Allogeneic Hematopoietic Stem Cell Transplantation: State of the Art in 2018

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Overview:

- Update on allogeneic transplantation for malignant and nonmalignant diseases: state of the art in 2018
- Choosing the optimal stem cell donor
- New tools to prevent and treat CMV
- First FDA-approved drug approved to treat chronic GVHD

Major Improvements in Transplant Outcomes Over the Past 2 Decades

Historical Problem	Solution
• Conditioning regimens too toxic	• Development of safer conditioning regimens (IV busulfan)/use of lung shielding • Development of reduced intensity conditioning regimens
• Older patients ineligible due to prohibitive risk of mortality	
• Death from invasive fungus and CMV	• Advent of voriconazole, PCR to detect early CMV reactivation with use of empiric gancyclovir. Letermovir for CMV prophy
• Lack of donors precludes the use of the procedure	• Growth of unrelated registry, increasing use MUDS, cord transplants and haplo-identical donors

In the era of precision medicine, why do we still perform these dangerous allogeneic transplants?

- **Remains only curative modality for certain diseases associated with short survival with conventional therapy**
  - **Relapsed AML**
  - **Relapsed ALL**
  - **High Risk MDS**

- **Is the only curative modality for many non-malignant debilitating diseases**
  - Sickle cell Anemia
  - Aplastic Anemia- Relapsed refectory to IST

We have Made Advances in Diseases Like MDS But Most Patients with High-Risk Disease Will Die from their Disease Without a Transplant

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JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Randomized Phase II Study of Azacitidine Alone or in Combination With Lenalidomide or With Vorinostat in Higher-Risk Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia: North American Intergroup Study SWOG S1117

Mikkael A. Sekeres, Megan Othus, Alan F. List, Olatoyosi Odenike, Richard M. Stone, Steven D. Gore, Mark R. Litzow, Rena Buckstein, Min Fang, Diane Roulston, Clara D. Bloomfield, Anna Moseley, Aziz Nazha, Yanming Zhang, Mario R. Velasco, Rakesh Gaur, Ehab Atallah, Eyal C. Attar, Elina K. Cook, Alyssa H. Cull, Michael J. Rauh, Frederick R. Appelbaum, and Harry P. Erba

Author affiliations and support information (if applicable) appear at the end of this article.

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Clinical trial information: NCT01522976.

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ABSTRACT

Purpose
Azacitidine is standard, first-line therapy in higher-risk myelodysplastic syndromes (MDS). Whether azacitidine-based combinations with lenalidomide or vorinostat produce superior overall response rates (ORRs) to azacitidine is not known.

Patients and Methods
North American Intergroup Study S1117 is a phase II/III trial that randomly assigned patients with higher-risk MDS and chronic myelomonocytic leukemia (CMML) 1:1:1 to azacitidine (75 mg/m^2/day on days 1 to 7 of a 28-day cycle); azacitidine plus lenalidomide (10 mg/day on days 1 to 21); or azacitidine plus vorinostat (300 mg twice daily on days 3 to 9). The primary phase II end point was improved ORR.

Results
Of 277 patients from 90 centers, 92 received azacitidine, 93 received azacitidine plus lenalidomide, and 92 received azacitidine plus vorinostat. Median age was 70 years (range, 28 to 93 years), 85 patients (31%) were female, and 53 patients (19%) had CMML. Serious adverse events were similar across arms, although combination-arm patients were more likely to undergo nonprotocol-defined dose modifications ($P < .001$).With a median follow-up of 23 months (range, 1 to 43 months), the ORR was 38% for patients receiving azacitidine, 49% for azacitidine plus lenalidomide ($P = .14$ *v* azacitidine), and 27% for azacitidine plus vorinostat ($P = .16$ *v* azacitidine). For patients with CMML, ORR was higher for azacitidine plus lenalidomide versus azacitidine (68% *v* 28%, $P = .02$) but similar for all arms across cytogenetic subgroups, as was remission duration and overall survival. ORR was higher with mutations in *DNMT3A* and lower for *SRSF2*, whereas ORR duration improved with fewer mutations. Lenalidomide dose reduction was associated with worse overall survival (hazard ratio, 1.30; $P = .05$).

Conclusion
Patients with higher-risk MDS treated with azacitidine-based combinations had similar ORR to azacitidine monotherapy, although patients with CMML benefitted from azacitidine plus lenalidomide. The efficacy of combination regimens may have been affected by dose modifications.

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ASSOCIATED CONTENT

See accompanying Editorial on page 2729

Appendix
DOI: https://doi.org/10.1200/JCO.2015.66.2510

Data Supplement
DOI: https://doi.org/10.1200/JCO.2015.66.2510

DOI: https://doi.org/10.1200/JCO.2015.66.2510

INTRODUCTION

The myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemias (CMML; an MDS/myeloproliferative neoplasm [MPN] overlap) comprise a spectrum of distinct bone marrow disorders associated with cytopenias, a consequent increased risk of bleeding and infection, and, in higher-risk subtypes, a high likelihood of transformation to acute myeloid leukemia.[1-3] They are the most common myeloid malignancies, with approximately 15,000 to 20,000 new diagnoses in the United States yearly, 25% to 30% of which constitute higher-risk disease.[4]

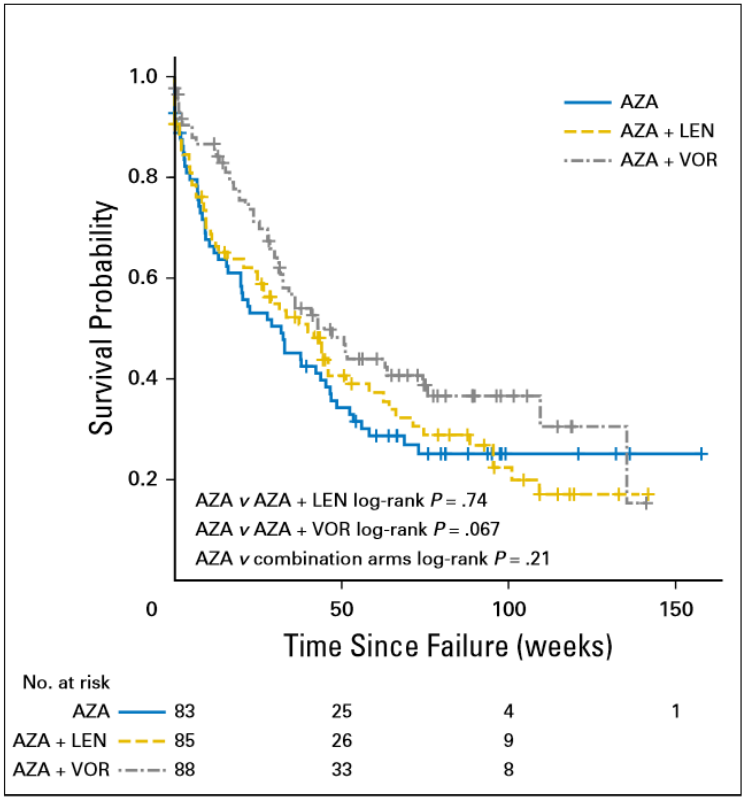
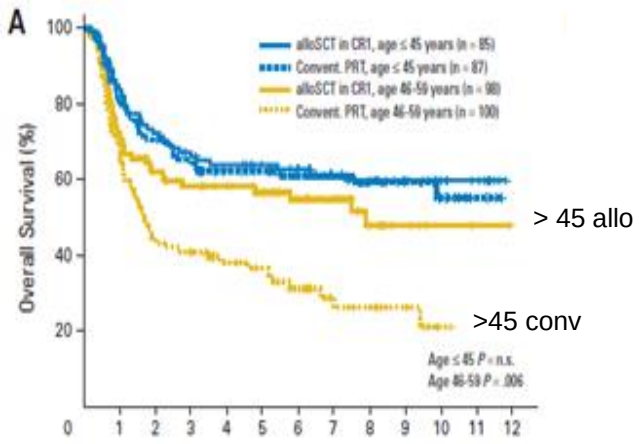


Fig 3. Overall survival after failure. AZA, azacitidine; LEN, lenalidomide; VOR, vorinostat.

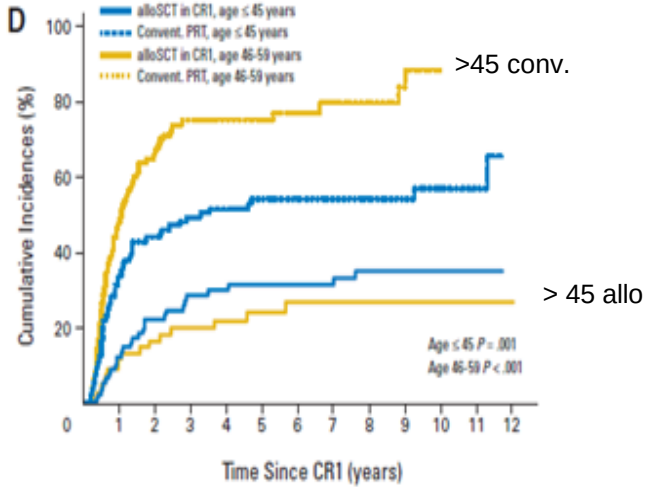
Allogeneic Transplant For AML in CR1 Decreases Relapse Risk and Improves Survival for Select Patients

Outcomes superior for older pts with allogeneic HCT

Survival



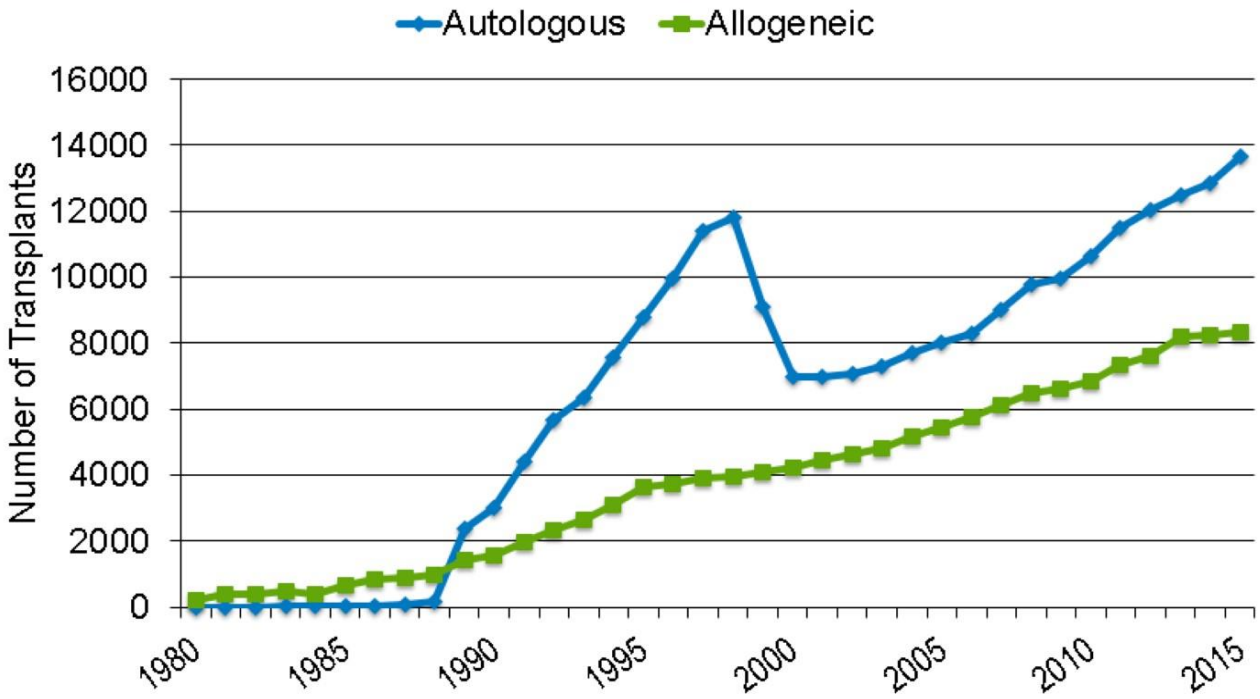
Relapse



Stelljes et al JCO 2014:32(4)

Transplant Numbers are Increasing in the U.S.

Annual Number of HCT Recipients in the US by Transplant Type



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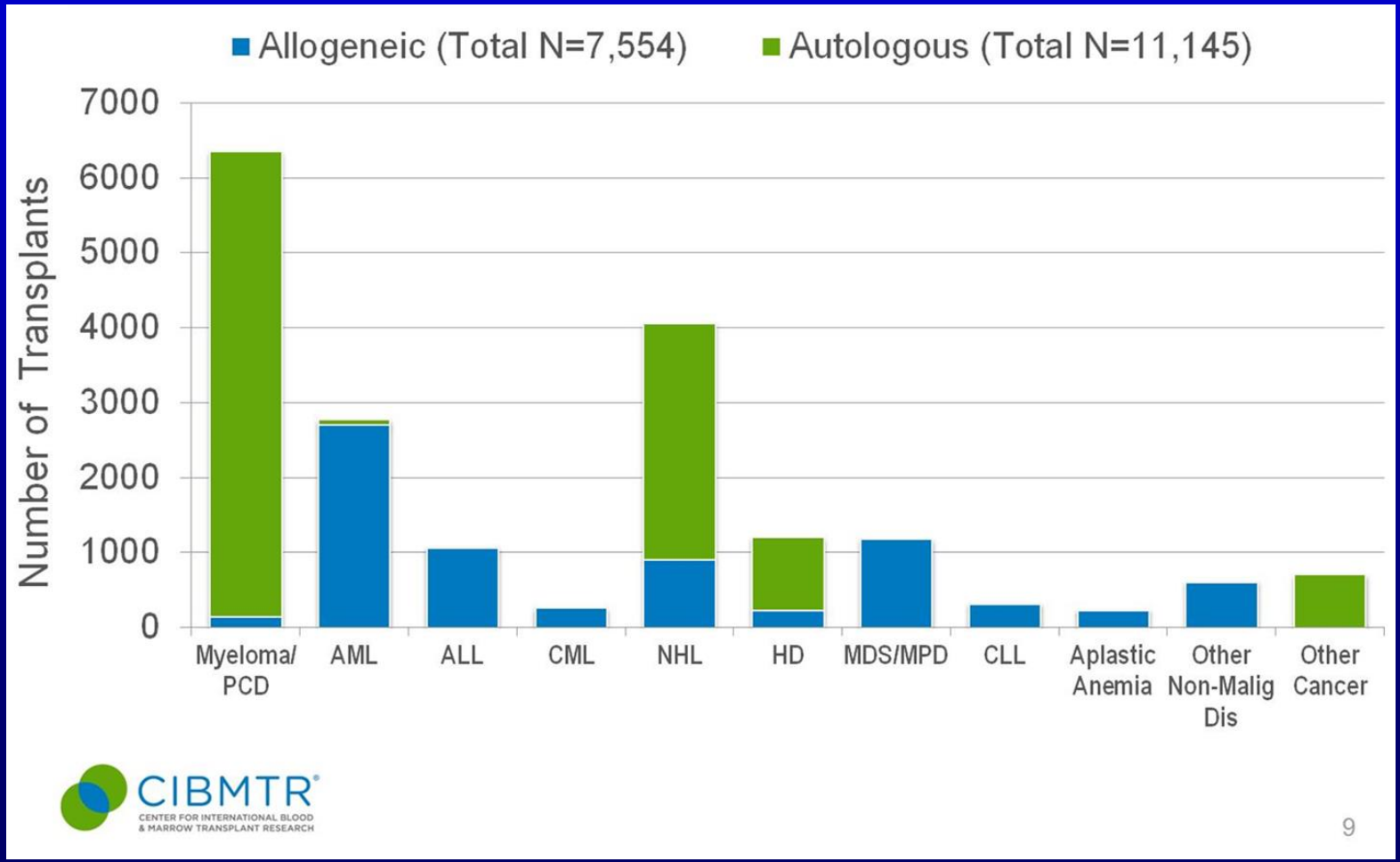
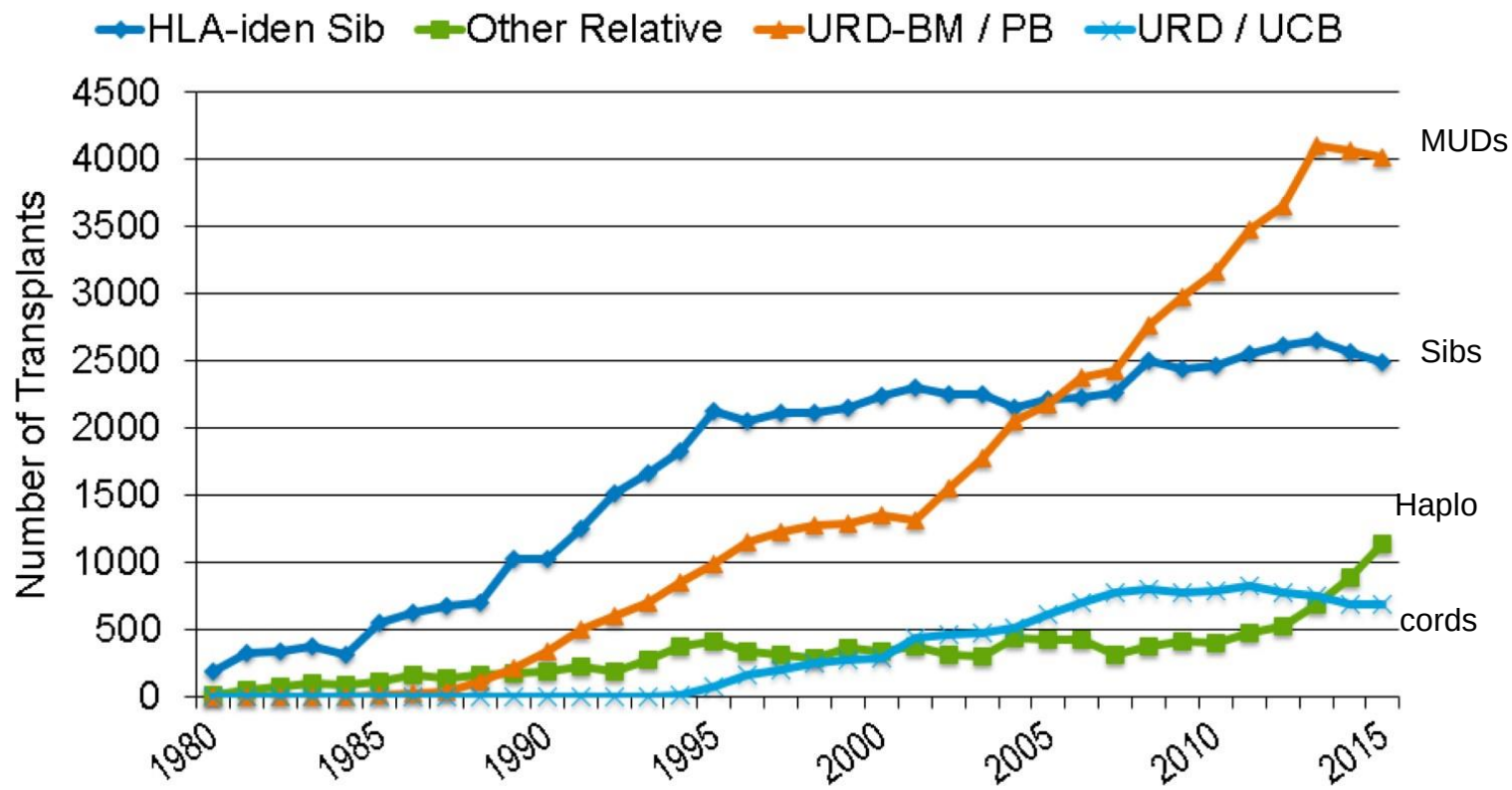
Most Common Indications for an Hematopoietic Cell Transplant (HCT) in the U.S.



