Supplementary Appendix

Blinatumomab for minimal residual disease in adults with B-precursor acute lymphoblastic leukemia

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Table of Contents

SUPPLEMENTARY METHODS

A. Eligibility Criteria

Inclusion Criteria

A patient was eligible for study participation only if all of the following criteria were met:

1. Patients with B-precursor acute lymphoblastic leukemia (ALL) in complete hematologic remission (CR) defined as less than 5% blasts in bone marrow after at least 3 intense chemotherapy blocks. Intense chemotherapy treatment was defined as age-appropriate treatment given with the intention to achieve a CR and the best long-term outcome in the judgment of the treating physician (eg, GMALL induction I-II/consolidation I, induction/intensification/consolidation or 3 blocks of Hyper-CVAD [cyclophosphamide, vincristine, doxorubicin, and dexamethasone]).
2. Presence of minimal residual disease (MRD) at a level of $\geq 10^{-3}$ (molecular failure or molecular relapse) in an assay with a minimum sensitivity of 10^{-4} documented after an interval of at least 2 weeks from last systemic chemotherapy.
3. For evaluation of MRD, patients must have had at least 1 molecular marker based on individual rearrangements of immunoglobulin (Ig) or T-cell receptor (TCR) genes or a flow cytometric marker profile evaluated by a national or local reference lab approved by the sponsor.
4. Bone marrow or peripheral blood specimen from primary ALL diagnosis/diagnosis of ALL relapse; a sufficient amount of DNA (or a respective amount of cell material) for clone-specific MRD assessment must be received by central MRD lab and lab must confirm that the sample is available.
5. Hematologic criteria for remission as defined below:
    - <5% blasts
    - Absolute neutrophil count ≥1,000/μL
    - Platelets ≥50,000/μL (transfusion permitted)

- Hemoglobin level ≥9 g/dL (transfusion permitted)

6. Renal and hepatic function as defined below:
   - Aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase <2 × upper limit of normal (ULN)
   - Total bilirubin <1.5 × ULN
   - Creatinine clearance ≥50 mL/min (calculated according to Cockroft & Gault)
7. Negative human immunodeficiency virus (HIV), hepatitis B virus surface antigen (HbsAg), and hepatitis C virus (anti-HCV) tests.
8. Negative pregnancy test in women of childbearing potential.
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
10. Age ≥18 years.
11. Ability to understand and willingness to sign a written informed consent.
12. Signed and dated written informed consent.

Exclusion Criteria

A patient was not eligible to participate in this study if any of the following criteria applied:

1. Presence of circulating blasts or current extramedullary involvement by ALL.
2. History of relevant central nervous system (CNS) pathology or current relevant CNS pathology (eg, seizure, paresis, aphasia, cerebrovascular ischemia/hemorrhage, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis, or coordination or movement disorders).
3. Current infiltration of cerebrospinal fluid by ALL.
4. History of or active relevant autoimmune disease.
5. Prior allogeneic hematopoietic stem cell transplantation (HSCT).
6. Eligibility for treatment with tyrosine kinase inhibitors (ie, Philadelphia chromosome [Ph]–positive patients with no documented treatment failure of or intolerance/contraindication to at least 2 tyrosine kinase inhibitors).

7. Systemic cancer chemotherapy within 2 weeks prior to study treatment (except for intrathecal prophylaxis).
8. Radiotherapy within 4 weeks prior to study treatment.
9. Autologous HSCT within 6 weeks prior to study treatment.
10. Therapy with monoclonal antibodies (eg, rituximab, alemtuzumab) within 4 weeks prior to study treatment.
11. Treatment with any investigational product within 4 weeks prior to study treatment.
12. Previous treatment with blinatumomab.
13. Known hypersensitivity to Ig's or to any other component of the study drug formulation.
14. Active malignancy other than ALL with the exception of basal cell or squamous cell carcinoma of the skin, or carcinoma in situ of the cervix. (In Germany only: History of malignancy other than ALL within 5 years prior to treatment start with blinatumomab, with the exception of basal cell or squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix).
15. Active infection or any other concurrent disease or medical condition that was deemed to interfere with the conduct of the study as judged by the investigator.
16. Nursing women or women of childbearing potential not willing to use an effective form of contraception during participation in the study and at least 3 months thereafter or male patients not willing to ensure effective contraception during participation in the study and at least 3 months thereafter.

B. Study Design and Treatment

CNS and Cytokine Release Syndrome (CRS) Prophylaxis

CNS ALL prophylaxis (intrathecal dexamethasone 4 mg or equivalent, methotrexate 15 mg, and cytosine arabinoside 40 mg) was recommended before cycle 1 and after cycles 2 and 4. All patients received prednisone 100 mg or equivalent ≤1 hour before each cycle as prophylaxis for

neurologic events and CRS. If neurologic or CRS events occurred, blinatumomab infusion was interrupted and patients could receive dexamethasone (24 mg/d for up to 3 days, then tapered over 4 days).

