Allogeneic Transplantation for Hodgkin Lymphoma *(past, present and future)*

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Allogeneic HSCT for HL

More is less … NRM 40-65%

- 100 HLA identical sibling allografts
- median age 28 yr
- TRM 61%
- Relapse 65%
- DFS 15%

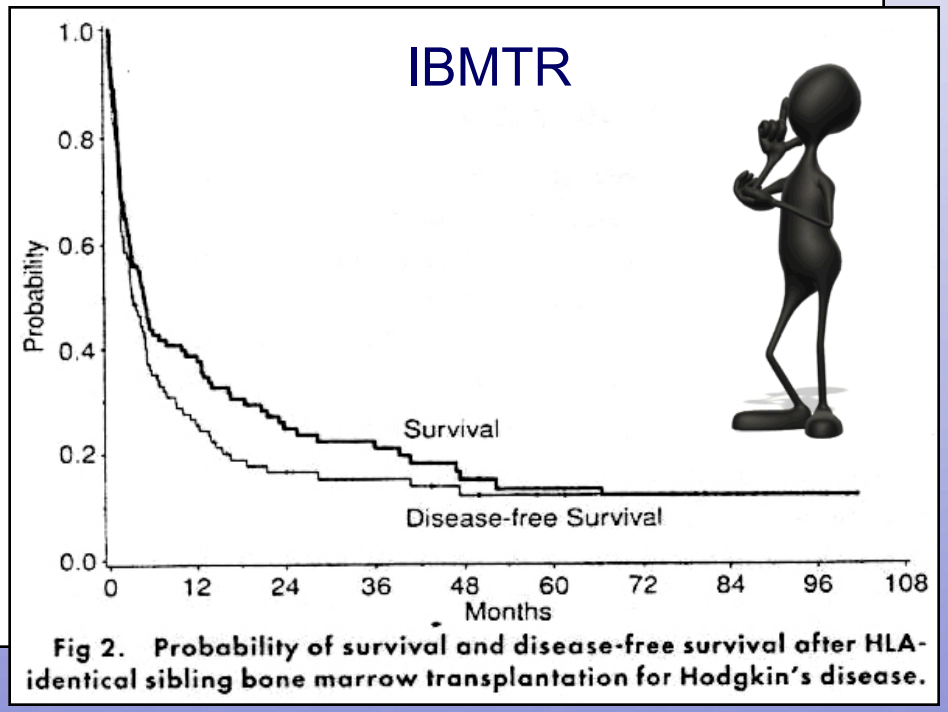


Fig 2. Probability of survival and disease-free survival after HLA-identical sibling bone marrow transplantation for Hodgkin's disease.

Gajewski et al. ***JCO*** 1996;14:572

Allogeneic HSCT for HL

More is less …

- Matched pair study - 45 pts in each group
  - sex, age, status at Tx, time D - T[illegible]SI

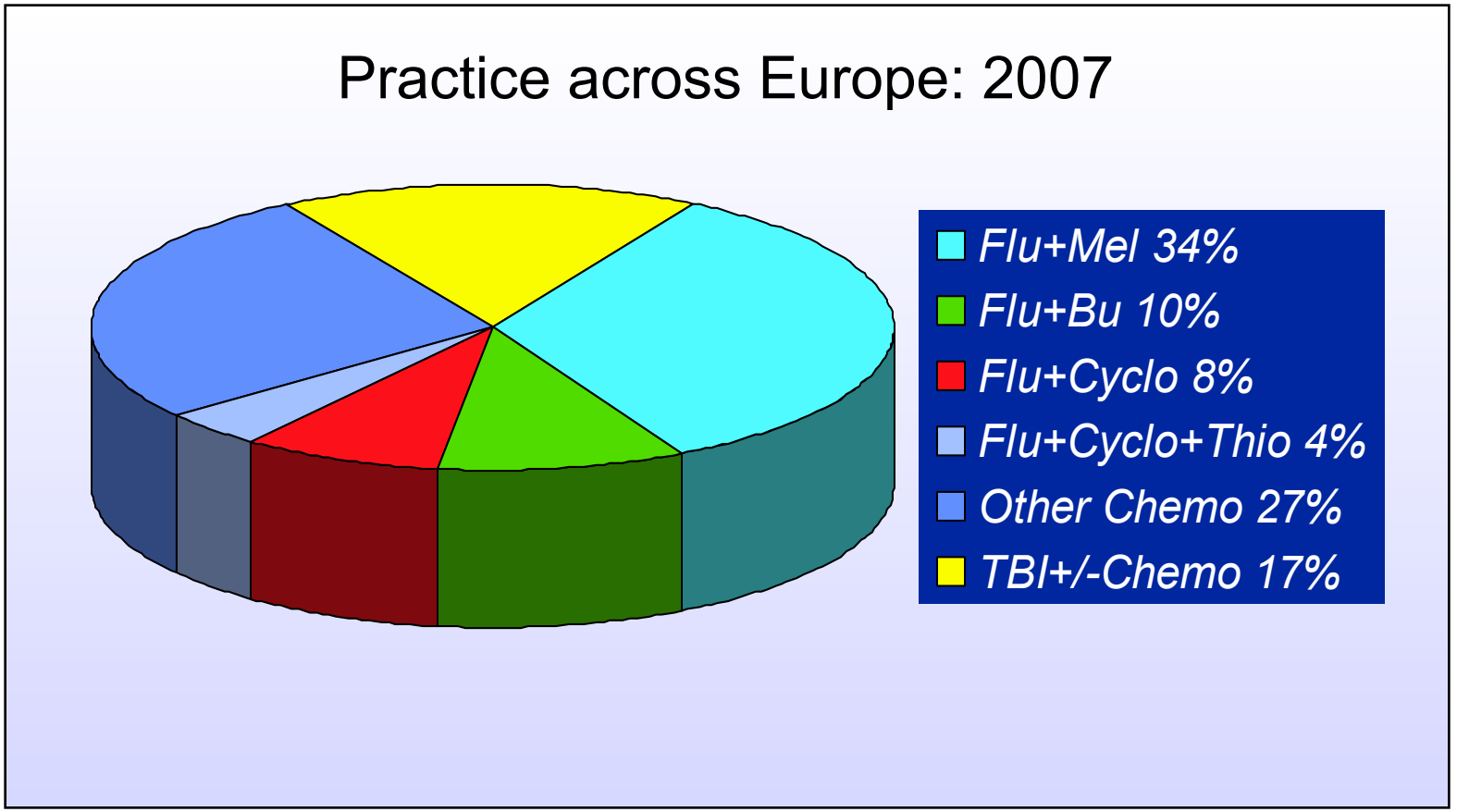
		Allo
TRM	12%	65%
Chemosen[illegible]	64%	30%

- Acute GV[illegible]
  - [illegible]isk of relapse
  - [illegible]wer overall survival

"allogeneic HSCT not recommended"

