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Excellent Outcomes With Reduced Frequency of Vincristine and Dexamethasone Pulses in Standard-Risk B-Lymphoblastic Leukemia: Results From Children's Oncology Group AALL0932

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abstract

PURPOSE AALL0932 evaluated two randomized maintenance interventions to optimize disease-free survival (DFS) while reducing the burden of therapy in children with newly diagnosed NCI standard-risk (SR) B-acute lymphoblastic leukemia (B-ALL).

METHODS AALL0932 enrolled 9,229 patients with B-ALL; 2,364 average-risk (AR) patients were randomly assigned (2 × 2 factorial design) at the start of maintenance therapy to vincristine/dexamethasone pulses every 4 (VCR/DEX4) or every 12 (VCR/DEX12) weeks, and a starting dose of once weekly oral methotrexate of 20 mg/m^2 (MTX20) or 40 mg/m^2 (MTX40).

RESULTS Five-year event-free survival and overall survival (OS) from enrollment, for all eligible and evaluable SR B-ALL patients (n = 9,226), were 92.0% (95% CI, 91.1% to 92.8%) and 96.8% (95% CI, 96.2% to 97.3%), respectively. The 5-year DFS and OS from the start of maintenance for randomly assigned AR patients were 94.6% (95% CI, 93.3% to 95.9%) and 98.5% (95% CI, 97.7% to 99.2%), respectively. The 5-year DFS and OS for patients randomly assigned to receive VCR/DEX4 (n = 1,186) versus VCR/DEX12 (n = 1,178) were 94.1% (95% CI, 92.2% to 96.0%) and 98.3% (95% CI, 97.2% to 99.4%) *v* 95.1% (95% CI, 93.3% to 96.9%) and 98.6% (95% CI, 97.7% to 99.6%), respectively (P = .86 and .69). The 5-year DFS and OS for AR patients randomly assigned to receive MTX20 versus MTX40 were 95.1% (95% CI, 93.3% to 96.8%) and 98.8% (95% CI, 97.9% to 99.7%) versus 94.2% (95% CI, 92.2% to 96.1%) and 98.1% (95% CI, 97.0% to 99.2%), respectively (P = .92 and .89).

CONCLUSIONS The NCI-SR AR B-ALL who received VCR/DEX12 had outstanding outcomes despite receiving one third of the vincristine/dexamethasone pulses previously used as standard of care on Children's Oncology Group (COG) trials. The higher starting dose of MTX of 40 mg/m^2 once weekly did not improve outcomes when compared with 20 mg/m^2 once weekly. The decreased frequency of vincristine/dexamethasone pulses has been incorporated into frontline COG B-ALL trials to decrease the burden of therapy for patients and their families.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy.[1] NCI standard-risk (SR) B-acute lymphoblastic leukemia (B-ALL) patients comprise approximately 55% of children with ALL, and those treated on Children's Oncology Group (COG) regimens between 2000 and 2005 achieved 5-year overall survival (OS) rates of 95.0% ± 0.4%.[1] However, treatment-related morbidity can extend into adulthood.[2]

Historically, COG B-ALL therapy has included once every 4 weeks vincristine/corticosteroid (steroid) pulses during maintenance. CCG-161, which enrolled patients from 1978 to 1983 and used less intensive premaintenance therapy than given today, showed improved event-free survival (EFS) in lower-risk patients randomly assigned to receive monthly vincristine/prednisone pulses.[3] Contemporary therapy is more effective, and current risk classification based on leukemia cytogenetics

CONTEXT

Key Objective

Can maintenance therapy in patients with newly diagnosed National Cancer Institute (NCI) standard-risk (SR) B-acute lymphoblastic leukemia (B-ALL) be optimized to improve disease-free survival (DFS) and reduce the burden of therapy?

Knowledge Generated

In the context of modern Children's Oncology Group (COG) therapy, vincristine/dexamethasone pulses administered every 12 weeks demonstrated excellent outcomes. Increasing the starting dose of oral methotrexate from 20 to 40 mg/m^2 once weekly in maintenance did not improve DFS.

Relevance

Excellent treatment outcomes in NCI SR B-ALL have been achieved with a decreased frequency of vincristine/dexamethasone pulses while decreasing the burden of therapy. COG has adopted this change in new B-ALL trials.

and minimal residual disease (MRD) defines a more rigorous SR population.[4] CCG-1891 demonstrated no advantage to every 3 weeks versus every 4 weeks maintenance vincristine/prednisone pulses in intermediate risk B-ALL patients treated with a single delayed intensification (DI) phase.[5] A prospective trial conducted between 1995 and 2000 showed that intermediate-risk patients did not benefit from six versus no vincristine/dexamethasone maintenance pulses (each containing two vincristine doses) on a Berlin-Frankfurt-Muenster (BFM) backbone.[6] By contrast, the European Organization for Research and Treatment of Cancer (EORTC) 58951 study showed superior outcomes in patients with average-risk (AR) B-ALL and non-Hodgkin lymphoma randomly assigned to receive six maintenance vincristine/steroid pulses with a 6-year disease-free survival (DFS) of 90.6% $\pm$ 2.1% versus 82.8% $\pm$ 2.8% ($P = .027$) with no pulses. Interestingly, some of the EORTC patients were included in the above BFM trial that showed no benefit to pulses in a much larger patient cohort.[7] A Childhood ALL Collaborative Group meta-analysis demonstrated improved EFS with vincristine/prednisone pulses but not vincristine/dexamethasone pulses; however, neither improved OS.[8] Given studies showing that dexamethasone was more effective than prednisone, the lack of benefit of vincristine/dexamethasone pulses was presumed to be related to the more intense premaintenance chemotherapy rather than the steroid used.[8,9] Intensified premaintenance therapy, refinements in genetic and MRD-based risk stratification, and better supportive care have improved outcomes on COG ALL trials,[1] making the optimal frequency of maintenance pulses in modern ALL therapy uncertain.

Maintenance therapy is based on antimetabolites including daily 6-mercaptopurine (6-MP) and once weekly methotrexate.[10-12] Methotrexate is usually administered orally, but is sometimes given intravenously or subcutaneously.[13,14] Incomplete absorption occurs at all dose levels, with absorption saturation occurring at oral doses of approximately 40 mg/m^2, suggesting that higher oral doses might deliver more methotrexate.[15,16] This may enhance efficacy, either directly or through xanthine oxidase inhibition, which may decrease the first-pass effect on oral 6-MP and increase bioavailability.[17-21] Weekly methotrexate 40 mg/m^2 has been given intravenously and orally without excessive toxicity.[14,22]

COG ALL trials include daily 6-MP and weekly methotrexate during maintenance, with dosing guidelines designed to minimize severe myelosuppression and infectious complications because of the large intrapatient variability in drug absorption and metabolism, and genetic polymorphisms in *TPMT* or *NUDT15*, that increase phosphorylated 6-MP metabolites.[23,24] Titrating doses based on maintenance absolute neutrophil (ANC) and platelet counts potentially maximizes antileukemic effect and reduces relapse.[24-27] Poor compliance with maintenance therapy is associated with a 2.5-fold increased risk of relapse, highlighting the importance of optimizing maintenance chemotherapy.[23,28]

Following a three-drug induction, COG AALL0932 risk-stratified patients with SR B-ALL and those classified as AR then received a low-intensity 4-week consolidation phase without high-dose methotrexate or asparaginase intensification, and two interim maintenance phases separated by a single DI. Patients were then eligible for two maintenance random assignments examining the efficacy of reduced frequency of vincristine/dexamethasone pulses and starting oral methotrexate doses of 40 versus 20 mg/m^2 once weekly.

METHODS

Patients

Eligible B-ALL patients had newly diagnosed NCI SR B-ALL (age 1-9.99 years and initial WBC $<$ 50,000/μL).[29] Patients with CNS3 ($\geq$ 5 WBC/μL CSF with blasts), testicular leukemia, or prior cytotoxic chemotherapy were excluded.

Institutional review board approval was obtained at participating institutions prior to patient enrollment. Written informed consent and assent (where appropriate) were obtained from each patient and their parent/guardian before starting therapy. AALL0932 was registered at ClinicalTrials.gov identifier NCT01190930.

