Table S1. Response to treatment of T-ALL patients included in the aging cluster and in the resistance cluster.

	Patients resistance cluster (n=17)	Patients no-resistance cluster (n=99)	P	Patients aging cluster (n= 15)	Patients no-aging cluster (n=101)	P
Slow response at day +14	13/16 (81%)	35/83 (42%)	0·006	12/14 (86%)	36/85 (42%)	0·003
N. of induction cycles to CR						
1	9 (53%)	84 (85%)	0·006	9 (60%)	84 (83%)	0·075
2	8 (47%)	15 (15%)		6 (40%)	17 (17%)	
CR (Ind-1 + Ind-2)	13 (77%)	89 (90%)	0·124	9 (60%)	93 (92%)	0·003
Exitus Ind-1 or Ind-2	4 (24%)	7 (7%)	0·055	5 (33%)	6 (6%)	0·005

Results expressed as number of cases/total cases (percentage). CR: complete remission; +14: fourteen days after induction treatment; d+35: thirty-five days after induction treatment; P: p value.

Table S2. Clinical-biological characteristics and response to treatment of T-ALL patients grouped according to the GOG mutational profile.

	Genetic group		
	GOG$^-$ (n = 97)	**GOG$^+$ (n =19)**	**P**
Patient-related features			
Median age, y (range)	37 (16-61)	38 (16-59)	0·618
Gender, M/F	70/27	16/3	0·393
Disease-related features			
Median WBC, 10^9/L (range)	52.8 (0·5-525·4)	95.1 (6·5-414·6)	0·271
ECOG			
0	36/95 (38%)	7/17 (41%)	0·939
1	45/95 (47%)	8/17 (47%)	
2	12/95 (13%)	2/17 (12%)	
≥3	2/95 (2%)	0	
Adenopathies	48/82 (59%)	7/16 (44%)	0·276
Splenomegaly	31/93 (33%)	8/18 (44%)	0·366
Hepatomegaly	21/92 (23%)	4/18 (22%)	1·000
Mediastinal mass	38/94 (40%)	11/19 (58%)	0·161
CNS involvement	13/91 (14%)	1/19 (5%)	0·457
Immunophenotype			
ETP-ALL	22/92 (24%)	0	0·112
Pre-T	14/92 (15%)	4/18 (28%)	
Cortical	38/92 (41%)	9/18 (50%)	
Mature	18/92 (20%)	4/18 (22%)	
Cytogenetics			
0-2 abn.	56/97 (58%)	10/19 (53%)	0·431
CK≥3	9/97 (9%)	1/19 (5%)	
NE	32/97 (33%)	8/19 (42%)	
Response-related features			
Slow response at day +14	44/86 (51%)	4/13 (31%)	0·170
N. of induction cycles to CR			
1	76/97 (78%)	17/19 (90%)	0·357
2	21/97 (22%)	2/19 (10%)	
CR post Ind-1	77/97 (79%)	18/19 (95%)	0·190
CR (Ind-1 + Ind-2)	84/97 (87%)	18/19 (95%)	0·461
MRD <0·1% at day +35	60/72 (83%)	14/17 (82%)	1·000
Treatment			
Chemotherapy	56/67 (69%)	13/15 (87%)	0·213
Allo-SCT	21/67 (31%)	2/15 (13%)	

