ORIGINAL ARTICLE

Blinatumomab vs historic standard-of-care treatment for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukaemia

Nicola Gökbuget1 | Hervé Dombret2 | Sebastian Giebel3 | Monika Brüggemann4 | Michael Doubek5 | Robin Foa6 | Dieter Hoelzer7 | Christopher Kim8 | Giovanni Martinelli9 | Elena Parovichnikova10 | Josep Maria Ribera11 | Marieke Schoonen12 | Catherine Tuglus13 | Gerhard Zugmaier14 | Renato Bassan15

1 University Hospital, Goethe University, Frankfurt, Germany
2 Hôpital Saint-Louis, University Paris Diderot, Paris, France
3 Maria Skłodowska-Curie Institute—Oncology Center, Gliwice, Poland
4 University Hospital Schleswig-Holstein, Kiel, Germany
5 University Hospital and CEITEC Masaryk University, Brno, Czech Republic
6 ‘Sapienza’ University of Rome, Rome, Italy
7 J.W. Goethe University Hospital, Frankfurt, Germany
8 Center for Observational Research, Amgen Inc, Thousand Oaks, CA, USA
9 Policlinico S Orsola Istituto Seragnoli, Bologna, Italy
10 National Research Center for Hematology, Moscow, Russia
11 ICO Hospital Germans Trias i Pujol, Jose Carreras Research Institute, Barcelona, Spain
12 Centre for Observational Research, Amgen Ltd, Uxbridge, UK
13 Biostatistics, Amgen Inc, Thousand Oaks, CA, USA
14 Clinical Development, Amgen (Europe) GmbH, Munich, Germany
15 UOC Ematologia, Ospedale dell’Angelo, Mestre-Venezia, Italy

Abstract

Objectives: Survival outcomes from a single-arm phase 2 blinatumomab study in patients with minimal residual disease (MRD)-positive B-cell precursor (BCP)-acute lymphoblastic leukaemia (ALL) were compared with those receiving standard of care (SOC) in a historic data set.

Methods: The primary analysis comprised adult Philadelphia chromosome (Ph)-negative patients in first complete haematologic remission (MRD \( \geq 10^{-3} \)). Relapse-free survival (RFS) and overall survival (OS) were compared between blinatumomab- and SOC-treatment groups. Baseline differences between groups were adjusted by propensity scores.

Results: The primary analysis included 73 and 182 patients from the blinatumomab and historic data sets, respectively. When weighted by age to the...
Minimal residual disease (MRD) in acute lymphoblastic leukaemia (ALL) is the presence of leukaemic blasts at submicroscopic levels in patients with complete haematologic remission (CR).1-4 MRD can be detected at a sensitivity of $10^{-4}$ using standardised methods such as allele-specific real-time polymerase chain reaction (PCR) and multiparameter flow cytometry immunophenotyping.1,2,5,6 Approximately 30-50% of adult ALL patients have MRD despite haematologic CR after induction/consolidation chemotherapy.7,12 MRD is an important risk factor for early haematologic relapse in ALL.1,2,6-11,13-20 Patients who are MRD-positive after front-line induction/consolidation chemotherapy (persistent MRD) experience poorer outcomes than those who become MRD-negative,7-10,16,18-21 as do patients who subsequently become MRD-positive after previous MRD-negativity (relapsed MRD).9,11,13-17

Although there is no standardised treatment protocol for patients with MRD-positive ALL, MRD status can guide treatment decisions, including selecting patients who may benefit from allogeneic haematopoietic stem cell transplantation (HSCT), and clinical practice guidelines support the use of MRD status to inform postinduction treatment decisions.1,2,6,11,13-20 Indeed, MRD-positive patients who receive HSCT tend to experience better outcomes than those who do not.7,9,22,26,27 Furthermore, patients who are MRD-positive before HSCT may be more likely to relapse and have poorer outcomes after transplantation than those who are MRD-negative before HSCT.22,28-32

To understand the prognostic implications of MRD in real-world clinical practice, a retrospective study of adult MRD-positive patients who received standard-of-care (SOC) treatment between 2000 and 2014 was recently conducted using European ALL study group databases.33 Median relapse-free survival (RFS) was 12.4 months (95% confidence interval [CI]: 10.0-19.0), and median overall survival (OS) was 32.5 months (95% CI: 23.6-48.0) from baseline MRD detection in the historic data set among patients in first CR.33

Blinatumomab, an engineered bispecific T-cell engager (BiTE8) antibody construct that targets CD3-expressing T cells to CD19-expressing B cells to facilitate tumour cell lysis,34 has been investigated in the setting of MRD.12,35-37 Blinatumomab elicited high MRD response rates and long-lasting RFS in a single-arm, phase 2 study of adults with MRD-positive ALL.35-37 A subsequent larger, confirmatory, single-arm, phase 2 study included 116 patients, with 65% in first CR (CR1). Of the 113 patients evaluable for MRD response, 78% (95% CI: 69-85) had a complete MRD response after one cycle of blinatumomab treatment.12 After a median follow-up of 30 months, median RFS was 18.9 months (95% CI: 12.3-35.2), and median OS was 36.5 months (95% CI: 19.8-not reached).12

