High Molecular Remission Rate in Pediatric Patients With Relapsed/Refractory B-cell Precursor Acute Lymphoblastic Leukemia Treated With Blinatumomab: RIALTO, an Open-label, Multicenter, Expanded Access Study

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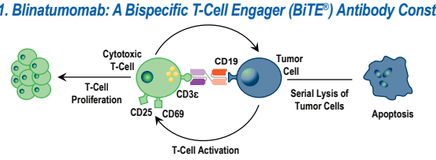
BACKGROUND

Outcomes Are Poor for Pediatric Patients With Relapsed/Refractory B-Cell Precursor Acute Lymphoblastic Leukemia (r/r Bcp-ALL)

- Although 99% of children with newly diagnosed ALL achieve a first remission with current risk-adapted protocols, approximately 15% will relapse and 8–10% will eventually die from disease progression or treatment-related complications[1]
- Long-term survival rates after marrow relapse for children with r/r Bcp-ALL range from less than 30% for early relapses to 50–60% for late relapses[2,3]
- Current standard-of-care treatments for relapsed ALL are associated with severe acute and long-term toxicities[4,5]
- New active agents with reduced toxicity are needed to improve outcomes for children with r/r Bcp-ALL

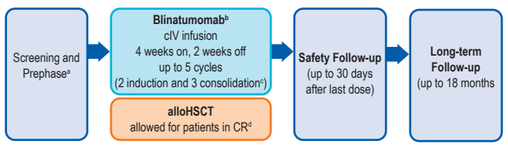
Figure 1. Blinatumomab: A Bispecific T-Cell Engager (BiTE®) Antibody Construct



- Blinatumomab redirects CD3-positive cytotoxic T-cells to lyse CD19-positive B-cells[6]
- A CR rate of 39% was achieved with blinatumomab monotherapy in pediatric patients with r/r Bcp-ALL in a phase 1b/2 study[7]
- Here we present results of an open-label, expanded access study of blinatumomab in pediatric patients with r/r Bcp-ALL (ClinicalTrial.gov NCT02187354)

RIALTO: EXPANDED ACCESS STUDY

Figure 2. Study Design: An Open-Label, Multicenter Expanded Access Study in Pediatric Patients with r/r Bcp-ALL



[a]Prephase 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 prephase medication. [b]Dosing: If <25% blasts at screening: 15 µg/m²/day; if ≥25% blasts at screening: 5 µg/m²/day on days 1–7 in cycle 1, then 15 µg/m²/day thereafter. [c]If patients achieve CR within first 2 cycles. [d]CR defined as no evidence of circulating blasts or extramedullary disease and <5% blasts in bone marrow. Patients could proceed to alloHSCT at any stage during treatment or follow-up. alloHSCT, allogeneic hematopoietic stem cell transplantation; cIV, continuous intravenous; CR, complete response; r/r Bcp-ALL, relapsed/refractory B-cell precursor acute lymphoblastic leukemia.

METHODS

Table 1. Patient Eligibility

Key Inclusion Criteria	• Age >28 days and <18 years • CD19-positive Bcp-ALL with ≥5% blasts in the bone marrow or <5% blasts and MRD level ≥10^{-3} • Relapsed/refractory disease defined as – Second or greater bone marrow relapse – Any relapse after allogeneic (allo) HSCT; or – Refractory to other treatments (chemotherapy/alloHSCT) • Adequate liver function defined as – ALT ≤135 IU/L in the European Union and Switzerland – ALT <5 times the upper limit of normal for age in the United States • Prior treatment with blinatumomab was allowed, provided the patient was not blinatumomab-refractory or intolerant, and leukemic cells were CD19 positive
Key Exclusion Criteria	• Clinically relevant CNS pathology • Chemotherapy within 2 weeks, radiotherapy within 4 weeks, or immunotherapy within 6 weeks of blinatumomab initiation • Grade 2–4 acute GvHD or active chronic GvHD • Immunosuppressive agents to prevent or treat GvHD within 2 weeks

ALT, alanine transaminase; CNS, central nervous system; GvHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease.

