Original Article

Blinatumomab Compared With Standard of Care for the Treatment of Adult Patients With Relapsed/Refractory Philadelphia Chromosome–Positive B-Precursor Acute Lymphoblastic Leukemia

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BACKGROUND: A single-arm, phase 2 trial demonstrated the efficacy and safety of blinatumomab, a bispecific T-cell–engaging antibody construct, in patients with relapsed/refractory (r/r) Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL), a rare hematologic malignancy with limited treatment options. This study compared outcomes with blinatumomab with those of a historical control treated with the standard of care (SOC). **METHODS:** The blinatumomab trial enrolled adult patients with Ph+ ALL who were r/r to at least 1 second-generation tyrosine kinase inhibitor (n = 45). Propensity score analysis (PSA) was used to compare outcomes with blinatumomab with those of an external cohort of similar patients receiving SOC chemotherapy (n = 55). The PSA mitigated confounding variables between studies by adjusting for imbalances in the age at diagnosis and start of treatment, sex, duration from diagnosis to most recent treatment, prior allogeneic hematopoietic stem cell transplantation, prior salvage therapy, and number of salvage therapies. Bayesian data augmentation was applied to improve power to 80% with data from a phase 3 blinatumomab study in r/r Philadelphia chromosome–negative ALL. **RESULTS:** In the PSA, the rate of complete remission or complete remission with partial hematologic recovery was 36% for blinatumomab and 25% for SOC, and this resulted in an odds ratio of 1.54 (95% confidence interval [CI], 0.61-3.89) or 1.70 (95% credible interval [CrI], 0.94-2.94) with Bayesian data augmentation. Overall survival favored blinatumomab over SOC, with a hazard ratio of 0.81 (95% CI, 0.57-1.14) or 0.77 (95% CrI, 0.61-0.96) with Bayesian data augmentation. **CONCLUSIONS:** These results further support blinatumomab as a treatment option for patients with r/r Ph+ ALL. ***Cancer* 2020;126:304-310**.

KEYWORDS: blinatumomab, Philadelphia chromosome–positive acute lymphoblastic leukemia, propensity score analysis, remission, standard of care, survival.

INTRODUCTION

The development of BCR-ABL1 protein–specific tyrosine kinase inhibitors (TKIs) has significantly improved outcomes in Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL).[1-3] The standard of care (SOC) for de novo Ph+ ALL is induction with conventional or attenuated chemotherapy in combination with a TKI.[2,3] Most patients achieve complete remission (CR) and proceed to allogeneic hematopoietic stem cell transplantation (allo-HSCT).[4] However, relapse can occur and is commonly associated with TKI-resistant mutations in the kinase domain of the *BCR-ABL1* oncogene.[5] There is no definitive evidence of a sustained response or long-term survival with TKIs after a relapse, with overall survival (OS) ranging from approximately 4 to 6 months.[4,6,7] Compounding these challenges, Ph+ ALL is rare,[8] and this limits most clinical trials evaluating new treatments to single-arm studies.[2,3]

Blinatumomab is a bispecific T-cell–engaging antibody construct that binds simultaneously to CD3-positive cytotoxic T cells and CD19-positive B cells and allows endogenous T cells to recognize and eliminate CD19-positive ALL blasts.[9]

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Prior studies have established the efficacy and safety of blinatumomab in relapsed/refractory (r/r) Philadelphia chromosome–negative (Ph–) ALL.[10] Both Ph– and Ph+ B-precursor leukemic cells express CD19; therefore, blinatumomab was assessed in a single-arm, phase 2 study of patients with r/r Ph+ ALL who had received a second-generation TKI.[11] Of the 45 patients enrolled, 36% achieved CR or complete remission with partial hematologic recovery (CRh). The median OS was 7.1 months.

