When Should Patients Be Referred to a Clinical Trial?

Kenneth C. Anderson, MD
Kraft Family Professor of Medicine
Harvard Medical School
Chief, Division of Hematologic Neoplasia
Director, LeBow Institute for Myeloma Therapeutics
Director, Jerome Lipper Center for Multiple Myeloma
Vice Chair, Program in Transfusion Medicine
Department of Medical Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

MMRF
Multiple Myeloma Research Foundation

Cancer Drug Development: 14 New Drugs in 2004; Cost, $40 Billion

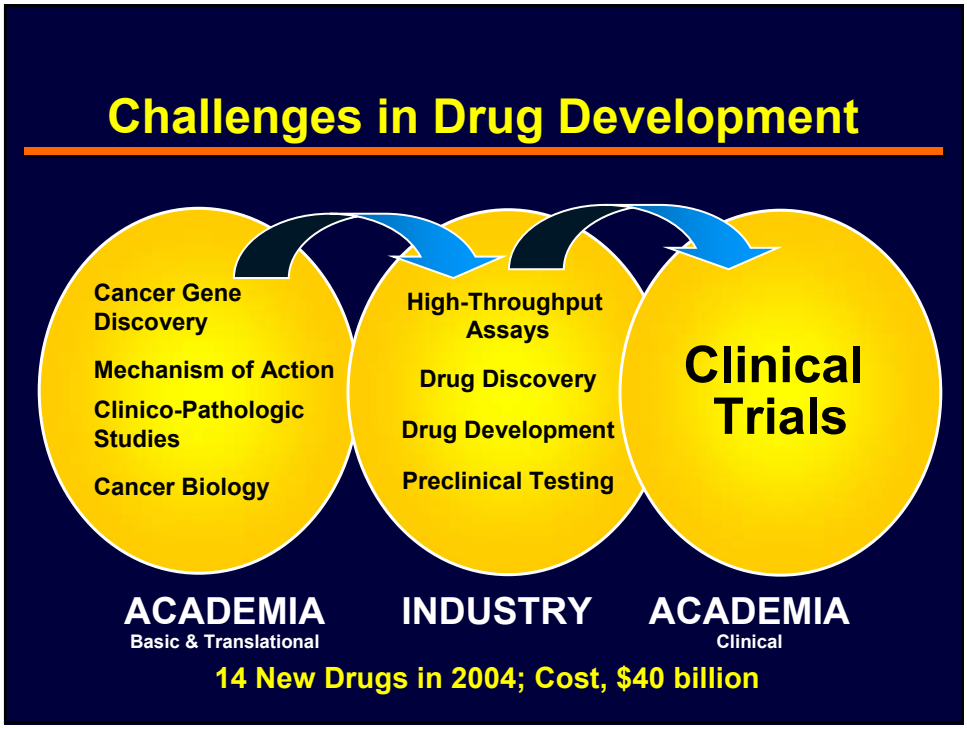
Preclinical Cancer Drug Candidates

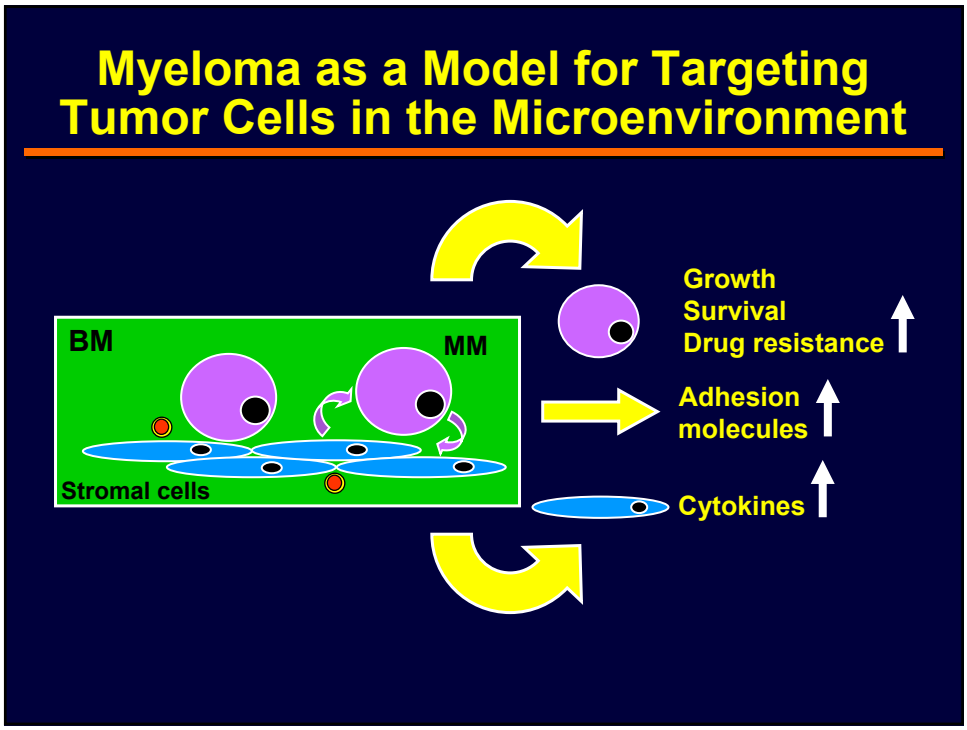
5% Success to market in 7–10 years

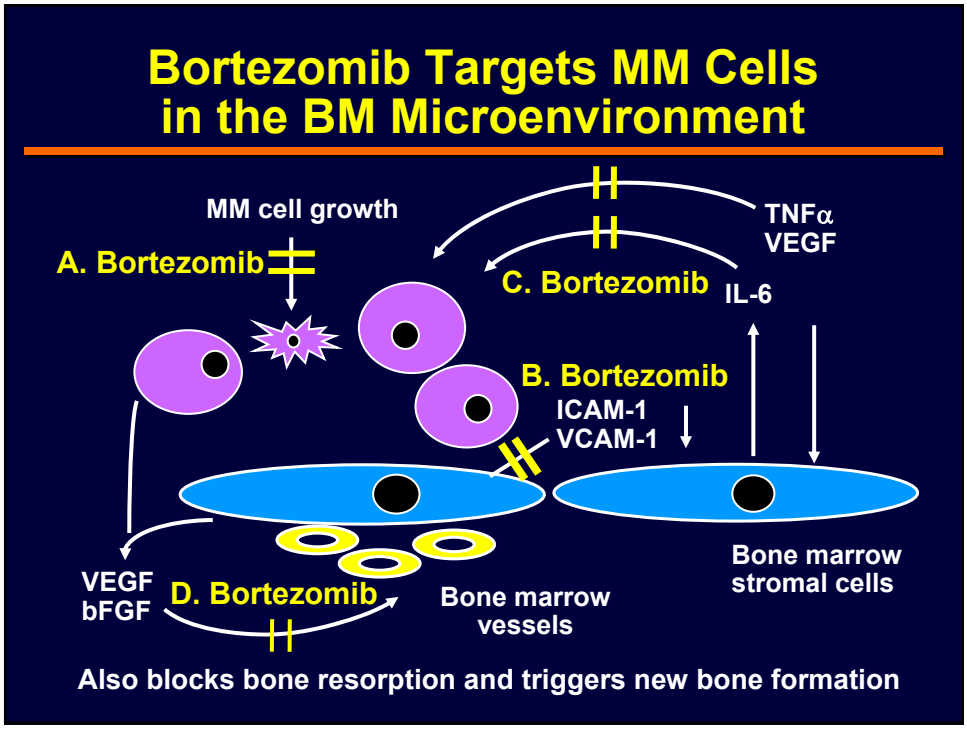
>60% Fail due to lack of efficacy

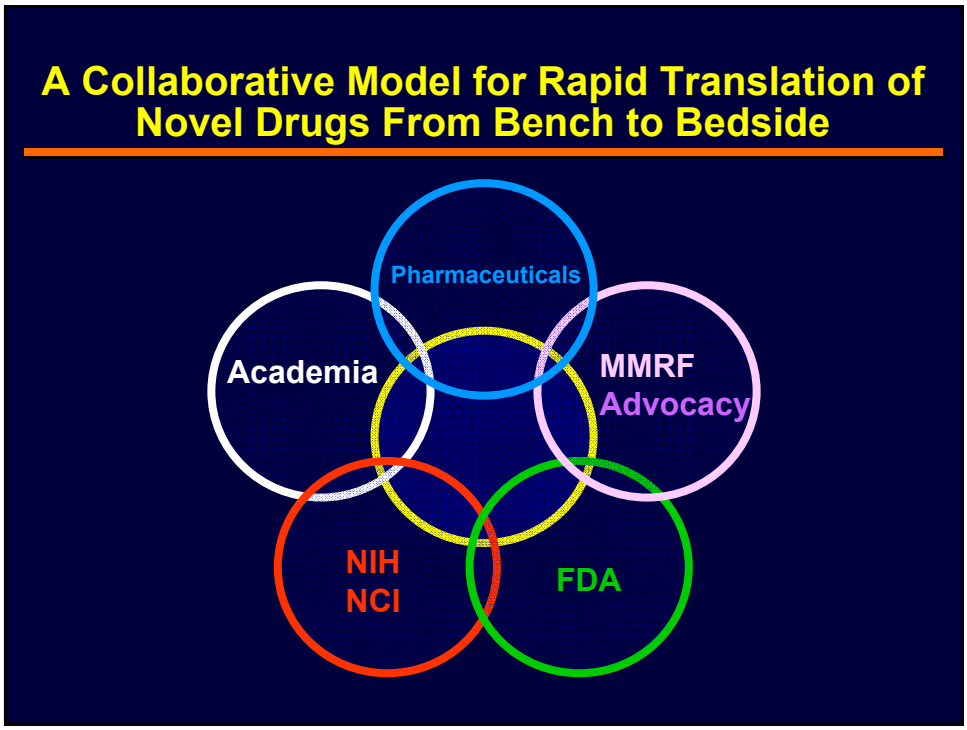
Effective FDA-Approved Cancer Drug

Preclinical testing	Oncology Compounds: Number Entering	Oncology Compounds: Success Rate	All Compounds: Number Entering	All Compounds: Success Rate
Phase 1	100	61	100	63
Phase 2	61	28	63	40
Phase 3	17	43	25	58
Registration	7	70	15	77
Approval	5		11	


Challenges in Drug Development
Cancer Gene Discovery
Mechanism of Action
Clinico-Pathologic Studies
Cancer Biology
High-Throughput Assays
Drug Discovery
Drug Development
Preclinical Testing
Clinical Trials
ACADEMIA
Basic & Translational
INDUSTRY
ACADEMIA
Clinical
14 New Drugs in 2004; Cost, $40 billion


Myeloma as a Model for Targeting Tumor Cells in the Microenvironment
BM
MM
Stromal cells
Growth
Survival
Drug resistance
Adhesion molecules
Cytokines


Bortezomib Targets MM Cells in the BM Microenvironment
MM cell growth
A. Bortezomib
TNFα
VEGF
C. Bortezomib
IL-6
B. Bortezomib
ICAM-1
VCAM-1
