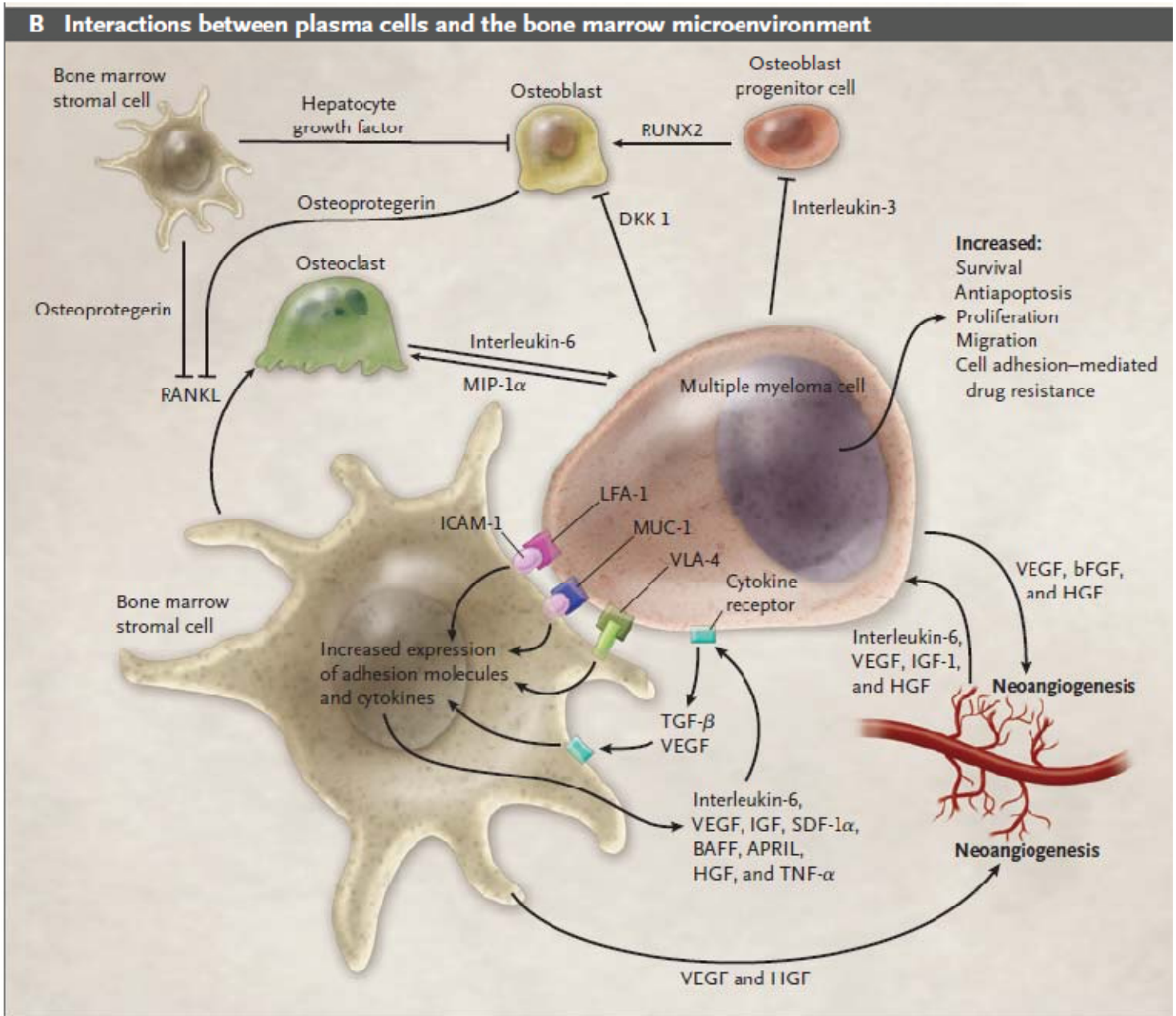
AIH septembre 2009, Nantes

Nouveaux agents dans le myélome, mode d'action

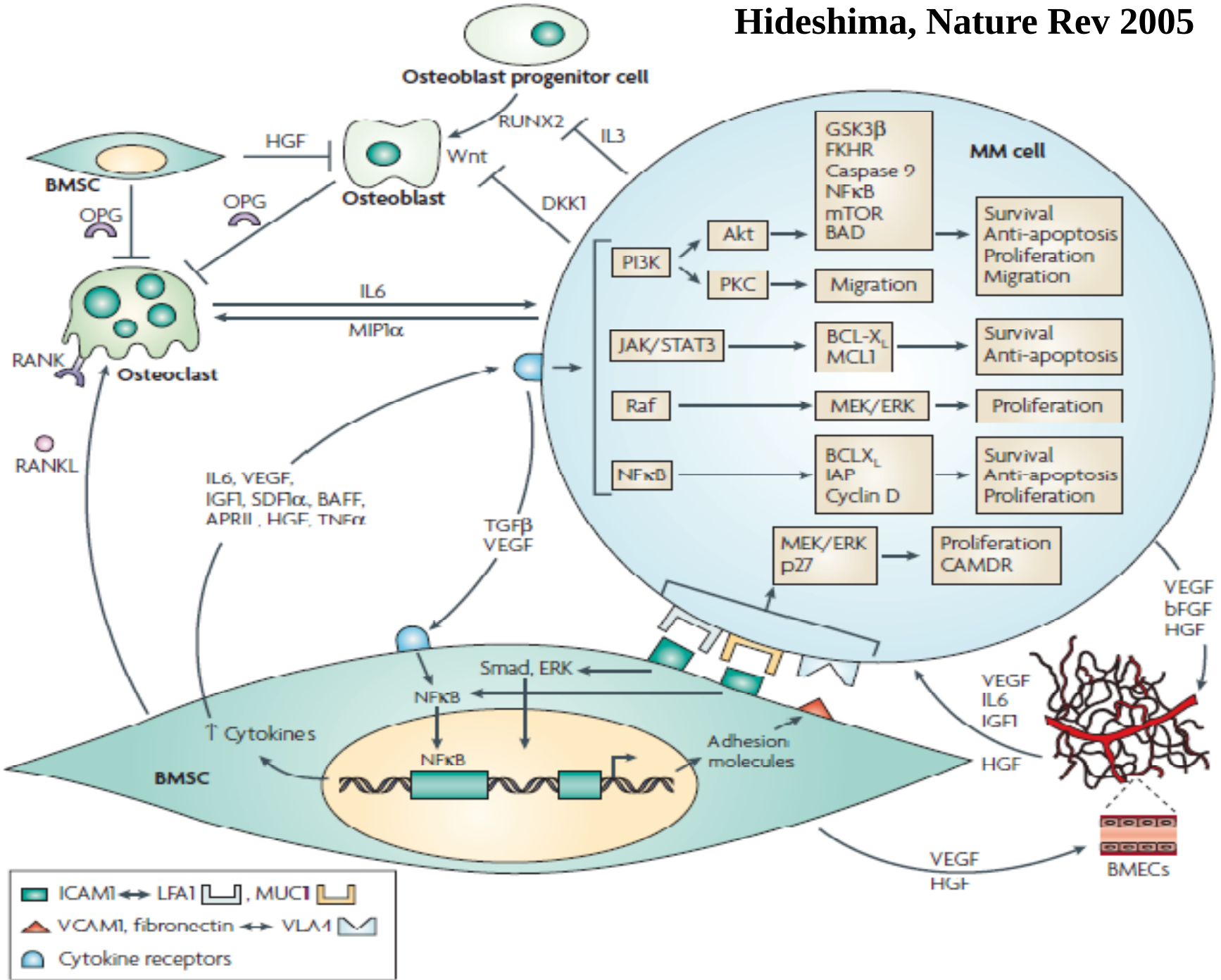
Pr Philippe Moreau

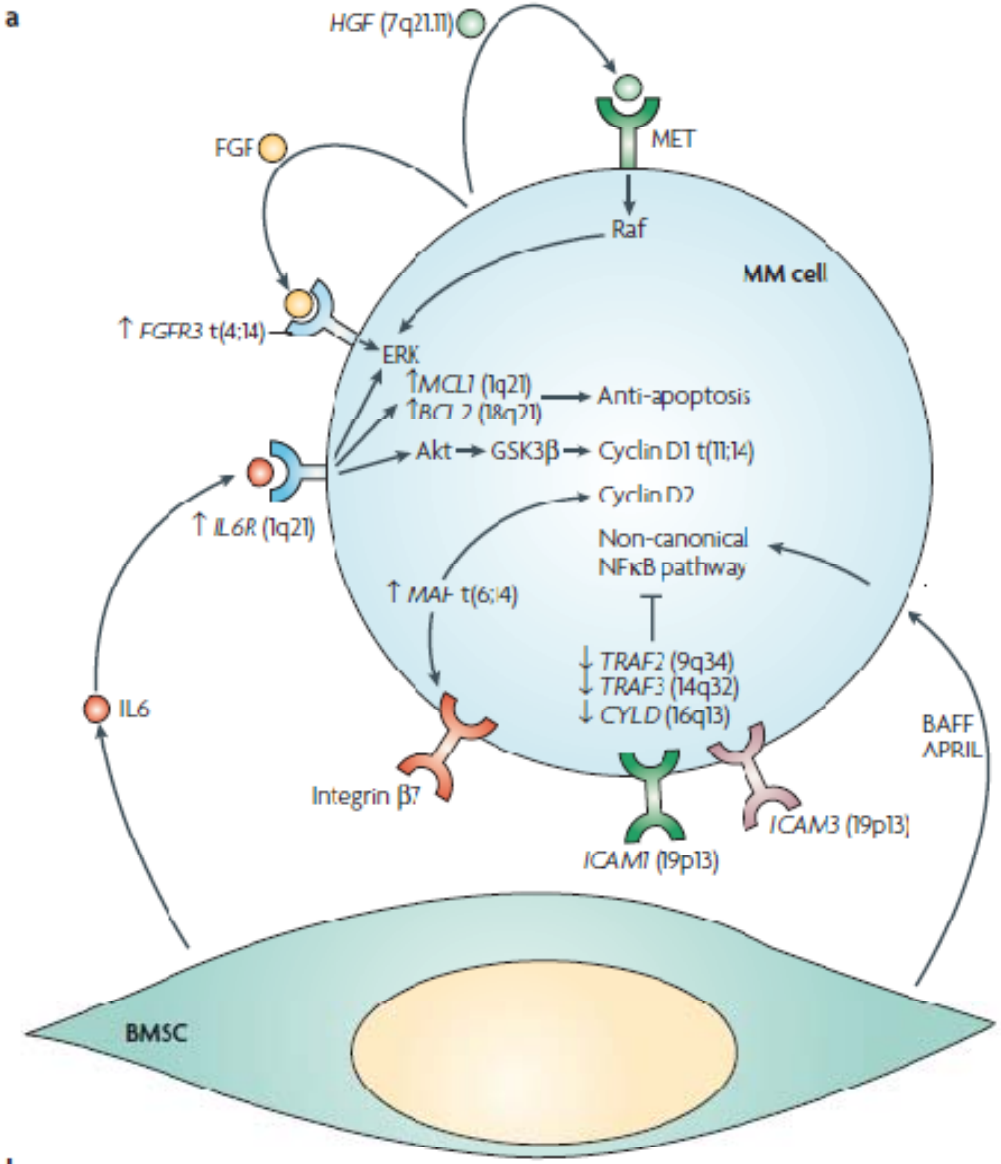
CENTRE HOSPITALIER
UNIVERSITAIRE DE NANTES

Harousseau JL, Moreau P – New Engl J Med 2009



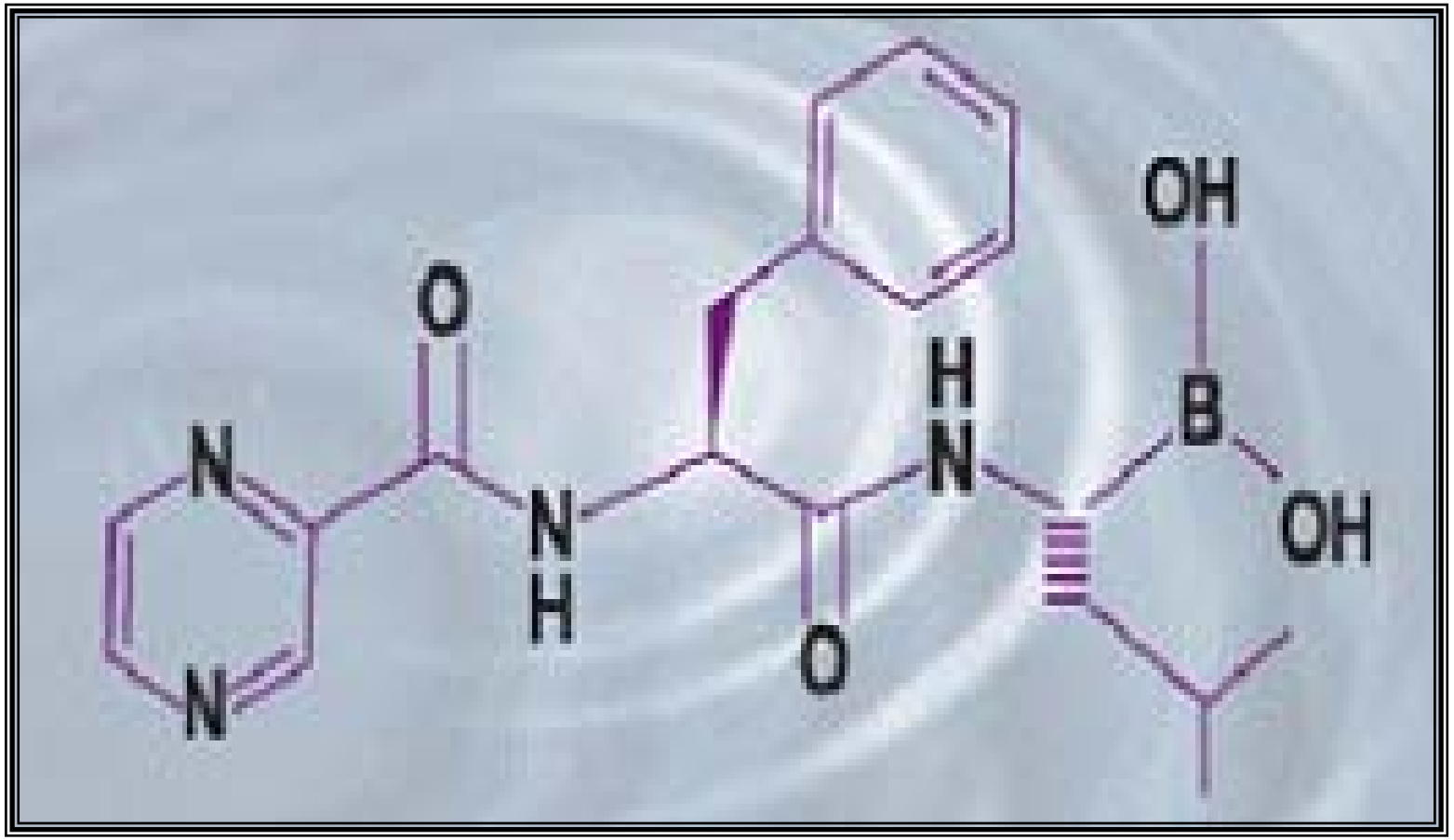
Hideshima, Nature Rev 2005





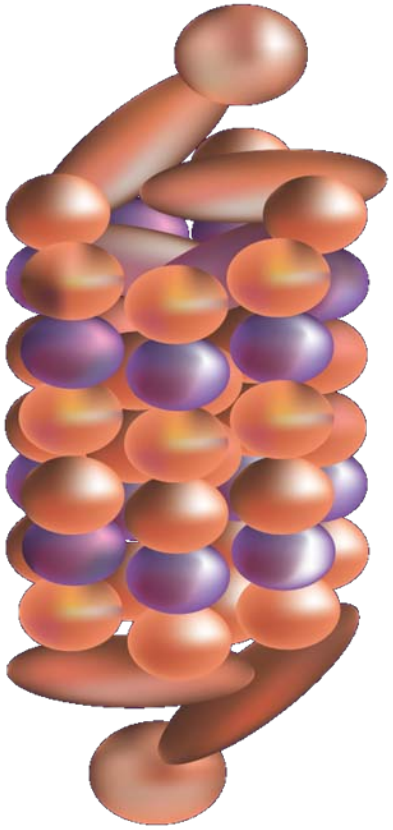
Transcriptional changes triggered in multiple myeloma cells by their interaction with the bone marrow milieu

- Proliferation, ↓apoptosis: ↑IL6, HGF, IGF1, MCL1, HSPs
- Angiogenesis: ↑IL8, VEGF
- Bone resorption: ↑IL6, VEGF, IL1β
- Adhesion: ↑integrins, other CAMs, ECM proteins



Dipeptidyl boronic acid ; bortezomib ; PS341

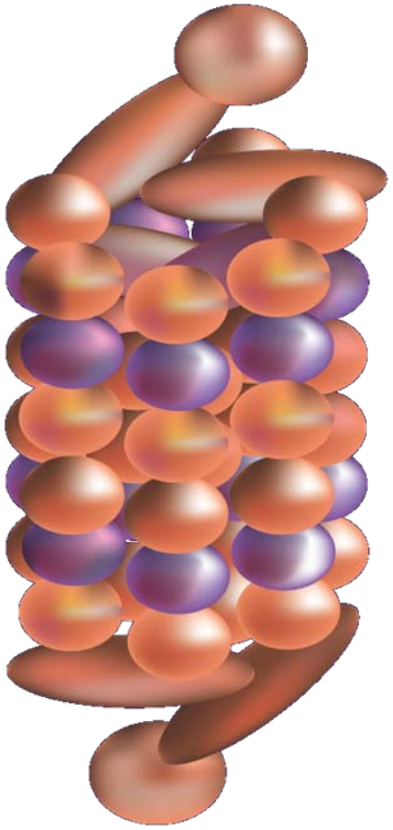
Protéasome



- Complexe enzymatique catalytique
- Dans le noyau et le cytoplasme de toutes les cellules eucaryotes
- Initialement : recyclage de protéines endommagées
- Rôle majeur dans le cycle cellulaire et survie
- Rôle principal : dégradation protéique

Rivett Arch Biochem Bioph 1989; Tanaka FEBS Lett 1988 ; Matthews PNAS 1989; Arrigo Nature 1989; Kisseley Chem Biol 2001

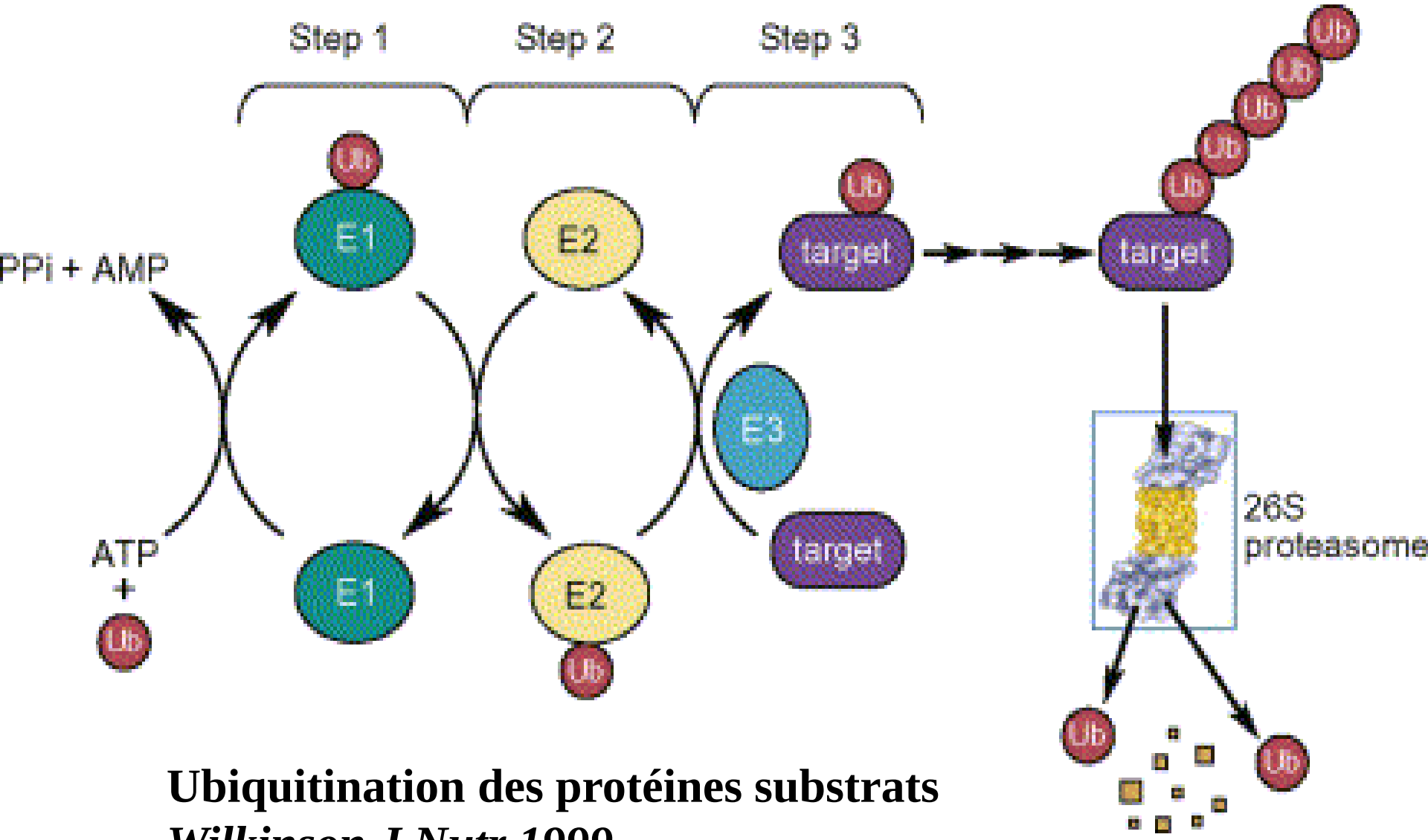
Protéasome



- **Substrats : molécule signaling, régulateurs cycle cellulaire, facteurs transcription, protéines anti-apoptotiques…**

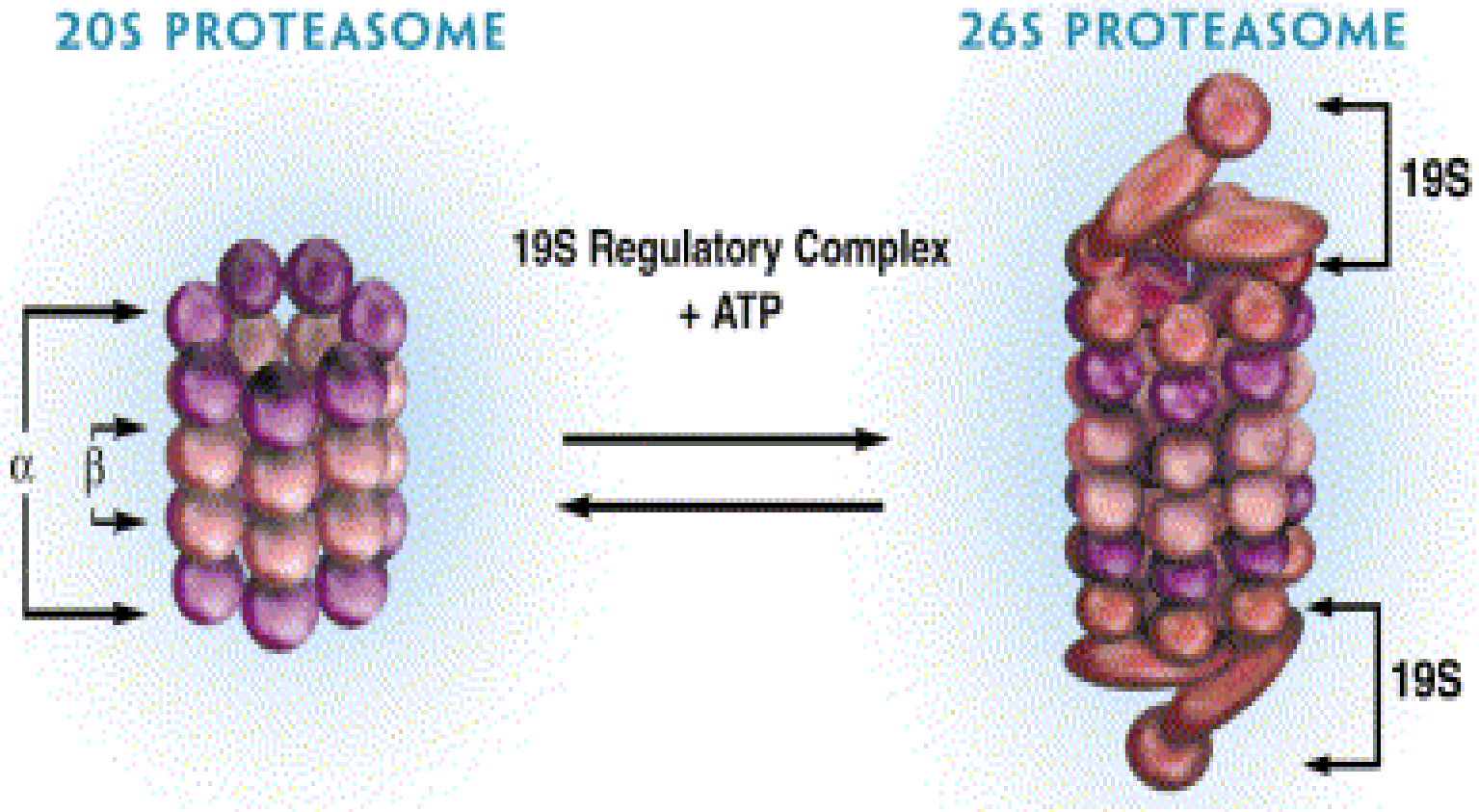
- **Dégradation interrompue : intérêt potentiel contre cellules cancéreuses**

  Kumatori *PNAS* 1990. *Abnormally high expression of proteasomes in human leukemic cells*



