HHS Public Access

Author manuscript

*Leukemia*. Author manuscript; available in PMC 2015 June 01.

Published in final edited form as:

*Leukemia*. 2014 December ; 28(12): 2336–2343. doi:10.1038/leu.2014.142.

# A Revised Definition for Cure of Childhood Acute Lymphoblastic Leukemia

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## Abstract

With improved contemporary therapy, we re-assess long-term outcome in patients completing treatment for childhood acute lymphoblastic leukemia to determine when cure can be declared with a high degree of confidence. In 6 successive clinical trials between 1984 and 2007, 1291(84.5%) patients completed all therapy in continuous complete remission. The post-therapy cumulative risk of relapse or development of a second neoplasm and the event-free survival rate and overall survival were analyzed according to the presenting features and the three treatment periods defined by relative outcome. Over the three treatment periods, there has been progressive increase in the rate of event-free survival (65.2% vs. 74.8% vs. 85.1% [P<0.001]) and overall survival (76.5% vs. 81.1% vs. 91.7% [P<0.001]) at 10 years. The most important predictor of outcome after completion of therapy was the type of treatment. In the most recent treatment period, which omitted the use of prophylactic cranial irradiation, the post-treatment cumulative



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**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

**AUTHOR CONTRIBUTIONS**

CHP, CC, DP and WHL designed, analyzed and interpreted the study. DC, SCR, and ECS performed the laboratory research. CHP, DC, WHL and WEE wrote the manuscript. CHP, JTS, WPB, MMH, RCR, SJ, SCH, DB, HI, JER, MLM, and TAG provided clinical data. All authors critically reviewed the manuscript and gave their final approval.

risk of relapse was 6.4%, death in remission 1.5%, and development of a second neoplasm 2.3% at 10 years, with all relapses except one occurring within 4 years off therapy. None of the 106 patients with the t(9;22)/*BCR-ABL1*, t(1;19)/*TCF3-PBX1* or t(4;11)/*MLL-AFF1* had relapsed after 2 years from completion of therapy. These findings demonstrate that with contemporary effective therapy that excludes cranial irradiation, approximately 6% of children with acute lymphoblastic leukemia may relapse after completion of treatment, and those who remain in remission at 4 years post-treatment may be considered cured (i.e., less than 1 % chance of relapse).

**Keywords**

acute lymphoblastic leukemia; cure; off-therapy relapse

## INTRODUCTION

An objective definition of cure for children and adolescents with acute lymphoblastic leukemia (ALL) has been elusive. If eradication of the leukemic clone is the sole criterion, patients who maintain complete remission for a prolonged time after receiving all scheduled therapy may be considered “cured” of their disease. However, this definition does not take into account the possibility of a second cancer or other treatment-related complication that may jeopardize both the quality and length of the individual’s post-treatment survival.

In a previous study of 856 childhood ALL patients treated between 1962 and 1992 who were event-free survivors for 10 years after the induction of remission, we found that the cumulative risk of relapse at 30 years from the date of complete remission was extremely low (0.6%).[1] This finding was similar to that in another study of 1134 survivors who had been event-free for 10 years post-treatment at 20 years of follow-up.[2] However, we noted that among long-term survivors who had received radiation therapy, the development of second neoplasms continued well beyond 20 years of follow-up, without reaching a plateau,[1] a finding that has since been confirmed by other groups.[3-5] As a result, the irradiated group had a significantly lower survival rate than that of the non-irradiated 10-year event-free survivors, whose probability of survival was identical to that of the general population.[1,4] Based on these observations, we suggested a working definition of cure – 10 years or more of event-free survival – emphasizing that patients who meet this standard and did not receive radiation therapy have a normal survival expectancy.[1]

Improvement in the efficacy of treatment, together with the decreasing use of carcinogenic therapy, especially prophylactic cranial irradiation, has increased 5-year event-free survival rates to 80% to 87%.[6-10] This progress is likely to have an impact on long-term survival expectancy and may change the timing at which a child with ALL can be considered cured. We therefore re-examined the results of stopping therapy for patients enrolled in six consecutive clinical trials between the mid-1980s and the mid-2000s, a period in which the 5-year event-free survival rates increased from 68% to 87%.

# MATERIALS AND METHODS

## Study Population and Treatment Protocols

From February 1984 to October 2007, 1527 consecutive patients, 18 years or younger, with newly diagnosed ALL were enrolled in six successive clinical trials (Total Therapy studies 11, 12, 13A, 13B, 14 and 15) at St. Jude Children's Research Hospital.[7,11-15] The clinical and biologic features of these patients are shown in the Supplementary Table 1, while the general characteristics of the different treatment protocols are summarized in the Supplementary Table 2. Briefly, prophylactic cranial irradiation was given to a decreasing proportion of patients in each successive trial because of improving systemic and intrathecal therapy: 64% in study 11, 37% in study 12, 22% in study 13A, 12% in study 13B and none in studies 14 and 15. In study 15, epipodophyllotoxins were omitted in all but 6% of the patients, who required intensification of therapy prior to hematopoietic stem cell transplantation. The treatment protocols were approved by the institutional review board, with signed informed consent obtained from the parents or guardians and assent from the patients, as appropriate. Long-term follow-up has been a major research emphasis in these trials. Survivors who have been in remission for 5 years or more are evaluated annually in our After Completion of Therapy Clinic. Through our Cancer Registry, questionnaire is mailed each year to the alumni survivors who are 18 years of age or older. Since 2007, alumni survivors have also been eligible for periodic cancer-related risk-based consultations as part of the St. Jude Lifetime Cohort Study.

## Statistical Analysis

Event-free survival and survival from diagnosis or the completion of treatment in continuous complete remission were estimated by the method of Kaplan-Meier. The cumulative incidence functions of post-treatment failure due to a specific cause (relapse, development of a second neoplasm, or death in remission) were estimated by the method of Kalbfleisch and Prentice,[16] and compared using Gray's test. Deaths in remission and second neoplasms were considered competing events in the estimation of cumulative incidence of relapse. The confidence intervals of failure probabilities were constructed using the normal approximation.[16] In a few cases where this method created a negative lower limit, a nonparametric method[17] was applied. The Fine and Gray model for competing risks and Cox regression model were used to identify independent risk factors for relapse and event-free survival, respectively. The proportion hazards assumption for each variable included in the model was checked using the Schoenfeld residuals. The Hochberg and Benjamini adaptive step-down Bonferroni method was used to adjust for multiple comparisons.[18] The actuarial risk of failures among survivors in study 15 was estimated with the Poisson model. The upper confidence bound of the expected number of failures in a given amount of person-year follow up was determined by using the exact upper confidence bound of the Poisson rate based on the observed number of failures and person-year follow-up. To provide a conservative estimate of the actuarial risk of relapse among 4-year post-treatment event-free survivors, a sensitivity analysis was performed on the unlikely assumption of up to 4 additional hypothetical relapses occurring during 2 additional years of follow-up. The database updated on August 23, 2013 was used for this analysis. The median follow-up time for patients remaining in continuous remission was 15.8 years (range, 1.3 to 29.4 years) in

all studies and 8.2 years (range, 1.3 to 12.9 years) for those in study 15. At the time of analysis, 95% of the survivors had had a follow-up visit within 2 years; only 2.0% of the patients lacked a documented contact within the previous 5 years.

