Auto/Allo for DLBCL

Koen van Besien, MD
ill Cornell Medical College, NY

Topics

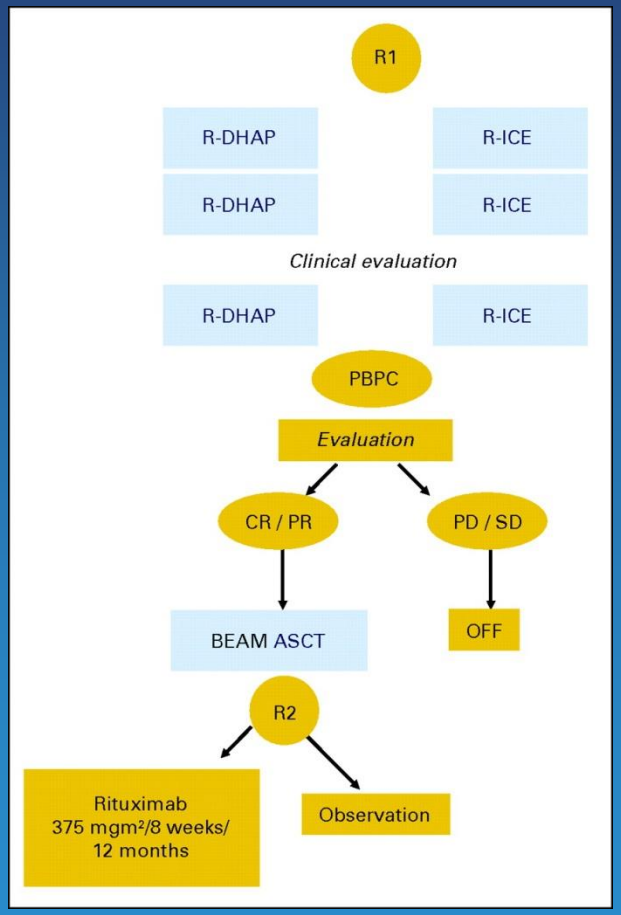
- Autologous SCT: Current standards
  - Parma
  - Coral
  - Age
  - Salvage
  - Conditioning
- Auto in CR1
  - Historical
  - Double Hit Lymphoma
- Auto for Partial Response
- Allogeneic Transplantation
  - Controversial role
  - Improving access and outcomes.

Clinical factors at relapse influence outcome following autoSCT

- Chemorefractory disease
  - Pts achieving less than a PR?
  - Pts with PD?
- > 3 prior regimens
- Elevated LDH
- Time to relapse < 12 months
- High disease burden
- Bulky disease (> 10 cm)
- Prior Rituximab

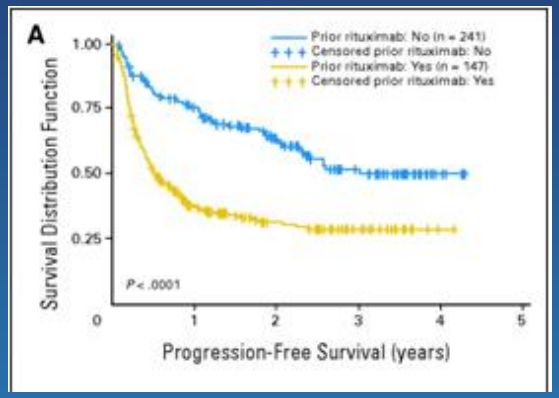
Van Besien BMT 2001
Vose JCO 1993
Prince Br J Hem 1996
Guglielmi JCO 1998
Moskowitz BMT 1999

Coral Study

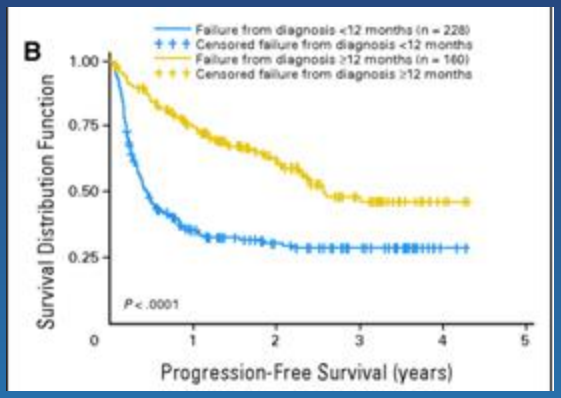


Gisselbrecht C et al. JCO 2010;28:4184-4190
Horwitz, Blood, 2004

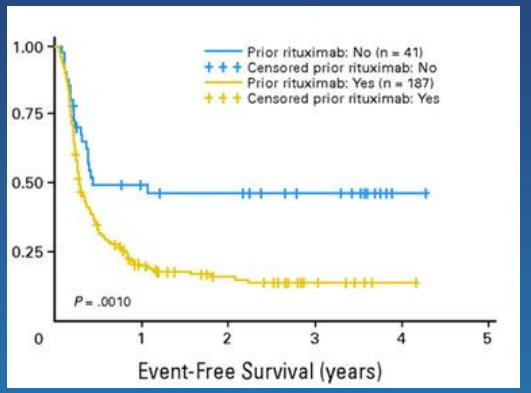
Coral Study outcomes depending on prior rituximab and duration of initial remission



Prior Rituximab vs Not



Initial remission >< 12 mo



Prior rituximab and CR1<12 months

Gisselbrecht C et al. JCO 2010;28:4184-4190

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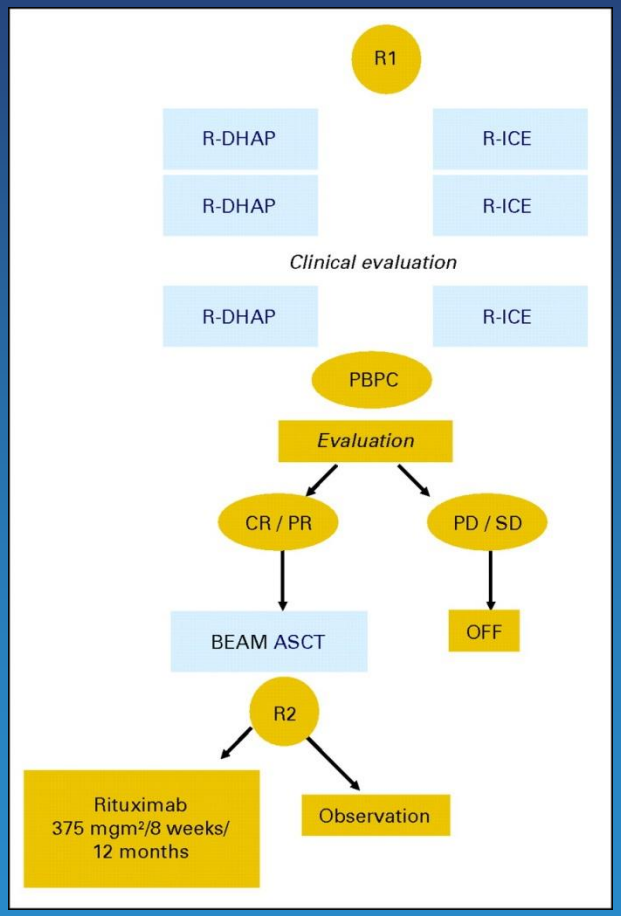
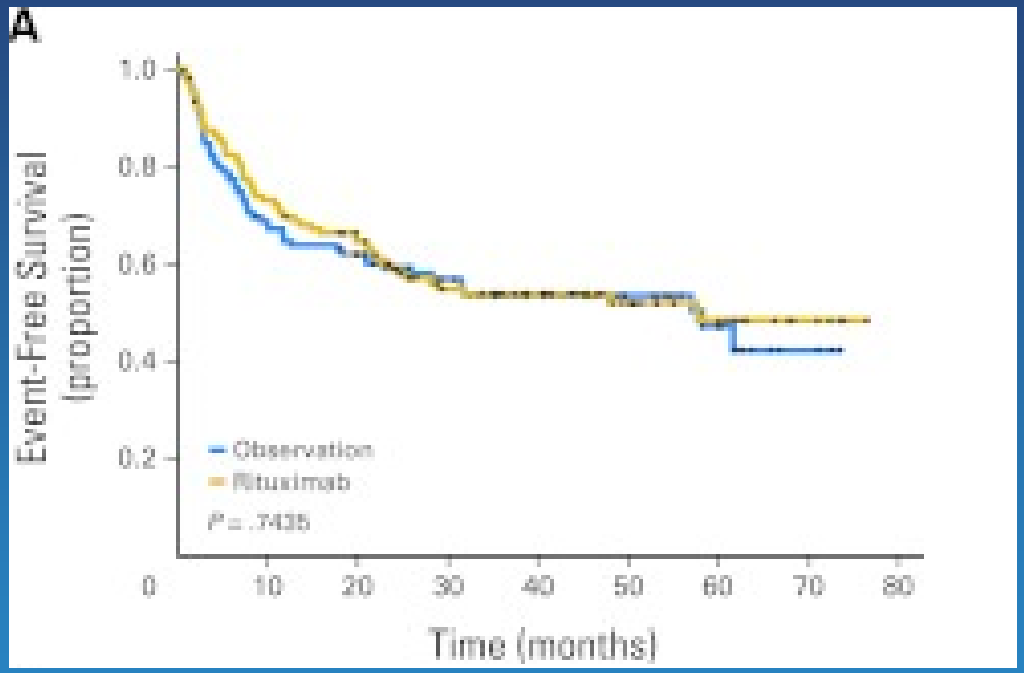
Maintenance Rituximab after ASCT for DLBCL





Gisselbrecht C et al. JCO 2012

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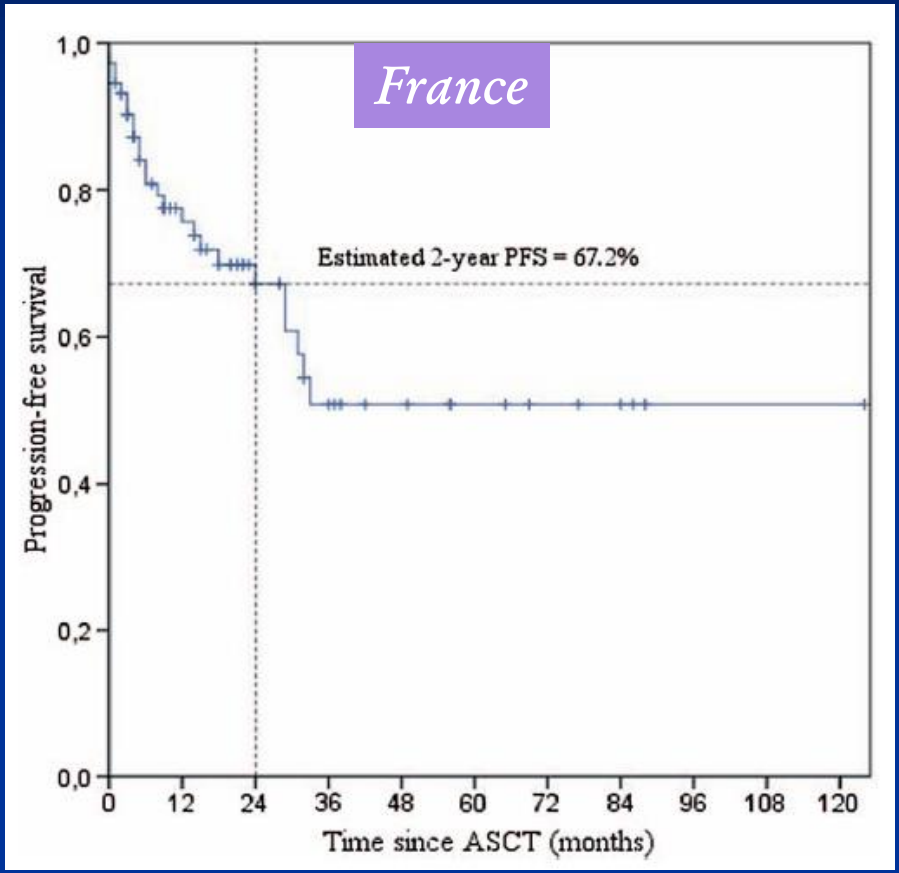
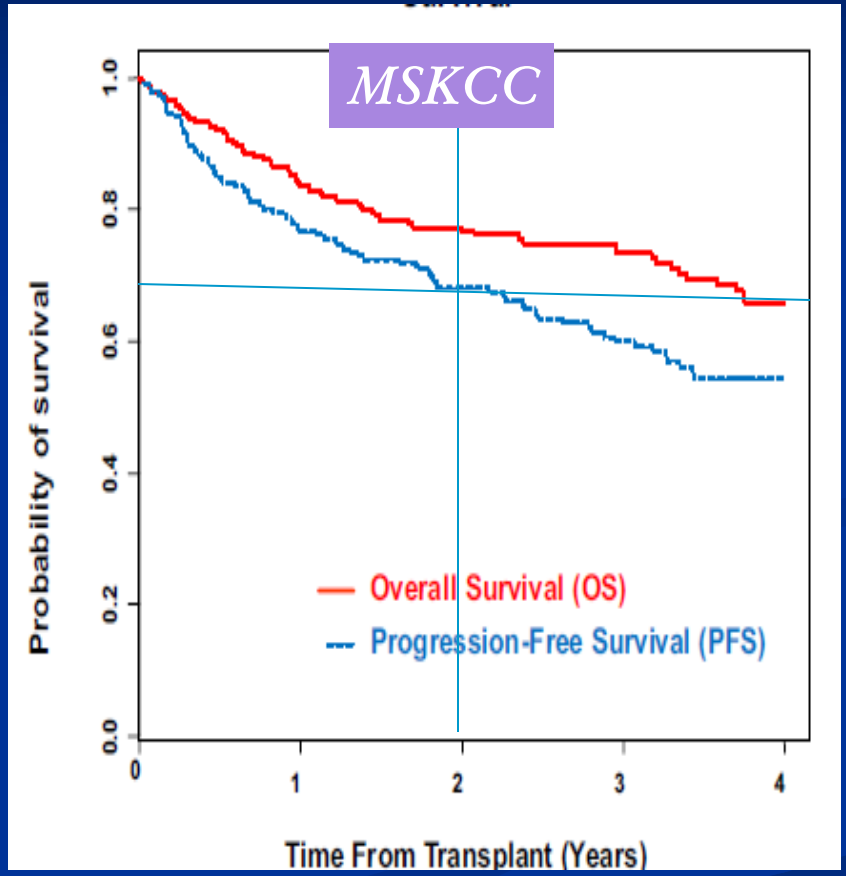
PFS after ASCT in older NHL



