XIX CONGRESSO NAZIONALE SIES 2026

Ectopic activation of *FOXF1* and *FENDRR* by t(14;16)(q32;q24) identifies a high-risk T-ALL/MPAL subtype.

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Palazzo degli Affari

Disclosures of Danika Di Giacomo

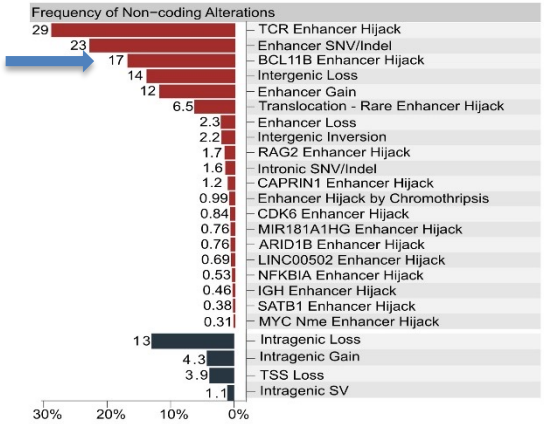
No conflicts of interest to disclose.

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

ACUTE LEUKAEMIAS OF MIXED OR AMBIGUOUS LINEAGE

- Acute leukemia of ambiguous lineage (ALAL) and mixed-phenotype acute leukaemia (MPAL) are grouped under a single category in view of their overlapping clinical features.

→ ALAL with *BCL11B-r* *(Di Giacomo et al 2021, Montefiori et al. 2021)*



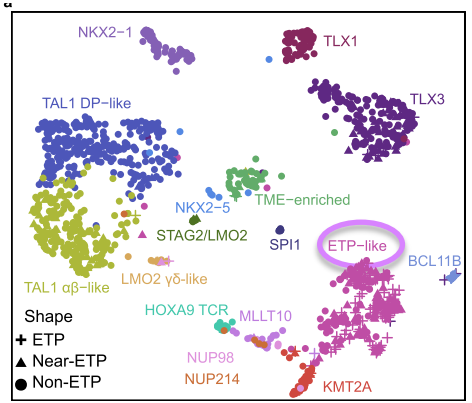
(Polonen et al 2024)

- the *BCL11B* enhancer is one of the most hijacked regulatory elements in T-ALL

EARLY T-CELL PRECURSOR ALL, ETP-ALL

- High-risk immature T-ALL, with a distinctive immunophenotype (cCD3$^+$, CD7$^+$, CD1a$^-$, CD8$^-$, myeloid/stem markers) and no unifying cytogenetic marker.

- Identification of novel oncogenic drivers has led to the expansion of ETP-ALL to “ETP-like” T-ALL with comparable gene expression profiles despite different immunophenotypes *(Polonen et al 2024)*.



(Polonen et al 2024)

Methods - Patients cohort

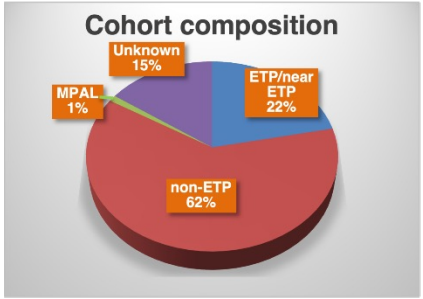
Cohort 1 - University of Perugia	
Total cases	**510***
Adults (>18y)	277
Childrens (≤18y)	233
Age range	1-78
M/F	380/130

*La Starza et al. 2020; Di Giacomo et al. 2021; unpublished cases

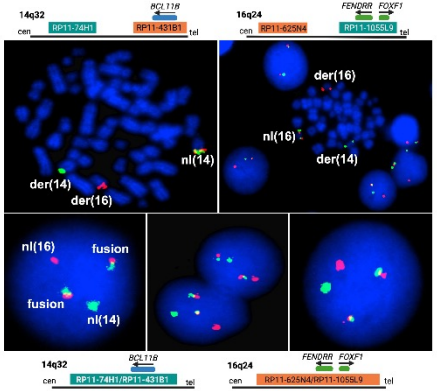
Cohort 2 - SJCRH	
Total cases	**1321****
Adults (>18y)	60
Childrens (≤18y)	1261
Age range	1-29
M/F	979/342

