Original Article

Long-Term Survival of Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia Treated With Blinatumomab

Max S. Topp, MD[1]; Nicola Gökbuget, MD[2]; Gerhard Zugmaier, MD, PhD[3]; Anthony S. Stein, MD[4]; Hervé Dombret, MD[5]; Yuqi Chen, PhD[6]; Josep-Maria Ribera, MD, PhD [7]; Ralf C. Bargou, MD[8]; Heinz-August Horst, MD, PhD[9]; and Hagop M. Kantarjian, MD [10]

BACKGROUND: Blinatumomab is a CD19 BiTE (bispecific T-cell engager) immuno-oncology therapy that mediates the lysis of cells expressing CD19. **METHODS:** A pooled analysis of long-term follow-up data from 2 phase 2 studies that evaluated blinatumomab in heavily pretreated adults with Philadelphia chromosome–negative, relapsed/refractory B-cell precursor acute lymphoblastic leukemia was conducted. **RESULTS:** A total of 259 patients were included in the analysis. The median overall survival (OS) among all patients, regardless of response, was 7.5 months (95% confidence interval [CI], 5.5-8.5 months); the median follow-up time for OS was 36.0 months (range, 0.3-60.8 months). The median relapse-free survival (RFS) among patients who achieved a complete remission (CR) or complete remission with partial hematologic recovery (CRh) in the first 2 cycles (n = 123) was 7.7 months (95% CI, 6.2-10.0 months); the median follow-up time for RFS was 35.0 months (range, 9.5-59.5 months). OS and RFS plateaued with 3-year rates of 17.7% and 23.4%, respectively. The cumulative incidence function of the time to relapse, with death not due to relapse considered a competing risk, for patients who achieved a CR/CRh within 2 cycles of treatment also plateaued with a 3-year relapse rate of 59.3%. For patients who achieved a CR/CRh with blinatumomab followed by allogeneic hematopoietic stem cell transplantation while in continuous CR, the median OS was 18.1 months (95% CI, 10.3-30.0 months) with a 3-year survival rate of 37.2%. **CONCLUSIONS:** These data suggest that long-term survival is possible after blinatumomab therapy. ***Cancer* 2021;127:554-559**.

LAY SUMMARY:

- Immuno-oncology therapies such as blinatumomab activate the patient's own immune system to kill cancer cells.
- This study combined follow-up data from 2 blinatumomab-related clinical trials to evaluate long-term survival in patients with relapsed and/or refractory B-cell precursor acute lymphoblastic leukemia at high risk for unfavorable outcomes.
- Among patients who achieved a deep response with blinatumomab, one-third lived 3 years or longer. These findings suggest that long-term survival is possible after treatment with blinatumomab.

KEYWORDS: acute lymphoblastic leukemia (ALL), bispecific T-cell engager (BiTE), blinatumomab, overall survival.

INTRODUCTION

Patients with relapsed/refractory (R/R) B-cell precursor acute lymphoblastic leukemia (ALL) have a poor prognosis, with allogeneic hematopoietic stem cell transplantation (HSCT) generally viewed as the only curative option.[1-3] However, immuno-oncology therapy with blinatumomab, BiTE (a bispecific T-cell engager) molecule, has led to long-term survival among responders even in the absence of HSCT.[4] In a phase 3 study of heavily pretreated adults with R/R ALL, the median overall survival (OS) was 7.7 months in the blinatumomab group and 4.0 months in the chemotherapy group ($P = .01$). The median duration of follow-up was 11.7 and 11.8 months, respectively. The study was stopped early because the threshold for an OS benefit was met at the interim analysis.[5]

We pooled long-term follow-up data from 2 single-arm, phase 2 studies (NCT01209286 and NCT01466179) to assess the durability of response to blinatumomab in patients with R/R ALL.[6,7] In the primary analyses of the 2 phase 2 studies, the median durations of follow-up for OS and relapse-free survival (RFS) were relatively short: 12.1

Corresponding Author: Gerhard Zugmaier, MD, PhD, Amgen GmbH, Munich, Germany (gerhardz@amgen.com).

