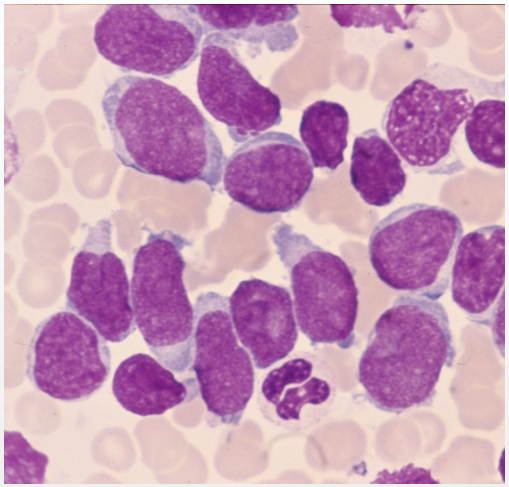
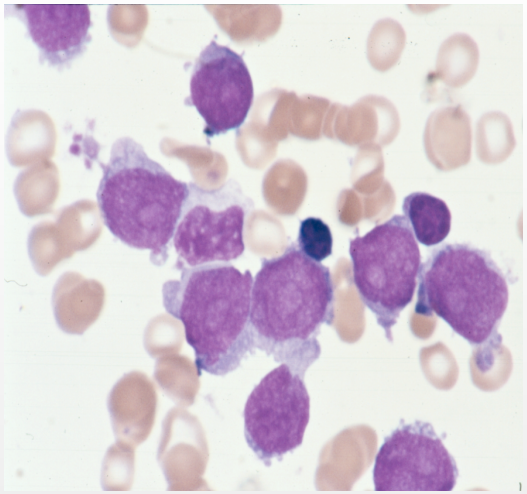
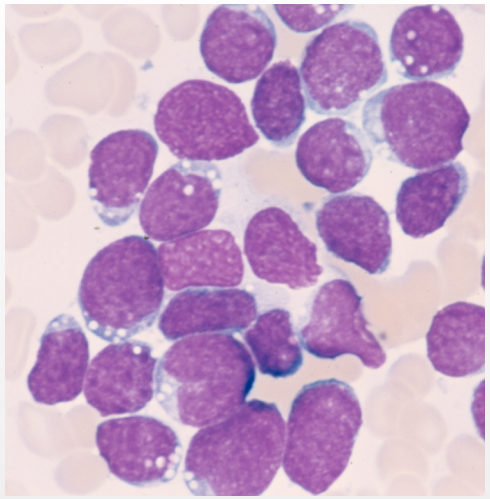
Leucemia Acuta Linfoblastica

La terapia del giovane adulto

Alessandro Rambaldi

Bologna, 13 Maggio 2016

UNIVERSITÀ DEGLI STUDI DI MILANO

Azienda Ospedaliera Papa Giovanni XXIII Bergamo

Disclosures

Honoraria and Scientific Advisory Board

- Amgen
- Pierre Fabre
- Mundipharma

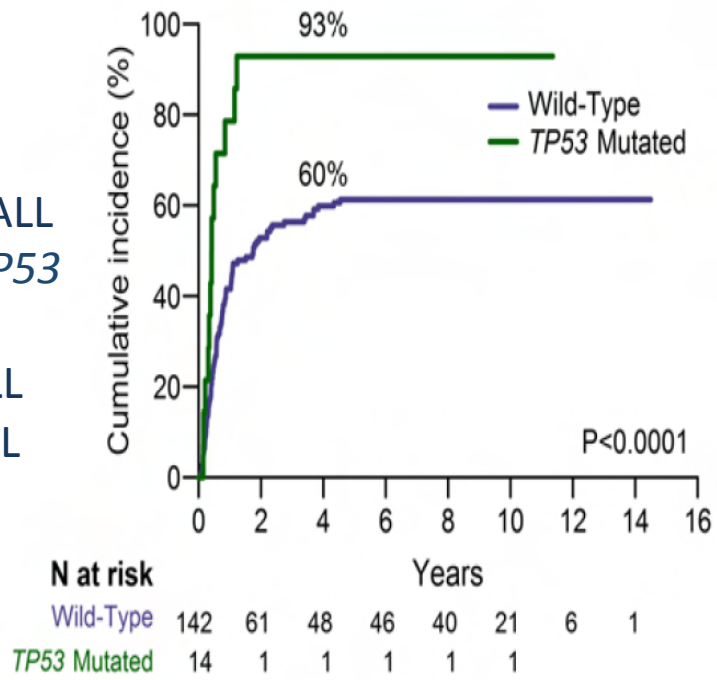
Predicting risk factors in ALL

Patient-related	Disease-related	Treatment-related*
Age (>35-55 years)	WBC (>30 [B], >100 [T])	Steroid prephase response
Performance status (ECOG >1)	Immunophenotype (pro-B, CD1a-negative early pre-T and early/mature)	Induction day 14 bone marrow response
Significant comorbidity	Cytogenetics (high-risk)*	Late CR (>cycle 1)
	Genetics/genomics (high-risk)	MRD
Miscellaneous	CNS involvement	

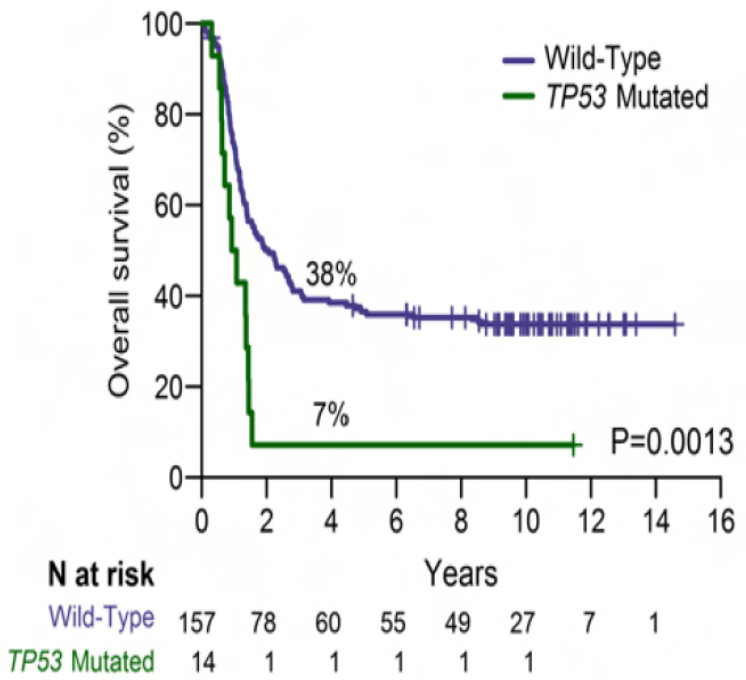
* t(9;22)/Philadelphia chromosome, t(4;11), t(1;19), t(8;14), abn 11q23, +8, -7, del6q, low hypodiploidy with 30-39 chromosomes, near triploidy with 60-78 chromosomes, complex with ≥5 unrelated anomalies