**Pölönen et al. 2024; Zhang et al. 2012

1831 T-ALL/MPAL cases



Molecular cytogenetics



WGS
6 cases

t(14;16)(q32;q24):
7 cases

M/F=10/3, 7-37 years old

Extramedullary localization in 10/13

Immunophenotype:

CD38+, cCD3+, CD7+, CD13+, CD10, cyCD79 and/or CD19 (10/11).

CD34-, CD1a-, CD4-; TdT- (9/11) CD8- (8/11)

Diagnosis: 7 ETP-ALL, 2 ETP-like, 4 MPAL

Refractory to frontline therapies

Methods - Molecular characterization of a novel t(14;16)(q32;q24)

Multiomic approach

Genomics
- WGS/Custom NGS

Mutations, CNV, Chromosome rearrangements

Transcriptomics
- RNA-seq
- scRNA-seq

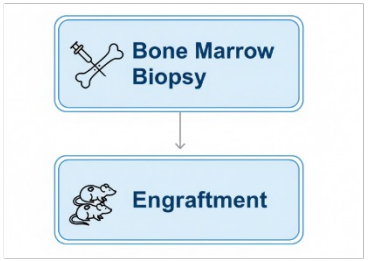
Clustering, Differential Expression Analysis, Clonal heterogeneity

Epigenomics
- H3K27ac HiChIP
- ATAC-seq
- ChIP-seq

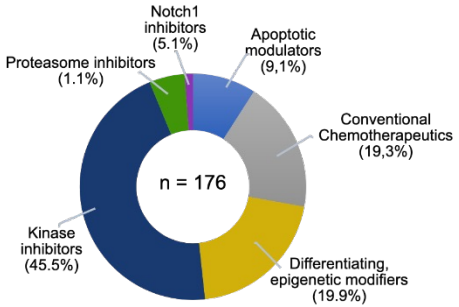
Long-range interactions
Chromatin accessibility
Binding site mapping

Therapeutic vulnerability assessment

PDX generation



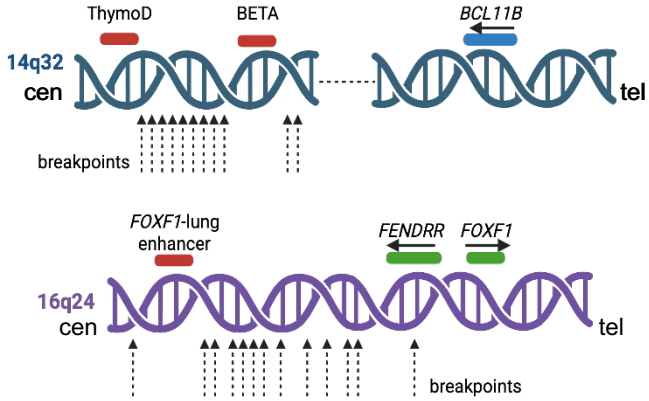
Drug Response Profiling



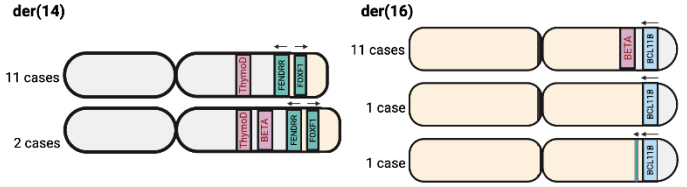
Ex vivo validation of selected compounds and cellular signaling dependencies

Results - The t(14;16)(q32.2;q24) juxtaposes *FOXF1/FENDRR* with the *BCL11B* enhancer on der(14)

Breakpoints were located between the ThymoD enhancer and *BCL11B* on chr14 and centromeric to *FOXF1* on chr16 in all 13 cases.



