CITTA' DI SAN GIOVANNI ROTONDO RETE CIVICA 2.0 · GITMO · Rete Ematologica Pugliese · SIE "Società Italiana di Ematologia" · fondazione GIMEMA onlus

"Real World Evidence"

Nuovi target terapeutici in ematologia

Presidente del Convegno
Nicola Cascavilla

Auditorium "Fra Agostino Daniele"
San Giovanni Rotondo
8 - 9 Novembre 2018

Blinatumumab, Inotuzumab e LLA: l'esperienza real world della REP

Lorella Melillo

High CR rates are seen after front-line therapy in adults with ALL, but relapse is common

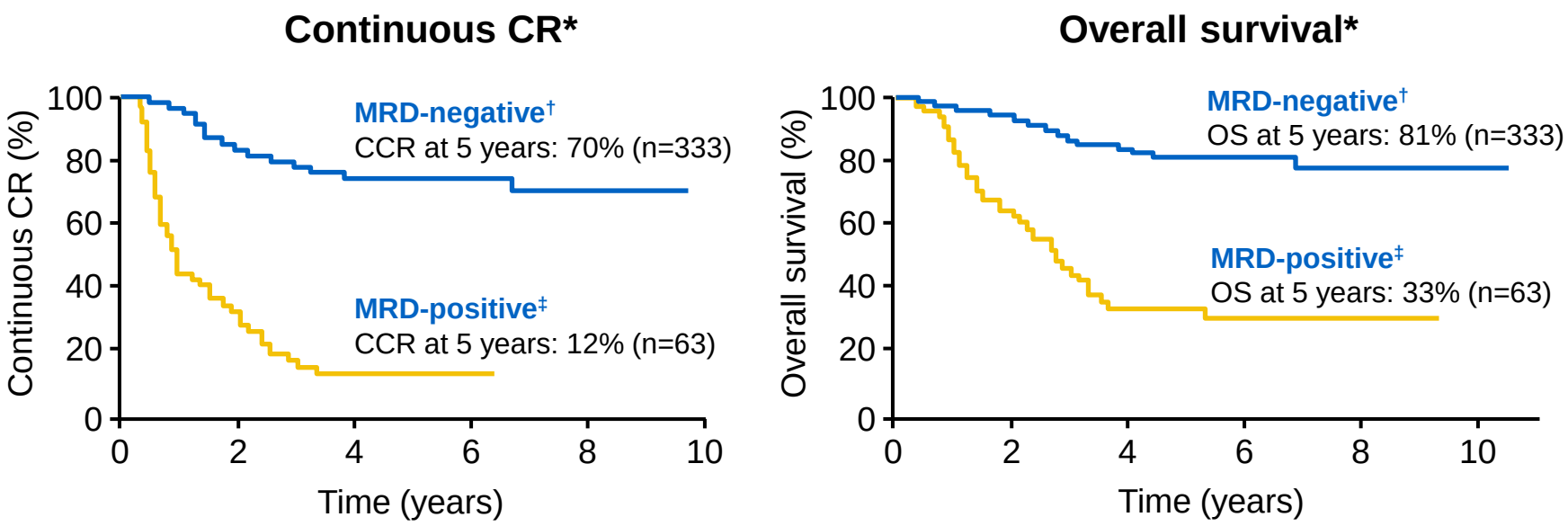
Study	Year	N	Median age, years	CR rate, %	OS, % at year
CALGB 9111	1988	198	35	85	50%, 3 years
SWOG 8417/8419	2001	353	32	62	35%, 8 years
NILG 08/96	2001	121	35	84	48%, 3 years
JALSG 93	2002	263	31	78	30%, 6 years
Sweden	2002	153	42	86	28%, 5 years
GIMEMA 02/86	2002	767	28	82	27%, 9 years
MDACC	2004	288	40	92	38%, 5 years
EORTC ALL3	2004	340	33	74	36%, 6 years
LALA 94	2004	922	33	84	36%, 5 years
GOELAL 02	2004	198	33	86	41%, 6 years
PETHEMA ALL-93	2005	222	27	82	34%, 5 years
GMALL 07	2007	713	34	89	54%, 5 years
MRC-ECOG	2008	1646	NRP	90	39%, 5 years

CR, complete response; NRP, not reported; OS, overall survival

Bassan R, et al. *J Clin Oncol* 2011;29:532–43.

MRD-negativity is a marker of improved outcome following induction therapy in adult ALL

Impact of MRD status at Week 16 on response in Ph-negative adult ALL patients following induction/consolidation therapy



Patients MRD-negative at Week 16 had significantly higher probability of CCR and OS at 5 years (P<0.0001 for both endpoints) than those who remained MRD-positive. Achievement of MRD negativity is therefore a potentially useful clinical endpoint

*Patients with HSCT in CR1 excluded;
†MRD-negativity with an assay sensitivity of ≥10^{-4};
‡Persistent quantifiable MRD positivity within the quantitative range (≥10^{-4});
CCR, continuous CR; MRD, minimal residual disease; Ph, Philadelphia chromosome; HSCT, Haematopoietic stem cell transplant

Adapted from Gökbuget N, et al. *Blood* 2012;120:1868–76.

Relapse/refractory rate in 2015 was projected to be around 50% in adult Ph-negative B-ALL

Projected incidence range of adult B-lineage ALL in the US and EU in 2015

	US	EU5*
B-lineage ALL *80% of adult ALL*	1720–1900	1540–1700
Precursor B-cell (BCP) ALL *75% of adult ALL*	1610–1780	1440–1600
Ph-negative BCP-ALL *77% of B-cell adult ALL*	1240–1370	1120–1230
Relapsed/refractory (r/r) after 1st line chemotherapy *~50% of Ph-negative adult BCP-ALL*	620–685	560–615

*Combined incidence ranges from ‘European Union Five’ countries (France, Germany, Italy, Spain and UK)

Katz AJ, et al. *Cancer Causes Control* 2015;26:1627–42.

EUROPEAN HEMATOLOGY ASSOCIATION
Ferrata Storti Foundation

Haematologica 2016
Volume 101(12):1524-1533

International reference analysis of outcomes in adults with B-precursor Ph-negative relapsed/refractory acute lymphoblastic leukemia

Nicola Gökbuget,[1] Hervè Dombret,[2] Jose-Maria Ribera,[3] Adele K. Fielding,[4] Anjali Advani,[5] Renato Bassan,[6] Victoria Chia,[7] Michael Doubek,[8] Sebastian Giebel,[9] Dieter Hoelzer,[1] Norbert Ifrah,[10] Aaron Katz,[7] Michael Kelsh,[7] Giovanni Martinelli,[11] Mireia Morgades,[3] Susan O'Brien,[12] Jacob M. Rowe,[13] Julia Stieglmaier,[14] Martha Wadleigh[15] and Hagop Kantarjian[12]

[1]University Hospital, Goethe University, Frankfurt, Germany; [2]Hôpital Saint-Louis, Paris, France; [3]ICO-Hospital Germans Trias I Pujol, Jose Carreras Research Institute, Barcelona, Spain; [4]UCL Cancer Institute, London, UK; [5]Cleveland Clinic, Ohio, USA; [6]UOC Ematologia, Ospedale dell'Angelo, Mestre-Venezia, Italy; [7]Center for Observational Research, Amgen, USA; [8]University Hospital, Brno, Czech Republic; [9]Maria Sklodowska Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland; [10]Center Hospitalier Universitaire, Angers, France; [11]Policlinico Sant'Orsola, Istituto Seragnoli, Bologna, Italy; [12]University of Texas, MD Anderson Cancer Center, Houston, USA; [13]Rambam Medical Center, Haifa, Israel; [14]Clinical Development, Amgen, Germany and [15]Dana Farber Cancer Institute, Boston, Massachusetts, USA

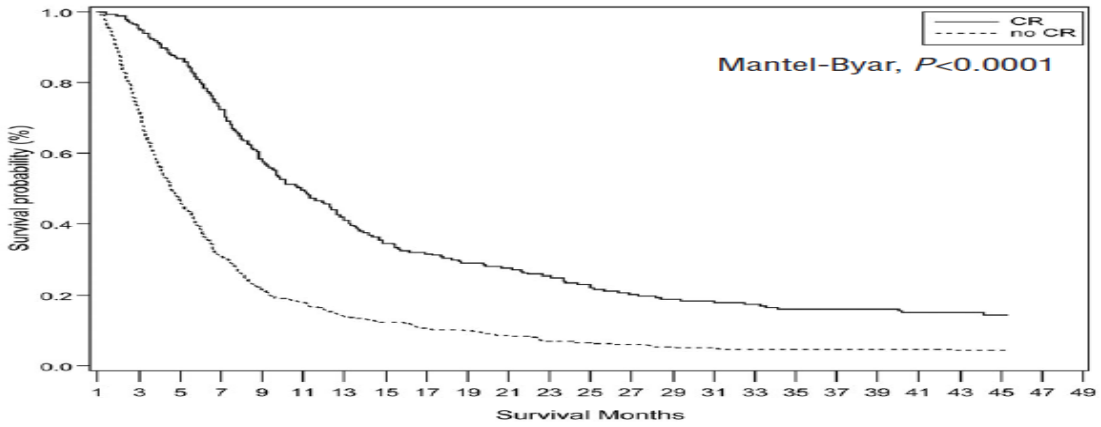


Figure 3. Overall survival by CR status among adult Ph-negative relapsed/refractory B-precursor ALL patients in first salvage. The CR survival curve includes only those patients who achieved CR with the first salvage therapy. Patients who achieved CR but for whom no date of CR was available were excluded from the analysis. Survival between groups is assessed beginning at 36 days after the start of first salvage (the median time to CR) and therefore patients who died or whose data were censored before 36 days are not included in the comparison. At 36 days, 137 patients had achieved CR with first salvage and 563 patients had not. Thirty patients who achieved CR with first salvage and 17 patients who did not remained alive and uncensored at 4 years.

