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Late isolated central nervous system relapse in childhood B-cell acute lymphoblastic leukemia treated with intensified systemic therapy and delayed reduced-dose cranial radiation: A report from the Children's Oncology Group study AALL02P2

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Abstract

Background: Patients with late, ≥18 months post-diagnosis, isolated central nervous relapse (iCNS-R) of B-acute lymphoblastic leukemia (ALL) have excellent outcomes with chemotherapy plus cranial radiotherapy, with 5-yr overall survival (OS) approaching 80% in POG 9412. Subsequent relapse and radiation-related morbidity remain the causes of treatment failure and

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Conflict of Interest:

SPH has received consulting fees from Novartis, honoraria from Amgen and Jazz, and owns stock in Amgen. The remaining authors declare that there is no conflict of interest.

long-term sequelae. COG AALL02P2 aimed to maintain outcomes in patients with late iCNS-R using intensified chemotherapy and a decrease in cranial irradiation from 1800 to 1200 cGy.

Procedures: COG AALL02P2 enrolled 118 eligible patients with B-ALL and late iCNS-R who received intensified systemic therapy, triple intrathecal chemotherapy and 1200 cGy cranial irradiation delivered at 12 months, with maintenance chemotherapy continuing until 104 weeks post-diagnosis.

Results: The 3-yr event-free and overall survival (EFS) and OS were 64.3±4.5% and 79.6±3.8%, with 46.1% (18/39) of second relapses including the CNS. Of the 112 patients who completed therapy, 78 received protocol-specified radiation. Study enrollment was closed after interim monitoring analysis showed inferior EFS compared to POG 9412. Patients with initial NCI standard risk classification fared better than high risk patients.

Conclusions: COG AALL02P2 showed inferior EFS but similar OS compared to POG 9412. Limitations included a small sample size, more intensive prior therapies, and a significant number of patients (34/118, 29%) who did not receive protocol-directed radiation due to early relapse prior to 1 year or did not otherwise follow the treatment plan. New approaches are needed to improve outcome for these patients and determine the optimal timing and dose of cranial radiation in the treatment of iCNS-R.

Keywords

CNS relapse; leukemia; childhood

Introduction

The central nervous system (CNS) is involved in 30% of relapses (isolated or in combination with bone marrow or other site) of pediatric Acute Lymphoblastic Leukemia (ALL) and remains a major obstacle to improving survival.[1–4] Isolated CNS relapse (iCNS-R) occurs in 2–5% of patients in recent clinical trials, predominantly in patients without prior overt CNS disease.[5–20]

Improved outcomes following iCNS-R are the result of intensified systemic therapy with drugs that effectively treat CNS leukemia (high-dose (HD) methotrexate, HD cytarabine, dexamethasone, and pegaspargase), in addition to CNS-directed treatment including intrathecal chemotherapy and cranial (CRT) or craniospinal radiotherapy (CSI). These strategies have been successfully applied to front-line protocols seeking to reduce and/or eliminate CNS radiation in at risk patients (CNS2, CNS3, and those with traumatic taps and presumed introduction of circulating blasts into the cerebrospinal fluid [CSF]) without compromising survival.[9–11,14,21–24] However, patients receiving cranial radiotherapy (CRT) have an increased prevalence of acute and long-term neurotoxicity, endocrinopathies, second cancers, neurocognitive deficits, late mortality, and impaired quality of life.[13,25–33]

Pediatric Oncology Group (POG) trials for children with CNS-R conducted in the 1990s (9061 and 9412) aimed to limit the use of CSI and delayed radiotherapy to enable a longer period of time to deliver effective systemic chemotherapy without inducing excessive marrow toxicity.[19,34] These strategies yielded impressive long-term second remissions with

4-year event-free survival (EFS) rates of 70–80%.[19,20,34] Compared to POG 9061, 9412 reduced CRT dose from 2400 to 1800 cGy, eliminated spinal radiation (1500 cGy), and delayed radiation from 6 to 12 months.[20] The 4-year EFS for POG 9412 B-ALL iCNS-R patients with CR1 ≥18 months was 78%±6%. Both studies identified length of first remission as a major prognostic indicator, and on POG 9412, National Cancer Institute (NCI) risk group[35] at time of their initial diagnosis was an independent prognostic variable.

Based on these encouraging results, Children's Oncology Group (COG) AALL02P2 aimed to further decrease CRT dose to 1200 cGy and delay its delivery until completion of 12 months of further intensified systemic chemotherapy in patients with late iCNS-R (≥18 months after initial diagnosis). It was hypothesized that this decreased exposure to radiation would decrease adverse events of CRT, while preserving POG 9412 outcomes.

Patients and Methods

Patients

From November 1, 2004 to January 7, 2011, COG AALL02P2 enrolled patients 18 months to <30 years old at the time of relapse with B-or T-ALL and first iCNS-R or testicular relapse occurring ≥18 months from the date of initial diagnosis. Only patients with <5% marrow blasts by morphology assessed locally were eligible. Children with Down syndrome were excluded, as were those who underwent bone marrow transplant in first remission. Patients with known optic nerve and or retinal involvement were not eligible because they could not delay radiotherapy for 12 months.

COG AALL02P2 included modifications to the POG 9412 backbone aimed at providing intensified systemic therapy for 12 months prior to radiation to address the issue of subsequent marrow relapse, as well as optimize use of drugs known to better target the CNS compartment including dexamethasone, with HD cytarabine and methotrexate (dose increased from 1 to 5 g/m^2 per cycle), plus 1200 cGy CRT. Additionally, pegaspargase was given (POG 9412 used native E. coli asparaginase). A secondary objective was to determine if the frequency and level of bone marrow involvement via flow-cytometry at the time of extramedullary relapse, and to assess if the level of pre-treatment minimal residual disease (MRD) correlated with outcomes.