- This analysis focuses on the first 98 pediatric and adolescent patients enrolled into the expanded access study
- Data cutoff was March 9, 2018

Primary Endpoint: Safety

- Treatment-emergent adverse events (AE) and treatment-related AEs

Key Secondary Endpoints: Efficacy

- CR within the first 2 cycles
  - CR was defined as <5% blasts in the bone marrow, and was subclassified on the basis of peripheral blood count recovery
- Minimal residual disease (MRD) response within the first 2 cycles
  - MRD response was defined as <10^{-4} leukemic blasts measured by PCR or flow cytometry
- Relapse-free survival (RFS)
- Overall survival (OS)
- Rate of alloHSCT after CR

RESULTS

Table 2. Demographics and Baseline Characteristics

	All Patients (N=98)
Age, median (range), years	8.5 (0.4–17.0)
Age group, years, n (%)	
0–1	13 (13)
2–6	26 (27)
7–17	59 (60)
Male, n (%)	57 (58)
Blast category, n (%)	
<5%	9 (9)
5–49%	49 (50)
≥50%	40 (41)
Recurrent genetic abnormalities,[a] n (%)	
MLL rearranged	15 (15)
t(9;22) BCR-ABL	4 (4)
t(17;19)	2 (2)
t(12;21)/ETV6-RUNX1	8 (8)
Hypo/hyperdiploidy	1 (1)/5 (5)
Other	16 (16)
Constitutional trisomy 21 (Down syndrome), n (%)	4 (4)
Disease history, n (%)	
Primary refractory disease	14 (14)
Refractory to reinduction therapy	20 (20)
Second or greater relapse	55 (56)
Relapse after alloHSCT	41 (42)

[a]More than one type of genetic abnormality can be selected for the same patient. alloHSCT, allogeneic hematopoietic stem cell transplantation

- Median number of cycles started and completed: 2 (range, 1−5)
  - 37% of patients completed 2 cycles of blinatumomab
  - 4% of patients completed all 5 cycles of blinatumomab
- Primary reasons for discontinuation of blinatumomab included disease progression (26%), proceeding to alloHSCT (21%), >25% blasts at the end of cycle 1 (8%), AE (8%), hematological or extramedullary relapse subsequent to CR (7%), and study completion (5%)

Table 3. Safety Summary

Event, n (%)	Treatment-Emergent (N=98)	Treatment-Related (N=98)
AE, any grade	97 (99)	75 (77)
Grade ≥3	63 (64)	25 (26)
Grade ≥4	29 (30)	4 (4)
Serious AE	45 (46)	21 (21)
AE leading to treatment interruption	24 (24)	19 (19)
AE leading to treatment discontinuation	8 (8)	4 (4)
Fatal AE	9 (9)	0

AE, adverse event.

Table 4. Treatment-Emergent AEs (Any Grade) Occurring in ≥10% of Patients

Event, n (%)	All Patients (N=98)
Pyrexia	81 (83)
Vomiting	26 (27)
Headache	24 (24)
Anemia	19 (19)
Cough	16 (16)
Cytokine release syndrome	16 (16)
Nausea	16 (16)
Pain	15 (15)
Neutropenia	12 (12)
Abdominal pain	11 (11)
Fluid balance positive	11 (11)
Hypokalemia	11 (11)
Pain in extremity	11 (11)
Platelet count decreased	11 (11)
Back pain	10 (10)
Febrile neutropenia	10 (10)
Hypotension	10 (10)
Rash	10 (10)
Thrombocytopenia	10 (10)

AE, adverse event.

