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Clinical Trials and Observations

Antimetabolite therapy for lesser-risk B-lineage acute lymphoblastic childhood: a report from Children's Oncology Group Study P9201

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Abstract

Pediatric Oncology Group (POG) protocol 9201 enrolled children with lesser-risk B-linea lymphoblastic leukemia (ALL) defined by age (1-9), white blood cell count (WBC) less th (50 000/μL), DNA findings of trisomies 4 and 10 (or DNA index > 1.16), and lack of over nervous system (CNS) leukemia. After vincristine, prednisone, and asparaginase inducti eligible patients attained remission (3 induction deaths) and received 6 courses of intrav methotrexate (1 g/m^2) with daily mercaptopurine. Weekly intramuscular methotrexate v during maintenance; pulses of vincristine and prednisone were administered with perio chemotherapy. Treatment duration was 2.5 years. No alkylators, epipodophylotoxins, an radiation were given. The 6-year event-free survival (EFS) was 86.6% with overall surviv 97.2%. Patients with less than 5% marrow blasts on induction day 15 had superior EFS. reaching conventional statistical significance (P = .068) was noted for superior outcome with trisomies of chromosomes 4 and 10 versus those lacking double trisomies. Sex, ethn status, and WBC were not predictive. This indicates the great majority of children with le B-lineage ALL are curable without agents with substantial late effects.

Introduction

B-lineage acute lymphoblastic leukemia (ALL) is the most common childhood malignanc industrialized countries.[1] Multiple different treatments have produced cures for a majori with ALL.[2,3] A wide variety of prognostic factors have been used to separate patients intc risk and higher risk. The Pediatric Oncology Group (POG) previously recognized patient: "favorable" age and initial white blood cell count (WBC) by National Cancer Institute cor group criteria[4] whose blasts have an elevated DNA index or trisomy of both chromosome their leukemic cells to have an exceptionally good prognosis when treated with antimetal a finding supported by other studies.[6,7] Because of the potential short- and long-term bu therapy, POG 9201 was designed to extend this observation to a larger set of patients, att clearly define a group of patients with an excellent prognosis even when treated with less treatment.

Patients, materials, and methods

Patients

The POG 9201 protocol opened as a limited institution pilot study in June 1992 and as a single-arm phase 3 group-wide study in November 1994. The study met accrual goals an patient enrollment in November 1999. Patients eligible for enrollment were diagnosed w ALL (confirmed by a central POG laboratory), aged 1 to 9 years, and had an initial WBC l 10^9/L (50 000/μL). Evidence of trisomies 4 and 10 was required if cytogenetics were abr (informative); it was assumed that "normal" cytogenetic studies might reflect lack of cell division in the sample, and demonstration of a DNA index more than 1.16 was allowed as marker; DNA index was determined by a POG reference laboratory and all cytogenetics v determined centrally or centrally reviewed by one of the authors (A.J.C.). Fluorescence in hybridization (FISH), to determine trisomies of chromosomes 4 and 10, was performed c by another central POG reference laboratory (M.J.P.); these results were not used in dete eligibility for the study but are used in analysis of outcomes. Initial cerebrospinal fluid (C no leukemic cells (CNS1) or, if blasts were present, had a total WBC less than 5 (CNS2). A traumatic initial spinal taps in patients with circulating peripheral blasts were included i category even if no blasts were noted in the CSF itself provided the CSF WBC was less tha with initial CNS3 status or testicular leukemia were excluded. During the years 1997 to 1(POG had open studies for all patients with B-lineage ALL, this study accrued approximat (276/1374) of protocol registrations for patients older than 1 year. Informed consent for classification studies and registration on POG induction therapy was obtained from legal all patients prior to the initiation of treatment. A separate consent for POG 9201 was req of induction. All informed consent documents were approved by the local institutional re all institutions entering patients on this protocol, followed then-current POG guidelines, with the Declaration of Helsinki. This study (POG-9201) is registered with the National C (http://www.cancer.gov/clinicaltrials).

Between June 1992 and November 1999, a total of 658 patients were enrolled and initiat the POG 9400 classification study as described in this report. Two patients were biologic due to cytogenetic findings and 3 others were administratively ineligible due to improper

signing of informed consent. Three patients died prior to completing induction (2 from c sepsis present at the time of diagnosis and the third from unclear cause), and an additior developed biopsy-proven glomerulonephritis during induction and was not registered or treatment. Thus 653 of the 656 patients who were biologically eligible attained remissior induction treatment, with the only failures being 3 induction deaths. Excluding patients for treatment on this protocol, the remaining 649 patients, all of whom attained remissic induction, are included in this report. All data received by the statistical office and/or stu as of April 29, 2004, were included in the analyses. Data through end of treatment or firs available for all patients with the exception of 4 who were removed from protocol therap family relocations, 1 due to uncontrolled emesis, and 1 due to parental preference for car physician. These patients were censored at that time point. Fifty-six percent of patients v 68.6% white, 17% Hispanic, 6.6% African American, and 7.8% other races. Median age a was 3.9 years (range: 1.0-9.9 years). Fifty-four patients had CNS2 involvement or a traur (red blood cell count 10 or more) at diagnosis. Seventy-three percent of patients had a W $\times 10^9$/L (10 000/μL).

Treatment plan

Initial induction therapy for all patients included vincristine (1.5 mg/m^2 with 2.0 mg ma intravenously on days 1, 8, 15, and 22; prednisone 40 mg/m^2 per day in 3 divided doses and L-asparaginase 6000 international units/m^2 intramuscularly on days 2, 5, 8, 12, 15, patients received age-based intrathecal chemotherapy on days 1 and 15; patients with CN treated identically to CNS1 patients except for also receiving IT chemotherapy on days 8 induction. The initial protocol used triple intrathecal chemotherapy (methotrexate, hydr cytosine arabinoside). This was changed to methotrexate alone when therapeutic modific made to address CNS toxicity on companion protocols, although there was no indication toxicity in this study. The number of circulating blasts present on day 8 was recorded for patients who had circulating blasts present at the time of diagnosis. Percent residual blas determined by bone marrow morphology on days 15 and 29 of induction.

