Transplantation for Myeloma

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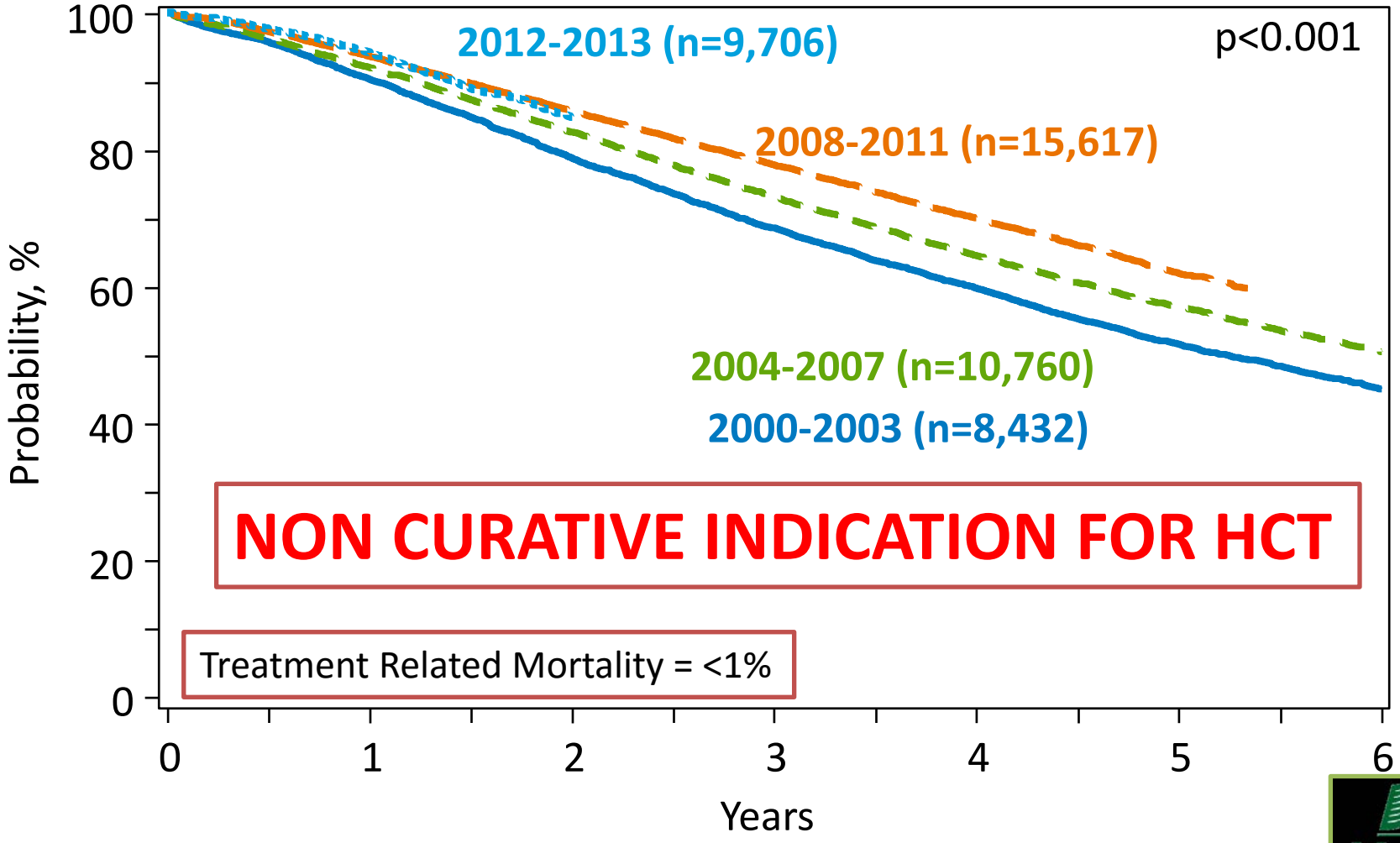
Survival after Auto transplant for Myeloma, 2003-2013



By Year of Transplant

CIBMTR Summary Slides 2015

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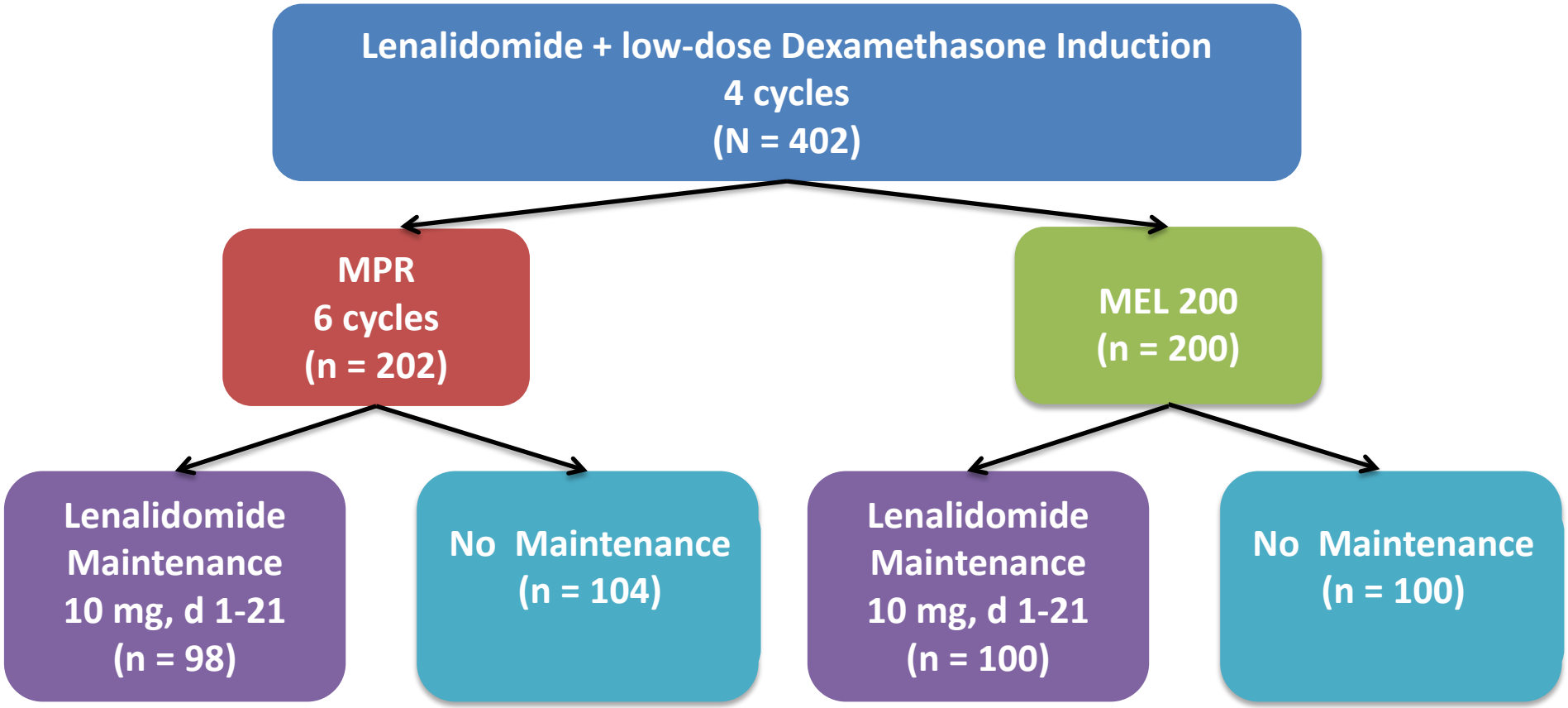
Transplant for MM: Is it still needed? If so, when… (still upfront or ok to wait)?

