Blinatumomab e TMO

Raffaella Cerretti
Rome Transplant Network
Università di Roma Tor Vergata

Policlinico S.Orsola –Malpighi
Bologna, 13 maggio 2013

RTN
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Blinatumomab e TMO

- ALL patients in 1st CR
- ALL patients in Relapse/Refractory disease
- ALL patients in Relapse after HSCT

ALL patients in 1st CR

Adult ALL patients and comparison donor – no donor

Reference	Patients		TRM NRM		Relapse		Disease-Free Survival	
LALA94 Thomas et al, 2004	HR Donor	100	18	@3y, *P*=0.01	36	@5y, *P*=.001	45	@ 5 y, *P*=0.007
	HR No Donor	159	7		62		18	
GOELAL02 Hunault et al, 2004	HR Donor	41	15	@ 6 months	12	@6y, *P*=.0001	75	@ 6 y, *P*=.0004
	HR No Donor	106	7		56		33	
PETHEMA Ribera et al, 2005	HR Donor	72	10	@ 6 months	51	@5y,	37	@ 5 y, *P*=.NS
	HR No Donor	84	2		62		46	
HOVON Cornelissen et al, 2009	Donor	96	16	@ 5 y, *P*=.002	24	@5y, *P*=.0001	60	@ 5 y, *P*=.01
	No Donor	161	3		55		42	
MRCUKALLXII ECOG2993 Goldstone AH, Blood 2008	Donor	443	HR: 35 SR: 19	@ 2y	HR: 37 SR: 24	@5y, *P*=.0005	53	@ 5 y OS, *P*=.01
	No Donor	588	HR: 13 SR: 7		HR: 63 SR: 49		45	

HR=high risk, SR=standard risk

ALL patients in 1st CR

Biological and clinical risk factors for ALL at diagnosis

White Blood Count:	**>30x10^9/L for B-ALL; >100x10^9/L for T-ALL**
Phenotype:	**very immature, pro B-ALL, pro and pre T-ALL, mature T-ALL (EGIL BI, TI, TII, TIV)**
Cytogenetics:	**t(9;22), t(4;11), t(1;19), t(8;14), abn 11q23, +8, -7, del6q, low hypodiploidy, near triploidy, complex Karyotype**
Molecular mutations:	**BCR/ABL1, CLRF2/JAK mutations (Ph+ like ALL), IKZF1 deletion, wild-type NOTCH1/FXBW7, altered RAS/PTEN, p53, MYC**
Age > 35 y	
Late Complete Remission	

**Minimal Residual Disease (MRD):
clonal IgG and T-cell receptor gene rearrangement**

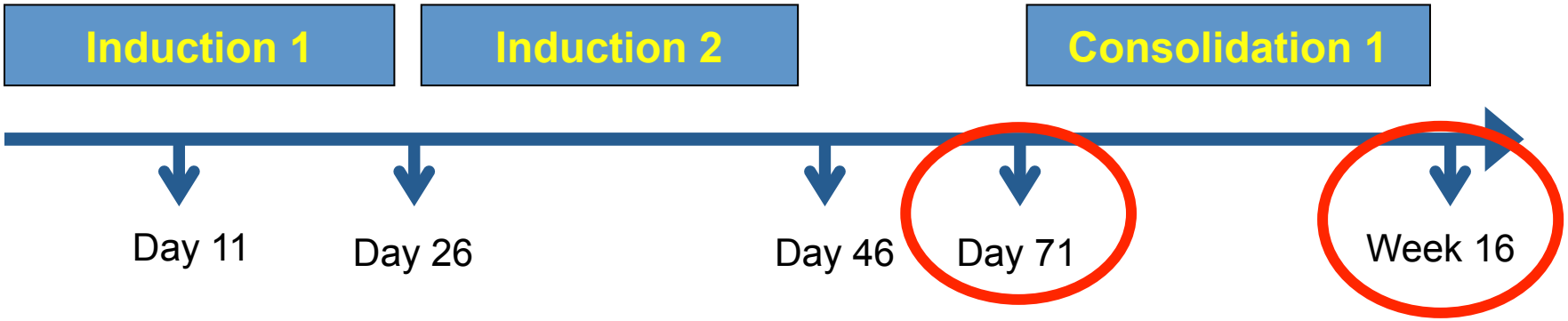
Impact of Minimal Residual Disease (MRD) in adult ALL patients

GMALL 06/99 and 07/03 Trials – 1999-2009
Age: 15-55 y
Standard Risk (SR): n=975
High Risk (HR): n=673

MRD: quantitative PCR of leukemia-specific Ig and TCR gene rearrangements

Molecular CR: MRD negativity, $< 10^{-4}$ Molecular failure or relapse: MRD $\geq 10^{-4}$

Time points



Patients: n=580 **Molecular CR: n=335**

70%

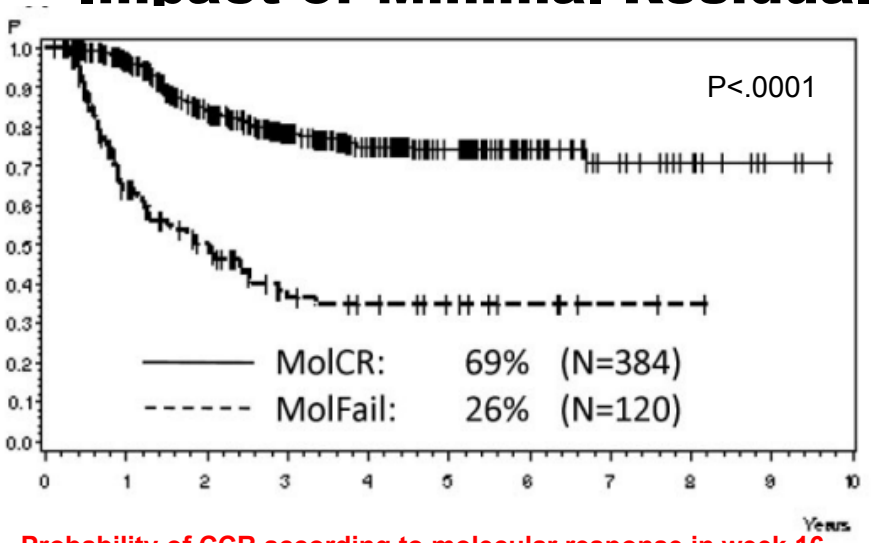
Standard Risk: 77% - High Risk: 51%

***p*<.0001**

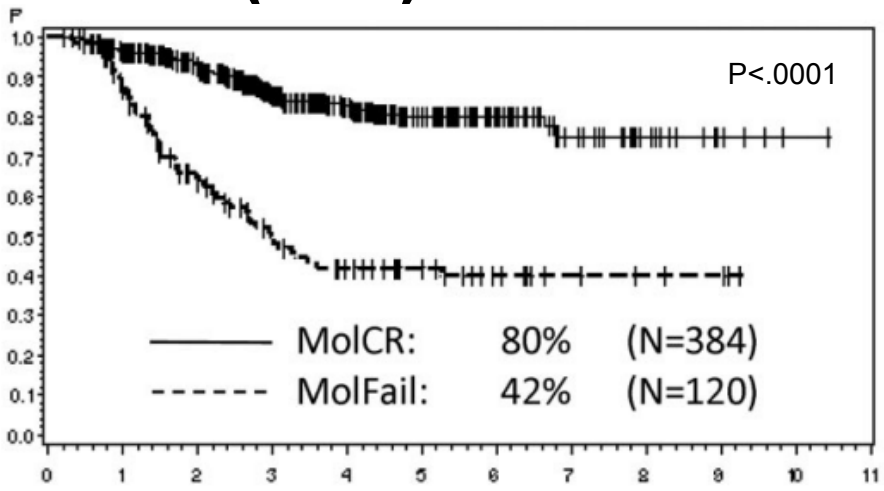
Gökbudget N et al, Blood 2012
German Multicenter Study Group for GMALL

ALL patients in 1st CR

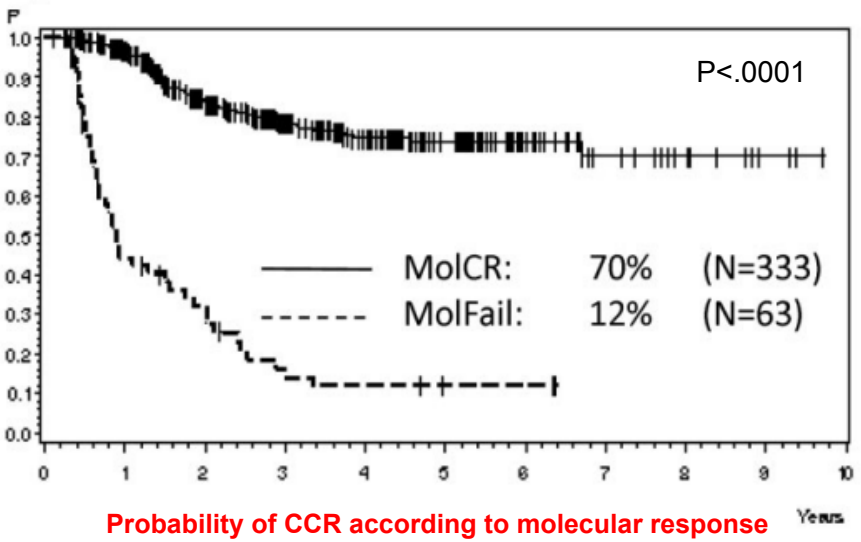
Impact of Minimal Residual Disease (MRD) in adult ALL



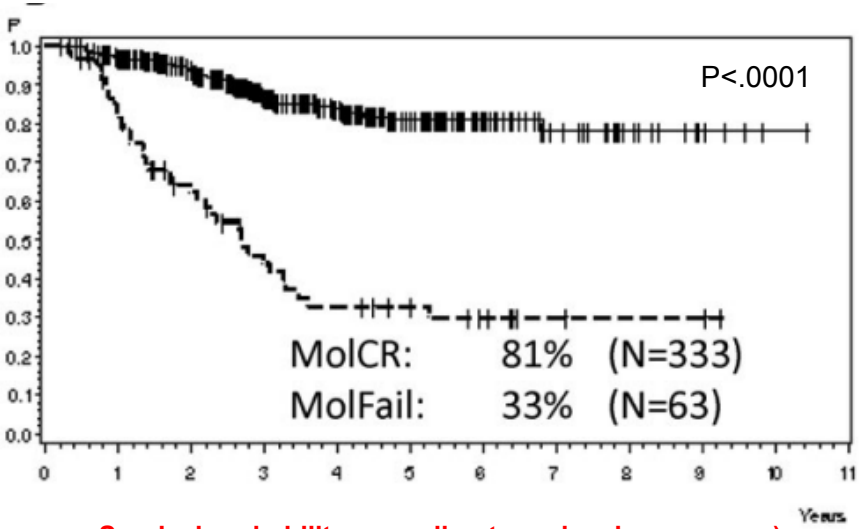
Probability of CCR according to molecular response in week 16



Survival probability according to molecular response in week 16



Probability of CCR according to molecular response excluding SCT in first CR



Survival probability according to molecular response) excluding SCT in first CR

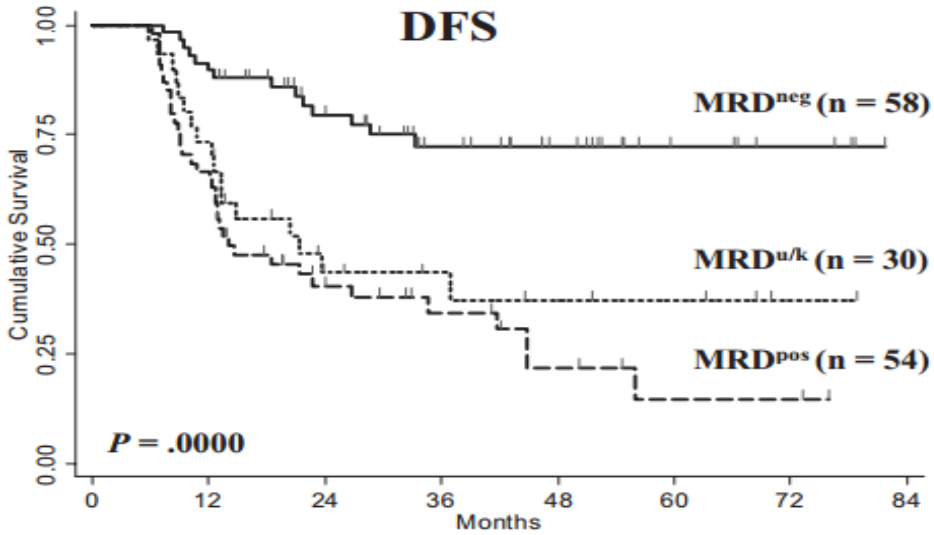
CCR: continuous complete remission probability

