Calling All Super Heroes

AML: Fast track to transplant

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November 10, 2018

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Disclosures

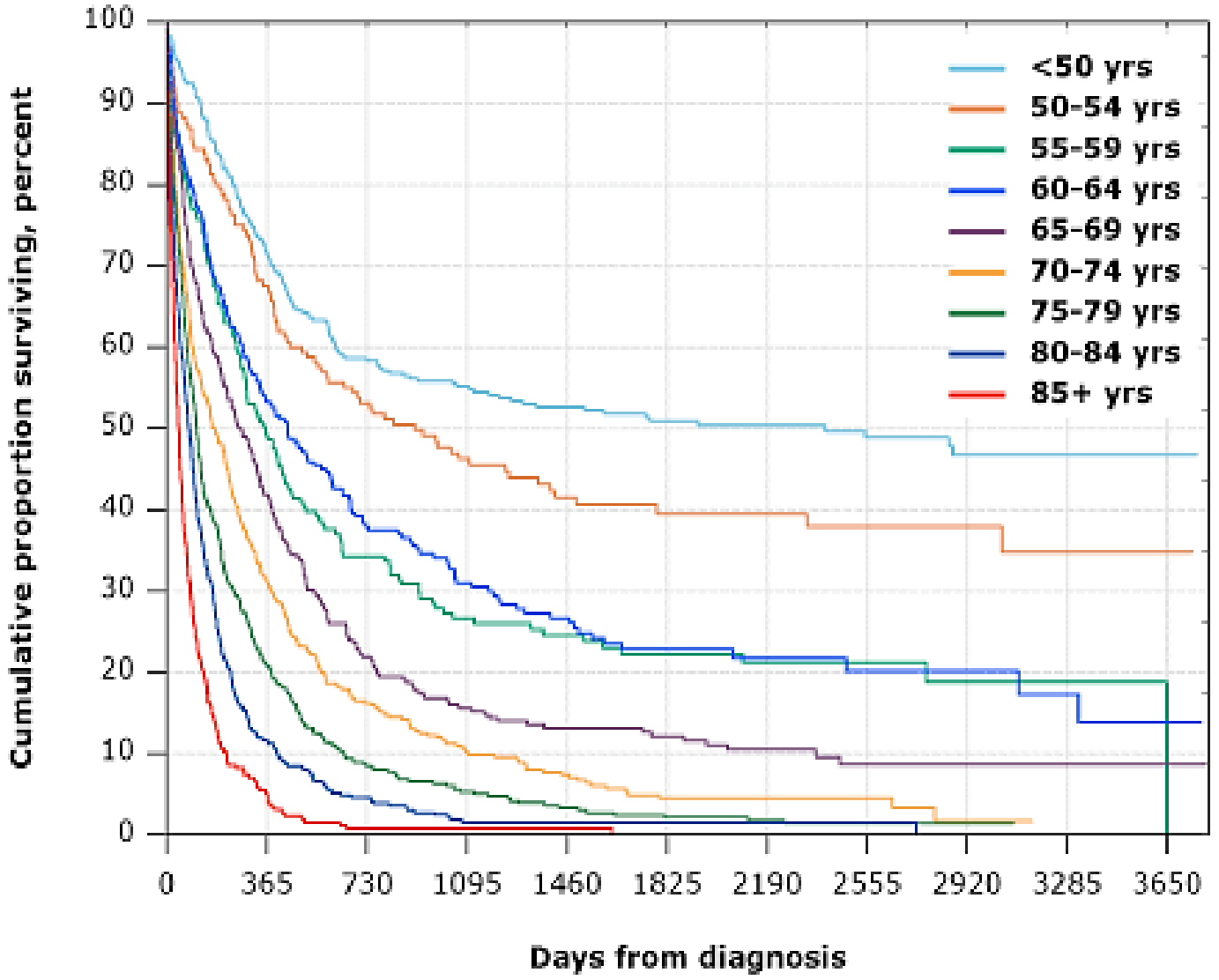
The following faculty and planning committee staff have the following financial disclosures:

Name	Institution	Disclosure
John M. Pagel, M.D., Ph.D.	Swedish Cancer Institute	Actinium Pharmaceuticals
Steve Spellman, MBS	CIBMTR	None
Misty Evans	Vanderbilt University	Jazz Pharmaceuticals, Monetary, Speakers Bureau
Maria Brown	CIBMTR	None

Learning Objectives

- At the conclusion of this session, attendees will be able to:
  - Describe the diagnosis of AML and Risk assessment
  - List traditional treatment options
  - Understand outcomes with allogeneic transplantation using different donor stem cell sources
  - Evaluate results of SWOG 1203 trial
  - Recall Intervention at diagnosis opportunities

Survival in Acute Myeloid Leukemia



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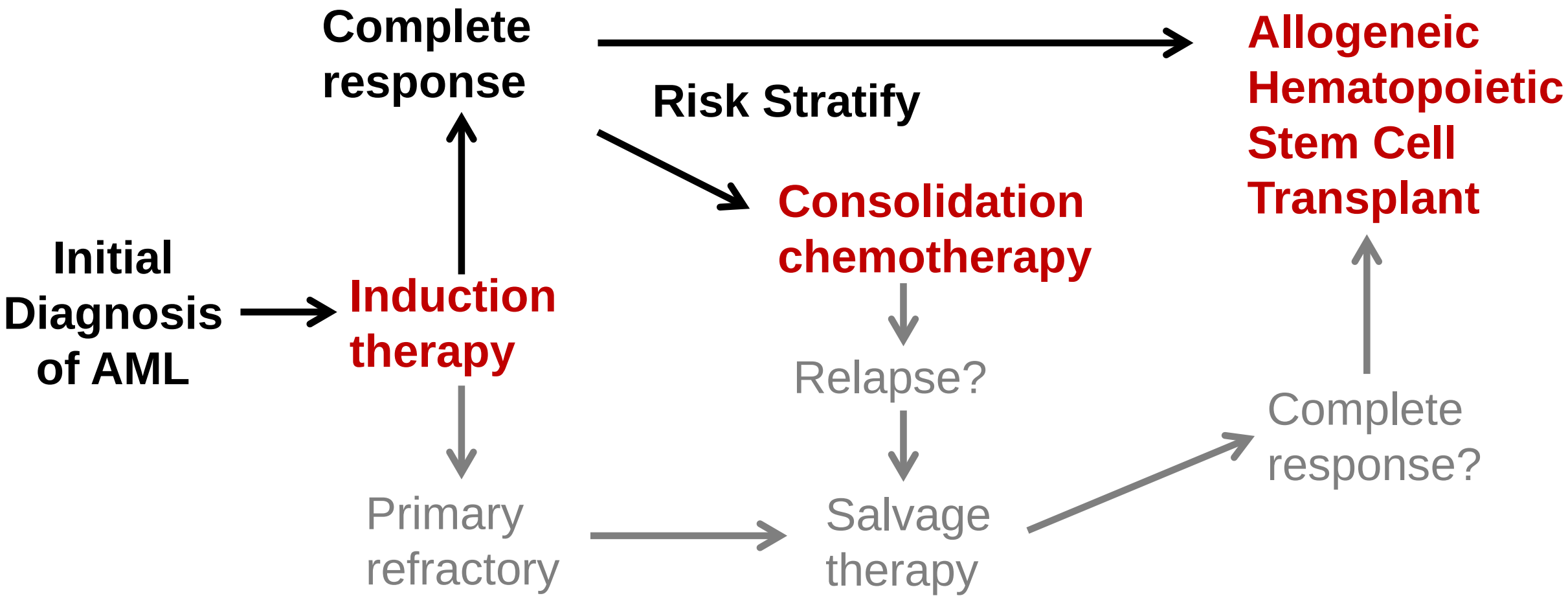
Juliusson G *et al. Blood* 2009;113:4179-4187.

Initial Therapy for Adult AML Patient Fit for Curative Therapy

- 49 year old woman with hypertension
- Presented for evaluation of fever, weight loss
- WBC 53,840 with 44% blasts, HgB 8.5 gram/dL, PLT 68,700
- Bone marrow biopsy: AML with del(5q)
- Neutrophilic dermatosis, grade 3 transaminase elevation prior to induction

Current Paradigm for the Initial Treatment of AML



SWOG S1203: A Randomized Phase III Study of Standard Cytarabine Plus Daunorubicin (7+3) Therapy Versus Idarubicin with High Dose Cytarabine (IA) with or without Vorinostat (IA+V) in Younger Patients with Previously Untreated Acute Myeloid Leukemia (AML)

G Garcia-Manero, M Othus, JM Pagel, JP Radich, M Fang, DA Rizzieri, G Marcucci, SA Strickland, M Litzow, ML Savoie, BC Medeiros, MA Sekeres, TL Lin, GL Uy, BL Powell, JE Kolitz, RA Larson, RM Stone, DF Claxton, J Essell, S Luger, SR Mohan, A Moseley, FR Appelbaum, and HP Erba

S1203: Treatment Arms

- 7+3:
  - Induction: Ara-C 100 mg/m^2 CI IV daily x 7 and Daunorubicin* 90 mg/m^2 IV QD days 1-3
  - Consolidation: Ara-C 3 gram/m^2 IV every 12 hours on days 1, 3, and 5 x 4 cycles

- IA+V Induction:
  - Vorinostat 500 mg po TID QD X 3 days (days 1-3), Idarubicin 12 mg/m^2 QD x 3 (days 4-6), Ara-C 1.5 gram/m^2 CI QD X 4 (days 4-7)

- IA+V Consolidation (x 4 cycles):
  - Vorinostat 500 mg po TID QD X 3 days (days 1-3), Idarubicin 8 mg/m^2 QD x 2 (days 4-5), Ara-C 0.75 gram/m^2 CI QD X 3 (days 4-6)
  - Maintenance: vorinostat 200 mg po TID x 14 days every 28 days

- IA as IA+V (without vorinostat)

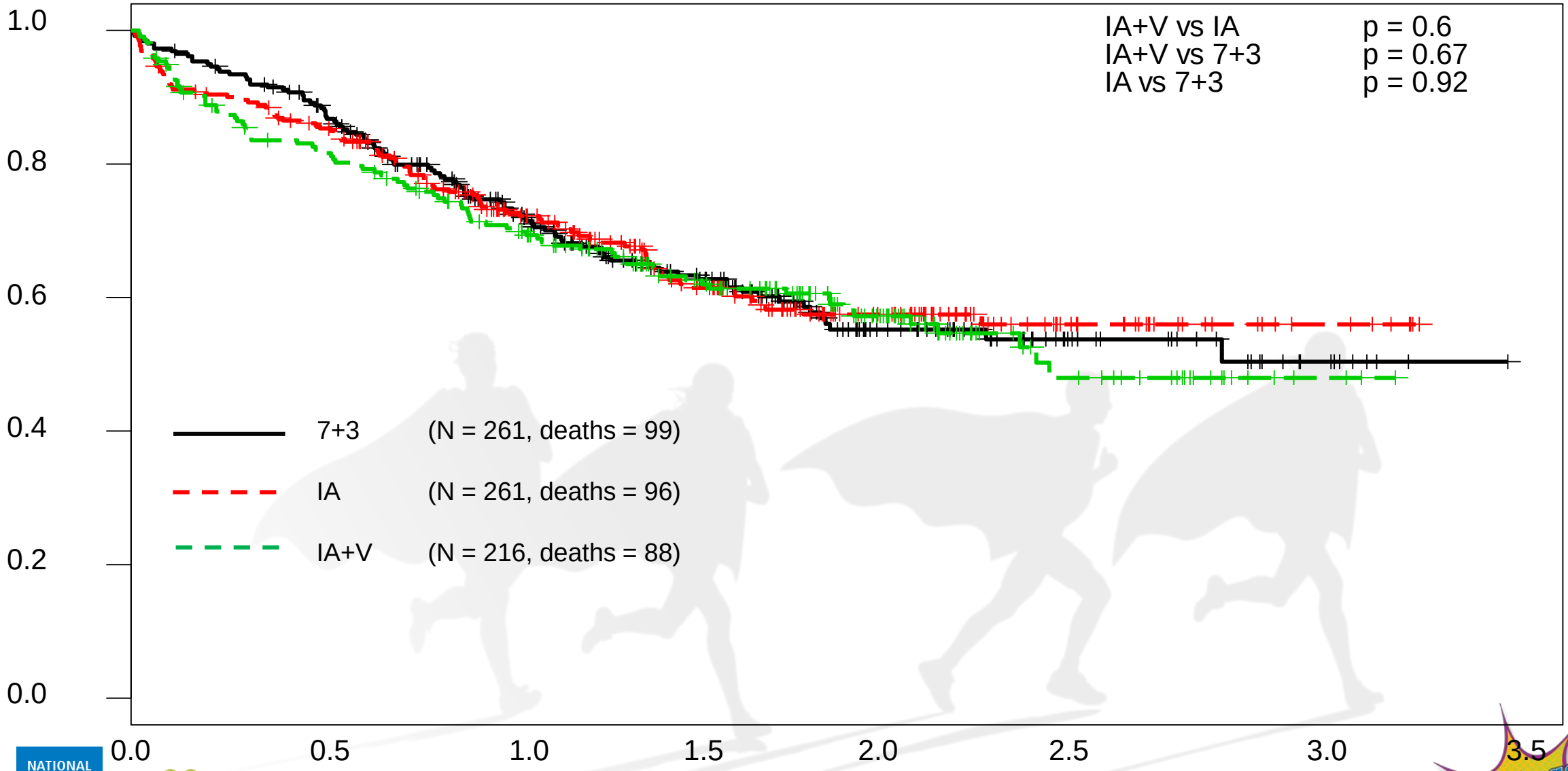
S1203: Response Summary

	All	7+3 (N=261)	IA (N=261)	IA+V (N=216)	P
CR	460 (62%)	164 (63%)	166 (64%)	130 (60%)	0.58
CRi	111 (15%)	33 (13%)	41 (16%)	37 (17%)	
Failure	167 (23%)	64 (25%)	54 (21%)	49 (23%)	

S1203: Early mortality

	ALL	7+3	IA	IA+V	P
Died ≤ day 30	31 (4)	7 (3)	16 (6)	8 (4)	0.013
Died ≤ day 60	53 (7)	12 (5)	22 (9)	19 (9)	0.097

S1203: Overall Survival



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Cytogenetics remains the most common and reproducible estimate of prognosis for patients with AML

- Using cytogenetics, patients can be categorized as having favorable, intermediate, or unfavorable (high) risk disease
- The unfavorable risk group comprises ~30% of all patients
  - Has a first CR1 rate of 54% and an estimated survival at 5 years of 11%
    - outcomes that were significantly worse than seen in intermediate- or favorable-risk patients
- Among patients with high-risk disease allogeneic transplantation has a ~44% survival at 5 years with allogeneic transplantation *versus* 15% with chemotherapy alone
- Unfortunately only 40% of patients assigned to allogeneic HCT are actually transplanted.
- Allogeneic transplantation has been recommended for adults age ≤60 years with high-risk AML in CR1

Current Use and Trends in Hematopoietic Cell Transplantation in the United States

- The number of both autologous and allogeneic transplants for treatment of malignant diseases continues to increase.
- Between 1991 and 1997, 7% of allogeneic HCTs were performed in patients age ≥50 years
  - Between 2000 and 2015, this percentage increased to 38%.
- In 2015, 25% of all allogeneic HCT recipients were age ≥60 years, up from 5% in 2000
  - 4.4% were age ≥70 years in 2015, compared with 0.4% in 2000

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D'Souza et al, BBMT, 2017

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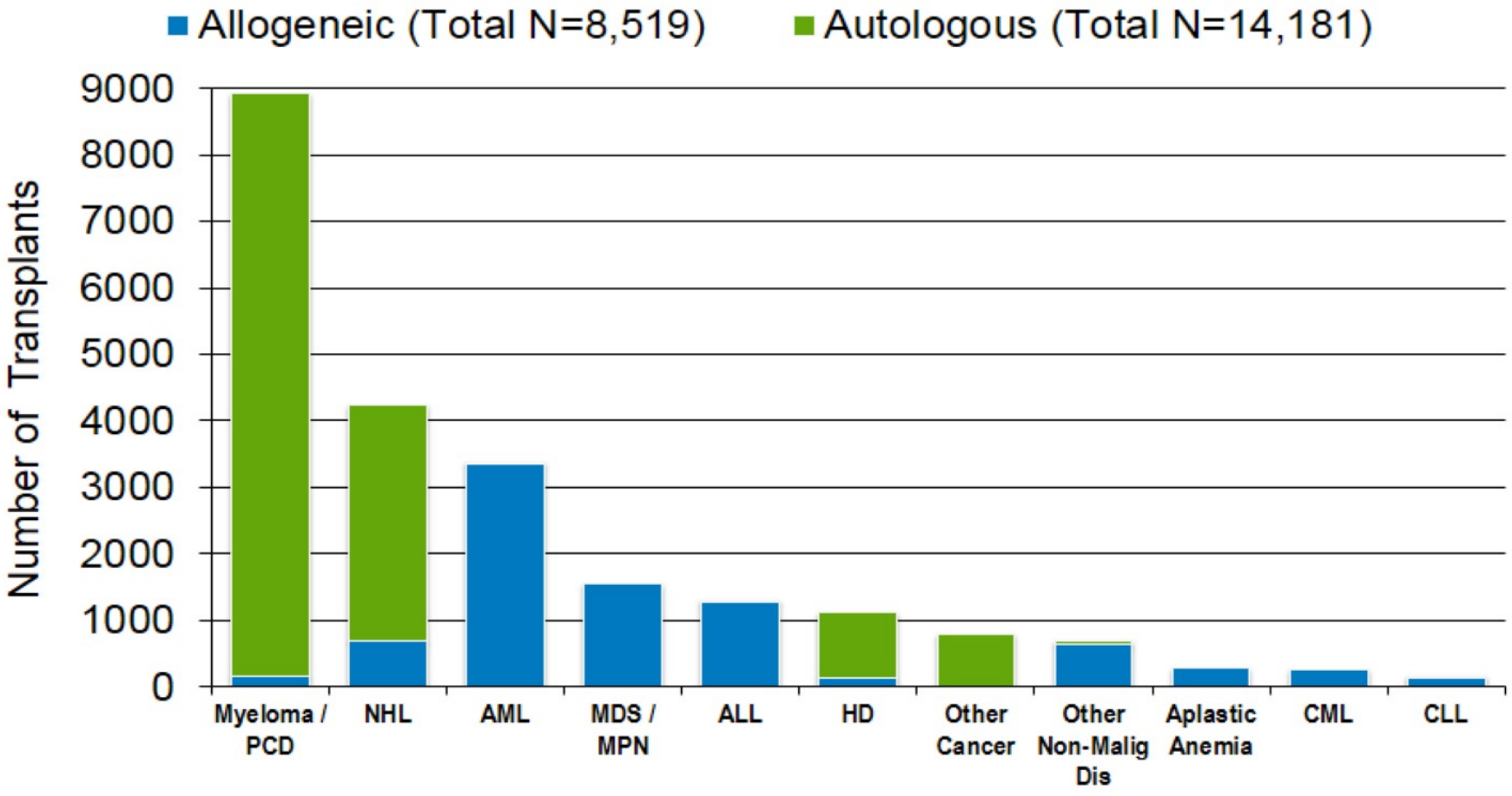
Indications for Hematopoietic Cell Transplant in the US, 2016



