Blinatumomab compared with standard of care for the treatment of adult patients with Philadelphia chromosome–positive relapsed/refractory B-precursor acute lymphoblastic leukemia

Short Running Title*:* Blinatumomab in Ph+ relapsed/refractory ALL

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Precis

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. Using propensity score analysis, we demonstrate that efficacy outcomes (complete remission and overall survival) from the phase 2 trial with blinatumomab compare favorably with a cohort of similar patients with r/r Ph+ ALL treated with standard-of-care chemotherapy.

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Abstract

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. We compared outcomes with blinatumomab to a historical control treated with standard of care (SOC).

Methods

The blinatumomab trial enrolled adult patients with Ph+ ALL who were r/r to at least one second-generation tyrosine kinase inhibitor (*N*=45). We used propensity score analysis (PSA) to compare outcomes with blinatumomab to an external cohort of similar patients receiving SOC chemotherapy (*N*=55). PSA mitigated confounding variables between studies by adjusting for imbalances in 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 augmentation was applied to improve power to 80% using data from a Phase 3 blinatumomab study in Ph− r/r ALL.

Results

In the PSA, rate of complete remission or complete remission with partial hematologic recovery was 36% for blinatumomab and 25% for SOC, resulting 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 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 augmentation.

Conclusions

These results further support blinatumomab as a treatment option for patients with Ph+ r/r ALL.

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

Total number of each:
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Introduction

The development of BCR-ABL1 protein-specific tyrosine kinase inhibitors (TKI) 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 (alloHSCT).[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 sustained response or long-term survival with TKIs after relapse, with overall survival (OS) ranging from approximately 4 to 6 months.[4,6,7] Compounding these challenges, Ph+ ALL is rare,[8] limiting 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, allowing endogenous T cells to recognize and eliminate CD19-positive ALL blasts.[9] Prior studies established the efficacy and safety of blinatumomab in Philadelphia chromosome–negative (Ph–) relapsed/refractory (r/r) 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 Ph+ r/r ALL who had received a second-generation TKI.[11] Of the 45 patients enrolled, 36% achieved CR or CR with partial hematologic recovery (CRh). 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 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 to demonstrate 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, enabling less biased comparison of outcomes.

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

Methods

External SOC

The external SOC cohort was identified and developed from existing clinical databases at centers in Italy (Ospedale Papa Giovanni XXIII; Policlinico Sant'Orsola, Istituto Seragnoli) and Spain (ICO-Hospital

Germans Trias i Pujol, Josep Carreras Research Institute). To align with the eligibility criteria of the Phase 2 blinatumomab trial, patients with Ph+ r/r ALL included in the external SOC cohort were ≥18 years of age, r/r to at least one second-generation TKI (dasatinib, nilotinib, bosutinib, 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 salavage 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 present analysis (see Supporting Information Figure s1). 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 Ph+ r/r 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 of age were eligible for enrollment provided they were r/r to at least one second-generation TKI, had >5% bone marrow blasts, and had an Eastern Cooperative Oncology Group performance status of ≤2. Exclusion criteria included alloHSCT within 12 weeks before the start of blinatumomab, active acute or chronic (Grade 2 to 4) graft-versus-host disease, systemic treatment of graft-versus-host disease within 2 weeks of starting blinatumomab, 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/day in Week 1 of Cycle 1 and 28 μg/day thereafter. For each treatment cycle, blinatumomab was administered for 4 weeks followed by 2 weeks off treatment. Patients who achieved a CR/CRh could receive up to three 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 censored at the time they were lost to follow-up or alive. CR was defined as ≤5% bone marrow blasts, with platelets >100,000/µl, absolute neutrophil count >1000/µl and no evidence of extramedullary disease. CRh was defined as ≤5% bone marrow blasts, with platelets >50,000/µl and absolute neutrophil count >500/µl. Response was determined within the first two treatment cycles in the blinatumomab study (~70 days) but varied for the SOC cohort depending on the treatment (median time to response was 48 days).

