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High Remission Rates In Pediatric Patients With Resistant Acute Lymphoblastic Leukemia Treated With Blinatumomab: Updated Analysis Of An Expanded Access Study (RIALTO)

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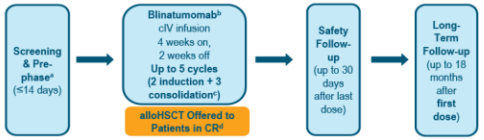
BACKGROUND

- Relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL) remains a leading cause of cancer-related deaths in pediatric patients[1]
- Approximately 1 in 5 children and adolescents diagnosed with ALL will have R/R disease and need to undergo salvage treatment[1]
- Children and adolescents with high-risk features of genetic abnormalities at baseline have an even worse prognosis[2]

Study Design: An Open-label, Multicenter Expanded Access Study in Pediatric Patients With R/R ALL (NCT02187354)



[a]Pre-phase period is permitted for the administration of dexamethasone or hydroxyurea to reduce tumor burden and the incidence of tumor lysis syndrome. For patients with blasts <50% at screening, dexamethasone is mandatory as [a]pre-phase medication.
[b]Dosing: If <25% blasts at baseline: 15 µg/m²/day; if ≥25% blasts at baseline: 5 µg/m²/day on days 1–7 in cycle 1, then 15 µg/m²/day thereafter.
[c]If patients achieve CR within the first 2 cycles.
[d]CR defined as no evidence of circulating blasts or extramedullary disease and <5% blasts in bone marrow; CR was subclassified on the basis of recovery of peripheral blood counts. Patients could proceed to alloHSCT at any stage during treatment or follow-up.
R/R ALL, relapsed/refractory acute lymphoblastic leukemia; CR, complete response; cIV, continuous intravenous; alloHSCT, allogeneic hematopoietic stem cell transplantation

OBJECTIVE

- Report safety and efficacy of blinatumomab in an open-label, single-arm, expanded access study of pediatric patients with CD19-positive R/R ALL

PATIENTS AND METHODS

Key Patient Eligibility

Inclusion	• Age >28 days and <18 years • CD19-positive B-precursor ALL with ≥5% blasts in the bone marrow or <5% blasts but with MRD level $\geq 10^{-3}$ • Relapsed/refractory disease defined as any of the following: – ≥2 relapses – relapse after alloHSCT – refractory to prior treatments • Prior treatment with blinatumomab was allowed, provided the patient was not blinatumomab-refractory or intolerant, and leukemic cells were CD19 positive
Exclusion	• Clinically relevant CNS pathology • Chemotherapy within 2 weeks, radiotherapy within 4 weeks, or immunotherapy within 6 weeks • Grade 2 – 4 acute GvHD or active chronic GvHD • Immunosuppressive agents to prevent or treat GvHD within 2 weeks

ALL, acute lymphoblastic leukemia; CD, cluster of differentiation; CNS, central nervous system; GvHD, graft-versus-host disease; alloHSCT, allogeneic hematopoietic stem cell transplantation; MRD, minimal residual disease

Endpoints

- This primary analysis focuses on 110 pediatric and adolescent patients enrolled into an expanded access study
- Data cutoff: September 27, 2018

Primary: Safety

- Treatment-emergent adverse events and treatment-related adverse events

Secondary: Efficacy

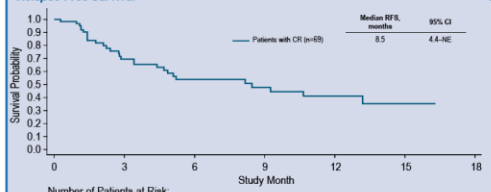
- Complete response (CR) within the first 2 cycles
- MRD remission within the first 2 cycles
- Relapse-free survival (RFS)
- Overall survival (OS)
- Rate of allogeneic hematopoietic stem cell transplant (alloHSCT) after CR

Statistical Analysis

- Reporting of this study is descriptive
- Survival endpoints were estimated by the Kaplan-Meier method or the Simon-Makuch method, with a 42-day landmark.

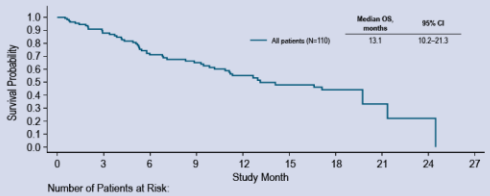
RESULTS

Relapse-Free Survival



Median follow-up time: 6.1 months. RFS is based only on responders and calculated from the time of CR. Survival estimates calculated by Kaplan-Meier method.
CI, confidence interval; CR, complete response; NE, not estimable; OS, overall survival; RFS, relapse-free survival

Overall Survival



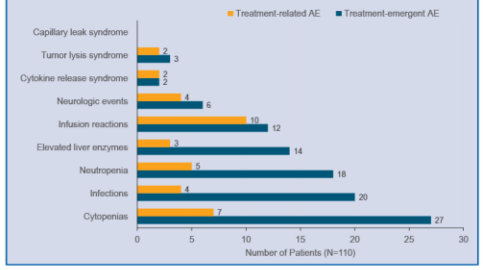
Median follow-up time: 16.2 months. Survival estimates calculated by Kaplan-Meier method.
CI, confidence interval; OS, overall survival.

Safety Summary

Event, n (%)	Treatment Emergent N=110	Treatment Related N=110
AE, any grade	109 (99)	81 (74)
Grade ≥ 3	71 (65)	29 (36)
Grade ≥ 4	31 (28)	3 (4)
Serious AE	50 (46)	21 (26)
AE leading to treatment interruption	25 (23)	18 (22)
AE leading to treatment discontinuation	7 (6)	4 (5)
Fatal AE	9 (8)	0

AE, adverse event

Treatment-Emergent and Treatment-Related Adverse Events (AE) of Interest, Grade ≥3



Demographics and Baseline Characteristics

Characteristic	All Patients (N=110)
Age, median (range), years	8.5 (0.4–17.0)
Age group,[a] years, n (%)	
0–1	13 (12)
2–6	31 (28)
7–17	66 (60)
Male, n (%)	62 (56)
Blast category, n (%)	
<5% with MRD $\geq 10^{-3}$	12 (11)
5%–49%	55 (50)
≥50%	42 (38)
Unknown	1 (1)
Recurrent genetic abnormalities,[b] n (%)	
MLL re-arrangement	18 (16)
t(9;22) BCR-ABL	5 (5)
t(17;19)	2 (2)
t(12;21)/TEL-AML1	9 (8)
Hypo/hyperdiploidy	1 (1)/6 (6)
Other	12 (11)
Constitutional trisomy 21 (Down syndrome), n (%)	4 (4)
Disease history, n (%)	
Primary refractory disease	17 (16)
Refractory to re-induction therapy	23 (21)
Second or greater relapse	61 (56)
Relapse after alloHSCT	44 (40)

