Transplants for Multiple Myeloma

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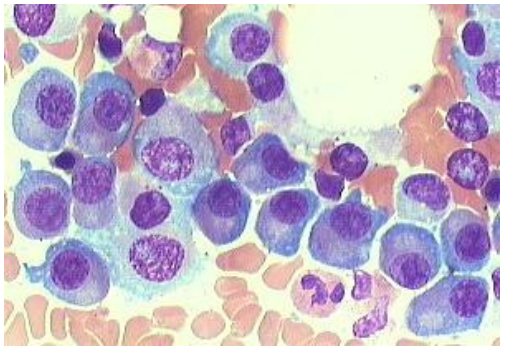
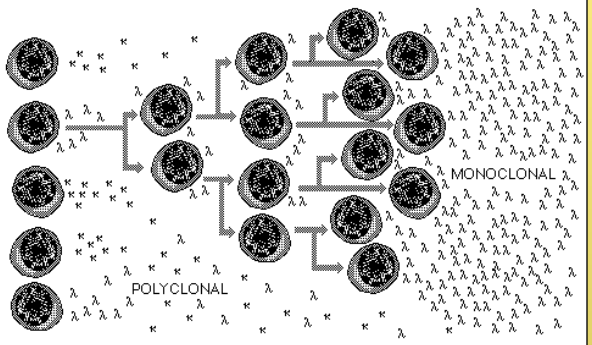
Transplants for Multiple Myeloma



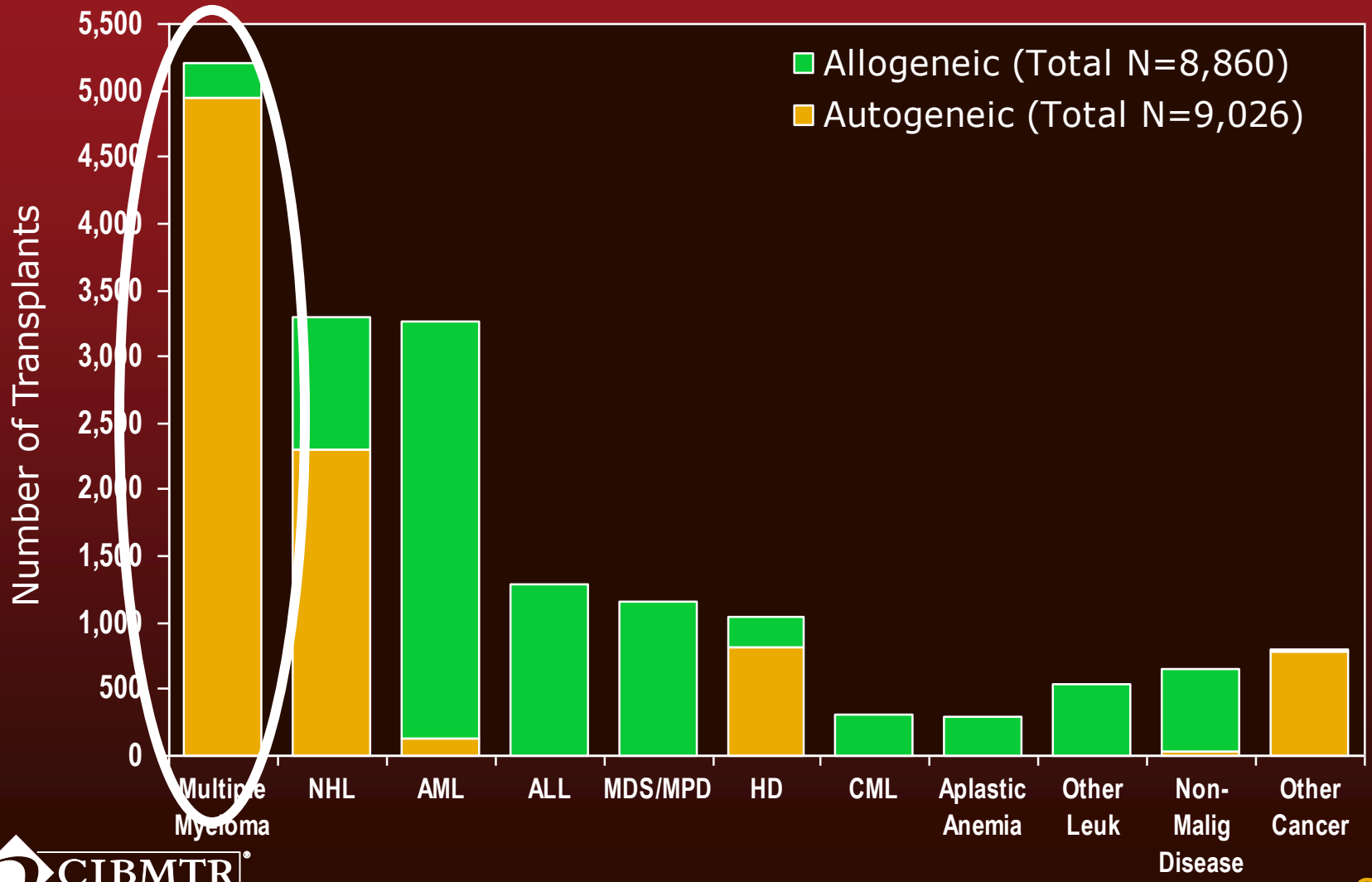
- Multiple myeloma is an incurable plasma cell disorder.
- Clinical presentation includes:
  - Anemia, lytic bone lesion, kidney failure, hypercalcemia and repetitive infections
- Most common indication of autologous transplants
- Many new regimens available for disease control.

TOPICS



- Impact of novel agents on myeloma outcomes
- Trends in treatment practices
- Is transplant needed at all?
- Role of allogeneic transplant

Indications for Hematopoietic Stem Cell Transplants in the United States, 2010



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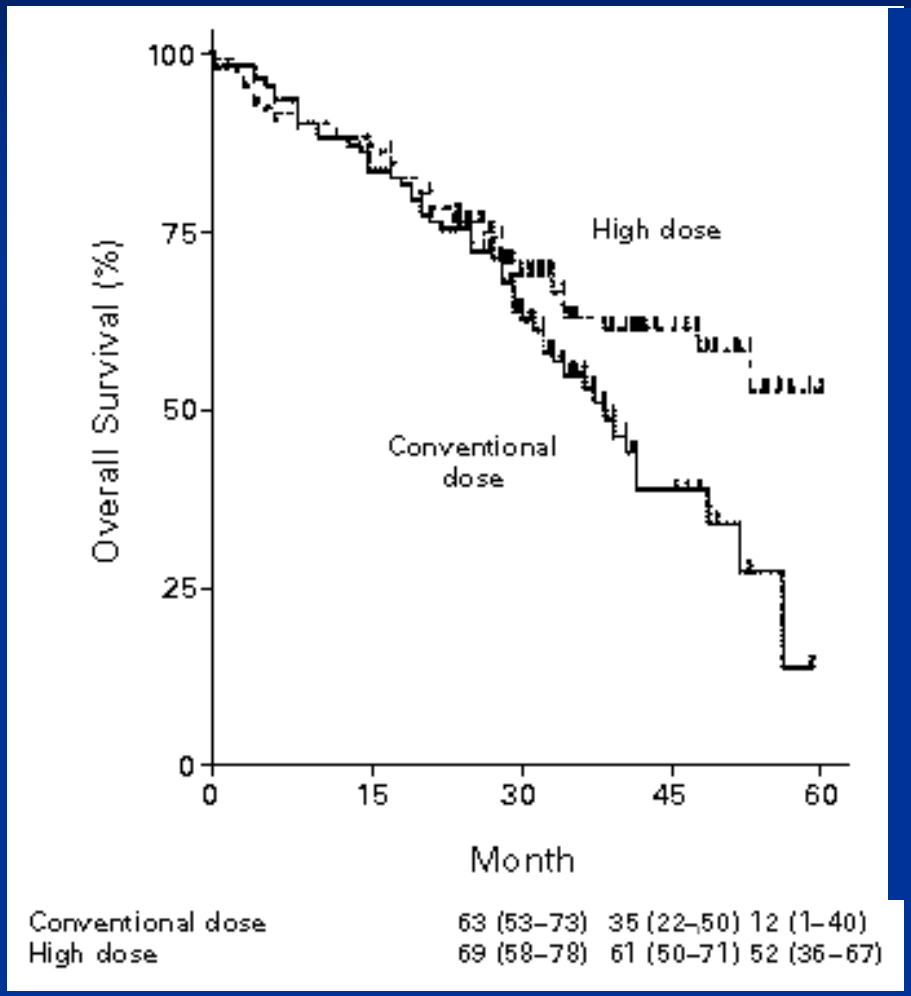
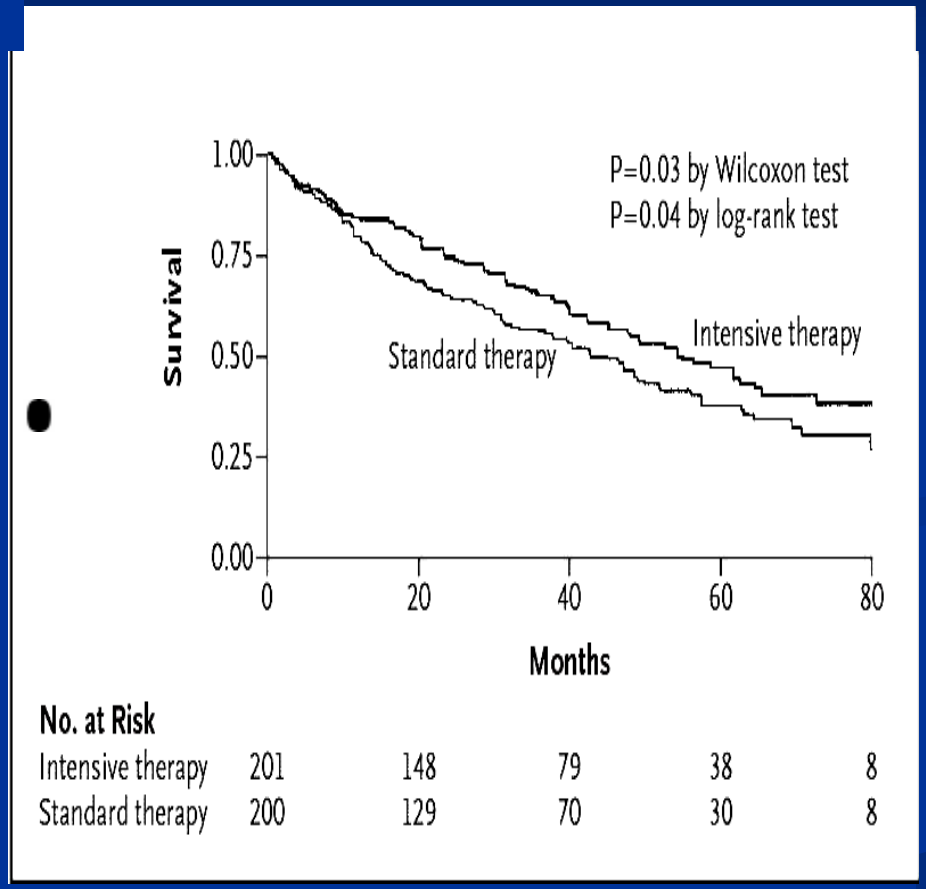
Autologous HCT vs. Chemotherapy