Gökbudget N et al, Blood 2012
German Multicenter Study Group for GMALL

ALL patients in 1st CR

Risk classification and treatment based on MRD (neg<10^{-4}) in adult ALL

NILG ALL 09/00 Trial: 280 pts, median age 38 y (16-65)



72%

14%

Multivariate analysis for DFS and risk of relapse

Risk factors	DFS		Relapse	
	HR (95%CI)	*P*	HR (95%CI)	*P*
MRD^{pos}	5.88 (2.86-12.08)	.001	5.33 (2.38-11.96)	.001
WBC>100	5.13 (2.06-12.75)	.001	4.32 (1.56-11.99)	.005
WBC >30	2.57 (1.32-5.02)	.006	2.27 (1.04-4.96)	.04
HR cytogenetics	1.04 (0.52-2.12)	.9	0.96 (0.42-2.21)	.93
Age >55 y	1.36 (0.52-3.59)	.5	1.44 (0.49-4.29)	.5

Bassan R, Blood 2009

ALL patients in 1st CR

Molecular levels of post-induction MRD predicts HSCT outcome in adult Ph- ALL

NILG Trial 09/00

CMR (complete molecular remission): n= 64 (47%) → Maintenance

Quantitative MRD levels:

MR ,molecularly responsive: MRD< 10^{-4}: n= 21 (15%)

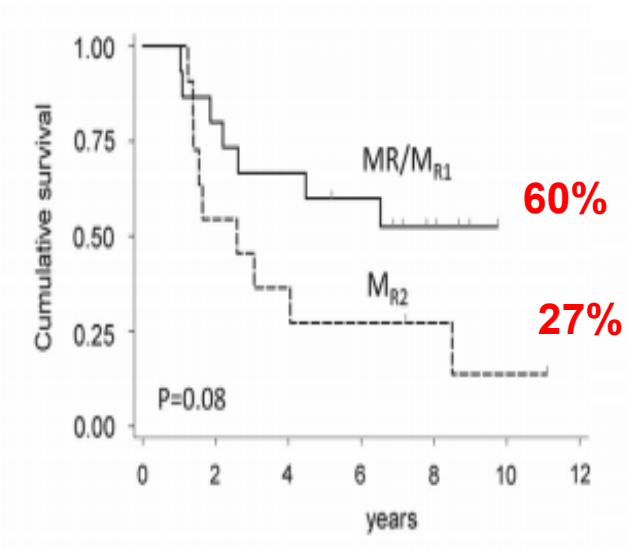
MR1, molecularly resistant 1: MRD 10^{-4}-10^{-3}: n=17 (13%)

MR2 , molecularly resistant 2: MRD ≥10^{-3}: n=34 (25%)

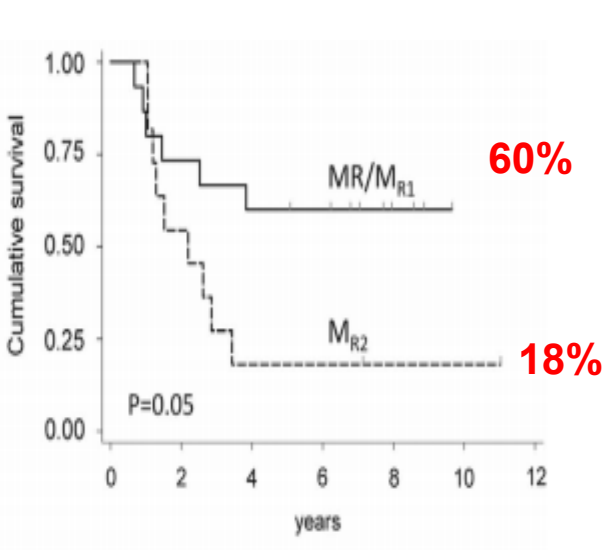
} Allogeneic SCT, chemotherapy, autoSCT

Outcomes by MRD levels in patients receiving allogeneic SCT (n=26)

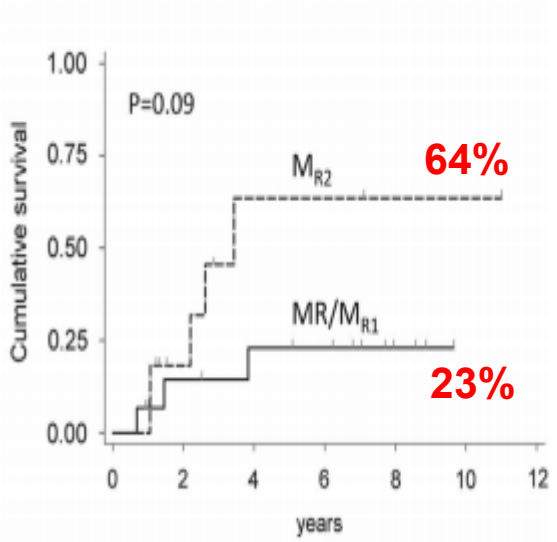
Overall survival



DFS



Relapse incidence



Bassan R, Br Cancer J 2014

ALL patients in 1st CR

Blinatumomab in patients with MRD^{pos} ALL: confirmatory, Phase II study

Inclusion criteria: B-ALL adult patients in hematological CR after ≥3 chemotherapy treatments and MRD^{pos}(≥10^{-3})
Primary endpoint: MRD^{neg} rate (≤10^{-4})

Responders:
- **Allo-HSCT after ≥1 cycle (n=90, 78%)**
- ≤ 4 cycles

Total Response Rate: 90/116 (80%)

>1st course of Blina: 88/116 (78%)

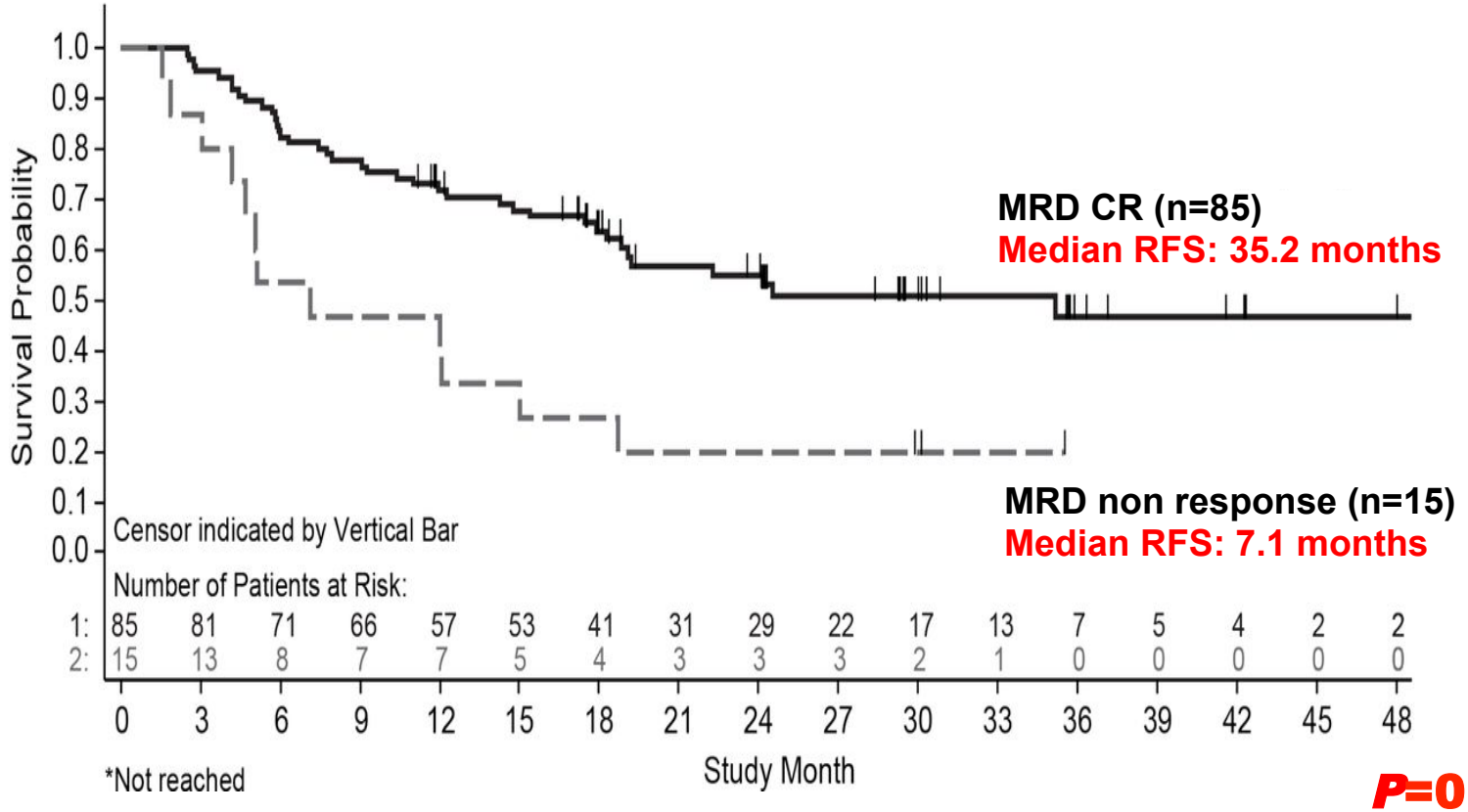
N=116	N (%)	Response (%)
CR before Blinatumomab:		
first	75 (65)	82
second	39 (34)	71
third	2 (1)	50
MRD levels before Blinatumomab*		
≥10^{-1} to <1	9 (8)	67
≥10^{-2} to <10^{-1}	45 (39)	82
≥10^{-3} to <10^{-2}	52 (45)	78

* 10 patients (8%) had MRD level <10^{-3}, below the lower limit of quantification or unknown

Gökbuget N, ASH 2015

ALL patients in 1st CR

Blinatumomab in patients with MRD^{pos} ALL: confirmatory, Phase II study



***P*=0.002**

Kaplan-Meier analysis of RFS inpatients with or without CR after blinatumomab
(Pts with RFS >45 days)

blood

Nicola Gökbuget et al. Blood 2015;126:680

ALL patients in 1st CR

- **MRD positivity is significantly associated with worse outcome.**

- **The Blinatumomab determines a high response rate in achieving MRD negativity (< 10^{-4}) in patients with MRD positivity after induction chemotherapy.**

- **Blinatumomab allows higher number of MRD positive patients undergoing allogeneic transplantation after achieving MRD negativity.**

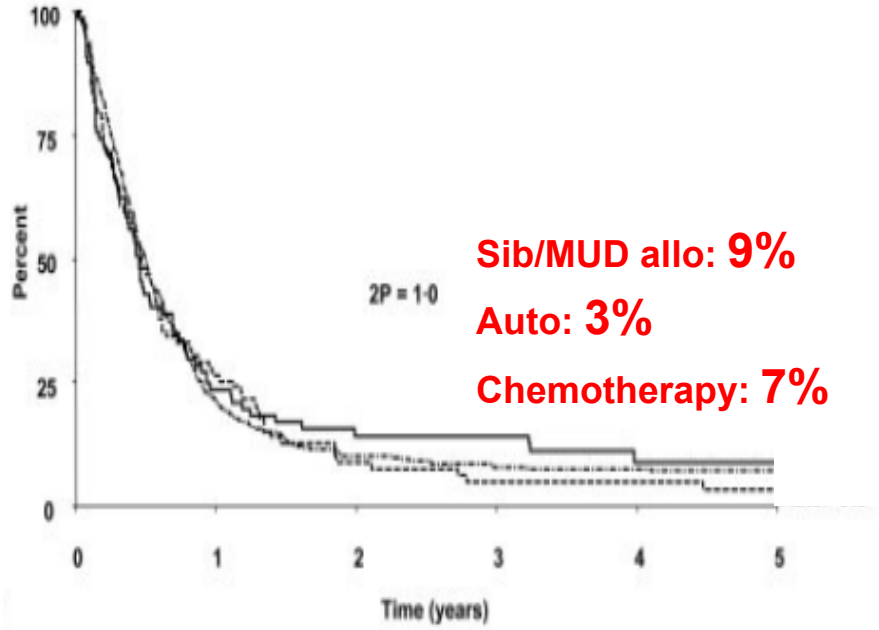
ALL patients in Relapse/Refractory Disease

MRC UKALLXII/ECOG2993 Trial: Outcome after relapse of adult ALL

Patients (15-60 y) relapsed after front line therapy: n=609

Overall survival: @1y 22%; @2 y 7%.

