

Do we still need TBI?

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Corso di Formazione **GITMO**

**Trapianto e
terapie cellulari:
cellule, donatori e
condizionamenti**

Udine, 8-9 Ottobre 2026

Aula Polifunzionale Ospedale di Udine

Disclosures of Michele Massa

Company name

Research support

Employee

Consultant

Stockholder

Speakers bureau

Advisory board

Other

I have no conflicts of interest to disclose.

*Personal disclosure:
I'm a pediatrician. Please be gentle with the questions!*



Where it all began?

INTRAVENOUS INFUSION OF BONE MARROW IN PATIENTS RECEIVING RADIATION AND CHEMOTHERAPY*

E. DONNALL THOMAS, M.D.,† HARRY L. LOCHTE, JR., M.D.,‡ WAN CHING LU, PH.D.,§
AND JOSEPH W. FERREBEE, M.D.¶

COOPERSTOWN, NEW YORK, AND BOSTON, MASSACHUSETTS

<< Since cases of radiation disaster may occur, and since bone-marrow deficiency from radiation or chemotherapy does occur in the normal course of clinical medicine, an effort has been made to determine the availability and usefulness of bone-marrow infusions for the treatment of these conditions in man. >>

N Engl J Med. 1957;257:491-496



Almost 70 years later... Do we still need TBI?

Why is TBI so hard to replace?



disease control vs. lifetime toxicity

Ideal condition

Desired feature

Antileukaemic

Host immunos

Sanctuary-site

Controllable treatment delivery

Minimal acute and late toxicity

TBI



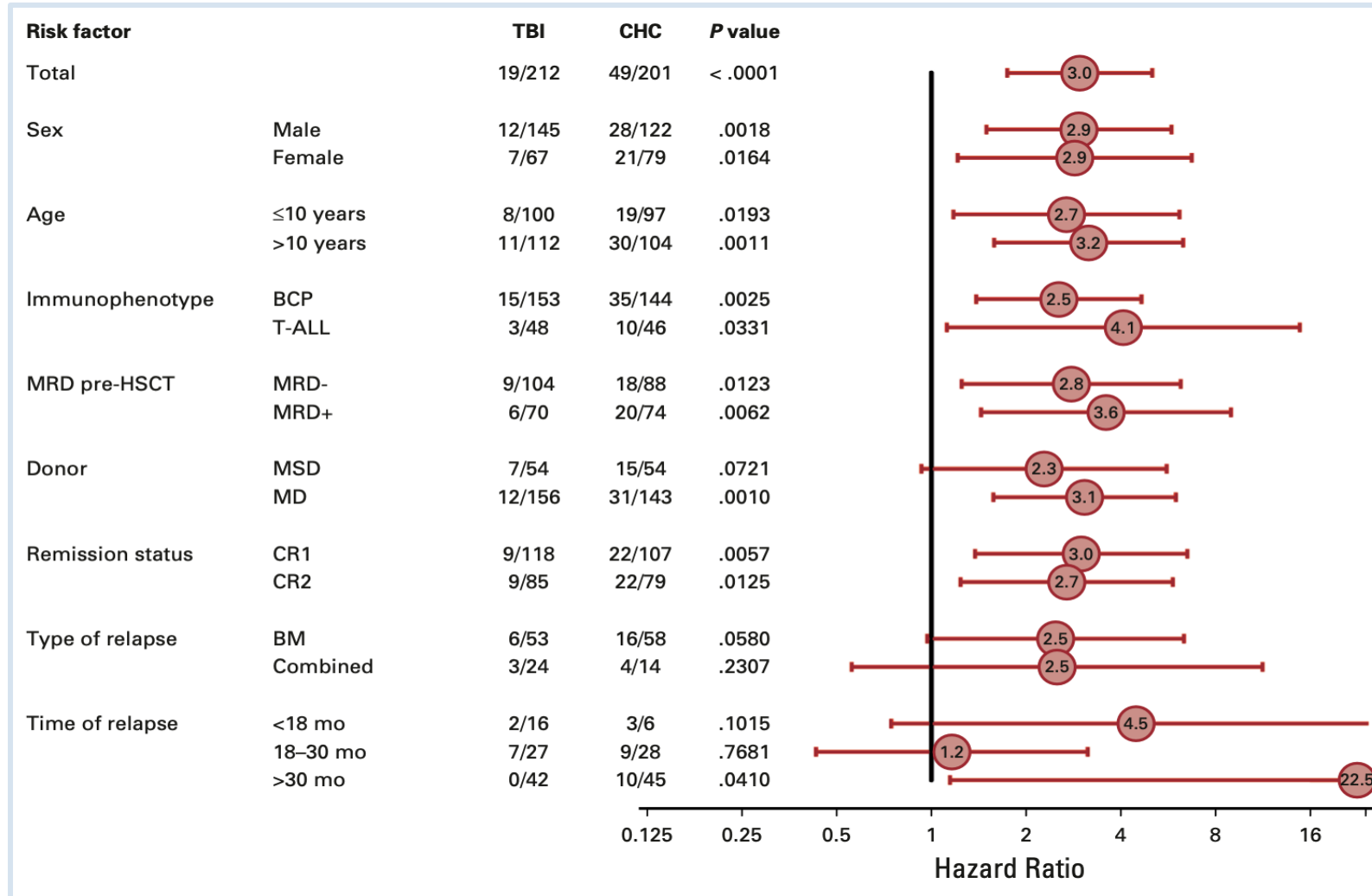
Shimoni et al. The EBMT Handbook. 2024; Ch. 13 ; Hoebe et al. Front Pediatr. 2021;9:774348.

