Long-term results of St. Jude Total Therapy studies 11, 12, 13A, 13B and 14 for childhood acute lymphoblastic leukemia

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Abstract

We analyzed the long-term outcome of 1011 patients treated in five successive clinical trials (Total Therapy Studies 11, 12, 13A, 13B and 14) between 1984 and 1999. The event-free survival improved significantly (p=0.003) from the first two trials conducted in the 1980s to the three more recent trials conducted in the 1990s. Approximately 75% of patients treated in the 1980s and 80% in the 1990s were cured. Early intensive triple intrathecal therapy, together with more effective systemic therapy, including consolidation and reinduction treatment (Studies 13A and 13B) as well as dexamethasone (Study 13A), resulted in a very low rate of isolated central-nervous-system relapse rate (<2%), despite the reduced use of cranial irradiation. Factors consistently associated with treatment outcome were age, leukocyte count, immunophenotype, DNA index, and minimal residual disease level after remission induction treatment. Because of concerns about therapy-related secondary myeloid leukemia and brain tumors, in our current trials we reserve the use of etoposide for patients with refractory or relapsed leukemia undergoing hematopoietic stem cell transplantation, and cranial irradiation for those with CNS relapse. The next main challenge is to further increase cure rates while improving quality of life for all patients.

Keywords

B-lineage ALL; T-lineage ALL; CNS relapse; prognostic factors; leukemia; chemotherapy
Introduction

The St. Jude Total Therapy program for childhood acute lymphoblastic leukemia (ALL) has spanned over four decades. The first nine studies, conducted from 1962 to 1979, established the importance of combination systemic chemotherapy in full doses and central-nervous-system (CNS)-directed therapy. Total Therapy Study 10 (1979 to 1983), the first to apply risk-directed therapy, showed the efficacy of high-dose methotrexate and the feasibility of reducing the use of cranial irradiation.2 In Study 11 (1984-1988), the use of early treatment intensification improved outcome, and the schedule-dependent leukemogenic effects of epipodophyllotoxins were identified.3-5 Study 12 (1988-1991) proved the benefits of individualized therapy based on pharmacokinetics.6 In Study 13A (1991-1994), early intensification of intrathecal therapy substantially reduced CNS relapse hazard, allowing further reduction of cranial irradiation.7 This study also disclosed the pharmacodynamic basis of differences in methotrexate disposition between various phenotypic and genotypic subtypes of ALL.8-12 The long-term results of these 13 studies were reported in the December 2000 issue of Leukemia,13 together with those of 11 other groups.

In Study 13B (1994-1998), the efficacy of early intensification of intrathecal therapy was confirmed,14 paving the way to the total elimination of prophylactic cranial irradiation in subsequent Total Therapy studies.15-17 Study 13B demonstrated that host pharmacogenetics affects treatment toxicity as well as antileukemic outcome,18,19 and also represented the first leukemia trial to apply pharmacogenetics in therapy;20 that is, the dose of mercaptopurine during continuation therapy was based on polymorphisms of the gene encoding thiopurine methyltransferase to reduce the hematopoietic toxicity and the risk of secondary cancer.21-23 Study 14 (1998-1999) attempted to find optimal doses of methotrexate for various subtypes of ALL.15 Study 15 tested whether prophylactic cranial irradiation could be safely omitted in all children with newly diagnosed ALL, and its encouraging results have recently been published.17 In this report, we update the results of Studies 11 to 14.

Materials and methods

From 1984 to 1999, 1011 consecutive patients aged 18 years or younger with newly diagnosed ALL were enrolled in five successive treatment protocols (Total Therapy Studies 11, 12, 13A, 13B and 14) at St. Jude Children’s Research Hospital.3,6,7,14,15 Patients were not eligible for the studies if they had received more than 1 week of prior therapy or any treatment other than glucocorticoids, vincristine or emergency mediastinal irradiation. The diagnosis of ALL was based on immunophenotyping with panels of monoclonal antibodies directed toward lineage-associated antigens. Cytogenetic and molecular genetic studies and DNA index determination were performed with methods described previously.14 All protocols were approved by Institutional Review Board; Studies 11, 12 and 13B were also reviewed and approved by the National Cancer Institute. Written informed consent and assent were obtained from all parents and/or patients as appropriate.
Treatment

Details of Total Therapy Studies have been described in earlier publications.3,6,7,14,15 In Study 11, 3 patients received 6-week remission induction with prednisone, vincristine, daunorubicin, asparaginase, teniposide and cytarabine, followed by consolidation therapy with 2 weekly doses of high-dose methotrexate at 2 g/m². At the completion of consolidation therapy, lower-risk patients were stratified and randomized to receive antimitabolite-based therapy or four pairs of drugs (etoposide plus cyclophosphamide, mercaptopurine plus methotrexate, teniposide plus cytarabine, and prednisone plus vincristine) rotated weekly for 120 weeks, whereas higher-risk patients were stratified and randomized to receive the same four pairs of drugs in rotation weekly or every 6 weeks for 120 weeks. Triple intrathecal therapy was given on days 2, 22 and 43 of remission induction (additional doses on days 8 and 15 for patients with CNS leukemia [CNS 3] at diagnosis), and then every 8 weeks during the first year of continuation therapy. Cranial irradiation and five intrathecal treatments were added for 64% of the patients with higher-risk leukemia (18 Gy) or CNS leukemia at diagnosis (24 Gy). Overall, lower-risk cases received 9 doses of triple intrathecal therapy and higher-risk cases 13 to 15 doses.

In Study 12, 6 patients received remission induction therapy identical to that in Study 11. Upon attaining complete remission, patients were stratified (by age, leukocyte count, age and DNA index) and randomized to receive either conventional doses (based on body surface area) or individualized doses (targeted to achieve an area under the plasma concentration-versus-time curve between the 50th and 90th percentiles of that in the conventional arm) of high-dose methotrexate, and teniposide plus cytarabine, given as alternating pulses for 5 courses each during the first year of 120 weeks of continuation therapy with mercaptopurine and methotrexate. Intrathecal therapy during remission induction was identical to that in Study 11, and was then given on day 1 of each of the 10 courses of pulse therapy. Cranial irradiation plus 5 intrathecal treatments were given to 37% of the patients with high-risk leukemia (18 Gy) or CNS leukemia at diagnosis (24 Gy) during weeks 59 to 61 of continuation therapy. The number of intrathecal therapy ranged from 13 to 20 doses in this study. In addition, three of the six patients with Philadelphia chromosome-positive leukemia underwent allogeneic hematopoietic stem cell transplantation.

In Study 13A, 7 patients were stratified and randomized to receive high-dose (1 g/m²) or lower-dose (30 mg/m² every 6 hours for 4 doses) methotrexate up-front, followed by 6 weeks of remission induction therapy similar to that used in the preceding two trials (except that etoposide was substituted for teniposide). All patients received 2 weeks of consolidation therapy with 2 weekly doses of high-dose methotrexate (2 g/m²) and daily mercaptopurine. Continuation therapy was risk-directed. Lower-risk patients received antimitabolite-based therapy for 120 weeks with pulses of high-dose methotrexate every 8 weeks (for the first year) and prednisone plus vincristine pulse every 4 weeks. Higher-risk cases received weekly rotation continuation therapy similar to that in Study 11, with the addition of asparaginase, high-dose methotrexate, and a reinduction phase during the first year. Recognizing the increased risk of CNS relapse in patients with CNS 2, CNS 3, or traumatic lumbar puncture with blasts had led to intensified intrathecal therapy in these patients as
well as some CNS 1 cases with other high-risk features. These patients received 2 additional weekly doses of intrathecal therapy during remission induction and then every 4 weeks during the first year of continuation therapy. Cranial irradiation plus 5 intrathecal treatments were given to 22% of the patients with CNS 3 status (24 Gy) or high-risk leukemia (18 Gy). The number of intrathecal therapy doses administered was 15 for lower-risk cases and ranged from 22 to 26 for higher-risk cases. Only one of the 6 patients with Philadelphia chromosome-positive leukemia underwent transplantation.

After 2 days of treatment with mercaptopurine alone or mercaptopurine plus high-dose or lower-dose methotrexate, patients in Study 13B received the same 6-week remission induction and 2 weeks of consolidation as those in Study 13A. Lower-risk cases received mercaptopurine and methotrexate continuation therapy, reinforced by high-dose methotrexate every 8 weeks for the first year, dexamethasone plus vincristine pulse every 4 weeks, and reinduction therapy during weeks 16 to 21 after remission induction. Post-remission therapy for higher-risk cases was similar to that in Study 13A with some modifications (dexamethasone was substituted for prednisone, and asparaginase was used only during reinduction and omitted during continuation therapy). CNS-directed therapy was similar to that in Study 13A except that cranial irradiation plus 5 intrathecal treatments were given to only 12% of patients who have T-cell ALL and initial leukocyte count over 100 × 10⁹/L (18 Gy), or CNS 3 status (24 Gy). The total number of intrathecal treatments ranged from 13 in lower-risk cases to 26 in high-risk cases who received cranial irradiation. Eleven patients were transplanted: 4 each for Philadelphia chromosome-positive or t(4;11) ALL and 3 for other conditions.

