩾ 30,000/mm^3, Hb ⩾ 7.0 g/dL	ANC ⩾ 1000/mm^3, platelets ⩾ 50,000/mm^3	ANC ⩾ 1000/mm^3, Hb ⩾ 8.0 g/dL, platelets ⩾ 50,000/mm^3	WBCs ⩾ 1500/mm^3, ANC ⩾ 1000/mm^3, Hb ⩾ 7.5 g/dL, platelets ⩾ 30,000/mm^3	ANC ⩾ 1000/mm^3, Hb ⩾ 8.0 g/dL, platelets ⩾ 50,000/mm^3	ANC ⩾ 1000/mm^3, Hb ⩾ 8.0 g/dL, platelets ⩾ 50,000/mm^3	ANC ⩾ 1000/mm^3, Hb ⩾ 8.0 g/dL, platelets ⩾ 50,000/mm^3
Organ function	Adequate hepatic function; CrCl ⩾ 50 mL/min	Adequate hepatic function; CrCl ⩾ 20 mL/min	Adequate hepatic function; CrCl > 30 mL/min	Adequate hepatic function; CrCl ⩾ 50 mL/min	Adequate hepatic function; CrCl ⩾ 15 mL/min	Adequate hepatic function; CrCl ⩾ 15 mL/min	Adequate hepatic function; CrCl ⩾ 15 mL/min	Adequate hepatic function; CrCl ⩾ 30 mL/min
Dosing schedule	QD × 2[b]	QD × 2[b]	QD × 2[c]	QD × 2[b]	QD × 2[b]	QD × 2[b]	QD × 2[c]	QW[d]
Carfilzomib dose, cycle 1 (mg/m^2)	15, 20, or 20 on D1, 2 only, then 27 thereafter (dose-escalation phase); 20 on D1, 2, then 27 thereafter (dose-expansion phase)	20 on D1, 2, then 36–70 thereafter (dose-escalation phase) or 45–56 thereafter (dose-expansion phase)	20 on D1, 2, then 20–45 thereafter (dose-escalation phase) or 36 thereafter (dose-expansion phase)	20 on D1, 2, then 27 thereafter	20 on D1, 2, then 27 thereafter	20 on D1, 2, then 56 thereafter	20 on D1 & 2 of cycle 1, then 36 thereafter	20 on D1 of cycle 1, then 45–88 thereafter (dose-escalation phase); or MTD thereafter (dose-expansion phase)
Carfilzomib dose, cycle 2 and beyond (mg/m^2)	15, 20, or 27 (dose-escalation phase) or 27 (dose-expansion phase) through cycle 12, then biweekly (D1, 2, 15, and 16) for subsequent cycles	36–70 (dose-escalation phase); 45–56 (dose-expansion phase)	20–45 (dose-escalation phase); 36 (dose-expansion phase)	27 through cycle 12, then biweekly (D1, 2, 15, and 16) for cycles 13–18	27; may begin biweekly dosing (D1, 2, 15, and 16) in cycle 10 at investigator discretion	56	36	45–88 (dose-escalation phase); MTD (dose-expansion phase)
Additional treatment	Lenalidomide (10, 15, 20, or 25 mg [dose-escalation phase]; 25 mg [dose-expansion phase] on D1–21) and low-dose dexamethasone (40 mg/week)	None; or weekly low-dose dexamethasone (40 mg) from cycle 1 onwards	Melphalan (9 mg/m^2) and prednisone (60 mg/m^2) on D1–4	Lenalidomide (25 mg on D1–21) and low-dose dexamethasone (40 mg/week) for all cycles	None	Low-dose dexamethasone (40 mg/week)	Melphalan (9 mg/m^2) and prednisone (60 mg/m^2) on D1–4	Low-dose dexamethasone (40 mg on D1, 8, 15, and 22 of cycle 1–8, and on D1, 8, 15 of cycle 9 and beyond)
Infusion time, min	2–10	2–10; or 30	30	2–10	2–10	30	30–60	30

ANC, absolute neutrophil count; CrCl, creatinine clearance; D, day; ECOG, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; min, minutes; MM, multiple myeloma; MTD, maximum tolerated dose; QD, consecutive days; QW, once-weekly dosing; WBCs, white blood cells; y, year.

[a] Patients with solid tumors and refractory or rituximab-intolerant lymphoma were also enrolled.

[b] D1, 2, 8, 9, 15, 16 of 28-day cycle.

[c] D1, 2, 8, 9, 22, 23, 29, 30 of 42-day cycle.

[d] D1, 8, 15 of 28-day cycle.

