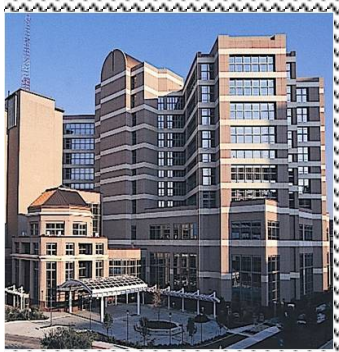
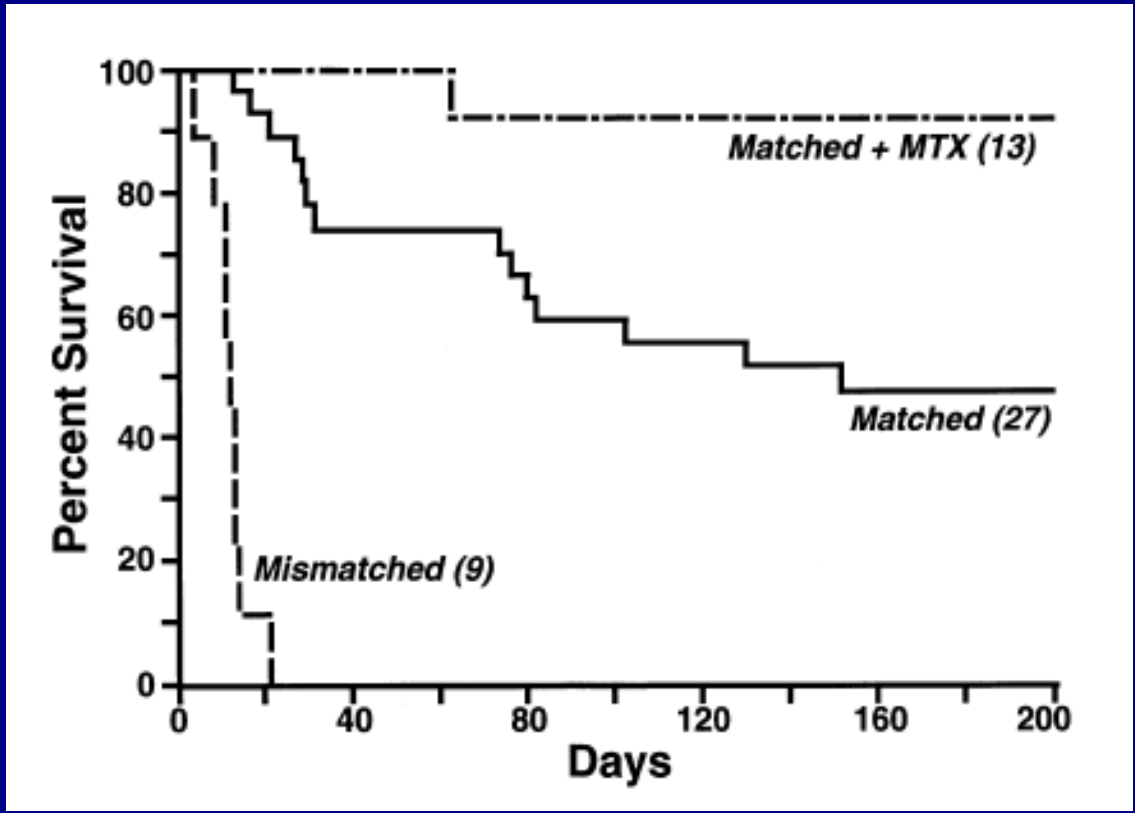
AML: Transplant or ChemoTherapy?



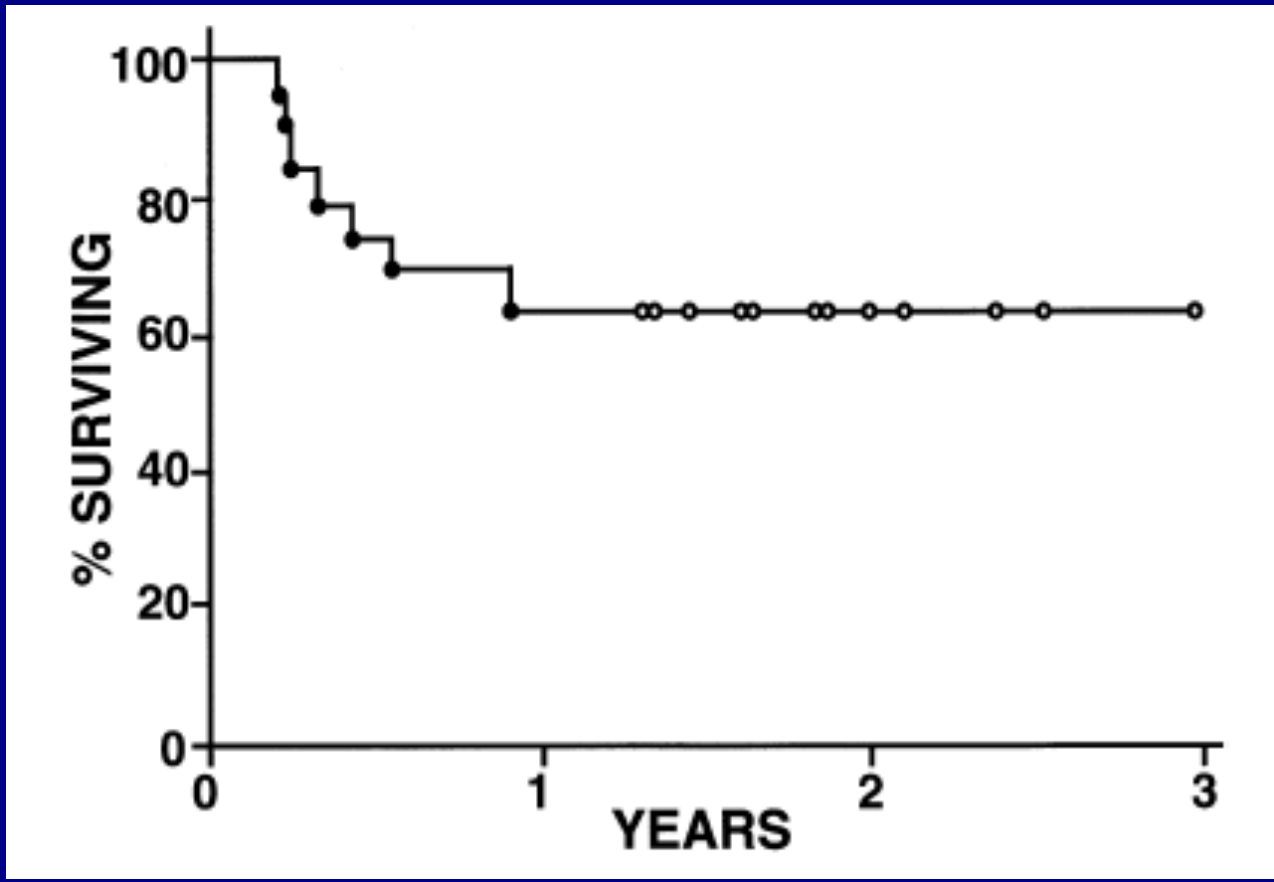
1960's: Importance of HLA type in Animal Models



Survival of Dogs Given 1000 RAD TBI and a Marrow Infusion from a Littermate Matched or Mismatched for Dog Leucocyte Antigens (Epstein 1968, Storb 1971)

Thomas: A History of Haemopoietic Cell Transplantation, Brit J Haematol, 1999, 105, 330-339

1970's: HLA-identical Sibling as a Curative Therapy in CR 1 given Cy-TBI and (n=19)

