Transplant in Ph- B ALL

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COIs

Disclosures (last and current year)	
advisory board membership	Gilead, MSD, Novartis
travel support	Amgen, Gilead, MSD, Menarini
honoraria	Amgen, MSD, Bristol, Genesis, Gilead
consultancy	Abbvie, Novartis, Prime View
research support	Takeda, Abbvie
Disclaimers for this presentation	NO

Transplantation and Cellular Therapy 28 (2022) 791–792

ELSEVIER

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

ASTCT
American Society for Transplantation and Cellular Therapy

The Bottom Line

To Transplant or Not To Transplant in First Remission Acute Lymphoblastic Leukemia? Study group data give some answers, but not all

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As a hematologist specializing in allogeneic hematopoietic cell transplantation (HCT), I have to make predictions. I want to offer the best chance of cure to my patients but at the same time I know that a transplantation can end in a tragedy. In most cases I know which path I should recommend.

The “really tough choice” comes when I consult potential candidates for allogeneic HCT with Acute Lymphoblastic Leukemia (ALL) who have attained a first remission. Chemotherapy alone can be curative in up to 30 percent of adult patients and even more in adolescents and the so-called young adults [1,2].

Allogeneic HCT provides the best chance for durable disease control for adults with ALL, but how can I justify a treatment with high risk of morbidity and mortality when it is not obvious that conventional chemotherapy has failed?

In the face of such uncertainties, I prefer to enroll my patients into a national or international network study-group trial with a recommended treatment pathway which is prospectively evaluated and adjusted.

Long-Term Results of Allogeneic Stem Cell Transplantation in Adult Ph- Negative High-Risk Acute Lymphoblastic Leukemia

- adult patients (18-55 years of age) with ALL, GMALL, April 1999 and June 2013.
- 76% realization of HCT, median 148d (2/3 MUD)

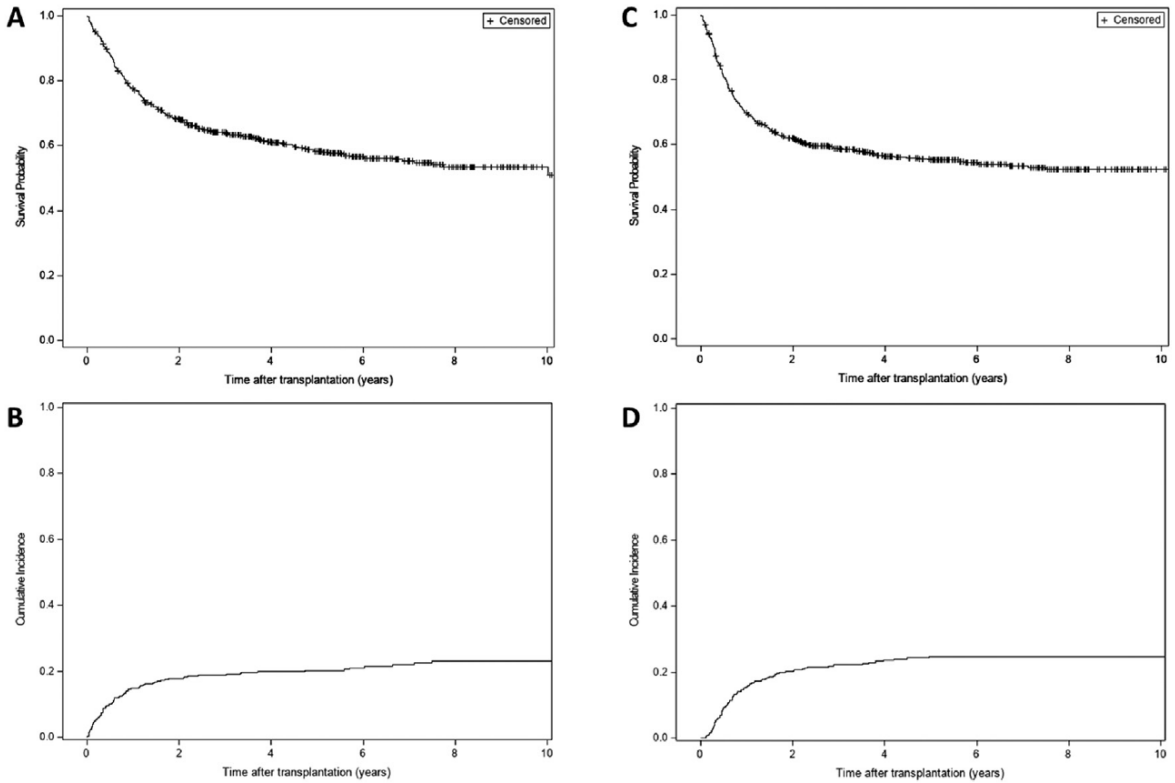


Figure 1. (A) Overall survival (OS). (B) Disease-free survival (DFS). (C) NRM. (D) Relapse risk (RR). (A) OS: Evaluable patients (N = 542), 5-year probability 0.58 (95% CI, 0.54-0.63). (B) DFS: Evaluable patients (N = 542), 5-year probability 0.55 (95% CI, 0.51-0.59). (C) NRM: Evaluable patients (N = 542), 5-year cumulative risk 0.20 (95% CI, 0.17-0.24). (D) RR: Evaluable patients (N = 542), 5-year cumulative risk 0.25 (95% CI, 0.21-0.28).

HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Reduced 8-Gray Compared to Standard 12-Gray Total Body Irradiation for Allogeneic Transplantation in First Remission Acute Lymphoblastic Leukemia: A Study of the Acute Leukemia Working Party of the EBMT

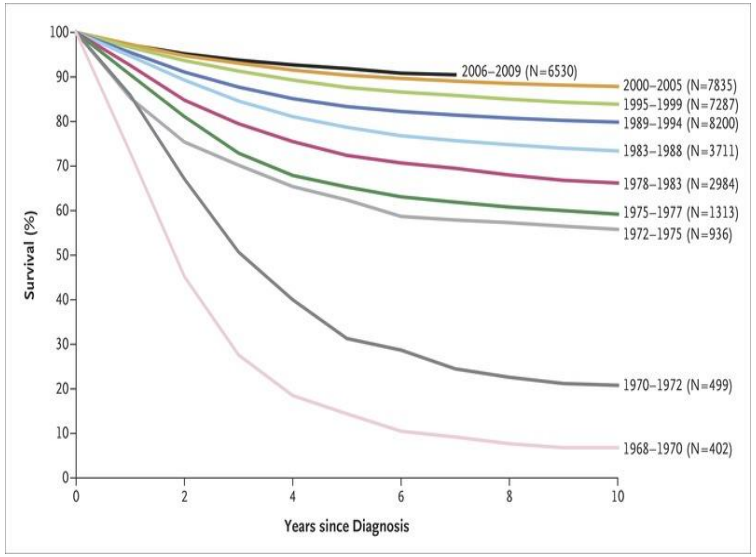
Correspondence: Alexandros Spyridonidis (spyridonidis@upatras.gr).

Transplant in Ph- B ALL

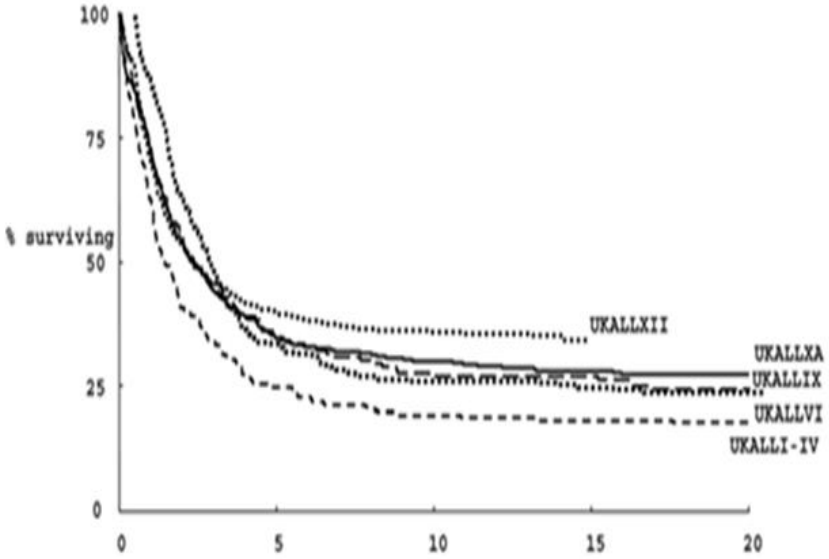
- Yes or no?
- Who and when?
- How?
- How I provide counselling to the patient with ALL referred to my transplant unit

Goal treatment is cure. It becomes harder to treat and cure as the patient ages.

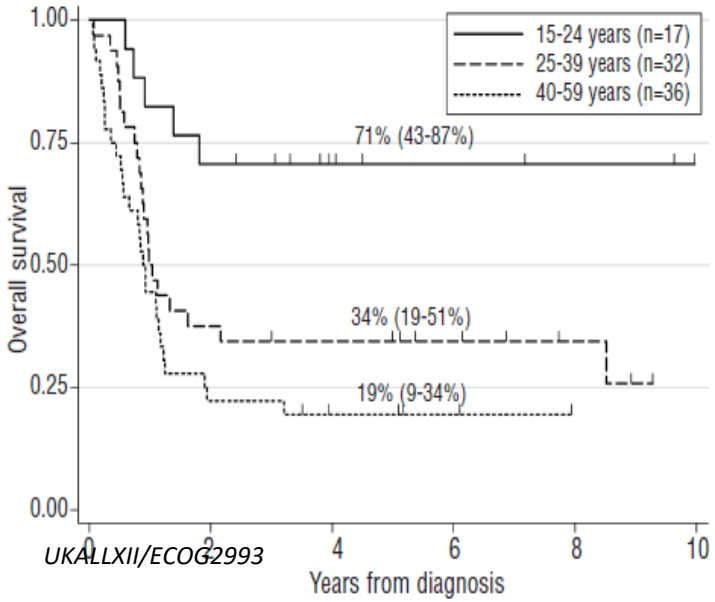
ALL - survival
has changed in children!



ALL survival
isn't changing a lot in adults!



