Transplant in the Era of Effective Induction Therapy

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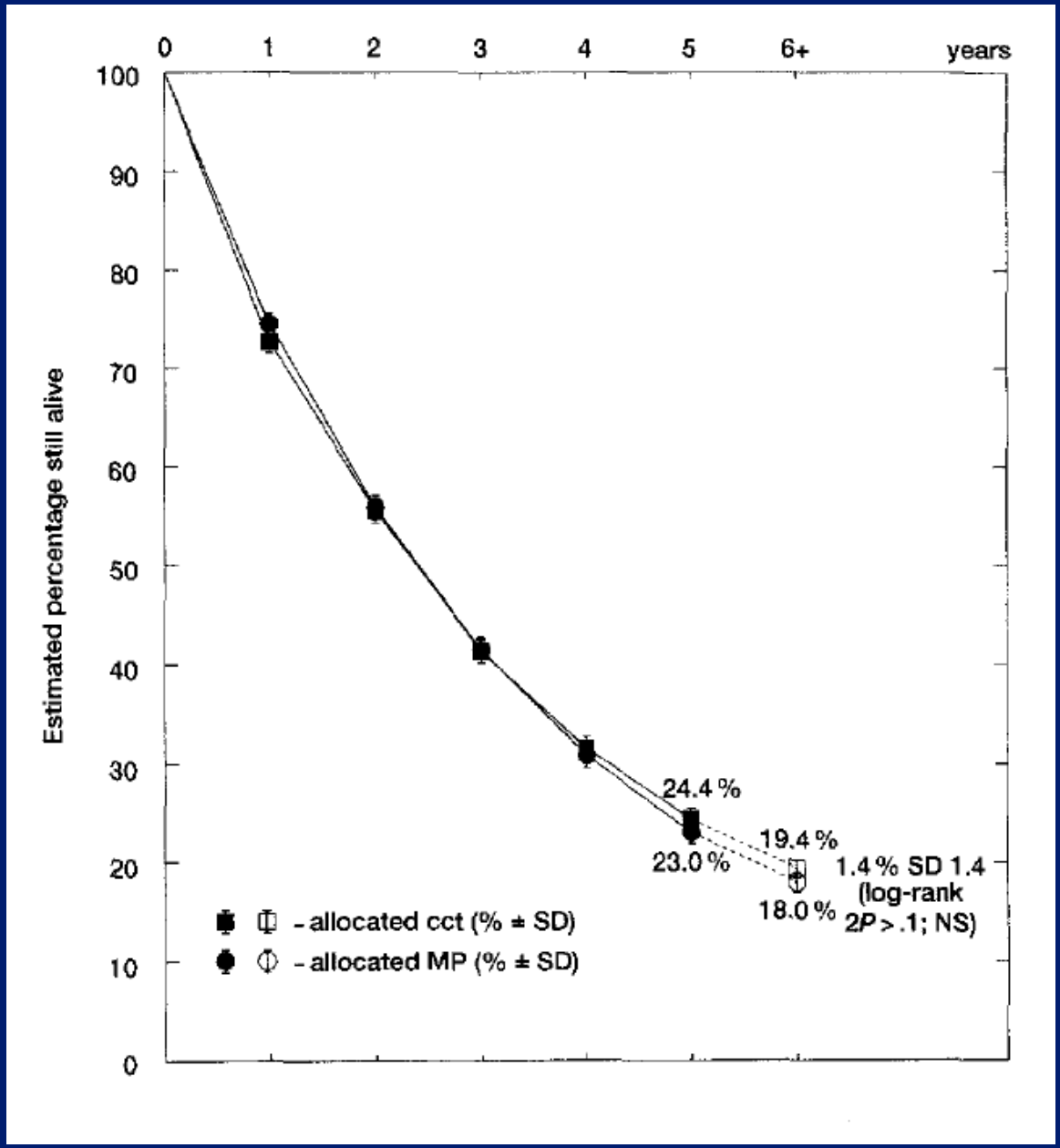
Providing Extraordinary Care

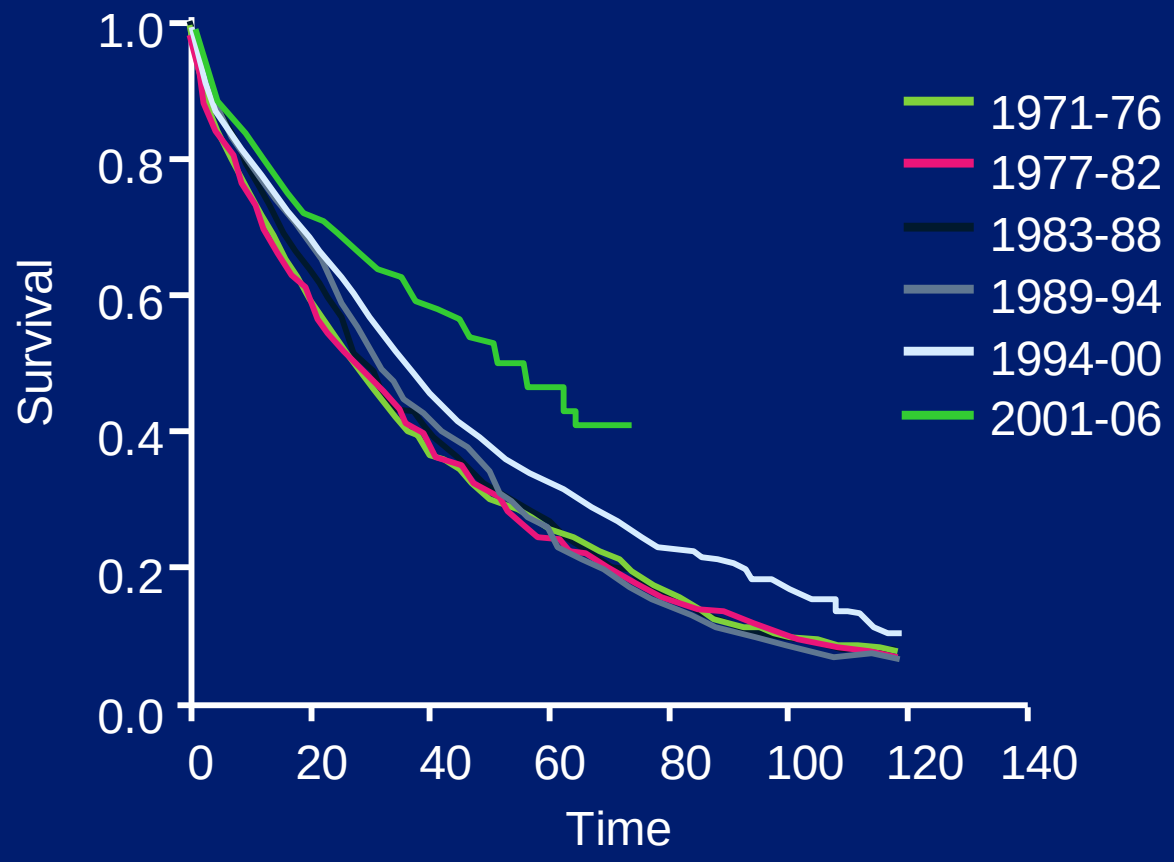
No Improvement in Therapy for Patients with Myeloma in 30 years



Myeloma Trialists J Clin Oncol 1998; 16: 3832-42

Overall Survival has Improved in the Past Decade

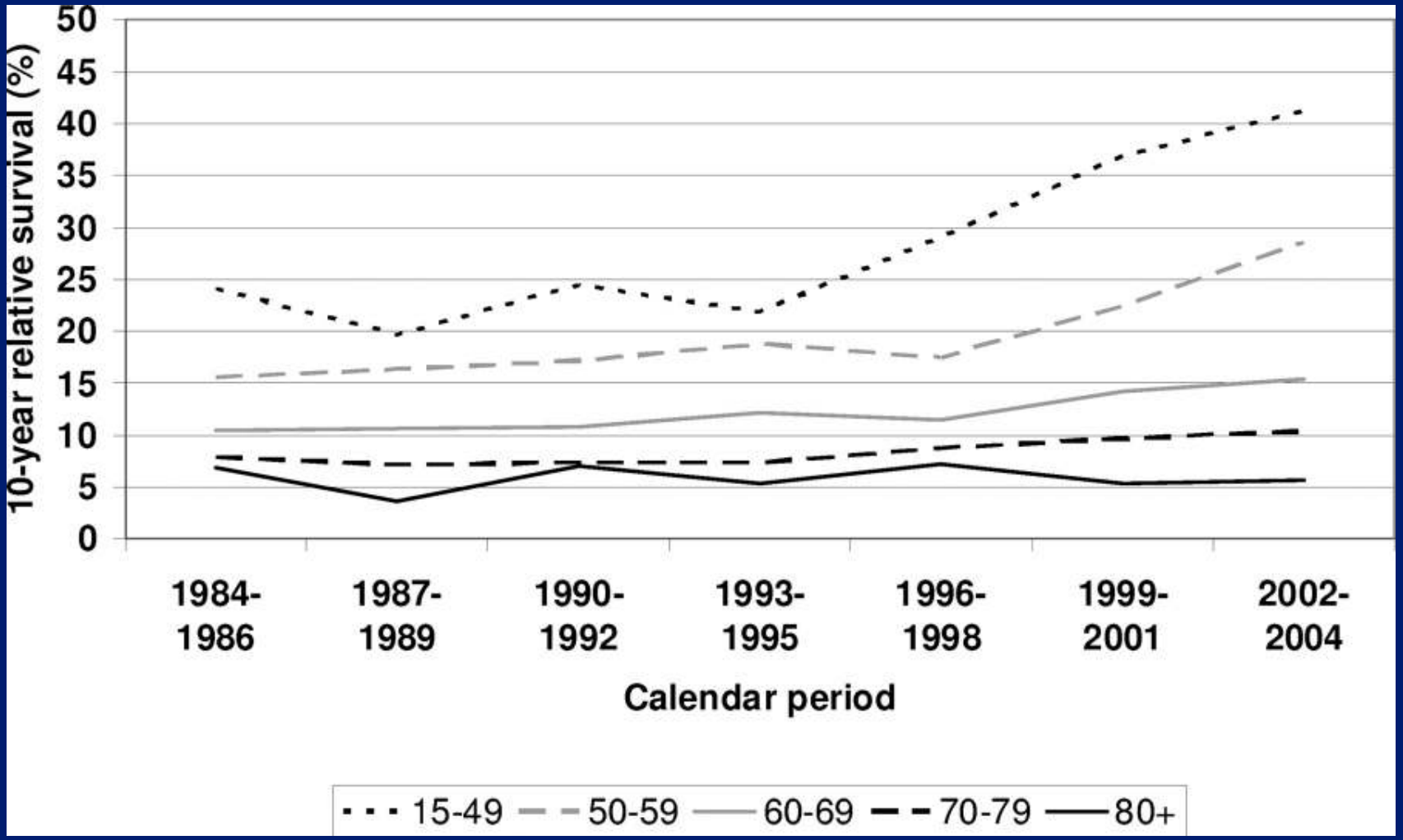
OS in Multiple Myeloma Based Year of Diagnosis



Overall Survival from the time of diagnosis grouped into 6-year intervals based on the date of diagnosis.

