Optimal Management of Newly Diagnosed Transplant Eligible Multiple Myeloma

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Multiple Myeloma(MM): Not One Disease

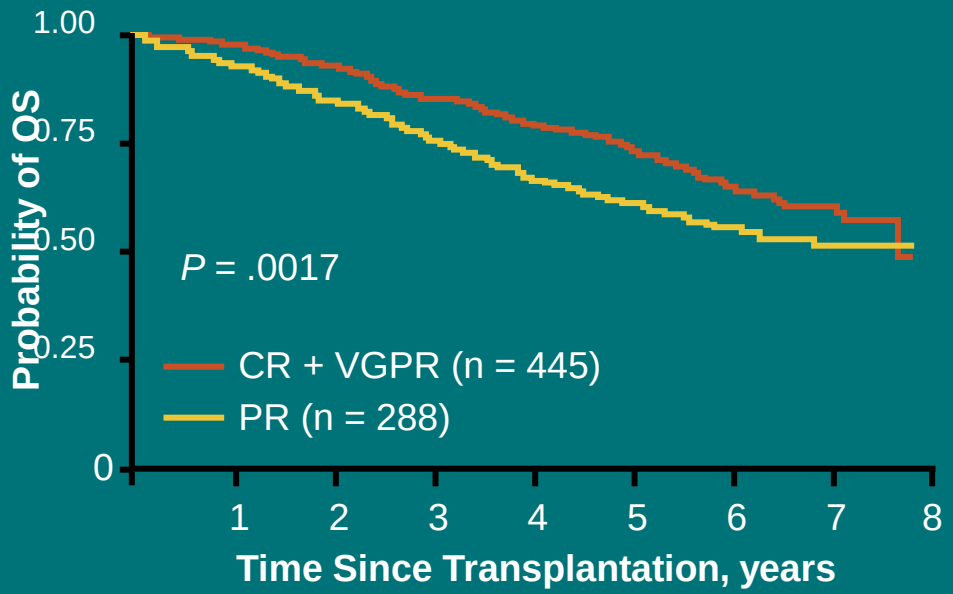
- MGUS to Active MM transition period is different among patients.
- Diagnosis is made at variable time-points during the transition, so degree of end organ damage is different.
- Management strategies are focusing on changing myeloma in to a chronic illness for majority of patients, probably curative for a subset. [Martinez-Lopez J et al Blood 2011;Usmani et al Leukemia 2012
- Good and standard risk patients make up ~80%, benefiting most from strategy combining novel agents and high dose melphalan/stem cell rescue. [Chng et al Leukemia 2013]

Goals of Induction Therapy

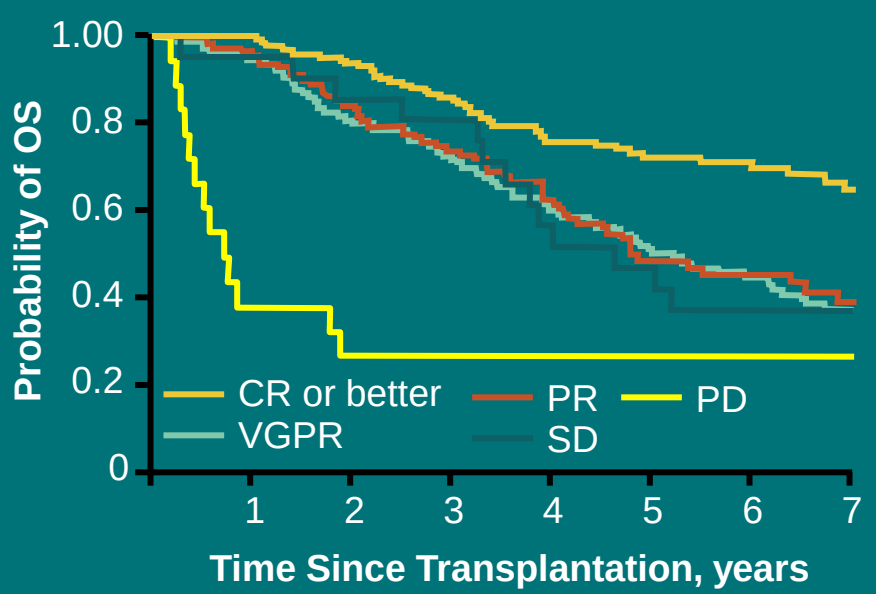
- High response rate; rapid response
- Improve performance status
- Minimize negative effect on QoL
- Not limit PBSC mobilization
- Achieving maximal response
  - > VGPR > CR > sCR > ?? MRD-ve
    - MRD Assessment requires optimization and not ready for prime time