[1]Universitätsklinikum Würzburg, Würzburg, Germany; [2]Goethe University, Frankfurt, Germany; [3]Amgen GmbH, Munich, Germany; [4]Gehr Family Center for Leukemia Research, City of Hope, Duarte, California; [5]Saint Louis Hospital, University of Paris, Paris, France; [6]Amgen, Inc, Thousand Oaks, California; [7]Catalan Institute of Oncology–Germans Trias I Pujol Hospital, Josep Carreras Leukemia Research Institute, Badalona, Spain; [8]Comprehensive Cancer Center Mainfranken, University Hospital Würzburg, Würzburg, Germany; [9]University Hospital of Schleswig-Holstein, Kiel, Germany; [10]The University of Texas MD Anderson Cancer Center, Houston, Texas

We thank Kathryn Boorer, PhD (KB Scientific Communications, LLC, supported by Amgen, Inc), and Julie Gegner, PhD (Amgen, Inc), for writing and editorial assistance in the preparation of this article and Robert Dawson (Cactus Communications, Inc, supported by Amgen, Inc) for assistance in editing and formatting the figures.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.33298, **Received:** July 1, 2020; **Revised:** September 11, 2020; **Accepted:** October 1, 2020, **Published online** November 3, 2020 in Wiley Online Library (wileyonlinelibrary.com)

and 9.7 months, respectively, in the exploratory phase 2 study (n = 36)[7] and 9.8 and 8.9 months, respectively, in the confirmatory phase 2 study (n = 189).[6] An additional analysis of the 36 adults in the exploratory study after a median follow-up of 32.6 months found that a plateau was reached for both RFS and OS.[8] Here, we report the long-term RFS and OS from the pooled phase 2 studies to further substantiate long-term survival outcomes after therapy with blinatumomab.

MATERIALS AND METHODS

The design and conduct of the 2 studies included in this analysis have been published.[6,7] In brief, both were open-label, single-arm, phase 2 studies in adult patients with R/R B-cell precursor ALL. The study protocols were approved by the independent ethics committee of each study site, and all patients provided written informed consent before any study-specific procedures were performed. Overall, 259 patients with Philadelphia chromosome–negative disease were included in this analysis; 2 patients with Philadelphia chromosome–positive disease from the confirmatory study were excluded.

In both studies, a treatment cycle consisted of a continuous intravenous infusion of blinatumomab for 4 weeks followed by a 2-week treatment-free interval.[6,7] Patients in the dose-finding part of the exploratory study received blinatumomab at 15 μg/m^2/d over the entire treatment period; at 5 μg/m^2/d in week 1 and then at 15 μg/m^2/d thereafter; or at 5 μg/m^2/d in week 1, at 15 μg/m^2/d in week 2, and at 30 μg/m^2/d thereafter.[7] Patients in the confirmatory study received blinatumomab at 9 μg/d in week 1 and at 28 μg/d thereafter.[6]

Kaplan-Meier estimates of median OS and median RFS and rates of OS and RFS were determined for the overall patient population; the Kaplan-Meier estimate of median OS was also determined for patients who underwent HSCT. Because a failure to consider competing risks can lead to biased results when the follow-up period is long, the cumulative incidence function of the time to relapse, with death not due to relapse considered a competing risk, was determined for patients who achieved a complete remission (CR) or complete remission with partial hematologic recovery (CRh) within 2 cycles.

Patient clinical outcomes are presented by survival status: <36-month OS or ≥36-month OS (alive at the month 36 follow-up). Most events occur within 24 months of treatment initiation.[1] The evaluated clinical outcomes were the best overall response in the first 2 cycles, the minimal residual disease (MRD) response after blinatumomab (<10^{-4} detectable blasts by quantitative polymerase chain reaction), the proportion of patients who underwent HSCT, and the proportions of relapse-free survivors with and without HSCT. Cox regression modeling was used to explore the relationship between baseline and postbaseline factors and OS and RFS; postbaseline factors were modeled as time-dependent covariates.

