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MUTATIONS OF UNKNOWN SIGNIFICANCE IN THE FOXO AND EGFR SIGNALING PATHWAYS IN PATIENTS WITH CML

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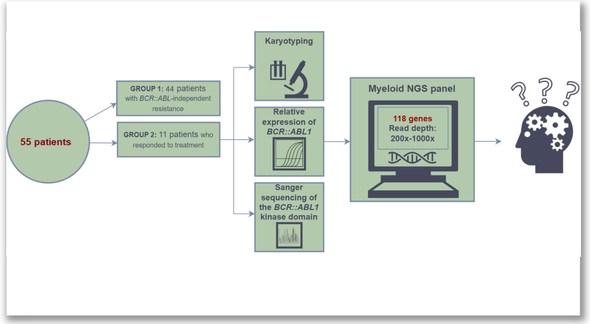
INTRODUCTION

To overcome *BCR::ABL* inhibition, alternative signaling pathways may be activated in Ph-positive cells to compensate for the loss of *BCR::ABL* kinase activity. Therefore, Ph-positive cells will be able to proliferate and survive despite effective *BCR::ABL* inhibition. Various mutations in participating genes can lead to the activation of alternative signaling pathways.

AIM

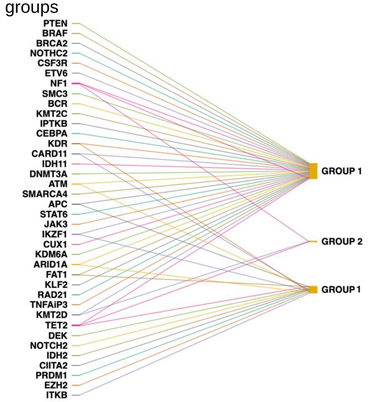
Using NGS data annotation, identify *BCR::ABL*-independent genes with mutations of unknown clinical significance (VUS) and evaluate their impact on the development of resistance to tyrosine kinase inhibitor therapy.

METHOD

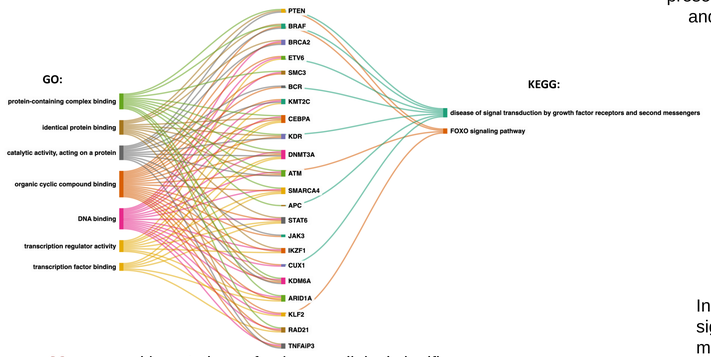


RESULTS

Mutations in the ***TET2, KMT2D*** and ***NF1*** genes occur in all groups

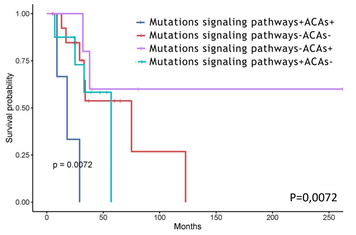


Annotation of genes with mutations of unknown clinical significance



29 genes with mutations of unknown clinical significance
31% of genes are associated with FOXO and EGFR pathways

Event-free survival of patients in group 1 depending on the presence of mutations in genes participating in the FOXO and EGFR and ACAs signaling pathways and ACAs



In 60% of patients with VUS in the FOXO or EGFR signaling pathways, MMR was never achieved despite multiple lines of therapy (p=0.023). It has also been noted that patients with FOXO or EGFR mutations have more than two ACAs.

CONCLUSIONS

The presence of mutations of unknown significance in genes involved in the FOXO and EGFR signaling pathways in combination with ACAs significantly reduces overall and event-free survival, which emphasizes their importance in the formation of resistance to TKIs.

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