Newer drugs :
Carfilzomib
Pomalidomide
Elotuzumab
Daratumumab
Panabinostat

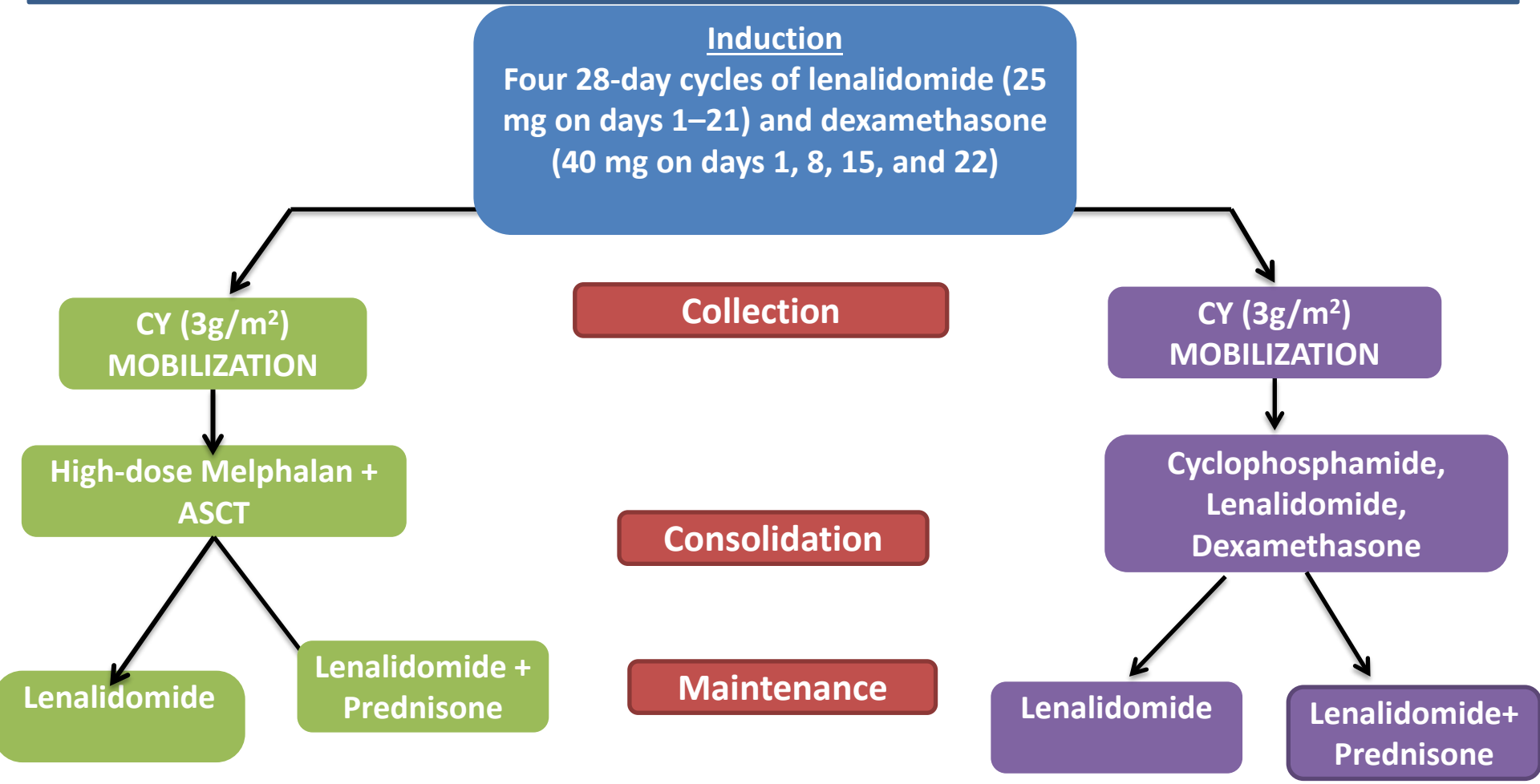
Phase 3 MPR Consolidation vs Tandem MEL200



GIMEMA NEJM 2014	402	RD x4	MPR x6 ASCT x2	22mo median 43mo* PFS	65% 4y 81%* OS

Palumbo, et al. *N Engl J Med.* 2014;371:895-905.

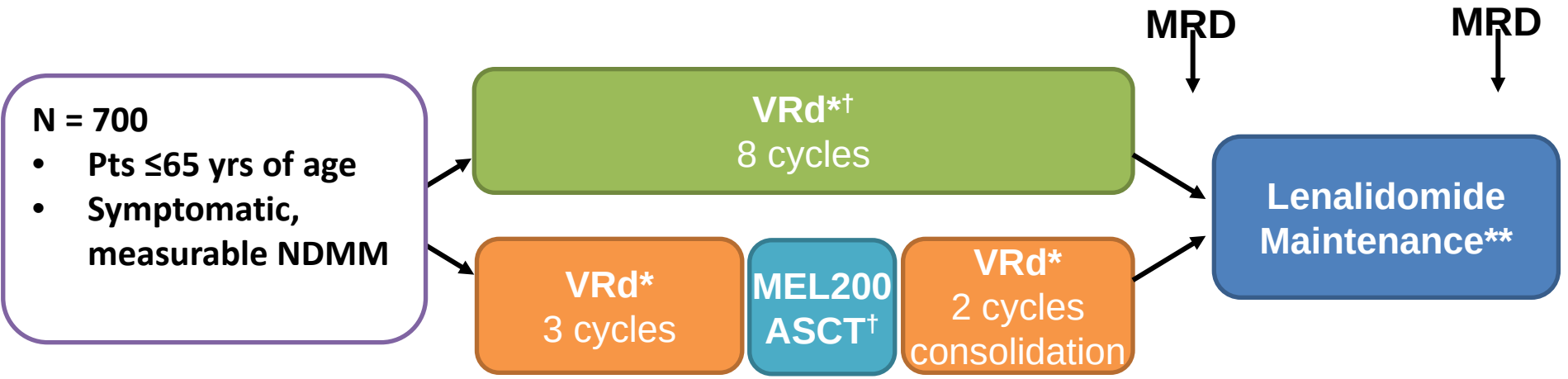
High-dose Melphalan - ASCT vs Chemotherapy



Gay, et al. *Lancet Oncol.* 2015;16:1617-1629.

