BCR-ABL1-like cases in pediatric acute lymphoblastic leukemia: a comparison between DCOG/Erasmus MC and COG/St. Jude signatures

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SUPPLEMENTAL MATERIAL
for
***BCR-ABL1*-Like Cases in Pediatric Acute Lymphoblastic Leukemia: a Comparison Between DCOG/Erasmus MC and COG/St. Jude Signatures**

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Content

SUPPLEMENTAL METHODS

Patient cohorts

This study comprised children with newly diagnosed BCP-ALL enrolled in consecutive Dutch Childhood Oncology Group trials (DCOG ALL-8, ALL-9 and ALL-10)[1] and German Cooperative ALL trials (COALL 06-97 and 07-03),[2] here referred to as DCOG/COALL. These patient cohorts were described and analyzed together previously.[3,4] Written informed consent was obtained from parents or guardians and institutional review boards approved the use of excess of diagnostic material for research purposes. These studies were conducted in accordance with the Declaration of Helsinki. In addition, this study comprised the US Childhood Oncology Group (COG) P9906 cohort described previously.[5,6] This cohort contains high-risk cases only, and one of the risk criteria was older age: over age 12 (boys) or 16 (girls). Since signature comparisons of HC vs. PAM were performed within each cohort and not across cohorts, a difference in patient characteristics between DCOG/COALL and COG P9906 does not affect our conclusions. A summary of patient characteristics is shown in Supplemental Table S1.

Identification of *BCR-ABL1*-like samples using expression profiles

Affymetrix U133 Plus 2.0 files were exchanged between Erasmus MC and St. Jude Children's Research Hospital. The Hierarchical Clustering (HC) signature was applied to DCOG/COALL and COG cases by Den Boer at Erasmus MC, and the Prediction Analysis of Microarrays (PAM) was applied to DCOG/COALL and COG cases by Mullighan at St. Jude.

Only nine probe sets were identical in both signatures (Supplemental Table S2). Although *BCR-ABL1*-positive ALL is characterized by high ABL1 mRNA levels, the expression of *ABL1* is not increased in *BCR-ABL1*-like cases (Supplemental Figure S1), and as such cannot be used to identify *BCR-ABL1*-like cases.

Hierarchical clustering (HC)

Identification of *BCR-ABL1*-like samples using HC was performed at Erasmus MC as described previously.[3,4] Affymetrix U133 Plus 2.0 expression data from two independent cohorts of patients were used: 452 patients enrolled in the DCOG/COALL study,[3,4] and 207 patients enrolled in the P9906 COG cohort.[5] Briefly, Affymetrix U133 2.0 CEL files for 107 microarrays of the original ALL validation cohort[3] (DCOG; GSE13351), and one of the test cohorts were read into R[7] version 2.13.0 using the affy package[8] version 1.30.0. Probes were background-corrected and summarized into probe sets with MAS 5.0, followed by variance stabilization normalization[9] using the vsn package version 3.20.0 and batch correction by ComBat.[10] Next, the expression data for the 110 classifier probe sets[3] were selected.

For HC, each time a single sample was added to the reference cohort of 107 DCOG samples. The vsn-normalized log2 intensity data were centered to the mean expression per gene over the 108 samples, and scaled by root mean square. Hierarchical clustering was performed by cosine distance and average linkage. We clustered 146 DCOG/COALL cases as well as 143 P9906 cases without the recurrent cytogenetic aberrations *BCR-ABL1*, *MLL* rearrangement, *TCF3* rearrangement, *ETV6-RUNX1*, or high-hyperdiploidy (51-67 chromosomes), i.e. B-other. Samples clustering with the known *BCR-ABL1*-positive and *BCR-ABL1*-like samples were called *BCR-ABL1*-like, and BCP-ALL samples without recurrent known aberrations (*BCR-ABL1* or *ETV6-RUNX1* translocation, *MLL* or *TCF3* rearrangement, high-hyperdiploidy) falling in other clusters were called non-*BCR-ABL1*-like B-other. Samples with known recurrent aberrations were clustered as a control, and each of the samples belonging to the *ETV6-RUNX1*-translocated, *TCF3*- or *MLL*-rearranged subtypes joined their correct cluster. R code for performing the clustering procedure is available upon request.

