Forum in Ematologia: novità biologiche e terapeutiche
Bari, 6-7 Ottobre 2016

Immunoterapia e nuove strategie di trattamento delle LAL Ph-

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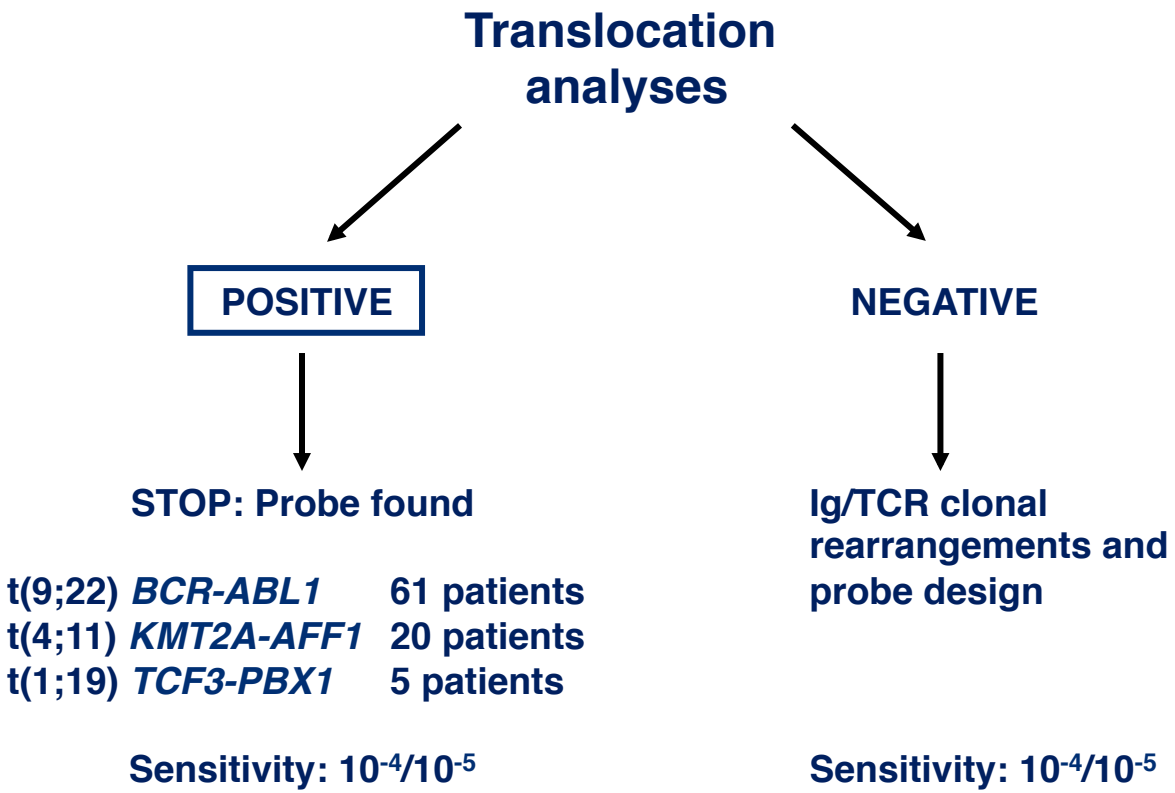
Program overview

1. MRD strategy and results of recent trials
2. How to improve the outcome of MRD- and MRD+ patients
    a. Rituximab
    b. Blinatumomab
    c. Inotuzumab

alloHSCT, allogeneic haematopoietic stem cell transplant; MRD, minimal residual disease

Identification of leukaemia-specific probes at diagnosis

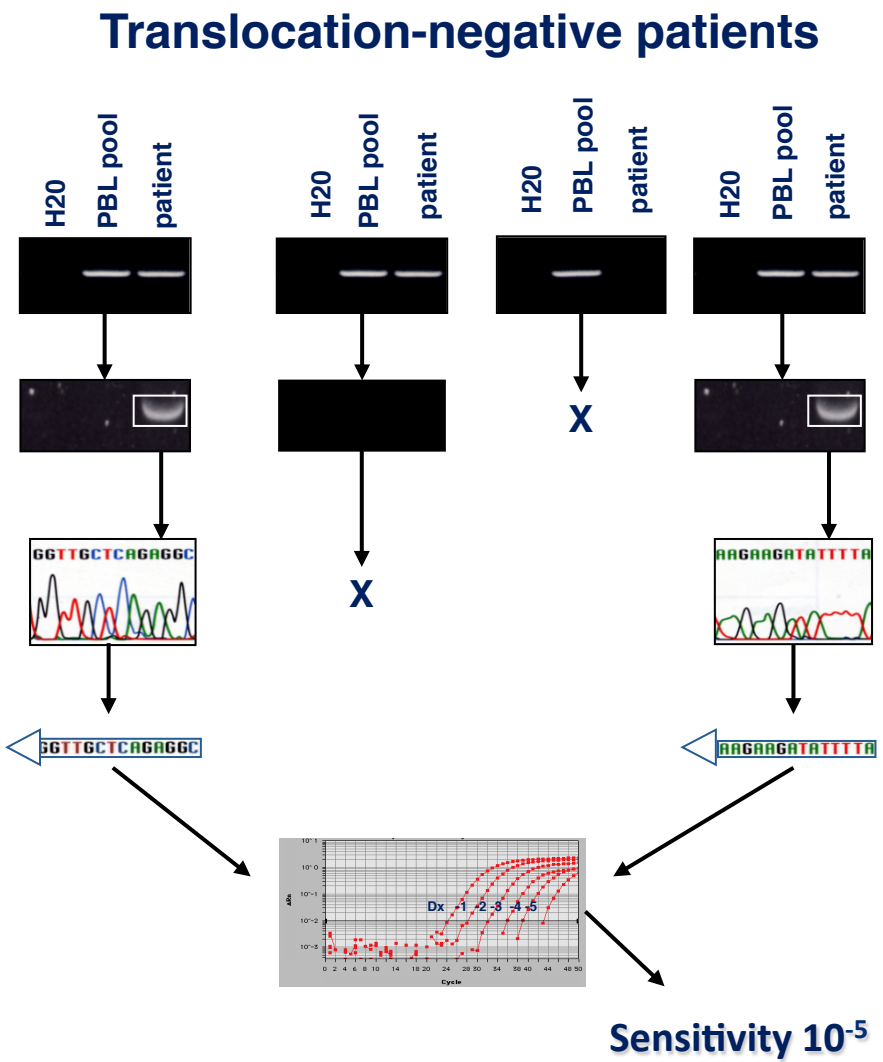


Ig, immunoglobulin; TCR, T cell receptor

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

Identification of leukaemia-specific probe at diagnosis

1. Rearrangements PCR Panel (36)
2. Homo-heteroduplex clonality test
3. Direct Sanger Sequence
4. Design of patient-specific primers
5. Primer sensitivity test at different temperatures



PBL, peripheral blood leukocyte

EuroMRD
a division of ESLHO

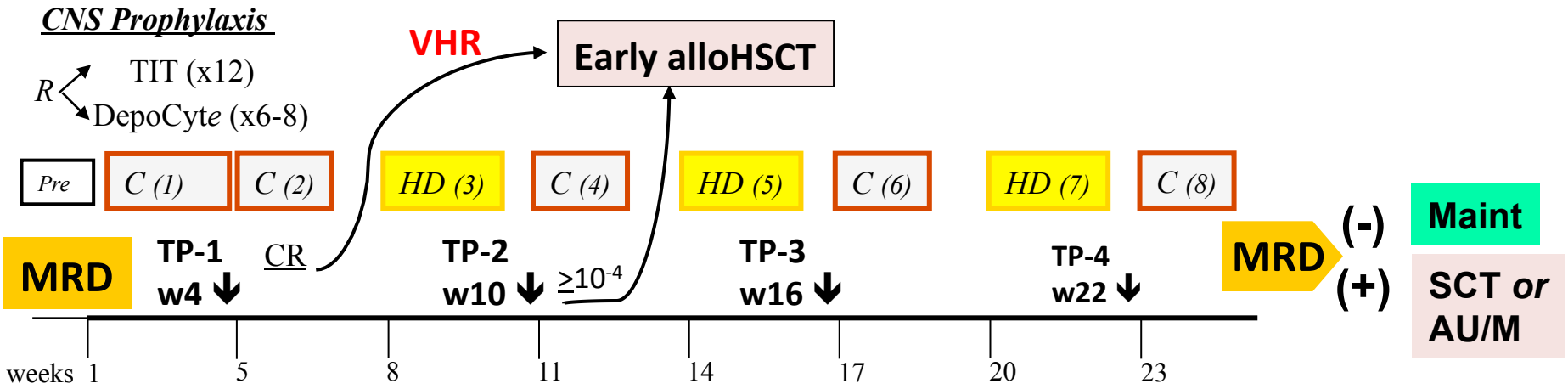
Molecular probes generated for the MRD study