Treatment and Assessments

The AALL02P2 chemotherapy backbone for this study has been previously reported[36] with some minor differences based on site of relapse. Induction included 4 weeks of systemic therapy plus weekly intrathecal triple (ITT) chemotherapy (Table 1). CNS remission was defined as two consecutive lumbar punctures with no morphologic blasts evident on CSF analysis. Induction failure was defined as failure to achieve CNS remission following six weekly ITT. Following Induction, patients received Consolidation, Intensification I, Reinduction, and Intensification II, with concomitant ITT chemotherapy. These phases were designed to last 50 weeks, following which patients with iCNS-R received a 3-week block of chemotherapy with 1200 cGy cranial radiation given as 8 daily fractions of 150 cGy. AALL02P2 was designed to allow radiation to be delayed up to 2 months to allow

completion of the intensive chemotherapy phases. Following irradiation, patients received five 10-week cycles of intensified maintenance, each including 4 doses of cyclophosphamide 300 mg/m^2 given weekly. Cyclophosphamide doses were omitted if the absolute neutrophil count was <500/microliter or platelet count was <75,000/microliter. No further intrathecal therapy was given during maintenance, but diagnostic lumbar punctures were performed on day 1 of each maintenance cycle.

Bone marrow samples taken prior to treatment initiation were assessed for MRD via flow cytometry,[37] at a single central reference laboratory at the University of Washington.

Protocol Amendments

Several amendments altered eligibility or therapy during the conduct of AALL02P2. Amendment 1 (March 2007) expanded eligibility to include patients with first isolated CNS or testicular relapse of lymphoblastic lymphoma, changed methotrexate administration from intramuscular to oral during maintenance, and the age for discontinuous dexamethasone (7 days of therapy, 7 days without and 7 days of therapy) administration during Reinduction and the Cranial Irradiation phase was decreased from ≥13 years to ≥10 years. Amendment 2 (August 2008) implemented discontinuous dexamethasone during these phases for all patients based on increased rates of osteonecrosis observed in COG AALL0232.[15] Amendment 4 (June 2010) removed T-ALL and lymphoblastic lymphoma from the eligibility criteria as only 4 patients had been enrolled among 143. In December 2010 an interim monitoring showed inferior outcomes to POG 9412, resulting in enrollment being suspended and study closure in January 2011 (see below). Amendment 5 (February 2011) was implemented after study closure and recommended that patients who had not yet received cranial irradiation should receive 1800 cGy, and methotrexate administration in maintenance was changed back to intramuscular.

Adverse Event Reporting

Adverse events (AEs) were reported using NCI CTCAE v4.0. Routine reporting included all Grade 3 and higher AEs with the exception of CNS AEs (Grade 2 and higher) and osteonecrosis (referred to as avascular necrosis, AVN) AEs (Grade 1 and higher). Reportable hematologic AEs were any Grade 3 or higher event that resulted in therapy delay >1 week or hospitalization.

Study Design and Statistical Methods

The primary endpoint for AALL02P2 was EFS as compared to historical outcomes on POG 9412 and POG 9061, which had 3-year EFS rates for late iCNS-R of approximately 75%. AALL02P2 was designed to accrue 143 patients with late iCNS-R over 5.72 years. If at least 41 events (induction failures, relapse, second malignancy, or death) occurred among the 143 (assuming a binomial distribution to model the number of events at three years), it would be concluded that the 3-year EFS is less than 75%. With this design there is a 17.9% chance of erroneously concluding that there is a decrease in EFS when in fact the true three-year EFS is 75%. The probability is 95.5% of concluding there is a decrease in EFS when the true three-year EFS is 65%. The study had interim monitoring conducted to protect against poor EFS. Under the exponential assumption, three-year EFS of 75% translates to a hazard

rate of relapse of 0.096. Interim analysis was be based on the estimated hazard rate. The alpha × t^2 spending function was used to maintain an overall one-sided Type I error rate of 18%. A total of 113 of the expected 143 eligible patients with iCNS-R had been accrued at the time of the third protocol specified interim monitoring for EFS. The 3-year EFS rate for these patients was 60.27±7.18 %, with a 3-year overall survival rate of 75.20±6.24%. Thirty of the expected 41 events had occurred. Using an alpha × t^2 spending function, the p-value required would be less than or equal to 0.084. The observed p-value of 0.02 was less than 0. 084. Hence the monitoring boundary was crossed indicating that the outcomes on this study were inferior to those seen on P9412 leading the COG Data monitoring committee to permanently close AALL02P2.

EFS was calculated as the time from enrollment to first event (induction death, induction failure, relapse at any site, second malignant neoplasm or remission death from any cause) or last contact, and OS was defined as the time from enrollment to death from any cause or last contact. Survival rates were estimated using the Kaplan-Meier method and corresponding standard errors were based on the method of Peto, et al.[38,39] The two-sided log-rank test was used for comparison of survival curves between groups. *P*-values < 0.05 were considered statistically significant. Data frozen as of September 30, 2016 are included in this report.

Results

Patient Characteristics

One hundred and sixty-eight patients enrolled on AALL02P2; of these, 2 were ineligible, 42 had an isolated testicular relapse (ITR), 122 had isolated CNS-R, and 2 had concurrent CNS and testicular relapse (Figure 1). Of the 122 isolated CNS-R patients, 118 had B-ALL and 4 had T-ALL. Results for patients with ITR have been reported previously.[36] This report is limited to the iCNS-R patients with B-ALL.

The mean age at initial ALL diagnosis was 5.6 years, and mean age at enrollment on AALL02P2 was 8.1 years. At initial diagnosis, 35% (40 of 115 patients with data available regarding NCI risk group at initial diagnosis) of patients were classified as high risk (HR ALL) and 65% (75/115) as standard risk (SR ALL) based on NCI/Rome criteria (SR: age 1–9.9 years of age with leukocyte count <50 × 10^9/L; HR: age ≥10 years and/or leukocyte count ≥50 × 10^9/L).

Response to Induction Therapy

At the end of Induction, 112/118 (94.9%) of iCNS-R patients attained remission, with one induction failure, 2 induction deaths (influenza A H1N1 and *Pseudomonas jirovecii* pneumonia with acute respiratory distress syndrome), and 3 patients removed from therapy due to toxicity and/or physician discretion (Figure 1).

Outcomes: EFS and OS

The 3-year EFS and OS for patients on COG AALL02P2 (n=118) are 64.3±4.5% and 79.6±3.8%, respectively (Figure 2A). The initial concern for an inferior EFS on AALL02P2

compared to POG 9412 that led to the premature study closure was confirmed with additional follow-up. Compared to late CNS-R B-ALL patients (n=50) on POG 9412, the 3-year EFS for COG AALL02P2 was significantly inferior (64.3±4.5% vs. 79.9±5.8%; p=0.03). Though the interim analysis was focused on EFS, it was noted that the OS rates were not statistically different (79.6±3.8% vs. 85.8±5.1%; p=0.35) (Figures 2B, 2C).