[a]Includes 63 children aged between 2 and 12 years and 34 adolescents aged between 12 and 17 years.
[b]More than one type of genetic abnormality can be selected for the same patient.
MRD, minimal residual disease; alloHSCT, allogeneic hematopoietic stem cell transplant

Best Response During First 2 Cycles of Blinatumomab

Efficacy Response	Patients with ≥5% blasts at baseline (N=98) n (%)	95% CI
CR in first 2 cycles	58 (59)	48.8–69.0
CR with full recovery of peripheral blood counts	39 (67)	30.0–50.2
CR with incomplete recovery of peripheral blood counts	6 (10)	2.3–12.9
CR without recovery of peripheral blood counts	13 (22)	7.3–21.6
MRD response	46 (47)	36.8–57.3
MRD non-responsive	19 (19)	21.1–28.6
Proceeded to alloHSCT	36 (62)	48.4–74.5
Non-CR		
Stable disease	5 (5)	1.7–11.5
Progressive disease	20 (20)	12.9–29.7
Not evaluable	1 (1)	0.0–5.6
No response data	13 (13)	7.3–21.6
Prior alloHSCT	45 (46)	35.9–56.3
Genetic abnormality	30 (31)	21.9–40.9
	Patients with <5% blasts with MRD $\geq 10^{-3}$ at baseline (N=12)	
CR in first 2 cycles	11 (92)	61.5–99.8
CR with full recovery of peripheral blood counts	3 (27)	5.5–57.2
CR with incomplete recovery of peripheral blood counts	0	0.0–26.5
CR without recovery of peripheral blood counts	8 (73)	34.9–90.1
MRD response	11 (92)	61.5–99.8
Non-CR		
Progressive disease	1 (8)	0.0–26.5
Prior alloHSCT	0	0.0–30.1
Genetic abnormality	2 (17)	2.9–49.1

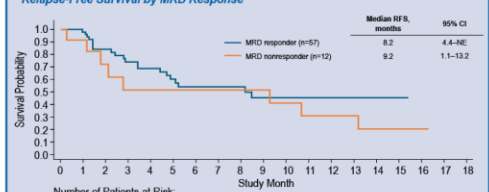
CI, confidence interval; CR, complete response; alloHSCT, allogeneic hematopoietic stem cell transplant; MRD, minimal residual disease

Best Responses by Subgroup During First 2 Cycles of Blinatumomab

Patient Subgroup	CR n/N1	CR %	CR With Full Hematologic Recovery n/N1	Recovery %	MRD n/N1	MRD %
Baseline blast category						
<5%	11/12	92	3/12	25	11/12	92
5%–49%	39/55	71	26/55	47	33/55	60
≥50%	19/42	45	13/42	31	13/42	31
Genetic abnormality						
Yes	17/32	53	11/32	34	11/32	34
No	52/78	67	31/78	40	46/78	59
t(17;19)	2/2	100	2/2	100	2/2	100
Down syndrome	4/4	100	2/4	50	4/4	100
Prior alloHSCT						
Yes	28/45	62	19/45	42	22/45	49
No	41/65	63	23/65	35	35/65	54
Prior blinatumomab	4/4	100	4/4	100	3/4	75
Prior relapses						
1	17/30	57	12/30	40	13/30	43
≥2	42/63	67	24/63	38	36/63	57

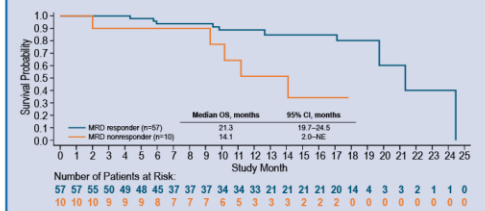
alloHSCT, allogeneic hematopoietic stem cell transplant; CR, complete response; MRD, minimal residual disease
n/N1, number of responders/total number of patients with evaluable data under each category

Relapse-Free Survival by MRD Response



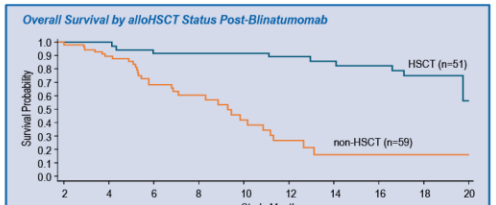
RFS by MRD response is based only on responders and calculated from time of CR, by Kaplan-Meier method.
CI, confidence interval; CR, complete response; MRD, minimal residual disease; NE, not estimable; RFS, relapse-free survival.

Overall Survival by MRD Response



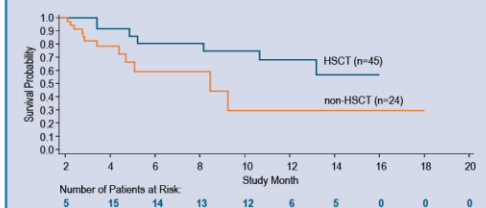
OS by MRD response is based only on responders and calculated from time of CR by Kaplan-Meier method.
CI, confidence interval; CR, complete response, MRD, minimal residual disease; NE, not estimable; OS, overall survival

Overall Survival by alloHSCT Status Post-Blinatumomab



Survival estimates calculated by Simon-Makuch .
OS, overall survival; HSCT, hematopoietic stem cell transplant

Relapse Free-Survival by alloHSCT Status Post-Blinatumomab



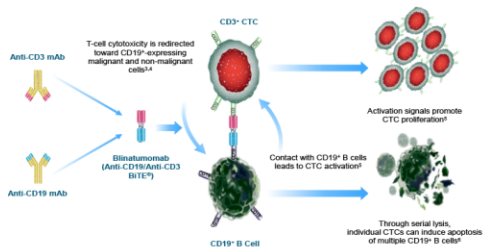
Survival estimates calculated by Simon-Makuch.
RFS, relapse-free survival; HSCT, hematopoietic stem cell transplant

KEY TAKEAWAYS

- **Safety profile of blinatumomab was tolerable and consistent with that recorded in other studies**
- **High-risk patients (defined as having persistent MRD and genetic disorders at baseline) achieved high rates of CR and MRD responses with low rates of relapse and disease progression**
- **Response rate inversely correlated with the leukemia burden**
- **Best outcomes (ie, CR and MRD responses) were observed in patients given allogeneic HSCT after blinatumomab treatment**
- **Blinatumomab is a suitable treatment option for pediatric patients with R/R ALL**

Mechanism of Action

Blinatumomab: CD3/CD19 Bispecific T-cell Engager (BiTE®) Immuno-oncology Therapy



BiTE®, bispecific T-cell engager; CD, cluster of differentiation; CTC, cytotoxic T cell; mAb, monoclonal antibody.