## RESULTS

Of the 1527 patients enrolled in Total Therapy studies 11 to 15, 1291 (84.5%) were in continuous complete remission at the end of treatment including patients who underwent hematopoietic stem cell transplantation in first complete remission (Figure 1). As shown in Table 1, treatment outcome (event-free survival, survival and cumulative risk of any relapse) did not differ significantly between patients treated in studies 11 and 12, or among those treated in studies 13A, 13B, and 14, leading us to combine these cohorts into two groups for subsequent analyses. Patients treated in study 15 had a superior treatment outcome compared to those in studies 13A, 13B and 14, and therefore constituted a third comparison group. The 10-year event-free survival rate increased progressively over the three treatment periods ($P<0.001$): 65.2% (95% CI, 61.3% - 69.1%) vs. 74.8% (95% CI, 70.9% - 78.7%) vs. 85.1% (95% CI, 79.0% - 91.2%). The improved result in study 15 extended to NCI standard-risk B-ALL ($p=0.006$), NCI high-risk B-ALL ($p<0.0001$), and T-ALL ($p<0.001$) (data not shown). This improvement was also apparent in the analysis of overall survival ($P<0.001$): 76.5% (95% CI, 73.0% - 80.0%) vs. 81.1% (95% CI, 77.6% - 84.6%) vs. 91.7% (95% CI, 87.0% - 96.4%).

### Major adverse events after completion of therapy

Of the 191 major post-therapy adverse events, hematological relapse in 104 cases (79 isolated and 25 combined with extramedullary relapse) was the most common, followed by the development of a second neoplasm in 44 cases (20 acute myeloid leukemias, 4 myelodysplastic syndromes, 1 chronic myeloid leukemia, 14 brain tumors and 5 solid tumors), and 17 extramedullary relapses (9 central-nervous-system, 5 testicular and 3 other sites). The remaining events comprised 26 deaths in remission due to various causes (10 accidents, 6 infections, 3 graft-versus-host disease, 3 multi-organ failure, 2 suicides, and 1 each of seizure and complications of ataxia-telangiectasia),12 of the deaths resulting from complications of hematopoietic stem cell transplantation. In study 15, 27 patients relapsed, 7 died in remission (3 graft-versus-host disease, 3 infections, and 1 accident), and 3 developed a second neoplasm (1 glioblastoma multiforme, 1 myelodysplastic syndrome, and 1 malignant fibrous histiocytoma) after completion of therapy among the 455 patients who completed all treatment in continuous complete remission.

Most of the adverse events (76 cases, 39.8%) occurred in the first year after completion of treatment, 40 (20.9%) in the second year, 13 (6.8%) in the third, 16 (8.4%) in the fourth, 7 (3.66%) in the fifth, 25 (13.09%) between the sixth and the tenth years, and 14 (7.33%) beyond 10 years (Supplementary Figure 1). Of the adverse events occurring after 10 years, 2 were leukemic relapses, 3 brain tumors, 2 solid tumors, and 7 deaths in remission.

### Factors associated with the risk of a post-therapy adverse event

There was steady improvement in the proportion of patients who remained event-free after completion of therapy (p=0.004): 82.4 (95% CI, 78.9% - 85.9%) in studies 11 and 12 vs. 84.1% (95% CI, 80.6% - 87.6%) in studies 13A, 13B and 14 vs. 90.0% (95% CI, 84.6% - 93.3%) in study 15 at 10 years. DNA index ≥1.16, hyperdiploidy>50, absence of the t(9;22)/*BCR-ABL1* or t(4;11)/*MLL-AFF1*, lack or low levels of minimal residual disease at day 19 of induction or the end of remission induction, and treatment according to study 15 were each associated with a higher post-therapy event-free survival rate (Supplementary Table 1). Treatment according to study 15, absence of t(9;22)/*BCR-ABL1*, hyperdiploidy>50, and lack of minimal residual disease at the end of remisson induction were independently associated with a favorable long-term outcome in a multivariate analysis (Supplementary Table 3).

In view of the decreasing use of carcinogenic treatment (i.e., epipodophyllotoxins and prophylactic cranial irradiation) in successive Total Therapy studies, we also compared the cumulative risk of a second neoplasm among the different groups (Figure 2A): 5.0% (95% CI, 3.0% to 7.1%) in studies 11 and 12 vs. 3.5% (95% CI, 1.7% to 5.5%) in studies 13A, 13B and 14 vs. 2.3% (95% CI, 0.5% to 6.6%) in study 15 at 10 years (p=0.003).

The cumulative risk of any relapse following completion of therapy was 12.1% (95% CI, 9.0% to 15.2%) in studies 11 and 12, 9.8% (95% CI, 6.9% to 12.8%) in studies 13A, 13B and14, and 6.4% (95% CI, 4.0% to 8.8%) in study 15 at 10 years (p=0.026; Figure 2B). A lower risk of post-therapy relapse was associated with treatment according to study 15, female sex and the absence of t(9;22)/*BCR-ABL1* in both univariate (Table 2) and multivariate (Table 3) analyses. Among the subgroup of 629 patients with data on minimal residual disease, only the lack (<0.01%) and low level (0.01% to <0.1%) of minimal residual disease at the end of remission induction therapy were associated with lower risk of post-therapy relapse (Table 3).

### Time to relapse

The time to relapse varied widely according to the clinical or biologic factors examined (Table 2). Notably, no relapses beyond 2 years were observed in the 106 patients with the t(9;22)/*BCR-ABL1*, t(1;19)/*TCF3-PBX1* or t(4;11)/*MLL-AFF1* (Table 2).

Analysis of the conditional probability of post-therapy relapse for each treatment group (Figure 3) showed that there was still an estimated risk of relapse of 0.65% (95% CI, 0.04% to 1.17%) beyond 10 years after completion of therapy in studies 11 and 12, whereas no relapse was observed beyond 10 years in studies 13A, 13B and 14. In study 15, there were 13 relapses in the first year after completion of treatment, 7 between 1 and 2 years, 4 between 2 and 3 years, 2 between 3 and 4 years, and 1 at 6 years. Of the 418 patients in study 15 who completed all treatment and remained alive and event-free at the time of analysis, 313 (75%) had been followed for 4 years or more after completion of therapy. With 827.6 person-years of follow-up (after completion of therapy for 4 years) of the 313 patients, the 95% and 99% upper confidence bound of the expected number of relapse per 100 person-years of follow-up beyond 4 years after completion of treatment are 0.57 and 0.8, respectively. To provide a conservative estimate of the future risk of relapse among the 4-

year post-treatment event-free survivors, we performed a sensitivity analysis covering a range of likely to unlikely scenarios, in which 1 to 4 hypothetical additional relapses will occur during 2 additional years of follow up. The analyses showed the 99% upper confidence bound of the actuarial risk of 0.42 to 0.74 relapse per 100 person-years of follow-up (Supplementary Table 4), indicating an extremely low risk of further relapse.

