Alessandro Rambaldi

Nuove terapie ed indicazioni nella leucemia linfoblastica acuta B

Modena, 18 Maggio 2017

UNIVERSITÀ DEGLI STUDI DI MILANO

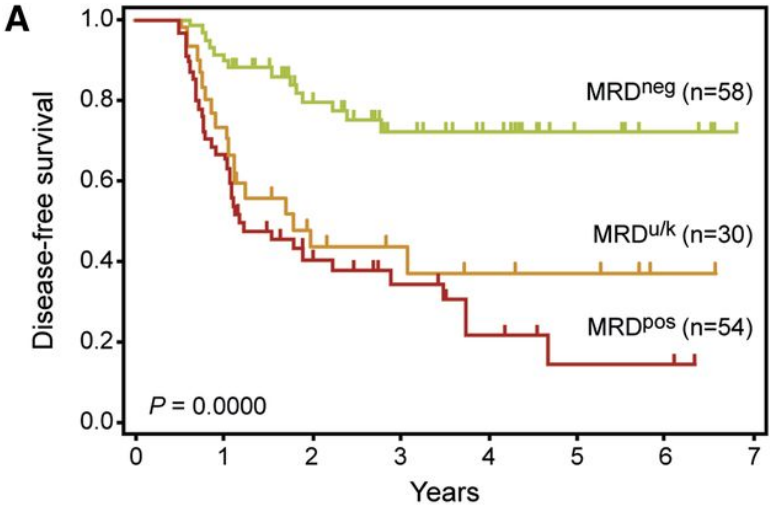
Azienda Ospedaliera Papa Giovanni XXIII Bergamo

Agenda

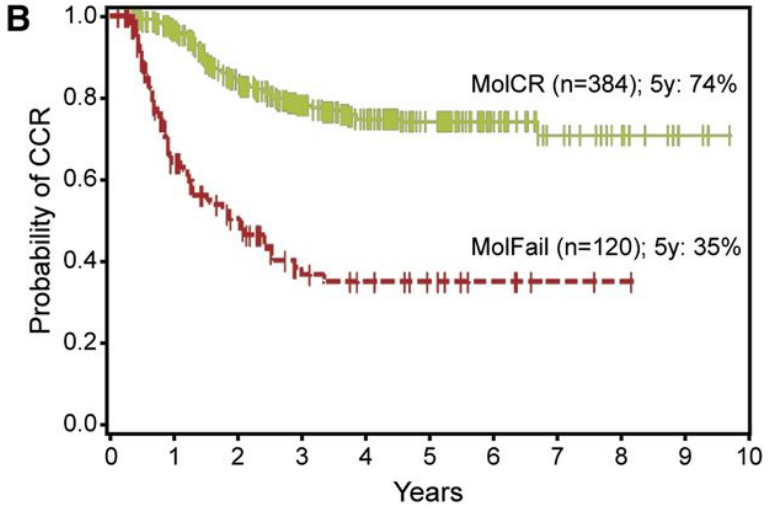
- Incorporating MRD into ALL treatment
- When treatment fails
- Treatment in older ALL
- Future perspectives

Results of prospective clinical trials on adult Ph-ALL according to MRD response.

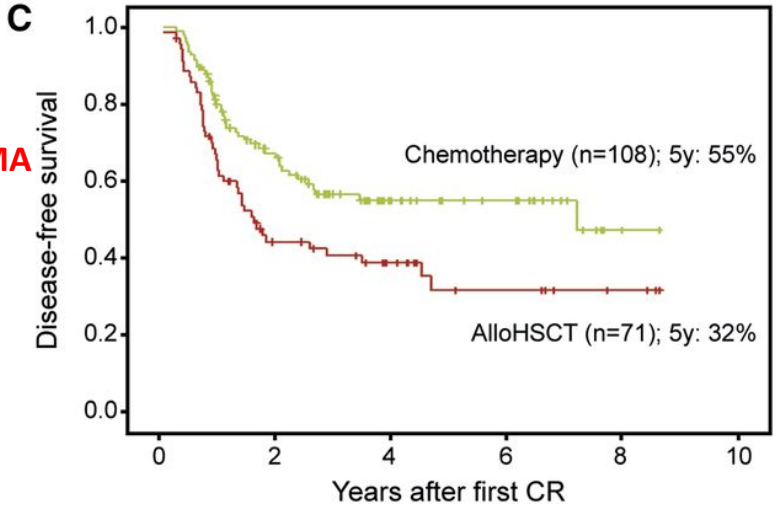
NILG



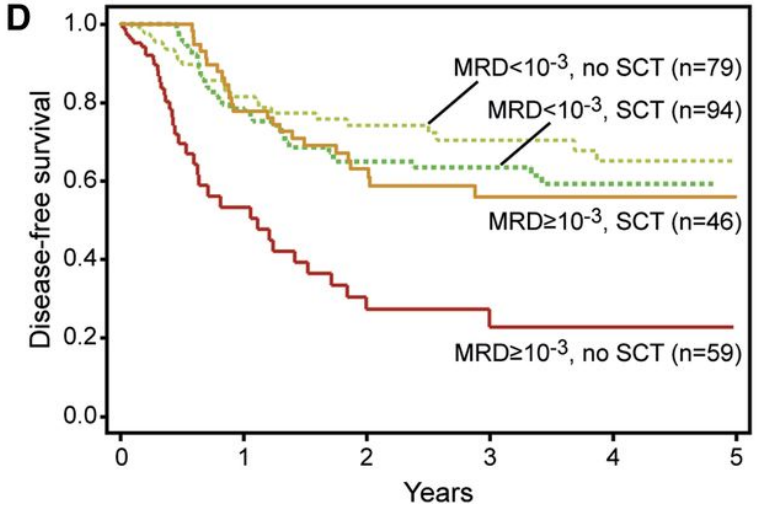
GMALL



PETHEMA



GRAAL



Jacques J. M. van Dongen et al. Blood 2015;125:3996-4009

blood

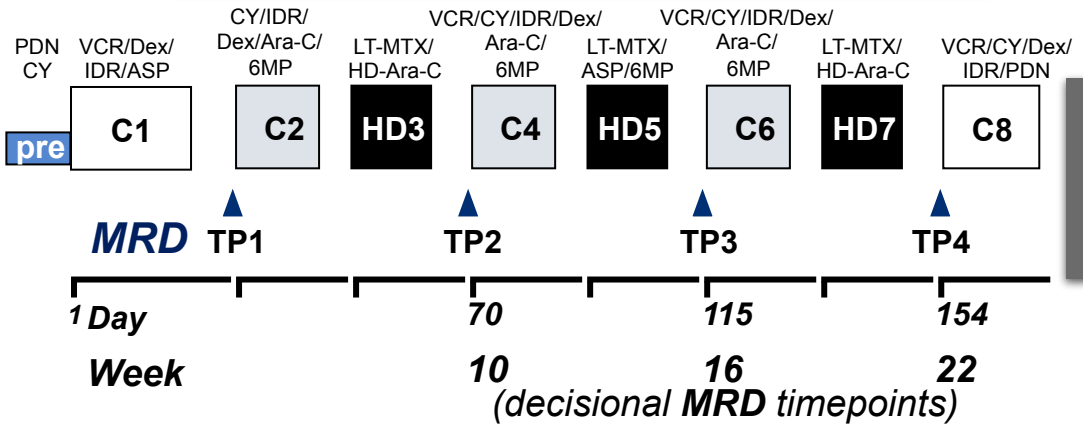
Trial design (Ph- ALL)

SR	HR	VHR
• No risk feature	• WBC 30-100 • Pro-B • Late CR	• WBC >100 • Early/ mature-T • Highly adverse cytogenetics*

1. Risk Stratification

*t(4;11)/MLL, abn q23, +8, -7, del6q, t(8;14), low hypodiploid/ near triploidy, complex

2. Induction/Consolidation and MRD Study



3. Risk/ MRD-Specific Therapy

- **VHR** all
- **SR/HR MRD** ≥10^{-4} w10 ≥10^{-4} w16, positive w22
- **HR** **MRD** unknown

(***EARLY HCT*** *after HD3)* (***HCT*** *after C8)*

Allogeneic HCT (RD/URD)

Maintenance (2-Y)

(after C8)

- **SR/HR** **MRD** <10^{-4} w10-16, negative w22
- **SR** **MRD** unknown

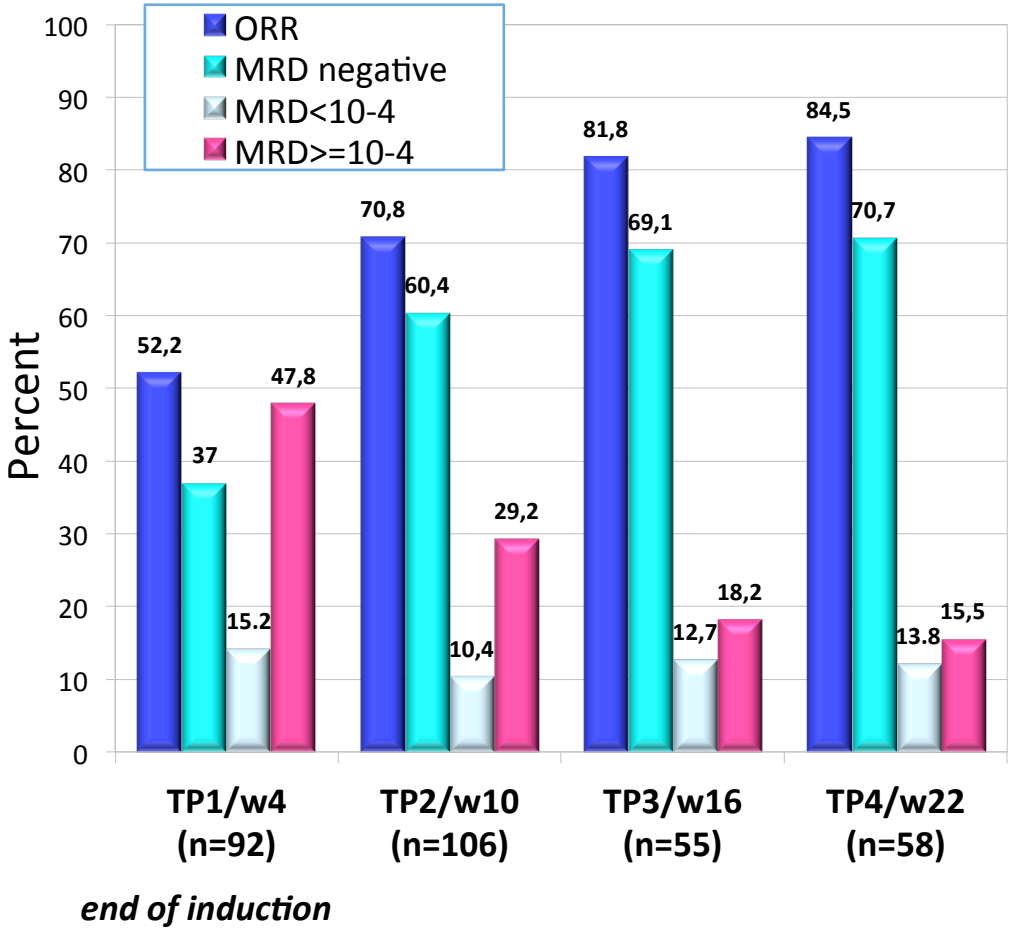
- **HLA testing** to identify RD/URD at diagnosis
- Radiation-free, CNS prophylaxis **(triple IT vs IT liposomal cytarabine)**

BFM-type: C2,C4,C5 **L[redacted]age-targeted MTX**: HD3,HD5,HD7
(B-ALL 2.5 g/m^2; T-ALL 5 g/m^2; 1.5 g/m^2 if age >55 years)

ClinicalTrials.gov NCT-00795756

MRD study and risk classification

- **MRD study** with 1-2 case-specific sensitive molecular probe(s) (*sensitivity 10^{-4} or greater*) generated in 109/142 CR patients (77%)



end of induction

- **Integrated clinical – MRD risk classification** for allocation of 142 CR patients to **HCT** *or* **Maintenance**