Determination Trial—Phase III IFM/DFCI

Role of Early vs Delayed Transplant in the Era of Novel Agents

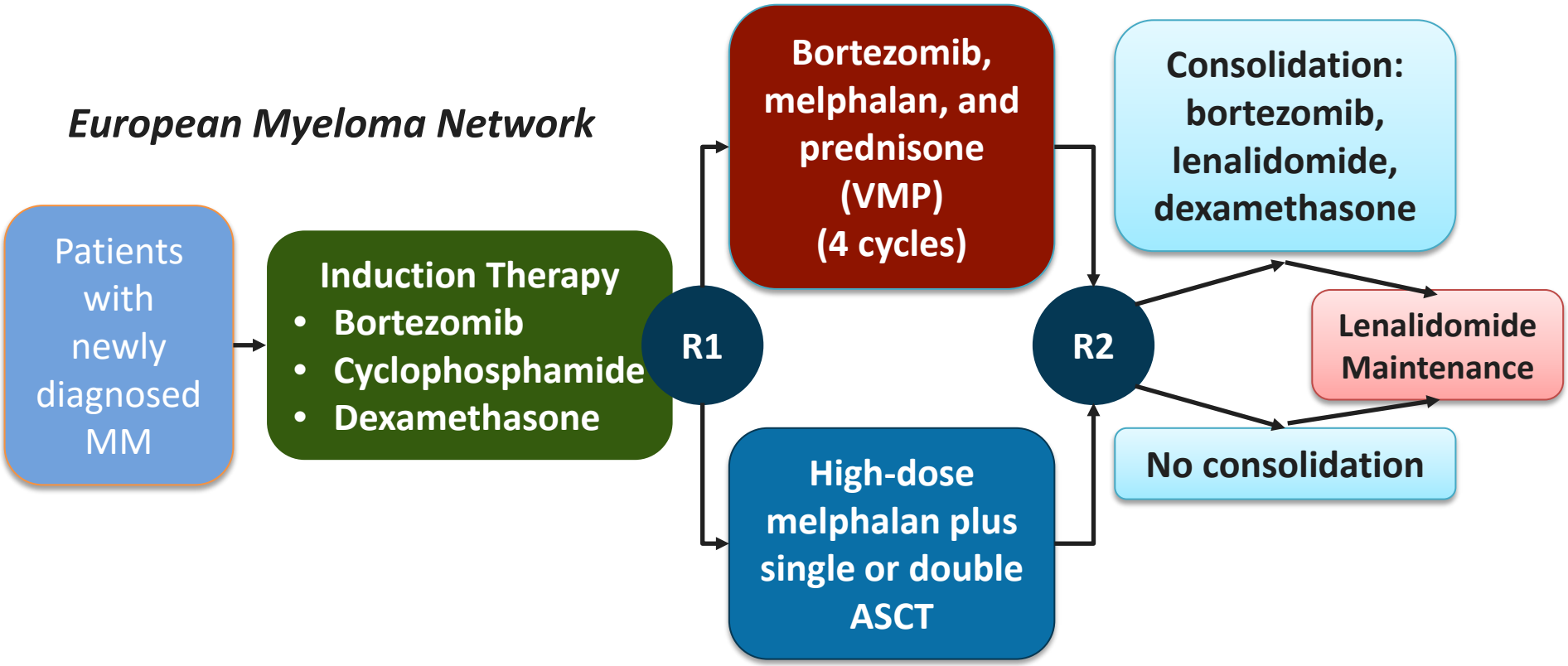


- Primary objective: PFS
- Secondary objectives: ORR, MRD, TTP, OS, Safety

**VRD: bortezomib 1.3 mg/m^2 IV on Days 1, 4, 8, 11 + lenalidomide 25 mg on Days 1-14 + dexamethasone 20 mg on Days 1, 2, 4, 5, 8, 9, 11, 12.*
*** till POD in US trial and 12 months in IFM trial*
†Included PBSC collection with cyclophosphamide 3 g/m^2 + G-CSF after cycle 3.

Avet-Loiseau H, et al. ASH 2015. Abstract 191.

EMN02/H095
ASCT vs VMP After CyBorD Induction



Cavo M, et al. *J Clin Oncol*. 2016;34(suppl). Abstract 8000.

New drug vs. Auto-Transplant Studies

Group	No	Induction	Comparator	> VGPR	PFS	OS
GIMEMA NEJM 2014	402	RD x4	MPR x6 ASCT x2	63 59	22mo median 43mo*	65% 4y 81%*
MultiCenter Lancet Oncol 2015	389	RD x4	CDR x6 ASCT x2	50 54	29mo 43mo*	68% 4y 77%*
IFM 2009 ASH 2015	700	VRD x3	VRD x5 ASCT + VRD x2	78 88*	34mo 43mo*	83% 4y 81%
EMN ASH 2016	1192	VCD x3-4	VMP x4 ASCT 1 or 2	74 85*	57% @ 3 yrs 65% HR 0.73*	NS (short fu)

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EMN02/HO95 Results

PFS from first randomization – ASCT vs VMP

	Study Population		High Risk	
	ASCT n=695	VMP n=497	ASCT n=133	VMP n=87
PFS, months	NR	42.5	42.3	20.3
3-year PFS Rate	65%	57.1%	52.4%	29.5%
HR (95% CI)	0.73 (0.61-0.88)		0.53 (0.37-0.76)	
P value	.001		.001	

Median follow-up 25 months.

- Patients with high-risk cytogenetics derived the most significant benefit
- Adverse events included GI concerns and mucositis

ASCT improves PFS over high dose therapy for MM patients

Cavo M, et al. *Blood.* 2016;128. Abstract 673.

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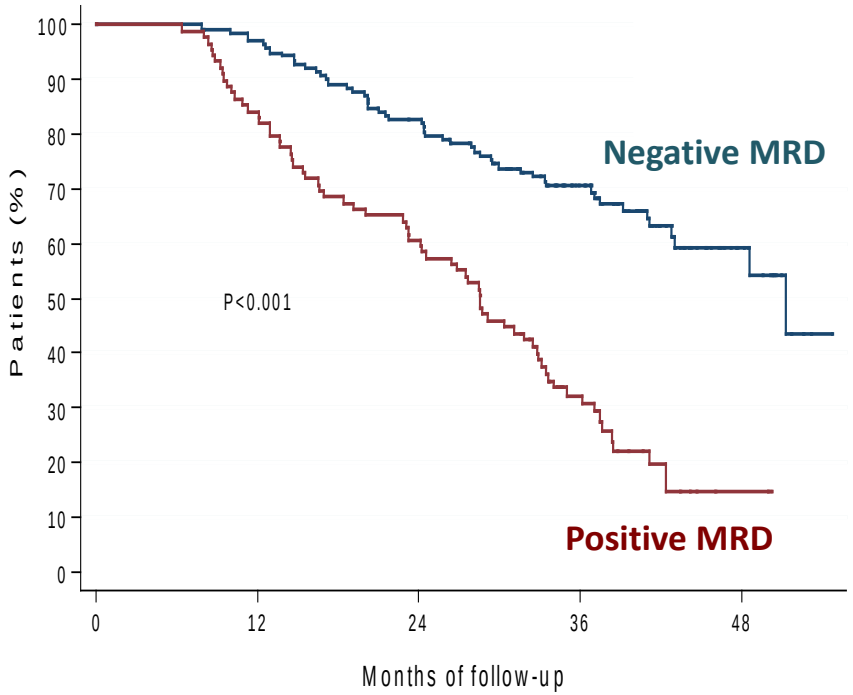
IFM/DFCI—PFS According to MRD (FCM) Post Consolidation

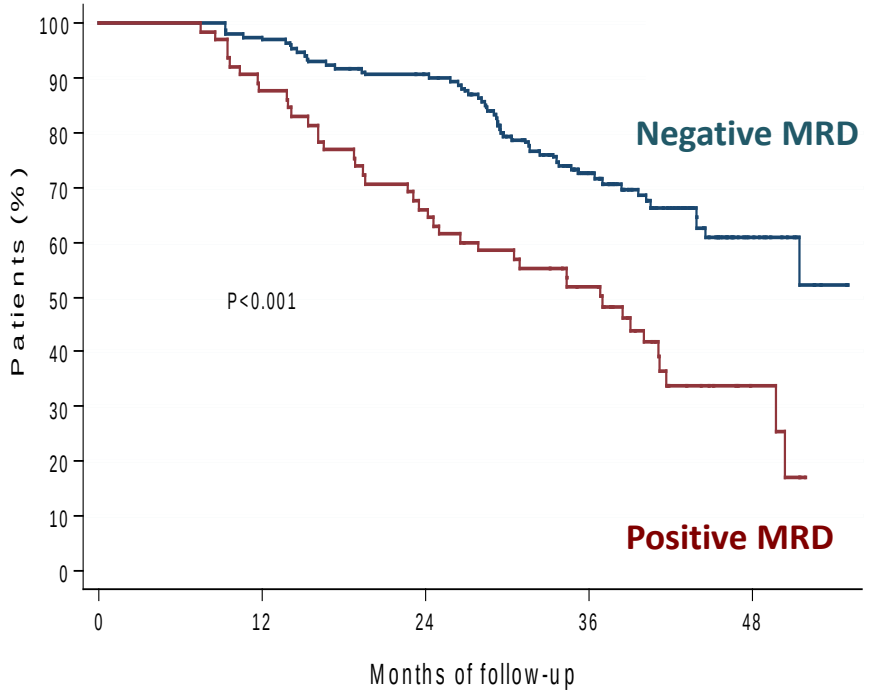
VRD Arm



N at risk

MRD pos	89	75	54	22	2
MRD neg	140	135	113	72	14

Transplant Arm



N at risk

MRD pos	65	57	43	30	4
MRD neg	172	166	151	86	17

Attal, et al. *Blood.* 2015 126:391

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Beyond Auto Transplantation for Myeloma