Historical results in R/R BCP-ALL

An international survey

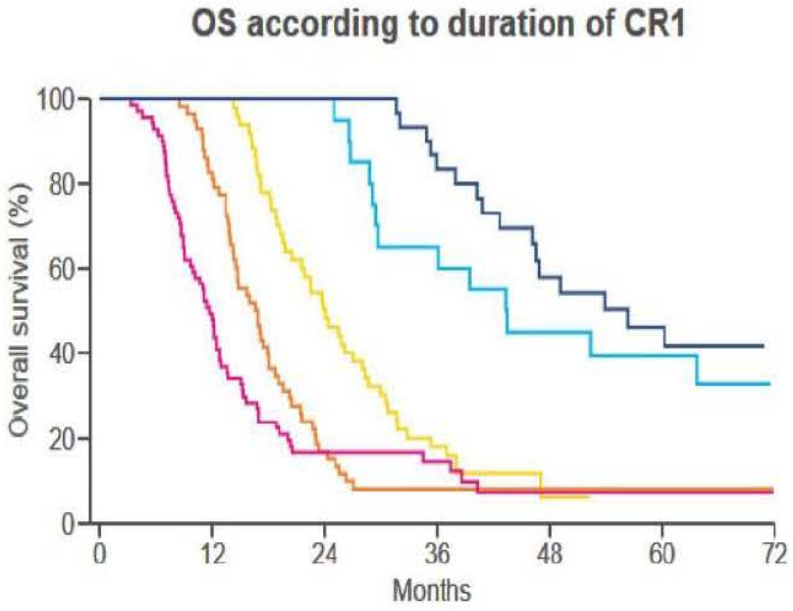
- Poor prognosis among adults with R/R acute lymphoblastic leukaemia treated with standard of care (SOC) chemotherapy
- Prognostic factors for a better outcome:
  - Younger age and lower WBC at primary diagnosis
  - Longer duration of first remission
  - Salvage 1 vs Salvage 2–3
  - No prior allogeneic HSCT
  - Possibility of performing allogeneic HSCT after salvage
  - More recent period primary (diagnosis from 2005 onward)

N=1706 Ph-negative R/R ALL	No prior salvage (S1)	One prior salvage (S2)	Two or more prior salvages (S3)
Complete remission rate (95% CI)	40% (37%–44%)	21% (16%–26%)	11% (6%–18%)
Median OS, months (95% CI)	5.8 (5.5–6.2)	3.4 (2.8–4.2)	2.9 (2.6–3.4)

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

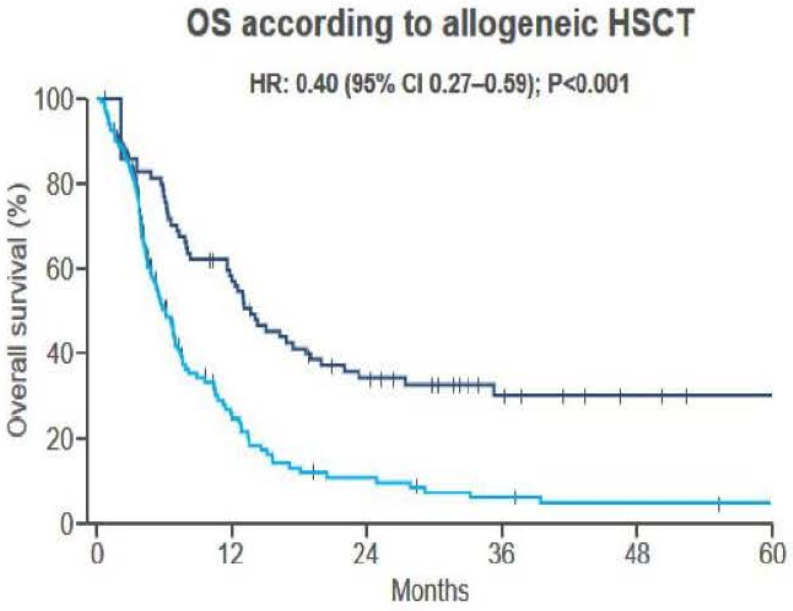
Younger adults with ALL in first relapse (GRAALL data)

Impact of CR1 duration



Patients at risk:							
<6 months	71	33	12	7	3	2	2
6–12 months	58	47	10	3	2	2	2
12–18 months	50	50	25	9	1	0	0
18–24 months	20	20	20	13	9	6	4
≥24 months	30	30	30	24	15	11	9

Impact of post-relapse HSCT



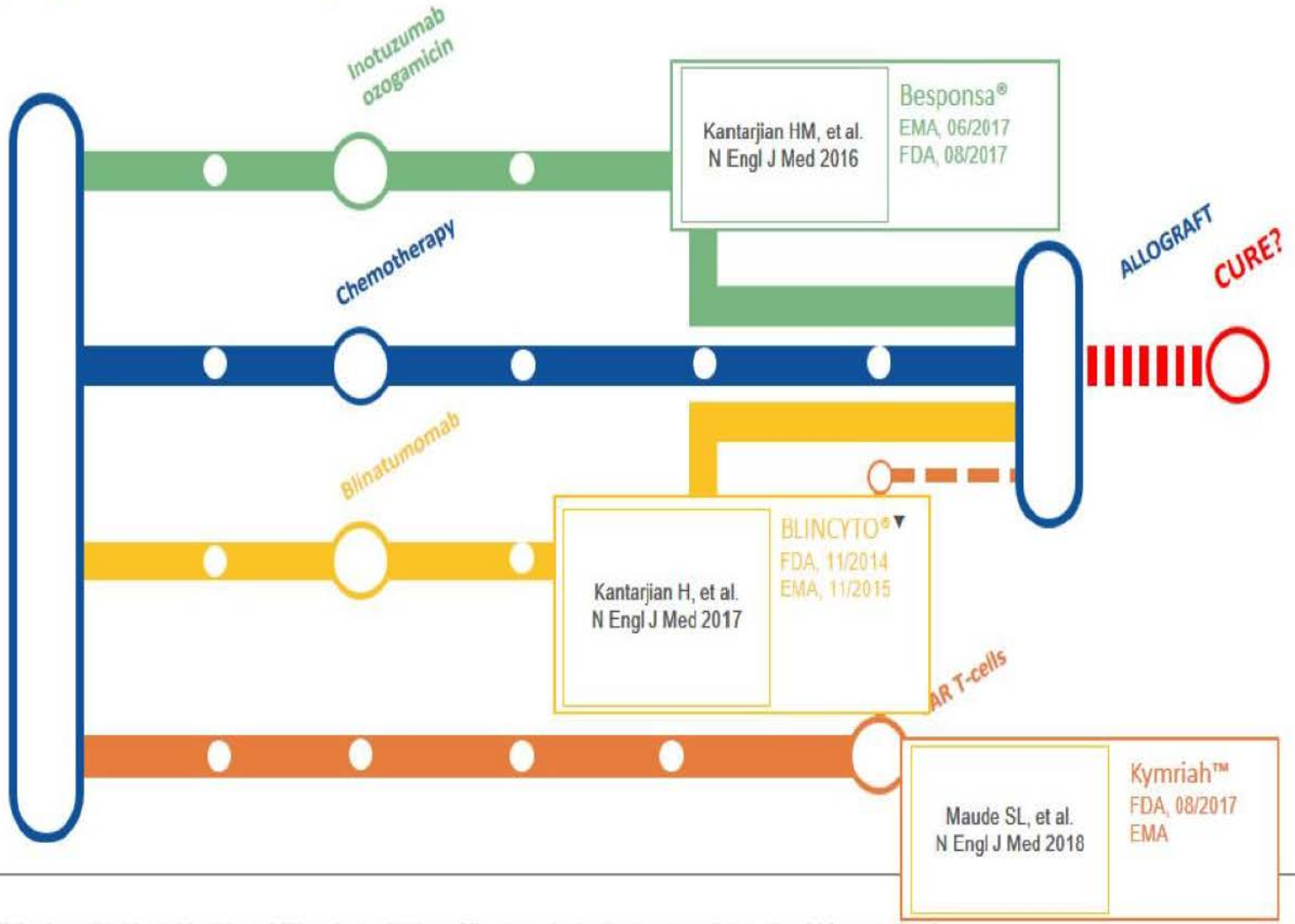
Patients at risk:						
No HSCT	194	24	10	5	3	2
HSCT	0	44	23	12	7	5

Adapted from Desjonquères A, et al. Blood Cancer J 2016;6:e504.

CI, confidence interval; HR, hazard ratio.

The journey of a patient with R/R BCP-ALL

Newly approved therapies



▼This medicinal product is subject to additional monitoring. All suspected adverse reactions should be reported.

Three R/R BCP-ALL studies

Patient populations

Experimental arms	INO-VATE[1] Phase 3 Inotuzumab ozogamicin (INO) CD22	TOWER[2,3] Phase 3 Blinatumomab CD19	ELIANA[4] Phase 2 Tisagenlecleucel CD19
Patients, N	109	271	75
Median age	**47 years**	**37 years**	**11 years (3–23)**
Age ≥55 years, N (%)	43 (39%)	67 (25%)	0 (0%)
Overt ALL, %	100%	100%	100% (at screening)
Ph+ ALL, N (%)	14 (13%)	0 (0%)	NR
First salvage, N (%)	**73 (67%)**	**114 (42%)**	**NR**
Prior allogeneic HSCT, N (%)	**17 (16%)**	**94 (35%)**	**46 (61%)**

The patient populations in the 3 studies differ, therefore the outcomes cannot be directly compared

1. Kantarjian HM, et al. N Engl J Med 2016;375:740–53; 2. Topp MS, et al. EHA 2016; Abstract S149 and oral presentation;
3. Kantarjian H, et al. N Engl J Med 2017;376:836–47; 4. Maude SL, et al. N Engl J Med 2018;378:439–48.

NR, not reported.

Incorporating Immunotherapy Into the Treatment Strategies of B-Cell Adult Acute Lymphoblastic Leukemia: The Role of Blinatumomab and Inotuzumab Ozogamicin

Hagop Kantarjian, MD, and Elias Jabbour, MD

OVERVIEW

TABLE 1. Blinatumomab Activity in Acute Lymphoblastic Leukemia

	Ph-Positive	Ph-Negative		Positive MRD
Parameter	Pivotal Phase II (ALCANTARA)	Confirmatory Phase II	Tower Phase III	BLAST Phase II
No. of Patients	45	189	271	116
CR/CRh/ CRi, %	36	43	45	NA
MRD* negativity, %	88	82	76	78
OS, median, mo	7.1	6.1	7.7	36

TOWER Phase 3 study design

Patients ≥18 years with R/R Ph-negative pre-B ALL:

- Refractory to intensive combination chemotherapy (initial or salvage)
- Untreated first relapse (remission <12 months)
- Untreated second or greater relapse
- Relapse at any time after allo-HSCT

2:1 randomisation (N=405)

Stratified by age, prior salvage and prior allo-HSCT

Blinatumomab* (n=271)

- Continuous infusion; 4 weeks on, 2 weeks off; 9 µg/day for 7 days, then 28 µg/day during weeks 2–4
- Then continuous infusion; 4 weeks on, 8 weeks off; 28 µg/day

SC chemotherapy (n=134)

Investigator choice:

- FLAG ± anthracycline; HiDAC-based; high-dose MTX-based; or clofarabine-based

- **Primary endpoint:** OS
- **Key secondary endpoints:** CR in induction; CR/CRh/CRi in induction; EFS
- **Other secondary:** Duration of CR, molecular remission, allo-HSCT realisation, AEs

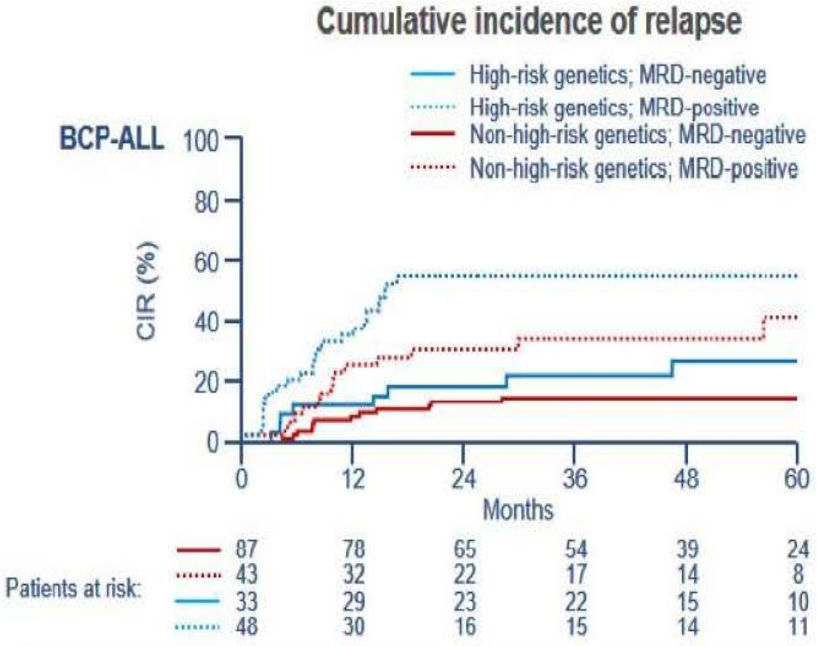
The **induction phase** consisted of two cycles of assigned protocol-specified therapy. The **consolidation phase** consisted of three cycles of assigned protocol-specified therapy in patients who achieved a bone marrow response at the end of the induction phase;
*Dexamethasone was given pre-dose to prevent cytokine-release syndrome.