To assess the relevance of the blinatumomab study results within the wider context of available treatment options, we compared the treatment outcomes with those of an external control population. For rare diseases without a satisfactory SOC, regulatory agencies support the use of external controls as a method for demonstrating the efficacy of new treatments.[12] A problem with this approach is the substantial variability among patients in the external control cohort. Propensity score analysis (PSA) provides a better balance between patients receiving the treatment of interest and the external control with respect to relevant baseline factors, and it enables a less biased comparison of outcomes.

Here we report the results of a PSA comparing efficacy data from the phase 2 blinatumomab study and those of an external population: patients with r/r Ph+ B-precursor ALL who had received SOC after the failure of or resistance to treatment with second-generation TKIs.

MATERIALS AND METHODS

External SOC

The external SOC cohort was identified and developed from existing clinical databases at centers in Italy (Pope John XXIII Hospital [Bergamo] and Sant'Orsola Policlinic [Bologna]) and Spain (Josep Carreras Research Institute, Hospital Germans Trias i Pujol, Catalan Oncology Institute [Barcelona]). To align with the eligibility criteria of the phase 2 blinatumomab trial, patients with r/r Ph+ ALL included in the external SOC cohort were 18 years old or older, were r/r to at least 1 second-generation TKI (dasatinib, nilotinib, bosutinib, or ponatinib), and had >5% bone marrow blasts. Patients were excluded if they had a history of malignancy other than ALL within 5 years of initiating salvage SOC, central nervous system or extramedullary disease, or prior therapy with blinatumomab. There were no restrictions on qualifying salvage therapy.

Data collection began in August 2017 and ended in January 2018. Fifty-five patients met all eligibility criteria and were included in the current analysis (see Supporting Fig. 1). The baseline period started from the initial diagnosis of ALL and ended at the start of the qualifying salvage therapy, and data were collected from diagnosis until the date of death or last follow-up. Investigators received approval from an institutional review board or ethics committee of participating centers.

Blinatumomab Ph+ ALL study

The blinatumomab study was an open-label, single-arm, multicenter, phase 2 clinical trial of blinatumomab in adults with r/r Ph+ ALL (ClinicalTrials.gov identifier NCT02000427). The study was conducted at 19 centers in Europe and the United States. Details of this study have been previously reported.[11] Patients with Ph+ B-precursor ALL who were 18 years old or older were eligible for enrollment provided that they were r/r to at least 1 second-generation TKI, had >5% bone marrow blasts, and had an Eastern Cooperative Oncology Group performance status of 2 or lower. Exclusion criteria included allo-HSCT within the 12 weeks before the start of blinatumomab, active acute or chronic (grade 2-4) graft-versus-host disease, systemic treatment of graft-versus-host disease within 2 weeks of starting blinatumomab, a history or presence of clinically relevant central nervous system pathology (including central nervous system ALL), isolated extramedullary disease, and a history of malignancy other than ALL within 5 years. Blinatumomab was administered as a continuous intravenous infusion at a dose of 9 μg/d in week 1 of cycle 1 and at a dose of 28 μg/d thereafter. For each treatment cycle, blinatumomab was administered for 4 weeks, which was followed by 2 weeks off treatment. Patients who achieved CR/CRh could receive up to 3 additional cycles of treatment. The baseline period for patients began in January 2014, and the study ended in May 2015. All patients provided informed consent, and the study was approved by the institutional review boards of participating centers.

Efficacy Endpoints

Efficacy endpoints for the PSA included OS and CR/CRh. For time-to-event analyses, patients were followed from the start date of blinatumomab or SOC therapy to the event or were censored at the time they were lost to follow-up or alive. CR was defined as ≤5% bone marrow blasts, with a platelet count >100,000/μL, an absolute neutrophil count >1000/μL, and no evidence of extramedullary disease. CRh was defined as ≤5% bone marrow blasts, with a platelet count >50,000/μL and an absolute neutrophil count >500/μL. The response was determined within the first 2 treatment cycles in the blinatumomab study (approximately 70 days) but varied for the SOC cohort with the treatment (the median time to a response was 48 days).

