

Supplementary Information

Supplementary Table 1 – Baseline characteristics and clinical response of patients of the GRAALL/FRALLE cohorts

	<i>PI3KS^{ALT}</i>	<i>PI3KS^{WT}</i>	Overall	<i>p-value</i> ²
Variable	n = 87 (18%)	n = 389 (82%)	n = 476	
Age (y) ¹	14.6 (3.2-57.2)	15.3 (1.1-59.1)	15.3 (1.1-59.1)	0.21
Male	66 / 87 (76%)	291 / 389 (75%)	357 / 476 (75%)	0.89
Median WBC (G/l) ¹	116 (1-770)	51 (0-980)	64 (0-980)	<0.001
CNS Involvement	14 / 86 (16%)	37 / 388 (10%)	51 / 474 (11%)	0.082
Immunophenotype				<0.001
Immature (IM0/δ/γ)	5 / 75 (7%)	84 / 344 (24%)	89 / 419 (21%)	
IMβ/pre-αβ	33 / 75 (44%)	178 / 344 (52%)	211 / 419 (50%)	
Mature TCRγδ	7 / 75 (9%)	46 / 344 (13%)	53 / 419 (13%)	
Mature TCRαβ	30 / 75 (40%)	36 / 344 (10%)	66 / 419 (16%)	
ETP phenotype	7 / 59 (12%)	49 / 248 (20%)	56 / 307 (18%)	0.19
Oncogenetic classification				<0.001
<i>CALM-AF10</i>	4 / 87 (5%)	9 / 389 (2%)	13 / 476 (3%)	
<i>TLX1</i>	5 / 87 (6%)	49 / 389 (13%)	54 / 476 (11%)	
<i>TLX3</i>	7 / 87 (8%)	65 / 389 (17%)	72 / 476 (15%)	
<i>SIL-TAL1</i>	29 / 87 (33%)	28 / 389 (7%)	57 / 476 (12%)	
Negative	34 / 87 (39%)	185 / 389 (48%)	219 / 476 (46%)	
ND	8 / 87 (9%)	53 / 389 (14%)	61 / 476 (13%)	
Risk Classifier N/F/R/P				
High-risk	72 / 87 (83%)	137 / 389 (35%)	209 / 476 (44%)	<0.001
Treatment Response				
Corticosenstivity	35 / 83 (42%)	224 / 384 (58%)	259 / 467 (55%)	0.010
Chemosensitivity	68 / 85 (80%)	269 / 382 (70%)	337 / 467 (72%)	0.083
Complete Remission	83 / 87 (95%)	357 / 389 (92%)	440 / 476 (92%)	0.37
MRD1 > 10 ⁻⁴	23 / 64 (36%)	100 / 276 (36%)	123 / 340 (36%)	>0.99
Allo-SCT	19 / 84 (23%)	82 / 372 (22%)	101 / 456 (22%)	0.89
Outcome				
5-year CIR, SHR [95% CI]	39% [27;49]	27% [22;31]	29% [25;33]	0.01
5-year OS, HR [95% CI]	58% [47;70]	74% [70;79]	71% [67;75]	0.007

¹Statistics presented: Median (Minimum-Maximum)

²Statistical tests performed: Fisher's exact test; Wilcoxon rank-sum test.

p-values < 0.05 are indicated in bold

MRD1 corresponds to MRD evaluation after induction and was performed by allele-specific oligonucleotides polymerase chain reaction. T-cell receptor status and oncogenic were performed as described in supplemental methods.