Full dose BEAM
*N=73, m age 67 (65-74) , **D100 TRM 3%***
Martin et al, LL 2015
France



BEAM 74%
*N=202, m age 65 (60-74) , **D100 TRM 4%***
Dahi et al, BBMT 20, 2004, 2014
MSKCC

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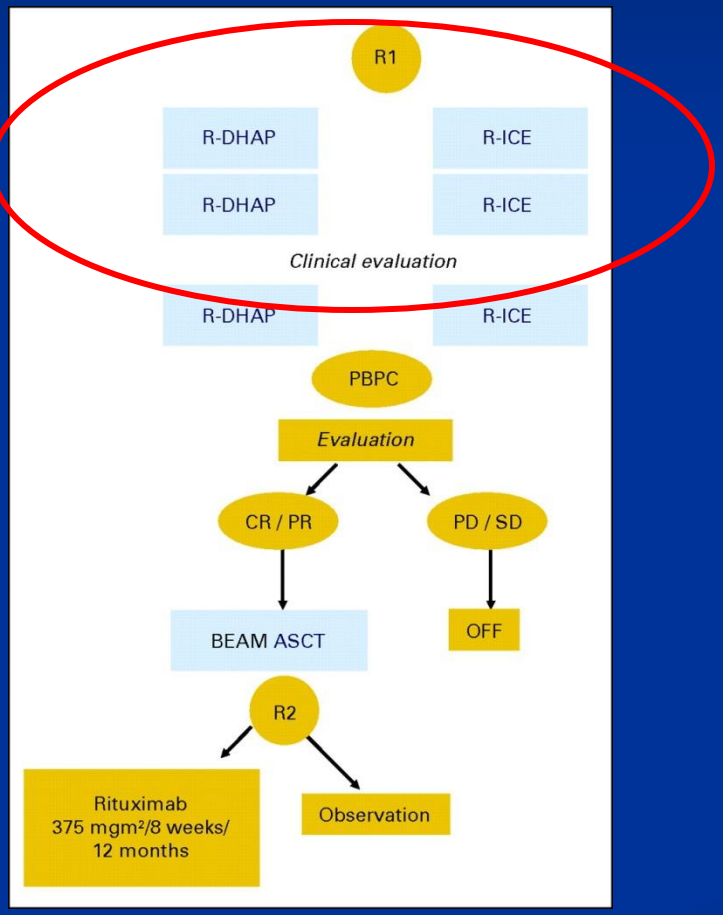
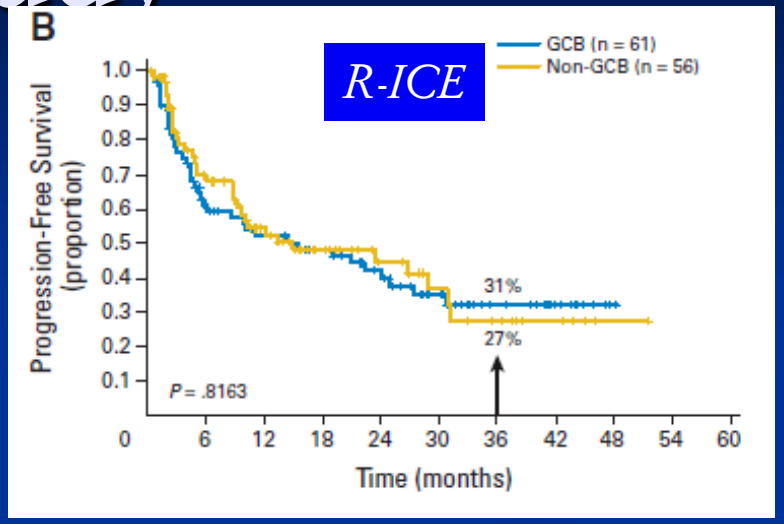
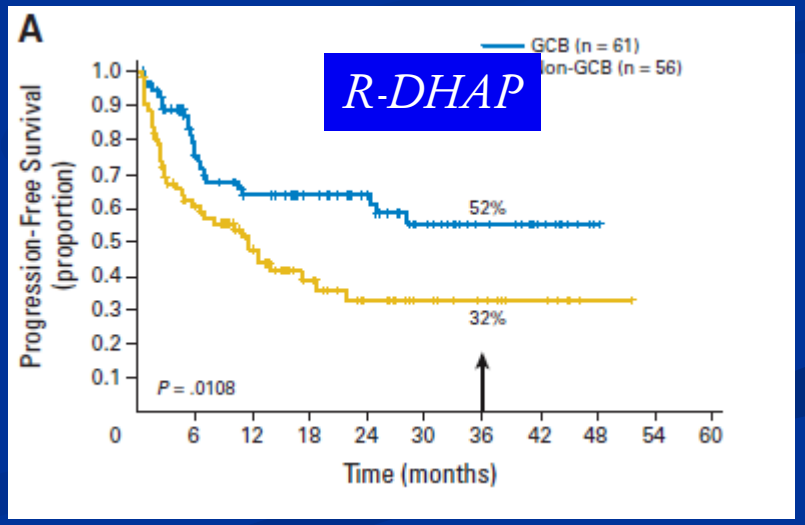
Coral Study

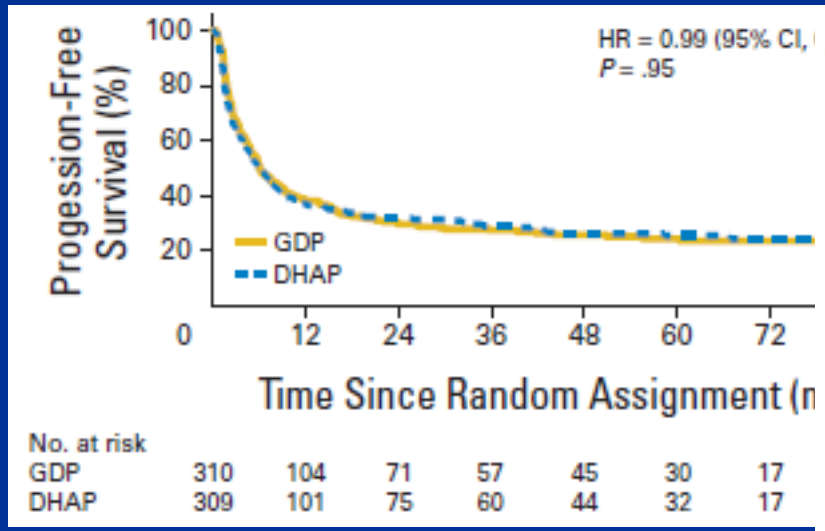


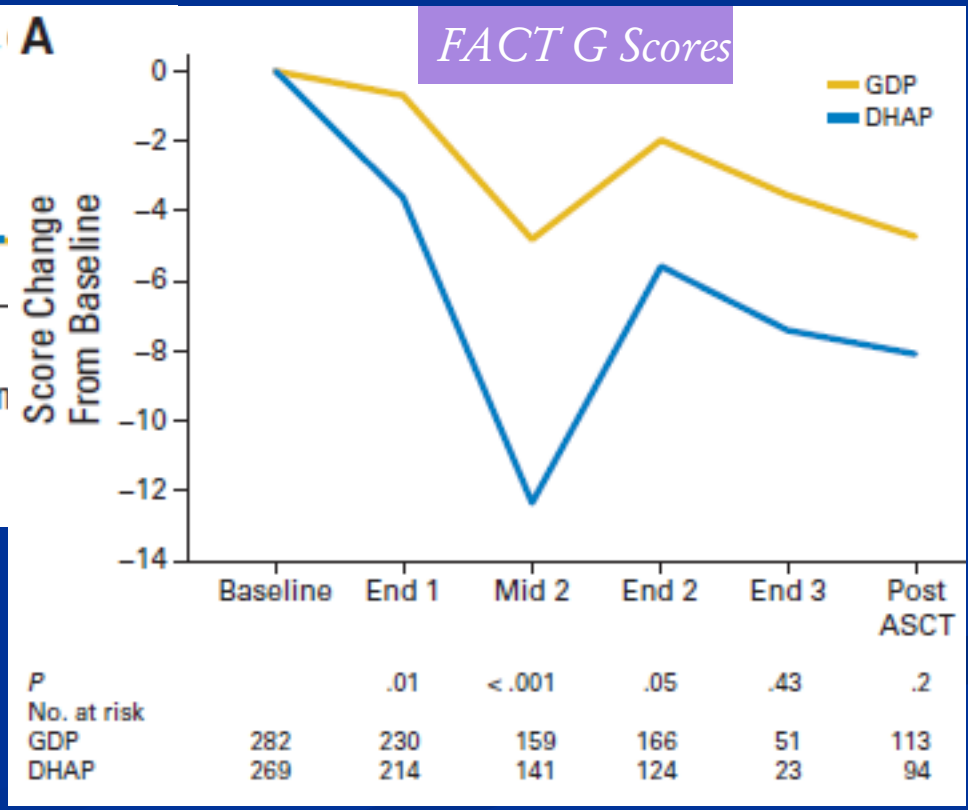




Gisselbrecht C et al. JCO 2010;28:4184-4190
Thieblemont, JCO 2011

Randomized Comparison of Gemcitabine, Dexamethasone, and Cisplatin Versus Dexamethasone, Cytarabine, and Cisplatin Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed and Refractory Aggressive Lymphomas: NCIC-CTG LY.12





Crump et al, JCO 32, 3940, 2014

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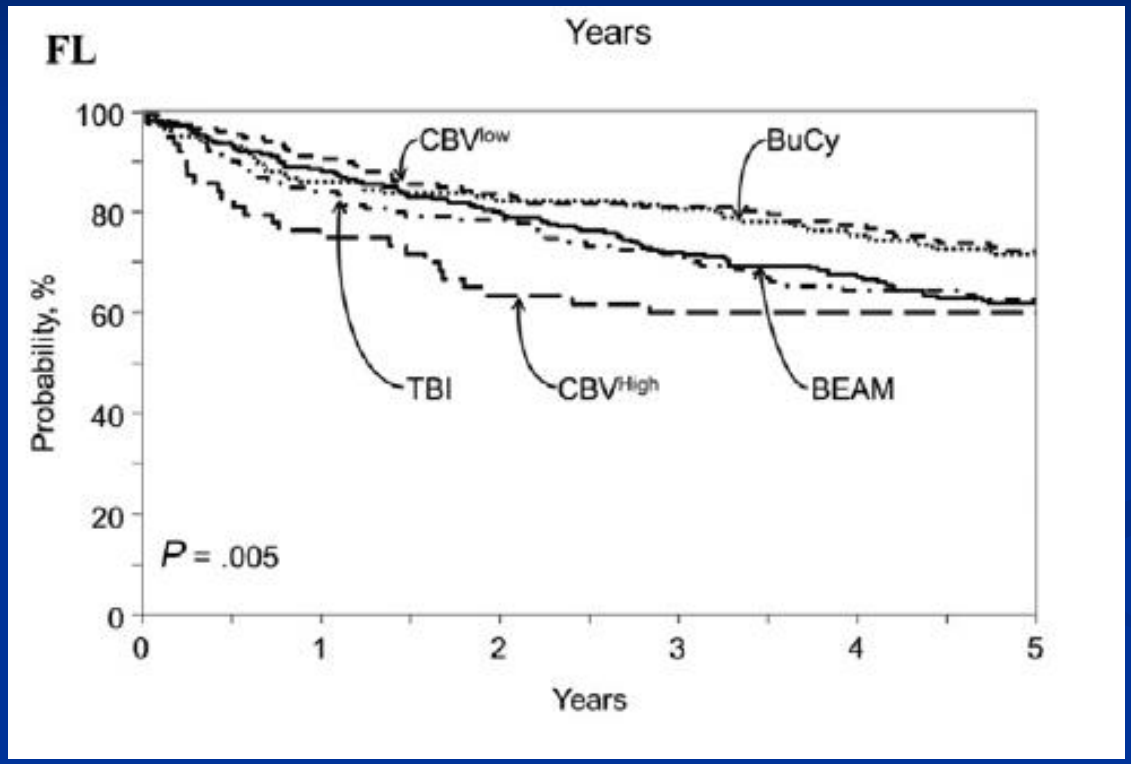
Conditioning Regimens