Achieving ≥ VGPR/CR = Better Outcomes

Achieving ≥ VGPR[1]

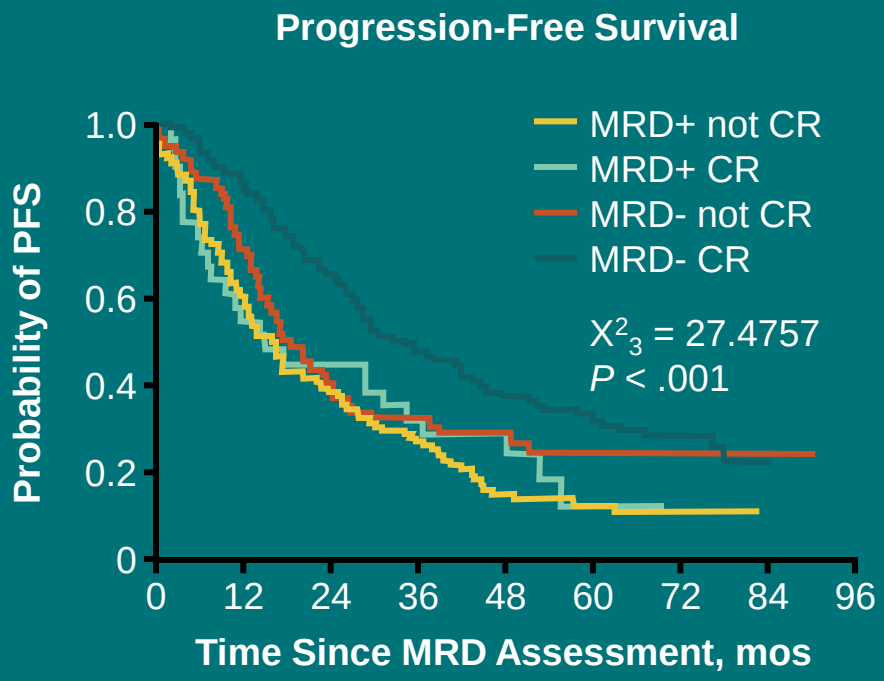


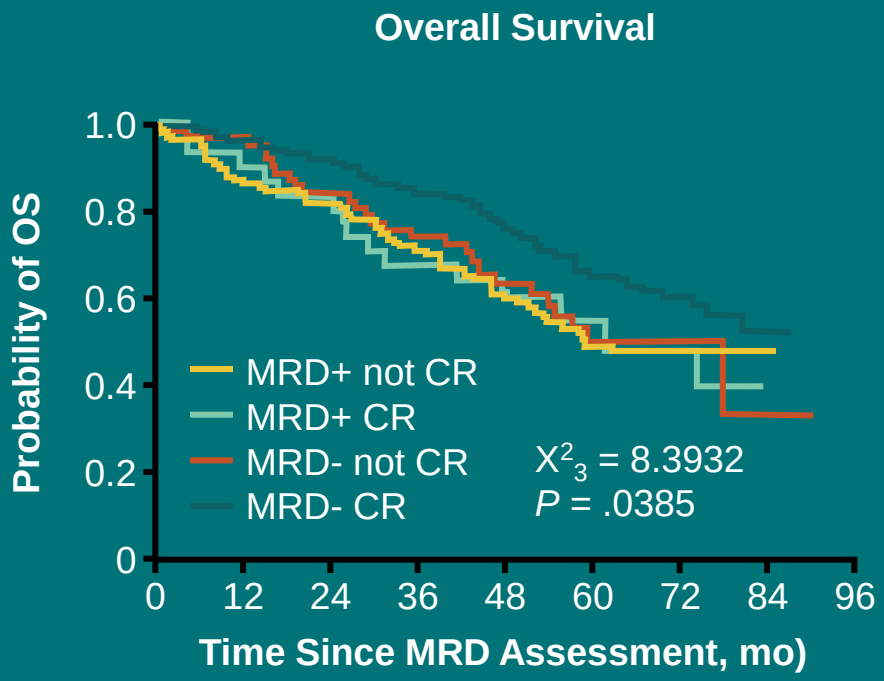
Achieving CR[2]



