



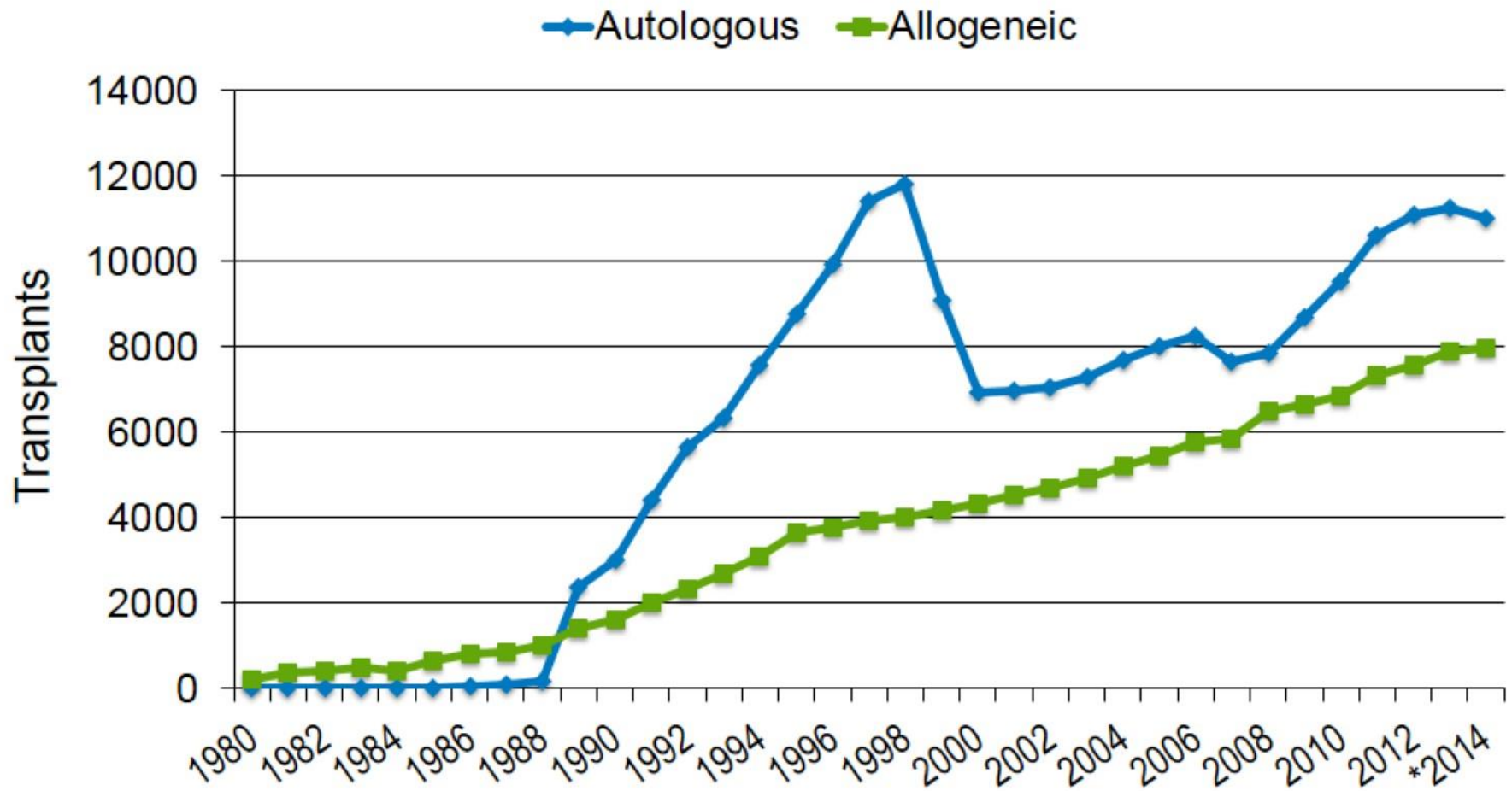
11. ULUSAL AFEREZ KONGRESİ

03-06 Kasım 2016 - THE MARMARA TAKSİM / İSTANBUL

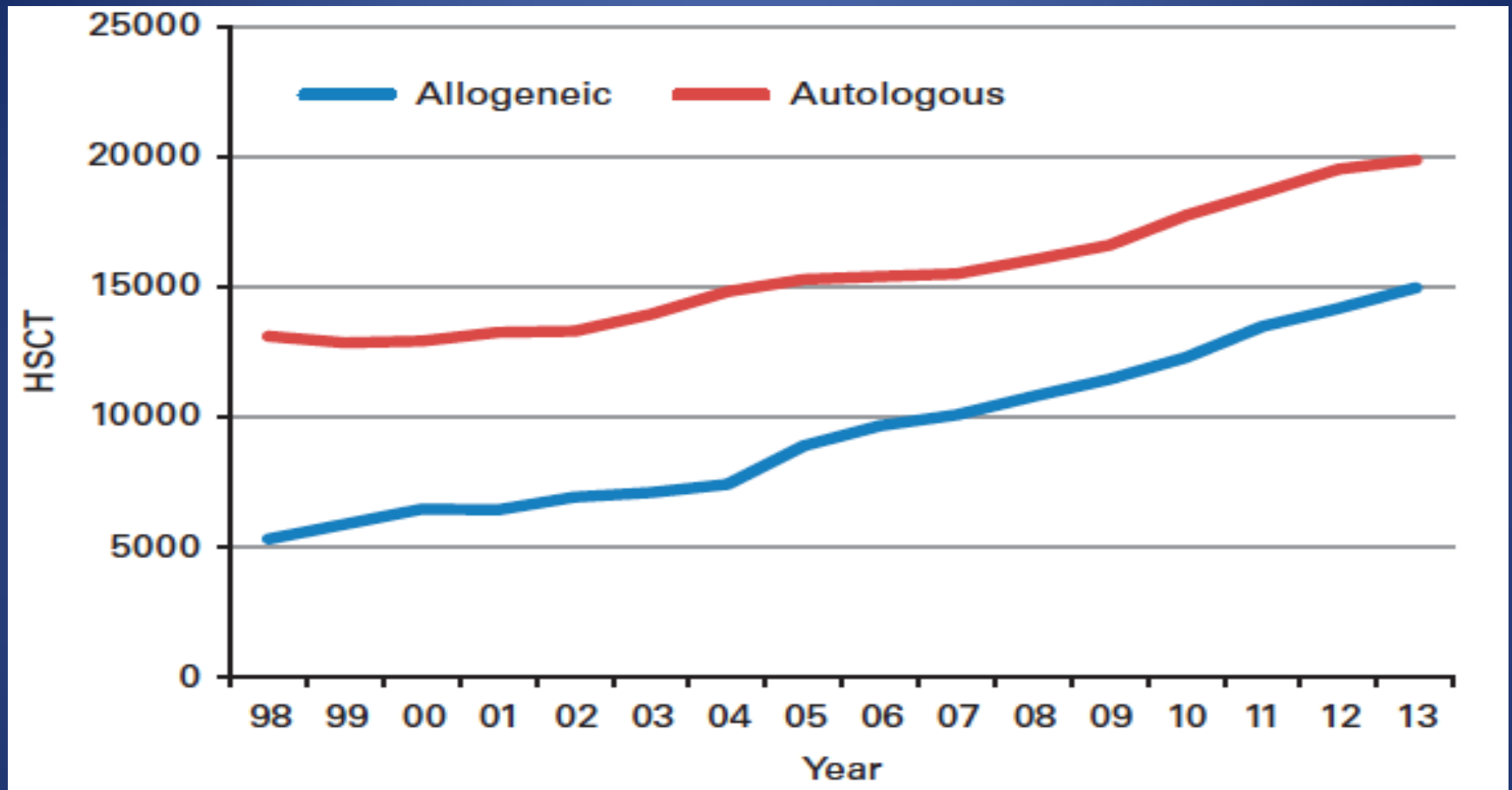
HKHN: BAŞARIYI ETKİLEYEN FAKTÖRLER

Dr. Emre Tekgündüz
Ankara Onkoloji Hastanesi
Hematoloji ve Kök Hücre Nakil Kliniği

Annual Number of Transplant Recipients in the US by Transplant Type



EBMT-2013



EBMT 2014 Report: 40829 HCT

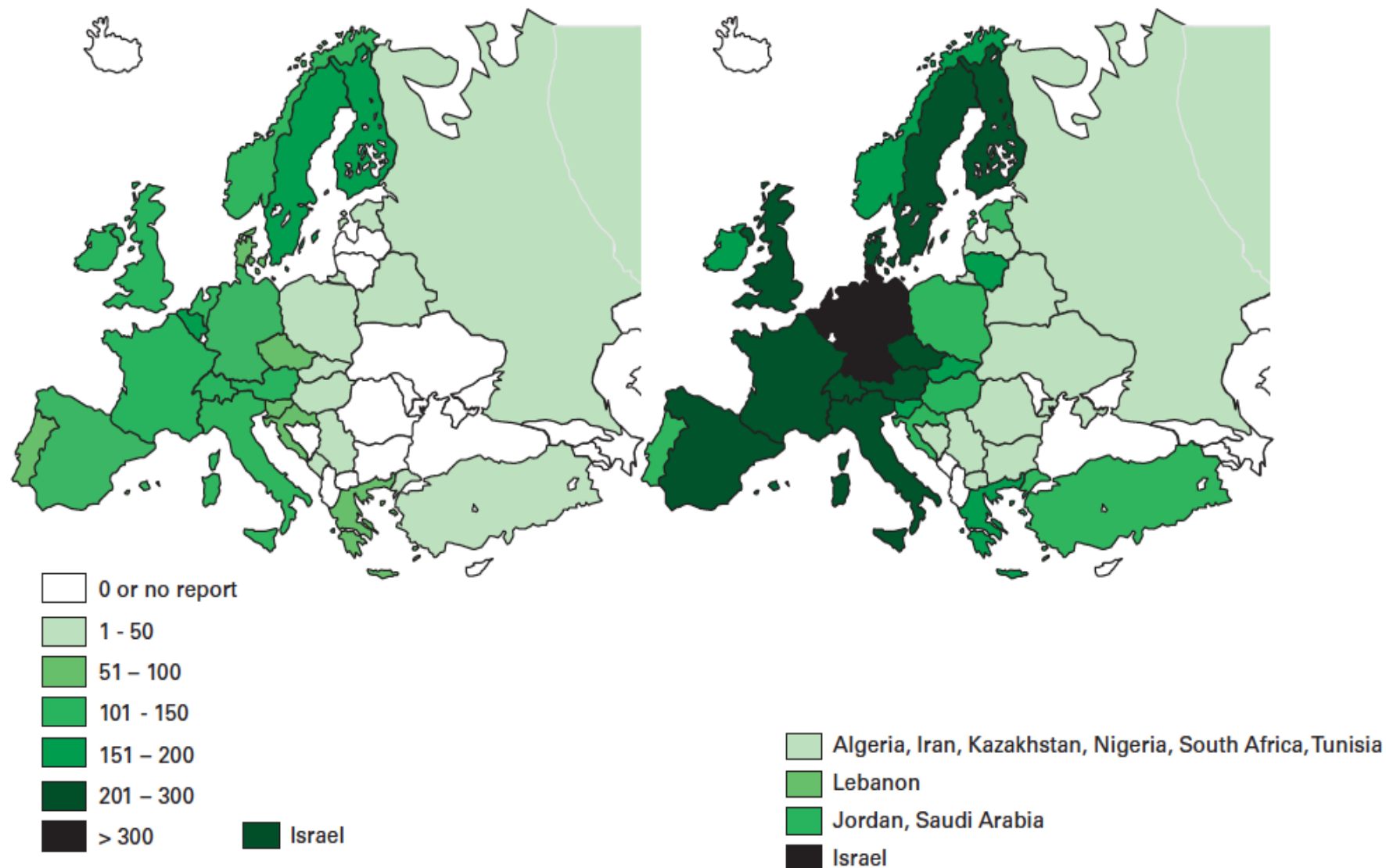
Bone Marrow Transplantation 2015; 50: 476-82
Bone Marrow Transplantation 2016; 51: 786-92