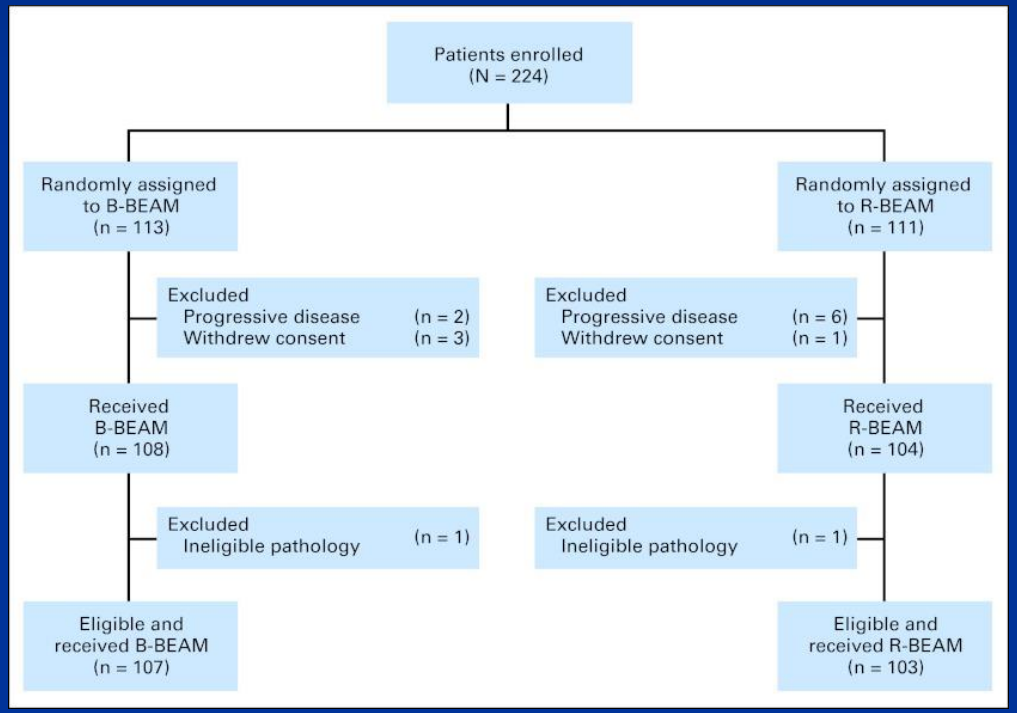


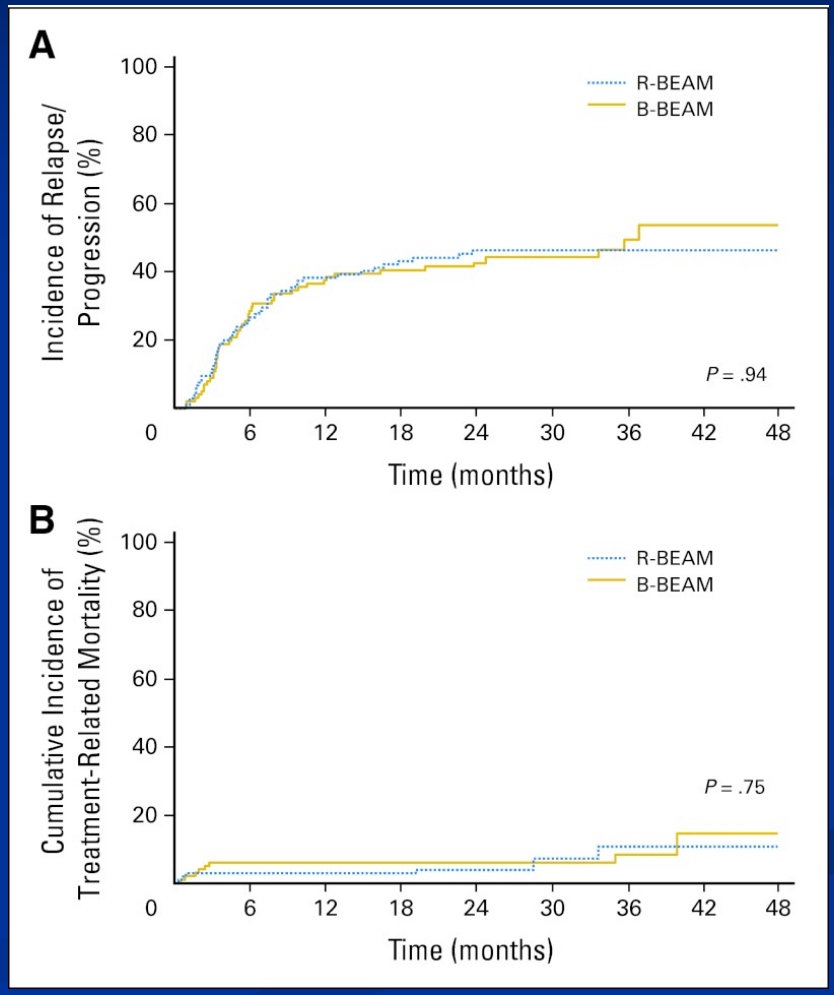
Risk for IPS		
	RR	P
CBV~450	1.88	0.003
CBV~300	1.1	
BuCy	1.25	
TBI	2	0.002

R-BEAM is the standard
There is worse… not better

Chen et al, BBMT 2015

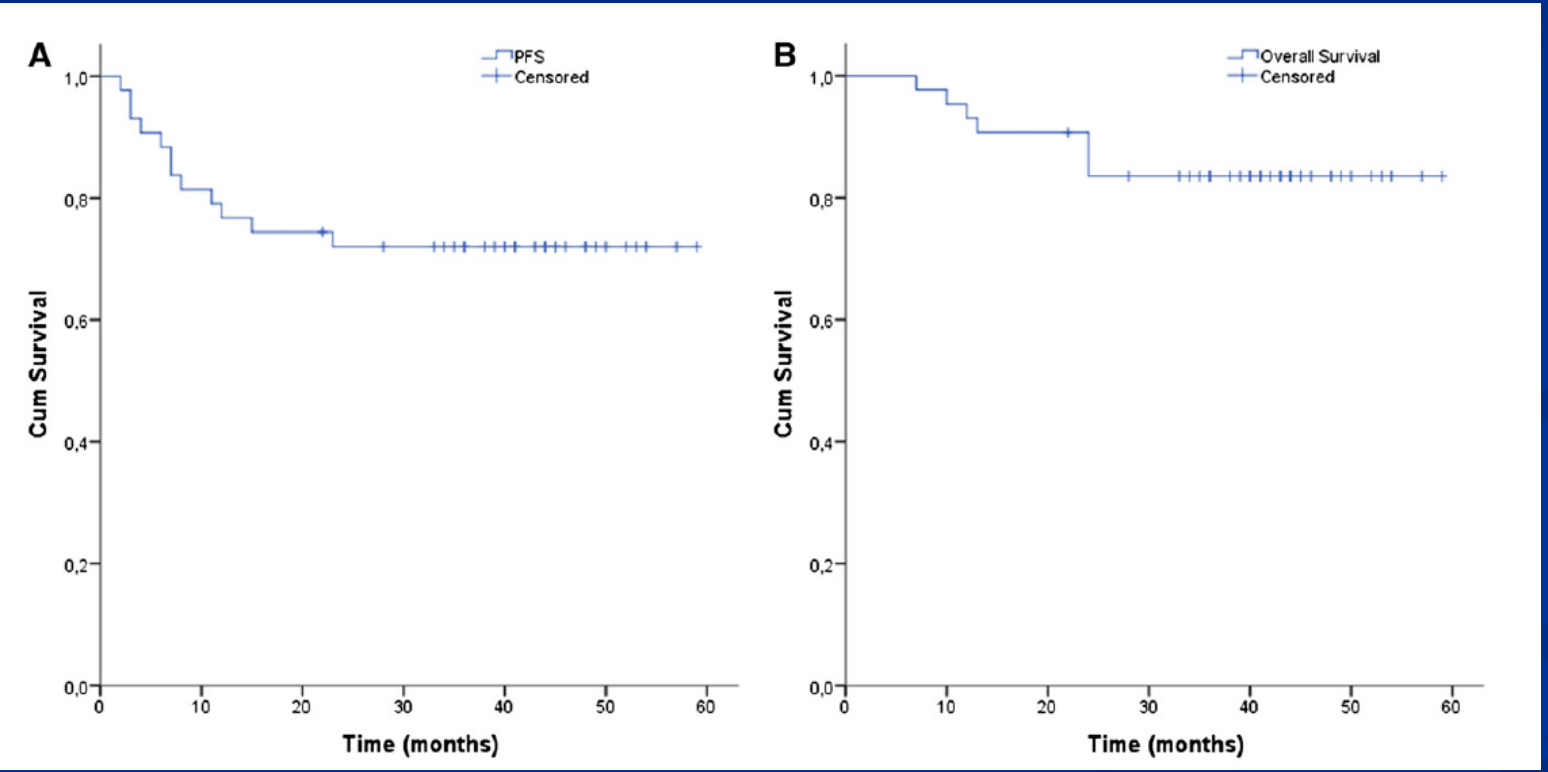
Phase III randomized study of RBEAM compared with iodine-131 tositumomab/BEAM psed diffuse large B-cell lymphoma: results from the BMT CTN 0401 trial





Vose JCO, 2013

Bendamustine EAM



Capria et al, Blood 124,3030, 2014

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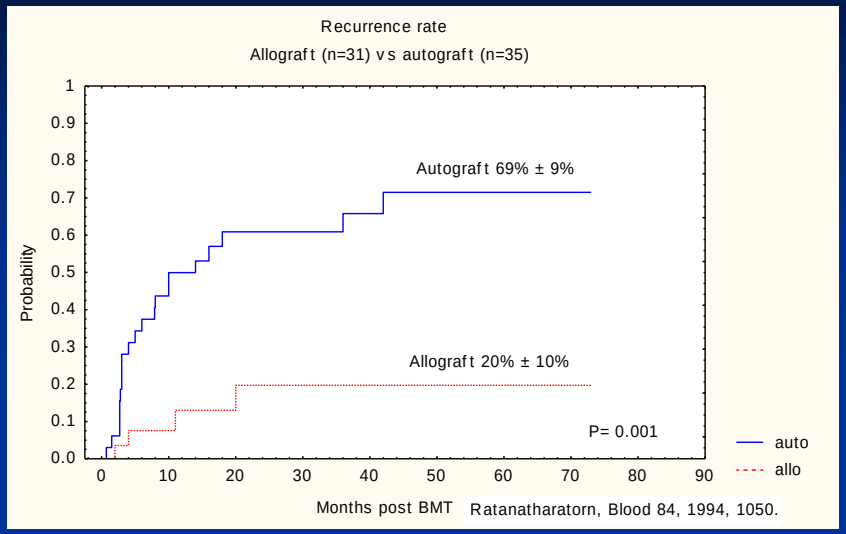
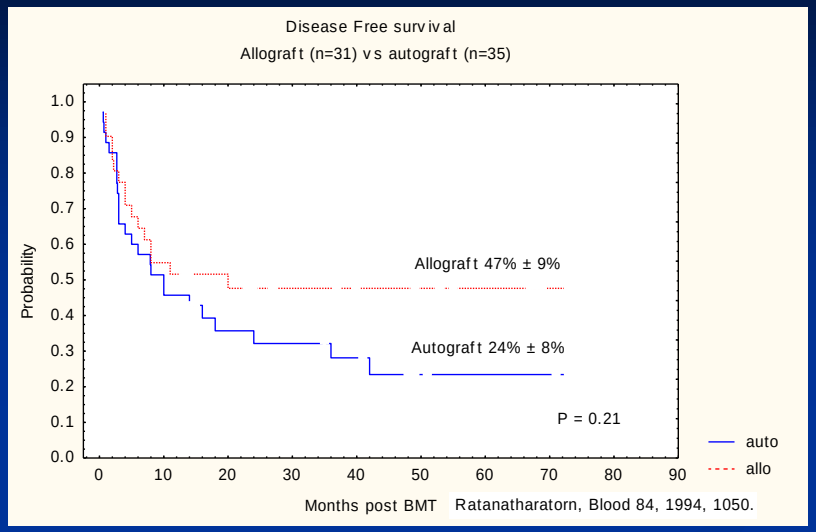
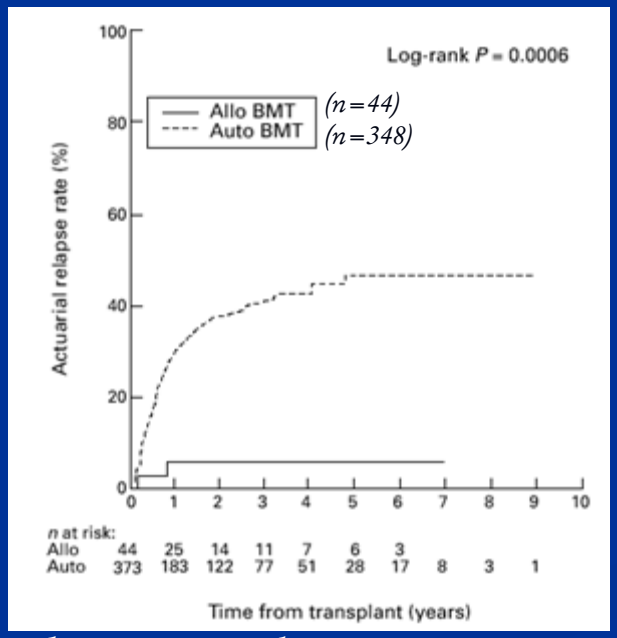
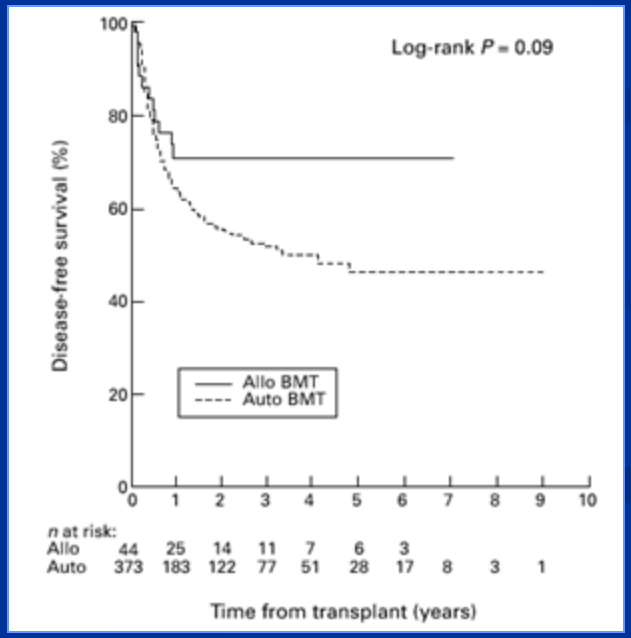
Allo vs auto BMT for lymphoma









