Bone Marrow Transplantation in Hematologic Malignancies: Hodgkin's and non Hodgkin's Lymphomas Leukemias and Myeloma

Michele Malagola

Chair of Hematology – University of Brescia
Bone Marrow Transplant Unit – AO Spedali Civili - Brescia

Bone Marrow Transplantation in Acute Leukemia[1]

E. D. Thomas and R. B. Epstein

Department of Medicine, University of Washington School of Medicine, Seattle, Washington

Cancer Res 1965

TABLE 2

Allogenic Marrow Grafts in the Dog

All dogs were given 1500 r and an allogenic marrow infusion. The 2nd group of dogs received methotrexate in the first 10 days after irradiation. The 3rd group of dogs also received methotrexate; in this group donors and recipients were matched for 6 red cell antigens.

Treatment	No. of dogs	No. of "takes"	No. of graft rejections	No. living beyond 150 days
Irradiation: random donor and recipient	10	8	5	1
Irradiation and methotrexate: random donor and recipient	10	10	2	4
Irradiation and methotrexate donor and recipient matched for RBC antigens	10	10	3	5

Summary of Some Published Observations on the Results of Whole-Body Irradiation and Marrow Infusion in Patients with Acute Leukemia

Author	Reference	Type of marrow			Evidence of homologous marrow engraftment	Evidence of secondary syndrome	Remission[a]
		Allogenic	Isogenic	Fetal			
Andrews *et al.*	1	7					2
Arient *et al.*	2	1					
Atkinson *et al.*	3		1				1
Beard *et al.*	6	1					
Clinicopathologic Conference	27	1					
Haurani *et al.*	15	9					1
King	18	1	1				1
Kurnick	19		2				
Mathé *et al.*	20[b]	10			7	7	3
McGovern *et al.*	23	2	2				1
Pegg *et al.*	25	2					
Thomas and Ferrebee	31	15	4	3[c]	1		5
Total		46	10	3	6	5	14

MAIN TOPICS - Radiotherapy and SCTs

Preparative regimen for

Autologous SCT

Allogeneic SCT

1. Myeloablative

2. Non-Myeloablative

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Autologous SCT .....in NHLs

Allogeneic SCT

1. Myeloablative

2. Non-Myeloablative

RT-based *vs* CHT-based conditioning in ASCT for NHLs

Author	Pts	SCs	TBI +C+/-E	CHT	Acute Tox	TRM	Outcome
Philip '87	100	BM=100%	39 (39%)	61 (61%)	=	=	=
Stockerl '96 (Stanford)	221	-	-	-	-	=	> OS (TBI)
Salar' 01 (Spain)	359 (DLBCL) 1983-1999	BM=38% PB=62%	47 (4%)	348 (96%)	> aplasia (TBI)	> in TBI	< OS/DFS (TBI)
Delgado '01 (Seattle)	351 1990-1998	BM=25% PB=75%	221 (63%)	130 (37%)	=	=	=
Liu '09 (Canada)	73 1994-2005	PB=100%	26 (36%)	47 (64%)	=	=	=

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Liu '09 (Canada)	73 1994-2005	PB=100%	26 (36%)	47 (64%)	=	=	=

Long-term OS	30 – 65%
Long-term DFS	30 – 55%
TRM	4 – 16%
Incidence of second malignancies	3 – 20% @ 5 yrs

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Autologous SCT ..... in HLs

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Nademadee '95 (City of Hope)	85 1988-1993	BM=29% PB=26% BM+PB=45%	22 (26%)	63 (74%)	=	=	=
Horning '97 (Stanford)	119 1987-1995	PB=37% BM+/-PB=63%	26 (22%)	93 (78%)	=	=	=
Subira '00 (Spain)	56 1987-1997	BM=71% PB=29%	11 (20%)	45 (80%)	=	>in TBI	<< in TBI
Delgado '03 (Seattle)	92 1990-1998	BM=42% PB=58%	42 (46%)	50 (54%)	=	=	=

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Long-term OS	50 – 80%
Long-term DFS	20 – 60%
TRM	5 – 36%
Incidence of second malignancies	<5% @ 5 yrs

RT-based conditioning in Allo-SCT

- Destroy residual neoplastic cells
- Clear the host marrow to allow repopulation with donor marrow cells
- Provide immunosuppression to avoid allograft rejection

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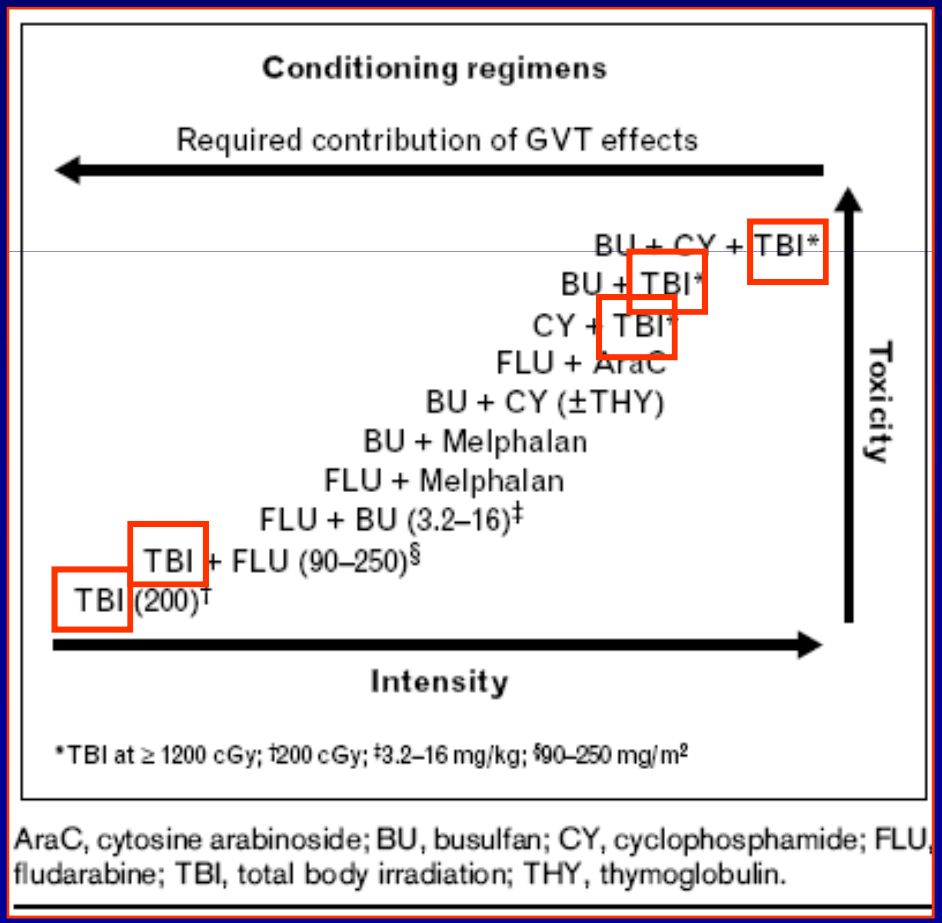

