Does conditioning intensity matter?

the NO position

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The ideal transplant platform

What can we expect from a modern transplant platform (conditioning regimen + GVHD prophylaxis?)

- Engraftment (do we always need myeloablation?)
- Low extrahematological toxicity
- High anti-leukemia efficacy to let time for GVL effect to take over
- Low rates of aGVHD, no grade 3-4 aGVHD
- No or mild cGVHD

The dilemma of dose intensity – the conditioning intensity axiom

The conditioning intensity axiom:

- Reduced intensity has the rationale of reduced non-relapse mortality (NRM)

- Increased intensity results in reduced relapse (REL)

- NRM and REL are inversely proportional

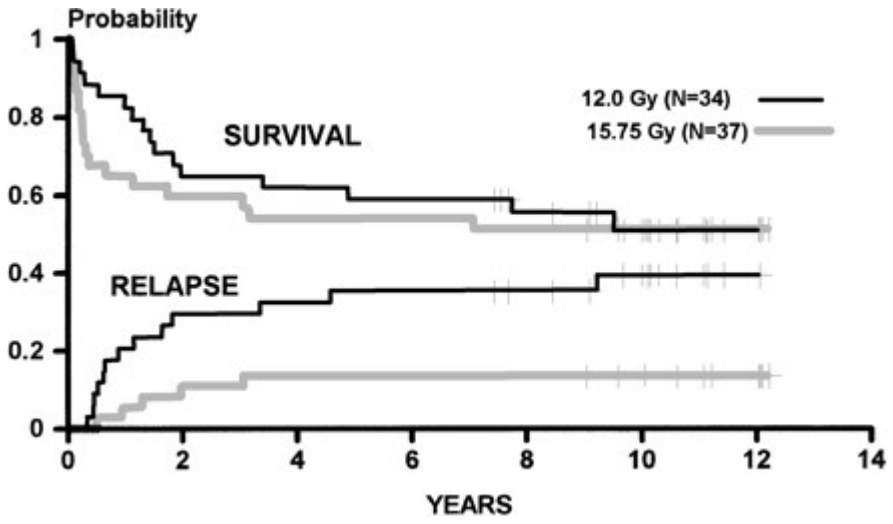
- Survival depends on the sum of the competing factors NRM + REL

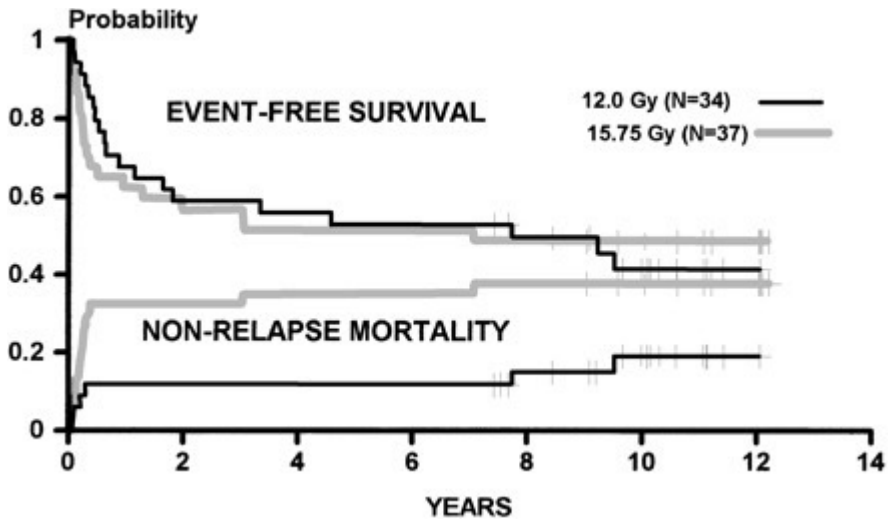
The survival equation:

$$OS = 1 - (NRM + REL)$$

$$NRM * REL = k$$

The dilemma of dose intensity – a paradigmatic example





Let's solve the equation:

TBI 15.75 Gy

OS = 1 – (NRM + REL)
= 1 – (0.4 + 0.1)
= 1 – 0.5
= 0.5

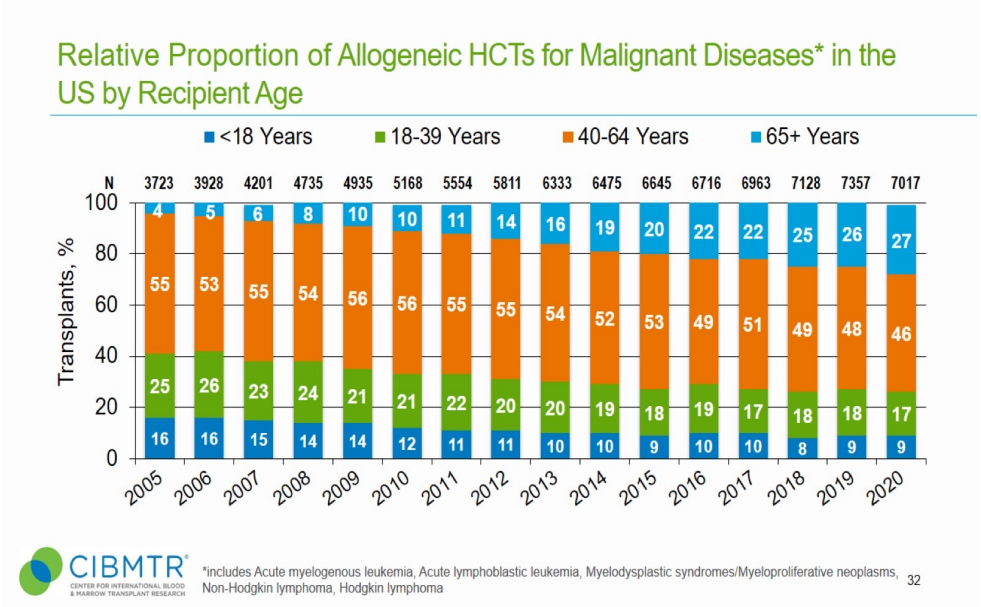
TBI 12 Gy

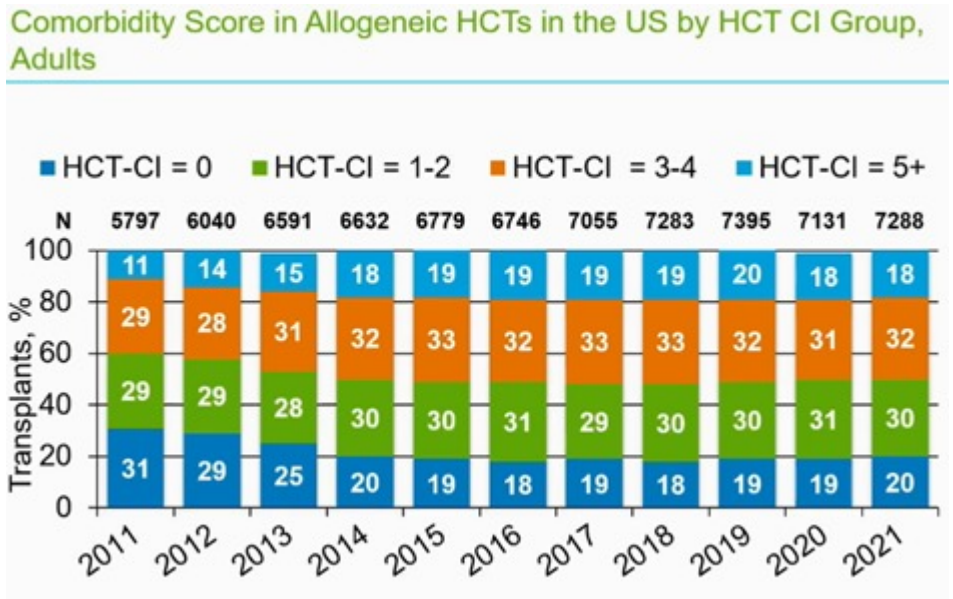
OS = 1 – (NRM + REL)
= 1 – (0.1 + 0.4)
= 1 – 0.5
= 0.5

Different intensity: similar survival

Clift, blood 1998

The evolving concept of transplant elegibility





Higher flexibility in transpant elegibility

Older/unfit patients: intensity = toxicity

We are forced to de-escalate intensity in this population

Can we prove the axiom wrong?

What do we need intensity for?

1. To engraft stem cells: no need for high intensity in AML

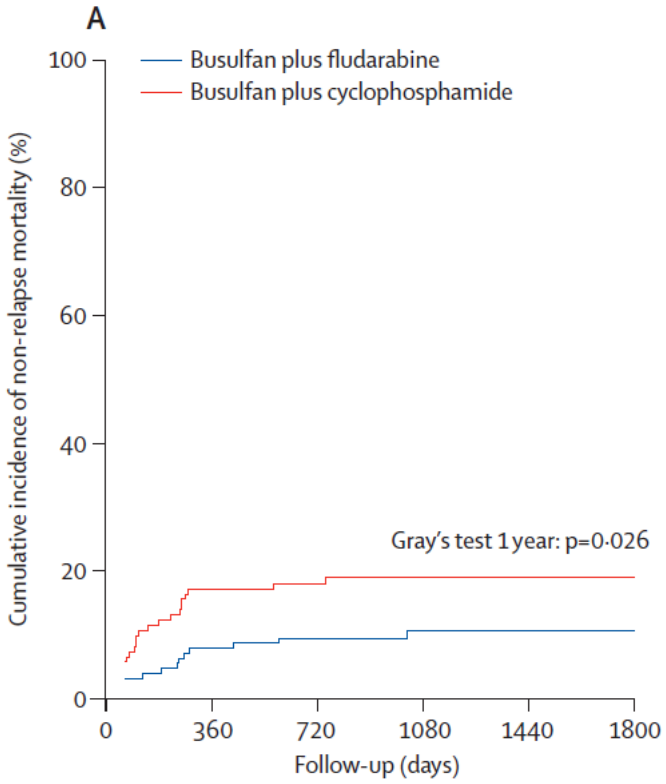
2. To eradicate residual disease: does intensity really matters?