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AUTHOR DISCLOSURES

- F. Locatelli reports speakers' bureau and consulting fees from Amgen
- G. Zugmaier is employed by, holds stock in, and has patents/royalties/other intellectual property with Amgen
- P. Bader reports speakers' bureau and consulting fees from Novartis and Amgen (Brasil), patents, royalties, and research funding from Medac, research funding from Riemser and Neovii, and consulting fees from Celgene
- C. Rossig reports advisory board fees from Amgen, Celgene, EUSA Pharma, Genetech, Novartis, and Roche, and speaker honoraria from BMS, Pfizer, and Roche
- J-P. Bourquin reports travel support from Servier
- B. Brethon reports invitation to meetings, remunerations for oral presentations, and advices for the record of blinatumomab in pediatrics in France with Amgen
- R. Handgretinger reports speaker honorarium from Amgen
- S. Jeha, P-G. Schlegel, and C. Chen-Santel have nothing to disclose

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Treatment of Adults with Relapsed/Refractory Philadelphia Chromosome Negative Acute Lymphoblastic Leukemia with Blinatumomab in a Real-World Setting: Results from the NEUF Study

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BACKGROUND

- Blinatumomab is approved in Europe for the treatment of adult and pediatric patients (pts) with relapsed and/or refractory Philadelphia chromosome negative B-cell precursor acute lymphoblastic leukemia (R/R Ph- BCP-ALL), and adult pts with minimal residual disease (MRD)-positive Ph-BCP-ALL[1]
- Prior to country-specific reimbursement, blinatumomab was made available to pts who met pre-specified criteria via an expanded access program (EAP): this included both adult and pediatric pts with diagnoses of R/R Ph- BCP-ALL, R/R Ph+ BCP-ALL, or MRD-positive Ph-/Ph+ ALL
- The NEUF study is a retrospective observational study of pts enrolled in the EAP in selected European countries (France, Italy, Russia, Spain, and the UK)

OBJECTIVE

- We describe pt characteristics, and blinatumomab usage and effectiveness in adult R/R Ph- BCP-ALL enrolled in the NEUF study

METHODS

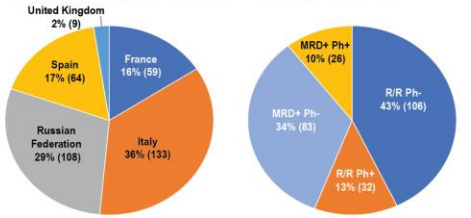
- Eligible pts initiated blinatumomab in the EAP between 1 Jan 2014 and 31 Dec 2016
- Data was extracted from medical notes using a dedicated electronic case report form (eCRF) and stored in a secure database. Where necessary data was not recorded in the medical notes, it was entered as "missing"; missing data was excluded from calculation of percentages in the analyses
- Patients were followed from blinatumomab initiation until: death; entry into a clinical trial; end of available follow-up in the medical notes, or the end of the study period (30 June 2017), whichever occurred first
- Adverse events were reported separately, according to local regulations. Safety data was not collected in this study
- Analysis was purely descriptive: no formal hypothesis was tested. Patient data was analysed on an intention-to-treat basis
- Time-to-event analysis was undertaken using Kaplan Meier (KM) methodology (inverse KM estimates being used to calculate follow-up time)
- MRD response was defined as MRD level $<10^{-4}$ within the first, and first two cycles of blinatumomab treatment. MRD assessment was undertaken as per local clinical practice, including flow cytometry and polymerase chain reaction (PCR): MRD status was then extracted from the patient medical record
- Cumulative incidence function analysis was used to evaluate mortality not due to disease relapse following allogeneic hematopoietic stem cell transplant (HSCT): relapse and death-due to undocumented relapse were treated as competing risks and KM estimates of mortality calculated

RESULTS

Demographics of the NEUF Study

- A total of 253 adult pts were enrolled in NEUF, with the most in Italy (n = 113) and fewest in the UK (n = 9) (**Figure 1a**)
- At enrolment, 106 pts had a diagnosis of R/R Ph- BCP-ALL, 32 pts had a diagnosis of R/R Ph+ BCP-ALL, and 109 had a diagnosis of MRD positive ALL (either Ph- or Ph+) as illustrated in **Figure 1b**. A total of 6 pts had diagnosis data missing

Figure 1. NEUF Study Adult Population by Country (a) or Diagnosis (b)



1a. By Country 1b. By Diagnosis

Baseline Characteristics of R/R Ph- BCP ALL Adult Patients

- Among the 106 R/R Ph- BCP-ALL, 47% were female and median age at blinatumomab initiation was 36.5 years (interquartile range [IQR]: 24.0, 52.0), as illustrated in **Table 1**
- A total of 43 (41%) pts had HSCT prior to blinatumomab initiation (4 pts with autologous HSCT, and the remainder having ≥1 allogeneic HSCT)
- At time of blinatumomab initiation, 44 (46%) pts had blast count ≥50%, and 20 (19%) pts had extramedullary disease. A total of 64 (60%) pts were in hematologic relapse, with the remainder being refractory to therapy
- The median number of salvage therapies was 1 (IQR: 0, 2), i.e. most patients started blinatumomab as third-line therapy. Over half (51.1%, n = 34) of relapsed pts had not been treated with salvage therapy, and over one quarter (28.5%, n = 12) had been treated with ≥ 2 salvage therapies (**Figure 2**)
- Before receiving blinatumomab, over half (53%, n = 54) of pts were treated with pre-phase dexamethasone, and 89% (n = 93) with pre-dose dexamethasone

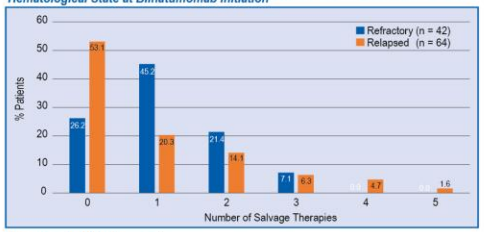
RESULTS (Continued)