Propensity score analysis

PSA was planned and pre-specified prior to conducting endpoint analyses. PSA creates a balance between the blinatumomab and external SOC cohorts with respect to available baseline covariates that determine both the propensity for a patient to be treated (with blinatumomab) and a patient's prognosis.[13-15] Baseline covariates included age at diagnosis and treatment, sex, time from diagnosis to most recent treatment (months), prior alloHSCT (yes, no), prior salvage therapy (yes, no) and number of prior salvage therapies (0, 1, 2, 3 and ≥4). An estimated propensity score (i.e., the predicted probability of participating in the blinatumomab Phase 2 trial) was assigned to each patient based on the selected covariates. The balance of covariates between patients in the blinatumomab trial and patients in the external cohort was determined by calculation of standardized differences in each covariate before and after propensity score adjustment 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 using inverse probability of treatment weighting (IPTW) methods.[16] The objective was to estimate the average treatment effect (ATE) from moving the entire population from untreated to treated.[17] Sensitivity analyses explored use of stabilized IPTW (sIPTW), which accounts for potential instability caused by very large weights,[18] and average treatment effect of treated weights (ATT).[19] Covariates with a standardized difference of >0.20 after IPTW adjustment were added to statistical models as a covariate.

CR/CRh rates were analyzed using a logistic regression model with a single-treatment indicator covariate and propensity score–based weights to adjust for differences between 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 (CI) to evaluate the probability of CR/CRh. Similarly, OS was analyzed via a Cox

proportional hazards model with a single-treatment indicator covariate and using propensity score–based IPTW or sIPTW weights to adjust for differences.

Given 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 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 Ph– r/r B-cell precursor ALL.[10] For Bayesian models, point estimates and 95% credible intervals (CrI) were estimated using 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 completing sensitivity analyses with pre-specified lower levels of 'borrowing' (i.e. power levels of 70% and 75%). Statistical programming was conducted in SAS 9.4 (SAS Institute, Cary, NC).

Results

Patient characteristics are presented in Table 1. All but 1 patient in each of the cohorts were enrolled based on Ph+ r/r 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, while 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 gender 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 was prior treatment with ≥3 TKIs (16% vs. 38%) and prior alloHSCT (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%), while 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 TKI (29%), and TKI alone (31%) (see Supporting Information Table s1). Common chemotherapy agents included mercaptopurine, vincristine, cytarabine, cyclophosphamide, and mitoxantrone. Generally, chemotherapy included combination regimens, such as HAM (high-dose cytarabine and mitoxantrone), MEC (mitoxantrone, etoposide and cytarabine), and hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone). Other treatments (18%) included

aurora kinase inhibitor, bortezomib, and donor leukocyte infusion, used alone or as part of a combination chemotherapy regimen, and salvage alloHSCT. Use of corticosteroids was common. Fifteen patients (27%) in the external SOC cohort achieved CR/CRh with their qualifying salvage therapy, with 14 (25%) achieving a CR and 1 (2%) achieving a CRh (Table 2). Of 51 patients for whom OS data were available, median OS was 6.0 (95% CI 4.4–9.2) months (Supporting Information Fig s2).

The primary analysis of the blinatumomab study has been previously reported.[11] The CR/CRh rate was 36% after two cycles, with 14 patients (31%) achieving a CR and 2 patients (4%) achieving a CRh. Median OS was 7.1 months (95% CI 5.6–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, indicating that most patients in the external SOC would have been eligible to receive blinatumomab treatment (Supporting Information Fig s3). Two covariates had >0.20 standardized difference between the cohorts: prior alloHSCT and no prior salvage therapy (Supporting Information Table s2). After adjustment with IPTW, the standardized difference became 0 for no prior salvage therapy and was reduced from –0.33 to –0.23 for prior alloHSCT. Because the difference remained >0.20, the propensity score models incorporated IPTW-ATE adjustment with prior alloHSCT as a covariate.

The Bayesian-augmented (80% power) odds ratio estimate for CR/CRh was 1.70 (95% CrI 0.94–2.94), favoring blinatumomab over the external SOC (Table 3). Corresponding CR/CRh rate estimates for the blinatumomab and the 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 OS of blinatumomab with the external SOC was 0.77 (95% CrI 0.61–0.96), suggesting a statistically significant 23% reduction in the risk of death associated with blinatumomab compared with external SOC. The non-Bayesian (65% power) hazard ratio was 0.81 (95% CI 0.57–1.14) (Table 4; Fig 1).

Sensitivity analyses of less borrowing for Bayesian augmentation were consistent with these analyses (see Supporting Information Table s3 [CR/CRh] and Fig s4 [OS]), as were ATT sensitivity analyses (Supporting Information Table s4 [CR/CRh] and Table s5, Figs s4 and s5 [OS]) and sIPTW analyses (Supporting Information Fig s6 [OS]).