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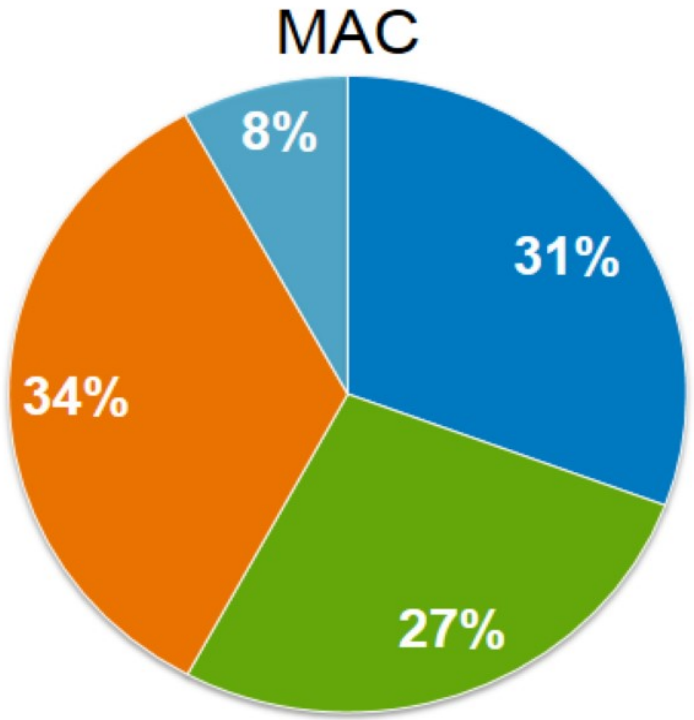
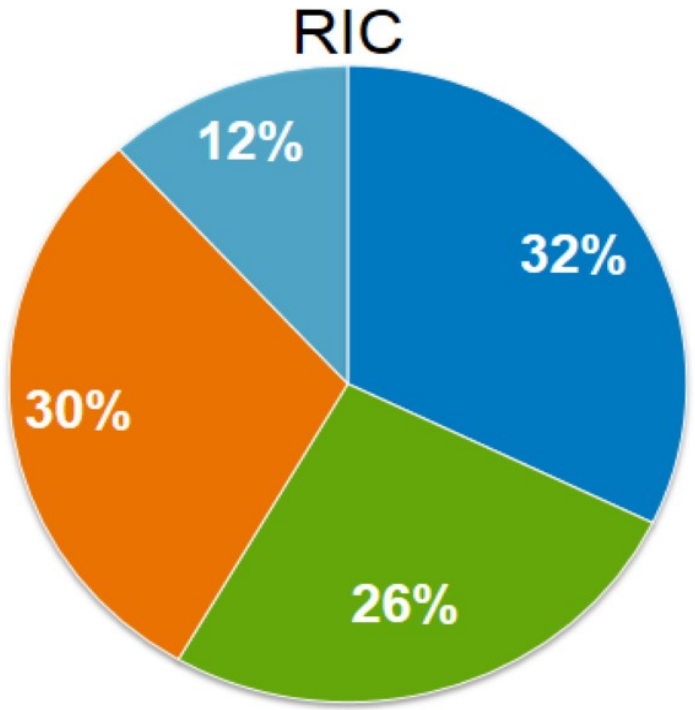
Common Conditioning Regimens in AML or MDS Allogeneic HCT in the US in 2000-2015





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Patient Eligibility: Factors associated with transplant-related problems

Disease-related

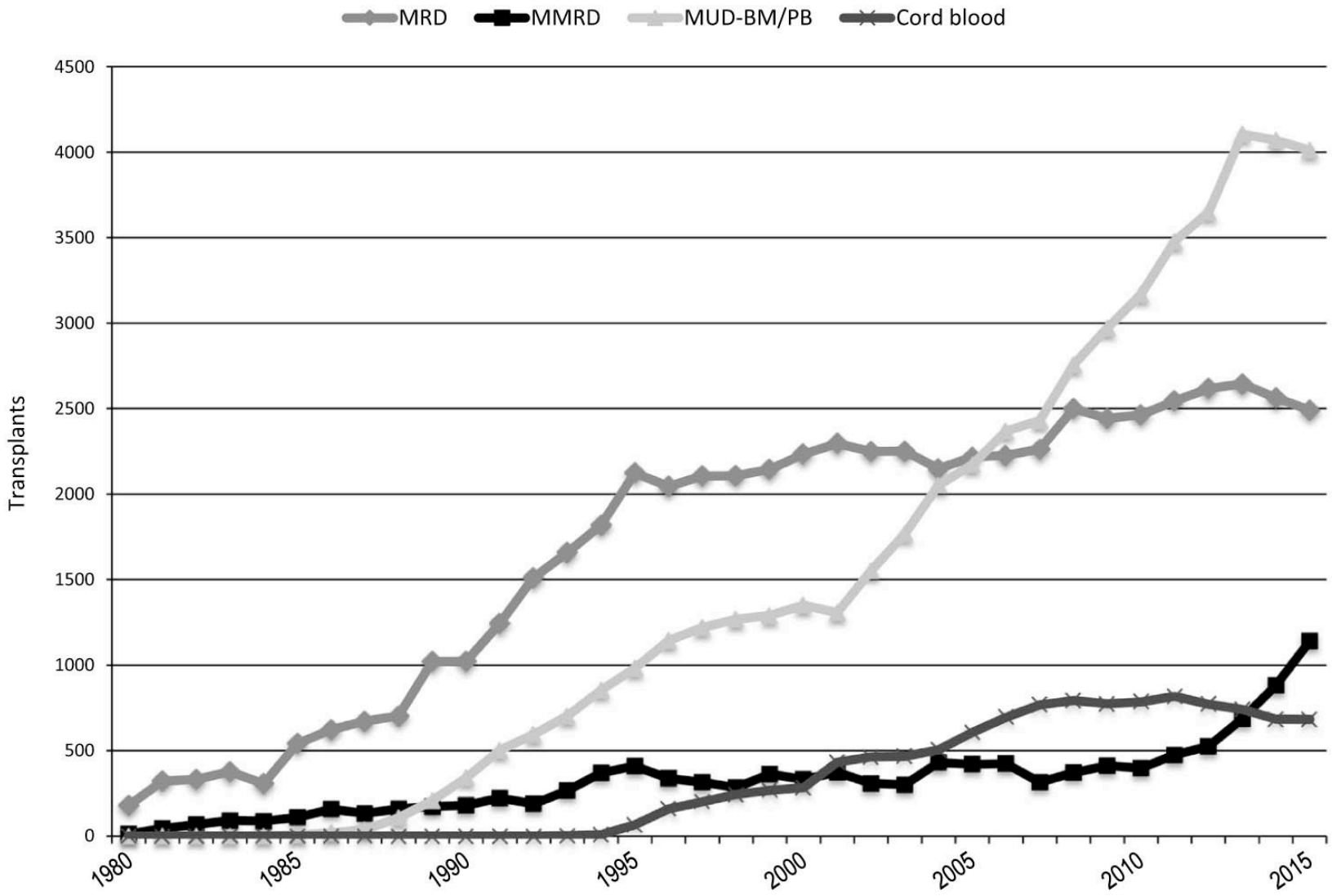
- Diagnosis & molecular characteristics
- Prior therapy
- Remission vs Relapse
- Early vs late in disease course

Patient-related

- Age
- Performance status
- Co-morbidities

Treatment-related

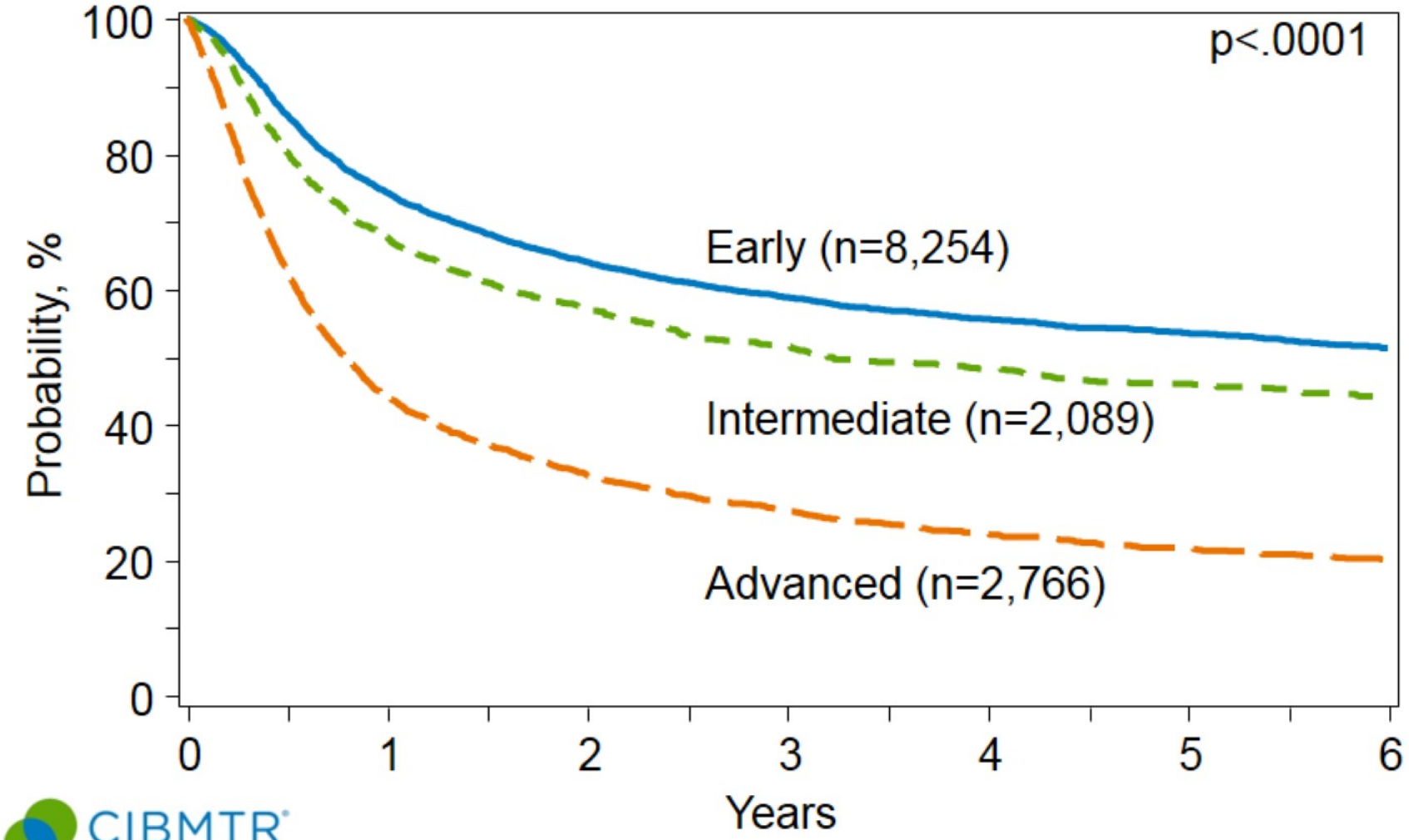
- Intensity of the conditioning regimens
- Stem cell source



Legend: MRD- matched related donor; MMRD- mismatched related donor; MUD-BM/PB- matched unrelated donor-bone marrow/peripheral blood

Biology of Blood and Marrow Transplantation 2017 23, 1417-1421DOI: (10.1016/j.bbmt.2017.05.035)

Survival after HLA-Matched Sibling Donor HCT for AML, 2005-2015



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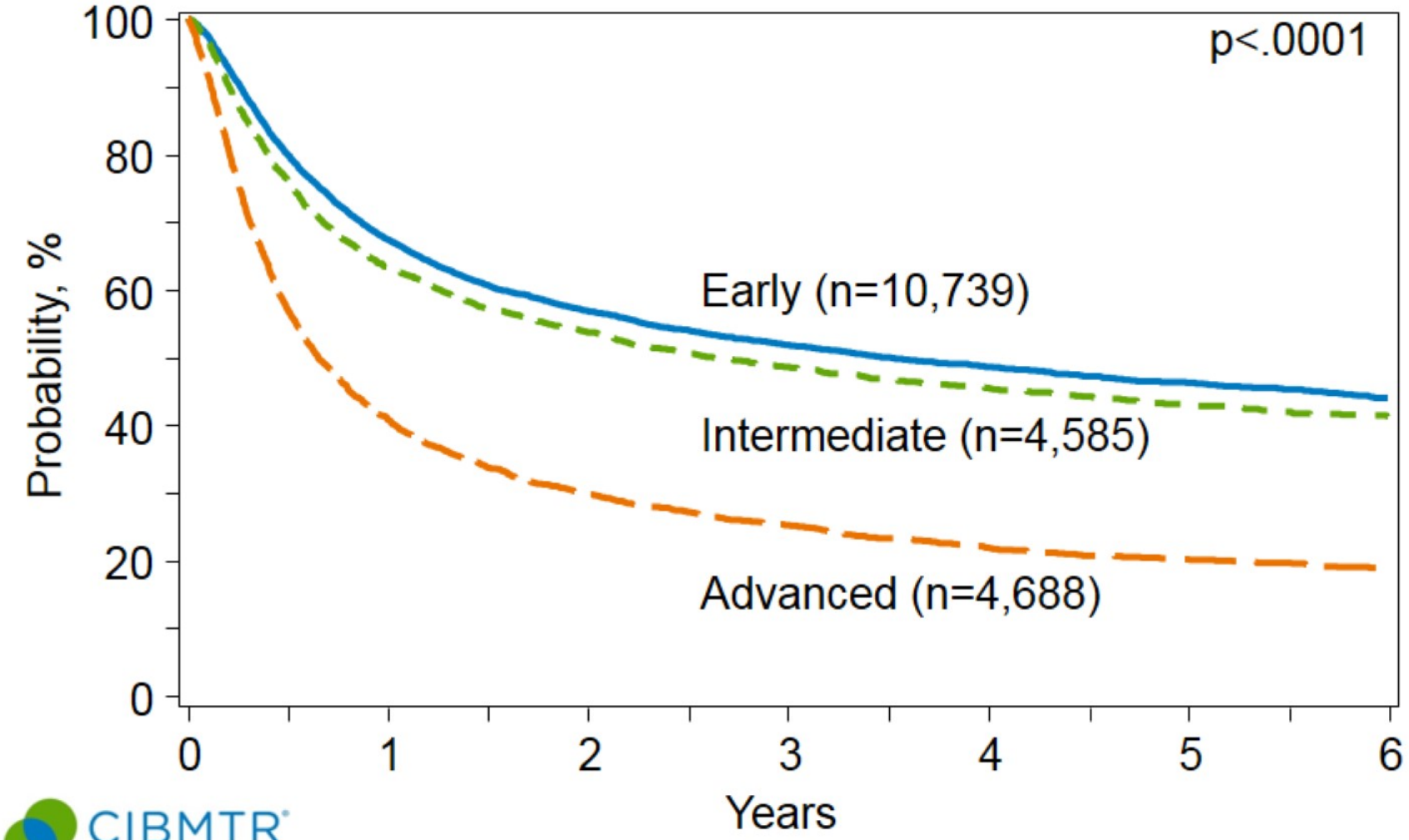
Survival after Unrelated Donor HCT for AML, 2005-2015