Survival according to front line therapy

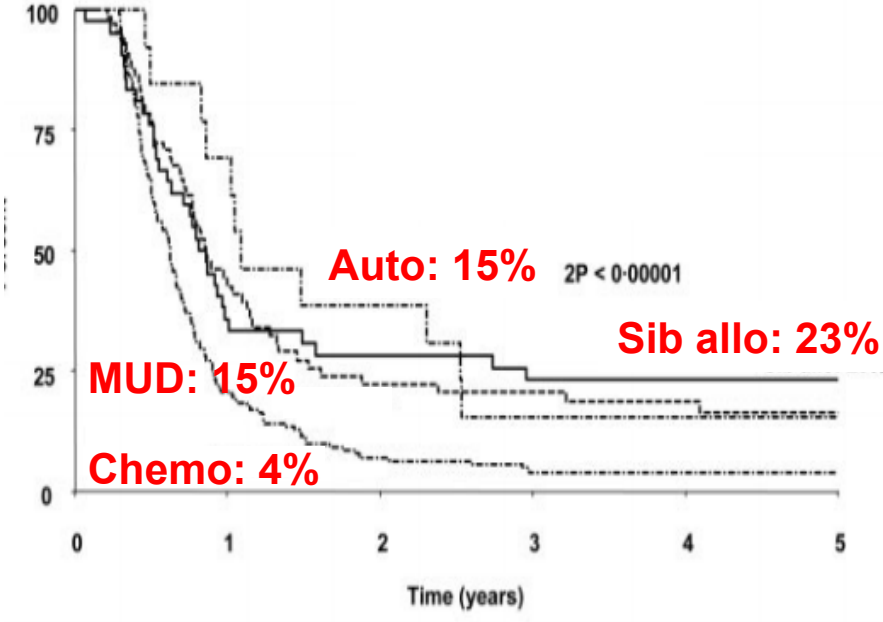


Sib/MUD allo: 9%

Auto: 3%

Chemotherapy: 7%

Survival according to therapy for relapse*



Auto: 15%

Sib allo: 23%

MUD: 15%

Chemo: 4%

* Patients who received transplantation in CR1 excluded

Fielding AK, Blood 2007

ALL patients in Relapse/Refractory Disease

Blinatumomab for relapsed or refractory B-ALL: Multicentre, Single-Arm, Phase 2 study

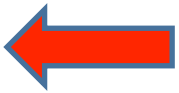
Europe: 23 Centers; USA: 14 Centers

N=189

Inclusion criteria:

- Primary refractory
- Relapse ≤12 months of CR1
- Relapse ≤12 months of HSCT
- ≥ 1 salvage therapy

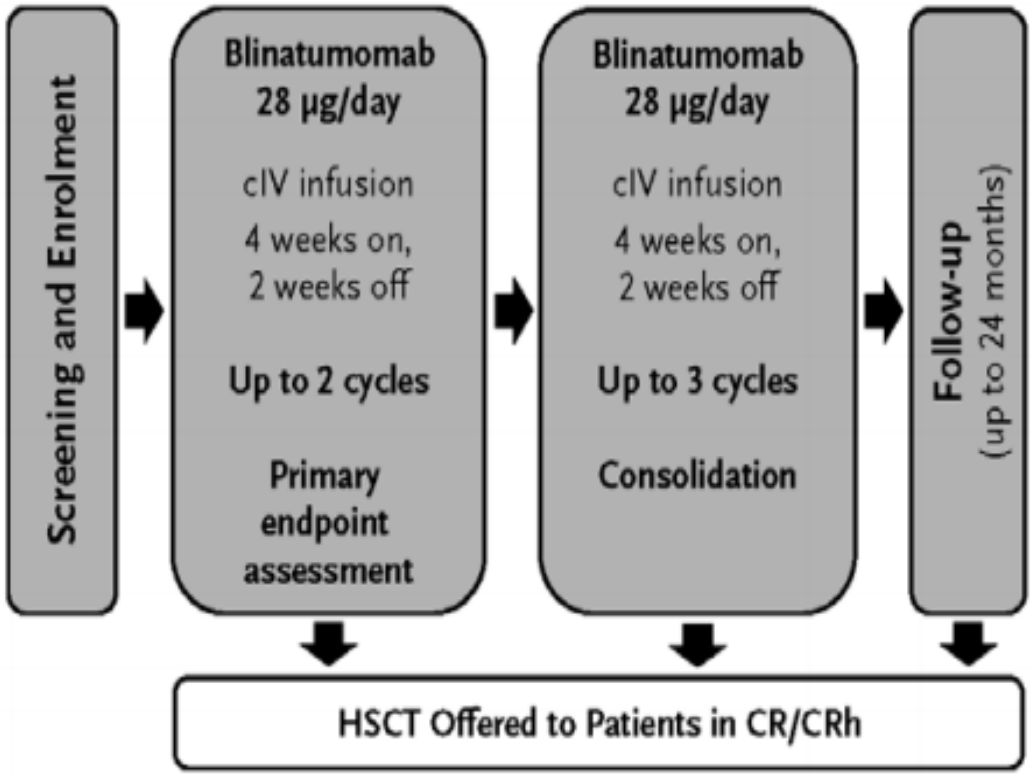
Previous alloHSCT	**64 (34%)**
No previous alloHSCT	**125 (66%)**
no previous salvage therapy	**29 (15%)**
1 previous salvage therapy	**55 (29%)**
≥ 2 previous salvage therapy	**41 (22%)**



Topp MS, Lancet Oncol 2015

ALL patients in Relapse/Refractory Disease

Blinatumomab for relapsed or refractory B-ALL: Multicentre, Single-Arm, Phase 2 study



Study Endpoints

Primary
- CR/CRh during the first two cycles

Secondary included
- CR, CRh
- Relapse-free survival
- Overall survival
- HSCT realization
- Incidence of adverse events

Exploratory included
- Minimal residual disease response by PCR during the first two cycles

Topp MS, Lancet Oncol 2015

ALL patients in Relapse/Refractory Disease

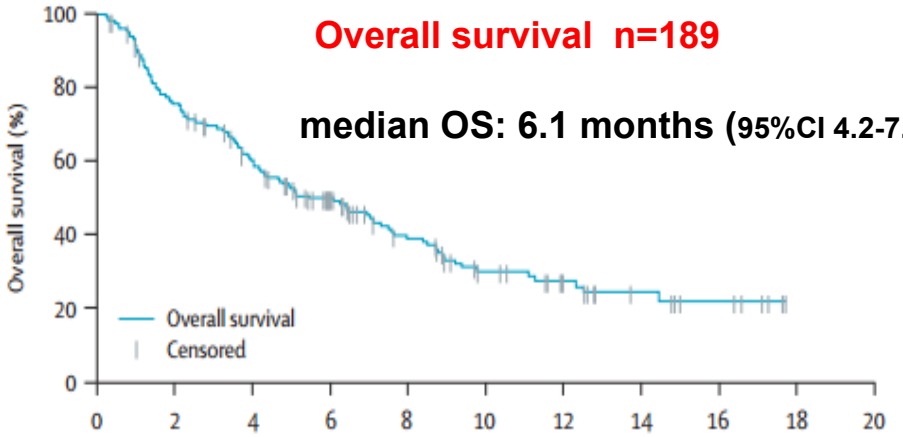
Blinatumomab for relapsed or refractory B-ALL: Multicentre, Single-Arm, Phase 2 study

Response	Patients	Rate
CR/CRh within 2 cycles	**81/189**	**43%**
CR	**63**	**33%**
CRh	**18**	**10%**
No response	**90**	**48%**
Not evaluable*	**18**	**10%**
MRD response during first 2 cycles in patients with CR/ CRh§	**60/73**	**82%**
Allogeneic HSCT after CR/CRh	32/81	**40%**
Patients previously transplanted	5/29	17%
Patients not previously transplanted	27/52	52%
Transplant-related mortality at 100 days (95% CI)	-	**11 (0-23)**

*early death (9), early discontinuation following Adverse Events (9)
§ 8 patients among the 81 responders had no MRD assessment in the primary analysis

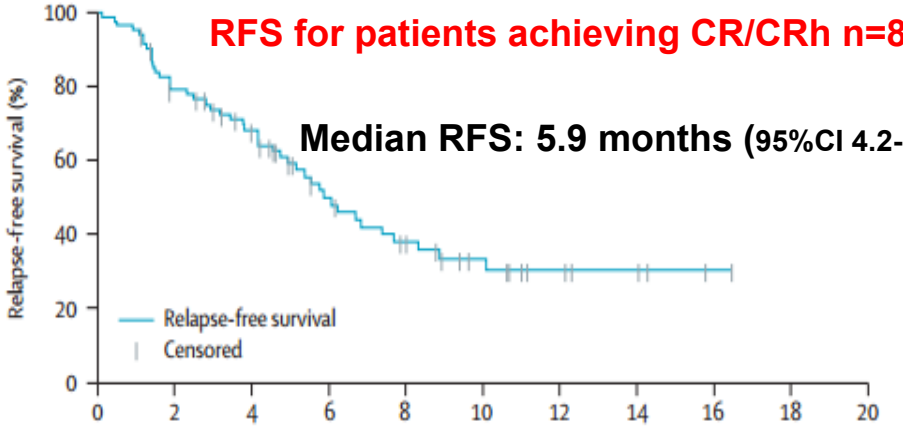
Overall survival n=189

median OS: 6.1 months (95%CI 4.2-7.5)



RFS for patients achieving CR/CRh n=81

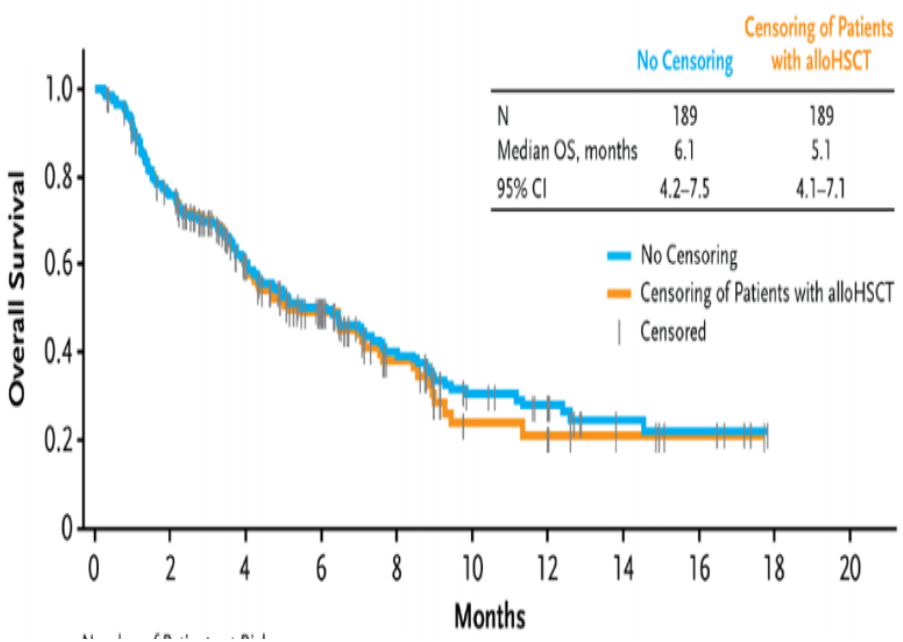
Median RFS: 5.9 months (95%CI 4.2-7)