Discussion

In the single-arm Phase 2 blinatumomab trial, adult patients with Ph+ r/r 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 compared 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 that of the blinatumomab study, a similar patient population was selected for comparison. Both patient populations were heavily pretreated and balanced for most baseline covariates. In the external SOC, the CR/CRh rate was 26% and median OS was 6.0 months, consistent with historical Ph+ ALL studies.[4,6,7]

PSA adjusted for imbalances in prognostic covariates and Bayesian augmentation was applied to improve statistical power. Bayesian-augmented PSA demonstrated a 70% increase in the odds of achieving remission with blinatumomab compared with 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 compared with SOC, and sensitivity analyses were consistent with these findings. For future salvage treatment strategies, these observations are of great importance, particularly among patients for whom an alloHSCT is planned only in second remission.[20,21]

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 one treatment-emergent adverse event (AE) and 82% experienced a Grade ≥3 AE, but these were generally manageable as only 7% of patients discontinued treatment due to an AE.[11] The most common Grade ≥3 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, as the combination may provide additional benefit to patients with Ph+ ALL.[22] There is also evidence in Ph– ALL to support the use of blinatumomab at earlier stages of treatment, including patients who have achieved CR/CRh with induction therapy but still have minimal residual disease (MRD).[10,23] In the Phase 2 trial, 18/45 patients with Ph+ r/r ALL who received blinatumomab achieved an MRD response, with the median OS not reached for MRD responders compared with 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 development of novel treatments for rare malignancies.[12,24] However, there are limitations. While the PSA mitigates the impact of known confounders and bias, it is not a replacement for randomization. In the propensity score model, one can only consider known covariates that are measured in both studies. The use of PSA cannot address imbalances in unmeasured/unknown covariates or post-baseline variables. We did not have data on ECOG performance status or kinase domain mutations for the external SOC cohort, and post-treatment alloHSCT was more frequent with blinatumomab than with external SOC (15% vs. 9%). Other limitations include the small sample size of the cohorts, response assessment by centralized (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, while 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 was 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 Ph+ r/r ALL compared with external SOC. These data further support blinatumomab as a treatment option for patients with Ph+ r/r ALL.

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Table 1. Baseline characteristics

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

alloHSCT, allogeneic hematopoietic stem cell transplantation; SOC, standard of care; TKI, tyrosine kinase inhibitor.

*Prior to start of qualifying salvage therapy for the external SOC cohort.

†Spain (*n* = 14), Italy (*n* = 41).

‡One patient had ALL 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,* n (%)		
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 (17)	6 (13)
Proceeded to alloHSCT, n (%)	8 (15)	4 (9)
Median overall survival, months (95% CI)	6.0 (4.4–9.2)†	7.1 (5.6–NE)

CI, confidence interval; alloHSCT, allogeneic hematopoietic stem cell transplantation; NA, not available; NE, not estimable; SOC, standard of care.

*Response within first two cycles of treatment for blinatumomab study.

†Overall survival data available for 51 patients (4 missing treatment start or last follow-up date).

Table 3. Summary of CR/CRh analysis with and without Bayesian augmentation and adjusted by inverse probability of treatment weighting (IPTW) – average treatment effect (ATE)

Endpoint	External SOC (*N* = 55)	Blinatumomab study (*N* = 45)
Non-Bayesian (65% power)	OR 1.54 (95% CI 0.61–3.89); *P* = 0.26	
CR/CRh (95% CI)	26% (16%–40%)	36% (22%–52%)
Bayesian augmentation (80% power)	OR 1.70 (95% CrI 0.94–2.94); *P* = 0.076	
CR/CRh (95% CrI)	25% (17%–34%)	36% (28%–46%)

CI, confidence interval; CR, complete remission; CRh, complete remission with partial hematologic recovery; CrI, credible interval; OR, odds ratio; SOC, standard of care.

Table 4. Summary of OS analysis with and without Bayesian augmentation and adjusted by inverse probability of treatment weighting (IPTW) – average treatment effect (ATE)

