

The conditioning platform in lymphoid diseases

TBI, chemotherapy and beyond: from ALL to lymphoma



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Disclosures

Francesco Saraceni has the following relationships to disclose:

Company	Advisory board	Travel grants
Medac	✓	✓
Sanofi	—	✓
Sobi	✓	—

Open issues in conditioning for lymphoid malignancies

1

Why is lymphoid disease different?

Radiosensitivity, sanctuary sites, peculiar graft-versus-ALL/lymphoma effect

2

ALL: is TBI still the gold standard – and for whom?

Myeloablative TBI vs chemotherapy, TBI dose, MRD

3

Lymphoma: does intensity really matter?

Reduced intensity, non-myeloablative and low-dose TBI platforms

4

What's next?

MRD-guided de-escalation, TBI-sparing regimens, targeted irradiation

Why is lymphoid disease different?



Radiosensitivity

Lymphoblasts and lymphocytes are highly radiosensitive: TBI has been the historical backbone of ALL conditioning



Sanctuary sites

CNS and testis: TBI does not depend on drug penetration. Chemo alternatives must cross the blood–brain barrier (thiotepa, busulfan)



GVL gradient

Graft-versus-lymphoma is strong in indolent lymphoma/MCL, weaker in aggressive lymphoma and ALL



Measurable disease

MRD in ALL and PET status in lymphoma modulate the intensity we need

Indolent lymphoma / MCL → Aggressive lymphoma → ALL *decreasing GVL • increasing need for intensity*

1. ALL: how much intensity (TBI) do we need? 2. Lymphoma: how little intensity can we afford?

Conditioning regimen - the dilemma of dose intensity

The conditioning intensity axiom:

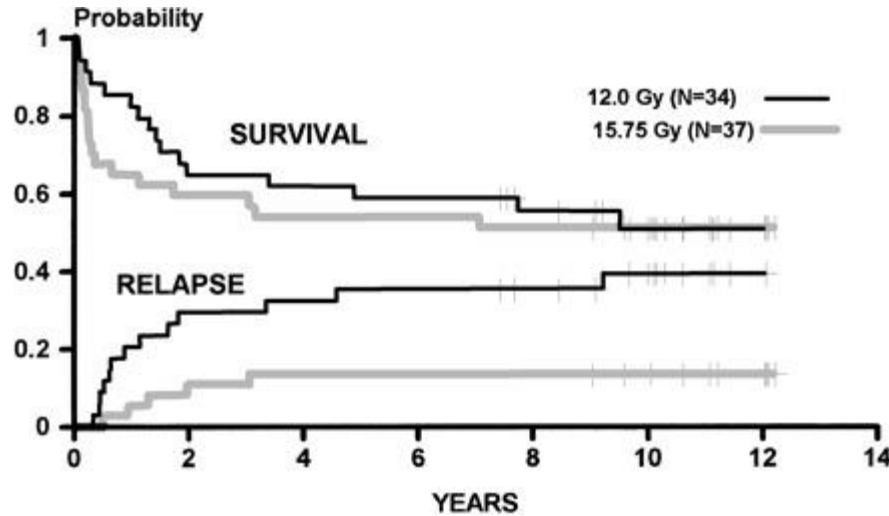
- Reduced intensity results in reduced non-relapse mortality (NRM)
- Increased intensity results in reduced relapse (REL)
- NRM and REL are inversely proportional
- Survival depends on the sum of the competing factors NRM + REL

The survival equation:

$$\text{OS} = 1 - (\text{NRM} + \text{REL})$$

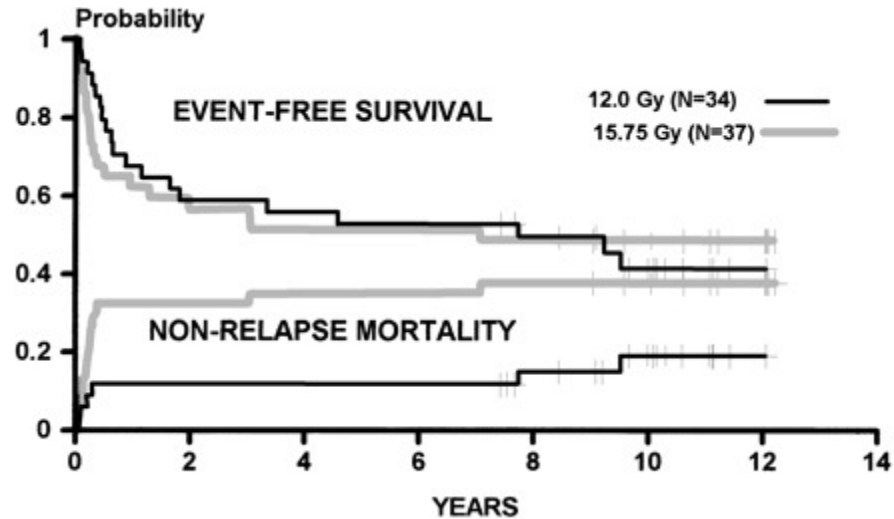
$$\text{NRM} * \text{REL} = k$$

The dilemma of dose intensity – a paradigmatic example



TBI 15.75 Gy

$$\begin{aligned} \text{OS} &= 1 - (\text{NRM} + \text{REL}) \\ &= 1 - (0.4 + 0.1) \\ &= 1 - 0.5 \\ &= 0.5 \end{aligned}$$



TBI 12 Gy

$$\begin{aligned} \text{OS} &= 1 - (\text{NRM} + \text{REL}) \\ &= 1 - (0.1 + 0.4) \\ &= 1 - 0.5 \\ &= 0.5 \end{aligned}$$

Different intensity: similar survival
(TBI: identical survival may hide a quite different quality of life)

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ALL: TBI as the myeloablative standard

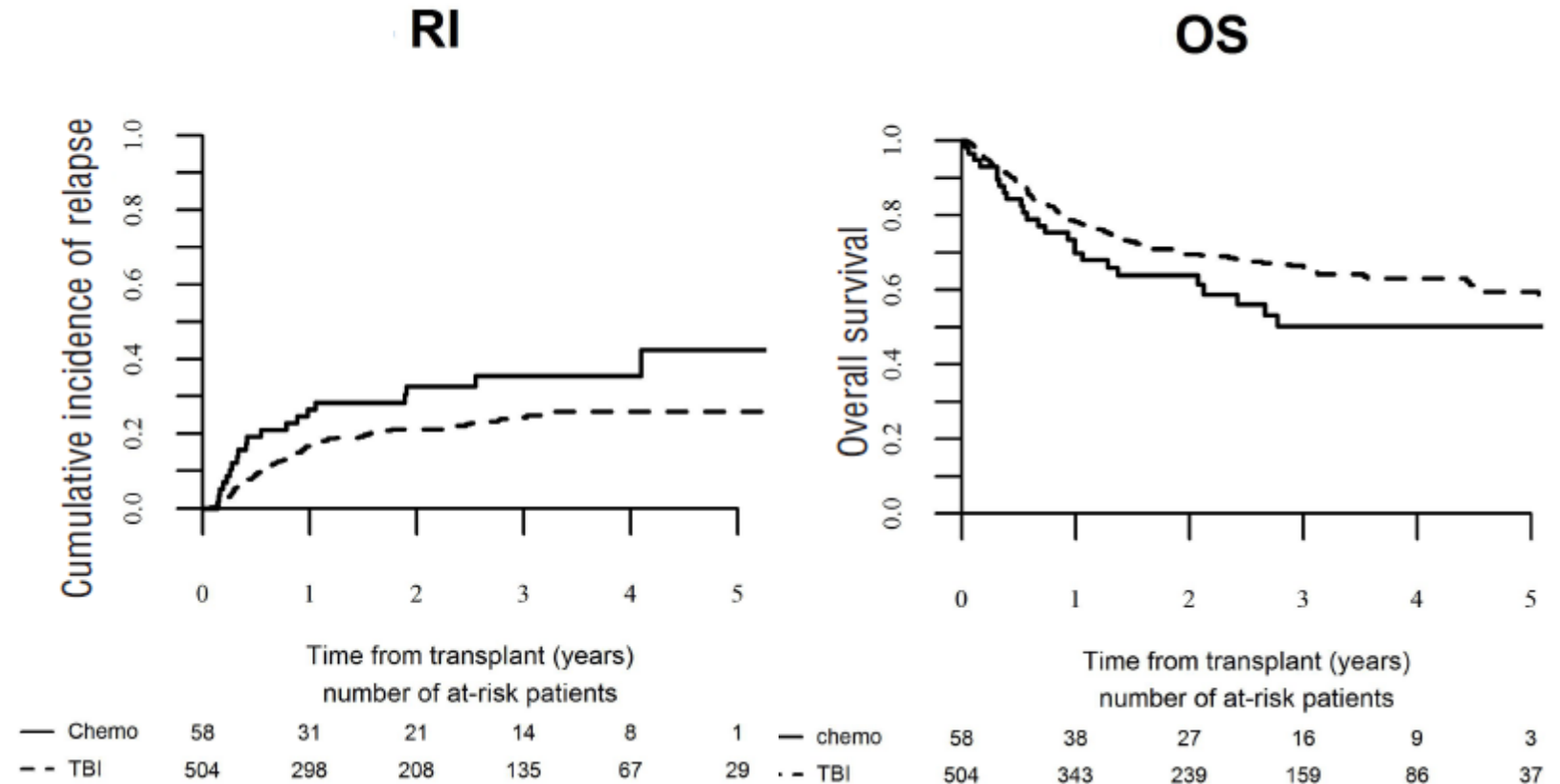
ALWP/EBMT pivotal data

- 4859 adults, ALL in CR1
- MSD/MUD · curves: 2008–12, TBI 504 vs chemo 58
- TBI vs chemo-based conditioning
- 1993–2007 vs 2008–2012:
NRM and relapse decreased over time

Lower Relapse with TBI-based MAC (2008–2012, HR 0.48
p=0.004)

Higher LFS (p=0.02)

OS trend favours TBI (p=0.14)



TBI-based MAC (12 Gy): the preferable myeloablative regimen for adult, fit ALL patients

Which partner for TBI?