C. Criteria for Discontinuation and Interruption of Blinatumomab

Criteria for Treatment Discontinuation

Treatment with blinatumomab was discontinued in the event of any of the following:

- Hematologic relapse
- Investigator's decision that a change of therapy was in the patient's best interest
- Patient or investigator not compliant with the study protocol
- Progression of a medical condition that, in the opinion of the investigator, should lead to treatment discontinuation
- Administration of relevant nonpermitted concomitant medication(s)
- Occurrence of an adverse event (AE) that made discontinuation from treatment desirable or necessary in the investigator's and/or the patient's opinion
- Central laboratory determination that the patient's screening bone marrow demonstrated that the patient was ineligible for study treatment owing to MRD negativity at the time of enrollment

Protocol amendments dated February 17, 2012, and July 11, 2012 added the following criteria for treatment discontinuation:

- Extramedullary relapse
- Infusion interruption of more than 2 weeks due to an AE
- Occurrence of a neurologic event meeting 1 or more of the following criteria:
  - More than 1 seizure

- Neurologic event of grade 4 severity, per the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (May 28, 2009)
- Neurologic event leading to treatment interruption that needed more than 1 week to resolve to CTCAE grade ≤1

Treatment Interruption/Dose Modification Due to AEs

The severity of AEs was assessed according to the CTCAE version 4.0 (May 28, 2009). The investigator was responsible for determining causality (relation to investigational drug).

In the case of clinically relevant persistent nonhematologic AEs of CTCAE grade 3 or 4 that could not be promptly controlled by appropriate medical management the administration of blinatumomab was stopped.

Blinatumomab could be restarted after recovery from the AE to CTCAE grade ≤2; the treatment cycle was continued at the same dose. An infusion stop of more than 2 weeks led to permanent discontinuation. Reappearance of the same grade 3 or 4 clinically relevant nonhematologic events in the same patient resulted in permanent discontinuation of treatment.

The following special treatment modifications applied if neurologic events occurred:

- In the case of neurologic events, dexamethasone was administered at a dose of at least 24 mg/d for up to 3 days. The dexamethasone dose was then stepwise reduced over up to 4 days.
- Diagnostic measures were conducted to exclude potential infectious causes after neurologic events of CTCAE grade ≥3. In case of CTCAE grade 3 neurologic events, the infusion of the investigational drug was stopped immediately and the following investigations were performed: physical examination, vital signs, safety laboratory

evaluation, cranial magnetic resonance imaging, and assessment of cerebrospinal fluid (if appropriate). If the event decreased to CTCAE grade ≤1 within 1 week, treatment could be restarted within 2 weeks, but not earlier than 72 hours (3 days) after the infusion was stopped.

- In the case of a CTCAE grade 4 neurologic event, the infusion of the blinatumomab was stopped immediately and treatment was permanently discontinued and not restarted.

Protocol amendments dated February 17, 2012, and July 11, 2012, added the following criteria for treatment interruption in case of neurologic events:

- If the neurologic event was a seizure, appropriate prophylactic anticonvulsant treatment with a therapeutic dose of, for example, phenytoin or levetiracetam was administered during restart and during start of the following new treatment cycle.
- For patients with neurologic events of CTCAE grade 3 that resolved to grade 1 (see above), the infusion was restarted at the lower dose level of 5 μg/m^2/d. Infusion was restarted in the hospital, under supervision of the investigator, and the patient remained hospitalized for at least 2 days. After dose reduction to 5 μg/m^2/d, reescalation to 15 μg/m^2/d was not permitted.
- In the case of an interruption due to clinically relevant CTCAE grade 2 neurologic events, blinatumomab could be restarted after recovery from the AE to CTCAE grade ≤1; the treatment cycle could be continued at the same dose or at the reduced dose level of 5 μg/m^2/d, at the investigator's discretion. Infusion was restarted in the hospital, under supervision of the investigator. However, after dose reduction to 5 μg/m^2/d, re-escalation to 15 μg/m^2/d was not permitted. Hence, this restriction was taken into consideration when deciding on dose reduction due to clinically relevant neurologic events of CTCAE grade 2 severity.

- In the case of an occurrence of more than 1 seizure, blinatumomab infusion was stopped immediately and treatment was permanently discontinued and not restarted.

In the case of any clinical/laboratory AEs considered medically relevant, treatment could be interrupted or permanently discontinued at the discretion of the investigator.

Retreatment Following MRD Relapse

Patients who completed the initial 4-cycle treatment, had a complete MRD response of ≥4 weeks' duration, did not receive HSCT/chemotherapy, and had MRD relapse within 18 months of treatment start could receive blinatumomab retreatment if they still met eligibility criteria. Blinatumomab retreatment was not offered to patients who experienced hematologic relapse.

D. Key Protocol Amendments

Protocol Amendment 3 (February 17, 2012)

Clarified and modified procedures to be followed in the event of grade ≥3 neurologic events (see above).

Protocol Amendment 4 (July 11, 2012)

Clarified criteria for treatment discontinuation (see above).

