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POSTER ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Proteomic Profiling Identifies Unique IDH Mutant Signatures and Novel Therapeutic Opportunities in Adult Acute Myeloid Leukemia Patients

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INTRODUCTION Patients with IDH mutations are common in adult Acute Myeloid Leukemia (AML), with selective IDH inhibitors (IDHi) being recommended, but they do not always respond. We evaluated the proteome of IDH mutant AML patients to identify prognostic signatures and therapeutic targets.

METHODS The expression of 429 proteins (339 total, 90 post-translational modified) were measured by Reverse Phase Protein Array in fresh samples from 805 newly diagnosed AML patients, and normalized to normal CD34+ cells. We analyzed 151 patients with IDH mutations (IDH1 = 56, IDH2 = 76, both = 19), treated with AraC-based combination therapy (N=71, including 5 with IDHi, 11 with Venetoclax (VTX)) or Hypomethylating agent based (HMA, N=65, + IDHi=5, +VTX=11, or both=2) and 3 received IDHi monotherapy, Proteins prognostic for Overall Survival (OS) were identified using pairwise LogRank tests ($p<0.05$) adjusted for False Discovery Rate (FDR), followed by unbiased hierarchical clustering. Continuous and categorial variables were compared with Wilcoxon, Kruskal-Wallis (KS) or Fisher's Exact test with simulated p-values (10000 replicates). Cox proportional hazards models (CoxPH) were developed for Uni-(UV) and Multi-variate (MV) analysis. Differentially expression (DE) analysis was performed using the KS test and pairwise Dunn's tests with p-values adjusted with FDR ($p<0.01$). Deep neural network analysis using random forest models identified proteins most predictive of cluster assignment.

RESULTS 97 proteins were individually prognostic for OS, and formed 3 patient clusters (Fig. 1: C1=red, C2=blue, C3=green). Most clinical and molecular features were not biased between clusters, however C2 had more cases with primary AML, diploid karyotype (kar.), intermed. cytogenetic (cyto.) risk, and IDH+FLT3_ITD or NPM1 mutants, while C3 has more cases with unfavorable cyto. risk, complex kar., and mutations in IDH+EZH2 or TP53, and ASLX1+IDH combination were more frequent in C1. Of note, C1 has the largest proportion of VTX-treated patients, while C3 has the largest proportion of IDHi-treated ones. The OS (Fig. 2) of C1 patients was better (Median: C1=42.2mo, C2=18.3mo, C3=10.7mo; p=0.0021), but no difference was noted for Complete Remission Duration (CRD) (Median: C1=72.3mo, C2=21.6mo, C3=33.4mo; p=0.7). The OS was similar when patients were filtered by specific mutations or combinations, e.g. IDH1, IDH2, and IDH combined with ASLX1, RUNX1 or TET2, or by other features, e.g. 56-70 age group, males, primary AML, intermed. cyto. risk, diploid kar., VTX or HMA without IDHi and/or VTX (HMA-TX) therapies.
CoxPH models showed only C1 and C3 predictive for OS in the UV analysis (HR=1, 1.5, 2.3; p=ref., 0.22, <0.001), along with age, secondary AML, complex, diploid and del12 kar., HMA-TX, and IDH1, IDH2, NPM1, TP53, DNMT3a and JAK2 mutations. In the MV analysis, C1, C2 and C3 (HR=1, 2.6, 3.4; p=ref., 0.019, <0.001), age, secondary AML, complex and diploid kar., HMA-TX and IDH1 mutation predicted OS. Regarding CRD, no cluster was predictive in the UV model (HR=1, 1.2, 1.4; p=ref., 0.65, 0.41), but age, secondary AML, complex kar., HMA-TX, and ASLX1, EZH2 and IDH2 mutants were. In contrast, C1 and C3 (HR=1, 2.3, 2.6; p=ref., 0.13, 0.046) predicted CRD in the MV model, as well as secondary AML, HMA-TX and IDH2 mutation.

Most frequent biological processes observed among the predictive proteins were epigenetics, DNA damage response, cell cycle and metabolism, with 23, 12, 12, and 11 proteins. DE analysis identified 133 proteins among 429, including: ADM,

LCK and BTK up-, and TP53BP1 and PRMT1 down-regulated in C1; ANXA1 up-, and PTK2 and SRC down-regulated in C2. In C3, TGM2 is higher than normal, although lower than in C1. Inhibitors for upregulated proteins are in clinical development, potentially working as synergistic agents. Furthermore, a set of 5 proteins (SMARCB1, SMARCA2, WTAP, PIK3CB and RAD50) predicted cluster membership with 97% of accuracy, useful for quickly identifying patients and personalizing therapy.