In Study 14, upfront methotrexate at various doses was given before remission induction treatment identical to that of Study 13B. Consolidation therapy consisted of 2 weekly doses of high-dose methotrexate (5 g/m² for higher-risk and 2.5 g/m² for lower-risk cases) together with daily mercaptopurine and triple intrathecal therapy. Post-remission therapy was similar to that in Study 13B with some modifications (high-dose methotrexate was given at 5 g/m² for higher-risk cases and 2.5 g/m² for lower-risk cases; polyethylene glycol-conjugated asparaginase was given at days 1, 8 and 15 and idarubicin was given at days 1 and 8 of reinduction treatment together with weekly vincristine and dexamethasone). The total number of triple intrathecal treatments ranged from 16 in lower-risk cases to 23 in higher-risk cases with CNS 2, CNS 3, or traumatic lumbar puncture with blasts status at diagnosis. None of the patients received prophylactic cranial irradiation, regardless of CNS status or other features at diagnosis. Two patients with poor early response were transplanted: one infant with t(4;11) ALL and the other with Philadelphia chromosome-positive ALL.

### Statistical analysis

The duration of event-free survival was defined as the time from diagnosis until the date of failure (induction failure, relapse, death, or the development of a second malignancy) or until the date of last contact for all event-free survivors. Patients who did not attain a complete remission were considered failures at time zero. Event-free survival and overall survival rates were estimated by the method of Kaplan Meier and were compared with the
Mantel-Haenszel test. The Cox proportional hazards model was used to identify independent prognostic factors with respect to event-free survival and overall survival. All analyses were performed on the basis of “intent-to-treat.”

For patients who achieved complete remission, cumulative incidence functions of isolated CNS or any (isolated plus combined) CNS relapse, as well as testicular relapse, therapy-related second malignancy, and death from toxicity, were estimated by the method of Kalbfleisch and Prentice, and the functions were compared with Gray’s test, adjusting for competing events. An isolated CNS relapse was defined as one without simultaneous relapse at another site, while a combined CNS relapse was one in the CNS accompanied by relapse in the bone marrow or any other extramedullary site. The database last updated on January 23, 2009, was used for analyses.

The routine follow-up procedures for long-term survivors at our institution have been described previously. Briefly, after completion of therapy, remission status and late effects are comprehensively assessed at least annually. Patients who are at least 18 years old and remain in remission for at least 10 years after diagnosis are discharged from the institution and followed thereafter by the community physicians. The status of these patients is monitored by a questionnaire mailed annually by the institution’s tumor registry. No patients have been lost to follow-up during treatment. When the databases were frozen for analyses, 79%, 80%, 90%, 91% and 98% of event-free survivors in studies 11, 12, 13A, 13B and 14, respectively, had been seen within 12 months, and 8%, 8%, 2.6%, 2.6% and 2.4% had not been seen or contacted for more than 5 years.

**Results**

The event-free survival improved significantly from the clinical trials conducted in the 1980s (Studies 11 and 12) to those in the 1990s (Studies 13A, 13B and 14) (p=0.003, Table 1). However, the overall survival was similar between the studies (p=0.32), with the exception of Study 13B which had a better result. Late failures occurring beyond 10 years from diagnosis were uncommon (<2%).

**Protocol-specific treatment outcome**

**Study 11**—Event-free survival at 15 years for the 358 evaluable patients was 68.4±2.5%, and overall survival was 75.7±2.3% (Fig. 1). Median follow-up was 21.6 years (range, 9.5 to 24.4 years) for the 268 survivors (243 free of adverse events). The cumulative risk estimates for isolated CNS and any CNS relapses at 15 years were 6.1±1.3% and 7.6±1.4% , respectively. Of the 186 male patients, three developed testicular relapse (isolated in one patient, combined with hematologic relapse in another, and combined with hematologic and CNS relapse in the third) with a cumulative incidence of 1.7±1.0% at 10 years. The type of post-remission continuation therapy had no impact on the complete remission duration for either the lower-risk or higher-risk group (Fig. 2).

Secondary neoplasms included acute myeloid leukemia (AML) in 10 patients, brain tumor in 2, and Ewing sarcoma, carcinoma, and basal cell carcinoma in the three remaining patients. The cumulative risk of any secondary neoplasms was 3.2±1.0% at 10 years and 3.8±1.0% at
15 years; that of secondary myeloid malignancies plateaued at 2.9±0.9% at 10 years. None of the patients in the lower-risk group developed secondary AML. In the higher-risk group, patients treated with drug pairs rotated every 6 weeks had a significantly higher rate of secondary AML than those who received the same drug pairs rotated weekly (p=0.03; 8.2±3.0% vs. 2.0±1.2%).

**Study 12**—Event-free survival and overall survival estimates at 15 years for the 188 evaluable patients were 59.5±3.9% and 77.6±3.3%, respectively, (Fig. 3). Of the 146 survivors (112 free of adverse events), the median follow-up duration was 17.4 years (range, 8.4 to 19.8 years). Compared to other Total Therapy Studies, Study 12 had the highest rates of CNS relapse: 10.4±2.3% for isolated CNS relapse and 14.8±2.6% for any CNS relapse at 15 years (p<0.001). It also had the highest rate of any testicular relapse (isolated in 2 boys and combined with hematologic relapse in 3 others) with a cumulative risk of 5.1±2.2% at 10 years. Individualized doses of high-dose methotrexate tended to improve event-free survival in patients with B-lineage ALL (p=0.08) but not in those with T-lineage ALL (p=0.91, Fig. 4). Overall survival estimates did not differ between patients treated with individualized or conventional therapy for both B-lineage ALL (p=0.86; 79.3±5.1% vs. 80.5±4.7% at 15 years) and T-lineage ALL (p=0.28; 69.2±13.6% vs. 85.7±9.8% at 15 years).

Secondary neoplasms included 10 cases of brain tumor, 3 AML, and 2 myelodysplastic syndrome, with a cumulative risk of 8.3±2.1% at 15 years. Notably, this study had the highest rate of secondary brain tumor: 5.5±1.7% at 15 years. Not surprisingly, all brain tumors developed among the 71 patients who had received cranial irradiation, resulting in a cumulative risk of 14.1±4.2% at 15 years; none of the 113 non-irradiated patients had this complication (p<0.0001). The risk was especially high among the 7 irradiated patients with thiopurine methyltransferase deficiency: 42.9±20.6%.

**Study 13A**—Among 165 evaluable patients, the event-free survival was 70.2±5.8% and overall survival 76.9±5.2% at 15 years (Fig. 5). The median follow-up duration of the 127 survivors (116 free of events) was 14.6 years (range, 7.4 to 17.0 years). Isolated and any CNS relapse rates were only 1.2±0.9% and 4.9±1.7% at 15 years. Only 1 of 92 boys developed a combined testicular and hematologic relapse (cumulative risk, 1.1±1.1% at 10 years).

Secondary leukemias (10 AML, 2 ALL and 1 myelodysplastic syndrome) occurred in 13 patients, brain tumors in 2 and osteosarcoma in 1. The cumulative risk of any second neoplasm was 9.9±2.4% at 10 years and 15 years. The cumulative risk of secondary myeloid malignancy was 6.8±2.0% at 10 years, the highest rate among all Total Therapy Studies.

**Study 13B**—Event-free survival at 10 years for the 247 evaluable patients was 77.6±2.9%, and overall survival was 83.7±2.5% (Fig. 6). Median follow-up was 11.4 years (range, 2.4 to 14.2 years) for the 206 survivors (191 event-free). The cumulative risk of isolated CNS relapse at 10 years was only 1.7±0.8% and that of any CNS relapse was 3.3±1.2%. Of the 144 boys, only one developed an isolated testicular relapse (cumulative risk at 10 years, 0.7±0.7%).

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Eight patients have developed secondary myeloid malignancies (4 AML, 3 myelodysplastic syndrome and 1 chronic myeloid leukemia) with a cumulative risk of 3.3±1.2% at 10 years. To date, none of the patients has developed other types of second neoplasms.

**Study 14**—Because of excessive toxicities encountered during remission induction, the protocol was terminated early, after enrolling 53 patients. Event-free survival was 77.4±5.7% at 5 years and 77.4±16.5% at 10 years; the overall survival was 81.1±5.3% and 79.2±16.1%, respectively (Fig. 7). Two patients developed a combined CNS and hematologic relapse (cumulative risk, 4.0±2.8% at 10 years). To date, none of the patients has developed an isolated CNS relapse, any testicular relapse, or a secondary neoplasm.