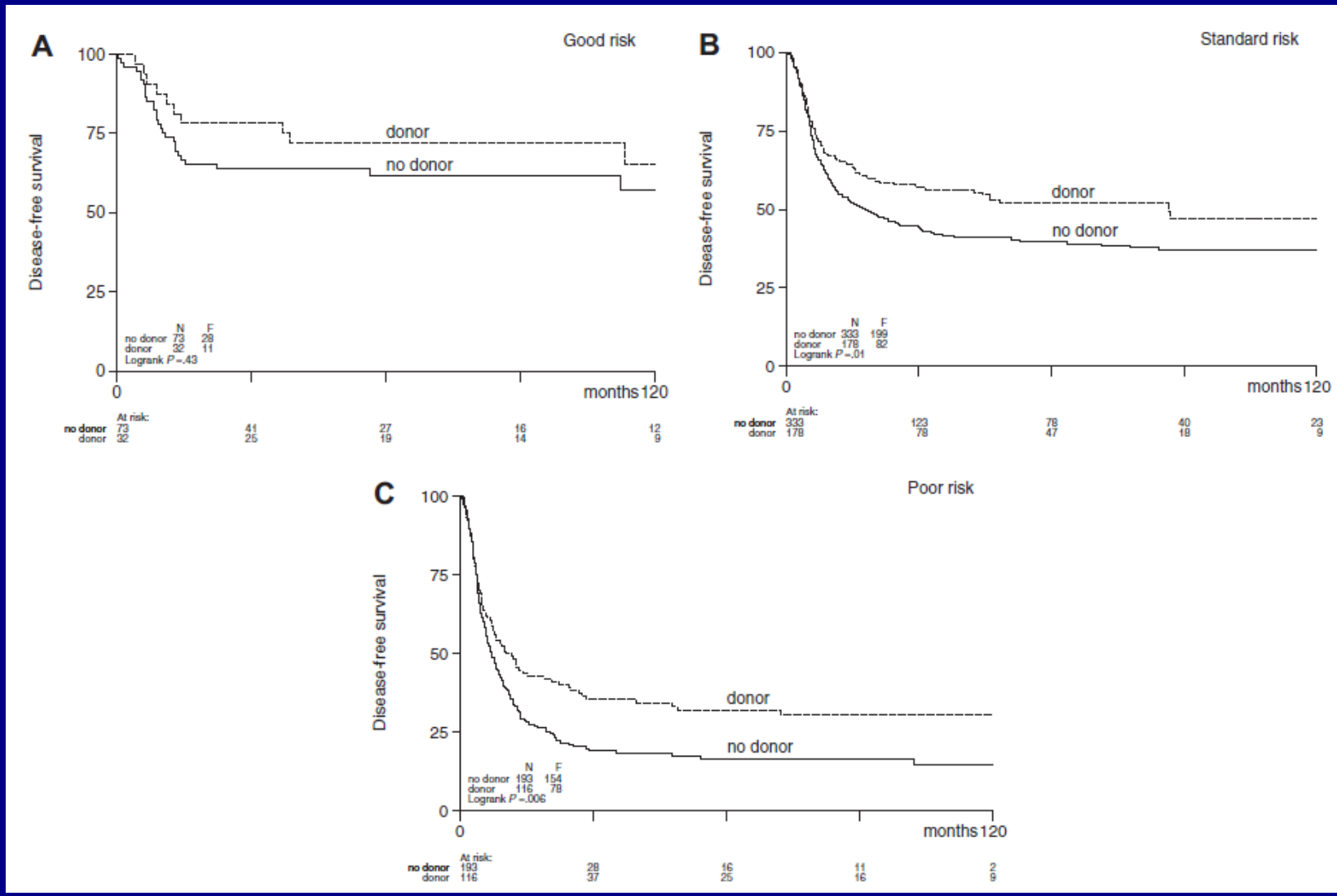


Thomas, NEJM, 301, 597, 1979

AML: Currently effective modalities of RX

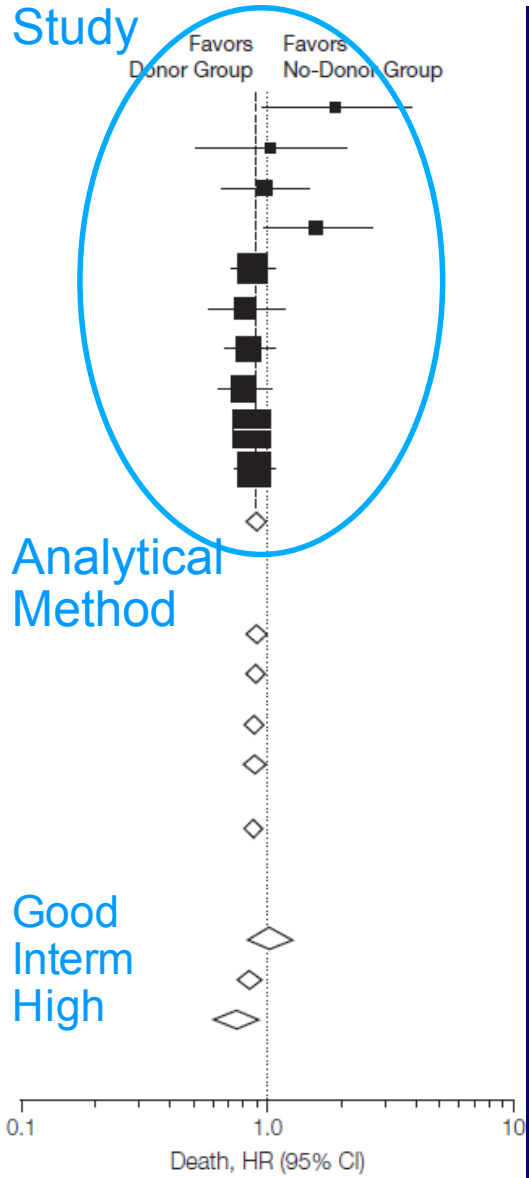
- Cytotoxic chemotherapy
- Chemo +/- radiotherapy + allogeneic donor cells

Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle-aged adults: benefits for whom?



Allogeneic Stem Cell Transplantation for Acute Myeloid Leukemia in First Complete Remission

Systematic Review and Meta-analysis of Prospective Clinical Trials

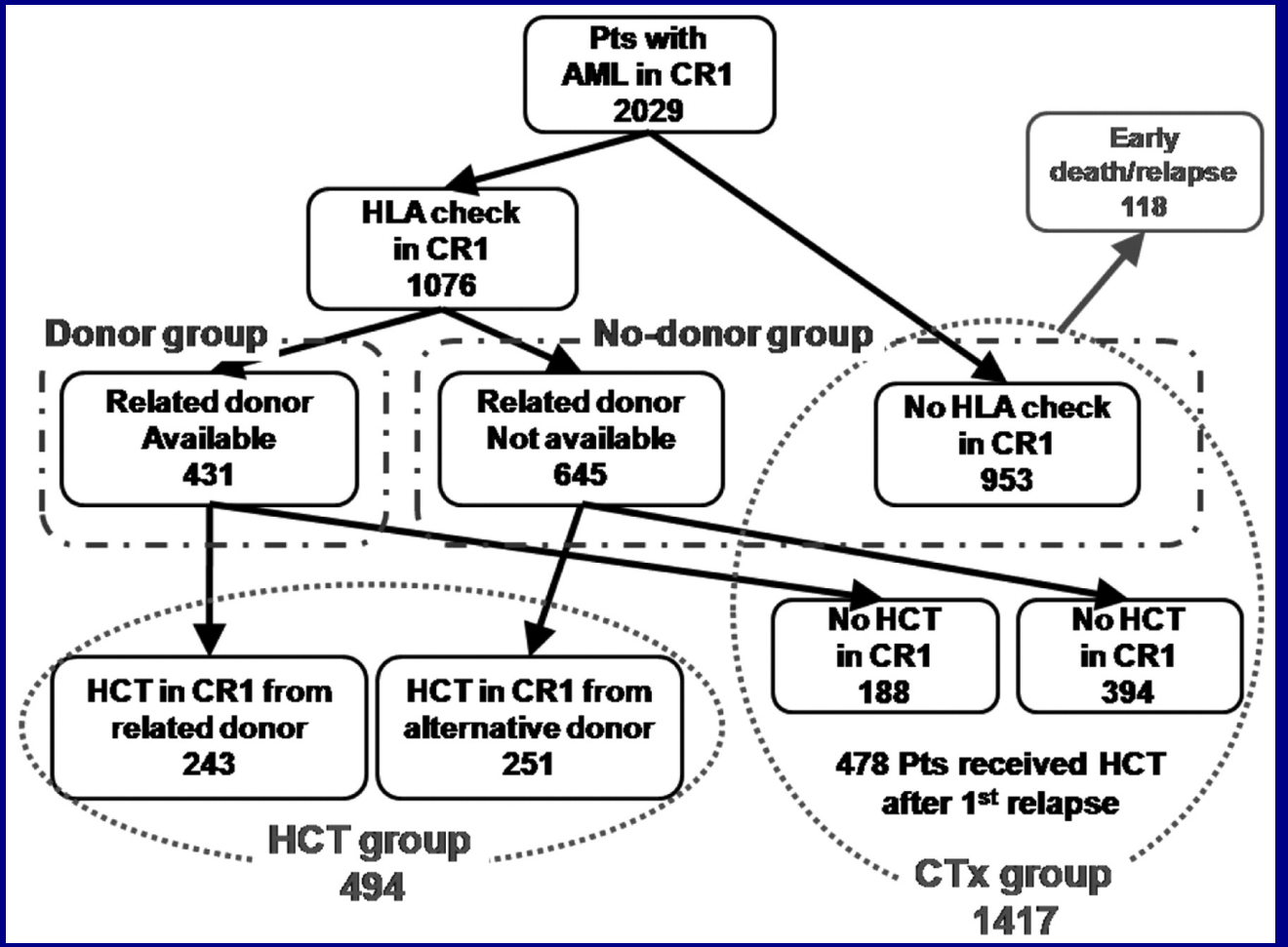


24 prospective trials- over 5,000 patients

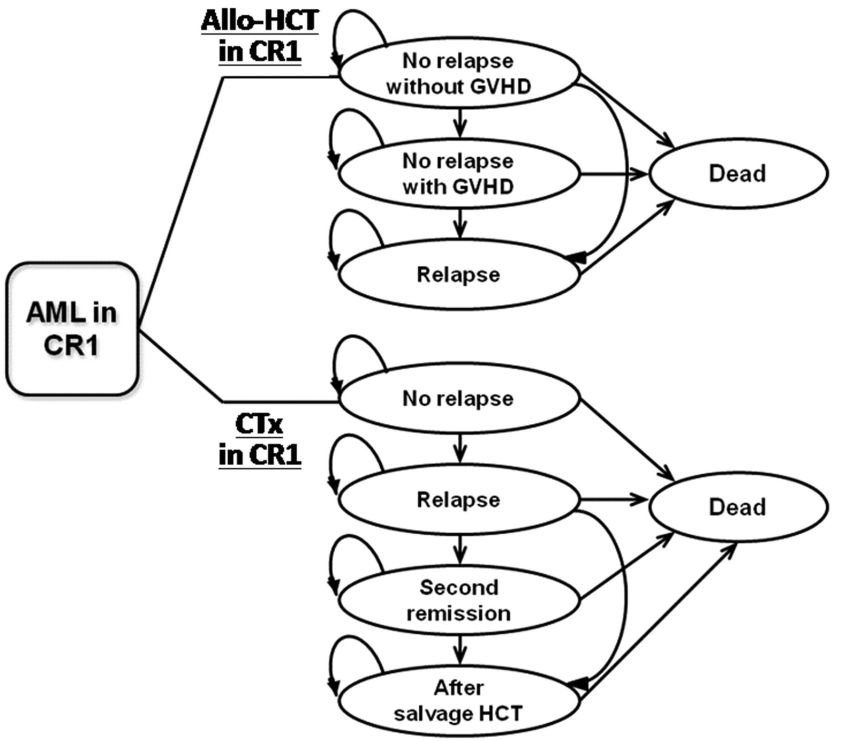
- Allo transplant beneficial in poor and intermediate risk, but not good risk AML
- There are very few situations where allo transplant is inferior!