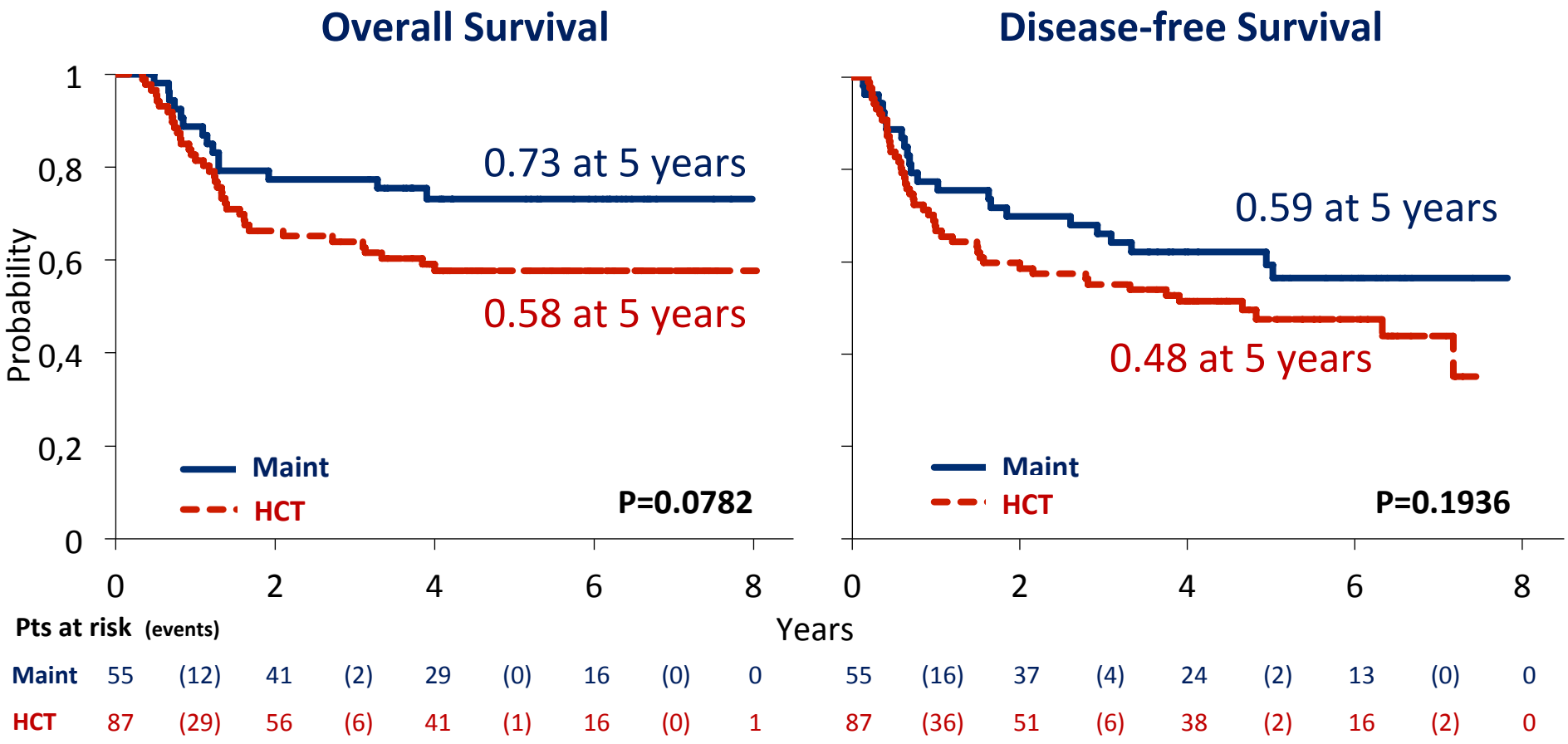
– **HCT allocation cohort (N = 87, 61.2%)**

- VHR (all) 61
- HR *and* MRD >10^{-4}/pos 8
- SR *and* MRD >10^{-4}/pos 14
- HR MRD unknown 4

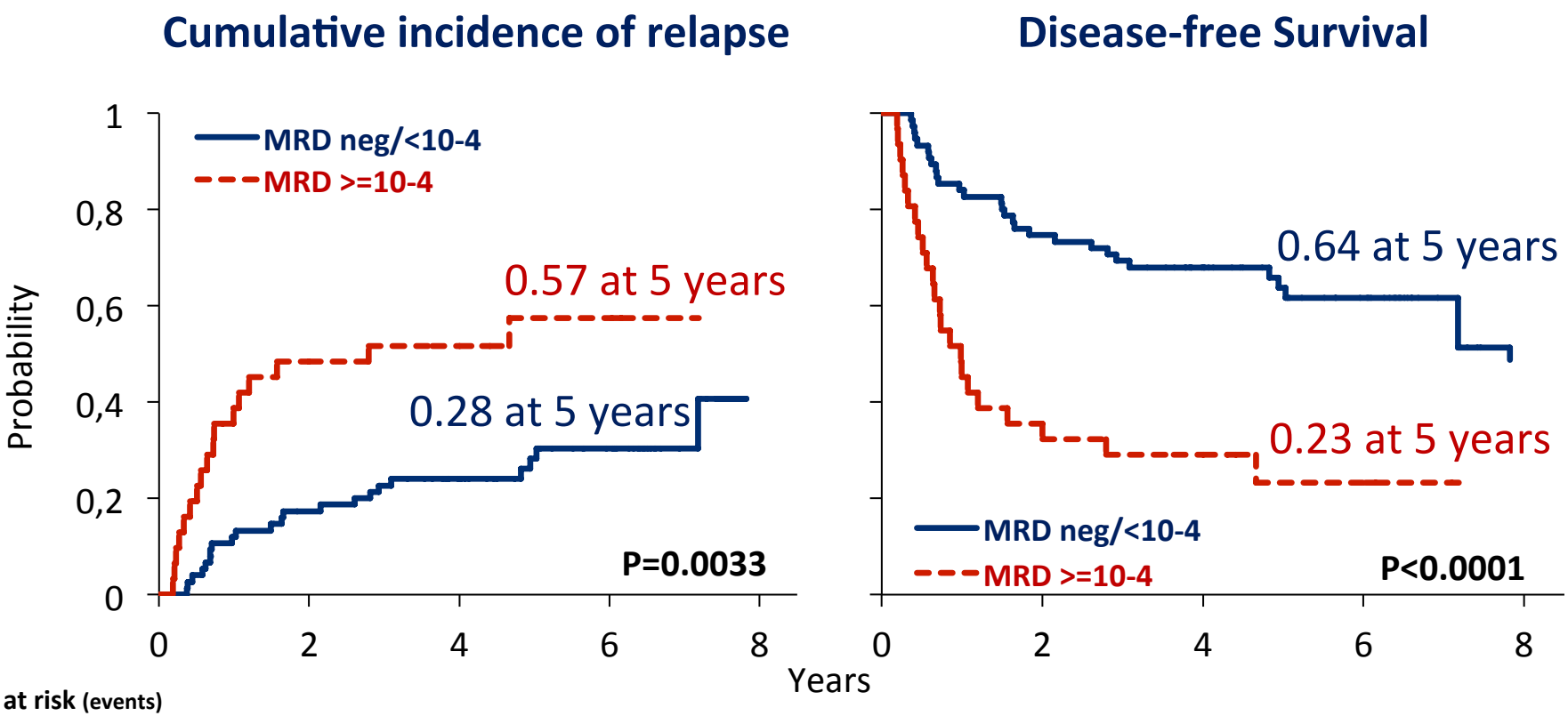
– **Maintenance allocation cohort (N = 55, 38.8%)**

- SR *and* MRD <10^{-4}/neg 35
- HR *and* MRD <10^{-4}/neg 6
- SR MRD unknown 14

Main outcomes by treatment allocation (ITT analysis)



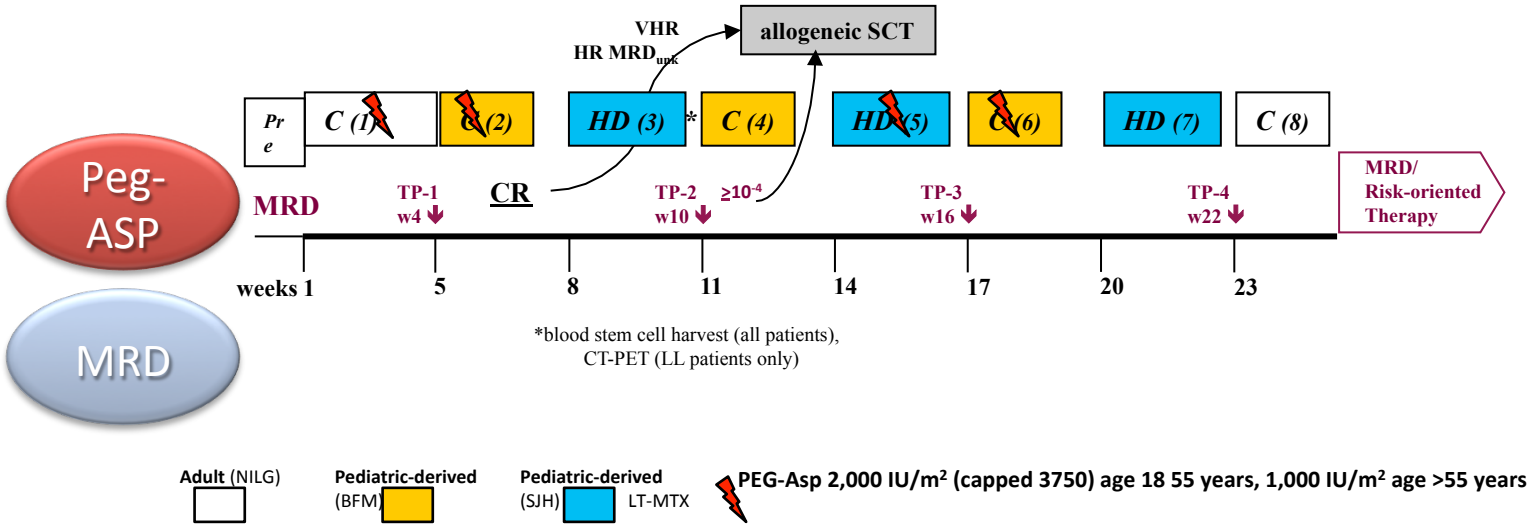
MRD at timepoint 2 (w10): CIR and DFS



Pts at risk (events)																
MRD neg/<10^{-4}	75	(13)	56	(5)	41	(3)	21	(1)	0	75	(19)	56	(5)	41	(3)	21	(1)	0
MRD >=10^{-4}	31	(15)	10	(1)	8	(1)	4	(0)	0	31	(21)	10	(1)	8	(1)	4	(0)	0

GIMEMA LAL 1913

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, Gruppo Italiano Malattie Ematologiche dell'Adulto

https://clinicaltrials.gov/ct2/show/NCT02067143

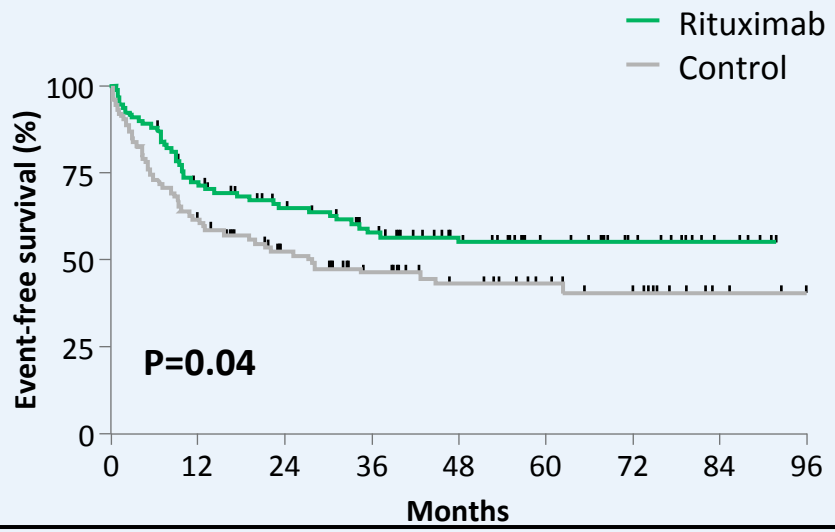
Merits and limits of the MRD driven strategy

- High predictive power of Week 10 MRD
- MRD-driven strategy failing in 25% of MRD-negative patients
- Poor results with alloHSCT (high NRM)

