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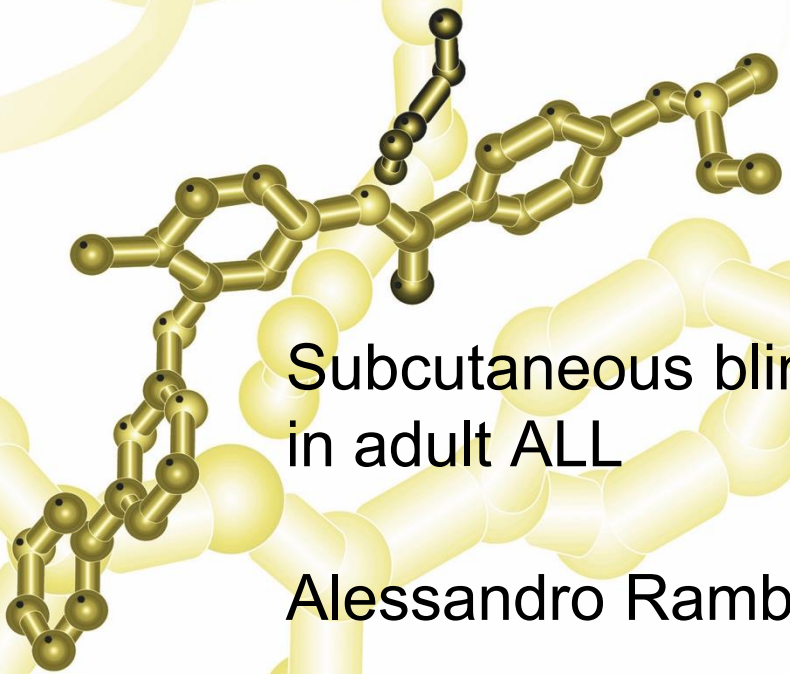

Subcutaneous blinatumomab in adult ALL

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New Drugs in Hematology

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Disclosures of Alessandro Rambaldi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen			✓			✓	✓
Pfizer			✓				
Novartis			✓			✓	
Kite Gilead			✓			✓	✓
Jazz			✓			✓	✓
Omeros			✓			✓	✓

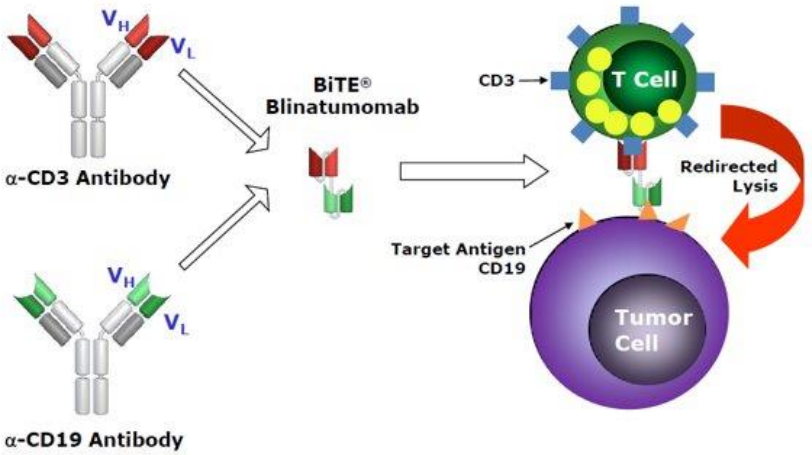
BACKGROUND

Blinatumomab is a bispecific T-cell engager (BiTE®) that redirects $CD3^+$ T cells to engage and lyse $CD19^+$ target cells.

Blinatumomab is approved for the treatment of adults and children with R/R and MRD positive BP-ALL in more than 50 countries, including USA and EU.

The approved route of administration of blinatumomab is by continuous intravenous (cIV) infusion, for which hospitalization is recommended for up to 9 days.