Sensitivity	N	%
10^{-5}	156	51
10^{-4}	119	39
10^{-3}	33	10

- **≥1 Probe: 90%**
- **2 Probes: 65%**
- **Probe sensitivity of $\geq 10^{-4}$: 90%**

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

NILG study 10/2007



C (1),(2),(4),(6),(8) = *Conventional-dose cycles (no. 2,4,6: **Paediatric-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

VHR:

- 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

Bassan R, et al. Haematologica 2015;100:786–93; https://clinicaltrials.gov/ct2/show/NCT00795756

NILG 10/07 protocol: patients characteristics

		ALL Ph(-) n=163	
		TCP-ALL n=44	BCP-ALL n=119
Age	Median(range)	38 (17 - 65)	42 (17 - 67)
Gender M/F	N(%)	28/16 (63.6)	66/53 (55.5)
Risk stratification	N(%)		
Standard-risk		11 (25.0)	62 (52.1)
High-risk		0 (0.0)	22 (18.5)
Very high risk		33 (75.0)	35 (29.4)

BCP, B-cell precursor; NR, no response; TCP, T-cell precursor

A Rambaldi, personal communication

NILG 10/07 protocol: haematological response*

	Ph- ALL (N=163)	
	TCP-ALL (n=44)	BCP-ALL (n=119)
CR	43 (98%)	99 (83%)
NR	1 (2%)	6 (5%)
ED	0	14 (12%)

*Evaluated after 2 cycles
BCP, B-cell precursor; NR, no response; TCP, T-cell precursor

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MRD evaluation at different time points

MRD EVALUATION		Ph- (N=163)	
		TCP-ALL (n=44)	BCP-ALL (n=119)
TP2 (W10)	N	41	93
	Evaluable	36 (88%)	75 (81%)
	MRD≥10^{-4}	9 (25%)	23 (31%)
	MRD neg/≤10^{-4}	27 (75%)	52 (69%)
TP3 (W16)	N	18	61
	Evaluable	14 (78%)	40 (66%)
	MRD≥10^{-4}	3 (21%)	5 (12.5%)
	MRD neg/≤10^{-4}	11 (79%)	35 (87.5%)
TP4 (W22)	N	18	61
	Evaluable	14 (78%)	44 (72%)
	MRD≥10^{-4}	4 (29%)	13 (30%)
	MRD neg/≤10^{-4}	10 (71%)	31 (70%)

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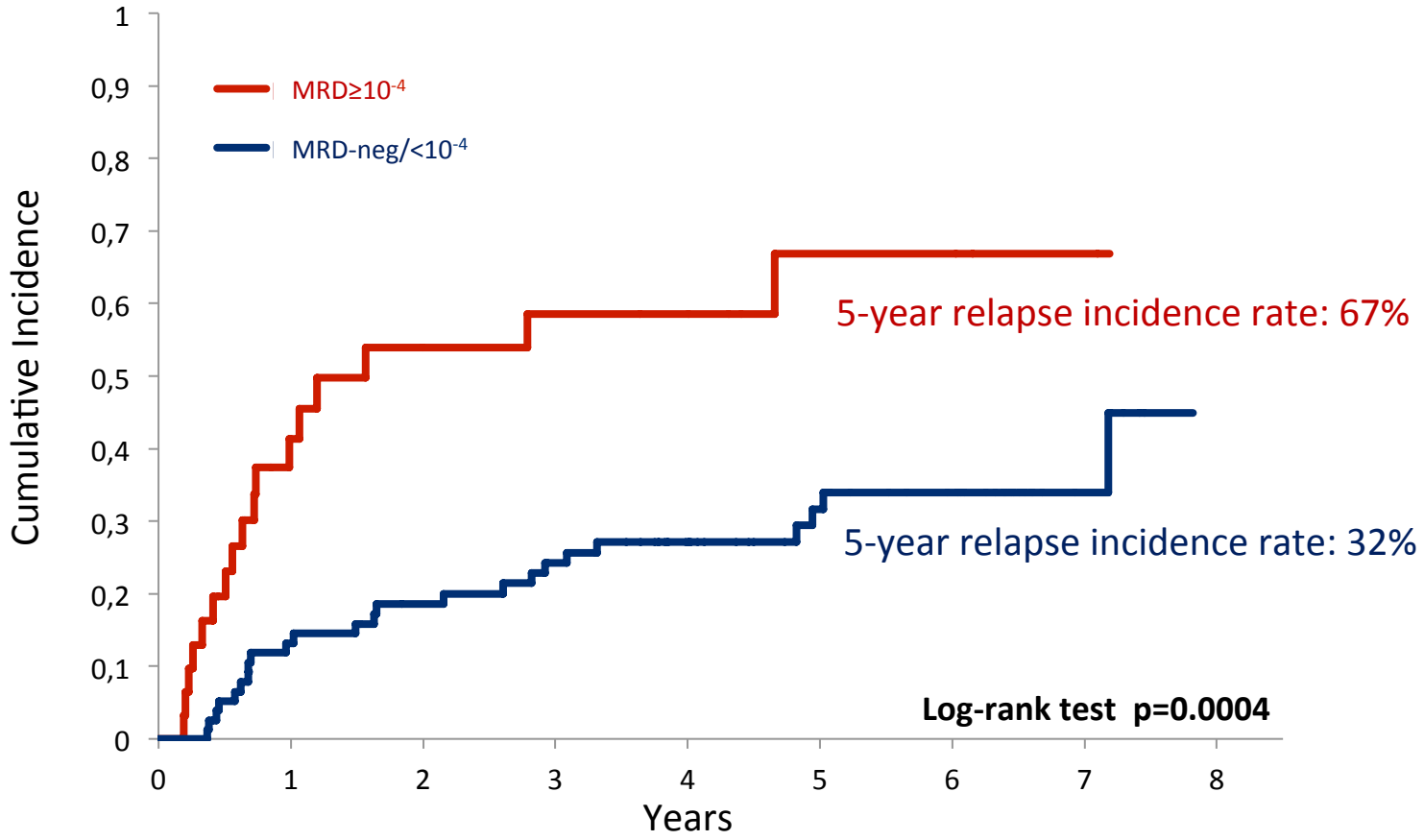
CIR by TP2 MRD in Ph- ALL



Patients at risk (events)

MRD≥10-4	31	(12)	14	(3)	10	(1)	9	(0)	8	(1)	4	(0)	4	(0)	2	(0)	0	**HSCT: 18 (58%)**
MRD-neg/<10-4	78	(10)	65	(4)	58	(4)	53	(2)	41	(2)	30	(1)	21	(0)	6	(1)	0	**HSCT: 31 (40%); 25 VHR**

CIR, cumulative incidence of relapse

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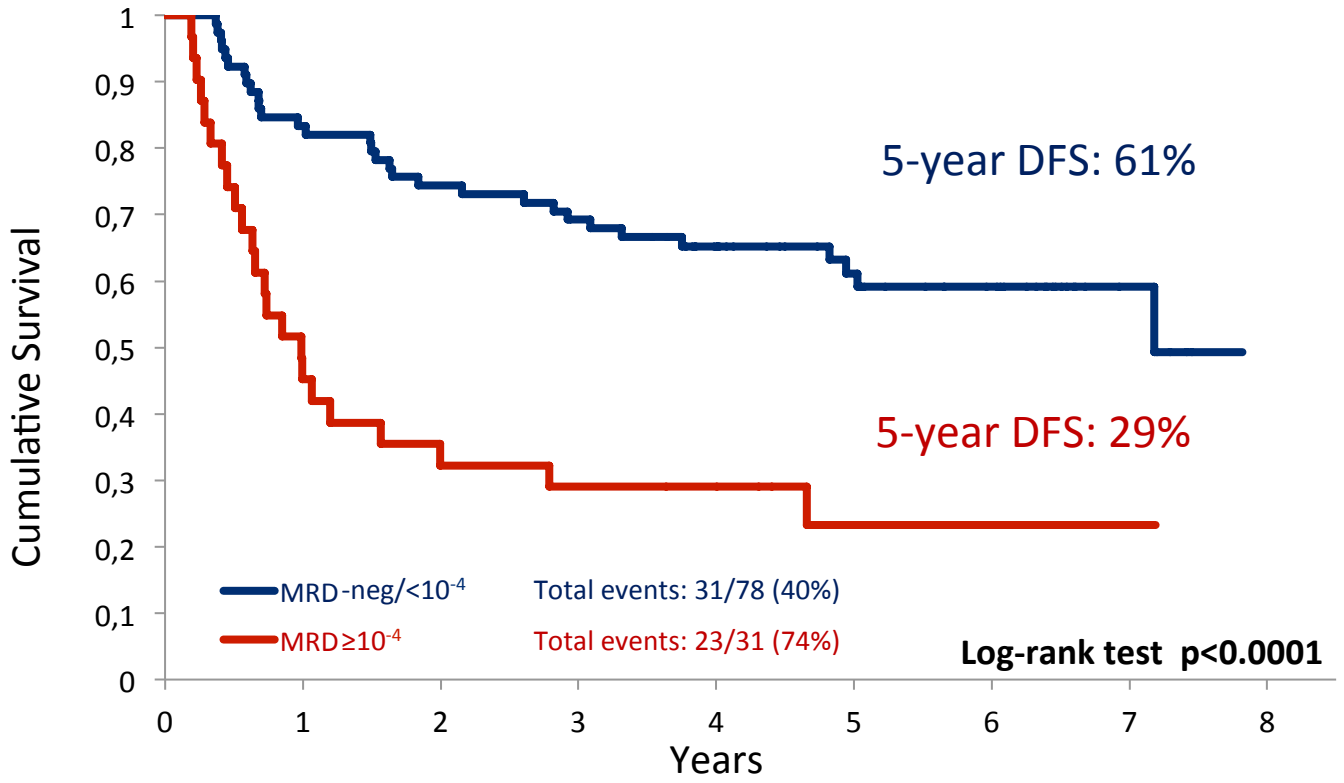
DFS by TP2 MRD in Ph- ALL