## DISCUSSION

This study demonstrates that the improvement in treatment of childhood ALL since the mid-1980s has significantly reduced not only the risk of leukemic relapse but also the risk of developing a second neoplasm. Indeed, the cumulative risk of any relapse at 10 years after completion of therapy was reduced from 12.1% in studies 11 and 12 to 9.8% in studies 13A, 13B and 14 to only 6.4% in study 15. Equally important, the duration of risk of relapse after completion of treatment also decreased progressively, with only one of the 313 patients in study 15 who had been off treatment and event-free for 4 years relapsing beyond this time point. Even with additional follow-up, the actuarial risk of relapse should not exceed 1 per 100 person-year follow up for the 4-year post-treatment event-free survivors in this study.

Undoubtedly, the complete omission of prophylactic cranial irradiation and the restriction of administration of epipodophyllotoxins to patients undergoing transplantation were crucial in reducing the risk of a second neoplasm to a very low level in study 15. Among 498 patients treated in that study, we observed only one case each of myelodysplastic syndrome,[7] primary malignant fibrous histiocytoma and glioblastoma multiforme after cessation of treatment. Although antimetabolite treatment has been associated with the development of secondary myeloid neoplasm, especially in patients with thiopurine methyltransferase deficiency,[19] the child who developed myelodysplastic syndrome had normal thiopurine methyltransferase activity. The patient who developed glioblastoma multiforme had received total-body irradiation as part of the preparative regimen for transplantation. In this regard, prophylactic cranial irradiation as low as 12 Gy can be associated with the development of brain tumor.[20] Whether the patient who developed a malignant fibrous histiocytoma has underlying genetic susceptibility to develop cancer is unknown.

Late relapse of ALL has been variously attributed to the outgrowth of a minor drug-resistant subclone, acquisition of additional genetic abnormalities by a resilient preleukemic clone, or the de novo development of secondary ALL.[21-27] Conceivably, early intensification with asparaginase and dexamethasone as well as high-dose methotrexate, which were applied to all patients and at higher doses for those with high-risk B-ALL and T-ALL, likely eliminated a higher proportion of mutant stem-cell lines in study 15 than did therapies administered in the five preceding trials (see Supplementary Table 2). The restriction of epipodophyllotoxins might also have prevented de novo development of secondary ALL in this study.

The presence of the t(9;22)/*BCR-ABL1* was one of the factors significantly associated with the post-treatment relapse hazard. However, ABL tyrosine kinase inhibitors, effective agents for t(9;22)/*BCR-ABL1*-positive ALL,[28,29] were available for only the last few patients enrolled in study 15. The presence of minimal residual disease at the end of remission

induction is one of the strongest prognostic factors in childhood ALL and correlated with a high cumulative risk of relapse in virtually all clinical trials.[30-35] In a Children's Oncology Group study, detectable minimal residual disease at the end of remission induction was also associated with a greater risk of relapse at 3 years or more after diagnosis,[32] a finding confirmed in our study.

In the Children's Oncology Group study, the presence of favorable genetic features such as *ETV6-RUNX1* or trisomies of chromosomes 4 and 10 provided additional prognostic information beyond the absence of minimal residual disease at the end of remission induction.[32] However, neither *ETV6-RUNX1* nor hyperdiploidy >50 (which is associated with trisomies of chromosomes 4 and 10) was independently related to the risk of post-treatment relapse in the current analysis. As reported previously,[36] gender remained a risk factor in this study.

The biologic subtypes of ALL can have a major influence on the time to relapse. Late relapse is well recognized in *ETV6-RUNX1*-positive and T-cell ALL,[25,37-39] and has been attributed to a second, independent malignant transformation of a preleukemic clone that was not eradicated during initial treatment. While we also observed late relapses in 4 patients with *ETV6-RUNX1*-positive ALL treated in studies 12, 13A and 13B at 5.1, 5.6, 9.1 and 9.2 years after completion of treatment, none of the 59 patients with *ETV6-RUNX1*-positive ALL treated in study 15 relapsed beyond 4 years after completion of treatment, suggesting that more effective treatment can eradicate preleukemic clones in such patients. Finally, relapses were not observed beyond 2 years after completion of therapy among 106 patients with the t(9;22)/*BCR-ABL1*, t(1;19)/*TCF3-PBX1* or t(4;11)/*MLL-AFF1* in any of our Total Therapy studies, indicating that these patients may be declared cured earlier than patients with other biologic subtypes of ALL.

Our results allow us to revise the timing for an objective definition of cure. We propose that, with use of effective treatment similar to that in study 15, a patient who did not receive cranial irradiation and remains in complete remission for at least 4 years after the completion of antileukemic therapy should practically be considered cured because the likelihood of subsequent late event is exceedingly rare. This new definition should be applicable to contemporary clinical trials that shared similar treatment approach with intensified dexamethasone and asparaginase and achieved 5-year event-free survival rates of 85% or higher and 5-year survival rates of 90% or more.[6-10] It should also alleviate much of the uncertainty and stress surrounding elective cessation of therapy following prolonged continuation treatment,[40] and help to overcome barriers to insurance coverage and health-care access experienced by many long-term survivors.[1,41,42] Finally, the omission of cranial irradiation will contribute to preserving global cognitive abilities, including intellectual functioning, academic abilities, learning and memory, as reported for patients treated in study 15.[43]

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGEMENTS

This work was funded in part by the NCI grant CA21765, CA36401, and U01 GM92666, and the American Lebanese and Syrian Associated Charities (ALSAC).

