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Blood 142 (2023) 6037–6039

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

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

Exploring Potential Molecular Mechanisms of Drug Response in FLT3-ITD Negative AML Patients Treated with Quizartinib Vs Placebo Plus Standard Chemotherapy in the 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], *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], *Jorge Labrador*[35], *David Martinez Cuadron*[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, Spain
[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] CIMA LAB Diagnostics, Universidad de Navarra, 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 Universitario de Burgos, Universidad Isabel I, Burgos, ESP
[36] Hospital Universitari i Politecnic La Fe, Valencia, Spain
[37] Hospital Universitari i Politecnic la Fe, Valencia, Spain

Introduction
Wild-type FLT3 AML presents significant therapeutic challenges due to limited treatment options. The QUIWI trial investigated quizartinib (Quiz) combined with standard chemotherapy, showing promising results. To understand drug response and refractoriness, we conducted a correlative analysis, exploring differential expression patterns among distinct patient groups. We reasoned that the molecular fingerprints of good responders to Quiz plus chemotherapy would be different with respect to patients who respond only to standard chemotherapy, helping to elucidate critical molecular mechanisms associated with Quiz response. Our study provides a basis for personalized therapeutic strategies in FLT3-ITD negative AML.

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, out of which 55 cases were FLT3-ITD and were discarded for this analysis. For this analysis, only samples with a minimum of 20% blasts were considered. The sequences were aligned to the GRCh37 reference genome using the Hisat algorithm. Differential expression was assessed with the DESeq2 algorithm, using Blast proportion to adjust for disparities among the samples. P-values were adjusted for multiple testing using the FDR method. OS was defined as time from start of screening to death. Gene ontology and pathways analysis were performed using the WebGestalt portal.

Results
In this study, we compared the gene expression profiles of Quiz versus placebo-treated patients categorized as good responders, defined arbitrarily as those who continue alive and have a minimum follow-up of 6 months after diagnosis. Out of 82 eligible patients, we identified 100 (q-value < 0.05) and 172 (q-value < 0.1) differentially expressed genes between the Quiz and Placebo groups. Notably, 132 genes were overexpressed in the Quiz group, while 40 genes showed overexpression in the placebo group. Moreover, we observed a highly significant overexpression of ribosomal genes in the Quiz group (17 overlaps, KEGG pathways q-value $< 2.2 \times 10^{-16}$), and a significant overexpression of genes related to the attenuation of the heat shock protein transcriptional response, which is involved in protein folding, in the placebo group (Reactome q-value, 0.008; gene ids: *HSPA1A*, *HSPA1B* and *DNAJB1*). Additionally, the Quiz group exhibited a significant overexpression of transmembrane receptor protein tyrosine phosphatase-related genes (Gene Ontology Molecular Function q-value, 0.02; gene ids: *PTPRB*, *PTPRG* and *PTPRU*).

Conclusion
This correlative analysis of the Quiwi trial revealed critical molecular mechanisms associated with Quiz response. The overexpression of ribosomal and transmembrane receptor protein tyrosine phosphatase-related genes in good responders within the Quiz group, along with the overexpression of the heat shock pathway genes in the placebo group, aligns with existing knowledge about the FLT3 pathway biology and the molecular determinants to tyrosine-kinase inhibitors. These findings offer potential biomarkers for personalized therapeutic approaches to improve clinical outcomes in this challenging AML population.

Disclosures Mosquera Orgueira: *Janssen:* Consultancy; *AstraZeneca:* Consultancy. **Bergua Burgues:** *Fundesalud. Grants of Europena funds.Daychii:* Research Funding; *Daychii:* Consultancy; *Hospital San Pedro de Alcántara. Servicio de Hematologia. Cáceres. SPAIN:* Current Employment. **Tormo:** *MSD:* Honoraria; *BMS:* Honoraria; *Astellas:* Honoraria; *Pfizer:* Honoraria; *AbbVie:* Honoraria. **Salamero:** *Abbvie:* Consultancy, Honoraria; *Astellas:* Consultancy, Honoraria; *Pfizer:* Consultancy, Honoraria; *Jazz:* Consultancy, Honoraria; *BMS:* Consultancy, Honoraria. **Ayala:** *Novartis:* Consultancy, Speakers Bureau; *Incyte:* Consultancy; *Astellas, BMS:* Speakers Bureau. **Montesinos:** *INCYTE:* Consultancy; *NERVIANO:* Consultancy; *Celgene:* Consultancy; *Jazz pharma:* Consultancy, Research Funding, Speakers Bureau; *Menarini-Stemline:* Consultancy, Research Funding; *Astellas:* Consultancy, Speakers Bureau; *BEIGENE:* Consultancy; *OTSUKA:* Consultancy; *Janssen:* Speakers Bureau; *BMS:* Consultancy, Other, Research Funding; *Daiichi Sankyo:* Consultancy, Research Funding; *Kura oncology:* Consultancy; *GILEAD:* Consultancy; *Abbvie:* Consultancy, Research Funding, Speakers Bureau; *Takeda:* Consultancy, Research Funding; *Novartis:* Consultancy, Research Funding; *Ryvu:* Consultancy; *Pfizer:* Consultancy, Research Funding, Speakers Bureau.

