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Original Research

Long-term follow-up of blinatumomab in patients with relapsed/refractory Philadelphia chromosome–positive B-cell precursor acute lymphoblastic leukaemia: Final analysis of ALCANTARA study

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KEYWORDS
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Philadelphia chromosome–positive

Abstract ***Aim:*** To evaluate long-term durability of blinatumomab, a BiTE® (bispecific T-cell engager) molecule, in adults with relapsed/refractory (R/R) Philadelphia chromosome–positive (Ph+) B-cell precursor acute lymphoblastic leukaemia (ALL).
Methods: In this final analysis of an open-label, single-arm, phase 2, multicentre ALCANTARA study (NCT02000427), adults (age ≥18 years) with Ph+ ALL who had relapsed or were refractory to at least one TKI were included. The primary endpoint was the proportion of patients who achieved complete remission (CR)/CR with partial haematologic recovery (CRh) during the first two cycles of blinatumomab treatment.

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Results: The final analysis included 45 patients who completed the study between 3rd January 2014 and 6th January 2017, of which 16 (35.6%; 95% CI, 21.9%–51.2%) achieved CR/CRh within the first two blinatumomab cycles. After a median follow-up of 16.1 months, median relapse-free survival (RFS) was 6.8 (95% CI, 4.4–not estimable [NE]) months. Median overall survival (OS) was 9.0 (95% CI, 5.7–13.5) months with a median follow-up of 25.1 months. Median OS in patients with CR (19.8 [95% CI, 12.1–NE] months) was greater than in those without CR (6.0 [95% CI, 2.9–7.1] months). Of 16 patients with CR/CRh, 14 achieved complete minimal residual disease (MRD) response; the median duration of complete MRD response was 9.7 (95% CI, 5.2–NE) months. Treatment-related adverse events were consistent with those previously reported.

Conclusion: Long-term durability of responses to blinatumomab was demonstrated in patients with R/R Ph+ ALL.

1. Introduction

The Philadelphia (Ph) chromosome, characterised by t(9;22)(q34;q11) translocation, is the most common cytogenetic abnormality found in patients with acute lymphoblastic leukaemia (ALL) [1,2]. Approximately 25% of adults with B-cell precursor (BCP) ALL constitutes Ph chromosome–positive (Ph+) ALL characterised by a *BCR-ABL1* fusion gene formed on the Ph chromosome [1,3]. This gene encodes a tyrosine kinase with dysregulated activity and is responsible for leukaemia [4]. BCR-ABL1 protein-specific tyrosine kinase inhibitors (TKIs) play a key role in the treatment of Ph+ ALL [5]. Although complete remission (CR) rates > 90% were reported when TKIs were either included in conventional induction therapy or used alone, relapse occurred in 14%–48% of patients and was associated with resistance substitutions in the ABL kinase domain [6–11]. Hence, alternative therapies are needed for the treatment of patients with relapsed/refractory (R/R) Ph+ ALL.

Blinatumomab, a BiTE® (bispecific T-cell engager) molecule, is engineered to engage cytotoxic T cells with CD19 expressing B cells, thereby leading to the lysis of the targeted B cells [12]. Blinatumomab is indicated for the treatment of adults and children with R/R BCP ALL and BCP ALL with minimal residual disease (MRD) [13]. Results from the primary analysis of a phase 2 study in patients with Ph+ BCP ALL who had relapsed or were refractory to TKIs reported that blinatumomab was efficacious with adverse events (AEs) consistent with previous experience in patients with Ph^- BCP ALL [3]. A propensity score analysis of these data compared with historical control data of patients who received standard of care (i.e., induction chemotherapy plus TKI) after the failure of or resistance to treatment with second-generation TKIs further supports blinatumomab as a treatment option in patients with R/R Ph+ ALL [14]. As an extension of the primary analysis [3], we report findings from the final analysis after a long-term follow-up period.