**Treatment results according to presenting features**

Prognostic factors were analyzed for all studies except Study 14 because of its limited enrollment. High-risk B-lineage according to the NCI/Rome criteria (age <1 or >10 years with leukocyte count >50×10^9/L) and T-cell phenotype were consistently adverse prognostic factors, whereas DNA index ≥1.16 was a favorable factor for event-free survival in all 4 studies analyzed (Tables 2 to 5). Initial leukocyte count and Philadelphia chromosome had prognostic significance in most studies, and age was consistently associated with overall survival in the 4 studies. The use of intensified intrathecal treatment in Studies 13A and 13B abolished the adverse prognostic significance of CNS 2 and of traumatic lumbar puncture with blasts observed in previous studies. With the improvement in event-free survival for B-lineage cases in Studies 13A and 13B, the favorable prognostic impact of ETV6-RUNX1 (also known as TEL-AML1) fusion was less noticeable. Notably, systematic minimal residual disease measurement was initiated in Study 13B, and this factor had independent prognostic impact for both event-free survival and overall survival.

Independent risk factors for isolated CNS relapse in Study 11 were high leukocyte counts, the presence of Philadelphia chromosome and the presence of blasts in cerebrospinal fluid (non-CNS1 status); in Study 12, non-CNS1 status was the only factor. There were too few events in Studies 13A and 13B for analysis.

**Discussion**

Our single-institution experience reported here shows that risk-directed therapy cured approximately 75% of children with ALL in the 1980s and up to 80% in the 1990s. The rarity of late relapses observed in this analysis supports our previous working definition of cure of childhood ALL, i.e., 10 or more years of event-free survival.27 With advances in therapy, testicular and other extramedullary relapse outside of CNS has become very rare. However, CNS control remains a therapeutic challenge. The cumulative risk of any CNS relapse was 7.6% in Study 11 and 14.8% in Study 12. The high rate of CNS relapse in Study 12 can be attributed not only to inadequate intrathecal therapy during remission induction and early postremission therapy, but also to the relatively low intensity of systemic therapy (e.g., lack of consolidation and reinduction therapy as well as a lack of glucocorticoid pulses). Study 12 yielded a reasonably good long-term survival rate owing, at least in part, to the high retrieval rate of CNS relapse. However, patients who received salvage therapy
including cranial or craniospinal irradiation for CNS relapse would have been more prone to late treatment-related sequelae than those remaining in first remission.

Starting from Study 13A, early intensive intrathecal therapy has been administered to patients at high risk of CNS relapse, including those with any amount of blasts in cerebrospinal fluid at diagnosis (even from traumatic lumbar puncture).29-31 and reinduction treatment has become an integral component of therapy. With these treatment modifications, and in spite of reductions in cranial irradiation, 10-year rates of isolated and any CNS relapse have decreased to 1.2% and 4.9% in Study 13A, and to 1.7% and 3.3% in Study 13B. In turn, this has boosted 10-year event-free survival to 71.5% and 77.6%, respectively. Because of the improvements in CNS control and the high salvage rate of CNS relapse, together with the risk of devastating radiation-associated late effects (second cancers in particular)27,32 we decided to omit the use of prophylactic CNS irradiation in all patients. Instead, we have relied on effective intrathecal and systemic therapy (such as high-dose methotrexate, intensive asparaginase, dexamethasone) for CNS control since 1998, beginning with Study 14. More recently, special precautions have also been taken to decrease the rate of traumatic lumbar puncture.33 The results of Studies 14 and 15 showed that with effective risk-adjusted chemotherapy, prophylactic cranial irradiation can be safely omitted in all patients because CNS relapse rate remained low and those who developed isolated CNS relapse have a very high salvage rate. For patients who are at risk of CNS relapse with contemporary therapy including those with any CNS involvement, T-cell immunophenotype and t(1;19)[TCF3-PBX1],17,34 we further intensify early intrathecal treatment in our current clinical trial (Study 16).

The development of secondary neoplasm was one of the major causes of treatment failure in our clinical trials with a 10-year cumulative risk ranging from 3.2% to 9.9%, albeit none occurred in Study 14 thus far. Because the latency period of radiation-induced second neoplasm is generally over 10 years,27,32 we expect that this could occur in additional patients, especially among those enrolled in Studies 11 and 12, where two thirds and one third of the patients received CNS irradiation, respectively. We identified several risk factors that potentiate the development of second malignancy. Weekly administration of etoposide or teniposide for an extended period increased the risk of secondary AML.5 Concomitant intensive antimetabolite and asparaginase treatment, as well as the use of granulocyte colony-stimulating factor therapy, can potentiate the risk of epipodophyllotoxin-induced secondary AML.35-37 Intensive use of antimetabolites prior to and during cranial radiation can increase the risk of radiation-related brain tumor, especially among patients with thiopurine methyltransferase deficiency.21 In this regard, patients with a deficiency in this enzyme have a higher risk of developing second cancer than those with wild type activity.38 In our recently Study 15 (2000-2007), we prospectively analyzed genetic polymorphism and activity of this enzyme, decreasing the starting dose of mercaptopurine to 60 mg/m² in patients with heterozygous deficiency; limited the use of epipodophyllotoxins only in those who will undergo allogeneic transplantation for very high-risk ALL; and totally omitted the use of prophylactic cranial irradiation.17 With a median follow-up time of 4.0 years (range, 1.2 to 8.4), the 5-year survival rate for the 498 evaluable patients was 93.5% (95%
confidence interval, 89.8 to 97.2), and thus far only one patient developed a myelodysplastic syndrome.

Given the overriding prognostic impact of treatment,39,40 it is not surprising that there are only a few presenting features consistently predictive of outcome: age, leukocyte count, T-lineage and DNA index for event-free survival, and only age for overall survival. In contrast to the results in collaborative study groups, race has no prognostic significance in our studies, a result that we attribute to the access to effective treatment offered at our institution irrespective of the patients’ insurance status.41 Minimal residual disease measurement is one of the most important predictors of treatment outcome because it accounts for leukemic genetic abnormality, host pharmacogenetics and pharmacodynamics, and treatment compliance.17,42-49 We have been using this measure for risk-directed therapy not only to improve cure rates but also in efforts to avert excessive toxicities. The recent application of genome-wide microarray and high-throughput sequencing methodologies has identified new high-risk subgroups, such as early T-cell precursor leukemia50 and B-cell precursor ALL with genetic alteration of IKZF1,51-53 a gene that encodes the lymphoid transcription factor IKAROS. These patients typically also have high levels of minimal residual disease at the end of remission induction. For these high-risk patients, innovative treatment strategies are needed to improve their outcome.54,55 Finally, while the acquired genetic abnormalities of leukemic cells play a critical role in drug responsiveness, it is also important to study inherited genetic variations which are associated not only with host drug disposition but also with leukemic cell biology.56

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Fig. 1.
Event-free survival (EFS), survival and cumulative incidence of isolated or any CNS relapse in Total Therapy Study 11.
Fig. 2.
Duration of continuous complete remission according to postremission therapy in patients with low-risk or higher-risk ALL in Total Therapy Study 11.
Fig. 3.
Event-free survival (EFS), survival and cumulative incidence of isolated or any CNS relapse in Total Therapy Study 12.
Fig. 4.
Duration of continuous complete remission according to postremission therapy for B-lineage and T-lineage cases, respectively.
Fig. 5.
Event-free survival (EFS), survival and cumulative incidence of isolated or any CNS relapse in Total Therapy Study 13A.
Fig. 6.
Event-free survival (EFS), survival and cumulative incidence of isolated or any CNS relapse in Total Therapy Study 13B.
Fig. 7.
Event-free survival (EFS), survival and cumulative incidence of isolated or any CNS relapse in Total Therapy Study 14.
### Table 1

**Treatment Outcome According to Total Therapy Studies**

| Total Therapy Studies | Total 11 | Total 12 | Total 13A | Total 13B | Total 14 |
|-----------------------|---------|---------|----------|----------|---------|
| **Year**              | 1984-1988 | 1988-1991 | 1991-1994 | 1994-1998 | 1998-1999 |
| **No. of Patients**   | 358     | 188     | 165      | 247      | 53      |
| **Induction failure (toxic death)** | 15 (8) | 6 (3) | 3 (3) | 5 (3) | 3 (2) |

