Measurable Residual Disease-dependent Unfavorable Outcomes in Pediatric PAX5-rearranged B-ALL

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AIEOP
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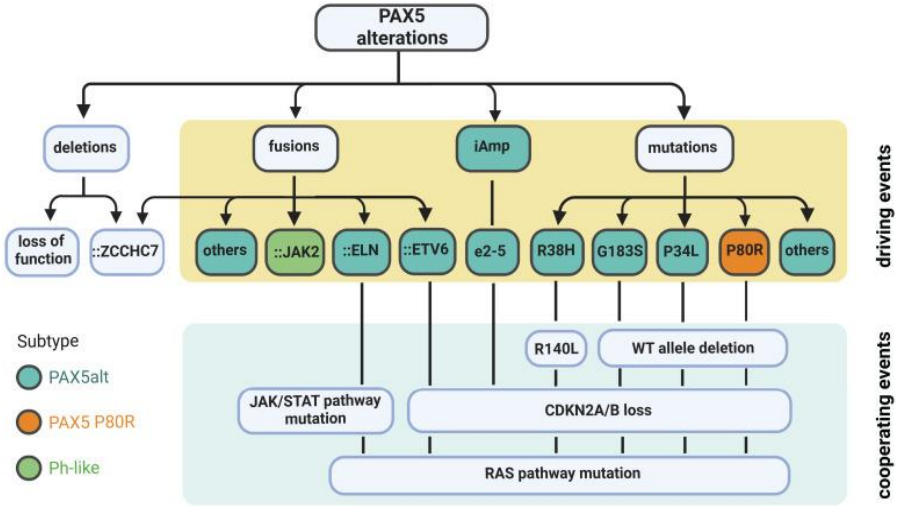
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Disclosures of Nicolò Peccatori

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

Background

- *PAX5*: a master regulator of B-cell development and leukemogenesis
- *PAX5* alterations in 30% of B-ALL
- Two novel molecular ALL subtype:
  - *PAX5 P80R*
  - *PAX5*-Alt
- Intermediate outcomes for *PAX5*-Alt
- Limited evidence on the prognostic value of *PAX5* fusion genes in pediatric ALL



PAX5-driven ALL AIEOP Cohort

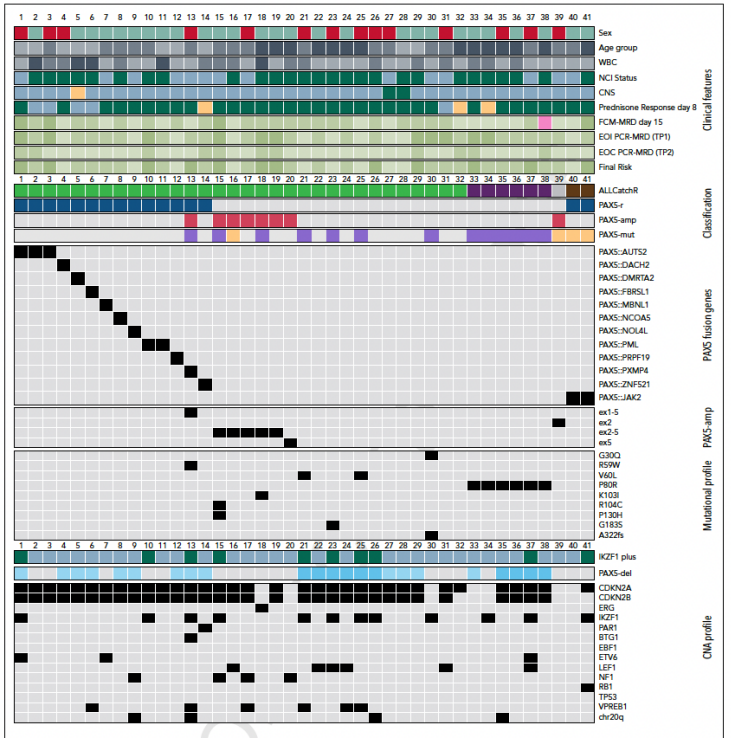
Comprehensive genetic analyses (RNA-seq+CNA) on 465 newly-diagnosed B-ALL pts