2. Methods

2.1. Patients

As previously described [3], this was an open-label, single-arm, phase 2, multicentre study to evaluate the efficacy and safety of blinatumomab in patients with R/R Ph+ ALL conducted across 19 centres in France, Germany, Italy, the United Kingdom and the United States (NCT02000427). In this final analysis, safety and efficacy analyses were re-run and updated from the primary analysis. Adults (age ≥ 18 years) with Ph+ ALL BCP ALL who had relapsed after or were refractory to at least one second-generation or later TKI (dasatinib, nilotinib, bosutinib and ponatinib), or were intolerant to second-generation or later TKIs and intolerant or refractory to imatinib mesylate were included in the study. Key exclusion criteria were history or presence of clinically relevant central nervous system (CNS) pathology, active CNS ALL, active acute or chronic (grades 2–4) graft-versus-host disease, systemic treatment of graft-versus-host disease within 2 weeks before treatment start, allogeneic haematopoietic stem cell transplantation (alloHSCT) within 12 weeks before the start of blinatumomab treatment, and isolated extramedullary disease. Any TKI therapy, anti-tumour therapy other than blinatumomab, chronic systemic high-dose corticosteroid therapy, or other immunosuppressive therapies were prohibited during treatment. Appropriate protocol approvals were obtained from the ethics committee at each study site. The studies were conducted in conformance with Good Clinical Practice standards. All patients provided written informed consent before the start of the study.

2.2. Study design and procedures

The study included a 3-week screening and pre-phase period, an induction treatment period, a consolidation treatment period, and a safety follow-up visit 30 days after treatment. Each treatment cycle consisted of 4 weeks of continuous intravenous (cIV) infusion of blinatumomab followed by a 2-week treatment-free interval. In the first cycle, blinatumomab was administered as a cIV infusion in adult patients at 9 μg/day in week 1 followed by 28 μg/day during weeks 2–4. In subsequent cycles, patients received blinatumomab at 28 μg/day during weeks 1–4. Patients received two cycles initially for induction of remission. CR was defined as ≤ 5% bone marrow blasts, platelets > 100,000/μL, and absolute neutrophil count (ANC) > 1000/μL. CR with partial haematologic recovery (CRh) was defined as ≤ 5% bone marrow blasts, platelets > 50,000/μL, and ANC > 500/μL. Three additional consolidation cycles were administered to patients who had achieved CR/CRh during the induction treatment period. A total of six long-term follow-up visits (every 3 months for 18 months) were scheduled after the safety follow-up visit to evaluate overall survival (OS) and response duration. Additional details of the treatment cycles, including those of blinatumomab and dexamethasone administration, have been reported previously [3]. MRD response was determined by *BCR-ABL1* quantification only for patients achieving CR/CRh. Complete MRD response was defined as no detectable *BCR-ABL1* transcripts by allele-specific real-time quantitative polymerase chain reaction (RT-PCR) with an internal *ABL* amplification control as established by a central laboratory (LabCorp, Burlington, NC, USA; assay sensitivity ≥ 10^{-5}; 0.00% *BCR-ABL1*/*ABL1*).

2.3. Endpoints and statistical analysis

Safety and efficacy analyses were performed on a full analysis set that included all patients who received at least one dose of blinatumomab infusion. In cycles 1–5, 45 (100%), 28 (62%), 12 (27%), nine (20%) and seven (16%) patients started blinatumomab treatment cycles, respectively. The primary endpoint was to evaluate the proportion of patients who achieved CR/CRh during the first two cycles of blinatumomab treatment, wherein an exact binomial 95% confidence interval (CI) was provided. The sample size was calculated for Simon's two-stage design based on a one-sided type I error of 0.025 and a power of 90% to detect the effective response rate assumption of ≥ 30% over an ineffective treatment rate of ≤ 10%.