Protocol Amendment 5 (March 6, 2014)

Modified the key secondary endpoint of relapse-free survival (RFS) by censoring at the time of allogeneic HSCT, rather than analyzing only the subset of patients who did not receive HSCT within 18 months of initiating treatment with blinatumomab.

E. MRD Assessments

MRD was centrally assessed by real-time quantitative polymerase chain reaction (RQ-PCR) of individual Ig and/or TCR gene rearrangements, or by flow cytometry. The central reference laboratory (University of Kiel, Germany) used allele-specific oligonucleotide RQ-PCR of clonally rearranged TCR and/or Ig genes to assess MRD response and MRD relapse.

F. Study Oversight

The study was designed by N.G., R.B., M.S.T., and G.Z. (the investigators) in collaboration with Amgen, Inc. (the sponsor) and was conducted in accordance with the provisions of the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. An independent Data Monitoring Committee regularly reviewed safety data and the progress of the study. The institutional review board/ethics committee at each participating center approved the protocol. All authors vouch for the accuracy and completeness of the reported data and for the fidelity of the study to the protocol and approved the decision to submit the manuscript for publication. Writing and editing assistance was provided by the sponsor, PharmaScribe, LLC and Complete Healthcare Communications, LLC (both contracted by the sponsor). The study was registered with ClinicalTrials.gov (identifier, NCT01207388) and with EudraCT (number, 2010-018314-75).

SUPPLEMENTARY RESULTS

A. Treatment Realization

The median (range) number of completed cycles among patients who completed at least 1 cycle of blinatumomab was 2 (1-4). Treatment cycles, withdrawals, and interruptions are illustrated in **Figure 1**. Overall 8 patients had any antileukemic treatment in ongoing remission after blinatumomab.

B. Outcomes by Remission Status

MRD Response

In patients with complete MRD response OS, RFS, and duration of hematologic remission were significantly longer in patients treated in first vs later CR (**Supplementary Table S3, Supplementary Figure S2, Figure 3E**). Median RFS was 11.0 vs 24.6 months among patients who achieved complete MRD response within later CR vs first CR (CR1) (unadjusted hazard ratio = 2.09; 95% CI, 1.26- 3.48; *P* = .004) (**Figure 3D**), and OS was significantly longer for patients treated in CR1 (**Supplementary Figure S2**). The impact of other baseline covariates on OS, RFS, and duration of hematologic remission is summarized in **Supplementary Table S3**.

HSCT Realization

Fifty-five patients in the key secondary endpoint analysis set received HSCT in CR1 and 19 in second or greater CR. The median age of transplanted patients was 42.1 years (range, 18-67). Seventeen (15%) patients relapsed or died of disease progression following HSCT, 20 (18%) died in CR and 36 (33%) remained in CR. Among 55 patients transplanted in CR1, 10 (18%) relapsed, 15 (27%) died without relapse in CR, 29 (53%) remained in CR, and 1 (2%) died due to disease progression. Overall, 55 patients had myeloablative conditioning, 14 patients had reduced intensity conditioning, and the conditioning regimen was not recorded for 5 patients. Seventeen patients received HSCT from a matched related donor (23%), 20 from a matched unrelated donor (27%); 25 were classified as mismatched (34%) and 12 as unknown (16%).

OS in Patients With and Without Post-blinatumomab HSCT

For patients in the key secondary endpoint analysis set treated in CR1 an ad hoc Mantel-Byar analysis of OS revealed no significant difference between transplanted (n = 74) and nontransplanted patients (n = 36) (odds ratio [OR] = 1.83; 95% CI, 0.69-4.9; *P* = .24). For patients treated in second or later CR the outcome of nontransplanted patients was inferior (OR = 0.31; 95% CI, 0.12-0.83; *P* = .02). The Simon-Makuch plot for all patients is given in **Supplementary Figure S5**. Among all patients who received HSCT, 14.5% died after relapse compared with 45.0% who died after relapse without receiving HSCT. Similarly, the overall death rate in patients with HSCT was lower (42.1%) than without HSCT (52.5%). Due to the decreasing number of patients evaluated over the follow-up period, these data should be interpreted with caution.

C. Treatment Interruptions Due to Neurologic AEs

Patients with grade 4 neurologic events were required to permanently discontinue blinatumomab treatment. Twelve (10%) patients interrupted treatment per protocol because of grade ≥3 neurologic events, including 2 patients who discontinued therapy prior to a protocol amendment dated July 11, 2012, that permitted restarting treatment at a reduced dose after a grade 3 neurologic event. Subsequent to the amendment, 7 patients resumed treatment at a lower dose: 5 had no further treatment interruptions, but 2 stopped treatment for another neurologic event. Tremor (n = 5), aphasia, seizure, and encephalopathy (n = 3 each) were the most common neurologic events leading to discontinuation.

