Transplantation for Leukemia: How much regimen intensity is needed?

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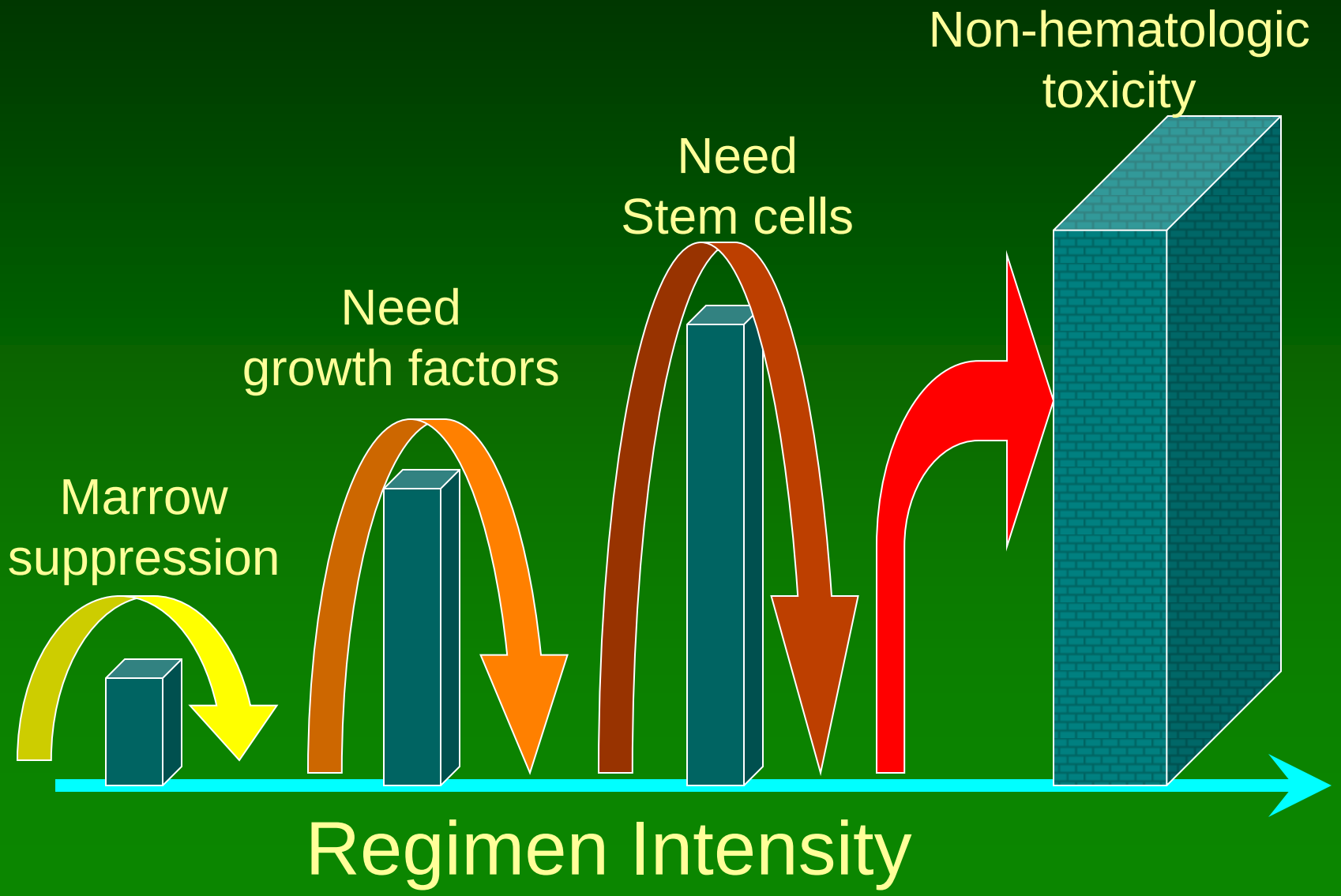
Capetown, 2014

