Transplantation for Leukemia: How much regimen intensity is needed?

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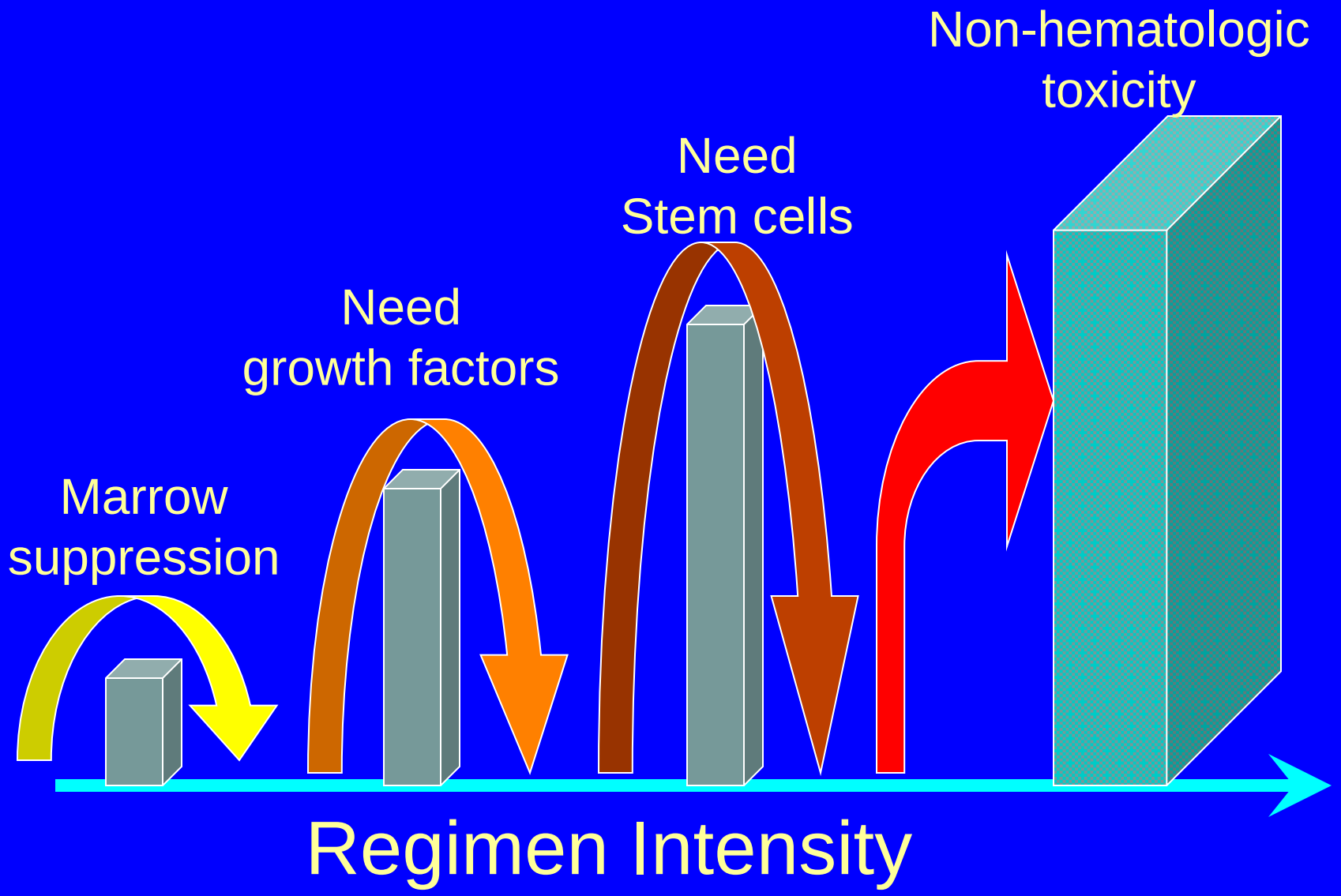
Riyadh, 2017