ALWP/EBMT registry

- 2255 adults, CR1 83% / CR2, 2010–2020
- TBI 12 Gy + Cy (n=2105) vs + Flu (n=150)
- MSD/MUD, no haplo
- Matched-pair analysis: 132 vs 132

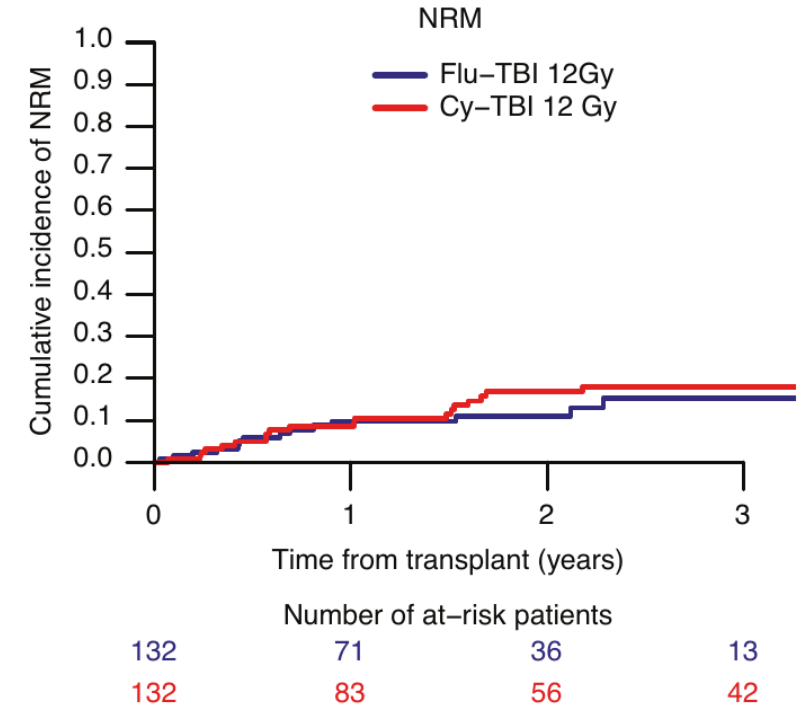
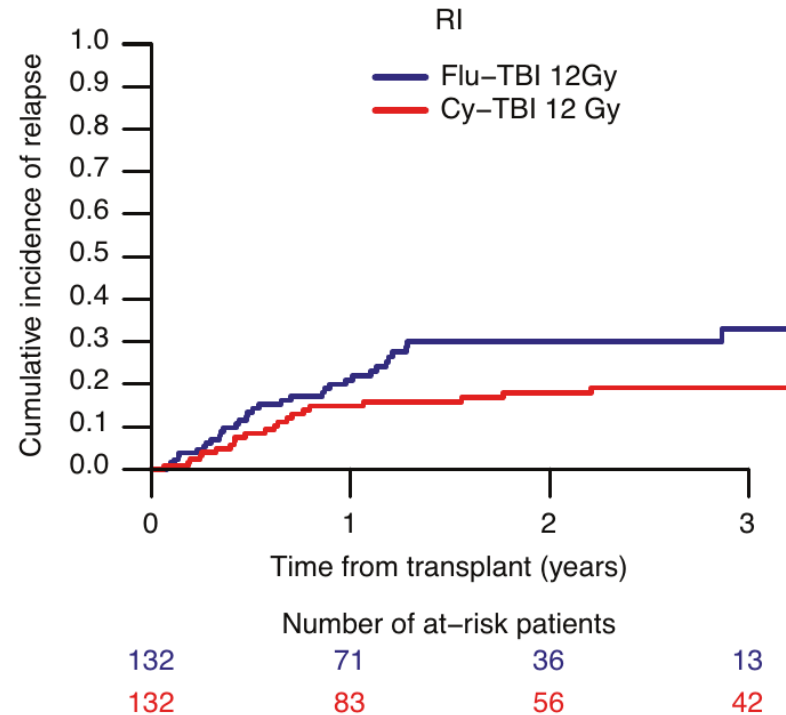
Lower relapse with TBI/Cy, matched pairs
(2-y 18% vs 30%, HR 0.5, $p=0.015$)

Similar NRM 17% vs 11% ($p=0.69$)

LFS 65% vs 59% · OS 73% vs 68% (NS)

Whole cohort: RI HR 0.69 ($p=0.049$)

More aGVHD 2–4 with Cy (HR 1.57)



TBI/Cy remains the reference backbone in fit patients: Flu costs relapses without sparing toxicity

The young, T-ALL case: TBI best playground

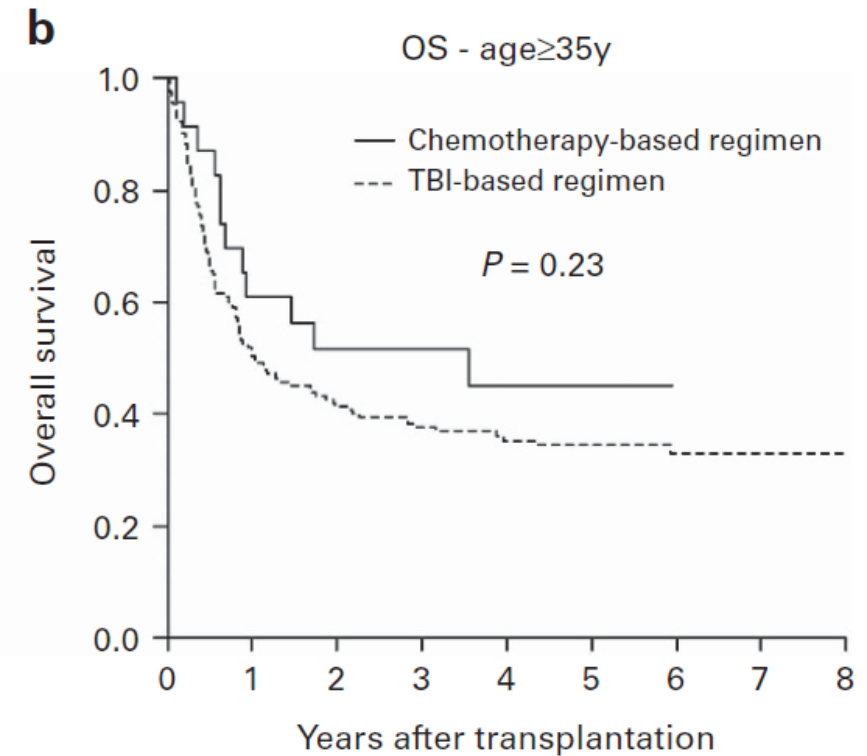
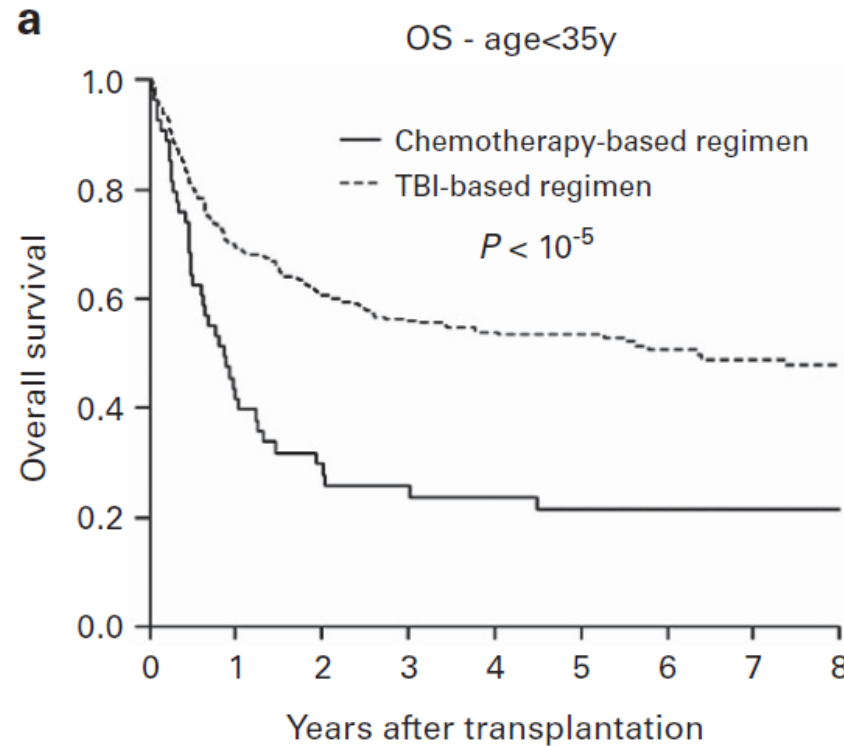
ALWP/EBMT registry

- 601 adults with T-ALL, MAC allo-SCT
- CR1 69% · CR2 15% · advanced 16%
- TBI (n=523) vs chemo (n=78)
- Chemo: Bu IV/Cy in 46 of 78
- Median age 30 y, follow-up 58 months

Lower relapse with TBI
(multivariable, $p=0.0002$)

<35 y: relapse 30% vs 60%
<35 y: NRM 21% vs 22% (NS)
LFS HR 0.55

Higher OS with TBI only in patients <35 y
≥35 y: NRM 38% vs 9% with TBI
($p=0.01$)



TBI for young adults with T-ALL; from 35 y onwards the relapse gain is lost to NRM

Sanctuary sites: TBI as the only possible weapon

ALWP/EBMT registry

- 547 adults with ALL in CR1, 2009–2019
- .CNS+ at diagnosis (n=96) vs CNS–
- CNS+: younger (31 vs 40 y)
- MAC in 82–86%

Higher LFS with TBI-MAC in CNS+ patients

(multivariable, HR 0.43, p=0.01)

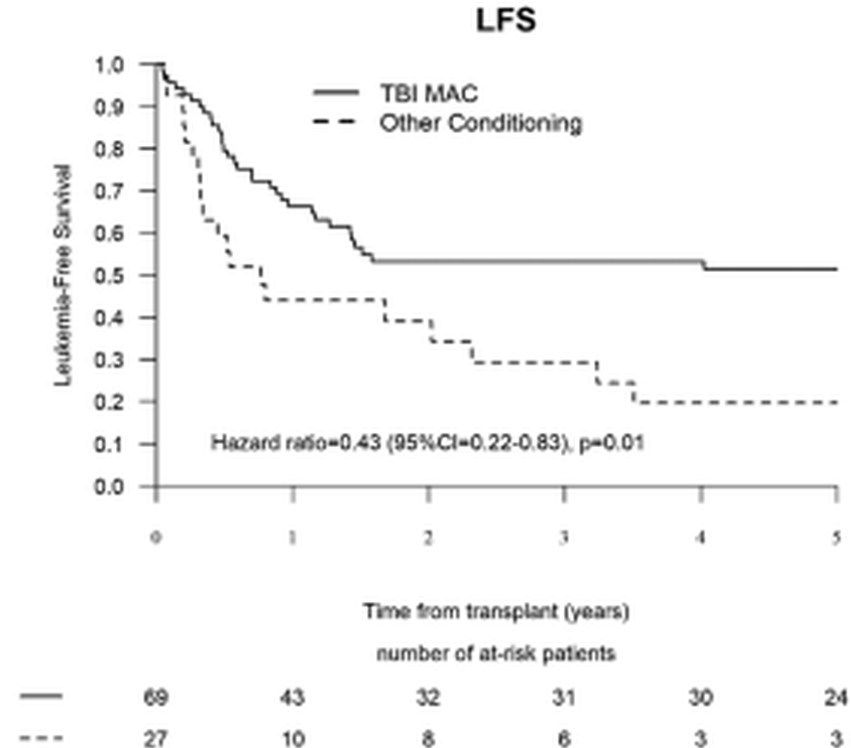
CNS+: relapse HR 0.35 with TBI

CNS+ vs CNS–: relapse HR 1.58

Ph– ALL: CNS relapse HR 0.12¹

CNS–: less relapse, no LFS/OS gain

CNS+ patients only



CNS-positive ALL: a strong indication for TBI-based myeloablative conditioning

Same sanctuary, different biology: CNS+ ALL vs CNS+ AML

TBI- vs chemotherapy-based conditioning · CNS involvement at diagnosis · allo-HCT in CR1