SUPPLEMENTARY TABLES

Table S1. Summary of enrollment by country

Country	Number of patients enrolled
Austria	4
Belgium	10
Czech Republic	1
France	12
Germany	56
Italy	15
Netherlands	1
Romania	3
Russia	2
Spain	5
United Kingdom	7

Table S2. Analysis sets for response evaluation

Data set	Patient number	Definition	Analysis
Full analysis set (FAS)	116	All patients who received at least 1 dose of blinatumomab	Patient characteristics Safety Overall outcome
Primary endpoint FAS (EP-FAS)	113	Patients from FAS with MRD test and sensitivity of MRD test of at least 10^{-4}	Complete MRD response after cycle 1 (primary endpoint)*
Primary endpoint efficacy set (EP-ES)	103	All patients from EP-FAS with hematologic CR and MRD > 10^{-3}	MRD response
Key secondary endpoint FAS	110	All patients from FAS with Ph-negative ALL and hematologic CR	Relapse-free survival (key secondary endpoint) All other outcome analyses

ALL, acute lymphoblastic leukemia; CR, complete remission; MRD, minimal residual disease; Ph, Philadelphia chromosome.

*Data on complete MRD response after cycle 1 were available for 112 patients; 1 patient died in cycle 1 due to pneumonia without postbaseline MRD evaluation.

Table S3. Efficacy endpoints: analysis by covariates

	Overall survival (for all patients treated)				Hematologic relapse-free survival‖				Duration of hematologic remission¶			
	n/N	Median* (95% CI)	Estimated probability at 18 months* (95% CI)*	*P*†	n/N	Median* (95% CI)	Estimated probability at 18 months* (95% CI)*	*P*†	n/N	Median‡ (95% CI)	Estimated probability at 18 months† (95% CI)*	*P*§
Sex												
Men	28/68	NR (19.8-NR)	0.68 (0.55-0.77)	.27	34/64	22.3 (12.1-NR)	0.56 (0.43-0.67)	.45	24/64	NR (24.3-NR)	0.69 (0.57-0.80)	.61
Women	25/48	20.6 (15.8-NR)	0.60 (0.45-0.73)		28/46	18.1 (7.1-35.2)	0.50 (0.35-0.63)		15/46	NR (NR-NR)	0.72 (0.58-0.84)	
Age, years												
18-54	36/77	36.5 (18.7-NR)	0.64 (0.52-0.73)	.79	39/73	24.2 (12.0-NR)	0.56 (0.44-0.67)	.40	25/73	NR (NR-NR)	0.73 (0.62-0.82)	.72
≥55	17/39	NR (17.1-NR)	0.67 (0.50-0.79)		23/37	17.9 (7.4-35.2)	0.48 (0.32-0.63)		14/37	NR (17.9-NR)	0.65 (0.49-0.80)	
MRD level at baseline#												
$<10^{-2}$	24/60	NR (18.7-NR)	0.68 (0.55-0.78)	.33	28/57	35.2 (14.8-NR)	0.58 (0.44-0.69)		16/57	NR (NR-NR)	0.74 (0.62-0.84)	.43
$\geq 10^{-2}$ to $<10^{-1}$	24/45	23.1 (13.1-40.4)	0.60 (0.44-0.73)		26/42	18.9 (7.8-25.1)	0.52 (0.36-0.66)	.45	16/42	NR (24.3-NR)	0.71 (0.57-0.84)	
$\geq 10^{-1}$ to <1	4/9	NR (10.5-NR)	0.67 (0.28-0.88)		6/9	15.0 (7.1-NR)	0.44 (0.14-0.72)		5/9	22.3 (7.4-NR)	0.56 (0.26-0.89)	
Relapse history												
First CR	30/75	36.5 (20.6-NR)	0.69 (0.58-0.78)	.084	36/75	24.6 (18.7-NR)	0.62 (0.50-0.72)	.004	20/75	NR (NR-NR)	0.79 (0.69-0.87)	.004
Second/third CR	23/41	19.1 (11.9-NR)	0.56 (0.40-0.70)		26/35	11.0 (6.8-15.4)	0.34 (0.19-0.50)		19/35	19.1 (7.4-NR)	0.51 (0.36-0.69)	

CI, confidence interval; CR, hematologic complete remission; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease; NR, not reached; Ph, Philadelphia chromosome.
*Kaplan-Meier estimate.
†Log-rank test *P* value.
‡1 − cumulative incidence function estimate of hematologic relapse with death due to other causes as competing risk.
§Gray's test *P* value.
‖Relapse-free survival in patients with Ph-negative disease in CR at baseline, without censoring at HSCT or post-blinatumomab chemotherapy.

¶Duration of hematologic remission in patients with Ph-negative disease in CR at baseline, without censoring at HSCT or post-blinatumomab chemotherapy is evaluated by 1 − cumulative incidence function of hematological relapse with death due to other causes as a competing event.
#Two patients did not have evaluable baseline MRD measurements.