TP53 mutations in adult ALL (by NGS)

- 14/171 (8%) ALL positive for *TP53*
- 9.7% in Bp-ALL
- 5.3% in Tp-ALL



Cumulative incidence of relapse



Overall survival

Salmoiraghi, S et al. Haematologica 2016; Epub ahead of print

haematologica
the hematology journal

In adult ALL treatment intensity matters

Pediatric-inspired intensified programs
vs
conventional therapy

blood
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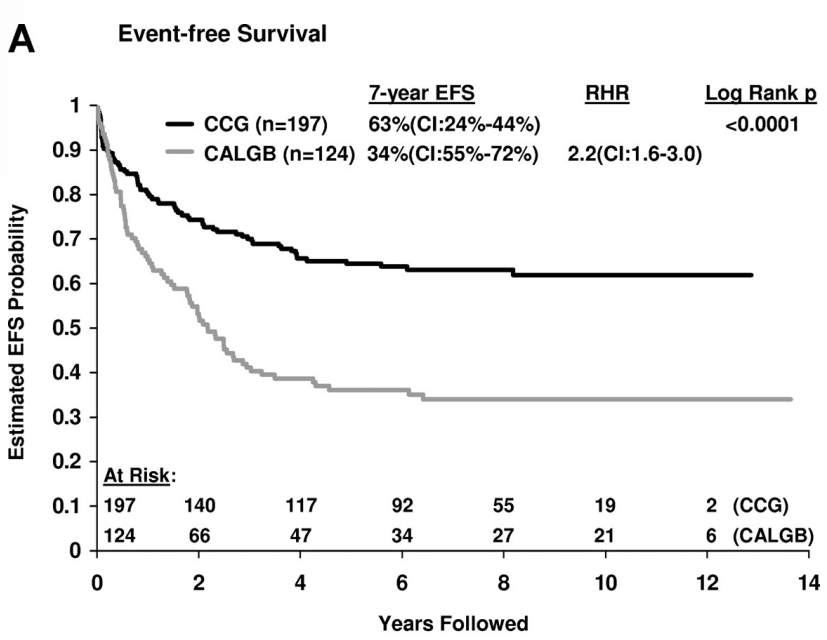
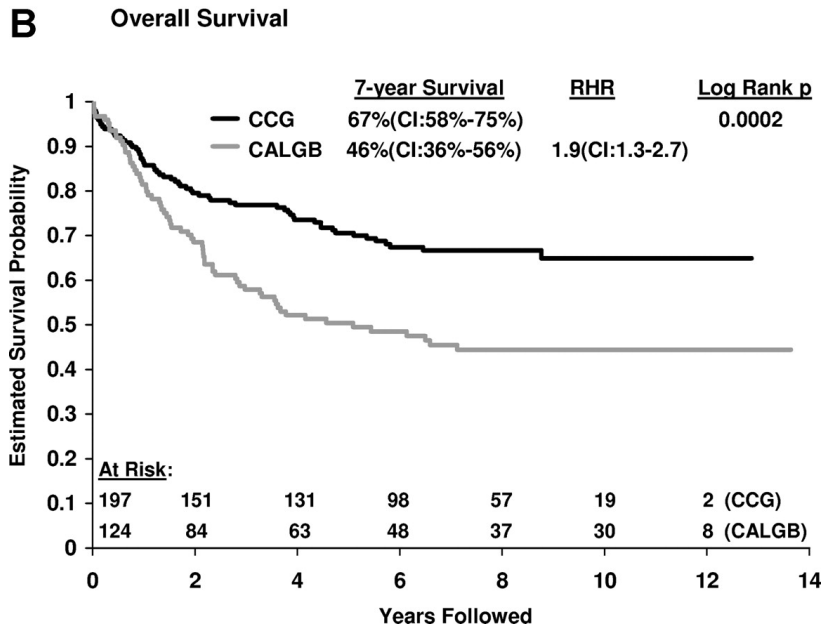
Comparison among CALGB and CCG patients





Event Free Survival

Overall Survival

Stock, W. et al. Blood 2008;112:1646-1654

Principles of pediatric-type therapy

	Pediatric-type (compared to adult therapy)
Chemotherapy	•Corticosteroids: more, dexamethasone •VCR: more •L-asparaginase: more, pegylated •Antimetabolites: more (MTX, 6-thiopurines, ara-C), higher-dose MTX (2.5-5 g/m^2)
Treatment intensity/ adherence	•Higher, no/minimal dose reductions and treatment delay (dedicated, well trained staff)
SCT	•Limited use (MRD/risk class)

In Europe: *BFM → GMALL; AIEOP → GIMEMA; FRALLE → GRAALL etc.*

Application to adults: *variable/modified or unmodified, difficult (age limit: 25/35 – 50 – 60 ?)*

Frequenza e sensibilità delle sonde molecolari generate dallo studio del riarrangiamento dei geni Ig e TCR

Sensibilità	n	%
10^{-5}	156	51
10^{-4}	119	39
10^{-3}	33	10

90%

The outcome of adult ALL patients achieving MRD negativity is reproducibly good without alloHSCT!

