Nuovi farmaci e trapianto
Aula Magna Kolbe
Università di Udine
21 gennaio 2016

GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

Inibitori delle tirosin kinasi nelle Ph+ ALL dell'adulto: prima, dopo o in alternativa al trapianto allogenico

Alessandro Rambaldi

Azienda Ospedaliera
Papa Giovanni XXIII
Bergamo

UNIVERSITÀ DEGLI STUDI DI MILANO

Agenda

1. Overcome primary refractory resistance and early relapse
2. Achieve (before allo) and maintain (after allo) a complete molecular remission
3. Impact of the conditioning regimen and the stem cell source
4. AlloHSCT for every patient in CR1?

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CLINICAL OUTCOME OF Ph+ ALL PATIENTS TREATED IN A PRE-IMATINIB ERA (1990 - 2000)

N	80
CR	63/80 (79%)
Allo TRX	16 (20%)

Disease Free Survival (n=63)

Overall Survival (n=80)

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nilg northern italy leukemia group

Overcome primary refractory resistance and early relapse

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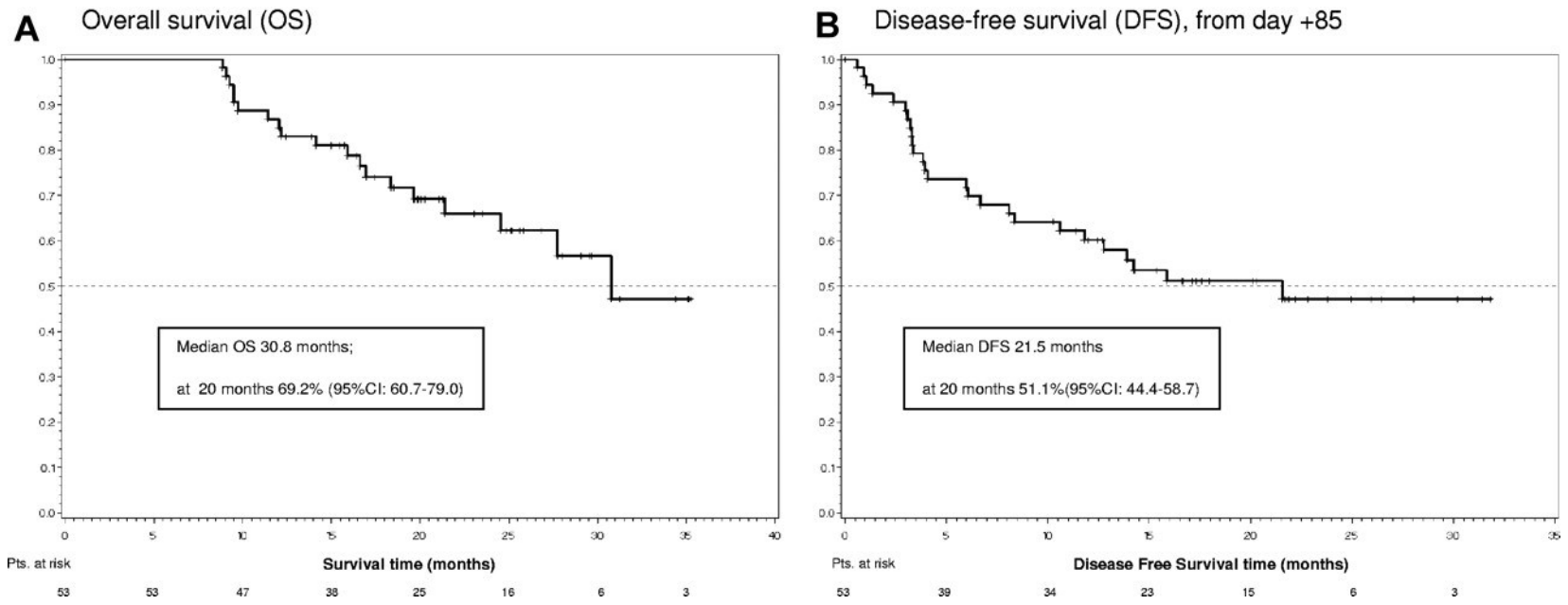
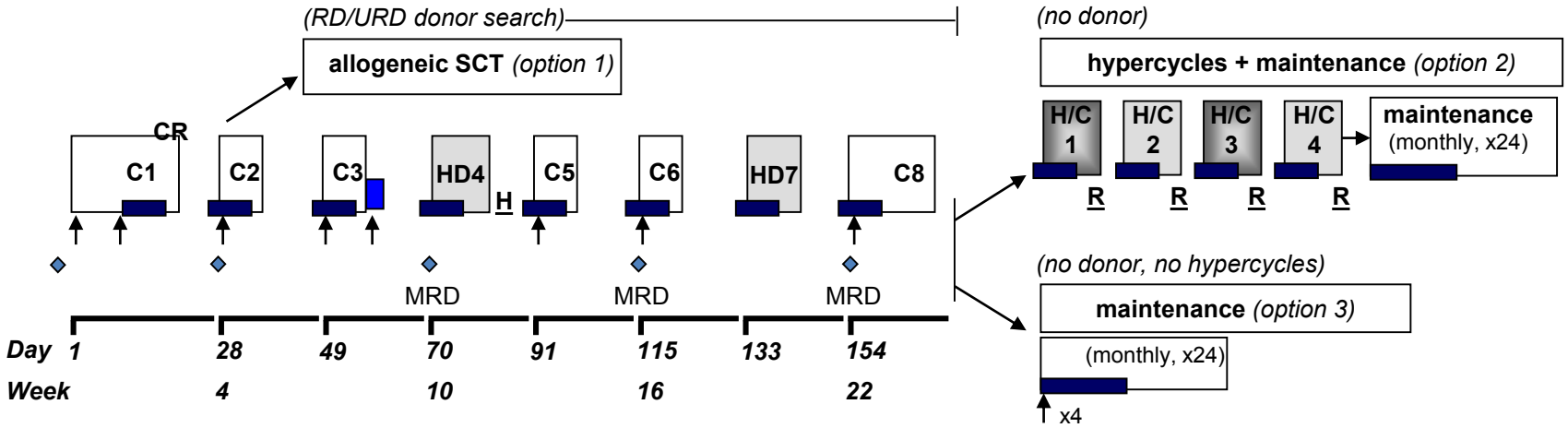
Survival after treatment with Dasatinib and steroids in older Ph+ ALL



Robin Foà et al. Blood 2011;118:6521-6528

Chemotherapy-Phased Imatinib Pulses for Adult Patients with Ph+ ALL
Northern Italy Leukemia Group Protocol 09/00



Key:

◇ = bone marrow examination

↑ = intrathecal prophylaxis (MTX/Ara-C/PDN)

MRD = minimal residual disease analysis

▮ = cranial irradiation (18 Gy)

▬ = 7-day imatinib pulse (600 mg/d)

C = standard chemotherapy cycle
(1: IDR/VCR/L-Asp/PDN;
2,3,5,6: IDR/VCR/CY/DXM;
8: IDR/VCR/PDN)

