ORIGINAL ARTICLE

Blinatumomab Added to Chemotherapy in Infant Lymphoblastic Leukemia

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ABSTRACT

BACKGROUND

KMT2A-rearranged acute lymphoblastic leukemia (ALL) in infants is an aggressive disease with 3-year event-free survival below 40%. Most relapses occur during treatment, with two thirds occurring within 1 year and 90% within 2 years after diagnosis. Outcomes have not improved in recent decades despite intensification of chemotherapy.

METHODS

We studied the safety and efficacy of blinatumomab, a bispecific T-cell engager molecule targeting CD19, in infants with *KMT2A*-rearranged ALL. Thirty patients younger than 1 year of age with newly diagnosed *KMT2A*-rearranged ALL were given the chemotherapy used in the Interfant-06 trial with the addition of one postinduction course of blinatumomab (15 μg per square meter of body-surface area per day; 28-day continuous infusion). The primary end point was clinically relevant toxic effects, defined as any toxic effect that was possibly or definitely attributable to blinatumomab and resulted in permanent discontinuation of blinatumomab or death. Minimal residual disease (MRD) was measured by polymerase chain reaction. Data on adverse events were collected. Outcome data were compared with historical control data from the Interfant-06 trial.

RESULTS

The median follow-up was 26.3 months (range, 3.9 to 48.2). All 30 patients received the full course of blinatumomab. No toxic effects meeting the definition of the primary end point occurred. Ten serious adverse events were reported (fever [4 events], infection [4], hypertension [1], and vomiting [1]). The toxic-effects profile was consistent with that reported in older patients. A total of 28 patients (93%) either were MRD-negative (16 patients) or had low levels of MRD ($<5\times10^{-4}$ [i.e., <5 leukemic cells per 10,000 normal cells], 12 patients) after the blinatumomab infusion. All the patients who continued chemotherapy became MRD-negative during further treatment. Two-year disease-free survival was 81.6% in our study (95% confidence interval [CI], 60.8 to 92.0), as compared with 49.4% (95% CI, 42.5 to 56.0) in the Interfant-06 trial; the corresponding values for overall survival were 93.3% (95% CI, 75.9 to 98.3) and 65.8% (95% CI, 58.9 to 71.8).

CONCLUSIONS

Blinatumomab added to Interfant-06 chemotherapy appeared to be safe and had a high level of efficacy in infants with newly diagnosed *KMT2A*-rearranged ALL as compared with historical controls from the Interfant-06 trial. (Funded by the Princess Máxima Center Foundation and others; EudraCT number, 2016-004674-17.)

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Infant acute lymphoblastic leukemia (ALL) is a rare disease with dismal outcomes. Although event-free survival among older children has shown improvements with time and is currently more than 85%,[1,2] infants with ALL diagnosed in their first year of life continue to have a poor prognosis, with 6-year event-free survival of 46% and overall survival of 58%.[3] In particular, infants with a rearrangement of the gene encoding histone–lysine *N*-methyltransferase 2A (*KMT2A*, formerly known as mixed-lineage leukemia [*MLL*]), which is found in 75% of infants with ALL, have the worst outcomes, with 6-year event-free survival of only 36% in Interfant-06, the largest clinical trial involving this population to date.[3] Similar outcomes in infants with *KMT2A*-rearranged ALL have been reported in the Interfant-99, Children's Cancer Group 1953, and Children's Oncology Group P9407 and AALL0631 studies.[4-7]

In the Interfant-06 trial, 90% of all relapses occurred during the 2 years of treatment, with 66% occurring in the first year after diagnosis,[3] which illustrates the aggressiveness of this specific type of ALL. Survival after relapse is only 20%.[8] Other than in the Japanese MLL-10 study, in which 3-year event-free survival was 66%,[9] intensification of chemotherapy and the use of allogeneic hematopoietic stem-cell transplantation (HSCT) has not improved outcomes in infants with *KMT2A*-rearranged ALL over the past two decades.[3,7]

Blinatumomab is a bispecific single-chain molecule designed to link CD19+ B cells and CD3+ T cells, resulting in T-cell activation and a cytotoxic T-cell response against CD19+ B cells. Leukemic cells in infant ALL are immature B-lineage cells that express CD19. Studies have shown that blinatumomab is a safe and efficacious treatment for older children and adults with relapsed or refractory B-lineage ALL after intensive chemotherapy.[10-13] We therefore hypothesized that one course of blinatumomab could be safely added to the Interfant-06 backbone regimen and improve outcomes among infants with *KMT2A*-rearranged ALL.