Kumar SK, et al. *Blood*. 2008;111:2516-2520.

Estimate of 10-yr OS in Pts with MM by Age in Defined Time Periods: 1984 to 2004



Brenner, H. et al. Blood 2008;111:2521-2526

Transplant Outcomes with “old” Conventional Therapy

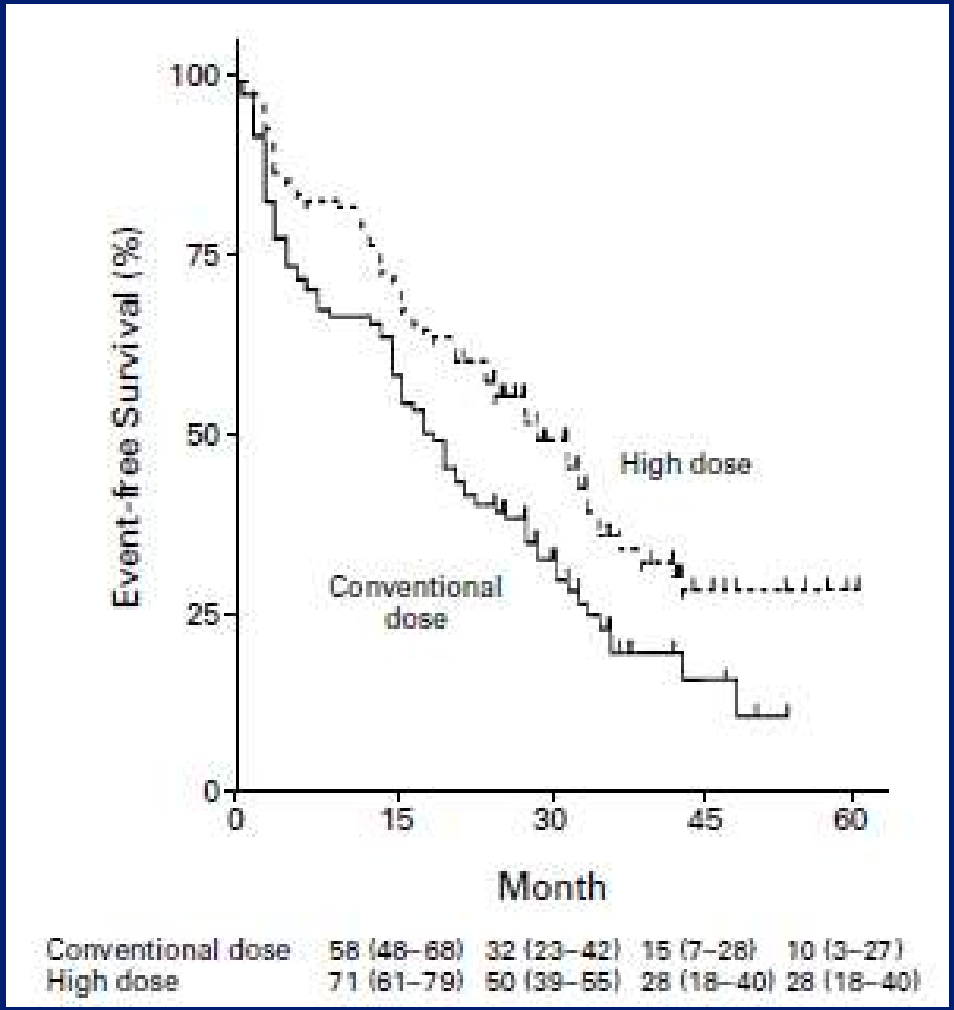
No Improvement in Survival for Patients with Multiple Myeloma for 30 Years Until…

A PROSPECTIVE, RANDOMIZED TRIAL OF AUTOLOGOUS BONE MARROW TRANSPLANTATION AND CHEMOTHERAPY IN MULTIPLE MYELOMA

TABLE 2. RESPONSE RATES ACCORDING TO TREATMENT GROUP.*

TYPE OF RESPONSE	CONVENTIONAL DOSE (N = 100)	HIGH DOSE (N = 100)
	no. of patients	
Complete	5	22
Very good partial	9	16
Partial	43	43
Minimal	18	7
Progressive disease	25	12

*P<0.001 for the comparison of the various response categories between the two groups by the chi-square test. Seventy-four patients in the high-dose group underwent autologous bone marrow transplantation.



Attal M, et al. *N Engl J Med*. 1996;335:91-97.

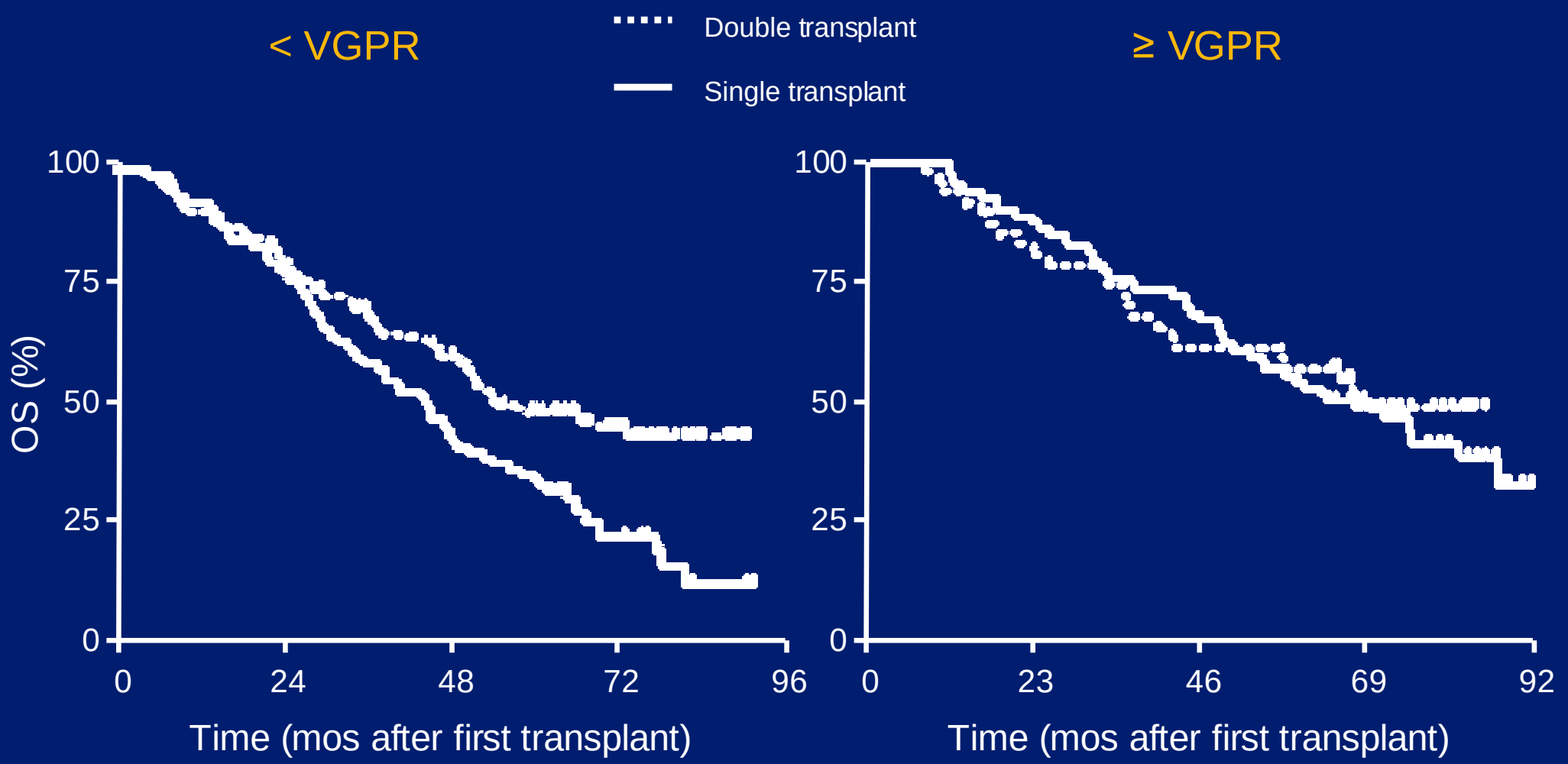
ASCT Vs. CCT: Historical Data

		Patients (n)	CR (%)	PFS (median mos)	OS (median mos)
Attal et al, 1996	CCT	100	5	18	44
	HDT	100	22	28	57
Fermand et al, 2005	CCT	96	4	18.7	50.4
	HDT	94	6	24.3	55.3
Blade et al, 2005	CCT	83	11	34.3	66.9
	HDT	81	30	42.5	67.4
Child et al, 2003	CCT	200	8.5	19.6	42.3
	HDT	201	44	31.6	54.8
Barlogie et al, 2006	CCT	252	15	21	53
	HDT	258	17	25	58

CCT = conventional chemotherapy; ND = newly diagnosed; HDT = high-dose chemotherapy; PFS = progression-free survival.
Adapted from Kumar, 2009.