a

Allogeneic transplants per 10 million population in

1998

2013

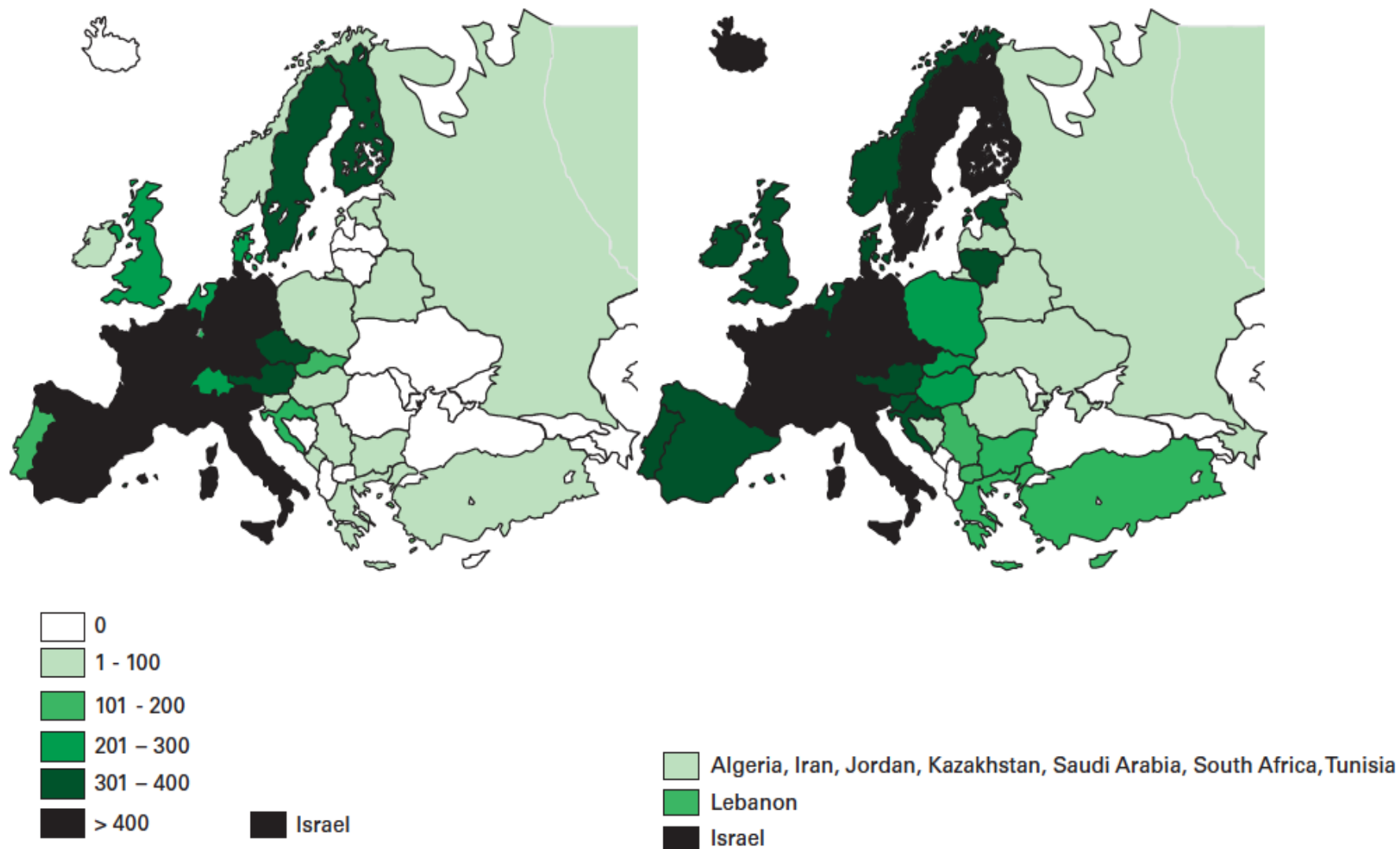


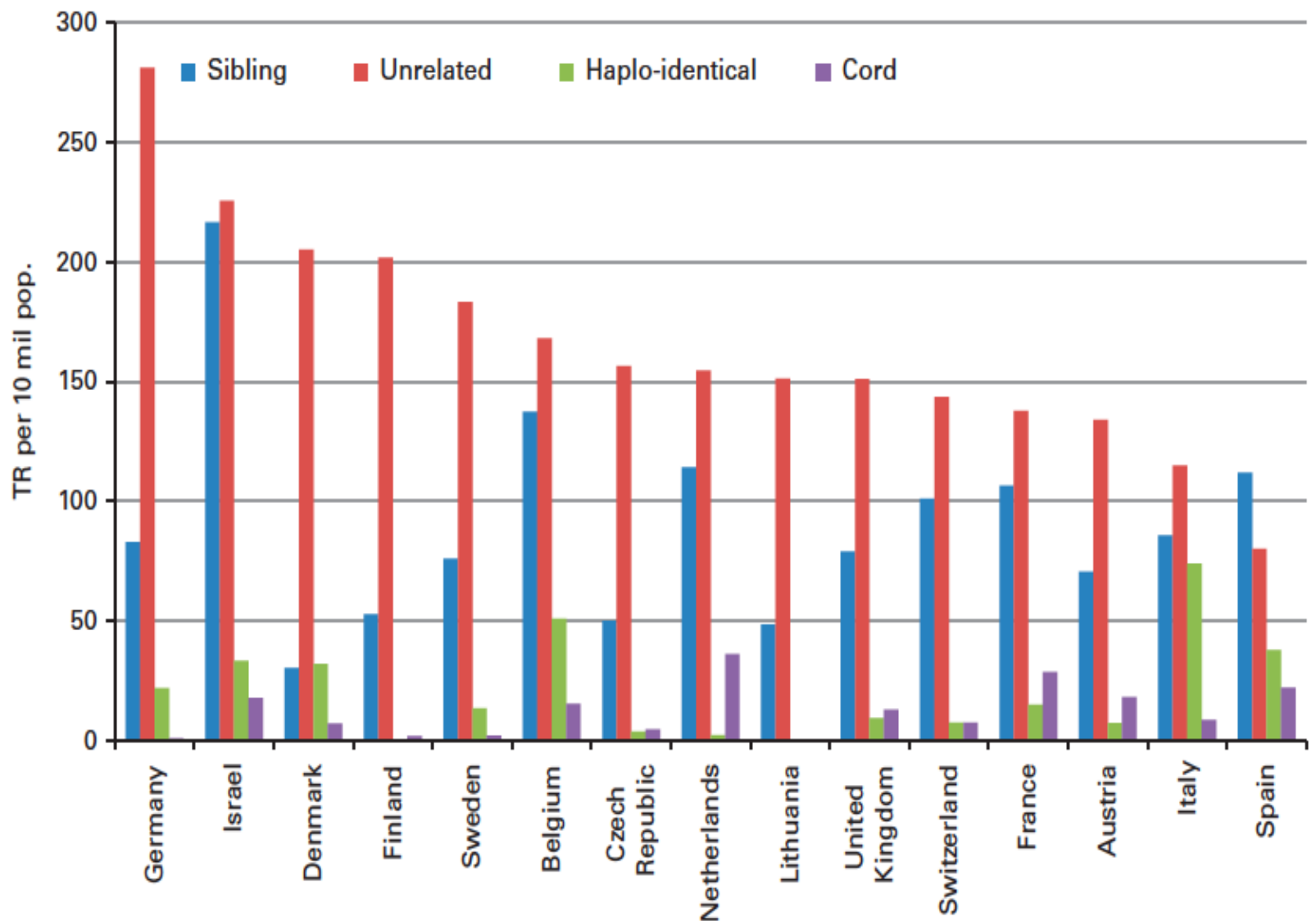
b

Autologous transplants per 10 million population in

1998

2013

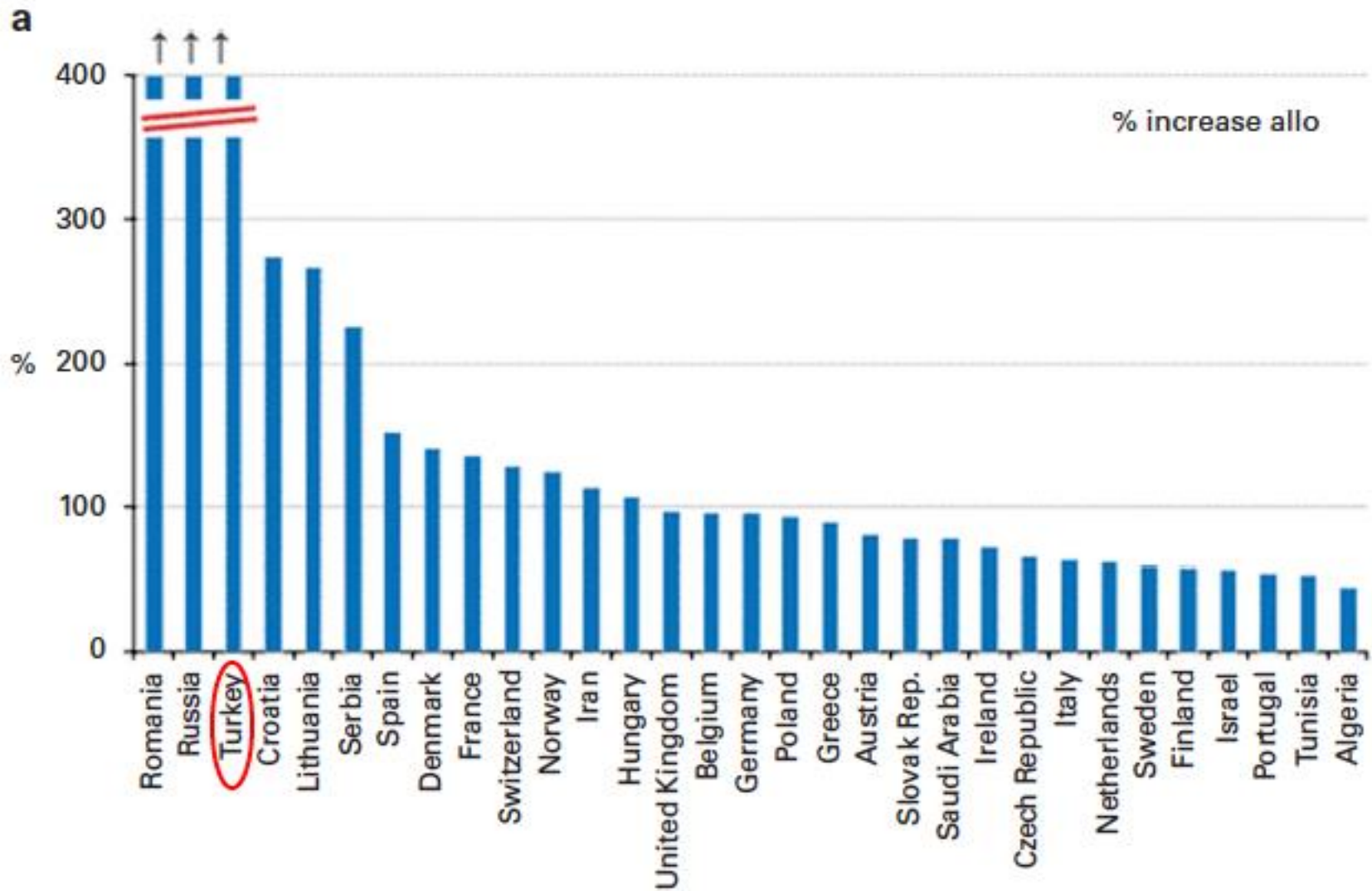




TR Allo	387	494	275	257	275	372	215	308	200	253	260	288	230	283	252
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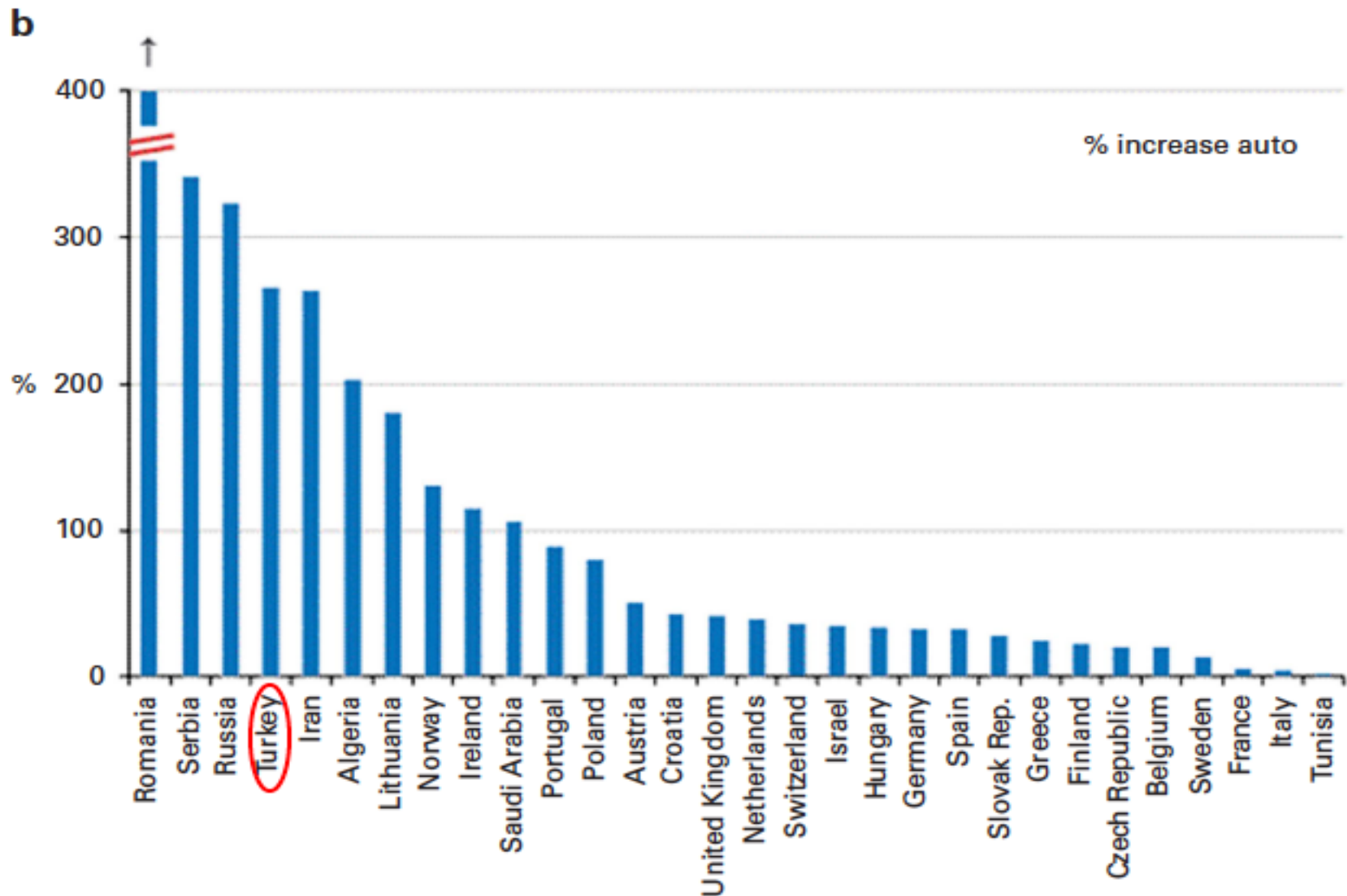
EBMT 2014 Survey:

Turkey is one of the emerging countries in terms of increased HCT activity in the last 10 years



EBMT 2014 Survey:

Turkey is one of the emerging countries in terms of increased HCT activity in the last 10 years



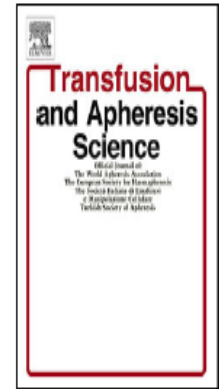


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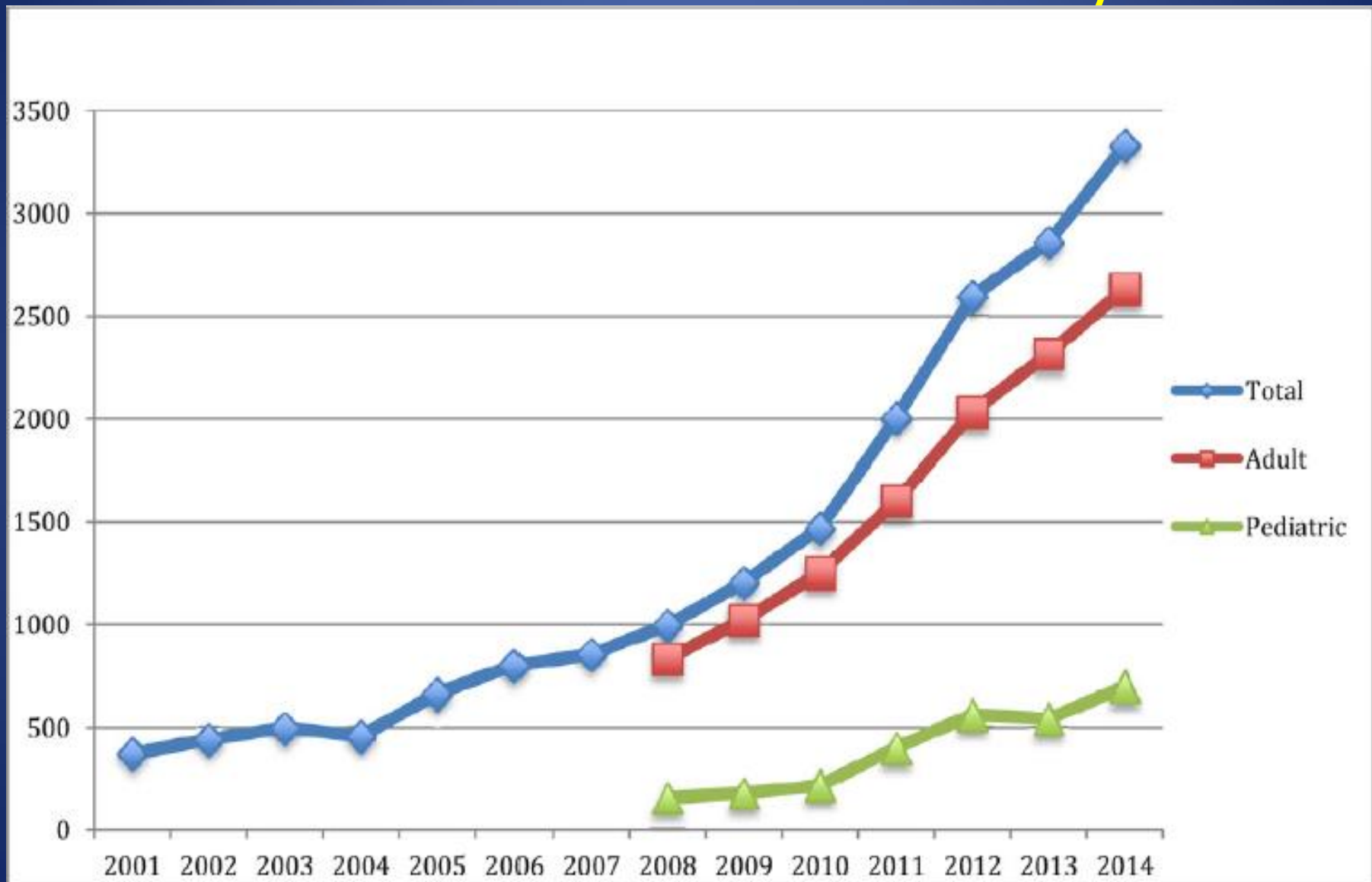


Hematopoietic cell transplantation activity of Turkey in 2014: Ongoing increase in HCT rates

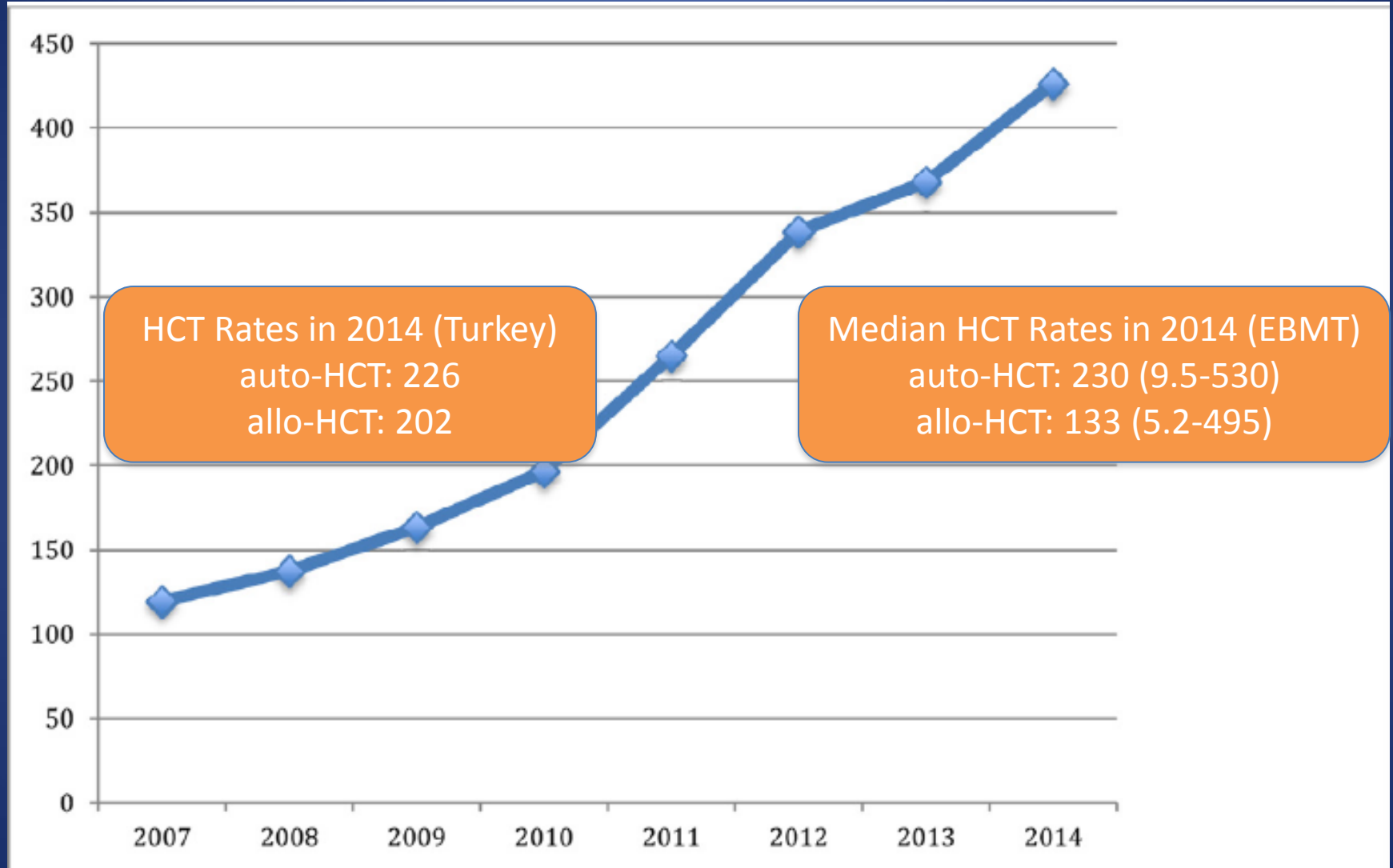


Emre Tekgündüz^a, İrfan Şencan^b, Arif Kapuağası^{b,*}, Doğan Ünal^b,
Murat Öztürk^b, Eyüp Gümüş^b, Hakan Göker^c, Emine Betül Tavil^d,
Mehmet Ertem^e, Mustafa Çetin^f, Mutlu Arat^g, Teoman Soysal^h,
Osman Karakaşlı^b, Halil Yılmaz Surⁱ, Akif Yeşilipek^j, Burhan Ferhanoğlu^k,
Duygu Uçkan^d, Osman İlhan^l, Fevzi Altuntaş^m

Number of total HCT Activity

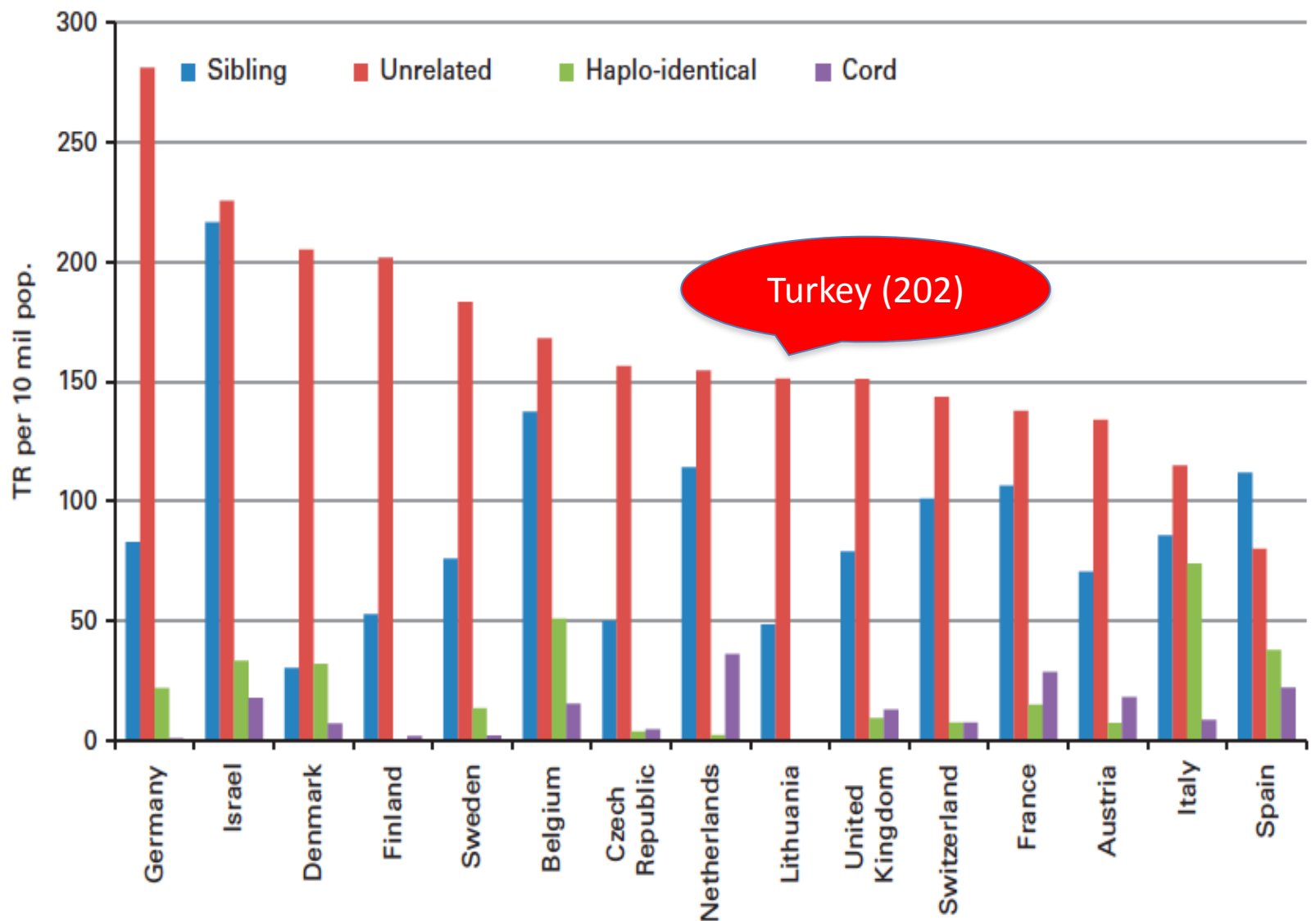


HCT Rates: 2007-2014



Transfus Apher Sci 2016; 54: 53-9

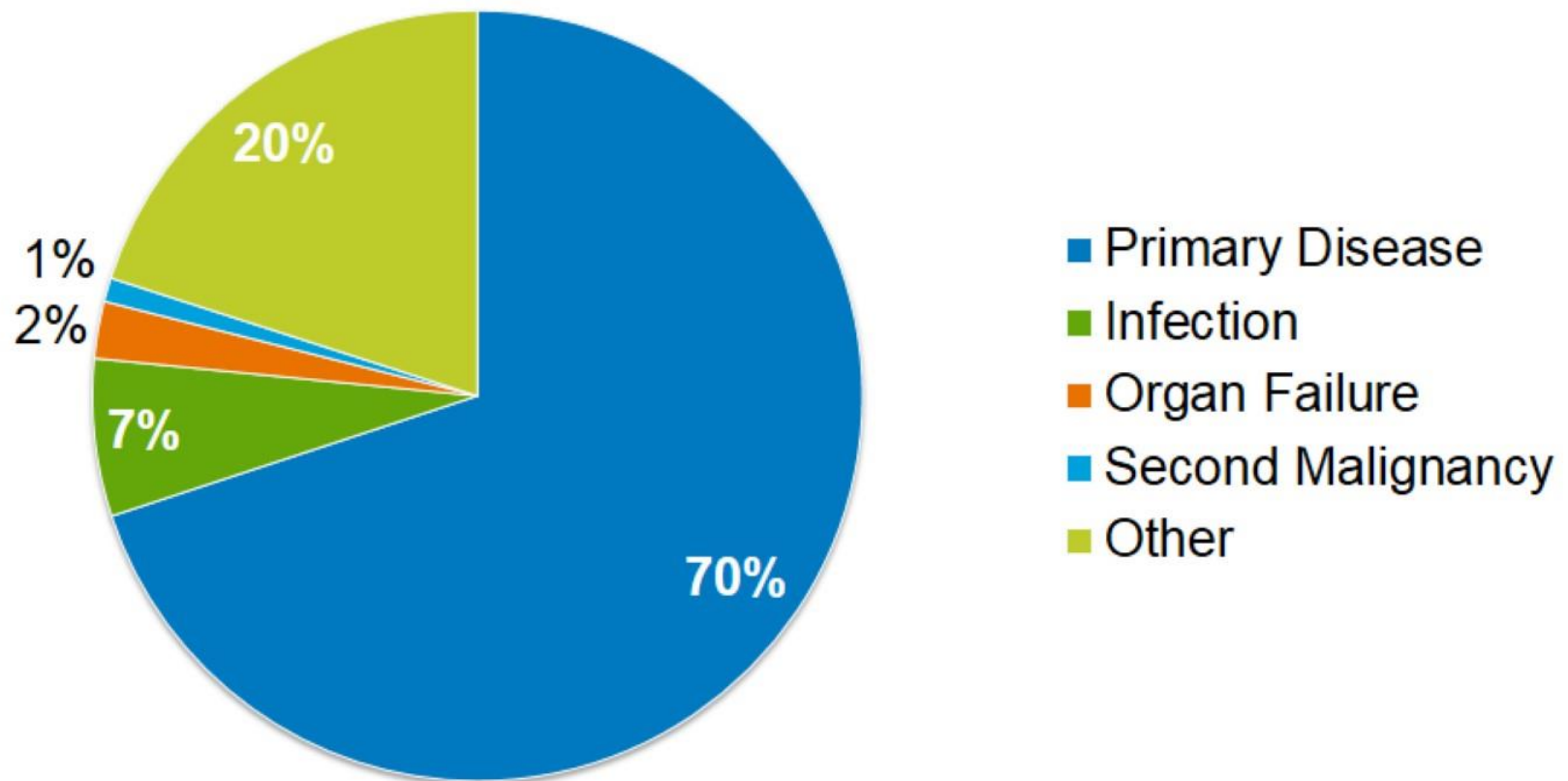
Bone Marrow Transplantation 2016; 51: 786-92



