XIX CONGRESSO NAZIONALE SIES 2026

L'ASSENZA DI ESPRESSIONE DI CD38 CARATTERIZZA UN SOTTOGRUPPO DI LEUCEMIA LINFOBLASTICA ACUTA Ph-LIKE CON PROGNOSI PARTICOLARMENTE INFAUSTA

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Disclosures of L. V. Cappelli

No conflicts to declare

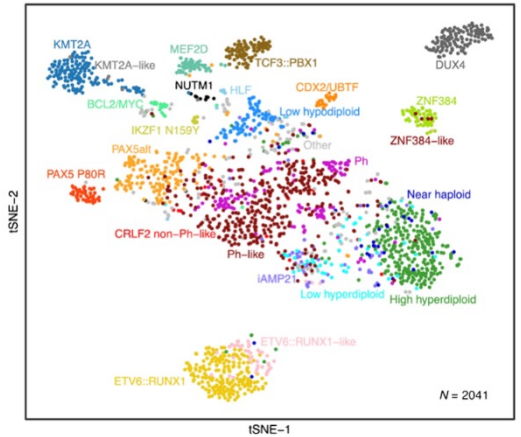
Acute lymphoblastic leukemia (ALL)

WHO, 5th edition[1]

Precursor B-cell neoplasms
B-cell lymphoblastic leukaemias/lymphomas
B-lymphoblastic leukaemia/lymphoma, NOS
B-lymphoblastic leukaemia/lymphoma with **high** hyperdiploidy
B-lymphoblastic leukaemia/lymphoma with hypodiploidy
B-lymphoblastic leukaemia/lymphoma with iAMP21
B-lymphoblastic leukaemia/lymphoma with *BCR*::*ABL1* fusion
B-lymphoblastic leukaemia/lymphoma with *BCR*::*ABL1*-like features
B-lymphoblastic leukaemia/lymphoma with *KMT2A* rearrangement
B-lymphoblastic leukaemia/lymphoma with *ETV6*::*RUNX1* fusion
B-lymphoblastic leukaemia/lymphoma with *ETV6*::*RUNX1*-like features
B-lymphoblastic leukaemia/lymphoma with *TCF3*::*PBX1* fusion
B-lymphoblastic leukaemia/lymphoma with *IGH*::*IL3 fusion*
B-lymphoblastic leukaemia/lymphoma with *TCF3*::*HLF* fusion
B-lymphoblastic leukaemia/lymphoma with other defined genetic abnormalities

ICC 2022[2]

B-ALL
B-ALL with recurrent genetic abnormalities:
B-ALL with t(9;22)(q34.1;q11.2)/BCR::ABL1
with lymphoid only involvement
with multilineage involvement
B-ALL with t(v;11q23.3)/*KMT2A* rearranged
B-ALL with t(12;21)(p13.2;q22.1)/*ETV6*::*RUNX1*
B-ALL, hyperdiploid
B-ALL, low hypodiploid
B-ALL, near haploid
B-ALL with t(5;14)(q31.1;q32.3)/*IL3*::*IGH*
B-ALL with t(1;19)(q23.3;p13.3)/*TCF3*::*PBX1*
B-ALL, *BCR*::*ABL1*–like, *ABL-1* class rearranged
B-ALL, *BCR*::*ABL1*–*like*, *JAK-STAT* activated
B-ALL, *BCR*::*ABL1*–like, NOS
B-ALL with iAMP21
B-ALL with *MYC* rearrangement
B-ALL with *DUX4* rearrangement
B-ALL with *MEF2D* rearrangement
B-ALL with *ZNF384*(362) rearrangement
B-ALL with *NUTM1* rearrangement
B-ALL with *HLF* rearrangement
B-ALL with *UBTF*::*ATXN7L3*/*PAN3*,*CDX2* ("CDX2/UBTF")
B-ALL with mutated *IKZF1* N159Y
B-ALL with mutated *PAX5* P80R
Provisional entity: B-ALL, *ETV6*::*RUNX1*-like
Provisional entity: B-ALL, with *PAX5* alteration
Provisional entity: B-ALL, with mutated *ZEB2* (p.H1038R) /*IGH*::*CEBPE*
Provisional entity: B-ALL, *ZNF384* rearranged-like
Provisional entity: B-ALL, *KMT2A* rearranged-like
B-ALL, NOS



