Chromosome abnormalities at onset of complete remission are associated with worse outcome in patients with acute myeloid leukemia and an abnormal karyotype at diagnosis: CALGB 8461 (Alliance)

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Supplementary Appendix

Chromosome abnormalities at onset of complete remission are associated with worse outcome in patients with acute myeloid leukemia and an abnormal karyotype at diagnosis: CALGB 8461 (Alliance)

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Participating institutions

The following Cancer and Leukemia Group B (CALGB)/Alliance for Clinical Trials in Oncology (Alliance) institutions participated in this study. For each of these institutions, the current or last principal investigator and the cytogeneticists who analyzed the cases are listed as follows:

North Shore University Hospital, Manhasset, NY: Daniel R. Budman, Prasad R. K. Koduru, Ayala Aviram-Goldring and Chandrika Sreekantaiah; The Ohio State University Medical Center, Columbus, OH: Richard M. Goldberg, Karl S. Theil, Diane Minka and Nyla A. Heerema; Wake Forest University School of Medicine, Winston-Salem, NC: Heidi Klepin, P. Nagesh Rao, Wendy L. Flejter and Mark Pettenati; Dana Farber Cancer Institute, Boston, MA: Harold J. Burstein, Cynthia C. Morton and Paola Dal Cin; Washington University School of Medicine, St. Louis, MO: Nancy L. Bartlett, Jaime Garcia-Heras, Peining Li and Shashikant Kulkarni; Weill Medical College of Cornell University, New York, NY: Scott Tagawa, Prasad R.K. Koduru and Ayala Aviram-Goldring; University of Chicago Medical Center, Chicago, IL: Hedy L. Kindler, Katrin M. Carlson, Yanming Zhang and Michelle M. LeBeau; University of North Carolina, Chapel Hill, NC: Thomas C. Shea and Kathleen W. Rao; Ft. Wayne Medical Oncology/Hematology, Ft. Wayne, IN: Sreenivasa Nattam and Patricia I. Bader; Duke University Medical Center, Durham, NC: Jeffrey Crawford and Barbara K. Goodman; Mount Sinai School of Medicine, New York, NY: Lewis R. Silverman and Vesna Najfeld; SUNY Upstate Medical University, Syracuse, NY: Stephen L. Graziano and Constance K. Stein; University of Maryland Cancer Center, Baltimore, MD: Martin J. Edelman and Yi Ning; University of Iowa Hospitals, Iowa City, IA: Daniel A. Vaena and Shivanand R. Patil; Long Island Jewish Medical Center, Lake Success, NY: Daniel R. Budman, Ayala Aviram-Goldring and Prasad R. K. Koduru; Massachusetts General Hospital, Boston, MA: David Ryan, Justin Gainor, Cynthia C. Morton and Paola Dal Cin; University of Massachusetts Medical Center, Worcester, MA: William V. Walsh, Vikram Jaswaney, Michael J. Mitchell and Patricia Miron; Vermont Cancer Center, Burlington, VT: Steven M. Grunberg and Mary Tang;

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Treatment protocols

The patients analyzed in this study were enrolled onto one of the CALGB multicenter front-line treatment studies. Younger patients (aged <60 years) enrolled onto the CALGB 8525 protocol (n=5) were treated with cytarabine and daunorubicin induction chemotherapy and were randomly assigned to four cycles of consolidation with low, intermediate or high doses (HiDAC) of cytarabine followed by maintenance treatment with four cycles of low dose cytarabine combined with daunorubicin.[1] Patients enrolled onto CALGB 9022 (n=5) received induction chemotherapy similar to that on CALGB 8525 followed by consolidation with one cycle of HiDAC, a cycle of cyclophosphamide and etoposide, and one cycle of mitoxantrone and diaziquone.[2] Treatment for patients on protocol CALGB 9222 (n=10) was similar, except that different doses of mitoxantrone were explored, and the consolidation treatment was randomized to three cycles of monotherapy

with HiDAC or consolidation with one cycle of HiDAC, a cycle of cyclophosphamide and etoposide, and one cycle of mitoxantrone and diaziquone.[3]