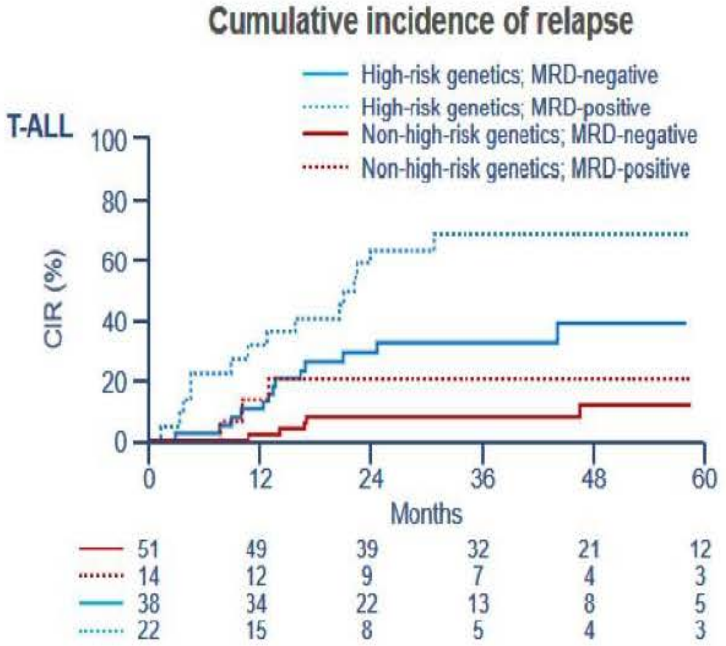
Kantarjian H, et al. N Engl J Med 2017;376:836–47.

Independent value of MRD and genetics

The GRAALL study

- Post-induction MRD at the 10^{-4} cut-off
- High-risk genetic features:
  - *KMT2A* rearrangement and/or focal *IKZF1* deletion in BCP-ALL
  - No *NOTCH1/FBXW7* mutation and/or *N/KRAS* mutation or *PTEN* anomaly in T-ALL





Adapted from Beldjord K, et al. Blood 2014;123:3739–49.

BLAST Phase 2 study design

Blinatumomab for MRD+ BCP-ALL patients

MRD+ BCP-ALL

Transplantable and non-transplantable patients

Blinatumomab
15 μg/m²/day cIV over 4 weeks
with up to 3 consolidation cycles

Primary endpoint

Proportion of patients achieving a CMR in the first cycle
i.e. MRD negative
(minimum sensitivity 10^{-4})

MRD eligibility

- Patients in haematological CR with detectable MRD, defined as a level of $\geq 10^{-3}$ in an assay with a minimum sensitivity of 10^{-4}
- In molecular failure/relapse after a minimum of 3 blocks of intensive chemotherapy

MRD evaluation

- A reference lab confirmed MRD status at inclusion by quantitative PCR according to standardised methodology
- MRD response was analysed solely in the reference lab

Gökbuget N, et al. Blood 2018;131:1522–31.

CMR, complete MRD response.

blood®

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia

Nicola Gökbuget,[1] Hervé Dombret,[2] Massimiliano Bonifacio,[3] Albrecht Reichle,[4] Carlos Graux,[5] Christoph Faul,[6] Helmut Diedrich,[7] Max S. Topp,[8] Monika Brüggemann,[9] Heinz-August Horst,[9] Violaine Havelange,[10] Julia Stieglmaier,[11] Hendrik Wessels,[11] Vincent Haddad,[12] Jonathan E. Benjamin,[13] Gerhard Zugmaier,[11] Dirk Nagorsen,[13] and Ralf C. Bargou[14]

[1]University Hospital, Frankfurt, Germany; [2]University Hôpital Saint-Louis, Assistance Publique-Hôpitaux de Paris, University Paris Diderot, Paris, France; [3]Department of Medicine, Section of Hematology, Verona University, Verona, Italy; [4]University Hospital Regensburg, Regensburg, Germany; [5]Université Catholique de Louvain, CHU UCL Namur (Godinne), Yvoir, Belgium; [6]University Hospital and Comprehensive Cancer Center Tübingen, Universitätsklinikum Tübingen, Tübingen, Germany; [7]Department of Hematology and Oncology, Medizinische Hochschule, Hannover, Germany; [8]Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany; [9]Klinik für Innere Medizin II, Universitätsklinikum Schleswig-Holstein, Kiel, Germany; [10]Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; [11]Amgen Research (Munich), GmbH, Munich, Germany; [12]Amgen, Ltd., Cambridge, United Kingdom; [13]Amgen, Inc., Thousand Oaks, CA; and [14]Comprehensive Cancer Center Mainfranken, Uniklinikum Würzburg, Würzburg, Germany

KEY POINTS

- Among adults with MRD-positive ALL in hematologic remission after chemotherapy, 78% achieved a complete MRD response with blinatumomab.
- Complete MRD response after blinatumomab treatment in this population was associated with significantly improved OS.

Table 2. Overall long-term outcomes and by MRD complete response and nonresponse in cycle 1 (key secondary end point full analysis set)

	All patients	MRD responders*	MRD nonresponders*
OS			
Patients with events, n/N	48/110	31/85	14/22
Median† (95% CI)	36.5 (19.8-NR)	38.9 (33.7-NR)	12.5 (3.2-NR)
Estimated probability at 18 months (95% CI)†	0.67 (0.58-0.75)	0.70 (0.59-0.79)	0.34 (0.15-0.54)
P‡	—	.002	
Hematologic RFS			
Patients with events, n/N	62/110	40/85	12/15
Median† (95% CI)	18.9 (12.3-35.2)	23.6 (17.4-NR)	5.7 (1.6-13.6)
Estimated probability at 18 months (95% CI)†	0.53 (0.44-0.62)	0.58 (0.46-0.68)	0.20 (0.05-0.42)
P‡	—	.002	
Duration of hematologic remission§			
Patients with events, n/N	38/110	23/85	7/15
Median† (95% CI)	NR (NR-NR)	NR (NR-NR)	NR (3.7-NR)
Estimated probability at 18 months (95% CI)†	0.70 (0.61-0.78)	0.77 (0.67-0.85)	0.53 (0.30-0.80)
P¶	—	.14	

ı, patients with events (deaths for OS, death in CR, or relapse for RFS and relapse for duration of hematologic remission); N, patients at risk; NR, not reached.

‡Landmark analysis includes patients in both the key secondary full analysis set and the primary end point analysis set and excludes patients with an event (death or relapse) or censored before day 45.

·Kaplan-Meier estimate.

:Log-rank test *P* value compared with MRD nonresponders.

¡Duration of hematologic remission is evaluated by 1 − cumulative incidence function of hematologic relapse with death in CR as a competing event.

¶Gray's test *P* value compared with MRD nonresponders.

FDA approval for MRD+ ALL

March 2018

- Accelerated FDA approval to blinatumomab for the treatment of adult and paediatric patients with BCP-ALL who are in remission but still have MRD [1]

Based on the results of two Phase 2 studies

- The BLAST study (116 patients) [2]
- The pilot MT103-202 study (21 patients) [3]

1. FDA press release. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm603151.htm (accessed June 2018);
2. Gökbuget N, et al. Blood 2018;131:1522–31; 3. Topp MS, et al. J Clin Oncol 2011;29:2493–98.

Blinatumomab for MRD+ ALL in CR1 or beyond CR1 (no prior allo-HSCT): BLAST trial (n=116)

Primary endpoint efficacy set (n=103)*	Patients, n (%)	Molecular CR rate, n (%)
Age range (y)	18–76	
Evaluable patients	103	91 (88)
After 1 cycle of blinatumomab	103	82 (80)
CR1 patients	66	55 (83)
MRD level at baseline		
$\geq 10^{-2}$	52	42 (81)
$\geq 10^{-3}$ to $<10^{-2}$	51	40 (78)
BCR-ABL	4	3 (75)
t(4;11)/*KMT2A-AFF1*	4	2 (50)

- 74/110 patients had post-blinatumomab allo-HSCT (67%)
  - Similar overall survival as no HSCT patients (P = NS)

*Patients in haematological CR and with MRD $>10^{-3}$ at baseline.

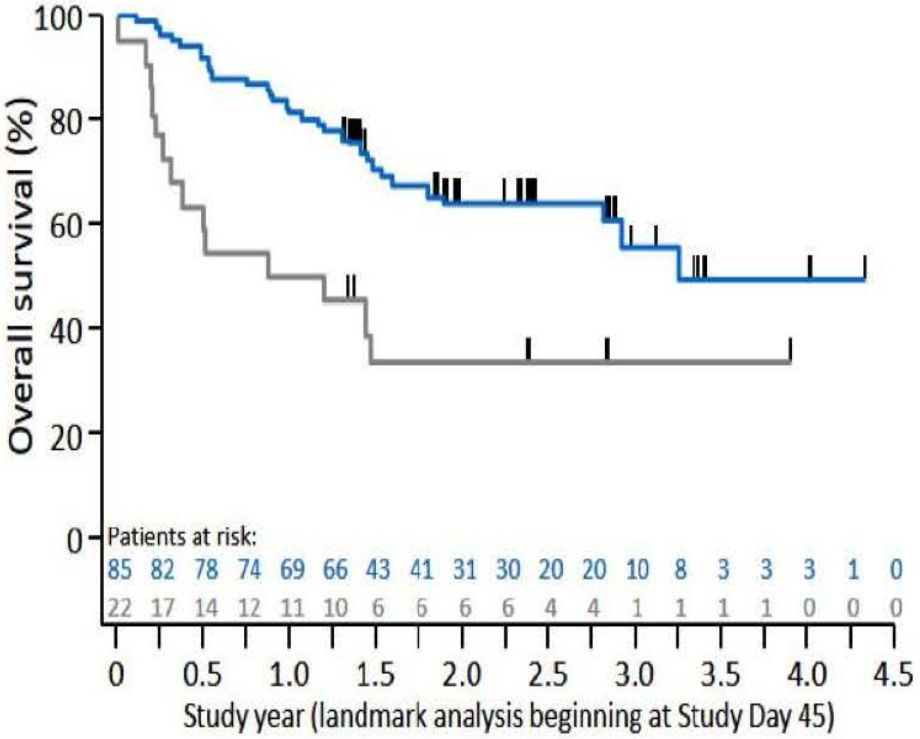
Gökbuget N, et al. Blood 2018;131:1522–31.

