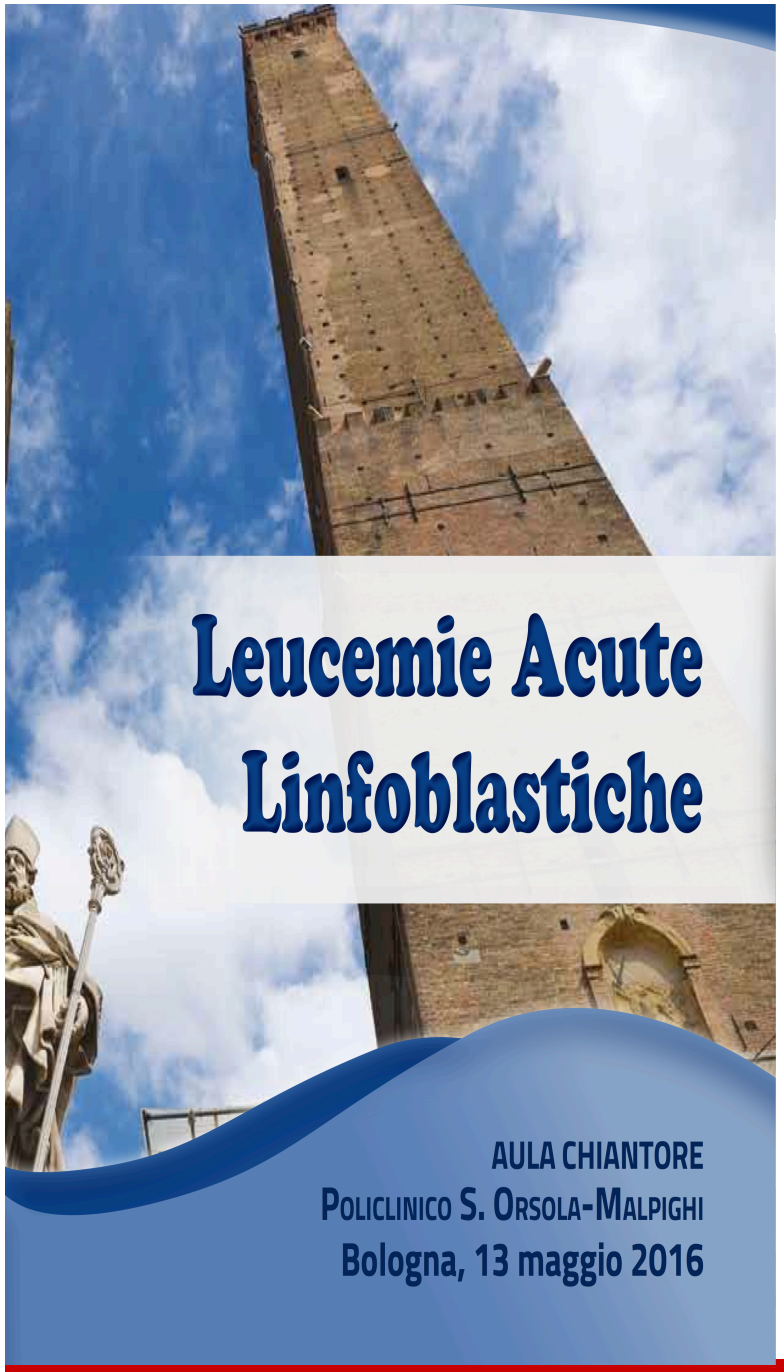

Blinatumomab in Ph+ ALL patients

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DIMES

University of Bologna

Ph+ ALL: background

- Ph+ is the most common single cytogenetic abnormality in B-precursor ALL
  - ~25% of adult ALL is Ph+
  - frequency of Ph+ disease increases with age

- Ph+ ALL patients historically have a poor prognosis

- TKIs have improved outcomes:
  - Addition to firstline therapy has increased response rates and likelihood of achieving alloHSCT (Fielding AK, et al. *Blood* 2014)

  - Sequential use of chemotherapy ± alternative TKIs is the dominant approach to treating Ph+ R/R ALL when alloHSCT is not an option