Patients on CALGB 9621 (n=28) were randomly assigned to receive induction chemotherapy with cytarabine, daunorubicin and etoposide with or without a multidrug resistance protein inhibitor PSC-833 (valspodar).[4] Postremission therapy depended on whether the patient had core-binding factor acute myeloid leukemia (CBF-AML) or not, with CBF-AML patients who harbored t(8;21)(q22;q22) or inv(16)(p13.1q22)/t(16;16)(p13.1;q22) receiving three courses of HiDAC, and non-CBF-AML patients assigned to postremission therapy with HiDAC and etoposide for stem-cell mobilization and myeloablative treatment with busulfan and etoposide for autologous hematopoietic stem-cell transplantation (HSCT).[4] Patients not eligible for autologous HSCT were administered two cycles monotherapy with HiDAC. Maintenance immunotherapy consisted of either a sequence of alternating low and high dose recombinant interleukin-2 (rIL2) or no therapy. Patients on protocols CALGB 19808[5] (n=79) and CALGB 10503[6] (n=47) were treated similarly to those on CALGB 9621. However, on CALGB 10503, PSC-833 was eliminated from induction treatment and maintenance therapy consisted of decitabine, a DNA methyltransferase inhibitor.[6]

Patients with *FLT3*-ITD or *FLT3*-TKD enrolled on CALGB 10603 (n=11) were randomized to receive induction with cytarabine and daunorubicin and consolidation with four cycles of HiDAC in combination with either the multi-kinase inhibitor PKC-412 (midostaurin) or placebo, followed by, respectively, one year maintenance with PKC-412 monotherapy or placebo.[7] Patients diagnosed with CBF-AML enrolled on CALGB 10801 (n=11) were administered induction chemotherapy with cytarabine, daunorubicin and the multikinase inhibitor dasatinib, followed by consolidation treatment consisting of four courses of HiDAC with dasatinib. Patients remaining in complete remission (CR) received one-year maintenance with dasatinib or placebo.[8]

Older patients (aged ≥60 years) enrolled onto CALGB 8923 (n=2) received cytarabine and daunorubicin induction treatment similar to CALGB 8525 and were then randomized to receive postremission therapy of four cycles of low dose cytarabine alone or two cycles of intermediate

dose cytarabine in combination with mitoxantrone.[9] Twenty-one patients were enrolled onto CALGB 9720, which evaluated multidrug resistance modulation by PSC-833 during induction and consolidation therapy with cytarabine, daunorubicin, and etoposide. However, the PSC-833 arm was closed after random assignment of 120 patients because of a high number of early deaths.[10] Enrollment continued for patients on the chemotherapy-only control arm. Postremission therapy consisted of a single cytarabine, daunorubicin and etoposide consolidation course also with PSC-833 until arm closure and the patients were subsequently randomly assigned to receive or not receive rIL2 maintenance therapy similar to CALGB 19808.[10]

Patients on CALGB 10201 (n=25) received induction chemotherapy consisting of cytarabine and daunorubicin, with or without the *BCL2* antisense oblimersen sodium. The consolidation regimen included two cycles of HiDAC with or without oblimersen.[11] For patients on CALGB 10502 (n=8), bortezomib was added to both induction consisting of cytarabine and daunorubicin and to consolidation with two cycles of intermediate-dose cytarabine.[12]

In the CALGB 11001 trial for older AML patients with *FLT3*-ITD or *FLT3*-TKD, the patients (n=5) received induction chemotherapy that consisted of cytarabine, daunorubicin and the oral multikinase inhibitor sorafenib, and consolidation consisted of intermediate-dose cytarabine with sorafenib, followed by one year maintenance with sorafenib.[13] Patients on CALGB 11002 (n=1) received induction therapy with two cycles of decitabine, followed by maintenance therapy with decitabine with or without the addition of the proteasome inhibitor bortezomib for both induction and maintenance.[14]

Definition of clinical endpoints

Complete remission required that a bone marrow aspirate with a cellularity of >20% had maturation of all cell lines, < 5% blasts and undetectable Auer rods. In the peripheral blood, the absolute neutrophil count had to be ≥1.5 x 10^9/L and the platelet count ≥100 x 10^9/L, with no detectable leukemic blasts. There had to be no evidence of extramedullary leukemia. All of the aforementioned characteristics had to persist for at least 1 month.[15] Relapse was defined as ≥5% blasts in the bone marrow aspirate, or the re-appearance of circulating blasts not attributed to "overshoot" following recovery from myelosuppressive therapy, or the development of extramedullary leukemia. Disease-free survival was measured from the documented date of CR until date of relapse or death from any cause, with censoring of patients alive and relapse-free at last follow-up. Overall survival was measured from the date of enrollment in the study until date of death, with censoring of patients alive at last follow-up.

