Stem cell transplantation and immunotherapy

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Post-ASH 2011 meeting, 6-1-2012

Transplantation Abstracts

1886

* Oral > poster
* Randomized, prospective trials
* Studies with impact on daily practice

Immunotherapy Abstracts

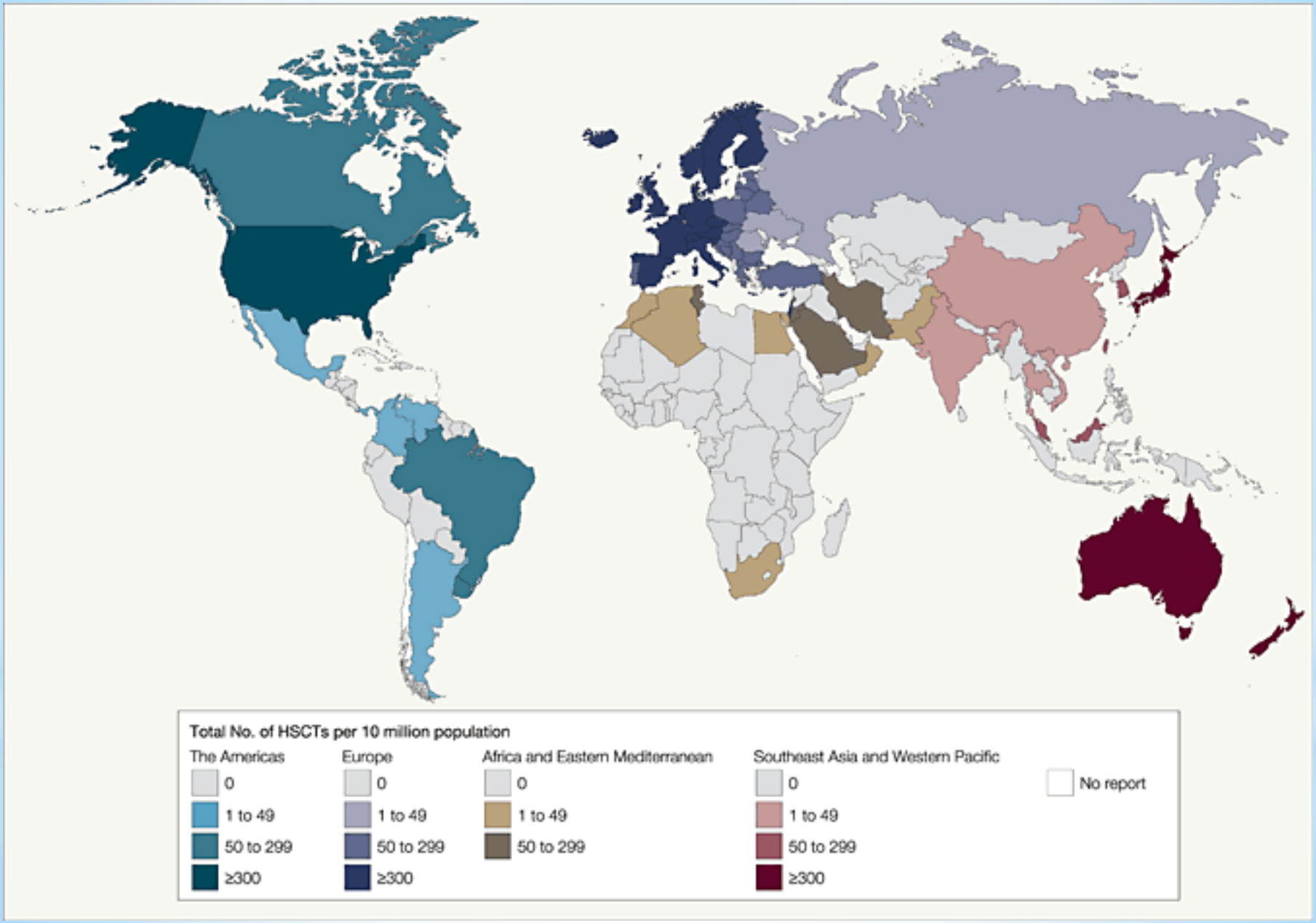
192

* **Autologous stem cell transplantation**
  * Indications: New? Old? Identify ideal candidates?
  * Mobilization
  * Conditioning?
  * Management of relapse post transplant?
* **Allogeneic stem cell transplantation**
  * Indications: New? Old? Identify ideal candidates?
  * Stem cell source?
  * Conditioning
  * GVL/GVT balance
  * Post transplant strategies to improve outcome
  * Management of relapse post transplant?
  * Acute GVHD
  * Chronic GVHD
* **Immunotherapy**

*Overview

If stem cell transplantation is dying, it sure is enjoying it's final days…

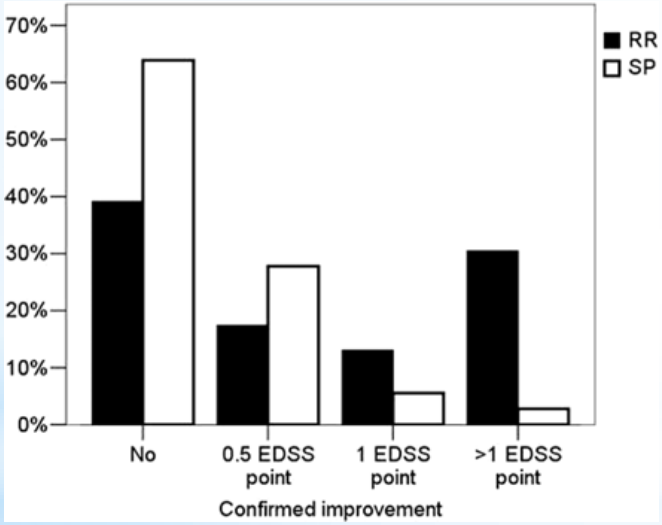
Michael Bishop, ASH News Daily, Monday December 12, 2011



Gratwohl, JAMA, 2008

* New indications?

- Auto-immune diseases (Tyndall, educational HSCT I):
  - Auto HSCT for scleroderma: change in angiogenic niche
  - Auto/allo MSCT for Crohn (fistulae) (Ciccociupo, Gut, 2011) and lupus nephritis (randomized trials ongoing)
- Multiple sclerosis (Abstracts #334, #2020, #3075)
  - > 600 MS pts worldwide have undergone ASCT, >> retrospective trials, 10 small controlled trials, BEAM+ATG, CD34 selection
  - **#334 (Saccardi)**: prospective, multicenter, n=74 (MS unresponsive to conventional R/), CY/G-CSF mob PBSC, condit BEAM-ATG, median FU=48 m
    - @5y: 60% alive, PFS@5y: RR (71%), SP (62%), TRM: 3,3%
    - condition stable/improved, feasible, better QOL



RR= relapsing remittent
SP=secondary progressive

Valuable R/ option for young pts in early phase MS

  - **#2020 (Chen)**: retrospective, n=25, G-CSF mob PBSC, CD34-selected grafts, condit BEAM-ATG: PFS@3y: 74%, @6y: 65%, @9y: 48%; neurological improvement
  - **#3075 (Nash)**: Phase II, prospective, highly active RR MS, n=25: EFS@1y: 96%, @2y: 77%

* Auto SCT: indications

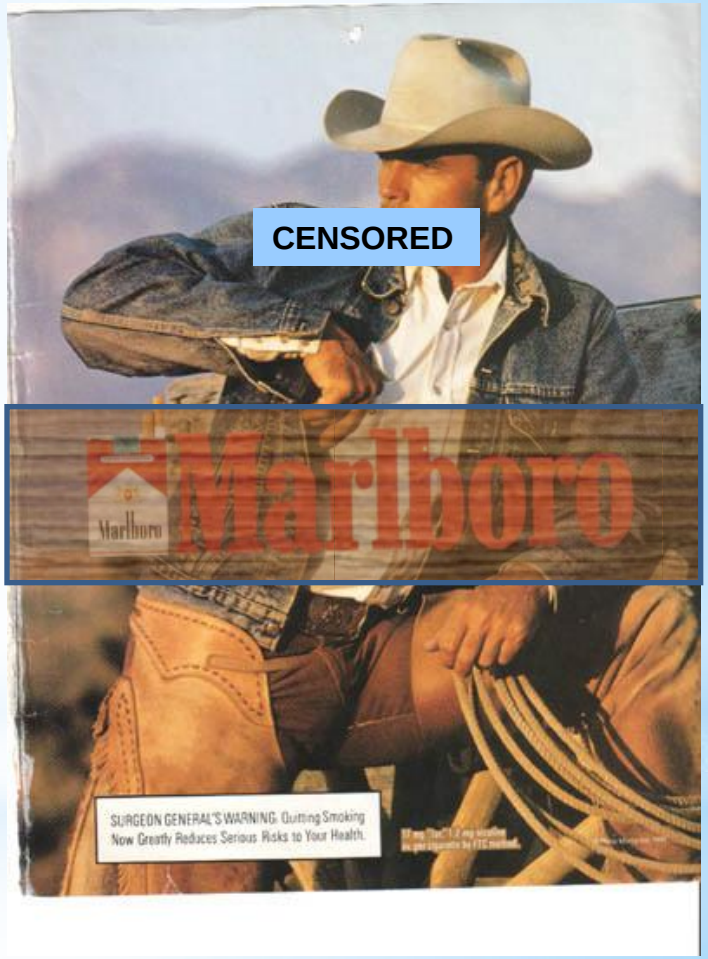
* Impact of nicotine exposure to mobilization (**# 1934, Haile**): retrospective, single centre, male patients with MM, n=137 (9.5% nicotine exposure during mobilization): improved mobilization in patients with nicotine exposure

