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CD371-positive pediatric B-cell acute lymphoblastic leukemia: propensity to lineage switch and slow early response to treatment

This is a pre print version of the following article:

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/2008230> since 2024-08-29T12:26:47Z

Published version:

DOI:10.1182/blood.2023021952

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Table 1: Patients and leukemia main features at diagnosis in the AIEOP cohort

Variable	Total pts		CD371+ pts		CD371- pts		P-value
	N	%	N	%	N	%	
Total	843	100	76	9.0	767	91.0	
Age							< 0.001
1-9 years	676	80.2	41	54.0	635	82.8	
10-17 years	167	19.8	35	46.0	132	17.2	
Gender							0.770
Male	457	54.2	40	52.6	417	54.4	
Female	386	45.8	36	47.4	350	45.6	
WBC count							0.240
< 20 x 10 ⁹ /L	611	72.6	61	80.3	550	71.8	
20-99 x 10 ⁹ /L	186	22.1	11	14.5	175	22.8	
≥ 100 x 10 ⁹ /L	45	5.3	4	5.2	41	5.4	
DNA index							< 0.001
= 1.00	511		66		445		
≠ 1.00	324		9		315		
Translocations							
<i>ETV6-RUNX1</i>	191	23.1	1	1.4	190	25.2	< 0.001
<i>TCF3-PBX1</i>	30	3.7	0	0.0	30	4.1	0.100
<i>KMT2A-AFF1</i>	6	0.7	1	1.4	5	0.7	0.430
Immunophenotype at diagnosis (EGIL)							<0.001
BI-ALL	22	2.6	10	13.2	12	1.6	
BII-ALL	635	75.3	66	86.8	569	74.2	
BIII-ALL	186	22.1	0	0.0	186	24.2	
Ambiguous leukemia							
BAL (EGIL)	7	0.8	1	1.3	6	0.8	0.490
MPAL (WHO)	24	2.8	3	4.0	21	2.7	0.540

Data not available: WBC count: 1 patient; DNA index: 8 patients; BAL: 2 patients

Abbreviations: pts: patients; N: number; %: percentage; WBC: white blood cell; ALL: acute lymphoblastic leukemia; BAL: biphenotypic leukemia; MPAL: mixed-phenotype leukemia

Table 2: Immunophenotype at diagnosis: distribution of antigen expression intensity in CD371+ and CD371- BCP-ALL

Variable	AIEOP cohort					P	iBFM flow network cohort					P	P*
	Total n°	CD371 pos n°	%	CD371 neg n°	%		Total n°	CD371 pos n°	%	CD371 neg n°	%		
Total	843	76	9.02	767	90.98	-	969	84	8.67	885	91.33	-	0.795
CD45						<0.001						<0.001	
STRONG	258	50	19.38	208	80.62		169	30	17.75	139	82.25		0.674
WEAK	457	24	5.25	433	94.75		200	5	2.50	195	97.50		0.114
PP	2	1	50.00	1	50.00		-						
NEG	124	1	0.81	123	99.19		63	0	0.00	63	100.00		1.000
NOT DONE	2	0		2			537	49		488			
CD19						0.099						0.199	
STRONG	819	74	9.04	745	90.96		963	83	8.62	880	91.38		0.757
WEAK	23	1	4.35	22	95.65		4	0	0.00	4	100.00		1.000
PP	1	1	100.00	0	0.0		-						
NEG	0						2	1	50.00	1	50.00		
CD10						<0.001						<0.001	
STRONG	786	55	7.00	731	93.00		909	63	6.93	846	93.07		0.211
WEAK	22	9	40.91	13	59.09		34	14	41.18	20	58.82		0.984
PP	13	2	15.38	11	84.62		-						
NEG	22	10	45.45	12	54.54		26	7	26.92	19	73.08		0.186
CD58						0.014						0.380	
STRONG	749	73	9.75	676	90.25		687	64	9.32	623	90.68		0.077
WEAK	82	1	1.22	81	98.78		12	2	16.67	10	83.33		0.042
PP	1	1	100.00	0	0.00		-						
NEG	8	1	12.50	7	87.50		1	0	0.00	1	100.00		1.000
NOT DONE	3	0		3			270	18		252			
CD34						0.013						<0.001	
STRONG	645	68	10.54	577	89.46		659	78	11.84	581	88.16		0.459
WEAK	67	0	0.00	67	100.00		150	4	2.67	146	97.33		0.314
PP	45	6	13.33	39	86.67		-						
NEG	79	2	2.53	77	97.47		160	2	1.25	158	98.75		0.601
NOT DONE	7	0		7			-						
CD2						<0.001						<0.001	
STRONG	16	14	87.50	2	12.50		30	27	90.00	3	10.00		1.000
WEAK	17	16	94.12	1	5.88		84	20	23.81	64	76.19		<0.001
PP	8	8	100.00	0	0.00		-						
NEG	800	38	4.75	762	95.25		855	37	4.33	818	95.67		0.680
NOT DONE	2	0		2			-						
CD56						<0.001						<0.001	
STRONG	7	4	57.14	3	42.86		13	4	30.77	9	69.23		0.356
WEAK	13	7	53.85	6	46.15		67	14	20.90	53	79.10		0.014
PP	1	1	100.00	0	0.00		-						
NEG	811	64	7.89	747	92.11		889	66	7.42	823	92.58		0.717
NOT DONE	11	0		11			-						
MYELOID ANTIGENS**						<0.001						<0.001	
YES	289	42	14.53	247	85.47		636	70	11.01	566	88.99		0.128
NO	554	34	6.14	520	93.86		333	14	4.20	319	95.80		0.218