TR Allo	387	494	275	257	275	372	215	308	200	253	260	288	230	283	252
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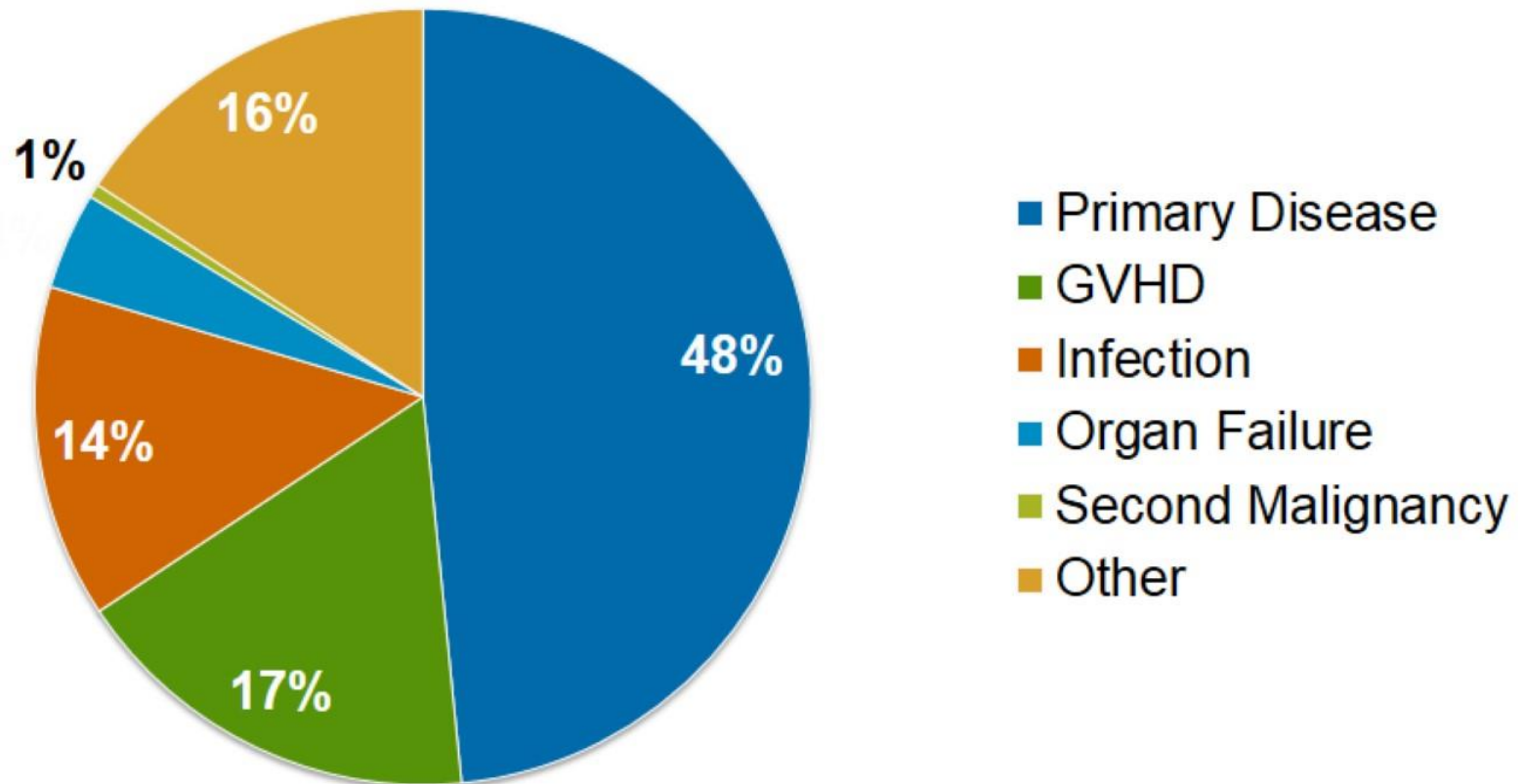
HKHN: MORTALİTE NEDENLERİ

Causes of Death after Autologous Transplants done in 2012-2013

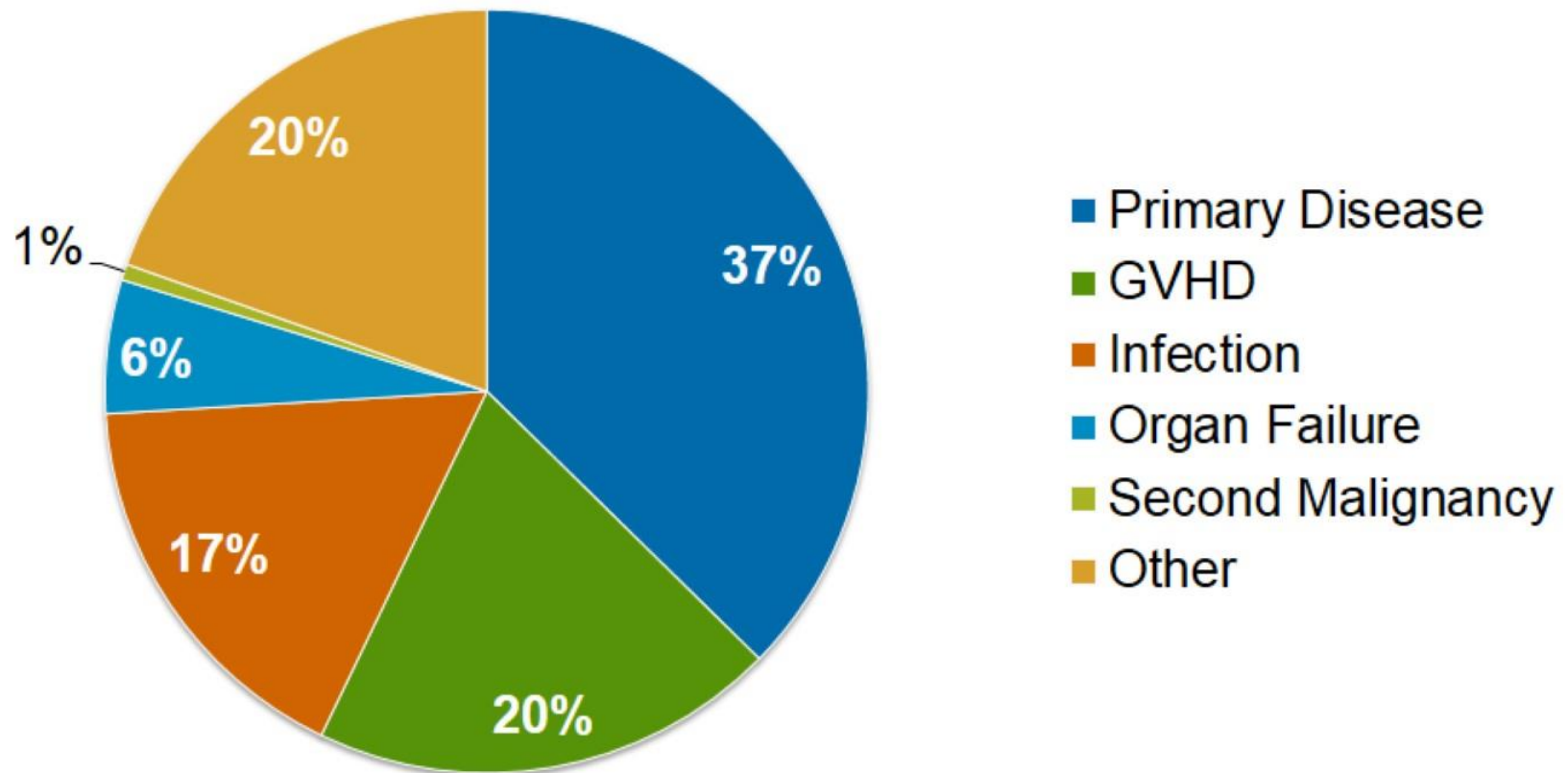


Causes of Death after HLA Match

Sibling Transplants done in 2012-2013

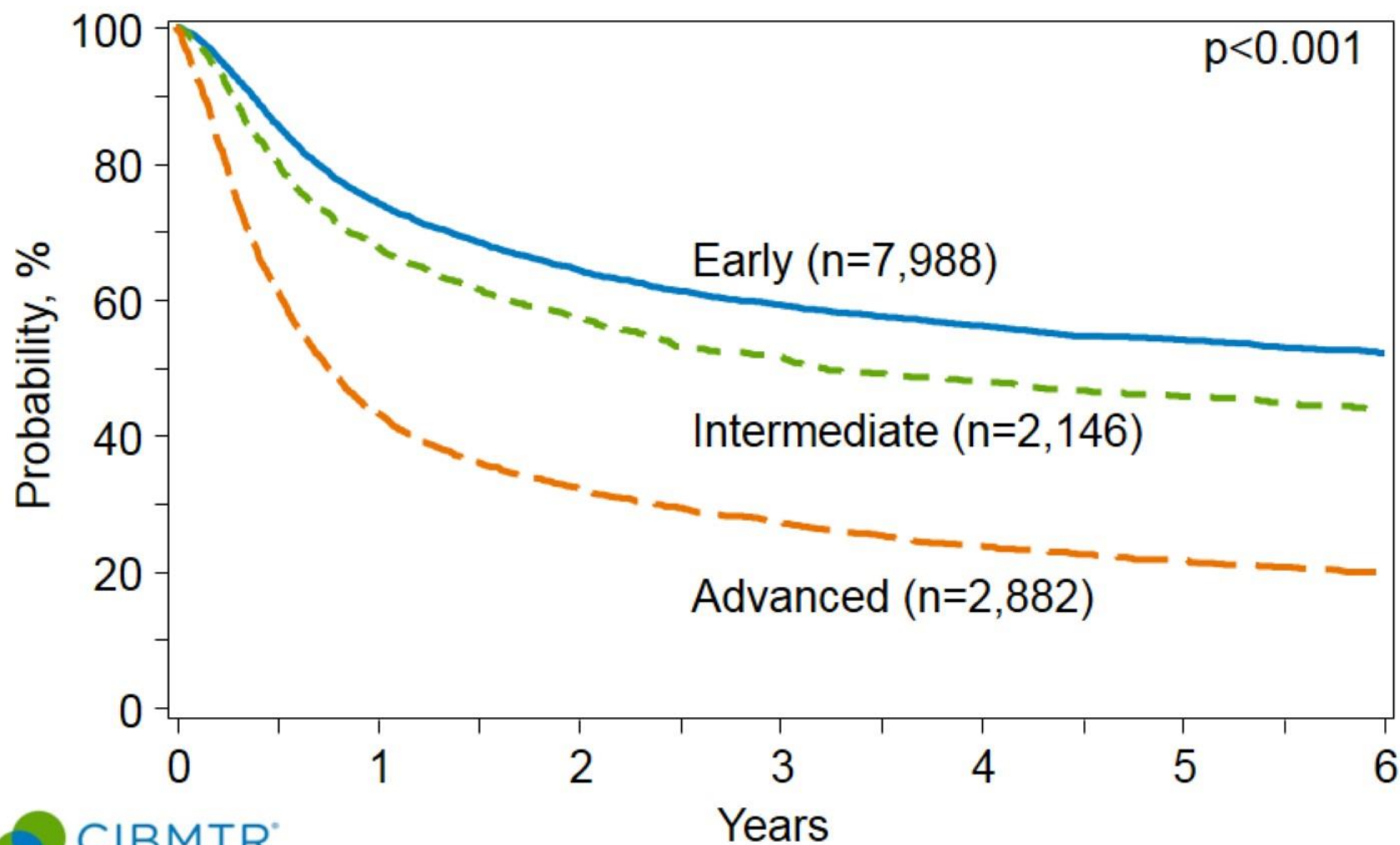


Causes of Death after Unrelated Donor Transplants done in 2012-2013

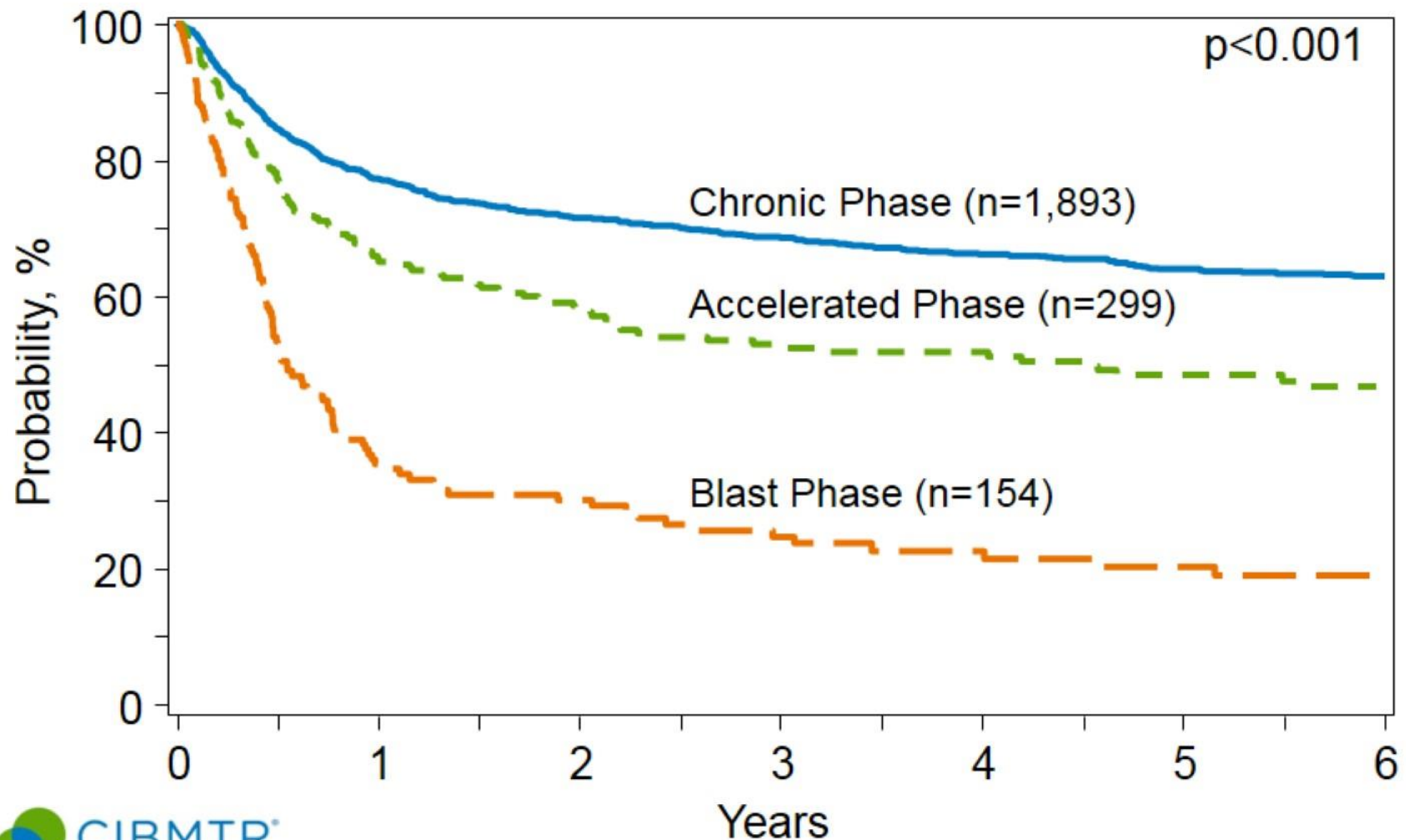


HASTALIK EVRESİ

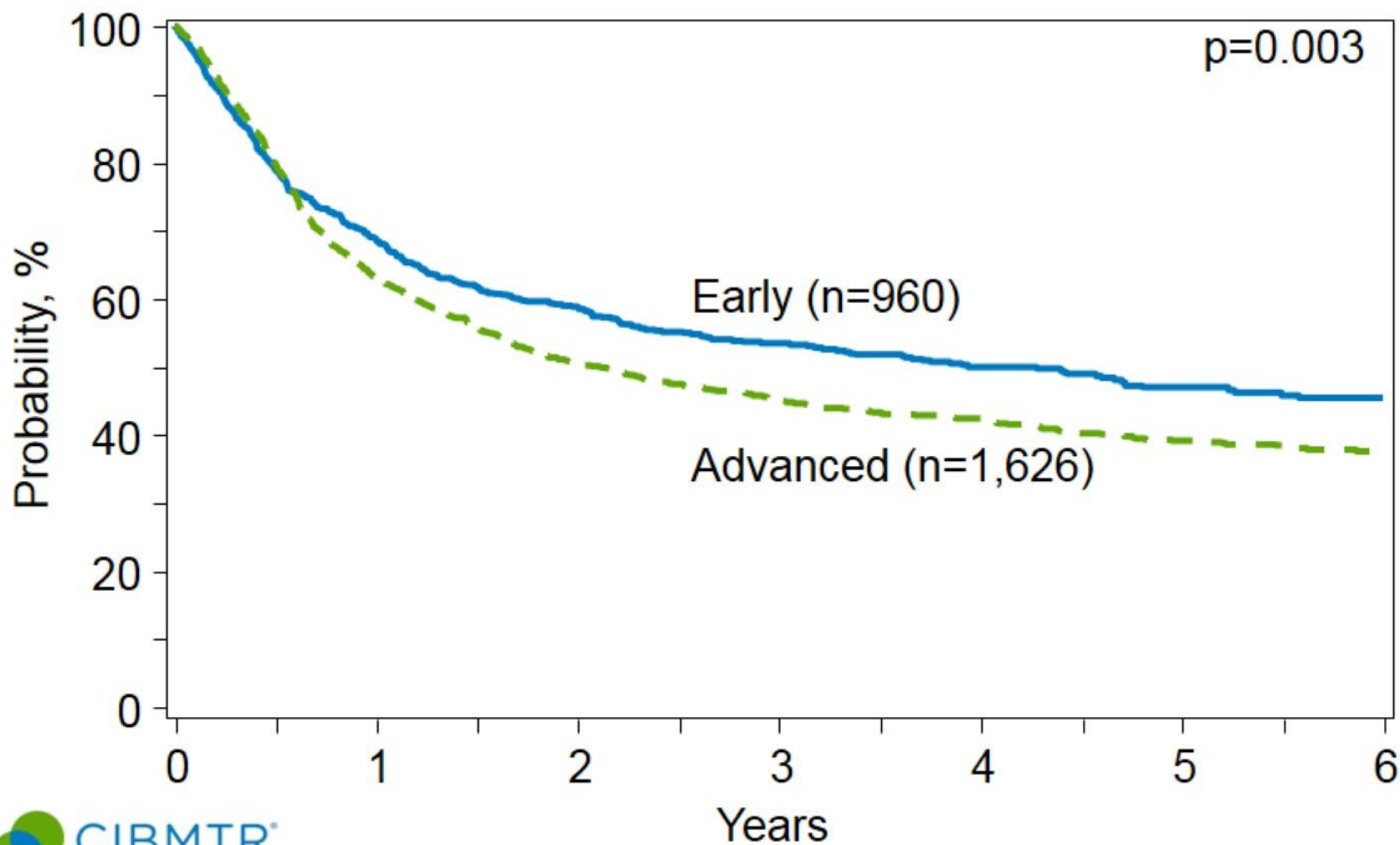
Survival after HLA Match Sibling Donor Transplants for AML, 2003-2013