Bone marrow stromal cells
VEGF
bFGF
D. Bortezomib
Bone marrow vessels
Also blocks bone resorption and triggers new bone formation


A Collaborative Model for Rapid Translation of Novel Drugs From Bench to Bedside
Pharmaceuticals
Academia
MMRF
Advocacy
NIH
NCI
FDA

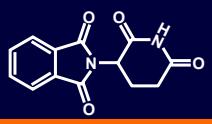
Integration of Novel Therapy Into Myeloma Management

- Bortezomib, lenalidomide, thalidomide, pegylated liposomal doxorubicin
- Treatment of relapsed/refractory MM (single agent/combinations)
- Induction/First-line therapy
- Transplant/Maintenance

Bench to Bedside Development of Bortezomib in Myeloma

2000	Phase 1 trials: safe and has anti-MM activity
2000	Targets MM cell in BM microenvironment
2001	Phase 2 trial in relapsed/refractory MM
2003	FDA approved: 35% responses (CRs), duration 12 months, clinical benefit
2004	Phase 3 trial vs Dex in relapsed MM
2005	FDA approved: prolonged TTP and OS
2006	High OR and CR rates as initial therapy
2006	Novel proteasome inhibitors and combinations
2007	Phase 3 trials in newly diagnosed MM
2008	FDA approved as initial therapy

Thalidomide in Myeloma

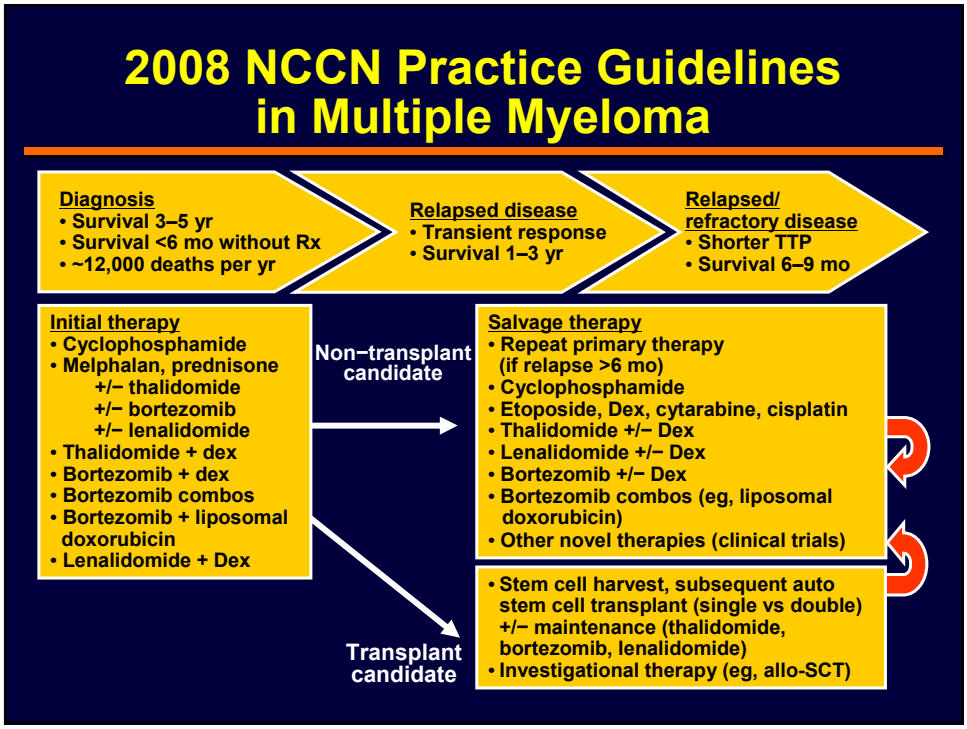


- ≥50% decrease in paraprotein in 30% relapsed and/or refractory MM patients
- 47% response when combined with Dex in Dex-refractory MM
- 63% response when combined with Dex vs 41% to Dex as initial therapy; FDA May 2006
- Does not compromise subsequent PBSC mobilization and collection
- 80%–90% response combined with MP vs 48% to MP as initial therapy of elderly patients
- Improved EFS (28 mo) and OS (54 mo) after MPT compared with MP and MEL-100 × 2
- Improves OR, CR, PFS, OS in patients >75 yr compared with MP