Schimmer et al Bone Marrow Transplant.26:859-64, 2000

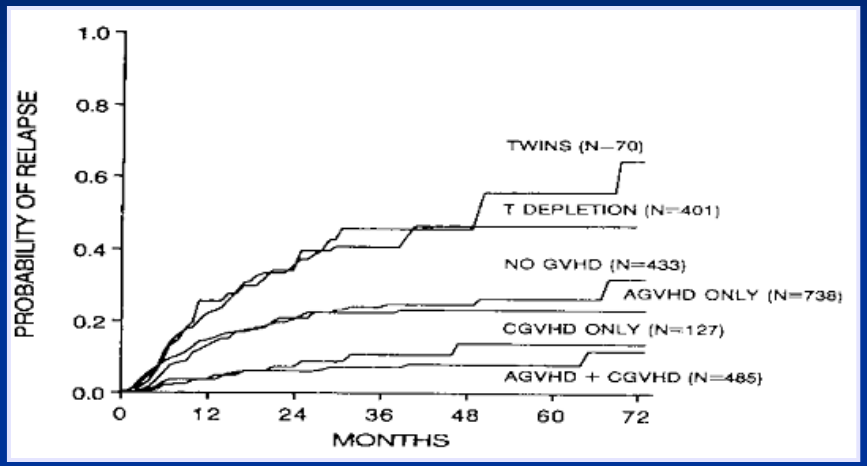
An Endangered Species

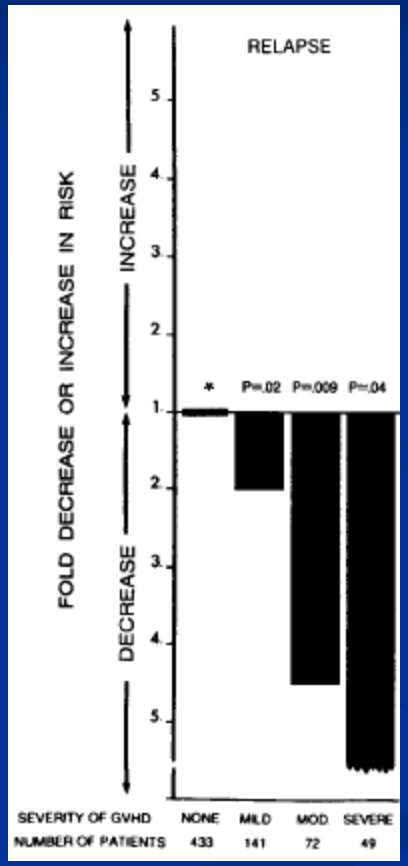
- "The outcomes of allogeneic transplantation are horrible"
- "As far as allogeneic transplantation is concerned, I am a nihilist"
- "I send patients for two second opinions before recommending an allo transplant"

Why this bad reputation?

- Concern over TRM
- Concern over disease recurrence
- **Concern over chronic GVHD**
  - **Transplant benefit is often attributed to GVL effects and GVHD considered a necessary evil.**

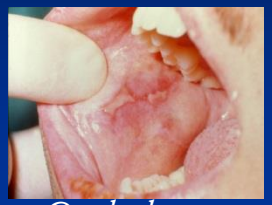
Is chronic GVHD Good or Bad?
Relative Risk of Treatment Failure (death or relapse) after allo transplant for good risk leukemia as a function of GVHD



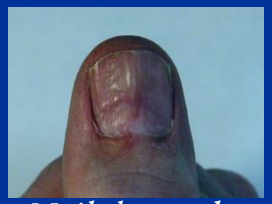


Horowitz et al: Blood 1990; 75:555-562

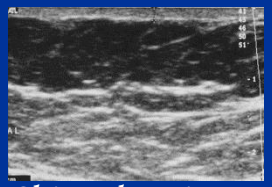
Ocular sicca



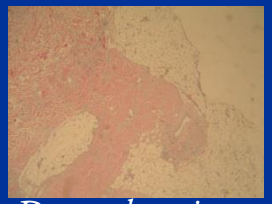
Oral ulcers



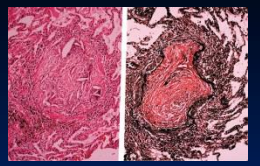
Nail dystrophy



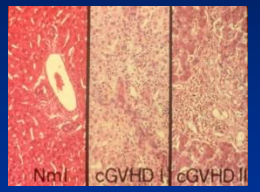
Skin sclerosis



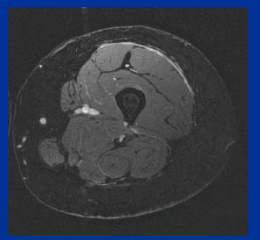
Deep sclerosis



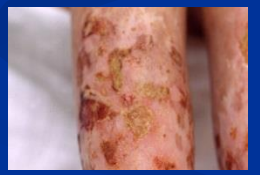
Bronchiolitis obliterans



Loss of bile ducts



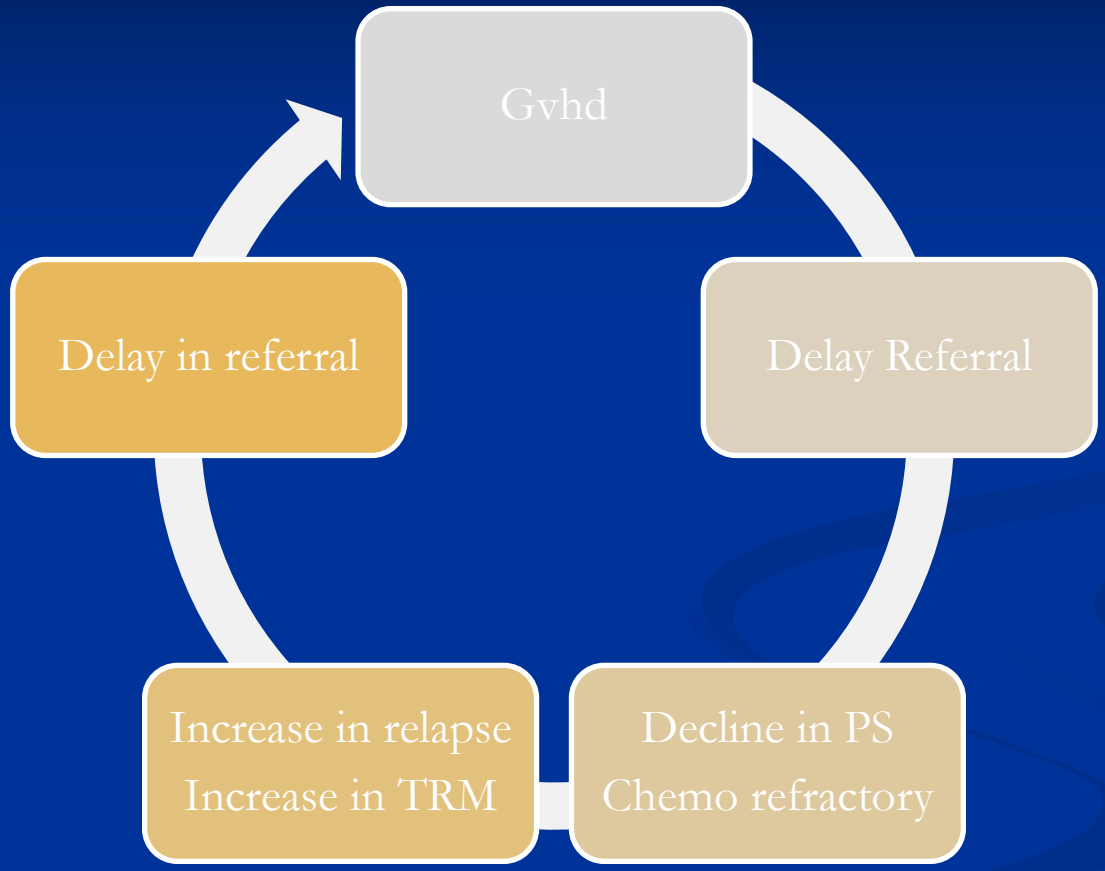
Fasciitis



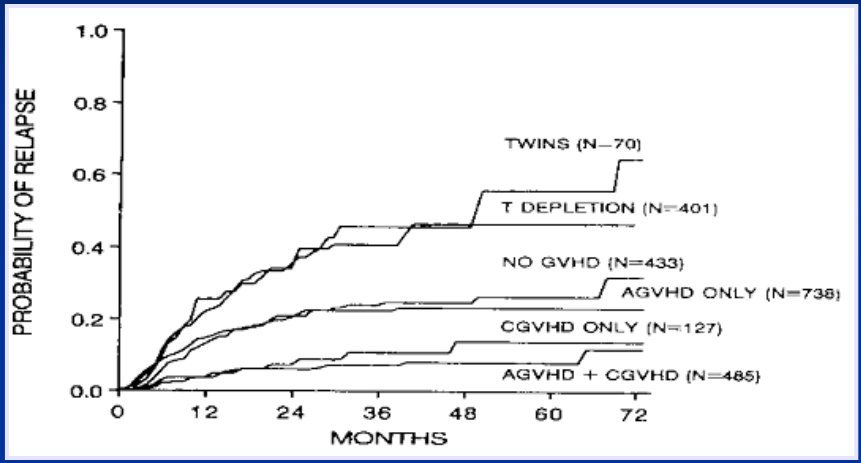
Skin ulcers

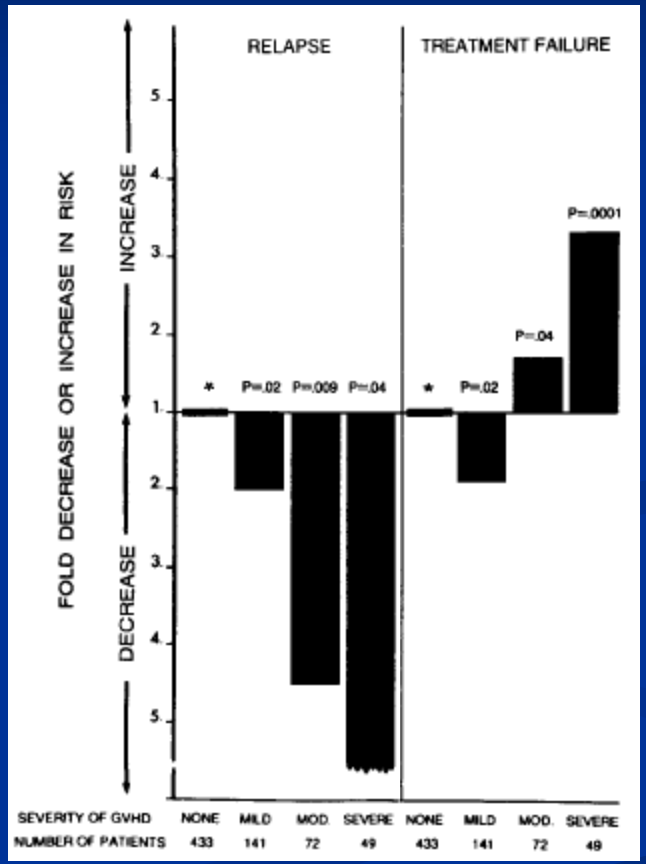
Infections
Disability
Quality of life
Endocrine
Metabolism
Nutrition
Pain