Allogeneic HCT Recipients in the US, by Donor Type



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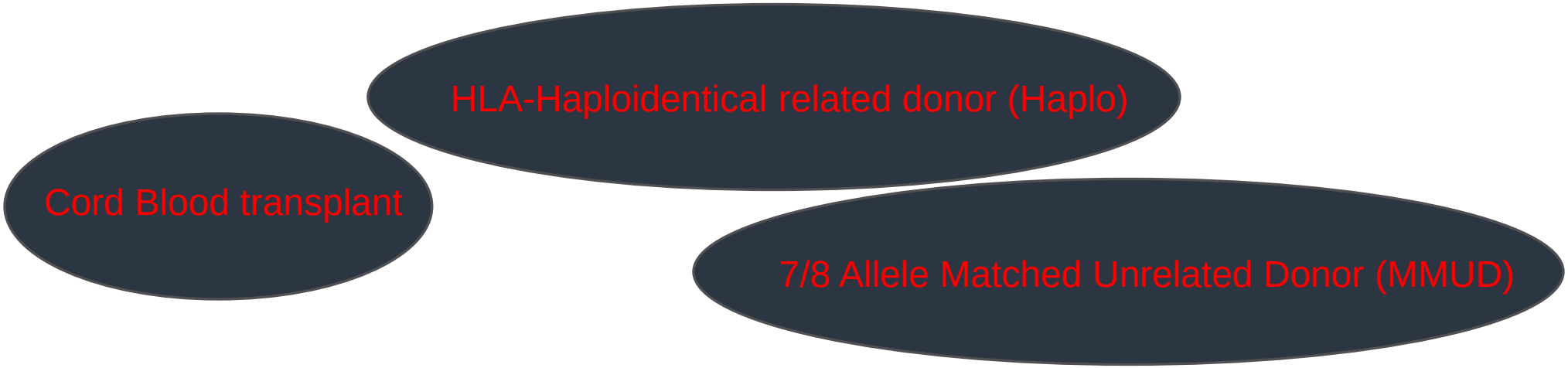
Donor Sources- who to choose?

1) HLA Identical Sibling (SIB)

2) 8/8 Allele Matched Unrelated Donor (MUD)

3) see below



Donor Selection Starts at Referral

Choosing the best donor:

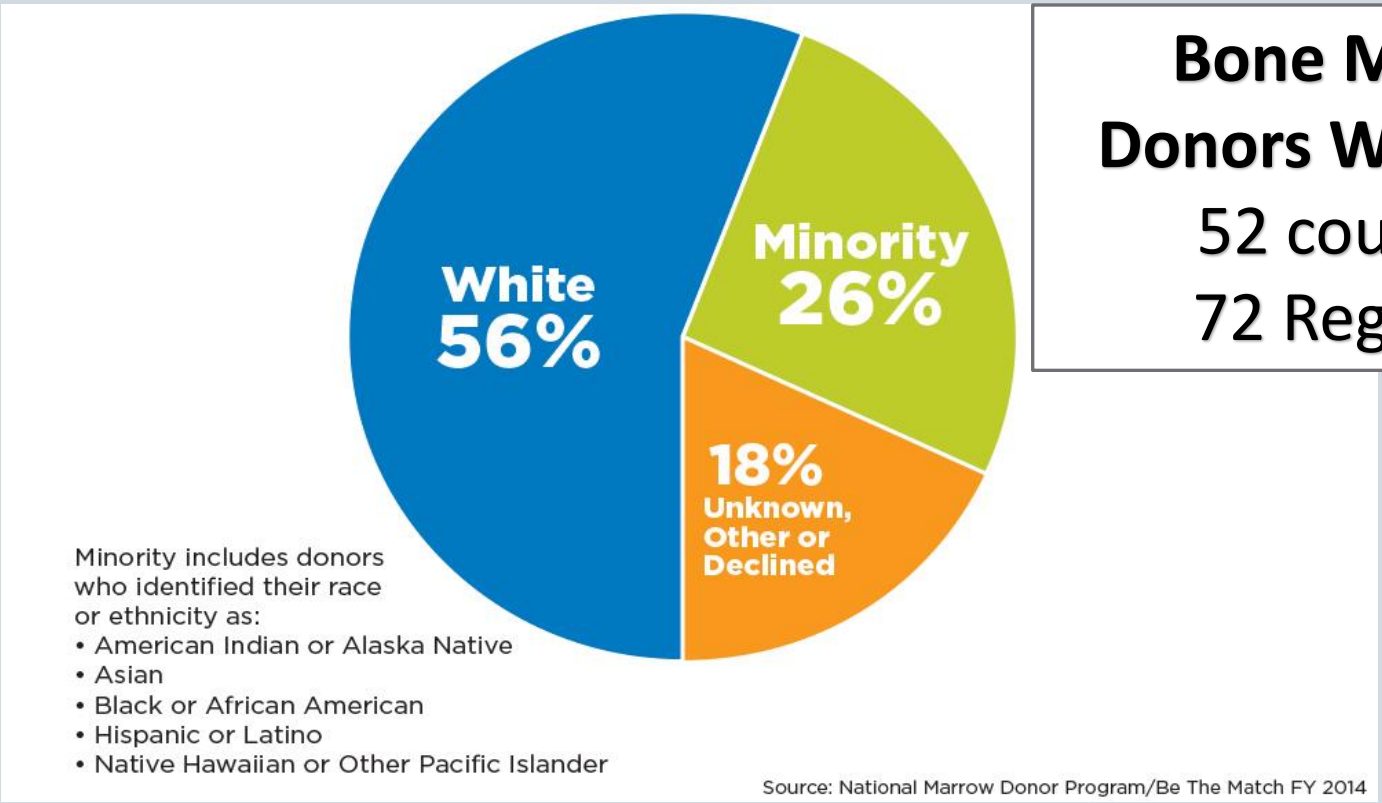
Factors to consider-Urgency of Transplant
- Aggressive disease
- Malignant versus Non-Malignant Disease

Primary Factors
- HLA Match
  - 8/8 allele match still preferred
  - Need to not have Donor-Specific HLA Antibodies in the case of mismatched transplant
- ***Availability of Donor in time needed***

Secondary Factors (in no particular order!)
- Age
- CMV Status
- ABO Match
- Gender

Other Selection Factors
- DPB1 Matching, NK Alloreactivity, Viral Exposure

Diversity of Adult Donors on the Be The Match Registry® 2014



Bone Marrow Donors Worldwide

52 countries

72 Registries

Haploidentical BM Transplants

- Transplants that utilize stem cells collected from a relative who only matches for half of the HLA tissue antigens

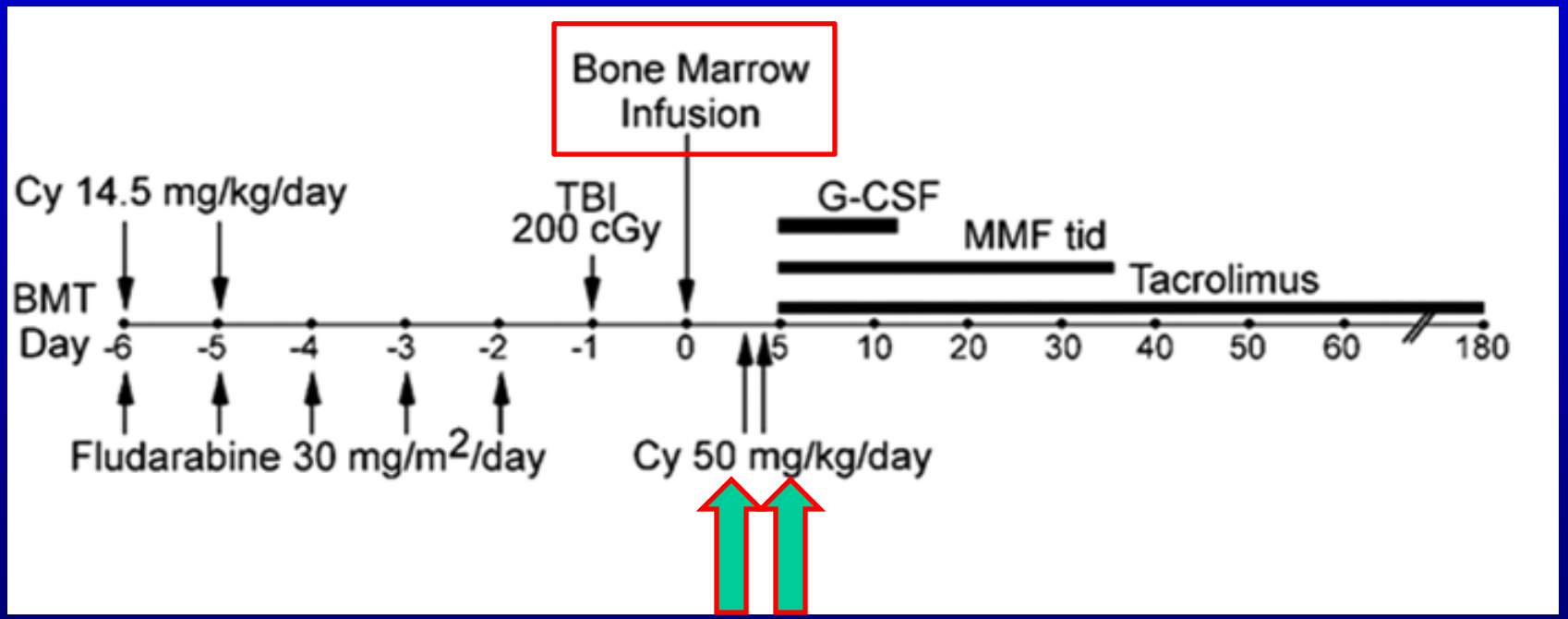
  •Advantages;

  Virtually every patient will have a haplo-identical relative to serve as a stem cell donor

  •Disadvantages:

  - Higher incidence of graft versus host disease
  - Obligates use of T-cell depleted transplants
  - T-cell depletion increases the risk of
    - graft rejection
    - infection
    - disease relapse.

Post Transplant Cyclophosphamide Following T-cell Replete Haploidentical Transplantation of BM or PBSC to Prevent GVHD



Fuchs E. et al JHU

Haploidentical Transplant With Post-Transplant Cyclophosphamide vs MUD Donors For AML

Survival

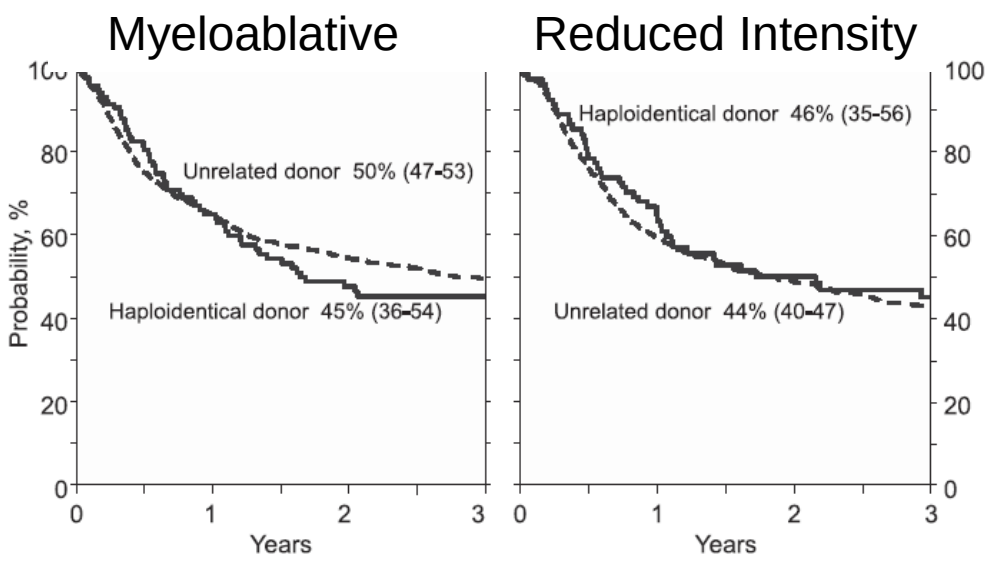


Figure 3. Overall survival. (A) The probability of OS by donor type after myeloablative conditioning regimen, adjusted for age and disease risk index. (B) The probability of OS by donor type after reduced intensity conditioning regimen, adjusted for disease risk index and secondary AML.

Ciurea S. et al Blood 2015 126:8:1033-40

Haploidentical Transplant With Post-Transplant Cyclophosphamide vs MUD Donors For AML

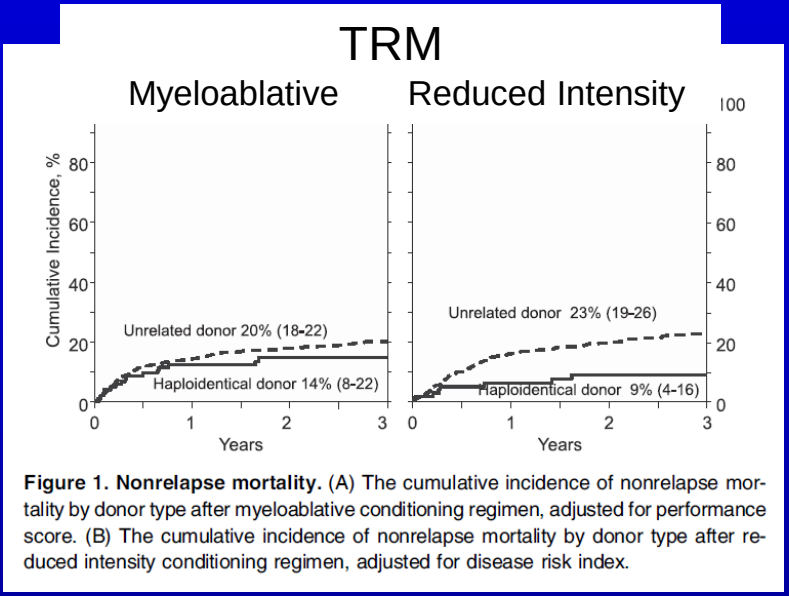


Figure 1. Nonrelapse mortality. (A) The cumulative incidence of nonrelapse mortality by donor type after myeloablative conditioning regimen, adjusted for performance score. (B) The cumulative incidence of nonrelapse mortality by donor type after reduced intensity conditioning regimen, adjusted for disease risk index.