It can be challenging to recruit enough patients with uncommon diseases such as MRD-positive B-cell precursor (BCP)-ALL to power randomised controlled trials adequately. Furthermore, in patients who have very poor outcomes with SOC, it may be considered unethical to perform a randomised trial without an effective control arm. Therefore, single-arm studies are often conducted to provide valuable information about treatment efficacy.38 The use of data from patients treated historically with SOC provides an opportunity for the retrospective comparison of outcomes with a new treatment investigated in a single-arm study.39 Patient-level historic data have previously been used to compare outcomes between blinatumomab and SOC treatment in patients with relapsed/refractory Ph-negative BCP-ALL.39 In that analysis, both weighted and propensity score methods were used to create a balance between the two patient groups to enable statistical comparisons,39,40 and the results closely mirrored the results from the confirmatory randomised phase 3 study.41 This propensity score method is intended to mimic the effects of randomisation.42 Similarly, other studies evaluating treatment outcomes among ALL patients have also used propensity score adjustment to compare two distinct study populations.43,44 Overall, the approach of using historic controls and propensity score statistical methods has provided important context for the effect of novel treatments in rare diseases with unmet need.43-45

The objective of this study was to compare RFS and OS between patients with MRD-positive BCP-ALL treated with blinatumomab in a single-arm, phase 2 study12 and patients with MRD-positive disease from a historic data set who were treated with SOC,33 employing weighted and propensity score analyses. The primary
analysis study population included patients in CR1 only, and sensitivity analyses used data from patients treated in CR1 and later CRs. These analyses provide context for interpreting the efficacy of blinatumomab in adults with MRD-positive Ph-negative BCP-ALL.

2 | METHODS

2.1 | Historic data set

Full details of the historic data set are described elsewhere. The study population was assembled from ALL study group databases in Europe that included prospective MRD testing in their treatment protocols. Patients with MRD-positive Ph-negative BCP-ALL in CR were included in the study if MRD was detected at a national reference laboratory by PCR at a level of $\geq 10^{-4}$ or by flow cytometry at a level of $\geq 10^{-3}$; they were aged $\geq 15$ years at the time of ALL diagnosis; they were diagnosed between 2000 and 2014; they were treated at participating study group sites; a history of ALL treatment was available; and a history of relapse status and disease follow-up after MRD detection was available. Exclusion criteria included the following: presence of extramedullary disease at the time of MRD detection; treatment with blinatumomab within 18 months of MRD detection; and allogeneic HSCT before MRD detection. In the historic data set, SOC treatments were given at the discretion of the treating physician and details were not captured for this analysis. It can be expected that, depending on the national protocols, either chemotherapy was continued in MRD-positive patients or patients may have been referred to stem cell transplantation as outlined in Gökbuget et al.

2.2 | Blinatumomab study

Full details of the blinatumomab study are described elsewhere. Patients were treated with blinatumomab (15 µg/m²/infusion over 4 weeks followed by a 2-week treatment-free period) for up to four cycles. Eligible patients could receive HSCT at any time after the first cycle. Patients with MRD-positive BCP-ALL in CR1 or later CR were included if MRD was detected at a central reference laboratory by PCR at a level of $\geq 10^{-3}$ and they were aged $\geq 18$ years at study entry. Exclusion criteria included the following: active extramedullary disease; a history of clinically relevant central nervous system pathology; previous allogeneic HSCT; and patients with Ph-positive ALL who were eligible for tyrosine kinase inhibitor therapy. The data cut-off for the study was mid-2015.

2.3 | Combined study population

Several analysis sets were defined (Figure S1). The primary analysis study population (primary analysis set [PAS]) comprised patients from both the historic data set and blinatumomab study who met the following criteria: a diagnosis of Ph-negative BCP-ALL in first complete haematologic remission (CR1) only; quantifiable MRD-positive disease at a level of $\geq 10^{-3}$, independent of the detection method; no missing baseline covariates required for propensity score derivation; and aged $\geq 18$ years at the time of MRD detection. Patients from the blinatumomab study were required to have received at least one blinatumomab dose. To control for immortal time bias, patients from the historic data set were required not to have relapsed during the 14 days after baseline MRD detection, which reflected the median screening time between baseline MRD detection and first blinatumomab dose in the blinatumomab study. The restriction of the PAS to patients in CR1 predominantly affected the blinatumomab group because approximately one-third of these patients were enrolled in second or third complete haematologic remission (CR2 or CR3), and the restriction of patient age to $\geq 18$ years at study entry only affected the SOC group because age $\geq 18$ years was an inclusion criterion in the blinatumomab study.

For sensitivity analyses, two additional analysis sets were defined in the same way as the PAS but with additional criteria applied. The full analysis set (FAS) included patients in any CR (CR1, CR2 or CR3). The PCR-only analysis set (PCRAS) included patients in CR1 who had MRD detected by PCR but excluded patients who had MRD detected by flow cytometry. This extra criterion affected the SOC group because patients from the historic data set had MRD assessed by PCR or flow cytometry.

2.4 | Outcome measures

The primary endpoint was RFS and the secondary endpoint was OS. The baseline date for both outcomes was the date of first blinatumomab treatment, or 14 days after the date of baseline MRD detection for SOC-treated patients. RFS was defined as the time from the baseline date until haematologic relapse or death due to any cause, whichever occurred first. Patients who did not relapse or die were censored on the date of their last follow-up. OS was defined as the time from the baseline date until death from any cause. Patients without death reported were censored on the last date they were known to be alive.