Table 2: Simple Logistic Regression Analysis for Predicting Day1 CD 34Cell Count ≥ 4 million/kg

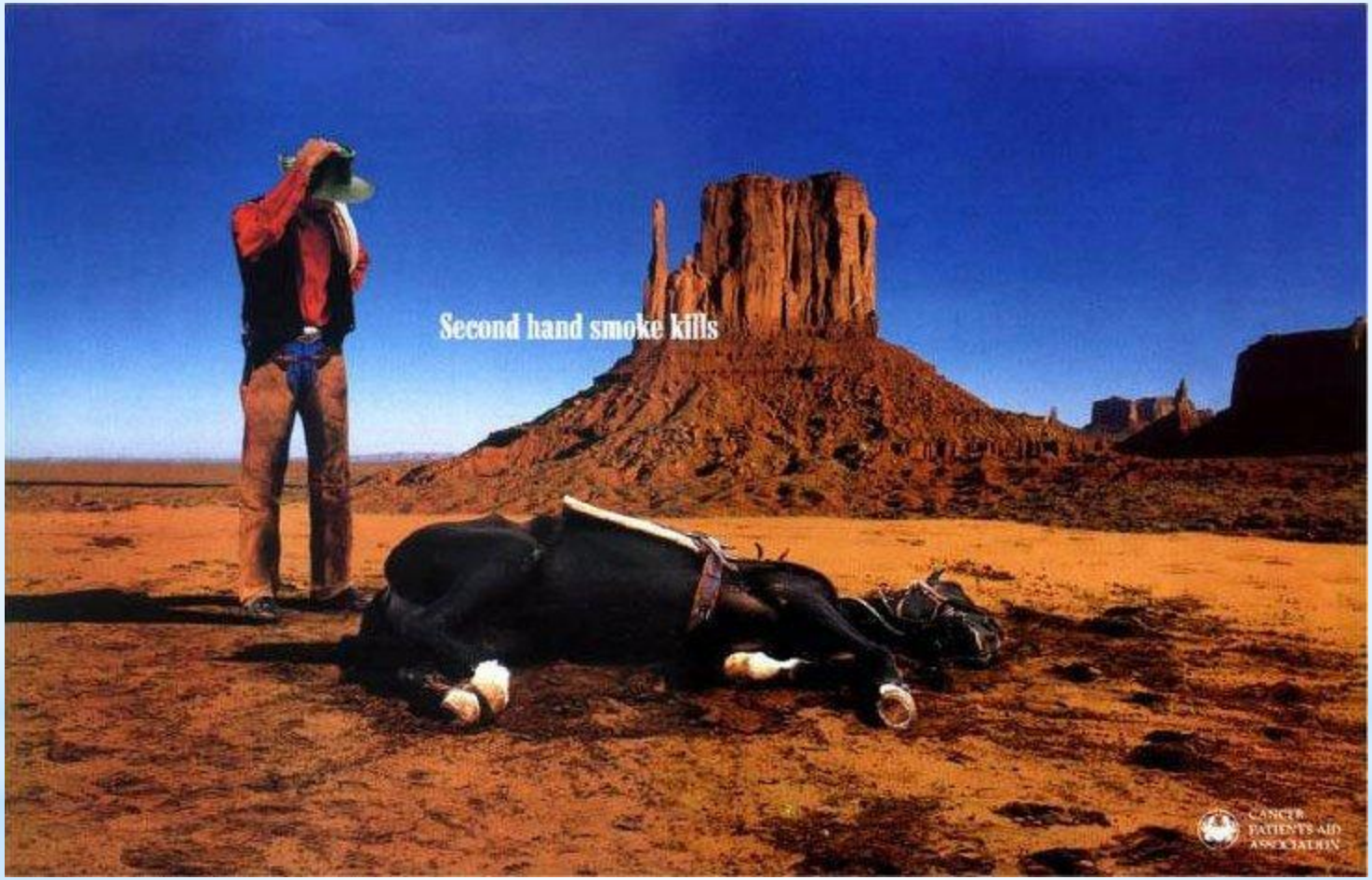
Variable	Coefficient (β)	Standard Error	Wald (χ^2)	p-Value
Age <65	0.444	0.291	2.330	0.1269
Nicotine Use	0.626	0.297	4.452	0.0349
No Prior alkylating agent	0.543	0.391	1.933	0.1644
No Prior radiation therapy	0.220	0.228	0.937	0.3332
Response at transplant (>PR)	0.479	0.290	2.730	0.0985
lenalidomide use	–0.085	0.258	0.109	0.7418
Durie-Salmon stage 1 & 2 vs. 3	–0.014	0.261	0.003	0.9578

Table 3: Multiple Logistic Regression Analysis for Predicting Day1 CD 34Cell Count ≥ 4 million/kg

Variable	Coefficient (β)	Standard Error	Wald (χ^2)	p-Value
Nicotine Use	0.624	0.301	4.308	0.0379
Age <65	0.441	0.295	2.236	0.1348



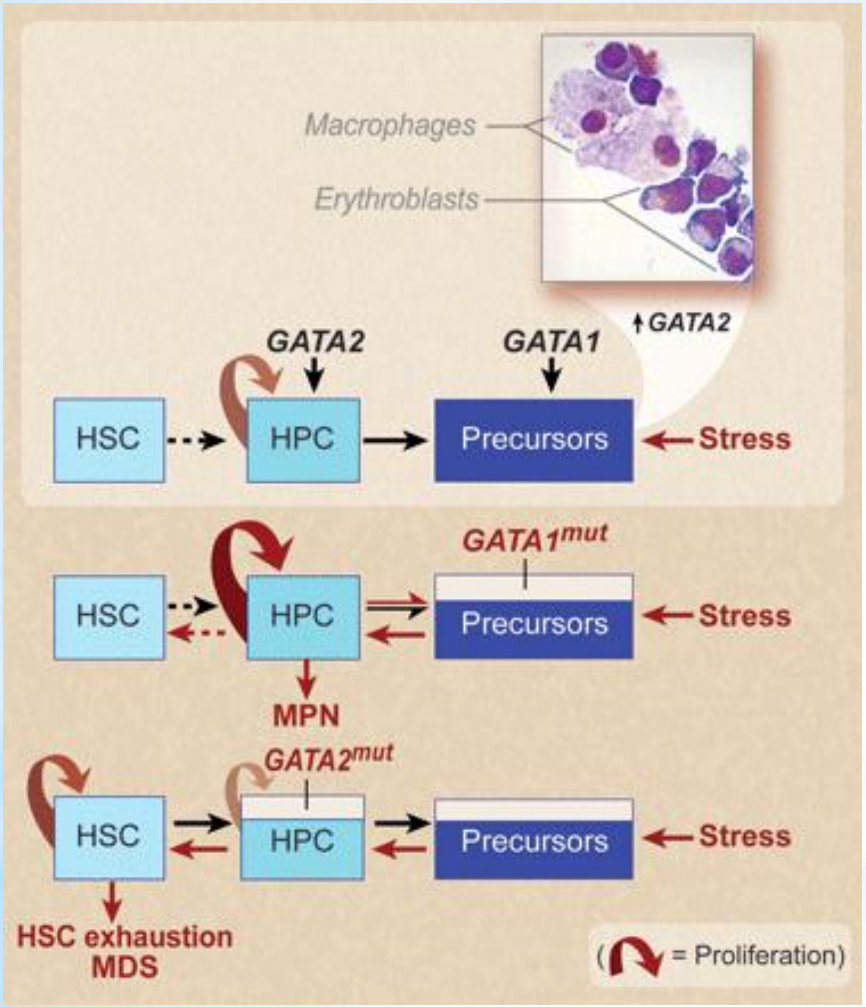
* Auto SCT: mobilisation



*Auto SCT: mobilisation

* Allo SCT: indications

* New indications?
  - GATA-2 deficiency (Holland, scientific session on PID)