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

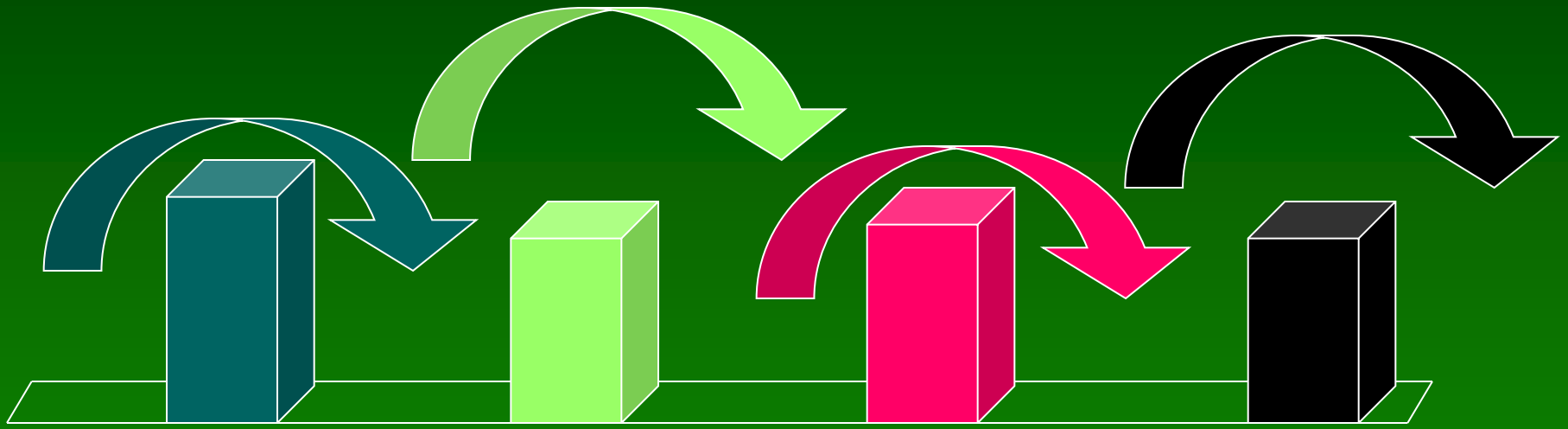
Dose-intensity may not prevent relapse

AML - beyond CR1
bad cytogenetics

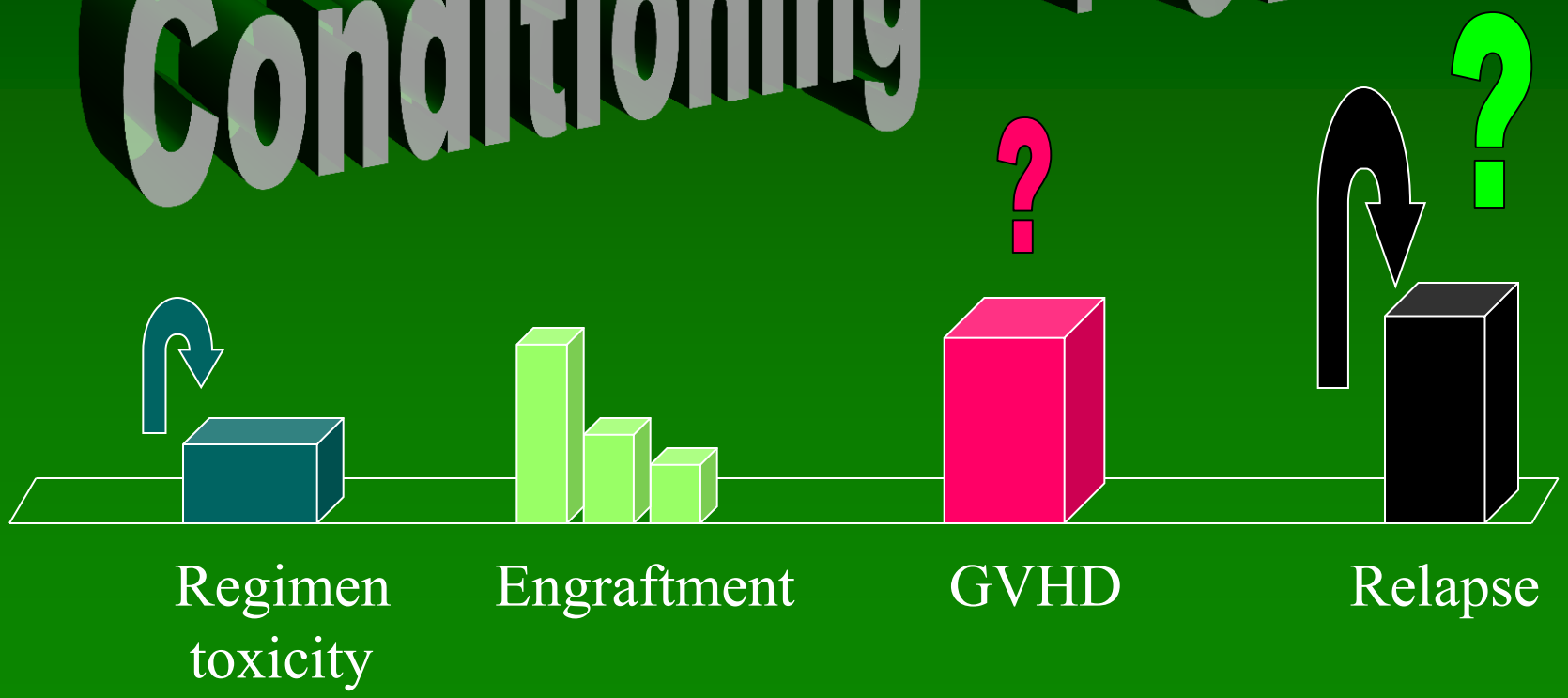
ALL-most except standard risk CR2

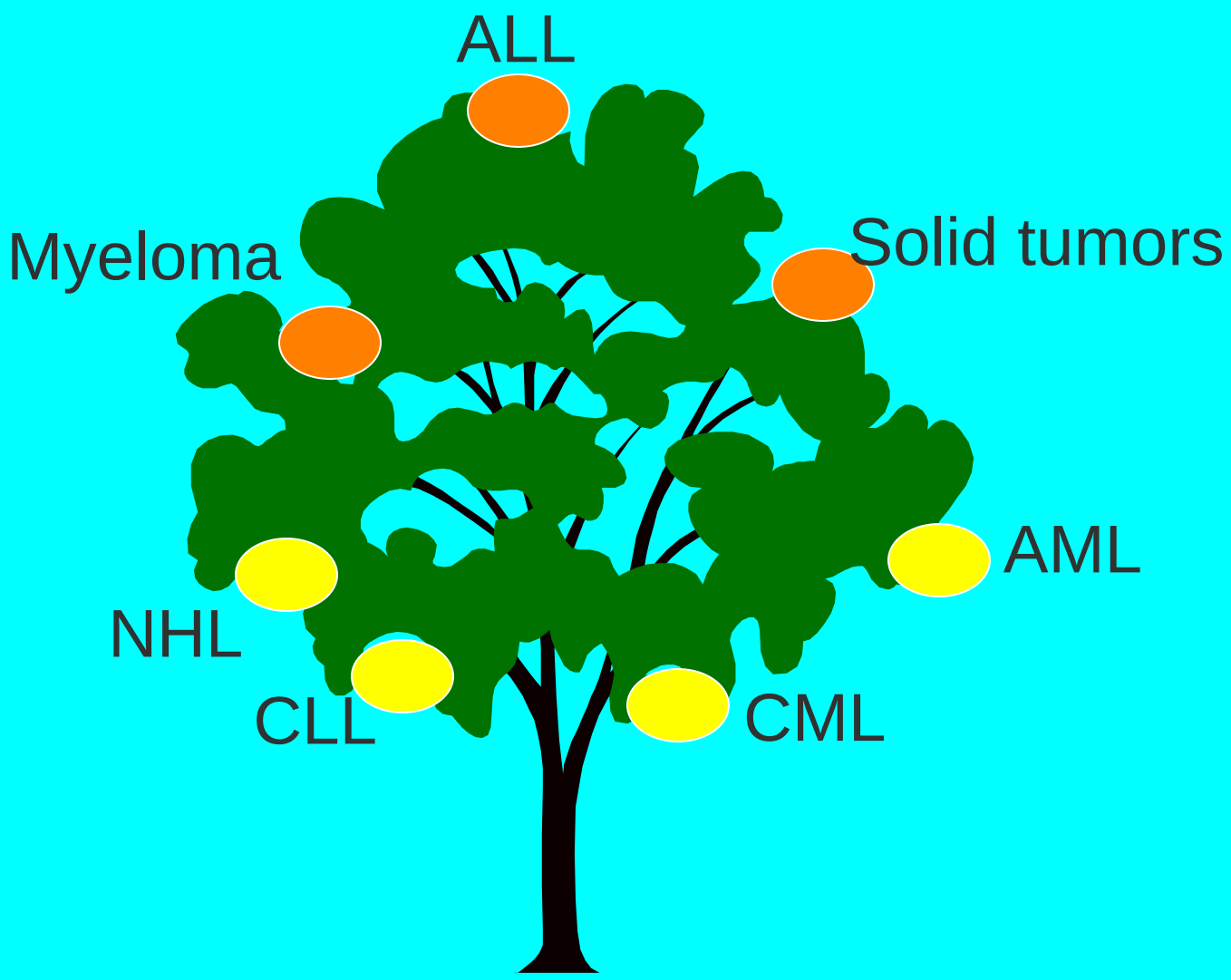
High grade NHL, Myeloma,
Solid tumors

Barriers to Transplant Success

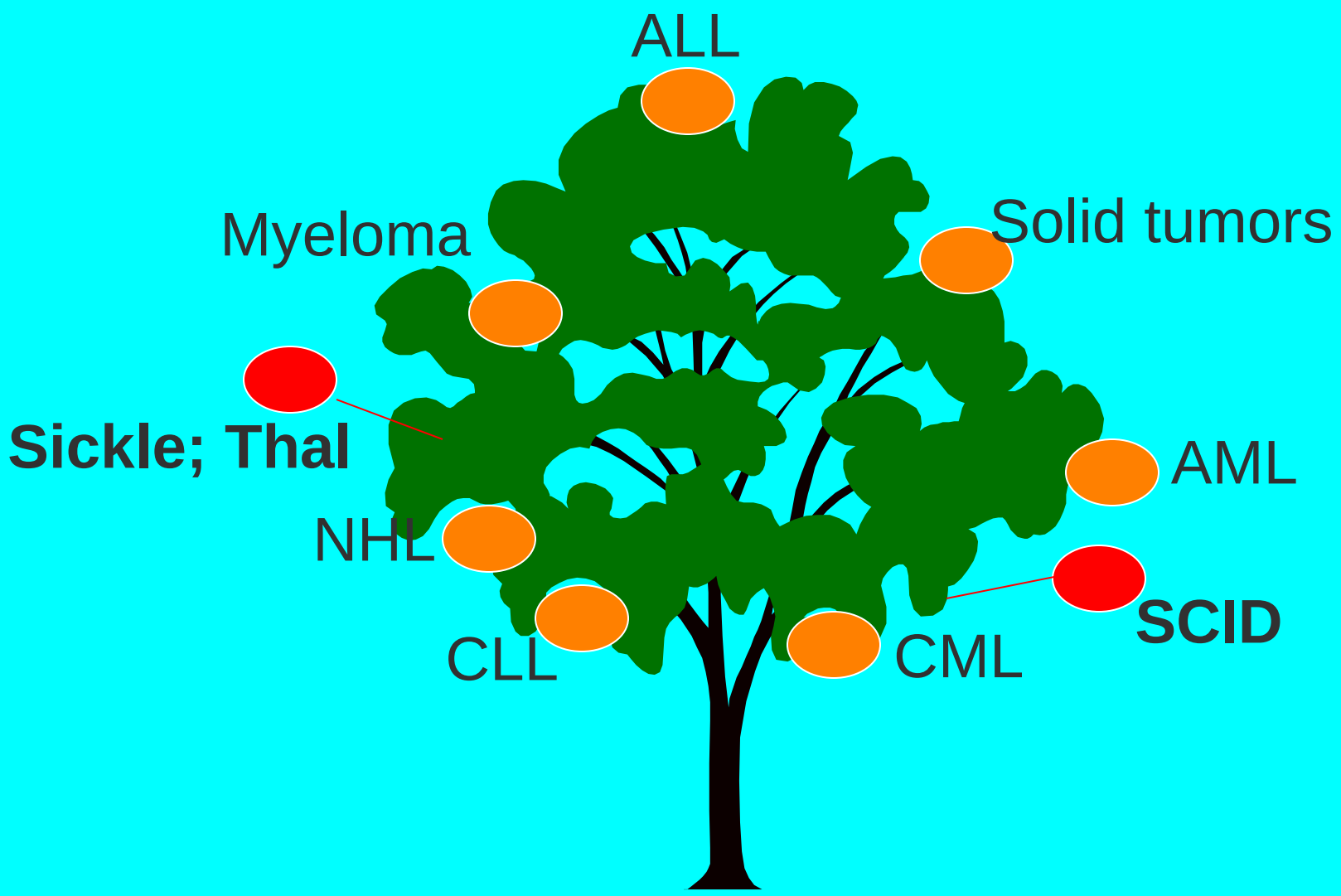