Transplants for Cancer

Stem cells are Restorative

Conditioning designed for
- Therapeutic Index
- Not for leukemia efficacy

Dose Intensity for BMT



Anti-cancer effects of BMT

Kill the cancer cells

Save the patient

Restore immunocompetence

Prevent Infection

Prevent cancer recurrence {GVL}

Anti-cancer effects of BMT

Kill the cancer cells

Save the patient

Restore immunocompetence

- Undesired tissue toxicity
- Undesired enhancement of GVHD

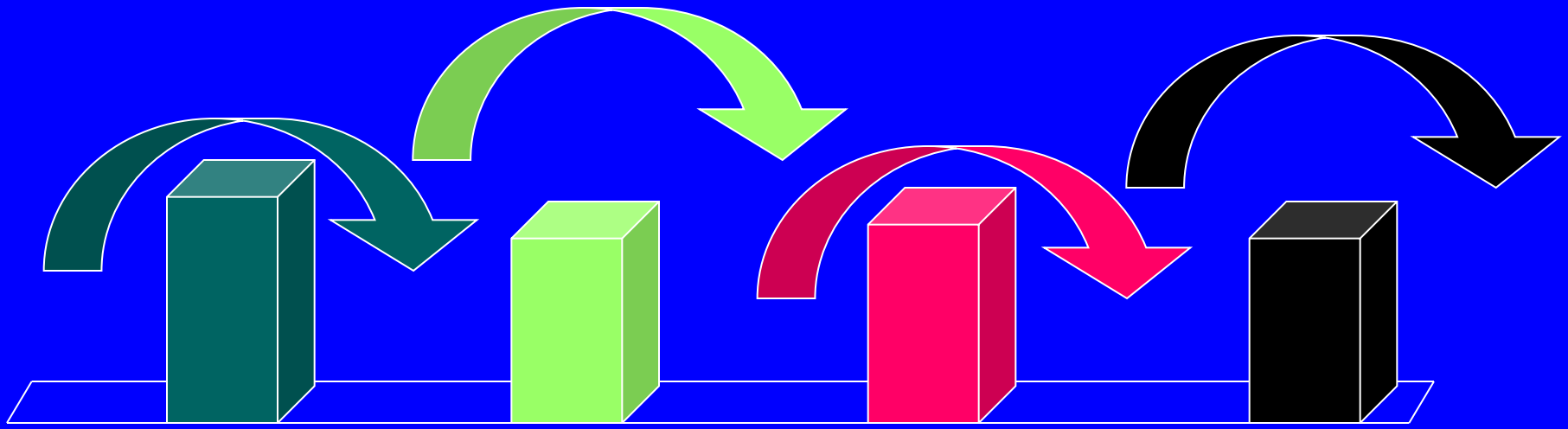
Dose-limiting toxicities

Cyclophosphamide
gut, bladder, heart

TBI
mucosa, lung

Busulfan
lung, gut, liver

Barriers to Transplant Success: Conditioning Intensity influences them all

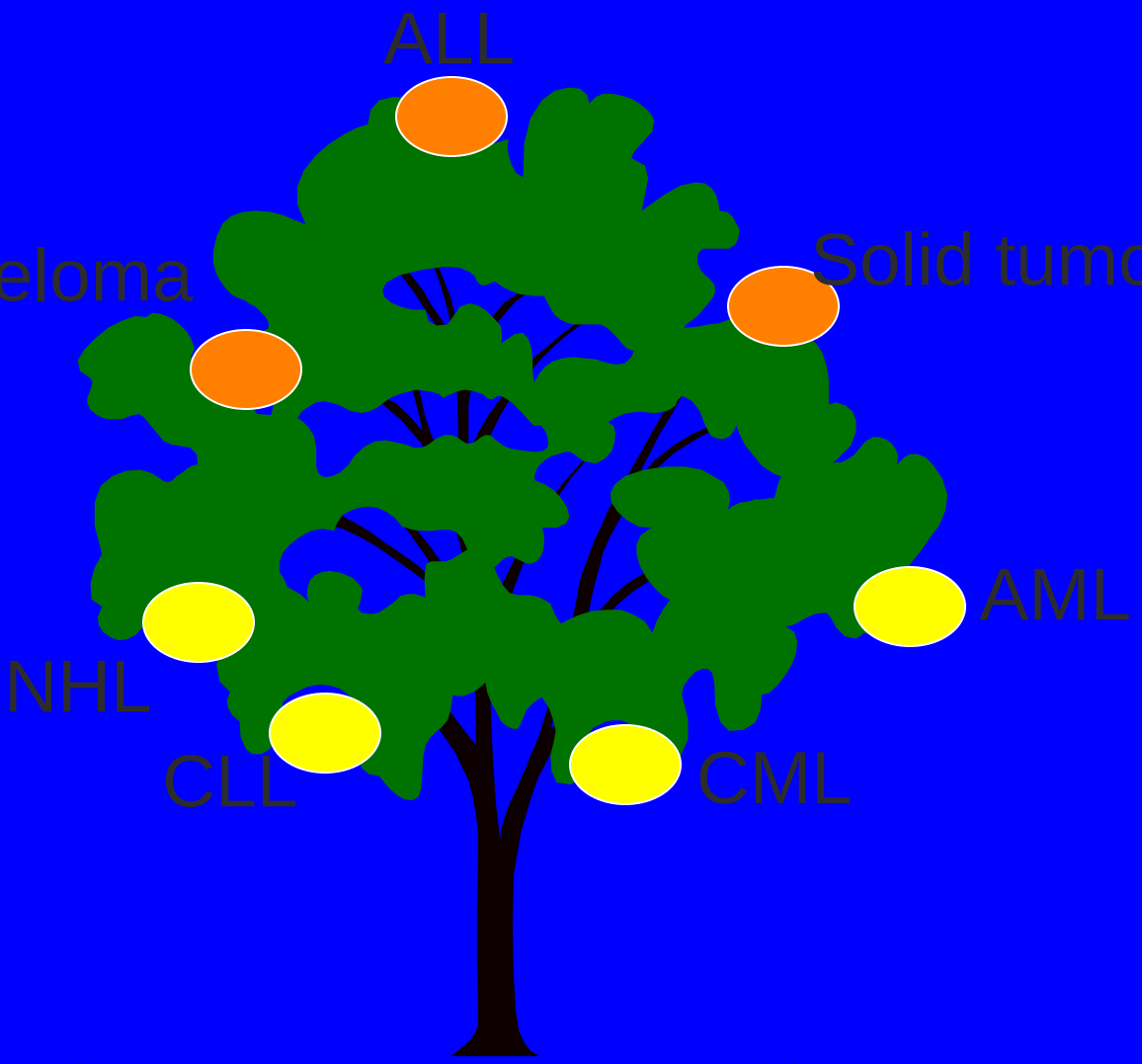


Dose-intensity may not prevent relapse

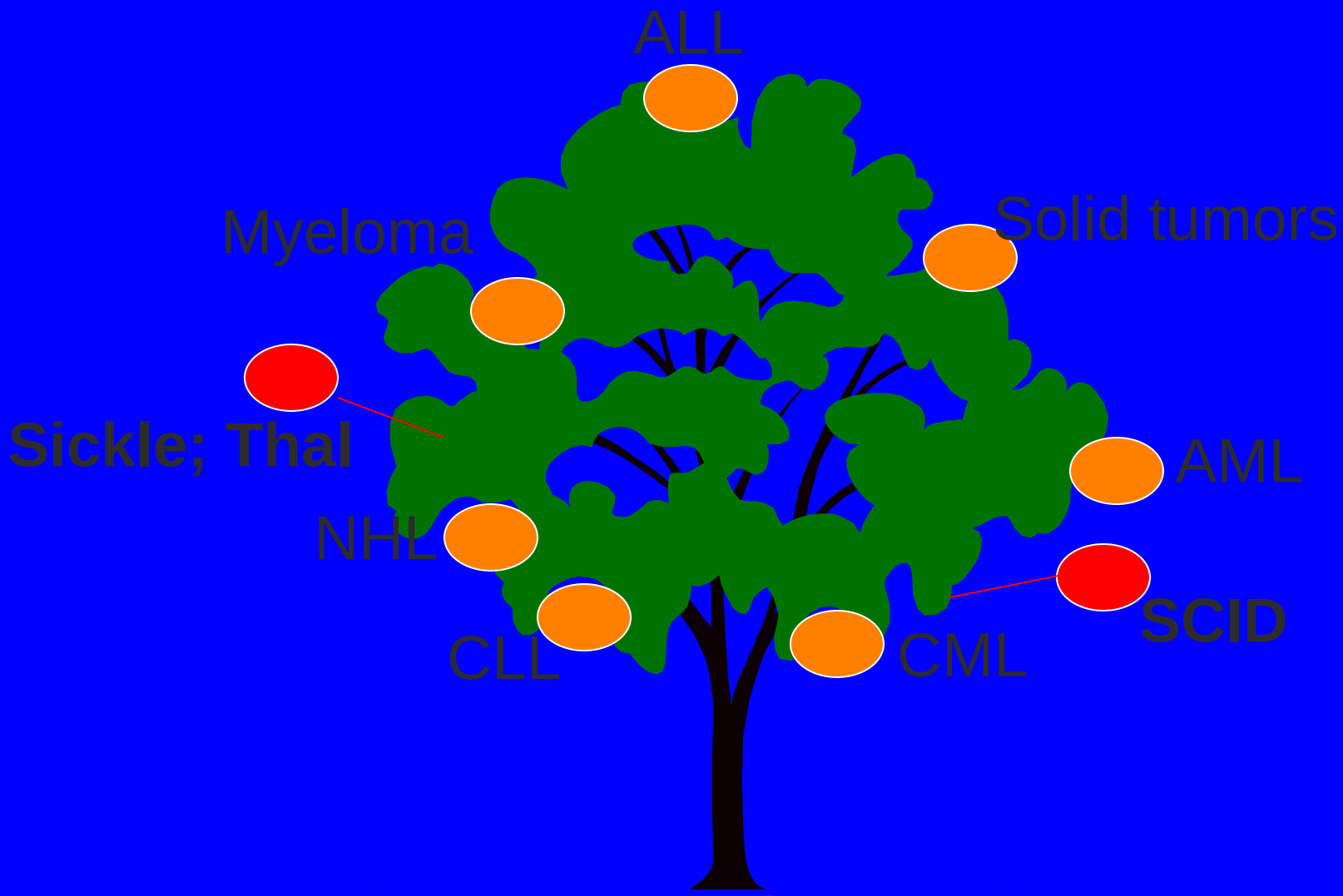
AML - beyond CR1
bad cytogenetics

ALL-most except standard risk CR2

High grade NHL, Myeloma,
Solid tumors



Graft vs Tumor Effects



Graft vs Trouble Effects

Similar Outcomes Using Myeloablative vs. Reduced Intensity and Non-Myeloablative Allogeneic Transplant Preparative Regimens for AML or MDS