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   - TBI 1200 cGy
2. Non-Myeloablative
   - TBI 200 cGY

ACUTE MYELOID LEUKEMIA

TBI + CTX

1977 100 **refractory/relapsed pts** treated with TBI (12 Gy) + CTX (120)

Long term DFS @ 13 yrs: 11%

Thomas ED, Blood 1977 - Seattle

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1979 19 pts in **1° CR** treated with TBI (12 Gy) + CTX (120)

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1990 72 pts in **1° CR** treated with TBI (15.75 Gy *vs* 12 Gy) + CTX (120)

	12 Gy	15.75 Gy	P
TRM @ 3yrs	12%	32%	0.04
RR @ 3 yrs	35%	12%	0.06
aGVHD (III-IV)	21%	48%	0.02

Clift et al, Blood 1990 - Seattle

ACUTE MYELOID LEUKEMIA

Bus+ CTX

1983 51 AML pts all phases (35% 1° CR) → Bus 16 mg/Kg + CTX 200 mg/Kg

OS @ 2 yrs: 44% (1° CR)

Santos GW et al, NEJM 1983 – Johns Hopkins

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1989 99AML pts all phases (50% 1° CR) → Bus 16 mg/Kg + CTX 200 mg/Kg

Overall TRM:	62%
DFS @ 3 yrs:	38%
OS @ 3 yrs:	40%

Geller et al, Blood 1989 – Johns Hopkins

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Overall TRM: 62%
DFS @ 3 yrs: 38%
OS @ 3 yrs: 40%

Geller et al, Blood 1989 – Johns Hopkins

1987 50 pts with leukemias (58% ALs) → Bus 16 mg/Kg + CTX 120 mg/Kg
RFS @ 3 yrs: 65%
OS @ 3 yrs: 65%

Tutschka P et al, Blood 1987 - Columbus

ACUTE LEUKEMIAS – published trials

TBI/Cy *vs* Bus/Cy

Author	Pts	TRM		aGVHD (≥ 2)		cGVHD		DFS		OS	
		TBI	CHT	TBI	CHT	TBI	CHT	TBI	CHT	TBI	CHT
Blaise '92 (France)*	101 AML Random	8%	27%	=	=	=	=	72%	47%	75%	51%
Ringden '94 (Sweden)*	107 ALs Random	9%	28%	4%	15%	35%	45%	=	=	76%	62%
Ringden '96 (Sweden)	782 ALs Retrospective	=	=	=	=	=	=	=	=	=	=
Granados '00 (Spain)	156 ALL Retrospective	=	=	=	=	=	=	43%	22%	-	-
Sociè '01 (France) *Long term f up**	172 AML Random	=	=	=	=	=	=	=	=	=	=
Litzow '02 (USA)	581 AML Retrospective	=	=	=	=	=	=	=	=	=	=

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		TBI	CHT	TBI	CHT	TBI	CHT	TBI	CHT	TBI	CHT
Blaise '92 (France)*	101 AML Random	**8%**	27%	=	=	=	=	**72%**	47%	**75%**	51%
Ringden '94 (Sweden)*	107 ALs Random	**9%**	28%	**4%**	15%	**35%**	45%	=	=	**76%**	62%
Ringden '96 (Sweden)	782 ALs Retrospective	=	=	=	=	=	=	=	=	=	=
Granados '00 (Spain)	156 ALL Retrospective	=	=	=	=	=	=	**43%**	22%	-	-
Sociè '01 (France) *Long term f up**	172 AML Random	=	=	=	=	=	=	=	=	=	=
Litzow '02 (USA)	581 AML Retrospective	=	=	=	=	=	=	=	=	=	=

ACUTE LEUKEMIAS – Toxicity

TBI/Cy *vs* Bus/Cy

Author	VOD		IP		Cysitits		Cataracts		Permanent Alopecia	
	TBI	CHT	TBI	CHT	TBI	CHT	TBI	CHT	TBI	CHT
Blaise '92 (France)*	=	=	=	=	NE	NE	NE	NE	NE	NE
Ringden '94 (Sweden)*	1%	12%	=	=	8%	24%	31%	10%	11%	38%
Rindgen '96 (Sweden)	3%	7%	12.5%	6%	2%	7%	NE	NE	NE	NE
Granados '00 (Spain)	=	=	=	=	=	=	NE	NE	NE	NE
Sociè '01 (France) *Long term f up**	=	=	=	=	=	=	=	=	Low	High
Litzow '02 (USA)	6%	13%	=	=	NE	NE	NE	NE	NE	NE

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	TBI	CHT	TBI	CHT	TBI	CHT	TBI	CHT	TBI	CHT
Blaise '92 (France)*	=	=	=	=	NE	NE	NE	NE	NE	NE
Ringden '94 (Sweden)*	**1%**	12%	=	=	**8%**	24%	**31%**	10%	**11%**	38%
Rindgen '96 (Sweden)	**3%**	7%	**12.5%**	6%	**2%**	7%	NE	NE	NE	NE
Granados '00 (Spain)	=	=	=	=	=	=	NE	NE	NE	NE
Sociè '01 (France) *Long term f up**	=	=	=	=	=	=	=	=	**Low**	High
Litzow '02 (USA)	**6%**	13%	=	=	NE	NE	NE	NE	NE	NE

CHRONIC MYELOID LEUKEMIA

TBI/Cy *vs* Bus/Cy

Author	Pts	TRM		aGVHD (≥ 2)		cGVHD		DFS		OS	
		TBI	CHT	TBI	CHT	TBI	CHT	TBI	CHT	TBI	CHT
Clift '94 (F Hutc)*	142 Random	=	=	48%	35%	=	=	=	=	=	=
Ringden '94 (Sweden)*	57 Random	=	=	=	=	=	=	=	=	=	=
Devergie '95 (France)*	120 Random	=	=	=	=	=	=	=	=	=	=
Kroger '01 (German)	50 (MUD) Random	=	=	=	=	30%	65%	=	=	=	=
Sociè '01 (France) *Long term f up* *	324 Random	=	=	=	=	=	=	=	=	=	=

CHRONIC MYELOID LEUKEMIA

TBI/Cy *vs* Bus/Cy

Author	Pts	TRM		aGVHD (≥ 2)		cGVHD		DFS		OS	
		TBI	CHT	TBI	CHT	TBI	CHT	TBI	CHT	TBI	CHT
Clift '94 (F Hutc)*	142 Random	=	=	**48%**	35%	=	=	=	=	=	=
Ringden '94 (Sweden)*	57 Random	=	=	=	=	=	=	=	=	=	=
Devergie '95 (France)*	120 Random	=	=	=	=	=	=	=	=	=	=
Kroger '01 (German)	50 (MUD) Random	=	=	=	=	**30%**	65%	=	=	=	=
Sociè '01 (France) *Long term f up* *	324 Random	=	=	=	=	=	=	=	=	=	=