Non myeloablative Conditioning + GVL



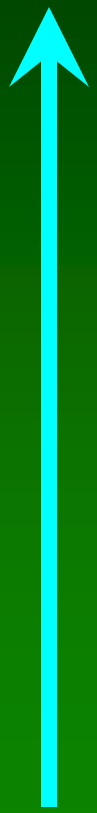


Graft vs Tumor Effects



Graft vs Trouble Effects

Allogeneic Immune Susceptibility



CML
CLL/low grade NHL
AML
Hodgkins disease, Myeloma
ALL/High grade NHL

Solid tumors

Reduced Intensity Transplants

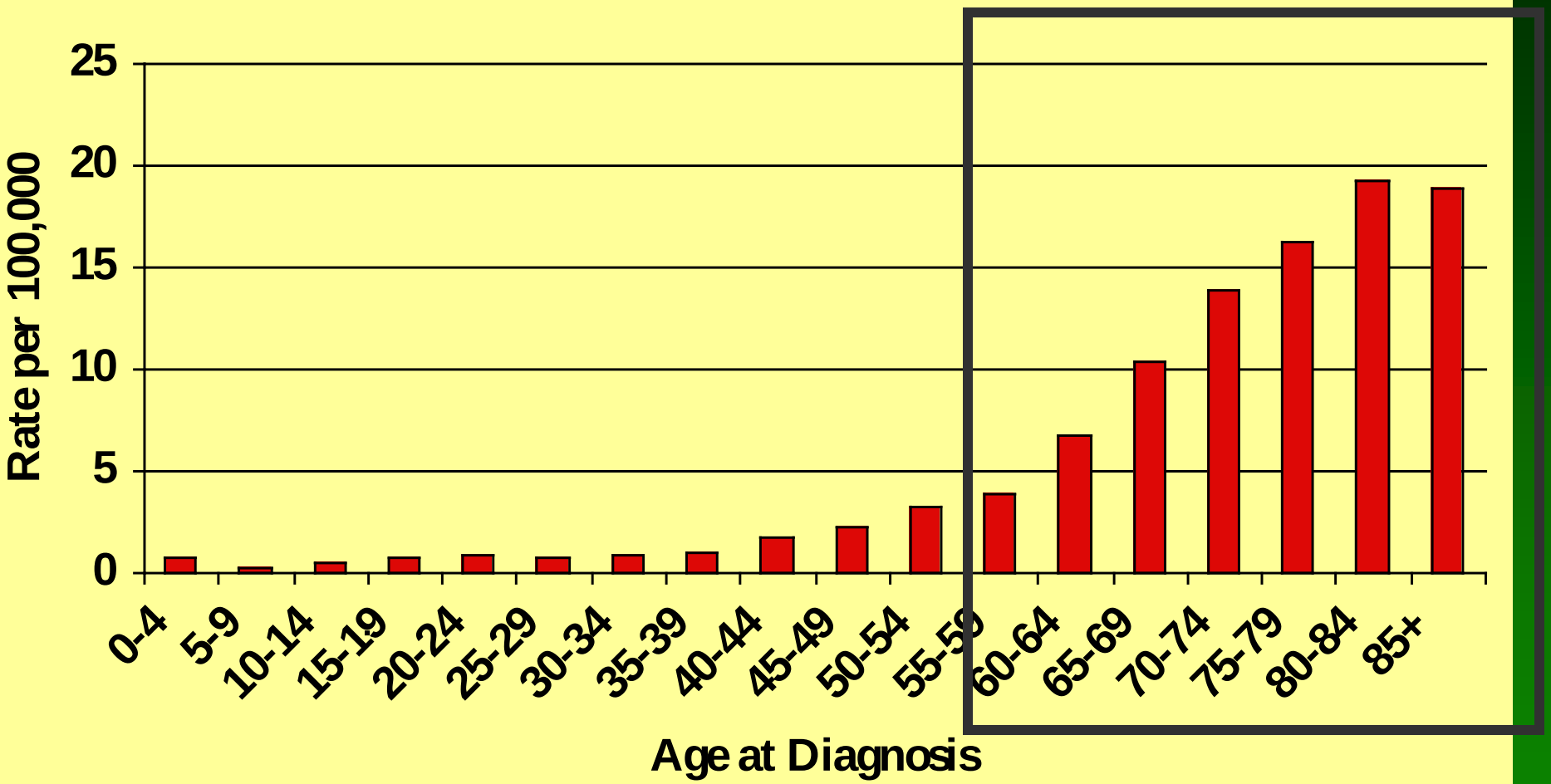
Limit conditioning toxicity
Retain the allogeneic anti-tumor effects

Establish a lymphoid graft

Immunoablation --- lymphodepletion

lymphoid space

AML: Age Specific Incidence



SEER Data 1973-1997

AGE <54 = ~ 25% OF ALL AML CASES

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

Luger, Pulsipher et al

BMT, 2012

Patient Selection

- **Allogeneic bone marrow and/or PBSC**
- **HLA-identical sibling or URD HCT**
- **AML or MDS, reported to the CIBMTR, 1997-2004**
- **Age 18-70 years**