Luger, Pulsipher et al

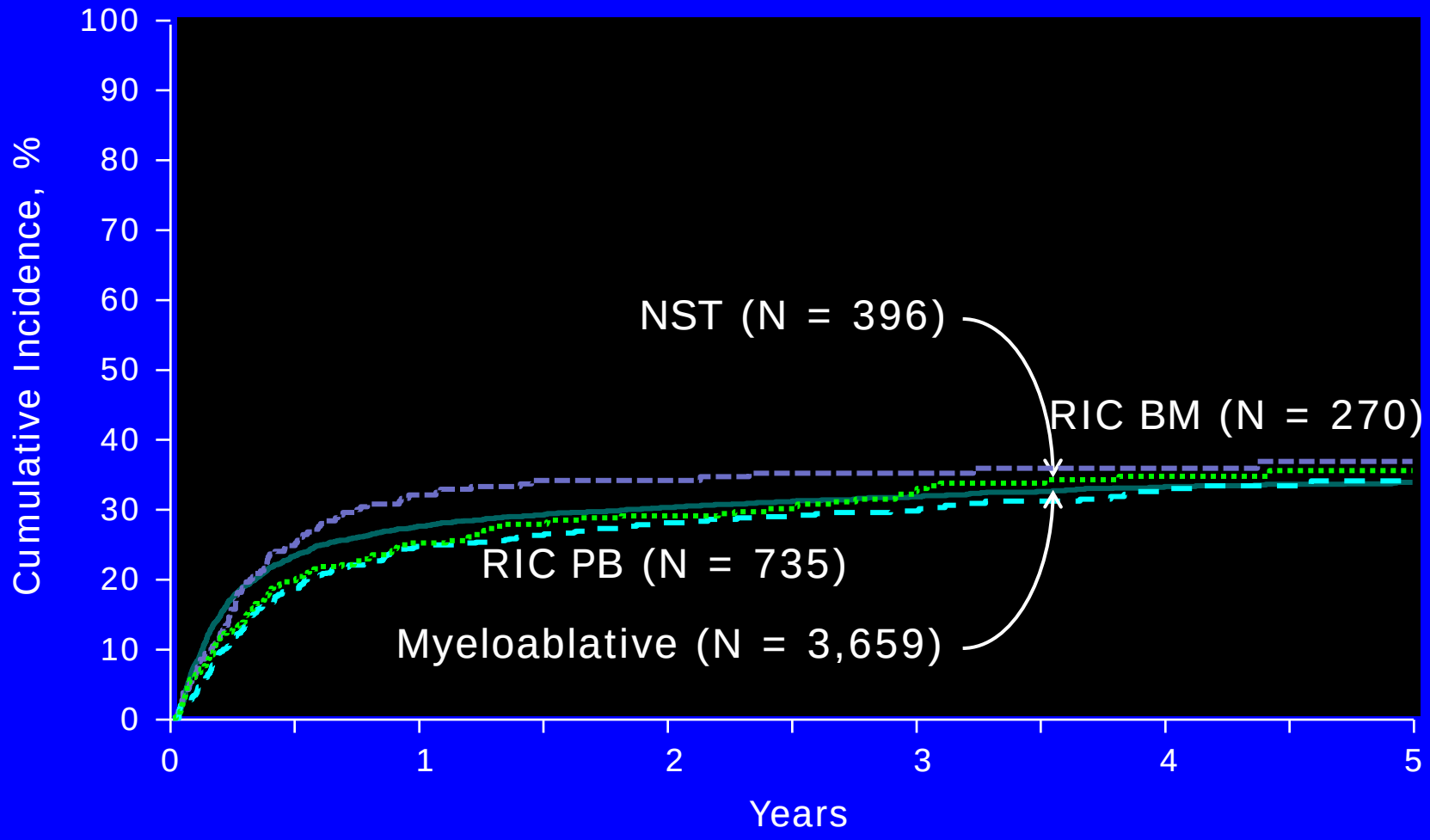
BMT, 2012

Patient Characteristics

Variable	MA	RIC	NST
N	3731	1041	407
Age, y	42 (18-68)	55 (18-70)	57 (18-70)

AML/MDS
1997-2004 Sib/URD BM/PBSC

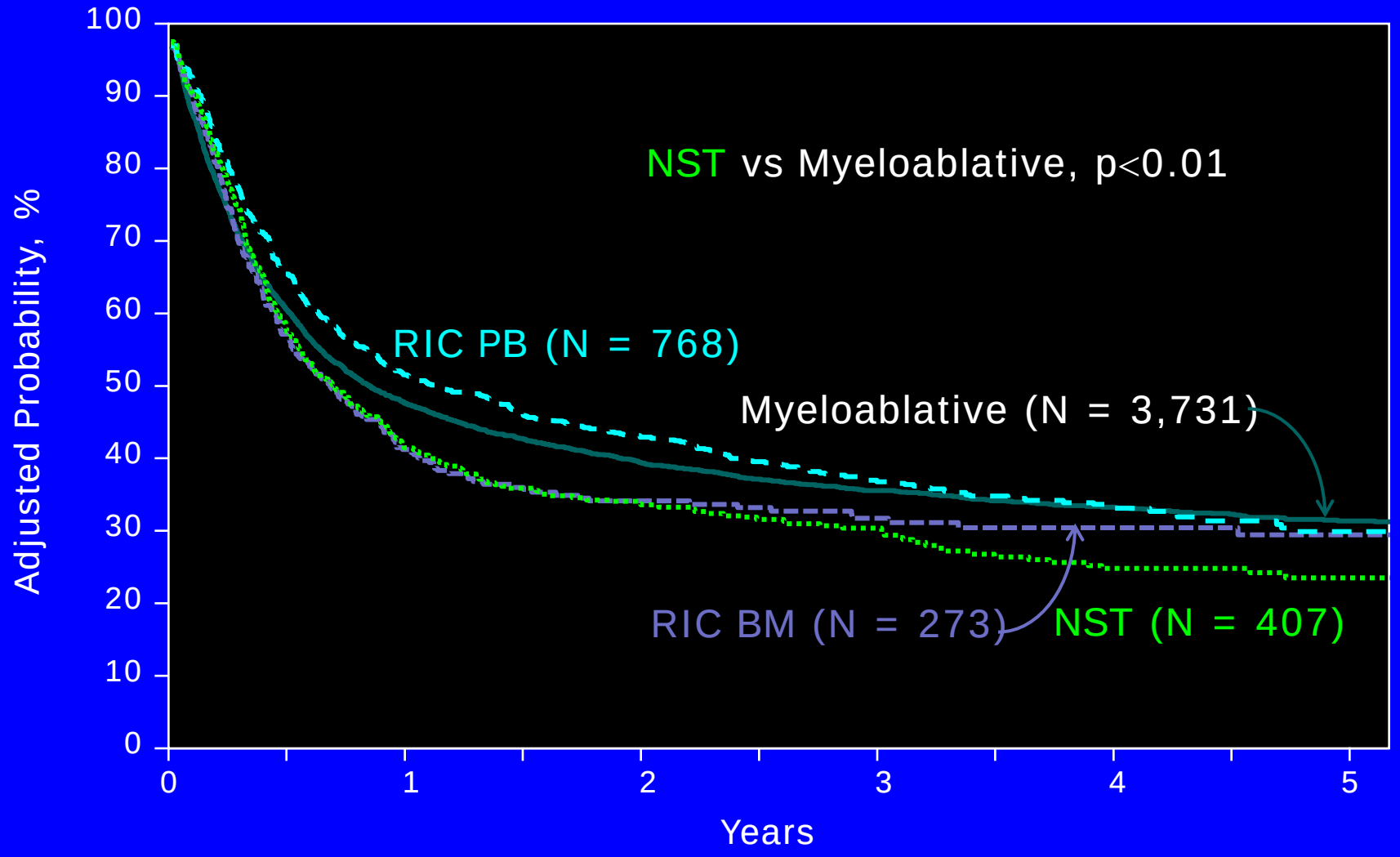
Cumulative Incidence of Treatment-Related Mortality



Relative Risk of Relapse

Variables	N	RR (95% CI)	P
Myeloablative	3659	1.00	
RIC BM	270	1.51 (1.23-1.85)	<0.001
RIC PB	735	1.06 (0.92-1.22)	0.44
NST	396	1.65 (1.40-1.96)	<0.001