METHODS

STUDY OVERSIGHT

We conducted a prospective, single-group, international, multicenter, phase 2 study involving patients with newly diagnosed *KMT2A*-rearranged ALL in the first year of life. The study was conducted in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, International Council for Harmonisation Guidelines for Good Clinical Practice, and the Declaration of Helsinki. The study protocol, available with the full text of this article at NEJM.org, was approved by the institutional review board of each participating center. The parents or guardians of the patients provided written informed consent. The study was investigator-initiated; Amgen provided some funding for monitoring and provided blinatumomab free of charge but did not have any other role in the study. The authors were responsible for the collection and assembly of data; the first author wrote the first draft of the manuscript, and all the authors had input in reaching a final version. No one who is not an author contributed to writing the submitted manuscript. The authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

A Quick Take is available at NEJM.org

PATIENTS

Patients younger than 1 year of age with newly diagnosed *KMT2A*-rearranged, CD19+, B-precursor ALL that had been treated according to the Interfant-06 protocol with less than 25% leukemic blasts in the bone marrow at the end of induction were eligible for participation. Exclusion criteria included a clinically relevant central nervous system (CNS) condition requiring treatment (e.g., unstable seizure disorder) and evidence of CNS involvement at the end of induction. Additional eligibility criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org. The risk classification for the infants with *KMT2A*-rearranged ALL was in accordance with that used in the Interfant-06 trial: high risk was defined as an age of less than 6 months at diagnosis with a white-cell count of at least 300×10^9 per liter at diagnosis or a poor response to prednisone; all other patients with *KMT2A*-rearranged ALL in the study were classified as being at medium risk. The Interfant-06 treatment schedule has been described previously.[3]

THERAPY

After 1 month of the induction therapy used in Interfant-06, patients received one cycle of blinatumomab (15 μg per square meter of body-surface

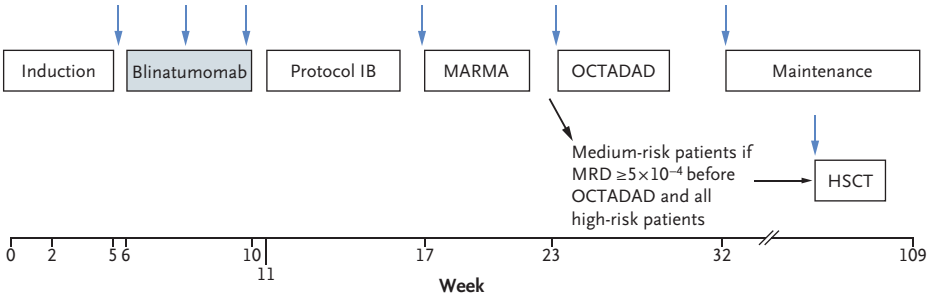


Figure 1. Treatment Protocol.

Light blue arrows indicate time points at which minimal residual disease (MRD) was measured: at the end of induction, during the blinatumomab infusion (day 15 and day 29 of the infusion), before MARMA, before OCTADAD or hematopoietic stem-cell transplantation (HSCT), and before maintenance treatment. Intrathecal prophylaxis was administered on day 15 of the blinatumomab infusion. Protocol IB consists of cyclophosphamide, cytarabine, and mercaptopurine; MARMA consists of high-dose cytarabine, high-dose methotrexate, mercaptopurine, and asparaginase; OCTADAD consists of vincristine, dexamethasone, asparaginase, daunorubicin, thioguanine, cytarabine, and cyclophosphamide; and maintenance treatment consists of mercaptopurine and methotrexate.

area per day) as a 4-week continuous infusion (Fig. 1). Dexamethasone (5 mg per square meter) was administered intravenously 30 minutes before starting the blinatumomab infusion. Intrathecal prophylaxis (methotrexate and prednisolone) was administered on day 15 of the blinatumomab infusion. After the blinatumomab infusion, patients continued treatment in accordance with the Interfant-06 protocol, with consecutive courses of protocol IB (cyclophosphamide, cytarabine, and mercaptopurine), MARMA (high-dose cytarabine, high-dose methotrexate, mercaptopurine, and asparaginase), OCTADAD (vincristine, dexamethasone, asparaginase, daunorubicin, thioguanine, cytarabine, and cyclophosphamide), and maintenance therapy (mercaptopurine and methotrexate).[3] All high-risk patients and medium-risk patients with minimal residual disease (MRD) of at least 5×10^{-4} before OCTADAD were candidates for HSCT in the first complete remission.