Milpied et al. ***JCO*** 1996;14:1291

Present: 2000s 'Reduced intensity' transplants



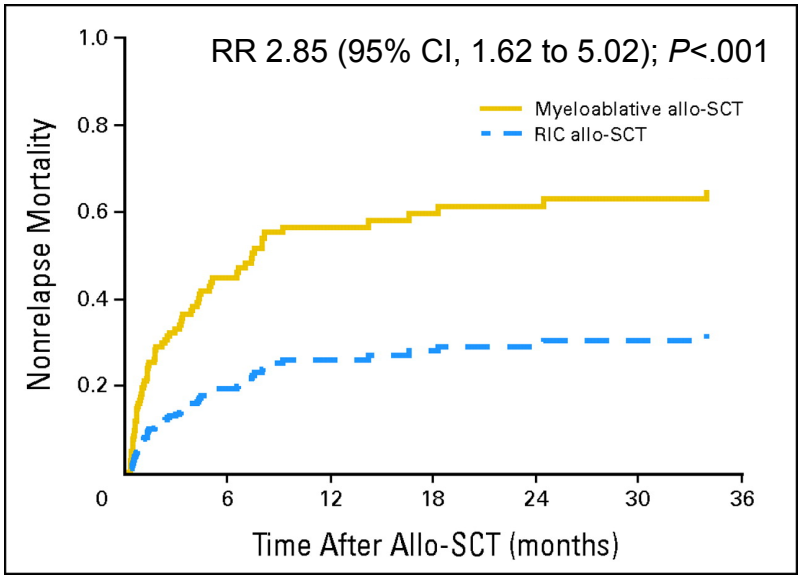
Summary of early RIC experience

Study	n	TRM	Relapse	PFS	PFS Refractory	OS
EBMT	401	22% (2yr)	53% (3yr)	26% (3yr)	7% (3yr)	41% (3yr)
UK (MF-A)	49	16% (2yr)	45% (3yr)	39% (4yr)	22% (4yr)	56% (4yr)
Spain (MF)	40	25% (1yr)	44% (3yr)	32% (2yr)	10% (2yr)	48% (2yr)
FHCRC (F-TBI)	35	??	>70% (3yr)	8% (3yr)	??	35% (3yr)
UMN (F-TBI-Bu/C)	21	25% (6m)	??	20% (2yr)	??	48% (2yr)
GITMO (CFT)	32	3% (3yr)	81% (3yr)	16% (3yr)	??	32% (3yr)
MDACC (MF)	58	15% (2yr)	55% (2yr)	32% (2yr)	12% (3yr)	64% (2yr)
DFCI (F-Bu)	36	15% (3yr)	63% (3yr)	22% (3yr)	??	56% (3yr)
			45-80%	*10-40%*		*30-60%*

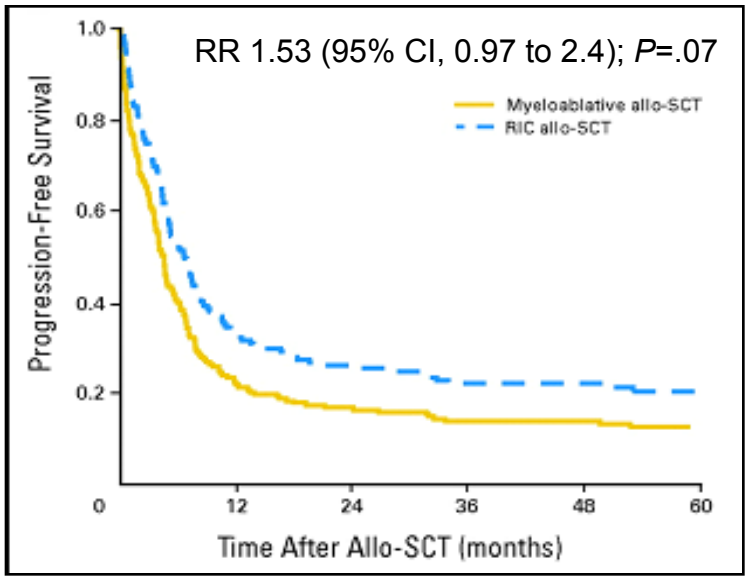
Relapse has become the commonest cause for treatment failure

RIC compared with conventional allogeneic SCT in relapsed or refractory Hodgkin Lymphoma

Non-relapse mortality (n=168)



Progression free survival (n=168)



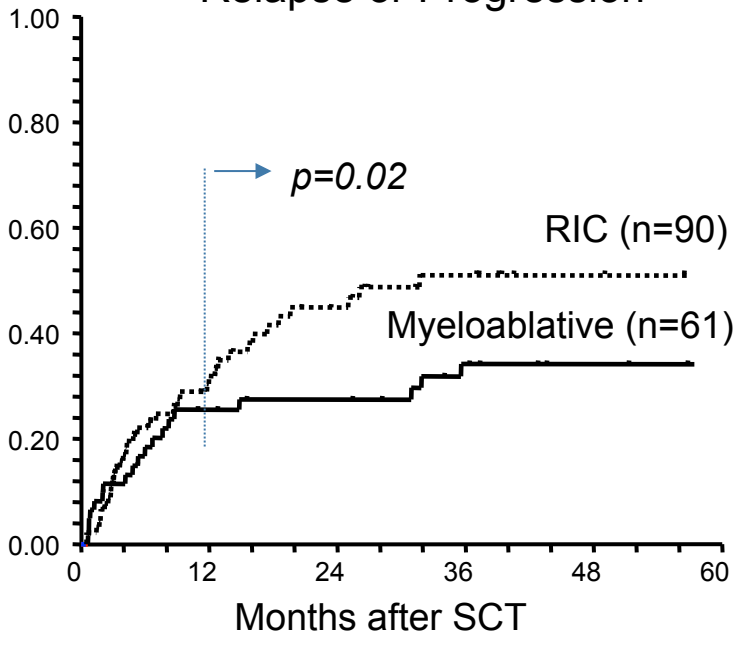
52% failed ASCT

*Sureda et al. **J Clin Oncol**. 2008; 26:455-62*

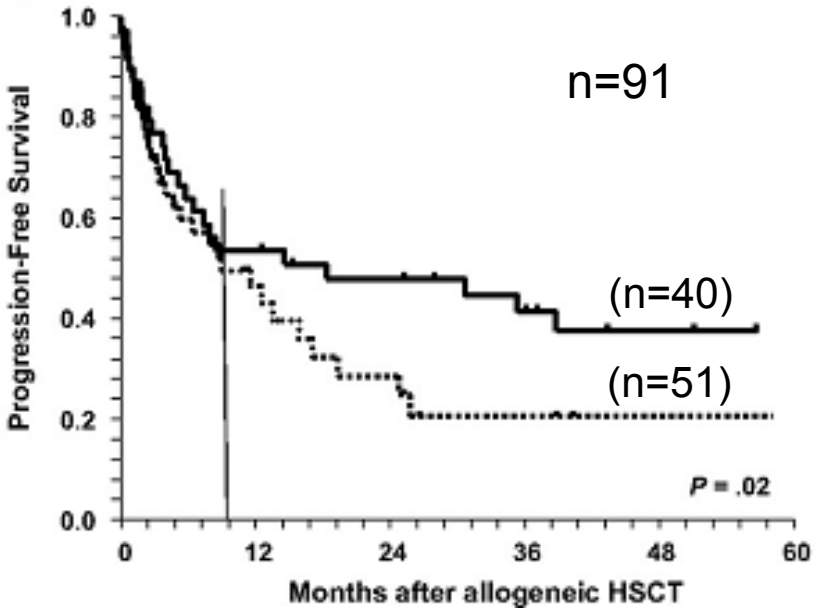
Allogeneic HSCT in children and adolescents with recurrent Hodgkin Lymphoma