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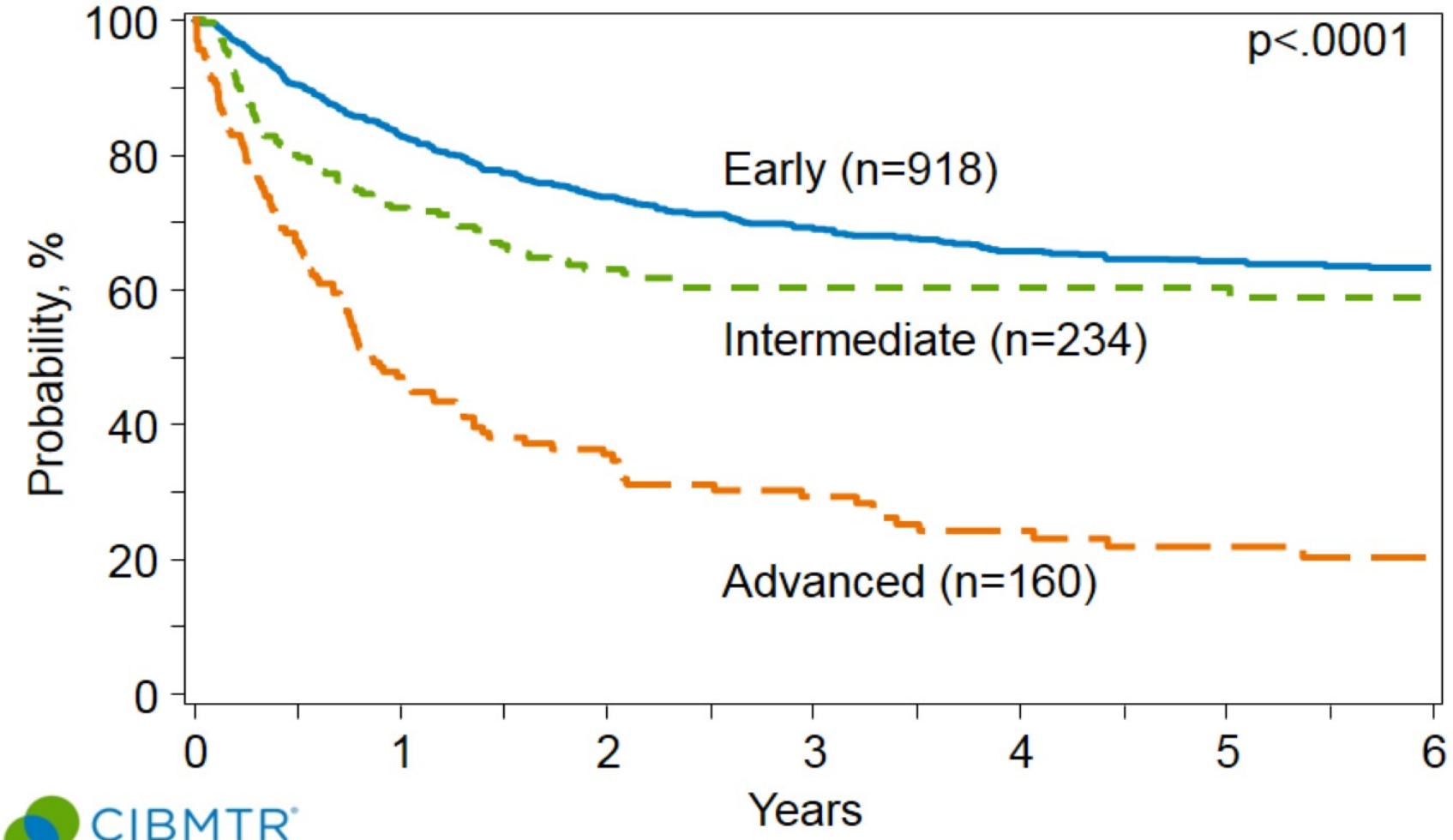
Survival after HLA Matched Sibling Donor HCT for AML, Age <18 Years, 2005-2015



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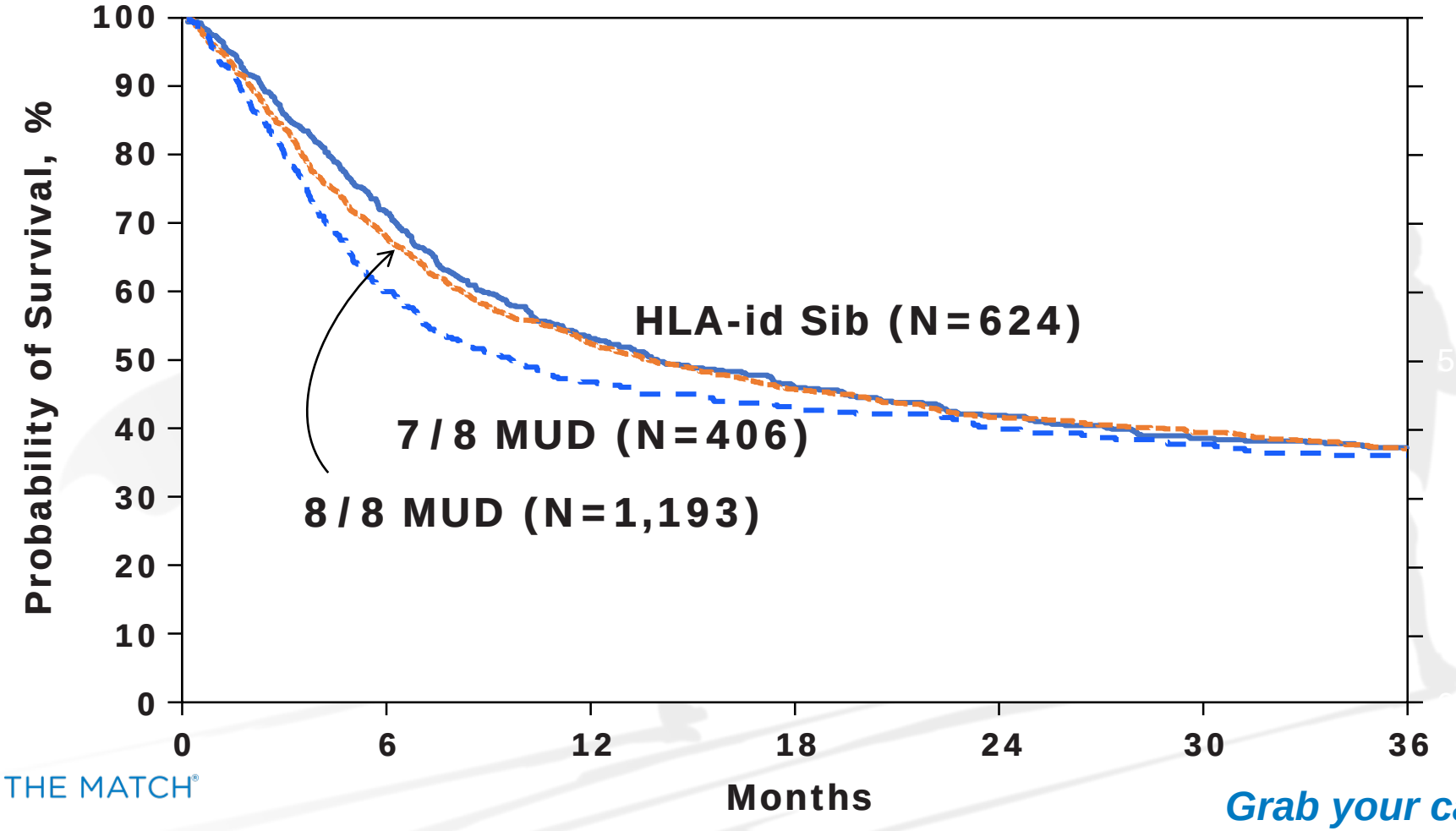
Adjusted Probability of Survival After Transplantation for AML



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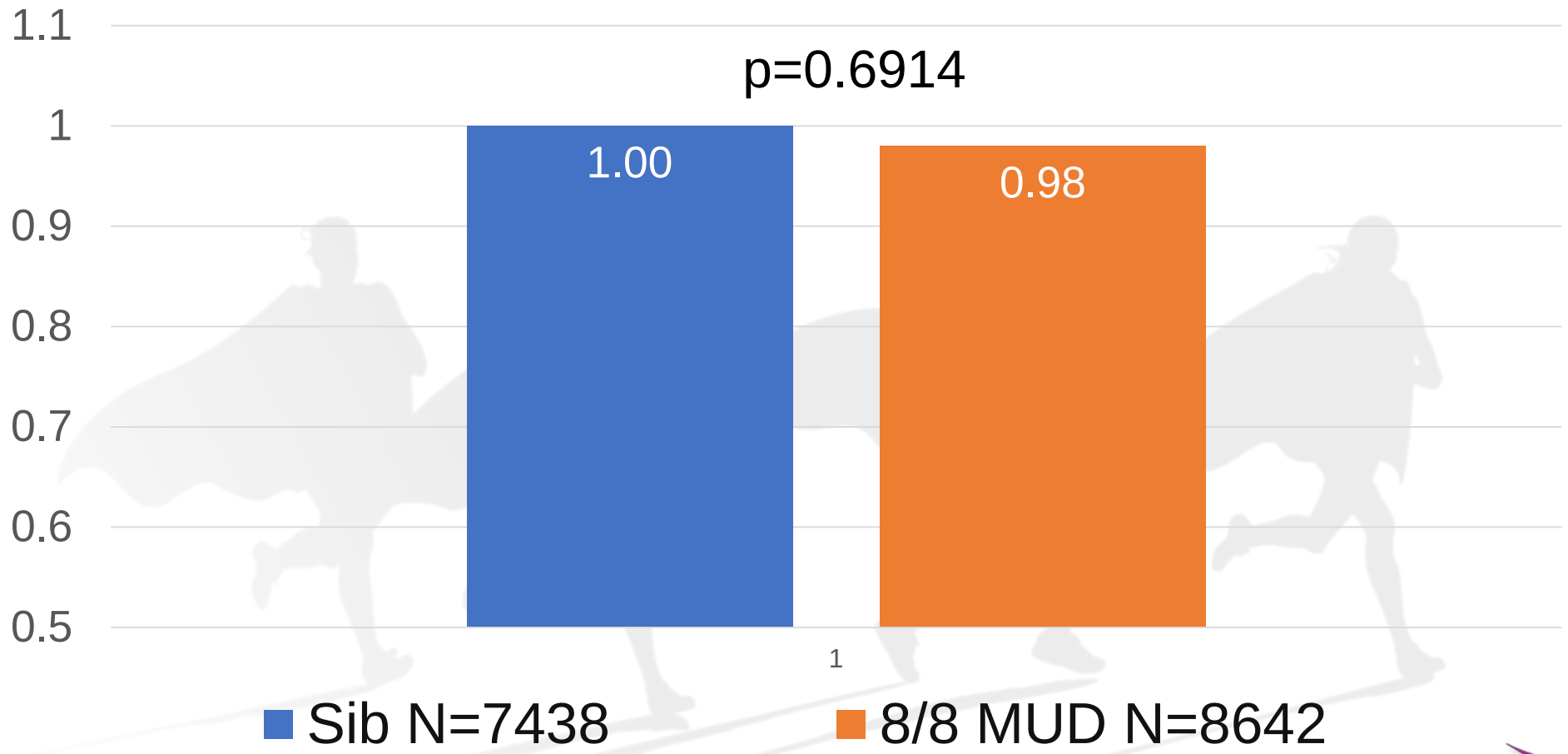
Saber, et al. Blood 2012

Impact of Donor Type on one-year mortality of after HCTs done in 2013-2015



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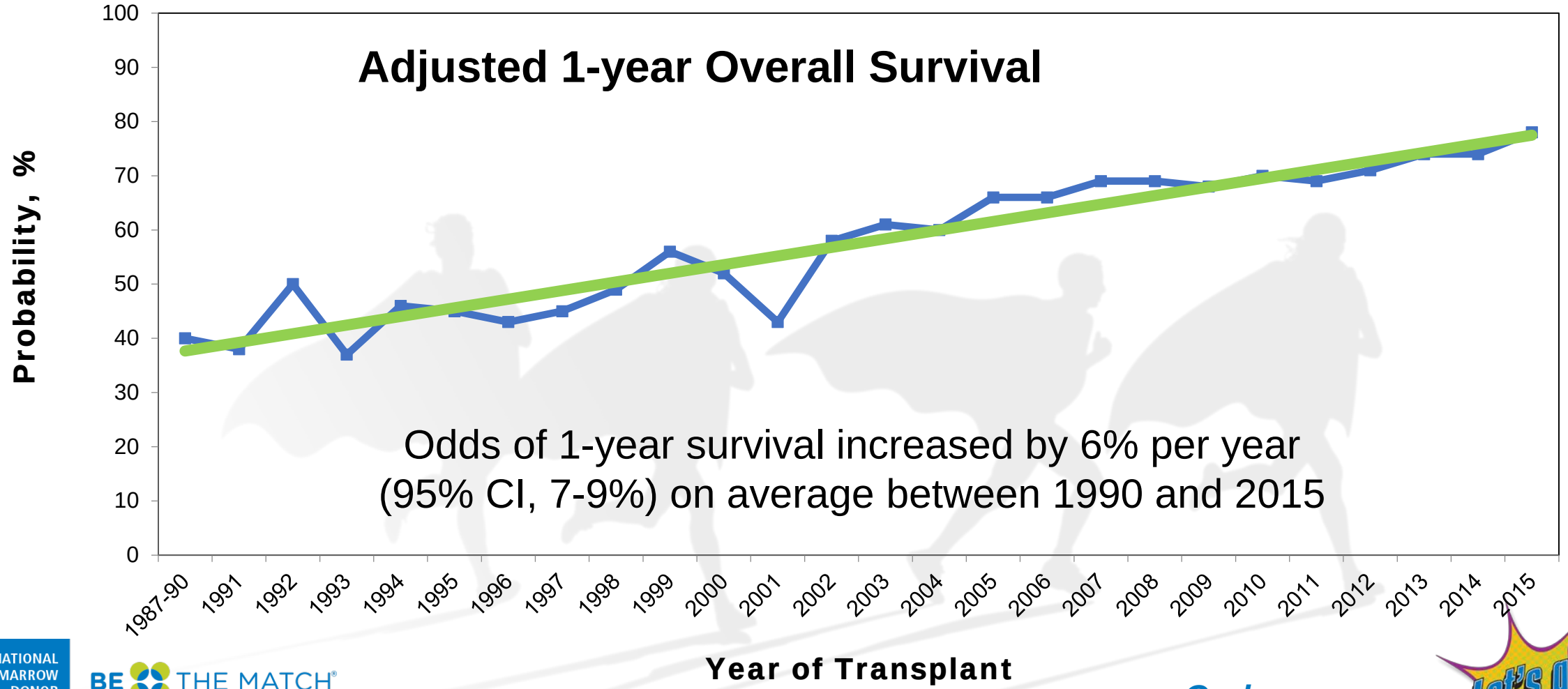
Survival After Unrelated Donor Transplantation

Age <50 years, myeloablative conditioning, acute leukemia in remission or MDS



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Is a hapolidentical donor the best option for AML in the absence of HLA-identical donor?

- Haplo is gaining ground because of:
  - Rapid availability of donor in a high-risk disease
  - Potential budgetary advantages
  - Less transplant related mortality?
- But still open questions:
  - Long term reports still scarce
  - Higher rate of relapse?

AML CR1; Haploidentical *versus* Matched Sibling

Characteristics	Haploidentical (n=231)	Identical sibling (n=219)
Age, y, median (range)	28 (15-57)	40 (17-60)
Cytogenetic risk group,* no. (%)		
Intermediate, normal	99 (43)	110 (50)
Intermediate, abnormal	84 (36)	77 (35)
High	48 (21)	32 (15)
Courses required for CR (%)		
1	155 (67)	156 (71)
2	60 (26)	50 (23)
3-4	16 (7)	13 (6)
Graft type, no. (%)		
BM + PB cell	231 (100)	124 (57)
BM		14 (6)
PB cell		81 (37)
Follow-up time from CR, mo		
No. of evaluable patients	188 (81%)	184 (84%)
Median (range)	36 (16-63)	37 (14-66)

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Wang et al., *Blood* 2015; 125: 3956-3962

Myeloablative Conditioning for Sibling vs Haplo

- HLA-haploidentical related:
  - Cytarabine (4 g/m2/d -10, -9)
  - Busulfan (3.2 mg/kg/d -8, -7, -6)
  - cyclophosphamide (1.8 g/m2/d -5, -4)
  - Me-CCNU (250 mg/m2/d -3)
  - ATG (2.5mg/kg/d -5 to -2)
- HLA-identical sib:
  - hydroxycarbamide (80mg/kg -10)
  - cytarabine (2 g/m2/d -9)
  - Rest of regimen the same without ATG
- GVHD prophylaxis: CSP, MMF, MTX

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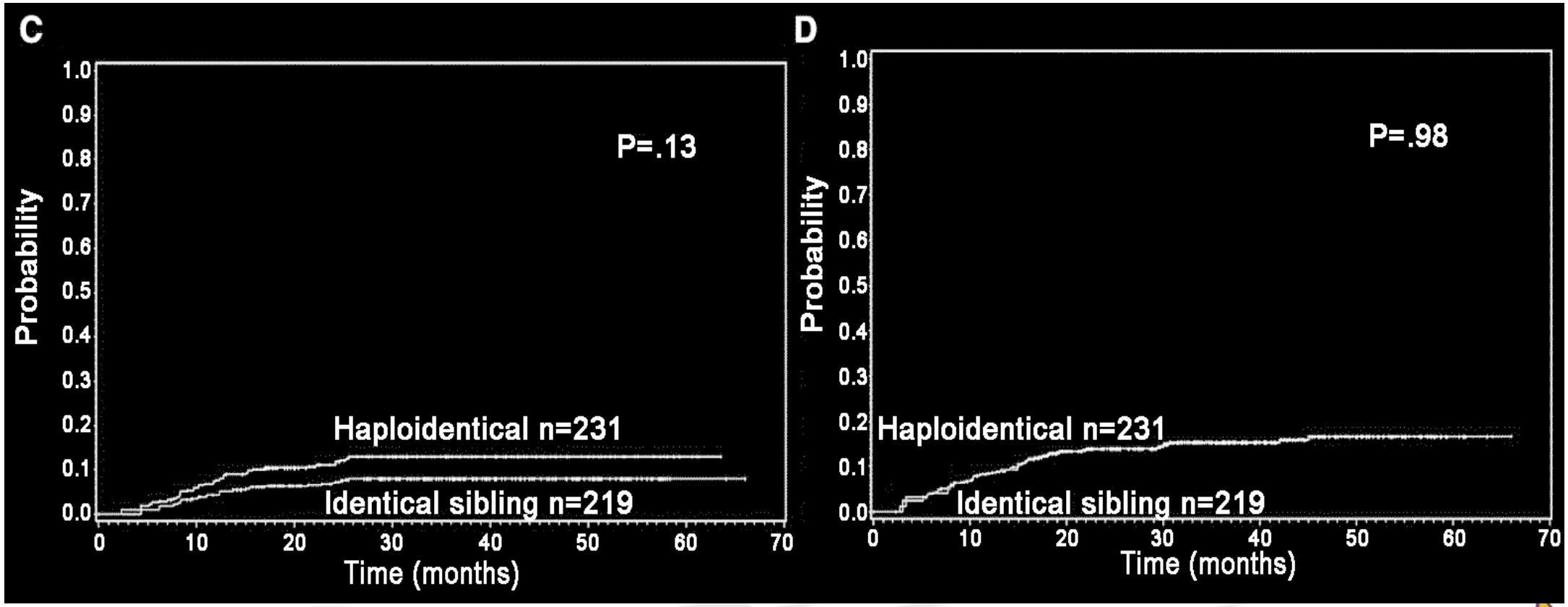
Wang et al., *Blood* 2015; 125: 3956-3962