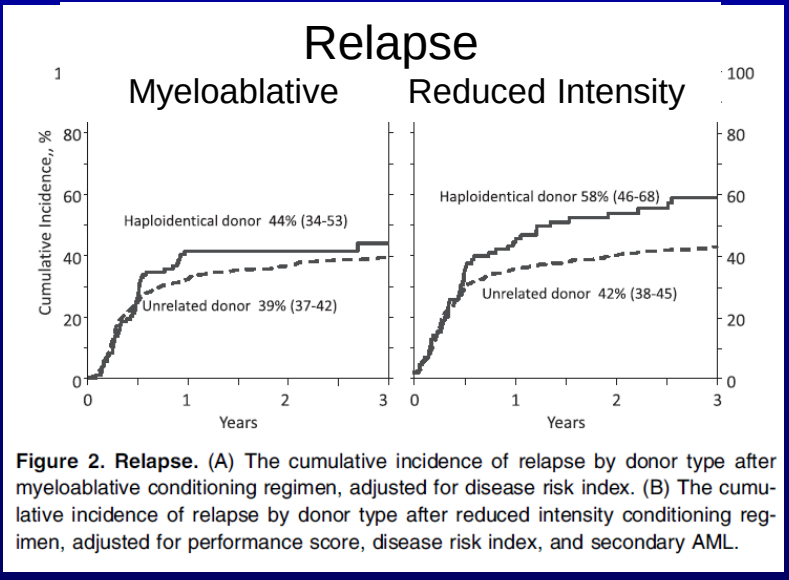


Figure 2. Relapse. (A) The cumulative incidence of relapse by donor type after myeloablative conditioning regimen, adjusted for disease risk index. (B) The cumulative incidence of relapse by donor type after reduced intensity conditioning regimen, adjusted for performance score, disease risk index, and secondary AML.

Table 5. Multivariate analysis (subset): risks of acute and chronic GVHD, nonrelapse mortality, relapse, and OS by donor type

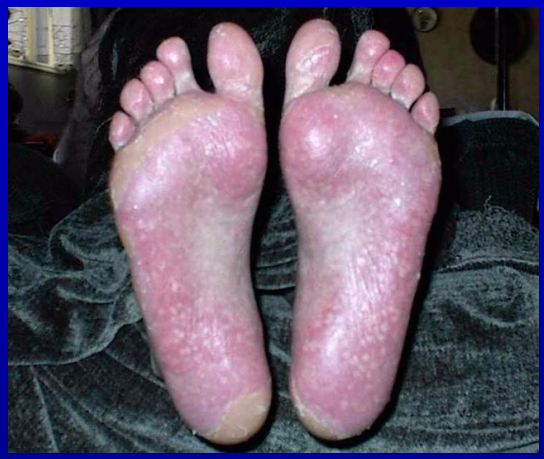
	Transplant conditioning regimen intensity	
Outcome	Myeloablative* Hazard ratio (95% CI)	Reduced intensity† Hazard ratio (95% CI)
Grade 2-4 acute GVHD		
Matched unrelated donor	1.00	1.00
Haploidentical donor	0.37 (0.23-0.61) $P = .0001$	0.71 (0.44-1.15) $P = .16$
Grade 3-4 acute GVHD		
Matched unrelated donor	1.00	1.00
Haploidentical donor	0.33 (0.14-0.81) $P = .02$	0.21 (0.05-0.86) $P = .03$
Chronic GVHD		
Matched unrelated donor	1.00	1.00
Haploidentical donor	0.44 (0.29-0.66) $P = .0001$	0.45 (0.28-0.71) $P = .0006$
Nonrelapse mortality		
Matched unrelated donor	1.00	1.00
Haploidentical donor	0.93 (0.54-1.61) $P = .83$	0.59 (0.27-1.29) $P = .19$
Relapse		
Matched unrelated donor	1.00	1.00
Haploidentical donor	1.28 (0.911.81) $P = .16$	1.53 (1.08-2.22) $P = .02$
Overall mortality		
Matched unrelated donor	1.00	1.00
Haploidentical donor	1.19 (0.87-1.61) $P = .28$	1.06 (0.76-1.51) $P = .70$

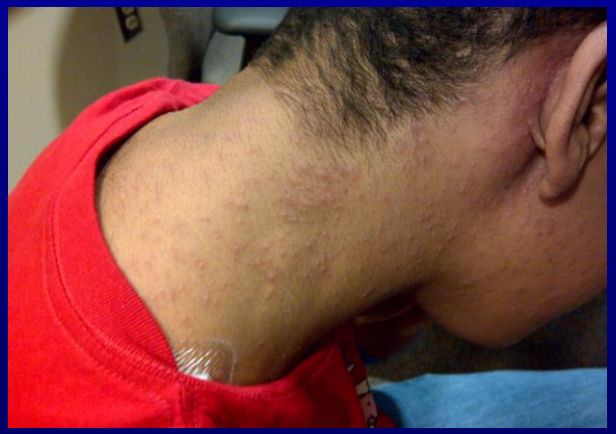
Ciurea S. et al Blood 2015 126:8:1033-40

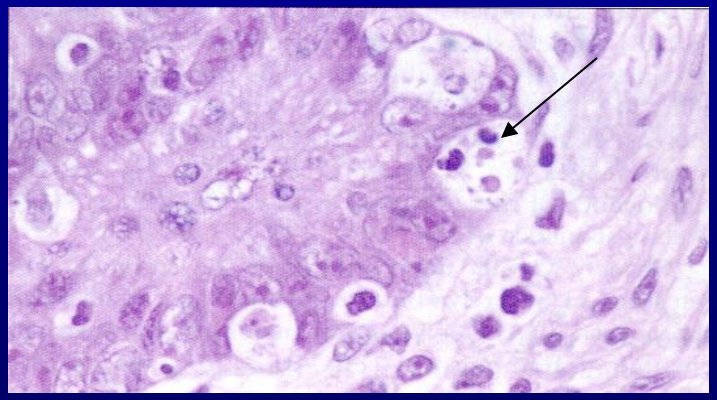
GVHD Remains a Major Contributor to Transplant Related Mortality

Acute GVHD

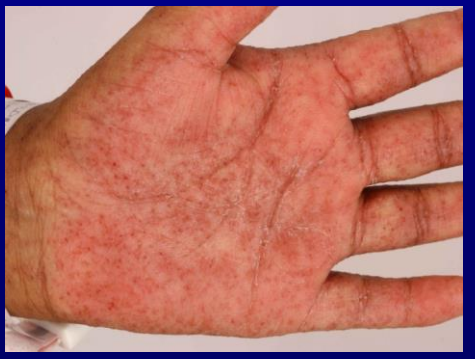
1. GI Tract: Diarrhea
2. Liver: Jaundice
3. Skin: Rash





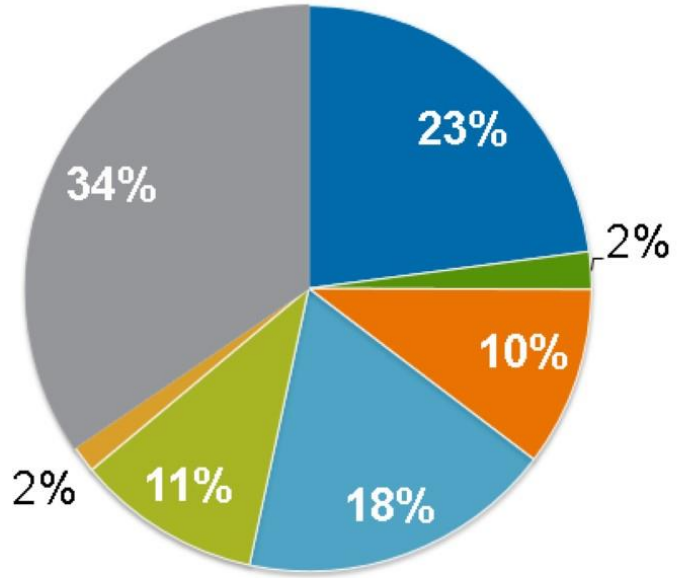


GVHD of the Colon

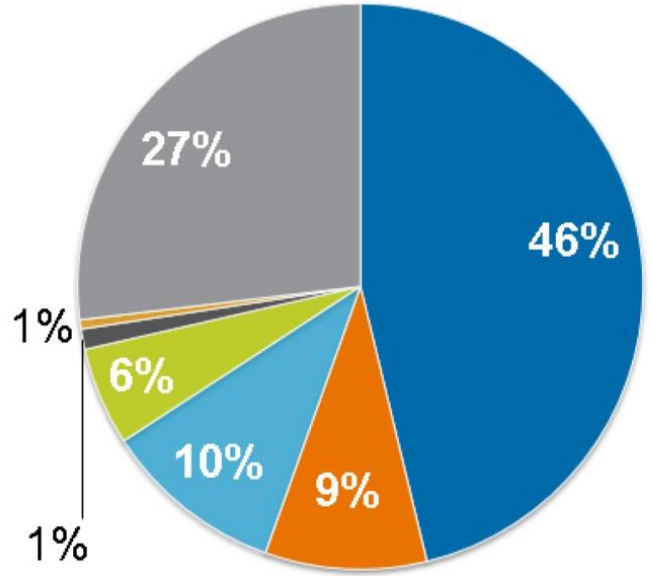


Causes of Death after Unrelated Donor HCT done in 2013-2014

Died within 100 days post-transplant



Died at or beyond 100 days post-transplant



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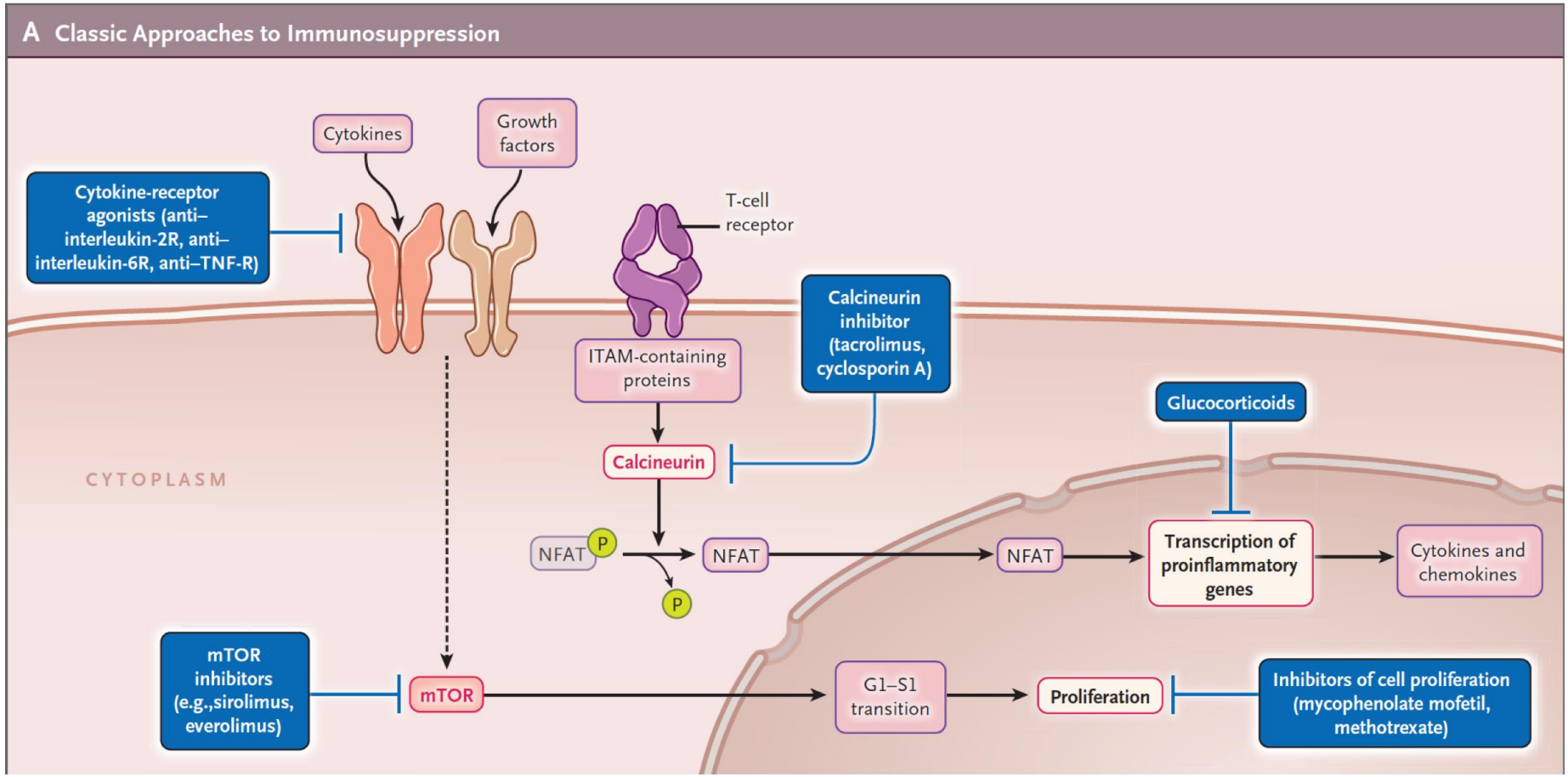
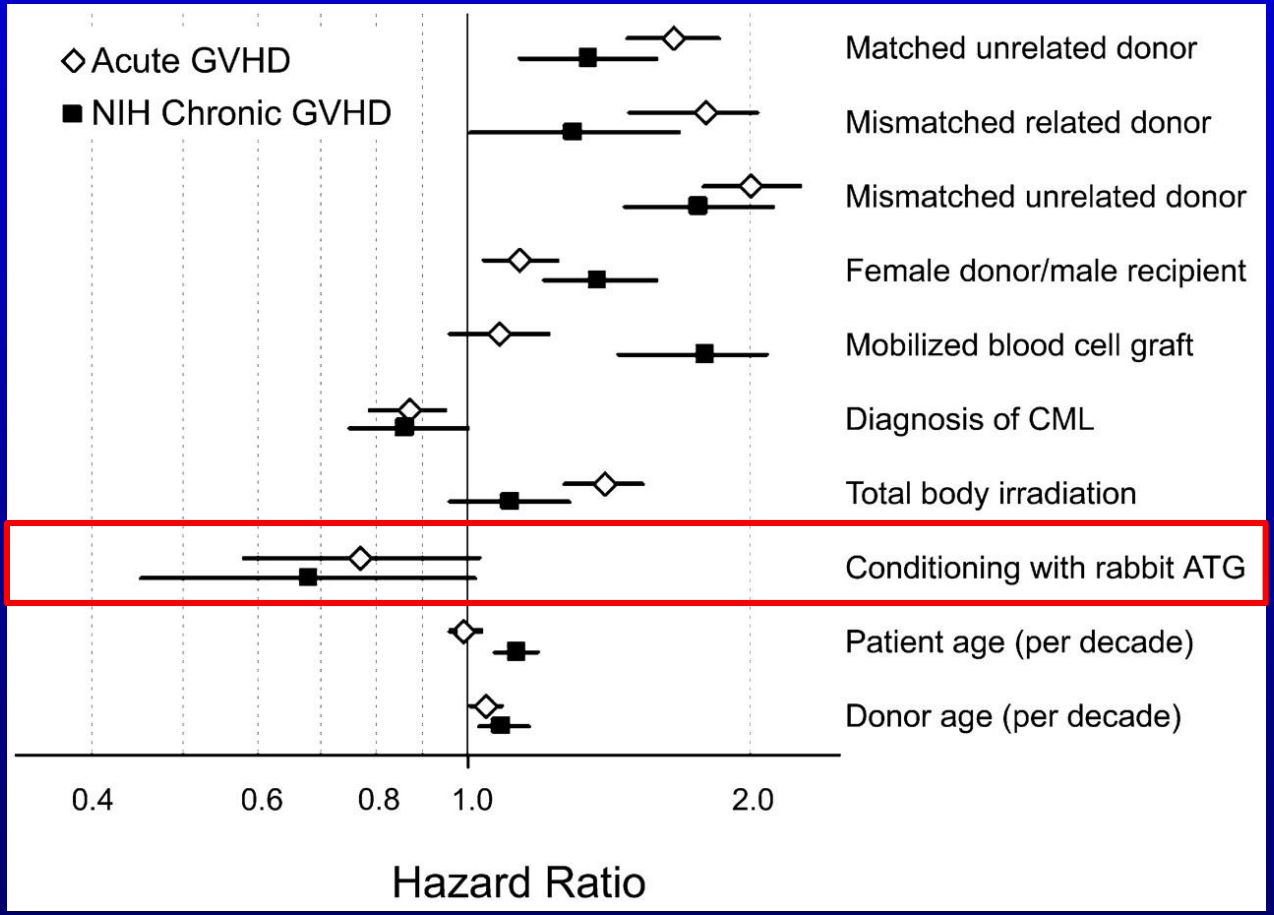
Classical treatment approach for GVHD prevention



