

# Combination targeted strategies: Choosing rational designs

Jesus San-Miguel



Institute of Biomedical Research  
Hematology Department



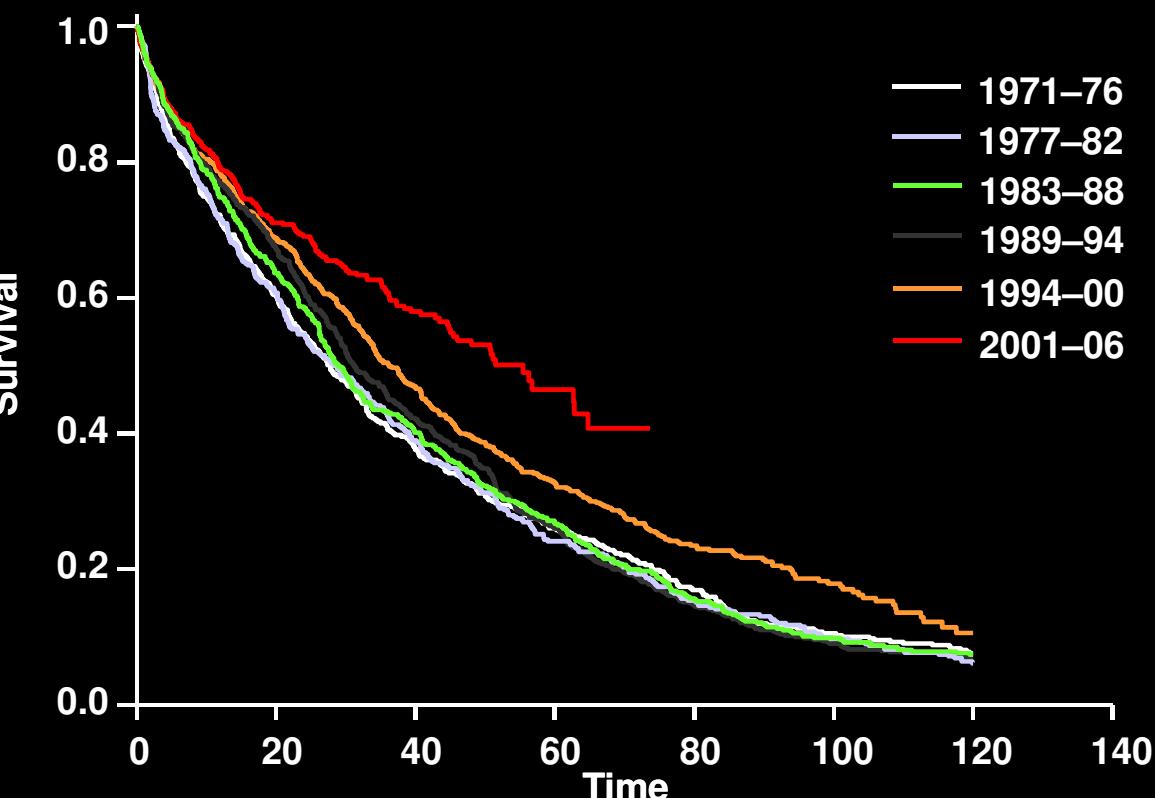
University of Salamanca



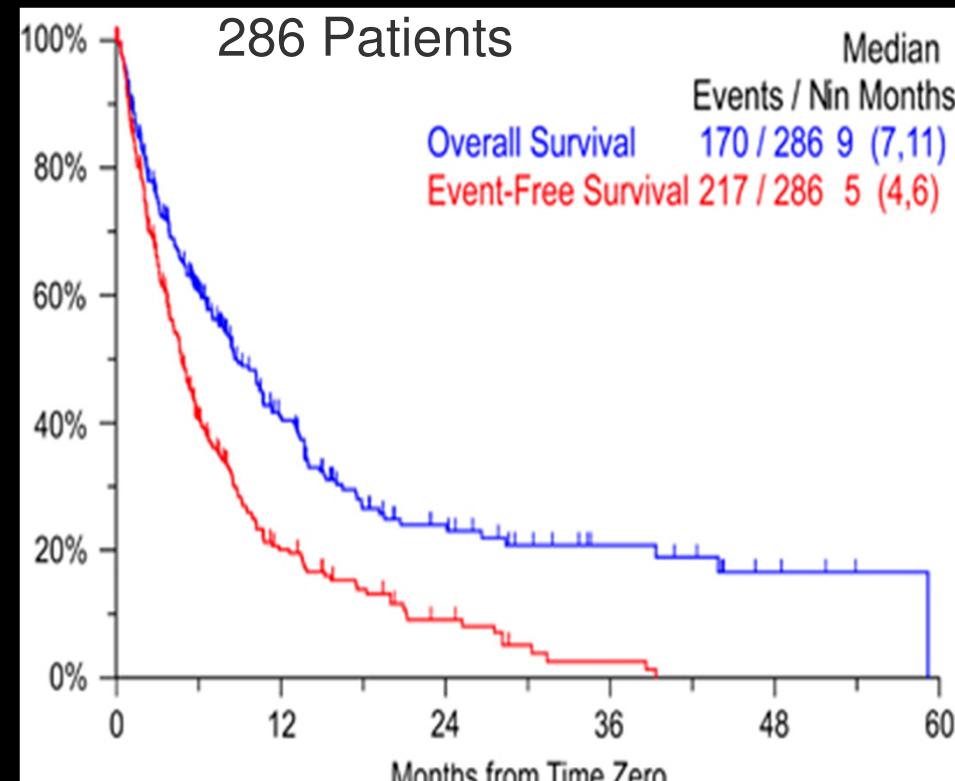
Cancer Research Center

# Outcome of Myeloma Patients

Changes in OS from 1970-2006



Refractory to BTZ & relapsed/ refractory or ineligible to receive an IMiD



*Despite the benefit observed with novel agents in the last years,  
... other drugs are still needed for relapsed/refractory patients*

# Novel Drugs in MM

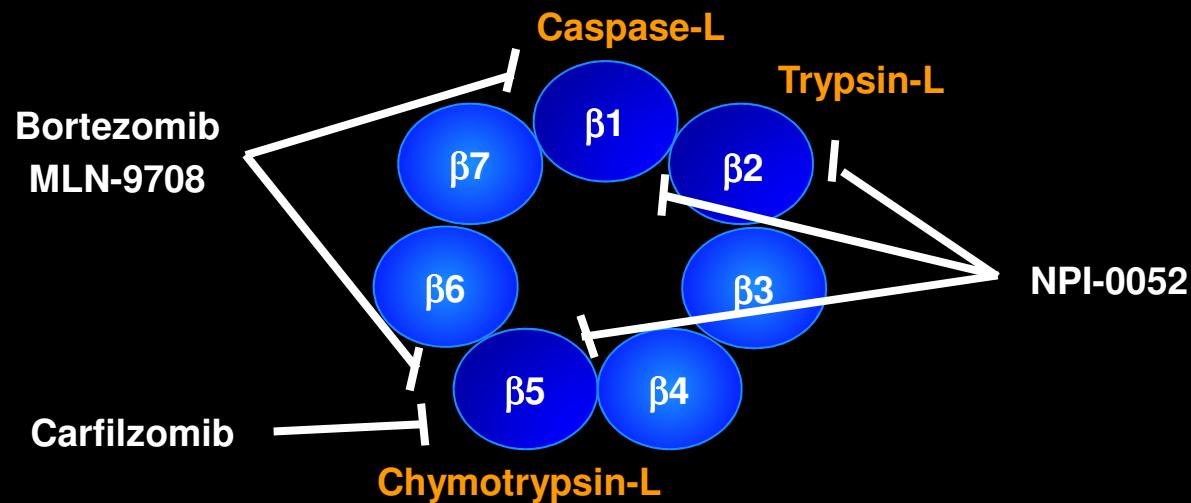
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- *Derivatives from the already approved*
  - Novel Proteasome Inhibitors
  - Novel IMIDs
  - Novel Alkylators
- *Novel Mechanisms of action*
  - MoAb: anti CS1 & anti-CD38
  - Deacetylase Inhibitors
  - Pi3K/AKT/mTOR
  - KSP inhibitors

# Proteasome inhibitors: MoA

- The proteasome is an intracellular enzyme complex responsible for the degradation of regulatory & misfolded and potentially toxic proteins.
- Biological effects of proteasome inhibition:**
  - Inhibition of Proliferation
  - Cell Cycle Arrest
  - ER stress and unfolded protein response
  - Blockade of NF $\kappa$ B pathway

$\beta$ -subunit ring of the proteasome: Catalytic sites



	Type	Catalytic inhibition			Reversibility	po/iv	Dosing
		Chymotryp	Casp.	Tryp.			
<b>Bortezomib</b>	Boronate	X	X		Reversible	iv	1, 4, 8, 11
<b>Ixazomib MLN-9708</b>	Boronate	X	X		Reversible	po	1, 4, 8, 11
<b>Carfilzomib</b>	Epoxi-ketone	X			Irreversible	iv	1-2, 8-9, 15-16
<b>Oprozomib</b>	Epoxi-ketone	x			irreversible	po	BID
<b>Marizomib</b>	Salinospore	X	X	X	Irreversible	iv	1, 4, 8, 11
<b>CEP-18770</b>	Boronate	X	X		Reversible	i.v	1, 4, 8, 11

# Carfilzomib in Relapsed MM

➤ Single Agent<sup>1,2,3</sup>

$\geq$ PR	BTZ-naïve	Btz-refr	
20 mg	42%		PFS. 3,7m; OS: 15,6m
20/27 mg*	52%	17-19%	

G 3/4) AEs: Hematological toxicity (24%); No PN: 1% (12% G 1/2

➤ Combinations

- Carfz + Len + Dex 52 patients<sup>4</sup> ..... ORR 78% (18% CR/nCR)
- Carfz + Pom + Dex 32 patients<sup>5</sup> ..... ORR 50% PFS 7.4 m,
  - Phase III randomized trial in R patients (ASPIRE) Len-Dex +/- CFZ

1. Siegel. Blood 2012

4. Wang. ASCO 2011. Abs. 8025

2. Vij. BJH 2012

5.. Shah et al. ASH 2012 , Abstr 74 (Dose escalation)