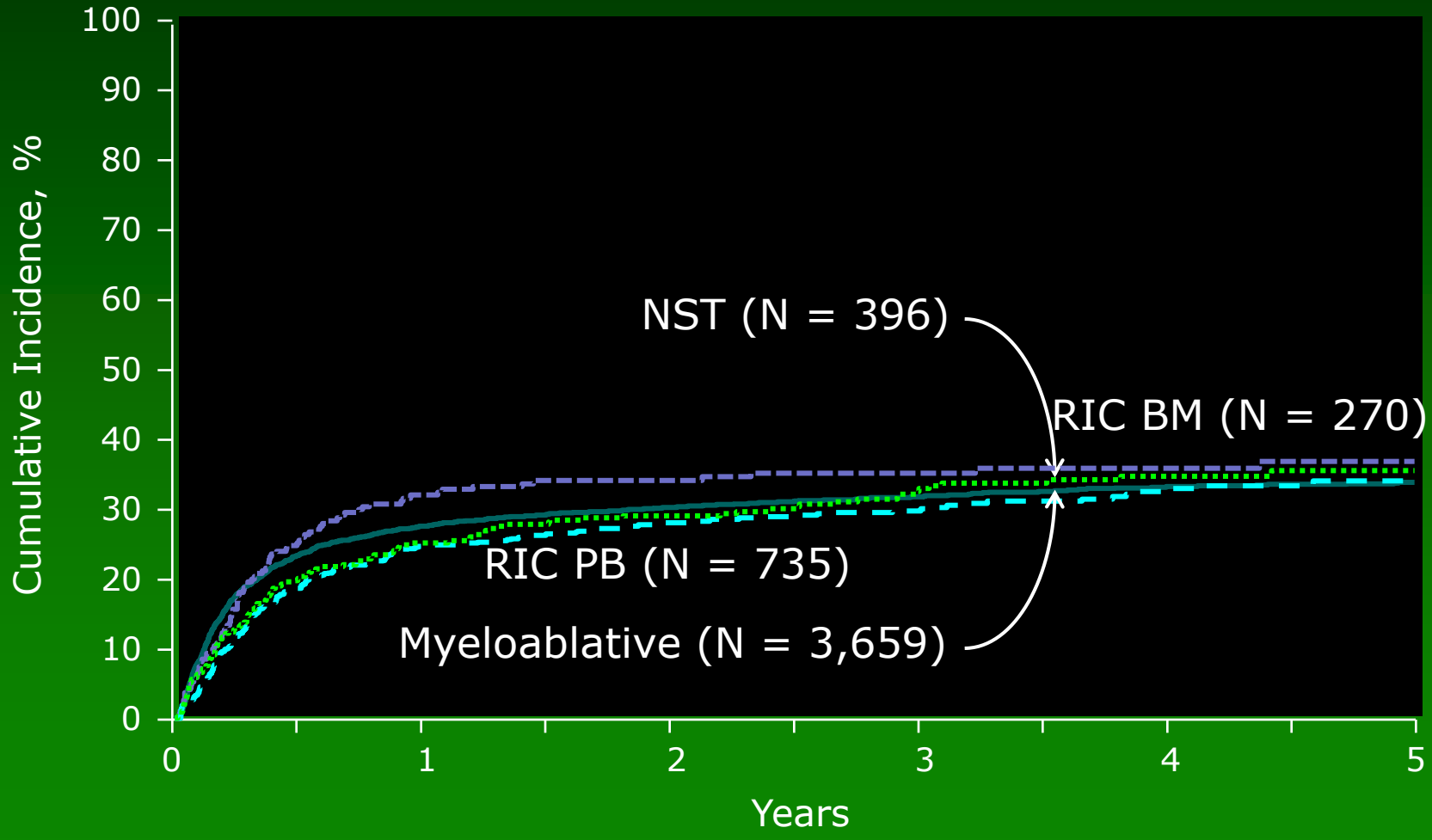
Patient Characteristics

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

Conditioning Regimen Intensity: CIBMTR Categories

- **Myeloablative (MA) n=3731**
  - Cy/TBI (n=1635), Bu/Cy (n=1575)
  - TBI ≥500 cGy, or >800 cGy fx (n=144)
  - Mel ≥150 mg/m^2 (n=57)
  - Bu >9 mg/kg (n=320)
- **Reduced-intensity (RIC) n=1041**
  - TBI <500 cGy, or <800 cGy fx (n=149)
  - Mel ≤150 mg/m^2 (n=378)
  - Bu ≤9 mg/kg (n=514)
- **Non-myeloablative (NST) n=407**
  - TBI 200 cGy (n=34), Flu/TBI 200 cGy (n=245)
  - Flu/Cy (n=128)