Koreth J et al, JAMA 301,2349, 2009

A Markov decision analysis of allo SCT vs chemo in AML CR1



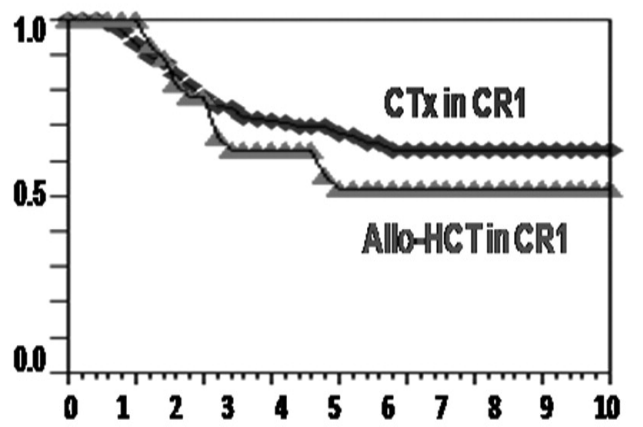
Kurosawa S et al. Blood 2011;117:2113-2120

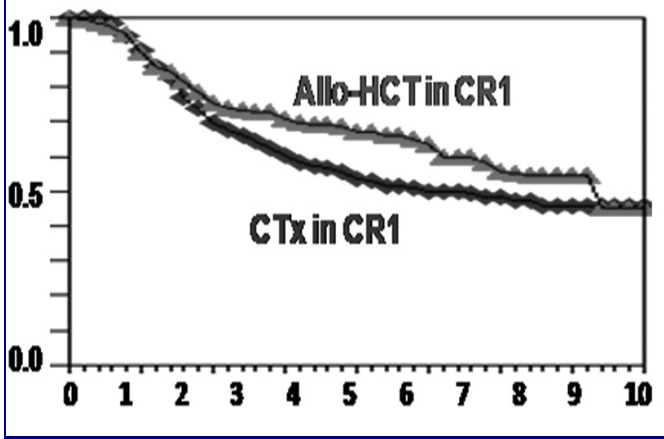


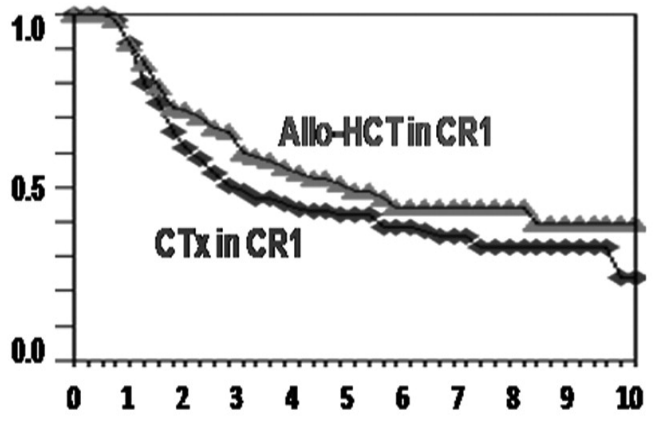
A Markov decision analysis of allo SCT vs chemo in AML CR1

Table 1. Quality-of-life utilities

	Median	Range
Allo-HCT in CR1		
No relapse without GVHD	0.90	0.60-1.00
No relapse with GVHD	0.60	0.40-0.80
Relapse	0.30	0.20-0.70
Chemotherapy in CR1		
No relapse	0.90	0.80-1.00
Relapse	0.50	0.20-0.80
Second remission	0.80	0.40-0.95
After salvage allo-HCT	0.66	0.10-1.00







Favorable | Intermediate | Poor Risk

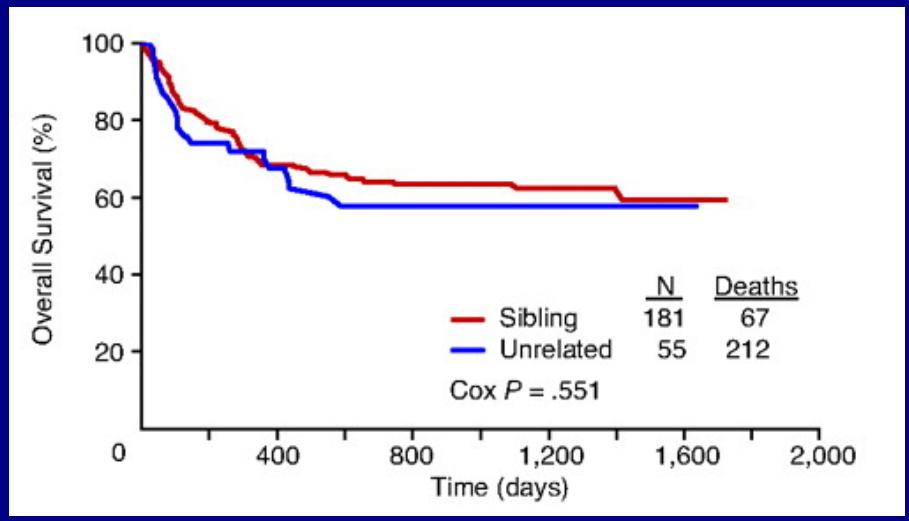
SCT has most impact in younger patients with Poor Risk Leukemia and in older patients

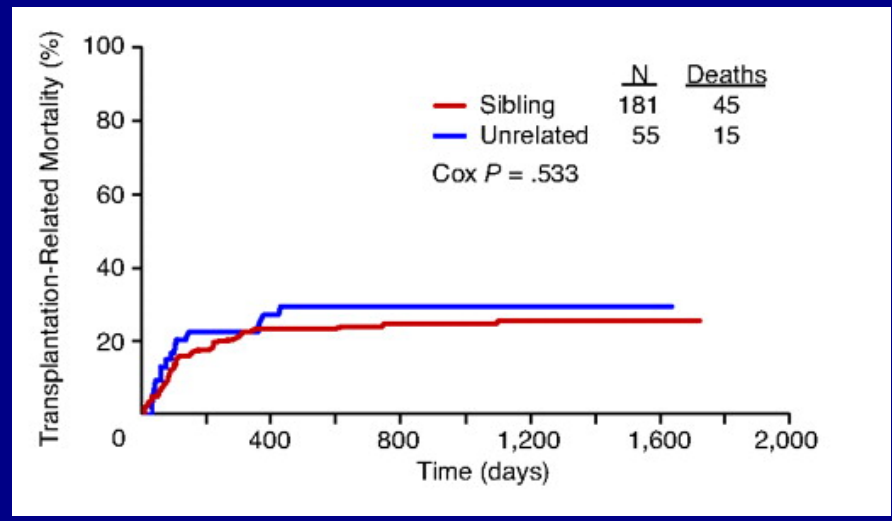
Kurosawa S et al. Blood 2011;117:2113-2120

Why then is transplant not more commonly used?

- Why Not???....
- They don't have a donor....
- They don't think about it...
- They are too old....
- It is too toxic.....

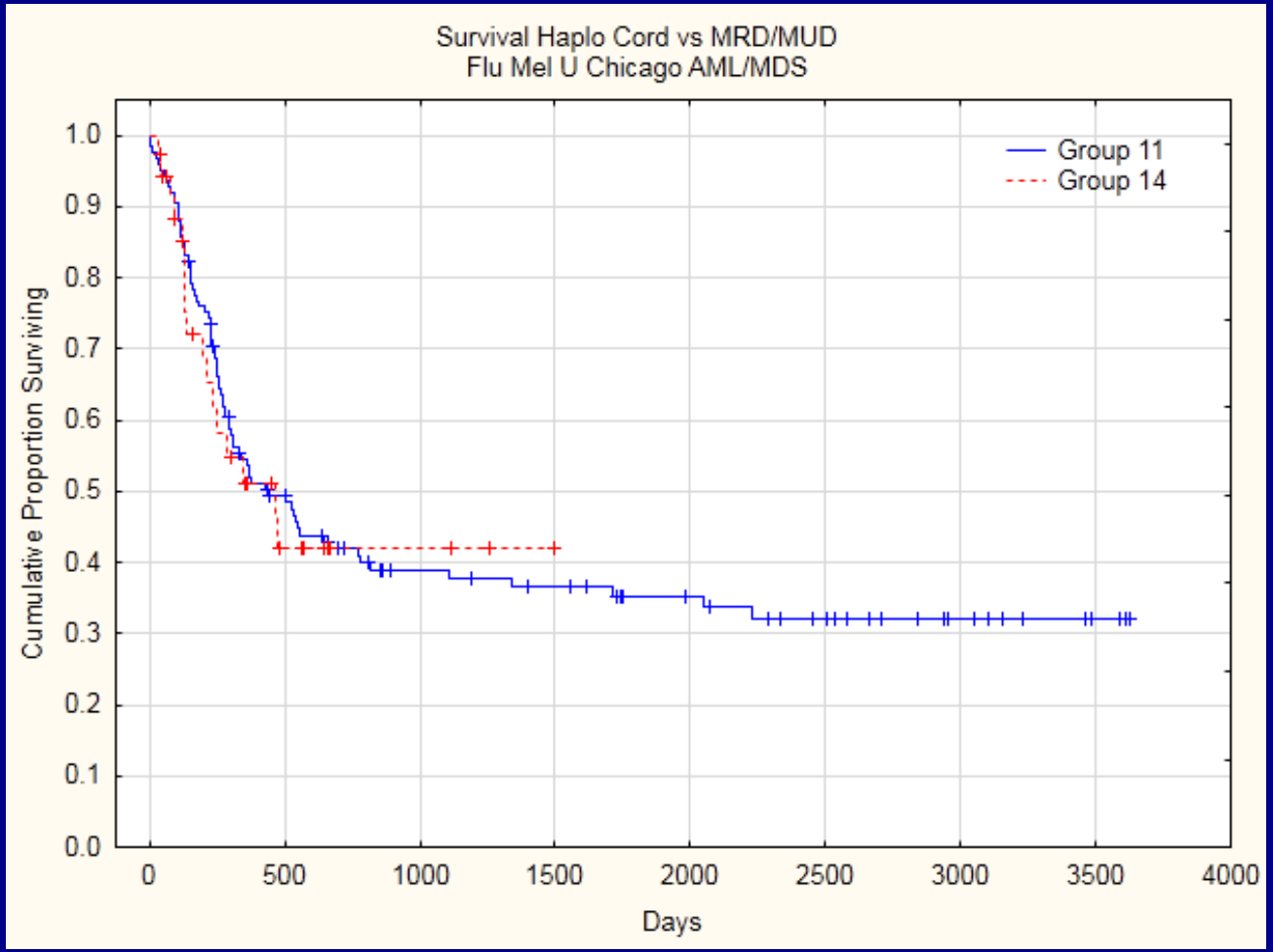
Overall survival and Transplant Related Mortality in AML CR1 undergoing Sibling vs matched Unrelated Donor Transplantation





Yakoub-Agha, I. et al. J Clin Oncol; 24:5695-5702 2006

Survival is similar after Haplo-Cord vs Related/Unrelated donor transplant



Unpublished Data

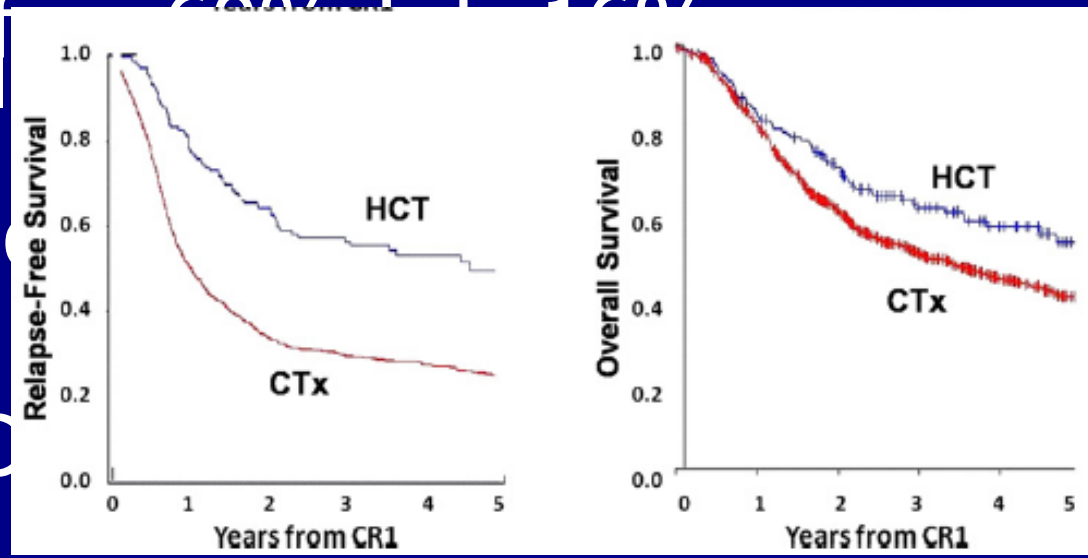
Why then is transplant not more commonly used?