Bortezomib (APEX)  $\geq$  PR 43%

3. Vij. Blood 2012

# Combinations of Carfilzomib in Newly Diagnosed MM

- **Carfz+ Thal + Dex** (n=50)<sup>1</sup> ..... ORR **91%** (18% sCR/CR) (44% post Cons)  
4 induct+ ASCT+4 Consolid  
AE G3: 2% PN; 6% Cardiac, 12% Skin
  - **Carfz + Len + Dex** (n=53)<sup>2</sup> ..... ORR **98%** (42% sCR) PFS @ 2 y: 92%  
PN: 23% G 1/2
  - **Carfz + Cycl + Dex** (n=58)<sup>3</sup> ..... ORR **98%** (23% sCR)\* PFS @ 1 y: 88%  
Elderly: 9 Induct (36mg)+ Maintenance (/15d)  
AE G3: 0% PN; 5% Cardiac, 10% Infect; 12% discont  
\* ORR in High vs Standard Risk : 91% vs 78% ( nCR 45 vs 15%)
  - **Carfz + Thal +Cycl + Dex** (n=38)<sup>4</sup> ..... ORR **96%** (23% sCR)  
AE G3: 0% PN; 5% Cardiac, 15% DVT

# Activity of MLN 9708 (Ixazomib): oral

## ➤ ***Relapse /Refractory***

- <b>Weekly</b> (n=32, 97% Btz) <sup>1</sup> .....	<b>11% ≥PR</b>	<b>PN G1/2 : 9%</b>
- <b>Bi- weekly</b> (n=56, 88% Btz) <sup>2</sup> .....	<b>13% ≥PR</b>	<b>PN G1/2 : 11%</b>

## ➤ ***Newly diagnosed*** <sup>3</sup>

- (W) + <b>LD</b> (n=65) .....	<b>92% ≥ PR</b> (28% CR/nCR)	<b>PN G2 : 9%;</b>
<b>G3: 3%*</b>		PFS@1y: 93%

**Relapsed:** LD+/-MLN (Phase 3) ;    **NwD:** MP+MLN;    **Maintenance:** L+MLN;    **SMM:** MLN+D

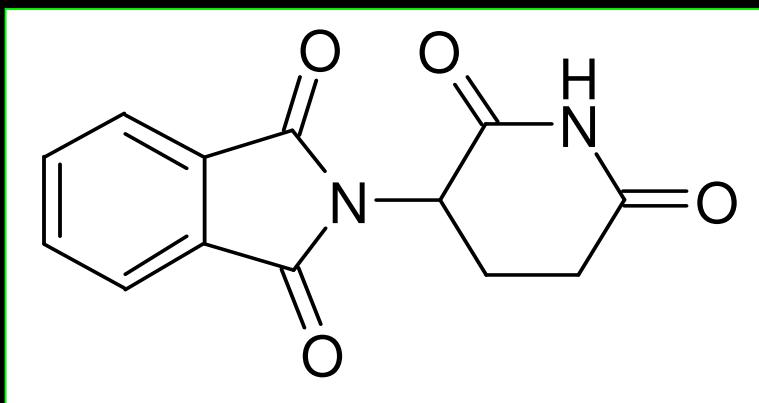
<sup>1-2</sup> Fatigue (30-40%), Thrombocytopenia (30-40%), Nausea (30%), Diarrhea (25%), Rash (18%)

\* PN solved in one and reduced to G1 in an other.

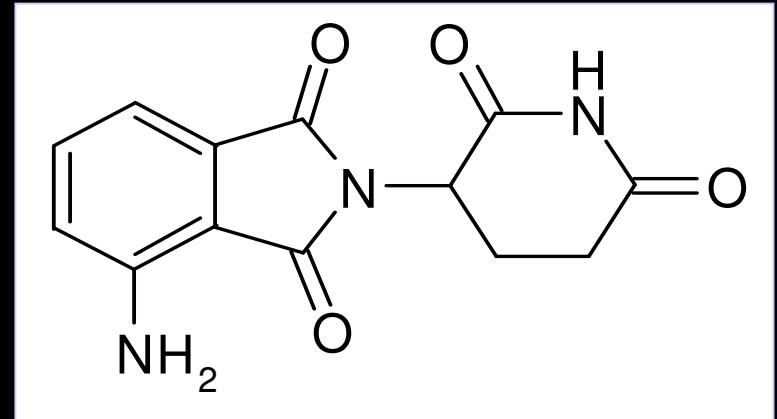
# 2<sup>nd</sup> Generation of Novel Drugs in MM

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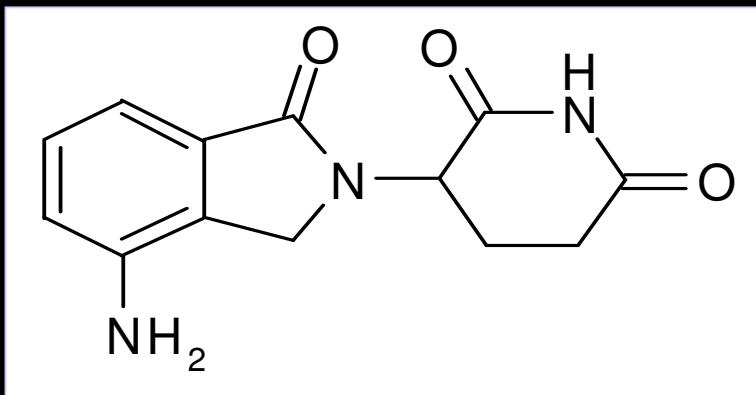
# Immunomodulatory Drugs



**Thalidomide**



**Actimid™ (pomalidomide)** 60-  
70%RR, 1y PFS; 25% RR in Lena refractory pts



**Revlimid™ (lenalidomide)**  
60%RR; 12months PFS

# Differences in Mechanism of Action of IMIDs

10

Effect	Relative potency += potency factor of 10		
	Thalidomide	Lenalidomide	Pomalidomide
Immune modulation CD4+ and CD8+	+	++++	+++++
Tregs suppression	-	+	+
Th1 cytokine production	+	++++	+++++
NK and NKT cell activation	+	++++	+++++
Antibody-dependent cellular cytotoxicity (ADCC)	-	++++	+++
Anti-angiogenesis	++++	+++	+++
Anti-inflammatory properties	+	++++	+++++
Direct anti-tumour effects Anti-proliferative Activity	+	+++	+++
Elimination	Primarily urinary excretion; <3% as parent	Primarily urinary excretion; ~80% as parent	Urinary excretion; ~2% as parent
Rate limiting toxicities	PN, constipation, somnolence, DVT	Myelosuppression, DVT	Myelosuppression

# Activity of Pomalidomide + dex

	n	Population	Dose	$\geq PR$	PFS/TTP/DOR
Lacy <sup>1,2,3</sup>	60	62% prev IMIDs	2 mg (1-28)	65 %	PFS 13 m
Lacy <sup>3,4</sup>	34	Len refr	2 mg (1-28)	32 %	PFS 4.7 m
Lacy <sup>3</sup>	60	Len refr	4 mg (1-28)	37%	PFS 7.9 m
Leleu <sup>5</sup>	84	Len & Btz refr	4 mg (1-21)	35 %	TTP 9.2 m
			4 mg (1-28)	34 %	TTP 7.3 m
Lacy <sup>3,6</sup>	70	Len & Btz refr	2 mg (1-28)	26 %	PFS 6.5 m
			4 mg (1-28)	29 %	PFS 3.3 m
Richardson <sup>7</sup>	113	Prev Len & Btz. Refr to last line	4 mg (1-21)	34 %	PFS 4.7 m

Dex 40 mg weekly

Lenalidomide + Dex<sup>8,9</sup>  $\geq PR$ : 60% (15% CR) TTP: 11.2 m

Schey (JCO 2004): 24 pts (2mg): 54%PR

1. Lacy. JCO. 2009 2. Mikhael. ASH 2011. Abst 2942 3. Lacy. ASH 2011. Abst 3963 4. Lacy. Leukemia. 2010 5. Leleu ASH 2011. Abstract 812 6. Lacy Blood 2011