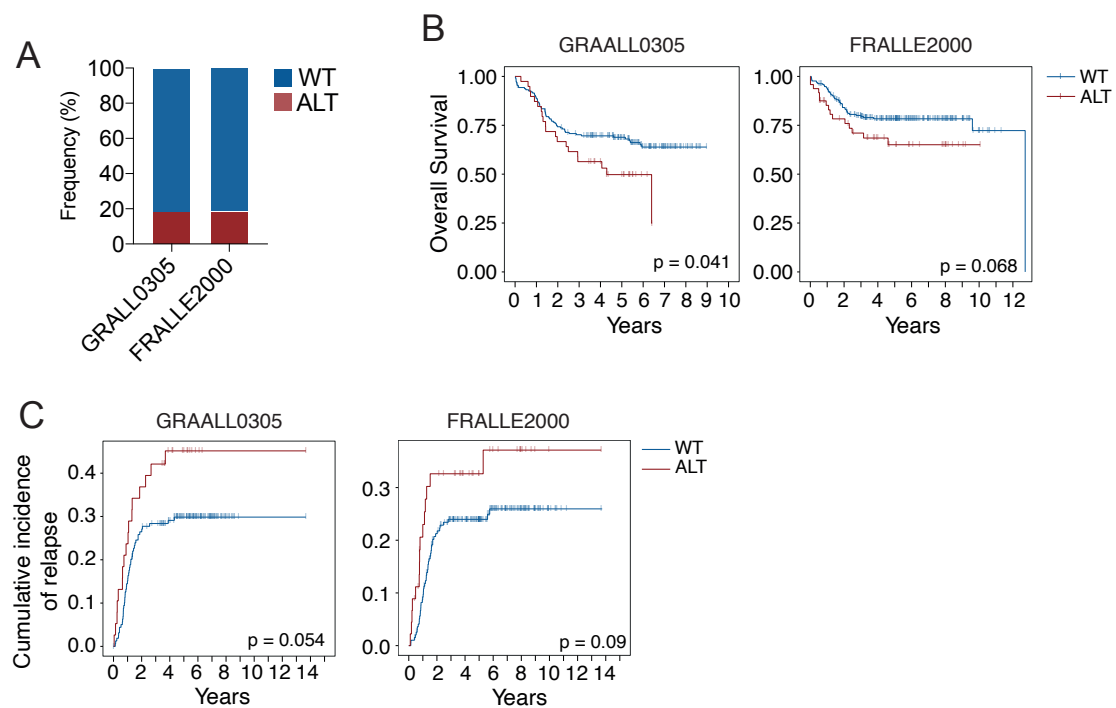
T-ALL: T-cell acute lymphoblastic leukemia; WBC, white blood count; CNS, central nervous system; ETP, early thymic precursor; High Risk classifier, *NOTCH1/FBXW7-RAS/PTEN* classifier as previously described¹; CR, complete remission; MRD, minimal residual disease; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; CIR, cumulative incidence of relapse; OS, overall survival; HR: hazard ratio, SHR: specific hazard ratio, CI: confidence interval

Supplementary Table 2 – Baseline characteristics and clinical response of the five patients treated with erwinase and temsirolimus