Outcomes after Transplantation According to Donor Source

Non-relapse Mortality

Relapse



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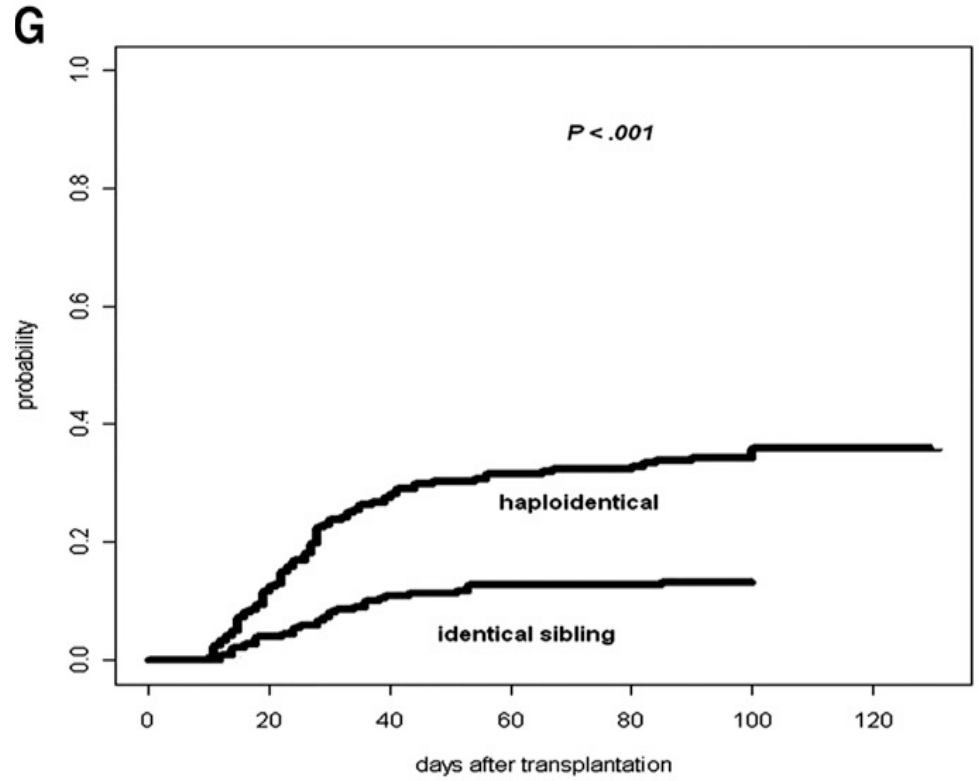
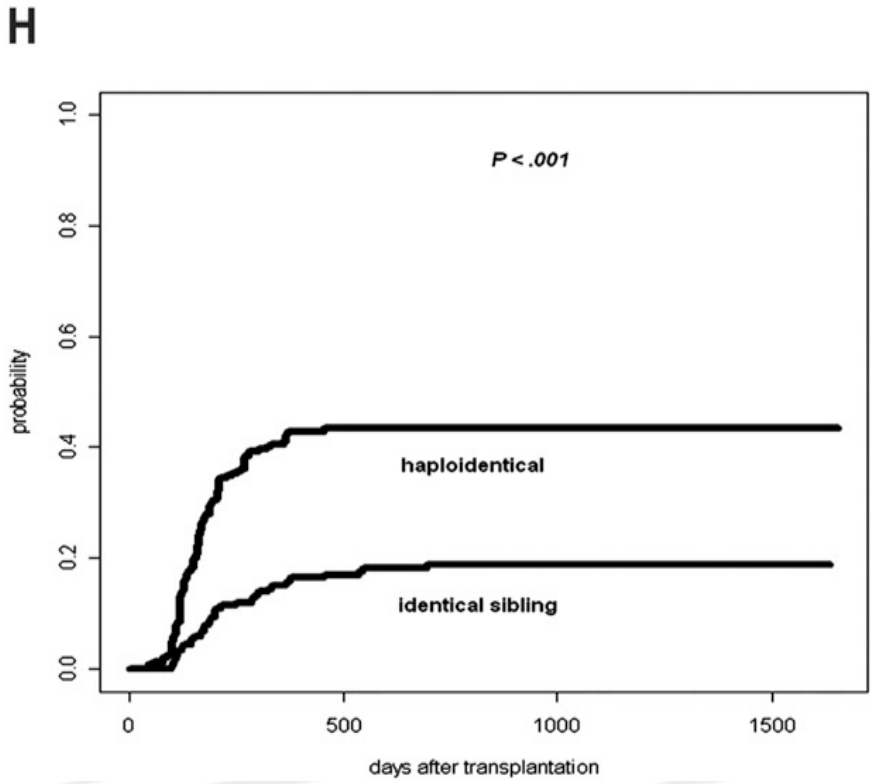
Wang et al., *Blood* 2015; 125: 3956-3962

GvHD According to Donor Source

Acute GVHD Grades II-IV



Chronic GVHD



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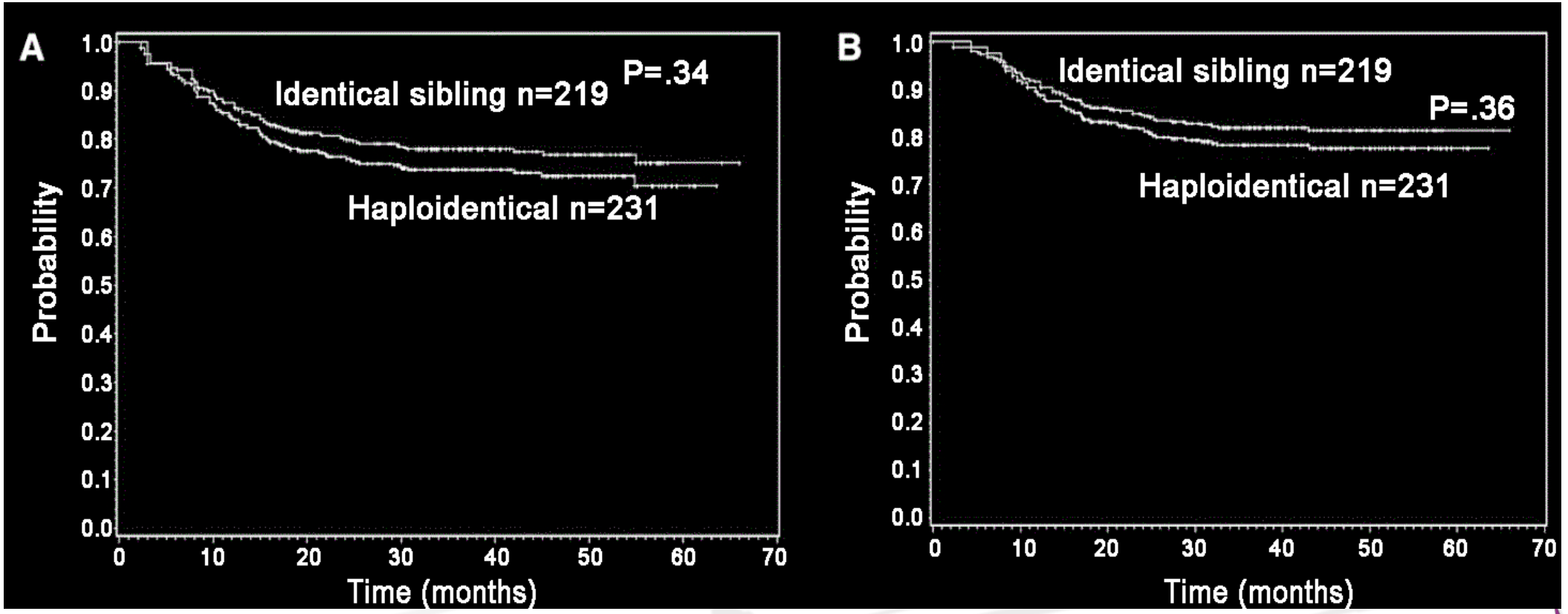
Wang et al., *Blood* 2015; 125: 3956-3962

Survival According to Donor Source

Disease-free

Overall



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Wang et al., *Blood* 2015; 125: 3956-3962

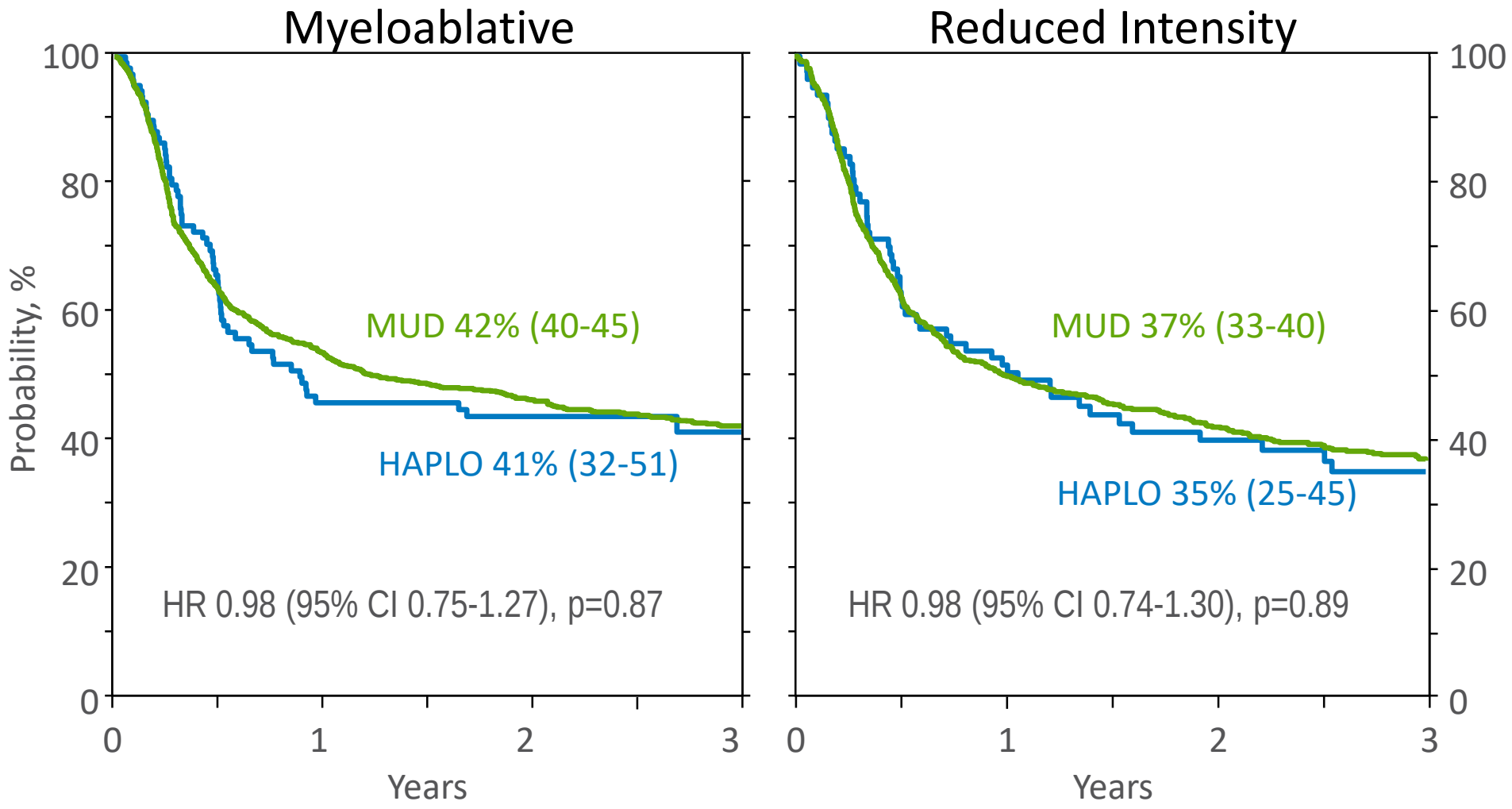
Outcomes Haplo vs MUD for AML – CIBMTR

- 2,174 pts with AML (21-70 yrs) transplanted between 2008-2012
- 1,982 pts had 8/8 MUD, 192 pts haplo with postCy
- **MA** - 1245 had MUD, 104 haplo
- **RIC/NMA** - 737 had MUD, 88 haplo
- Very similar characteristics except:
  - RIC MUD transplants older (median 62 vs. 57 yrs), more likely to have a PS< 80%
  - Haplo transplants less likely to be in CR1 an had longer interval diagnosis – transplant
- Median follow-up – approx. 3 years for all groups
- No transplant center effect on survival