Mono-MAC syndrome
- Monocytopenia
- Low B cell/NK cell count
- HPV infections
- Atypical mycobacteria
- Myelodysplasia

GATA-2 mutations
Indication for allo-SCT after RIC (Flu/TBI), Cuellar-Rodriguez, Blood, 2011

#2045 (Sturgess): 10 pts: high risk of death, 7 pts died, 3 pts alive, 2/3 underwent SCT
No aGVHD post SCT: no host DC's

* BM vs PBSC **(#1, C. Anasetti)**: (BMT CTN protocol 0201)
  - Phase III, prospective, randomized trial (n=550): MUD, >>MAC, BM vs PBSC
  - OS/NRM/DFS/relapse @ 2y =; aGVHD =; cGVHD: 48%(PBSC) vs 32%(BM), p=0.02 (20-50x T in PB); infections: more in BM; graft failure: 8%(BM) vs 3%(PB)
  - Conclusion (MUD, MAC): PBSC preferred for pts at risk for graft failure or early infections, all others: BM (pt/donor preferences)
* BM vs PBSC **(#319, Mielcarek)**: MRD, update on Bensinger, NEJM, 2001

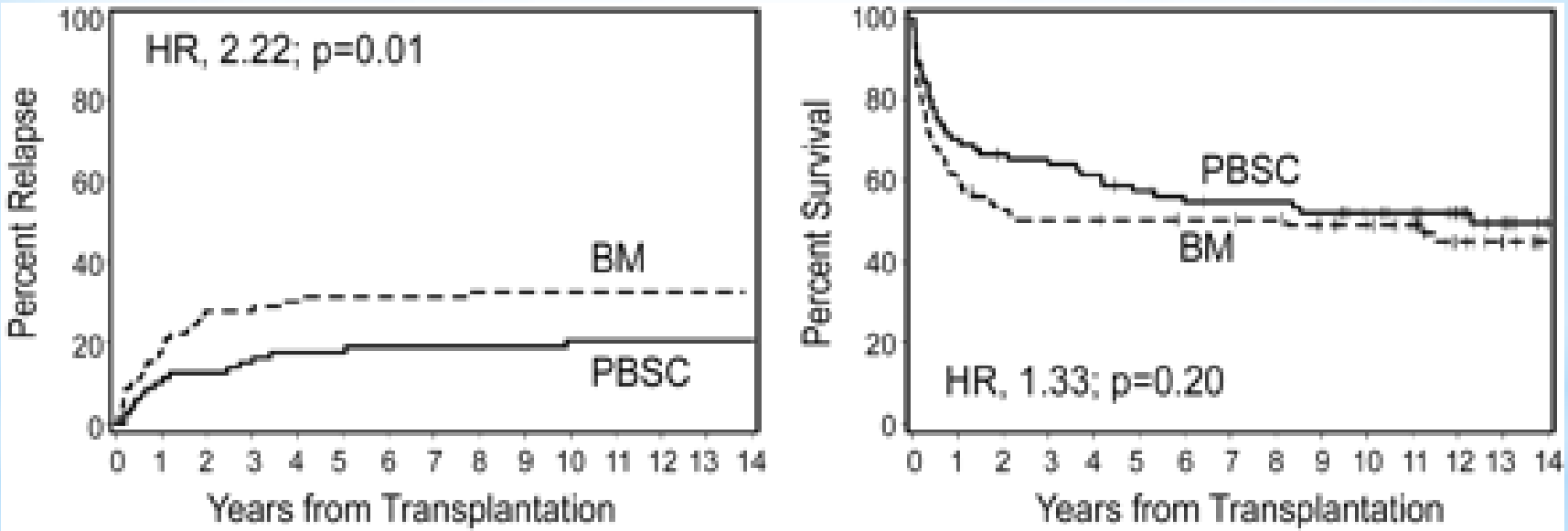


Figure 1: *Left panel:* cumulative incidence of relapse. *Right panel:* Kaplan-Meier survival estimates.

* Allo SCT: stem cell source

Allo SCT: stem cell source

* Double CB **(#836, Ruggeri)**: Retrospective (EBMT), n=134, de novo AML in CR1: LFS@2y: 52% → valid R/ if no HLA-identical donor available, optimal conditioning not clear

* Double CB **(#653, Cutler)**: Phase Ib trial, n=11, Flu/Mel/ATG, sir/tac
  - 2 CB: 1 CB R/ FT-1050 (PGE2) 2h, then IV, 1 CB infused untreated 2h later
  - 9/11: PGE2-treated CB dominant source, @D+14, long-term
  - PGE2: increased homing (CXCR4/SDF-1), proliferation, cell cycle entry, less apoptosis

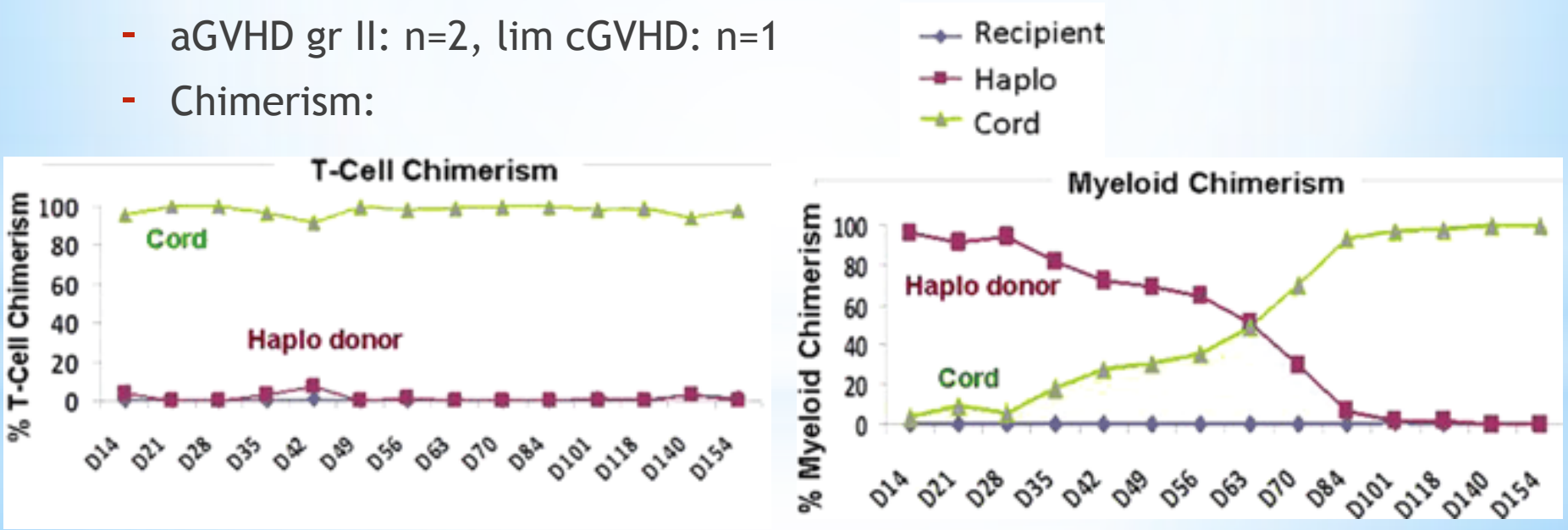
* Single expanded CB **(#486, Milpied)**: Prospective clinical trial, n=8, RIC, adults
  - CD34+: expanded (SCF/Flt-3L/TPO/G-CSF) for 12 days → injected
  - CD34-: frozen, injected 8h after expanded fraction
  - Rapid, sustained engraftment

* Allo SCT: stem cell source

* Haplo+CB in SAA **(#654, Gormley)**: prospective, single arm, n=8, SAA, ANC<500, refractory to ≥2 IS agents, no HLA-matched donor
  - CB SCT in SAA: disappointing results (EBMT/Eurocord, Perrault de Latour, BBMT, 2011: OS@3y: 38%, engraftment: 51%)
  - Conditioning: Cy (120 mg/kg), flu (125 mg/m²), horse ATG (160 mg/kg), TBI (200 cGy)

RESULTS: @9m: 7 pts alive, transfusion independent, 1 pt died @14m (CMV pneumonitis)