Adjusted Probability of Overall Survival



Conclusions: MA vs RIC vs NST for AML/MDS

Similar rates of engraftment and acute GVHD

TRM lower for RIC early, but similar by 36 months

Equal MA and RIC relapse rates Equal 5-yr OS

Non-ablative lower OS

Prospective Randomized Trial BMT CTN 0901

AML/MDS adults

MAC: Flu Bu2 vs BuCy vs CyTBI

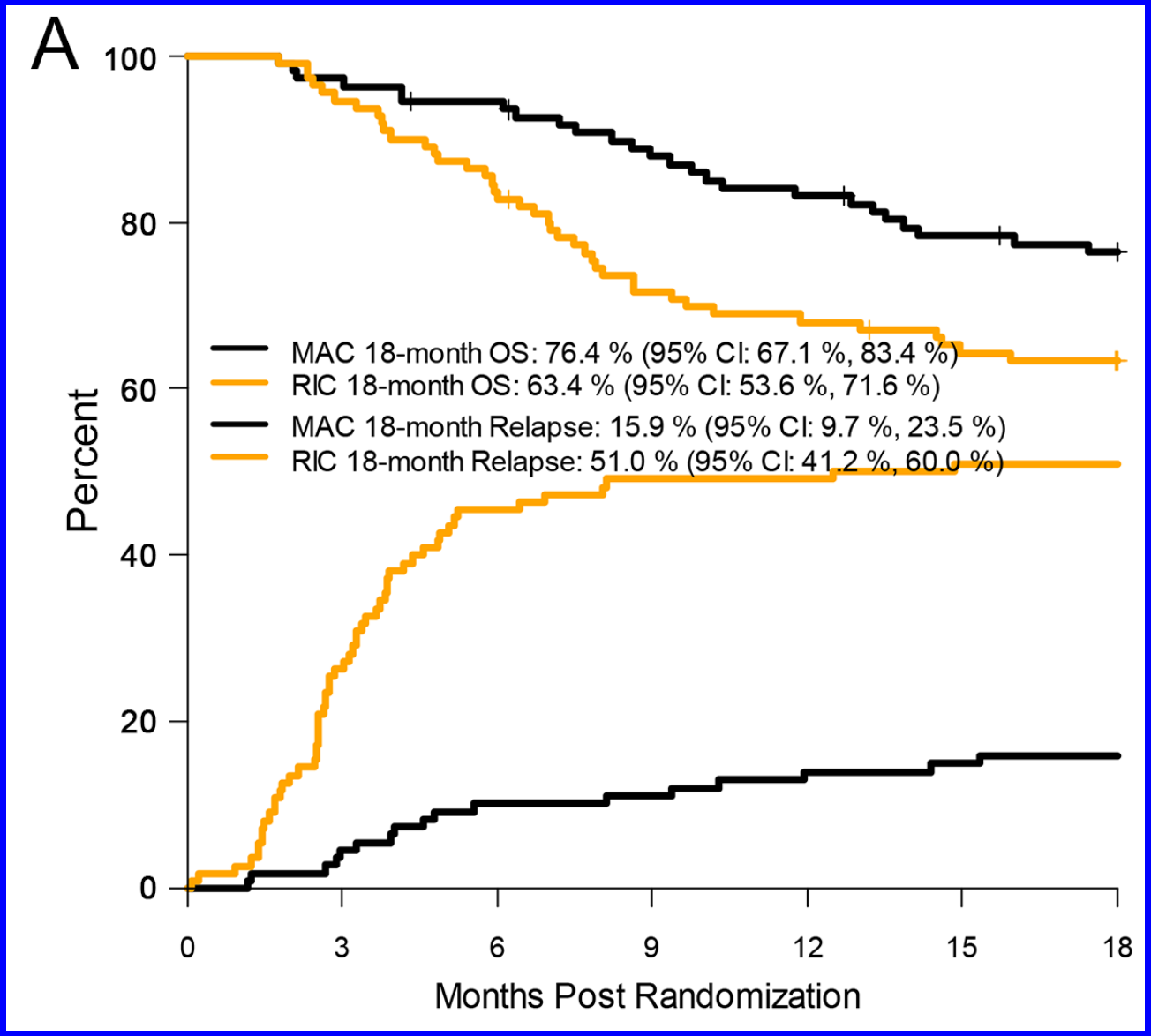
RIC: Flu Bu4 vs FluMel

N=356 planned;
272 enrolled in 34 months

Stopped for excess relapse with RIC

Scott et al, 2017

OS & Relapse for AML: MAC better than RIC



76.4%

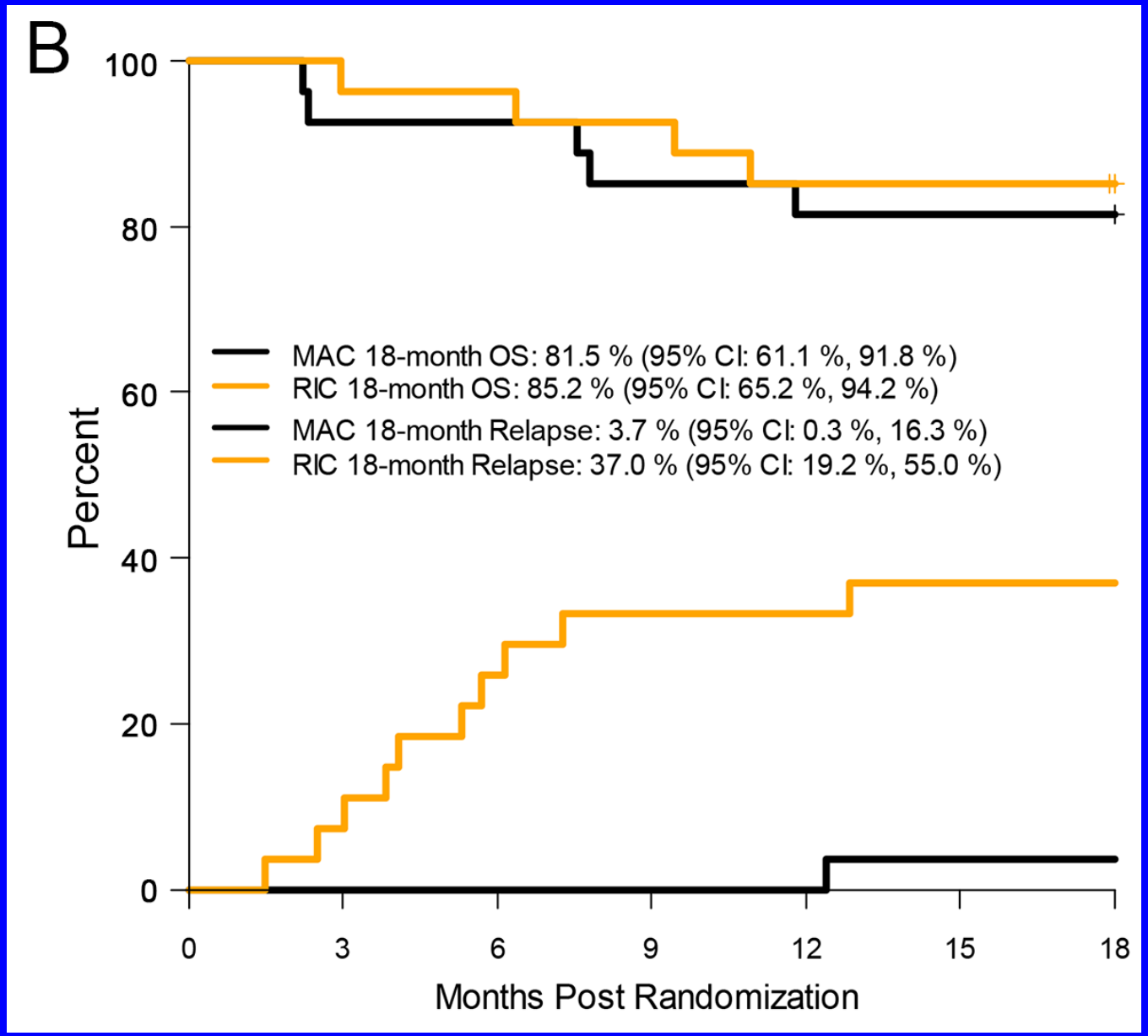
63.4

51%

15.9%

Scott et al, 2017

OS & Relapse for MDS: MAC = RIC



85.2%

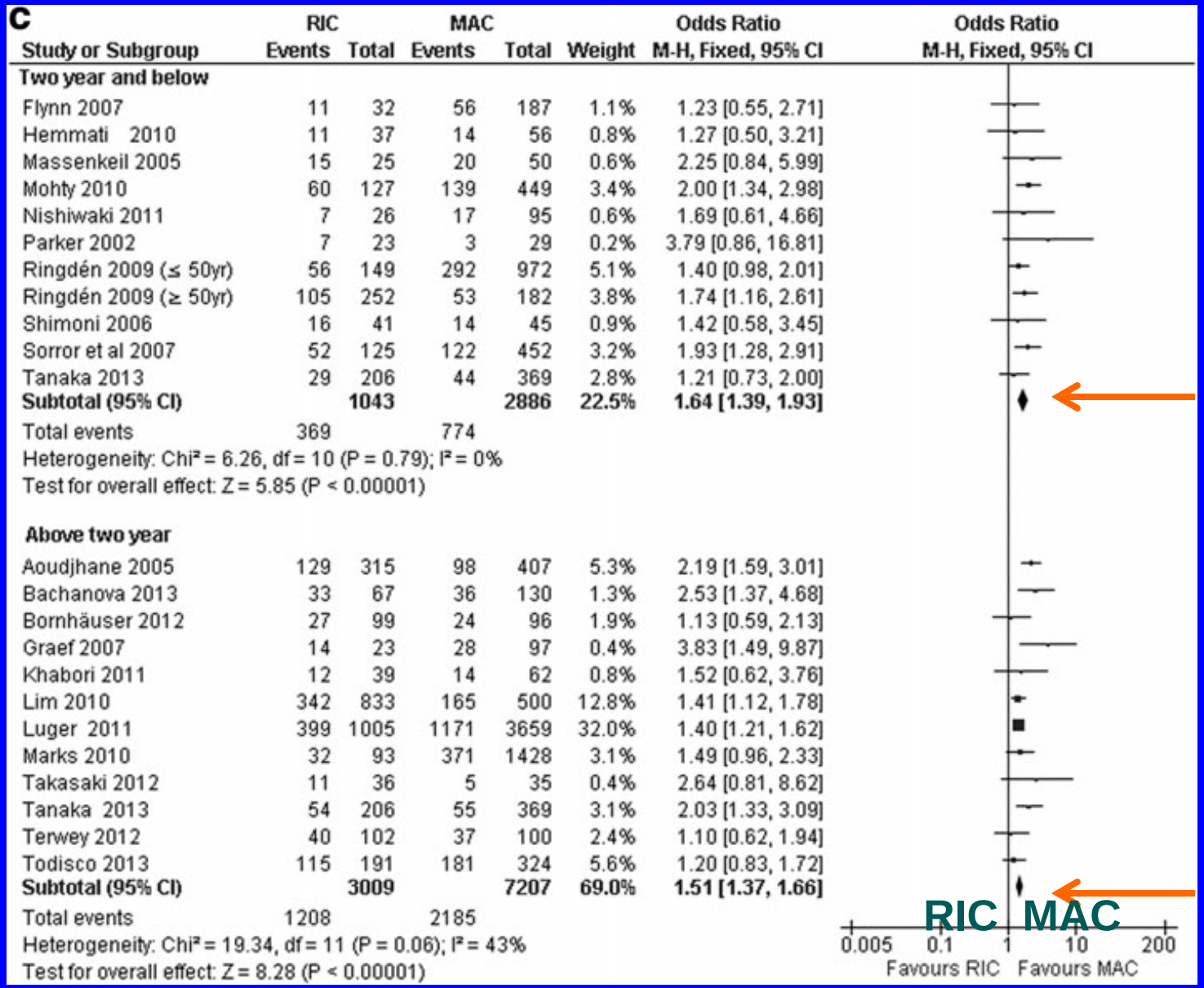
81.5%

37%

3.7%

Scott et al, 2017

Relapse RIC worse than MAC for Acute Leukemia



C	RIC		MAC			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Two year and below							
Flynn 2007	11	32	56	187	1.1%	1.23 [0.55, 2.71]	
Hemmati 2010	11	37	14	56	0.8%	1.27 [0.50, 3.21]	
Massenkeil 2005	15	25	20	50	0.6%	2.25 [0.84, 5.99]	
Mohty 2010	60	127	139	449	3.4%	2.00 [1.34, 2.98]	
Nishiwaki 2011	7	26	17	95	0.6%	1.69 [0.61, 4.66]	
Parker 2002	7	23	3	29	0.2%	3.79 [0.86, 16.81]	
Ringdén 2009 (≤ 50yr)	56	149	292	972	5.1%	1.40 [0.98, 2.01]	