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Supplementary Table S1. Karyotypes at diagnosis and at complete remission of 32 AML patients who had abnormal cytogenetics at diagnosis and at complete remission.

Pt. no.	Age/ sex	Karyotype*		ELN Genetic Group†
		Pretreatment	Complete remission	
1	59/M	45,X,-Y,t(8;21)(q22;q22),del(9)(q12q22)[17]/46,XY[3]	45,X,-Y[11]/46,XY[9]	Favorable
2	69/M	46,XY,t(8;21)(q22;q22),del(11)(q21q23)[17]/46,XY[3]	45,X,-Y[7]/46,XY[13]	
3	44/M	46,XY,inv(16)(p13.1q22)[18]/47,idem,+8[2]	47,XY,+8,inv(16)(p13.1p22)[1]/46,XY[22]	
4	62/F	46,XX,inv(16)(p13q22)[3]/46,XX[17]	46,XX,t(2;3)(q11.2;p26)[2]/46,XX[18]	
5	47/F	47,XX,+8[8]/46,XX[7]	47,XX,+8[1]/46,XX[49]	Intermediate-II
6	54/F	47,XX,+8[20]	47,XX,+8[2]/46,XX[18]	
7	64/M	47,XY,+8[19]/48,idem,+15[1]	45,X,-Y[4]/46,XY[16]	
8	69/M	47,XY,+8[16]/46,XY[4]	46,XY,del(20)(q11.2)[2]/46,idem,del(16)(q12.1q24)[1]/ 46,XY[17]	
9	53/M	46,XY,del(7)(q21q36)[18]/46,XY[2]	42,XY,-6,del(7)(q21q36),-11,-12,-16[1]/46,XY[29]	
10	70/F	46,XX,del(7)(q11.2q36)[3]/46,XX[27]	46,XX,del(7)(q11.2q36)[1]/46,XX,del(7)(p15)[1]/ 46,XX[24]	
11	54/M	46,XY,del(20)(q12)[20]	46,XY,del(20)(q12)[4]/46,XY[5]	
12	77/M	46,XY,del(20)(q11.2q13.3)[23]/92,idemx2[2]/46,XY[3]	46,XY,del(20)(q11.2q13.3)[1]/46,XY[29]	
13	76/M	46,XY,t(3;21)(q26.2;q22)[20]	46,XY,t(3;21)(q26.2;q22)[10]/46,XY[10]	
14	70/M	46,XY,inv(3)(p13p25)[19]/45,idem,-18,add(19)(q13.1)[1]	46,XY,inv(3)(p13p25)[3]/46,XY[17] Blood: 46,XY,inv(3)(p13p25)[11]	
15	71/F	47,XX,+8[3]/48,XX,+8,+13[5]/47,XX,+13[1]/47,XX,+21[1]/ 46,XX[10]	47,XX,+21[1]/46,XX[36]	
16	65/F	46,XX,del(7)(q32q36),del(9)(q12q3?1)[20]	46,XX,del(7)(q32q36),del(9)(q12q3?1)[4]/46,XX[16] Blood: 46,XX[20]	
17	78/M	46,XY,del(20)(q11.2q13.1)[6]/45,X,-Y[6]/46,XY[8]	45,X,-Y[8]/46,XY[12] Blood: 46,XY[8]	
18	75/M	45,X,-Y[4]/46,idem,+12[16]	45,X,-Y[19]/46,XY[1]	
19	31/F	46,XX,t(6;9)(p23;q34)[23]	46,XX,t(6;9)(p23;q34)[11]/46,XX[11]	Adverse
20	29/M	46,XY,t(6;11)(q27;q23)[15]/46,XY[7]	46,XY,t(6;11)(q27;q23)[5]/46,XY[15]	
21	25/M	45,XY,inv(3)(p21q26),-7[20]	46,XY,inv(3)(p21q26)[2]/45,idem,-7[2]/46,XY[23]	
22	45/M	45,XY,-7[12]/46,idem,+mar[8]	46,XY,-7,+mar[1]/46,XY[19]	
23	59/M	44,XY,del(5)(q13q33),-7,dic(12;19)(p11.2;p13.1)[9]/ 45,idem,+mar[4]	44,XY,del(5)(q13q33),-7,dic(12;19)(p11.2;p13.1)[5]/ 46,XY[16]	
24	58/M	48,XY,+1,der(1;7)(q10;p10),+9,+21[17]/46,XY[3]	48,XY,+1,der(1;7)(q10;p10),+9,+21[3]/46,XY[5] Blood: 48,XY,+1,der(1;7)(q10;p10),+9,+21[2]/46,XY[18]	
25	59/M	46,XY,add(5)(q11.2),-7,add(8)(q24.1),-16,-17,-21,+r,+mar1, +mar2,+mar3[20]	45,XY,add(5)(q11.2),-7,-15,-17,-21,-22,+mar1,+mar2, +mar3,+mar4[1]/46,XY[20]	