Zeiser and Blazar,
NEJM 2017

Multivariate Analysis Identifies ATG in Conditioning as Reducing Risk of grade 2-4 acute and chronic NIH GVHD (N=2941)



Flowers et al BLOOD, 2011

The NEW ENGLAND JOURNAL of MEDICINE

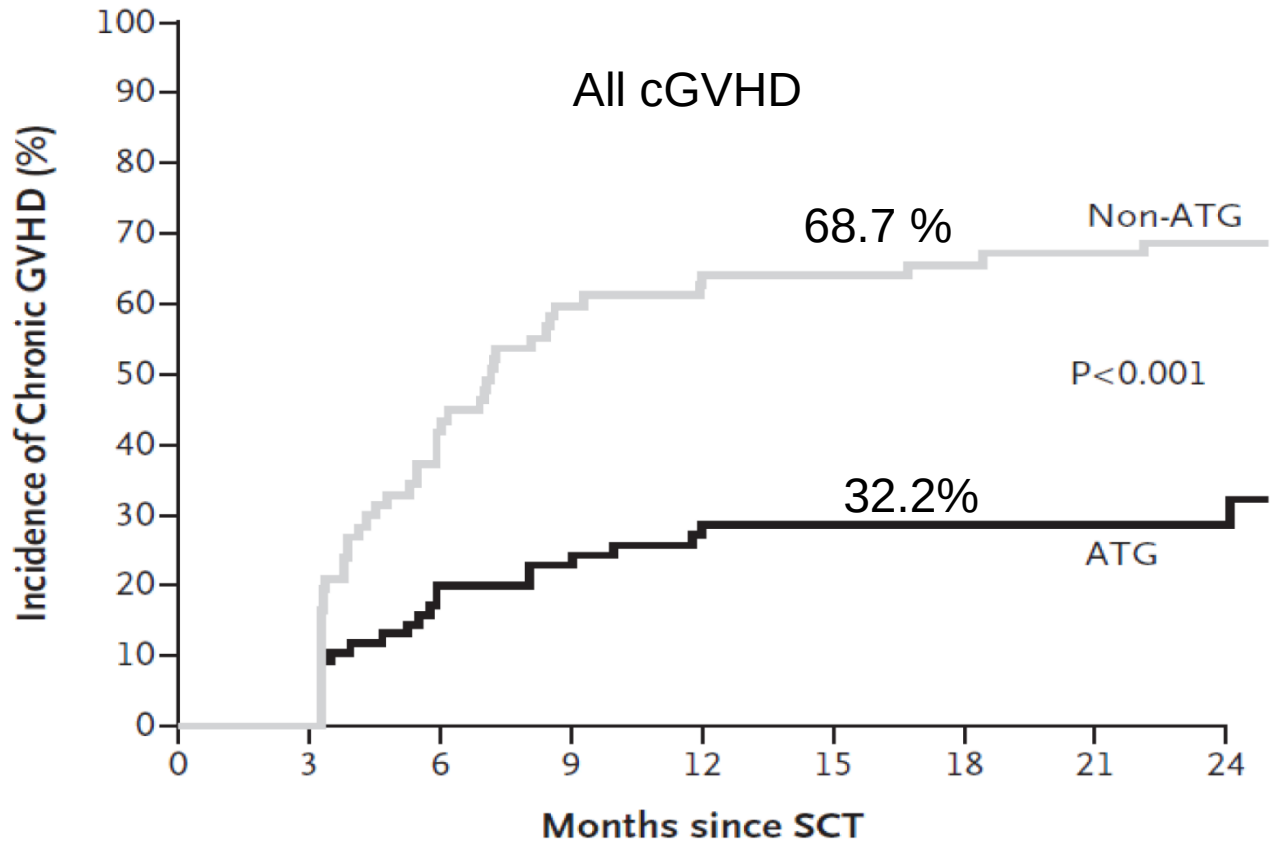
ORIGINAL ARTICLE

Antilymphocyte Globulin for Prevention of Chronic Graft-versus-Host Disease

Nicolaus Kröger, M.D., Carlos Solano, M.D., Christine Wolschke, M.D., Giuseppe Bandini, M.D., Francesca Patriarca, M.D., Massimo Pini, M.D., Arnon Nagler, M.D., Carmine Selleri, M.D., Antonio Risitano, M.D., Ph.D., Giuseppe Messina, M.D., Wolfgang Bethge, M.D., Jaime Pérez de Oteiza, M.D., Rafael Duarte, M.D., Angelo Michele Carella, M.D., Michele Cimminiello, M.D., Stefano Guidi, M.D., Jürgen Finke, M.D., Nicola Mordini, M.D., Christelle Ferra, M.D., Jorge Sierra, M.D., Ph.D., Domenico Russo, M.D., Mario Petrini, M.D., Giuseppe Milone, M.D., Fabio Benedetti, M.D., Marion Heinzelmann, Domenico Pastore, M.D., Manuel Jurado, M.D., Elisabetta Terruzzi, M.D., Franco Narni, M.D., Andreas Völp, Ph.D., Francis Ayuk, M.D., Tapani Ruutu, M.D., and Francesca Bonifazi, M.D.

Kroger et al,
NEJM, 2016

GVHD prophylaxis in allo PBSCT MRD: ATG added to myelo-ablative regimen. Phase 3 RCT. N=155. Patient with AML/CLL.



No. at Risk									
ATG	83	78	55	46	42	40	38	38	25
Non-ATG	72	68	34	23	21	20	18	17	9

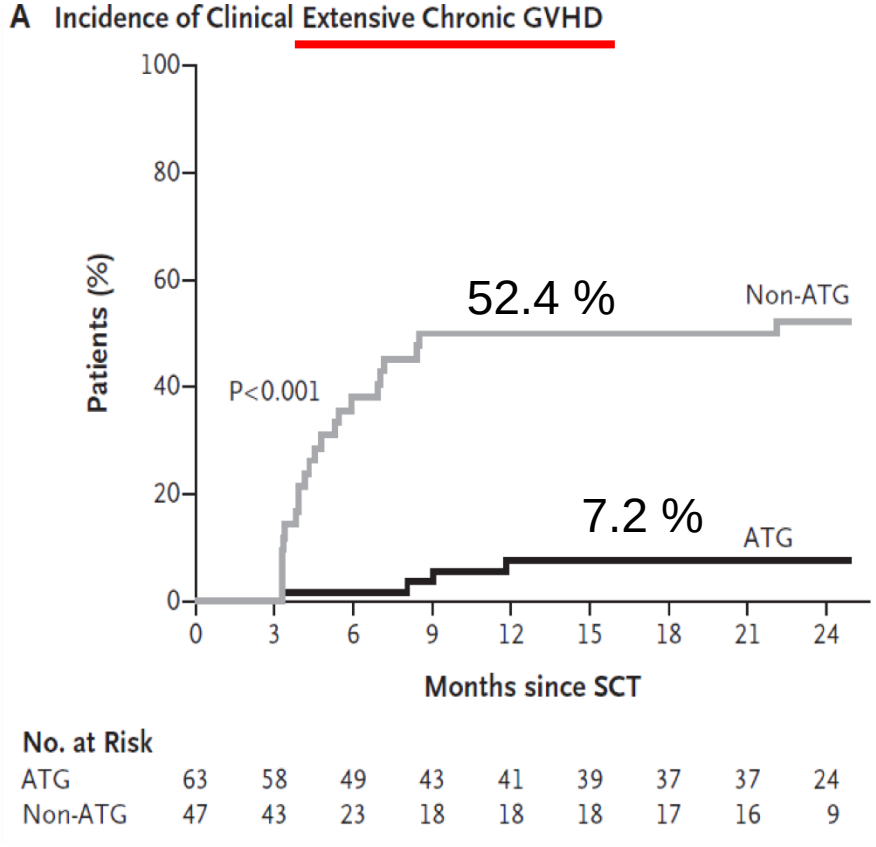
Cumulative incidence of cGVHD at 2 years.
Conditioning regimens:

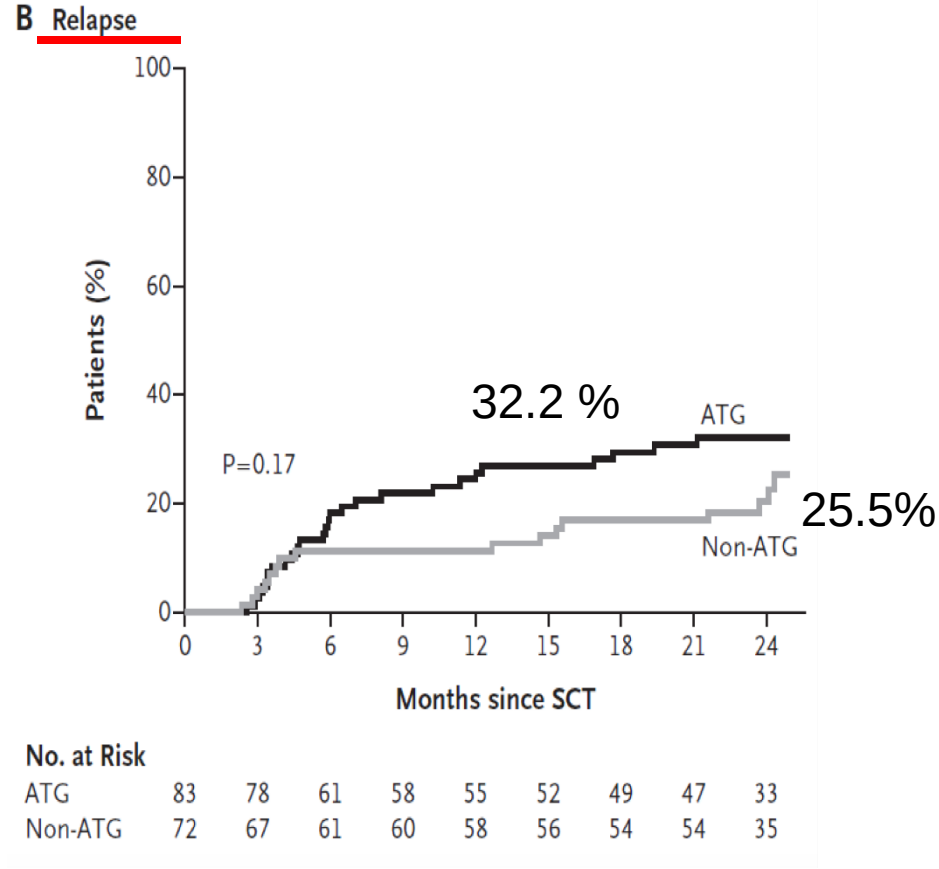
1. TBI (12gy)+Cytoxan
2. Busulfan + Cytoxan
3. Etoposide+ TBI