Study Design

This phase III multicenter, randomized trial opened to accrual in August 2010. Enrollment on AALL08B1 (ClinicalTrials.gov identifier: NCT01142427), the risk-classification trial, was required. Patients received a three-drug induction (Appendix Table A1, online only).[30] Patients without Down syndrome (DS) and who were Philadelphia chromosome (Ph)–negative were risk stratified at the end of induction (EOI) into four risk groups: low risk (LR), AR, high risk, or very high risk (VHR) based on induction day 8 peripheral blood (PB) flow cytometry-based MRD, day 29 bone marrow (BM) MRD, blast genetics, CNS status, and steroid pretreatment (Appendix Table A2, online only). DS patients were classified as SR-DS or high-risk DS based on similar factors (Appendix Table A3, online only). Ph-positive patients were not eligible for postinduction therapy. Favorable genetics included simultaneous trisomies of chromosome 4 and 10 (double trisomy; DT) or *ETV6/RUNX1* fusion. Unfavorable genetics were intrachromosomal amplification of chromosome 21, *KMT2A* (*MLL*) rearrangements, or hypodiploidy (< 44 chromosomes and/or DNA index < 0.81). This report focuses on the primary objectives in AR SR B-ALL patients to determine (i) if vincristine/dexamethasone pulses could be given every 12 weeks versus every 4 weeks without adversely impacting DFS; and (ii) if a starting maintenance oral methotrexate dose of 40 mg/m^2 once weekly would improve DFS compared with 20 mg/m^2 once weekly.

AR patients had day 29 BM MRD < 0.01% and either favorable genetics (without unfavorable genetics) and day 8 PB MRD ≥ 0.01%; steroid pretreatment; CNS2 (CSF WBC < 5/μL with blasts) status; or neutral cytogenetics with day 8 PB MRD < 1%. After completing pre-maintenance therapy (Fig 1), AR patients were randomly assigned using a 2 × 2 factorial design to one of four maintenance regimens as follows: (arm A) vincristine/dexamethasone pulses every 4 weeks (VCR/DEX4), and starting oral methotrexate dose 20 mg/m^2/week (MTX20); (arm B) every 4 week pulses and methotrexate 40 mg/m^2/week (MTX40); (arm C) every 12 week pulses and methotrexate 20 mg/m^2/week; (arm D) every 12 week pulses and methotrexate 40 mg/m^2/week. All arms included intrathecal methotrexate every 12 weeks, with oral methotrexate held that week. Maintenance cycles were repeated until completion of therapy, which was two (girls) or three (boys) years from starting interim maintenance I (Appendix Table A1). AALL0932 included guidelines (Data Supplement, online only) for adjusting 6-MP and methotrexate based on ANC and platelet count, and *TPMT* and *NUDT15* genotypes (incorporated mid-trial), which increased or decreased doses of 6-MP and methotrexate to target ANC 750-1,500/μL and platelets > 75,000/μL.

In January 2017, the Data Safety Monitoring Committee determined that a futility boundary had been crossed and that the study could not demonstrate that a 40 mg/m^2/week methotrexate starting dose was superior to 20 mg/m^2/week. Thus, all patients randomly assigned to MTX40 had their dose lowered to 20 mg/m^2/week, the standard of care, and 6-MP and methotrexate doses were subsequently adjusted based on tolerability following protocol guidelines.

Statistical Analysis

Study data frozen from June 30, 2019, are included in this report. For the overall NCI SR B-ALL cohort, EFS and OS were calculated from study enrollment to first event (EFS: induction failure, relapse, second malignant neoplasm, or remission death; OS: death) or censored at last follow-up. For randomly assigned patients, DFS and OS were calculated from random assignment (start of maintenance) to first event (for DFS: relapse, second malignant neoplasm, or remission death) or censored at last follow-up. Median follow-up was calculated using the reverse Kaplan-Meier method.[31] Survival rates were estimated by the method of Kaplan-Meier[32] with 95% CIs calculated using SEs of Peto et al.[33] The methotrexate dosing random assignment was powered (93% at one-sided $\alpha = .05$) to detect a difference in 5-year DFS from 93% *v* 96% for the MTX20 and MTX40 groups, respectively. The VCR/DEX pulse frequency random assignment was powered (90% at one-sided $\alpha = .10$) to detect a difference in 5-year DFS from 93% *v* 90% for VCR/DEX4 versus VCR/DEX every 12 weeks (VCR/DEX12), respectively. Both random assignments had interim monitoring for efficacy using an $\alpha^* t^2$ spending function, and futility monitoring for the methotrexate dosing question was based on the method of Fleming et al[34] with first interim analysis scheduled when 20% of expected DFS events were observed. A Cox proportional hazard model was fit to test for a possible interaction between the methotrexate dose and vincristine/dexamethasone pulse frequency random assignments using a two-sided 0.05 significance level threshold. Toxicities were graded according to NCI Common Toxicity Criteria Version 4 with targeted toxicity rates summarized by treatment arm and therapy period. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Graphics were generated with R Version 3.0.1.[35]

RESULTS

Patient Characteristics

AALL0932 enrolled 9,298 B-ALL patients from 224 institutions between August 2010 and March 2018. Sixty-nine were ineligible because of incorrect risk classification (12), inadequate sample collection (10), incorrect informed consent (6), ineligibility for the AALL08B1 (9), prior therapy (2), timing of enrollment/start of therapy (16), wrong diagnosis (13), or wrong enrollment (1). Three of 9,229 eligible SR ALL patients did not receive any induction treatment and were deemed unevaluable. After completing induction, 1,210 patients were risk-classified as LR and 236 as SR-DS and will be reported separately. One thousand, two hundred and sixty-one patients were risk classified as high risk, 83 as high-risk DS, 1,041 as VHR, 99 as

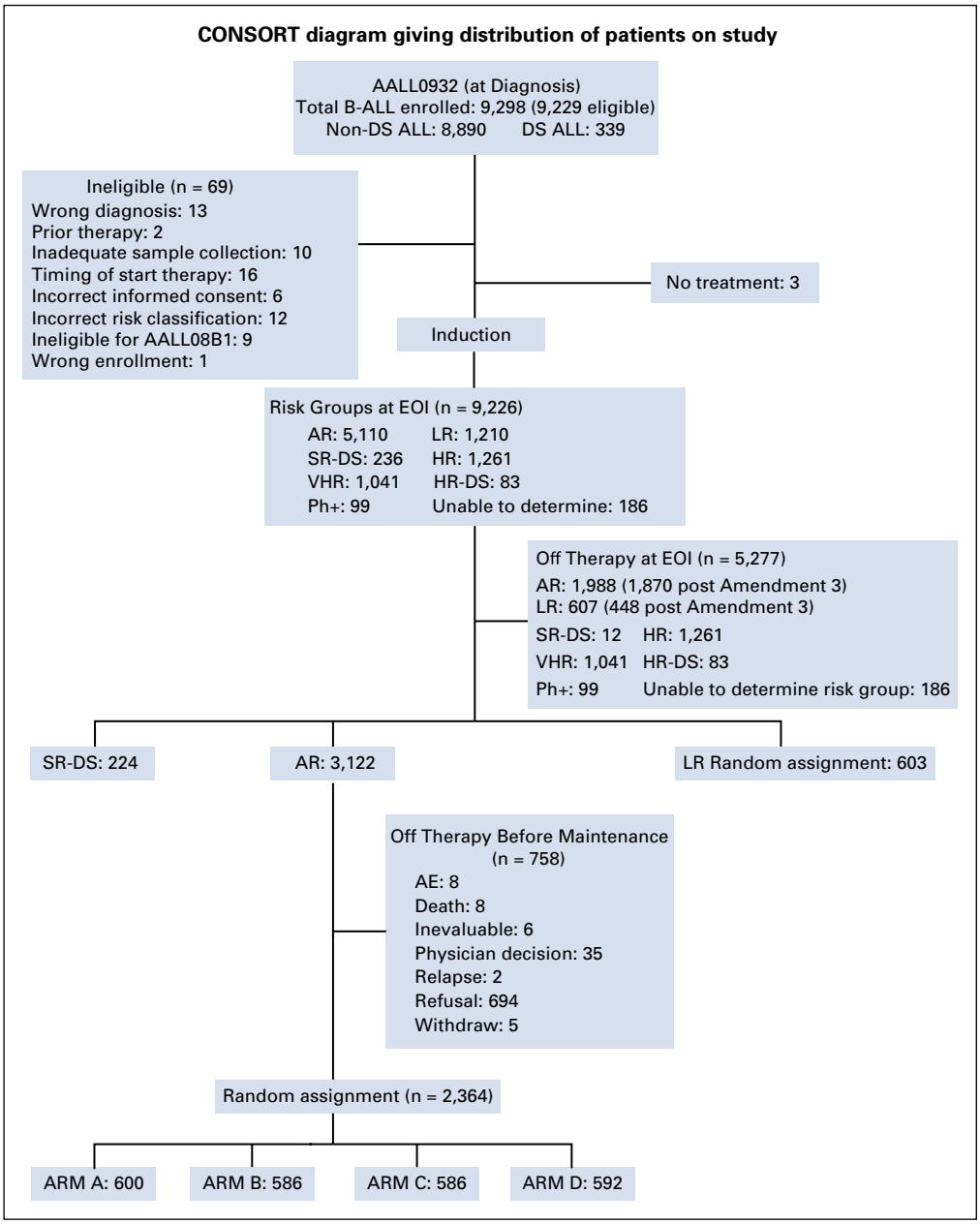

FIG 1. CONSORT diagram for Children's Oncology Group AALL0932. AE, adverse event; AR, average risk; B-ALL, B-acute lymphoblastic leukemia; DS, Down syndrome; EOI, end of induction; HR, high risk; LR, low risk; Ph, Philadelphia chromosome; SR, standard risk; VHR, very high risk.