BLAST trial (n=116)

OS by MRD response during Cycle 1*

	n	Median OS (95% CI)
MRD complete responder at Cycle 1	85	**38.9** (33.7–NR)
MRD non-responder at Cycle 1	22	**12.5** (3.2–NR)

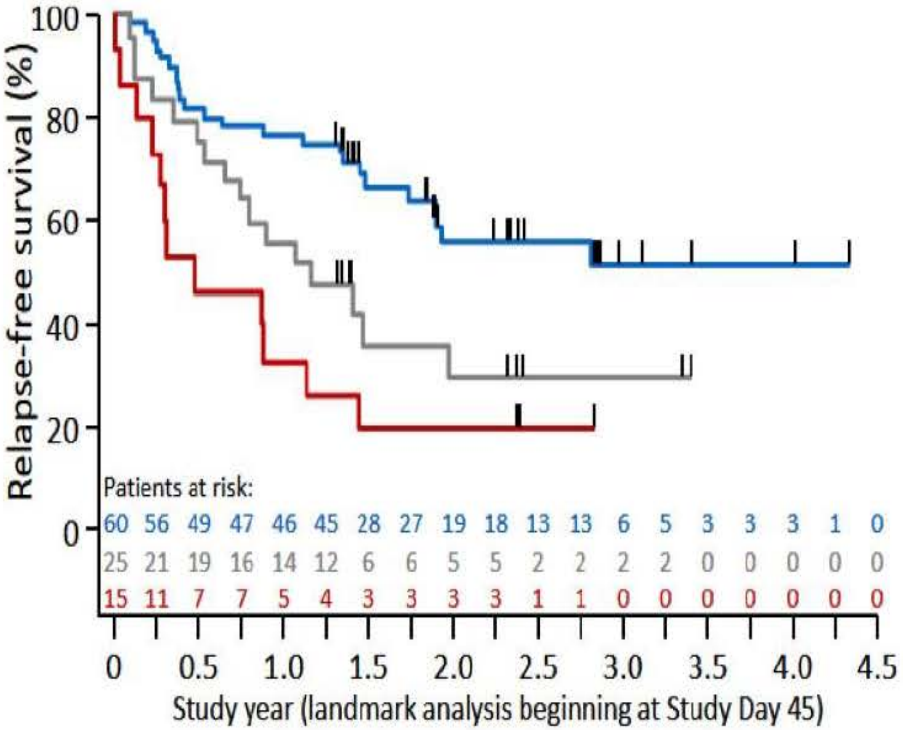
Hazard ratio (95% CI): **2.63** (1.40–4.96); P=0.002



RFS by remission status at screening and responder status*

	n	Median RFS (95% CI)
MRD responder at Cycle 1 in 1st CR	60	**NR** (20.8–NR)
MRD responder at Cycle 1 in 2nd or 3rd CR	25	**13.9** (7.8–NR)
MRD non-responder at Cycle 1	15	**5.7** (1.6–13.6)

Hazard ratio (95% CI) for 2 vs 1: **2.02** (1.07–3.81); for 3 vs 1: **3.34** (1.66–6.71); P=0.001



*Without censoring at allogeneic HSCT and post-blinatumomab chemotherapy.

Gökbuget N, et al. Blood 2018;131:1522–31.

VOLUME 35 · NUMBER 16 · JUNE 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Complete Hematologic and Molecular Response in Adult Patients With Relapsed/Refractory Philadelphia Chromosome–Positive B-Precursor Acute Lymphoblastic Leukemia Following Treatment With Blinatumomab: Results From a Phase II, Single-Arm, Multicenter Study

Giovanni Martinelli, Nicolas Boissel, Patrice Chevallier, Oliver Ottmann, Nicola Gökbuget, Max S. Topp, Adele K. Fielding, Alessandro Rambaldi, Ellen K. Ritchie, Cristina Papayannidis, Lulu Ren Sterling, Jonathan Benjamin, and Anthony Stein

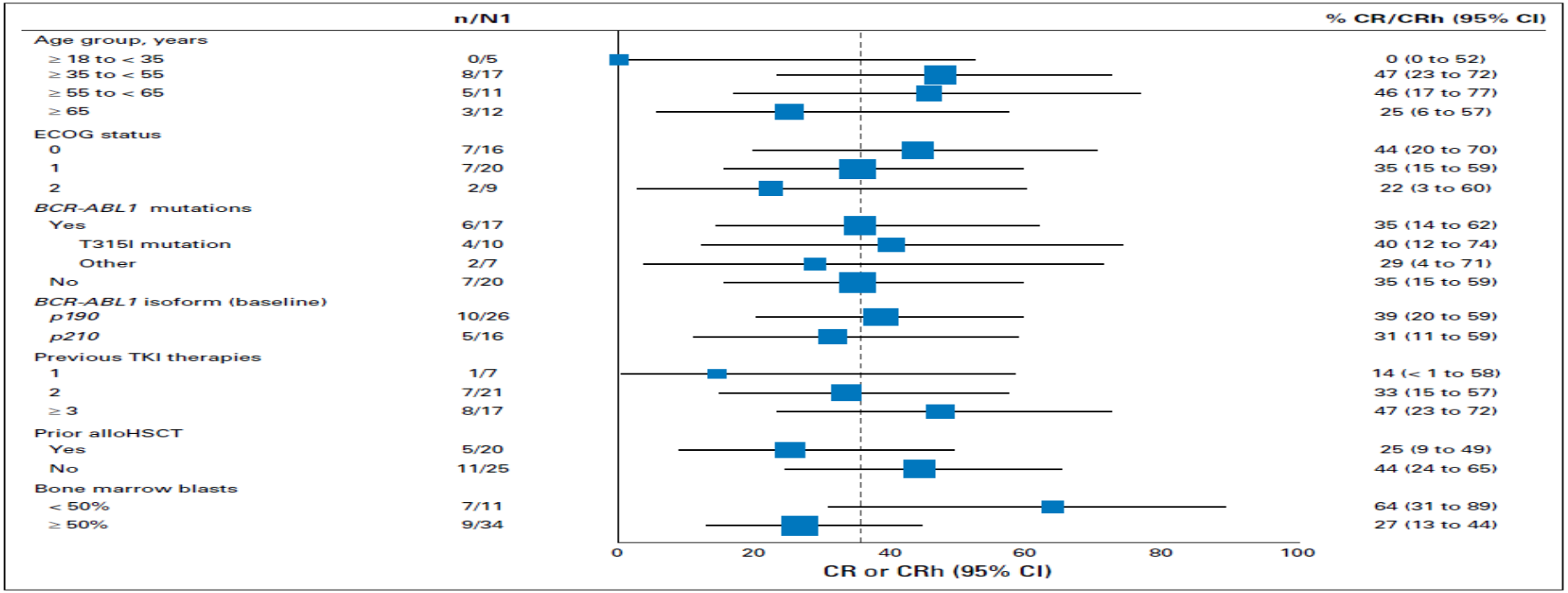
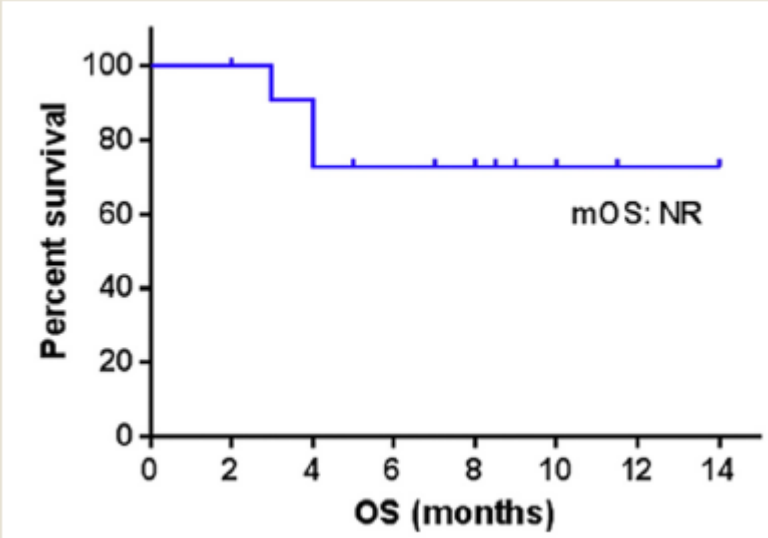


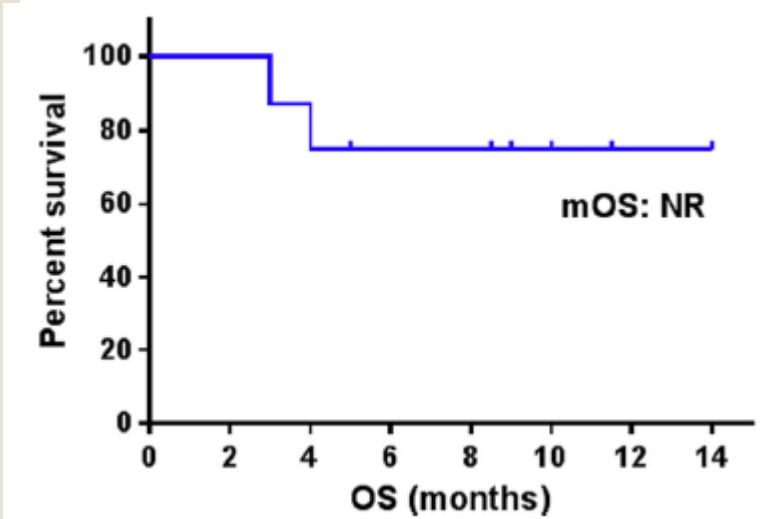
Fig 1. Overall responses (complete remission/complete remission with partial hematologic recovery [CR/CRh]) during the first two treatment cycles among prespecified patient subgroups. The dashed line represents the point estimate for CR/CRh for the entire patient population, and the box size indicates the relative population weight. n/N1, number of responders/total number of patients with evaluable responses within each category. alloHSCT, allogeneic hematopoietic stem-cell transplantation; ECOG, Eastern Cooperative Oncology Group; TKI, tyrosine kinase inhibitor.

Safety and Efficacy of Blinatumomab in Combination With a Tyrosine Kinase Inhibitor for the Treatment of Relapsed Philadelphia Chromosome-positive Leukemia

Rita Assi, Hagop Kantarjian, Nicholas J. Short, Naval Daver, Koichi Takahashi, Guillermo Garcia-Manero, Courtney DiNardo, Jan Burger, Jorge Cortes, Nitin Jain, William Wierda, Salim Chamoun, Marina Konopleva, Elias Jabbour

Figure 1 OS of Patients Treated With Blinatumomab and All Tyrosine Kinase Inhibitors (Top, n = 12) and Those Treated With Blinatumomab and Ponatinib (Bottom, n = 8). In Both Cases, the mOS was Not Reached (NR)





Incorporating Immunotherapy Into the Treatment Strategies of B-Cell Adult Acute Lymphoblastic Leukemia: The Role of Blinatumomab and Inotuzumab Ozogamicin