P*: comparison of variables distribution between AIEOP and iBFM Flow Network cohorts

**Any myeloid antigen of CD11b, CD14, CD15, CD33, CD64, CD65, MPO, LYSO, CD13, CD117

Abbreviations: POS: positive; STRONG: strong positivity; WEAK: weak positivity; PP: partial positivity; NEG: negative; YES: any positivity (weak, strong, partial positive); NO: negativity of all myeloid antigens.

Figure 1: Myelomonocytic switch in CD371 positive BCP-ALL. With the beginning of steroid as per AIEOP-BFM ALL 2009 protocol, surface antigen expression of residual lymphoblastic cells showed a myelomonocytic switch. It displayed two different patterns: **a-** single population of blast cells with heterogeneous expression of CD19 (single population pattern: orange population); **b-** a two-populations pattern: the first population keeping the immunophenotype of the diagnosis (blue population); the second population showing a downregulation of CD19 and CD34, an upregulation of CD45, and an increase of SSC (orange population).

Figure 1a

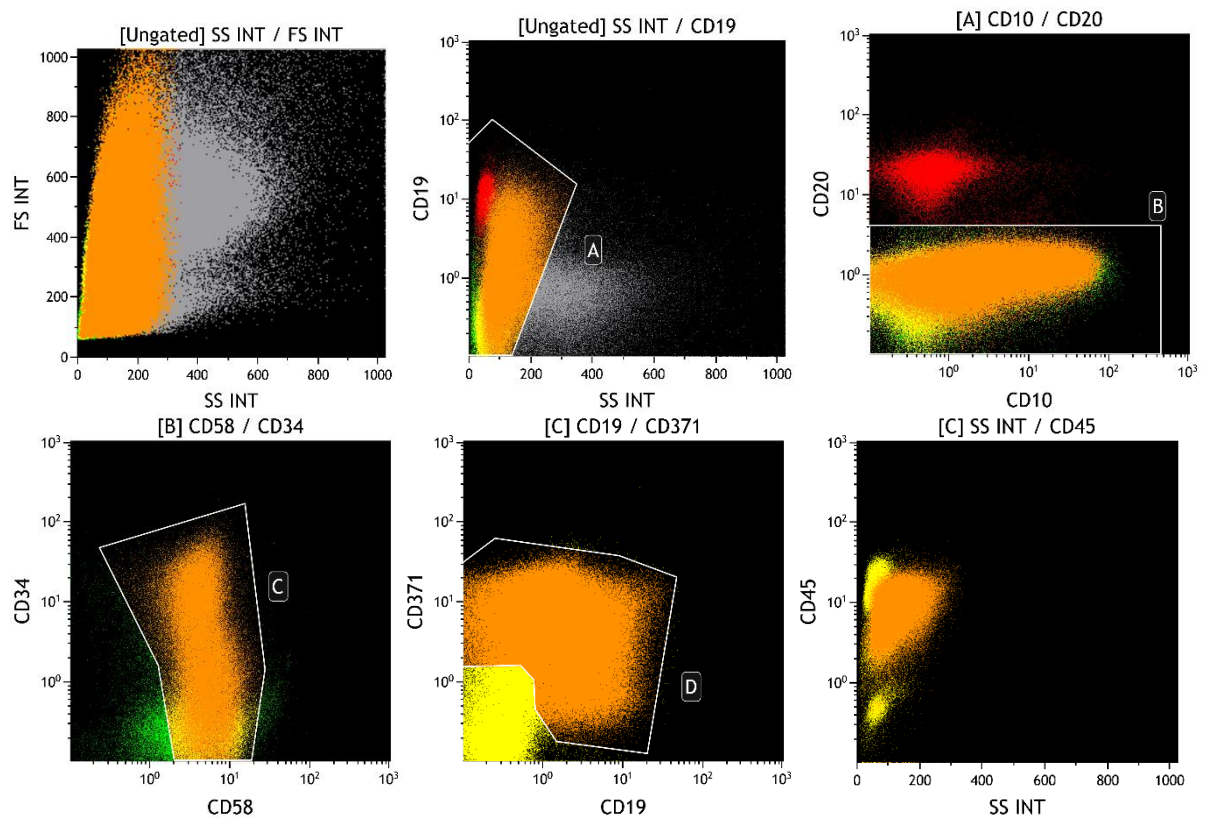


Figure 1b

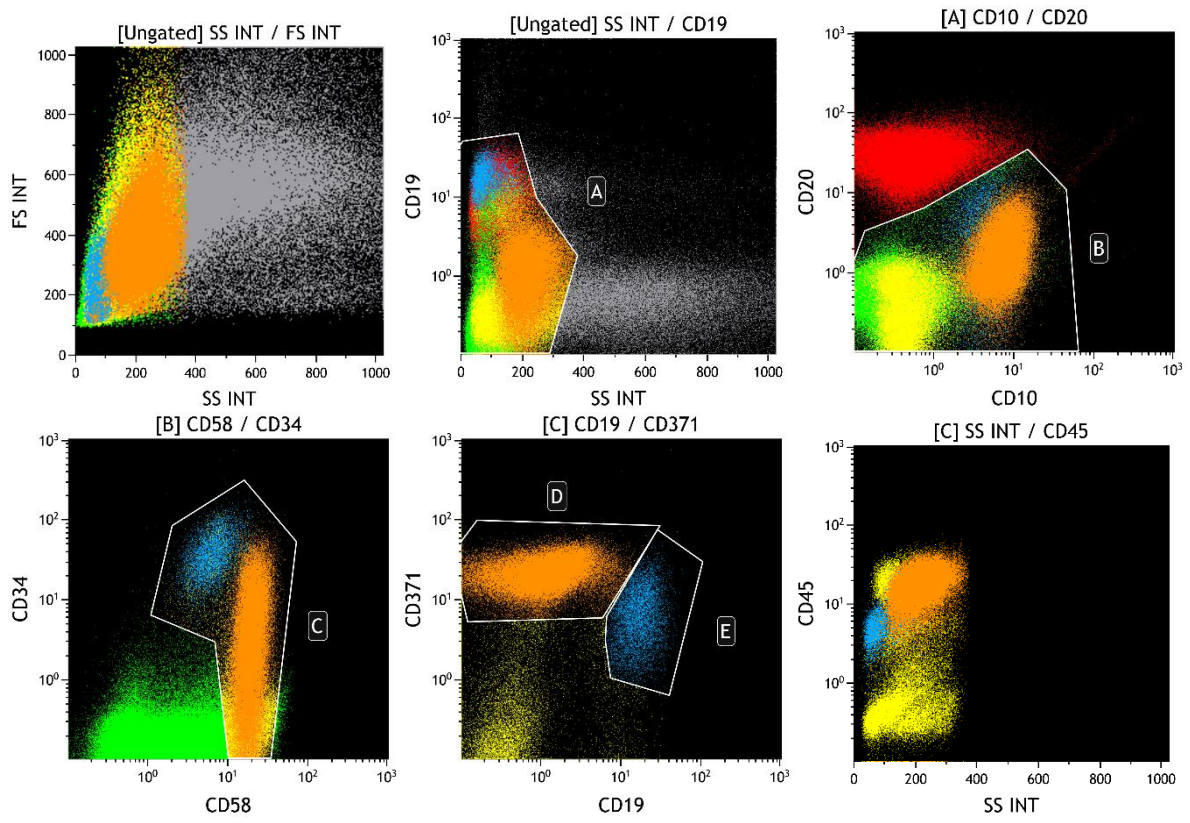


Figure 2: CD371+ BCP-ALL: peripheral blood samples on Day 8 of Induction therapy. Standard morphology revealed a population of monocytes at different maturation stages.