This intent to treat analysis of 118 patients included 34 (29%) patients who did not receive protocol-directed chemotherapy and CNS radiation. The decision to come off therapy for some patients was related to the amendment and premature closure. Of those patients who came off protocol directed therapy, 11 received radiation, 5 in association with a second relapse (dose and site not captured).

The rate of second relapses was non-significantly higher for NCI HR ALL (16/40; 40%) compared to those with SR ALL (23/75; 31%) (Table 2) with 3-year cumulative incidence of relapse rates of 26.7±5.2% and 35.1±7.7% for NCI SR and HR, respectively (p=0.1901) (Supplemental Figure 1).

The EFS differences between COG AALL02P2 and POG 9412 were most notable for patients who were NCI SR at initial diagnosis (Figure 3). The 3-year EFS for patients initially classified as HR were similarly poor (p=0.83) for both POG 9412 (58.3±15.4%; n=12) and AALL02P2 (59.9±7.9%). Overall survival rates were also similar (p=0.97) for 9412 and AALL02P2, 66.7±14.6% and 67.2±7.6%, respectively. In both studies, patients initially classified as SR did better than their respective HR counterparts, but the 3-year EFS for SR patients on POG 9412 (86.7±5.6%, n=38) was superior (p=0.0149) to those treated on COG AALL02P2 (65.3±5.5%; n=75). In contrast, 3-year OS rates for the SR patients were not statistically different between 9412 and AALL02P2, 92±15.9% vs 85.3±4.1% (p = 0.29), respectively. Of note, 24% of 9412 patients (12/50) were initially NCI HR compared to 35% (40/115) on AALL02P2. The total number of patients on both trials were small, but this discrepancy likely influenced outcome comparisons between the two.

EFS Events

Of the 112 eligible patients, 78 received protocol-prescribed cranial radiation (1200 cGy in 64 and 1800 cGy in 14 patients following the amendment). Thirty-two patients did not receive protocol prescribed cranial radiation as they came off protocol prior to that timepoint for the following reasons: physician or patient discretion (19), relapse (10), and death (3). An additional 2 patients completed the protocol-prescribed chemotherapy but did not receive radiation.

EFS events are summarized in Table 2 and Supplemental Table 1. Of the 6 remission deaths, 1 occurred post-radiation. Of the 39 patents who experienced a subsequent relapse, 19 received chemotherapy without protocol-prescribed radiation and 20 received radiation and chemotherapy as per protocol - 2 during the radiation reporting period and 18 while in Maintenance. Patients who had an event prior to scheduled radiation at 12 months are included in the group of 19 patients. Of the 20 relapsed patients who received protocol prescribed radiation, 15 received 1200 cGy and 5 received 1800 cGy (post amendment).

Toxicity

Toxicities for iCNS-R patients treated on AALL02P2 were those expected with 12 months of intensified systemic chemotherapy. There were 6 reports of avascular necrosis (AVN, three Grade 3, three Grade 2), however collection of these data began with a 2008 protocol amendment and may therefore have not included any occurrences of AVN prior to this time. Four patients came off therapy (1 in Induction and 3 prior to radiation) due to intolerable toxicity. These patients each experienced multiple toxicities, including Grade 4 myelosuppression, infection (Rubella, pseudomonas necrotizing fasciitis), peripheral neuropathy, and drug allergy. The most common combined Grade 3 and 4 toxicities reported were: febrile neutropenia (187), mucositis (30) diarrhea (22), hyperglycemia (21), anaphylaxis (20), dehydration (18), sepsis (7), and a thromboembolic event (6). In addition to the 2 Induction deaths, 4 deaths were reported as first events on treatment or within one month of end of treatment, including 3 patients from infectious causes (probable cytomegalovirus and *Streptococcus pneumoniae* sepsis, *Escherichia coli* bacteremia, *Pseudomonas aeruginosa* sepsis), and 1 death at home of unknown cause. Two additional remission deaths were reported as first events at 3 years due to multi-organ failure, and 4 years due to multiorgan failure and graft versus host disease.

MRD Assessments

Detectable bone marrow MRD was present at diagnosis in 15/76 (19.7%) patients tested at a threshold of 0.01% and 13/79 (16.5%) at a threshold of 0.1%. The event-free (p=0.9332) and overall survival (p=0.9522) rates were superimposable for both MRD cut-offs (Supplemental Figure 2).

Discussion

Reduction of CNS radiation ALL patients with iCNS-R continues to be a challenge, yet remains an important goal given the late effects of CNS radiation and limited options for treatment following subsequent relapse. Excellent outcomes reported in POG 9061/9412 in patients with late CNS-R were attributed to a treatment approach reliant on the use of effective anti-leukemia agents with good CNS activity facilitated by a delay in delivery of CNS radiation that had previously limited chemotherapy delivery because of prolonged myelosuppression. Specifically, POG 9061 delayed CNS radiation for six months after relapse and POG 9412 then intensified the chemotherapy, delayed CNS radiation for 12 months after relapse and reduced the dose of CRT from 2400 to 1800 cGy. COG AALL02P2 was designed to test one year of further intensified systemic therapy, followed by CRT at a reduced dose of 1200 cGy. AALL02P2 encountered a number of challenges with lower than expected enrollment given continued success with frontline therapies and decreasing CNS-R rates, as well as a large number of enrolled patients who did not complete protocol-prescribed therapy. The study was closed before reaching planned accrual when an interim analysis crossed predefined monitoring boundaries and showed inferior EFS compared to POG 9412.

With respect to overall survival, this treatment strategy with COG AALL02P2 did prove as effective for patients with late relapse and NCI SR ALL as the predecessor POG 9412 study,

however, EFS was markedly inferior for this cohort compared to the prior trial. NCI HR patients fared equally poorly on both trials, without meaningful differences in outcomes.