Prediction Analysis of Microarrays (PAM)

CEL files for 216 newly analyzed U133 plus 2.0 DCOG/COALL ALL samples representing all subtypes were sent to St. Jude for identification of Philadelphia-like cases using PAM as described previously for the P9906 cohort.[6,11] Briefly, the CEL files of each of the test cohorts were co-normalized with the CEL files of the AALL0232 training cohort (n=325) using the default MAS 5.0 normalization.[12] The classifier was trained on *BCR-ABL1*-positive samples in the AALL0232 training cohort (n=21), and applied to each test cohort. When the PAM coefficient was ≥ 0.5, the sample was assigned to 'Ph-like', otherwise to 'Non Ph-like' group.[6,11] Ph-like samples identified in the DCOG/COALL data did not carry known recurrent aberrations; among the P9906 Ph-like samples was one sample with high-hyperdiploidy.[6]

Molecular aberrations

For DCOG/COALL samples, copy number aberrations in B-cell development genes were identified as described[4] using SALSA P335 version A3 ALL-IKZF1 MLPA assay (MRC-Holland), including 8 probes for *IKZF1* (exons 1-8), 4 probes for *BTG1* (exons 1-2 and downstream region), 5 probes for *RB1* (exons 6, 14, 19, 24, 26), 6 probes for *PAX5* (exons 1, 2, 5, 6, 8, 10), 3 probes for *CDKN2A* (exons 2a and 4) and *CDKN2B* (exon 2), 4 probes for *EBF1* (exons 1, 10, 14, 16), and 6 probes for *ETV6* (exons 1, 2, 3, 5, 8). For *PAX5*, intragenic amplifications were coded with the deletions as they are predicted to be functionally equivalent.[13] Comparative genomic hybridization (SurePrint G3 180K array, Agilent) was used to identify intrachromosomal amplification of chromosome 21 (iAMP21) and co-deletion of chromosome arms 9p and 20q indicative of dic(9;20). Exons 16 and 20 of *JAK2* were screened for mutations using Sanger sequencing. Abnormalities in *CRLF2* were identified by expression of Affymetrix U133 Plus 2.0 probe set 208303_s_at, above the 90th percentile of the total BCP-ALL group.[4] Kinase-activating fusion genes involving *ABL1*, *ABL2*, *PDGFRB*, *CSF1R* or *JAK2* kinases were identified by split-signal FISH and RT-PCR.[14]

For the COG samples, molecular aberrations have been described.[6,11,15] Affymetrix SNP arrays were used to detect copy number abnormalities in *IKZF1*, *VPREB1*, *RB1*, *PAX5*, *CDKN2A*, *CDKN2B*, *EBF1* and *ETV6*;[5] Sequencing to detect mutations in *IKZF1*, *RB1*, *PAX5*, *CDKN2A*, *CDKN2B*, *ETV6*, *JAK1*, *JAK2*, *JAK3*, *FLT3*, *IL7R*;[6,11,15] Gene expression followed by FISH, RT-PCR and RACE to detect *CRLF2* translocations;[16] and RNA sequencing, karyotyping, FISH and RT-PCR to detect translocations of *ABL1*, *PDGFRB* and *JAK2*.[6] Fisher's Exact test was used to test differences in the proportion of aberrations between groups.

Association with clinical outcome

Cumulative incidence of relapse (CIR) was estimated using a competing risks model. We considered relapse as event, and death as competing event. To test for equality of CIRs, Gray's test has been applied. The CIR probability (pCIR) with standard error was reported. Outcome analyses were performed in R 3.0.1, using the packages cmprsk[17] version 2.2-6, mstate[17] version 0.2.6[18], and survival[19] version 2.37-4.

SUPPLEMENTAL TABLES

Supplemental Table S1. Overlapping probe sets between the PAM and HC signatures for identification of *BCR-ABL1*-like cases

Probe set	Gene symbol
200953_s_at	*CCND2*
201810_s_at	*SH3BP5*
201811_x_at	*SH3BP5*
202123_s_at	*ABL1*
203372_s_at	*SOCS2*
208892_s_at	*DUSP6*
214181_x_at	*LST1*
214574_x_at	*LST1*
218825_at	*EGFL7*

Supplemental Table S2. Characteristics of cased included in the signature comparison study

