

Key Questions in Myeloma Research



Brian G.M. Durie
Cedars-Sinai Samuel
Oschin Cancer
Center- Los Angeles,
CA, USA

Vienna
October 15, 2010



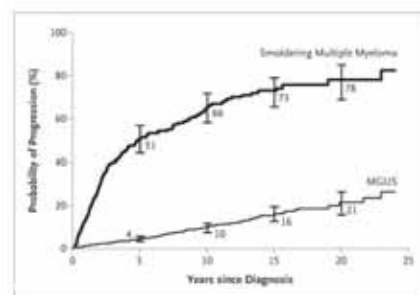
6 Key Questions

- Should we treat high risk smoldering MM?
- What depth of response is needed?
- Which treatments are best in 2010?
- Does higher risk make a difference?
- Is consolidation/maintenance required?
- Which new drugs are promising?

Should High Risk SMM Be Treated?

- Current criteria identify:
50% progression in 2 years
- Early use of Rev/Dex promising

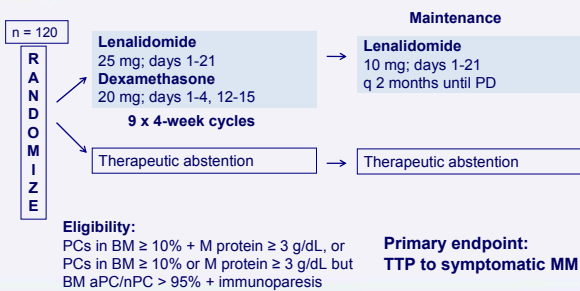
Probability of Progression to Active Multiple Myeloma or Primary Amyloidosis in Patients With Smoldering Multiple Myeloma or Monoclonal Gammopathy of Undetermined Significance (MGUS)



Kyle RA, et al. N Engl J Med. 2007;356:2582-2590.



Lenalidomide Plus Dexamethasone in High-Risk Smoldering MM



Mateos et al. ASH 2009; abstract 614.

Lenalidomide Plus Dexamethasone in High-Risk SMM

Response	Lenalidomide/Dexamethasone Arm	
	Intent-to-Treat (n = 40)	Pts With 9 Cycles (n = 23)
Median # cycles	4 (range, 1-9)	NA
ORR	81%	91%
sCR/CR	3%/11%	4%/17%
\geq VGPR	30%	38%

	Len/Dex Arm	Abstinence Arm
TTP, median (n = 94)*	Not reached	19.3 months [†]
OS, 2-year rate (n = 94)*	100%	96%

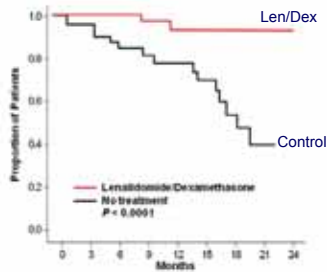
* Median follow-up 14 months

[†] P < .0001

Mateos et al. ASH 2009; abstract 614.

PFS: Len/Dex vs. Control

Control Median PFS 19.3 Months



Mateos ASH 2009

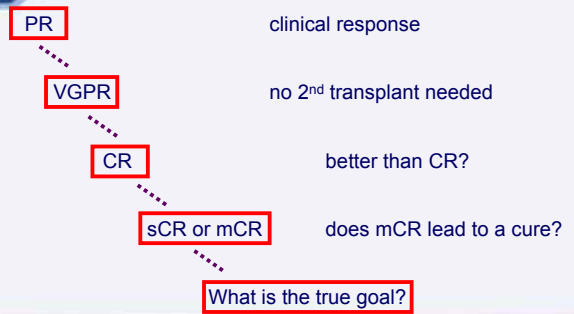
What's Needed Now?

- Criteria predicting:
 - 90% progression in 2 years
- Studies of several types of treatments
 - REV
 - REV/DEX
 - VRD to increase VGPR/CR rate?
 - What other options?

Concerns

- Early response will not translate into survival benefit
- Drug resistance could emerge
- Simple treatment may be insufficient for high risk disease

What depth of response is required?



Fundamental philosophies

CURE

- Use all available options early

or

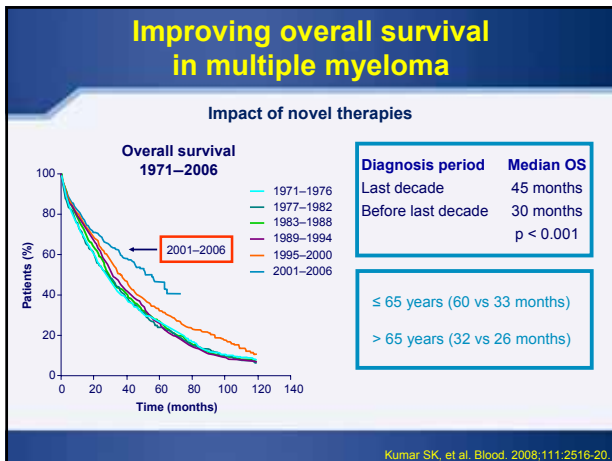
- Use treatments sequentially over time

CHRONIC CONTROL

Control With Chronic Trimming...