**Relapses**

|                    | Total 11 | Total 12 | Total 13A | Total 13B | Total 14 |
|--------------------|---------|---------|----------|----------|---------|
| **Hematological only** | 48      | 19      | 17       | 24$^f$   | 4       |
| **CNS only**        | 21      | 19      | 2        | 7$^f$    | 0       |
| **Hematological + CNS** | 4       | 8       | 6        | 2        | 2       |
| **Testicular only**  | 1       | 2       | 0        | 1        | 0       |
| **Hematological + Testicular** | 1     | 3       | 1        | 0        | 0       |
| **Hematological + CNS + Testicular** | 1  | 0       | 0        | 0        | 0       |
| **Other relapses sites** | 2       | 1       | 0        | 1        | 1       |

**Second Cancer**

|                   | Total 11 | Total 12 | Total 13A | Total 13B | Total 14 |
|-------------------|---------|---------|----------|----------|---------|
| 15                 | 15      | 16      | 8        | 0        |

**Infectious death in remission**

|                   | Total 11 | Total 12 | Total 13A | Total 13B | Total 14 |
|-------------------|---------|---------|----------|----------|---------|
| 4                 | 2       | 1       | 4        | 1        |

**Other causes of remission deaths**$^g$

|                   | Total 11 | Total 12 | Total 13A | Total 13B | Total 14 |
|-------------------|---------|---------|----------|----------|---------|
| 3                 | 1       | 3       | 4        | 1        |

**10-year cumulative risk of death in remission (%)**

|                   | Total 11 | Total 12 | Total 13A | Total 13B | Total 14 |
|-------------------|---------|---------|----------|----------|---------|
| 1.7±0.7            | 1.6±0.9 | 1.9±1.1 | 3.3±1.2  | 4.0±2.8  |

**10-year event-free survival ± SE (%)**

|                   | Total 11 | Total 12 | Total 13A | Total 13B | Total 14 |
|-------------------|---------|---------|----------|----------|---------|
| 69.6±2.4          | 61.2±3.6 | 71.5±3.5 | 77.6±2.9 | 77.4±16.5 |

**10-year overall survival ± SE (%)**

|                   | Total 11 | Total 12 | Total 13A | Total 13B | Total 14 |
|-------------------|---------|---------|----------|----------|---------|
| 76.5±2.2          | 78.7±3.0 | 78.2±3.2 | 83.7±2.5 | 79.2±16.1 |

$^f$ Hematological relapse was associated with mediastinal relapse in one case.

$^g$ CNS relapse was associated with mediastinal relapse in one case and with ocular relapse in another case.

$^g$ One case involved the kidney and one the lymph nodes in Study 11; one involved the mediastinum in Study 12; one bilateral eyes in Study 13B; and one in the orbit in Study 14.

$^g$ One died of suicide, one of an accident, and one of a neurologic event in Study 11; one died of an accident in Study 12; two died of accidents and one of suicide in Study 13A; two died of graft-versus-host diseases, 1 of an accident and one of liver failure associated with cystic fibrosis in Study 13B; and one patient died of graft-versus-host disease in Study 14.
## Table 2

Treatment results according to presenting features in patients treated in Study 11

| Factors     | No. of patients | Event-free survival ± SE (%) | Overall survival ± SE (%) |
|-------------|-----------------|------------------------------|----------------------------|
|             |                 | Year 5       | Year 10      | Year 15      | p-value | Year 5       | Year 10      | Year 15      | p-value |
| B-lineage   |                 |              |              |              |         |              |              |              |         |
| NCI Standard| 183             | 85.2 ± 2.6   | 82.0 ± 2.8   | 81.4 ± 2.9   | <.0001  | 89.1 ± 2.3   | 86.9 ± 2.5   | 85.8 ± 2.6   | 0.0001 |
| NCI High    | 113             | 62.8 ± 4.5   | 61.1 ± 4.6   | 60.2 ± 4.7   | 73.5 ± 4.1 | 69.9 ± 4.3   | 69.0 ± 4.5   |             |         |
| T-lineage   |                 |              |              |              |         |              |              |              |         |
| NCI Standard| 10              | 40.0 ± 13.9  | 40.0 ± 15.5  | 40.0 ± 15.5  | 0.69    | 40.0 ± 13.9  | 40.0 ± 15.5  | 40.0 ± 15.5  | 0.21   |
| NCI High    | 52              | 51.9 ± 6.8   | 50.0 ± 6.8   | 46.0 ± 6.9   | 63.5 ± 6.6 | 61.5 ± 6.6   | 61.5 ± 6.9   |             |         |
| Sex         |                 |              |              |              |         |              |              |              |         |
| Male        | 186             | 68.3 ± 3.4   | 64.5 ± 3.5   | 63.4 ± 3.6   | 0.06    | 74.7 ± 3.2   | 71.5 ± 3.3   | 70.4 ± 3.4   | 0.03   |
| Female      | 172             | 76.2 ± 3.2   | 75.0 ± 3.3   | 73.8 ± 3.4   | 83.7 ± 2.8 | 82.0 ± 2.9   | 81.4 ± 3.0   |             |         |
| Age at diagnosis (yrs.) | | | | | | | | | |
| <1          | 11              | 45.5 ± 13.7  | 45.5 ± 13.7  | 36.4 ± 13.0  | 0.0007  | 63.6 ± 13.6  | 63.6 ± 13.6  | 63.6 ± 13.6  | 0.006  |
| 1-9         | 257             | 76.3 ± 2.6   | 73.5 ± 2.8   | 72.7 ± 2.8   | (0.01)* | 82.5 ± 2.4   | 80.2 ± 2.5   | 79.4 ± 2.6   |         |
| >10         | 90              | 63.3 ± 5.0   | 61.1 ± 5.1   | 60.0 ± 5.3   | 71.1 ± 4.7 | 67.8 ± 4.9   | 66.6 ± 5.1   |             |         |
| Race        |                 |              |              |              |         |              |              |              |         |
| White       | 314             | 72.9 ± 2.5   | 70.4 ± 2.6   | 69.4 ± 2.6   | 0.26    | 79.9 ± 2.3   | 77.7 ± 2.4   | 76.7 ± 2.4   | 0.20   |
| Black       | 43              | 65.1 ± 7.1   | 62.8 ± 7.2   | 60.4 ± 7.5   | 72.1 ± 6.7 | 67.4 ± 7.0   | 67.4 ± 7.3   |             |         |
| Other       | 1               | 100 ± 0.0    | 100 ± 0.0    | 100 ± 0.0    | 100 ± 0.0 | 100 ± 0.0    | 100 ± 0.0    |             |         |
| WBC×10^9/L  |                 |              |              |              |         |              |              |              |         |
| <10         | 154             | 80.5 ± 3.2   | 78.6 ± 3.3   | 77.9 ± 3.4   | <.0001  | 84.4 ± 2.9   | 83.1 ± 3.0   | 82.5 ± 3.1   | 0.0001 |
| 10-49       | 109             | 76.1 ± 4.1   | 72.5 ± 4.3   | 71.5 ± 4.3   | 81.7 ± 3.7 | 78.0 ± 3.9   | 76.1 ± 4.1   |             |         |
| 50-99       | 30              | 66.7 ± 8.4   | 63.3 ± 8.6   | 63.3 ± 8.8   | 83.3 ± 6.7 | 76.7 ± 7.6   | 76.7 ± 7.7   |             |         |
| >100        | 65              | 47.7 ± 6.1   | 46.2 ± 6.1   | 42.9 ± 6.2   | 60.0 ± 6.0 | 58.5 ± 6.0   | 58.5 ± 6.4   |             |         |
| Cell lineage|                 |              |              |              |         |              |              |              |         |
| Factors          | No. of patients | Event-free survival ± SE (%) | Overall survival ± SE (%) |
|------------------|-----------------|-------------------------------|---------------------------|
|                  | Year 5          | Year 10                       | Year 15                    | Year 5          | Year 10                       | Year 15                    | p-value | Year 5          | Year 10                       | Year 15                    | p-value |