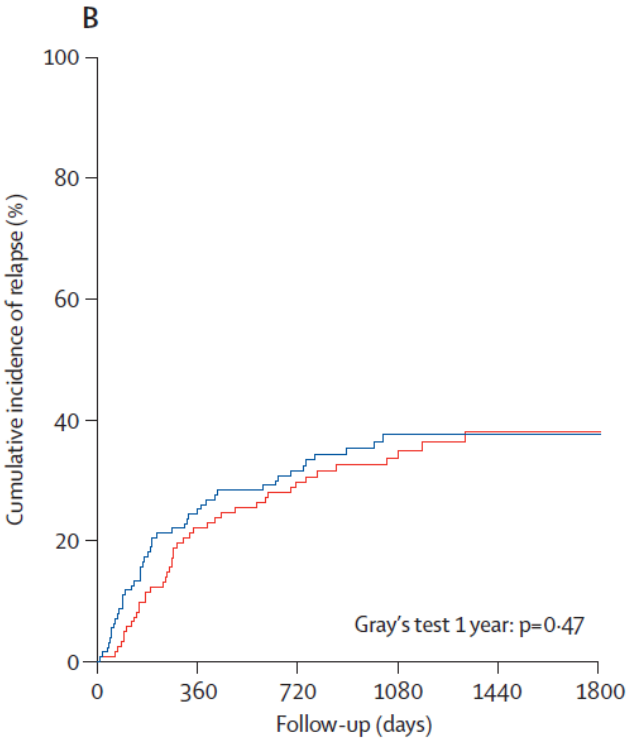
Let’s get rid of dose intensity!

Let’s prove the axiom wrong - we need randomized studies

Let's get rid of dose intensity – 1

GITMO phase III, randomized trial. Pivotal study
Bu-Cy vs Bu-FLU (2 vs 1 alkylator)
AML 40-65y, HLA matched related or UD (>=9/10)





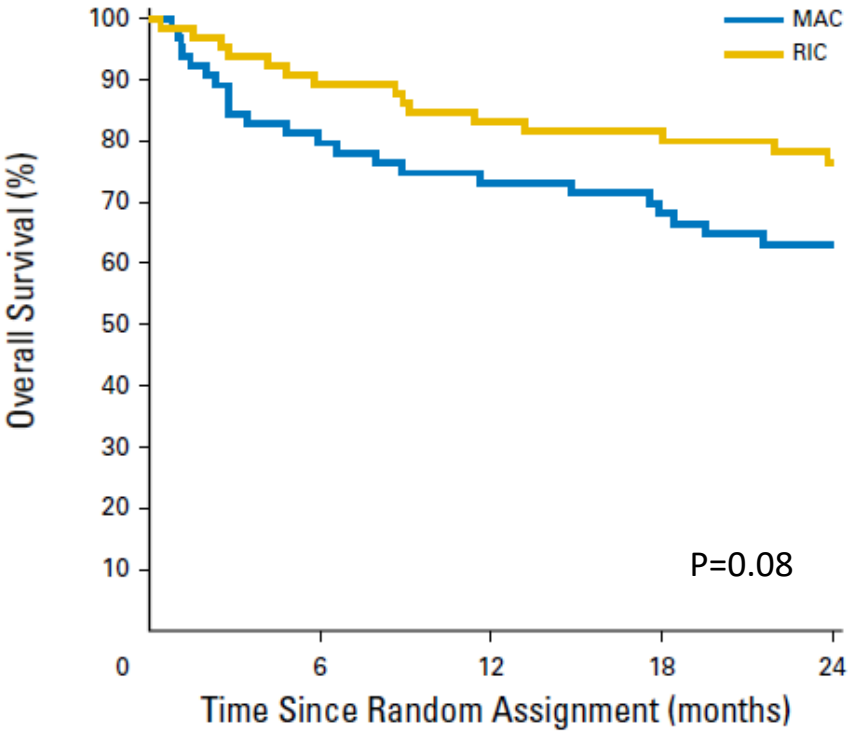
Primary endpoint: 1 year NRM: met
NRM: 19% (BuCy) vs 10% (BuFlu)
Organ failure: 7% (BuCy) vs less than 1% (BuFlu)
No difference in survival

Reduced NRM, however REL not increased

Rambaldi, Lancet Oncol 2015

Let's get rid of dose intensity - 2

RICMAC EBMT trial, Phase III, randomized
RIC vs MAC (Bu2-Flu vs Bu-Cy)
MDS + secondary AML
HLA matched related or UD (>=9/10)



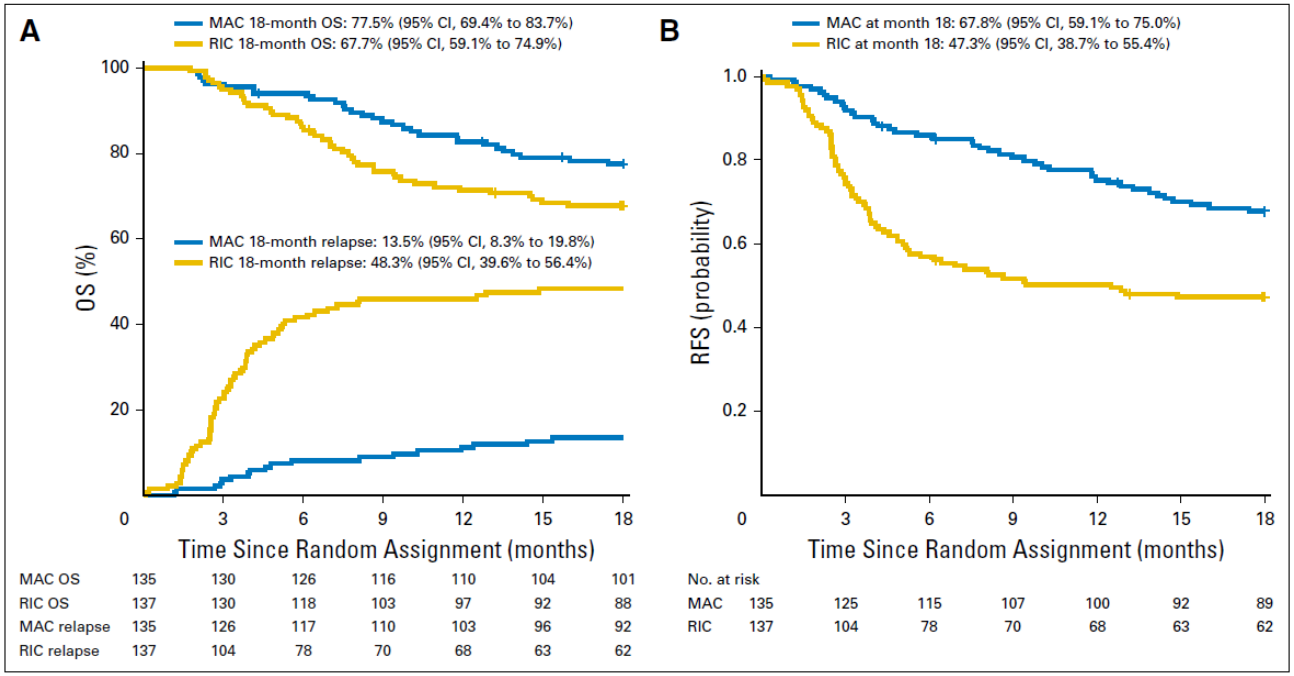
RIC: trend for better OS compared to MAC (in MDS)

