French & German SFGM-TC Day

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Total body irradiation (TBI) in conditioning regimen for acute lymphoblastic leukemia

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TBI in conditioning regimen for ALL

❖ Total body irradiation is commonly used in conditioning regimen for patients with ALL

Reference	Design	Age	Hemopathy	OS	EFS	Relapse	TRM
Ringdén et al., Blood, 1994 *Randomized trial*	TBI + CY (n = 79) Bu + CY (n = 88)	1-55 y.o. (median = 35)	AML (n = 69) ALL (n = 38) CML (n = 57) NHL (n = 4)	**TBI: 3y-OS 76%** Bu: 3y-OS 62%	**TBI: 3y-EFS 67%** Bu: 3y-EFS 56%	TBI: 3y-CIR 26% Bu: 3y-CIR 22%	TBI: 3y-TRM 9% **Bu: 3y-TRM 28%**
Davies et al., JCO, 2000 *Retrospective study*	TBI + CY (n = 451) Bu + CY (n = 176)	< 20 y.o.	ALL	**TBI: 3y-OS 55%** Bu: 3y-OS 40%	**TBI: 3y-EFS 50%** Bu: 3y-EFS 35%	TBI: 3y-CIR 35% Bu: 3y-CIR 41%	TBI: 3y-TRM 15% **Bu: 3y-TRM 23%**
Bunin et al., BMT, 2003 *Randomized trial*	TBI + ETO + CY (n = 22) Bu + ETO + CY (n = 21)	< 21 y.o.	ALL	**TBI: 3y-OS 67%** Bu: 3y-OS 47%	**TBI: 3y-EFS 58%** Bu: 3y-EFS 29%	TBI: 7/22 Bu: 9/21	TBI: 2/22 **Bu: 5/21**

❖ Significantly improved OS with TBI, regardless of the conditioning intensity

Marks et al., Blood, 2010 *(retrospective study)*

93 Ph- ALL patients (CR1 or CR2), > 16 y.o.

. *Full-intensity* (n = 1428): TBI ≥ 13 Gy 30% / TBI < 13 Gy 60%

. vs *RIC* (n = 93): TBI < 13 Gy 40%

Table 4. Multivariate analysis of treatment failure (death or relapse) and death

Variable	N	RR	Lower CL	Upper CL	*P*
Treatment failure, main effect					
Full intensity	1421	1.00			
RIC	92	1.05	0.78	1.41	.75
Treatment failure, other significant factors					
TBI as part of conditioning regimen					
Yes	1285	1.00			
No	228	1.40	1.16	1.68	.001

TBI in conditioning regimen for ALL

- Long-term side effects of TBI are a major concern:
  - impaired growth and intellectual development
  - pneumonitis
  - cataracts
  - endocrinologic disturbances
  - secondary malignancies

- With improved genetic testing, GvHD prophylaxis and other advances,

  could chemoconditioning replace TBI in ALL?

For Omitting Radiation Under Majority age

- International multicenter **randomized phase III noninferiority study**
- Pediatrics patients with high-risk ALL
- 88 centers in 21 countries
- 2013-2018

original reports

Total Body Irradiation or Chemotherapy Conditioning in Childhood ALL: A Multinational, Randomized, Noninferiority Phase III Study

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JCO, 2020; https://doi.org/10.1200/JCO.20.02529

- Inclusion criteria:
  - < 18 y.o. at diagnosis, 4-21 y.o. at HSCT
  - CR pre-HSCT
  - MSD or MUD/MMUD
- Exclusion criteria:
  - CNS involvement
  - Pre-HSCT cranial radiation
  - Prior HSCT

Random assignment

❖ TBI arm: (n = **212**)

TBI 12 Gy over 3 days + **ETO** 60 mg/kg D-3

❖ Chemoconditioning arm: (n = **201**)