  - All pts: donor engraftment (ANC>500@D+42): 7/8: CB, 1/8: haplo (@25m)
  - TTN recovery: 10 d (10-18)
  - aGVHD gr II: n=2, lim cGVHD: n=1
  - Chimerism:



* Allo SCT: stem cell source

* Haplo+CB after RIC **(#830, Liu)**: prospective, single arm, n=45, high risk hematological diseases (58% active disease @SCT), median FU of survivors=330d, conditioning: Flu/Mel/rabbit ATG

RESULTS:

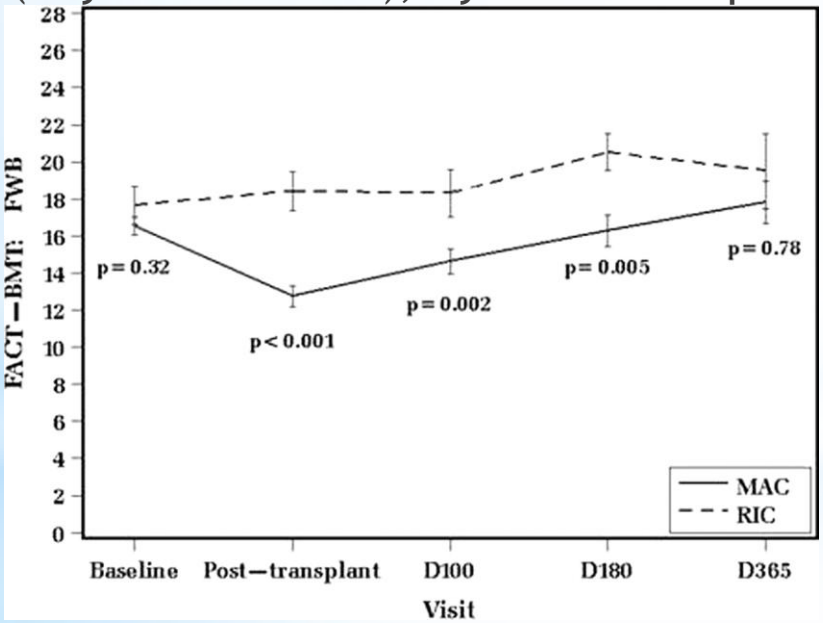
- Cum incid neutrophil recovery @D+50: 95%, median TTN engraf: 11 d (9-15d)
- Cum incid platelet recovery @D+100: 83%, median TTP engraf: 19 d (15-33)
- Chimerism

	Haplo	CB
D+30	86%	10%
D+100	22%	78%
D+180	2%	95%

- aGVHD II-IV: 25%; cGVHD @1y: 6%
- TRM@D+100: 9%, TRM@1y: 28%, relapse@D+100: 11%, relapse@1y: 30%
- OS@1y: 55%, PFS@1y: 42% (disease @SCT: tendency to ↓PFS, but ns, p=0.06)
- CMV viremia: 42%, CMV dis: n=4; EBV viremia: 42%, PTLD: 11%

*Allo SCT: conditioning

* QOL in MAC vs RIC **(#843, Lazaryan)**: prospective, n=192, AML (n=130), MDS (n=52), MPD (n=10), median FU=34m
  - MAC (n=154) vs RIC (n=38): comparable for gender, race, HCT-CI, #prior chemo, donor relation, length of FU, QOL baseline; sign different for age (61 for RIC, 48 for MAC), SC source (95% PBSC in RIC, 19% in MAC), TBI containing conditioning (95% in RIC, 24% in MAC), CD34 dose (5.2 in RIC, 2.2 in MAC), GVHD profylaxis)
  - QOL and psycho-social functioning: longitudinal assessment (day100/180/365), by validated questionnaires



RIC sign better than MAC until 6m, comparable @1y

* IS: sir/tac vs MTX/tac **(#323, Pidala)**: prospective, randomized, phase II, n=74, AML (23), ALL (15), MDS (9), MM (8), NHL (8), CLL (7), CMl (2), MPD (2), donor: MRD (n=35), MUD (n=39), MAC

  - Sir (1 year)+ tac (until D60) vs MTX (D1, 3, 6, 11) + tac (until D60)

  - Tregs: $CD4^{+}CD25^{++}CD127^{-}$ (foxp3+)

	Sir/tac	MTX/tac	p
%Treg/CD4 @D30	16.3	9.9	<0.0001
%Treg/CD4 @D90	14.6	9.7	0.0009
Abs#Treg @D30	more		Sign
Abs#Treg @D90	more		Sign
Cum inc aGVHD II-IV@D+100	43%	89%	<0.0001
aGVHD III-IV	16%	13%	0.16
cGVHD	51%	67%	0.56
Moderate-severe cGVHD	20%	63%	0.013
TTN engraftment	16d (11-22)	16d (12-28)	0.57
TTP engraftment	12d (6-20)	16d (10-33)	0.012

* Allo SCT: conditioning

Allo SCT: conditioning

* IS: sir/tac vs CSA/MMF **(#890, Perez-Simon)**: prospective, multicenter, MUD, RIC (Flu (150 Mg/m²)/Bu (10 mg/kg)/Mel (140 mg/m²)), n=90, CR (41%), PR (30%), active disease (29%)

CSA/MFF: n=45 (2002-2007)

Sir/tac: n=45 (2008-2010)

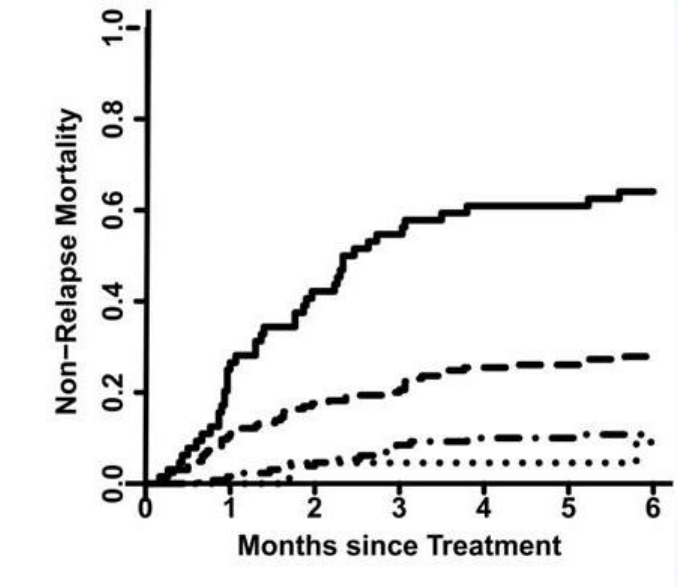
	Sir/tac	CSA/MMF	p
Micro-angiopathy	12%	-	-
aGVHD II-IV	49%	50%	ns
aGVHD III-IV	15%	26%	ns
Gut aGVHD ≥ II	18%	55%	0.007
cGVHD	55%	88%	0.0002
Extensive cGVHD	27%	52%	0.03
NRM @D+100	10%	20%	ns
NRM @1y	19%	40%	0.028
EFS @2y	59%	35%	0.008
OS @2y	72%	48%	0.018

*Allo SCT: GVL/GVT

* Azacitidine **(#324, Dennis):** Prospective, single arm, n=27, AML (18 CR1, 7 CR2, 2 relapse),time matched control population
  - Flu/Mel/Alemtuzumab → Azacitidine post allo-SCT #D+42: 36 mg/m^2 x 5d every 28d (for 12m)
  - Moderate toxicity, 3 grade II aGVHD, 2 limited cGVHD
  - Increased Treg (4+25+foxp3+127lo) @3m (sign more than matched pop), not @9/12m
  - Increased CD8+ T cell response to tumor Ags (WT1, CTA)
    - Pre-SCT: 1/22, post-SCT: 14/16
    - Effector memory phenotype (CCR7- RA-)
    - In vitro functionality: specific, IFN-γ, TNFα, IL-2, CD107

* Biomarkers for aGVHD **(#152, Vander Lugt)**: IPAS approach to identify biomarkers of aGVHD (Paczesny, Blood, 2009) to predict response to treatment @D+28 and survival @D+180 after treatment

  - ST2 = decoy receptor (IL-33 receptor) that drives Th phenotype from Th2 → Th1 (pathofysiology of R/-resistant aGVHD)