As in POG 9412, COG AALL02P2 continued to show a difference in outcomes between the NCI HR and SR ALL groups. The overall survival showed a trend towards better survival in the NCI SR group. Similar results are seen in this recent trial with EFS for NCI HR vs SR. Barredo et al, previously reported in POG 9412 that NCI SR ALL status was an independent favorable prognostic factor in addition to length of CR1 suggesting that the NCI/Rome criteria serve as a clinical surrogate for inherent biological differences.[20] There were 11 relapses with 8 attributable to CNS relapse in POG 9412, suggesting a need for further improvement in CNS (and marrow) control. Interestingly, in AALL02P2, NCI SR ALL patients fared far worse with respect to EFS than the similar cohort in POG 9412. This may be related to several factors including differences in frontline treatments with more intensified therapies thereby rendering these patients more difficult to treat, as well as a large number of patients on COG AALL02P2 who did not receive the protocol-prescribed radiation. Treatment delays and toxicities did not appear to influence outcomes. These patients (26% of the total enrolled) that did not follow the protocol-directed therapy included 10 patients who had events prior to the timing of radiation, as well as patients, and/or clinicians, who chose not to continue with the protocol post amendment.

Novel therapies to reduce the risk of second relapse and treatment providing safer and less toxic CNS directed therapy are needed. Consideration of other factors in addition to CNS penetration of drugs is needed; the CNS is thought to be an immunologic sanctuary not just a physical barrier.[40] Subclinical seeding of the CNS from other sites, particularly the BM, is implicated in subsequent BM relapse and improved methods of eradicating disease systemically are needed. While delay of CNS irradiation has proven to be an important part of relapse therapy, this study emphasizes the necessity of ensuring adequate delivery of CRT. The results of AALL02P2 suggest that cranial radiation is a critical and necessary component of relapse therapy for iCNS-R of B-ALL in the context of chemotherapy-driven regimens. Nevertheless, emerging data using immunotherapy (chimeric antigen receptor T-cells) in the setting of extramedullary disease at diagnosis or relapse of ALL may provide an alternative strategy to decrease or eliminate CNS irradiation.[41–44]

While baseline bone marrow MRD data were only available from 64% (76/118) patients, MRD analysis was not predictive of either EFS or OS. Within the sensitivity of 0.01%, 19.7% of patients were MRD-positive, though it is certainly possible that rates would be higher with more sensitive MRD technologies.

The incidence of isolated CNS relapse has decreased with contemporary strategies, and several trials have shown that cranial irradiation can be omitted in newly diagnosed ALL patients.[14,21,23,24] However, the individual trials conducted to date have included relatively few patients with overt CNS disease. A large study from the Ponte de Legno group aggregated data from 16,623 children (<18 years) with ALL treated by 10 cooperative groups between 1996 and 2007.[24] In that study, cranial radiotherapy was associated with a reduced risk of CNS relapse only in the small subgroup of 406 patients with CNS3 status, and the overall event rate did not differ between those that did or did not receive

radiotherapy. In parallel to newly diagnosed ALL, there is great interest in reducing radiotherapy dose, or eliminating it entirely, in patients with CNS-R due to the long-term adverse impact of cranial irradiation on CNS outcomes, secondary brain tumors, and quality of life.[9,30,45–47] Toward this end, earlier studies from the POG and others demonstrated that it was possible to preserve outcomes in patients with late CNS-R by intensifying systemic chemotherapy while reducing radiation dose and limiting it to the cranial fossa (eliminating spinal irradiation). However, despite further intensification of systemic chemotherapy, COG AALL02P2 showed inferior EFS compared to POG 9412 when the cranial radiation dose was reduced to 1200 cGy, intended to be delivered at 12 months from onset of recurrence. Limitations in the current study included a small sample size due to increasing rarity of iCNS-R, early study closure and a substantial number of patients, 34/118 (29%), who did not receive protocol directed radiation either due to early relapse prior to 1 year or decision to not follow the treatment plan. It is also possible that cranial irradiation may need to be administered earlier after relapse, and that further intensifying systemic cytotoxic therapy is counterproductive.

The overall goal to limit cranial radiotherapy in patients with iCNS-R remains important. Future studies might also incorporate newer immunotherapies or more sensitive marrow MRD technologies and/or CNS response measures to attempt to identify which patients with iCNS-R might be cured without irradiation, and whether different subgroups might require lower or higher doses of radiotherapy. To gain adequate power to address these questions, future trials will likely require international collaboration.

Children’s Oncology Group Data Sharing Statement:

The Children’s Oncology Group Data Sharing policy describes the release and use of COG individual subject data for use in research projects in accordance with National Clinical Trials Network (NCTN) Program and NCI Community Oncology Research Program (NCORP) Guidelines. Only data expressly released from the oversight of the relevant COG Data and Safety Monitoring Committee (DSMC) are available to be shared. Data sharing will ordinarily be considered only after the primary study manuscript is accepted for publication. For phase 3 studies, individual-level de-identified datasets that would be sufficient to reproduce results provided in a publication containing the primary study analysis can be requested from the NCTN/NCORP Data Archive at https://nctn-data-archive.nci.nih.gov/. Data are available to researchers who wish to analyze the data in secondary studies to enhance the public health benefit of the original work and agree to the terms and conditions of use. For non-phase 3 studies, data are available following the primary publication. An individual-level de-identified dataset containing the variables analyzed in the primary results paper can be expected to be available upon request. Requests for access to COG protocol research data should be sent to: datarequest@childrensoncologygroup.org. Data are available to researchers whose proposed analysis is found by COG to be feasible and of scientific merit and who agree to the terms and conditions of use.

For all requests, no other study documents, including the protocol, will be made available and no end date exists for requests. In addition to above, release of data collected in a

clinical trial conducted under a binding collaborative agreement between COG or the NCI Cancer Therapy Evaluation Program (CTEP) and a pharmaceutical/biotechnology company must comply with the data sharing terms of the binding collaborative/contractual agreement and must receive the proper approvals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS:

ALL	Acute lymphoblastic leukemia
CNS	central nervous system
CNS-R	central nervous system relapse
iCNS-R	isolated central nervous system relapse
B-ALL	B cell acute lymphoblastic leukemia
T-ALL	T cell acute lymphoblastic leukemia
COG	Children's Oncology Group
cGy	centigray
EFS	event free survival
OS	overall survival
POG	Pediatric Oncology Group
HD	high dose
CRT	cranial radiotherapy
CSI	craniospinal radiotherapy
NCI	National Cancer Institute
MRD	minimal residual disease
ITT	intrathecal triple (chemotherapy)
CSF	cerebral spinal fluid
CTCAE	common terminology for adverse events
HR ALL	high risk acute lymphoblastic leukemia

SR ALL	standard risk acute lymphoblastic leukemia
ITR	isolated testicular relapse
AVN	avascular necrosis