Early resistance does not occur



Overall survival as an end-point

Best new early Target

→ Early Response in ≥ 90%

“If you’re not alive early, you won’t be alive later.”

... Reduce early toxicities

Crucial Follow Up Target

→ Longest Survival with best QOL

“If you’re alive later, would you have been alive anyway with less or different treatment?”

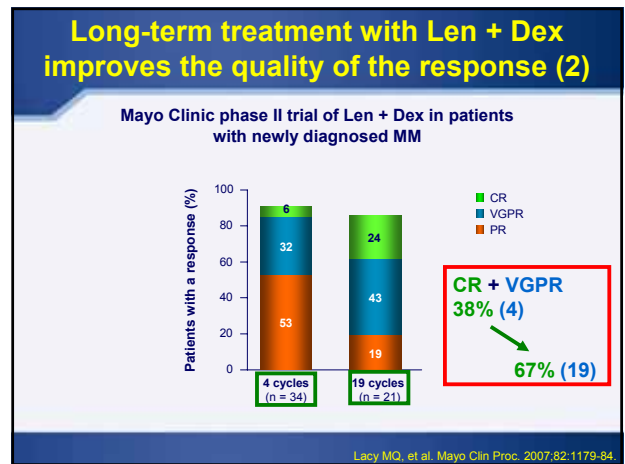
... Study long survivors

Assessment of early overall survival

- 1-Year survival now steadily improving

– ECOG	Thal + Dex	80–83%
– Palumbo	MPT	87%
– IFM	ASCT	88%
– ECOG	RD	88%
– San Miguel	VMP (VISTA)	90%
– Barlogie	TT2	92%
– ECOG	Rd	96%
– Richardson	VRD	97%

Barlogie B, et al. N Engl J Med. 2006;354:1021-30; Facon T, et al. Lancet. 2007;370:1209-18; Palumbo A, et al. Lancet. 2006;367:825-31; Rajkumar SV, et al. J Clin Oncol. 2006;24:431-8; Rajkumar SV, et al. J Clin Oncol. 2008;26:2117-7; Rajkumar SV, et al. Presented at ASH/ASCO symposium, ASH 2008; San Miguel JF, et al. N Engl J Med. 2008;359:906-17.

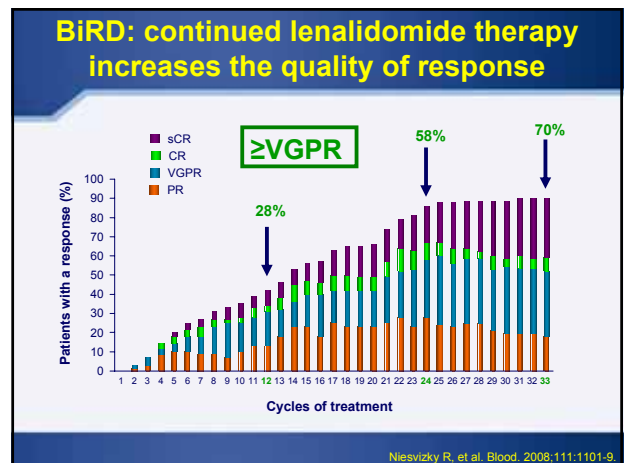


ECOG-E4A03: quality of response improves with continued treatment

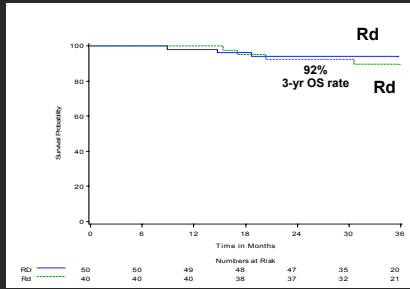
ECOG-E4A03: phase III trial of Len + standard-dose versus low-dose Dex

	Response in 4 cycles, %	Best overall response, %
RD		
Response (≥ PR)	79	81
≥ VGPR within 4 cycles	42	51
CR (IF ⁻)	4	17
Rd		
Response (≥ PR)	68	70
≥ VGPR	24	40
CR (IF ⁻)	2	14

Rd = lenalidomide + low-dose dexamethasone; RD = lenalidomide + standard-dose dexamethasone. Presented at ASH/ASCO symposium, ASH 2008. Rajkumar SV, et al.