NRM, non-relapse mortality

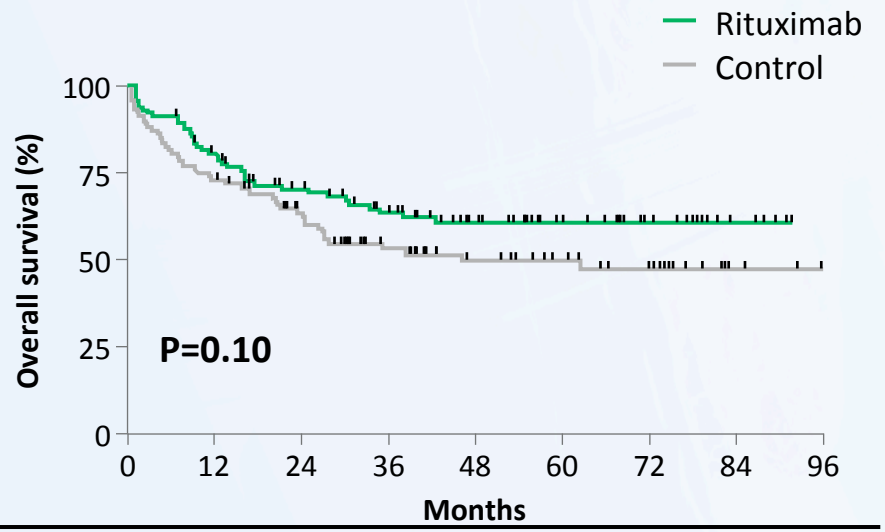
Event-free survival and cumulative incidence of relapse in the rituximab and control groups

Event-free survival



No. at risk:									
Control	104	63	45	34	25	19	14	6	3
Rituximab	105	73	58	47	35	26	18	10	5

Overall survival



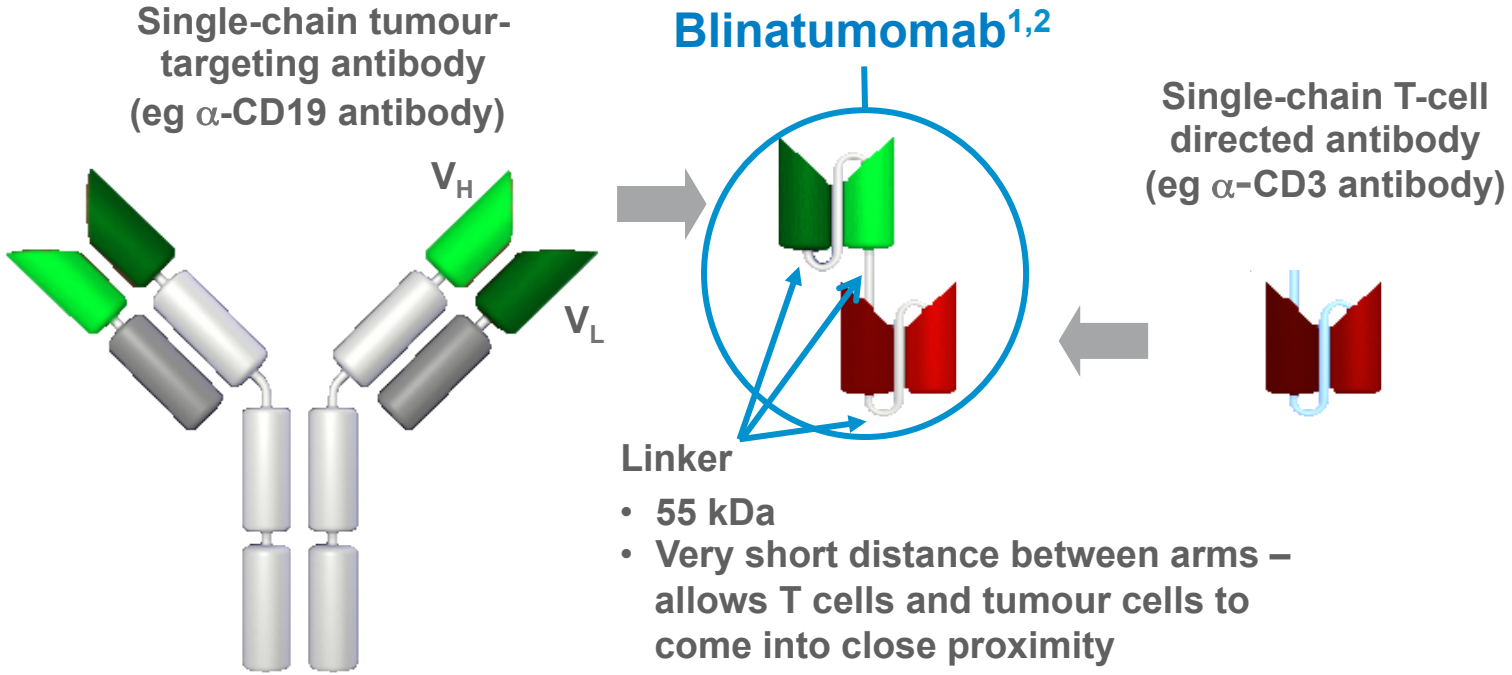
No. at risk:									
Control	104	75	57	38	28	22	16	6	3
Rituximab	105	82	64	51	39	28	19	10	5

Rituximab is not approved for the treatment of ALL

Maury S *et al. N Engl J Med* 2016;375:1044–1053

BiTE® antibody blinatumomab: designed to direct T cells to ALL cells

BiTE® = **Bi**specific **T** cell **E**ngager



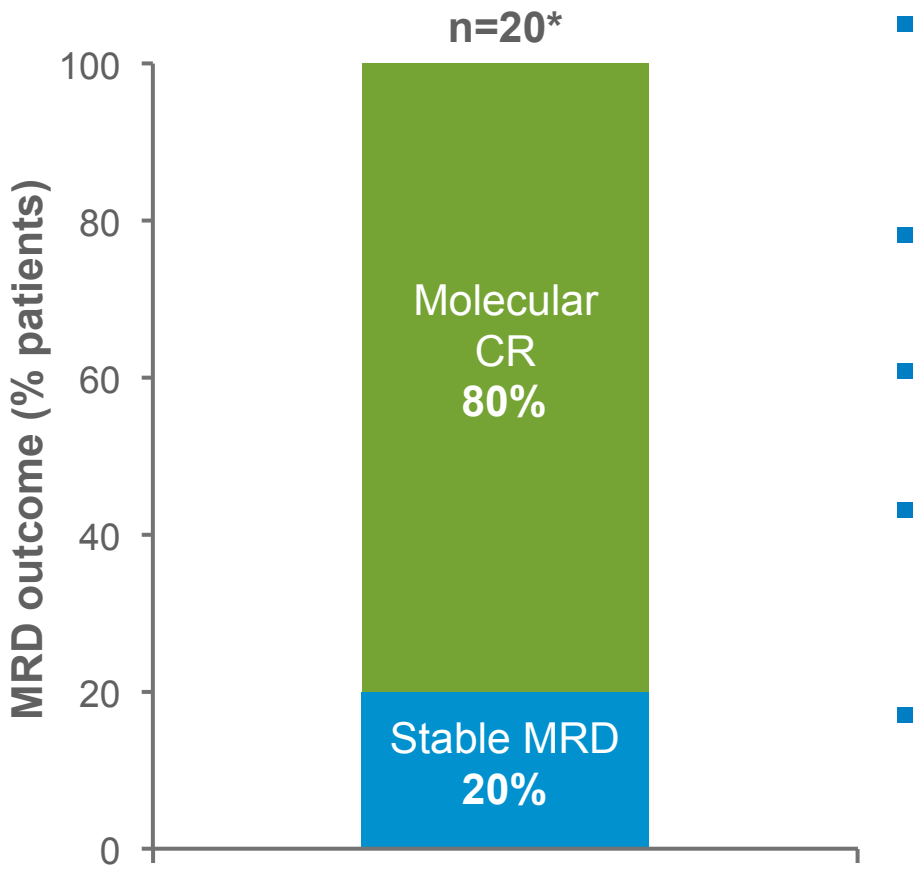
- 55 kDa
- Very short distance between arms – allows T cells and tumour cells to come into close proximity

95–100% of B-precursor ALL tumours are CD19+[3]

1. Nagorsen D, Baeuerle PA. Exp Cell Res 2011;317:1255–60;
2. Baeuerle PA, Reihnardt C. Cancer Res 2009;69:4941–4;
3. Hoelzer D. Hematology Am Soc Hematol Educ Program 2011;2011:243–9

kDa, kiloDaltons

Phase II study of blinatumomab in patients with MRD+ B-precursor ALL



*1 patient not evaluable: <1 treatment cycle and lack of response assessment

- Responses were rapid
  - All responses occurred within the first cycle of treatment
- Four patients had stable MRD levels as best response
- No MRD increase was observed during treatment
- Responders included:
  - 3/5 patients were Ph(+)
  - 1/2 patients were t(4;11)+
- Majority of AEs transient
  - Lymphopenia most common grade 3/4 AE (seen in 33%)
  - No CRS observed

Topp MS, et al. J Clin Oncol 2011;29:2493–8

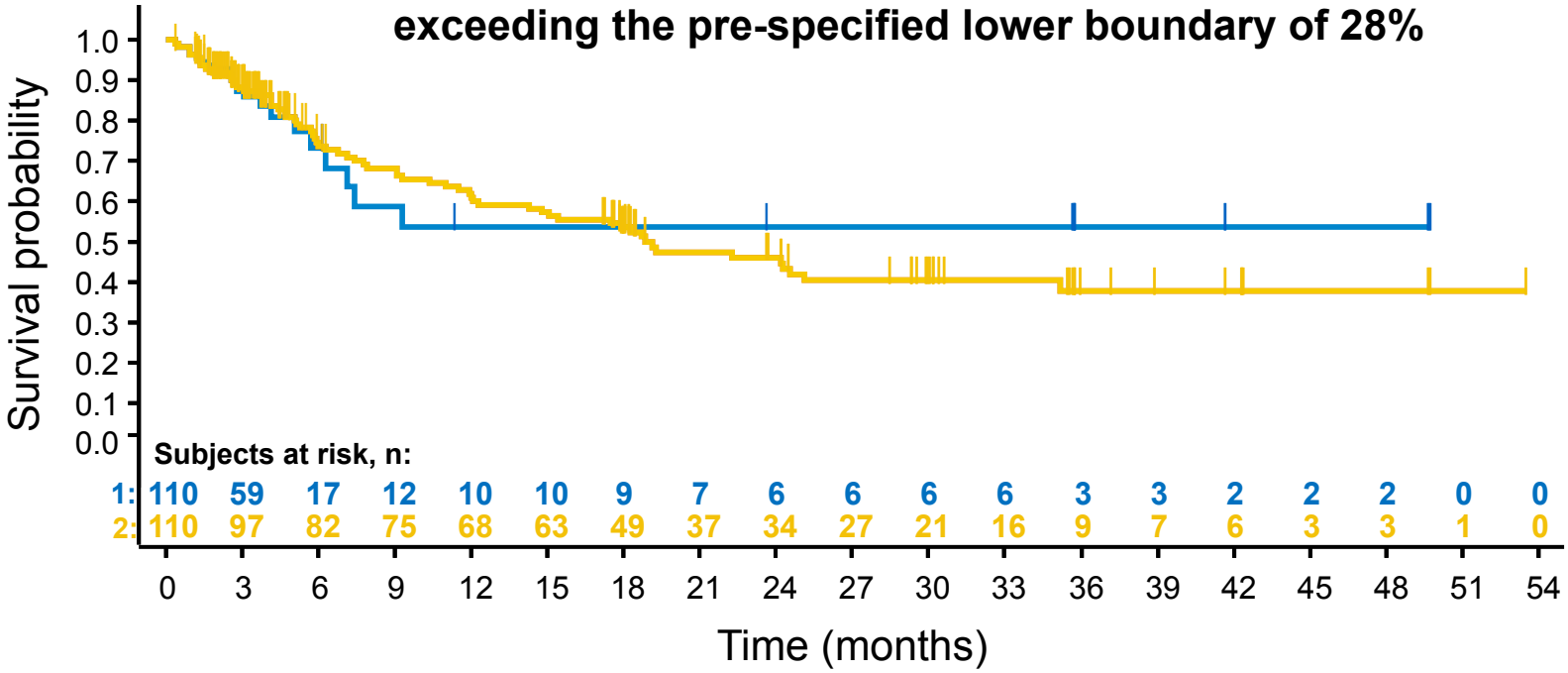
Blinatumomab for MRD positivity: always a bridge to transplant?