END POINTS

The primary end point was clinically relevant toxic effects, defined as any toxic effect that is possibly or definitely attributable to blinatumomab and results in permanent discontinuation of blinatumomab or death. Secondary end points for toxicity and feasibility included serious adverse events graded according to Common Terminology Criteria for Adverse Events, version 4.03; the number of treatment interruptions; and the percentage of patients who received a full course (4 weeks) of blinatumomab. The secondary efficacy end points were measures of antileukemic activity, including MRD response; the percentage of medium-risk patients with MRD of at least 5×10^{-4} (i.e., ≥5 leukemic cells per 10,000 normal cells) before OCTADAD; and long-term outcomes. MRD was measured by polymerase chain reaction (PCR) with the use of the *KMT2A* genomic breakpoint fusion sequence and the immunoglobulin and T-cell receptor (TCR) gene rearrangements as targets at the end of induction, during the blinatumomab infusion (day 15 and day 29 of the infusion), before MARMA, before OCTADAD or HSCT, and before maintenance treatment (Fig. 1). The highest level of MRD was used when results for more than one PCR marker were reported. MRD negativity was defined as undetectable MRD. Measurement of MRD was not mandated after HSCT. Data on adverse events were collected from the start of the blinatumomab infusion until the start of the next chemotherapy course (protocol IB). Outcome data were compared with historical control data from the Interfant-06 trial.

STATISTICAL ANALYSIS

Interfant-06 historical controls were selected on the basis of the inclusion and exclusion criteria used in the current study and available data on MRD at the end of induction (Fig. S2). A Fisher's exact test (two-sided) was performed to compare

the level of MRD before MARMA among the patients in this study with those among Interfant-06 historical controls, and 95% exact confidence intervals for the difference of proportions were calculated at different time points for the evaluation of MRD response. Disease-free survival was defined as the time from study entry to relapse, death from any cause, or second cancer, whichever occurred first. Patients who withdrew (i.e., patients who permanently discontinued blinatumomab because of disease progression or for safety reasons) were defined as having had treatment failure in the sensitivity analysis. Overall survival was defined as the time from study entry to death from any cause. Data were censored at the date of last contact when no event was observed. Survival curves were computed according to the Kaplan–Meier estimator, and 95% confidence intervals were based on Greenwood's standard error. Comparison with selected Interfant-06 historical controls was based on the estimated hazard ratio and 95% confidence interval from an adjusted Cox regression model (see the Supplementary Appendix).[14] A weighted Kaplan–Meier analysis for individually matched data was also applied (see the Supplementary Appendix).[15] Confidence intervals have not been adjusted for multiplicity and cannot be used in place of hypothesis tests. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

Thirty patients were enrolled from July 2018 through July 2021 at 12 sites in 9 countries (Fig. S1). The final follow-up was on August 31, 2022. The baseline characteristics of the patients are shown in Table S2; there were no significant differences between the patients in our study and the selected Interfant-06 historical controls. No withdrawals occurred, but five patients had deviations from protocol-prescribed therapy. Two medium-risk patients underwent HSCT at the investigator's discretion despite not having the protocol-defined indication for HSCT (i.e., the MRD before OCTADAD was not $\geq 5\times10^{-4}$), one of whom also received part of the Interfant-06 myeloid-style consolidation treatment (a course of cytarabine, daunorubicin, and etoposide [ADE]) instead of protocol IB. Three patients received alternative schedules after the blinatumomab infusion: one high-risk patient underwent HSCT immediately after the blinatumomab infusion, another high-risk patient received the full Interfant-06 myeloid-style consolidation (courses of ADE and of mitoxantrone, cytarabine, and etoposide [MAE][3]) instead of protocol IB before transplantation, and one medium-risk patient who did not undergo HSCT received ADE and MAE instead of protocol IB, followed by MARMA, OCTADA (i.e., OCTADAD without daunorubicin), and maintenance treatment. Overall, eight of nine high-risk patients underwent HSCT in the first complete remission (the remaining patient died in complete remission just before planned HSCT). None of the medium-risk patients in our study (as compared with 20% in the Interfant-06 trial) had MRD levels before OCTADAD that were high enough to make them eligible for HSCT in the first complete remission.

TOXIC EFFECTS

In terms of the primary end point, we did not observe any toxic effects that were possibly or definitely attributable to blinatumomab and that resulted in permanent discontinuation of blinatumomab or in death. All the patients received the full 4-week course of blinatumomab. One patient had a treatment interruption for 2 days because of a hypertensive crisis; the patient had also been treated for a hypertensive crisis during induction. The infusion was restarted at a reduced dose of 5 μg per square meter per day and was subsequently increased after 2 days to 15 μg per square meter per day without further complications.