Pt. no.	Age/ sex	Karyotype*		ELN Genetic Group†
		Pretreatment	Complete remission	
26	57/M	61,XY,+X,+1,+5,+8,+9,+10,+11,+12,+13,del(17)(p11), -18,+19,+20,+21,+21,+22,+22,+mar[19]/46,XY[1]	46,XY,del(17)(p11)[4]/91,XXYY,-14,del(17)(p11)[1]/ 46,XY[15]	Adverse
27	84/M	48,XY,+1,del(5)(q22q33),+8,+10,-17[11]/48,idem,der(14) t(14;17)(p12;q21)[4]/46,XY[5]	48,XY,+1,del(5)(q22q33),+8,+10,der(14)t(14;17) (p12;q21),-17[1]/46,XY[19] Blood: 46,XY,t(2;8)(q27;p11.2)[1]/46,XY[19]	
28	66/M	43,XY,-5,-7,add(9)(q34),-14,psu dic(17;16)(p1?2;q2?3), der(19)t(14;19)(q11.2;q13.3),+mar1[5]/44,idem,+mar2[4]/ 46,XY[11]	43,XY,-5,-7,add(9)(q34),-14,psu dic(17;16)(p1?2;q2?3), der(19)t(14;19)(q11.2;q13.3),+mar1[1]/45,XY,add(9) (q34),-14,psu dic(17;16)(p1?2;q2?3),der(19)t(14;19) (q11.2;?q13.3),+mar2[1]/46,XY[18]	
29	76/M	Blood: 43,XY,dup(1)(p36.3p21),del(5)(q22q35),-7,der(8)t(8;8)(p23; q11),psu dic(12;13)(p13;p11.1),add(16)(q22),dic(16;17) (p11.2;p11.2),add(18)(p11.2),-21,+22[2]/ 43,idem,+del(20)(q11.2q13.1),-22[2]/44,idem,-add(18),+21, +mar1[2]/43,idem,-Y,-17,+del(20)(q11.2q13.1),add(22)(q13), +mar1[4]/46,XY[10]	Blood: 46,XY[18] BM: 43,X,-Y,dup(1)(p36.3p21),del(5)(q22q35),-7,der(8) t(8;8)(p23;q11),psu dic(12;13)(p13;p11.1),add(16)(q22), dic(16;17)(p11.2;p11.2),-17,add(18)(p11.2),+del(20) (q11.2q13.1),-21,+add(22)(q13),+mar1[1]/46,XY[19]	
30	84/F	43-45,XX,add(4)(q21),-5,i(8)(q10),add(11)(p15),der(12)t(?1;12) (p22;p13),add(15)(q15),der(16)t(?1;16)(p22;q22),-17[cp11]/ 42-44,X,-X,-5,add(9)(q34),der(9)t(9;21)(p13;q11.2), psu dic(12;11)(p13;p13),-15,-16,-17,-18,-19,-21,+der(?) (7pter→7p11.2::?→cen→?::15q21→15qter),+mar1,+mar2x2, +2-3mar[cp7]/40-43,idem,psu dic(?;13)(?;p11.2)[cp2]	44-45,XX,add(4)(q21),-5,add(11)(p15),der(12)t(?1;12) (p22;p13),add(15)(q15),der(16)t(?1;16)(p22;q22),-17[5]/ 44,idem,i(8)(q10)[3]/41,X,-X,-5,add(9)(q34),der(9)t(9;21) (p13;q11.2),add(11)(q23),psu dic(12;11)(p13;p13),-15, -16,-17,-18,-19,-21,+der(?)(7pter→7p11.2::?→cen→?: :15q21→15qter),+mar1,+mar3[1]/46,XX[6]	
31	61/M	45-47,XY,t(3;17)(p13;p13),del(5)(q11.2q35),-20,+mar1[5]/ 48,idem,-der(3)t(3;17),+20,add(20)(q11.2),+22,+mar2[8]/ 76-97,idemx2,-der(3)t(3;17),-der(3)t(3;17),-5,+20,+20, add(20)(q11.2)x2,+22,+22,+mar2x2[cp4]/120-134,idemx3, -der(3)t(3;17),-der(3)t(3;17),-t(3;17),-5,-del(5),-6,-11,-12, -16,+20,+20,add(20)(q11.2)x3,-21,+mar2x3[cp2]/46,XY[1]	46,XY,t(3;17)(p13;p13),del(5)(q11.2q35),-20,+mar[2]/ 46,XY[18]	
32	74/M	44-45,XY,add(1)(p13),del(5)(q13q33),-7,add(12)(p1?3),-17, der(17)t(7;17)(q11.21;p13)[cp2]/42-45,idem,+dic(17;18)(p13; p11.2),-18,+mar[cp4]/43,idem,+dic(17;18)(p13;p11.2),-18, dic(20;22)(q13.1;p11.2)[2]/44,idem,+dic(17;18)(p13;p11.2), -18,dic(20;22)(q13.1;p11.2),+22[2]/44,idem,+dic(17;18)(p13; p11.2),-18,dic(20;22)(q12.1;p11.2),+idic(22)(p13)[cp4]/45,idem, +dic(17;18)(p13;p11.2),-18,del(20)(q13.1),+idic(22)(p13)[2]/ 44,idem,+17,dic(17;22)(p13;p13),-18,+trc(18;22;20)(p11.2; q13p11.2;q13.1)[1]/44,idem,+17,dic(17;18),dic(20;22),+dic(20; 22)[1]/45,idem,+17,dic(17;18),dic(20;22),+22,+idic(22)[1]/ 45,idem,+17,del(4)(q27),dic(17;18),+dic(18;22)(p11.2;p13), dic(20;22),+dic(20;22)[1]	44,XY,add(1)(p13),del(5)(q13q33),-7,add(12)(p1?3), der(17)t(7;17)(q11.21;p13),dic(17;18)(p13;p11.2),-20, idic(22)(p13),+2mar[1]/41,idem,-6,-14,+dic(20;22) (q13.1;p11.2),-idic(22),-2mar[1]/46,XY[18]	