Confirmatory Phase 2 study of blinatumomab in adults with MRD-positive B-precursor ALL: relapse-free survival
Ph-negative patients in haematological CR

Median (95% CI) follow-up: 29.9 (24.2, 30.6) months

The key secondary endpoint was met:

- **18-month Kaplan–Meier estimate of RFS = 54% (95% CI: 33%, 70%) exceeding the pre-specified lower boundary of 28%**



1: RFS censoring at alloSCT and post-blinatumomab chemotherapy (N=110); median 95% CI NR (6.3, NR)

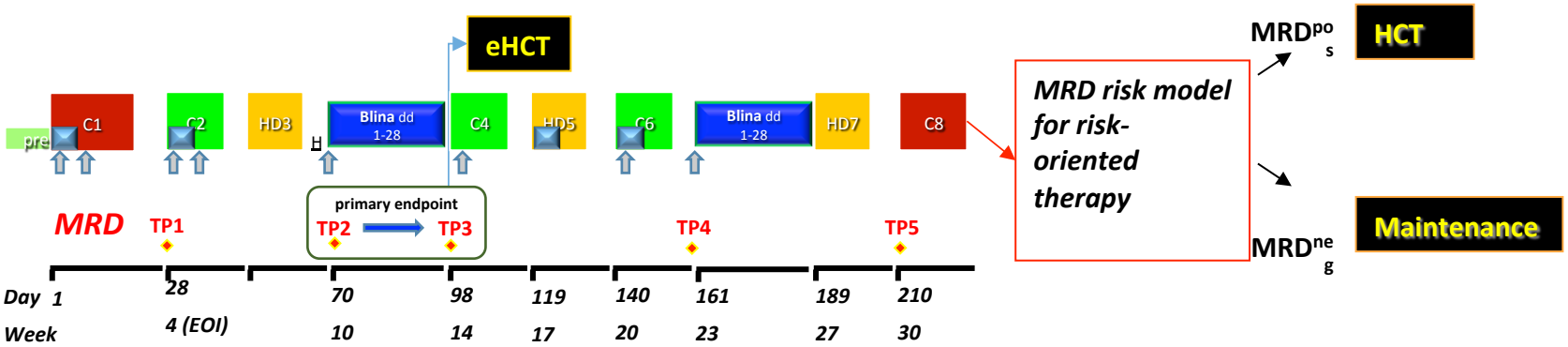
2: RFS not censoring at alloSCT and post-blinatumomab chemotherapy (N=110); median 95% CI 18.9 (12.3, 35.2)

SCT in continuous CR: 67%

AMGEN®
Oncology

Gökbuget N, et al. ASH 2015: Abstract 680 and oral presentation

Protocol GIMEMA Ph- BCP ALL «Blinatumomab»



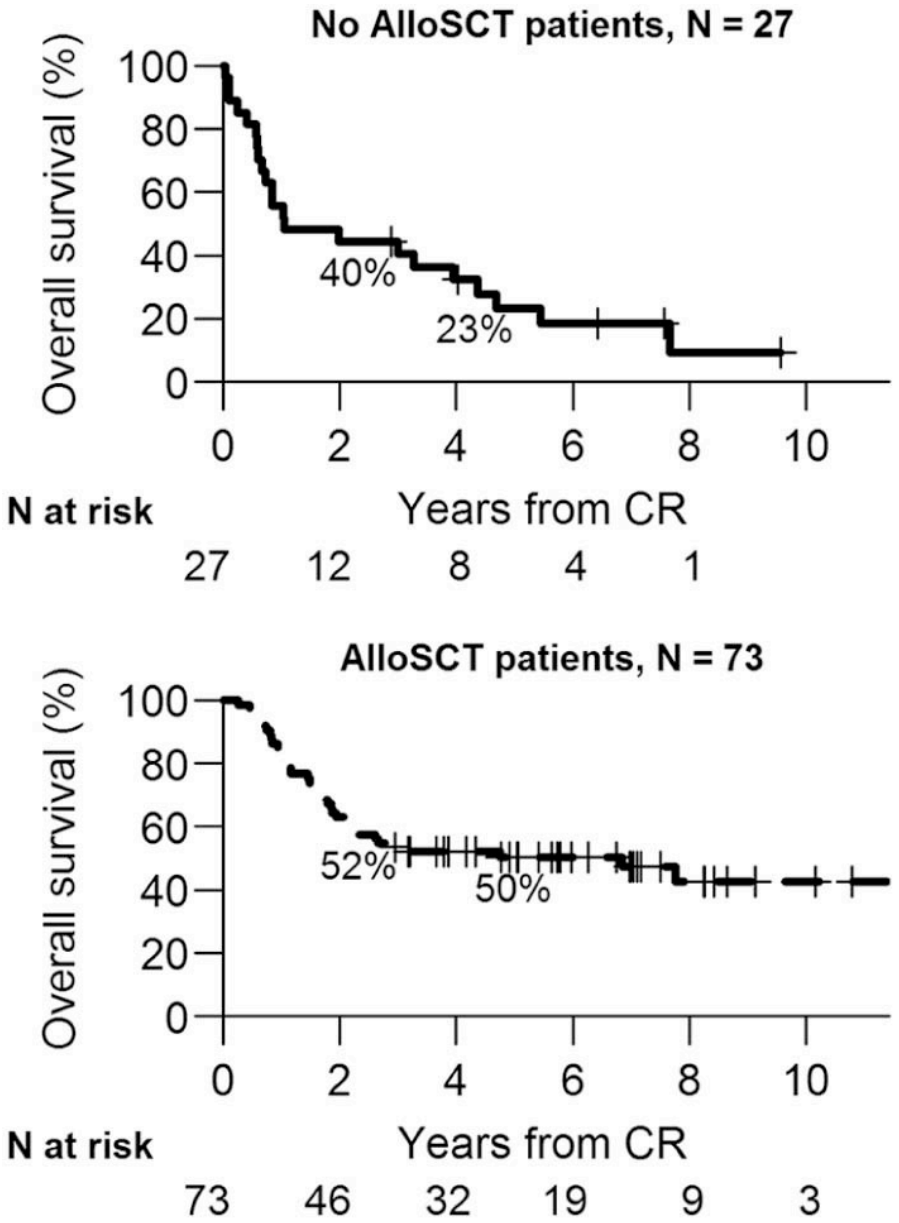
Treatment elements

- ADULT CONVENTIONAL (pre: CY; VCR, Dex, IDR)
- TRIPE IT
- Pegylated- ASP
- BLINATUMOMAB
- PEDIATRIC-TYPE (IDR-CY-DXM-6MP-AraC)
- PEDIATRIC-TYPE (HD MTX-AraC or HD MTX-ASP-6MP) with lineage-targeted MTX (B: 2.5 g/m^2)

eHCT , early hematopoietic cell Tx (after Blinatumomab), for **vHR*** or **TP2 MRD ≥ 10^{-4}**

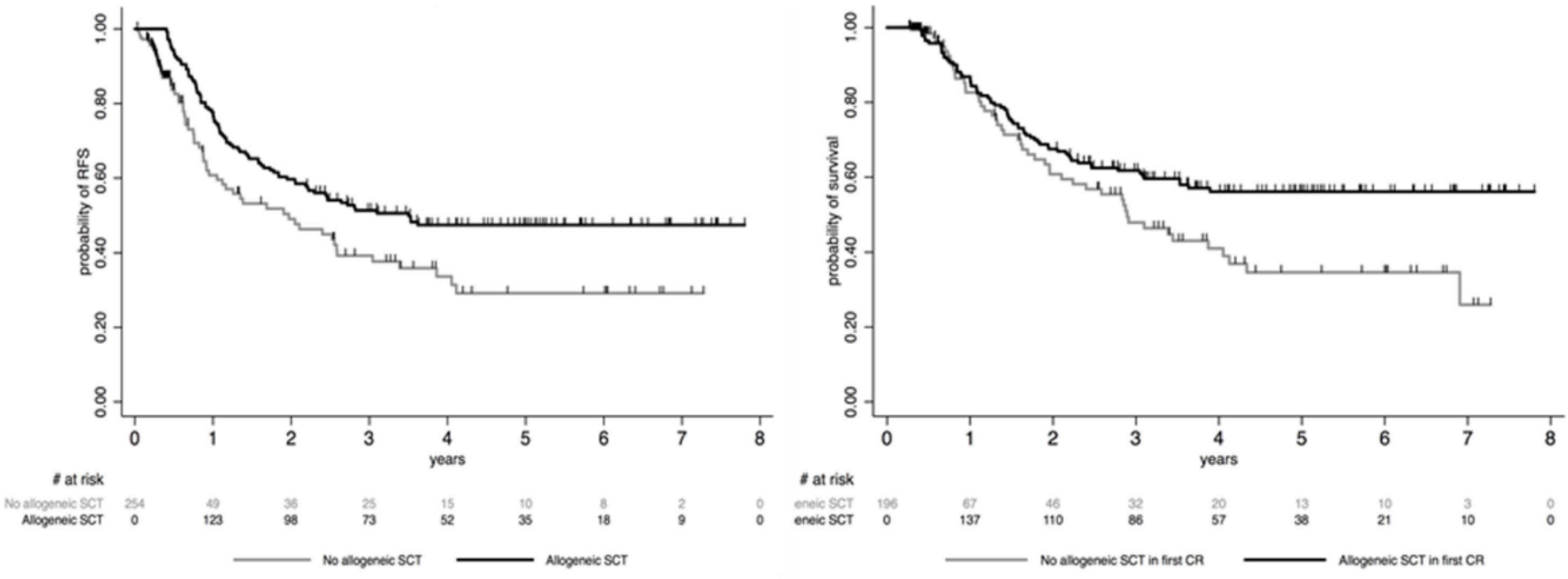
**WBC >100, highly adverse cytogenetics*

AlloHSCT for every Ph+ ALL patient in CR1?



Federico Lussana, Biology of Blood and Marrow Transplantation Volume 22, Issue 11, Pages 1983-1987 (November 2016)

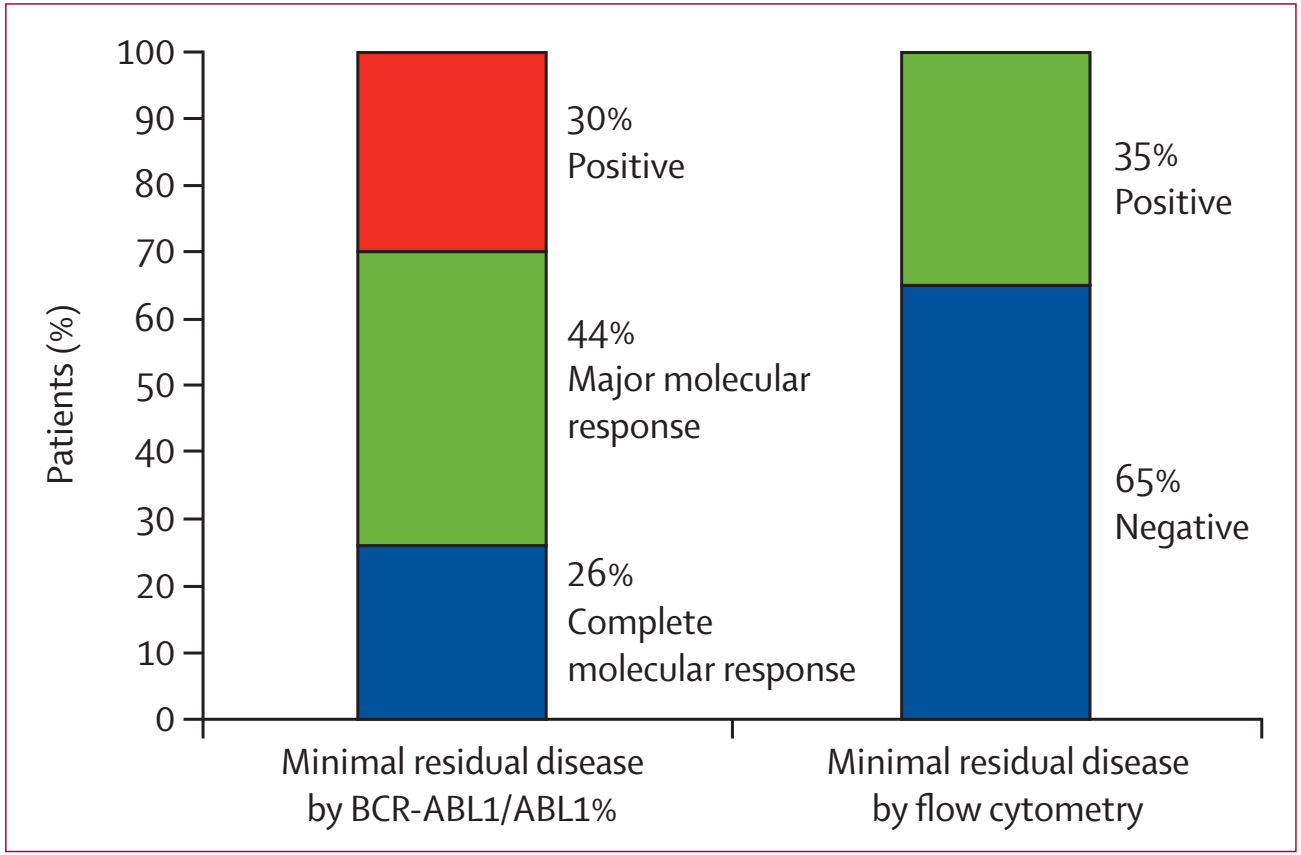
Simon-Makuch plots for RFS in CR patients. *t0 was the time of hematological CR* achievement