Lenalidomide + high (RD) vs. low-dose dex (Rd)
Phase III ECOG trial : OS: Transplant following 4 cycles of RD/Rd

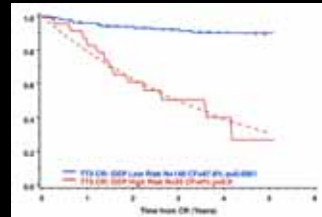


Rajkumar et al Lancet Oncology 2010; 11: 29-37

Total Therapy: towards the cure

All active treatment tools through induction, consolidation & maintenance

Total Therapy 3 (303 pts) : VTD-PACE (x2)→ASCT (x2)→VTD-PACE (x2)→VTD (monthly during 1 y)→TD (2 y)



TT3
 Low Risk [Blue]
 High Risk [Red]

Nair B. Blood 2010

Key Point

Improving
 &
 Sustaining
 Response

...Over Time
 (e.g. ≥ 2 years)

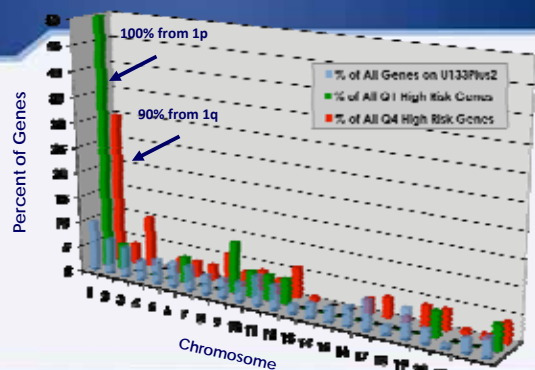
Best Treatment in 2010

	Transplant or Not	Non-Transplant Only
2 Drug	TD VD Rd	MP
3 Drug	VTD VRD VCD CTD BIRD	MPT VMP MPR...
4 Drug	VCRD (Evolution) VCTD.....Total Rx	VMPT...

Does higher risk make a difference?

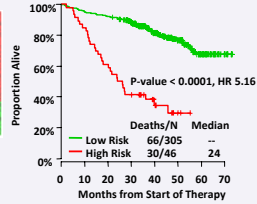
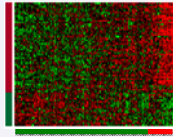
- YES
 - T(4;14) improved with V and maybe R
 - 17p- still poor risk
- What about GEP?

70-Genes Model Driven by Chr 1 Genes



GEP70-Gene Model Defines High Risk in ~20% of Newly Diagnosed MM

GEP70-Gene Model



Validations

Chng et al., *Leukemia*, 2008
Zhan et al., *Blood*, 2008
Decaux et al., *JCO*, 2008
Nair et al., *Blood*, 2009
Dickens et al., *Clin Can Res*, 2010
Hose et al., submitted, 2010

Shaughnessy et al., *Blood*, 2007

What about GEP?

- Within ~ 20% "high risk" patients

Only 70% are truly high risk

- Thus can highly aggressive treatment be justified?
- GEP "not ready for prime time"

Continue to stratify by risk

What about consolidation and maintenance?

- Results with consolidation promising
 - e.g. IFM Revlimid post-transplant
- Revlimid maintenance also very promising
 - IFM (Attal)
 - CALGB (McCarthy)
 - MPR-R (Palumbo)

New Post-Transplant Data: ASCO 2010

- **IFM**
 - 614 patients
 - Age <65; ≤6 months post-ASCT
 - Revlimid® 10-15mg QD or placebo
 - 3 year PFS 68% vs. 35%
 - 3 year OS 88% vs. 80%
- **CALGB**
 - 418 patients
 - Age <70; ≤1 year from diagnosis
 - Revlimid® 10-15mg daily or placebo
 - Events 29/210 vs. 58/208
 - TTP 25 months for placebo; deaths 11/17 so far

ASCO 2010: Attal et al., (#8018); McCarthy et al., (#8017)

Assessing New Drugs 2010

- **Most Promising**
 - Carfilzomib
 - Pomalidomide
 - Elotuzimab...
- **How to show benefit?**
 - Unmet need in relapse/refractory patients
 - Need benchmark comparison or randomized trial

New Protocols

- Carfilzomib + Pomalidomide
- Elotuzimab + Revlimid

IMWG Benchmark Analysis 2009/2010 Relapse/Refractory Myeloma

Natural History of Multiple Myeloma Relapsing After Therapy with IMiDs and Bortezomib: A Multicenter International Myeloma Working Group Study

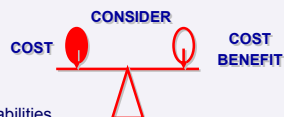
Shaji Kumar, Joan Blade, John Crowley, Hartmut Goldschmidt, Antje Hoering, Sundar Jagannath, Juan Lahuerta, Jacob Laubach, Philippe Moreau, Gareth Morgan, Robert Oriowski, Antonio Palumbo, Paul Richardson, Jesus San Miguel, Orhan Sezer, David Siegel, Pieter Sonneveld, Jackie Szymonifka, S. Vincent Rajkumar, Brian G.M. Durie

ASH 2009 Abstract



Innovation in Challenging Times

- Many new drug targets are available
- Investment in research and drug development is crucial
 - Improved quality of life
 - Extended survival
 - Increased productivity
 - Reduced hospitalization/disabilities



Lesson: Improved outcomes are key.

What To Expect 2010-2015??

- **New Novel Agents Available**
 - Revlimid 2010
 - Carfilzomib 2012?
 - Pomalidomide 2012?
- **New Drugs/Targets**
 - Elotuzimab
 - Vorinostat (other HDAC)
 - Other...