Survival after HLA Match Sibling Transplants for CML, 2003-2013

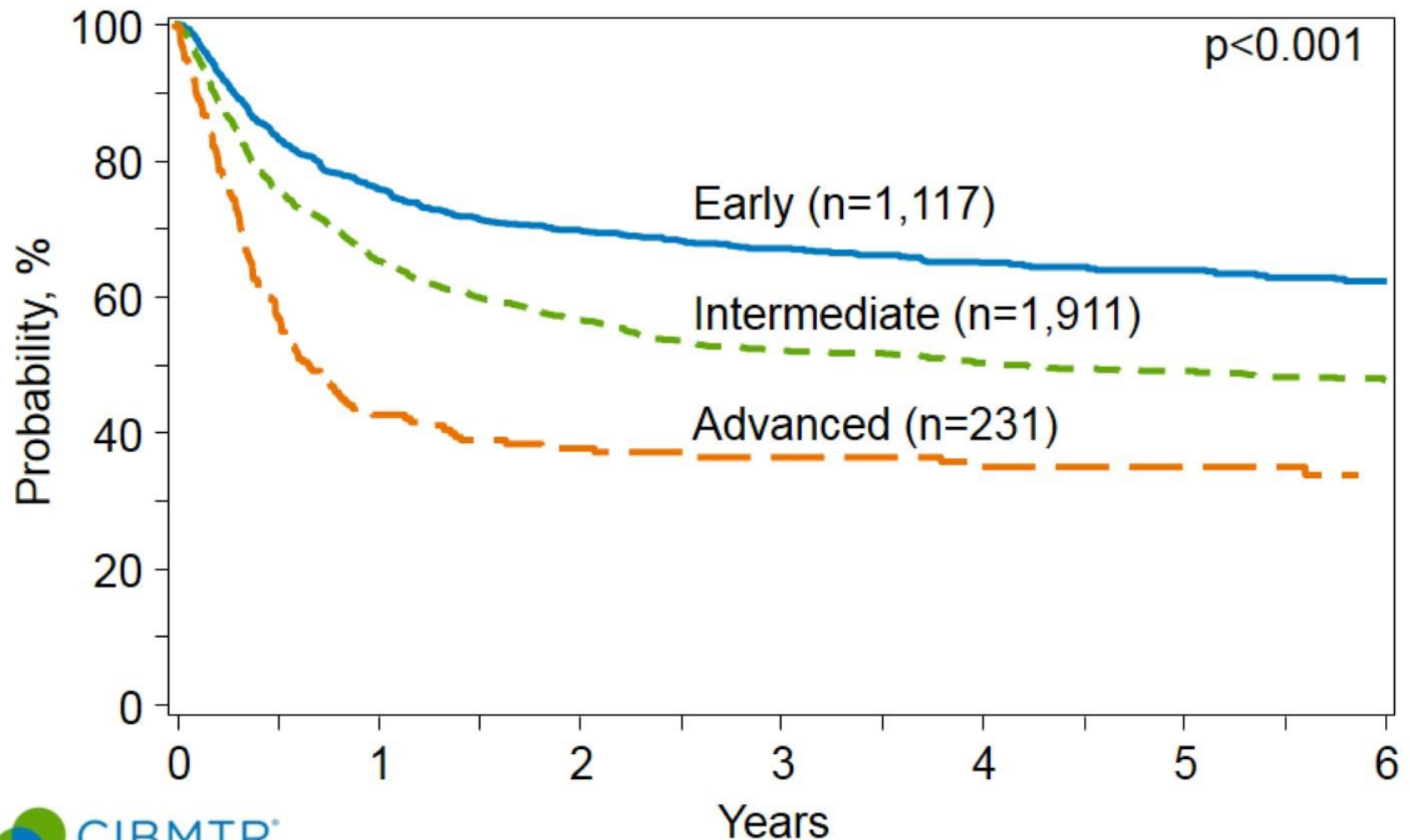


Survival after Allogeneic Transplants for Myelodysplastic Syndrome (MDS), 2003-2013

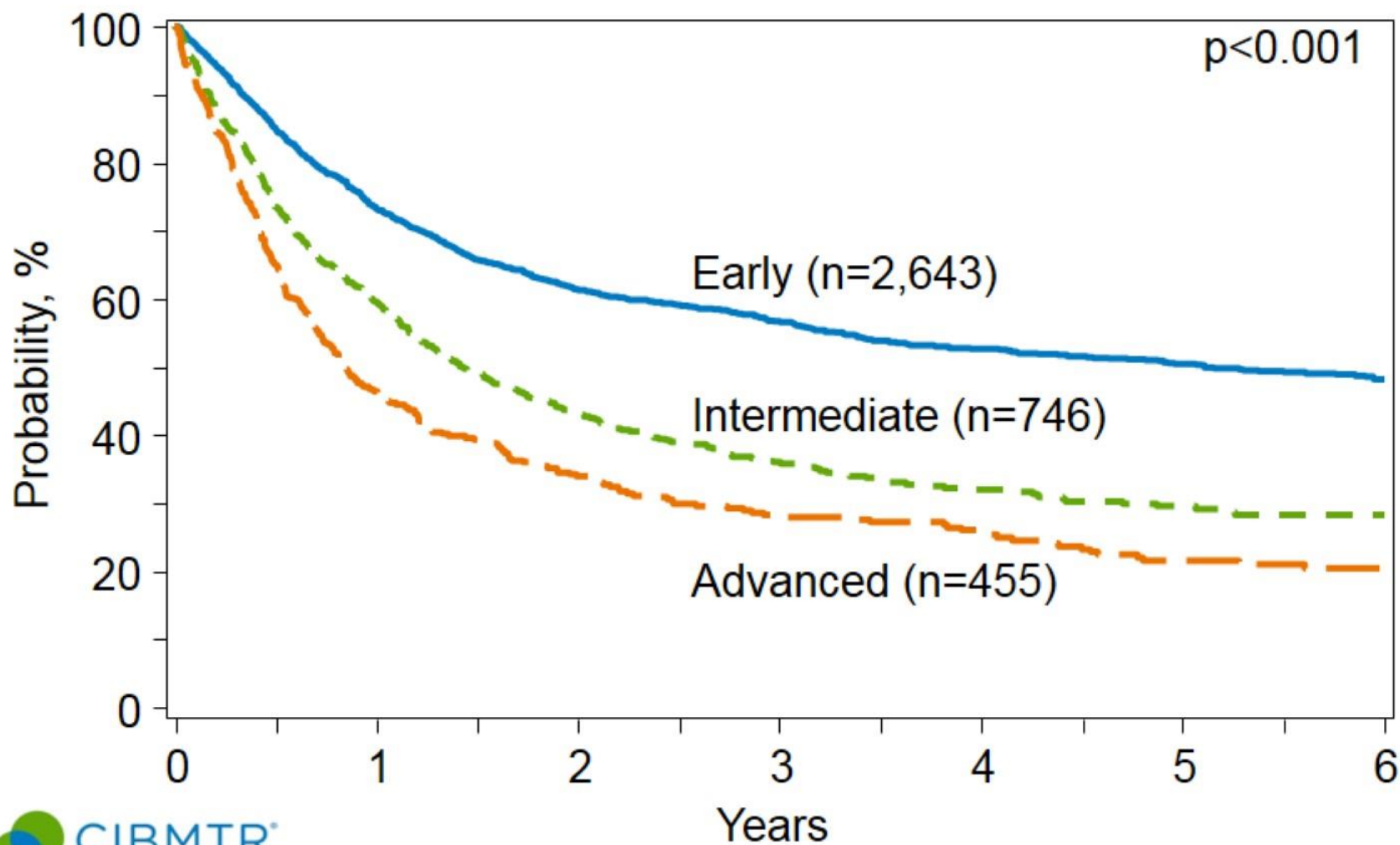


YAŞ

Survival after Unrelated Donor Transplants for ALL, Age <20 years, 2003-2013



Survival after HLA Match Sibling Donor Transplants for ALL, Age ≥ 20 Years, 2003-2013



DOKU UYUMU

GvHD-Risk Faktörleri

Donör	Konak
HLA uyumu (akraba/akraba dışı)	Yaş
Cinsiyet uyumsuzluğu (♀ → ♂)	Hazırlık rejimi
Alloimmunizasyon (parite/transfüzyonlar)	GvHD proflaksisi
Kök hücre kaynağı (PBSC > BM > CB)	CMV, mikrobiyal çevre
NK-hücre alloreaktivitesi	Genetik yatkınlık

HLA uyumu-akut GVHD

Table 97-9 Incidence of Grades III-IV Acute Graft-Versus-Host Disease According to Number of Mismatched Class I HLA-A, -B, and -C and Class II DRB1, DQB1 Alleles

Number of Mismatches	0 Class I	1 Class I	≥2 Class I
0 Class II	77/237 (32%)	28/94 (30%)	21/59 (36%)
1 Class II	13/29 (45%)	4/14 (29%)	11/20 (55%)
≥2 Class II	6/9 (67%)	2/3 (67%)	6/7 (86%)

This summary is restricted to 472 patients who underwent myeloablative conditioning and unrelated bone marrow transplantation for the treatment of chronic myeloid leukemia. The number of mismatched class I and class II alleles is displayed so that the effect of increasing numbers of class I alleles on graft-versus-host disease incidence can be viewed within a fixed number of class II mismatches. Similarly, the effect of increasing numbers of class II mismatches can be compared within a fixed number of class I mismatches (E. Petersdorf, unpublished).

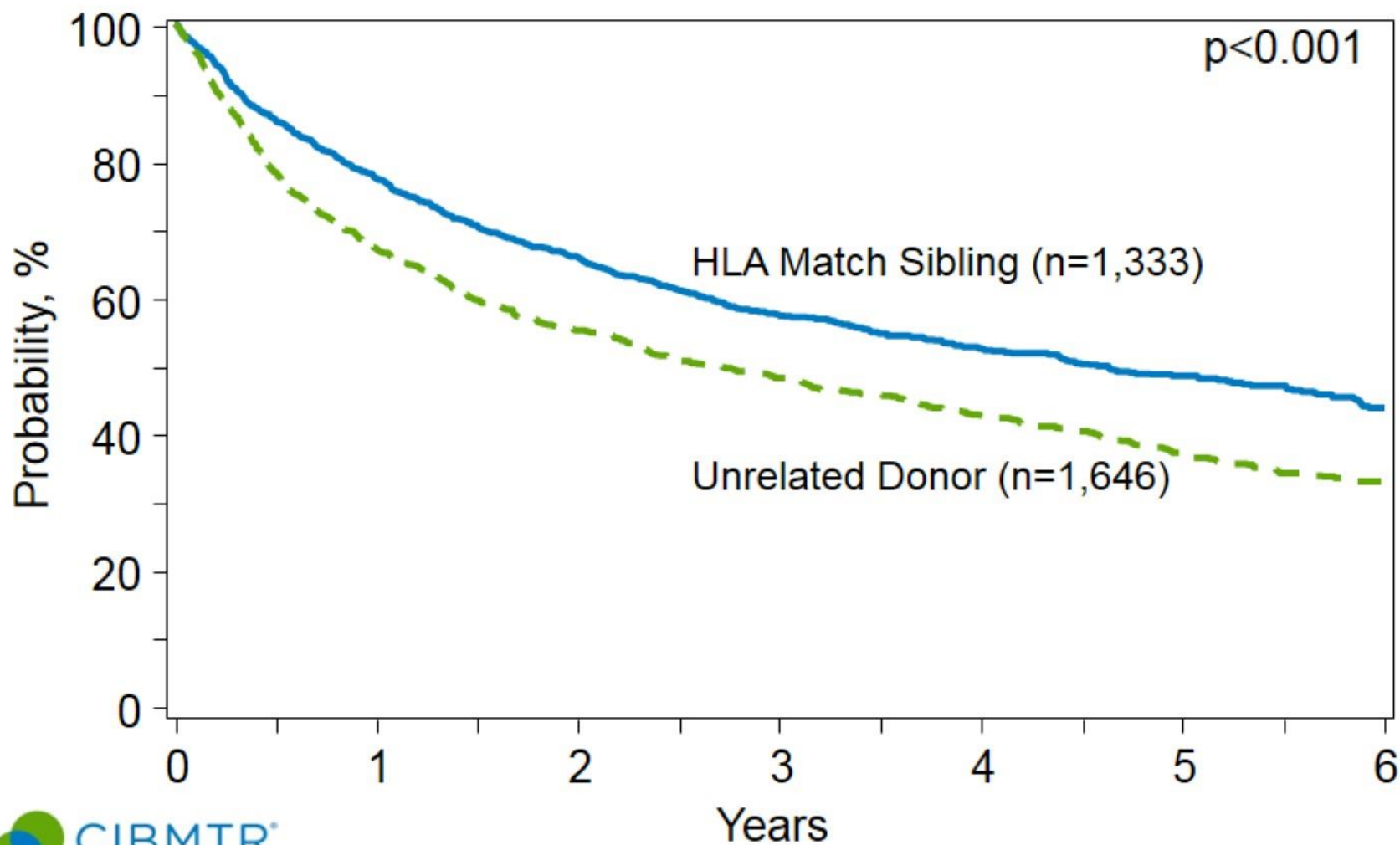
HLA uyumu-mortalite

Table 97-10 Hazard Ratio for Mortality According to Class I HLA-A, -B, and -C and Class II DRB1, DQB1 Match Status

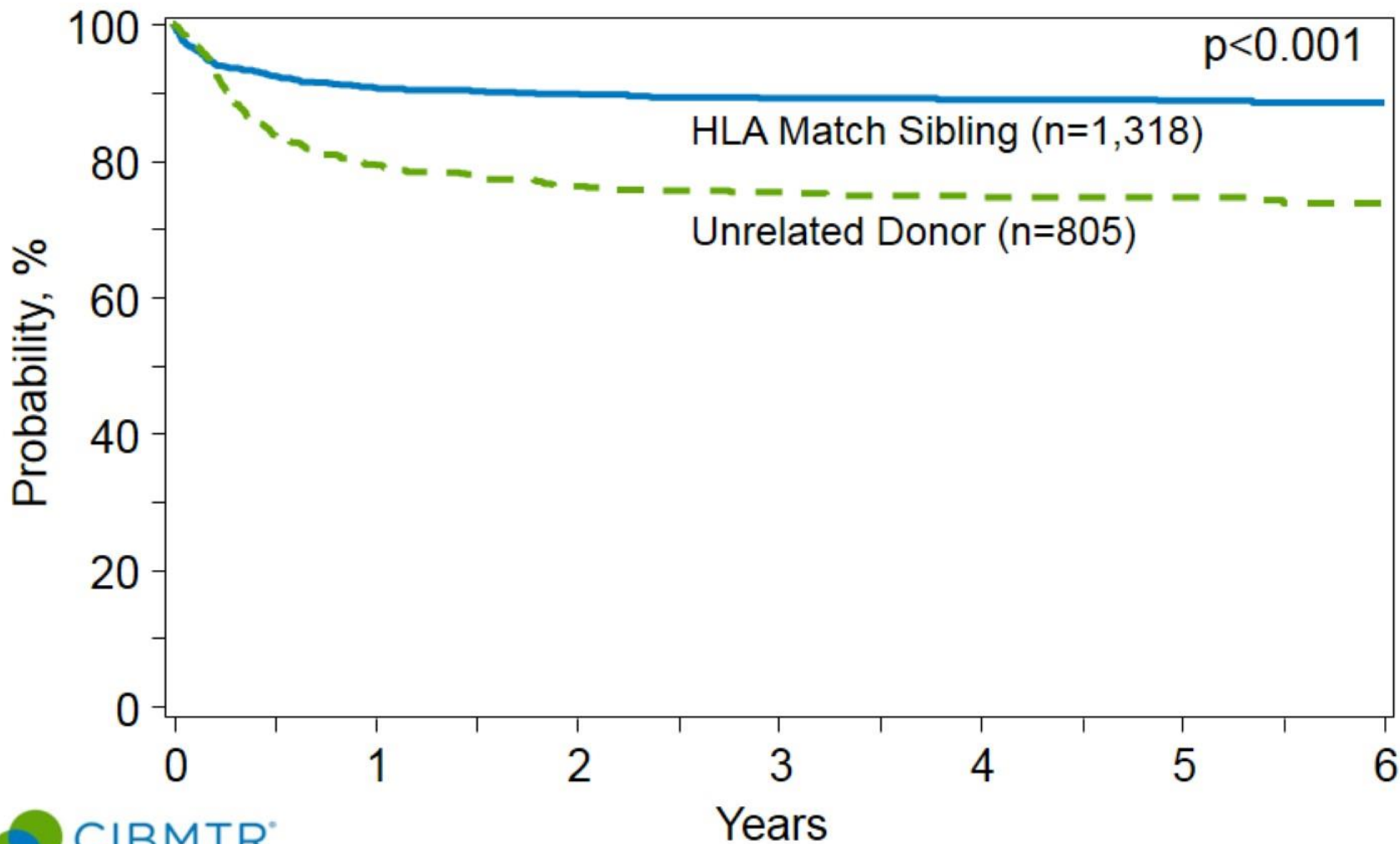
Number of Mismatches	0 Class I	1 Class I	≥2 Class I
0 Class II	1 (n = 231)	1.4 (n = 96)	1.9 (n = 64)
1 Class II	1.1 (n = 33)	3.0 (n = 12)	1.8 (n = 23)
≥2 Class II	1.5 (n = 9)	4.3 (n = 3)	4.4 (n = 7)

This study population is identical to that described in Table 97-9 with the exception that availability of acute graft-versus-host disease grading information was not required for evaluation of mortality. Hazard ratios reflect adjustments for stage of disease, age at transplant, time from diagnosis to transplant, and use of cytomegalovirus and fungal prophylaxis (E. Petersdorf, unpublished).

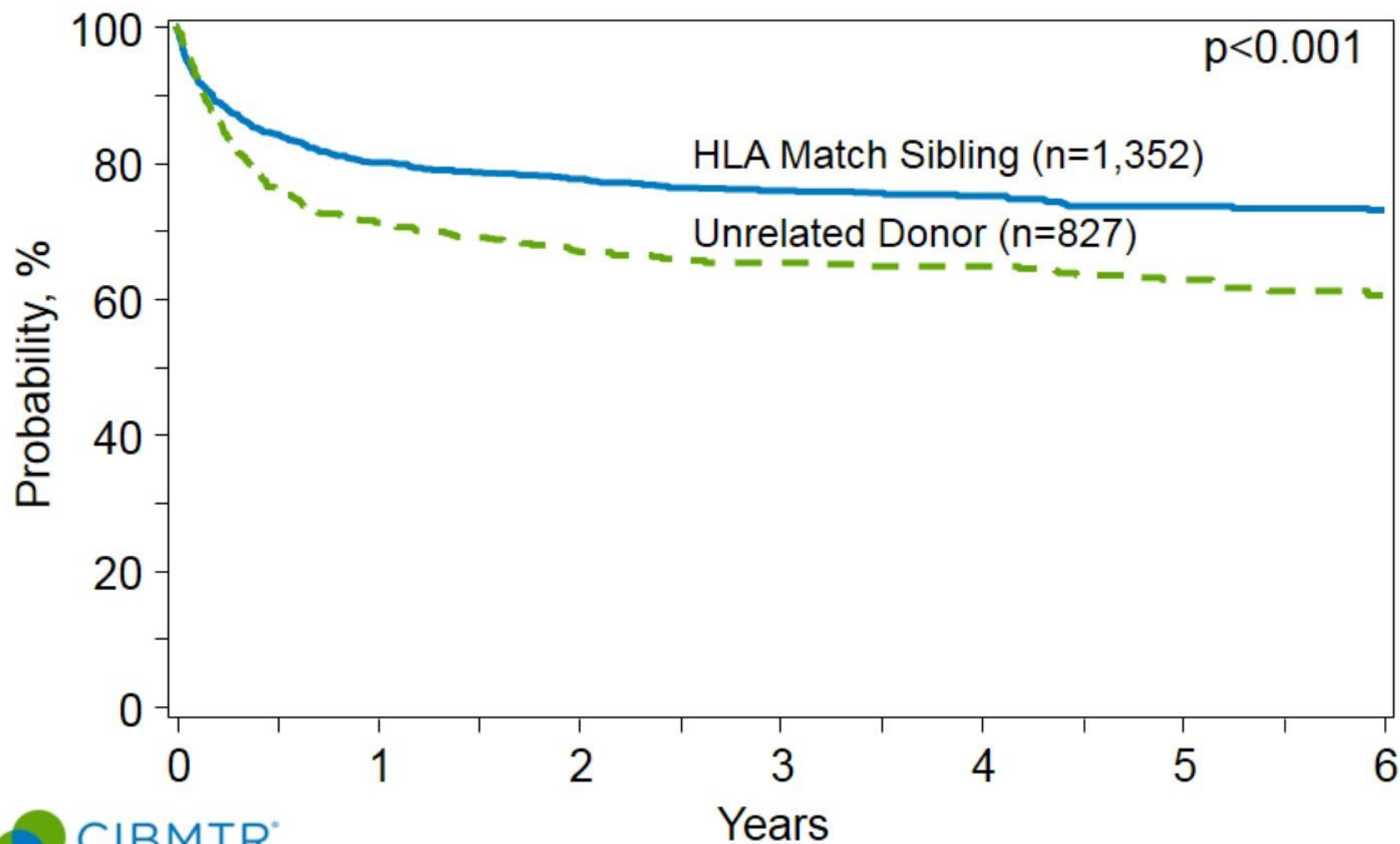
Survival after Allogeneic Transplants for Chronic Lymphocytic Leukemia (CLL), 2003-2013



Survival after Allogeneic Transplants for Severe Aplastic Anemia, <20 Years, 2003-2013