Ph-positive, and 186 as risk group unable to be determined, primarily because of lack of required MRD or cytogenetic data, and came off protocol therapy (Fig 1). Five thousand, one hundred and ten patients were classified as AR; 1,870 of these came off protocol therapy at the EOI because AR random assignment accrual goals had been met. An additional 118 patients were removed at EOI for other reasons including refusal or withdrawal of consent (n = 73) and physician determines it is in patient's best interest (n = 33). Those AR patients still on protocol therapy were approached before maintenance to consent to the AR maintenance random assignment, with 2,364 randomly assigned to one of the four maintenance arms: A [VCR/DEX4, MTX20] (n = 600), B [VCR/DEX4, MTX40] (n = 586), C [VCR/DEX12, MTX20] (n = 586), or D [VCR/DEX12, MTX40] (n = 592) (Fig 1). Consistent with the predicted 25% estimation of random assignment dropout, 22.3% of parents declined to participate in the maintenance random assignment. The 5-year DFS (P = .8291) and OS (P = .5201) of patients who declined random assignment were similar to those who participated. Presenting features of the four groups were similar (Table 1).

TABLE 1. Overall Demographic Table for B-ALL Patients and AR-Randomly Assigned Patients

Demographic Category	Total Eligible (N = 9,229)	Arm A VCR/DEX4 MTX20 (n = 600)	Arm B VCR/DEX4 MTX40 (n = 586)	Arm C VCR/DEX12 MTX20 (n = 586)	Arm D VCR/DEX12 MTX40 (n = 592)	Total AR-Randomized (n = 2,364)
Sex						
Female	4,259 (46.1%)	284 (47.3%)	259 (44.2%)	269 (45.9%)	285 (48.1%)	1,097 (46.4%)
Male	4,970 (53.9%)	316 (52.7%)	327 (55.8%)	317 (54.1%)	307 (51.9%)	1,267 (53.6%)
Race						
American Indian or Alaska	94 (1.0%)	6 (1.0%)	3 (0.5%)	5 (0.9%)	1 (0.2%)	15 (0.6%)
Asian	425 (4.6%)	31 (5.2%)	28 (4.8%)	21 (3.6%)	29 (4.9%)	109 (4.6%)
Black or African American	498 (5.4%)	36 (6.0%)	40 (6.8%)	29 (4.9%)	32 (5.4%)	137 (5.8%)
Native Hawaiian or other	48 (0.5%)	6 (1.0%)	3 (0.5%)	0 (0.0%)	0 (0.0%)	9 (0.4%)
Multiple races	60 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unknown	1,300 (14.01%)	66 (11.0%)	77 (13.1%)	78 (13.3%)	84 (14.2%)	305 (12.9%)
White	6,804 (73.7%)	455 (75.8%)	435 (74.2%)	453 (77.3%)	446 (75.3%)	1,789 (75.7%)
Ethnic						
Hispanic or Latino	2,119 (23.0%)	130 (21.7%)	150 (25.6%)	129 (22.0%)	152 (25.7%)	561 (23.7%)
Not Hispanic or Latino	6,672 (72.3%)	459 (76.5%)	414 (70.6%)	436 (74.4%)	426 (71.9%)	1,735 (73.4%)
Unknown	438 (4.7%)	11 (1.8%)	22 (3.8%)	21 (3.6%)	14 (2.4%)	68 (2.9%)
Age group						
< 3	2,415 (26.2%)	164 (27.3%)	153 (26.1%)	172 (29.4%)	165 (27.9%)	654 (27.7%)
3-5	3,514 (38.1%)	234 (39.0%)	240 (41.0%)	224 (38.2%)	239 (40.4%)	937 (39.6%)
5-10	3,300 (35.7%)	202 (33.7%)	193 (32.9%)	190 (32.4%)	188 (31.7%)	773 (32.7%)
Cytogenetics						
Favorable	5,274 (57.1%)	376 (62.7%)	380 (64.8%)	387 (66.0%)	362 (61.1%)	1,505 (63.7%)
Neutral	3,541 (38.4%)	224 (37.3%)	206 (35.2%)	199 (34.0%)	230 (38.9%)	859 (36.3%)
Unfavorable	414 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
WBC group						
< 10,000	5,693 (61.7%)	378 (63.0%)	359 (61.3%)	341 (58.2%)	344 (58.1%)	1,422 (60.1%)
10,000-30,000	2,751 (29.8%)	170 (28.3%)	188 (32.1%)	199 (34.0%)	202 (34.1%)	759 (32.1%)
30,000-50,000	785 (8.5%)	52 (8.7%)	39 (6.7%)	46 (7.8%)	46 (7.8%)	183 (7.8%)
CNS						
CNS1	8,455 (91.6%)	554 (92.3%)	533 (90.9%)	524 (89.4%)	554 (93.6%)	2,165 (91.6%)
CNS2	742 (8.0%)	45 (7.5%)	52 (8.9%)	55 (9.4%)	35 (5.9%)	187 (7.9%)
Unknown	32 (0.4%)	1 (0.2%)	1 (0.2%)	7 (1.2%)	3 (0.5%)	12 (0.5%)

Abbreviations: AR, average risk; B-ALL, B-acute lymphoblastic leukemia; MTX20, methotrexate of 20 mg/m^2/week; MTX40, methotrexate of 40 mg/m^2/week; VCR/DEX12, vincristine/dexamethasone pulses every 12 weeks; VCR/DEX4, vincristine/dexamethasone pulses every 4 weeks.

Treatment Outcomes

The 5-year EFS (CI) and OS from enrollment for the 9,226 eligible B-ALL patients were 92.0% (95% CI, 91.1% to 92.8%) and 96.8% (95% CI, 96.2% to 97.3%), respectively (Fig 2A). There was a significant difference in EFS and OS between boys and girls; 5-year EFS (hazard ratio [HR], 1.28 [95% CI, 1.08 to 1.51], $P = .003$) and OS (HR, 1.38 [95% CI, 1.06 to 1.80], $P = .015$) in boys were 91.2% (95% CI, 90.0% to 92.5%) and 96.4% (95% CI, 95.5% to 97.2%) *v* 92.8% (95% CI, 91.6% to 94.0%) and 97.2% (95% CI, 96.4% to 98.0%) in girls, respectively (Appendix Fig A1, online only). The induction death and failure (M3) rates were 0.37% and 0.12%, respectively.

The 5-year DFS and OS from the start of maintenance for the 2,364 randomly assigned AR patients were 94.6% (95% CI, 93.3% to 95.9%) and 98.5% (95% CI, 97.7% to 99.2%), respectively, with a median follow-up of 4.8 years (Fig 2B).