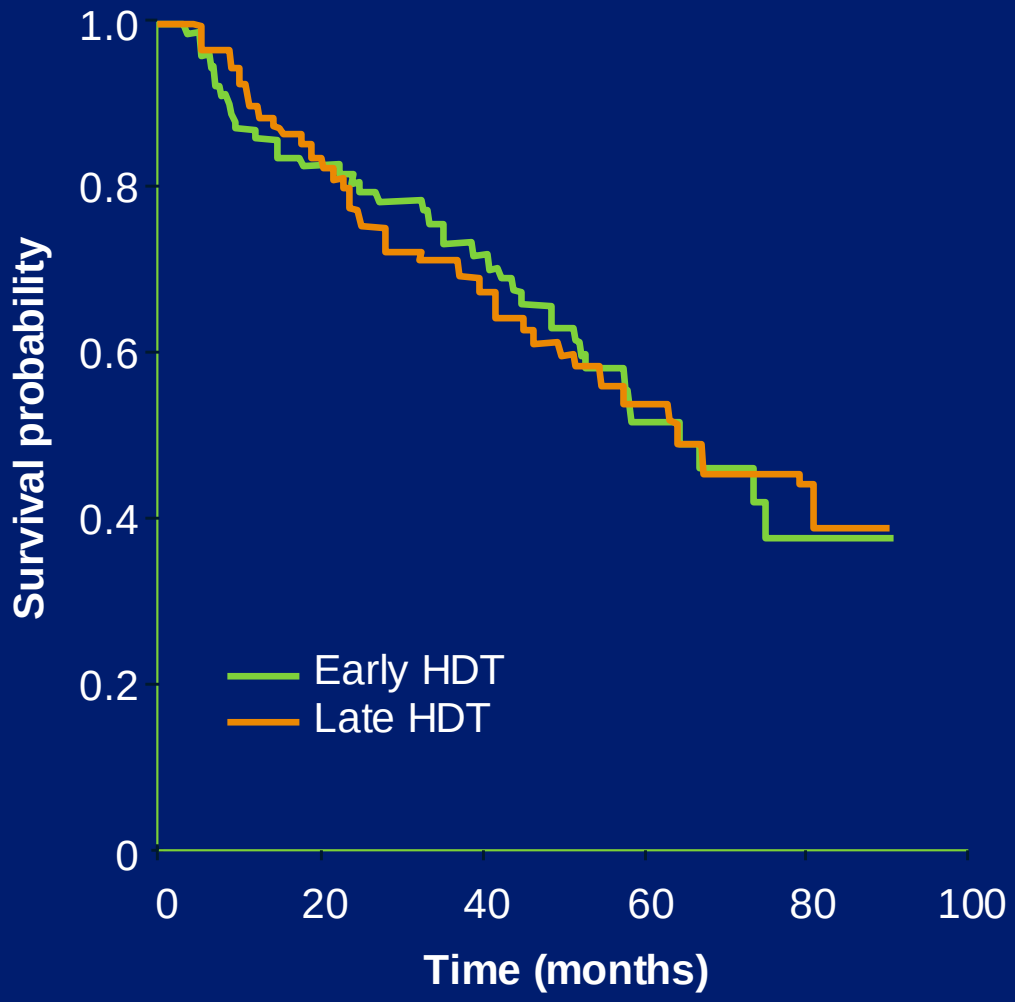
Single Vs. Double Transplant: Overall Survival

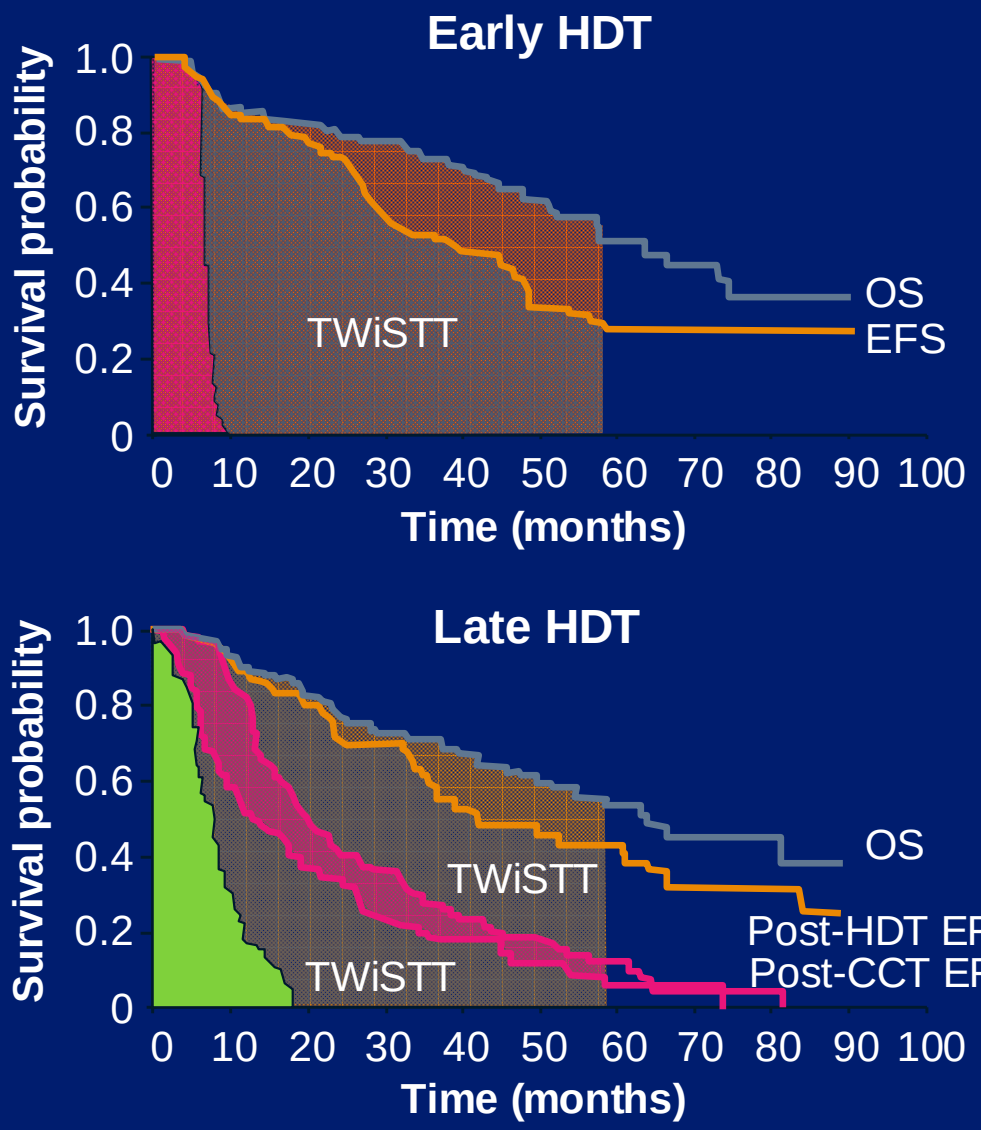
IFM 94



IFM = Intergroupe Francophone du Myélome.
Attal et al, 2003.

Timing of Transplant: Early vs Late Transplant





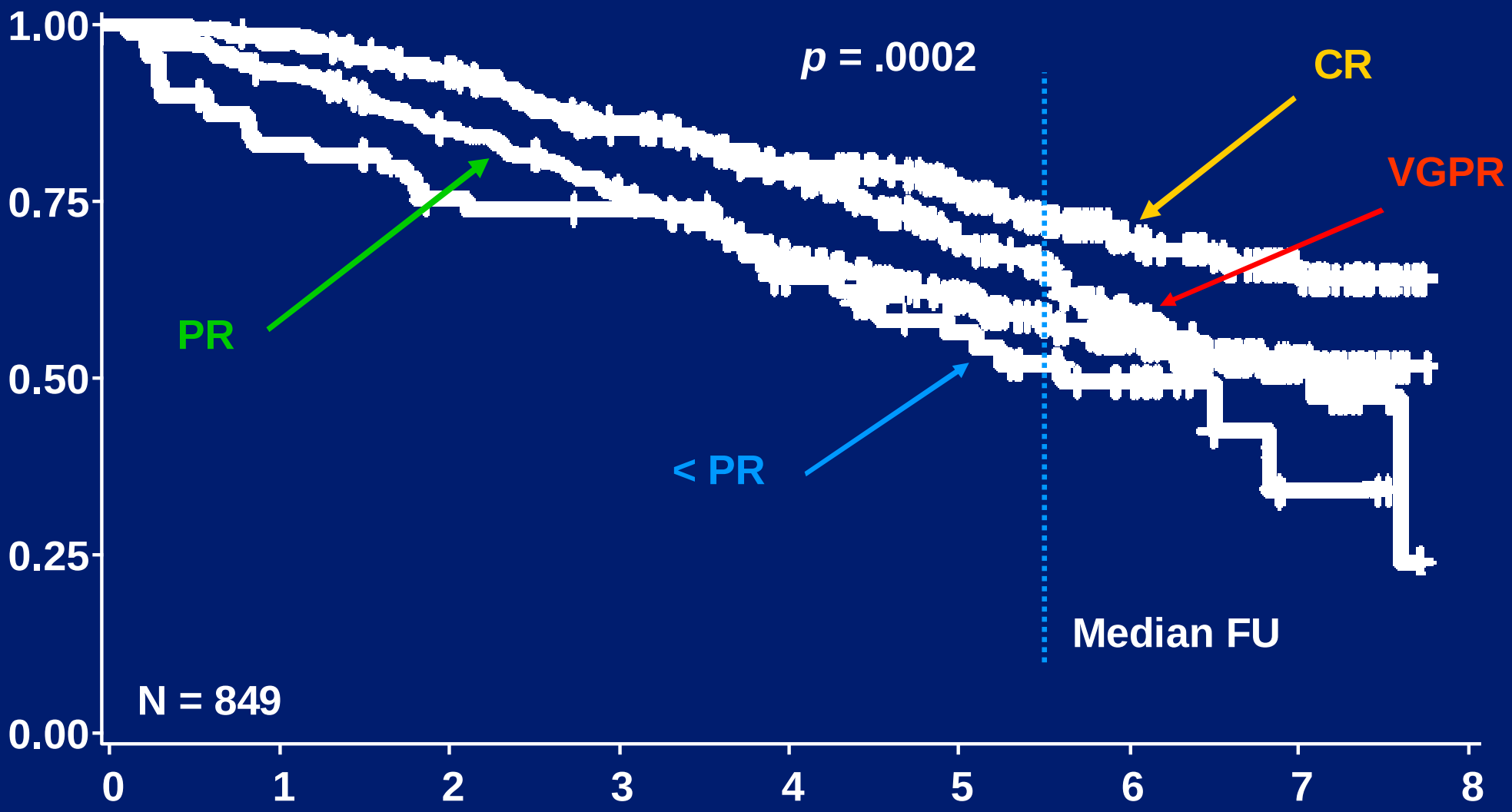
HDT = high-dose therapy; TWiSTT = time without symptoms, treatment, or treatment toxicity.

Fermand J-P, et al. Blood. 1998;92:3131-6.