Can we replace TBI? For Omitting Radiation Under Majority age (FORUM)



FORUM
Stem Cell Transplantation

Phase III non-inferiority trial. High-risk ALL. Age 4-21 years at HSCT



Outcome	TBI-VP16	Cht	P value
OS	91%	75%	<0.0001
EFS	86%	58%	<0.0001
CIR	12%	33%	<0.0001
TRM	2%	9%	0.0269

Peters C et al. J Clin Oncol. 2021;39:295–307.

Adult ALL: not a universal answer

RANDOMIZED NON-INFERIORITY TRIAL

Selected B-ALL in CR1

n = 550; 14-65 years; HLA-matched
Standard-risk cytogenetics; 13 centres

REGIMENS

TBI 9 Gy (2 × 4.5 Gy) + Cy 120 mg/kg

vs IV Bu 12.8 mg/kg + Cy 120 mg/kg

Not the 12 Gy / etoposide FORUM regimen

2-YEAR OVERALL SURVIVAL

TBI-Cy		BuCy
79.4%	vs	76.6%

OS comparison: P = 0.457

BuCy non-inferior: P = 0.022

CIBMTR - RETROSPECTIVE REGISTRY

Myeloablative regimens

n = 1,118; 18-60 years; CR1 / CR2

Matched donors; TBI n = 819 / IV Bu n = 299

REGIMENS

TBI 9-16 Gy + Cy or etoposide

vs IV Bu + Flu / clofarabine / Cy / Mel

Bu: median 11.5 mg/kg; PK-guided in 80%

ADJUSTED 3-YEAR OUTCOMES

	TBI	IV Bu	P
Relapse	28%	37%	0.0074
TRM	25%	19%	0.039
OS	53%	57%	0.35

Less relapse; no significant OS difference.

Zhang H et al. J Clin Oncol. 2023;41:343–353

Kebriaei P et al. BBMT. 2018;24:726–733.

Adult ALL: not a universal answer

EBMT - RETROSPECTIVE REGISTRY

8 Gy beyond age 45

n = 501; CR1; transplants 2005-2020; MSD or 9-10/10 unrelated donors
INTERMEDIATE-INTENSITY REGIMENS

Flu + TBI 8 Gy

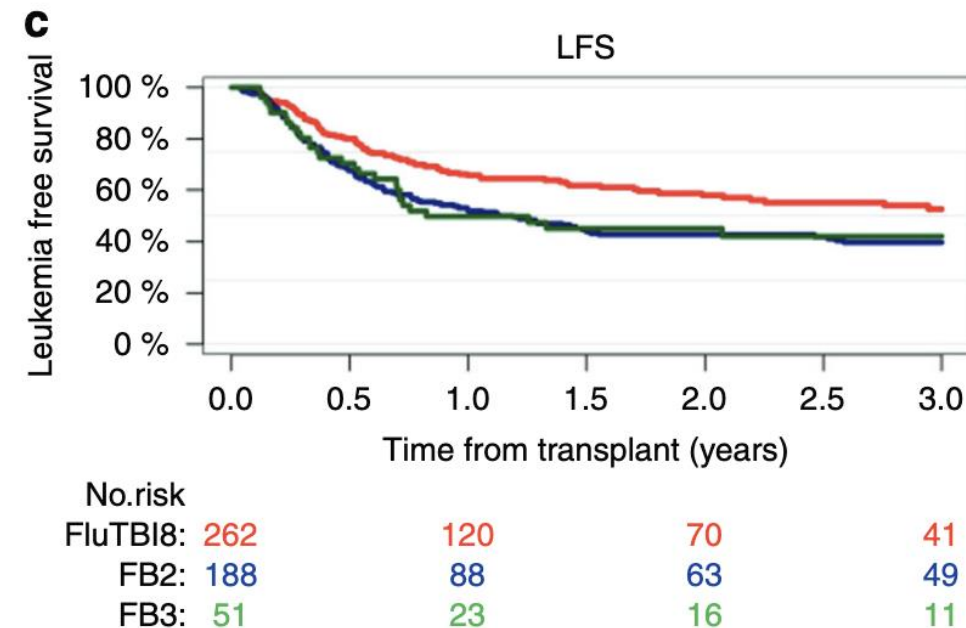
vs Flu + IV Bu 6.4 mg/kg n = 262
or Flu + IV Bu 9.6 mg/kg n = 188
n = 51

ADJUSTED LFS HR - REF: Flu-TBI8

IV Bu dose	HR (95% CI)	P
6.4 mg/kg	1.56 (1.09–2.23)	0.014
9.6 mg/kg	1.63 (1.02–2.58)	0.039

OS and NRM: no significant differences.