+/- R-ATG

Kroger et al, NEJM, 2016

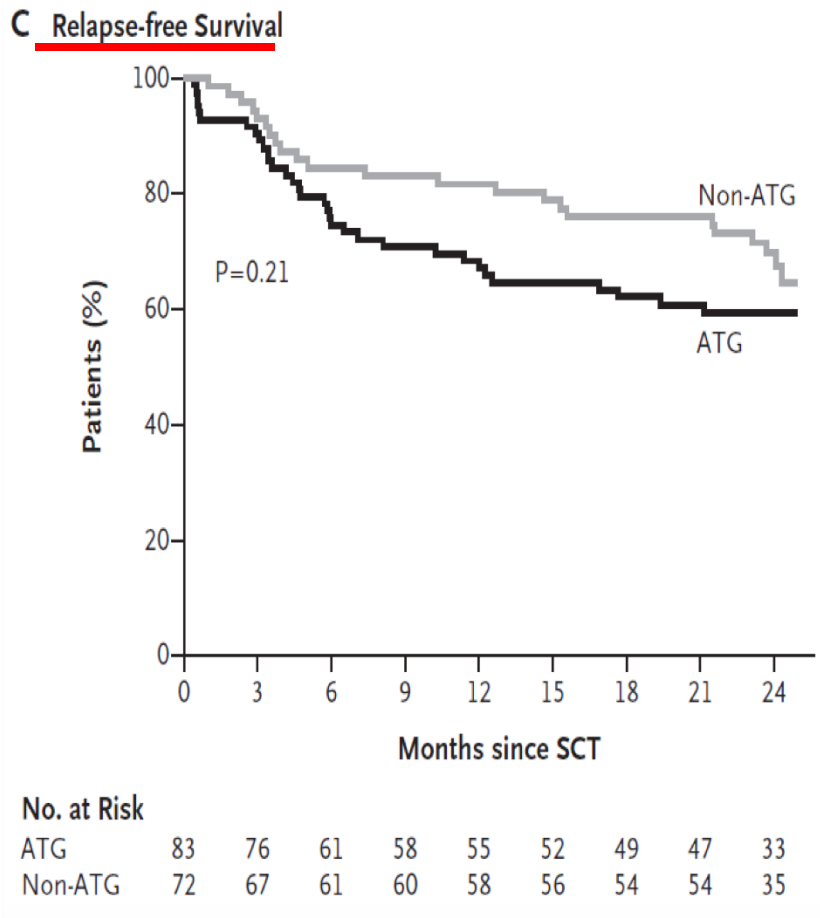
GVHD prophylaxis in MRD HSCT: ATG

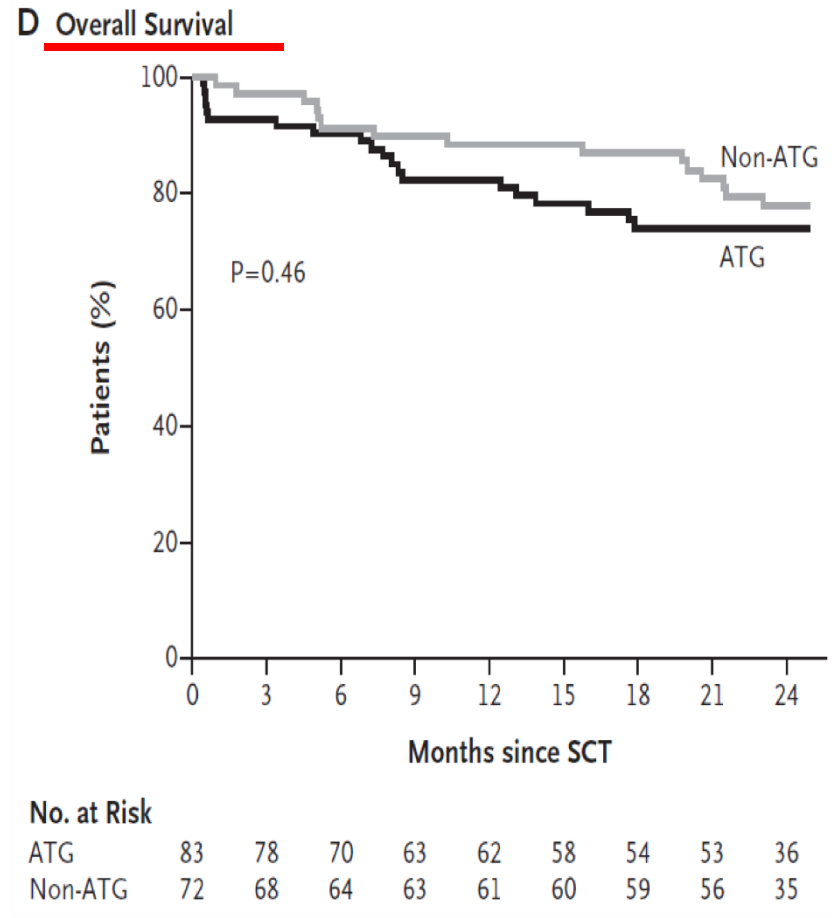




Kroger et al, NEJM, 2016

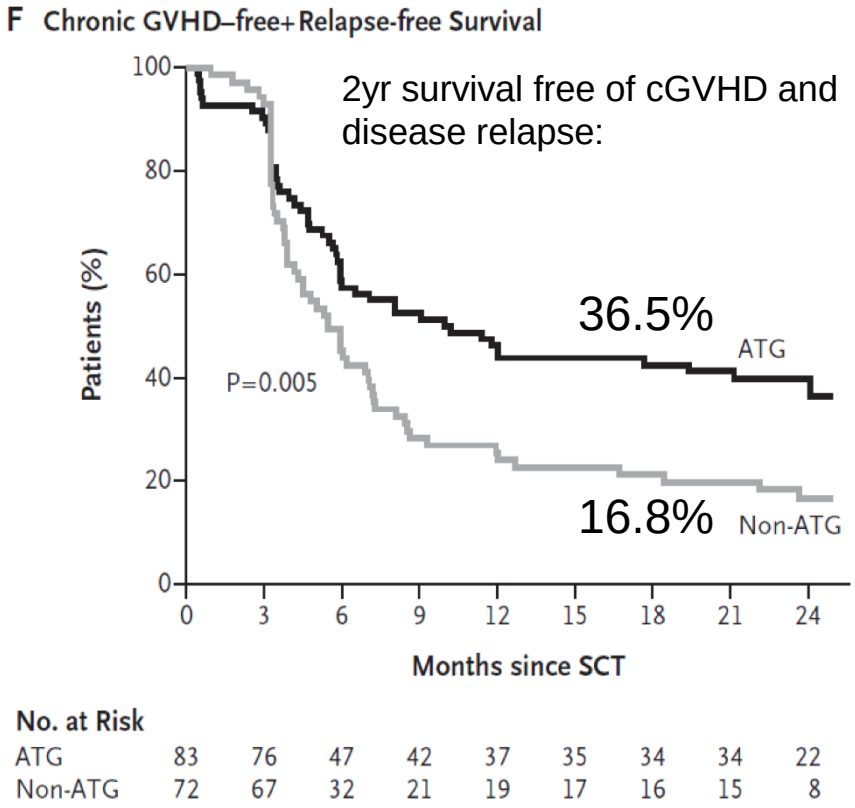
GVHD prophylaxis in MRD HSCT: ATG





Kroger et al,
NEJM, 2016

GVHD prophylaxis in MRD HSCT: ATG



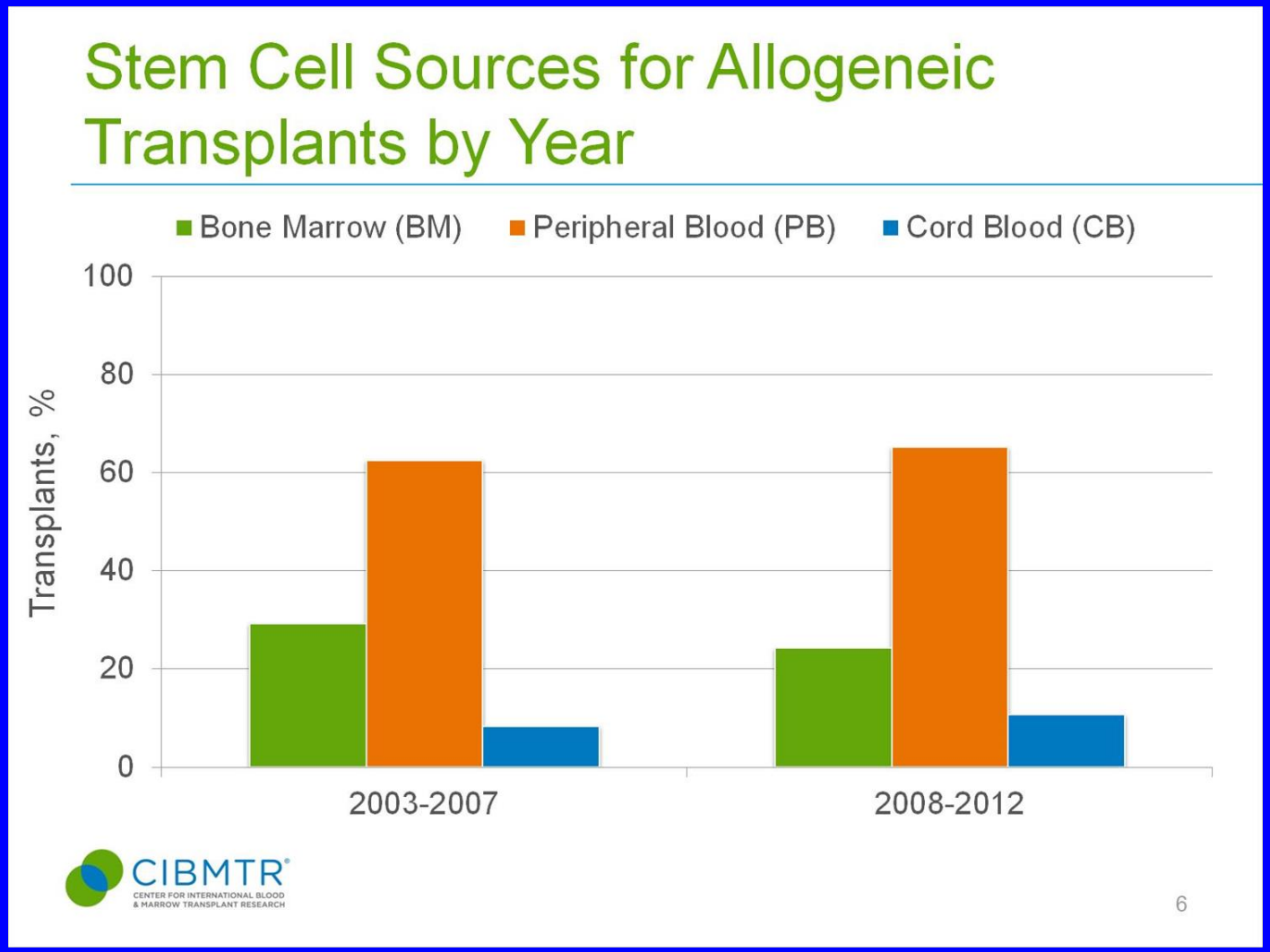
- This randomized trial defines a clear role for the use of ATG in conditioning regimens to prevent cGVHD

Kroger et al, NEJM, 2016

Graft Source

- PBSC is the most common graft source
- BM is associated with a lower risk of GVHD compared to PBSC
- Cord Blood transplants, despite HLA mismatching, are associated with a low incidence off GVHD

Peripheral Blood Stem Cell Transplants (PBSCs) are the Most UtilizedGraft Cell Source for Allogeneic Transplants



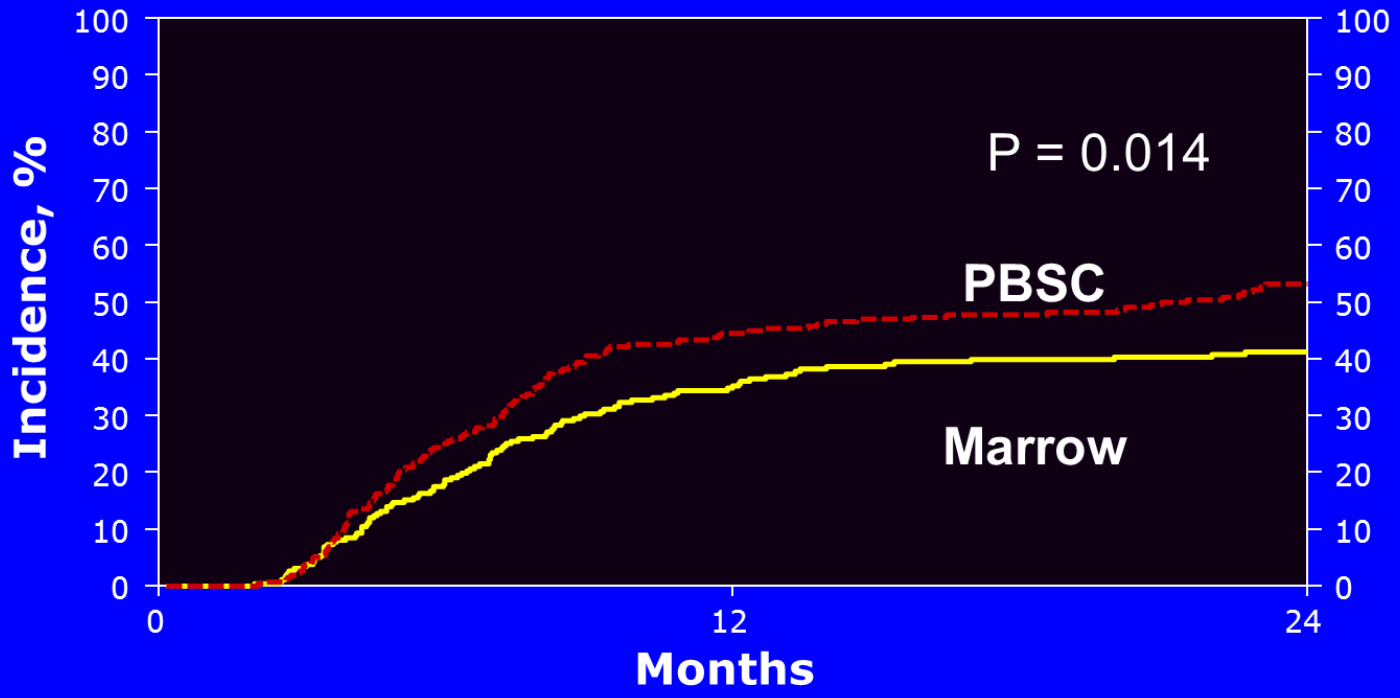
Pros of PBSCs:

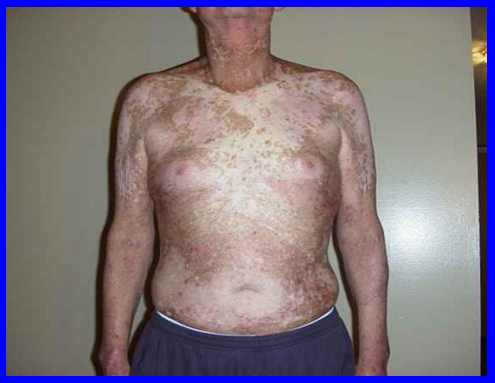
1. Easy to collect
2. Higher CD34+ Cell dose
3. Lower graft rejection rate

Cons of PBSCs

1. Higher cGVHD risk

PBSCs Associated with Higher Incidence of cGVHD than BM Transplants





- **Extensive chronic GVHD 32% BM vs 48% PBSC (p=0.001)**

Anasetti et al; NEJM 2012: 367:1487

What Transplant Stem Source is Optimal for Haplo-Transplants Using Post Transplant Cyclophosphamide: Bone Marrow vs. PBSC?

Bashey et al. JCO 2017

Mobilized Peripheral Blood Stem Cells Versus Unstimulated Bone Marrow As a Graft Source for T-Cell–Replete Haploidentical Donor Transplantation Using Post-Transplant Cyclophosphamide

Asad Bashey, Mei-Jie Zhang, Shannon R. McCurdy, Andrew St. Martin, Trevor Argall, Claudio Anasetti, Stefan O. Ciurea, Omotayo Fasan, Sameh Gaballa, Mehdi Hamadani, Pashna Munshi, Monzr M. Al Malki, Ryotaro Nakamura, Paul V. O'Donnell, Miguel-Angel Perales, Kavita Raj, Rizwan Romee, Scott Rowley, Vanderson Rocha, Rachel B. Salit, Melhem Solh, Robert J. Soiffer, Ephraim Joseph Fuchs, and Mary Eapen

A B S T R A C T

Purpose

T-cell–replete HLA-haploidentical donor hematopoietic transplantation using post-transplant cyclophosphamide was originally described using bone marrow (BM). With increasing use of mobilized peripheral blood (PB), we compared transplant outcomes after PB and BM transplants.

Patients and Methods

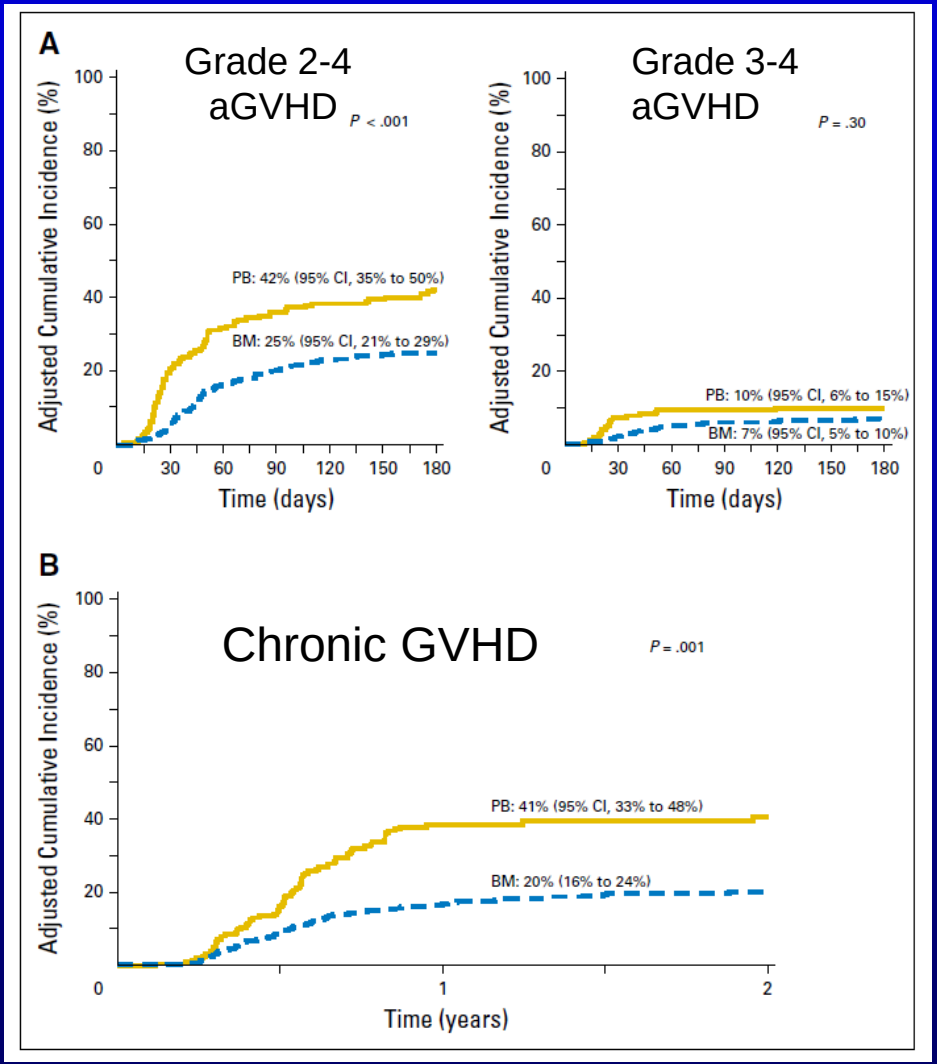
A total of 681 patients with hematologic malignancy who underwent transplantation in the United States between 2009 and 2014 received BM (n = 481) or PB (n = 190) grafts. Cox regression models were built to examine differences in transplant outcomes by graft type, adjusting for patient, disease, and transplant characteristics.

