SUPPLEMENTAL DATA

Clinical and biological features of PTPN2 deleted adult and pediatric T-cell acute lymphoblastic leukemia

Contents:

SUPPLEMENTARY METHODS

Clinical trials

Patients aged from 15 to 59 years old were enrolled in the GRAALL-2003 and GRAALL-2005 protocols. The study design is provided as a supplementary PDF file.

Patients, from 1 to 14 years old, with a diagnosis of T-ALL were treated according the FRALLE 2000 T guidelines (FRALLE study group, Supplemental Figure 1). Diagnosis of T-ALL was performed using cytomorphology, cytochemistry and flow cytometry.

Definitions: Good prednisone response (GPR) was defined as < 1000 circulating blasts/µL on day 8, poor prednisone response (PPR) when ≥ 1000 circulating blasts/µL on day 8. Morphologic assessment of a bone marrow aspirate was done at day 21. A chemosensitivity was represented by ≤ 5% blasts, a chemoresistance by > 5%. Complete remission (CR) was defined as: absence of physical signs of leukemia, bone marrow with active hematopoiesis and < 5% leukemic blast cells (identified morphologically), and normal cerebrospinal fluid. Patients were stratified into two groups.

Treatment stratification: Standard risk group (T1) was defined by the presence of all the following criteria: good prednisone response (GPR) at day 8, chemosensitivity (CHs) at day 21, MRD < 10-2 at day 35. High risk group (T2) was defined by the presence of one of the following criteria: poor prednisone response (PPR) at day 8, chemoresistance at day 21 or MRD ≥ 10-2 at day 35. Patients treated according to T2 group were eligible for allogeneic stem cell transplantation (SCT) after late intensification n°1 when a matched sibling or unrelated donor was available.

Microarray-based comparative genomic hybridization (array CGH)

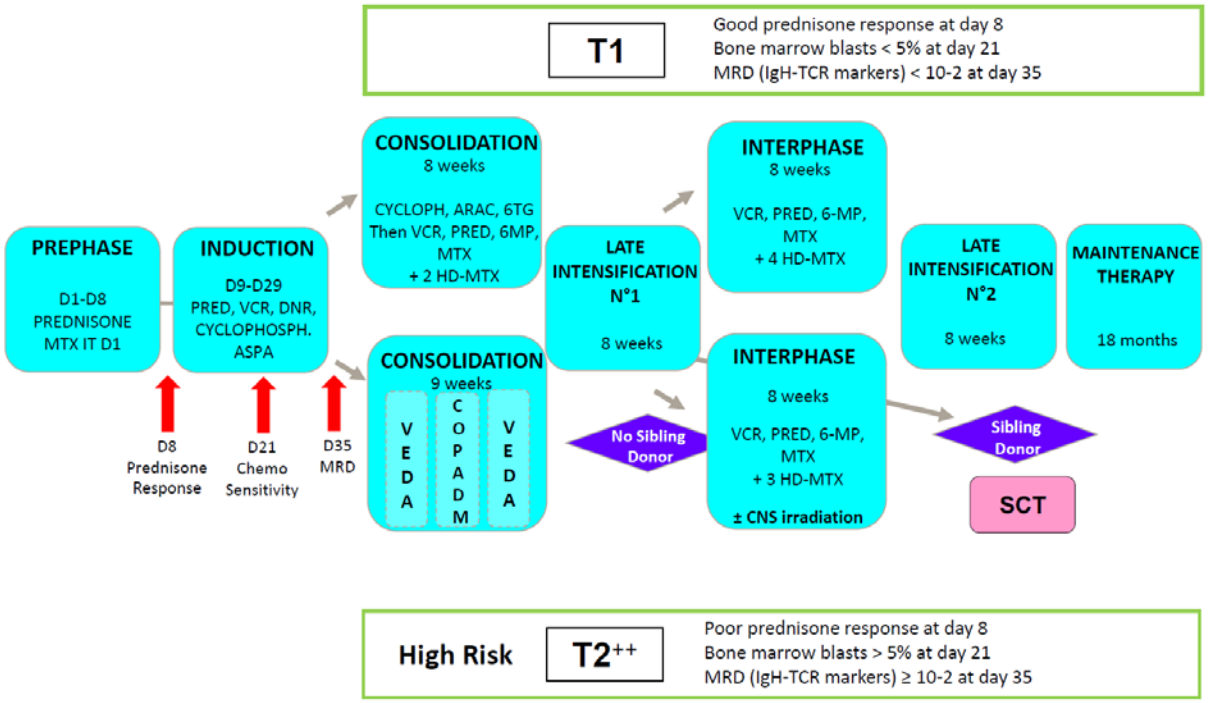
Diagnostic DNA was hybridized on Affymetrix (Santa Clara, CA) Cytogenetics Whole-Genome 2.7M Array, according to the manufacturer's directions. Data were analyzed with the Chromosome Analysis Suite (ChAS) software (Affymetrix®).