LFS favoured TBI: P = 0.014 / 0.039 (Bu6.4 / Bu9.6).



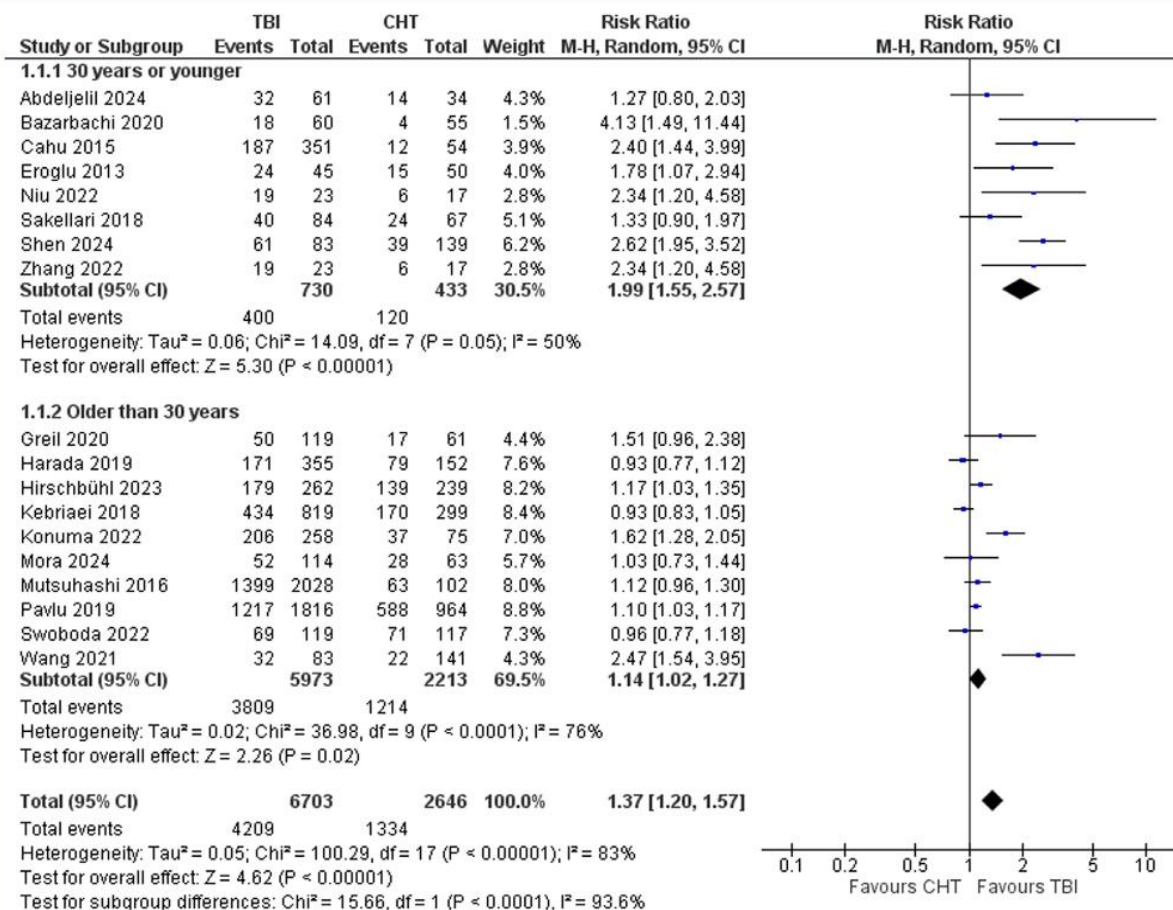
A relapse-control signal is also seen with 8 Gy. Not only with high-dose TBI.

Observational comparisons do not establish equal biological intensity or an intensity-independent effect.