Patients at risk (events)

MRD-neg/<10^{-4}	78	(13)	65	(7)	58	(4)	53	(3)	41	(2)	30	(1)	21	(0)	6	(1)	0
MRD≥10^{-4}	31	(17)	14	(4)	10	(1)	9	(0)	8	(1)	4	(0)	4	(0)	2	(0)	0

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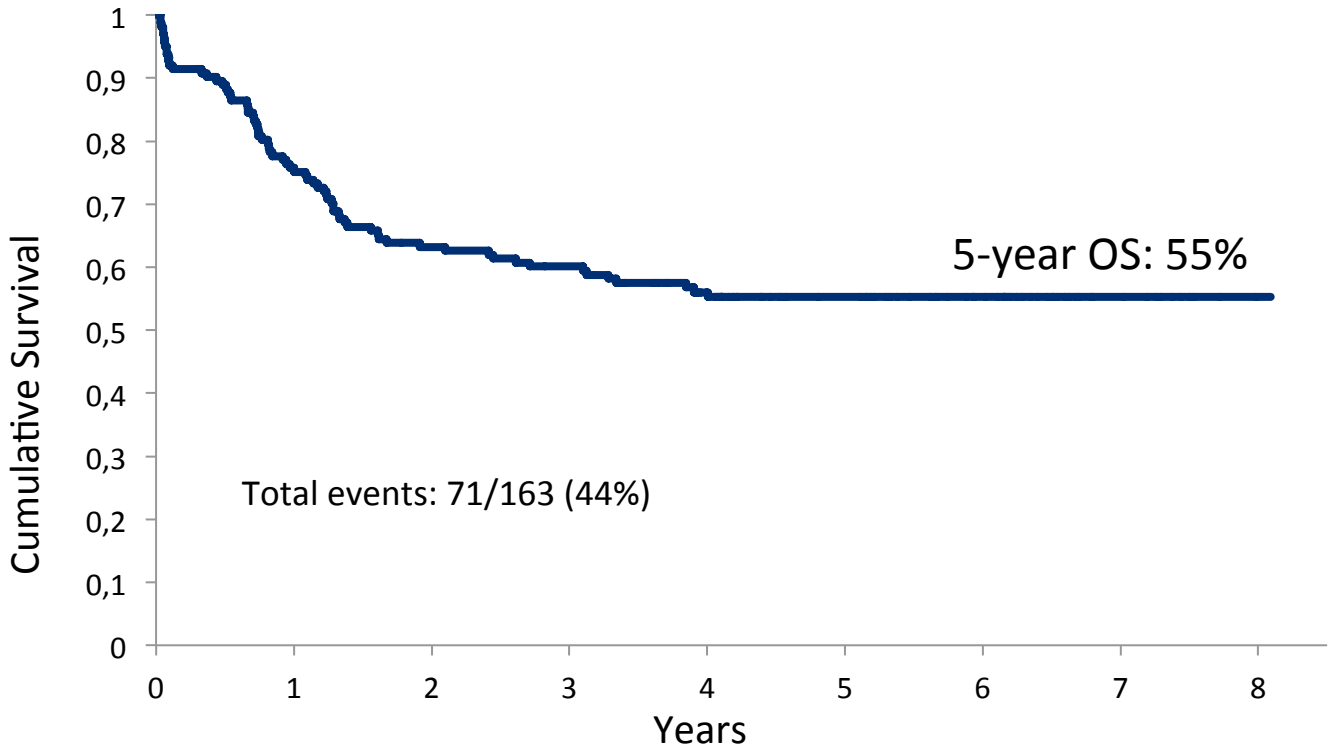
Overall Survival in Ph- ALL



Patients at risk (events)	163	(40)	120	(19)	100	(5)	94	(6)	70	(1)	49	(0)	32	(0)	11	(0)	1

OS, overall survival

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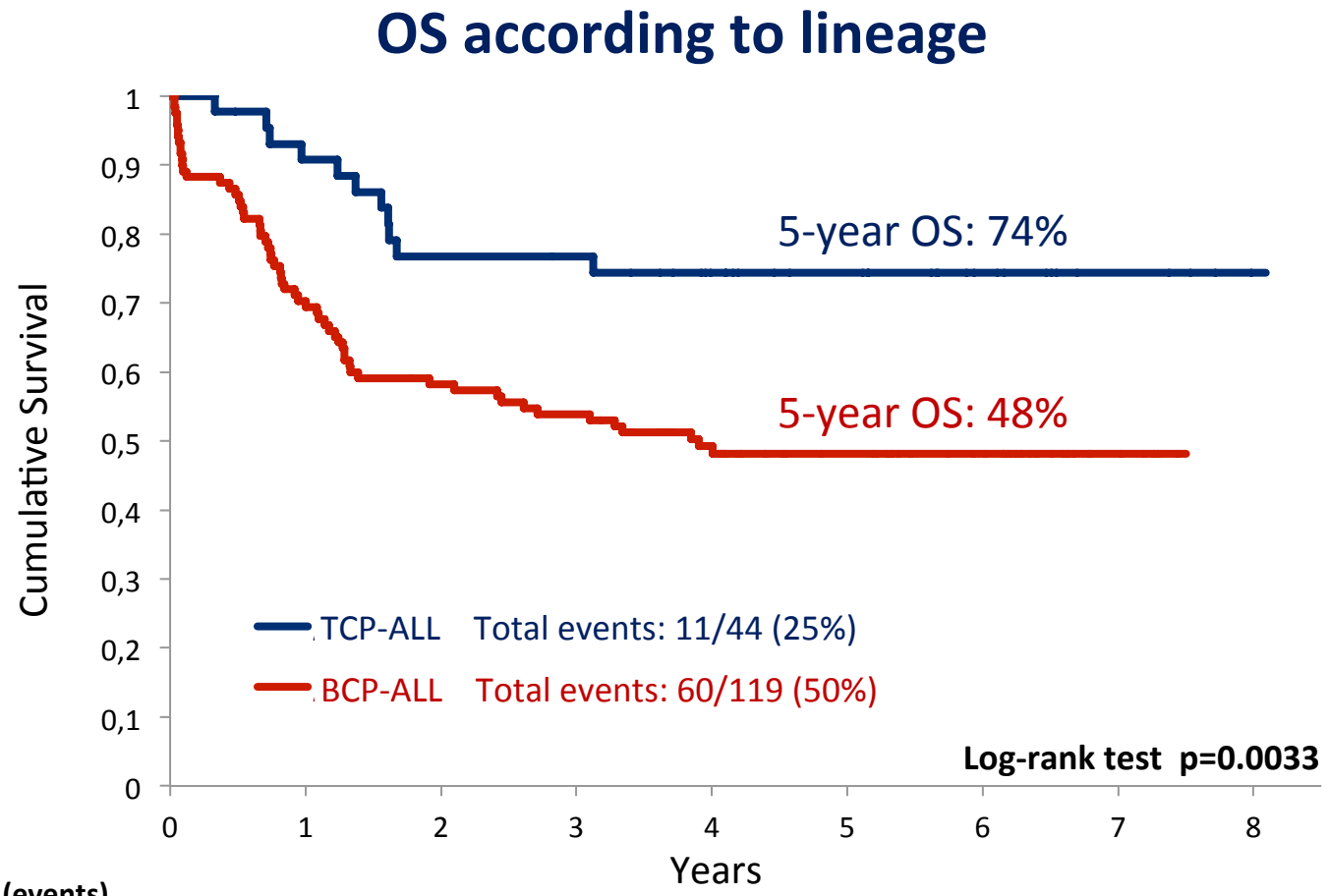
OS in Ph- ALL according to lineage