Ubiquitination des protéines substrats

Wilkinson J Nutr 1999

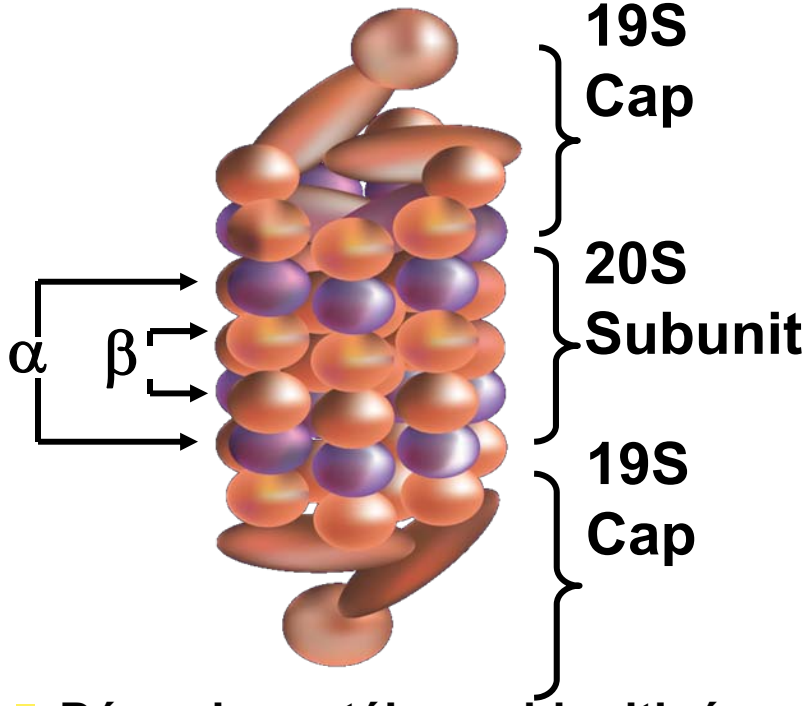


- 700 kDa
- Broad substrate specificity

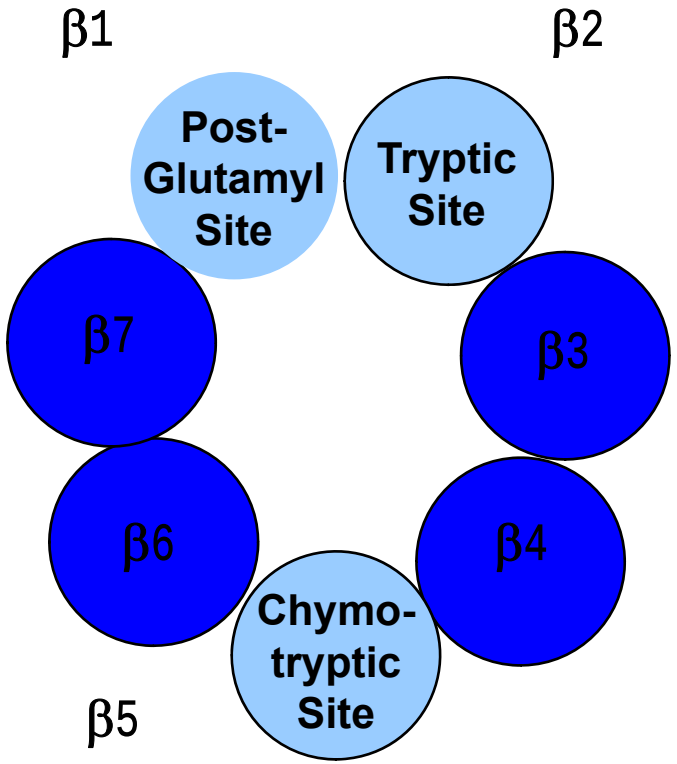
- 2,000 kDa

Structure du protéasome

26S Protéasome



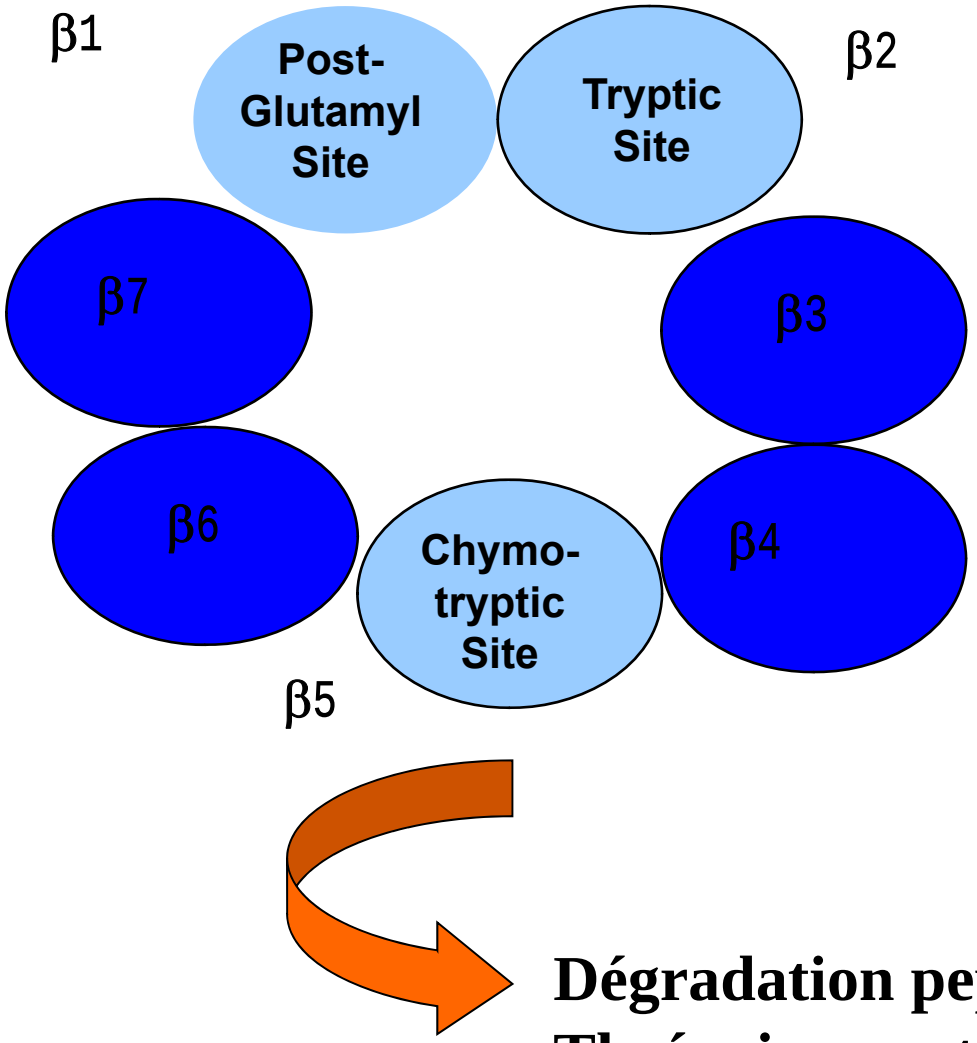
Coupe anneau β



- **Dégrade protéines ubiquitinées**
- **Protéolyse ATP-dépendante**

1. *J Bio Chem.* 1999; 274(32): 22123-22126. 2. *Science.* 1995; 268(5210) 579-582. 3. *Bioorg Med Chem Lett.* 1998; 8(4): 333-338.

Coupe anneau β



Dégradation peptides 3 – 25 AA
Thréonine-protéase

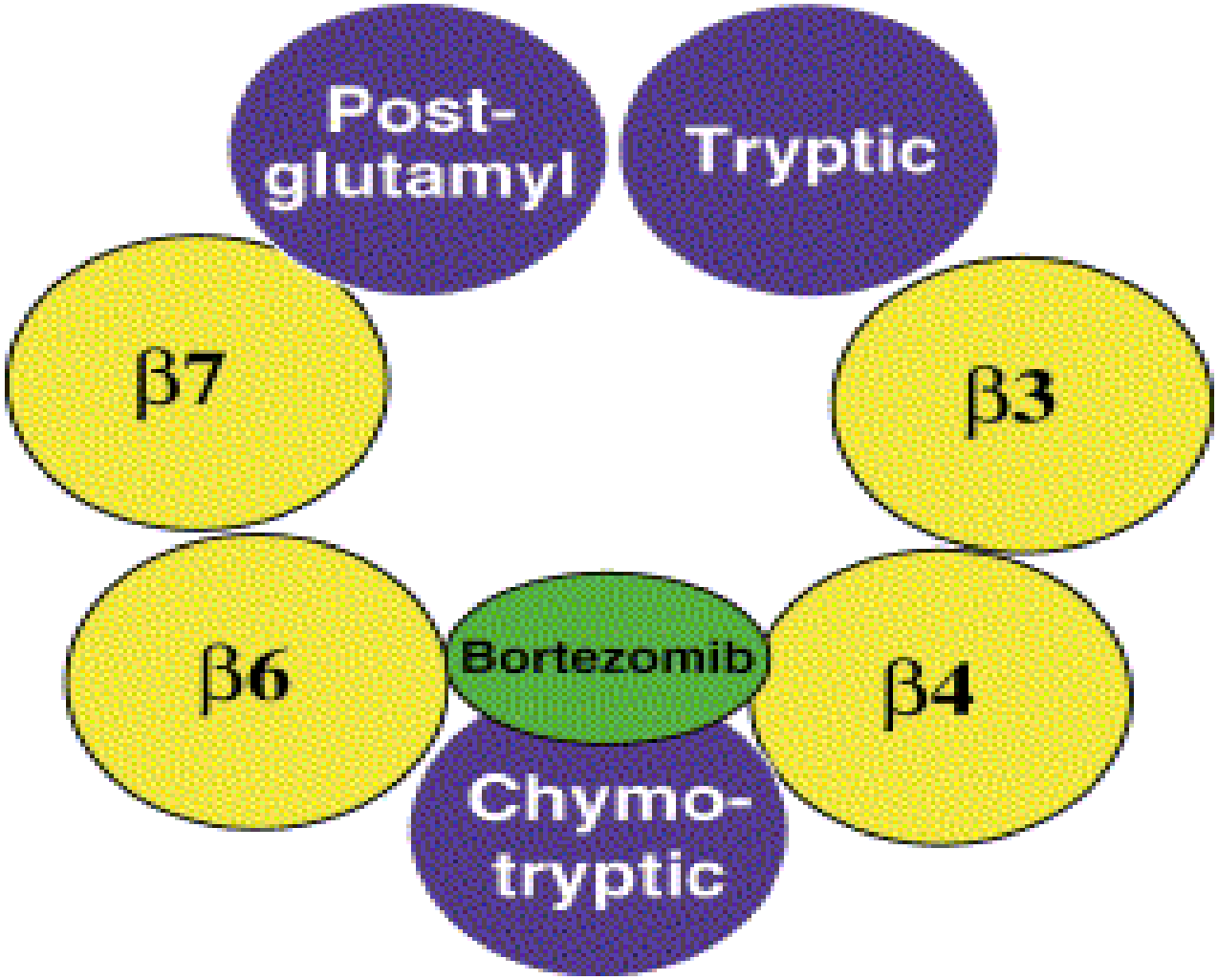
Inhibiteurs du protéasome

- Fixation +/- réversible avec 20S

- MG132;PSI; lactacystin; NLVS; epoxomicin

Pb stabilité, fixation irréversible

→ peptide boronic acids



Bortezomib, fixation sélective, réversible, bloque site activité chymotrypsique, dissociation lente, petit poids moléculaire, synthèse facile

Effet de l'inhibition du protéasome sur la stabilité de différentes protéines régulatrices du cycle cellulaire bien établi :

- cyclines
- CDKI : p21, p27
- suppresseur tumeur : p53
- NF-KB

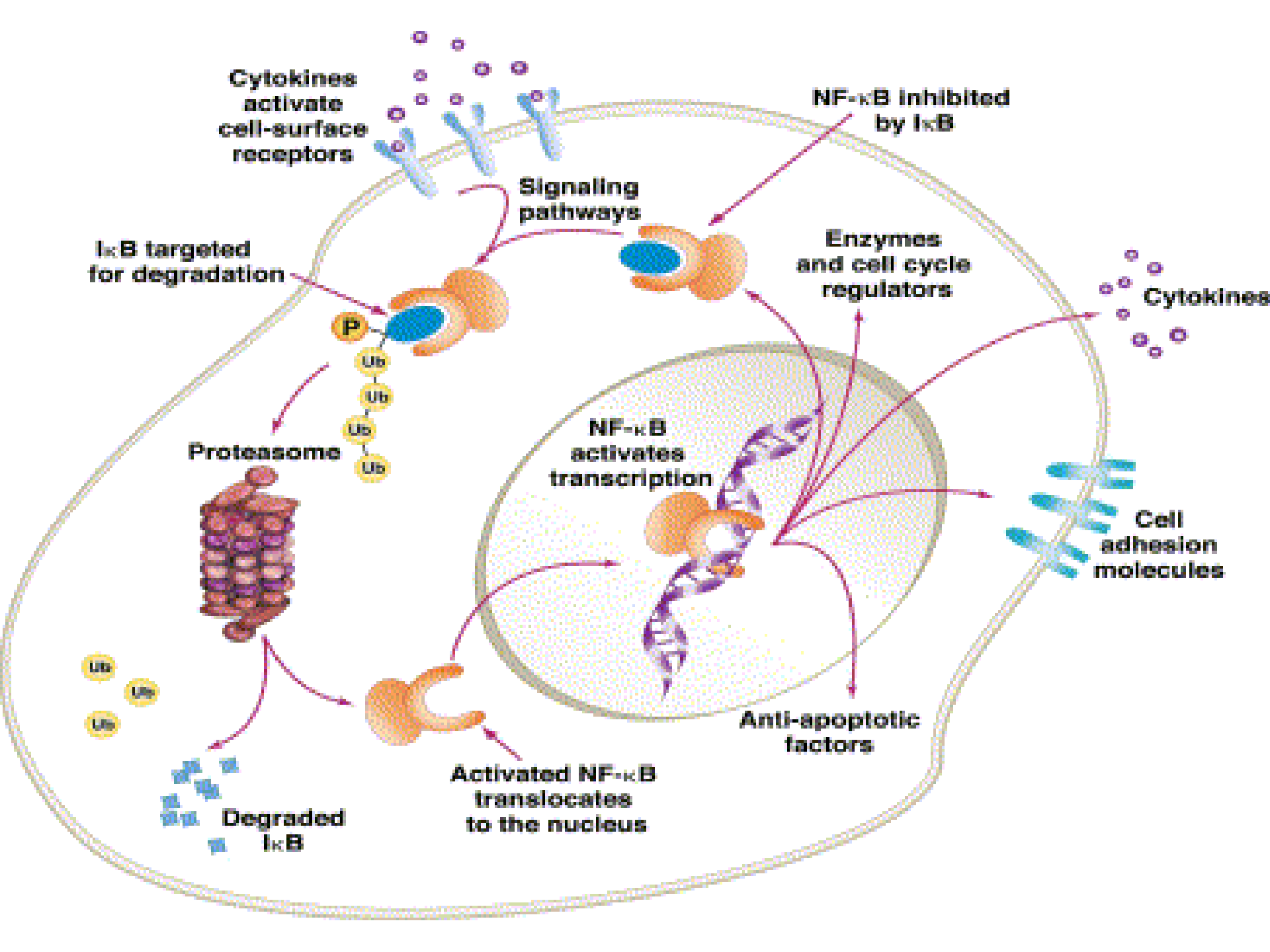
Hideshima Cancer Res 2001; Adams Cancer Res 1999

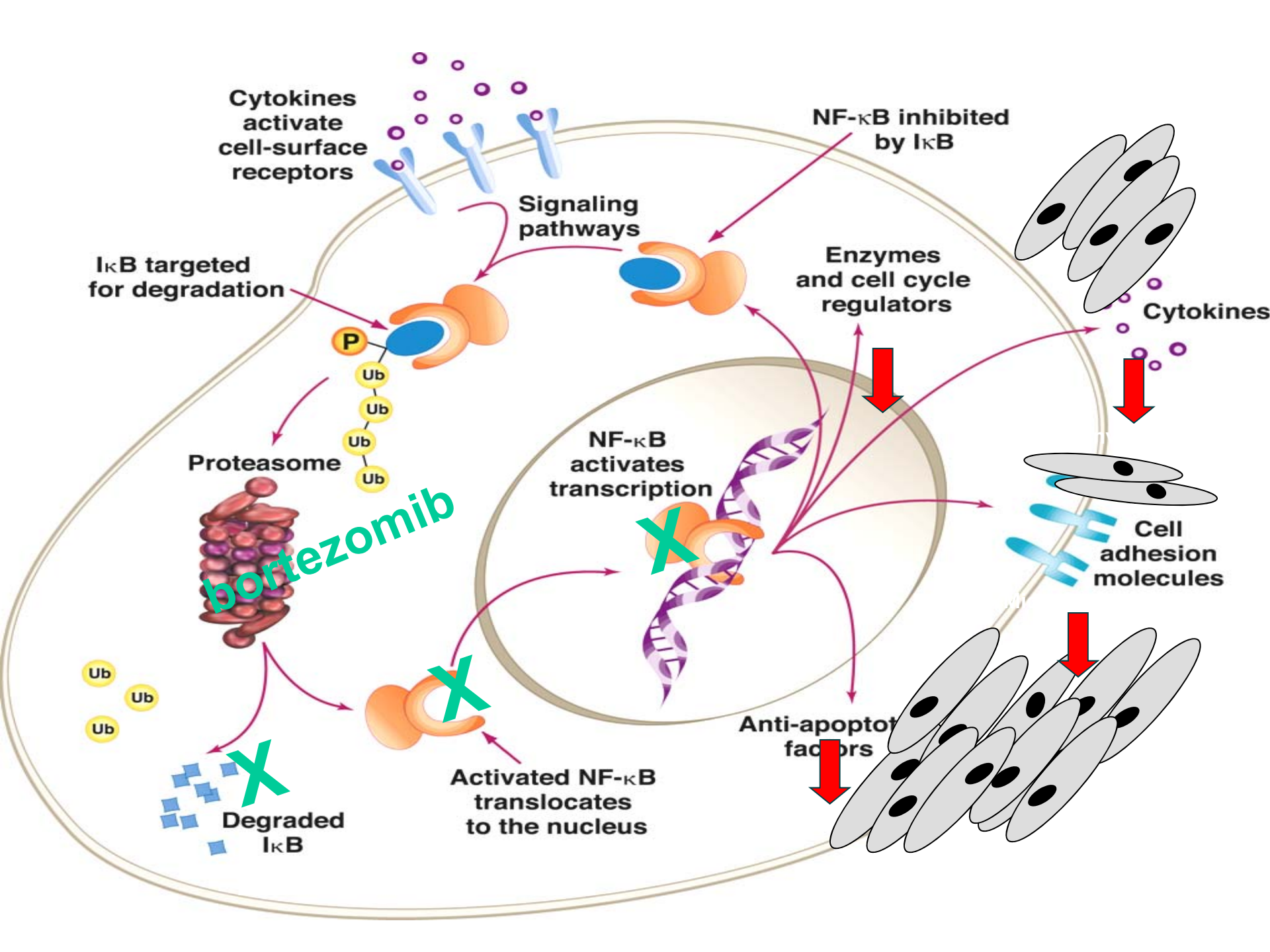
p53

- Facteur de transcription, régulateur du cycle cellulaire

- Empêche les cellules dont ADN endommagé de se diviser

- Dégradation dépendante d'une enzyme Mdm2, E3 ubiquitine-ligase → surexprimée dans certains cancers


Cytokines activate cell-surface receptors
NF-κB inhibited by IκB
Signaling pathways
IκB targeted for degradation
Enzymes and cell cycle regulators
Cytokines
P
Ub
Ub
Ub
Ub
Proteasome
NF-κB activates transcription
Cell adhesion molecules
Ub
Ub
Ub
Anti-apoptotic factors
Activated NF-κB translocates to the nucleus
Degraded IκB


Cytokines activate cell-surface receptors
NF-κB inhibited by IκB
Signaling pathways
IκB targeted for degradation
Enzymes and cell cycle regulators
Cytokines
P
Ub
Ub
Ub
Ub
Proteasome
bortezomib
NF-κB activates transcription
Cell adhesion molecules
Ub
Ub
Ub
Anti-apoptot
fac rs
Degraded IκB
Activated NF-κB translocates to the nucleus

NFKB

- Activation constitutive dans certains cancers
(Wang *Science* 1998, Kordes *Leukemia* 2000)

- Promotion de survie tumorale
(Jeremias *Blood* 1998)

- Diminution de la chimiosensibilité et sensibilité à la radiothérapie
(Wang *Mol Cell Biol* 1999, Um *Oncogene* 2001, Russo Int J Radiat Oncol Biol Phys 2001)

Programme NCI sur 60 lignées tumorales
Adams Cancer Res 1999;59:2615

→ myélome
→ pancréas
→ prostate
→ tête & cou
…/…

Le mécanisme d'action n'est pas univoque

Mitsiades et al

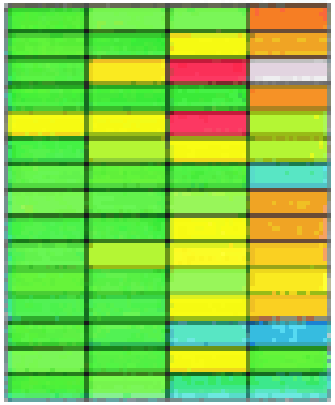
***PNAS* 2002;99:14374-14379**

Molecular sequelae of proteasome inhibition in human multiple myeloma cells

Lignée MM.1S + PS341 (100 nM de 0 à 8 h)

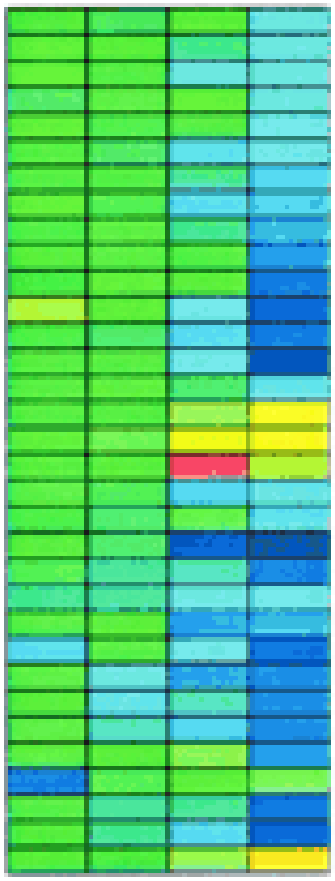
Apoptosis related

growth arrest and DNA-damage-inducible, alpha
growth arrest and DNA-damage-inducible, beta
growth arrest and DNA-damage-inducible, gamma
TRAIL Receptor DR5
Fas
Fas Ligand
Tosa inhibitor of Fas-mediated apoptosis
death associated protein 3
BH3 interacting domain death agonist
caspase 8
caspase 7
caspase 1
Bcl-2
BCL2-antagonist/killer 1
defender against cell death 1



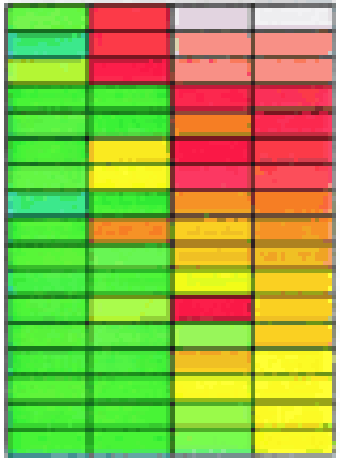
Growth signaling/Cell cycle

mitogen-activated protein kinase kinase kinase 4
chemokine (C-X-C motif), receptor 4 (fusin)
chemokine (C-C motif) receptor 1
casein kinase 1, gamma 2
c-src tyrosine kinase
insulin receptor substrate 1
casein kinase 1, gamma 2
pim-1 oncogene
p21/Cdc42/Rac1-activated kinase 1
stathmin 1/oncoprotein 18
insulin receptor substrate 1
insulin-like growth factor binding protein 3
insulin-like growth factor 1 (somatomedin C)
insulin-like growth factor 1 receptor
syndecan 1
cyclin C
cyclin-dependent kinase 7
retinoblastoma-binding protein 8
cyclin-dependent kinase inhibitor 3
Fanconi anemia, complementation group G
E2F transcription factor 5, p130-binding
cyclin A2
cyclin B1
cyclin B2
cyclin E1
cyclin E2
cyclin F
cell division cycle 2, G1 to S and G2 to M
cell division cycle 2-like 1 (PITSLRE proteins)
cyclin-dependent kinase 6
cyclin-dependent kinase 2
proliferating cell nuclear antigen
p21/WAF1



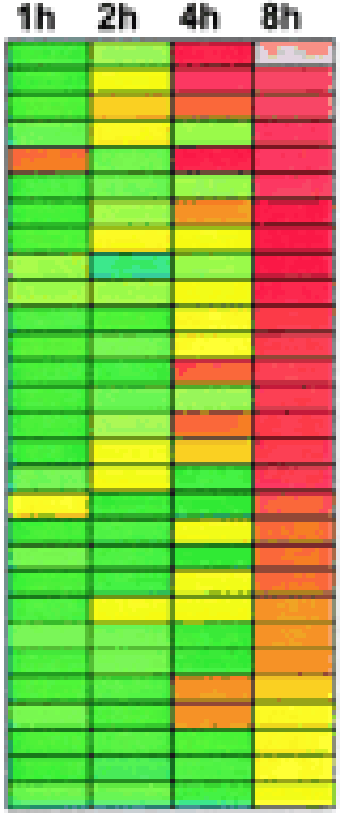
Heat Shock Proteins

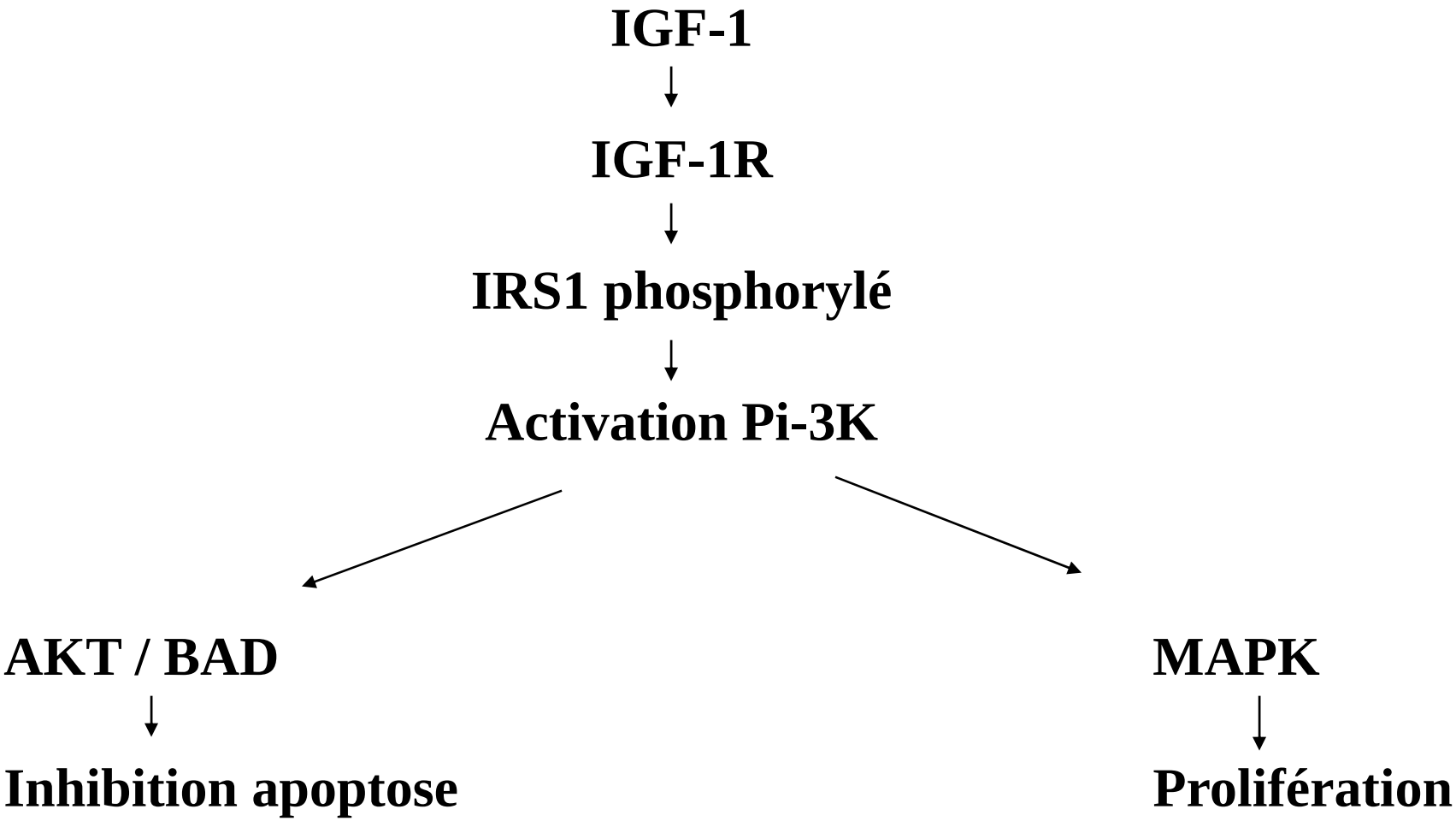
heat shock 70kD protein 6 (HSP70B')
heat shock 70kD protein 1B
heat shock 70kD protein 1A
heat shock 27kD protein 1
heat shock protein 47, member 2
DnaJ (Hsp40) homolog, subfamily B, member 1
dual specificity phosphatase 1
DnaJ (Hsp40) homolog, subfamily B, member 4
heat shock 70kD protein 1B
heat shock 90kD protein 1, alpha
heat shock 70kD protein 4
DnaJ (Hsp40) homolog, subfamily B, member 4
DnaJ (Hsp40) homolog, subfamily B, member 2
DnaJ (Hsp40) homolog, subfamily A, member 1
stress-induced-phosphoprotein 1
DnaJ (Hsp40) homolog, subfamily B, member 6
heat shock 10kD protein 1 (chaperonin 10)