Yes, we can! The axiom was wrong: Reduced NRM does not necessary lead to increased REL

Kroger, J Clin Oncol 2017

De-escalating dose intensity for all patients? RIC for everybody!

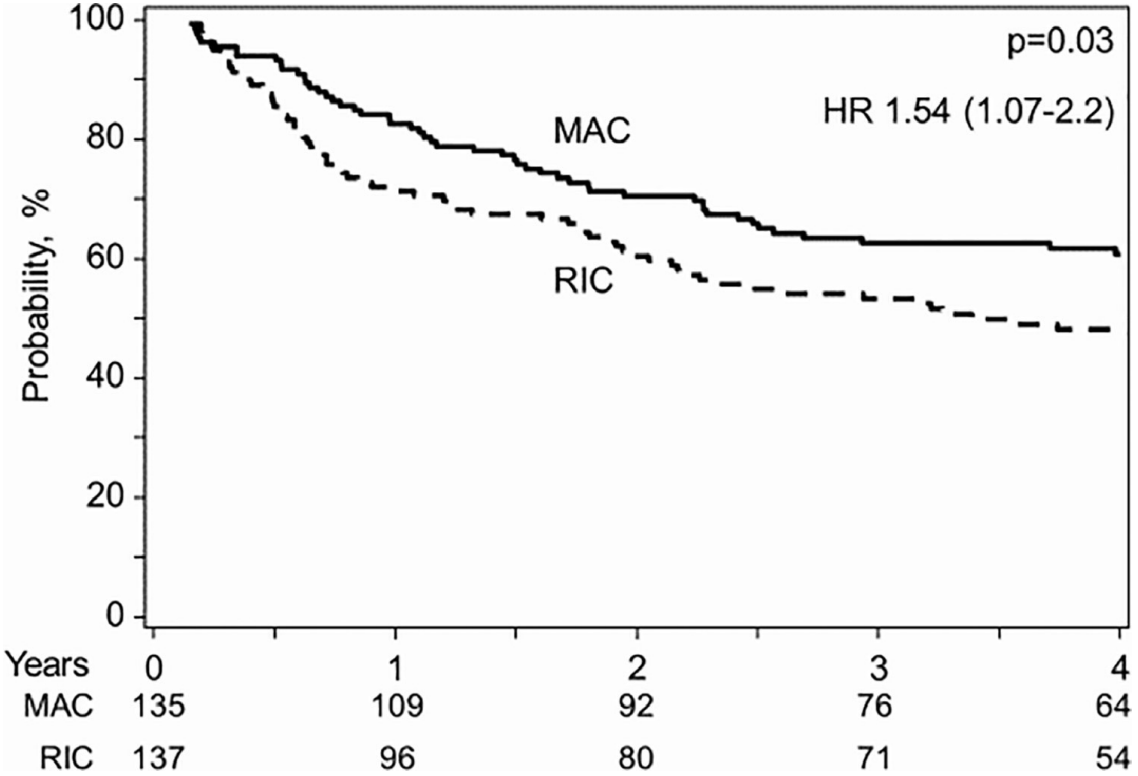
US-CTN 0901 study, Phase III randomized trial, MAC vs RIC
271 patients with AML or MDS
Age 18-65, HCT-CI max 4
MAC: Bu/Cy or Cy/TBI; RIC: Bu2/Flu or Flu/Mel



Increased relapse in AML (not in MDS): 48% (RIC) vs 14% (MAC)
Increased LFS MAC vs RIC

Scott, J Clin Oncol 2017

De-escalating dose intensity for all patients? NO, we can't



MAC vs RIC: improved survival (AML only)

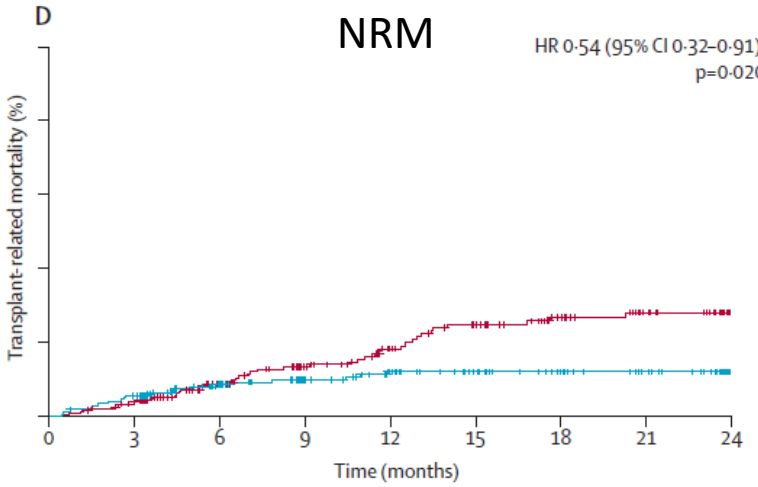
Was the axiom right, after all?