		DCOG/COALL **n=146**		***P9906*** **n=143**	
		N	**%**	**N**	**%**
Gender					
	Female	72	49.3	43	30.0
	Male	74	50.7	100	70.0
Age (years)					
	<10	94	64.4	46	32.2
	≥10	52	35.6	97	67.8
Ethnicity*					
	White			84	58.7
	Hispanic/Latino			37	25.9
	Other			22	15.4
White blood cell count (cells x 10^9/L)					
	<50	93	63.7	71	49.7
	≥50	53	36.3	72	50.3
***BCR-ABL1*-like**					
	BCR-ABL1-like HC and/or PAM	87	59.6	58	40.6
	Non-*BCR-ABL1*-like B-other	59	40.4	85	59.4
Treatment arm					
	Non-high risk	73	50.0	-	-
	High risk	73	50.0	143	100

* Ancestry of the DCOG/COAL not recorded; expected to be in large majority Caucasian.

Supplemental Table S3. Enrichment of NCI-Rome high risk cases among *BCR-ABL1*-like identified cases in the DCOG/COALL cohort using the HC signature and using the PAM signature

		***BCR-ABL1*-like by HC**		**P=0.02**	***BCR-ABL1*-like by PAM**		**P=0.2**
		Yes	**No**	**Total**	**Yes**	**No**	**Total**
NCI-Rome*	**High risk**	57	35	92	24	68	92
	Standard risk	22	32	54	9	45	54
	Total	79	67	146	33	113	146

*Risk group according to the NCI-Rome criteria: white blood cell count ≥ 50/nl and/or age ≥ 10 years.

Supplemental Table S4. Frequencies of molecular aberrations in the groups identified by the two *BCR-ABL1*-like signatures in the total DCOG/COALL cohort

DCOG/ COALL	HC total (79)			PAM total (33)			Both HC and PAM (25)			HC only (54)			PAM only (8)			Others[a] (59)		Total (146)	
	cases/ tested	%	pval[b]	cases/ tested	%	pval	cases/ tested	%	pval	cases/ tested	%	pval	cases/t ested	%	pval	cases/ tested	%	cases/ tested	%
IKZF1 del	34/75	45	0.05	19/32	59	0.006	14/24	58	0.01	20/51	39	0.2	5/8	63	0.1	15/54	28	54/137	39
iAMP21	11/68	16	0.01	10/28	36	0.0001	9/23	39	0.0001	2/45	4	0.6	1/5	20	0.2	1/52	2	13/125	10
RB1 del	10/75	13	0.2	7/32	22	0.03	6/24	25	0.02	4/51	8	0.7	1/8	13	0.4	3/55	5	14/138	10
JAK2 mut	2/72	3	1	5/28	18	0.09	1/20	5	1	1/52	2	0.6	4/8	50	0.002	2/51	4	8/131	6
CRLF2 high	11/79	14	0.4	14/33	42	0.0003	8/25	32	0.02	3/54	6	0.7	6/8	75	0.0001	5/59	8	22/146	15
Kin fusion[c]	11/58	19	0.003	8/24	33	0.0002	8/20	40	0.0001	3/38	8	0.2	0/4	0	1	0/38	0	11/100	11
PAX5 del[d]	33/75	44	0.9	9/32	28	0.3	7/24	29	0.3	26/51	51	0.4	2/8	25	0.5	23/55	42	58/138	42
CDKN2A/B	40/75	53	0.5	11/32	34	0.4	8/24	33	0.3	32/51	63	0.08	3/8	38	0.7	25/55	45	67/138	49
EBF1 del	15/75	20	0.4	9/32	28	0.09	7/24	29	0.1	8/51	16	0.8	2/8	25	0.3	7/55	13	24/138	17
ETV6 del	14/75	19	1	5/32	16	0.8	5/24	21	1	9/51	18	0.8	0/8	0	0.3	11/55	20	25/138	18
dic(9;20)	18/68	26	0.001	2/28	7	0.6	2/23	9	0.6	16/45	36	0.0001	0/5	0	1	2/52	4	20/125	16
BTG1 del	4/75	5	0.3	5/32	16	0.5	2/24	8	1	2/51	4	0.3	3/8	38	0.08	6/55	11	13/138	9

[a] Precursor B-ALL patients without recurrent genomic aberrations and not identified as *BCR-ABL1*-like by the HC or PAM signatures.

[b] Fisher's Exact Test p-value comparing the indicated group with the 59 remaining B-other cases.

[c] Kinase-activating fusions: *EBF1-PDGFRB* (3), *ZMIZ1-ABL1*, *ABL1* with unknown partner, *RCSD1-ABL2*, *SSBP2-CSF1R*, *PAX5-JAK2* (2), *JAK2* with unknown partner (2).