H / R = autologous blood stem cell harvest / reinfusion

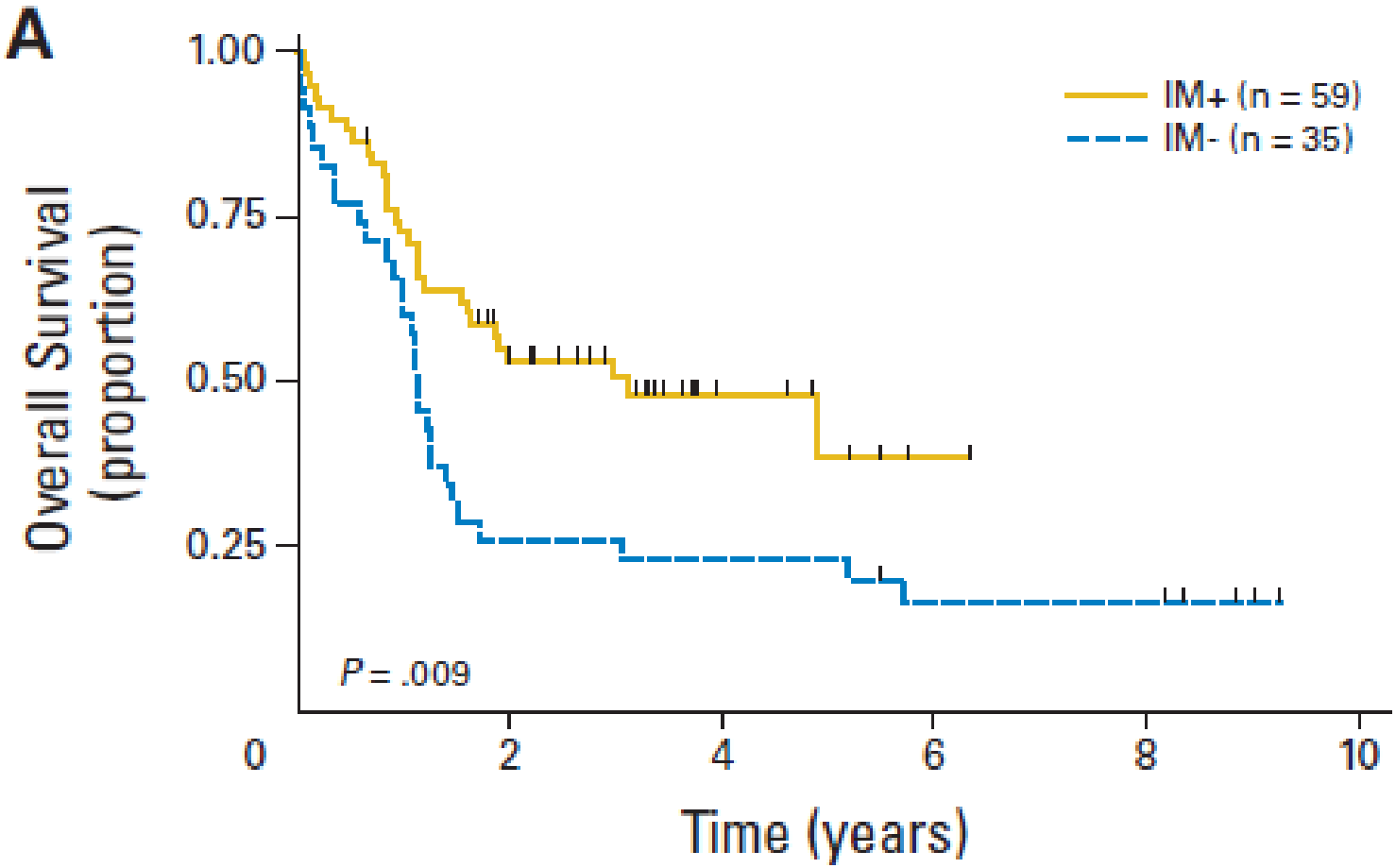
HD = high dose chemotherapy cycle (MTX/Ara-C)

H/C = hypercycle with autologous blood stem cell support
(1, 3: high dose L-PAM/VP16/6MP;
2, 4: high dose MTX/Ara-C)

▬ = 14-day IM pulse (600 mg/d)

Bassan R et al.: Journal of Clinical Oncology, 2010

Chemotherapy-Phased Imatinib Pulses for Adult Patients with Ph+ ALL
Northern Italy Leukemia Group Protocol 09/00



Bassan R et al.: J Clin Oncol 28:3644-3652. 2010

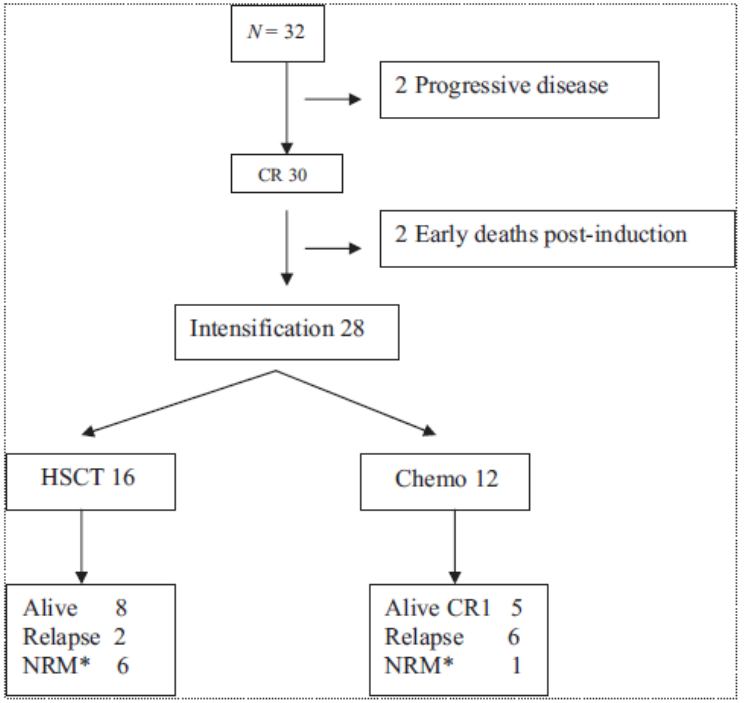
bjh research paper

Treatment of Philadelphia chromosome-positive acute lymphoblastic leukaemia with imatinib combined with a paediatric-based protocol

Santhosh Thyagu,[1] Mark D. Minden,[1] Vikas Gupta,[1] Karen W.L. Yee,[1] Aaron D. Schimmer,[1] Andre C. Schuh,[1] Jeffrey H. Lipton,[1] Hans A. Messner,[1] Wei Xu[2] and Joseph M. Brandwein[1]

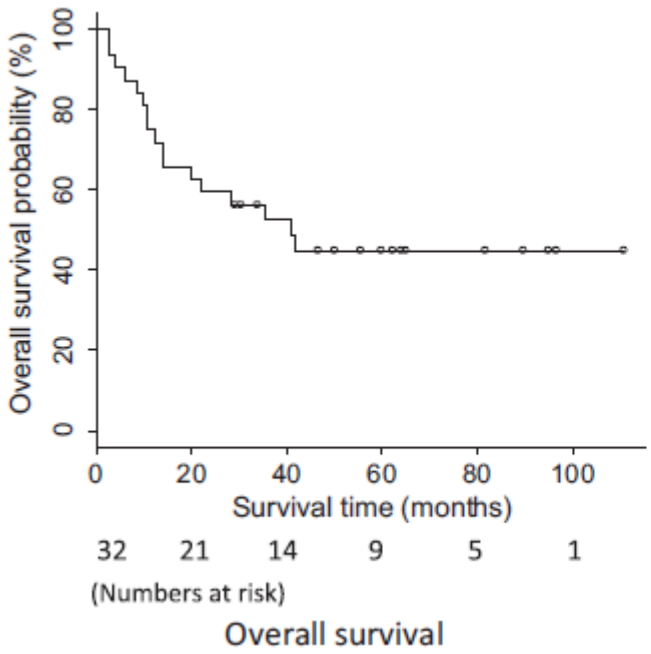
[1]Department of Medical Oncology and Hematology, and [2]Department of Biostatistics, Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada

Patient characteristic	Number
Age, years: median (range)	46 (18–60)
Age subgroups: 18–40 years/41–60 years	11/21

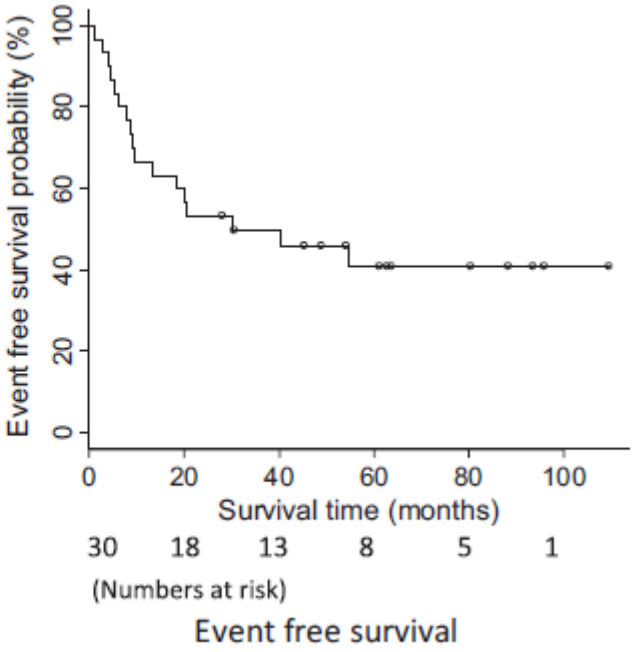


British Journal of Haematology, 2012, **158,** 506–514

Treatment of Philadelphia chromosome-positive acute lymphoblastic leukaemia with imatinib combined with a paediatric-based protocol