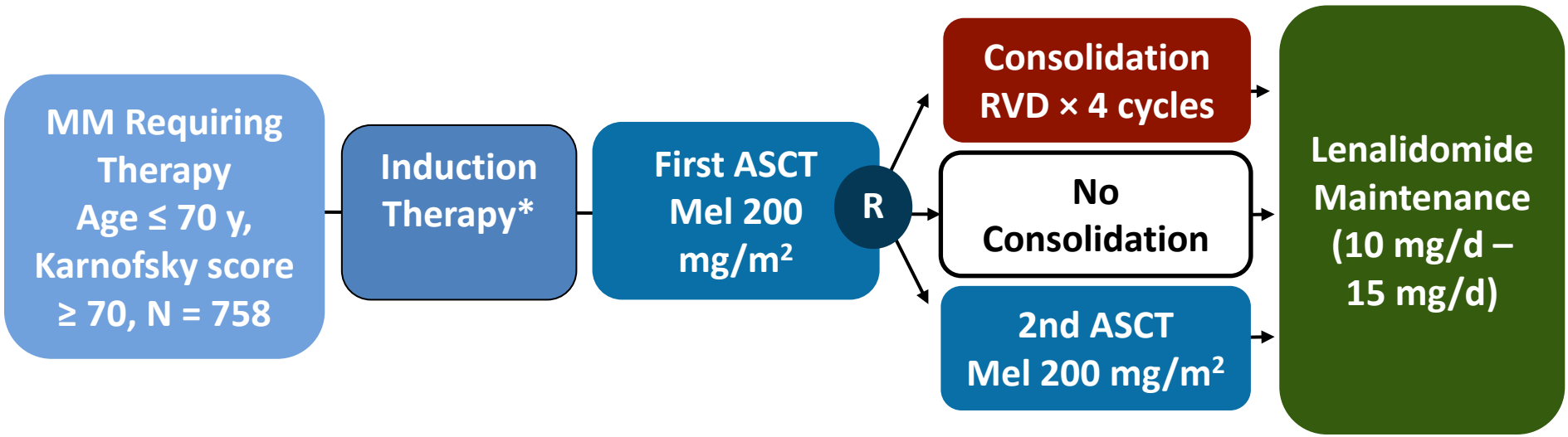
Approaches to prevent relapse

CONSOLIDATION

MAINTENANCE

ALLOTRANSPLANT & IMMUNE THERAPY

BMT CTN 0702 STAMINA Study



*Induction therapy was not specified. Patients must have had ≥ 2 cycles of systemic therapy, within 2-12 mos of therapy initiation and Available autograft ≥ 4×10^6 CD34+ cell/kg.

Median follow-up: 37.8 mos

ClinicalTrials.gov. NCT01109004.

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Stamina Study Results

No significant difference between the study arms

Post induction + ASCT-1 followed by:	R Maint only n=257	RVD→R n=254	Double ASCT→R n=247
Median PFS, mos	52.2	56.7	56.5
Median OS, mos	83.4	85.7	82.0
High-risk patients, n	59	65	57
Median PFS, mos	40.2	48.3	42.2
Median OS, mos	79.5	77.5	79.3

Post induction + ASCT-1 followed by:	R Maint only n=257	RVD→R n=254	Double ASCT→R n=247
Second malignancies, n	10	15	14
Cumulative incidence, %	4.0	6.0	5.9

ClinicalTrials.gov. NCT01109004.

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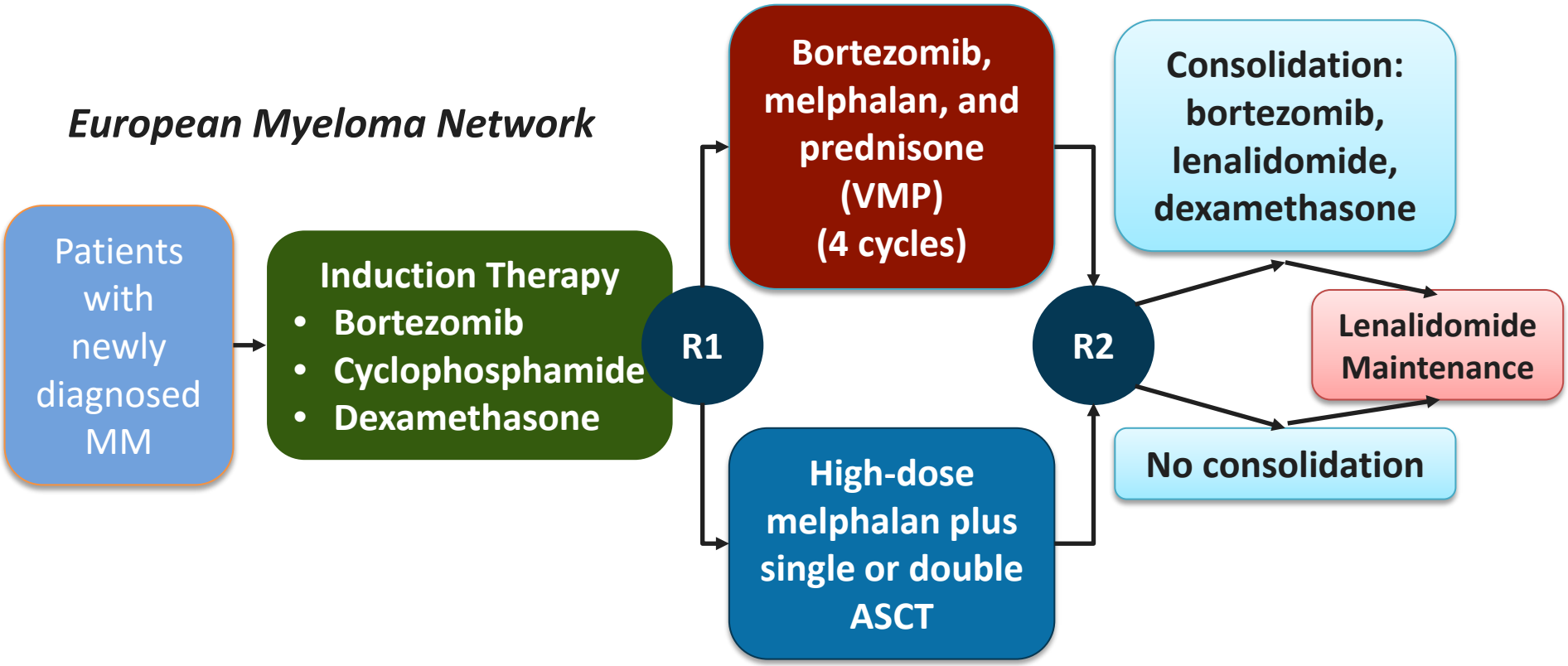
EMN02/H095
ASCT vs VMP After CyBorD Induction



Cavo M, et al. *J Clin Oncol*. 2016;34(suppl). Abstract 8000.

EMN02/HO95
Consolidation

- PFS from second randomization (R2) – consolidation with VRD vs no consolidation
  - 3-year PFS from R2 = 62%
    - 65% VRD vs 60% without consolidation
    - Median PFS not reached
  - Prolonged PFS after adjustment for R1 with an HR=0.78; *P*=.13
- 3-year OS 86% vs 87%
- PFS benefit in subgroups

Subgroup	HR,	*P* value
R-ISS stage III	.67	.26
VMP at R1	.76	.19
HDM at R1	.79	.13
Low-risk cytogenetics	**.68**	**.03**
High-risk cytogenetics	1.03	

Consolidation improves PFS for most subgroups, but there was no benefit for high risk patients

Sonneveld P, et al. *Blood.* 2016;128. Abstract 242.

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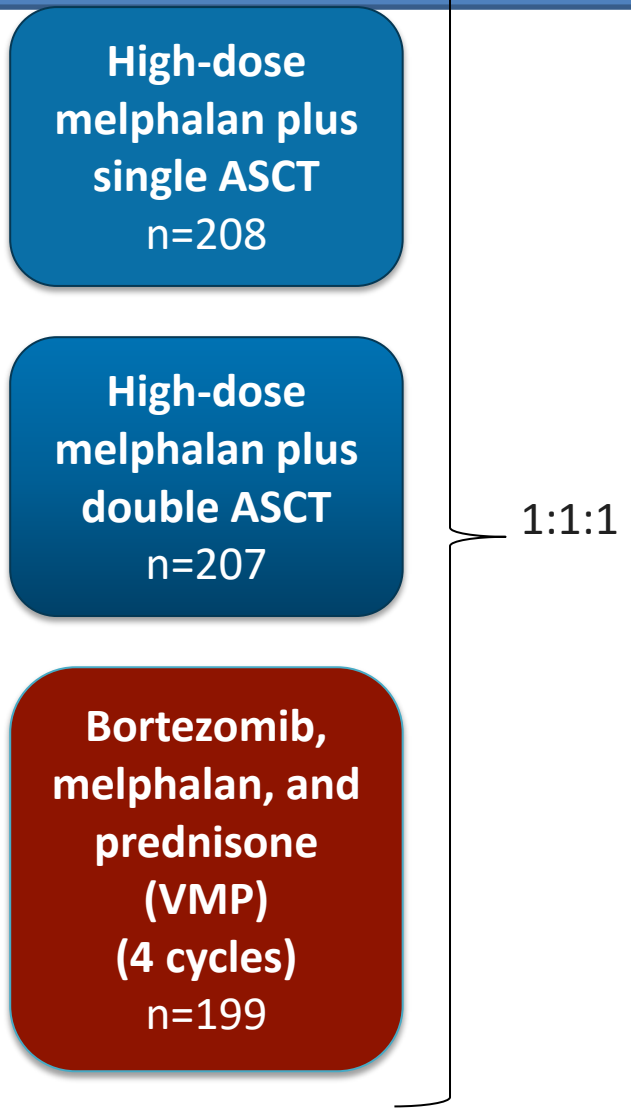
EMN02/H095 Single vs Double ASCT



- PFS ITT population, single vs double
  - 45 mo vs NR
- 3-year PFS rate single vs double:
  - 60% vs 73% (HR=0.66; *P*=.030)
- Patients with high-risk cytogenetics benefit most from double ASCT

Cavo M, et al. *Blood.* 2016;128. Abstract 991.