- **Thiotepa** 5 mg/kg bid for 1 day

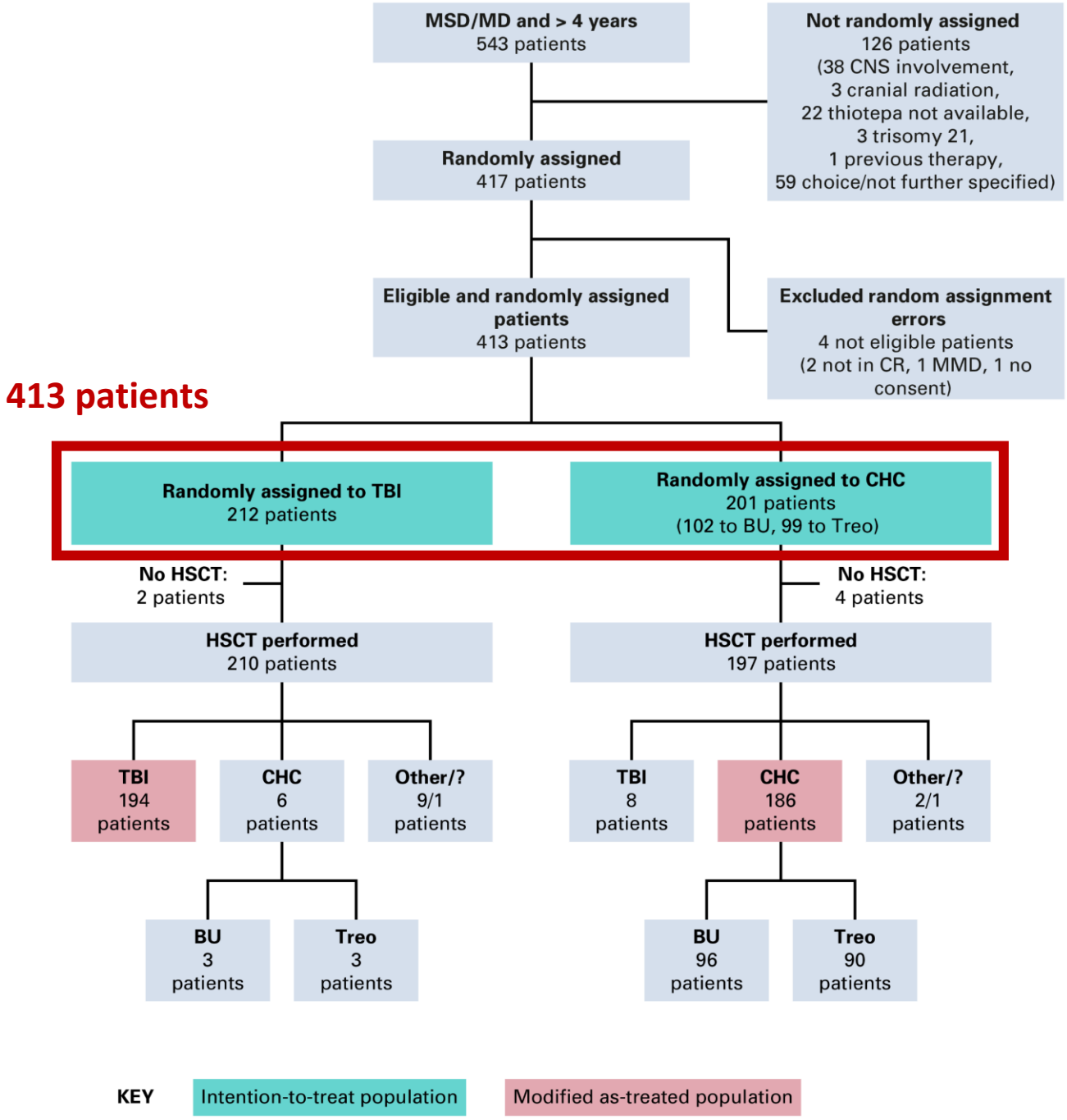
- **Fludarabine** 30 mg/m²/d for 5 days

- either **treosulfan** 14 g/m²/d for 3 days

or **busulfan** over 4 days

❖ GvHD prophylaxis:

- MSD = cyclosporine A (CsA) only
- MUD/MMUD = CsA + MTX + ATG



FORUM study

Patient and Disease Characteristic, n (%)	All (N = 413)	TBI (n = 212)	Chemoconditioning		
			Total (n = 201)	Busulfan (n = 102)	Treosulfan (n = 99)
Stem cell source[c]					
Bone marrow	337 (82%)	174 (82%)	163 (81%)	78 (76%)	85 (86%)
Peripheral blood[d]	51 (12%)	25 (12%)	26 (13%)	14 (14%)	12 (12%)
Cord blood	16 (4%)	9 (4%)	7 (3%)	7 (7%)	0 (0%)
Remission status					
CR1	225 (54%)	118 (56%)	107 (53%)	47 (46%)	60 (61%)
CR2	164 (40%)	85 (40%)	79 (39%)	46 (45%)	33 (33%)
CR3	18 (4%)	7 (3%)	11 (5%)	7 (7%)	4 (4%)
MRD pre-HSCT[a]					
MRD-negative (PCR)	135 (33%)	72 (34%)	63 (31%)	40 (39%)	23 (23%)
MRD-positive (PCR)	132 (32%)	61 (29%)	71 (35%)	31 (30%)	40 (40%)
MRD-negative (flow cytometry)	57 (14%)	32 (15%)	25 (12%)	20 (20%)	5 (5%)
MRD-positive (flow cytometry)	12 (3%)	9 (4%)	3 (1%)	3 (3%)	0 (0%)

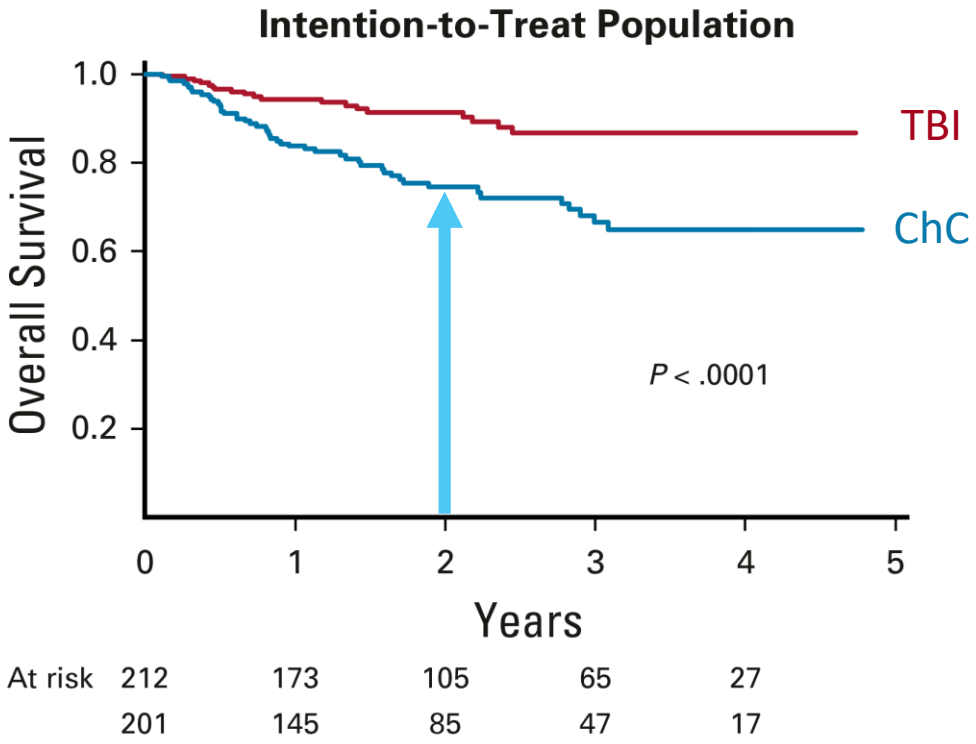
MRD- 57%
MRD+ 43%

- MRD was assessed 2 weeks before conditioning therapy (bone marrow):