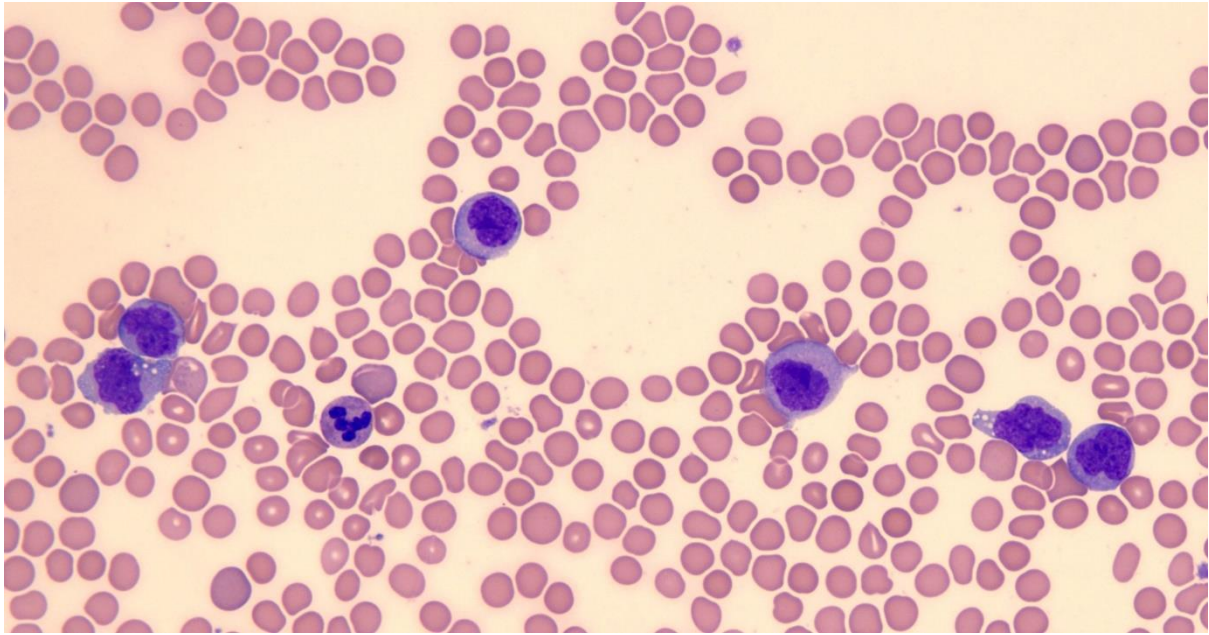
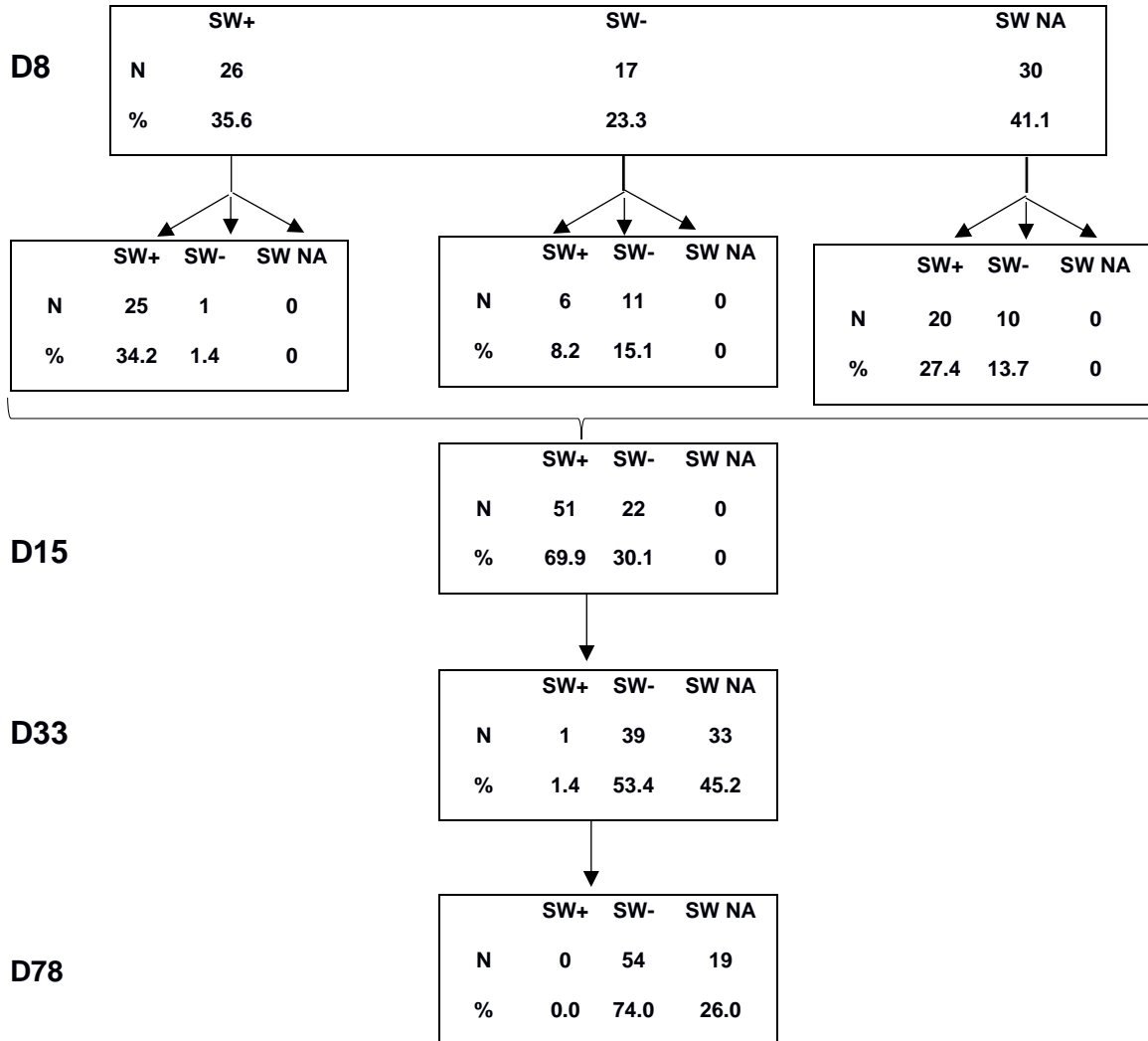