The translocation moves *FOXF1/FENDRR* onto der(14), with *BCL11B* reciprocally relocated to der(16).



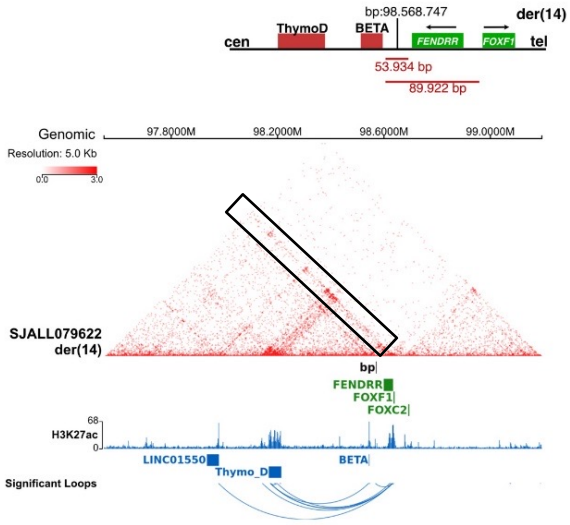
- cryptic in 12 of 13 cases
- mutually exclusive with all established cytogenetic subtype-defining alterations in T-ALL, suggesting it is the ***primary oncogenic driver alteration***.

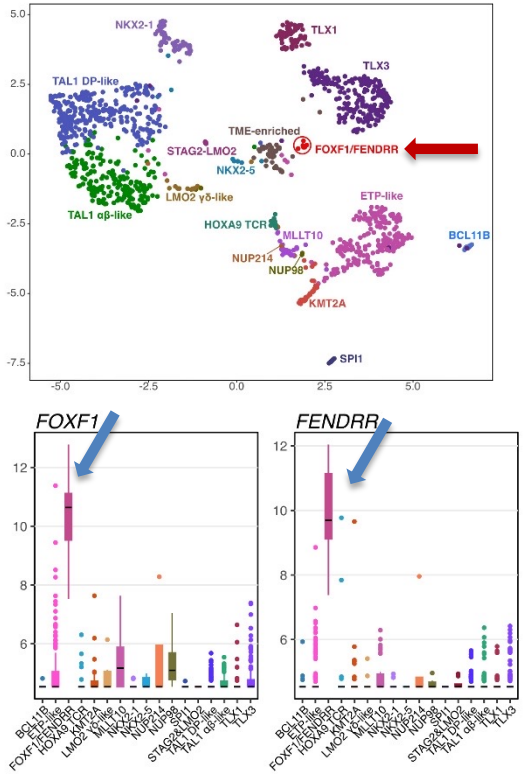
ThymoD: *BCL11B* enhancer

BETA: *BCL11B Enhancer Tandem Amplification – BCL11B*-a

Results - The t(14;16)(q32.2;q24) enables aberrant long-range enhancer–promoter interactions and identifies a distinct molecular subgroup.

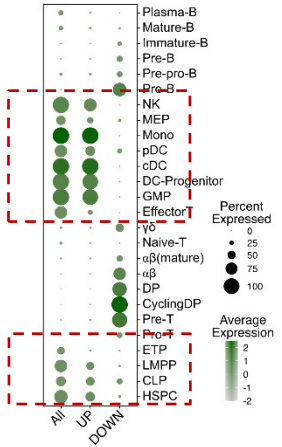
Regulatory long-rage interaction between ***BCL11B*** elements and the ***FOXF1/FENDRR*** locus on der(14).