Propensity Score Analysis

The PSA was planned and prespecified before endpoint analyses were conducted. The PSA created a balance between the blinatumomab and external SOC cohorts with respect to available baseline covariates that determined both the propensity for a patient to be treated (with blinatumomab) and a patient's prognosis.[13-15] The baseline covariates included the age at diagnosis and treatment, sex, time from diagnosis to most recent treatment (months), prior allo-HSCT status (yes or no), prior salvage therapy status (yes or no), and number of prior salvage therapies (0, 1, 2, 3, or ≥4). An estimated propensity score (ie, the predicted probability of participating in the blinatumomab phase 2 trial) was assigned to each patient on the basis of the selected covariates. The balance of covariates between patients in the blinatumomab trial and patients in the external cohort was determined by the calculation of standardized differences in each covariate before and after propensity score adjustments and box plot overlap in propensity scores.

In the estimation of treatment effects, propensity scores were used to adjust for differences between patients in the blinatumomab and external SOC cohorts via inverse probability of treatment weighting (IPTW) methods.[16] The objective was to estimate the average treatment effect (ATE) from moving the entire population from an untreated status to a treated status.[17] Sensitivity analyses explored the use of stabilized inverse probability of treatment weighting (sIPTW), which accounts for potential instability caused by very large weights,[18] and the average treatment effect of treated weights (ATT).[19] Covariates with a standardized difference >0.20 after IPTW adjustment were added to statistical models as covariates.

CR/CRh rates were analyzed with a logistic regression model with a single-treatment indicator covariate and propensity score–based weights to adjust for differences between the blinatumomab and external SOC cohorts. The model's coefficient for treatment effect was used to obtain an odds ratio, and a robust variance estimation (applied with a generalized estimating equation) was used to construct 95% confidence intervals (CIs) to evaluate the probability of CR/CRh. Similarly, OS was analyzed via a Cox proportional hazards model with a single-treatment indicator covariate and with propensity score–based IPTW or sIPTW weights to adjust for differences.

Because of the small sample sizes, the PSA had a statistical power of 65% to detect an assumed hazard ratio of 0.75 favoring blinatumomab treatment. To increase power, Bayesian data augmentation was applied to endpoint analyses using distributions of OS and the odds ratio of CR/CRh from the phase 3 trial of blinatumomab versus SOC in patients with r/r Ph– B-cell precursor ALL.[10,20] For Bayesian models, point estimates and 95% credible intervals (CrIs) were estimated with summary statistics and the relative highest posterior density interval of the posterior distributions for model parameters of interest. Bayesian models used enough "borrowing" from the phase 3 trial to achieve a power of 80%. Potential bias was assessed by the completion of sensitivity analyses with prespecified lower levels of borrowing (ie, power levels of 70% and 75%). Statistical programming was conducted in SAS 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Patient characteristics are presented in Table 1. All but 1 patient in each of the cohorts were enrolled on the basis of r/r Ph+ ALL to a second-generation TKI. One patient in the external SOC cohort was intolerant to a second-generation TKI and had failed or was intolerant to imatinib, whereas 1 patient in the blinatumomab cohort was resistant to imatinib but had not received a second-generation TKI (protocol deviation).

The study populations were generally similar with respect to sex and age, but differences were noted for geographic region and prior treatments. The proportion of patients with no prior salvage therapy was higher in the blinatumomab cohort (13% vs 31%), as were the proportions with prior treatment with 3 or more TKIs (16% vs 38%) and prior allo-HSCT (33% vs 44%). Dasatinib was the most common prior TKI in both cohorts (89% vs 87%). Prior treatment with imatinib was more common in the external SOC cohort (87% vs 56%), whereas prior treatment with ponatinib was more common in the blinatumomab cohort (13% vs 51%).