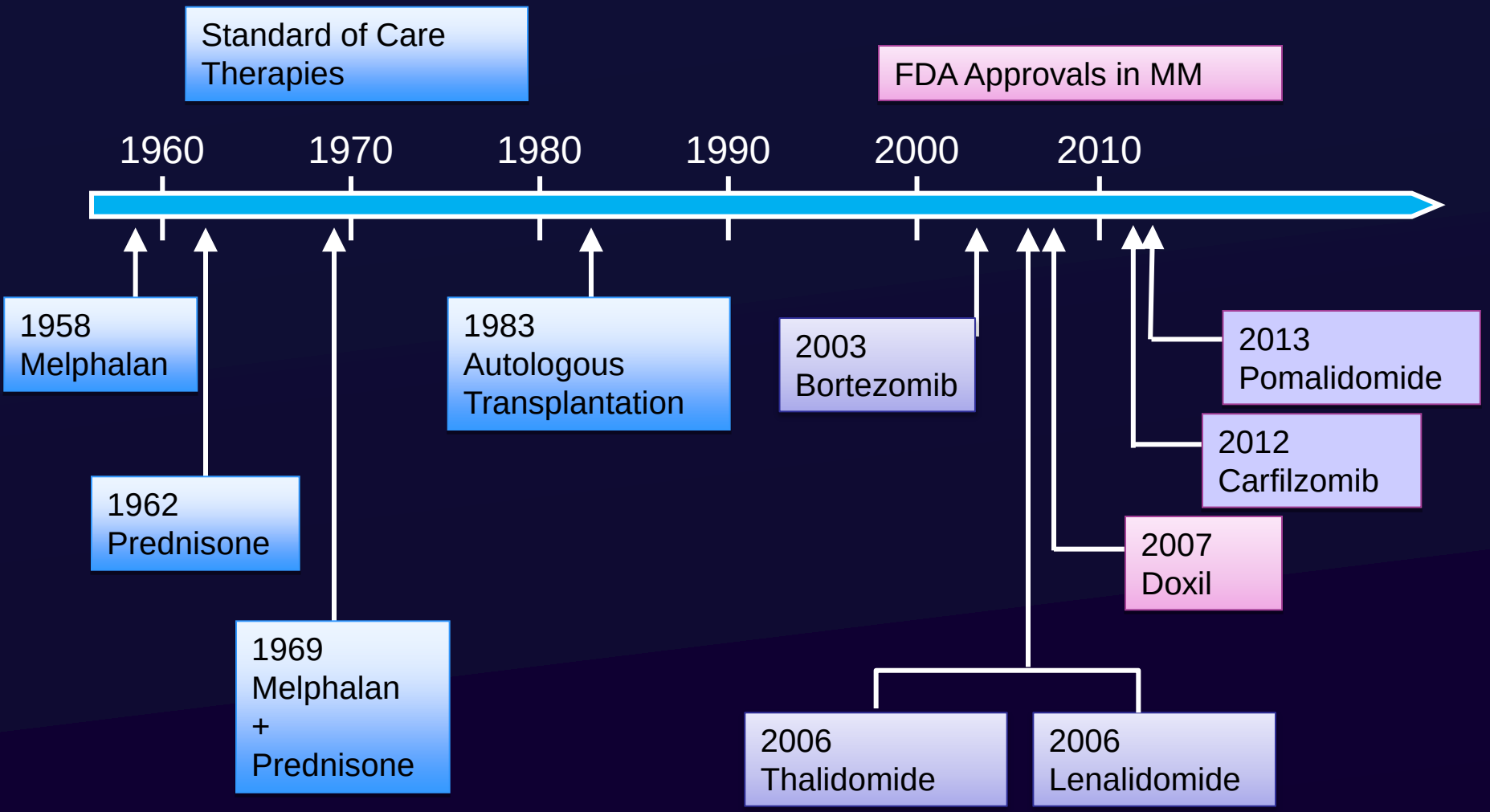




Attal M. N Engl J Med 1996; 335:97

Child J. N Engl J Med 2003; 348:1875

History Myeloma Therapy

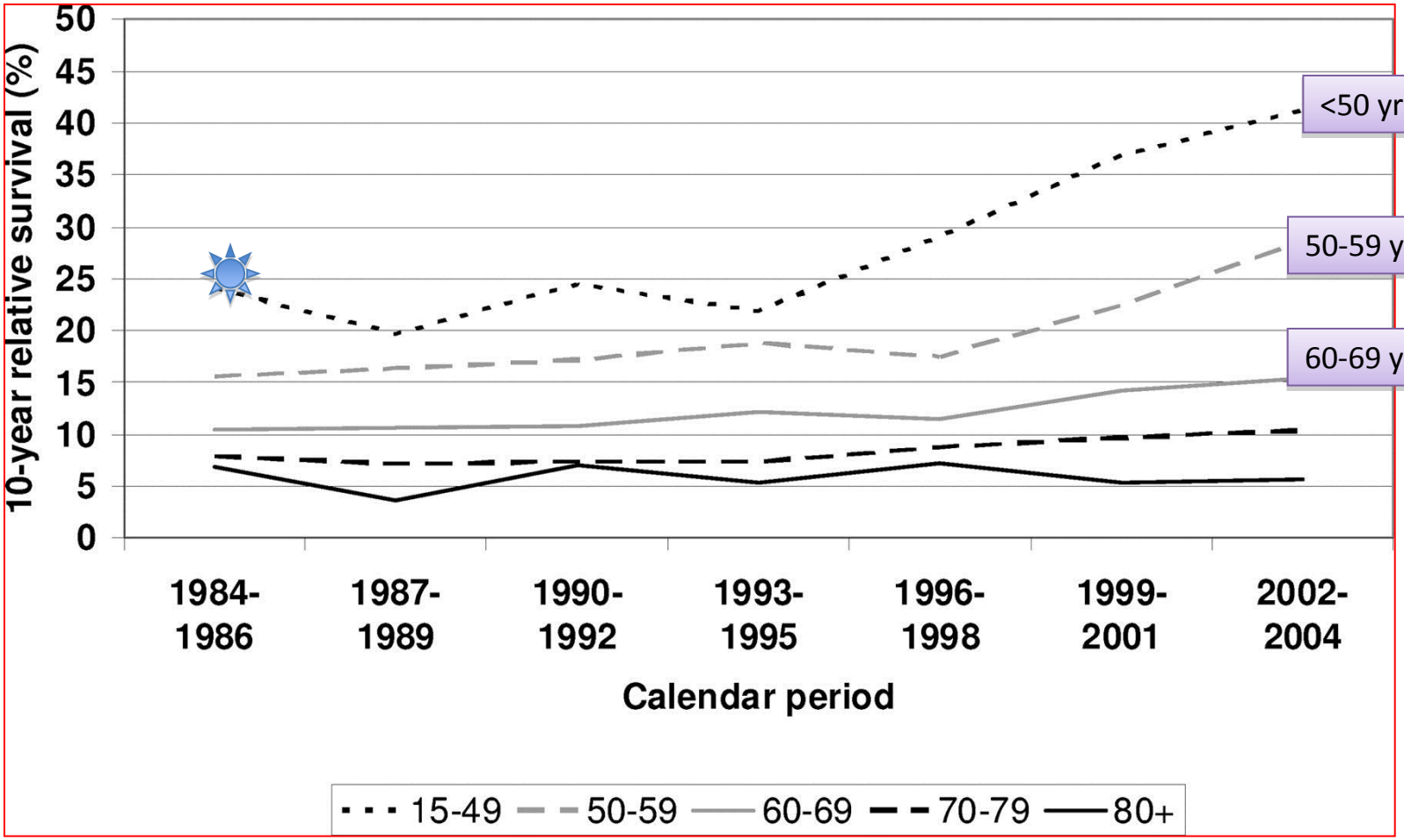


Adapted from Kumar SK et al. *Blood*. 2008;111:2516–2520.

Major Question
Time to abandon autotransplant?

- Excellent Outcomes of newer drug induction
- OS advantage of autotransplant was proven in comparison to "old" conventional chemotherapy
- Is there evidence of benefit in the modern era?

MYELOMA SURVIVAL
Over Time



Reasons????

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

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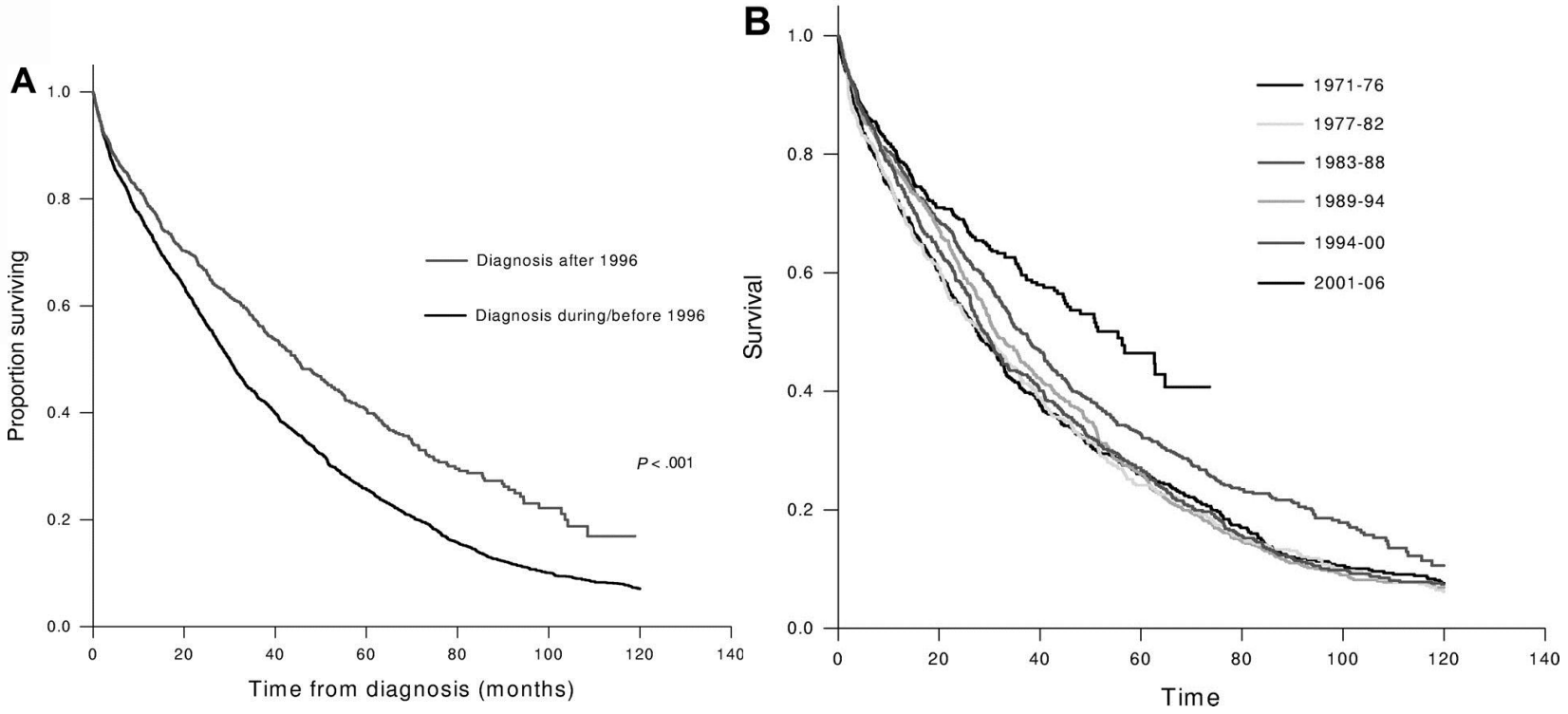
blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Overall survival from diagnosis of multiple myelomas.



Kumar S K et al. Blood 2008;111:2516-2520

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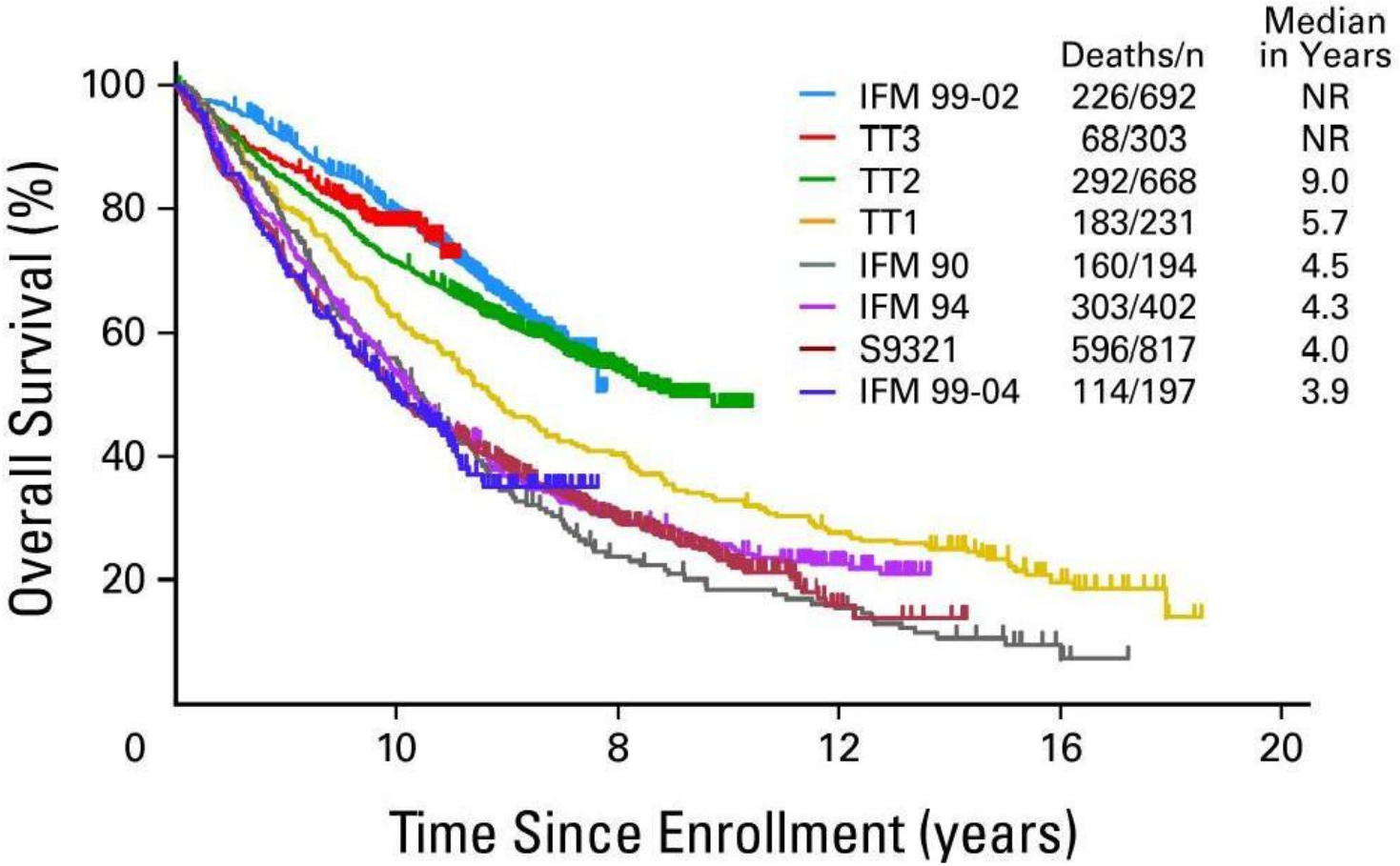
Overall Survival of Autotransplantation in MM



Barlogie B, et al. *J Clin Oncol.* 2010;28(7):1209-1214.

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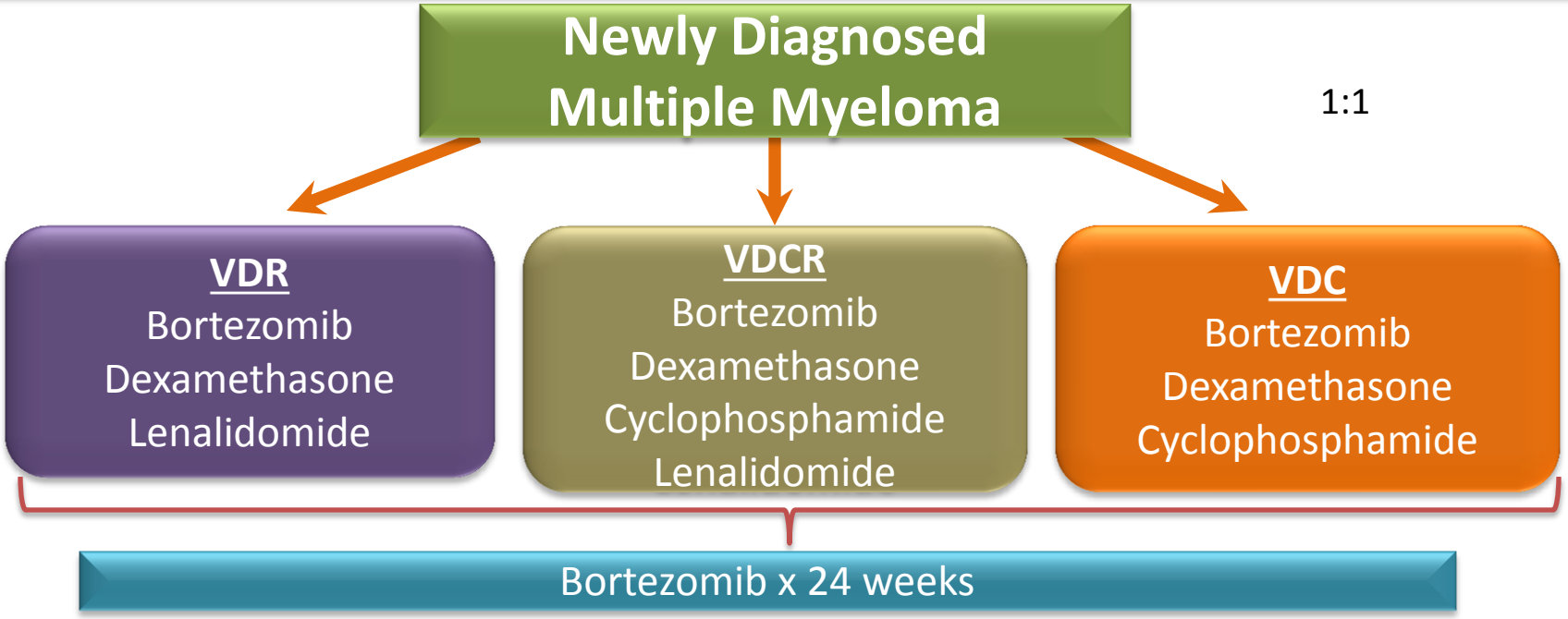
EVOLUTION, Phase II

Kumar et al. Accepted by JCO



	VDCR N = 41	VDR N = 42	VDC N = 32	VDC-modified* N = 15
CR	20%	24%	22%	40%
≥ VGPR	**59%**	**55%**	**47%**	**60%**
≥ PR	93%	93%	91%	93%

Compare to RVD regimen phase II – 67-74% VGPR rate. Richardson et al JCO 2011

Abstract 127.