41 *PAX5-driven* patients

- 6 PAX P80R patients
- 33 PAX5-alt patients (PAX5-r, -amp, -mut) (6%)
- 2 *PAX5::JAK2* patients (Ph-like)

Outcomes (3-years EFS)

- PAX5 P80R → 100%
- *PAX5*-alt → 76.7±7.8%
- *PAX5*-r → 67.3±14%



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Multinational retrospective study to investigate clinical and prognostic value of PAX5-r in pediatric ALL

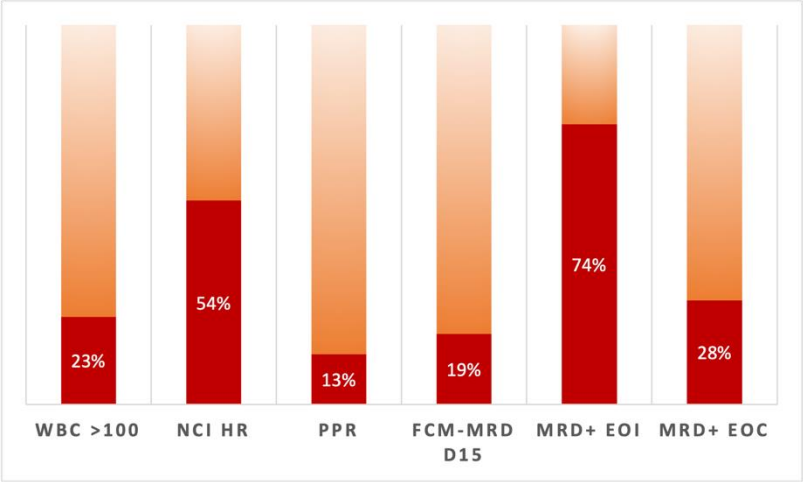
- 159 newly diagnosed pediatric *PAX5*-r ALL patients
- Consecutive AIEOP-BFM ALL trials (2000, 2009, 2017)
- 2002-2024 in Italy, Germany and Austria

- *PAX5* fusion genes were identified
  - Retrospectively by cytogenetics, FISH, SNP-array or targeted RNA-seq until 2018
  - Prospectively by WTS or targeted RNA-seq from 2018 onwards

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Clinical and biological features of *PAX5*-r ALL

- Median age 3.4 years; males 66.7%
- High rates of hyperleukocytosis and NCI HR
- Tendency toward slow treatment response



- Enrichment in IKZF1plus profile (15.7%)
- 60 different PAX5 fusion gene partners (JAK2, NOL4L, AUTS2, ETV6…)

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Comparative analyses in the AIEOP-BFM ALL 2017 trial