Results of prospective, MRD-based clinical trials in Ph- ALL

Study, year (reference)	Patients	MRD method	MRD study (level for negativity)	Outcomes MRD negative	Outcomes MRD positive
Bassan, R 2009	280 adult ALL patients	RQ-PCR	MRD≤10^{-4}	5-year OS 75% 5-year DFS 72%	5-year OS 33% 5-year DFS 14%
Gökbuget, N 2012	580 Ph- adult ALL patients	RQ-PCR	MRD≤10^{-4}	5-year OS 80% 5-year DFS 67%	5-year OS 42% 5-year DFS 25%
Beldjoord, 2014	423 Ph- ALL paients	RQ-PCR	MRD≤10^{-4}	5- year RI 23%	5- year RI rate 60%
Ribera, JM, 2014	326 HR Ph- adult ALL patients	Flow cytometry	Patients with MRD< 1×10^{-3} after induction and < 5×10^{-4} after early consolidation	5-year OS 56% 5-year DFS 51%	5-year OS 17% 5-year DFS 0%

Lussana F and Rambaldi A MJHID, 2014

Should we transplant every possible case in CR1?
(based on clinical risk factors)

SCT for no one

MRD negative (with acceptable risk profile)

SCT for everyone

MRD positive *or*

MRD negative **without*** acceptable risk profile

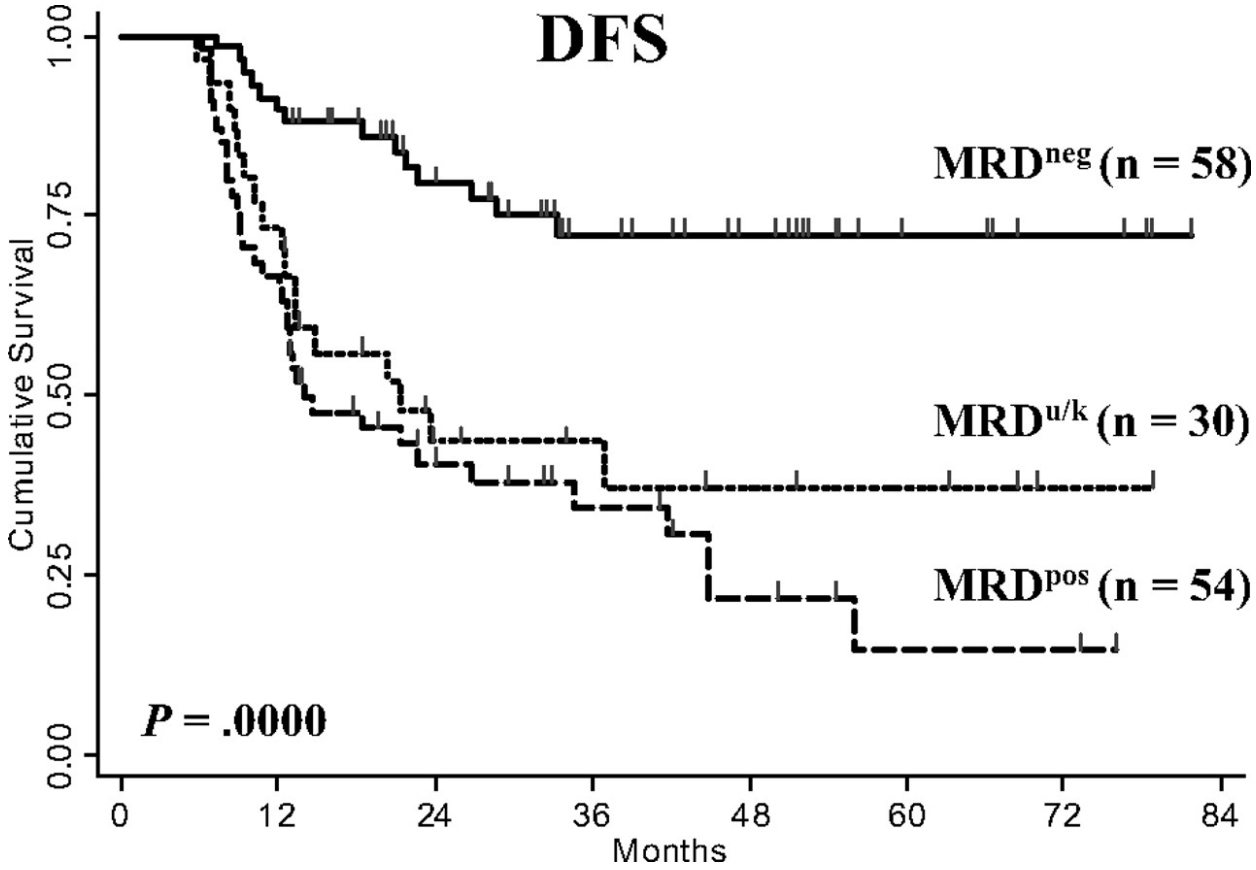
any of: Ph+, t(4;11), t(1;19), t(8;14), abn 11q23, +8, -7, del6q, low hypodiploidy, near triploidy, complex

How to improve the outcome of adult ALL

1. **Reduce the failure of the MRD driven strategy**
2. **Improve the outcome of alloHSCT**

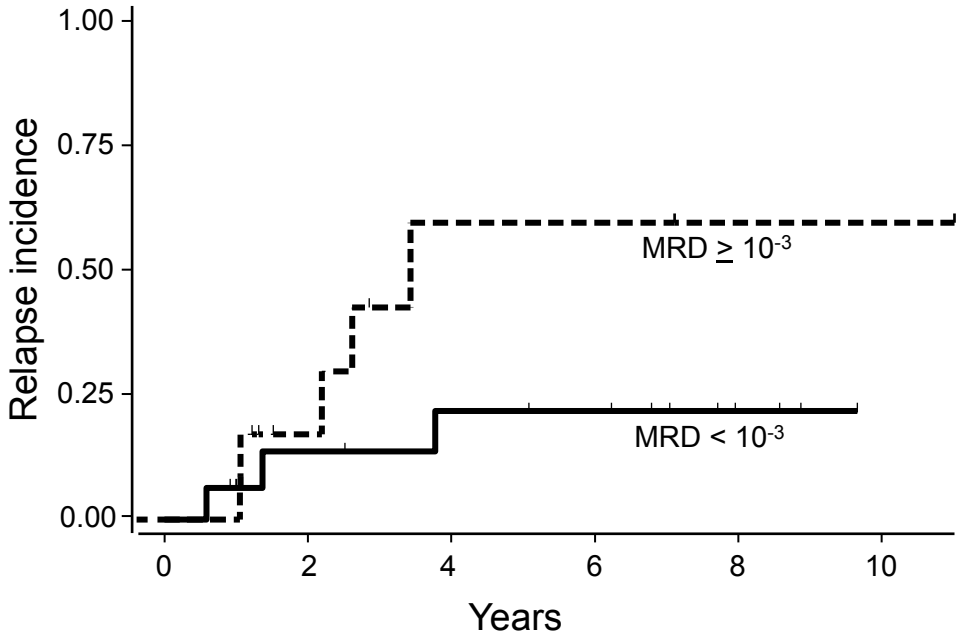
blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Figure 3 DFS according to MRD study results

