Role of Stem Cell Transplantation in Multiple Myeloma: The Changing Landscape

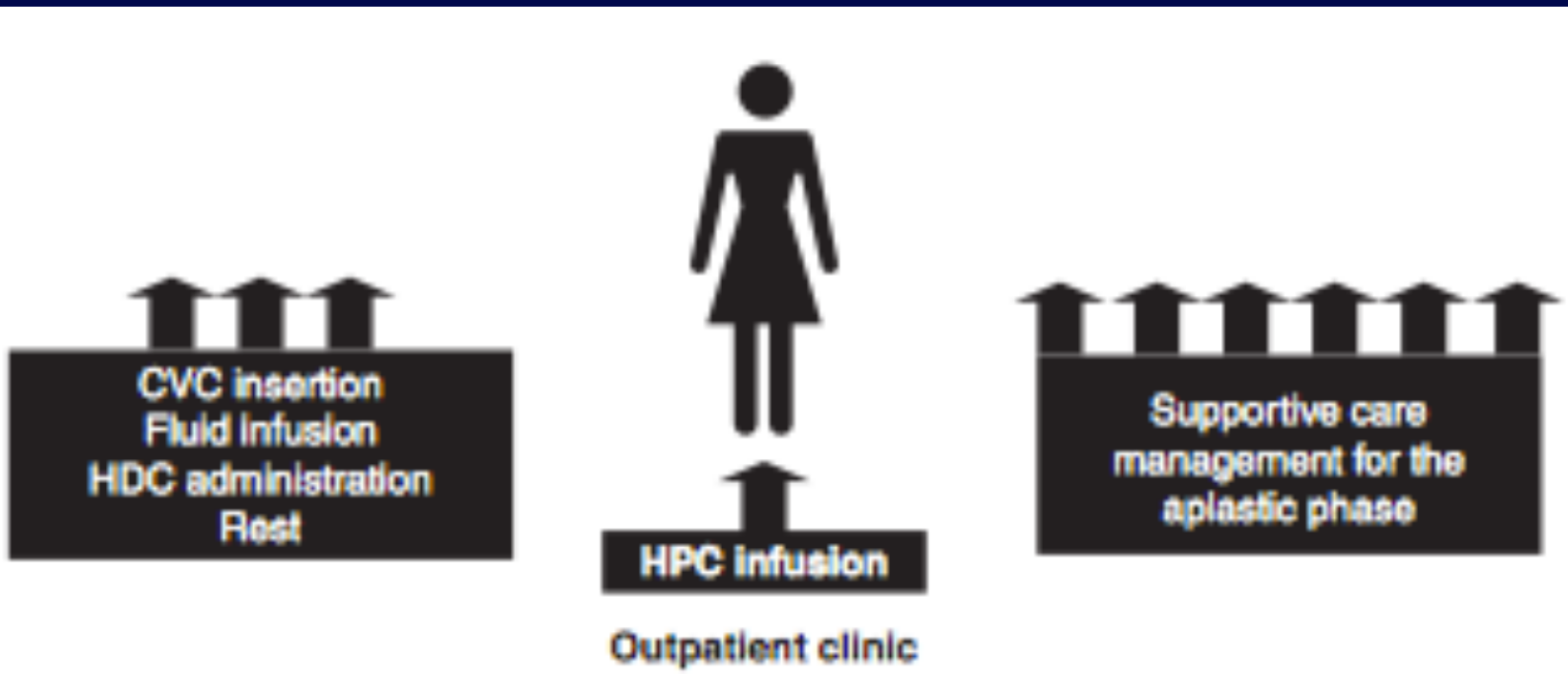
Simrit Parmar, MD
MDACC
Houston, TX, USA

Why Transplant in the Era of Novel Therapy?

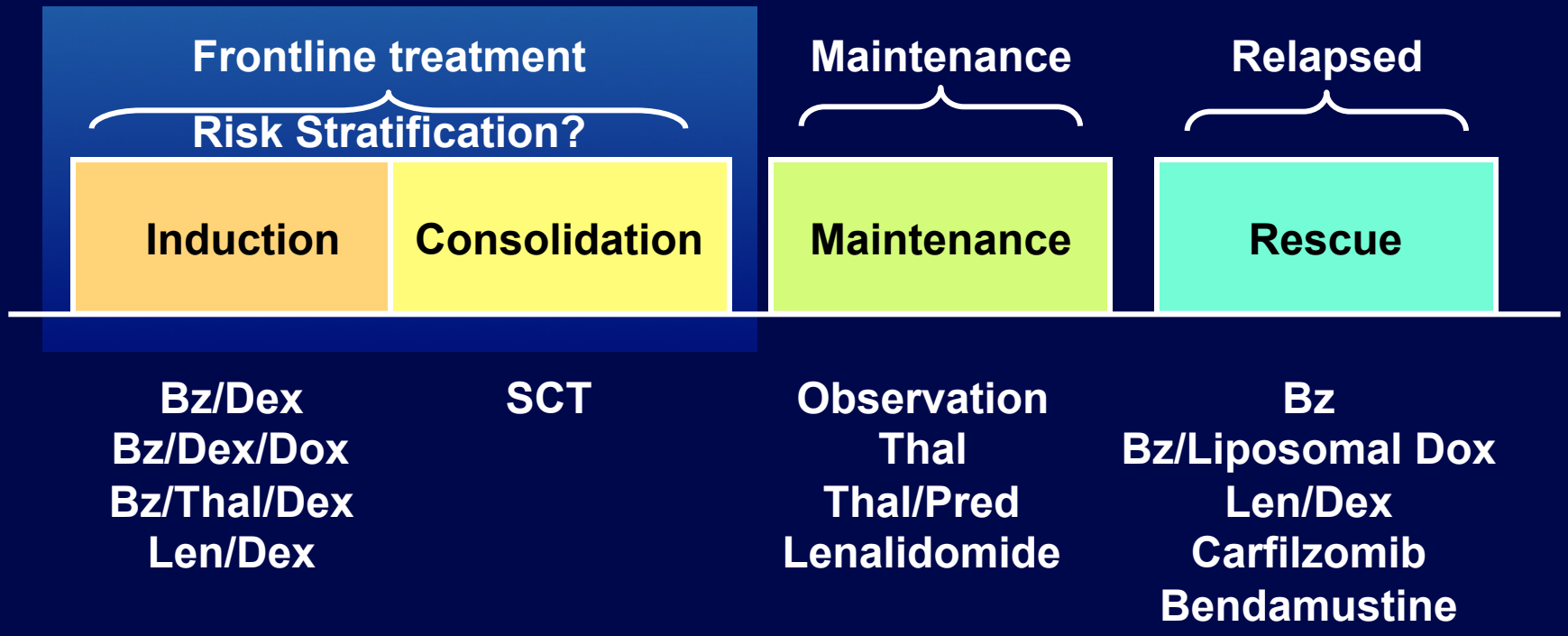
- Safe (TRM <2%)
- Highest CR rates before novel agents
- Higher CR rates when used in combination with novel agents
- Mature data on the durability of response
- Longer PFS and better QOL in patients receiving Auto HCT early
- Comparable cumulative cost