Overall survival



Event free survival

Impact of TKIs before transplant

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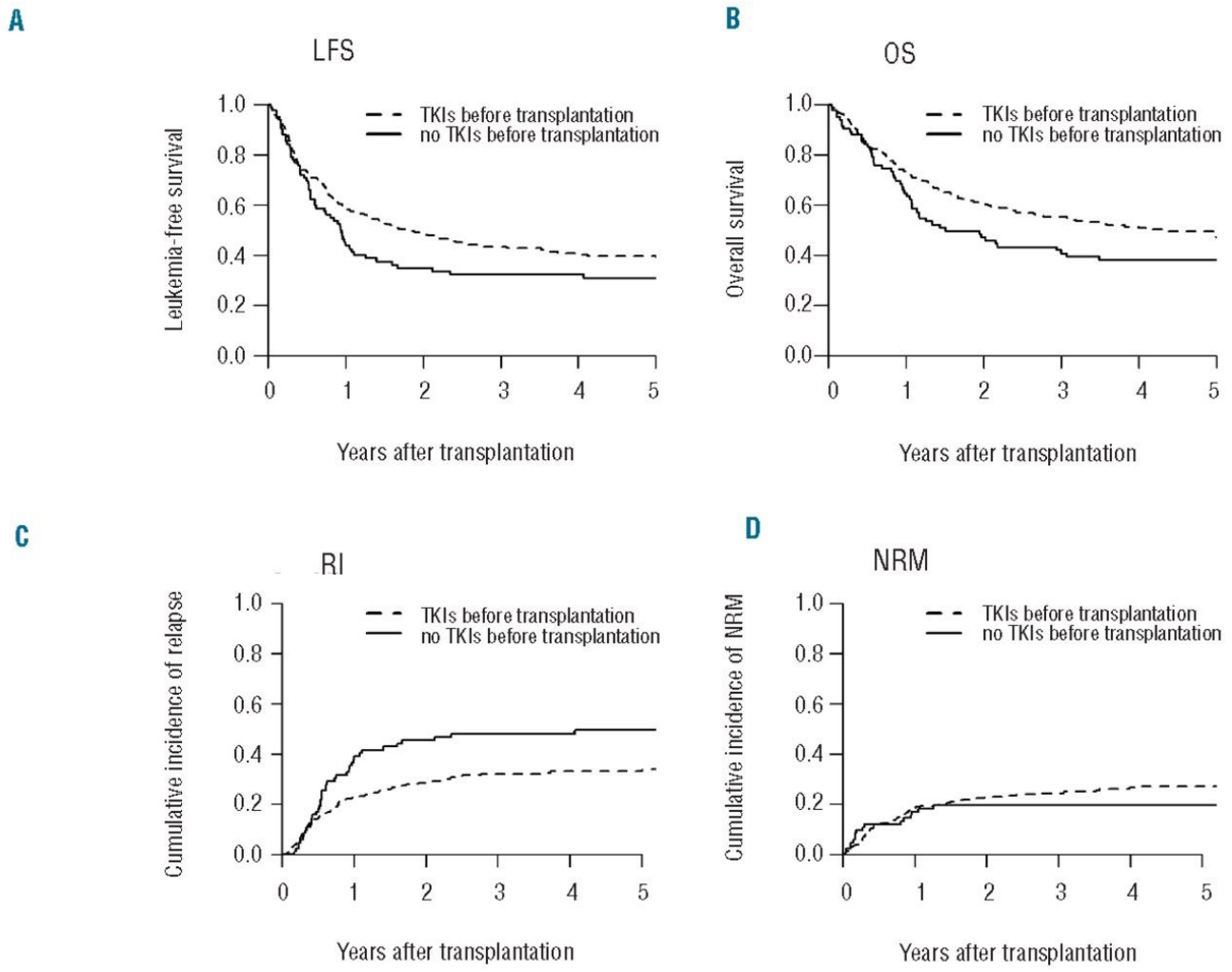
Probability of (A) leukemia-free survival (LFS), (B) overall survival (OS), (C) relapse incidence (RI), and (D) non-relapse mortality (NRM) in allografted patients with Ph+ALL in first complete remission with TKIs before allogeneic stem cell transplantation



Eolia Brissot et al. Haematologica 2015;100:392-399

Impact of MRD at time of conditioning

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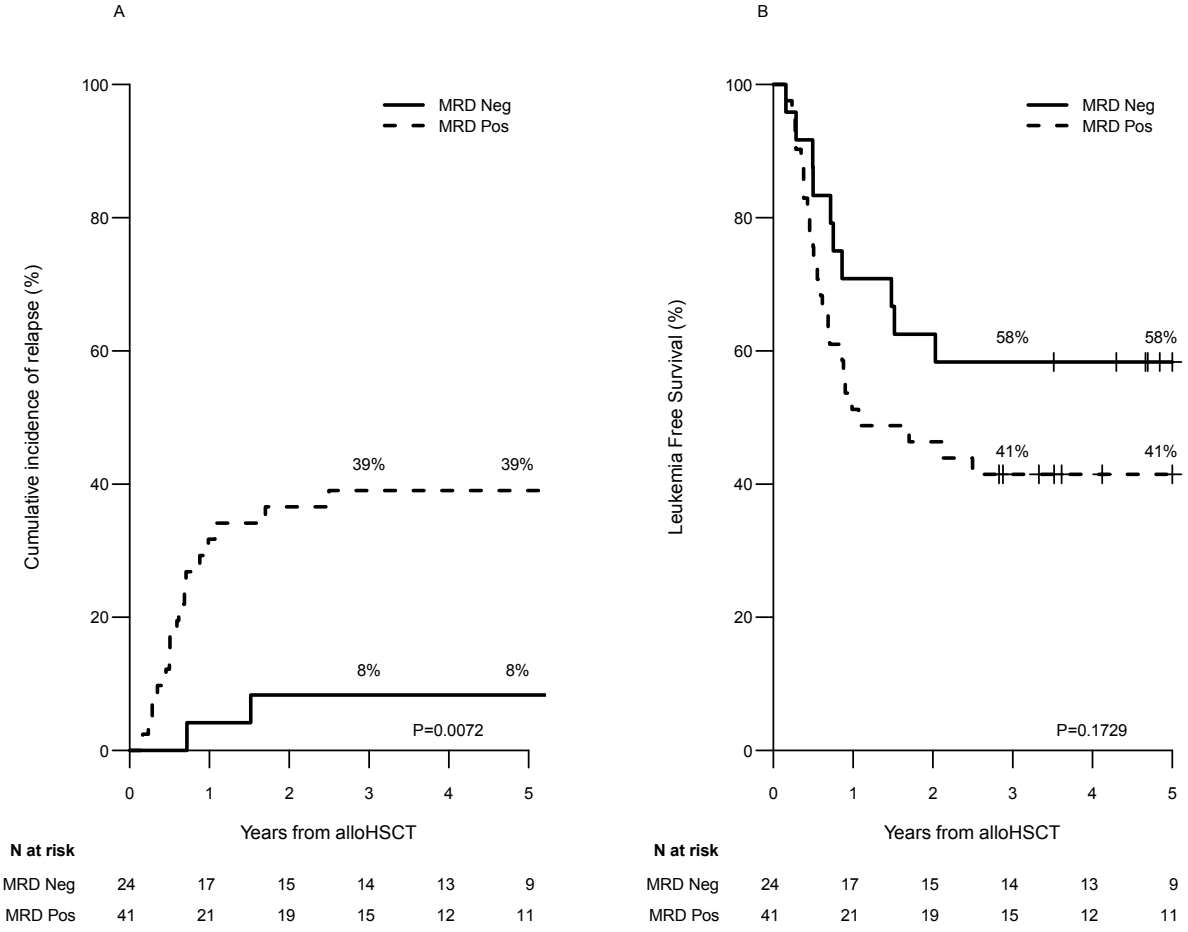
Allogeneic transplantation for adult Ph+ ALL: impact of MRD status at conditioning



Lussana et al.: ASH 2015

Impact of MRD after transplant

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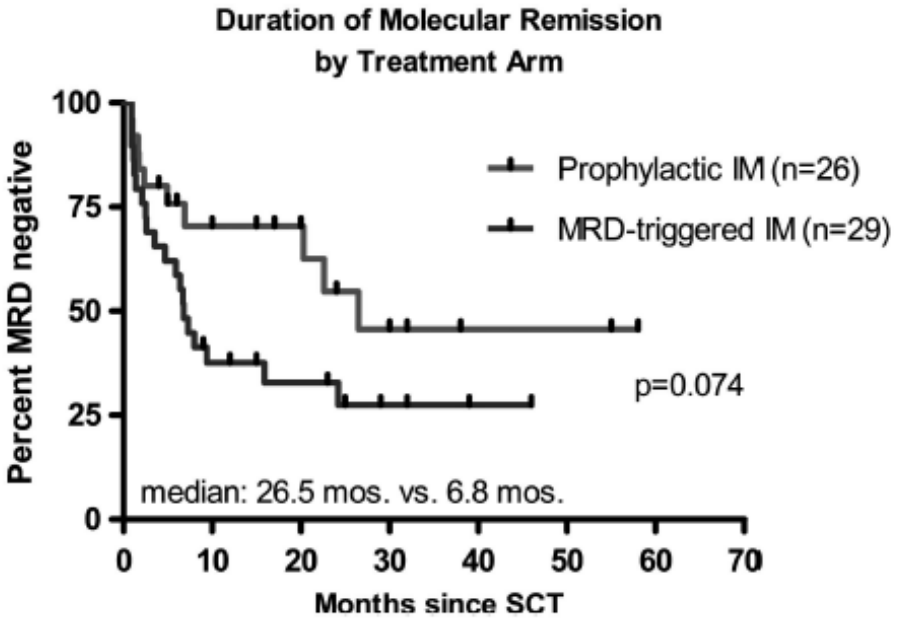
Randomized comparison of prophylactic and MRD-triggered imatinib after alloHSCT for Ph+ ALL