| B                | 296             | 76.7 ± 2.5                    | 74.0 ± 2.5                 | 73.3 ± 2.6               | <.0001          | 83.1 ± 2.2                    | 80.4 ± 2.3                 | 79.4 ± 2.4 | <.0001          | 83.1 ± 2.2                    | 80.4 ± 2.3                 | 79.4 ± 2.4 | <.0001          |
| T                | 62              | 50.0 ± 6.3                    | 48.4 ± 6.4                 | 44.9 ± 6.4               | (0.04)          | 59.7 ± 6.1                    | 58.1 ± 6.3                 | 58.1 ± 6.4 | (0.03)          | 59.7 ± 6.1                    | 58.1 ± 6.3                 | 58.1 ± 6.4 | (0.03)          |
| CNS status       |                 |                               |                             |                          |                 |                               |                           |           |                 |                             |                          |           |                 |
| CNS 1            | 260             | 78.8 ± 2.5                    | 76.2 ± 2.6                 | 75.0 ± 2.8               | <.0001          | 83.8 ± 2.3                    | 81.5 ± 2.4                 | 80.3 ± 2.5 | 0.007           | 83.8 ± 2.3                    | 81.5 ± 2.4                 | 80.3 ± 2.5 | 0.007           |
| CNS 2            | 48              | 56.2 ± 7.0                    | 56.2 ± 7.0                 | 54.2 ± 7.1               | (0.03)          | 68.7 ± 6.6                    | 64.6 ± 6.8                 | 64.6 ± 6.8 |                 | 68.7 ± 6.6                    | 64.6 ± 6.8                 | 64.6 ± 6.8 |                 |
| CNS 3            | 14              | 35.7 ± 11.7                   | 35.7 ± 11.7                | 35.7 ± 11.7              |                 | 64.3 ± 12.1                   | 64.3 ± 12.1                | 64.3 ± 12.8 |                 | 64.3 ± 12.1                   | 64.3 ± 12.1                | 64.3 ± 12.8 |                 |
| Traumatic with blasts | 36        | 58.3 ± 8.0                    | 52.8 ± 8.1                 | 52.8 ± 8.1               |                 | 63.9 ± 7.8                    | 61.1 ± 7.9                 | 61.1 ± 7.9 |                 | 63.9 ± 7.8                    | 61.1 ± 7.9                 | 61.1 ± 7.9 |                 |
| DNA index        |                 |                               |                             |                          |                 |                               |                           |           |                 |                             |                          |           |                 |
| 1.16-1.60        | 66              | 87.9 ± 4.0                    | 84.8 ± 4.4                 | 84.8 ± 4.5               | 0.007           | 89.4 ± 3.8                    | 84.8 ± 4.4                 | 84.8 ± 4.5 | 0.03            | 89.4 ± 3.8                    | 84.8 ± 4.4                 | 84.8 ± 4.5 | 0.03            |
| Other            | 292             | 68.5 ± 2.7                    | 66.1 ± 2.8                 | 64.7 ± 2.8               |                 | 76.7 ± 2.5                    | 74.7 ± 2.5                 | 73.6 ± 2.6 |                 | 76.7 ± 2.5                    | 74.7 ± 2.5                 | 73.6 ± 2.6 |                 |
| t(9;22)          |                 |                               |                             |                          |                 |                               |                           |           |                 |                             |                          |           |                 |
| Present          | 12              | 41.7 ± 13.0                   | 41.7 ± 13.0                | 41.7 ± 13.0              | 0.01            | 41.7 ± 13.0                   | 41.7 ± 13.0                | 41.7 ± 13.0 | 0.002           | 41.7 ± 13.0                   | 41.7 ± 13.0                | 41.7 ± 13.0 | 0.002           |
| Absent           | 346             | 73.1 ± 2.4                    | 70.5 ± 2.5                 | 69.3 ± 2.5               | (0.01)          | 80.3 ± 2.1                    | 77.7 ± 2.2                 | 76.9 ± 2.3 | (0.002)         | 80.3 ± 2.1                    | 77.7 ± 2.2                 | 76.9 ± 2.3 | (0.002)         |
| t(1;19)          |                 |                               |                             |                          |                 |                               |                           |           |                 |                             |                          |           |                 |
| Present          | 13              | 69.2 ± 12.1                   | 69.2 ± 12.1                | 69.2 ± 12.1              | 0.95            | 76.9 ± 11.1                   | 69.2 ± 12.1                | 69.2 ± 12.1 | 0.59            | 76.9 ± 11.1                   | 69.2 ± 12.1                | 69.2 ± 12.1 | 0.59            |
| Absent           | 345             | 72.2 ± 2.4                    | 69.6 ± 2.5                 | 68.4 ± 2.6               |                 | 79.1 ± 2.2                    | 76.8 ± 2.3                 | 75.9 ± 2.4 |                 | 79.1 ± 2.2                    | 76.8 ± 2.3                 | 75.9 ± 2.4 |                 |
| ETV6-RUNX1       |                 |                               |                             |                          |                 |                               |                           |           |                 |                             |                          |           |                 |
| Present          | 14              | 100 ± 0.0                     | 92.9 ± 6.6                 | 92.9 ± 6.9               | 0.05            | 100 ± 0.0                     | 100 ± 0.0                  | 100 ± 0.0 | 0.04            | 100 ± 0.0                     | 100 ± 0.0                  | 100 ± 0.0 | 0.04            |
| Absent           | 344             | 70.9 ± 2.4                    | 68.6 ± 2.5                 | 67.4 ± 2.6               |                 | 78.2 ± 2.2                    | 75.6 ± 2.3                 | 74.7 ± 2.4 |                 | 78.2 ± 2.2                    | 75.6 ± 2.3                 | 74.7 ± 2.4 |                 |
| t(4;11)          |                 |                               |                             |                          |                 |                               |                           |           |                 |                             |                          |           |                 |
| Present          | 3               | 33.3 ± 19.2                   | 33.3 ± 19.2                | 33.3 ± 19.2              | 0.23            | 66.7 ± 22.2                   | 33.3 ± 19.2                | 33.3 ± 19.2 | 0.10            | 66.7 ± 22.2                   | 33.3 ± 19.2                | 33.3 ± 19.2 | 0.10            |
| Absent           | 355             | 72.4 ± 2.4                    | 69.9 ± 2.4                 | 68.7 ± 2.5               |                 | 79.2 ± 2.2                    | 76.9 ± 2.2                 | 76.0 ± 2.3 |                 | 79.2 ± 2.2                    | 76.9 ± 2.2                 | 76.0 ± 2.3 |                 |