	G-CSF Mob. + ASCT	Revlimid +Velcade +Dex (6 cycles)	Velcade + Dex (6 cycles)
Cost	155K	150K	126K

AutoSCT in Outpatient Setting

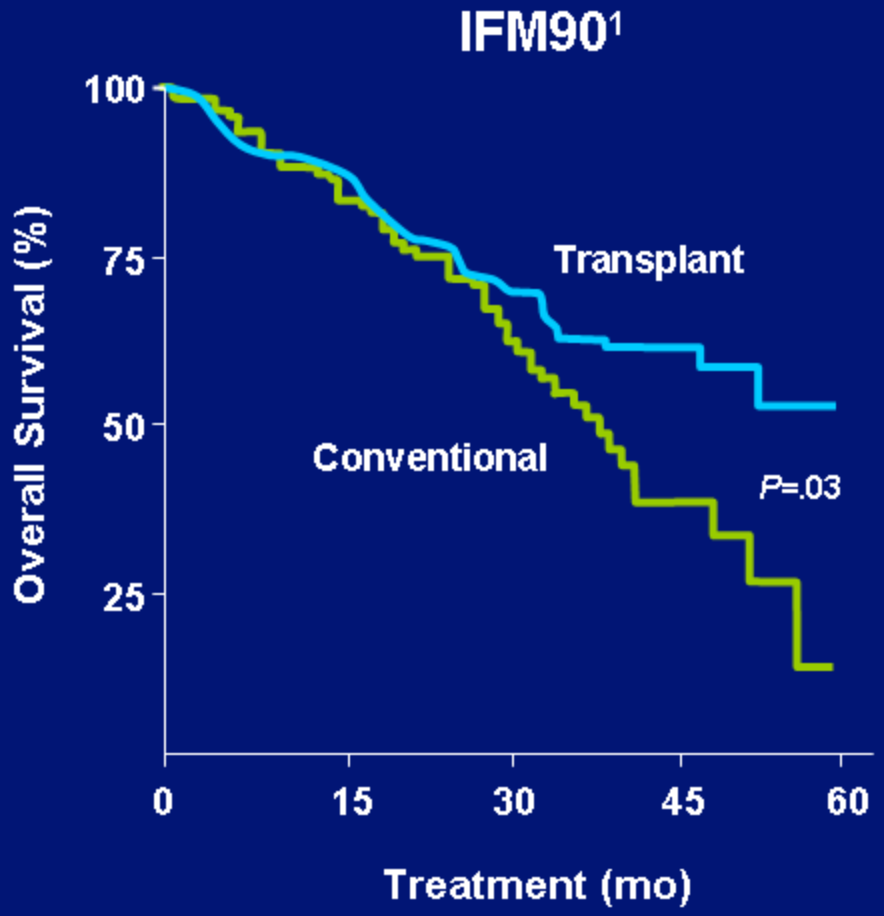


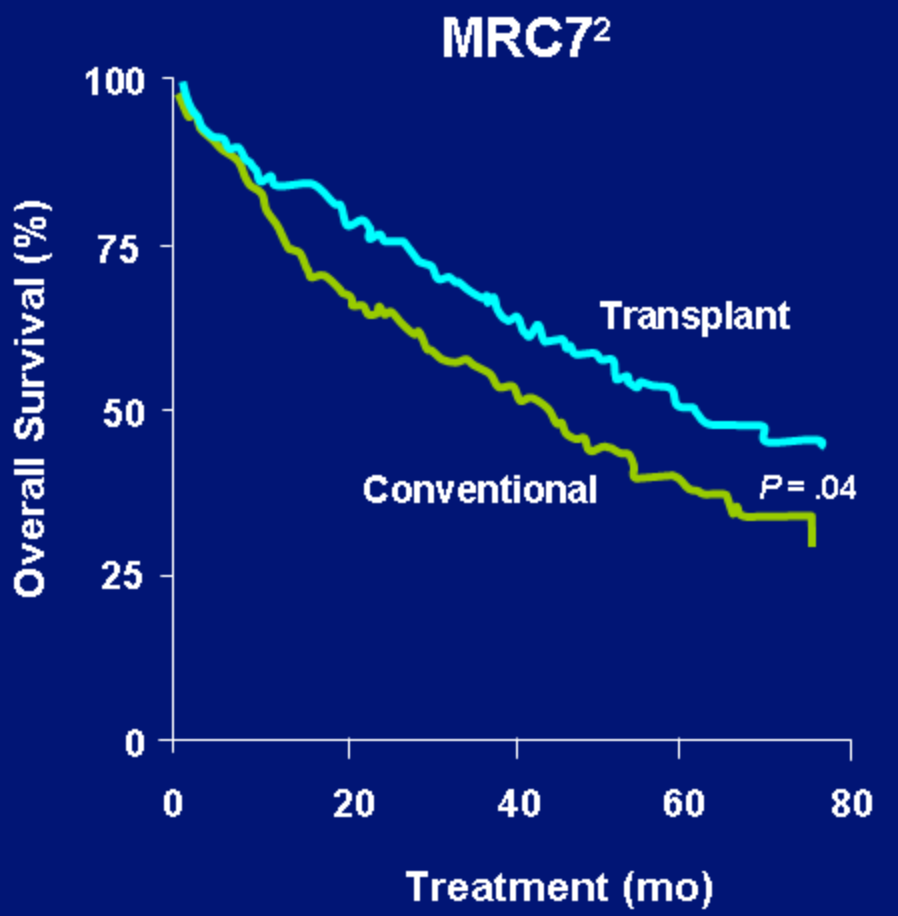
Multiple Myeloma Treatment Lines in Transplant-Eligible Patients
Current Paradigm



National Comprehensive Cancer Network. The NCCN Clinical Practice Guidelines in Oncology Multiple Myeloma (Version 1.2011). http://www.nccn.org/. Accessed October 13, 2010.

Early Myeloablative Therapy in Autologous BM Transplant Patients





1. Adapted with permission from Attal M et al. *N Engl J Med*. 1996;335:91
2. Adapted with permission from Child JA et al. *N Engl J Med*. 2003;348:1875

THE TRANSPLANT QUESTIONS FOR 2012

- Focusing on reducing burden of treatment
  - Does everybody need triple therapy induction?
    - Would a doublet (Rd or Vd) be sufficient for standard risk disease?
    - Is VRD the new standard?
      - No randomized trial data available
  - Optimal duration of induction?
    - 2 cycles vs 4 cycles vs “best response”?
- Define Timing of SCT
  - Is SCT optional for patients achieving a CR?
  - Should salvage SCT be offered to all relapsing patients SCT naïve or not?
- Focusing on improving therapy
  - Incorporating new agents into conditioning regimens
  - Reducing morbidity
  - Preventing relapse: Maintenance Therapy

Tumor Burden Reduction

- **CR or VGPR has emerged as the most important factor associated with a prolonged progression- free survival (PFS) and overall survival (OS)**

- **The sensitivity to the initial chemotherapy, measured by the M-protein reduction at the time of transplantation, is the most important predictor of residual disease after ASCT**

Lahuerta ,JCO 2008

Luskin et al 4134

- VRD → AutoSCT
- At 100 days post-ASCT, 33% showed improvement in disease response.
- PFS at 12 months post-ASCT is 85%

Randomized Phase III HOVON-65/ GMMG-HD4 Trial

	VAD (%) N=414	PAD (%) N=413	p-value
Complete Response	2	7	<0.001
≥ nCR	5	11	<0.001
≥ VGPR	14	42	<0.001
≥ PR	54	78	<0.001
After HDM			
Complete Response	9	21	<0.001
≥ nCR	**15**	**31**	<0.001
≥ VGPR	36	62	<0.001
≥ PR	75	88	<0.001