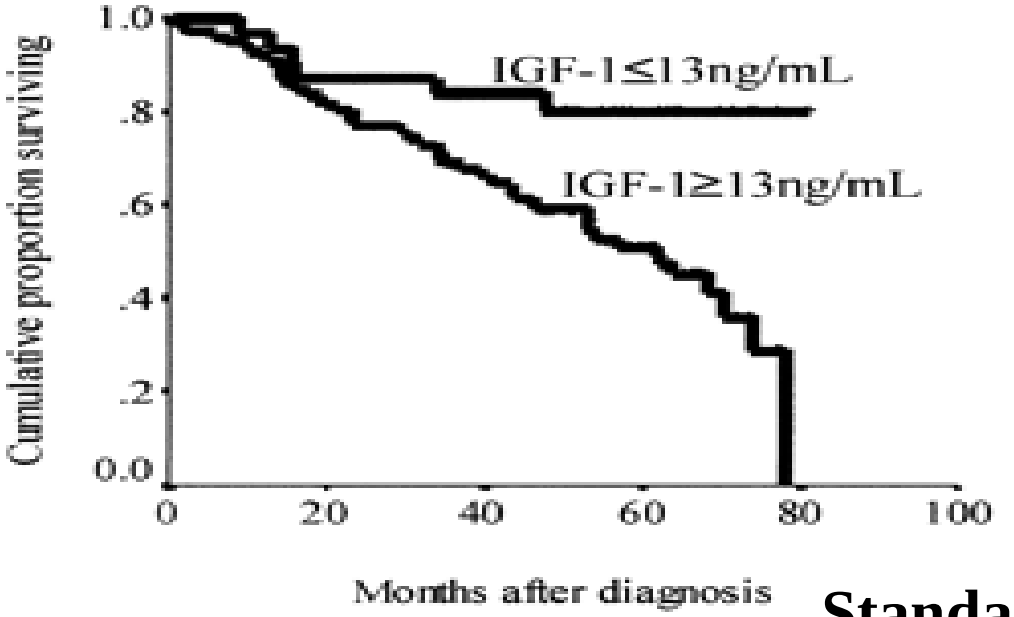


Proteasome pathway

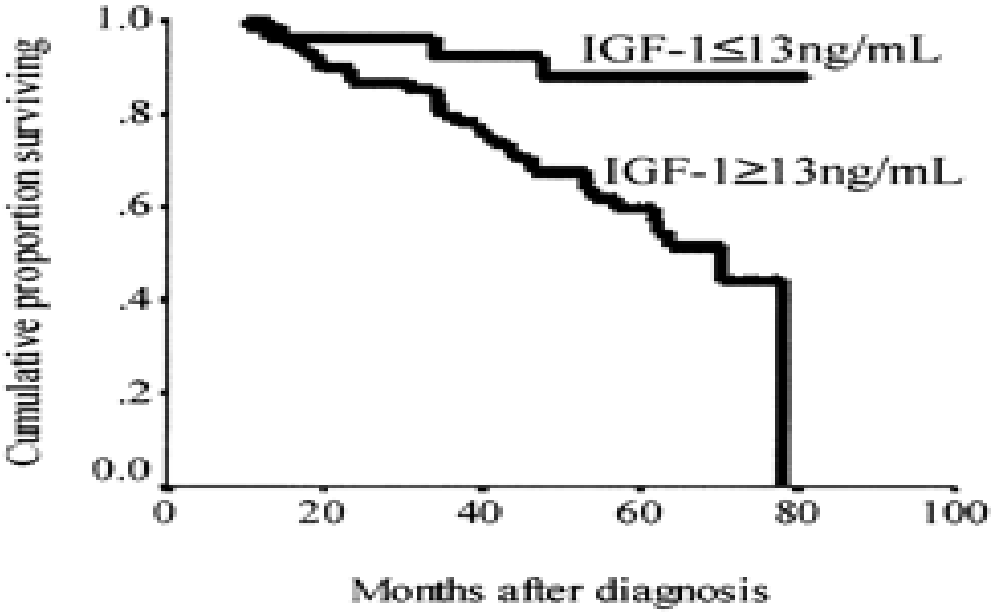
proteasome 26S subunit, ATPase, 4
proteasome 26S subunit, non-ATPase, 12
proteasome 26S subunit, ATPase, 6
proteasome 26S subunit, non-ATPase, 8
proteasome 26S subunit, non-ATPase, 13
proteasome subunit, beta type, 7
proteasome subunit, beta type, 7
proteasome subunit, alpha type, 5
proteasome subunit, beta type, 3
proteasome subunit, alpha type, 6
proteasome 26S subunit, non-ATPase, 8
proteasome 26S subunit, non-ATPase, 2
ubiquitin specific protease 5 (isopeptidase T)
proteasome subunit, beta type, 2
proteasome 26S subunit, non-ATPase, 11
proteasome 26S subunit, ATPase, 1
proteasome 26S subunit, ATPase, 3
proteasome 26S subunit, non-ATPase, 10
proteasome 26S subunit, non-ATPase, 1
proteasome subunit, beta type, 4
proteasome subunit, beta type, 6
proteasome subunit, alpha type, 3
proteasome subunit, beta type, 4
proteasome subunit, beta type, 5
proteasome 26S subunit, ATPase, 2
proteasome 26S subunit, non-ATPase, 3
proteasome subunit, beta type, 1
proteasome subunit, alpha type, 1
proteasome 26S subunit, non-ATPase, 7



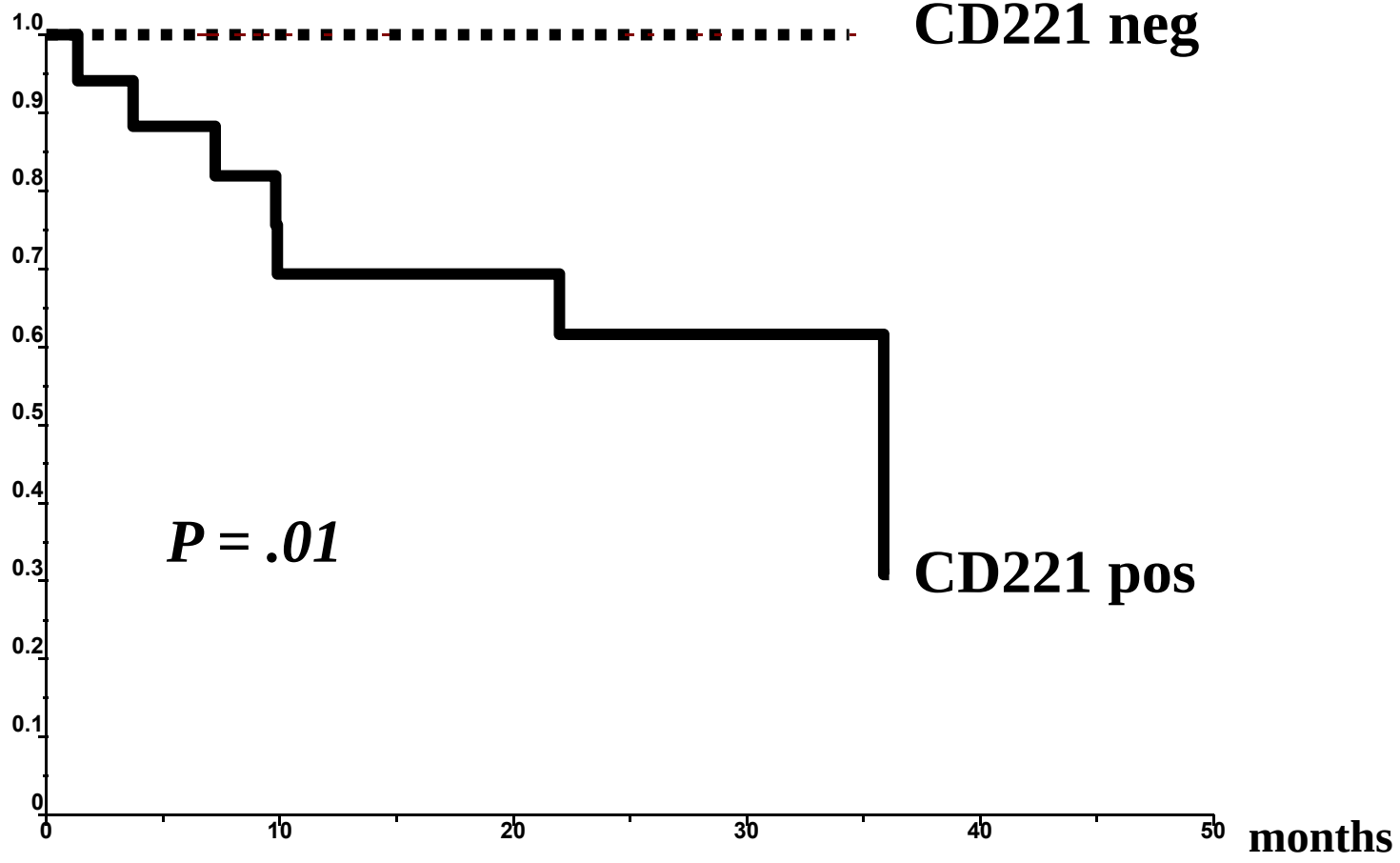

IGF-1
IGF-1R
IRS1 phosphorylé
Activation Pi-3K
AKT / BAD
Inhibition apoptose
MAPK
Prolifération



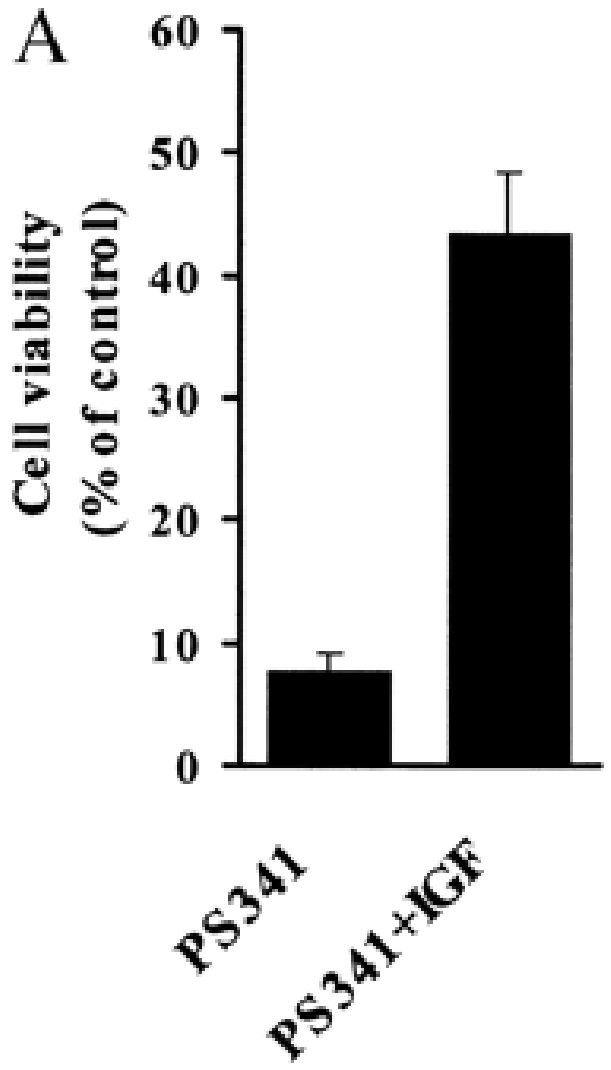
Standal , Blood 2002

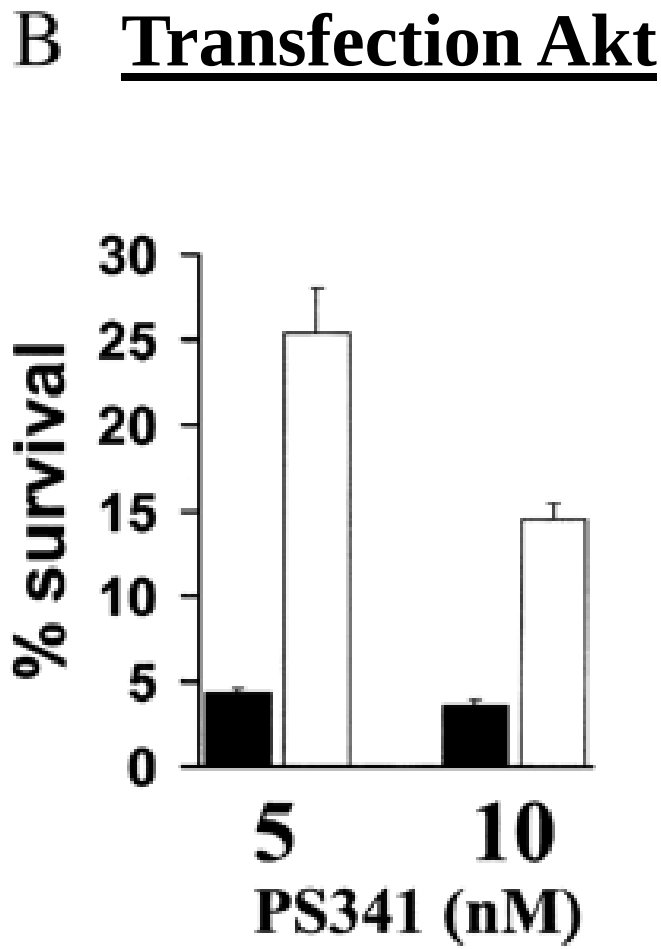


Bataille R & Moreau P, Haematologica 2005



Overall survival according to CD221 phenotype





IGF1 peut minorer les effets de PS341

Apoptosis related

growth arrest and DNA-damage-inducible, alpha
growth arrest and DNA-damage-inducible, beta
growth arrest and DNA-damage-inducible, gamma
TRAIL Receptor DR5
Fas
Fas Ligand
Tosa inhibitor of Fas-mediated apoptosis
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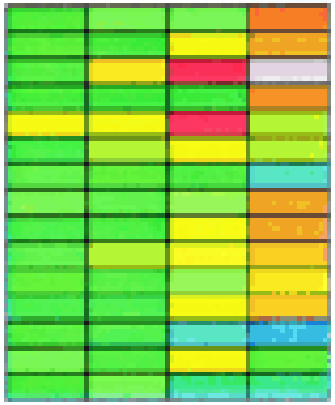
caspase 7
caspase 1
Bcl-2
BCL2-antagonist/killer 1
defender against cell death 1



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casein kinase 1, gamma 2
pim-1 oncogene
p21/Cdc42/Rac1-activated kinase 1
stathmin 1/oncoprotein 18
insulin receptor substrate 1
insulin-like growth factor binding protein 3
insulin-like growth factor 1 (somatomedin C)
insulin-like growth factor 1 receptor
syndecan 1
cyclin C
cyclin-dependent kinase 7
retinoblastoma-binding protein 8
cyclin-dependent kinase inhibitor 3
Fanconi anemia, complementation group G
E2F transcription factor 5, p130-binding
cyclin A2
cyclin B1
cyclin B2
cyclin E1
cyclin E2
cyclin F
cell division cycle 2, G1 to S and G2 to M
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cyclin-dependent kinase 6
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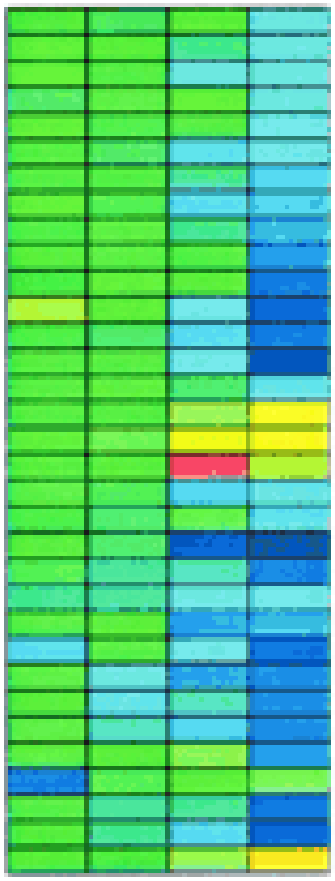

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DnaJ (Hsp40) homolog, subfamily B, member 2
DnaJ (Hsp40) homolog, subfamily A, member 1
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DnaJ (Hsp40) homolog, subfamily B, member 6
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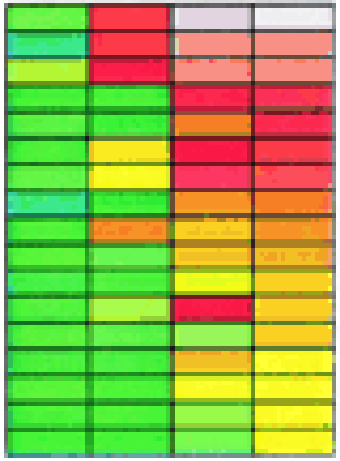

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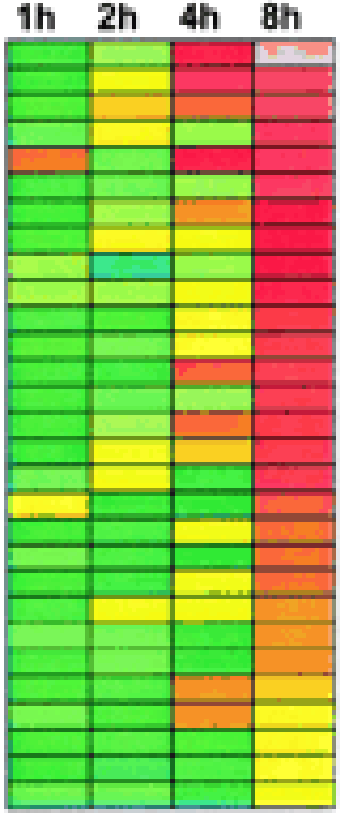
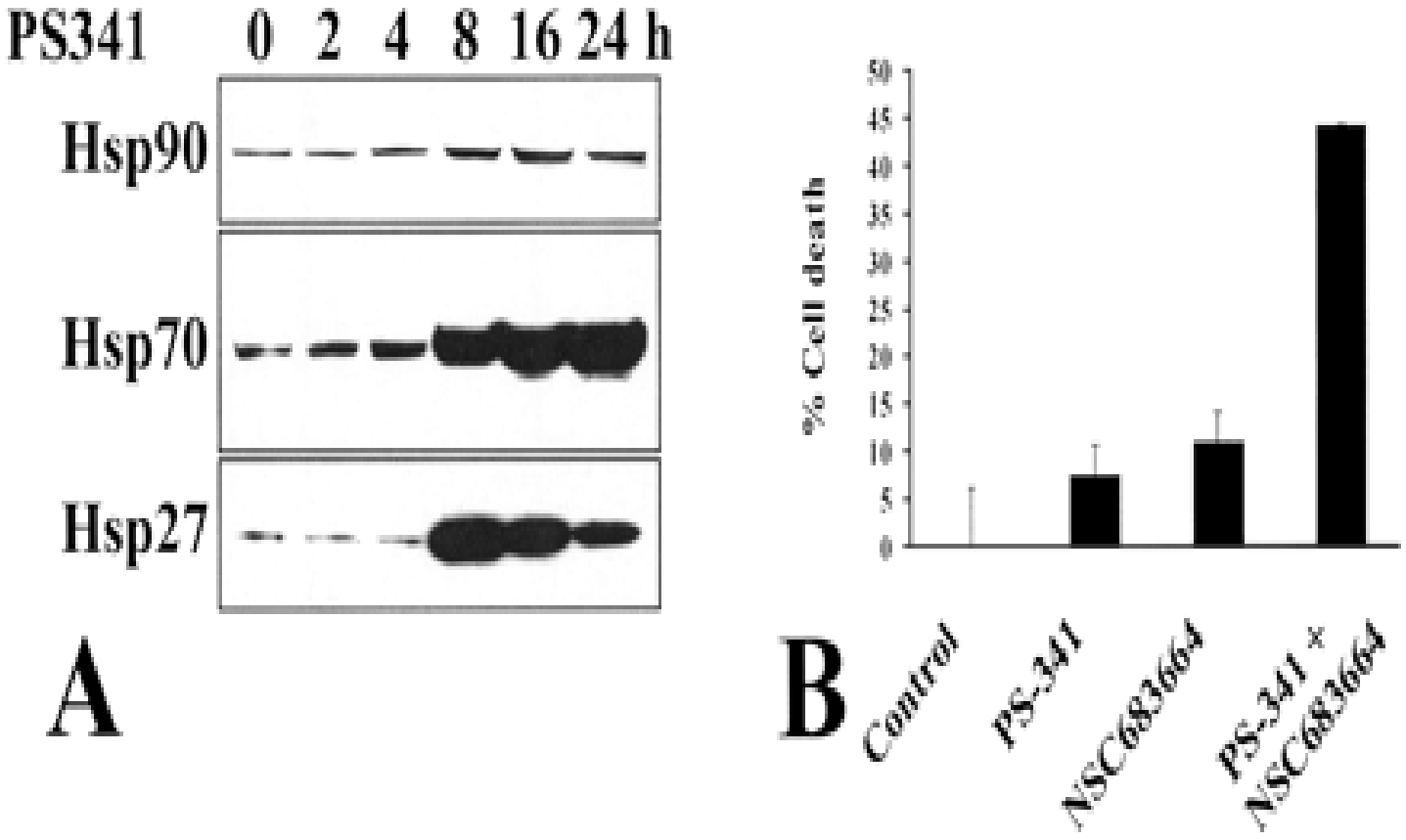
proteasome 26S subunit, non-ATPase, 13
proteasome subunit, beta type, 7
proteasome subunit, beta type, 7
proteasome subunit, alpha type, 5
proteasome subunit, beta type, 3
proteasome subunit, alpha type, 6
proteasome 26S subunit, non-ATPase, 8
proteasome 26S subunit, non-ATPase, 2
ubiquitin specific protease 5 (isopeptidase T)
proteasome subunit, beta type, 2
proteasome 26S subunit, non-ATPase, 11
proteasome 26S subunit, ATPase, 1
proteasome 26S subunit, ATPase, 3
proteasome 26S subunit, non-ATPase, 10
proteasome 26S subunit, non-ATPase, 1
proteasome subunit, beta type, 4
proteasome subunit, beta type, 6
proteasome subunit, alpha type, 3
proteasome subunit, beta type, 4
proteasome subunit, beta type, 5
proteasome 26S subunit, ATPase, 2
proteasome 26S subunit, non-ATPase, 3
proteasome subunit, beta type, 1
proteasome subunit, alpha type, 1
proteasome 26S subunit, non-ATPase, 7





PS341 induit synthèse de protéines chaperones, protectrices des cellules tumorales

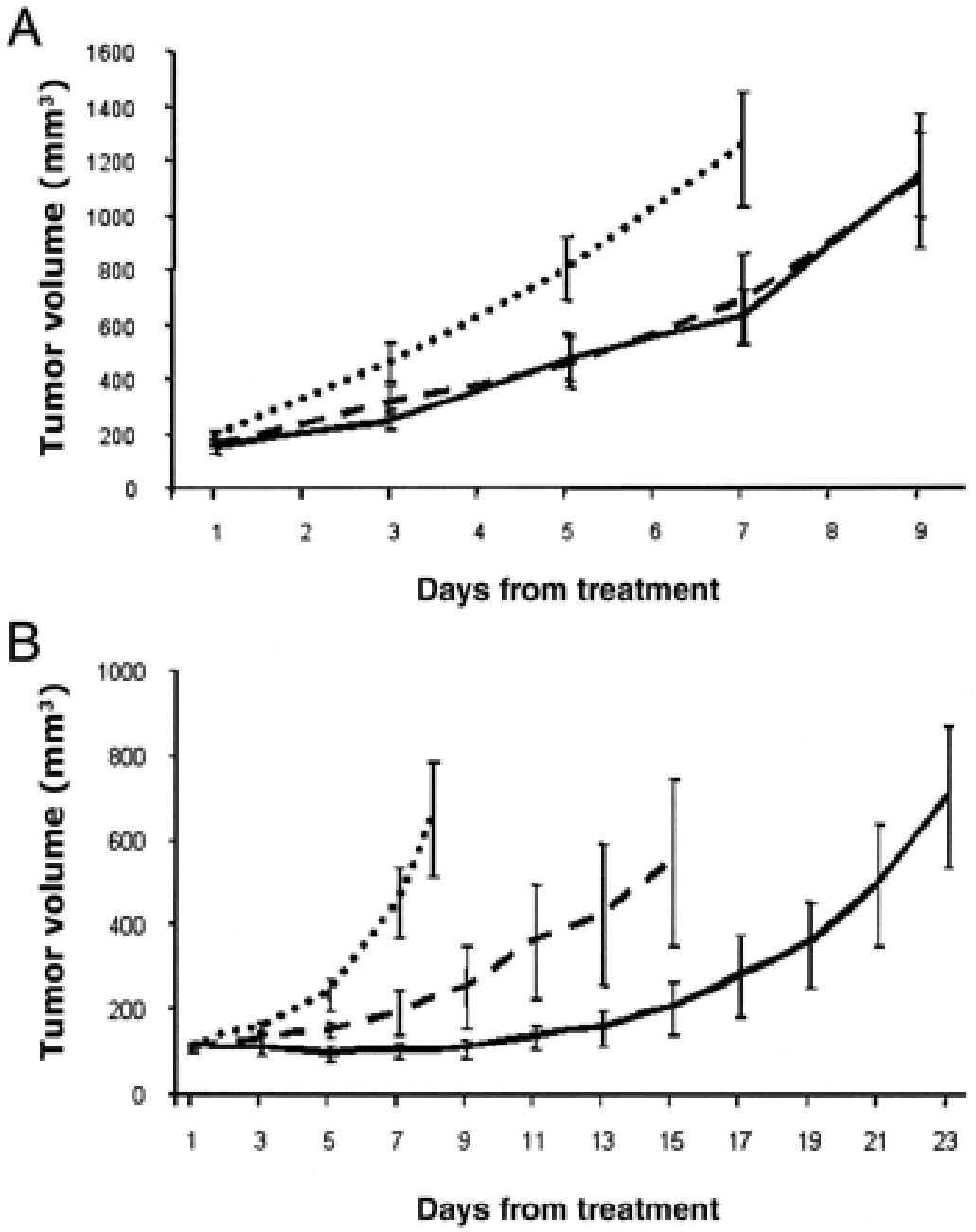
Efficacité in vitro sur *lignées cellulaires*

Mais aussi dans *modèles animaux*

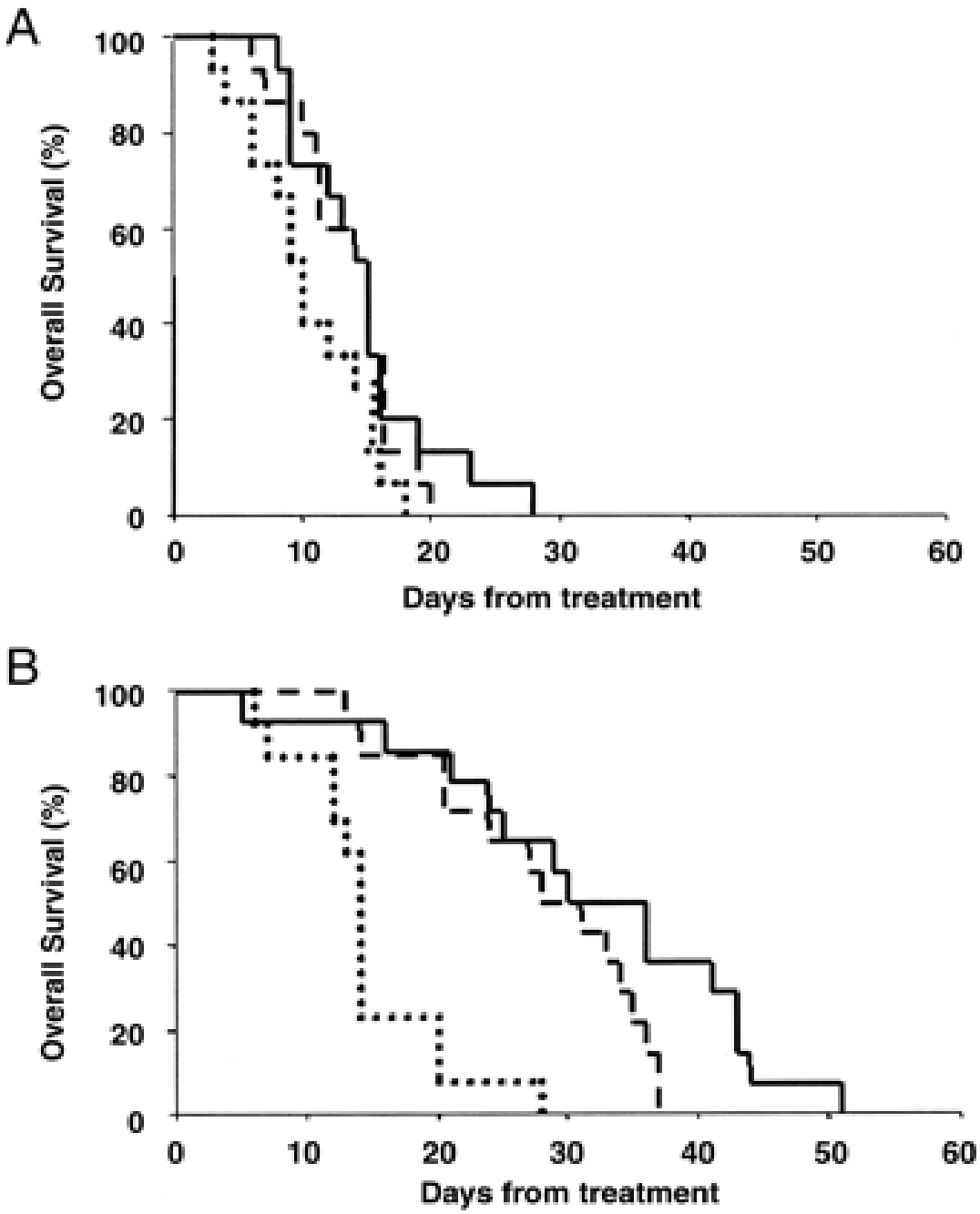
→ seul
Myélome, LeBlanc Cancer Res 2002;62:17