ALL, CNS+

ALWP/EBMT registry · n=96 (of 547)

TBI-based MAC: better outcomes

LFS: HR 0.43 (p=0.01)

Relapse: HR 0.35

OS: HR 0.44

CNS relapse (Ph-): HR 0.12¹

Kharfan-Dabaja, HemaSphere 2022

AML, CNS+

ALWP/EBMT registry · n=278, propensity-matched

TBI (n=96) vs chemo (n=182): no gain

2-y LFS: 57% vs 64% (HR 1.03, p=0.85)

Relapse: 26% vs 24% (HR 0.99)

OS: 62% vs 70% (HR 1.14, p=0.50)

Price: more cGVHD, 44% vs 33% (HR 1.69, p=0.02)

Wang, Saraceni, Brissot et al., ASH 2026 oral presentation

TBI is a good weapon for the radiosensitive lymphoblast, not for the sanctuary per se

The price of TBI: expected late effects

Second cancers

17% vs 3%

Breast cancer after allo-HCT, TBI vs no TBI (median latency 12.5 y)

Gonads

~100%

Ovarian failure in females ≥ 13 y after fractionated TBI

Eyes

60% vs 7%

10-y cataracts: single-dose TBI vs >6 fractions

Thyroid

~30%

Overt hypothyroidism in long-term follow-up

Brain

$>40\%$

Persisting neurocognitive deficits at 5 y; TBI a key risk factor

Metabolism

2×

Diabetes and dyslipidemia vs general population; TBI raises the risk

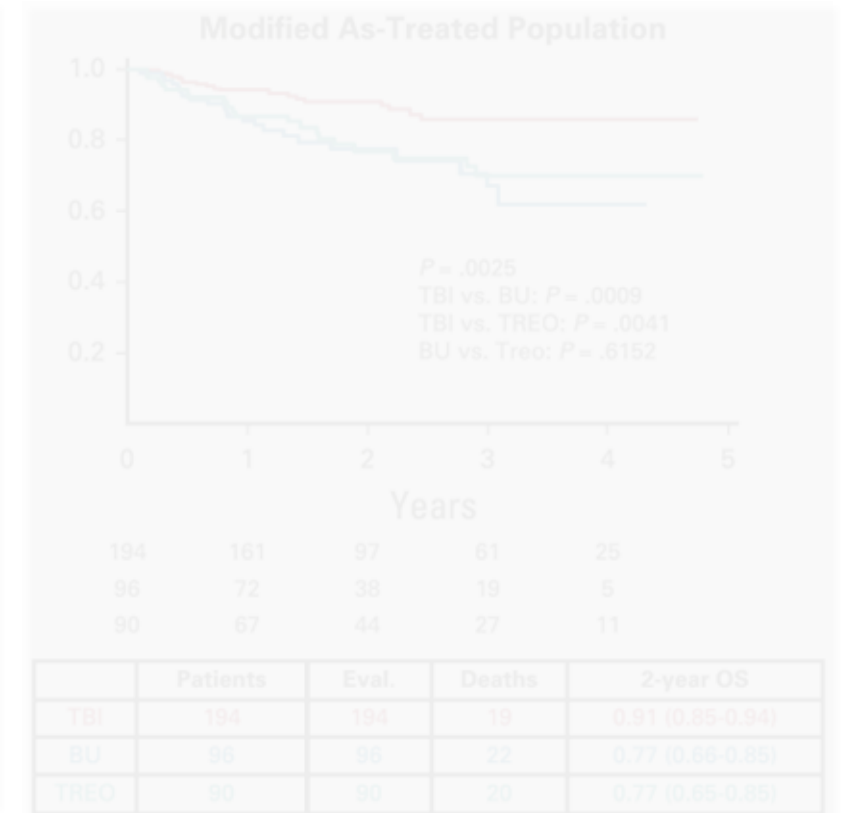
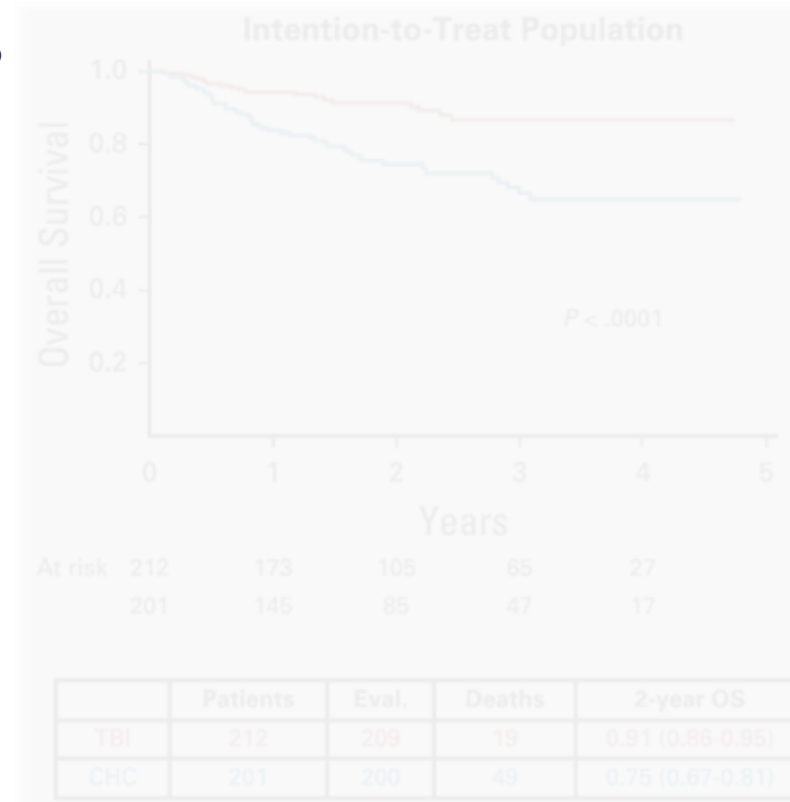
Also: interstitial pneumonitis, renal dysfunction, osteonecrosis, growth impairment in children

The price of TBI is paid by healthy organs: do we really still need to irradiate the whole body in 2026?

Chemo vs TBI conditioning in children: the FORUM randomized trial

I-BFM / IntReALL / EBMT-PDWP

- Phase III RCT, non-inferiority
- 413 children 4–21 y, CR1/CR2+
- **TBI 12 Gy + VP16 vs**
Flu/Thio + Bu or Treo



NO SPOILER! the results are 1 talk away, same channel, in 15 minutes, stay tuned

Chemo vs TBI conditioning in adults: the chinese randomized trial

Chinese phase III RCT

- 13 centers, non-inferiority
- .545 adults 14–65 y (median 26)
- .Standard-risk B-ALL, CR1
- . BuCy vs TBI 9 Gy (4.5 Gy × 2)/Cy
- MSD/MUD, PBSC grafts

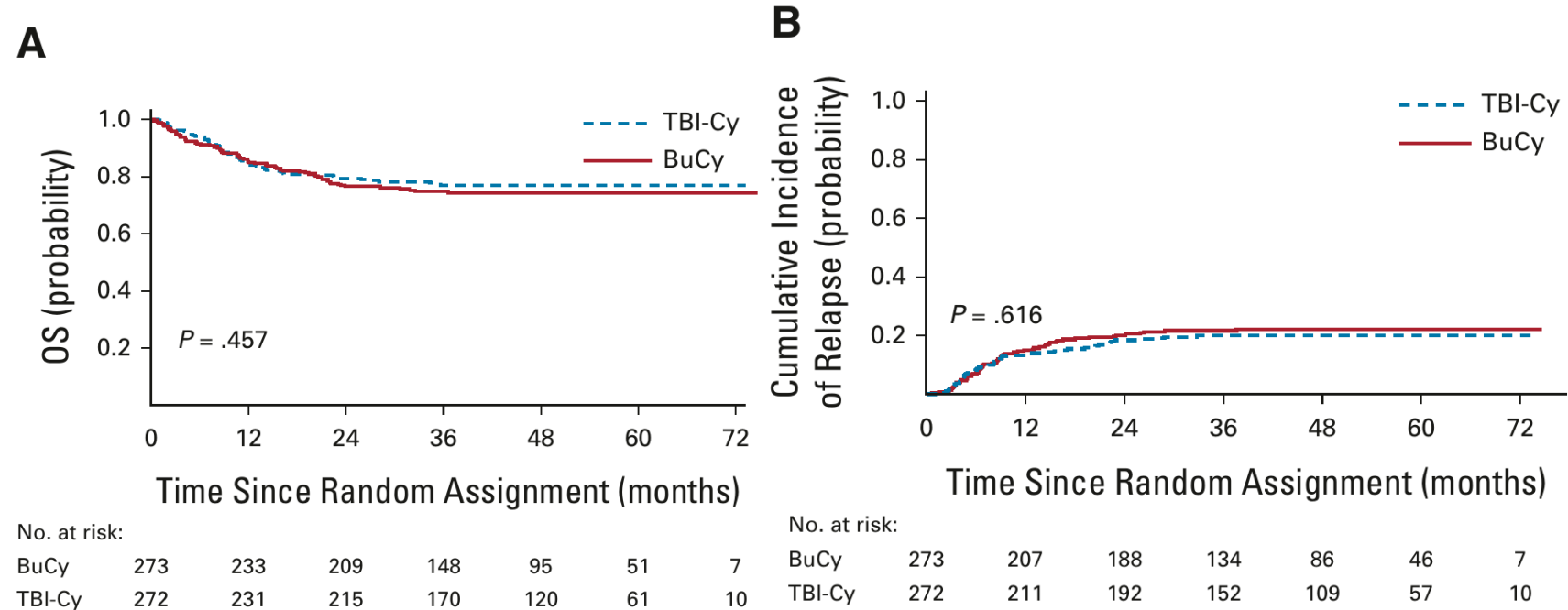
Similar OS

2-y OS 76.6% vs 79.4%
(non-inferiority $p=0.022$)

Relapse 20.2% vs 18.4% ($p=0.62$)

NRM 11.0% vs 11.0% ($p=0.99$)

DFS 68.9% vs 70.6% ($p=0.64$)



BuCy non-inferior – but vs TBI 9 Gy, in standard-risk, mostly MRD– adults

Chemo vs TBI in adults – retrospective data: Thiotepea-based regimens

GETH (Spanish multicenter)

- 177 adults, MAC allo-HSCT, 2002–2018
- TBI 12–13 Gy + Cy/Flu (n=114)
vs Thio/Bu + Cy or Flu (TTB, n=63)
- Median follow-up 83 months

Relapse vs NRM = OS (the axiom, again!)