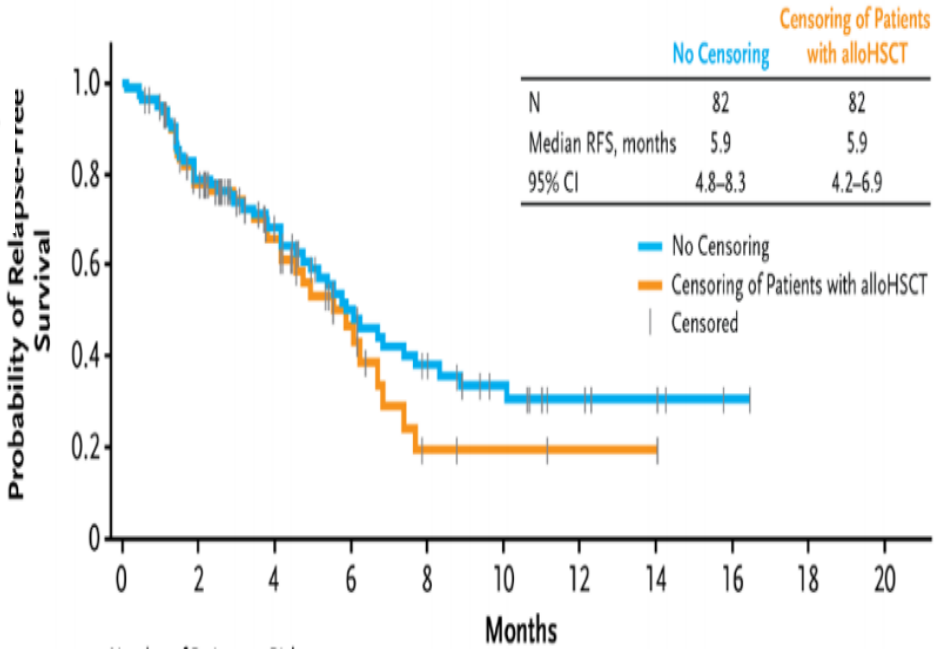


Topp MS, Lancet Oncol 2015

ALL patients in Relapse/Refractory Disease

Blinatumomab for relapsed or refractory B-ALL: Multicentre, Single-Arm, Phase 2 study





Topp MS, Lancet Oncol 2015

ALL patients in Relapse/Refractory Disease

HSCT in adult patients with relapsed/refractory ALL achieving remission with blinatumomab: exploratory analysis

Primary objective:

to assess the efficacy of **blinatumomab as a bridge to transplant** in adults with relapsed/refractory ALL

Among patients who received allo-HSCT after achieving CR/CRh with blinatumomab, this exploratory analysis investigated:

- Relapse-free survival
- Overall survival
- Mortality within 100 days after transplant

The patients who relapsed (n=7) or received chemotherapy (n=2) after blinatumomab and before transplant were excluded

ALL patients in Relapse/Refractory Disease

HSCT in adult patients with relapsed/refractory ALL achieving remission with blinatumomab: exploratory analysis

Characteristics of patients	Allo HSCT n=34
Median cycles of Blinatumomab before alloHSCT, n (range	2 (1-5)
Median time from last Blinatumomab dose to first conditioning regimen, days (range)	23 (8-60)
Conditioning regimen, n (%) Myeloablative Reduced intensity Unknown	 15 (44) 12 (35) 7 (21)
Donor type, n (%) Haploidentical Sibling Unrelated	 1 (3) 7 (21) 23 (68)

Stein AS
EBMT 2016

ALL patients in Relapse/Refractory Disease

HSCT in adult patients with relapsed/refractory ALL achieving remission with blinatumomab: exploratory analysis

RFS, 12-months estimate median follow-up, months (range)	**54%** 13.9 (8.5-17.1)
OS, 12-months estimate median follow-up, months (range)	**62.1%** 13.4 (9.4-14.6)

Mortality within 100 days after alloHSCT

Category	Cause of death	N=4	Days after alloHSCT
Infection	Sepsis Sepsis Septic shock	1 1 1	75 59 8
GVHD	Skin and gut	1	42

Stein AS
EBMT 2016

ALL patients in Relapse/Refractory Disease

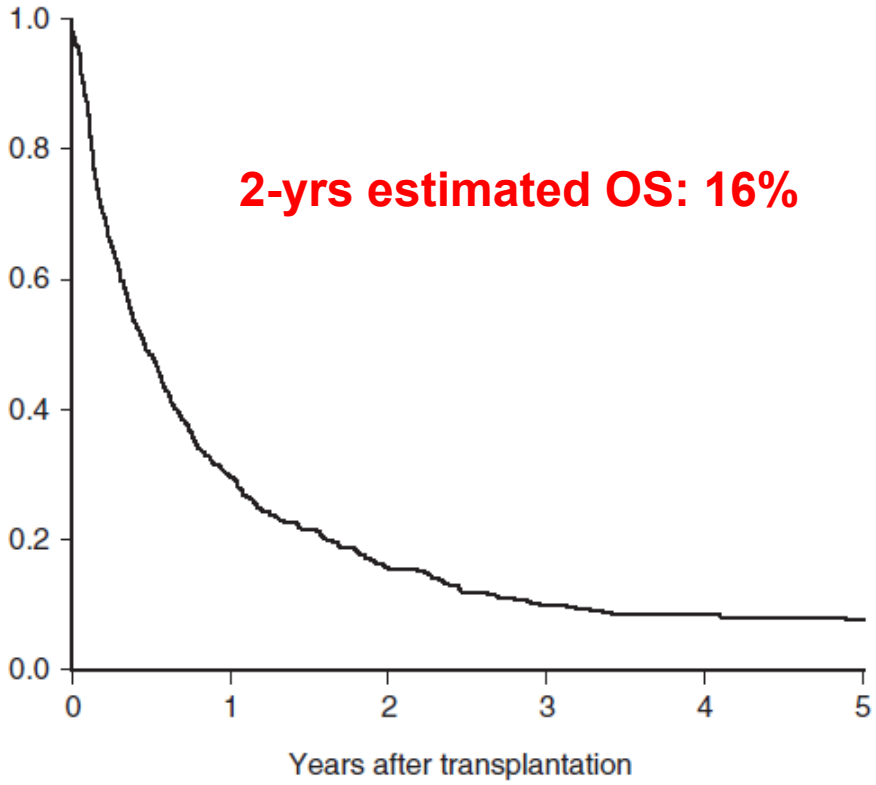
- **Blinatumomab can be considered effective as salvage therapy and bridge to transplant**
- **There is no evidence of relevant or unexpected transplant-related mortality or morbidity in patients receiving allo-SCT after blinatumomab**
- **Whether allo-HSCT after blinatumomab-induced remission can really improve the long-term outcome needs to be confirmed in larger series of patients and on a longer follow-up.**

ALL patients in Relapse after Allogeneic SCT

Outcomes of adults with ALL who relapse after allogeneic Hematopoietic Stem Cell Transplant (allo-HSCT). An analysis on behalf of the ALWP of EBMT

Allo-HSCT in CR between 1995-2006
n=465
median age: 32 y (range: 18-66)

Distribution of post-relapse therapies n=465	
Supportive care	62 (13%)
Cytoreductive therapy only	202 (43%)
GVL-based	108 (23%)
Second transplant	93 (20%)



2-yrs estimated OS: 16%

Spyridonidis A, Leukemia 2012

ALL patients in Relapse after Allogeneic SCT

Blinatumomab in adult patients relapsed after Allogeneic Hematopoietic Stem Cell Transplantation – Exploratory Analysis

Inclusion criteria

- Adult patients with Philadelphia chromosome negative B-ALL
- Primary refractory disease
- Early relapse (duration of first remission ≤ 12 months)
- Relapse within 12 months of allo-HSCT
- Any relapse or refractory disease after first salvage therapy
- ≥ 10% bone marrow blasts +/- etramedullary disease
- ECOG performance status ≤ 2

Stein AS ,
EBMT 2016

ALL patients in Relapse after Allogeneic SCT

Blinatumomab in adult patients relapsed after Allogeneic Hematopoietic Stem Cell Transplantation – Exploratory Analysis

Characteristics	n=64
Median age, y (range)	32 (19-74)
Salvage therapies before blinatumomab, n (%) 0 1 2 ≥ 3	 9 (14) 22 (34) 13 (20) 20 (31)
Donor type, n (%) Haploidentical Sibling Unrelated Sibling/Unrelated* Haploidentical/Unrelated*	 1 (2) 29 (45) 31 (48) 2 (3) 1 (2)
Myeloablative Conditioning, n (%)	34 (59)
Previous acute or chronic GVHD, n (%)	19 (30)

*patients who received 2 transplant procedures before blinatumomab

Stein AS ,
EBMT 2016

ALL patients in Relapse after Allogeneic SCT

Blinatumomab in adult patients relapsed after Allogeneic Hematopoietic Stem Cell Transplantation – Exploratory Analysis

Results	n=64	
Hematological Response		
CR/CRh in first 2 cycles	29/64	45%
CR	18/64	28%
CRh	11/64	17%
Blast-free hypo/aplastic bone marrow	4/64	6%
Failure	31/64	48%
Molecular response ($<10^{-4}$)*	16/18 CR	89%

* Based on the number of patients who had achieved CR or CRh within the first two cycles and had evaluable MRD data (n=18)

Stein AS ,
EBMT 2016

ALL patients in Relapse after Allogeneic SCT

Blinatumomab in adult patients relapsed after Allogeneic Hematopoietic Stem Cell Transplantation – Exploratory Analysis

Transplant outcome	**n=64**	95% CI
Median Relapse-free Survival, months (median follow-up: 12.4 months)	**7.4**	5-10.1
Median Overall Survival, months (median follow-up: 16.6 months)	**8.5**	4.2-11.2

Stein AS ,
EBMT 2016

ALL patients in Relapse after Allogeneic SCT

- **The outcome of patients relapsed after Allo-HSCT is extremely poor.**

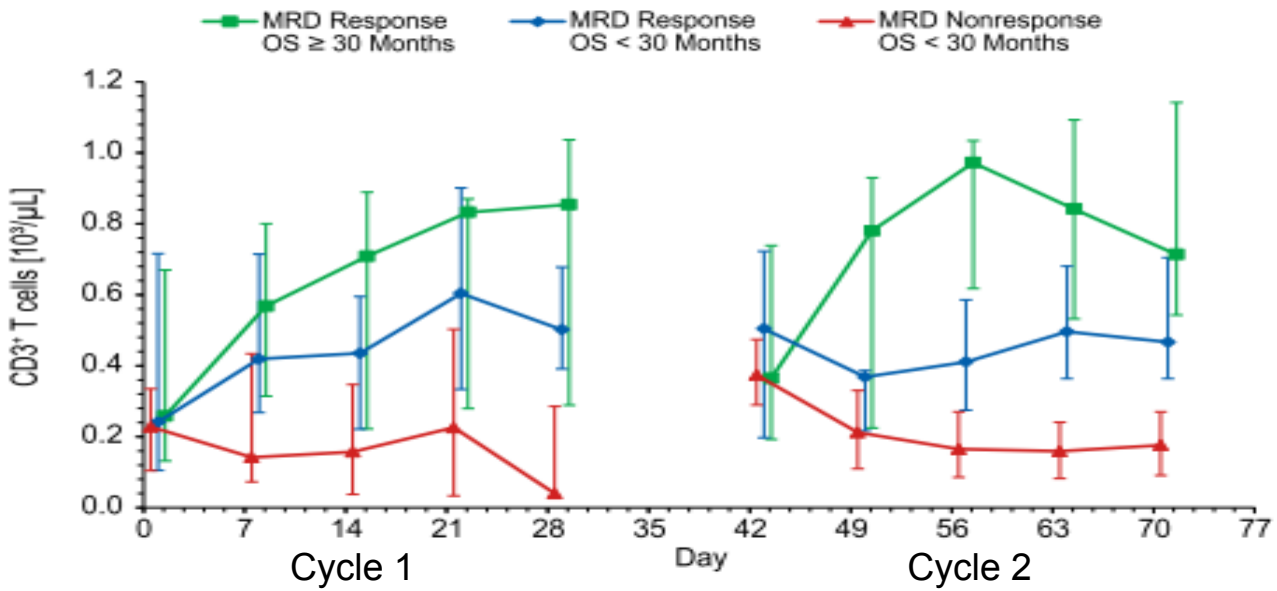
- **The blinatumomab can rescue 45% of patients relapsed after transplant and allows to achieve a molecular response is 88%of responders.**