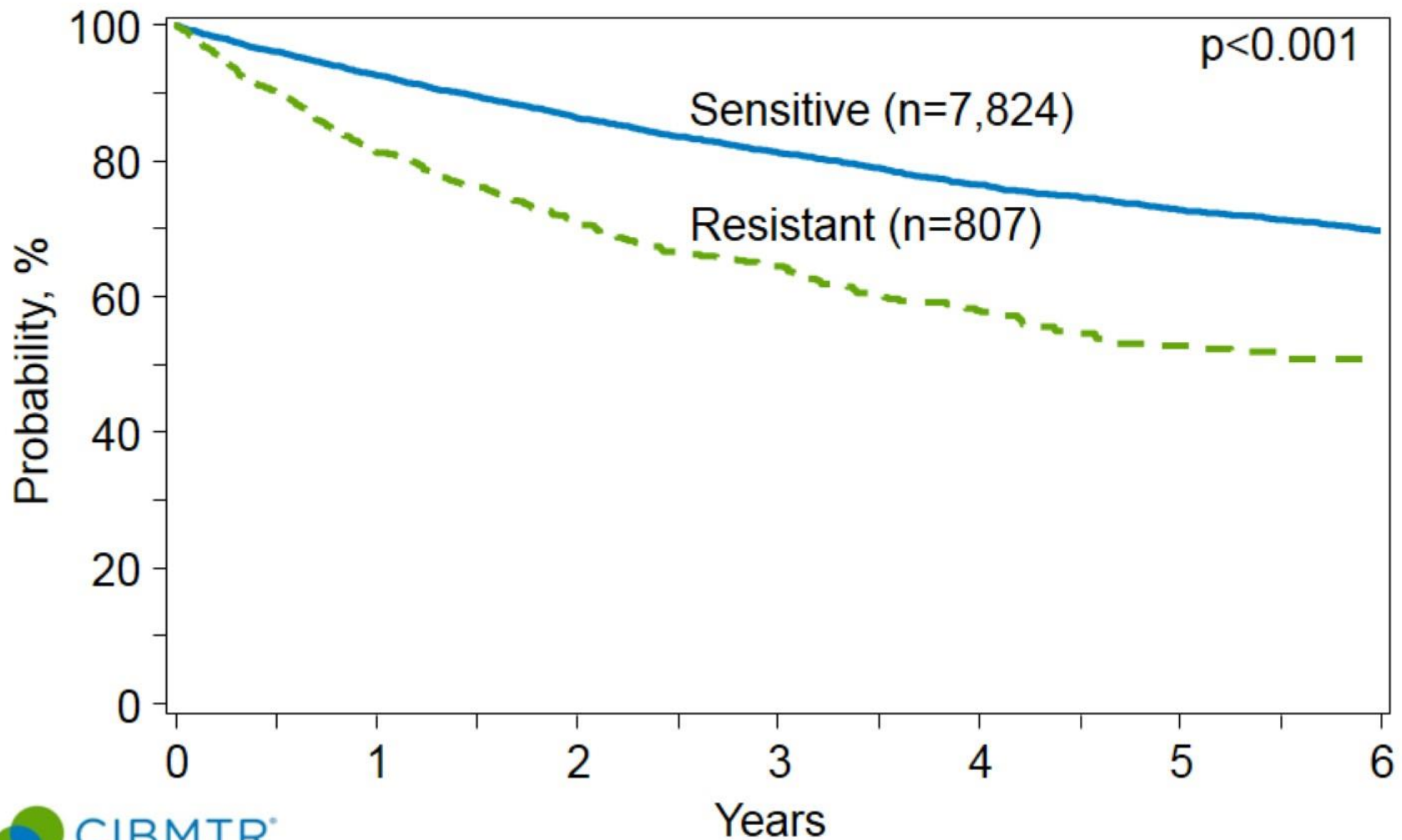


Survival after Allogeneic Transplants for Severe Aplastic Anemia, ≥ 20 Years, 2003-2013

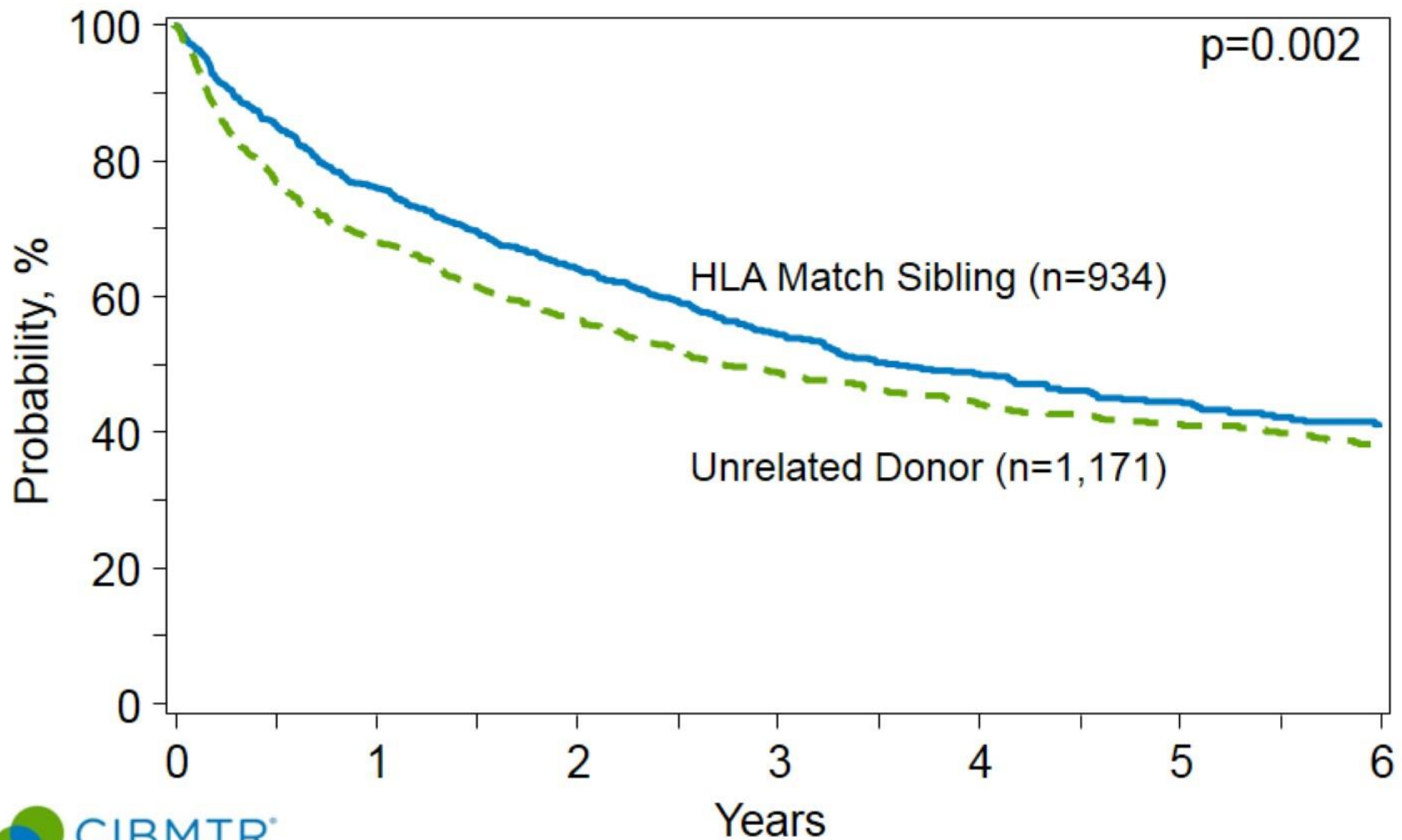


KEMOSENSITIVITE

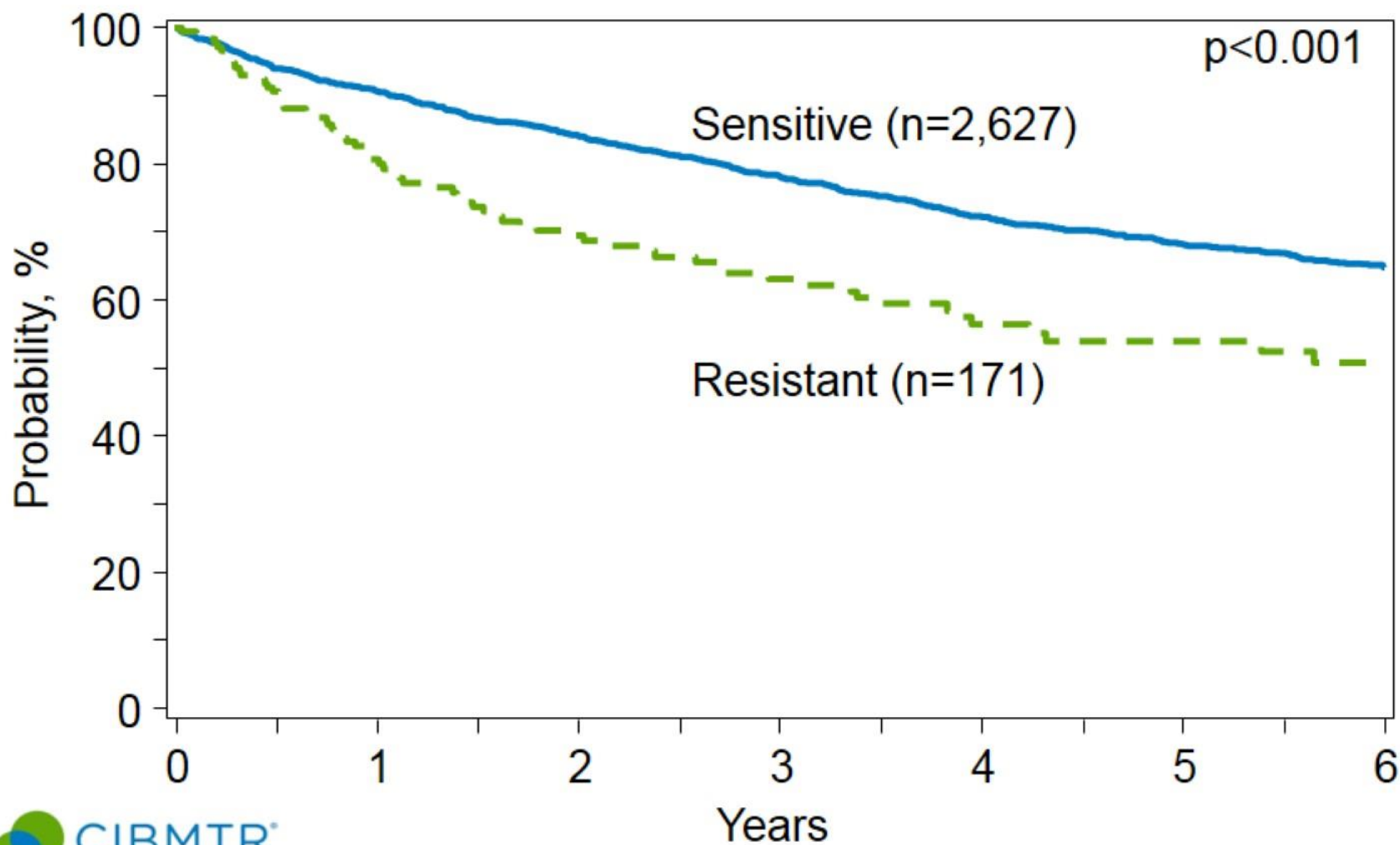
Survival after Autologous Transplants for Hodgkin Lymphoma, 2003-2013



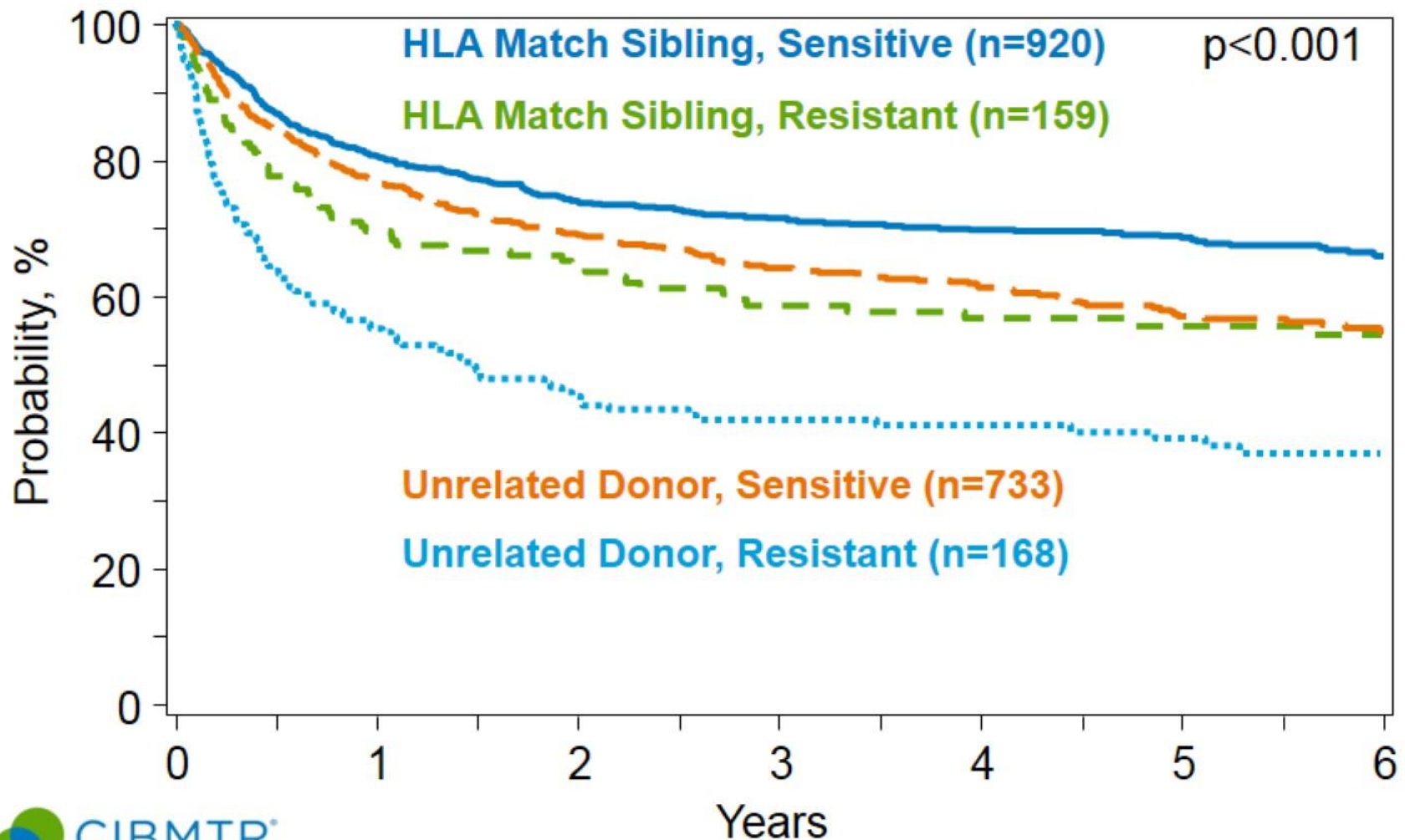
Survival after Allogeneic Transplants for Hodgkin Lymphoma, 2003-2013



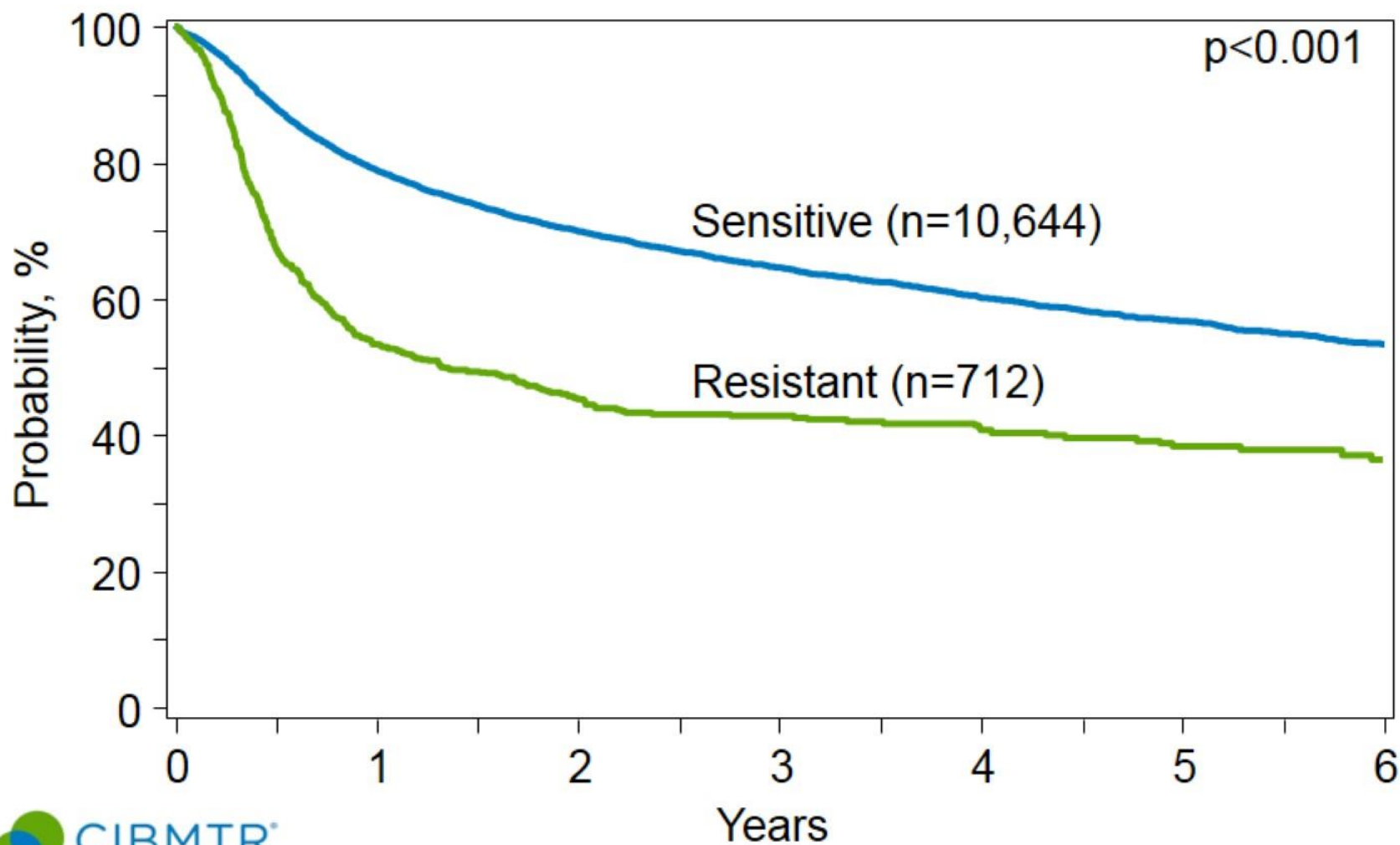
Survival after Autologous Transplants for Follicular Lymphoma, 2003-2013



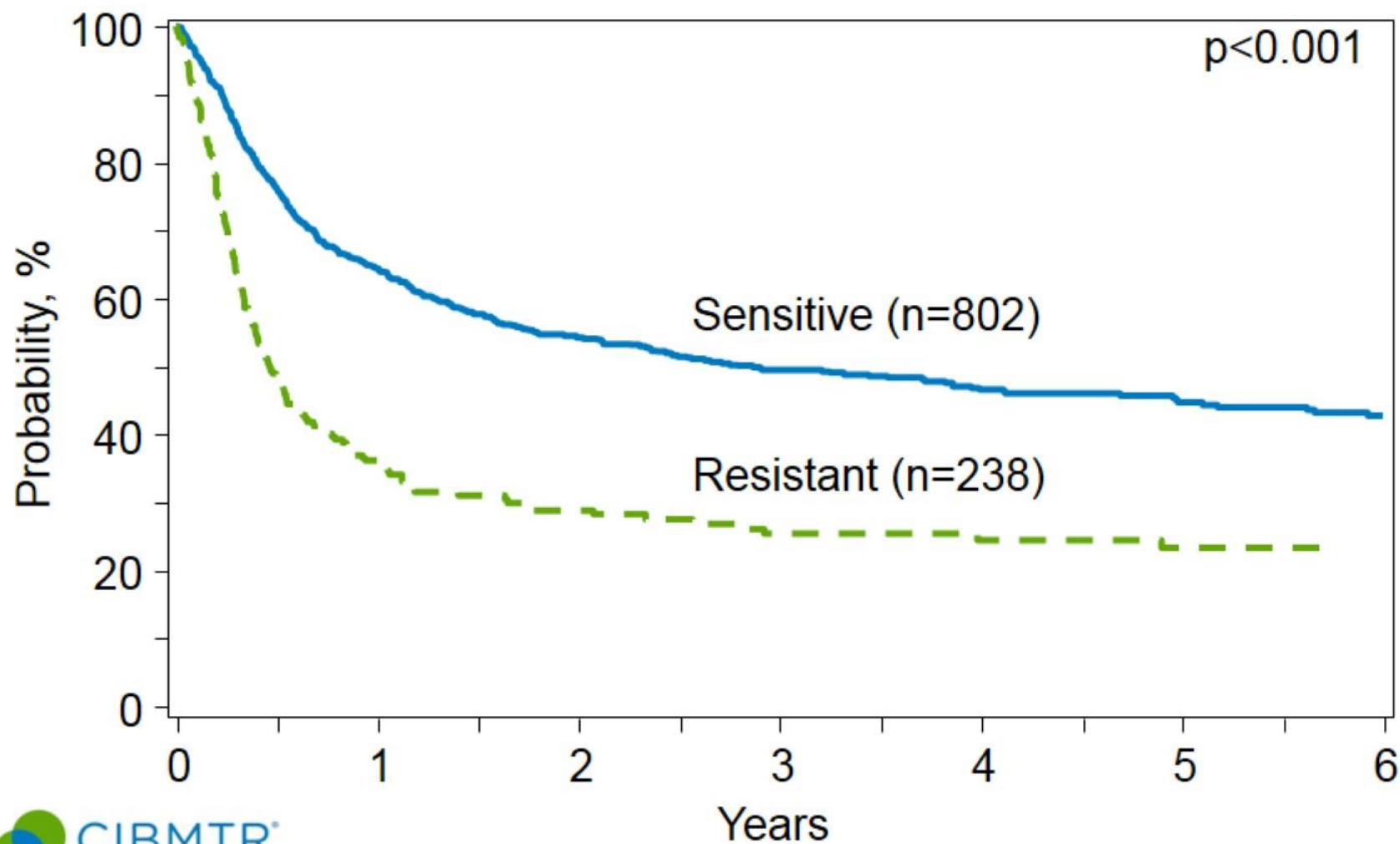
Survival after Allogeneic Transplants for Follicular Lymphoma, 2003-2013



Survival after Autologous Transplants for Diffuse Large B-cell Lymphoma (DLBCL), 2003-2013