Table 1. Baseline Characteristics of R/R Ph- B-Cell Adult Patients

			Adults N = 106 n	Adults N = 106 %
Sex	Female		50	47.2
Age at Blinatumomab Initiation	Median (IQR)		36.5 (24.0, 52.0)	
Number of Salvage Therapies	Median (IQR)		1.0 (0.0, 2.0)	
Disease Status at Blinatumomab initiation	Hematologic Relapse		64	60.4
	Refractory		42	39.6
HSCT Prior to Blinatumomab	Number of Patients		43	40.6
	Time between HSCT and Initation (months): median (IQR)		13.0 (7.2, 20.0)	
Response Prior to Blinatumomab	CR/CRh/CRi at Frontline Therapy		84	79.2
Blast Count at Binatumomab Initiation (%)	≤ 5		14	14.6
	> 5 and < 10		5	5.2
	> 10 and < 50		33	34.4
	≥ 50		44	45.8
	Unknown		10	-
Extramedullary Disease	Yes	Any	20	19.2
		Central Nervous System	4	3.8
		Testis	4	3.8
		Spleen	2	1.9
		Liver	1	1.0
		Other	12	11.5
	No		84	80.8
	Unknown		2	-
Comedications with Blinatumomab	Dexamethasone	Pre-phase	54	52.9
		Unknown	4	-
		Pre-medication	93	89.4
		Unknown	2	-
	Tyrosine Kinase	Any	1	0.9
		Unknown	0	-
	Donor Lymphocyte Infusion	Yes	13	12.9
		Unknown	0	-
	Chemotherapy	Any	10	9.4
		Unknown	0	-

-: Not applicable; CR: complete remission with full recovery of peripheral blood counts; CRh: Complete remission with partial recovery of peripheral blood counts; CRi: complete remission with incomplete recovery of peripheral blood counts; IQR: interquartile range; HSCT: hematopoietic stem cell transplant

Figure 2: Percentage Distribution of Patients by Number of Salvage Therapies and Hematological State at Blinatumomab Initiation



Response to Blinatumomab

- Within two cycles of blinatumomab, 54 (51%) pts achieved hematological response defined as complete remission CR/CRh/CRi (**Table 2**), of whom 91% (49/54) achieved complete remission (CR)
- A total of 28 (26%) pts were documented as being refractory to blinatumomab at two cycles
- A further 21 (16%) pts were documented as "other", defined in the eCRF as: no change in dose/planned dose increase/dose reduction/permanent treatment interruption/temporary treatment interruption. These pts may have been refractory although they were not categorized as such by the treating clinician
- Three patients died before completing two cycles of blinatumomab

Table 2: Hematological Response in the First Two Cycles of Blinatumomab

	Adults N = 106 n	Adults N = 106 % (95% CI)
Best Hematological Response in First Two Blinatumomab Cycles		
CR/CRh/CRi	54	50.9 (41.0, 60.8)
CR	49	46.2 (36.5, 56.2)
CRh	3	2.8 (0.6, 8.0)
CRi	2	1.9 (0.2, 6.6)
Refractory	28	26.4 (18.3, 35.9)
Unknown	0	-
Patients Deceased within 2 Cycles	3	2.8 (0.6, 8.0)
Other*	21	19.8 (13.0, 29.0)

CR: complete remission; CRh: complete remission with partial recovery of peripheral blood counts; CRi: Complete remission with incomplete recovery of peripheral blood counts
*Other was defined in the eCRF as: no change in dose/planned dose increase/dose reduction/permanent treatment interruption/temporary treatment interruption

- Among the 54 pts with CR/CRh/CRi within the first two cycles of blinatumomab, 33 pts had evaluable MRD response (**Table 3**)
- The percentage of pts with complete MRD or MRD response was 85% (n/N = 28/33). Over half of these 28 pts had non-detectable MRD (defined using a test with minimum sensitivity $>10^{-4}$), i.e. complete MRD (57%, n/N = 16/28), with the remainder having MRD $<10^{-4}$, i.e. MRD response (43%, n/N = 12/28)

Table 3: Minimal Residual Disease Response among Evaluable Patients with CR/CRh/CRi in the First Two Cycles of Blinatumomab

	Adults n = 38 n	Adults n = 38 % (95% CI)[a]
Evaluable MRD	33	
Complete MRD[b]/MRD Response[c]	28	84.8 (68.1, 94.9)
Complete MRD[b]	16	48.5 (30.8, 66.5)
MRD response[c]	12	36.4 (20.4, 54.9)
MRD Failure[d]	5	15.2 (5.1, 31.9)
MRD Relapse[e]	0	0.0
Unknown	3	-

MRD: minimal residual disease
[a]Three patients were recorded as having evaluable MRD by the treating clinician, but response was not entered: these patients ('unknown') were not included in the calculation of percentages
[b]Complete MRD includes pts in complete remission and MRD not detectable by sensitive molecular probe(s) (sensitivity 10^{-4})
[c]MRD response includes pts in complete remission, not in complete MRD response, with low-level non-quantifiable MRD ($<10^{-4}$/0.01%) assessable by multiparameter flow cytometry (lower detection limit, between 10^{-3} and 10^{-4} higher sensitivity with 8–12 colour techniques)
[d]MRD failure includes pts in complete remission, not in MRD response or complete MRD, with quantifiable MRD (10^{-4}/0.01%) assessable by multiparameter flow cytometry (lower detection limit, between 10^{-3} and 10^{-4})
[e]MRD relapse includes pts in complete remission, that were in a prior complete MRD or MRD response, and subsequently had a loss of complete MRD or MRD response, with quantifiable MRD (10^{-4}/ 0.01%) assessable by multiparameter flow cytometry (lower detection limit, between 10^{-3} and 10^{-4})

Outcomes Following Blinatumomab in Patients Achieving CR/CRh/CRi

- Following blinatumomab, 33 out of 43 pts who proceeded to transplant (77%) achieved a CR/CRh/CRi prior to transplant. Median time from CR/CRh/CRi to transplant was 4.6 months (min, max: 0.2, 7.4)
- Median relapse free survival (RFS) was 11.0 (min, max: 0.0, 15.4: **Figure 3a**) over a median follow-up time of 16.2 months (min, max: 0.7, 29.7). When censoring at time of HSCT, median RFS was 11.0 months (min, max: 0.0, 15.4: **Figure 3b**) over a median follow-up of 3.93 months (min, max: 0.2, 29.7)
- In sensitivity analysis, KM estimates for RFS at 24 months were calculated for various subgroups. KM estimates were similar in patients who had: HSCT prior to blinatumomab compared to those who did not (29.9% vs 28.4%); MRD response compared to those who did not (35.0% vs 28.6%, and; patients with bone marrow blasts < 50% at blinatumomab initiation compared to those with blasts ≥ 50% (33.2% vs 31.5%) as illustrated in **Figure 3c**. These differences were more pronounced for HSCT prior to blinatumomab, and molecular response, when censoring at time of HSCT (data not shown)

Figure 3. Relapse Free Survival[a] in R/R Ph- B-Cell Adult Patients (n = 54): Time-to-event Analysis (a) and After Additional Censoring at Time of HSCT (b)