Quantitative real-time reverse transcription-polymerase chain reaction (qRT-PCR)

One µg of total RNA was converted to cDNA in a random primed synthesis with the SUPERSCRIPT III reverse transcriptase (Life Technologies). PTPN2 expression was analyzed with a specific Mix 20X (reference Hs00959888_g1, Thermo Fisher Scientific) following the manufacturer's instructions. PTPN2 expression was normalized on GAPDH expression (reference Hs02786624_g1, Thermo Fisher Scientific). An ABI PRISM 7900 Sequence Detection System (Life Technologies) was used to perform the PCR reactions and measure fluorescence at each cycle. Generated data were analyzed using $2^{-\Delta\Delta Ct}$ method.[1]

SUPPLEMENTAL FIGURES

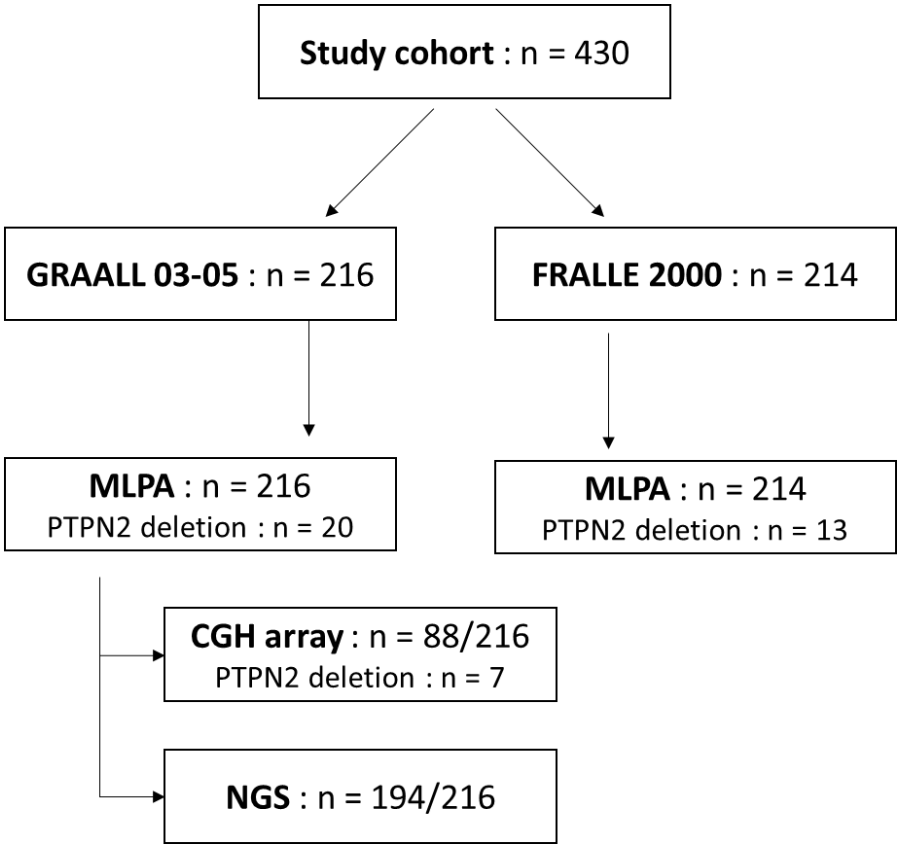
Supplemental Figure 1



++ Patients treated according T2 group were eligible for SCT after late intensification n°1 when a sibling donor was available

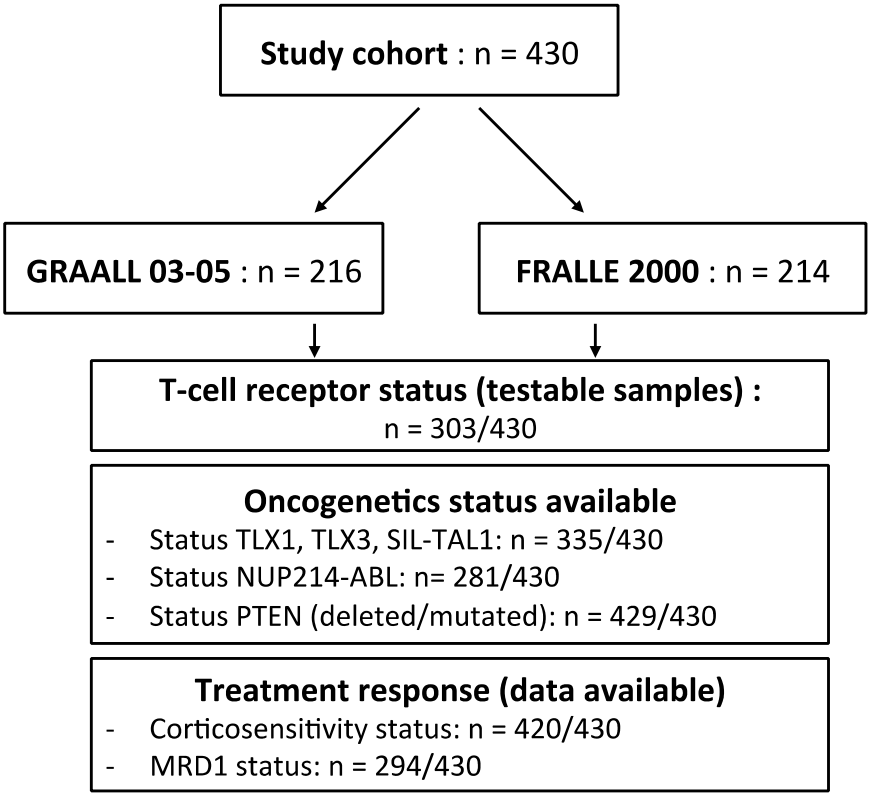
Supplemental Figure 1. General design of FRALLE 2000 T guidelines.