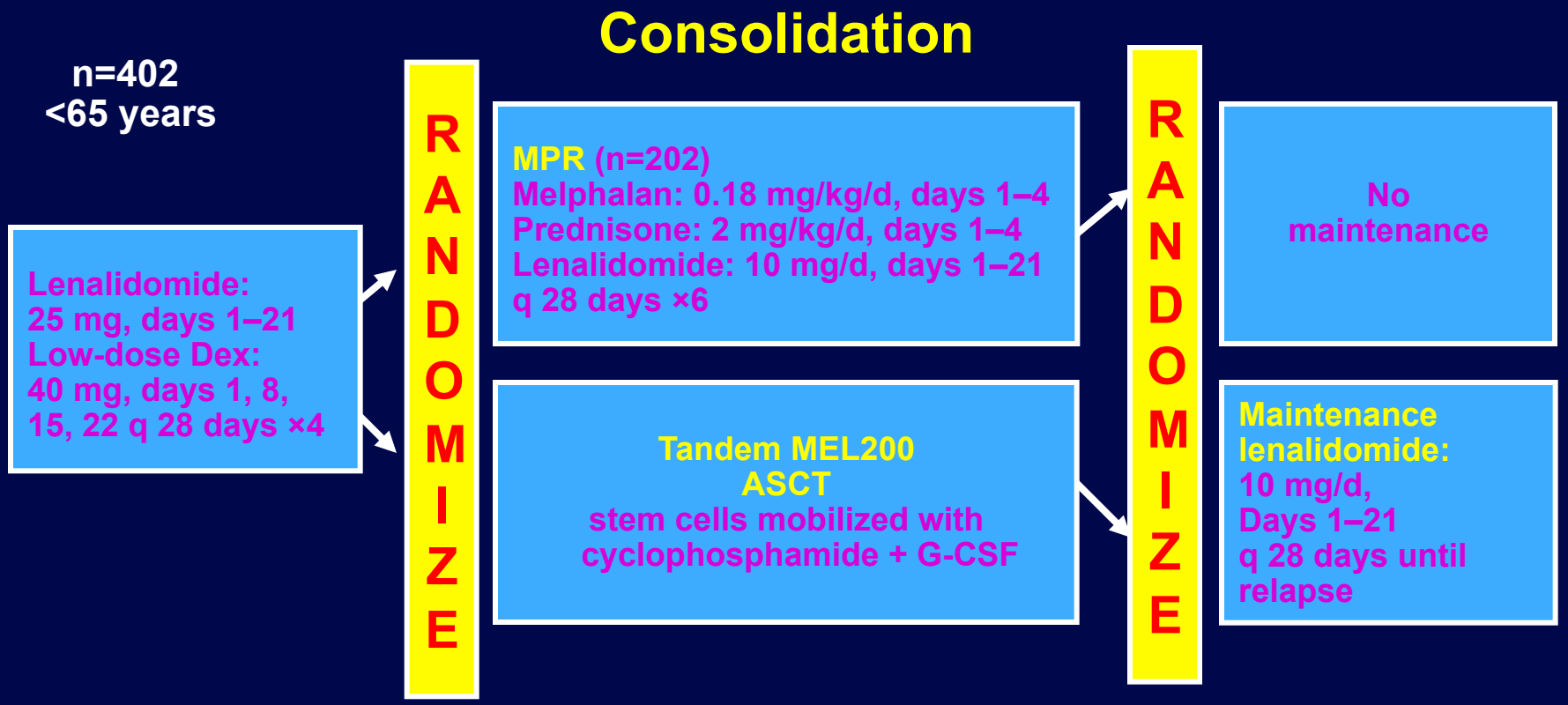
Sonneveld, JCO2012

Phase 3 PETHEMA/GEM study

	VTD (n=130)	TD (n=127)	VBMCP/ VBAD/B (n=129)
CR	35%	14%	21%
PFS	56.2 mos	28.2 mos	35.5 mos
After HDM			
CR	46%	24%	38%

Rosinol, Blood 2012