CHRONIC MYELOID LEUKEMIA

TBI/Cy *vs* Bus/Cy

WARNINGS

TBI

- Higher renal toxicity
- Higher number of
  1. days of fever
  2. hospitalization
  3. positive blood cultures

Clift et al, Blood 1994

- Higher RR

Devergie et al, Blood 1995

- Longer neutropenia

Kroger et al, BMT 2001

- Higher cataracts
- Higher avascular osteonecrosis

Sociè et al, Blood 2001

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TBI/Cy *vs* Bus/Cy

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Kroger et al, BMT 2001

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Sociè et al, Blood 2001

CHT

- Higher hepatic toxicity
- More hemorrhagic cystitis
- More mucositis

Kroger et al, BMT 2001
Ringden O et al, Blood 1994

- More VOD

Ringden O et al, Blood 1994

- Trend to higher graft failure

Devergie et al, Blood 1995

TBI plus CTX versus BUS plus CTX as conditioning regimen for pts with leukemia undergoing allo-SCT: a meta analysis

Shi-Xia et al, Leuk & Lymph 2010

18 trials (1990 / 2009)
3172 pts

TBI in AML / ALL

- Lower rates of leukemia relapse
- Lower TRM
- Higher DFS

TBI in CML

- Higher rate of leukemia relapse
- Lower TRM
- Similar DFS

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- Lower TRM
- Similar DFS

✓ NO differences in terms of aGHVD and cGVHD

✓ **TBI**
1. Higher cataracts
2. Higher IP
3. Higher growth problems

✓ **BUS**
1. Higher VOD
2. Higher hemorrhagic cystitis

MAIN TOPICS - Radiotherapy and SCTs

Preparative regimen for

Autologous SCT

Allogeneic SCT

1. Myeloablative
   - TBI 1200 cGy
2. Non-Myeloablative

HAEMATOLOGICAL MALIGNANCIES

TBI 200 cGy

Author	Pts	Other drugs	Durable donor chim	TRM @ day 100	aGVHD ≥ II	cGVHD	Long term outcome
McSweeney '01	45	-	80%	6 %	47%	74%	OS: 70% (1 yr)
Maris '03	89	Fluda	85%	11%	52%	37%	OS: 52% (1 yr)
Mielcarek '03	44	Fluda	89%	-	64%	73%	OS: 68% (1 yr)
Maloney '03	54 MM	-	100%	2%	38%	46%	OS: 78% (2 yrs)
Niederwieser '03	52	Fluda	88%	11%	63%	30%	OS: 40% (1 yr)
Diaconescu '04	73	Fluda	-	3%	16%	43%	-
Sorror '04	60	Fluda	-	12%	77%	53%	OS: 50% (2 yrs)
Baron '05	21 CML	Fluda	57%	0%	82%	72%	OS: 85% (2 yrs)
Sorror '05	64 CLL	+/- Fluda	95%	11%	55%	50%	OS: 60% (2 yrs)
Hegenbart '06	122 AML	+/- Fluda	95%	3%	40%	36%	OS: 48% (2 yrs)
Kahl '07	834	+/- Fluda	-	18% (2 yrs)	-	-	OS: 43% (3 yrs)
Laport '08	148 MDS/AML	+/- Fluda	75%	21% (200 d)	39%	37%	OS: 27% (3 yrs)
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Mielcarek '03	44	Fluda	89%	-	64%	73%	OS: 68% (1 yr)
Maloney '03	54 MM	-	100%	2%	38%	46%	OS: 78% (2 yrs)
Niederwieser '03	52	Fluda	88%	11%	63%	30%	OS: 40% (1 yr)
Diaconescu '04	73	Fluda	-	3%	16%	43%	-
Sorror '04	60	Fluda	-	12%	77%	53%	OS: 50% (2 yrs)
Baron '05	21 CML	Fluda	57%	0%	82%	72%	OS: 85% (2 yrs)
Sorror '05	64 CLL	+/- Fluda	95%	11%	55%	50%	OS: 60% (2 yrs)
Hegenbart '06	122 AML	+/- Fluda	95%	3%	40%	**36%**	OS: 48% (2 yrs)
Kahl '07	834	+/- Fluda	-	18% (2 yrs)	-	-	OS: 43% (3 yrs)
Laport '08	148 MDS/AML	+/- Fluda	75%	21% (200 d)	39%	37%	OS: 27% (3 yrs)
Sorror '08	152 CLL	Fluda	-	25% (3 yrs)	-	-	OS: 53% (3 yrs)

HAEMATOLOGICAL MALIGNANCIES

TBI 200 cGy

Author	Pts	Other drugs	Durable donor chim	TRM @ day 100	aGVHD ≥ II	cGVHD	Long term outcome
McSweeney '01	45	-	80%	6 %	47%	74%	OS: 70% (1 yr)
Maris '03	89	Fluda	85%	11%	52%	37%	OS: 52% (1 yr)
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Reduced-intensity conditioning using fludarabine with either antithymocyte globulin and BU, or low-dose TBI allowing allogeneic hematopoietic SCT

C Cable[1,6], MP Buzzeo[2,6], JD Schold[3], S Khan[1], H Leather[1], J Moreb[1], K Jamieson[1], J Scornik[4], RJ Amdur[5], JR Wingard[1] and V Reddy[1]

BMT 2010

- 66 pts with different malignancies
- Median age 55 yrs (17-70)
- 25/66 (38%) → AML
- 70% of pts in "early phase"
- 53% MUD

- 25 pts (38%): TBI 200 cGy + Fluda
- 41 pts (62%): Fluda + ATG + Bus

- GVHD prophylaxis: Tacrolimus (+ MMF in TBI group)