Data on adverse events were collected from the start of the blinatumomab infusion until the start of the next treatment block (protocol IB). Ten serious adverse events were reported in 9 patients (fever, grade 1 [4 events]; infection, grade 3 or 4 [4 events]; hypertension, grade 3 [1 event]; and vomiting, grade 3 [1 event]) (Table 1). No fatal adverse events were reported, and no patients had neurologic events. In total, 78 adverse events of any grade occurred (61 events when only the highest grade of a given event in each patient is counted). The most frequent grade 3 or higher adverse events were febrile neutropenia (in 7% of the patients), anemia (in 17%), neutropenia (in 7%), and elevated γ-glutamyltransferase levels (in 7%) (Table 1). The most frequent grade

Table 1. Adverse Events.*

Event	All Patients (N=30)
Any serious adverse event — no. of patients (%)	9 (30)
Infection, grade 3 or 4	4 (13)
Fever, grade 1	3 (10)†
Hypertension, grade 3	1 (3)
Vomiting, grade 3	1 (3)
No. of adverse events leading to permanent discontinuation of blinatumomab	0
No. of adverse events of any grade	61
No. of adverse events of CTCAE grade ≥3	16
Adverse events of CTCAE grade ≥3 — no. of patients (%)	
Anemia	5 (17)
Febrile neutropenia	2 (7)
Pharyngitis	1 (3)
Hypertension	1 (3)
Decreased neutrophil count	2 (7)
Decreased white-cell count	1 (3)
Increased alanine aminotransferase level	1 (3)
Increased γ-glutamyltransferase level	2 (7)
Hypoproteinemia	1 (3)

* Patients who had the same adverse event multiple times were counted once, and the highest grade is reported. If a patient had episodes in different adverse event categories, it is counted in each category. CTCAE denotes Common Terminology Criteria for Adverse Events.
† Fever of grade 1 occurred twice in one patient.

1 or 2 adverse events were hypertension (in 13% of the patients), vomiting (in 13%), and diarrhea (in 13%). Twelve patients received intravenous immune globulin, and 2 received granulocyte colony-stimulating factor.

MRD

MRD response is shown in Figure 2 and Table S3. After 2 weeks and 4 weeks of blinatumomab, 53% of the patients (16 of 30) were MRD-negative. Of the 22 patients who were MRD-positive at the end of induction, 9 became MRD-negative after the blinatumomab infusion. The percentage of patients who were MRD-negative at the start of MARMA was 54%, increasing to 94% before maintenance treatment. At the end of the blinatumomab infusion, 93% of the patients (28 of 30) were MRD-negative or had only low levels of MRD ($<5\times10^{-4}$); before MARMA, 93% (26 of 28) were MRD-negative or had only low levels of MRD, as compared with 83% of the patients in the Interfant-06 trial (P=0.26). All the patients had MRD levels of less than 5×10^{-4} before OCTADAD, as compared with 83% of the patients in the Interfant-06 trial.

Figure 3 shows the MRD responses and outcomes in individual patients. Two medium-risk patients underwent HSCT at the investigator's discretion. All 19 medium-risk patients who continued chemotherapy became MRD-negative during further treatment.

MRD negativity at the end of the blinatumomab infusion was more frequent among medium-risk patients than among high-risk patients (67% vs. 22%) and more common among patients who had had low MRD levels ($<5\times10^{-4}$) at the end of induction than among those who had had high levels (78% vs. 17%). However, the majority of high-risk patients and patients with high levels of MRD at the end of induction still had a response to blinatumomab, with 78% (7 of 9) and 92% (11 of 12), respectively, becoming MRD-negative or having low levels of MRD after the blinatumomab infusion.

DISEASE-FREE AND OVERALL SURVIVAL

After a median follow-up of 26.3 months (range, 3.9 to 48.2), 2-year disease-free survival was 81.6% (95% confidence interval [CI], 60.8 to 92.0) and 2-year overall survival was 93.3% (95% CI, 75.9 to 98.3) (Fig. 4A). The 2-year event-free and overall survival in the Interfant-06 trial (484 patients) were 42.4% (95% CI, 37.9 to 46.8) and 54.5% (95% CI, 49.9 to 58.9), respectively (Fig. S3). A direct comparison, considering only the patients in the Interfant-06 trial who met the inclusion criteria used in the current study and for whom data were available on MRD at the end of induction (214 patients), is shown in Figure 4B and 4C. In this analysis, 2-year disease-free survival in the Interfant-06 trial was 49.4% (95% CI, 42.5 to 56.0) and 2-year overall survival was 65.8% (95% CI, 58.9 to 71.8); the corresponding hazard ratios for the comparison of the infants in our study with the historical controls were 0.22 (95% CI, 0.09 to 0.34) and 0.15 (95% CI, 0.04 to 0.62). Similar results were obtained with an additional analysis in which Interfant-06 historical comparators were selected to match the individual characteristics of patients in this study (2-year disease-free survival, 46.2%; 95% CI, 37.2 to 57.3) (Fig. S4).