Blinatumomab, is the front runner of the BiTE® antibody class



Dirk Nagorsen and Patrick A. Baeuerle. Exp Cell Res 2011 May 15;317(9):1255-60

Subcutaneous Administration of Blinatumomab: background

- SC blinatumomab has been tested for safety and tolerability in R/R indolent non-Hodgkin's lymphoma in a phase 1b trial (NCT02961881); a favorable safety profile was obtained and SC blinatumomab was well tolerated[1].

- The encouraging safety profile observed in this previous trial of the SC mode of administration prompted the evaluation of SC blinatumomab in patients with R/R B-ALL.

- This ongoing phase 1b, multicenter, single-arm, open-label, dose-escalation study (NCT04521231) evaluated the safety and tolerability of SC blinatumomab in patients with R/R B-ALL.

[1] Rossi G, et al. Poster presented: 63rd Annual Meeting of the American Society of Hematology; December 2021; Atlanta, USA

Subcutaneous Administration of Blinatumomab: rationale

- SC administration of blinatumomab (SC blinatumomab) can
  - simplify administration, improve convenience, reduce the treatment burden, and decrease the cost for patients
  - eliminate the need for a central line or continuous venous access and infusion device (pump)
  - abrogate the risk of device-related complications such as overdose caused by incorrect pump settings, dose interruptions from intravenous line occlusion, and line infections
  - deliver earlier target dose (cycle 1 day 1) and overall higher dose of blinatumomab to patients
  - improve the overall health-related quality of life of patients

Patient Eligibility

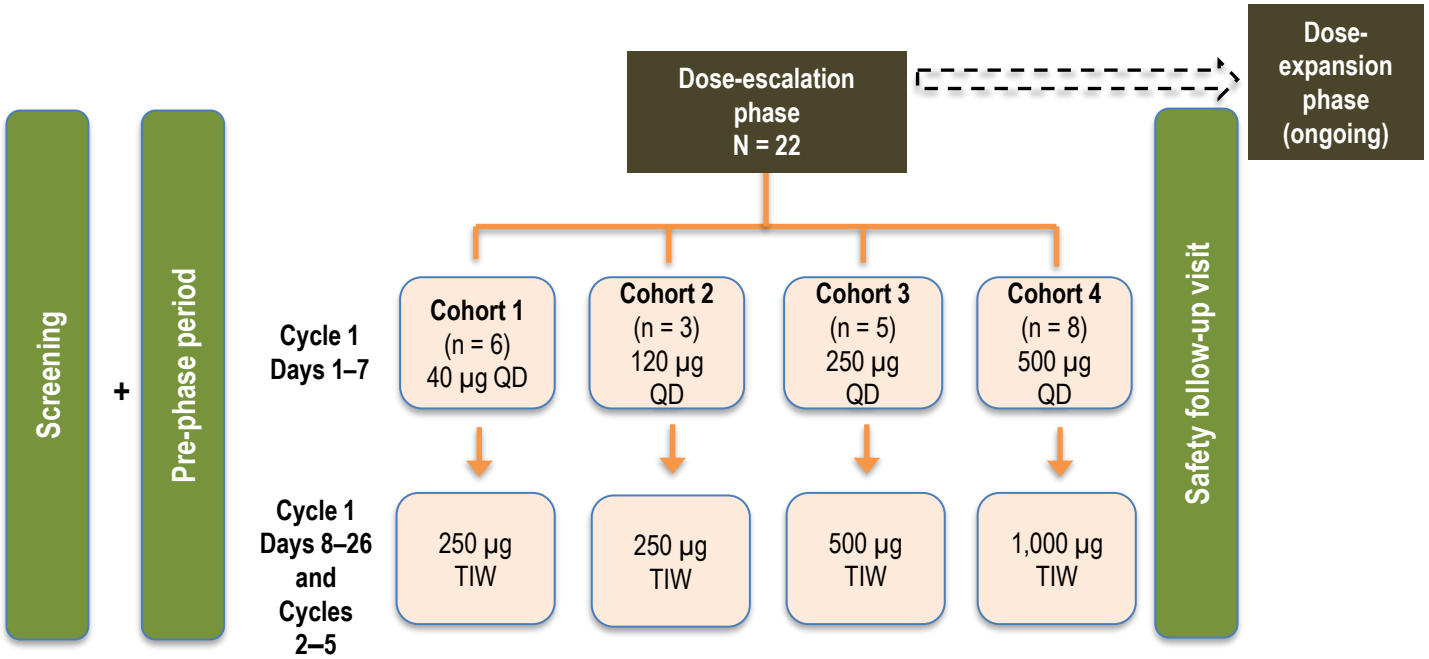
- Age ≥ 18 years
- Diagnosis of B precursor-ALL
- Refractory to primary induction therapy or salvage therapy
- Relapsed disease including
  - untreated relapse (any stage)
  - refractory relapse or relapse after any salvage therapy
  - relapse after allogenic hematopoietic stem cell transplant (HSCT)
- Eastern Cooperative Oncology Group performance status score ≤ 2
- ≥ 5% blasts in the bone marrow