2.5 | Statistical analyses

2.5.1 | Weighted analysis

Relapse-free survival and OS estimates for the historic data set patients who were treated with SOC were stratified by age group, and strata-specific estimates were pooled into a combined estimate, with each stratum weighted according to the proportion of patients observed in that age stratum in the blinatumomab study.
2.5.2 Propensity score analysis

To control for potential confounding created by imbalance in baseline characteristics, covariates that were available in both data sets were chosen based on likely clinical influence on prognosis, potential differences in medical practices by region or whether a patient would be able to receive blinatumomab treatment. The candidate covariates comprised age at primary diagnosis (years); gender (male, female); cytogenetic abnormality t(4;11)/KMT2A-AFF1 translocation (yes, no/unknown); time from primary diagnosis to baseline MRD date (months); baseline MRD level (<1 × 10−3, ≥1 × 10−3 to <1 × 10−2, ≥1 × 10−2 to <1 × 10−1, ≥1 × 10−1); white blood cell (WBC) count at diagnosis (≤30 000/µl, >30 000/µl); and type of previous chemotherapy (German multicentre ALL [GMALL] regimen, other). The candidate covariates and two-way interaction terms were tested stepwise in a logistic regression model with blinatumomab treatment as a binary dependent variable. The threshold for retaining covariates in the model was a P value < .30. The covariates included in the final model comprised age at primary diagnosis; time from primary diagnosis to baseline MRD level; baseline MRD level; an indicator for GMALL as the previous chemotherapy regimen; and an interaction term between the indicator for GMALL and the time from primary diagnosis to baseline MRD level (baseline MRD level was treated as a continuous covariate).

With adequate balance between the patient groups, the inverse probability of treatment (IPT) weighting (IPTW) method for propensity score adjustment was used in the statistical analysis of the study endpoints (Figures S2 and S3). The weighting method used was the average treatment effect (ATE), and an exploratory sensitivity analysis was conducted using average treatment effects of treated (ATT) weights. Disproportionate influence of large IPT weights was addressed using stabilised IPTW. Further details on the propensity score analysis can be found in the Appendix S1.

Relapse-free survival and OS were analysed using Cox proportional hazards regression models with input data weighted according to the methods already described and including blinatumomab or SOC treatment as an independent variable. A time-dependent covariate for HSCT was included in the models because the clinical use of HSCT had increased in the period between the historic study and more recent blinatumomab study. Further sensitivity analyses were conducted by excluding the HSCT covariate. Robust variance estimation was applied to all models, and HRs and 95% CIs were calculated. Survival rates were estimated at 12, 18, 24 and 30 months based on the Cox regression models, without adjustment for HSCT, and Kaplan-Meier (KM) curves were produced. Median RFS, OS and follow-up were estimated from the KM curves. P values were calculated using two-sample z tests.

3 RESULTS

3.1 Patient characteristics

Of the 116 patients enrolled in the blinatumomab study who received blinatumomab treatment, 73 patients were eligible for inclusion in the PAS. The PCRs included all 73 patients from the PAS because all patients in the blinatumomab study had MRD detected by PCR. The FAS also included the 34 patients in CR2 or later CR; 107 patients in total. The median follow-up of the blinatumomab study was 30 months.

Of 287 patients included in the historic study with data spanning from 2000 to 2014, 272 were evaluated for RFS and OS; 270 were in CR1. One hundred and eighty-two patients were eligible for inclusion in the PAS. The PCRs included 130 patients. The median follow-up in the historic study was 23 months. Figure S1 is a consort diagram of the two study populations.

Compared with patients in the SOC group of the PAS, patients treated with blinatumomab were older (median: 46.5 vs 33.0 years, P < .001), were diagnosed with ALL more recently (79.5% vs 8.8% in the year 2011 or later, P < .001), and had a longer time between primary diagnosis and baseline MRD detection (median: 4.64 vs 4.77 months, P < .001) (Table 1). Baseline MRD levels and WBC counts were statistically similar between the two groups. Patients in both studies received at least three cycles of intensive chemotherapy prior to the detection of MRD; a mean of five cycles was received in the blinatumomab study but this was not reported in the historic study.

3.2 Weighted analysis

Patient data from the SOC group of the PAS were stratified by age group, and the outcomes obtained for each stratum were weighted to obtain a pooled estimate according to the proportion of patients observed in each age stratum in the blinatumomab study. Weighted to the blinatumomab study population, median RFS in the SOC group was 7.8 months (95% CI: 6.4-12.4), and median OS was 25.9 months (95% CI: 17.0-39.1), whereas in the blinatumomab group, median RFS was 35.2 months (95% CI: 18.9-not evaluable [NE]), and median OS was NE (95% CI: 24.2-NE) (Table 2). Of note, median RFS and OS decreased with increasing patient age in the SOC group, but median was typically not reached in the blinatumomab group (Table 2).

3.3 Propensity score analysis

The balance of baseline factors (model covariates) between patients in the SOC and blinatumomab groups of the PAS, before and after propensity score adjustment using sIPTW, is shown in Figure S2. The distribution of propensity scores between the two treatment groups was relatively similar (Figure S3), and there were few outliers (Figure S4). Additional details of the covariate balance assessment are available in the Appendix S1.