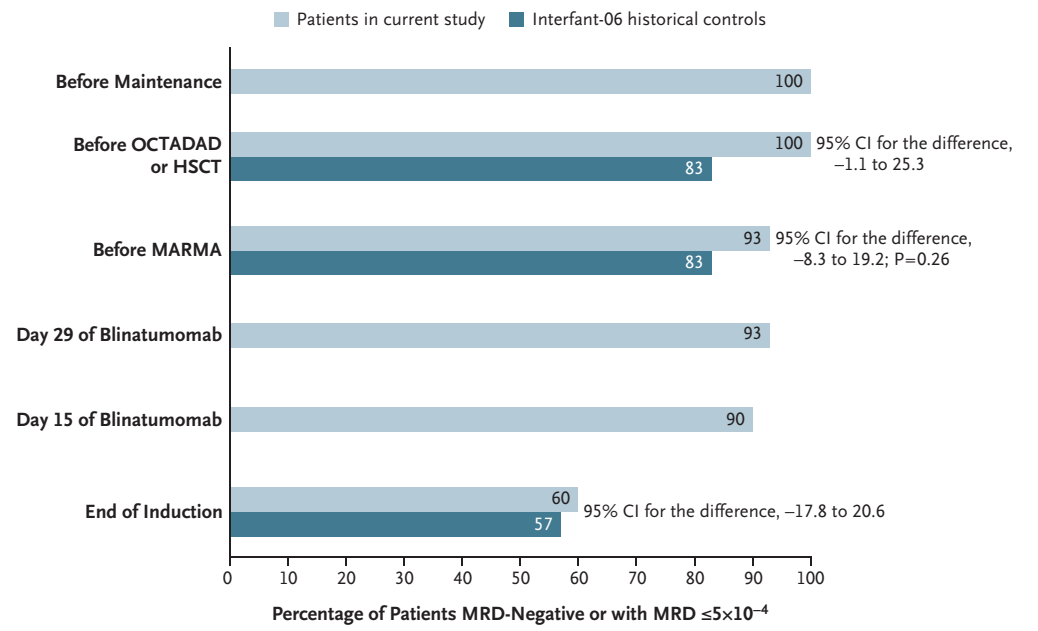


Figure 2. MRD at Time Points Throughout the Study.

MRD was measured by polymerase chain reaction (PCR) with the use of the *KMT2A* genomic breakpoint fusion sequence and the immunoglobulin and T-cell receptor (TCR) gene rearrangements as targets. The highest MRD result was used if both PCR targets were measured. The figure shows the percentages of patients who were negative for MRD (i.e., in whom MRD was undetectable) or had MRD of less than 5×10^{-4} (i.e., <5 leukemic cells per 10,000 normal cells) among the patients in the current study and among 214 historical controls in the Interfant-06 trial; 95% exact confidence intervals (CIs) are shown for the differences in these percentages between the two populations. A two-sided Fisher's exact test was performed to compare the level of MRD before MARMA among the patients in this study with those among Interfant-06 historical controls, and 95% exact confidence intervals for the difference of proportions were calculated at different time points for the evaluation of MRD response. The numbers of patients included at each time point in the current study were 30 patients at the end of induction, day 15 of the blinatumomab infusion, and day 29 of the blinatumomab infusion; 28 patients before MARMA; 24 patients before OCTADAD; and 18 patients before maintenance treatment (medium-risk patients only).