BM: bone marrow; F: female; M: male; no.: number; Pt.: patient.

* Karyotypes listed are from bone marrow specimens unless indicated otherwise.

† European LeukemiaNet Genetic Groups.[16]

Supplementary Table S2. Karyotypes at diagnosis and at complete remission of 16 AML patients with an abnormal karyotype at diagnosis who had a normal karyotype at complete remission that contained one or two cells with nonclonal, pretreatment-unrelated chromosome abnormalities.

Pt. no.	Age/ sex	Karyotype*		ELN Genetic Group†
		Pretreatment	Complete remission	
33	34/M	45,X,-Y,t(8;21)(q22;q22)[10] Blood: 45,X,-Y,t(8;21)(q22;q22)[10]	184,XXXXYYYY[1]/46,XY[19]	Favorable
34‡	30/M	45,X,-Y,t(8;21)(q22;q22),del(20)(q11.2q13.1)[22]/ 46,XY[2]	46,XY,t(5;18)(q12;q12)[1]/46,XY[29]	
35	54/F	46,XX,t(8;21)(q22;q22)[20]	46,XX,t(1;1)(p36;q21)[1]/46,XX[19]	
36	40/F	46,XX,inv(16)(p13q22)[19]/46,XX[1]	45,XX,+X,+1,+1,-2,+5,+5,-6,-7,-7,+8,-9,-11, +12,+12,-13,-14,-18,+19,+19,-22,-22[1]/ 46,XX[19]	
37	36/F	46,XX,inv(16)(p13.1q22)[25]/46,idem,del(10)(p13)[1]	46,XX,t(3;10)(p21;p14)[1]/46,XX[19]	
38‡	43/M	47,XY,+8[30]	45,XY,t(2;13)(q21;q21),-19[1]/47,XY,+2[1]/ 46,XY[28]	Intermediate-II
39‡	43/M	47,XY,+8[20]	46,XY,del(11)(q24)[1]/46,XY[19]	
40	31/M	46,XY,add(7)(q32)[12]	46,XY[20] Blood: 46,XY,del(1)(q21),add(14)(q22),add(15)(q22), -21,+mar[1]/46,XY[19]	
41‡	72/F	46,XX,add(7)(q22)[7]/92,idemx2[cp3]/46,XX[10]	46,XX,t(1;5)(p22;q33)[1]/46,XX[19]	
42‡	69/F	46,XX,del(9)(q13q22)[20] Blood: 46,XX,del(9)(q13q22)[20]	46,XX[23] Blood: 46,XX,t(2;16)(p?13;p13)[1]/46,XX[19]	
43‡	50/M	47,XY,+8[9]/48,XY,+8,+13[2]/46,XY[9] Blood: 47,XY,+8[1]/46,XY[6]	46,XY,t(1;18)(p10;p10)[1]/46,XY[19] Blood: 46,XY[8]	
44‡	52/F	47,XX,t(7;19;11)(q11.2;q13.3;q23),+8[20] Blood: 47,XX,t(7;19;11)(q11.2;q13.3;q23),+8[20]	47,XX,+20[1]/46,XX[19]	Adverse
45	70/F	46,XX,ins(11;10)(q23;p15p11.2)[20] Blood: 46,XX,ins(11;10)(q23;p15p11.2)[19]/47,idem,+8[1]	46,XX,del(16)(q22)[1]/46,XX[19] Blood: 46,XX[3]	