Hagop Kantarjian, MD, and Elias Jabbour, MD

OVERVIEW

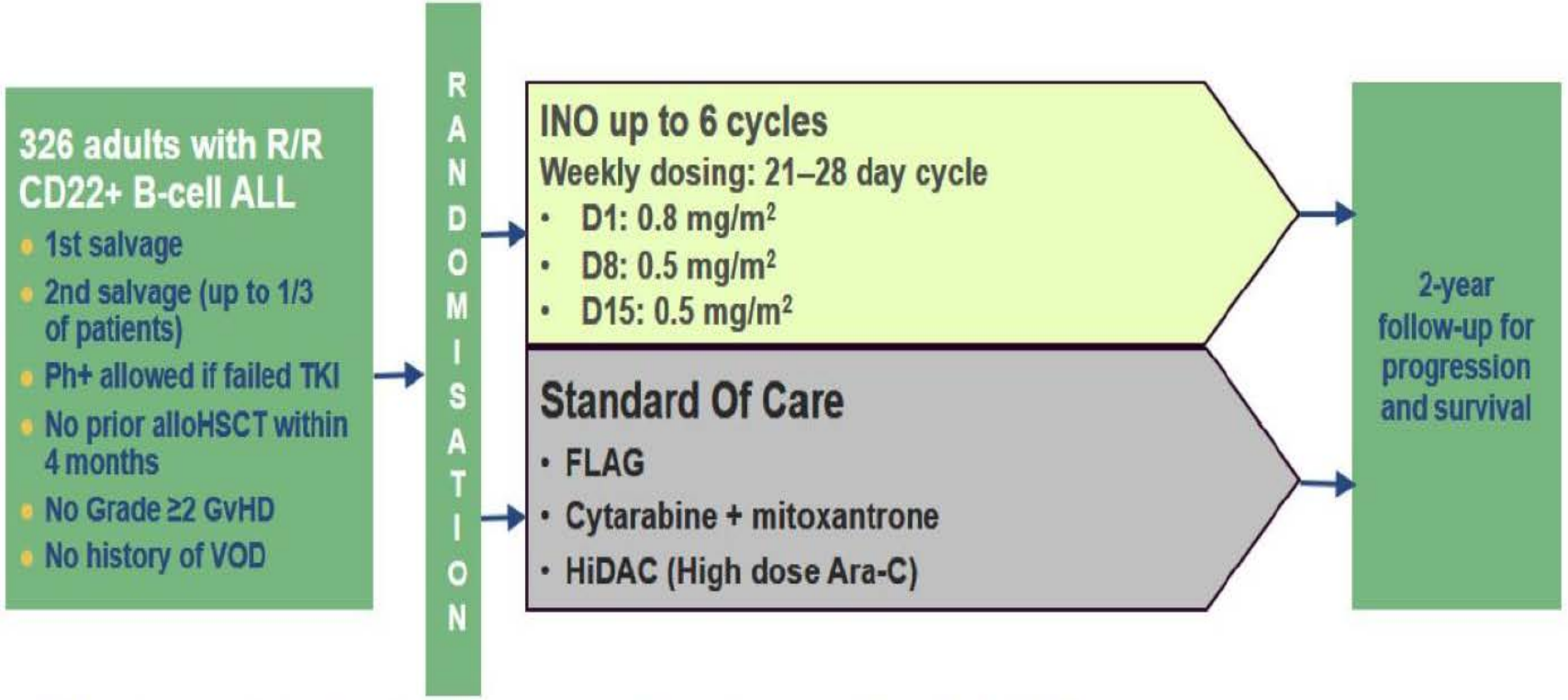
KANTARJIAN AND JABBOUR

TABLE 2. Inotuzumab Ozogamicin Activity in Acute Lymphoblastic Leukemia

Parameter	Single Dose Phase II	Weekly Dose Phase II	Weekly Dose Multicenter Phase II	INO-VATE Phase III	INO + Mini-Hyper-CVD R/R	INO + Mini-Hyper-CVD Frontline Elderly
No. of patients	49	41	35	109	70	52
INO dose/schedule	1.8 mg/m² D1 q 3–4 weeks	0.8 mg/m² D1	0.8 mg/m² D1	0.8 mg/m² D1	1.3–1.8 mg/m² in cycle 1 followed by 1.0–1.3 mg/m² for cycles 2–4	1.3–1.8 mg/m² in cycle 1 followed by 1.0–1.3 mg/m² for cycles 2–4
		0.5 mg/m² D8, 15	0.5 mg/m² D8, 15	0.5 mg/m² D8, 15		
Results						
ORR, %	57	59	68	88	77	97
CR, %	18	20	31	36	59	80
MRD negativity, %	68	71	84	78	81	96
Median survival, mo	5	7.3	7.4	7.7	11	Not reached

INO-VATE Phase 3 study

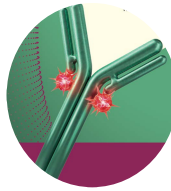
R/R CD22+ BCP-ALL



- INO reduced to 1.5 mg/m²/cycle once the patient achieved CR/CRi
- 2 co-primary endpoints: CR (CR + CRi) and OS

Kantarjian HM, et al. N Engl J Med 2016;375:740–53.

Take home messages: BESPONSA vs SOC



- Fewer hematological side effects
- Reduced hospitalisation
- Easy administration
- Improved QoL

DOUBLED 2-YEAR SURVIVAL RATE

(23%)

MORE PATIENTS PROCEEDING TO SCT

(40%)

HIGHER MRD NEGATIVITY RATE IN RESPONDERS

(80%)

HIGHER CR/CRi RATES

(80%)

Kantarjian HM *et al. N Engl J Med* 2016;375:740–753

CONCLUSION

After adjusting for heterogeneity in patient characteristics between the trial populations, blinatumomab exhibited a similar CR rate as InO and a potential survival benefit, with statistically significantly longer RMST at 12 months

Indirect treatment comparison of blinatumomab▼ vs inotuzumab ozogamicin for treating adult patients with relapsed or refractory acute lymphoblastic leukaemia receiving zero or one prior salvage therapy

Jinlin Song[1], Qiufei Ma[2], Wei Gao[1], Ze Cong[2], Jipan Xie[1], Zachary Zimmerman[2], Laura Belton[3], Janet Franklin[2], Stephen Palmer[4]

[1]Analysis Group, Inc., Boston, MA 02199, USA; [2]Amgen Inc., Thousand Oaks, CA 91320, USA; [3]LB Biostatistics, London, UK; [4]University of York, York, YO105DD, UK

Incorporating Immunotherapy Into the Treatment Strategies of B-Cell Adult Acute Lymphoblastic Leukemia: The Role of Blinatumomab and Inotuzumab Ozogamicin

Hagop Kantarjian, MD, and Elias Jabbour, MD

OVERVIEW

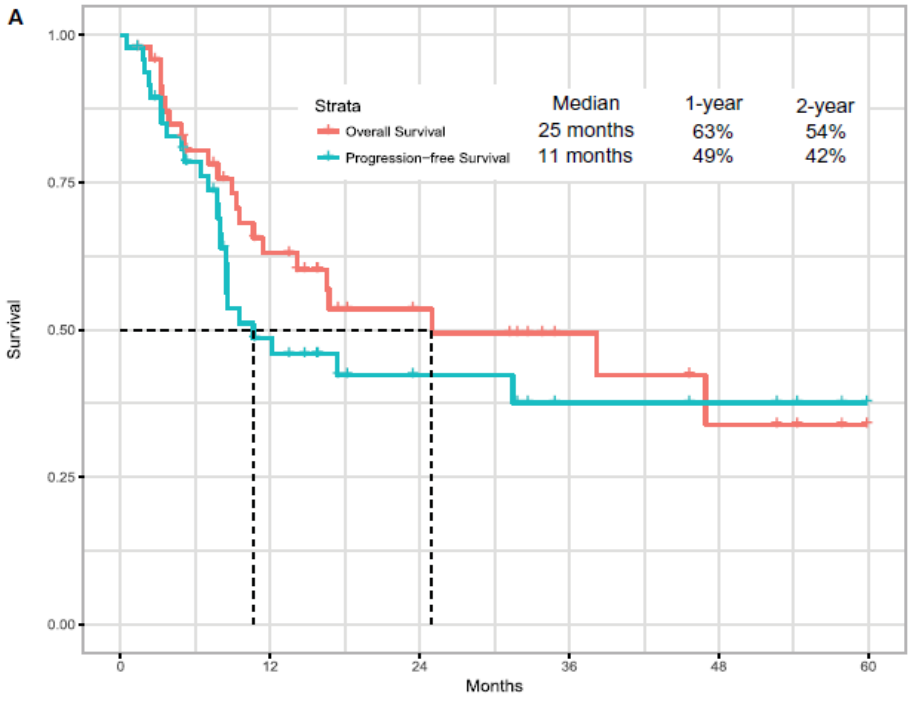
KANTARJIAN AND JABBOUR

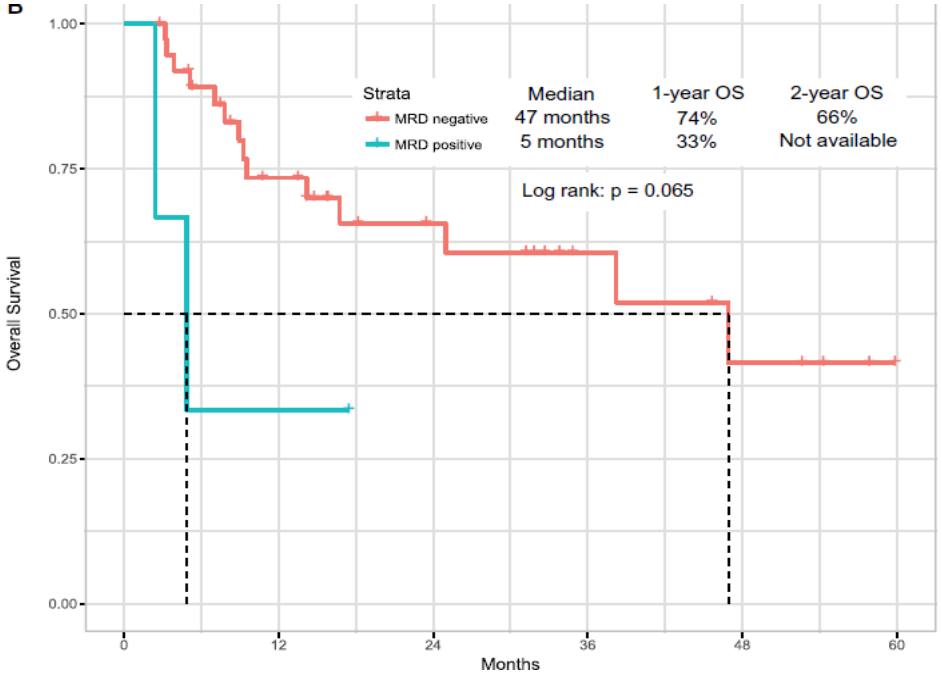
TABLE 2. Inotuzumab Ozogamicin Activity in Acute Lymphoblastic Leukemia

Parameter	Single Dose Phase II	Weekly Dose Phase II	Weekly Dose Multicenter Phase II	INO-VATE Phase III	INO + Mini-Hyper-CVD R/R	INO + Mini-Hyper-CVD Frontline Elderly
No. of patients	49	41	35	109	70	52
INO dose/schedule	1.8 mg/m² D1 q 3–4 weeks	0.8 mg/m² D1	0.8 mg/m² D1	0.8 mg/m² D1	1.3–1.8 mg/m² in cycle 1 followed by 1.0–1.3 mg/m² for cycles 2–4	1.3–1.8 mg/m² in cycle 1 followed by 1.0–1.3 mg/m² for cycles 2–4
		0.5 mg/m² D8, 15	0.5 mg/m² D8, 15	0.5 mg/m² D8, 15		
Results						
ORR, %	57	59	68	88	77	97
CR, %	18	20	31	36	59	80
MRD negativity, %	68	71	84	78	81	96
Median survival, mo	5	7.3	7.4	7.7	11	Not reached

Chemoimmunotherapy With Inotuzumab Ozogamicin Combined With Mini-Hyper-CVD, With or Without Blinatumomab, Is Highly Effective in Patients With Philadelphia Chromosome–Negative Acute Lymphoblastic Leukemia in First Salvage