Supplemental Figure 2



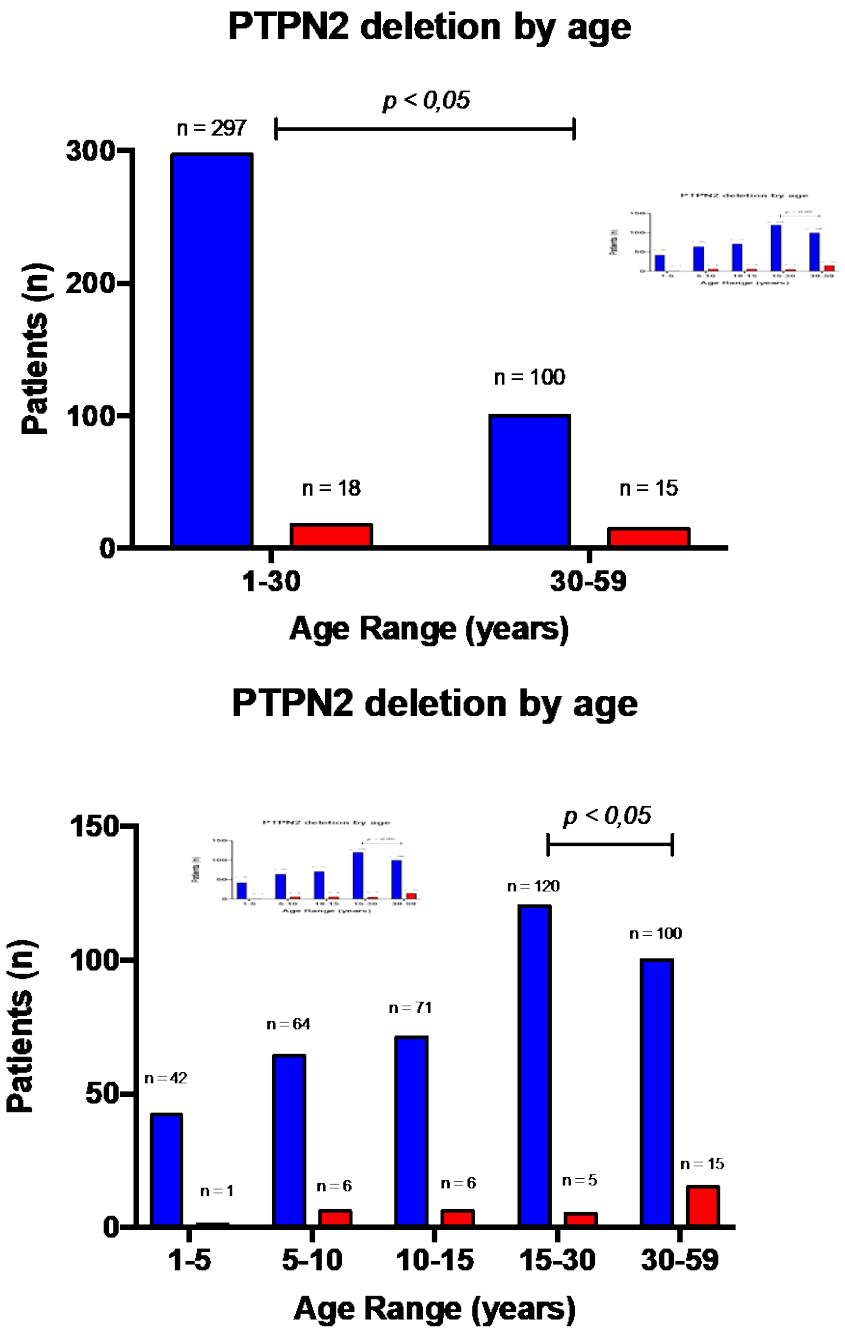
Supplemental Figure 2. Flow chart displaying the molecular characterization

Supplemental Figure 3



Supplemental Figure 3. Flow chart displaying the molecular data available

Supplemental Figure 4.



<u>Supplemental Figure 4</u>. PTPN2 deletions sorted by age

Schematic representation of PTPN2 deletions frequency according to age.

SUPPLEMENTAL TABLES

Supplemental Table 1. Chemotherapy in the standard risk group T1.