Don't even think about RIC in young, fit AML patients!

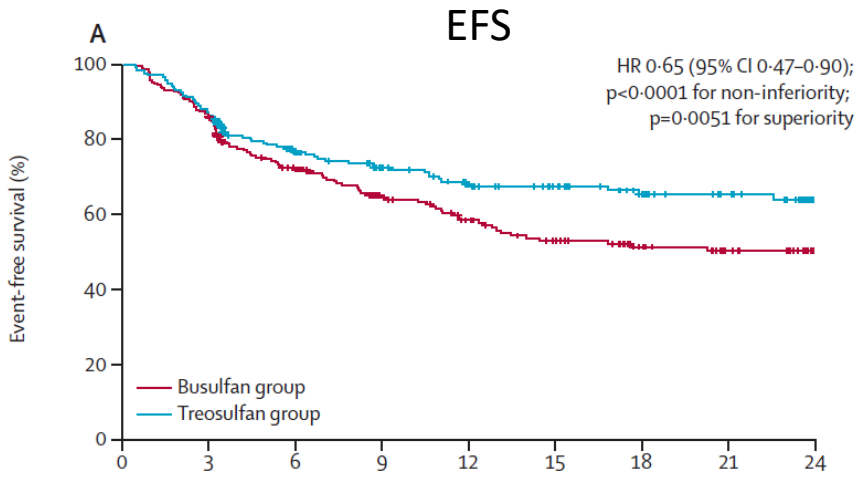
Scott, Transplantation and cellular therapy 2021

Can we improve over conventional RIC regimens? Treosulfan

Randomized, phase III Trial (MC-FludT.14/L Trial), Bu-Flu vs Treo-Flu
18–70 years, AML CR or MDS
HLA-matched related or UD (>=9/10)
Key inclusion criteria: considered inelegible for Myeloablative regimen based on:
- **Age >= 50y**
And/or **HCT-CI >2**
Treo 10 g/m2 (3 days) vs Bu 3,2 mg/kg (2 days)
+ Fludarabine 30 mg/m2 (5 days)