- n=151 (1987-2005); failed ASCT: 55%
- Median age at diagnosis: 15 yrs (2-18); at SCT: 17 yrs (4-21)

Relapse or Progression



PFS



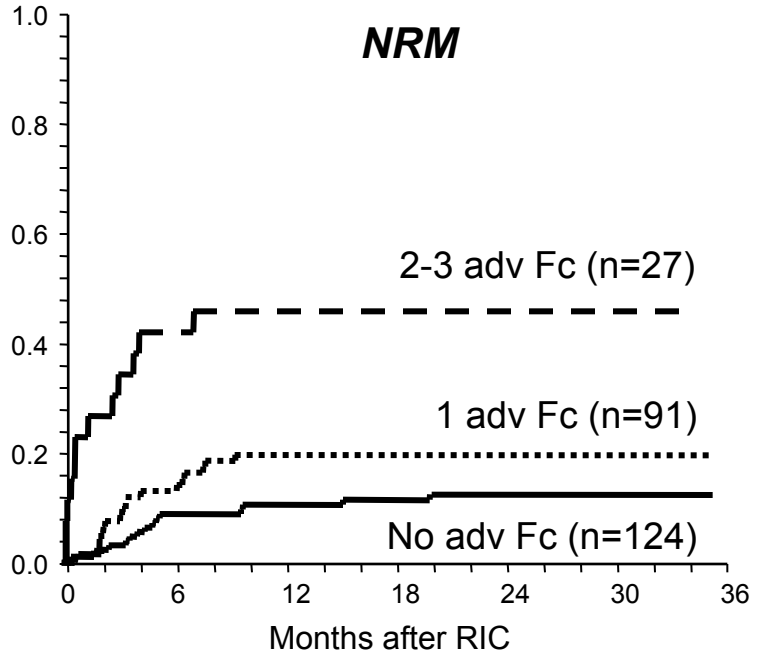
Same NRM, but increased RR following RIC, with a trend to lower PFS

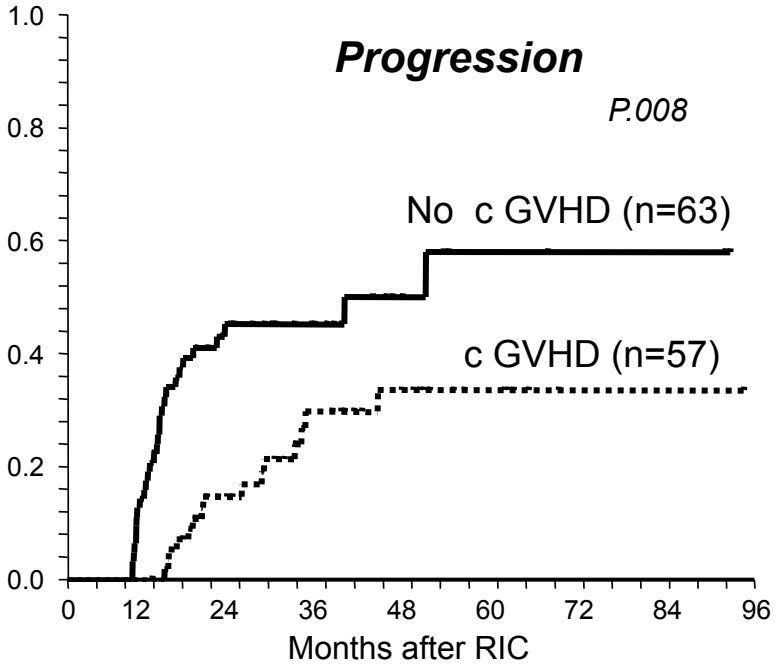
Claviez et al. ***Blood*** *2009; 114(10):2060-67*

Defining prognostic factors: EBMT

Adverse Fc for NRM:
- age ≥ 45 years
- poor performance
- chemorefractory

Risk of progression after 9 months of RIC according to cGVHD (Landmark analysis)





Prior Transplant, Donor Relation and TCD: ns

TCD no significant impact

Sureda et al. **JCO** 2008; 26:455-62

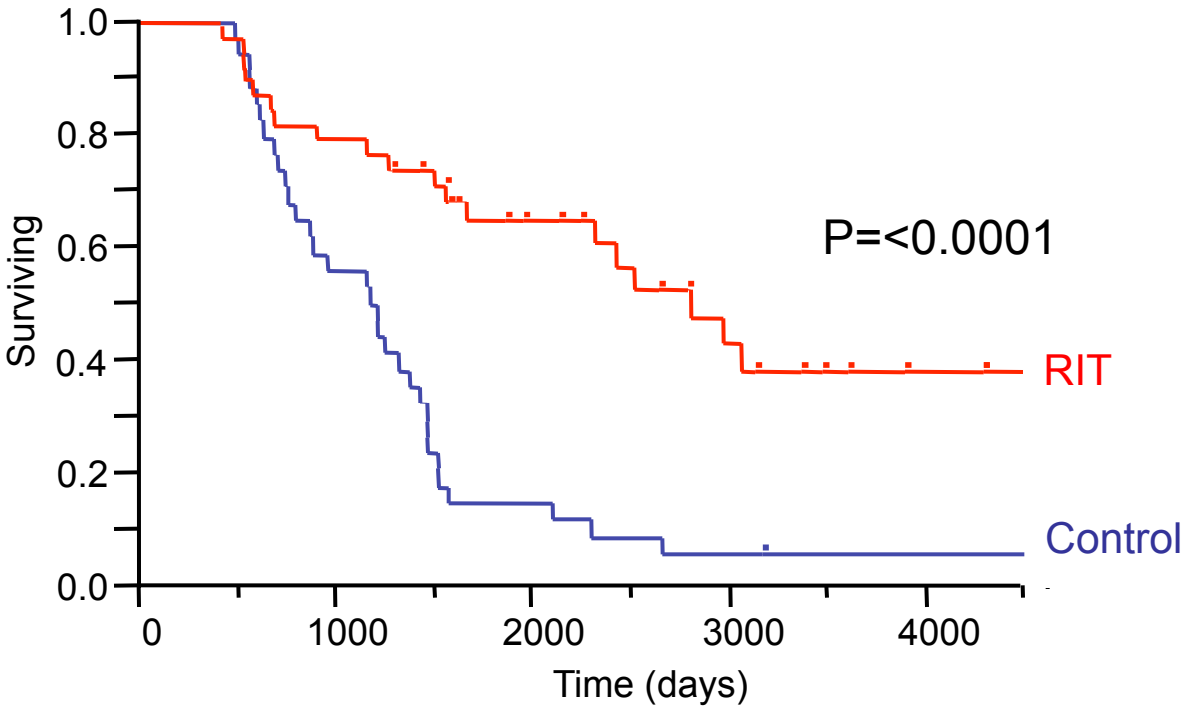
RIC to salvage autograft failure

Outcome for relapsed HL post-autologous transplant is poor: median survival <24 months

- RIT group: 1998-2004, 7 UK centres
  (n=38) all autograft failures
  34% chemorefractory
  related 63%, unrelated 37%
- Control group: autograft 1990-1997
  (n=34) all autograft failures
  all chemosensitive at relapse
  survival >12m from relapse