- Why Not???....
- They don't have a donor....
- They don't think about it...
- They are too old....
- It is too toxic....

Comparison of allo tx and chemo as consolidation for elderly non M3 AML in CR1

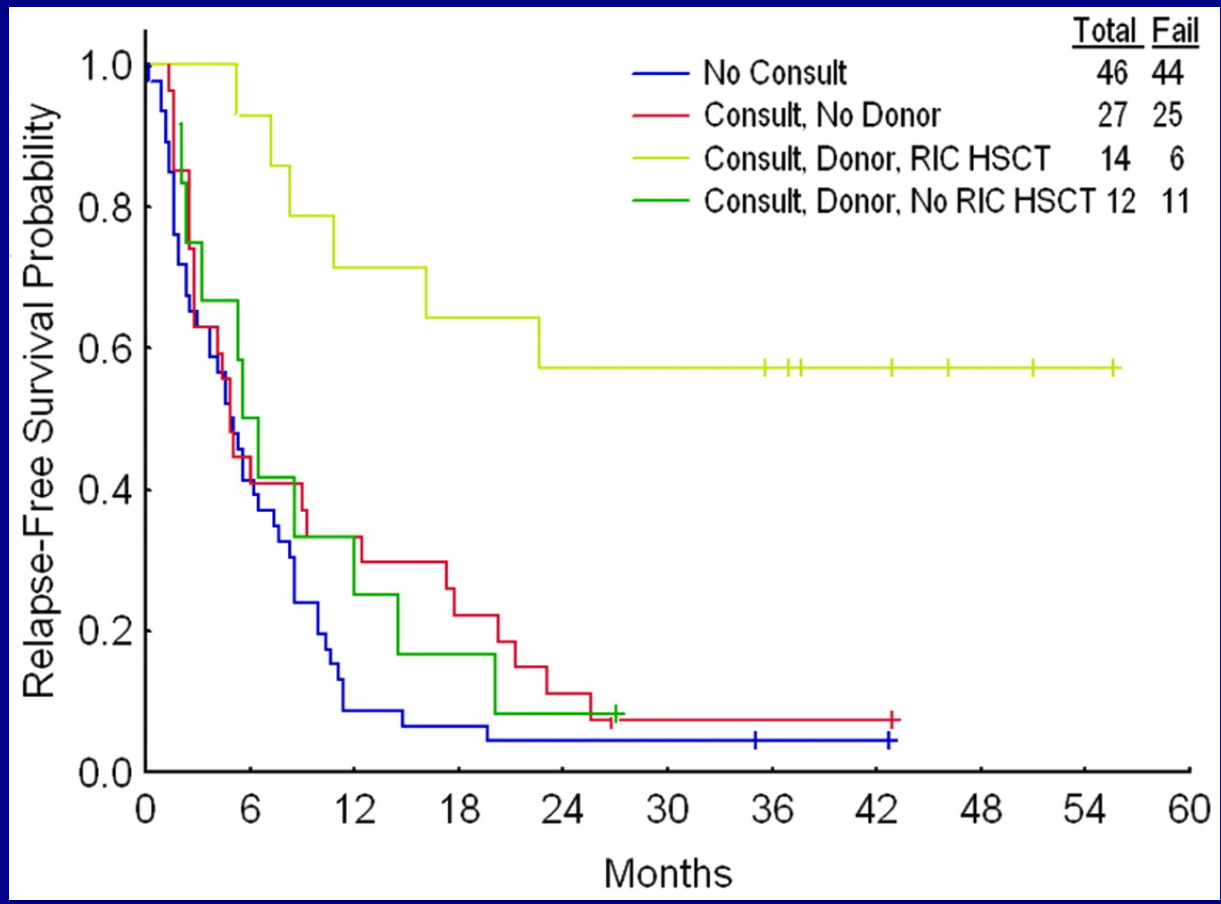
- 1036 AML CR1pts age 50-70 from 67 centers,
- MFU 3.6 yrs
- Karyotype: 16% f[illegible] 16%
- 9%

	3y RFS	3y OS
CTx	31%	53%
HCT	56%	62%
CTX non fav kx		51%
HCT non fav kx		61%



Kurosawa, BBMT 17, 401-411, 2011

Prospective feasibility analysis of RIC in elderly (>50) patients with newly diagnosed AML and MDS and adverse features



Estey E et al. Blood 2007;109:1395-1400

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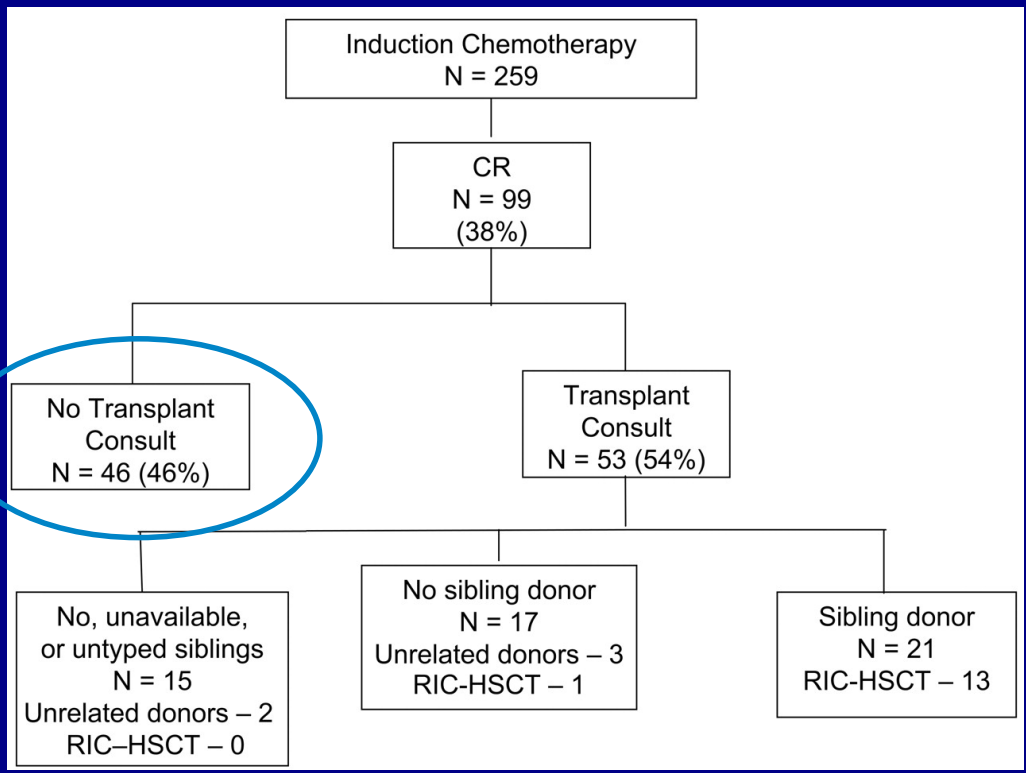


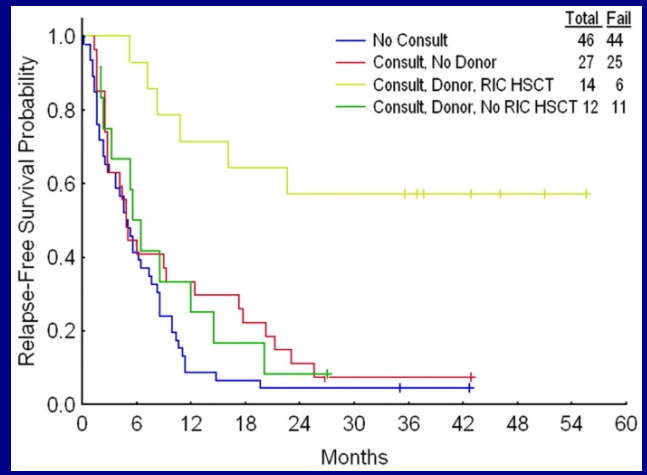
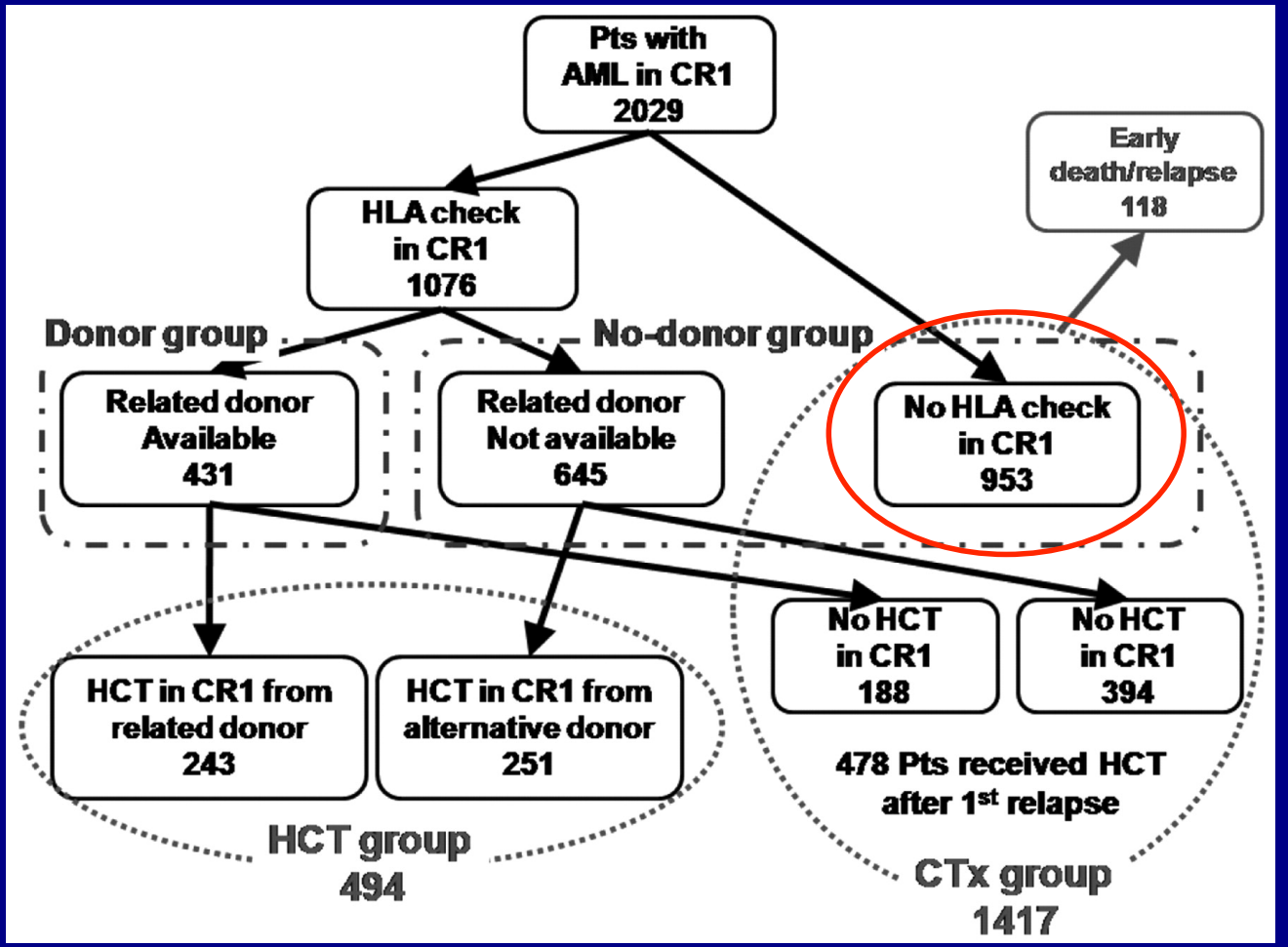