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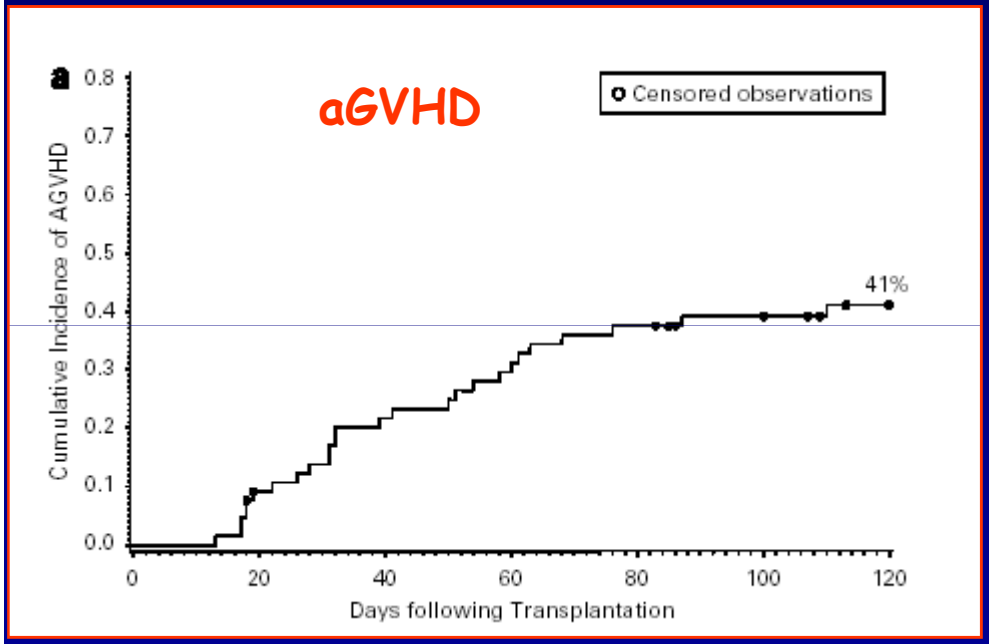
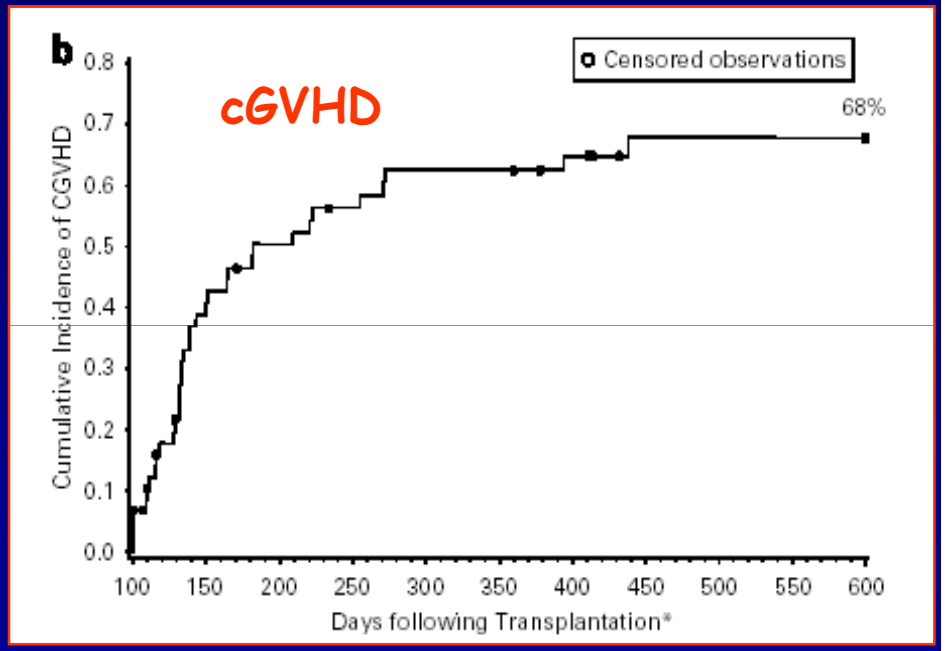
BMT 2010





Median onset +32 (13 – 110)

Median onset +134 (100 - 438)

Reduced-intensity conditioning using fludarabine with either antithymocyte globulin and BU, or low-dose TBI allowing allogeneic hematopoietic SCT

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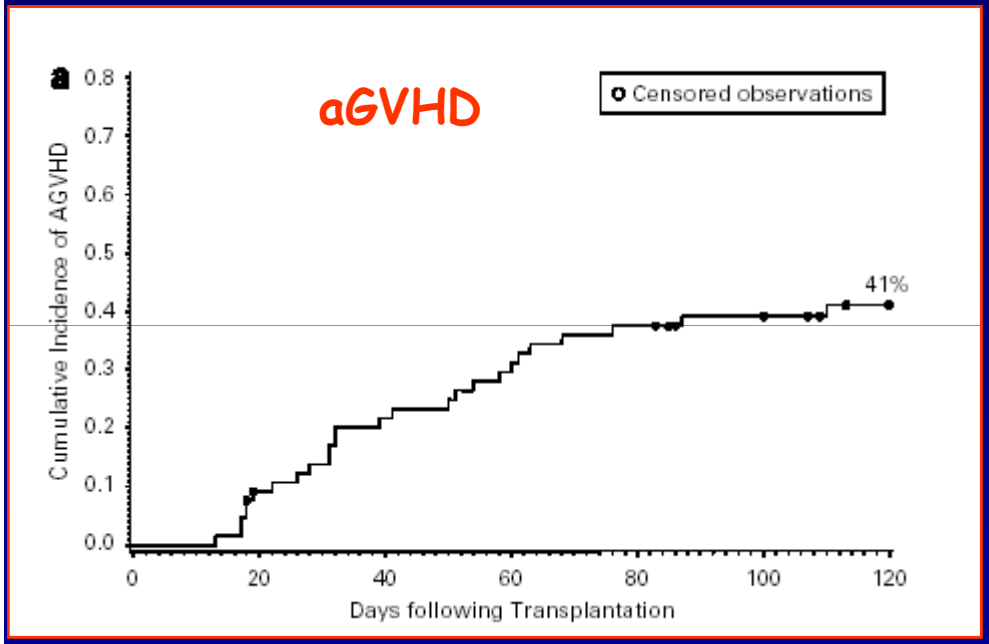
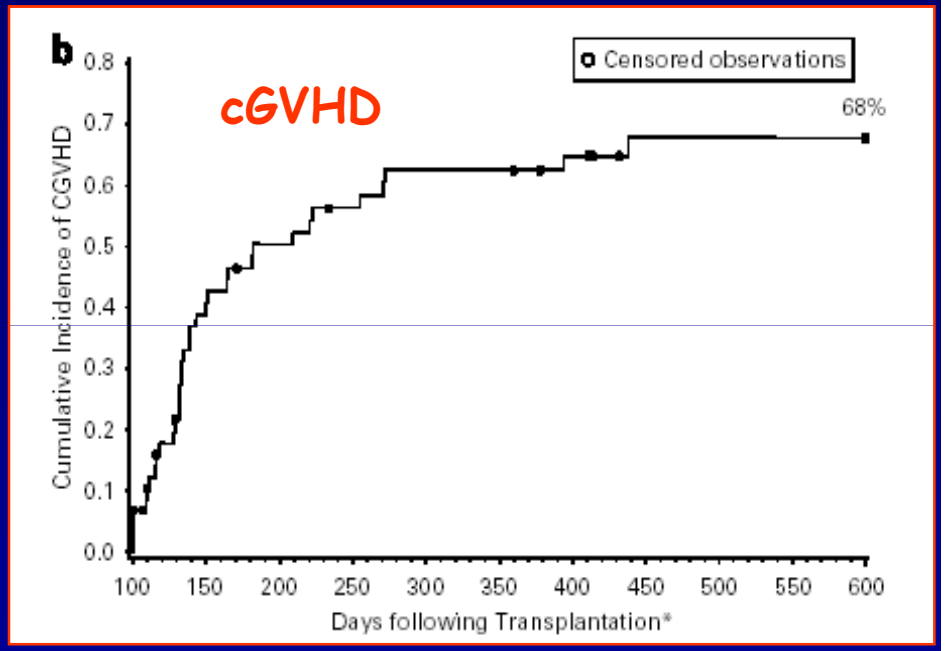