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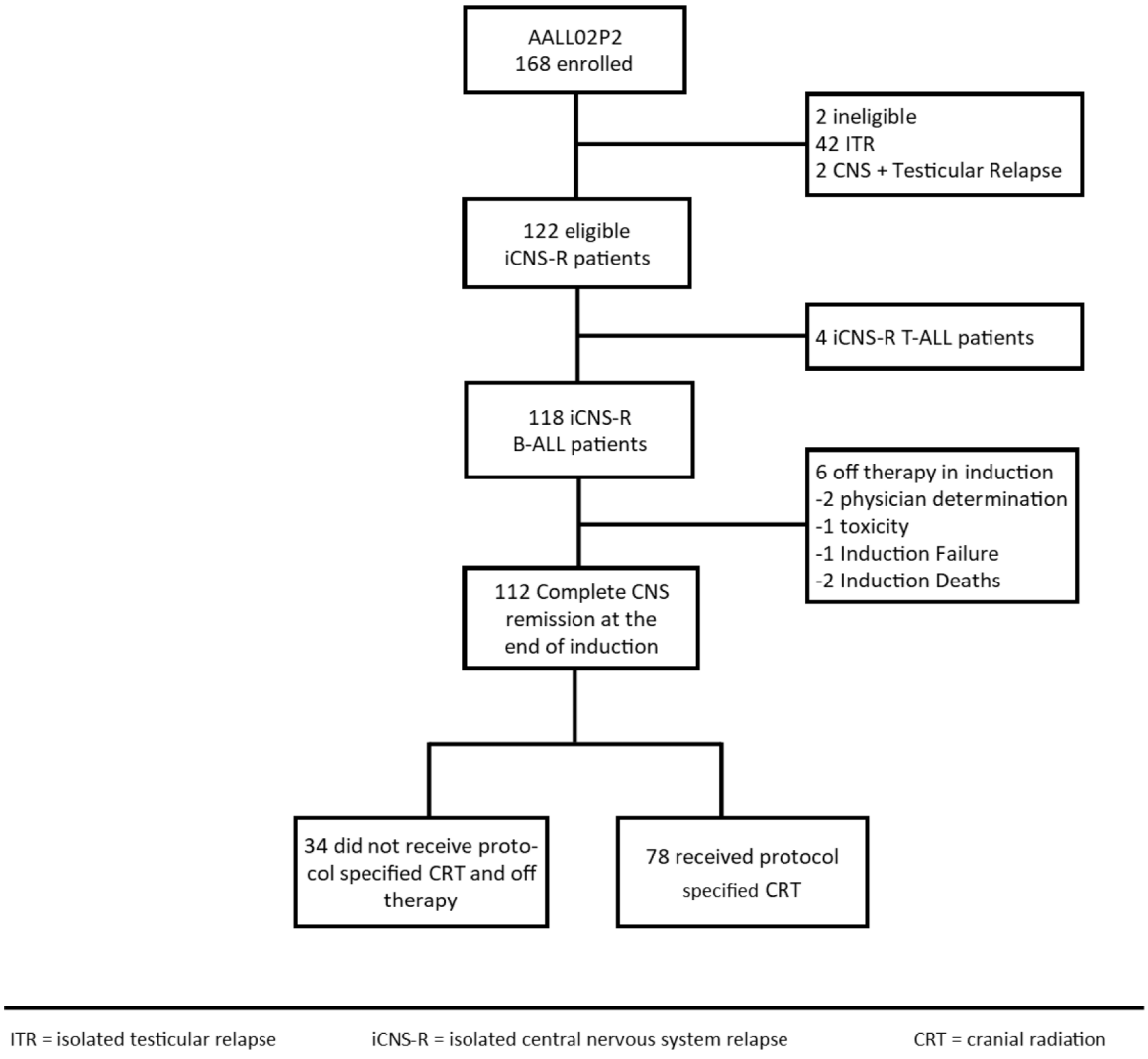
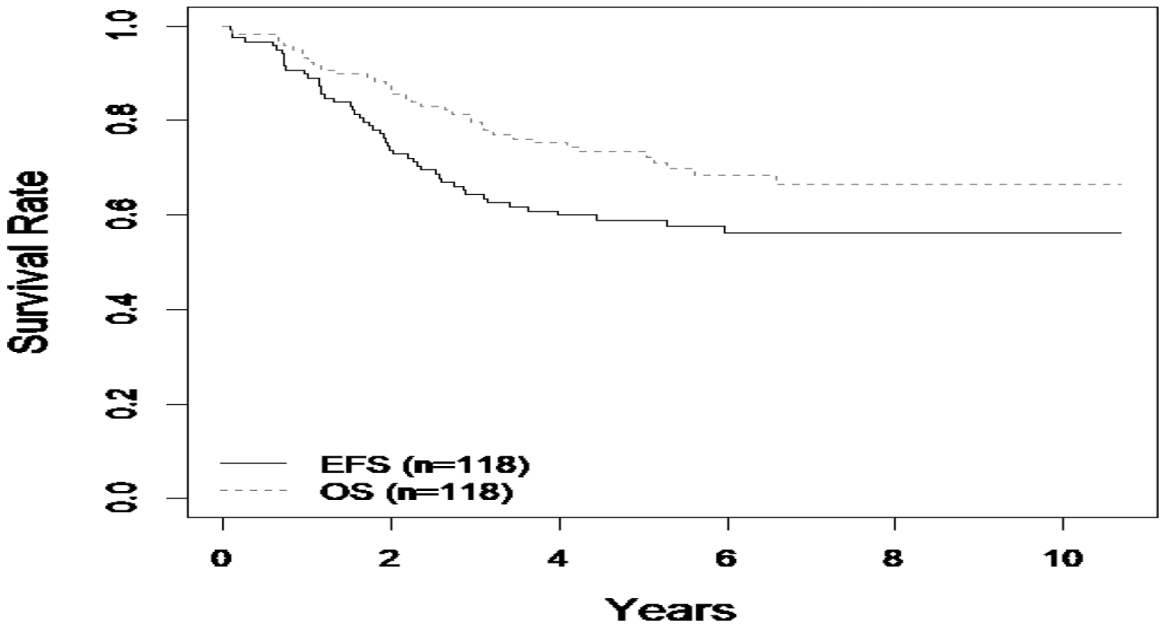
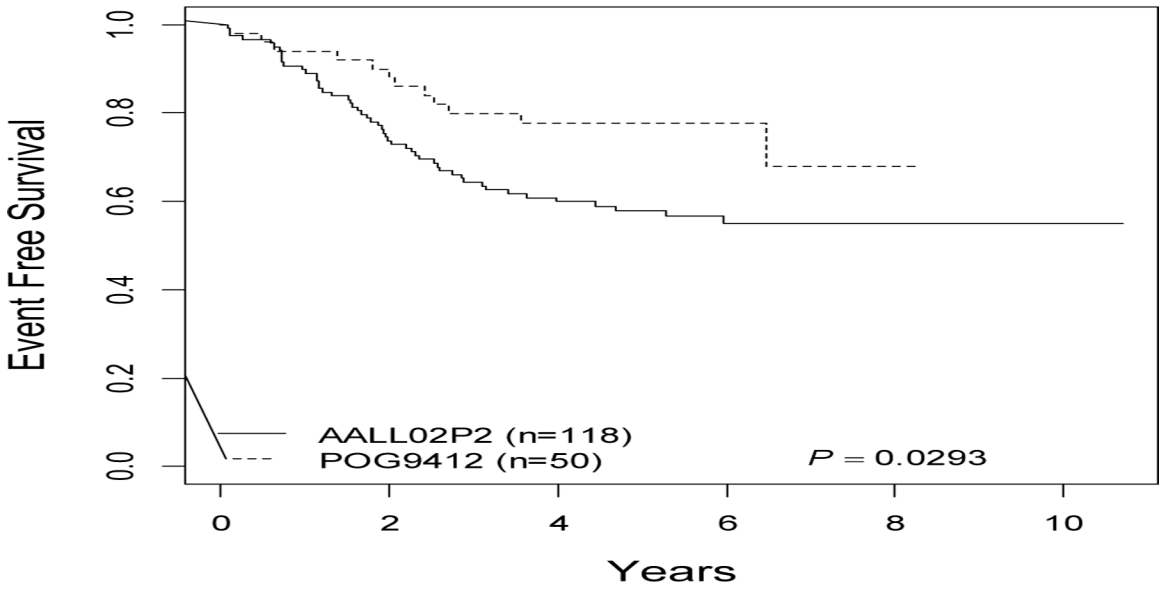