Bashey et al. JCO 2017

PBSC vs BM Following Haplo-Transplantation with Post-transplant Cytoxan

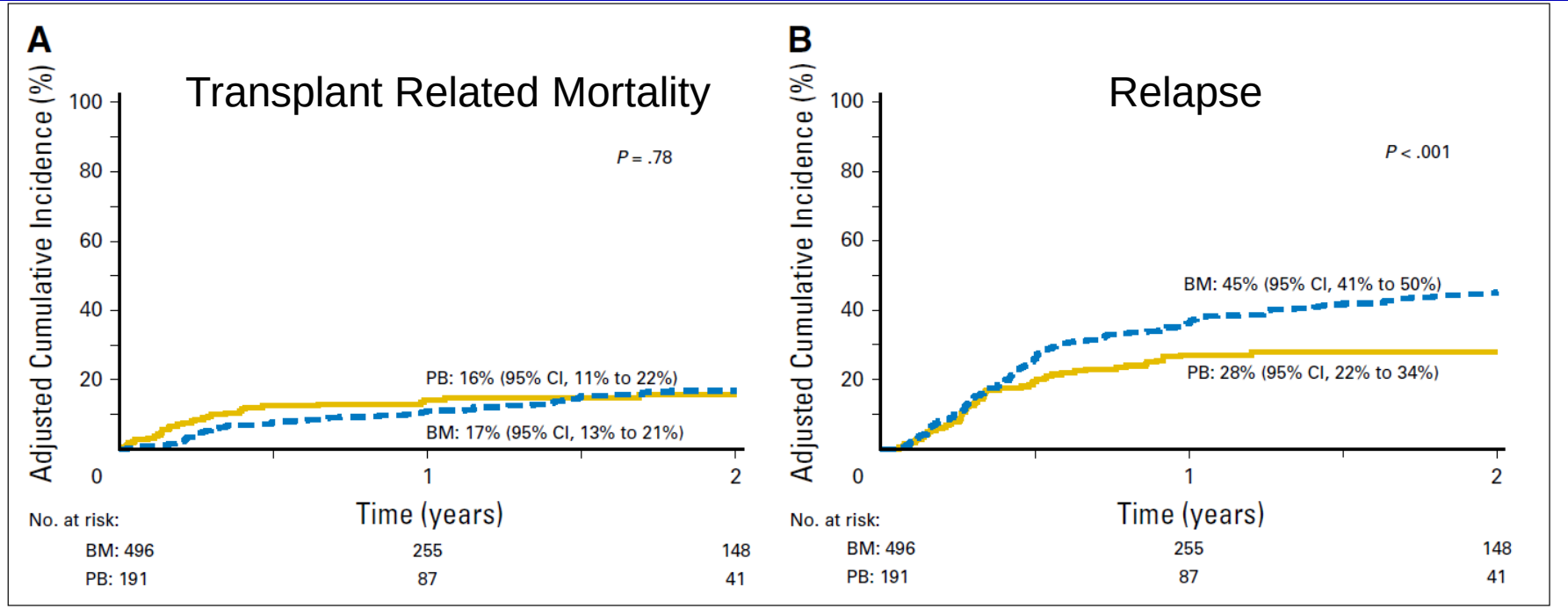
681 haplo-transplant pts

N=481 bone marrow
N=191 PBSC



Bashey et al. JCO 2017

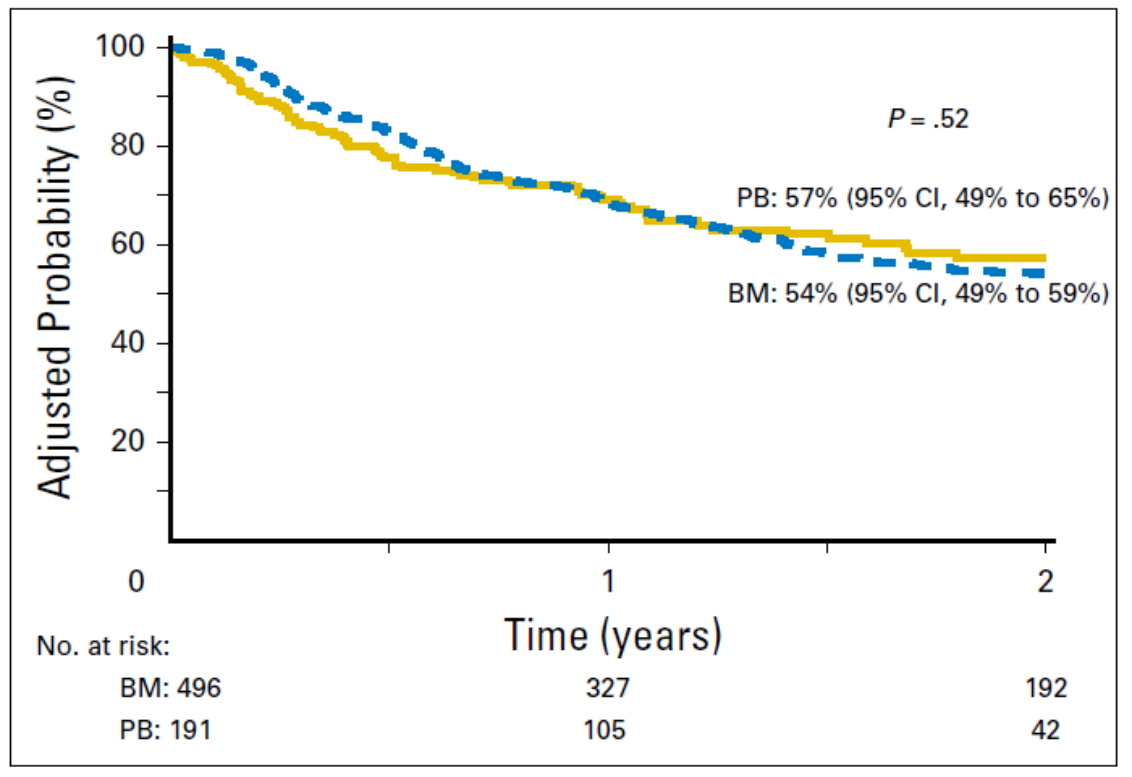
PBSC vs BM Following Haplo-Transplantation with Post-transplant Cytoxan



Bashey et al. JCO 2017

PBSC vs BM Following Haplo-Transplantation with Post-transplant Cytoxan

Survival



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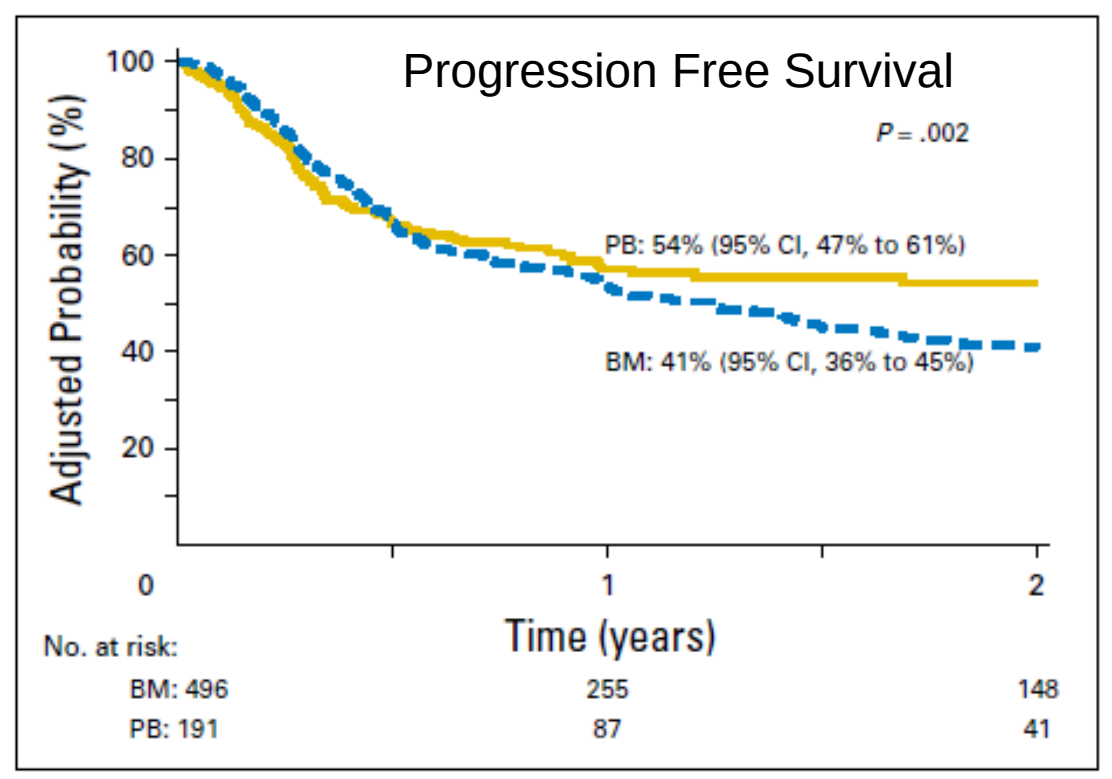
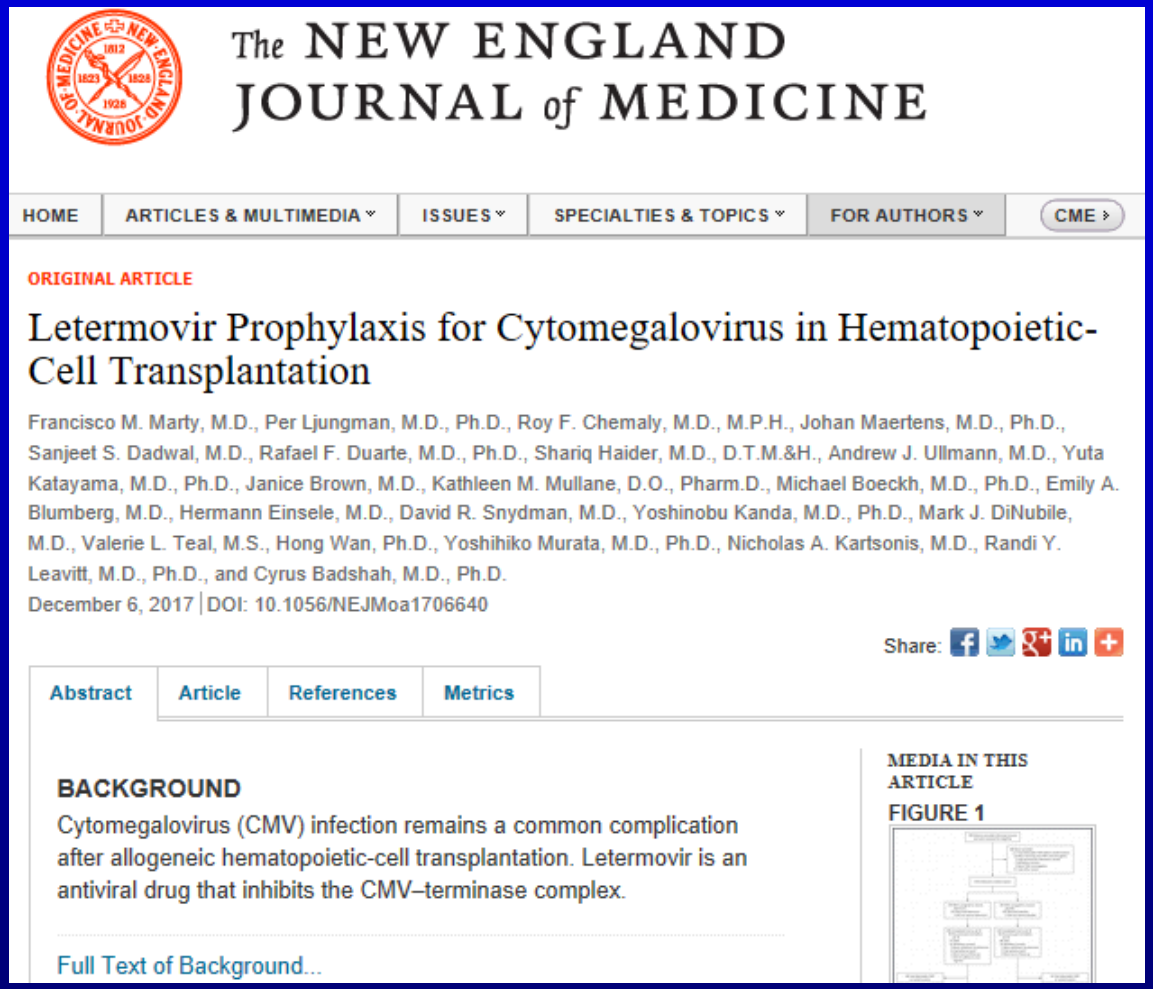
PBSC vs BM Following Haplo-Transplantation with Post-transplant Cytoxan



BM and PBSC both viable stem cell options post Haplo transplant
Longer follow-up needed to discern if PFS advantage with PBSC improves survival

New Tools To Treat Transplant Related Complications



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ORIGINAL ARTICLE

Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation

Francisco M. Marty, M.D., Per Ljungman, M.D., Ph.D., Roy F. Chemaly, M.D., M.P.H., Johan Maertens, M.D., Ph.D., Sanjeet S. Dadwal, M.D., Rafael F. Duarte, M.D., Ph.D., Shariq Haider, M.D., D.T.M.&H., Andrew J. Ullmann, M.D., Yuta Katayama, M.D., Ph.D., Janice Brown, M.D., Kathleen M. Mullane, D.O., Pharm.D., Michael Boeckh, M.D., Ph.D., Emily A. Blumberg, M.D., Hermann Einsele, M.D., David R. Snydman, M.D., Yoshinobu Kanda, M.D., Ph.D., Mark J. DiNubile, M.D., Valerie L. Teal, M.S., Hong Wan, Ph.D., Yoshihiko Murata, M.D., Ph.D., Nicholas A. Kartsonis, M.D., Randi Y. Leavitt, M.D., Ph.D., and Cyrus Badshah, M.D., Ph.D.

December 6, 2017 | DOI: 10.1056/NEJMoa1706640

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Abstract | Article | References | Metrics

BACKGROUND

Cytomegalovirus (CMV) infection remains a common complication after allogeneic hematopoietic-cell transplantation. Letermovir is an antiviral drug that inhibits the CMV–terminase complex.

Full Text of Background...

MEDIA IN THIS ARTICLE

FIGURE 1

Letermovir- a non-nucleoside CMV inhibitor targeting viral terminase complex preventing viral replication

Randomized trial n=570 patients

- **n=376 received prophy letermovir**
- **n=192 received placebo**
- **14 weeks of study drug**
- **Dose 480 mg/day off CSA**
- **Dose 240 mg/day on CSA**

- **Study endpoint- CMV reactivation week 24**

F. Marty et al. NEJM Dec 2017

OUTCOMES

Table 2. Efficacy End Points (Primary Efficacy Population).*

End Point	Letermovir Group (N=325)	Placebo Group (N=170)	Difference (95% CI)	P Value
	number of patients (percent)		*percentage points*	
Primary end point at wk 24 after transplantation	122 (37.5)	103 (60.6)	−23.5 (−32.5 to −14.6)	<0.001
Clinically significant CMV infection	57 (17.5)	71 (41.8)		
Initiation of preemptive therapy	52 (16.0)	68 (40.0)		
CMV disease†	5 (1.5)	3 (1.8)		
Discontinued trial before wk 24	56 (17.2)	27 (15.9)		
Owing to adverse event	6 (1.8)	1 (0.6)		
Owing to death without CMV	28 (8.6)	12 (7.1)		
Owing to other reason‡	22 (6.8)	14 (8.2)		
Missing outcome in wk 24 visit window	9 (2.8)	5 (2.9)		
Key secondary end point at wk 14 after transplantation	62 (19.1)	85 (50.0)	−31.3 (−39.9 to −22.6)	<0.001
Clinically significant CMV infection	25 (7.7)§	67 (39.4)		
Initiation of preemptive therapy	24 (7.4)	65 (38.2)		
CMV disease†	1 (0.3)	2 (1.2)		
Discontinued trial before wk 14	33 (10.2)	16 (9.4)		
Owing to adverse event	5 (1.5)	1 (0.6)		
Owing to death without CMV	14 (4.3)	6 (3.5)		
Owing to other reason‡	14 (4.3)	9 (5.3)		
Missing outcome in wk 14 visit window	4 (1.2)	2 (1.2)		

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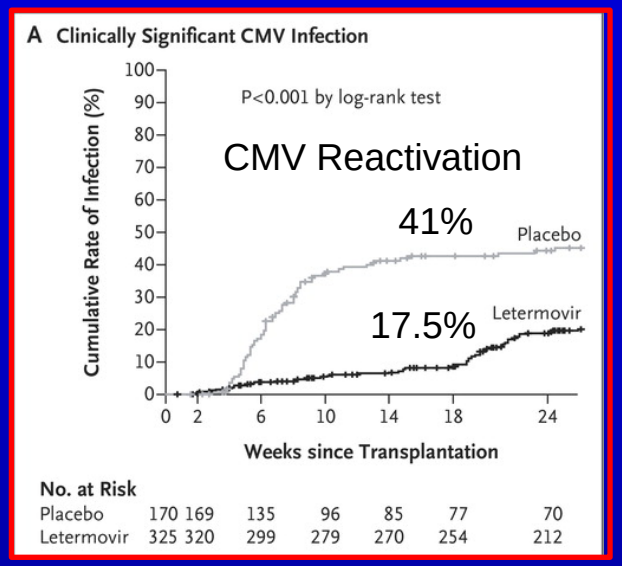
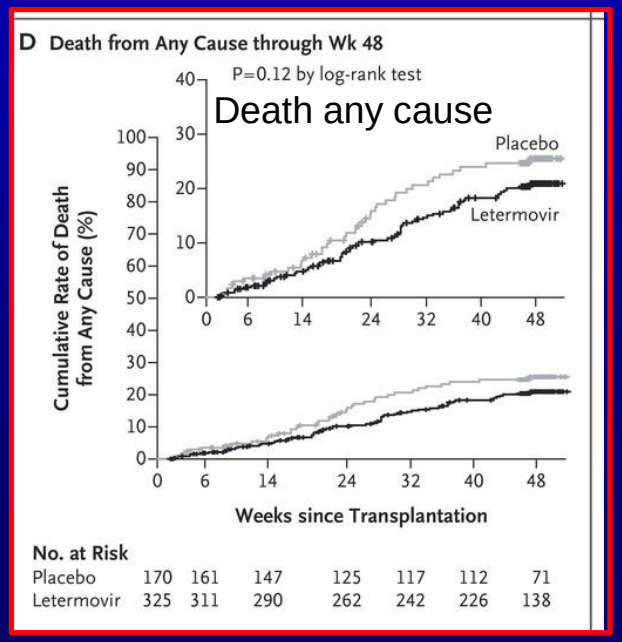
OUTCOMES





- FDA approves letermovir Nov 2017 for CMV prophylaxis post transplant

- Letermovir is well tolerated
  - ❖ No marrow suppression unlike ganciclovir
  - ❖ No renal toxicity unlike foscarnet
- ❖ Use of drug to treat CMV reactivation being studied