3.3.1 Relapse-free survival

Regarding RFS, a 50% reduction in risk of relapse or death was associated with blinatumomab compared with SOC treatment in the PAS (HR: 0.50 [95% CI: 0.32-0.78], P = .002) (Table 3). Similar results were
Table 1: Patient and disease characteristics, including MRD status, from the primary analysis set

| Characteristic                        | Patients in historic (SOC) data set (N = 182) | Patients in blinatumomab study (N = 73) | P value |
|--------------------------------------|-----------------------------------------------|---------------------------------------|---------|
| Gender, n (%)                        |                                               |                                       | .99     |
| Female                               | 80 (44.0)                                     | 32 (43.8)                             |         |
| Agea, y                               | Mean (SD) 36.3 (13.6)                         | 44.8 (16.6)                           | <.001   |
| Median (range)                       | 33.0 (18, 65)                                 | 46.5 (18, 76)                         |         |
| Age groupb, n (%)                    |                                               |                                       |         |
| 15-34 y                              | 98 (53.9)                                     | 20 (27.4)                             | <.001   |
| 35-54 y                              | 56 (30.8)                                     | 27 (37.0)                             |         |
| 55-64 y                              | 27 (14.8)                                     | 17 (23.3)                             |         |
| ≥65 y                                | 1 (0.6)                                       | 9 (12.3)                              |         |
| Year of ALL diagnosis, n (%)         |                                               |                                       | <.001   |
| 2000-2004                            | 59 (32.4)                                     | 0 (0)                                 |         |
| 2005-2010                            | 107 (58.8)                                    | 15 (20.5)                             |         |
| 2011 or later                        | 16 (8.8)                                      | 58 (79.5)                             |         |
| Country, n (%)                       |                                               |                                       | .083    |
| Germany                              | 70 (38)                                       | 38 (52)                               |         |
| Italy                                | 47 (26)                                       | 10 (14)                               |         |
| France                               | 25 (14)                                       | 6 (8)                                 |         |
| Spain                                | 8 (4)                                         | 2 (3)                                 |         |
| Other                                | 32 (18)                                       | 17 (23)                               |         |
| Chemotherapy protocol, n (%)         |                                               |                                       | .035    |
| GMALL                                | 76 (42)                                       | 42 (57)                               |         |
| GRAALL                               | 25 (14)                                       | 7 (10)                                |         |
| NILG                                 | 27 (15)                                       | 3 (4)                                 |         |
| Other                                | 54 (29)                                       | 21 (29)                               |         |
| WBC count at diagnosis               |                                               |                                       | .220    |
| ≥30 000/µl, n (%)                    | 51 (28.0)                                     | 15 (20.5)                             |         |
| Cytogenetic/molecular aberrations, n (%)|                                   |                                       | .709    |
| t(4;11)/KMT2A-AFF1 translocation     | 15 (8.2)                                      | 5 (6.8)                               |         |
| Time from primary diagnosis to baseline MRD date, mo | | | | .001 |
| Mean (SD)                            | 6.6 (6.1)                                     | 12.8 (14.3)                           |         |
| Median (range)                       | 4.77 (1.3, 60.8)                              | 6.46 (3.2, 68.7)                      |         |
| MRD level at baseline, n (%)         |                                               |                                       | .810    |
| ≥10^−6                               | 2 (1.1)                                       | 0 (0)                                 |         |
| ≥1 × 10^−2 to <10^−6                 | 11 (6.0)                                      | 3 (4.1)                               |         |
| ≥1 × 10^−2 to <10^−1                 | 65 (35.7)                                     | 25 (34.3)                             |         |
| ≥1 × 10^−2 to <10^−2                 | 104 (57.1)                                    | 38 (52.1)                             |         |

Abbreviations: ALL, acute lymphoblastic leukaemia; CR, complete haematologic remission; GMALL, German multicentre acute lymphoblastic leukaemia; GRAALL, French-Swiss-Belgian Group for Research on Adult Acute Lymphoblastic Leukaemia; MRD, minimal residual disease; NILG, Northern Italy Leukaemia Group; SD, standard deviation; SOC, standard of care; WBC, white blood cell.

a Age at primary diagnosis in the historic data set and age at study entry in the blinatumomab study.

obtained across the other analysis sets and sensitivity analyses, including analyses in which patients in CR1 and later CRs were included (FAS); MRD was detected by PCR only (PCRAS); different IPT weighting methods were used for the propensity score adjustments; HSCT was excluded as a time-dependent covariate from the regression models (Figure S5).

The 18-month RFS (unadjusted for HCST) was estimated at 39% (95% CI: 33%-48%) for the SOC group compared with 67% (95% CI:...
58%-78%) for the blinatumomab group (P < .001) (Table 3). The KM estimate of median RFS (unadjusted for HSCT) was 8.3 months (95% CI: 6.2-11.8) for the SOC group, compared with 35.2 months (95% CI: 24.2-NE) for the blinatumomab group (P = .002) (Figure 1).

### 3.3.2 Overall survival

Regarding OS, there was a non-statistically significant improvement associated with blinatumomab compared with SOC treatment in the PAS (HR: 0.76 [95% CI: 0.47-1.24]) (Table 3). Similar results were obtained across the analysis sets and sensitivity analyses, including the FAS, PCRAS and analyses that excluded HSCT as a time-dependent covariate from the regression models (Figure S6).

The 18-month OS (unadjusted for HCST) was estimated at 55% (95% CI: 48%-63%) for the SOC group and 71% (95% CI: 62%-81%) for the blinatumomab group (P = .002) (Figure 2).

### 3.3.3 Exploratory analysis

A sensitivity analysis was conducted using the ATT method and the covariates after adjustment were less balanced than using ATE: three covariates had a standardised difference >0.20 after propensity score adjustment. The HRs for RFS and OS, both with and without adjustment for HSCT, were similar to those from the ATE analysis (Figure S7).