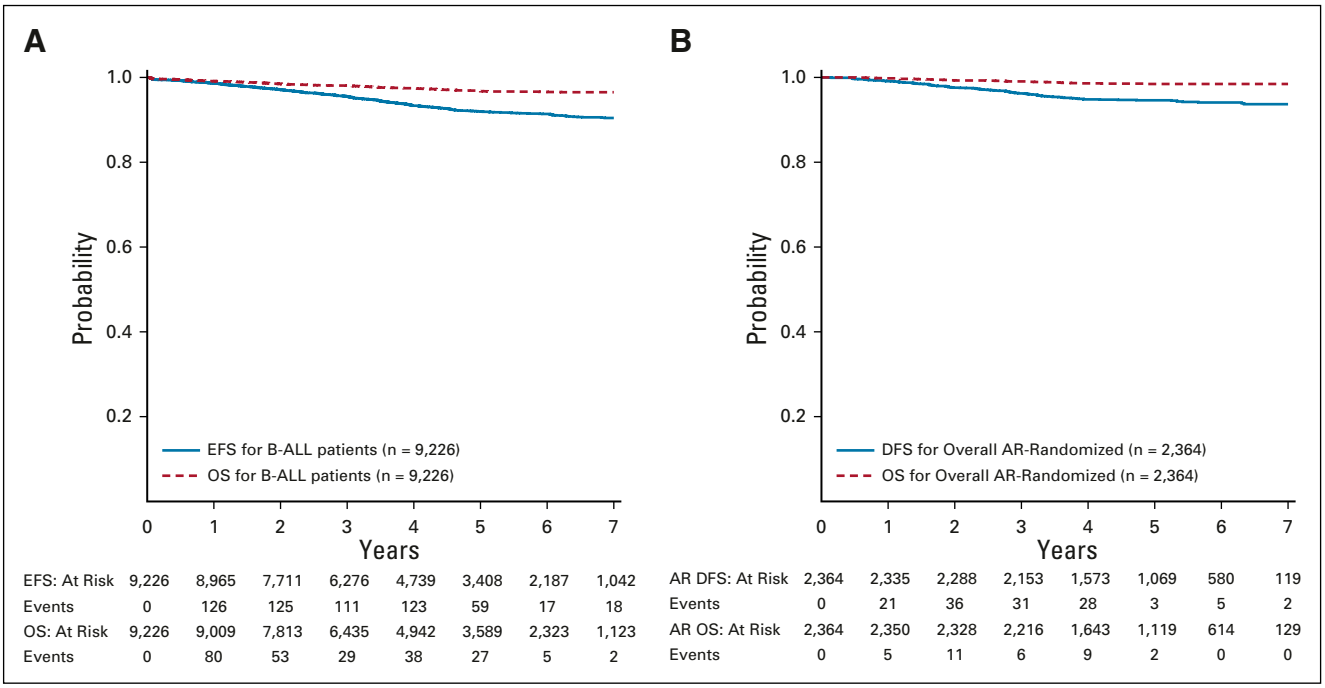

FIG 2. (A) EFS and OS from enrollment for all eligible B-ALL patients; (B) DFS and OS from start of maintenance for the randomly assigned AR patients. AR, average risk; B-ALL, B-acute lymphoblastic leukemia; DFS, disease-free survival; EFS, event-free survival; OS, overall survival.

There was no difference in outcome by sex; 5-year DFS (HR, 1.20 [95% CI, 0.84 to 1.70], $P = .31$) and OS (HR, 1.32 [95% CI, 0.68 to 2.65], $P = .43$) in boys were 94.2% (95% CI, 92.3% to 96.1%) and 98.3% (95% CI, 97.2% to 99.3%) *v* 95.1% (95% CI, 93.3% to 96.9%) and 98.7% (95% CI, 97.7% to 99.7%) in girls, respectively (Appendix Fig A2, online only).

Results of Randomized Maintenance Therapy Questions

Five-year DFS for AR patients randomly assigned to receive vincristine/dexamethasone pulses every 12 (n = 1,178) versus every 4 weeks (n = 1,186) was 95.1% (95% CI, 93.3% to 96.9%) and 94.1% (95% CI, 92.2% to 96.0%), respectively (HR, 0.83 [95% CI, 0.58 to 1.17], $P = .86$; Fig 3A) and 5-year OS was 98.6% (95% CI, 97.7% to 99.6%) and 98.3% (95% CI, 97.2% to 99.4%), respectively (HR, 0.84 [95% CI 0.42 to 1.67], $P = .69$; Fig 3B).

The 5-year DFS was 95.1% (95% CI, 93.3% to 96.8%) for MTX20 and 94.2% (95% CI, 92.2% to 96.1%) (HR, 0.78 [95% CI, 0.55 to 1.11], $P = .92$; Fig 3C) for MTX40, with a 5-year OS of 98.8% (95% CI, 97.9% to 99.7%) to 98.1% (95% CI, 97.0% to 99.2%), respectively (HR, 0.65 [95% CI, 0.32 to 1.30], $P = .89$; Fig 3D).

Five-year DFS for patients on maintenance arms A, B, C, and D was 95.4% (95% CI, 93.0% to 97.8%), 92.8% (95% CI, 89.7% to 95.8%), 94.7% (95% CI, 92.1% to 97.3%), and 95.6% (95% CI, 93.1% to 98.0%), respectively ($P = .06$; Fig 4A), and the 5-year OS was 98.7% (95% CI, 97.4% to 100%), 97.9% (95% CI, 96.2% to 99.5%), 98.9% (95% CI, 97.7% to 100%), and 98.4% (95% CI, 96.9% to 99.9%), respectively ($P = .61$; Fig 4B). The 5-year DFS and OS by sex were comparable for the four maintenance regimens (Appendix Table A4, online only). Per trial design, a Cox proportional hazard model was used to examine possible significant interaction between the methotrexate starting dose and vincristine/dexamethasone pulse frequency random assignments. The result of $P = .056$, based on the prespecified criteria, indicated a lack of evidence; the dose level effect depends on pulse frequency and, conversely, that the pulse frequency effect depends on dose level. Exploratory simple effect comparisons (using contrasts in the Cox model) were made comparing factor levels controlling for the other factor and showed that arm B (MTX40 and VCR/DEX4) could have higher risk than arm A (MTX20 and VCR/DEX4; HR, 1.76 [95% CI, 1.09 to 2.86], $P = .02$), and arm B (MTX40 and VCR/DEX4) could have higher risk than arm D (MTX40 and VCR/DEX12; HR, 1.66 [95% CI, 1.03 to 2.68], $P = .04$). This is not clinically relevant as the higher methotrexate dose provided no advantage.

Sites of relapse are shown in Tables 2 and 3 and in the Appendix Table A5, online only. There was no significant difference noted in the cumulative incidence of relapse by random assignments (Appendix Fig A3, online only).

Adverse Events

Therapy was well tolerated. The incidences of targeted toxicities were at expected rates (Appendix Tables A6 and A7, online only). No differences were observed in targeted toxicities associated with vincristine (motor or sensory neuropathy, ileus) or methotrexate (mucositis/stomatitis, or elevated bilirubin) between maintenance

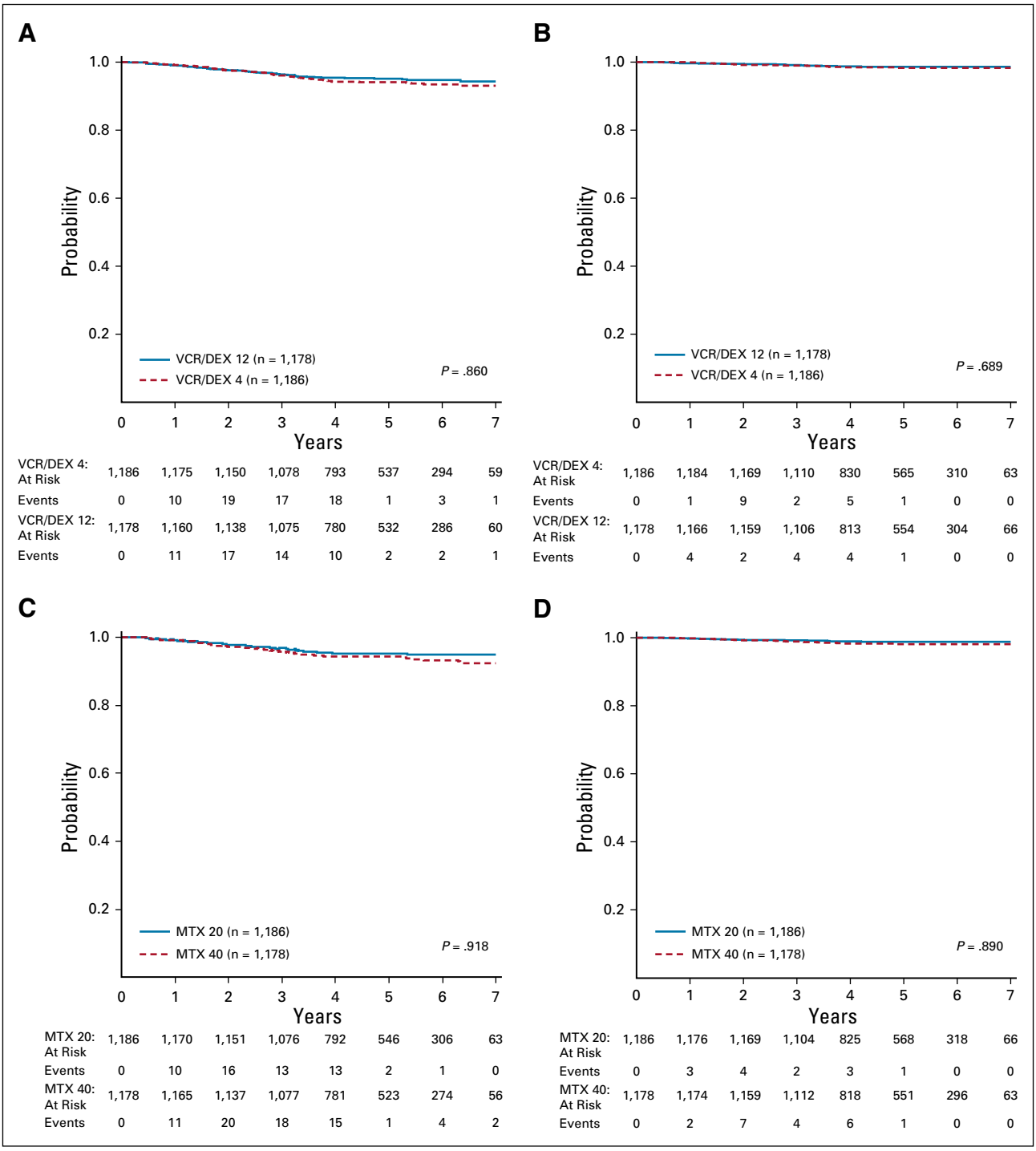

FIG 3. (A) DFS for the AR subset of patients randomly assigned to receive VCR/DEX12 *v* VCR/DEX4; (B) OS for AR patients randomly assigned to receive VCR/DEX12 *v* VCR/DEX4; (C) DFS for the AR subset of patients randomly assigned to receive MTX20 *v* MTX40; (D) OS for the AR subset of patients randomly assigned to receive MTX20 *v* MTX40. AR, average risk; DFS, disease-free survival; MTX20, methotrexate of 20 mg/m^2/week; MTX40; methotrexate of 40 mg/m^2/week; OS, overall survival; VCR/DEX12, vincristine/dexamethasone pulses every 12 weeks; VCR/DEX4, vincristine/dexamethasone pulses every 4 weeks.

arms. However, the rate of neuropathy was lower for patients receiving pulses every 12 versus every 4 weeks, 1.8% *v* 3.4%, $P = .015$, respectively.