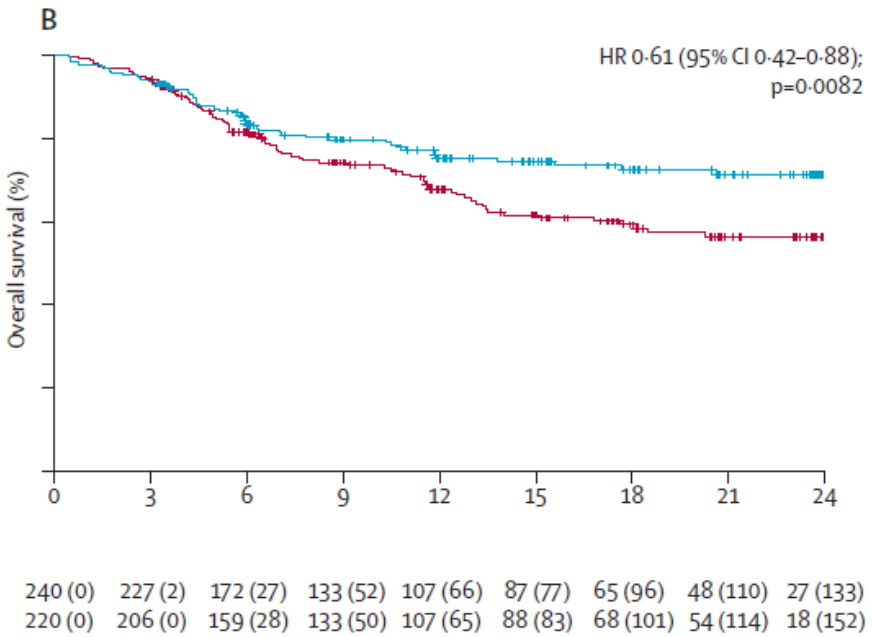
NRM gap widens beyond 6 months



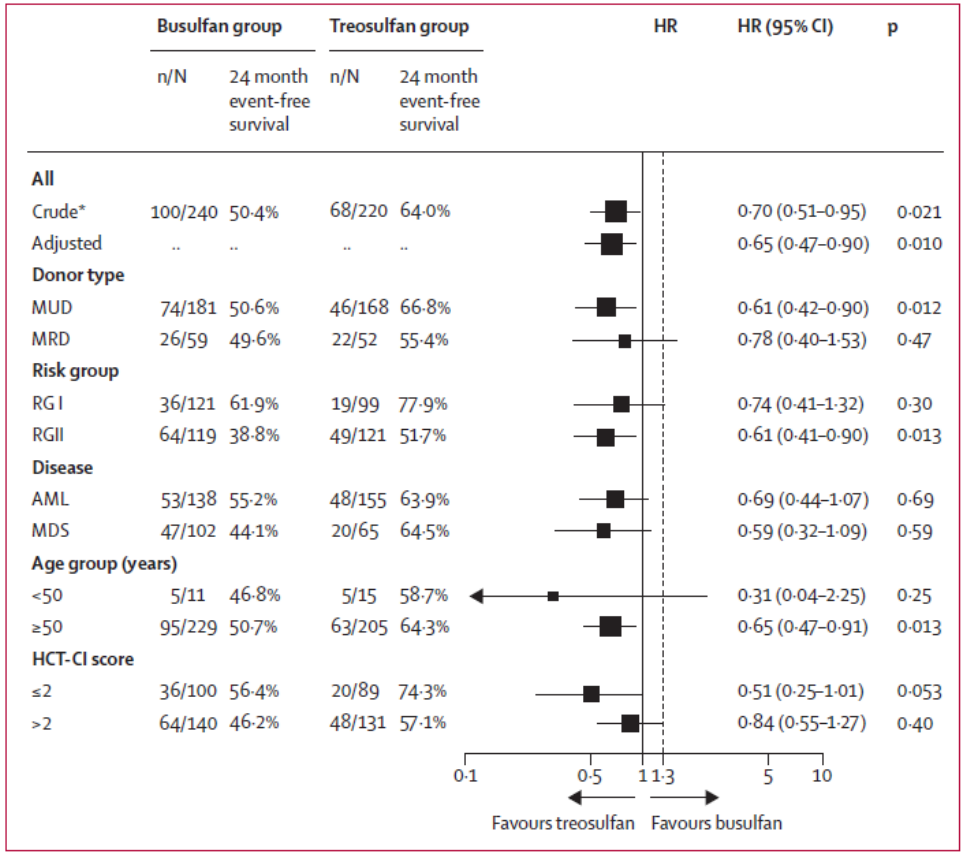
Primary endpoint: met. Improved EFS

Beelen, Lancet Hematol 2020

Can we improve over conventional RIC regimens? Treosulfan



Improved OS



Beelen, Lancet Hematol 2020

After all, is conditioning intensity the right focus?

Conditioning intensity is the result of the combination of:

1. The inherent pharmacodynamic properties of the single conditioning agents
2. The resultant toxicity to that given patient

   (patient-related variables as, Age/comorbidities/dynamic fitness

   previous chemotherapy, alkylator dosing in obese pts, drug-drug interactions etc.)

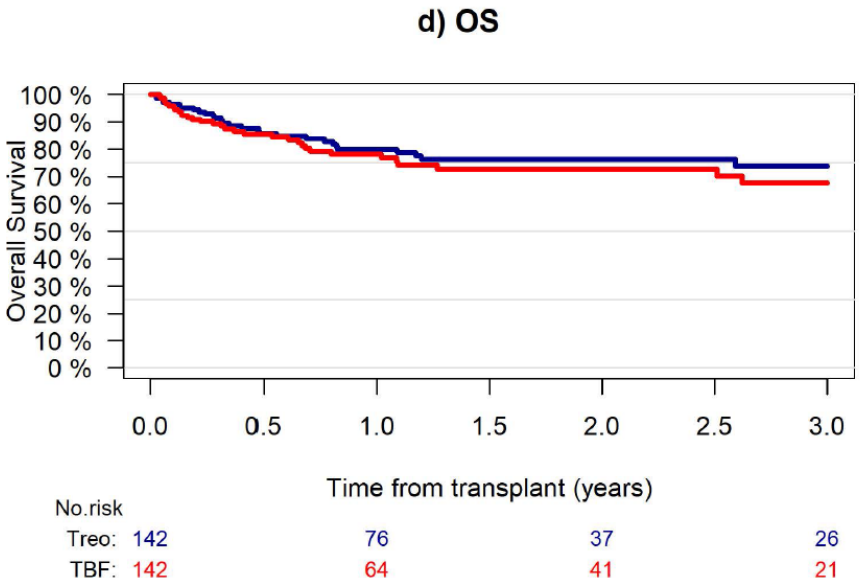
+ GVHD prophylaxis should be taken into account (ptCY vs ATG/MTX/CSA vs T-cell depleted HSCT)

The ptCY case:

i.e.
Myeloablative TBI-based conditioning + ptCY
Double alkylator conditioning + ptCY

High toxicity is expected

Treosulfan as an alternative to double alkylator in ptCY haplo for AML



	2-years OS
Treo	76%
TBF	73%
P	0.53

RIC subgroup

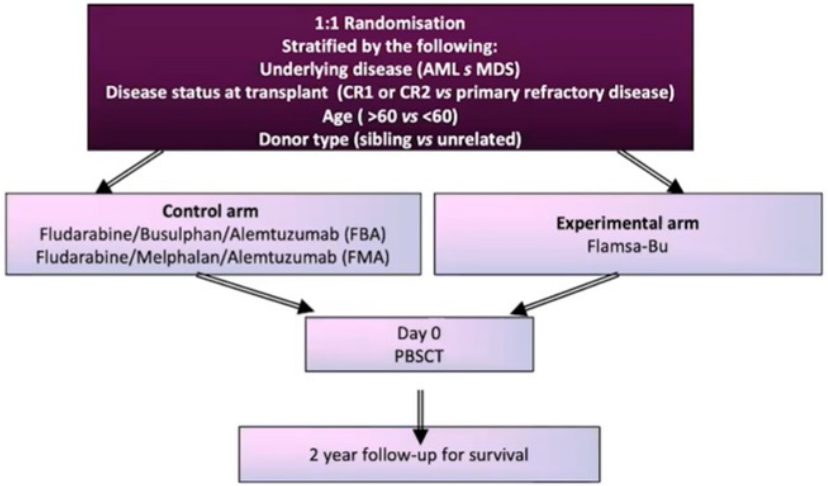
2y	NRM	RI
Treo	**13%**	**20%**
TBF	24%	13%
	P=0.2	P=0.7

