

## The Search for New Myeloma Drugs

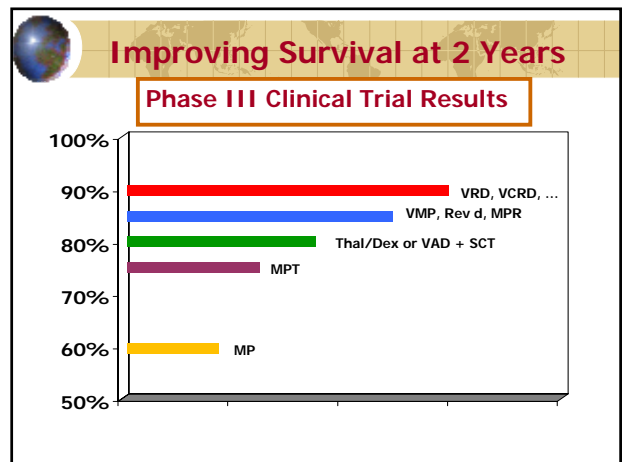
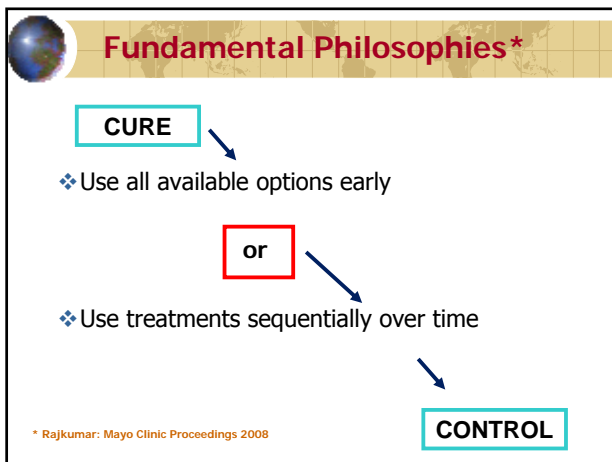
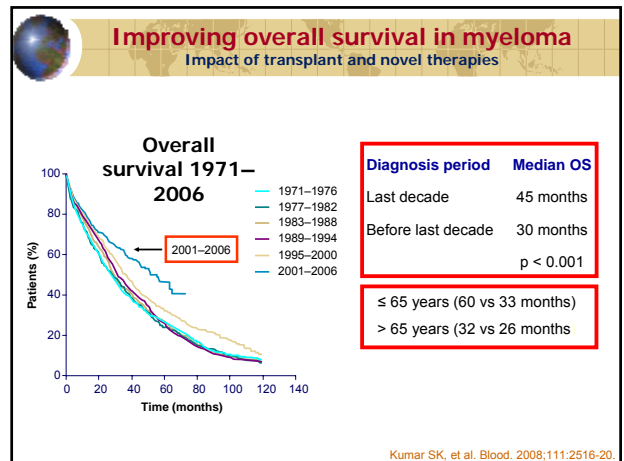
Friday, October 15, 2010  
Vienna, Austria

**Brian G.M. Durie, M.D.**




APTIVM  
DIALYSIS

CEDARS-SINAI



## Staging and Prognostic Factors

### Staging

Durie-Salmon

ISS (Sβ<sub>2</sub>M/Alb)