* Significant difference in multivariate analysis
## Table 3

Treatment results according to presenting features in patients treated in Study 12

| Factors           | No. of patients | Event-free survival ± SE (%) | Overall survival ± SE (%) |
|------------------|-----------------|------------------------------|---------------------------|
|                  |                 | Year 5 | Year 10 | Year 15 | p-value | Year 5 | Year 10 | Year 15 | p-value |
| **B-lineage**    |                 |        |         |         |          |        |         |         |          |
| NCI Standard     | 99              | 78.8 ± 4.1 | 71.7 ± 4.5 | 70.7 ± 4.9 | 0.002 | 89.9 ± 3.0 | 84.8 ± 3.6 | 82.7 ± 4.1 | 0.06 |
| NCI High         | 60              | 56.7 ± 6.3 | 51.7 ± 6.5 | 48.2 ± 7.1 | 0.51  | 75.0 ± 5.5 | 71.6 ± 5.8 | 71.6 ± 6.4 | 0.06 |
| **T-lineage**    |                 |        |         |         |          |        |         |         |          |
| NCI Standard     | 5               | 60.0 ± 19.0 | 60.0 ± 19.0 | 60.0 ± 19.0 | 0.51  | 80.0 ± 16.0 | 80.0 ± 16.0 | 80.0 ± 17.9 | 0.68 |
| NCI High         | 24              | 50.0 ± 9.8 | 41.7 ± 9.6 | 41.7 ± 10.6 | 0.13  | 79.2 ± 8.1 | 70.8 ± 9.0 | 70.8 ± 9.9 | 0.61 |
| **Sex**          |                 |        |         |         |          |        |         |         |          |
| Male             | 102             | 62.7 ± 4.8 | 55.9 ± 4.9 | 54.9 ± 5.4 | 0.001 | 81.4 ± 3.8 | 77.5 ± 4.1 | 76.3 ± 4.6 | 0.61 |
| Female           | 86              | 73.3 ± 4.7 | 67.4 ± 5.0 | 65.0 ± 5.5 | 0.001 | 86.0 ± 3.7 | 80.2 ± 4.3 | 79.0 ± 4.7 | 0.61 |
| **Age at diagnosis (yrs.)** |             |        |         |         |          |        |         |         |          |
| <1               | 8               | 25.0 ± 12.5 | 25.0 ± 12.5 | 25.0 ± 12.5 | 0.005 | 50.0 ± 15.8 | 50.0 ± 15.8 | 50.0 ± 17.7 | 0.002 |
| 1-9              | 128             | 75.0 ± 3.8 | 68.8 ± 4.1 | 66.4 ± 4.5 | 0.001 | 89.8 ± 2.7 | 85.2 ± 3.1 | 83.5 ± 3.5 | 0.003 |
| >10              | 52              | 55.8 ± 6.8 | 48.0 ± 6.9 | 48.0 ± 7.6 | 0.001 | 73.1 ± 6.1 | 67.2 ± 6.5 | 67.2 ± 7.1 | 0.003 |
| **Race**         |                 |        |         |         |          |        |         |         |          |
| White            | 170             | 68.8 ± 3.5 | 61.8 ± 3.7 | 59.9 ± 4.0 | 0.001 | 82.4 ± 2.9 | 78.2 ± 3.2 | 77.0 ± 3.5 | 0.001 |
| Black            | 17              | 52.9 ± 11.5 | 52.9 ± 11.5 | 52.9 ± 13.7 | 0.001 | 94.1 ± 5.5 | 82.4 ± 8.9 | 82.4 ± 10.4 | 0.001 |
| Other            | 1               | 100 ± 0.0 | 100 ± 0.0 | No Data | 0.001 | 100 ± 0.0 | 100 ± 0.0 | No Data | 0.001 |
| **WBC×10⁹/L**    |                 |        |         |         |          |        |         |         |          |
| <10              | 88              | 75.0 ± 4.6 | 71.6 ± 4.8 | 71.6 ± 5.1 | 0.001 | 87.5 ± 3.5 | 86.4 ± 3.7 | 85.1 ± 4.0 | 0.001 |
| 10-49            | 58              | 67.2 ± 6.1 | 56.9 ± 6.4 | 55.2 ± 7.1 | 0.001 | 84.5 ± 4.7 | 74.1 ± 5.7 | 72.4 ± 6.3 | 0.001 |
| 50-99            | 16              | 68.8 ± 11.1 | 62.5 ± 11.5 | 56.2 ± 13.2 | 0.001 | 81.2 ± 9.4 | 75.0 ± 10.4 | 75.0 ± 11.3 | 0.001 |
| >100             | 26              | 42.3 ± 9.3 | 34.6 ± 8.9 | 30.8 ± 9.7 | 0.001 | 69.2 ± 8.8 | 65.4 ± 9.1 | 65.4 ± 10.3 | 0.001 |
| **Cell lineage** |                 |        |         |         |          |        |         |         |          |
| B                | 159             | 70.4 ± 3.6 | 64.2 ± 3.8 | 62.2 ± 4.2 | 0.001 | 84.3 ± 2.9 | 79.9 ± 3.2 | 78.5 ± 3.5 | 0.001 |
| Factors | No. of patients | Year 5 | Year 10 | Year 15 | p-value | Year 5 | Year 10 | Year 15 | p-value |
|---------|----------------|--------|---------|---------|---------|--------|---------|---------|---------|---------|
| CNS status |               |        |         |         |         |        |         |         |         |         |
| T       | 29            | 51.7 ± 9.0 | 44.8 ± 9.0 | 44.8 ± 9.0 | 79.3 ± 7.4 | 72.4 ± 8.1 | 72.4 ± 9.0 | 81.4 ± 7.5 | 0.22 |
| CNS 1   | 125           | 73.6 ± 3.9 | 67.2 ± 3.9 | 64.7 ± 4.6 | 0.03 | 87.2 ± 3.0 | 83.2 ± 3.3 | 81.5 ± 3.7 | 0.15 |
| CNS 2   | 34            | 52.9 ± 8.3 | 41.2 ± 8.3 | 41.2 ± 9.5 | 80.0 ± 6.8 | 67.6 ± 7.9 | 67.6 ± 9.3 | 80.0 ± 9.3 | 0.22 |
| CNS 3   | 10            | 63.2 ± 10.6 | 63.2 ± 10.6 | 63.2 ± 11.1 | 68.4 ± 10.3 | 68.4 ± 10.3 | 68.4 ± 10.7 | 68.4 ± 10.7 | 0.22 |
| Other   | 19            | 35.8 ± 10.3 | 35.8 ± 10.3 | 35.8 ± 11.1 | 68.4 ± 10.3 | 68.4 ± 10.3 | 68.4 ± 10.7 | 68.4 ± 10.7 | 0.22 |
| T(9;22) | 6             | 66.7 ± 19.2 | 66.7 ± 19.2 | 66.7 ± 27.2 | 81.3 ± 13.9 | 66.7 ± 19.2 | 66.7 ± 27.2 | 66.7 ± 27.2 | 0.45 |
| Absent  | 182           | 67.4 ± 3.5 | 61.0 ± 3.5 | 61.0 ± 3.5 | 84.0 ± 2.7 | 79.4 ± 3.0 | 79.4 ± 3.3 | 79.4 ± 3.3 | 0.22 |
| DNA index |                |        |         |         |         |        |         |         |         |         |
| 1.16-1.60 | 35            | 80.0 ± 6.6 | 71.4 ± 7.0 | 73.9 ± 8.7 | 0.05 | 91.4 ± 4.7 | 86.6 ± 5.3 | 85.3 ± 6.8 | 0.20 |
| 0.922   | 15            | 64.7 ± 3.8 | 57.4 ± 4.0 | 56.2 ± 4.2 | 81.7 ± 3.4 | 76.6 ± 3.4 | 75.7 ± 3.7 | 75.7 ± 3.7 | 0.22 |
| 0.01   | 182           | 67.4 ± 3.5 | 61.0 ± 3.5 | 61.0 ± 3.5 | 84.0 ± 2.7 | 79.4 ± 3.0 | 79.4 ± 3.3 | 79.4 ± 3.3 | 0.22 |
| ETV6-RUNX1 |              |        |         |         |         |        |         |         |         |         |
| Present | 7             | 71.4 ± 15.6 | 71.4 ± 15.6 | 71.4 ± 15.6 | 71.4 ± 17.1 | 71.4 ± 17.1 | 71.4 ± 17.1 | 71.4 ± 17.1 | 0.63 |
| Absent  | 181           | 67.4 ± 3.5 | 61.0 ± 3.5 | 61.0 ± 3.5 | 84.0 ± 2.7 | 79.4 ± 3.0 | 79.4 ± 3.3 | 79.4 ± 3.3 | 0.22 |
| t(1;19) | 7             | 66.7 ± 19.2 | 66.7 ± 19.2 | 66.7 ± 27.2 | 81.3 ± 13.9 | 66.7 ± 19.2 | 66.7 ± 27.2 | 66.7 ± 27.2 | 0.45 |
| Present | 3             | 33.3 ± 19.2 | 33.3 ± 19.2 | 33.3 ± 19.2 | 66.7 ± 22.2 | 66.7 ± 22.2 | 66.7 ± 27.2 | 66.7 ± 27.2 | 0.45 |
| Absent  | 185           | 68.1 ± 3.4 | 61.6 ± 3.6 | 59.9 ± 3.9 | 83.8 ± 2.7 | 78.9 ± 3.0 | 77.7 ± 3.3 | 77.7 ± 3.3 | 0.22 |

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*Significant difference in multivariate analysis.
## Table 4

Treatment results according to presenting features in patients treated in Study 13A