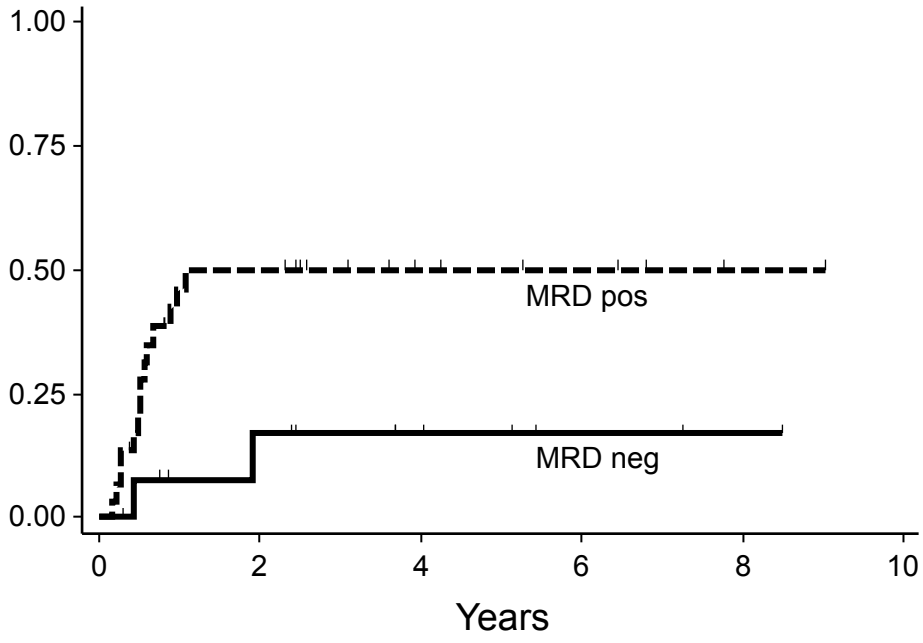


Bassan, R. et al. Blood 2009;113:4153-4162

Allogeneic transplantation for adult ALL: impact of MRD status at conditioning



Ph-

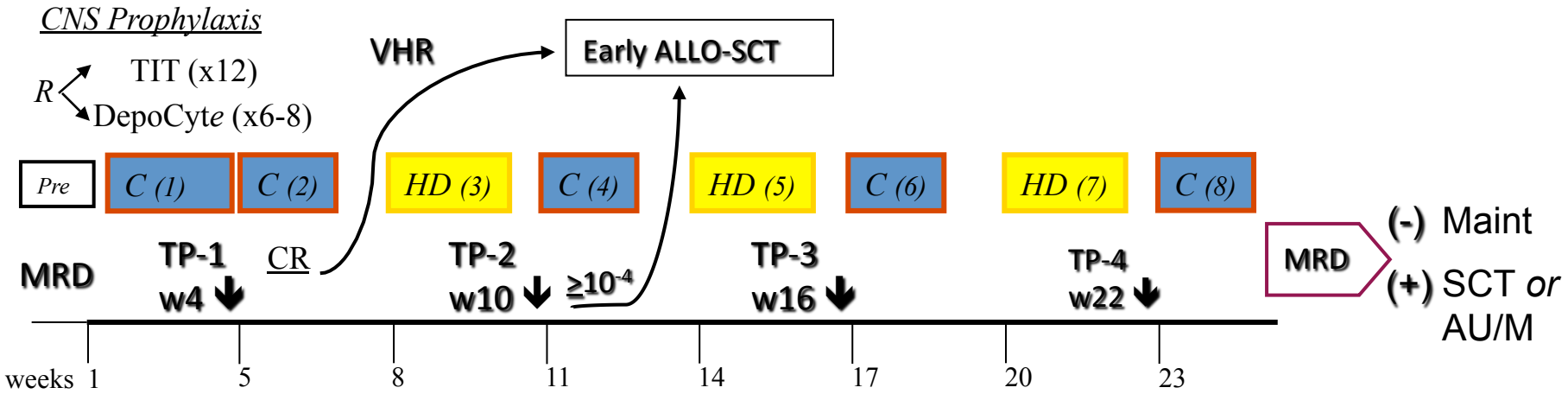


Ph+

Lussana F and Rambaldi A. Haematologica 2015;9:369–76

haematologica
the hematology journal

NILG study 10/2007



C (1),(2),(4),(6),(8) = *Conventional-Dose Cycles (no. 2,4,6: Pediatric-type AIEOP-derived)*