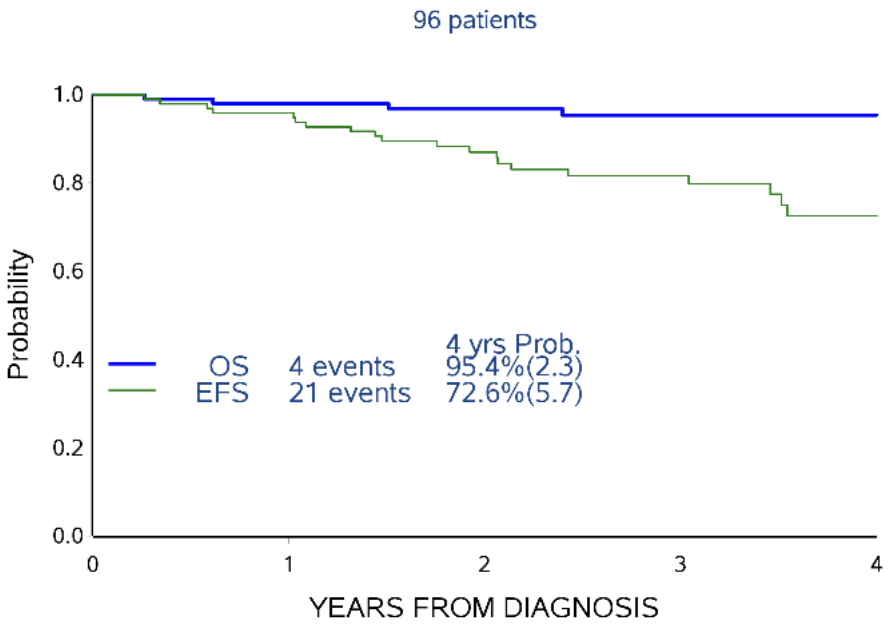
Characteristics	Expanded PAX5-r cohort (n = 159)	AIEOP-BFM ALL 2017		P value*
		PAX5-r ALL (n = 96)	Non-PAX5-r ALL (n = 1948)	
Sex				
Male	66.0% (105/159)	63.5% (61/96)	54.9% (1069/1948)	.096
Female	34.0% (54/159)	36.5% (35/96)	45.1% (879/1948)	
Age at diagnosis, y				
<1	3.8% (6/157)	6.3% (6/96)	3.6% (70/1948)	**.32** (<1 vs 1-9 vs 10-17 y)
1-5	64.3% (101/157)	63.5% (61/96)	55.7% (1085/1948)	
6-9	12.7% (20/157)	9.4% (9/96)	16.1% (314/1948)	
10-17	19.1% (30/157)	20.8% (20/96)	24.6% (479/1948)	
Not known	2/159	—	—	
WBC at diagnosis $\times 10^9$/L				
Median (range)	22.3 (0.48-537)	25.6 (0.7-537)	9.9 (0.1-1000)	**<.001**
<20	46.5% (73/157)	44.8% (43/96)	65.9% (1283/1946)	**<.001** (<100 vs ≥100)
20-100	30.6% (48/157)	32.3% (31/96)	26.1% (507/1946)	
≥100	22.9% (36/157)	22.9% (22/96)	8.0% (156/1946)	
Not known	2/159	—	2/1948	
NCI criteria†				
Standard	46.5% (74/159)	42.7% (41/96)	60.9% (1186/1948)	**<.001**
High	53.5% (85/159)	57.3% (55/96)	39.1% (762/1948)	
CNS involvement				
No (CNS1/2)	96.7% (145/150)	95.6% (87/91)	97.6% (1808/1852)	.28
Yes (CNS3)	3.3% (5/150)	4.4% (4/91)	2.4% (44/1852)	
Not known	9/159	(5/96)	(96/1948)	
IKZF1^{plus}‡				
Negative	84.0% (100/119)	85.3% (81/95)	92.2% (1742/1889)	**.015**
Positive	16.0% (19/119)	14.7% (14/95)	7.8% (147/1889)	
Not known	40/159	(1/96)	(59/1948)	
Prednisone response, day +8§				
Good	86.5% (134/155)	85.1% (80/94)	94.3% (1763/1870)	**<.001**
Poor	13.5% (21/155)	14.9% (14/94)	5.7% (107/1870)	
Not known	4/159	(2/96)	(78/1948)	
Flow cytometry MRD, day +15				
<0.1%	29.8% (39/131)	30.0% (27/90)	34% (636/1869)	.43
0.1%-10%	51.1% (67/131)	51.1% (46/90)	51.7% (966/1869)	
≥10%	19.1% (25/131)	18.9% (17/90)	14.2% (267/1869)	
Not known	28/159	(6/96)	(79/1948)	