Qualifying salvage therapies in the external SOC cohort included chemotherapy (22%), chemotherapy plus a TKI (29%), and a TKI alone (31%; see Supporting Table 1). Common chemotherapy agents included mercaptopurine, vincristine, cytarabine, cyclophosphamide, and mitoxantrone. Generally, chemotherapy included combination regimens such as high-dose cytarabine and mitoxantrone (HAM), mitoxantrone, etoposide, and cytarabine (MEC), and cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD). Other treatments (18%) included an aurora kinase inhibitor, bortezomib, and donor leukocyte infusion, used alone or as part of a combination chemotherapy regimen, and salvage allo-HSCT. Use of corticosteroids was common. Fifteen patients (27%) in the external SOC cohort achieved CR/CRh with their qualifying salvage therapy,

TABLE 1. Baseline Characteristics

Characteristic	External SOC (n = 55)	Blinatumomab Study (n = 45)
Age, median (range), y[a]	53 (20-82)	55 (23-78)
Age category, No. (%)[a]		
18-34 y	9 (16)	5 (11)
35-54 y	22 (40)	17 (38)
≥55 y	24 (44)	23 (51)
Sex, No. (%)		
Male	28 (51)	24 (53)
Female	27 (49)	21 (47)
Geographic region/country, No. (%)		
United States	0	11 (24)
European Union	55 (100)[b]	34 (76)
Lines of prior salvage treatment, No. (%)		
0	7 (13)	14 (31)
1	31 (56)	12 (27)
≥2	17 (31)	19 (42)
No. of prior TKI treatments, No. (%)		
1	6 (11)	7 (16)
2	41 (75)	21 (47)
≥3	8 (15)	17 (38)
Prior TKIs, No. (%)[a]		
Imatinib	48 (87)	25 (56)[c]
Dasatinib	49 (89)	39 (87)
Ponatinib	7 (13)	23 (51)
Nilotinib	10 (18)	16 (36)
Multiple TKIs	49 (89)	38 (84)
Prior allo-HSCT, No. (%)		
Yes	18 (33)	20 (44)
No	37 (67)	25 (56)

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; SOC, standard of care; TKI, tyrosine kinase inhibitor.
[a]Before the start of qualifying salvage therapy for the external SOC cohort.
[b]Spain (n = 14) and Italy (n = 41).
[c]One patient had acute lymphoblastic leukemia resistant to imatinib and was never exposed to a second-generation or later TKI.

TABLE 2. Treatment Outcomes

	External SOC (n = 55)	Blinatumomab Study (n = 45)
Response to treatment, No. (%)[a]		
Overall complete remission	15 (27)	16 (36)
Complete remission	14 (25)	14 (31)
Complete remission with partial hematologic recovery	1 (2)	2 (4)
Complete remission with incomplete hematologic recovery	1 (2)	2 (4)
Blast-free hypoplastic or aplastic bone marrow	NA	3 (7)
Partial remission	1 (2)	2 (4)
No response	NA	12 (27)
Refractory/progressive disease/ early death	28 (51)	4 (9)
Unknown/missing	10 (18)	6 (13)
Proceeded to allo-HSCT, No. (%)	8 (15)	4 (9)
Overall survival, median (95% CI), mo	6.0 (4.4-9.2)[b]	7.1 (5.6 to NE)

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; CI, confidence interval; NA, not available; NE, not estimable; SOC, standard of care.
[a]Response within the first 2 cycles of treatment for the blinatumomab study.
[b]Overall survival data were available for 51 patients (4 were missing the treatment start or last follow-up date).

TABLE 3. Summary of CR/CRh Analysis With and Without Bayesian Data Augmentation and With IPTW-ATE Adjustments

Endpoint	External SOC (n = 55)	Blinatumomab Study (n = 45)
Non-Bayesian data augmentation (65% power)	OR, 1.54 (95% CI, 0.61-3.89); *P* = .26	
CR/CRh, % (95% CI)	26 (16-40)	36 (22-52)
Bayesian data augmentation (80% power)	OR, 1.70 (95% CrI, 0.94-2.94); *P* = .076	
CR/CRh, % (95% CrI)	25 (17-34)	36 (28-46)

Abbreviations: ATE, average treatment effect; CI, confidence interval; CR, complete remission; CRh, complete remission with partial hematologic recovery; CrI, credible interval; IPTW, inverse probability of treatment weighting; OR, odds ratio; SOC, standard of care.

with 14 (25%) achieving CR and 1 (2%) achieving CRh (Table 2). For the 51 patients for whom OS data were available, the median OS was 6.0 months (95% CI, 4.4-9.2 months; Supporting Fig. 2).