Drug/Administration route	mg/m2/day	Day
Prephase		
Prednisone/po-iv	60	1-7
MTX/it	By age*	1
Induction		
Prednisone/po-iv	40	8–28 then tapered
Vincristine/iv	1.5 (max: 2 mg)	8, 15, 22, 29
Daunorubicin/iv	40	8, 9, 10, 15
L-Asparaginase/iv	6,000 IU/m2	8, 10, 12, 15, 17, 19
Cyclophosphamide/iv	1000	8
MTX-ARAC-PRED/i.t	By age**	8, 15
Consolidation		
Tioguanine/po	60	1-22
Cyclophosphamide/iv	1000	1-15
Aracytine/sc	30/12h	1-2, 8-9, 15-16
Prednisone/po-iv	40	29-35
Mercaptopurine/po	50	29-49
Vincristine/iv	1.5 (max: 2 mg)	29, 43
Methotrexate/iv	5000	29, 42
Methotrexate/po	25	36
Leucovorin rescue	15/6h	36h after start HD-MTX
MTX-ARAC-PRED/i.t	By age**	1, 15, 29, 43
Delayed intensification n°1		
Dexamethasone/po-iv	10	1-14 then tapered
Vindesine/iv	3 (max: 4 mg)	1, 8, 15
Adriamycine/iv	25	1, 8, 15
L-Asparaginase/iv	6,000 IU/m2	3, 5, 8, 10, 12, 15
Tioguanine/po	60	29-49
Etoposide	150	29, 36, 43
Aracytine/sc	30/12h	29-30, 36-37, 43-44
MTX-ARAC-PRED/i.t	By age**	3, (± 15[§]), 30, (± 43[§])
Interphase		
Prednisone/po-iv	40	1-7, 29-35
Mercaptopurine/po	50	1-49
Vincristine/iv	1.5 (max: 2 mg)	1, 15, 29, 43
Methotrexate/iv	5000	1, 15, 29; 43
Methotrexate/po	25	8, 22, 36
Leucovorin rescue	15/6h	36h after start HD-MTX
MTX-ARAC-PRED/i.t	By age**	1, 15, 29, 43[§§]

Cranial irradiation	18 or 24 Gy [&]	40-45
Delayed intensification n°2		
Prednisone/po-iv	40	1-14 then tapered
Vincristine/iv	1.5 (max: 2 mg)	1, 8, 15
Daunorubicin/iv	40	1, 8, 15
L-Asparaginase/iv	6,000 IU/m2	3, 5, 8, 10, 12, 15
Tioguanine/po	60	29-49
Cyclophosphamide/iv	1000	29
Aracytine/sc	30/12h	29-30, 36-37, 43-44
MTX-ARAC-PRED/i.t	By age**, §§	3, 30
Maintenance (18 months)		
Prednisone/po-iv	40	1-7 every 4 weeks ***
Mercaptopurine/po	50	daily
Methotrexate/po	25	weekly
Vincristine/iv	1.5 (max: 2 mg)	Every 4 weeks ***
MTX-ARAC-PRED/i.t	By age**, §§	Every 3 months, 3 times

<u>Supplemental Table 1.</u> Chemotherapy in the standard risk group T1.

Abbreviations: iv, intravenous; po, per os; i.t., intrathecal; sc: subcutaneous

* Age-adjusted doses of intrathecal methotrexate: ≥1 and < 2 years: 8 mg; ≥2 and < 3 years: 10 mg; ≥3 and < 10 years: 12 mg; ≥10 years: 15 mg

** Age-adjusted doses of triple intrathecal MTX, ARA-C and methylprednisolone respectively: ≥ 1 and < 2 years: 8, 15 and 20 mg; ≥ 2 and < 3 years: 10, 20 and 20 mg; ≥ 3 years and < 10 years: 12, 25 and 20 mg; ≥10 years: 15, 20 and 20 mg

*** 12 times, then stopped

§ in case of CNS involvement

& Preventive use: 18 Gy only for patients ≥ 4 years with WBC ≥ 100 G/L at diagnosis; Therapeutic use (CNS involvement at diagnosis): 18 Gy for patients <4 years, 24 Gy for patients ≥ 4 years

§§ Except for irradiated patients

Supplemental Table 2. Chemotherapy in the high risk group T2.

Drug/Administration route	mg/m2/day	Day
Prephase		
Prednisone/po-iv	60	1-7
MTX/it	By age*	1
Induction		
Prednisone/po-iv	40	8–28 then tapered
Vincristine/iv	1.5 (max: 2 mg)	8, 15, 22, 29
Daunorubicin/iv	40	8, 9, 10, 15
L-Asparaginase/iv	6,000 IU/m2	8, 10, 12, 15, 17, 19
Cyclophosphamide/iv	1000	8
MTX-ARAC-PRED/i.t	By age**	8, 15
Consolidation		
VEDA n°1		
Dexamethasone/po-iv	20	1-5
Vincristine/iv	1.5 (max: 2 mg)	1
Aracytine/iv	2000/12h	1, 2
Etoposide/iv	150	3, 4, 5
MTX-ARAC-PRED/i.t	By age**	5
COPADM		
Prednisone/po-iv	40	1-5
Vincristine/iv	1.5 (max: 2 mg)	1
Adriamycine/iv	25	2
Methotrexate/iv	5000	1
Leucovorin rescue	15/6h	36h after start HD-MTX
Cyclophosphomide	500/12h	2, 3
MTX-ARAC-PRED/i.t	By age**	2
VEDA n°2		
identical to n°1		
Delayed intensification n°1		
Dexamethasone/po-iv	10	1-14 then tapered
Vindesine/iv	3 (max: 4 mg)	1, 8, 15
Adriamycine/iv	25	1, 8, 15
L-Asparaginase/iv	6,000 IU/m2	3, 5, 8, 10, 12, 15
Tioguanine/po	60	29-49
Etoposide	150	29, 36, 43