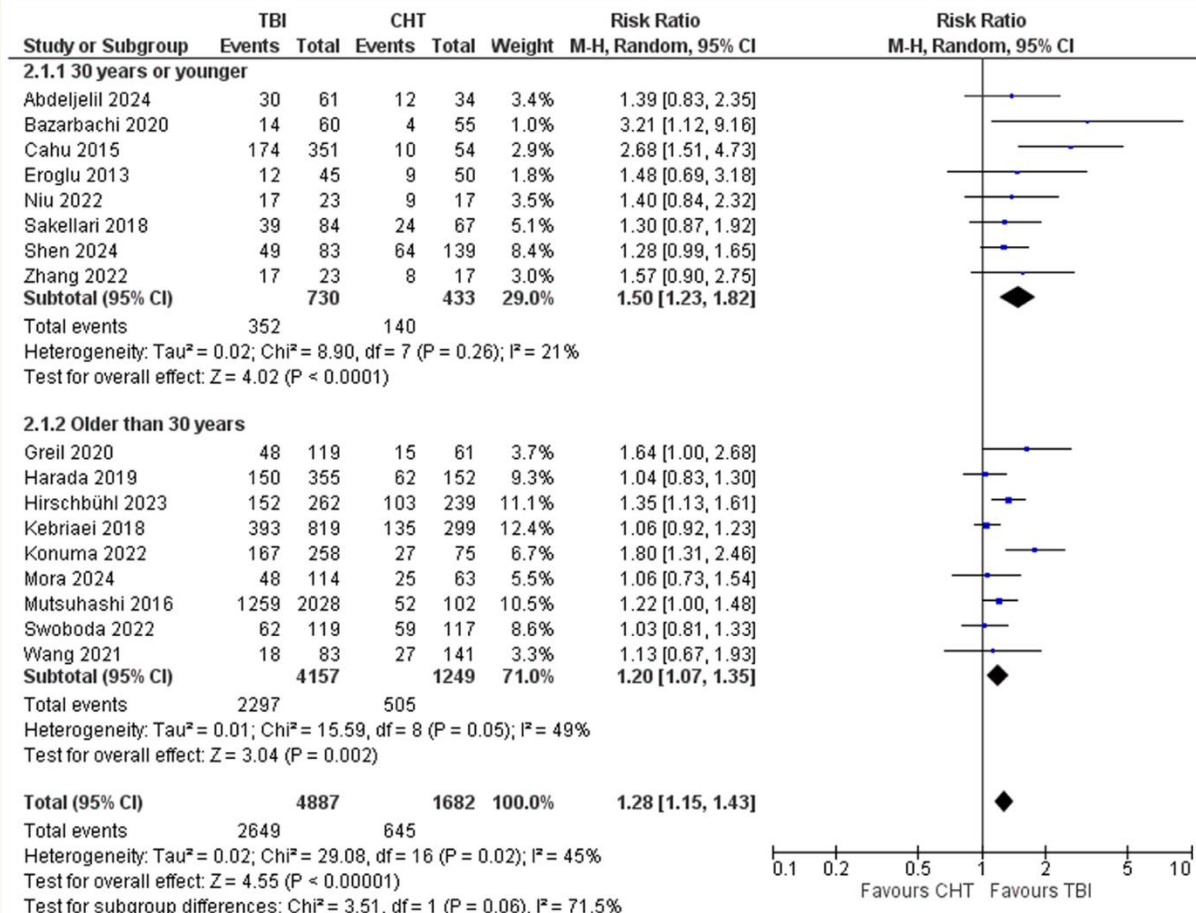
Hirschbühl K et al. BMT. 2023;58:874–880

Adult ALL: can we replace TBI?