Bench to Bedside Development of Lenalidomide

- Preclinical (2000): targets tumor (caspase-8–mediated apoptosis) and microenvironment *in vitro* and *in vivo* in animal model
- Phase 1 trial (25 patients, 2001): MTD 25 mg; favorable toxicity; stable disease or response in 79% of patients
- Phase 2 trials (324 patients, 2002–2003): confirmed responses and decreased neuropathy, constipation, and somnolence compared with thalidomide; Dex improved responses
- Two phase 3 trials (700 patients, 2003–2004): lenalidomide/Dex vs Dex/placebo in relapsed myeloma: FDA approved June 2006 for relapsed myeloma (OR, CR, TTP, OS)
- Phase 2 trial (34 patients, 2005): 91% responses, with 6% CR and 32% nCR as initial therapy for transplant candidates; MPR promising for non–transplant candidates
- Phase 3 trials in newly diagnosed MM

2008 NCCN Practice Guidelines in Multiple Myeloma

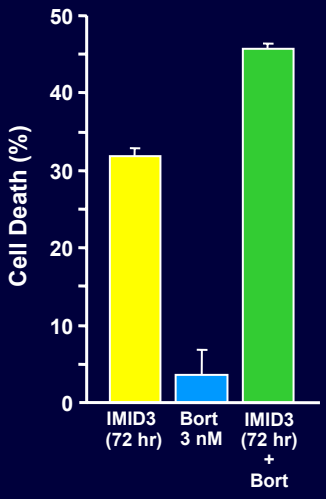


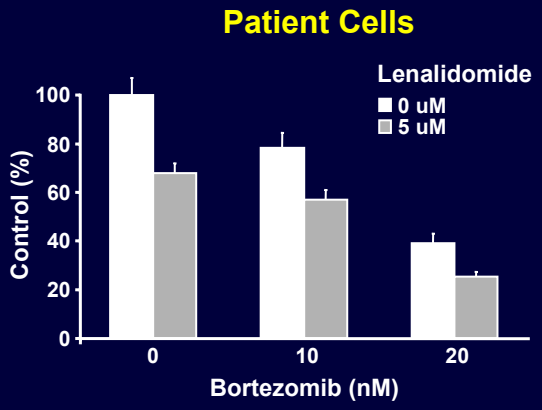
Integration of Novel Therapy Into Myeloma Management

5 FDA drug approvals in last 5 years

Median survival prolonged from 3—7 years (especially in younger patients)

Combination of Lenalidomide + Bortezomib





Mitsiades CS et al. *Blood* 2002;99:4525.

Bortezomib and Lenalidomide Therapy

- Lenalidomide induces caspase-8–mediated apoptosis of MM cells in BM *in vitro* and *in vivo*; Dex (caspase-9) enhances response
- Synergistic MM cell toxicity of lenalidomide with bortezomib *in vitro* and *in vivo* (dual apoptotic signaling)
- Phase 1/2 trials show that majority (58%) of patients refractory to either agent alone respond to the combination
- Phase 1/2 trials show 100% response, with 71% CR/VGPR when used as initial therapy

Richardson PG et al. ASCO 2008.

Multiple Myeloma Research Consortium

1. **Member institutions**
   - City of Hope
   - Dana-Farber Cancer Institute
   - Emory University
   - Hackensack U. Medical Center
   - Mayo Clinic
   - H. Lee Moffitt Cancer Center
   - Ohio State University
   - Roswell Park
   - Saint Vincent's Cancer Center
   - UHN/Princess Margaret Hospital
   - University of Chicago
   - University of Michigan
   - Washington University
   - UCSF
   - Indiana University
2. **Linked by genomics, validation, and clinical trials cores**
3. **GLP tissue bank**

Multiple Myeloma Research Consortium

- **Goal: Bring the best treatments to patients faster**
- **Preclinical validation at multiple sites**
- **Uniform clinical trial agreements**
- **Cores**
  - **Genomics/GLP tissue bank: aCGH profiling; portal**
  - **Validation: PI3K inhibitor SF1126: validation to clinical trial**
  - **Clinical trials**

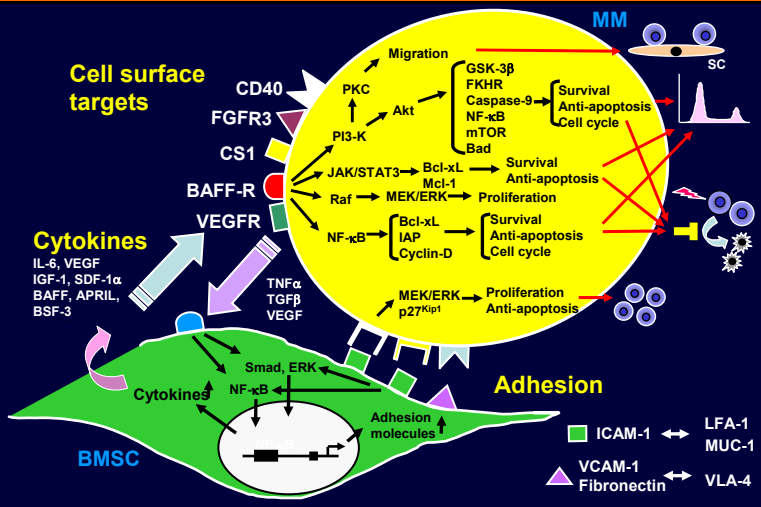
    Phase 1: proteasome inhibitor NPI-0052

    Phase 2: proteasome inhibitor carlfizomib

    Phase 1/2: combination mTOR inhibitor CCI-779/bortezomib

    Phase 1/2: combination LBH 589/bortezomib

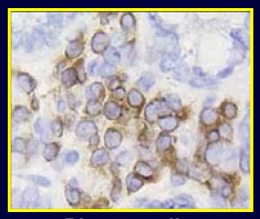
Growth of the MM Cell in the BM Microenvironment



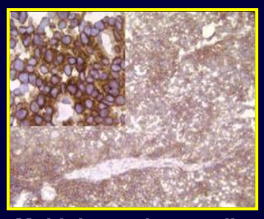
Hideshima T, Anderson KC. *Nature Rev Cancer*. 2002;2:927.
Hideshima T et al. *Blood*. 2004;104:607.