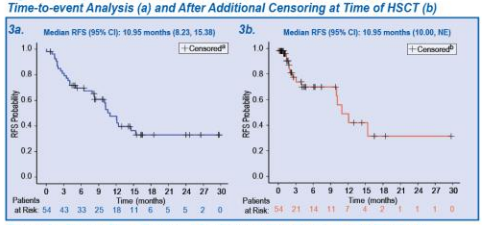
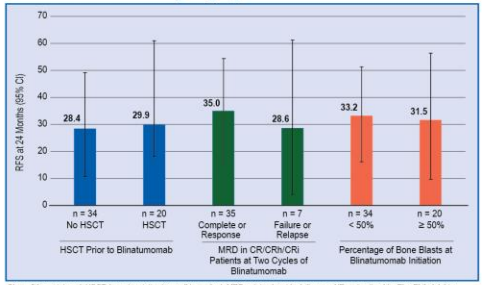


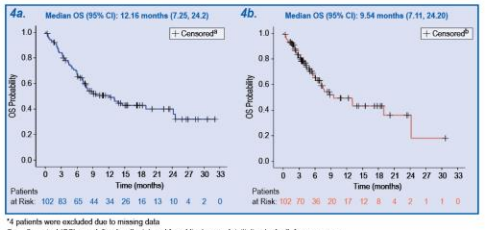
Figure 3c. Kaplan Meier Estimates for Relapse Free Survival at 24 Months in R/R Ph- B-Cell Adult Patients by Subgroup



CI: confidence interval; HSCT: hematopoietic stem cell transplant; MRD: minimal residual disease; NE: not estimable; Ph-: Philadelphia chromosome negative status; Ph+: Philadelphia chromosome positive status; RFS: relapse free survival
[a]Relapse free survival was defined as the interval from the time of achieving CR/CRh/CRi (best response within first 2 cycles) until the date of: relapse or; M2 marrow or; death, whichever occurred first
[b]Time-to event-analysis is censored if: patient is alive at the end of the study, clinician decision, and loss to follow-up of HSCT; [b]Additional censoring at time of HSCT

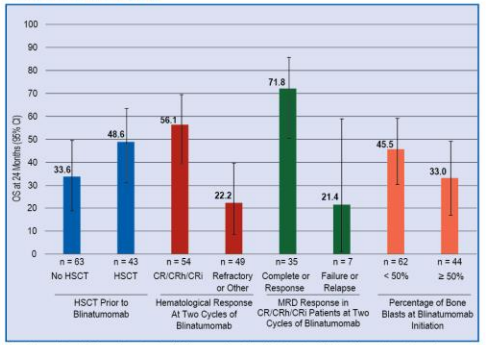
- Median overall survival (OS) was 12.2 months (min, max: 0.2, 24.6; **Figure 4a**) over a median follow-up time of 17.3 months (min, max: 0.4, 32.1). When censoring for HSCT, median OS was 9.5 months (min, max: 0.2, 24.2; **Figure 4b**) over a median follow-up of 6.6 months (min, max: 0.4, 30.7)
- In sensitivity analysis, KM estimates for OS at 24 months were calculated for various subgroups. KM estimates were higher in patients who had: HSCT prior to blinatumomab compared to those who did not (48.6% vs 33.6%); hematologic response i.e. CR/CRh/CRi vs no hematologic response (56.1% vs 22.2%); MRD response compared to those who did not (71.8% vs 21.4%, and; patients with bone marrow blasts <50% at blinatumomab initiation compared to those with blasts ≥50% (45.4% vs 33.0%) as illustrated in **Figure 4c**. These differences were more pronounced for HSCT prior to blinatumomab, and MRD response, when censoring at time of HSCT (data not shown)

Figure 4. Overall Survival in R/R Ph- B-Cell Adult Patients (n = 102): Time-to-event Analysis (a) and After Additional Censoring at Time of HSCT (b)*



*4 patients were excluded due to missing data
Overall survival (OS) was defined as the interval from blinatumomab initiation to death from any cause
[a]Time-to event-analysis is censored if: patient is alive at the end of the study, clinician decision, and loss to follow-up of HSCT; [b]Additional censoring at time of HSCT

Figure 4c. Kaplan Meier Estimates for Overall Survival at 24 Months in R/R Ph- B-Cell Adult Patients by Subgroup



CI: confidence interval; CR: complete remission with full recovery of peripheral blood counts; CRh: Complete remission with partial recovery of peripheral blood counts; CRi: complete remission with incomplete recovery of peripheral blood counts; HSCT: hematopoietic stem cell transplant; MRD: minimal residual disease; OS: overall survival
Other was defined in the eCRF as: no change in dose/planned dose increase/dose reduction/permanent treatment interruption/temporary treatment interruption

Outcomes Following Post-Blinatumomab HSCT

- Following blinatumomab, 43 (41%) pts proceeded to HSCT (one patient with autologous HSCT), among whom 33 (77%) achieved CR/CRh/CRi prior to transplant
- In a survival analysis following allogeneic HSCT in patients who achieved CR/ CRh/CRi at any time and proceeded to transplant without any intervening other anti-cancer therapy (n = 29): median survival was 17.8 months (min, max: 1.1, 17.8) over a median follow-up of 13.9 months (min. max: 0.0, 29.2) (data not shown)
- At 1 year, the KM estimate for survival after HSCT was 55.8% (95% CI: 32.5, 73.8) (data not shown)
- In sensitivity analysis, the KM estimate for survival at 1 year in pts who achieved complete MRD or MRD response (75%.6, 95% CI: 37.8, 92.3) was greater than the estimate in pts who did not (25.0%, 95% CI: 0.9, 66.5), (data not shown)
- Where relapse and death-due-to-undocumented relapse were competing risks, median time to death (not due to relapse) was not reached: the cumulative incidence function estimate for non-relapse mortality at 3 months was 10.7% (95% CI: 3.9, 29.4), and at 12 months was 19.3% (95% CI: 8.7, 42.8) (**Table 4**)

Table 4. Mortality after Allogeneic HSCT in R/R Ph- B-Cell ALL Adult Patients[a] (n = 29[b])

	Adults n = 29 n	Adults n = 29 %
Number of Patients with Event (Death Not Due to Relapse)	5	17.2
Number of Patients with Competing Risk (Relapse/Death due to Undocumented Relapse/Death due to Unknown Causes	10	34.5
Number of Censored Patients	14	48.3
Cumulative Incidence Function Estimate for Death Not Due to Relapse[c], % (95% CI)		
3 months	10.7 (3.9, 29.4)	
12 months	19.3 (8.7, 42.8)	

[a]Patients who achieved CR/CRh/CRi at any time following blinatumomab therapy and proceeded to transplant without any other intervening myelosuppressive therapy; [b]Four pts were excluded due to missing data; [c]Relapse and death-due to undocumented relapse treated as competing risks