Table 3: Distribution of myelomonocytic switch at different disease reevaluation time points in CD371 positive BCP-ALL

	Total		AIEOP		iBFM		<i>P</i>
	n°	%	n°	%	n°	%	
Total CD371+ at diagnosis	157		73		84		
Switch on Day 8							0.217
Yes	42	65.6	26	60.5	16	76.19	
No	22	34.4	17	39.5	5	23.81	
NA	103		30		63		
Switch on Day 15							0.265
Yes	100	65.4	51	69.9	49	61.25	
No	53	34.6	22	30.1	31	38.75	
NA	4		0		4		
Switch on Day 33							0.317
Yes	4	5.6	1	2.5	3	9.38	
No	68	94.4	39	97.5	29	90.63	
NA	95		33		52		
Switch on Day 78							
Yes	0	0.0	0	0.0	0	0.00	
No	86	100.0	54	100.0	32	100.00	
NA	81		19		52		

Abbreviations: n: number of samples; %: percentage; Switch +: presence of myelomonocytic switch; Switch -: absence of myelomonocytic switch.

Figure 3: Myelomonocytic switch evolution in all 73 evaluable CD371 positive BCP-ALL during Induction and Consolidation Therapy as per AIEOP-BFM ALL 2009 protocol. Myelomonocytic switch could be observed (detection limit 1×10^{-4}) since the first re-evaluation time point on Day 8 or later on Day 15 and Day 33. It was never detected on Day 78 in the AIEOP cohort.