Figure 1:

CONSORT diagram: Patient treatment and outcomes. Pathway followed by all patients enrolled on the Children's Oncology Group (COG) AALL02P2.





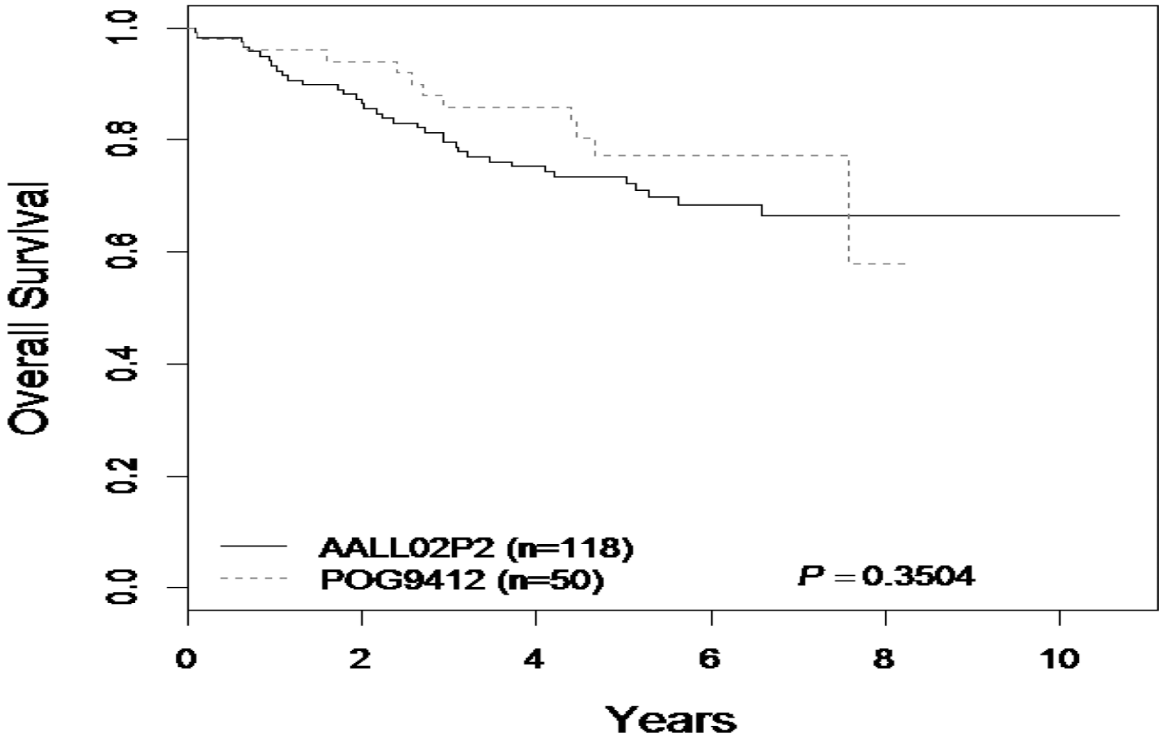


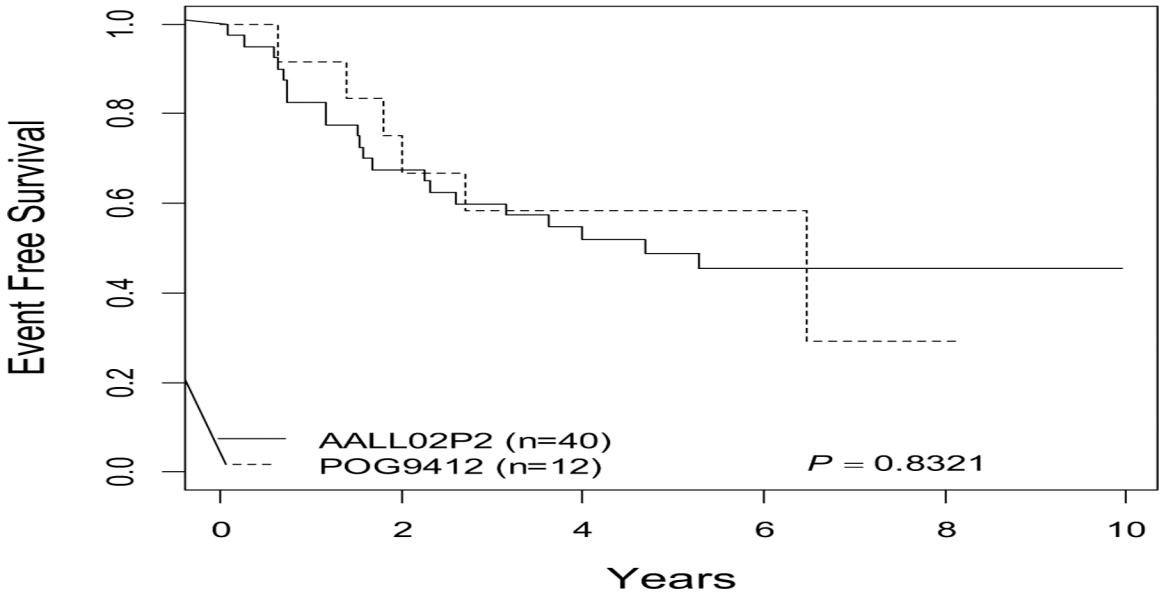
Figure 2:

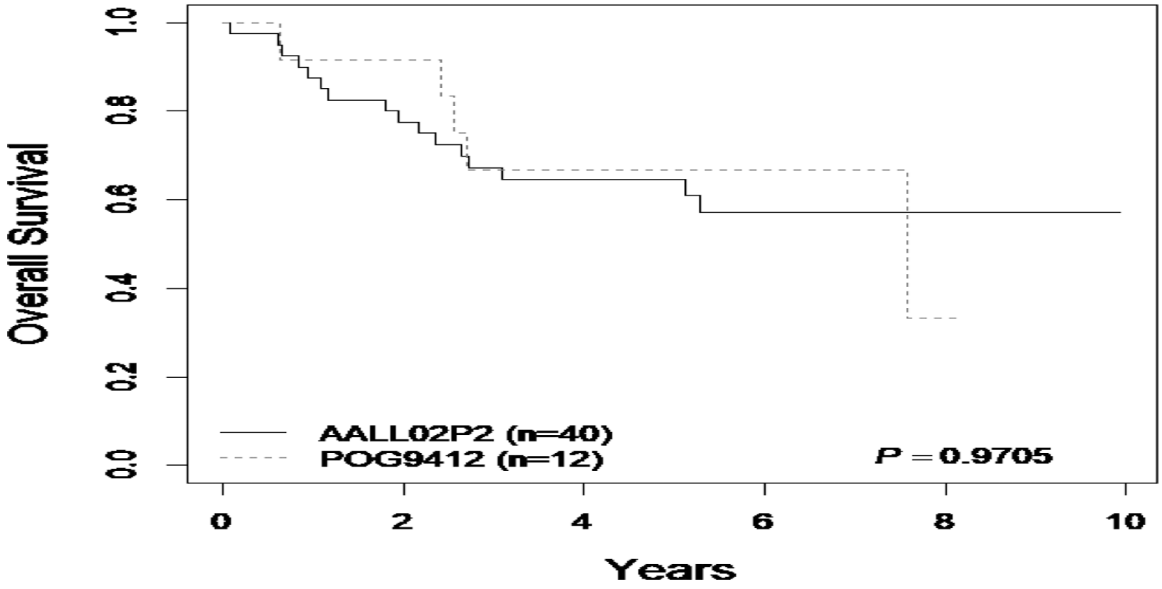
Event free survival (EFS) and overall survival (OS) of COG AALL02P2, and comparison to historical outcomes

Figure 2A Event free survival (EFS) and overall survival (OS) of isolated late CNS-R patients with B-ALL enrolled and treated on COG AALL02P2

Figure 2B EFS COG AALL02P2 compared to historical outcomes of similar patients treated on POG 9412

Figure 2C OS COG AALL02P2 compared to historical outcomes of similar patients treated on POG 9412