Ringdén 2009 (≥ 50yr)	105	252	53	182	3.8%	1.74 [1.16, 2.61]	
Shimoni 2006	16	41	14	45	0.9%	1.42 [0.58, 3.45]	
Sorror et al 2007	52	125	122	452	3.2%	1.93 [1.28, 2.91]	
Tanaka 2013	29	206	44	369	2.8%	1.21 [0.73, 2.00]	
Subtotal (95% CI)		**1043**		**2886**	**22.5%**	**1.64 [1.39, 1.93]**	
Total events	369		774				
Heterogeneity: Chi² = 6.26, df = 10 (P = 0.79); I² = 0%							
Test for overall effect: Z = 5.85 (P < 0.00001)							
Above two year							
Aoudjhane 2005	129	315	98	407	5.3%	2.19 [1.59, 3.01]	
Bachanova 2013	33	67	36	130	1.3%	2.53 [1.37, 4.68]	
Bornhäuser 2012	27	99	24	96	1.9%	1.13 [0.59, 2.13]	
Graef 2007	14	23	28	97	0.4%	3.83 [1.49, 9.87]	
Khabori 2011	12	39	14	62	0.8%	1.52 [0.62, 3.76]	
Lim 2010	342	833	165	500	12.8%	1.41 [1.12, 1.78]	
Luger 2011	399	1005	1171	3659	32.0%	1.40 [1.21, 1.62]	
Marks 2010	32	93	371	1428	3.1%	1.49 [0.96, 2.33]	
Takasaki 2012	11	36	5	35	0.4%	2.64 [0.81, 8.62]	
Tanaka 2013	54	206	55	369	3.1%	2.03 [1.33, 3.09]	
Terwey 2012	40	102	37	100	2.4%	1.10 [0.62, 1.94]	
Todisco 2013	115	191	181	324	5.6%	1.20 [0.83, 1.72]	
Subtotal (95% CI)		**3009**		**7207**	**69.0%**	**1.51 [1.37, 1.66]**	
Total events	1208		2185				
Heterogeneity: Chi² = 19.34, df = 11 (P = 0.06); I² = 43%							
Test for overall effect: Z = 8.28 (P < 0.00001)							