## REFERENCES

1. Pui CH, Cheng C, Leung W, et al. Extended follow-up of long-term survivors of childhood acute lymphoblastic leukemia. N Engl J Med. 2003; 349:640–649. [PubMed: 12917300]
2. Vora A, Frost L, Goodeve A, et al. Late relapsing childhood lymphoblastic leukemia. Blood. 1998; 92:2334–2337. [PubMed: 9746771]
3. Maule M, Scélo G, Pastore G, et al. Risk of second malignant neoplasms after childhood leukemia and lymphoma: an international study. J Natl Cancer Inst. 2007; 99:790–800. [PubMed: 17505074]
4. Mody R, Li S, Dover DC, et al. Twenty-five-year follow-up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. Blood. Jun 15.2008 111:5515–5523. [PubMed: 18334672]
5. Taylor AJ, Little MP, Winter DL, et al. Population-based risks of CNS tumors in survivors of childhood cancer: the British Childhood Cancer Survivor Study. J Clin Oncol. 2010; 28:5287–5293. [PubMed: 21079138]
6. Pui CH, Mullighan CG, Evans WE, Relling MV. Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? Blood. 2012; 120:1165–1174. [PubMed: 22730540]
7. Pui CH, Campana D, Pei D, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med. 2009; 360:2730–2741. [PubMed: 19553647]
8. Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. J Clin Oncol. 2012; 30:1663–1669. [PubMed: 22412151]
9. Vrooman LM, Stevenson KE, Supko J, et al. Postinduction dexamethasone and individualized dosing of Escherichia coli L-asparaginase each improve outcome of children and adolescents with newly diagnosed acute lymphoblastic leukemia: results from a randomized study - Dana-Farber Cancer Institute ALL Consortium Protocol 00-01. J Clin Oncol. 2013; 31:1202–1210. [PubMed: 23358966]
10. Vora A, Goulden N, Wade R, et al. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. Lancet Oncol. 2013; 14:199–209. [PubMed: 23395119]
11. Rivera GK, Raimondi SC, Hancock ML, et al. Improved outcome in childhood acute lymphoblastic leukaemia with reinforced early treatment and rotational combination chemotherapy. Lancet. 1991; 337:61–66. [PubMed: 1670723]
12. Evans WE, Relling MV, Rodman JH, et al. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. N Engl J Med. 1998; 338:499–505. [PubMed: 9468466]
13. Pui CH, Mahmoud HH, Rivera GK, et al. Early intensification of intrathecal chemotherapy virtually eliminates central nervous system relapse in children with acute lymphoblastic leukemia. Blood. 1998; 92:411–415. [PubMed: 9657739]
14. Pui CH, Sandlund JT, Pei D, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIIIB at St Jude Children's Research Hospital. Blood. 2004; 104:2690–2696. [PubMed: 15251979]
15. Pui CH, Pei D, Sandlund JT, et al. Long-term results of St Jude Total Therapy Studies 11, 12, 13A, 13B, and 14 for childhood acute lymphoblastic leukemia. Leukemia. 2010; 24:371–382. [PubMed: 20010620]
16. Kalbfleisch, JD.; Prentice, RL. The Statistical Analysis of Failure Time Data. Second edition. Wiley; New York, NY: 2002. p. 247
17. Choudhury JB. Non-parametric confidence interval estimation for competing risk analysis: application of to contraceptive data. Statist Med. 2002; 21:1129–1144.

18. Hochberg Y, Benjamini Y. More powerful procedures for multiple significance testing. Stat Med. 1990; 9:811–818. [PubMed: 2218183]
19. Schmiegelow K, Al-Modhwahi I, Andersen MK, et al. Methotrexate/6-mercaptopurine maintenance therapy influences the risk of a second malignant neoplasm after childhood acute lymphoblastic leukemia: results from the NOPHO ALL-92 study. Blood. 2009; 113:6077–6084. [PubMed: 19224761]
20. Schrappe M, Reiter A, Ludwig WD, et al. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90. Blood. 2000; 95:3310–3322. [PubMed: 10828010]
21. Li A, Zhou J, Zuckerman D, et al. Sequence analysis of clonal immunoglobulin and T-cell receptor gene rearrangements in children with acute lymphoblastic leukemia at diagnosis and at relapse: implications for pathogenesis and for the clinical utility of PCR-based methods of minimal residual disease detection. Blood. 2003; 102:4520–4526. [PubMed: 12946997]
22. van Vlierberghe P, Meijerink JP, Lee C, et al. A new recurrent 9q34 duplication in pediatric T-cell acute lymphoblastic leukemia. Leukemia. 2006; 20:1245–1253. [PubMed: 16673019]
23. Ford AM, Fasching K, Panzer-Grümayer ER, et al. Origins of “late” relapse in childhood acute lymphoblastic leukemia with TEL-AML1 fusion genes. Blood. 2001; 98:558–564. [PubMed: 11468150]
24. Konrad M, Metzler M, Panzer S, et al. Late relapses evolve from slow-responding subclones in t(12;21)-positive acute lymphoblastic leukemia: evidence for the persistence of a preleukemic clone. Blood. 2003; 101:3635–3640. [PubMed: 12506024]
25. Mullighan CG, Phillips LA, Su X, et al. Genomic analysis of the clonal origins of relapsed acute lymphoblastic leukemia. Science. 2008; 322:1377–1380. [PubMed: 19039135]
26. Zuna J, Cave H, Eckert C, et al. Childhood secondary ALL after ALL treatment. Leukemia. 2007; 21:1431–1435. [PubMed: 17460701]
27. Szczepanski T, Van der Velden VH, Waanders E, et al. Late recurrence of childhood T-cell acute lymphoblastic leukemia frequently represents a second leukemia rather than a relapse: first evidence for genetic predisposition. J Clin Oncol. 2011; 29:1643–1649. [PubMed: 21357790]
28. Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children’s oncology group study. J Clin Oncol. 2009; 27:5175–5181. [PubMed: 19805687]
29. Biondi A, Schrappe M, De LP, et al. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. Lancet Oncol. 2012; 13:936–945. [PubMed: 22898679]
30. van Dongen JJ, Seriu T, Panzer-Grümayer ER, et al. Prognostic value of minimal residual disease in acute lymphoblastic leukaemia in childhood. Lancet. 1998; 352:1731–1738. [PubMed: 9848348]
31. Coustan-Smith E, Behm FG, Sanchez J, et al. Immunological detection of minimal residual disease in children with acute lymphoblastic leukaemia. Lancet. 1998; 351:550–554. [PubMed: 9492773]
32. Borowitz MJ, Devidas M, Hunger SP, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children’s Oncology Group study. Blood. 2008; 111:5477–5485. [PubMed: 18388178]
33. Conter V, Bartram CR, Valsecchi MG, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood. 2010; 115:3206–3214. [PubMed: 20154213]
34. Stow P, Key L, Chen X, et al. Clinical significance of low levels of minimal residual disease at the end of remission induction therapy in childhood acute lymphoblastic leukemia. Blood. 2010; 115:4657–4663. [PubMed: 20304809]
35. Schrappe M, Valsecchi MG, Bartram CR, et al. Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study. Blood. 2011; 118:2077–2084. [PubMed: 21719599]
36. Pui CH, Pei D, Sandlund JT, et al. Risk of adverse events after completion of therapy for childhood acute lymphoblastic leukemia. J Clin Oncol. 2005; 23:7936–7941. [PubMed: 16258093]

37. Ford AM, Fasching K, Panzer-Grümayer ER, et al. Origins of “late” relapse in childhood acute lymphoblastic leukemia with TEL-AML1 fusion genes. Blood. 2001; 98:558–564. [PubMed: 11468150]

38. Konrad M, Metzler M, Panzer S, et al. Late relapses evolve from slow-responding subclones in t(12;21)-positive acute lymphoblastic leukemia: evidence for the persistence of a preleukemic clone. Blood. 2003; 101:3635–3640. [PubMed: 12506024]