A 3-month RFS landmark period (median time from CR to transplantation) was used here, as patients should be alive but also in first CR to be actually transplanted. This landmark minimizes the bias related to early relapses

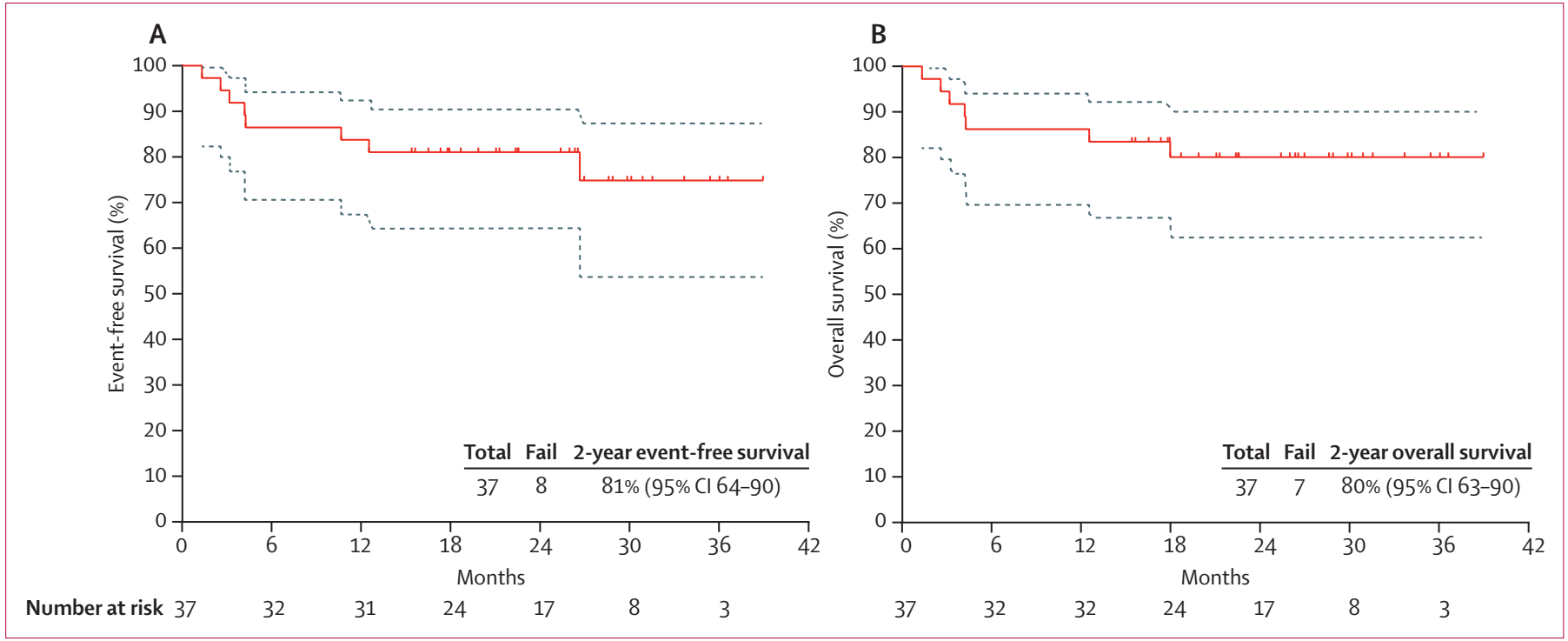
Chalandon I.: Blood First Edition Paper, prepublished online April 15, 2015

MRD levels after one cycle of protocol therapy in CR



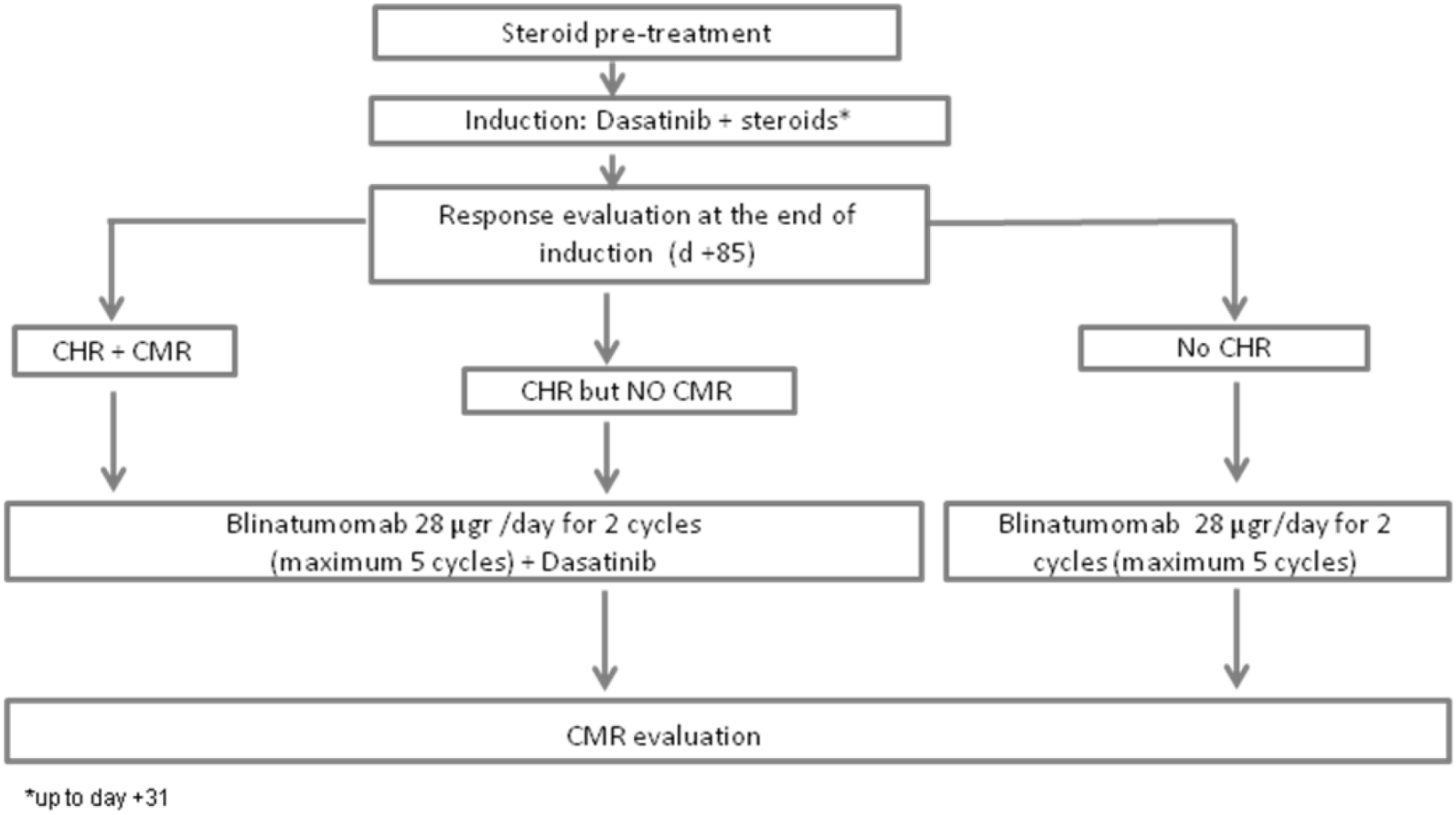
Jabbour, E et al. Lancet Oncol 2015

Clinical Outcomes



Jabbour, E et al. Lancet Oncol 2015

GIMEMA LAL2116



*up to day +31

PI: Prof R.Foà

EudraCT number 2016-001083-11
Clinical Trial Number NTC02744768

When treatment fails

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

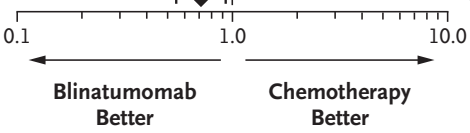
Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

Hagop Kantarjian, M.D., Anthony Stein, M.D., Nicola Gökbuget, M.D., Adele K. Fielding, M.B., B.S., Ph.D., Andre C. Schuh, M.D., Josep-Maria Ribera, M.D., Ph.D., Andrew Wei, M.B., B.S., Ph.D., Hervé Dombret, M.D., Robin Foà, M.D., Renato Bassan, M.D., Önder Arslan, M.D., Miguel A. Sanz, M.D., Ph.D., Julie Bergeron, M.D., Fatih Demirkan, M.D., Ewa Lech-Maranda, M.D., Ph.D., Alessandro Rambaldi, M.D., Xavier Thomas, M.D., Ph.D., Heinz-August Horst, M.D., Ph.D., Monika Brüggemann, M.D., Wolfram Klapper, M.D., Ph.D., Brent L. Wood, M.D., Ph.D., Alex Fleishman, M.S., Dirk Nagorsen, M.D., Ph.D., Christopher Holland, M.S., Zachary Zimmerman, M.D., Ph.D., and Max S. Topp, M.D.

Kantarjian, HM et al.: NEJM 2017

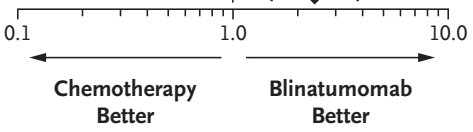
A Prespecified Subgroup Analysis of Overall Survival

Subgroup	Median Survival				Hazard Ratio (95% CI)
	Blinatumomab		Chemotherapy		
	no. of patients	*mo*	*no. of patients*	*mo*	
Age					
<35 yr	123	9.9	60	4.5	0.70 (0.46–1.06)
≥35 yr	148	5.6	74	3.8	0.77 (0.55–1.08)
Salvage-treatment phase					
First	114	11.1	65	5.3	0.60 (0.39–0.91)
Second	91	5.1	43	3.3	0.59 (0.38–0.91)
Third or later	66	3.7	26	3.0	1.13 (0.64–1.99)
Previous allogeneic stem-cell transplantation					
Yes	94	7.7	46	5.3	0.81 (0.51–1.29)
No	177	7.7	88	3.7	0.70 (0.51–0.96)
Bone marrow blasts					
<50%	84	11.5	38	6.8	0.60 (0.35–1.03)
≥50%	18	5.0	96	3.7	0.82 (0.61–1.10)
Overall	271	7.7	134	4.0	0.71 (0.55–0.93)



B Prespecified Subgroup Analysis of Remission Rate

Subgroup	Blinatumomab	Chemotherapy	Odds Ratio (95% CI)
	no. of events/no. of patients (%)		
Age			
<35 yr	53/123 (43.1)	15/60 (25.0)	2.27 (1.15–4.50)
≥35 yr	66/148 (44.6)	18/74 (24.3)	2.50 (1.34–4.66)
Salvage-treatment phase			
First	60/114 (52.6)	23/65 (35.4)	2.03 (1.08–3.80)
Second	36/91 (39.6)	7/43 (16.3)	3.37 (1.35–8.38)
Third or later	23/66 (34.8)	3/26 (11.5)	4.10 (1.11–15.12)
Previous allogeneic stem-cell transplantation			
Yes	38/94 (40.4)	5/46 (10.9)	5.56 (2.02–15.36)
No	81/177 (45.8)	28/88 (31.8)	1.81 (1.06–3.09)
Bone marrow blasts			
<50%	55/84 (65.5)	13/38 (34.2)	3.65 (1.63–8.17)
≥50%	64/186 (34.4)	20/96 (20.8)	1.99 (1.12–3.55)
Overall	119/271 (43.9)	33/134 (24.6)	2.40 (1.51–3.80)



Kantarjian, HM et al.: NEJM 2017

Outcomes of Hematopoietic Stem Cell Transplantation (HSCT) Among Adults With Relapsed/Refractory (r/r) ALL Achieving Remission With Blinatumomab