Melphalan/Prednisone/Lenalidomide (MPR) vs MEL200/ASCT Following Lenalidomide/ Dexamethasone (Ld) Induction



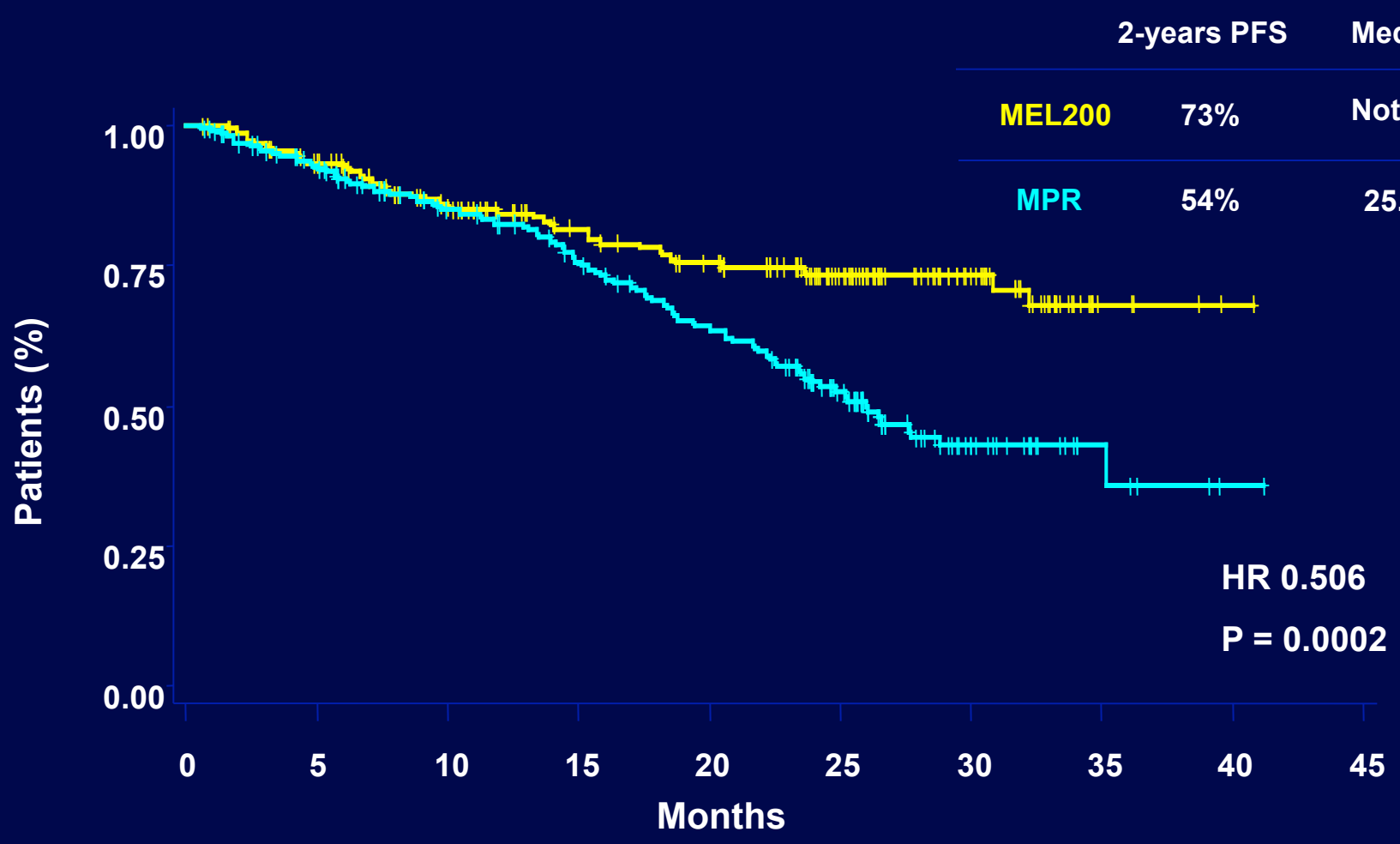
Primary end point: PFS

Palumbo A et al. *Blood*. 2009;114:Abstract 350.