TABLE 1. Baseline Characteristics

Baseline Characteristic	Total Patients (n = 259)
Age, median (range), y	38 (18-79)
Sex, No. (%)	
Male	160 (61.8)
Female	99 (38.2)
Race, No. (%)	
White	205 (79.2)
Asian	8 (3.1)
Black (or African American)	7 (2.7)
American Indian or Alaska Native	1 (0.4)
Native Hawaiian or other Pacific Islander	1 (0.4)
Other	12 (4.6)
Unknown	25 (9.7)
Primary refractory, No. (%)	25 (9.7)
Prior relapses, No. (%)	
1	146 (56.2)
≥2	88 (34.0)
Prior HSCT, No. (%)	
Yes	88 (34.0)
No	171 (66.0)
Bone marrow blasts	
No.	255
Mean (SD), %	66.7 (31.1)
Bone marrow blasts, No. (%)	
≤5%	6 (2.3)
>5 to <10%	10 (3.9)
10 to <50%	61 (23.6)
≥50%	178 (68.7)
Unknown	4 (1.5)
Cytogenetic factors, No. (%)	
t(4;11)	16 (6.2)
ECOG performance status, No. (%)	
0	90 (34.7)
1	129 (49.8)
2	38 (14.7)
Unknown	2 (0.8)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HSCT, hematopoietic stem cell transplantation; SD, standard deviation.

RESULTS

In this pooled analysis of 259 patients, the baseline characteristics were similar to those of patients in individual trials (Table 1).[6,7] The baseline characteristics, the number of treatment cycles, and the outcomes by RFS and OS status with and without HSCT are provided in the supporting information (Supporting Tables 1 and 2). The median OS was 7.5 months (95% confidence interval [CI], 5.5-8.5 months) after a median follow-up duration of 36.0 months (range, 0.3-60.8 months; Fig. 1A). The median RFS for those who achieved a CR/CRh in the first 2 cycles (n = 123) was 7.7 months (95% CI, 6.2-10.0 months)