| Factors          | No. of patients | Year 5 | Year 10 | Year 15 | *p-value | Year 5 | Year 10 | Year 15 | *p-value |
|------------------|-----------------|--------|---------|---------|----------|--------|---------|---------|----------|
| **B-lineage**    |                 |        |         |         |          |        |         |         |          |
| NCI Standard     | 84              | 88.1 ± 3.5 | 83.3 ± 4.1 | 82.1 ± 6.6 | 0.003 | 89.3 ± 3.4 | 86.9 ± 3.7 | 86.9 ± 5.7 | 0.02 |
| NCI High         | 58              | 69.0 ± 6.0 | 62.0 ± 6.4 | 60.1 ± 10.5 | 0.10 | 81.0 ± 5.1 | 72.4 ± 5.9 | 70.3 ± 9.3 |        |
| **T-lineage**    |                 |        |         |         |          |        |         |         |          |
| NCI Standard     | 2               | 50.0 ± 25.0 | 50.0 ± 25.0 | 50.0 ± 35.4 | 0.91 | 100 ± 0.0 | 50.0 ± 25.0 | 50.0 ± 35.4 | 0.97 |
| NCI High         | 21              | 61.9 ± 10.2 | 52.4 ± 10.4 | 52.4 ± 16.2 | 0.20 | 61.9 ± 10.2 | 61.9 ± 10.2 | 57.1 ± 16.7 |        |
| **Sex**          |                 |        |         |         |          |        |         |         |          |
| Male             | 92              | 71.7 ± 4.7 | 68.5 ± 4.8 | 66.2 ± 7.7 | 0.20 | 79.3 ± 4.2 | 75.0 ± 4.5 | 73.7 ± 6.9 | 0.29 |
| Female           | 73              | 84.9 ± 4.2 | 75.2 ± 5.0 | 75.2 ± 8.4 | 0.20 | 87.7 ± 3.8 | 82.1 ± 4.5 | 80.8 ± 7.6 |        |
| **Age at diagnosis (yrs.)** | | | | | | | | | |
| <1               | 5               | 20.0 ± 12.6 | 20.0 ± 12.6 | 20.0 ± 17.9 | <.0001 | 40.0 ± 17.9 | 40.0 ± 17.9 | 40.0 ± 21.9 | <.0001 |
| 1-9              | 117             | 87.2 ± 3.1 | 82.6 ± 3.6 | 81.1 ± 6.0 | (<0.001) * | 89.7 ± 2.8 | 86.3 ± 3.2 | 85.4 ± 5.3 | (0.002) * |
| >10              | 43              | 58.1 ± 7.4 | 48.8 ± 7.4 | 46.4 ± 10.7 | 0.07 | 69.8 ± 6.9 | 60.5 ± 7.3 | 57.7 ± 10.4 |        |
| **Race**         |                 |        |         |         |          |        |         |         |          |
| White            | 139             | 79.9 ± 3.4 | 73.3 ± 3.7 | 71.8 ± 6.1 | 0.18 | 85.6 ± 3.0 | 79.8 ± 3.4 | 78.3 ± 5.4 | 0.07 |
| Black            | 23              | 69.6 ± 9.3 | 65.2 ± 9.9 | 65.2 ± 15.7 | 0.07 | 73.9 ± 8.9 | 73.9 ± 9.2 | 73.9 ± 14.3 |        |
| Other            | 3               | 33.3 ± 19.2 | 33.3 ± 19.2 | 33.3 ± 27.2 | 0.07 | 33.3 ± 19.2 | 33.3 ± 19.2 | 33.3 ± 27.2 |        |
| **WBC×10^9/L**   |                 |        |         |         |          |        |         |         |          |
| <10              | 71              | 80.3 ± 4.7 | 74.6 ± 5.2 | 71.7 ± 8.1 | 0.06 | 83.1 ± 4.4 | 80.3 ± 4.7 | 78.7 ± 7.3 | 0.15 |
| 10-49            | 50              | 78.0 ± 5.8 | 72.0 ± 6.3 | 72.0 ± 10.2 | 0.06 | 82.0 ± 5.4 | 76.0 ± 6.0 | 76.0 ± 9.3 |        |
| 50-99            | 20              | 90.0 ± 6.5 | 85.0 ± 8.0 | 85.0 ± 14.7 | 0.06 | 95.0 ± 4.8 | 90.0 ± 6.7 | 90.0 ± 11.6 |        |
| >100             | 24              | 58.3 ± 9.7 | 50.0 ± 9.8 | 50.0 ± 14.4 | 0.06 | 75.0 ± 8.6 | 66.7 ± 9.3 | 62.5 ± 14.5 |        |
| **Cell lineage** |                 |        |         |         |          |        |         |         |          |
| B                | 142             | 80.3 ± 3.3 | 74.6 ± 3.7 | 73.1 ± 6.0 | 0.02 | 85.9 ± 2.9 | 81.0 ± 3.3 | 80.2 ± 5.2 | 0.004 |
| Factors          | No. of patients | Event-free survival ± SE (%) | Overall survival ± SE (%) |
|------------------|----------------|-----------------------------|---------------------------|
|                  |                | Year 5 | Year 10 | Year 15 | * p-value | Year 5 | Year 10 | Year 15 | * p-value |
| **T**            | 23             | 60.9 ± 9.8 | 52.2 ± 10.0 | 52.2 ± 16.1 | 65.2 ± 9.6 | 60.9 ± 9.8 | 56.5 ± 16.7 | (0.02)* |
| **CD 10**        | **Positive**   | 127    | 89.0 ± 2.8 | 82.6 ± 3.4 | 81.8 ± 5.6 | 92.1 ± 2.4 | 89.0 ± 2.8 | 87.3 ± 4.7 | <.0001   |
|                  | **Negative**   | 22     | 40.9 ± 9.9 | 36.4 ± 9.7 | 36.4 ± 13.0 | 54.5 ± 10.2 | 45.5 ± 10.1 | 45.5 ± 13.7 |           |
| **CNS status**   |                |        |          |         |           |          |          |          |          |
| **CNS 1**        | 101            | 83.2 ± 3.7 | 75.2 ± 4.3 | 73.1 ± 7.2 | 0.34 | 85.1 ± 3.5 | 79.2 ± 4.0 | 77.0 ± 6.6 | 0.89 |
| **CNS 2**        | 42             | 71.4 ± 6.9 | 69.0 ± 7.0 | 69.0 ± 10.7 | 83.3 ± 5.7 | 78.6 ± 6.2 | 78.6 ± 9.4 |           |
| **CNS 3**        | 6              | 50.0 ± 17.7 | 50.0 ± 17.7 | 50.0 ± 20.4 | 66.7 ± 17.2 | 66.7 ± 17.2 | 66.7 ± 19.2 |           |
| **Traumatic with blasts** | 16  | 68.8 ± 11.1 | 61.9 ± 12.1 | 61.9 ± 22.1 | 75.0 ± 10.4 | 75.0 ± 10.8 | 75.0 ± 18.8 |           |
| **DNA index**    |                |        |          |         |           |          |          |          |          |
| **1.16-1.60**    | 32             | 93.8 ± 4.2 | 93.8 ± 4.3 | 93.8 ± 7.4 | 0.003 | 96.9 ± 3.0 | 96.9 ± 3.1 | 96.9 ± 5.4 | 0.005 |
| **Other**        | 133            | 73.7 ± 3.8 | 66.1 ± 4.1 | 64.6 ± 6.5 | (0.009)* | 79.7 ± 3.5 | 73.7 ± 3.8 | 72.1 ± 5.9 | (0.03)* |
| **t(9;22)**      |                |        |          |         |           |          |          |          |          |
| **Present**      | 6              | 33.3 ± 15.7 | 16.7 ± 10.8 | No Data | 0.0002 | 50.0 ± 17.7 | 50.0 ± 17.7 | 50.0 ± 20.4 | 0.05 |
| **Absent**       | 159            | 79.2 ± 3.2 | 73.5 ± 3.5 | 72.2 ± 5.7 | (0.008)* | 84.3 ± 2.9 | 79.2 ± 3.2 | 77.9 ± 5.2 |           |
| **t(1;19)**      |                |        |          |         |           |          |          |          |          |
| **Present**      | 8              | 100 ± 0.0 | 100 ± 0.0 | 100 ± 0.0 | 0.09 | 100 ± 0.0 | 100 ± 0.0 | 100 ± 0.0 | 0.14 |
| **Absent**       | 157            | 76.4 ± 3.4 | 70.0 ± 3.7 | 68.7 ± 5.9 | 82.2 ± 3.0 | 77.1 ± 3.4 | 75.7 ± 5.3 |           |
| **ETV6-RUNX1**   |                |        |          |         |           |          |          |          |          |
| **Present**      | 42             | 88.1 ± 4.9 | 83.3 ± 5.7 | 81.0 ± 10.2 | 0.06 | 90.5 ± 4.5 | 85.7 ± 5.3 | 85.7 ± 9.0 | 0.11 |
| **Absent**       | 123            | 74.0 ± 3.9 | 67.4 ± 4.2 | 66.5 ± 6.7 | 80.5 ± 3.6 | 75.6 ± 3.9 | 73.8 ± 6.0 |           |
| **t(4;11)**      |                |        |          |         |           |          |          |          |          |
| **Present**      | 4              | 25.0 ± 15.3 | 25.0 ± 15.3 | 25.0 ± 15.3 | 0.006 | 75.0 ± 18.8 | 50.0 ± 20.4 | 50.0 ± 20.4 | 0.18 |
| **Absent**       | 161            | 78.9 ± 3.2 | 72.6 ± 3.5 | 71.3 ± 5.8 | 83.2 ± 2.9 | 78.9 ± 3.2 | 77.5 ± 5.3 |           |

*Significant difference in multivariate analysis.