Progression Free Survival

49.4% Reduced Risk of Progression

Median follow-up 26 months

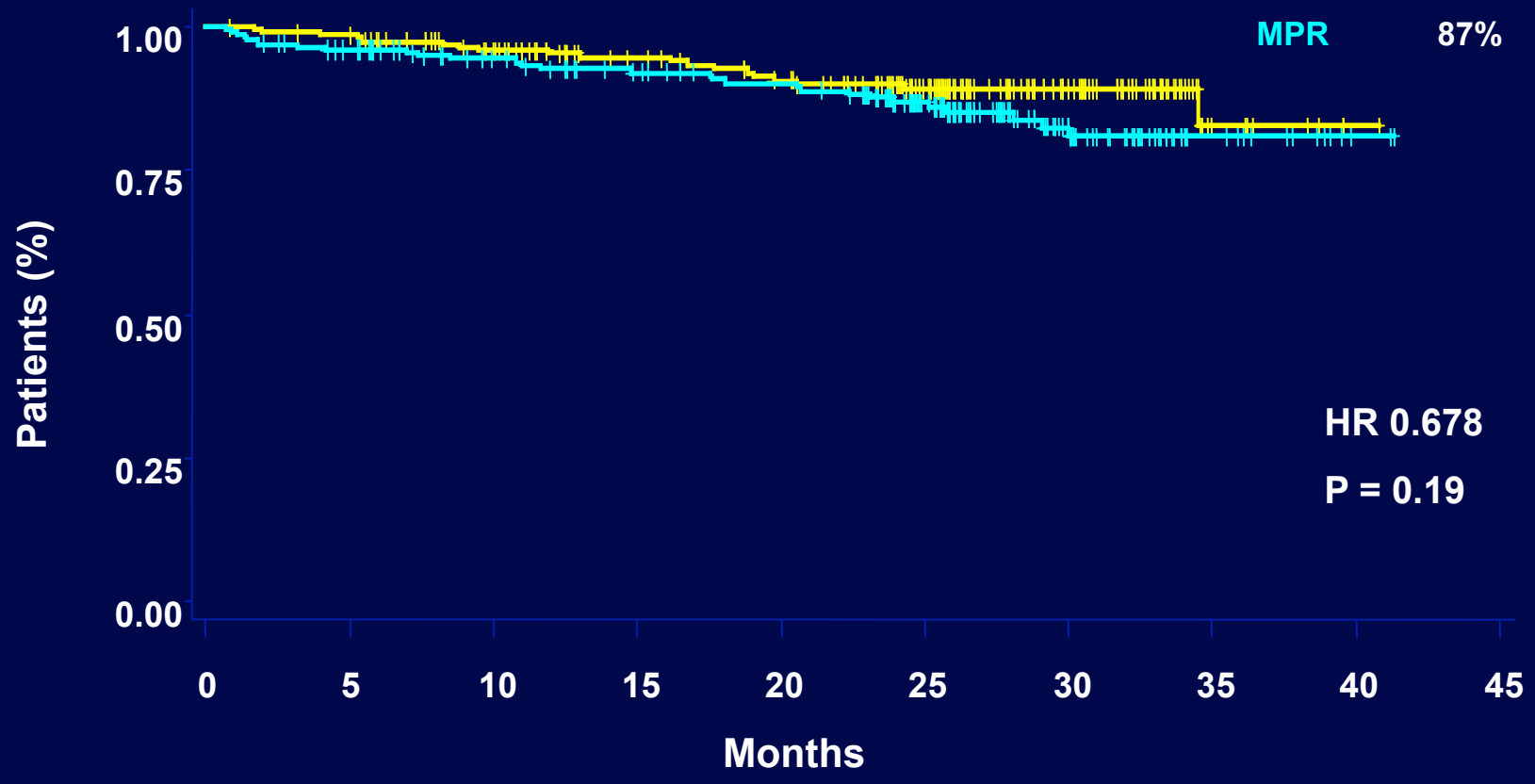


MPR, melphalan-prednisone-lenalidomide; MEL200, melphalan 200 mg/m^2; PFS, progression free survival; HR, hazard ratio; mos, months

