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ORAL ABSTRACTS

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

The FLT3-like Gene Expression Signature Predicts Response to Quizartinib in Wild-Type FLT3 Acute Myeloid Leukemia: An Analysis of the Pethema Quiwi Trial

Adrian Mosquera Orgueira[1], *Manuel Perez Encinas*[2], *Jose Angel Diaz Arias*[3], *Rebeca Rodriguez Veiga, MD*[4], *Juan Miguel Bergua Burgues*[5], *Jesús Lorenzo Algarra*[6], *Carmen Botella*[7], *Jose Antonio Perez Simon*[8], *Teresa Bernal*[9], *Mar Tormo, MD*[10], *Maria Calbacho*[11], *Olga Salamero, MD*[12], *Josefina Serrano, MD*[13], *Victor Noriega*[14], *Juan Antonio Lopez Lopez*[15], *Susana Vives*[16], *Mercedes Colorado*[17], *Jose Luis Lopez Lorenzo, MD*[18], *Maria Vidriales Vicente*[19], *Raimundo Garcia Boyero*[20], *Maria Teresa Olave Rubio*[21], *Pilar Herrera Puente*[22], *Olga Arce*[23], *Manuel Barrios Garcia*[24], *Maria Jose Sayas Lloris*[25], *Marta Polo*[26], *Maria Isabel Gomez Roncero*[27], *Eva Barragan, PhD*[28], *Rosa Ayala, MD PhD*[29], *Carmen Chillon*[30], *Maria Jose Calasanz, PhD*[31], *Blanca Boluda*[32], *Andres Peleteiro Raindo*[33], *Raquel Amigo*[34], *David Martinez Cuadron*[35], *Jorge Labrador*[36], *Pau Montesinos, PhDMD*[37]

[1] University Hospital of Santiago de Compostela, Department of Hematology, IDIS, SANTIAGO DE COMPOSTELA, Spain
[2] University Hospital of Santiago de Compostela, Department of Hematology, IDIS, SANTIAGO, ESP
[3] University Hospital of Santiago de Compostela, Department of Hematology, IDIS, A Coruña, Spain
[4] Hospital Universitary i Politecnic La Fe, VALENCIA, ESP
[5] Hospital San Pedro de Alcántara, Cáceres, Spain
[6] Hospital General de Albacete, Albacete, ESP
[7] Hospital General Universitario de Alicante, Alicante, Spain
[8] University Hospital Virgen del Rocío, Sevilla, Spain
[9] Hospital Universitario Central De Asturias, Oviedo, ESP
[10] Hospital Clínico Universitario de Valencia, Instituto de Investigación Sanitaria INCLIVA, Valencia, Spain
[11] Hospital Universitario 12 de Octubre, Madrid, Spain
[12] Hospital Vall d'Hebron, Barcelona, Barcelona, ESP
[13] Hospital Universitario Reina Sofía, IMIBIC, Cordoba, ESP
[14] Hospital Clínico de A Coruña, A Coruña, Spain
[15] Hospital Universitario de Jaen, Jaen, Spain
[16] Hospital Germans Trias i Pujol, Badalona, ESP
[17] Hospital Universitario Marqués De Valdecilla, Santander, Spain
[18] Fundacion Jimenez Diaz, Madrid, ESP
[19] Hospital Universitario de Salamanca, IBSAL, CIBER-ONC number CB16/12/00233 y Centro de Investigación, Salamanca, Spain
[20] Hospital General Universitario de Castellon, Castellon, Spain
[21] Hospital Clinico Universitario Lorenzo Blesa, Zaragoza, ESP
[22] Hospital Universitario Ramon y Cajal, Madrid, ESP
[23] Hospital Universitario de Basurto, Bilbao, Spain
[24] Hospital Universitario Regional de Malaga, Malaga, Spain
[25] Hospital Dr. Peset, ZARAGOZA, ESP
[26] Hospital Clinico San Carlos, Madrid, ESP
[27] Hospital Virgen de la Salud, Toledo, Spain
[28] Hematology Research Group, Instituto de Investigación Sanitaria La Fe, Valencia, Spain
[29] Hospital Universitario 12 de Octubre, I+12, CNIO, Complutense University, CIBERONC, Madrid, Spain
[30] Hospital Universitario de Salamanca; (CIC, IBMCC USAL-CSIC), Salamanca, ESP
[31] Cancer Center Clinica Universidad de Navarra, Centro de Investigación Médica Aplicada (CIMA), IDISNA, CIBER-ONC number CB16/12/00369 and CB16/12/00489, Pamplona, Spain
[32] Hospital Universitari I Politècnic La Fe, Valencia, ESP