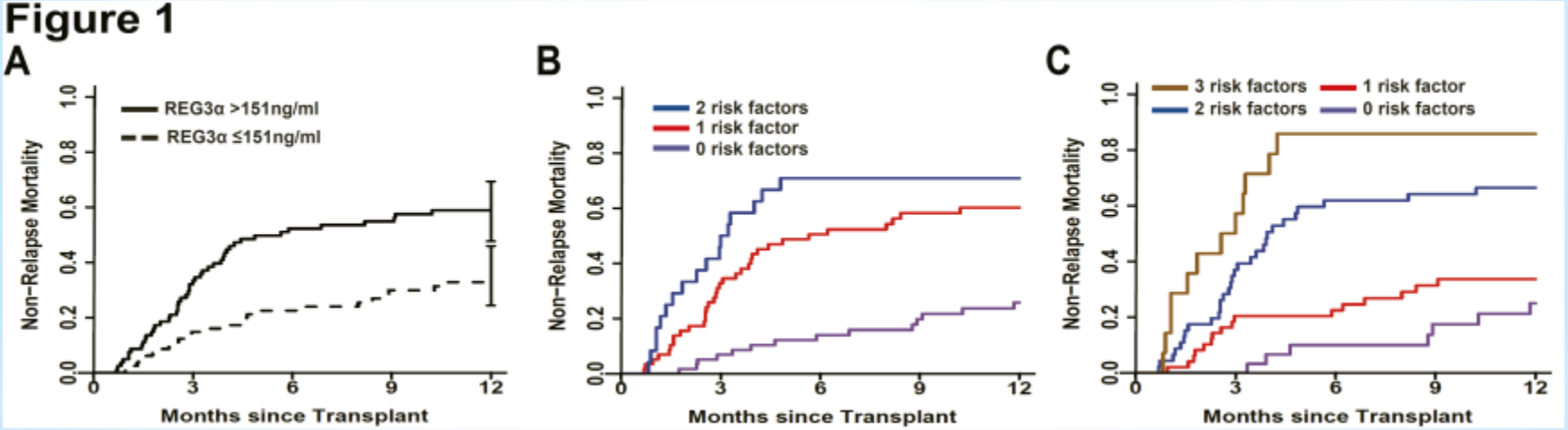


Onset GVHD grade & D0 ST2	D180 post-therapy NRM	Hazard Ratio compared to (a)	p-value
(a) Low ST2 & Grade 1-2 (·—·– N=130)	11%		
(b) Low ST2 & Grade 3-4 (····· N=22)	9%	0.8	0.80
(c) High ST2 & Grade 1-2 (– – – N=165)	28%	2.9	<0.001
(d) High ST2 & Grade 3-4 (——— N=64)	64%	9.0	<0.001

* Allo SCT: acute GVHD

* Biomarkers for aGVHD **(#153, Harris)**: n=140, identification of markers:
  REG3α = plasma biomarker of lower GI aGVHD

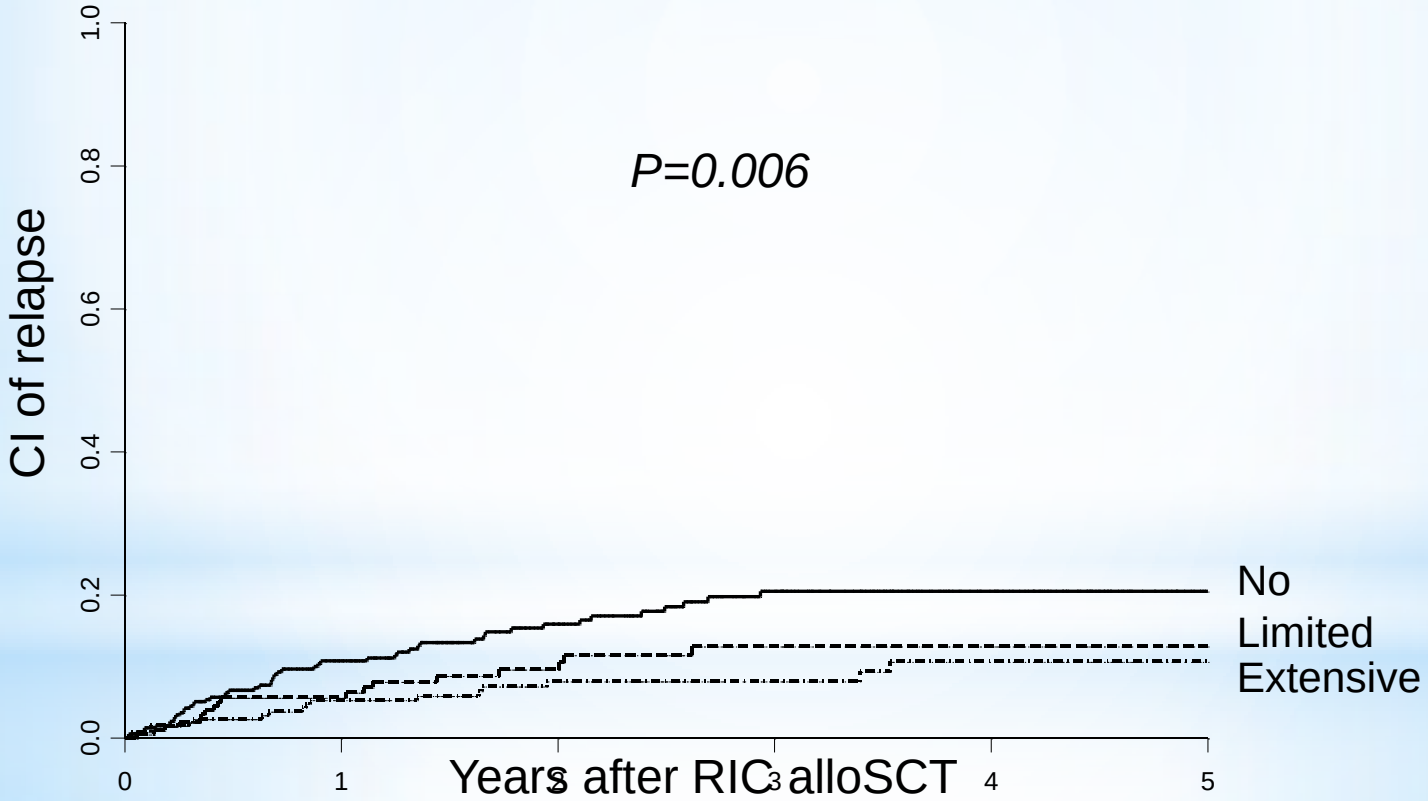
  better identification of high risk patients in whom standard treatment might not be sufficient



* Allo SCT: acute GVHD

* Allo SCT: chronic GVHD

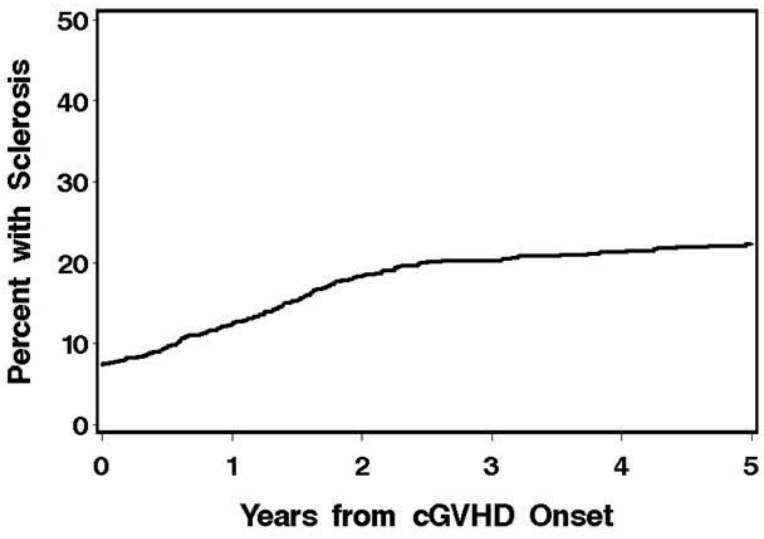
* Impact of cGVHD on outcome **(#321, Baron)**: Retrospective analysis (EBMT), n=1859, AML in CR1/2, RIC, PBSC, MRD (n=1208), MUD (n=651)
  - cGVHD: less RR
  - Extensive cGVHD: increased long-term NRM
  - Limited cGVHD: increased OS



* Sclerotic cGVHD **(#322, Inamoto)**: Retrospective analysis, n=986, Multivariate analysis for risk factors for development of sclerotic cGVHD (cutaneous sclerosis, fasciitis, joint contractures)