Consolidation therapy from weeks 5 to 25 included intravenous methotrexate 1 g/m^2 as infusion at weeks 7, 10, 13, 16, 19, and 22 with delayed leucovorin rescue along with oral 6-mercaptopurine (6MP), 50 mg/m^2 daily. Simultaneous intrathecal therapy was admin 10, 13, 16, 19, and 22. Pulses with 2 weekly doses of intravenous vincristine (1.5 mg/m^2 w maximum dose) and 7 days of oral prednisone (40 mg/m^2 per day, in 3 divided doses tal maximum daily dose 60 mg) were given from weeks 8 to 9 and 16 to 17.

Continuation therapy from weeks 25 to 130 included oral 6MP 75 mg/m^2 daily and IM m mg/m^2 weekly. Pulses of vincristine and prednisone, as in consolidation, were given at w 41 to 42, 57 to 58, 73 to 74, 89 to 90, and 105 to 106. Intrathecal chemotherapy was giver initially every 8 weeks through week 105, which was later modified (due to toxicity on co protocols) to every 12 weeks to week 109. The original treatment schema is shown in Fig above, some changes were made in intrathecal therapy for consistency with alterations ir studies felt to have excess toxicity. Patients with initial CNS1 status thus received 14 to 2

treatments. There was no indication of a difference in outcome or toxicity related to the c intrathecal prophylaxis schedule or drugs. Patients received Pneumocystis prophylaxis w trimethoprim/sulfamethoxazole, pentamidine, or dapsone from attainment of remission following the completion of therapy. A diagnostic lumbar puncture and bone marrow asp with a physical examination and routine complete blood count (CBC) were required at th treatment (weeks 130-131). A routine testicular biopsy was not required. Diagnostic spin planned at 4, 8, and 12 months off treatment while no off-treatment bone marrow aspira required in the absence of a clinical suspicion of relapse.

Statistical analyses

This was a single-arm nonrandomized study. Event-free survival (EFS) and overall survi were computed for all eligible patients on study. Time to an adverse event was defined as date of diagnosis until first relapse, second malignancy, or death from any cause. Patient experiencing an event were censored as of the date of last contact. The EFS and OS estim computed using the Kaplan-Meier method[8] and standard errors of the estimates were de according to Peto and Peto.[9]

Toxicity grading

Toxicity was graded according to Common Toxicity Criteria (CTC) version 2.0: grade 3 ir severe; grade 4, unacceptable or life-threatening toxicity; and grade 5, lethal toxicity.[10] A were reviewed and scored by the primary study coordinator. Grade 1 and 2 toxicities (mi moderate) were generally not considered significant, but all grade 2 or greater neurotoxi recorded.

Results

The 6-year EFS and OS were 86.6% ± 1.8% (± standard error) and 97.2% ± 0.87%, respe Figure 2). The highest risk for relapse was between 2 and 5 years from diagnosis.

Data were available from day-15 marrow aspirates on 571 patients (others did not have n aspirations or the quality was inadequate for interpretation). Patients with 5% or fewer b marrows (n = 525) had superior EFS (87.6% ± 2.0%) compared with those (n = 46) with blasts (76.1% ± 9.3%) with a *P* value of .010 as shown in Figure 3. This supports multiple observations regarding the prognostic value of early response, whether measured by peri on day-8 or day-15 bone marrow aspiration.[11,12] In this study, only 9 patients had more t blasts/μL at day 8, too few to allow meaningful statistical analysis, although 2 of these 9 relapsed.

There were no statistically significant differences in EFS based upon sex, CNS status, eth WBC value (< 10 $\times 10^9$/L versus 10-50 $\times$ 10^9/L [< 10 000 μ/L versus 10 000–50 000 μ/L majority of patients on this study were CNS1 (595/649 or 91.7%). They had a 6-year EFS 1.8% compared with 76.8% ± 8.3% for those who were either CNS2 or had traumatic CSI = 54). With this small sample size, results favoring CNS1 patients did not reach standard statistical significance in EFS (*P* = .072). Separate analysis of the 28 patients with conve

disease (blasts present with red cell count < 10) demonstrated 6-year EFS of 79.6%, prov
indication of this group having a worse outcome than the entire 54 patients recognized w
measure of CNS involvement. Likewise, comparison of EFS (P = .54) between white and
showed no significant differences.

Patients with proven trisomies of chromosomes 4 and 10 (by cytogenetics or FISH) show
nonsignificant trend toward better EFS compared with those lacking the double trisomie
techniques (6-year EFS of 87.4% vs 82.5%, P = .068) (Figure 4). The difference in overal
(97.7% vs 94.5%) was not significant (P = .11). Further, the "most favorable" subset of pa
who had trisomies 4 and 10, an M1 marrow on day 15, and were CNS1 at diagnosis had a
88.9% ± 1.9% and an OS of 97.7% ± 0.9%, demonstrating that this fails to select patients
outcomes.

Salvage therapy and outcomes

Of the 79 relapses on this study, 13 occurred on treatment (3 CNS, 9 marrow, and 1 marr
and 10 were identified via end of treatment evaluation (6 CNS, 3 marrow, and 1 testicula
relapses were noted between 2 to 46 months after end of treatment; 2 occurred in patien
been removed from protocol therapy.

Outcomes for relapsed patients are summarized below, grouped by site of relapse.

Isolated testicular relapse (n = 7). Isolated testicular relapse was the initial event for 7 patie
physical examination, and confirmed by biopsy. A single relapse was noted at the end of
between 3 to 8 months off treatment and 1 at 14 months off treatment. These patients in
retreated with systemic chemotherapy and testicular radiation; all are alive and well in s
remission, off treatment 16 to 54 months. The other patient refused conventional treatm
alternative medications for 6 months until he had a marrow relapse. This patient is curre
remission on treatment. Since all were late testicular relapses, they would be expected to
excellent salvage rate.[13]

Isolated CNS relapse (n = 12). There were 12 patients with isolated CNS relapse as their ini
whom 3 were diagnosed on treatment at weeks 84, 97, and 97. Routine end of treatment
relapses. The other 3 were identified on routine LPs per protocol 5 to 13 months off treat
patient had headaches for a week prior to the end of treatment LP, while all others were
at the time of CNS relapse.