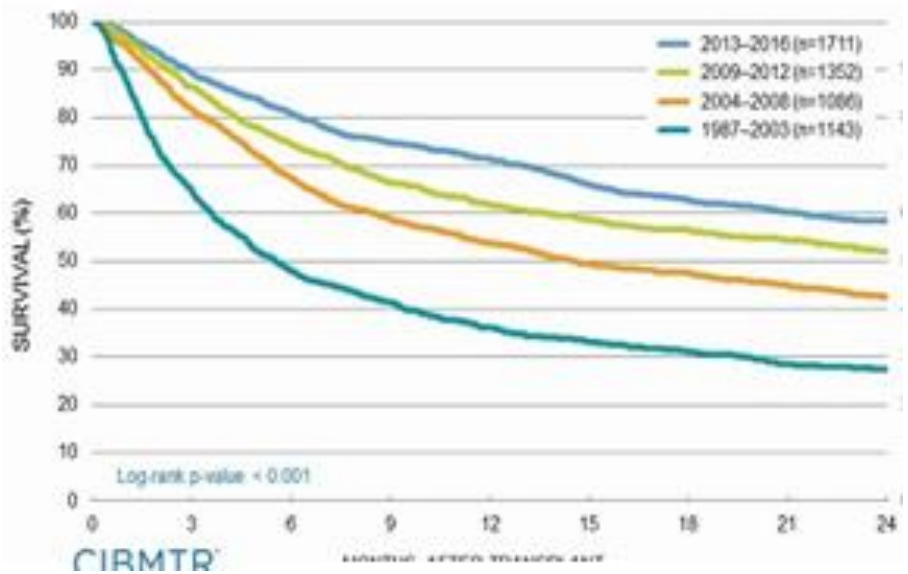
ALL survival
according to age

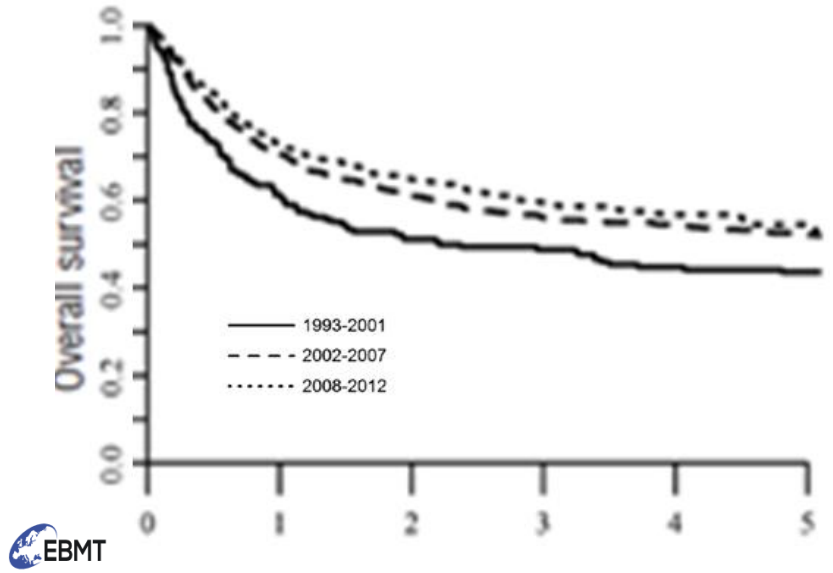


UKALLXII/ECOG2993

Marks DI, et al. Haematologica 2013;98:945–52

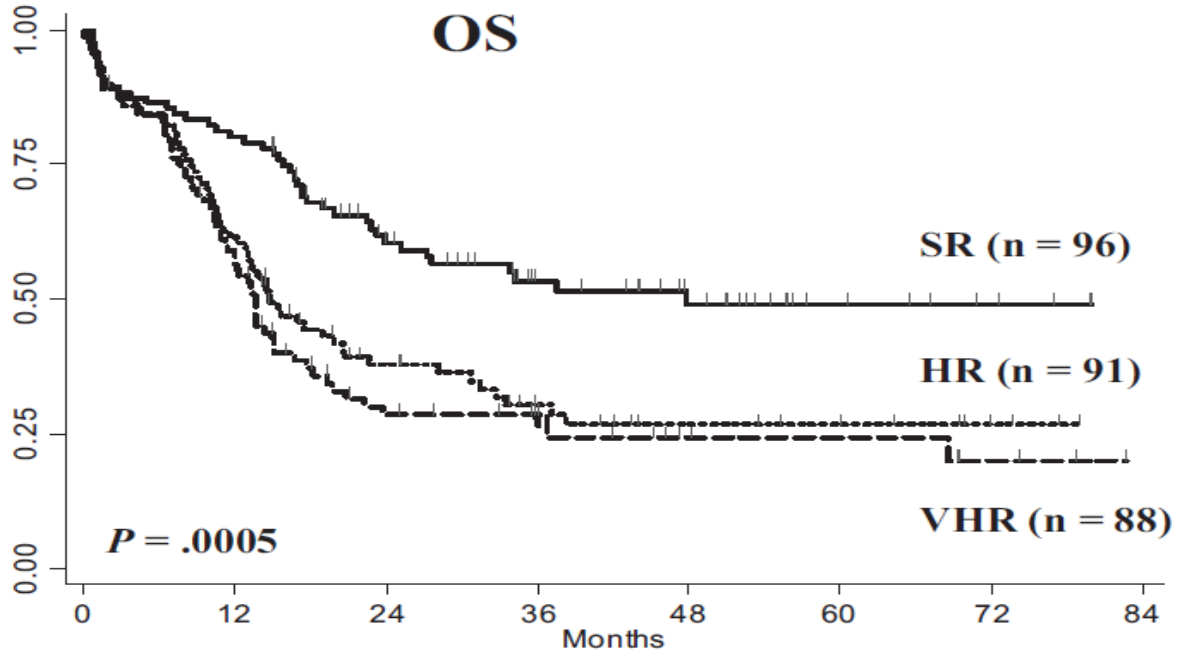
ALL-survival has changed in SCT adults





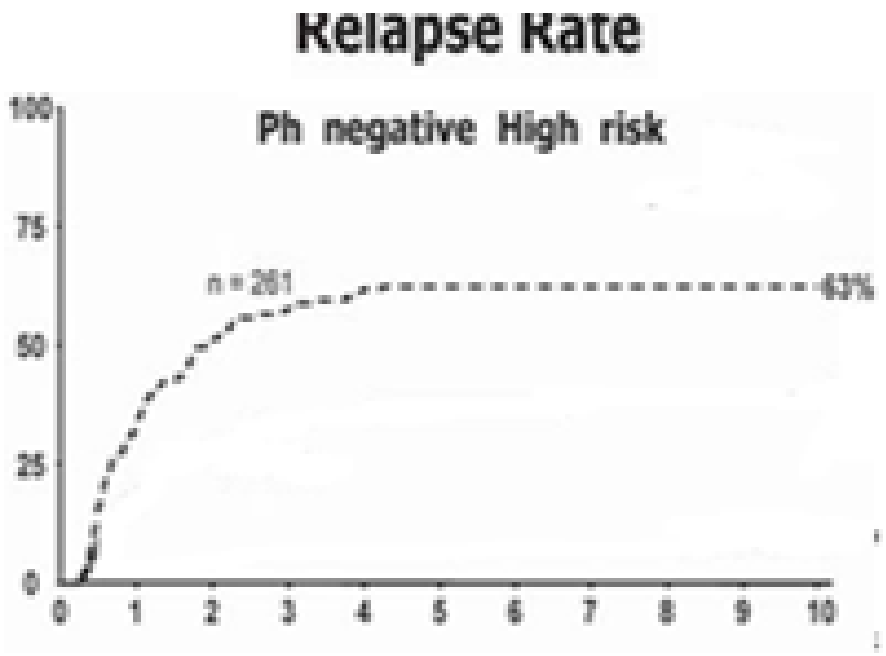
Giebel S, et al. Haematologica 2017;102(1):139–49

Not all ALL are the same. Some 20-40% patients can be cured without HCT. Some pts can be cured only with allo-HCT.



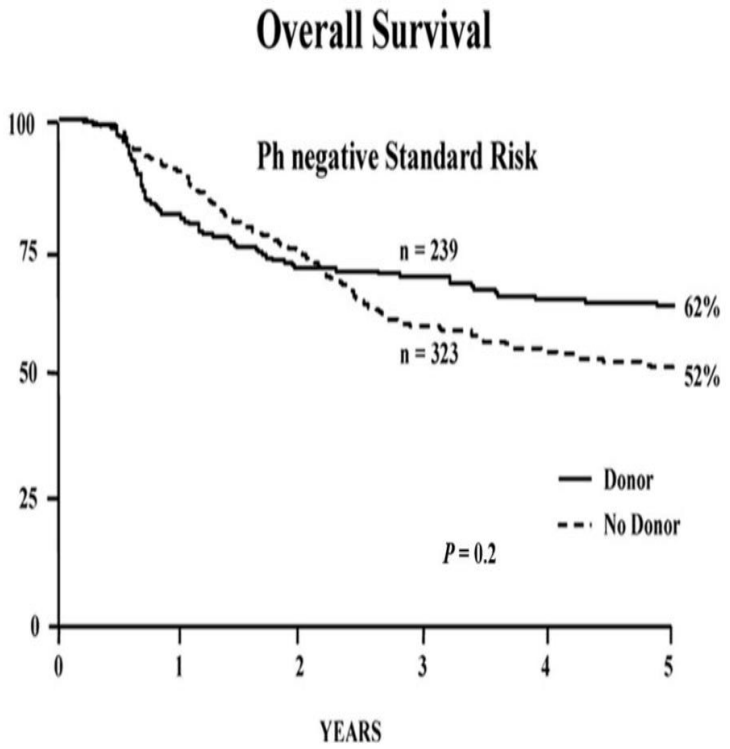
why to Tranpslant at CR1 (preimmunotherapy era)

5y OS <40% w/o HCT



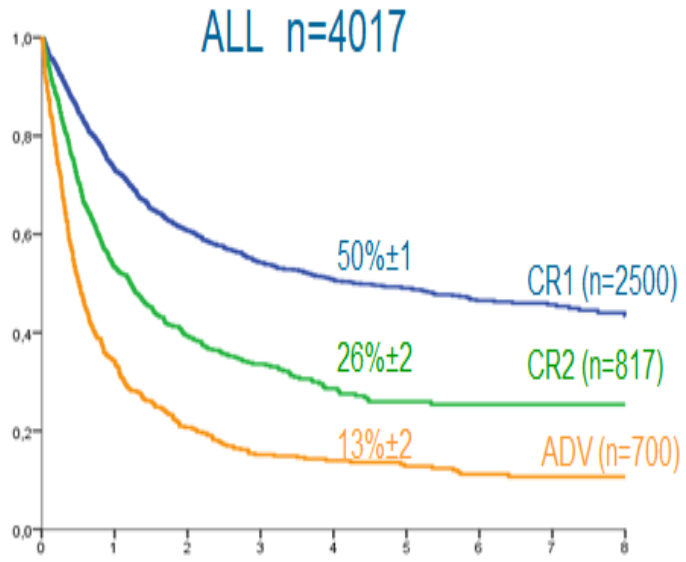
Sant et al. Eur J Cancer. 2009;45(6):931-91

HCT at CR1: yes



Goldstone AH, et al. Blood 2008;111:1827–33

Minimal salvage at CR2



CIBMTR

The field moves fast. Best treatment is a clinical trial

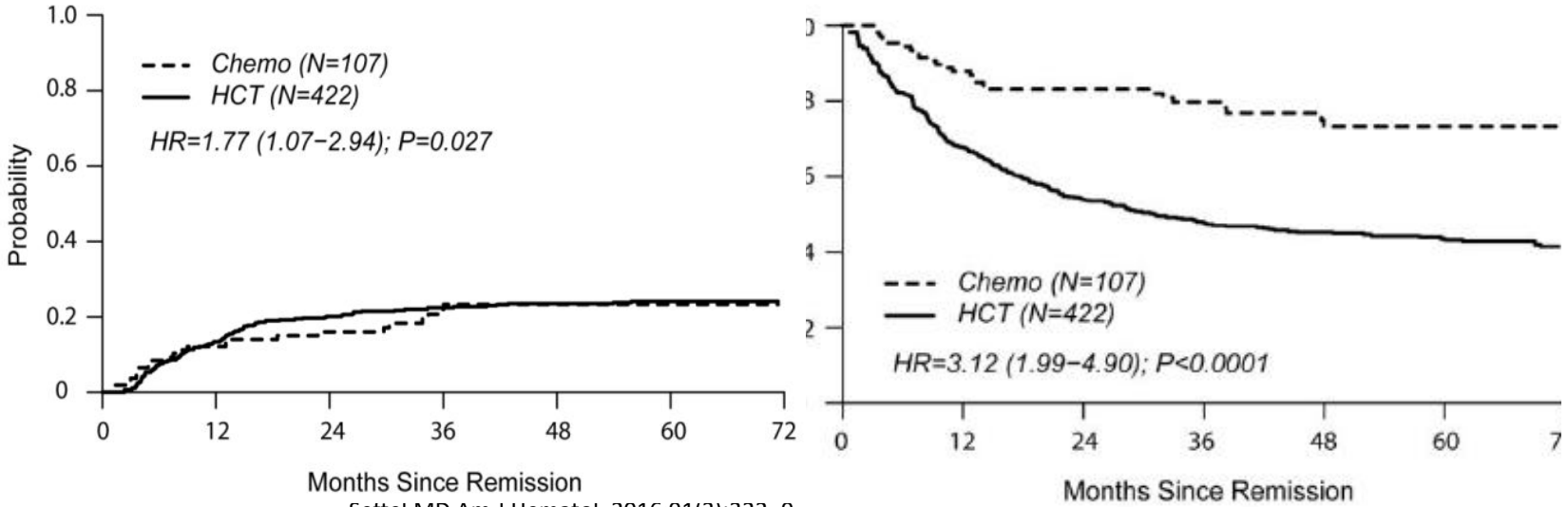
New drugs and technologies	Open questions
Better frontline therapies	Pediatric intensified protocols are enough?
Better prognostic markers (MRD, oncogenetics)	Not standardized, more validation needed
Better salvage immunotherapies for REL ALL or MRD	Blina, inotuzumab, CAR-T as standalone therapy?
Immunotherapies as first line / maintenance ?	In clinical studies

How I decide for transplant?

Has the patient received adequate frontline therapy without delays?