Anthony S Stein,[1] Max S Topp,[2] Nicola Gökbuget,[3] Ralf C Bargou,[4] Hervé Dombret,[5] Richard A Larson,[6] Alessandro Rambaldi,[7] Gary Schiller,[8] Gerhard Zugmaier,[9] Lulu Sterling,[10] Jonathan Benjamin,[10] Hagop Kantarjian,[11] Stephen J Forman[1]

[1]Gehr Leukemia Center, City of Hope, Duarte, CA, USA; [2]Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany; [3]Department of Medicine II, Goethe University, Frankfurt, Germany; [4]Comprehensive Cancer Center Mainfranken, Universitätsklinikum Würzburg, Würzburg, Germany; [5]University Paris, Hôpital Saint Louis, Paris, France; [6]University of Chicago, Chicago, IL, USA; [7]Department of Hematology, Hematology and Bone Marrow Transplant Unit, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; [8]University of California Los Angeles, Los Angeles, CA, USA; [9]Amgen (Research) Munich GmbH, Munich, Germany; [10]Amgen Inc., Thousand Oaks, CA, USA; [11]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

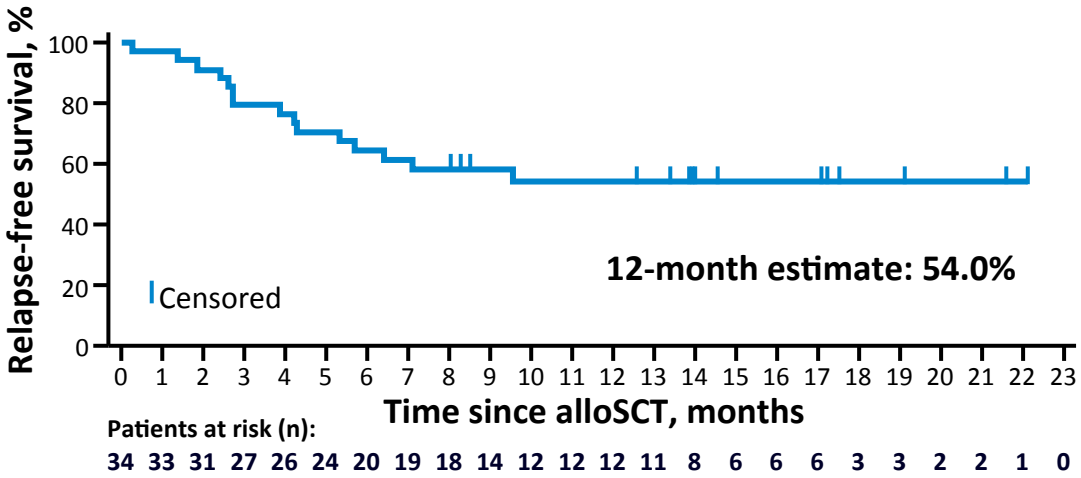
Stein AS, et al. ASBMT Meeting, 2016

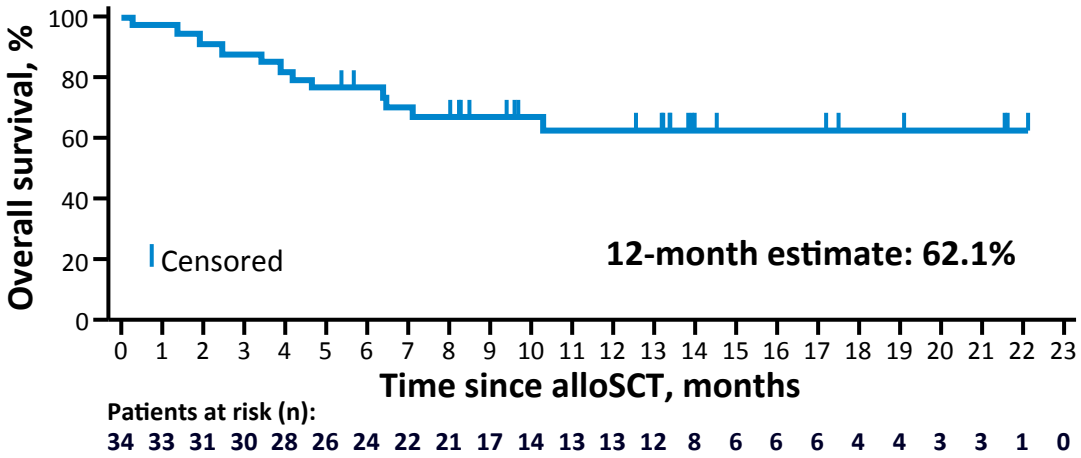
Objectives of this exploratory analysis

- The primary objective was to assess blinatumomab as a bridge to transplant in adults with r/r ALL
- Among patients who went on to receive alloSCT after achieving CR/CRh, this exploratory analysis investigated:
  - Relapse-free survival
  - Overall survival
  - Mortality within 100 days after alloHCT
- Patients who relapsed before alloSCT and patients who had other antileukemic therapy after blinatumomab but before alloSCT were excluded from this analysis

Stein AS, et al. ASBMT Meeting, 2016

Relapse-free and overall survival in patients receiving alloSCT after achieving CR/CRh with blinatumomab





	N=34
Median RFS, months	NE
95% CI	5.3–NE
RFS events, n	15
Relapse	9
Death without relapse	6
Patients censored, n	19

Median follow-up: 13.9 (8.5–17.1 months)

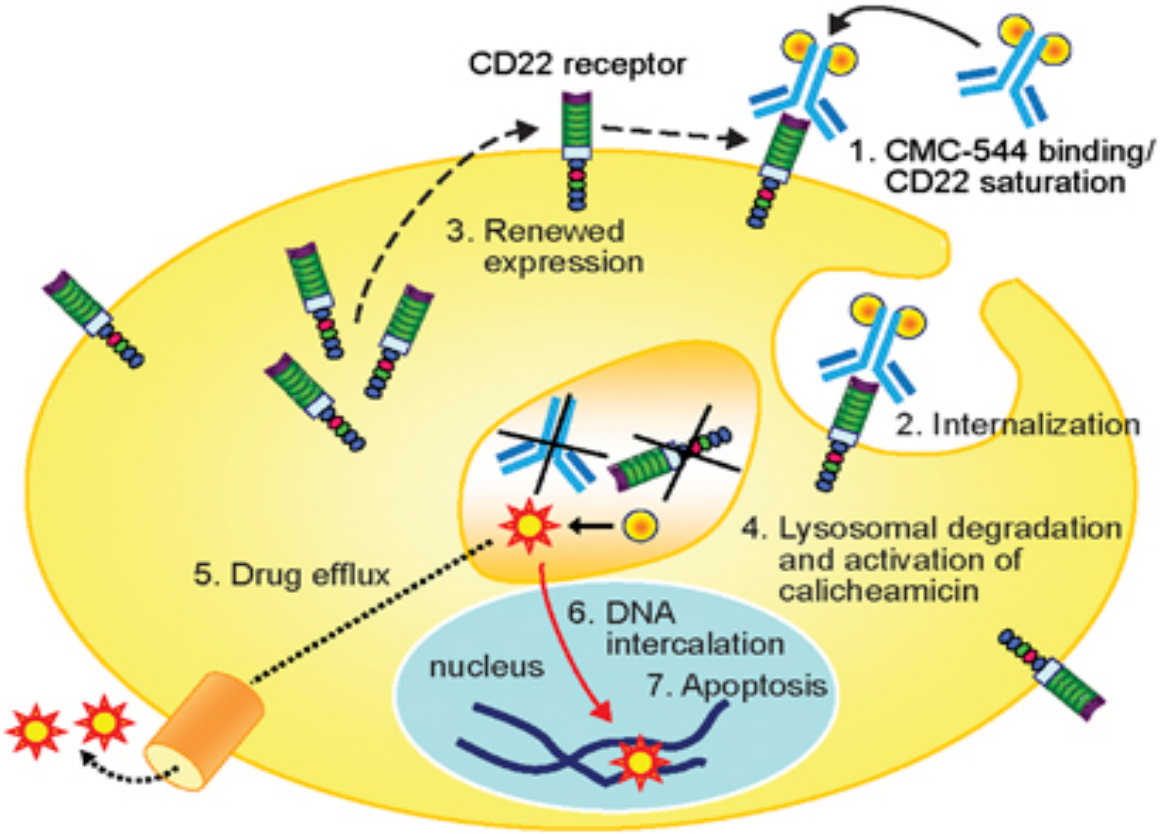
	N=34
Median OS, months	NE
95% CI	7.1–NE
OS events, n	12
Patients censored, n	22

Median follow-up: 13.4 (9.4–14.6) months

NE, not estimable; RFS, relapse-free survival

Stein AS, et al. ASBMT Meeting, 2016

Inotuzumab Ozogamicin: a novel calicheamicin-conjugated CD22 antibody



JF de Vries, Leukemia 2012

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

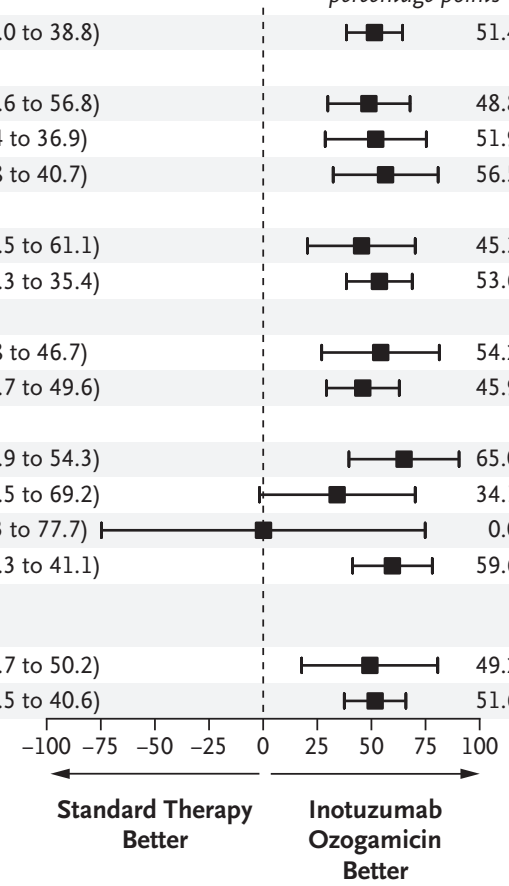
Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia

Hagop M. Kantarjian, M.D., Daniel J. DeAngelo, M.D., Ph.D., Matthias Stelljes, M.D., Giovanni Martinelli, M.D., Michaela Liedtke, M.D., Wendy Stock, M.D., Nicola Gökbuget, M.D., Susan O'Brien, M.D., Kongming Wang, Ph.D., Tao Wang, Ph.D., M. Luisa Paccagnella, Ph.D., Barbara Sleight, M.D., Erik Vandendries, M.D., Ph.D., and Anjali S. Advani, M.D.