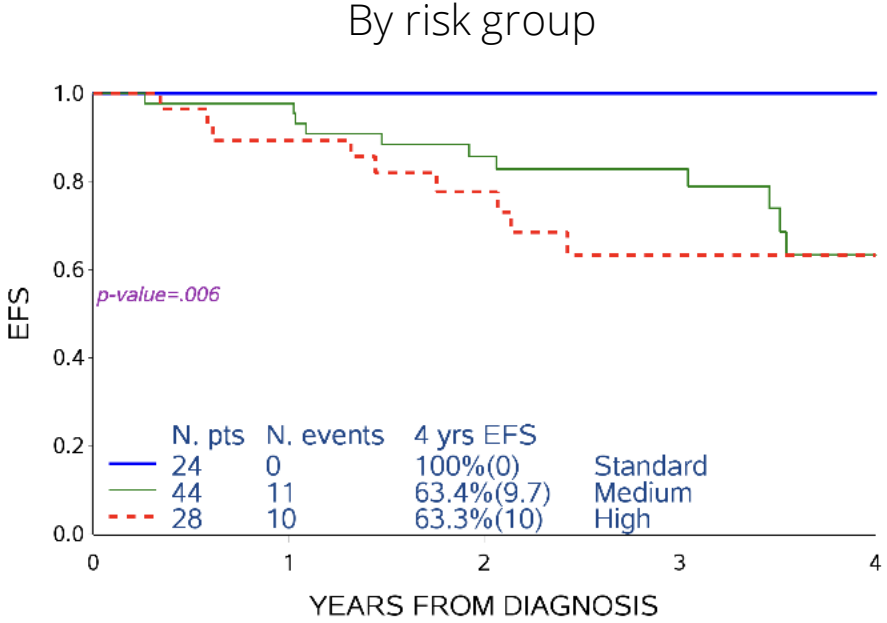
- 96 *PAX5*-r *vs* 1948 non-*PAX5*-r ALL patients
- Hyperleukocytosis, NCI HR and IKZF1^{plus} status were statistically significant higher in the *PAX5*-r ALL
- No differences in terms of MRD-based treatment response and risk stratification