39. Forestier E, Heyman M, Andersen MK, et al. Outcome of ETV6/RUNX1-positive childhood acute lymphoblastic leukaemia in the NOPHO-ALL-1992 protocol: frequent late relapses but good overall survival. Br J Haematol. 2008; 140:665–672. [PubMed: 18241254]

40. Wakefield CE, McLoone JK, Butow P, et al. Parental adjustment to the completion of their child’s cancer treatment. Pediatr Blood Cancer. 2011; 56:524–531. [PubMed: 21298736]

41. Park ER, Li FP, Liu Y, et al. Health insurance coverage in survivors of childhood cancer: the Childhood Cancer Survivor Study. J Clin Oncol. 2005; 23:9187–9197. [PubMed: 16361621]

42. Ginsberg JP. Health insurance for survivors of childhood cancer: a pre-existing problem. Pediatr Blood Cancer. 2009; 53:928–930. [PubMed: 19606458]

43. Conklin HM, Krull KR, Reddick WE, et al. Cognitive outcomes following contemporary treatment without cranial irradiation for childhood acute lymphoblastic leukemia. J Natl Cancer Inst. 2012; 104:1386–1395. [PubMed: 22927505]

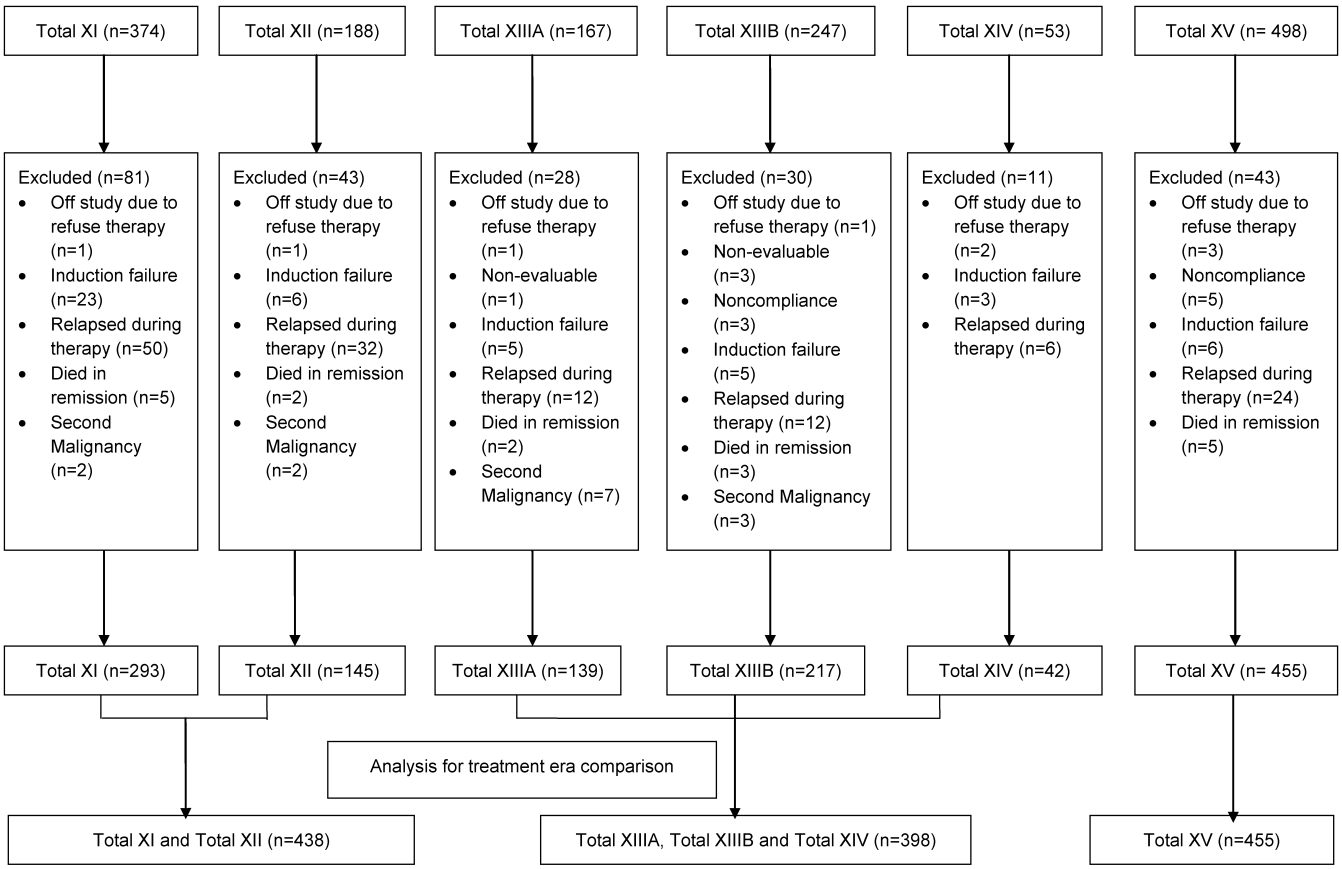
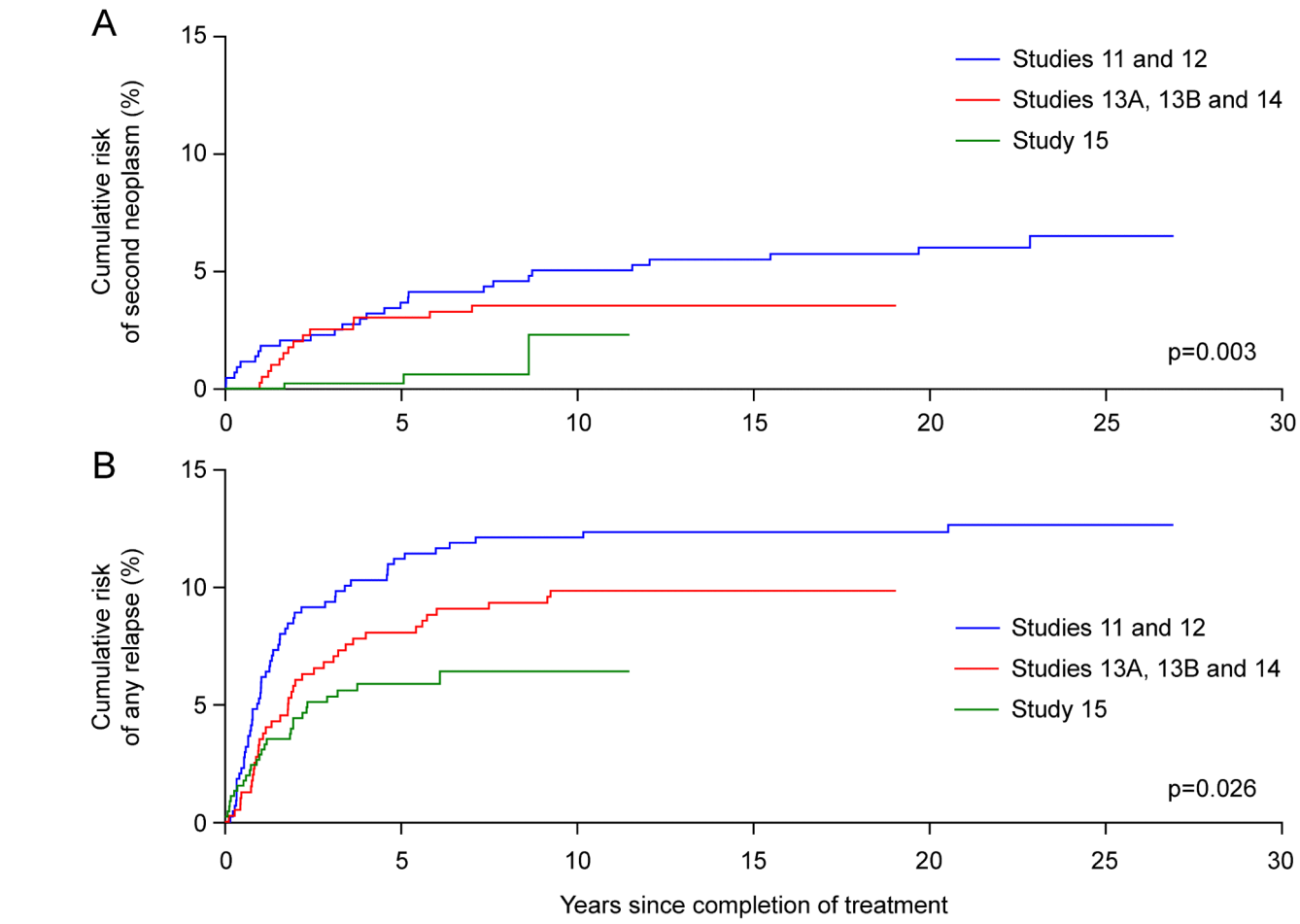