Spectrum of manifestations in chronic GVHD


Gvhd
Delay Referral
Decline in PS
Chemo refractory
Increase in relapse
Increase in TRM
Delay in referral

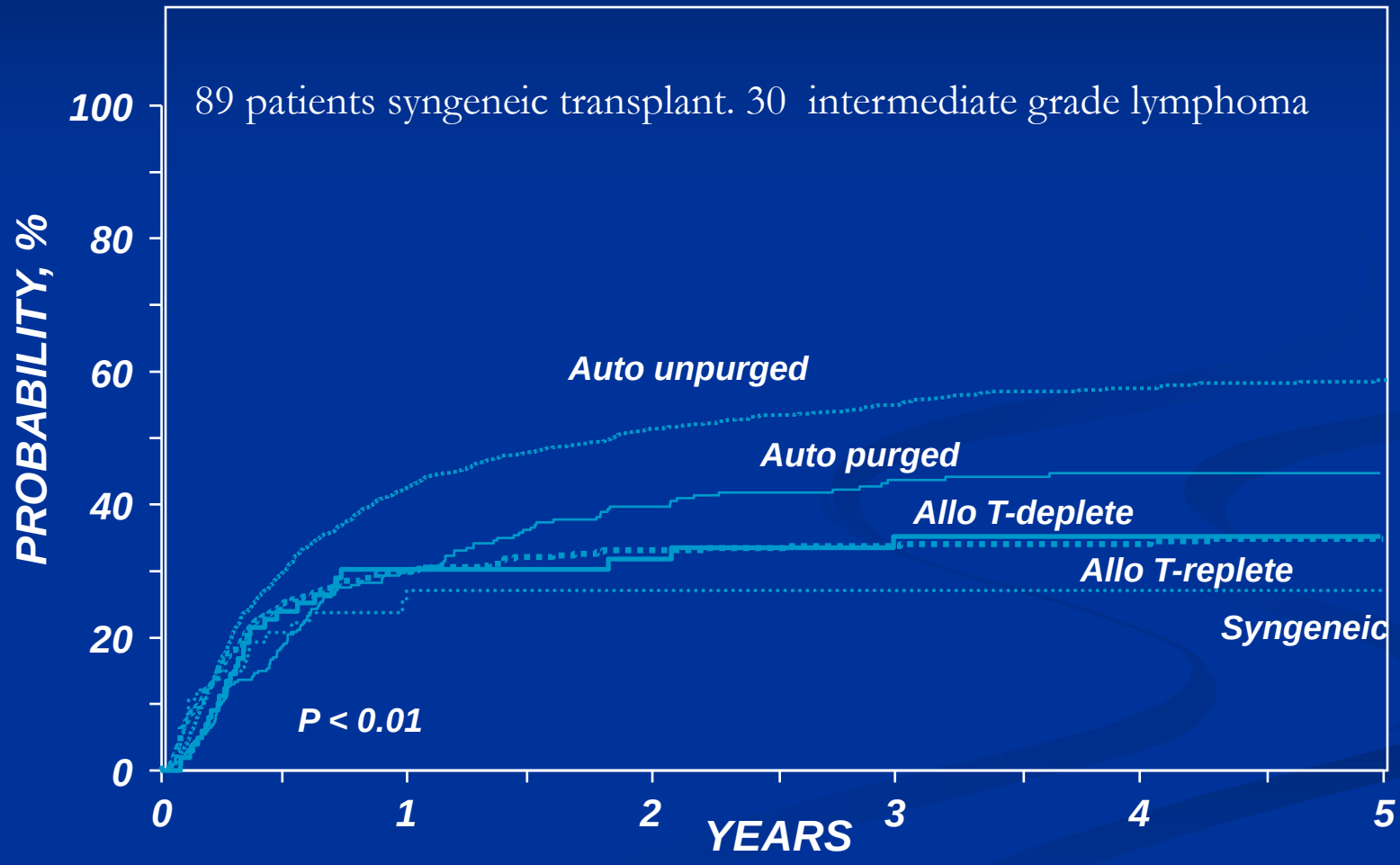
Is chronic GVHD Good or Bad?
Relative Risk of Treatment Failure (death or relapse) after allo transplant for good risk leukemia as a function of GVHD





Horowitz et al: Blood 1990; 75:555-562

Probability Of Relapse After Syngeneic Transplantation



Bierman et al, J Clin Oncol 21, 3744, 2003

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Graft-Versus-Tumor Effects After Allogeneic Hematopoietic Cell Transplantation With Nonmyeloablative Conditioning

J Clin Oncol 23:1993-2003. © 2005

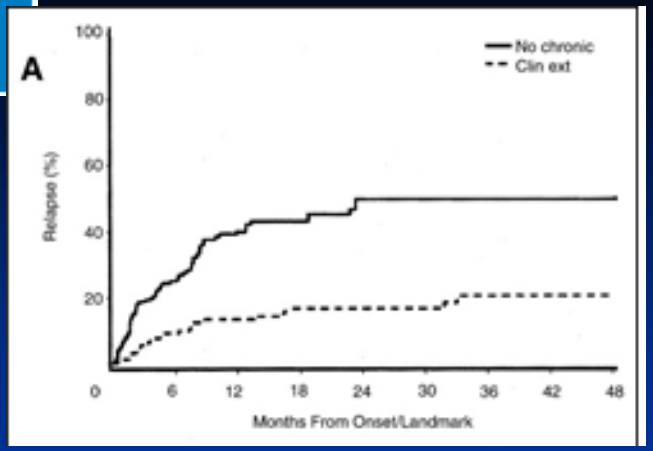
Frédéric Baron, Michael B. Maris, Brenda M. Sandmaier, Barry E. Storer, Mohamed Sorror, Razvan Diaconescu, Ann E. Woolfrey, Thomas R. Chauncey, Mary E.D. Flowers, Marco Mielcarek, David G. Maloney, and Rainer Storb

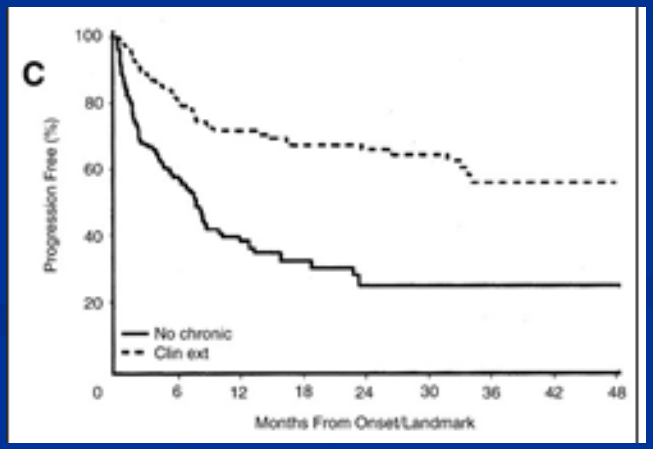
Patients and Methods

We analyzed GVT effects in 322 patients given grafts from HLA-matched related (n = 192) or unrelated donors (n = 130).

Results

Of the 221 patients with measurable disease at HCT, 126 (57%) achieved complete (n = 98) or partial (n = 28) remissions. In multivariate analysis, there was a higher probability trend of achieving complete remissions in patients with chronic extensive graft-versus-host disease (GVHD; $P = .07$). One hundred eight patients (34%) relapsed or progressed. In multivariate analysis, achievement of full donor chimerism was associated with a decreased risk of relapse or progression ($P = .002$). Grade 2 to 4 acute GVHD had no significant impact on the risk of relapse or progression but was associated with increased risk of nonrelapse mortality and decreased probability of progression-free survival (PFS). Conversely, extensive chronic GVHD was associated with decreased risk of relapse or progression ($P = .006$) and increased probability of PFS ($P = .003$).





Graft-Versus-Host Disease and Graft-Versus-Tumor Effects After Allogeneic Hematopoietic Cell Transplantation

J Clin Oncol 31. © 2013

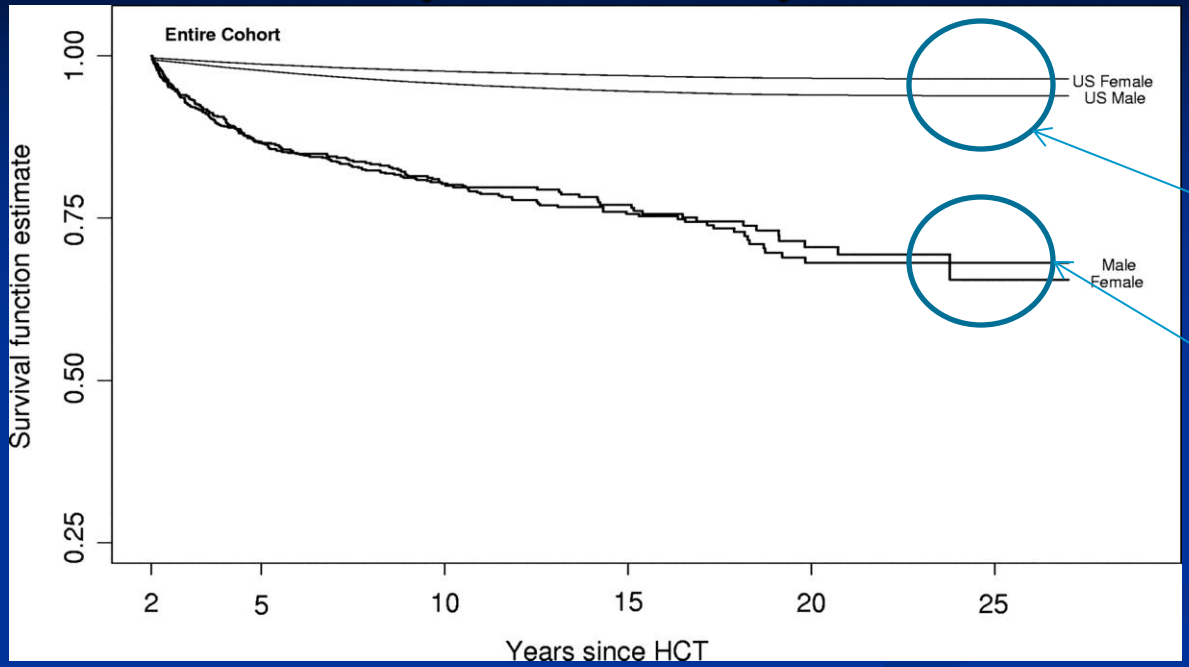
Patients and Methods

Patients received low-dose total-body irradiation ± fludarabine before HCT from HLA-matched related (n = 611) or unrelated (n = 481) donors, followed by mycophenolate mofetil and a calcineurin inhibitor to aid engraftment and control GVHD. Median patient age was 56 years (range, 7 to 75 years). Forty-five percent of patients had comorbidity scores of ≥ 3. Median follow-up time was 5 years (range, 0.6 to 12.7 years).

Results

Depending on disease risk, comorbidities, and GVHD, lasting remissions were seen in 45% to 75% of patients, and 5-year survival ranged from 25% to 60%. At 5 years, the nonrelapse mortality (NRM) rate was 24%, and the relapse mortality rate was 34.5%. Most NRM was a result of GVHD. The most significant factors associated with GVHD-associated NRM were serious comorbidities and grafts from unrelated donors. Most relapses occurred early while the immune system was compromised. GVT effects were comparable after unrelated and related grafts. Chronic GVHD, but not acute GVHD, further increased GVT effects. The potential benefit associated with chronic GVHD was outweighed by increased NRM.