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Outcomes

96 PAX5-r ALL pts enrolled in the AIEOP-BFM ALL 2017 trial (median FU 3.2 yrs)

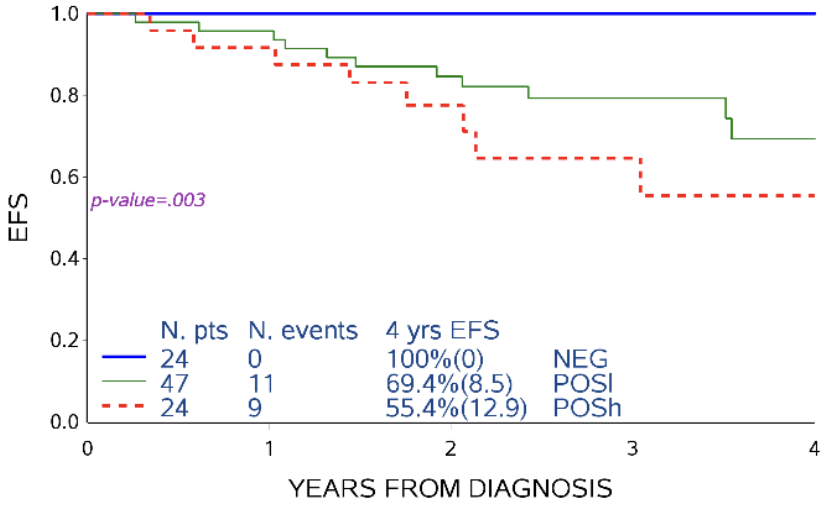




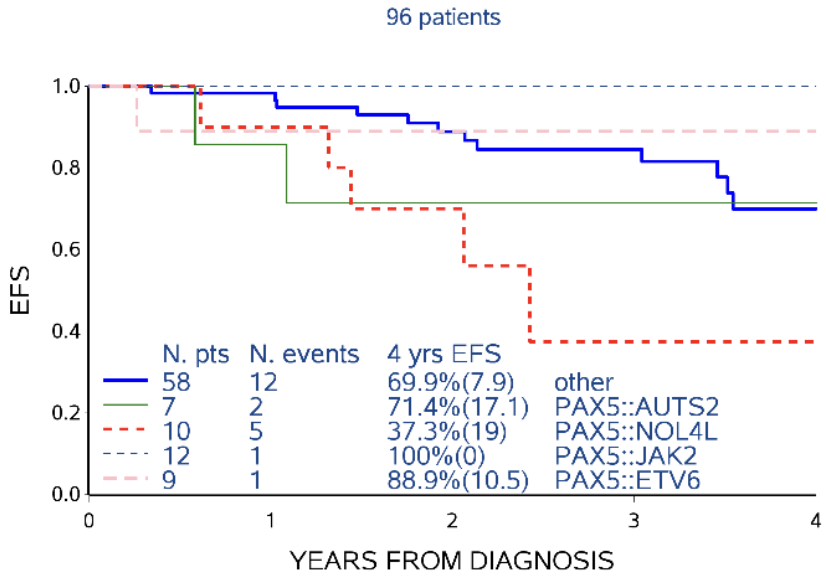
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Outcomes