ISS & FISH

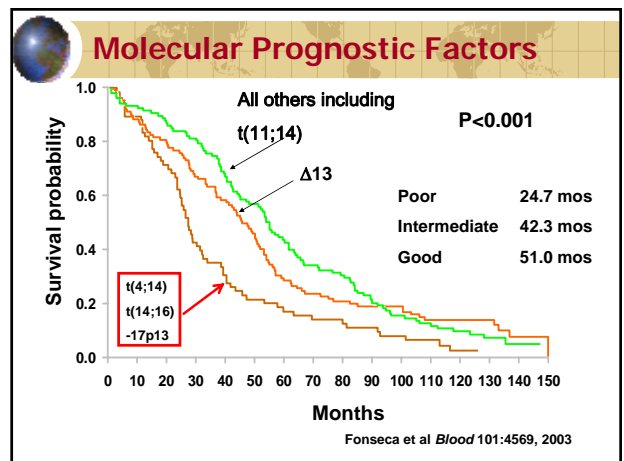
### Prognostic Factors

FISH

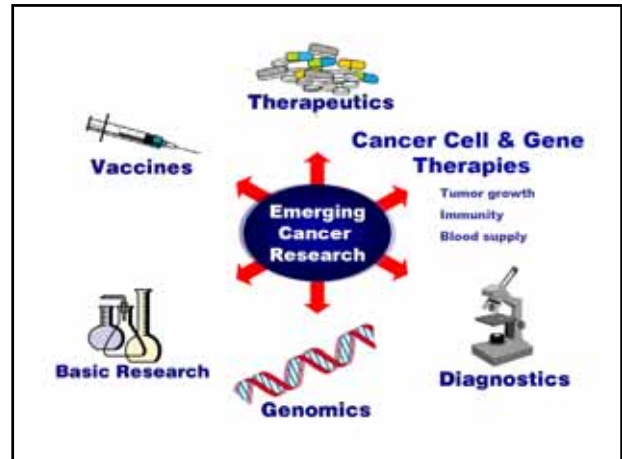
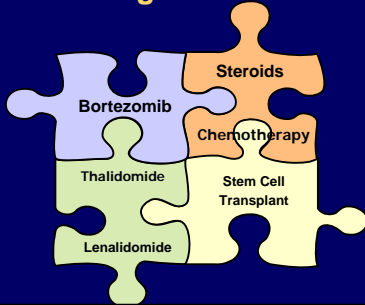
- del 17p
- t (4;14)
- t (14; 16)

Chromosomes

- del 13
- Hypodiploidy



How do we put together the puzzle pieces to come up with best treatments for myeloma?  
How do we get new treatments?



### What's Best in 2010

VRD (Velcade / Revlimid / Dexamethasone)

VCRD...

What's Next???

### Updated Analysis of Phase I/II Trial of VRD in Newly Diagnosed Multiple Myeloma

Phase 1 up to eight 3-wk cycles at 5 dose levels; phase II dose: 25 mg/1.3 mg/m<sup>2</sup> lenalidomide/bortezomib + 20-mg dexamethasone

Patients with ≥ PR could proceed to ASCT after ≥ 4 cycles

After 8 cycles, responding patients could receive maintenance – 3-wk cycles of lenalidomide (Days 1-14), and wklly bortezomib (Days 1, 8), at doses tolerated at end of cycle 8 plus dexamethasone 10 mg (Days 1, 2, 6, 9)

Anderson KC, et al. ASCO 2010. Abstract 8016. Reprinted with permission.

### What's Next?

VRD + Cytoxan: "Evolution"

5 drugs

New Drugs

### Types of New Drug Trials

Phase I Safety

Phase II Response

Phase III Longer Term Benefit

- Single Agent (Relapsed Refractory)
  - Response
- Randomized (1-3 Relapses)
  - Response
  - PFS
  - Survival

Randomized against "accepted comparator\*" (e.g. Revlimid/Velcade...)

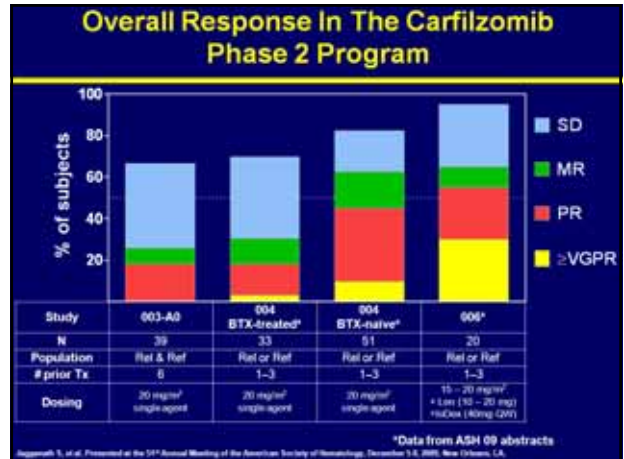
## Current Drugs

**“Potential” FDA approval**

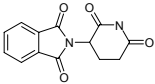
- Carfilzomib
- Palmaridomide

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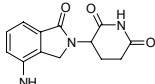
- Elotuzimab
- Vorinostat/Panobinostat (HDAC)



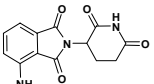
### Molecular Structure of Thalidomide, Lenalidomide and Pomalidomide



**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


### Response Rates

Confirmed Response Rate (≥PR)		26%
Best Response		
VGPR	5 (14%)	} 54%
PR	6 (17%)	
MR	8 (23%)	
SD	11 (31%)	
PD	2 (6%)	
NE	3 (9%)	