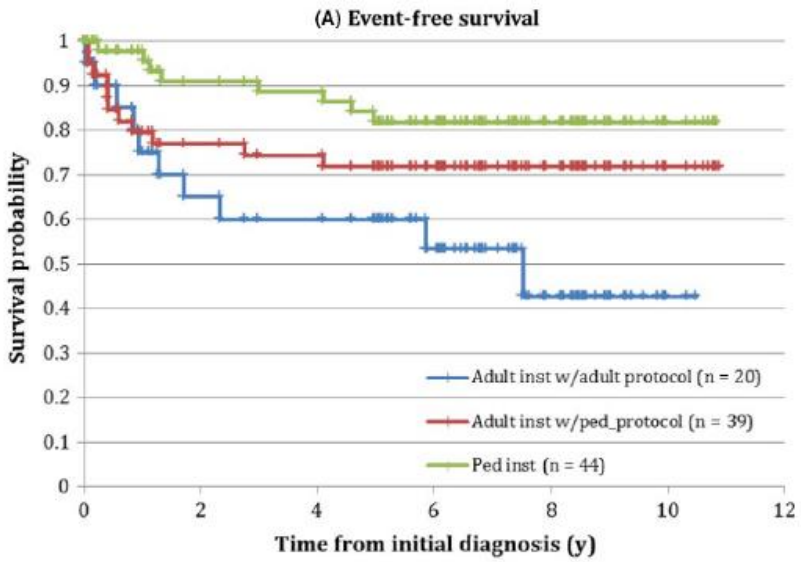
Pediatric inspired protocol may result in durable remissions also in adults
DFCI trials vs CIBMTR allo HCT retrospective , 2002-2011, 18-50y

Median age 30 y
Median age 34 y



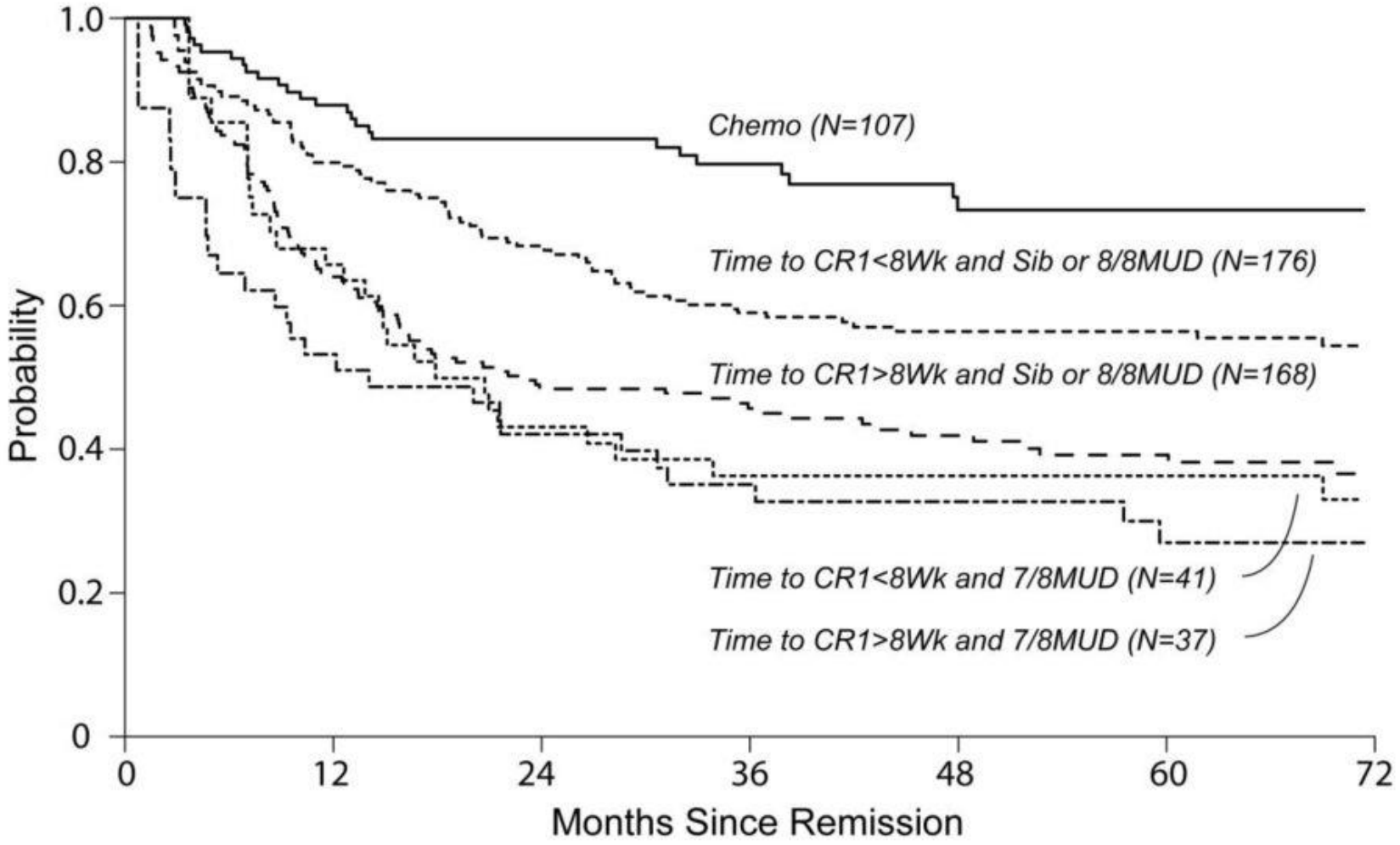
Settel MD Am J Hematol. 2016;91(3):322–9.

Chemo delivery wo delays may play a role
Canada 15-21 y ALL 1992-2011, Locus of care



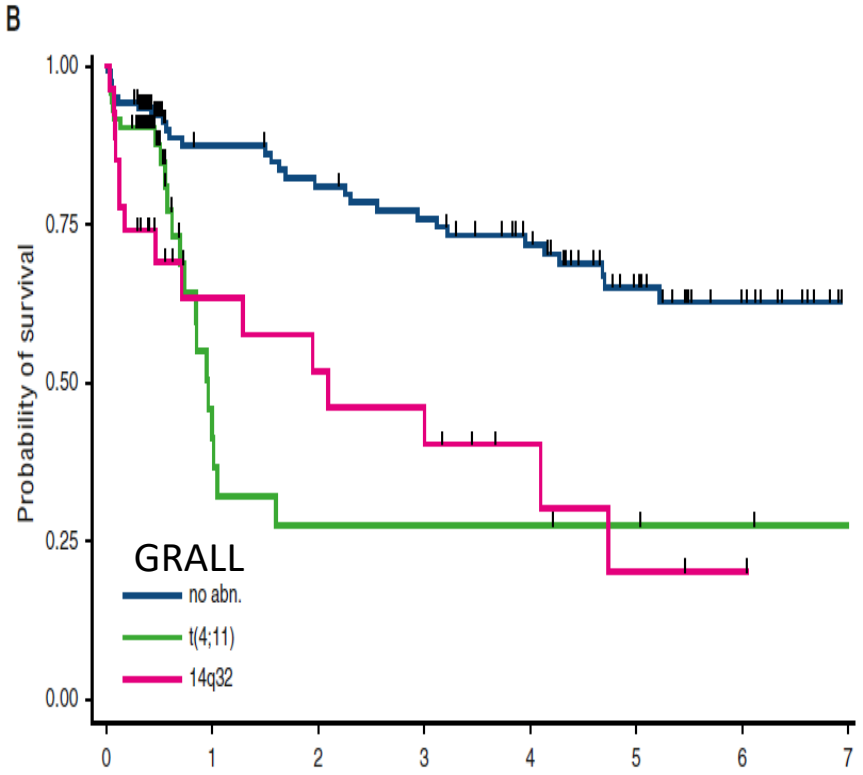
Cancer Medicine. 2019;8:2095–2103.

Response dynamics. Has the patient reached CR1 quickly?



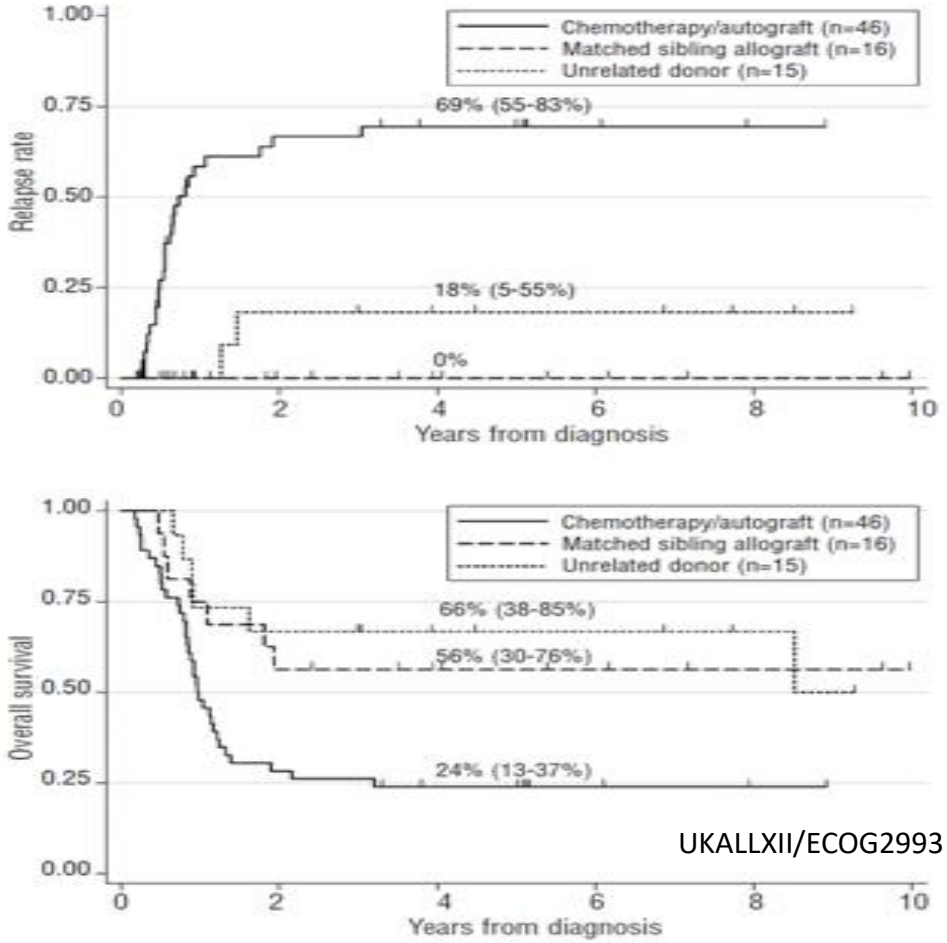
Seftel MD Am J Hematol. 2016;91(3):322–9.

High risk genetics? (e.g. t(4;11) / MLL)



(Blood. 2017;130(16):1832-1844)

Allo-HCT may overcome HR cytogenetics

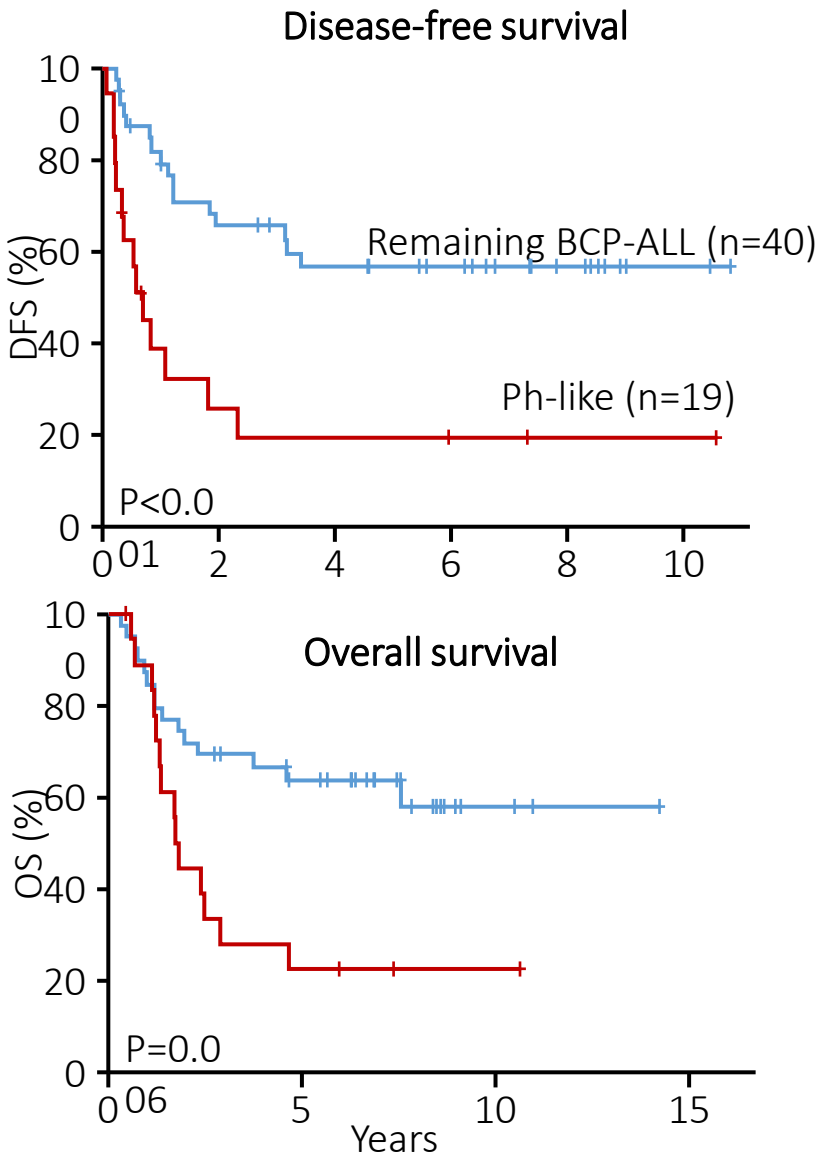


UKALLXII/ECOG2993 t(4;11)

Marks DI, et al. Haematologica 2013;98:945–52

High risk BCR-ABL1 (Ph)-like ALL?