All-cause mortality in 1479 2+y survivors after allo HCT



Age Matched Controls

Transplant Survivors

	No GVHD 10 y	GVHD 10y	RR NRM
AML	92%	73%	3.4

blood
THE JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Bhatia S et al. Blood 2007;110:3784-3792

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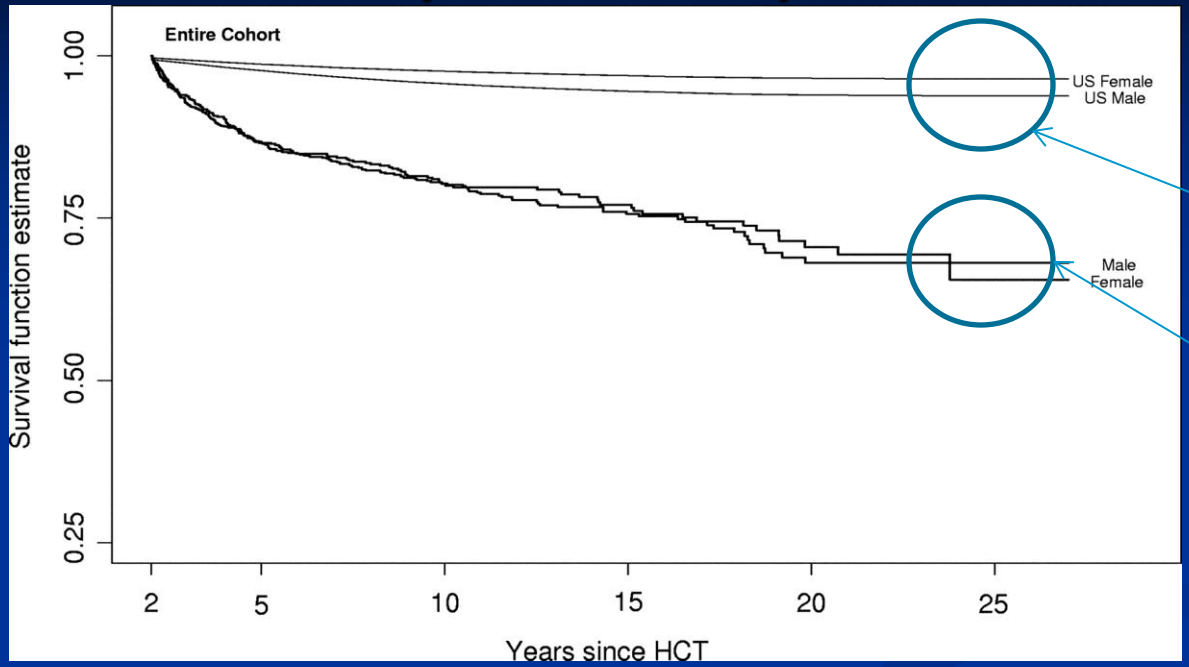

Age Matched Controls

Transplant Survivors

	No GVHD 10 y	GVHD 10y	RR NRM	RR RRM
AML	92%	73%	3.4	1.8

blood
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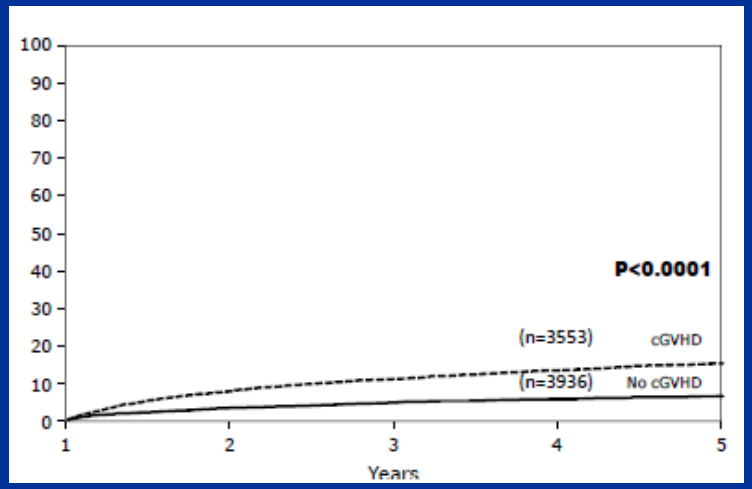
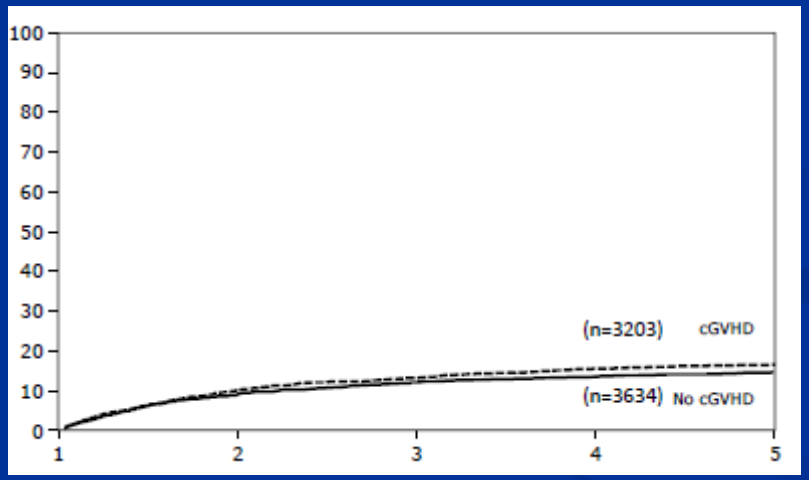
Impact of chronic graft-versus-host disease on late relapse and survival on 7489 patients after myeloablative allogeneic hematopoietic cell transplantation for leukemia

Michael Boyiadzis,[1] Mukta Arora,[2] John P. Klein,[3] Anna Hassebroek,[4] Michael Hemmer,[3] Alvaro Urbano-Ispizua,[5] Joseph H. Antin,[6] Brian J. Bolwell,[7] Jean-Yves Y. Cahn,[8] Mitchell S. Cairo,[9] Corey S. Cutler,[6] Mary E. Flowers,[10] Robert P. Gale,[11] Roger Herzig,[12] Luis M. Isola,[13] David A. Jacobsohn,[14] Madan H. Jagasia,[15] Thomas R. Klumpp,[16] Stephanie J. Lee,[10] Effie W. Petersdorf,[10] Stella Santarone,[17] Stephen R. Spellman,[4] Harry C. Schouten,[18] Leo F. Verdonck,[19] John R. Wingard,[20] Daniel J. Weisdorf,[2] Mary M. Horowitz,[3] Steven Z. Pavletic[21]

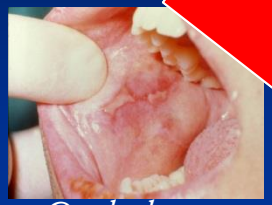




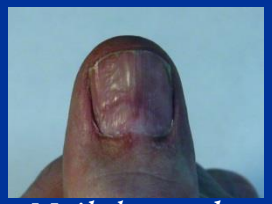
Conclusions: These results indicate that clinically relevant anti-leukemia effects of cGVHD on late relapses are present only in CML but not in AML, ALL or MDS. Chronic GVHD in patients who are one year survivors after myeloablative allogeneic HCT is primarily associated with higher TRM and inferior survival.

Clin Cancer Res. 2014

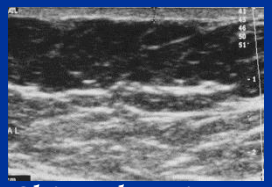
Ocular sicca



Oral ulcers

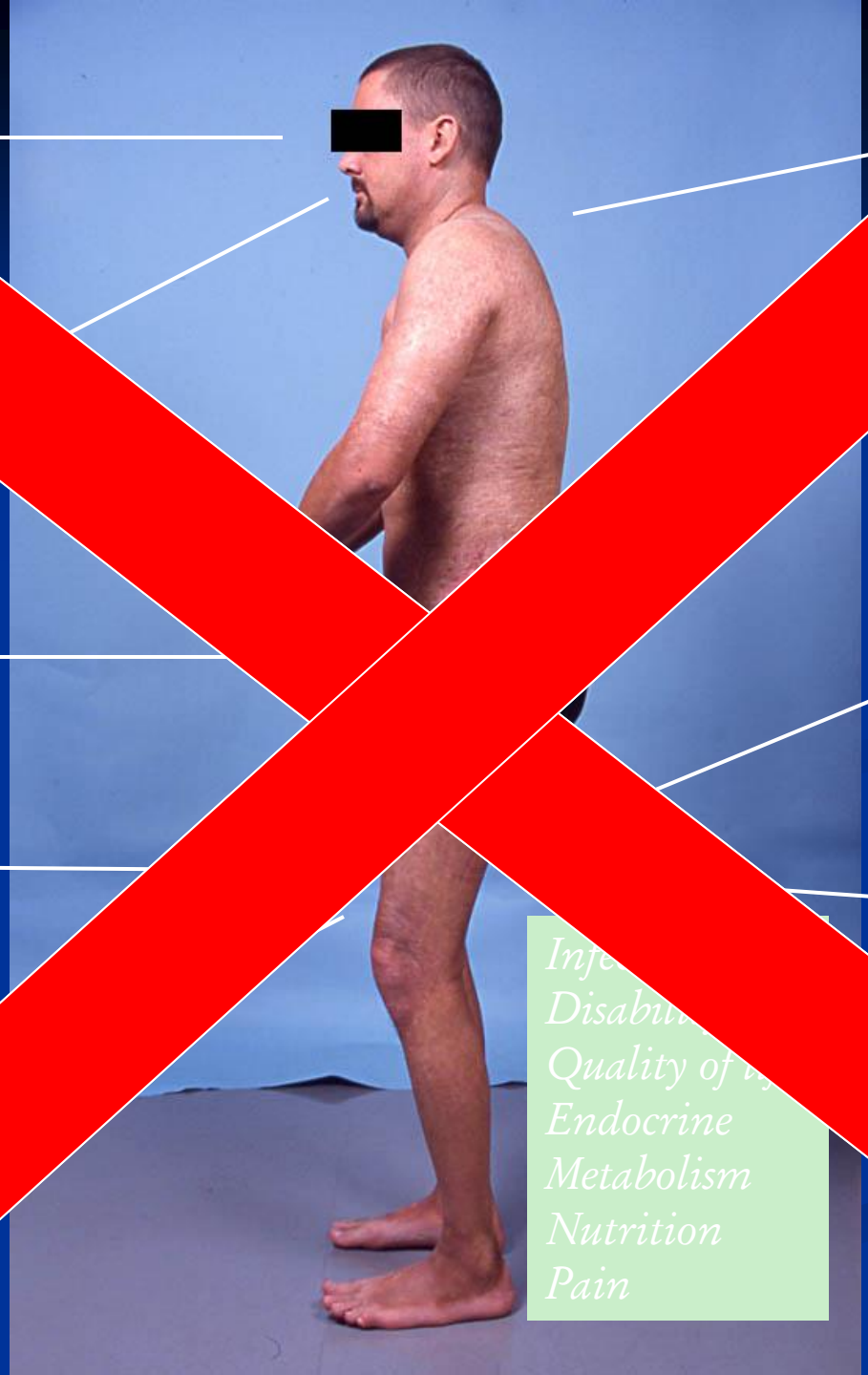


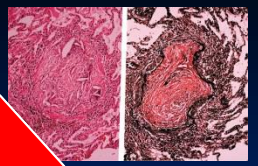
Nail dystrophy



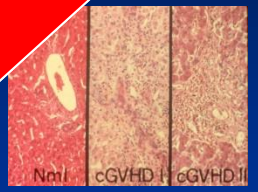
Skin sclerosis

Deep sclero

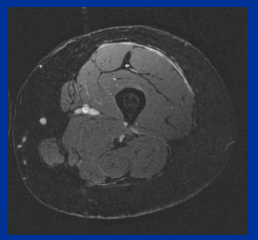




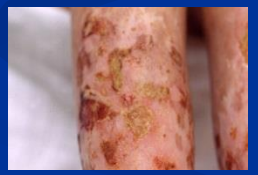
olitis obliterans



Loss of bile ducts



Fasciitis



Skin ulcers

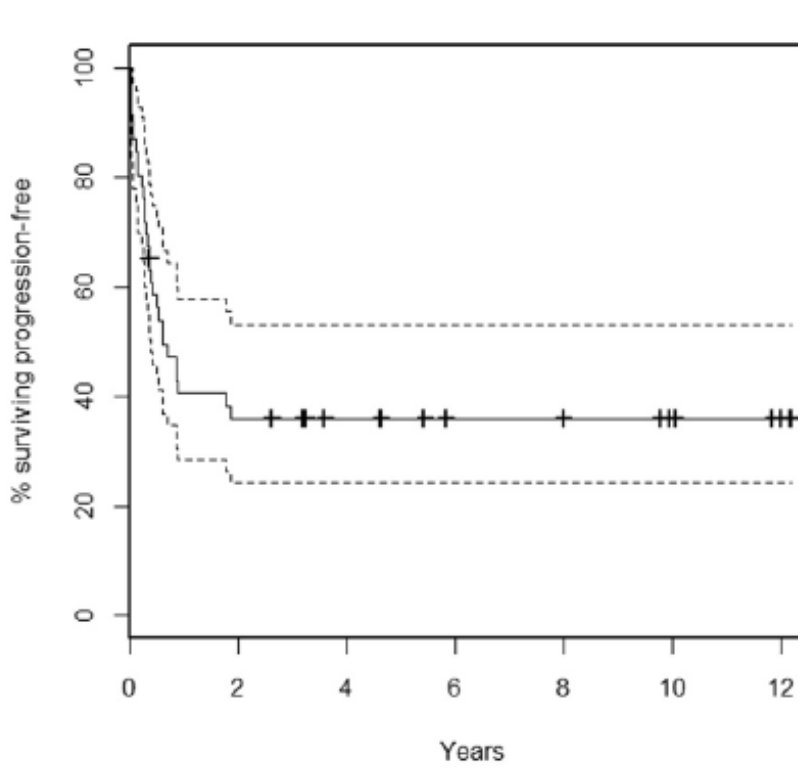
Inf
Disabil
Quality of
Endocrine
Metabolism
Nutrition
Pain