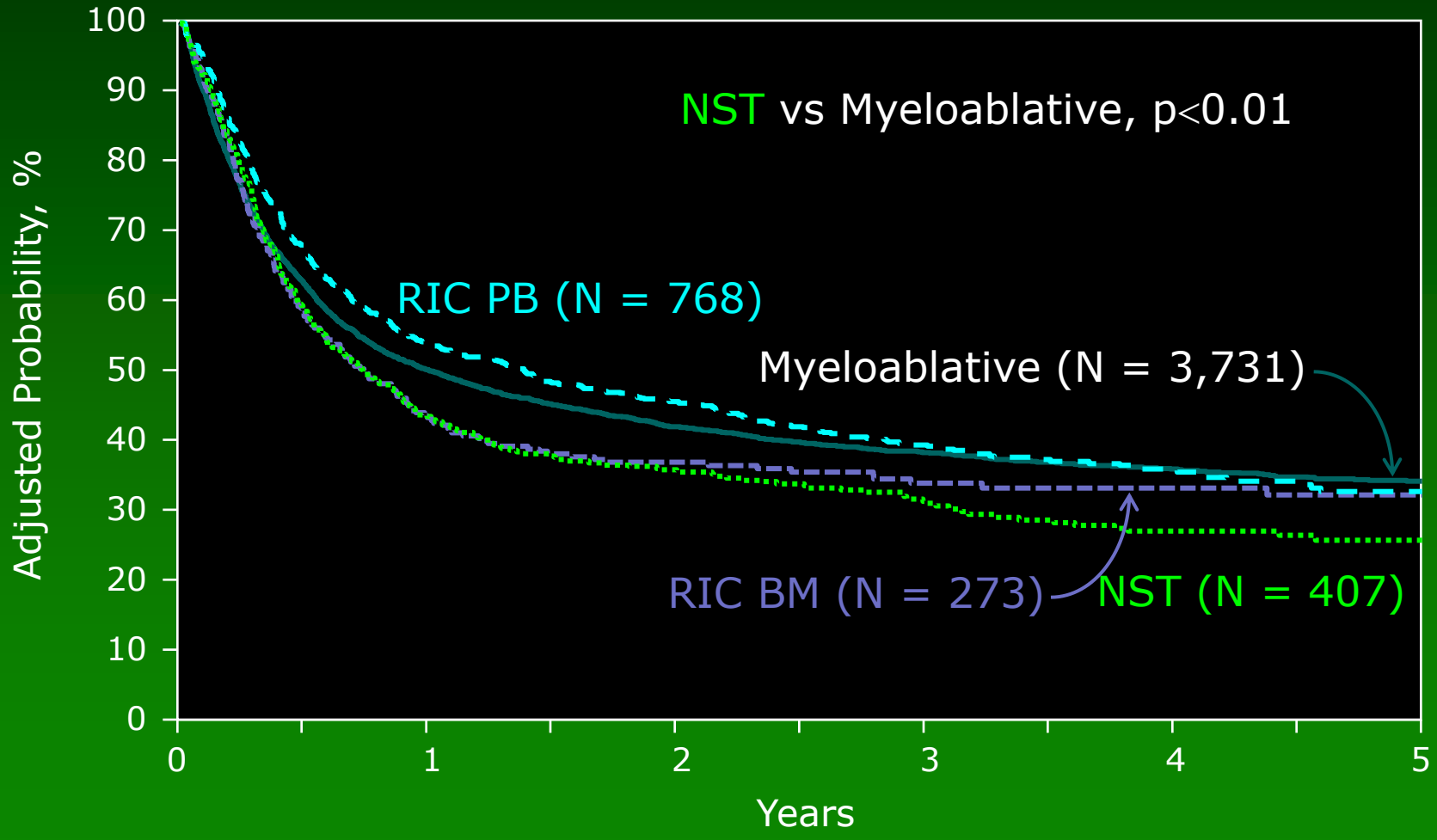
Cumulative Incidence of Treatment-Related Mortality



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

- **Rates of engraftment and acute GVHD similar**
- **TRM lower for RIC early, but similar by 36 months**

Conclusions

- **More relapse with NST**
- **MA and RIC relapse rates are similar**
- **5-yr OS using each approach similar;**

But

slightly higher mortality with NST

MA vs. RIC for Adult Ph- ALL

- Allogeneic HCT BM or PBSC
- HLA-identical sibling or unrelated donor 1995-2007
- Age ≥ 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

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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%

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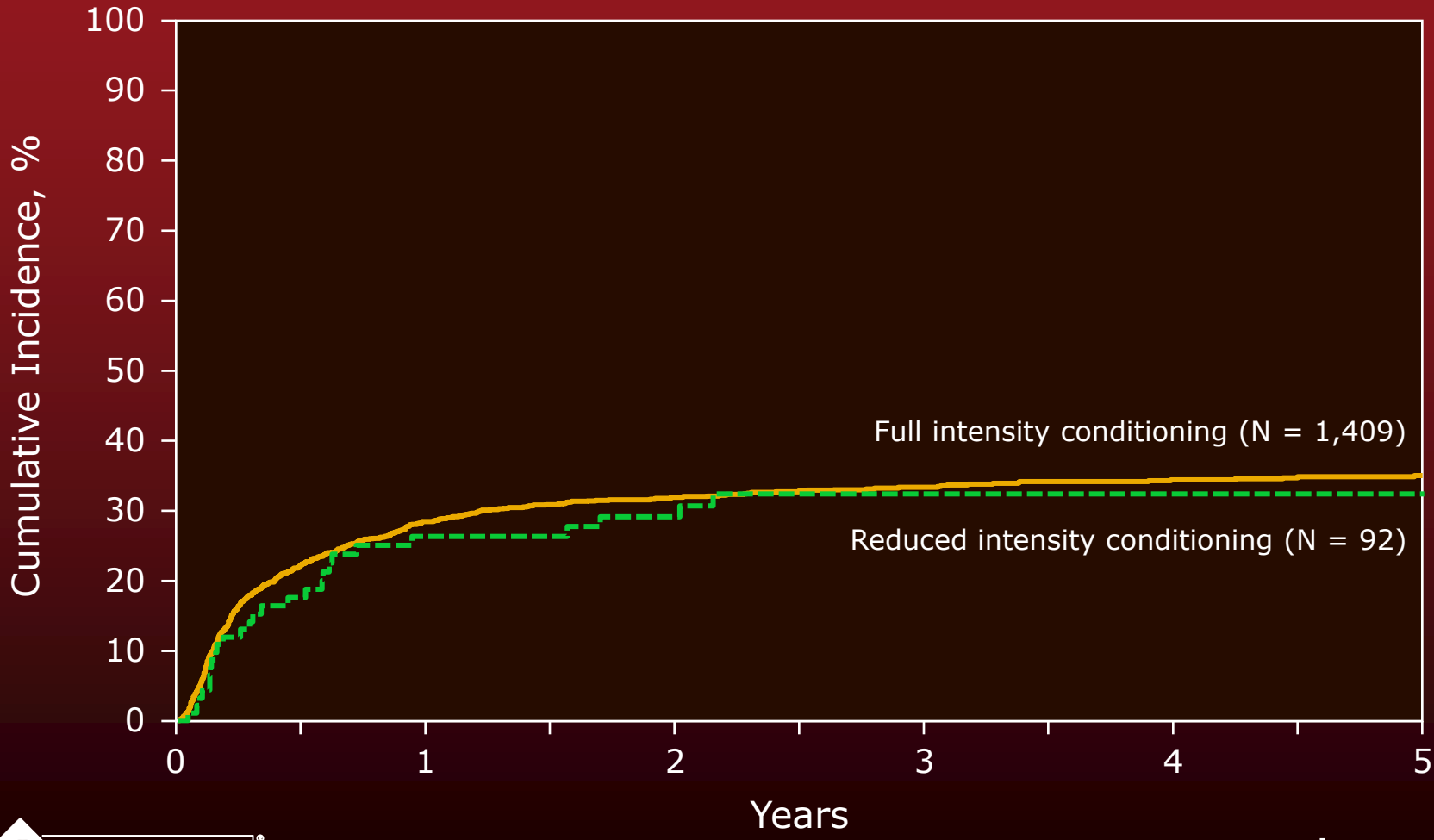
Marks et al