Elias Jabbour, MD [1]; Koji Sasaki, MD, PhD [1]; Farhad Ravandi, MD[1]; Xuelin Huang, PhD[2]; Nicholas J. Short, MD[1]; Maria Khouri[1]; Partow Kebriaei, MD[3]; Jan Burger, MD[1]; Joseph Khoury, MD[4]; Jeffrey Jorgensen, MD, PhD[4]; Nitin Jain, MD[1]; Marina Konopleva, MD, PhD[1]; Guillermo Garcia-Manero, MD[1]; Tapan Kadia, MD [1]; Jorge Cortes, MD[1]; Jovitta Jacob, BS[1]; Kathryn Montalbano, RN[1]; Rebecca Garris, MS[1]; Susan O'Brien, MD[5]; and Hagop Kantarjian, MD [1]





Cancer,2018

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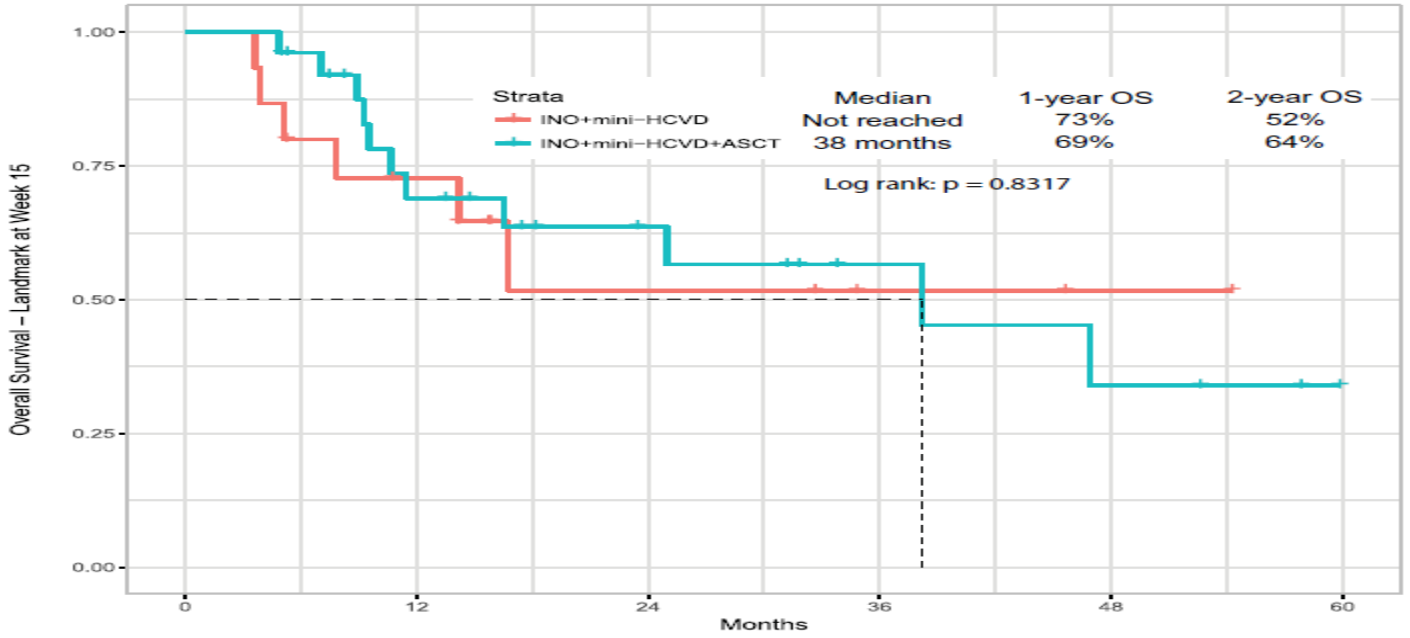

Cancer,2018

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Inotuzumab ozogamicin in combination with low-intensity chemotherapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia: a single-arm, phase 2 study

Hagop Kantarjian, Farhad Ravandi, Nicholas J Short, Xuelin Huang, Nitin Jain, Koji Sasaki, Naval Daver, Naveen Pemmaraju, Joseph D Khoury, Jeffrey Jorgensen, Yesid Alvarado, Marina Konopleva, Guillermo Garcia-Manero, Tapan Kadia, Musa Yilmaz, Gautam Bortakhur, Jan Burger, Steven Kornblau, William Wierda, Courtney DiNardo, Alessandra Ferrajoli, Jovitta Jacob, Rebecca Garris, Susan O'Brien, Elias Jabbour

Lancet Oncol 2018; 19: 240–48
Published Online
January 15, 2018
http://dx.doi.org/10.1016/S1470-2045(18)30011-1

Summary

Background Inotuzumab ozogamicin, an anti-CD22 monoclonal antibody bound to a toxin, calicheamicin, has shown single-agent activity in relapsed or refractory acute lymphoblastic leukaemia. We aimed to assess the activity and safety of inotuzumab ozogamicin in combination with low-intensity chemotherapy in older patients with acute lymphoblastic leukaemia.

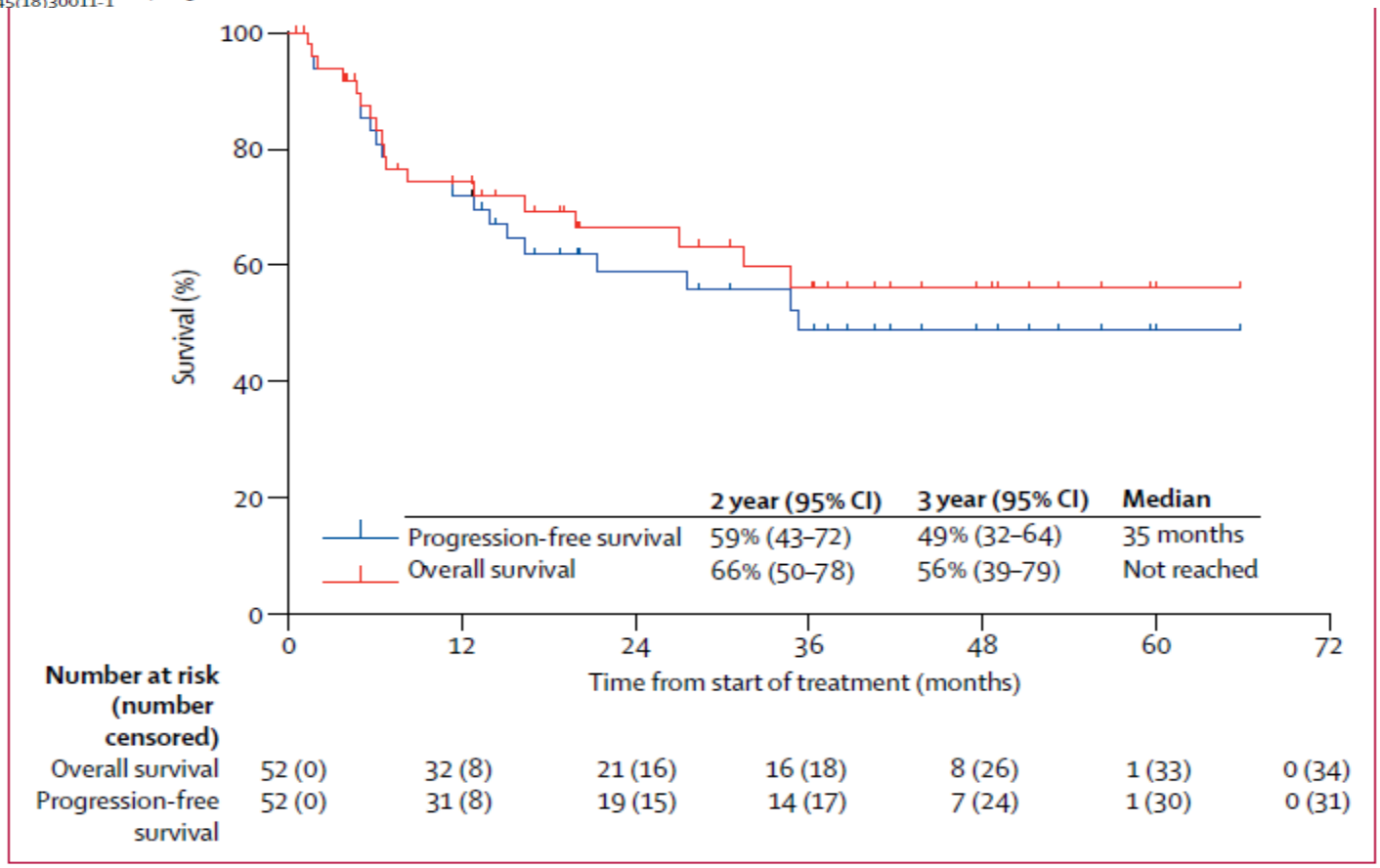


Figure 2: Progression-free and overall survival

Review Article

Toward the Potential Cure of Leukemias in the Next Decade

Hagop M. Kantarjian, MD; Michael J. Keating, MB, BS; and Emil J Freireich, MD

Historically, progress in leukemia research has been slow, but it has accelerated recently as a result of understanding the pathophysiology of leukemias and implementing more effective and targeted therapies. This review summarizes the progress across leukemia subsets and projects the potential cure of most leukemias in the next decade. ***Cancer* 2018;000:000-000**. © *2018 American Cancer Society.*

KEYWORDS: cure, leukemias, targeted, therapy, treatments.

INTRODUCTION

Young oncologists take for granted the steadfast progress toward the cure of leukemias in the past 2 decades. By contrast, leukemia research veterans, who have seen both sides of the leukemia research coin, are continually amazed at the major shifts in therapeutic research and improved outcomes of patients with different subsets of leukemia.

Progress in leukemia research has been historically slow and saccadic but accelerated recently as a result of better understanding of the pathophysiology of different leukemias. Hence, the subtle benefits that have accumulated over decades may have gone unnoticed by nonleukemia and younger oncologists. This review provides a state-of-the-art, high-level overview of progress in research across multiple leukemias for medical researchers and practitioners, within and outside the field of leukemia.

We divide the leukemias into 3 categories. The *easy leukemias* comprise 4 subsets in which progress has been substantial and we are close to an ideal curative therapy: hairy cell leukemia (HCL), acute promyelocytic leukemia (APL), core binding factor (CBF) leukemia, and chronic myeloid leukemia (CML). The *intermediate leukemias* are those undergoing a therapeutic revolution in slow motion: acute lymphocytic leukemia (ALL) and chronic lymphocytic leukemia (CLL). The third category includes the *more difficult leukemias*—acute myeloid leukemia (AML) and the related disorder myelodysplastic syndrome (MDS)—for which we believe there are finally important tools with curative potential.