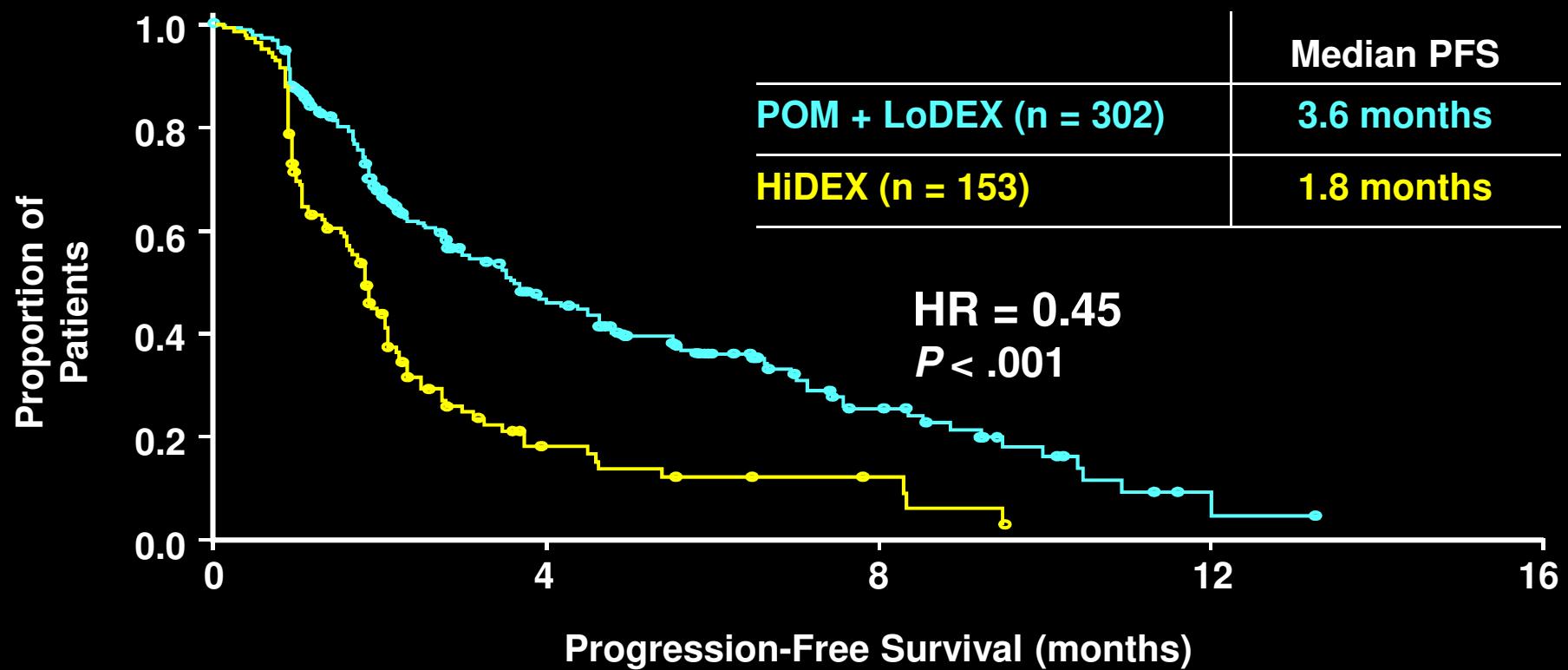
7. Richardson ASH 2011. Abst 634

8. Weber D, NEJM 2007, \*Updated ASH 2007, Abstr 412 9. Dimopoulos M, NEJM 2007, \*Upd. ASH 2007, Abstr 412

# MM-003 Design: POM + LoDEX vs HiDEX (455patients)

*Refractory MM Pts Who Have Failed BORT and LEN*

**PFS: ITT Population**

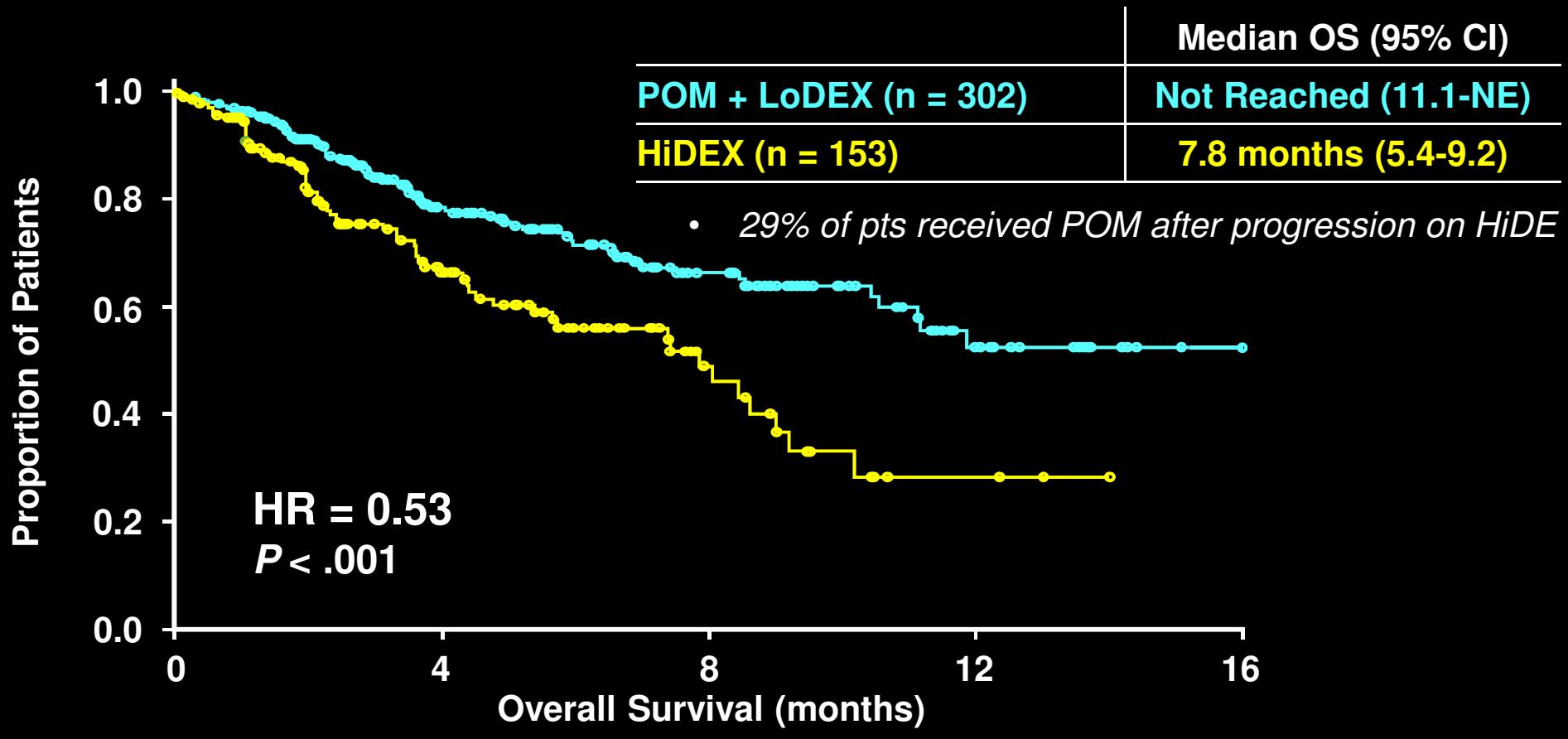


In Patients refractory to both LEN and BORT : 3,2 vs 1,7m; HR 0,48, p< 0,001

**ORR ( $\geq PR$ ): 21% vs 3%; ( $\geq MR$ ): 37% vs 8%**

*PFS of  $\geq MR$  in POM + LoDEX: 8.5 months*

## MM-003: Overall Survival: *ITT Population*

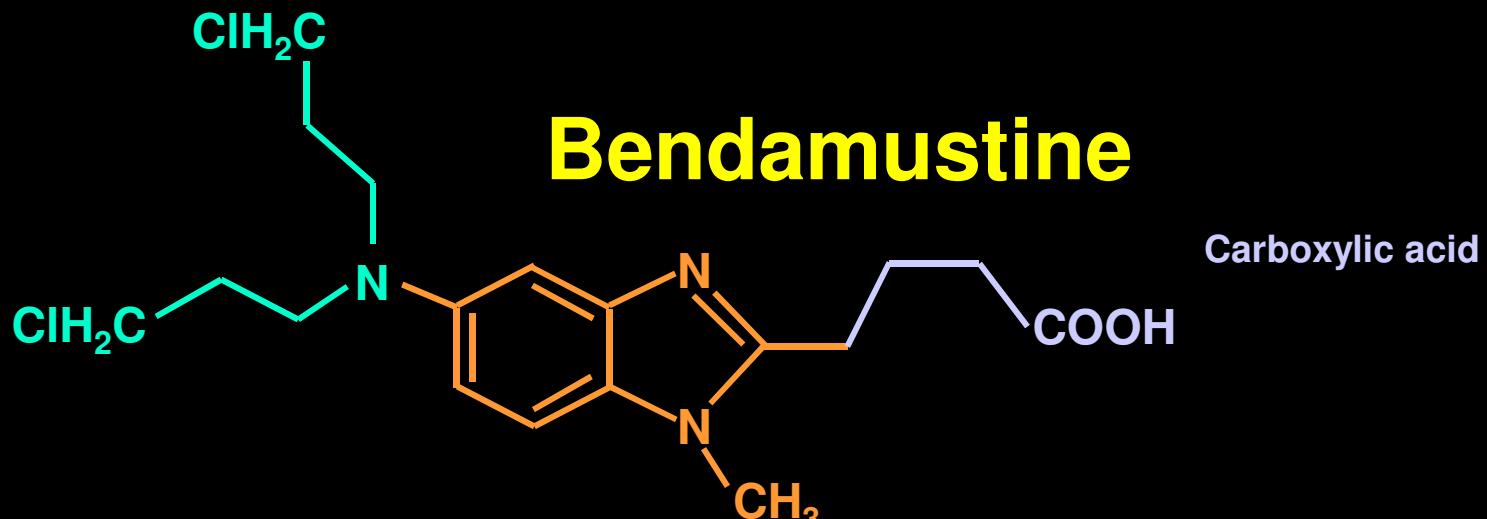


In Patients refractory to Both LEN and BORT : NR vs 7,4m; HR 0,58, p< 0,003

*Combinations in R/R with Cycloph, Clarytro, Bortez, Carfilz.....50-73% RR \**

Dimopoulos ASH 2012, Abstr ( LBA 6

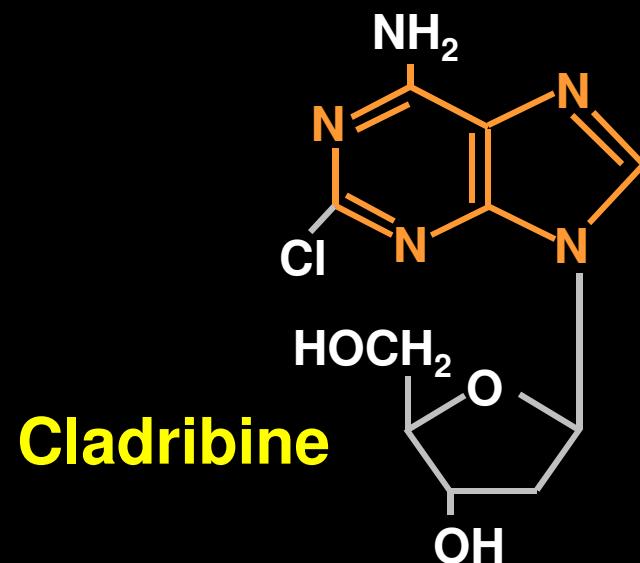
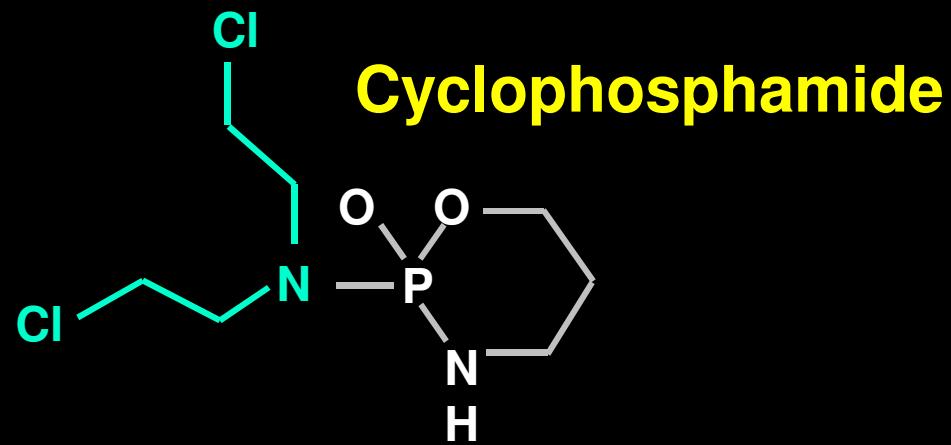
# Bendamustine: an old-new drug



Nitrogen mustard

Benzimidazole ring

Carboxylic acid



# Bendamustine in R/R MM

- **Single agent<sup>1</sup>** (31 patients relapsing HDT)      ORR: 31% (7% CR);      PFS: 6m
  - **Benda-Bortz-Dex<sup>3</sup>** (40 patients)      ORR: 72% (25% VGPR)
  - **Benda-Bort-Dex<sup>4</sup>** (74 patients)      ORR: 65% (21% CR)      PFS: 9.7m
  - **Benda-Bort-Pred<sup>5</sup>** (46 patients)      ORR: 75% (15% nCR)
  - **Benda-Thal-Pred<sup>6</sup>** (28 patients *2 prior lines*)      ORR: 86% (14% CR)
  - **Benda-Thal-Dex<sup>7</sup>** (23 patients *5 prior lines*)      ORR: 26% (4% CR)
  - **Benda-Len-Dex<sup>8</sup>** (36 patients)      ORR: 52% (24% VGPR)