**Figure 1.**

CONSORT diagram. Of the 562 patients treated in studies 11 and 12, 467 in study 13A, 13B and 14, and 498 in study 15, 438, 398, and 455 patients, respectively, remained in continuous complete remission upon the completion of treatment.

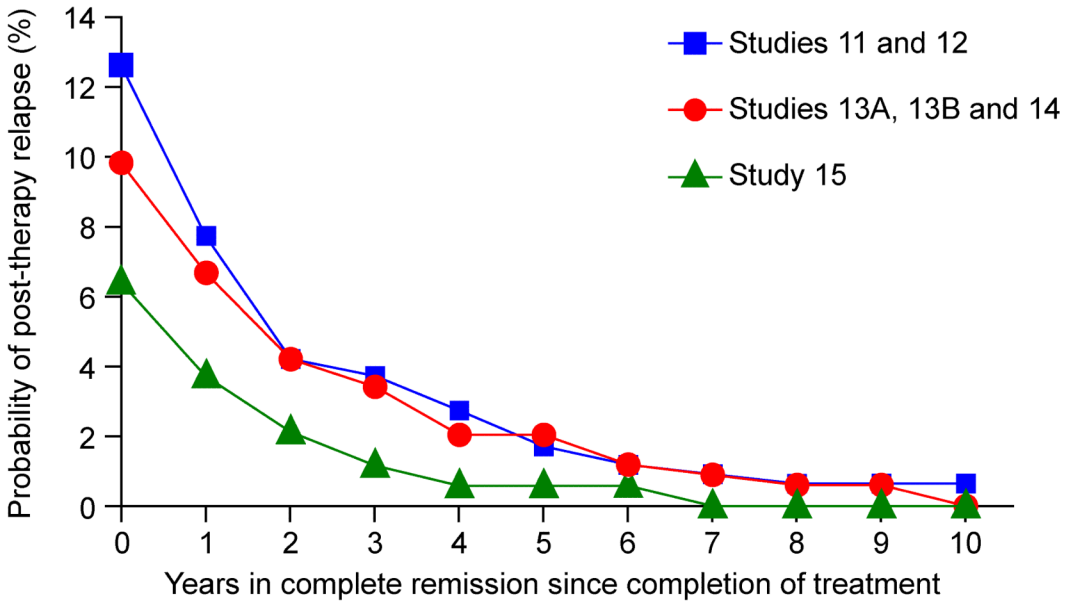



No. at risk:

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Studies 11 and 12 | 438 | 405 | 388 | 385 | 378 | 371 | 367 | 366 | 362 | 356 | 356 | 354 | 353 | 351 | 348 | 346 | 343 | 340 | 334 | 318 | 290 | 252 | 207 | 158 | 115 | 59 | 24 |
| Studies 13A, 13B and 14 | 398 | 376 | 358 | 353 | 346 | 345 | 339 | 338 | 335 | 332 | 328 | 315 | 275 | 232 | 177 | 135 | 94 | 46 | 15 | 2 | | | | | | | |
| Study 15 | 455 | 432 | 418 | 387 | 313 | 250 | 183 | 128 | 86 | 41 | 2 | 1 | | | | | | | | | | | | | | | |

**Figure 2.**

Cumulative risk of development of a second neoplasm (A) or relapse (B) after completion of therapy for patients in continuous remission according to Total Therapy study. The numbers of patients who remained event-free and were at risk of developing second neoplasm or relapse at any given year after completion of treatment for the three cohorts were provided in the bottom of the figure. Note the significant decrease in both adverse events for each successive treatment group.




| No. at risk: | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Studies 11 and 12 | 438 | 405 | 388 | 385 | 378 | 371 | 367 | 366 | 362 | 356 | 356 |
| Studies 13A, 13B and 14 | 389 | 376 | 358 | 353 | 346 | 345 | 339 | 338 | 335 | 332 | 328 |
| Study 15 | 455 | 432 | 418 | 387 | 313 | 250 | 183 | 128 | 86 | 41 | 2 |

**Figure 3.**

Conditional probability of relapse for patients remaining in continuous complete remission for the given years after completion of treatment by Total Therapy study. Note the progressive decrease in the probability of off-therapy relapse for each successive treatment group, and the absence of relapse in patients remaining in remission at 4 years off therapy in study 15.