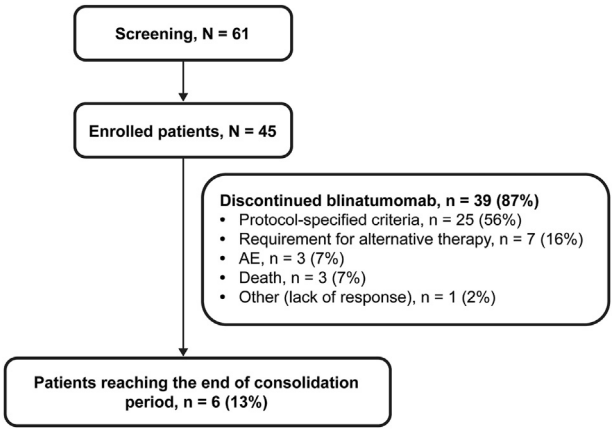

Fig. 1. Patient disposition. AE, adverse event.

The secondary endpoints included MRD responses during the first two cycles of treatment, relapse-free survival (RFS), duration of CR/CRh, OS, alloHSCT after blinatumomab-induced remission and 100-day mortality rate after alloHSCT. Endpoints have been defined previously [3]. The Kaplan-Meier method was used to estimate the duration of CR/CRh, RFS, OS and 100-day mortality rate following alloHSCT.

3. Results

3.1. Patient disposition, demographics and baseline characteristics

The final analysis involved all patients who completed the study between 3rd January 2014 and 6th January 2017. Of the 61 patients screened, 45 patients (74%) were enrolled in the study. A majority of the patients discontinued treatment due to protocol-specified criteria (56%), including premature end of the induction phase due to disease, or clinical progression without prior CR/CRh/CR with incomplete haematologic recovery (27%), intention to receive alloHSCT (13%), failure to achieve response within two blinatumomab cycles (9%) and occurrence of haematologic or extramedullary relapse subsequent to achieving response on treatment (7%); six patients completed the consolidation treatment period (13%; Fig. 1). A total of eight patients (18%) completed the study, and 37 patients (82%) had died by the end of the study.

Demographics and baseline characteristics of patients who were enrolled in the study were reported previously [3]. The median age of patients was 55 years (range, 23–78 years). A majority of patients had received ≥ 2 prior TKIs, including 39 (87%) patients treated with dasatinib. A total of 34 (76%) patients had ≥ 50% bone

marrow blasts, and 20 (44%) patients underwent prior alloHSCT.

3.2. Response

3.2.1. Best overall response of CR/CRh within the first two cycles

The data pertaining to the primary efficacy endpoint were similar to the outcomes of primary analysis in the full analysis set (N = 45) [3]. In the primary analysis, 16 (35.6%; 95% CI, 21.9%–51.2%) patients achieved CR/CRh within the first two cycles of blinatumomab treatment; the result remained unchanged at the time of the final analysis. Of these, 14 (31.1%; 95% CI, 18.2%–46.6%) patients achieved CR and two (4.4%; 95% CI, 0.5%–15.1%) achieved CRh.

3.2.2. MRD response during the first two cycles

The MRD response data were similar in the primary and final analysis for patients in the full analysis set. A complete MRD response was observed in 14 of the 16 (87.5%; 95% CI, 61.7%–98.4%) CR/CRh responders, of which 12 (85.7%) patients had a CR and two (100%) patients had a CRh.

3.3. Survival

3.3.1. RFS

The median RFS was 6.8 (95% CI, 4.4–not estimable [NE]) months, with a median follow-up of 16.1 (95% CI, 10.6–22.6) months in patients with a CR/CRh. Of the 16 responders after two blinatumomab cycles, five (31%) patients were relapse-free, ten (63%) had a relapse and one patient died. A sensitivity analysis that censored prior to transplant showed similar results (Fig. 2). Median RFS in patients with CR/CRh in the first two blinatumomab cycles with P190 isoform of *BCR-ABL1* (n = 10) was 6.7 (95% CI, 3.7–NE) months and was NE with P210 isoform.