Table 5. Treatment-Emergent and Treatment-Related Adverse Event Categories of Interest, Grade ≥3

	All Patients (N=98)	
Event, n (%)	**Treatment-Emergent**	**Treatment-Related**
Cytopenias	30 (31)	9 (9)
Infections	16 (16)	0
Elevated liver enzymes	12 (12)	3 (3)
Infusion reactions	9 (9)	7 (7)
Neurologic events	5 (5)	4 (4)
Cytokine release syndrome	2 (2)	2 (2)
Tumor lysis syndrome	2 (2)	1 (1)
Capillary leak syndrome	0	0

Table 6. Best Response During the First 2 Cycles of Blinatumomab

	n (%)
All patients (N=98)	
CR during the first 2 cycles	59 (60)
CR with full recovery of peripheral blood counts	39 (40)
CR without full recovery of peripheral blood counts	20 (20)
Non-CR	
Hypoplastic or acellular bone marrow	1 (1)
Partial remission	1 (1)
Stable disease	4 (4)
Progressive disease	16 (16)
No response data or non-evaluable	17 (17)
Patients who achieved CR during first 2 cycles (N=59)	
MRD response during the first 2 cycles[a]	47 (80)
Proceeded to alloHSCT	27 (46)

alloHSCT, allogeneic hematopoietic stem cell transplantation; CR, complete response; MRD, minimal residual disease

Table 7. Best Response by Subgroup During the First 2 Cycles of Blinatumomab

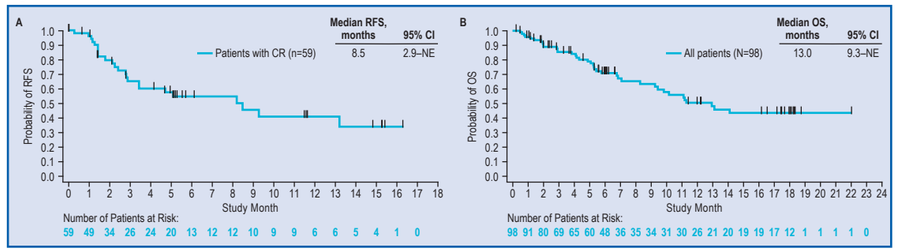
Patient Subgroup[a]	CR		CR With Full Hematologic Recovery		MRD	
	n/N1	%	n/N1	%	n/N1	%
Baseline blast category						
<5%	7/9	78	2/9	22	7/9	78
5–49%	35/49	71	25/49	51	29/49	59
≥50%	17/40	43	12/40	30	11/40	28
Genetic abnormality						
Yes	25/47	53	18/47	38	18/47	38
No	34/50	68	21/50	42	29/50	58
t(17;19)	2/2	100	2/2	100	2/2	100
Down syndrome	3/4	75	2/4	50	3/4	75
Prior alloHSCT						
Yes	26/43	60	19/43	44	20/43	47
No	33/55	60	20/55	36	27/55	49
Prior blinatumomab	3/4	75	3/4	75	2/4	50
Prior relapses						
1	15/26	58	10/26	38	10/26	38
≥2	36/57	63	23/57	40	31/57	54

[a]Response data unavailable or unevaluable for 17 patients in the full analysis set (N=98). alloHSCT, allogeneic hematopoietic stem cell transplantation; CR, complete response; MRD, minimal residual disease; n/N1, number of responders/total number of patients in each category

Efficacy Outcomes During the First 2 Cycles of Blinatumomab

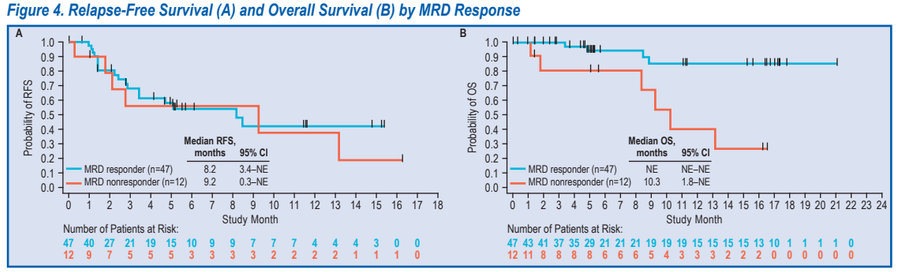
- Of 59 patients with a CR during the first 2 cycles, 47 (80%) had a molecular response and 27 (46%) proceeded to alloHSCT
  - 19 patients relapsed and 5 died after a median follow-up of 5.3 months
- Of 89 patients with ≥5% blasts at baseline, 52 (58%) achieved CR during the first 2 cycles; of these, 40 (77%) also had an MRD response
- Among patients with a CR in the first 2 cycles (n=59), median RFS was 9.2 months (95% confidence interval [CI] 3.4–not evaluable [NE]) for those with <50% blasts at baseline, and 5.1 months (2.1–13.2) for those with ≥50% blasts at baseline
  - Median OS was NE (95% CI, 11.1–NE) for patients with <50% blasts, and 7.1 months (95% CI, 5.1–11.3) for patients with ≥50% blasts at baseline