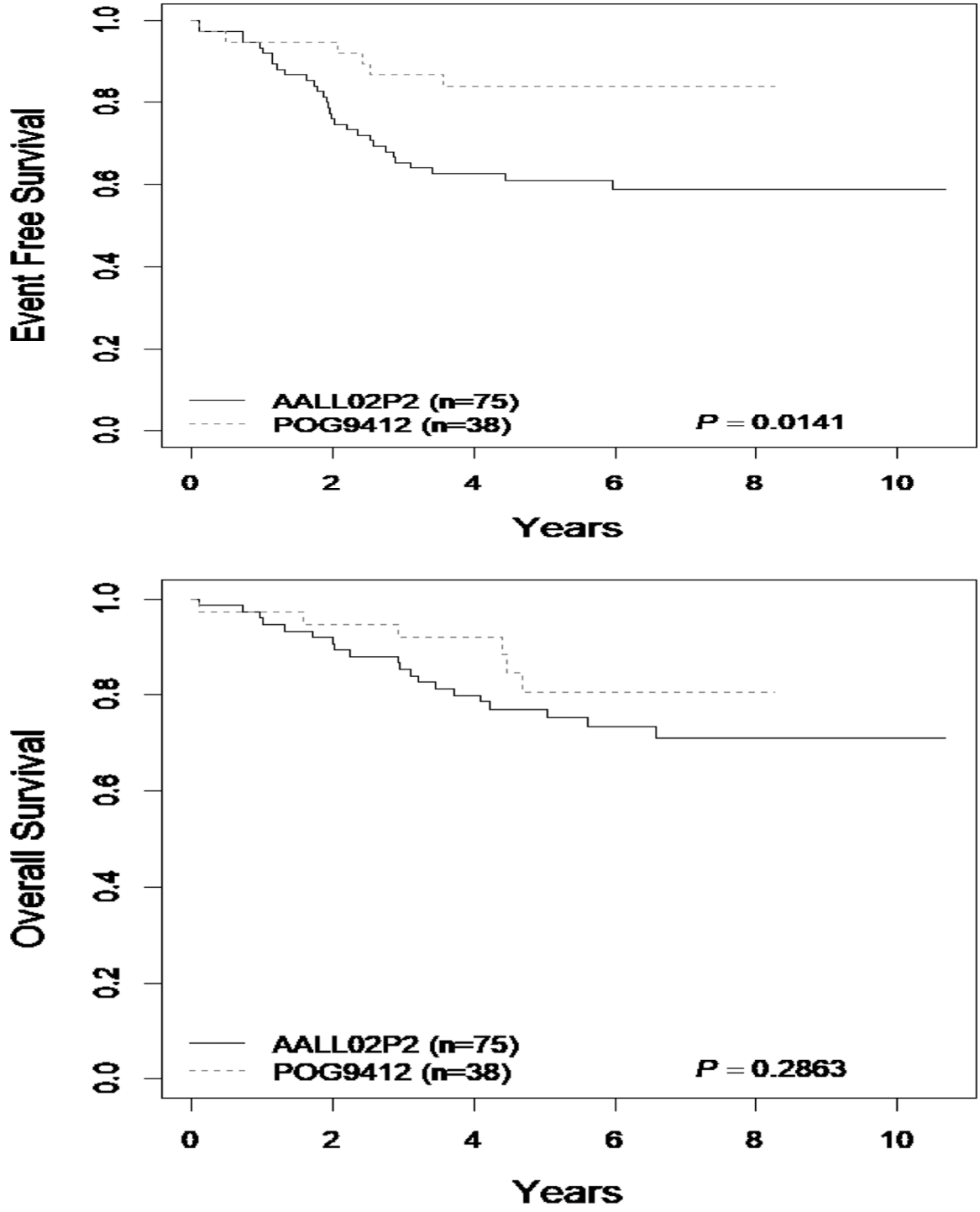


Figure 3:

Event free survival (EFS) and overall survival (OS) of isolated CNS-R patients with B-ALL on COG AALL02P2, stratified by NCI risk group and compared to historical outcomes of similar patients on POG 9412

Figure 3A EFS NCI HR patients, comparison between COG AALL02P2 and POG 9412

Figure 3B OS NCI HR patients, comparison between COG AALL02P2 and POG 9412
Figure 3C EFS NCI SR patients, comparison between COG AALL02P2 and POG 9412
Figure 3D OS NCI SR patients, comparison between COG AALL02P2 and POG 9412

Table 1:

COG AALL02P2 protocol design

Treatment	Dosage	Timing
Induction (weeks 1–4)		
Dexamethasone (DEX)	10 mg/m^2/day PO daily	Weeks 1 – 4
Vincristine (VCR)	1.5 mg/m^2 IV weekly	Weeks 1, 2, 3, 4
Daunorubicin (DNR)	25 mg/m^2 IV weekly	Weeks 1, 2, 3
ITT (intrathecal triple, Methotrexate/Hydrocortisone/ Cytarabine, MTX/HC/ARA-C)	age adjusted	Weeks 1, 2, 3, 4 (5, 6) *
Consolidation (weeks 5–10)		
Cytarabine (ARA-C)	3000 mg/m^2 IV every 12 h × 4	Weeks 5, 8
PEG-Asparaginase	2500 IU/M^2 IM	Weeks 5, 8
Intensification I (weeks 11–22)		
HDMTX	5 g/m^2 IV over 24 h with LV rescue	Weeks 11, 14, 17, 20
6-Mercaptopurine (MP)	50 mg/m^2 PO daily days 2–6	Weeks 11, 14, 17, 20
Etoposide (ETOP)	300 mg/m^2 IV	Weeks 12, 15, 18, 22
Cyclophosphamide (CPM)	500 mg/m^2 IV	Weeks 12, 15, 18, 22
ITT	age adjusted	Weeks 13, 16, 19, 22
Reinduction (weeks 23–26)		
DEX pulses **	10 mg/m^2/day PO × 7 days	Weeks 23, 25
VCR	1.5 mg/m^2 IV weekly	Weeks 23, 24, 25, 26
DNR	25 mg/m^2 IV weekly	Weeks 23, 24, 25
Intensification II (weeks 27–50)		
ARA-C	3000 mg/m^2 IV every 12 h × 4	Weeks 27, 33, 39, 45