- Approx. 10%-20% cases of B- ALL. Heterogenous group
- Difficult to diagnose, a FISH panel could be used
- Poor prognosis
- Fewer MRD- remissions
- High Relapse risk even if MRD- has been achieved
- Responsive to TKIs



Herold T, et al. Haematologica 2017;102:130–8

Major established High-risk genetics in Ph –ALL

Genetics	Risk group	
t(4;11) (11q23/MLL)	Poor, very HR	MRC-ECOG, SWOG, NILG-ALL, North UK, GIMEMA
CK (>5)	Poor, very HR	MRC-ECOG, NILG-ALL, North UK
low hypodiploidy	Poor, very HR	MRC-ECOG, NILG-ALL, North UK
−7, t(8;14)	HR, Unfavorable	MRC-ECOG, SWOG, North UK,
Bcr abl like	Poor, very HR	MRC-ECOG, SWOG, GIMEMA
high hyperdiploidy	Good, SR	MRC-ECOG

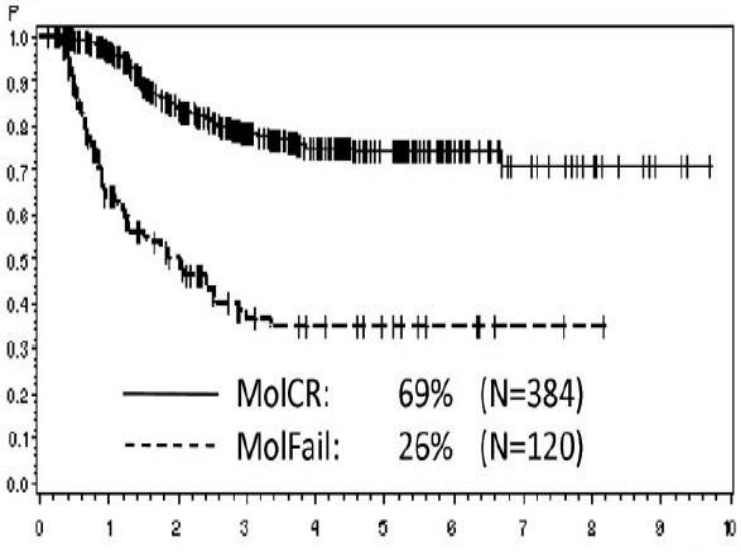
MRC-ECOG Ph III, SWOG Ph III North UK Observational, NILG-ALL Ph II , GIMEMA Phase II

(Moorman et al. Blood 2007, Pullarkatet al. Blood 2008, Bassan et al. Blood 2009, Moorman et al Blood 2010, Manciniet al. Blood 2005

MRD
The utmost key factor that predicts ALL relapse

Persistent MRD. Prognostic impact In metanalyses

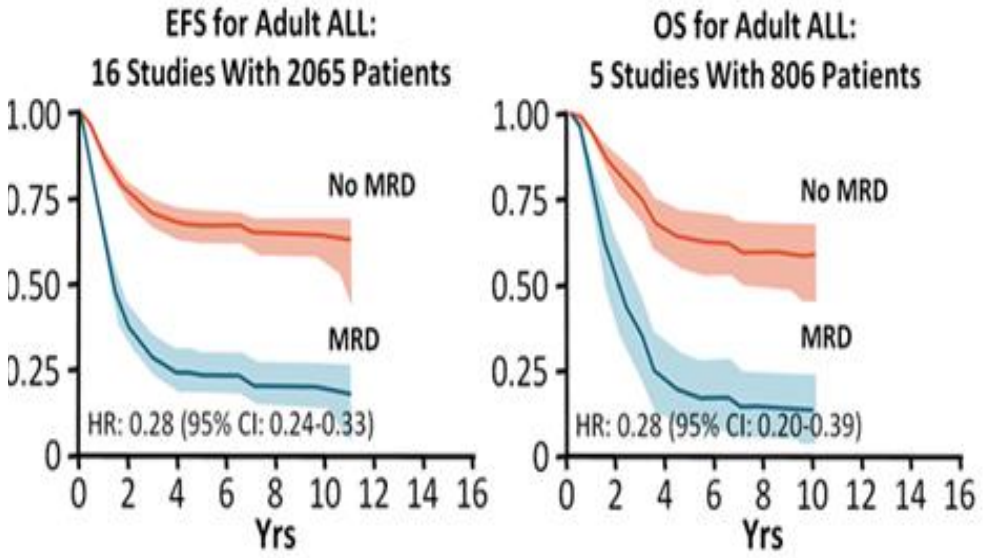
PROSPECTIVE STUDIES



MRD at Week 16 (GMALL 08)

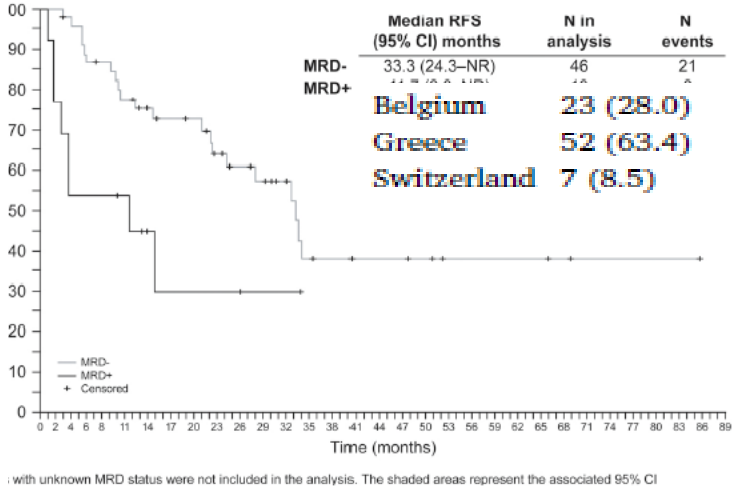
Goekbuget et al. Blood 2012

METANANALYSIS



Berry DA, et al. JAMA Oncol. 2017;3:e170580

CLINICAL PRACTICE



with unknown MRD status were not included in the analysis. The shaded areas represent the associated 95% CI

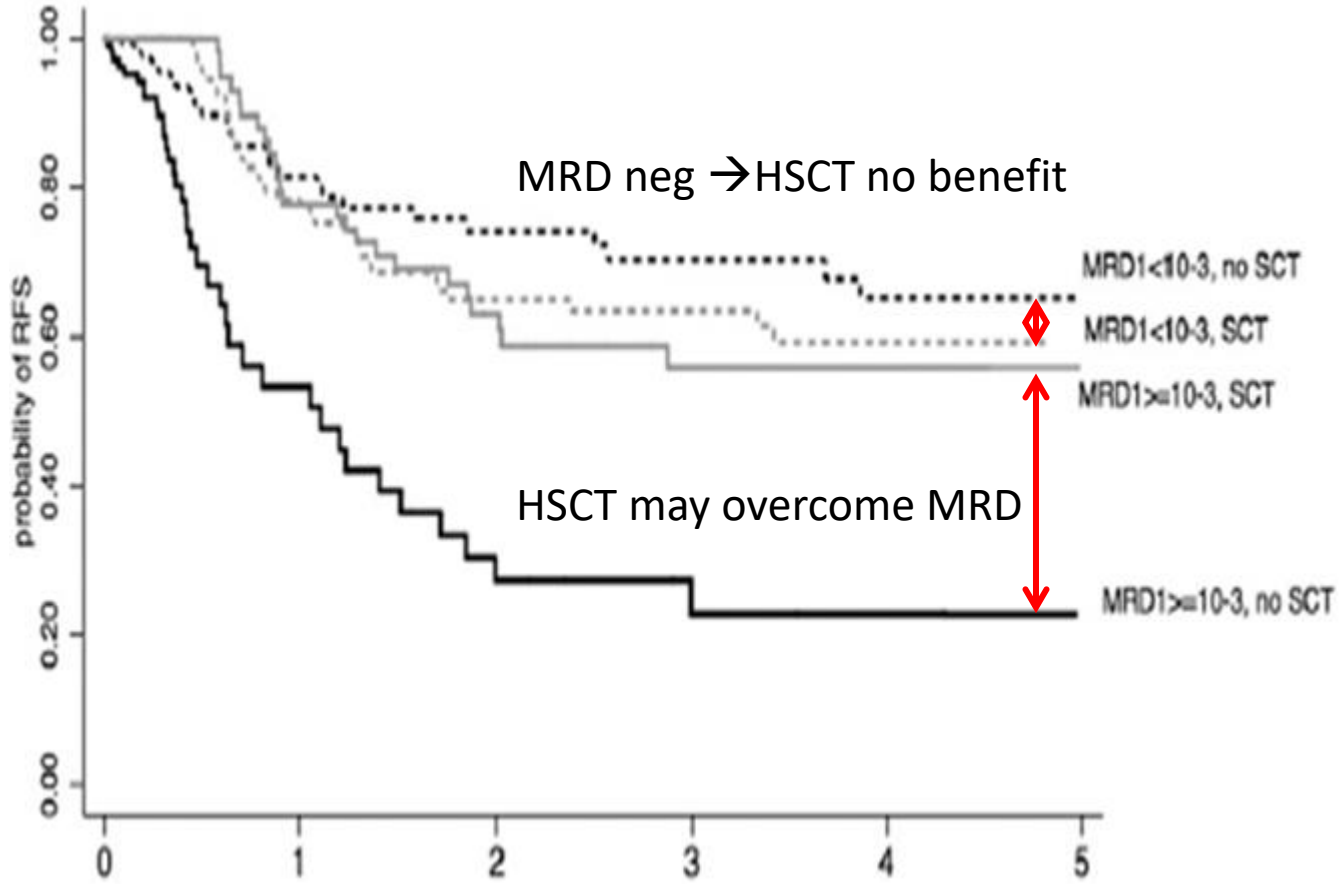
Fig. 1. RFS from CRh (A) for all patients with ALL and (B) by MRD status[a].