Targeting Cell Surface CS1 in Multiple Myeloma

- Universal gene expression in multiple myeloma
- Confirmed CS1 protein expression by flow cytometry and immunohistochemistry with anti-CS1 antibodies
- Normal tissue staining showing exclusive expression only in tissue plasma cells



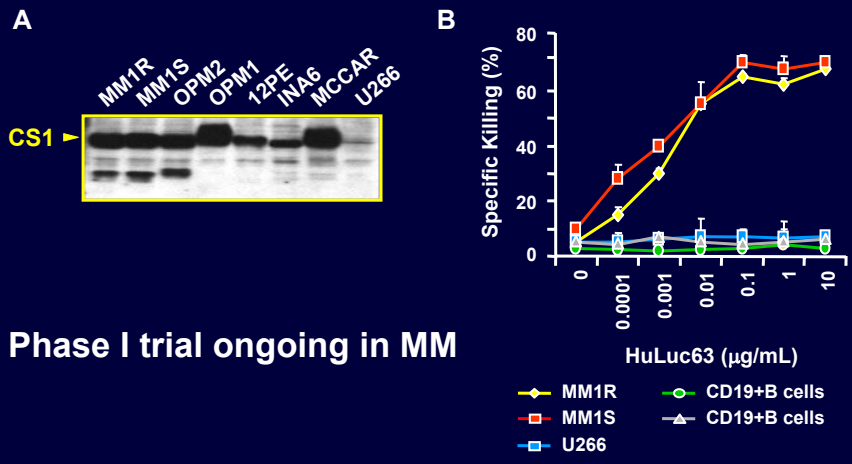
Plasma cells in normal gut



Multiple myeloma cells in a plasmacytoma

Staining was performed with HuLuc63 humanized anti-CS1 monoclonal antibody

HuLuc63 Anti-CS1 Antibody Induces Specific MM Cell Lysis

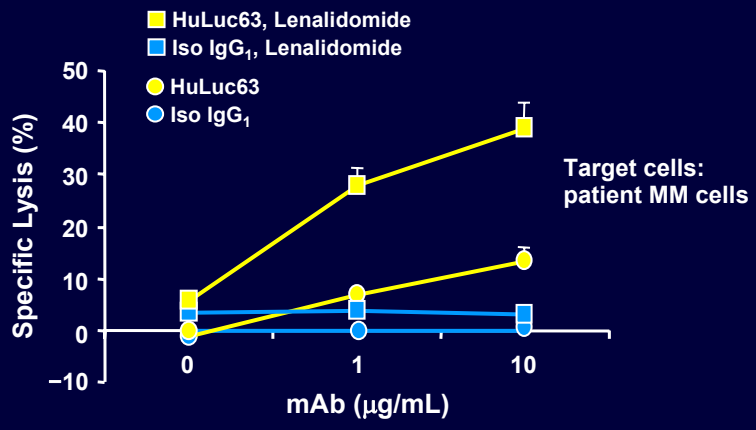


Phase I trial ongoing in MM

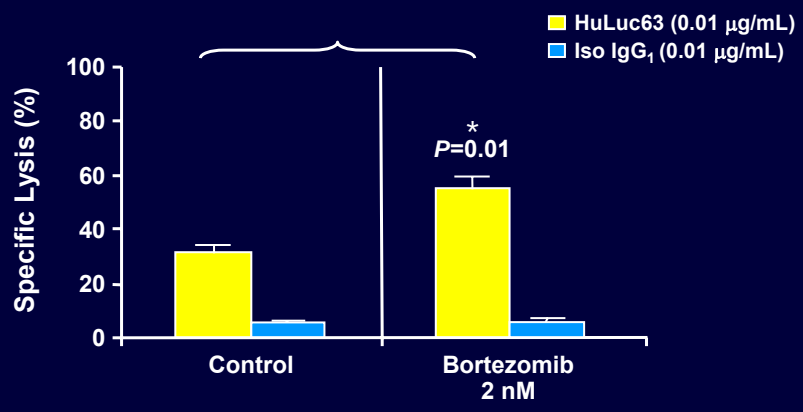
Tai YT et al. *Blood*. 2008;112:1329.
Tai YT et al. *Blood*. 2007;110:Abstract 109.

Lenalidomide Enhances HuLuc63-Induced ADCC Against Patient MM Cells

Phase 1 Trial Ongoing in MMRC



Bortezomib Increases HuLuc63-Induced ADCC Against MM1R Cells



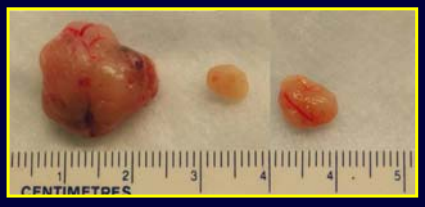
Phase 1 trial of combination ongoing in MMRC

Targeting Cytokines FGFR3 (TK1258A) Tyrosine Kinase Inhibitor Blocks Human Myeloma Growth

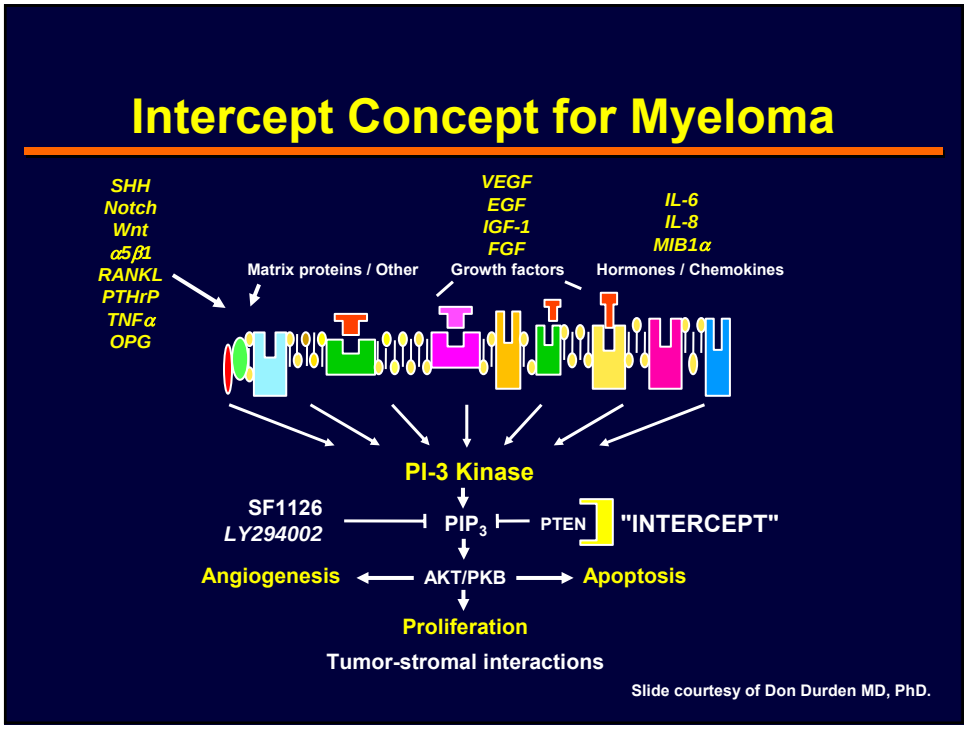
Phase 1/2 trial completed in MMRC:

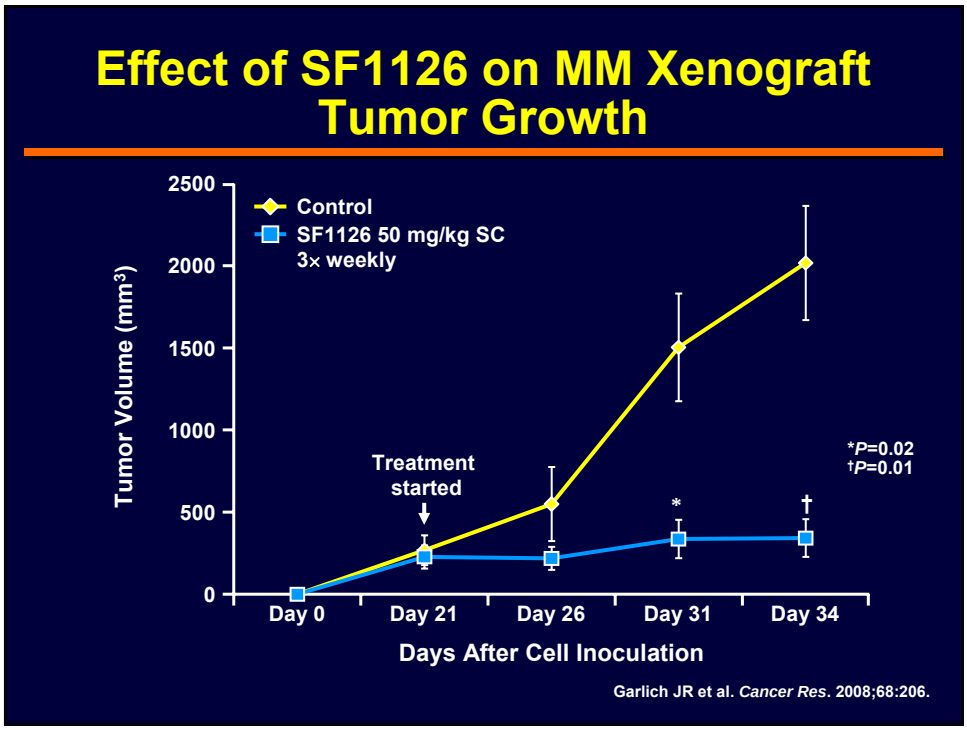
No responses

Placebo 60 mg/kg 30 mg/kg



Trudel S et al. *Blood.* 2005;105:2941.

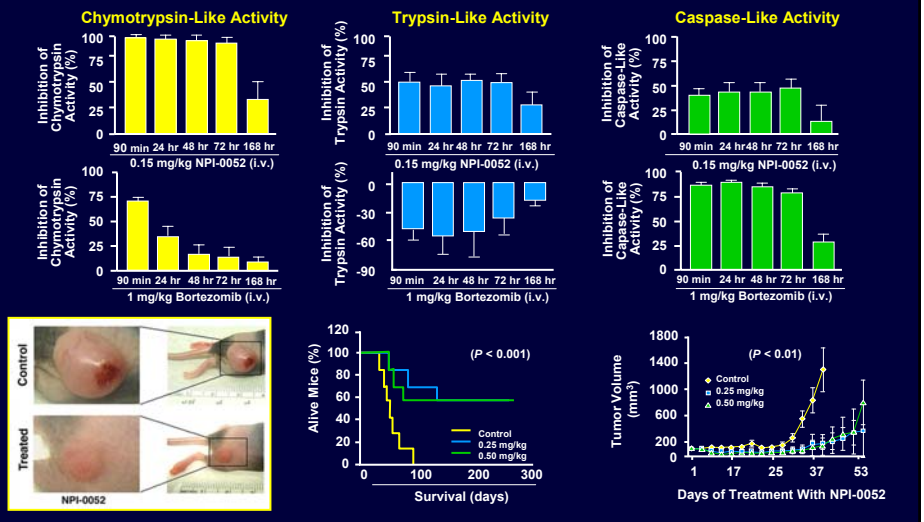

Intercept Concept for Myeloma
SHH
Notch
Wnt
α5β1
RANKL
PTHrP
TNFα
OPG
VEGF
EGF
IGF-1
FGF
IL-6
IL-8
MIB1α
Matrix proteins / Other
Growth factors
Hormones / Chemokines
PI-3 Kinase
SF1126
LY294002
PIP3
PTEN
"INTERCEPT"
Angiogenesis
AKT/PKB
Apoptosis
Proliferation
Tumor-stromal interactions
Slide courtesy of Don Durden MD, PhD.


Effect of SF1126 on MM Xenograft Tumor Growth
Control
SF1126 50 mg/kg SC 3× weekly
Tumor Volume (mm3)
2500
2000
1500
1000
500
0
Treatment started
*P=0.02
†P=0.01
Day 0
Day 21
Day 26
Day 31
Day 34
Days After Cell Inoculation
Garlich JR et al. Cancer Res. 2008;68:206.

Phase 1 Clinical Trial of SF1126 in MMRC

- Phase 1 trial of SF1126 in relapsed/refractory MM
- Escalation with overdose control (EWOC) phase 1 design
  - Allows for fewer patients treated with ineffective doses of study drug
- Once MTD defined, 10 patients will be treated with SF1126 and bortezomib, based on preclinical data

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

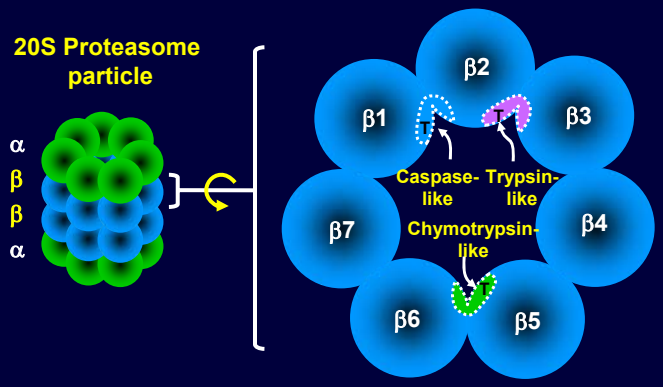


Chauhan D et al. *Cancer Cell*. 2005;8:407.