One death during first remission occurred just before HSCT; this death was considered to be unrelated to blinatumomab (tracheal bleeding due to a tracheal cannula). Four relapses occurred (Table S4). Two medium-risk patients had a combined bone marrow–CNS relapse during maintenance treatment and are in continuous second complete remission. Another medium-risk patient had a CNS relapse during protocol IB and is in second complete remission after MARMA and HSCT. The fourth relapse occurred in a high-risk patient who had a combined bone marrow–CNS relapse 2 months after HSCT. All relapses were CD19+, but the high-risk patient also had a CD19− clone in the CNS at relapse. This patient had a good response to blinatumomab (MRD, $<10^{-4}$) but underwent HSCT immediately after the blinatumomab infusion. The cumulative incidence of relapse is shown in Figure S5. Molecular reappearance of disease occurred in one high-risk patient after HSCT; this patient subsequently became MRD-negative after chimeric antigen receptor (CAR) T-cell therapy. Sensitivity analysis showed that when data from the five patients who had deviations from the treatment protocol were censored, 2-year disease-free survival was 83.4% (95% CI, 61.3 to 93.4) and 2-year overall survival was 96.2% (95% CI, 75.7 to 99.4).

DISCUSSION

In this study, adding blinatumomab to the standard chemotherapy backbone in infants with newly diagnosed *KMT2A*-rearranged ALL was feasible and appeared to be safe. Our data indi-

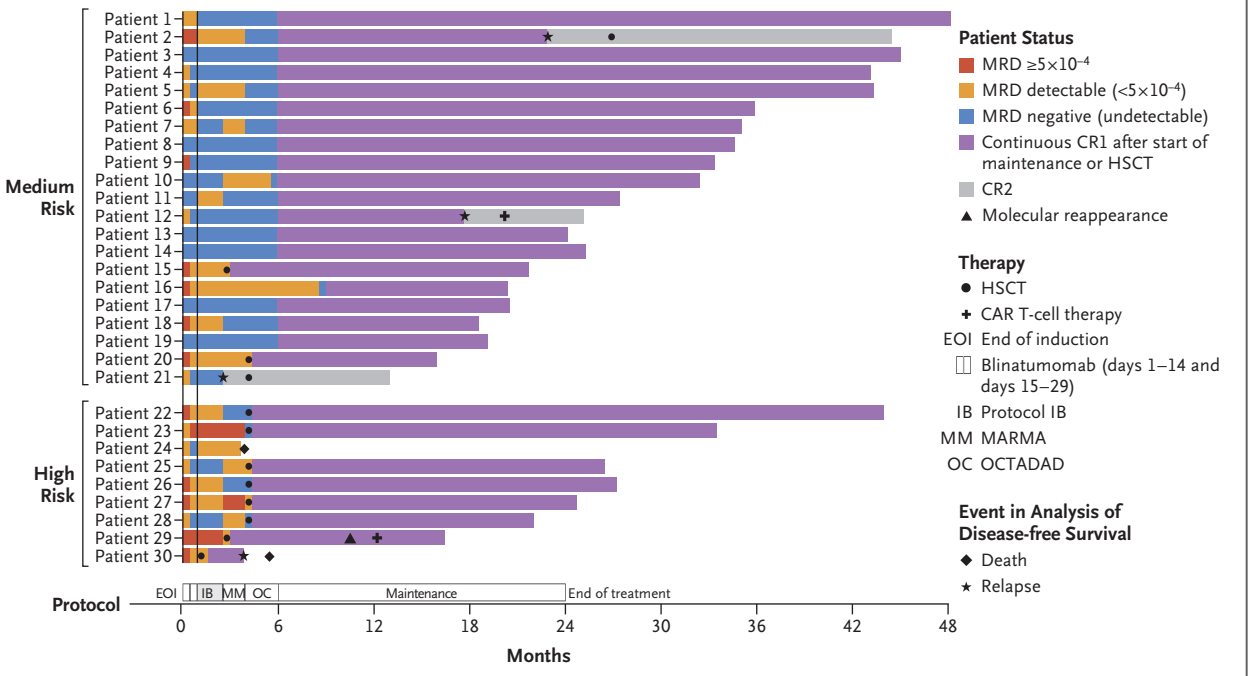


Figure 3. Swimmer Plot of MRD Response and Outcomes in Individual Patients.

The time line is synchronized for the different chemotherapy blocks according to protocol time lines. The actual time of starting a block for individual patients may differ. The vertical line indicates the end of the blinatumomab infusion. Patients with relapsed disease who reached second complete remission are shown in gray (starting at relapse, because the date of second complete remission is unknown). Patient 16 had been *KMT2A* MRD-negative since before OCTADAD but remained immunoglobulin–TCR MRD-positive at a very low level ($<5\times10^{-5}$) at the start of maintenance treatment and became immunoglobulin–TCR MRD-negative during maintenance treatment. CAR denotes chimeric antigen receptor, CR1 first complete remission, and CR2 second complete remission.

cate a higher level of antileukemic activity than the Interfant-06 protocol, as reflected by good responses with respect to MRD and improved short-term survival. Although the follow-up time was relatively short, it included the period historically defined as the period of increased risk of relapse. These outcome data are very promising, given the poor survival and lack of improvements in outcomes among infants with *KMT2A*-rearranged ALL in recent decades.