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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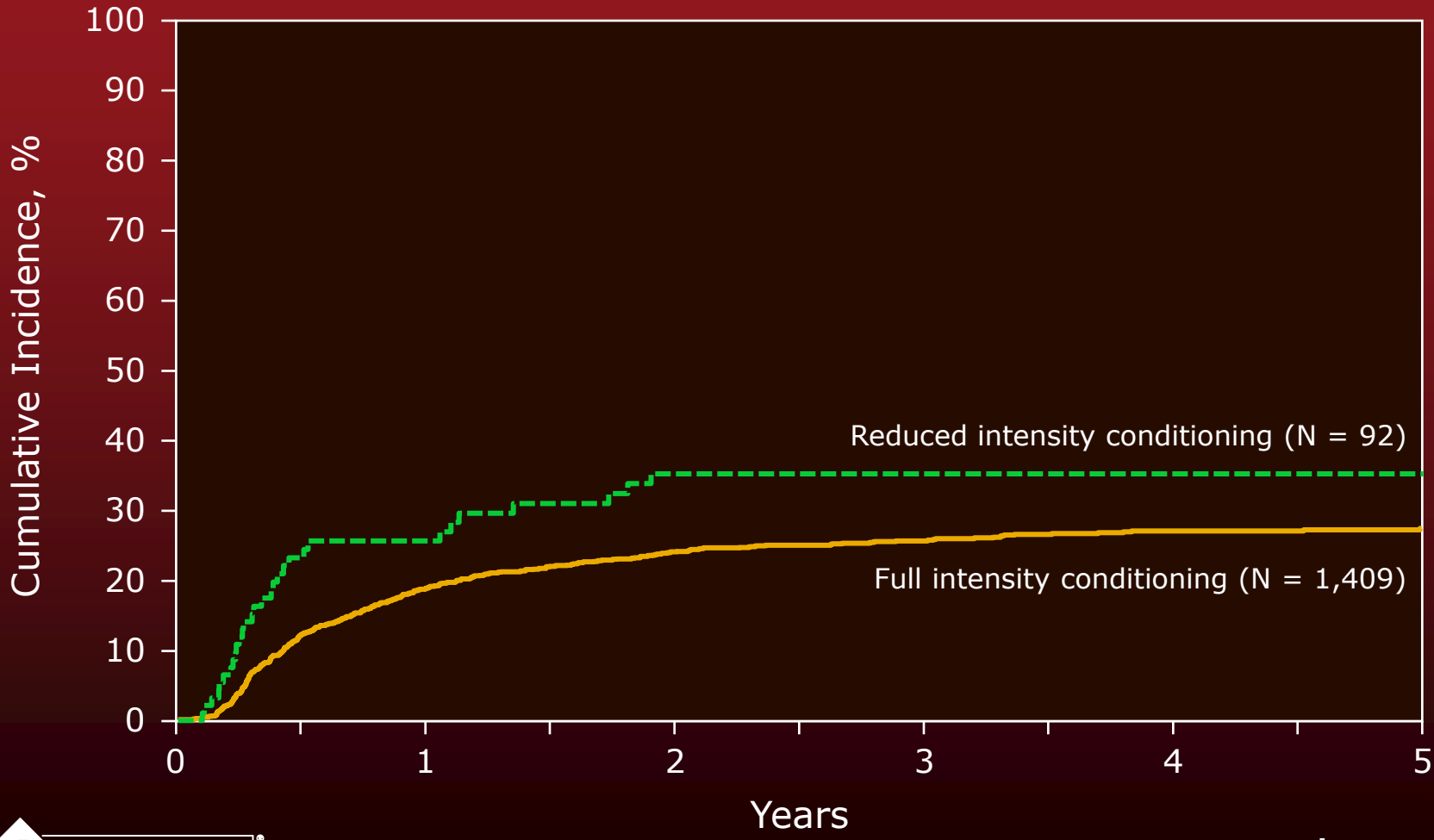
Marks et al

Cumulative Incidence of Relapse



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Marks et al

Relative Risk of Relapse

Factor	RR	P-value
RIC vs. MA	**1.34**	**0.15**
Other factors:		
< 12 months CR1	2.74	<0.01
Acute GVHD, Grades II-IV	0.54	0.02
Chronic GVHD	0.80	0.08