Table 2. Reasons for failure to undergo RIC-HSCT (85 patients)

	No. patients
"Too ill"	15*
Refused	5
No siblings	11
Siblings "too ill" or unavailable for HLA typing	7
Siblings typed without identification of donor†	12
Unclear‡	35

Estey E et al. Blood 2007;109:1395-1400

A Markov decision analysis of allo SCT vs chemo in AML CR1

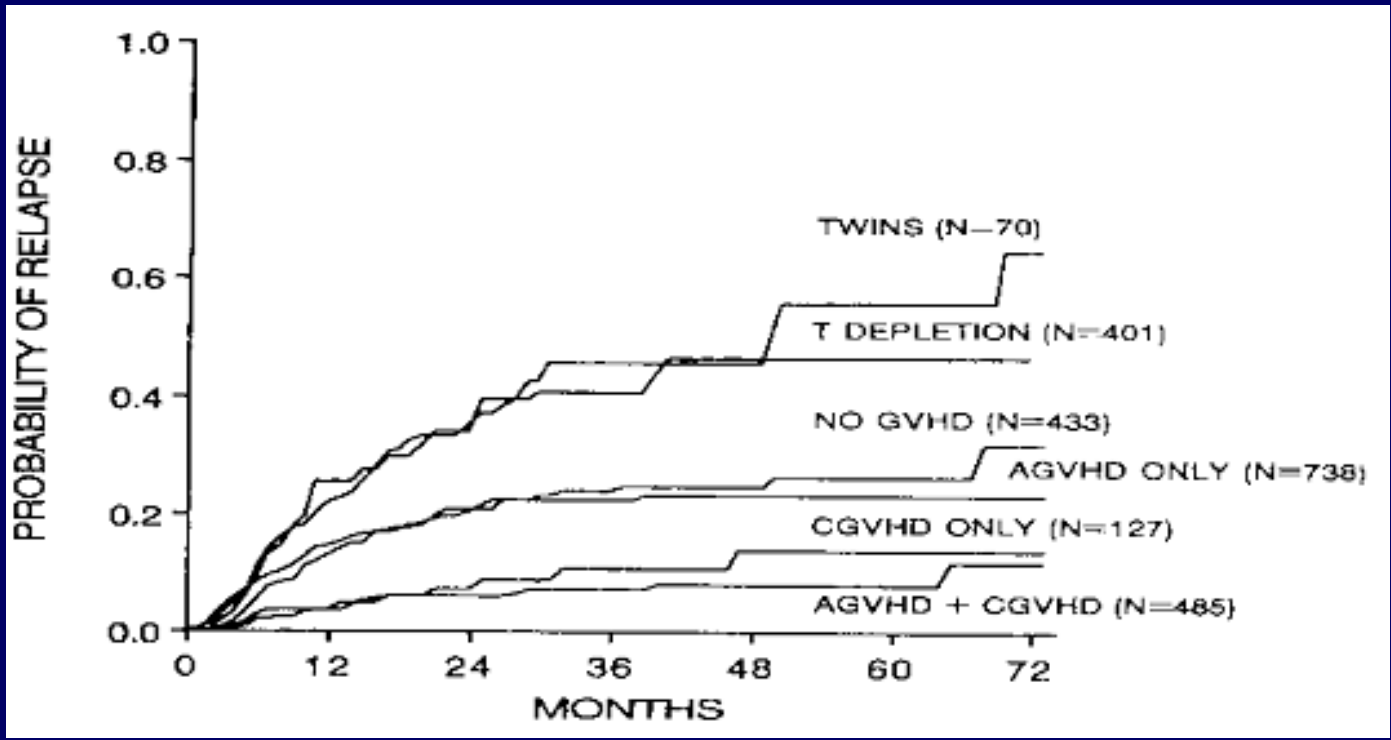


Kurosawa S et al. Blood 2011;117:2113-2120

Overview

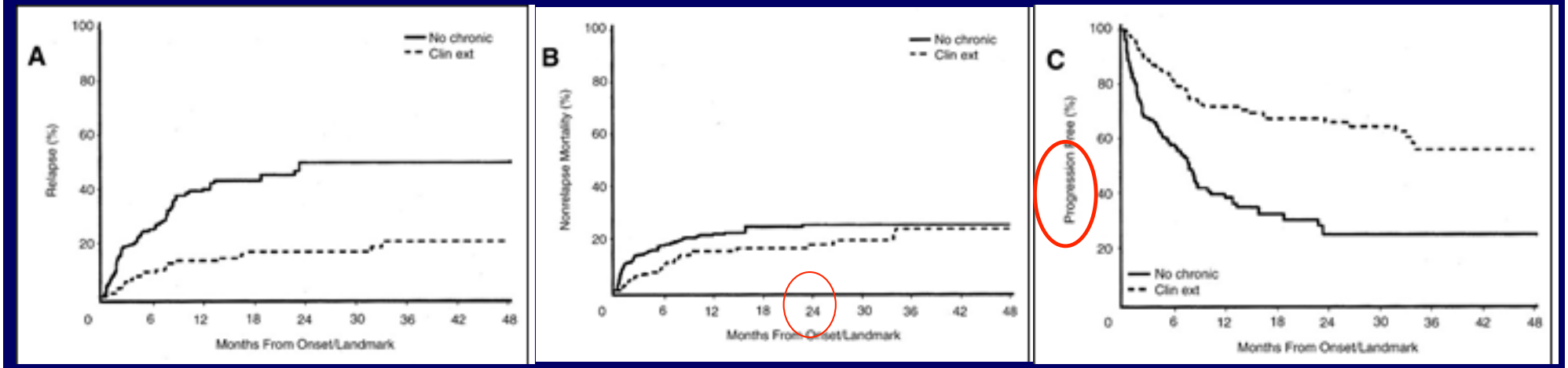
- Why Not???....
  - They don't have a donor....
  - They are too old....
  - It is too toxic.... The issue of chronic GVHD!

Actuarial probability of relapse after allo transplant for good risk leukemia as a function of GVHD



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

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



Median follow up 23 months (3-72)