- **The efficacy of blinatumomab in patients relapsed after alloHSCT should be confirmed in further prospective studies, with more patients and longer follow-up**

ALL patients in Relapse after Allogeneic SCT

Blinatumomab in relapsed/refractory adult B-ALL patients. Phase II Study

T-cell kinetics after cycle 1 and 2 of Blinatumomab



- Increase of T-cell reproduces a natural T-cell response consisting of T-cell activation, expansion and contraction phase.
- T-cell expansion consisted mainly of increasing number of effector memory T cells(T_{EM}), which play a role in blinatumomab-induced apoptosis
- **Expansion of T-cells was predominant in MRD responders with OS≥ 30months**

Topp MS, Blood 2015

ALL patients in Relapse after Allogeneic SCT

Relapsed B-ALL after allo-HSCT : concurrent blinatumomab and DLI

Pt	Age at SCT	Donor	Time to relapse (days)	DLI dose (CD3+/Kg)	DLI with Blinatumomab	Best response	Outcome
1	35	MSD	136	$5x10^7$	2	MFC, Cytogenetics, 100%donor chimerism	Death, relapse 12 months after Blina
2	71	MUD	106	$1x10^7$	1	MFC, Cytogenetics	Continued CR
3	61	MUD	359	$1x10^7$	1	MFC, molecular CR	Continued CR
4	64	MSD	436	$1x10^7$	1	Progressive disease	Progression

The engagement of donor T lymphocytes when blinatumomab is given concomitantly with DLI might increase the anti-leukemic effect of both therapeutic strategies

Ueda M, USA
Bone Marrow Transplantation, 2016

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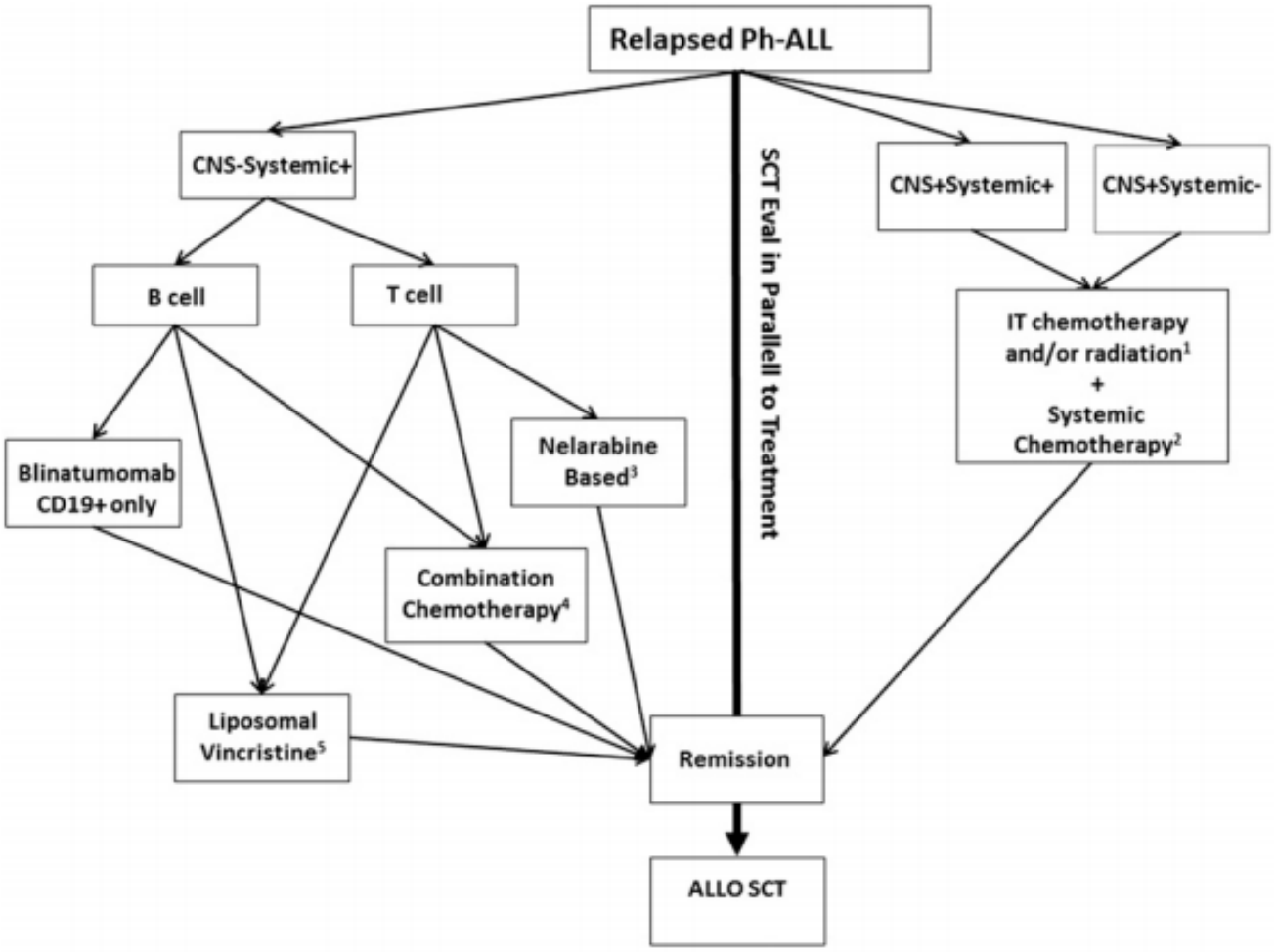
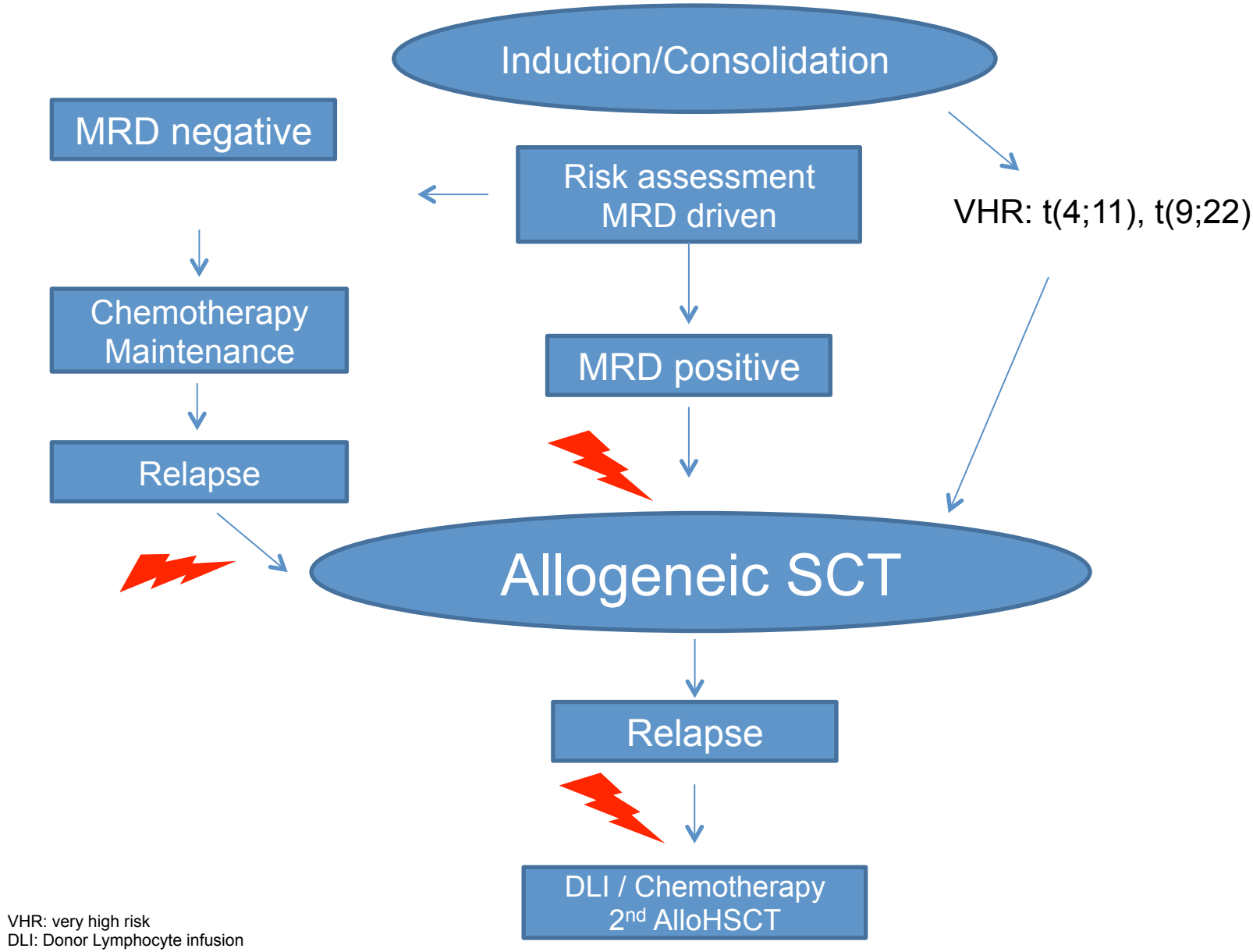


Frey NV and Luger SM, USA
How I treat relapsed or refractory Ph- ALL
Blood 2015

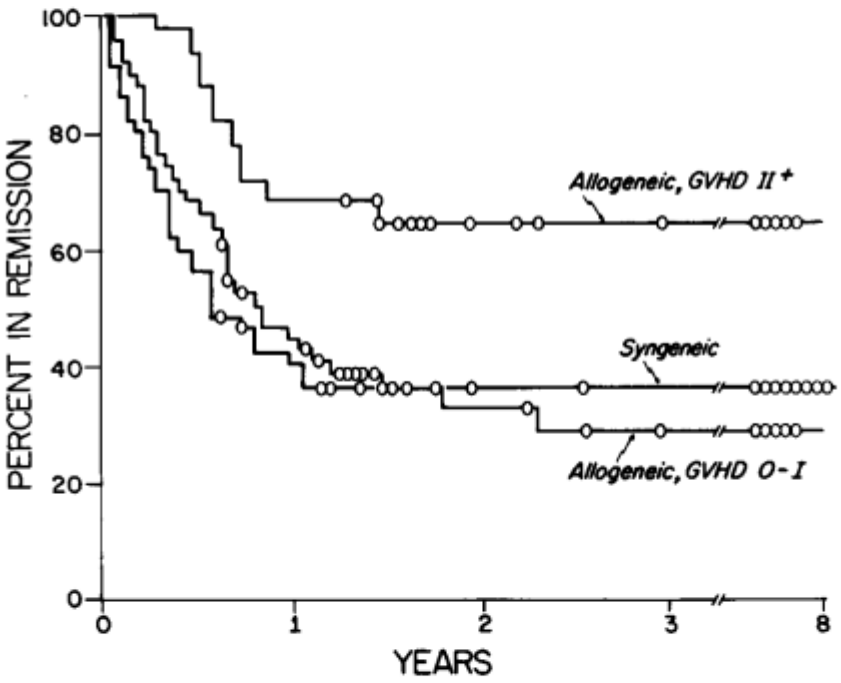
Algorithm for treatment of adult B-ALL: risk assessment MRD-based