[d] For *PAX5*, intragenic amplifications were coded with the deletions as they are predicted to be functionally equivalent.

Supplemental Table S5. Frequencies of molecular aberrations in the groups identified by the two *BCR-ABL1*-like signatures in the NCI-Rome high risk cases of the DCOG/COALL cohort

DCOG/ COALL	HC total (57)			PAM total (24)			Both HC and PAM (19)			HC only (38)			PAM only (5)			Others[a] (30)		Total (92)	
NCI-HR	cases/ tested	%	pval[b]	cases/ tested	%	pval	cases/ tested	%	pval	cases/ tested	%	pval	cases/ tested	%	pval	cases/ tested	%	cases/ tested	%
IKZF1 del	26/54	48	0.03	16/23	70	0.001	12/18	67	0.005	14/36	39	0.2	4/5	80	0.02	6/27	22	36/86	42
iAMP21	5/49	10	0.2	6/21	29	0.005	5/17	29	0.006	0/32	0	1	1/4	25	0.1	0/26	0	6/79	8
RB1 del	6/54	11	0.7	5/23	22	0.2	4/15	22	0.2	2/36	6	1	1/5	20	0.4	2/28	7	9/87	10
JAK2 mut	1/53	2	1	2/20	10	0.2	0/19	0	1	1/38	3	1	2/5	40	0.02	0/26	0	3/84	4
CRLF2 high	8/57	14	0.2	11/24	46	0.0002	7/14	37	0.004	1/38	3	1	4/5	80	0.0005	1/30	3	13/92	14
Kin fusion[c]	8/40	20	0.045	7/16	44	0.002	7/18	50	0.0008	1/26	4	1	0/2	0	1	0/19	0	8/61	13
PAX5 del [d]	27/54	50	0.2	7/23	30	0.8	6/18	33	1	21/36	58	0.08	1/5	20	0.6	10/28	36	38/87	44
CDKN2A/B	34/54	63	0.5	10/23	43	0.6	8/18	44	0.8	26/36	72	0.2	2/5	40	0.7	15/28	54	51/87	59
EBF1 del	8/54	15	1	8/23	35	0.1	6/18	33	0.2	2/36	6	0.4	2/5	40	0.2	4/28	14	14/87	16
ETV6 del	12/54	22	1	4/23	17	1	4/18	22	1	8/36	22	1	0/5	0	0.6	6/28	21	18/87	21
dic(9;20)	13/49	27	0.03	1/21	5	1	1/17	6	1	12/32	38	0.003	0/4	0	1	1/26	4	14/79	18
BTG1 del	3/54	6	0.06	4/23	17	1	1/18	6	0.2	2/36	6	0.1	3/5	60	0.1	6/28	21	12/87	14

[a] Precursor B-ALL patients without recurrent genomic aberrations and not identified as *BCR-ABL1*-like by the HC or PAM signatures.

[b] Fisher's Exact Test p-value comparing the indicated group with the 59 remaining B-other cases.

[c] Kinase-activating fusions: *EBF1-PDGFRB* (2), *ABL1* with unknown partner, *RCSD1-ABL2*, *SSBP2-CSF1R*, *PAX5-JAK2*, *JAK2* with unknown partner (2).

[d] For *PAX5*, intragenic amplifications were coded with the deletions as they are predicted to be functionally equivalent.

Supplemental Table S6. Frequencies of molecular aberrations in the groups identified by the two *BCR-ABL1*-like signatures in the COG P9906 cohort

