## Abstract: P397

# Title: IKZF1 ALTERATIONS HAVE A NEGATIVE IMPACT ON EARLY MOLECULAR RESPONSE AND SURVIVAL OF ADULT PATIENTS WITH B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH GMALL 07/2003 PROTOCOL IN CZECHIA

**Abstract Type: Poster Presentation**

**Session Title: Acute lymphoblastic leukemia - Clinical**

**Background:**

Alterations of *IKZF1* encoding IKAROS are associated with poor outcome of high risk B-progenitor acute lymphoblastic leukemia (ALL) including *BCR::ABL1*-positive (Ph+) and Ph-like ALL patients (review Churchman and Mullighan 2017). Co-occurrence of *IKZF1* deletions (*IKZF1*$^{del}$) with at least one other gene deletion (*CDKN2A, CDKN2B*, *PAX5* or *PAR1*) in the absence of *ERG* deletion was defined as *IKZF1*$^{plus}$. Presence of *IKZF1*$^{plus}$ represented a very-poor prognostic factor of outcome in pediatric ALL (Stanulla et al 2018).

**Aims:**

This work of the Czech Leukemia Study Group for Life is focused on 79 adult B-ALL patients treated with GMALL 07/2003 protocol (and with imatinib in Ph+ ALL). The aim is to analyse prognostic significance of *IKZF1* alterations on molecular response at week 11 (W11) and overall survival (OS).

**Methods:**

MLPA was performed in 38 Ph+ and 41 Ph-negative (Ph-) ALL patients using kits P335, P202 and Coffalyser software (MRC Holland). Patients were divided into 4 groups: *IKZF1*$^{plus}$, *IKZF1*$^{del}$, MLPA positive excluding *IKZF1* (MLPA$^{pos}$) and MLPA negative (MLPA$^{neg}$). Molecular response was evaluated by quantification of clone-specific IG/TCR rearrangements or *BCR::ABL1* transcript. Measurable residual disease (MRD) achievement was defined as negative or positive quantifiable. Log-rank test, Kaplan-Meiers survival curves and Chi-square test were used for statistical evaluations.

**Results:**

*IKZF1*$^{del}$ and *IKZF1*$^{plus}$ had higher frequency in Ph+ ALL patients (42% and 34%, respectively) compared to Ph- ALL (7% and 7%, respectively). MLPA$^{plus}$ was detected more frequently in Ph- (29%) compared to Ph+ patients (11%).

OS was significantly shorter in Ph+ patients with *IKZF1*$^{plus}$ compared to other groups ($P$=0.04). All five MLPA$^{neg}$ patients are alive. The probability to achieve MRD at W11 was not significantly decreased in Ph+ patients with *IKZF1*$^{plus}$ and *IKZF1*$^{del}$ compared to MLPA$^{pos}$ and MLPA$^{neg}$. OS of patients not achieving MRD at W11 was reduced in *IKZF1*$^{plus}$ and *IKZF1*$^{del}$ group compared to MLPA$^{pos}$ and MLPA$^{neg}$ ($P$=0.07 and 0.08, respectively). However, despite achieving MRD at W11, *IKZF1*$^{plus}$ and *IKZF1*$^{del}$ patients had low probability of OS with a worse trend in *IKZF1*$^{plus}$.

Despite low numbers of Ph- patients with *IKZF1*$^{plus}$ (n=3) and *IKZF1*$^{del}$ (n=3), there was a clear trend to worse outcome in this group that is comparable to MLPA$^{pos}$ and contrasting with MLPA$^{neg}$ patients. A significant difference was found between *IKZF1*$^{plus}$ and MLPA$^{neg}$ patients ($P$=0.003). The probability to reach MRD at W11 was significantly lower in patients with *IKZF1*$^{plus}$ and MLPA$^{pos}$ ($P$=0.003). Irrespective of *IKZF1* status, all Ph- patients who did not achieve MRD at W11 had low probability of OS. Patients with *IKZF1* alterations and MRD response had lower probability of OS.

**Summary/Conclusion:**

*IKZF1* alterations were more frequent in Ph+ ALL. Their detection correlated with shorter OS in both Ph+ and Ph- ALL adults treated with GMALL 07/2003 protocol. Individuals with *IKZF*$^{plus}$ had the worse outcome. Importantly, *IKZF1* alterations were proven as a poor prognostic factor for OS despite the achievement of MRD at W11. *IKZF1* profiling should be performed regularly in B-ALL as there is a room for treatment intensification in *IKZF1*-altered patients.

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**Keywords:** Ph+ ALL, B cell acute lymphoblastic leukemia, ALL, Ikaros