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STaMINA and EMN02/H095 *Differences*

- Pre-transplant induction regimen differences
  - Patients in the European study received bortezomib, cyclophosphamide, Dex
  - Most patients on the CTN study received RVD induction

Post induction + ASCT-1 followed by:	**R Maint only n=257**	**RVD→R n=254**	**Double ASCT→R n=247**
Initial Therapy			
RVD, %	**57.1**	**52.8**	**55.6**
CyBorD, %	**13.4**	**13.8**	**15.6**
Rd, %	9.7	11	8.6
Vd, %	11.3	12.6	12.5
Other, %	8.5	9.8	7.8

- Longer term follow-up needed

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What should be the standard of care?

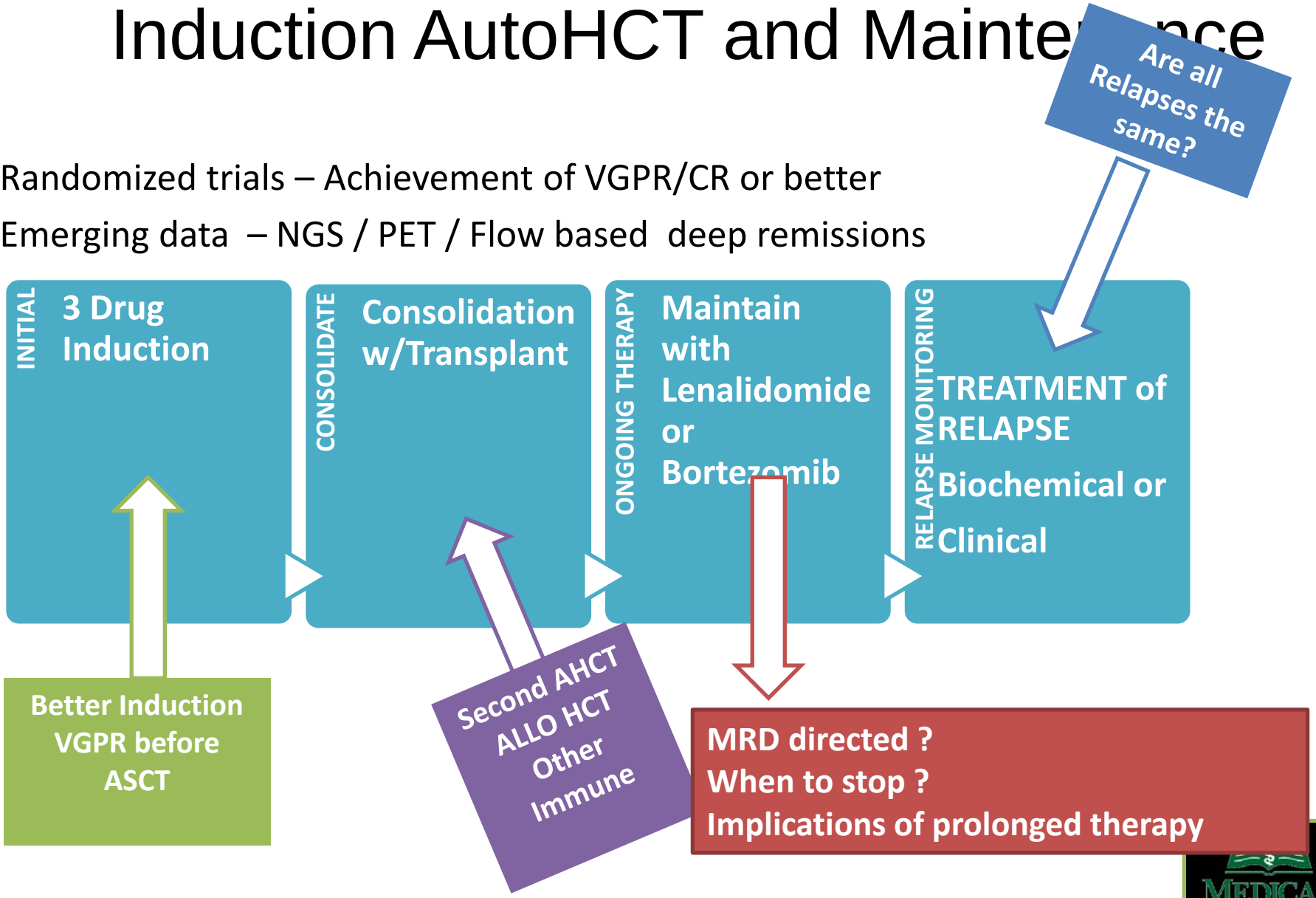
- Proteasome Inhibitor + IMID + Steroid induction
- Single auto transplant
- Lenalidomide Maintenance
    - Who should no maintenance? Bortezomib ? For how long?

For patients not in CR after 4 cycles of initial therapy, further induction should be attempted to induce VGPR or CR pre transplant

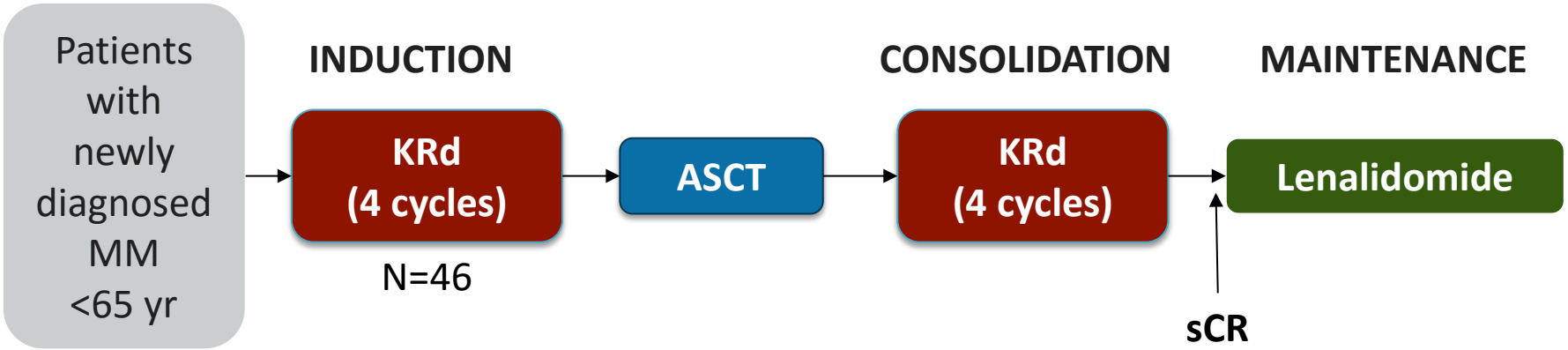
True or False?