HD (3),(5),(7) = *Lineage-Targeted HD-MTX Infusion Cycles (SJH-derived)*

B-lin: 2.5 g/m²

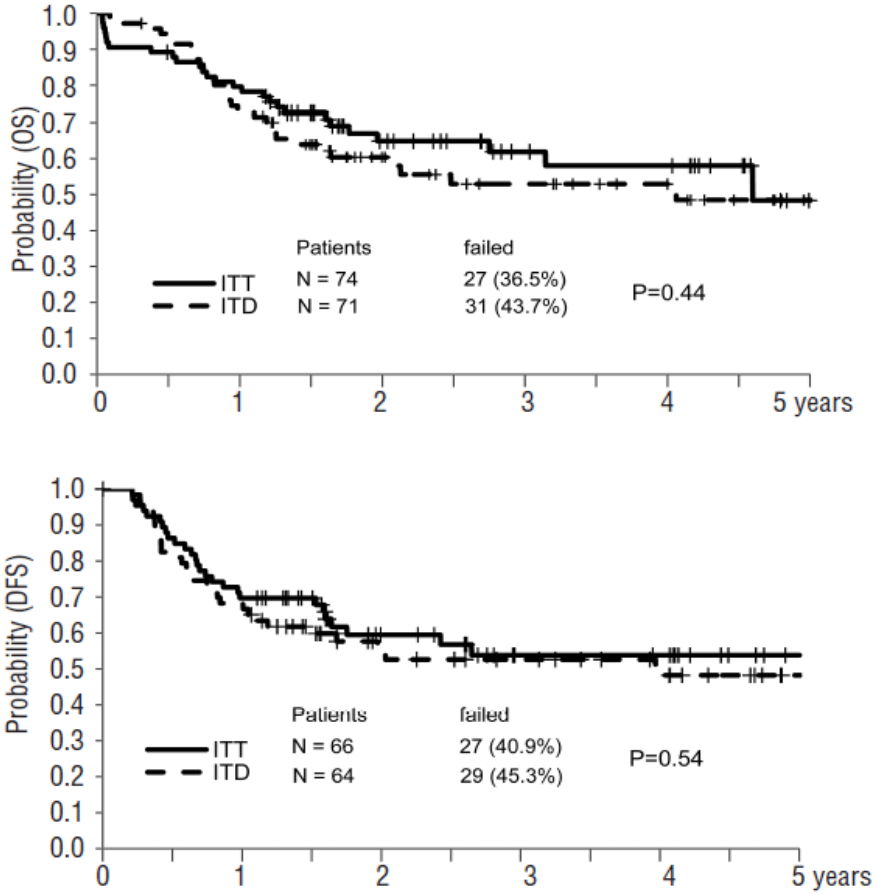
T-lin: 5 g/m²

NB: age >55: 1.5 g/m²

- WBC >100x10⁶ cells/µL
- Early/mature T
- Adverse cytogenetics: Ph, MLL at q23, +8, -7, del6q, t(8;14), NTr (60-78), low hypo (30-39), complex

Intrathecal triple therapy vs liposomal cytarabine CNS prophylaxis in ALL

Outcome estimates by randomisation arm



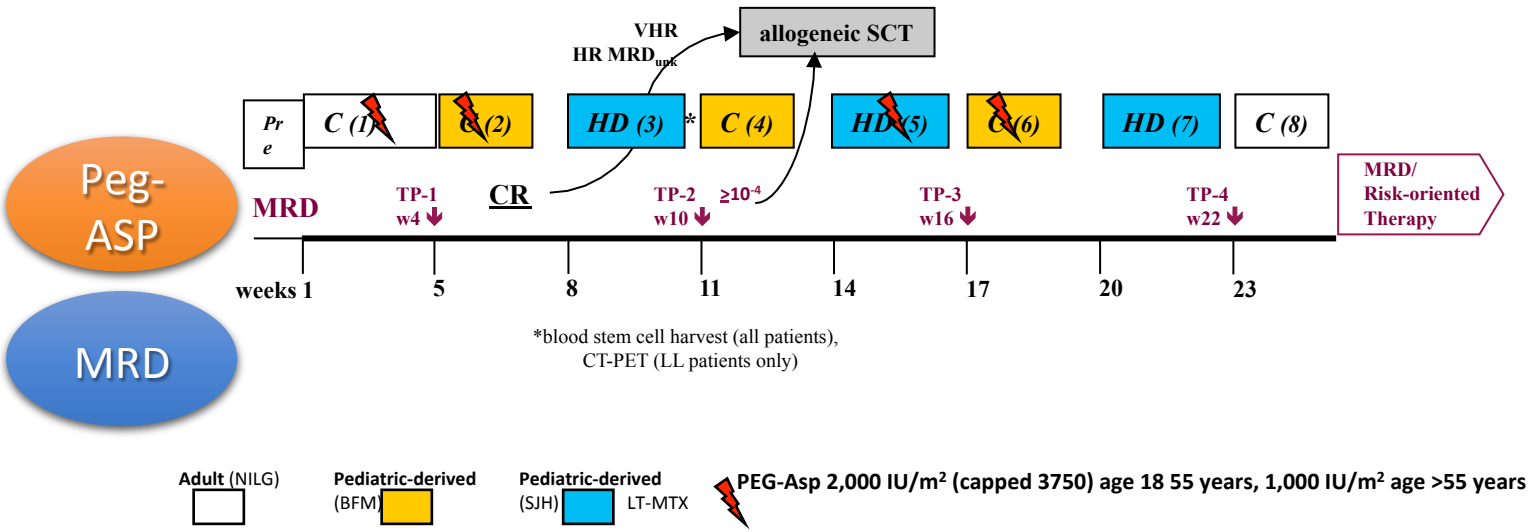
ITD, intrathecal liposome-encapsulated cytarabine; ITT, intrathecal triple therapy

Bassan R, et al. Haematologica 2015;100:786–93

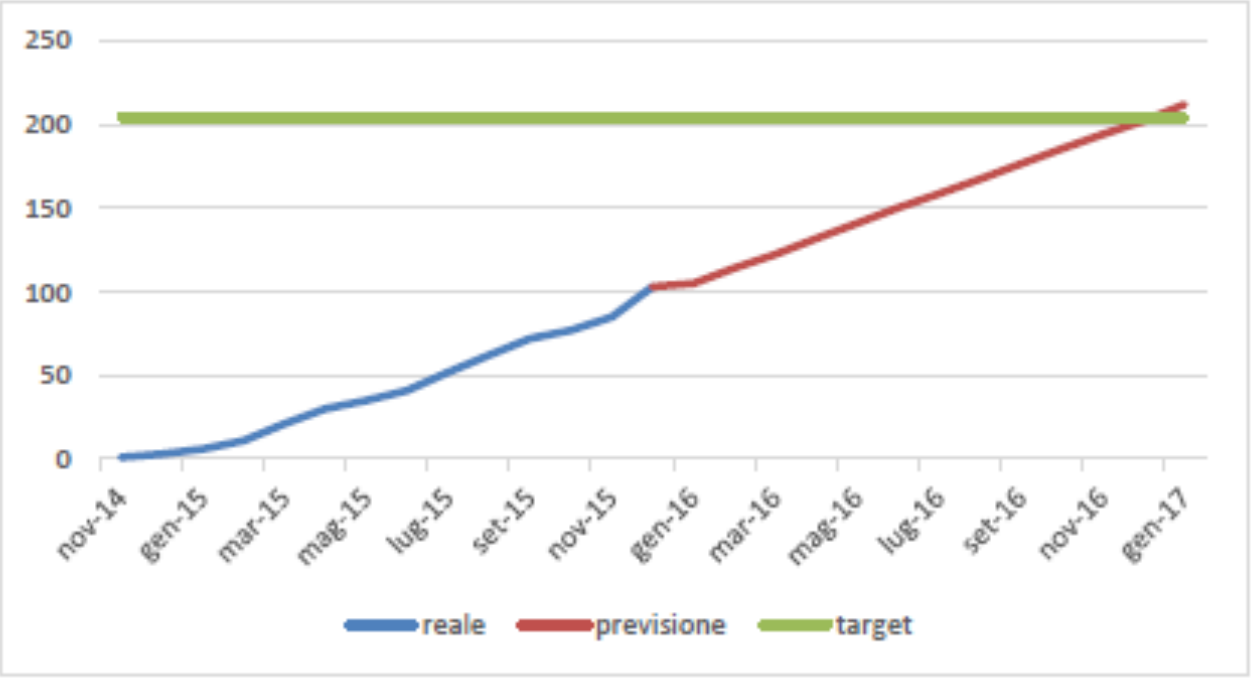
haematologica
the hematology journal

National Treatment Program of Philadelphia Chromosome-negative Adult Acute Lymphoblastic Leukemia with Pegylated Asparaginase Added to a Lineage-Targeted Risk- and Minimal Residual Disease-Oriented Strategy