[33] University Hospital of Santiago De Compostela, Department of Hematology, IDIS, SANTIAGO DE COMPOSTELA, ESP
[34] Instituto de Investigaciones Santiarias La Fe, Valencia, Spain
[35] Hospital Universitari i Politecnic La Fe, Valencia, Spain
[36] Hospital Universitario de Burgos, Universidad Isabel I, Burgos, ESP
[37] Hospital Universitari i Politecnic la Fe, Valencia, Spain

Background
The identification of predictive biomarkers is crucial for guiding treatment decisions in acute myeloid leukemia (AML). Previously, we identified a FLT3-like gene expression signature in FLT3 wild-type AML patients, which clustered a variable proportion of FLT3 wild-type patients with FLT3-ITD and TKD mutated patients. The QUIWI trial was a randomized, placebo-controlled, phase II study preliminary showing a significant increase in overall survival (OS) in wild-type FLT3 AML patients treated with the FLT3 inhibitor quizartinib (Quiza) plus standard chemotherapy. This preplanned correlative study was designed to assess the value of the FLT3-like signature to predict responses to Quiza.

Methods
We performed RNA sequencing (RNAseq) analysis on a subset of patients from the clinical trial. RNA was extracted using standard methods, followed by assessment of nucleic acid integrity (TapeStation) and quantification (Qubit). Total mRNA sequencing was performed using polyA RNAseq with TruSeq technology. A total of 206 adequate samples from bone marrow and peripheral blood were sequenced (161 from FLT3-ITD negative enrolled in QUIWI; and 55 from FLT3-ITD positive patients who were screen failure of the QUIWI trial by this reason). The sequences were aligned to the GRCh37 reference genome using the Hisat algorithm. Gene expression quantification was performed using the Bioconductor workflow, and gene expression estimates (FPKM) were obtained. The gene expression estimates were log2 normalized. Finally, those genes mapping to the original FLT3-like signature (595 genes) were selected for downstream analysis. Clustering was based on the hierarchical method, using standard euclidean distance metrics. OS was defined as time from start of screening to death. Event-free survival (EFS) was defined as time from randomization to failure to achieve CR/CRi after 1 or 2 cycles, death in CR/CRi, or relapse (whichever occurred the first). Relapse-free survival was defined as time from randomization to disease relapse or death by any cause.

Results
Among the total 206 patients, a cluster of 54.37% (N=112) was enriched in FLT3-mutant cases (71.11% of cases, **Figure 1A**). This subgroup comprised 49.67% of wild-type FLT3 cases (N=80), hereafter FLT3-like patients. In the group of not FLT3-like patients, no differences were identified between the placebo and Quiza group in the total number of deaths (Fisher's p-value, 0.63), EFS (cox p-value, 0.83; HR 1.07 [0.56-2.06]), RFS (cox p-value 0.76; HR 0.88 [0.38-2.01]) and OS (cox p-value, 0.62; HR 1.22 [0.55-2.67]). Among FLT3-like patients, significant differences were identified in the total number of deaths (Fisher's p-value, 0.004), EFS (cox p-value, 0.009; HR 0.45 [0.25-0.82], RFS (cox p-value 0.01, HR 0.37 [0.18-0.79]) and OS (cox p-value 0.01, HR, 0.41 [0.20-0.84]) (**Figure 1B**). No statistically significant association was observed between the FLT3-like pattern and the ELN-17 classification: 30.4% were low risk, 40.5% intermediate risk, 29.1% high risk.