Median onset +32 (13 – 110)

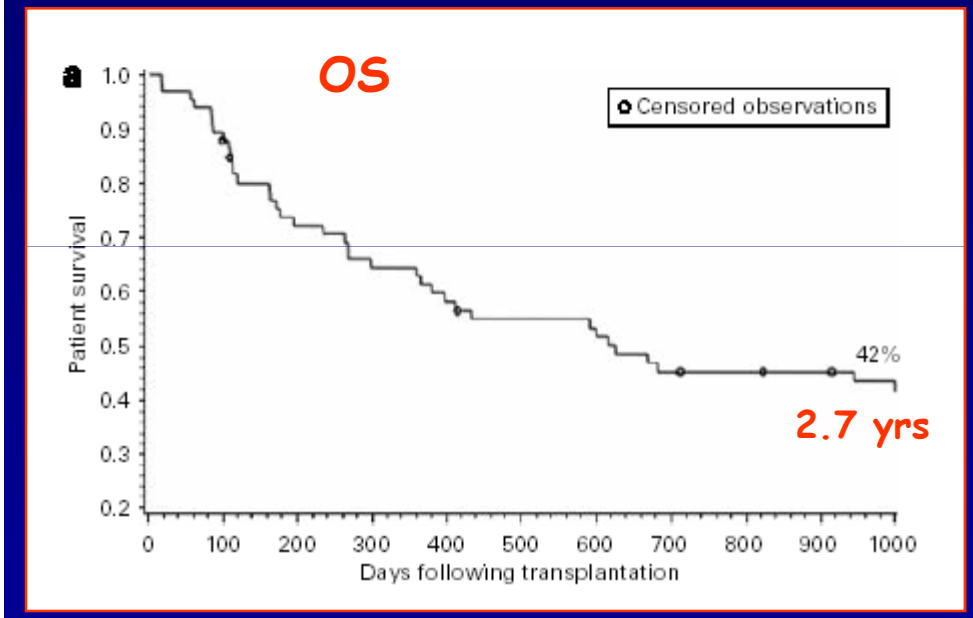
Median onset +134 (100 - 438)

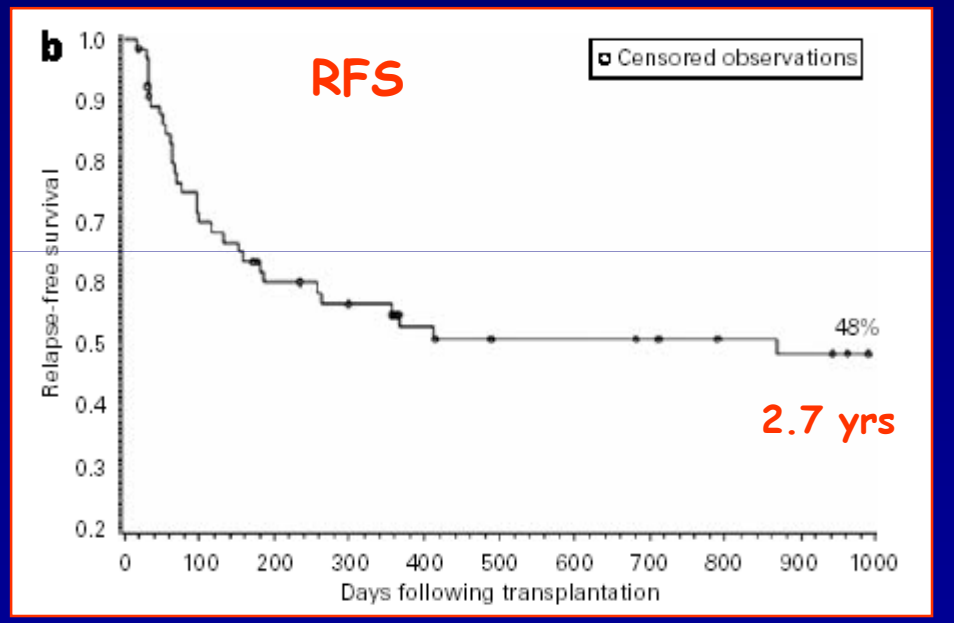
- CMV infection: 33%
- 100% donor chimerism (+30): 62%
- IFI: 10/66 pts (1.5%)
- TRM @ day +100: 6%

Reduced-intensity conditioning using fludarabine with either antithymocyte globulin and BU, or low-dose TBI allowing allogeneic hematopoietic SCT

C Cable[1,6], MP Buzzeo[2,6], JD Schold[3], S Khan[1], H Leather[1], J Moreb[1], K Jamieson[1], J Scornik[4], RJ Amdur[5], JR Wingard[1] and V Reddy[1]

BMT 2010





No differences within the two regimens

Pts achieving full donor chimerism @ +30 in TBI group → better survival *vs* no TBI group

Reduced-intensity conditioning using fludarabine with either antithymocyte globulin and BU, or low-dose TBI allowing allogeneic hematopoietic SCT