1. Knop et al. *Hematologica* 2005, 90:1287
2. Berenson. *ASH 2011 Abstract* 1857
3. Hrusowsky et al *ASH 2007 Abstract* 4851

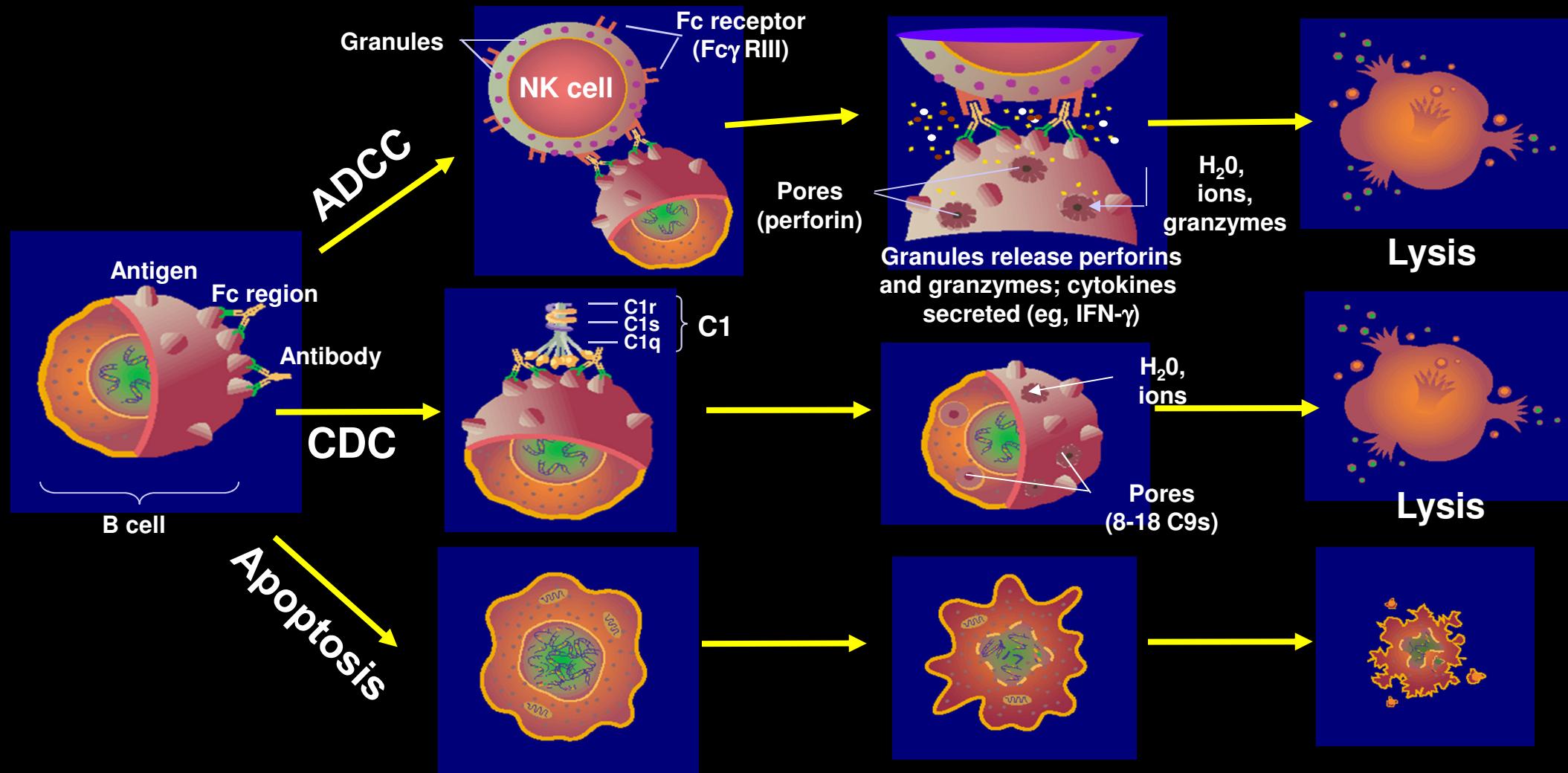
- 4. Ludwig H. ASH 2012 Abstract 943**
- 5. Pönisch et al. Lugano 2008**
- 6. Pönisch et al. BJH 2008, 143: 191-2**

**7. Grey-Davies E. BJH 2011  
8. Lentzsch. ASH 2011 Abstract 304**

# 2<sup>nd</sup> Generation of Novel Drugs in MM

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# Mechanism of action of monoclonal antibodies



1. ADCC: Antibody-dependent cellular cytotoxicity

2. CDC Complement-dependent lysis

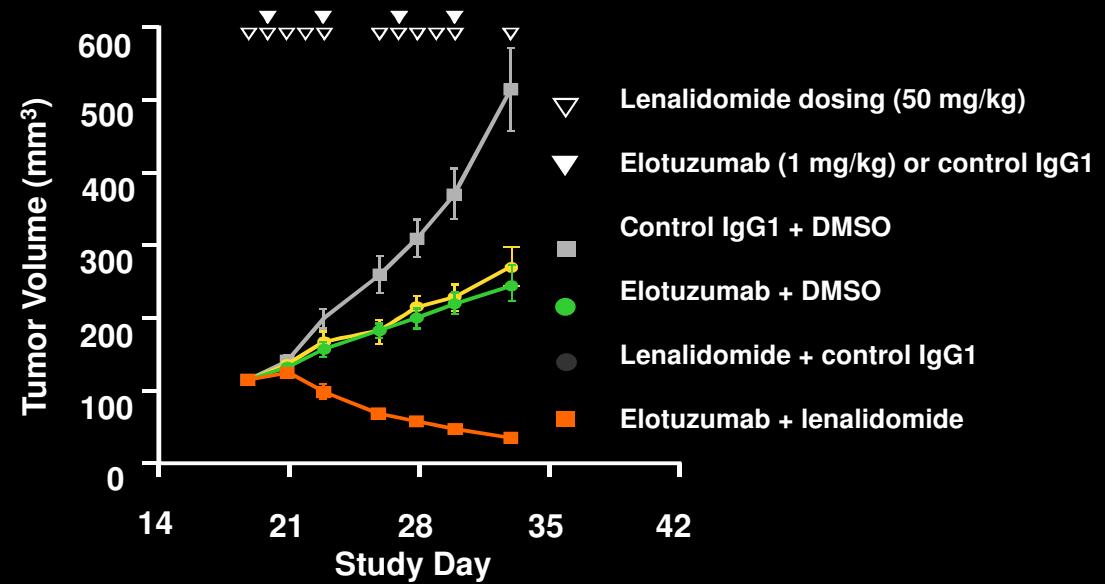
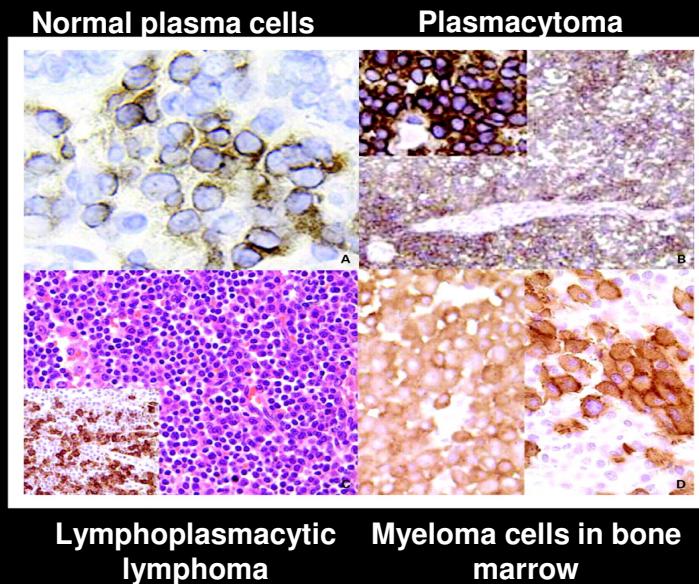
# Elotuzumab (Anti-CS1 MoAb) in MM

Elotuzumab is a humanized IgG1 mAb targeting human CS1, a cell surface glycoprotein<sup>1,2</sup>

CS1 is highly expressed on >95% of MM cells<sup>1-3</sup>

- Lower expression on NK cells
- Little to no expression on normal tissues

- MoA of elotuzumab is primarily through NK cell-mediated ADCC against myeloma cells<sup>1,2</sup>
- In a MM xenograft mouse model, the combination of elotuzumab + lenalidomide significantly reduced tumor volume compared with either agent alone<sup>4</sup>



DCC = antibody-dependent cellular cytotoxicity;

MED = maximum efficacious dose;; MoA = mechanism of action; 1. Hsi ED et al. Clin Cancer Res. 2008;14:2775-2784; 2. Tai YT et al. Blood. 2008;112:1329-1337