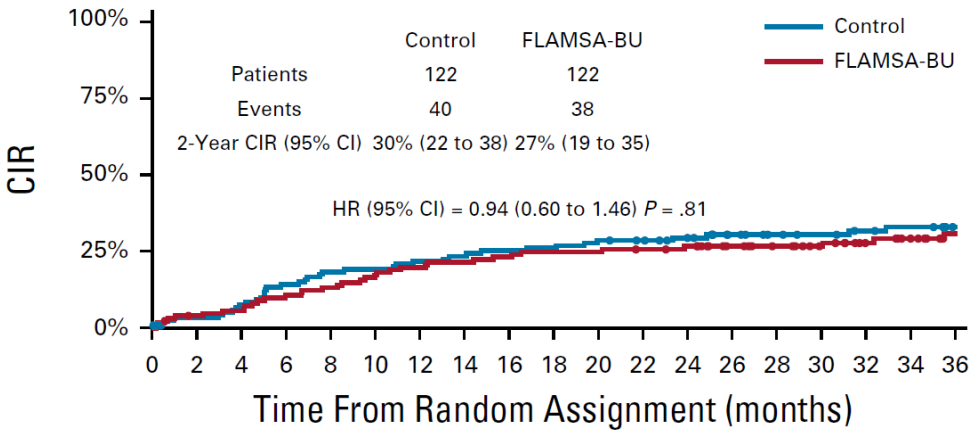
2y	LFS	OS
Treo	67%	**77%**
TBF	64%	68%
	P=0.6	P=0.3

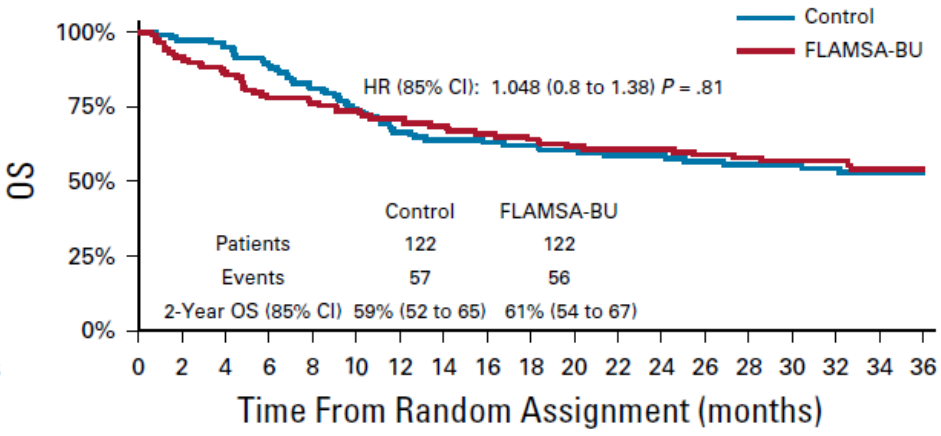
Saraceni, *submitted*

Don’t forget we are in 2023, we have MRD! The FIGARO trial

Phase III, randomized trial
244 AML or MDS patients
Not eligible to MAC
RIC vs intensified sequential conditioning
MRD prospectively evaluated by MFC





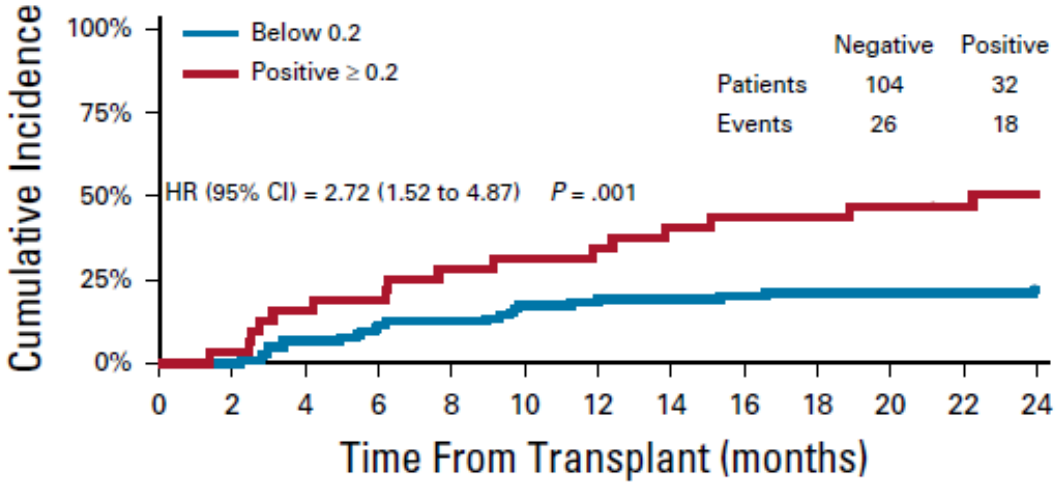


Intensified regimen did not improve outcome
Relapse rate 25-30% as expected, different from US-CTN 0901 trial

Craddock, J Clin Oncol 2020

FIGARO UK trial - MRD

Detrimental effect of pre-transplant MRD (0,2% cutoff) on cumulative incidence of relapse