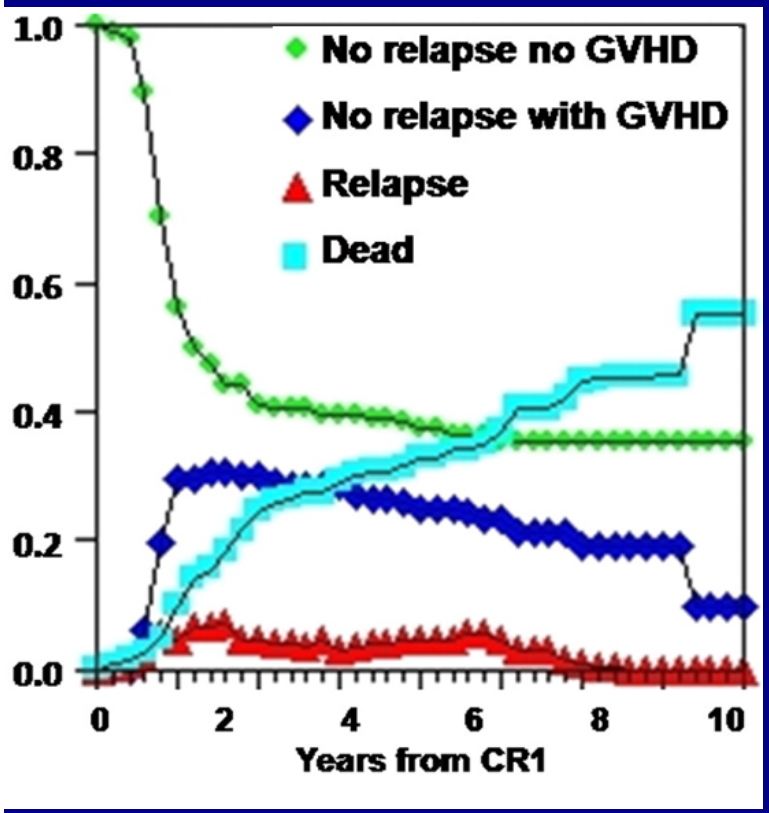
Baron F et al. JCO 2005;23:1993-2003

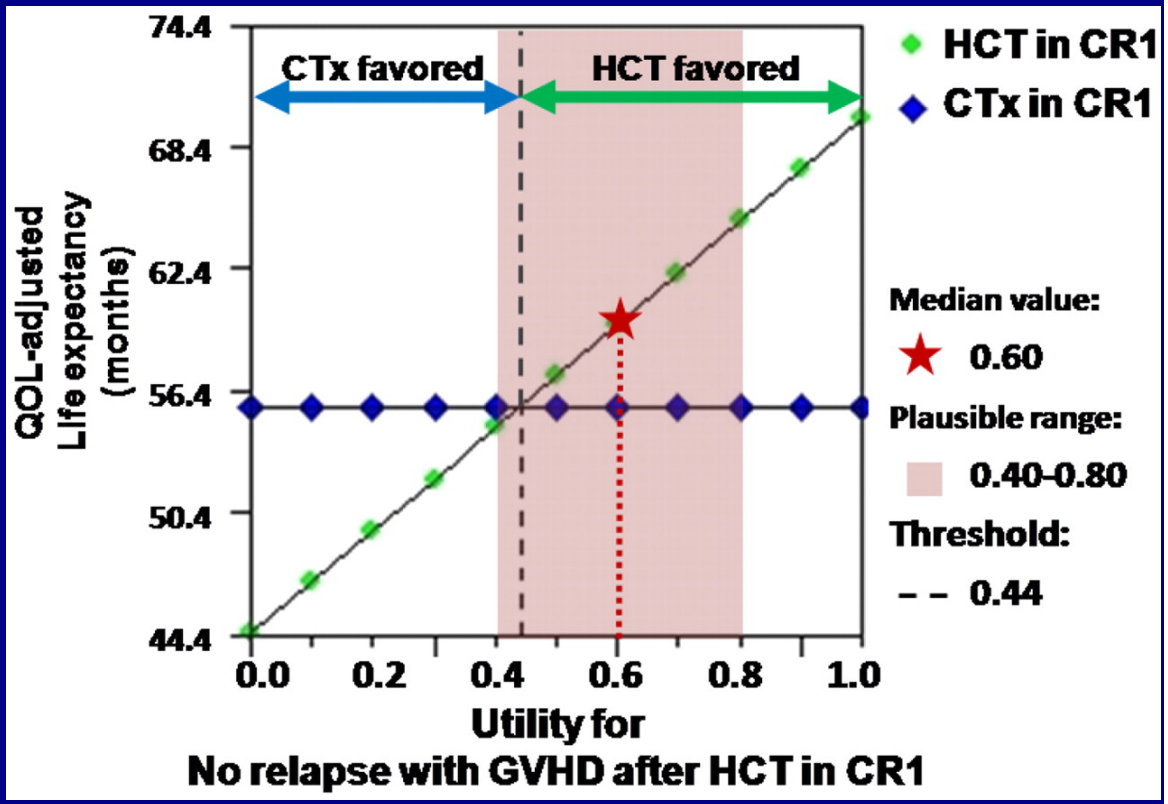
JOURNAL OF CLINICAL ONCOLOGY

Chronic GVHD

- Affects quality of life
- Does not affect relapse rates in AML
- Shortens life

Allo SCT vs chemo in AML CR1: Utility of Transplant Depends on Impact of GVHD





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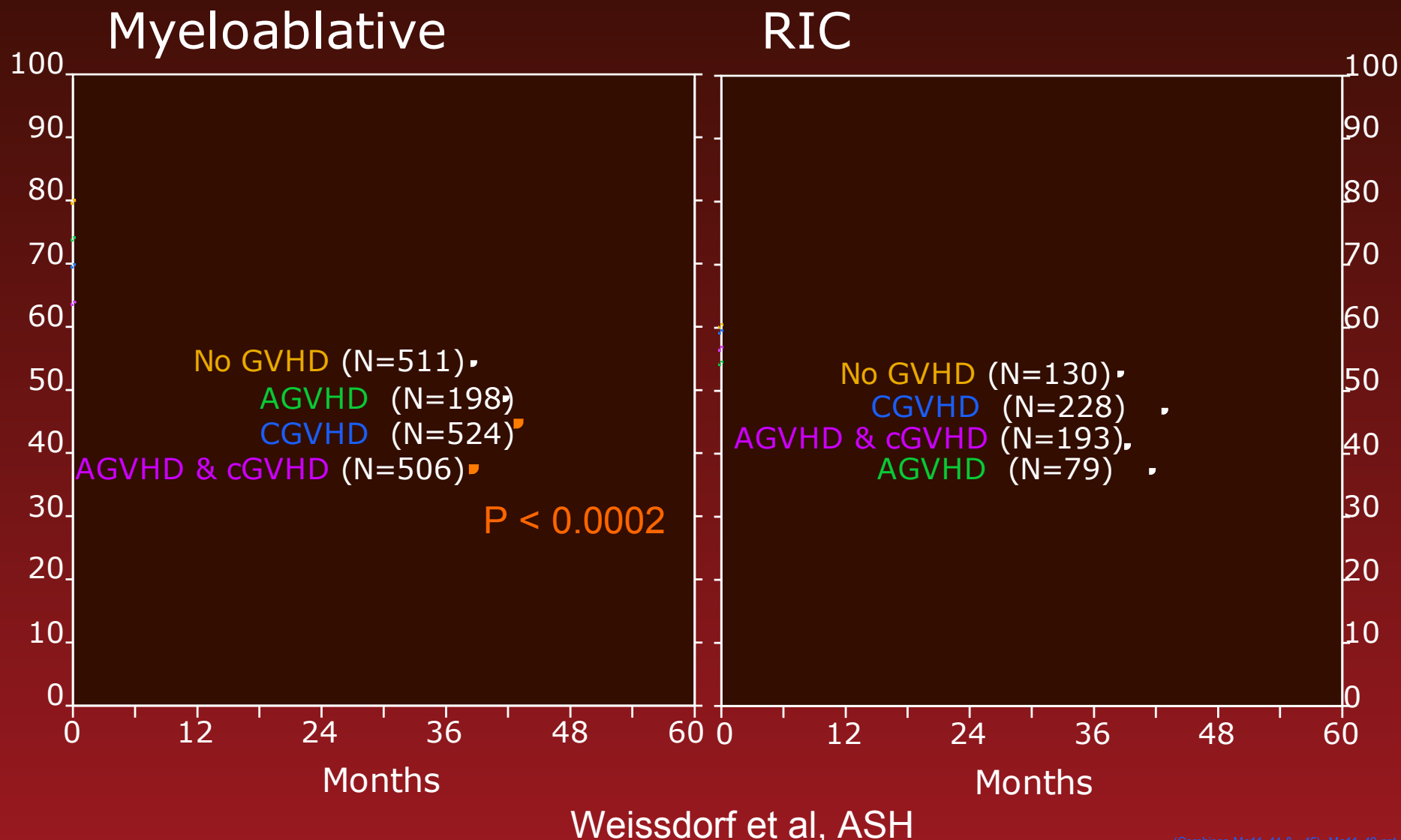
Unfavorable impact of GVHD on DFS



Weissdorf et al, ASH 2011

Flu-Mel (MDACC)

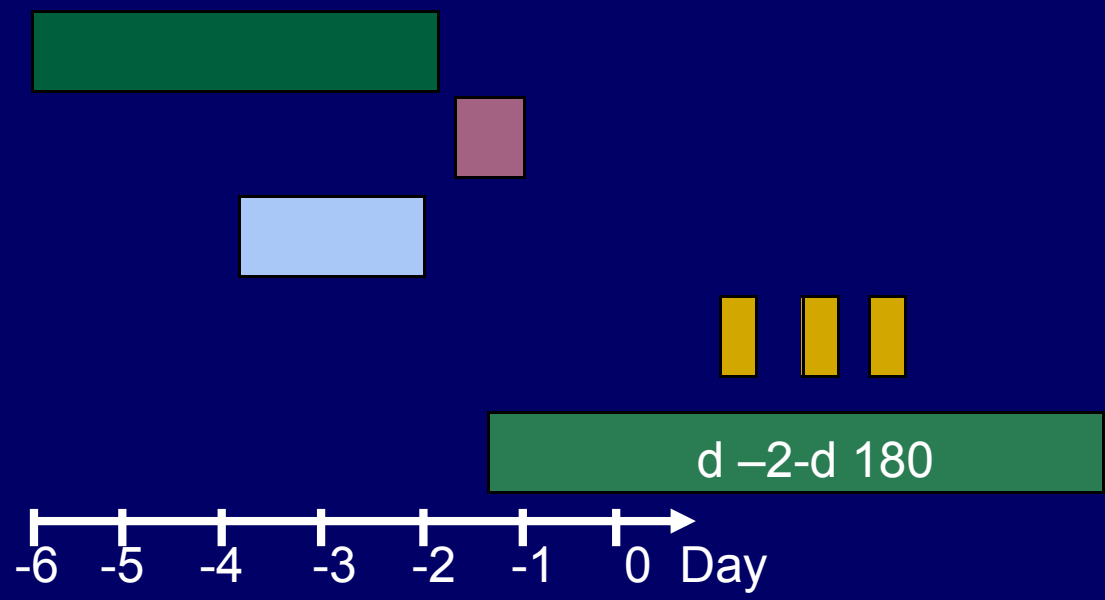
Fludarabine* (30 mg/m2/day)

Melphalan (100-140-180 mg/m2)

ATG (in MUD)

Methotrexate

Tacrolimus



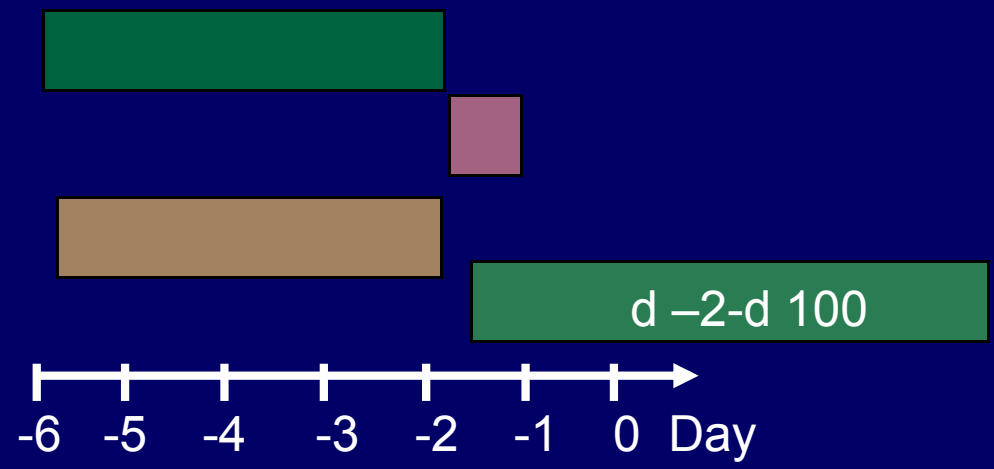
Flu-Mel-Campath (UC)

Fludarabine* (25 mg/m2/day)