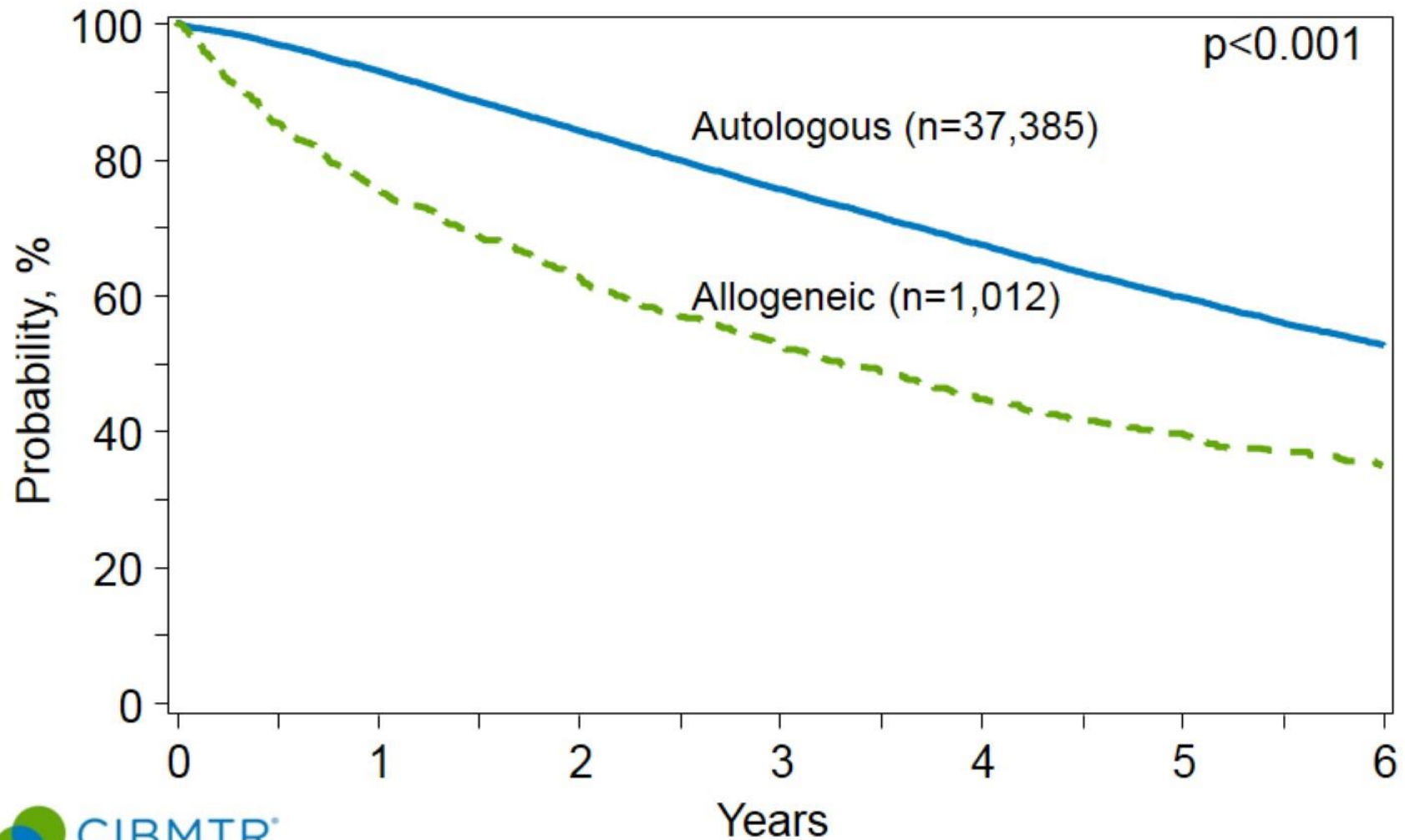


Survival after HLA Match Sibling Transplants for Diffuse Large B-cell Lymphoma (DLBCL), 2003-2013

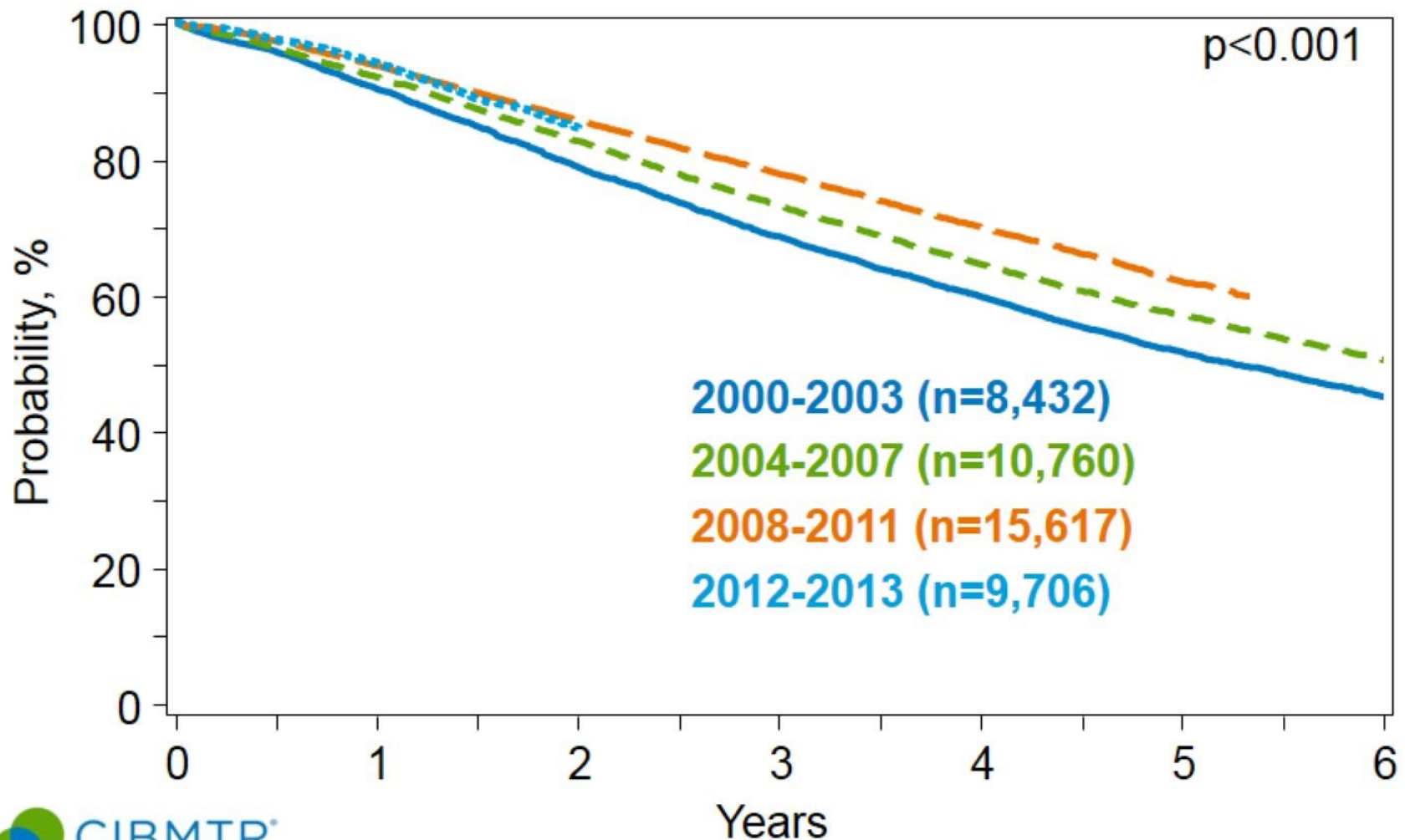


TRANSPLANT DÖNEMİ-TİPİ

Survival after Transplants for Multiple Myeloma, 2003-2013



Survival after Autologous Transplants for Multiple Myeloma, 2000-2013



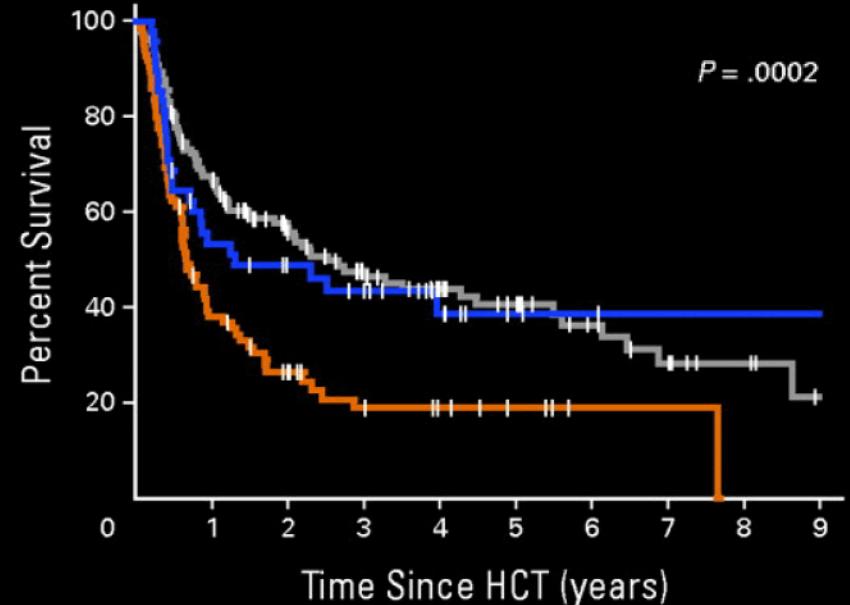
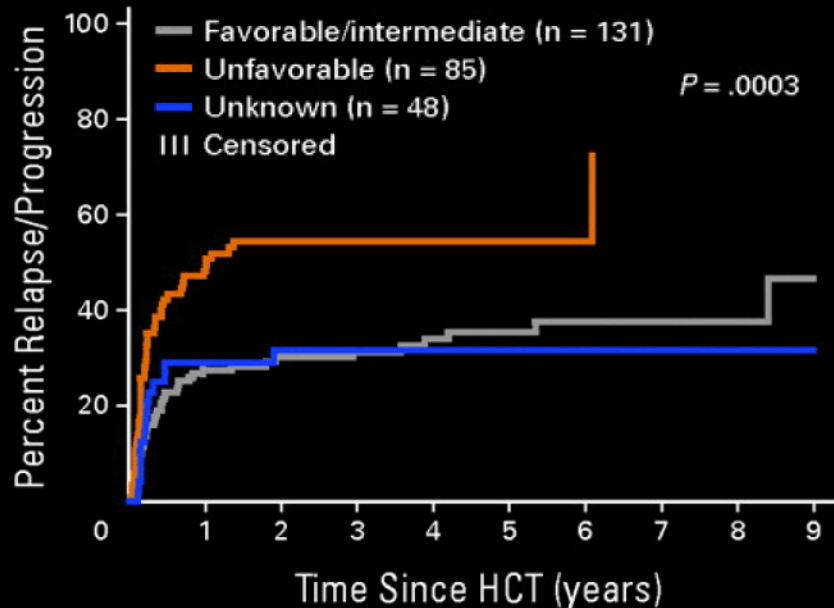
SİTOGENETİK-MOLEKÜLER GENETİK

Sitogenetik

Patients = 274
Median age = 60 years

Relapse/progression

Overall survival

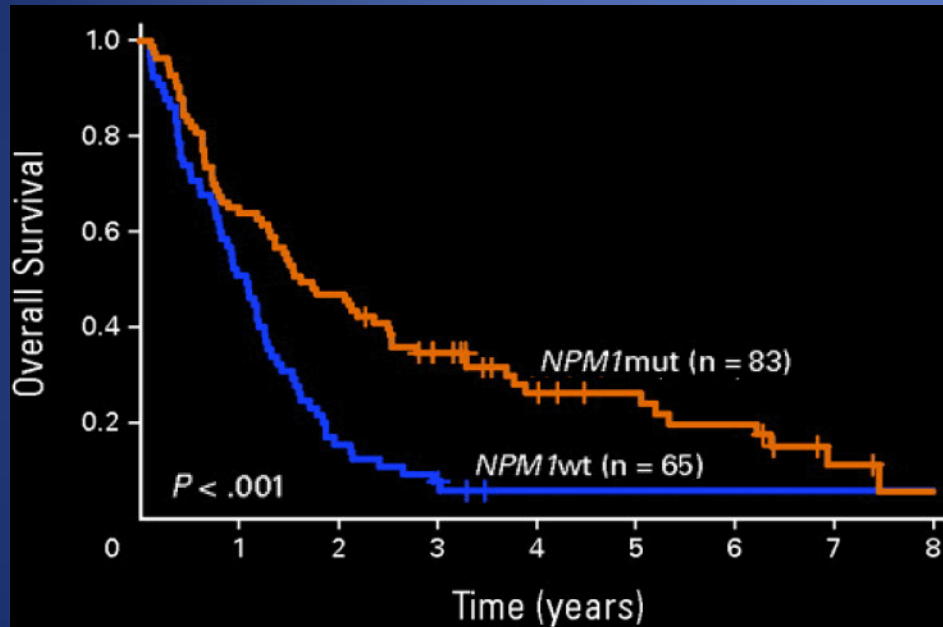


Gyurkocza B et al. JCO 2010;28:2859-2867

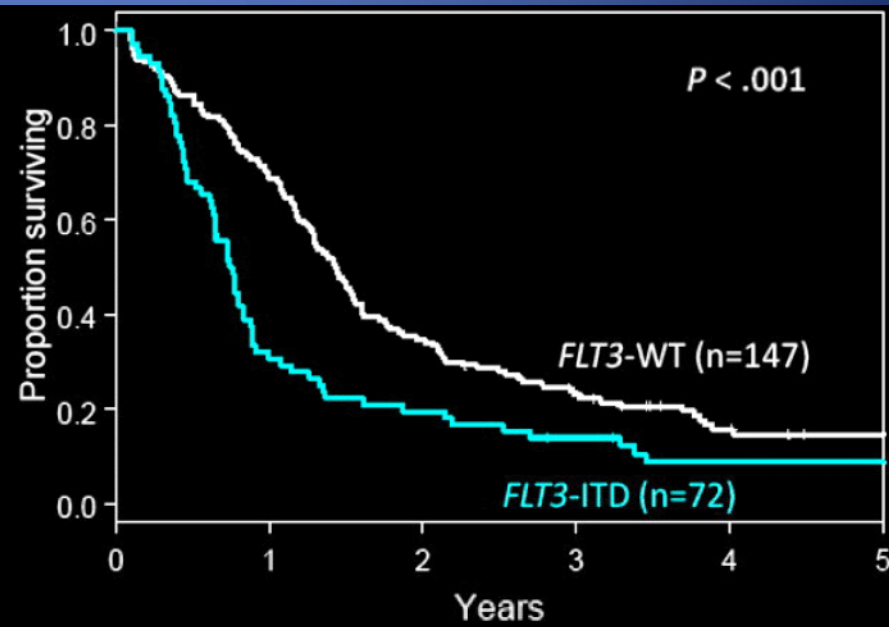
Moleküler Belirteçler

CLGB çalışmaları-yaşlı hastalar

Nucleophosmin geni
(NPM-1)



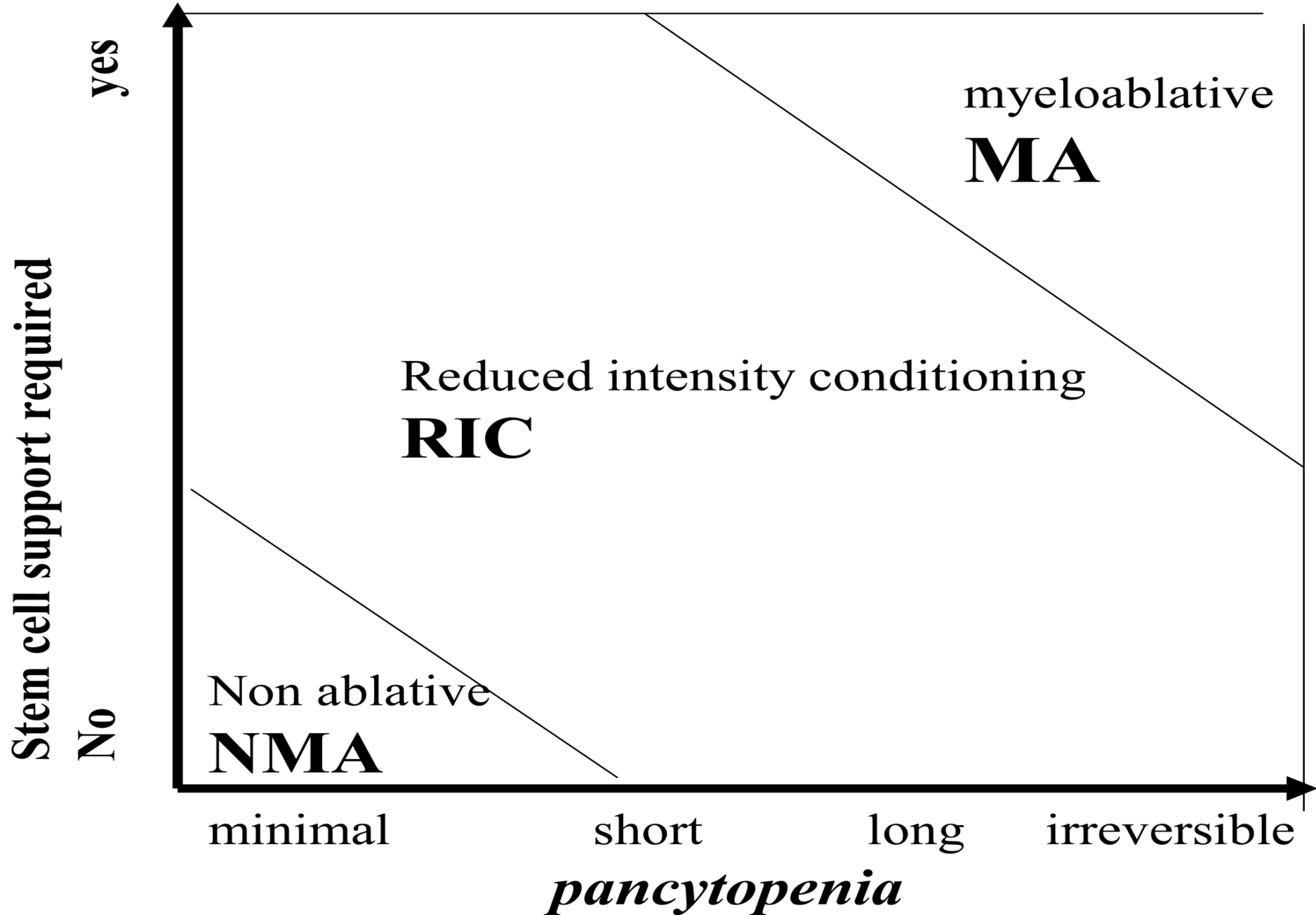
FMS-like tyrosine kinase geni
(FLT3 ITD)



Becker H et al. JCO 2010;28:596-604

Whitman S P et al. Blood 2010;116:3622-26

HAZIRLAMA REJİMLERİ



UCB HKHN: MAC vs RIC

- Erişkin ALL; UCB-HKHN; retrospektif; 1996-2011
- Ph+ALL (n: 433); Ph-ALL (n: 115)
- Medyan yaş: 33 (18-66)
- Anormal karyotip: %76
- dUCBT: %43
- Medyan TNC dozu: $4.02 \times 10^7/\text{kg}$
- Sonuçlar: Ph+ALL ile Ph-ALL farksız

	MAC-CR1 (n:107)	MAC-CR2 (n:70)	RIC-CR1 (n:49)	RIC-CR2 (n:24)
İZLEM (ay)	26	35	31	34
NRM (%; 2 yıl)	41	49	22	17
Relaps (%; 2 yıl)	24	22	30	47
LFS (%; 2 yıl)	35	30	49	36
aGvHD (%)	43	37		

Multivaryant analizde LFS üzerine etkili faktörler:

- yaş < 44 (HR: 0.6; p: 0.04)
- transplant sırasında CR1 (HR: 0.6; p: 0.05)
- RIC (HR: 0.6; p: 0.015)

CIBMTR: IV BU vs TBI TEMELLİ MAC

- Prospektif, çok merkezli: AML, KML, MDS
- IV BU (n: 1025) vs TBI (n:458)