### 4 DISCUSSION

Minimal residual disease is associated with treatment resistance,3,9,12,33,47 earlier relapse and worse prognosis in patients with ALL.1,2,6-11,13-20 Treatment with blinatumomab achieved high conversion rates from MRD-positive to MRD-negative status in the single-arm, phase 2 blinatumomab study: 78% of patients achieved a complete MRD response after one cycle of blinatumomab.12 Furthermore, a landmark analysis showed that a complete MRD response in cycle 1 was associated with longer RFS and OS than in patients who remained MRD-positive despite blinatumomab treatment (median RFS: 23.6 vs 5.7 months, P = .002; median OS: 38.9 vs 12.5 months, P = .002).12 Although results of the blinatumomab study appeared promising,12 it was difficult to place them in the context of SOC, which typically consists of continued chemotherapy and/or HSCT. Historic data gathered before the availability of new treatments provide an opportunity for comparison with new treatments. Weighted age-stratified and propensity score-adjusted analyses were conducted, therefore, to compare blinatumomab with SOC treatment.

Patients treated historically with SOC who closely matched the eligibility criteria of the blinatumomab study12 were compared with patients treated with blinatumomab. Propensity score-adjusted analysis showed that patients with MRD who were treated in CR1 in the blinatumomab study12 had longer RFS and OS than those treated with SOC, although the difference was not statistically significant for OS (median RFS: 35.2 vs 8.3 months, P = .002; median OS: 36.5 vs 27.2 months, P = .27). Additionally, the probability of RFS at 30 months in the blinatumomab group was nearly double that in the SOC group, and the probability of OS at 30 months was also higher for blinatumomab than SOC; both point estimates were statistically significant.
Our analyses demonstrated that blinatumomab treatment led to an improvement in RFS and OS in patients with MRD-positive B-precursor ALL. In addition to blinatumomab, other immunotherapies may also be effective in MRD-positive B-precursor ALL. A favourable outcome has been reported in patients treated with CD19-specific chimeric antigen receptor (CAR) T cells who had a low leukaemia burden. Treatment with CAR T cells induced a high rate of MRD-negative CR in over 80% of patients. No data are currently available for the use of inotuzumab in MRD-positive ALL. At present, inotuzumab and CAR T cells have a marketing authorisation for full cytologic relapse only. Clinical trials are underway to understand the role of these novel agents in treatment sequencing to achieve MRD-negative remissions for patients with ALL.

These results were consistent across all analysis sets and sensitivity analyses, suggesting that the results are robust. In an age-stratified analysis, estimates of median RFS and OS were longer for younger patients than for older patients, which is consistent with age being a well-established prognostic factor in ALL. Adjustment for age was important because the blinatumomab study patient population was substantially older than the historic data set. The age-stratified analysis was a simple way of demonstrating that patient age had an important influence on outcomes in the two studies. Estimates of median RFS and OS from the age-stratified analysis were similar to those from the propensity score analysis.

As part of the process of producing comparable blinatumomab and SOC groups in the propensity score analysis, it was important to consider the balance of available key prognostic factors between the two groups. Previous work identified that age at primary diagnosis, baseline MRD status (persistent vs relapsed MRD), baseline MRD level, and WBC count at diagnosis were associated with RFS and that age at primary diagnosis, WBC count at diagnosis and year of primary diagnosis were associated with OS in patients with MRD-positive ALL. These are established baseline prognostic factors and also reflect the more recently established importance of response-based assessments, such as MRD. Use of IPT weighting by propensity score successfully created a balance in these assessed covariates between patients treated with blinatumomab and SOC. This approach is intended to mimic the effects of randomising patients with respect to treatment assignment and enables statistical comparisons between two patient groups based on measured covariates. Other covariates that could have influenced outcome and might have been able to account for medical practice, regional or inter-person differences between the study groups (eg country and prior chemotherapy protocol), were also balanced after adjustment. Of the factors found to have statistically significant associations with RFS and OS in the historic study, only year of primary diagnosis and MRD relapse vs persistence were not tested as candidate covariates in the propensity score models: there was too little overlap in year of diagnosis, and MRD relapse vs persistence was not available for the blinatumomab study.

In the absence of randomised data, the use of propensity score adjustment can provide context for a single-arm study. The prior comparison between blinatumomab and historic SOC treatment in patients with relapsed/refractory Ph-negative BCP-ALL was similar to the results in the randomised phase 3 study. Additionally, other studies have also compared novel treatment combinations to historic data to evaluate clinical benefit. The age-stratified and propensity score analyses using data from the PAS reflected the experience of adults in CR1 because

### Table 3: Summary of endpoints from the primary analysis set after propensity score adjustment using stabilised inverse probability of treatment weightings

| Endpoint | SOC | Blinatumomab | HR (95% CI) | P value |
|----------|-----|--------------|-------------|---------|
| Relapse-free survival, HSCT-adjusted | 0.50 (0.32-0.78) | 0.47 (0.30-0.73) | <.001 |
| Relapse-free survival* (95% CI) | 0.47 (0.30-0.73) | 0.47 (0.30-0.73) | <.001 |
| Probability at 12 mo | 0.42 (0.35-0.50) | 0.70 (0.61-0.80) | <.001 |
| Probability at 18 mo | 0.39 (0.33-0.48) | 0.67 (0.58-0.78) | <.001 |
| Probability at 24 mo | 0.35 (0.28-0.43) | 0.63 (0.53-0.76) | <.001 |
| Probability at 30 mo | 0.29 (0.23-0.37) | 0.52 (0.41-0.65) | .001 |
| Overall survival, HSCT-adjusted | 0.76 (0.47-1.24) | 0.68 (0.42-1.09) | .27 |
| Overall survival* (95% CI) | 0.68 (0.42-1.09) | 0.68 (0.42-1.09) | .11 |
| Probability at 12 mo | 0.67 (0.60-0.75) | 0.80 (0.72-0.88) | <.001 |
| Probability at 18 mo | 0.55 (0.48-0.63) | 0.71 (0.62-0.81) | .019 |
| Probability at 24 mo | 0.52 (0.44-0.60) | 0.67 (0.57-0.79) | .029 |
| Probability at 30 mo | 0.48 (0.41-0.56) | 0.62 (0.52-0.74) | .043 |

**Abbreviations:** CI, confidence interval; HR, hazard ratio; HSCT, haematopoietic stem cell transplantation; SOC, standard of care.