VHR: very high risk
DLI: Donor Lymphocyte infusion

Antileukemic effect of graft-versus-host disease in human recipients of allogeneic marrow grafts

1970-1977
N° of pts: 242
ALL: 126
ANLL: 116
Donor: syngeneic n=46
HLA-id n=196
Disease Status: Relapse/ resistant: 175
Remission: 67
Conditioning regimen: TBI-Cy
GVHD prophylaxis: MTX



Patients	Donor/Grade of GVHD	Probability of relapse @ 1 y	*P* value
Acute nonlymphocytic leukemia	Syngeneic Allogeneic: 0-I Allogeneic II-IV or chronic	0.55 0.44 0.33	0.14
Acute lymphocytic leukemia	Syngeneic Allogeneic: 0-I Allogeneic II-IV or chronic	0.62 0.65 0.31	0.002

Weiden PL, NEJM, 1979

HLA identical sibling transplantation in adult ALL in first CR

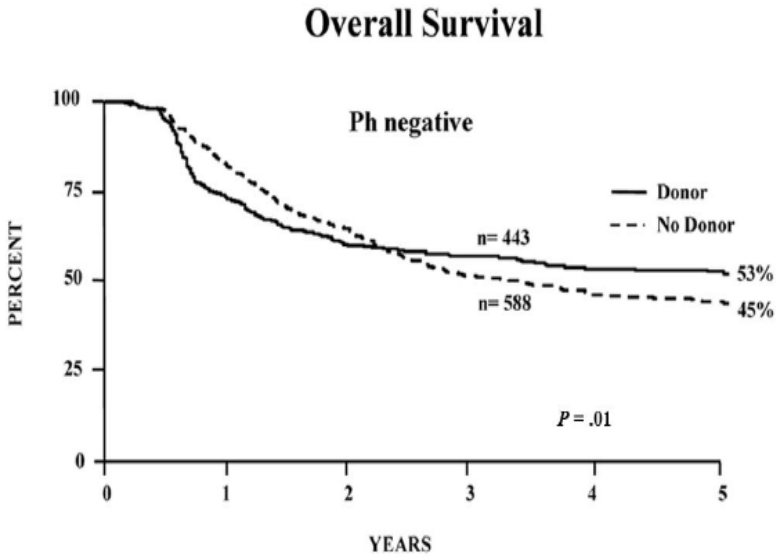
MRC UKALL XII / ECOG 2993

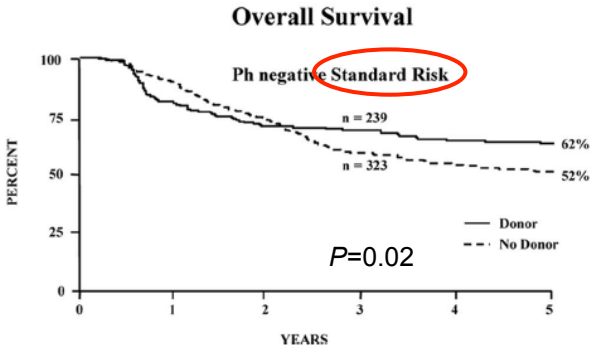
Adult ALL: 15-59 y; enrollment 1993-2006

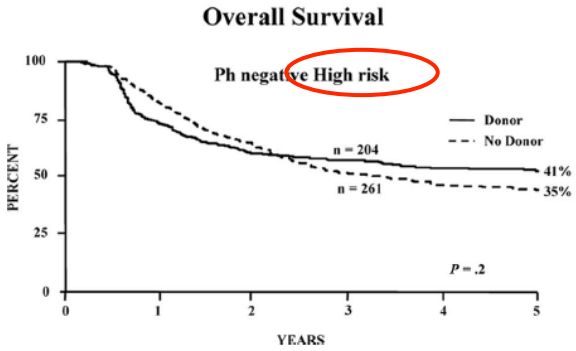
Donor group: HLA identical SCT

No Donor group: chemotherapy or autoSCT

High Risk: > 35 years old; Ph+ALL; B-ALL >30x10^9/L WBC; T-ALL >100x10^9/L







	NRM @2y	Relapse Rate @6y
High Risk		
Donor	35%	37%
No Donor	13%	63%
Standard Risk		
Donor	19%	24%
No Donor	7%	49%

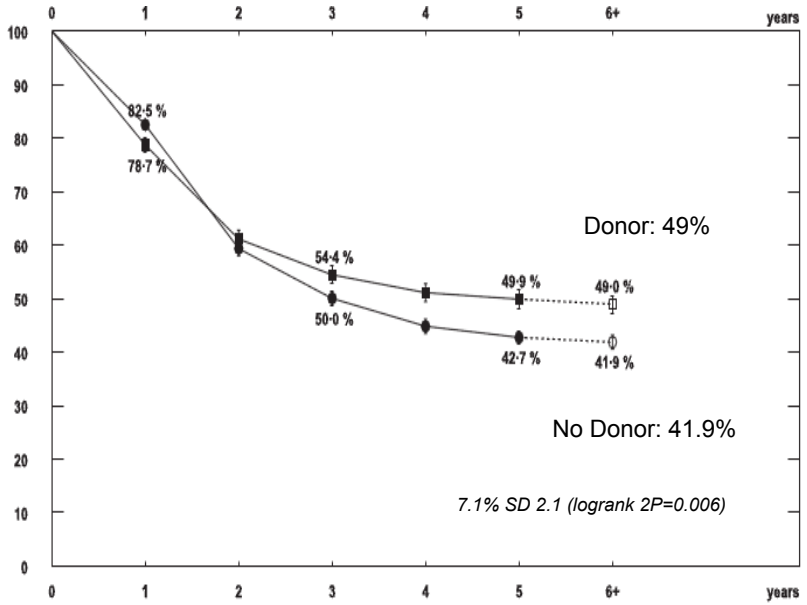
Goldstone AH, Blood 2008

HLA identical sibling transplantation in adult ALL in first CR

Allogeneic vs autologous SCT/chemotherapy: a systematic review and meta-analysis of prospective and selected retrospective trials, based on Individual Patient Data

Allogeneic myeloablative transplantation from HLA-identical sibling provides:

- significantly lower incidence of relapse (OR=0.58; 95% CI, 0.52-0.65; *P*=.00001)
- significantly higher non-relapse mortality (OR=2.36; 95% CI, 1.94-2.86; *P*<.00001)
- Significantly longer survival (OR=0.87; 95% CI, 0.79-0.96; *P*=.006)



Only patients <35 y old show a significant survival benefit in the donor group (OR=0.79; 95% CI, 0.70-0.90; *P*=.0003)

Gupta V et al, Blood 2013
Acute Leukemia Stem Cell Transplantation Trialists' Collaborative Group

ALL patients in 1st CR

Impact of Minimal Residual Disease (MRD) in adult ALL patients

Multivariate analysis of prognostic factors:
Variables included: age, immunophenotype, risk group, molecular response

Endpoint	Multivariate analysis
CCR	**16w molecular response** **HR 4.5, *P*<.0001**
OS	**Age** **HR 1.3, *P*=.007**
OS	**16w molecular response** **HR 4, *P*<.0001**

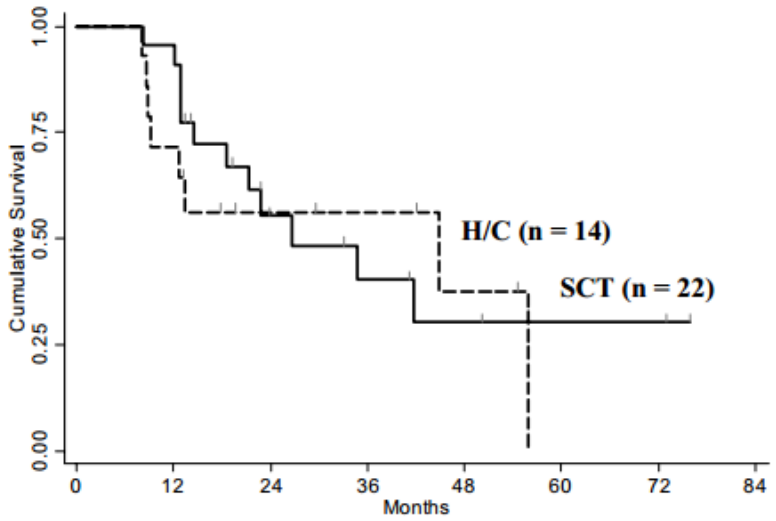
5-years outcomes of patients with molecular failure after consolidation (week 16): effect of SCT

Endpoint	no SCT n=35	SCT n=25	*P*
CCR	17 ±7	73 ±10	<.0001
DFS	16 ±7	50 ±7	=.004

Landmark analysis: patients with remission duration shorter than 232 days (median time to transplant + 1 month) were excluded

Gökbudget N et al, Blood 2012
German Multicenter Study Group for GMALL

Risk classification and treatment based on MRD in adult ALL



DFS of MRD^{pos} group in patients undergoing allogeneic SCT or H/C

- MRD is the best parameter predicting relapse and outcome, and it can be used to optimize therapeutic strategy
- Allogeneic SCT represents the salvage option for patients MRD^{pos}

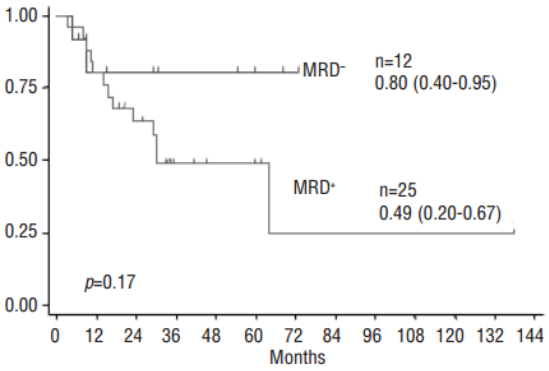
Bassan R, Blood 2009

Clearance of MRD and outcome after allogeneic SCT in adult high-risk ALL patients

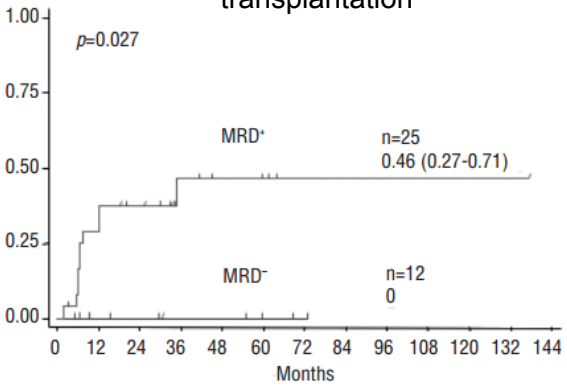
NILG –ALL 08/96 and 09/00
Adult ALL: n=43, median age 30 (18-63)
B-ALL/T-ALL: 37/7
HLAid sibling/Matched Unrelated Donor: 24/19
CR1 for MRD+ post-induction or High Risk: 29
CR2: 8
Active disease: 6

Results:
36 months OS: 48% (95% CI 31-63)
G+30: 71% (20/28) converted MRD+ → MRD-