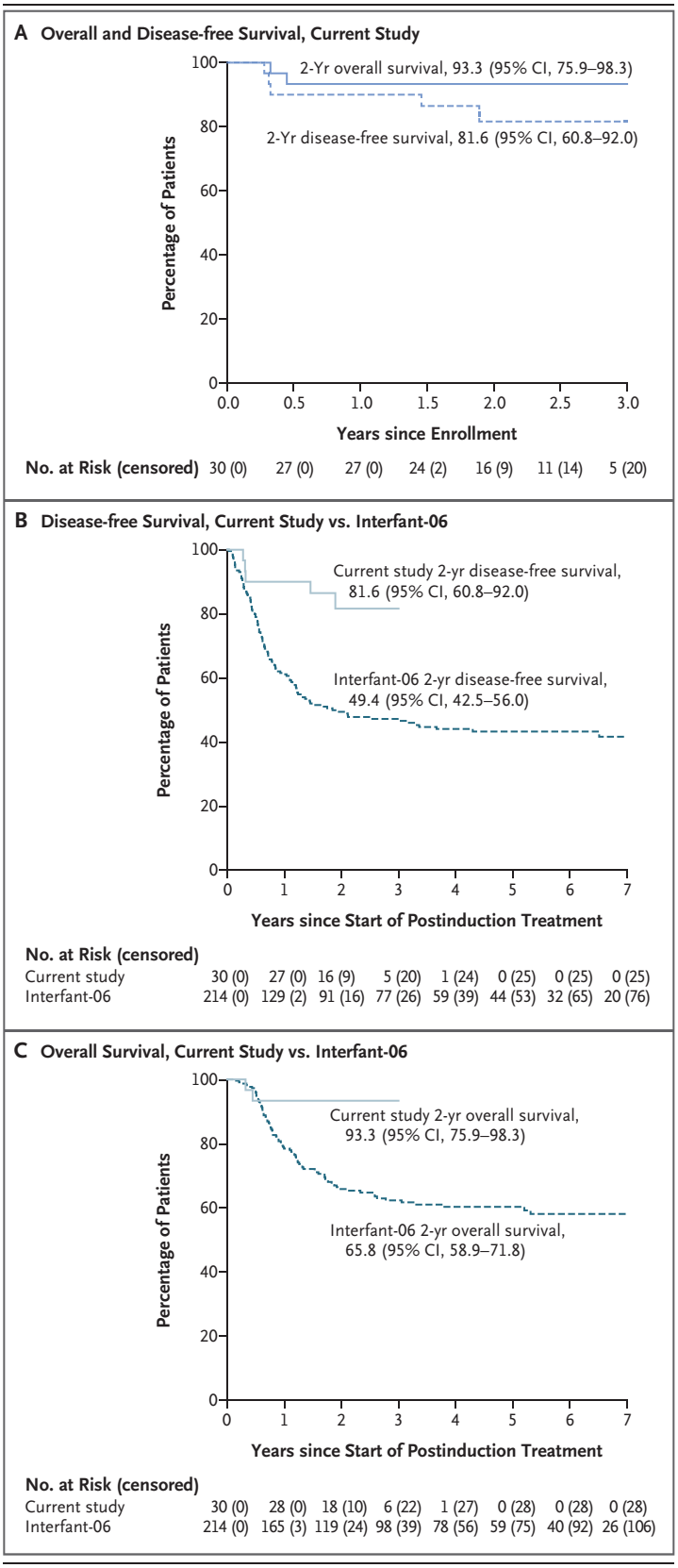
The design of our study was based on two hypotheses. First, because of the early events that are known to occur during therapy, we hypothesized that new interventions should be implemented early in treatment. Second, we hypothesized that higher response rates and a lower incidence of side effects would be associated with a low leukemia burden at the time of blinatumomab administration.[10,11,16] Blinatumomab was therefore added immediately after induction therapy.

In general, blinatumomab has fewer acute adverse effects than chemotherapy. The toxic-effects profile in our infant cohort was consistent with that in previous studies of blinatumomab in older children and adults.[10,11,16-18] We used a fixed dose of 15 μg per square meter per day, without dose reductions for age. The starting dose was also not reduced in patients with M2 marrow (5 to 25% blasts). Because of the low tumor burden, no severe cytokine release syndrome occurred; only one patient had cytokine release syndrome (grade 1), and three patients had grade 1 fever, which could be attributed to cytokine release syndrome or an infusion reaction. Moreover, no neurologic events were reported in our cohort, although we cannot rule out underreporting of mild neurologic symptoms that may have been unrecognized in infants.