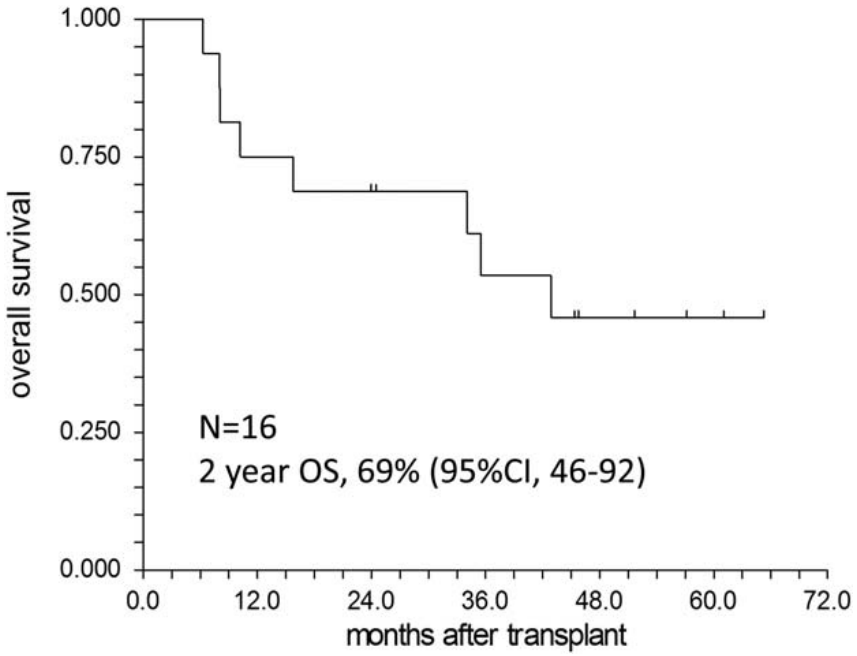
- MRD after allogeneic SCT for Ph+ ALL is predictive of relapse and Imatinib may prevent it
- imatinib was administered either prophylactically or following detection of MRD
- Prophylactic imatinib significantly reduced the incidence of molecular recurrence (40% vs 69%; P=0.046)



Pfeifer, H : Leukemia, 2012

Phase 1/2 study of nilotinib prophylaxis after alloHSCT in patients with advanced CML or Ph+ ALL

- Prophylactic nilotinib maintenance started at a median of 38 days after alloHSCT
- Most patients achieved or maintained a complete MR, and only 1 of them later relapsed
- With a median follow-up of 46 months the 2-year OS and PFS rates were 69% and 56%, respectively



Shimoni A et al. Cancer **121 (6), 863–871, 2015**

Impact of the conditioning regimen and the stem cell source

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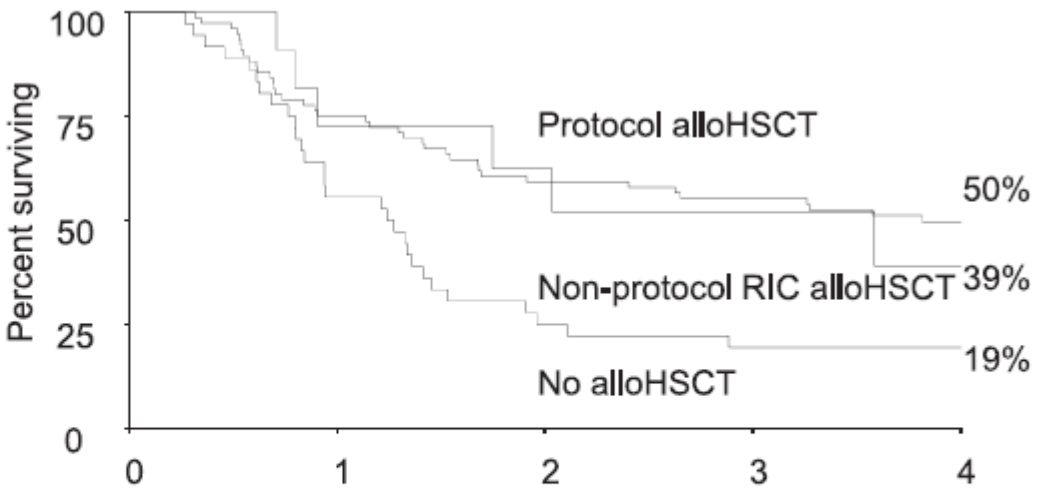
blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Protocol myeloablative sibling/MUD alloHSCT, nonprotocol RIC alloHSCT or no alloHSCT



At risk:					
Protocol alloHSCT	76	57	45	42	31
Non-protocol RIC alloHSCT	11	8	6	5	3
No alloHSCT	38	20	9	7	6

Fielding A K et al. Blood 2014;123:843-850

AlloHSCT for every patient in CR1?

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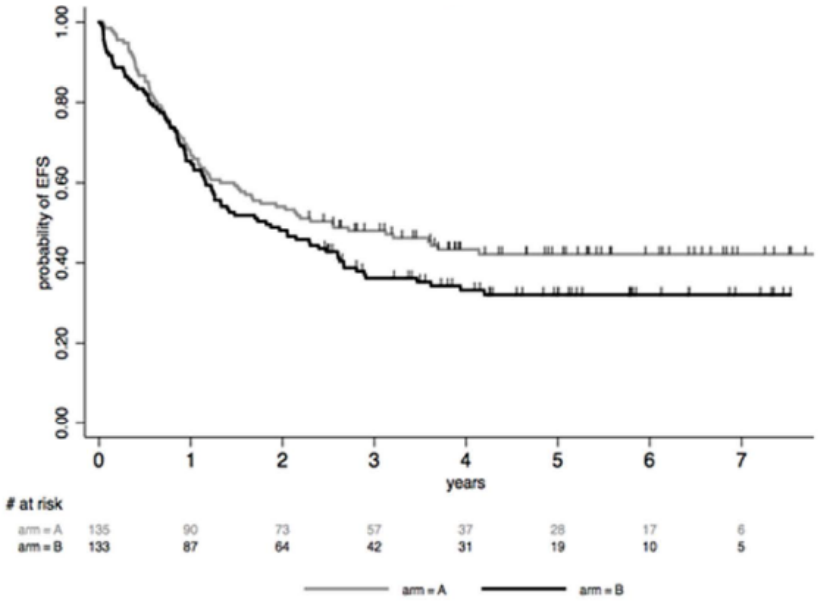
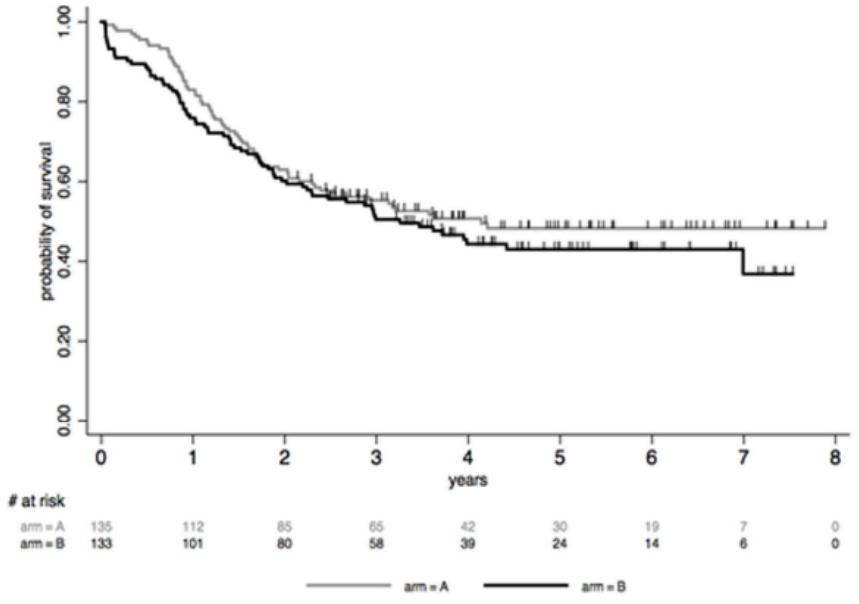
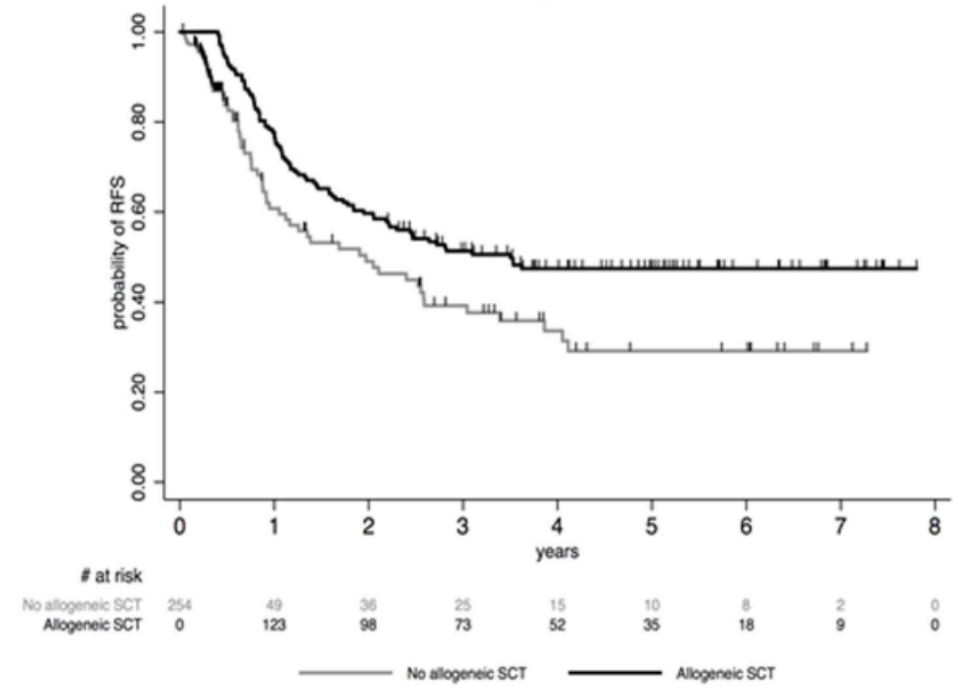
Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia.