→ association
Cusack Cancer Res 2001;61:3535

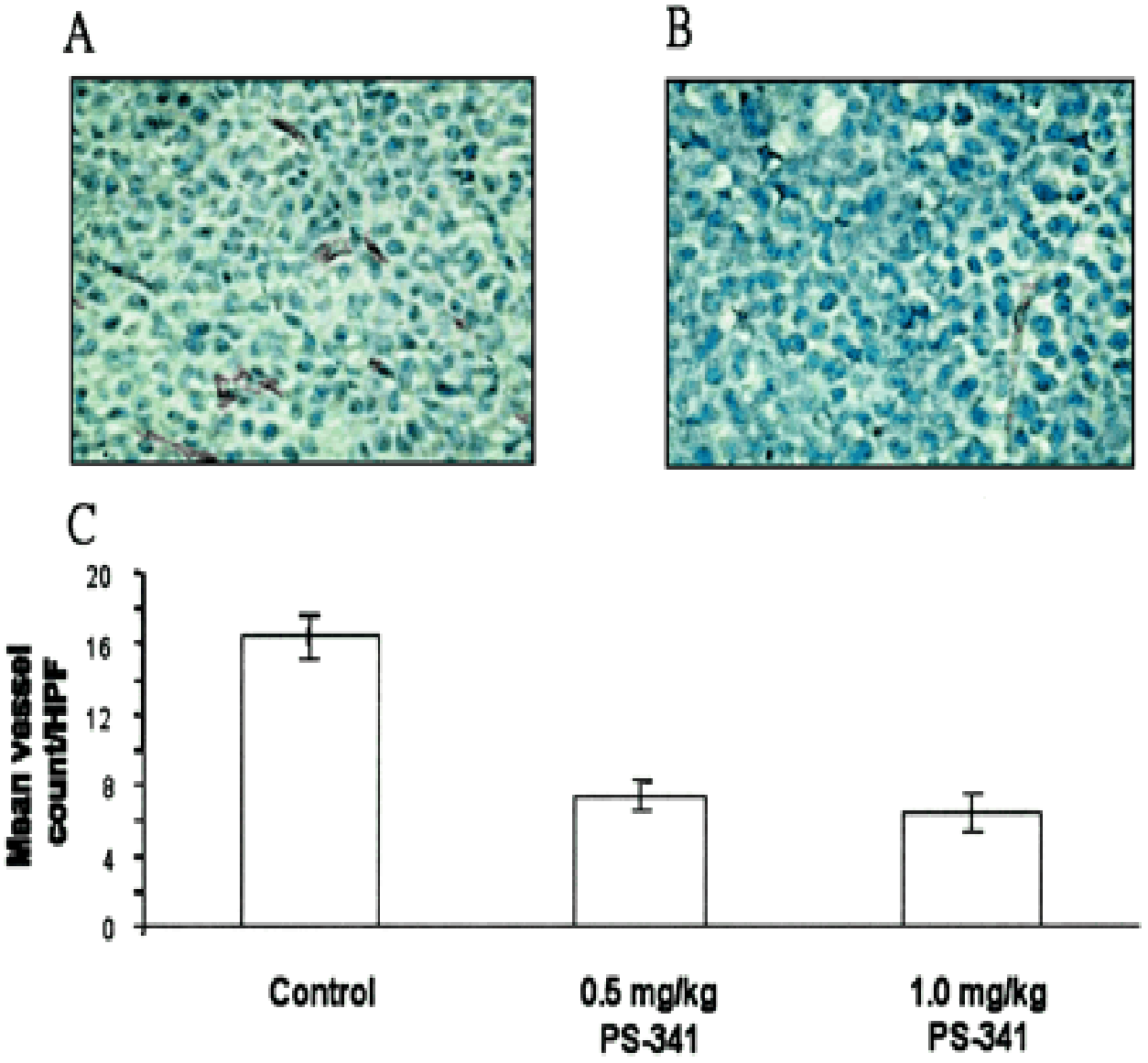
LeBlanc et al,
Cancer Res 2002



LeBlanc et al,
Cancer Res 2002



LeBlanc et al,
Cancer Res 2002



Synergie in vitro lignées cellulaires,

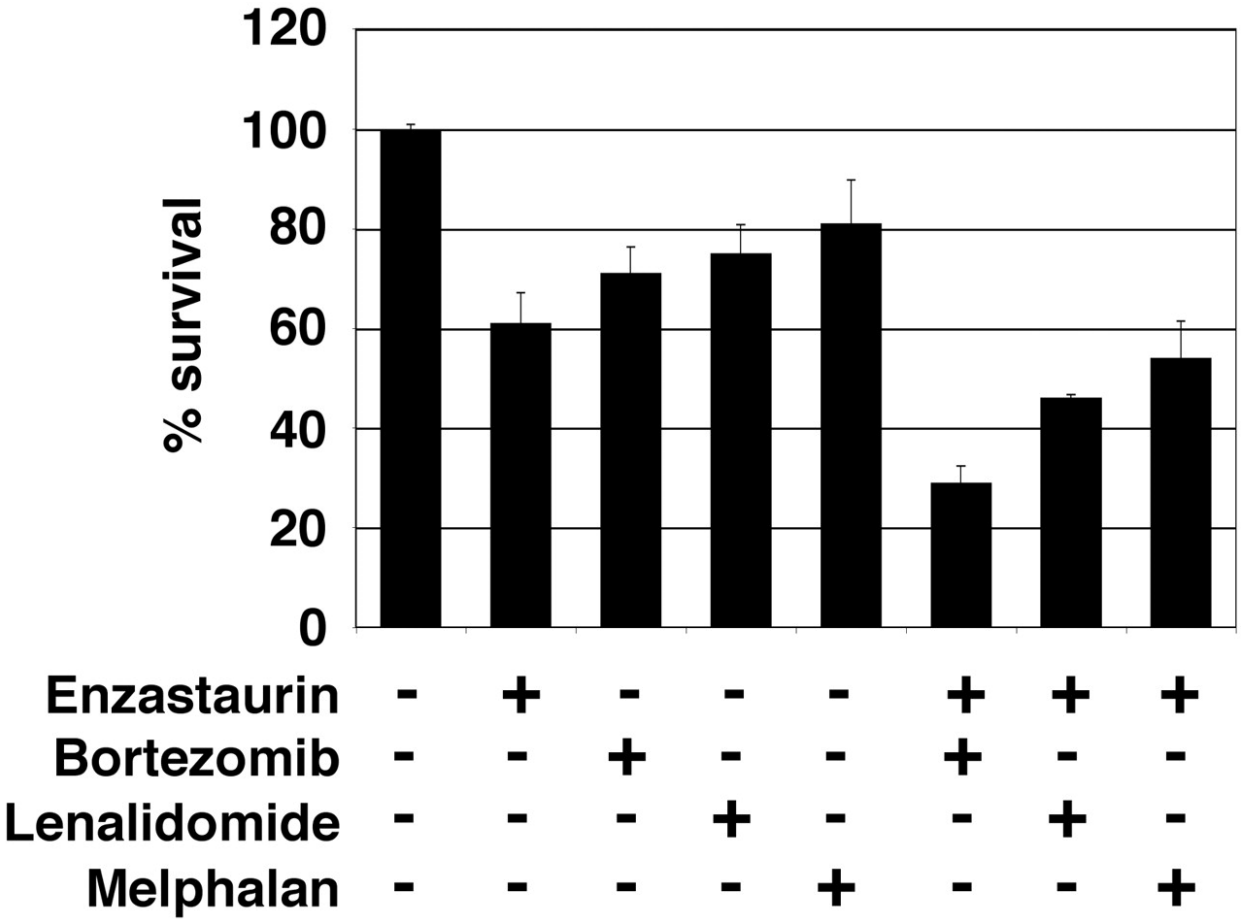
→ antisens (BCl2)

→ inhibiteur Hsp (Mitsiades)

→ dex (Hideshima Cancer Res 2001)

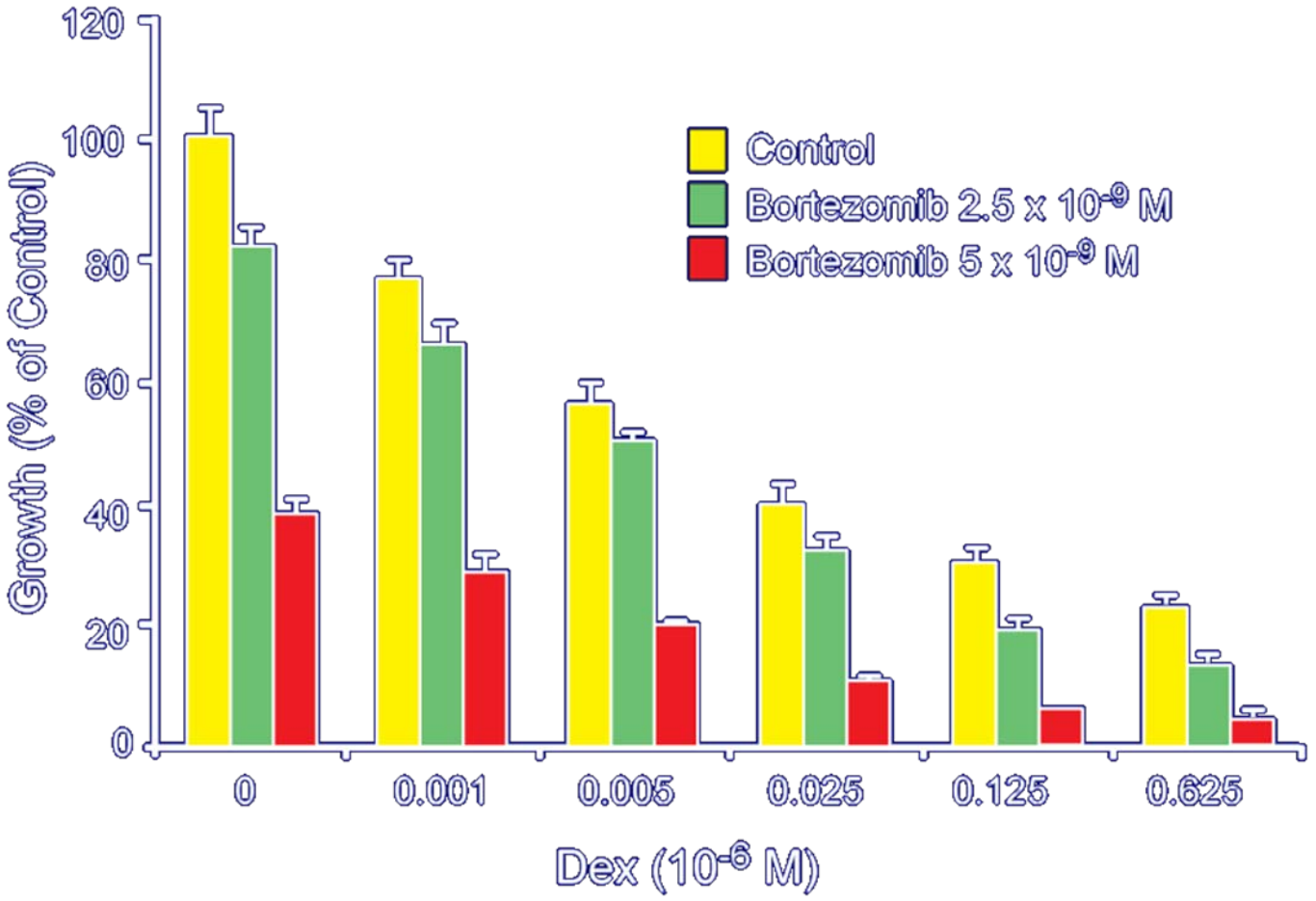
→ Melphalan et doxo (Hideshima Blood 2003)

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY



Podar, K. et al. Blood 2007;109:1669-1677

Additive Effect of Dex To Bortezomib



Hideshima et al. *Cancer Res*. 2001;61:3071.

Phase I, 43 patients, Aghajanian et al, Clin Cancer Res 2002
2 x /semaine pdt 2 semaines puis repos une semaine

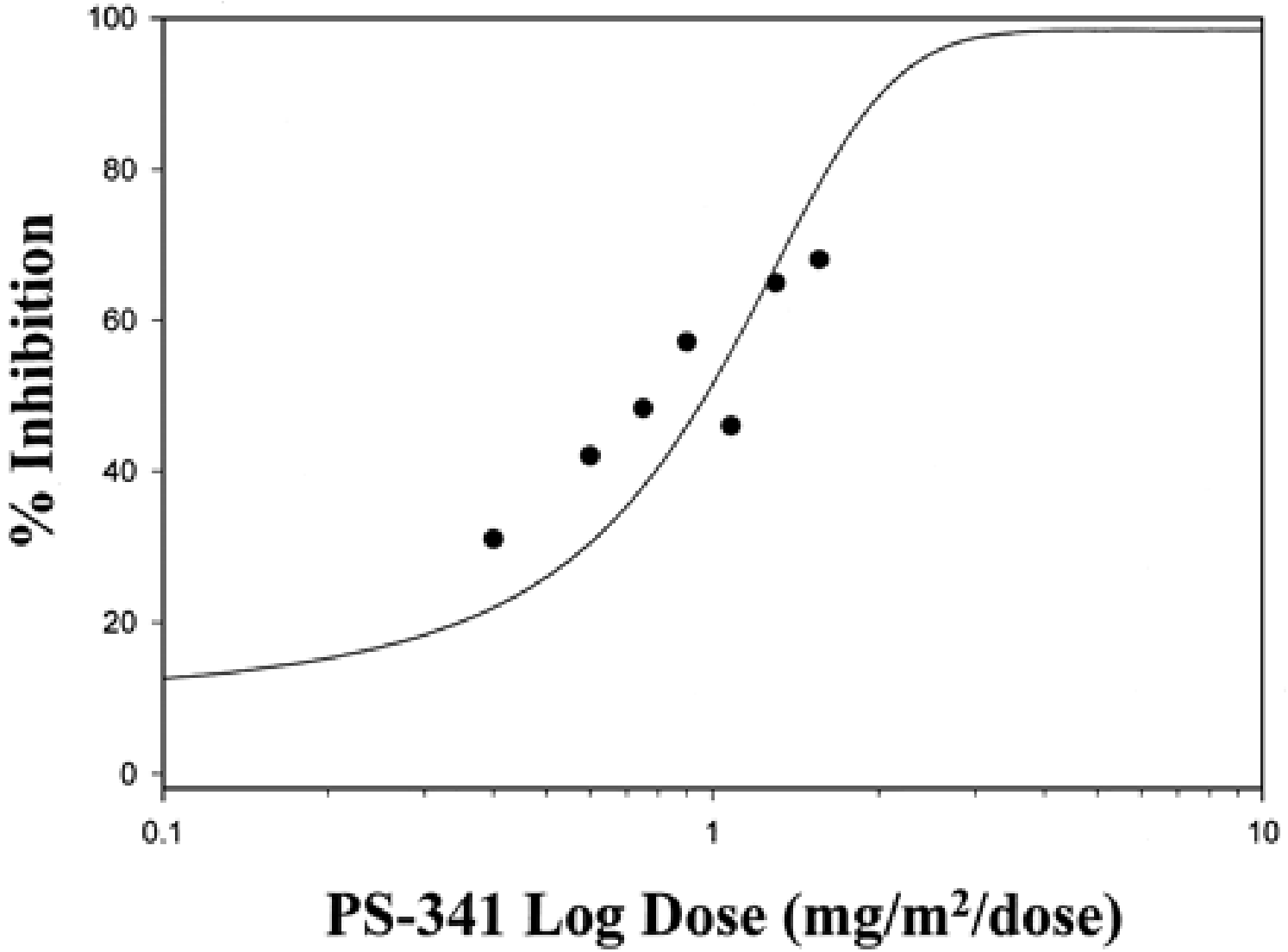
Dose levels (mg/m^2), no. of patients	Total no. of cycles	Hemoglobin				Platelets				Neutrophils			
		1	2	3	4	1	2	3	4	1	2	3	4
0.13, *n* = 3	6	0	1	0	0	0	0	0	0	0	0	0	0
0.25, *n* = 4	9	0	1	0	0	0	0	0	0	0	0	0	0
0.40, *n* = 5	8	0	4	0	0	0	0	0	0	0	0	0	0
0.60, *n* = 4	8	0	0	0	0	0	0	0	0	0	0	0	0
0.75, *n* = 3	9	1	1	0	0	0	0	0	0	0	0	0	0
0.90, *n* = 6	17	1	0	0	0	1	1	0	0	0	0	1	0
1.08, *n* = 3	6	0	2	0	0	1	0	0	0	0	1[a]	0	0
1.30, *n* = 3	7	2	0	1	0	1	1	0	0	0	0	0	0
1.56, *n* = 12	19	5	3	1	0	3	2	2	0	0	0	1	0

Toxicité non hématologique : 2 dose-limiting

- Diarrhées : 2/12 pts grade 3 à 1.56 mg/m2 + 4/12 grade 2 et 1/12 grade 1.

- Neuropathie sensitive : 2/12 grade 3 à 1.56 mg/m2 (préexistantes) + 1/12 grade 2 (préexistante)

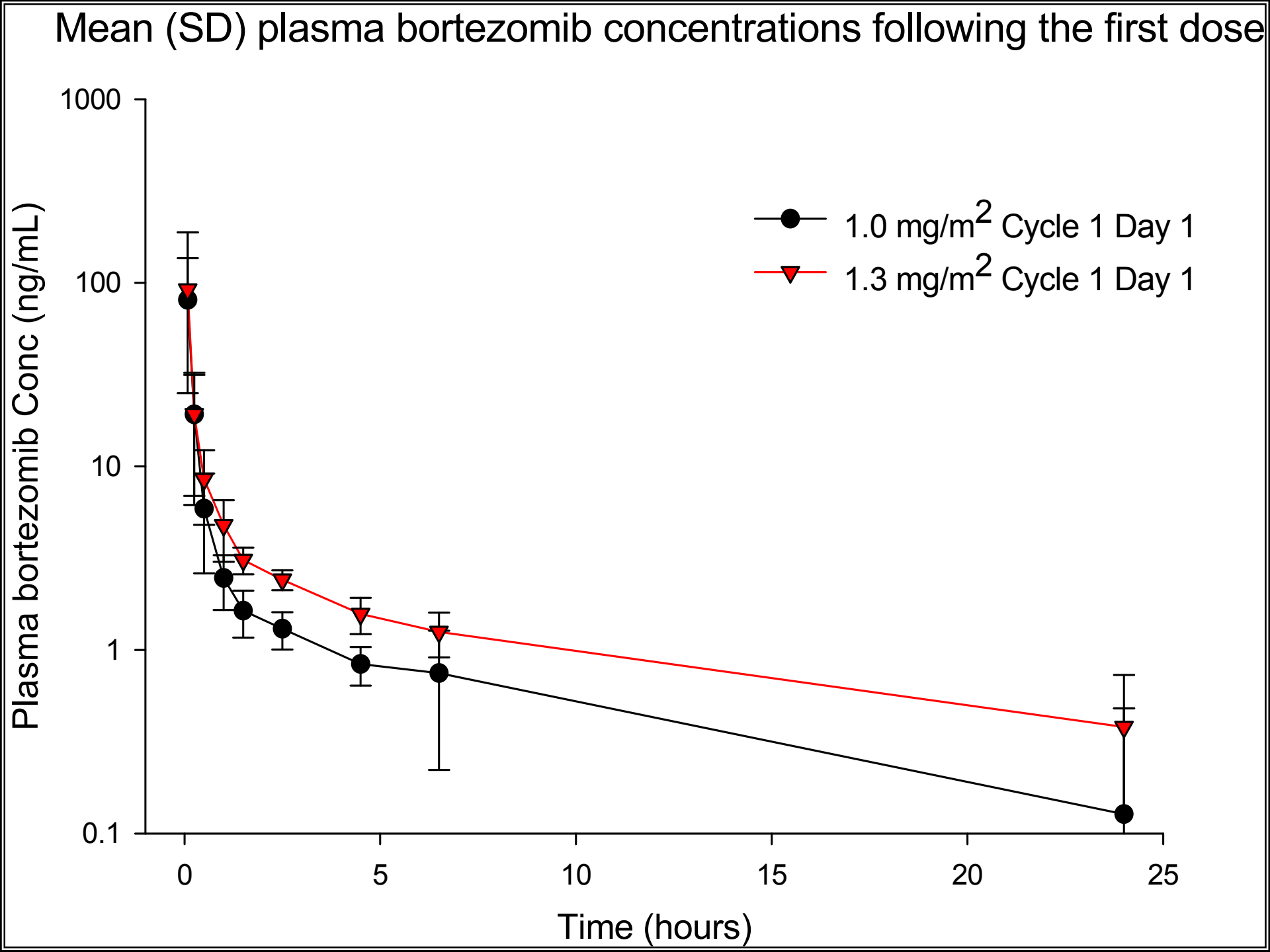
Clin Cancer Res 2002, Aghajanian et al

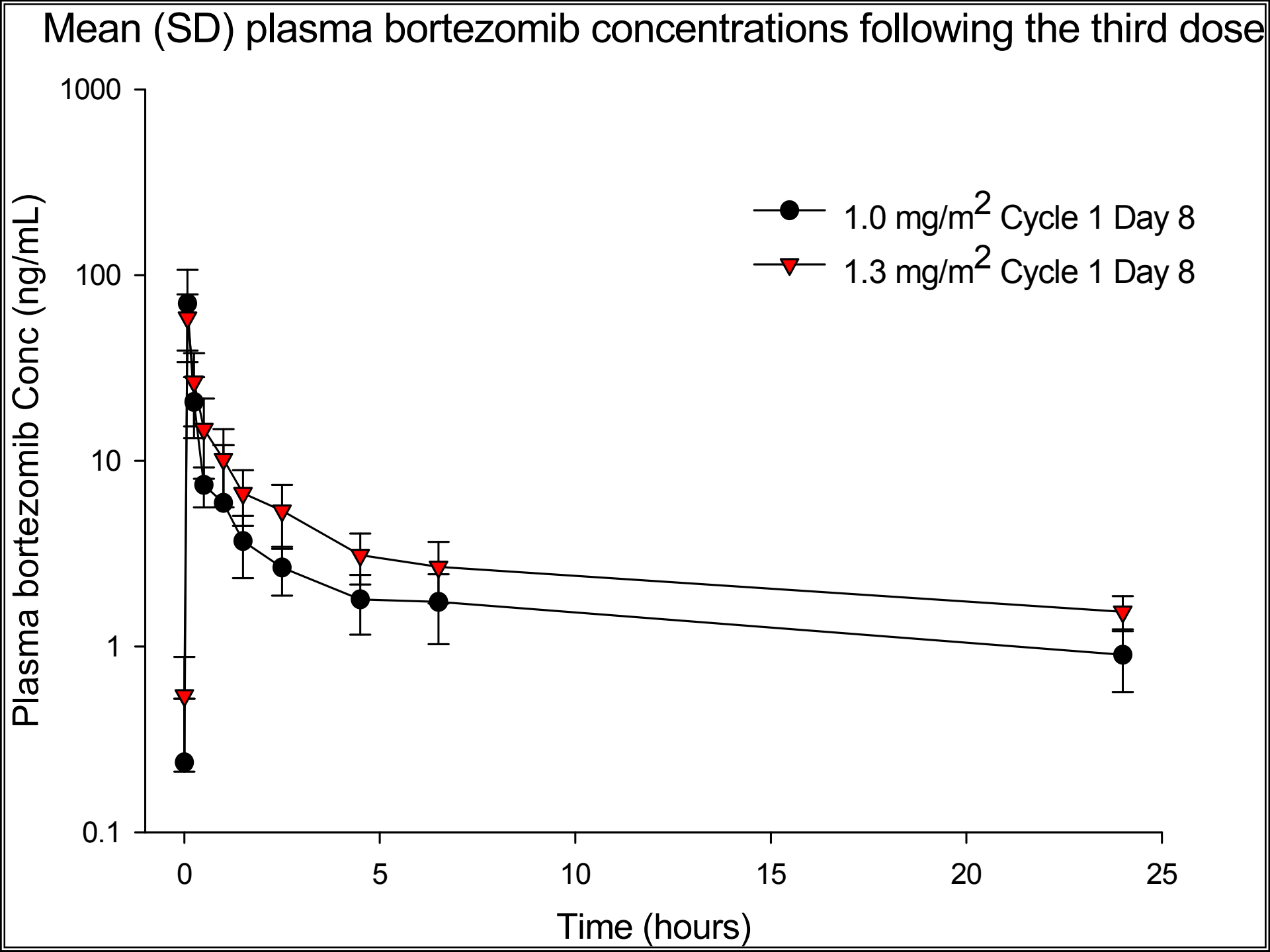


Dose	At 1 hour	At 24 hours
0.4 mg/m²	31%	6.5%
0.6 mg/m²	42%	6%
0.75 mg/m²	46%	17.5%
0.9 mg/m²	—	29.5%
1.08 mg/m²	—	24.8%
1.3 mg/m²	65%	32.8%
1.56 mg/m²	68%	32.8%

- Pas de différence entre J1, 4, 8, 11

- Retour normale à 72h


Mean (SD) plasma bortezomib concentrations following the first dose
1000
100
10
1
0.1
Plasma bortezomib Conc (ng/mL)
1.0 mg/m2 Cycle 1 Day 1
1.3 mg/m2 Cycle 1 Day 1
0
5
10
15
20
25
Time (hours)


Mean (SD) plasma bortezomib concentrations following the third dose
1000
100
10
1
0.1
Plasma bortezomib Conc (ng/mL)
1.0 mg/m2 Cycle 1 Day 8
1.3 mg/m2 Cycle 1 Day 8
0
5
10
15
20
25
Time (hours)