Study Objectives

- The primary objective was to evaluate the safety and tolerability of SC blinatumomab in patients with R/R B-ALL.

- The secondary objectives were to assess
  - pharmacokinetics (PK)
  - pharmacodynamics (PD), and
  - efficacy of SC blinatumomab in patients with R/R B-ALL

Study Design



Bone marrow evaluation was performed on day 27 of each cycle and additionally on day 12 of cycle 1 in cohorts 3 and 4.
QD, once daily; R/R B-ALL, relapsed/refractory B-cell acute lymphoblastic leukemia; SC, subcutaneous; TIW, three times weekly.

Pilar Martínez-Sánchez et al.: ASH 2022

Efficacy assessments

- Complete remission with full hematologic recovery (CR) was defined as
  - less than 5% blasts in the bone marrow; no evidence of disease, and
  - full recovery of peripheral blood counts
    - platelet count > 100,000/µL
    - absolute neutrophil count > 1,000/µL
- Complete remission with only partial hematological recovery (CRh) was defined as
  - less than 5% blasts in the bone marrow; no evidence of disease, and
  - partial recovery of peripheral blood counts:
    - platelet count > 50,000/µL
    - absolute neutrophil count > 500/µL
- An MRD-negative response was defined as the presence of $< 10^{-4}$ leukemic blasts detectable by flow cytometry or polymerase chain reaction.

Demographics and baseline characteristics of patients with R/R B-ALL treated with SC blinatumomab

	Total (N = 22)	Cohort 1 (n = 6)	Cohort 2 (n = 3)	Cohort 3 (n = 5)	Cohort 4 (n = 8)
Age in years, (median) range	50.0 (19–83)	63.5 (38–83)	64.0 (31–72)	37.0 (19–70)	39.5 (26–71)
Age group, years, n (%)					
18–54	12 (54.5)	2 (33.3)	1 (33.3)	4 (80.0)	5 (62.5)
55–64	3 (13.6)	1 (16.7)	1 (33.3)	0 (0.0)	1 (12.5)
≥ 65	7 (31.8)	3 (50.0)	1 (33.3)	1 (20.0)	2 (25.0)
Sex, n (%)					
Male	12 (54.5)	3 (50.0)	1 (33.3)	1 (20.0)	7 (87.5)
Race, n (%)					
White	16 (72.7)	4 (66.7)	3 (100.0)	4 (80.0)	5 (62.5)
Other[a]	5 (22.7)	2 (33.3)	0 (0.0)	1 (20.0)	2 (25.0)
Data not available	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
Ethnicity, n (%)					
Hispanic/Latino	7 (31.8)	0 (0.0)	1 (33.3)	2 (40.0)	4 (50.0)
Not Hispanic/Latino	13 (59.1)	5 (83.3)	2 (66.7)	3 (37.5)	3 (59.1)
Data not available	2 (9.1)	1 (16.7)	0 (0.0)	0 (0.0)	1 (12.5)
Extramedullary disease, n (%)					
Yes	2 (9.1)	1 (16.7)	1 (33.3)	0 (0.0)	0 (0.0)
Central nervous system	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other sites	2 (9.1)	1 (16.7)[b]	1 (33.3)[c]	0 (0.0)	0 (0.0)
No	20 (90.9)	5 (83.3)	2 (66.7)	5 (100.0)	8 (100.0)