Gu Z, et al, Nat Genet 2019

1: Alaggio R, et al. Leukemia 2022;
2: Arber DA, et al. Blood 2022

Methods and objectives

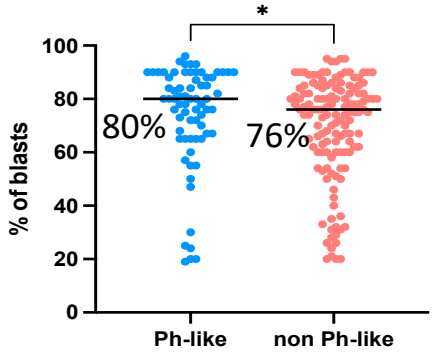
- Retrospective multicentric study based on three GIMEMA protocols (LAL1913[1], LAL2317[2] e ALL2922[3])
- Inclusion criteria: available clinical, phenotypical, molecular data→ 204 adult B-ALL patients
- *BCR::ABL1* predictor[4]: 70 Ph-like (34%) vs 144 non Ph-like (66%)
- **Objective**: Integrating clinical, phenotypic, and molecular data to identify outcome predictors
- Molecular studies:
  - Multiplex Ligation-dependent Probe Amplification (MLPA)
  - Targeted RNA-seq
- Statistical studies: Fisher's/Mann-Whitney, Kaplan-Meier (log-rank), Cox proportional hazards model.
- Endpoints: DFS, OS

1. Bassan R, et al. Blood Adv 2023
2. Bassan R, et al. Blood 2025
3. Chiaretti S, et al. SIE 2025
4. Chiaretti S, et al. BJH 2018

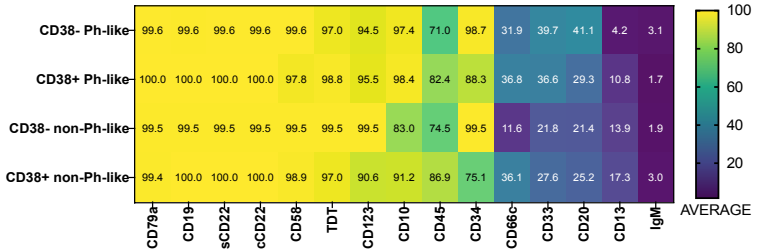
Ph-like *vs* non-Ph-like: immunophenotypic differences

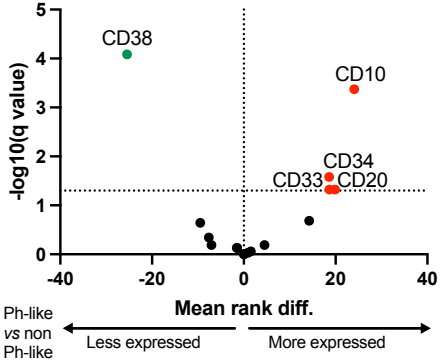
Ph-like patients are more frequently CD38 negative[2,3] (~30% vs 7%, p<0.0001)

- B-common pts: 175/204 (86%)
- Euroflow Consortium[1]



Antigen	Mean_Ph_like	Mean_Ph_neg	q_value_FDR
CD38	67,67	93,08	0,000099
CD10	98,05	81,03	0,007618
CD34	91,53	74,39	0,017520
CD33	37,60	25,43	0,038459
CD20	32,99	24,54	0,017520