Table S4. Adverse events of all grades occurring in >3% of patients*

	Patients (N = 116)		
	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with AEs	116 (100)	36 (31.0)	31 (26.7)
Any grade AE occurring in >3% of patients			
Pyrexia	103 (88.8)	9 (7.8)	0 (0)
Headache	44 (37.9)	4 (3.4)	0 (0)
Tremor	35 (30.2)	6 (5.2)	0 (0)
Chills	30 (25.9)	0 (0)	0 (0)
Fatigue	28 (24.1)	0 (0)	0 (0)
Nausea	27 (23.3)	0 (0)	0 (0)
Vomiting	26 (22.4)	0 (0)	0 (0)
Diarrhea	23 (19.8)	1 (0.9)	0 (0)
Hypokalemia	18 (15.5)	2 (1.7)	0 (0)
Neutropenia	18 (15.5)	4 (3.4)	16 (13.8)
Insomnia	17 (14.7)	1 (0.9)	0 (0)
Aphasia	15 (12.9)	1 (0.9)	0 (0)
Arthralgia	15 (12.9)	0 (0)	0 (0)
Cough	15 (12.9)	0 (0)	0 (0)
Hypotension	14 (12.1)	0 (0)	1 (0.9)
Constipation	13 (11.2)	0 (0)	0 (0)
Rash	11 (9.5)	0 (0)	0 (0)
Back pain	10 (8.6)	1 (0.9)	0 (0)
C-reactive protein increased	10 (8.6)	3 (2.6)	0 (0)
Dizziness	9 (7.8)	1 (0.9)	0 (0)
Device-related infection	8 (6.9)	3 (2.6)	0 (0)
Leukopenia	8 (6.9)	5 (4.3)	2 (1.7)
Nasopharyngitis	8 (6.9)	0 (0)	0 (0)
Pain in extremity	8 (6.9)	0 (0)	0 (0)
Alanine aminotransferase increased	7 (6.0)	2 (1.7)	4 (3.4)
Anemia	7 (6.0)	3 (2.6)	1 (0.9)
Ataxia	7 (6.0)	0 (0)	0 (0)
Hypertension	7 (6.0)	0 (0)	0 (0)
Night sweats	7 (6.0)	0 (0)	0 (0)
Paresthesia	7 (6.0)	0 (0)	0 (0)
Weight increased	7 (6.0)	1 (0.9)	0 (0)
Blood immunoglobulin G decreased	6 (5.2)	1 (0.9)	0 (0)
Confusional state	6 (5.2)	1 (0.9)	0 (0)
Encephalopathy	6 (5.2)	3 (2.6)	2 (1.7)

	Patients (N = 116)		
	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Hypomagnesemia	6 (5.2)	0 (0)	0 (0)
Thrombocytopenia	6 (5.2)	2 (1.7)	3 (2.6)
Upper respiratory tract infection	6 (5.2)	0 (0)	0 (0)
Aspartate aminotransferase increased	5 (4.3)	1 (0.9)	3 (2.6)
Decreased appetite	5 (4.3)	1 (0.9)	0 (0)
Dysgraphia	5 (4.3)	0 (0)	0 (0)
Myalgia	5 (4.3)	0 (0)	0 (0)
Oropharyngeal pain	5 (4.3)	0 (0)	0 (0)
Overdose	5 (4.3)	0 (0)	0 (0)
Stomatitis	5 (4.3)	2 (1.7)	0 (0)
Tachycardia	5 (4.3)	0 (0)	0 (0)
Vertigo	5 (4.3)	0 (0)	0 (0)
Abdominal pain	4 (3.4)	0 (0)	0 (0)
Anxiety	4 (3.4)	1 (0.9)	0 (0)
Asthenia	4 (3.4)	1 (0.9)	0 (0)
Blood lactate dehydrogenase increased	4 (3.4)	3 (2.6)	0 (0)
Catheter site erythema	4 (3.4)	0 (0)	0 (0)
Cytokine release syndrome†	4 (3.4)	2 (1.7)	0 (0)
Dyspepsia	4 (3.4)	0 (0)	0 (0)
Intention tremor	4 (3.4)	0 (0)	0 (0)
Neck pain	4 (3.4)	0 (0)	0 (0)
Pruritus	4 (3.4)	0 (0)	0 (0)
Rhinitis	4 (3.4)	0 (0)	0 (0)
Staphylococcal infection	4 (3.4)	3 (2.6)	0 (0)

AE, adverse event; CRS, cytokine release syndrome; MedDRA, Medical Dictionary for Regulatory Activities.
*Treatment-emergent AEs were coded using MedDRA version 17.0.
†Two grade 1 CRS (patients with baseline MRD levels 2×10^{-2} and 8×10^{-2}) and 2 grade 3 CRS (patients with baseline MRD levels 1×10^{-1} and 3×10^{-3}).

Table S5. Overall survival, relapse-free survival, and duration of response by baseline remission status*

	Patients in first CR (N = 75)	Patients in second or greater CR (N = 35)
Overall survival		
n events (death)	30	18
Median, months	36.5	23.1
Hazard ratio (95% CI)†	1.37 (0.76-2.46)	
P‡	<.30	
Relapse-free survival§		
n events (death in CR or relapse)	36	26
Median, months	24.6	11.0
Hazard ratio (95% CI)†	2.09 (1.26-3.48)	
P‡	.004	
Duration of hematologic remission‖		
n events (relapse)	20	19
Median, months	NR	19.1
Hazard ratio (95% CI)†	0.39 (0.21-0.73)	
P¶	.004	

CI, confidence interval; CR, complete remission; HSCT, hematopoietic stem cell transplantation; Ph, Philadelphia chromosome.