Unlike outcomes in older children, outcomes in infants with *KMT2A*-rearranged ALL have not improved over two successive Interfant studies,

Figure 4. Disease-free Survival and Overall Survival among Infants in This Study and Selected Historical Controls.

The comparisons shown in Panels B and C include 214 patients from the Interfant-06 trial who met the inclusion criteria used in the current study and for whom data were available on MRD at the end of induction.



with 6-year event-free survival of 36.4% and overall survival of 48.0%.[3,7] The addition of blinatumomab to the standard chemotherapy backbone in the present study resulted in an improved MRD response and in better short-term disease-free and overall survival. In the current study, 2-year disease-free survival was 81.6%, as compared with 49.4% in the Interfant-06 trial. Although longer-term follow-up is awaited, this improved disease-free survival is of importance because 90% of relapses in this patient population occur within 2 years after diagnosis. HSCT was performed in 8 of 9 high-risk patients, whereas 46% of high-risk patients in Interfant-06 had an event before HSCT. None of the 21 medium-risk patients received HSCT because of persistent high levels of MRD. In addition, none of the 3 patients with M2 marrow at the end of induction had an event, whereas all the patients in Interfant-06 who had M2 or M3 marrow at the end of induction died.

The number of relapses was low; however, all the patients who had a relapse had CNS involvement at relapse. This underscores the need for adequate intrathecal chemotherapy during the blinatumomab infusion, because the efficacy of blinatumomab for the treatment of CNS leukemia may be limited.[19]

KMT2A-rearranged ALL is associated with a propensity for lineage switch to acute myeloid leukemia. In the Interfant-06 trial, lineage switches were uncommon, reported in 1% of patients. The selective pressure from CD19-directed therapy such as blinatumomab may confer a further predisposition to this phenotypic switch; however, phenotypic switch has mainly been described in case reports.[20,21] In two retrospective case series of patients with relapsed or refractory infant *KMT2A*-rearranged ALL, lineage switch was identified in 1 of 11 patients in one study and in 1 of 9 patients in the other.[22,23] An increased incidence of lineage switch has been reported after CD19-directed CAR T-cell therapy for *KMT2A*-rearranged ALL.[24-26]

No lineage switches occurred in our cohort of 30 infants treated with blinatumomab, and therefore the benefit of improved survival with blinatumomab may outweigh the small risk of lineage switch.

MRD response fluctuated in some patients. This may be explained in part by discrepancies between measurements of MRD with *KMT2A* PCR as compared with immunoglobulin–TCR PCR, which could be due to false positivity for immunoglobulin–TCR PCR targets in regenerating bone marrow.[27,28] The *KMT2A* genomic breakpoint fusion sequence will be the preferred target for PCR measurement of MRD in future trials.[29]

This study has several limitations. The follow-up time was relatively short. A randomized design was not possible because of the rarity of the disease and the unsatisfactory outcomes that would have occurred in a control group of patients who did not receive blinatumomab. Blinatumomab was therefore added in a single-group study design to the Interfant-06 chemotherapy backbone. The data on MRD and outcomes in patients in the historical control group who were treated with the same chemotherapy backbone were well established in the Interfant-06 trial, which involved a large cohort of infants.[3,29] Five treatment deviations were reported in our study, all in patients who had high levels of MRD at the end of induction. Two medium-risk patients underwent HSCT in the absence of a protocol-defined indication, and four patients received myeloid-style consolidation therapy (ADE or ADE plus MAE) or no consolidation therapy before HSCT, instead of protocol IB and MARMA. We recently showed that infants with high levels of MRD at the end of induction benefit from myeloid-style consolidation (ADE plus MAE), whereas those with low levels of MRD at the end of induction benefit from lymphoid-directed consolidation (protocol IB).[29] A sensitivity analysis showed that these treatment deviations did not affect outcomes.

Blinatumomab added to the Interfant-06 backbone appeared to be safe and had promising efficacy in terms of short-term disease-free survival and the percentage of patients with a complete MRD response. Longer follow-up is awaited, but the low incidence of relapse after treatment with blinatumomab is remarkable, given that in historical controls relapses occur frequently and early during therapy. It may be useful to focus future work on identifying whether additional courses of blinatumomab will improve outcomes further and whether HSCT will continue to be necessary to cure high-risk patients.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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