SONUÇ	N	HR	P
OS	1439	0.82	0.026
TRM	1434	0.81	0.15
RELAPS	1434	0.93	0.43

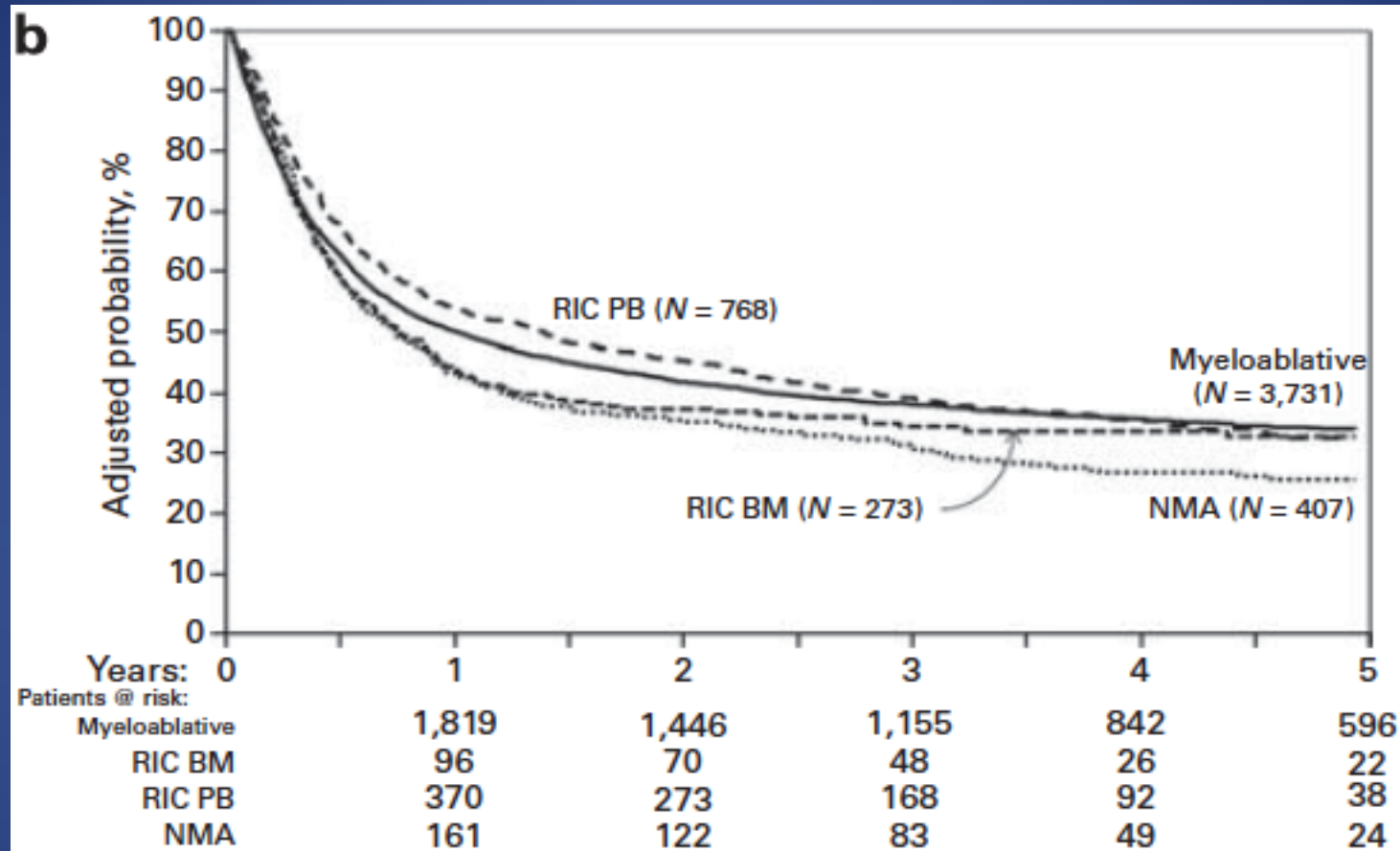
TBI ile karşılaştırıldığında;

- IV BU ile genel sağkalım artar
- Relaps veya TRM değişmez
- Engrafman, grade II-IV aGvHD ve kronik GvHD benzer

AML/MDS: MAC vs RIC/NMA

- CIBMTR
- AML/MDS
- MAC (n. 3731); RIC/NMA (n: 1448)
- Retrospektif
- 1997-2004

CIBMTR: GENEL SAĞKALIM



- 5 yıllık sağkalım: MAC (%34); RIC (%33); NMA (%26)
- Sağkalım: MAC = RIC > NMA

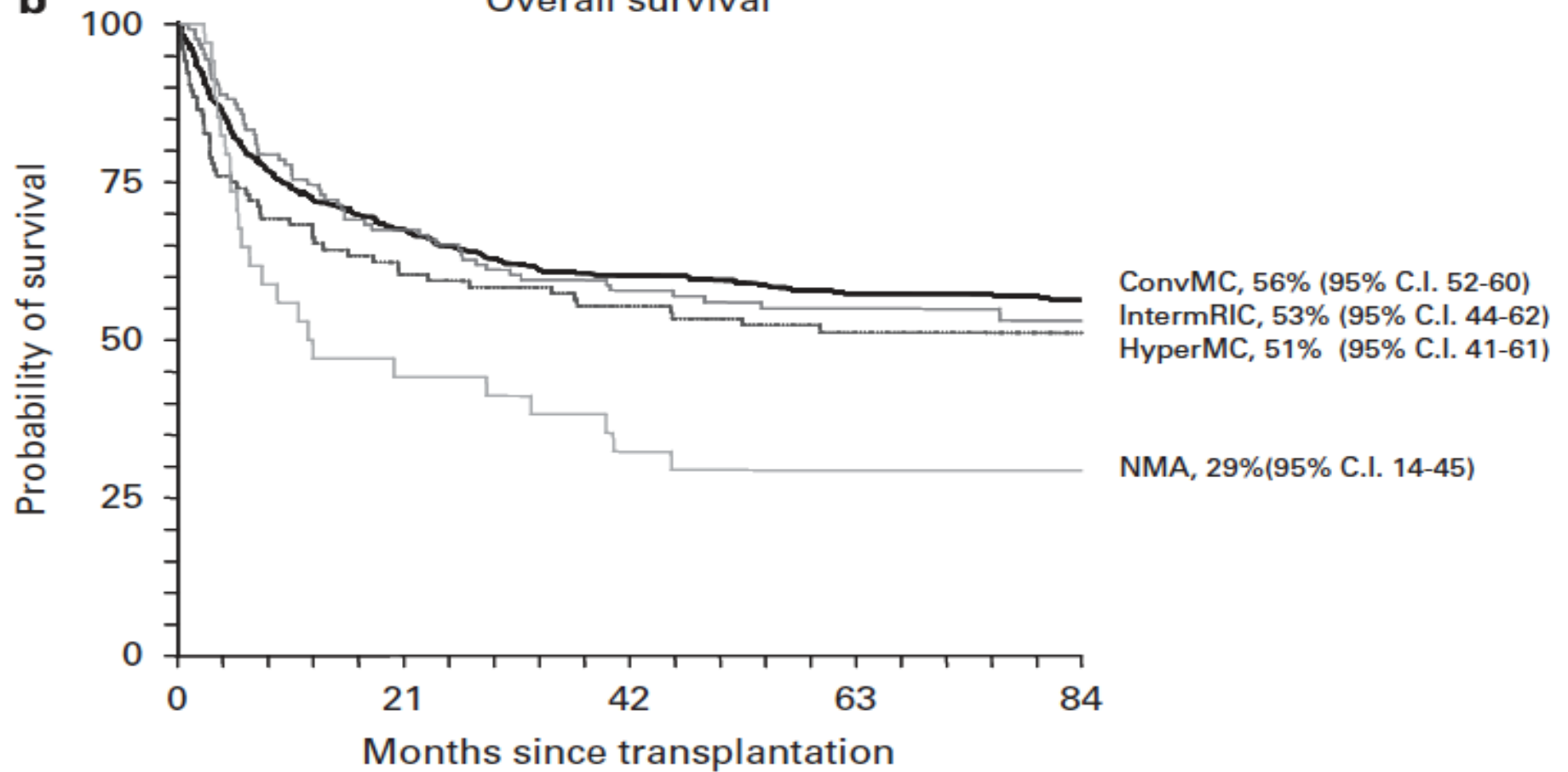
AML/MDS: MAC vs RIC/NMA

- EBMT
- AML/MDS: < %10 BLAST
- HLA TAM UYUMLU KARDEŞ
- MAC_{konvansiyonel}; MAC_{yoğun}; RIC, NMA
- n: 878
- Retrospektif
- 1998-2004

EBMT ÇALIŞMASINDA TANIMLAR

TANIM	REJİM
MAC _{konvansiyonel}	Yüksek doz-tek ajan (Cy, Etoposid, Tiotepa, Mel, Ida, AraC) + TBI (>10 Gy)
MAC _{yoğun}	Bu-Cy
RIC	Flu + Bu (< 9 mg/kg) Flu-Mel Flu + Cy veya thiotepa veya treosulfan Cy + thiotepa
NMA	Flu + TBI (2 Gy) Flu-Bu ₄

b Overall survival



7 yıllık sağkalım: $MAC_{konvansiyonel} = MAC_{yoğun} = RIC > NMA$

SKORLAMA SİSTEMLERİ

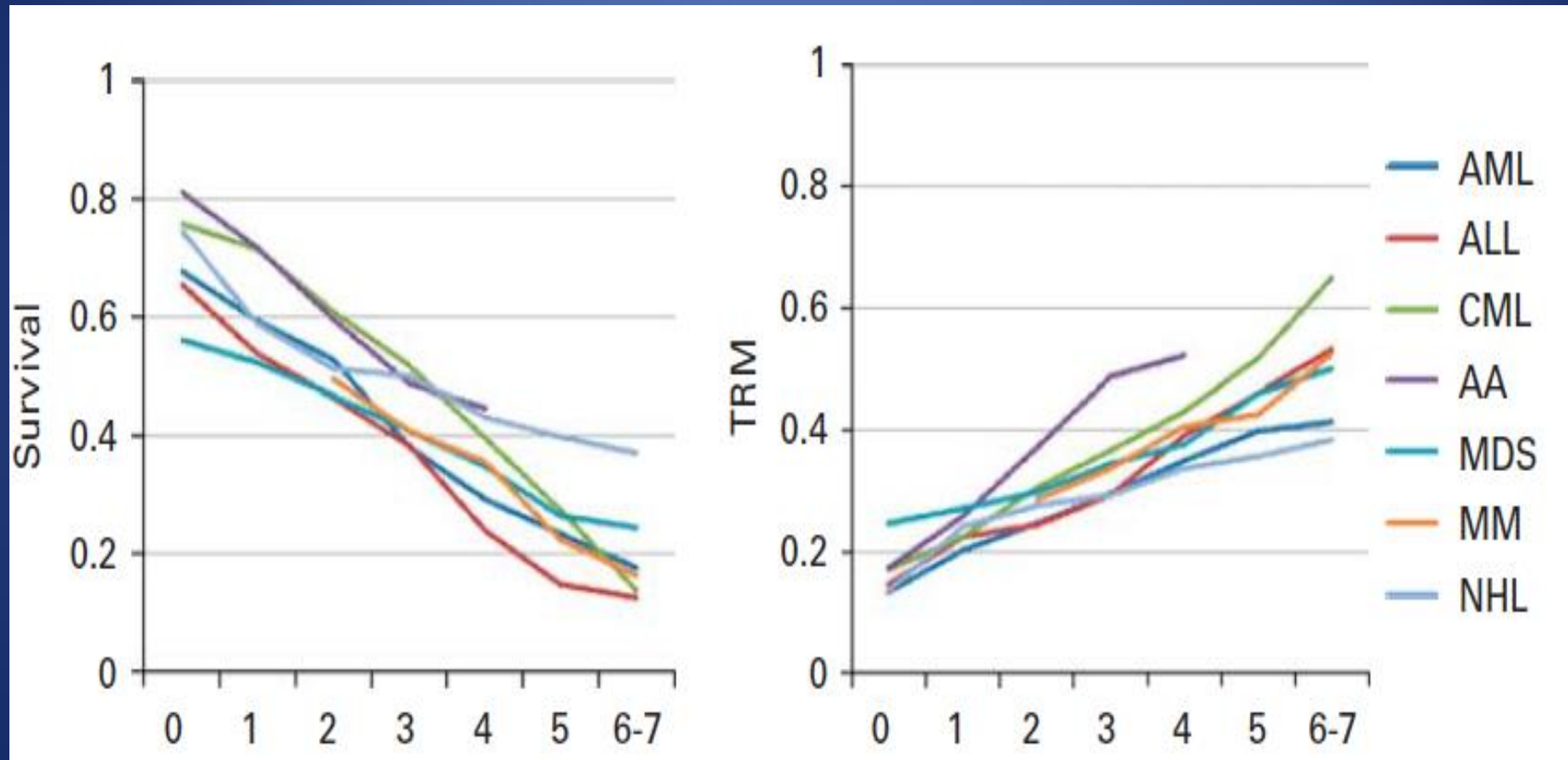
EBMT, HCT-CI, aHCT-CI, DRI

GRATWOHL RİSK SKORU

Risk faktörleri	Puan
Donör uyumu	
HLA-tam uyumlu	0
MUD/HLA-uyumsuz akraba	1
Evre	
Kronik faz	0
Akselere faz	1
Blastik faz	2
Hasta yaşı	
< 20	0
20-40	1
> 40	2
Donör/hasta cinsiyet uyumu	
Kadın donör/erkek hasta	1
Diğer	0
Tanı-transplant arası süre	
< 12 ay	0
≥ 12 ay	1

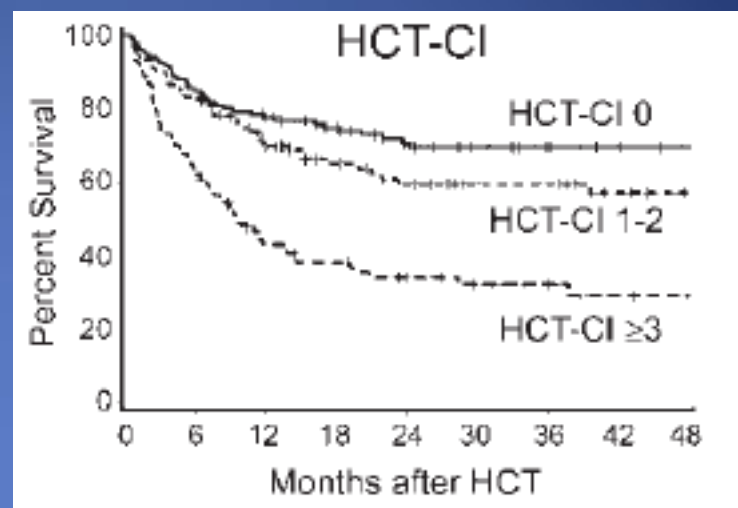
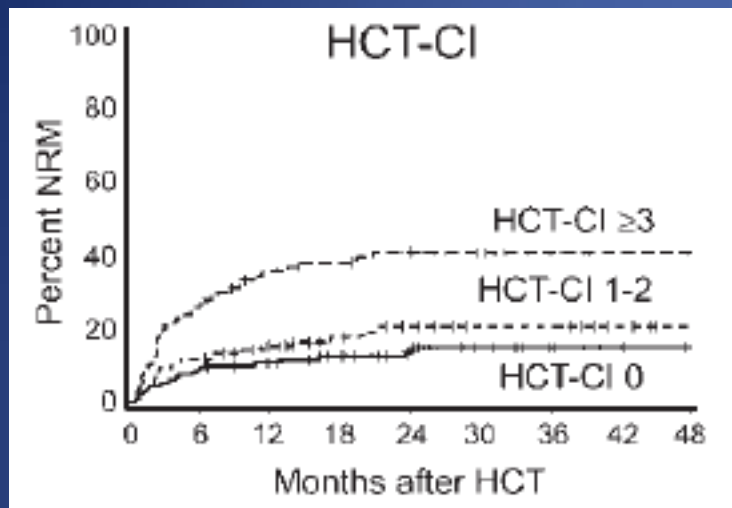
Skor	% Mortalite	% Sağkalım
0	< 25	>70
1	> 25	>60
2	40	50
3-4	>50	< 40
5-7	70-75	< 25

EBMT skoru KML dışında da geçerli!



HCT-CI

Comorbidity	Definitions of comorbidities included in the new HCT-CI	HCT-CI weighted scores
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac‡	Coronary artery disease,§ congestive heart failure, myocardial infarction, or $EF \leq 50\%$	1
Inflammatory bowel disease	Crohn disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance†	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild‡	Chronic hepatitis, bilirubin $> ULN$ to $1.5 \times ULN$, or AST/ALT $> ULN$ to $2.5 \times ULN$	1
Obesity†	Patients with a body mass index $> 35 \text{ kg/m}^2$	1
Infection†	Requiring continuation of antimicrobial treatment after day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal‡	Serum creatinine $> 2 \text{ mg/dL}$, on dialysis, or prior renal transplantation	2
Moderate pulmonary‡	DLco and/or FEV_1 66%-80% or dyspnea on slight activity	2
Prior solid tumor‡	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Severe pulmonary‡	DLco and/or $FEV_1 \leq 65\%$ or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic‡	Liver cirrhosis, bilirubin $> 1.5 \times ULN$, or AST/ALT $> 2.5 \times ULN$	3



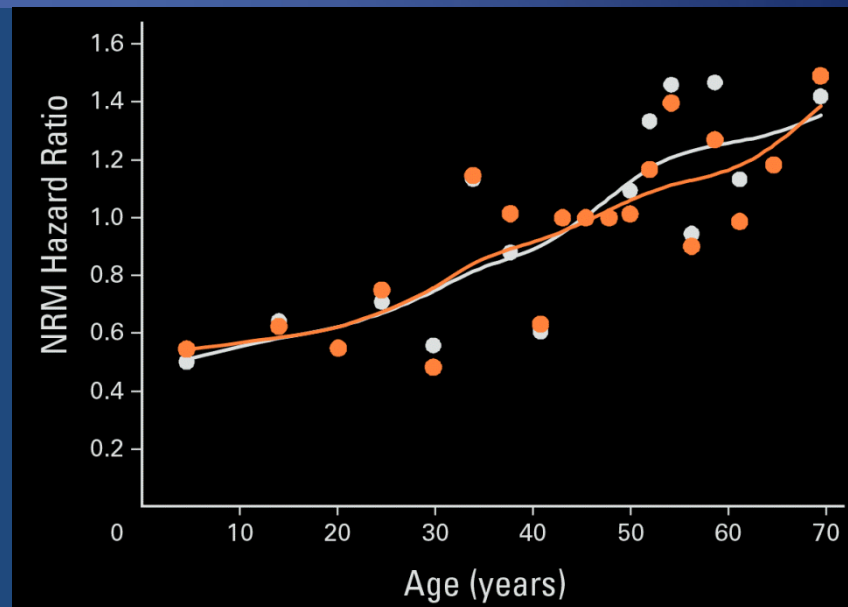
HCT-CI	NRM (2 yil)	OS (2 yil)
0	14	71
1-2	21	60
≥ 3	41	34

Could Age be Incorporated into the HCT-CI?

Training set, (n) = 1853

NRM

Age, yrs	HR	<i>p</i>
≤19	1.0	
20-39	1.21	0.29
40-49	1.48	0.04
50-59	1.75	0.004
≥60	1.84	0.005



Age ≥ 40 years = score of 1

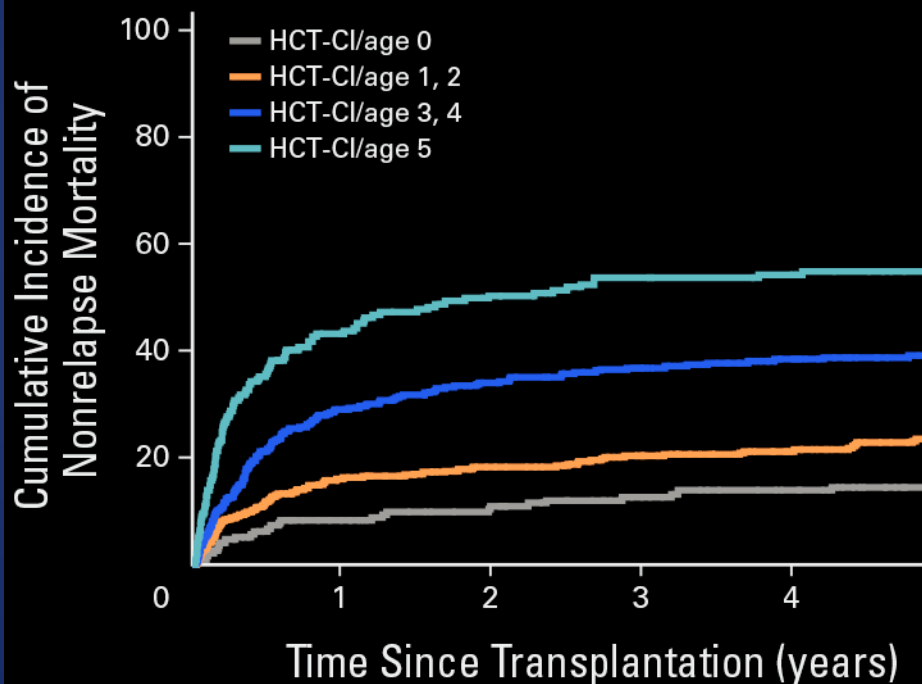
Adjusted for HCT-CI scores, diagnoses, disease status, CMV sero-status, KPS, prior regimens, conditioning intensity, ATG, donor type, and stem cell source.