Ciurea SO, et al. Blood. 2015; 126:1033

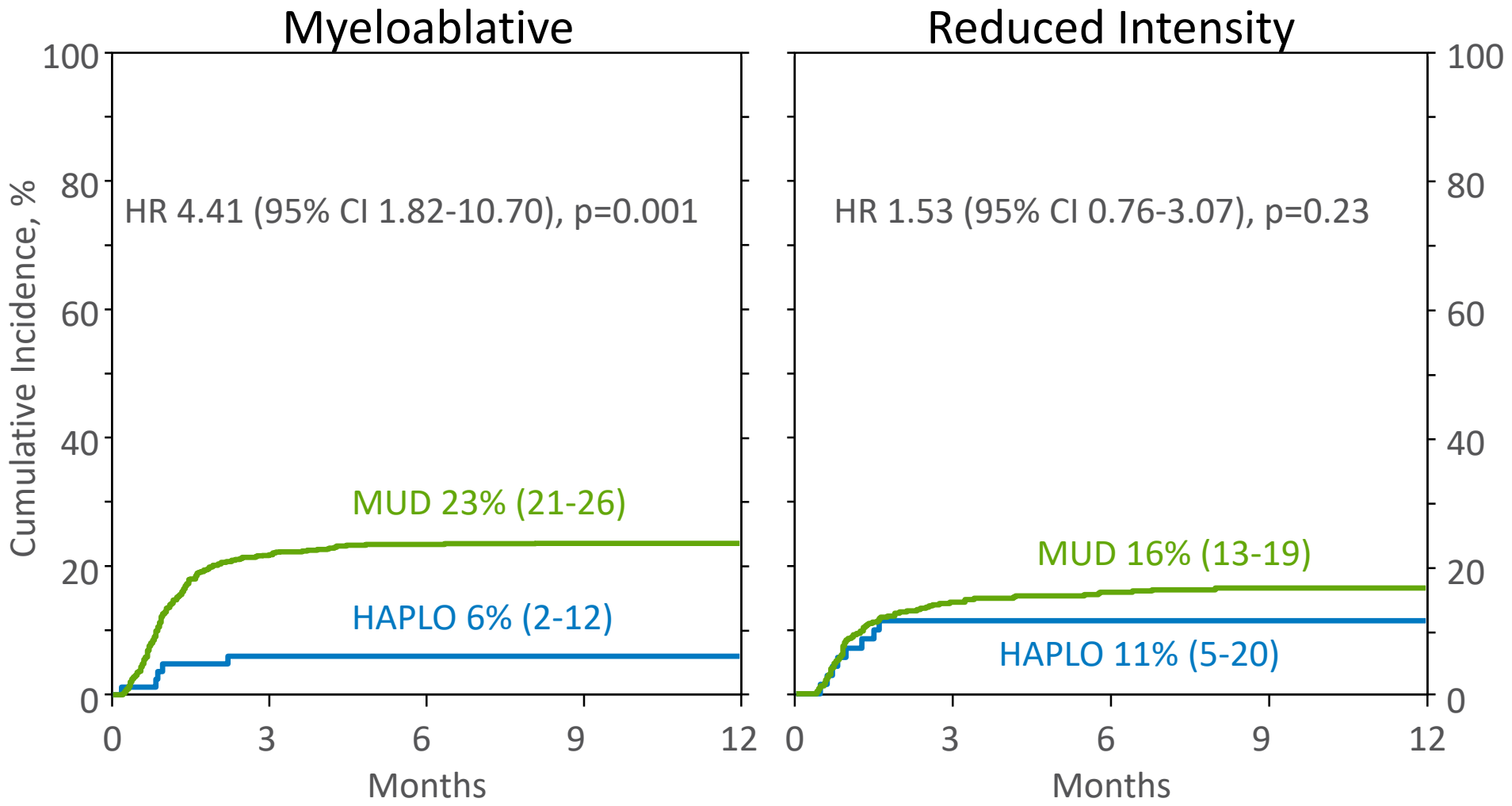
Leukemia-Free Survival

Adjusted for DRI, performance score, secondary AML



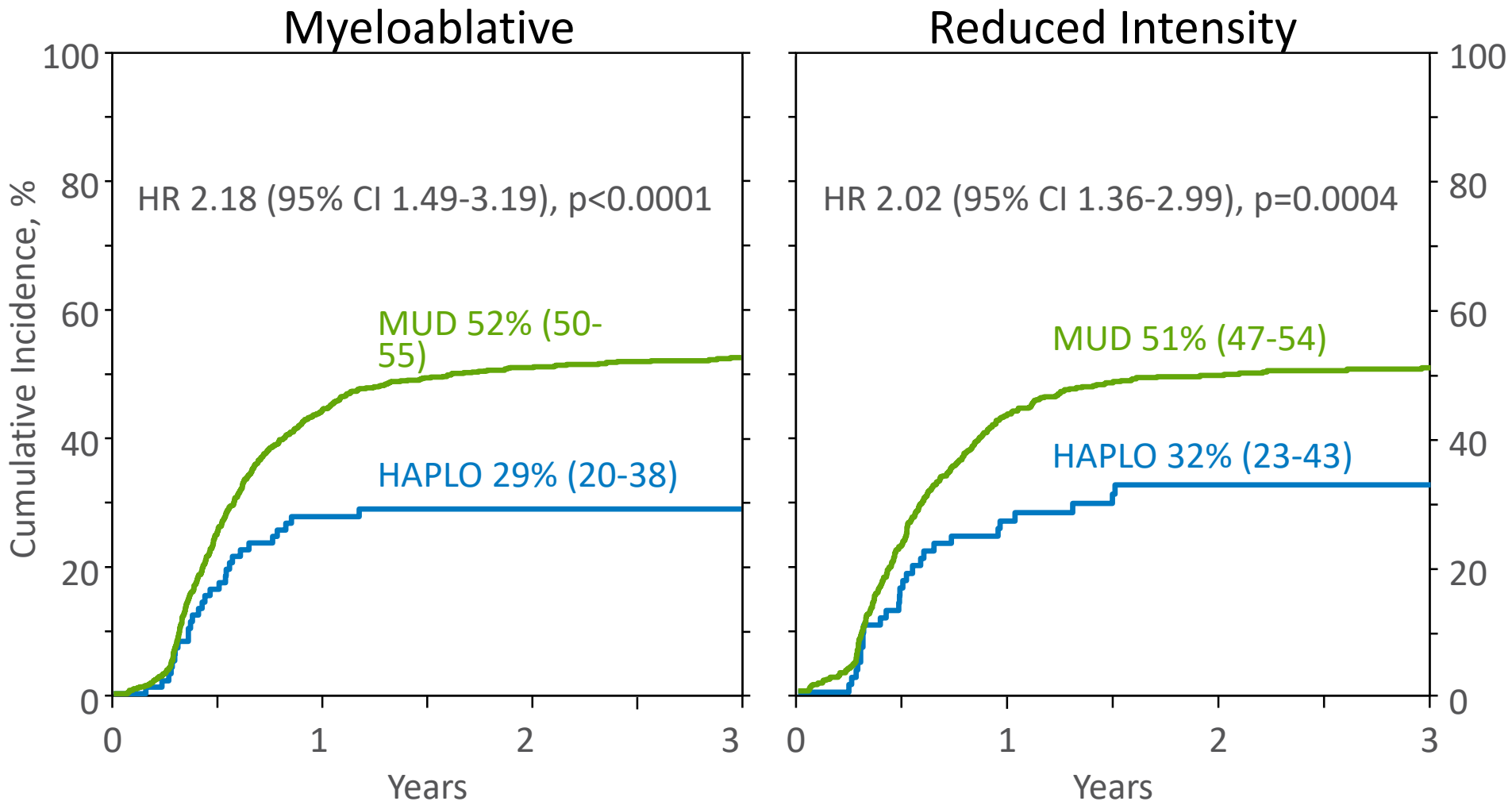
Ciurea SO, et al. Blood. 2015; 126:1033

Grade II-IV Acute Graft vs Host Disease



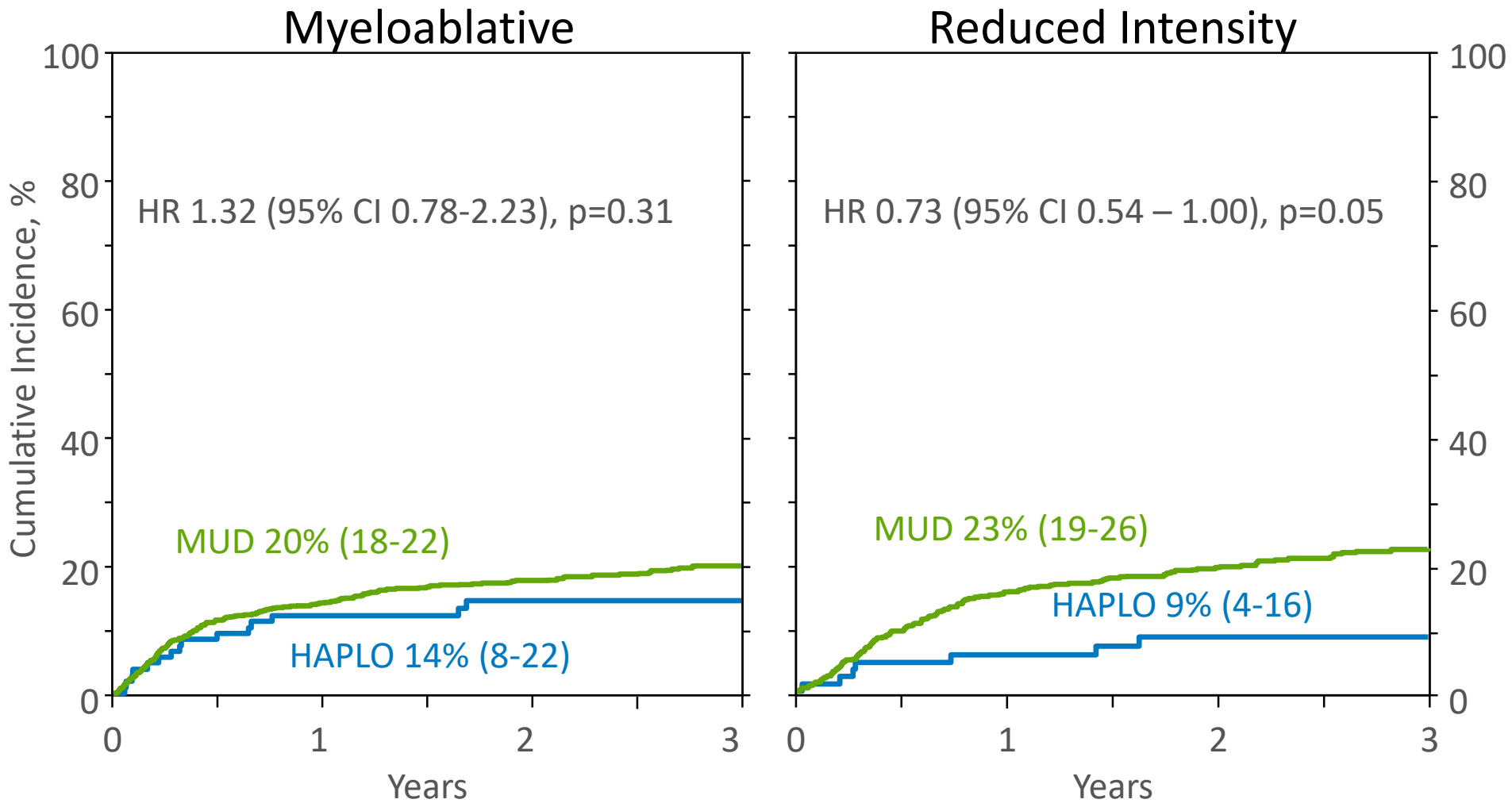
Ciurea SO, et al. Blood. 2015; 126:1033

Chronic Graft vs. Host Disease



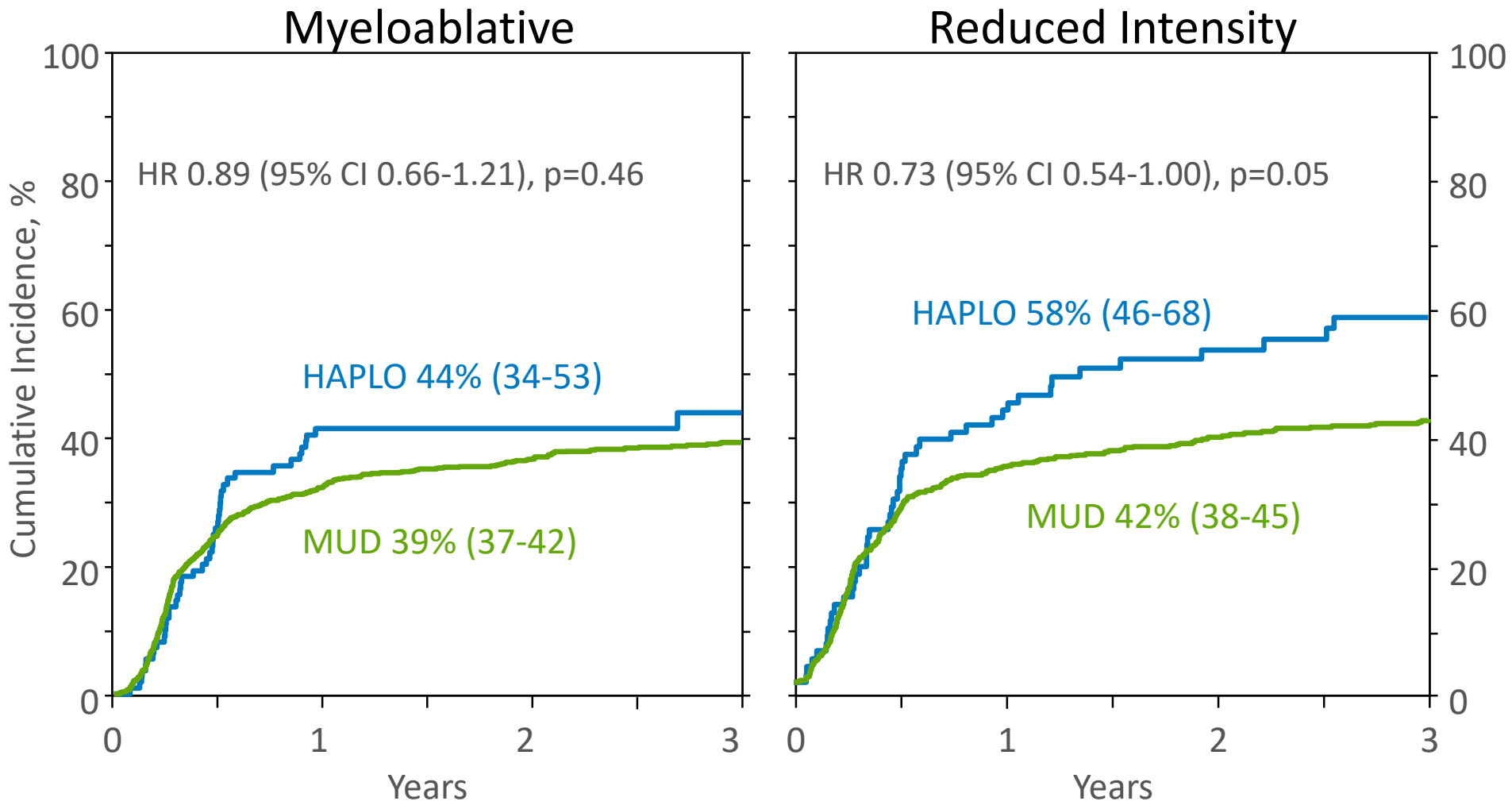
Ciurea SO, et al. Blood. 2015; 126:1033

Non Relapse Mortality



Ciurea SO, et al. Blood. 2015; 126:1033

Relapse



Ciurea SO, et al. Blood. 2015; 126:1033

Umbilical Cord Blood Stem Cell Grafts

- Advantages
  - Readily available stem cells source
  - Tolerance across HLA barriers
  - Nearly 30 year of experience
  - Less chronic GvHD vs. Matched Unrelated donor
    - *Eapen M et al Lancet 2010*
  - Potent anti-tumor activity
    - *Milano F et al NEJM 2016*
- Disadvantages
  - Low stem cell dose
    - Delayed hematopoietic recovery
    - Delayed immunologic recovery
  - Increased resource utilization

Potential Solution

Ex-vivo Expansion Cord Blood Stem Cells

Strategies to improve outcomes after SCT in AML

- **Pre-HCT strategies**
  - Improving conditioning regimens
  - graft engineering
  - Donor selection
- **Post-HCT strategies**
  - Prophylactic and preemptive chemotherapeutic approaches
  - Prophylactic and preemptive immune-mediated approaches

Background

- AML patients with high-risk cytogenetics have a significantly worse survival
  - compared to similarly treated intermediate- or favorable-risk patients
- Better outcome in high-risk AML patients in CR1 who undergo allogeneic HCT
  - compared with consolidation chemotherapy
  - only 40% of patients proceed to HCT
- Alternative donors are available for the large majority of high-risk AML patients
  - outcomes after allogeneic HCT from URD are similar to those following MRD transplantation
  - the lack of a matched sibling donor (available in about 33%) should not be a barrier to HCT

Feasibility of Allogeneic HCT Among High-Risk AML Patients in First Complete Remission

Results of the Transplant Objective from the SWOG (S1203) Randomized Phase III Study of Induction Therapy Using Standard 7+3 Therapy or Idarubicin with High-Dose Cytarabine (IA) *versus* IA plus Vorinostat

Clinical Trials Registry: NCT #01802333

John M. Pagel, Megan Othus, Guillermo Garcia-Manero, Min Fang, Jerald P. Radich, David A. Rizzieri, Guido Marcucci, Stephen A. Strickland, Mark R. Litzow, M. Lynn Savoie, Stephen R. Spellman, Dennis L. Confer, Jeffrey W. Chell, Maria Brown, Bruno C. Medeiros, Mikkael A. Sekeres, Tara L. Lin, Geoffrey Uy, Bayard L. Powell, Jonathan E. Kolitz, Richard A. Larson, Richard M. Stone, David Claxton, James Essell, Selina M. Luger, Sanjay R. Mohan, Anna Moseley, Harry P. Erba, Frederick R. Appelbaum

SWOG 1203 Transplant Objectives

- To determine if a prospective organized effort could rapidly identify alternative donors to improve the historical 40% allogeneic HCT rate

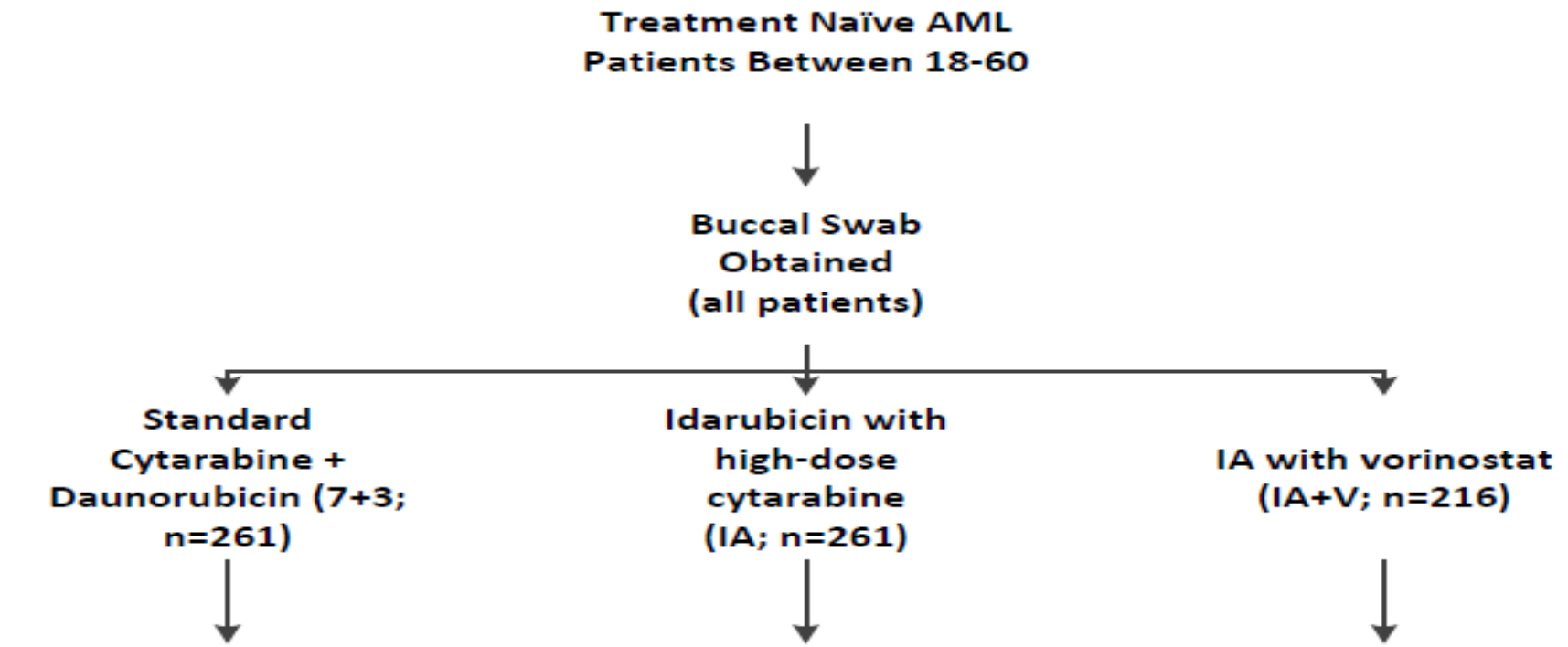
Primary Objective

- To determine whether it is possible to get 60% or more of adults ≤ age 60 with high-risk AML in CR1 to allogeneic HCT