There was one death from brain herniation shortly after an end of treatment CNS relapse
patient with headaches). All others had second systemic treatment including cranial or c
radiation with one having a second CNS relapse. This patient is well 11 months following
unrelated transplantation. All other patients are alive and well from 1 to 48 months off s
treatment. This is in accord with anticipated salvage rates after late (> 18 months after d
isolated CNS relapse.[14]

Combined CNS and testicular relapse (n = 1). A single patient had a CNS and testicular relap
off therapy and is in second remission 2 years off retreatment with chemotherapy and ra

Other extramedullary relapse sites (n = 4). Less common extramedullary relapse occurred ir first was an extradural, lymphomatous mass (with flow cytometry identical to the origina patient is more than a year off treatment in second remission. Another patient had a cort relapse 29 months off therapy with 5% marrow blasts marking like the original ALL and remission on chemotherapy 13 months after relapse. The third patient relapsed in a prea node 32 months off treatment and is in second remission after 3 months of treatment. Tl had an orbital relapse 7 months off therapy, received alternative treatments, had a marrc died after a transplantation.

Extramedullary relapses with abnormal marrows (n = 3). There was one testicular relapse 2 n treatment with 7% marrow blasts. This patient was retreated with chemotherapy and tes radiation, remaining on treatment 23 months after relapse. Another patient had CNS dis routine LP 9 months off treatment and 8% marrow blasts. This patient had a marrow tra relapsed 21 months later, and had a second transplantation. He is free of disease 46 mon transplantation. The third patient had an ovarian relapse 22 months off treatment with ç marrow and is off treatment, 44 months after relapse.

Bone marrow ± other sites (n = 50). There were 39 patients with isolated marrow relapse; 9 and 3 identified at end of treatment evaluation. Of these 12, 9 have died, 4 prior to and 5 transplantation; 3 survivors are 32 to 56 months after transplantation.

The 27 patients experiencing a posttreatment isolated marrow relapse did so 9 to 38 mor treatment. In this group, 11 had transplantations with 3 deaths, 1 in relapse, and 7 in rem months after transplantation. There were 16 treated with intensive chemotherapy and 15 remission 10 to 66 months after relapse, while 1 is on treatment in third remission after a

Marrow relapse was combined with extramedullary relapse in 11 patients, 8 having CNS each CNS and testicular, testicular, and scalp relapses. One patient relapsed at week 61 a transplantation, while the others, relapsing 4 to 46 months off treatment remain alive 1 t after relapse, 2 after transplantations.

Relapses in patients previously removed from study (n = 2)

A patient off study for spinal myelopathy at week 23 received alternative chemotherapy a testicular relapse; he is 14 months off second treatment. Another patient transferred to a noncooperative group physician at week 69, received unknown treatment, and died after relapse. Both were counted as failing at relapse.

Toxicities

The therapy was generally well tolerated. While 560 (86.3%) of the patients had at least (grade 4 hematologic toxicity after induction, there were no episodes of fatal sepsis. The n nonhematologic toxicity was elevated transaminases with 340 (52%) of patients having a episode of grade 3 or 4 toxicity. All of these were reversible and no patient was removed f therapy or had therapy withheld for an excessive period of time as a result.

Neurotoxicity

Acute neurotoxicity was noted in 57 patients (8.8%) during treatment. The great majorit
although 2 patients developed major paralysis. The first had clinical findings compatible
Guillain-Barré syndrome shortly after bacterial sepsis. This patient developed spinal my
has stable paraplegia with a neurogenic bladder. The other patient developed acute quad
week 73 intrathecal medications as did 2 patients on other studies treated on the same d
institution; no additional intrathecal medications were given and the patient remains in
Extensive investigation failed to identify a cause (anonymous by request, oral personal c
October 8, 1997).

Seizures occurred in 14 (2.2%) patients with 4 during induction, 2 having scans indicatin
microthrombi, likely related to asparaginase. Of the remaining 10 seizures, 2 were attribu
infection: 1 with bacterial sepsis and 1 with erlichiosis in blood and CSF. Another was fel
febrile convulsion and one a new onset seizure disorder (focal seizure by electroencephal
weeks after most recent intrathecal medication with normal magnetic resonance imaging
remaining 6 (one with neurofibromatosis) had seizures within 10 days of intrathecal mec
no other risk factors identified.

The relatively low seizure frequency may have been due to the fact that when intrathecal
were given 3 weeks apart during consolidation, 5 of 6 were administered concurrently wi
methotrexate and followed by intravenous fluids and leucovorin rescue, unlike some oth
studies with a higher incidence of seizures in which more frequent intrathecal medicatio
administered, cranial radiation was given, and/or no intrathecal medications were imme
by leucovorin rescue.[15–17] This also differs from the seizure frequency on companion PO
separated intravenous methotrexate and intrathecal chemotherapy and provided no leuc
after any intrathecal medications.[18] A currently open Children's Oncology Group study is
issue in greater detail through studies of neurologic outcomes of patients on differing stu

Grade 2 or 3 headaches were reported in 5 patients, while 4 had transient motor weakne
ataxia, and/or visual complaints; all of these 9 resolved.

There were 31 patients with motor or peripheral nerve toxicities related to vincristine, 6
significance. Peripheral neurotoxicity at least transiently impacting normal activity occu
whom 3 were proven to have Charcot-Marie Tooth (CMT) disease.[19] Of these patients, 18
vincristine dosing, and 1 patient (with CMT) received no vincristine after induction. All p
CMT required physical therapy; 2 had long-lasting disabilities.

Deaths in remission

There were 2 deaths in remission, both due to varicella shortly after the week-73 to -74 p
pulse. Neither patient was neutropenic or lymphopenic at the time and both were treated
within 24 hours of hospital admission. A detailed review of all 110 cases of varicella on th
found that more severe infections were seen in patients who received prednisone near th
varicella infection.[20]

Second malignancies

Myelodysplasia characterized by monosomy 7 developed in 2 patients; in neither case wa cytogenetic finding observed at original diagnosis. While this is unusual as a side effect o treatments, it has been reported.[21] Both patients have had marrow transplantations and remission. It is noteworthy that one of these patients had a sibling develop ALL followed 7 (Paul Bowman, MD, Cook Children's Hospital, Fort Worth, TX, personal communicatic 2003), which may imply a genetic link[22] even though monosomy 7 was not identified at

Discussion

It is clear that patients with high hyperdiploidy by virtue of trisomies of chromosomes su 17 or 4, 10, and 18 potentially have a superior outcome.[5,23,24] The United Kingdom grou 5-year EFS of 86% for low-risk females and a 5-year overall survival of 96% for all patien years with trisomies 4 and 18.[25] However, some studies have shown that lesser-risk child may actually have results similar to those in standard- and higher-risk groups if their the sufficiently intense.[26,27] It is therefore critical to maintain sufficient intensity to preserve excellent outcomes seen in this group of patients.