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Aggressive Induction Choices - Summary

- Transplant "eligible"
  - 3 drug combination excellent VGPR rate in phase II
  - RVD = CVD (CyBorD) with D15 Cytoxan
  - Another 3 drug regimen PAD (Bz+Doxo+Dex)
  - Comparison to 2 drug combination unlikely to happen in US.
  - 4 drugs – CVRD or RVDD (anthracycline) – no evidence of benefit at this time
  - 4 drugs regimens maybe a role in relapsed setting / plasma cell leukemia induction
  - Caveat –
    - NO data with SQ Bortezomib or weekly Bortezomib in combination

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Were novel agents the sole responsible for improvement in myeloma survival?

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Len + High-Dose Dex vs. Low-Dose Dex in Patients with Newly Diagnosed Myeloma

Trial primary end-point:
Response rate and adverse events

Patients
(n = 445)

Len + high-dose Dex, 4 cycles, cycle length 28 days
Len 25 mg/day, days 1–21
Dex 40 mg/day, days 1–4, 9–12, 17–20

Len + low dose Dex, 4 cycles
Len 25 mg/day, days 1–21
Dex 40 mg/day, days 1, 8, 15, 22

Survival rate in patients ≥ 65 years old

	Patients (n)	2-year survival probability (95% CI)	
RD	119	0.67 (0.56–0.77)	p = 0.009
Rd	114	0.82 (0.74–0.91)	

Rajkumar SV, et al. *Lancet Oncology*

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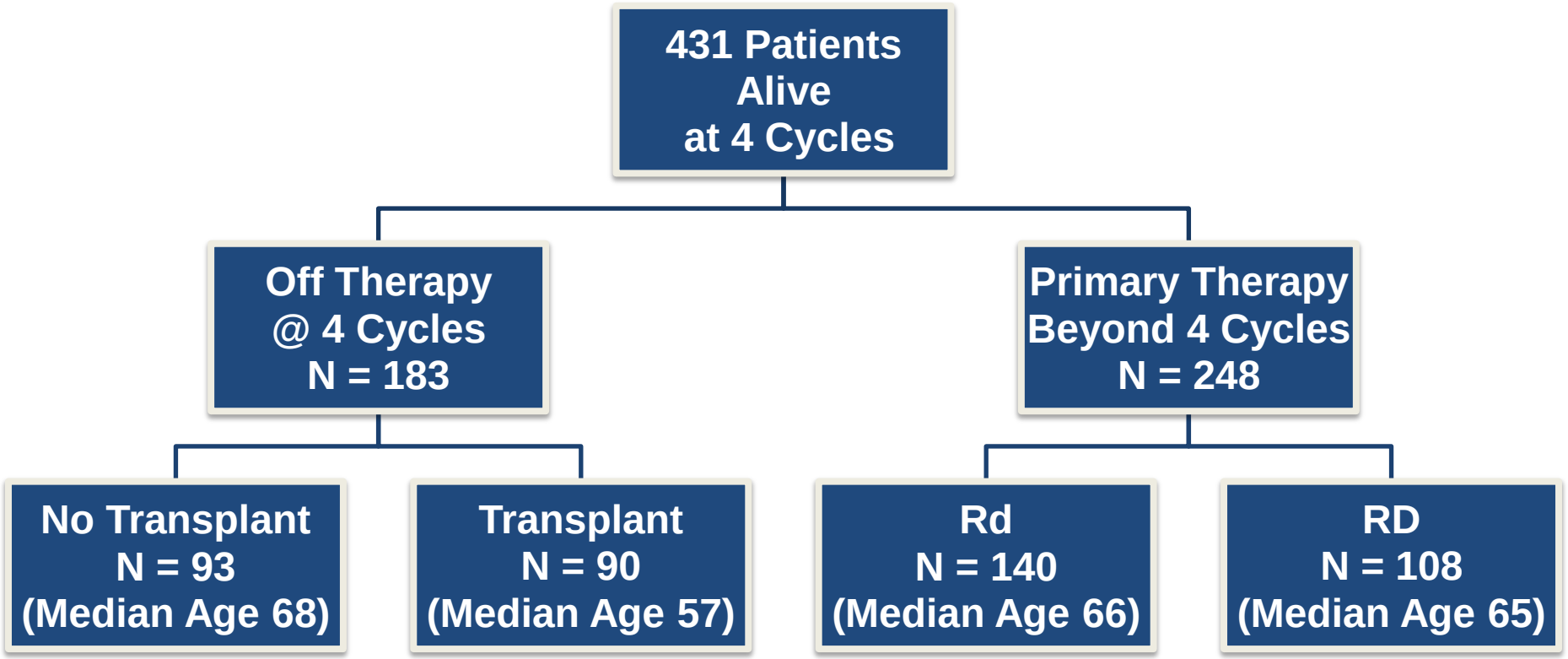
ECOG E4A03: Landmark Analysis



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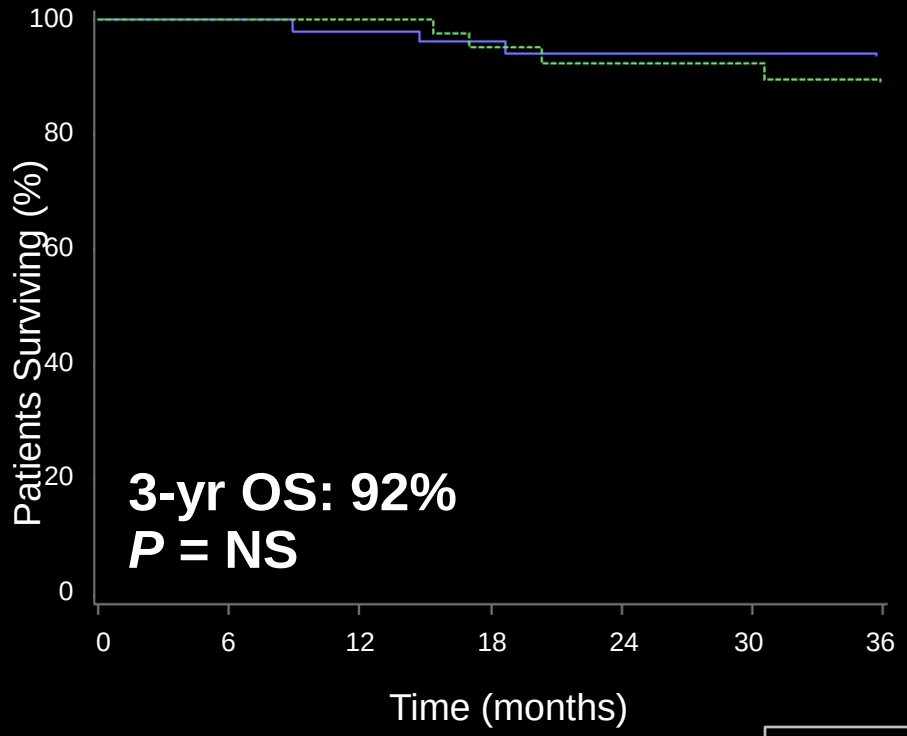
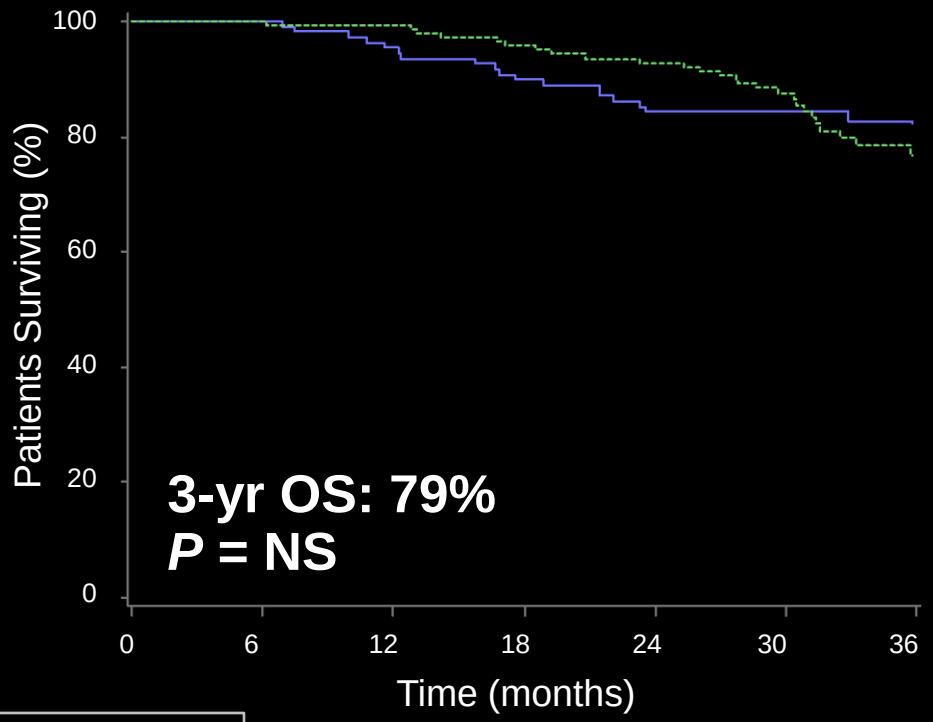
ECOG E4A03: Overall Survival

SCT After 4 Therapy Cycles



Continued Primary Therapy (Beyond 4 Cycles)

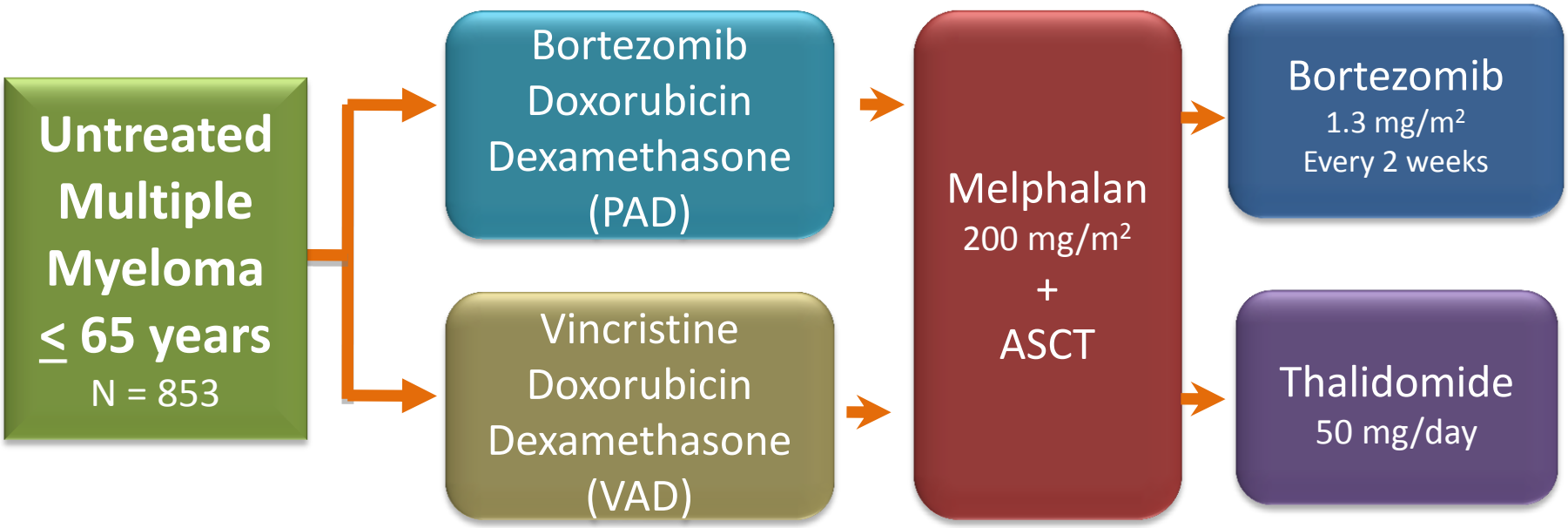


Rd RD

Unplanned analysis, includes unbalanced arms

Rajkumar SV. Presented at the ASH/ASCO Joint Symposium. December 7, 2008; San Francisco, CA.

HOVON-65 / GMMG-HD4, VAD vs PAD



Response	VAD n = 150	PAD n = 150	P
≥ VGPR pre ASCT	15%	42%	<0.001
≥ VGPR after ASCT	50%	80%	0.002

Neben K et al Blood. 2012 Jan 26;119(4):940-8.

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Rd → MPR vs Rd → MEL200 / ASCT

Thromboprophylaxis : randomized between aspirin and low molecular weight heparin

Median follow-up = 20 months.

Response to Protocol	MPR n = 130	MEL200 n = 143	P
CR	20%	25%	0.49
≥ VGPR	60%	37%	0.24
24-month PFS	**59%**	**73%**	**0.003**

Palumbo A, et al. *J Clin Oncol Annual Meeting Abstracts.* 2011;28(15S). Abstract 8020.

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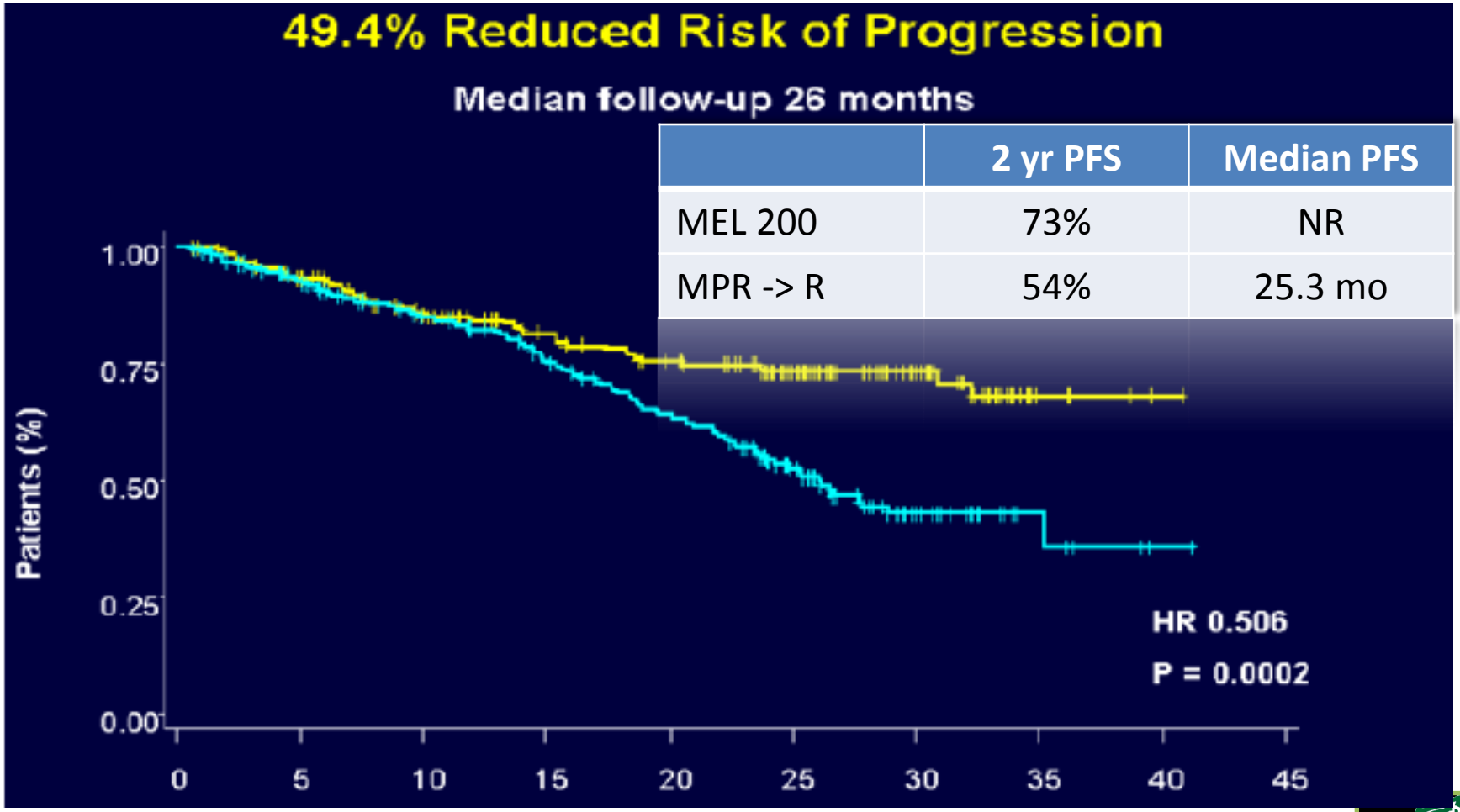
Progression Free Survival



Overall Survival is no different

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How did this data impact practice?