23 trials
N>10000

Relapse
< 2 years

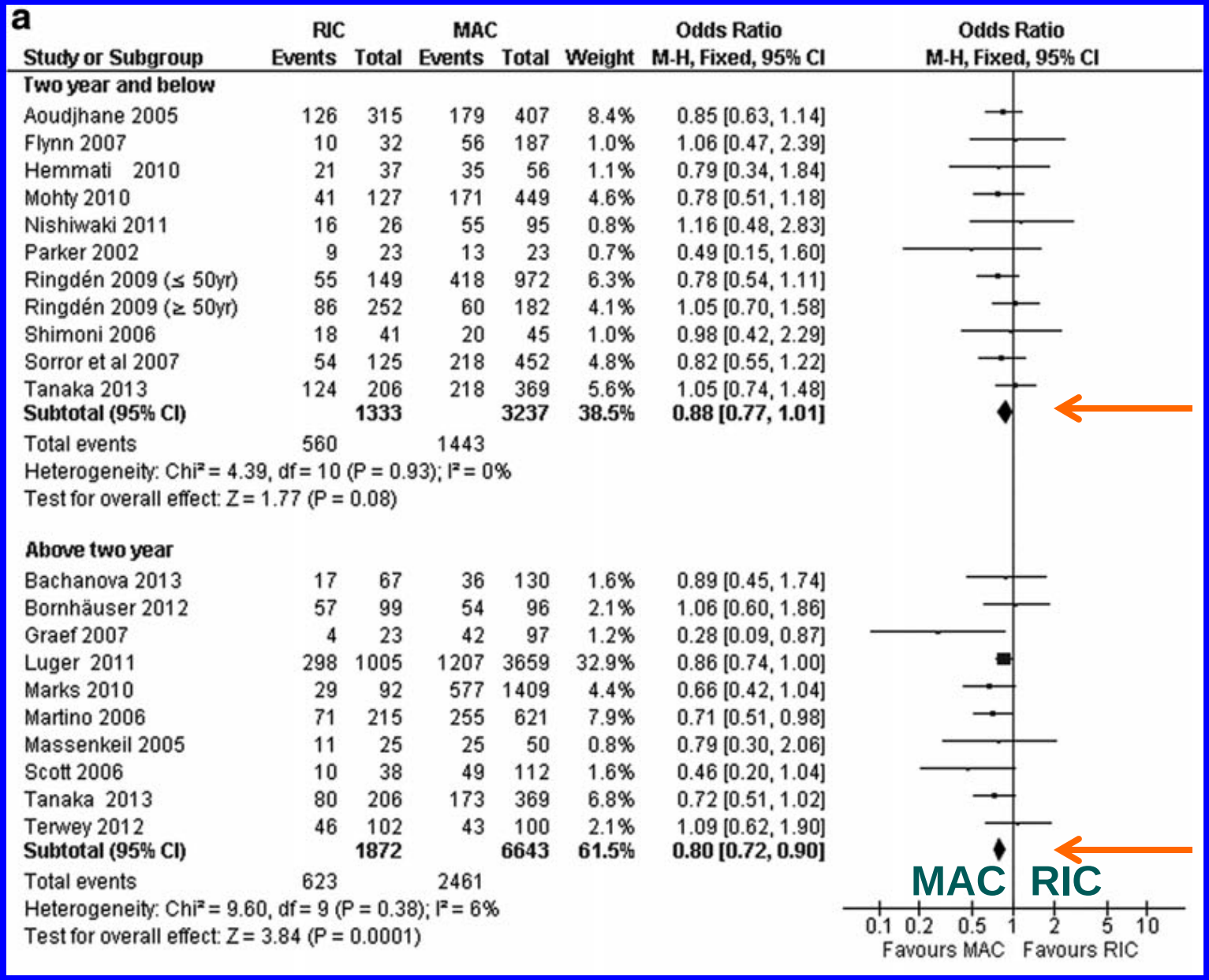
P=0.00001

Relapse
> 2 years

P=0.00001

Abdul Wahid, 2014

PFS RIC ~worse than MAC for Acute Leukemia



PFS
< 2 years

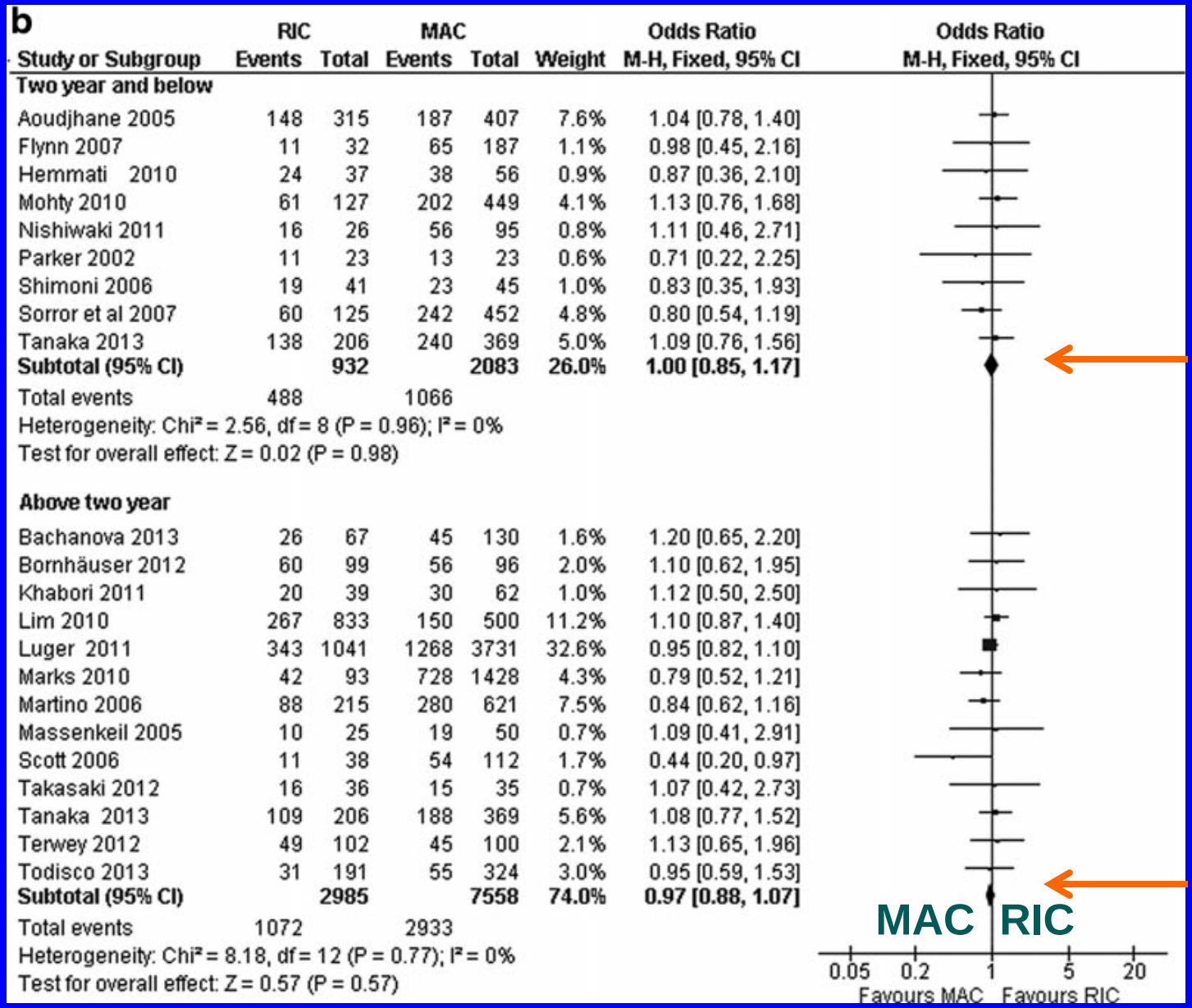
P=0.08

PFS
> 2 years

P=0.0001

Abdul Wahid, 2014

OS RIC = MAC for Acute Leukemia



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Study or Subgroup	RIC Events	RIC Total	MAC Events	MAC Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Two year and below						
Aoudjhane 2005	148	315	187	407	7.6%	1.04 [0.78, 1.40]
Flynn 2007	11	32	65	187	1.1%	0.98 [0.45, 2.16]
Hemmati 2010	24	37	38	56	0.9%	0.87 [0.36, 2.10]
Mohty 2010	61	127	202	449	4.1%	1.13 [0.76, 1.68]
Nishiwaki 2011	16	26	56	95	0.8%	1.11 [0.46, 2.71]
Parker 2002	11	23	13	23	0.6%	0.71 [0.22, 2.25]
Shimoni 2006	19	41	23	45	1.0%	0.83 [0.35, 1.93]
Sorror et al 2007	60	125	242	452	4.8%	0.80 [0.54, 1.19]
Tanaka 2013	138	206	240	369	5.0%	1.09 [0.76, 1.56]
Subtotal (95% CI)		**932**		**2083**	**26.0%**	**1.00 [0.85, 1.17]**
Total events	488		1066			
Heterogeneity: Chi² = 2.56, df = 8 (P = 0.96); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.98)						
Above two year						
Bachanova 2013	26	67	45	130	1.6%	1.20 [0.65, 2.20]
Bornhäuser 2012	60	99	56	96	2.0%	1.10 [0.62, 1.95]
Khabori 2011	20	39	30	62	1.0%	1.12 [0.50, 2.50]
Lim 2010	267	833	150	500	11.2%	1.10 [0.87, 1.40]
Luger 2011	343	1041	1268	3731	32.6%	0.95 [0.82, 1.10]
Marks 2010	42	93	728	1428	4.3%	0.79 [0.52, 1.21]
Martino 2006	88	215	280	621	7.5%	0.84 [0.62, 1.16]
Massenkeil 2005	10	25	19	50	0.7%	1.09 [0.41, 2.91]
Scott 2006	11	38	54	112	1.7%	0.44 [0.20, 0.97]
Takasaki 2012	16	36	15	35	0.7%	1.07 [0.42, 2.73]
Tanaka 2013	109	206	188	369	5.6%	1.08 [0.77, 1.52]
Terwey 2012	49	102	45	100	2.1%	1.13 [0.65, 1.96]
Todisco 2013	31	191	55	324	3.0%	0.95 [0.59, 1.53]
Subtotal (95% CI)		**2985**		**7558**	**74.0%**	**0.97 [0.88, 1.07]**
Total events	1072		2933			
Heterogeneity: Chi² = 8.18, df = 12 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.57 (P = 0.57)						

OS
< 2 years
P=0.98

OS
> 2 years
P=0.57

Abdul Wahid, 2014

MA vs. RIC for Adult Ph- ALL

- Allogeneic HCT BM or PBSC
- HLA-identical sibling or unrelated donor 1995-2007
- Age $\geq$ 16 years
- CR1 or CR2

Marks et al
Blood, 2010

CIBMTR®

Clinical Characteristics

	RIC	MA	P-value
Number	93	1428	
Age, yr	45 (17-66)	28 (16-62)	<0.001
Age > 50 yr	43%	7%	<0.001
KPS < 80%	14%	7%	0.07
CR1	59%	52%	0.20
HLA-Id sibling	41%	32%	0.09
PBSC grafts	73%	43%	<0.001
2002-2007	73%	51%	<0.001

CIBMTR®

Marks et al

Similar Outcomes

Outcome	RIC	MA
Acute GVHD @ 100d (grades II-IV)	39%	46%
Chronic GVHD @ 3 years	34%	42%
TRM @ 3 years	32%	33%