Patients at risk (events)

TCP-ALL	44	(4)	39	(6)	33	(0)	32	(1)	25	(0)	19	(0)	11	(0)	5	(0)	1
BCP-ALL	119	(36)	81	(13)	67	(5)	62	(5)	45	(1)	30	(0)	21	(0)	6	(0)	0

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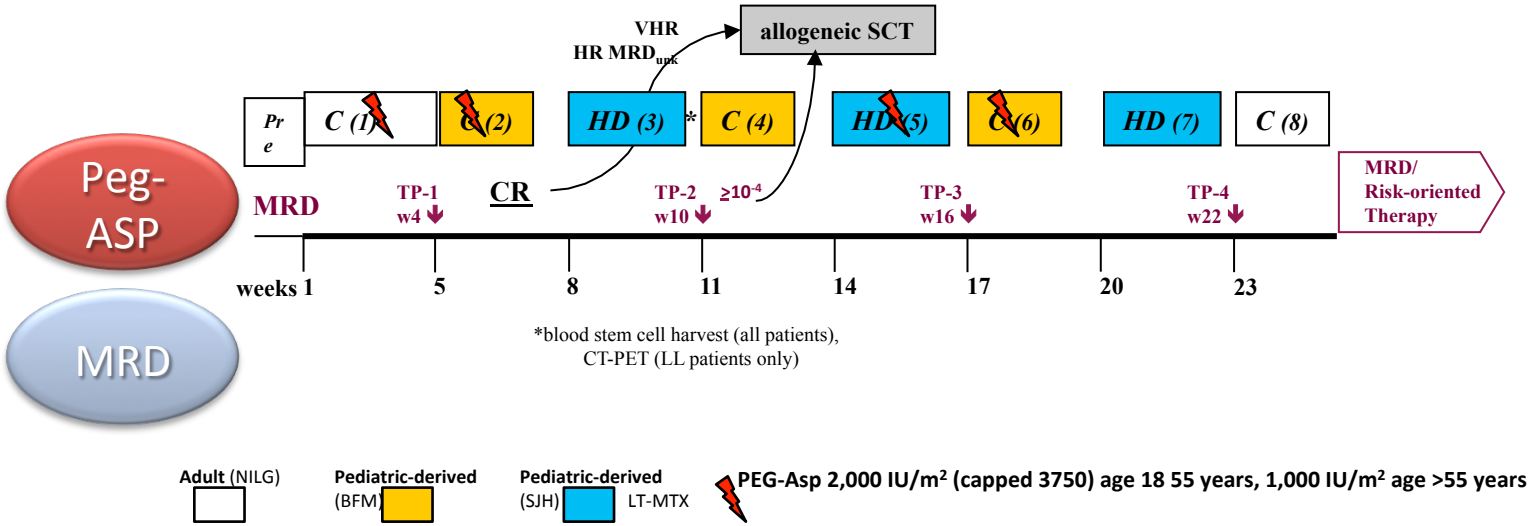
GIMEMA LAL 1913

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

Molecular probes generated for the MRD study (GIMEMA study LAL 1913: Ph- ALL)

Sensitivity	N	%
10^{-5}	45	61
10^{-4}	29	39

- **≥1 probe: 94%**
- **2 probes: 87%**
- **Probe sensitivity of ≥10^{-4}: 100%**

3 Labs involved: Bergamo, Roma, Palermo

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Role of HSCT

HSCT for no one

MRD-negative (with acceptable risk profile)

HSCT for everyone

MRD positive *or*

MRD negative **without*** acceptable risk profile

*Any of: Ph+, t(4;11), t(1;19), t(8;14), abnormal 11q23, +8, -7, del6q, low hypodiploidy, near triploidy or complex karyotype

Limits of the MRD driven strategy

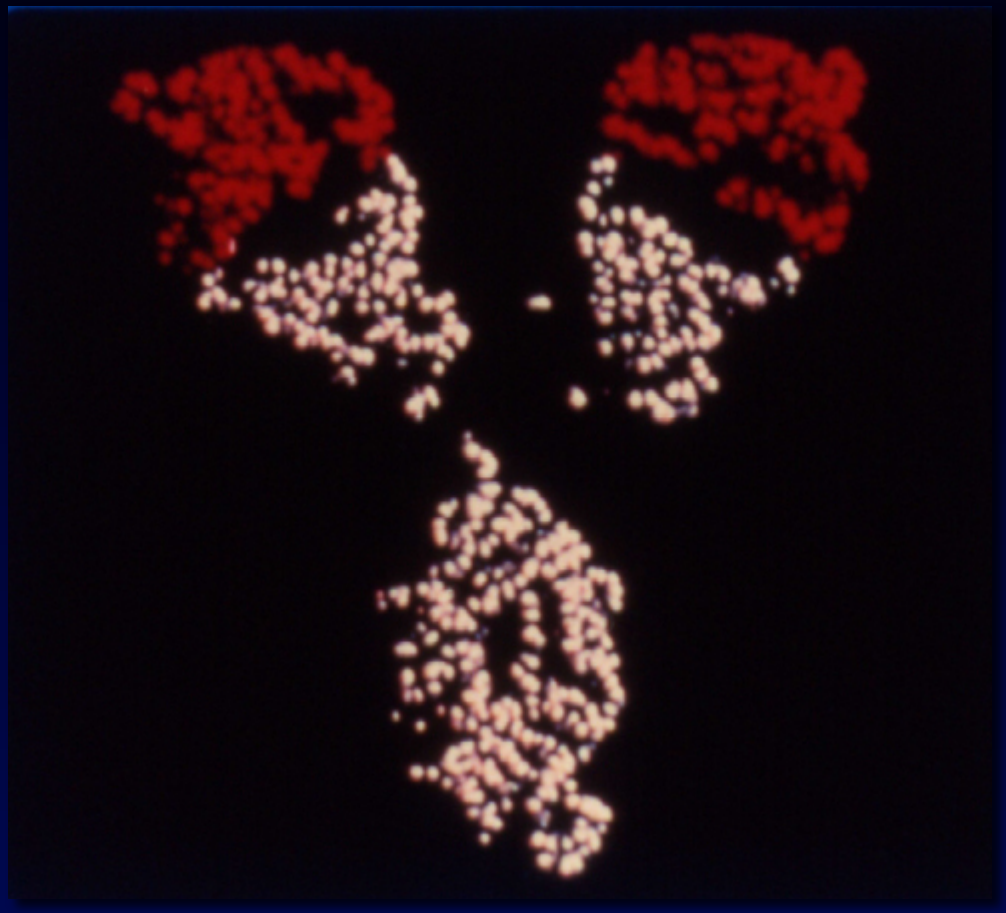
- MRD- patients relapse in 25% of cases
- Poor results with alloHSCT (negative selection)

Program overview

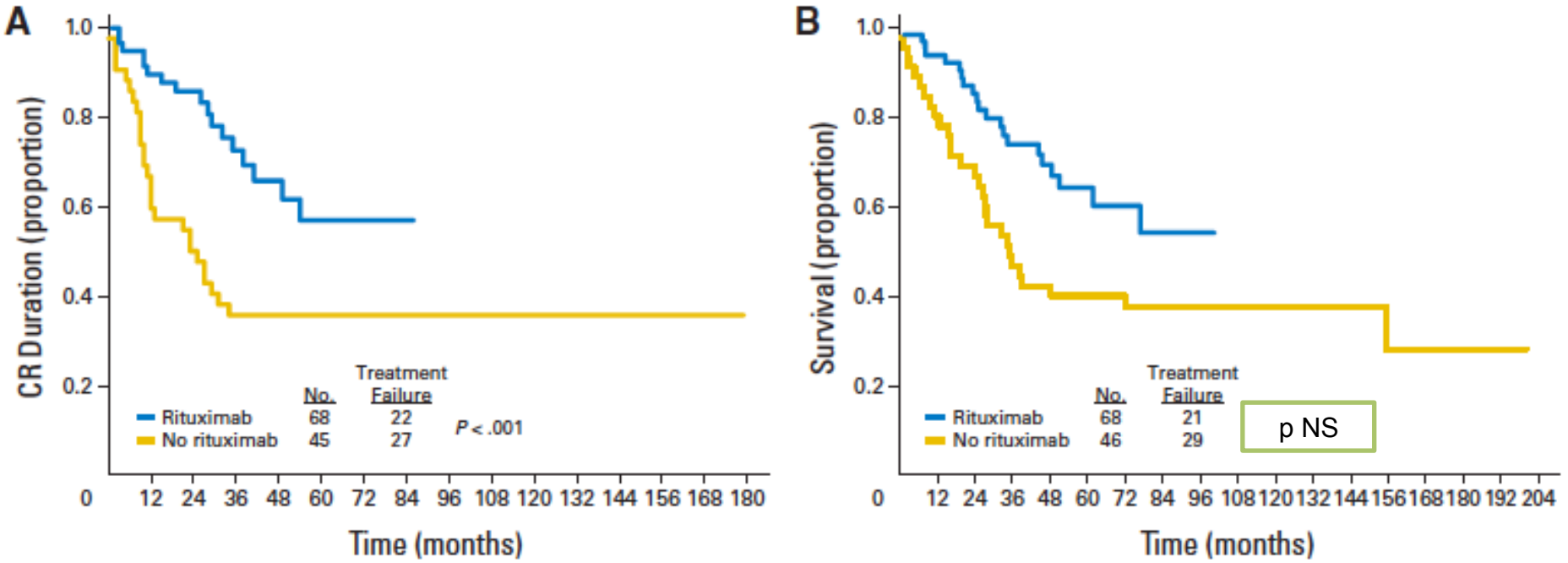
1. Rationale, MRD strategy and results of recent trials