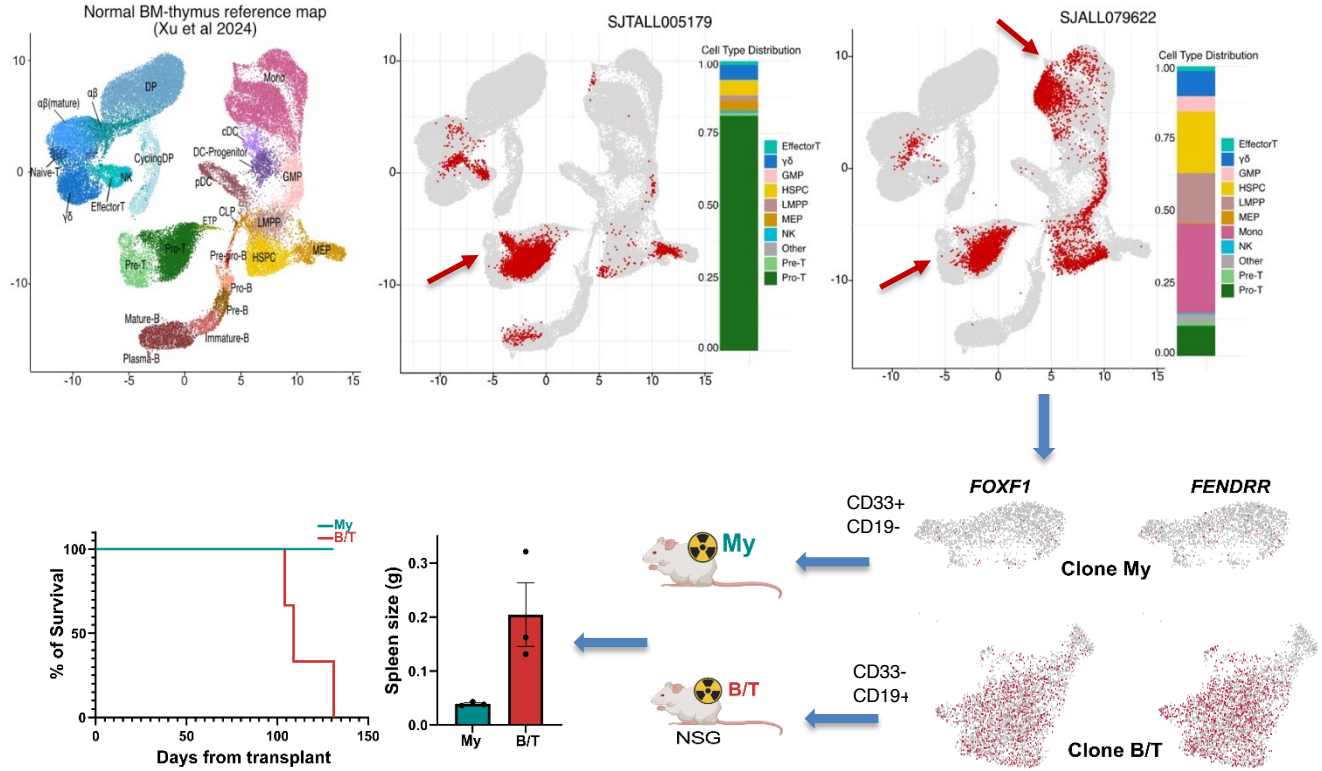
The upregulation of *FOXF1* and *FENDRR* characterizes this subtype

"*FOXF1/FENDRR*" ALL



- Early developmental arrest
- Shift towards non-T programs

Results - *FOXF1/FENDRR* leukemia shows clonal heterogeneity and lineage plasticity

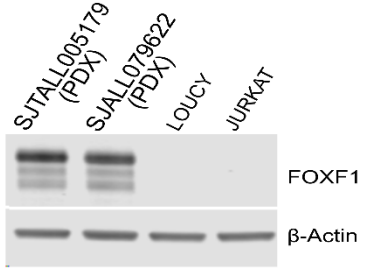


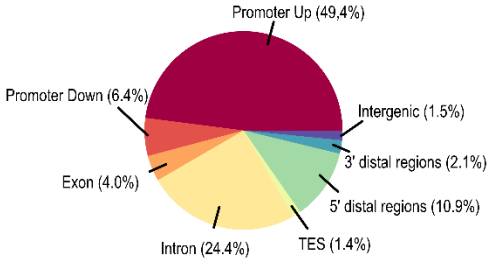
- Intra-tumoral and inter-sample transcriptomic variability
- Pro-T transcriptional signature