This study demonstrates that moderately-intensive antimetabolite-based chemotherapy than 90% long-term survival in young children with lesser-risk ALL, comprising approxi childhood cases of B-lineage ALL as noted above. It is noteworthy that none of these chil radiation, anthracyclines or alkylating agents, dexamethasone, or topoisomerase inhibitc their initial treatment protocol. Results from Holland, the Nordic group, and several Uni studies have demonstrated 5-year EFS of approximately 85% in their lowest-risk groups radiation was omitted, further supporting this approach to CNS prophylaxis[5,24,28–30] fo A meta-analysis of worldwide trials including almost 3000 patients also showed equivale radiotherapy and long-term intrathe-cal therapy.[31]

Intravenous methotrexate and intrathecal prophylaxis have been associated with long-te neurocognitive dysfunction,[17,32] though the degree to which any one child is affected is h Encouraging studies, describing populations of adults, treated for ALL during childhood cranial radiation, have found that the likelihood of being employed, married, and insure with that of the general population.[33] The relatively low seizure frequency in this study n due to the fact that when intrathecal medications were given 3 weeks apart during conso were administered concurrently with intravenous methotrexate and thus were followed h fluids and leucovorin rescue as noted above.

Vincristine has been associated with long-term neuropathies, but the cumulative dose or low, as was the cumulative steroid dose. In this young population treated with prednison dexamethasone, there were no reports of avascular necrosis recorded on the off-therapy submitted by participating institutions.[34]

Thus it is likely that the great majority of the patients in this study will not only be long-t but will do so with a minimum of significant late effects.

The issue of CNS2 status has been controversial with some noting this as an adverse prog feature[35] and others finding these patients having outcomes identical to those of CNS1 p

This may relate to the fact that patients with initial traumatic CSF have also been noted t
outcomes[37,38]; they were thus grouped with CNS2 patients in this study. In these lesser-
with the addition of 2 intrathecal chemotherapy treatments during induction, there was
difference between the CNS1 patients and those in the CNS2 group, as also seen in the St
Therapy XIIIB, which used a similar strategy.[39] This finding remained true when only th
with CNS2 status as defined by Burger et al[37] and Gajjar et al[38] were considered. Whethe
result in this defined patient group would have been obtained without this slight intensif
therapy is unknown. The number of CNS2 patients was small enough that a substantial d
outcome would have been required to reach statistical significance.

Many previous studies have found differences in outcome based upon ethnic group,[40–4
studies have not confirmed this,[43] and the issue when corrected for disease biology rema
Males have historically been reported to have an inferior prognosis,[45,46] although recent
focused on lesser-risk patients have found no significant differences related to sex.[39,47] N
sex was predictive of outcome in this study. There have been no deaths among the 44 Afr
enrolled; the 6-year EFSs for males and females are 84.8% and 88.5%, respectively, with
OSs of 96.4% and 98.2%. One assumes that this is due to the relative uniformity of this le
of patients, defined by age, WBC at diagnosis, favorable cytogenetics, and the absence of
Thus, these host and disease characteristics are the more critical determinants of outcom

A critical challenge remains, to identify patients at higher risk of relapse who might pote
from more aggressive therapy. Even among this group of lesser-risk patients, greater tha
patients had an event of some type by years 7 to 8. The patients without trisomies 4 and
about 80% and patients with more than 5% residual blasts on day-15 marrows had an EF
Patients with both of these unfavorable features (n = 6) had an EFS of 50%. Thus, an acc
assessment of blast cytogenetics and the use of early morphologic response to augment t
have improved the EFS and overall survival for the group as a whole, especially for those
favorable group who are identified as having some higher-risk features.[48] Whether the u
dexamethasone (instead of prednisone) or a delayed intensification phase would improv
unknown. Some randomized studies, with excellent overall results, have demonstrated th
dexamethasone,[49,50] while other trials have not.[51] A delayed intensification commonly i
outcome among standard-risk patients, but also adds anthracycline, an alkylating agent
increased risk of infection.[30]

It should be noted that our study did not include patients with the TEL:AML1[12,21] transl
is now believed to also confer a generally favorable prognosis, except for slow molecular
These patients very rarely have hyperdiploidy and would largely represent a distinct grou
from those who were eligible for this study.[53] Whether those with this translocation wou
outcomes with this therapy is addressed by a subsequent study, POG 9904.

The patients in our study had an overall 7- to 8-year survival of more than 95%. This is in
smaller prior studies of patients selected for favorable host and disease characteristics.[5,
Further improvements in outcome, without increasing the burden of care for all, will res
identification of prognostic features, such as the presence of minimal residual disease, w

so that selective intensification can be applied. Since significant late toxicities were unco
care must be taken in regard to any reduction of therapy.[26,27,48] However, it is clear the
of patients, identified in this study by the lack of trisomies of both chromosomes 4 and 1
response, or both, that has potential to benefit from further intensification of therapy. D
microarrays, gene expression profiling, and other molecular measures of early response
more sensitive techniques for the identification of such slow responders.[54,55] Conversely
that rapid disappearance of minimal residual disease, measured by techniques more sen
microscopy, would be associated with an even better outcome than reported here, althou
selected for most favorable features by the techniques available in this study did not hav
significantly better than the entire population.

Supplementary Material

[Supplemental Appendix]

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Footnotes

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The online version of this article contains a data supplement.

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Authorship

Contribution: A.R.C. designed the study, reviewed all patient data in detail, and was the

of the paper; P.L.M. was the secondary coordinator, answered queries when A.R.C. was a contributed to the design, and reviewed all amendments; S.B.L. and M.D. performed the analyses; B.A.B. coordinated a companion protocol and worked closely with the first autl all the amendments and review of outcome data; J.K. coordinated a companion protocol closely with the first author regarding all amendments and overall study design; J.P. coo POG 9400 classification protocol to assure assignment of patients to the correct treatme reviewed questions regarding this study during the time of patient accrual; M.J.P. perfor analysis on all study patients, coordinated submission of results to the statistical office, a karyotype review; A.J.C. performed karyotypes on large numbers of patients and reviewe results for each patient entered in the study; J.J.S. designed statistical aspects of the stuc all the amendments; B.C., working with the first author on this matter, contributed to th and as POG ALL Chair, oversaw all aspects of the study; he also contributed extensively t paper.