Overall Survival



Event-Free Survival



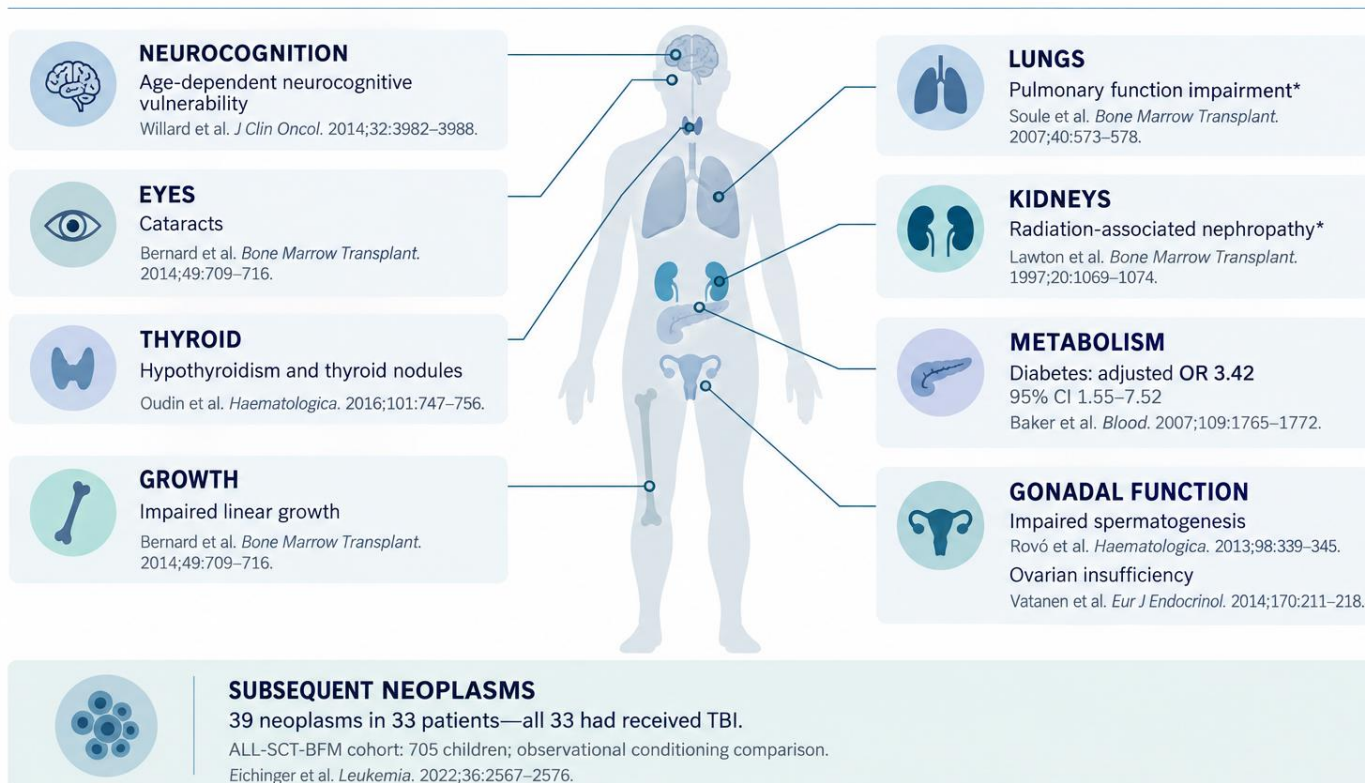
Hasaan Ans et al., 2025

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TBI toxicity: beyond early mortality



Selected cohorts; estimates are population- and regimen-specific.

*Post-HCT toxicity is multifactorial. Age, dose, fractionation, organ exposure, other treatments and GVHD modify risk.

Late effect	Study population	Key finding
Growth impairment and cataracts	LEA: 240 childhood leukaemia survivors; median follow-up 10.1 years	More late complications after TBI: 3.01 vs 2.35 per survivor; $P=0.03$. Lower odds of growth impairment and cataracts after busulfan. ¹
Impaired spermatogenesis	EBMT: 224 male allo-HCT recipients; median assessment 5.3 years after HCT	Detectable sperm in 18% of TBI recipients; TBI was the strongest predictor of azoospermia. ²
Diabetes mellitus	BMTSS: 1,089 HCT survivors; mean follow-up 8.6 years	TBI exposure associated with diabetes: OR 3.42; 95% CI 1.55–7.52. ³
Subsequent neoplasms	ALL-SCT-BFM: 705 children with ALL; 558 received TBI	39 neoplasms in 33 patients—all TBI-exposed. Whole-cohort cumulative incidence: 2% at 5 years → 13% at 10 years. ⁴

¹ Bernard F et al. *Bone Marrow Transplant.* 2014;49:709–716.

² Rovó A et al. *Haematologica.* 2013;98:339–345.

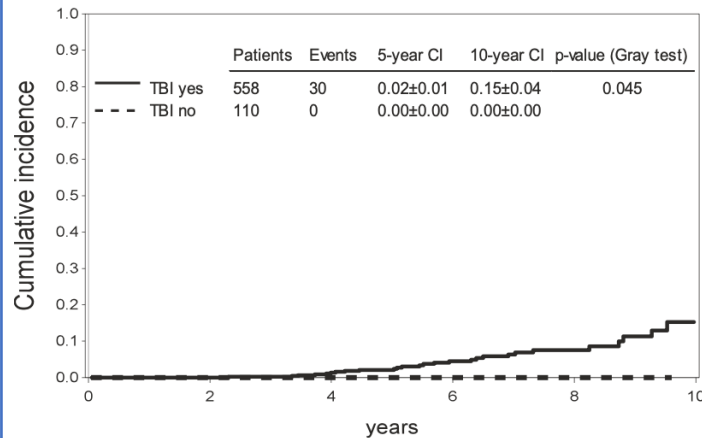
³ Baker KS et al. *Blood.* 2007;109:1765–1772.

⁴ Eichinger A et al. *Leukemia.* 2022;36:2567–2576.

Subsequent neoplasm after TBI

ALL-SCT-BFM 2003 + registry

705 children. 558 TBI 12 Gy / etoposide; 110 chemo; 37 unspecified



at risk (censored)

	0	2	4	6	8	10
TBI yes	558	381 (177)	287 (265)	162 (380)	71 (465)	13 (518)
TBI no	110	58 (52)	36 (74)	16 (94)	5 (105)	2 (108)

- 39 neoplasms in 33 patients; all 33 had received TBI.
- CI SMN TBI group: 5 years= 2%;
10 years: 15%.

Eichinger et al., Leukemia 2022

ALL-SCT-BFM 2003 + FORUM

Type of SM	Total n = 46	TBI n = 45	CHEMO n = 1
Thyroid cancer	18 (39%)	18 (40%)	—
MDS	4 (9%)	4 (9%)	—
Osteosarcoma	4 (9%)	3 (7%)	1 (100%)
Basal cell carcinoma	3 (7%)	3 (7%)	—
Glioblastoma	3 (7%)	3 (7%)	—

Lawitschka et al., ASH 2023.