“Improving the Modern Triple Sequence” Induction AutoHCT and Maintenance

- Randomized trials – Achievement of VGPR/CR or better
- Emerging data – NGS / PET / Flow based deep remissions



KRd Induction and Consolidation



- Efficacy
  - Median PFS not reached
  - 2-year PFS 91%
  - 78% VGPR at ASCT
  - 70% MRD negative after consolidation
- Safety
  - 17% cardiac and vascular AE

Response after Consolidation	n/N	%
sCR	26/46	57
sCR + CR	28/46	61
MRD - CMF	32/46	70
MRD - NGS	23/34	68

KRd induction and consolidation is effective; cardiac toxicity is a concern

Zimmerman et al. ASH abstract 2016

Transplant is the most cost effective therapy in MM

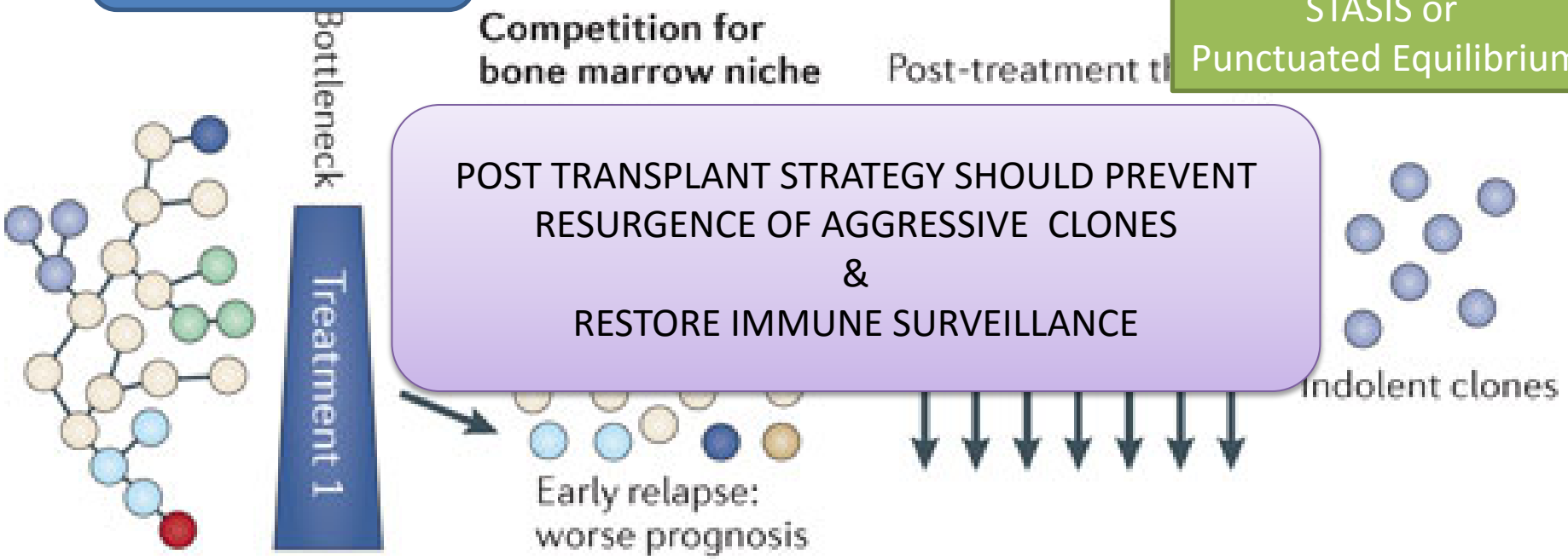
- KRD or VRD in the USA :
  - Approximate monthly cost – 30-50 000 USD/mo
  - Addition of Daratumumab – 12-23 000 USD more
  - Recurring nature of the cost
  - Limitation of Time without treatment

Why is Autotransplant for MM still important?

AUTO TRANSPLANT
DEBULKING
LYMPHODEPLETION

Maintenance/Consolidation

STASIS or
Punctuated Equilibrium



POST TRANSPLANT STRATEGY SHOULD PREVENT
RESURGENCE OF AGGRESSIVE CLONES
&
RESTORE IMMUNE SURVEILLANCE

Multiclonal disease with clonal heterogeneity

Morgan et al Nat Rev Cancer. 2012 Apr 12

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Immunotherapy after AutoHCT

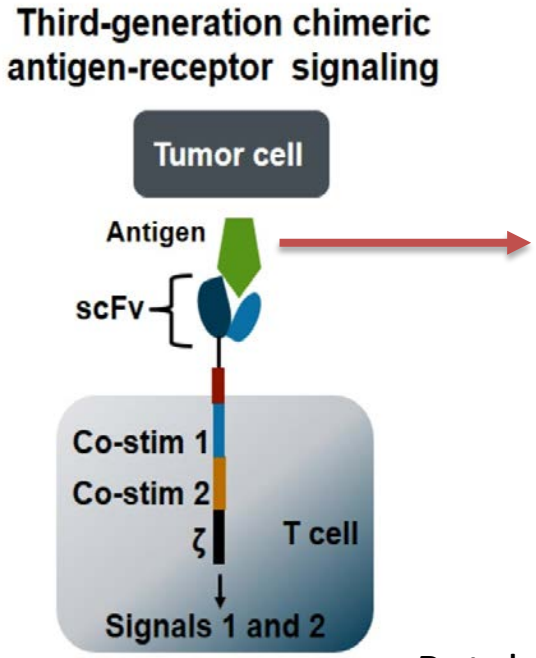
- Minimal TRM
- Immune effect without GVHD

Immune therapy is ideal for post AUTO HCT SETTING

- Minimal residual disease state
- Elimination of competing and suppressor cells
- Tumor antigen release from high dose chemotherapy
- Favorable cytokine milieu

Adoptive Cellular Therapy

- Autologous marrow derived myeloma Infiltrating Lymphocytes
- NK cell therapies (from donors or expanded third party)
- Re-engineered T cells
- Vaccines – BMT CTN 1401 study



Antigenic targets for CAR – T cells :
BCMA – B cell Maturation Antigen
NY ESO -1 / LAGE
SLAM F7
CD 56
NKG2L
Kappa Light Chain
CD19 / CD38 / CD70 / CD138

Rotolo A et al; Br. Journal of Haem. 2016;173: 350

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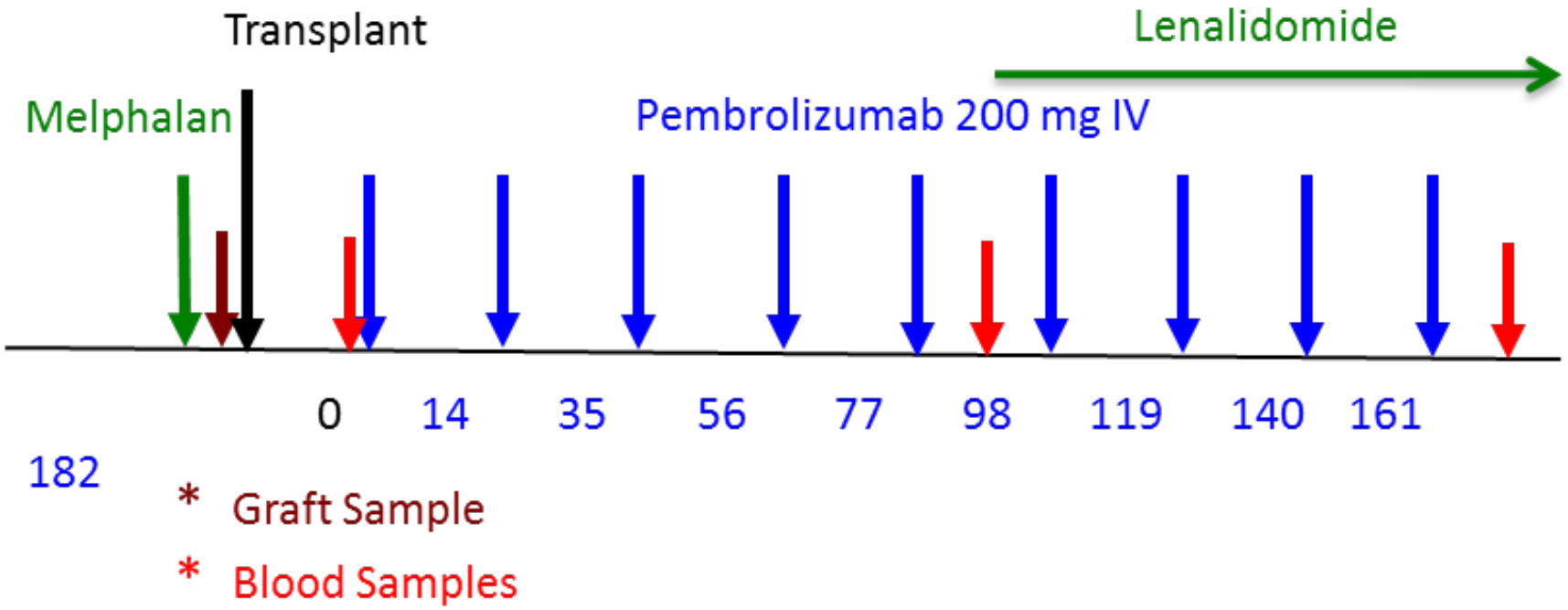
PD-1 inhibition after Auto



- Effects of anti-PD-1 on T- and NK-cell function
- Correlation of immune cell phenotypes in the autologous graft and outcomes

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To Cryopreserve or Not?