*Among patients with Ph-negative disease in hematologic remission at baseline.

†The hazard ratio estimates are obtained from the Cox model with subjects in the first remission at baseline as the reference level.

‡Log-rank test *P* value.

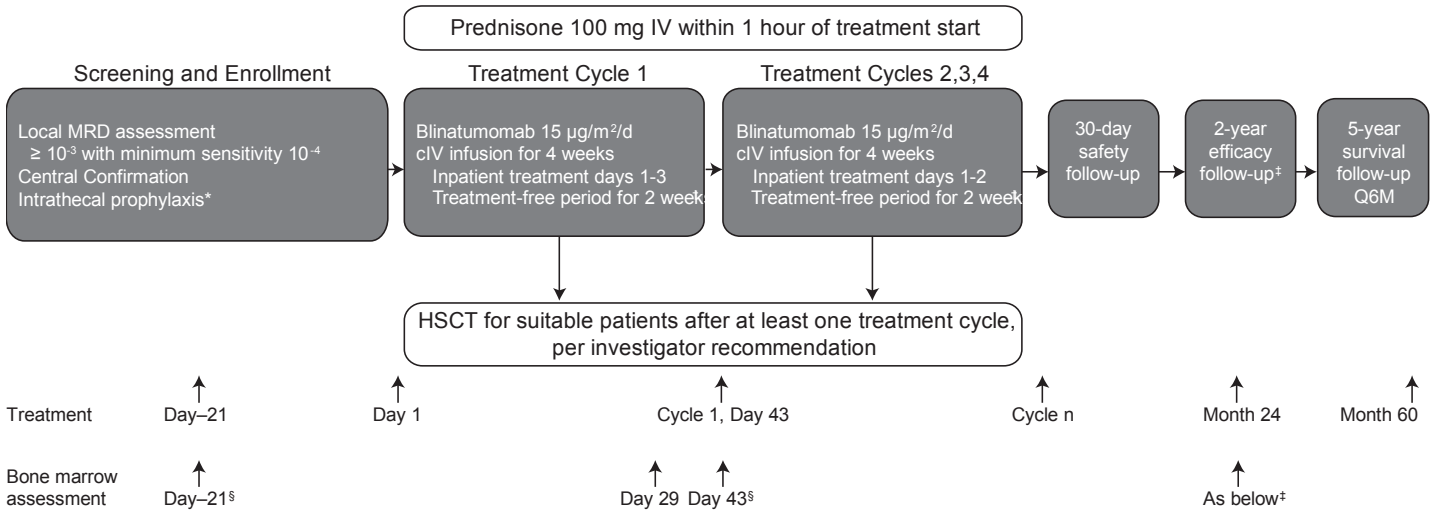
§Relapse-free survival in patients with Ph-negative disease in CR at baseline, without censoring at HSCT or post-blinatumomab chemotherapy.

‖Duration of hematologic remission in patients with Ph-negative disease in CR at baseline, without censoring at HSCT or post-blinatumomab chemotherapy is evaluated by 1 − cumulative incidence function of hematological relapse with death due to other causes as a competing event.

¶Gray's test *P* value.

SUPPLEMENTAL FIGURES

Figure S1. Study schema



cIV, continuous IV; HSCT, hematopoietic stem cell transplantation; IV, intravenous; LLOQ, lower limit of quantitation; MRD, minimal residual disease; Q6M, once every 6 months.