**Table 1**

Treatment Outcome According to Total Therapy Study

| Total Therapy Studies | Total 11 | Total 12 | Total 13A | Total 13B | Total 14 | Total 15 |
|---|---|---|---|---|---|---|
| Year | 1984-1988 | 1988-1991 | 1991-1994 | 1994-1998 | 1998-1999 | 2000-2007 |
| No. of patients | 374 | 188 | 167 | 247 | 53 | 498 |
| Age (years) | 0-18 | 0-18 | 0-18 | 0-18 | 0-18 | 1-18 |
| Event-free survival % (95% CI) | | | | | | |
| 5 years | 70.0(65.3-74.7) | 67.6(60.9-74.3) | 76.7(70.2-83.2) | 80.0(74.9-85.1) | 77.4(66.2-88.6) | 87.3(84.4-90.2) |
| 10 years | 67.3(62.6-72.0) | 61.2(54.3-68.1) | 70.7(63.8-77.6) | 77.5(72.2-82.8) | 75.5(64.1-86.9) | 85.1(79.0-91.2) |
| Overall survival % (95% CI) | | | | | | |
| 5 years | 78.1(74.0-82.2) | 83.5(78.2-88.8) | 82.1(76.4-87.8) | 86.1(81.8-90.4) | 81.1(70.7-91.5) | 93.5(91.3-95.7) |
| 10 years | 75.4(71.1-79.7) | 78.7(72.8-84.6) | 77.4(71.1-83.7) | 84.1(79.4-88.8) | 79.2(68.4-90.0) | 91.7(87.0-96.4) |
| Off-therapy events | | | | | | |
| Hematological relapse | 25 | 8 | 9 | 17 | 1 | 19 |
| CNS relapse | 3 | 3 | 0 | 2 | 0 | 1 |
| Hematological + CNS relapse | 3 | 5 | 4 | 2 | 1 | 5 |
| Testicular relapse | 0 | 2 | 0 | 1 | 0 | 2 |
| Hematological + testicular relapse | 1 | 2 | 1 | 0 | 0 | 0 |
| Hematological + CNS + testicular relapse | 1 | 0 | 0 | 0 | 0 | 0 |
| Other relapse | 1 | 1 | 0 | 1 | 0 | 0 |
| Second malignancy | 14 | 13 | 9 | 5 | 0 | 3 |
| Death in remission | 3 | 2 | 6 | 6 | 2 | 7 |
| Off-therapy outcome % (95% CI) | | | | | | |
| 5-yr event-free survival | 86.7(82.8-90.6) | 80.7(74.2-87.2) | 86.4(80.7-92.1) | 86.5(82.0-91.0) | 90.5(76.6-96.3) | 92.4(89.3-95.5) |
| 10-yr event-free survival | 85.3(81.2-89.4) | 76.5(69.6-83.4) | 82.1(75.8-88.4) | 84.2(79.3-89.1) | 90.5(76.6-96.3) | 90.0(84.6-93.3) |
| 5-yr survival | 91.5(88.4-94.6) | 91.0(86.3-95.7) | 90.0(85.1-94.9) | 91.6(87.9-95.3) | 92.9(79.5-97.6) | 95.9(93.5-98.3) |
| 10-yr survival | 90.4(87.1-93.7) | 88.3(83.0-93.6) | 87.9(82.4-93.4) | 90.2(86.3-94.1) | 92.9(79.5-97.6) | 95.1(92.3-96.8) |
| 5-yr cumulative risk of relapse | 10.2(6.8-13.7) | 13.1(7.6-18.6) | 7.9(3.4-12.3) | 9.3(5.4-13.2) | 2.4(1.2-12.2) | 5.9(3.7-8.1) |

| Total Therapy Studies | Total 11 | Total 12 | Total 13A | Total 13B | Total 14 | Total 15 |
|---|---|---|---|---|---|---|
| 10-yr cumulative risk of relapse | 11.3(7.6-14.9) | 13.8(8.2-19.4) | 10.0(5.0-15.0) | 10.7(6.6-14.8) | 4.8(1.2-12.2) | 6.4(4.0-8.8) |
| 5-yr cumulative risk of second malignancy | 2.7(0.9-4.6) | 5.5(1.8-9.2) | 5.0(1.4-8.6) | 2.3(0.3-4.3) | 0 | 0.2(0.2-1.8) |
| 10-yr cumulative risk of second malignancy | 3.1(1.1-5.1) | 9.0(4.3-13.7) | 6.4(2.3-10.5) | 2.3(0.3-4.3) | 0 | 2.3(0.5-6.6) |
| 5-yr cumulative risk of death in remission | 0.3(0.05-1.4) | 0.7(0.1-2.8) | 0.7(0.4-3.9) | 1.9(0.7-3.9) | 4.8(1.2-12.3) | 1.5(0.4-2.7) |
| 10-yr cumulative risk of death in remission | 0.3(0.50-1.4) | 0.7(0.1-2.8) | 1.4(0.4-3.9) | 2.8(1.4-5.1) | 4.8(1.2-12.3) | 1.5(0.4-2.7) |

CNS central nervous system

**Table 2**

Factors associated with cumulative risk of any post-therapy relapse and time to relapse

| Factor | No. Patients | No. Patients with Post-Therapy Relapse | Median time to Post-Therapy Relapse (range) in Years | Estimate % (95% CI) Year 5 | Year 10 | P Value |
|---|---|---|---|---|---|---|
| NCI risk group (B- ALL) | | | | | | |
| Standard | 671 | 55 | 1.36(0.07-9.23) | 7.6(5.6-9.6) | 8.6(6.4-10.8) | 1.00 |
| High | 418 | 43 | 1.15(0.00-9.14) | 8.9(6.2-11.7) | 10.8(7.7-13.9) | |
| NCI risk group (T- ALL) | | | | | | |
| Standard | 25 | 3 | 0.73(0.52-20.51) | 8.0(0.0-18.9) | 8.0(0.0-18.9) | 1.00 |
| High | 145 | 14 | 1.17(0.15-10.15) | 8.4(3.8-12.9) | 9.2(4.4-14.1) | |
| Sex | | | | | | |
| Male | 688 | 81 | 1.15(0.07-20.5) | 10.4(8.1-12.7) | 12.2(9.6-14.7) | 0.02 |
| Female | 603 | 40 | 1.34(0.00-7.10) | 6.2(4.2-8.1) | 6.8(4.8-8.8) | |
| Age at Diagnosis | | | | | | |
| Infant | 20 | 2 | 0.72(0.54-0.91) | 10.0(0.0-23.6) | 10.0(0.0-23.6) | 1.00 |
| 1-10 years | 1005 | 94 | 1.26(0.07-20.51) | 8.4(6.6-10.1) | 9.6(7.7-11.4) | |
| Older than 10 | 266 | 25 | 1.32(0.00-7.48) | 8.5(5.1-11.9) | 10.0(6.2-13.7) | |
| Leukocyte count at Diagnosis | | | | | | |
| $<10 \times 10^9$/L | 604 | 54 | 1.30(0.13-9.23) | 8.2(6.0-10.4) | 9.3(6.9-11.7) | 1.00 |
| 10 to 49 $\times 10^9$/L | 387 | 38 | 1.81(0.07-20.51) | 8.7(5.9-11.6) | 10.1(7.0-13.2) | |
| 50 to 99 $\times 10^9$/L | 142 | 11 | 1.12(0.44-5.60) | 6.5(2.4-10.6) | 8.2(3.5-12.9) | |
| ≥100 × 109/L | 158 | 18 | 0.55(0.00-10.15) | 10.2(5.4-14.9) | 11.0(6.0-16.0) | |
| Race | | | | | | |
| White | 1059 | 93 | 1.32(0.00-20.51) | 7.9(6.2-9.5) | 9.0(7.2-10.8) | 1.00 |
| Black | 180 | 20 | 0.82(0.16-9.14) | 10.1(5.7-14.6) | 11.8(6.8-16.7) | |
| Other | 52 | 8 | 1.47(0.44-6.09) | 13.5(4.1-22.8) | 15.8(5.6-26.1) | |
| Immunophenotype | | | | | | |
| B | 1089 | 98 | 1.26(0.00-9.23) | 8.1(6.5-9.8) | 9.5(7.7-11.3) | 1.00 |