Elimination biphasique
t 1 / 2 α < 10 min
t 1 / 2 β : 5 à 10 heures

Vd : 400-600 l

AUC : augmentation proportionnelle à la dose 1 ou 1.3 mg/m2

Pas d'accumulation plasmatique dans le temps

The NEW ENGLAND JOURNAL of MEDICINE

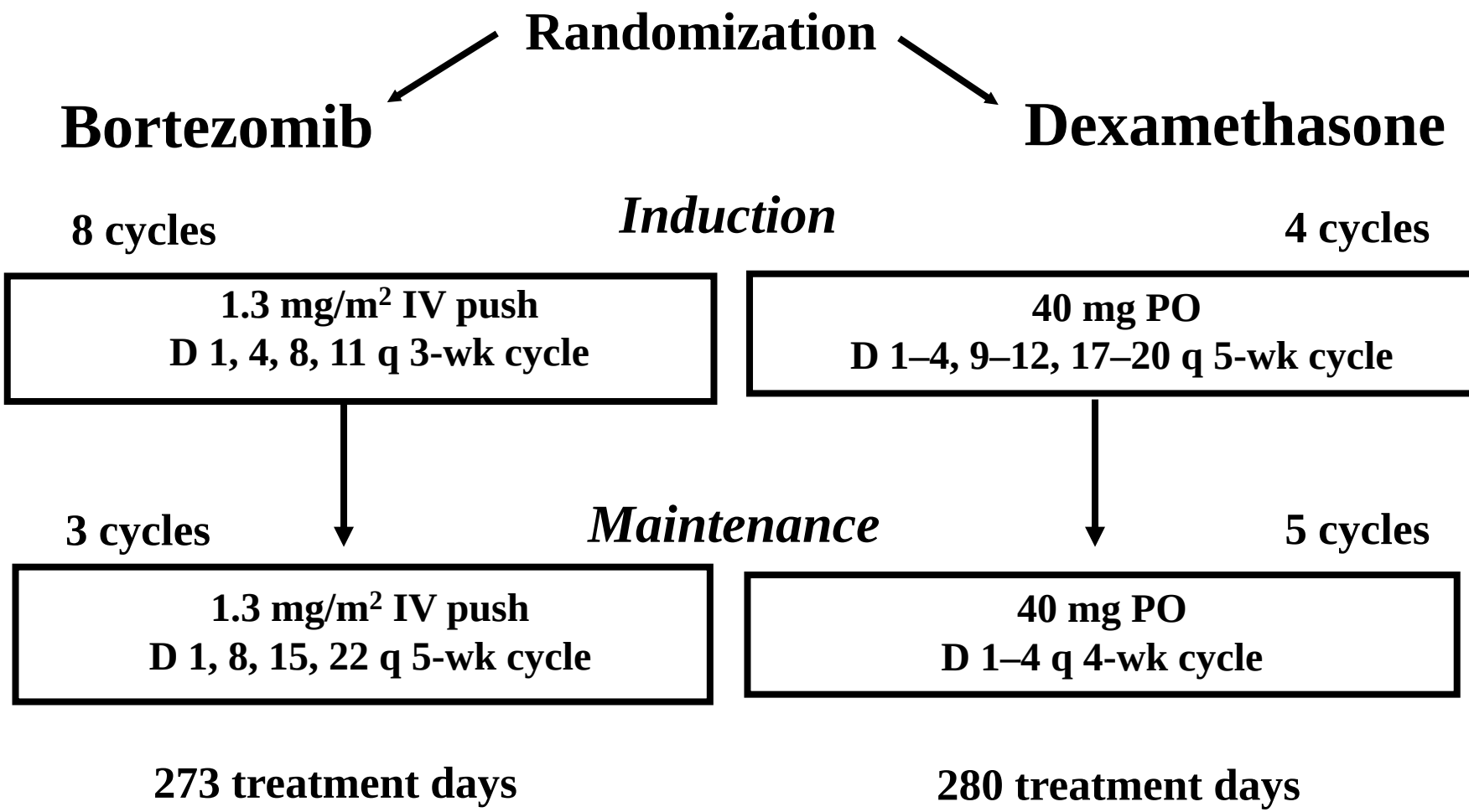
N ENGL J MED 352;24 WWW.NEJM.ORG JUNE 16, 2005

ORIGINAL ARTICLE

Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma

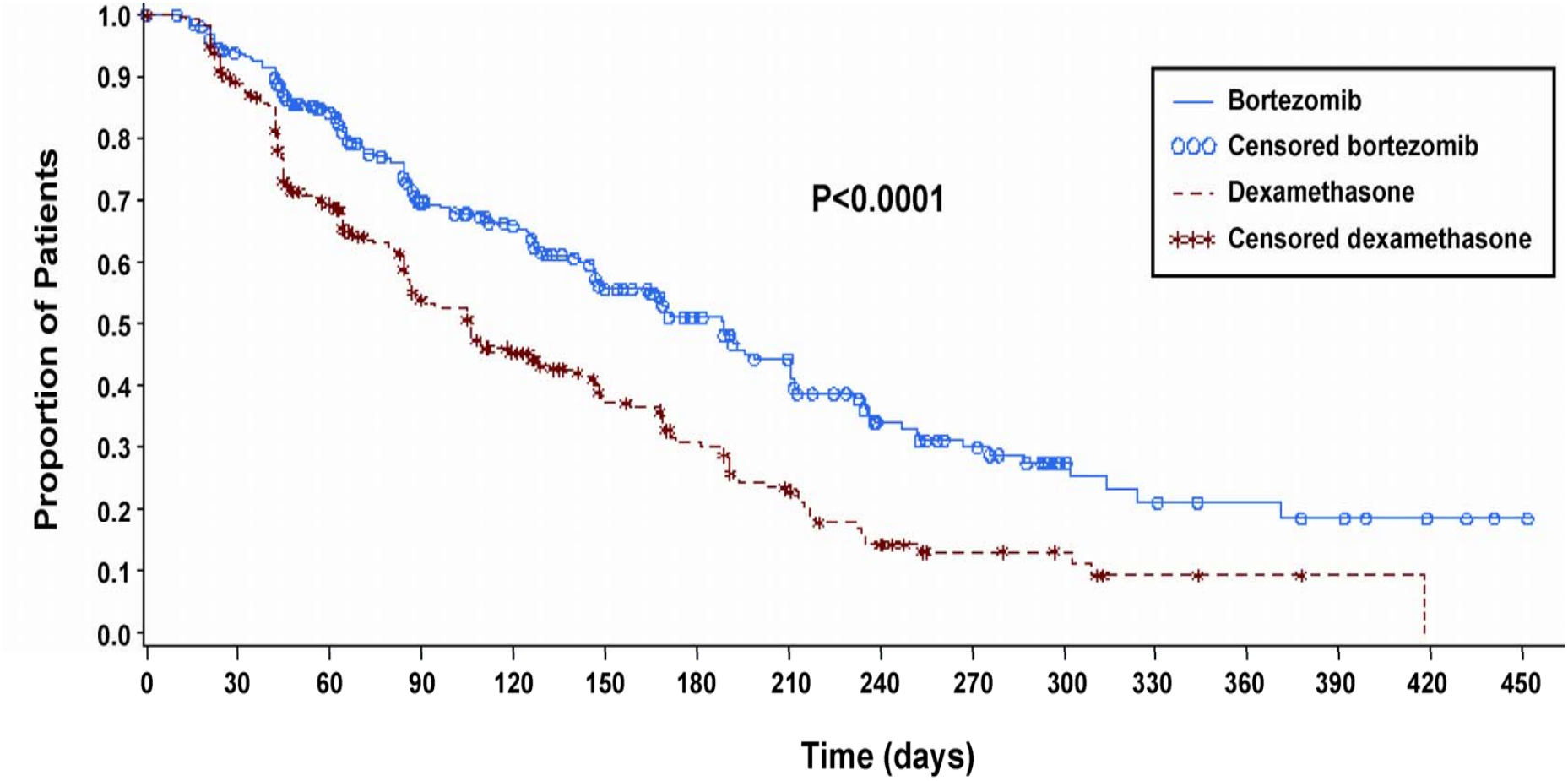
Paul G. Richardson, M.D., Pieter Sonneveld, M.D., Michael W. Schuster, M.D., David Irwin, M.D., Edward A. Stadtmauer, M.D., Thierry Facon, M.D., Jean-Luc Harousseau, M.D., Dina Ben-Yehuda, M.D., Sagar Lonial, M.D., Hartmut Goldschmidt, M.D., Donna Reece, M.D., Jesus F. San-Miguel, M.D., Joan Bladé, M.D., Mario Boccadoro, M.D., Jamie Cavenagh, M.D., William S. Dalton, M.D., Anthony L. Boral, M.D., Ph.D., Dixie L. Esseltine, M.D., Jane B. Porter, M.S., David Schenkein, M.D., and Kenneth C. Anderson, M.D., for the Assessment of Proteasome Inhibition for Extending Remissions (APEX) Investigators*

APEX: TREATMENT PLAN



Time to progression (*n* = 669)

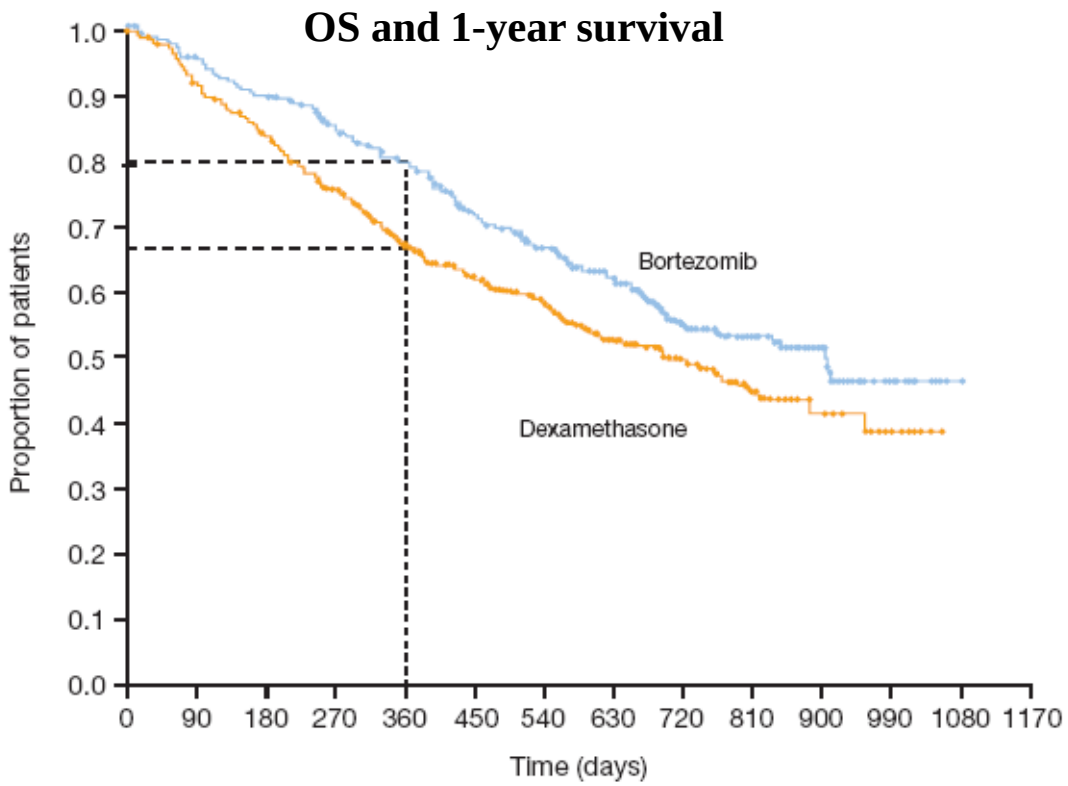
78% improvement in median TTP with bortezomib



Median TTP: bortezomib 6.2 mois; dexamethasone 3.5 mois

Updated APEX survival data

- **Superior TTP 6.2m vs 3.5 m**
- **Superior survival despite cross-over**
  - **Median OS: bortezomib 29.8 months vs 23.7 months for high-dose Dex (*P* = 0.0272)**
  - **1-year survival rate: 80% vs 67% (*P* = 0.0002)**



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

- Essai randomisé, international, phase III VMP vs MP Chez MM de novo inéligible pour une intensification autogreffe
- ≥65 yrs or <65 yrs et inéligible pour une autogreffe; KPS ≥60%

RANDOMISE

VMP = MP plus Bortezomib

Cycles 1-4: Bortezomib 1.3 mg/m^2 IV: days 1,4,8,11,22,25,29,32

Cycles 5-9: Bortezomib 1.3 mg/m^2 IV days 1,8,22,29

MP

Cycles 1-9

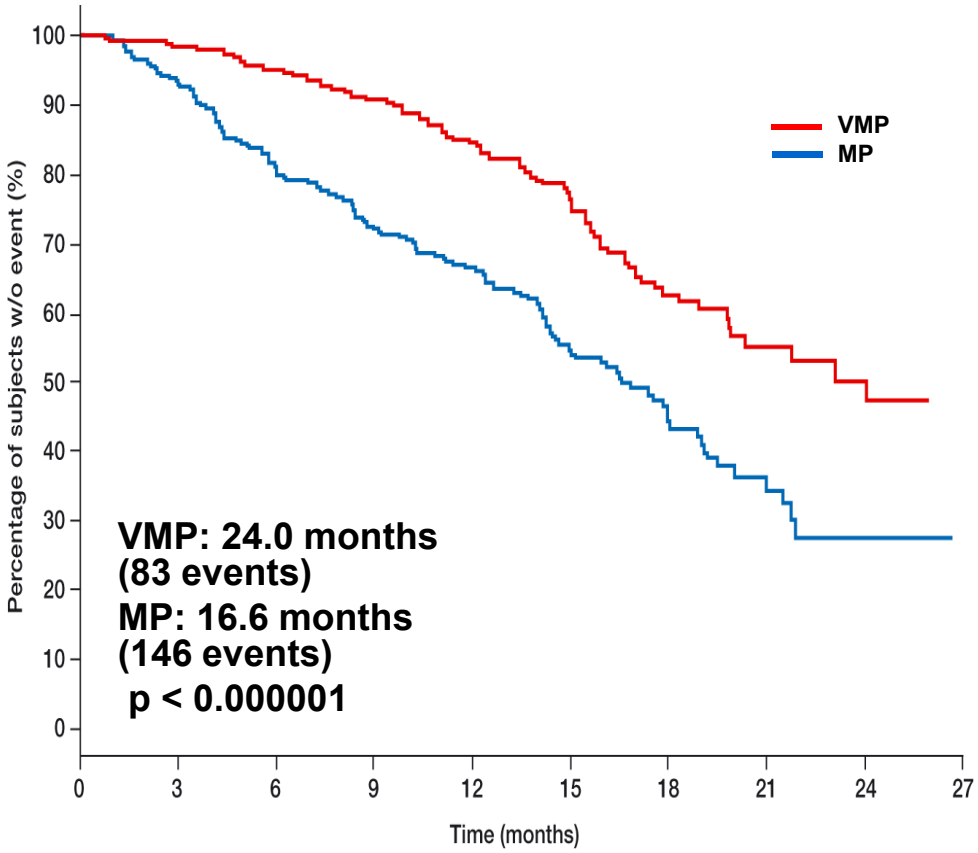
Melphalan 9 mg/m^2

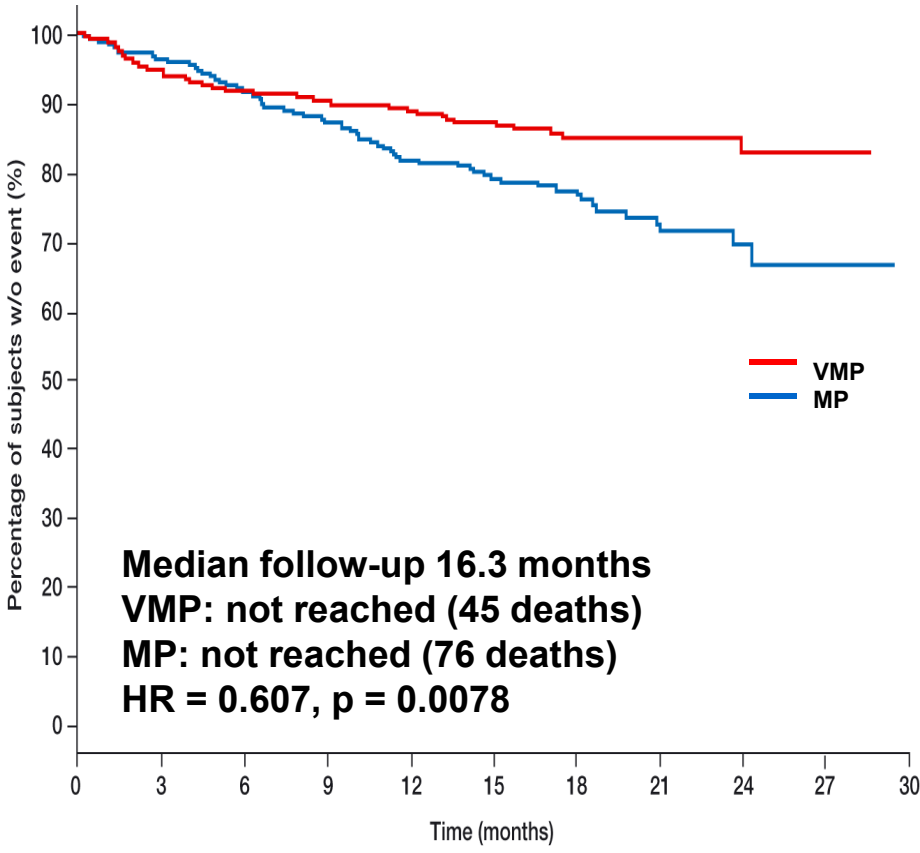
Prednisone 60 mg/m^2 days 1-4

Objectif primaire: TTP

9 cycles de 6 semaines (54 weeks) dans les 2 bras

Survie sans progression et globale





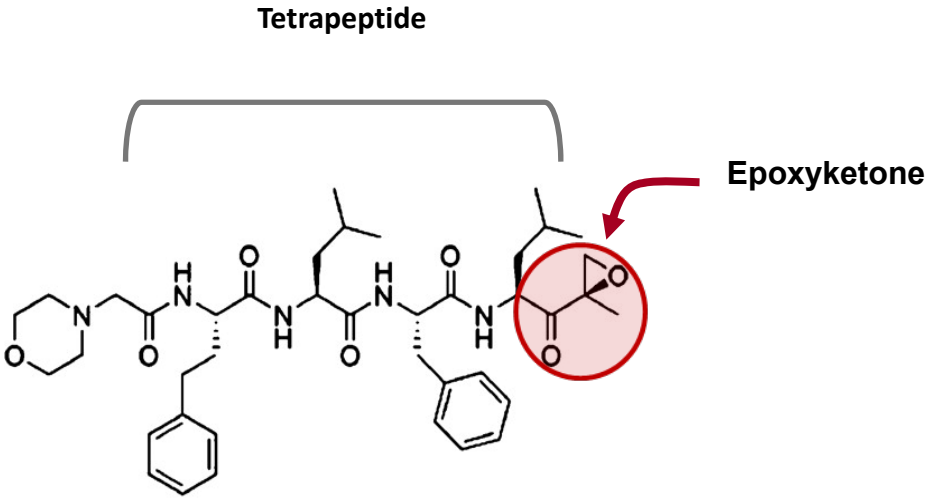
Survie sans progression

Survie globale

- **Survie Globale @ 2-years 82.6% in VMP vs 69.5% in MP**

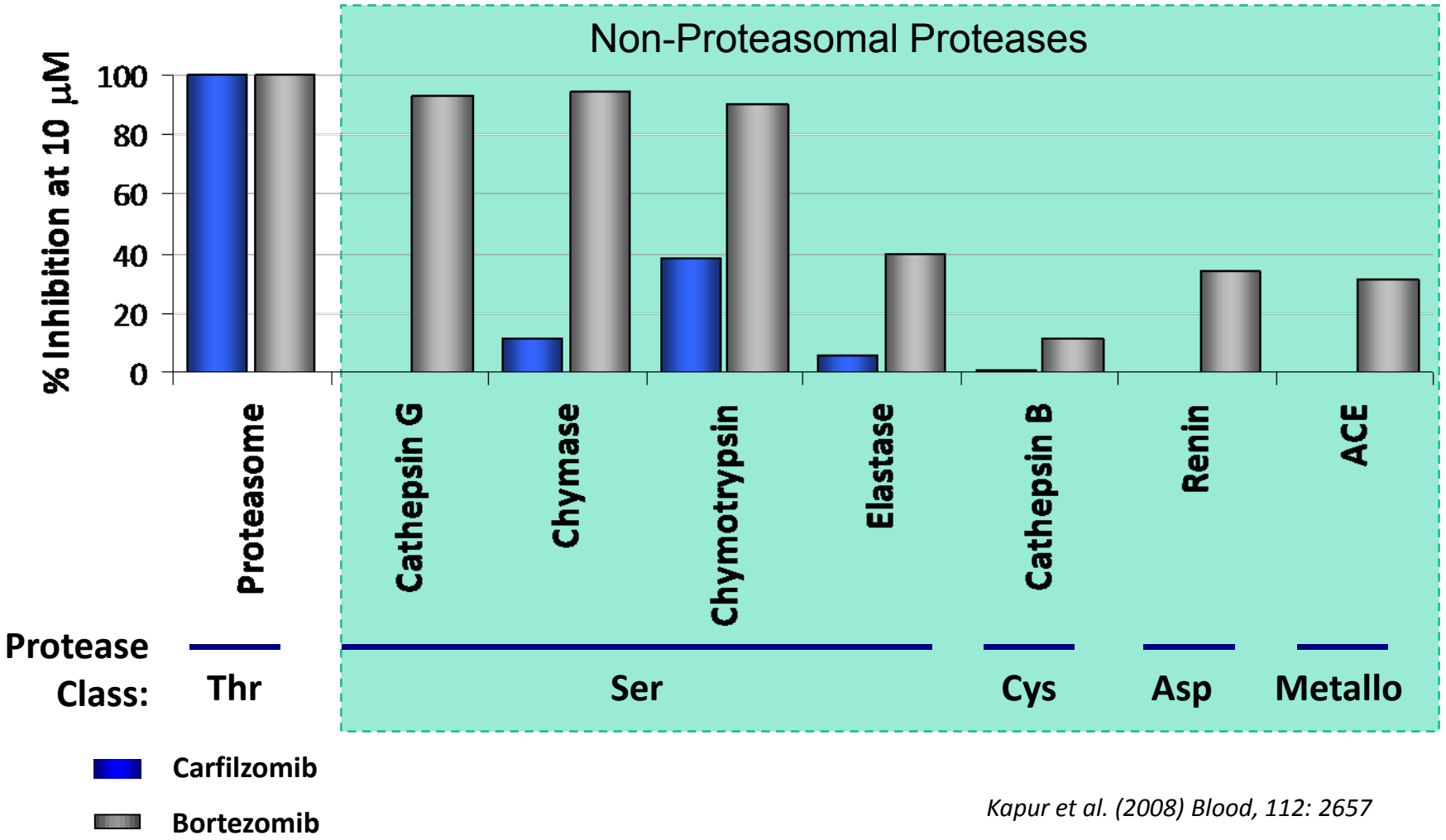
Carfilzomib:
Selective and Irreversible Proteasome Inhibitor

Carfilzomib is the first in a new class of selective and irreversible proteasome inhibitors that are associated with prolonged target suppression, improved antitumor activity and low neurotoxicity



Carfilzomib is Highly Selective for the Proteasome

Minimal off target activity across all classes of proteases

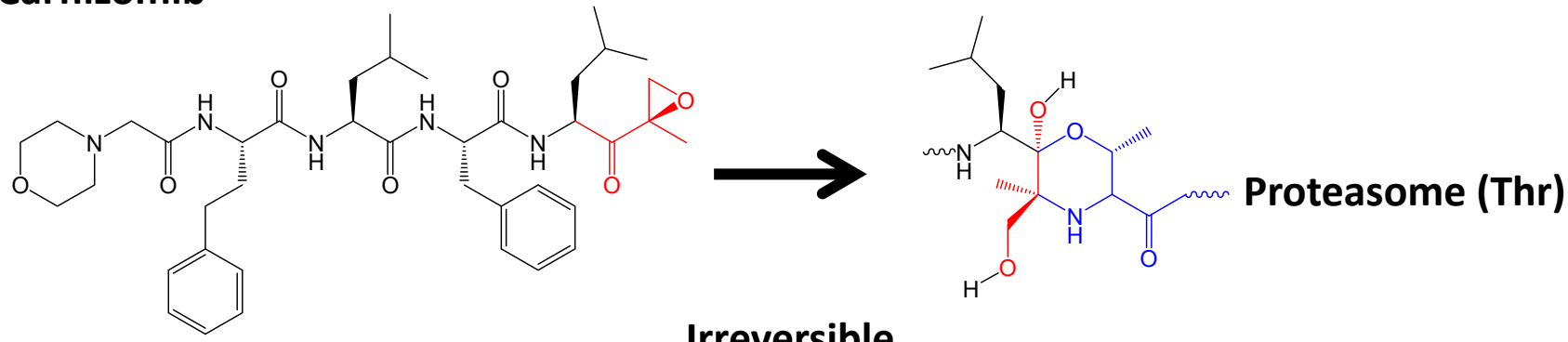


Kapur et al. (2008) Blood, 112: 2657

Mechanism of Binding to Active Site

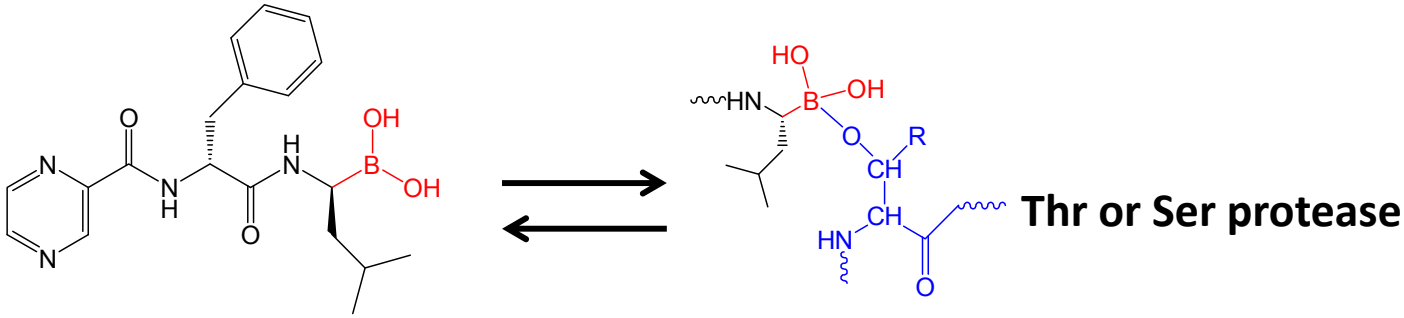
Unique chemistry drives selectivity and prolonged inhibition

Carfilzomib



Irreversible

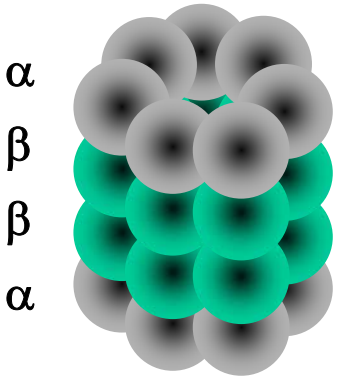
Bortezomib

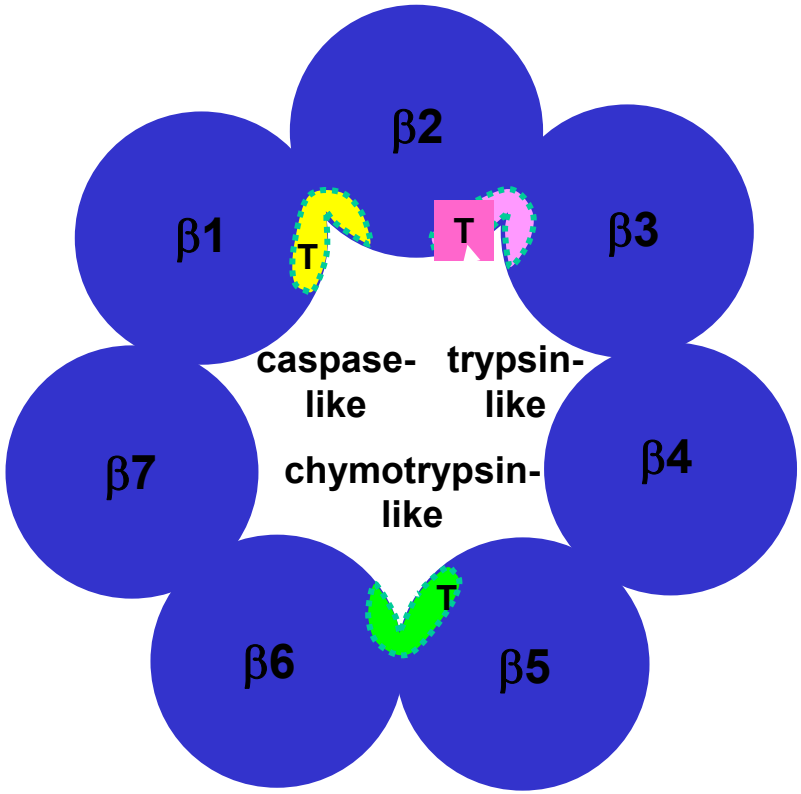


Slowly reversible

Carfilzomib

20S proteasome particle





β-subunit ring

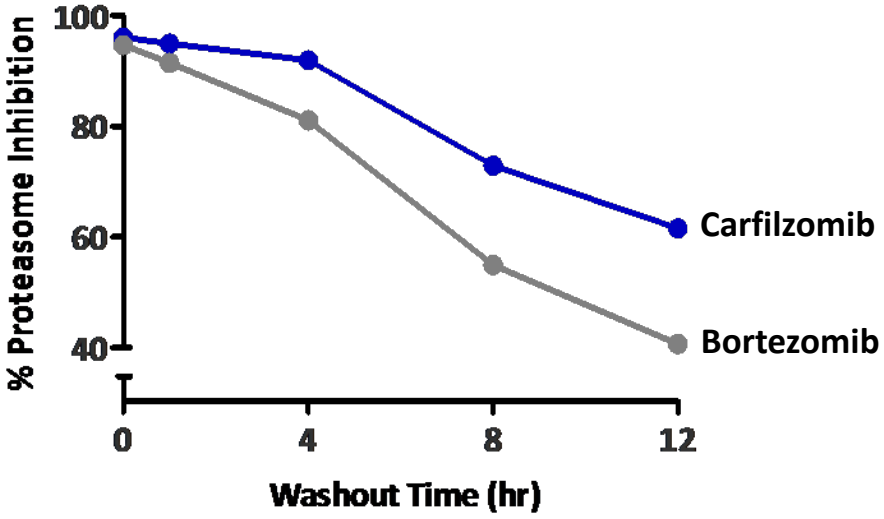
Three distinct N-terminal threonine protease active sites