2. **How to improve the outcome of MRD- and MRD+**

Rituximab: the very good, old friend



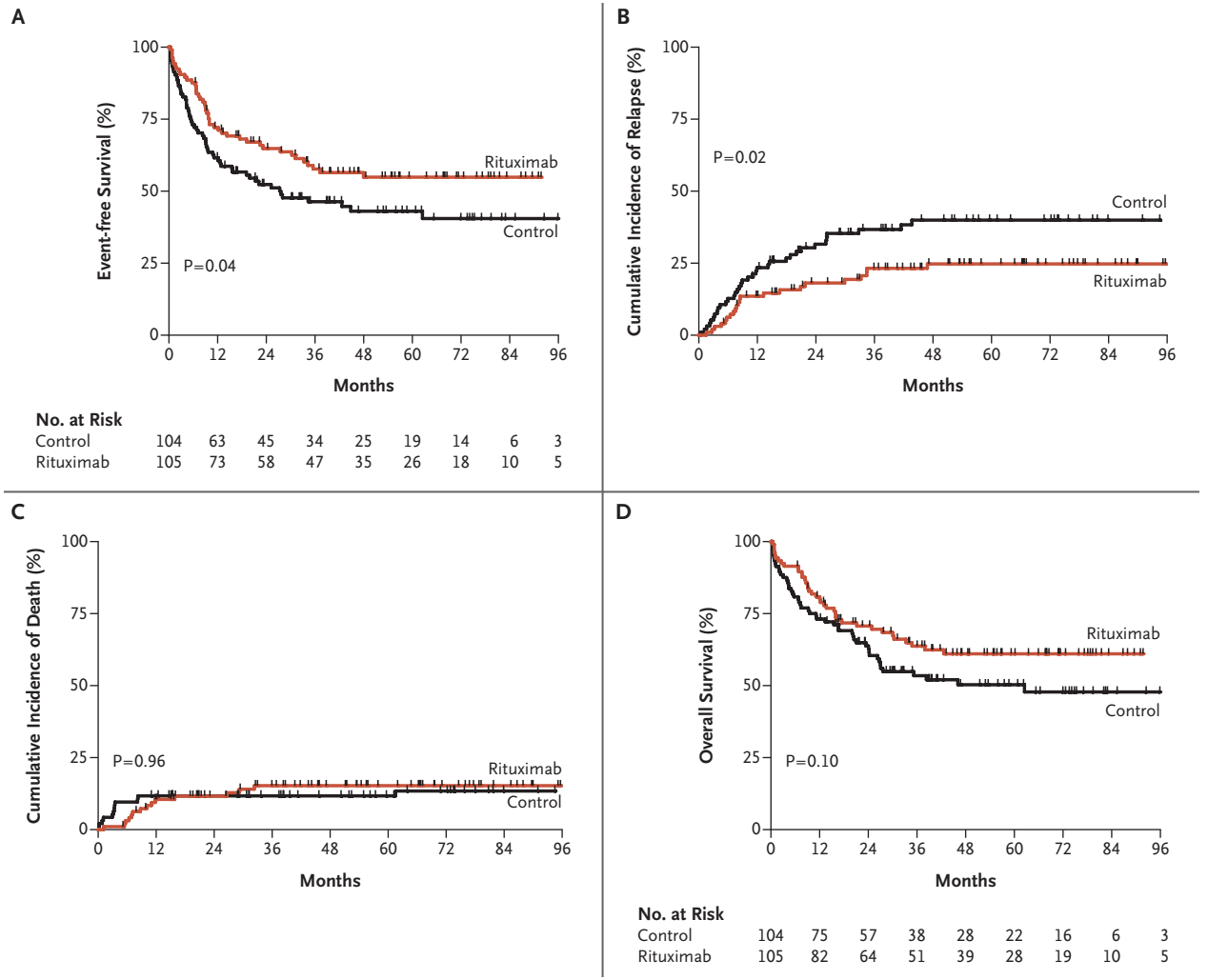
Chemo-immunotherapy with a modified Hyper-CVAD and Rituximab Regimen improves outcome in de novo Ph- BCP-ALL



Outcomes in patients <60 years old. Comparison with an historical cohort.
No significant differences in OS