The HCT-CI/Age Composite Index

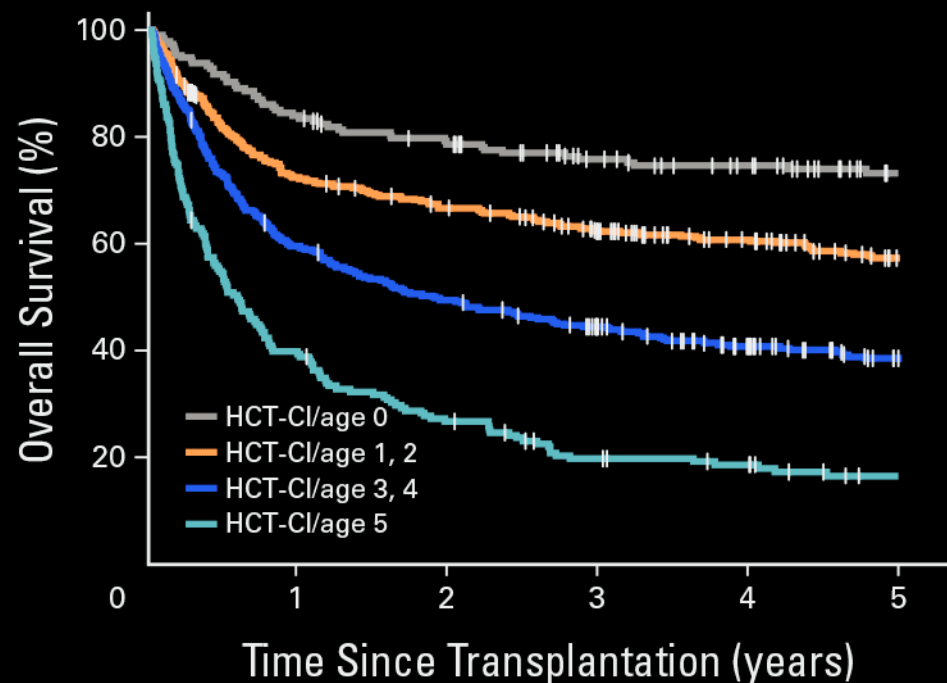
	Score
Age ≥ 40 years	1
Arrhythmia	1
Cardiac	1
Inflammatory bowel	1
Diabetes	1
Cerebro-vascular	1
Depression/anxiety	1
Hepatic-mild	1
Morbid obesity	1
Infection	1
Rheumatologic	2
Peptic ulcer	2
Renal-moderate/severe	2
Pulmonary-moderate	2
Prior Solid tumor	3
Heart Valve disease	3
Pulmonary-severe	3
Hepatic-moderate/severe	3

Validation of The Composite Comorbidity/Age Index

NRM



Overall Survival

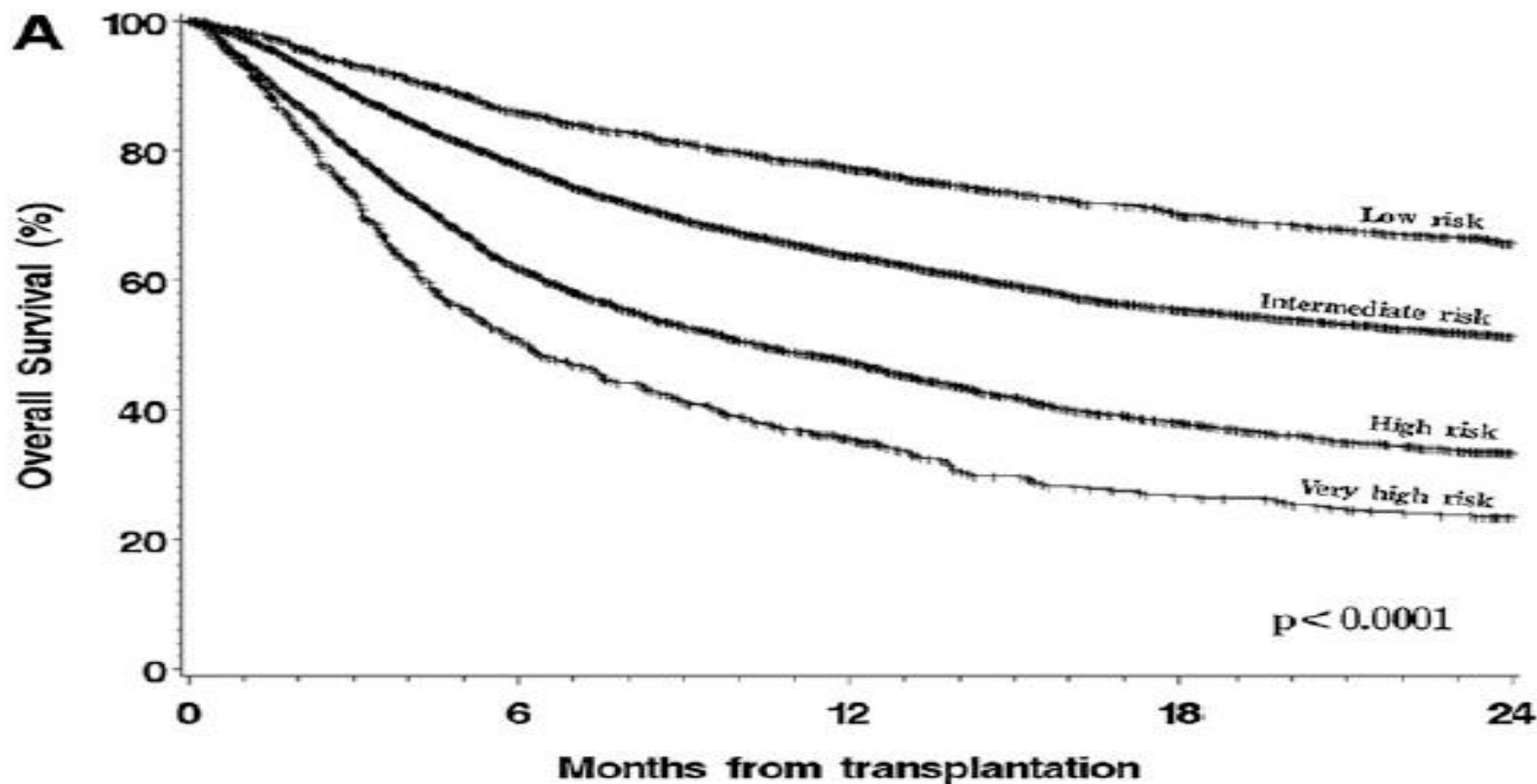


HASTALIK-EVRE	RİSK GRUBU
HL (CR) KLL (CR) Mantle hücreli NHL (CR) Indolen NHL (CR) KLL (PR) KML 1. veya 2. kronik faz	düşük
KML ileri evre Mantle hücreli NHL (PR) Myeloproliferatif neoplaziler-tümü AML-orta sitogenetik risk (CR) ALL (CR1) T hücreli NHL (CR/PR) MM (CR/VGPR/PR) Agresif NHL (CR) Düşük risk MDS-orta sitogenetik (erken/ileri evre) Düşük risk MDS-kötü sitogenetik (erken evre) Yüksek risk MDS-orta sitogenetik (erken evre) HL (PR) İndolen NHL (ileri evre) KLL (ileri evre) Agresif NHL (PR)	orta
T hücreli NHL (ileri evre) AML-iyi sitogenetik (ileri evre) HL (ileri evre) Yüksek risk MDS-orta sitogenetik (ileri evre) Yüksek risk MDS-kötü sitogenetik (erken/ileri evre) ALL-CR2/CR3 AML-kötü sitogenetik (CR) Mantle hücreli NHL (ileri evre) BL (CR) MM (ileri evre) Düşük risk MDS-kötü sitogenetik (ileri evre) AML-orta sitogenetik (ileri evre)	yüksek
KML blastik faz ALL (ileri evre) Agresif NHL (ileri evre) AML-kötü sitogenetik (ileri evre) BL (PR) (ileri evre)	çok yüksek

TRANSPLANTATION

Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation

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KÖK HÜCRE DOZU-KAYNAĞI

Kök Hücre Dozu: Otolog

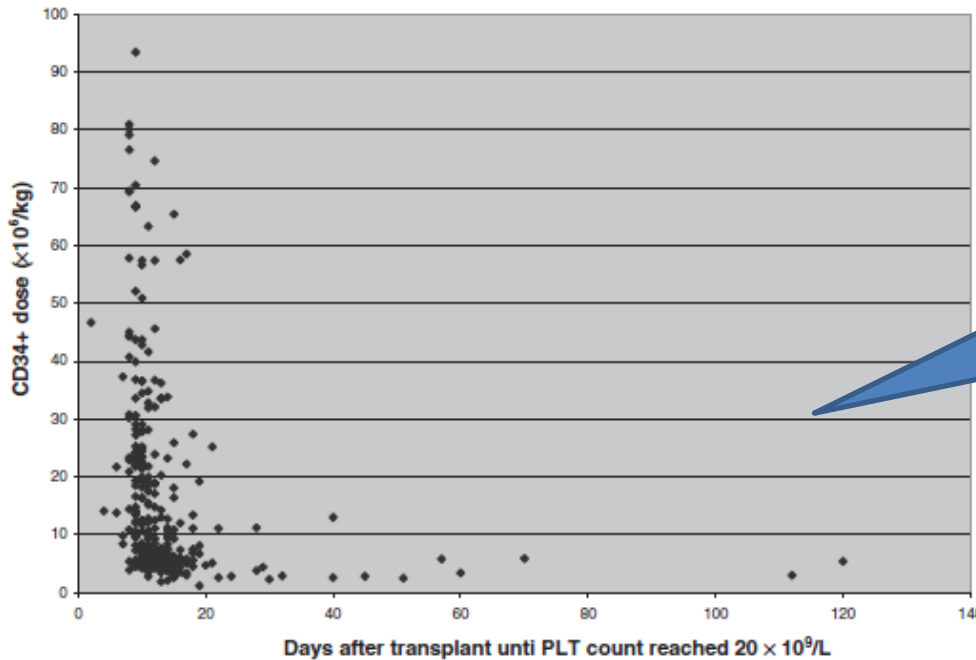
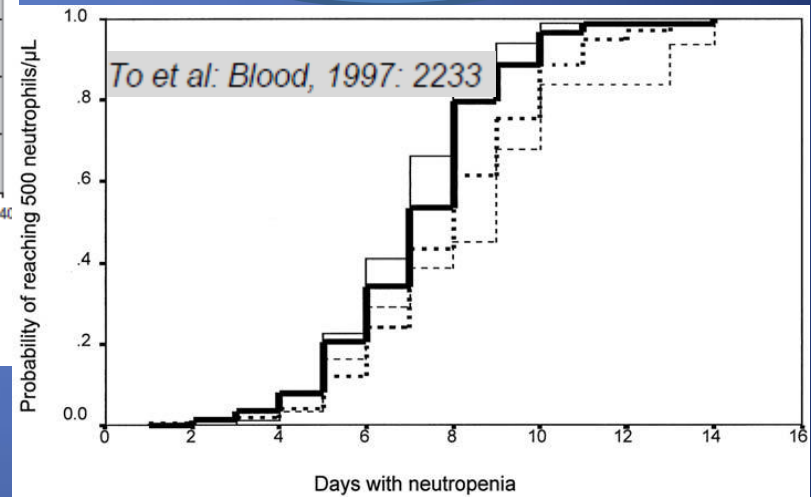


Fig. 2. Relationship between CD34+ dose and days to recovery of PLTs to more than 20×10^9 per L without further need of transfusion.

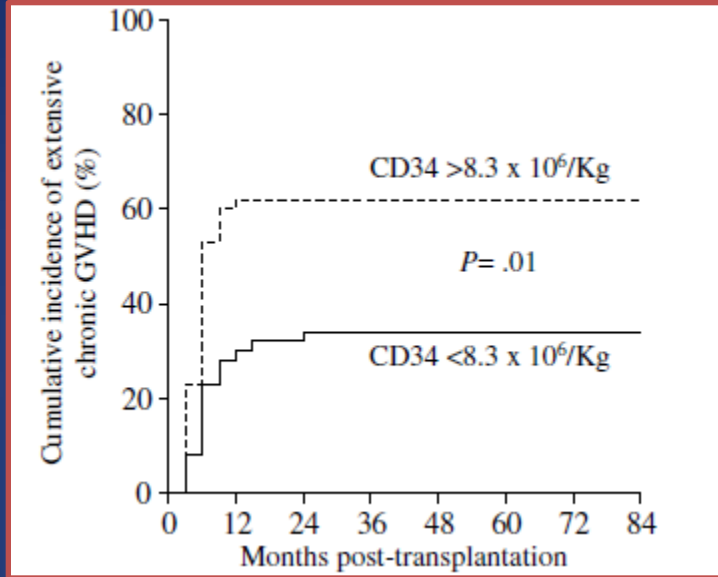
The results of this study show that the median dose of CD34+ cells infused into the recipients of autologous transplants was 8.4×10^6 per kg. It is obvious that a high dose of PBPCs mostly results in very rapid hematologic recovery and a low need for transfusion products.⁵⁻⁷ The

Otolog nakillerde
> 5×10^6 CD34+
hücre/kg hücre dozu
ile daha hızlı
engrafman



— $5-8 \times 10^6$ CD34/kg
- - $2-5 \times 10^6$ CD34/kg
..... $< 2 \times 10^6$ CD34/kg

Kök hücre dozu: allogeneik



Mobilization and collection of peripheral blood progenitor cells for transplantation

Ramakrishna L. Reddy *

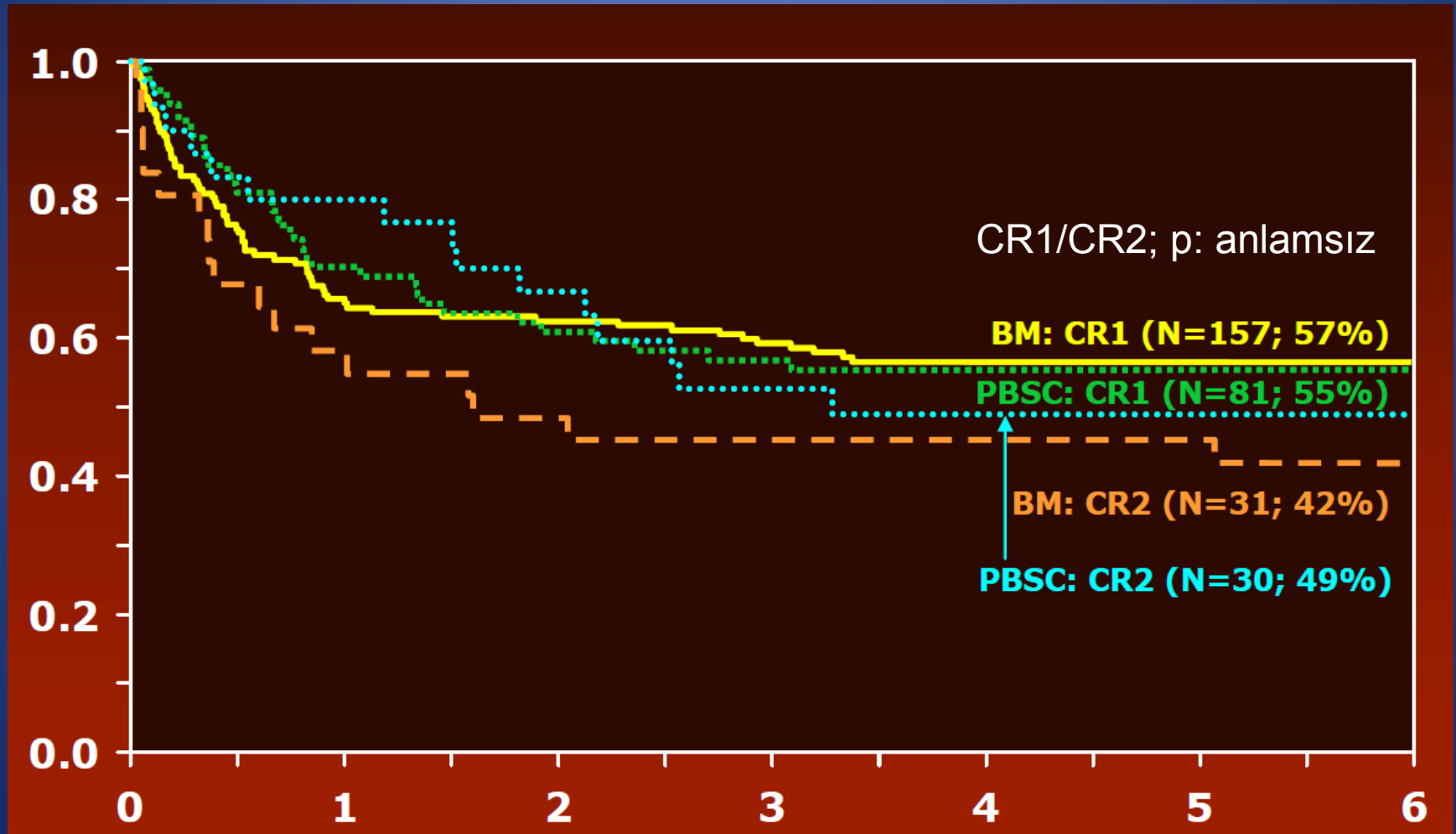
Transfusion and Apheresis Science 32 (2005) 63–72

Though increased CD34+ cell dose leads to faster neutrophil and platelet engraftment, increasing the cell dose above a certain threshold may have other complications particularly in allogeneic transplants. In HLA identical sibling transplantation with PBPC, infusion of higher dose $>8.3 \times 10^6/\text{kg}$ CD34+ cells was associated with increased mortality from chronic GVHD. Efforts to accelerate neutrophil recovery with higher CD34+ cell dose must be counter balanced with the risk of chronic GVHD [35].

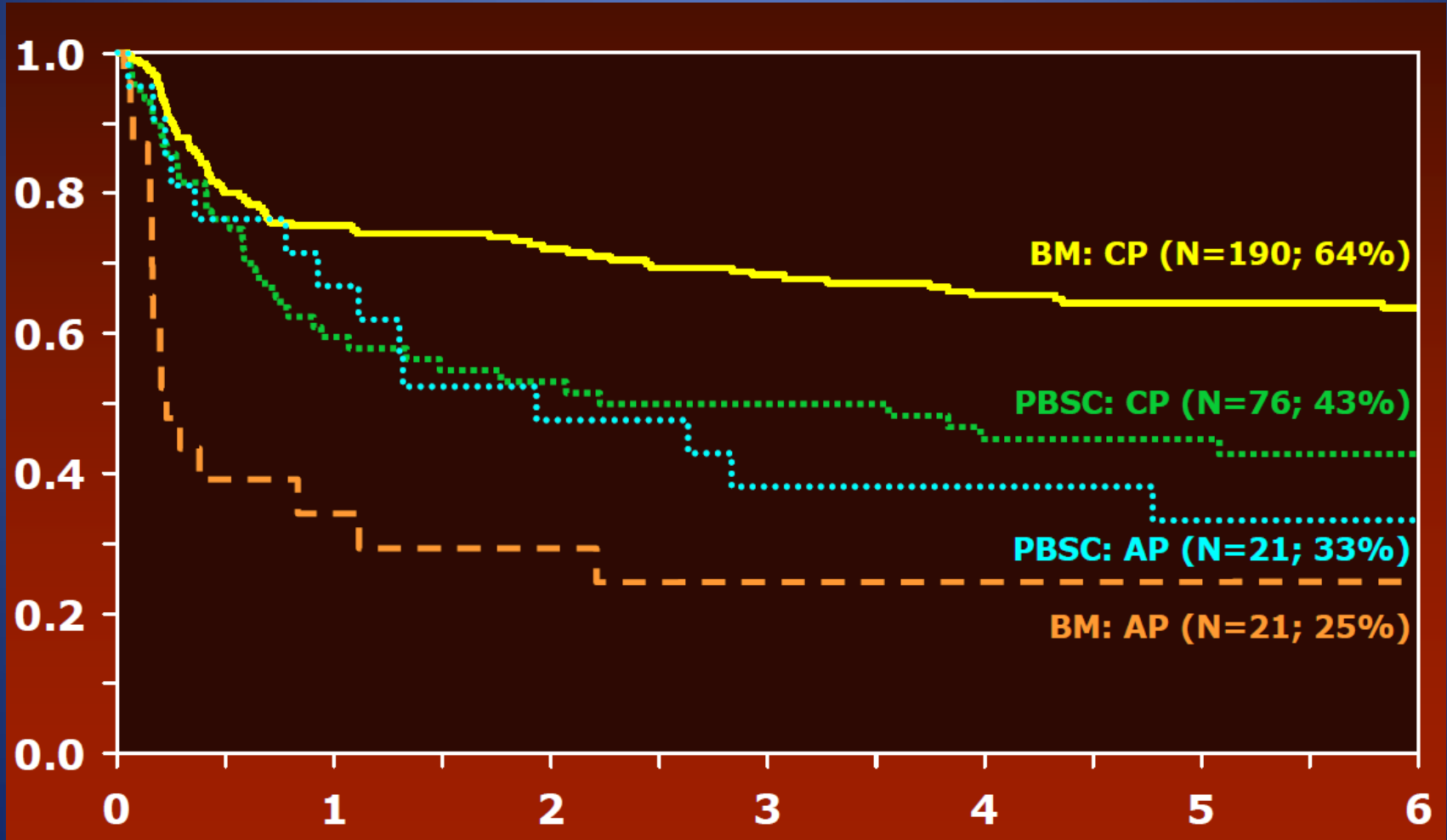
Allojeneik
nakillerde $> 8 \times 10^6$
CD34+ hücre/kg
ile kronik GvHH' ye
bağlı mortalitede
artış

Higher doses of CD34+ peripheral blood stem cells are associated with increased mortality from chronic graft-versus-host disease after allogeneic HLA-identical sibling transplantation

Akut lösemi-genel sağkalım -kök hücre kaynağına göre-



Kronik lösemi-genel sağkalım -kök hücre kaynağına göre-



Lösemilerde kök hücre kaynağı

- PKH kullanımı kronik GvHD sıklığını artırır
- PKH: İleri evre lösemilerde TRM↓ (erken mortalite ↓)
- PKH: Erken evre lösemilerde TRM↑ (geç mortalite ↑)
- PKH: İleri evre KML' de sağkalım avantajı
- Kİ: Erken evre KML' de sağkalım avantajı
- Kİ/PKH: Relaps farksız
- Ki/PKH: Akut lösemilerde LFS, genel sağkalım farksız

HAZIRLAMA REJİMİ DIŞINDA HKHN BAŞARISINA ETKİLİ FAKTÖRLER

DEĞİŞKEN	YORUM
Hasta ilişkili faktörler	Yaş, eşlik eden hastalıklar, performans
Hastalık ilişkili faktörler	Tanı (malign – benign) GVT etkisine duyarlılık (KML, FL, KLL) Evre Kurtarma tedavisine yanıt İlk remisyon süresi Tanı-HKHN arası süre
Hasta-donör ilişkisi	HLA uyumu, gebelik sayısı
Peri-transplant dönem	GvHD profilaksisi, CMV profilaksisi
Graft	Kök hücre kaynağı Graft manipülasyonu (T hücre depleasyonu) Kök hücre dozu
Post-transplant dönem	İzlem süresi, immun manipülasyon (DLI)
İstatistik	Analiz yöntemi, çalışma dizaynı (prospektif-retrospektif)