1. Harousseau JL, et al. J Clin Oncol. 2009;27:5720. 2. Kapoor P, et al. J Clin Oncol. 2013;31:4529-4535.

MRD Flow Cytometry Helps Predict Outcomes Post Transplant



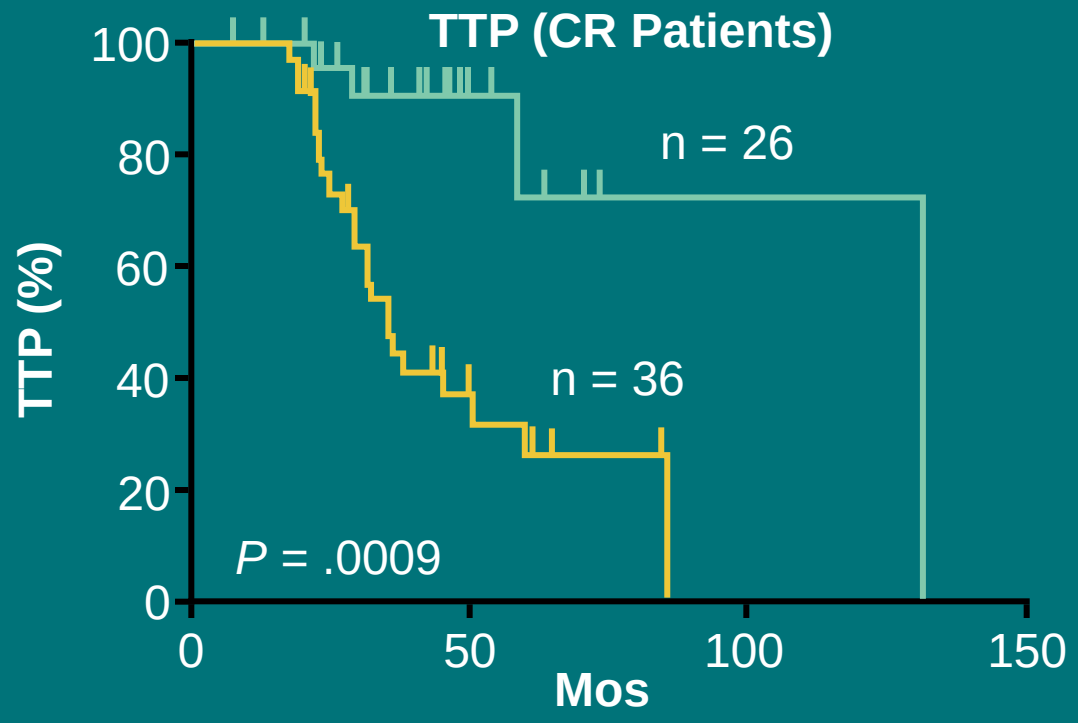


International Myeloma Foundation is leading a multi-center, standardization effort.

Rawstron AC, et al. J Clin Oncol. 2013;31:2540-2547.

MRD by High-Throughput Sequencing Predicts Prognosis in Patients With CR

- Quantitative; with amplification and sequencing of immunoglobulin gene segments using consensus primers for: immunoglobulin heavy-chain locus complete (IGH-VDJH), IGH incomplete (IGH-DJH), and immunoglobulin κ locus (IGK)