CONCLUSIONS

- **The NEUF study includes the largest documented cohort of R/R Ph- BCP-ALL patients treated with blinatumomab in real world clinical practice**
- **A high proportion of adult patients achieved hematological response to blinatumomab, and over one-third then proceeded to HSCT**
- **Over one-third of patients were still alive 24 months after blinatumomab initiation**
- **At one year, mortality not due to disease relapse following HSCT was estimated to be approximately 20%**
- **Outcomes were better in patients with hematologic response compared to those without, and in patients with MRD response compared to those without**
- **These results are widely consistent with published results from clinical trial[2], and confirm the effectiveness of blinatumomab in a real world setting**

REFERENCES

1. European Medicines Agency. Blincyto® (blinatumomab) Summary of Product Characteristics. 2019
2. Kantarjian H, et al. *NEJM* 2017;376:836-47

DISCLOSURES

Nicolas Boissel has received honoraria from Amgen, Pfizer, Shire, Servier, Jazz and Ariad
Josep-Maria Ribera has received research funds and honoraria, and served on advisory boards, for Amgen, Pfizer, Shire, and Ariad
Sabina Chiaretti has received honoraria for advisory boards from Amgen Inc, Incyte, Pfizer and Shire
Alessandro Rambaldi received support from Amgen, Pfizer, Novartis, and Celgene for travel, sponsored lectures, and advisory board meetings
Renato Bassan has received honoraria for advisory boards from Amgen Inc., Incyte, Pfizer and Shire
Cristina Papayannidis has received honoraria from Amgen, Pfizer, Novartis, Shire and Teva for travel, sponsored lectures and advisory board meetings
Robin Foà has received honoraria for speaker bureau and advisory boards for Amgen Inc., Pfizer, Novartis, Shire, Janssen, Incyte
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Treatment of Adults with Minimal Residual Disease (MRD) Positive Acute Lymphoblastic Leukemia with Blinatumomab in a Real-World Setting: Results from the NEUF Study

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BACKGROUND

- In November 2015, the European Medicines Agency (EMA) granted conditional approval for blinatumomab for the treatment of adults with relapsed and/or refractory Philadelphia chromosome-negative B-cell acute lymphoblastic leukaemia (R/R Ph- BCP-ALL); this was converted to final approval in June 2018
- Approval was later widened to include pediatric R/R Ph- BCP-ALL patients (August 2018), and adult minimal residual disease (MRD)-positive Ph- BCP-ALL (January 2019)[1]
- Prior to country-specific reimbursement, blinatumomab was made available to patients (pts) who met pre-specified criteria via an expanded access program (EAP); this included both adult and pediatric pts with diagnoses of R/R and MRD-positive BCP-ALL (either Ph- or Ph+)
- The NEUF study is a retrospective observational study of pts enrolled in the EAP in selected European countries (France, Italy, Russia, Spain, and the UK)

OBJECTIVE

- We describe pt characteristics, and blinatumomab usage and effectiveness in adult MRD-positive Ph-/Ph+ BCP-ALL enrolled in the NEUF study

METHODS

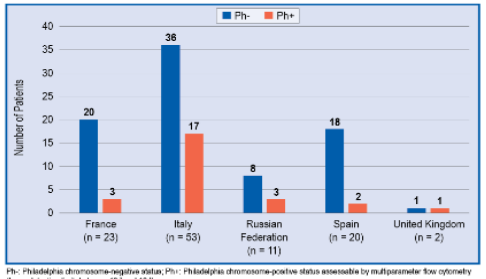
- Pts who initiated blinatumomab in the EAP between 01 Jan 2014 and 31 Dec 2016 were eligible for inclusion in the NEUF study
- A specially designed electronic case report form (eCRF) was used to extract data from patient medical notes. If data was not recorded in the original record, it was entered as "missing" in the eCRF. Missing data was not included in the calculation of percentages in the analyses
- Enrolled pts were followed up from blinatumomab initiation until: death; entry into a clinical trial; end of follow-up, or; end of the study period (30 June 2017), whichever occurred first
- MRD response was defined as MRD level $<10^{-3}$ within the first, and first two cycles of blinatumomab treatment. MRD assessment was undertaken as per local clinical practice, including flow cytometry and polymerase chain reaction (PCR): MRD status was then extracted from the patient medical record
- Disease-free survival (DFS) was defined as time from initiation of blinatumomab until date of relapse (blasts in bone marrow >5%, or extramedullary relapse, after documented response) or death, whichever occurred first
- Adverse events were reported separately, according to local regulations. Safety data was not collected in this study
- The analyses are purely descriptive. No formal hypothesis was tested. Patient data was analysed on an intention-to-treat basis
- Time-to-event analysis was undertaken using Kaplan Meier (KM) methodology (inverse KM estimates being used to calculate follow-up time)
- Cumulative incidence function analysis was used to evaluate mortality not due to disease relapse, following hematopoietic stem cell transplant (HSCT): relapse and death-due to undocumented relapse were treated as competing risks and KM estimates of mortality calculated

RESULTS

Demographics and Characteristics of the MRD-positive Patients

- A total of 373 pts were enrolled in the NEUF study: 109 were MRD-positive of which 83 (76.1%) were Ph- and 26 (23.9%) were Ph+
- Amongst the MRD-positive pts, 53 were enrolled in Italy, 23 in France, 20 in Spain, 11 in Russia, and 2 in the UK (**Figure 1**)

Figure 1. Distribution of Philadelphia Chromosome Status in Adult MRD-Positive Patients



Ph-: Philadelphia chromosome-negative status; Ph+: Philadelphia chromosome-positive status assessable by multiparameter flow cytometry (lower detection limit, between 10^{-3} and 10^{-4})

RESULTS (Continued)

- A total of 45 (41%) pts were female, and median age across all patients was 43 years (interquartile range [IQR]: 27, 55), as illustrated in **Table 1**

Table 1. Baseline Characteristics of MRD-Positive Adult Patients

		Adults n = 109	
		n	%
Sex			
Female		45	41.3
Age at Blinatumomab Initiation			
Median (IQR)		43.0 (27.0, 55.0)	
Disease Status at Blinatumomab Initiation			
Molecular Failure		77	70.6
Molecular Relapse		32	29.4
HSCT Prior to Blinatumomab			
Number of Patients		17	15.6
Time Between HSCT and Initiation (Months): Median (IQR)		10.2 (3.8, 24.9)	
Number of Previous Salvage Therapies			
Median (IQR)		0.0 (0.0, 1.0)	
Blast Count at Blinatumomab Initiation (%)			
< 50		90	95.7
≥ 50		4	4.3
Unknown		15	-
Comedications with Blinatumomab			
Dexamethasone			
	Pre-phase	36	34.6
	Unknown	5	-
	Pre-medication	92	86.8
	Unknown	3	-
Tyrosine Kinase Inhibitors (TKIs)			
	Any TKI	12	12.3
	Missing	3	-
Donor lymphocyte Infusion (DLI)			
	Yes	4	3.8
	Unknown	3	-
Chemotherapy			
	Yes	7	6.5
	Missing	2	-