Leukemia Research 91 (2020) 106334

MRD+ pts benefit from allo HCT

GRALL

- Intensified frontline protocol (92% CR)
- SCT> High Risk (WBC, genetics, MRD)
- SCT > Sibling donor vs no donor



BLOOD, 16 APRIL 2015 x VOLUME 125,

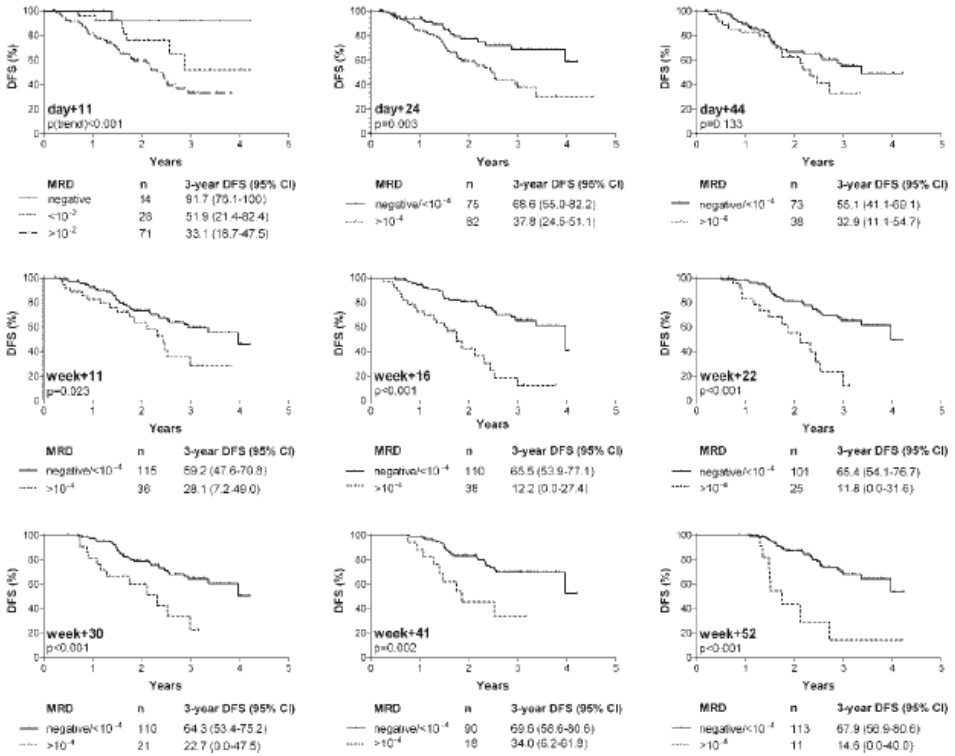
Persistent MRD. Indication for transplant

Data from prospective MRD-oriented trials					
Study (year started)	**MRD+**	**MRD+ to allo-SCT**	**allo-SCT (5youtcome)**	**No allo-SCT (5y outcome)**	**P**
GMALL (1999)	120 SR+HR	57 (47%)	DFS 44% OS 54%	DFS 11% OS 33%	<0.001 0.06
NILG (2000)	60 SR+HR	26 (43%)	DFS 42%	DFS 12%	0.0001
PETHEMA (2003)	24 HR	24 (100%)	DFS 24% OS 31%	-	-
GRAALL (2003)	105 HR	59 (56%)	DFS 55% OS 65%	DFS 22% OS 30%	0.001 0.002

1Gökbuget N, et al. Blood. 2012;120:1868–76; 2. Bassan R, et al. Blood Cancer J 2014; 2014;4:e225 and supplementary information; Ribera J, et al. J Clin Oncol 2014;32:1595–04; 4. Dhédin N, et al. Blood 2015;125:2486–96

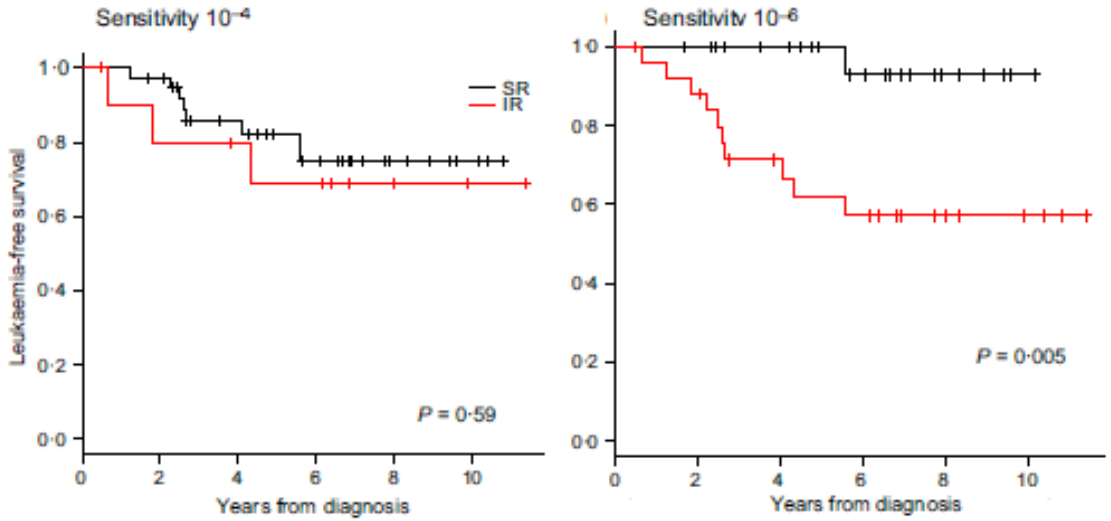
MRD≠ MRD ≠ MRD
any MRD predicts outcome

MRD at any time point



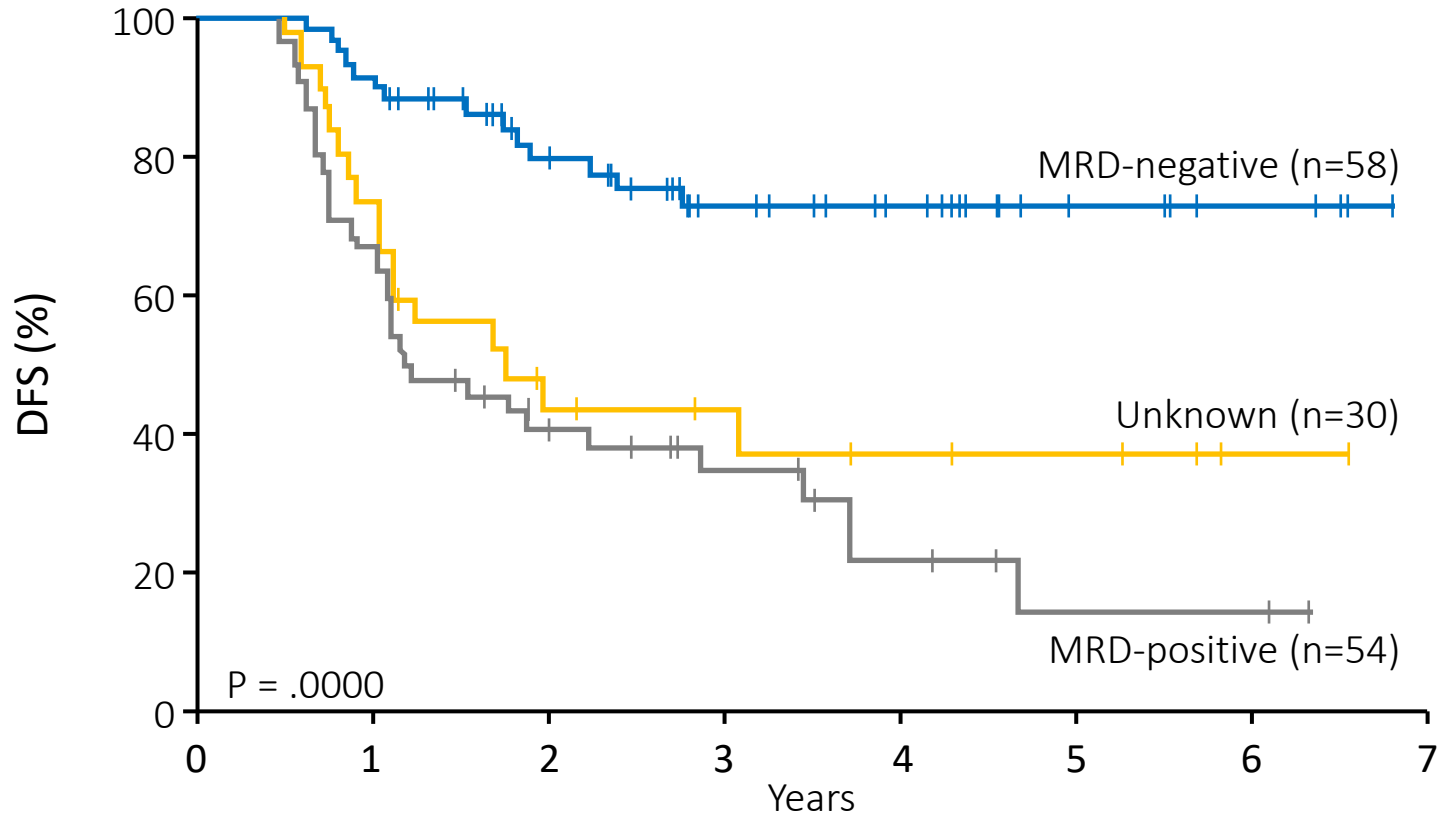
Blood. 2006; 107:1116-1123

Even low MRD



British Journal of Haematology, 2017, 176, 248–257

Can allograft be spared in MRD negative pts?

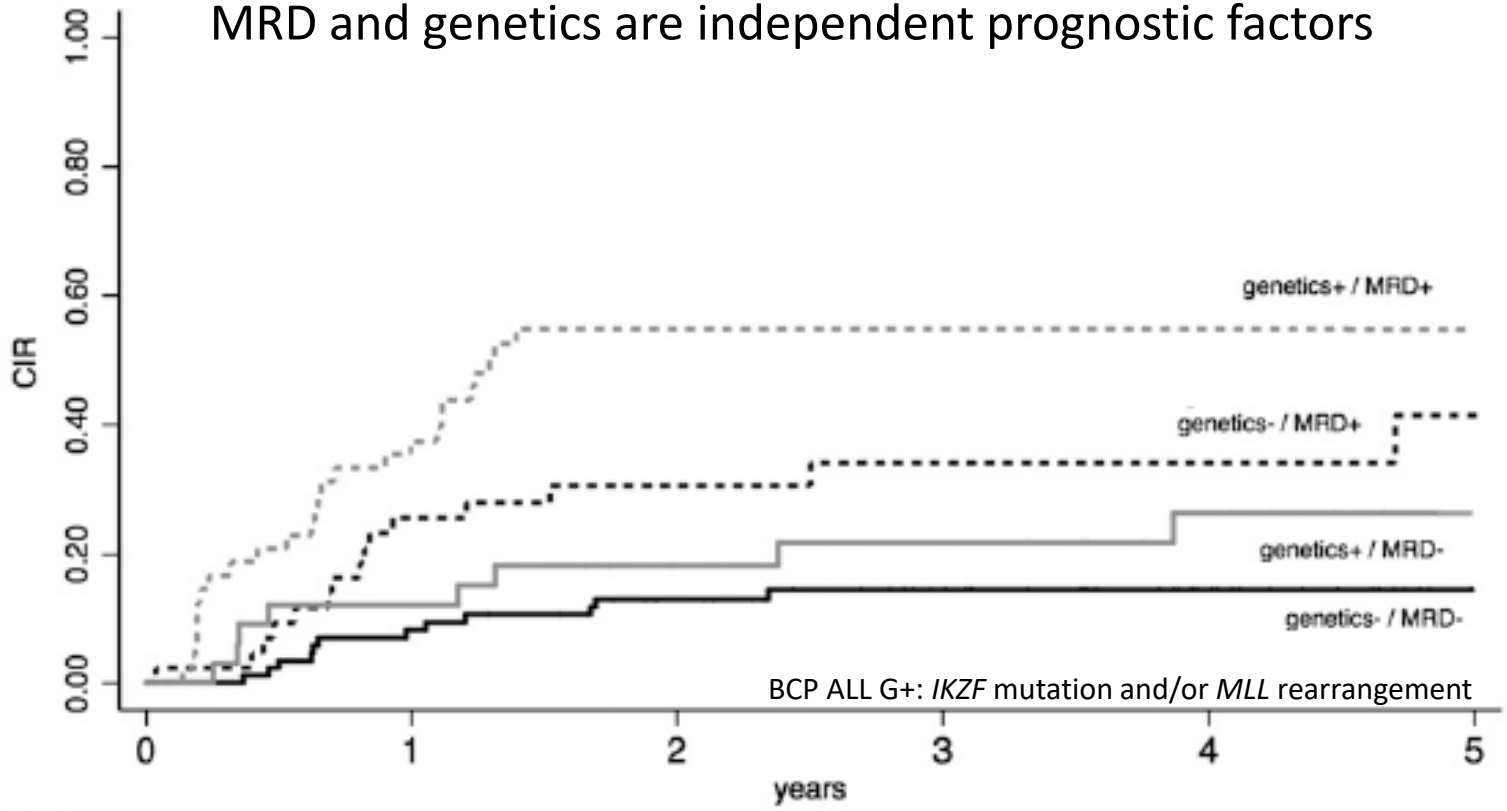


1. Bassan R, et al. Blood 2009;113:4153–62

What is the meaning of MRD levels in the context of different genotypes?