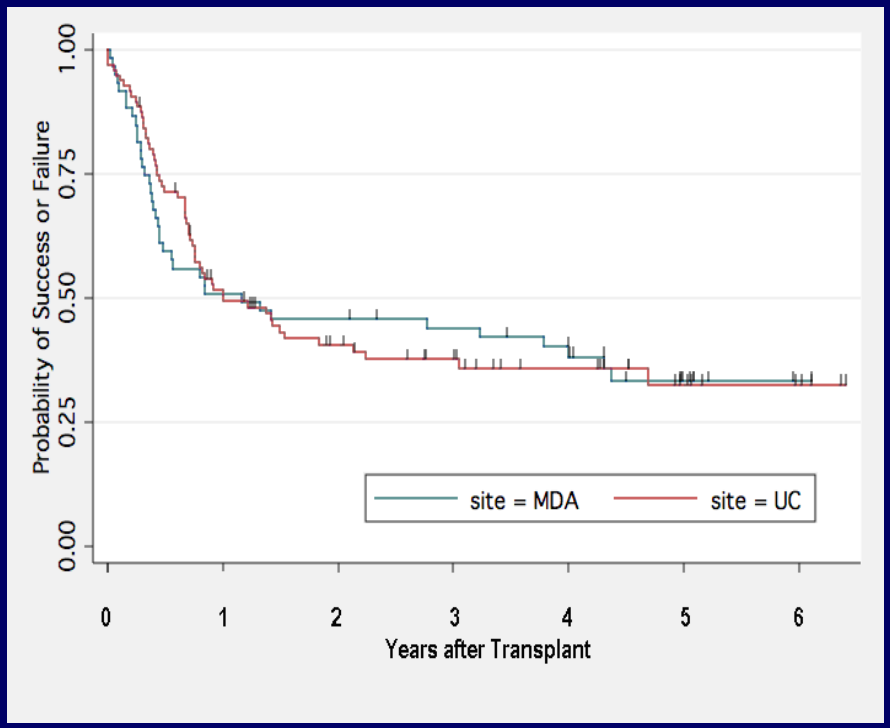
Melphalan (70 mg/m2/day)

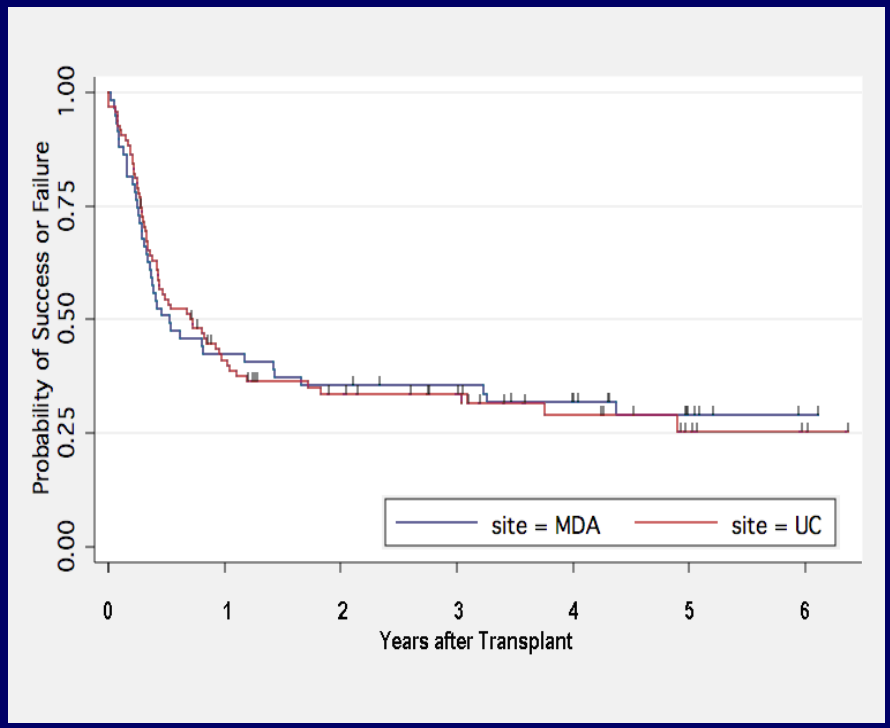
Campath (20 mgday)

Tacrolimus



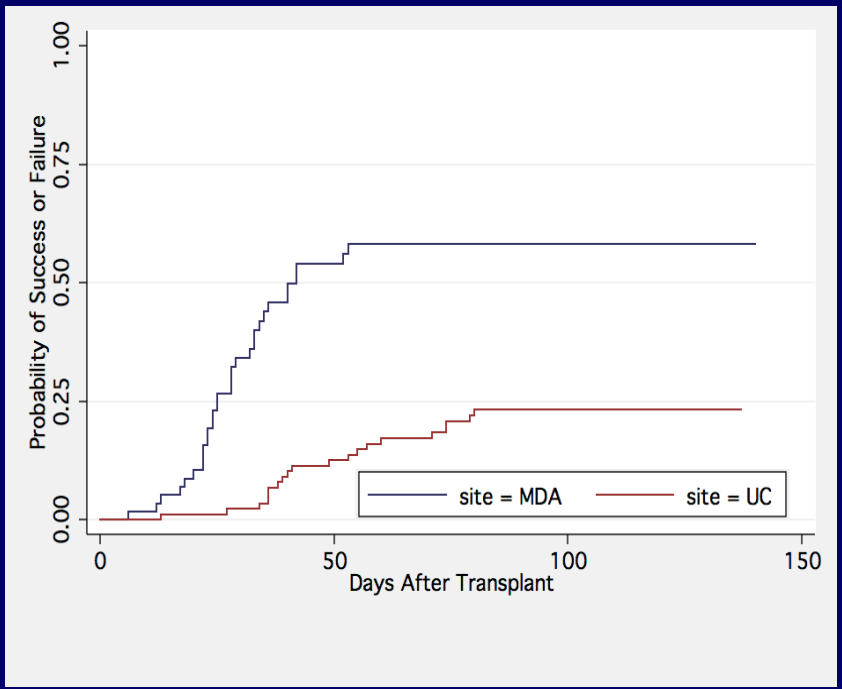
MDACC –UC: Survival - PFS

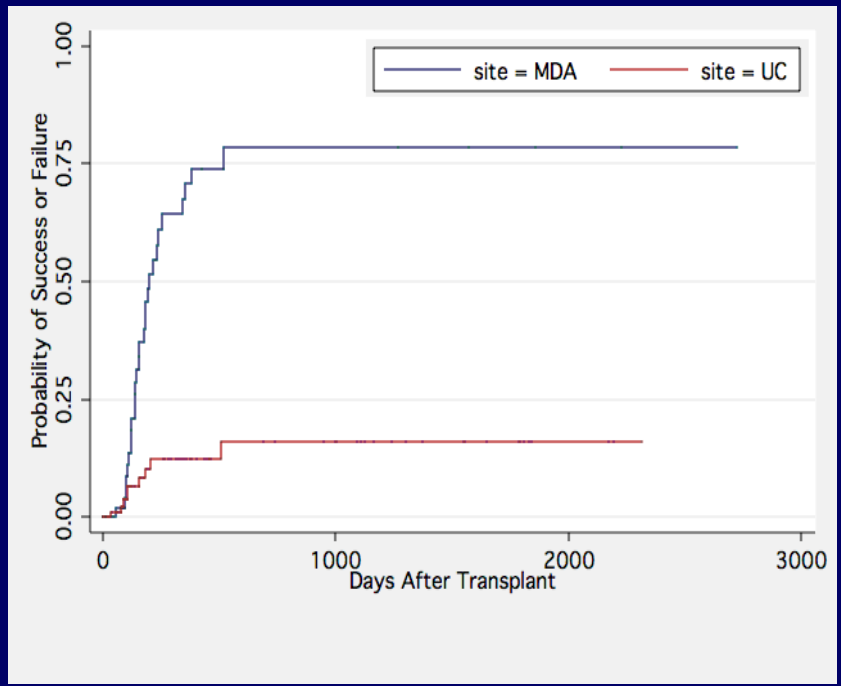




Biol Blood Marrow Transplant.15:610-7, 2009.

MDACC – UC: Acute and Chronic GVHD





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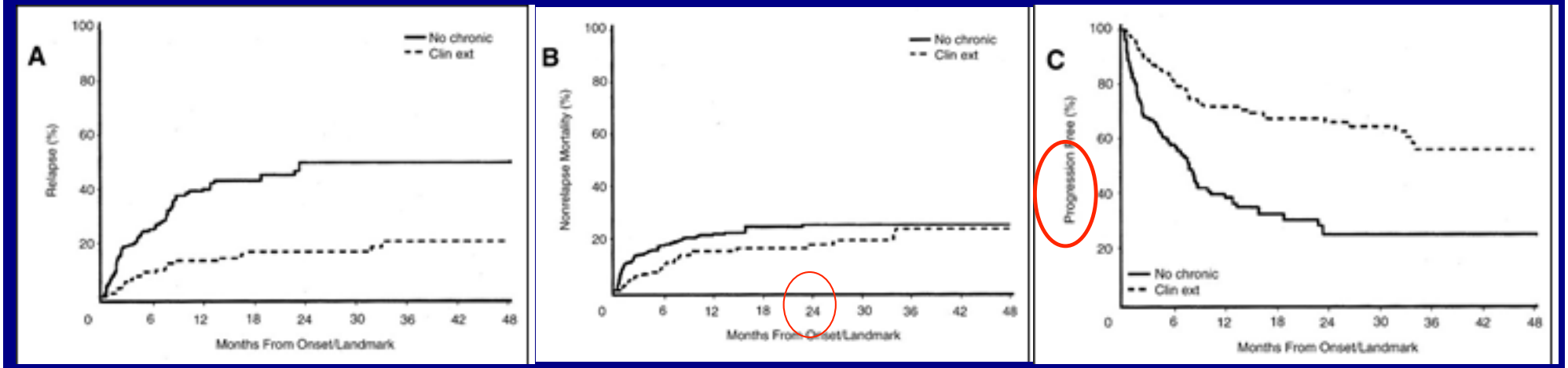

Median follow up 23 months (3-72)