P9906	HC total (43)			PAM total (40)			Both HC and PAM (25)			HC only (18)			PAM only (15)			Others[a] (85)		Total (143)	
	cases/ tested	%	pval[b]	cases/ tested	%	pval	cases/ tested	%	pval	cases/ tested	%	pval	cases/ tested	%	pval	cases/ tested	%	cases/ tested	%
Hispanic/Latino	15	35	0.02	20	50	<0.0001	11	44	0.005	4	22	0.5	9	60	0.0006	13	15	37	26
IKZF1 del	21	49	0.009	25	63	<0.0001	16	64	0.0005	5	28	0.8	9	60	0.01	21	25	51	36
VPREB del	24	56	0.0004	19	48	0.01	15	60	0.001	9	50	0.04	4	27	0.8	20	24	48	34
RB1 del	4	9	1	4	10	1	2	8	1	2	11	1	2	13	0.7	9	11	15	10
JAK2 mut	10	23	0.0003	14	35	<0.0001	9	36	<0.0001	1	6	0.4	5	33	0.0007	2	2	17	12
CRLF2 high	14	33	<0.0001	20	50	<0.0001	11	44	<0.0001	3	17	0.1	9	60	<0.0001	4	5	27	19
Kin fusion[c]	9	21	<0.0001	10	25	<0.0001	9	36	<0.0001	0	0	1	1	7	0.2	0	0	10	7
Other kin mut[d]	11	26	0.09	12	30	0.03	7	28	0.1	4	22	0.3	5	33	0.06	11	13	27	19
PAX del[e]	18	42	0.6	11	28	0.4	9	36	1	9	50	0.3	2	13	0.1	31	36	51	36
CDKN2A/B	28	65	0.2	23	58	0.6	16	64	0.4	12	67	0.3	7	47	0.8	44	52	79	55
EBF1 del	7	16	0.0003	10	25	<0.0001	7	28	<0.0001	0	0	1	3	20	0.003	0	0	10	7
ETV6 del	6	14	1	3	8	0.4	2	8	0.5	4	22	0.5	1	7	0.7	12	14	19	13
dic(9;20)	3	7	0.4	1	3	1	1	4	1	2	11	0.2	0	0	1	3	4	6	4
BTG1 del	10	23	0.06	9	23	0.06	8	32	0.009	2	11	0.7	1	7	1	8	9	19	13

[a] Precursor B-ALL cases without recurrent genomic aberrations and not identified as *BCR-ABL1*-like by the HC or PAM signatures

[b] Fisher's Exact Test p-value comparing the indicated group with the 85 remaining B-other cases

[c] Kinase-activating fusions: *NUP214-ABL1* (2), *EBF1-PDGFRB*, *BCR-JAK2*, *STRN3-JAK2*, *IGH@-EPOR*,[6] *IGK-EPOR*, *MYH9-IL2RB*, *PAX5-JAK2*, and *SNX2-ABL1*[14]

[d] Other kinase-activating lesions, including *JAK1*, *JAK3*, *FLT3*, and *IL7R* mutations[6,11,15]

[e] For *PAX5*, intragenic amplifications were coded with the deletions as they are predicted to be functionally equivalent

Supplemental Table S7. Cumulative incidence of relapse estimates in the *BCR-ABL1*-like signature groups

A

DCOG ALL-9/10	total	relapses	5-yr CIR (SE)	Gray p
HC total	54	17	30% ± 6%	0.07
PAM total	25	6	20% ± 8%	0.4
HC and PAM	19	5	22% ± 10%	0.3
HC only	35	12	34% ± 8%	0.047
PAM only	6	1	17% ± 17%	0.8
Other (ref)	31	4	10% ± 5%	