IQR: interquartile range; HSCT: hematopoietic stem cell transplant

- A total of 17 (15.6%) pts had prior HSCT, including 2 pts who had ≥1 autologous transplant
- Among the 26 MRD-positive Ph+ pts, 23 (88.5%) were treated with tyrosine kinase inhibitors (TKIs) as first-line therapy. TKIs were then used as salvage therapy in 15 (93.8%) of the 17 pts with data available. The most commonly used TKI in first line was imatinib, and in salvage was dasatinib (data not shown)
- The median number of salvage therapies prior to blinatumomab across MRD-positive patients was 0 (IQR: 0.0, 1.0)
- Among the 60 pts who did not receive salvage therapies, 8.3% (n = 5) had prior HSCT. This proportion was 25% (n = 12) among the 49 pts who used ≥1 salvage therapy
- Blast count at blinatumomab initiation was ≥50% in 4 (4.3%) pts. It is plausible that these patients were MRD-positive at the time of the EAP application, but disease progression occurred between the application and receipt of blinatumomab
- Pre-phase dexamethasone was given before blinatumomab in 36 (34.6%) pts: it was used as pre-medication in 92 (86.8%) pts

Response to Blinatumomab

- Of the 82 pts who had evaluable MRD response in the first 2 blinatumomab cycles, 66 (82.5%) achieved MRD response (2 pts excluded due to missing data): among these patients, 73% (n/N = 48/66) had complete MRD response (undetectable MRD) and 27% (n/N = 18/66) had MRD response (MRD $<10^{-3}$), as illustrated in **Table 2**

Table 2. Minimal Residual Disease Response to Blinatumomab

	Response in First Blinatumomab Cycle n = 84		Response in First Two Blinatumomab Cycles n = 82	
	n	%[a]	n	%[a]
Evaluable MRD				
Complete MRD[b]/MRD Response[c]	**54**	**87.1 (76.1, 94.3)**	**66**	**82.5 (72.4, 90.1)**
Complete MRD[b]	38	61.3 (48.1, 73.4)	48	60.0 (48.4, 70.8)
MRD Response[c]	16	25.8 (15.5, 38.5)	18	22.5 (13.9, 33.2)
MRD Failure[d]	**8**	**12.9 (5.7, 23.9)**	**14**	**17.5 (9.9, 27.6)**
MRD Relapse[e]	**0**	**0.0**	**0**	**0**
Unknown	**2**	**-**	**2**	**-**

MRD: minimal residual disease
[a]Two patients were recorded as having evaluable MRD by the treating clinician, but response was not entered: these patients ("unknown") were not included in the calculation of percentages
[b]Complete MRD includes pts in complete remission and MRD not detectable by sensitive molecular probe(s) (sensitivity 10^{-5})
[c]MRD response includes pts in complete remission, not in complete MRD response, with low level non-quantifiable MRD (<10-<0.01%) assessable by multiparameter flow cytometry (lower detection limit, between 10^{-3} and 10^{-4} higher sensitivity with 8–12 colour techniques)
[d]MRD failure includes pts in complete remission, not in MRD response or complete MRD, with quantifiable MRD (≥10-≥0.01%) assessable by multiparameter flow cytometry (lower detection limit, between 10^{-3} and 10^{-4})
[e]MRD relapse includes pts in complete remission, that were in a prior complete MRD or MRD response, and subsequently had a loss of complete MRD or MRD response, with quantifiable MRD (≥-≥0.01%) assessable by multiparameter flow cytometry (lower detection limit, between 10^{-3} and 10^{-4})

- Among the 66 Ph- patients with evaluable MRD, 57 (89.1%) pts achieved a complete MRD or MRD response in the first two cycles of blinatumomab (2 pts excluded due to missing data). Only 16 Ph+ had evaluable MRD: 9 (56.3%) pts achieved a complete MRD or MRD response in the first two cycles

Outcomes Following Blinatumomab

- A total of 74 (68.1%) pts proceeded to HSCT following blinatumomab (2 with autologous transplants). The median time to HSCT from CR was 2.4 months (min, max: 0.2, 16), over a median follow-up of 14.8 months (min, max: 1.6, 32.5)
- Median DFS was 27.6 months (min, max: 0.4, 33.0; **Figure 2a**) over a median follow-up of 18.3 months (min, max: 1.8, 34.8). When censoring at time of HSCT, median DFS was 33.0 months (min, max: 0.4, 33.0; **Figure 2b**) over a median follow-up of 3.7 months (min, max: 1.3, 33.4)
- In sensitivity analysis, KM estimates for DFS at 24 months were calculated for various subgroups (**Figure 2c**). These KM estimates were similar for the following subgroups:
  - Pts who had HSCT prior to blinatumomab vs those who did not: 56.1% vs 54.8, respectively
  - Ph+ vs Ph-: 57.7% vs 54.1% respectively
- The KM estimate for DFS was numerically higher in pts who achieved a complete MRD or MRD response in the first two cycles of blinatumomab compared with those who did not (61.2% vs 36.9%) (**Figure 2c**)
- Subgroup analyses for DFS censored at time of HSCT showed similar results, with just a reversal of the KM estimates at 24 months for Ph- pts (54.1%) and Ph+ pts (57.7%) (data not shown)

Figure 2. Disease Free Survival in MRD-Positive Adult Patients (n = 108): Time-to-event Analysis (a) and After Additional Censoring at Time of HSCT (b)*

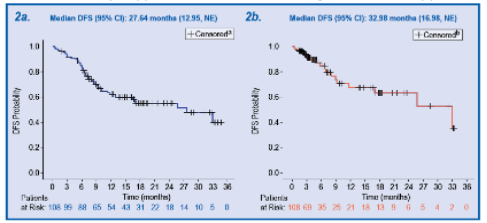
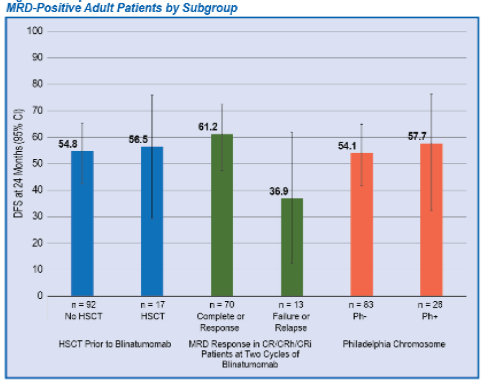