By EOI-MRD



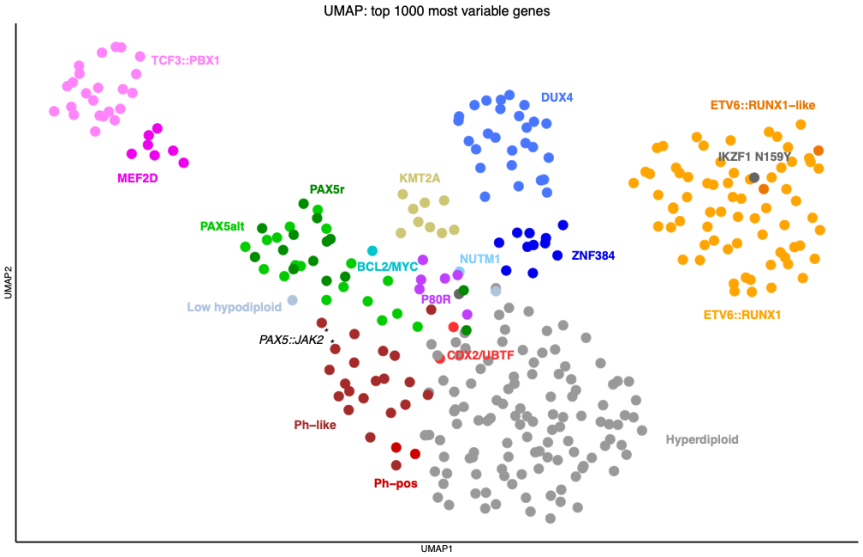
By PAX5 fusion gene partner

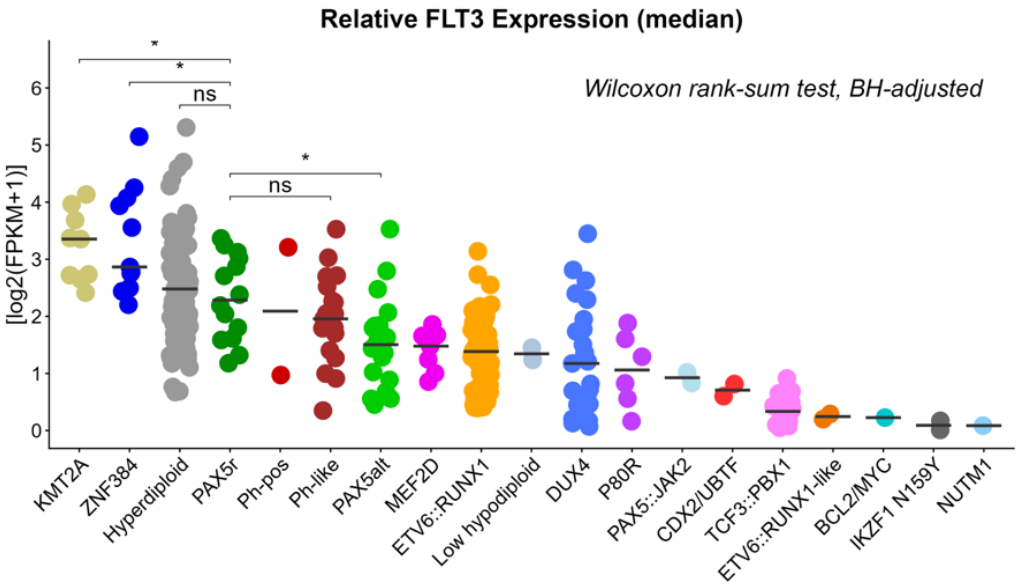


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FLT3 as a potential target in PAX5-r ALL

Gene expression profiling of *PAX5*-r ALL in the AIEOP cohort

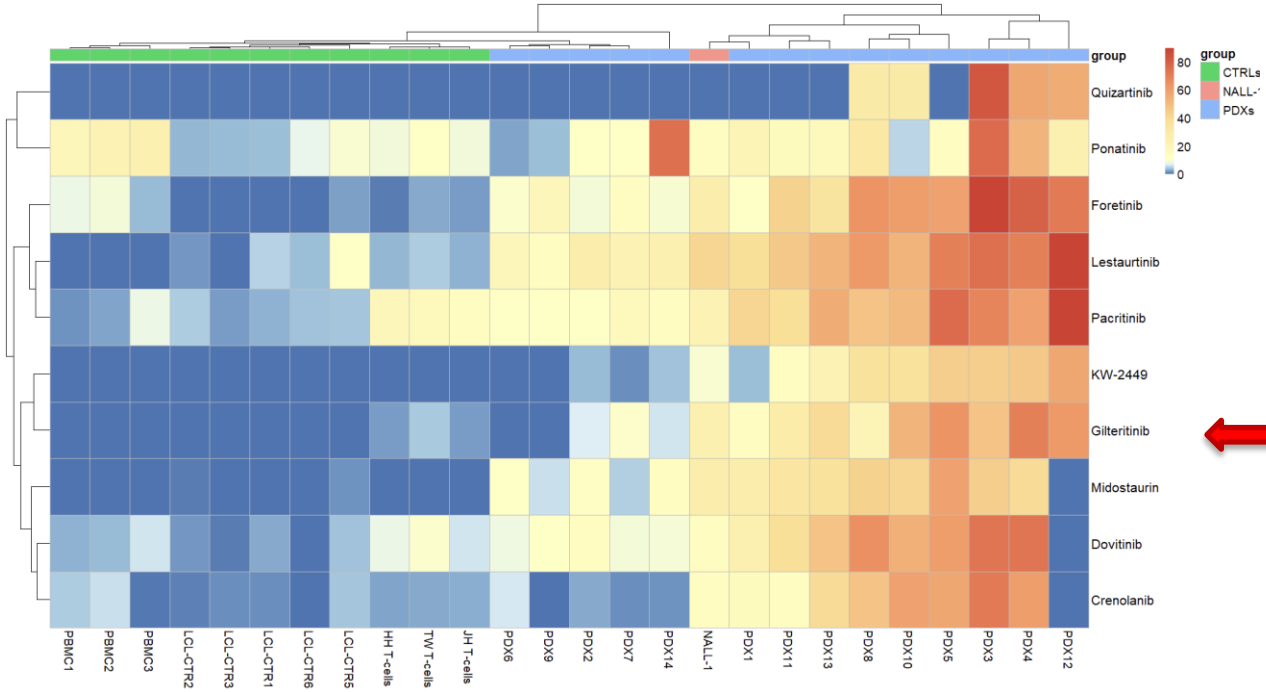




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FLT3 targeting in *PAX5*-r ALL