Aracytine/sc	30/12h	29-30, 36-37, 43-44
MTX-ARAC-PRED/i.t	By age**	3, 30, (± 43§)
Interphase		
Prednisone/po-iv	40	1-7, 29-35
Mercaptopurine/po	50	1-49
Vincristine/iv	1.5 (max: 2 mg)	1, 15, 29 (± 43§)
Methotrexate/iv	5000	1, 15, 29 (± 43§)
Methotrexate/po	25	8, 22, 36
Leucovorin rescue	15/6h	36h after start HD-MTX
MTX-ARAC-PRED/i.t	By age**	1, 15, 29 (± 43§)
Cranial irradiation	18 to 24 Gy &	40-45
Delayed intensification n°2		
Prednisone/po-iv	40	1-14 then tapered
Vincristine/iv	1.5 (max: 2 mg)	1, 8, 15
Daunorubicin/iv	40	1, 8, 15
L-Asparaginase/iv	6,000 IU/m2	3, 5, 8, 10, 12, 15
Tioguanine/po	60	29-49
Cyclophosphamide/iv	1000	29
Aracytine/sc	30/12h	29-30, 36-37, 43-44
MTX-ARAC-PRED/i.t	By age**, §§	3, 30
Maintenance (18 months)		
Prednisone/po-iv	40	1-7 every 4 weeks ***
Mercaptopurine/po	50	daily
Methotrexate/po	25	weekly
Vincristine/iv	1.5 (max: 2 mg)	Every 4 weeks ***
MTX-ARAC-PRED/i.t	By age**, §§	Every 3 months, 3 times

Supplemental Table 2. Chemotherapy in the high risk group T2.

Abbreviations: iv, intravenous; po, per os; i.t., intrathecal; sc: subcutaneous

* Age-adjusted doses of intrathecal methotrexate: ≥1 and < 2 years: 8 mg; ≥2 and < 3 years: 10 mg; ≥3 and < 10 years: 12 mg; ≥10 years: 15 mg

** Age-adjusted doses of triple intrathecal MTX, ARA-C and methylprednisolone respectively: ≥ 1 and < 2 years: 8, 15 and 20 mg; ≥ 2 and < 3 years: 10, 20 and 20 mg; ≥ 3

years and < 10 years: 12, 25 and 20 mg; ≥10 years: 15, 20 and 20 mg

*** 12 times, then stopped

§ in case of CNS involvment

& Preventive use: 18 Gy for patients ≥ 4 years; Therapeutic use (CNS involvement at diagnosis): 18 Gy for patients <4 years, 24 Gy for patients ≥ 4 years

§§ Except for irradiated patients

Supplemental Table 3. Clinicobiologic characteristics of adult patients with T-ALL (GRAALL protocol) according to PTPN2 status.

	PTPN2 del 20 (9%)*	PTPN2 WT 196 (91%)	Total 216 (100%)	p-value
Clinical Subsets Analyzed				
Male	14/20 (70%)	140/196 (71%)	154/216 (71%)	1
Median Age, Years	36.9	30.4	30.8	**0.02**
(Range)	(23.4 – 57.0)	(16.3 – 59.1)	(16.3 – 59.1)	
WBC, Median	24.6	32.6	31.7	0.2
(Range)	(4.1 – 233)	(0.9 – 645)	(0.9 – 645)	
CNS involvement	1/20 (5%)	25/193 (13%)	26/213 (12%)	0.26
T-cell receptor status				
Immature (IM0, IMD, IMG)	2/18 (11%)	53/170 (31%)	55/188 (29%)	0.06
αβ lineage (IMB, pré-αβ, TCRαβ)	15/18 (83%)	99/170 (58%)	114/188 (61%)	**0.03**
γδ lineage (TCR γδ)	1/18 (6%)	18/170 (11%)	19/188 (10%)	0.43
Oncogenetics				
TLX1	10/19 (53%)	33/185 (18%)	43/204 (21%)	**0.001**
TLX3	4/19 (21%)	22/185 (12%)	26/204 (13%)	0.21
SIL-TAL1	1/19 (5%)	19/185 (10%)	20/204 (10%)	0.7
NUP214-ABL	4/20 (20%)	10/195 (5%)	14/215 (6%)	**0.03**
PTEN deleted/mutated	0/20	25/195 (13%)	25/215 (12%)	0.14
NOTCH1/FBXW7 mutated	16/20 (80%)	132/196 (67%)	148/216 (68%)	0.3
Treatment response				
Corticosensitivity	15/20 (75%)	105/196 (54%)	120/216 (56%)	0.1
CR	19/20 (95%)	180/196 (92%)	199/216 (92%)	1
MRD1 $\geq 10^{-4}$**	2/15 (13%)	35/109 (32%)	37/124 (30%)	0.2

<u>Supplemental Table 3.</u> Clinicobiologic characteristics of adult patients with T-ALL (GRAALL protocol) according to PTPN2 status.