Figure 3. Relapse-Free Survival (A) and Overall Survival (B)



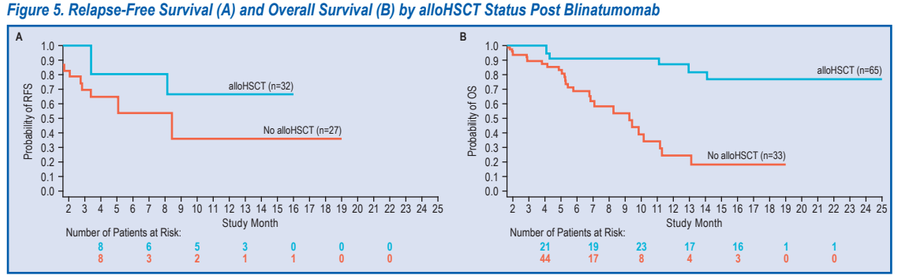
RFS is based only on responders and calculated from time of CR. Survival estimates calculated by Kaplan-Meier method. CI, confidence interval; CR, complete response; NE, not estimable; OS, overall survival; RFS, relapse-free survival.

Figure 4. Relapse-Free Survival (A) and Overall Survival (B) by MRD Response



RFS and 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; RFS, relapse-free survival.

Figure 5. Relapse-Free Survival (A) and Overall Survival (B) by alloHSCT Status Post Blinatumomab



Survival estimates calculated by Simon-Makuch method using a 42-day landmark. alloHSCT, allogeneic hematopoietic stem cell transplantation.

CONCLUSIONS

- In this expanded access study, single-agent blinatumomab resulted in a CR rate of 58% in pediatric patients with r/r Bcp-ALL who had ≥5% blasts at baseline
  - 77% of patients who achieved a CR with blinatumomab also had an MRD response during the first 2 cycles
  - Of 9 patients who had CR at baseline (with MRD ≥10^{-3}), 7 achieved an MRD response during the first 2 cycles
  - 46% of responders proceeded to alloHSCT
  - We observed a higher response rate among patients with lower tumor burden at baseline (<50% blasts)
  - Among responders, the OS probability was better if MRD response was achieved
- The safety profile of blinatumomab was consistent with prior studies[7,8]
  - Adverse events (including cytokine release syndrome and neurologic events) were consistent with those previously reported for r/r Bcp ALL
  - Discontinuation due to treatment-related AEs was infrequent
- These data further support the use of blinatumomab for children and adolescents with CD19 positive Bcp-ALL

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AUTHOR DISCLOSURES

F. Locatelli reports speakers' bureau and consulting fees from Amgen Inc. G. Zugmaier is employed by, holds stock in, and has patents/royalties/other intellectual property with Amgen Inc. P. Bader reports speakers' bureau and consulting fees from Novartis, patents, royalties and research funding from Medac, research funding from Riemser and Neovii, and consulting fees from Celgene. C. Rossig reports honoraria and consulting fees from Amgen and honoraria from Pfizer. S. Jeha, P.-G. Schlegel, J-P. Bourquin, R. Handgretinger, B. Brethon, and C. Chen-Santel have nothing to disclose.

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