3.3.2. OS

The median OS was 9.0 (95% CI, 5.7–13.5) months with a median follow-up of 25.1 (95% CI, 20.8–25.9) months. Of the 45 patients included in the analysis, eight (18%) were alive. The median OS was not impacted when censoring for alloHSCT (9.0 [95% CI, 5.7–13.5] months) with a similar median follow-up duration (24.8 [95% CI, 10.9–25.9] months). Additionally, the median OS in patients with CR/CRh (23.0 [95% CI, 12.6–NE] months) was greater than that in patients without CR/CRh (5.7 [95% CI, 3.4–6.5] months); median OS for the 14 patients with complete MRD response was not estimable (Fig. 3).

In a subgroup of patients with *BCR-ABL1* mutations (n = 17), the median OS was 6.5 (95% CI, 4.2–NE) months. Median OS was not estimable for 10 patients with T315I mutations and was 5.6 (95% CI, 0.8–12.1) months in seven patients with mutations other than T315I. In a subgroup of patients with P190 (n = 26) and P210 isoforms (n = 16) of *BCR-ABL1*, the median OS was 12.1 (95% CI, 5.3–NE) months and 6.4 (95% CI, 2.9–NE) months, respectively.

3.3.3. Duration of remission

The median time to haematologic relapse (duration of remission) for the 16 CR/CRh responders was 6.8 (95% CI, 4.5–NE) months. Eleven of 16 CR/CRh responders received TKIs during the long-term follow-up period. Censoring prior to the time of alloHSCT did not alter the duration of remission (6.7 [95% CI, 3.8–NE] months). The duration of remission was 9.7 (95% CI, 5.2–NE) months for the complete MRD responders

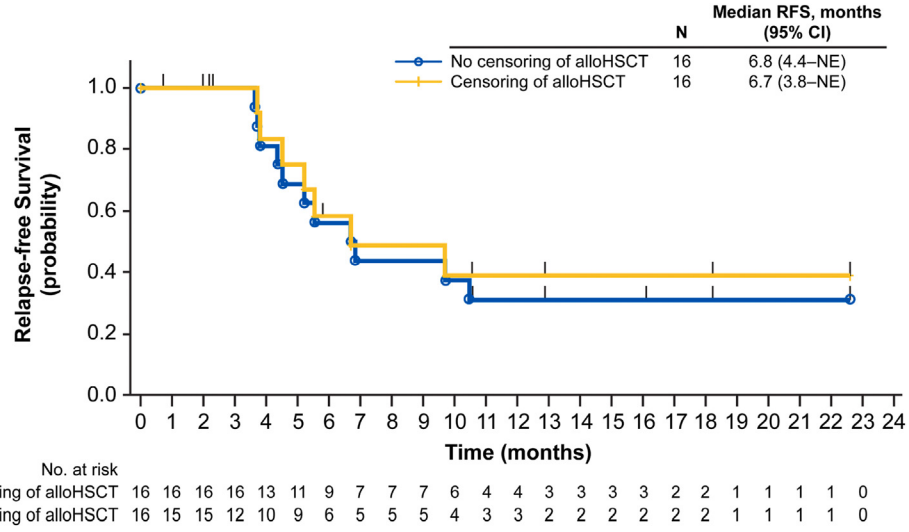

Fig. 2. Relapse-free survival. Vertical bars indicate censoring. alloHSCT, allogeneic haematopoietic stem cell transplantation; CI, confidence interval; NE, not estimable; RFS, relapse-free survival.