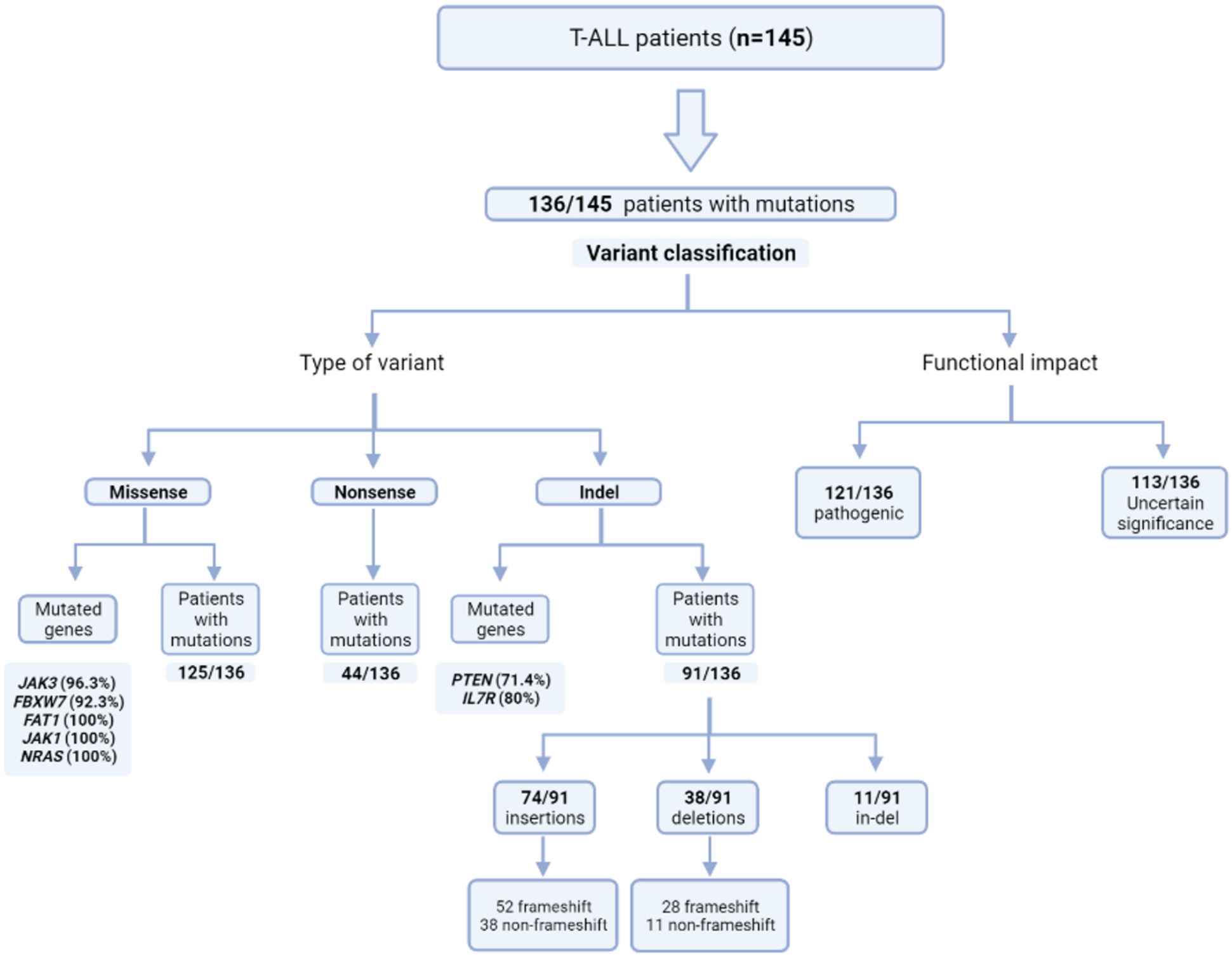
Results expressed as number of cases/total cases (percentage). MRD values were considered for those patients that reach CR. Y: years; CNS: central nervous system; ETP-ALL: early T-cell precursor acute lymphoblastic leukaemia; CR: complete remission; abn: abnormalities; CK: complex karyotype; MRD: measurable residual disease; d+14: fourteen days after induction treatment; d+35: thirty-five days after induction treatment; Allo-SCT: allogeneic stem cell transplantation; P: p value.

Table S3. Prognostic factors for cumulative incidence of relapse identified in the univariable analyses in the PETHEMA adult T-ALL cohort.

		Univariable analyses	
Disease/patient feature	**N**	**HR (95% CI)**	**P**
Age*	102	0·986 (0·965 – 1·009)	0·230
WBC count (x10^9/L)*	100	1·001 (0·998 – 1·003)	0·510
CNS involvement			
No	87	Reference	0·380
Yes	10	0·644 (0·239 – 1·736)	
ETP-ALL			
No ETP-ALL	78	Reference	0·340
ETP-ALL	17	1·365 (0·725 – 2·571)	
Karyotype			
0-2 abn.	62	Reference	0·150
CK≥3	7	1·929 (0·794 – 4·688)	
PETHEMA treatment protocol			
ALL-AR-03	27	Reference	0·580
ALL-HR-11	75	1·196 (0·632 – 2·262)	
N/KRAS			
Non-mutated	92	Reference	0·026
Mutated	10	2·550 (1·121 – 5·800)	
MRD at day +35			
<0·1%	74	Reference	0·110
≥0·1%	15	1·772 (0·871 – 3·608)	