Conclusion
The FLT3-like gene expression signature successfully identified a subset of patients who derived the most benefit from Quiz, while patients without the FLT3-like signature did not demonstrate a benefit compared with placebo. These findings support the use of the FLT3-like signature as a potential biomarker to identify those wild-type FLT3 AML patients who may benefit from Quiz, providing a valuable insight for personalized treatment in AML.

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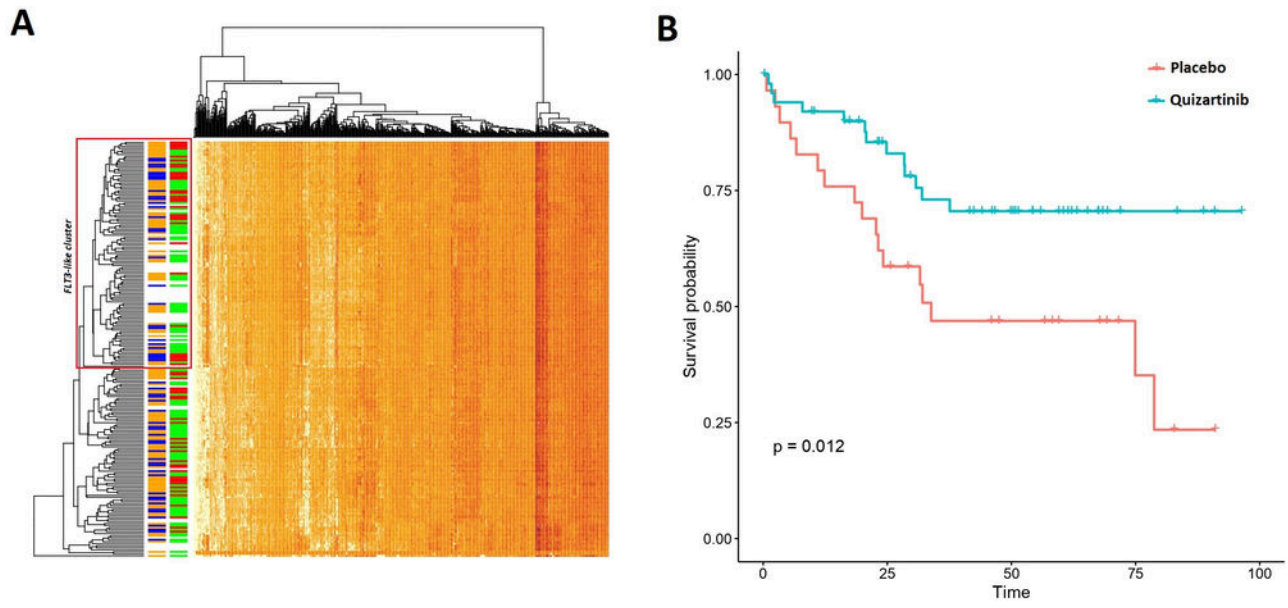

Figure 1. A) Heatmap representing the 595-signature in the 206 patients available for analysis. The top dendogram represents the hierarchical clustering of genes in the signature. The left side dendrogram represents the hierarchical clustering of samples according to the gene expression signature. Two colored row bars are represented. The left one represents the treatment arm in the clinical trial: quizartinib (orange), placebo (blue) and screening failure due to FLT3-mutation (white). The right one represents the status of patients at last follow-up: alive (green), death (red) and screening failure due to FLT3 mutation (white). The FLT3-like cluster is highlighted in the red box, an it is characterized by an enrichment in FLT3 mutant AML cases (71.1% of all FLT3-mutated cases). B) Kaplan-Meier plot representing the overall survival of patients in the FLT3-like cluster, indicating a superiority of quizartinib over placebo in this group.

Figure 1

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