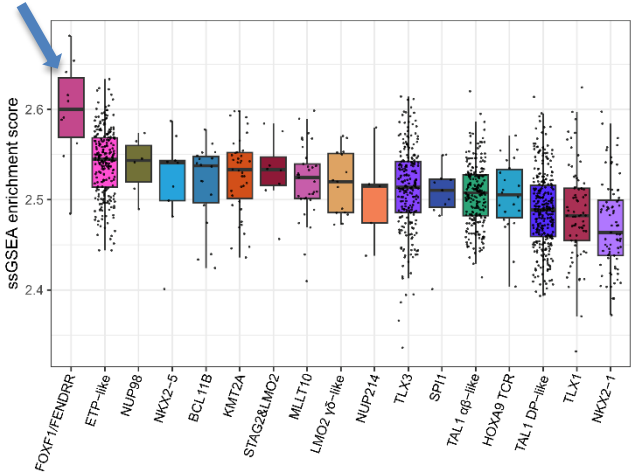
Engraftment of the lymphoid clone expressing *FOXF1/FENDRR*

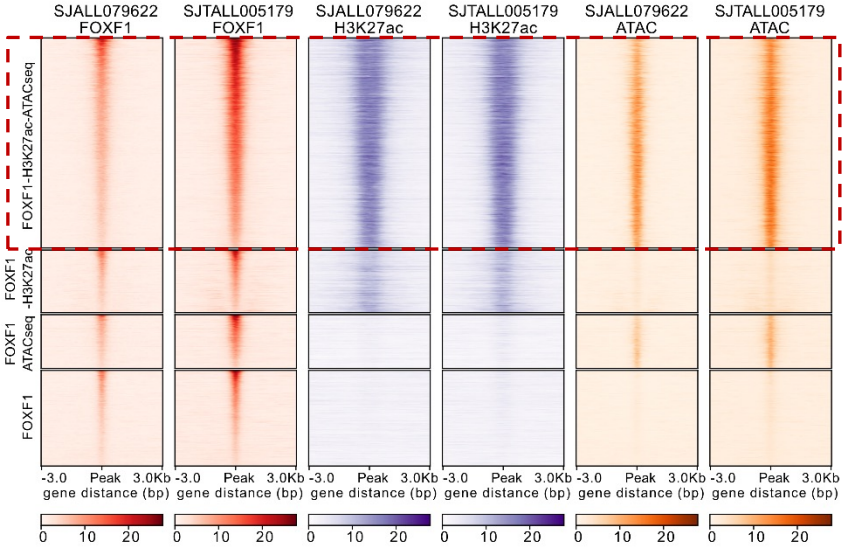
Results - FOXF1 drives the transcriptional program of *FOXF1/FENDRR* ALL

FOXF1 mostly binds at promoter regions (55,8%)