[a]Other implies races other than American Indian or Alaska Native, Asian, Black or African American, or Native Hawaiian or Other Pacific Islander. [b]Face mass. [c]Lymph node.
R/R B-ALL, relapsed/refractory B-cell acute lymphoblastic leukemia; SC, subcutaneous.

Demographics and baseline characteristics of patients with R/R B-ALL treated with SC blinatumomab

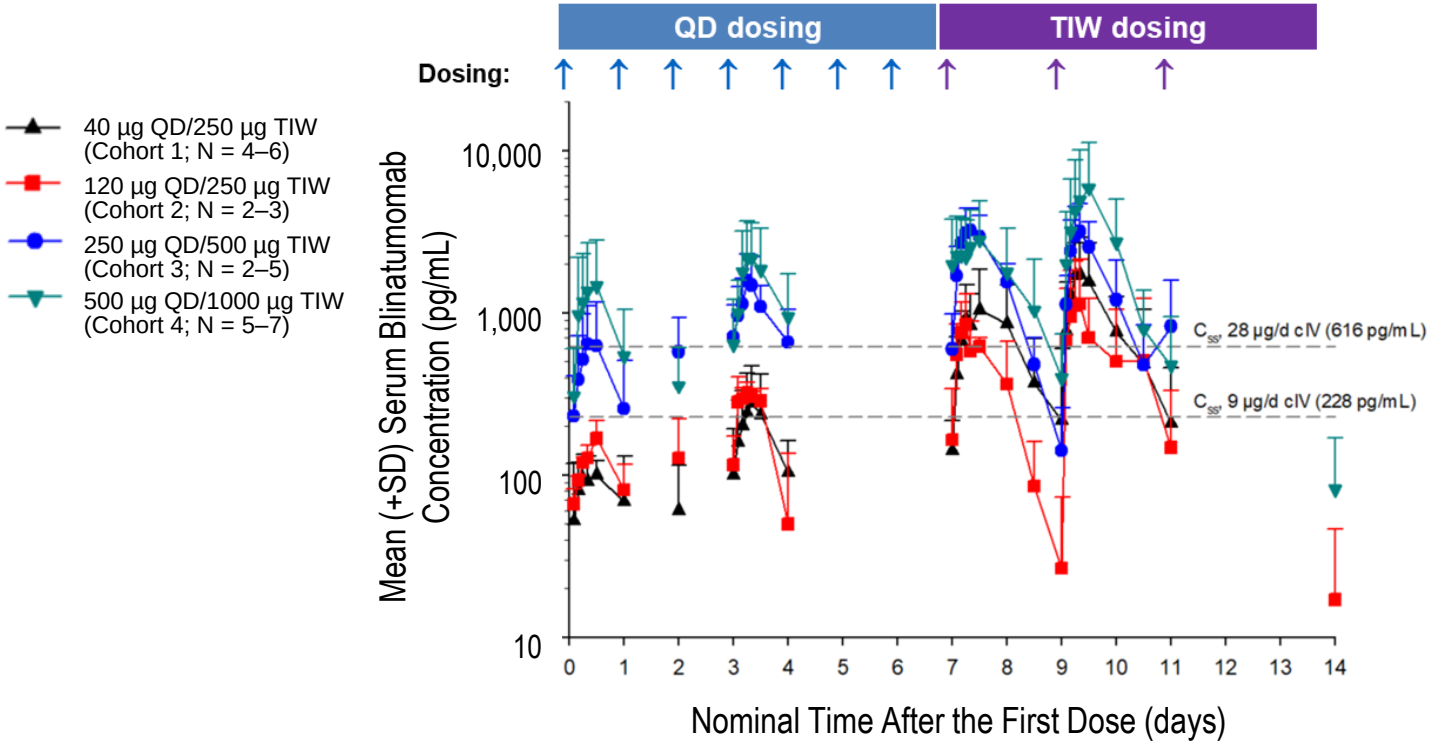
- The median bone marrow blast count at the start of the study was 76.5% (range, 6% to 100%).
- Five patients were primary refractory to frontline therapy.
- Nine patients had disease relapse after chemotherapy.
- One patient had refractory relapse.
- Four patients had disease relapse after HSCT.
- Disease relapse was observed in 1 patient after HSCT and anti-CD19 chimeric antigen receptor T cell therapy (antiCD19 CART).
- Disease relapse was observed in 1 patient after antiCD19 CART.
- Disease relapse was observed in 1 patient after two prior HSCTs and blinatumomab therapy
- The median number of cycles of SC blinatumomab received was 1 (range, 1 to 5).
- Seven patients received one cycle, two patients received two cycles, one patient received three cycles, one patient received four cycles, and three patients received five cycles. Eight patients ended the treatment during cycle 1.