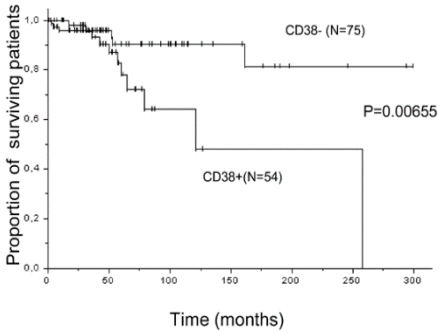


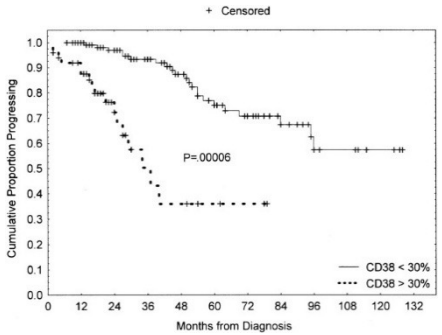


1: Theunissen P, et al. Blood 2017
2: Laganà A, et al. MJHID 2024
3: Paietta E, et al. Blood 2021

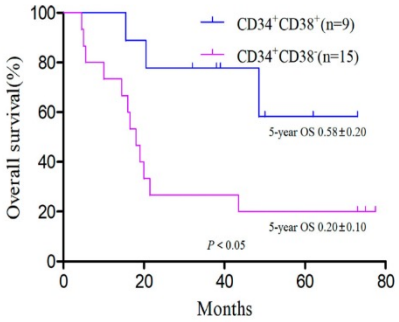
CD38: to be or not to be?

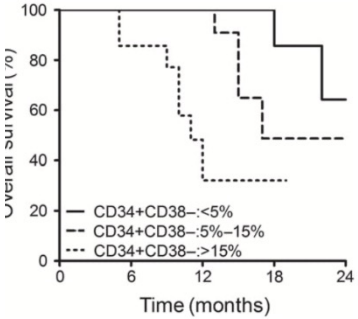
CD38 in CLL





Pediatric B-ALL





- Enzyme involved in T-cell signaling
- Tumor expression: incompetent T cell expansion
- Unfavorable prognosis in CLL

- CD38-/CD34+: more immature and stem-like phenotype (*leukemia-initiating cells* : LICs)

Wentao Li, et al. Biomedicine & Pharmacotherapy 2022
Bocuzzi V et al. Journ Transl Medicine 2024

Durig J et al, Leukemia 2002
Del Poeta G et al, Blood 2001

Zhao J, et al. Hematology 2022
Long J et al. Leuk & Lymphoma 2014

Results: Clinical differences between CD38-/CD38+ ALL

- No major clinical differences between CD38- vs CD38+ cases
- CD38-/CD38+: higher WBC (median 25.3 x10^3/mm3 vs 6.3 x10^3/mm3 [Ph-like]);