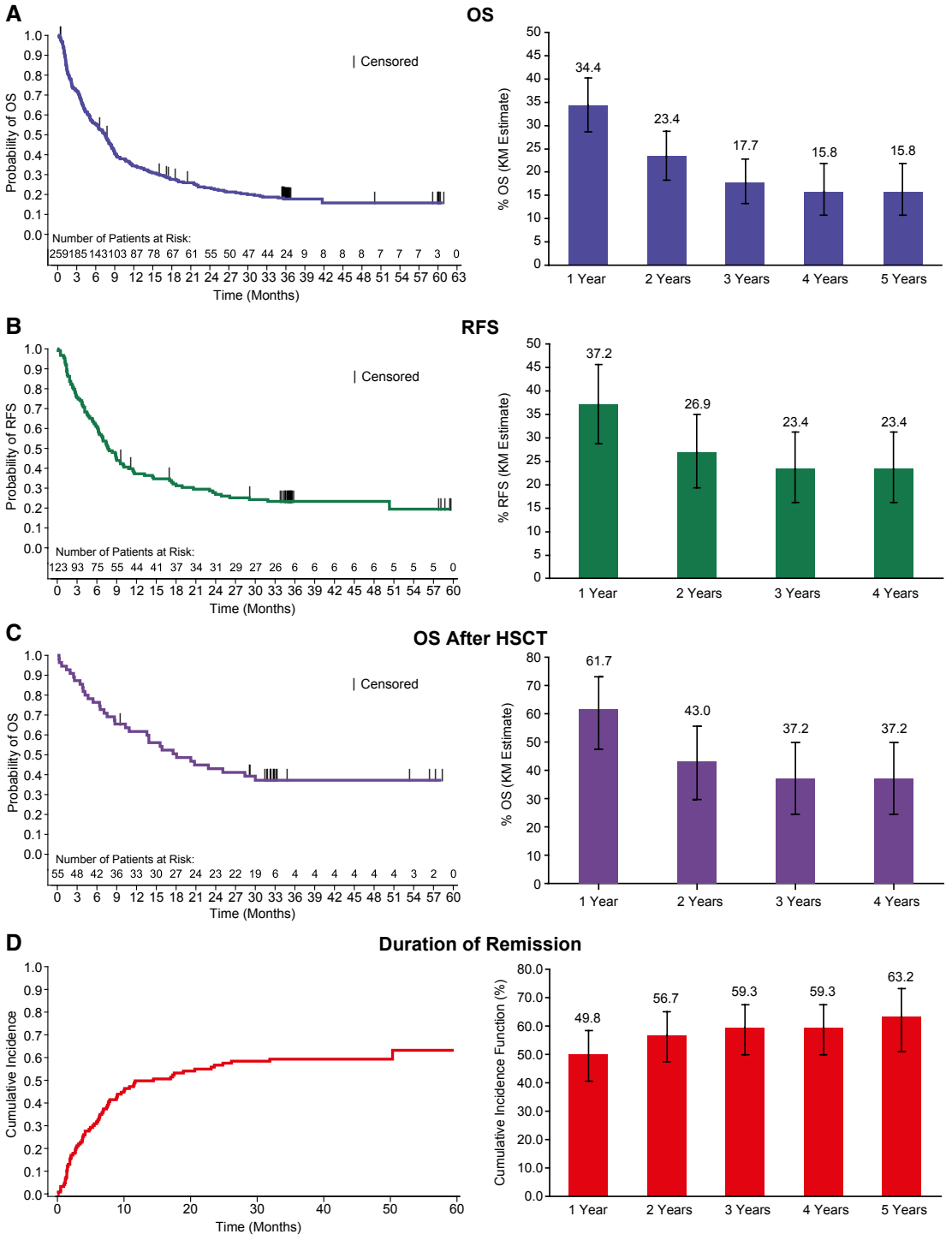

Figure 1. OS, RFS, and cumulative incidence function of the time to relapse: (A) OS KM curve and estimates at specific time points for the overall patient population, (B) RFS KM curve and estimates at specific time points for the overall patient population, (C) OS KM curve for patients who underwent HSCT after achieving a CR/CRh, and (D) cumulative incidence function of the time to relapse and estimates at specific time points for the overall patient population. OS was measured from the time of the first blinatumomab dose to death from any cause, and RFS was measured from the time of first CR or CRh within the first 2 cycles to hematologic or extramedullary relapse or death resulting from any cause. Patients who were alive were censored on the last documented visit date or the date of the last phone contact. The cumulative incidence function of the time to relapse with death from nonrelapse as a competing risk was determined for patients who achieved a CR/CRh within 2 cycles of treatment. Error bars represent 95% confidence intervals. CR indicates complete remission; CRh, complete remission with partial hematologic recovery; HSCT, allogeneic hematopoietic stem cell transplantation; KM, Kaplan-Meier; OS, overall survival; RFS, relapse-free survival.

TABLE 2. Clinical Outcomes After Blinatumomab Treatment

Clinical Outcome	Patients Who Survived ≥36 mo (n = 43)[a]	Patients Who Survived <36 mo (n = 216)	Total Patients (n = 259)
Best response within 2 cycles, No. (%)			
CR	27 (62.8)	60 (27.8)	87 (33.6)
CRh	9 (20.9)	27 (12.5)	36 (13.9)
Hypocellular bone marrow	1 (2.3)	2 (0.9)	3 (1.2)
MRD responders, No. (%)[b]	35 (81.4)	72 (33.3)	107 (41.3)
MRD response during cycle 1[c]	32 (91.4)	65 (90.3)	97 (90.7)
MRD response during cycle 2[c]	2 (5.7)	5 (6.9)	7 (6.5)
MRD response during cycle 3 and beyond[c]	1 (2.9)	2 (2.8)	3 (2.8)
HSCT after blinatumomab, No. (%)	24 (55.8)	56 (25.9)	80 (30.9)
In remission after achieving CR/CRh within 2 cycles	21 (48.8)	35 (16.2)	56 (21.6)
Achieved CR/CRh within 2 cycles but relapsed before HSCT	1 (2.3)	7 (3.2)	8 (3.1)
HSCT without CR/CRh within 2 cycles	2 (4.7)	14 (6.5)	16 (6.2)
Relapse-free survivor after blinatumomab, No. (%)	27 (62.8)	2 (0.9)[d]	29 (11.2)
Blinatumomab only	8 (18.6)	1 (0.5)	9 (3.5)
HSCT after blinatumomab in CCR	19 (44.2)	1 (0.5)	20 (7.7)