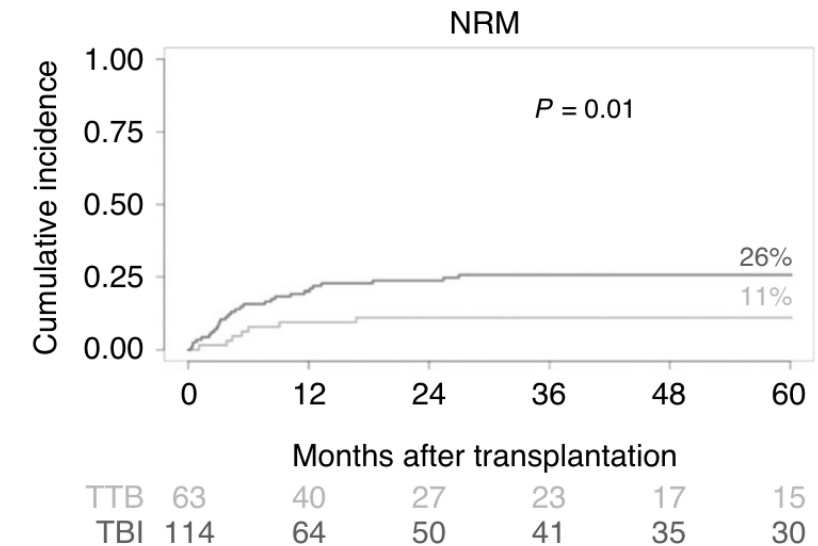
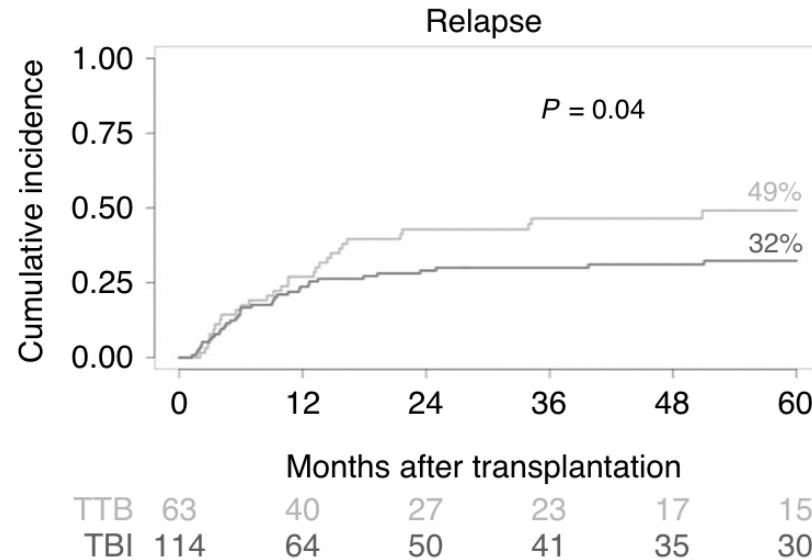
. **Relapse** with TTB vs TBI
(multivariable, $p=0.02$; 5-y 49% vs 32%)

. **NRM 26% vs 11% with TBI (HR 0.24)**

OS 46% vs 44% ($p=0.9$)

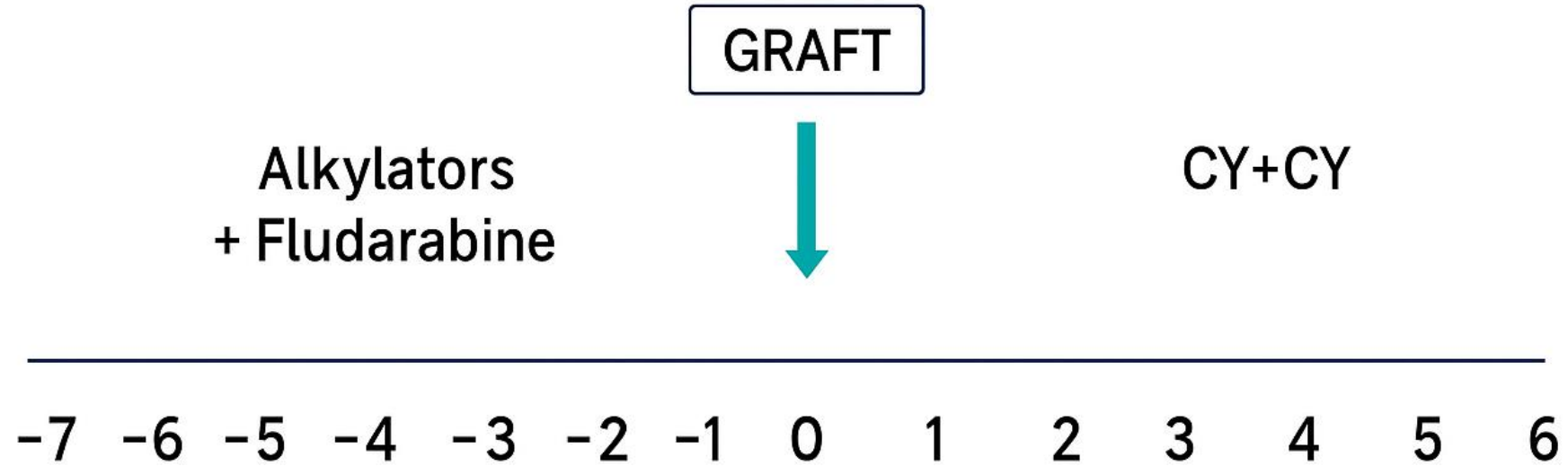
MRD+: relapse 41% vs 65% ($p=0.08$)

More cGVHD with TTB (62% vs 39%)



The axiom again: TBI = less relapse, thiotepea = less NRM, same survival

PTCy: the dose intensity dilemma, episode 2



A novel key player enters the scene: PTCy

If the focus was once all on pre-infusion, now everything starts to revolve around this post-graft infusion alkylating agent

So, we should compromise on what we administer pre-graft

When the Cy is already taken: PTCy haplo transplant, Flu-TBI vs TBF

ALWP/EBMT registry

- .236 adults, haplo-HCT + PTCy, 2010–2018
- .Flu-TBI ≥ 10 Gy (n=117)
vs Thio/Bu/Flu – TBF (n=119)
- .CR1 54%; active disease 10–19%

The axiom again!

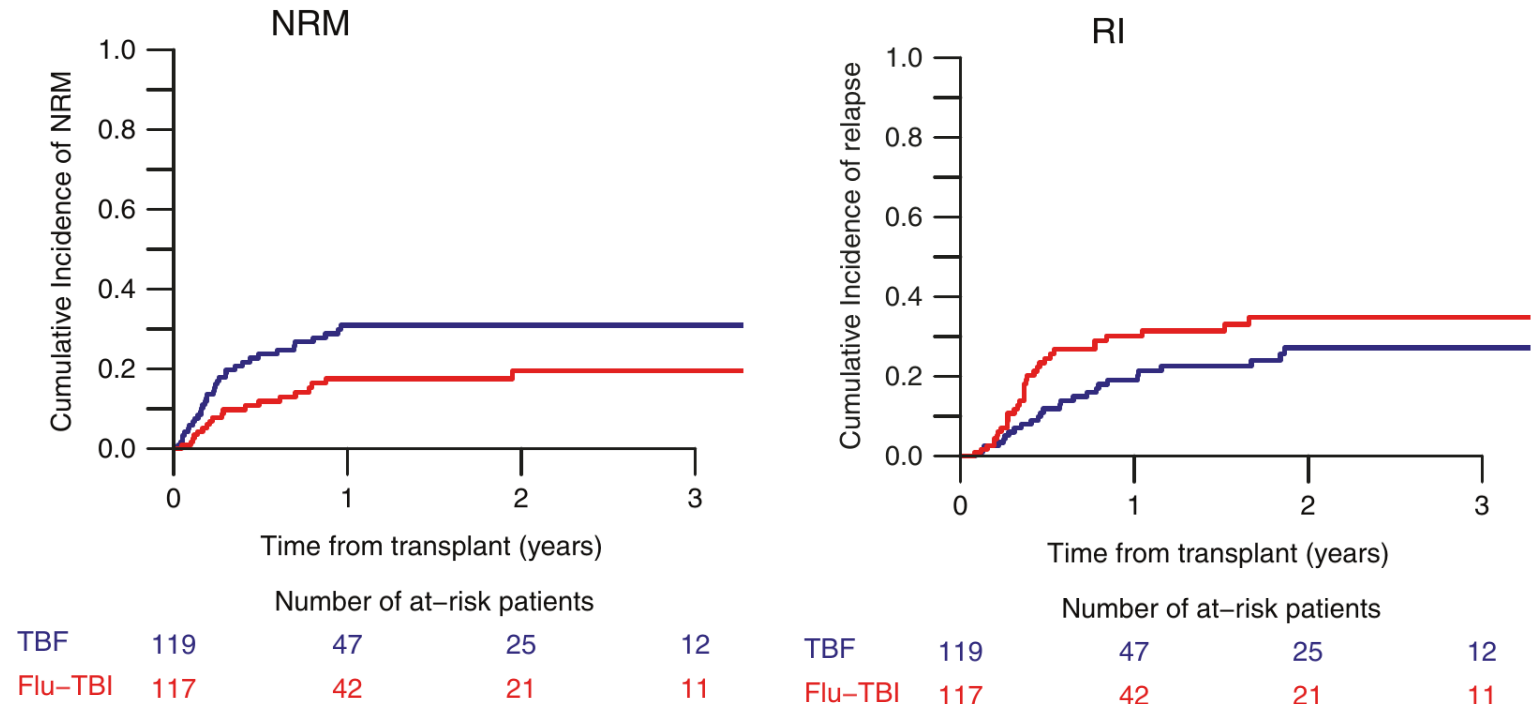
Higher NRM and lower relapse
with Flu-TBI vs TBF
(multivariable, $p=0.035$)

2-y NRM 19.5% vs 31% ($p=0.03$)

2-y relapse 35% vs 27% ($p=0.11$)

CR1/CR2: relapse HR 2.59 with Flu-TBI

2-y OS 54% vs 53% ($p=0.61$)