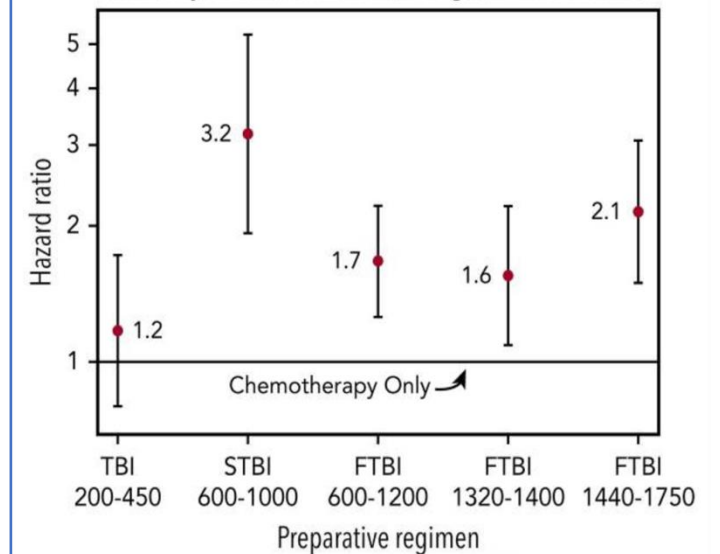
- TBI increases the risk of secondary neoplasms compared with chemotherapy conditioning.
- The magnitude of risk depends on dose and fractionation: highest with non-fractionated or high-dose TBI.
- Risk persists for decades, with a broad spectrum of solid malignancies.

Influence of dose and fractionation

Fred Hutchinson cohort 4,905 long-term survivors (>1y after HSCT)

581 neoplasms in 499 patients

Adjusted hazard ratios for risk of subsequent malignant neoplasms is dependent upon total body irradiation (TBI) dose (cGy) and fractionation (S=single, F=fractionated).



Baker et al. Blood. 2019;133:2790-2799.

Can we omit TBI?

How can we preserve disease control while reducing toxicity?

1) Reduce the dose

- **Yanagisawa et al., 2009:**
Feasibility and early tolerability
- **Komori et al., 2019: Late-effects rationale,** ovarian endocrine function can persist or recover after 8-Gy conditioning,
- **Spyridonidis et al., 2023:**
Retrospective EBMT registry study, no significant association between TBI dose and LFS, relapse, NRM or OS



8-Gy regimen is feasible;
reduced late toxicity is plausible; efficacy requires prospective confirmation

2) Redefine dose distribution

OPTIMISE DELIVERY

IMRT / VMAT / helical tomotherapy

- **Ladbury CL et al., 2022:** long-term OS and RFS preserved despite substantial organ sparing. Lower grade II-IV aGVHD
- **Hui et al., 2024:** VMAT-TBI: lower organ toxicity with no detected loss of disease control

ADAPT THE TARGET VOLUME

TMI / TMLI

- **Stein et al., Lancet Haematology 2026:** 20 Gy can be delivered to marrow/lymphoid targets with clinically acceptable toxicity