Pt. no.	Age/ Sex	Karyotype*		ELN Genetic Group†
		Pretreatment	Complete remission	
46‡	40/F	45,XX,-5,-11,t(16;16)(p13.1;q24),add(17)(p13),+mar[17]/ 46,idem,+6[3] Blood: 45,XX,-5,-11,t(16;16)(p13.1;q24),add(17)(p13),+mar[19]/ 46,idem,+6[1]	46,XX[20] Blood: 46,XX,del(13)(q22q32)[1]/46,XX[2]	
47‡	30/F	46,X,del(X)(p22.1),del(12)(p11.2p12)[1]/46,idem, del(4)(q21)[cp2]/46,XY[22] Blood: 46,X,del(X)(p22.1),del(12)(p11.2p12)[1]/46,idem, del(4)(q21)[cp2]/46,XX,t(12;14)(p13;q12),-14,+mar[1]/ 46,XX,tr(14;14;?)(q10;q10;?)[1]/46,XX[16]	47,XX,+mar[1]/46,XX[20]	Adverse
48‡	65/M	45,XY,-3,der(5)inv(5)(p15q13)add(5)(q31),add(6)(p21.3), +11,ider(11)(q10)del(11)(q13q14)x2,-17[16]/46,XY[5]	46,XY,del(6)(q15q25)[1]/46,XY[19]	

F: female; M: male; no.: number; Pt.: patient.

* Karyotypes listed are from bone marrow specimens unless indicated otherwise.

† European LeukemiaNet Genetic Groups.[16]

‡ Cytogenetic data on relapse sample are available. The nonclonal aberration or aberrations found at CR were not detected in the relapse sample.

Supplementary Table S3: Frequency of pretreatment cytogenetic abnormalities in AML patients with an entirely normal karyotype at the time of complete remission and in patients with a normal karyotype at complete remission that contained nonclonal, pretreatment-unrelated chromosome abnormalities.

Cytogenetic abnormalities at diagnosis	Entirely normal CR karyotype (n=210)	Normal CR karyotype with single cells with a nonclonal abnormality(s) unrelated to pretreatment karyotype (n=16)
	Number of patients (%)	Number of patients (%)
ELN Favorable*	**101 (48)**	**5 (31)**
t(8;21)(q22;q22)	39 (19)	3 (19)
inv(16)(p13q22)/t(16;16)(p13;q22)	62 (29)	2 (12)
ELN Intermediate-II*	**63 (30)**	**6 (38)**
t(9;11)(p22;q23)	8 (4)	0
Other abnormalities, including	55 (26)	6 (38)
Sole +8	11 (5)	2 (13)
Other sole trisomy	10 (5)	0
Sole chromosome loss other than –5 or –7	5 (2)	0
Sole del(7q) or add(7q)	4 (2)	2 (13)
Sole del(9q)	4 (2)	1 (6)
Other sole unbalanced abnormalities	5 (2)	0
Sole reciprocal translocation or inversion	7 (3)	0
Two abnormalities	9 (4)	1 (6)
ELN Adverse*	**46 (22)**	**5 (31)**
inv(3)(q21q26)/t(3;3)(q21;q26)	2 (1)	0
t(6;9)(p23;q34)	1 (<1)	0
t(v;11)(v;q23)	6 (3)	2 (12)
–5 or del(5q)	2 (1)	0
–7	2 (1)	0
Complex karyotype	33 (16)	3 (19)

CR: complete remission; ELN: European LeukemiaNet Genetic Groups.