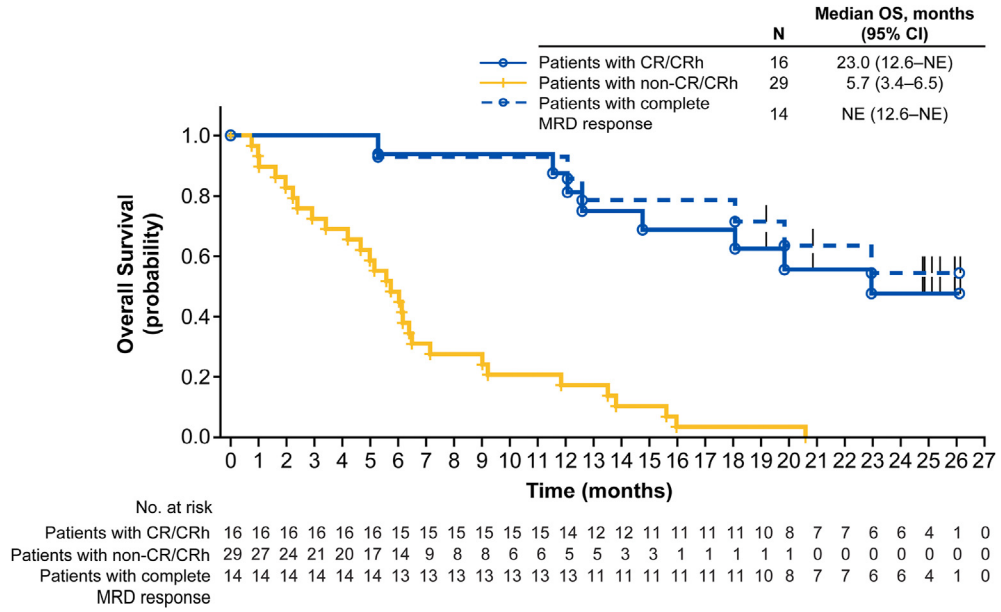

Fig. 3. Overall survival. Vertical bars indicate censoring. CI, confidence interval; CR, complete remission; CRh, CR with partial haematologic recovery; MRD, minimal residual disease; NE, not estimable; OS, overall survival.

(Fig. 4). Five patients were alive with no measurable disease at the end of the follow-up period. Of these five patients, four achieved durable responses without alloHSCT. Three of the four long-term survivors without alloHSCT received TKI therapy during the follow-up period; one remained MRD negative with neither alloHSCT nor additional TKI therapy.

3.4. AlloHSCT and 100-day mortality rate after alloHSCT

A total of nine patients (20%) received alloHSCT. Of these nine, four (8.9%) were in remission after CR/CRh within the first two cycles and received no anti-leukaemic medication after blinatumomab therapy (Table 1). The 100-day mortality rate in these four patients who received an alloHSCT while in blinatumomab-induced remission was 25% (one death). Additionally, the median survival after alloHSCT in these four patients was 15.9 (95% CI, 2.1–16.9) months.

3.5. Safety

The incidence of treatment-emergent AEs (TEAEs) and treatment-related AEs is summarised in Table 2. The most frequent treatment-related grade ≥ 3 AEs included febrile neutropenia (11%) and elevated levels of alanine aminotransferase (11%); the most frequent treatment-