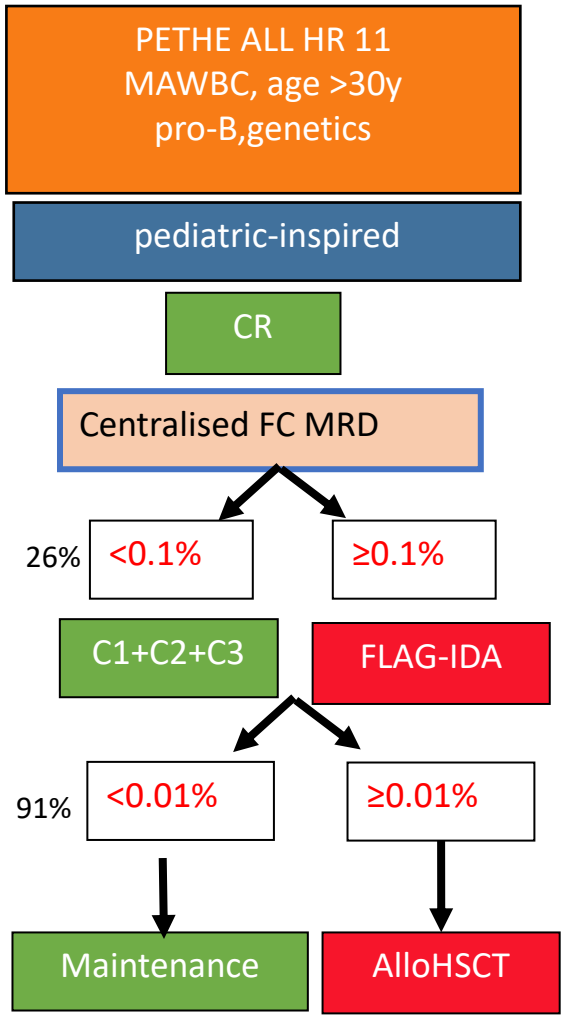
GRAALL

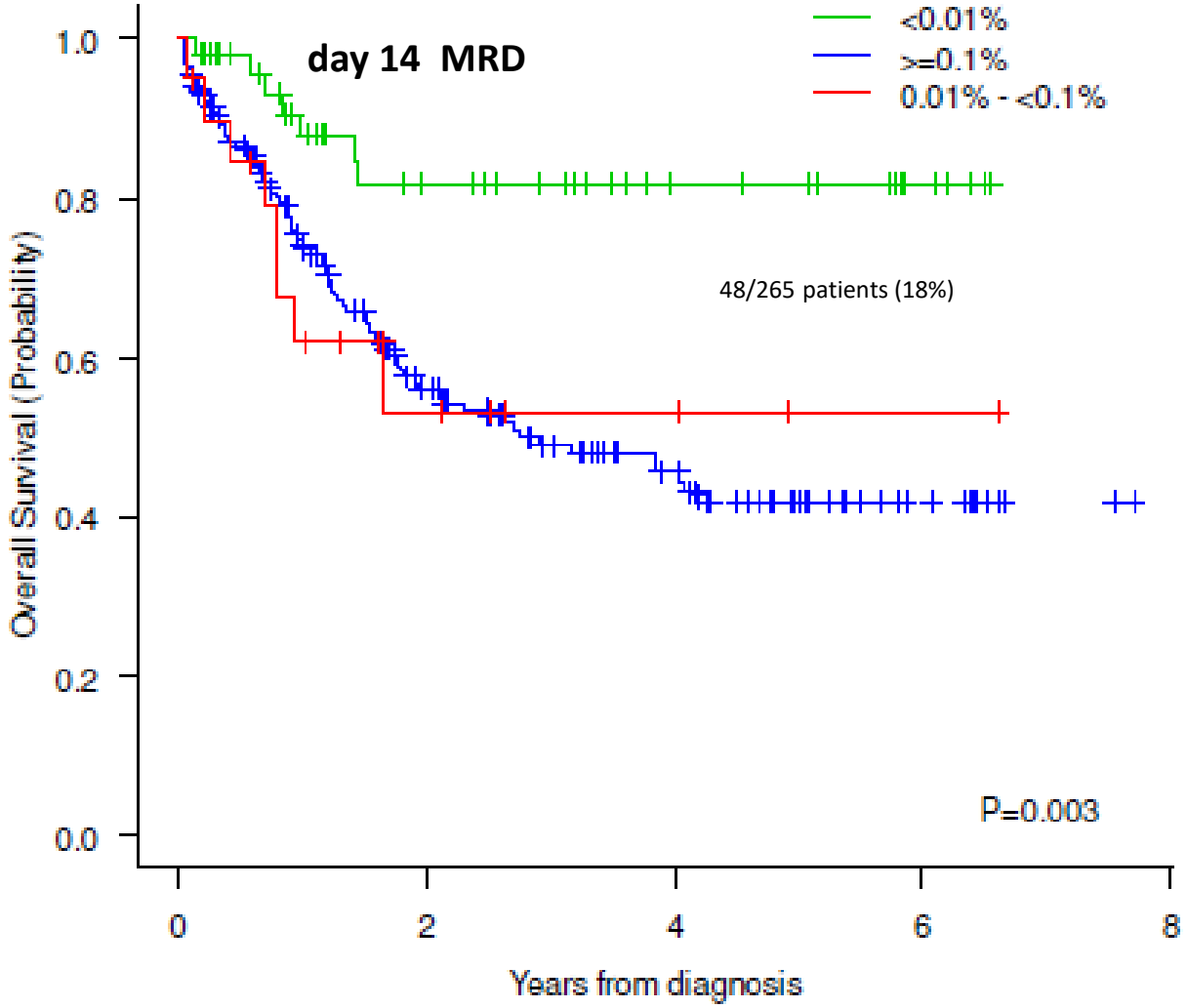
MRD and genetics are independent prognostic factors



Blood. 2014;123(24):3739-3749

MRD early responders: pts that do not need HCT





Blood 2021 Apr 8;137(14):1879-1894.

What do the experts suggest?

Indications for allo HCT in ALL CR1. In Europe

Study group	Diagnosis	Oncogenetics	MRD after Induction	MRD after Consolidation	MRD method
GMALL (Germany)	WBC, pro B ALL	MLL	No CR	MRD ≥10−4	PCR
HOVON (Netherlands)	WBC	adverse	No CR	MRD ≥10−4	FC
SVALL(Swed)/ FALL (Fin)	(opt WBC)	(opt MLL , Ho-T)	No CR	MRD ≥10−3	FC/ PCR
GIMEMA (Italy)	WBC, pro B ALL	MLL		MRD +	PCR
GRAALL (France)	**X**	**X**	MRD ≥10−3	MRD ≥10−4	PCR
PALG (Poland)	WBC, CNS	MLL,	MRD ≥10−3	MRD ≥10−4	FC/PCR
PETHEMA (Spain)	**X**	**X**	MRD ≥10−3	MRD ≥10−4	FC
UKALL (UK)	WBC, **>40 y**	MLL, CK, Ho-Tr	MRD ≥10−4		PCR

Bone Marrow Transplantation (2019) 54:798–809

In Europe

ESMO guidelines

clinical practice guidelines

Annals of Oncology 27 (Supplement 5): v69–v82, 2016
doi:10.1093/annonc/mdw025
Published online 7 April 2016

Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

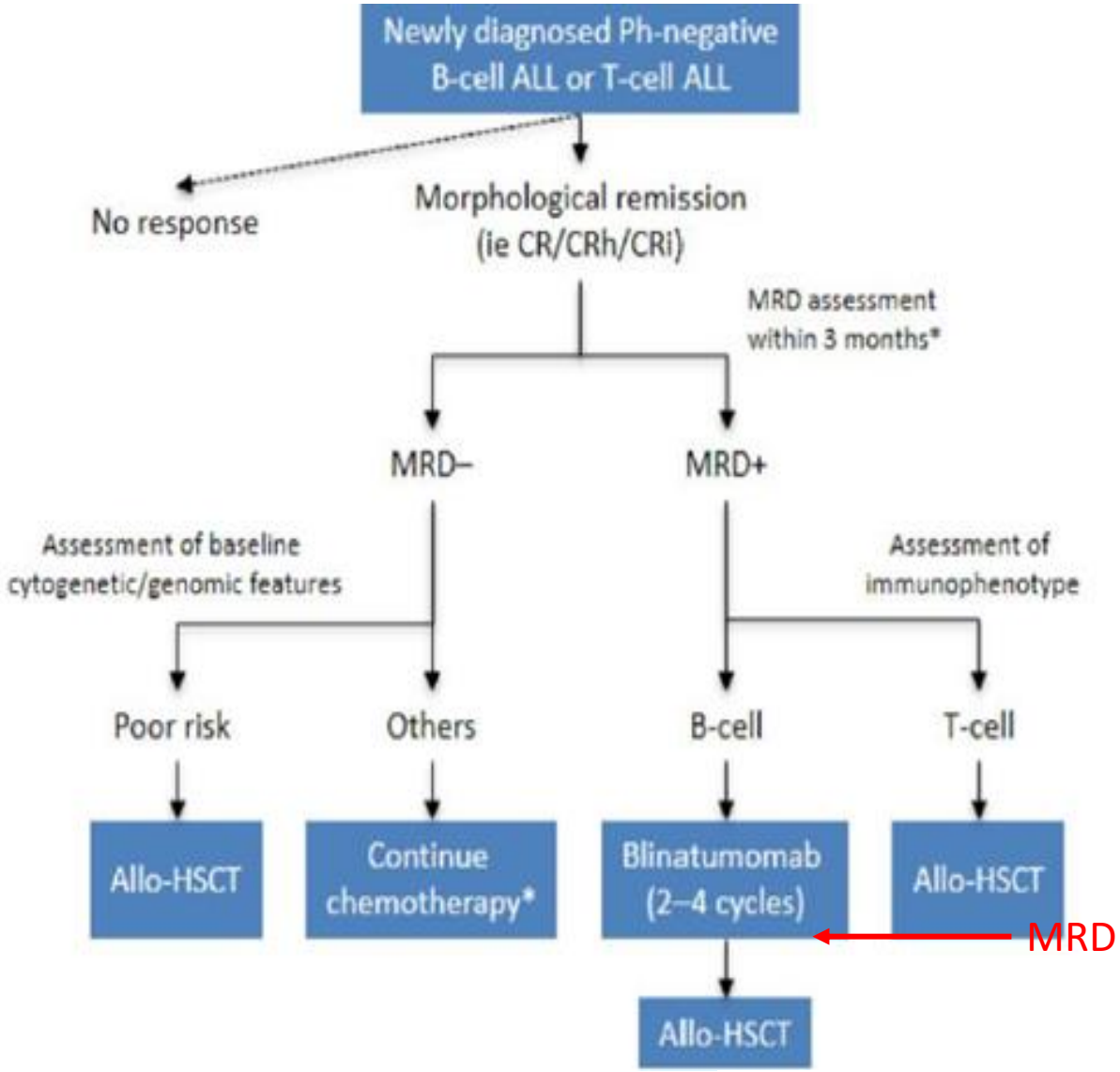
D. Hoelzer[1], R. Bassan[2], H. Dombret[3], A. Fielding[4], J. M. Ribera[5] & C. Buske[6] on behalf of the ESMO Guidelines Committee*

[1]ONKOLOGIKUM Frankfurt am Museumsufer, Frankfurt, Germany; [2]Hematology Unit, Ospedale dell'Angelo e Ospedale SS. Giovanni e Paolo, Mestre-Venezia, Italy; [3]Institut Universitaire d'Hematologie Hopital St Louis, Paris, France; [4]Cancer Institute, University College London, London, UK; [5]Department of Clinical Hematology, ICO-Hospital Germans Trias i Pujol, Jose Carreras Research Institute, Universitat Autonoma de Barcelona, Barcelona, Spain; [6]CCC Ulm, Institut für Experimentelle Tumorforschung, Universitätsklinikum Ulm, Ulm, Germany

Stage	Recommendations
CR1	– AlloSCT **recommended in all patients with poor early MRD response** – AlloSCT **not recommended in SR patients with sustained molecular response** – Indication **unclear in HR patients with sustained molecular response**
CR≥2	– AlloSCT superior