IC_{50}s (nM)	Chymotrypsin-like	Caspase-like	Trypsin-like
Carfilzomib	6	2400	3600
Bortezomib	7	74	4200

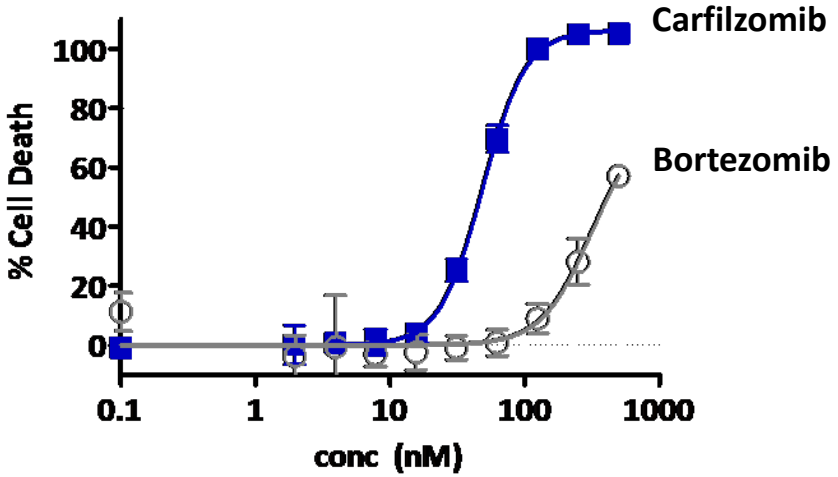
Prolonged Inhibition Enhances Tumor Cell Death

Irreversible binding of carfilzomib prolongs proteasome inhibition and triggers cell death at lower doses of drug

Proteasome inhibition in HT-29 cells following brief exposure to drug



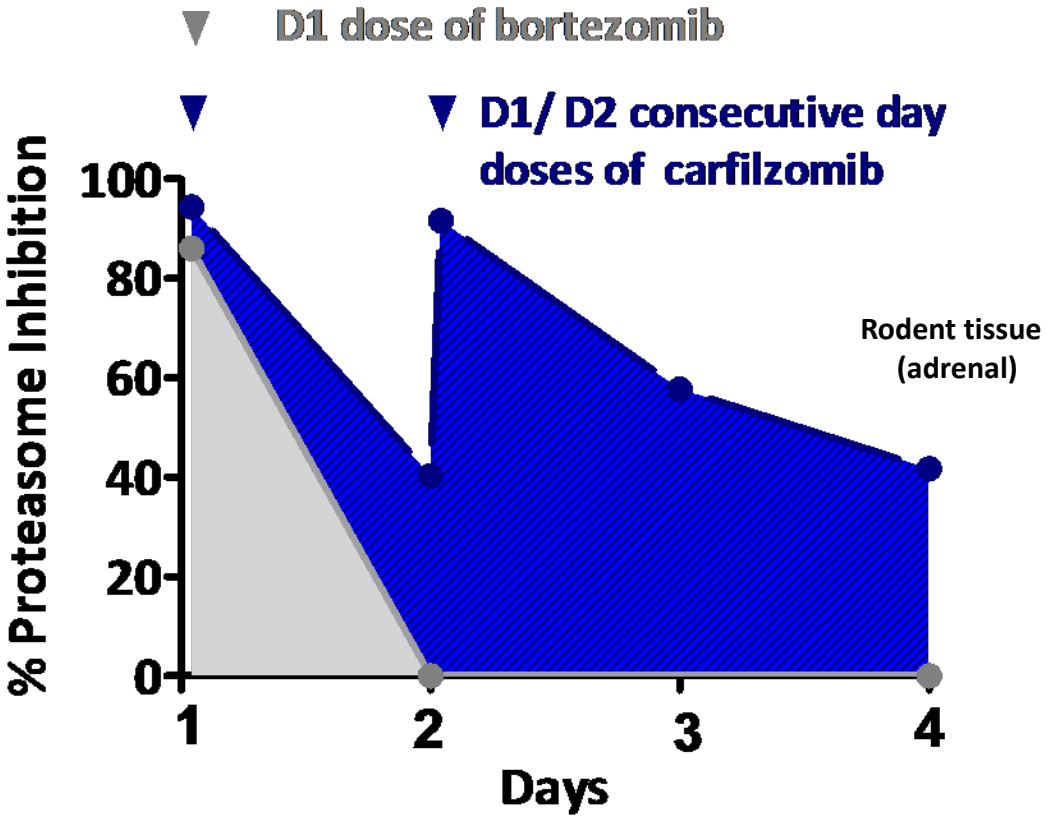
Cell viability measured in RPMI-8226 cells 24 hrs after brief exposure to drug



Demo et al. (2007), Cancer Research, 67:6383

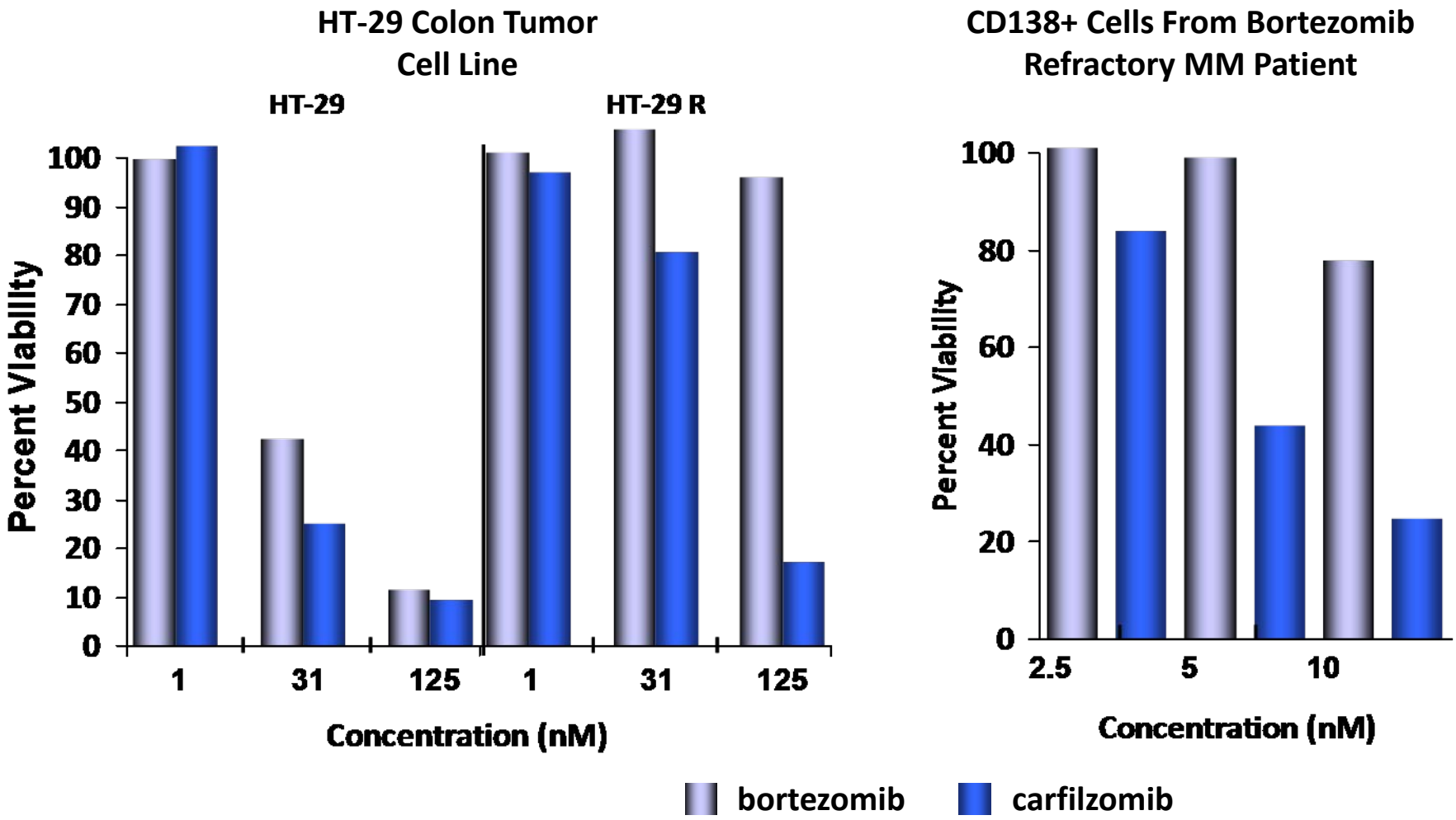
Tolerability Allows Consecutive Day Dosing

Carfilzomib can be dosed on consecutive days (D1/D2) to lengthen the time of proteasome inhibition



Demo et al. (2007), Cancer Research, 67:6383

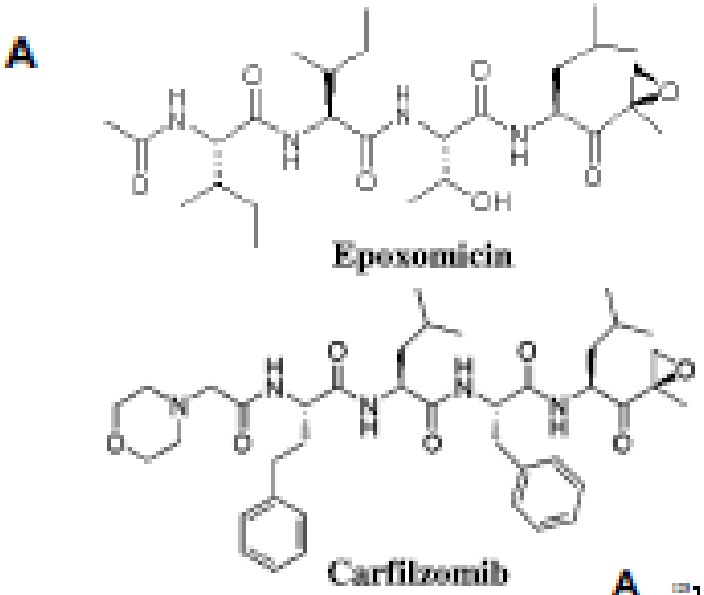
Carfilzomib is Active in Bortezomib-resistant Tumor Cells

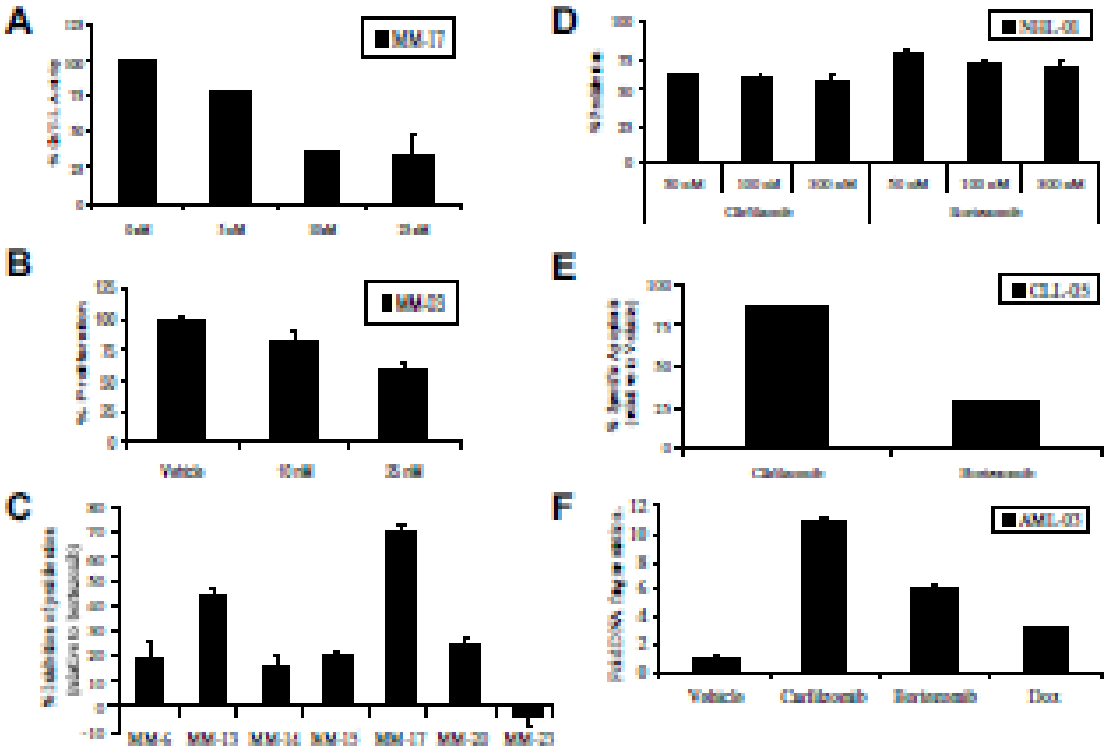


Demo et al. (2005) Blood, 106:1588, Kuhn et al.(2007), Blood, 110:3281

Carfilzomib

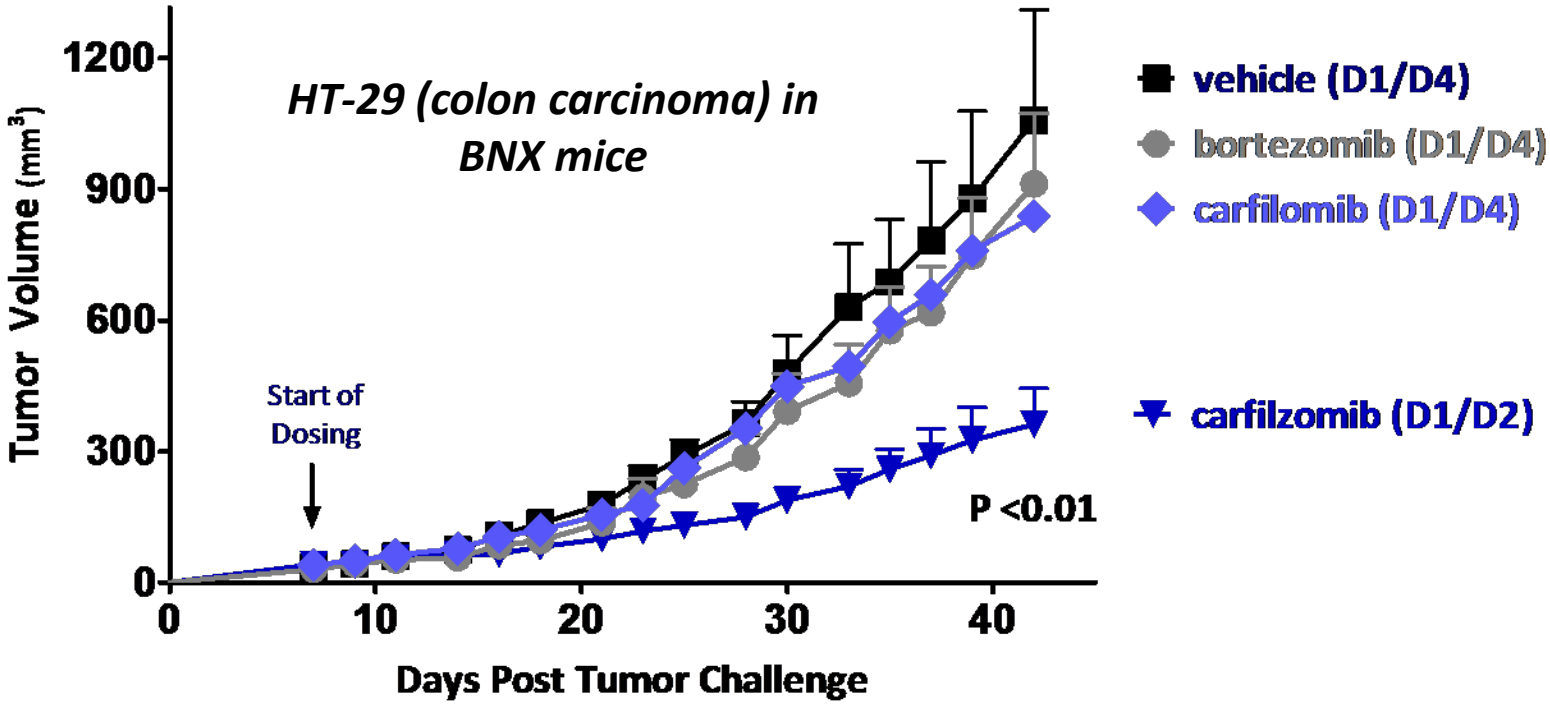
Kuhn et al, Blood 2007:110:3281





Improved Anti-Tumor Activity

Consecutive day dosing with carfilzomib prolongs proteasome inhibition and improves anti-tumor activity



Demo et al. (2007), Cancer Research, 67:6383

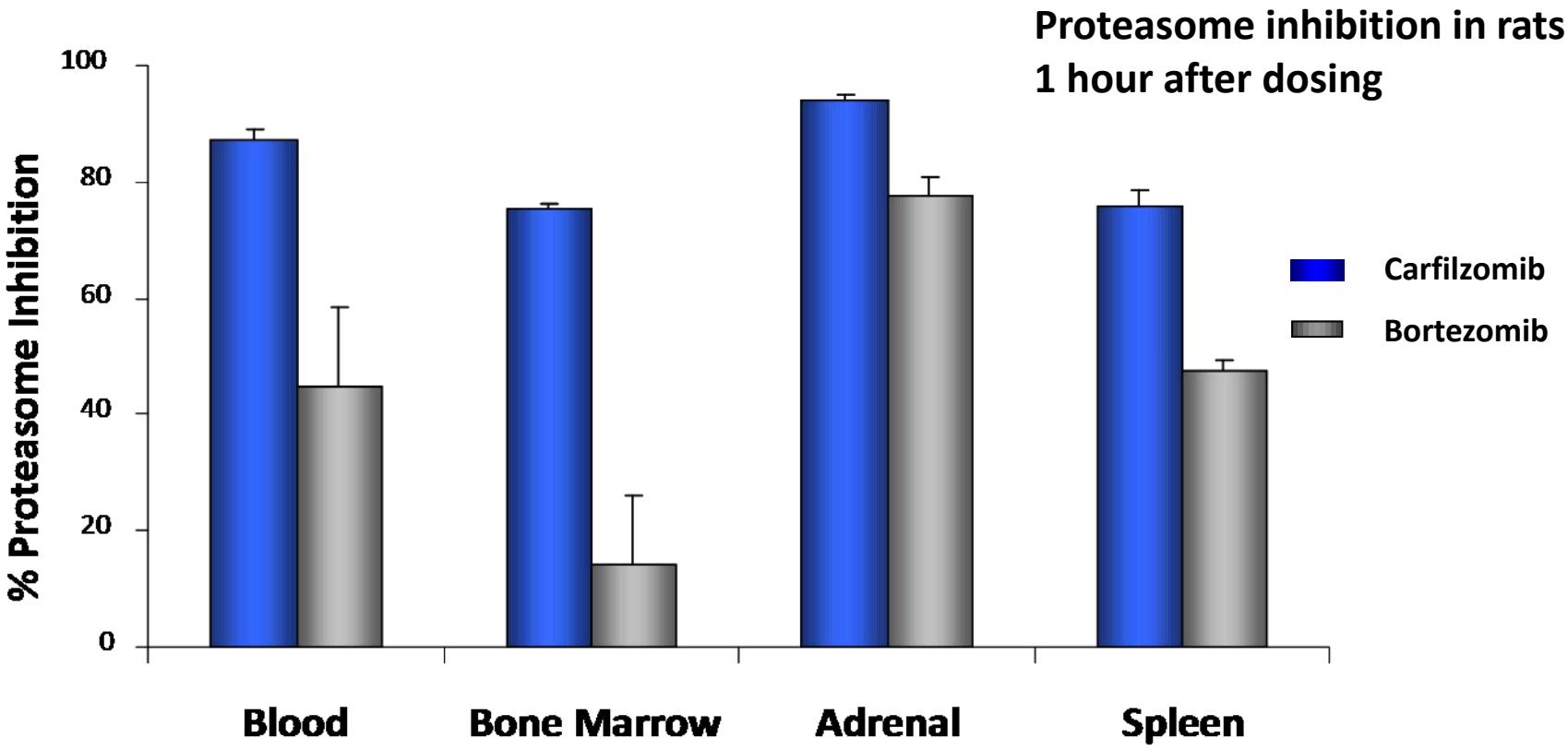
Carfilzomib Lacks Neurotoxicity and Neutropenia in Chronic Toxicity Studies

Chronic Toxicity Studies in Rats (6 months) and Monkeys (9 months)		
Toxicity	Bortezomib (D1/D4)	Carfilzomib (D1/D2)
Neurologic	Tremors and reduced motor activity Nerve degeneration Reduced nerve conduction velocity	***No neurobehavioral deficits*** ***No histological changes***
Hematologic	Decreased RBC & platelets, Decrease WBCs	Decreased platelets ***No WBC changes***
Gastrointestinal	Mucosal hyperplasia and inflammation	
Cardiovascular	Sporadic cardiac inflammation	
Renal	Chronic progressive nephropathy	

Kirk et al, (2008) Blood, 112: 2765; Bortezomib Summary Basis of Approval; Cavaletti G, (2007) Exp Neurology 204:317.

Greater Proteasome Inhibition

Carfilzomib dosing achieves more proteasome inhibition at the MTD



Bross, et al. (2005) Clinical Cancer Research 10:3954; Data on file, Proteolix.

Preclinical Profile of Carfilzomib

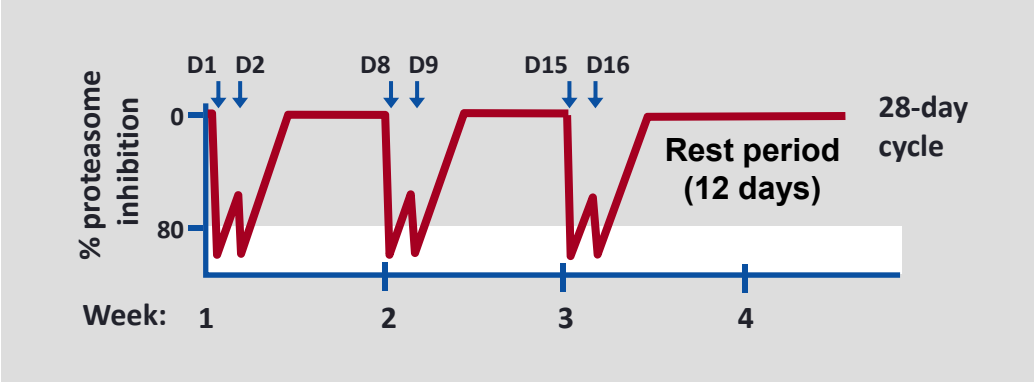
- **Novel chemical class: highly selective and irreversible proteasome inhibitors**
  - Minimal off target activity
  - Irreversible mechanism prolongs proteasome inhibition
  - Consecutive day dosing tolerated
- **Improved efficacy with consecutive day dosing**
  - D1/D2 dosing prolongs proteasome inhibition and improves anti-tumor activity
- **No neurotoxicity in animals**
  - No histological or behavioral neurotoxicity in animals was observed with chronic dosing
- **Active in bortezomib-resistant cells and tumor models**

PX-171-004 Carfilzomib Phase 2 Study Design

Design

- **Relapsed MM**
- **20 mg/m^2 IV push;**
- **12 cycles**
- **Premedication:**

dexamethasone 4 mg PO (Cycle 1 only)



Primary endpoint

- Overall response rate

Secondary endpoints

- DOR, PFS, TTP, OS
- Safety

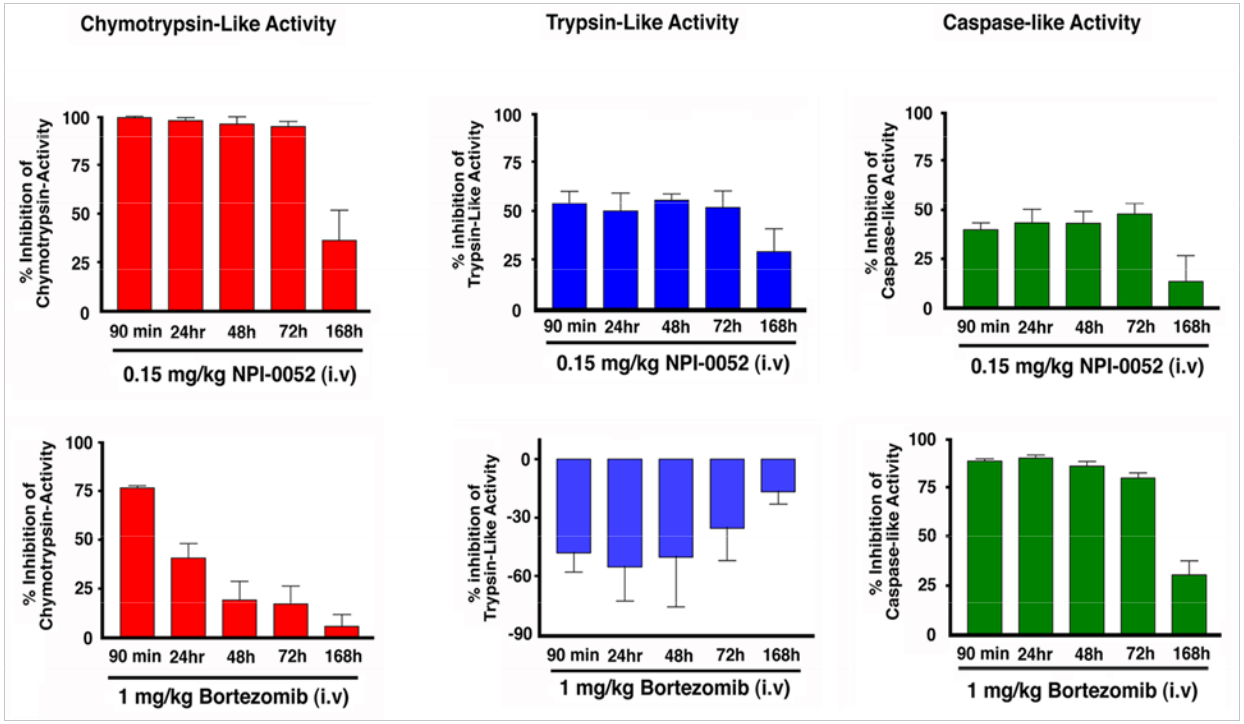
PX-171-003: Responses in Bortezomib Refractory Patients

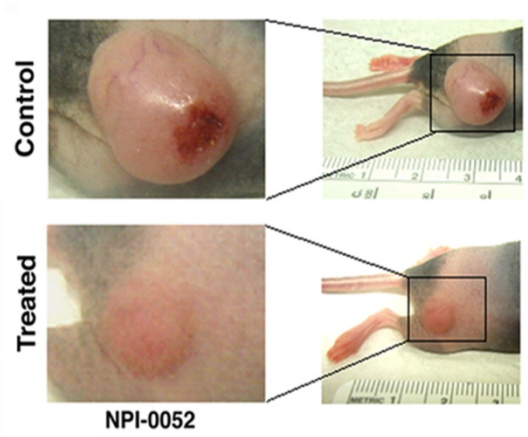
- 5 of 26 (19%) responded with MR or better to single-agent carfilzomib

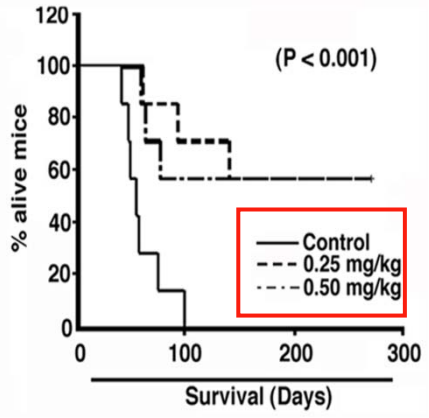
Last Therapy	Carfilzomib	
Regimen	Best Response	Days
BTZ + Len/Dex	PR	211
BTZ + Dex/Dox/Thal	MR	100
BTZ + Dox/Dex (BTZ/Dox/Thal maintenance)	MR	289
BTZ + Len	MR	332*
BTZ + Tanespimycin	MR	191