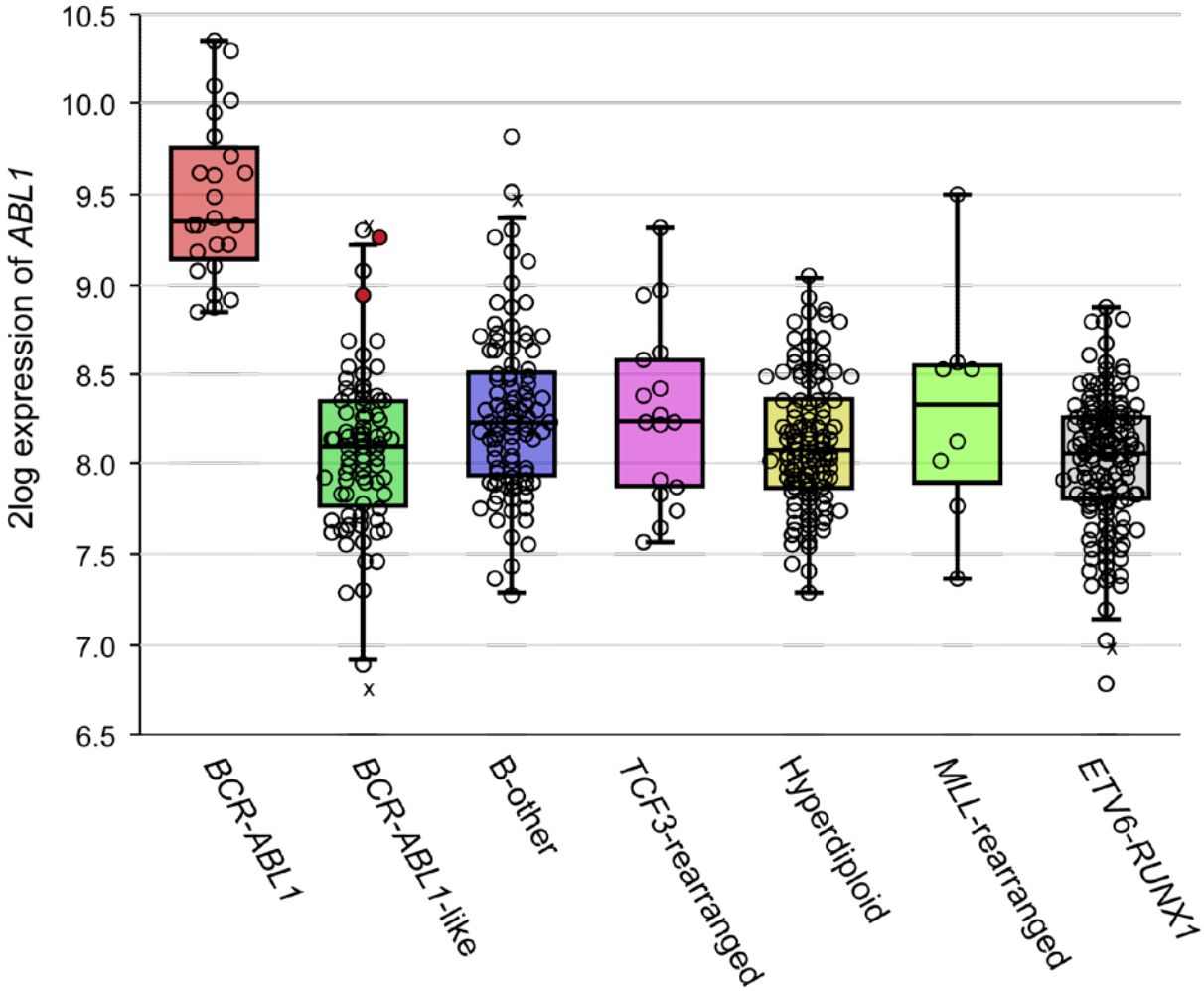
B

DCOG ALL-9/10 NCI-HR	total	relapses	5-yr CIR (SE)	Gray p
HC total	39	11	28% ± 7%	0.09
PAM total	17	3	19% ± 10%	0.4
HC and PAM	14	2	16% ± 11%	0.5
HC only	25	9	36% ± 10%	0.04
PAM only	3	1	NA	0.03
Other (ref)	15	1	7% ± 7%	