DISCUSSION

AALL0932 sought to improve outcomes and reduce toxicity and burden of therapy by optimizing maintenance therapy for

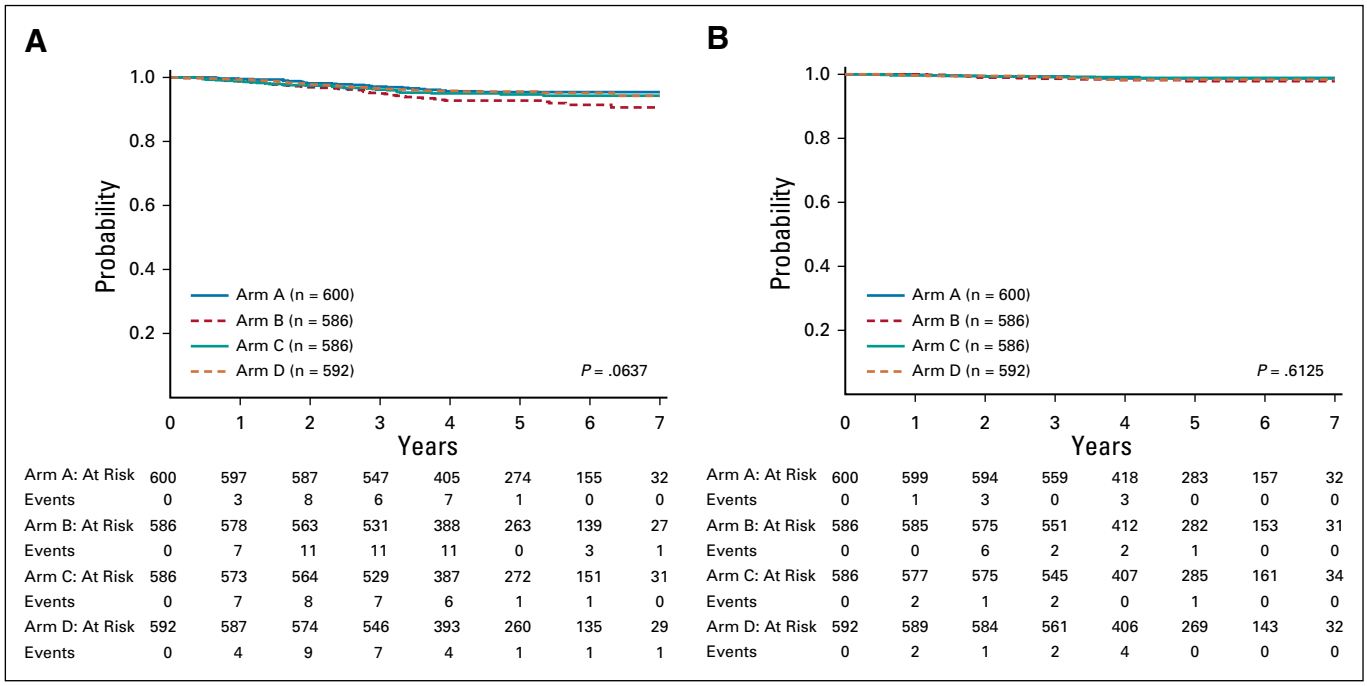

FIG 4. (A) Disease-free survival and (B) overall survival by average risk maintenance arm.

the AR subset of NCI SR B-ALL, defined using a combination of NCI risk group, sentinel somatic genetic lesions, clinical variables, and early treatment response. These AR patients had projected 5-year DFS rates of 90%-95% at the time of study design, and AALL0932 demonstrated outstanding outcomes with vincristine/dexamethasone maintenance pulses given every 12 weeks, with 5-year DFS/OS rates of 95.1% and 98.6%. AALL0932 was not designed as a classic noninferiority trial, which would have required many more years to complete, but the lower 5-year 95% confidence limits of 93.3% (DFS) and 97.7% (OS) with every 12 week pulses were well within prestudy expectations. Our data do not address whether any maintenance pulses are needed. The AALL0932-reduced vincristine/dexamethasone pulses arm still provides more vincristine/steroid exposure than the plus-pulses arm of the BFM prospective meta-analysis study, which showed that six vincristine/steroid pulses in maintenance did not improve the outcome. However, that study used the BFM backbone, which included much more intensive premaintenance therapy with a four-drug induction, intensive Ib consolidation phase, and four courses of high-dose methotrexate.[6,7]

TABLE 2. Sites of Relapse by Pulse Frequency Random Assignment

	Pulse Frequency		
Relapse Site	**VCR/DEX12**	**VCR/DEX4**	**Total**
BM	28	37	65
BM plus CNS	3	4	7
BM plus testicular	2	1	3
CNS	13	16	29
CNS plus PB	1	0	1
Testicular	1	2	3
Other extramedullary	1	1	2
Total	49	61	110

Abbreviations: BM, bone marrow; PB, peripheral blood; VCR/DEX12, vincristine/dexamethasone pulses every 12 weeks; VCR/DEX4, vincristine/dexamethasone pulses every 4 weeks.

Reducing maintenance vincristine/dexamethasone pulses by two thirds lessens the burden of therapy and may translate to improved quality of life. Glucocorticoids cause significant toxicities: myalgias, myopathies, infections, hyperglycemia, osteonecrosis, obesity, metabolic sequelae, adrenal axis suppression, and neurocognitive late effects.[36-39] Moreover, steroid exposure increases emotional lability and disruptive behaviors leading to missed days of school or daycare by patients and work by parents.[40,41] Vincristine is also associated with declines in fine motor and sensory-perceptual performance.[42,43] Early data regarding quality-of-life outcomes for AALL0932 have been reported, and longer-term data will be described separately.[44]

Because methotrexate doses of 40 mg/m^2 were well tolerated in previous trials, AALL0932 also explored the optimal starting dose of oral methotrexate during maintenance based on its poor oral bioavailability and known interpatient variability in plasma methotrexate levels following oral doses.[14-17,19,45] However, a futility boundary was

TABLE 3. Sites of Relapse by Oral Methotrexate Dose Random Assignment

	Dose Frequency		
Relapse Site	**MTX20**	**MTX40**	**Total**
BM	28	37	65
BM plus CNS	7	0	7
BM plus testicular	1	2	3
CNS	10	19	29
CNS plus PB	1	0	1
Testicular	1	2	3
Other extramedullary	1	1	2
Total	49	61	110

Abbreviations: BM, bone marrow; MTX20, methotrexate of 20 mg/m^2/week; MTX40, methotrexate of 40 mg/m^2/week; PB, peripheral blood.

crossed in January 2017, and patients who had been randomly assigned to receive a starting methotrexate dose of 40 mg/m^2/week had their dose lowered to 20 mg/m^2/week, the standard of care therapy, and their doses of 6-MP and MTX were adjusted based on tolerability as per protocol guidelines for all arms. These data were confirmed with analysis of mature data, with 5-year DFS of 95.1% and 94.2% ($P = .92$), and 5-year OS of 98.8% and 98.1% ($P = .89$) for those receiving MTX20 and MTX40, respectively.

To investigate potential confounding impacts of the increased starting dose of oral MTX, we reviewed detailed data regarding cumulative maintenance doses of 6-MP and MTX administered by arm to assess whether the higher methotrexate dose might have led to lower doses of 6-MP or more frequent holding of oral chemotherapy, which per protocol guidelines occurred when ANC was $< 500/\mu L$ or platelet count was $< 50{,}000/\mu L$. A comparison of 6-MP dosing showed nearly identical median doses administered on the MTX20 and MTX40 arms. For example, in the first month of maintenance cycle four, patients on MTX20 arms received a median (interquartile range [IQR]) of 95.2% (67.2%, 101.6%) of protocol 6-MP dosing compared with a median IQR of 95.2% (64.9%, 101.7%) on the MTX40 arms. As expected, the methotrexate dose administered on MTX40 arms was approximately double of that given on the MTX20 arms. However, the number of days chemotherapy was held was not collected; based on similar cumulative doses across arms, it seems unlikely that there were more interruptions in therapy on the MTX40 arms than on the MTX20 arms. As these doses were patient- or parent-reported and not confirmed by pill counts or MEMS cap, it is also possible that patients on the MTX40 arm were less compliant with oral chemotherapy.

