ENHANCED VALIDATION OF THE FLT3-LIKE GENE EXPRESSION SIGNATURE AS A PREDICTIVE BIOMARKER FOR QUIZARTINIB RESPONSE IN FLT3-ITD NEGATIVE ACUTE MYELOID LEUKEMIA: EXPANDED COHORT AND EXTENDED FOLLOW-UP FROM THE PETHEMA QUIWI-TRIAL

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INTRODUCTION

The identification of predictive biomarkers is crucial for guiding treatment decisions in acute myeloid leukemia (AML). Previously, we identified an ***FLT3-like* gene expression signature** in ***FLT3* wild-type AML** patients, which clustered a proportion of patients with *FLT3*-ITD and TKD mutated cases. The QUIWI trial, a randomized, placebo-controlled, phase II study (n=273), showed a significant increase in overall survival (OS) in *FLT3*-ITD negative AML patients treated with the *FLT3* inhibitor quizartinib (Quiza) plus intensive chemotherapy (3+7). Our initial study including 161 randomized patients in the QUIWI demonstrated that the *FLT3*-like signature could predict responses to Quiza, highlighting its potential as a biomarker for personalized treatment in AML.

AIM

- To evaluate the role of the *FLT3*-like profile in the original discovery cohort, using **extended follow-up** of patients treated with Quiza.
- To **validate** the *FLT3*-like profile in new patients from the QUIWI clinical trial, assessing its utility as a predictive biomarker for Quiza response.
- To explore the relationship between the *FLT3*-like profile and *NPM1* and *DNMT3A* mutations, determining how these interactions influence the predictive power for Quiza response.

RESULTS

The first step was to evaluate the outcomes of patients in the original training set (N=161) with longer patient follow-up (median follow-up of 3.20 years and median OS was not yet reached). Within the *FLT3*-like cluster (N=80), a significant benefit for Quiza over placebo was observed with a p-value of 0.002 and a hazard ratio (HR) of 0.34 (95% CI: 0.17-0.68). No benefit for Quiza over placebo was observed in the non-*FLT3*-like cluster (p-value=0.43, HR 1.35, 95% CI: 0.64-2.84).

Next, we used the *FLT3*-clusterization to identify *FLT3*-like patients among the 87 newly sequenced cases. 24 cases (27.6%) were identified as *FLT3*-like, and these patients showed a **significant benefit for Quiza over placebo (p-value 0.02, HR 0.08, 95% CI: 0.01-0.71).** Among these, 50% of cases harbored *NPM1* mutations, and 29% had concurrent *DNMT3A* mutations, but a tendency for better response to Quiza was observed independently of these mutations.

Finally, when merging the two cohorts (N=248), a significant benefit for Quiza over placebo was observed in the *FLT3*-like group (N=104) with a p-value<0.001, an HR of 0.27, and a 95% CI of 0.14-0.52. This effect was **independent of *NPM1* and *DNMT3A* mutations** (p-value <0.001).

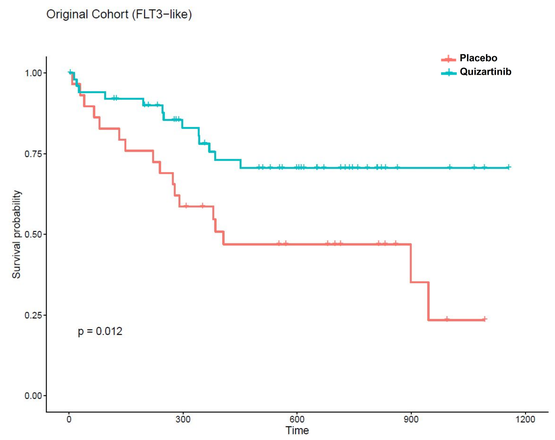

Figure 1: Kaplan-Meier plot of OS comparing Quiza and Plac. in FLT3-like patients from the original cohort with extended follow-up.

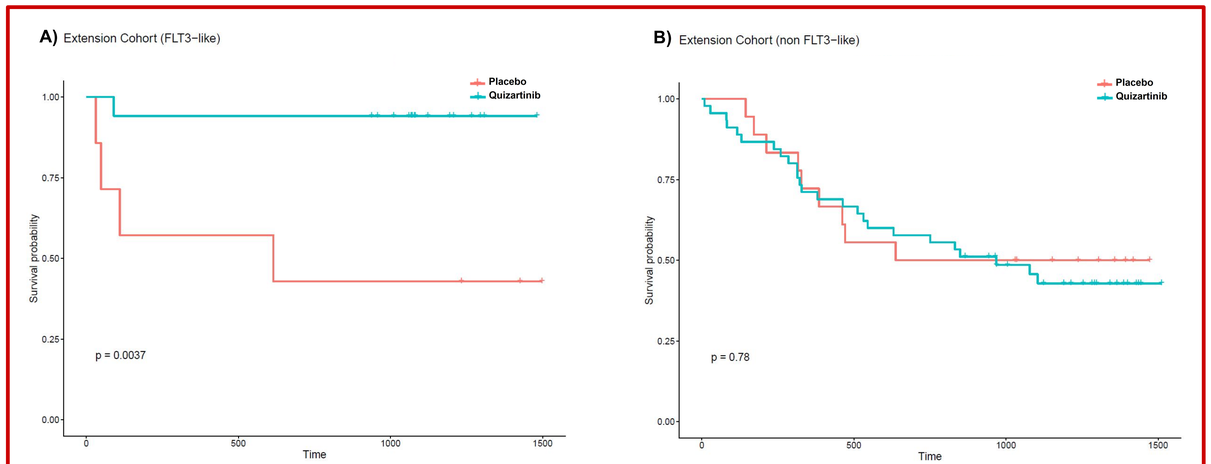

Figure 2: Kaplan-Meier comparison of overall survival between Quizartinib and Placebo in FLT3-like (**A**) and non-FLT3-like (**B**) patients from the expansion cohort.

METHODS

In this final report, we analyzed a total of 248 patients randomized in the QUIWI clinical trial, including an extended follow-up of the initial patient set (N=161) and an additional set of 87 patients included in the trial. RNA was extracted using standard methods, followed by an assessment of nucleic acid integrity (TapeStation) and quantification (Qubit). Total mRNA sequencing was performed using polyA RNA-seq with TruSeq technology. 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 and log2 normalized. The original *FLT3*-like signature (595 genes) was selected for downstream analysis. The method to assign new patients to predefined clusters involved calculating the distances between the new samples and the centroids of the existing groups, and then assigning the new samples to the group with the nearest centroid. OS was defined as the time from start of screening to death.

CONCLUSIONS

Our study **confirms the predictive value of the *FLT3*-like signature for identifying *FLT3*-ITD negative AML patients who benefit from Quiza**. The extended follow-up reinforces the significant survival benefit observed in *FLT3*-like patients treated with Quiza. Furthermore, the identification of new *FLT3*-like patients who exhibited superior response to Quiza over placebo validates the robustness of the *FLT3*-like clusterization method. This predictive strategy was effective regardless of *NPM1* or *DNMT3A* mutation status, supporting its potential use in personalized treatment approaches for *FLT3*-ITD negative AML.

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