3) Optimise the transplant strategy

BEFORE HSCT

- Improve disease control with blinatumomab
Peters et al., 2025

DURING CONDITIONING

- Individualise busulfan exposure
Ben Hassine et al., 2026

AFTER HSCT

- Study relapse prevention immunotherapy
FORUM2 P1 · <2 years, CD19+ B-ALL

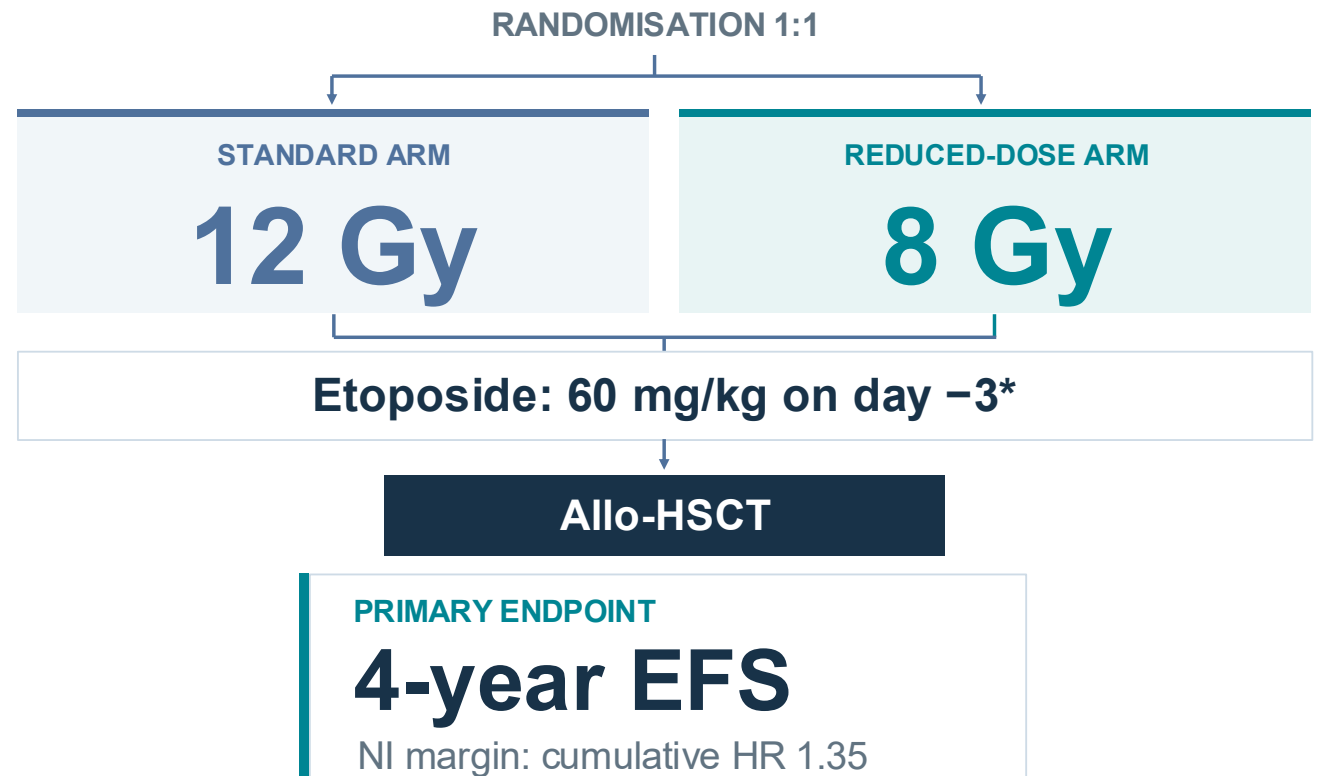
1) Reducing the dose: the FORUM 2 trial

Framework for Optimizing, Refining, and Unifying Management of HSCT in Pediatric ALL

Substudies Overview			
R1	R2	S1	P1
TBI: 8 vs 12Gy Etoposide	FOR-ux	Mismatched Family Donor	Baby FORUM PT-Blina
CR1, CR2, CR3	Treatment-naïve grade II-IV acute GvHD	PT-CY TBI 12 Gy / Eto (or chemo)	Chemo: Flu/Thio/Treo Flu/Thio/Bu
Treatment in pediatric centers participating in FORUM-2	Steroid vs Steroid + Ruxo	or	
	TBI/eto or Flu/Thio/Treo Flu/Thio/Bu	α/β T-cell depletion TBI12/TT/FLU	
Age: 2-25 years	Age: 3 mos-18 years	Age: 3 mos-25 years	Age: 3 mos-2 years
Donor: MD	Donor: MD	Donor: MMFD	Donor: MD, MMD

Phase III randomised non-inferiority trial. Planned enrolment: 1000 pts

ALL in remission . 2-25 years. MSD or 9/10-10/10 MUD



EU CT 2025-522052-13-00

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2) Optimising the volume

Delivery: IMRT, VMAT and helical tomotherapy; **target volume:** TMI and TMLI

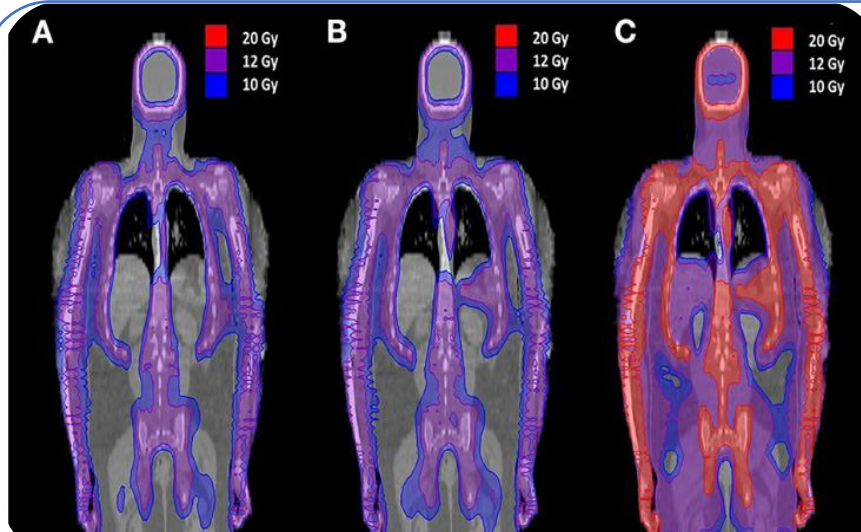
VMAT-TBI

**Matched retrospective cohort:
100 VMAT vs 100 2D-TBI**

Mixed diagnoses, MAC/NMA; median follow-up 14.3 months

	VMAT	2D-TBI	P
Pneumonitis	2%	12%	0.01
Nephrotoxicity	7%	34%	<0.01
1-year OS	86%	83%	0.26

Hui C et al. Front Oncol. 2024



Organ	TBI 12 Gy with lung blocks	TMLI 12 Gy (bone, lymph nodes, spleen, liver, and brain)
Lungs	8.2	4.7
Kidneys	12.0	6.1
Heart	11.1	4.6
Oral Cavity	11.9	2.9
Oesophagus	12.4	3.8
Gasto-Intestinal	12.1	3.7

Hoeben et al., 2021

TMI/TMLI

Goal: spare healthy organs; preserve or selectively intensify target irradiation

Stein A et al. Lancet Haematol. 2026;13 NCT02094794 trial.