Thomson et al. ***BMT*** 2008;41(9):365-70

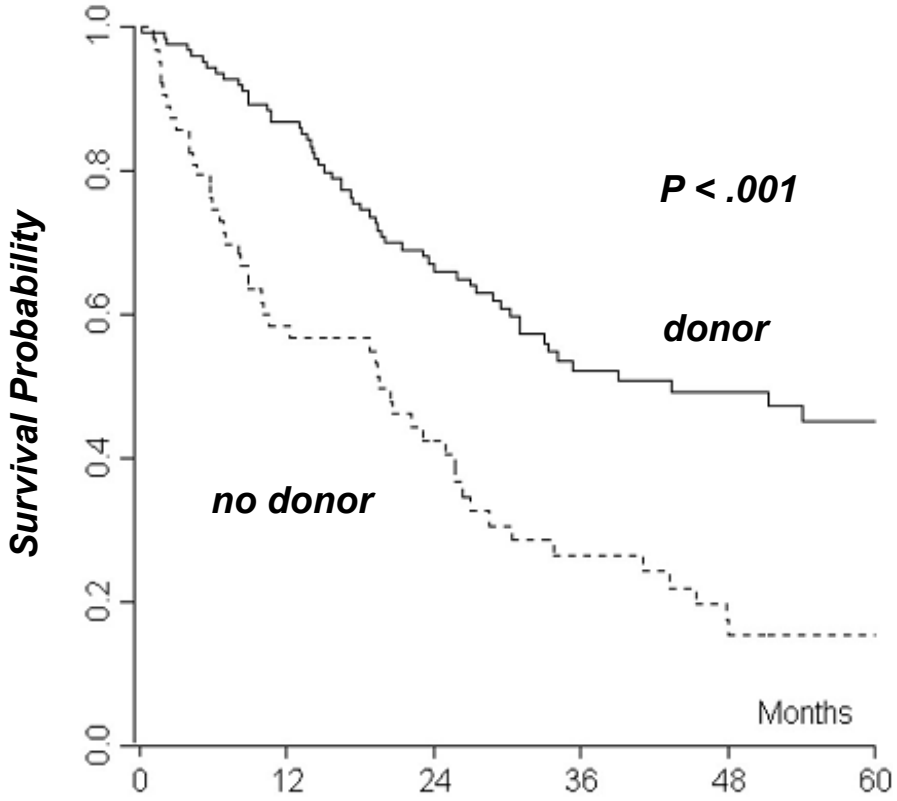
Overall survival from autograft



Outcome	RIT	Control	*P* value
OS at 10yrs from diagnosis	48%	15%	0.001
OS at 5yrs from autograft	65%	15%	<0.001

Thomson et al. ***BMT*** 2008;41(9):365-70

Overall survival from autograft



donor:	**122**	**102**	**67**	**40**	**27**	**17**
no donor:	**63**	**35**	**22**	**12**	**7**	**6**

Sarina et al. ***Blood*** 2010;115:3671-7

Addressing relapse - donor lymphocytes

- DLI are used to enhance alloreactivity in an attempt to enhance GvT
- Allo- and GvT-reactivity are closely aligned using current strategies
- Tumour-specific responses may occur

3 general strategies:

- Therapeutic
- Pre-emptive: targeted to e.g. mixed chimerism or MRD
- Prophylactic

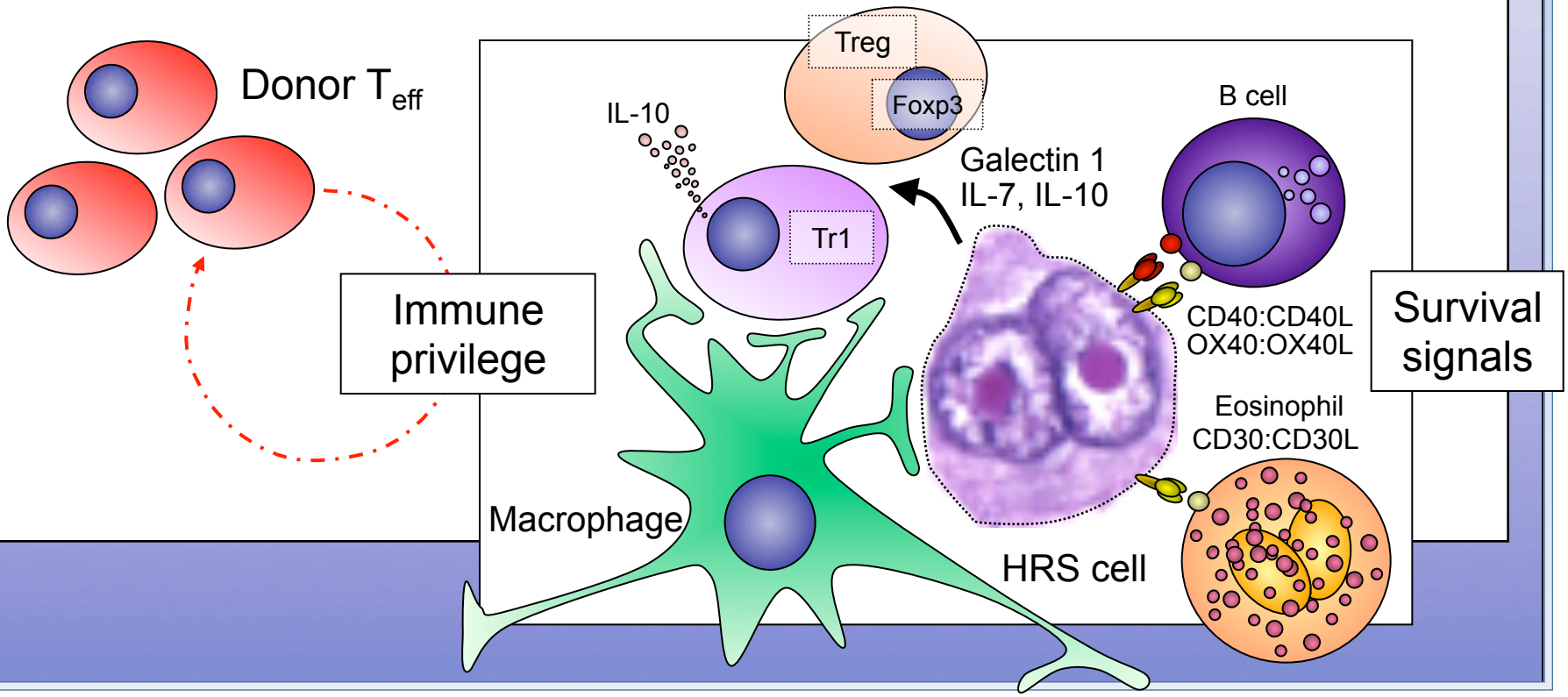
'Therapeutic' Donor Lymphocyte Infusions

Study	n	Preceding chemotherapy	CR/PR	Response rate	Response rate (DLI only)	Response at latest follow-up: time from last DLI
N. American survey (1999)	6	unknown	0/2	29%	unknown	2 PR 6+ and 18+ months
UK	24	10	14/5	79%	93%	9 CR, 2 PR median 4.6 yrs for CR
Spain	11	3	3/3	55%	N/A	None ongoing
UMN	2	unknown	0/2	100%	unknown	None ongoing
GITMO	9	0	3	33%	33%	unknown
MDACC	27	10	6/4	37%	29%	2 CR 8+ months
DFCI	13	unknown	2/0	15%	unknown	unknown
EBMT Registry	41	23	13	32%	44%	unknown
EBMT Registry (adolescent)	6	unknown	1/0	17%	unknown	1 CR 1 year