Safety: summary of treatment-emergent adverse events

	Total (N = 22)	Cohort 1 (n = 6)	Cohort 2 (n = 3)	Cohort 3 (n = 5)	Cohort 4 (n = 8)
TEAEs (any grade)	22 (100.0)	6 (100.0)	3 (100.0)	5 (100.0)	8 (100.0)
Grade ≥ 3 TEAEs	19 (86.4)	6 (100.0)	2 (66.7)	4 (80.0)	7 (87.5)
Serious TEAEs	18 (81.8)	4 (66.7)	2 (66.7)	5 (100.0)	7 (87.5)
Serious TEAEs leading to discontinuation of SC blinatumomab (excluding disease progression)	3 (13.6)	1 (16.7)	0 (0.0)	1 (20.0)	1 (12.5)
Fatal adverse events	3 (13.6)	1[a] (16.7)	0 (0.0)	1[b] (20.0)	1[c] (12.5)
Grade ≥ 3 TEAEs of interest					
Cytokine release syndrome	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	2[b] (25.0)
Blinatumomab-associated neurotoxicity[e]	6 (27.3)	1 (16.7)	0 (0.0)	1 (20.0)	4[f] (50.0)
Transient liver enzyme elevation	2 (9.1)	0 (0.0)	0 (0.0)	1 (20.0)	1 (12.5)

[a]Grade 5 herpes encephalitis unrelated to SC blinatumomab. [b]Progressive disease. [c]Refractory bleeding event unrelated to SC blinatumomab and disease progression. [d]Each event resolved within 48 h and subsequent cycle 1 dose was restarted. [e]At week 1 of treatment with SC blinatumomab. [f]Two patients with neurotoxicity in week 1 and two patients in week 4, one associated with nonresponse and the other with the concomitant use of psychotropic (antipsychotic) medications.
SC, subcutaneous; TEAE, treatment-emergent adverse event.