F. Marty et al. NEJM Dec 2017

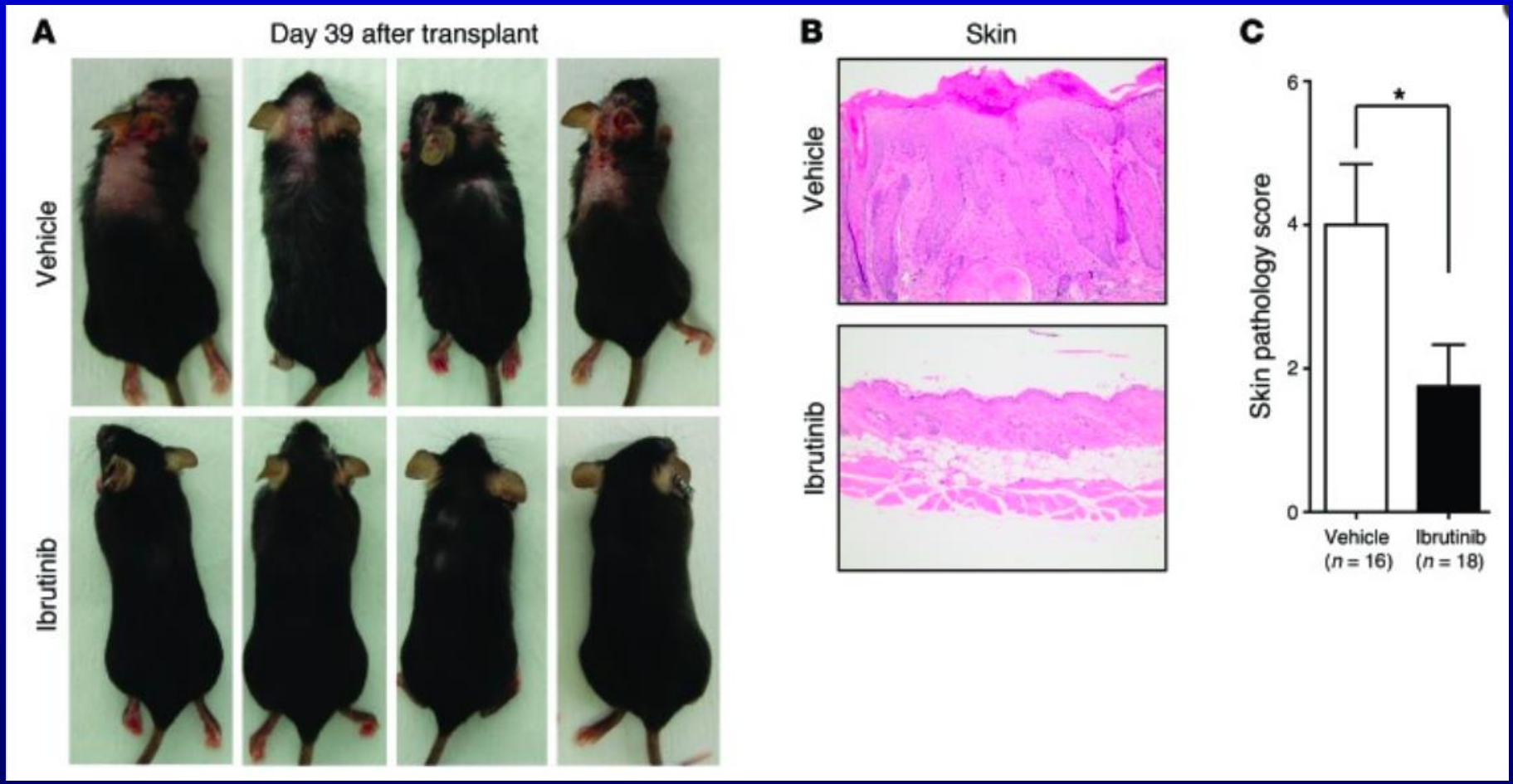
Ibrutinib for chronic GVHD after failure of prior therapy

Miklos, D et al, Blood-Sept 2017

cGVHD

- No standard 2nd line therapy for cGVHD (after corticosteroids)
- Ibrutinib inhibits BTK (which regulates B-cell survival)
- Ibrutinib also inhibits ITK (IL-2 inducible T-cell kinase, which drives immune reactivity toward healthy tissues)
- po daily dosing
- T ½ = ~5 hrs

Ibrutinib improved clinical manifestations of cGVHD in pre-clinical studies

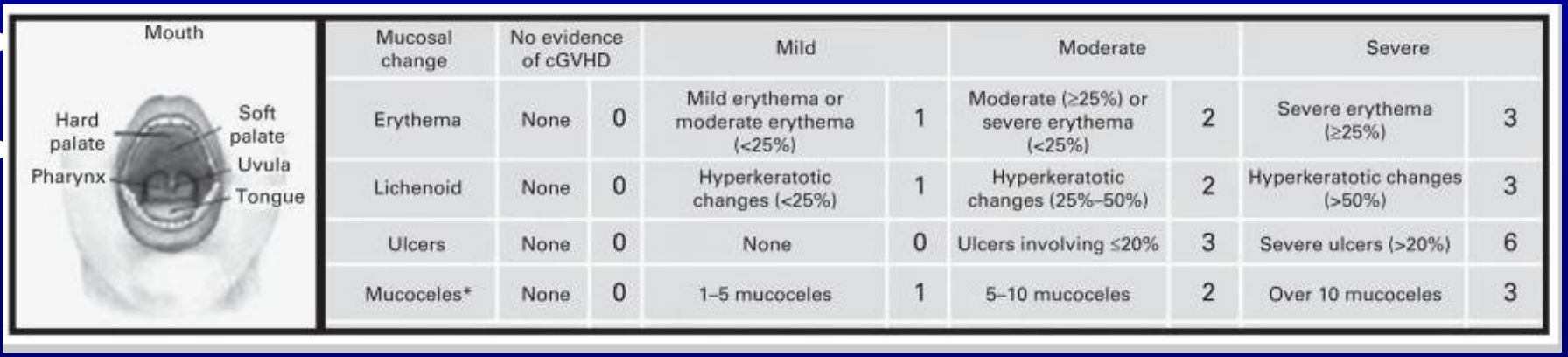


Study Design

- Phase 1b/ Phase 2
- Multicenter, Open Label
- Pharmacyclics company sponsored
- Enrollment 7/2014, Last follow-up 9/2016
- Sample size 40; assuming cGVHD response rate of 50%; Power 90% to show efficacy

Inclusion Criteria

- Adult
- Steroid dependent OR refractory cGVHD
  - Dependent = >0.25mg/kg/d Prednisone for ≥ 12 wks
  - Refractory = despite >0.25mg/kg/d Prednisone for ≥ 4 wks



Mouth

Mucosal change	No evidence of cGVHD		Mild		Moderate		Severe	
Erythema	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or severe erythema (<25%)	2	Severe erythema (≥25%)	3
Lichenoid	None	0	Hyperkeratotic changes (<25%)	1	Hyperkeratotic changes (25%–50%)	2	Hyperkeratotic changes (>50%)	3
Ulcers	None	0	None	0	Ulcers involving ≤20%	3	Severe ulcers (>20%)	6
Mucoceles*	None	0	1–5 mucoceles	1	5–10 mucoceles	2	Over 10 mucoceles	3

Methods

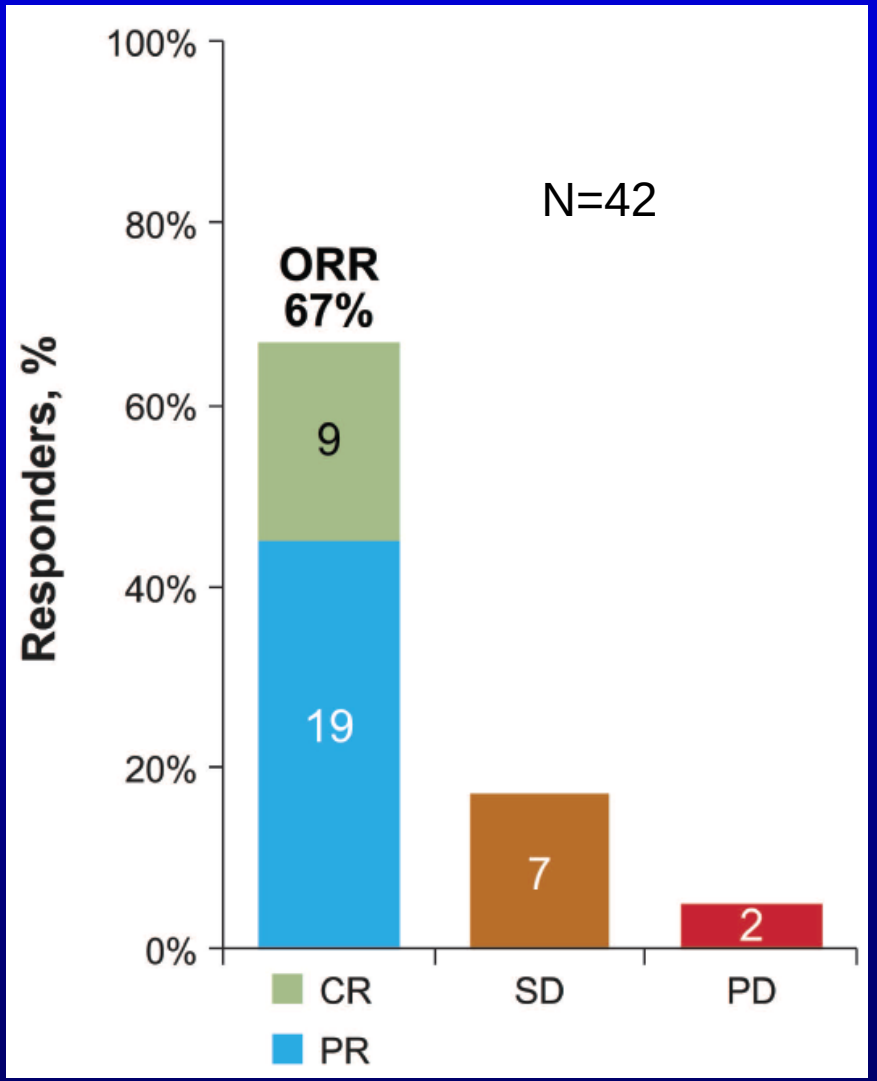
- All received CS before and during study + other IS allowed (as long as stable doses 14d prior to study) – drugs could be tapered
- 3+3 design
- Phase 1b: Started at dose 420mg; if DLT could reduce to 280mg or 140mg
  - N=6, No DLT, RP2D = 420mg
- Phase 2
  - N=42

Baseline Patient Characteristics

Characteristic	(N = 42)*
Median prior lines of treatment for cGVHD (range)	2 (1–3)
Mean prednisone dose at enrollment (range), mg/kg/d	0.31 (0.1–1.3)
Prior therapies for cGVHD	
Corticosteroids	42 (100)
Tacrolimus	21 (50)
Extracorporeal photopheresis/PUVA photochemotherapy	11 (26)
Rituximab	11 (26)
Mycophenolate mofetil	10 (24)
Cyclosporine	8 (19)
Sirolimus	7 (17)
Other immunosuppressants	2 (5)

ORR

- Steroid dependent: ORR 75%, CR 25%
- Steroid refractory: ORR 50%, CR 17%

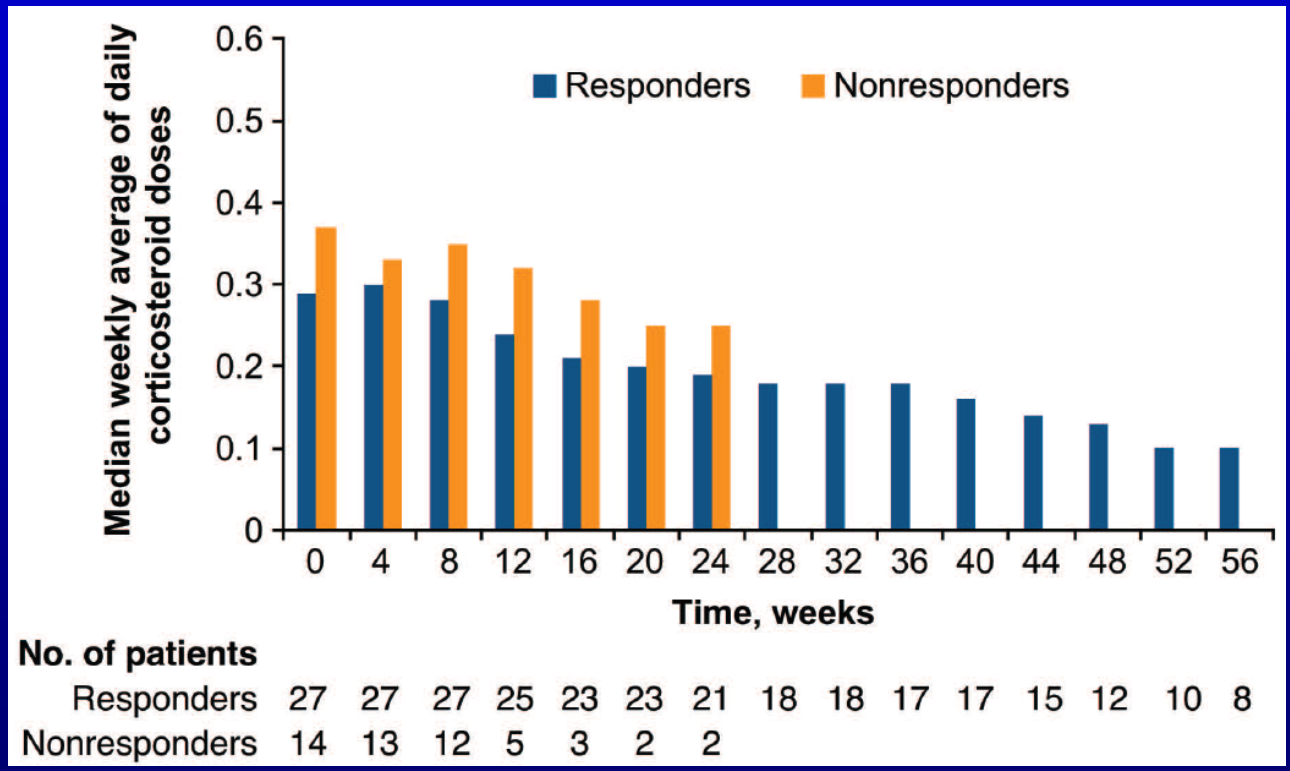


Response Rates

	No. of responders	Sustained response rate n (%)
Sustained response of ≥ 20 weeks	28	20 (71)
Organ	**No. of responders with organ involvement at baseline**	**Best overall response rate, n (%)**
Skin	24	21 (88)
Mouth	24	21 (88)
Gastrointestinal	11	10 (91)
Organs showing response	**No. of patients with ≥ 2 involved organs at baseline among responders**	**Best overall response rate, n (%)**
≥ 2 organs	25	20 (80)

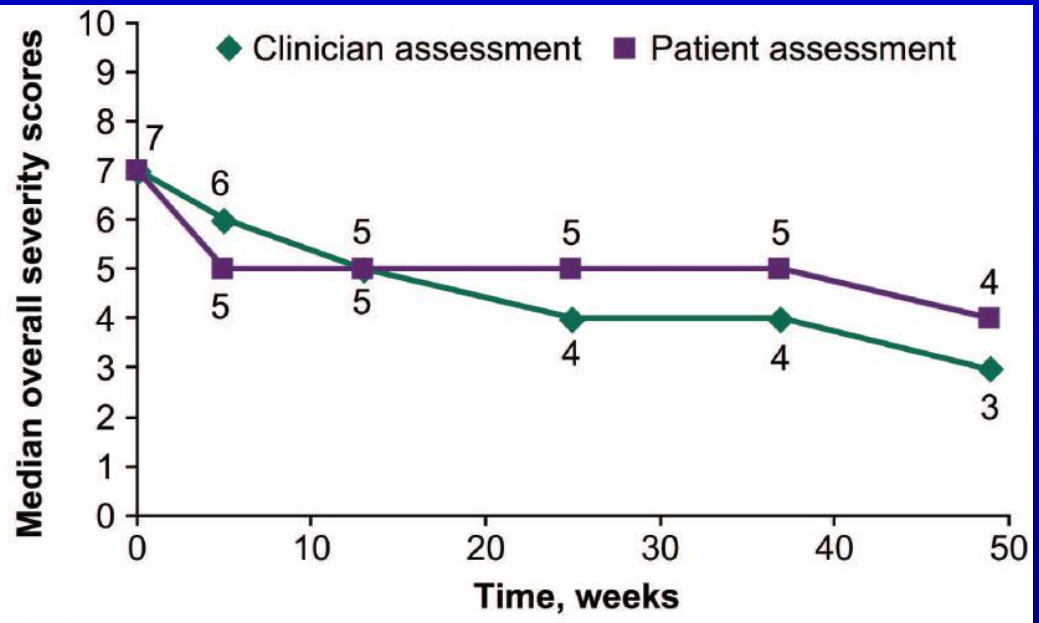
Ibrutinib Reduced Corticosteroid (CS) Usage

- Among responders, median CS use from 0.29 to 0.12 mg/kg/d
- 5 completely stopped CS



Ibrutinib Reduced GVHD Symptoms

- Lee GVHD Sx scale improved significantly in 61% of responders



Week	0	5	13	25	37	49
Clinician assessment	41	11	34	20	17	15
Patient assessment	42	10	31	18	16	14

Conclusion

- Ibrutinib demonstrated ORR 67% (CR=21%, PR=45%)
  - FDA approved for cGVHD – first drug approved for this indication
- Ibrutinib was largely safe to use, though:
  - 1/3 discontinued due to AE, though in a low PS population
- Phase 3 study underway for further validation