A complete list of Children's Oncology Group Study P9201 participating institutions is pı Document S1, available on the *Blood* website; see the Supplemental Appendix link at the online article.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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References

1. Gurney JG, Severson RK, Davis S, Robison LL. Incidence of cancer in children in the U sex-, race-, and 1-year age-specific rates by histologic type. Cancer. 1995;75:2186–2195. [PubMed: 7697611]

2. Pui CH, Evans WE. Acute lymphoblastic leukemia. N Engl J Med. 1998;339:605–615. [PubMed: 9718381]

3. Pui CH, Campana D, Evans WE. Childhood acute lymphoblastic leukaemia–current st perspectives. Lancet Oncol. 2001;2:597–607. [PubMed: 11902549]

4. Smith M, Arthur D, Camitta B, et al. Uniform approach to risk classification and treatı assignment for children with acute lymphoblastic leukemia. J Clin Oncol. 1996;14:18–24 [PubMed: 8558195]

5. Harris MB, Shuster JJ, Carroll A, et al. Trisomy of leukemic cell chromosomes 4 and 1 children with B-progenitor cell acute lymphoblastic leukemia with a very low risk of trea Pediatric Oncology Group study. Blood. 1992;79:3316–3324. [PubMed: 1596572]

6. Hann I, Vora A, Harrison G, et al. Determinants of outcome after intensified therapy c lymphoblastic leukaemia: results from Medical Research Council United Kingdom acute leukaemia XI protocol. Br J Haematol. 2001;113:103–114. [PubMed: 11328289]

7. Schrappe M, Reiter A, Zimmerman M, et al. Long-term results of four consecutive tria

ALL performed by the ALL-BFM study group from 1981-1995. Leukemia. 2000;14:2286-
[PubMed: 11187912]

8. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am S
1958;53:457–481.

9. Peto R, Peto J. Asymptotically efficient rank invariant test procedure. J Royal Stat Soc
1972;135:185–198.

10. National Cancer Institute. Common Toxicity Criteria (CTC). [Accessed December 11,
Available at: http://ctep.cancer.gov/forms/CTCv204-30-992.pdf.

11. Ganyon PS, Desai AA, Bostrom BC, et al. Early response to therapy and outcome in cl
lymphoblastic leukemia. Cancer. 1997;80:1717–1726. [PubMed: 9351539]

12. Sandlund JT, Harrison PL, Rivera G, et al. Persistence of lymphoblasts on day 15 and
of remission induction predicts a dismal treatment outcome in children with acute lympl
leukemia. Blood. 2002;100:43–47. [PubMed: 12070006]

13. Wofford MM, Smith SD, Shuster JJ, et al. Treatment of occult or late overt testicular
children with acute lymphoblastic leukemia: a Pediatric Oncology Group study. J Clin Oı
1992;10:624–630. [PubMed: 1548525]

14. Ritchey AK, Pollock BH, Lauer SJ, et al. Improved survival of children with isolated C
acute lymphoblastic leukemia: a pediatric oncology group study. J Clin Oncol. 1999;17:2
[PubMed: 10577846]

15. Chessells JM, Cox TCS, Kendall B, et al. Neurotoxicity in lymphoblastic leukemia: coı
and intramuscular methotrexate and two doses of radiation. Arch Dis Child. 1990;65:41
[PMCID: PMC1792187] [PubMed: 2346334]

16. Winick NJ, Bowman WP, Kamen BA, et al. Unexpected acute neurologic toxicity in th
children with acute lymphoblastic leukemia. J Natl Cancer Inst. 1992;84:252–256. [Publ

17. Mahoney DH, Shuster JJ, Nitschke R, et al. Acute neurotoxicity in children with B-pr
lymphocytic leukemia: an association with intermediate dose methotrexate and intrathe
therapy: a Pediatric Oncology Group study. J Clin Oncol. 1998;16:1712–1722. [PubMed:

18. Rodes S, Bell BA, Abish S, et al. A report of the event-free survival (EFS) and neuroto
children with newly diagnosed standard risk acute lymphoblastic leukemia (ALL) on Ped
Group (POG) protocol 9405 [abstract]. Blood. 2005;106:259a. Abstract 882.

19. Chauvenet AR, Shashi V, Selsky C, et al. Vincristine-induced neuropathy as the initial
Charcot-Marie-Tooth Disease in acute lymphoblastic leukemia: a Pediatric Oncology Gro
Pediatr Hematol Oncol. 2003;25:316–320. [PubMed: 12679647]

20. Hill G, Chauvenet AR, Lovato J, McLean TW. Recent steroid therapy increases severi
infections in children with lesser risk acute lymphoblastic leukemia. Pediatrics. 2005;116
[PubMed: 16199681]

21. Aquino VM, Schneider NR, Sandler E. Secondary myelodysplasia with monosomy 7 a
treatment for acute lymphoblastic leukemia in childhood. J Pediatr Hematol Oncol. 200
[PubMed: 11196270]

22. Carroll WL, Morgan R, Glader BE. Childhood bone marrow monosomy 7 syndrome:
disorder? J Pediatr. 1985;107:578–580. [PubMed: 3862804]

23. Sutcliffe MJ, Shuster JJ, Sather HN, et al. High concordance from independent studi
Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) associating favoral
with combined trisomies 4, 10 and 17 in children with NCI standard-risk B-precursor acu
lymphoblastic leukemia: a Children's Oncology Group (COG) initiative. Leukemia. 2005;
[PubMed: 15789069]

24. Heerema NA, Sather HN, Sensel MG, et al. Prognostic impact of trisomies of chromo
and 5 among children with acute lymphoblastic leukemia and high hyperdiploidy (> 50 c
J Clin Oncol. 2000;18:1876–1887. [PubMed: 10784628]

25. Moorman AV, Richards SM, Martineau M, et al. Outcome heterogeneity in childhood
high-hyperdiploid acute lymphoblastic leukemia. Blood. 2003;102:2756–2762. [PubMed