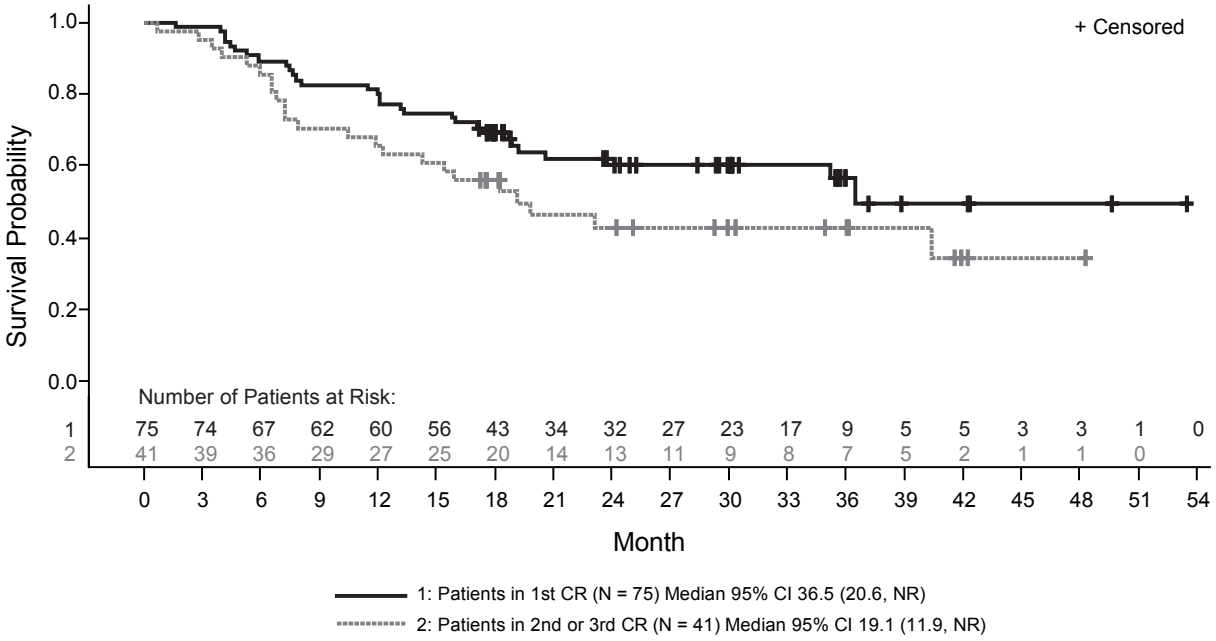
*During screening or within 4 weeks of treatment initiation; at day 29 of cycles 2 and 4; and every 3 months following treatment for up to 18 months. Treatment comprised dexamethasone 4 mg (or equivalent), methotrexate 15 mg, and cytosine arabinoside 40 mg.

†May be extended by up to 7 days.

‡At 3, 6, 9, 12, 18 and 24 months after treatment start.

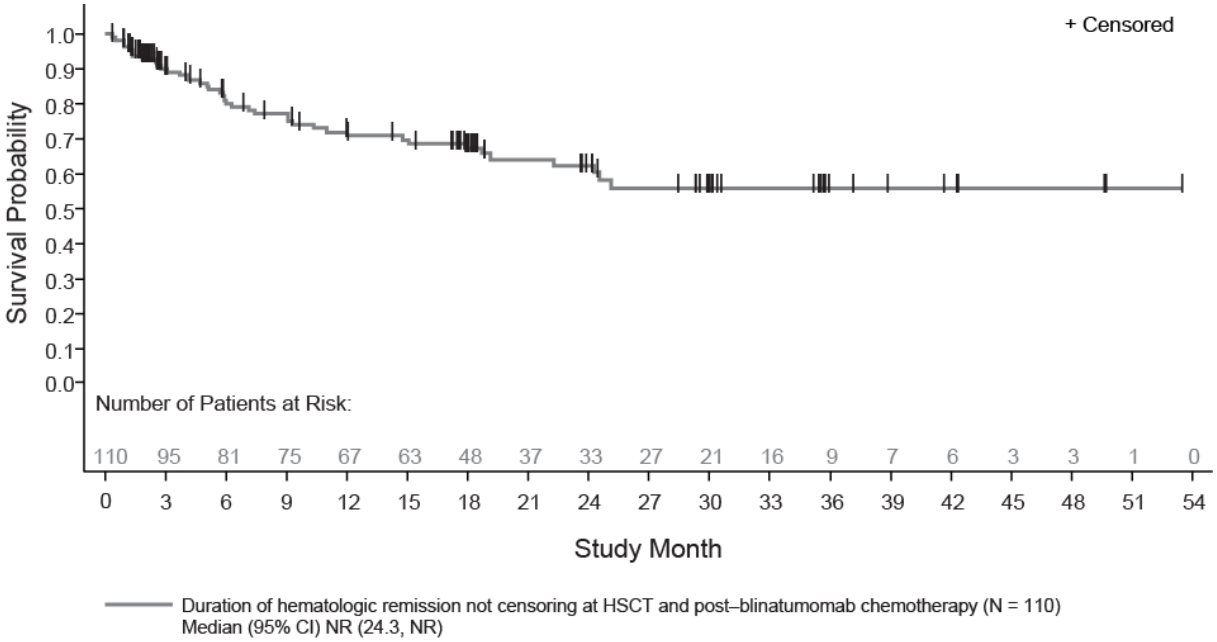
§Baseline bone marrow aspirations were obtained during screening or within 4 weeks prior to treatment start. Confirmatory bone marrow aspirations were performed on day 43 of cycle 1 if the central MRD result was not yet available or if there was an unclear MRD result (between LLOQ and sensitivity).