GOAL OF THERAPY:

COMPLETE REMISSION

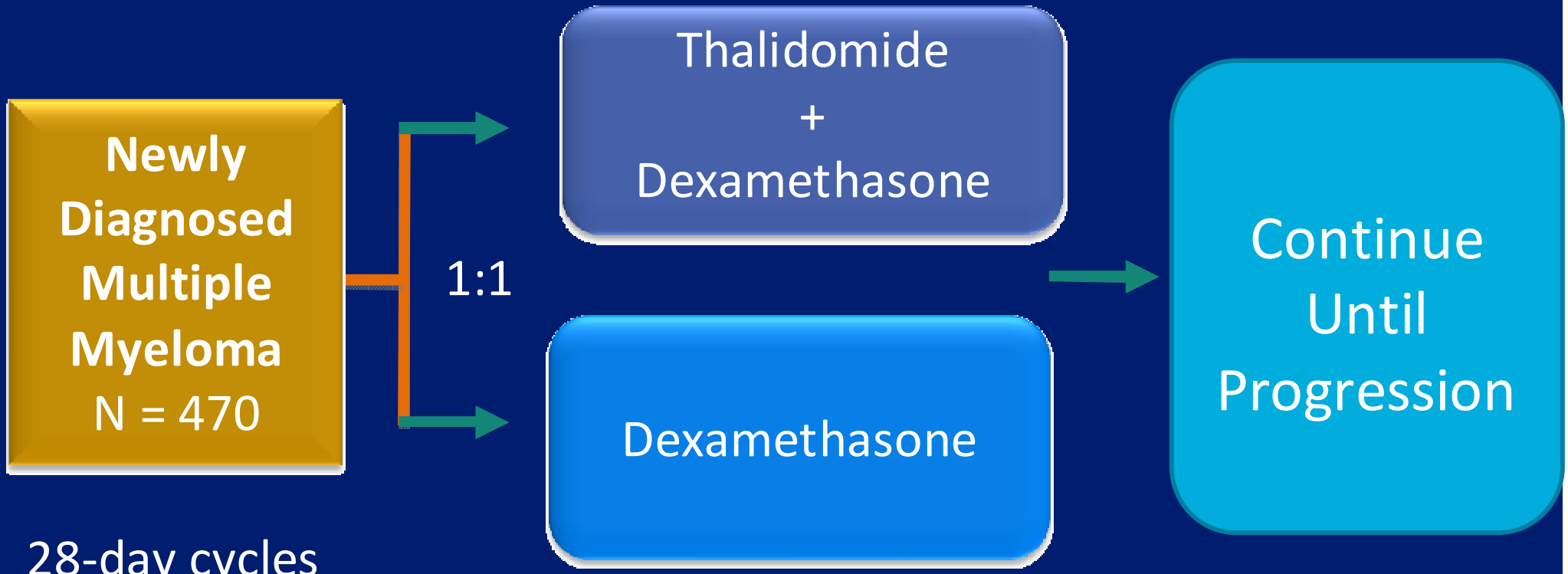
Impact of Response on Outcome: OS After 1 or 2 Transplants



PR = partial response; FU = follow-up.
Harousseau et al, 2006.

Outcomes with “Novel” Therapies

Phase III Thal/Dex vs Dex



28-day cycles

Thalidomide: 50 mg PO daily, d1-15; 100-200 mg d15, 200 mg/d, d1 cycle 2

Dexamethasone: 40 mg, d1-4, 9-12, 17-20

Rajkumar SV, et al. *J Clin Oncol.* 2008;26:2171-2177.

Phase III Thal/Dex vs Dex

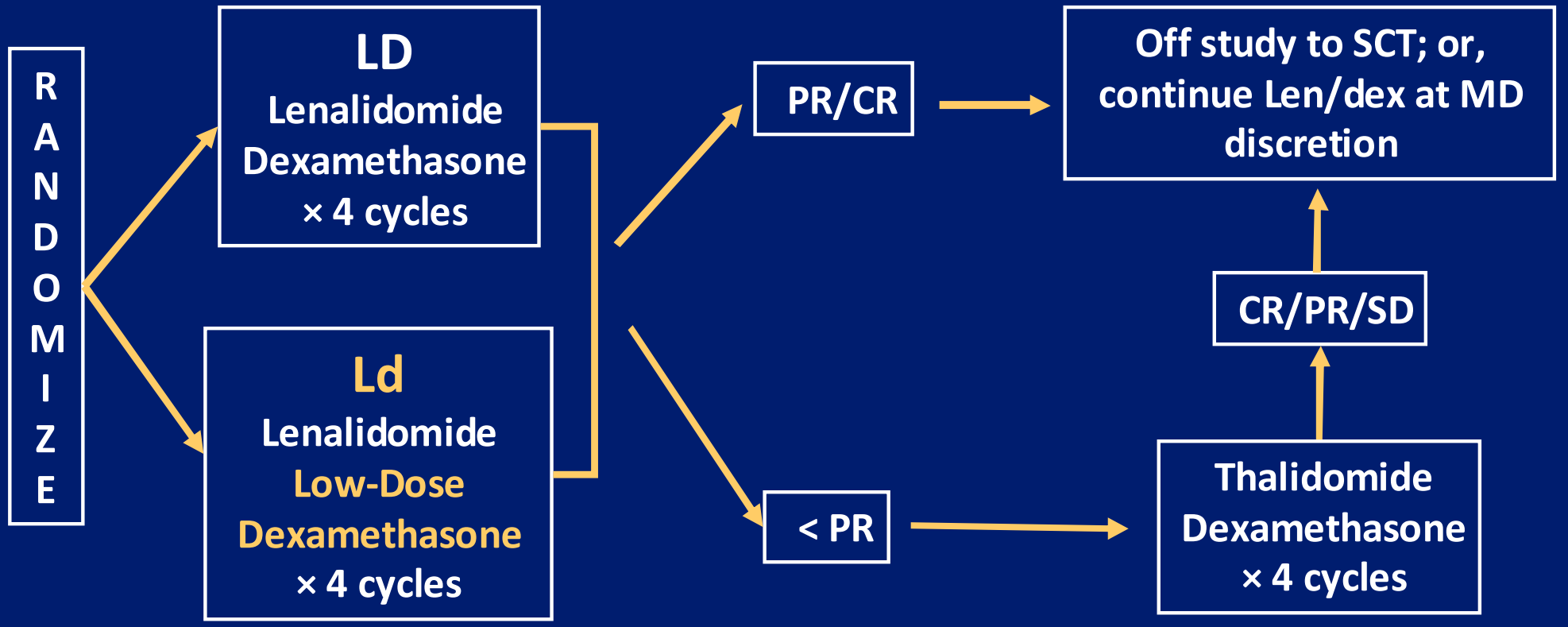
Response	Thal/Dex n = 235	Dex n = 235	*P*
ORR	63%	46%	< 0.001
CR	7.7%	2.6%	
PR	55.3%	43.4%	
CR + VGPR	43.8%	15.8%	< 0.001
Median TTP	22.6 months	6.5 months	< 0.001

Rajkumar SV, et al. *J Clin Oncol.* 2008;26:2171-2177.

Treatment of Elderly Transplant Candidates: Phase III Trials

Study	Regimen	N	TTP PFS/EFS	OS
Palumbo *(Blood 2008)*	MPT MP	129 126	22 15	45 vs. 48 p=0.79
Facon *(Lancet 2007)*	MPT MP	125 196	28 18	3y OS ~65% with MPT
San Miguel *(ASH 2008)*	VMP MP	344 338	24 17	3y OS ~72% with VMP
Rajkumar *(ASH 2008)*	RD Rd	445	22 23	3y OS: 75% with Rd in patients >65 yrs

Phase III E4A03 Trial: Lenalidomide Plus Standard (LD) or Low-Dose (Ld) Dexamethasone



Lenalidamide: 25 mg p.o. on days 1-21 of a 28-day cycle
Dexamethasone: 480 mg total per cycle (Regular Dose)
160 mg total per cycle (Low Dose)

Rajkumar et al. Lancet Oncology 11: 29 - 37, 2010

Results: LD vs. Ld

	LD	Ld
CR + PR	79%	68%
1 year OS	87%	96%
Grade 3 or worse AE	52%	35%

RD did not result in superior TTP, PFS, or OS compared to Rd

OS at 1-year was significantly better with Rd than RD, resulting in early closure of the trial

Rajkumar et al, 2010.

Survival Rate

	N	12 month survival Probability (95%CI)	24 month survival Probability (95%CI)
Len-High Dex (LD)	223	0.88 (0.84-0.92) 4 mo mortality 5.4%	0.78 (0.73-0.84)
Len-Low Dex (Ld)	222	0.96 (0.93-0.98) 4 mo mortality 0.5%	0.88 (0.84-0.93)

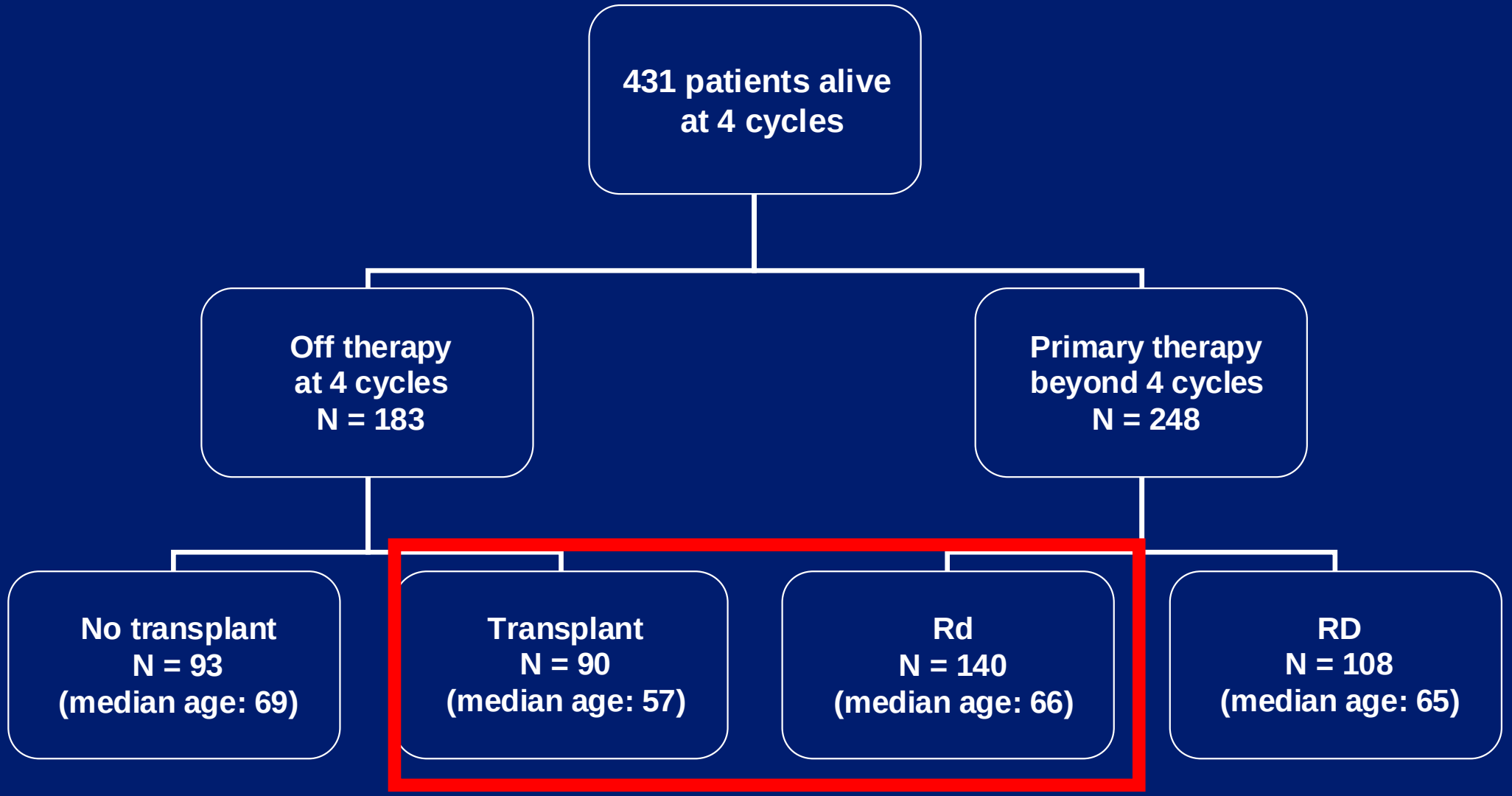
Based upon this data, the DSMB mandated a crossover of all patients currently being treated with High-Dose Dexamethasone (LD)