CONCLUSION Proteomics identified unique protein profiles that were independently prognostic for outcome in IDH mutant AML patients. We identified upregulated proteins for which inhibitors are in development, suggesting potential therapeutic synergies to improve outcomes. Finally, we defined 5 proteins that accurately stratifies IDH patients for novel treatment recommendations.

Disclosures No relevant conflicts of interest to declare.

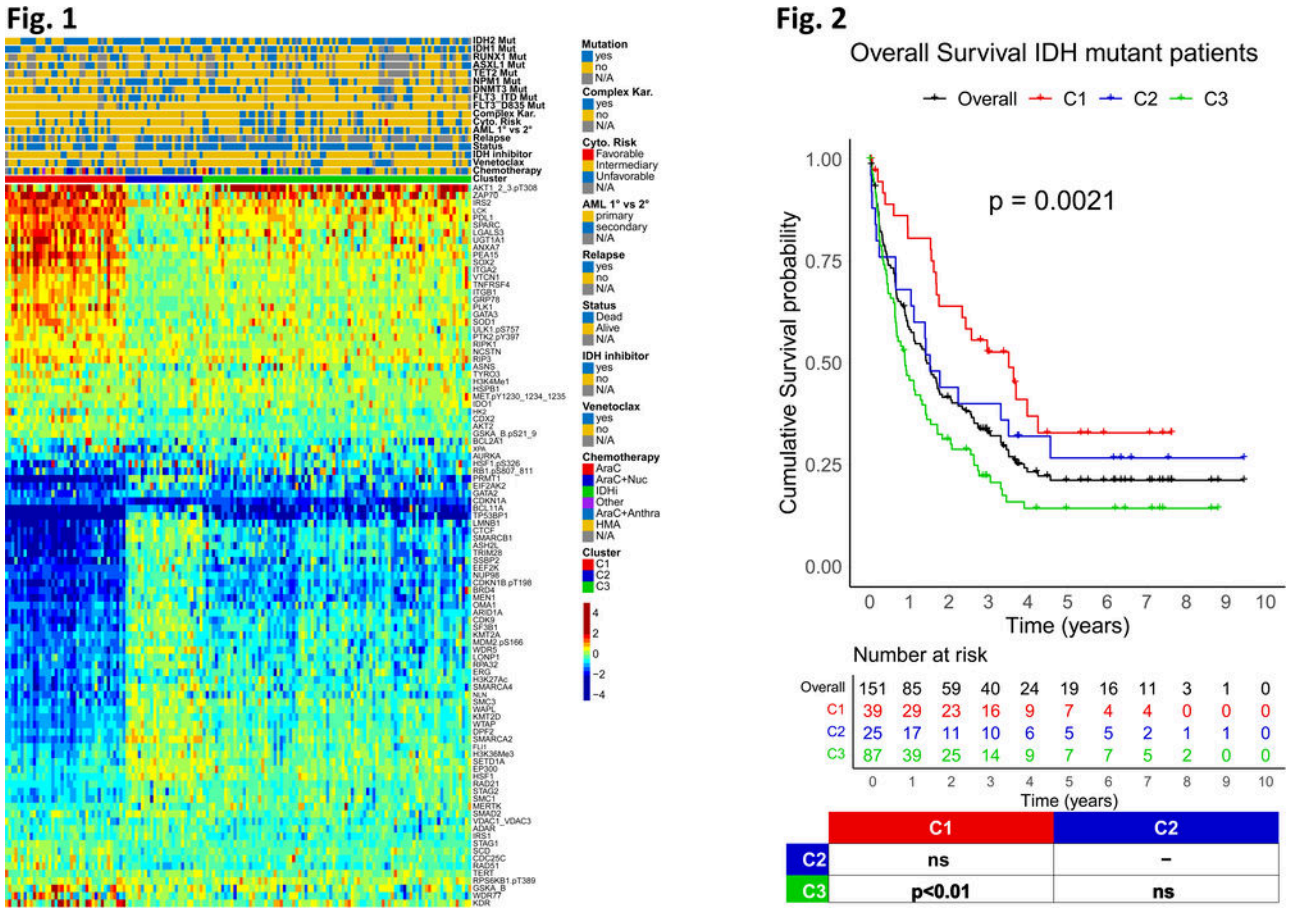

Figure 1

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