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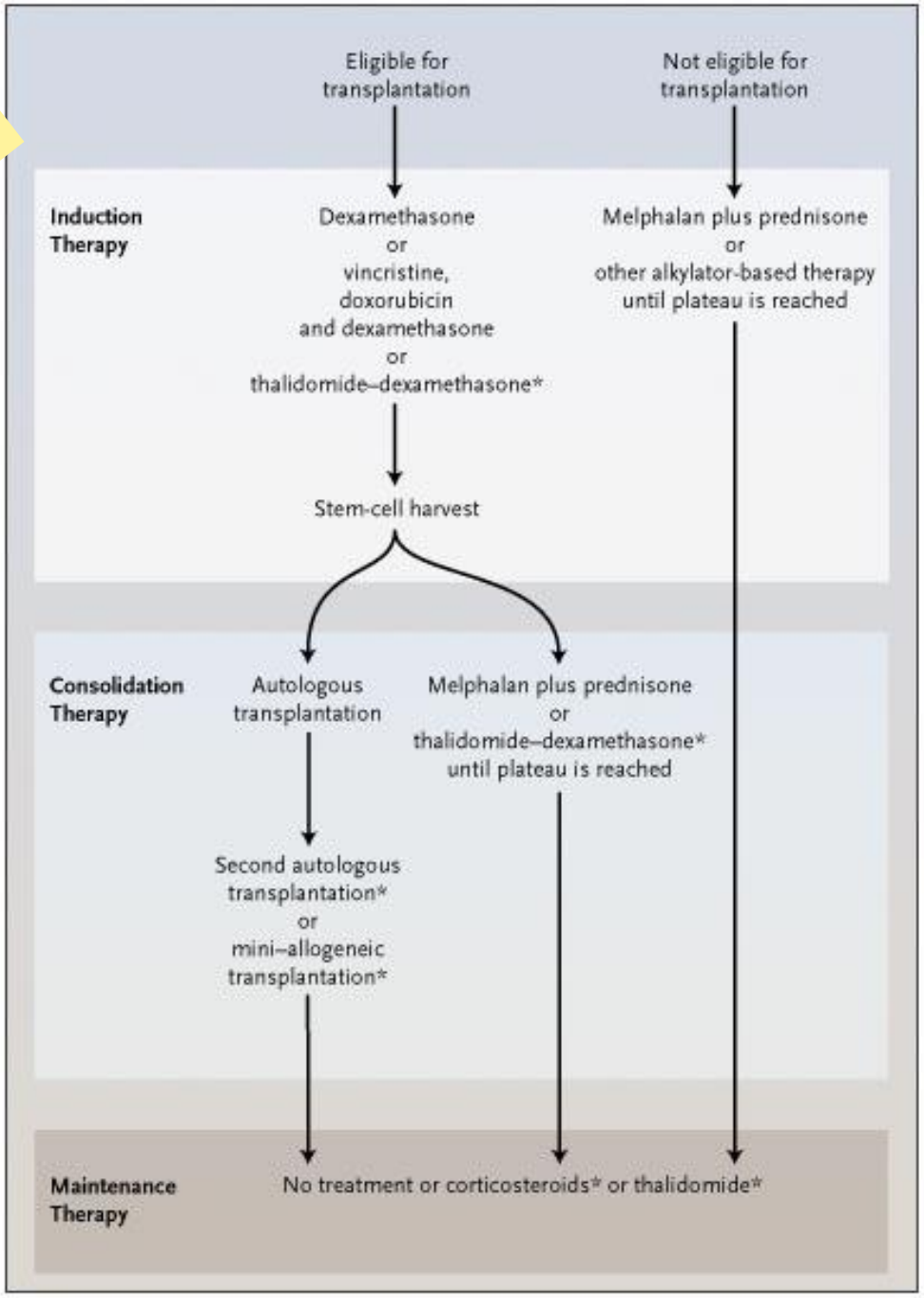
Recommendations In 2004



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)**	

Costa L. et al

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Subset of patients from Research CIBMTR centers

Characteristics of patients	1995-1999	2000-2004	2005-2010	P-value
Number of patients	686	1464	2223	
Cytogenetics				
Abnormal	26 (4)	57 (4)	487 (22)	
Normal	105 (15)	78 (5)	473 (21)	
Untested/Missing	555 (81)	1329 (91)	1263 (57)	
Disease status				
CR/PR	539 (79)	1273 (87)	1966 (88)	<0.001
Mobilization				
GCSF alone	167 (24)	358 (24)	921 (41)	<0.001
Conditioning regimen				
Melphalan alone	370 (54)	1363 (93)	2198 (99)	<0.001

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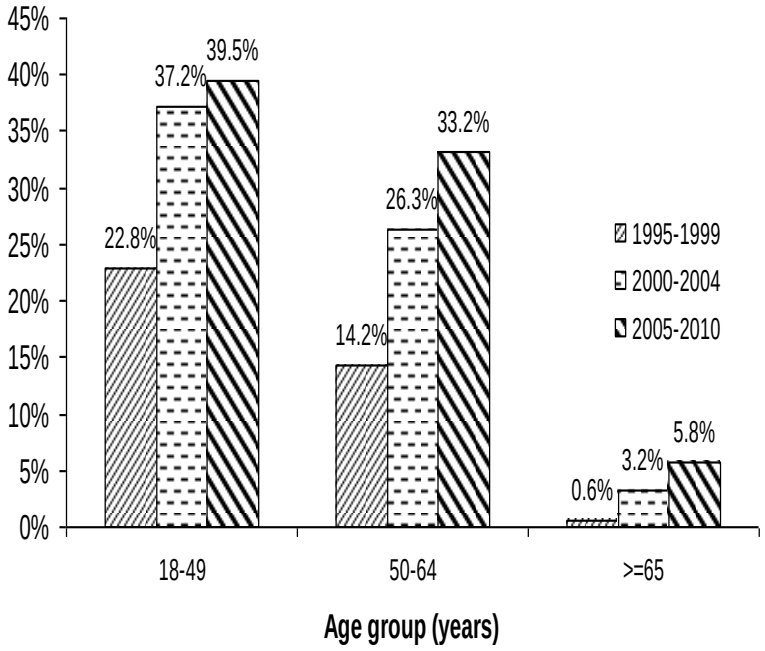
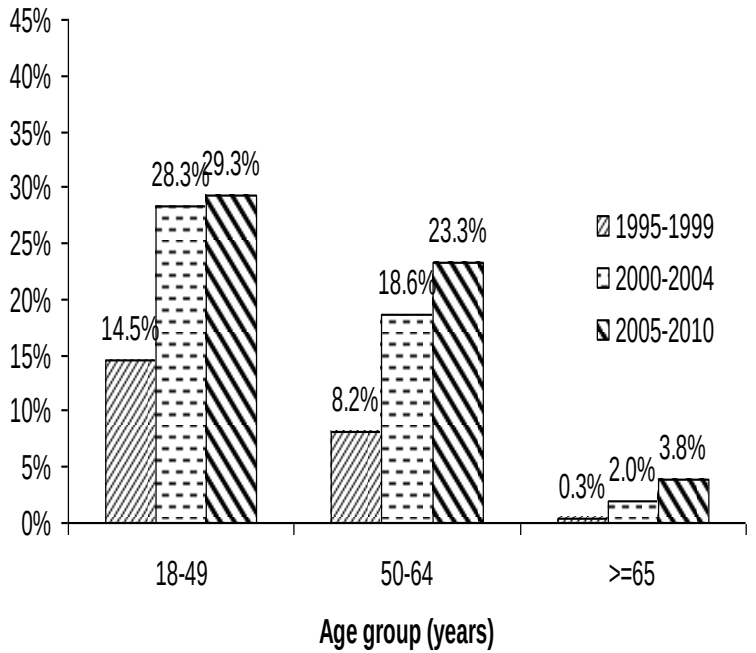
Ratio between first transplants/ newly diagnosed MM cases in U.S.A

a



Ratio between upfront transplants (<12 months)/ newly diagnosed MM cases in U.S.A.

b



Costa L. et al

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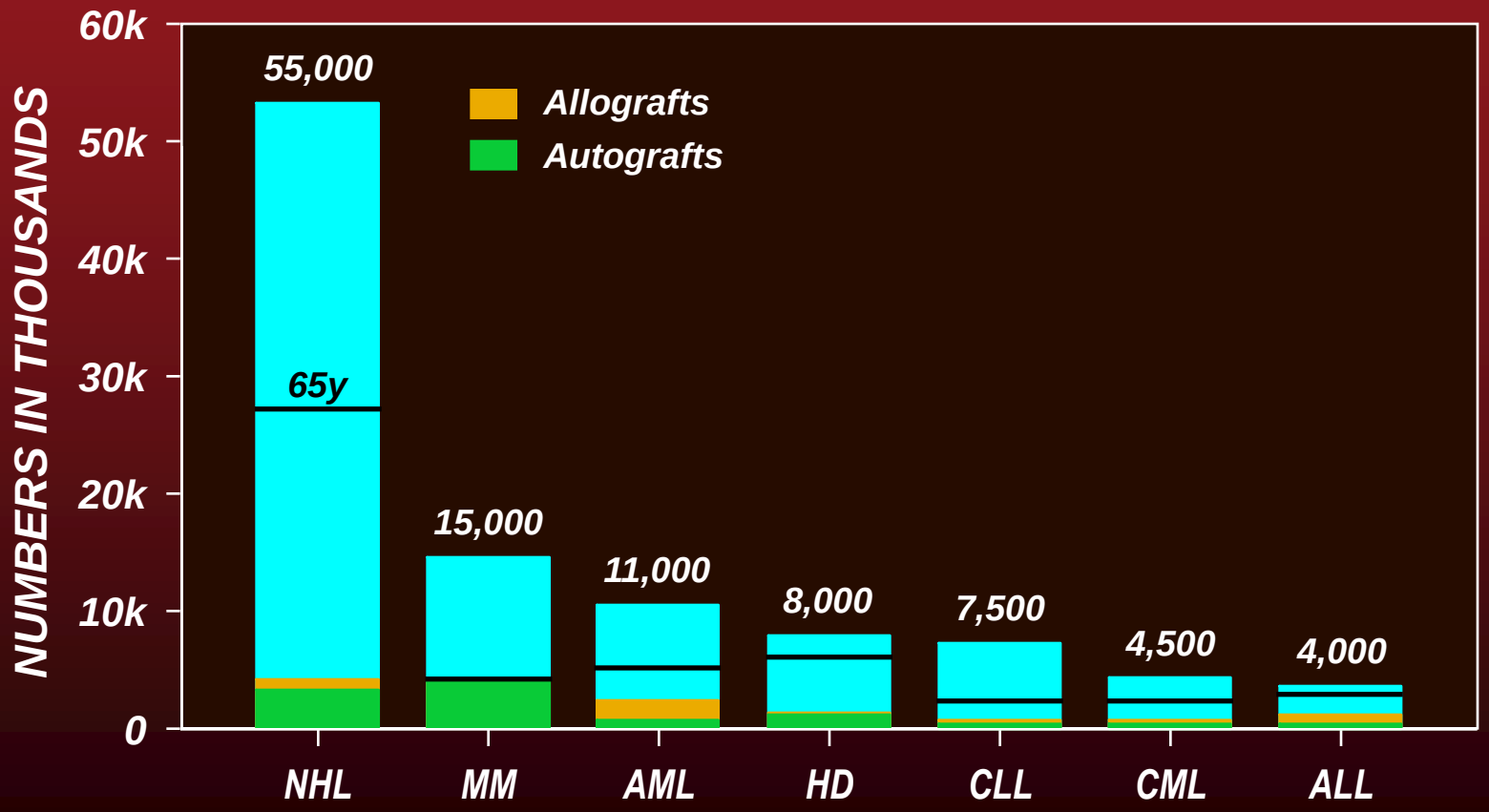
ESTIMATED NUMBERS OF POTENTIAL TRANSPLANT CANDIDATES vs TRANSPLANT RECIPIENTS IN U.S.



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Question
Is it time to abandon autotransplant?

- No clear evidence that transplant is worse
- Overall treatment related mortality is low (<1%)
- Relative benefit over non-transplant therapy may have decreased. But no proof for this.
- OS is improving over time but majority of benefit has gone to those of transplantable age.

  – **What are current outcomes and what can patients expect?**

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Summary of randomized trials – Novel agent induction followed by ASCT

Trial	Induction	ASCT	VGPR Rate	Median PFS	OS
IFM 2005	VD vs. VAD	1 or 2 ASCT	VAD – 37%	30 mo	77% at 3 yrs
			VD – 54%	36 mo	81% at 3 yrs
GMMG-HOVON	VAD vs. PAD	1 or 2	VAD- 61%	42% @ 3 yrs	71% @ 3 yrs
			PAD- 75%	48% @ 3 yrs	78% @ 3 yrs
IFM 2007	VD vs. vTD	1 or 2	VD – 59%	Not reported yet	
			vTD - 73%		
GIMEMA	TD vs. VTD	2	TD – 69%	75% @ 2 yrs	91% @ 2 yrs
			VTD – 87%	85% @ 2 yrs	96% @ 2 yrs

Majority did not mandate maintenance
Major triplet in the US – RVD – not included

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For those in VGPR or CR – can upfront ASCT be eliminated / delayed?

- Additional benefit from deeper reduction of MRD even for those in CR
- Collect PBSCT early but delay transplant till first relapse
- Early vs. Late transplant trial ongoing
- **Delayed ASCT:**
  - Does it improve QOL?
  - How many who plan to have a late ASCT actually receive it?