Overall Survival

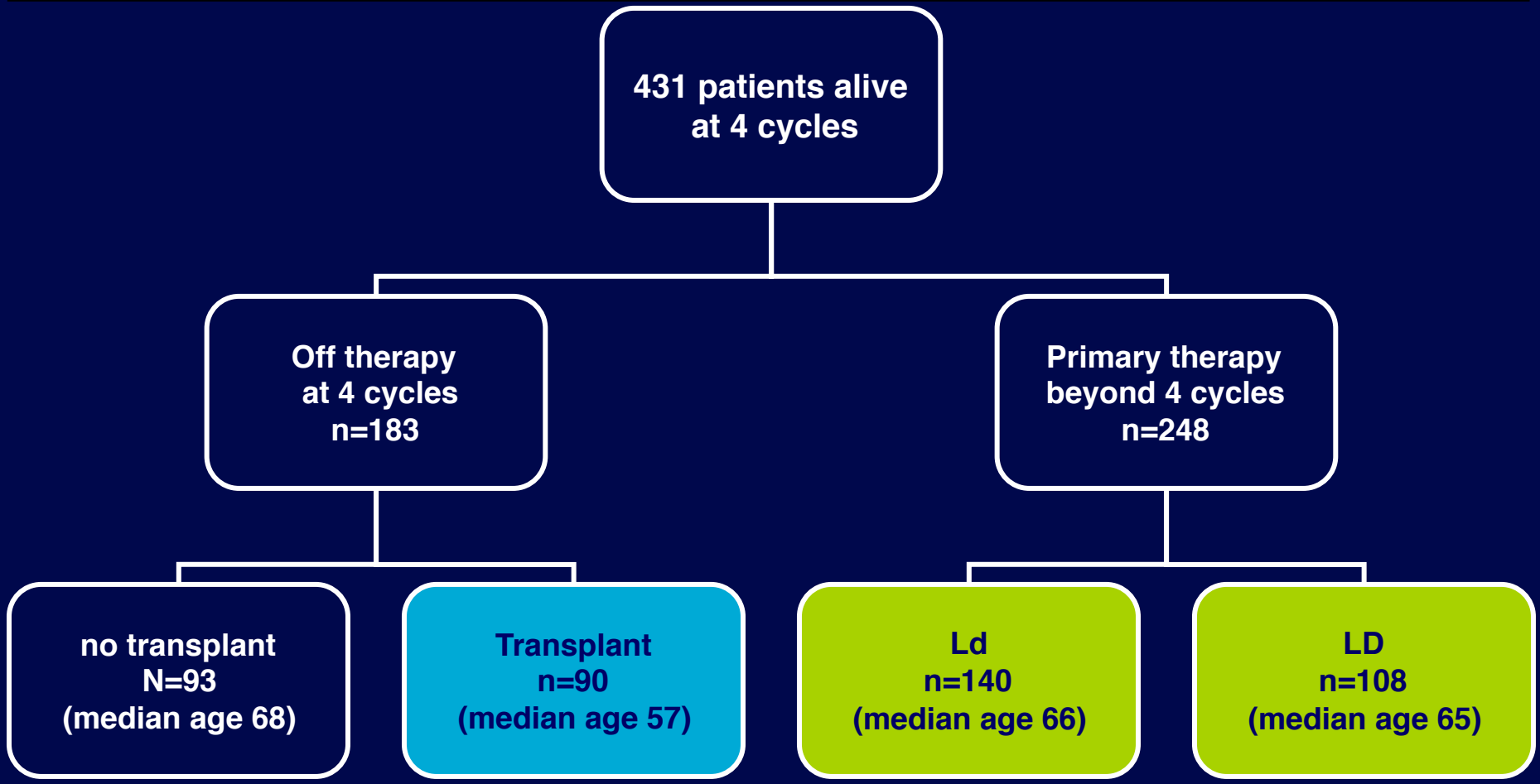
Median follow-up 26 months

	2-years OS
MEL200	90%
MPR	87%



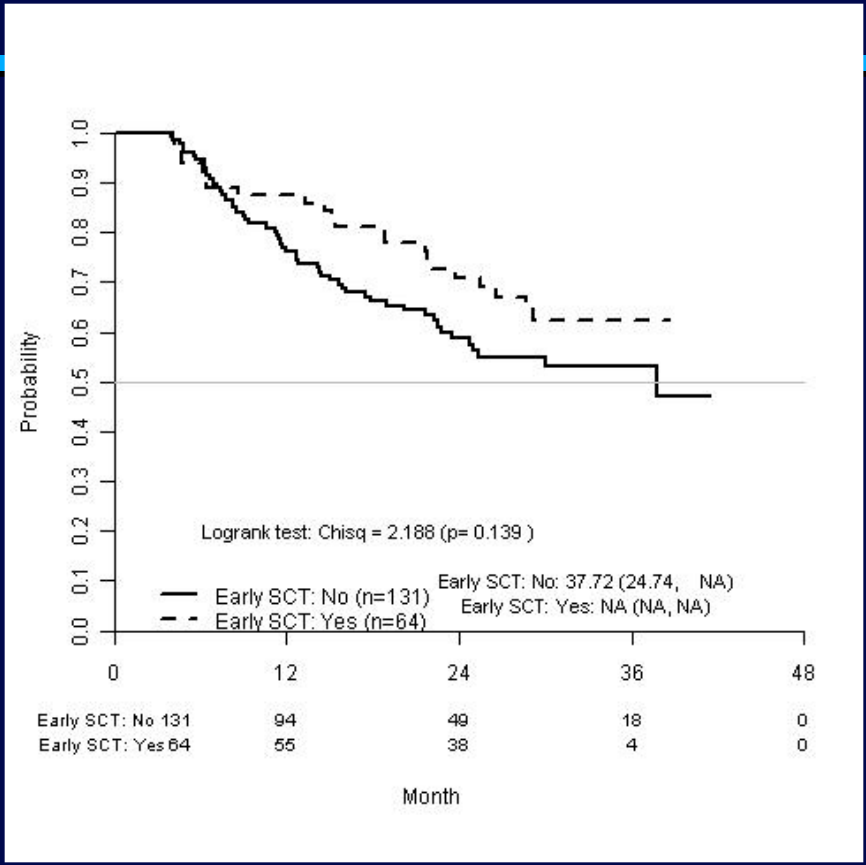
MPR, melphalan-prednisone-lenalidomide; MEL200, melphalan 200 mg/m^2; OS, overall survival; HR, hazard ratio