	HR (95% CI)	P
Covariates defined at transplant		
Stem cells		
Bone marrow	1.0	
PBSC	2.51 (1.4-4.6)	.003
Cord blood	-	ns
HLA and donor		
HLA-matched related	1.0	
HLA-matched unrelated	-	ns
HLA-mismatched	0.54 (0.3-0.9)	.02
Patient age	-	ns
Donor age	-	ns
Patient gender		
Male	1.0	
Female	1.61 (1.2-2.2)	.005
Donor gender pair	-	ns
Female donor to male recipient	-	ns
ABO mismatch		
None	1.0	
Minor	-	ns
Major	0.61 (0.4-0.9)	.02
Disease diagnosis	-	ns
Disease risk	-	ns
Conditioning intensity	-	ns
Total body irradiation		
None	1.0	
≤ 450 cGY	-	ns
> 450 cGY	1.84 (1.3-2.6)	.001
ATG in conditioning	-	ns
GVHD prophylaxis	-	ns
Covariates at onset of chronic GVHD		
Prior grade II-IV acute GVHD	-	ns
Prior stage 3 to 4 skin acute GVHD	1.88 (1.3-2.6)	.0002
Eosinophilia	-	ns
Platelets < 100 x10^9/L	-	ns
On steroids or progressive onset	-	ns
Skin involvement	-	ns
Extent of skin involvement	-	ns
Bronchiolitis obliterans	-	ns

ns, not statistically significant in univariate analysis and not included in multivariate model



* Allo SCT: chronic GVHD

* Vaccination trials post allo SCT (**Revzani**, educational HSCT II)

Author, year	Vaccine	No of patients	Histology	Status before vaccination	Comments
BCR-ABL vaccines, phase 1/2					
Pinilla-Ibarz, 2000[20]	p210 b3a2, pool of peptides + QS21	14	CML CP	Various levels of CyR	All patients developed DTH or CD4+ T-cell response; efficacy not demonstrated
Bocchia 2005[21]	b3a2 break point–derived peptides + QS21 + molgramostim	16	CML CP	MCyR on IM or INF-α	Patients continued on IM or I NF-alpha; 5 of 10 achieved CCyR (IM group)
Rojas 2007[22]	PADRE-linked b3a2 break point–derived peptides + GM-CSF	19	CML CP	MCyR on IM	Patients continued on IM; 1 log reduction in BCR-ABL transcripts in 13 of 14 patients in MCyR
PR1 vaccine, phase 1/2					
Qazilbash 2007[25]	PR1 peptide + montanide + GM-CSF	66	AML, CML, MDS	Measurable disease (53), CR (13)	Patients with immune response had better EFS: 8.7 versus 2.3 months ($P = .03$)
WT1 vaccines, phase 1/11					
Oka 2004[26]	WT1–235 natural or heteroclitic peptide + montanide	14	AML MDS	CR, PR, PD	WT-1-specific CD8+ T-cell responses in 9 of 13 evaluable objective responses or SD in 8 of 10 evaluable responses
Keilholz 2009[27]	WT1–126 peptide + KLH + GM-CSF	19	AML (17), MDS (2)	PR, PD	8 of 18 WT1-specific CD8+ T -cell responses; 6 of 10 objective responses or SD
Maslak 2010[28]	Polyvalent vaccine containing heteroclitic CD8 and CD4 peptide epitopes + montanide + GM-CSF	10	AML	CR	WT1 specific T-cells response in 7 of 8 who completed vaccine
Van Tendeloo 2010[29]	Autologous monocyte-derived DCs transfected with WT-1 mRNA	10	AML	CR, PR	2 patients in PR achieved CR; WT1 mRNA increase was reversed by additional DC vaccination; clinical responses correlated with WT1-specific CD8+ T cells
Combination of PR-1 and WT-1 peptide vaccines, phase 1/2					
Rezvani 2008[23]	PR-1 + WT1–126 peptide + montanide + GM-CSF	8	AML, MDS, CML	CR	PR1- or WT1-specific CD8+ T cells in 8 of 8 associated with transient reduction in MRD
Rezvani 2010[24]		6			
RHAMM vaccine, phase 1/2					
Schmitt 2008[30]	RHAMM/CD168-R3 peptide + montanide + GM-CSF	10	AML, MDS, MM	PR, PD	5 of 10 immunological response; 3 of 10 objective responses
Other approaches, phase 1/2					
Ho 2009[19]	K562/GM-CSF (GVAX)	28 recruited, 15 received at least 1 dose of vaccine	AML, MDS.	Post-HSCT in CR or PD	Durable CR in 9 of 15 at median of 26 mo (12-43 mo)
Borrello 2009[39]	GVAX accompanied by infusion of immunotherapy-primed lymphocytes after ASCT	54	AML	CR1	28 of 46 received 9 vaccinations; immune responses in 100% of vaccinated patients; RFS = 61.8% in immunotherapy-treated patients
Schuster 2009[31]	Id-KHL + GM-CSF (hybridoma)	177	FL	CR1, CR1u	PFS = 44.2 mo in vaccine group versus 30.6 mo in control arm ($P = .045$)

* Immunotherapy

*Immunotherapy

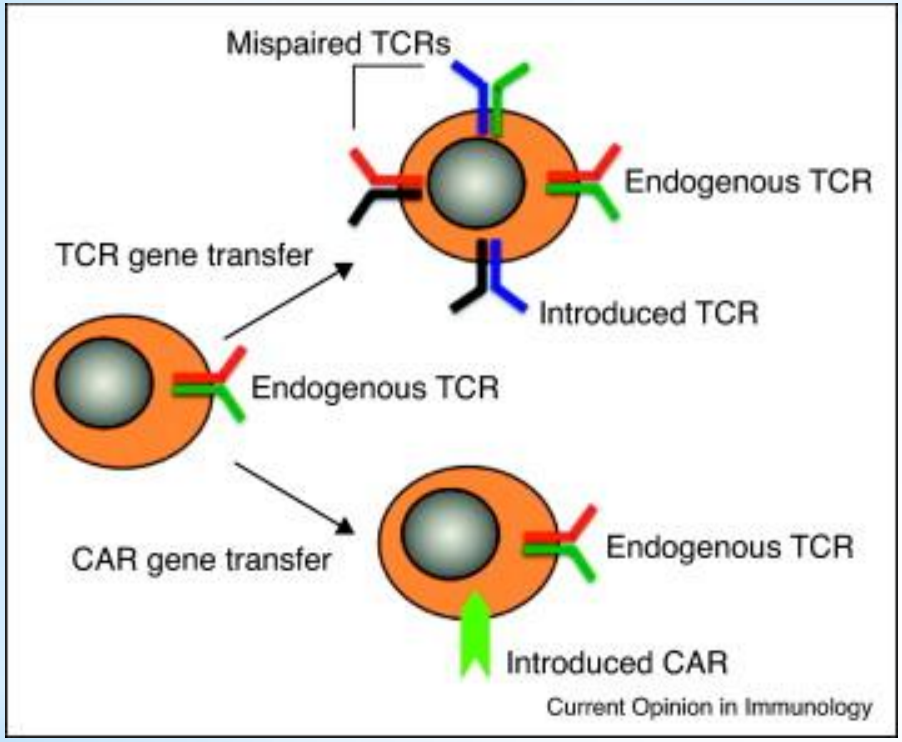
* Immunotherapy post CB SCT **(#155, Hanley),** Phase I, n=3, CB SCT
  - CB:→ 20%: generation of T cells ($5x10^6/m^2$ - $10^7/m^2$)

    → 80%: immediate infusion
  - T cells: 1 round of stimulation with autologous DC's (TD Ad5f35-pp65 vector) + IL-7, IL-12, IL-15; 2 rounds of weekly stimulation with autologous Ad5f35-pp65 TD EBV-LCL + IL-15 or IL-2)
  - Results: safe, reconstitution of virus-specific T cells, control of viral reactivation/infection

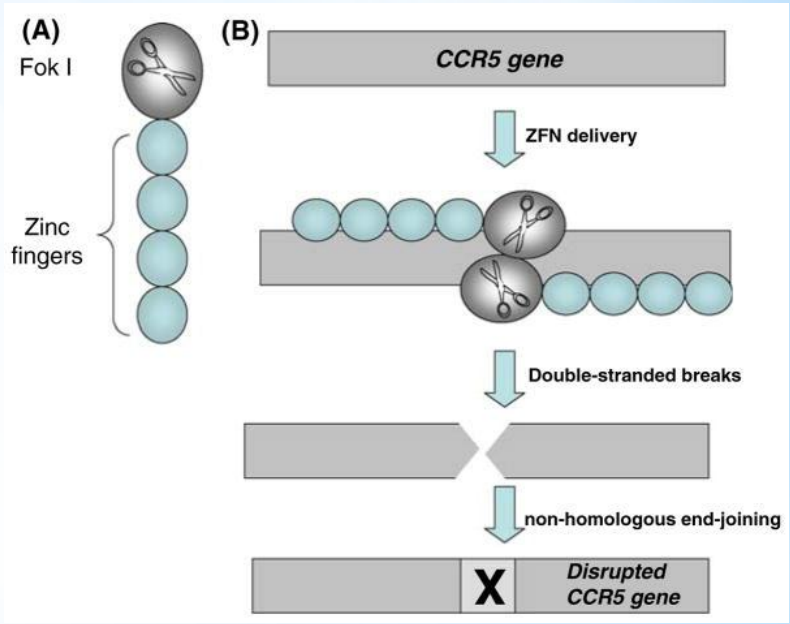
* MIL **(#647, Noonan),** Trial of HLA-matched allo SCT with post SCT Cy (specific depletion of allo-reactive T cells)
  - MIL=marrow infiltrating lymphocytes: in vitro expansion and activation with CD3/CD28 coated beads