Figure S2. Overall survival by baseline remission status



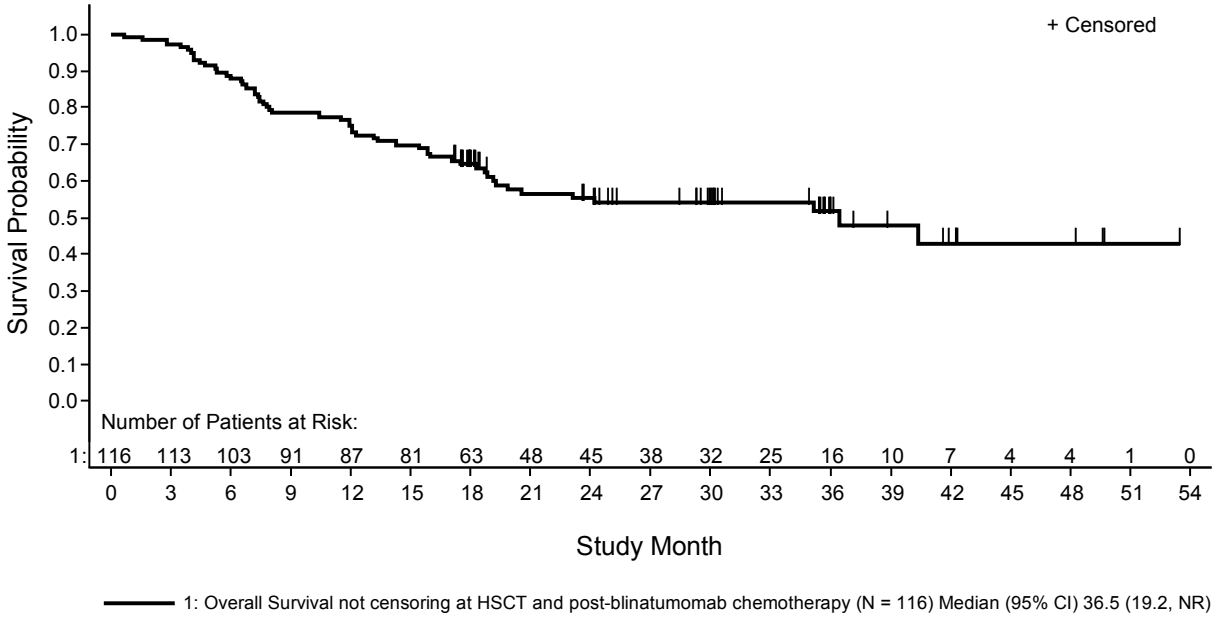
CI, confidence interval; CR, complete remission; NR, not reached.

Figure S3. Duration of hematologic remission



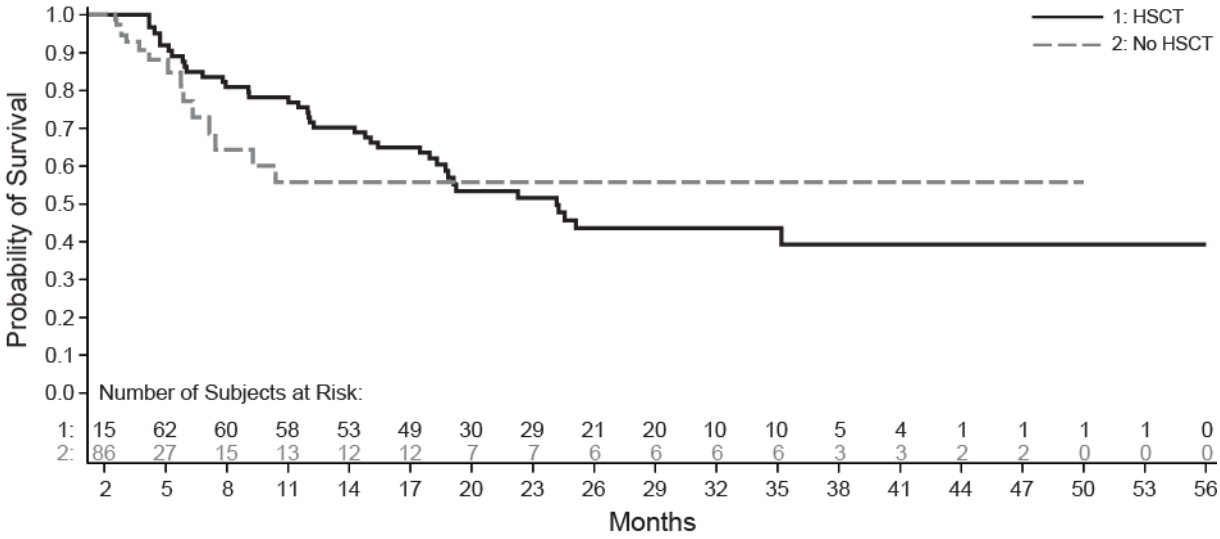
CI, confidence interval; HSCT, hematopoietic stem cell transplantation; NR, not reached.

Figure S4. Overall survival among all patients treated



The Kaplan-Meier estimate of median overall survival was 36.5 months (95% CI, 19.2-not estimable), with a median follow-up of 30.0 months (95% CI, 25.1-35.0).
CI, confidence interval; HSCT, hematopoietic stem cell transplantation; NR, not reached.

Figure S5. Simon-Makuch plot of relapse-free survival among all patients in the full analysis set by HSCT status



HSCT, hematopoietic stem cell transplantation.