26. Riehm H, Gadner H, Henze G, et al. Results and significance of six randomized trials
consecutive ALL-BFM studies. Haematol Blood Transfus. 1990;33:439–450. [PubMed:

27. Toyoda Y, Manabe A, Tsuchida M, et al. Six months of maintenance chemotherapy af
treatment for acute lymphoblastic leukemia of childhood. J Clin Oncol. 2000;18:1508–1
[PubMed: 10735899]

28. Kamps WA, Bokkerink JPM, Hakvoort-Cammel FGAJ, et al. BFM-oriented treatmen
with acute lymphoblastic leukemia without cranial radiation and treatment reduction for
patients: results of DCLSSG protocol ALL-8 (1991-1996). Leukemia. 2002;16:1099–1111.
[PubMed: 12040440]

29. Gustafson G, Schmiegelow K, Forestier E, et al. Improving outcome through two deca
childhood ALL in the Nordic countries: the impact of high-dose methotrexate in the redu
nervous system irradiation. Leukemia. 2000;14:2267–2275. [PubMed: 11187918]

30. Hutchinson RJ, Gaynon PS, Sather H, et al. Intensification of therapy for children wi
acute lymphoblastic leukemia: long-term follow-up of patients treated on Children's Can
1881. J Clin Oncol. 2003;21:1790–1797. [PubMed: 12721256]

31. Clarke M, Gaynon P, Hann I, et al. CNS-directed therapy for childhood acute lympho
leukemia: Childhood ALL Collaborative Group Overview of 43 randomized trials. J Clin
2003;21:1798–1809. [PubMed: 12721257]

32. Hill JM, Kornblith AB, Jones D, et al. A comparative study of the long term psychoso
of childhood acute lymphoblastic leukemia survivors treated by intrathecal methotrexate
without cranial radiation. Cancer. 1998;82:208–218. [PubMed: 9428499]

33. Pui C-H, Cheng C, Leung W, et al. Extended follow-up of long-term survivors of child

lymphoblastic leukemia. N Engl J Med. 2003;349:640–649. [PubMed: 12917300]

34. Mattano LA, Sather HN, Trigg ME, Nachman JB. Osteonecrosis as a complication of lymphoblastic leukemia in children: a report of the Children's Cancer Group. J Clin Onc 2000;18:3262–3272. [PubMed: 10986059]

35. Mahmoud HH, Rivera GK, Hancock ML, et al. Low leukocyte counts with blast cells i fluid of children with newly diagnosed acute lymphoblastic leukemia. N Engl J Med. 199 [PubMed: 8321259]

36. Gilchrist GS, Tubergen DG, Sather HN, et al. Low numbers of CSF blasts at diagnosis for the development of CNS leukemia in children with intermediate-risk acute lymphobl a Children's Cancer Group report. J Clin Oncol. 1994;12:2594–2600. [PubMed: 7989934

37. Burger B, Zimmermann M, Mann G, et al. Diagnostic cerebrospinal fluid examinatio with acute lymphoblastic leukemia: significance of low leukocyte counts with blasts or tr puncture. J Clin Oncol. 2003;21:184–188. [PubMed: 12525508]

38. Gajjar A, Harrison P, Dandlund J, et al. Traumatic lumbar puncture at diagnosis adv outcome in childhood acute lymphoblastic leukemia. Blood. 2000;96:3381–3384. [PubM

39. Pui C-H, Sandland JT, Pei D, et al. Improved outcome for children with acute lympho leukemia: results of Total Therapy Study XIIIB at St Jude Children's Research Hospital. 2004;104:2690–2696. [PubMed: 15251979]

40. Bhatia S, Sather H, Heerema N, et al. Racial and ethnic differences in survival of chil lymphoblastic leukemia. Blood. 2002;100:1957–1964. [PubMed: 12200352]

41. Pollock BH, DeBaun MR, Camitta BM, et al. Racial differences in the survival of child B-precursor acute lymphoblastic leukemia: a Pediatric Oncology Group study. Clin Onco 2000;18:813–823.

42. Kadan-Lottick NS, Ness K, Bhatia S, Gurney JG. Survival variability by race and ethn childhood acute lymphoblastic leukemia. JAMA. 2003;290:2008–2014. [PubMed: 1455

43. Pui C-H, Sunderland JT, Pei D, et al. Results of therapy for acute lymphoblastic leuk and white children. JAMA. 2003;290:2001–2007. [PubMed: 14559953]

44. Carroll WL. Race and outcome in childhood acute lymphoblastic leukemia. JAMA. 2003;290:2061–2063. [PubMed: 14559962]

45. Shuster JJ, Wacker P, Pullen J, et al. Prognostic significance of sex in childhood B-pr lymphoblastic leukemia: a Pediatric Oncology Group Study. J Clin Oncol. 1998;16:2854- [PubMed: 9704739]

46. Pui C-H, Boyette JM, Relling MV, et al. Sex differences in prognosis for children with lymphoblastic leukemia. J Clin Oncol. 1999;17:818–824. [PubMed: 10071272]

47. Silverman LB, Gelber RD, Dalton VK, et al. Improved outcome for children with acut leukemia: results of Dana-Farber Consortium Protocol 91-01. Blood. 2001;97:1211–1218.

[PubMed: 11222362]

48. Hunger SP, Winick NJ, Sather HN, Carroll WL. Therapy of low-risk subsets of childh lymphoblastic leukemia: when do we say enough? Pediatr Blood Cancer. 2005;45:876–8 [PubMed: 16007585]

49. Bostrom BC, Sensel MR, Sather HN, et al. Dexamethasone versus prednisone and da weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic report from the Children's Cancer Group. Blood. 2003;101:3809–3817. [PubMed: 12531

50. Mitchell CD, Richards SM, Kinsey SE, et al. Benefit of dexamethasone compared witl for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Counc randomized trial. Br J Haematol. 2005;129:734–745. [PubMed: 15952999]

51. Igarashi S, Manabe A, Ohara A, et al. No advantage of dexamethasone over prednisol outcome of standard- and intermediate-risk childhood acute lymphoblastic leukemia in Children's Cancer Study Group L95-14 protocol. J Clin Oncol. 2005;23:6489–6498. [PubMed: 16170158]

52. Madzo J, Zuna J, Muzikova K, et al. Slower molecular response to treatment predicts in patients with TEL/AML1 positive acute lymphoblastic leukemia. Cancer. 2003;97:105 [PubMed: 12491511]