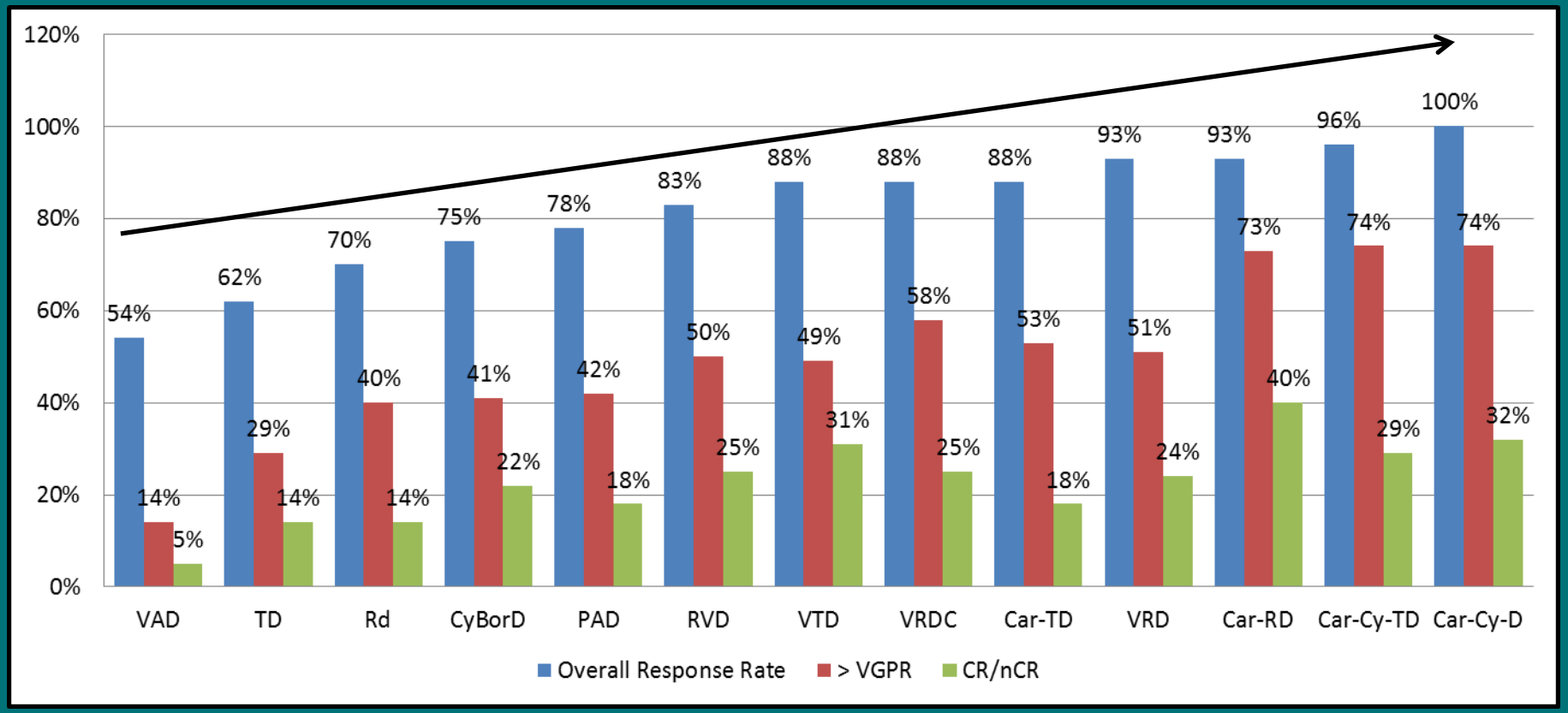


MRD negative
MRD positive
Threshold: 10^{-5}

MRD stratifies the CR population into 2 groups with strikingly different prognosis