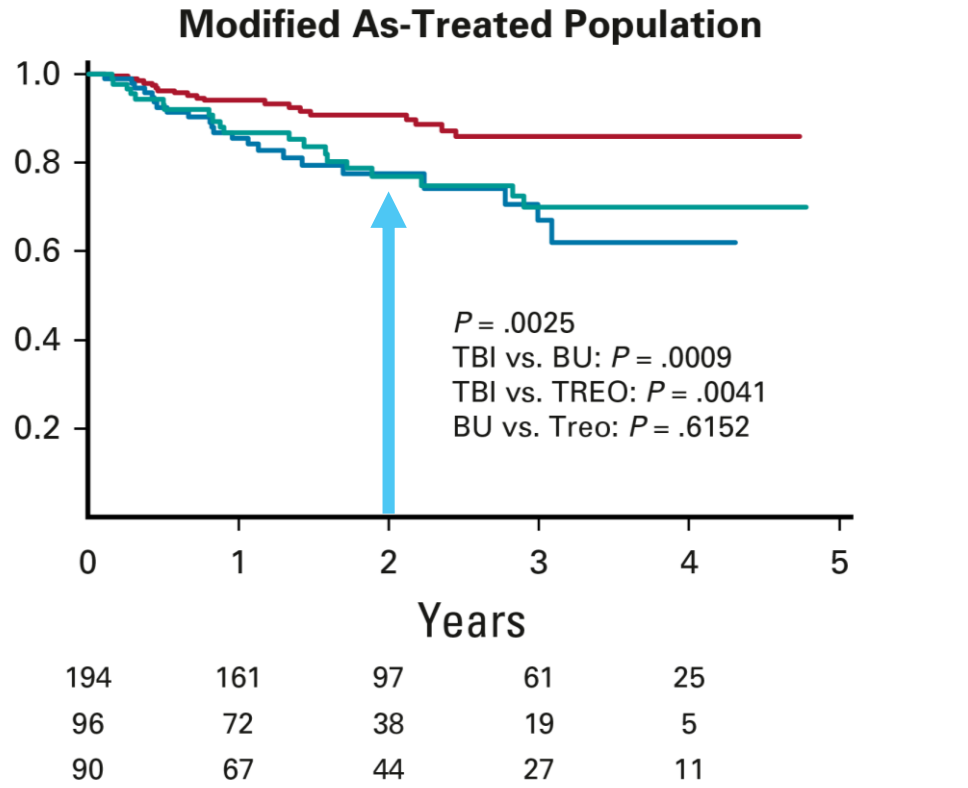
  defined as > 10^{-3} for flow cytometry and > 10^{-4} for PCR

FORUM study – Overall survival

Median follow-up: 2.1 years



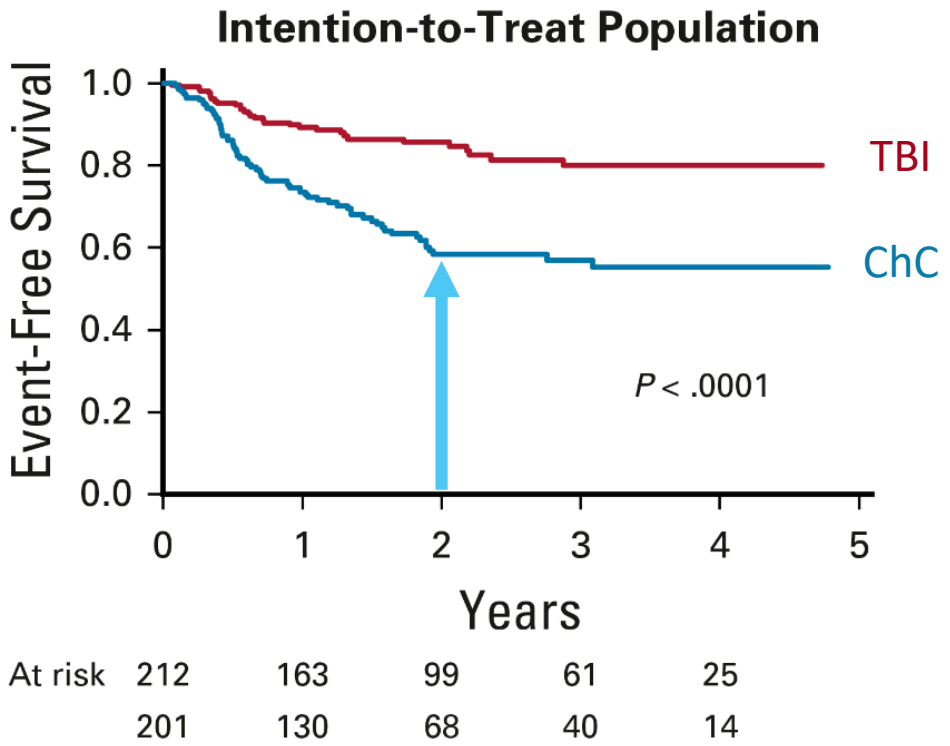
	Patients	Eval.	Deaths	2-year OS
TBI	212	209	19	0.91 (0.86-0.95)
CHC	201	200	49	0.75 (0.67-0.81)