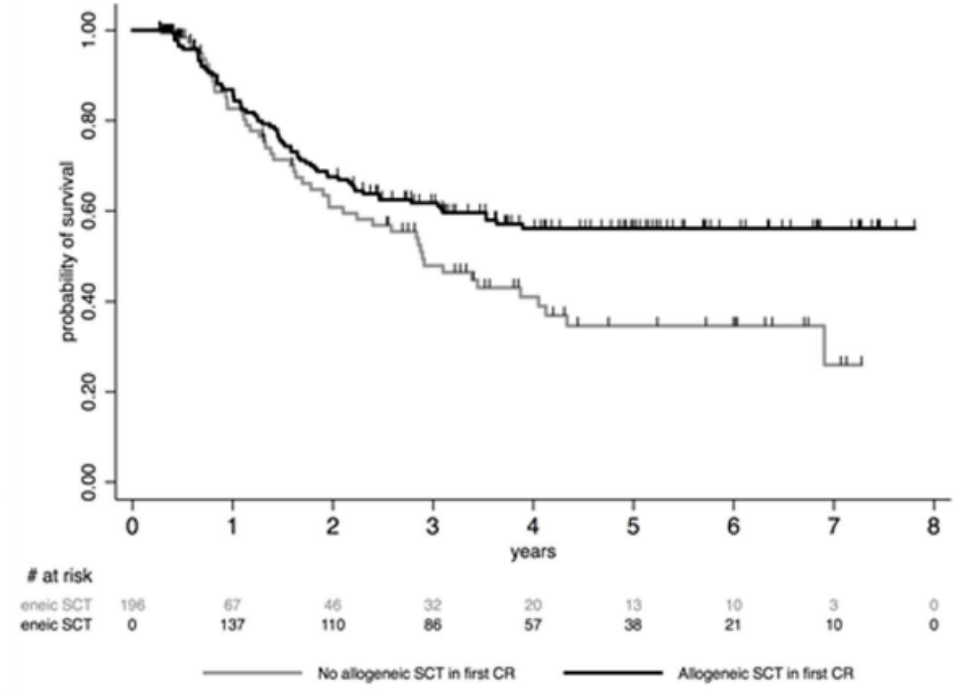




Chalandon I.: Blood First Edition Paper, prepublished online April 15, 2015

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

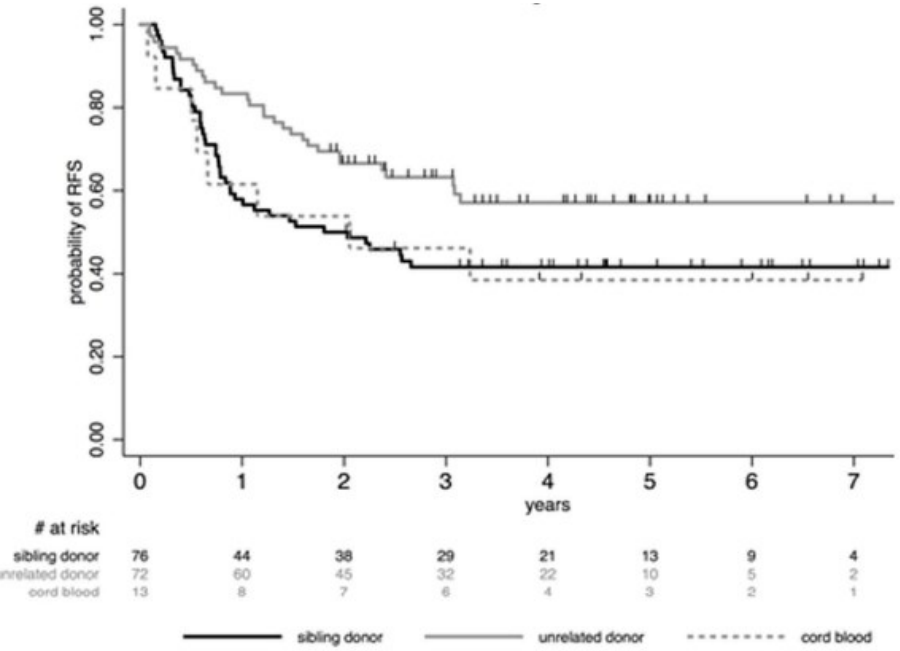


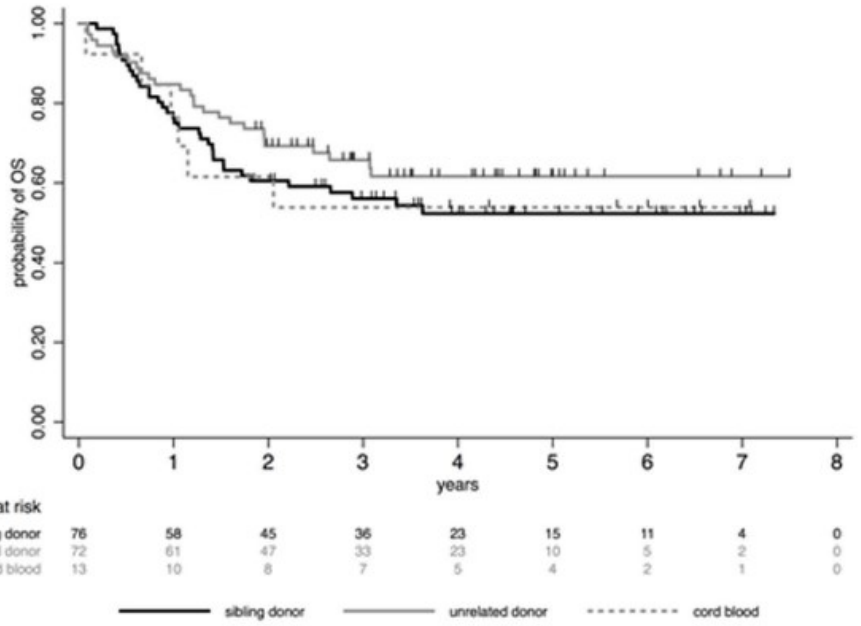


A 3-month RFS landmark period (median time from CR to transplantation) was used here, as patients should be alive but also in first CR to be actually transplanted. This landmark minimizes the bias related to early relapses

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

SCT outcome, by stem cell source





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

AlloHSCT for every patient in CR1?

Probably no!