E4A03: Landmark Analysis at Median Follow-up of 36 mo

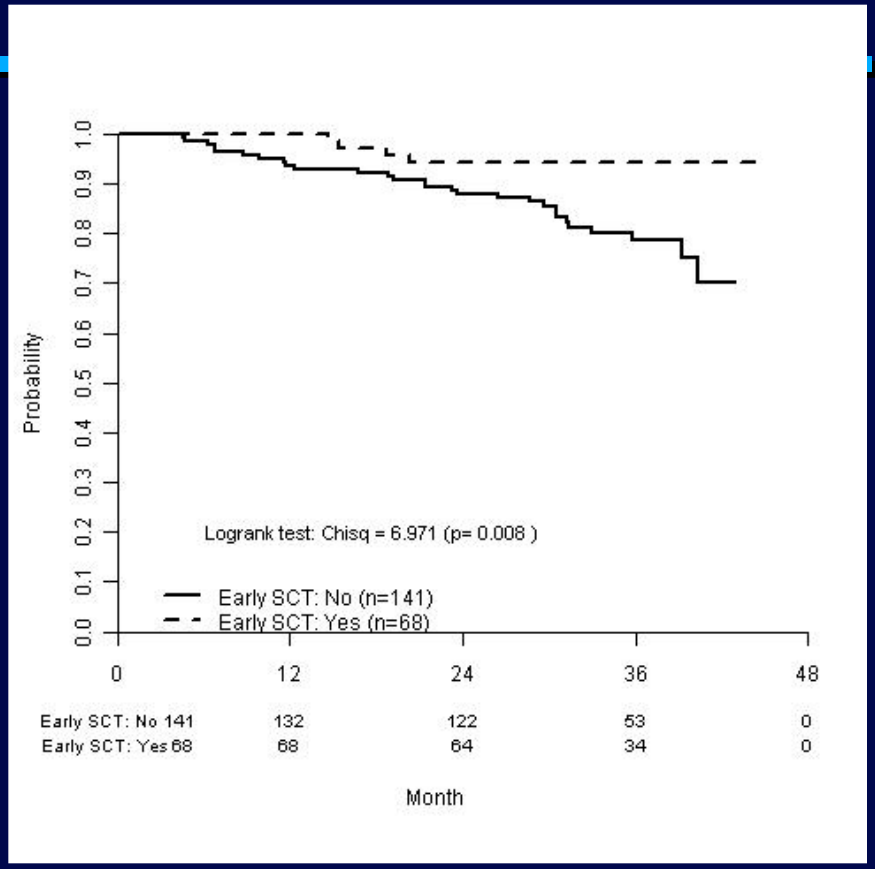


Rajkumar SV et al. The Lancet Oncology, Volume 11, Issue 1, Pages 29 - 37, January 2010

Outcomes in pts Age <65



Progression Free Survival



Overall Survival

Summary: Coventional Chemotherapy vs. Single Auto HCT

- OS benefit in at least 2 large, randomized trials
- Novel agents (lenalidomide, bortezomib) are not curative
- RCT incorporating the novel agents (VTD) as induction and/or consolidation with auto HCT are showing significant improvement in outcome (Harousseau et al. JCO 2010; Cavo et al. Lancet 2010)
- NCCN: Category 1 evidence supports proceeding straight to auto HCT after induction therapy

Thal Dex Maintenance: Brazilian Multiple Myeloma Study Group (BMMSG/GEMOH)

- VAD induction → MEL200 ASCT
- Randomize to Dex (n=52) or Thal/dex (n=56; 200 mg daily) for 12 mos or until ds progression
- Median follow-up 27 months
- ITT analysis; 2-year PFS of 30% vs. 64% (p= 0.002),
- In patients <VGPR, the 2-yr PFS 19% vs. 59% (P= 0.002)
- OS 70% vs. 85% (p=0.27)

Mailono , AJH 2012

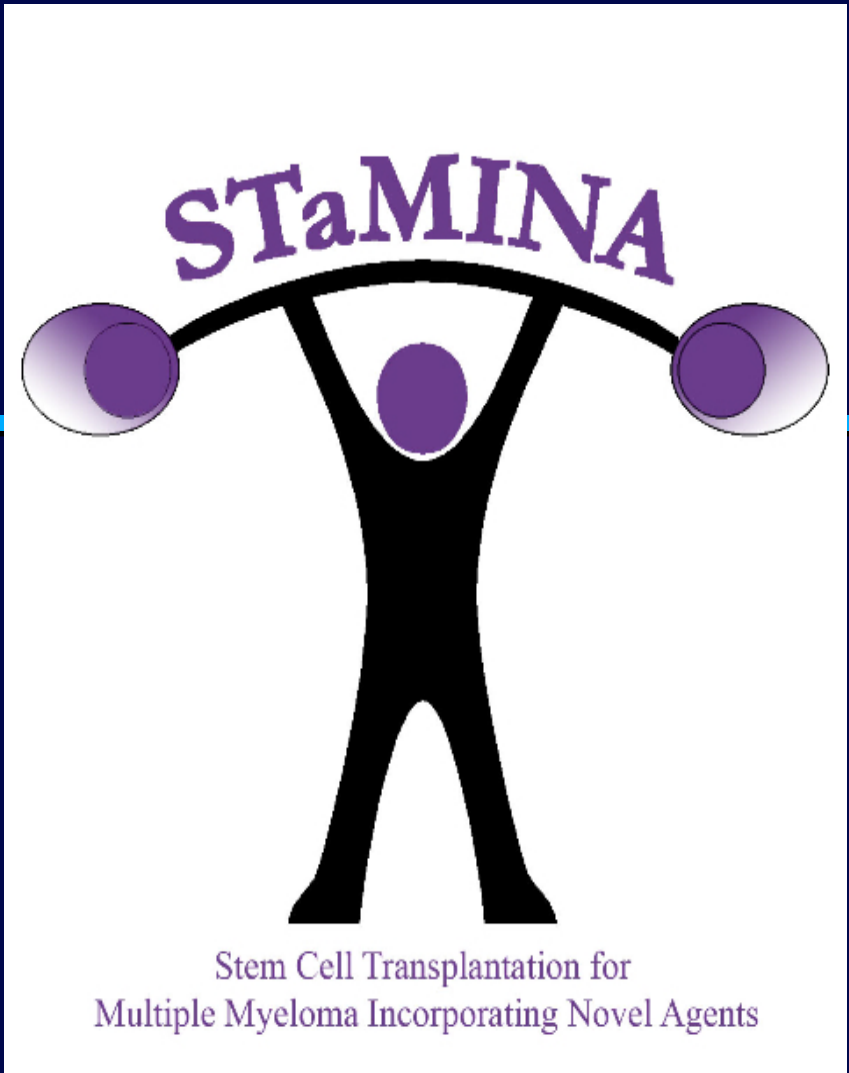
Role of Consolidation Therapy Hypothesis