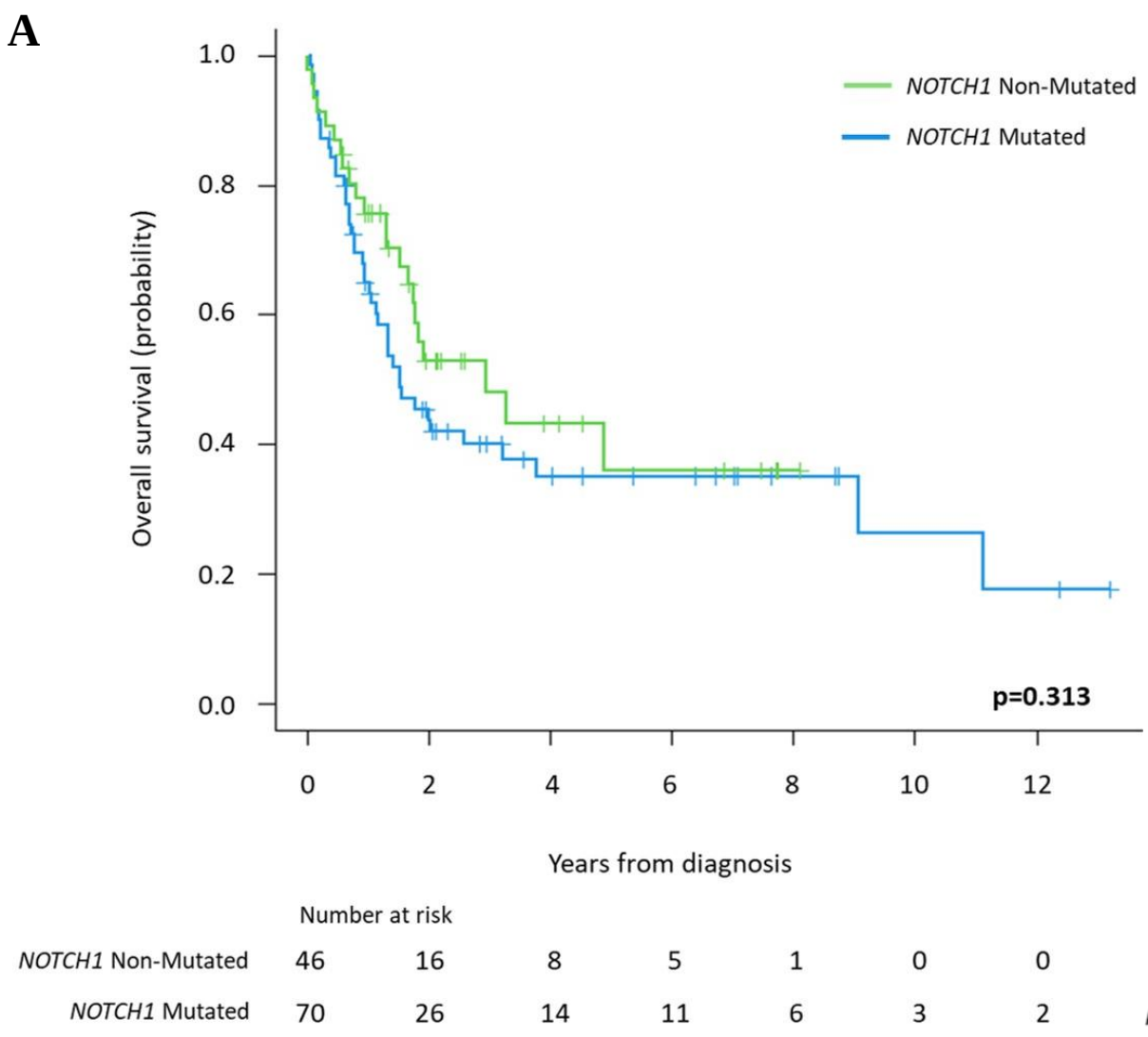
*Age and WBC were considered as continuous variables. N: number of cases; HR: hazard ratio; CI: confidence interval; OS: overall survival; WBC: white blood cell; ETP-ALL: early T-cell precursor acute lymphoblastic leukaemia; Abn: abnormalities; CK: Complex Karyotype; CNS: central nervous system; MRD: measurable residual disease P: p value.