Phase 1 MMRC Clinical Trial of NPI-0052

- Dose-escalation study of NPI 0052 given weekly for 3 weeks each cycle
- Early evidence of tolerability and clinical activity

Carfilzomib



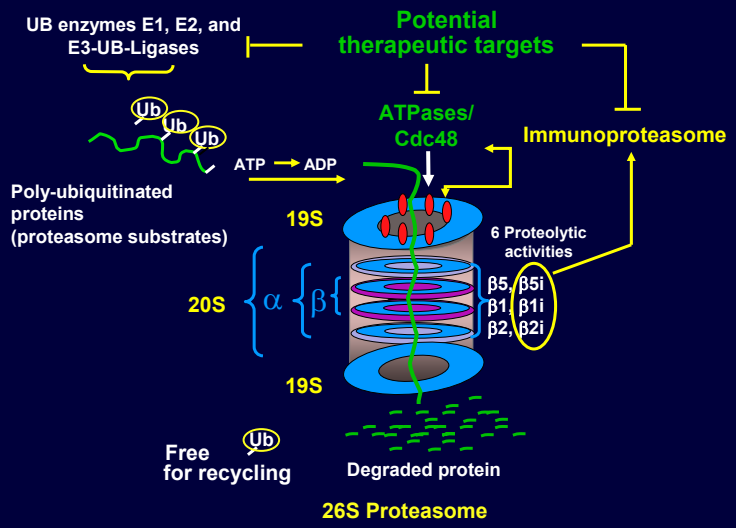
IC_{50}s (nM)	Chymotrypsin-Like	Caspase-Like	Trypsin-Like
PR-171	6	2400	3600
Bortezomib	7	74	4200

Clinical Activity of Carfilzomib

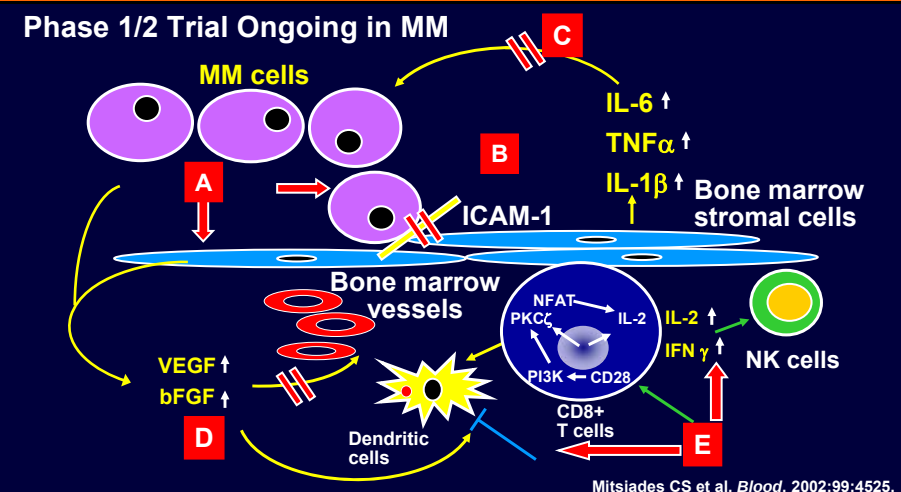
- Effective in bortezomib resistance
- Neuropathy not reported; dose-related thrombocytopenia
- Responses observed at 2 dose schedules: daily × 5 once per month, and daily × 2 each week for 3 weeks
- Two phase 2 trials ongoing in relapsed/ refractory MM in MMRC

Stewart KA et al. *J Clin Oncol.* 2007;25:Abstract 8003.

Proteasome: Present and Future Therapies



Pomalidomide in Myeloma



Hideshima T et al. *Blood.* 2000;96:2943.
Davies FE et al. *Blood.* 2001;98:210.
Gupta D et al. *Leukemia.* 2001;15:1950.

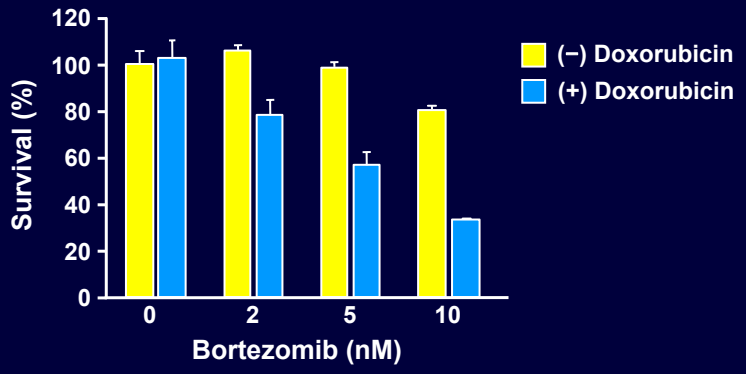
Mitsiades CS et al. *Blood.* 2002;99:4525.
Lentzsch S et al *Cancer Res.* 2002;62:2300.
LeBlanc R et al. *Blood.* 2004;103:1787.
Hayashi T et al. *Br J Haematol.* 2005;28:192.

Rationally Based Combination Therapies

- Bortezomib and doxorubicin
- Bortezomib, melphalan
- Bortezomib and Hsp90 inhibitor
- Bortezomib and NPI-0052
- Bortezomib and perifosine
- Bortezomib and LBH 589
- Bortezomib and Smac peptides
- Bortezomib and Bcl-2 inhibitor
- Bortezomib and p38 MAPK inhibitor
- Bortezomib and HuLuc63
- Lenalidomide and mTOR inhibitor
- Lenalidomide and anti-CD40 antibody
- Lenalidomide and doxorubicin
- Lenalidomide and HuLuc63
- Lenalidomide and LBH 589
- Lenalidomide and perifosine
- Lenalidomide and bevacizumab
- Lenalidomide and vaccine
- Lenalidomide and bortezomib

Preclinical Rationale for Combination Therapy in Clinical Trials

Low-Dose Bortezomib Enhances and Restores Sensitivity to DNA-Damaging Chemotherapy (Doxorubicin)



Mitsiades CS et al. *Blood* 2002;101:2377.

Phase 3 Study: Pegylated Liposomal Doxorubicin/Bortezomib Compared With Bortezomib Alone in Relapsed/Refractory MM

RANDOMIZATION

646 patients with relapsed and/or refractory myeloma

- Bortezomib 1.3 mg/m² days 11, 4, 8, 11 every 21 days for up to 8 cycles
- Bortezomib as above + pegylated liposomal doxorubicin 30 mg/m² on day 4

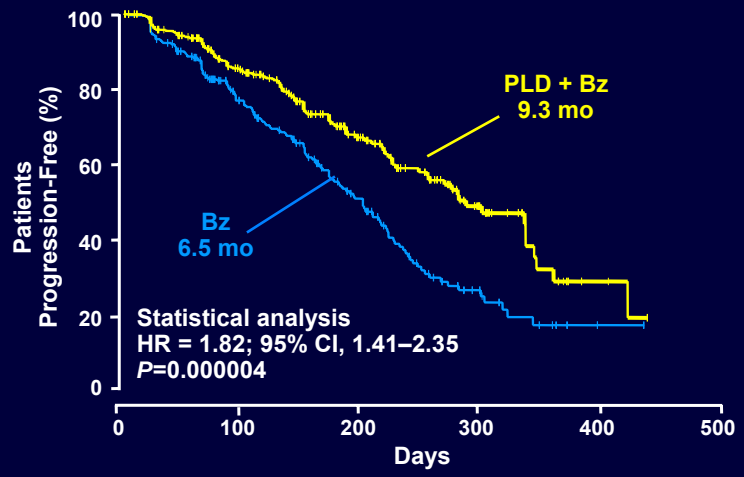
Primary end point: TTP
Secondary: OS, ORR, safety, resource utilization

Stratifications
- β_2m (≤2.5, >2.5 but ≤5.5, >5.5)
- Response vs progression on initial therapy

Orlowski RZ et al. *J Clin Oncol.* 2007;25:3892.