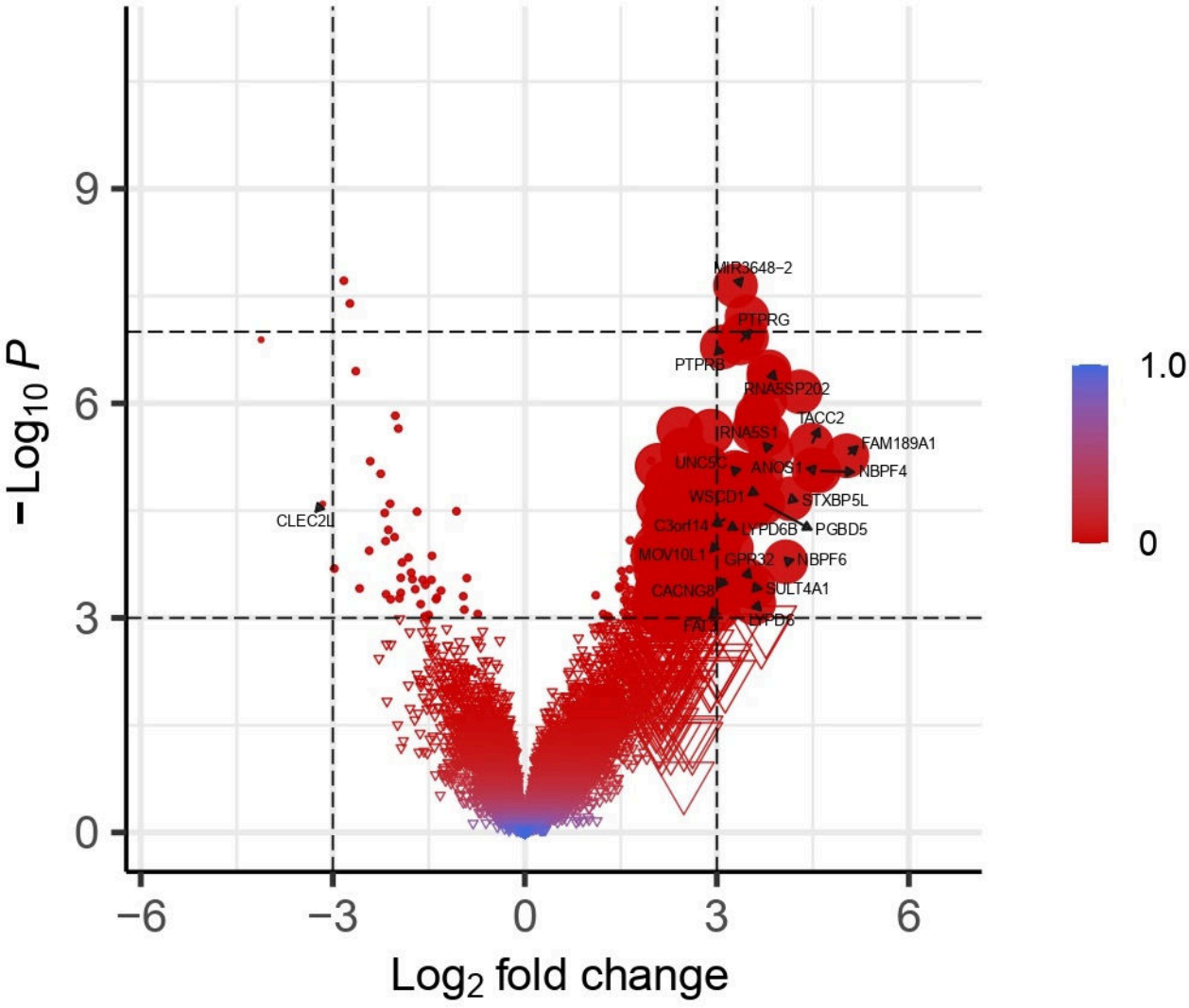

Figure 1. Volcano plot representing changes in gene expression between Quiz and Placebo good responders. Genes represented towards the righ of the plot were overexpressed in the Quiz group, and those towards the left were overexpressed in the Quiz group. Increasining point size and brighter red color correspond with lower p-values. The most significant genes with absolute Log2 fold changes >3 are indicated.

Figure 1

https://doi.org/10.1182/blood-2023-180710