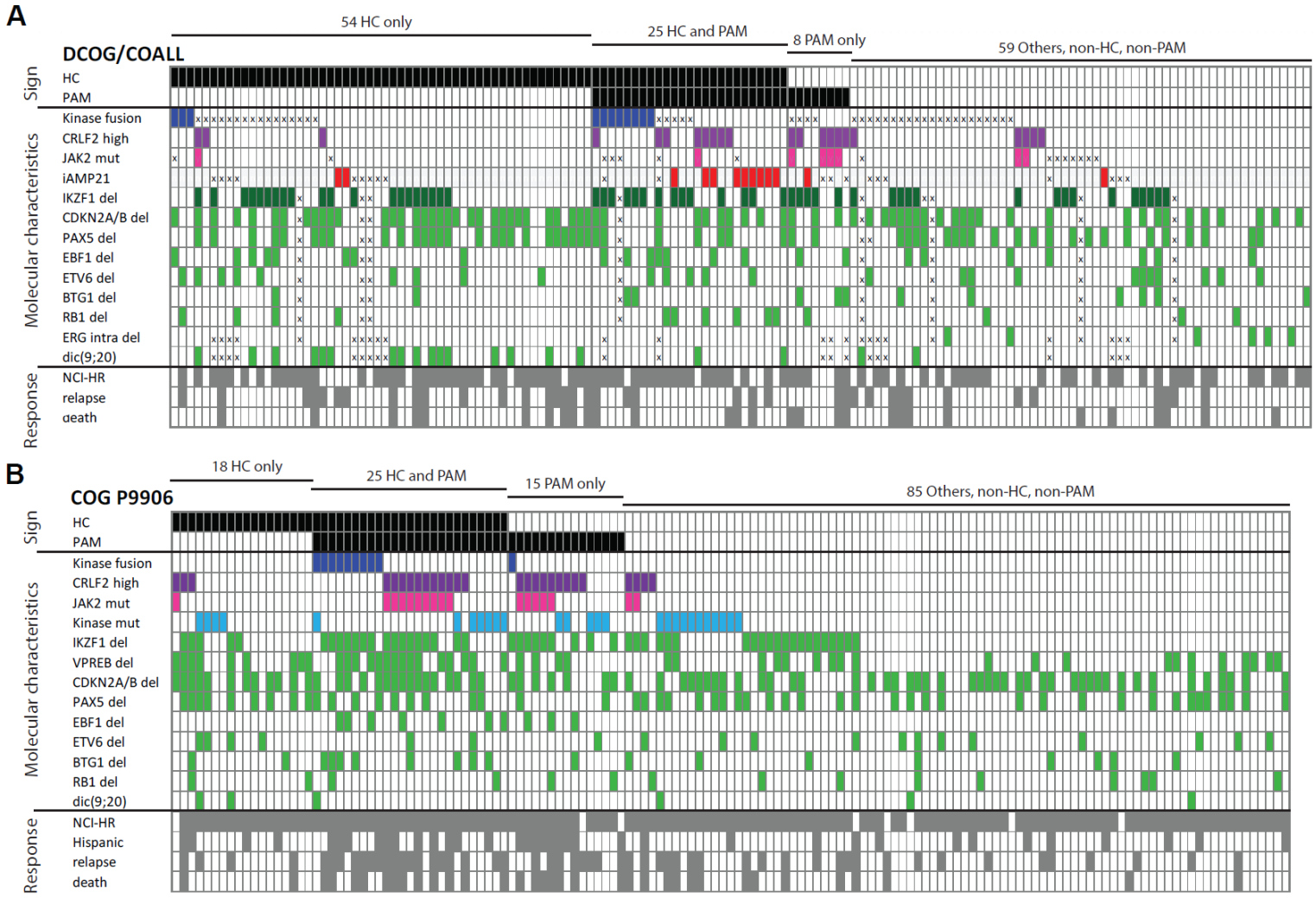
C

COG P9906	total	relapses	5-yr CIR (SE)	Gray p
HC total	43	23	52% ± 8%	0.005
PAM total	40	27	69% ± 8%	<0.0001
HC and PAM	25	19	73% ± 10%	<0.0001
HC only	18	4	22% ± 10%	0.6
PAM only	15	8	63% ± 16%	0.04
Other (ref)	85	24	28% ± 5%	