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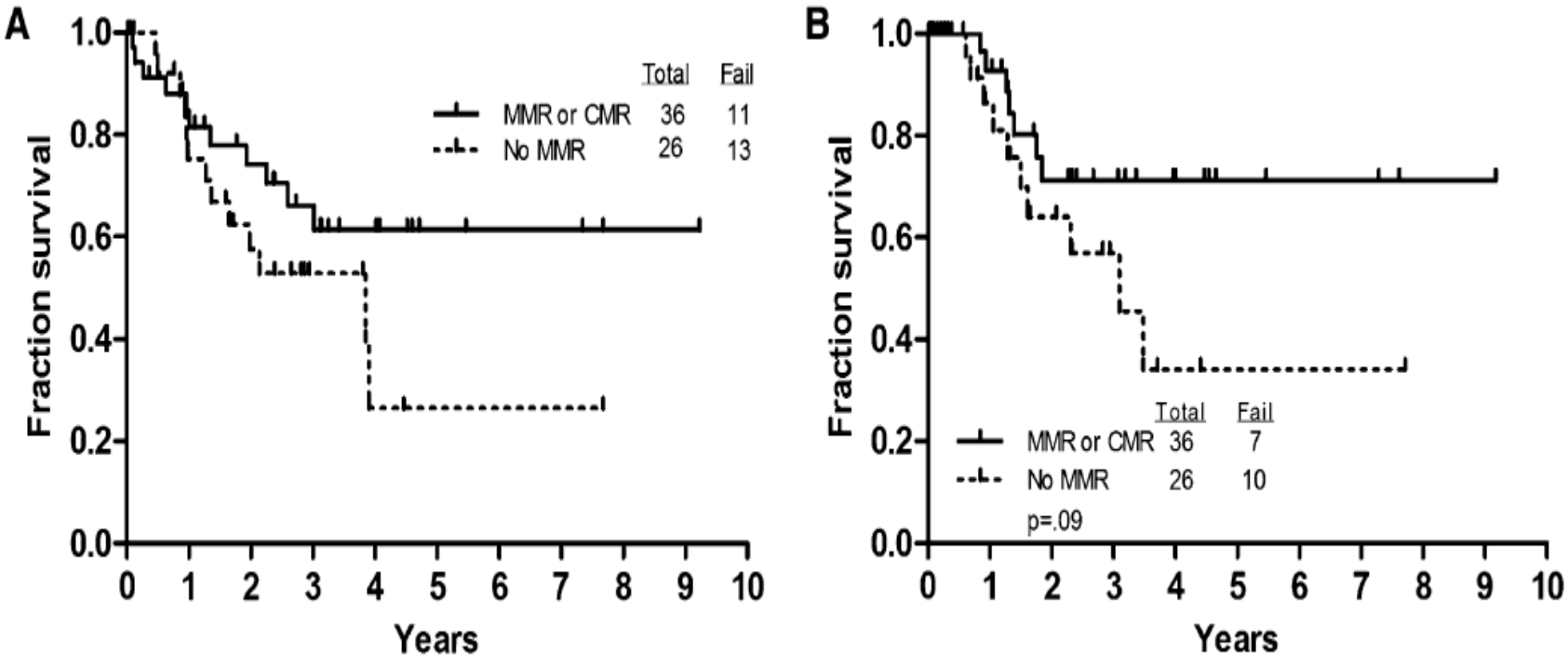
blood
2013 122: 1214-1221
doi:10.1182/blood-2012-11-466482 originally published online July 8, 2013

Detection of MRD may predict the outcome of patients with Philadelphia chromosome –positive ALL treated with tyrosine kinase inhibitors plus chemotherapy



OS **EFS**

Ravandi F et al. Blood, 2013

Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study

Elias Jabbour, Hagop Kantarjian, Farhad Ravandi, Deborah Thomas, Xuelin Huang, Stefan Faderl, Naveen Pemmaraju, Naval Daver, Guillermo Garcia-Manero, Koji Sasaki, Jorge Cortes, Rebecca Garris, C Cameron Yin, Joseph D Khoury, Jeffrey Jorgensen, Zeev Estrov, Zachary Bohannan, Marina Konopleva, Tapan Kadia, Nitin Jain, Courtney DiNardo, William Wierda, Vicky Jeanis, Susan O'Brien

	Participants (n=37)
Age	
Median (years)	51 (27–75)
≥50 years	20 (54%)
≥60 years	12 (32%)
Males	20 (54%)
ECOG performance status	
0–1	31 (84%)
2	6 (16%)
White blood cells (×10^9 per L)	8 (1–630)
CNS disease	3 (8%)
CD20-positive	11 (30%)
BCR-ABL1 transcript	
p190	27 (73%)
p210	10 (27%)
Cytogenetics	
Diploid	5 (14%)
Philadelphia chromosome-positive	32 (86%)
Baseline cardiovascular risk factors	
Hypertension	18 (49%)
Dyslipidaemia	4 (11%)
Coronary artery disease	4 (11%)
Peripheral arterial disease	1 (3%)

Data are n (%) or median (range). ECOG=Eastern Cooperative Oncology Group.

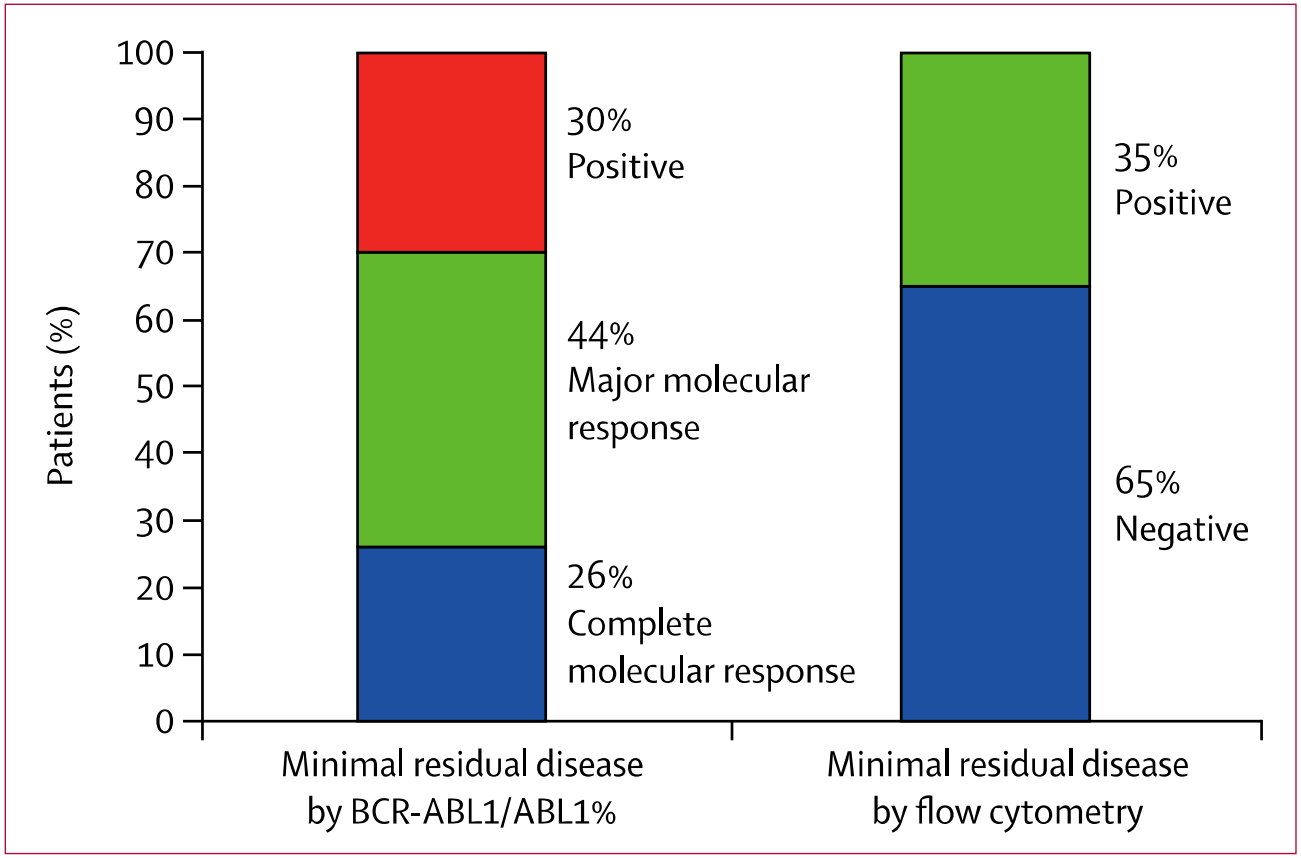
Table 1: **Patient characteristics**

	Number of patients (%)
Complete response*	36/36 (100%)
Complete cytogenetic response†	32/32 (100%)
Major molecular response	35/37 (95%)
Complete molecular response	29/37 (78%)
Flow cytometry negative‡	35/36 (97%)

Data are n/N (%). *One patient in complete response at beginning of study. †Five patients were diploid by conventional cytogenetics at beginning of study. ‡One patient had no sample sent to flow cytometry.