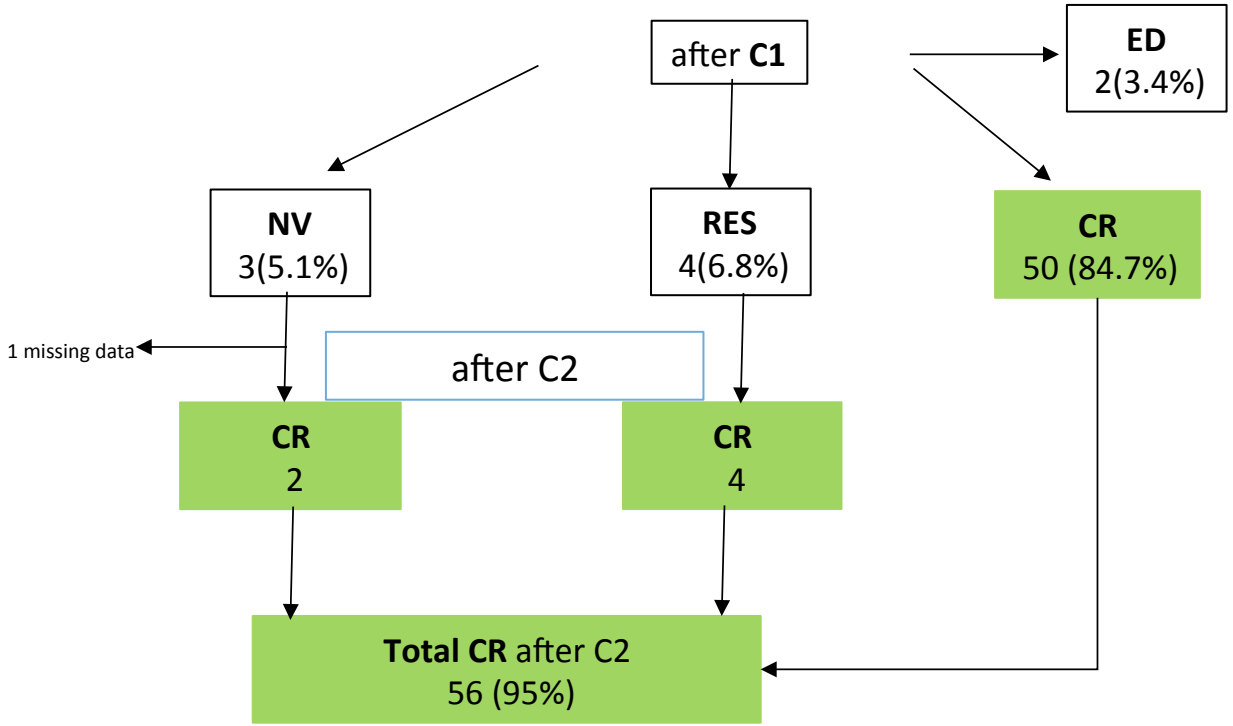
GIMEMA LAL 1913



GIMEMA LAL 1913



Treatment Response (n = 59)



Causes of death of these 2 patients
Infection
hyperbilirubinemia, hepatic dysfunction and alteration of coagulation after PEG-ASP administration

Deailsabout 4 patients RES after C1	
Age	≤55 (4), >55 (0)
Phenotype	B (3),T(1)
Risk	SR (3), No SR (1)

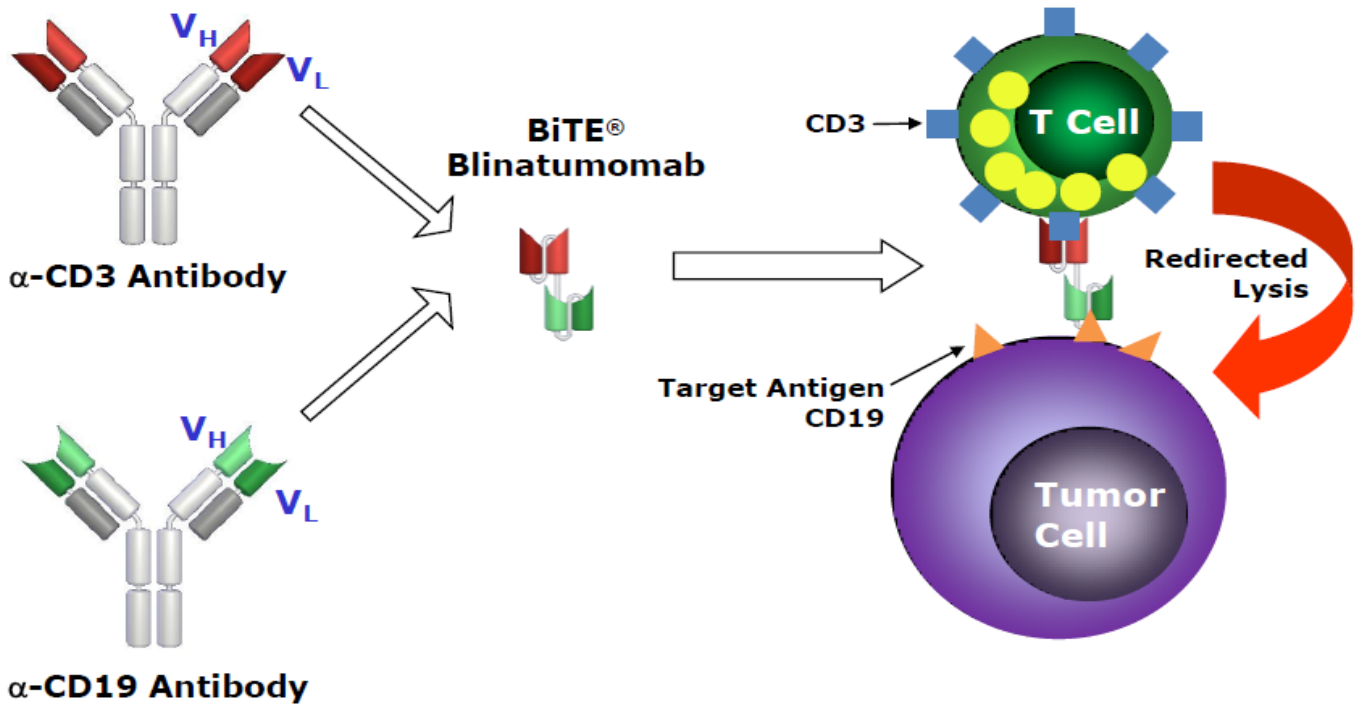
SAE correlate a Peg-ASP related SAE (excluding infections)