Genetic landscape of Ph-like ALL

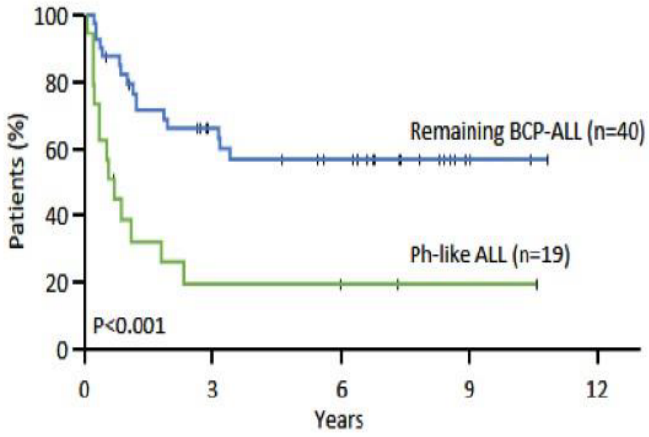
Subtype	Frequency
CRLF2-rearranged *JAK2* mutant	26.0%
CRLF2-rearranged *JAK2* WT	21.0%
Other mutations in JAK-STAT signalling	11.8%
ABL1-class rearrangements	11.5%
JAK2 rearrangements	6.9%
Ras mutations	5.7%
EPOR rearrangements	3.4%
Unknown alterations	13.7%

Adapted from Hunger SP, Mullighan CG. Blood 2015;125:3977–87.

Ph-like ALL outcome in adults

GMALL: 06/99 & 07/03[1]

DFS



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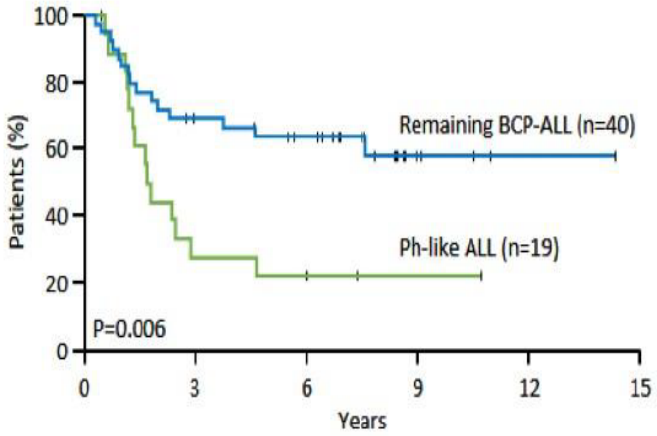
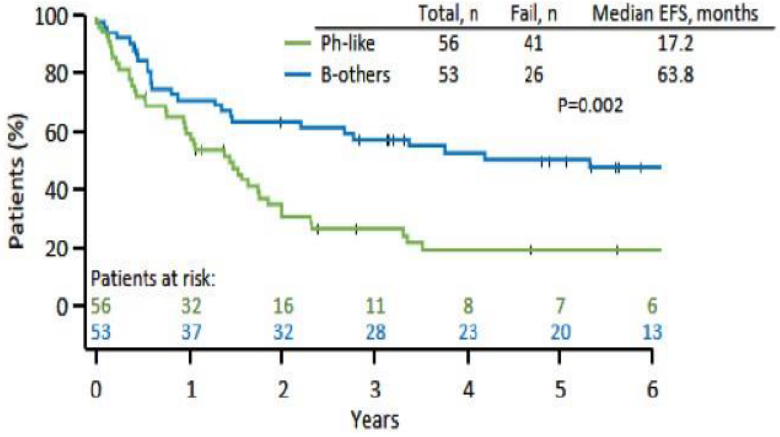


MDACC: HyperCVAD/A-BFM[2]

EFS



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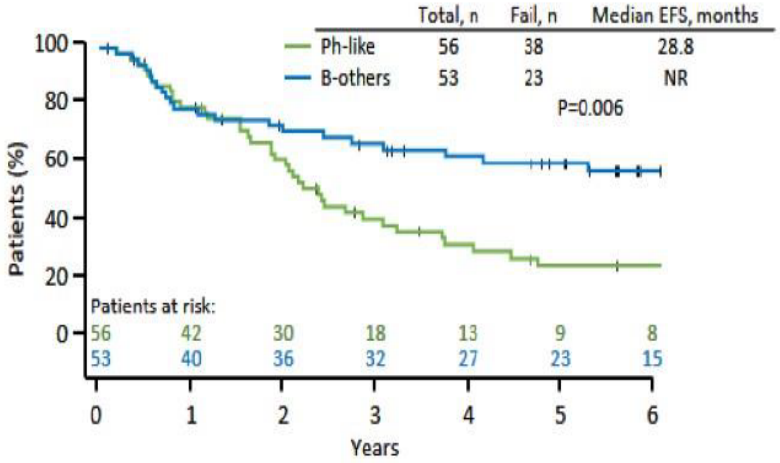

1. Herold T, et al. Haematologica 2017;102:130–8;
2. Jain N, et al. Blood 2017;129:572–81.

NR, not reached.

Ph-like ALL: conclusions

- Ph-like ALL is a heterogeneous group of B-ALL characterised by:
  - An increased frequency in AYA
  - A high rate of *IKZF1* intragenic deletion
  - Resistance to induction therapy (failure, high MRD levels)
- Lack of consensus approach who to screen and how
- Therapeutic options should be further evaluated:
  - Risk-adapted therapy based on MRD seems to be an option in children
  - Collaborative trials will be needed to determine the optimal targeted therapy for patients with rare kinase alterations
  - The respective role of targeted *vs* immunotherapy remains to be determined

Kinase rearrangements and therapeutic targets in Ph-like ALL

Kinase	TKI	Gene partners, n	Fusion partner genes
ABL1	Dasatinib	12	*CENPC, ETV6, FOXP1, LSM14, NUP214, NUP153, RCSD1, RANBP2, SNX2, SFPQ, SPTAN1, ZMIZ1*
ABL2	Dasatinib	3	*PAG1, RCSD1, ZC3HAV1*
CSF1R	Dasatinib	3	*SSBP2, MEF2D, TBL1XR1*
PDGFRB	Dasatinib	7	*ATF7IP, EBF1, ETV6, SSBP2, TNIP1, ZEB2, ZMYND8*
PDGFRA	Dasatinib	1	*FIP1L1*
CRLF2	JAK2 inhibitor	2	*IGH, P2RY8*
JAK2	JAK2 inhibitor	19	*ATF7IP, BCR, EBF1, ETV6, PAX5, PCM1, PPFIBP1, RFX3, SSBP2, STRN3, TERF2, TPR, USP25, ZNF274, GOLGA5, SMU1, HMBOX1, SNX29, ZNF340*
EPOR	JAK2 inhibitor	4	*IGH, IGK, LAIR1, THADA*
TSLP	JAK2 inhibitor	1	*IQGAP2*
DGKH	Unknown	1	*ZFAND3*
IL2RB	JAK1/3 inhibitor	1	*MYH9*
NTRK3	TRK inhibitor	1	*ETV6*
PTK2B	FAK inhibitor	3	*KDM6A, STAG2, TMEM2*
TYK2	TYK2 inhibitor	3	*MYB, SMARCA4, ZNF340*
FLT3	FLT3 inhibitor	1	*ZMYM2*
FGFR1	Sorafenib/dasatinib	1	*BCR*
BLNK	SYK/MEK inhibitor?	1	*DNTT*

Adapted from Pui CH, et al. Clin Lymphoma Myeloma Leuk 2017;17:464–70.

Available online at www.sciencedirect.com

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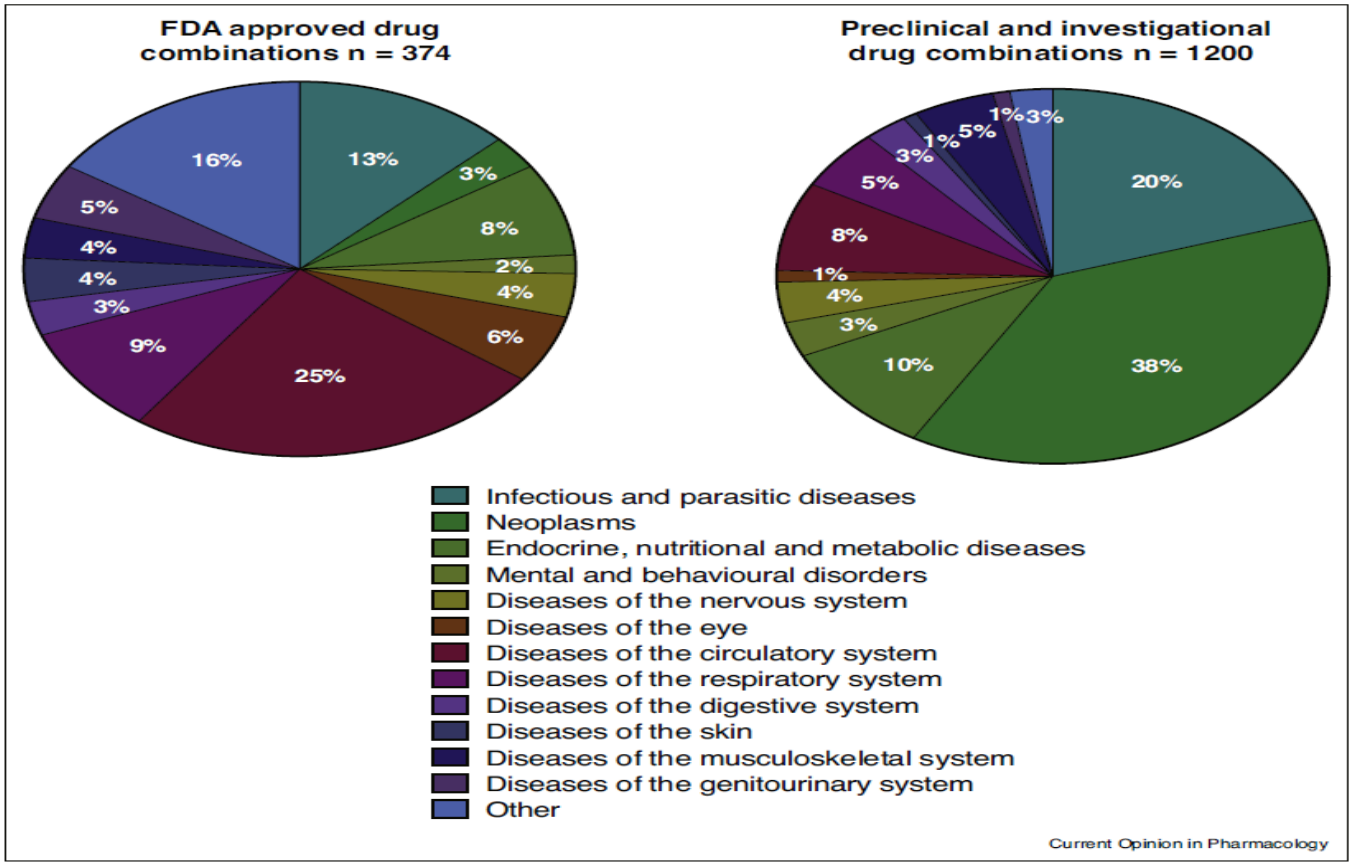
Current Opinion in Pharmacology

Recent advances in combinatorial drug screening and synergy scoring

Tea Pemovska[1,3], Johannes W Bigenzahn[1,3] and Giulio Superti-Furga[1,2]



Distribution of approved, preclinical and investigational drug combinations per disease area. The pie charts illustrate that currently most of the approved drug combinations are for treatment of infectious diseases (e.g. HIV, tuberculosis) whereas much of the research and development is targeting different cancer types. Data is retrieved from the Drug Combination Database (http://www.cls.zju.edu.cn/dcdb/) [52].