Comparison of the clinicobiologic characteristics of PTPN2 deleted and wild-type T-ALL patients in the adult cohort. Abbreviations: T-ALL, T-cell acute lymphoblastic leukemia; del, deleted; WT, wild-type; WBC, white blood count; CNS, central nervous system; CR, complete remission; MRD, minimal residual disease.

T-cell receptor status and oncogenetics were determined as previously described.[2–4]

* monoallelic 10/20, biallelic 10/20

** MRD was centrally assessed by real-time quantitative allele-specific oligonucleotide polymerase chain reaction and interpreted according to EuroMRD group guidelines.[5,6]

Supplemental Table 4. Clinical characteristics and outcome of the study cohort versus non-investigated patients (GRALL protocol)

GRAALL 03-05	**Study Cohort (N = 216)**	**Non-investigated Cohort (N = 121)**	**p-value**
Clinical Subsets Analyzed			
Male	154	85	0.9
Median Age, Years	30.8	33.5	0.16
(Range)	(16.3-59.1)	(17.6-59.5)	
WBC, Median	31.7	18	0.001
(Range)	(0.9-645.0)	(0.9-573.0)	
CNS involvement	26/216 (12%)	9/121 (7%)	0.2
Allo-SCT	76/216 (35%)	33/121 (27%)	0.14
Treatment Response			
Corticosensitivity	120/216 (56%)	85/121 (70%)	0.01
CR	199/216 (92%)	115/121 (96%)	0.25
5y-CIR, % (95%CI)	30% (24-37)	33% (25-43)	0.45
5y-OS, % (95%CI)	66% (59-72)	61% (51-69)	0.36

<u>Supplemental Table 4.</u> Clinical characteristics and outcome of the study cohort versus non-investigated patients (GRALL protocol)

Comparison of the clinicobiologic characteristics of the patients in the study cohort versus the non-investigated patients included in the GRAALL protocol.

Abbreviations: WBC, white blood cell count; CNS, central nervous system; CR, complete remission; CIR, cumulative incidence of relapse; OS, overall survival; CI, confidence interval; SCT, stem cell transplantation.

Supplemental Table 5. Clinicobiologic characteristics of pediatric patients with T-ALL (FRALLE protocol) according to PTPN2 status.

	PTPN2 del	**PTPN2 WT**	**Total**	**p-value**
	13 (6%)*	**201 (94%)**	**214 (100%)**	
Clinical Subsets Analyzed				
Male	8/13 (61%)	166/201 (83%)	174/214 (81%)	0.07
Median Age, Years	9.0	9.48	9.48	ns
(Range)	(4.3 – 14.3)	(1.1 – 19.5)	(1.1 – 19.5)	
WBC, Median	99	96.9	97.9	ns
(Range)	(7.6 – 574)	(0.3 – 980)	(0.3 – 980)	
CNS involvement	4/13 (31%)	12/201 (6%)	16/214 (7%)	**0.01**
T-cell receptor status				
Immature (IM0, IMD, IMG)	0/8	11/107 (10%)	11/115 (10%)	1
αβ lineage (IMB, pré-αβ, TCR αβ)	8/8 (100%)	75/107 (70%)	83/115 (72%)	0.1
γδ lineage (TCR γδ)	0/8	21/107 (20%)	21/115 (18%)	0.3
Oncogenetics				
TLX1	3/8 (37%)	6/123 (5%)	9/131 (7%)	**0.01**
TLX3	5/8 (63%)	30/123 (24%)	35/131 (27%)	**0.03**
SIL-TAL1	0/8	18/123 (15%)	18/131 (14%)	0.6
NUP214-ABL	1/4 (25%)	7/62 (11%)	8/66 (12%)	0.4
PTEN deleted/mutated	0/13	30/201 (15%)	30/214 (14%)	0.22
NOTCH1/FBXW7 mutated	12/13 (92%)	118/201 (59%)	130/214 (61%)	**0.02**
Treatment response				
Corticosensitivity	10/12 (83%)	112/192 (58%)	122/204 (60%)	0.1
CR	13/13 (100%)	194/201 (97%)	207/214 (97%)	1
MRD1 $\geq 10^{-4}$**	3/13 (23%)	74/176 (42%)	77/189 (41%)	0.2

<u>Supplemental Table 5.</u> Clinicobiologic characteristics of pediatric patients with T-ALL (FRALLE protocol) according to PTPN2 status.

Comparison of the clinicobiologic characteristics of PTPN2 deleted and wild-type T-ALL patients in the pediatric cohort. Abbreviations: T-ALL, T-cell acute lymphoblastic leukemia; del, deleted; WT, wild-type; WBC, white blood count; CNS, central nervous system; CR, complete remission; MRD, minimal residual disease.