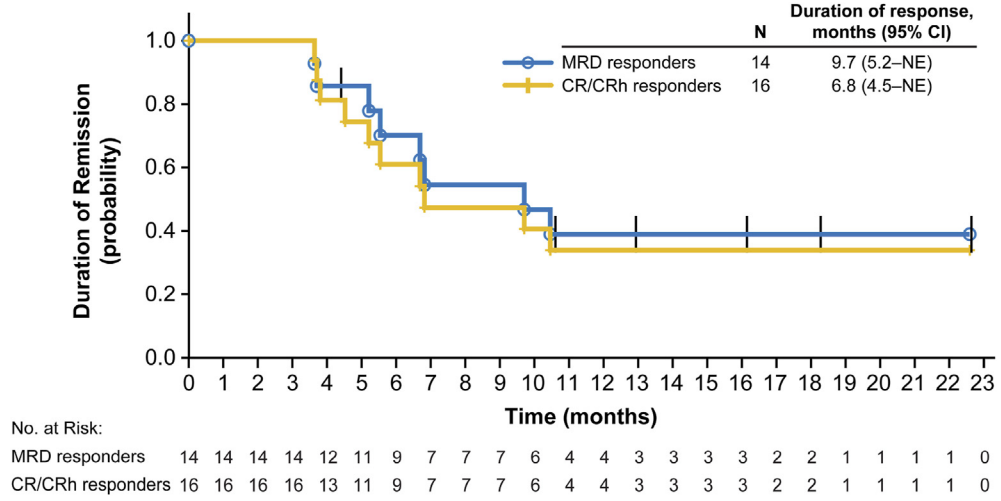

Fig. 4. Duration of remission in complete MRD responders. Vertical bars indicate censoring. CI, confidence interval; CR, complete remission; CRh, CR with partial haematologic recovery; MRD, minimal residual disease; NE, not estimable.

Table 1
Disease status at the time of alloHSCT.

	Blinatumomab (N = 45)
Disease status at the time of alloHSCT, n (%)	9 (20.0)
In remission after CR/CRh within the first two cycles and no anti-leukaemic medication after blinatumomab therapy[a]	4 (8.9)
In remission after CR/CRh within the first two cycles and with anti-leukaemic medication after blinatumomab therapy[a]	1 (2.2)
Not in remission after CR/CRh within the first two cycles	2 (4.4)
Not having reached CR/CRh within the first two cycles	2 (4.4)

alloHSCT, allogeneic haematopoietic stem cell transplantation; CR, complete remission; CRh, CR with partial haematologic recovery.
[a] Excluding conditioning regimens.

related serious AEs included tremor (7%) and febrile neutropenia (4%). Cytokine release syndrome occurred in four patients (9%), but none were grade ≥ 3 and led to treatment interruption or discontinuation. Neurologic events occurred in 28 (62%) patients, of which six (13%) were grade ≥ 3 and four (9%) led to treatment interruption.

Five patients (11%) had fatal AEs: multiple organ dysfunction syndrome, sepsis, septic shock, cerebral haemorrhage, and respiratory failure; one death due to septic shock was considered to be treatment-related by the investigator.

4. Discussion

In this final analysis of long-term outcomes following single-agent blinatumomab in heavily pretreated adults with R/R Ph+ ALL, responses to blinatumomab were durable with five of 16 (31%) CR/CRh responders remaining relapse-free, and no impact on median RFS or OS was detected when censoring for alloHSCT. In general, the efficacy and safety findings from the final analysis were consistent with that reported for the primary analysis; no new safety signals were observed [3].

Table 2
Incidence of AEs.

	Blinatumomab (N = 45)	
	TEAEs, n (%)	Treatment-related AEs, n (%)
All AEs	45 (100)	41 (91)
Grade ≥ 3	38 (84)	20 (44)
Grade ≥ 4	18 (40)	7 (16)
Serious AEs	28 (62)	12 (27)
Leading to discontinuation of blinatumomab	3 (7)	2 (4)
Serious	2 (4)	1 (2)
Leading to interruption of blinatumomab	17 (38)	12 (27)
Serious	13 (29)	7 (16)
Fatal AEs	5 (11)	1 (2)

AE, adverse event; TEAE, treatment-emergent AE.