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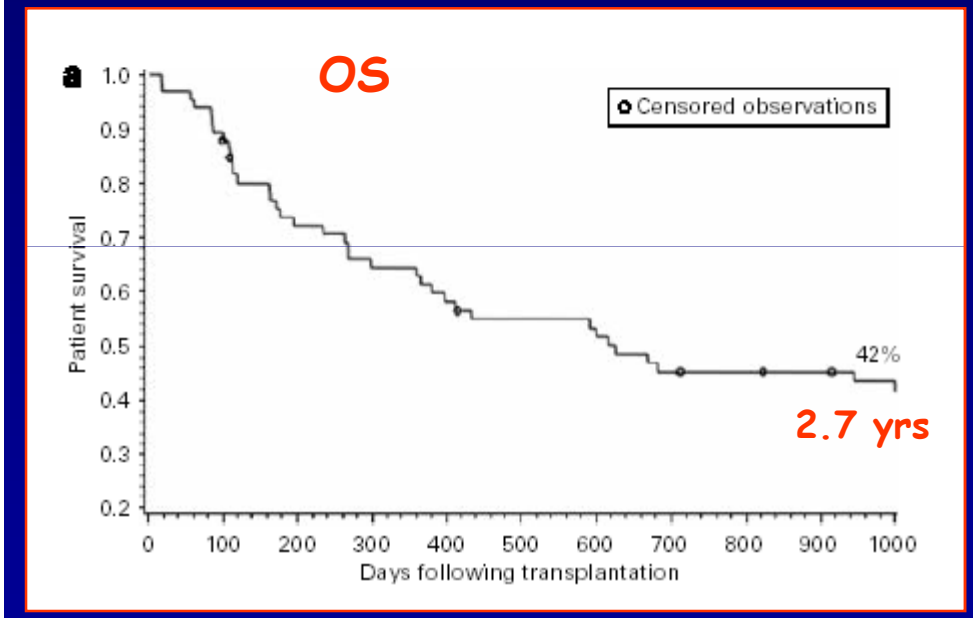
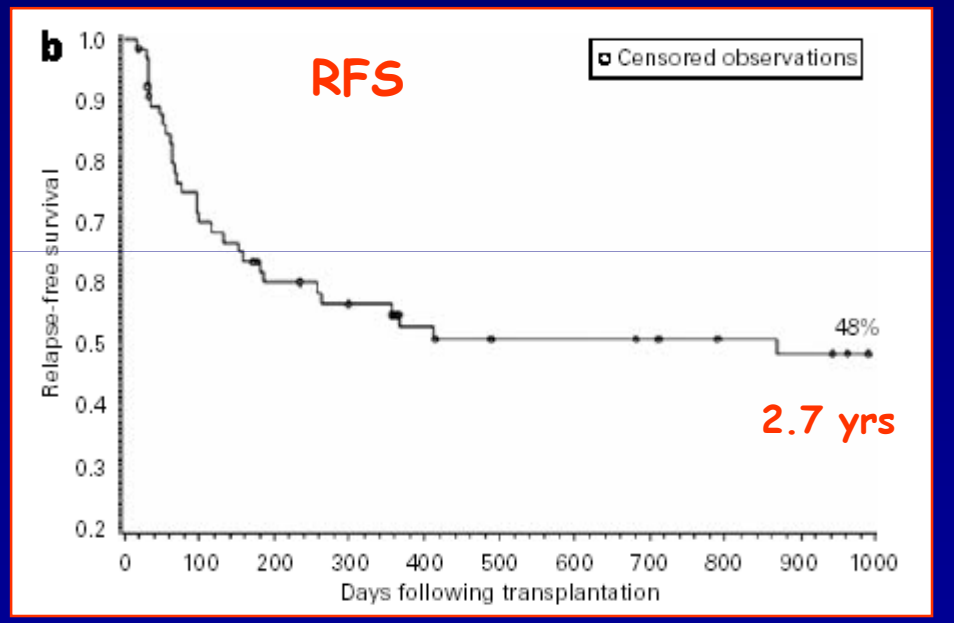




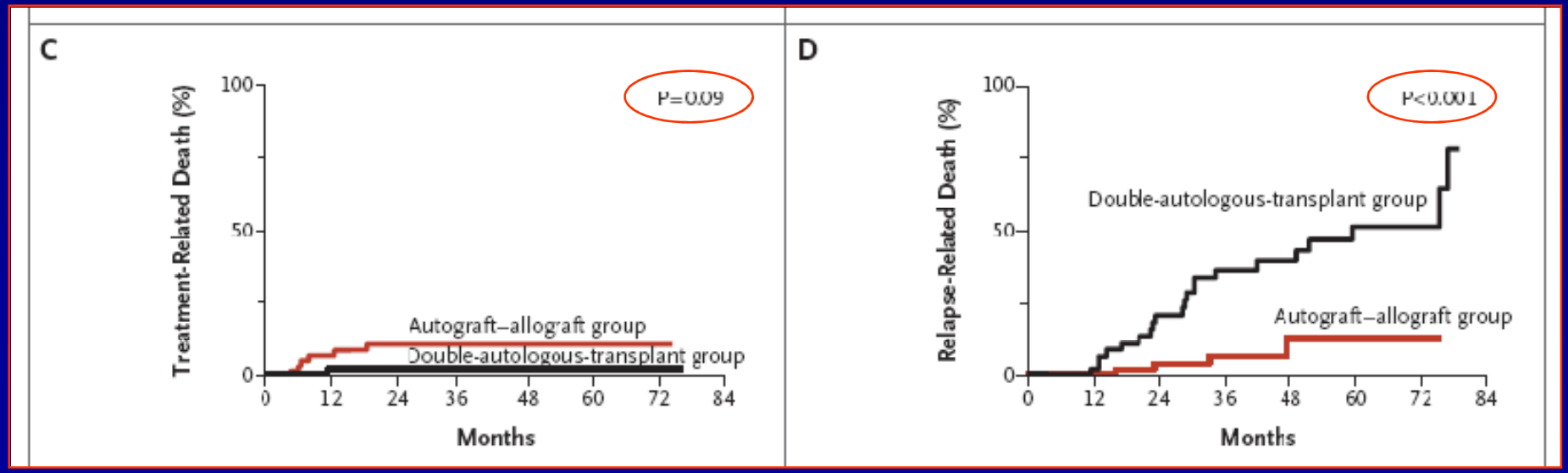
No differences within the two regimens

Pts achieving full donor chimerism @ +30 in TBI group → better survival *vs* no TBI group