T-cell receptor status and oncogenetics were determined as previously described.[2–4]

* monoallelic 6/13, biallelic 7/13

** MRD was centrally assessed by real-time quantitative allele-specific oligonucleotide polymerase chain reaction and interpreted according to EuroMRD group guidelines.[5,6]

Supplemental Table 6. Clinical characteristics and outcome of the study cohort versus non-investigated patients (FRALLE protocol)

FRALLE 2000T	**Study Cohort (N = 214)**	**Non-investigated Cohort (N = 191)**	**p-value**
Clinical Subsets Analyzed			
Male	NA	NA	
Median Age, Years	9.5	8.9	0.16
(Range)	(1.1-19.5)	(1.3-18.7)	
WBC, Median	101	72	0.7
(Range)	(0.3-980.0)	(0.9-900.0)	
CNS involvement	16/214 (8%)	25/191 (17%)	0.048
Allo-SCT	28/214 (13%)	30/191 (15%)	0.47
Treatment Response			
Corticosensitivity	122/204 (60%)	100/186 (54%)	0.26
CR	207/214 (97%)	168/191 (88%)	0.001
5y-CIR, % (95%CI)	25% (19-32)	25% (18-32)	0.72
5y-OS, % (95%CI)	79% (73-84)	74% (66-80)	0.18

Supplemental Table 6. Clinical characteristics and outcome of the study cohort versus non-investigated patients (FRALLE protocol)

Comparison of the clinicobiologic characteristics of the patients in the study cohort versus the non-investigated patients included in the FRALLE protocol.

Abbreviations: WBC, white blood cell count; CNS, central nervous system; CR, complete remission; CIR, cumulative incidence of relapse; OS, overall survival; CI, confidence interval; SCT, stem cell transplantation; NA, not available.

Supplemental Table 7. Genetic profile of PTPN2 deleted adult T-ALL.

	PTPN2 del N = 19	PTPN2 WT N = 175	Total N = 194	p-value
JAK-STAT signaling				
DNM2	**9/19 (47%)**	**29/175 (17%)**	**38/194 (20%)**	**0,004**
JAK3	5/19 (26%)	31/175 (18%)	36/194 (19%)	0,36
IL7R	4/19 (21%)	19/175 (11%)	23/194 (12%)	0,25
JAK1	1/19 (5%)	15/175 (9%)	16/194 (8%)	1
SH2B3	2/19 (11%)	11/175 (6%)	13/194 (7%)	0,37
STAT5B	1/19 (5%)	9/175 (5%)	10/194 (5%)	1
PI3K-AKT-mTOR signaling				
PTEN	0/19 (0%)	23/175 (13%)	23/194 (12%)	0,14
PIK3R1	1/19 (5%)	5/175 (3%)	6/194 (3%)	0,47
PIK3CA	1/19 (5%)	3/175 (2%)	4/194 (2%)	0,34
AKT1	0/19 (0%)	2/175 (1%)	2/194 (1%)	1
RAS signaling				
NRAS	2/19 (11%)	17/175 (10%)	19/194 (10%)	1
KRAS	1/19 (5%)	6/175 (3%)	7/194 (4%)	0,52
NF1	1/19 (5%)	4/175 (2%)	5/194 (3%)	0,41
BRAF	0/19 (0%)	3/175 (2%)	3/194 (2%)	1
PTPN11	0/19 (0%)	1/175 (1%)	1/194 (1%)	1
Epigenomic				
PHF6	**18/19 (95%)**	**71/175 (41%)**	**89/194 (46%)**	**<0,0001**
DNMT3A	0/19 (0%)	20/175 (11%)	20/194 (10%)	0,23
SUZ12	2/19 (11%)	16/175 (9%)	18/194 (9%)	0,69
CTCF	2/19 (11%)	11/175 (6%)	13/194 (7%)	0,37
KMT2D	1/19 (5%)	12/175 (7%)	13/194 (7%)	1
EP300	1/19 (5%)	11/175 (6%)	12/194 (6%)	1
KMT2A	1/19 (5%)	9/175 (5%)	10/194 (5%)	1
SETD2	1/19 (5%)	8/175 (5%)	9/194 (5%)	1
ASXL1	2/19 (11%)	8/175 (5%)	10/194 (5%)	0,25
EZH2	1/19 (5%)	6/175 (3%)	7/194 (4%)	0,52
TET2	0/19 (0%)	5/175 (3%)	5/194 (3%)	1
TET3	0/19 (0%)	5/175 (3%)	5/194 (3%)	1
IDH2	0/19 (0%)	5/175 (3%)	5/194 (3%)	1
EED	0/19 (0%)	4/175 (2%)	4/194 (2%)	1
IDH1	0/19 (0%)	3/175 (2%)	3/194 (2%)	1
HIST1H1B	0/19 (0%)	1/175 (1%)	1/194 (1%)	1
Notch signaling				
NOTCH1	17/19 (89%)	130/175 (74%)	147/194 (76%)	0,17
FBXW7	5/19 (26%)	32/175 (18%)	37/194 (19%)	0,37
Cell cycle/Apoptosis				
CDKN2A	0/19 (0%)	13/175 (7%)	13/194 (7%)	0,62