*HR and time point estimates do not include adjustment for HSCT as a time-dependent covariate.
only patients in CR1 were available in the historic data set. In the blinatumomab study, however, 35% of patients were in CR2 or CR3. RFS and OS were better for patients treated in CR1 than in those who were treated in later CRs in the blinatumomab study (median RFS: 24.6 months vs 11.0 months, $P = .004$; median OS: 36.5 months vs 19.1 months, $P = .084$).

Notably, the propensity score analyses using the FAS, which included patients treated in CR1 and later CRs, also found improvements in RFS with blinatumomab compared with SOC treatment (RFS HR: 0.582 [95% CI: 0.409-0.829]; OS HR: 0.728 [95% CI: 0.474-1.118]), despite the fact that all historic data set comparator patients were in CR1.

The improvement in RFS experienced by blinatumomab-treated patients with MRD-positive ALL compared with those treated historically with SOC did not translate into a statistically significant difference in OS in our analysis apart from point estimates at 18 months’ follow-up. The sample size for both groups was small, which limits statistical stability. It could also be that blinatumomab reduces risk of relapse, whereas OS is strongly influenced by HSCT; most patients underwent HSCT in the blinatumomab group, compared with fewer than half in the SOC group. Assessing the duration of remission could potentially address the influence of relapse reduction. Unfortunately, this was not feasible because competing risk regression cannot be conducted with propensity score adjustment using SAS software. Without appropriate adjustment for imbalance in baseline covariates between the blinatumomab and SOC groups, a comparison of duration of remission would lead to a biased estimate.$^{12,33}$

Of note, 67% of patients in the blinatumomab study received an HSCT during ongoing CR after blinatumomab treatment,$^{12}$ compared with 40% of patients in the historic data set who had an HSCT during CR after MRD detection (78% vs 44% of patients, respectively, in the PAS).$^{33}$ The HSCT rate observed in the historic study$^{33}$ was similar to that for the MRD non-responders in the blinatumomab study (45%).$^{12}$ No patients in the historic study received blinatumomab within 18 months of baseline MRD detection.$^{33}$ Improvements in RFS with blinatumomab were similar compared with SOC treatment irrespective of whether or not HSCT was adjusted for as a time-dependent covariate in the regression models.

Our approach has relevant limitations. All analyses were post-hoc and exploratory in nature. The small study population limits the power to detect differences between the two groups; however, the CIs reported and the extensive sensitivity analyses performed can serve as a guide to the significance and robustness of our results. Data completeness and quality varied between the two studies, and
only covariates that were reported in both data sets were included in the propensity score models; relapsed vs persistent MRD is a potentially relevant factor that was not recorded in the blinatumomab study.12 Unlike randomisation, propensity score analysis does not produce a balance between treatment groups with respect to all possible confounding variables. RFS did not appear to change dramatically over time in the historic study, although there was a difference in the proportion of patients who received HSCT over the historic study period, increasing from approximately 30% to 40% from 2000-2004 to 2005 onwards (P = .0608).23 The perception of the poor prognostic impact of MRD increased in the standard-of-care setting and may have contributed to an increasing proportion of patients referred to stem cell transplantation over time. Nevertheless, these analyses provide a useful context for interpreting the efficacy of blinatumomab in adults with MRD-positive Ph-negative BCP-ALL.

5 | CONCLUSIONS

This comparative analysis suggested that blinatumomab treatment followed by HSCT led to an improvement in RFS and a trend towards improved OS compared with SOC treatment in adults with MRD-positive Ph-negative BCP-ALL.

ACKNOWLEDGEMENTS

This study was funded by Amgen Inc, Thousand Oaks, CA, USA. Medical writing support, funded by Amgen Inc, was provided by Jack C. Dean of Oxford PharmaGenesis, Oxford, UK.

CONFLICT OF INTEREST

NG has received honoraria and research funding and has served on advisory boards, for Amgen, Pfizer, Celgene and Novartis; HD has received honoraria and/or research funding from Amgen, Agios, Seattle Genetics, Celgene, Sunesis, Roche, Pfizer, Ambit-Daiichi Sankyo, Shire-Baxalta, Ariad-Incyte, Karyopharm, Abbvie, Novartis, Kite, Otsuka, Celator-Jazz, Astellas, Menarini, Cellectis, Janssen, ImmunoGen and Servier; SG has received honoraria and has served on advisory boards for Amgen; MB has received honoraria and has served on advisory boards and at Speaker Bureaus for Amgen, Hoffman-La Roche and Incyte, and has received grant/research support from Affimed Therapeutics, Amgen Research, Celgene and Regeneron; MD has received honoraria and/or research funding from Abbvie, Amgen, AOP Orphan, Gilead, Janssen-Cilag, Novartis and Roche; RF has served on advisory boards and at Speaker Bureaus for Janssen, Abbvie, Celgene, Novartis, Amgen, Pfizer and Servier; DH declares no conflicts of interest; CK, MS, CT and GZ are employees and stockholders of Amgen; GM has served as an adviser to Amgen, Ariad-Incyte, Pfizer, Roche, Celgene, Janssen and Jazz Pharmaceuticals, and on Speaker Bureaus for Novartis, Pfizer and Celgene, and has received travel compensation from Daiichi Sankyo, Roche and Shire; EP has received research funds from Abbvie, Roche, Amgen, Novartis and Bristol; JMR has received honoraria and research funds and has served on advisory boards, for Amgen, Pfizer, Shire and Ariad; RB has received honoraria and has served on advisory boards for Amgen, Pfizer, Shire and Incyte.