In summary, AALL0932 achieved outstanding outcomes with a 5-year EFS of 92.0% and an OS of 96.8% $>$ 9,000 SR B-ALL patients. The AR patients had a 5-year DFS of 94.6% and an OS of 98.5% from the time of random assignment, and outcomes with maintenance vincristine/dexamethasone pulses given every 12 weeks were not proven to be inferior to outcomes with pulses given every 4 weeks. Because the study was not designed as a noninferiority trial, it was not demonstrated statistically that decreased pulse frequency resulted in outcomes as good as those with the every 4 weeks group. In addition, a higher starting dose of maintenance oral methotrexate did not improve DFS. Together, these results establish that in the modern era, a relatively low-intensity premaintenance backbone with a three-drug induction, no intensive 1b phase, and no high-dose methotrexate results in outstanding outcomes and that additional intensifications of traditional maintenance cytotoxic chemotherapy do not improve outcome. Based on these results and those of the BFM with no maintenance pulses,[6] COG B-ALL trials now use every 12 week vincristine/steroid pulses during maintenance, with efforts to improve survival focused on treatment interventions prior to starting maintenance therapy.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Excellent Outcomes With Reduced Frequency of Vincristine and Dexamethasone Pulses in Standard-Risk B-Lymphoblastic Leukemia: Results From Children's Oncology Group (COG) AALL0932

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APPENDIX

TABLE A1. Therapy Regimens for AR Patients at the Time of Study Initiation

Phase and Treatment	Dose
Induction (5 weeks)	
Dexamethasone	6 mg/m^2 per day PO, days 1-28
Cytarabine[a]	IT × 1 on days -2 to 1
Vincristine	1.5 mg/m^2 (maximum 2 mg) per dose, days 1, 8, 15, and 22
Methotrexate[b]	IT, days 8 and 29
PEG asparaginase	2500 IU/m^2 per dose IV, day 4
Consolidation (4 weeks)	
Mercaptopurine	75 mg/m^2 per day PO, days 1-28
Methotrexate[b]	IT, days 1, 8, and 15
Vincristine	1.5 mg/m^2 (maximum 2 mg) per dose, day 1
Interim maintenance (8 weeks)	
Vincristine	1.5 mg/m^2 (maximum 2 mg) per dose IV, days 1, 11, 21, 31, and 41
Methotrexate	100 mg/m^2 per day IV, days 1, 11, 21, 31, 41 (escalate by 50 mg/m^2 per dose)
Methotrexate[b]	IT day 31
Delayed intensification (8 weeks)	
Dexamethasone	10 mg/m^2 per day PO, days 1-7 and 15-21
Vincristine	1.5 mg/m^2 (maximum 2 mg) per dose IV, days 1, 8, and 15
Doxorubicin	25 mg/m^2 per day IV, days 1, 8, and 15
PEG asparaginase	2500 IU/m^2 per day IV, day 4
Methotrexate[b]	IT, days 1 and 29
Cyclophosphamide	1000 mg/m^2 per day IV, day 29
Thioguanine	60 mg/m^2 per day PO, days 29-42
Cytarabine	75 mg/m^2 per day SQ or IV, days 29-32 and 36-39
Interim maintenance II (8 weeks)	
Vincristine	1.5 mg/m^2 (maximum 2 mg) per dose IV, days 1, 11, 21, 31, and 41
Methotrexate	Starting dose of IV methotrexate is 2/3 of the maximum tolerated dose in interim maintenance I with same escalation rules, days 1, 11, 21, 31, and 41 (escalate by 50 mg/m^2 per dose)
Methotrexate[b]	IT days 1 and 31
Maintenance (12 weeks)[c]	Arm A
Vincristine	1.5 mg/m^2 per day IV, days 1, 29, and 57
Dexamethasone	6 mg/m^2 per day PO, days 1-5, 29-33, and 57-61
Mercaptopurine[d]	75 mg/m^2 per day PO, days 1-84
Methotrexate[d]	20 mg/m^2 per day PO, days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78
Methotrexate[b]	IT day 1
Maintenance (12 weeks)[c]	Arm B
Vincristine	1.5 mg/m^2 per day IV, days 1, 29, and 57
Dexamethasone	6 mg/m^2 per day PO, days 1-5, 29-33, and 57-61
Mercaptopurine[d]	75 mg/m^2 per day PO, days 1-84
Methotrexate[d]	40 mg/m^2 per day PO, days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78
Methotrexate[b]	IT day 1

(continued on following page)

TABLE A1. Therapy Regimens for AR Patients at the Time of Study Initiation (continued)

Phase and Treatment	Dose
Maintenance (12 weeks)[c]	Arm C
Vincristine	1.5 mg/m^2 per day IV, day 1
Dexamethasone	6 mg/m^2 per day PO, days 1-5
Mercaptopurine[d]	75 mg/m^2 per day PO, days 1-84
Methotrexate[d]	20 mg/m^2 per day PO, days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78
Methotrexate[b]	IT day 1
Maintenance (12 weeks)[c]	Arm D
Vincristine	1.5 mg/m^2 per day IV, day 1
Dexamethasone	6 mg/m^2 per day PO, days 1-5
Mercaptopurine[d]	75 mg/m^2 per day PO, days 1-84
Methotrexate[d]	40 mg/m^2 per day PO, days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78
Methotrexate[b]	IT day 1

Abbreviations: IV, intravenously; PO, orally; IT, intrathecally; SQ, subcutaneously.

[a]The doses were age-adjusted as follows: age 1 to 1.99 years, 30 mg; age 2 to 2.99 years, 50 mg; and age > 3 years, 70 mg.

[b]The doses were age-adjusted as follows: age 1 to 1.99 years, 8 mg; age 2 to 2.99 years, 10 mg; age 3 to 3.99 years, 12 mg; and age > 9 years, 15 mg.

[c]The cycles of maintenance therapy were repeated until the total duration of therapy, beginning with the first interim maintenance period, reached 2 years for girls and 3 years for boys.

[d]Mercaptopurine and methotrexate doses were adjusted to maintain an ANC between 500 and 1500 and platelet count >50 K; additional dose adjustments were made for patients with known *TPMT* mutations.

TABLE A2. COG AALL08B1 Classification System at the End of Induction for Patients With NCI SR Non-Down Syndrome B-Acute Lymphoblastic Leukemia Who Are Eligible for COG AALL0932

Risk Group	LR[c]	AR[d]		HR[e]		VHR	
NCI risk group	SR	SR	SR	SR	SR	SR	SR or HR
Favorable genetics[a]	Yes	Yes	No	Yes	No	No	Any
Unfavorable characteristics[b]	No	No	No	No	No	No	Yes
Day 8 PB MRD	< 0.01%	> 0.01%	< 1%	Any	≥ 1%	Any	Any
Day 29 BM MRD	< 0.01%	< 0.01%	< 0.01%	≥ 0.01%	< 0.01%	≥ 0.01%	Any

Abbreviations: AR, average risk; BM, bone marrow; COG, Children's Oncology Group; HR, high risk; LR, low risk; MRD, minimal residual disease; NCI, National Cancer Institute; PB, peripheral blood; SR, standard risk; VHR, very high risk.

[a]"Yes" is defined as the presence of double trisomy 4 and 10 OR *ETV6-RUNX1* fusion.

[b]Consists of patients with CNS3, hypodiploidy (< 44 chromosomes and/or DNA index < 0.81), *iAMP21*, Induction failure (M3 marrow day 29), or *KMT2A* (*MLL*) rearrangement (not *KMT2A* deletion) or *BCR-ABL1* positive.

[c]LR must have no steroid pretreatment and no CNS disease.

[d]NCI SR patients who are CNS2 may be included in AR but will not be eligible for the LR arm.

[e]All patients with testicular involvement will be assigned to be HR but may change to VHR if day 29 MRD ≥ 0.01%.

TABLE A3. COG AALL08B1 Classification System at the End of Induction for Patients With NCI SR-DS Who Are Eligible for COG AALL0932

Risk Status	SR-DS	HR-DS[b]
NCI risk group	SR	SR
Favorable genetics[a]	Any	Any
Day 8 PB MRD	Any	Any
Day 29 BM MRD	$< 0.01\%$	$\geq 0.01\%$

Abbreviations: BM, bone marrow; COG, Children's Oncology Group; DS, Down syndrome; HR, high risk; MRD, minimal residual disease; NCI, National Cancer Institute; PB, peripheral blood; SR, standard risk.