	Ph-like				Non Ph-like				
	Overall (n=70)	CD38− (n=21)	CD38+ (n=49)	p-value	Overall (n=134)	CD38− (n=9)	CD38+ (n=125)	p-value	p-value (Ph-like vs non Ph-like)
Age (years, median [range]	40,4 [18,2-65,2]	43,9 [19,8-63,3]	38,8 [18,2-65,2]	0,2827	40,5 [18,2-65,1]	46,19 [31,7-57,4]	38,1 [18,2-65,1]	0,1395	0,605
Sex – Male n (%)	42 (60%)	15 (71%)	27 (55%)	0,2879	69 (51%)	4 (29%)	65 (38%)	0,5764	0,3002
WBC (×10^9/L, median [range])	9,7 [0,22-461]	25,3 [0,4-461]	6,3 [0,2-317]	**0,0374**	5,7 [0,68-156]	6,6 [2,5-14]	5,7 [0,7-156,2]	0,8233	0,1469
Blasts % (median [range])	80 [20-96]	82 [24-93]	80 [20-96]	0,3469	75,5 [20-95]	76 [53-89]	75 [20-95]	0,8116	**0,0319**
Risk (SR, HR, VHR)	SR: 29 (57%), HR: 10 (20%), VHR: 12 (23%), NA: 19	SR: 8 (47%), HR: 5 (29%), VHR: 4 (23%), NA: 4	SR: 21 (62%), HR: 5 (15%), VHR: 8 (23%), NA: 15	0,3772	SR: 70 (60%), HR: 25 (22%), VHR: 21 (18%), NA: 18	SR: 4 (67%), HR: 1 (16,5%), VHR: 1 (16,5%), NA: 3	SR: 66 (60%), HR: 24 (22%), VHR: 20 (18%), NA: 15	1	0,7334
Allo-SCT n (%)	No: 37 (53%), Yes: 33 (47%)	No: 11 (52%), Yes: 10 (48%)	No: 26 (53%), Yes: 23 (47%)	1	No: 88 (76%), Yes: 28 (24%), NA: 18	No: 4 (67%), Yes: 2 (33%), NA: 3	No: 84 (76%), Yes: 26 (24%), NA: 15	0,6303	**0,002**
Follow-up (months, median [range])	14,2 [0,6-95,4]	13 [0,9-49,5]	16,1 [0,6-95,4]	0,7192	25,8 [0,6-90,8]	17,3 [6,6-44,7]	25,8 [0,6-90,8]	0,6945	0,1933

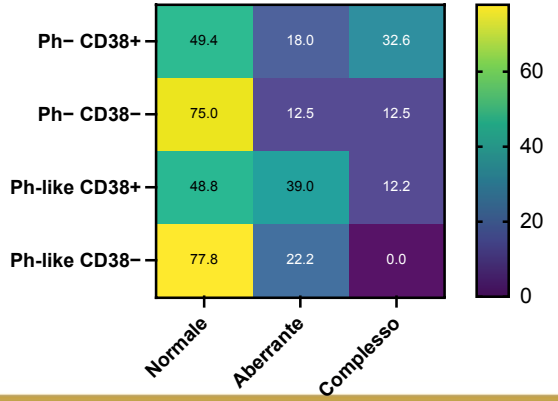
Results: Molecular differences between CD38-/CD38+ ALL

- CD38- patients have normal karyotype but unfavorable molecular aberrations (*IKZF1*^{plus} genotype, especially in the Ph-like subgroup)

Karyotype (129 samples, 63%)

	CD38-	CD38+
Normal	13 (76%)	54 (48%)
Aberrant	2 (12%)	25 (23%)
Complex	2 (12%)	33 (29%)

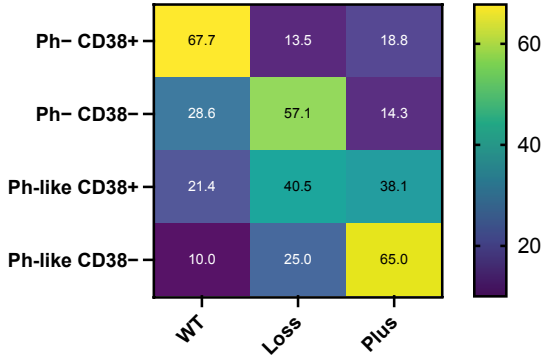
p=0.0375
OR: 0.29



MLPA (165 samples, 81%)

	CD38-	CD38+
IKZF1 WT	4 (15%)	74 (54%)
IKZF1 loss	9 (33%)	30 (22%)
IKZF1^{plus}	14 (52%)	34 (24%)