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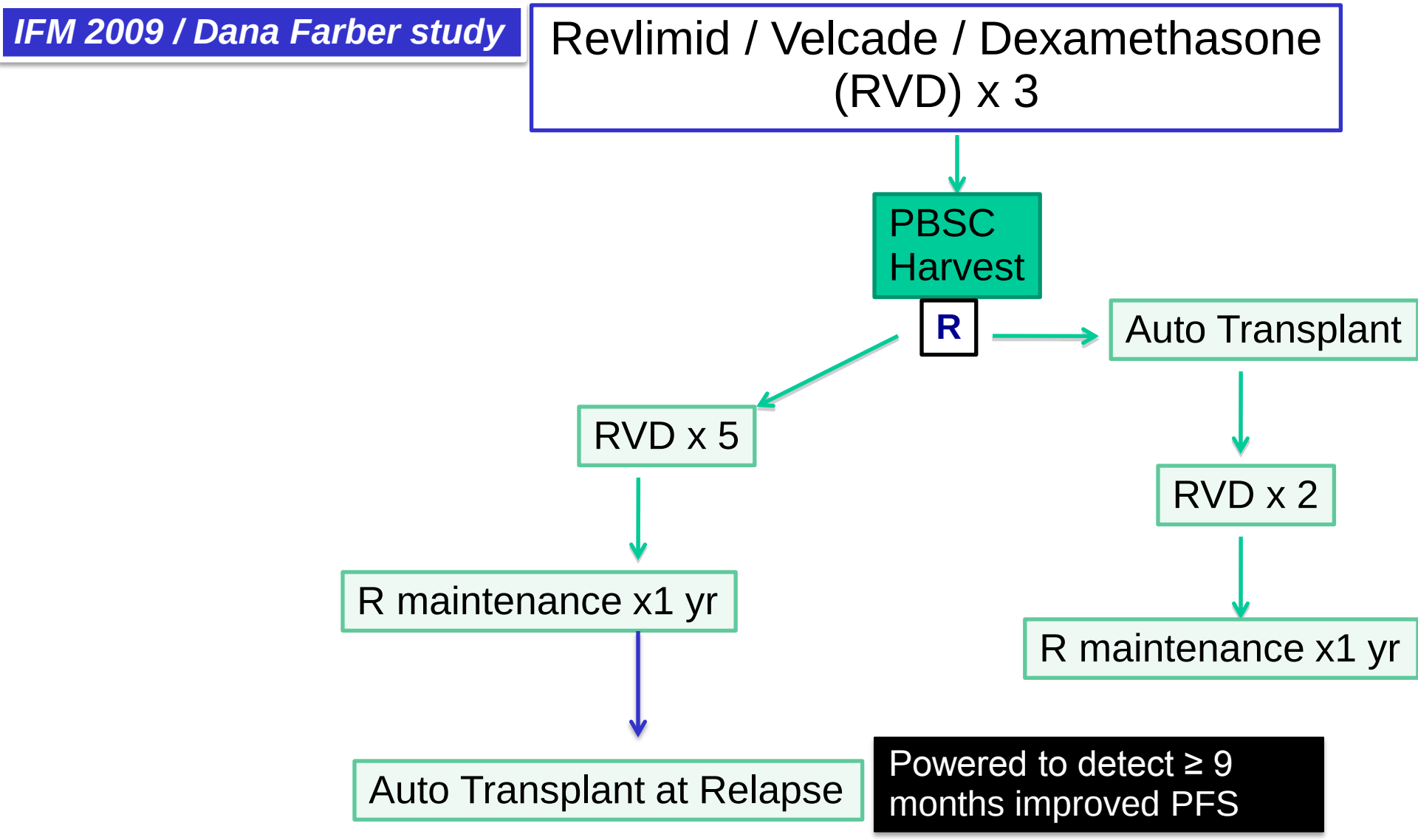
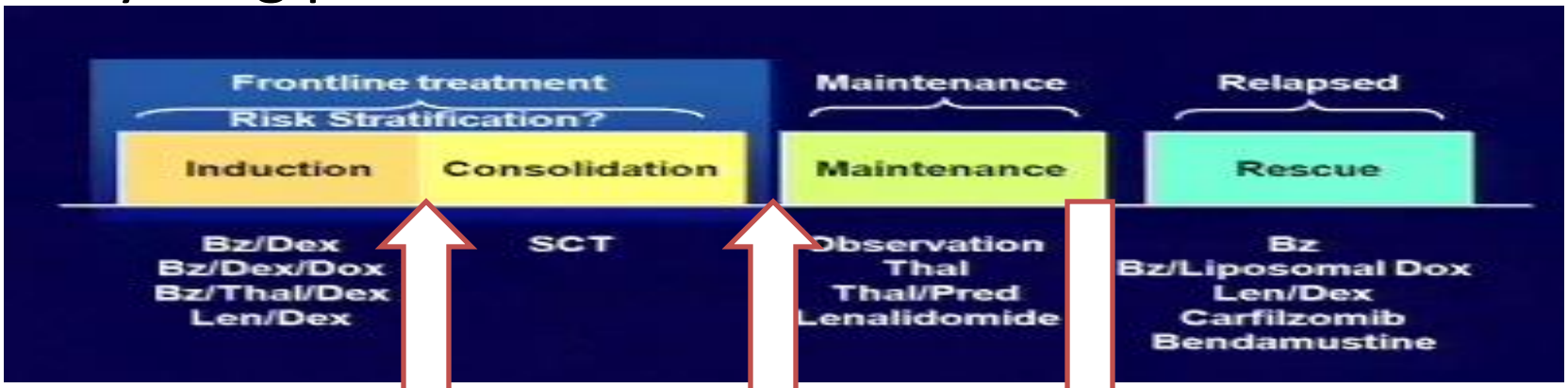
Role of up-front ASCT – current study



Goal of initial therapy in terms of Response

- Randomized trials – Achievement of VGPR or better
- Emerging data – PCR or Multicolor Flow Remission
- Standard Single Autotransplant may be changing esp. in young patients.



Better Induction
VGPR before
ASCT

Additional
Consolidation
VRD or VTD
Second ASCT

MRD directed ?
When to stop ?

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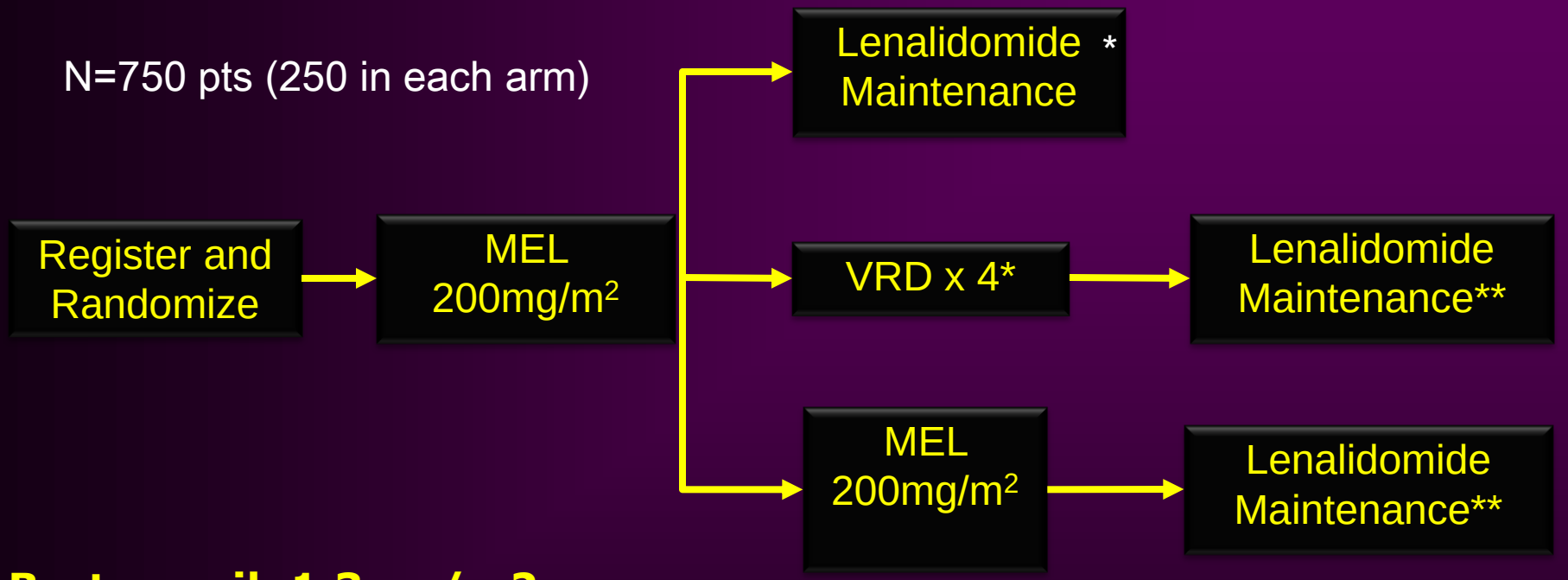
BMT CTN 0702 – STaMINA Trial: SCHEMA

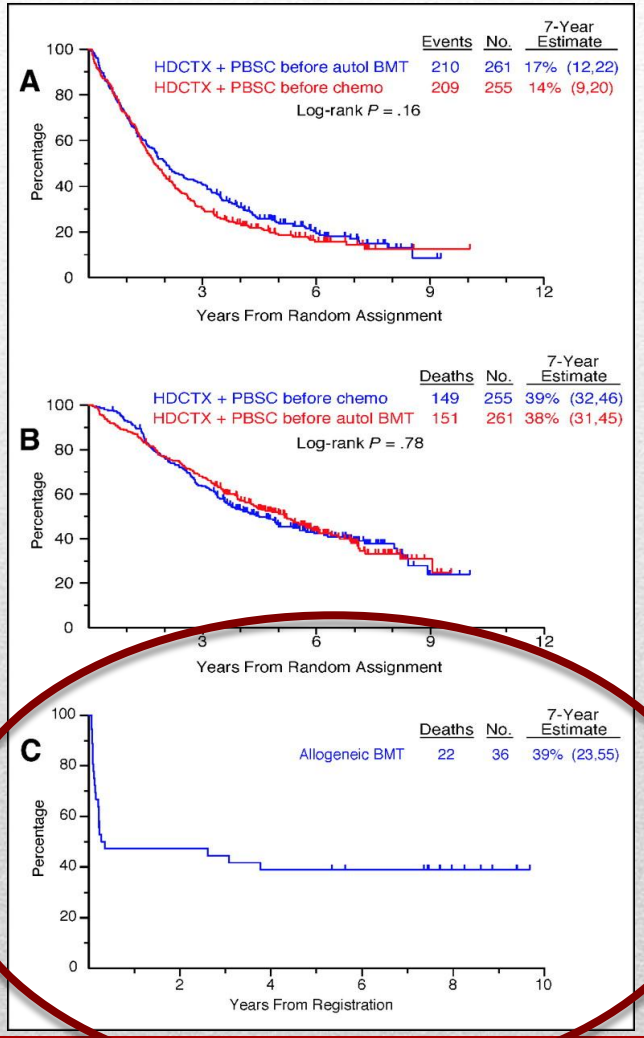


Bortezomib 1.3mg/m2 days 1, 4, 8,11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg days 1, 8, 15

****Lenalidomide x 3years : 10mg /d for 3 cycles , then 15 mg /d**

Allogeneic Transplants in Myeloma

Final Results of Phase III US Intergroup Trial S9321



PFS 7 years
Auto 17%
Chemo 14%

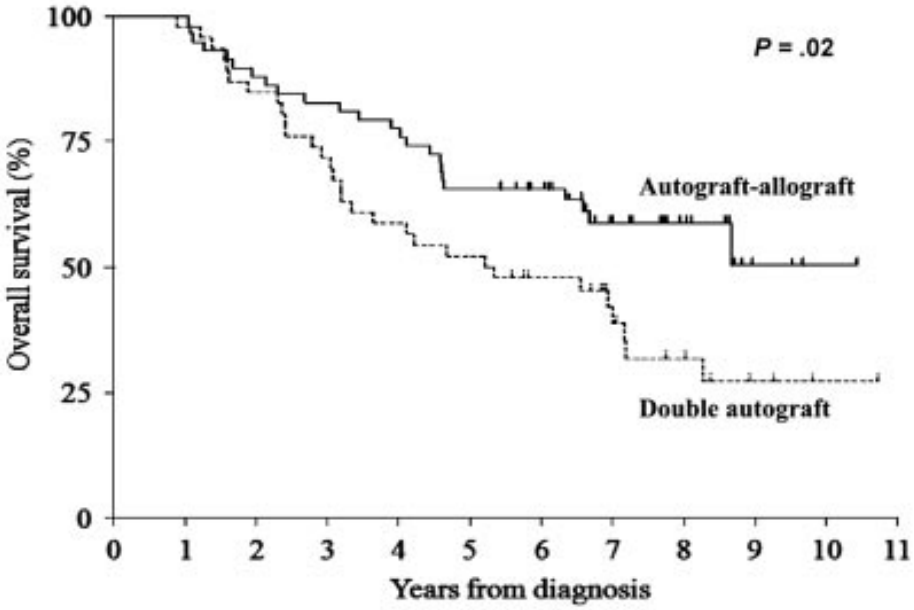
OS 7 years
Auto 39%
Chemo 38%

Allogeneic
7 years
PFS 22%
OS 39%

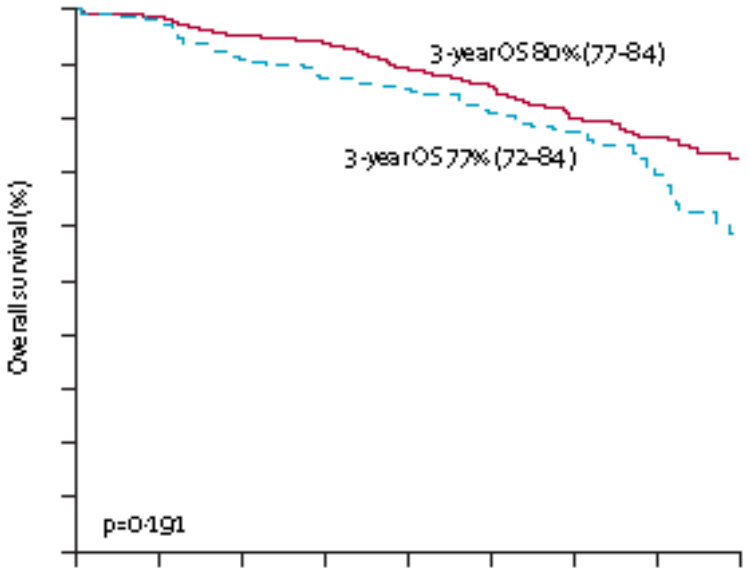
Barlogie et. Al. JCO 2006

Allogeneic Transplant

- Controversial
- US Trial – Negative (ASCT+ Allo no better than ASCTx2)
- European Trials – OS benefit esp. in high risk disease