DATA AVAILABILITY STATEMENT

Qualified researchers may request data from Amgen clinical studies. Complete data are available at the following: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/

ORCID

Nicola Gökbuget https://orcid.org/0000-0003-2291-8245

REFERENCES

1. Brüggemann M, Kotrova M. Minimal residual disease in adult ALL: technical aspects and implications for correct clinical interpretation. Blood Adv. 2017;1:2456-2466.
2. Brüggemann M, Raff T, Kneba M. Has MRD monitoring superseded other prognostic factors in adult ALL? Blood. 2012;120:4470-4481.
3. Bassan R, Hoelzer D. Modern therapy of acute lymphoblastic leukemia. J Clin Oncol. 2011;29:532-543.
4. Mopett J, Burke GA, Steward CG, Oakhill A, Goulden NJ. The clinical relevance of detection of minimal residual disease in childhood acute lymphoblastic leukaemia. J Clin Pathol. 2003;56:249-253.
5. Brüggemann M, Schrauder A, Raff T, et al. Standardized MRD quantification in European ALL trials: proceedings of the Second International Symposium on MRD assessment in Kiel, Germany, 18–20 September 2008. Leukemia. 2010;24:521-535.
6. van Dongen JJ, van der Velden VH, Brüggemann M, Orfao A. Minimal residual disease diagnostics in acute lymphoblastic leukaemia: need for sensitive, fast, and standardized technologies. Blood. 2015;125:3996-4009.
7. Bassan R, Spinelli O, Oldani E, et al. Improved risk classification for risk-specific therapy based on the molecular study of minimal residual disease (MRD) in adult acute lymphoblastic leukaemia (ALL). Blood. 2009;113:4153-4162.
8. Brüggemann M, Raff T, Flohr T, et al. Clinical significance of minimal residual disease quantification in adult patients with standard-risk acute lymphoblastic leukemia. Blood. 2006;107:1116-1123.
9. Gökbuget N, Kneba M, Raff T, et al. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. Blood. 2012;120:1868-1876.
10. Holowiecki J, Krawczyk-Kulis M, Giebel S, et al. Status of minimal residual disease after induction predicts outcome in both standard and high-risk Ph-negative adult acute lymphoblastic leukaemia. The Polish Adult Leukemia Group ALL 4–2002 MRD Study. Br J Haematol. 2008;142:227-237.
11. Raff T, Gökbuget N, Luschin S, et al. Molecular relapse in adult standard-risk ALL patients detected by prospective MRD monitoring during and after maintenance treatment: data from the GMALL 06/99 and 07/03 trials. Blood. 2007;109:910-915.
12. Gökbuget N, Dombret H, Benficio M, et al. Blinatumomab for minimal residual disease in adults with B-precursor acute lymphoblastic leukemia. Blood. 2018;131:1522-1531.
13. Berry DA, Zhou S, Higley H, et al. Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: a meta-analysis. JAMA Oncol. 2017;3:e170580.

14. Brüggemann M, Gökbüget N, Kneba M. Acute lymphoblastic leukemia: monitoring minimal residual disease as a therapeutic principle. Semin Oncol. 2012;39:47-57.

15. Mortuza FY, Papaoiannou M, Moreira IM, et al. Minimal residual disease tests provide an independent predictor of clinical outcome in adult acute lymphoblastic leukemia. J Clin Oncol. 2002;20:1094-1104.

16. Beldjord K, Chevret S, Asnafi V, et al. Oncogenetics and minimal residual disease are independent outcome predictors in adult patients with acute lymphoblastic leukemia. Blood. 2014;123:3739-3749.

17. Pemmaraju N, Kantarjian H, Jorgensen JL, et al. Significance of recurrence of minimal residual disease detected by multi-parameter flow cytometry in patients with acute lymphoblastic leukemia in morphological remission. Am J Hematol. 2017;92:279-285.

18. Vidriales MB, Perez JJ, Lopez-Berges MC, et al. Minimal residual disease in adolescent (older than 14 years) and adult acute lymphoblastic leukemias: early immunophenotypic evaluation has high clinical value. Blood. 2003;101:4695-4700.

19. Ravandi F, Jorgensen JL, O’Brien SM, et al. Minimal residual disease assessed by multi-parameter flow cytometry is highly prognostic in adult patients with acute lymphoblastic leukaemia. Br J Haematol. 2016;172:392-400.

20. Ribera JM, Oriol A, Morgades M, et al. Treatment of high-risk Philadelphia chromosome-negative acute lymphoblastic leukemia in adolescents and adults according to early cytologic response and minimal residual disease after consolidation assessed by flow cytometry: final results of the PETHEMA ALL-AR-03 trial. J Clin Oncol. 2014;32:1595-1604.

21. Patel B, Rai L, Buck G, et al. Minimal residual disease is a significant predictor of treatment failure in non-T-lineage adult acute lymphoblastic leukaemia: final results of the international trial UKALL XII/ECOG2993. Br J Haematol. 2010;148:80-89.

22. Schrappe M. Detection and management of minimal residual disease in acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2014;2014:244-249.