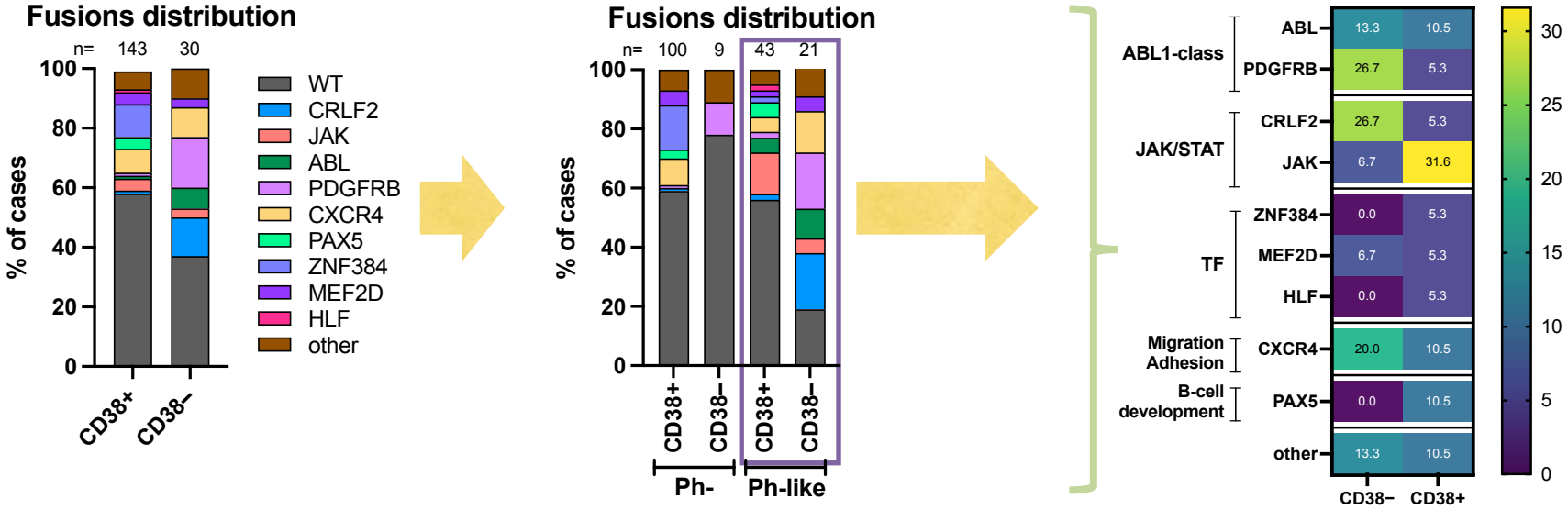
p=0.0002
OR: 6.64



Results: Molecular differences between CD38-/CD38+ ALL

- **CD38- have more prognostically unfavorable pathogenic fusions(>Ph-like)**

Targeted RNA-seq (174 campioni, 85%)



63% CD38- vs 42% in CD38+, **p=0.043, OR 2.39**

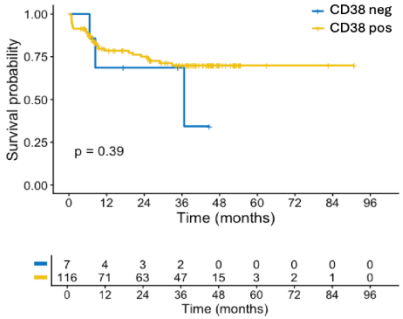
Ph-like: 81% CD38- vs 44% in CD38+, **p=0.0072, OR 5.37**