Giaccone et al 2011 117: 6721-6727



Krishnan et al Lancet Oncol 2011; 12: 1195–203

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Study	Transplant type	TRM	CR rate	EFS/PFS	OS	Relapse rate
Garban et al[9]*	tandem auto HCT	5%		35 m	47.2 m (P = .07)	
	auto/allo HCT	10.9% at 100-day		31.7 m	35 m	
Bruno et al[47]	tandem auto HCT	2% (CI at 2-yr)	26%	29 m	**54 m**	
	auto/allo HCT	10% (CI at 2-yr)	55% (P = .004)	35 m (P = .02)	**80 m (P = .01)**	
Knop et al[53]	tandem auto HCT	-	32%		72% (P = .22)	
	auto/allo HCT	12.7%	59% (P = .003)		60%	
Rosiñol et al[50]	tandem auto HCT	5%	11%	31 m	58 m	
	auto/allo HCT	16% (P = .07)	40% (P = .001)	not reached (P = .08)	not reached (P = .9)	
Krishnan et al[52]	tandem auto HCT	4% (CI at 3-yr)	45%	46% (P = .671)	80% (P =.191)	
	auto/allo HCT	11% (CI at 3-yr)	58% (P = .007)	43%	77%	
Björkstrand et al[55,56]	tandem auto HCT	3% (CI at 6-yr)	44% within 60m	12% at 96 m	**36% at 96 m**	82% (P = .0002)
	auto/allo HCT	18% (CI at 6-yr; P < .001)	56% within 60m (P = .007)	22% at 96 m (P = .027)	**49% at 96 m (P = .03)**	60%
Lokhorst et al[54]**	tandem auto HCT & maintenance post 1st auto HCT	3%	37%	22% at 6 ys	55% at 6 yr	77%
	auto/allo HCT	16% (P < .001)	43% (P = .67)	28% at 6 yr	55% at 6 yr	55%

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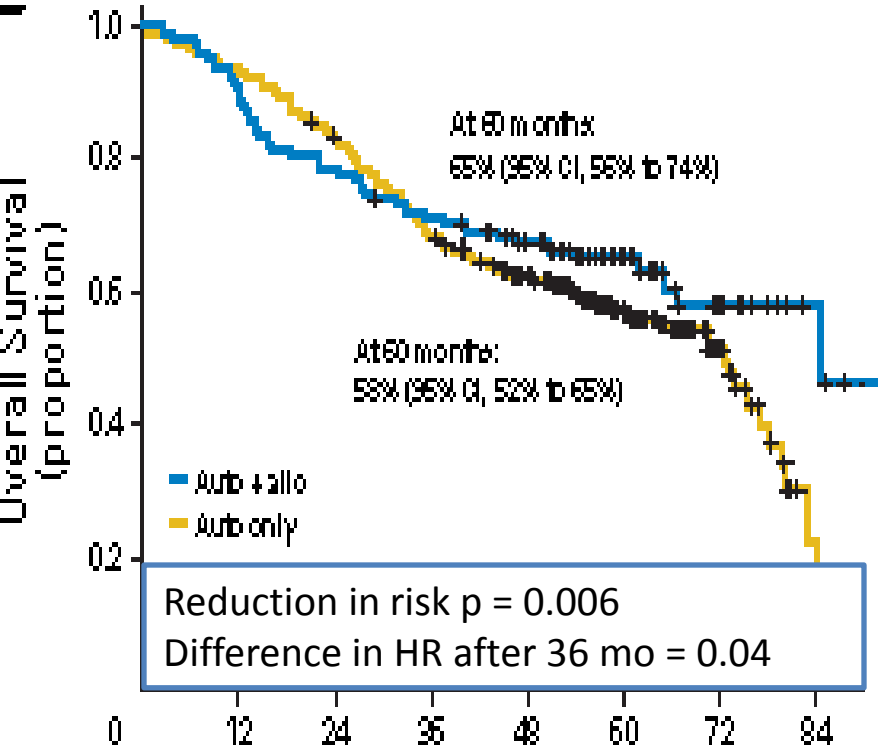
Why not give up Allotransplant?



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
- **New trial being planned**

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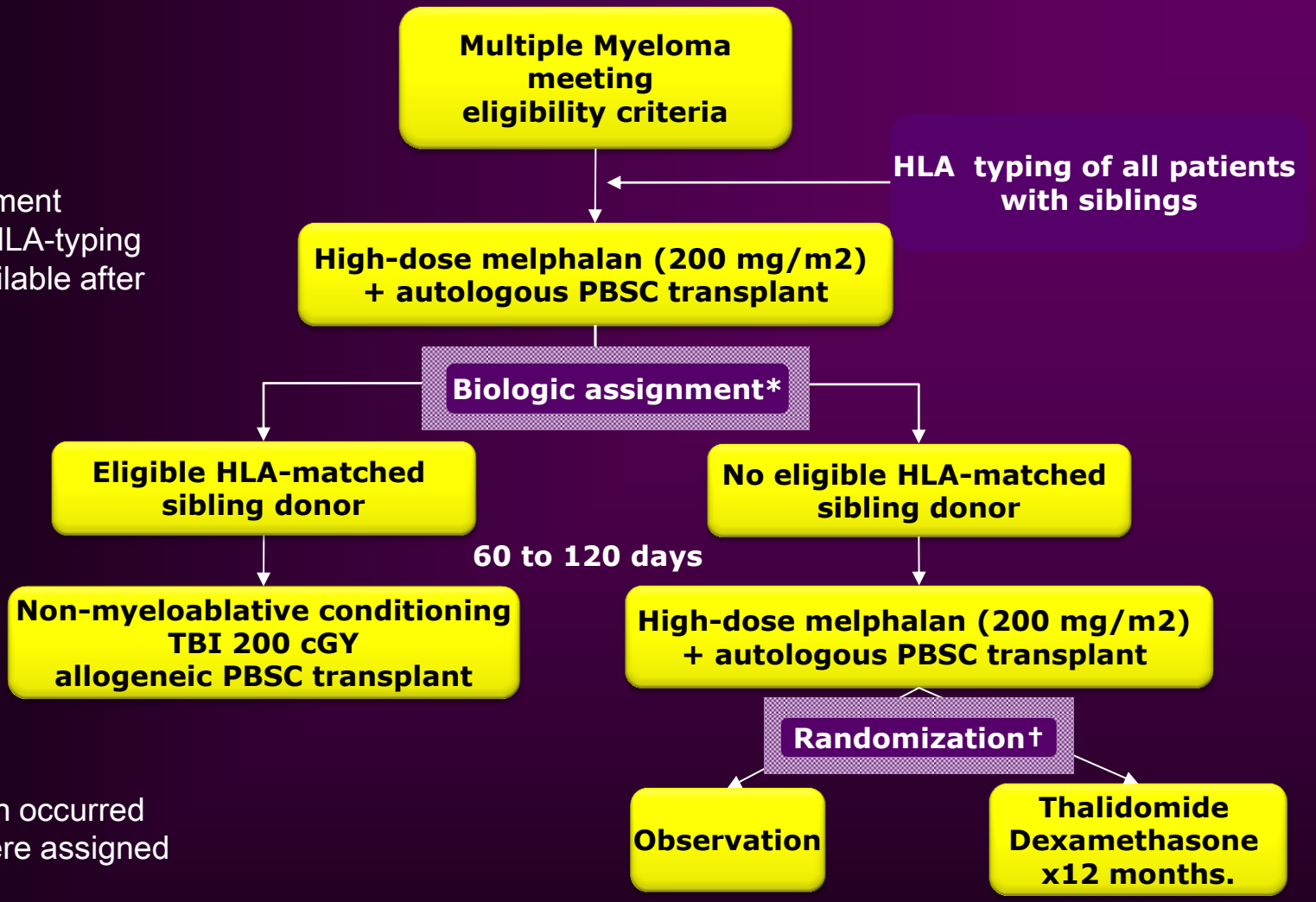
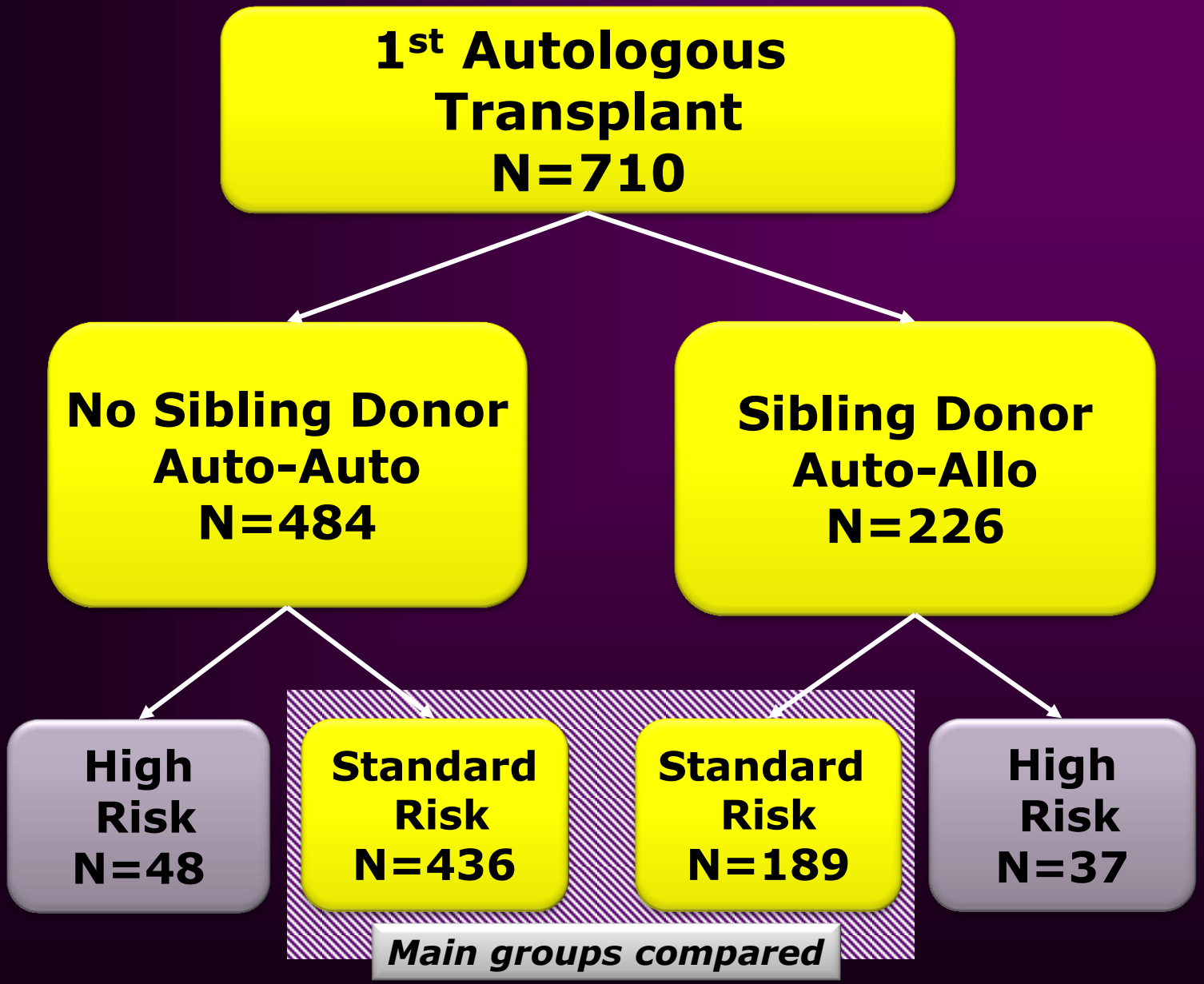
BMT CTN 0102 Study Schema



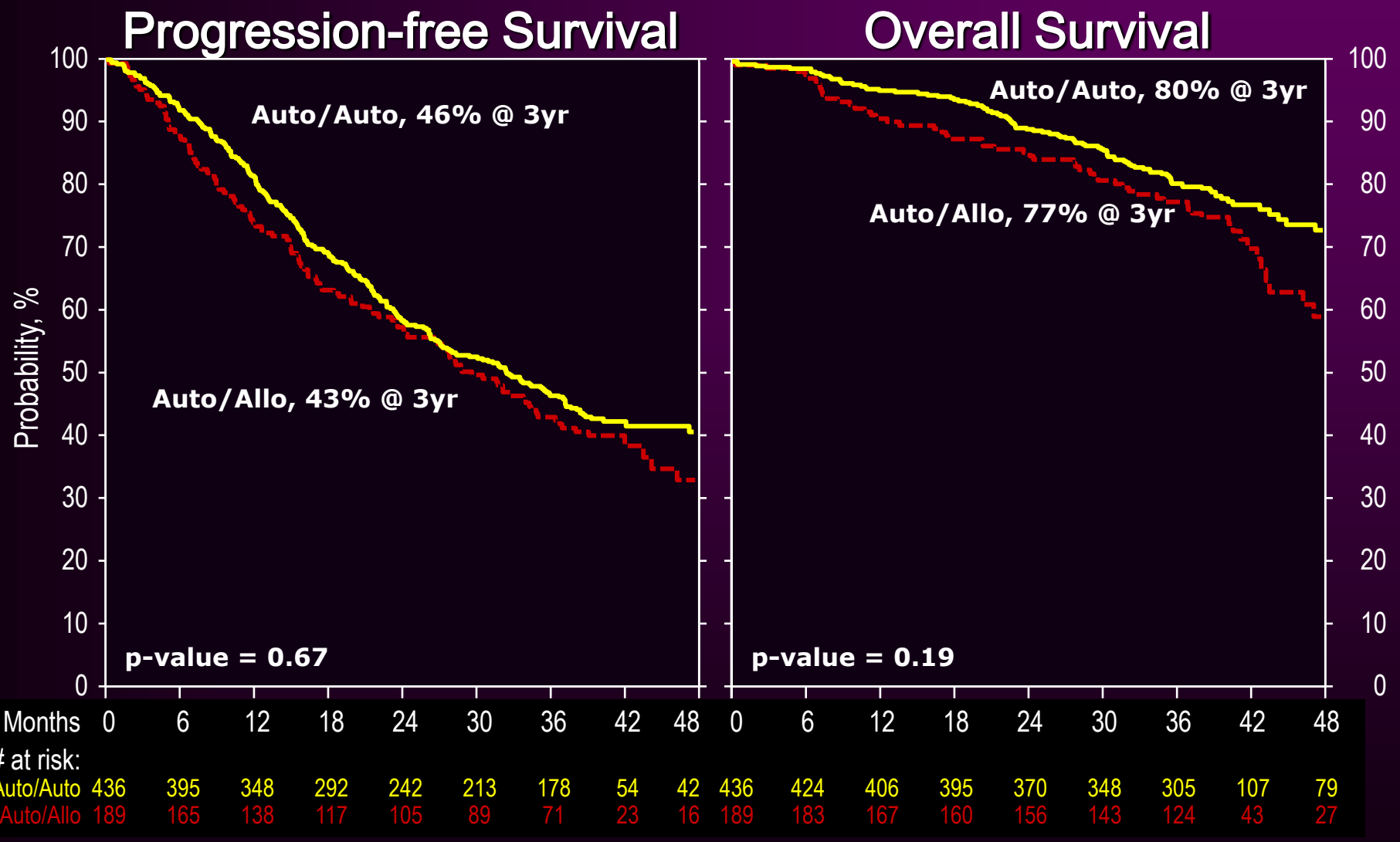
*Biologic assignment occurred when HLA-typing results were available after enrollment.