The axiom again: Flu-TBI = less NRM, TBF = less relapse, same survival. TBF+PTCy: 1+1+1=3 alkylators

TBI is flexible - the dose defines the goal: irradiate wisely

Increasing anti-leukemic effect – and increasing toxicity

≤ 2 Gy

Non-myeloablative

Flu/TBI 2 Gy $\pm$ Cy (PTCy)

Goal: Immunosuppression for engraftment; cure relies on GVL

Setting: Lymphoma, elderly/unfit

In ALL: Not enough: relapse ~40%

4–8 Gy

Intermediate

Flu/TBI 8 Gy

Goal: Anti-leukemic activity with reduced toxicity

Setting: Older/unfit ALL; GMALL standard over 45

Price: NRM ~20–25% in older patients

12 Gy

Myeloablative

6 $\times$ 2 Gy + Cy or VP16

Goal: Myeloablation + maximal anti-leukemic effect

Setting: Young, fit ALL (standard)

Price: Pneumonitis, late effects

Above 12 Gy: Less relapse, more NRM, same OS

TBI can be individualized: different doses, different goals – and different toxicities

Elderly/unfit patients: is 8 Gy enough? TBI 8 vs 12 Gy in CR1

ALWP/EBMT registry

- .639 adults with ALL in CR1, 2009–2020
- .Flu as sole partner of TBI
- .TBI 8 Gy (n=494) vs 12 Gy (n=145)
- 8 Gy: older (56 vs 40 y), more TCD

2-y LFS: 61% vs 62%

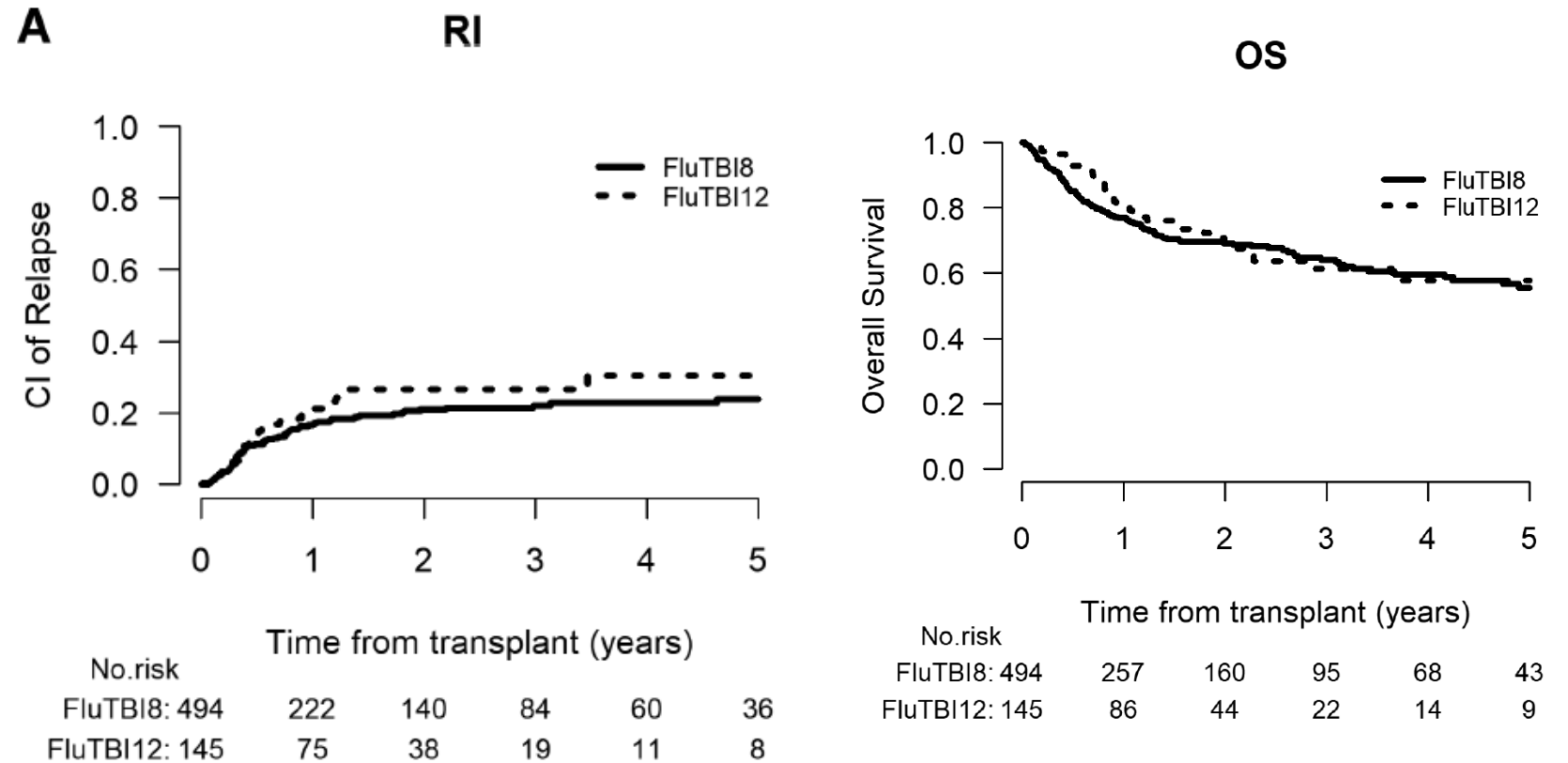
8 vs 12 Gy (p=0.65)
(multivariable HR 1.18, p=0.5)

OS 69% vs 69% (p=0.41)

Relapse 21% vs 27% (p=0.19)

NRM 18% vs 12% (p=0.056)

<55 y: LFS 66% vs 64% (p=0.91)



In CR1, 8 Gy is enough: TBI keeps an edge on relapse even at reduced intensity

Elderly/unfit patients : RIC chemo (busulfan) vs TBI

ALWP/EBMT registry

- .501 adults >45 y, ALL in CR1, 2005–2020
- Intermediate intensity, MSD/MUD
- .Flu/TBI 8 Gy (n=262) vs Flu/Bu
- Bu 6.4 (n=188) or 9.6 mg/kg (n=51)

**Higher relapse with Flu/Bu 6.4
vs Flu/TBI 8 Gy**

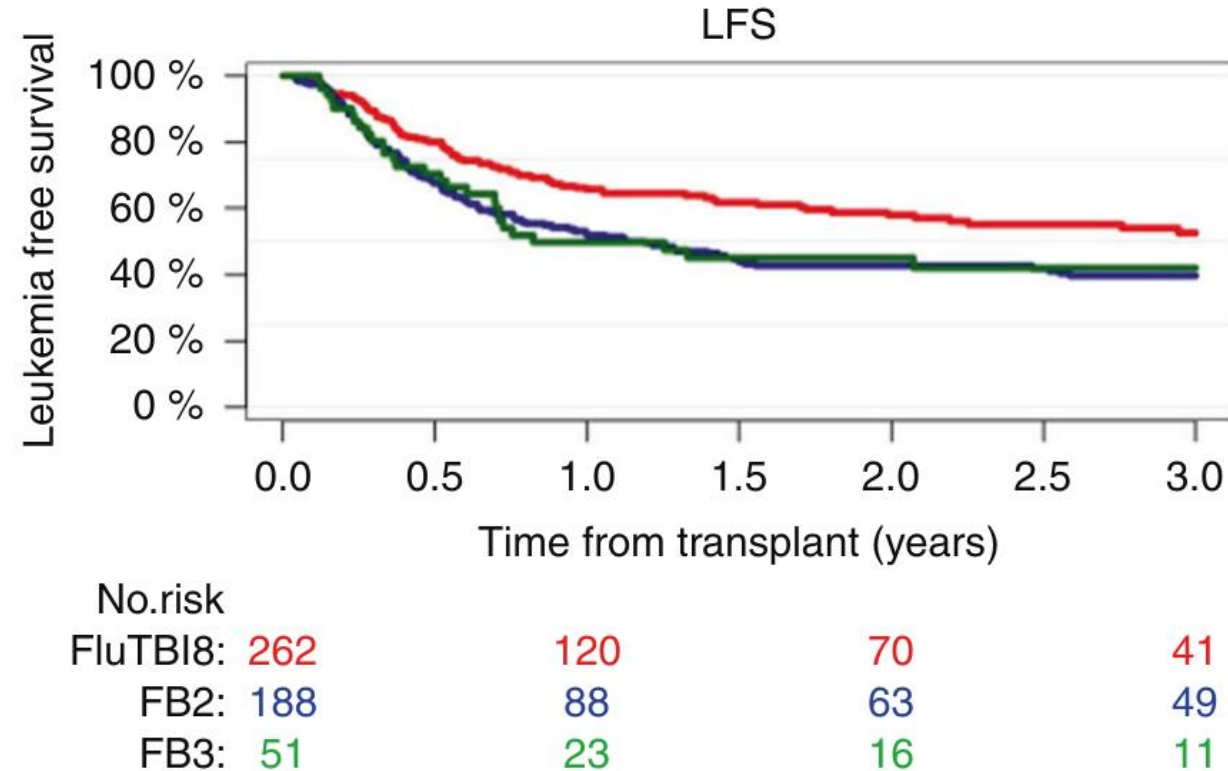
(multivariable, $p=0.01$)

2-y LFS 58% vs 43% vs 45% ($p=0.003$)

LFS HR 1.56 (Bu 6.4) · 1.63 (Bu 9.6)

NRM 17% vs 20% vs 24% ($p=0.38$)

OS 68.5% vs 57% vs 62% ($p=0.06$)



TBI beats chemo#1: Over 45: Flu/TBI 8 Gy beats Flu/Bu on relapse, at no cost in NRM