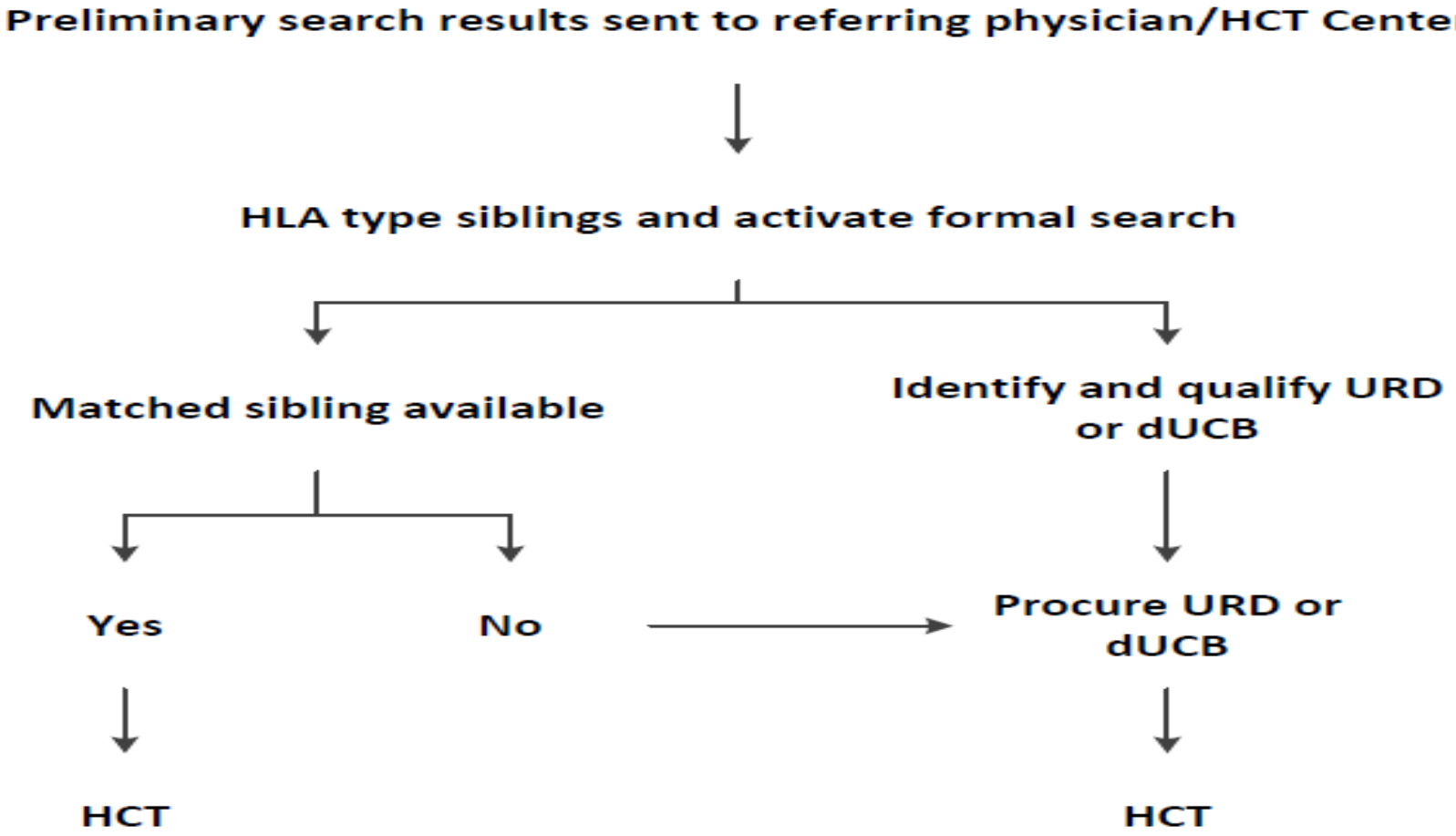
Secondary Objective

- To determine if transplanting significantly more adults with high-risk AML in CR1 would lead to an improved outcome compared with the historical RFS of 22%

Patients and Methods



Expedited Donor Identification and HCT



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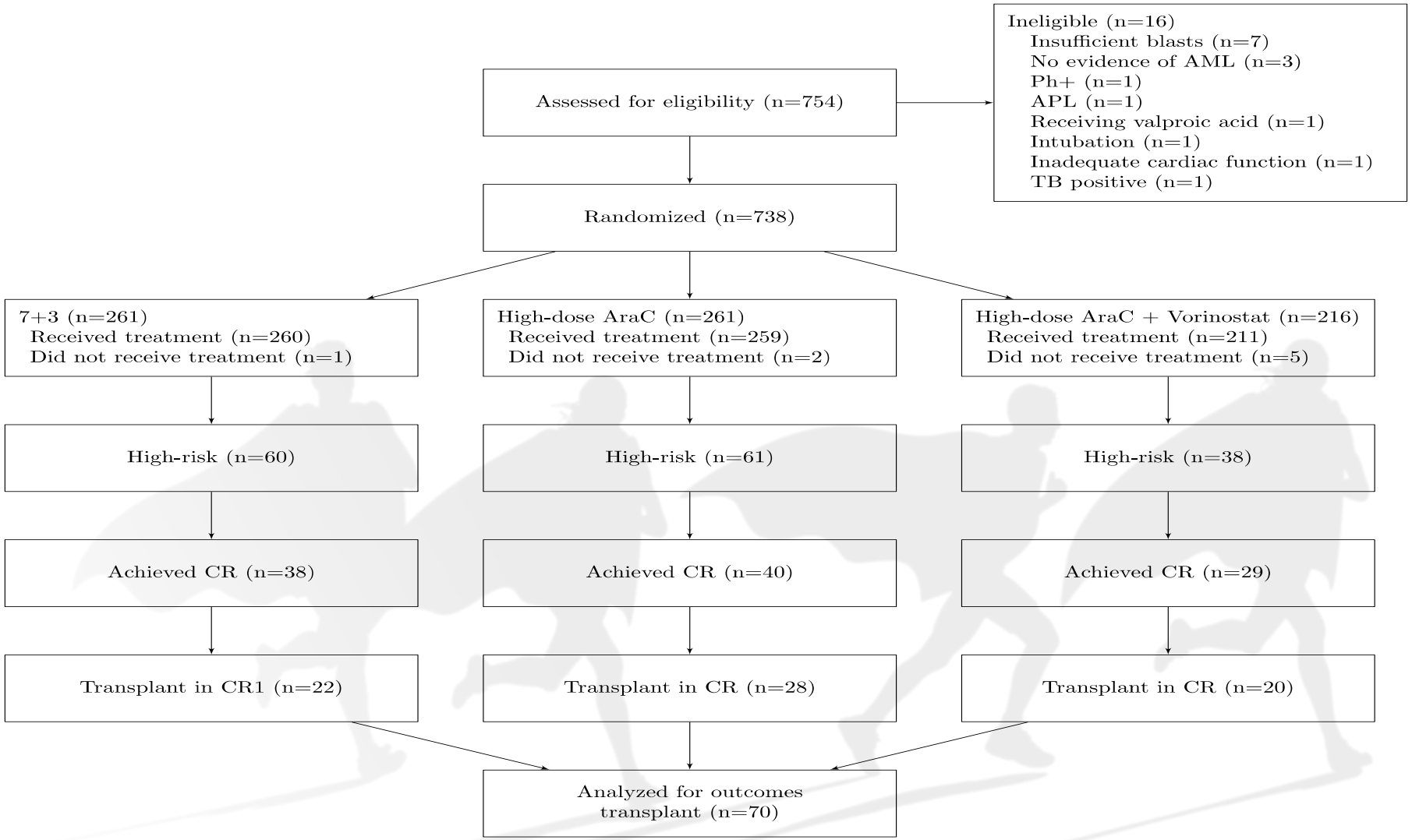
Consort Flow Diagram Displaying Randomization and Distribution of Patients



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Frequency of HCT in CR1 Among High-Risk AML

- 738 eligible patients
  - median age 49 years (range, 18-60)
  - 159 (22%) had high-risk cytogenetics
    - 60 (38%) 7+3
    - 61 (38%) IA
    - 38 (24%) IA+V
- HCT in 317 of all 738 patients (43%)
- 107 of 159 high-risk patients achieved CR/CRi (67%)
  - 68 (64%) of the high-risk patients received a HCT in CR1
    - $p<0.001$ compared to historical rate of 40%
  - 39 high-risk CR1 patients did not receive a transplant in CR1

Reasons for 39 high-risk CR1 patients not receiving a transplant in CR1

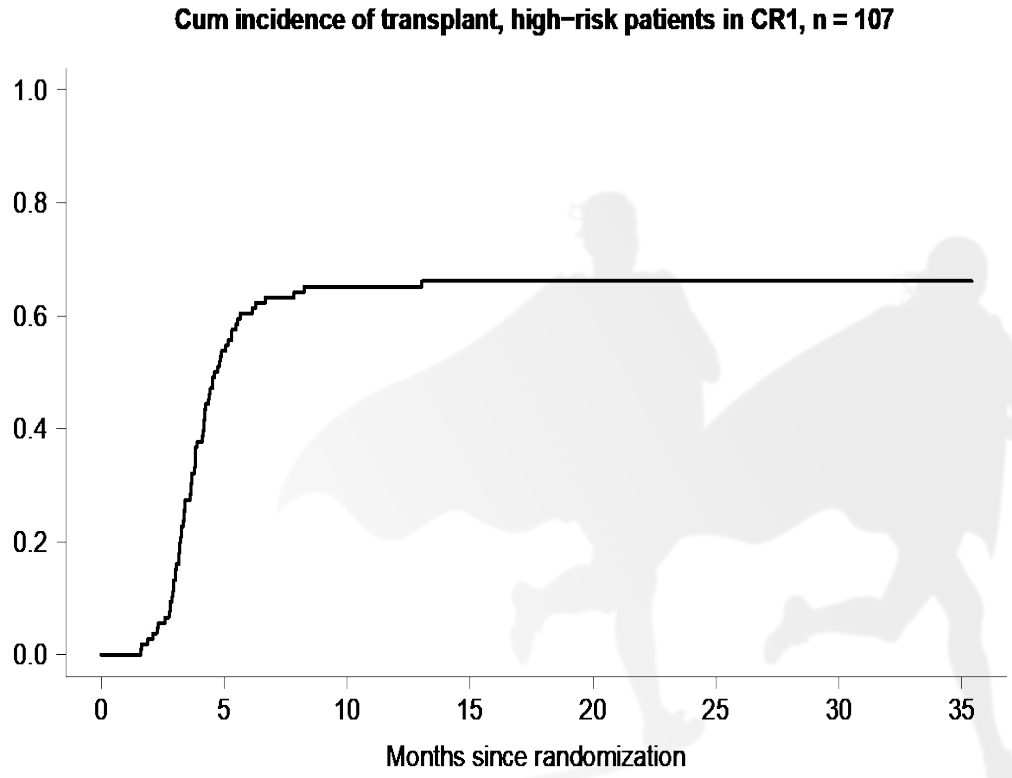
Reason	N
Co-morbidities	1
Death	6
No insurance	1
No donor	1
Physician decision	3
Patient decision	3
Relapse	6
Other	10
Unknown	8

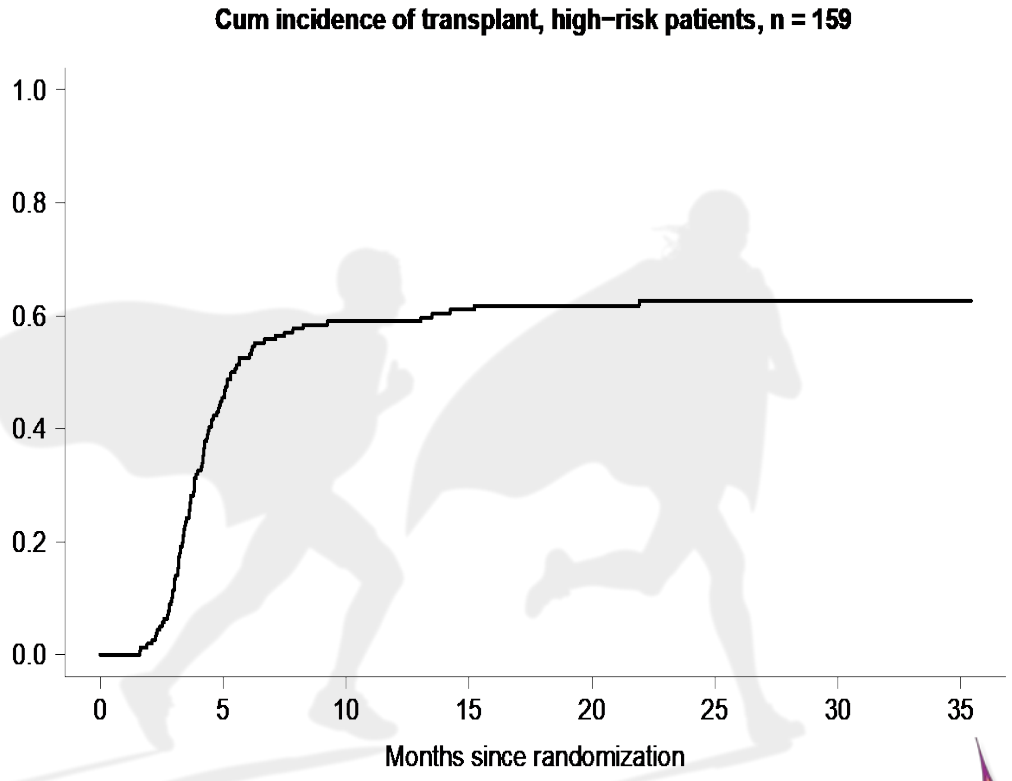
Transplant Data

HCT Donor Status	N (%)
MRD	25 (37%)
MUD	31 (45%)
Mismatched related donor	3 (4%)
Mismatched unrelated donor	8 (12%)
UCB	1 (1%)

- 66 high-risk patients transplanted in CR/CRi have detailed data
  - Median time to HCT from CR1 was 76 days (range, 20-365)
  - 57 patients (86%) received a myeloablative regimen
  - 9 (14%) received reduced-intensity conditioning

Cumulative Incidence of Transplant among High-Risk Patients in CR1 and all High-risk Patients





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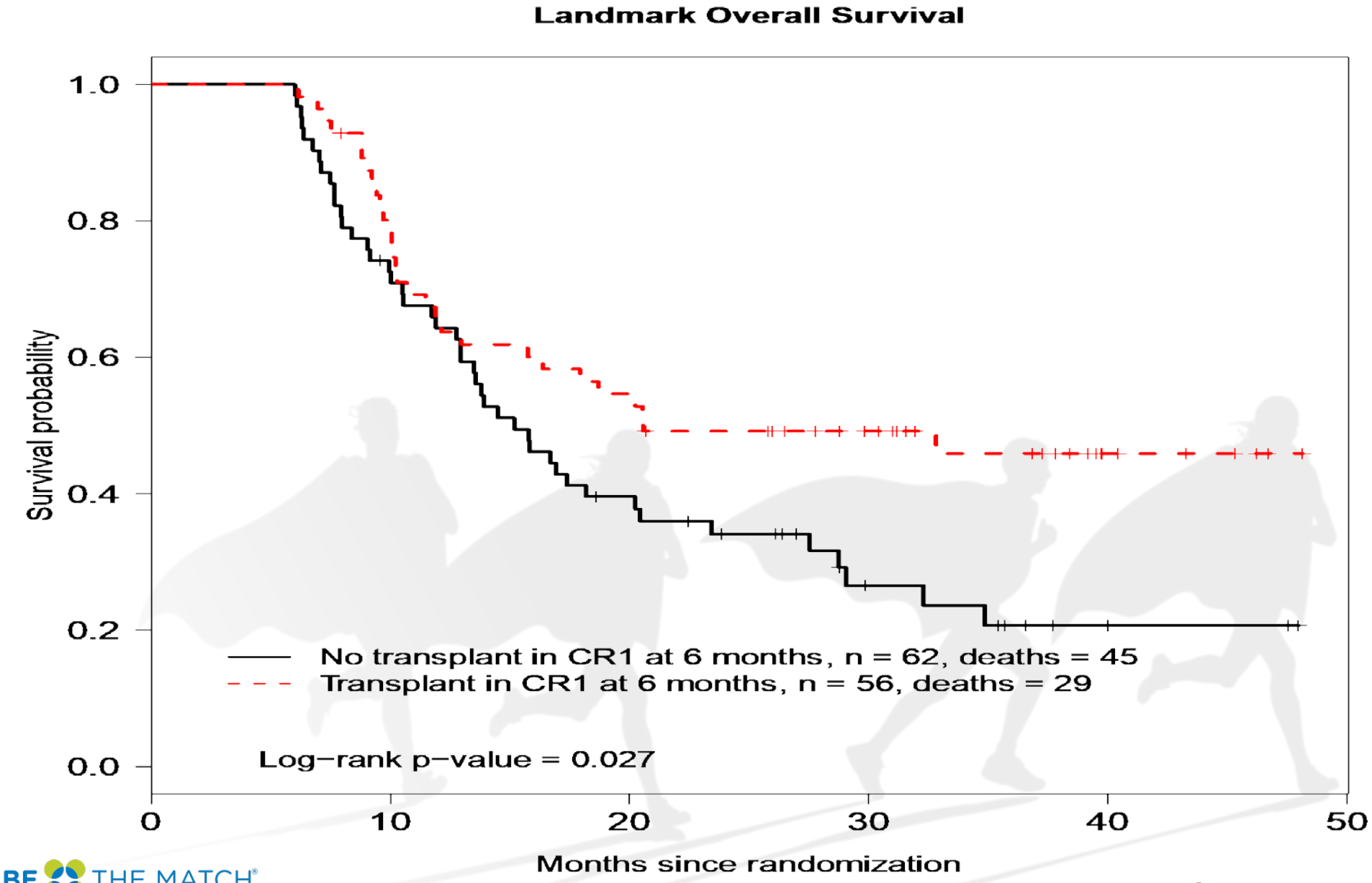