Ph+ ALL: open issues

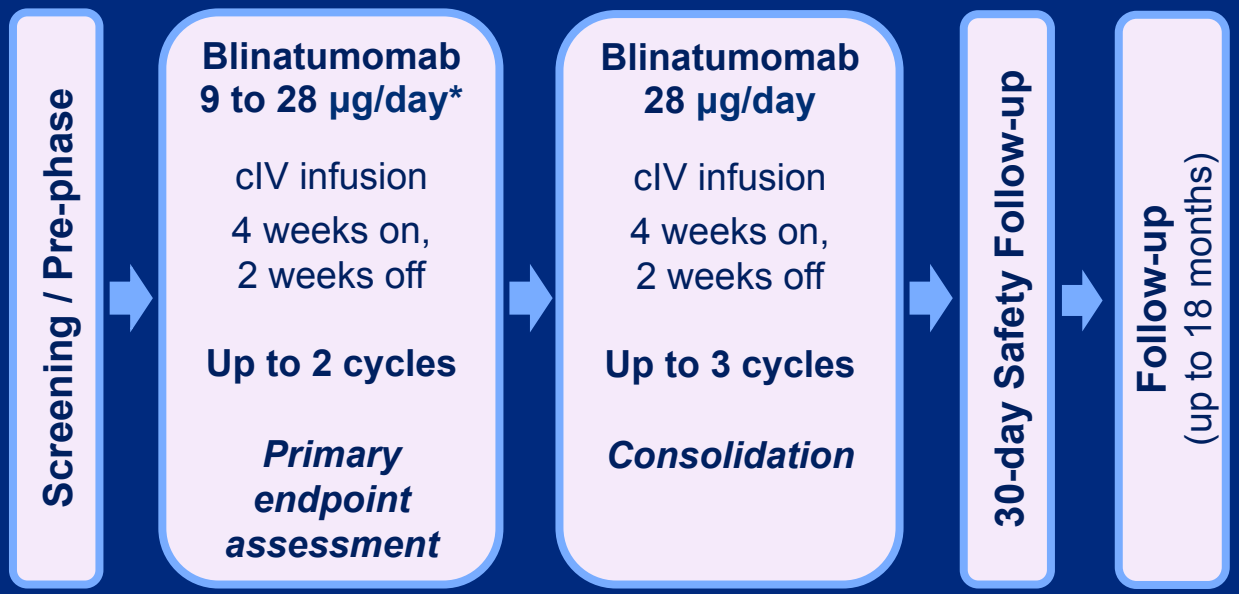
- Emergence of single and compound point mutations in *BCR-ABL* is responsible for a significant proportion of TKI resistance (Zabriskie MS, et al. *Cancer Cell* 2014;26:428-442)

TKI monotherapy	**Nilotinib[1] (N = 41)**	**Dasatinib[2] (N = 36)**	**Ponatinib[3] (N = 32)**
Complete hematologic response	45%	33%	41% (MHR)
Median overall survival (OS) OS at 1 year	5.2 months 27%	3.3 months* NA	8.0 months 40%

- Which options could be offered to these patients?

1. Ottmann OG, et al. *Leukemia* 2013;27:1411-1413.
2. Ottmann OG, et al. *Blood* 2007;110(7):2309-2315.
3. Cortes JE, et al. *N Eng J Med* 2013;369(19):1783-1796.

Open-Label, Single-Arm, Multicenter Phase 2 Study in Ph+ R/R ALL



Study Endpoints

Primary

- CR/CRh during the first 2 cycles

Key Secondary

- Minimal residual disease response by PCR of *BCR-ABL* during the first 2 cycles
- CR, CRh, and duration
- Relapse-free survival
- Overall survival
- HSCT realization
- Incidence of adverse events and antibody formation

* Only cycle 1, days 1 to 7: 9 µg/day

CR, complete remission; CRh, complete remission with partial hematological recovery of peripheral blood counts (platelets > 50,000/µL and ANC > 500/µL); cIV, continuous intravenous; HSCT, hematopoietic stem cell transplantation

Complete Molecular and Hematologic Response in Adult Patients With Relapsed/Refractory (R/R) Philadelphia Chromosome-Positive B-Precursor Acute Lymphoblastic Leukemia (ALL) Following Treatment With Blinatumomab: Results From a Phase 2 Single-Arm, Multicenter Study (ALCANTARA)

Giovanni Martinelli,[1] Hervé Dombret,[2] Patrice Chevallier,[3] Oliver Ottmann,[4] Nicola Gökbuget,[5] Max S. Topp,[6] Adele K. Fielding,[7] Lulu Ren Sterling,[8] Jonathan Benjamin,[9] Anthony Stein[10]

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Eligibility

Key Inclusion Criteria

- Adults (≥ 18 years) with Ph+ B-precursor ALL
  - Relapsed or refractory to at least one 2+ generation TKI or
  - Intolerant to 2+ generation TKI and intolerant/refractory to imatinib
- > 5% bone marrow blasts
- ECOG performance status ≤ 2