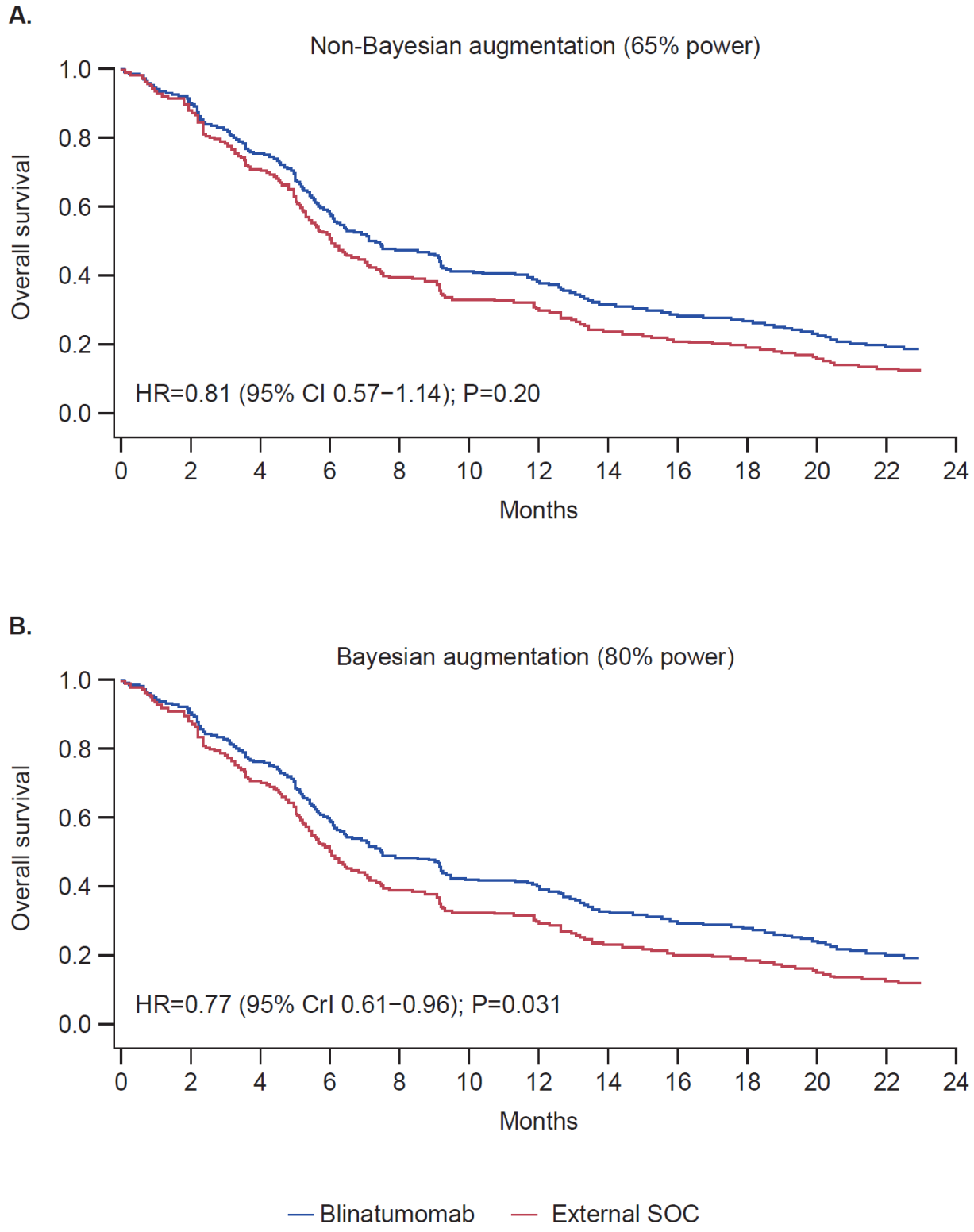
Endpoint	External SOC	Blinatumomab study
Non-Bayesian (65% power)	HR 0.81 (95% CI 0.57–1.14); *P* = 0.20	
OS probability (95% CI)		
3-month	79% (70%–89%)	83% (74%–93%)
6-month	52% (40%–68%)	59% (47%–74%)
9-month	39% (27%–57%)	47% (35%–64%)
12-month	32% (20%–50%)	40% (28%–57%)
Bayesian augmentation (80% power)	HR 0.77 (95% CrI 0.61–0.96); *P* = 0.031	
OS probability (95% CrI)		
3-month	79% (77%–81%)	83% (82%–85%)
6-month	51% (47%–55%)	60% (57%–63%)
9-month	39% (34%–43%)	48% (44%–52%)
12-month	31% (26%–35%)	41% (37%–44%)

CI, confidence interval; CrI, credible interval; HR, hazard ratio; OS, overall survival; SOC, standard of care.

Figure Legend

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

Figure 1.


A.
Non-Bayesian augmentation (65% power)
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
HR=0.81 (95% CI 0.57−1.14); P=0.20
0
2
4
6
8
10
12
14
16
18
20
22
24
Months
B.
Bayesian augmentation (80% power)
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
HR=0.77 (95% CrI 0.61−0.96); P=0.031
0
2
4
6
8
10
12
14
16
18
20
22
24
Months
Blinatumomab
External SOC