Abbreviations: CCR, continuous complete remission; CR, complete remission; CRh, complete remission with partial hematologic recovery; HSCT, allogeneic hematopoietic stem cell transplantation; MRD, minimal residual disease.
[a]Patients known to be alive after 35 months were considered long-term survivors in the analysis to account for a ±4-week window for the month 36 survival follow-up.
[b]At any time during treatment with blinatumomab.
[c]Percentages are based on the number of MRD responders.
[d]Two patients in the <36-month group in whom disease had not relapsed were lost to follow-up before their final visit and could not be considered long-term survivors.

after a median follow-up duration of 35.0 months (range, 9.5-59.5 months; Fig. 1B). OS and RFS rates plateaued after 3 years of follow-up with 2-, 3-, 4-, and 5-year rates of 23.4%, 17.7%, 15.8%, and 15.8%, respectively, for OS and with 2-, 3-, and 4-year rates of 26.9%, 23.4%, and 23.4%, respectively, for RFS (Fig. 1A,B). The median OS of patients who achieved a CR/CRh with blinatumomab followed by HSCT while in continuous CR was 18.1 months (95% CI, 10.3-30.0 months; Fig. 1C).

The cumulative incidence function of the time to relapse, with death not due to relapse considered a competing risk, for patients who achieved a CR/CRh within 2 cycles of treatment also plateaued with 2-, 3-, 4-, and 5-year relapse rates of 56.7%, 59.3%, 59.3%, and 63.2%, respectively (Fig. 1D).

Long-term survivors (those surviving for ≥36 months) were more likely to have achieved a CR/CRh, to have an MRD response, and to have undergone HSCT than those surviving for <36 months (Table 2). In univariate analyses, the Eastern Cooperative Oncology Group performance status at the baseline, achieving a CR/CRh during the study, and achieving an MRD response during the study were associated with OS. In the multivariate analysis, achieving a CR/CRh during the study and achieving an MRD response during the study were associated with OS (Table 3). Twenty-seven of the 43 long-term survivors (62.8%) were relapse free at 36 months. Nineteen of the 27 relapse-free survivors (70.4%) underwent HSCT after blinatumomab while in continuous CR, and 8 (29.6%) survived relapse free after blinatumomab without HSCT. In univariate analyses, race, t(4;11) status at the baseline, and achieving an MRD response during the study were associated with RFS. In the multivariate analysis, race and t(4;11) status at the baseline were associated with RFS (Table 3).

DISCUSSION

Immuno-oncology therapy is a major advancement in the treatment of patients with previously incurable disease. This is especially true for patients with R/R ALL enrolled in blinatumomab phase 2 trials because they are at high risk for an unfavorable outcome, a short time to first relapse, prior HSCT, and later lines of salvage therapy.[6,7] In this pooled analysis, OS and RFS plateaued after 3 years of follow-up with encouraging long-term survival rates in light of the historically poor rates with conventional chemotherapy.[1,9] The cumulative incidence function of the time to relapse, with death not due to relapse considered a competing risk, also plateaued. Because mortality unrelated to relapse may be substantial during a long follow-up period, this analysis suggests that more than one-third of patients who achieve a CR/CRh with blinatumomab therapy meet the criteria for a cure.[10] When the relationships between various factors and survival were explored, achieving a CR/CRh and achieving an MRD response were strong predictors of OS. The survival

TABLE 3. Relationship Between Factors and OS and RFS

Factor (Numerator/Denominator of HR)	HR (95% CI)	
	Univariate Analysis[a]	Multivariate Analysis[a]
OS		
Baseline		
Age (additional year/year)	1.00 (1.00-1.01)	
Sex (male/female)	1.00 (0.76-1.33)	
Race (White/other)	0.69 (0.45-1.06)	
Prior HSCT (yes/no)	0.92 (0.69-1.23)	
Primary refractory (yes/no)	0.74 (0.45-1.24)	
Salvage line (1st/2nd+)	0.78 (0.57-1.06)	
Central bone marrow (additional %/%)	1.01 (1.00-1.01)	
t(4;11) (yes/no)	1.53 (0.91-2.58)	
ECOG (0/1+)	0.59 (0.44-0.79)	
Postbaseline outcome		
CR/CRh (yes/no)	0.29 (0.21-0.40)	0.43 (0.25-0.74)
MRD responder (yes/no)	0.47 (0.31-0.72)	0.54 (0.33-0.87)
HSCT (yes/no)	0.64 (0.38-1.06)	
RFS		
Baseline		
Age (additional year/year)	1.00 (0.99-1.01)	
Sex (male/female)	1.23 (0.81-1.87)	
Race (White/other)	0.39 (0.22-0.71)	0.39 (0.20-0.77)
Prior HSCT (yes/no)	1.20 (0.78-1.84)	
Primary refractory (yes/no)	0.74 (0.34-1.61)	
Salvage line (1st/2nd+)	0.68 (0.42-1.10)	
Central bone marrow (additional %/%)	1.00 (0.99-1.01)	
t(4;11) (yes/no)	2.56 (1.14-5.74)	3.14 (1.36-7.28)
ECOG (0/1+)	0.68 (0.45-1.04)	
Postbaseline outcome		
MRD responder (yes/no)	0.55 (0.31-0.99)	
HSCT (yes/no)	0.63 (0.38-1.06)	