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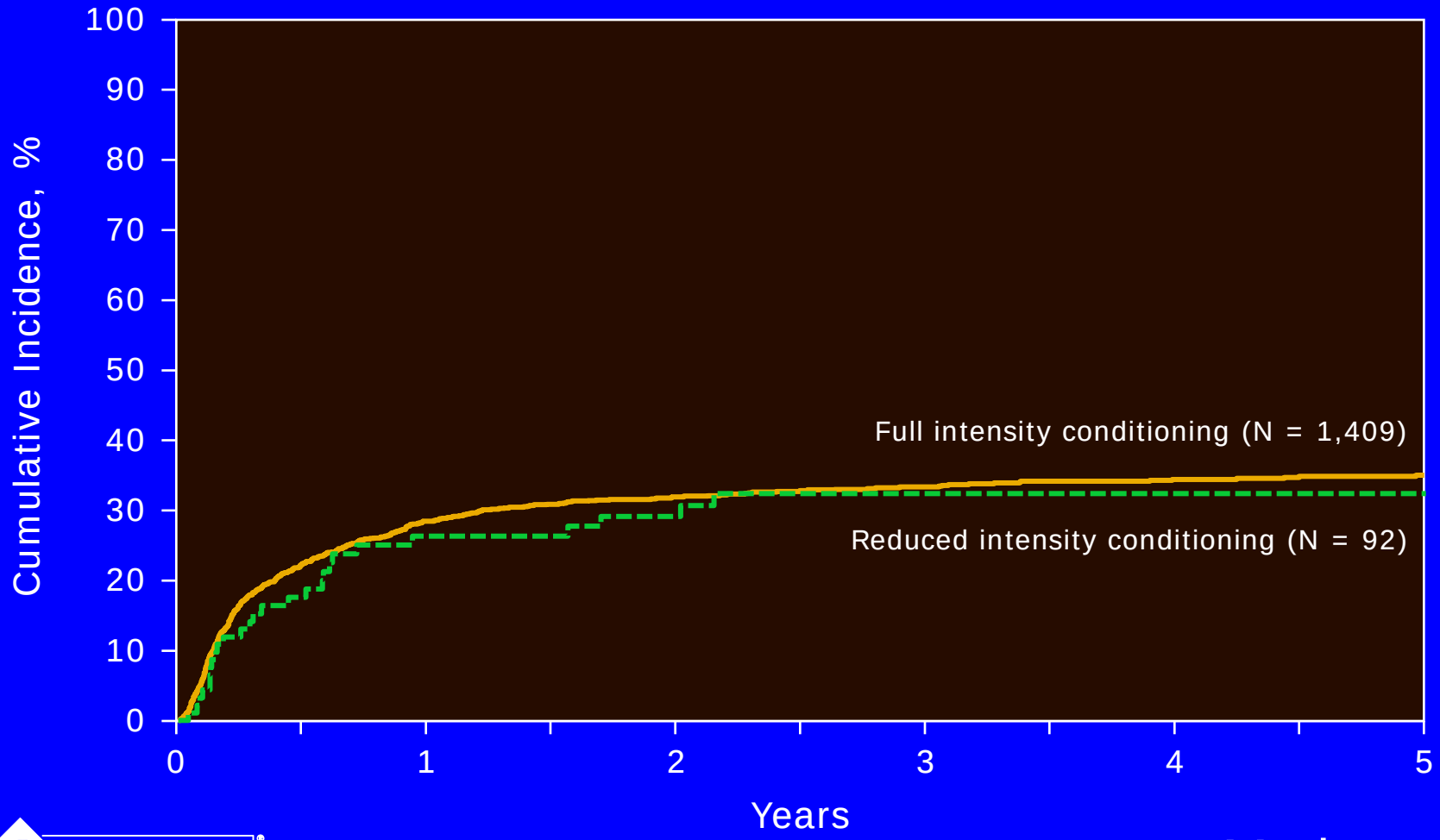
Marks et al

Cumulative Incidence of Treatment-related Mortality



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Marks et al

Similar Outcomes

Outcome	RIC	MA
Acute GVHD @ 100d (grades II-IV)	39%	46%
Chronic GVHD @ 3 years	34%	42%
TRM @ 3 years	32%	33%
Relapse @ 3 years	35%	26%
Overall Survival @ 3 years	38%	43%

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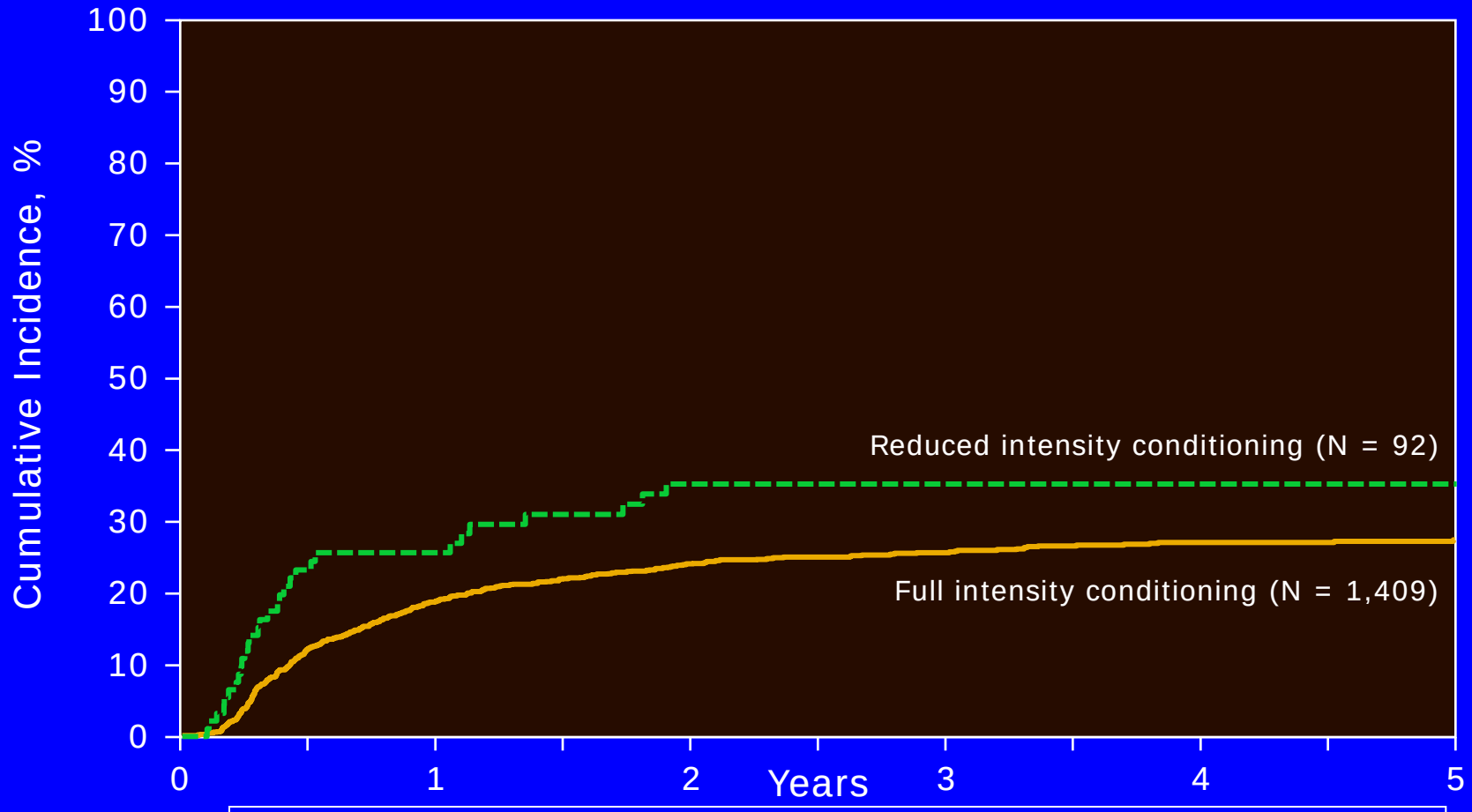
Marks et al