Key Exclusion Criteria

- Allogeneic HSCT within 12 weeks prior to start of blinatumomab
- Active acute or active chronic (grade 2−4) GvHD, or systemic treatment for GvHD within 2 weeks before treatment start
- History or presence of clinically relevant CNS pathology (epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis)

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; GvHD, graft-versus-host disease

Patient Characteristics

	All patients (N = 45)	
	n / N*	
Male	24 / 45	53%
Median age (range), years	55 (23–78)	
Age group		
18 to < 55 years	22 / 45	49%
55 to < 65 years	11 / 45	24%
≥ 65 years	12 / 45	27%
Cytogenetics and molecular analyses		
Philadelphia + other cytogenetic abnormalities	22 / 38	58%
ABL kinase domain mutations	17 / 37	46%
T315I mutation	10 / 37	27%
Prior relapses		
0 (primary refractory)	3 / 45	7%
1	25 / 45	56%
2	13 / 45	29%
≥ 3	4 / 45	9%
Prior allogeneic HSCT	**20 / 45**	**44%**
Prior tyrosine kinase inhibitors	45 / 45	100%
Imatinib	25 / 45	56%
Dasatinib	39 / 45	87%
Nilotinib	16 / 45	36%
Ponatinib	23 / 45	51%
Bone marrow blasts (central review)		
< 50%	11 / 45	24%
≥ 50%	34 / 45	76%

* Number of patients with evaluable data
HSCT, hematopoietic stem cell transplantation