The primary analysis of the blinatumomab study has been previously reported.[11] The CR/CRh rate was 36% after 2 cycles, with 14 patients (31%) achieving CR and 2 patients (4%) achieving CRh. The median OS was 7.1 months (95% CI, 5.6 to not estimable).

Propensity Score Analysis

All propensity scores for the external SOC control were contained within the 95% range of the propensity scores for blinatumomab, and this indicated that most patients in the external SOC would have been eligible to receive blinatumomab treatment (Supporting Fig. 3). Two covariates had a >0.20 standardized difference between the cohorts: prior allo-HSCT and no prior salvage therapy (Supporting Table 2). After adjustments with IPTW, the standardized difference became 0 for no prior salvage therapy and was reduced from –0.33 to –0.23 for prior allo-HSCT. Because the difference remained >0.20, the propensity score models incorporated an IPTW-ATE adjustment with prior allo-HSCT as a covariate.

The Bayesian-augmented (80% power) odds ratio estimate for CR/CRh was 1.70 (95% CrI, 0.94-2.94) and favored blinatumomab over the external SOC (Table 3). Corresponding CR/CRh rate estimates for the blinatumomab and external SOC cohorts were 36% (95% CrI, 28%-46%) and 25% (95% CrI, 17%-34%), respectively. The non-Bayesian (65% power) odds ratio was 1.54 (95% CI, 0.61-3.89).

The Bayesian-augmented (80% power) hazard ratio comparing the OS of blinatumomab with the OS of the external SOC was 0.77 (95% CrI, 0.61-0.96), and this suggested a statistically significant 23% reduction in the

TABLE 4. Summary of OS Analysis With and Without Bayesian Data Augmentation and With IPTW-ATE Adjustments

Endpoint	External SOC	Blinatumomab Study
Non-Bayesian data augmentation (65% power)	HR, 0.81 (95% CI, 0.57-1.14); $P = .20$	
OS probability, % (95% CI)		
3 mo	79 (70-89)	83 (74-93)
6 mo	52 (40-68)	59 (47-74)
9 mo	39 (27-57)	47 (35-64)
12 mo	32 (20-50)	40 (28-57)
Bayesian data augmentation (80% power)	HR, 0.77 (95% CrI, 0.61-0.96); $P = .031$	
OS probability, % (95% CrI)		
3 mo	79 (77-81)	83 (82-85)
6 mo	51 (47-55)	60 (57-63)
9 mo	39 (34-43)	48 (44-52)
12 mo	31 (26-35)	41 (37-44)

Abbreviations: ATE, average treatment effect; CI, confidence interval; CrI, credible interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; OS, overall survival; SOC, standard of care.

risk of death associated with blinatumomab in comparison with the external SOC. The non-Bayesian (65% power) hazard ratio was 0.81 (95% CI, 0.57-1.14; Table 4 and Fig. 1).

Sensitivity analyses of less borrowing for Bayesian data augmentation were consistent with these analyses (see Supporting Table 3 [CR/CRh] and Supporting Fig. 4 [OS]), as were ATT sensitivity analyses (Supporting Tables 4 [CR/CRh] and 5 and Supporting Figs. 4 and 5 [OS]) and sIPTW analyses (Supporting Fig. 6 [OS]).