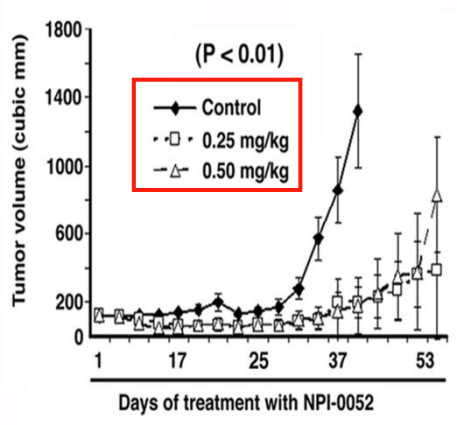
*Subject completed 12 cycles of carfilzomib treatment, as per protocol

Novel Proteasome Inhibitor NPI-0052 Inhibits Human MM Cell Growth and Prolongs Survival in a Murine Model





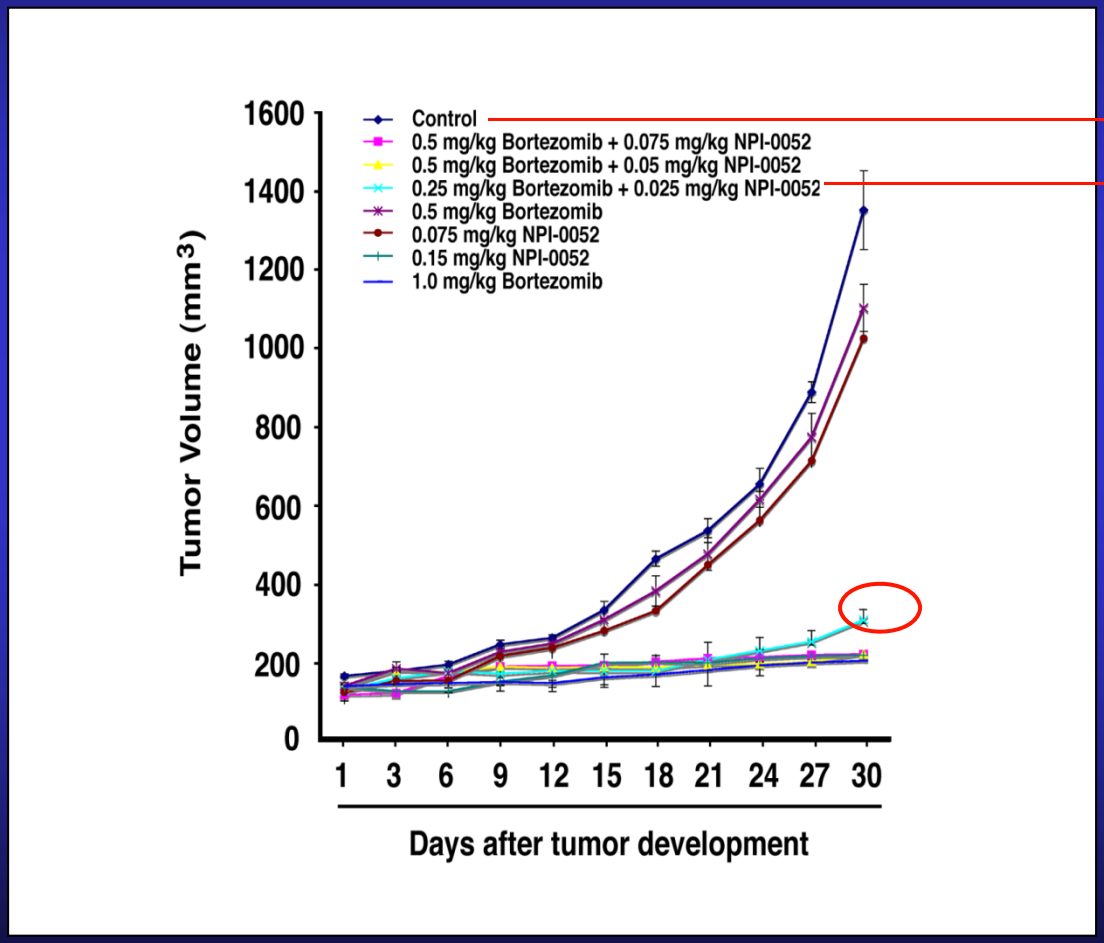




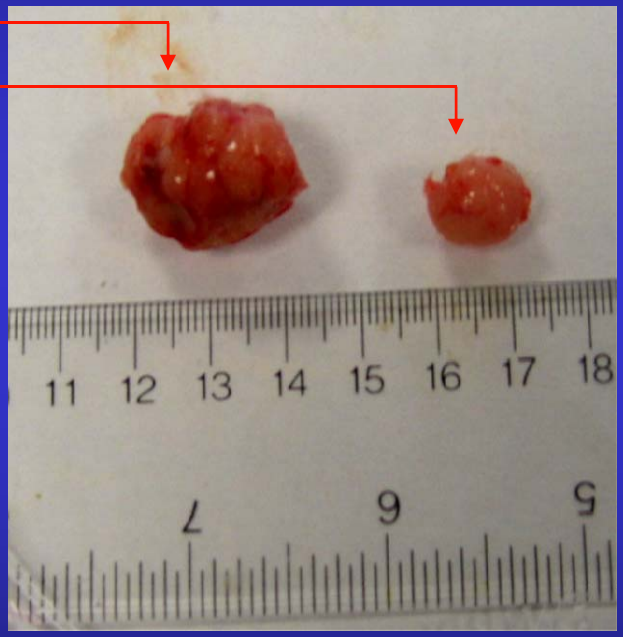
Phase I clinical trial in myeloma 11/06

Chauhan et al, Cancer Cell, 2005

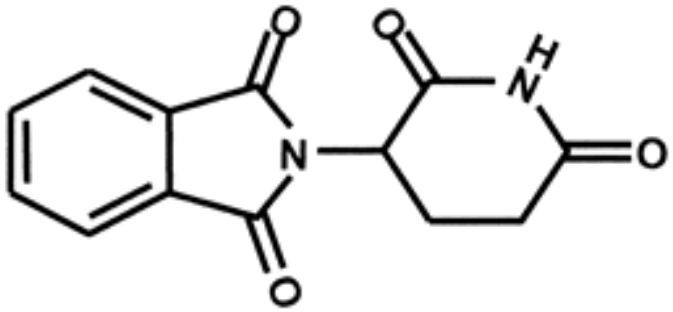
Combination of Bortezomib and NPI-0052 Inhibits Human Plasmacytoma Growth in Immune-Deficient BNX Mice



Control Treated

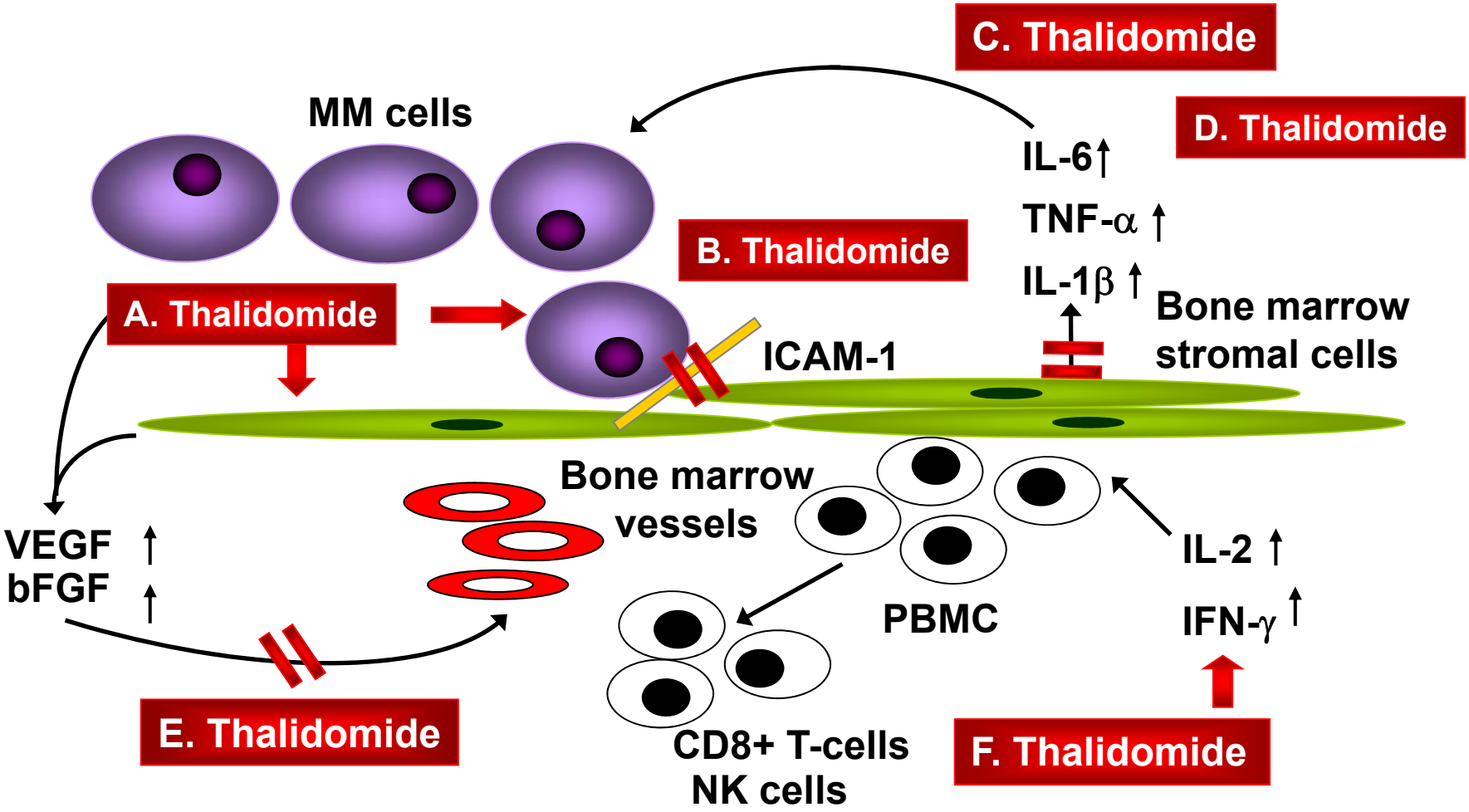


Chauhan et al., 2007



thalidomide

Thalidomide: multiple pathways, multiple targets



Adapted with permission from Richardson PG, et al. Blood. 2002;100:3063. ©Am Soc Hematol.

ORIGINAL ARTICLE

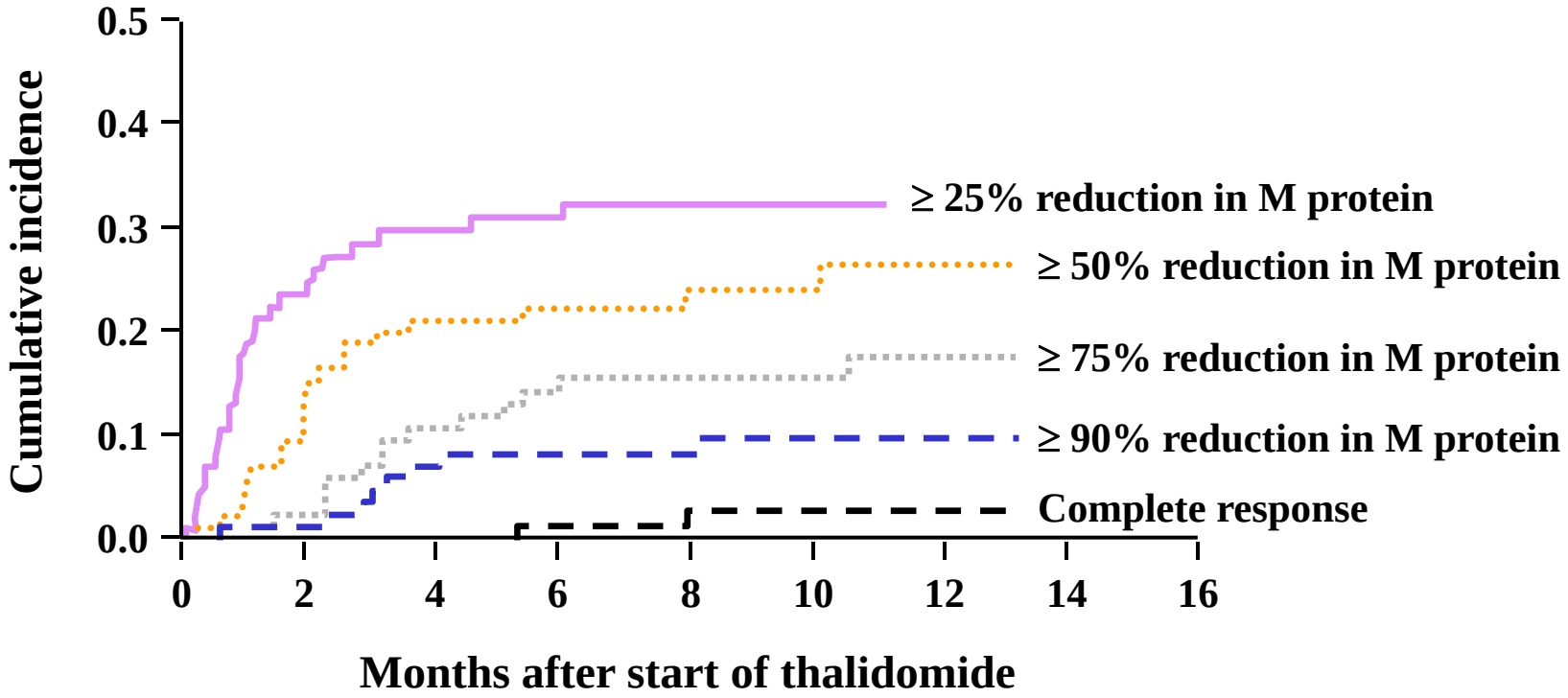
The NEW ENGLAND JOURNAL of MEDICINE

1999;341:1565

Antitumor Activity of Thalidomide in Refractory Multiple Myeloma

Seema Singhal, et al

Single-agent thalidomide salvage therapy in MM



SYSTEMATIC REVIEW OF PHASE II TRIALS OF THALIDOMIDE MONOTHERAPY IN RELAPSED MM

Glasmacher A, Br J Haematol 2005

- 42 communications (24 full papers)
- 1629 patients
- median dose > 200 mg/d in 86% of cases

CR or VGPR (> 90%)	1.6	
PR (>50%)	27.8	43.2%
MR	13.8	

- Survival data

1 year EFS 35 %, median EFS : 3 to 16 months

1 year SV 60 %, median SV : 14 months

Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99–06): a randomised trial

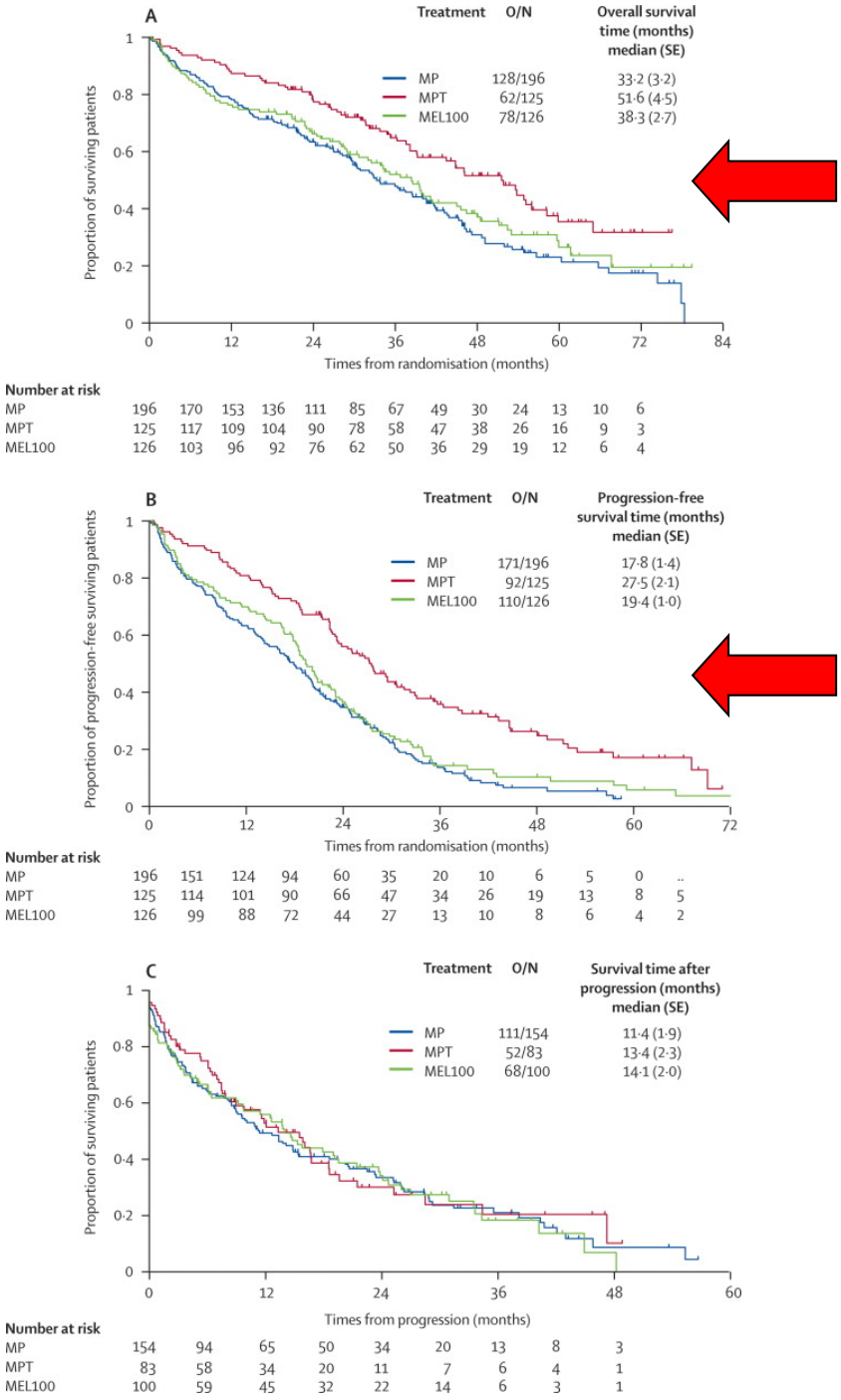
Thierry Facon, Jean Yves Mary, Cyrille Hulin, Lotfi Benboubker, Michel Attal, Brigitte Pegourie, Marc Renaud, Jean Luc Harousseau, Gaëlle Guillerm, Carine Chaleteix, Mamoun Dib, Laurent Voillat, Hervé Maisonneuve, Jacques Troncy, Véronique Dorvaux, Mathieu Monconduit, Claude Martin, Philippe Casassus, Jérôme Jaubert, Henry Jardel, Chantal Doyen, Brigitte Kolb, Bruno Anglaret, Bernard Grosbois, Ibrahim Yakoub-Agha, Claire Mathiot, Hervé Avet-Loiseau, on behalf of the Intergroupe Francophone du Myélome

Lancet 2007

MP vs MPThal vs high-dose therapy

prospective, randomized,
436 patients, 65-75 years

Facon et al , Lancet 2007



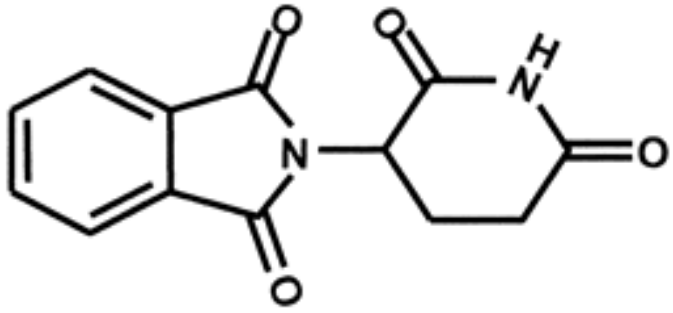
THE LANCET

Volume 370 · Number 9594 · Pages 1189–1282 · October 6–12, 2007 www.thelancet.com

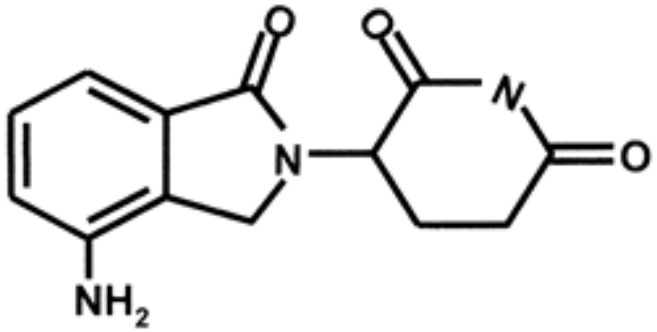
"The use of thalidomide in combination with melphalan and prednisone should be the reference treatment for previously untreated elderly patients with multiple myeloma."

See Articles page 1209

Thalidomide



Lenalidomide



blood
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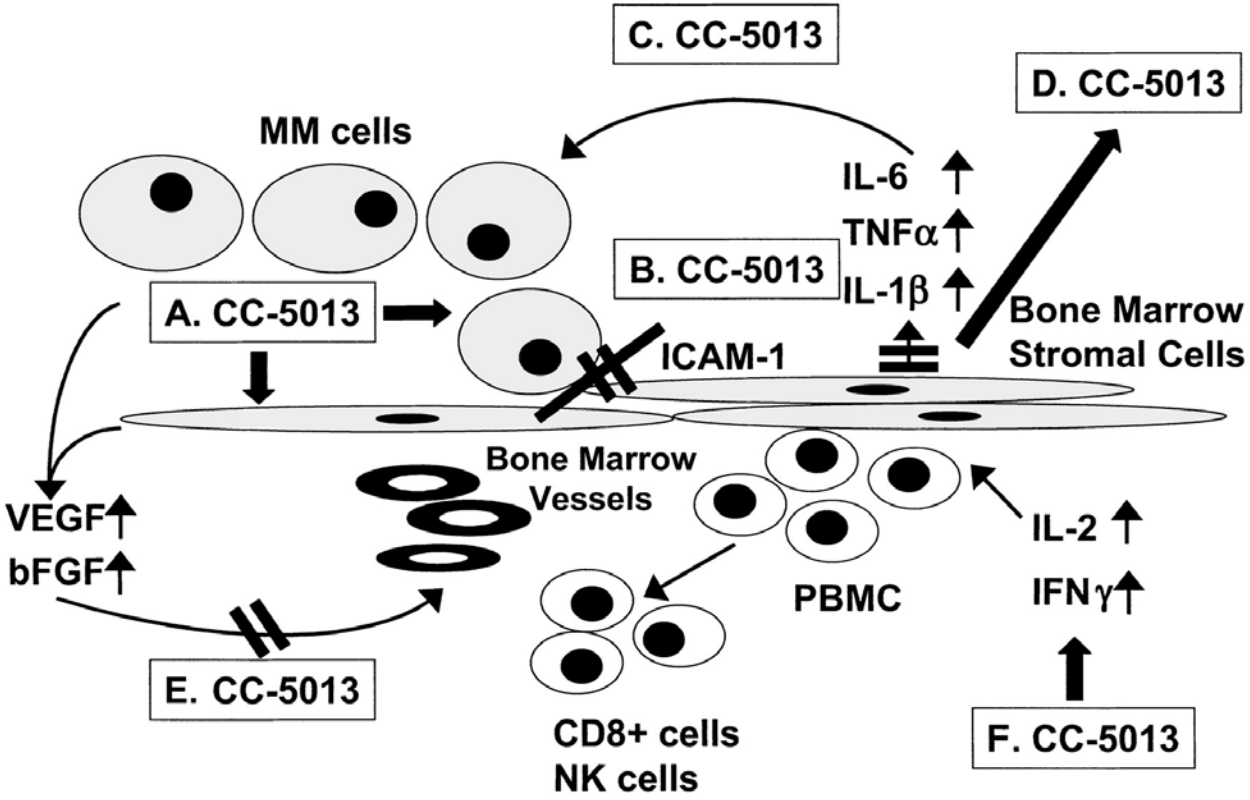
Figure 1.



Richardson, P. G. et al. Blood 2002;100:3063-3067

Lenalidomide plus Dexamethasone for Relapsed or Refractory Multiple Myeloma

Meletios Dimopoulos, M.D., Andrew Spencer, M.D., Michael Attal, M.D., H. Miles Prince, M.D., Jean-Luc Harousseau, M.D., Anna Dmoszynska, M.D., Jesus San Miguel, M.D., Andrzej Hellmann, M.D., Thierry Facon, M.D., Robin Foà, M.D., Alessandro Corso, M.D., Zvenyslava Masliak, M.D., Marta Olesnyckyj, R.N., Zhinuan Yu, Ph.D., John Patin, M.S., Jerome B. Zeldis, M.D., Ph.D., and Robert D. Knight, M.D., for the Multiple Myeloma (010) Study Investigators*

N Engl J Med 2007;357:2123

Table 2. Response among Patients in the Intention-to-Treat Population and in Selected Subgroups.*

Variable	Lenalidomide (N=176)	Placebo (N=175)	P Value
Response in the intention-to-treat population — no. (%)			
Overall response	106 (60.2)	42 (24.0)	<0.001
Complete response	28 (15.9)	6 (3.4)	<0.001
Near-complete response	15 (8.5)	3 (1.7)	
Partial response	63 (35.8)	33 (18.9)	
Stable disease	53 (30.1)	97 (55.4)	
Progressive disease	3 (1.7)	25 (14.3)	
Response could not be evaluated	14 (8.0)	11 (6.3)	
Overall response in subgroups — no./total no. (%)†			
Previous exposure to thalidomide			
Yes	26/53 (49.1)	11/67 (16.4)	0.002
No	80/123 (65.0)	31/108 (28.7)	<0.001
β_2-microglobulin — mg per liter			
<2.5	36/51 (70.6)	18/48 (37.5)	<0.001
≥2.5	70/125 (56.0)	24/127 (18.9)	<0.001
Previous no. of therapies			
1	37/56 (66.1)	17/57 (29.8)	<0.001
≥2	69/120 (57.5)	25/118 (21.2)	<0.001
Previous stem-cell transplantation			
Yes	60/97 (61.9)	27/95 (28.4)	<0.001
No	46/79 (58.2)	15/80 (18.8)	<0.001

* P values were calculated with the use of a continuity-corrected Pearson chi-square test. There was no subgroup-by-treatment interaction for response rates with the use of the Breslow–Day test for homogeneity.
† Percentages are for the rate of overall response among patients in selected subgroups of the intention-to-treat population.

A

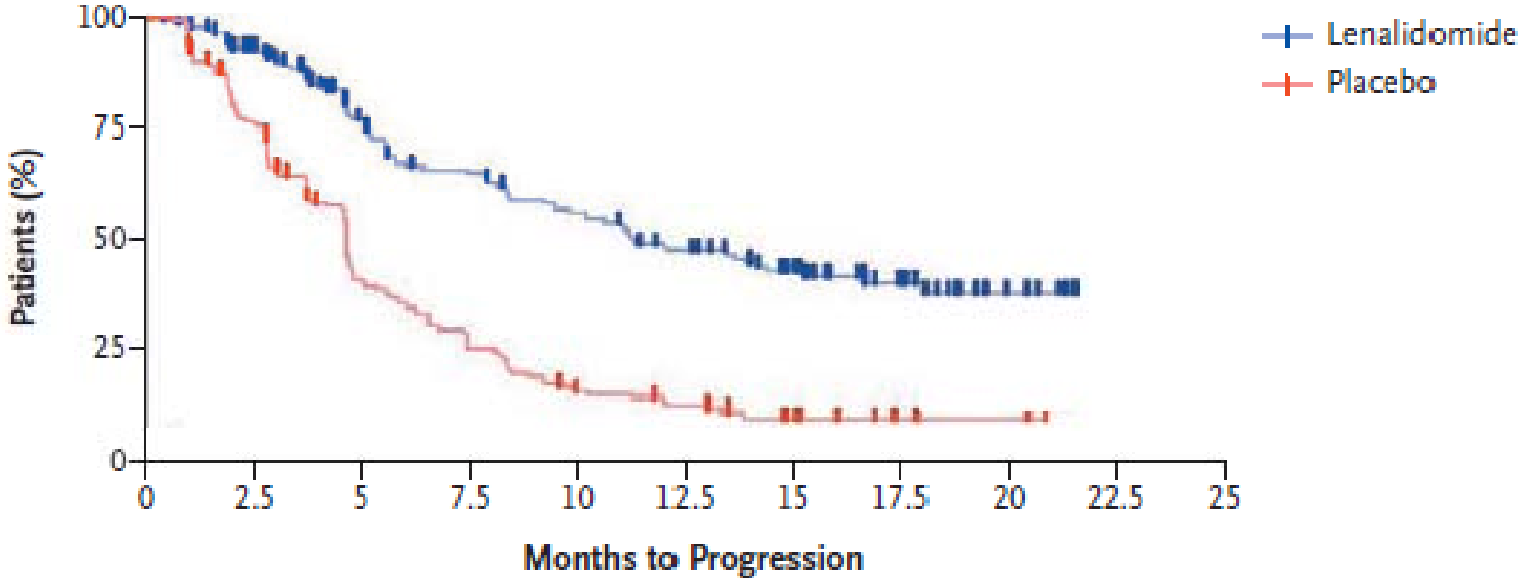


Figure 1. Kaplan–Meier Curves for the Time to Disease Progression among All Patients and in Subgroups with and without Previous Exposure to Thalidomide.