Elderly/unfit patients: RIC chemo (treosulfan) vs TBI

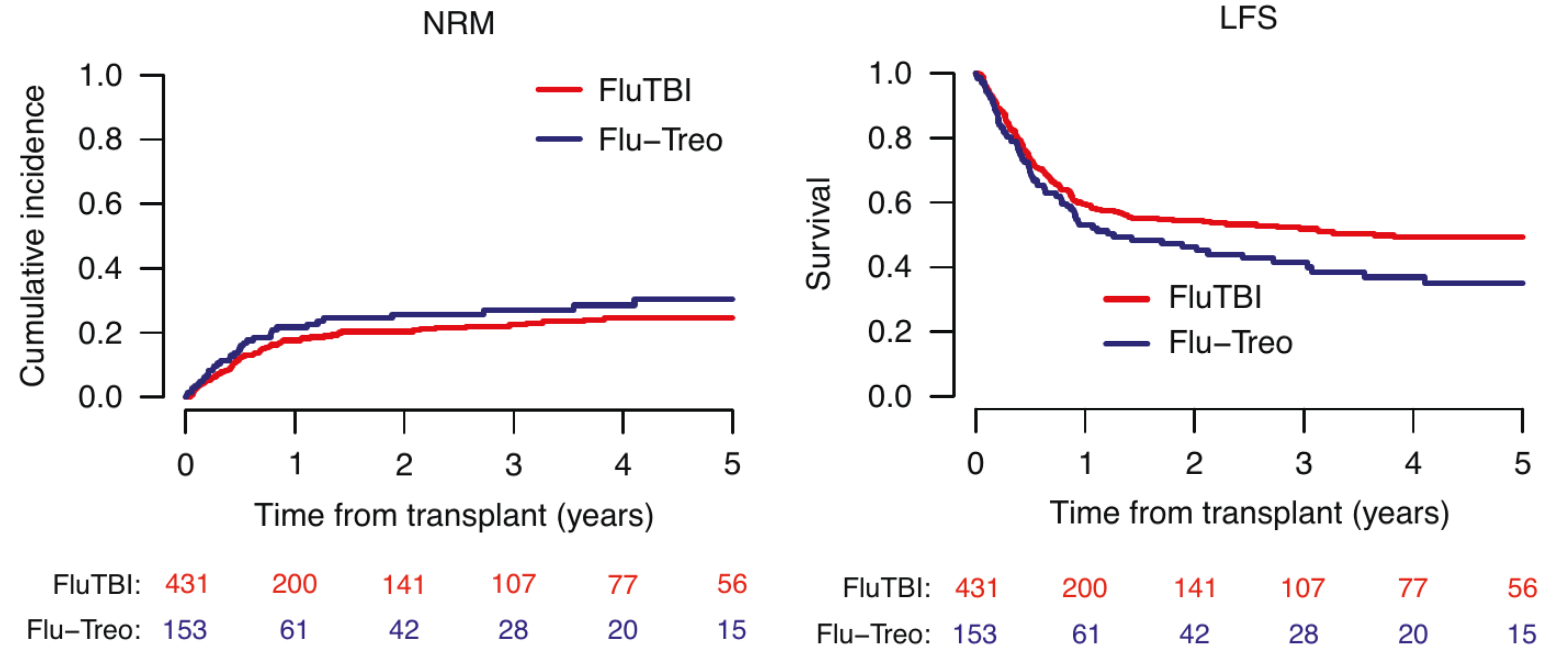
ALWP/EBMT matched-pair analysis

- Adults with ALL in CR1/CR2, 2006–2022
- Flu-Treo 30–42 g/m² (n=153)
- vs Flu-TBI 8–12 Gy (n=431; 8 Gy 67%)
- Median age 56.5 vs 54.1 y

2y LFS: trend in favour of TBI

LFS: Flu-Treo vs Flu-TBI:
2-y 46% vs 55%, p=0.10;

NRM 25.6% vs 20.4% (HR 1.19, NS)
Relapse 28.1% vs 25.1% (HR 1.31, NS)
OS 55% vs 61% (HR 1.19, NS)
No MRD data



TBI “beats” chemo#2: Treosulfan: a valid option when TBI is contraindicated, not yet a replacement

Elderly/unfit patients: RIC chemo (thiotepa) vs TBI

ALWP/EBMT registry

- 265 adults ≥ 40 y, ALL in CR1, 2000–2020
- .RIC thiotepa (n=148; TBI in 88)
vs RIC TBI 4–6 Gy (n=117)
- Median age 59 vs 56 y; Ph+ 55–59%

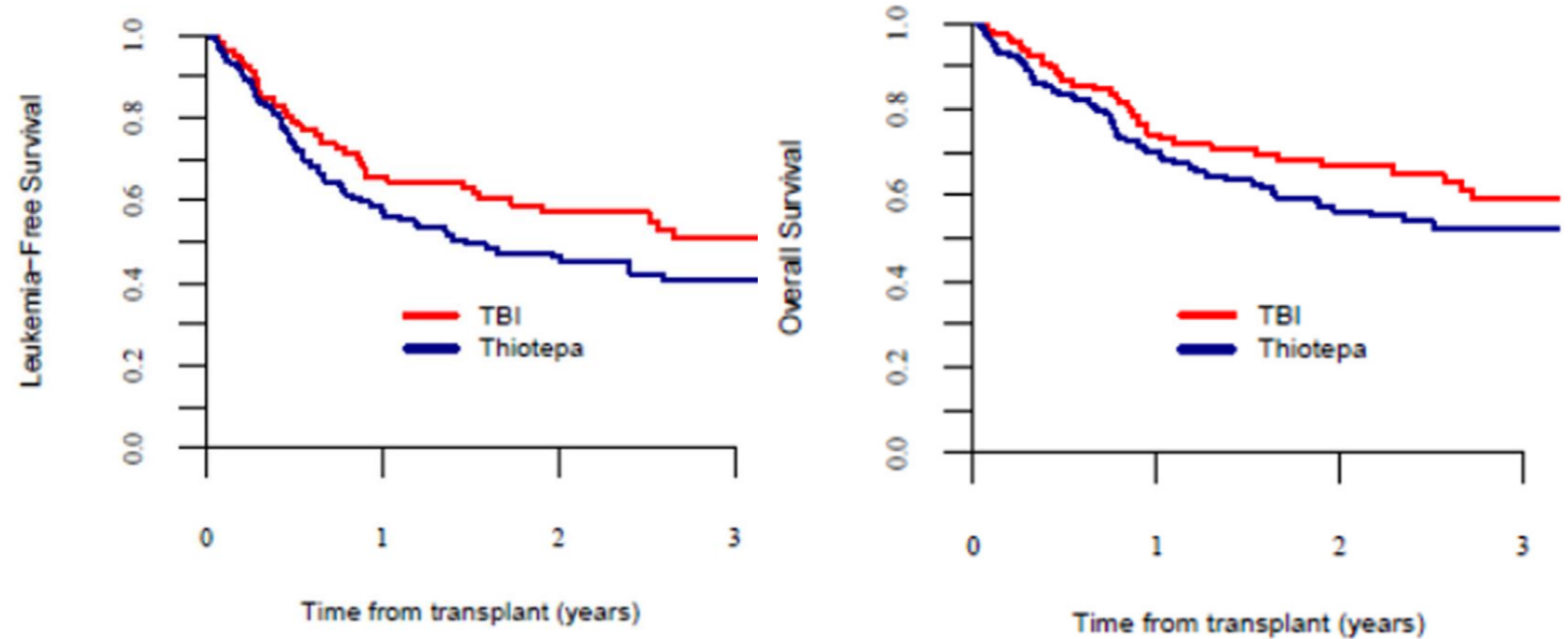
Thio vs TBI: similar LFS
(p=0.28)

2-y LFS 46% vs 57% (p=0.12)

2-y OS 56% vs 67% (p=0.18)

RI 28% vs 23% · NRM 26% vs 20% (NS)

cGVHD higher with TBI (43% vs 29%)



TBI (low dose) equals chemo: Over 40 with RIC: thiotepa is a valid alternative to low-dose TBI

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Non-myeloablative (2 Gy) TBI in lymphoma

CIBMTR registry

- 413 adults with NHL, RIC, 2008–2017
- MSD/MUD donors
- Flu/TBI 2 Gy (n=349) vs 4 Gy (n=64)

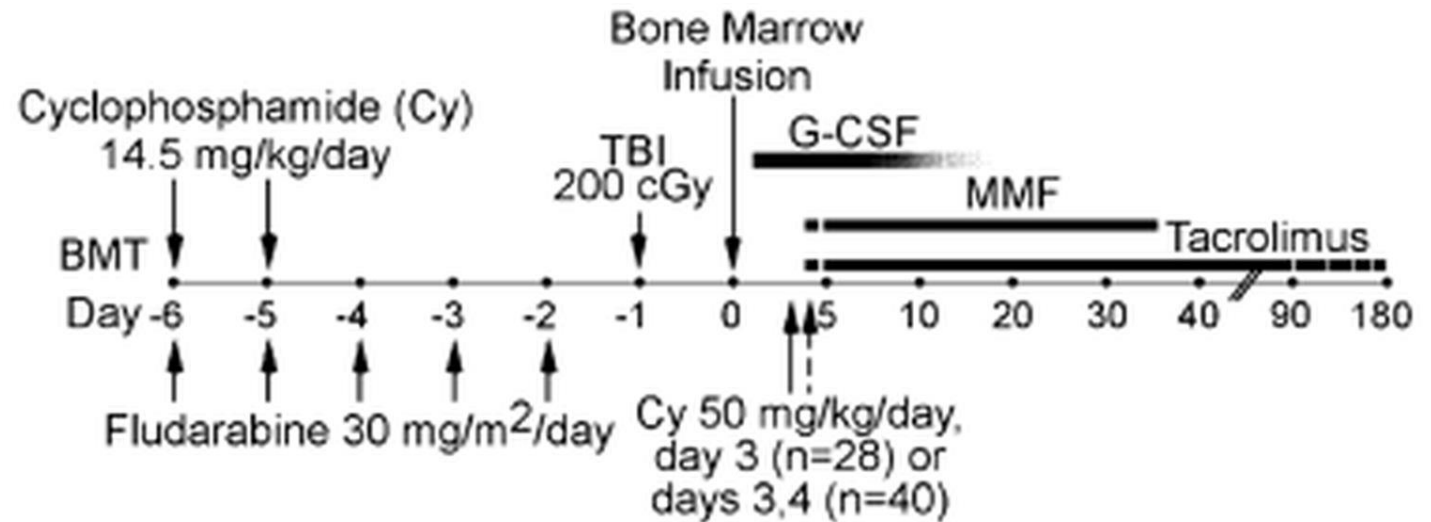
Higher NRM with TBI 4 vs 2 Gy
(multivariable, $p=0.03$)

5-y NRM 47% vs 28% ($p=0.005$)

5-y OS 31% vs 51% ($p=0.001$)

Relapse 29% vs 35% (NS)