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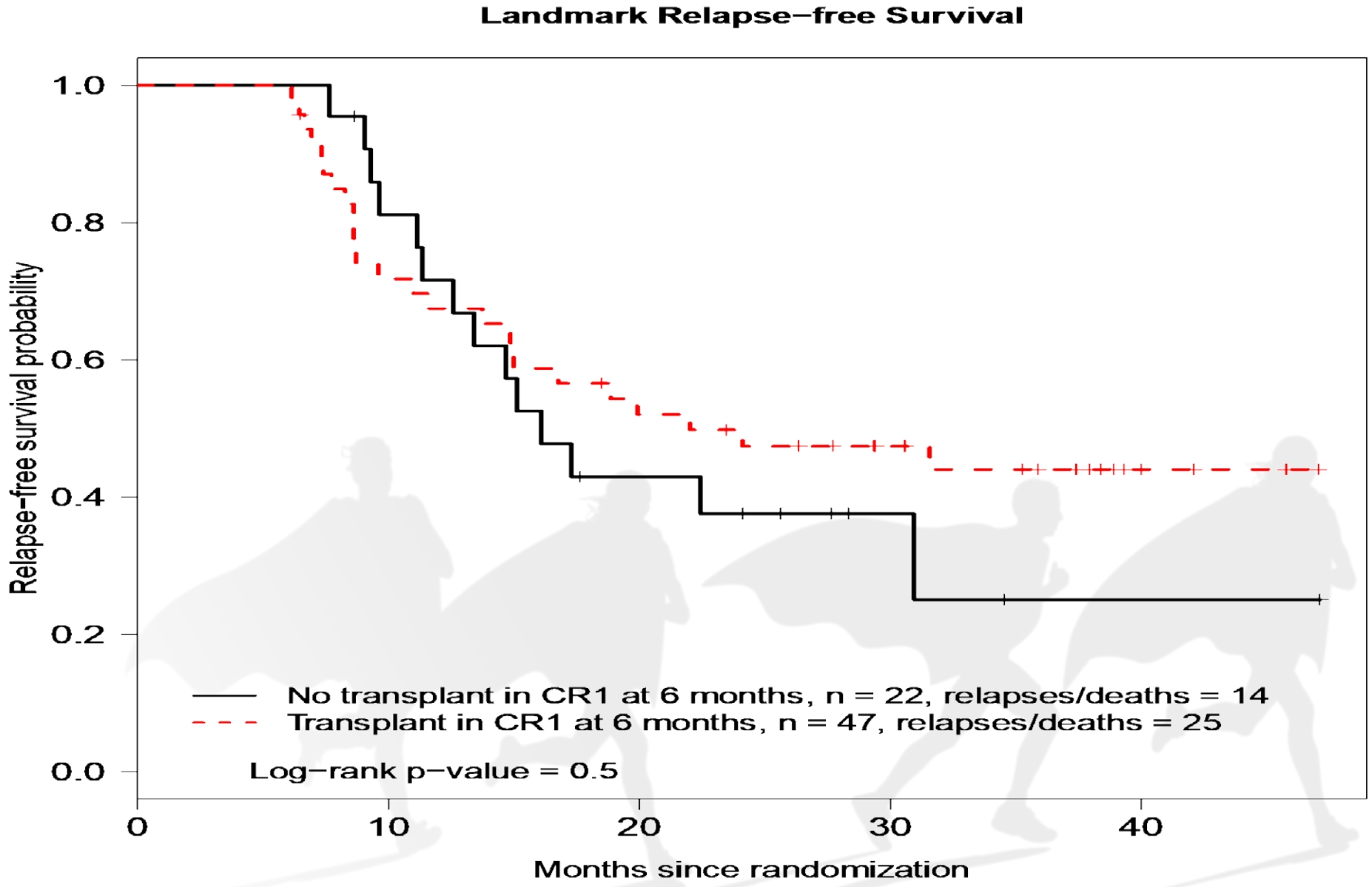

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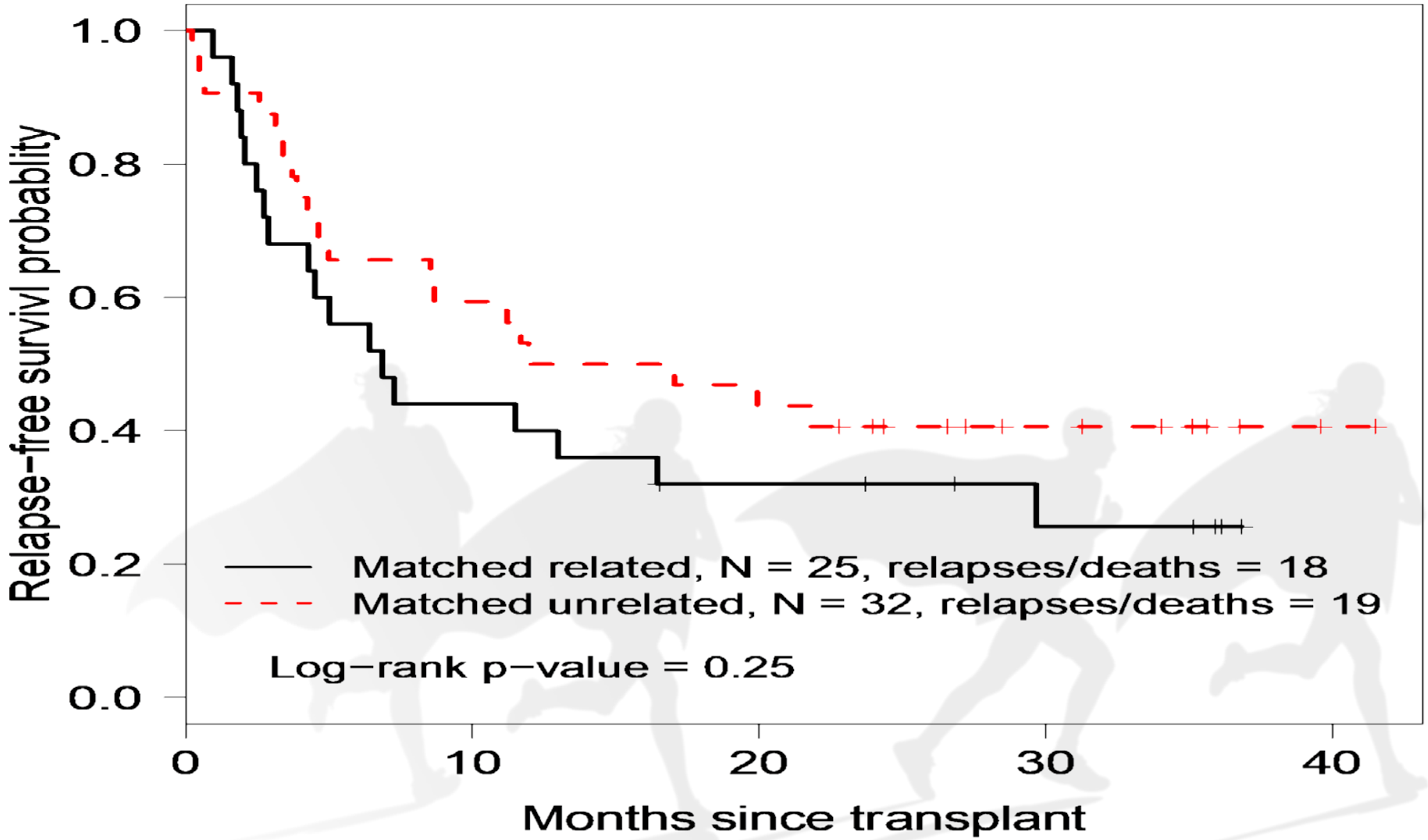
RFS after transplant in CR1, high−risk cohort



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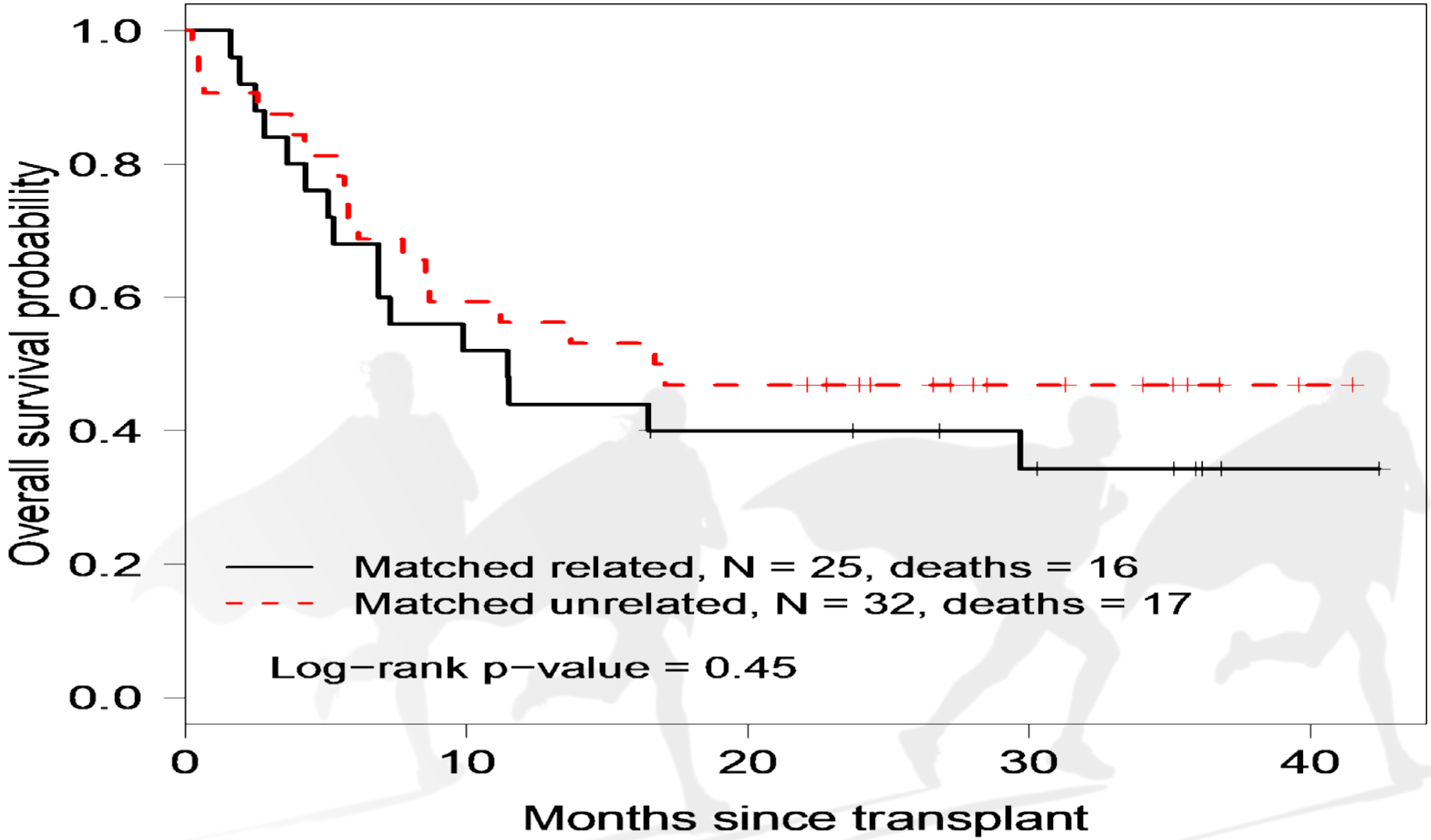
OS after transplant in CR1, high−risk cohort



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Transplant Survival Outcomes

- The 2-year RFS estimate in the entire high-risk cohort is 32%
  - significantly higher than the 22% historical rate (p=0.05)
- Median RFS in the high-risk CR1 cohort (n=107) was 10 months [range, 1-32* (censored) months]
- Median OS
  - among all patients in the high-risk cohort (n=159) was 12 months [range, 1-33* (censored) months]
  - 18 months [range 3-33* (censored) months] for those transplanted in CR1

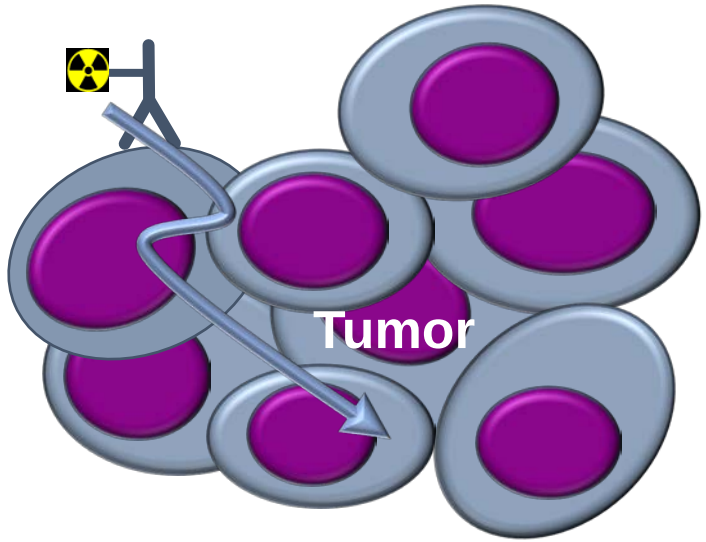
1 Year Estimates of Survival for High-Risk Patients Transplanted in CR1

	RFS (95% CI)	OS (95% CI)
MRD	40% (25%, 65%)	44% (28%, 69%)
MUD	50% (35%, 71%)	56% (41%, 76%)
The HR (reference = related) for RFS after transplant was 0.69 (0.36, 1.32) and for OS after transplant was 0.77 (0.39, 1.52)		

Conclusions

- In newly diagnosed adults with AML age 18-60 with early cytogenetic testing with an organized effort to identify a suitable allogeneic HCT donor
  - CR1 transplant rate of 64% in the high-risk group
  - significant improvement in RFS over historical controls

Approaches to Radioimmunotherapy for AML

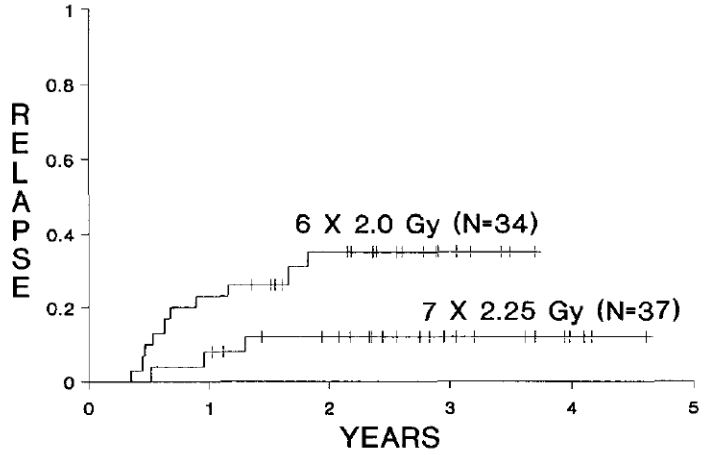


- Radioimmunoablation
- Targeted β particle therapy

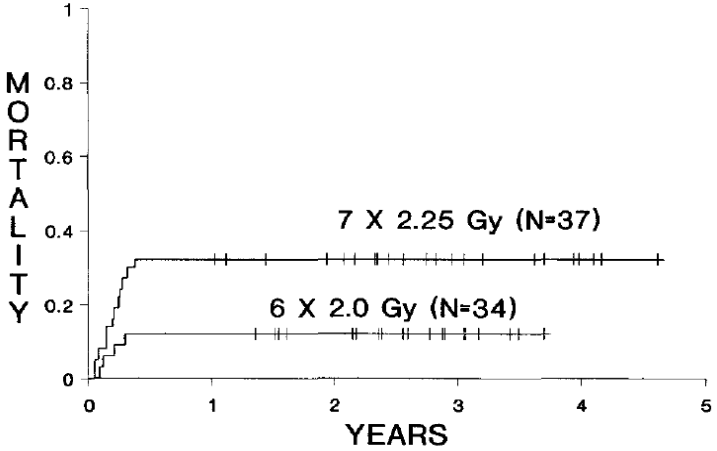
Rationale for RIT in HCT Regimens

- AML is highly radiosensitive.
- TBI is effective in HCT regimens at high doses.
- TBI dose cannot be escalated safely.
- RIT can increase radiation doses to bone marrow while minimizing exposure of normal tissues.

Probability of Relapse

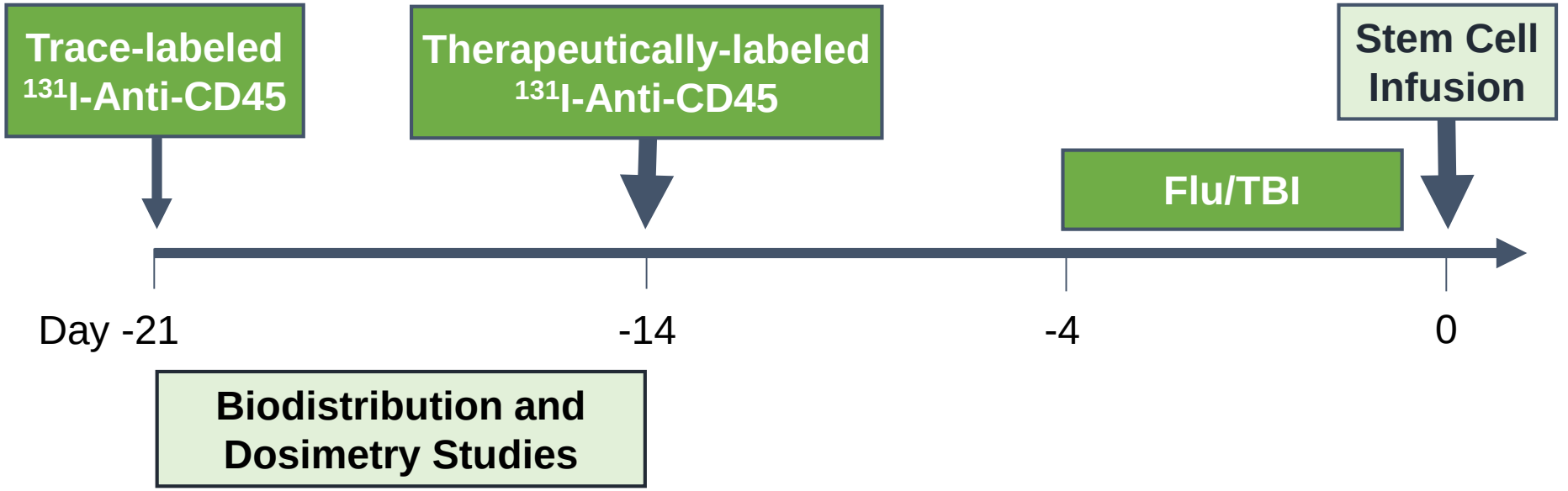


Probability of Mortality



Clift RA *et al. Blood* 1990; 76:1867-71.