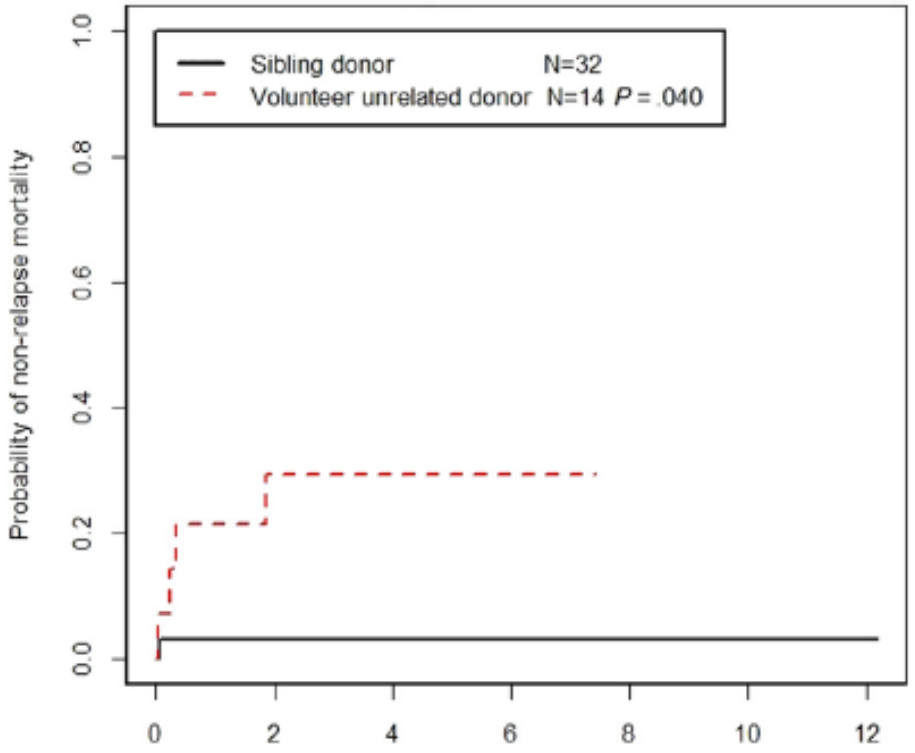
of
ns
GVHD

GVL and non-myeloablative tx

- GVL can induce/maintain remission in isolated cases
- IBMTR data on 2nd tx indicate that conditioning matters
- Syngeneic data suggest that GVL plays, on average, only a minor role in disease control
- Alternative approach:
  - Maintain intensity
  - Avoid GVHD, avoid TRM

BEAM Campath and aggressive NHL

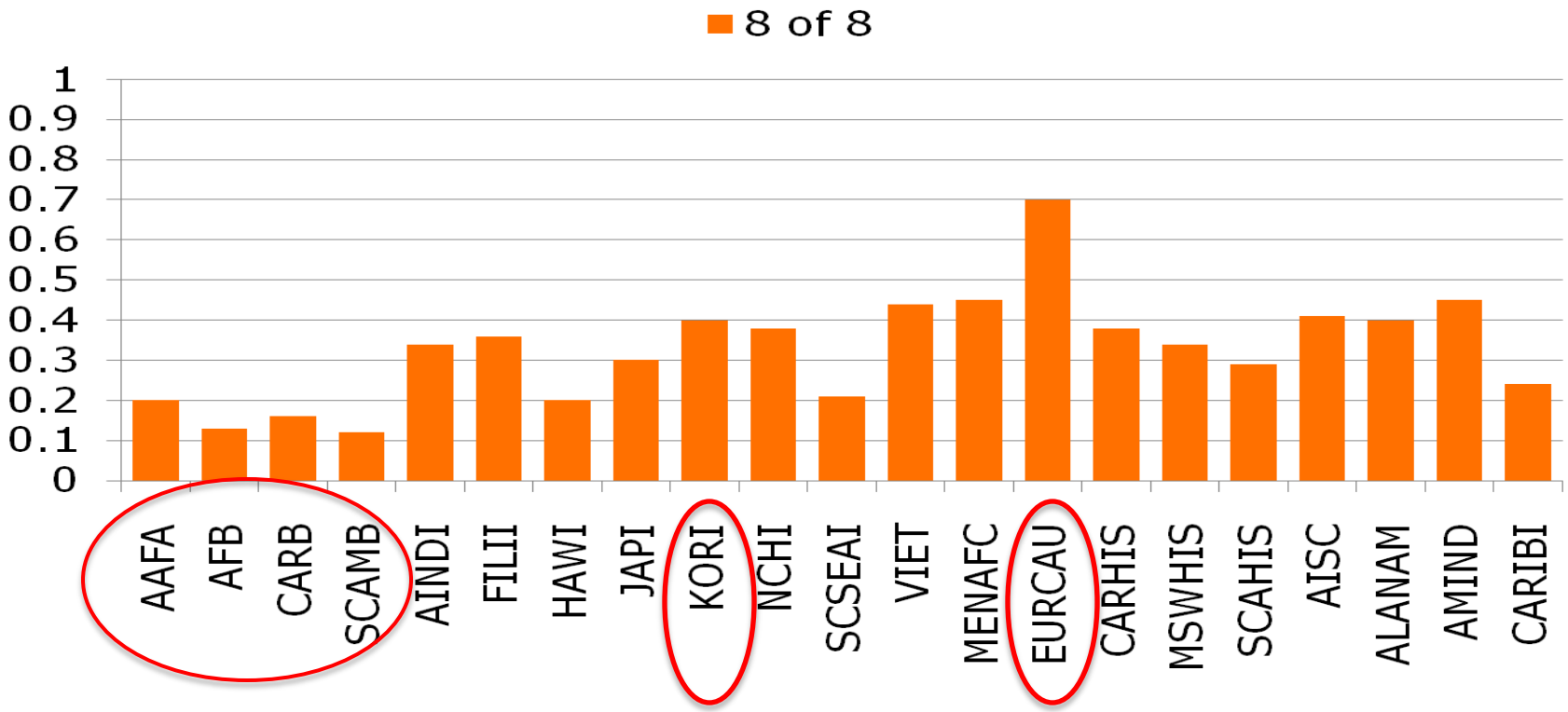


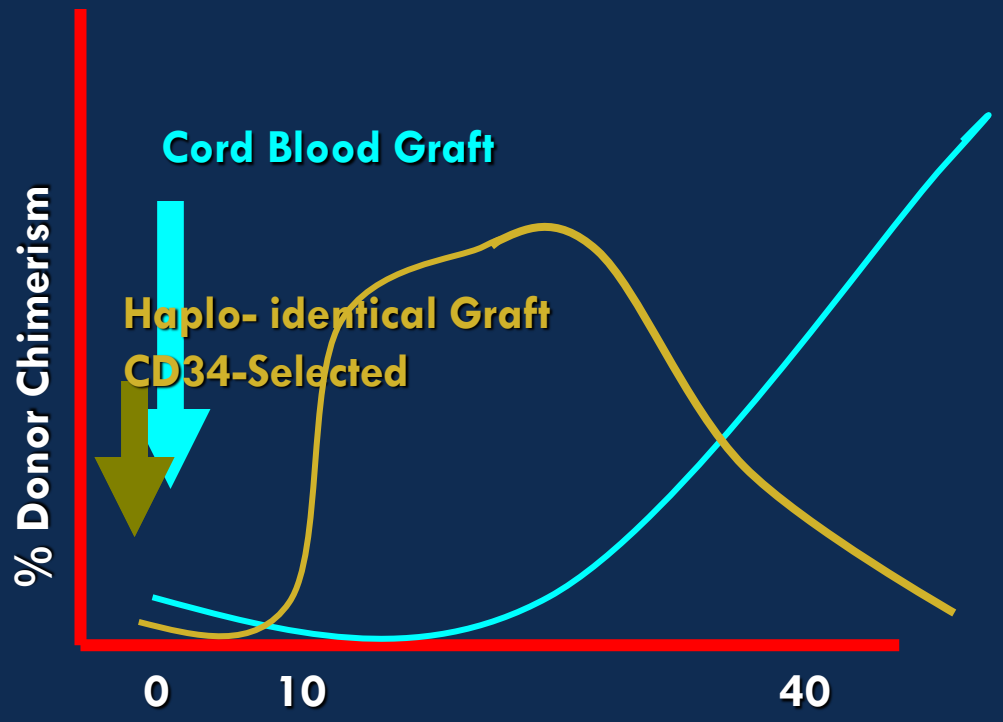


NRM
**3 MMURD*

Truelove et al, BBMT 21, 483, 2015

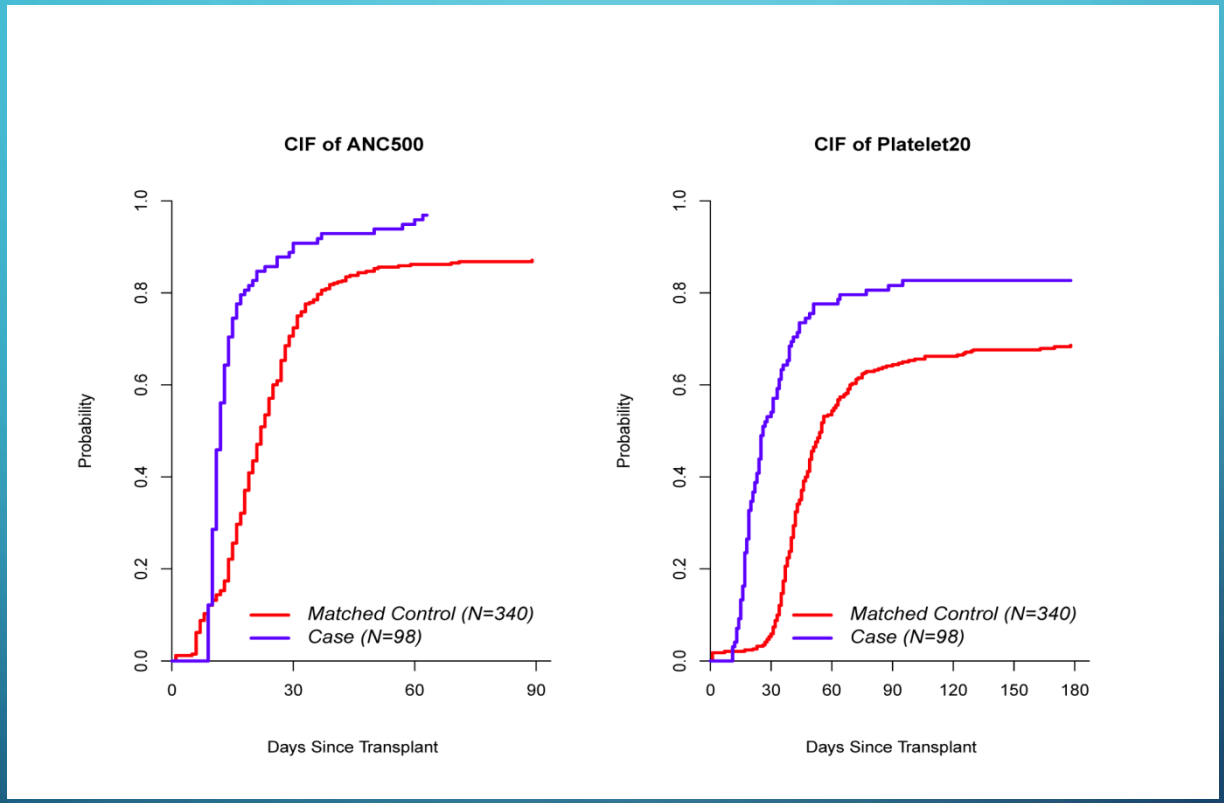
8/8 Allele, Available-Match Rates in the Adult Donor Registry





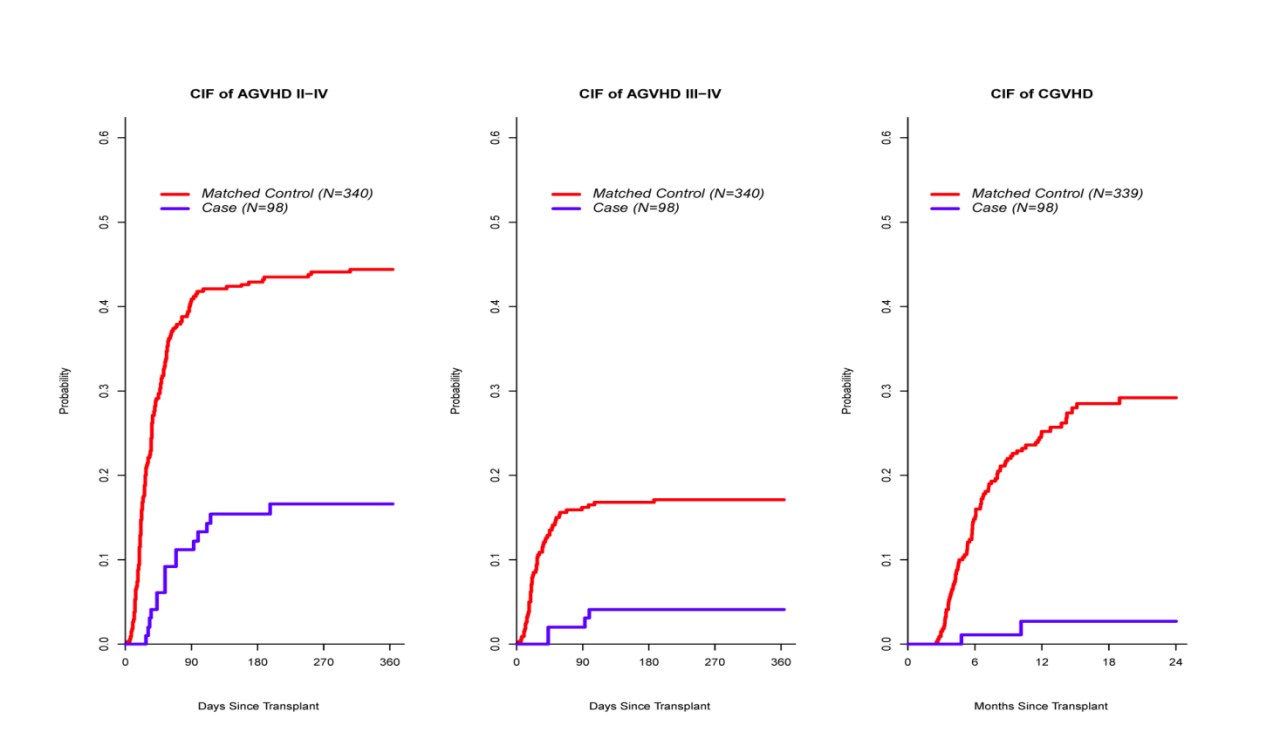
Fernandez, Exp Hematology 31, 535, 2003
Magro et al, Haematologica 91, 540, 2006,
Liu et al, Blood 118, 6438, 2011