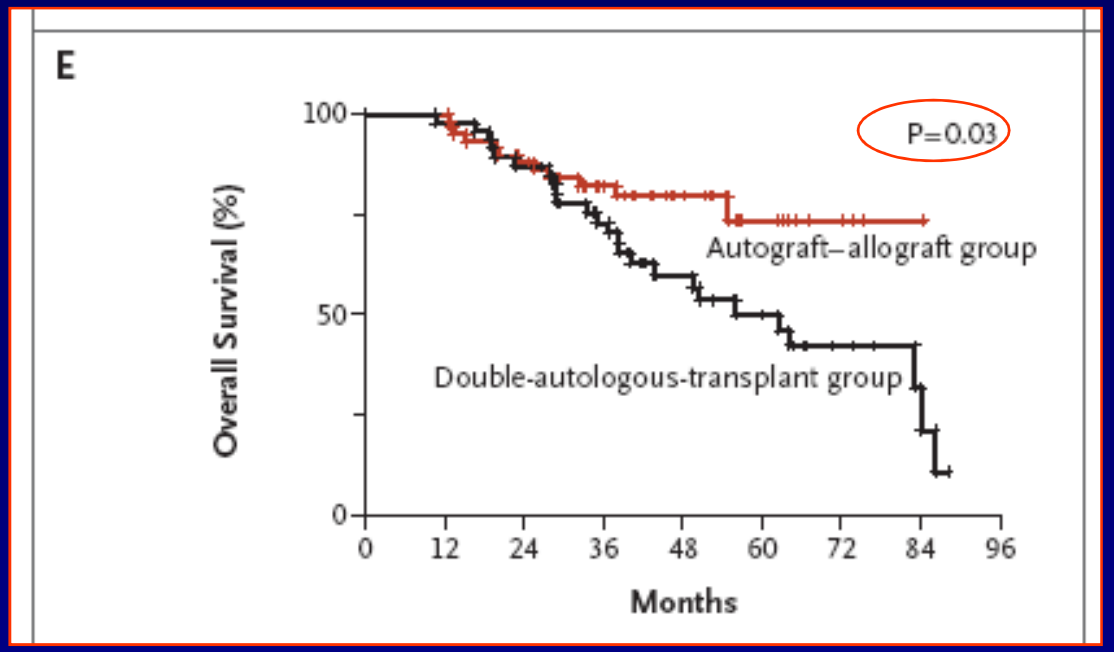
TBI-based RIC-ALLO-SCT for MM

Bruno et al, NEJM 2007

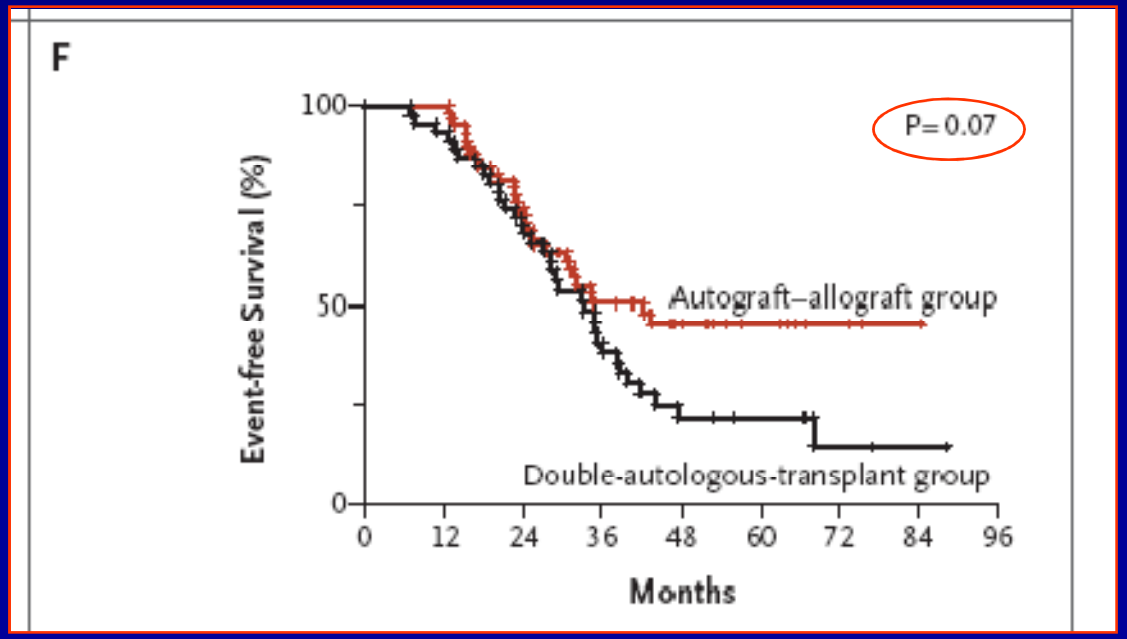
162 pts ≤ 65 yrs, newly diagnosed
VAD x 4 → EDX 4g/sqm + G-CSF + PBSC → I Auto-SCT
DONOR: Allo-SCT- RIC (TBI 200cGy)
NO DONOR: II Auto-SCT



OS


E
Overall Survival (%)
100
50
0
P=0.03
Autograft–allograft group
Double-autologous-transplant group
0
12
24
36
48
60
72
84
96
Months

EFS


F
Event-free Survival (%)
100
50
0
P=0.07
Autograft–allograft group
Double-autologous-transplant group
0
12
24
36
48
60
72
84
96
Months

Nonmyeloablative allografting for newly diagnosed multiple myeloma: the experience of the Gruppo Italiano Trapianti di Midollo