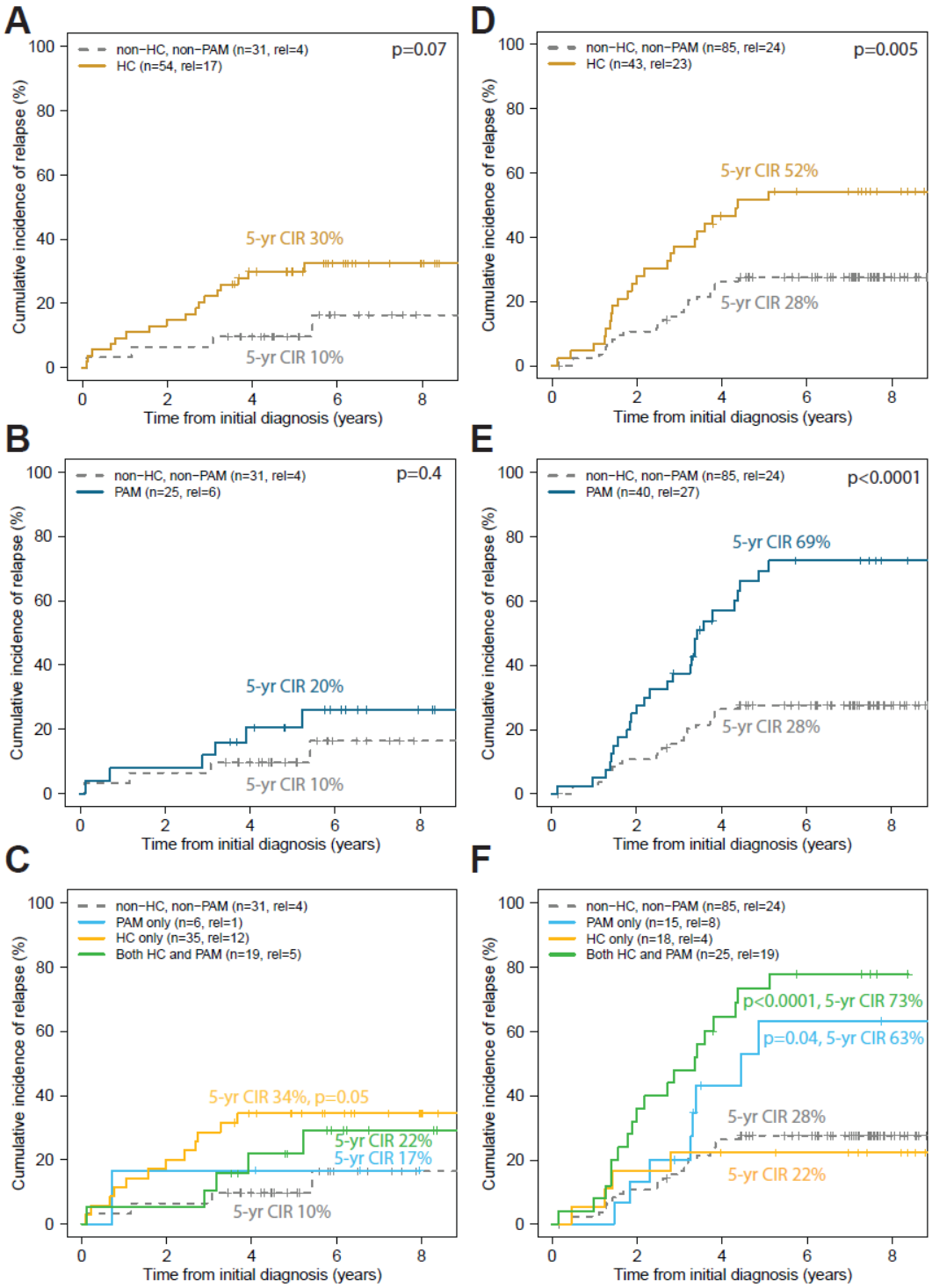
SUPPLEMENTAL FIGURES



Supplemental Figure S1. *ABL1* expression in BCP-ALL subtypes of the DCOG/COALL cohort
Box plot with circles for individual samples showing the expression of *ABL1* (probe set 202123_s_at) on the Affymetrix Plus U133 2.0 microarrays in the indicated BCP-ALL subtypes of the DCOG/COALL cohort. The *BCR-ABL1*-like cases have been identified by Hierarchical Clustering. Within the *BCR-ABL1*-like group, the two samples in red have *ABL1* fusions (*ZMIZ1-ABL1*, *ABL1* with unknown partner). Boxes contain the 1st quartile up to the 3rd quartile of the data values, the median is represented as a line within the box. Whiskers represent the values of the outer 2 quartiles. Values outside of the whiskers are indicated with 'o'. Box plot drawn in R2: microarray analysis and visualization platform (http://r2.amc.nl).



Supplemental Figure S2. Schematic representation of occurrence of molecular and clinical variables in (A) DCOG/COALL and (B) P9906 cohorts. Filled boxes indicate presence of parameter, x indicates unknown or inconclusive data.



Supplemental Figure S3. Cumulative incidence of relapse curves for PAM- and HC-identified *BCR-ABL1*-like groups. (A-C) CIR curves for the cases who were treated on the DCOG ALL-9/10 protocols, (**D-F**) CIR curves for the cases treated on the COG P9906 protocol. **(A, D)** HC-identified *BCR-ABL1*-like cases (brown), **(B, E)** PAM-identified *BCR-ABL1*-like cases (blue), **(C, F)** *BCR-ABL1*-like cases split up according to identification only by HC (orange), identification only by PAM (light-blue), and double-positive identification by both HC and PAM (green). The controls (gray) consist of non-*BCR-ABL1*-like B-other cases negative by either signature. For each group the 5-year CIR estimate is indicated. Gray test p-values below 0.1 are indicated. Abbreviations: n, total; rel, relapse. See Supplemental Table S7 for additional information.

SUPPLEMENTAL REFERENCES

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