Kantarjian, HM et al.: NEJM 2016

B **Rate According to Patient Characteristics at Baseline**

Subgroup	No. of Patients		Complete Remission		Between-Group Difference (97.5% CI)	P Value
	Inotuzumab Ozogamicin Group	Standard-Therapy Group	Inotuzumab Ozogamicin Group	Standard-Therapy Group		
			% (95% CI)		*percentage points*	
All patients	109	109	80.7 (72.1 to 87.7)	29.4 (21.0 to 38.8)	51.4 (38.4 to 64.3)	<0.001
Peripheral blasts						
0	42	48	90.5 (77.4 to 97.3)	41.7 (27.6 to 56.8)	48.8 (29.9 to 67.7)	<0.001
>0 to 1000	32	35	71.9 (53.3 to 86.3)	20.0 (8.4 to 36.9)	51.9 (28.5 to 75.3)	<0.001
>1000	34	25	76.5 (58.8 to 89.3)	20.0 (6.8 to 40.7)	56.5 (32.2 to 80.7)	<0.001
Bone marrow blasts						
<50%	30	29	86.7 (69.3 to 96.2)	41.4 (23.5 to 61.1)	45.3 (20.5 to 70.1)	<0.001
≥50%	77	78	77.9 (67.0 to 86.6)	24.4 (15.3 to 35.4)	53.6 (38.4 to 68.8)	<0.001
CD22 expression						
<90%	24	24	79.2 (57.8 to 92.9)	25.0 (9.8 to 46.7)	54.2 (27.0 to 81.3)	<0.001
≥90%	74	63	82.4 (71.8 to 90.3)	36.5 (24.7 to 49.6)	45.9 (29.1 to 62.8)	<0.001
Karyotype						
Normal	20	20	95.0 (75.1 to 99.9)	30.0 (11.9 to 54.3)	65.0 (39.6 to 90.4)	<0.001
Ph-positive	14	18	78.6 (49.2 to 95.3)	44.4 (21.5 to 69.2)	34.1 (–1.8 to 70.1)	0.08
t(4;11)-positive	3	6	33.3 (0.8 to 90.6)	33.3 (4.3 to 77.7)	0.0 (–74.7 to 74.7)	1.00
Other abnormalities	49	46	85.7 (72.8 to 94.1)	26.1 (14.3 to 41.1)	59.6 (41.3 to 78.0)	<0.001
Previous stem-cell transplantation						
Yes	17	22	76.5 (50.1 to 93.2)	27.3 (10.7 to 50.2)	49.2 (17.8 to 80.6)	0.004
No	92	87	81.5 (72.1 to 88.9)	29.9 (20.5 to 40.6)	51.6 (37.4 to 65.9)	<0.001

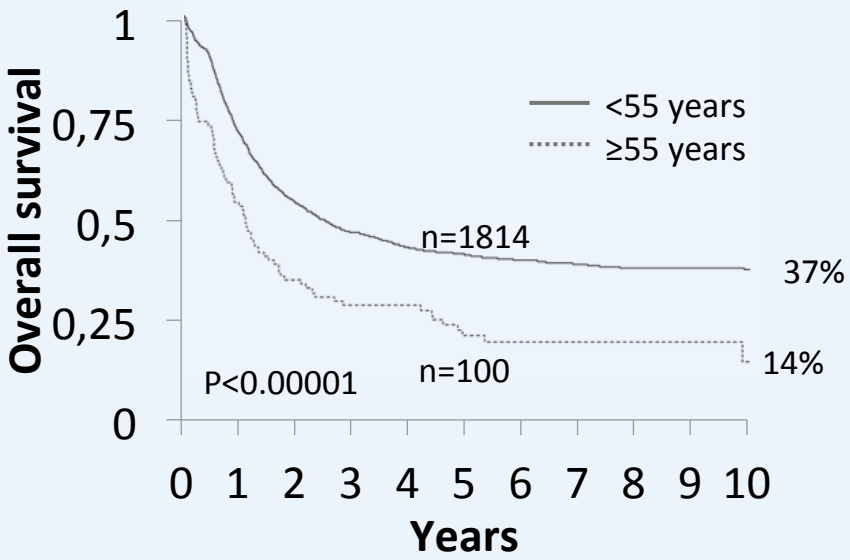


Kantarjian, HM et al.: NEJM 2016

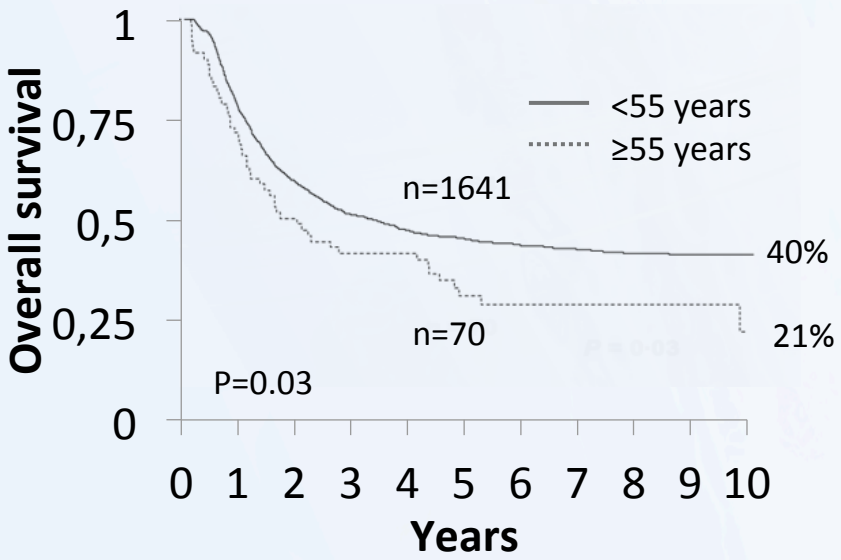
Treatment in older ALL

Survival in older ALL patients in the UKALLXII/ECOG2993 trial

Overall survival by age at entry

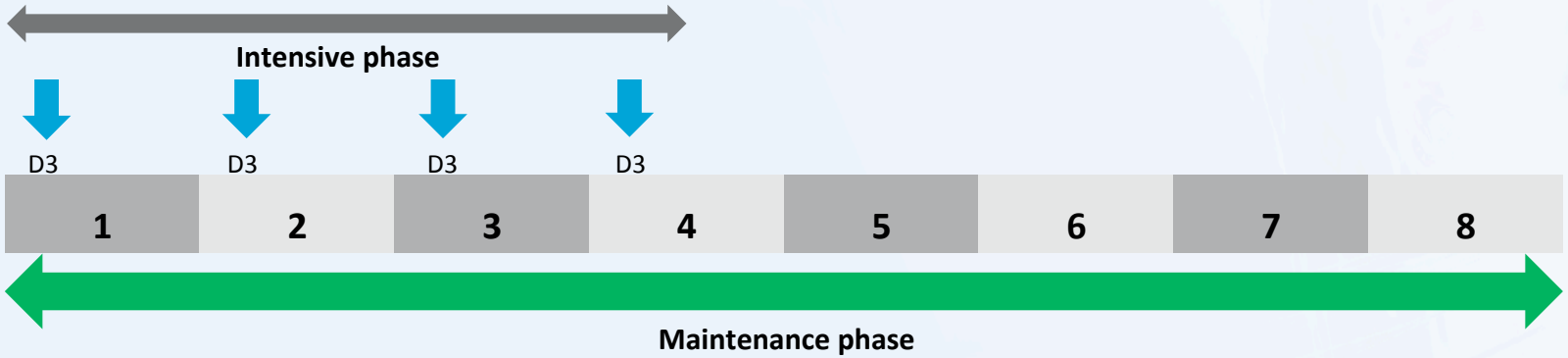


Overall survival of those who achieved CR by age at entry



Sive JI *et al. Br J Haematol* 2012;157:463–471

Study design



Mini HCVD cyclophosphamide (150 mg/m^2) and dexamethasone (20 mg) at 50% dose reduction

Mini-MTX-cytarabine methotrexate (250 mg/m^2) at 75% dose reduction, cytarabine (0.5 g/m^2) at 83% reduction

Inotuzumab

POMP maintenance (36 months)

Inotuzumab	First 6 patients	7 – 34	35 +
First cycle (mg/m2)	1.3	1.8	1.3
C2–4 (mg/m2)	0.8	1.3	1.0

- Inotuzumab dose reduction at start of study
- Rituximab and intrathecal chemotherapy were also given during the first 4 courses

Rituximab is not approved for the treatment of ALL
Sasaki K *et al.* Presented at ASH 2016 (Abstract 588)

Patient characteristics

Characteristic	Median (range) / n (%) N=47
Age (years), median (range)	68 (60–81)
Male sex, n (%)	29 (62)
ECOG PS ≥2, n (%)	7 (15)
WBC at diagnosis	
≥50, n (%)	3 (7)
Median (range)	3.0 (0.6–111.0)
Karyotype	
Diploid , n (%)	14 (30)
Complex , n (%)	19 (40)
Misc, n (%)	6 (13)
IM/ND, n (%)	8 (17)
Immunophenotype	
CD22 positive, median (range)	97 (72–100)
CD20 ≥20, n (%)	28 (60)

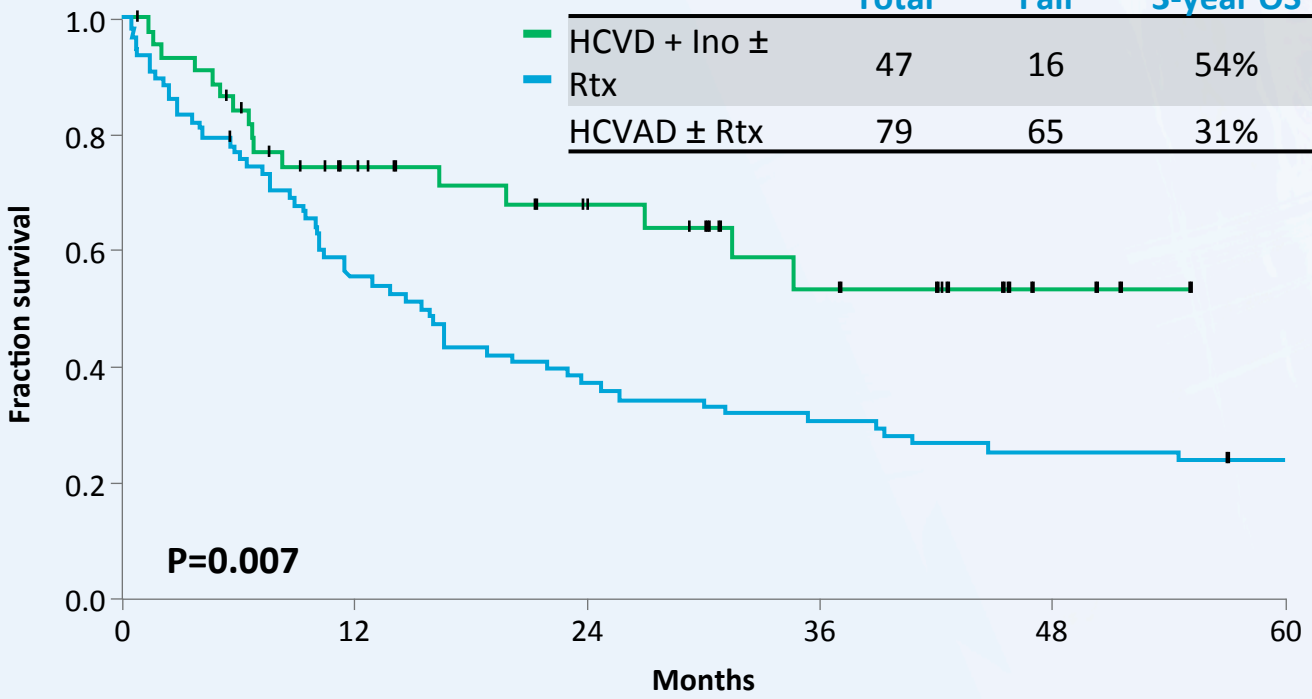
Sasaki K *et al.* Presented at ASH 2016 (Abstract 588)

Response rates

Response	N	%
CR	36	84
CRp	5	12
CRi	1	2
ORR	42	98
No response	1	2
Early death	0	0
Cytogenetic CR	22 abn at start (22/22)	100
Negative MRD*		
Day 21	31/41	76
Overall	44/46	96

*MRD assessed by 6-colour multiparameter flow
Sasaki K *et al.* Presented at ASH 2016 (Abstract 588)

Overall survival



	Total	Fail	3-year OS	Median
HCVD + Ino ± Rtx	47	16	54%	Not reached
HCVAD ± Rtx	79	65	31%	16 months