### Elotuzumab

Elotuzumab + Lenalidomide + Low-Dose Dexamethasone in Multiple Myeloma, Phase 1/2

- Humanized monoclonal IgG1 antibody targeting human CS1, a cell surface glycoprotein<sup>1,2</sup>
- CS1: highly and uniformly expressed on MM cells, restricted expression on NK cells, little to no expression on normal tissues<sup>1-3</sup>
- Preclinical data indicate MOA is mainly through NK-mediated ADCC<sup>1,2</sup>
- Elotuzumab monotherapy exhibited a manageable safety profile and SD in a number of patients with advanced MM<sup>4</sup>
  - ▶ Key toxicities included infusion reactions such as chills, pyrexia, headache, flushing, nausea, and vomiting
- 20/20 MM bone marrow cores and 8/8 plasmacytomas were positive for CS1 expression<sup>1</sup>



ADCC, antibody-dependent cellular cytotoxicity; MM, multiple myeloma; MOA, mechanism of action; NK, natural killer; SD, stable disease.  
<sup>1</sup>Hsi ED et al. Clin Cancer Res. 2008;14:2775-2784; <sup>2</sup>Tal YT et al. Blood. 2008;112:1329-1337; <sup>3</sup>van Rhee F et al. Mol Cancer Ther. 2009;8:2616-2624; <sup>4</sup>Zonder JA et al. Blood. 2008;112:2773.

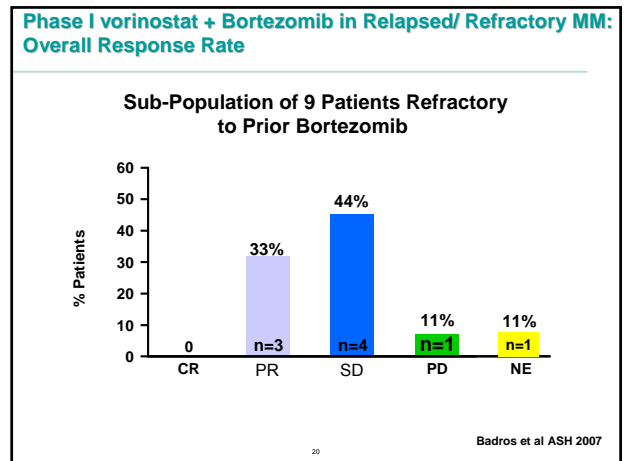
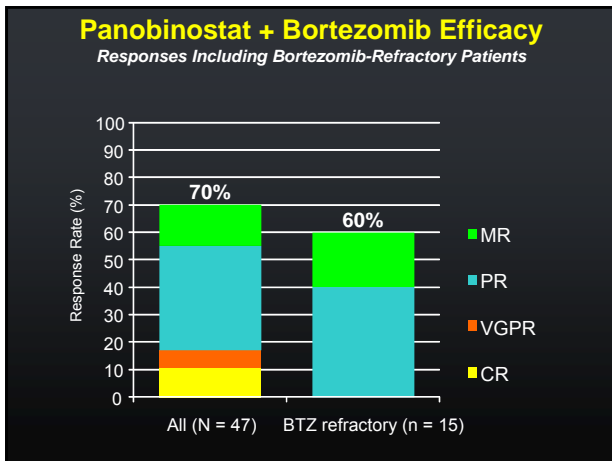
### Phase 1b: Efficacy

Elotuzumab + Lenalidomide + Low-Dose Dexamethasone in Multiple Myeloma, Phase 1/2

**Best Confirmed Response (IMWG Criteria)**

	Total Patients (%)	Lenalidomide-Naïve Patients (%)
Total ITT population	28	22
ORR (≥ PR)	23 (82)	21 (95)
CR	1 (4)	1 (5)
VGPR	7 (25)	6 (27)
PR	15 (54)	14 (64)
SD	4 (14)	1 (5)
PD	1 (4)	0

OR, complete response; IMWG, International Myeloma Working Group; ITT, intent-to-treat; ORR, objective response rate; PD, progressive disease; PR, partial response; VGPR, very good partial response.



**Relapse is the Next Step in Your Ongoing Care**

**Time is Your Friend**

### Conclusions

Best new treatment will emerge in relapse setting.

Need better criteria

- To identify new active drugs
- Obtain rapid approval
- Proceed with search for cure with better "tool bag"

### Long Survival???

YES!!

But cure- not yet...

...BUT, we may be one great drug away!!!