[a]Defined as the presence of double trisomy 4 and 10 OR *ETV6-RUNX1* fusion.

[b]All DS-ALL patients with CNS3 or testicular involvement will be assigned to the HR-DS study at the initial diagnosis. DS-ALL patients with MRD day 29 $\geq 0.01\%$, regardless of other factors will be classified as HR-DS.

TABLE A4. Five-Year DFS and OS by Sex by AR Maintenance Arm

Comparison Group	Arm A VCR/DEX4 and MTX20	Arm B VCR/DEX4 and MTX40	Arm C VCR/DEX12 and MTX20	Arm D VCR/DEX12 and MTX40
DFS boys	95.3% ± 1.8%	92.6% ± 2.1%	93.4% ± 2.0%	95.6% ± 1.7%
DFS girls	95.6% ± 1.7%	93.0% ± 2.3%	96.2% ± 1.7%	95.5% ± 1.8%
OS boys	98.3% ± 1.1%	96.8% ± 1.4%	99.4% ± 0.6%	98.6% ± 1.0%
OS girls	99.2% ± 0.8%	99.2% ± 0.8%	98.3% ± 1.1%	98.1% ± 1.2%

Abbreviations: AR, average risk; DFS, disease-free survival; MTX20, methotrexate of 20 mg/m^2/week; MTX40, methotrexate of 40 mg/m^2/week; OS, overall survival; VCR/DEX12, vincristine/dexamethasone pulses every 12 weeks; VCR/DEX4, vincristine/dexamethasone pulses every 4 weeks.

TABLE A5. Sites of Relapse by AR Maintenance Arm

Relapse Site	Arms				
Frequency	**Arm A**	**Arm B**	**Arm C**	**Arm D**	**Total**
BM	14	23	14	14	65
BM + CNS	4	0	3	0	7
BM + testicular	0	1	1	1	3
CNS	4	12	6	7	29
CNS + PB	0	0	1	0	1
Testicular	0	2	1	0	3
Other extramedullary	0	1	1	0	2
Total	22	39	27	22	110

Abbreviations: AR, average risk; BM, bone marrow; PB, peripheral blood.

TABLE A6. Targeted AEs for Induction, AR Postinduction, Premaintenance, and AR Maintenance

AE	Induction (N = 9,226)	AR Postinduction, Premaintenance (N =3,122)	AR Maintenance (N = 2,364)
1. CNS hemorrhage requiring medical intervention (grades 2, 3, 4, and 5)	18 (0.20%)	0 (0.00%)	0 (0.00%)
2. GI bleed requiring operative or interventional radiology intervention (grades 3, 4, and 5)	8 (0.09%)	3 (0.10%)	2 (0.08%)
3. Pancreatitis requiring medical intervention (grades 2, 3, 4, and 5)	94 (1.01%)	16 (0.51%)	14 (0.59%)
4. Osteonecrosis interfering with function (grades 2, 3, 4, and 5)	4 (0.04%)	5 (0.16%)	26 (1.10%)
5 Transient ischemic attacks (all grades)	2 (0.02%)	0 (0.00%)	0 (0.00%)
6. Stroke (all grades)	8 (0.09%)	1 (0.03%)	1 (0.04%)
7. Encephalopathy (grades 3, 4, and 5)	28 (0.30%)	13 (0.42%)	6 (0.25%)
8. Neuropathy; motor or sensory, interfering with ADL (grades 3, 4, and 5)	275 (2.98%)	139 (4.45%)	61 (2.58%)
9. Seizure (grades 2, 3, 4, and 5)	71 (0.77%)	53 (1.70%)	23 (0.97%)
10. Allergic reaction (grades 3, 4, and 5)	29 (0.31%)	63 (2.02%)	6 (0.25%)
11 Ileus (grades 3, 4, and 5)	36 (0.39%)	5 (0.16%)	5 (0.21%)
12. Mucositis/stomatitis; functional (grades 3, 4, and 5)	89 (0.96%)	356 (11.4%)	68 (2.88%)
13. Bilirubin (grades 3, 4, and 5)	111 (1.20%)	9 (0.29%)	136 (5.75%)
14. Thrombosis (grades 3, 4, and 5)	69 (0.75%)	19 (0.61%)	1 (0.04%)

Abbreviations: ADL, activities of daily living; AE, adverse event; AR, average risk.

TABLE A7. Targeted AEs for AR Maintenance by Treatment Arm

AE	AR Arm A (N = 600)	AR Arm B (N = 586)	AR Arm C (N = 586)	AR Arm D (N = 592)
1. CNS hemorrhage requiring medical intervention (grades 2, 3, 4, and 5)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
2. GI bleed requiring operative or interventional radiology intervention (grades 3, 4, and 5)	0 (0.00)	1 (0.17)	1 (0.17)	0 (0.00)
3. Pancreatitis requiring medical intervention (grades 2, 3, 4, and 5)	5 (0.83)	2 (0.34)	3 (0.51)	4 (0.68)
4. Osteonecrosis interfering with function (grades 2, 3, 4, and 5)	6 (1.00)	10 (1.71)	6 (1.02)	4 (0.68)
5 Transient ischemic attacks (all grades)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
6. Stroke (all grades)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.17)
7. Encephalopathy (grades 3, 4, and 5)	2 (0.33)	2 (0.34)	1 (0.17)	1 (0.17)
8. Neuropathy; motor or sensory, interfering with ADL (grades 3, 4, and 5)	17 (2.83)	23 (3.92)	12 (2.05)	9 (1.52)
9. Seizure (grades 2, 3, 4, and 5)	6 (1.00)	3 (0.51)	4 (0.68)	10 (1.70)
10. Allergic reaction (grades 3, 4, and 5)	5 (0.83)	1 (0.17)	0 (0.00)	0 (0.00)
11 Ileus (grades 3, 4, and 5)	1 (0.17)	0 (0.00)	1 (0.17)	3 (0.51)
12. Mucositis/stomatitis; functional (grades 3, 4, and 5)	17 (2.83)	23 (3.92)	16 (2.73)	12 (2.03)
13. Bilirubin (grades 3, 4, and 5)	39 (6.50)	34 (5.80)	33 (5.63)	30 (5.07)
14. Thrombosis (grades 3, 4, and 5)	0 (0.00)	0 (0.00)	1 (0.17)	0 (0.00)

Abbreviations: ADL, activities of daily living; AE, adverse event; AR, average risk.