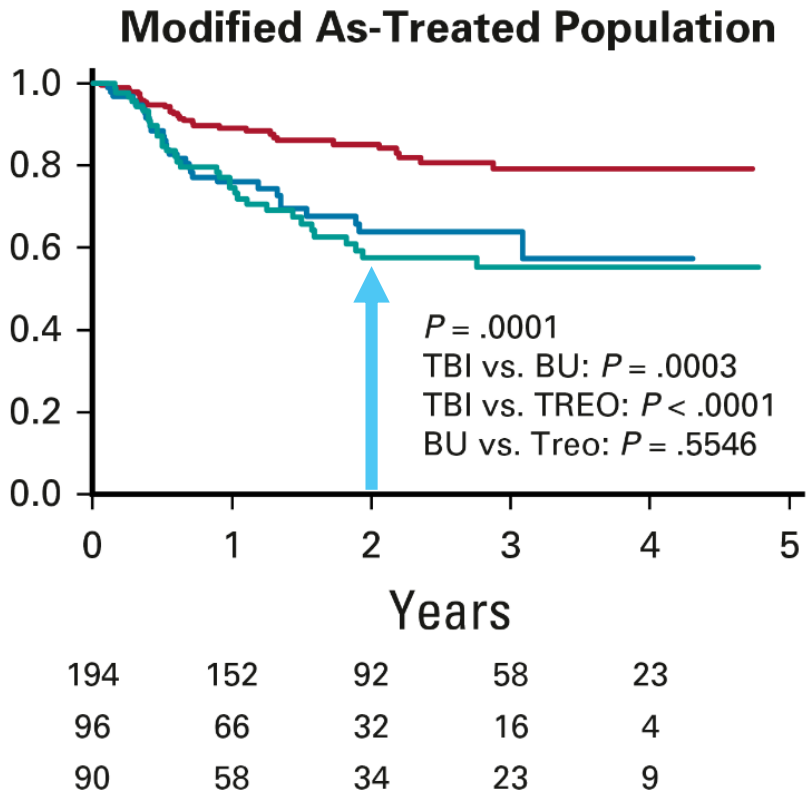


	Patients	Eval.	Deaths	2-year OS
TBI	194	194	19	0.91 (0.85-0.94)
BU	96	96	22	0.77 (0.66-0.85)
TREO	90	90	20	0.77 (0.65-0.85)