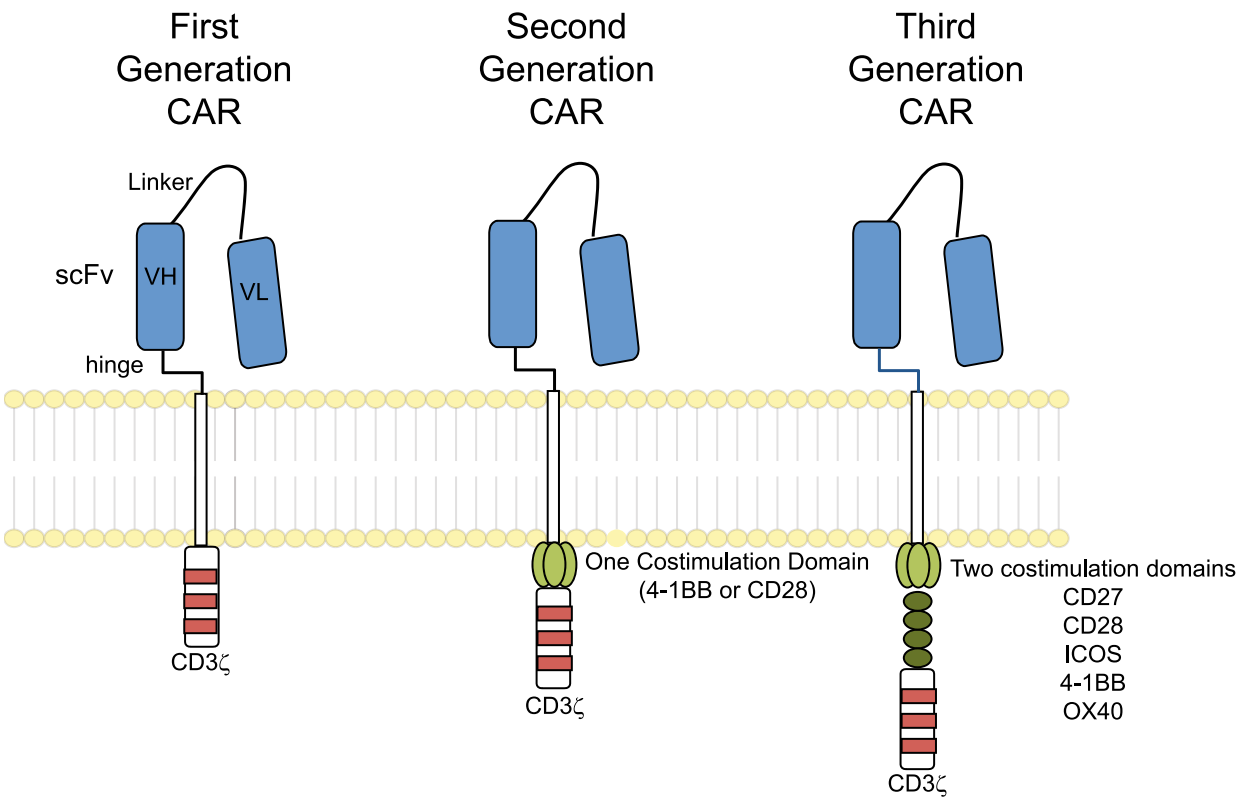
Sasaki K *et al.* Presented at ASH 2016 (Abstract 588)

Safety

≥10% Grade 3/4 AE	%
Prolonged thrombocytopenia	79
Infections during induction	53
Infections during consolidation	74
Hyperglycaemia	53
Hypokalemia	34
ALT/AST	19
Bilirubin	17
Haemorrhage	15
VOD	8

Sasaki K *et al.* Presented at ASH 2016 (Abstract 588)

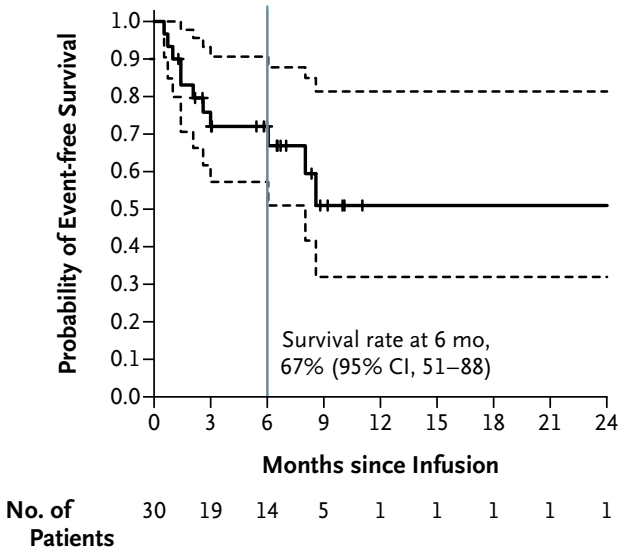
Chimeric antigen receptors

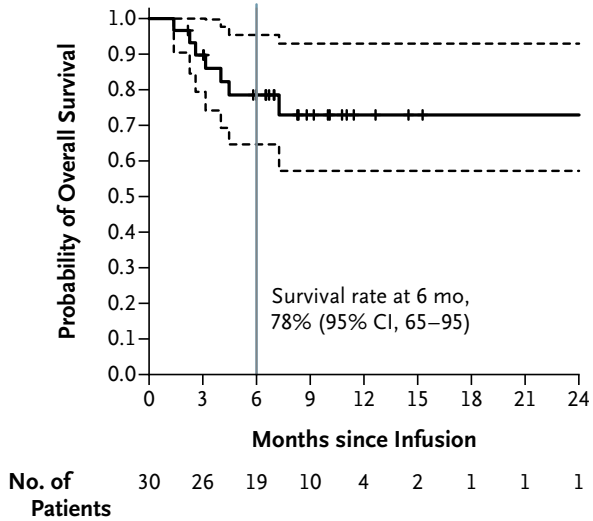


Maus, MV.:I Blood. 2014;123(17):2625-2635

ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia



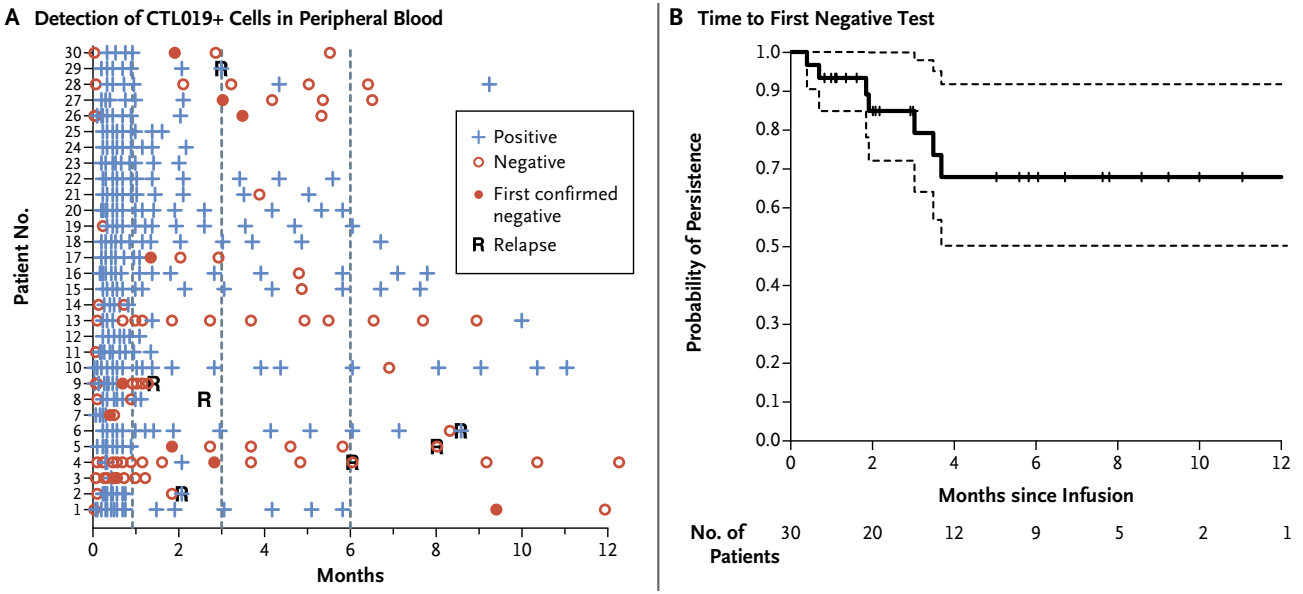


Maude SL.: N Engl J Med 2014;371:1507-17

ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

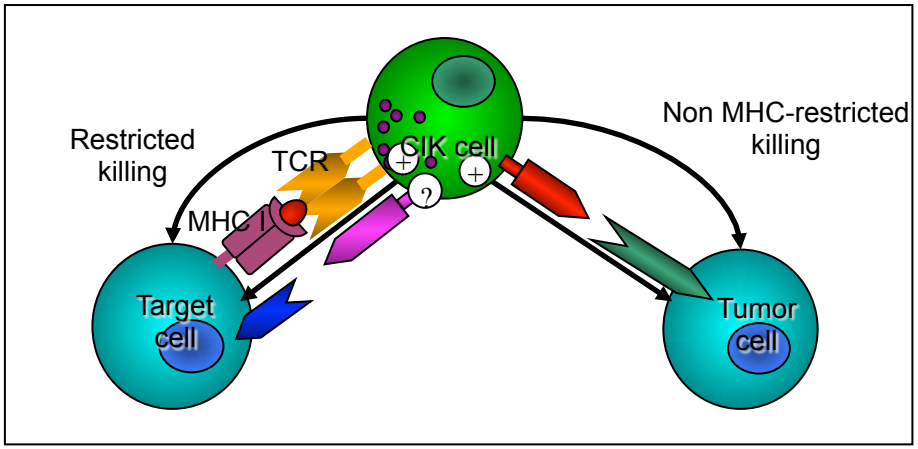
Persistence of CAR-T cells correlates with clinical outcome



Maude SL.: N Engl J Med 2014;371:1507-17

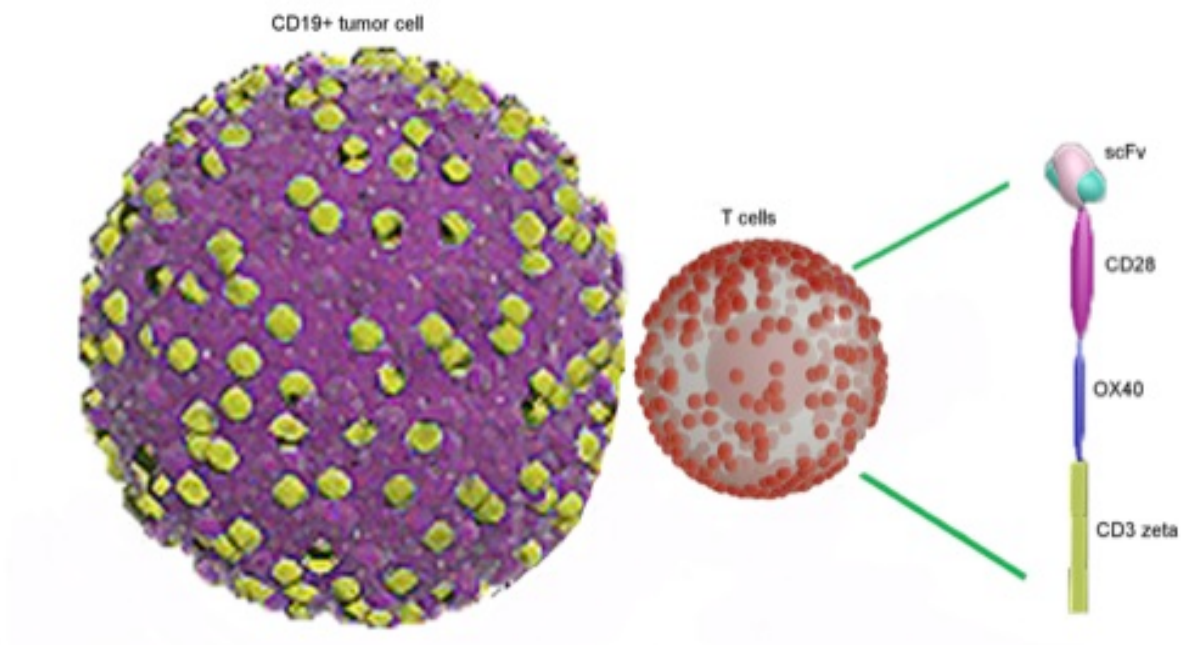
Cellular therapy with Cytokine Induced Killer (CIK) cells

- *CIK cells are NK-T cells (CD56+CD3+) expanded from peripheral blood mononuclear cells (first described in NK cell clones by T. Hercend)*
- *CIK cells show non-specific anti-tumor activity and home to tumors without significant GVHD in several animal models*
- *CIK cells can be reproducibly expanded in vitro under strict GMP conditions*



Introna et al, BMT, 2006
Marin et al, Exp. Hematol,2006
Franceschetti et al, Exp Hematol, 2009
Introna et al, BBMT, 2010
Pievani et al, Blood, 2011
Pievani et al, Blood, 2011

Open label, single arm, multicenter, dose escalation Phase I, trial to determine the safety of Allogeneic (donor derived) Cytokine Induced Killer (CIK) cells transduced with a transposon CD19 Chimeric Antigen Receptor (CAR) gene (CARCIK.CD19) in adult and pediatric patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL), after Hematopoietic Stem Cell Transplantation (HSCT)



CONCLUSIONS

MRD remains the most powerful predictor of outcome. Post-remissional therapy must be guided by MRD

AlloHSCT remains the post-remissional treatment of choice for HIGH RISK/MRD+ patients who must be allocated early to alloHSCT. Non relapse mortality remains a major problem

TKIs and chemotherapy may achieve long term remission even without a transplant consolidation to cure

New antibodies and TKIs may represent an effective innovative treatment approach to improve the cure rate and reduce treatment related toxicity and mortality

CART cells are an extraordinary investigational tool for future treatment of advanced ALL patients

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