† Randomization occurred once patients were assigned to auto-auto

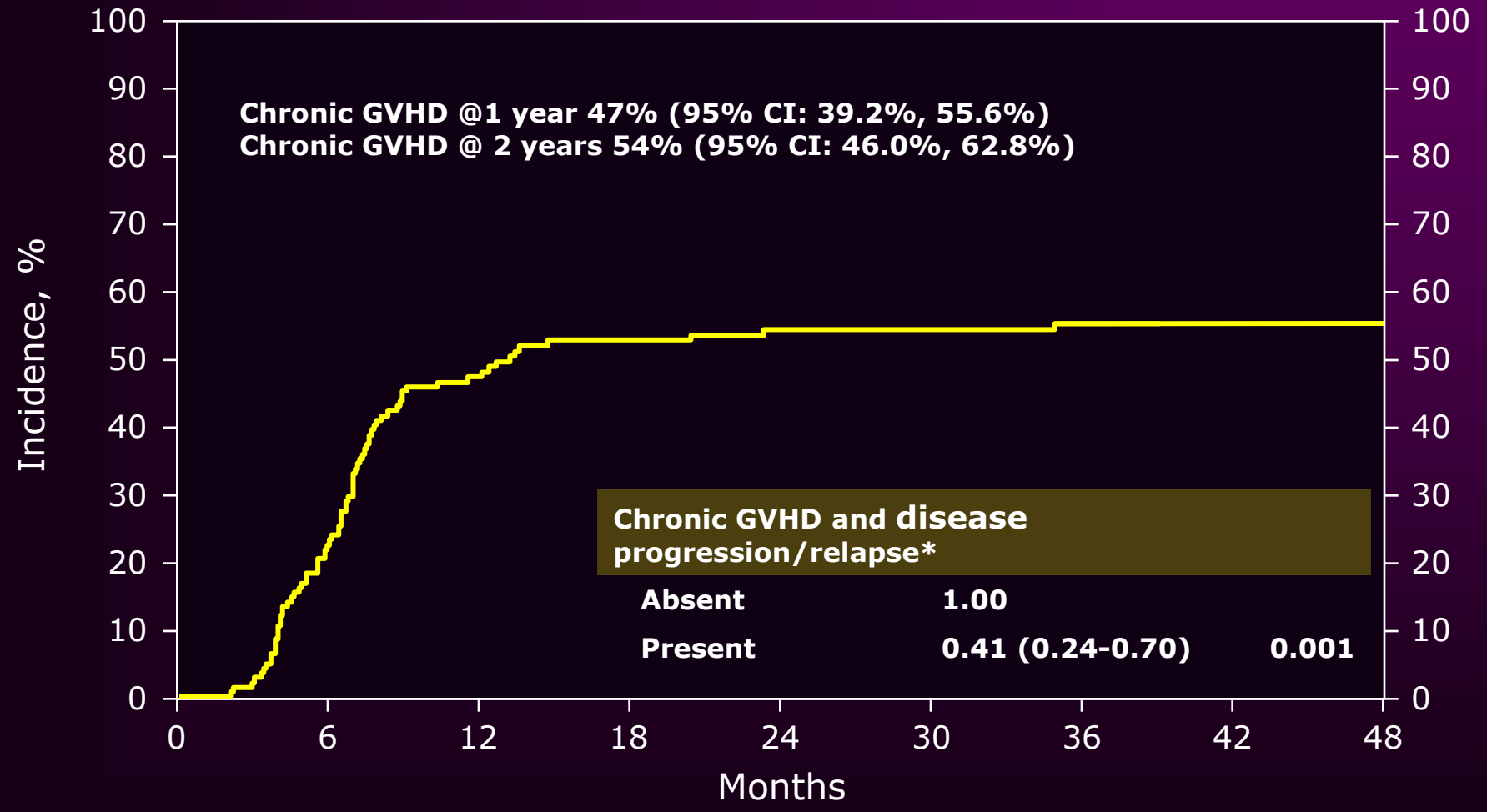
PRIMARY ENDPOINT : 3yr Progression Free Survival


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

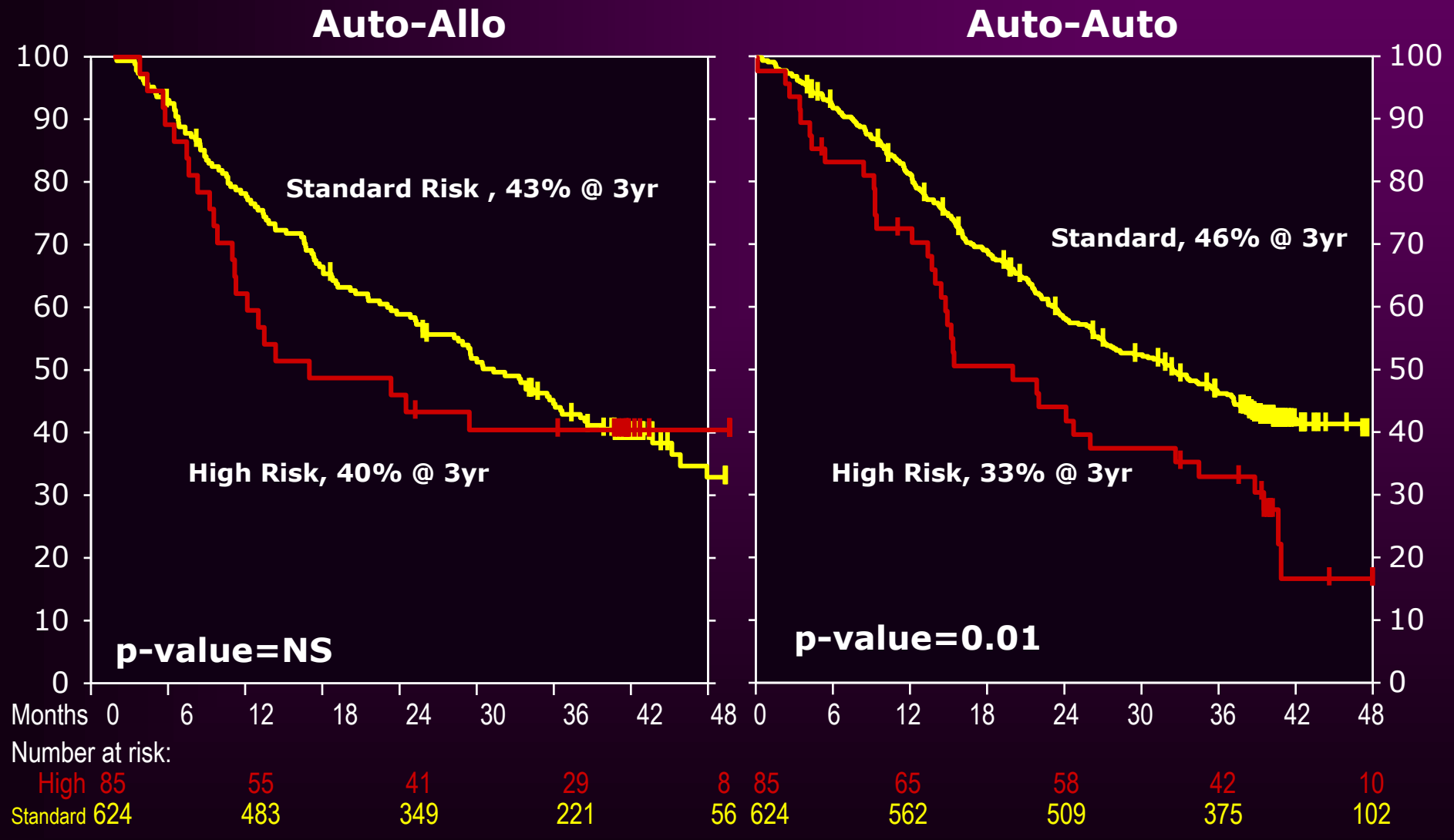


Cumulative Incidence of Chronic GVHD after Allogeneic Transplant



* Chronic GVHD treated as time-dependent covariate and adjusted for disease status at transplant.

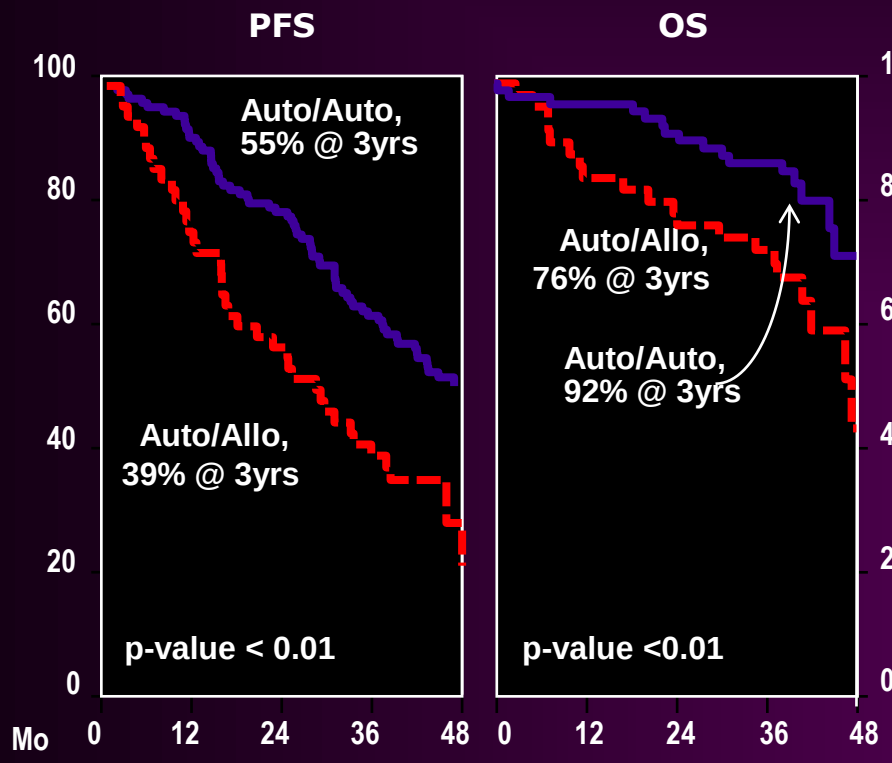
High Risk vs Standard Risk Myeloma as Defined in this Protocol did Predict for an Inferior PFS



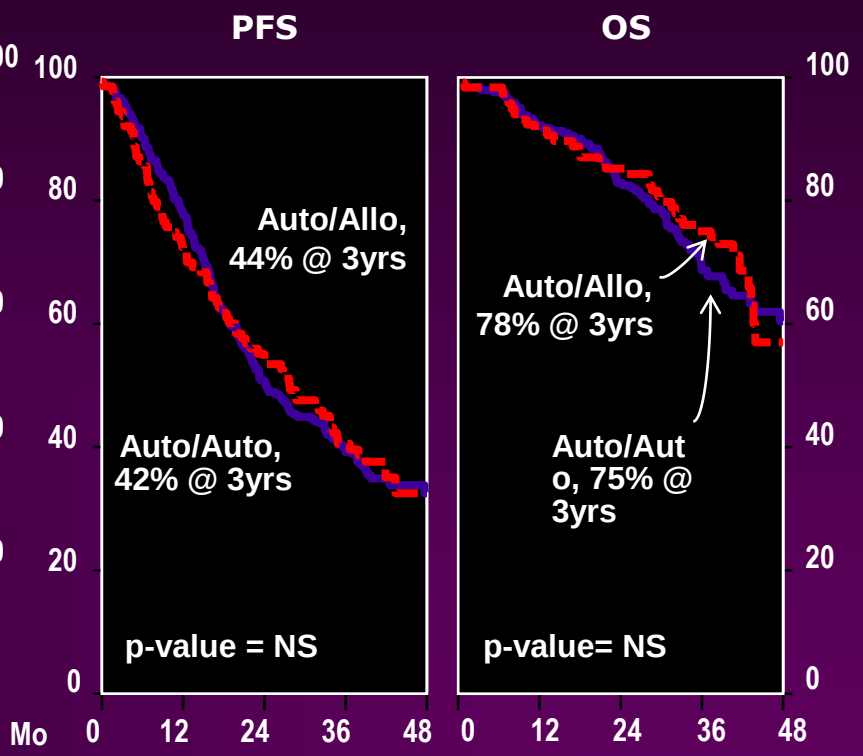
(Combines Mp10_34 & _35) Mp10_36.ppt

Tandem Autologous HCT (auto-auto) versus Single Autologous HCT Followed by HLA Matched Sibling Non-Myeloablative Allogeneic HCT (auto-allo) for Patients with Standard Risk Multiple Myeloma: Results from the BMT-CTN 0102 Trial

Durie-Salmon Stage I/II Patients



Durie-Salmon Stage III Patients



High Risk FISH abnormalities

Abnormality	Frequency	Prognosis
Hyperdiploidy	50%–60%	Good/neutral
t(4;14)	15%	Poor (neutral if bortezomib therapy ??)
t(11;14)	20%	Neutral
t(14;16)	3%	Poor/neutral
Monosomy 13	45%	Neutral if by FISH
del(17p)	8%	Poor
1q gain	35%	Poor
del(1p)	30%	Poor
5q gain	50%	Good
del(12p)	10%	Poor

The Impact of Genomics on the Management of Myeloma
Jill Corre and Hervé Avet-Loiseau - JNCCN Mar 2012 ; 10 (3)