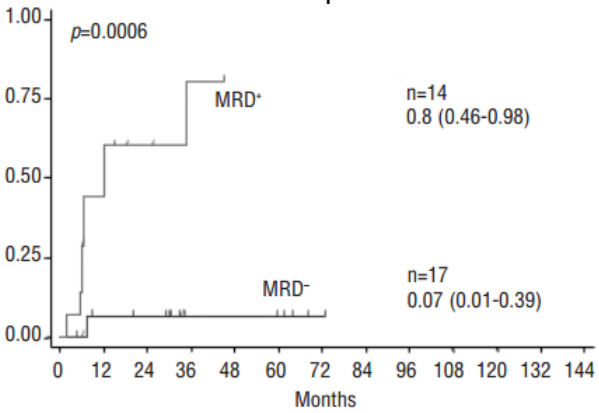
Overall Survival according to MRD status before transplantation



Cumulative incidence of relapse according to MRD status at transplantation



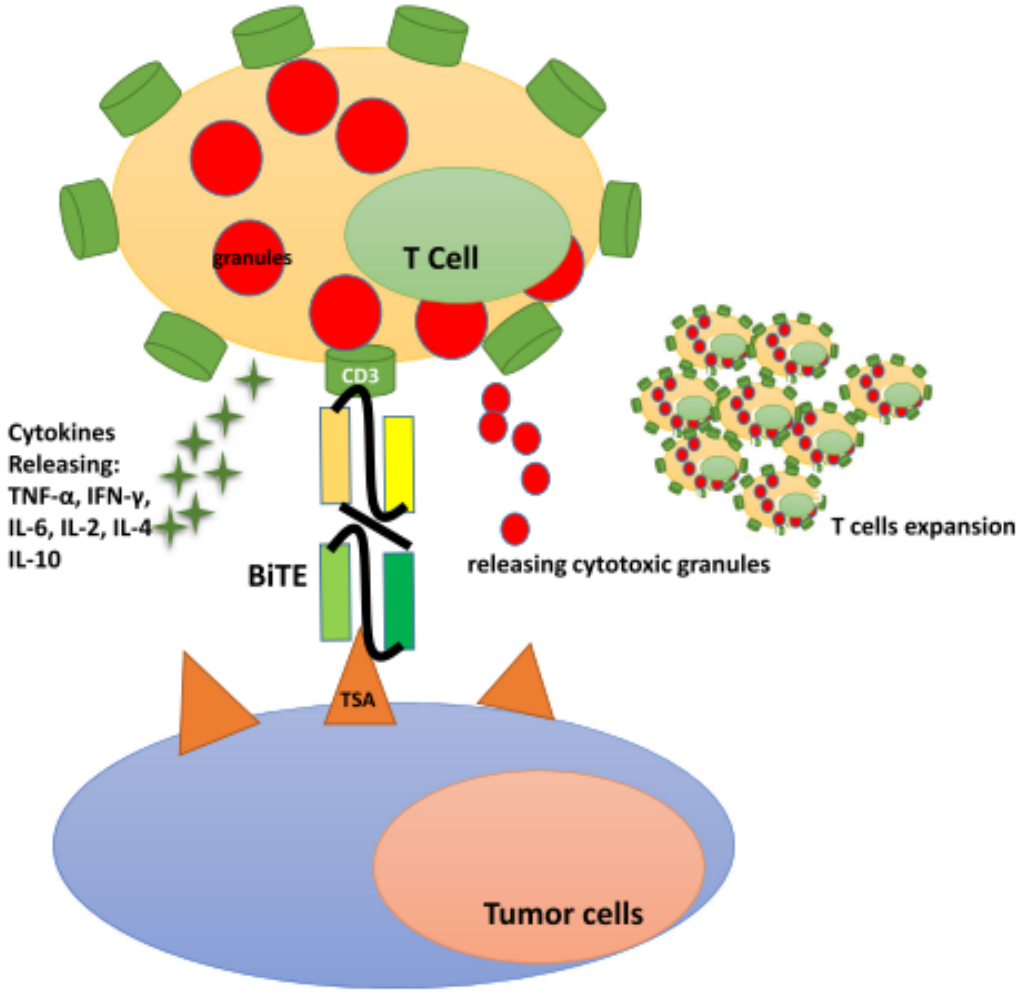
Cumulative incidence of relapse according to MRD status at day+100 after transplantation



- The achievement or maintenance of MDR^{neg} status within 3 months from transplant was significantly associated with a lower incidence of relapse
- By multivariate analysis only molecular complete remission before conditioning predicted complete remission at day+100

Spinelli O, Haematologica 2007

BiTE® antibodies redirect T cells to a tumor cells.



Fan G, J of Hematology & Oncology 2015

ALL patients in 1st CR

Blinatumomab in adult B-ALL patients in CR with MRD^{pos} status. Phase II Study

Patients characteristics:
Adult B-ALL, n=21; median age 47 (20-77)
Disease status: complete hematological remission with MRD^{pos} after consolidation or in molecular relapse

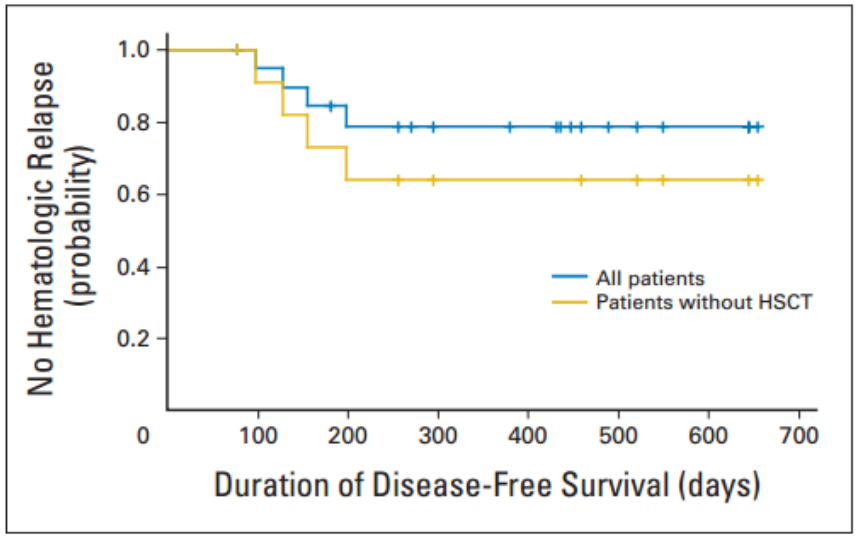
Treatment schedule:

Blinatumomab 15 mcg/m^2/24 h over 4 weeks

- Responders: 3 additional courses
- Allogeneic SCT n=8

Response after 4 weeks of treatment

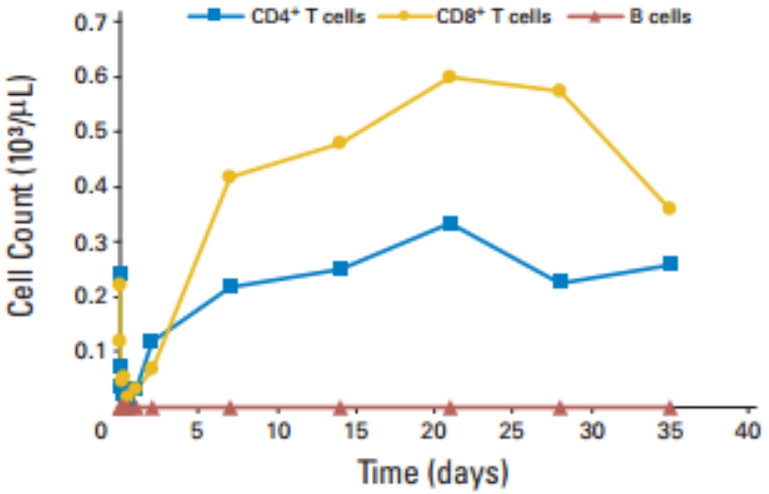
Category	N°	N° of responders	
Evaluable	20	16	80%
Molecularly refractory Molecular relapse	15 5	12 4	80%
Response according to MRD level before Blinatumomab			
≥ 10^{-2} < 10^{-3} to ≥ 10^{-3} <10^{-3} to ≥10^{-4}	11 5 4	10 4 2	91% 80% 50%



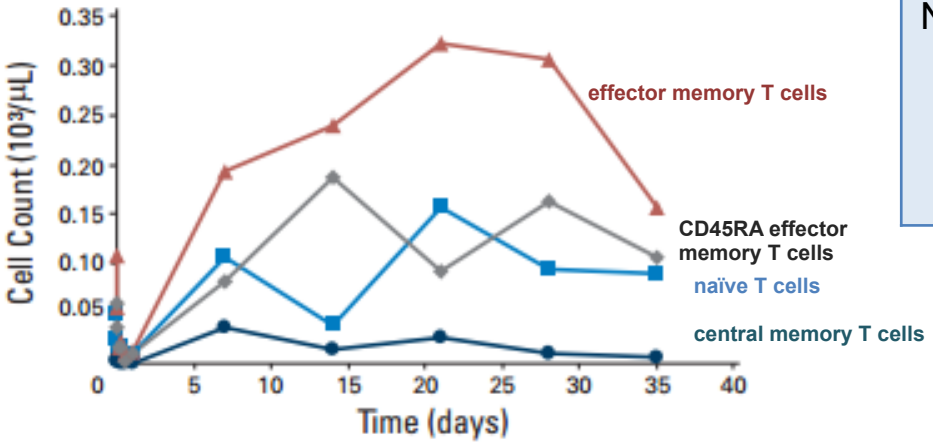
Median follow up for DFS: 276 d (78-655).
No relapse nor death in patients submitted to transplant

Topp MS, JCO 2011

Blinatumomab in adult B-ALL patients in CR with MRD^{pos} status. Phase II Study



CD8+ T-cells subset



Adverse Events Grade 3/4

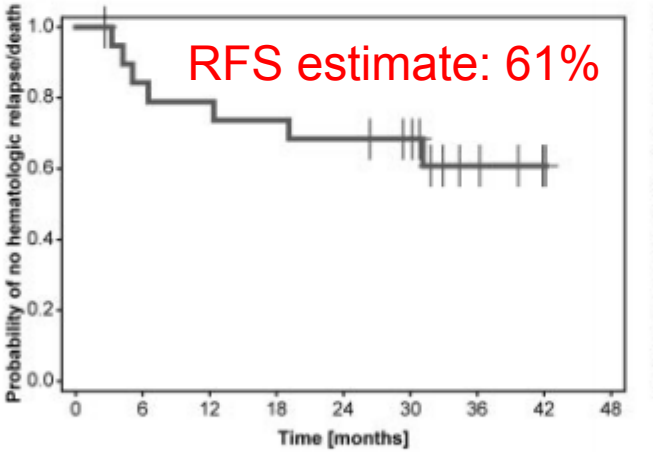
Adverse events	N° of patients N=21	%
Blood		
lymphopenia	7	33
leukopenia	2	9.5
Ig decreased	5	23.8
Nervous System		
syncope	1	4.8
seizure	1	4.8
headache	1	4.8
somnolence	1	4.8

Blinatumomab has the potential to induce durable molecular remission in patients in CR and MRD^{pos}.