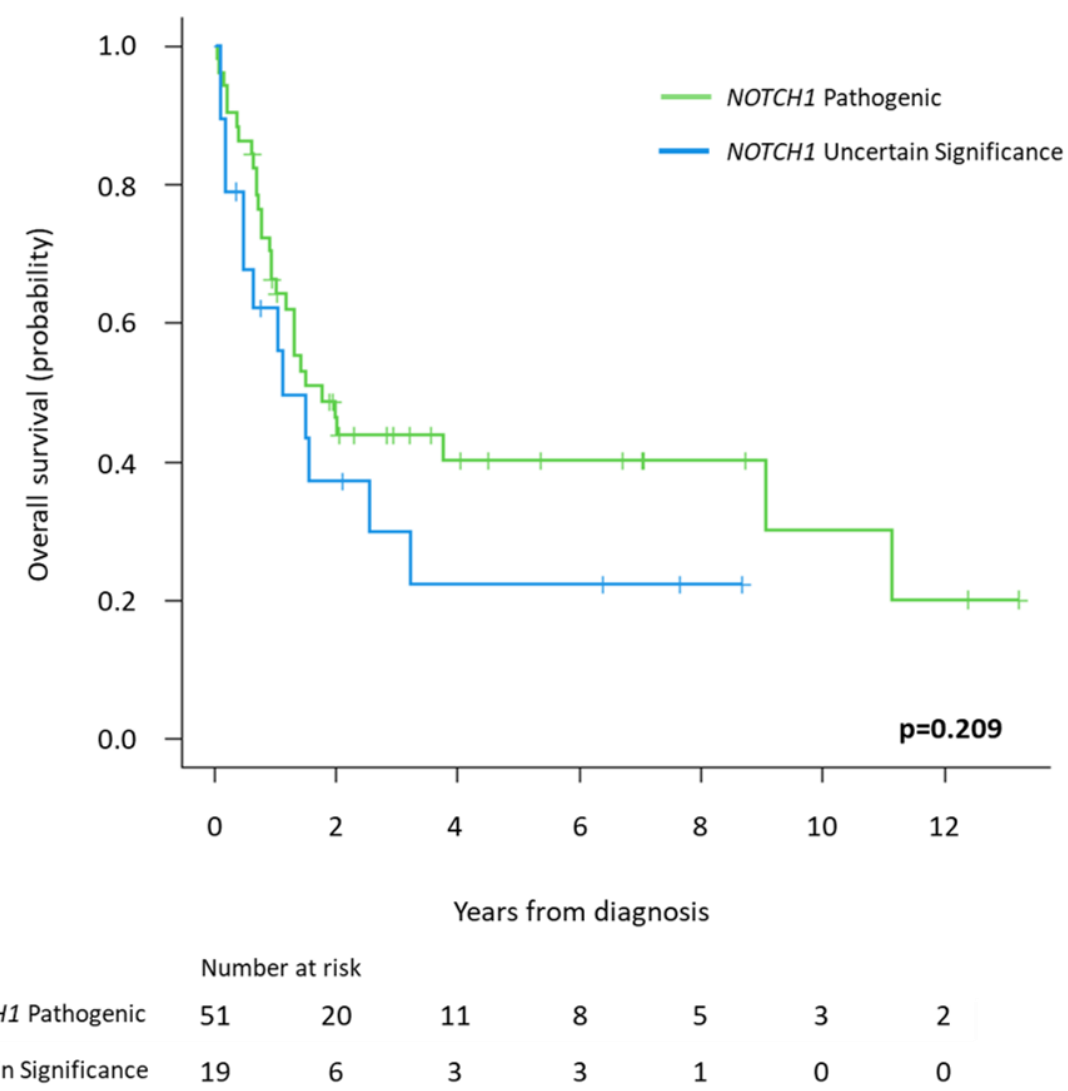
Supplemental Figure 1

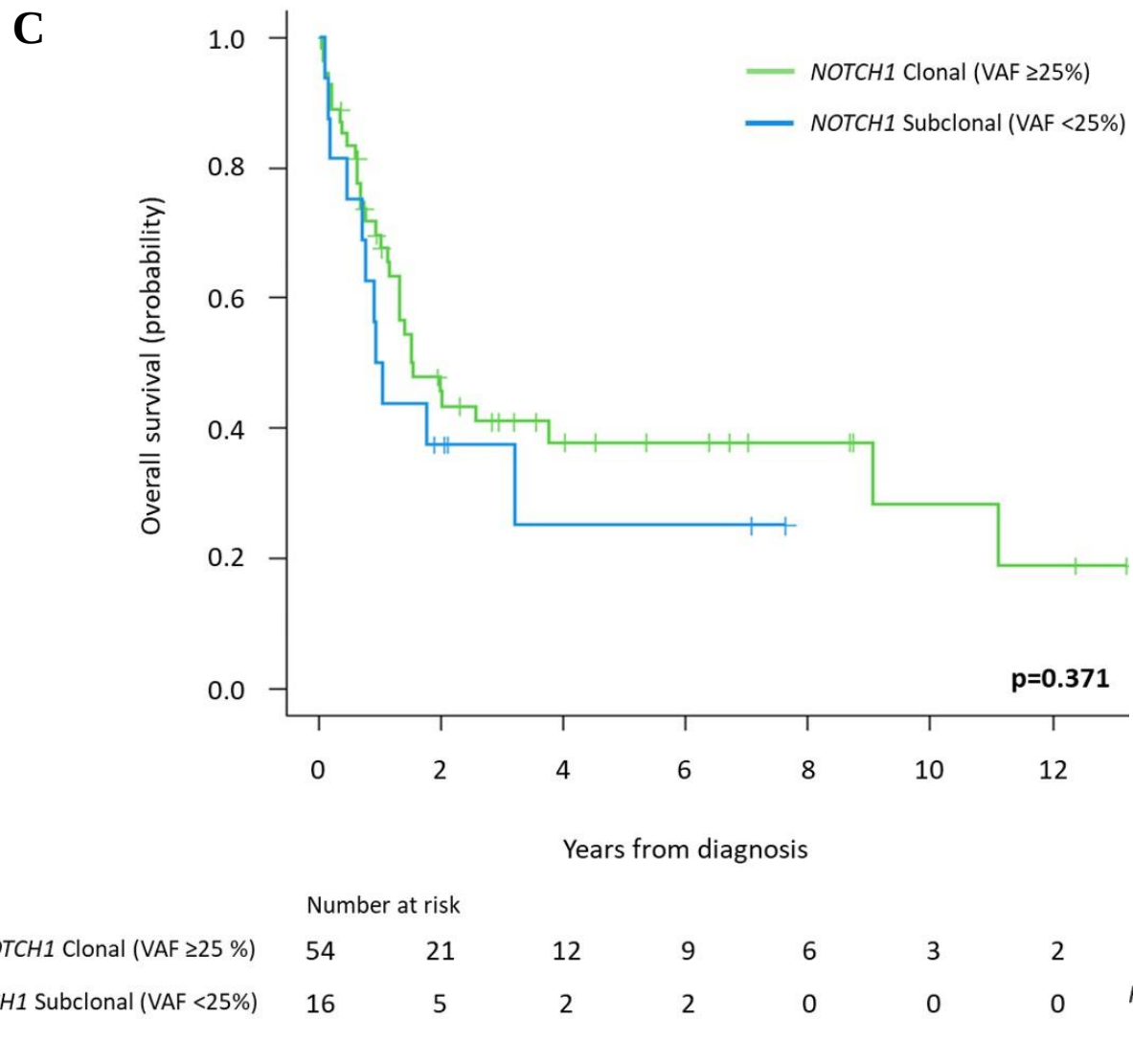