3. Van Rhee F et al. Mol Cancer Ther. 2009;8:2616-2624; 4. Lonial S et al. Blood. 2009;114:Abstract 432

# Elotuzumab (Anti-CS1 MoAb) in MM

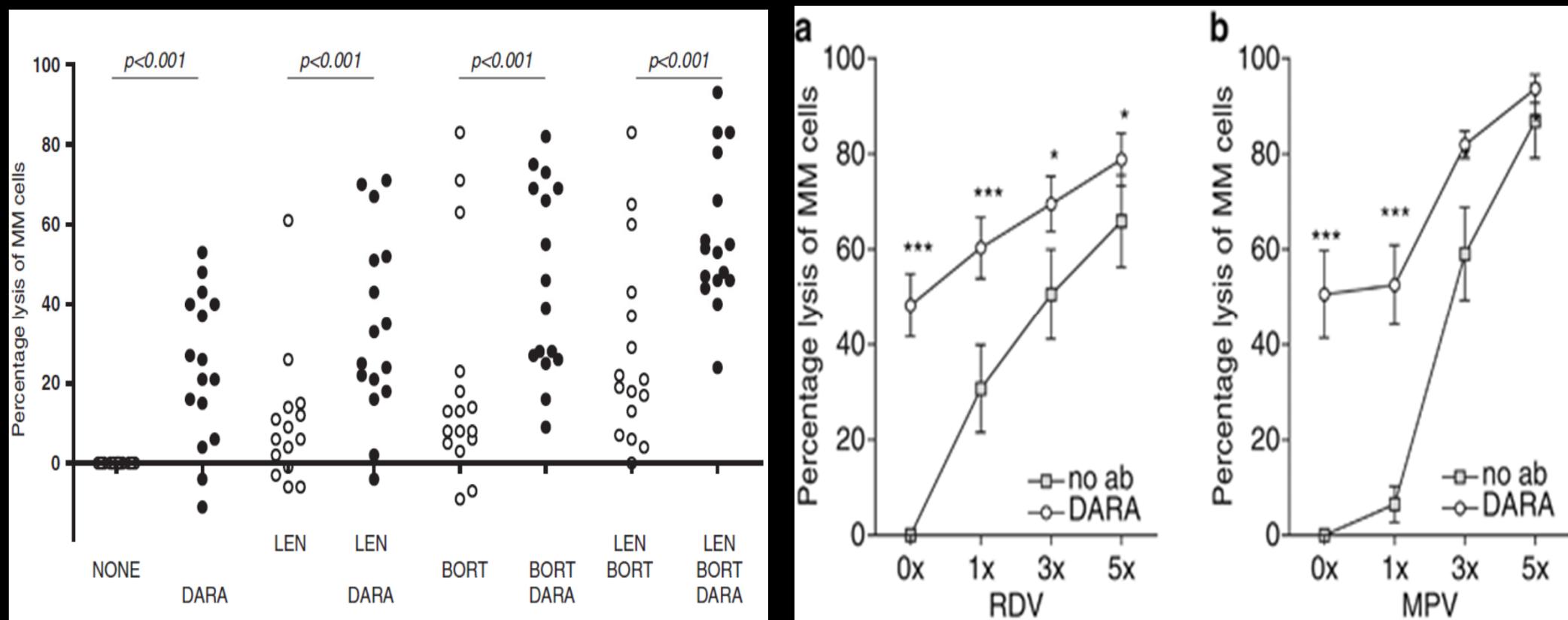
- Elotuzumab Monotherapy<sup>1</sup> → 26% SD
- Elotuz + Len + Dex : Len “prepares” immune cells & then Elotuzumab induces ADCC
  - Phase I<sup>2</sup> (28 pts) → ORR 82% TTP: NR @ 16 m
  - Phase II<sup>3</sup> n= 73 Len-naïve pts (2 doses of Elotuzumab 10 & 20 mg/Kg)

	10 mg	20 mg
≥PR	92%	76%

PFS: 26,9 m (10 mg/Kg) & 18,6 m (20 mg/Kg)
- Elotuz + Bortez + Dex      Phase I<sup>4</sup>      n=28 pts → ORR 48%

Phase III trials (Eloquent) in relapsed/refractory & Newly diagnosed: (LD+/- ELO)  
Phase II trials in R/R: Btz-Dex +/- ELO & Thal/Dex + ELO

# Anti-CD38: Daratumumab Enhances MM Killing by Key Anti-myeloma Agents



Ex vivo assays allows killing of tumor cells in bone marrow aspirates isolated from MM patients to be addressed.  
Daratumumab was tested as single agent and in combination with novel agents\*

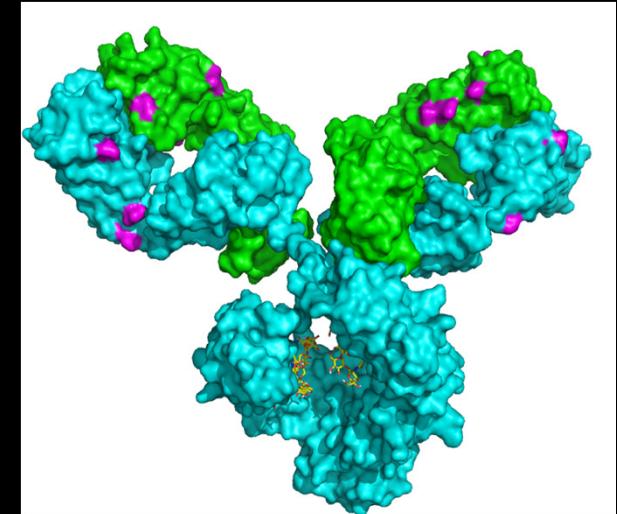
# Anti CD 38 (Daratumumab) : Results & Safety

- Weekly x 8 w followed by /14d up to week 24w (MTD: 8 mg/kg)
  - In 15 of 32 (47%)....**reduction in paraprotein** (following 8 w of darat in doses up to 24mg/kg)  
**4 PR (13%) + 6 MR (19%) + 5 SD**
  - At doses > 4mg/kg, 8 of the 12 (66%) had at least a MR
  - **AE:** Infusion-related reactions were observed during the initial infusions:  
*9% during the pre-dose infusion & 26% during the first full infusion; No dose relationship. & Five late reactions  
Two events grade 3, the remaining grade 1-2*
  - A dose-dependant decrease in NK cells was observed
- **Ongoing in R/R: Dara +LD or BD.....In NwD: Dara+VMP**

# SAR650984

## Naked humanized anti-CD38 mAb from Sanofi

- Unique pro-apoptotic activity seen in MM patient samples and cell lines
- In vivo anti-tumor activity as a single agent and in combination with myeloma therapies
- Single agent and combination clinical trials underway
  - Phase 1 in CD38+ hematological malignancies
  - Phase 1b combination with lenalidomide + dexamethasone
- *Poster presentation: P-288, April 4th, 08:00 - 17:00*



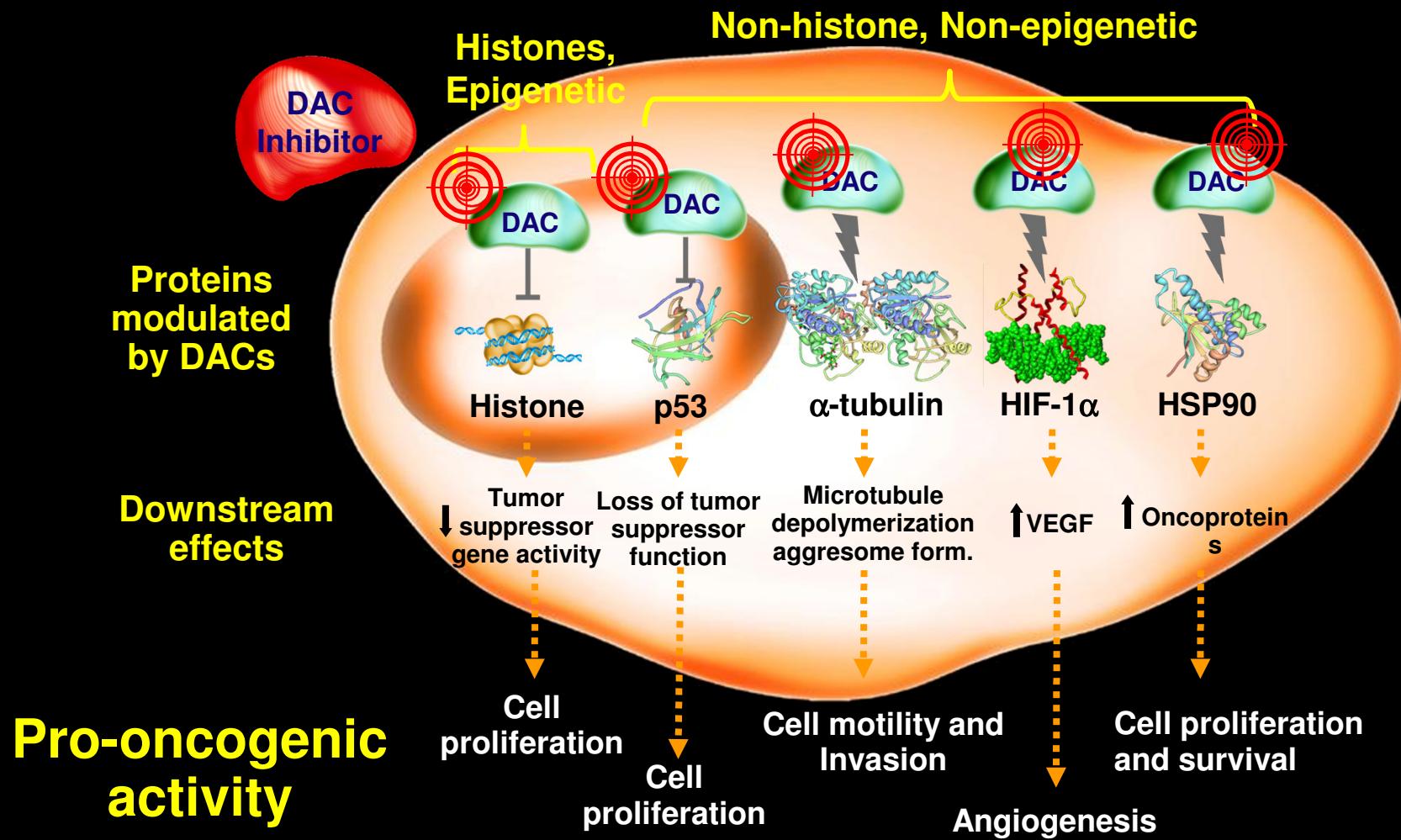
- Multiple mechanisms of action contribute to novel product profile:
  1. Antibody-dependent cellular cytotoxicity (ADCC)
  2. Complement-dependent lysis (CDC)
  3. Direct apoptosis

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# What are Deacetylases?

DACs are enzymes that remove acetyl groups from their client proteins and modulate their activity



# Activity of HDACi in monotherapy in MM

	n	ORR	Responses
Vorinostat <sup>1</sup> ( <i>SAHA</i> )	10	0%	1 MR, 9 SD
Panobinostat <sup>2</sup> ( <i>LBH589</i> )	38	3%	1PR, 1 MR, 1 SD
Givinostat <sup>3</sup> ( <i>ITF2357</i> )	19	0%	5 SD
Romidepsin <sup>4</sup> ( <i>FK228</i> )	12	0%	4 SD