Baltimore platform: Flu/Cy/TBI 2 Gy + PTCy



In lymphoma TBI 2 Gy opens the door to engraftment: the graft does the rest

Lymphoma: less is more

CIBMTR registry

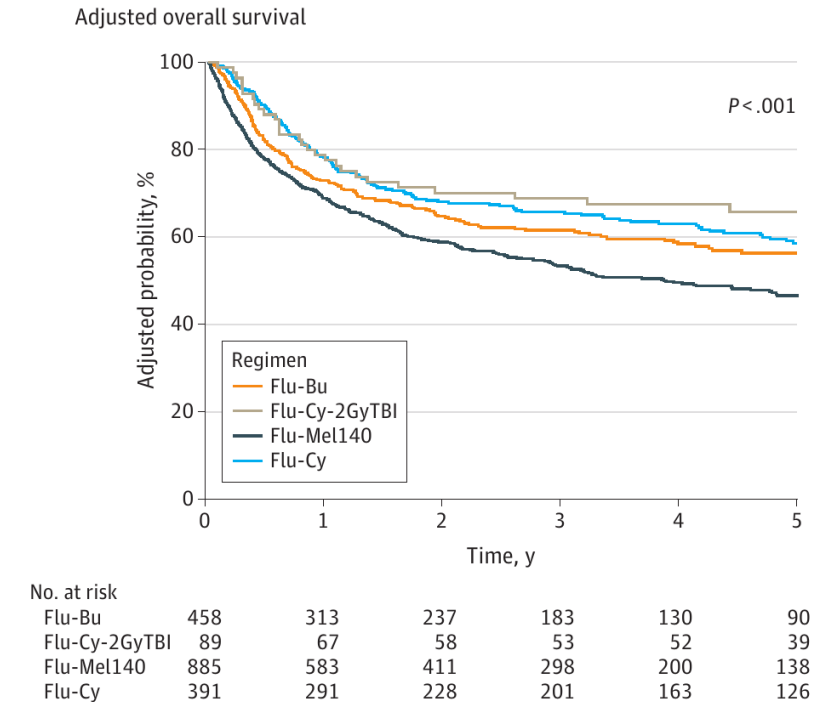
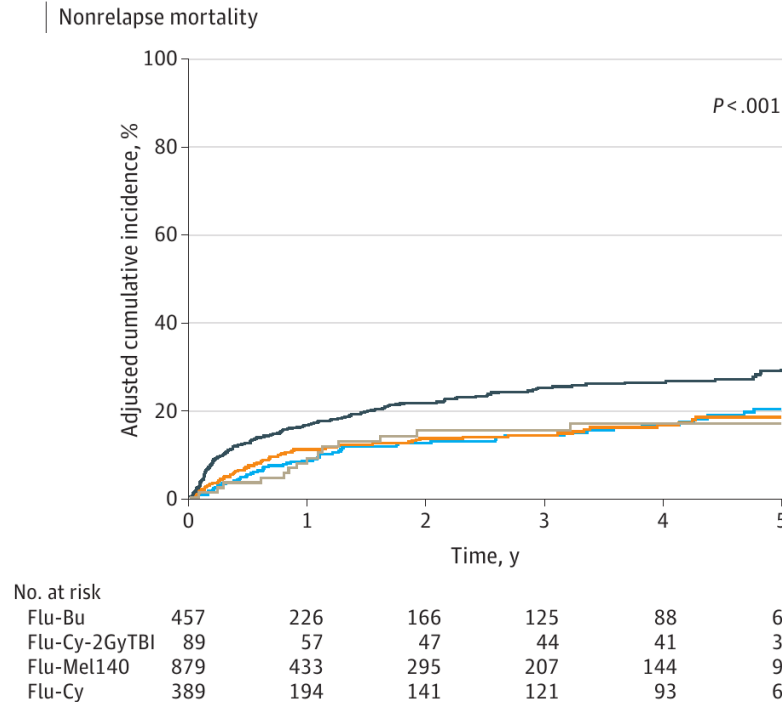
- . 1823 adults with NHL, 2008–2016
- RIC/NMA, MSD/MUD, PBSC
- . Flu-Bu (n=458) · Flu-Mel140 (n=885)
- . Flu-Cy (n=391) · Flu-Cy-TBI 2 Gy (n=89)

Higher mortality with Flu-Mel140 vs Flu-Cy-TBI 2 Gy (HR 1.82, $p < 0.01$)

.Relapse lowest with TBI 2 Gy (33%)

.4-y OS 67% (TBI 2 Gy) vs 49% (Flu-Mel)

4-y NRM 26% with Mel140 vs 16–17%



In lymphoma the axiom is reversed: the graft does the job

Advanced hodgkin lymphoma: the haplo graft does the job, again

Humanitas – Paoli-Calmettes

- .62 advanced HL, haplo + PTCy
- 85% prior HDC; 87% CR/PR at HCT
- .Flu/Cy/TBI 2 Gy (NMA) in 81%, thiotepa-based RIC 19%

3y PFS: 59%

(OS 63%, relapse 21%)

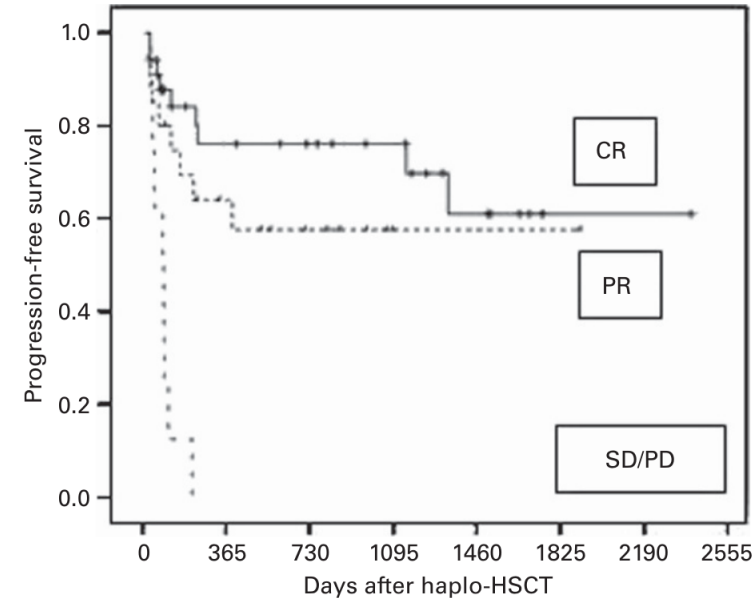
1-y NRM 20% (11% NMA TBI 2 Gy subgroup)

aGVHD III–IV 4%, cGVHD 16%

PBSC protective for OS (HR 0.24)

Update, 91 pts: PBSC vs BM OS HR 0.29¹

PFS by disease status at HCT



3-y PFS 76% · 58% · 0%

Relapse: 8% · 32% · 100%

Minimal conditioning, haploidentical graft: in Hodgkin lymphoma alloreactivity controls the disease

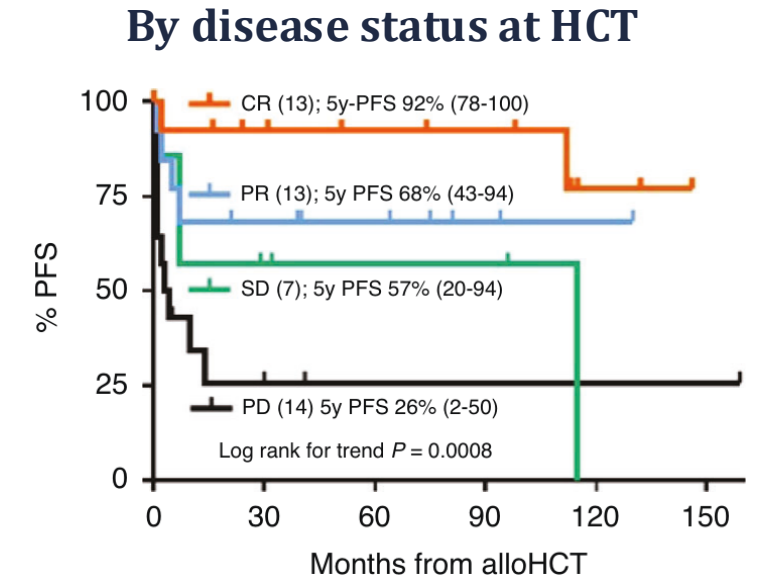
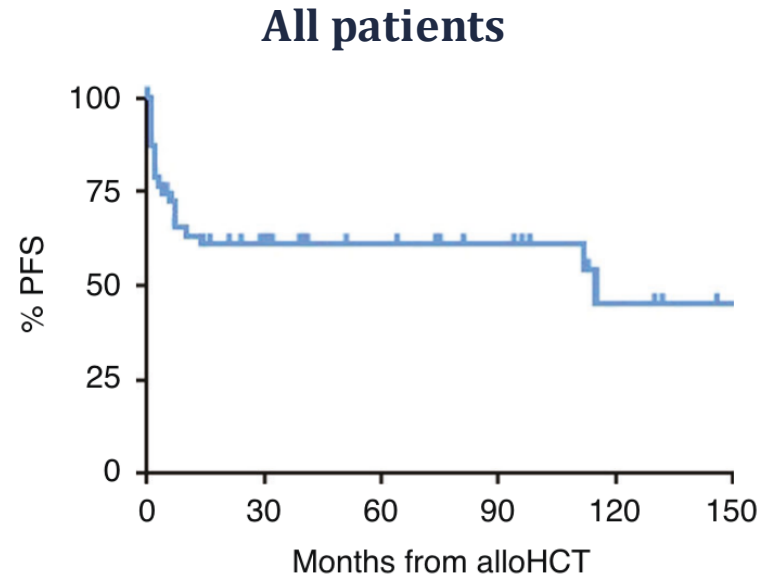
T-cell lymphoma: intermediate TBI is back

Heidelberg single-center

- .47 PTCL, 2010–2023, alloHCT
- .Flu/TBI, 8 Gy in 87%
- 45% chemoresistant at alloHCT
- Median follow-up 5.5 years

5y PFS 61%
(OS 65%)

5-y NRM 15% · relapse 24%
9/11 relapses within 6 months
No relapse after onset of cGVHD
PD at HCT: 5-y PFS 26%



Intermediate TBI bridges to GVL: no relapse after chronic GVHD

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ALL: MRD could change the question: TBI for whom?