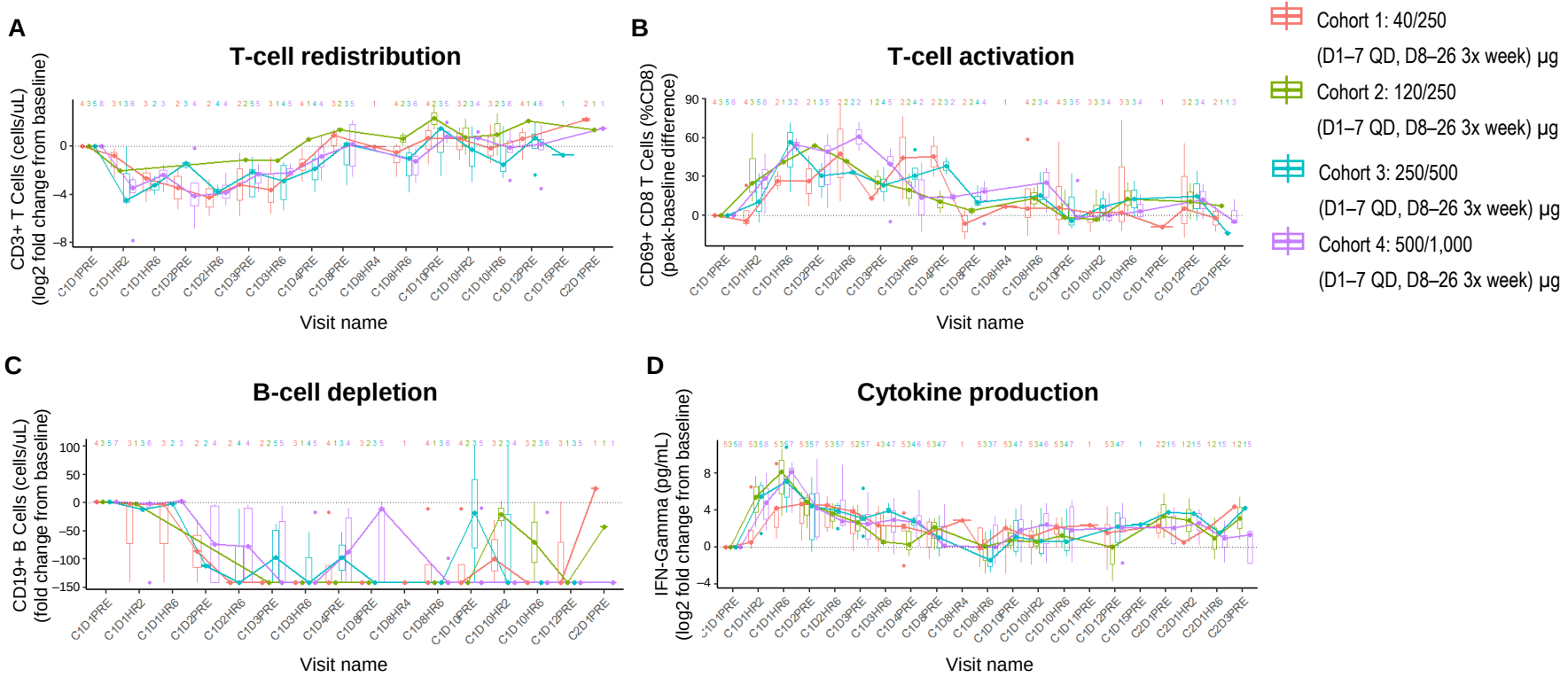
Pharmacokinetics: Mean (SD) concentration-time profiles of SC blinatumomab



- A dose-related increase was observed
- Gradual increase in exposure
- Peak concentrations achieved with a median of 6–12 h
- Apparent increase in half-life (observed mean of 8–19 h for SC compared with a short half-life of ~2 h for cIV).
- Encouraging estimated SC bioavailability
- Lack of impact of immunogenicity on bioavailability with multiple dosing.

Dashed horizontal lines represent the mean C_{ss} values of 228 and 616 pg/mL for 9 and 28 mg/day cIV doses, respectively, in patients with relapsed or refractory B-ALL[2].
B-ALL, B-cell acute lymphoblastic leukemia; cIV, continuous intravenous; C_{ss}, steady-state concentration; N, number of patients; QD, once daily; SC, subcutaneous; SD, standard deviation; TIW, three times weekly.