One-Year Survival Rate in Phase III Trials of Newly Diagnosed Patients

Study	Age	Phase	N	Regimen	1-yr Survival rate	Ref
Rajkumar, E1A00	Median=65	III	103	Thal Dex vs Dex	80%	JCO 2006
Rajkumar, MM003	Median=65	III	470	Thal Dex vs Dex	80%	ASH 06
Palumbo	Median=72	III	255	MPT vs MP	87%~	Lancet 06
Attal, IFM	<65	III	200	Auto vs Chemo	88%~	NEJM 1996
Child, MRC	<65	III	401	Auto vs Chemo	87%~	NEJM 2003
Barlogie, S9321	<=70	III	516	Auto vs Chemo	84%*	JCO 06
Attal, IFM	<60	III	399	Single vs Double Auto	90%~	NEJM 2003
Barlogie, TT II	**<75****	**III**	**668**	**TT2 +/-Thal**	**92%**	**NEJM 2006**
E4A03 Arm A	Median=65	223	223	Len + high-dose dex	87%	ASCO 2007
E4A03 Arm B	**Median=65**	**222**	**222**	**Len + low-dose dex**	**96%**	**ASCO 2007**

Rajkumar SV, et al. *J Clin Oncol.* 2007;25(Supplement):LBA8025.

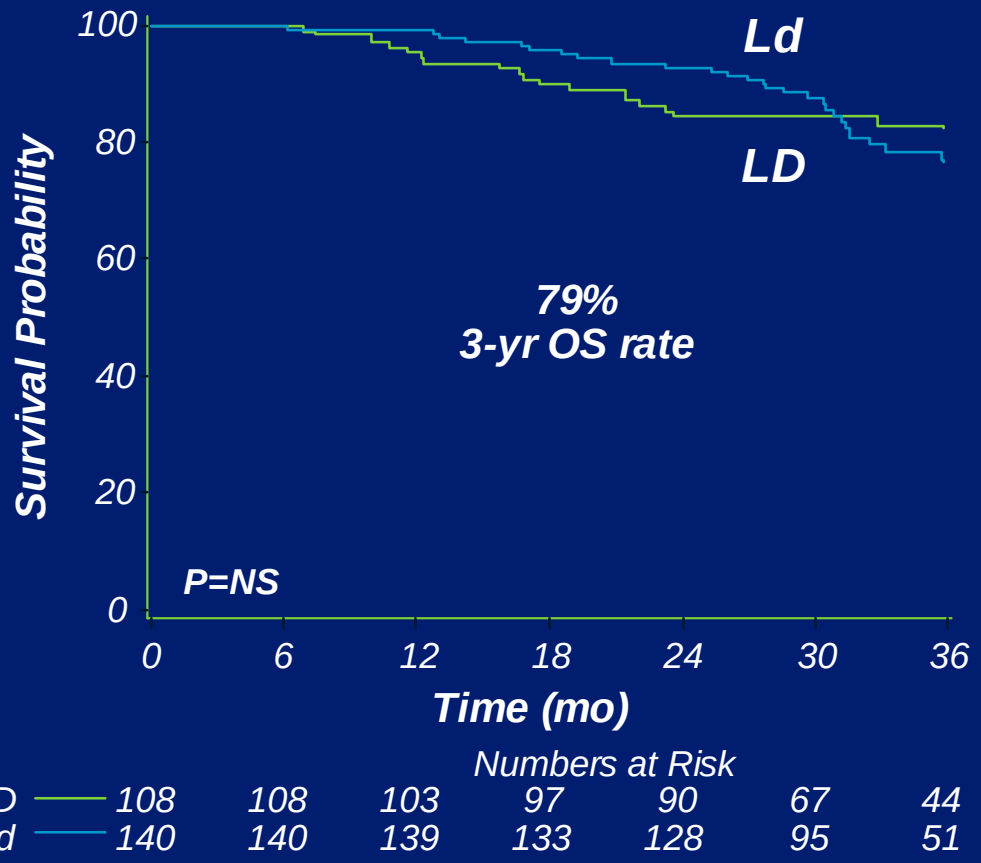
Landmark Analysis



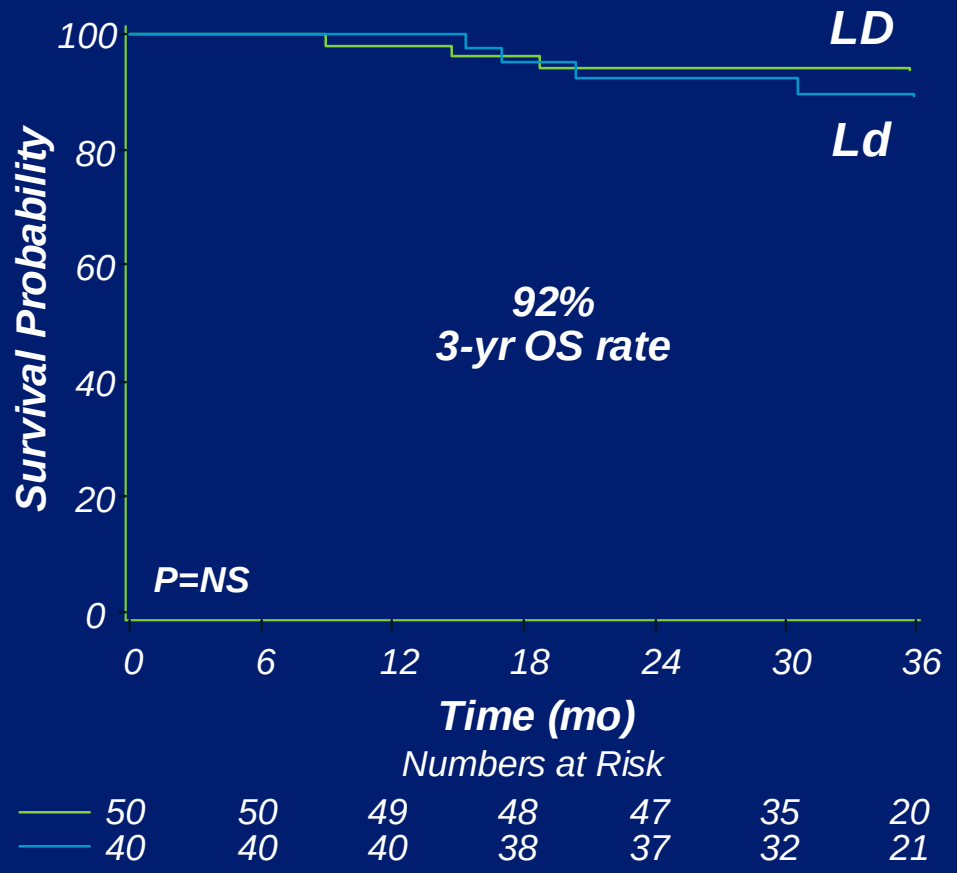
Rajkumar et al, 2010.