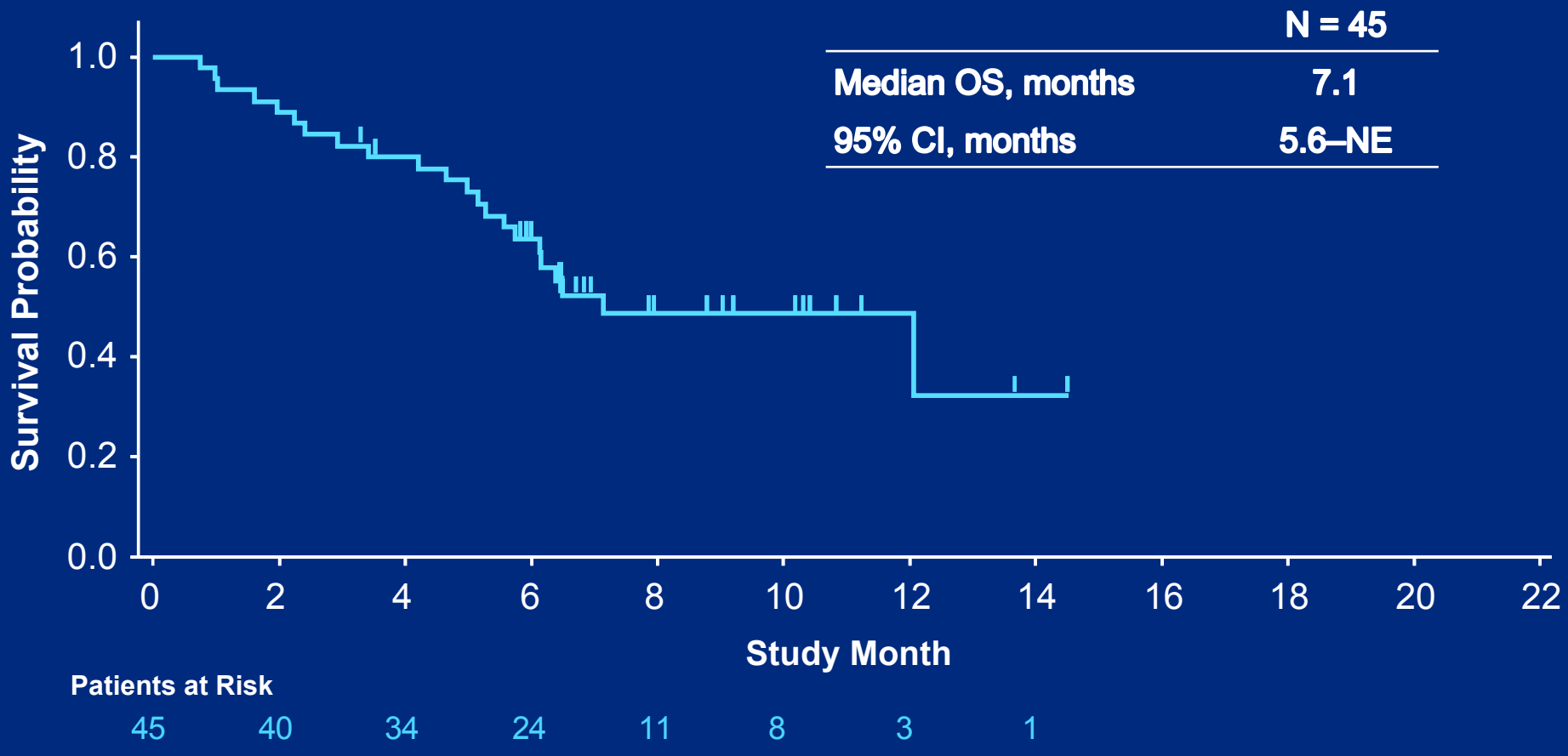
Response During First Two Cycles

	n / N		95% CI
Primary endpoint			
CR/CRh	16 / 45	**36%**	22–51
T315I mutation	4 / 10	40%	
≥ 2 prior 2+ generation TKI	11 / 27	41%	
Prior ponatinib treatment	8 / 23	35%	
Age 18 to < 55 years	8 / 22	36%	17–59
Age ≥ 55 years	8 / 23	35%	16–57
Secondary endpoints			
Best response			
CR	14 / 45	31%	18–47
CRh	2 / 45	4%	1–15
CRi (not qualifying for CRh)	2 / 45	4%	1–15
Complete MRD response*	14 / 16	**88%**	62–98
HSCT after blinatumomab-induced remission	4 / 16	**25%**	
100-day post-transplant mortality rate	1 / 4	25%	4–87

* Among CR/CRh responders only; includes all four CR/CRh patients with the T315I mutation.
Complete MRD response = no detectable PCR amplification of Ig or TCR genes in central lab with a sensitivity of 10^{-5}

CR, complete remission; CRh, complete remission with partial hematological recovery of peripheral blood counts;
CRi, complete response incomplete; MRD, minimal residual disease