- Overall response rates variable 30-80% (44/92 = 48%)
- A significant minority have durable responses (16/40 = 40%)

Donor Lymphocytes - Basic concepts

- If the major aim of HSCT is to foster GvT, modulation of the locally immunosuppressive microenvironment may be key to success, allowing access of effectors to the target population



Donor Lymphocytes - Basic concepts

- Minimally intensive regimens may fail to allow full benefit of alloreactivity (cf. Seattle and GITMO - highest relapse rates) i.e. dose intensity may be important for indirect immunological as well direct anti-tumour effects
- Furthermore, intervention at a state of minimal disease may be particularly important for 'therapeutic' DLIs when the tumour microenvironment is so critical to immunity

Donor Lymphocytes - Basic concepts

- Pre-emptive DLI for mixed chimerism remains controversial
- Based on the argument that MC = bidirectional tolerance, which can be broken using DLI: this may be the case in TCD but not T-replete protocols i.e. relevance of MC likely contextual
- In TCD setting MC potentially allows titration of alloreactivity with a readout that might allow dissociation of Gv-LymphoHaematopoietic system vs 'other GvHD' (lessons from CML)

- Potential impact on HL relapse may only be unmasked when the tumour environment is permissive to effector responses i.e. even if the relevance of MC were equivalent in TCD vs TCR, the outcome of DLI may not be

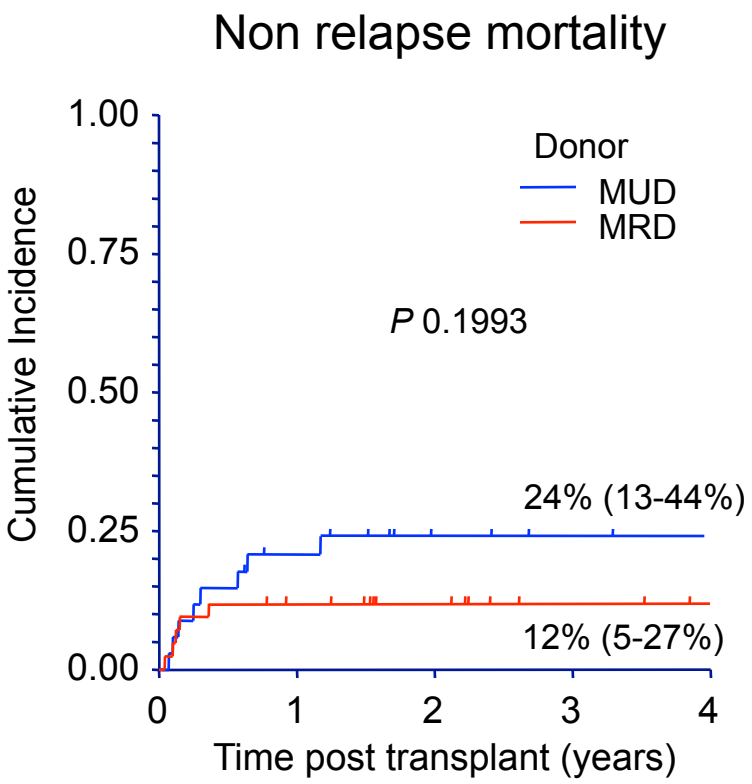
Donor Lymphocytes - Predictions

- Pre-emptive DLI for mixed chimerism will reduce relapse risk
- Monitoring the shift to full donor chimerism will allow titration of DLI dose to dissociate alloreactive GvHL effect from GvHD
- Therapeutic DLI will be more effective if intervention is directed earlier by functional imaging studies

RIC for Hodgkin Lymphoma: UCL experience

- n = 76 HL patients transplanted Oct ’97 - July ’09 at UCL

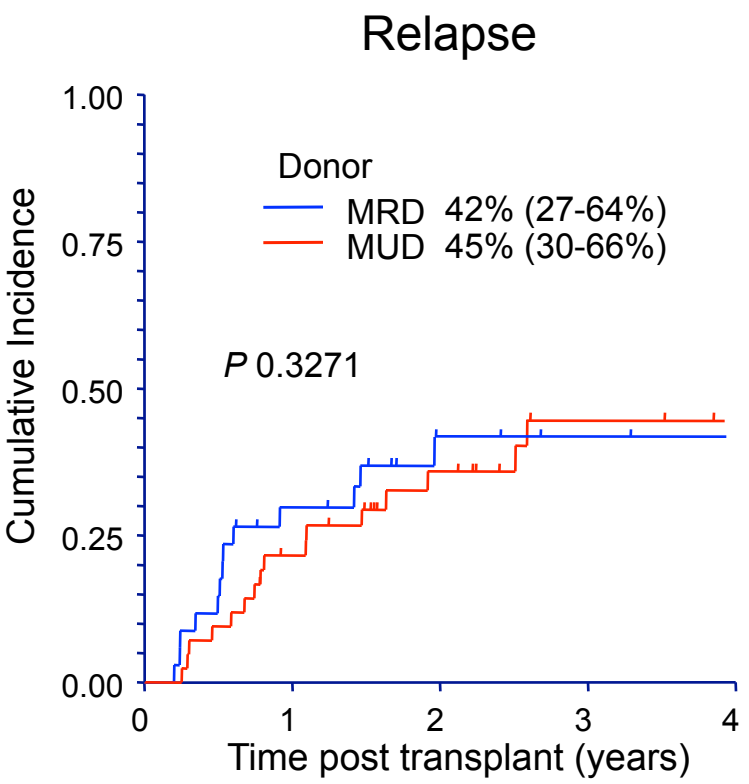
Characteristic		
Age		31 (13-59) yrs
Sex	M F	42 34
Primary resistant		50 (66%)
Failed autograft		45 (59%)
Prior lines		5 (2-10)
Status at Tx	CR PR Ref.	17 (22%) 33 (43%) 26 (34%)
Donor	MRD MUD MMUD	42 29 5 (8-9/10)
Follow-up (med, range)		2yrs (0.5-12.1)



Peggs et al. ***JCO*** 2011;41;29(8):971-8

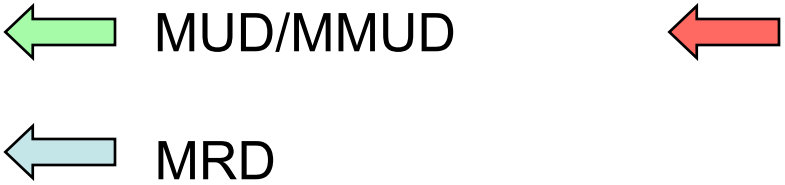
RIC for Hodgkin Lymphoma: Relapse

- aGvHD Gd II-III
  - MRD n=3/0, 7%
  - MUD n=8/2, 29%
- 31 relapses:
  - CR 5/17
  - PR 17/33
  - Refractory 9/26