* The ELN Favorable Genetic Group comprises cytogenetically abnormal-AML patients with t(8;21)(q22;q22)/*RUNX1-RUNX1T1* or inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB-MYH11*). Intermediate–II and ELN Adverse contain the remaining cytogenetically abnormal patients. The ELN Intermediate-II Genetic Group consists of patients with t(9;11)(p22;q23)/*MLLT3-KMT2A* or those with chromosome abnormalities not classified in the Favorable or Adverse Genetic Group. The ELN Adverse Genetic Group is defined by patients with inv(3)(q21q26.2) or t(3;3)(q21;q26.2)/*GATA2–MECOM*(*EVI1*); t(6;9)(p23;q34)/*DEK-NUP214*; t(v;11)(v;q23)/*KMT2A* rearranged; –5 or del(5q); –7; abnormalities of 17p; and a complex karyotype containing ≥3 cytogenetic abnormalities in the absence of one of the World Health Organization–designated recurring translocations or inversions — t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23), t(6;9), and inv(3)/t(3;3).[16]

Supplementary Table S4: Treatment outcomes of AML patients with an abnormal karyotype at diagnosis who had a normal karyotype at complete remission that contained one or two cells with nonclonal, pretreatment-unrelated chromosome abnormalities and of patients with an entirely normal karyotype at complete remission.

Outcome endpoint	Nonclonal, pretreatment-unrelated abnormalities present at CR (n=16)	Entirely normal CR karyotype (n=210)	*P*	HR (95%CI)
Disease-free survival			0.18	1.47 (0.83-2.59)
Median, years	0.8	1.0		
Disease-free at 3 years, % (95% CI)	19 (5-40)	35 (28-41)		
Disease-free at 5 years, % (95% CI)	19 (5-40)	31 (25-37)		
Overall survival			0.04	1.81 (1.02-3.21)
Median, years	1.4	2.5		
Alive at 3 years, % (95% CI)	25 (8-47)	48 (41-54)		
Alive at 5 years, % (95% CI)	25 (8-47)	42 (36-49)		

CI: confidence interval; CR: complete remission; HR: hazard ratio.

Supplementary Figure Legend

Figure S1. Disease-free survival (A) and overall survival (B) of *de novo* AML patients with abnormal pretreatment karyotype according to the presence or absence of nonclonal, pretreatment-unrelated chromosome abnormalities detected at the time of complete remission.