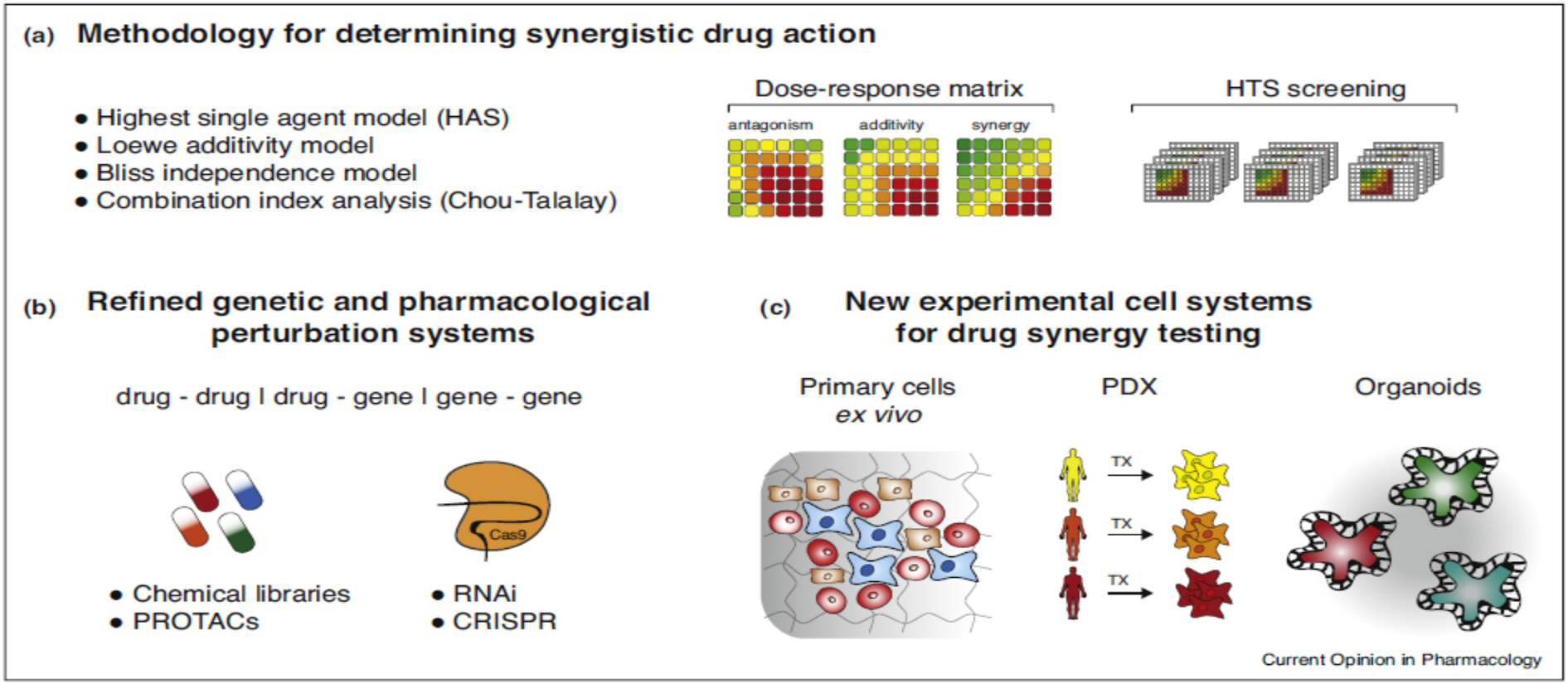
Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Recent advances in combinatorial drug screening and synergy scoring

Tea Pemovska[1,3], Johannes W Bigenzahn[1,3] and Giulio Superti-Furga[1,2]



Drug synergism analysis and technological advancements for drug combination screening. **(a)** Different methodologies for the statistical analysis and scoring of synergist drug effects, **(b)** functional genetic tools and novel drug candidates for the identification of combinatorial drug effects. RNAi: RNA interference, CRISPR: clustered regularly interspaced short palindromic repeats, PROTAC: proteolysis targeting chimera compounds, **(c)** novel cellular model systems for screening and identification of synergistic drug combinations, TX: transplant.

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"Real World Evidence"

Nuovi target terapeutici in ematologia

Presidente del Convegno
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Auditorium "Fra Agostino Daniele"
San Giovanni Rotondo
8 - 9 Novembre 2018

Blinatumumab e LLA: l'esperienza real world della REP

Table 2. **Adverse events.**	
Event	**No patients (%)**
Any adverse event	11 (78.6)
Event leading to discontinuation	4 (28.6)
Fatal serious adverse event ➔ Cerebral bleeding ➔ pneumonia	2 (15) 1 (7.5) 1 (7.5)
Any adverse event of grade ≥3 ➔ infection ➔ neutropenia ➔ thrombocytopenia ➔ Elevated liver enzymes ➔ Neurological events ➔ Cytokine release syndrome ➔ VOD ➔ TLS	10 (71.4) 6 (42.8) 3 (21.4) 3 (21.4) 3 (21.4) 2 (14.2) 1 (7.1) 0 0

BLAST trial: adverse events

Non-neurological AEs

Non-neurological AEs, n (%)	All patients (N=116)		
	Any grade	Grade 3	Grade 4
Any AE	116 (100)	38 (33)	31 (27)
Non-neurological AEs, worst Grade ≥3 occurring in ≥3% of patients			
Pyrexia	103 (89)	9 (8)	0 (0)
Headache	44 (38)	4 (3)	0 (0)
Neutropenia	18 (16)	2 (2)	16 (14)
Leukopenia	8 (7)	5 (4)	2 (2)
Anaemia	7 (6)	4 (3)	1 (1)
ALT increased	7 (6)	2 (2)	4 (3)
Thrombocytopenia	6 (5)	2 (2)	3 (3)
AST increased	5 (4)	1 (1)	3 (3)

Neurological AEs

Neurological AEs, n (%)	All patients (N=116)		
	Any grade	Grade 3	Grade 4
Any neurological AE	61 (53)	12 (10)	3 (3)
Neurological AEs, worst Grade ≥3			
Tremor	35 (30)	6 (5)	0 (0)
Aphasia	15 (13)	1 (1)	0 (0)
Dizziness	9 (8)	1 (1)	0 (0)
Confusional state	6 (5)	1 (1)	0 (0)
Encephalopathy	6 (5)	3 (3)	2 (2)
Seizure	3 (3)	1 (1)	1 (1)
Disorientation	3 (3)	1 (1)	0 (0)
Depressed level of consciousness	1 (1)	1 (1)	0 (0)
Generalised tonic-clonic seizure	1 (1)	1 (1)	0 (0)

Gökbuget N, et al. Blood 2018;131:1522–31.

RIEPILOGO STUDI

STUDI IN FASE DI PROGETTAZIONE

Codice	Tipo	Titolo dello studio	Età	Coordinatore
LAL2217	Osservazionale	Ancillary observational study of post front-Line Sequential Treatment of Adult Phila-delphia Chromosome Positive (Ph+) Acute Lymphoblastic Leukemia (ALL) Patients with Dasatinib and the Bispecific Monoclonal Antibody Blinatumomab	≥18 anni	Foà
ALL2518	Sperimentale	Asparaginase Activity Monitoring (AAM) in adult patients with Acute Lymphoblastic Leukemia (ALL)	18-65 anni	Vignetti, Testi
NP 17-282	Sperimentale	Ponatinib for the management of minimal residual disease (MRD) in adult Ph+ acute lymphoblastic leukemia (ph+ALL) patients	≥18 anni	Foà
NP 17-284	Sperimentale	A Phase 2 Study of Inotuzumab Ozogamicin (INO) Combined to Chemotherapy in Older Patients with Philadelphia Chromosome-negative CD22+ B-cell Precursor Acute Lymphoblastic Leukemia	>55 anni	Rousselot/Foà
NP 17-285	Sperimentale	Combination of Ponatinib plus chemotherapy as frontline approach for the treatment of patients with BCR/ABL1-like acute lymphoblastic leukemia (BCR/ABL1-like ALL)	≥18 anni	Foà

GIMEMA Care	Osservazionale prospettico e retrospettivo	Studio osservazionale, prospettico su pazienti affetti da LAL, LAM, LAP e Linfoma Linfoblastico registrati negli studi GIMEMA in 20 anni di attività della Fondazione al fine di valutarne gli esiti di follow-up a lungo termine	≥18 anni	La Sala
LAL2116 DALBA	Sperimentale	Front-Line Sequential Treatment of Adult Philadelphia Chromosome Positive (Ph+) Acute Lymphoblastic Leukemia (ALL) Patients with Dasatinib and the Bispecific Monoclonal Antibody Blinatumomab	≥18 anni	Foà
AML1301	Sperimentale	10-day decitabine versus conventional chemotherapy ("3+7") followed by allografting in AML patients ≥ 60 years	≥ 60 anni	Lübbert
APOLLO	Sperimentale	A randomized Phase III study to compare arsenic trioxide (ATO) combined to ATRA and idarubicin versus standard ATRA and anthracycLine-based chemotherapy (AIDA regimen) for patients with newLy diagnosed, high-risk acute prOmyelocytic leukemia – APOLLO-TRIAL	≥18 e ≤ 71 anni	Platzbecker Lo Coco
AML1516	Osservazionale	Italian Registry and set up of an Italian Molecular biology network for rapid identification of IDH1/IDH2 in Acute Myeloid Leukemia Patients	≥18 anni	Martinelli/ Voso
LAL2317	Sperimentale	National Treatment Program with Sequential Chemotherapy and Blinatumomab to Improve Minimal Residual Disease Response and Survival in Philadelphia Chromosome-negative B-Cell Precursor Adult Acute Lymphoblastic Leukemia	18-65 anni	Bassan

New Treatments for Adult ALL

Table A6. Registered or Ongoing trials (n = 12) With Innovative Therapeutics After HCT Relapse and After, During or Before HCT in Adult ALL*

Institution/Trial Denomination	ClinicalTrials.gov Identifier	Patient Age, Years (No.), ALL Subset	Study Drug	Associated Chemotherapy	Trial Design (phase)	Primary Objective/ Outcome Measures
After HCT relapse						
MSKCC/11-038	NCT01430390	Any age (12), CD19+ BCP ALL or lymphoma	Expanded EBV-specific allogeneic T-cytotoxic cells	No	I	Safety/persistence of escalating doses of allogeneic modified T cells
Masonic Cancer Center, University of Minnesota/ HM2013-12	NCT01885897	≥ 18 (61), ALL and other leukemias	ALT-803 (IL-15 superagonist complex)	No	I/II	Safety/efficacy, toxicity, incidence of acute and chronic GvHD
Case Comprehensive Cancer Center/CASE1916	NCT03104491	16-75 (44), CD22+ BCP ALL	Inotuzumab ozogamicin (calicheamicin-conjugated anti-CD22)	No	I/II	Maximum tolerated dose, posttransplant relapse, response rate
After HCT						
University of Colorado, Denver/ NCI-2013-00824	NCT01841333	≥ 18 (28), ALL and AML	PF-04449913 (Hedgehog inhibitor)	No	II	RFS and remission duration
Sidney Kimmel Comprehensive Cancer Center/IRB00125679	NCT03114865	≥ 18 (12), CD19+ BCP ALL, HR and/or MRD+ before HCT	Blinatumomab	No	I	OSOS, DFS, MRD response
MDACC/2015-0576	NCT02807883	18-70 (30), BCP ALL, HCT beyond CR1 or MRD+	Blinatumomab	No	II	Feasibility, OS and PFS

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Rete Ematologica Pugliese

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Grazie per l'attenzione

"Real World Eviden

Nuovi target terapeutici in ematologia

Presidente del Convegno
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