Hoelzer D. et al. Annals of Oncology 2016:27(S5); v69-v82

In North America

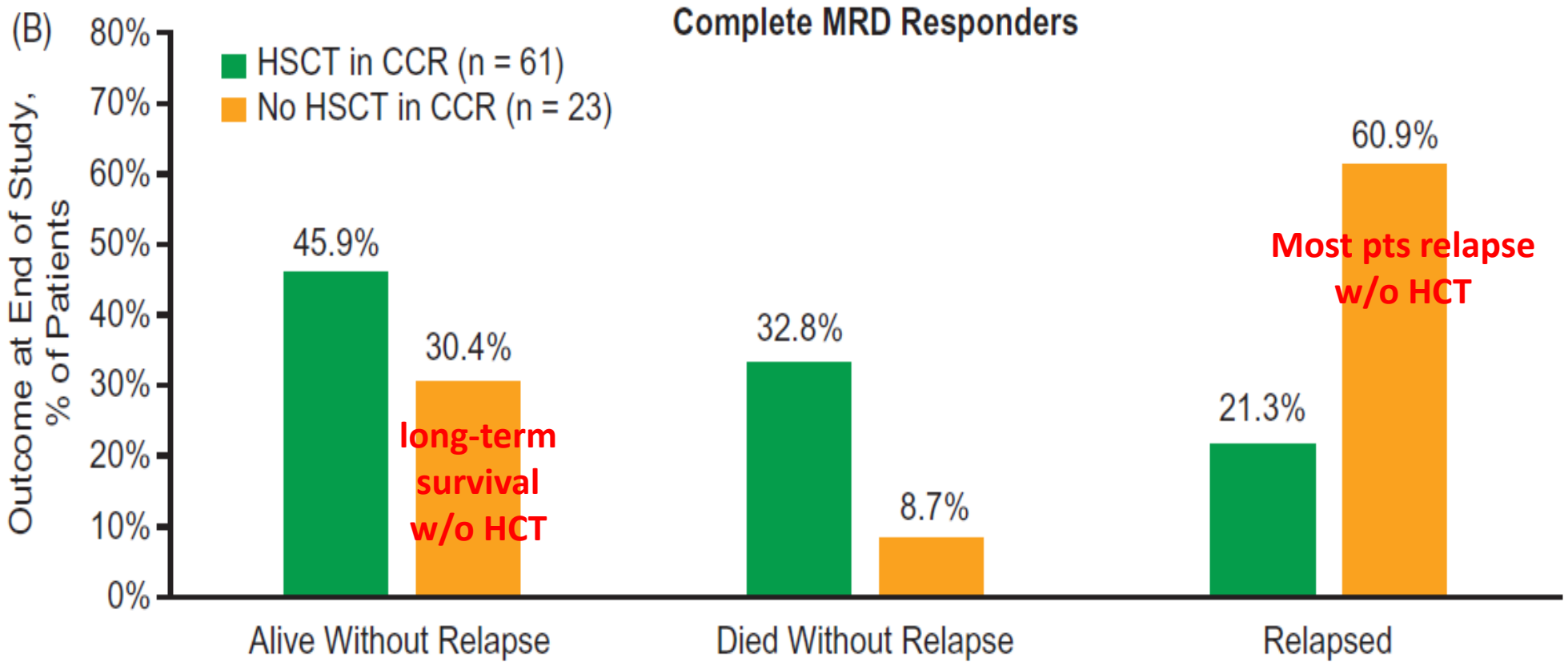


: Short NJ, et al. Am J Hematol 2019;94:257–65.

Conversion from MRD pos to negative, Need for allo-HCT consolidation?

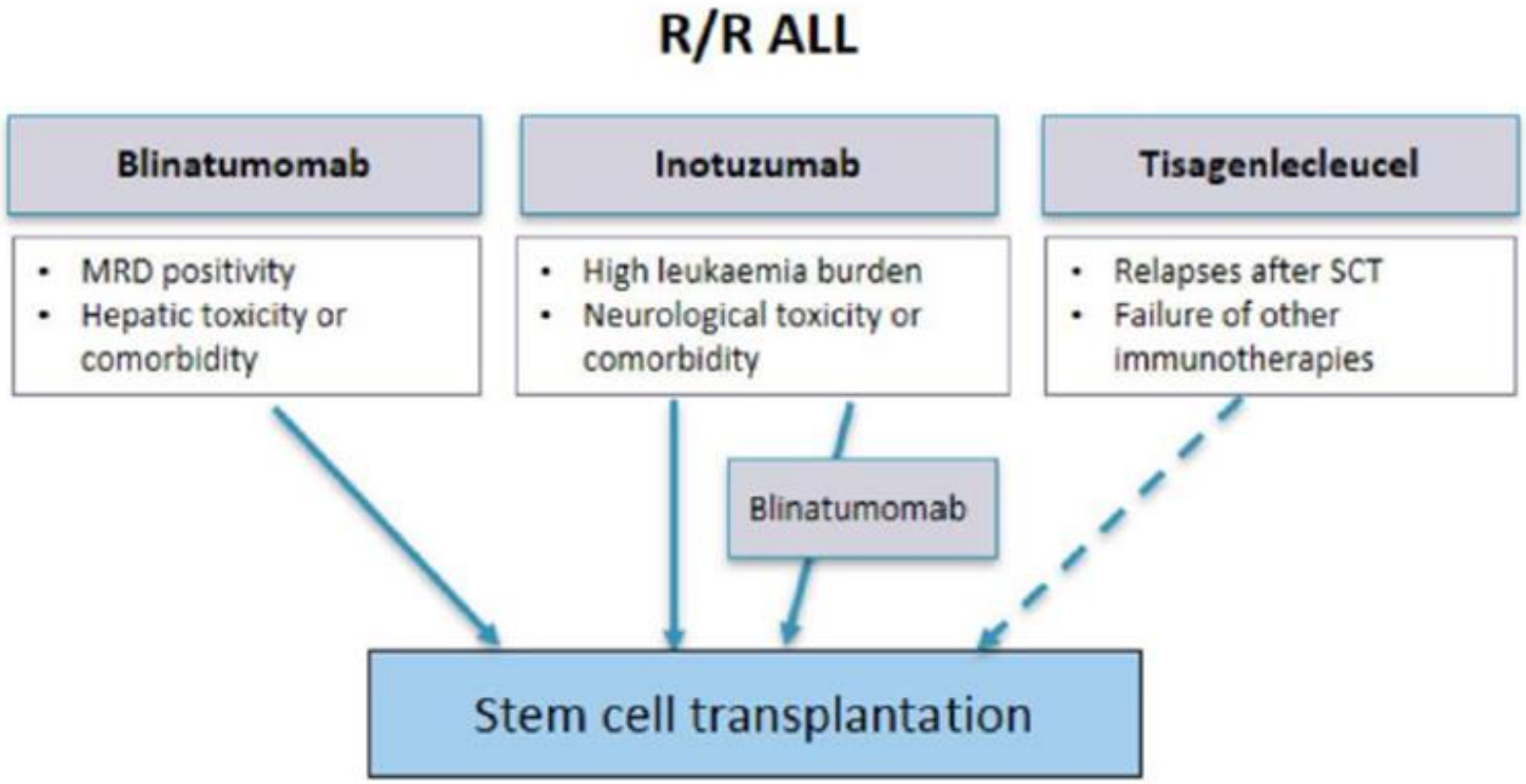
Should we transplant after MRD clearance with immunotherapy? YES!

BLAST trial 5-year follow-up



Leukemia & Lymphoma, 2020 61:11, 2665-2673

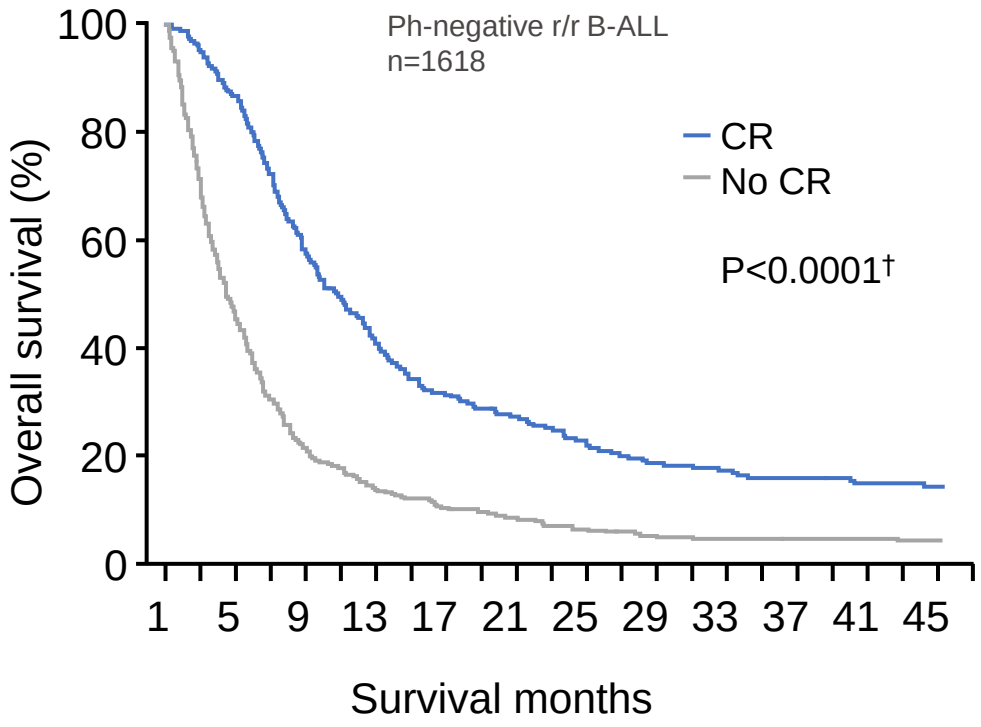
Do not transplant in CR1 But spare it for pts in CR-2



Adapted from Dhkal et al Leuk Lymphomaa 2020, 61:7-17

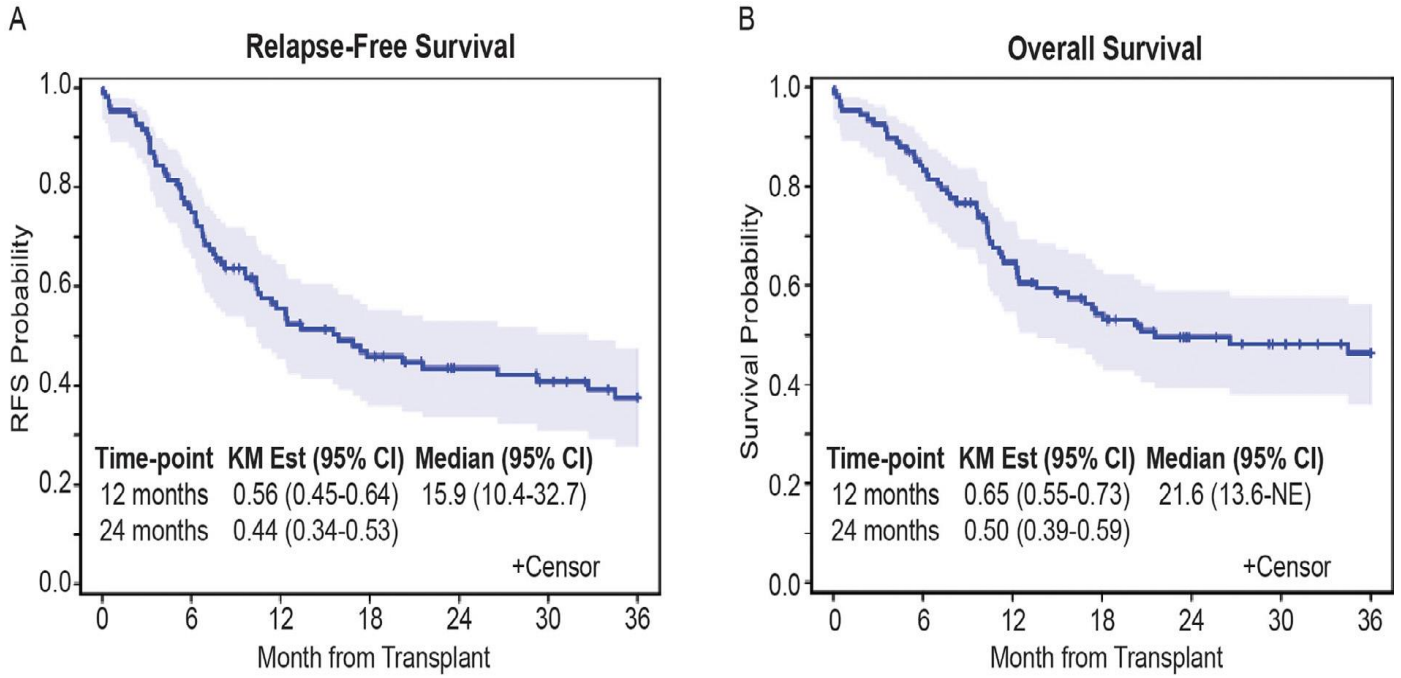
Nowadays there are better chances to be cured at CR2

r/r B-ALL salvage chemo



Gökbuget N, et al. Haematologica 2016;101:1524–33

Allogeneic Hematopoietic Cell Transplantation for Relapsed and Refractory Philadelphia Negative B Cell ALL in the Era of Novel Salvage Therapies