TP53	1/19 (5%)	3/175 (2%)	4/194 (2%)	0,34
FAS	0/19 (0%)	1/175 (1%)	1/194 (1%)	1
RB1	0/19 (0%)	1/175 (1%)	1/194 (1%)	1
Transcriptional regulation				
BCL11B	6/19 (32%)	26/175 (15%)	32/194 (16%)	0,1
WT1	**5/19 (26%)**	**17/175 (10%)**	**22/194 (11%)**	**0,047**
RUNX1	3/19 (16%)	13/175 (7%)	16/194 (8%)	0,2
LEF1	0/19 (0%)	5/175 (3%)	5/194 (3%)	1
ETV6	0/19 (0%)	6/175 (3%)	6/194 (3%)	1
CNOT3	0/19 (0%)	5/175 (3%)	5/194 (3%)	1
TAL1	0/19 (0%)	4/175 (2%)	4/194 (2%)	1
IKZF1	0/19 (0%)	3/175 (2%)	3/194 (2%)	1
ZEB1	1/19 (5%)	3/175 (2%)	4/194 (2%)	0,34
GATA3	0/19 (0%)	1/175 (1%)	1/194 (1%)	1
TBL1XR1	0/19 (0%)	1/175 (1%)	1/194 (1%)	1
CEBPA	0/19 (0%)	2/175 (1%)	2/194 (1%)	1
CUX1	0/19 (0%)	2/175 (1%)	2/194 (1%)	1
Ribosome				
RPL5	2/19 (11%)	5/175 (3%)	7/194 (4%)	0,14
RPL10	0/19 (0%)	3/175 (2%)	3/194 (2%)	1
RNA processing				
ZRSR2	0/19 (0%)	10/175 (6%)	10/194 (5%)	0,6
SF3B1	0/19 (0%)	3/175 (2%)	3/194 (2%)	1
U2AF1	0/19 (0%)	2/175 (1%)	2/194 (1%)	1
Signaling other				
ATM	0/19 (0%)	7/175 (4%)	7/194 (4%)	1
PTPRC	0/19 (0%)	6/175 (3%)	6/194 (3%)	1
RELN	0/19 (0%)	6/175 (3%)	6/194 (3%)	1
IRF4	0/19 (0%)	3/175 (2%)	3/194 (2%)	1
CARD11	0/19 (0%)	2/175 (1%)	2/194 (1%)	1
KIT	0/19 (0%)	1/175 (1%)	1/194 (1%)	1
FLT3	0/19 (0%)	1/175 (1%)	1/194 (1%)	1
Chemokines				
CXXC4	0/19 (0%)	4/175 (2%)	4/194 (2%)	1
CXCR4	0/19 (0%)	3/175 (2%)	3/194 (2%)	1
CCR4	0/19 (0%)	1/175 (1%)	1/194 (1%)	1
Ubiquitination				
HACE1	0/19 (0%)	1/175 (1%)	1/194 (1%)	1
CUL3	0/19 (0%)	1/175 (1%)	1/194 (1%)	1
Other				
SAMHD1	1/19 (5%)	1/175 (1%)	2/194 (1%)	0,19
CD58	0/19 (0%)	1/175 (1%)	1/194 (1%)	1
ECT2L	0/19 (0%)	1/175 (1%)	1/194 (1%)	1

<u>Supplemental Table 7.</u> Genetic profile of PTPN2 deleted adult T-ALL.

Comparison of the mutational genotypes of adult PTPN2 deleted (N = 19) and wild-type T-ALLs (N = 175). Percentage frequencies in each group and p-values are indicated. Genes are grouped by functional categories.

Abbreviations: T-ALL, T-cell acute lymphoblastic leukemia; del, deleted; WT, wild-type.

Supplemental Table 8. Significant co-occurring mutations.

	PTPN2 del	**PTPN2 WT**	**Total**	**p-value**
	19 (10%)	**175 (90%)**	**194 (100%)**	
Mutated gene / pathway				
IL7R/JAK-STAT*	14/19 (74%)	72/175 (41%)	86/194 (44%)	0.008
PHF6	18/19 (95%)	71/175 (41%)	89/194 (46%)	< 0.0001
WT1	5/19 (26%)	17/175 (10%)	22/194 (11%)	0.047

Supplemental Table 8. Significant co-occurring mutations.

Significant mutations co-occurring with PTPN2 deletions in adult T-ALL patients are highlighted. Percentage frequencies in each group and p-values are indicated.

Abbreviations: T-ALL, T-cell acute lymphoblastic leukemia; del, deleted; WT, wild-type

* IL7R, JAK1, JAK3, STAT5B, DNM2, SH2B3

Supplemental Table 9. Focus on IL7R/JAK/STAT pathway mutations in PTPN2 deleted patients

JAK-STAT signaling mutations in PTPN2 deleted patients					
	Coding (missense)	Stop (nonsense)	Frameshift	Non Frameshift	Splicing
DNM2 (n=9)	2	2	3	1	1
JAK3 (n=5)	5				
IL7R (n=4)			1	3	
JAK1 (n=1)	1				
SH2B3 (n=2)	1	1			
STAT5B (n=1)	1				

Supplemental Table 9. Focus on IL7R/JAK/STAT pathway mutations in PTPN2 deleted patients

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