E4A03: OS According to Transplant or No Further Treatment at 4 Cycles

E4A03: Primary Therapy Beyond 4 Cycles

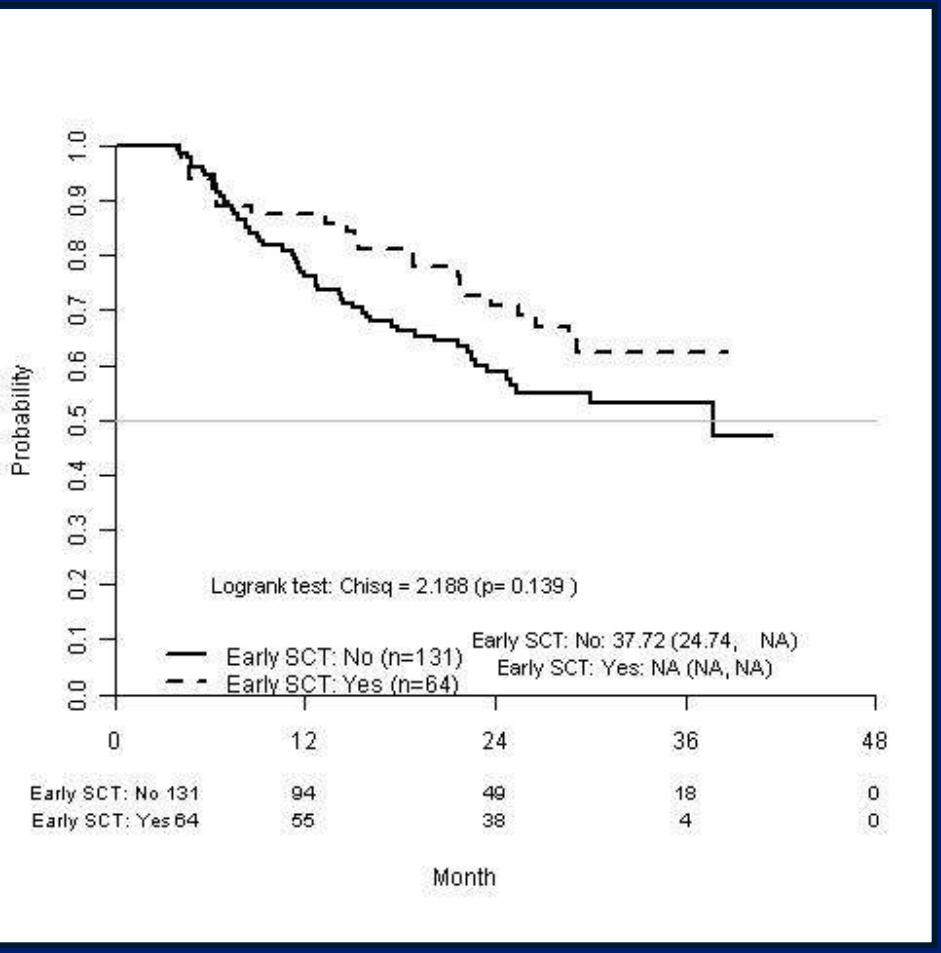


ASCT after 4 cycles LD or Ld

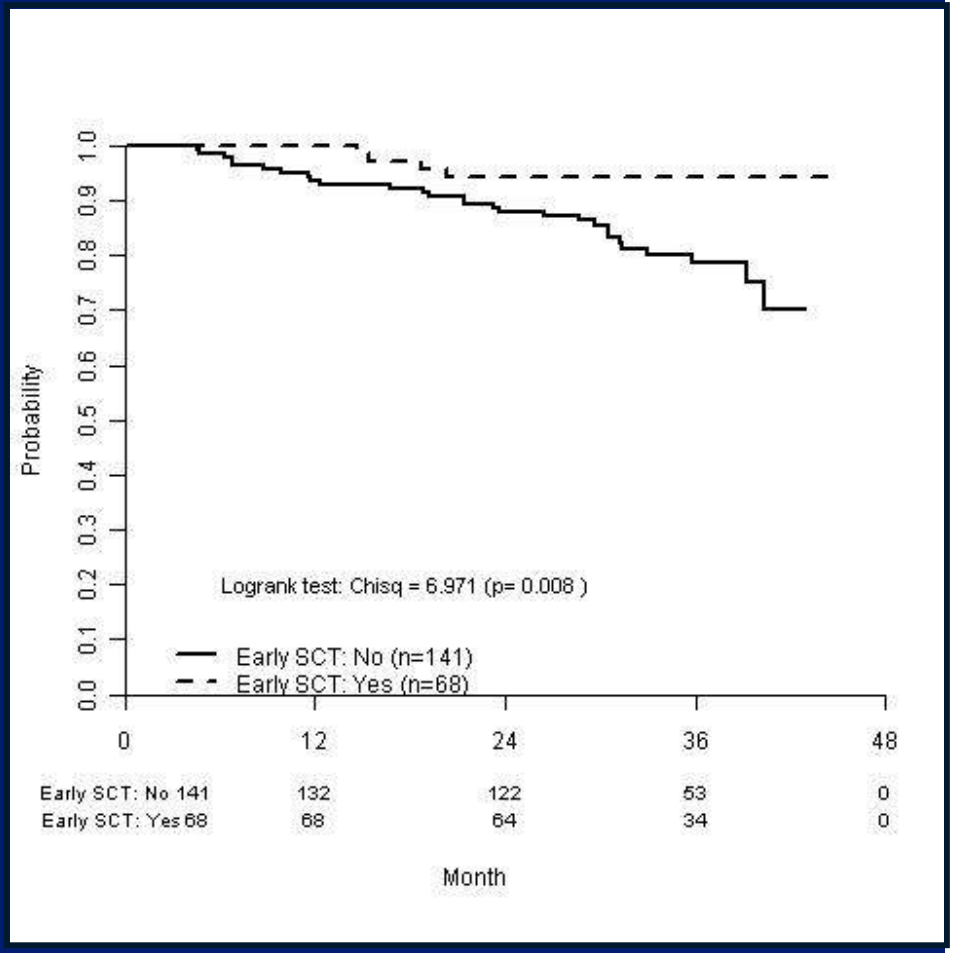


Rajkumar SV et al. Lancet Oncology, 11:29 - 37, 2010

Outcomes in pts Age <65



Progression Free Survival



Overall Survival

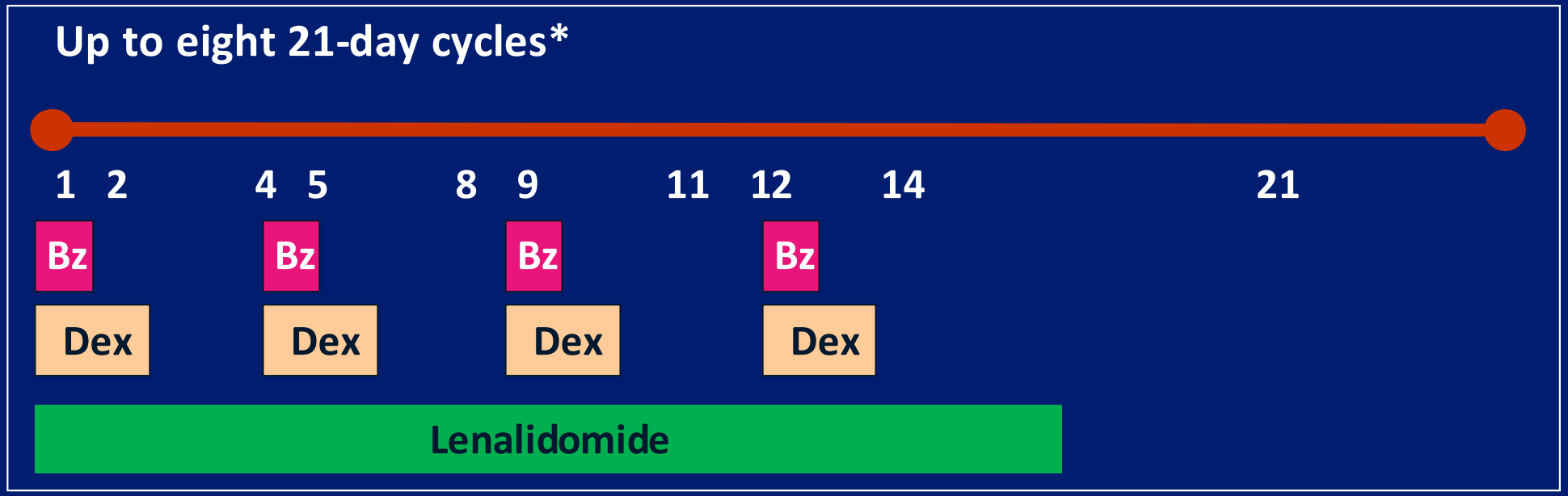
Toxicities

- Patients who discontinued the assigned therapy at 4 cycles were censored. Unable to assess treatment related morbidity.
- Given that the overwhelming majority of deaths occurring within 1 year were treatment related, this should be a good surrogate for TRM.

1-yr mortality

	No Early SCT:	Early SCT
Overall	0.94 (0.91, 0.96)	0.99 (0.97, 1.00)
Age <65	0.94 (0.90, 0.98)	0.99 (0.96, 1.00)
65≤ Age <70	0.96 (0.91, 1.00)	0.94 (0.83, 1.00)
Age ≥70	0.92 (0.88, 0.97)	1.00 (1.00, 1.00)

Lenalidomide/Bortezomib/Dex (RVD) as Induction



*Dex, 40 mg/day Days 1, 2, 4, 5, 8, 9, 11 and 12; 20 mg, cycles 5–8;
Amended to 20 mg/10 mg cycles 1–4/5–8 based on safety data

- Pts ≥PR may proceed to ASCT after ≥4 cycles
- Maintenance therapy permitted in pts ≥SD using weekly (days 1 and 8) schedule of Bz, and Dex on days 1, 2, 8, and 9
- Antithrombotic therapy with daily aspirin (81 or 325 mg)
- Antiviral therapy as prophylaxis against Herpes Zoster

Richardson et al Blood April 2010

Best Response to RVD

Response, n (%)	All pts (N=66)	Phase II (N=35)
CR	19 (29)	13 (37)
nCR	7 (11)	7 (20)
VGPR	18 (27)	6 (17)
PR	22 (33)	9 (26)
CR+nCR	26 (39)	20 (57)
(90% CI)	(29, 50)	(42, 71)
CR+nCR+VGPR	44 (67)	26 (74)
(90% CI)	(56, 76)	(59, 86)
At least PR	66 (100)	35 (100)
(90% CI)	(96, 100)	(92, 100)

- Response improvement seen in 42/56 pts (75%) from C4–8 and 20/38 pts (53%) beyond C8
- Median (range time to best overall response) was 2.1(0.6,20) mos

Lenalidomide / Bortezomib-Based

Response	RVD[2] N = 66	RVDD[3] N = 70	VDCR[4] N = 41
CR + nCR	39%	33%	32%
≥ VGPR	67%	59%	59%
≥ PR	100%	97%	93%

RVD: lenalidomide, bortezomib, dexamethasone; RVDD: RVD with pegylated liposomal doxorubicin; VDCR: RVD plus cyclophosphamide; VTD: bortezomib, thalidomide, dexamethasone

- Hematologic toxicity not cumulative
- Risk of DVT does not appear to be increased over lenalidomide alone
- Risk of PN does not appear to be increased over bortezomib alone

[1]Cavo M, et al. *Blood.* 2009:114(22). Abstract 351. [2]Anderson KC, et al. *J Clin Oncol.* 2010;28(15S). Abstract 8016. [3]Jakubowiak AJ, et al. *Blood*. 2009;114(22). Abstract 132. [4]Kumar S, et al. *Blood*. 2009:114(22). Abstract 127.

Phase II and III trials of doublet and triplet lenalidomide-based induction treatments for transplant-eligible patients

Regimen	N	After induction		PFS median	OS median	Author
		CR + PR (%)	CR/≥VGPR (%)			
RD vs Rd	223 222	81 70	5/50 4/40	19 mos 25 mos p=0.02	NR* NR p=0.4	Rajkumar et al
RVD	66	100	29 (39)*/67	75% @ 18 mo	97% @ 18 mo	Richardson et al
RVD vs VCD vs RVCD	42 32 42	83 75 86	24 (40)*/50 22 (31)*/41 24 (33)*/57	NR	NR	Kumar et al
RVDD	57	96	nr (30)*/58	NR	NR	Jakubowiak et al

*NR-not reached

Autologous Transplant Improves Responses After Traditional or Novel Induction

	Macro ASH 2006		Harousseau ASH 2009		Cavo ASH 2009	
	VAD (%)	ThalD (%)	VAD (%)	VelD (%)	ThalD (%)	VelThalD (%)
Induction ≥ VGPR	7	25	16	39	28	61
Transplant ≥ VGPR	42	44	37	54	64[a]	79[a]

[a]Tandem transplants.
ASH = American Society of Hematology.