- Is it worth investing in cryopreservation?
  - IMO – resounding YES!
  - Recover initial outlay in first transplant
  - Annual Cost 150 – 200 USD / year
  - Use cells at relapse in eligible patients
    - Reinduction / Transplant / Diff Maintenance
  - Multiply relapsed pts – cells to recover counts

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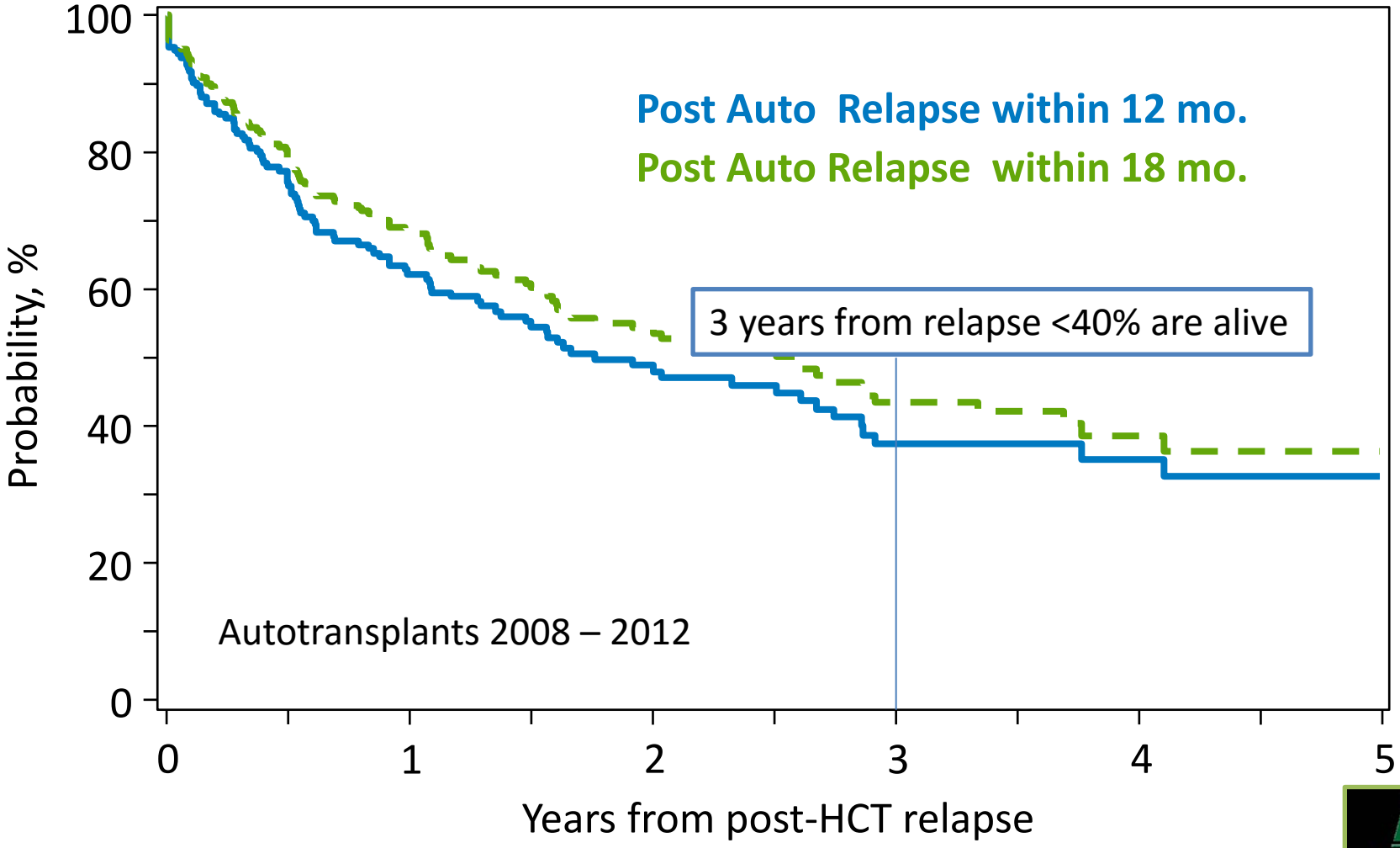
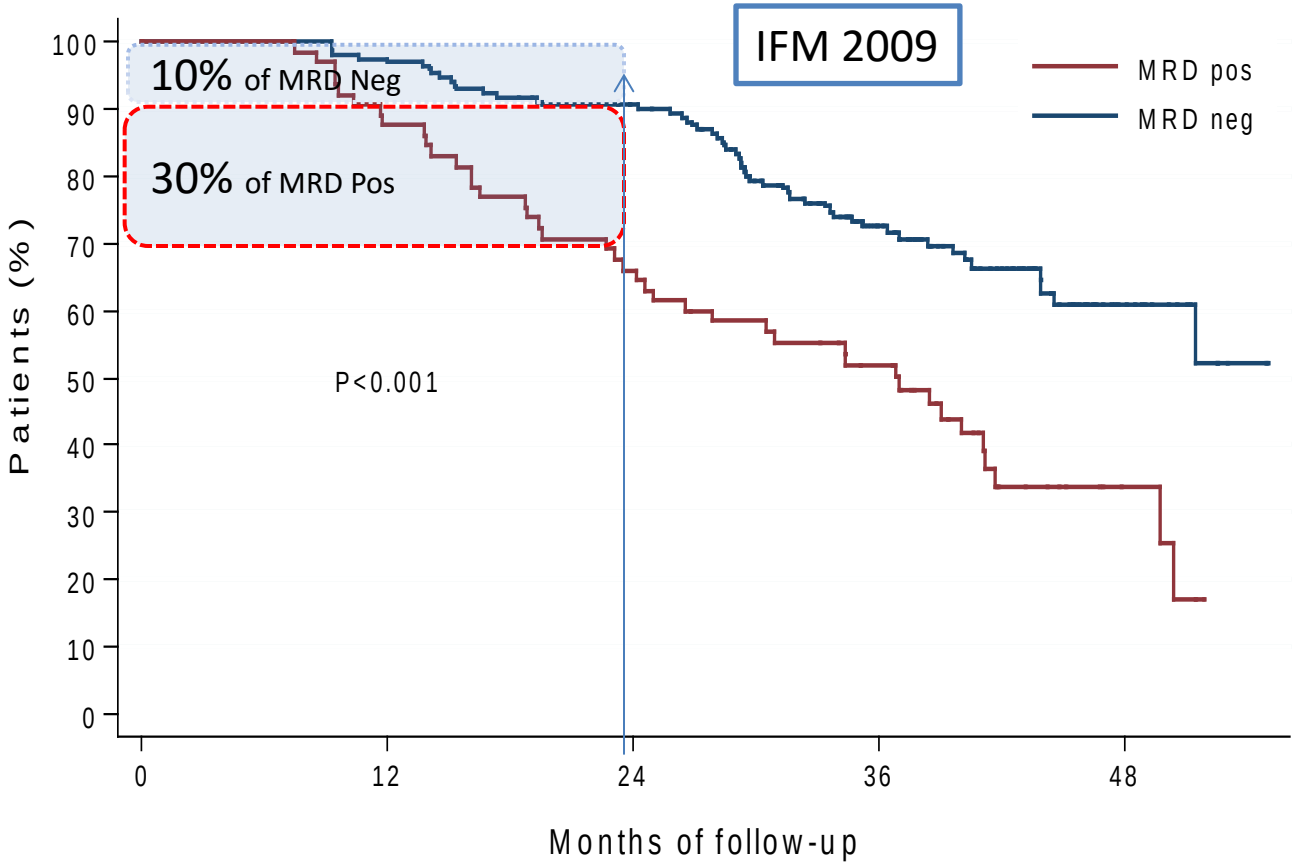
Second Salvage Transplants

- Freeze additional cells vs. Re-mobilize
  - What you gain in storage costs – will lose in Plerixafor
- Second transplant at relapse may be better than tandem upfront in the modern era
- IMWG consensus recommends salvage second transplant if PFS from first transplant is >18 mo