AE	N (%)/n1	/n2	outcome
CNS THROMBOSIS	4 (3.9)	(6.7)	Stable, NR, Stable, Stable
T.E. POLMONARE	1 (1.0)	(1.6)	Improved
COAGULOPATY	2 (1.9)	(3.3)	Improved, **Fatal***
ENCEFALOPATY	1 (1.0)	(1.6)	Improved
EPATOTOXICITY	5 (4.9)	(8.4)	Improved (2), Stable, NR, **Fatal**
PANCREATITIS	1 (1.0)	(1.6)	Stable

n1 = 103

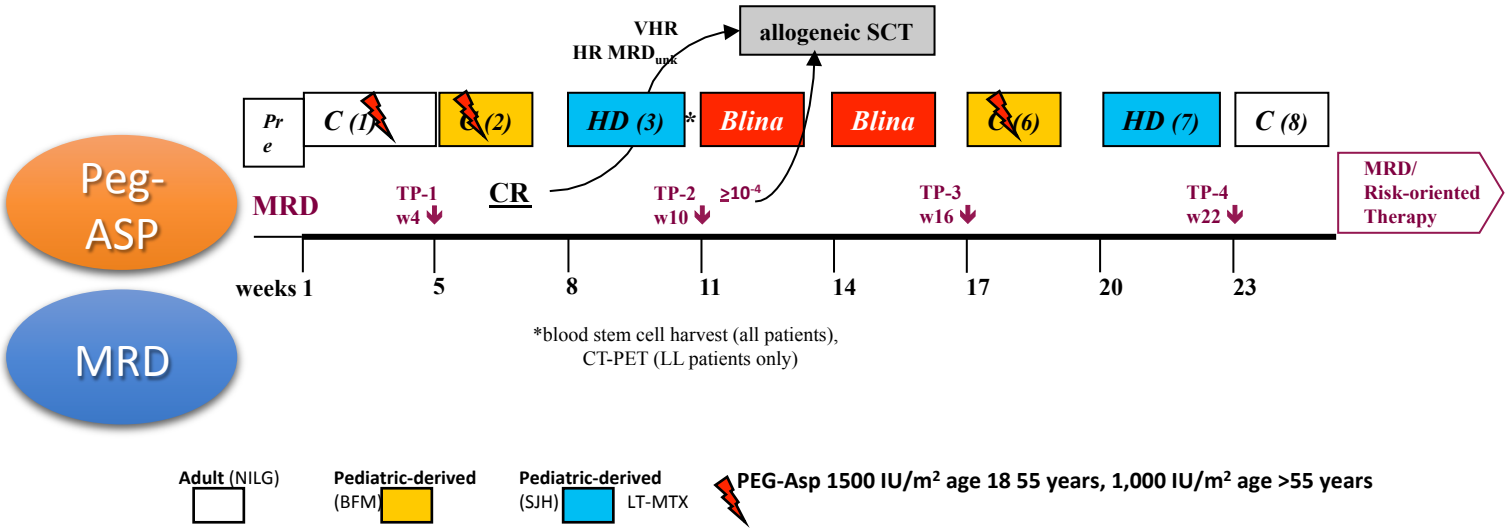
n2 = 59 (evaluable C1)

Blinatumomab:* a bispecific T-cell engaging (BiTE®) antibody construct



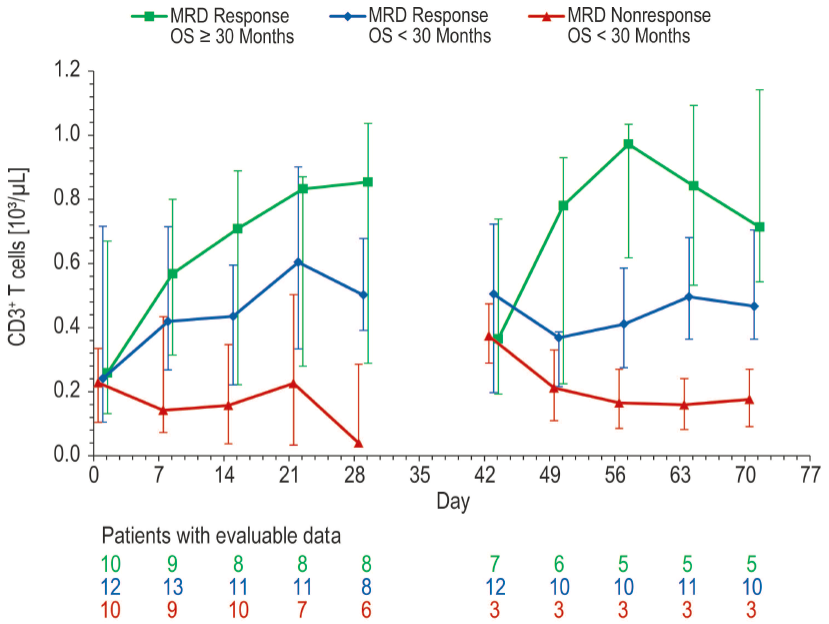
* ▼This medicinal product is subject to additional monitoring.
All suspected adverse reactions should be reported
Nagorsen D, Baeuerle PA. Exp Cell Res 2011;317:1255–60