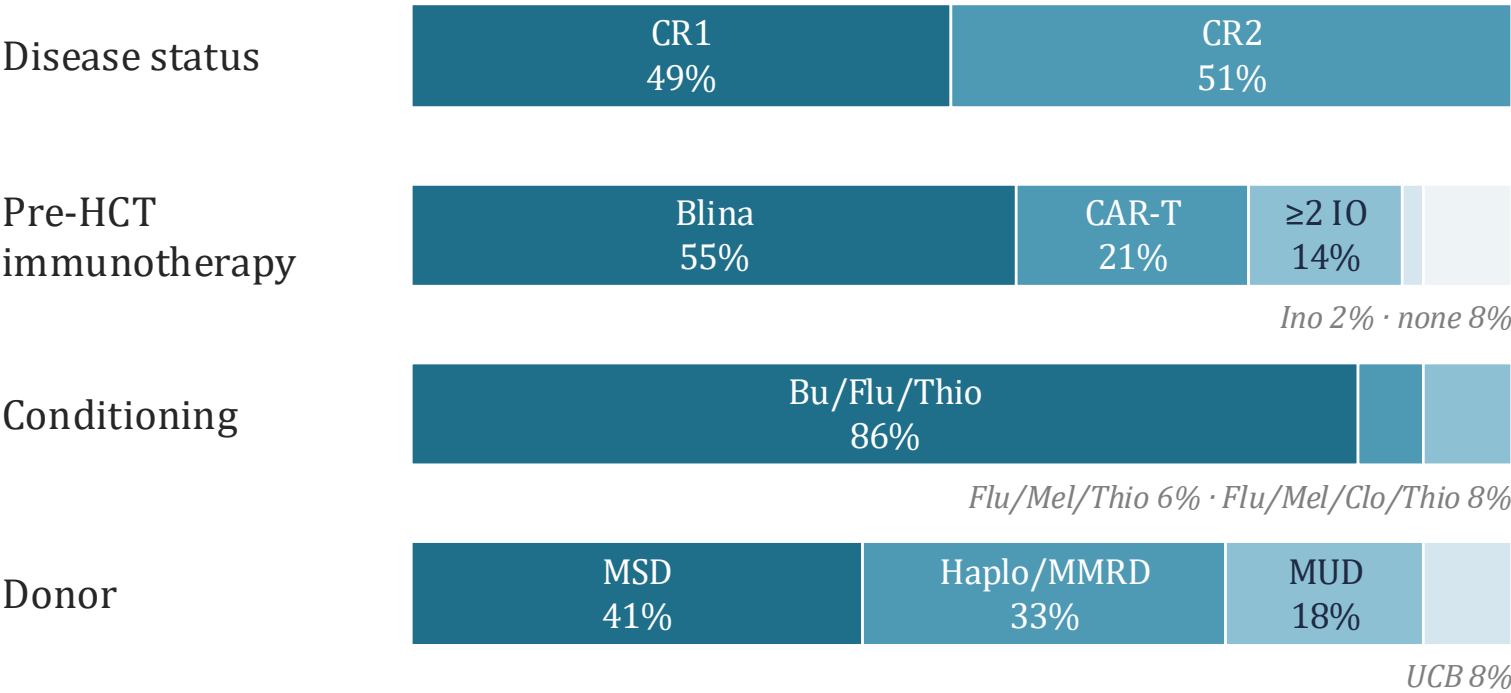
PTCTC phase II (EndRAD)

- .51 children/AYA, 1–31 y (median 13.5)
- .B-ALL in CR1 (49%) or CR2 (51%)
- .NGS-MRD negative before HCT
- Myeloablative, **no TBI** (mostly TBF)

2-y EFS 76%
primary endpoint met (>75%)

OS 82% at 2 years
NRM 12% (4 of 6 aged ≥14 y)
Relapse 6/51 (4 in CR2, 4 after MSD)
Day-100 TRM 2%

Who was transplanted without TBI



aGVHD 39% (III–IV 10%) · cGVHD 25% · BCR–/TCR+ in 5 patients: all alive, relapse-free

From "TBI for all" to "TBI for those who need it": MRD as the compass?

Irradiate smarter: TMLI

City of Hope (Duarte)

- >500 patients treated with TMI/TMLI
- IMRT on bone, nodes and spleen
- Spares lungs, liver, gut, lenses

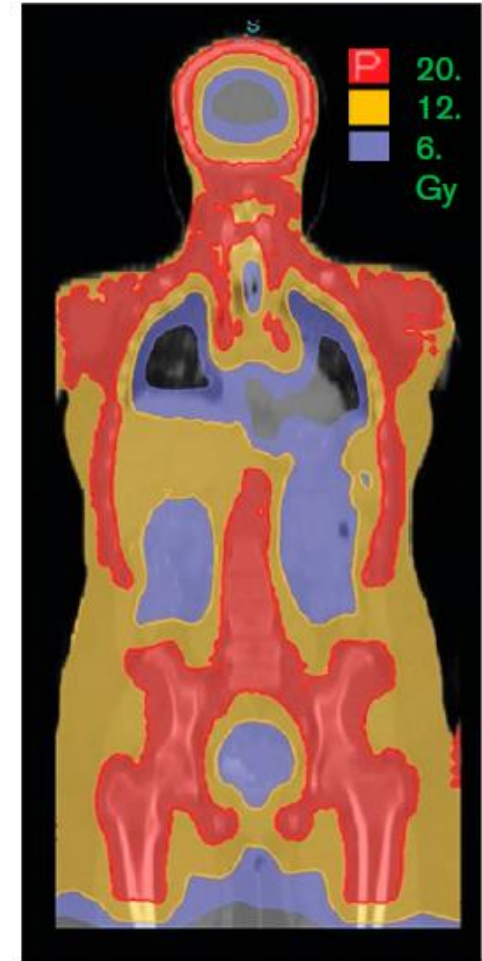
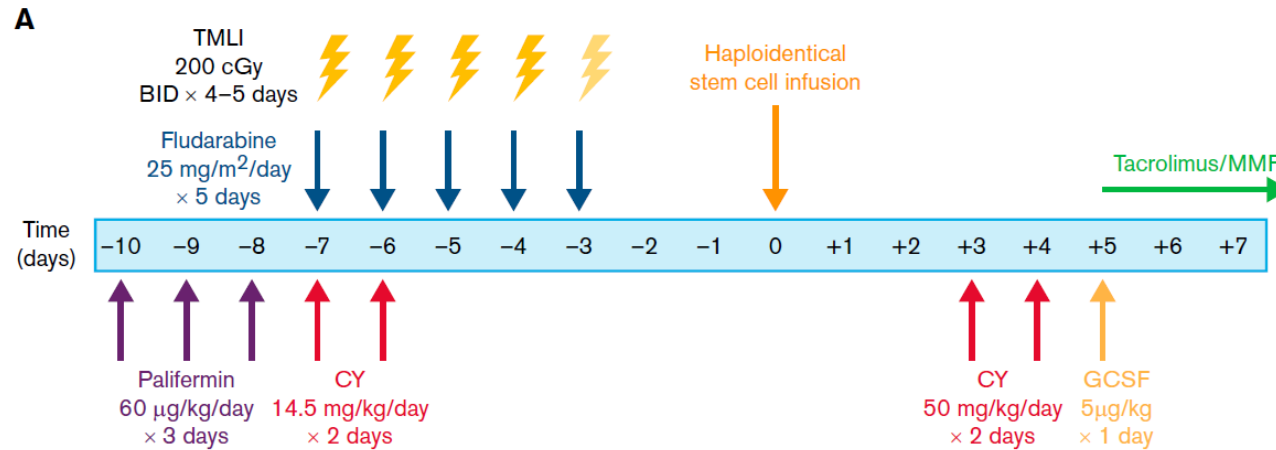
20 Gy

MTD in R/R acute leukemia (phase I)
1-y NRM 8% · day +30 CR 100% at 20 Gy

R/R leukemia + Cy/VP16: 2-y OS 48%

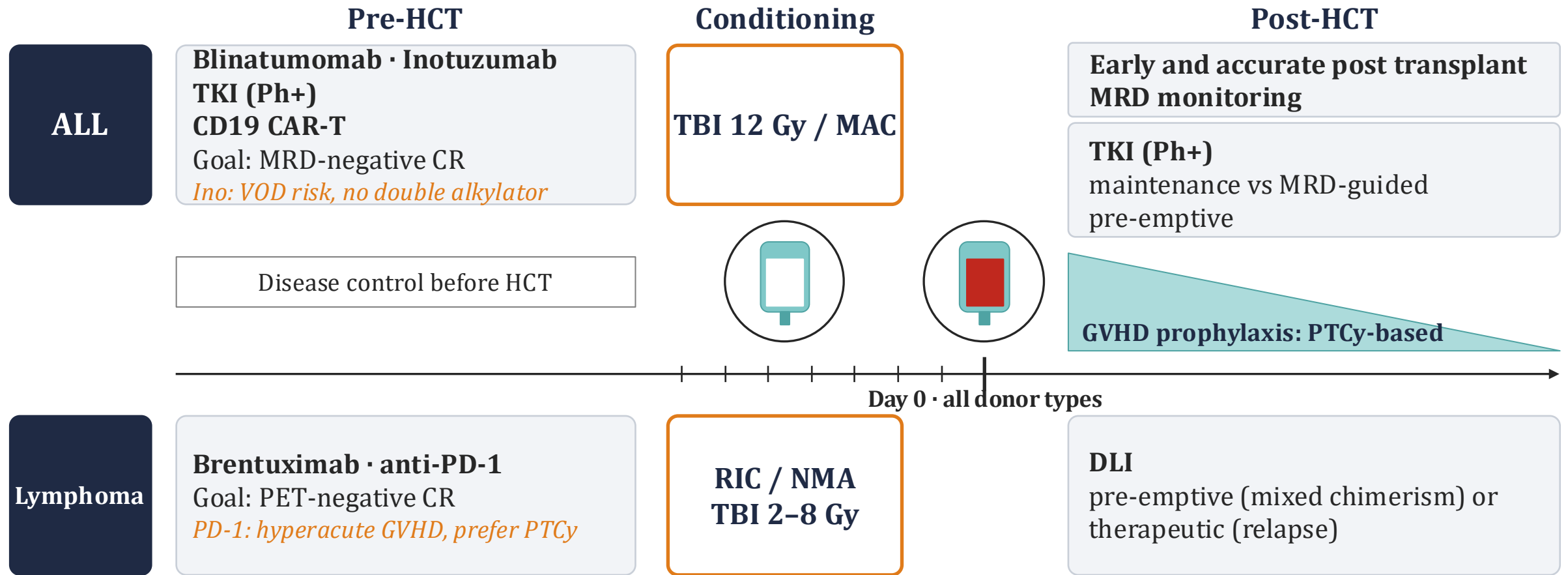
Haplo + PTCy: 2-y NRM 13%, 1-y OS 83%

AML in CR + PTCy: 2-y NRM 0%, OS 87%



Target the marrow, spare the organs: more dose where needed, less toxicity

The transplant platform: a wider view



Conditioning is one piece of a platform: what comes before and after shapes its design

Conclusions

- **ALL: TBI 12 Gy/Cy (or VP16) remains the myeloablative reference for fit patients**, especially in young adults, T-ALL, CNS-positive ALL.
- **Older or unfit patients in CR1: Flu/TBI 8 Gy** is as effective as 12 Gy and better than Flu/Bu. Thiotepa and treosulfan are options when TBI is not feasible.
- **Lymphoma: less is more**. RIC/NMA with TBI 2 Gy and PTCy lets the graft do the job, with intermediate TBI as an option in T-cell lymphoma.
- **Conditioning is part of a platform**: disease control before HCT, GVHD prophylaxis, post transplant interventions significantly influence outcome

Strike gently! Transplant is not all about conditioning. Heading towards a tailor made conditioning basing on single patient characteristics.

Thank you!