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Acute Leukemias

ABSENT CD38 EXPRESSION NEGATIVELY IMPACTS AND FURTHER DISCRIMINATES OUTCOME ON THE HIGH-RISK SUBGROUP PH-LIKE ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction: Ph-like acute lymphoblastic leukemia (ALL) is a B-ALL subtype lacking *BCR::ABL1* but sharing a transcriptomic profile similar to Ph+ ALL and being characterized by poor prognosis. Its genetic heterogeneity and lack of standardized diagnostic criteria hamper clinical management and risk stratification. Here we aimed at defining novel prognostic markers by integrating immunophenotypic and molecular data in adult B-lineage ALL.

Methods: We retrospectively analyzed 207 newly diagnosed adults (18–65 yrs) with B-ALL devoid of major molecular aberrations (*BCR::ABL1*, *TCF3::PBX1* and *KMT2A*) enrolled in the GIMEMA LAL1913, LAL2317 and ALL2922 trials (the latter designed specifically for Ph-like ALL). By applying the BCR/ABL1-like predictor (Chiaretti et al, BJH 2018), 70 cases were Ph-like and 137 were non-Ph-like (n=137). CNVs were assessed by MLPA and fusions by targeted RNA-seq.

Result: At baseline, antigen expression levels were similar between the two entities by immunophenotypic analysis (Figure 1A). However, Ph-like ALL cases expressed lower CD38 (67.7% vs 92.6%, p<0.0001) and higher CD10, CD34, CD33 and CD20 (Figure 1B). Associations between CD38+/- and Ph-like/Ph- status are reported in Table 1. Focusing on Ph-like cases, by MLPA analysis a higher frequency of the prognostically unfavorable *IKZF1*^{plus} genotype (Fedullo AL et al, Haematologica 2019) was found in CD38- (60%) compared to CD38+ Ph-like ALL cases (29%; p=0.027). RNA-sequencing analysis revealed a higher incidence of fusions in CD38- vs CD38+ Ph-like ALL cases (76% vs 37%, p=0.007), with CD38- cases being enriched in PDGFRB (25% vs 5% in CD38+, p=ns) and CRLF2 rearrangements (19% vs 10% in CD38+, p=ns) (Figure 1C). Finally, survival analysis on the global ALL cohort, showed that CD38- patients had a significantly inferior disease-free survival (DFS) (median 14.2 vs. 55.9 months, p=0.00041) and overall survival (OS) (median 48.7 months vs. not reached, p=0.024) compared to CD38+ cases. This was particularly evident in the Ph-like group (Figure 1D). Of note, extramedullary disease at both disease onset or relapse was significantly more common in CD38- patients (62%) compared to CD38+ ones (15%) (p=0.0066). Finally, multivariate analysis on the global cohort including known risk factors - age, gender, *IKZF1*^{plus} genotype - confirmed the lack of CD38 expression as an independent adverse prognostic factor for DFS (HR: 2.65, p=0.015) and OS (HR: 5.06, p=0.005) (Fig. 1E), together with advanced age (cut-off ≥55 years, DFS HR: 4.77, p=0.003, and OS HR: 6.86, p=0.004), while allogeneic stem cell transplant demonstrated a borderline significant protective effect on OS (HR: 0.37, p=0.053).

Conclusions: We identified a so far unrecognized Ph-like ALL subentity with absent CD38 (~30% of Ph-like ALL cases). These patients represent a distinct high-risk subgroup characterized by genomic aberrations and a markedly worse survival. Efforts are warranted to further define this entity molecularly.

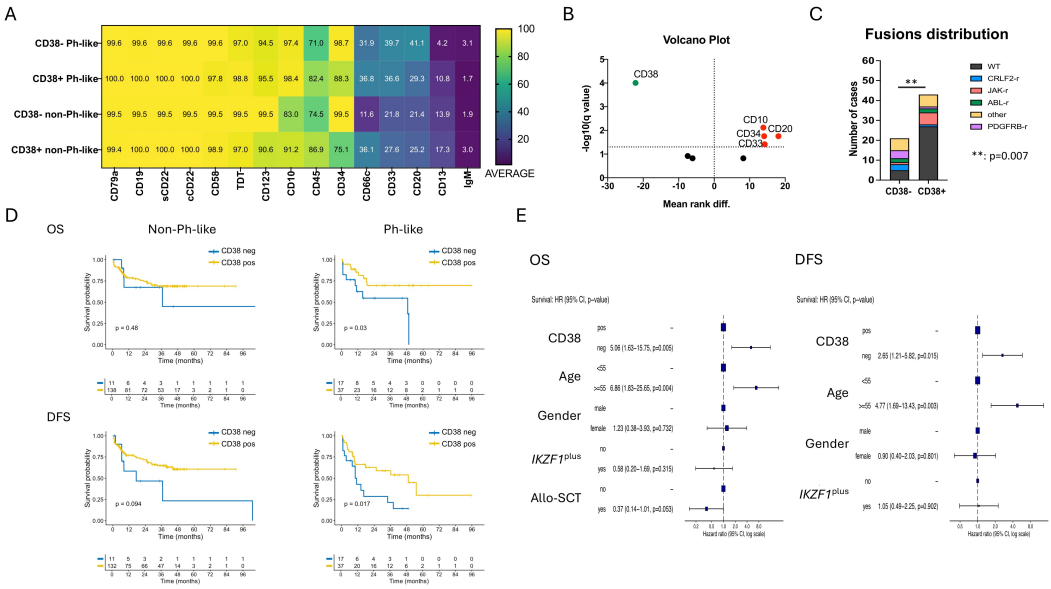

Fig. 1. (A) Heatmap depicting antigen expression levels assessed by immunophenotyping in Ph-like vs Ph- ALL CD38-/CD38+ samples. The mean value is indicated in each box. The first box from the left is the mean percentage of blasts detected by immunophenotype. **(B)** Volcano plot showing -log10(q values) of differentially expressed antigens between Ph-like and non-Ph-like cases. Antigens in green are significantly less expressed in Ph-like ALL while those in red are significantly more expressed than non-Ph-like ALL. P-values were calculated with Mann-Whitney test with adjustment for multiple comparisons. **(C)** Barplot depicting the distribution of gene fusions assessed by RNA-sequencing in CD38- vs CD38+ Ph-like ALL patients; p-value was calculated using Chi-square test. **(D)** Kaplan-Meier survival analysis showing disease-free survival (DFS) and overall survival (OS) outcomes in CD38- vs CD38+ non-Ph-like and Ph-like ALL patients; p-value was calculated using log-rank test. **(E)** Cox multivariate analysis showing the impact of CD38- on DFS and OS with other known clinical and molecular risk factors. Hazard ratios (HR), 95% confidence intervals (CI), and p-values are shown for each variable. P-values were calculated using the Wald test.