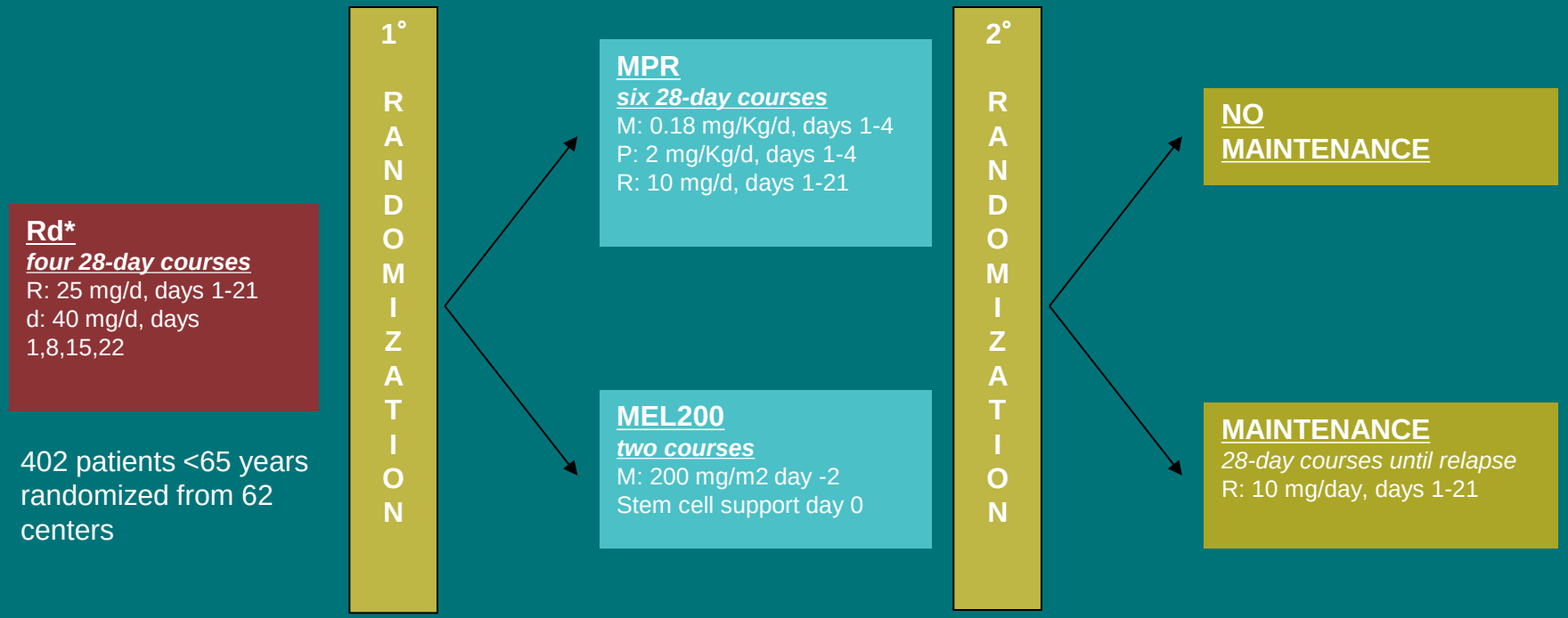
Martinez-Lopez, et al. Blood. 2014;123:3073-3079.

Good Combinations = Better Depth Of Response



Induction Regimens for Newly Diagnosed Transplant Eligible MM

Is Upfront High Dose Melphalan Important?



Median Follow-up: 51.2 months

	MPR	MEL200	p value
Median PFS	22.4 months	43 months	<0.0001
OS at 4 years	65.3%	81.6%	0.02

	R Maintenance	Observation	p value
Median PFS	21.6 months	41.9 months	<0.0001
OS at 3 years	88%	79%	NS

Palumbo A et al, NEJM 2014

Summary Of Abstract #8510

- Modern Total Therapy: KRd Induction x 4 cycles + ASCT + KRd Consolidation x 4 cycles + KRd Maintenance x 10 cycles
- Unprecedented Depth of Response
  - ? MRD Assessment
- AE/SAE: Acceptable
- ? Details of the High Risk Breakdown
  - Perhaps a better question in a larger cohort of patients
- ? Optimal Carfilzomib Dose/Schedule
  - Especially in light of ENDEAVOR trial data

Summary Of Abstract #8511

- Pooled data from 2 phase III studies with heterogeneous induction regimens
  - Non-bortezomib based regimen in majority of patients

- Primary endpoint for PFS met but too early for OS
  - Better depth of response post-consolidation
  - Benefit seen most in patients who were ‘high-risk’ and did not get bortezomib-based induction.