Phase III Studies of Thalidomide-based Combinations in Preparation for ASCT

Regimen	N	After induction		After ASCT		PFS	OS
		CR+PR (%)	CR/≥VGPR (%)	CR+PR (%)	CR/≥VGPR (%)		
TAD vs VAD	268 268	71 57	3/37 2/18	84 76	14/54 12/44	median 34 mos 22 mos p<0.001	median 73mos 60mos p=0.77
						5-yr	5-yr
TT2+THAL vs TT2 without THAL	323 345	NR NR	NR NR	NR NR	62/nr 43/nr	56% 44% p=0.01	65% 65% p=0.90
						4-yr	5-yr
Double ASCT+THAL vs Double ASCT without THAL	135 135	NR NR	NR/30 NR/15	NR NR	NR/68 NR/49	51% 31% p=0.001	69% 53% p=0.07

Phase III trials of bortezomib-based regimens in preparation for ASCT

Regimen	N	After induction		After ASCT		PFS	OS
		CR + PR (%)	CR/≥VGPR (%)	CR + PR (%)	CR/≥VGPR (%)		
VD vs VAD	223 218	78.5 63	6 (15)*/38 1 (6)*/15	80 77	16(35)*/54 9 (18)*/37	median 36 mos 30 mos p=0.06	3-yr 81% 77% p=0.5
VTD vs TD	236 238	93 79	19 (31)*/62 5 (11)*/28	93 84	42 (55)*/82 30 (41)*/64	3 yr 68% 56% p=0.005	3 yr 86% 84% p=0.03
VBMCP/VBAD+V vs VTD vs TD	129 130 127	75 85 62	21/36 35/60 14/29	73 77 58	38/51 46/65 24/40	median 38 mos 27 mos NR p=0.006	NR NR NR
PAD vs VAD	371 373	78 55	NR (11)*/42 NR (5)*/15	88 77	NR (30)*/61 NR (15)*/36	3 yr 36% 27% p=0.005	3 yr 78% 70% p=0.02
VD vs vTD	99 100	81 90	12 (22)*/35 13 (32)*/51	84 90	33 (54)*/59 30 (61)*/73	NR NR	NR NR

Total Therapy (TT) Trials: Treatment Schema

Phase	TT1	TT2	TT3
Randomization	–	±Thal (400 mg/day)	–
Induction	VAD × 3 ↓ HDCTX ↓ EDAP	VAD ↓ DCEP ↓ CAD ↓ DCEP	VDT-DPACE ↓ VDT-DPACE
ASCT 1	MEL200	MEL200	MEL200
ASCT 2	MEL200 MEL140 + TBI if <PR	MEL200 BEAM if <PR	MEL200
Consolidation	None	DCEP/CAD	VDT-PACE
Maintenance	IFN-α	IFN-α (+ D in 1st yr)	1st yr with VTD 2nd yr with T+D

Barlogie B et al. *Blood*. 1999;93:55; Shaughnessy J Jr et al. *Br J Haematol*. 2003;120:44;
Barlogie B et al. *Blood*. 2005;106:337a [abstract 1154]

Comparison of Total Therapy Regimens

	TT1 N = 231	TT2 N = 668	TT3 N = 303
Regimen	Phase II High-dose CT w/ IFN maintenance	Phase III High-dose CT ± thalidomide w/ post-SCT consolidation	Phase II bortezomib + thalidomide throughout therapy
Median FU	15.6 years	7.2 years	3.9 years
CR rate	40%	50%	60%
Median CR duration	2.5 years	5 years	3-year estimate 90%
Median EFS	2.6 years	4.8 years	3-year estimate 80%
Median OS	5.7 years	9 years	3-year estimate 85%
Projected cure fraction	9.0%	8.5%	74% (low-risk)

Barlogie B, et al. *J Clin Oncol*. 2009;27(15S). Abstract 8519.
Barlogie B, et al. *J Clin Oncol.* 2008;26(15S). Abstract 8516.

VRD induction, ASCT, VRD consolidation, lenalidomide maintenance
IFM 2008 Phase II Study

Induction treatment: 3 cycles VRD

Lenalidomide 25mg/d (days 1 to 14)
Bortezomib 1.3mg/m^2 (days 1, 4, 8, 11)
Oral Dexamethasone 40mg/d (days 1, 8, 14)

Response assessment

Peripheral Stem Cell Collection ≥ 5x10^6 /kg (cyclophosphamide 3g/m^2 and G-CSF 5µg/kg/d)

Response assessment — **Immunophenotypic analysis**

ASCT
Melphalan 200mg/m^2 on D-2 + Pegfilgrastim 6mg D2

Response assessment — **Immunophenotypic analysis**

Consolidation treatment = 2 cycles VRD

Response assessment — **Immunophenotypic analysis**

Maintenance therapy for 12 months: Lenalidomide

Lenalidomide 10mg/d for 3 months then 15mg/d if well tolerated

Response assessment according to IMWG criteria with immunophenotypic sCR

Roussel et al. ASH 2010 (Abstract 624)

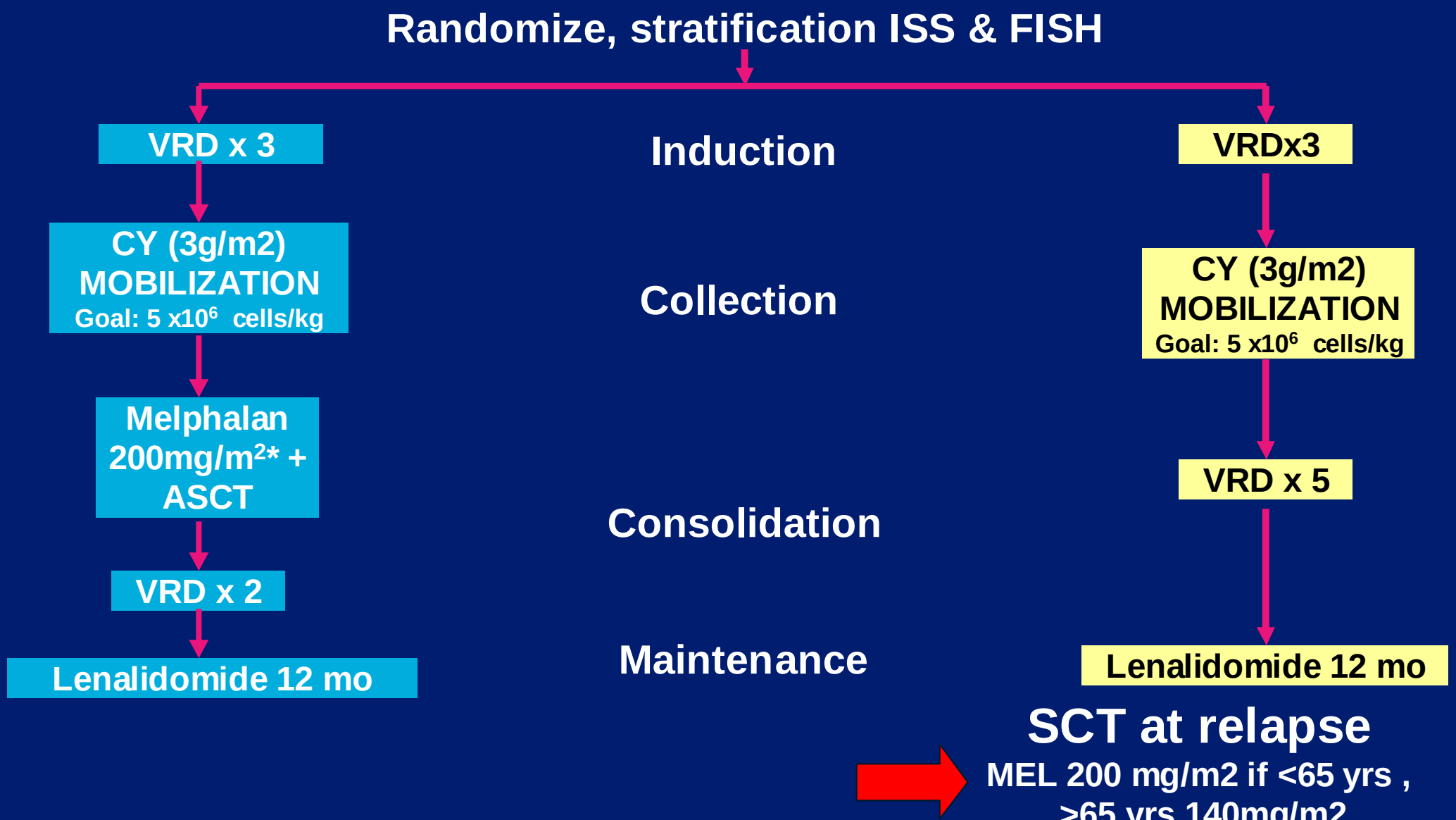
VRD induction, ASCT, VRD consolidation, lenalidomide maintenance IFM 2008 Phase II Study

- Patients (n=31), median age 58 years

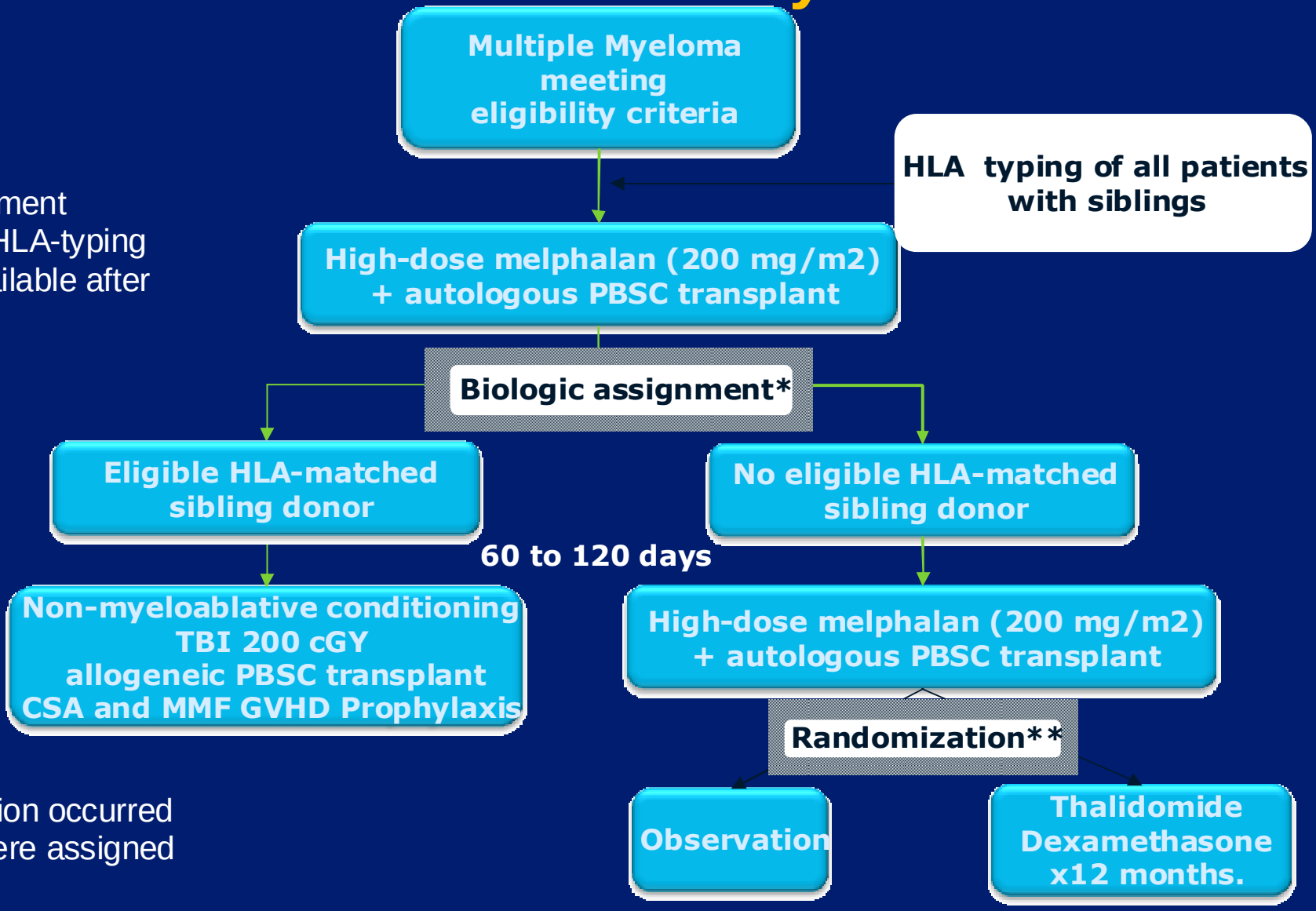
	After induction	After ASCT	After consolidation
	%	%	%
sCR	13	26	38
CR	10	10	10
CR+sCR	23	36	48
VGPR	**39**	**32**	**36**
≥ VGPR	62	68	84
PR	**32**	**23**	**10**
ORR	94	91	94