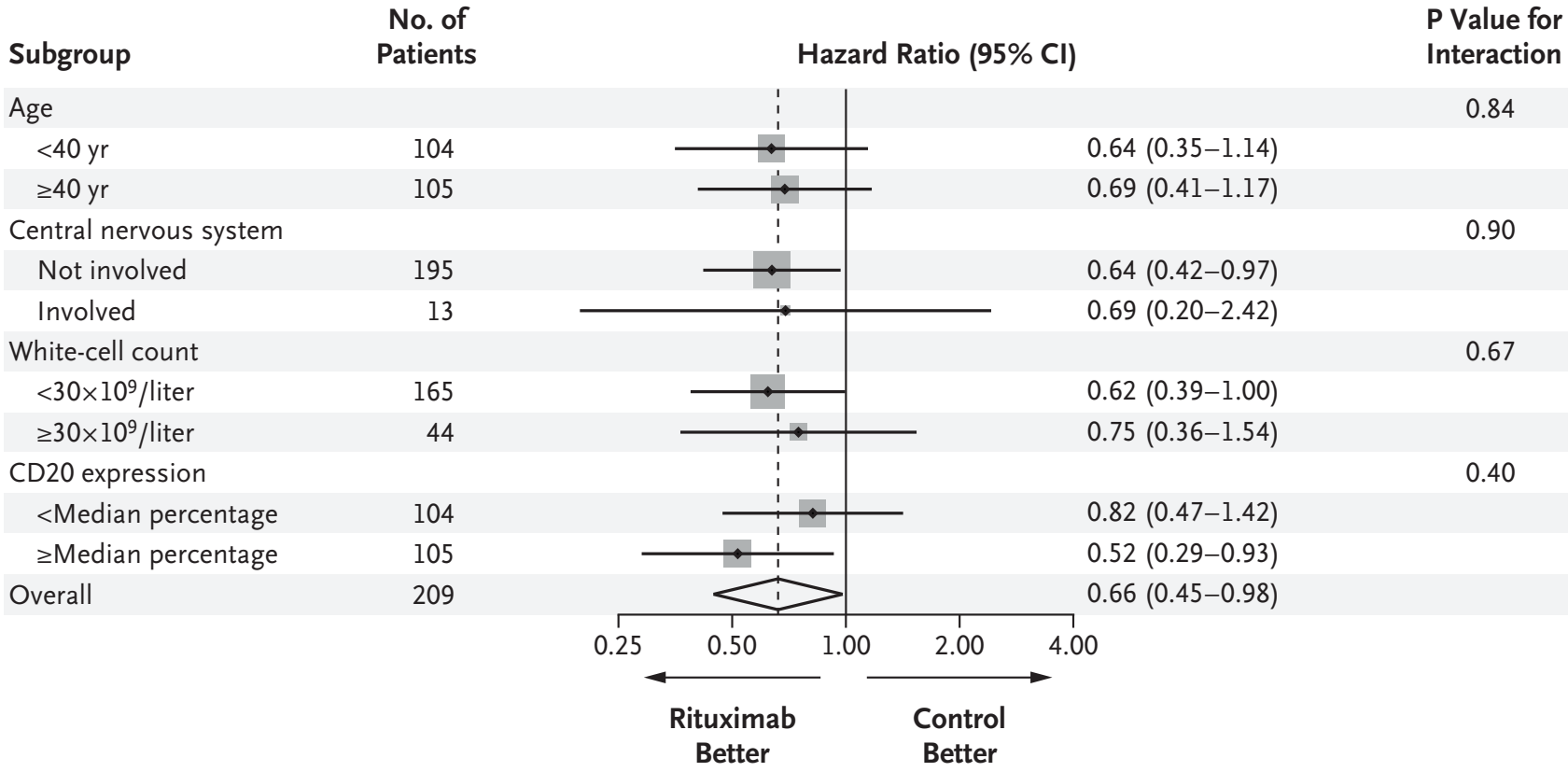
Thomas et al, JCO 2010

Rituximab in B-Lineage Adult ALL



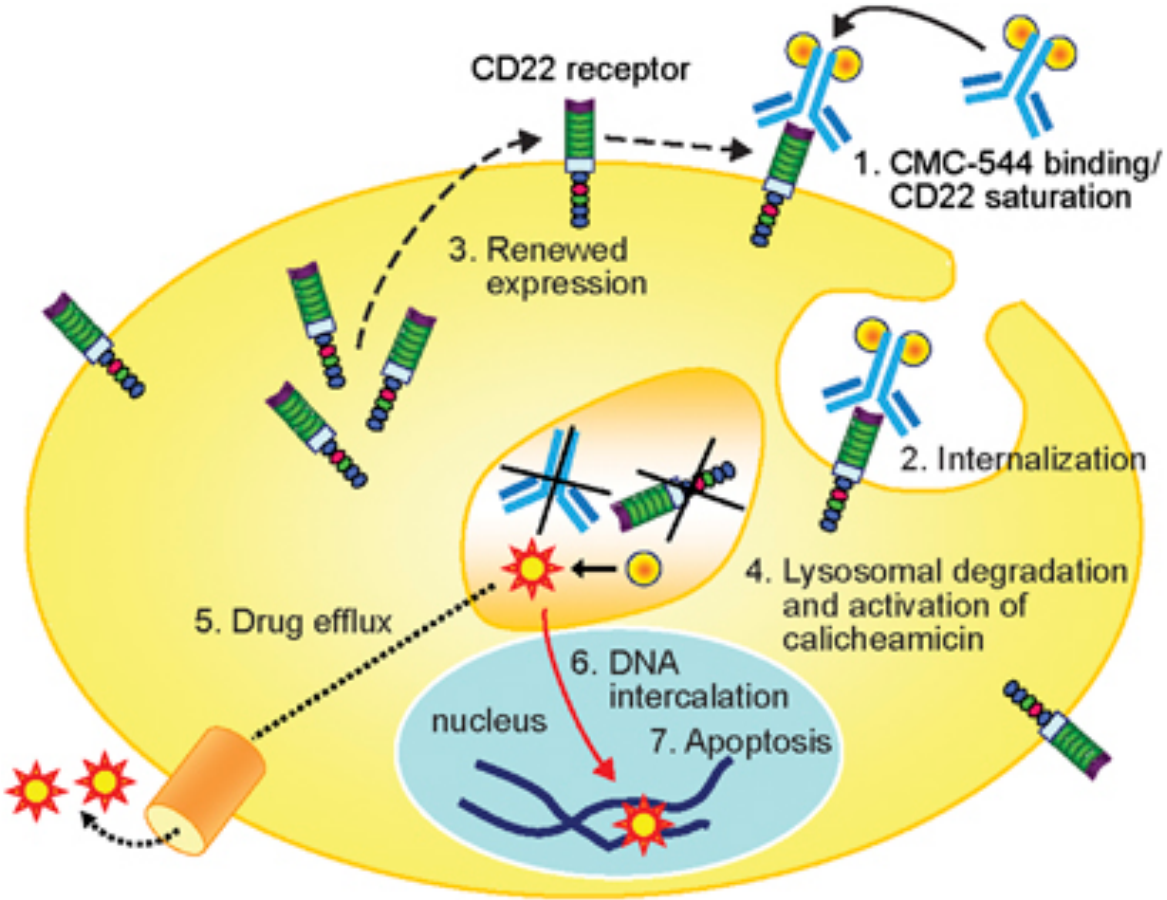
Maury S et al.,NEJM, 2016

Effect of Rituximab Treatment in Subgroups of Patients



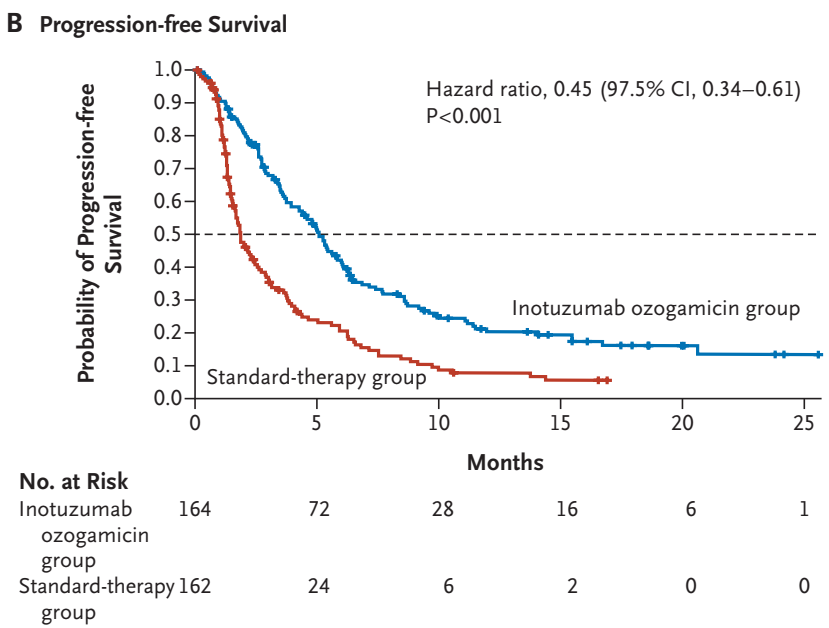
Maury S et al.,NEJM, 2016

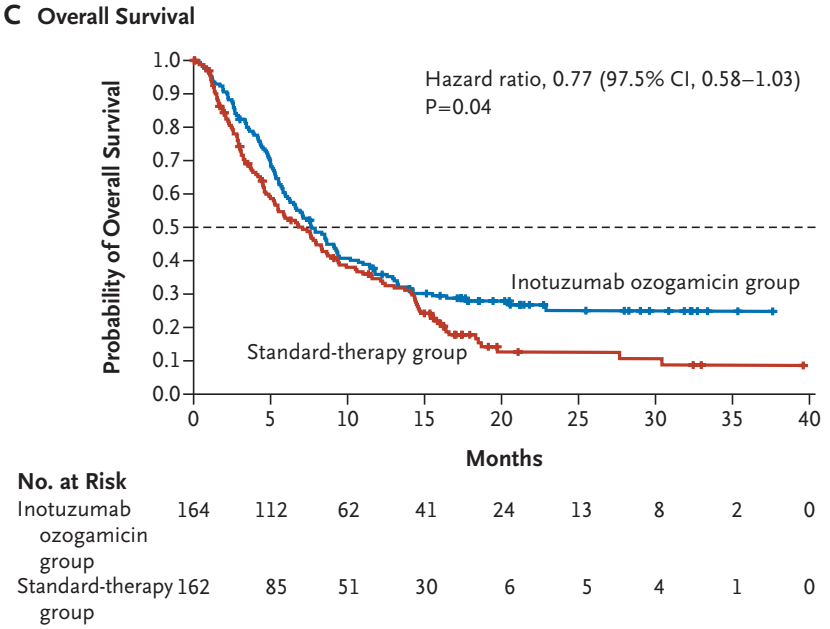
Inotuzumab Ozogamicin:
A novel calicheamicin-conjugated CD22 antibody