DISCUSSION

In the single-arm, phase 2 blinatumomab trial, adult patients with r/r Ph+ ALL receiving blinatumomab achieved a CR/CRh rate of 36% with a median OS of 7.1 months.[11] These results suggested an improvement in treatment outcomes with blinatumomab in comparison with historical studies but were limited by the single-arm trial design.[4,6,7] In the current analysis, PSA places these efficacy results into the context of available treatment options. By aligning the eligibility criteria of the external SOC with those of the blinatumomab study, we selected a similar patient population for comparison. Both patient populations were heavily pretreated and balanced for most baseline covariates. In the external SOC group, the CR/CRh rate was 26%, and the median OS was 6.0 months; this was consistent with historical Ph+ ALL studies.[4,6,7]

PSA, adjusted for imbalances in prognostic covariates and Bayesian data augmentation, was applied to improve statistical power. Bayesian-augmented PSA demonstrated a 70% increase in the odds of achieving remission with blinatumomab in comparison with the external SOC, a numerical benefit that did not reach statistical significance. The Bayesian-augmented analysis of OS showed a statistically significant 23% decrease in the hazard of death with blinatumomab treatment in comparison with SOC, and sensitivity analyses were consistent with these findings. For future salvage treatment strategies, these observations will be of great importance, particularly among patients for whom allo-HSCT is planned only in second remission.[21,22]

Although safety data for the external SOC were not available for comparison, treatment toxicity is a relevant concern. During the phase 2 blinatumomab study, all patients experienced at least 1 treatment-emergent adverse event (AE), and 82% experienced a grade 3 or higher AE, but these were generally manageable because only 7% of the patients discontinued treatment on account of an AE.[11] The most common grade 3 or higher AEs included febrile neutropenia (27%), thrombocytopenia (22%), and anemia (16%). One fatal AE (septic shock) was considered treatment-related by the investigator. Overall, blinatumomab was tolerable with manageable AEs.

Given the benefit-to-risk profile of blinatumomab in the phase 2 trial and across clinical trials in ALL,[10,11] future studies are looking to pair blinatumomab with TKIs because the combination may provide additional benefit to patients with Ph+ ALL.[23] There is also evidence in Ph– ALL to support the use of blinatumomab in patients at earlier stages of treatment, including patients who have achieved CR/CRh with induction therapy but still have minimal residual disease (MRD).[10,24] In the phase 2 trial, 18 of 45 patients with r/r Ph+ ALL who received blinatumomab achieved an MRD response, with the median OS not reached for MRD responders versus 3.9 months for MRD nonresponders.[11] MRD response data were not available for all patients in the external SOC cohort, so a comparison was not possible.

PSA has become an established method to support the development of novel treatments for rare malignancies.[12,25] However, there are limitations. Although PSA mitigates the impact of known confounders and bias, it is not a replacement for randomization. In the propensity score model, one can consider only known covariates that are measured in both studies. The use of PSA cannot address imbalances in unmeasured/unknown covariates or postbaseline variables. For the external SOC cohort, we did not have data for some of the eligibility criteria that defined the blinatumomab study population (eg, prior graft-versus-host disease, duration of remission with prior allo-HSCT, and Eastern Cooperative Oncology Group performance status) or data for other important prognostic