53. Rubnitz JE, Downing JR, Pui C-H, et al. TEL gene rearrangement in acute lymphobla new genetic marker with prognostic significance. J Clin Oncol. 1997;15:1150–1157. [PubM

54. Holleman A, Cheok MH, den Boer ML, et al. Gene-expression patterns in drug-resist lymphoblastic leukemia cells and response to treatment. N Engl J Med. 2004;351:533–5 [PubMed: 15295046]

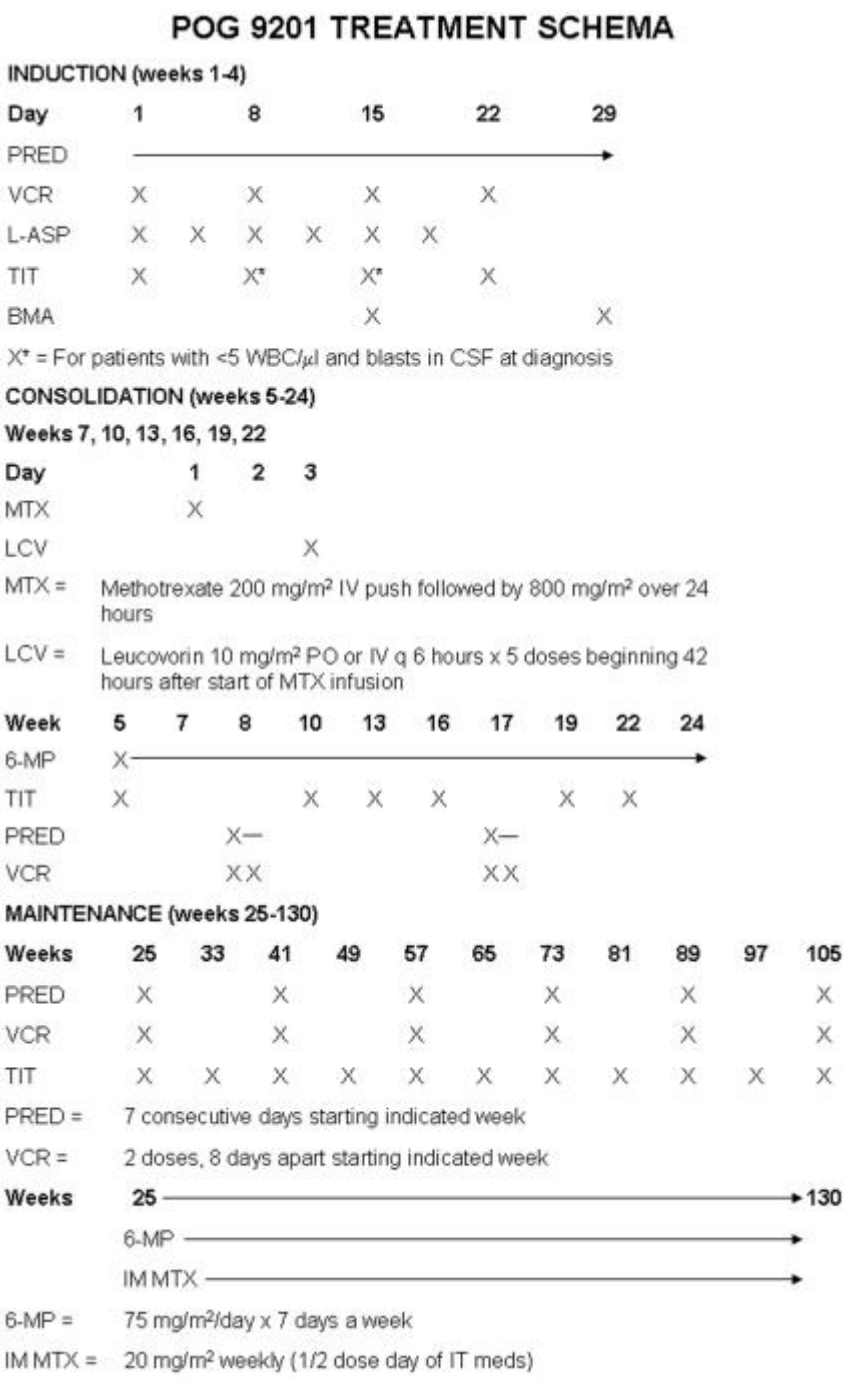
55. Pui C-H, Evans WE. Treatment of acute lymphoblastic leukemia. N Engl J Med. 200 [PubMed: 16407512]

56. Chauvenet A, Martin P, Bell B, et al. Anti-metabolite therapy for lesser-risk B-lineage lymphoblastic leukemia of childhood: Pediatric Oncology Group (POG) Study 9201. Ped 2005;44:567. Abstract 1717.

57. Chauvenet A, Martin P, Bell B, et al. Anti-metabolite therapy for lesser-risk b-lineage lymphoblastic leukemia of childhood: Pediatric Oncology Group (POG) Study 9201: Inte Society of Pediatric Oncology 2005. Ped Blood Cancer. 2005;45:421. Abstract O148.