* Safety of administered TCR transduced T cells

→ TCR mispairing: autoreactivity (Bendle, nature Medicine, 2010)



C. Turtle and S. Riddell, Curr Opin Immun, 2011



A. Varela-Rohena et al, Immunol Res, 2008

* Immunotherapy

* WT1-TCR / ZFN-autologous TCR **(Provasi, #667):** 2 ZFN-sets (TCRα/β)
  - T cells + ZFN: activation CD3/CD28 Ab beads + low doses IL-7/IL-15
  - CD3/TCR ↓: 34% $CD3^-$ after TRAC-ZFN, 30% $CD3^-$ after TRBC-ZFN: $CD3^-$ sort
  - TD with lentiviral vector encoding WT1-TCR → $CD3^+$

RESULTS

- In vitro (compared to conventional TCR transferred T cells): better recognition of WT1+ targets, no residual endogenous TCR activity, no autoreactivity
- Humanized GVHD mouse model: IV T cells → GVHD?

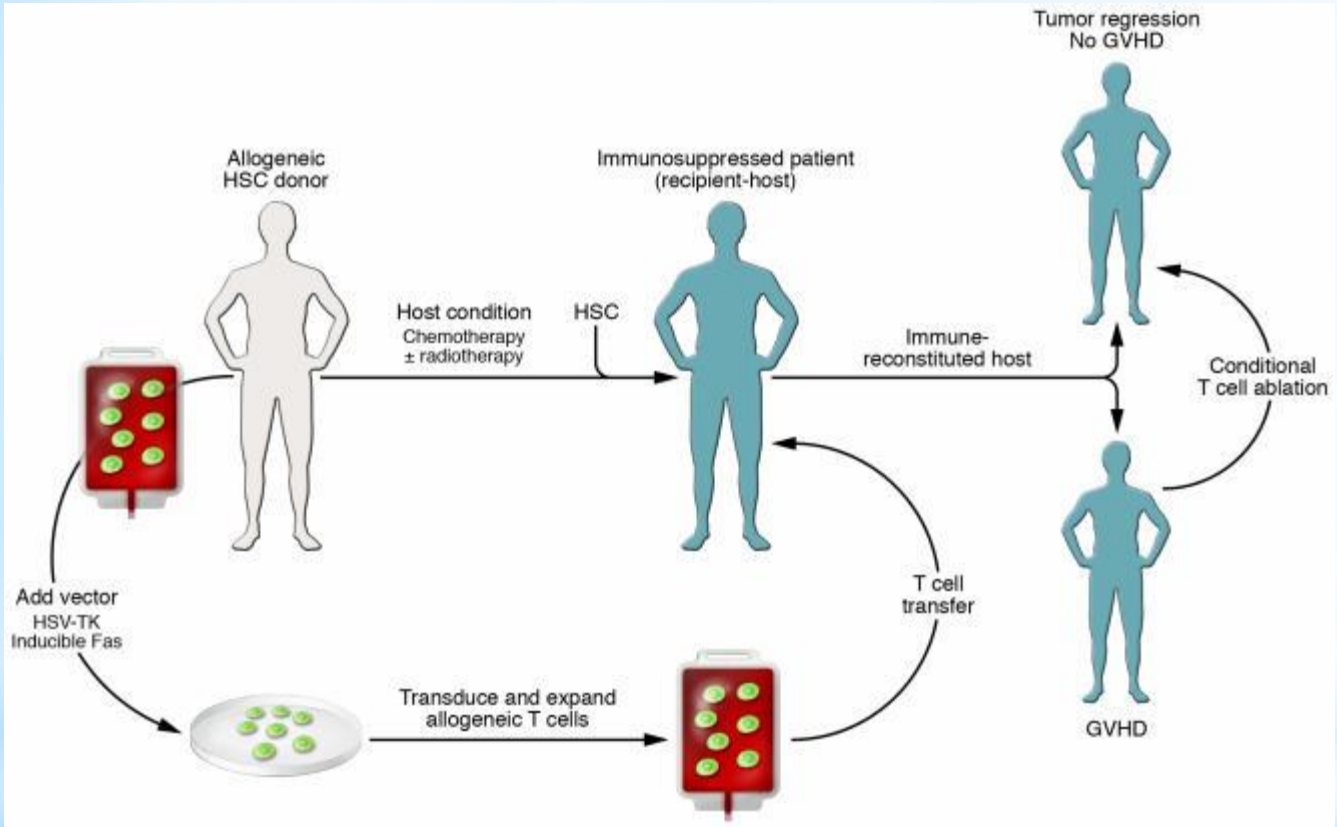
	GVHD	engraftment
Unmanipulated T cells	100% lethal GVHD	OK
TCR TD T cells	80% lethal GVHD	OK
TCR-ZFN TD T cells	No	OK

* WT1 specific CD4 T cell help **(Ochi, #645),** PB>pt: transduction with HLA-A*24:02 restricted WT1-TCRα/β (retroviral vector) with shRNA's for endogenous TCR (WT1-siTCR) in CD4 and CD8 T cells
  - CD4/ low foxp3 expression
  - WT1 peptide + TD CD4+ T cells → Th1 cytokines (IL-2, IFN-γ, TNF-α)
  - WT1 peptide + TD CD4+ T cells + TD CD8+ T cells:
    - ↑ CD107a expression
    - ↑ IFN-γ production
    - ↑ cytotoxicity
    - ↑ aantal
    - ↑ transition to memory phenotype (CD45RA-CD62L+): ↑ OX40 on TD CD4+, ↑ CCL3/4 on TD CD4+ (CCR5 on TD CD8+)
  - TD CD8+ T cells: efficient migration to CD4 in transwell
  - Response to autologous leukemia cells: stable

*Immunotherapy

* Safety of TCR transduced T cells: suicide genes

HSV-TK vector



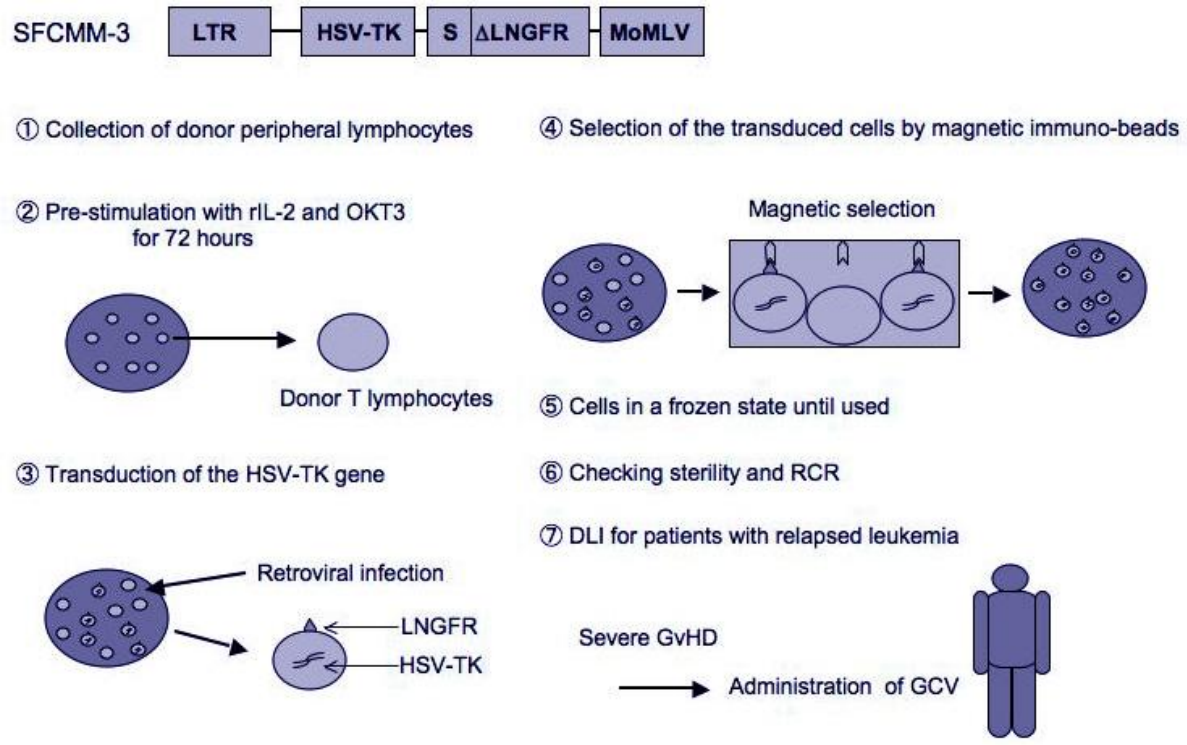
HSV-TK
- Marker gene = NGFR
- Can be activated by ganciclovir