Abbreviations: CI, confidence interval; CR, complete remission; CRh, complete remission with partial recovery of peripheral blood counts; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; HSCT, allogeneic hematopoietic stem cell transplantation; MRD, minimal residual disease; OS, overall survival; RFS, relapse-free survival.

[a]A stepwise variable selection was performed that included all factors with a predictive *P* value <.05 from the univariate models. A significance level of .05 was used for entry and removal criteria for candidate factors in the stepwise multivariate model.

advantage of achieving MRD negativity in both adults and children has been demonstrated in other studies, including a meta-analysis of 39 studies.[11]

Long-term results have also begun to emerge with other targeted therapies.[12,13] The reported OS rates for the anti-CD22 antibody-drug conjugate inotuzumab ozogamicin and CD19-directed chimeric antigen receptor T-cell therapy are difficult to compare with the current analysis because of the different patient populations in the blinatumomab, inotuzumab ozogamicin, and chimeric antigen receptor T-cell therapy studies. However, all these treatment regimens represent meaningful clinical advancements over standard chemotherapy.

Survival after blinatumomab compares favorably with published data evaluating chemotherapy after relapse.[9,14] Among relapsed patients with ALL treated with salvage chemotherapy, no patients without HSCT survived for more than 1 year after relapse.[1] Of the 43 long-term survivors reported here, 19 (44.2%) survived without HSCT, and 8 (18.6%) remained relapse free without HSCT for 3 or more years.

Although our results are strengthened by the large sample size and the long duration of follow-up, they are limited by the retrospective nature of the analysis and the inclusion of data pooled from 2 trials.

In summary, these long-term follow-up data suggest that a cure after blinatumomab therapy is most common in patients undergoing HSCT in CR, although a cure is possible in some patients after blinatumomab only, especially when MRD is eliminated.

FUNDING SUPPORT

This study was sponsored by Amgen, Inc. The trial sponsor was responsible for the study design, data collection, statistical analysis, and writing of the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit the manuscript for publication. The University of Texas MD Anderson Cancer Center is supported by the National Institutes of Health (grant P30 CA016672).

CONFLICT OF INTEREST DISCLOSURES

Max S. Topp reports a research grant and personal fees from Amgen. Nicola Gökbuget reports research funding, personal fees, and travel support from and participation in advisory boards for Amgen, Novartis, Pfizer, and Celgene. Gerhard Zugmaier is an employee and stockholder of Amgen and