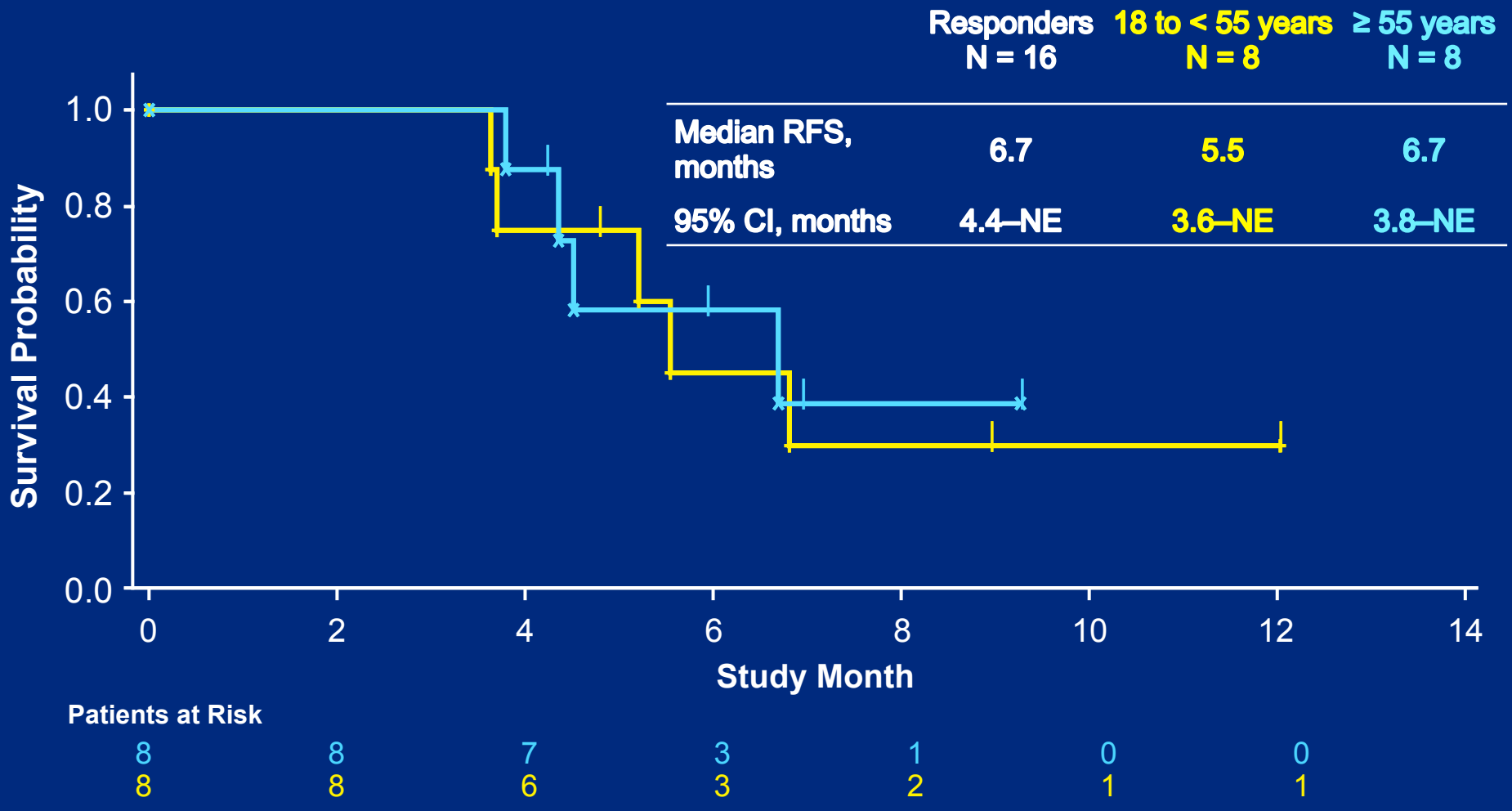
Overall Survival



NE, not estimable

Median follow-up: 8.8 months

Relapse-Free Survival



NE, not estimable

Median follow-up: 8.8 months

Adverse Events

Adverse events*, n (%)	All patients (N = 45)	
	Treatment emergent†	Treatment related‡
Worst grade < 3	8 (18)	21 (47)
Worst grade ≥ 3	37 (82)	20 (44)
Worst grade 5 (death)	5 (11)	1 (2)
Treatment interruption	16 (36)	12 (27)
Discontinuation due to AEs	3 (7)	2 (4)
Grade ≥ 3 occurring in ≥ 5% of patients, n (%)		
Febrile neutropenia	12 (27)	5 (11)
Thrombocytopenia	10 (22)	3 (7)
Anaemia	7 (16)	4 (9)
Alanine aminotransferase increased	5 (11)	5 (11)
Aspartate aminotransferase increased	5 (11)	4 (9)
Pyrexia	5 (11)	3 (7)
Pain	4 (9)	0 (0)
Sepsis	4 (9)	1 (2)
Device-related infection	3 (7)	1 (2)
Headache	3 (7)	0 (0)
Leukocytosis	3 (7)	0 (0)
Neutropenia	3 (7)	2 (4)

* CTCAE v4.03
** Cutoff based on treatment-emergent AE

† During treatment until 30 days post-treatment
‡ Investigator opinion

Neurologic Events and Cytokine Release Syndrome (Regardless of Causality)

	All patients (N = 45)		
	Any grade	**Grade 3**	**Grade 4**
Neurologic events, n (%)	21 (47)	3 (7)	0 (0)
Preferred terms with ≥ 5% frequency			
Paraesthesia	6 (13)	0 (0)	0 (0)
Confusional state	5 (11)	0 (0)	0 (0)
Dizziness	5 (11)	0 (0)	0 (0)
Tremor	4 (9)	0 (0)	0 (0)
Cytokine release syndrome, n (%)	4 (9)	0 (0)	0 (0)

Note: No grade 5 neurologic event or cytokine release syndrome was observed.

Conclusions

- The present study showed single-agent antileukemia activity of blinatumomab in patients with Ph+ R/R ALL who had failed 2+ generation TKI therapy, with a CR/CRh rate of 36% (95% CI, 22–51)
- Hematologic and molecular responses were independent of mutational status, including presence of the T315I mutation
  - Equivalent CR/CRh and RFS observed in patients < 55 and ≥ 55 years of age
- Among responders, 88% (14/16) achieved complete MRD response
  - Of these, 100% (6/6) with ABL-kinase domain mutations had complete MRD response
- Median OS of 7.1 months was observed in this poor prognostic Ph+ patient population
- Adverse events were consistent with previous blinatumomab treatment experience in the setting of Ph-negative R/R ALL

Thank you!

GRUPPO DI RICERCA
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SEVENTH FRAMEWORK PROGRAMME

NEXT GENERATION SEQUENCING for Targeted Personalized Therapy of Leukemia

AIL Bologna