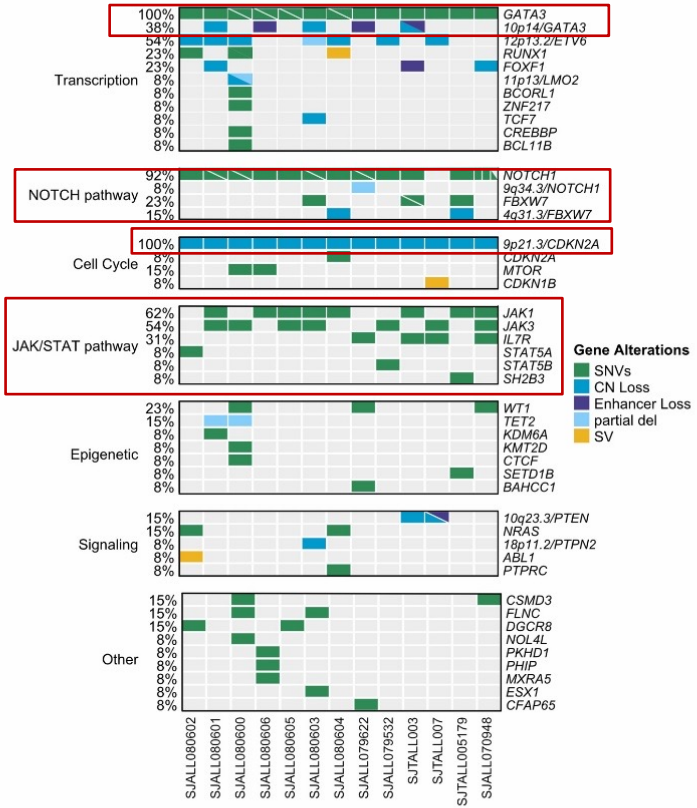




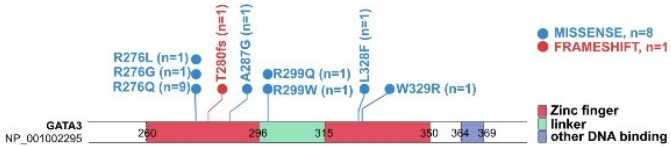
FOXF1 binds transcriptionally active genomic sites

FOXF1 targets are specifically enriched in the signature of the *FOXF1/FENDRR* ALL

Results – *FOXF1/FENDRR*-ALL cases share recurrent genomic lesions



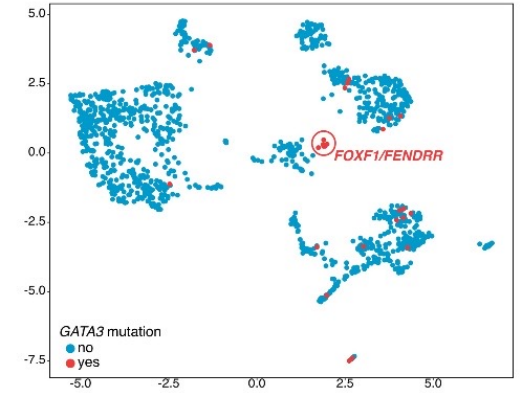
- *CDKN2A/B* del (13/13)
- JAK/STAT pathway mut (13/13)
- NOTCH1 pathway mut/del (12/13)
- *GATA3* mut/del (13/13)



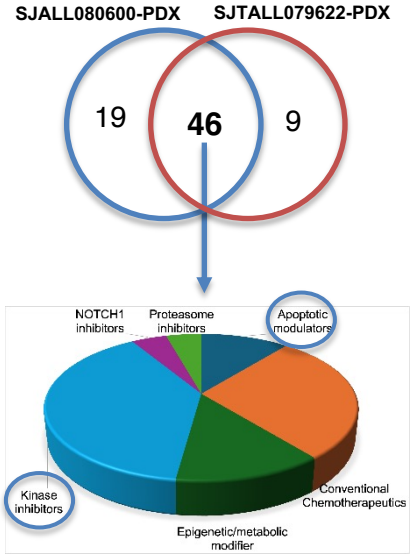
DNA binding domain

- *GATA3* bi-allelic inactivation in 5/13 cases

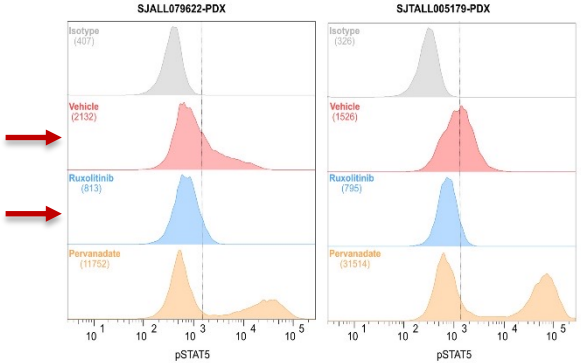
- *GATA3* mutations are specifically associated with the *FOXF1/FENDRR*-ALL subtype