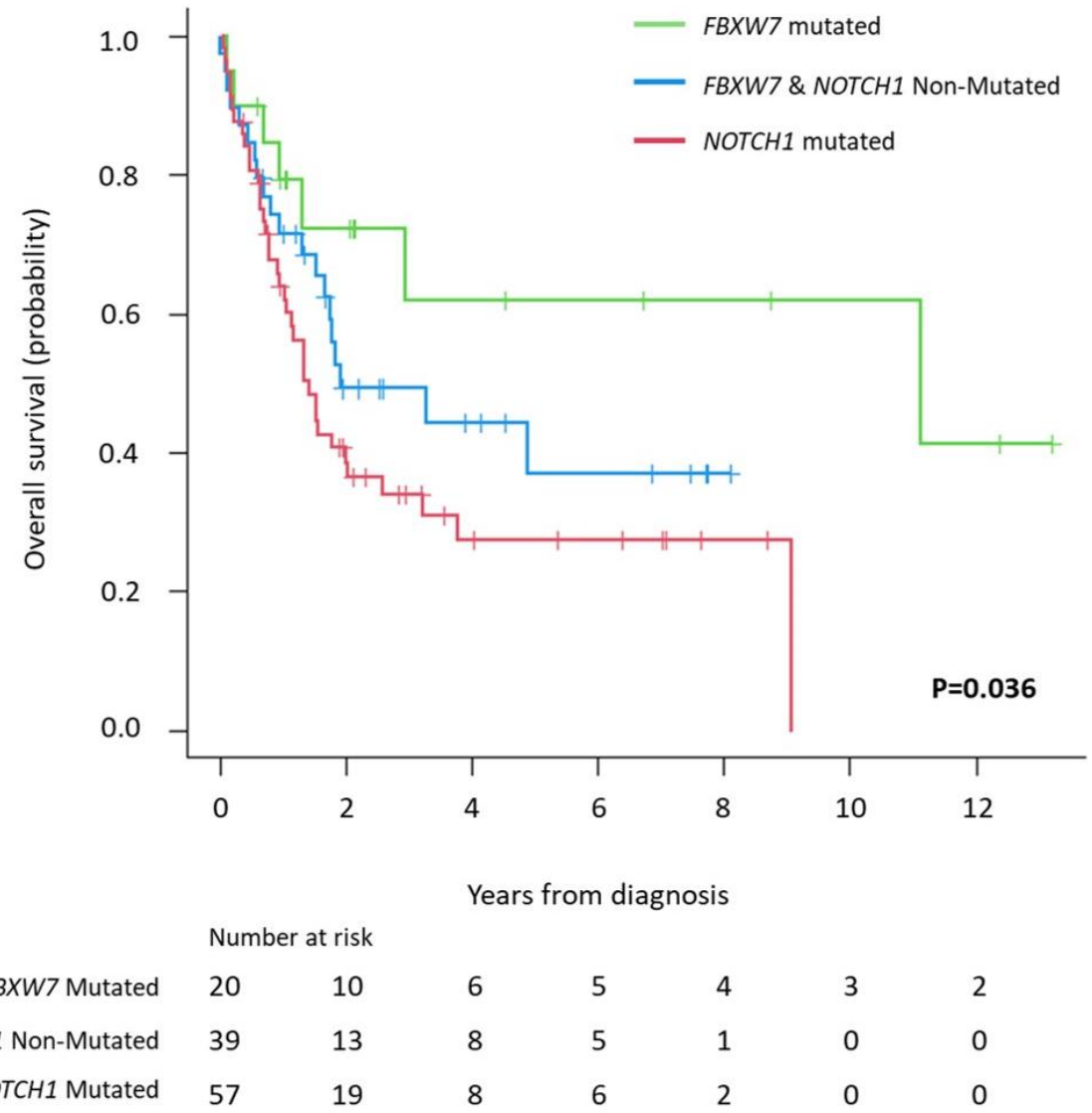
Supplemental Figure 1. Variant classification according to the type of variant detected (missense, nonsense, and indel) and their functional impact (pathogenic or uncertain significance). In-del: insertion and deletion.