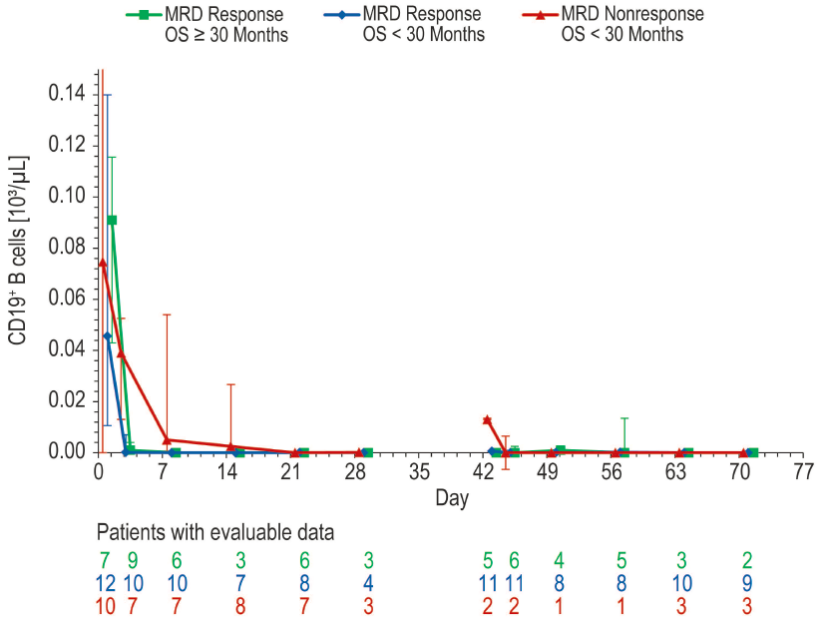
The next national trial
Option 1?

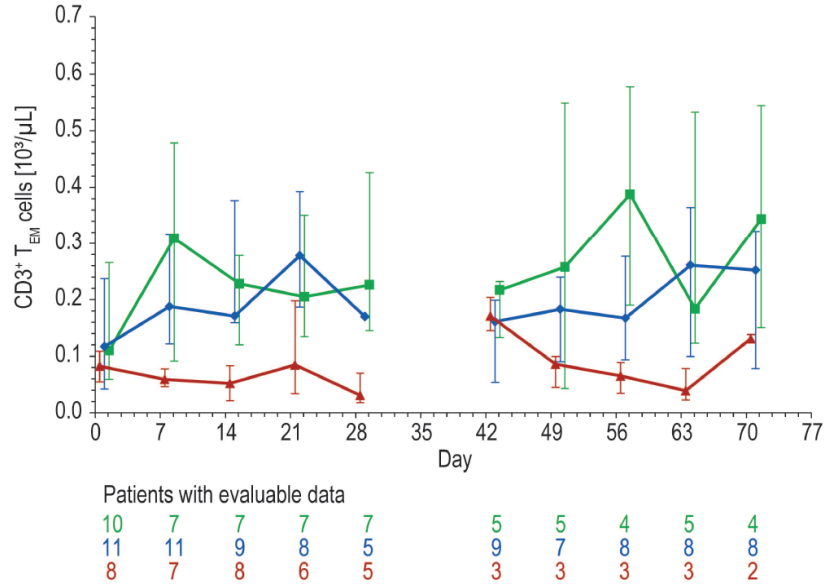


blood

T-cell and B-cell kinetics during cycle 1 (day 1 to 29) and cycle 2 (day 43 to 71) of blinatumomab treatment

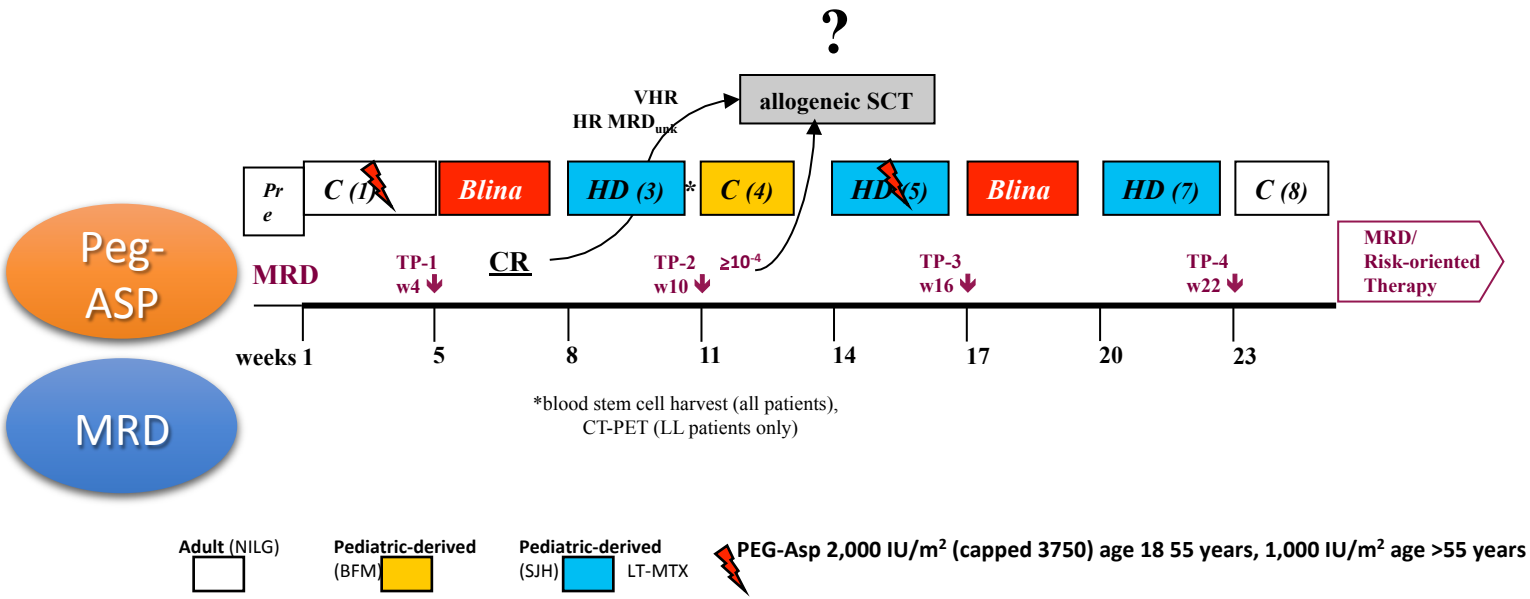






Zugmaier et al. Blood 2015;126:2578–84

The next national trial
Option 2?



Conclusions

- **Significant improvement in the outcome when intensified protocols are applied**

- **AlloHSCT should be reserved to very high risk patients (by molecular genetics) and those failing to achieve a molecular remission**

- **Innovative treatments are now available for the treatment of chemotherapy resistant/refractory (MRD positive) patients**