FORUM study – Event-free survival

Median follow-up: 2.1 years

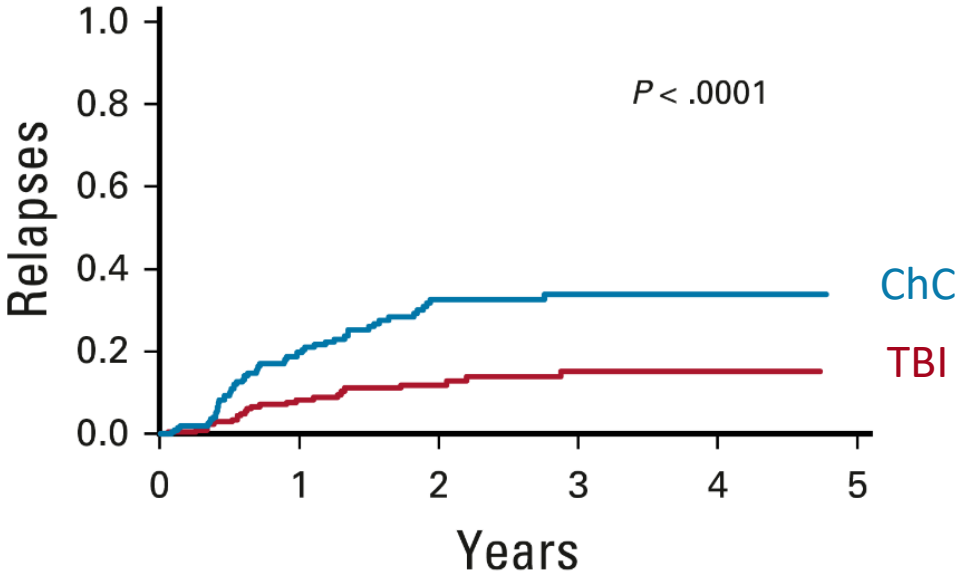




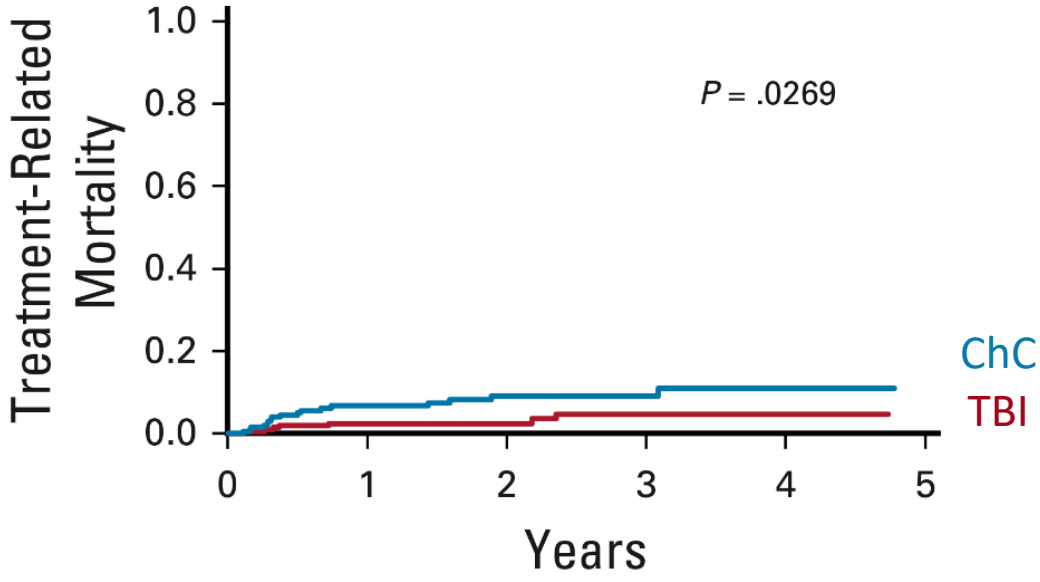
	Patients	Eval.	Events	2-year EFS
TBI	212	209	31	0.86 (0.79-0.90)
CHC	201	200	72	0.58 (0.50-0.66)

	Patients	Eval.	Events	2-year EFS
TBI	194	194	30	0.85 (0.79-0.90)
BU	96	96	30	0.64 (0.52-0.74)
TREO	90	90	33	0.58 (0.45-0.69)

FORUM study
Relapse incidence and Treatment-related mortality



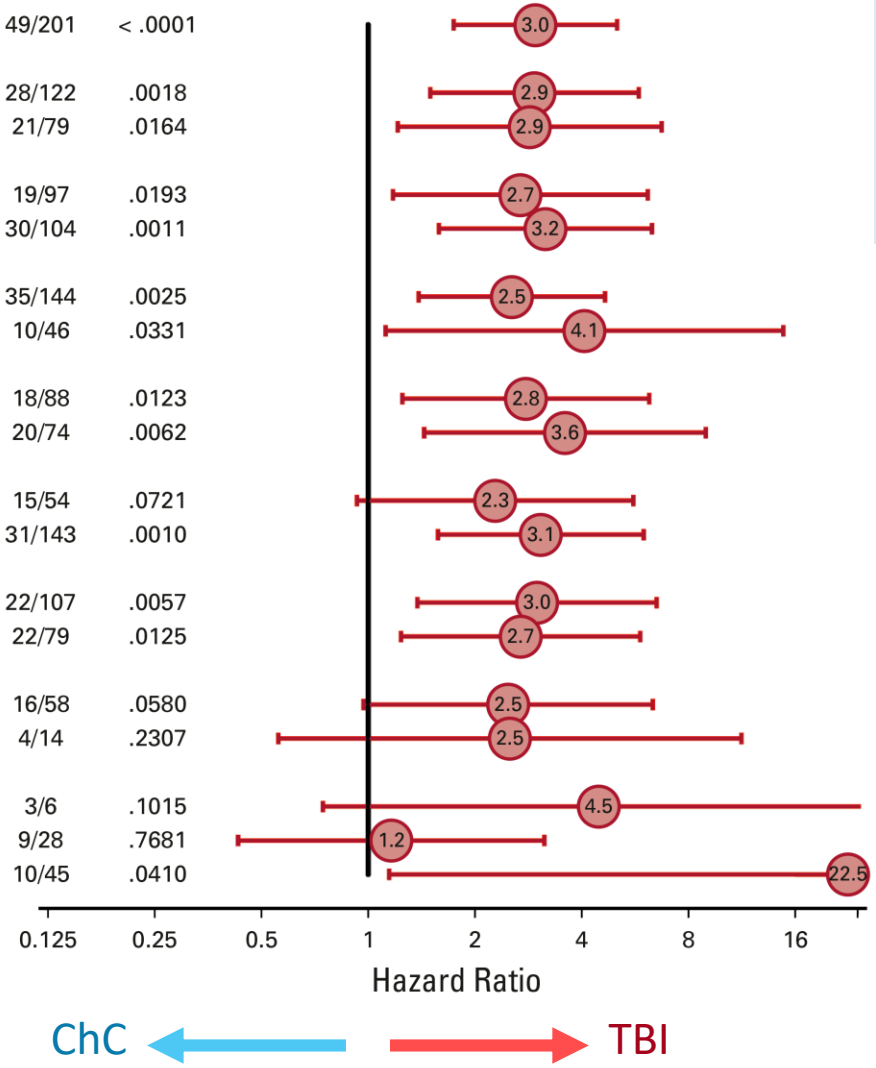
	Patients	Eval.	Relapses	2-year CIR
TBI	212	209	24	0.12 (0.08-0.17)
CHC	201	200	55	0.33 (0.25-0.40)