Incorporation of new agents as post transplant consolidation will improve EFS

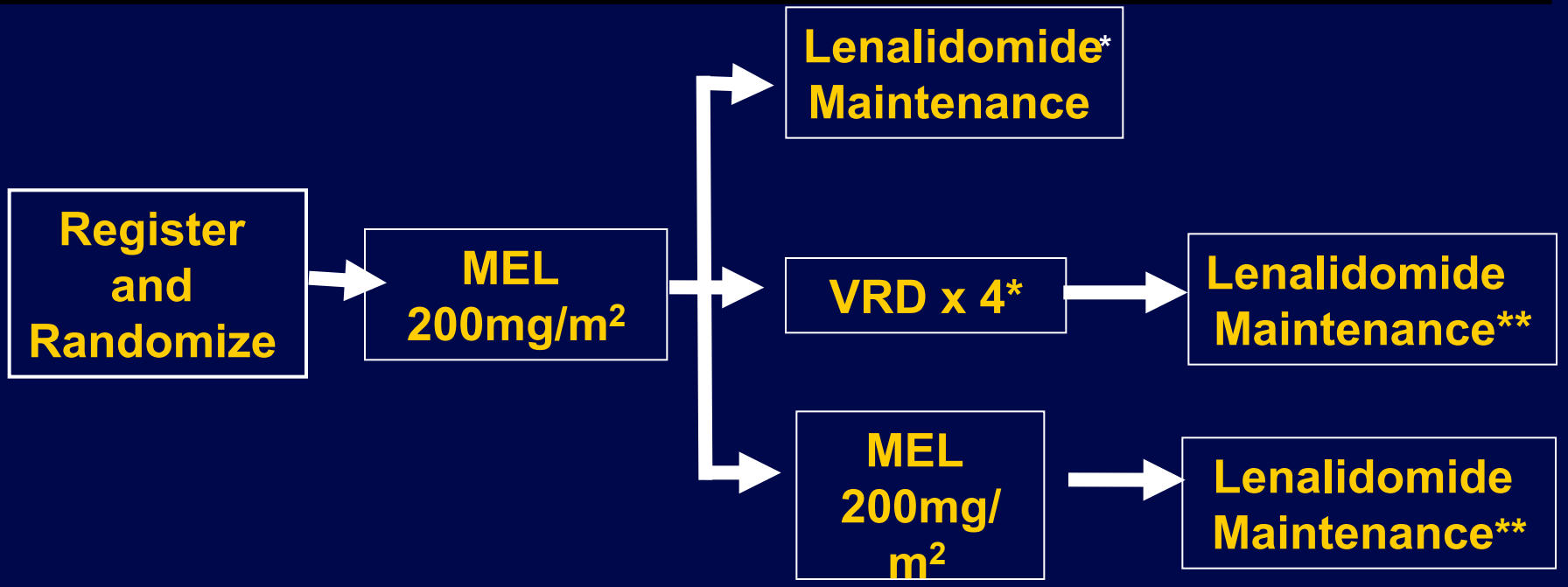
compared to

consolidation with second autologous HCT.

BMT CTN 0702
A Trial of Single Autologous Transplant with or without RVD Consolidation versus Tandem Transplant and Maintenance Therapy.



BMT CTN 0702: SCHEMA



* Bortezomib 1.3mg /m2 days 1, 4, 8,11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg days 1, 8, 15

**Lenalidomide 15 mg daily x 3years

STaMINA

Summary

- High dose melphalan with autologous stem cell support remains the standard of care for consolidation therapy for patients with chemosensitive disease
- Current therapy with high dose melphalan followed by maintenance therapy results in more than 70% major responses and median remission durations of around 3.5-4 years.
- Moving forward minimizing toxicities, developing more effective conditioning regimens and better risk stratification will allow us to provide each patient with the best chance of a long life with myeloma control, good quality of life with the least treatment burden

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Qaiser Bashir
Sairah Ahmed
APN's PharmD.
Research Nurses,
Data Managers, Fellows

Department of Lymphoma/Myeloma

Larry Kwak
Donna Weber
Michael Wang
Robert Orlowski
Raymond Alexanian
Sheeba Thomas
Jatin Shah

Symptom Research

Charles Cleeland
Shelley Wang
Lori Williams
Yvonne Dinh
Gabriela Rondon

We Thank
Our Patients and their Families