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Marks et al

HCT in CR2: Univariate Outcomes

	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

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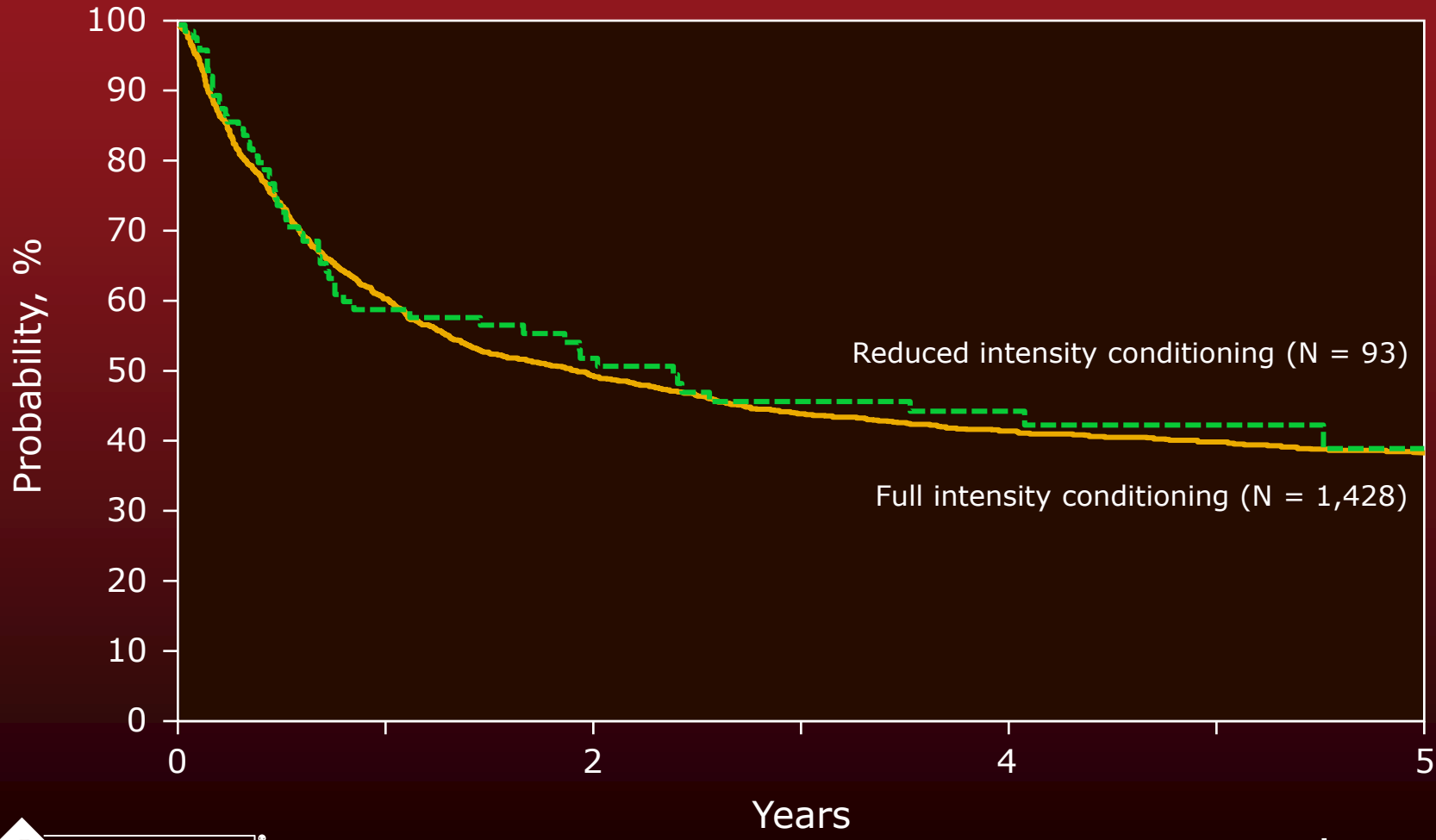
Adjusted Probability of Overall Survival



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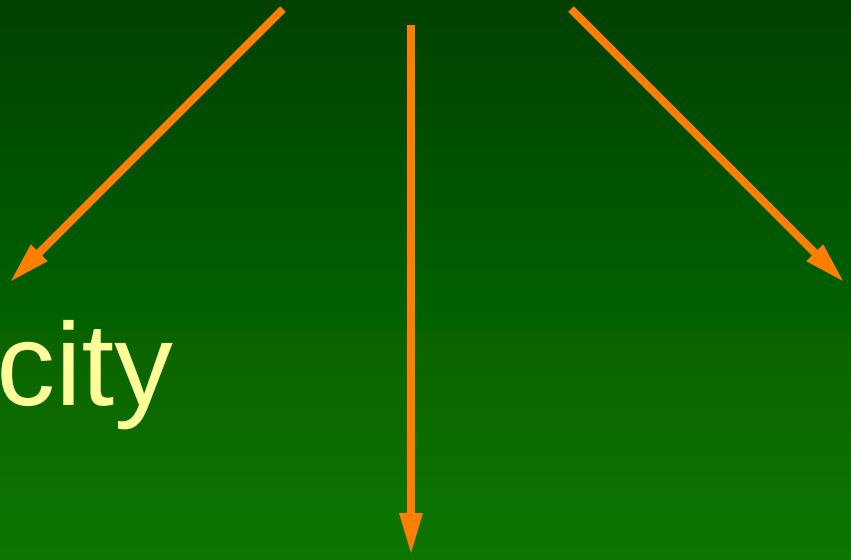
Can a Non-ablative prep?



Less toxicity

Enough GVL

Lymphodepletion for engraftment without excess GVHD

Clinical implications of less toxic BMT

Less morbidity & mortality

Applicable to older, sicker populations

Outpatient; less costly

Useful in newer clinical settings

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