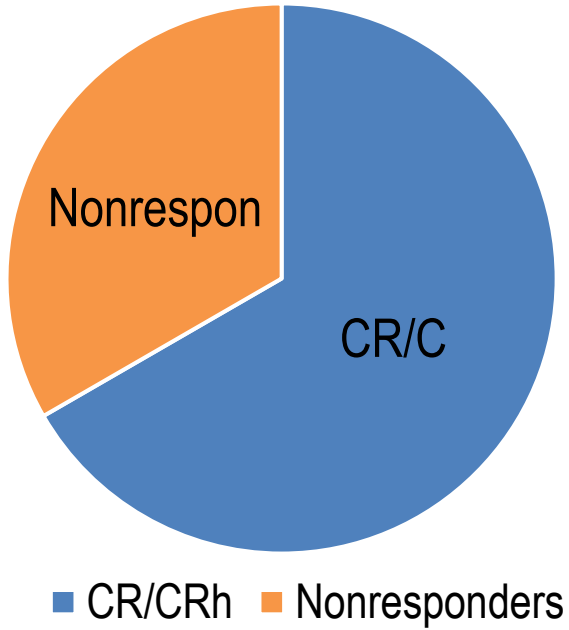
Pharmacodynamics: markers in response to SC blinatumomab treatment



The top, middle, and bottom of the boxes in A–D depict the third quartile, median, and first quartile, respectively.
C, cycle; cIV, continuous intravenous; D, day; HR, hour after SC blinatumomab dose; IFN, interferon; PRE, before SC blinatumomab dose; SC, subcutaneous.

Efficacy: Response rates with SC blinatumomab

- Response evaluation was available for only 21[a] of 22 patients.
- Fourteen of 21 (66.7%) evaluable patients achieved CR/CRh within one cycle of SC blinatumomab
  - Cohort 1, 3/6 (50.0%)
  - Cohort 2, 2/3 (66.7%)
  - Cohort 3, 4/5 (80.0%)
  - Cohort 4, 5/7 (71.4%)
    - Two patients who did not respond were underexposed to SC blinatumomab based on serum levels of blinatumomab.
- Thirteen of 14 patients with CR/CRh were MRD-negative after cycle 1 of SC blinatumomab
  - Eight of 14 patients underwent bone marrow evaluation at day 12, of which 100% of patients were MRD-negative on day 12.



[a]Response evaluation was not done for one patient either at day 12 or day 27 since he developed bleeding complications unrelated to SC blinatumomab and was taken off treatment. Additionally, bone marrow evaluation was not done as the patient was too sick.
CR, complete remission with full hematologic recovery; CRh, complete remission with partial hematologic recovery.

Efficacy: Response rates with SC blinatumomab

- At the data cut-off of September 15, 2023
  - 29 patients were treated: 14 at the 250µg/500µg dose and 13 at 500µg/1000µg dose. Data from two ineligible patients were excluded.
  - At the end of two cycles, 12 of 14 patients (85·7%) from the 250 µg/500 µg dose achieved CR/CRh of which nine patients (75·0%) were negative for measurable residual disease (MRD; $<10^{-4}$ leukemic blasts).
  - At the 500µg/1000µg dose, 12 of 13 patients (92·3%) achieved CR/CRh; all 12 patients (100·0%) were MRD-negative

Jabbour E. et al: American Journal of Hematology, 2024 in press

SUMMARY

- SC blinatumomab demonstrated
  - a manageable safety profile and acceptable antileukemic activity in heavily pretreated patients with R/R B-ALL,
  - PK exposures and PD profiles were consistent with those reported for the cIV regimen of blinatumomab, and
  - no evidence for immunogenicity to SC blinatumomab as all patients were negative for antiblinatumomab antibodies.
- These data validate the continued investigation of SC blinatumomab as a treatment option for patients with R/R B-ALL.

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