- Surprisingly low peripheral neuropathy

Impact of New Data On Current Practice

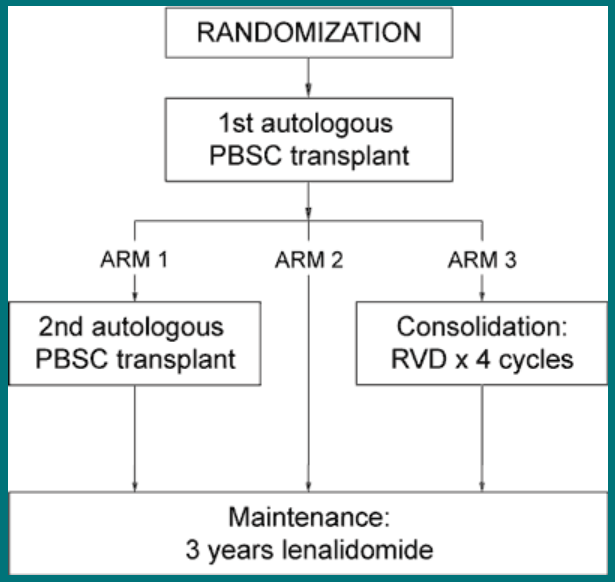
- Current Standard of Care in US:
  - Triplet Induction: Bortezomib used as part of induction from majority of US transplant eligible patients
  - ? Consolidation
  - Lenalidomide or bortezomib maintenance

- Impact of New Data: Not practice changing at the moment

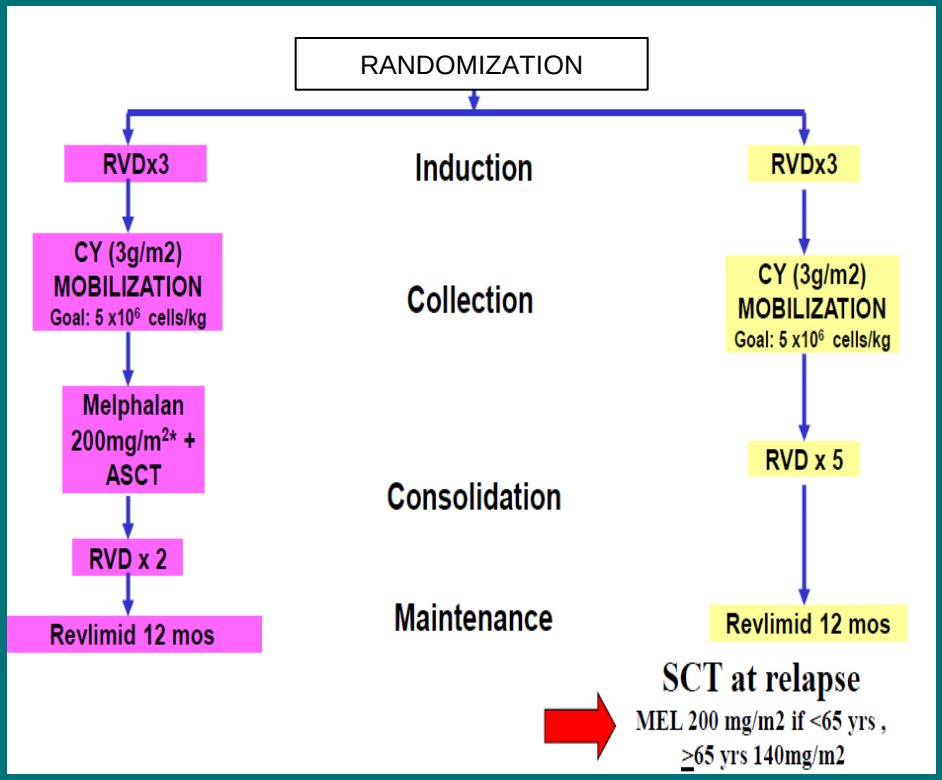
- Need head-to-head comparison of KRd and RVd using the modern ‘Total Therapy’ approach (Roussel et al JCO 2014)
  - Which MRD ‘Assay’ to Use?

Important Phase III Trials To Look Out For…

Schema for BMT-CTN 0702



Schema for IFM/DFCI 2009



Thank you for your attention!