Topp MS, JCO 2011

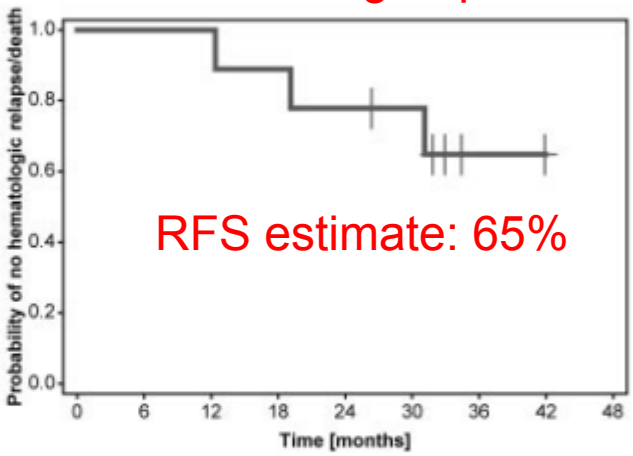
Blinatumomab in adult B-ALL patients in CR with MRD^{pos} status. Long-term result of the Phase II Study

All patients: n=20



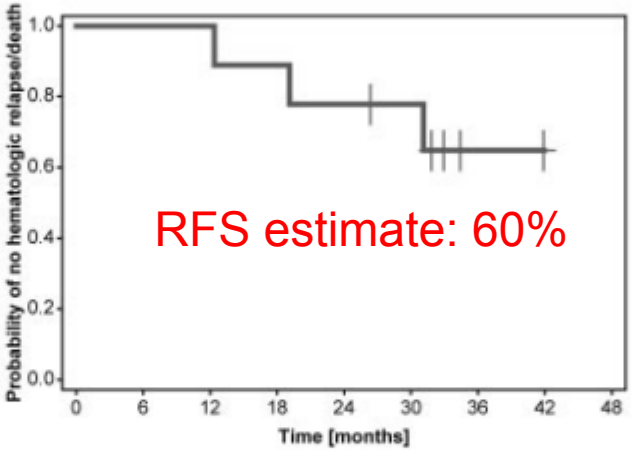
median follow-up: 32 months

Allo- HSCT group: n=9



median follow-up: 33 months

No- HSCT group: n=11



median follow-up: 31 months

- Blinatumomab can offer long-lasting complete remission and prolonged survival in MRD^{pos} patients
- The benefit in survival is observed even in patients who do not undergo to Allo-HSCT

Topp MS, Blood 2012

Blinatumomab in patients with MRD^{pos} ALL: confirmatory, Phase II study (BLAST)

Multivariate analysis

Endpoint	HSCT vs no HSCT HR (95% CI)	*P*
OS	1.39 (0.68-2.82)	0.36
RFS	0.89 (0.47-1.69)	0.73
Duration of response	0.36 (0.7-0.77)	0.008

Conclusions:

- Blinatumomab induces high rate of MRD responses (80%)
- MRD response after Blinatumomab is associated with significantly prolonged OS, RFS and duration of response
- The role of subsequent alloHSCT, which had been performed in a high proportion of patients, requires further investigation

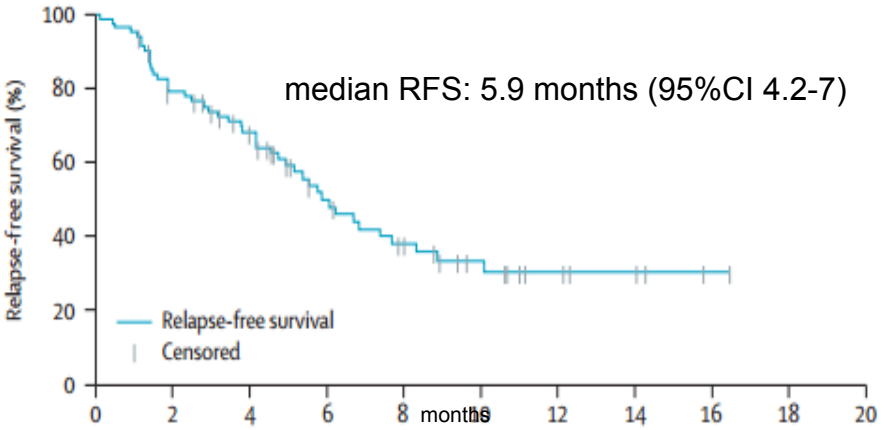
ALL patients in Relapse/Refractory Disease

Safety and activity of blinatumomab for adult patients with relapsed or refractory B-ALL: a Multicentre, Single-Arm, Phase 2 study

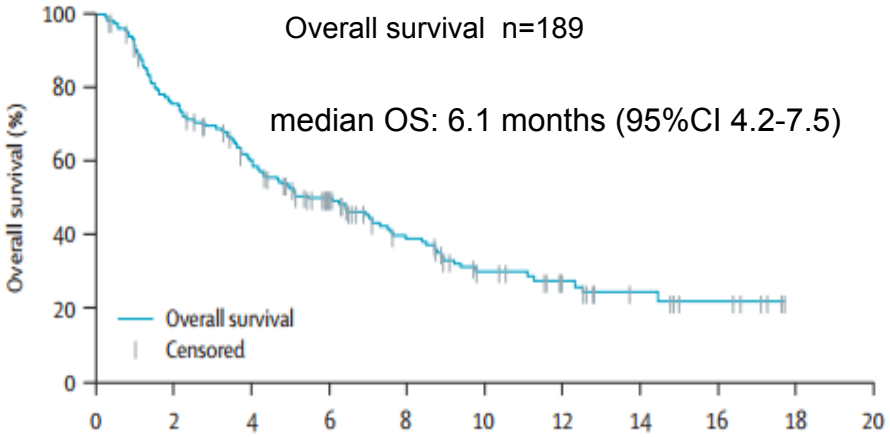
Response	Patients	Rate
CR/CRh within 2 cycles	81/189	43%
CR	63	33%
CRh	18	10%
No response	90	48%
Not evaluable*	18	10%
MRD response during first 2 cycles in patients with CR/CRh§	60/73	82%

*early death (9), early discontinuation following Adverse Events (9)
§ 8 patients among the 81 responders had no MRD assessment in the primary analysis

Kaplan-Meier survival estimates of patients achieving CR/CRh n=81



median RFS in CR patients: 6.9 months (95%CI 4.2-10.1)
median RFS in CRh patients: 5 months (95%CI 1.4-6.2)



Adverse Events	Patients, n=189	Rate
Pyrexia	113	60%
Headache	65	34%
Febrile neutropenia	53	28%
All neurologic events	98	52%
Grade 3-4 neurologic events	24	13%

Topp MS, Lancet Oncol 2015

Outcome of hematopoietic Stem Cell Transplantation (HSCT) in adult patients with relapsed/refractory ALL achieving remission with blinatumomab: exploratory analysis

Characteristics of patients

	AlloHSCT n=34	**No alloHSCT n=49**
Median age, y (range) 18 to <35 y, n (%) 35 to <55 y, n (%) 55 to <65 y, n (%) ≥ 65 y, n (%)	31 (18-65) 19 (56) 9 (26) 4 (12) 2 (6)	42 (19-75) 21 (43) 12 (24) 6 (12) 10 (20)
Relapses before Blinatumomab, n (%) 0 1 2 ≥ 3	 4 (12) 21 (62) 8 (24) 1 (3)	 3 (6) 30 (61) 10 (20) 6 (12)
Prior salvage therapies, n (%) 0 1 2 ≥ 3	 9 (27) 17 (50) 5 (15) 3 (9)	 10 (20) 20 (41) 9 (18) 10 (20)
AlloHSCT before Blinatumomab, n (%)	7 (21)	22 (45)
Overall alloHSCT realization in patients in CR after blinatumomab (n=83), n (%)	34 (41)	-
AlloHSCT realization in patients with prior transplant (n=54), n (%)	27 (50)	-
MRD response*, n (%) Complete MRD response§, n (%)	27 (79) 26 (77)	34 (69) 25 (51)

*<10^{-4};
§: blast not detectable at assay sensitivity ≤10^{-4})

Stein AS MS, ASBMT Meeting 2016
EBMT 2016

Treatment Options for relapsed ALL after allogeneic Stem cell Transplantation

Therapeutic strategies	Drawbacks/relevant issues
Conventional chemotherapy	• Toxicity • Low response rate • Limited duration of response
Second transplant	• Toxicity • Frequent subsequent relapse • Efficacy limited to selected categories of patients: younger or patients with long transplant-to-relapse interval • same or alternative donor choice
Donor Lymphocyte Infusion (DLI)	•Not effective in florid relapse •Response rate: 0-20%
Cell-based strategies: engineered T-cell therapy (CART-19)	• Promising results in ongoing trials • Feasibility limited to highly specialized facilities
Targeted therapies	•1st and 2nd generation TKIs for Ph+ ALL
Monoclonal antibodies	• Promising results in ongoing trials

Porter DL, Biol Blood Marrow Transpl 2010
NCI – International Workshop on Relapse after Allogeneic Hematopoietic Stem Cell Transplantation

Safety and activity of blinatumomab for adult patients with relapsed or refractory B-ALL: a Multicentre, Single-Arm, Phase 2 study

- Blinatumomab as single-agent showed a notable CR rate in very poor prognosis category of patients: adult relapsed/refractory B-ALL patients.
- The objective of allo-HSCT was reached in 40% of patients obtaining a CR after blinatumomab
- There is no evidence of relevant or unexpected transplant-related mortality or morbidity in patients receiving allo-SCT after blinatumomab
- Whether allo-HSCT after blinatumomab-induced remission can really improve the long-term outcome needs to be further investigated.

Topp MS, Lancet Oncol 2015

ALL patients in Relapse/Refractory Disease

Patients characteristics:

n=36; median age 32 (18-77)
Prior HSCT: n=15 (42%)
No prior HSCT: n=21 (58%)
Primary refractory: n=3 (8%)
Salvage after CR: n=11 (31%)
≥ Second salvage: n=7 (19%)

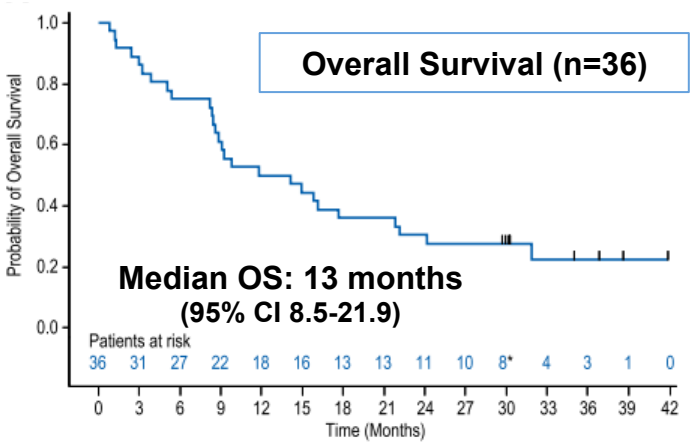
Response to treatment

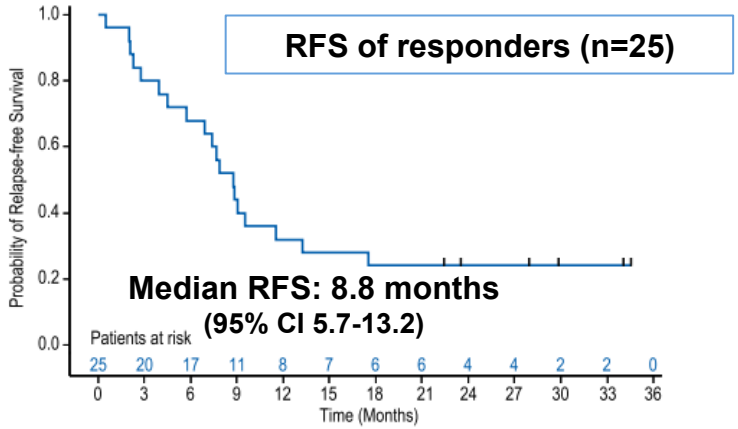
All patients: n=36	N°	% (95% CI)
Overall CR	25	69 (52-84)
CR	15	42 (26-59)
CRh	10	28 (14-45)
MRD response	22	88
End of cycle one	18	72
No MRD response	3	12

After CR/CRh 13 patients underwent allo-HSCT

Long-term survival

(Median follow-up: 32 months)





HSCT= hematopoietic stem cell transplant
CR=complete remission; CRh=CR with partial hematological recovery

Topp MS, JCO 2014
Topp MS, Blood 2015

ALL patients in 1st CR

Impact of Minimal Residual Disease (MRD) in adult ALL patients

Multivariate Analysis of Prognostic Factors:

age, immunophenotype, risk group, molecular response

Endpoint	Multivariate analysis
CCR	**16w molecular response** HR 4.5, *P*<.0001
OS	**Age** HR 1.3, *P*=.007
OS	**16w molecular response** HR 4, *P*<.0001

Gökbudget N et al, Blood 2012
German Multicenter Study Group for GMALL