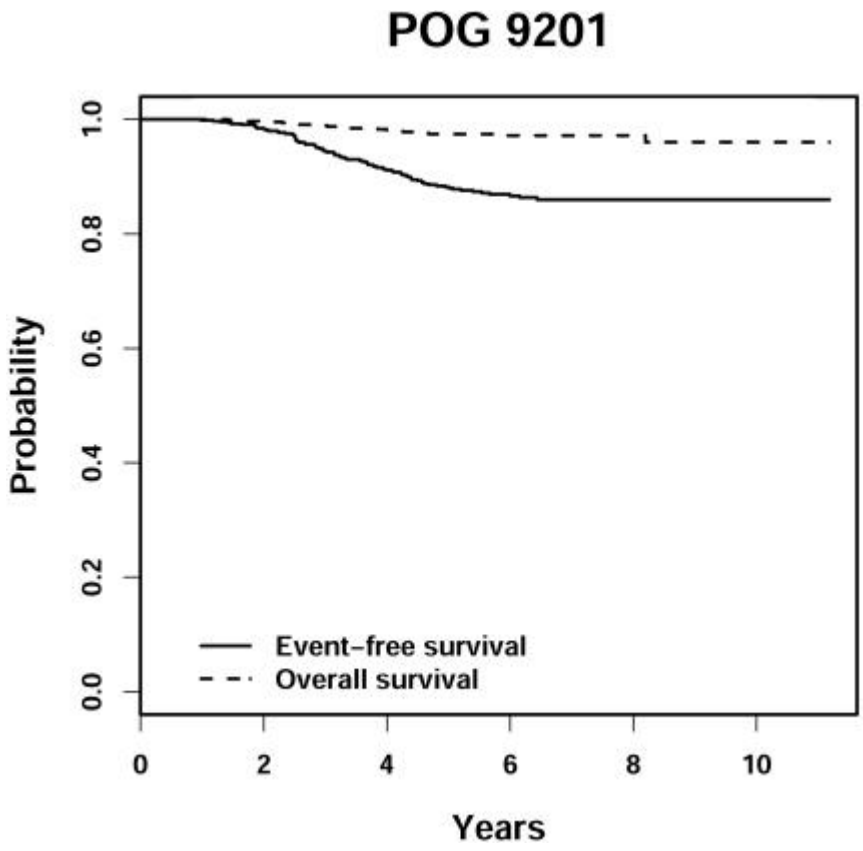
Figures and Tables

Figure 1



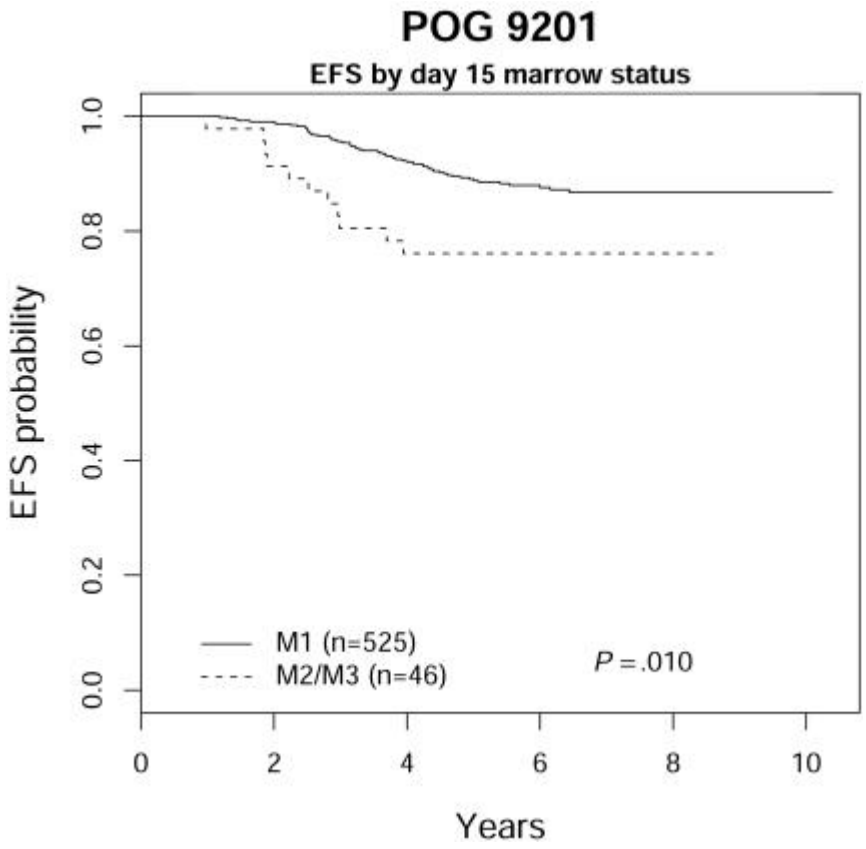
POG 9201 treatment schema.

Figure 2



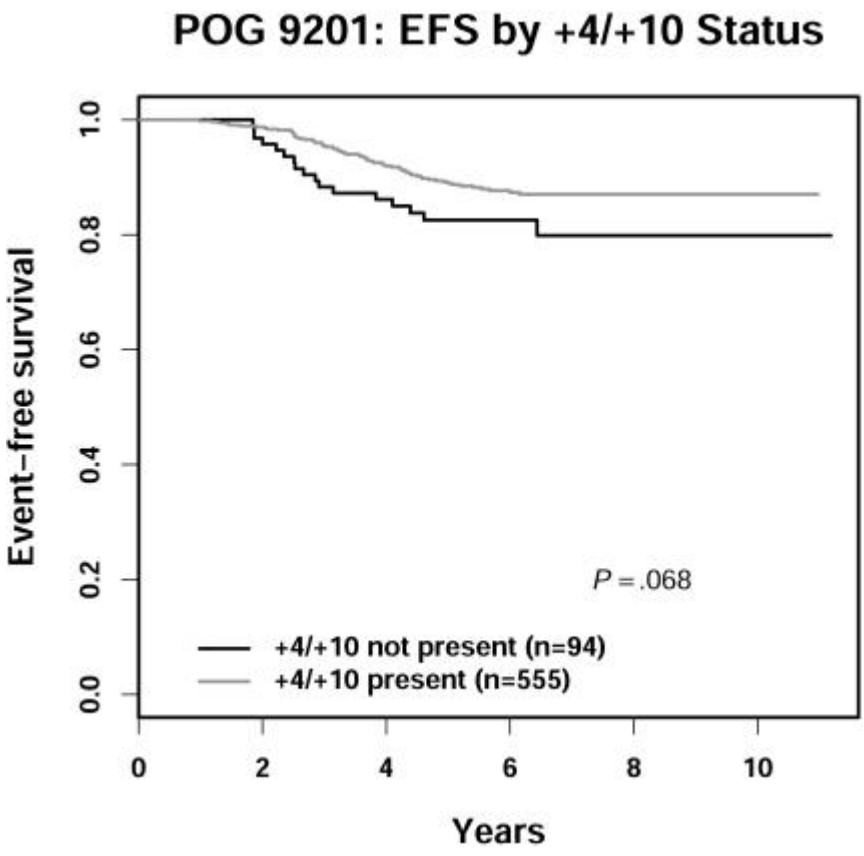
POG 9201 event-free and overall survival.

Figure 3



POG 9201 EFS by day-15 marrow status.

Figure 4



POG 9201 EFS by trisomy +4/+10 status.