No benefit of regimen intensification in positive MRD

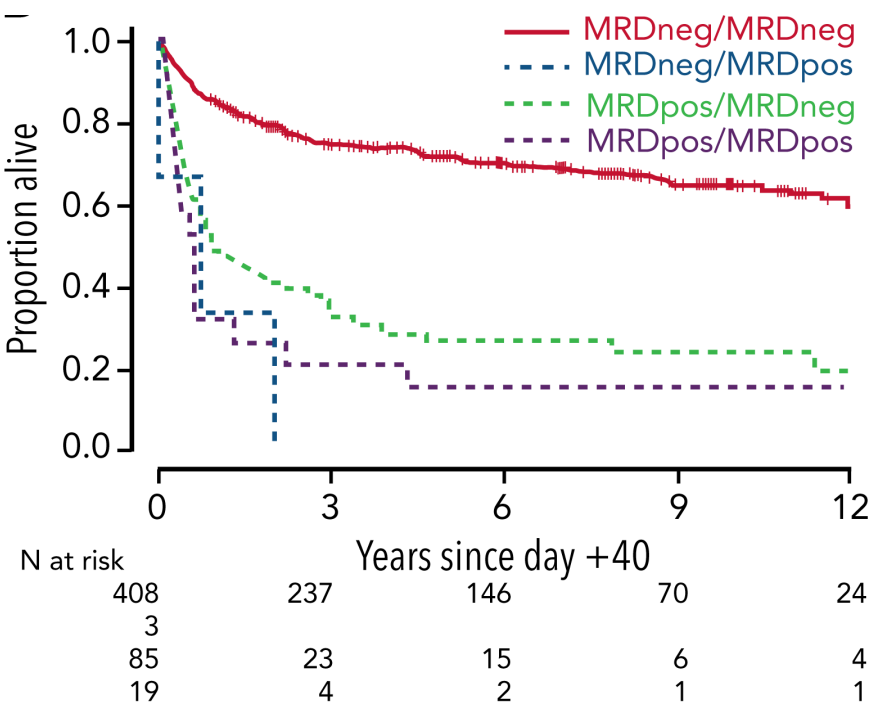
RIC MRDpos: relapse 40% (2y), survival 50% (2y)

RIC - HSCT is not futile in an elderly/unfit patient with positive MRD

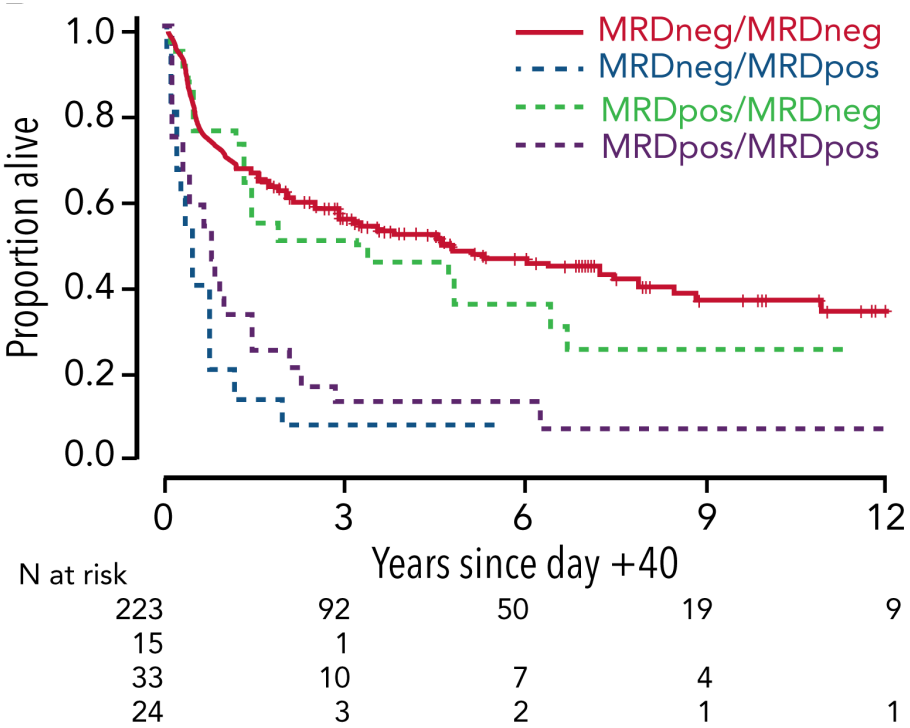
Craddock, J Clin Oncol 2020

Seattle – MAC vs NMA/RIC, MRD pre/post HSCT

810 AML CR1 or CR2; MAC vs non-MAC (RIC/NMA)
MRD by flow pre/post HSCT (peritransplant MRD)



MAC



NMA/RIC

Look at the green curve: RIC better than MAC in MRDpos (?)
RIC in MRDpos: 3y OS about 50%

Paras, blood 2022

Conclusion

- Crude conditioning intensity is not the best focus

- To design a patient-oriented HSCT platform (not just conditioning) is probably a better target

  (Donor choice, GVHD prophylaxis, AML therapy before HSCT, post-HSCT interventions significantly interact with conditioning intensity for NRM)

- To transplant an high risk >65y AML patient remains a main challenge

- Reduced intensity regimens represent a valid choice in patients not eligible for MAC

- RIC regimen can deliver good long term outcome even in high risk pts (i.e. MRDpos)

- Let's base our practice on good quality evidence, we have (few) data from randomized trials

Strike firmly but gently, transplant is not all about conditioning!

Grazie