R/R AML or ALL

n = 106; 16-60 years, single-centre, single-arm

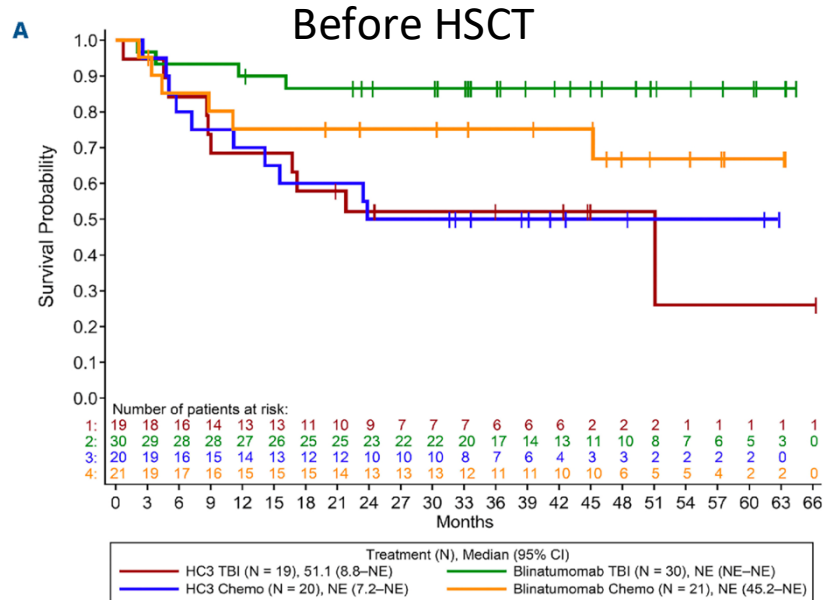
20 Gy TMLI

+ VP16 60 mg/kg + Cy 100 mg/kg

- **Dose escalation with acceptable toxicity to 20 Gy was achievable**
- **2-year PFS: 34%**

3) Can optimising the transplant strategy enable less TBI?

Immunotherapy



Blinatumomab is associated with better post-transplant outcome... irrespective of the conditioning regimen

Peters et al., 2025

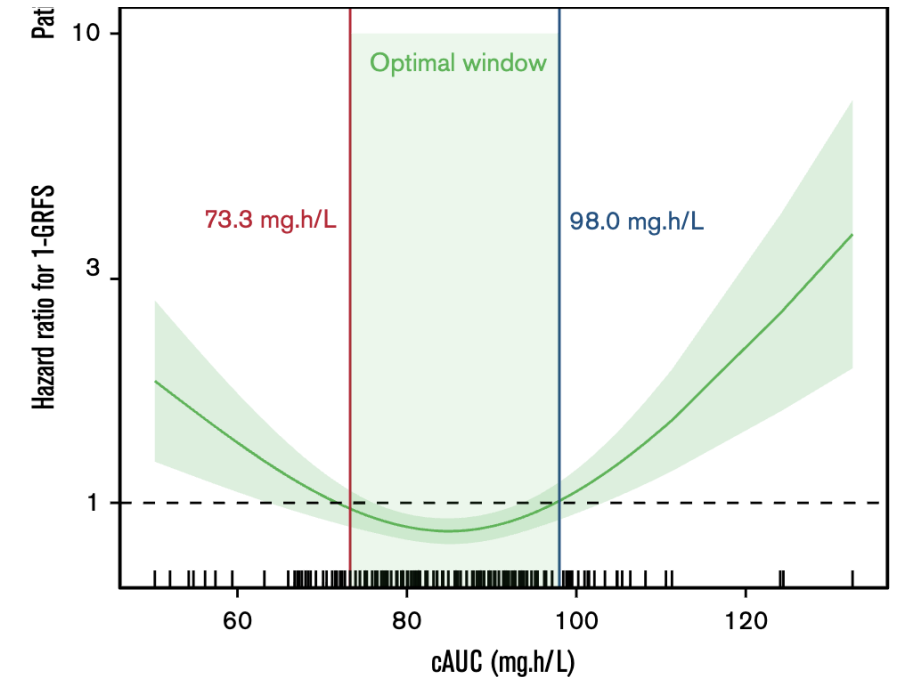
After HSCT

Figure 17-1. P1 substudy treatment plan



<2 years; CD19+ B-ALL; chemo-conditioning.
≤4 blinatumomab cycles from day +60 ±10

Optimise drug exposure



Optimized busulfan exposure (**cAUC 73.3–98.0 mg·h/L**): better EFS/GRFS; the exploratory matched comparison with TBI does not establish equivalence

Ben Hassine et al., 2026

Udine, 8-9 Ottobre 2026

Conclusions

- **TBI remains a reference conditioning strategy in ALL**, with the strongest evidence supporting superior relapse control and, in children/AYA, improved survival.
- **Its benefit is not universal or identical across all patients**, particularly in adults; age, disease risk, comorbidity and the alternative conditioning regimen all influence the net benefit.
- **Long-term toxicity remains the major trade-off**, especially endocrine/gonadal damage, growth impairment, cataracts and subsequent malignancies.
- **The future is likely to be TBI optimisation rather than simple omission**: lower doses, conformal delivery, selective target volumes, and stronger peri-transplant antileukaemic strategies.



Grazie per l'attenzione!