Figure 2c. Kaplan Meier Estimates for Disease Free Survival at 24 Months in MRD-Positive Adult Patients by Subgroup



*One patient was excluded from the analysis due to missing data
CI: confidence interval; CR: complete remission with full recovery of peripheral blood counts; CRh: Complete remission with partial recovery of peripheral blood counts; CRi: complete remission with incomplete recovery of peripheral blood counts; DFS: disease free survival; HSCT: hematopoietic stem cell transplant; MRD: minimal residual disease; NC: not estimable; Ph-: Philadelphia chromosome negative status; Ph+: Philadelphia chromosome-positive status
[a]Time to event analysis is censored if: patient is alive at the end of the study, clinician decision, and loss to follow up of HSCT
[b]Additional censoring at time of HSCT
Variation of numbers in each analysis is dependent on whether a pt experienced an event or was censored, and whether a pt was missing data information at or before the event or censoring

- Median overall survival (OS) and median OS censored at time of HSCT were not reached (over median follow-up times of 18.5 months, [min, max: 1.8, 34.8] and 4.0 months [min, max: 2.6, 13.7] respectively)
- At 24 months following blinatumomab initiation, the KM estimate for OS was 64.7% (95% CI: 52.8, 74.2) (Figure 3a). When censored at time of HSCT, the KM estimate was 77.6% (95% CI: 57.8, 88.9) (**Figure 3b**)
- In sensitivity analyses, KM estimates for OS at 24 months were calculated for various subgroups (**Figure 3c**):
  - OS was similar for pts who had HSCT prior to blinatumomab vs those who did not (67.0% vs 64.2% respectively)
  - OS was higher in pts who achieved a complete MRD or MRD response in the first two cycles of blinatumomab vs those who did not (71.5% vs. 57.1%)
  - OS was higher for Ph+ vs Ph- pts (71.7% vs 62.45%)
- Similar trends were seen in analyses censored at time for HSCT (data not shown)

Figure 3. Overall Survival in MRD-positive Adult Patients (n = 107): Time-to-Event Analysis (a) and After Additional Censoring at Time of HSCT (b)*

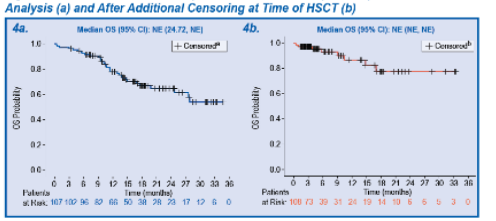
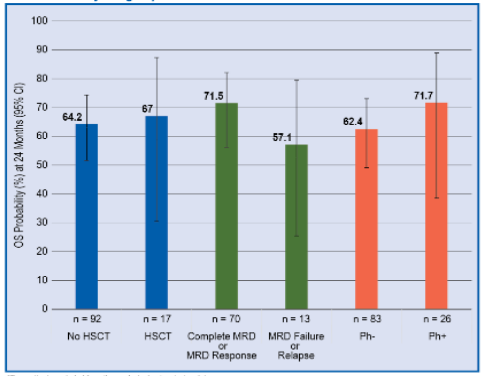


Figure 3c. Kaplan Meier Estimates for Overall Survival at 24 Months in MRD-Positive Adult Patients by Subgroup



*Two patients excluded from the analysis due to missing data
CI: confidence interval; HSCT: hematopoietic stem cell transplant; MRD: minimal residual disease; NC: not estimable; Ph-: Philadelphia chromosome negative status; Ph+: Philadelphia chromosome positive status; OS: overall survival
[a]Time-to-event analysis is censored if: patient is alive at the end of the study, clinician decision, and loss to follow-up of HSCT
[b]Additional censoring at time of HSCT

Outcomes Following Post-Blinatumomab HSCT

- In analysis of survival following allogeneic HSCT in pts who were not treated with any other myelosuppressive therapy between blinatumomab and transplant (n = 55), median survival was not reached (median-follow-up time of 15.5 months [min, max: 0.3, 33.0]) (data not shown)
- At 1 year, the KM estimate for survival after HSCT in pts without any intervening exposure to any other myelosuppressive therapy was 70.1% (95% CI: 54.8, 81.2) (data not shown)
- The KM estimate at 1 year in pts who achieved a complete MRD or MRD response in the first two blinatumomab cycles was 80.0% (95% CI: 62.3, 90.0), and 37.5% (95% CI: 8.7, 67.4) in pts who were in MRD failure or relapse (data not shown)
- Where relapse and death-due to-undocumented relapse were competing risks, median time to death was not reached: the cumulative incidence function estimate for non-relapse mortality at 3 months was 5.5% (95% CI: 1.9, 16.0), and at 12 months was 10.1% (4.3, 23.7), as illustrated in **Table 3**
- In pts who achieved complete MRD or MRD response in the first two blinatumomab cycles, the KM estimate for non-relapse death (relapse and death-due to undocumented relapse as competing risks) at 12 months was 10.7% (95% CI: 4.0, 28.6); pts with MRD failure or relapse the KM estimate was 11.8% (95% CI: 2.0, 68.3)

Table 3. Mortality After Allogeneic HSCT in MRD-Positive Adult Patients[a] (n = 55[b])

	Adults n = 55[c]	
	n	%
Number of Patients with Event (Death Not Due to Relapse)	6	10.7
Number of Patients with Competing Risk (Relapse/Death Due to Undocumented Relapse)	15	26.8
Number of Censored Patients	34	60.7
Cumulative Incidence Function Estimate for Death Not Due to Relapse[c], % (95%CI)		
3 months	5.5 (1.9, 16.0)	
12 months	10.1 (4.3, 23.7)	

[a]Patients who have not had any other myelosuppressive therapy between blinatumomab and transplant; [b]One pt was excluded from the analyses due to missing data; [c]Relapse and death-due to undocumented relapse treated as competing risks

CONCLUSIONS

- **In this large multi-country, multi-site study, blinatumomab was shown to induce MRD response within two cycles in the majority of MRD-positive patients who were evaluated**
- **The median DFS was over two years, while two-thirds of patients were still alive 24 months after initiation**
- **KM estimates of both DFS and OS at two years were consistently numerically higher in patients with MRD response compared to those without response**
- **This study demonstrates the real-world effectiveness of blinatumomab and is widely consistent with results from clinical study[2]**

REFERENCES

1. European Medicines Agency. Blincyto® (blinatumomab) Summary of Product Characteristics. 2019
2. Gökbuget, et al. *Blood*. 2018;131(14):1522-1531

DISCLOSURES

Nicolas Boissel has received honoraria from Amgen, Pfizer, Shire, Servier, Jazz and Ariad
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