1. Richardson PG, *Leuk Lymphoma* 2008

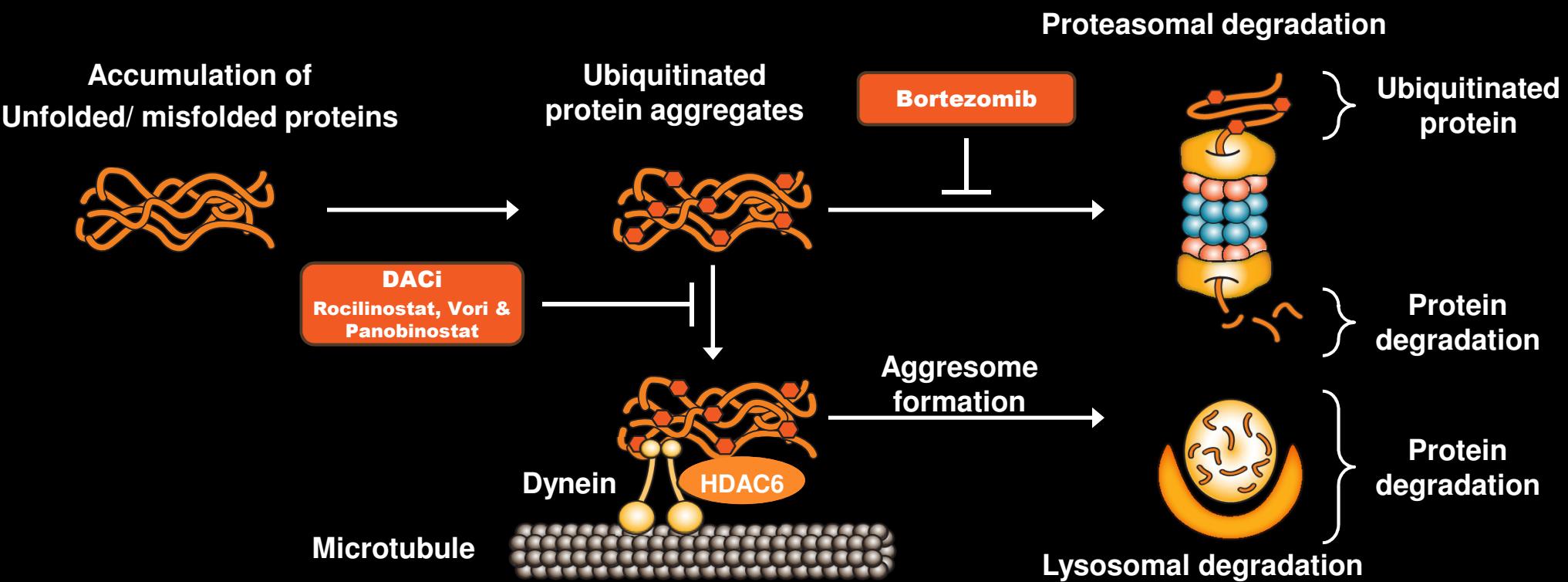
2. Wolf, ASH 2008. Abstract 2774

3. Galli M, *Ann Hematol* 2010

4. Niesvizky R, *Cancer* 2011

# Rationale for combining DACi + Bortezomib

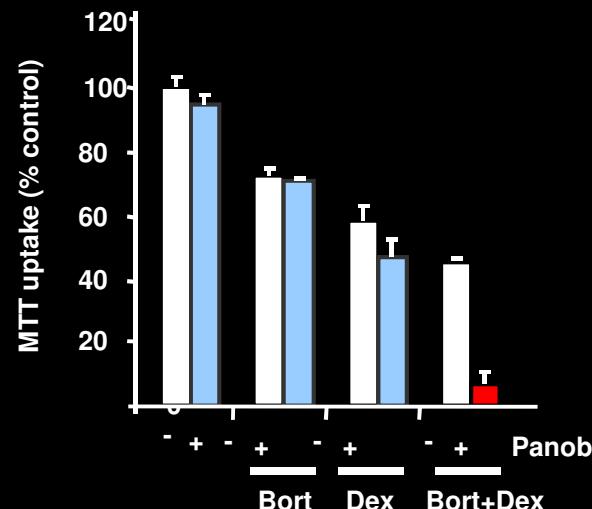
*Inhibition of the aggresome and proteasome pathways causes a buildup of intracellular misfolded cytotoxic proteins, leading to MM cell apoptosis<sup>1-4</sup>*



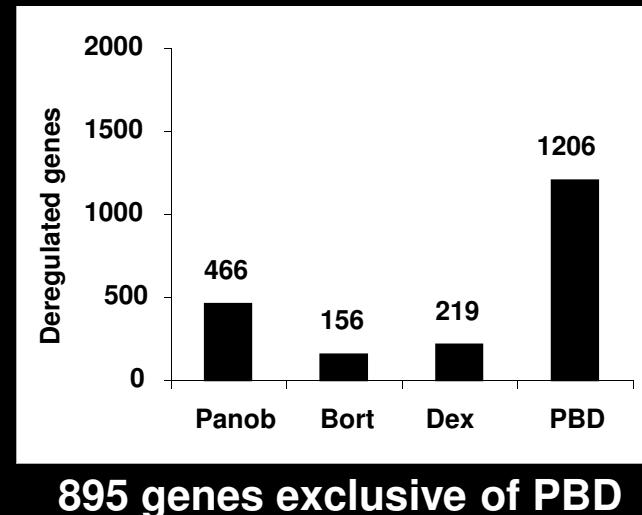
1. Hideshma T, et al. *Proc Natl Acad Sci USA*. 2005;102:8567-8572.
2. Ocio EM, et al. *Haematologica*. 2010;95:794-803.
3. Catley L, et al. *Blood*. 2006;108:3441-3449.
4. Hideshma T, et al. *Mol Cancer Ther*. 2011;10:2034-2042.

# Preclinical activity of HDACi + Bort + Dex in MM

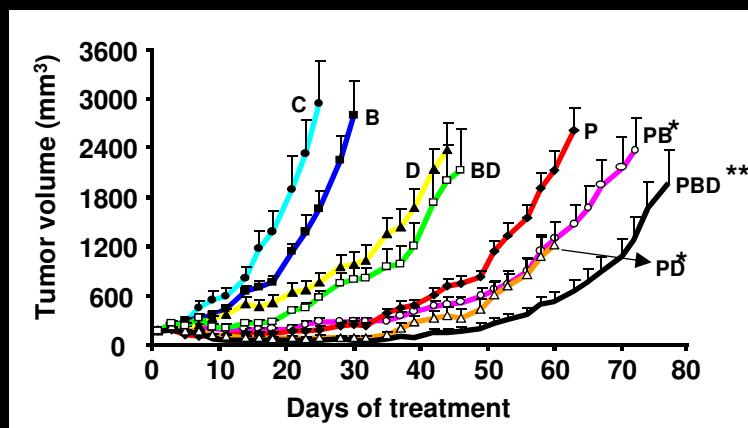
## Activity in vitro



## Changes in GEP

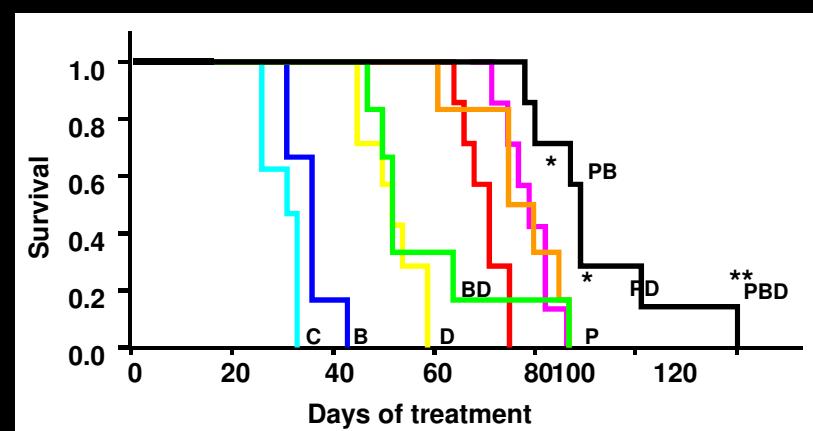


## Activity in vivo



\* p<0.05 related to singles

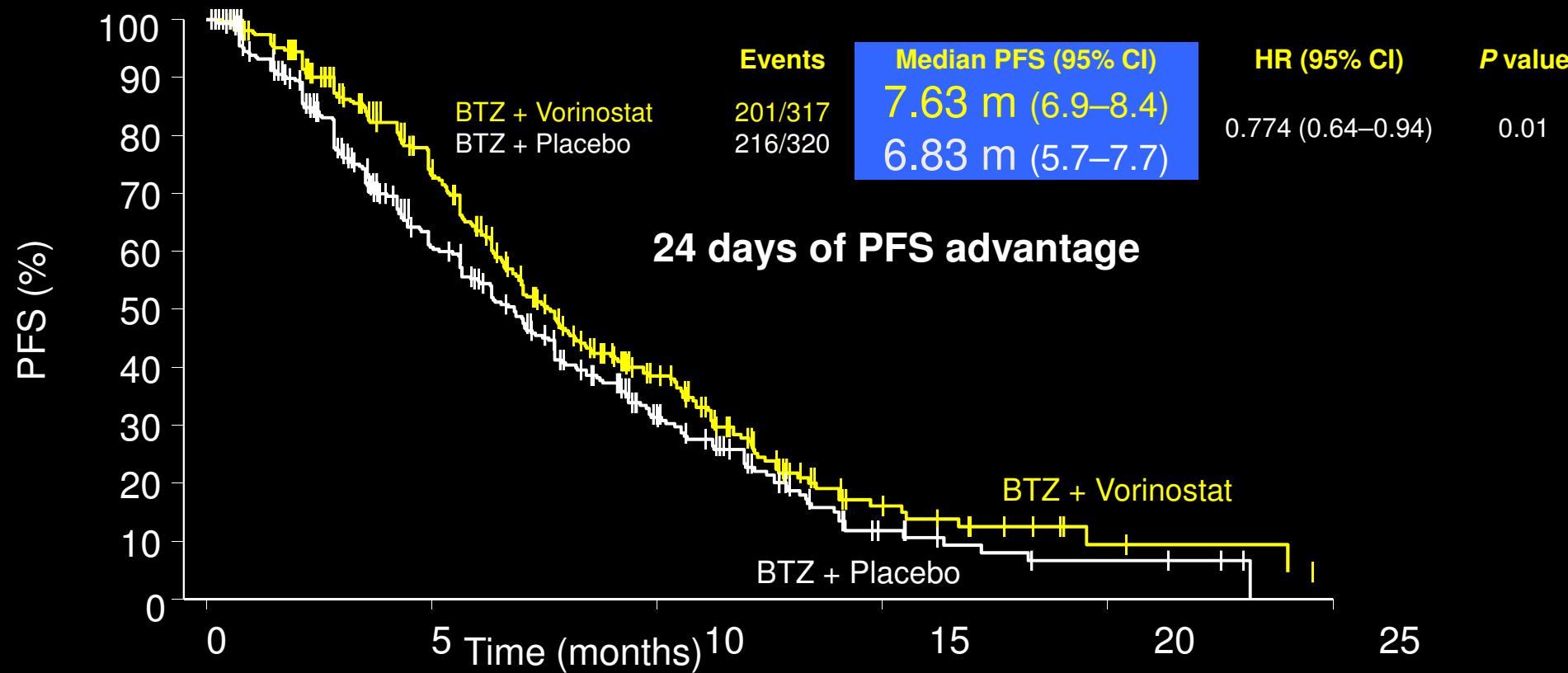
\*\* p<0.05 related to doubles



Maiso et al Cancer Res 2008; Ocio, Hematologica 2010

# Vorinostat+Btz vs Btz: Response Rate & PFS

ORR = 56% vs 41%,  $P<0.0001$



\***BTZ Refractory** (Vantage PN 095): RR = 33% (18% PR+ 15%MR) ; **DOR = 6.3 months**