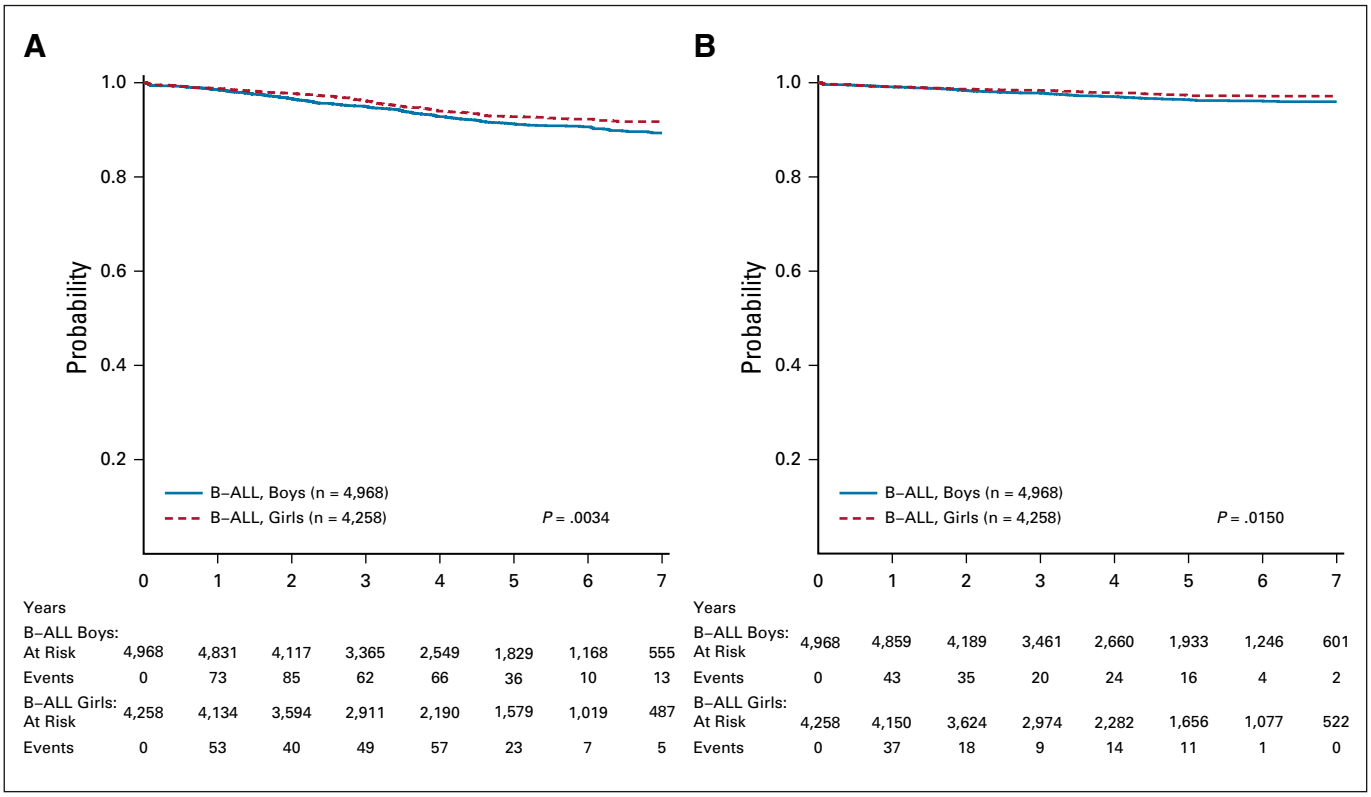

FIG A1. (A) EFS and (B) OS from enrollment for eligible B-ALL patients by sex. (B) OS from enrollment for the eligible B-ALL patients by sex. B-ALL, B-acute lymphoblastic leukemia; EFS, event-free survival; OS, overall survival.

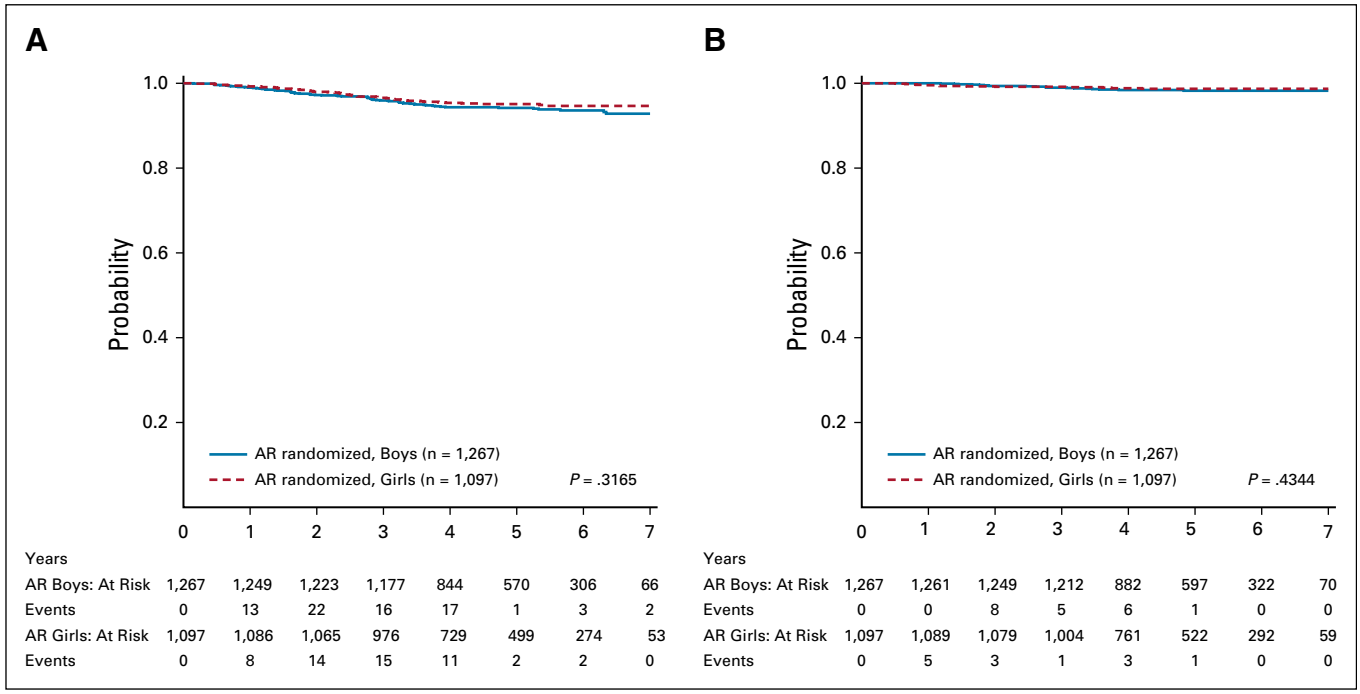

FIG A2. (A) DFS from the start of maintenance for the randomly assigned AR patients by sex. (B) OS from the start of maintenance for the randomly assigned AR patients by sex. AR, average risk; DFS, disease-free survival; OS, overall survival.

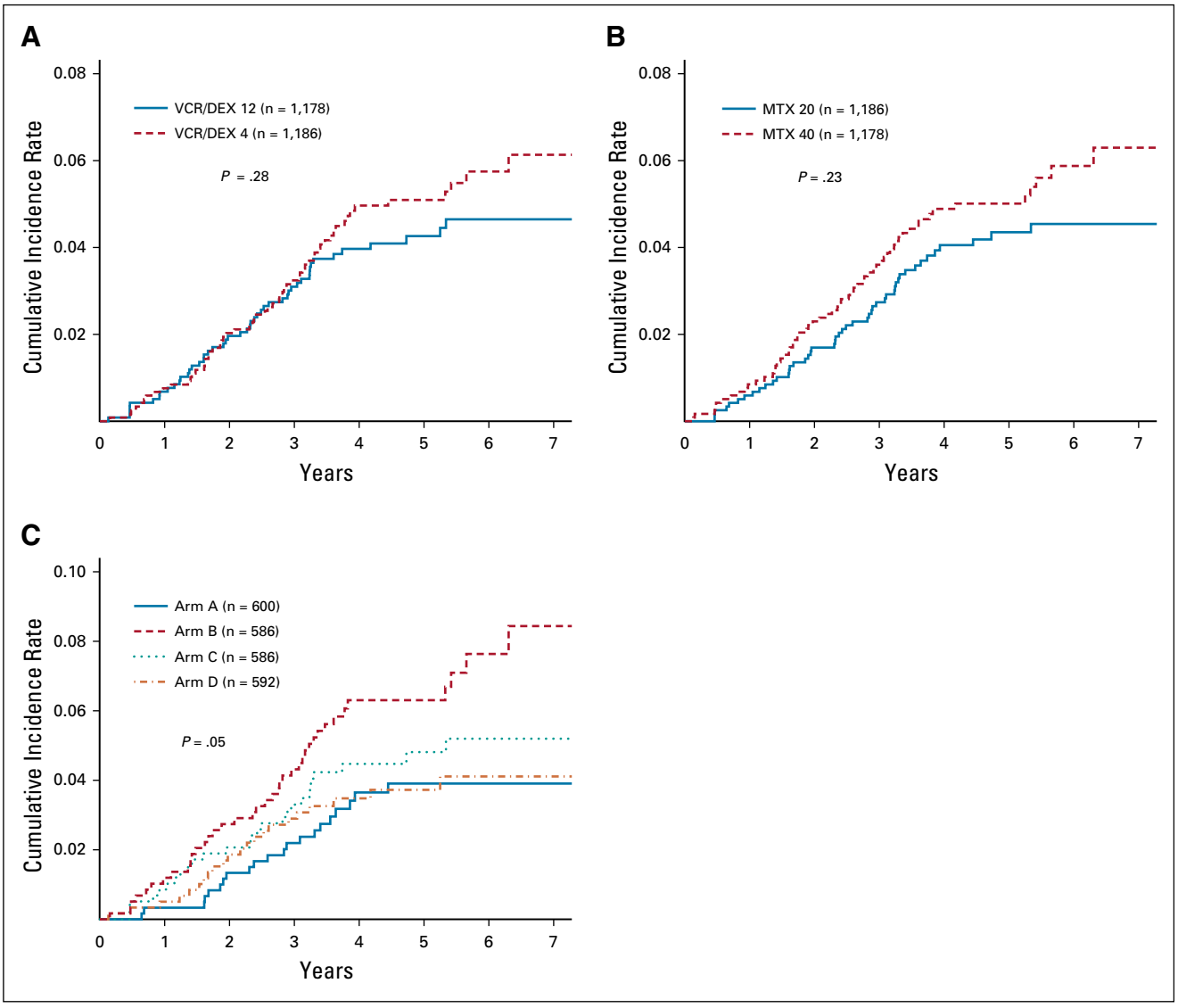

FIG A3. (A) Cumulative incidence of all relapses as first events by pulse frequency randomization. (B) Cumulative incidence of all relapses as first events by oral methotrexate dose random assignment. (C) Cumulative incidence of all relapses as first events by AR maintenance arm. AR, average risk.