DLI indications and schedule

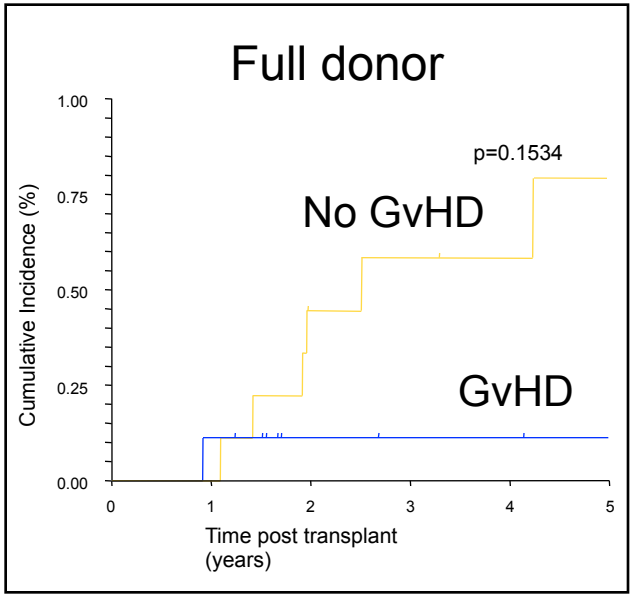
- DLI given for either mixed chimerism (from 6m) or relapse
- Relapse defined by recurrence or progression of FDG-avid lesions in sites of prior disease, with or without new sites
- If FDG-avid lesions only in new sites relapse confirmed by biopsy if accessible (n=12), otherwise an interval scan was performed at 6-8 weeks to confirm progression in the absence of other potentially causative pathology
- Dose escalation:
  - $1x10^6$ $CD3^+$/kg
  - $3x10^6$ $CD3^+$/kg
  - $1x10^7$ $CD3^+$/kg
  - $3x10^7$ $CD3^+$/kg
  - $1x10^8$ $CD3^+$/kg
  - $3x10^8$ $CD3^+$/kg



DLI for mixed chimerism

- 22 patients received DLI for mixed chimerism (18 MRD, 4 UD):
  - 20 converted to full donor
  - 2 stable at 5% following reduction from 30-40%

- Median time to 1st DLI: 287 days (9 months)
- GvHD:
  - acute: 1 Gd IV, 2 hepatitic
  - chronic: 4 limited, 1 extensive



Outcomes post relapse: n=31

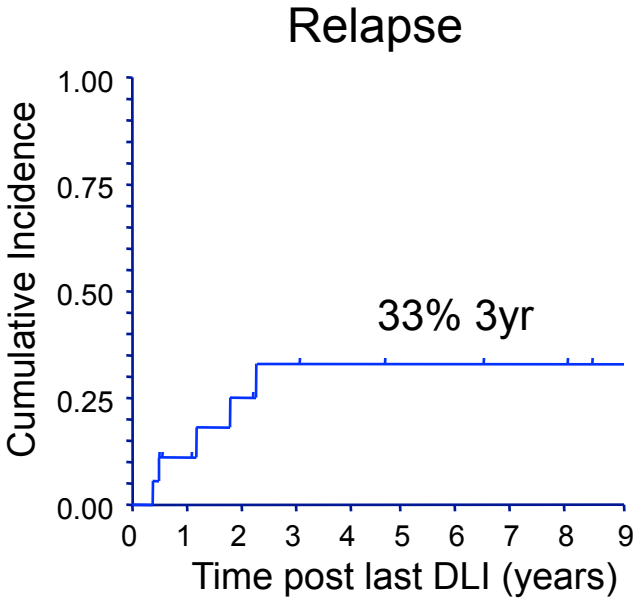
- 7 not given DLI:
  - 2 early progression (refractory)
  - 3 GvHD
  - 1 radiotherapy

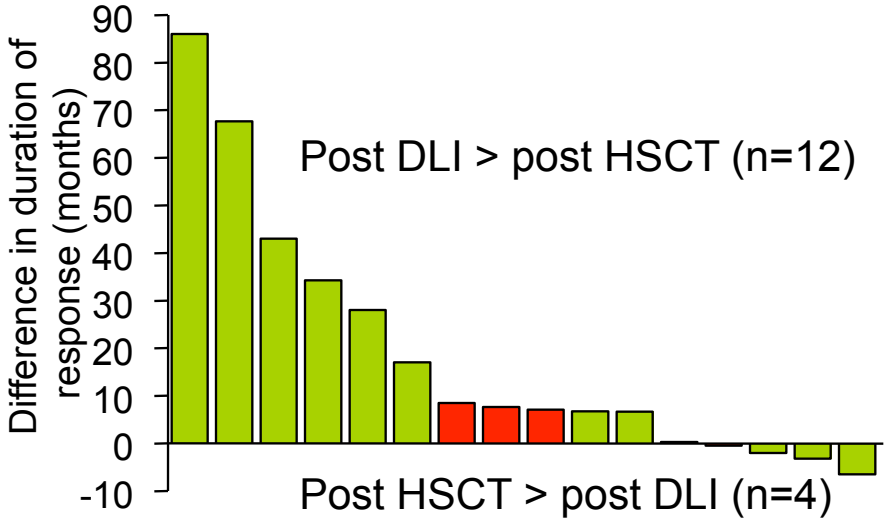
  } All dead at 45-494 days
  - 1 PR following CsA withdrawal, coincident with GvHD
- 24 received DLI
  - 13 MRD, 11 UD
  - 10 received cytoreduction prior to/between DLIs
    - gemcitabine, radiotherapy, ABVD, ESHAP, miniBEAM, IVE

DLI for relapsed disease

14 CR, 5 PR (79% response rate)

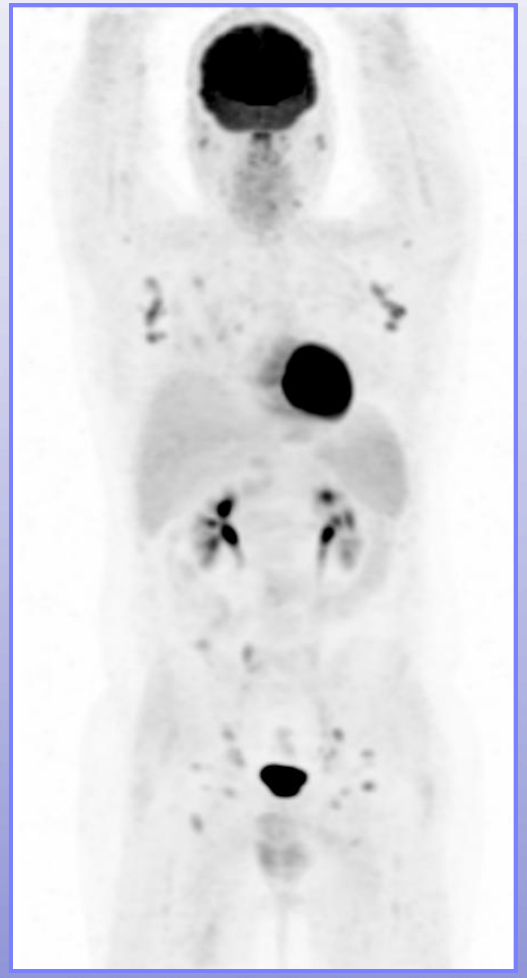
- MRD: 77% (9CR, 1PR, 3NR); UD: 82% (5CR, 4PR, 2NR)
- 13 responders (11CR) had no prior salvage