C June, JCO 2007

* Immunotherapy

Safety of TCR transduced T cells: suicide genes

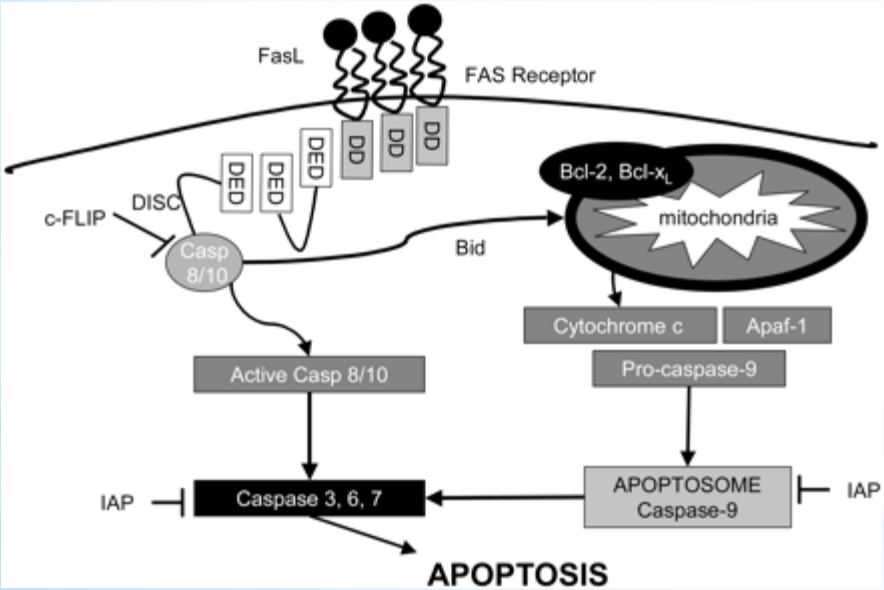
HSV-TK vector



- Inhibits host DNA → kills dividing cells (only activated cells)
- Effect can be very slow (↔ clinical studies, Bonini)
- Activated by therapeutic molecule

Onodera, Front Bioscience, 2008

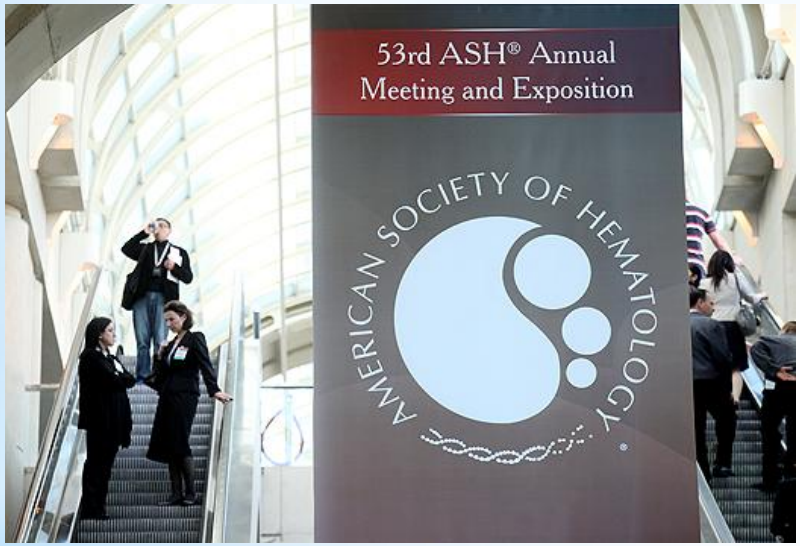
* Third party trispecific T cells **(#644, Zohren),** Preclinical study
  - Generation of multi-TAA-specific T cells (DC's loaded with PR1, PRAME, WT1 peptimix): CD4+ and CD8+
  - In vivo mouse model: functional → decreased tumor growth, increased survival
  - Transduction with iCaspase suicide gene: safe and effective



- iCasp9$_M$
- Marker gene = CD19 (truncated)
- Can be activated by AP1903 (or analogs) = small chemical inducer of dimerization; non-therapeutical

- Works on dividing and non-dividing cells
- Effect should be faster
- Small molecule is non-therapeutic

*Immunotherapy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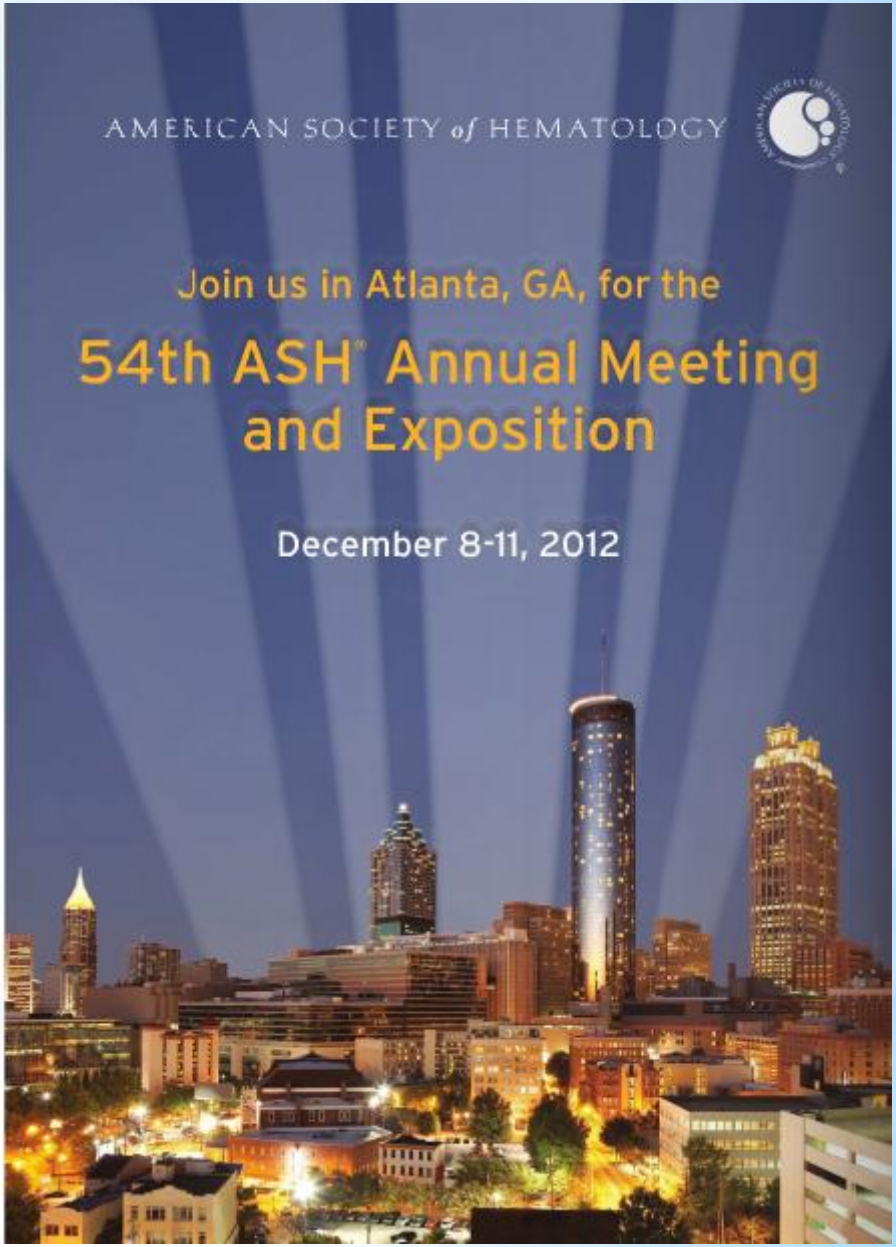
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