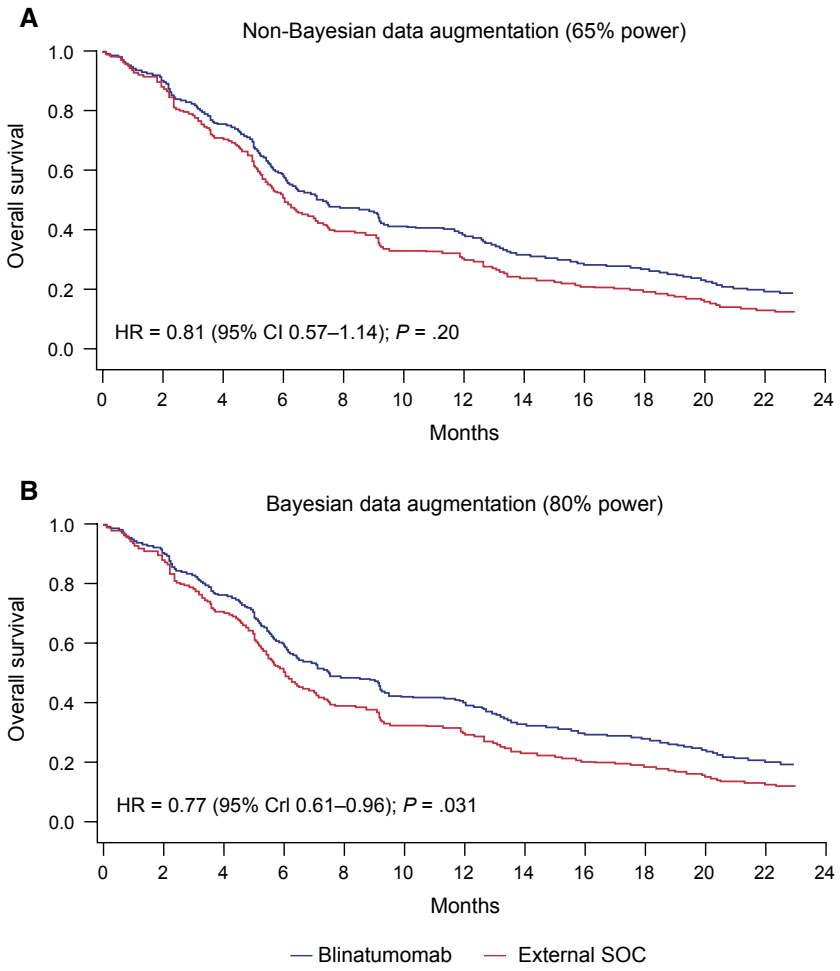

Figure 1. Cox proportional hazards model estimates of survival by treatment (A) with and (B) without Bayesian data augmentation (80% power). IPTW-ATE adjustments were made. Survival estimates were calculated with the proportion of prior hematopoietic stem cell transplantation: 0.327 for the control group and 0.4 for the blinatumomab group. ATE indicates average treatment effect; CI, confidence interval; CrI, credible interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; SOC, standard of care.

factors (eg, kinase domain mutations). Furthermore, post-treatment allo-HSCT was more frequent with blinatumomab than external SOC (15% vs 9%). Other limitations include the small sample sizes of the cohorts, response assessment by centralized review (blinatumomab study) versus investigator review (external SOC), and geographic and chronologic differences between the study cohorts. The blinatumomab study was conducted in the United States and Europe, whereas the external SOC included patients enrolled at centers in Italy and Spain, with some patients treated 9 years before the initiation of the blinatumomab study. Although differences in clinical practice could be present between these cohorts (eg, the use of newer TKIs such as ponatinib and nilotinib), general practice patterns for ALL over time and between regions were not dramatically different. Treatment with TKIs and chemotherapies were standard treatment options. Selecting for specific qualifying salvage therapies may have introduced additional bias.

In conclusion, the results from the PSA reported here suggest that blinatumomab improves treatment outcomes in patients with r/r Ph+ ALL in comparison with external SOC. These data further support blinatumomab as a treatment option for patients with r/r Ph+ ALL.

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AUTHOR CONTRIBUTIONS

Alessandro Rambaldi: Data acquisition, critical revision of the manuscript, and approval of the final version. **Josep-Maria Ribera:** Data acquisition, critical revision of the manuscript, and approval of the final version. **Hagop M. Kantarjian:** Data acquisition, critical revision of the manuscript, and approval of the final version. **Hervé Dombret:** Data acquisition, critical revision of the manuscript, and approval of the final version. **Oliver G. Ottmann:** Data acquisition, critical revision of the manuscript, and approval of the final version. **Anthony S. Stein:** Data acquisition, critical revision of the manuscript, and approval of the final version. **Catherine A. Tuglus:** Research design, analysis, and drafting of the manuscript. **Xiaoyue Zhao:** Analysis, critical revision of the manuscript, and approval of the final version. **Christopher Kim:** Research design, analysis, and drafting of the manuscript. **Giovanni Martinelli:** Data acquisition, critical revision of the manuscript, and approval of the final version.

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