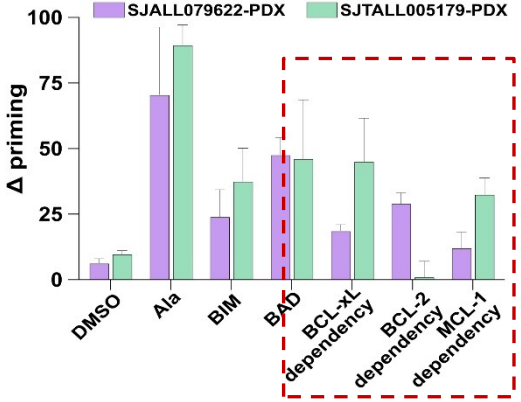
Results - *FOXF1/FENDRR* ALL show sensitivity to BCL-family and JAK/STAT pathway inhibitors

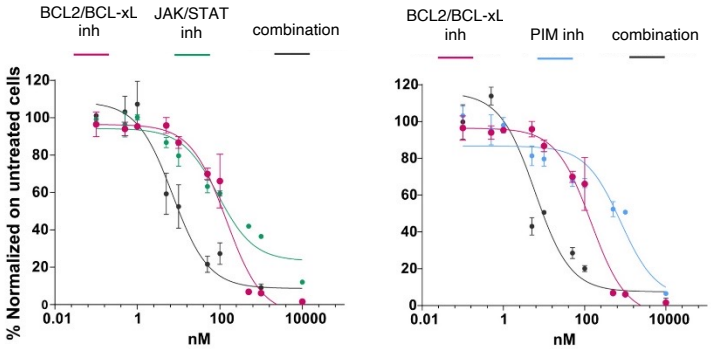


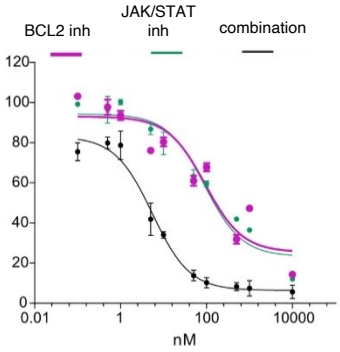
JAK/STAT dependency

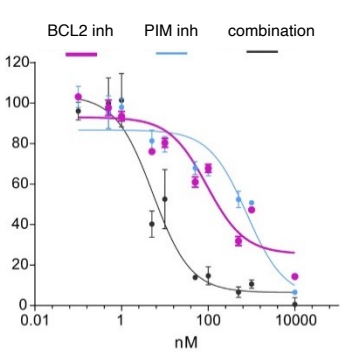


BCL-family dependency









Conclusions

- The **t(14;16)(q32;q24)** is the cytogenetic hallmark of a new subgroup of **high-risk** lineage ambiguous leukemia
- In this novel subtype *FOXF1/FENDRR* expression is de-regulated through juxtaposition to *BCL11B* regulatory elements: ***FOXF1/FENDRR*-ALL**
- FOXF1 genomic occupancy sustain the unique gene expression program of *FOXF1/FENDRR*-ALL
- *CDKN2A/B* deletion, *GATA3* loss of function, mutations affecting the JAK/STAT and NOTCH1 pathways are common co-occurring genomic events in this subtype
- Inactivation of **GATA3** has a role in the immunophenotypic and transcriptomic perturbations observed in *FOXF1/FENDRR* leukemia, resulting in the arrest of T-cell precursors at a pre-commitment stage.
- Combination therapies based on anti-apoptotic inhibitors targeting the BCL-family proteins and JAK/STAT inhibitors may represent a promising strategy in *FOXF1/FENDRR*-ALL.
- *FOXF1/FENDRR*-ALL is a clinically relevant entity that should be incorporated into the diagnostic workflow of immature acute leukemia

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