Superior Time to Progression With Combination of Bortezomib and PLD

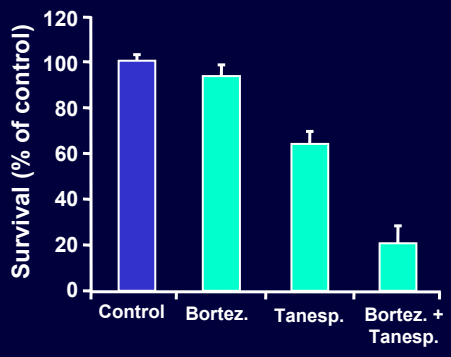
646 Patients With Relapsed/Refractory MM



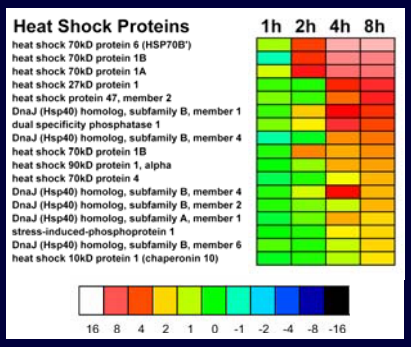
Orlowski RZ et al. *J Clin Oncol.* 2007;25:3892.

Tanespimycin + Bortezomib Synergistic Anti-MM Activity

In vitro **cytotoxicity model using MM cell lines suggests synergy**



Induction of Hsp70 seen at 2 hr; Hsp90 transcription increase ~4–8 hr following tanespimycin/BZ



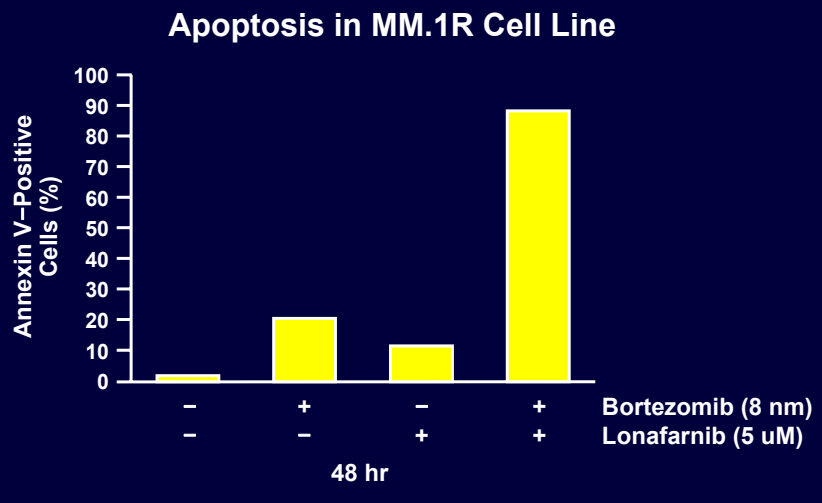
Transcription / Translation Regulation Signal Intensity

Mitsiades CS et al. *Blood.* 2006;107:1092.

Bortezomib and Hsp90 Inhibitor Therapy

- Hsp90 gene and protein overexpressed in MM; bortezomib further upregulates Hsp90 (2002)
- Hsp90 inhibitor + bortezomib induces synergistic cytotoxicity and overcomes bortezomib resistance *in vitro* and *in vivo* (2003–2004)
- Phase 1/2 clinical trials show safety and ability of Hsp90 inhibitor to sensitize or overcome resistance to bortezomib (2005–2006) (Richardson et al. ASH 2006)
- Phase 3 trial of bortezomib/Hsp90 inhibitor vs bortezomib in relapsed MM for FDA approval

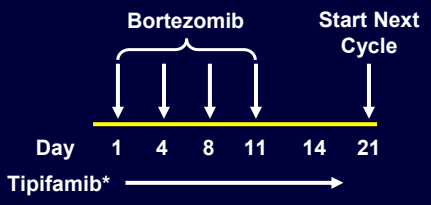
Bortezomib + Farnesyl Transferase Inhibitor Overcomes Dexamethasone Resistance



David E et al. *Blood.* 2005;106:4322.

Phase 1 MMRC Clinical Trial of Bortezomib + Tipifarnib

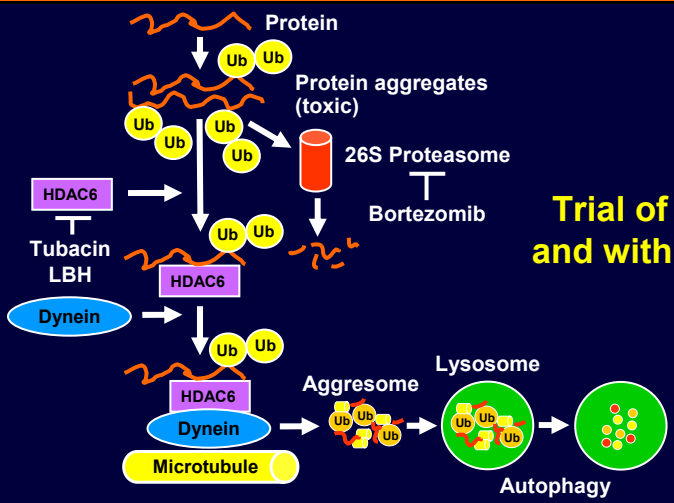
Dose Level	Bortezomib Dose (days 1,4,8,11)	Tipifarnib Dose (po b.i.d.)
–1	0.7 mg/m^2	100 mg
1	1.0 mg/m^2	100 mg
2	1.0 mg/m^2	200 mg
3	1.0 mg/m^2	300 mg
4	1.0 mg/m^2	400 mg



*First dose on day 2 following first bortezomib dose.

David E et al. *Blood*. 2005;106:4322.

Blockade of Ubiquitinated Protein Catabolism



Trial of LBH alone and with bortezomib

Hideshima T et al. *Clin Cancer Res*. 2005;11:8530.
Catley L et al. *Blood*. 2006;108:3441.

Novel Therapy Combinations With Bortezomib to Treat Multiple Myeloma

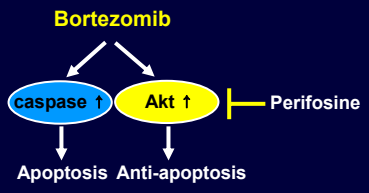
Drug	Drug Class	Results	Author	ASH 2007 Abstract No.
Suberoylanilide hydroxamic acid (SAHA) + bortezomib	Histone deacetylase (HDAC) inhibitor + proteasome inhibitor	n=17 4 PR 2 MR 11 SD	Weber et al	1172
		n=16 1 nCR 7 PR 6 SD	Badros et al	1168
Romidepsin + bortezomib	HDAC inhibitor + proteasome inhibitor	n=7 1 CR 3 PR 1 MR	Prince et al	1167

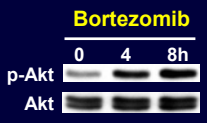
Clinical Trials of Combination Proteasome Inhibitor With Histone Deacetylase Inhibitor in MMRC

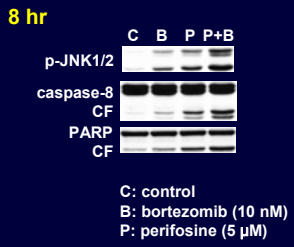
Relapsed/Refractory MM

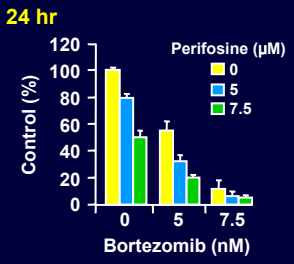
Phase 2 trial of bortezomib and SAHA
Phase 1/2 trial of bortezomib and LBH