The Future of Allogeneic BMT

- **Success of haplo-transplants:**
  - Will lead to more annual transplants world-wide

- **Reduced mortality of allotransplants**
  - Better drugs to prevent and treat GVHD (i.e. Ibrutinib/ruxolitinib for cGVHD)
  - Better drugs to prevent CMV reactivation
  - Transplants performed earlier in disease course- (i.e AML)- will reduce risk of disease relapse

- **More studies exploring investigational cellular therapies to improve transplant outcomes will be forthcoming**
  - **Viral reactive T-cells**
  - **Leukemia reactive T-cells**

Published Ahead of Print on February 19, 2013 as 10.1200/JCO.2012.44.3523
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2012.44.3523

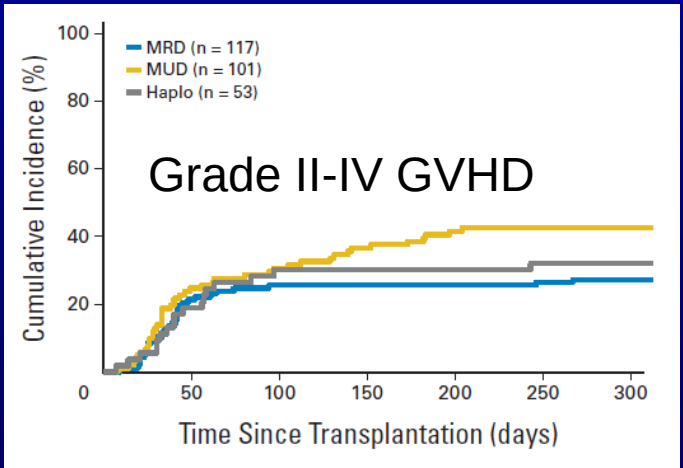
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

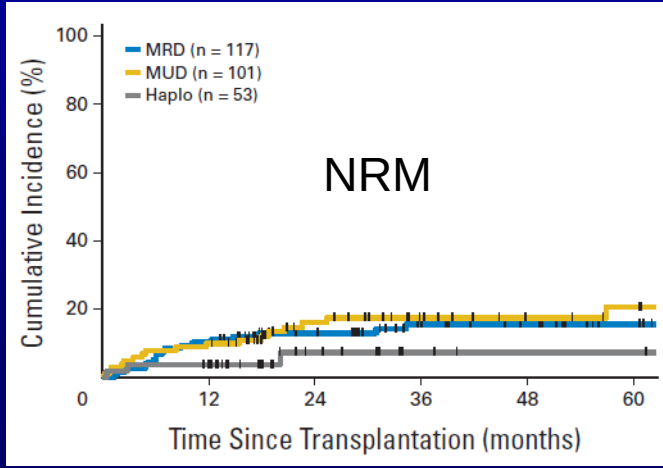
T-Cell–Replete HLA-Haploidentical Hematopoietic Transplantation for Hematologic Malignancies Using Post-Transplantation Cyclophosphamide Results in Outcomes Equivalent to Those of Contemporaneous HLA-Matched Related and Unrelated Donor Transplantation

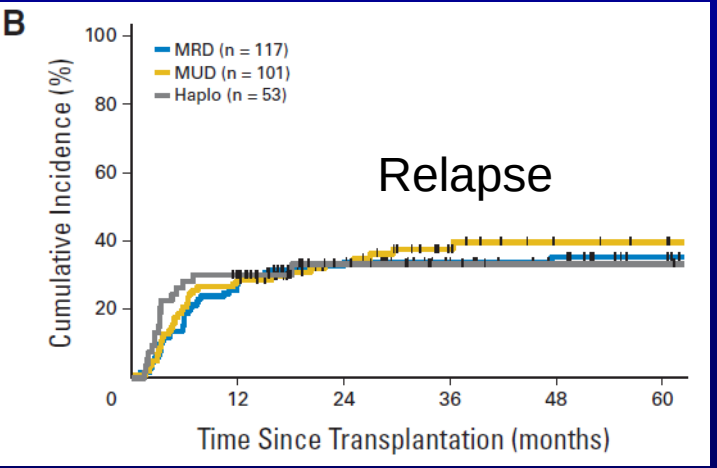
Asad Bashey, Xu Zhang, Connie A. Sizemore, Karen Manion, Stacey Brown, H. Kent Holland, Lawrence E. Morris, and Scott R. Solomon

271 patients hematological malignancies – Transplanted single center 2005-2010

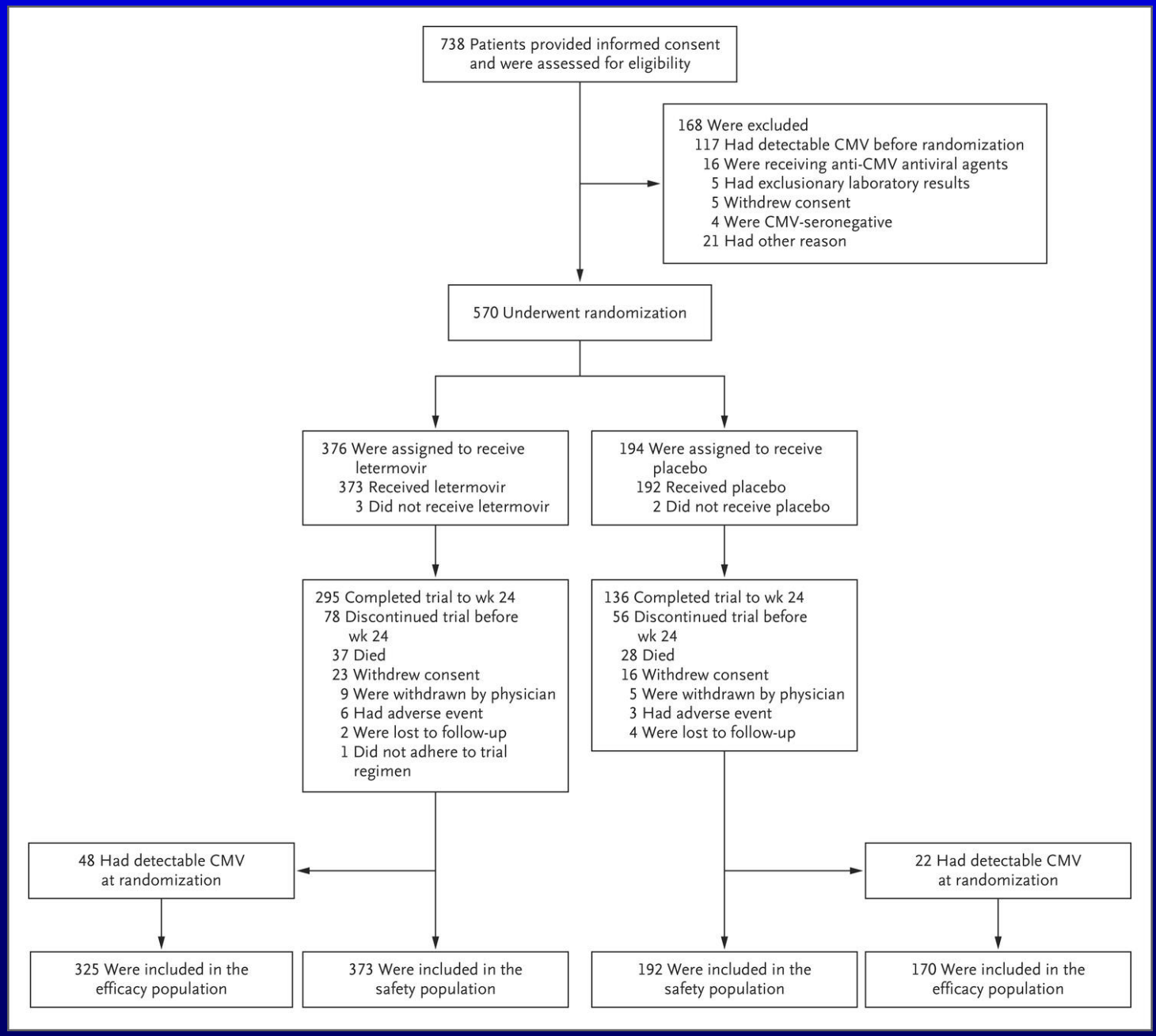
- 53 Haploidentical onors
- 117 MRDs
- 101 MUDS







Bashley et al; JCO 2013



F. Marty et al. NEJM Dec 2017

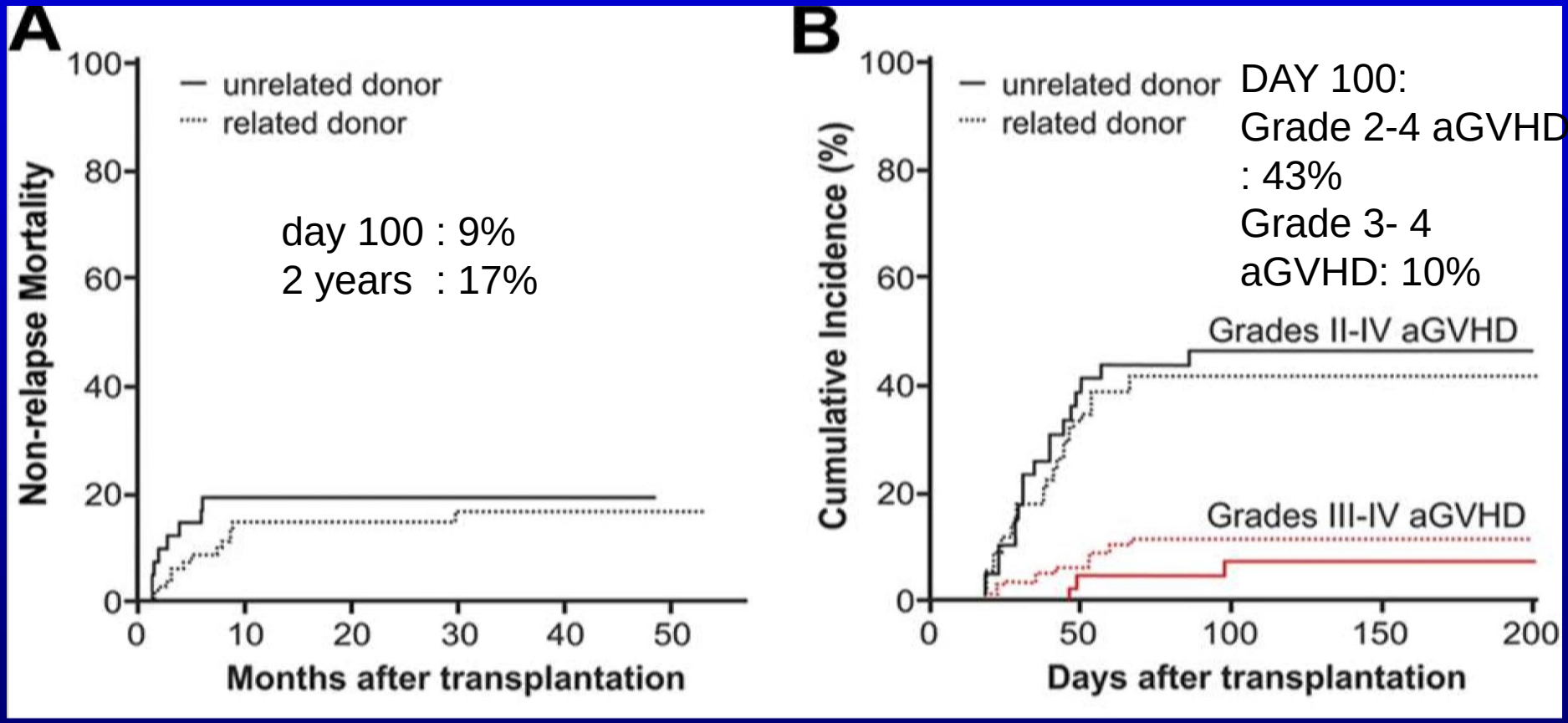
Who Should Get a Transplant?

Is the patient a good candidate for a transplant?

- Age-no longer limiting
- Medical co-morbidity- less limiting with RIC transplants
- Donor availability- no longer limiting

- Disease Status as a critical determinant for transplant eligibility.
  - Guiding principle- if the disease has a bad prognosis with conventional therapy then the risks of a transplant may be justifiable
    - This is a moving target for some diseases- i.e. P53 mutated CLL
    - This is easy for other diseases
      - Therapy related MDS/AML
      - AML in second CR
      - ALL in second CR

Single-agent cyclophosphamide : GVHD prophylaxis N=117 pts. 78 MRD, 39 URD. MAC: BuCy. Advanced hem malignancies



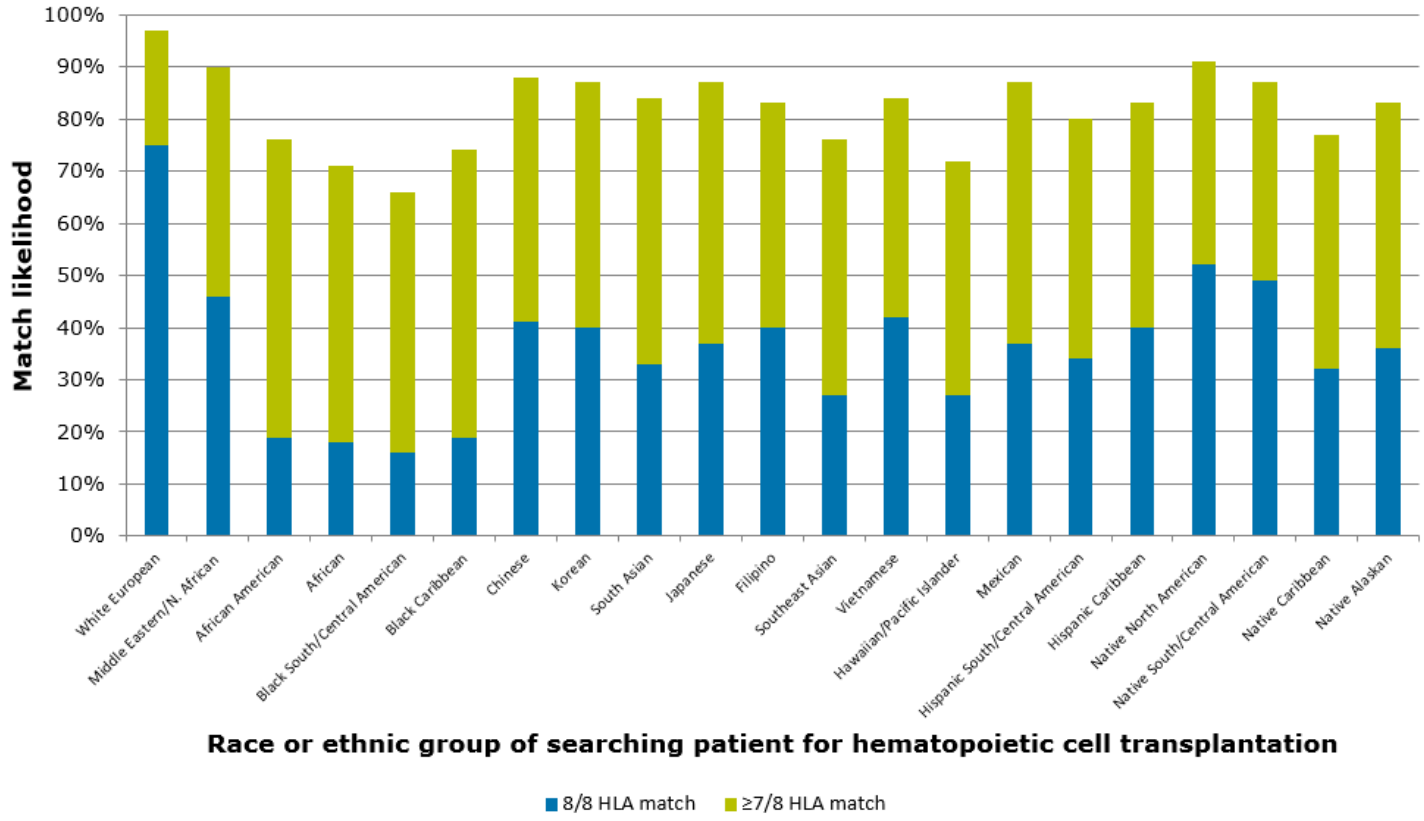
Luznik et al. Blood 2010

Results

	(N = 42)
Median time on study (range) — months	13.9 (0.5–24.9)
Median time on treatment (range) — months	4.4 (0.2–24.9)
Patients still on treatment — no. (%)	12 (29)
Reasons for treatment discontinuation, n (%)	
Adverse events (including death)*	14 (33)
Patient decision†	6 (14)
Progression of cGVHD	5 (12)
Recurrence or progression of original malignancy	2 (5)
Investigator decision†	2 (5)
Noncompliance with study drug	1 (2)

Likelihood of finding matched unrelated adult donor

Range 66-97%: *Available suitable match, by race/ethnic group, Be The Match Registry®*



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