NEUTROPHIL AND PLATELET ENGRAFTMENT



Presented by: Koen van Besien, MD, PhD

INCIDENCE OF ACUTE AND CHRONIC GVHD

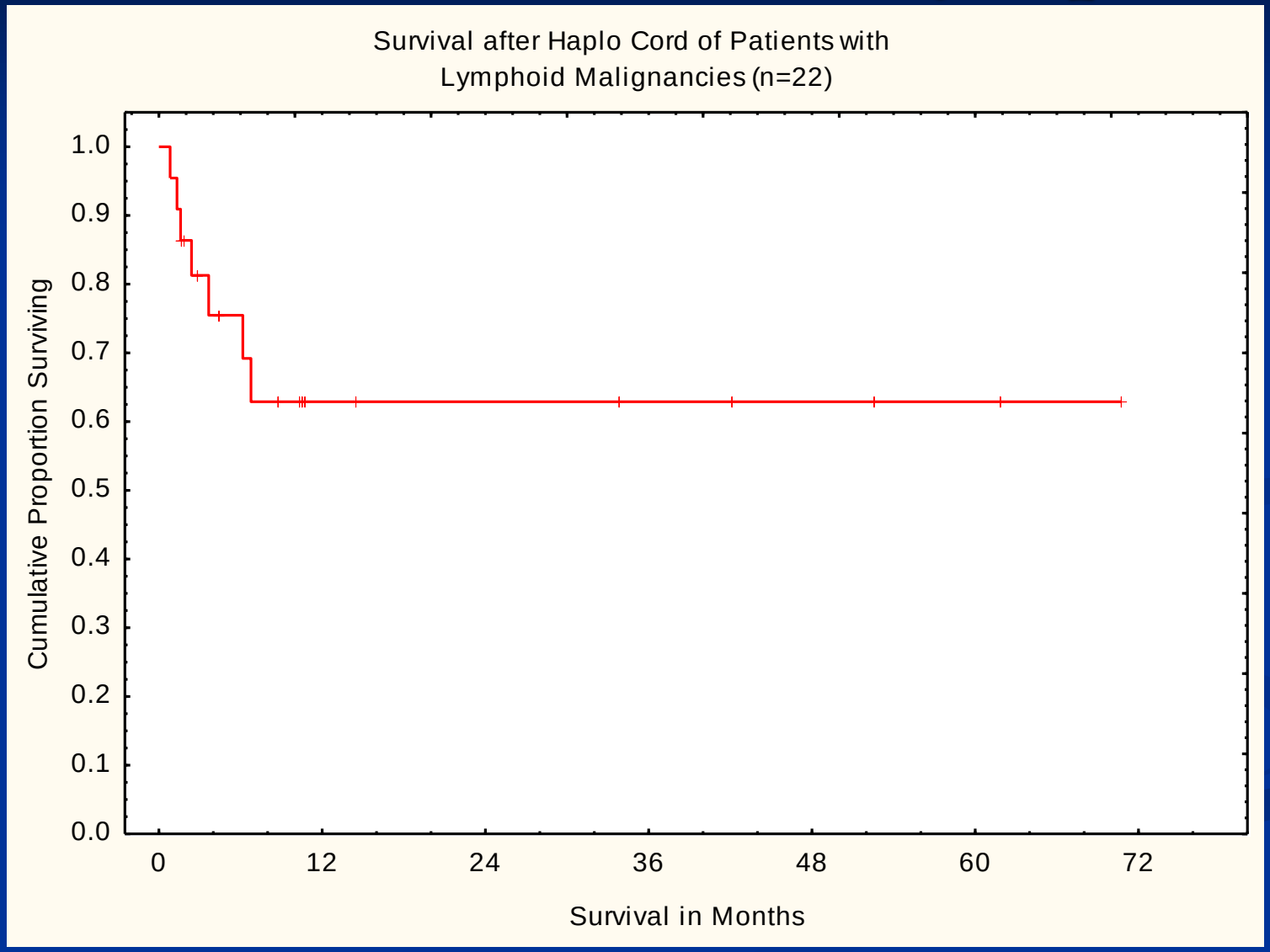


Haplo Cord for Lymphoma

	22
Age	54 (24-72)
Diagnosis	
HL	5
CLL	5 (1 Richter)
MCL	3 (2 Blastoid)
DLBCL (MYC)	2
FL Transformed	1
MF	2
PTCL	4 (ALCL, AngImm, HS)
Chemo Response	
Refractory (less than PR)	11
Chemo Sensitive	11

MFU Survivors: 11 months (2-71)

Survival after HC for lymphoma

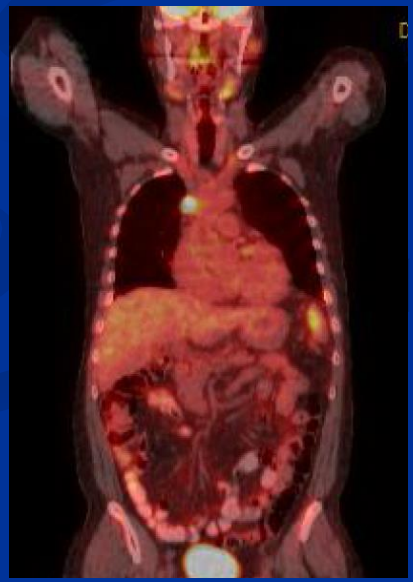


Case1: 36 y SC panniculitis like gamma delta T cell lymphoma

- 7/2012: SQ ,breast, liver, LN, spleen LDH 784 (nl250), hemophagocytosis
- EPOCH transient response, kinetic failure, ongoing hemophagocytosis.
- 11/2012: Flu-Mel-ATG +DUCBT
- Post tx: EBV neg B cell PTLD treated with rituximab.
- 10/2014: Ongoing remission. No GVHD

Pt 2: 64 y O Transformed lymphoma

- 11/09 stage 3 (BM negative) follicular grade II lymphoma (predominantly diffuse with sclerosis). watchful waiting)
- 11/11-4/12: **Benda rituxan** x6 with CR
- May 2013 relapse with LN, spleen pleural pericardial effusion. increased LDH.
- 4/2013- **R-CHOP x** 6. PR stomach SUV 5.8.
- Referred for auto BMT but fails collection.
- PET PD. → RICE x1 with PR
- Comorbidities: Afib, DM
- **1/2014: HC SCT Flu Mel ATG**
- 1/2015: Ongoing remission, no GVHD



Pt 3: 67 DLBCL Lymphoma

- 1995 DLBCL:CHOP + Bexxar (study)
- 2005: relapse: Intermittent rituxan
- 2013: bone marrow, PB, LDH 3000, t(8;14) MYC rearrangement, + additional cytogenetic abnormalities
- VIPERx 4→ residual marrow necrosis, LDH nl
- Comorbidities CHF, DM, PS: 60
- 12/2013: HC
- Multiple marrows with ongoing necrosis
- 03/2015: remission, limited cGVHD (vitiligo)

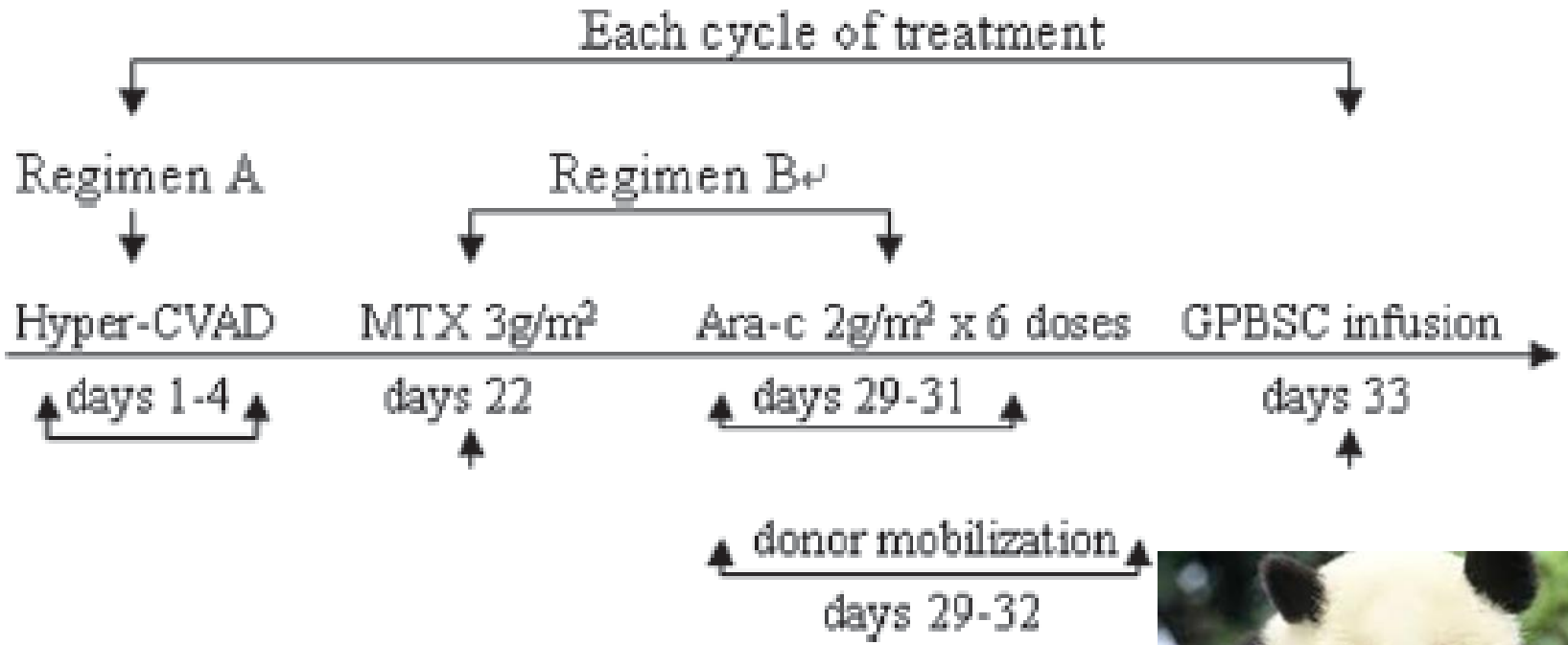
Allogeneic Transplantation

- Excellent treatment for pts unlikely to respond to autologous, failed autologous, failure to collect stem cells.
- GVHD is associated with worse survival, worse QOL and there is no evidence that it reduces relapse rates in lymphoma
- Age is not a contra-indication.
- Suitable donors can be identified for nearly all patients.
- LDH rather than PET may be predictor

LETTER TO THE EDITOR

Programmed haploidentical hematopoietic stem cell infusion combined with systemic chemotherapy improves the outcomes of patients with refractory or relapsed lymphoma

Zhao Hong-Xia[1], Sun Wan-Jun[1], Li Jie[1], Hu Hai-Lan[1] & Ai Hui-Sheng[2]



Leukemia & Lymphoma 2015

	Prior Rx	Duration of Previous R	Best Prior R	Cell Dose CD34/CD3	
MCL	RCHOP		PD	2.44/0.56	D 16 m PD
BL	CHOP	12	CR	1.51/0.9	DFS 41 m
T-LBL	VMCP	8	CR	2.1/0.7	DFS 41 m
T-LBL	VMCP	4	CR	2.7/0.9	DFS 31 mo
T-LBL	EPOCH	6	CR	2.8/1.8	DFS 28 mo
DLBCL	RCHOP		PD	.7/.9	D 4 m PD
DLBCL	RCHOP		PD	0.9/0.2	D 10 m PD
MCHL	ABVD		PD	0.8/0.7	DFS 31 mo
MCHL	MOPP ABVD BEACOPP	15	CR	2.6/0.6	D 3 m inf
MCHL	ABVD BEACOPP	10	CR	2.9/07	DFS 19 m