JF de Vries, Leukemia 2012

Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia



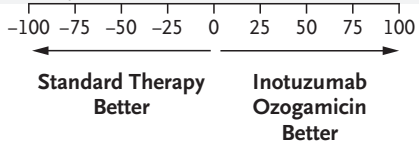


Kantarjian HM et al.,NEJM, 2016

Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia

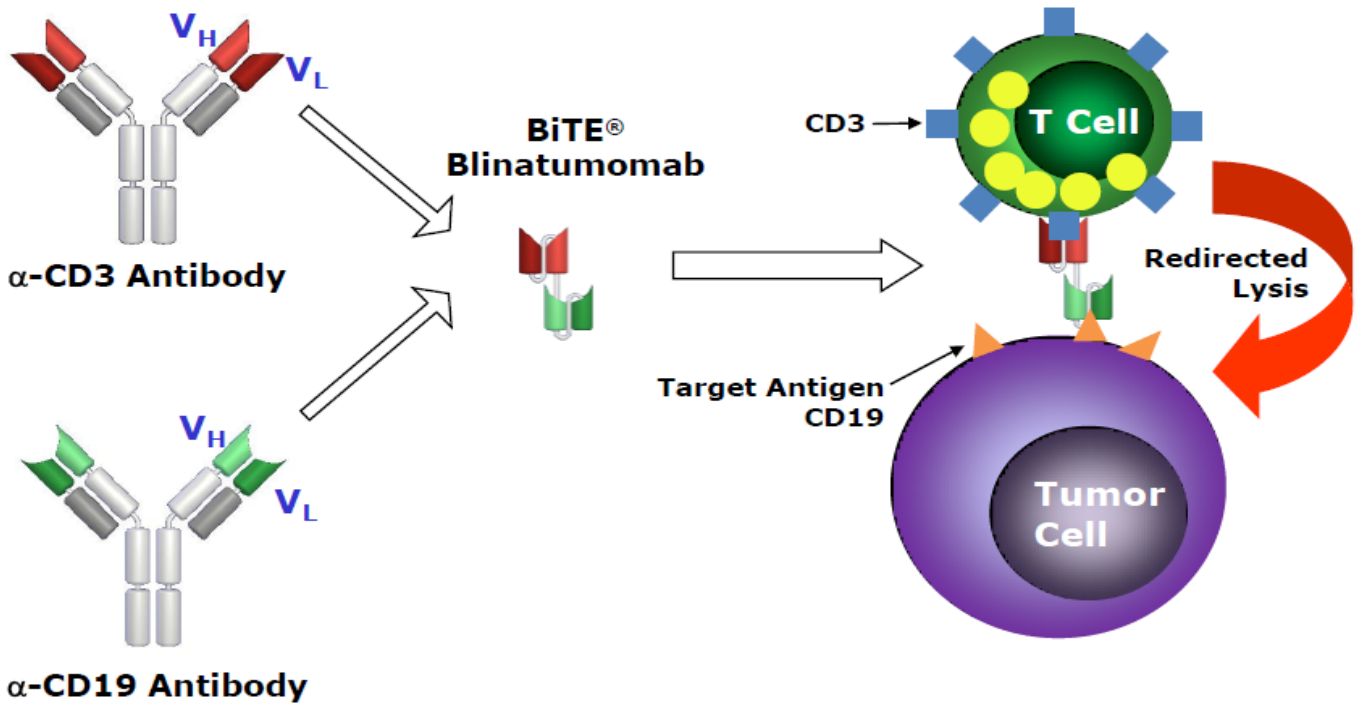
B **Rate According to Patient Characteristics at Baseline**

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

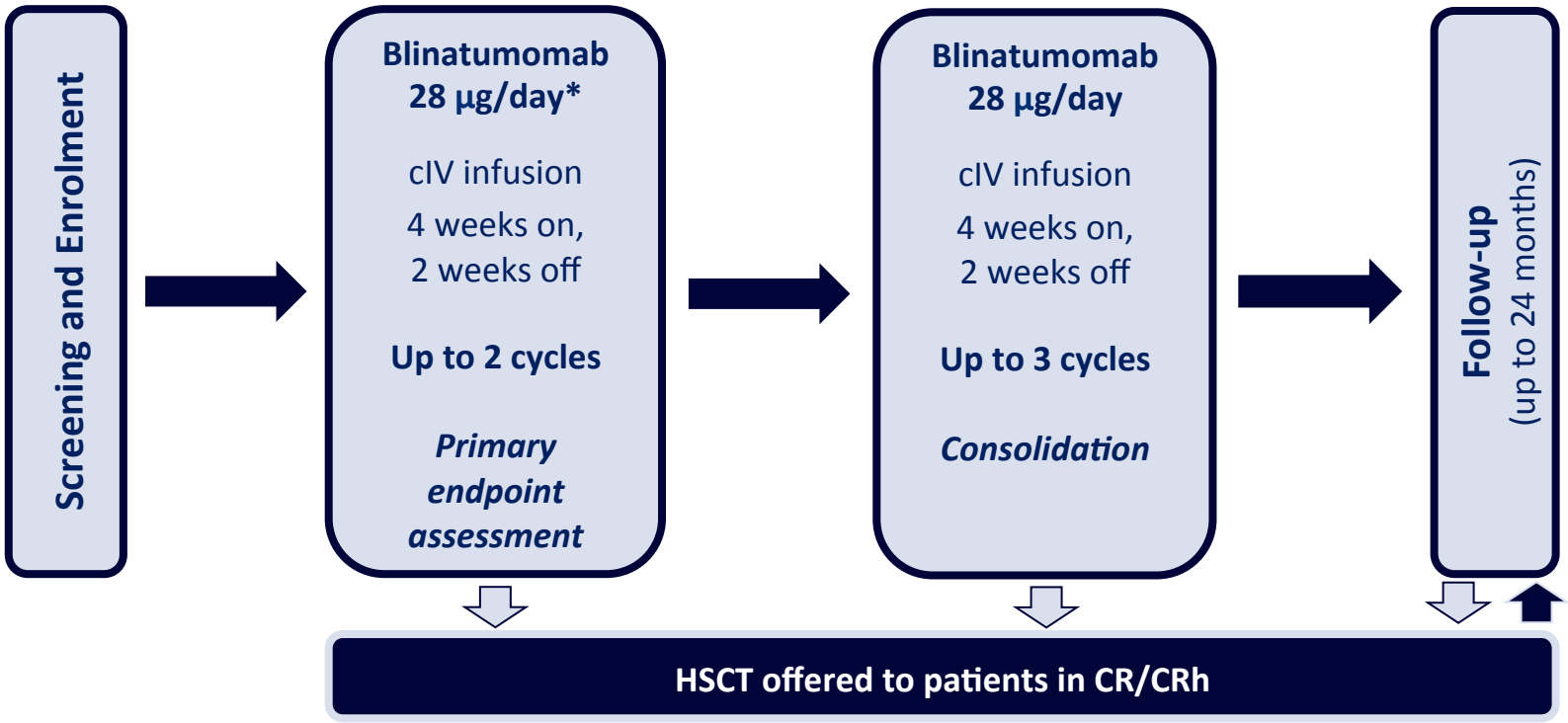
Blinatumomab:* a bispecific T-cell engaging (BiTE®) antibody construct



*▼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

Confirmatory open-label, single-arm, multi-centre Phase 2 Study in r/r Ph- ALL



*9 µg/day in Cycle 1 (Days 1–7)
cIV, continuous intravenous; CRh, complete response with partial recovery of peripheral blood counts (platelets >50,000/µL and absolute neutrophil count >500/µL); r/r, relapsed/refractory

Topp MS, et al. Lancet Oncol 2015;16:57–66

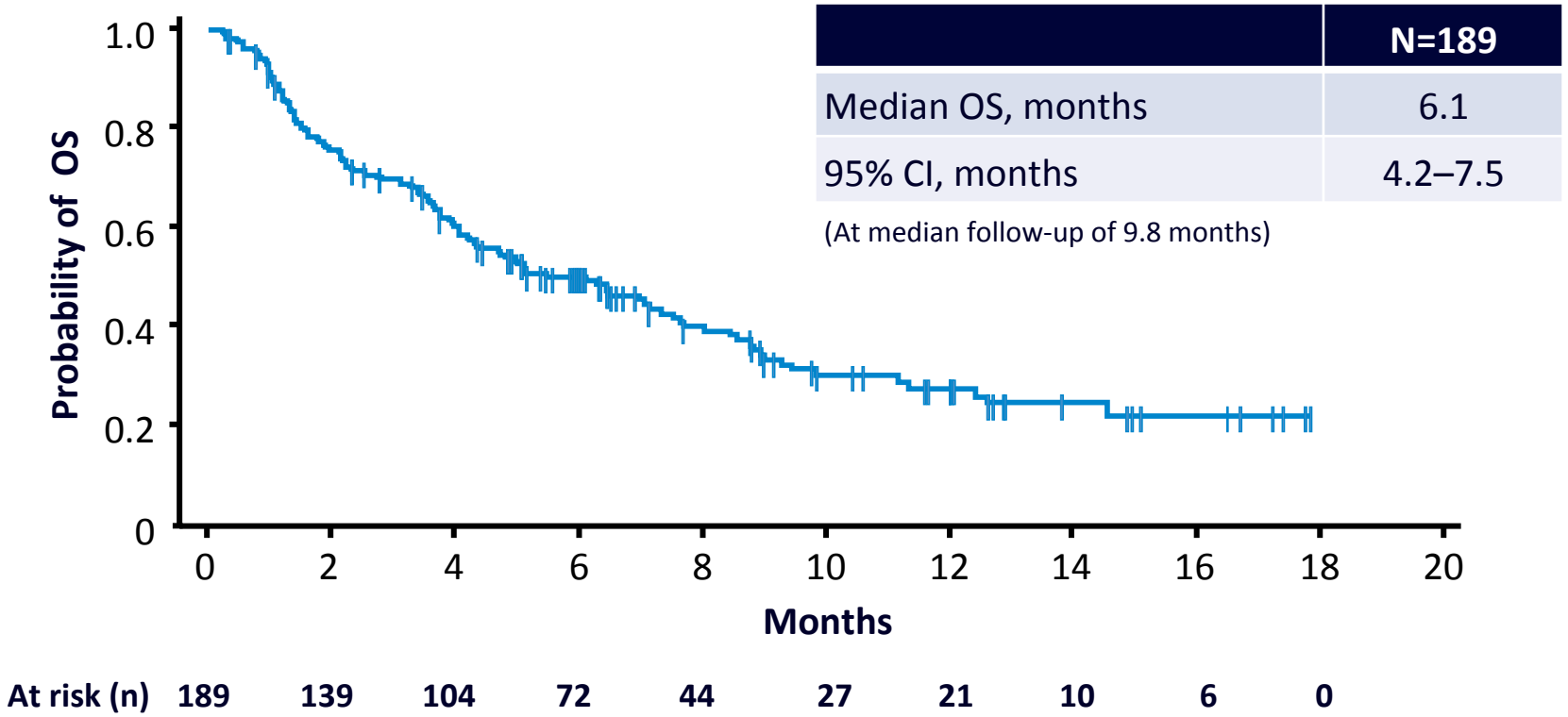
Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study