	Patients	Eval.	TRM	2-year TRM
TBI	212	209	7	0.02 (<0.01-0.05)
CHC	201	200	17	0.09 (0.05-0.14)

FORUM study – Overall survival

Risk factor		TBI	CHC	*P* value
Total		19/212	49/201	< .0001
Sex	Male	12/145	28/122	.0018
	Female	7/67	21/79	.0164
Age	≤10 years	8/100	19/97	.0193
	>10 years	11/112	30/104	.0011
Immunophenotype	BCP	15/153	35/144	.0025
	T-ALL	3/48	10/46	.0331
MRD pre-HSCT	MRD-	9/104	18/88	.0123
	MRD+	6/70	20/74	.0062
Donor	MSD	7/54	15/54	.0721
	MD	12/156	31/143	.0010
Remission status	CR1	9/118	22/107	.0057
	CR2	9/85	22/79	.0125
Type of relapse	BM	6/53	16/58	.0580
	Combined	3/24	4/14	.2307
Time of relapse	<18 mo	2/16	3/6	.1015
	18–30 mo	7/27	9/28	.7681
	>30 mo	0/42	10/45	.0410



There is no subgroup in which chemotherapy supplants TBI, even "favorable prognosis" groups!

FORUM study – Multivariable analyses

Variable	OS (52 Deaths/333 Evaluable Patients)		EFS (77 Events/333 Evaluable Patients)		Relapses (59 Events/333 Evaluable Patients)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Arm						
CHC *v* TBI	3.1 (1.7 to 5.7)	.0003	2.8 (1.7 to 4.6)	<.0001	2.5 (1.4 to 4.4)	<.0001
Donor						
MSD *v* MD	0.8 (0.4 to 1.4)	.3851	0.8 (0.5 to 1.4)	.5073	0.7 (0.4 to 1.1)	.1224
Remission phase (*v* CR1)						
CR2	1.5 (0.8 to 2.7)	.2078	1.7 (1.0 to 2.7)	.0371	1.7 (1.0 to 3.1)	.0572
CR3	0.7 (0.1 to 2.9)	.5785	0.6 (0.2 to 2.2)	.4834	0.3 (0.04 to 2.5)	.2684
MRD[a]						
Positive *v* negative	1.4 (0.8 to 2.4)	.2904	1.4 (0.9 to 2.3)	.1192	1.4 (0.8 to 2.4)	.2602
Age						
≥10 years *v* <10 years	1.8 (1 to 3.1)	.0480	1.5 (1 to 2.4)	.0799	1.2 (0.7 to 2.14)	.4327
Immunophenotype (*v* BCP)						
T-ALL	1.1 (0.5 to 2.3)	.8968	0.8 (0.4 to 1.6)	.4915	0.9 (0.4 to 1.9)	.7080
Other	1.1 (0.1 to 8)	.9584	0.6 (0.1 to 4.4)	.6160	NA	..

[a]MRD: defined as > 10^{-3} for flow cytometry and > 10^{-4} for PCR

FORUM study – Conclusions

- TBI was associated with lower risk of relapse and TRM than chemoconditioning
  - early termination of random assignment
- Thiotepa + fludarabine + busulfan/treosulfan have shown high efficacy compared with other conditioning regimens, and may be used when TBI isn't available
- MRD levels didn't affect EFS!
- The short follow-up time prevents any conclusion on long-term side effects

- Extrapolation of these results to adults?