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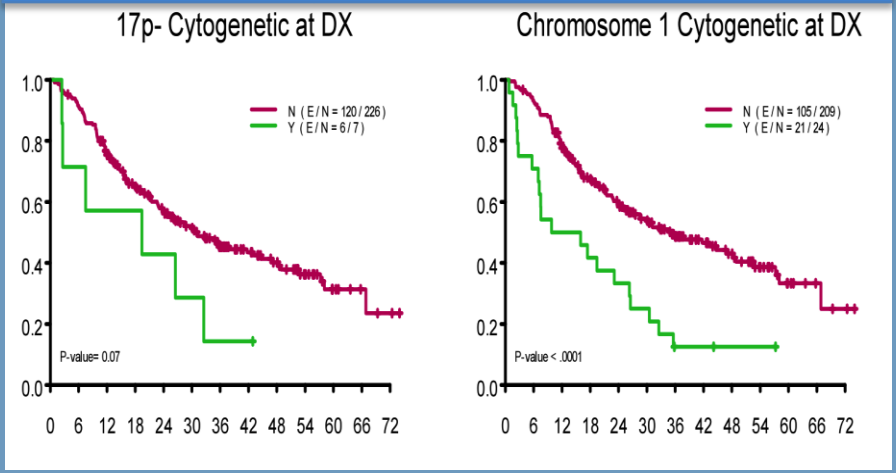
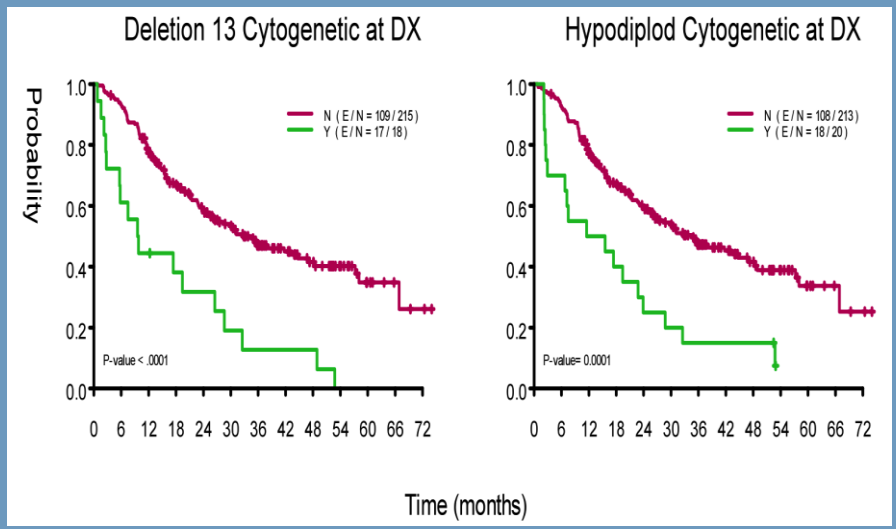
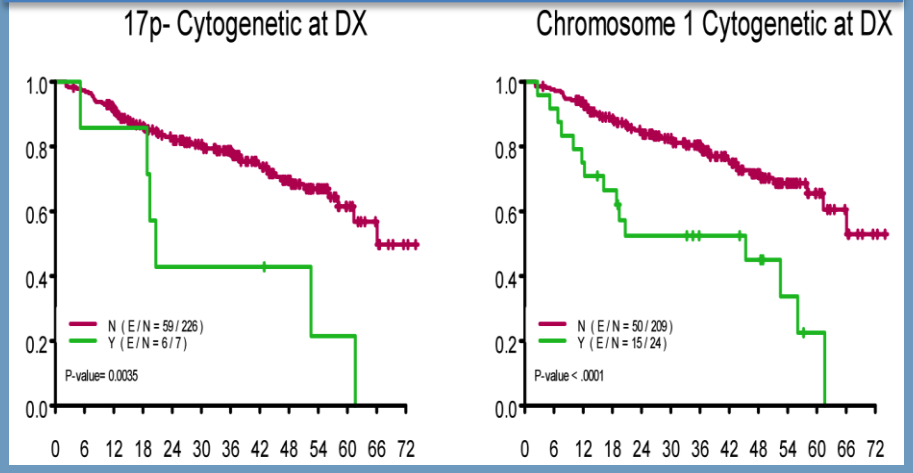
High-risk Chromosomal Abnormalities (MDACC; N=679; 2006 – 2010)

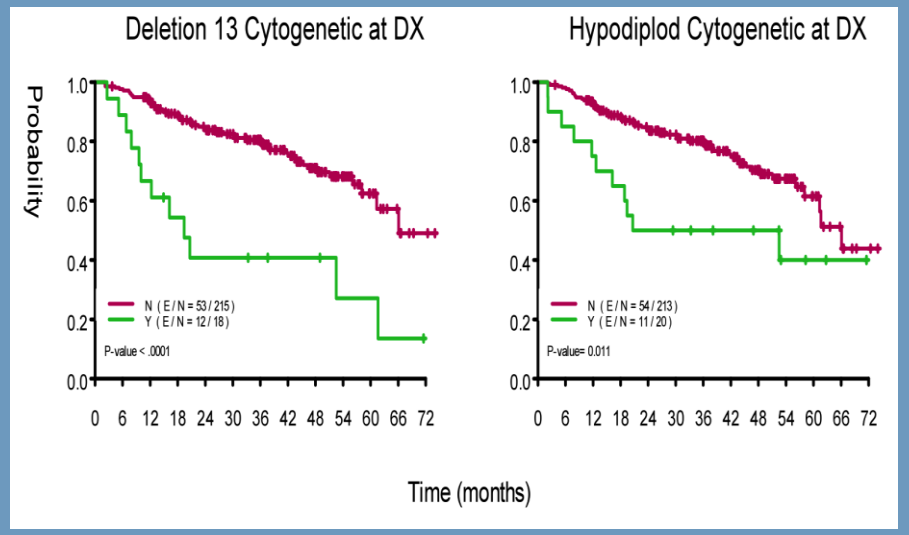
PFS





OS





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www.nature.com/leu

REVIEW

Plasma cell leukemia: consensus statement on diagnostic requirements, response criteria and treatment recommendations by the International Myeloma Working Group

C Fernández de Larrea[1], RA Kyle[2], BGM Durie[3], H Ludwig[4], S Usmani[5], DH Vesole[6], R Hajek[7], JF San Miguel[8], O Sezer[9], P Sonneveld[10], SK Kumar[2], A Mahindra[11], R Comenzo[12], A Palumbo[13], A Mazumber[14], KC Anderson[15], PG Richardson[15], AZ Badros[16], J Caers[17], M Cavo[18], X LeLeu[19], MA Dimopoulos[20], CS Chim[21], R Schots[22], A Noeul[23], D Fantl[24], U-H Melkqvist[25], O Landgren[26], A Chanan-Khan[27], P Moreau[28], R Fonseca[29], G Merlini[30], JJ Lahuerta[31], J Bladé[1], RZ Orlowski[32] and JJ Shah[32] on behalf of the International Myeloma Working Group[33]

Plasma cell leukemia (PCL) is a rare and aggressive variant of myeloma characterized by the presence of circulating plasma cells. It is classified as either primary PCL occurring at diagnosis or as secondary PCL in patients with relapsed/refractory myeloma. Primary PCL is a distinct clinic-pathological entity with different cytogenetic and molecular findings. The clinical course is aggressive with short remissions and survival duration. The diagnosis is based upon the percentage (≥20%) and absolute number ($\geq 2 \times 10^9$/l) of plasma cells in the peripheral blood. It is proposed that the thresholds for diagnosis be re-examined and consensus recommendations are made for diagnosis, as well as, response and progression criteria. Induction therapy needs to begin promptly and have high clinical activity leading to rapid disease control in an effort to minimize the risk of early death. Intensive chemotherapy regimens and bortezomib-based regimens are recommended followed by high-dose therapy with autologous stem cell transplantation if feasible. Allogeneic transplantation can be considered in younger patients. Prospective multicenter studies are required to provide revised definitions and better understanding of the pathogenesis of PCL.

Leukemia (2013) **27**, 780–791; doi:10.1038/leu.2012.336

Keywords: plasma cell leukemia; cytogenetics; bortezomib; transplantation; myeloma; prognosis

- 20% circulating plasma cells or >$2x10^9$/L absolute
- Consider plasma cell leukemia when:
  - 5% circulating plasma cells or >$0.5x10^9$/L absolute

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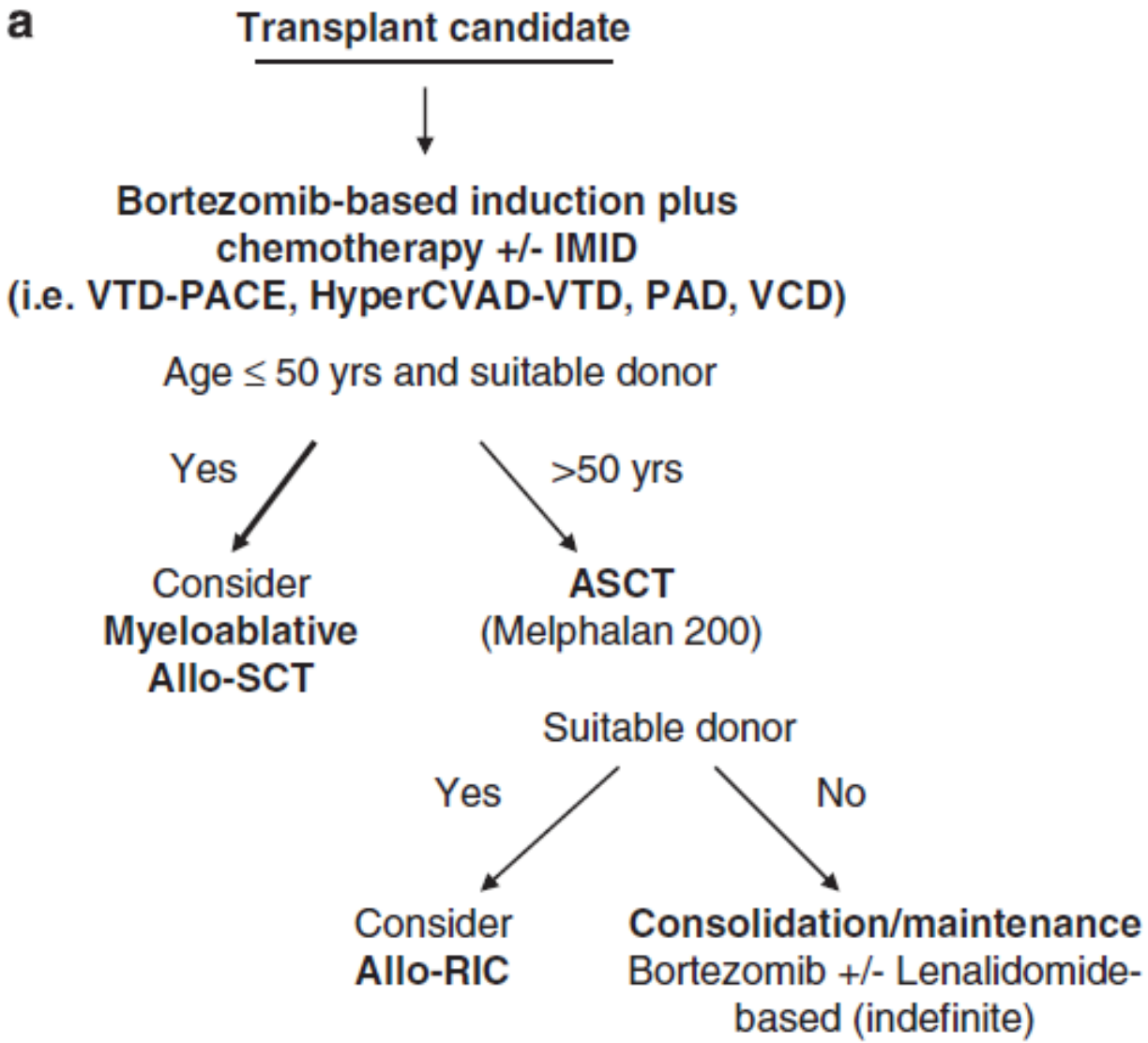

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High Risk MM & allogeneic Transplant

- Del17p and del 13q after allo (Flu/Mel+/-ATG, n=101): Schiling G et al Leukemia 2008
  - Higher relapse rate (HR 2.2)
  - Shorter event free survival (only del17p)
- Poor risk group (t(4;14), del17p, del13q, n=143)
  - No difference in PFS or OS between standard vs. poor risk groups. Ros-Weil, et al Haematologica 2011
- Del13q (EBMT NMAM-2000 study)
  - Auto/Allo with better PFS that Auto/Auto
  - No impact of del13q in the auto-allo cohort

Garthon, G et al Blood 2013

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Conclusions

- Transplant remains the main backbone for the treatment of myeloma.
- Myeloma outcomes are now much better with combination of novel agents and transplant
- Results of upfront autologous followed by allogeneic HCT are comparable to tandem autologous.
- High risk myeloma remains a challenge and novel approaches are needed

Merci

ขอบคุณ

תודה

Köszönettel

Obrigado!

Gracias

Bedankt

Vielen Dank

شكراً

Teşekkürler

Díky

Ευχαριστώ

cảm ơn bạn

Transplant considerations

Relapse

TRM

Scenario: Young patients with acute promyelocytic leukemia (APL)

Relapse

TRM

Scenario: Patient with AML with poor risk cytogenetics with a sibling donor

Autotransplants in AML

Pro

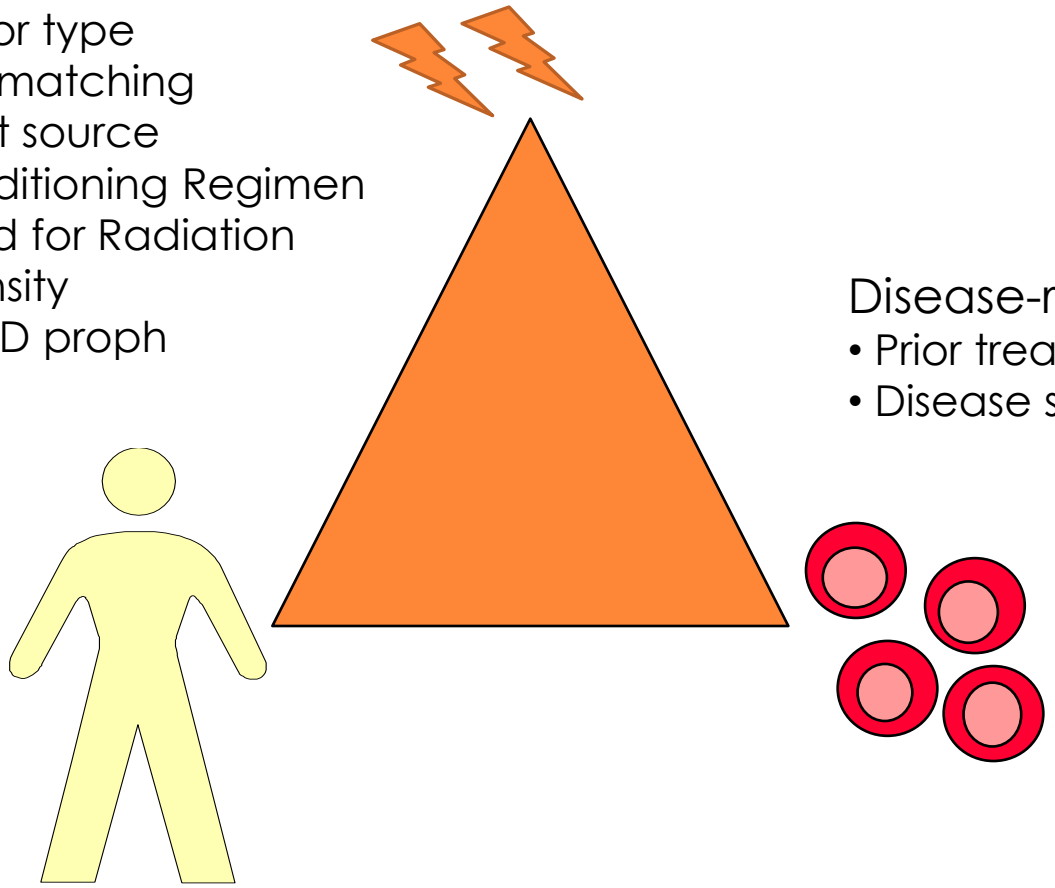
- Lower toxicity
- Use of PBSC and fast recovery
- Different AML subtypes might respond more beneficial to autoHCT

Con

- Lack of enthusiasm
- Relapse rates
- No graft versus leukemia effect.
- Toxicity

Determinants of transplant related toxicity

Transplant-related:
- Donor type
- HLA matching
- Graft source
- Conditioning Regimen
- Need for Radiation
- Intensity
- GVHD proph



Disease-related:
- Prior treatment
- Disease status

Patient-related:
- Age
- Weight
- Performance score
- Comorbidities
- Genetics

Transplant for Leukemia: Conclusions

- Most common indication but still many patients have no access to transplant
- Transplant still has a important role as curative therapy for leukemia
- Important to estimate the risk of disease relapse and transplant-related mortality
- Improvements in transplant related toxicity expanded the number of eligible patients.