Due to their efficacy against a malfunctioning tyrosine kinase encoded by *BCR-ABL1* fusion gene, BCR-ABL1 protein-specific TKIs play a key role in the treatment of Ph+ ALL. Inclusion of TKI in frontline treatment regimens has improved long-term survival in patients with newly diagnosed Ph+ BCP ALL [7,15,16]. Results from an open-label, multicentre, phase 2 trial (PACE) in patients with chronic myeloid leukaemia (CML) or Ph+ ALL treated with ponatinib, a third-generation TKI, demonstrated that 41% (95% CI, 24%–59%) of patients had a major haematologic response with a median duration of 3 (range, 2 to > 14) months, 47% had a major cytogenic response and 38% had a complete cytogenic response [17]. However, mutations in ABL kinase domain are associated with resistance to TKI therapy [18]. The targeted lysis of B cells by blinatumomab, which is achieved by engaging CD3+ cytotoxic T cells with CD19 expressing B cells, is independent of the presence of mutations in the ABL kinase domain. With its distinct mode of action, blinatumomab can thus overcome the resistance associated with TKI therapy, and the inclusion of blinatumomab in combination treatment regimens with TKIs could further improve treatment outcomes. In this regard, a retrospective study reported the efficacy and safety of a combination of blinatumomab with TKIs such as bosutinib, dasatinib, or ponatinib (n = 12) in patients with R/R heavily pretreated Ph+ ALL or CML in lymphoid blast crisis [19]. In another retrospective study (n = 13), eight of nine patients evaluable for response achieved complete molecular response (CMR) after a median of one cycle (range, one cycle to two cycles) of treatment with a combination of blinatumomab and TKIs. The median duration of follow-up among survivors was 10.8 (range, 3.5 to 20.0) months; three patients underwent alloHSCT in CMR [20]. Results from another retrospective study conducted across eight French centres (n = 15) indicated that 14 of 15 (93%) patients with R/R Ph+ ALL, who received a combination of blinatumomab and ponatinib, achieved a cytologic CR [21]. Additional trials evaluating the efficacy and safety of the combination of blinatumomab and TKIs with or without chemotherapy are ongoing [22–24].

Although the outcomes are encouraging, the small sample size of patients involved in this study limits our ability to draw firm conclusions. Another limitation of the study was the use of RT-PCR for the determination of MRD response. Although quantitative detection of clonal immunoglobulin and T-cell receptor gene rearrangements or flow cytometry analysis might have been better methods to analyse MRD status, RT-PCR was a more commonly used technique when this study was planned and conducted. In summary, the final analysis of the efficacy and safety data demonstrates the long-term durability of responses to single-agent blinatumomab in patients with R/R Ph+ ALL.

Data sharing and data accessibility

Qualified researchers may request data from Amgen clinical studies. Complete details are available at http://www.amgen.com/datasharing.

Author contributions

Giovanni Martinelli: Data curation, Investigation, Writing. **Nicolas Boissel:** Data curation, Investigation, Writing. **Patrice Chevallier:** Data curation, Investigation, Writing. **Oliver Ottmann:** Data curation, Investigation, Writing. **Nicola Gökbuget:** Data curation, Investigation, Writing. **Alessandro Rambaldi:** Data curation, Investigation, Writing. **Ellen K. Ritchie:** Data curation, Investigation, Writing. **Cristina Papayannidis:** Data curation, Investigation, Writing. **Catherine A. Tuglus:** Data curation, Formal Analysis, Product Administration, Writing, Validation. **Joan D. Morris:** Data curation, Product Administration, Writing, Validation. **Anthony Stein:** Data curation, Investigation, Writing.

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Conflict of interest statement

The authors declare the following financial interests/personal relationships, which may be considered as potential competing interests: Giovanni Martinelli declares no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper; Nicolas Boissel declares research funding and honoraria from Amgen; Patrice Chevallier reports honorarium from Amgen; Oliver Ottmann declares honoraria for advisory boards and research funding from Amgen, Incyte and Celgene, and honoraria for advisory boards from Roche, Fusion Pharma and Novartis; Nicola Gökbuget declares research support and honoraria from Amgen, Novartis and Pfizer, and is on advisory board of Amgen, Novartis and Pfizer; Alessandro Rambaldi reports personal fees from Amgen, Pfizer, Novartis, Kite Gilead, Celgene BMS, Astellas and Sanofi; Ellen K. Ritchie reports research support from Jazz and Pfizer, consulting fee from Celgene and Novartis, and is on speakers bureau and ad board of Incyte; Cristina Papayannidis reports honoraria from Amgen, Pfizer, Janssen, AbbVie and Novartis; Catherine Tuglus is an Amgen employee and holds Amgen stock; Joan Morris is an Amgen employee; Anthony Stein is on speakers bureau and advisory board of Amgen and Stemline.

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