Oral therapy for multiple myeloma: ixazomib arriving soon

MLN9708, ixazomib, is another boronate PI that is a reversible inhibitor of primarily the chymotrypsin-like activity of the 20S proteasome. However, in contrast to bortezomib, ixazomib has a shorter dissociation half-life, and in preclinical studies, it demonstrated greater tissue penetration compared with bortezomib.9 Most importantly, ixazomib is orally available. Pharmacokinetic examinations confirmed that ixazomib was rapidly absorbed (median Tmax was 1 hour), with a dose-proportional increase in plasma exposure. Pharmacodynamic studies in both trials indicated a dosedependent increase in whole blood 20S proteasome inhibition. The safety profile of ixazomib was favorable. With weekly dosing, drug-related grade $3 AEs were seen in 53% of the 60 patients treated, including thrombocytopenia (33%), neutropenia (18%), diarrhea (17%), and fatigue (8%).1 Thrombocytopenia appeared transient and cyclical. Of note, only 1 case of grade 3 PN was observed. With biweekly dosing, the most common drug-related grade $3 AEs overall in 60 treated patients were similar, including thrombocytopenia (37%), neutropenia (17%), skin rash (8%), and fatigue (7%).2 Interestingly, no grade 3 PN was reported. Disease response was also promising. Using weekly dosing, 8 of 30 (27%) response-evaluable patients treated at the MTD achieved a partial response.1 The median duration of response was 7.3 months. Of note, patients had received a median of 6 prior regimens, and nearly three quarters of them were refractory to their last prior therapy. With the biweekly regimen, 15% of 55 response-evaluable patients achieved PR or better, with 76% reaching at least stable disease, and 18% of the patients remained on treatment of $12 cycles.2

carfilzomib has produced robust and durable responses in clinical trials, and it has been approved in the United States for the treatment of relapsed and refractory MM.[6] Due to its favorable safety profile, carfilzomib is an

active sites of the 20S proteasome, with

setting, bortezomib is now predominantly

that ixazomib was rapidly absorbed (median

Table 2 Ongoing clinical trials of MLN9708 in multiple myeloma and amyloidosis

Trial	Stage	Identifier
Relapsed/refractory multiple myeloma		
Phase I pharmacokinetic study of oral MLN9708 plus lenalidomide and dexamethasone in adult Asian patients with relapsed and/or refractory multiple myeloma	Phase I	NCT01645930
Pharmacokinetic study of oral MLN9708 plus dexamethasone in relapsed/refractory multiple myeloma patients	Phase I/IB	NCT01830816
MLN9708 (ixazomib) in combination with panobinostat and dexamethasone in multiple myeloma	Phase I	NCT02057640
Pomalidomide and dexamethasone with or without ixazomib in patients with refractory multiple myeloma	Phase I/II	NCT02004275
Ixazomib plus pomalidomide and dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma	Phase I/II	NCT02119468
A Phase III study comparing oral MLN9708 plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with relapsed and/or refractory multiple myeloma	Phase III	NCT01564537
Newly diagnosed multiple myeloma		
Ixazomib, cyclophosphamide, and dexamethasone in treating patients with previously untreated symptomatic multiple myeloma	Phase I/II	NCT01864018
Study of oral MLN9708 in combination with melphalan and prednisone in patients with newly diagnosed multiple myeloma	Phase I/II	NCT01335685
Safety and efficacy study of a triplet combination of MLN9708, lenalidomide, and dexamethasone in the initial management of multiple myeloma (IFM2013-06)	Phase II	NCT01936532
Phase II study to evaluate the oral combination of MLN9708 with cyclophosphamide and dexamethasone in patients with newly diagnosed multiple myeloma	Phase II	NCT02046070
MLN9708 plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with newly diagnosed multiple myeloma	Phase III	NCT01850524
Smoldering multiple myeloma		
MLN9708 and dexamethasone for high-risk smoldering multiple myeloma	Phase II	NCT01660997
Systemic amyloidosis	Phase I	NCT01318902
Study of oral MLN9708 in adult patients with relapsed or refractory light-chain amyloidosis	Phase III	NCT01659658

Study Methods

- Treatment consisted of 6 induction cycles, then maintenance beginning 8 weeks after induction (given every 8 weeks for 8 cycles).
- Dose and schedule of **induction therapy**:
  - Carfilzomib (IV) 20 mg/m^2 (cycle 1), then 36 mg/m^2 (cycles 2 and beyond)
  - Dexamethasone (IV) 20 mg on days 1, 2, 8, 9
  - Rituximab 375 mg/m^2 on days 2, 9 of each 21-day cycle
- Dose and schedule of **maintenance therapy**:
  - Carfilzomib 36 mg/m^2, dexamethasone 20 mg on days 1, 2 and rituximab 375 mg/m^2 on day 2
- Patients with IgM level >4,000 mg/dL underwent plasmapheresis and/or had rituximab held until IgM <4,000 mg/dL to prevent symptomatic IgM flare.
- Patients received oral acyclovir (400 mg twice daily) and famotidine (20 mg twice daily) as concomitant medications.

Treon SP et al. *Proc ASH* 2013;Abstract 757 (abstract only).

Patient Characteristics

Characteristic (median)	n = 31
Age	61 years
Number of prior therapies	0 (range: 0-1)
Hematocrit levels	32.3%
Hemoglobin levels	10.7 g/dL
Serum IgM	3,375 mg/dL
Serum M-protein	2.185 g/dL
B2M	3.6 mg/L
Bone marrow disease involvement	60%
No prior therapy	87%

Treon SP et al. *Proc ASH* 2013;Abstract 757 (abstract only).