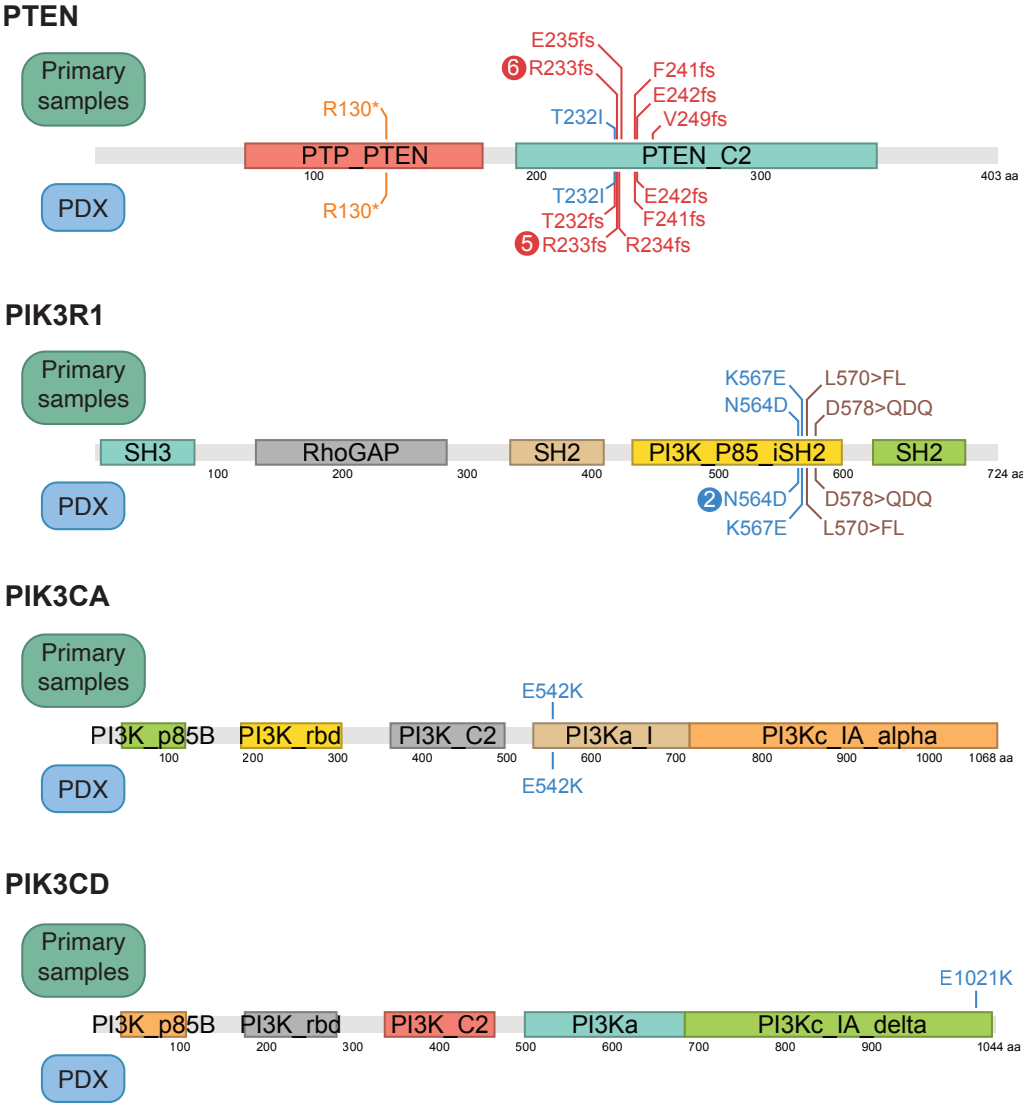
<i>Patient</i>	UPNT-1402	UPNT-1401	T-LL-147	T-LL-242	T-LL-244
Clinical characteristics					
Age at diagnosis	45 y	50 y	26 y	17 y	8 y
Sex	M	F	F	M	M
Disease characteristics					
T-ALL/LL	T-ALL	T-ALL	T-LL	T-LL	T-LL
Oncogenetics	<i>NA</i>	NEG	NEG	NEG	NEG
Immunophenotype	<i>NA</i>	IMB	pre-AB	<i>NA</i>	<i>NA</i>
ETP-ALL	0	1	0	0	0
WBC at diagnosis	290	353	-	-	-
CNS involvement	0	0	<i>NA</i>	1	0
PI3K alteration	<i>PTEN</i> ^{Mut+Del}	<i>PTEN</i> ^{Del}	<i>PTEN</i> ^{Mut+Del}	<i>PIK3R1</i> ^{Mut}	<i>AKT1</i> ^{Mut}
Prior treatment history					
Nb of prior lines of therapy	2	1	3	3	3
Allograft prior ET	yes	yes	no	no	no
Erwinase-Temsirolimus (ET)					
Nb of cycles of ET	2	2	2	1	2
Association with Venetoclax	0	1	0	1	1
Response evaluation to ET	MRD ^{Neg}	MRD ^{Neg}	Volumetric CR	Volumetric CR	Volumetric and Metabolic CR
Toxicity	Grade 3/4	Grade 2/3	Grade 1/2	Grade 1/2	Grade 1/2
Reason for ET discontinuation	Toxicity	Consolidation (DLI)	Consolidation (ASCT)	Supply restriction of Erwinase	Consolidation (ASCT)
Treatments following ET	Temsirolimus	DLI + Venetoclax	ASCT	Temsirolimus + Venetoclax	ASCT
Evolution					
Disease evolution after ET discontinuation	T-ALL Relapse	Persistent CR	ARDS post-ASCT	T-LL Progression	Persistent CR
Salvage treatment	Nelarabine	-	-	VPD	
Status	Died from disease progression	Alive (4y after DLI)	Died from ASCT related-toxicity	Died from disease progression	Alive (2 months post ASCT)