# Panobinostat + Bortezomib + (Dex) in Relapsed MM



## Phase Ib<sup>1</sup>

- 62 patients ..... **61% ≥ MR (51% PR)**
  - **Btz Refractory..... 32% ≥ MR (23% PR)**
- AE (G3) : *Thrombocytopenia 66%, Neutropenia 43, Fatigue 15% , PN 2% (expansion)*



## Phase II (Panorama 2)<sup>2</sup> (Btz-Refr. & at least 1 IMiD: Len 98%)

- 55 patients..... **35% PR PFS: 4.9 m**

*PAN + Btz + Dex can recapture responses in Btz-refractory*



## Phase III (Panorama 1): Btz-Dex +/- Panobinostat in Relapsed or R&R MM

1. San Miguel EHA 2011 (Abstr 314): 3w cycles x 8 (MTD: 20 mg PAN; 1.3 mg/m<sup>2</sup> Btz ) (2 wks on /1 w off) (47 in escalation & 15 in expansion phase)

2. Richardson ASH 2012 ( Abstr 1852) . Eight 3 w cycles PAN (20 mg) + Btz (1.3 mg/m<sup>2</sup> )+ Dex (20 mg)

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# Inhibitors of the PI3K/AKT/mTOR pathway

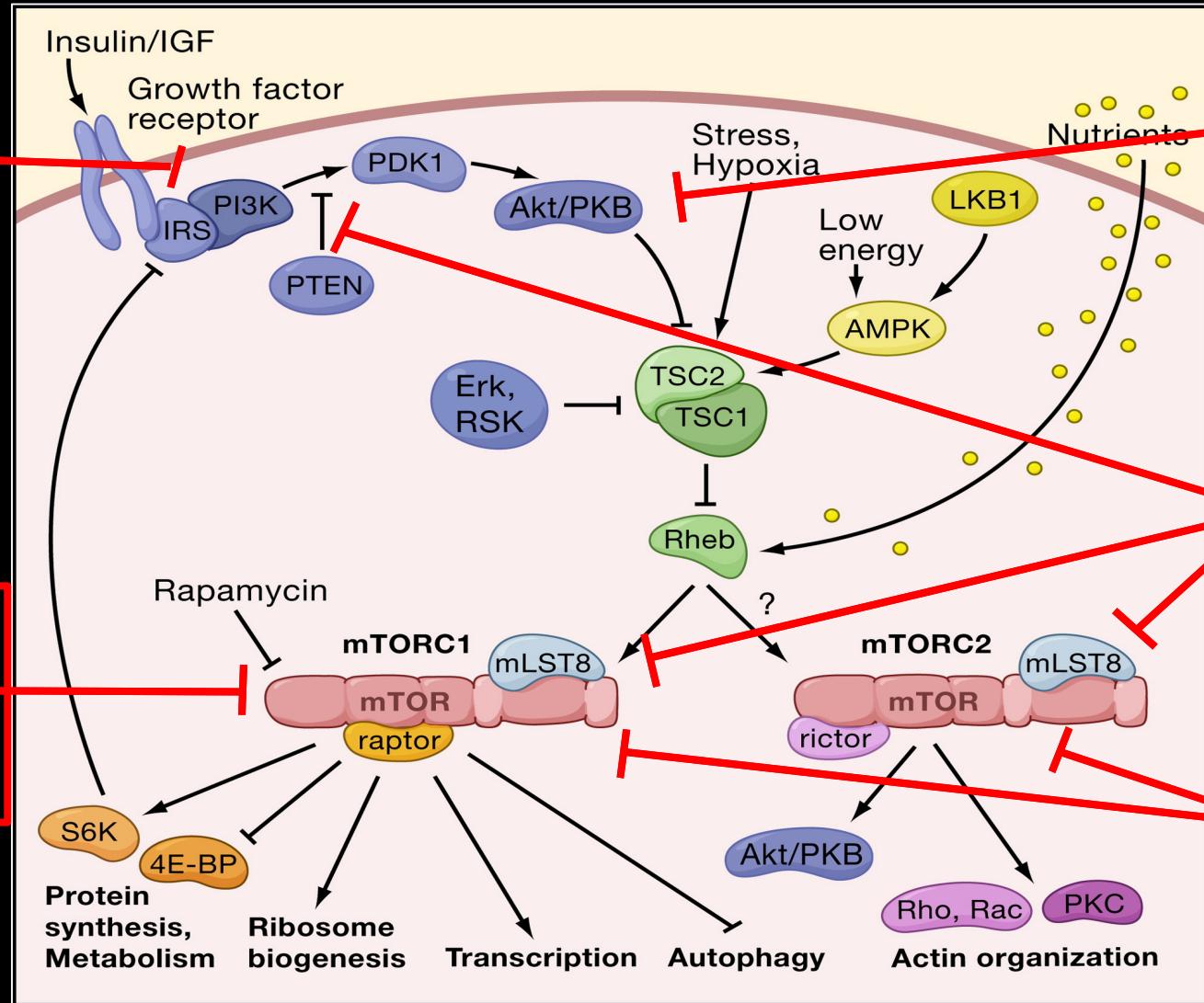
BKM120  
XL147  
GDC0941  
GSK1059615  
PX-866  
CAL101

Perifosine  
MK2206  
VQD-002  
XL418

Rapamycin  
CCI779 (Tensirol)  
RAD001 (Everol)  
AP23573

BEZ235  
BGT226  
XL765  
SF1126

AZD8055  
OSI-027  
CC-223



# PI3K/AKT/mTOR inhibitors in MM

$\geq MR$	Target	Alone	Bort	Len
<b>Perifosine</b>	AKT	38% <sup>1*</sup>	41% <sup>2*</sup>	70% <sup>3</sup>
<b>GSK2110183</b>		19% <sup>9</sup>		
<b>Everolimus</b>	mTORC1	7% <sup>4</sup>		58% <sup>5</sup>
<b>Temsirolimus</b>		38% <sup>6</sup>	38% <sup>7</sup> (47% @MTD)	38% <sup>8</sup> (50% @MTD)