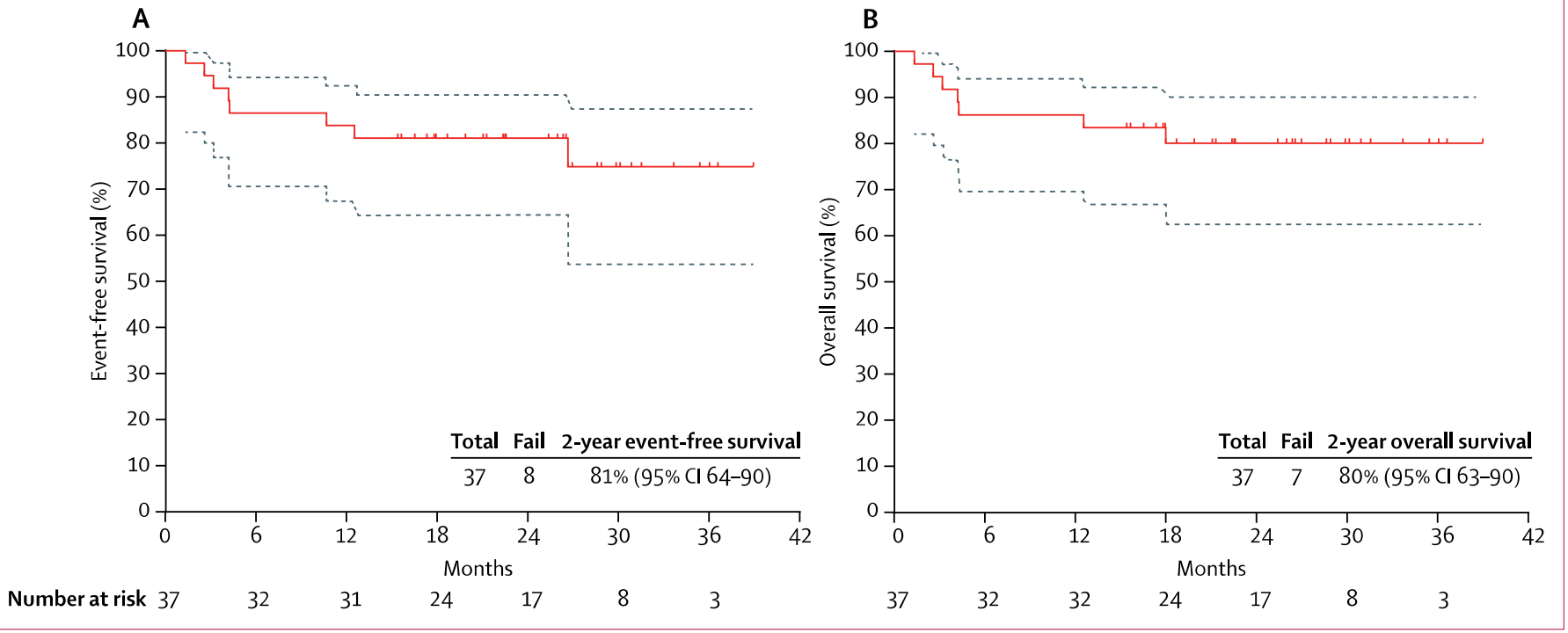
Jabbour, E et al. Lancet Oncol 2015

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

Why TKIs have improved the outcome?

- More patients in CR and less primary refractory diseases
- Less early death
- More patients achieving a molecular CR (> 40%)
- More patients to and better results after alloHSCT

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Research questions

- MRD before transplant matters! How to get it?
- Can we avoid chemotherapy?
- Can we avoid AlloHSCT?

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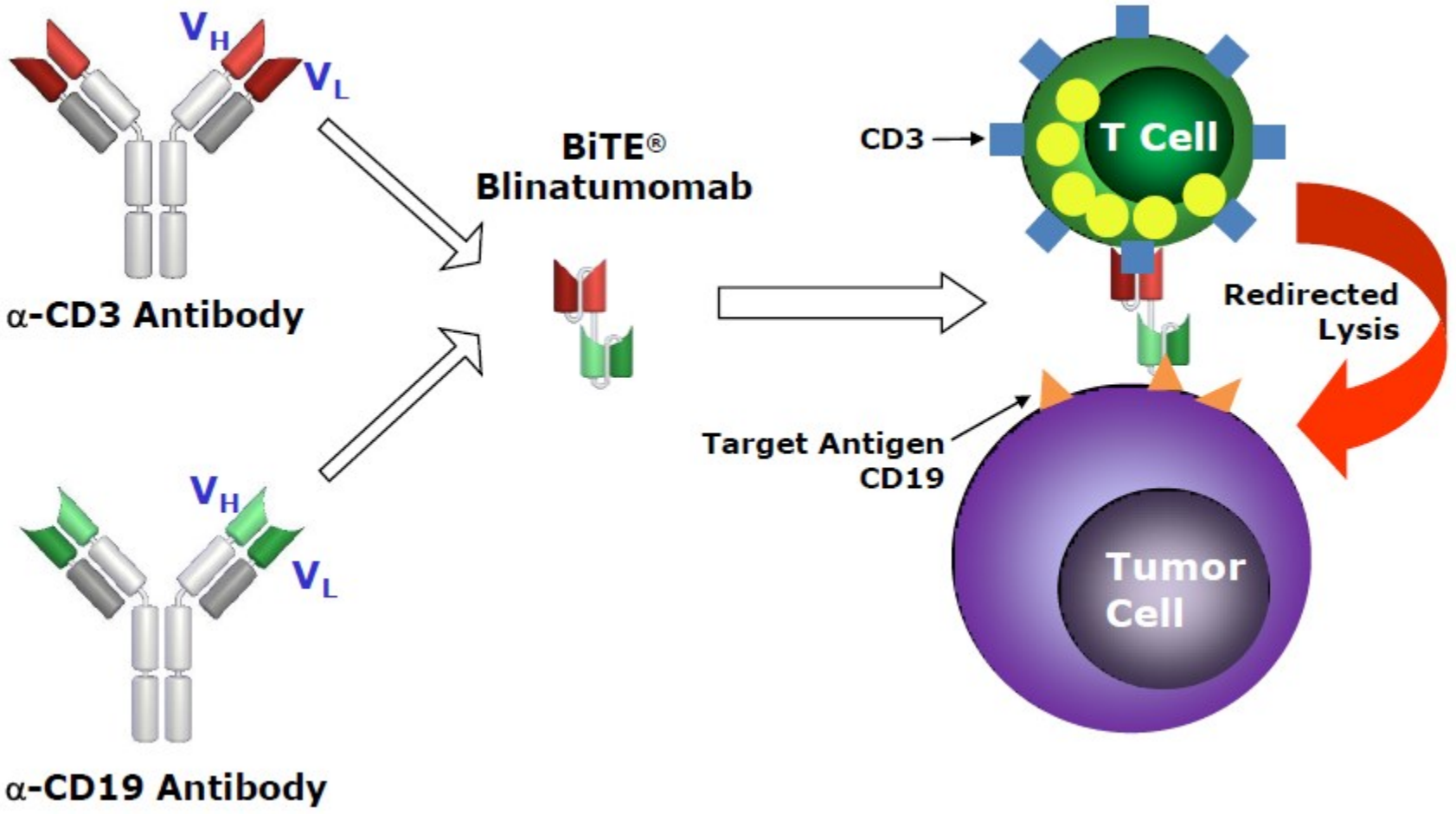
Blinatumomab , a Bispecific T-Cell Engaging (BiTE) Antibody



Dirk Nagorsen and Patrick A. Baeuerle
Experimental Cell Research

blood

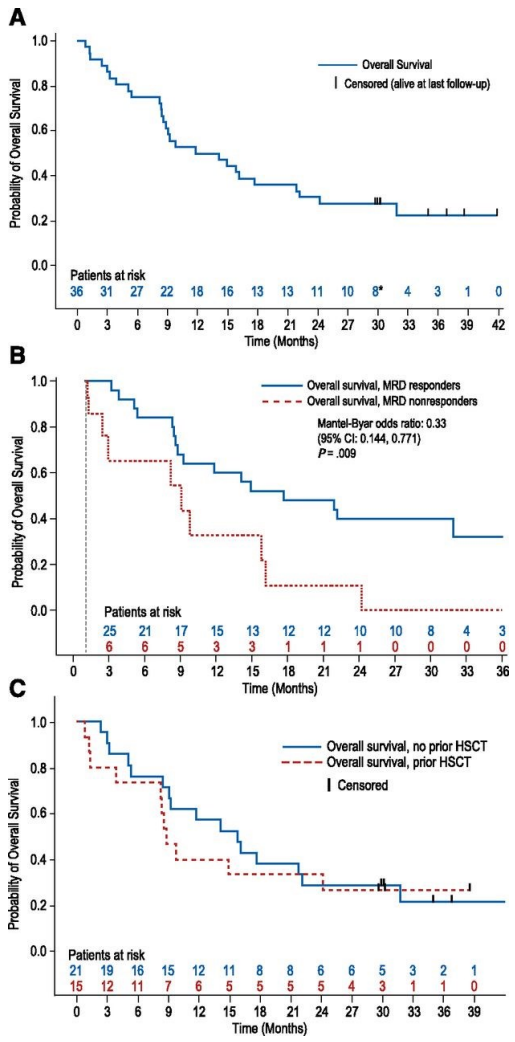
Prepublished online October 19, 2015;
doi:10.1182/blood-2015-06-649111 originally published online
October 19, 2015

Long-term survival and T-Cell kinetics in adult patients with relapsed/refractory B-precursor acute lymphoblastic leukemia who achieved minimal residual disease response following treatment with Anti-CD19 BiTE® antibody construct blinatumomab

Gerhard Zugmaier, Nicola Gökbuget, Matthias Klinger, Andreas Viardot, Matthias Stelljes, Svenja Neumann, Heinz-A. Horst, Reinhard Marks, Christoph Faul, Helmut Diedrich, Albrecht Reichle, Monika Brüggemann, Chris Holland, Margit Schmidt, Hermann Einsele, Ralf C. Bargou and Max S. Topp

- an open-label, multicenter, exploratory, single-arm, phase 2 study in adult patients with r/r B-precursor ALL conducted in collaboration with the German Study Group for ALL
- Ph negative and Ph-positive patients with primary refractory disease or relapse