Panel A shows estimates of the median time to disease progression for the intention-to-treat population (11.3 months in the lenalidomide group and 4.7 months in the placebo group) ($P<0.001$ by the log-rank test). Panel B shows the median time to disease progression among patients in the two study groups who received thalidomide before study entry and those who did not receive thalidomide (in the lenalidomide group, 13.5 months among patients who did not receive thalidomide and 8.4 months among those who did receive thalidomide; in the placebo group, 4.7 months and 4.6 months, respectively; $P<0.001$ by the log-rank test for both between-group comparisons of patients who did and those who did not receive thalidomide).

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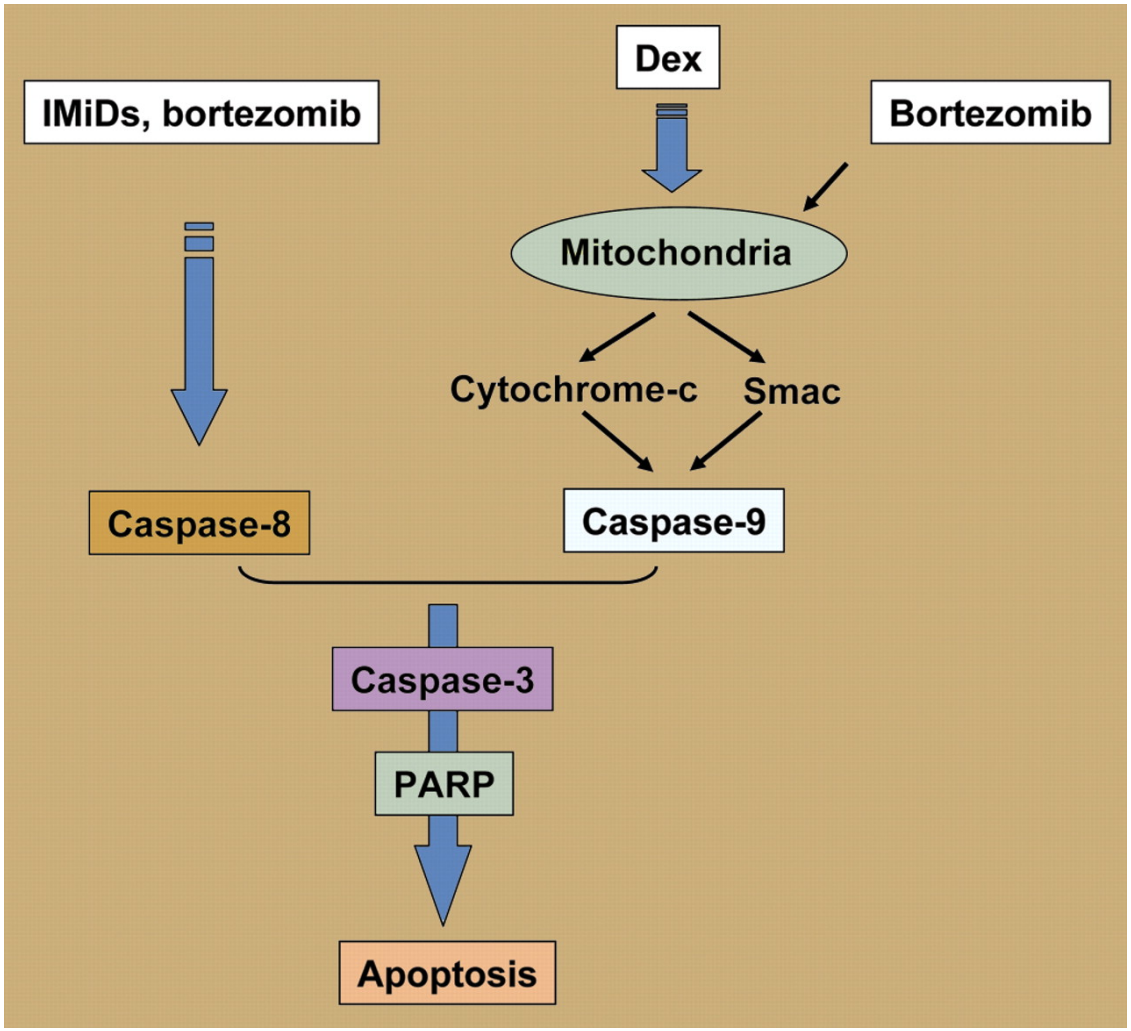
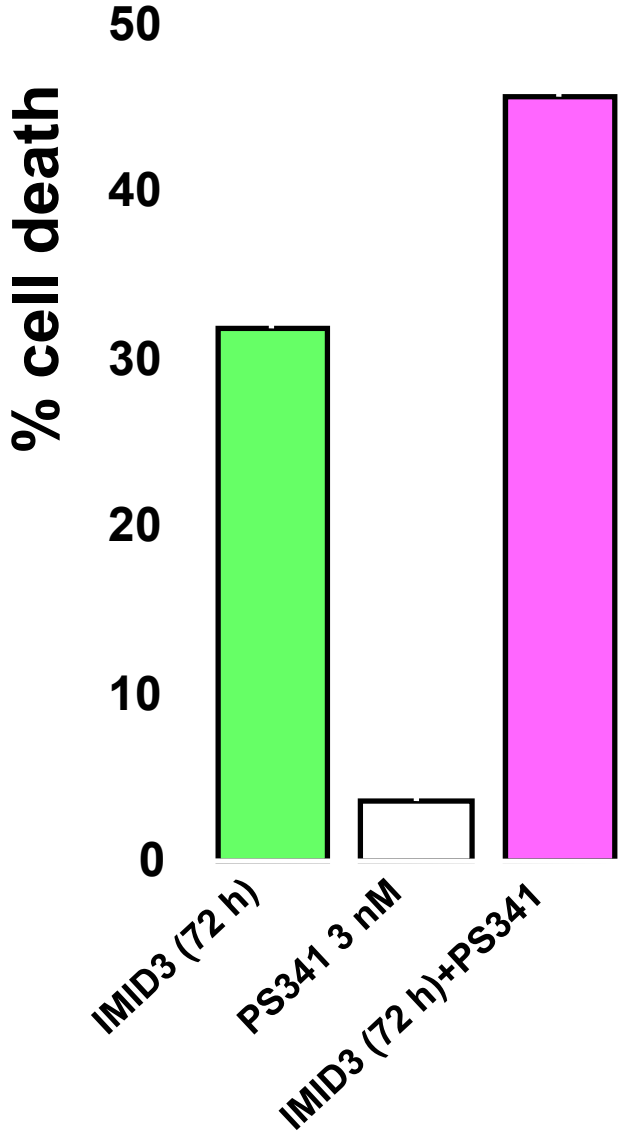
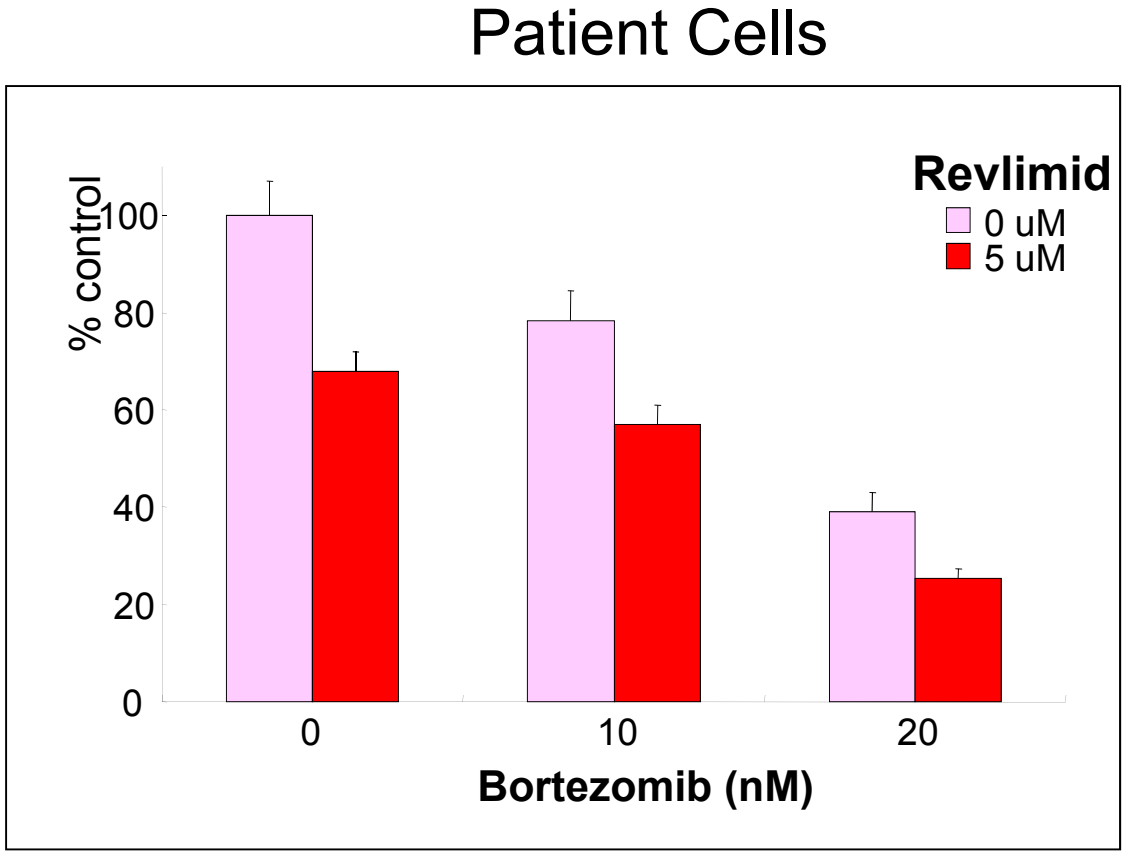
Toward a new therapeutic backbone in myeloma



Richardson, P. Blood 2007;109:2672-2673

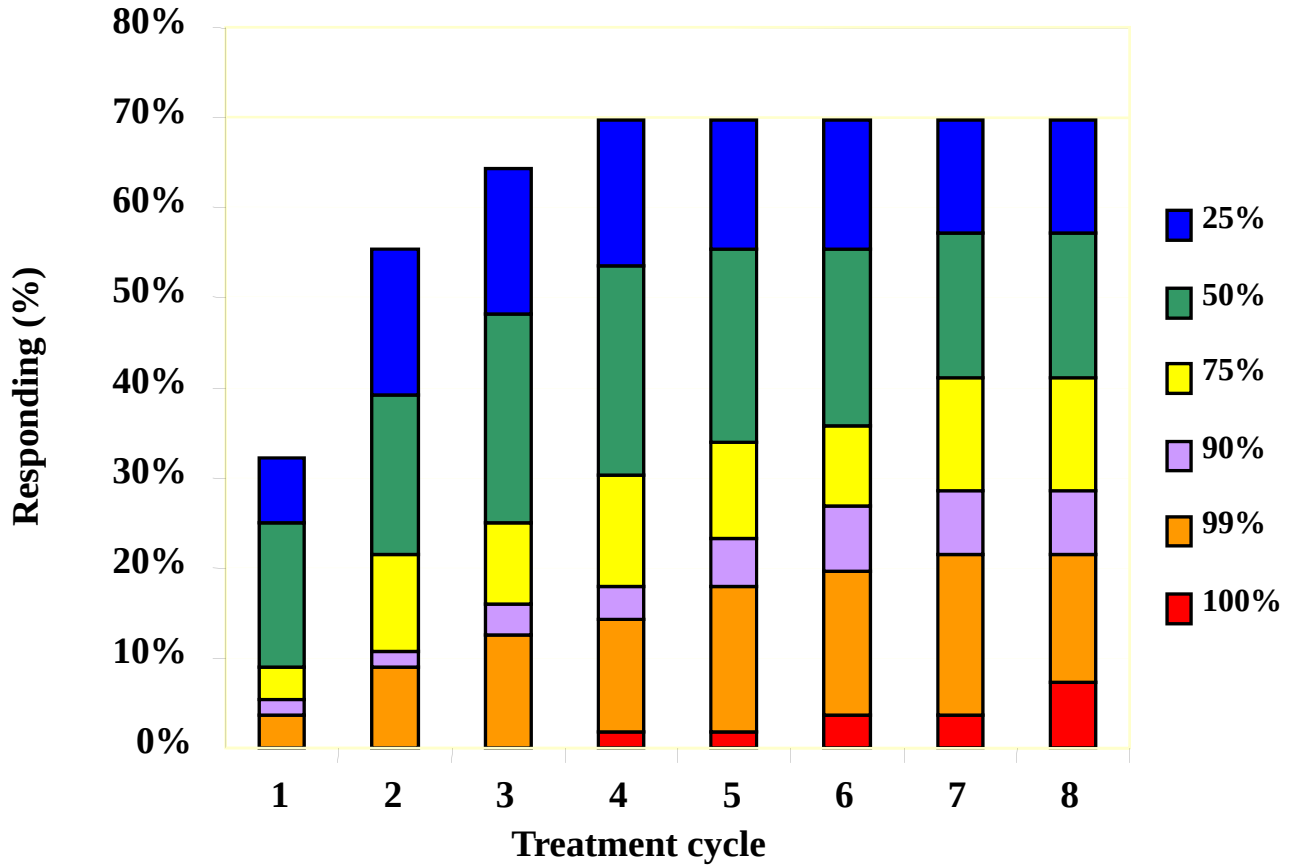
Combination Bortezomib + Lenalidomide





Mitsiades et al. Blood 2002; 99: 4525.

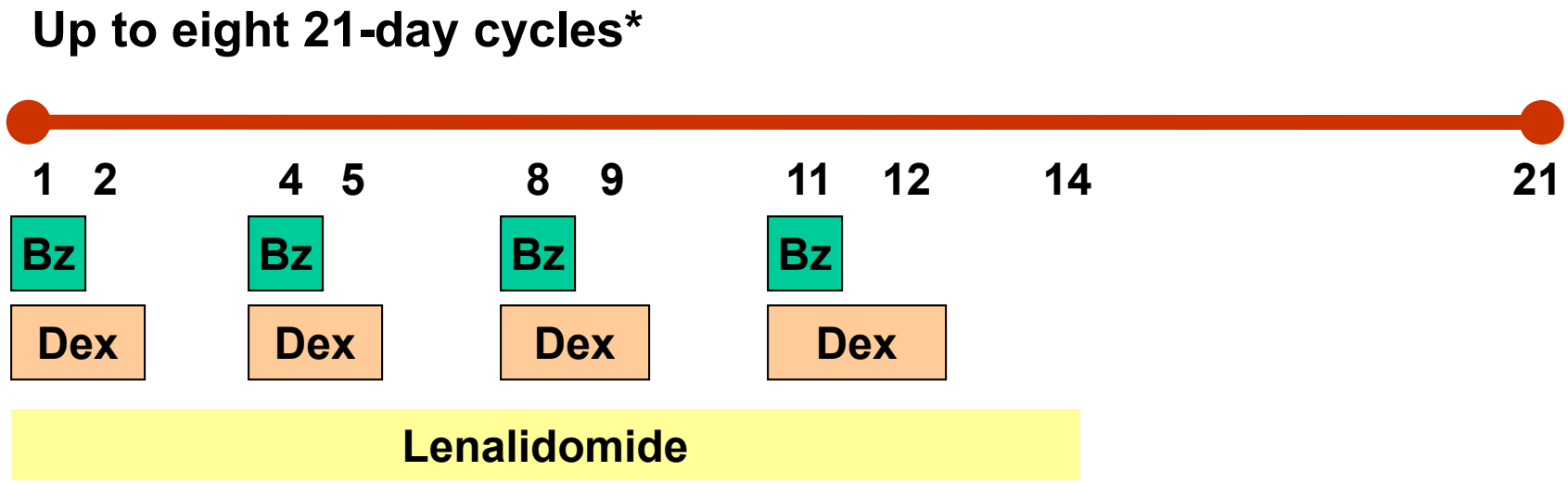
Bortezomib + thalidomide for post-transplant relapse: results



After 2 cycles, 55% ORR;
After 8 cycles, 22% CR & nCR
EFS: 7 m; OS: 21 m.

Zangari et al

Study Design



*Dex, 40 mg/day days 1, 2, 4, 5, 8, 9, 11, and 12; 20 mg, cycles 5–8; amended to 20 mg/10 mg cycles 1–4/5–8 based on safety data

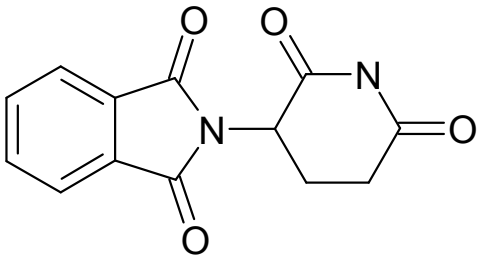
VTD combination therapy with bortezomib–thalidomide–dexamethasone is highly effective in advanced and refractory multiple myeloma

M Pineda-Roman[1], M Zangari[1], F van Rhee[1], E Anaissie[1], J Szymonifka[2], A Hoering[2], N Petty[1], J Crowley[2], J Shaughnessy[1], J Epstein[1] and B Barlogie[1]

Updated results on 85 patients

Leukemia 2008;22:1419-1427

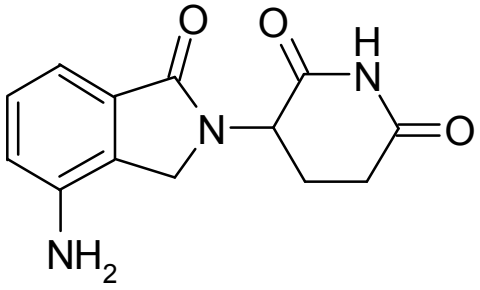
Molecular Structure of Thalidomide, Lenalidomide and Pomalidomide



Thalidomide

100-200 mg/d

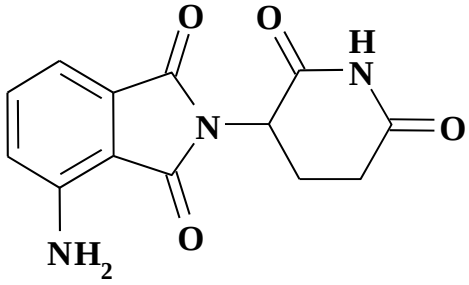
Neuropathy
Constipation
Sedation
DVT



Lenalidomide

15-25 mg/d

Myelosuppression
Skin rash
DVT



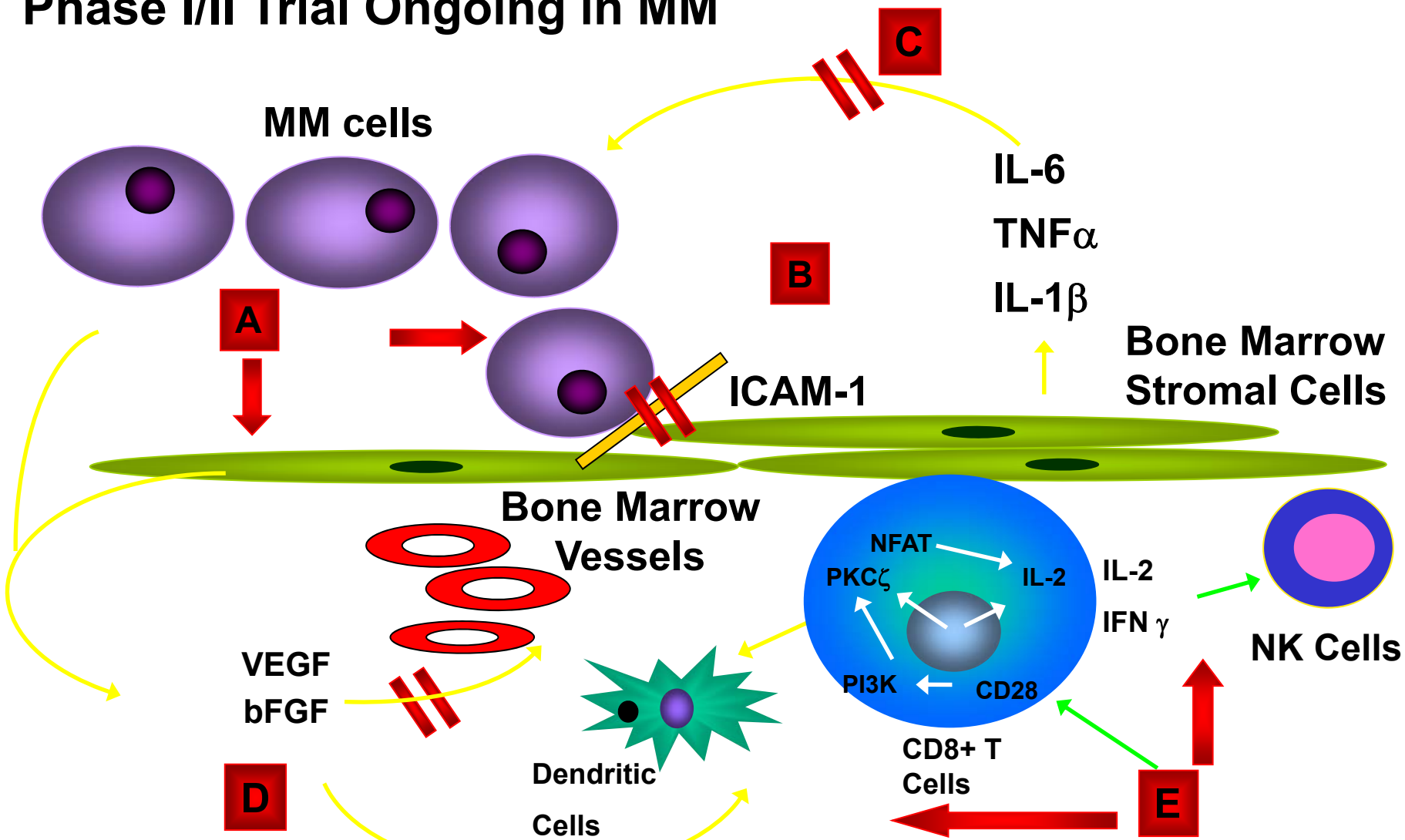
Pomalidomide

1-4 mg/d

Structurally similar, but functionally different both qualitatively and quantitatively

Pomalidomide in Myeloma

Phase I/II Trial Ongoing in MM



Hideshima et al. Blood 96: 2943, 2000
Davies et al. Blood 98: 210, 2001
Gupta et al. Leukemia 15: 1950, 2001

Mitsiades et al. Blood 99: 4525, 2002
Lentzsch et al Cancer Res 62: 2300, 2002
LeBlanc R et al. Blood 103: 1787, 2004
Hayashi T et al. Brit J Hematol 128: 192, 2005

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.

Phase I trials for Pomalidomide

	N	Dose	MTD	ORR
Schey JCO 2004	24	1-10 mg	2 mg	54%
Streetly BJH 2008	20	1-10* mg QOD	5 mg QOD	50%

* Nine patients also received dexamethasone

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.**

Lacy et al, IMW Washington 02/2009

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**

Best Responses

Confirmed Response	IMWG* response criteria N= 60	
CR	3 (5%)	CR +VGPR 33%
VGPR	17 (28%)	
PR	18 (30%)	ORR 63%
SD	18 (30%)	
PD	3 (5%)	
NE	1 (2%)	

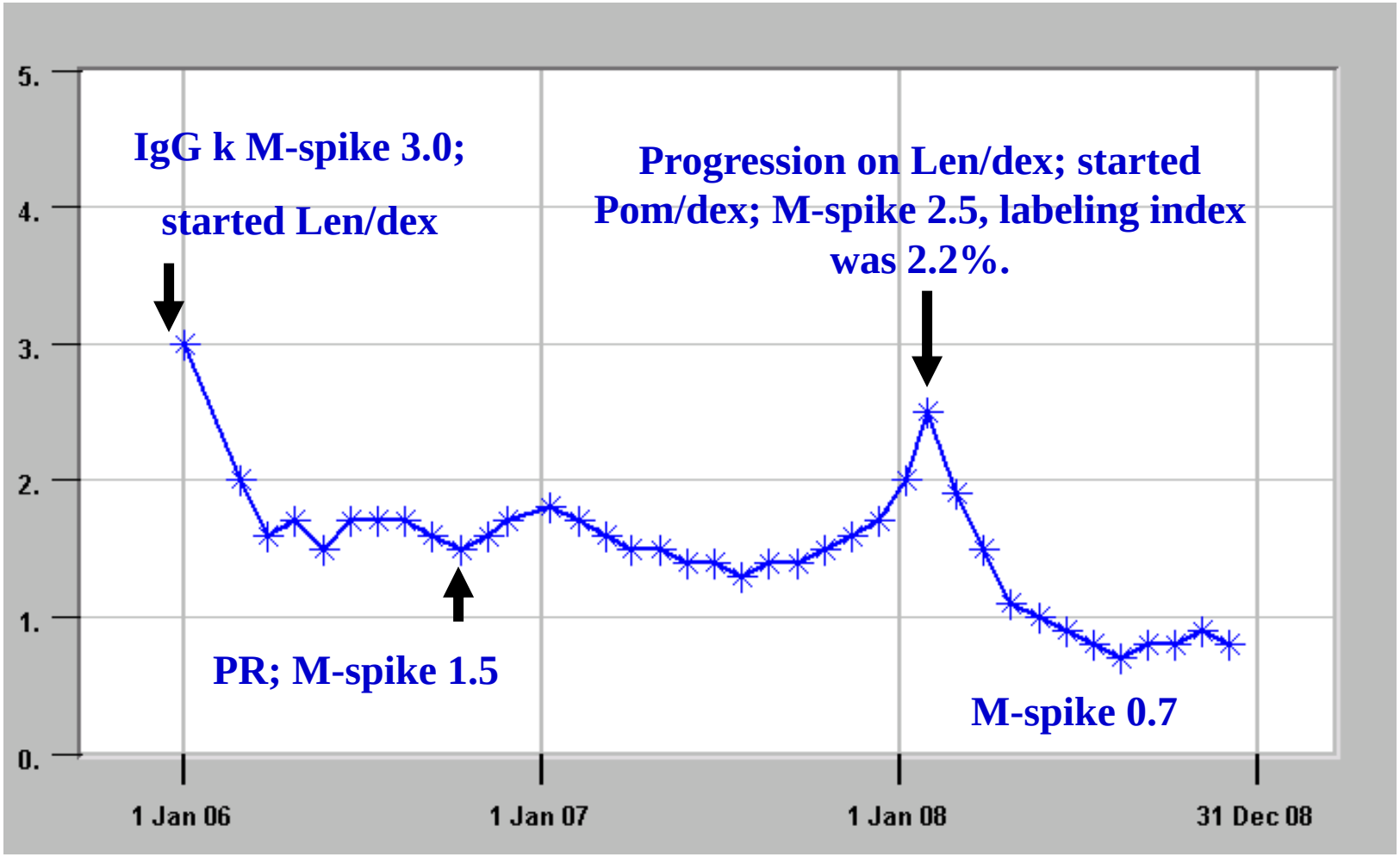
Median follow-up 7 months

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

Patient 1, Lenalidomide refractory
69 year old male



Patient 2, 67 year old female