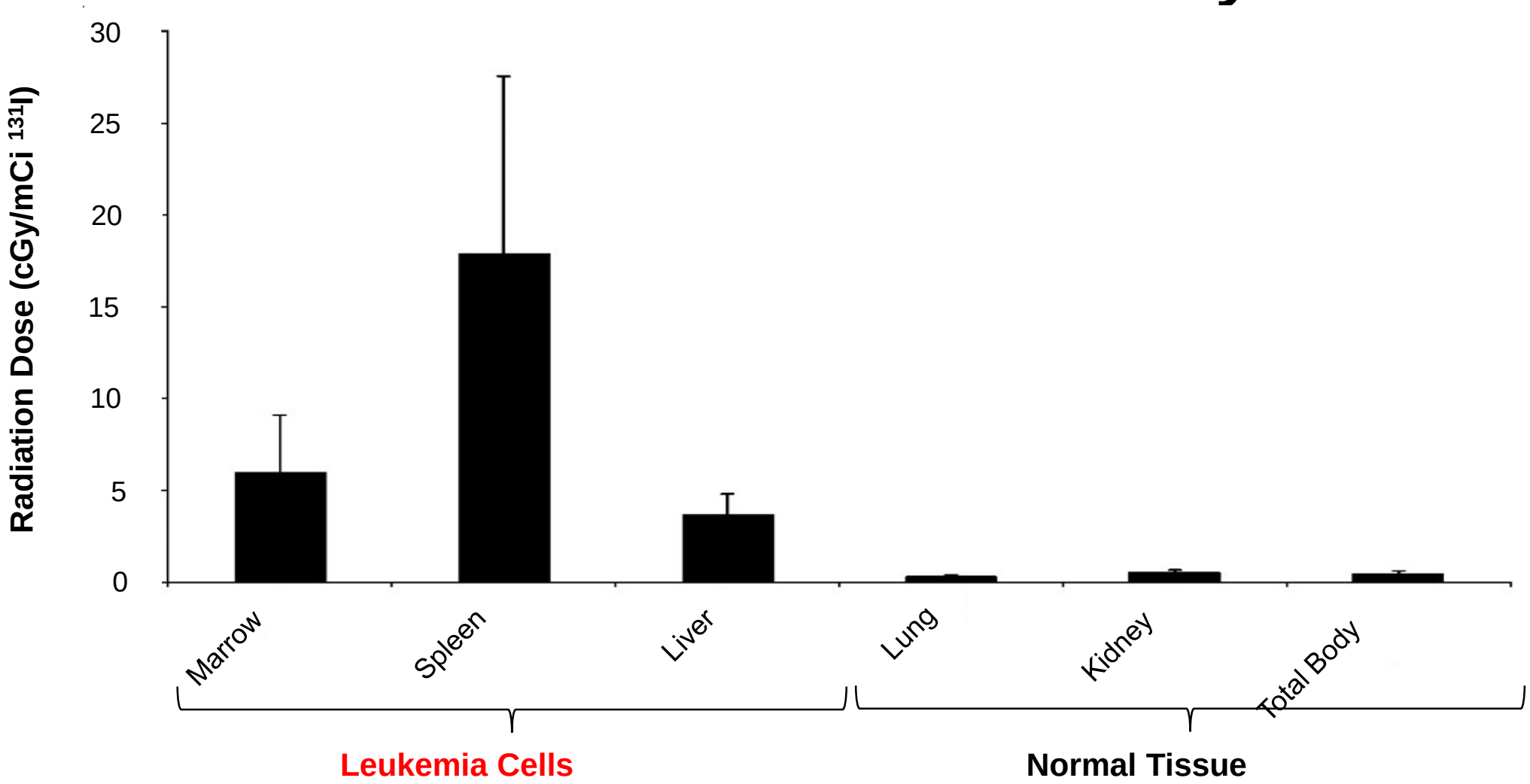
^{131}I-Anti-CD45/Flu/TBI Before Allogeneic Hematopoietic Transplant



- Recommended therapeutic dose delivered 24 Gy to the liver.
- Mean absorbed dose to bone marrow was 36 Gy.
- Mean absorbed dose to spleen was 101 Gy.

Pagel JM *et al. Blood* 2009;114:5444-5453.

^{131}I-Anti-CD45 Dosimetry



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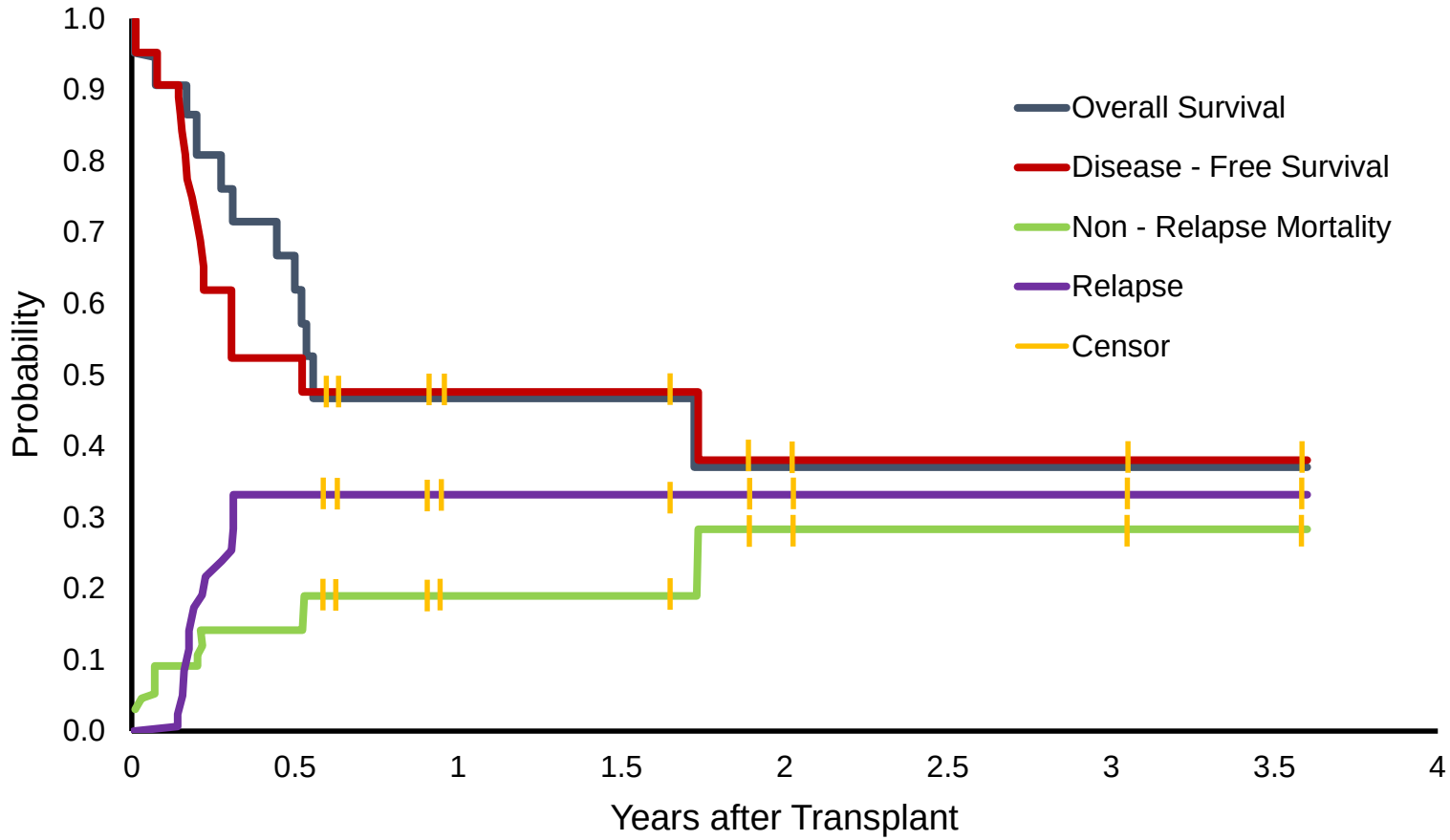
Pagel JM *et al. Blood* 2009;114:5444-5453.

Conditioning with ^{131}I-Anti-CD45/Flu/TBI: Outcomes of Patients Receiving MTD



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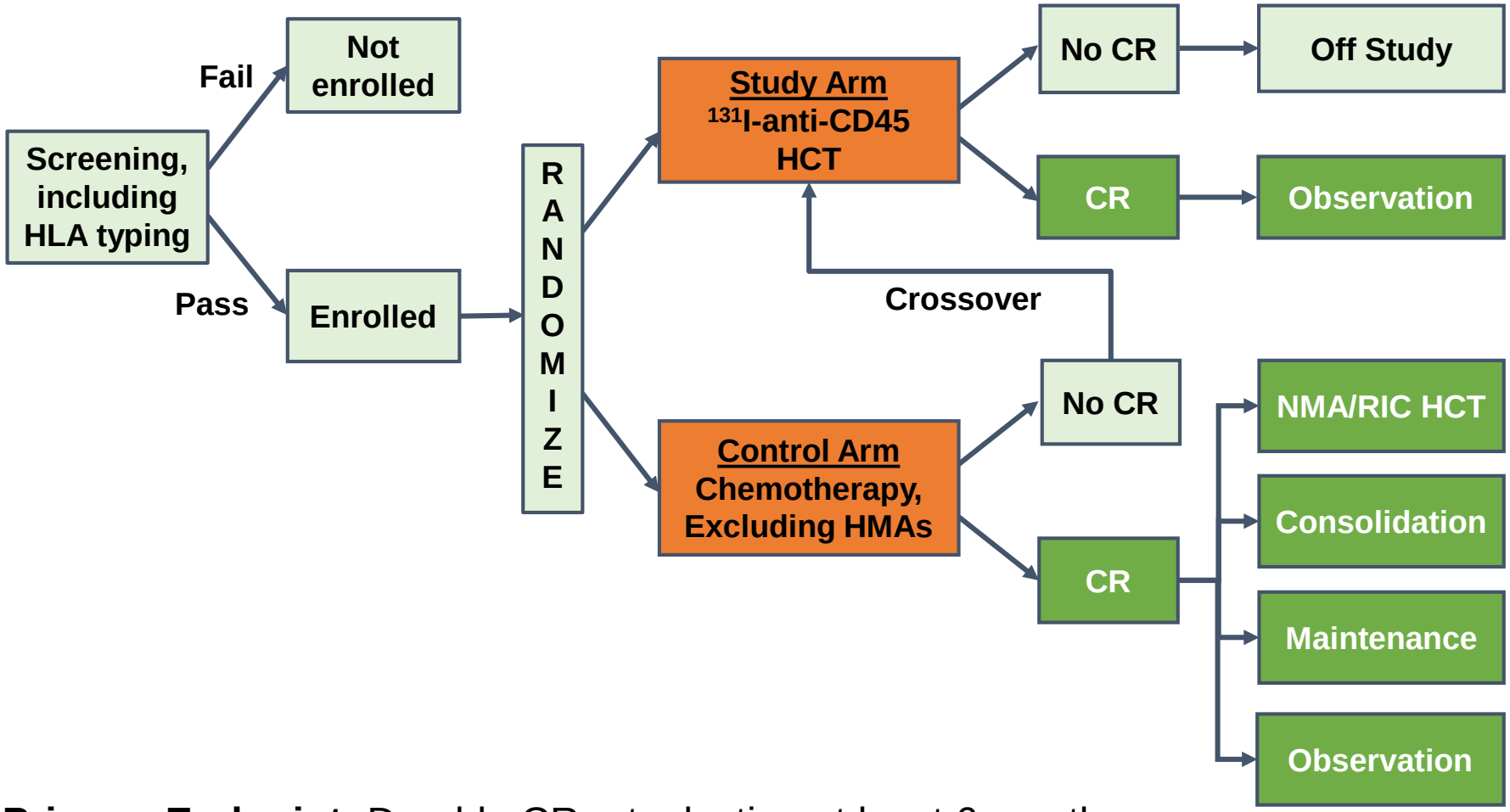
Pagel JM *et al. Blood* 2009;114:5444-5453.

^{131}I-Anti-CD45 Pivotal Trial Schema



Primary Endpoint: Durable CR rate, lasting at least 6 months.

Bone marrow aspirate and biopsy performed in all patients at ~1 and/or 2 months after the last day of intervention to determine response and at 6 months after CR has been established to confirm CR duration in groups labeled ■.

General Comments

- Relapse after HCT remains the leading cause of death for AML.
- Now almost all patients can have a donor.
- Matched sibling/unrelated donor are not the ONLY standards.
  - Haploidentical HCT
- Better outcomes in poor prognosis AML patients may be achieved simply by rapidly finding unrelated donors and performing allogeneic HCT in CR1 as soon as possible.

Our Vision

Democratize Cell Therapy

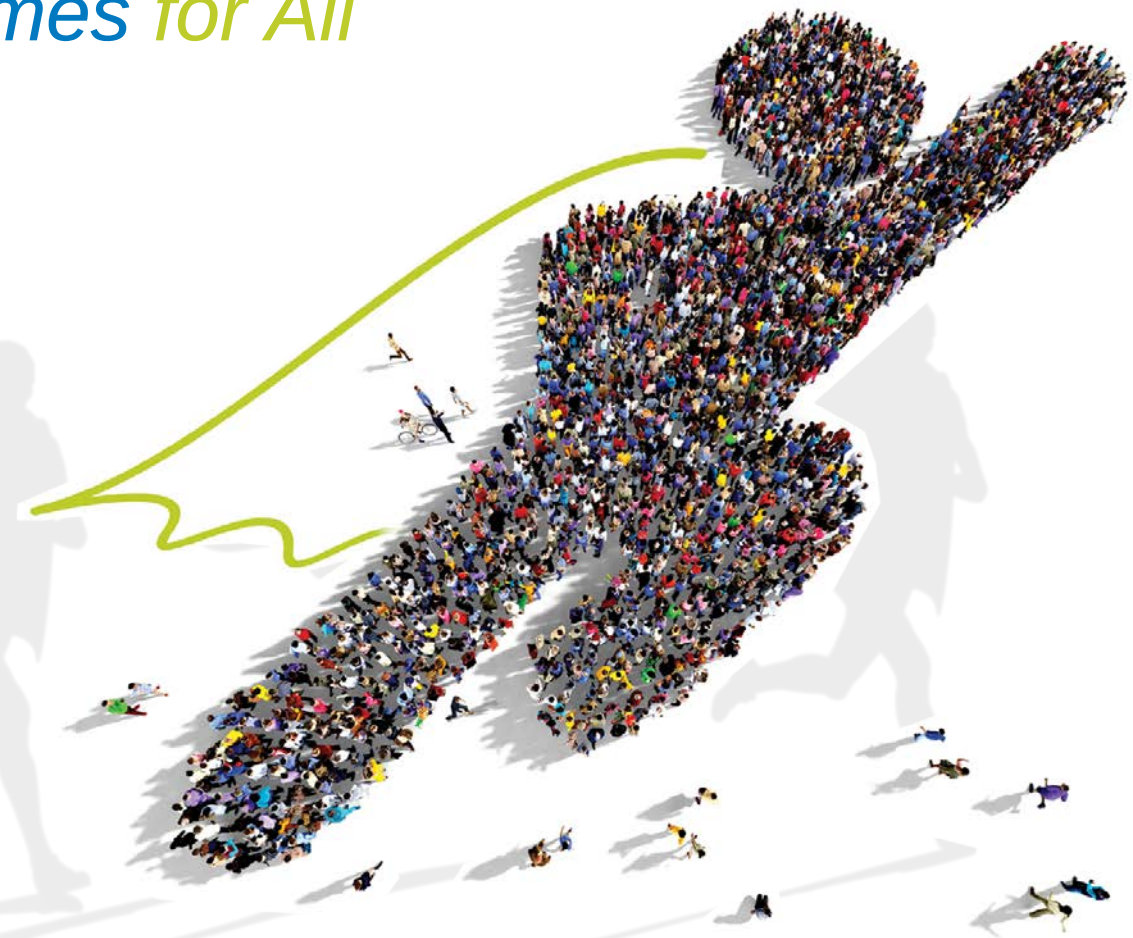
Equal Outcomes for All

INCREASE
Service level

INCREASE
Event–free survival

INCREASE
Volume

ELIMINATE
Disparity



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The **Strategic** Themes

Innovate

for the customer

Grow

with purpose

Simplify

everything

Be There

responsively serving

Simplify

everything

Intervention at Diagnosis

The Idea: HLA type and match every AML patient at the time of diagnosis and provide tools to identify high risk patients and to simplify the road from diagnosis to transplantation.

Equal Outcomes for All

Thank you!

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