High throughput drug screening

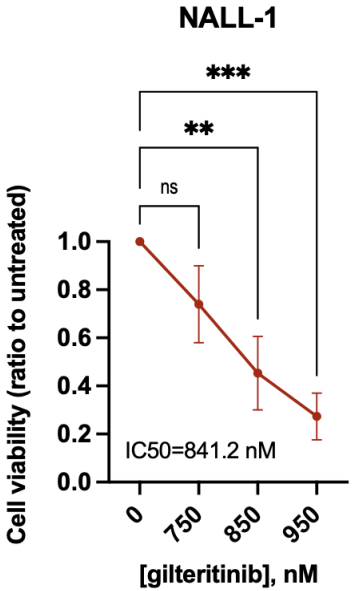


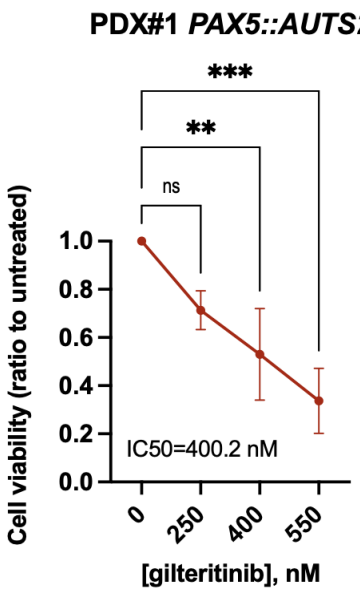
Gilteritinib showed favorable *in vitro* efficacy/hematologic toxicity profile

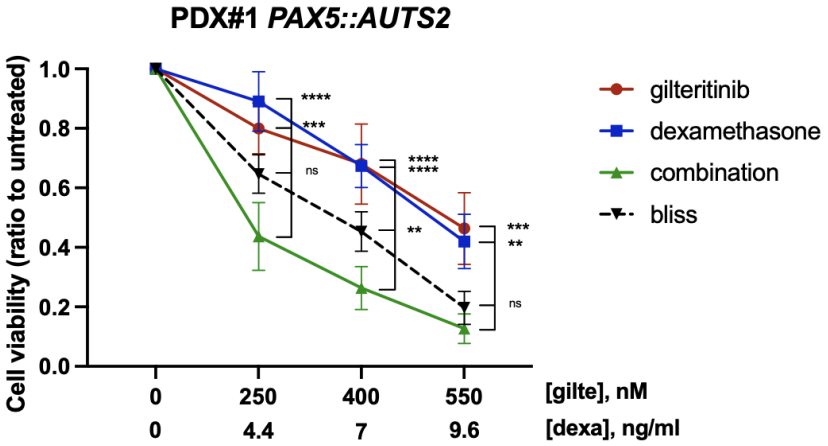
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In vitro and *ex vivo* efficacy of Gilteritinib

Cell viability experiments with gilteritinib







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Conclusions

- Our data define pediatric *PAX5*-r ALL as a high-risk molecular subgroup of B-ALL, characterized by an MRD-dependent poor prognostic profile.

- FLT3 overexpression emerged as a potential actionable target that warrants further investigation.

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LYMPHOID NEOPLASIA

Measurable residual disease–dependent unfavorable outcomes in pediatric *PAX5*-rearranged B-acute lymphoblastic leukemia

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SCAN ME

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Sistema Socio Sanitario Regione Lombardia
FONDAZIONE TETTAMANTI ONLUS
AIEOP-BFM ALL Study group
AIRC
UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA
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- Martin Zimmermann
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Austria-BFM group

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