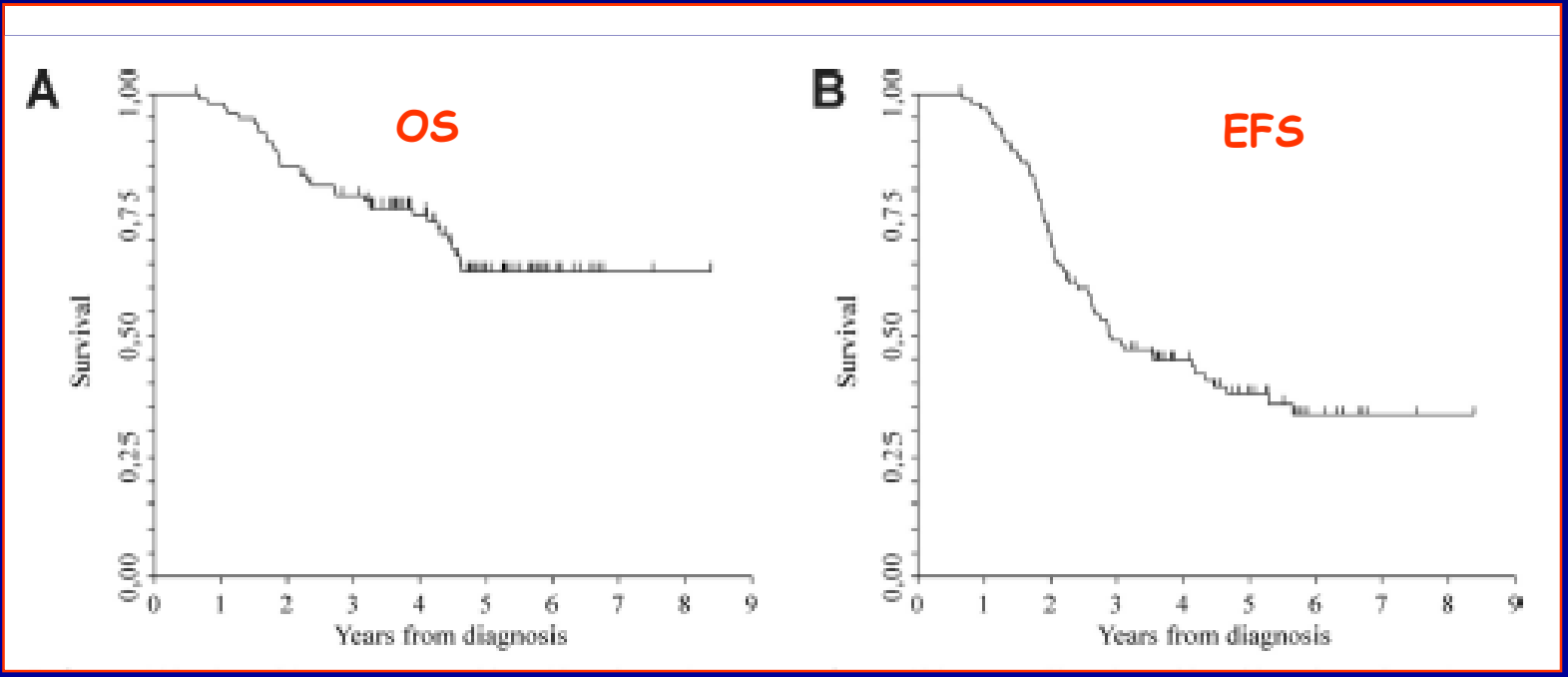
Bruno et al, Blood 2009

Table 1. Patient characteristics **100 pts**

Characteristic	Patients enrolled, no. (%)*
Male	52 (52)
Mean age, y (range)	54 (30-65)
Durie & Salmon stage II	29 (29)
Durie & Salmon stage III	67 (67)
International Staging System 2	22/92 (24)
International Staging System 3	14/92 (15)
IgG myeloma	57 (57)
IgA myeloma	18 (18)
IgD myeloma	1 (1)
Bence-Jones myeloma	18 (18)
Nonsecretory myeloma	6 (6)
β-2-microglobulin > 3.5 mg/dL	33/95 (35)
Albumin < 3.5 g/dL	21/95 (22)
Creatinine > 2 mg/dL	11 (11)
LDH above normal level	17/91 (19)
Presence of chromosome 13 deletion	14/43 (33)
HCT-specific comorbidity index ≥ 3	11 (11)

Nonmyeloablative allografting for newly diagnosed multiple myeloma: the experience of the Gruppo Italiano Trapianti di Midollo **Bruno et al, Blood 2009**

- VAD x 4 → EDX → Auto-SCT (Mel 200) → RIC allo-SCT (TBI 200cGy)
- Siblings
- aGVHD cumulative ≥ 2: 38%
- cGVHD cumulative: 50%
- TRM @ 2 yrs 11%



NON TBI-based RIC-ALLO-SCT for MM

Garban et al, Blood 2006

de novo MM, < 65 years
β2M > 3 mg/L and Δ13

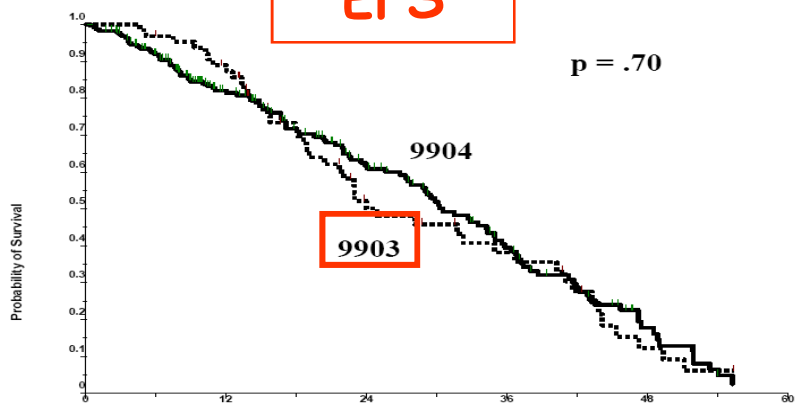
VAD x 4

Stem cell collection

HDM 200

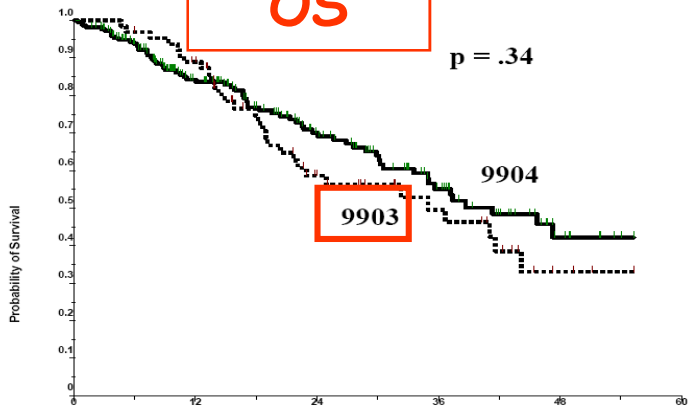
If HLA-sibling available Mini-allo Bu-Fluda-ATG	No donor available HDM 220 +/- anti-IL6
IFM9903 trial	**IFM9904 trial**

EFS



EFS intent-to treat : 64 vs 220 patients
IFM9903 vs 9904

OS



SURVIVAL Intent-to-treat : 64 vs 220 patients
IFM9903 vs 9904

HAEMATOLOGICAL MALIGNANCIES

Other TBI doses

400 cGy

103 refractory AML → Fluda/Amsacrina/AraC

TBI 400 cGy + CTX + ATG

Engraftment 100%

Median f up: 25 months

OS @ 4 yrs: 32%

LFS @ 4 yrs: 30%

NRM @ 1 yr: 17%

Schmid C et al, Blood 2006

HAEMATOLOGICAL MALIGNANCIES

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400 cGy

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OS @ 4 yrs: 32%

LFS @ 4 yrs: 30%

NRM @ 1 yr: 17%

Schmid C et al, Blood 2006

500/550 cGy

252 pts (different diseases, MUD/Sibling)

TBI 550 cGy + CTX 120

Engraftment: 86 - 100%

DFS @ 3 yrs: 21 - 77%

NRM @ 2 yrs: 7 - 42%

Khoury et al, BBMT 2001
Blum et al, BBMT 2002
Hallemeier et al, BBMT 2004
Girgis et al, Blood 2005

Can we draw some conclusions about TBI and SCT ?

- TBI in auto-SCT has been abounded in favour of CHT
  - same efficacy
  - same toxicity
  - CHT is easier to perform
  - with CHT → possibility of post transplant IF-RTT in HLs and NHLs

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  - extramedullary leukemias

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- TBI 12 Gy in allo-SCT is **comparable / superior to CHT**
- TBI 12 Gy in allo-SCT is usually preferred in
  - ALL
  - extramedullary leukemias
- Low dose TBI (200 cGy) is an excellent conditioning able to ensure sustained engraftment and hopefully Graft versus Tumor effect

Something new

TBI and Total Marrow Irradiation for pts with advanced haematologic Malignancies undergoing an allo-SCT: a pilot study

Corvò R, ……., Bacigalupo A *EBMT meeting 2010, P406*

- 12 Gy + CTX
- TMI with 2 Gy (delivered with Helical Tomotherapy (HT)
- 6 pts with advanced disease
- Efficient dose reduction on testes, brain, larynx, liver, lungs and kidney
- Bone marrow sites irradiated with an optimal conformity and an excellent dose homogeneity
- Feasible and safe