Perifos: 65% in BTz relapsed and 32% in BTz refractory

**Toxicity of Rapalogs: Hyperglycemia. Hypertriglyceridemia. Cytopenias**

\* + Dex

1. Richardson, ASH 2007. Abstract 1164

2. Richardson, JCO 2011

3. Jakubowiak, ASH 2010. Abstract 3064

4. Guenther, ASCO 2010. Abstract 8137

5. Mahindra, ASH 2010. Abstract 3051 & Yee, ASH 2011. Abstract 3966

6. Farag, Leuk Res 2009

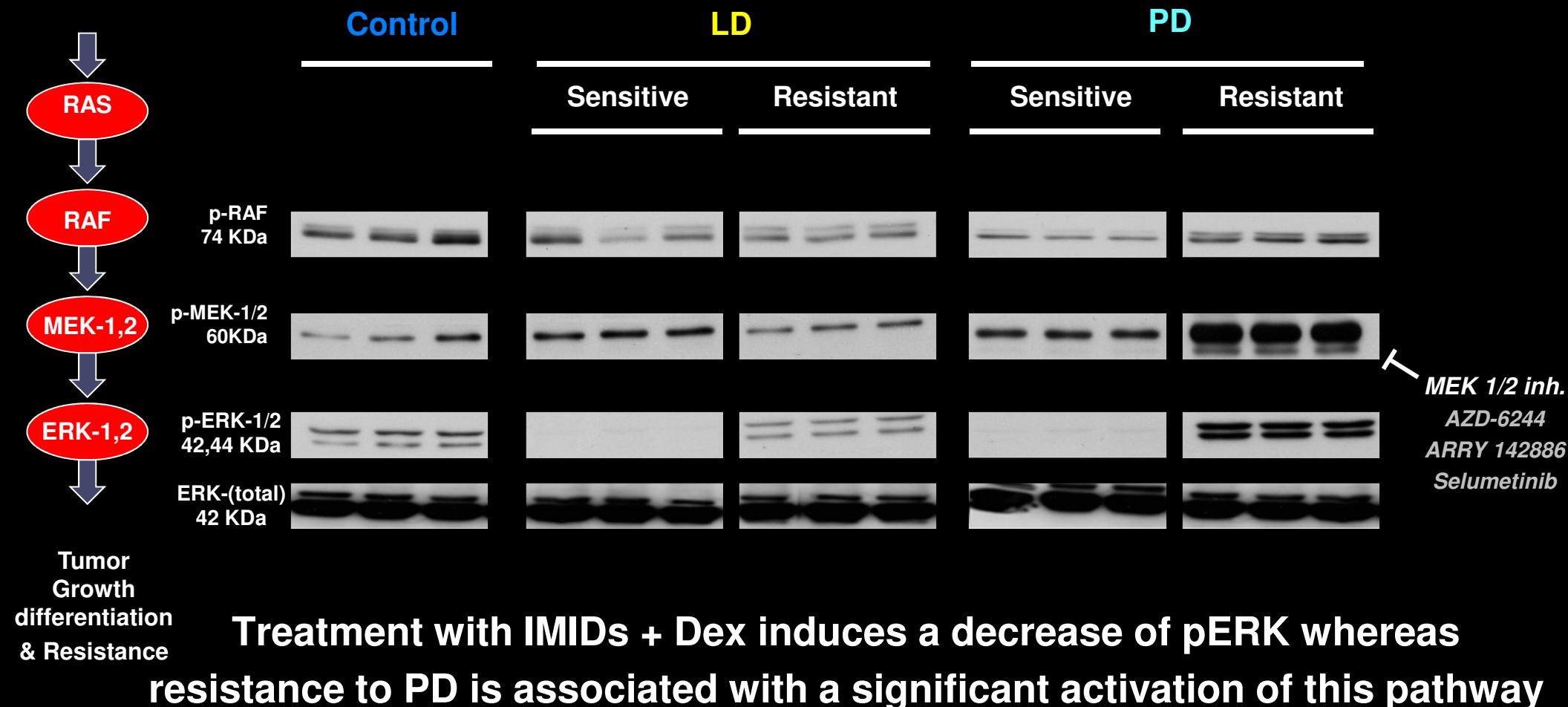
7. Ghobrial, Lancet Onc 2011

8. Hofmeister, JCO 2011

9. Spencer, ASH 2011. Abst 1856

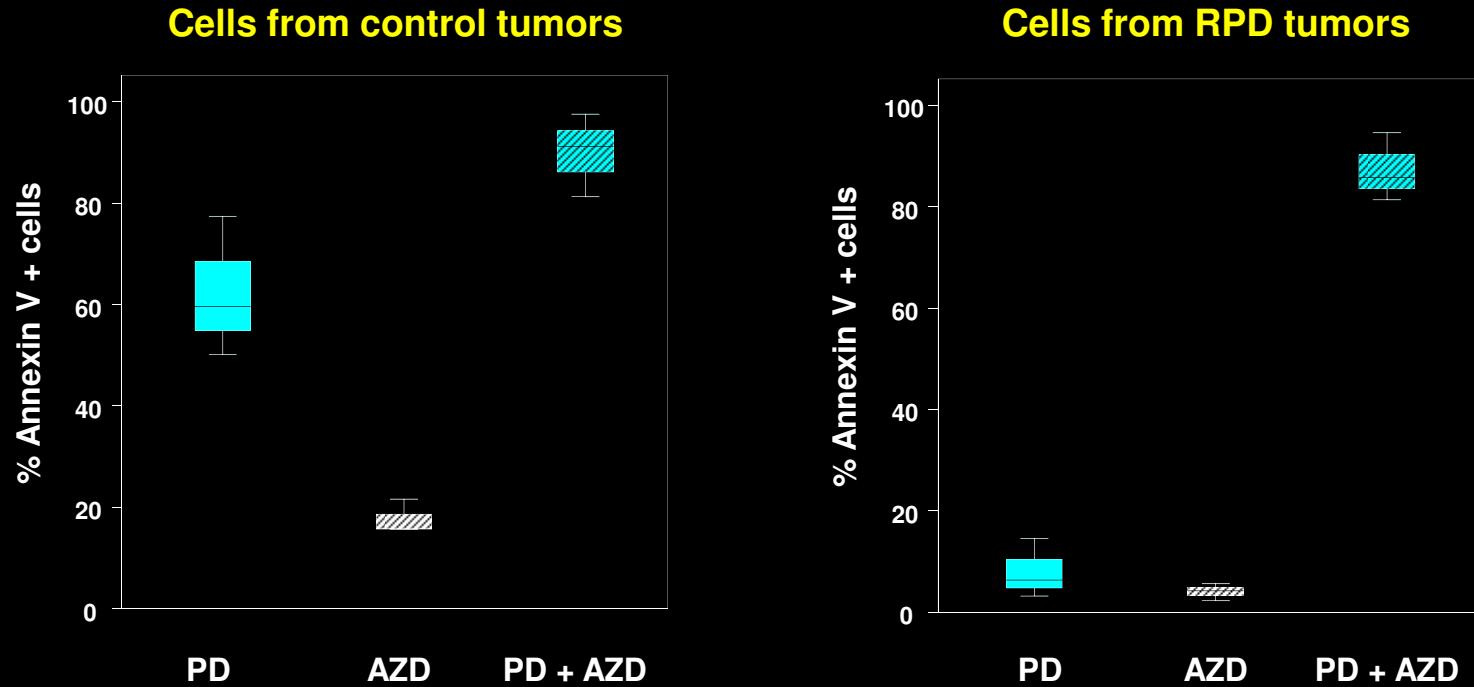
# Role of MEK/ERK pathway in IMIDs' activity & resistance

Fresh cells from untreated, sensitive and resistant tumors to LD & PD were extracted and different signaling pathways were analyzed by WB



# Ex vivo combination of MEK1/2 inhibitor + Pom-Dex

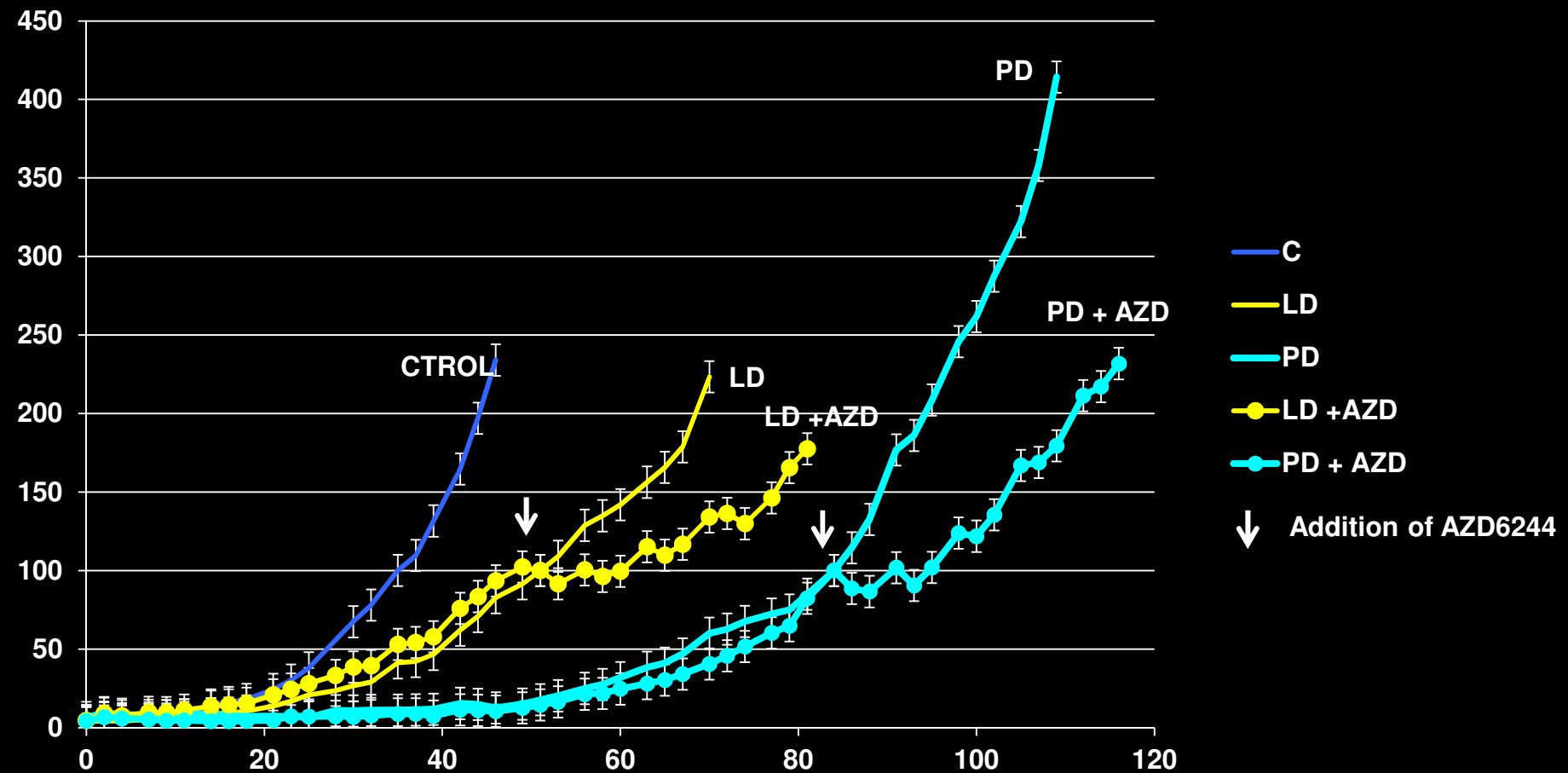
Cells from control tumors & tumors resistant to PD (RPD) were excised and ex vivo treated with PD +/- AZD 6244: Doses: Pomalidomide 10  $\mu$ M, Dex 10 nM & AZD-6244 100 nM (2 pulses) for 5 days



The MEK 1/2 inhibitor (AZD) little activity as single agent....but the addition completely overcomes the resistance to PD ex vivo

# Role of MEK/ERK inhibition in IMIDs' resistance

Treatment of Resistant Cells with the MEK inhibitor Selumetinib (AZD6244) + IMIDs



The addition of a MEK 1/2 inhibitor is able to slow down the growth of tumors resistant to LD or PD

# 2<sup>nd</sup> Generation of Novel Drugs in MM

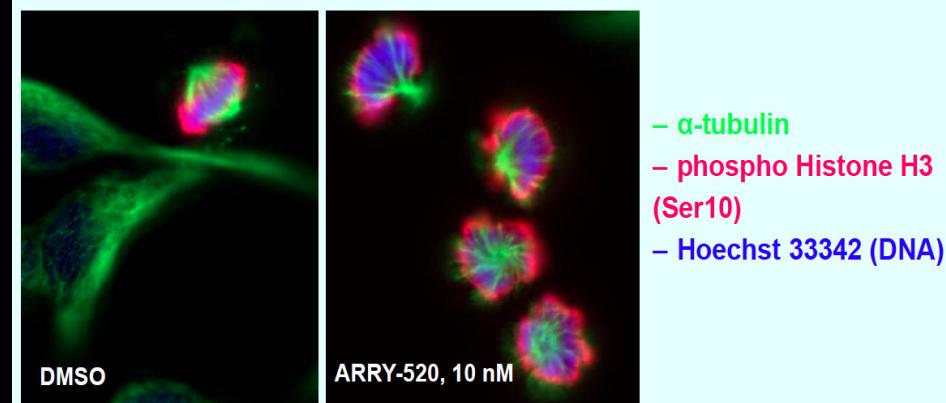
- *Derivatives from the already approved*
  - Novel Proteasome Inhibitors
  - Novel IMIDs
  - Novel Alkylators
- *Novel Mechanisms of action*
  - MoAb: anti CS1 & anti-CD38
  - Deacetylase Inhibitors
  - PI3K/AKT/mTOR
  - KSP inhibitors

# ARRY-520 (KSP inh) in MM

Kinesin spindle protein is required for cell cycle progression

- ARRY-520 induces mytotic arrest and subsequent apoptosis

## Formation of Monopolar Spindles



## Phase 2: (n=50) Exposed to Bortezomib and Len

Treatment:

Cohort 1: (exposed to BTZ & IMID)..... ARRY-520 + G-CSF  
Cohort 2: (Refractory to BTZ, Len, Dex).... ARRY-520 + G-CSF + low-dose Dex

## Results

**Cohort 1: ≥ MR 19%, PR 16%**

in pts refractory to Btz and Len: ≥ MR15%

**Cohort 2: ≥ MR 28%, ≥ PR 22%**

- *Prolonged TT Response: TT PR 3.7 months*

**Gr 3/4 AEs** (cohort 1, cohort 2): neutropenia (38%, 33%), thrombocytopenia (44%, 44%), anemia (28%, 50%), pneumonia (3%, 17%)

# Other Potential Agents

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- *Anti – BAFF (Tabalumab)*
- *CDK 4/6 Inhibitor (PD 0332991)*
- *Aplidin*
- *Zalypsis*
- .
- .
- .

# Current Treatment Approaches in Multiple Myeloma

**Progress in MM Cell Biology**



Prognostic factors

&

Myeloma subtypes\*

**Discovery of New Drugs**



Singular Mechanism of action

**Individualize & Tailor Treatment**

\* MM should not be considered a single entity