Cumulative Incidence of Relapse



Better with short CR1, GVHD

CIBMTR®

Marks et al

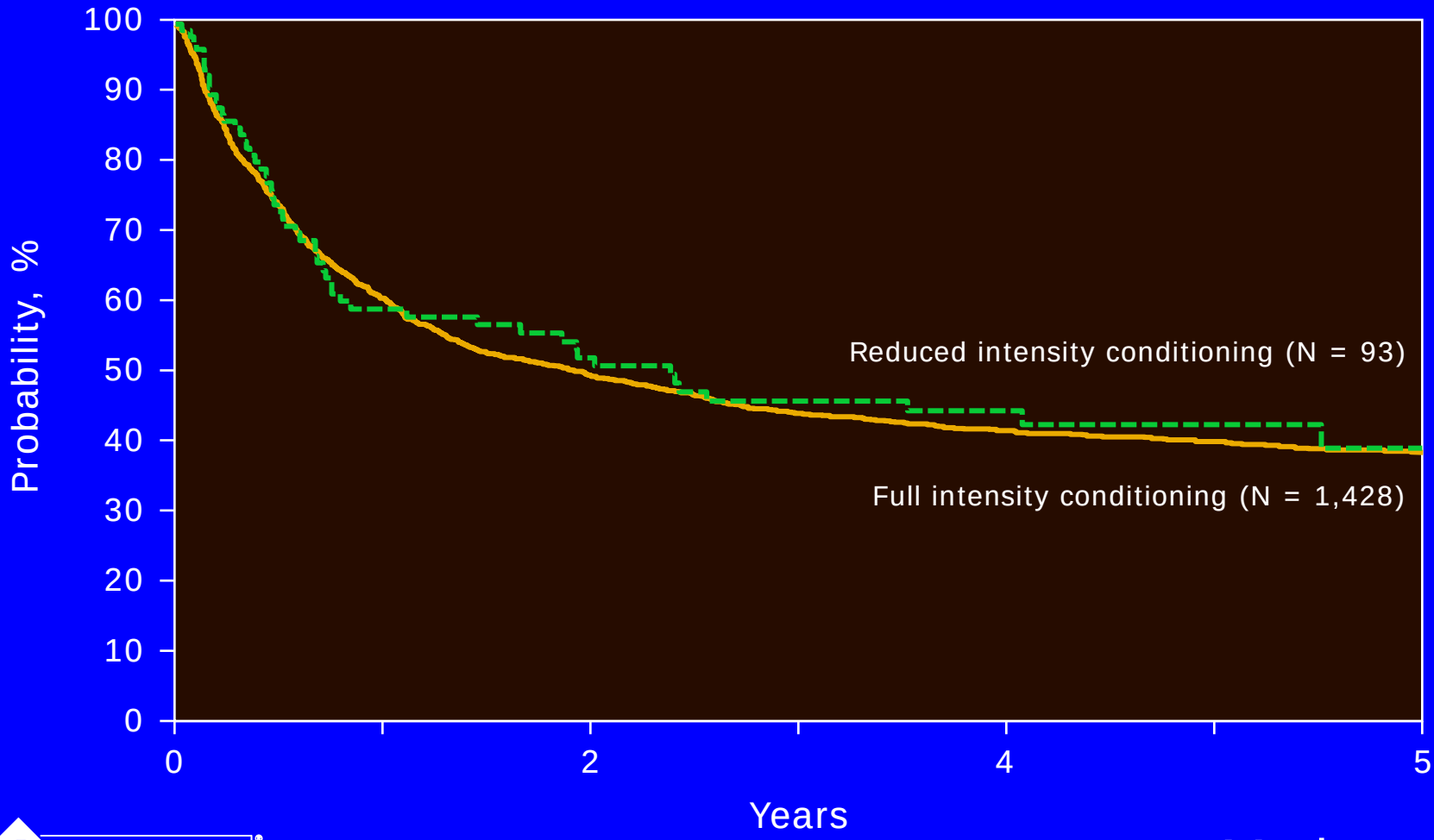
HCT for ALL CR2

	RIC	MA	P value
Relapse @ 3y	30 (17-46)	31 (28-35)	0.91
OS @ 3y	28 (14-44)	33 (30-37)	0.51

Marks et al
Blood, 2010

CIBMTR

Equal Adjusted Probability of Overall Survival



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Marks et al

Clinical implications of less toxic BMT

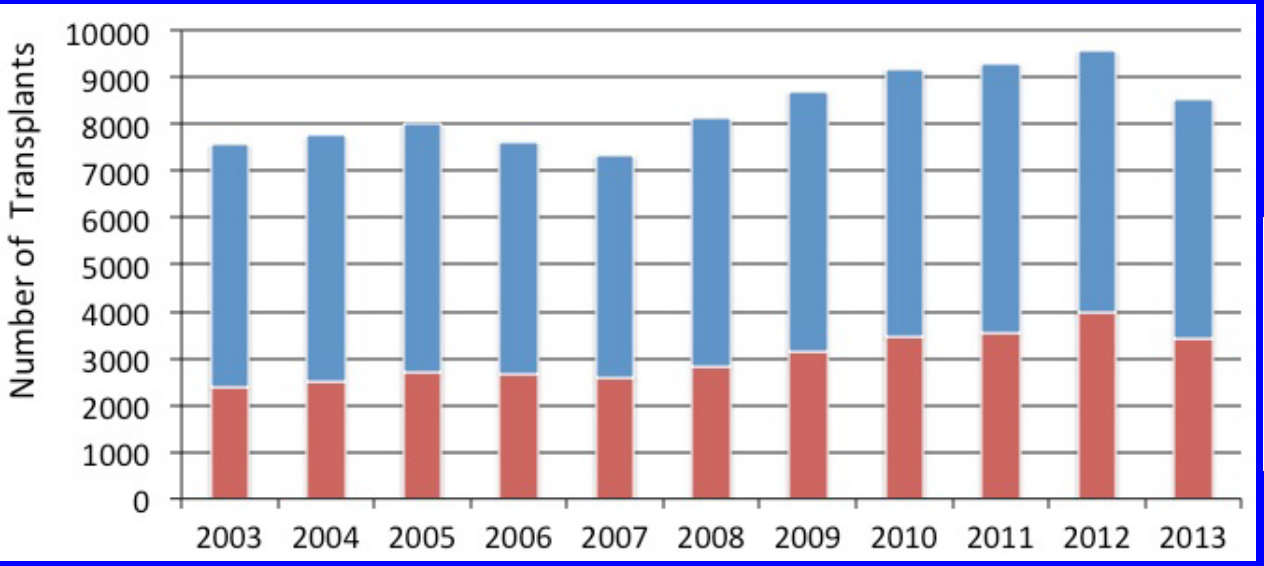
Less morbidity & mortality

Applicable to older, sicker populations

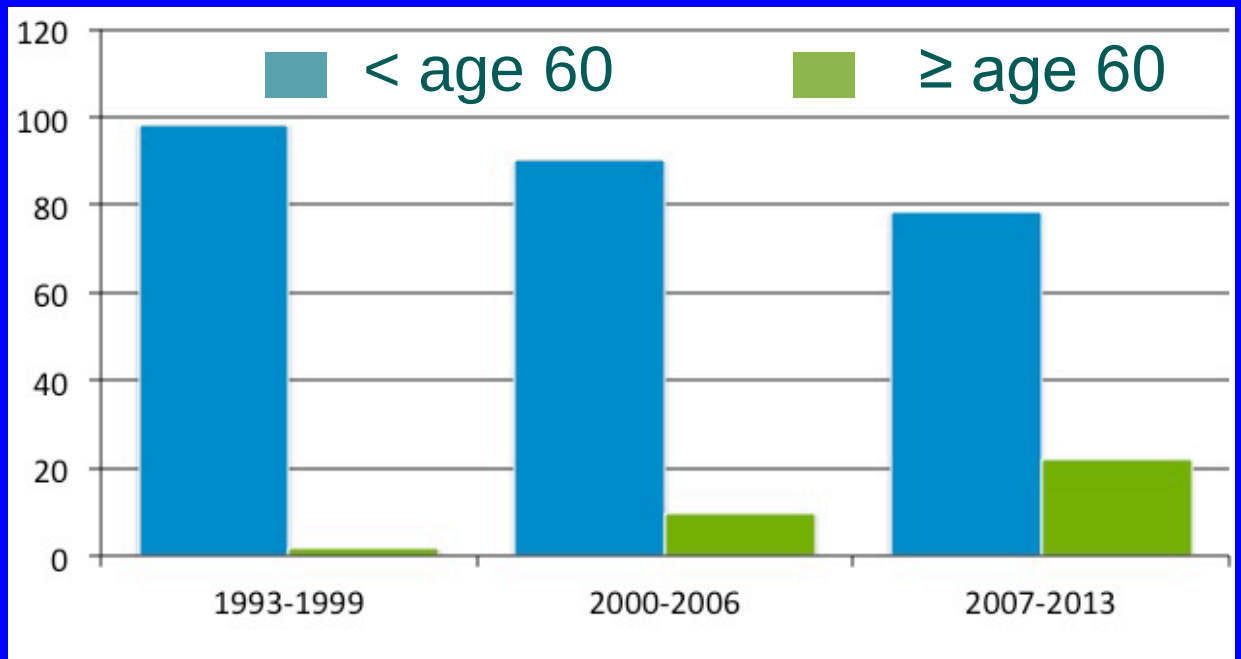
Outpatient; less costly

Useful in newer clinical settings

MAC RIC CIBMTR MAC:RIC Utilization



EMRO 2011-12
MAC 63%; RIC 9.5%
Aljurf, 2015



Situational choices for conditioning intensity in allotransplantation

Younger	*Tolerate more intense conditioning or GVHD*
Resistant tumor	*Need more GVL & more conditioning*
Pre-BMT infections	*Need faster immune recovery*

Modify graft & technique