Akt Inhibitor Perifosine Enhances Bortezomib-Induced Cytotoxicity in MM Cells







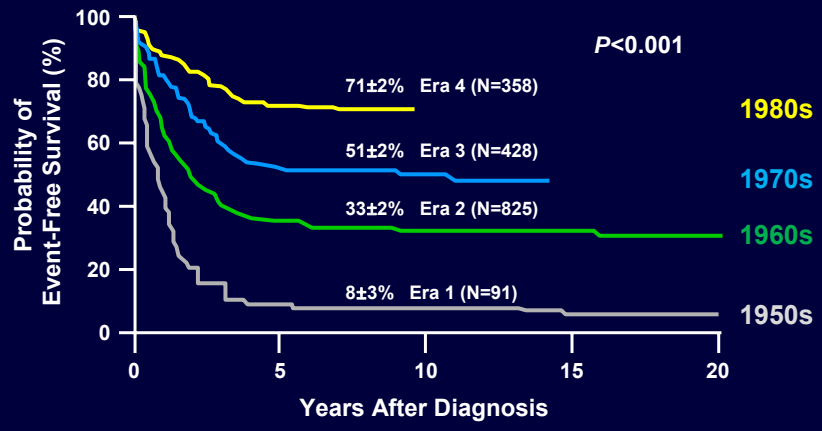


Hideshima T et al. *Blood*. 2006;107:4053.

Novel Therapy Combinations With Bortezomib to Treat Multiple Myeloma

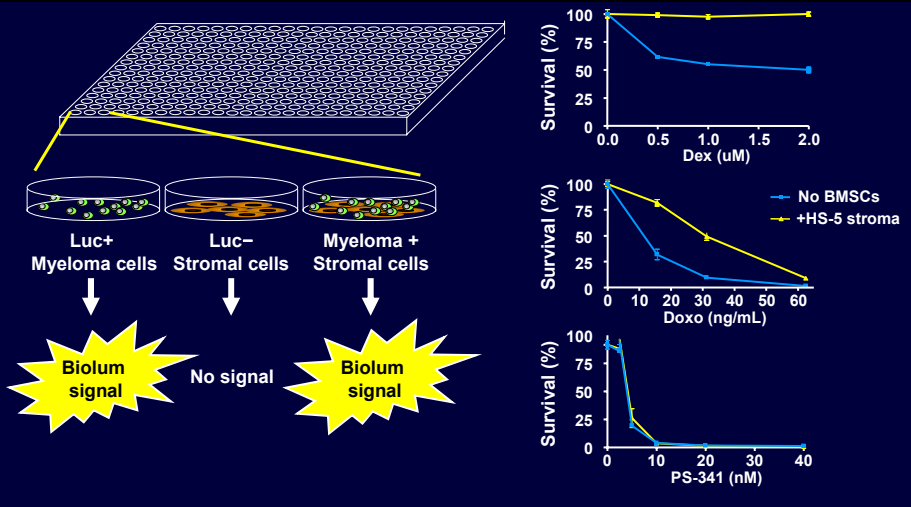
Drug	Drug Class	Results	Author	ASH 2007 Abstract No.
Perifosine (KRX-0401) + bortezomib	Alkyphospholipid + proteasome inhibtor	56% ORR 31% SD	Richardson et al	1170

Curative Combination Chemotherapy in Childhood ALL as a Model for MM



Pui CH. *N Engl J Med.* 1995;332:1618.

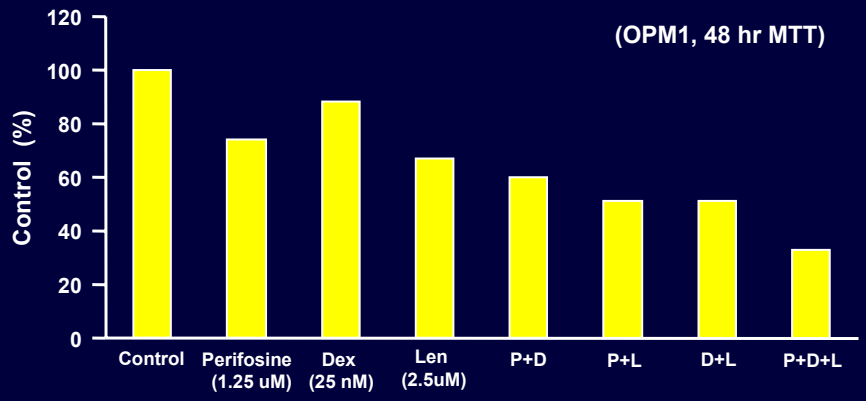
CS-BLI High-Throughput Screening of MM With BMSCs (SPORE to CACS)



CS-BLI, compartment-specific bioluminescence imaging.

McMillin DW et al. Haematologica. 2007:92:65. Abstract S11.5.

Perifosine Enhances MM Cell Cytotoxicity Induced by Lenalidomide + Dexamethasone



Hideshima T et al. Unpublished.

Phase 1 MMRC Study of 3 Drugs
Perifosine, Dexamethasone, Lenalidomide

- Relapsed or refractory MM (stage ≥I): 4–54 patients
- 4-week cycle
  1. Peri 50 mg + Dex 20 mg* + Len 15 mg** daily – 6 patients
  2. Peri 50 mg + Dex 40 mg* + Len 15 mg** daily – 6 patients
  3. Peri 100 mg + Dex 20 mg* + Len 15 mg** daily – 6 patients
  4. Peri 100 mg + Dex 40 mg* + Len 15 mg** daily – 6 patients
  5. Peri 50 mg + Dex 20 mg* + Len 25 mg** daily – 6 patients
  6. Peri 50 mg + Dex 40 mg* + Len 25 mg** daily – 6 patients
  7. Peri 100 mg + Dex 20 mg* + Len 25 mg** daily – 6 patients
  8. Peri 100 mg + Dex 40 mg* + Len 25 mg** daily – 6 patients

Phase 1 MMRC Study of 3 Drugs
Perifosine, Dexamethasone, Lenalidomide

- Relapsed myeloma
- Trial now completed within MMRC
- Well tolerated, with responses in the majority of patients

Four-Drug Combination
MMRC Clinical Trial

Newly Diagnosed Patients

Bortezomib
Dexamethasone
Doxorubicin
Lenalidomide

Sequential escalation of all 4 drugs

Conclusions and Future Directions

1. A new treatment paradigm targeting both the tumor cell and its microenvironment has already markedly improved OR, CR, EFS, and OS
2. Ongoing oncogenomic and proteomic studies are informing clinical protocol design and identifying novel therapeutic targets
3. Future molecularly based, rationally designed combination therapies (ie, immunomodulatory drug, proteasome inhibitor, Hsp90 inhibitor, HDAC inhibitor, and MoAb) will achieve durable CR in the majority of patients

Multiple Myeloma Research Consortium: A Collaborative Model for Rapid Translation of Novel Drugs From Bench to Bedside