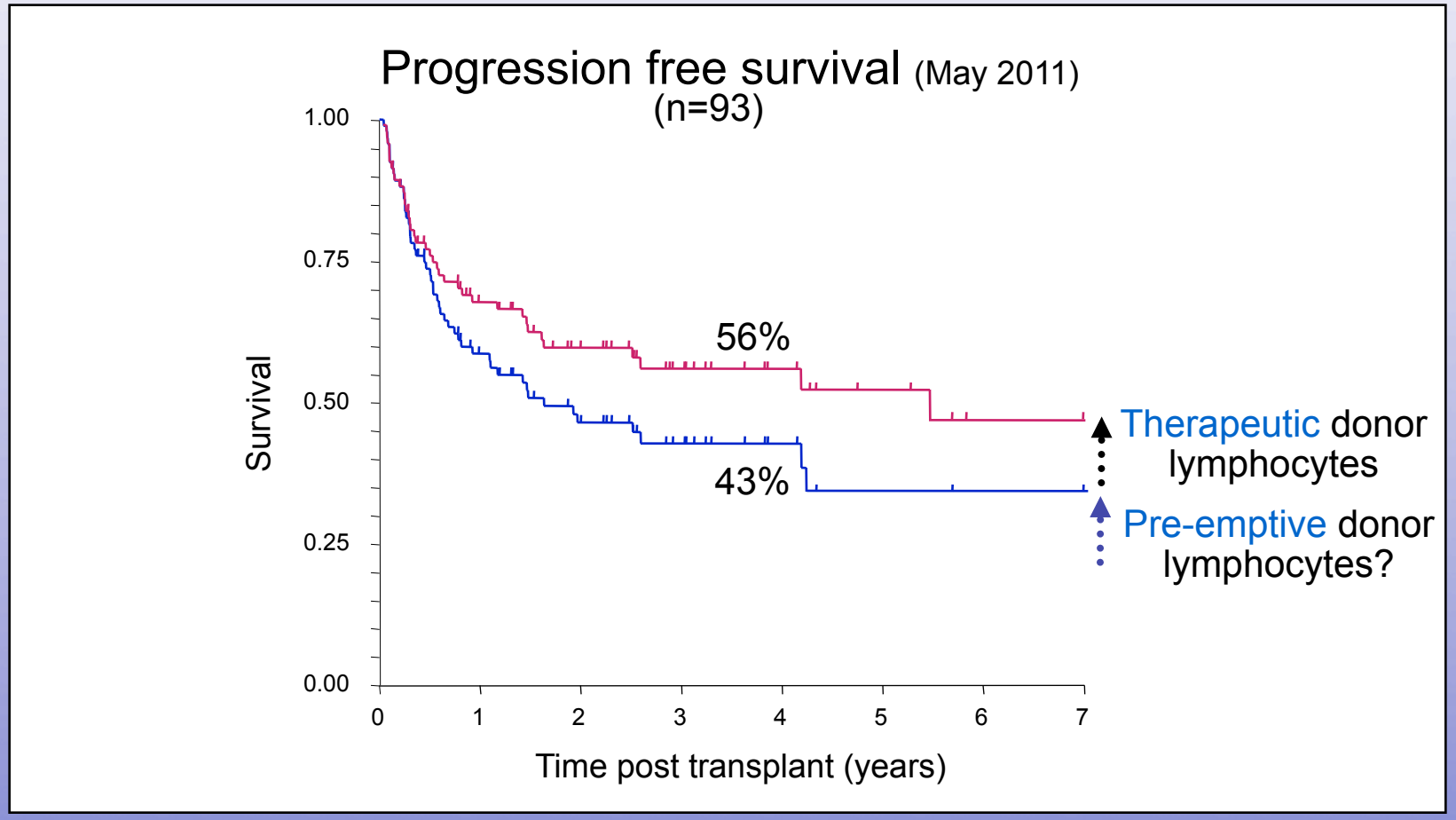
DLI for relapsed disease

Jan 03 - Aug 04



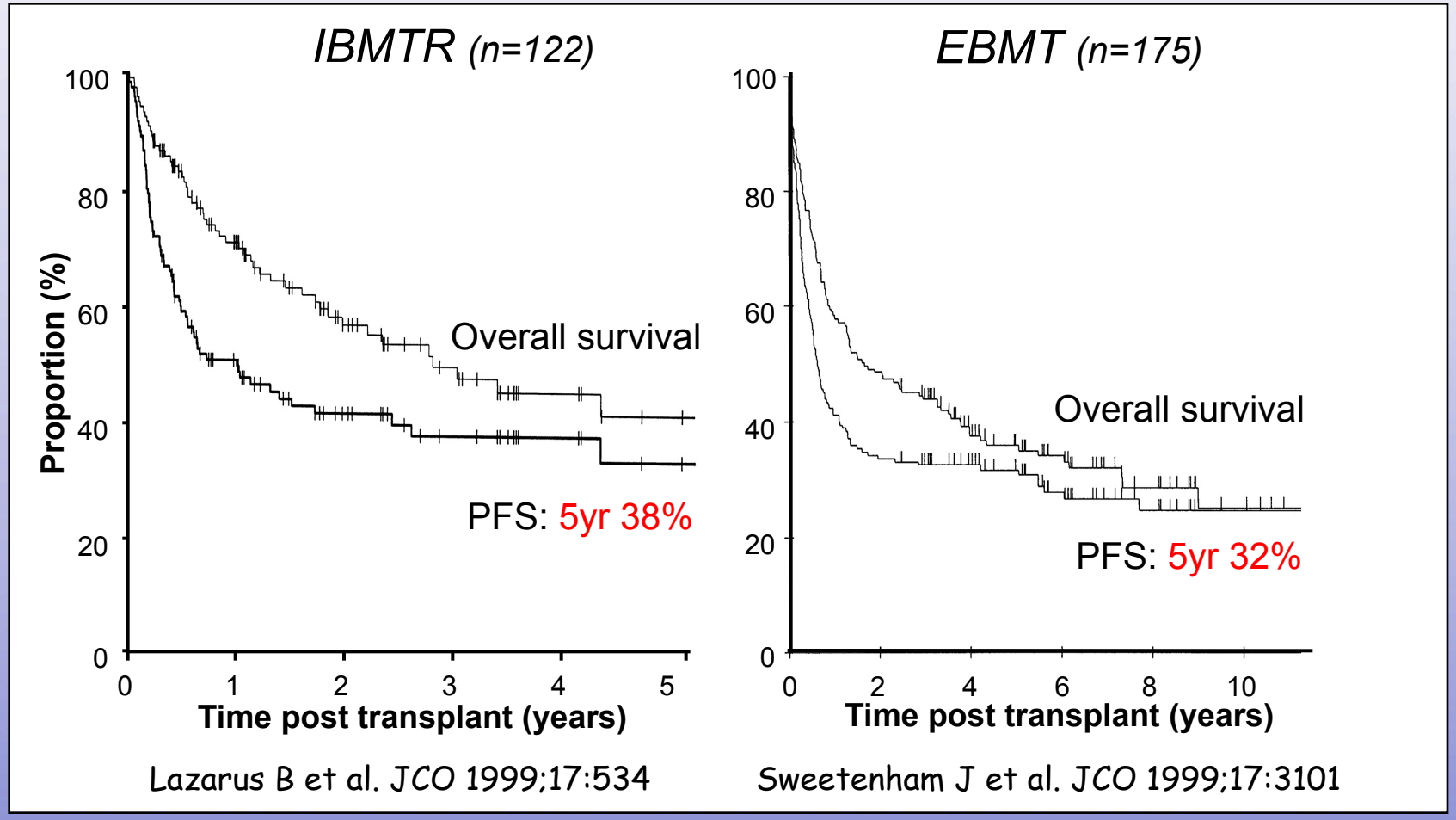
Nov 06 - Feb 08

Survival outcomes from transplant

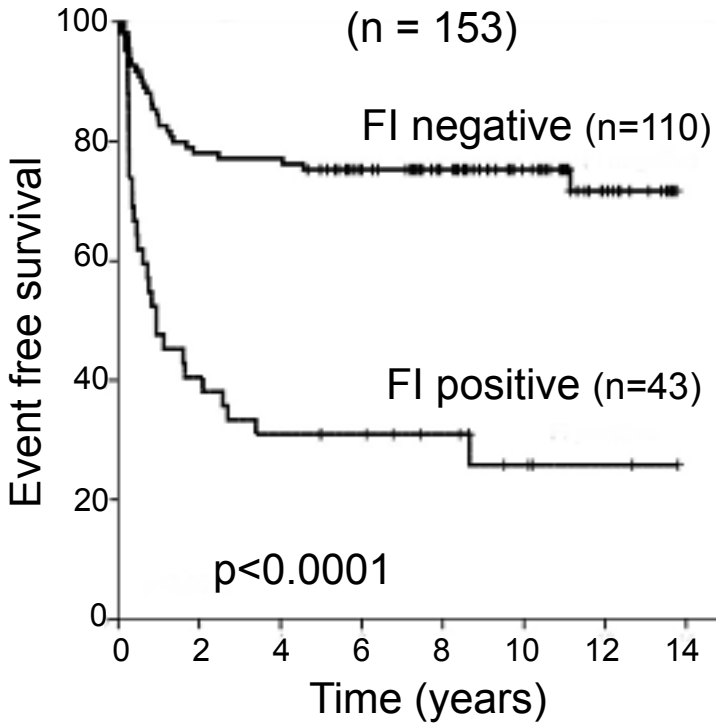


What next?

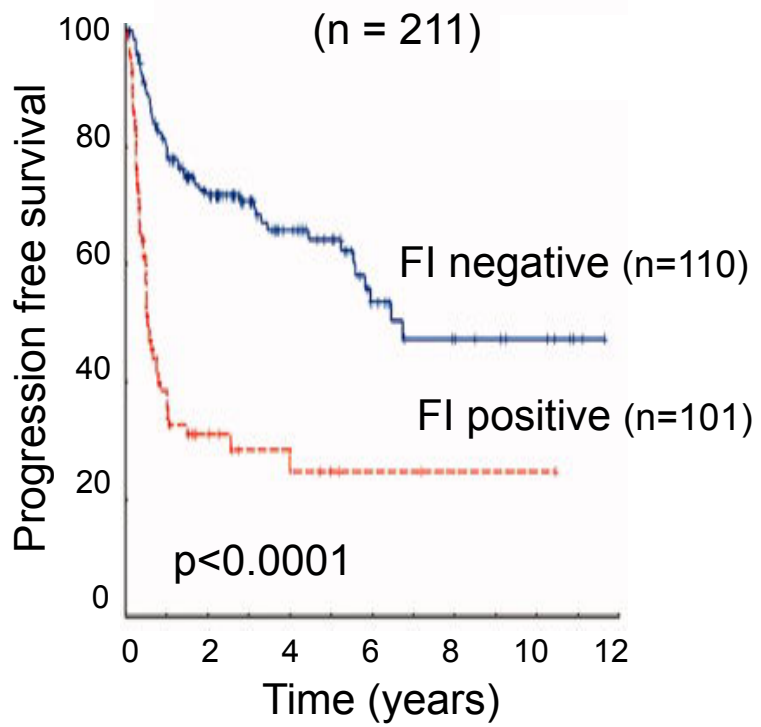
Autologous transplantation in primary refractory HL



Functional imaging predicts outcome post autograft



Moskowitz AJ. Blood 2010;116:4934



Jabbour E. Cancer 2007;109:2481

Tandem autografts

- Generally 2 ASCT within 1-3 months
  - OS 54-78%, PFS 49-59%
- GELA/SFGM H96 risk adapted strategy:
  - time to relapse <12 months
  - stage III-IV at relapse
  - relapse in previously irradiated site
- 0-1 = intermediate risk (n=95) 2-3 or PRHL = poor risk (n=150)
  - IR single ASCT: 5yr OS 85%, PFS 73%
  - HR tandem ASCT: 5yr OS 57%, PFS 46% (PRHL PFS 46%), TRM 6%

Tandem ASCT superior in poor risk patients with anything <CR to initial salvage?
Single ASCT for intermediate risk patients, or poor risk attaining CR?

A role for allografting?

- Alemtuzumab reduces long term GvHD-related morbidity and may modulate the tumour environment
- Aggressive treatment of MC may reduce relapse risk following TCD allogeneic HSCT