Figure S1A

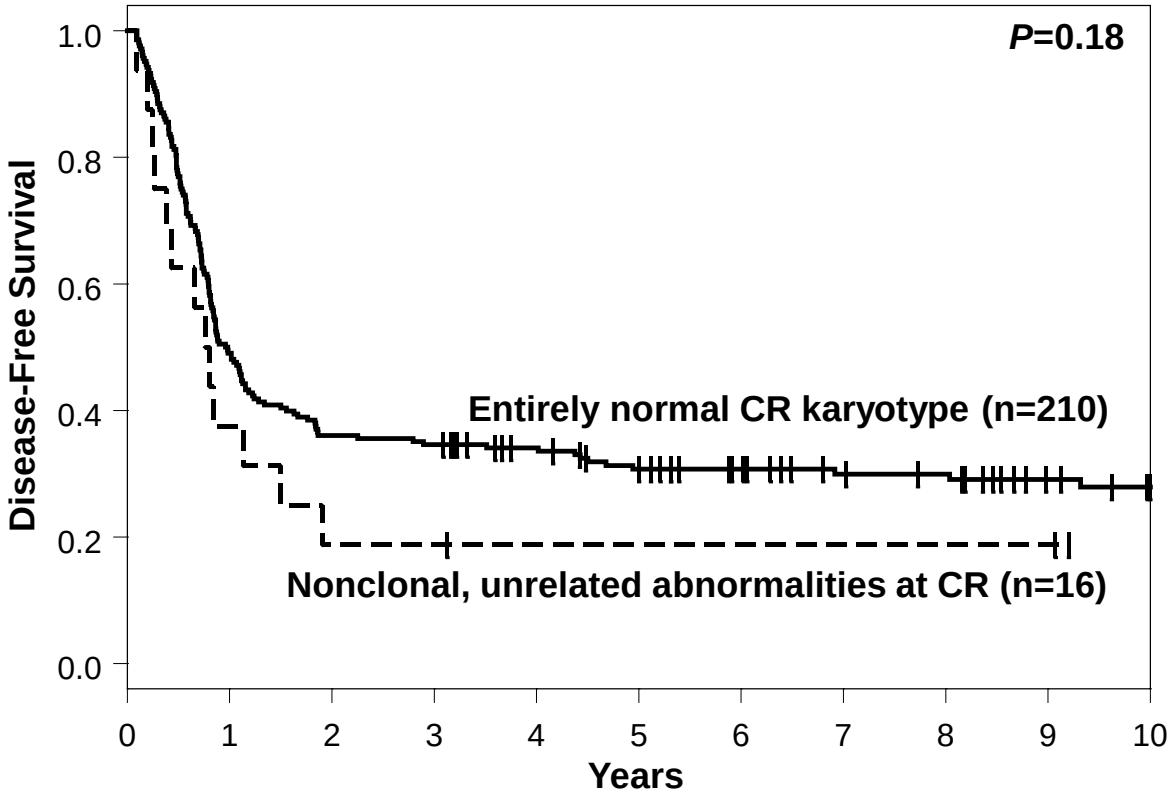
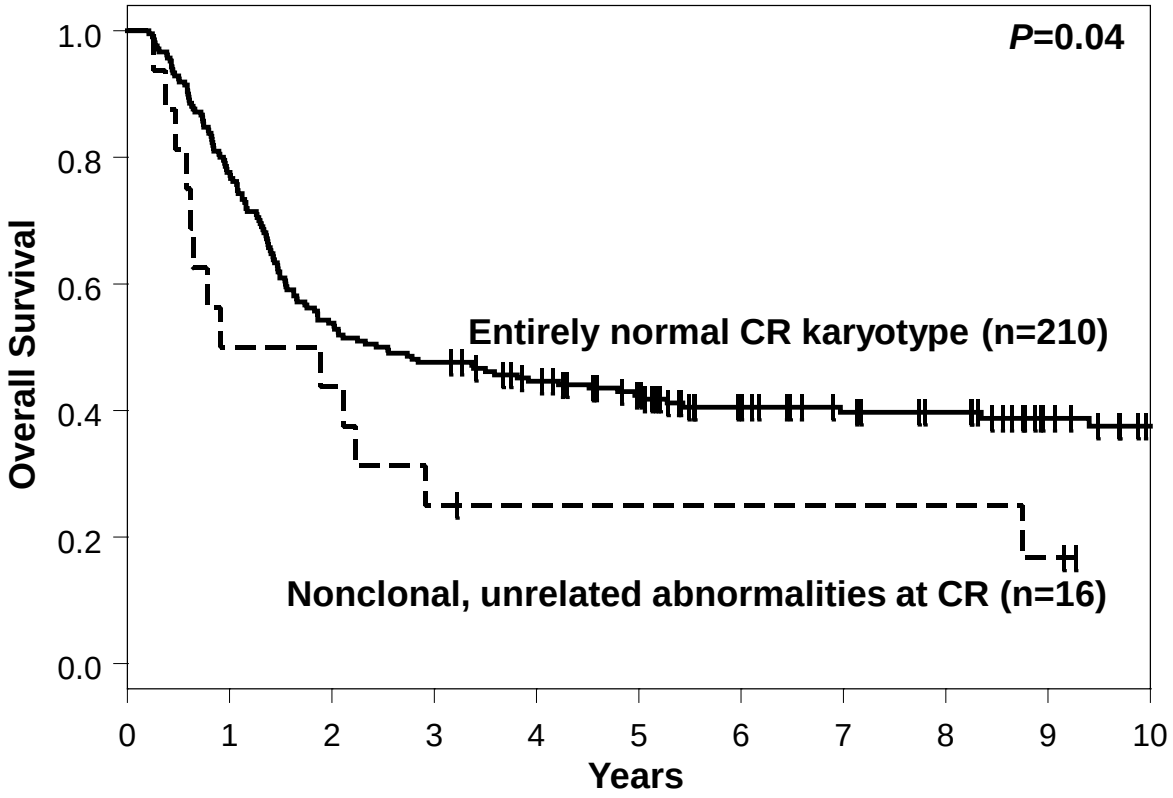

P=0.18
Disease-Free Survival
1.0
0.8
0.6
0.4
0.2
0.0
Entirely normal CR karyotype (n=210)
Nonclonal, unrelated abnormalities at CR (n=16)
0
1
2
3
4
5
6
7
8
9
10
Years

Figure S1B


P=0.04
Entirely normal CR karyotype (n=210)
Nonclonal, unrelated abnormalities at CR (n=16)
Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
6
7
8
9
10
Years