Max S Topp, Nicola Gökbuget*, Anthony S Stein, Gerhard Zugmaier, Susan O'Brien, Ralf C Bargou, Hervé Dombret, Adele K Fielding, Leonard Heffner, Richard A Larson, Svenja Neumann, Robin Foà, Mark Litzow, Josep-Maria Ribera, Alessandro Rambaldi, Gary Schiller, Monika Brüggemann, Heinz A Horst, Chris Holland, Catherine Jia, Tapan Maniar, Birgit Huber, Dirk Nagorsen, Stephen J Forman, Hagop M Kantarjian*

	Patients	Proportion (95% CI)
CR or CRh during the first two cycles	81/189	43% (36–50)
Best response during the first two cycles*		
CR	63/189	33% (27–41)
CRh	18/189	10% (6–15)
No response to therapy†	90/189	48%
Not evaluable‡	18/189	10%
Allogeneic HSCT after CR or CRh	32/81	40%
Allogeneic HSCT after CR	28/63	44%
Allogeneic HSCT after CRh	4/18	22%
100-day mortality from day of HSCT	..	11% (0–23)
MRD response during first two cycles in patients with CR or CRh§	60/73	82% (72–90)

Topp et al, Lancet Oncol 2015

Overall survival after blinatumomab in relapsed/ refractory ALL



	N=189
Median OS, months	6.1
95% CI, months	4.2–7.5

(At median follow-up of 9.8 months)

Topp MS, et al. Lancet Oncol 2015;16:57–66

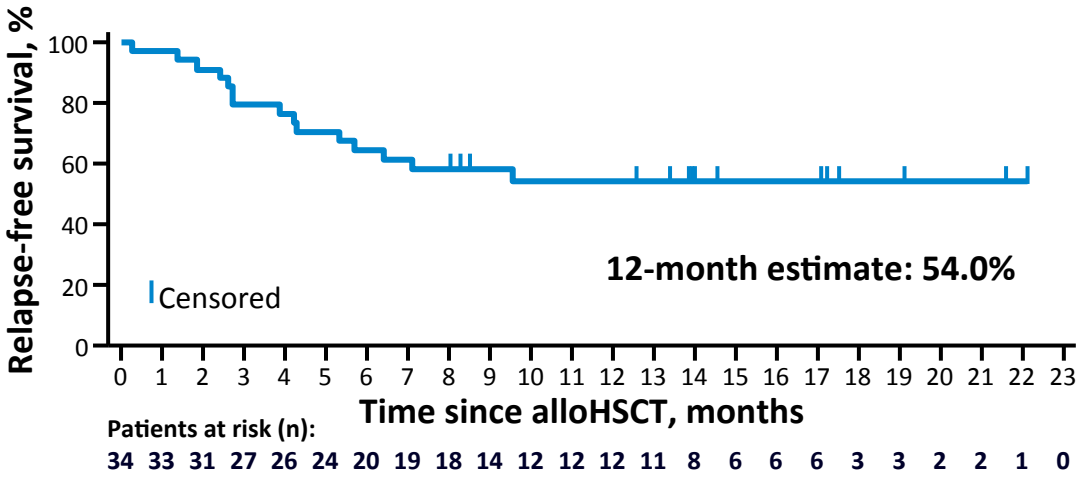
Outcomes of Hematopoietic Stem Cell Transplantation (HSCT) Among Adults With Relapsed/Refractory (r/r) ALL Achieving Remission With Blinatumomab

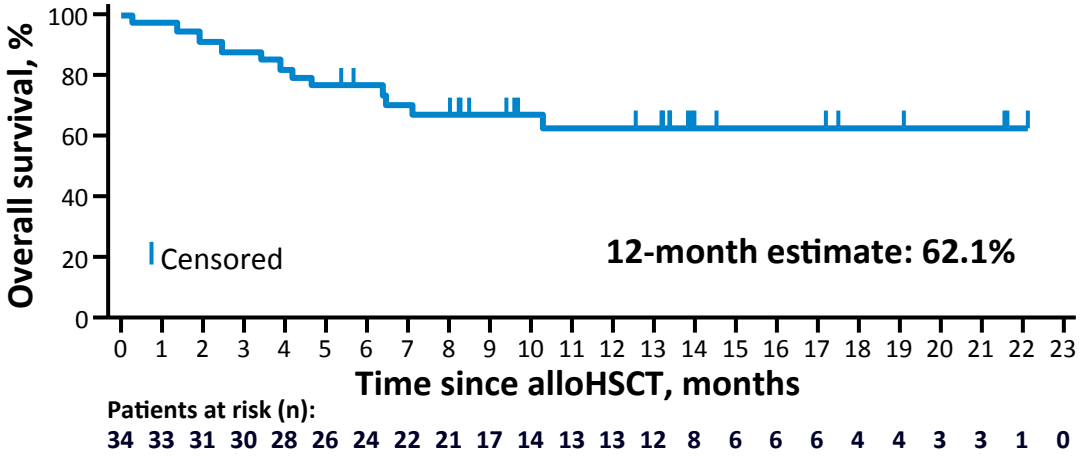
Anthony S Stein,[1] Max S Topp,[2] Nicola Gökbuget,[3] Ralf C Bargou,[4] Hervé Dombret,[5] Richard A Larson,[6] Alessandro Rambaldi,[7] Gary Schiller,[8] Gerhard Zugmaier,[9] Lulu Sterling,[10] Jonathan Benjamin,[10] Hagop Kantarjian,[11] Stephen J Forman[1]

[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

Relapse-free and overall survival in patients receiving alloHSCT 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

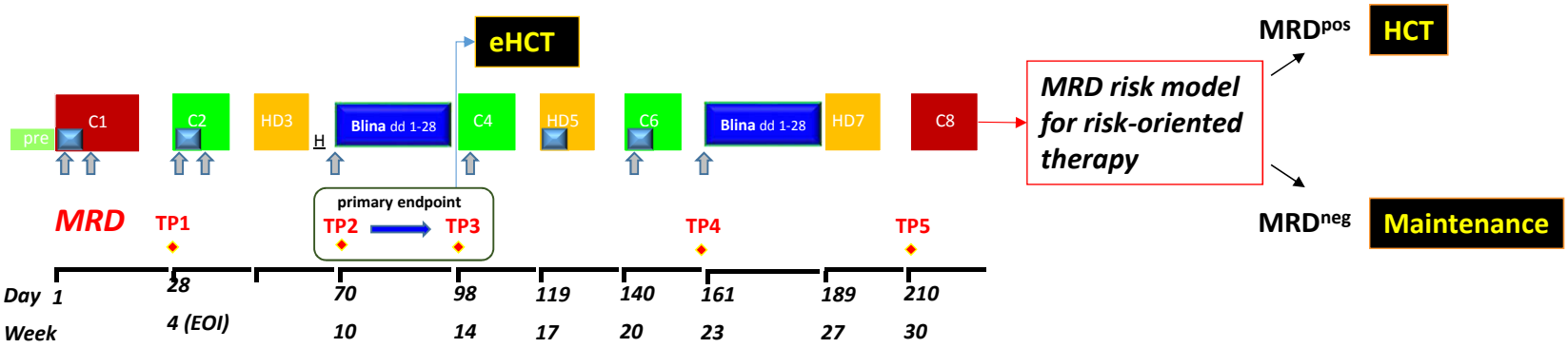
Median follow-up: 13.4 (9.4–14.6) months

CI, confidence interval; NE, not estimable; RFS, relapse-free survival

Stein AS, et al. ASBMT Meeting, 2016

The possible new national treatment program for adult ALL

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/m²)

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

**WBC >100, highly adverse cytogenetics*

Conclusions

- MRD guides a modern treatment strategy in adult ALL
- MRD helps to identify patients with chemo-resistant disease despite the use of intensified paediatric-like protocols
- 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 MRD-positive patients