**Data available in only a subset of patients.
Table 5
Treatment results according to presenting features in patients treated in Study 13B

| Factors            | Event-free survival ± SE (%) | Overall survival ± SE (%) |
|--------------------|------------------------------|----------------------------|
|                    | Year 5          | Year 10     | p-value | Year 5          | Year 10     | p-value |
| B-lineage          | NCI Standard   | NCI High    |         |                 |             |         |
| No. of patients    | 113            | 91          |         |                 |             |         |
|                    | 87.5 ± 3.1     | 75.8 ± 4.5  | 0.01    | 91.1 ± 2.7     | 81.3 ± 4.1  | 0.04    |
|                    | 85.7 ± 3.5     | 73.6 ± 5.0  |         | 89.2 ± 3.1     | 79.0 ± 4.6  |         |
| T-lineage          | NCI Standard   | NCI High    |         |                 |             |         |
| No. of patients    | 6              | 37          |         |                 |             |         |
|                    | 83.3 ± 13.9    | 67.4 ± 7.7  | 0.33    | 100 ± 0.0      | 78.2 ± 6.8  | 0.18    |
|                    | 83.3 ± 17.0    | 61.6 ± 8.3  |         | 100 ± 0.0      | 75.3 ± 7.3  |         |
| Sex                | Male           | Female      |         |                 |             |         |
| No. of patients    | 144            | 103         |         |                 |             |         |
|                    | 78.4 ± 3.4     | 82.4 ± 3.8  | 0.21    | 85.4 ± 3.0     | 86.3 ± 3.4  | 0.77    |
|                    | 74.8 ± 3.9     | 81.4 ± 4.1  |         | 83.9 ± 3.2     | 83.3 ± 4.0  |         |
| Age at diagnosis (yrs.) |                 |             |         |                 |             |         |
| <1                 | 10             | 161         |         |                 |             |         |
|                    | 70.0 ± 13.6    | 83.8 ± 2.9  | 0.08    | 70.0 ± 13.6    | 91.2 ± 2.2  | 0.006   |
|                    | 70.0 ± 13.6    | 81.2 ± 3.3  |         | 70.0 ± 13.6    | 89.3 ± 2.6  |         |
| 1-9                | 161            |             |         |                 |             |         |
| >10                | 76             | 76          |         |                 |             |         |
|                    | 73.6 ± 5.1     | 70.9 ± 5.6  | 0.03    | 76.2 ± 4.9     | 73.5 ± 5.5  |         |
| Race               | White          | Black       |         |                 |             |         |
| No. of patients    | 172            | 45          |         |                 |             |         |
|                    | 79.1 ± 3.1     | 86.5 ± 5.1  | 0.79    | 84.3 ± 2.8     | 90.9 ± 4.3  | 0.54    |
|                    | 77.3 ± 3.3     | 81.7 ± 6.5  |         | 83.1 ± 3.0     | 88.4 ± 5.3  |         |
|                    |                |             |         |                 |             |         |
| Other              | 30             |             |         |                 |             |         |
| WBC×10^9/L         |                |             |         |                 |             |         |
| <10                | 111            | 70          |         |                 |             |         |
|                    | 81.9 ± 3.7     | 88.6 ± 3.8  | 0.04    | 84.5 ± 3.4     | 94.3 ± 2.8  | 0.002   |
|                    | 80.9 ± 4.0     | 84.3 ± 4.6  |         | 82.6 ± 3.8     | 91.4 ± 3.5  |         |
| 10-49              | 28             | 38          |         |                 |             |         |
|                    | 78.6 ± 7.8     | 60.4 ± 7.9  | 0.003   | 92.9 ± 4.9     | 68.1 ± 7.5  | 0.18    |
|                    | 74.8 ± 8.6     | 57.5 ± 8.4  |         | 89.1 ± 6.1     | 68.1 ± 7.9  |         |
| >100               | 38             |             |         |                 |             |         |
| Cell lineage       | B              | T           |         |                 |             |         |
| No. of patients    | 204            | 43          |         |                 |             |         |
|                    | 82.3 ± 2.7     | 69.6 ± 7.0  | 0.03    | 86.7 ± 2.4     | 81.3 ± 5.9  | 0.18    |
|                    | 80.3 ± 3.0     | 64.7 ± 7.8  |         | 84.7 ± 2.7     | 78.8 ± 6.6  |         |
| Factors                      | Event-free survival ± SE (%) | Overall survival ± SE (%) |
|------------------------------|------------------------------|---------------------------|
|                              | Year 5                       | Year 10                   | Year 5                       | Year 10                   |
|                              | ± SE (%)                     | ± SE (%)                  | ± SE (%)                     | ± SE (%)                  |
|                              | p-value                      | p-value                   | p-value                      | p-value                   |
| CD 10 **                     |                              |                           |                              |                           |
| Positive                     | 198 84.8 ± 2.6               | 83.2 ± 2.9                | 0.10                         | 90.3 ± 2.1                | 88.8 ± 2.4                | 0.03                         |
| Negative                     | 32 75.0 ± 7.5                | 71.7 ± 8.1                |                              | 75.0 ± 7.5                | 75.0 ± 7.8                |                              |
| CNS status                   |                              |                           |                              |                           |                           |                              |
| CNS 1                        | 145 80.6 ± 3.3               | 77.1 ± 3.7                | 0.96                         | 85.4 ± 2.9                | 82.6 ± 3.4                | 0.82                         |
| CNS 2                        | 78 79.4 ± 4.6                | 78.0 ± 5.0                |                              | 85.8 ± 4.0                | 85.8 ± 4.2                |                              |
| CNS 3                        | 7 71.4 ± 15.6                | 71.4 ± 15.6               |                              | 71.4 ± 15.6               | 71.4 ± 15.6               |                              |
| Traumatic with blasts        | 17 82.4 ± 8.9                | 82.4 ± 9.6                |                              | 94.1 ± 5.5                | 88.2 ± 8.1                |                              |
| DNA index                    |                              |                           |                              |                           |                           |                              |
| 1.16-1.60                    | 46 91.3 ± 4.1                | 91.3 ± 4.3                | 0.01                         | 93.5 ± 3.6                | 91.3 ± 4.3                | 0.11                         |
| Other                        | 201 77.5 ± 3.0               | 74.4 ± 3.3                |                              | 84.0 ± 2.6                | 81.9 ± 2.9                |                              |
| t(9;22)                      |                              |                           |                              |                           |                           |                              |
| Present                      | 7 28.6 ± 13.9                | 28.6 ± 13.9               | <.0001                       | 42.9 ± 16.2               | 42.9 ± 16.2               | 0.0005                       |
| Absent                       | 240 81.6 ± 2.5               | 79.0 ± 2.8                | (<0.001)*                    | 87.0 ± 2.2                | 84.8 ± 2.5                | (<0.011)*                   |
| t(1;19)                      |                              |                           |                              |                           |                           |                              |
| Present                      | 10 80.0 ± 11.9               | 80.0 ± 14.6               | 0.80                         | 90.0 ± 9.0                | 90.0 ± 10.8               | 0.56                         |
| Absent                       | 237 80.1 ± 2.6               | 77.5 ± 2.9                | 85.6 ± 2.3                   | 83.4 ± 2.6                | 83.4 ± 2.6                |                              |
| ETV6-RUNX1                   |                              |                           |                              |                           |                           |                              |
| Present                      | 39 84.5 ± 5.9                | 81.7 ± 6.6                | 0.64                         | 86.8 ± 5.5                | 86.8 ± 5.8                | 0.49                         |
| Absent                       | 208 79.3 ± 2.8               | 76.8 ± 3.1                | 85.5 ± 2.4                   | 83.1 ± 2.8                | 83.1 ± 2.8                |                              |
| t(4;11)                      |                              |                           |                              |                           |                           |                              |
| Present                      | 7 42.9 ± 16.2                | 42.9 ± 16.2               | 0.002                        | 42.9 ± 16.2               | 42.9 ± 16.2               | <.0001                       |
| Absent                       | 240 81.2 ± 2.5               | 78.6 ± 2.8                | (0.007)*                     | 87.0 ± 2.2                | 84.8 ± 2.5                | (0.001)*                     |
| DAY 19 MRD                   |                              |                           |                              |                           |                           |                              |
| <0.01%                       | 62 87.1 ± 4.3                | 85.5 ± 4.8                | 0.003                        | 95.2 ± 2.7                | 93.5 ± 3.3                | 0.001                        |
| 0.01 to <1%                  | 37 70.3 ± 7.4                | 64.9 ± 8.4                |                              | 81.1 ± 6.3                | 75.7 ± 7.5                |                              |
| ≥1%                          | 28 60.7 ± 9.0                | 57.1 ± 9.7                |                              | 67.9 ± 8.6                | 64.3 ± 9.3                |                              |
| Factors       | No. of patients | Event-free survival ± SE (%) | Overall survival ± SE (%) |  p-value | Year 5 | Year 10 |  p-value |
|--------------|-----------------|------------------------------|---------------------------|----------|--------|--------|----------|
|              |                 | Year 5           | Year 10        |          | Year 5 | Year 10 |          |
| DAY 46 MRD  |                 |                 |                |          |        |        |          |
| <0.01%       | 102             | 86.3 ± 3.4       | 85.3 ± 3.8     | <.0001   | 94.1 ± 2.3 | 92.1 ± 2.9 | <.0001   |
| 0.01 to <1% | 29              | 75.7 ± 8.0       | 64.7 ± 9.3     |          | 82.6 ± 7.0 | 78.9 ± 7.9 |          |
| ≥1%          | 7               | 14.3 ± 9.4       | 14.3 ± 9.4     |          | 28.6 ± 13.9 | 14.3 ± 9.4 |          |

* Significant difference in multivariate analysis.

** Data available in only a subset of patients.