Supplemental Figure 2



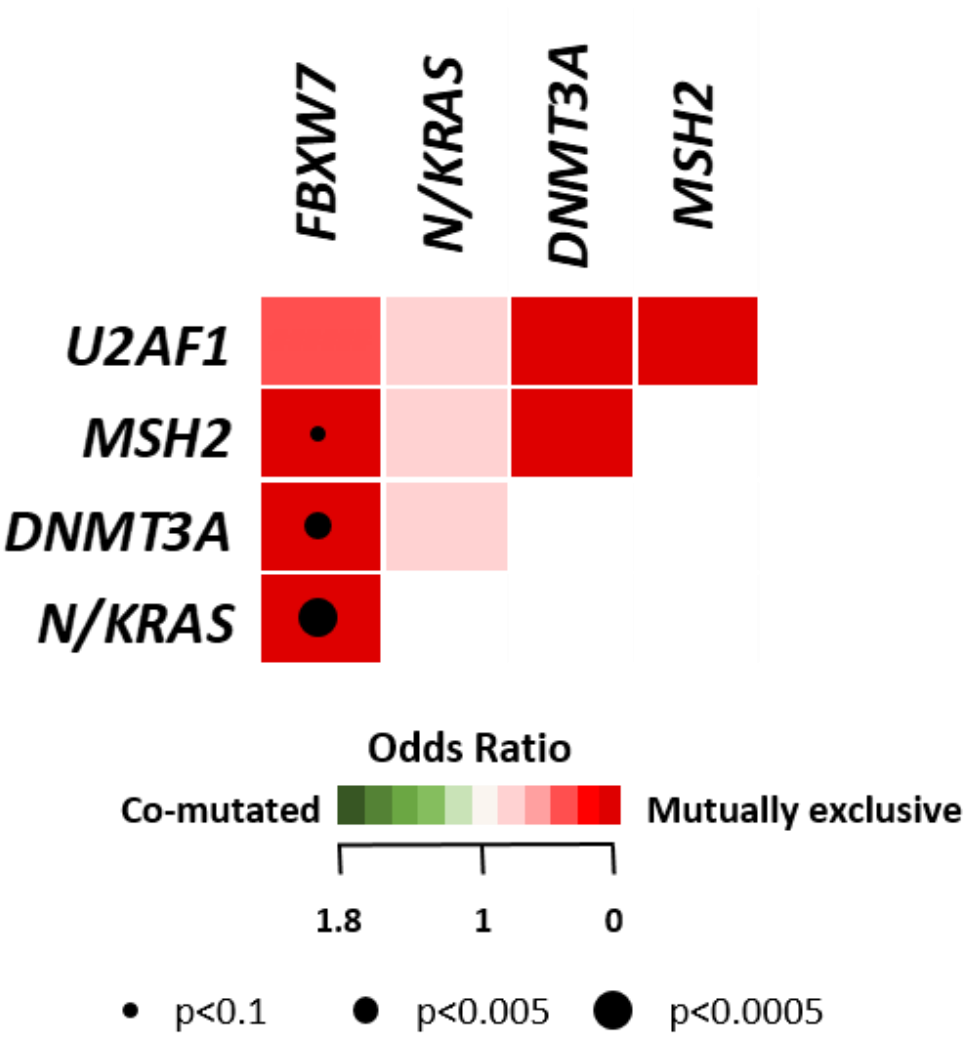






Supplemental Figure 2. Impact of *NOTCH1/FBXW7* mutations in OS. (A) OS from diagnosis according to *NOTCH1* global mutational status. OS (5y) was estimated of 35% (95% CI, 23%-47%) in *NOTCH1* mutated patients and 36% (95% CI, 16%-56%) in non-mutated patients (p=0.313). (B) OS from diagnosis according to the functional impact of the *NOTCH1* variants. OS (5y) was estimated of 40% (95% CI, 25% -55%) in patients with pathogenic *NOTCH1* variants and 22% (95% CI, 1%-43%) in patients with uncertain significance *NOTCH1* variants (p=0.243). (C) OS from diagnosis according to the *NOTCH1* variant clonality status. OS (5y) was estimated of 38% (95% CI, 24%-52%) in patients with clonal *NOTCH1* variants (VAF > 25%), compared with 25% (95% CI, 0%-50%) in patients with subclonal *NOTCH1* variants (VAF < 30%) (p=0.380). (D) OS from diagnosis according to *FBXW7* and *NOTCH1* mutational status. OS (5y) was estimated of 62% (95% CI, 9%-73%) in patients with *FBXW7* variants (with and without *NOTCH1* variants) compared with 27% (95% CI, 15%-41%) in patients with only *NOTCH1* variants (p=0.036). The OS of patients without *NOTCH1* and *FBXW7* mutations was 37% (95% CI 18%).

Supplemental Figure 3



Supplemental Figure 3. Co-ocurrence between genes with prognostic impact in the T-ALL cohort. Positive (odds ratio >1) and negative (odds ratio <1) correlations are depicted as green and red, respectively. Black circle diameters indicate the degree of significance.