Early Relapse After Auto HCT – is a high risk group



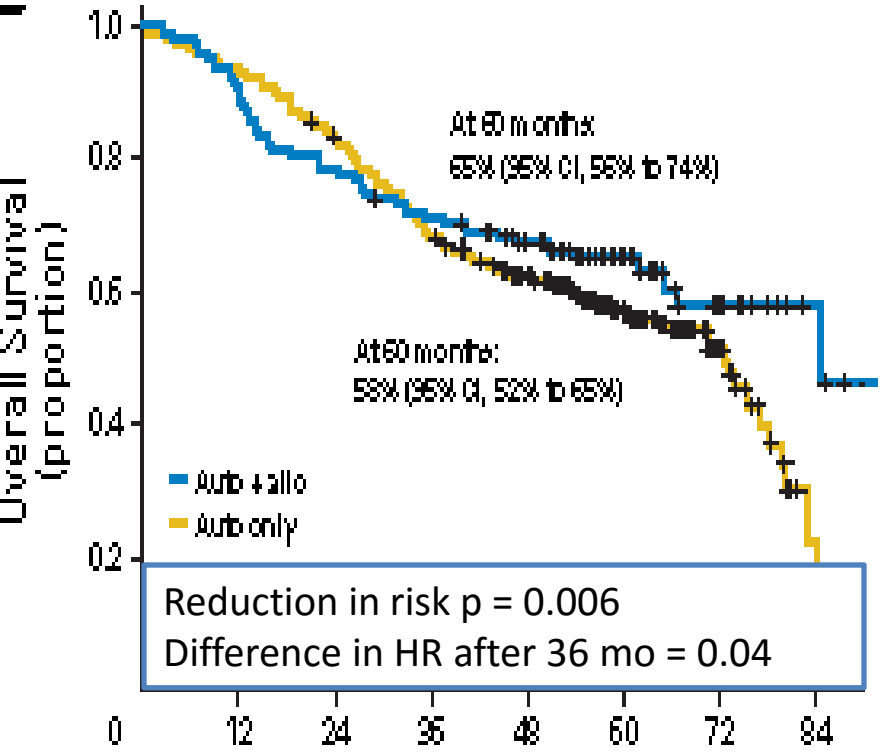
How many pts relapse early?



N at risk					
MRD pos	65	57	43	30	4
MRD neg	172	166	151	86	17

Attal M et al Blood 2015 126:391

Why not give up Allotransplant?



Bjorkstrand JCO 2011; 29: 3016 -22

- Intriguing European studies
- Longer follow up for a difference to show
- Young high risk pt – what to do?
- Low TRM - ~5% in the best centers
- Allo → Maintenance paradigm
- Backing off from “Mini” regimens

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Pay attention to Melphalan MEL Pharmacokinetics

- Inter-individual variability
  - Creatinine Clearance
  - Fat free mass
  - Hematocrit
- Higher MEL exposure—increased toxicity and efficacy
- Unbound MEL—sensitive predictor of toxicity and efficacy
- How do we optimize conditioning?

Nath, et al. *Br J Clin Pharmacol*. 2010;69:484-497.

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Autologous HCT for multiple myeloma in US and Canada within 12 months from diagnosis from 1995 to 2010 registered with CIBMTR

Characteristics of patients	1995-1999	2000-2004	2005-2010	P-value
Registered patients	**2226**	**6408**	**11644**	
Number of centers	189	195	174	
Median Age	54 (19-77)	57 (22-80)	58 (18-89)	
18-50 years	734 (33)	1445 (23)	2079 (18)	<0.001
50-65 years	1330 (60)	3875 (61)	6945 (60)	
65-80 years	**162 (7)**	**1088 (17)**	**2620 (23)**	

How old is too old?

Costa L. et al. BBMT

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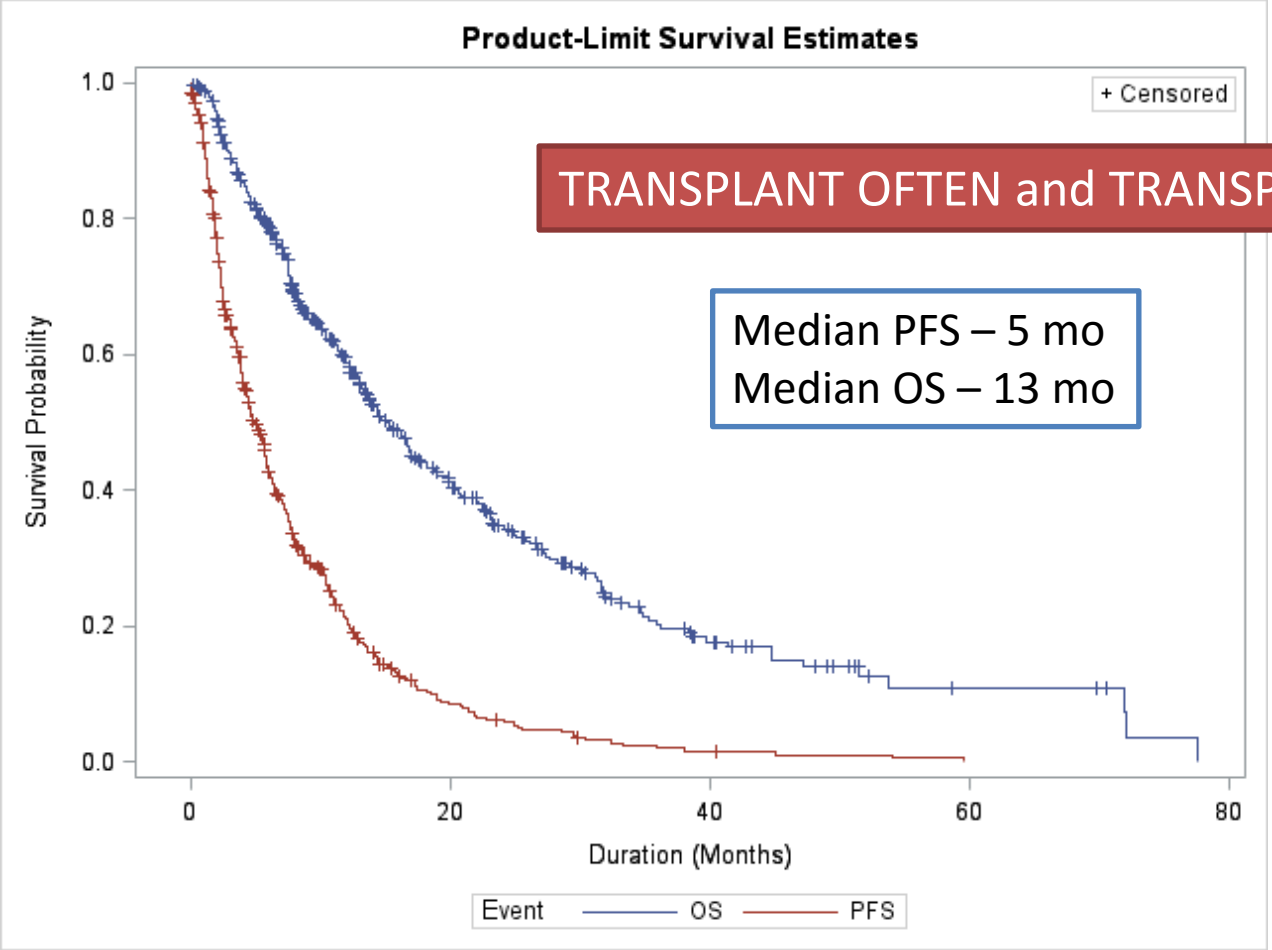
What We Know and Don't Know

- New drugs improve induction CRs → higher CRs after ASCT
  - Beyond VRD which drug combinations are optimal for pts proceeding to transplantation?
- Do higher response rates observed after novel drug combinations plus ASCT improve survival?
- If a pt achieves MRD neg CR after induction therapy is transplantation optional? Which MRD technique?

Gertz MA, Dingli D. Blood. 2014;124:882-890.
Giralt S, et al. Bio Blood Marrow Transplant. 2014;20:295-308.

Myeloma is still incurable: IMWG analysis of double refractory



TRANSPLANT OFTEN and TRANSPLANT EARLY

Median PFS – 5 mo
Median OS – 13 mo

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Milwaukee

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