| Factor | No. Patients | No. Patients with Post-Therapy Relapse | Median time to Post-Therapy Relapse (range) in Years | Estimate % (95% CI) | | P Value |
|---|---|---|---|---|---|---|
| | | | | Year 5 | Year 10 | |
| T | 170 | 17 | 1.02(0.15-20.51) | 8.3(4.1-12.5) | 9.0(4.7-13.4) | |
| CNS status | | | | | | |
| CNS-1 | 913 | 85 | 1.32(0.13-20.51) | 8.4(6.5-10.2) | 9.7(7.7-11.6) | 1.00 |
| CNS-2 | 251 | 26 | 1.40(0.00-10.15) | 8.8(5.3-12.4) | 10.5(6.5-14.4) | |
| Traumatic lumber puncture with blast | 89 | 5 | 1.50(0.11-3.56) | 5.8(0.8-10.8) | 5.8(0.8-10.8) | |
| CNS-3 | 33 | 4 | 0.78(0.27-1.15) | 12.1(0.8-23.5) | 12.1(0.8-23.5) | |
| DNA index | | | | | | |
| ≥1.16 | 295 | 20 | 1.64(0.31-4.59) | 6.9(4.0-9.9) | 6.9(4.0-9.9) | 0.95 |
| <1.16 | 996 | 101 | 1.15(0.00-20.51) | 8.9(7.1-10.6) | 10.4(8.5-12.4) | |
| Genetic abnormality | | | | | | |
| Hyperdiploidy >50 | | | | | | |
| Present | 381 | 30 | 1.39(0.07-6.37) | 7.5(4.8-10.1) | 8.1(5.3-10.9) | 1.00 |
| Absent | 856 | 82 | 1.02(0.00-20.51) | 8.3(6.4-10.2) | 9.8(7.8-11.9) | |
| t(9;22)/*BCR-ABL1* | | | | | | |
| Present | 31 | 9 | 0.43(0.11-1.84) | 29.0(12.7-45.4) | 29.0(12.7-45.4) | 0.002 |
| Absent | 1260 | 112 | 1.52(0.12-20.51) | 7.9(6.4-9.4) | 9.2(7.5-10.8) | |
| t(1;19)/*TCF3-PBX1* | | | | | | |
| Present | 60 | 1 | 0.97(0.97-0.97) | 1.7(0.0-4.9) | 1.7(0.0-4.9) | 0.52 |
| Absent | 1231 | 120 | 1.26(0.00-20.51) | 8.7(7.1-10.3) | 10.0(8.3-11.7) | |
| t(12;21)/*ETV6-RUNX1* | | | | | | |
| Present | 223 | 13 | 2.89(0.46-9.23) | 4.1(1.5-6.8) | 6.8(3.1-10.5) | 0.55 |
| Absent | 1068 | 108 | 1.13(0.00-20.51) | 9.3(7.6-11.1) | 10.3(8.4-12.1) | |
| t(4;11)/*MLL-AFF1* | | | | | | |
| Present | 15 | 2 | 1.08(0.91-1.25) | 13.3(0.02-31.3) | 13.3(0.03-31.3) | 1.00 |
| Absent | 1276 | 119 | 1.28(0.00-20.51) | 8.4(6.8-9.9) | 9.6(7.9-11.3) | |
| Minimal residual disease | | | | | | |
| On day 19 of induction | | | | | | |
| <0.01% | 255 | 15 | 1.80(0.12-5.73) | 5.7(2.8-8.6) | 6.4(3.2-9.5) | 1.00 |

| Factor | No. Patients | No. Patients with Post-Therapy Relapse | Median time to Post-Therapy Relapse (range) in Years | Estimate % (95% CI) | | P Value |
|---|---|---|---|---|---|---|
| | | | | Year 5 | Year 10 | |
| 0.01%-<0.1% | 126 | 7 | 1.99(0.13-9.14) | 4.8(1.0-8.6) | 8.9(0.1-17.7) | |
| ≥0.1% | 194 | 20 | 1.11(0.00-6.09) | 10.1(5.8-14.4) | 11.1(6.4-15.7) | |
| On remission date | | | | | | |
| <0.01% | 507 | 27 | 1.80(0.12-7.48) | 4.9(3.0-6.8) | 6.0(3.7-8.3) | <0.001 |
| 0.01%-<0.1% | 63 | 4 | 2.53(0.93-9.14) | 5.0(0.03-10.6) | 9.8(0.03-20.7) | |
| ≥0.1% | 59 | 15 | 1.08(0.00-3.63) | 25.9(14.4-37.3) | 25.9(14.4-37.3) | |
| Total Therapy Studies | | | | | | |
| 11 and 12 (1984-1991) | 438 | 55 | 1.15(0.15-20.51) | 11.2(8.2-14.1) | 12.1(9.0-15.2) | 0.026 |
| 13A, 13B and 14 (1991-1999) | 398 | 39 | 1.78(0.11-9.23) | 8.1(5.4-10.7) | 9.8(6.9-12.8) | |
| 15 (2000-2007) | 455 | 27 | 1.03(0.00-6.09) | 5.9(3.7-8.1) | 6.4(4.0-8.8) | |

**Table 3**

Independent risk factors for post-therapy relapse

| Features | Analysis excluding MRD | | Analysis including MRD | |
|---|---|---|---|---|
| | **Hazard ratios (95% CI)** | **P value** | **Hazard ratios (95% CI)** | **P value** |
| Study 15 | 0.61(0.4-0.96) | 0.03 | 0.66 (0.35-1.23) | 0.18 |
| *BCR-ABL1* Absent | 0.27 (0.12-0.57) | <0.001 | 0.44 (0.11-1.64) | 0.22 |
| Negative (<0.01%) MRD on remission date | --------- | ------- | 0.26(0.11-0.54) | <0.001 |
| 0.01%-<0.1% MRD on remission date | --------- | ------- | 0.27(0.08-0.87) | 0.028 |
| Female | 0.58(0.4-0.88) | 0.01 | 0.53(0.27-1.04) | 0.06 |

MRD denotes minimal residual disease, CI confidence interval