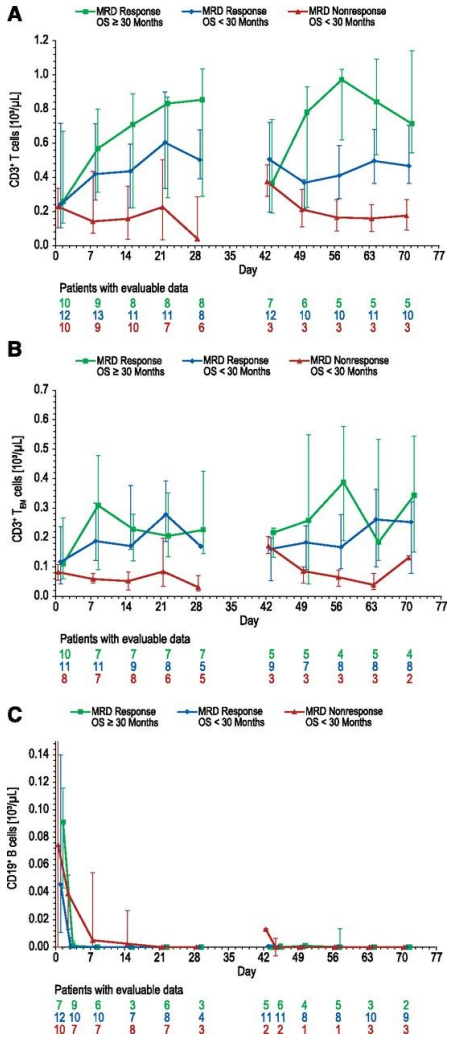
Overall Survival



Gerhard Zugmaier et al. Blood 2015;126:2578-2584

blood

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



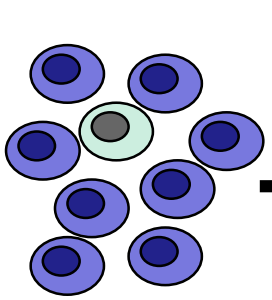
Gerhard Zugmaier et al. Blood 2015;126:2578-2584

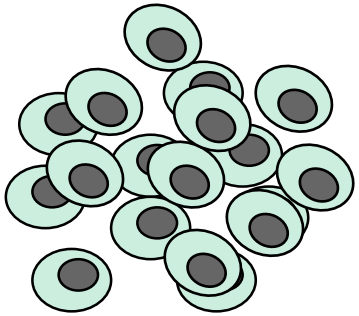
blood

Reasons of blinatumomab failure

- Loss od CD19 on the leukemic blast cell surface
- Lack of CD3+ effector cells

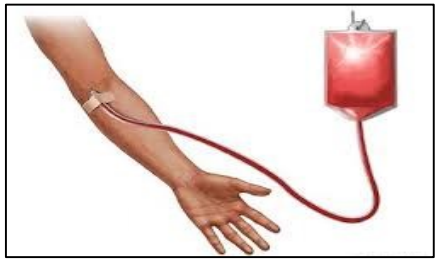
Expanding autologous polyclonal T cells in CLL for immunotherapy

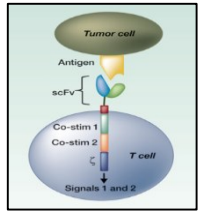


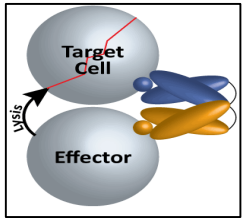


Immuno-reconstitution of CLL patients suffering life threatening infections after chemotherapy

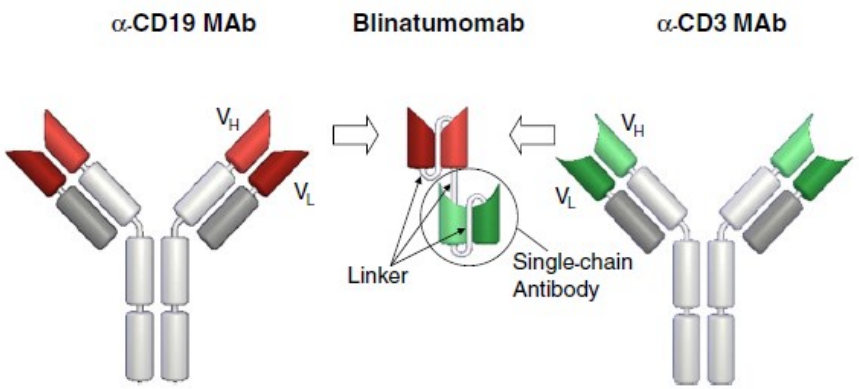
Immuno- therapy in combination with bispecific antibodies or CAR

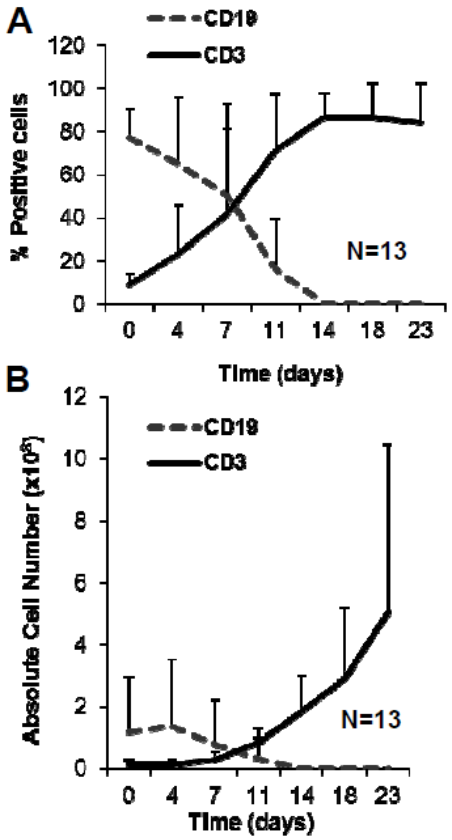






Expansion of T cells from CLL patients using blinatumomab and rhIL-2

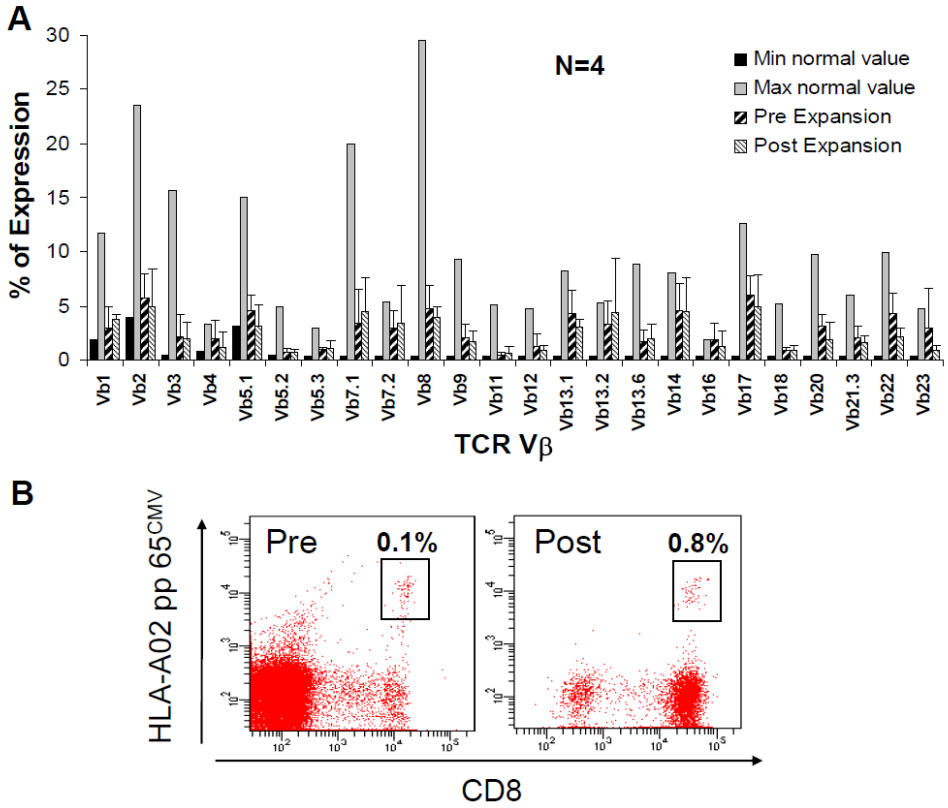




Golay J et al, The Journal of Immunology, 2014, 193: 4739–4747.

Blinatumomab Expanded T cells (BET)

- **Polyclonal**
- **contain virus specific T cell clones**



Golay J et al, The Journal of Immunology, 2014, 193: 4739–4747

CONCLUSIONS

- TKIs-based protocols improved the CR rate, the proportion of patients having an alloHSCT and the long-term outcome of adult Ph+ ALL
- MRD remains the most powerful predictor of outcome. Additional intensification with TKIs before and after transplantation could further improve the outcome
- AlloHSCT remains the post-remissional treatment of choice at least up to the age of 60. Non relapse mortality remains a major problem.
- TKIs and chemotherapy may achieve long term remission even without a transplant consolidation to cure
- Blinatumomab and TKIs may represent an effective innovative treatment approach

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