Abbreviations: SW+: presence of lineage switch; SW-: absence of lineage switch population; SW NA: MCF-MRD not available; N: number of samples; %: percentage; D: day

Table 4: Response to Induction and Consolidation Therapy and risk group stratification according to AIEOP-BFM ALL 2009 protocol criteria.

Variable	AIEOP cohort					P	iBFM flow network cohort					P*
	Total	CD371 pos		CD371 neg			Total	CD371 pos		CD371 neg		
	n°	n°	%	n°	%		n°	n°	%	n°	%	
Total	843	76	9.02	767	90.98		969	84	8.67	885	91.33	0.795
Prednisone response						0.470						<0.001
Good (PGR)	787	73	9.28	714	90.72		904	69	7.63	835	92.37	0.225
Poor (PPR)	55	3	5.45	52	94.55		56	15	26.79	41	73.21	0.004
NA	1	0		1			9	0		9		
MCF-MRD Day 15						0.008						<0.001
<0.1%	308	15	4.87	293	95.13		284	15	5.28	269	94.72	0.820
≥0.1-<10%	431	47	11.14	384	89.10		515	42	8.16	473	91.84	0.149
≥10%	88	11	12.50	77	87.50		103	21	20.39	82	79.61	0.147
NA	16	3		13			67	6		61		
Response to Induction IA						1.000						0.087
CR Day 33	825	75	9.09	750	90.91		950	80	8.42	870	91.58	0.618
Non-CR Day 33	10	0	0.00	10	100.00		6	2	33.33	4	66.67	0.125
NA	8	1		7			13	2		11		
PCR-MRD final						< 0.001						<0.001
Standard	273	11	4.03	262	95.97		337	6	1.78	331	98.22	0.094
Medium	443	41	9.26	402	90.74		487	38	7.80	449	92.2	0.428
MRD-SER	66	18	27.27	48	72.73		88	27	30.68	61	69.31	0.646
High	25	4	16.00	21	84.00		29	11	37.93	18	62.07	0.126
NA	36	2		34			28	2		26		
Final risk group						< 0.001						<0.001
Standard	277	12	4.33	265	95.67		314	6	1.91	308	98.09	0.088
Medium	390	37	9.49	353	90.51		431	34	7.89	397	92.11	0.416
High	176	27	15.34	149	84.66		216	44	20.37	172	79.63	0.200
NA	0						8	0		8		

P*: comparison of variables distribution between AIEOP and iBFM Flow Network cohorts

Abbreviations: CD371 pos: any positivity (strong, weak, partial positive) of CD371 antigen at diagnosis; CD371 neg: negativity of CD371 antigen at diagnosis; MFC: multiparametric flow cytometry; MRD: minimal residual disease; PCR: polymerase chain reaction; SER: slow early response.

Table 5: Patients and leukemia features at diagnosis in the iBFM Flow Network cohort

Variable	iBFM flow network cohort					P
	Total	CD371 pos		CD371 neg		
	n°	n°	%	n°	%	
Total	969	84	8.67	885	91.33	
Age						
Median	5.05	9.38		4.64		
Gender						0.286
Male	516	51	9.88	465	90.12	
Female	419	33	7.88	386	92.12	
NA	34	0		34	-	
Translocations						
ETV6-RUNX1	208	0	0.00	208	100.00	<0.001
TCF3-PBX1	27	0	0.00	27	100.00	0.152
KMT2A-AFF1	5	2	40.00	3	60.00	0.063
Immunophenotype at diagnosis (EGIL)						<0.001
BI-ALL	23	7	30.43	16	69.57	
BII-ALL	703	64	9.10	639	90.90	
BIII-ALL	232	12	5.17	220	94.83	
B-IV(non Burkitt)	5	0	0.00	5	100.00	
NA	6	1	-	5	-	
Ambiguous leukemia						
BAL (EGIL)	27	6	22.22	21	77.78	0.006
MPAL (WHO)	32	4	12.50	28	87.50	0.514

Abbreviations: pts: patients; n°: number; %: percentage; ALL: acute lymphoblastic leukemia; BAL: biphenotypic leukemia; MPAL: mixed-phenotype leukemia

Figure 4: Outcome analysis: 5-year event-free-survival of CD371^{pos} BCP-ALLs vs. CD371^{neg} BCP-ALLs