- Unrelated donors mismatched at up to 2/10 HLA-loci are a viable graft source following alemtuzumab-based conditioning
- FDG-PET may identify a group of patients with poor predicted outcome following autologous HSCT (PFS ~ 30% at 3-5 yrs)
- Transplant earlier in the disease pathway may be better tolerated allowing further reductions in NRM
- This may also allow consideration of escalating dose intensity

Dose Intensity

All series include significant nos. of refractory cases (33-50%)

PFS rates: 10-22% at 2-4 years in smaller series

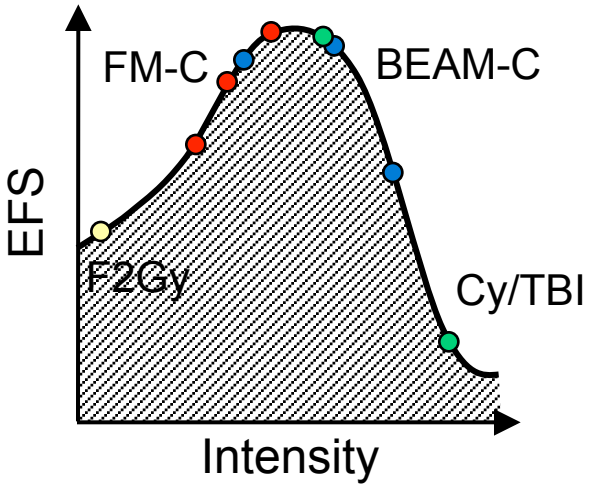
7% at 3 years in the EBMT analysis

PFS rates: Flu-Melph > less intensive Flu-Cy

(MDACC, Anderlini *et al*, 2005)

Some regimens are essentially devoid of anti-tumour activity

- particularly high relapse rates in GITMO and FHCRC



Conclusions

- Encouraging outcomes following BEAM-alemtuzumab allogeneic transplantation in a cohort predicted to have a relatively poor prognosis according to response to salvage
- Results require confirmation in a prospective multi-centre setting
- An appropriate subsequent comparison could be with a strategy of autologous transplantation (+/- brentuximab), with salvage consolidated by allogeneic transplantation in relapsing patients