reports patent royalties from Amgen. Anthony S. Stein reports participation in speakers' bureaus for Amgen and Celgene and personal fees from Amgen. Hervé Dombret is an advisor for, serves on a speakers' bureau for, and reports research support, consultancy, honoraria, and travel/accommodation support from Amgen; is an advisor for and reports research support and honoraria from Roche/Genentech; is an advisor for, serves on a speakers' bureau for, and reports honoraria and travel/accommodation support from Pfizer; is an advisor for, serves on a speakers' bureau for, and reports research support, honoraria, and travel/accommodation support from Ariad (Incyte); is an advisor for and reports research support and honoraria from Jazz Pharma and Kite Pharma; is an advisor for and reports honoraria from Novartis, Agios, Sunesis, Ambit (Daiichi Sankyo), Karyopharm, Menarini, Astellas, Janssen, Servier, Seattle Genetics, and Cellectis; and is a consultant and advisor for, serves on a speakers' bureau for, and reports honoraria from Celgene. Yuqi Chen is an employee and stockholder of Amgen. Josep-Maria Ribera reports research grants from Amgen, Novartis, and Pfizer and personal fees from Amgen, Celgene, Jazz Pharmaceuticals, Novartis, Pfizer, Shire, and Takeda. Ralf C. Bargou reports consultancy honoraria from AstraZeneca, Genmab, Pfizer, Amgen, Cellex, GEMoaB Monoclonals, Molecular Partners, and Novartis and royalty payments for a blinatumomab patent. Heinz-August Horst reports research funding and travel support from and participation in advisory boards for Amgen; participation in advisory boards for Pfizer, Jazz Pharmaceuticals, and Novartis; and research funding from Regeneron. Hagop M. Kantarjian reports research funding from AbbVie, Agios Pharmaceuticals, Amgen, Ariad Pharmaceuticals, Astex Pharmaceuticals, Bristol-Myers Squibb, Cyclacel Pharmaceuticals, Daiichi-Sankyo, ImmunoGen, Jazz Pharmaceuticals, Novartis, and Pfizer and honoraria from AbbVie, Actinium Pharmaceuticals, Agios Pharmaceuticals, Amgen, ImmunoGen, Orsenix, Pfizer, and Takeda.

AUTHOR CONTRIBUTIONS

Max S. Topp: Study design, data collection, data analysis, data interpretation, and writing or review of the article. **Nicola Gökbuget:** Study design, data collection, data analysis, data interpretation, and writing or review of the article. **Gerhard Zugmaier:** Study design, data analysis, data interpretation, and writing or review of the article. **Anthony S. Stein:** Data analysis, data interpretation, and writing or review of the article. **Hervé Dombret:** Data collection, data analysis, data interpretation, and writing or review of the article. **Yuqi Chen:** Data analysis, data interpretation, and writing or review of the article. **Josep-Maria Ribera:** Study design, data collection, data analysis, data interpretation, and writing or review of the article. **Ralf C. Bargou:** Study design, data collection, data analysis, data interpretation, and writing or review of the article. **Heinz-August Horst:** Data collection, data analysis, data interpretation, and writing or review of the article. **Hagop M. Kantarjian:** Study design, data collection, data analysis, data interpretation, and writing or review of the article.

DATA AVAILABILITY

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

REFERENCES

1. Gökbuget N, Stanze D, Beck J, et al. Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. *Blood*. 2012;120:2032-2041.
2. O'Brien S, Thomas D, Ravandi F, et al. Outcome of adults with acute lymphocytic leukemia after second salvage therapy. *Cancer*. 2008;113:3186-3191.
3. Tavernier E, Boiron JM, Huguet F, et al. Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial. *Leukemia*. 2007;21:1907-1914.
4. Jabbour EJ, Gokbuget N, Kantarjian HM, et al. Transplantation in adults with relapsed/refractory acute lymphoblastic leukemia who are treated with blinatumomab from a phase 3 study. *Cancer*. 2019;125:4181-4192.
5. Kantarjian H, Stein A, Gokbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med*. 2017;376:836-847.
6. Topp MS, Gokbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2015;16:57-66.
7. Topp MS, Gokbuget N, Zugmaier G, et al. Phase II trial of the anti-CD19 bispecific T cell–engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. *J Clin Oncol*. 2014;32:4134-4140.
8. Zugmaier G, Gokbuget N, Klinger M, et al. Long-term survival and T-cell kinetics in relapsed/refractory ALL patients who achieved MRD response after blinatumomab treatment. *Blood*. 2015;126:2578-2584.
9. Gokbuget 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.
10. Gidman W, Shah S, Zhang L, et al. Clinicians' perspectives on cure in adult patients with acute lymphoblastic leukemia with minimal residual disease: a Delphi study. *Adv Ther*. 2019;36:3017-3029.
11. 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.
12. 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.
13. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. *Cancer*. 2019;125:2474-2487.
14. Oriol A, Vives S, Hernandez-Rivas JM, et al. Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA study group. *Haematologica*. 2010;95:589-596.