CD38- Ph-like: Enrichment in ABL1-class, CRLF2 e CXCR4

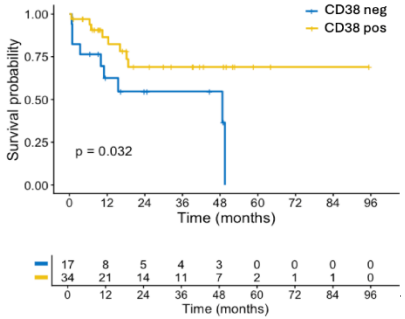
Results: prognosis in CD38-/CD38+ ALL

OS

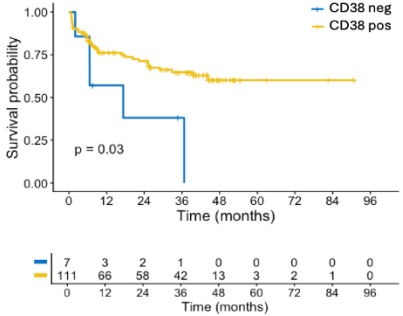
Non-Ph-like

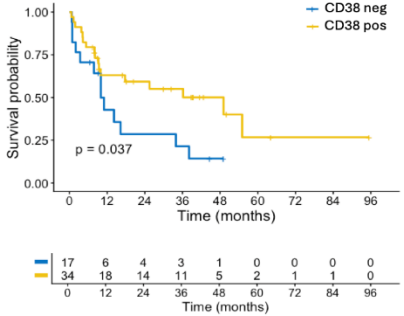


Ph-like

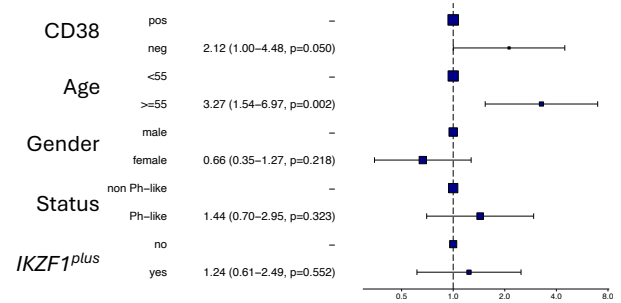


DFS

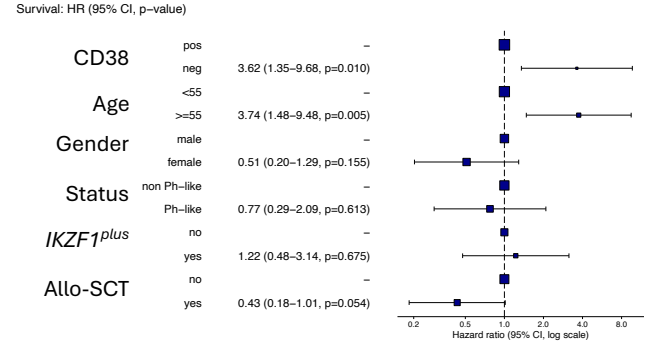




DFS



OS

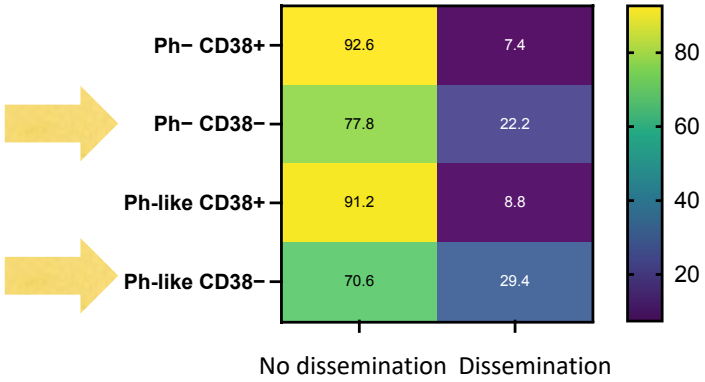


- **CD38- patients (especially Ph-like) have a more unfavorable prognosis (DFS, OS)**

CD38 expression and extramedullary dissemination

	No dissemination	Dissemination
CD38+	144 (92%)	12 (8%)
CD38-	19 (73%)	7 (27%)

p = 0.0084
OR = 4.42



- **CD38- patients have a greater tendency to disseminate to the CNS, regardless of Ph-like/non-Ph-like status**

Conclusions

- **New entity: Ph-like CD38-** (~30% of all Ph-like ALL)
- CD38-: normal karyotype but more molecular aberrations, i.e. *IKZF1*^{plus} and pathogenic fusions (ABL1-class, CRLF2 e CXCR4)

- Worse survival in DFS e OS in CD38- ALL
- More tendency to disseminate to extramedullary compartments
- **CD38- is associated with more immaturity and aggressiveness**

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