23. Stein A, Forman SJ. Allogeneic transplantation for ALL in adults. Bone Marrow Transplant. 2008;41:439-446.

24. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Acute lymphoblastic leukemia. Version 1.2018 2018. https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed October 2, 2019.

25. Hoelzer D, Bassan R, Dombret H, et al. Acute lymphoblastic leukemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27:v69-v82.

26. Dhedin N, Huynh A, Maury S, et al. Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia. Blood. 2015;125:2486-2496.

27. Eckert C, Henze G, Seeger K, et al. Use of allogeneic hematopoietic stem-cell transplantation based on minimal residual disease response improves outcomes for children with relapsed acute lymphoblastic leukemia in the intermediate-risk group. J Clin Oncol. 2013;31:2736-2742.

28. Spinielli O, Peruta B, Tosi M, et al. Clearance of minimal residual disease after allogeneic stem cell transplantation and the prediction of the clinical outcome of adult patients with high-risk acute lymphoblastic leukemia. Haematologica. 2007;92:612-618.

29. Zhou Y, Slack R, Jorgensen JL, et al. The effect of peritransplant minimal residual disease in adults with acute lymphoblastic leukemia undergoing allogeneic hematopoietic stem cell transplantation. Clin Lymphoma Myeloma Leuk. 2014;14:319-326.

30. Bassan R, Spinelli O, Oldani E, et al. Different molecular levels of post-induction minimal residual disease may predict hematopoietic stem cell transplantation outcome in adult Philadelphia-negative acute lymphoblastic leukemia. Blood Cancer J. 2014;4:e225.

31. Giebel S, Stella-Holowiecka B, Krawczyk-Kulis M, et al. Status of minimal residual disease determines outcome of autologous hematopoietic SCT in adult ALL. Bone Marrow Transplant. 2010;45:1095-1101.

32. Bar M, Wood BL, Radich JP, et al. Impact of minimal residual disease, detected by flow cytometry, on outcome of myeloablative hematopoietic cell transplantation for acute lymphoblastic leukemia. Leuk Res Treatment. 2014;2014:421723.

33. Gökbüget N, Dombret H, Giebel S, et al. Minimal residual disease level predicts outcome in adults with Ph-negative B-precursor acute lymphoblastic leukemia. Hematology. 2019;24:337-348.

34. Klinger M, Brandl C, Zugmaier G, et al. Immunopharmacologic response of patients with B-lineage acute lymphoblastic leukemia to continuous infusion of T cell-engaging CD19/CD3-bispecific BiTE antibody blinatumomab. Blood. 2012;119:6226-6233.

35. Topp MS, Kufer P, Gökbüget N, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J Clin Oncol. 2011;29:2493-2498.

36. Topp MS, Gökbüget N, Zugmaier G, et al. Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL. Blood. 2012;120:5185-5187.

37. Gökbüget N, Zugmaier G, Klinger M, et al. Long-term relapse-free survival in a phase 2 study of blinatumomab for the treatment of patients with minimal residual disease in B-lineage acute lymphoblastic leukemia. Haematologica. 2017;102:e132-e135.

38. Simon R, Blumenthal GM, Rothenberg ML, et al. The role of nonrandomized trials in the evaluation of oncology drugs. Clin Pharmacol Ther. 2015;97:502-507.

39. Gökbüget N, Kelsh M, Chia V, et al. Blinatumomab vs historical standard therapy of adult relapsed/refractory acute lymphoblastic leukemia. Blood Cancer J. 2016;6:e473.

40. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70:41-55.

41. Kantarjian H, Stein A, Gökbüget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med. 2017;367:836-847.

42. Imbens GW. Nonparametric estimation of average treatment effects under exogeneity: a review. Rev Econ Stat. 2004;86:4-29.

43. Jabbour E, Sasaki K, Ravandi F, et al. Chemoinmunotherapy with inotuzumab ozogamicin combined with mini-hyper-CVD, with or without blinatumomab, is highly effective in patients with Philadelphia chromosome-negative acute lymphoblastic leukemia in first salvage. Cancer. 2018;124:4044-4055.

44. Sasaki K, Jabbour EJ, Ravandi F, et al. Hyper-CVAD plus ponatinib versus hyper-CVAD plus dasatinib as frontline therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: A propensity score analysis. Cancer. 2016;122:3650-3656.

45. Lim J, Walley R, Yuan J, et al. Minimizing patient burden through the use of historical subject-level data in innovative confirmatory clinical trials: review of methods and opportunities. Ther Innov Regul Sci. 2018;52:546-559.

46. Hirano K, Imbens GW, Ridder G. Efficient estimation of average treatment effects using the estimated propensity score. Econometrica. 2003;71:1161-1189.

47. Choi S, Henderson MJ, Kwan E, et al. Relapse in children with acute lymphoblastic leukemia involving selection of a preexisting drug-resistant subclone. Blood. 2007;110:632-639.
48. Park JH, Riviere I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *N Engl J Med*. 2018;378:449-459.

49. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-Cell lymphoblastic leukemia. *N Engl J Med*. 2018;378:439-448.

50. Rowe JM. Prognostic factors in adult acute lymphoblastic leukaemia. *Br J Haematol*. 2010;150:389-405.

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

---

**How to cite this article:** Gökbuget N, Dombret H, Giebel S, et al. Blinatumomab vs historic standard-of-care treatment for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukaemia. *Eur J Haematol*. 2020;104:299–309. [https://doi.org/10.1111/ejh.13375](https://doi.org/10.1111/ejh.13375)