PEG-ASP	2500 IU/M^2 IM	Weeks 27, 33, 39, 45
ITT	age adjusted	Weeks 30, 36, 42, 48
MTX	5 g/m^2 IV over 24 h with LV rescue	Weeks 31, 37, 43, 49
MP	50 mg/m^2 PO daily × 5 days	Weeks 31, 37, 43, 49
ETOP	300 mg/m^2 IV	Weeks 32, 38, 44, 50
CPM	500 mg/m^2 IV	Weeks 32, 38, 44, 50
Chemotherapy (weeks 51–54)		
Cranial Radiation		
DEX	10 mg/m^2/day PO × 7 days	Weeks 51, 53
VCR	1.5 mg/m^2 IV weekly	Weeks 51, 52, 53
PEG-ASP	2500 IU/M^2 IM	Weeks 51, 53
Maintenance (weeks 55–104)		
10-week cycles × 5		
DEX	10 mg/m^2/day PO × 5 days	Weeks 55, 65, 75, 85, 95
MP	75 mg/m^2 PO daily, continuously	Weeks 55, 65, 75, 85, 95
MTX	20 mg/m^2 PO (IM ***) weekly, continuously	Weeks 55, 65, 75, 85, 95

Treatment	Dosage	Timing
VCR	1.5 mg/m^2 IV weekly	Weeks 61, 71, 81, 91, 101
CPM	300 mg/m^2 IV weekly	Weeks 61, 71, 81, 91, 101
Diagnostic LP	Day 1 of each cycle	Weeks 55, 65, 75, 85, 95

IV: intravenous
PO: oral
IM: intramuscular

*
weekly ITT in Induction, minimum 4 doses, up to 6 doses until 2 consecutive cytology negative for blasts; delay Consolidation to begin week 7 if week 6 ITT given

**
protocol amendment: changed discontinuous dexamethasone for patients ≤13years to all ages

***
protocol amendment change of PO to IM administration

Table 2

Summary of second relapses by NCI risk group and relapse site

	Relapse Site						
NCI Risk	**isolated BM**	**BM + CNS**	**BM + Testicular**	**isolated CNS**	**isolated Testicular**	**Other site**	**Total**
High Risk	4	2	1	7	0	2*	16
Standard Risk	7	3	1	11	1	0	23
Total	11	5	2	18	1	2*	39

* The 2 other relapse sites include ALL relapse in a paraspinal mass at T7–T9 and leukemic infiltrates of both eyes.