Roussel et al. ASH 2010 (Abstract 624)

IFM/DFCI 2009 Study
Newly Diagnosed MM Pts (SCT candidates)



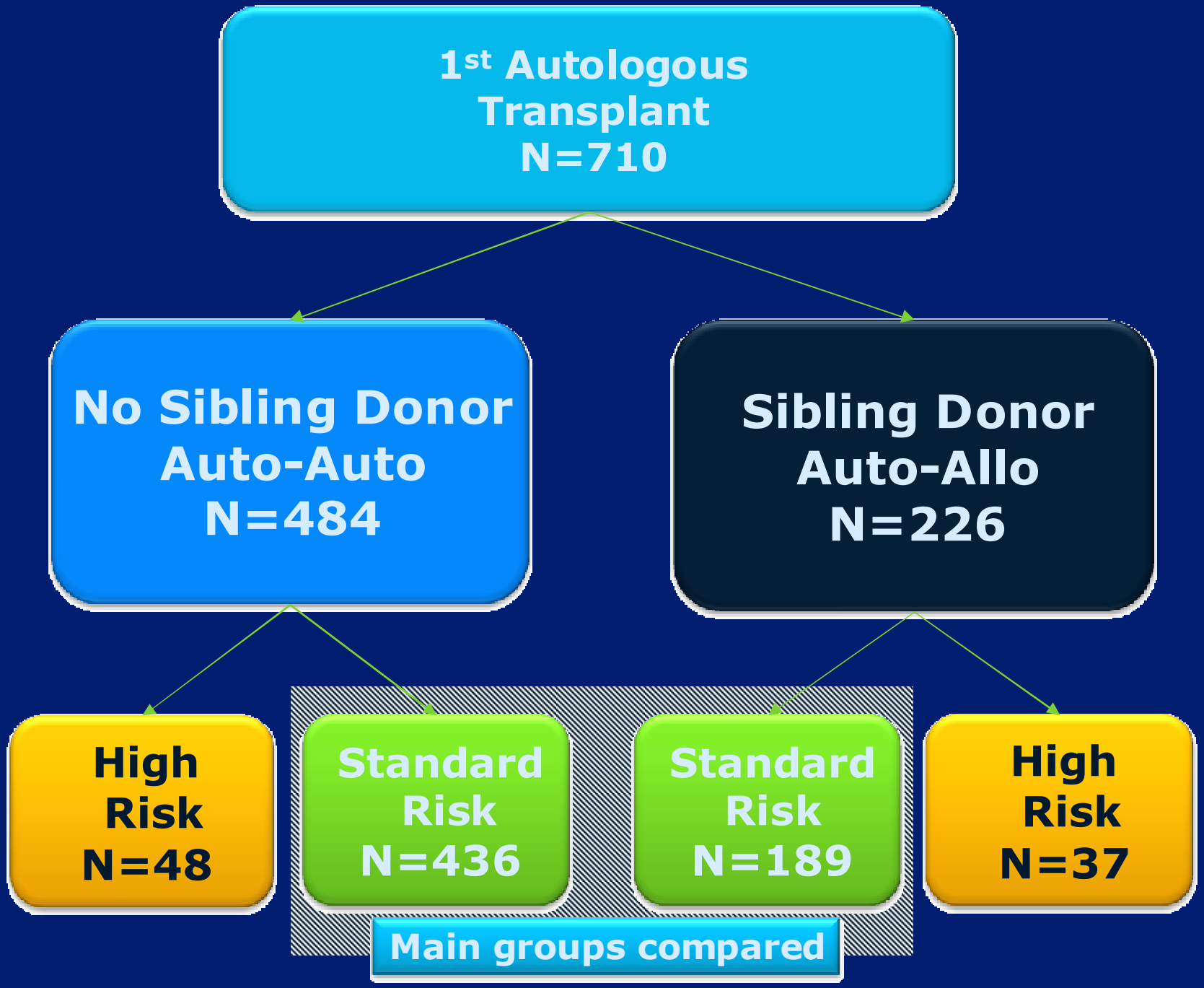
BMT CTN 0102 Study Schema



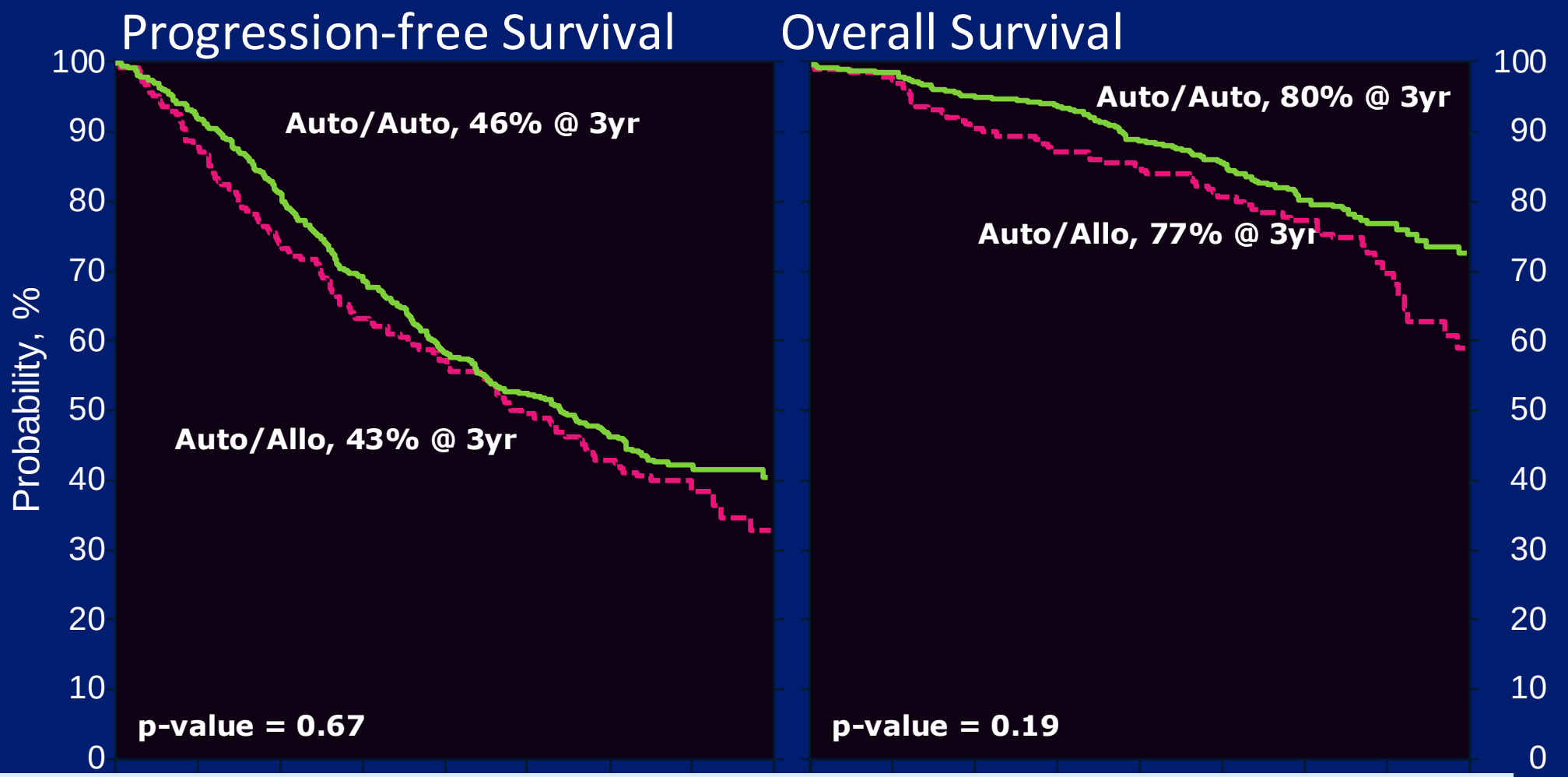
*Biologic assignment occurred when HLA-typing results were available after enrollment.

** Randomization occurred once patients were assigned to auto-auto

PRIMARY ENDPOINT : 3yr Progression Free Survival


1st Autologous Transplant N=710
No Sibling Donor Auto-Auto N=484
Sibling Donor Auto-Allo N=226
High Risk N=48
Standard Risk N=436
Standard Risk N=189
High Risk N=37
Main groups compared

Survival Outcomes after the First Transplant: Auto-Auto vs. Auto-Allo: Intent-to-treat analysis



Months	0	6	12	18	24	30	36	42	48	0	6	12	18	24	30	36	42	48
# at risk:																		
Auto/Auto	436	395	348	292	242	213	178	54	42	436	424	406	395	370	348	305	107	79
Auto/Allo	189	165	138	117	105	89	71	23	16	189	183	167	160	156	143	124	43	27

Conclusions

- Novel therapies improve induction response rates
  - Incidence of CR: 20-40%
- High dose therapy further improves response rates
  - Incidence of CR: 40-60%
- PFS appears to be longer in patients treated with induction therapy followed by transplant compared to continuation of initial therapy
- Maintenance therapy improves PFS