Baron F et al. JCO 2005;23:1993-2003

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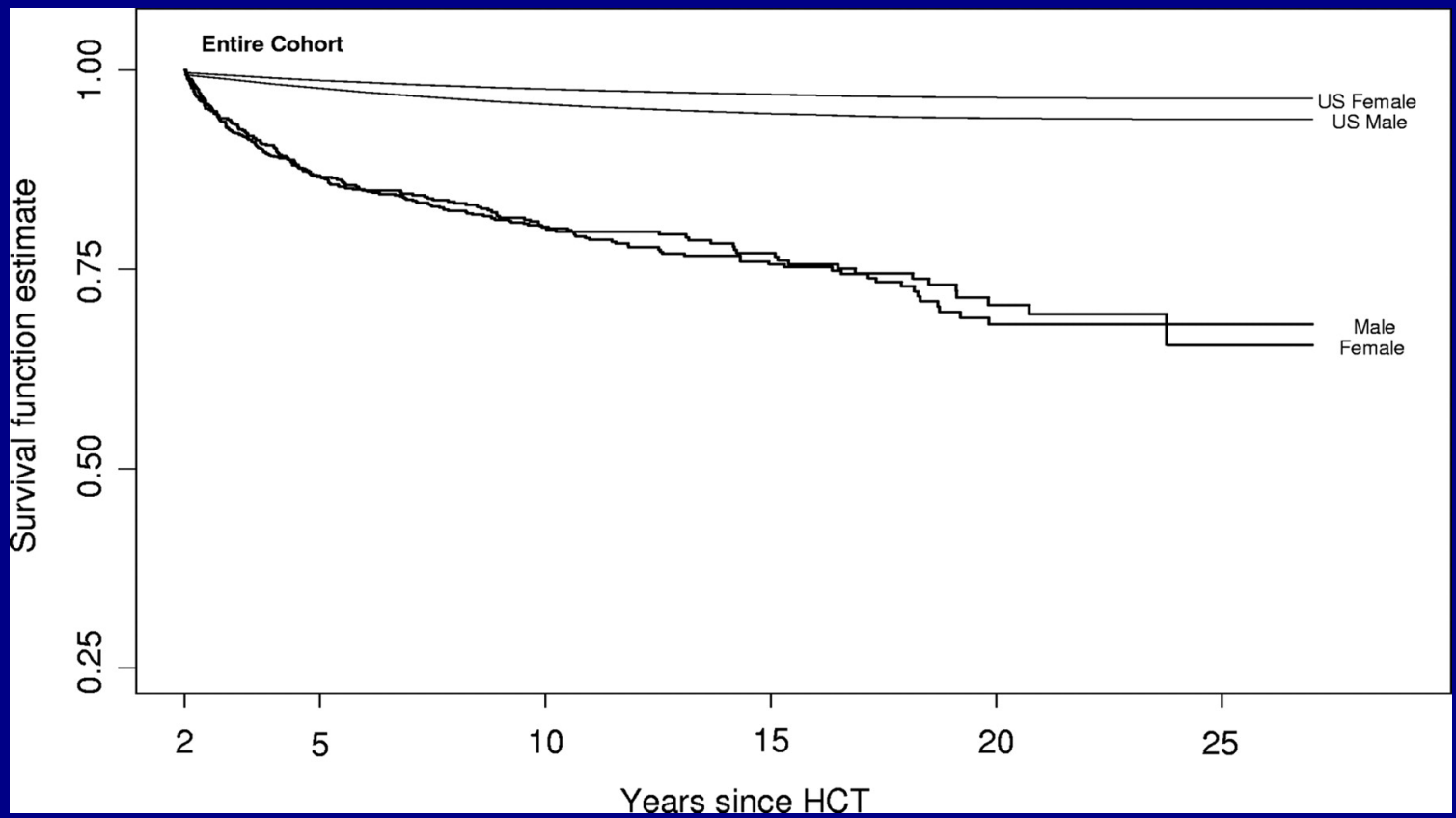
All-cause mortality in 1479 2+-year survivors after allo HCT



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

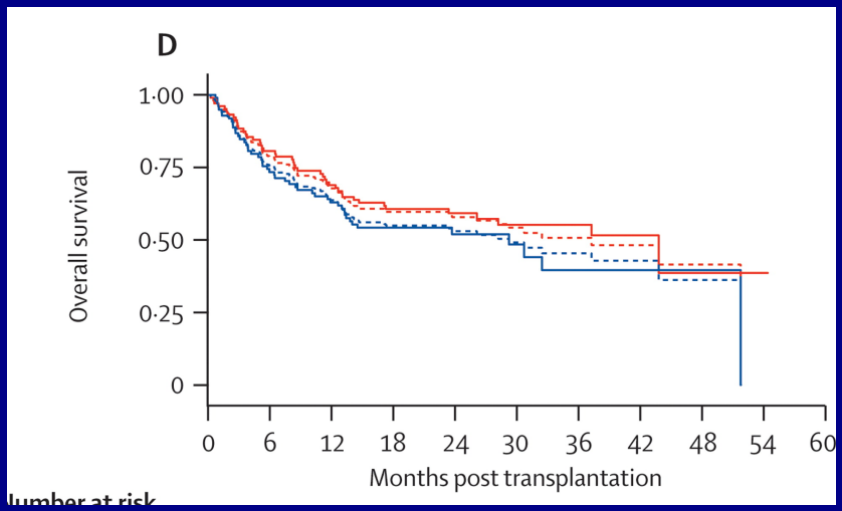
All-cause mortality in 1479 2+-year survivors after allo HCT

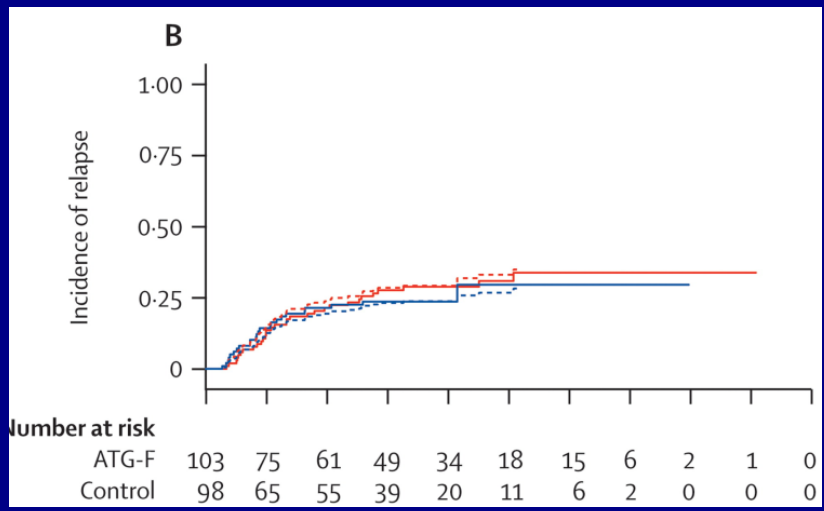
Table 2. Five- and 10-year overall survival by primary diagnosis and cGVHD status in patients surviving disease-free for 2 years after allogeneic HCT

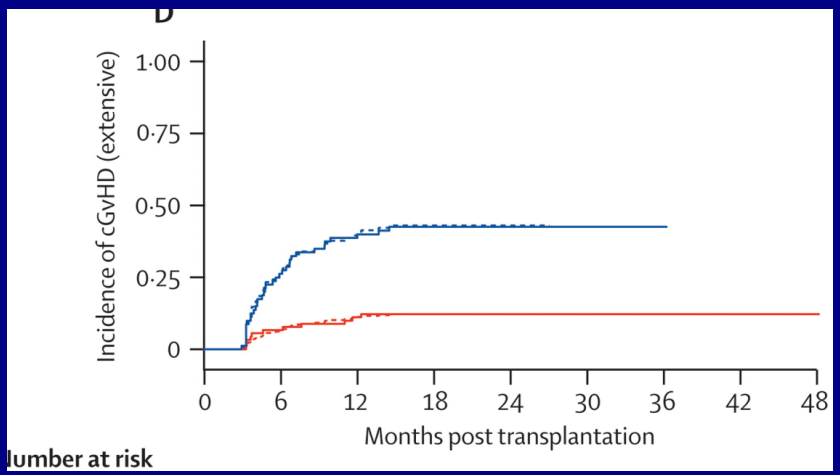
	Overall		Without cGVHD		With cGVHD	
Diagnosis	5-y	10-y	5-y	10-y	5-y	10-y
Entire cohort	90.2 (0.8)	84.6 (1.3)	95.1 (0.9)	91.0 (1.4)	85.5 (1.4)	78.1 (2.1)
Acute myeloid leukemia	89.3 (1.6)	82.8 (2.4)	95.5 (1.5)	92.1 (2.3)	83.0 (2.8)	73.2 (4.2)
Chronic myeloid leukemia	90.4 (1.5)	83.3 (2.5)	94.4 (1.9)	89.5 (3.5)	88.2 (2.1)	79.8 (3.4)
Acute lymphoblastic leukemia	88.5 (2.1)	83.9 (3.0)	93.6 (2.1)	86.7 (3.5)	82.5 (3.9)	81.5 (5.2)
Non-Hodgkin lymphoma	86.7 (5.5)	70.7 (10.6)	92.9 (7.9)	80.0 (14.7)	83.3 (7.3)	64.8 (14.5)
Severe aplastic anemia	95.9 (1.5)	93.8 (2.2)	99.1 (0.9)	99.1 (1.2)	90.7 (3.7)	85.5 (4.9)
Inborn errors of metabolism	89.1 (3.6)	86.4 (5.6)	92.3 (3.5)	90.5 (5.8)	77.8 (9.8)	72.2 (12.7)

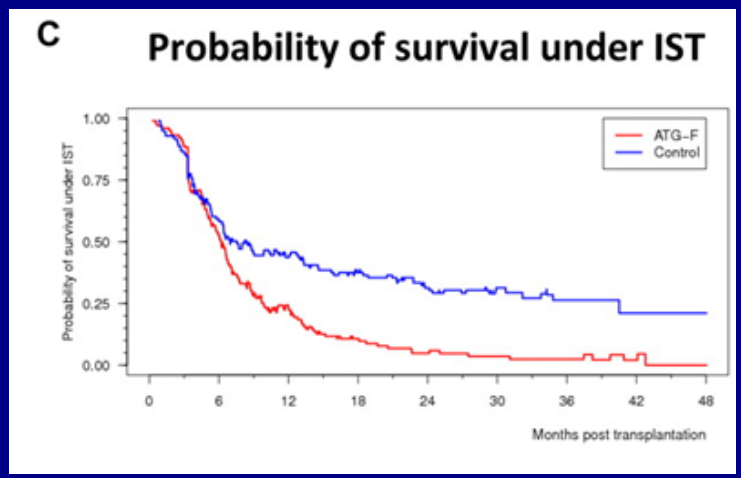
Bhatia S et al. Blood 2007;110:3784-3792

ATG vs no ATG after myeloablative Tx for AML in CR









Finke et al, Lancet Oncology 2009
Socié G et al. Blood 2011;117:6375-6382

Tx vs chemo for AML: Conclusions

- Allo Transplant is superior treatment for:
  - Young patients with intermediate risk disease
  - Older patients!!
- Donor availability is no longer an issue
- The benefits of transplant are diminished considerably by the detrimental long term effects of chronic GVHD.
- In 2012, there are compelling arguments for GVHD prevention by at least moderate T-cell depletion.

Conclusions (2)