Abbreviations : VPD: Vindesine / PEG-asparaginase/Daunorubicin, MRD^{Neg}: MRD negative, ASCT : allogeneic stem cell transplantation, CR : complete response, DLI : donor lymphocyte infusion, T-ALL: T-cell acute lymphoblastic leukemia, T-LL: T-cell lymphoblastic lymphoma, IMB: immature beta, pre-AB: pre alpha-beta, ETP: early thymic progenitor, Nb : number, ET : Erwinase / Temsirolimus, *PTEN*^{Mut}: PTEN mutation, *PTEN*^{Del}: PTEN deletion, *PIK3R1*^{Mut}: PIK3R1 mutation, WBC: white blood cells, CNS : central nervous system

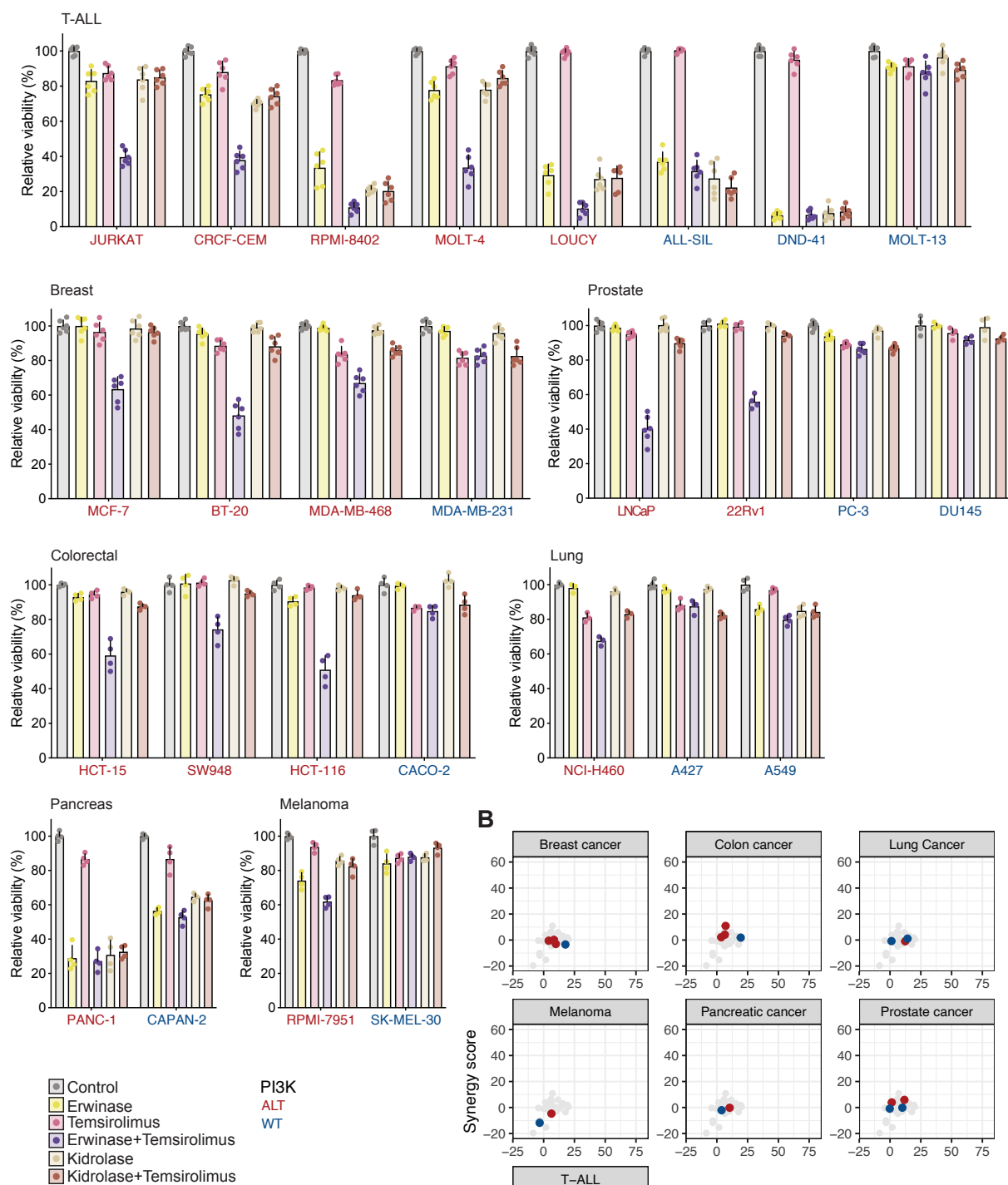
Supplementary Figure 1



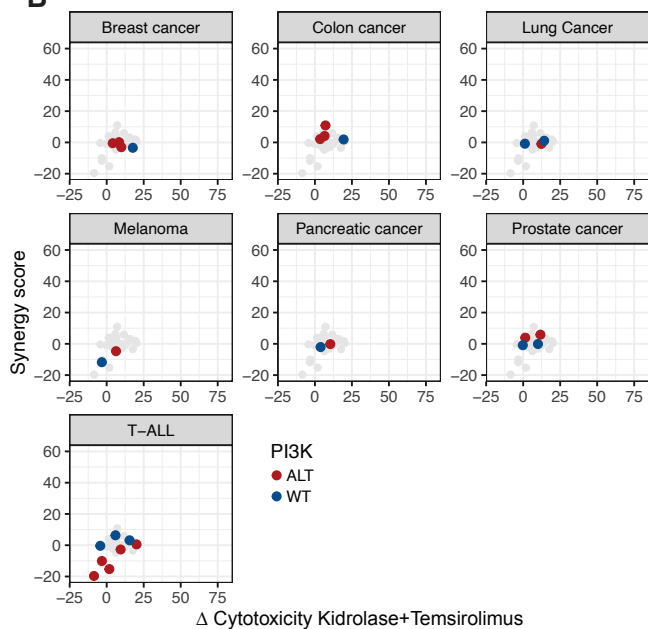
Supplementary Figure 2



A



B



Supplementary Figures Legends

Supplementary Figure 1

A. Incidence of PI3K signaling alterations in the adult and pediatric cohorts. B-C. Overall survival (B) and cumulative incidence of relapse (C) of the PI3KS^{WT} and PI3KS^{ALT} patients according to the protocol.

Supplementary Figure 2

Conservation of PI3K signaling core gene mutations evaluated by NGS in primary samples and PDX.

Supplementary Figure 3

A. Evaluation of the cytotoxicity of erwinase or kidrolase, and temsirolimus in a large spectrum of cancer cell lines. B. Correlation between the Δ cytotoxicity and the ZIP synergy score of kidrolase-temsirolimus stratified by cancer type.