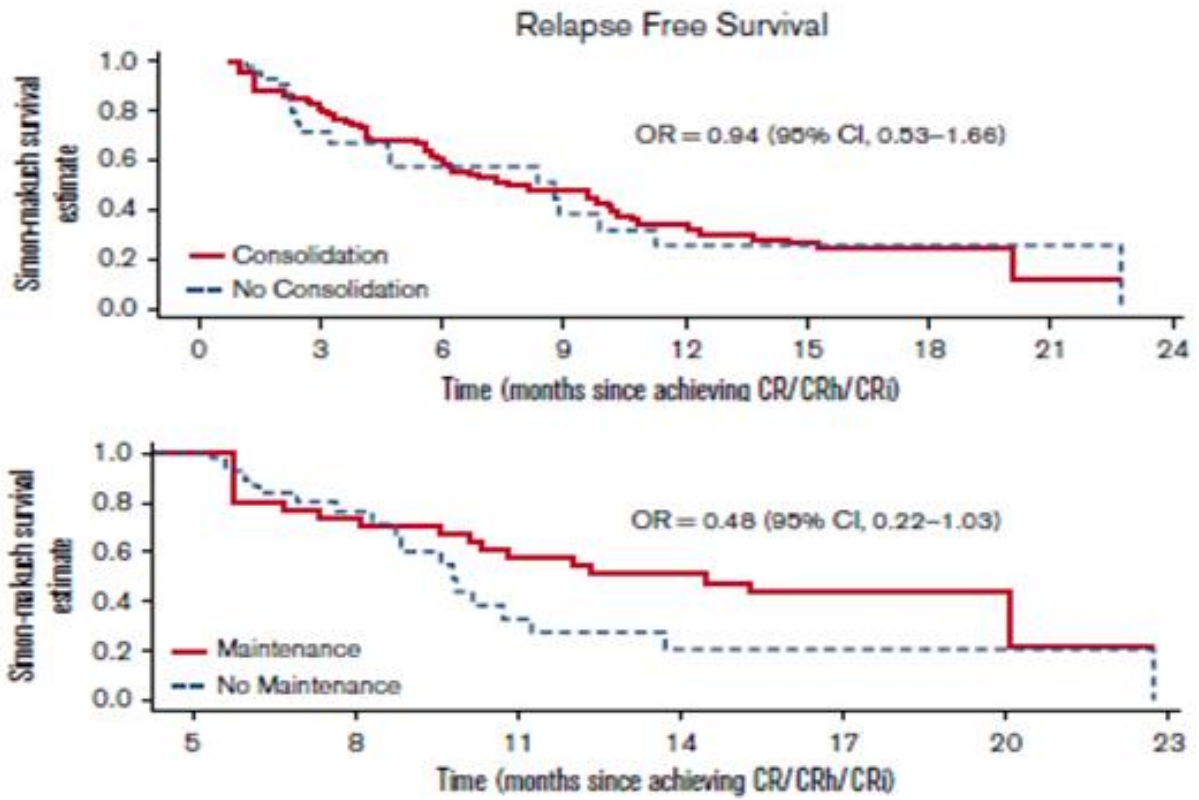


Transplantation and Cellular Therapy 27 (2021) 255.e1255.e9

Blina salvaged R/R ALL pts may profit from long term blina

86 pts consolidation
(3-5 cycles)

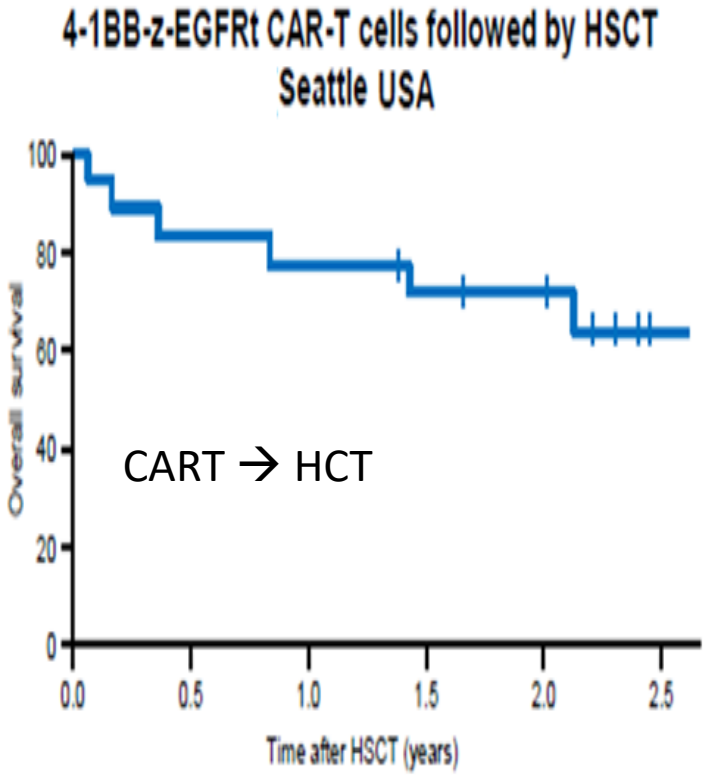
36 pts maintenance
(>=6 cycles)



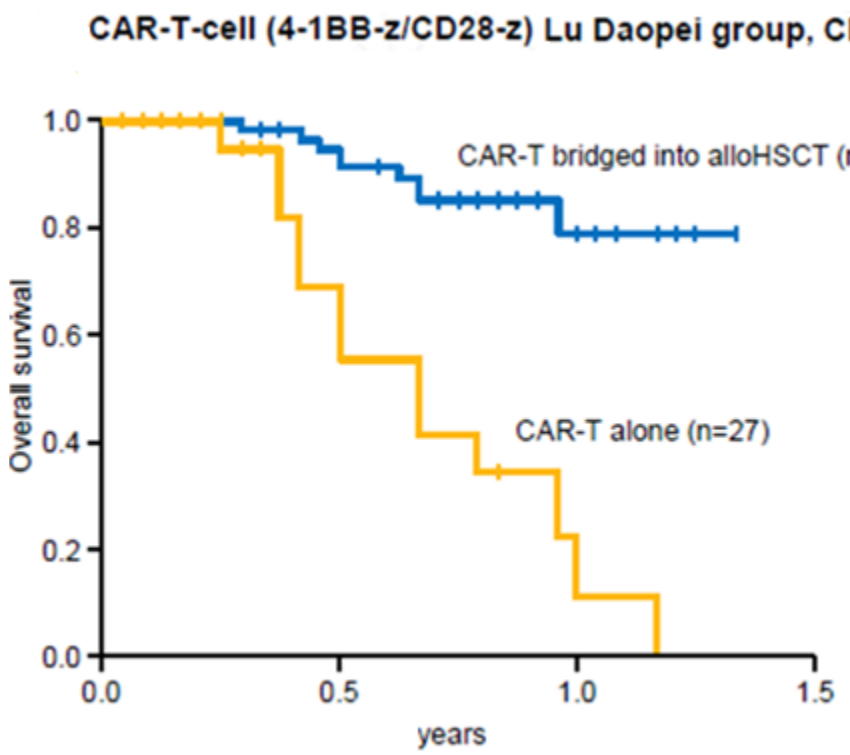
(Rambaldi A, et al. Blood Adv 2020;4:1518–25.)

Allo vs no Allo post CART
CART as a definitive salvage therapy or a bridging strategy?

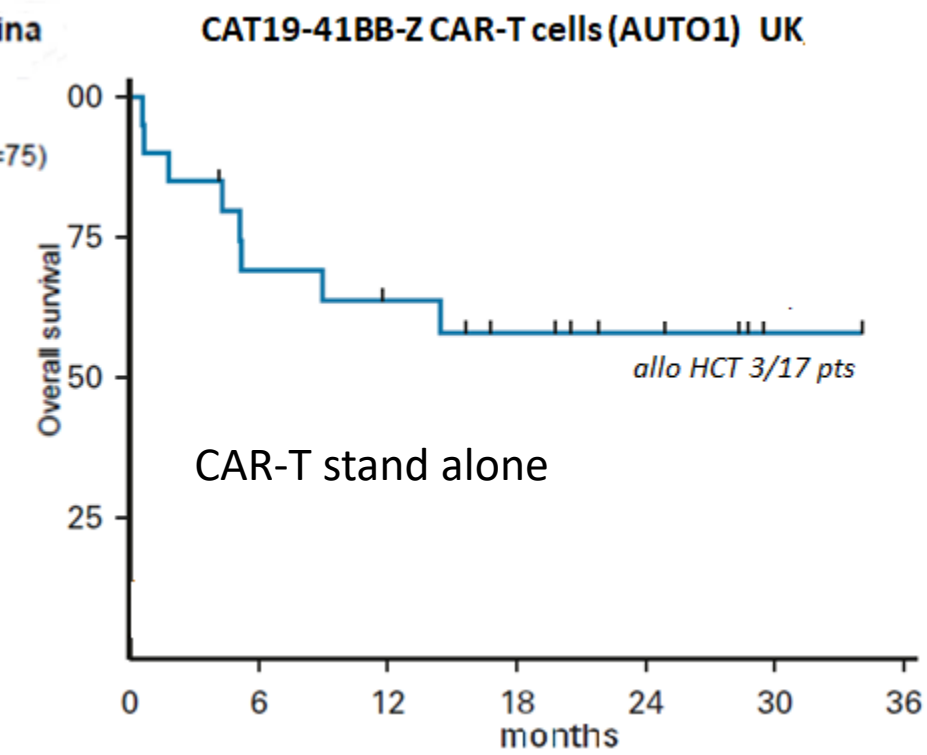
CAR-T ≠CAR-T≠ CAR-T.



Hay K, et al. Blood 2019;133:1652–63; 2



Zhang X, et al. Blood Adv 2020;4:2325–38.



JCO 2021 Aug 31;JCO2100917

Chemo + Blina in front line

Transplantation in ALL

- We are desperately trying to avoid/ replace transplant in ALL
- The challenge is to implement MRD and genetics in every day clinical practice
- Indications of HCT change with the new immunotherapeutic approaches administered in early phases and/ or as maintenance

Transplantation in ALL n CR-1

- **(Definitive) No for**

Intensified protocol + fast MRD clearance + no HR cytogenetics

- **Definitive yes**

MRD pos (try to convert MRD neg pr-Tx) or HR genetics

- **Probably yes**

MRD unknown

- **Open**

MRD neg with NGS (any time) (Blina or CART first line

Acute Leukemia Working Party

		Function in EBMT
CICERI	Fabio	Chair
MOHTY	Mohamad	Vice-Chair
GIEBEL	Sebastian	Secretary
BRISSOT	Eolia	secretary

	WP Governance
Study coordinators	Irma Khvedelidze Mohamed Houhou Emmanuelle Polge
Statisticians	Myriam Labopin Maud Ngoya Jacques-Emmanuel Galimard Christophe Peczynski

Name		Sub-committee	Function in EBMT
JORDI	Esteve	Molecular Markers	Leader
NAGLER	Arnon	Molecular Markers	Co-leader
GIEBEL	Sebastian	Acute Lymphoblastic Leukaemia	Leader
PERIC	Zina	Acute Lymphoblastic Leukaemia	Co-leader
SAVANI	Bipin	Conditioning	Leader
SPYRIDONIDIS	Alexandros	Conditioning	Co-leader
BARON	Frédéric	Cord blood	Leader
RUGGERI	Annalisa	Cord blood	Co-leader
SCHMID	Christoph	Immunotherapy and cellular therapy	Leader
MOHTY	Mohamad	Immunotherapy and cellular therapy	Co-leader
GORIN	Norbert-Claude	AUTO-SCT and graft composition	Leader
LANZA	Francesco	AUTO-SCT and graft composition	Co-leader
SHOUVAL	Roni	Data mining	Leader
VERSLUIS	Jurjen	Data mining	Co-leader
BUG	Gesine	Post-transplant pharmacologic modulation	Leader
BAZARBACHI	Ali	Post-transplant pharmacologic modulation	Co-leader
SANZ	Jaime	Alternative donor	Leader
PIEMONTESE	Simona	Alternative donor	Co-leader

PEOPLE

DONORS

FUNDING / SUPPORTERS

Co- financed by Greece and the European Union