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Mature plasmacytoid dendritic cell proliferations are also associated with T-cell acute lymphoblastic leukemia: towards an expanding range of associated neoplasms

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Plasmacytoid dendritic cells (pDC) are innate immune cells for which two neoplastic counterparts are described in the latest classification of the World Health Organization Classification of Haematolymphoid Tumours (WHO-HAEM5).[1] The first one is blastic pDC neoplasm (BPDCN) characterized by the proliferation of neoplastic pDC expressing aberrant markers such as CD56 or cytoplasmic (c)TCL1 for which a link with ultraviolet (UV) exposure was recently demonstrated.[2] The second entity is mature plasmacytoid dendritic cell proliferation (MPDCP) associated with myeloid neoplasm (MN). In MPDCP, clonal pDCs, with a phenotype close to mature physiological pDCs, accumulate in the bone marrow (BM) of patients diagnosed with chronic myelomonocytic leukemia (CMML)[3], acute myeloid leukemia (AML)[4,5] or, in a smaller proportion of cases, myelodysplastic syndromes (MDS).[6] In MPDCP associated with AML (pDC-AML), a clonal origin is shared between blast cells and pDC with a higher recurrence of *RUNX1* mutations compared with AML without MPDCP.[4,5] It is estimated that 3 to 5% of all AML (either at diagnosis or relapse) are associated with a pDC expansion, whose cut-off is currently defined as more than 2% of BM leukocytes.[4,7] MPDCP in the context of AML might be associated with an adverse prognosis, with an adverse risk according to the criteria of the European Leukemia Network (ELN) and data suggesting a worse relapse-free (RFS) and overall survival (OS) in patients in comparison with AML without MPDCP.[4] Despite few case-reports, MPDCP associated with lymphoid neoplasm (MPDCP-LN) are not currently mentioned in classification and little is known about these cases. [8, 9, 10, 11, 12, 13]

Here, we describe the immunophenotypic and molecular profiles of MPDCP-LN, particularly T-cell acute lymphoblastic leukemia (T-ALL), in order to highlight their similarities or differences with MPDCP-MN and the potentially clonal origin shared between lymphoblasts and pDCs.

This study included four patients that exhibited pDCs excess above 2% (the current threshold fixed to distinguish MPDCP from reactive or physiological conditions).[4] None of them met the criteria for BPDCN or MPDCP-MN (Table 1). All cases were centrally reviewed in the French ROMI network reference laboratory. Information was provided for all patients, and samples were stored anonymously as permitted by local authorities by using no-objection form implemented in our institutions. The use of clinical samples was conducted in accordance with the Declaration of Helsinki and the study was approved by the local ethic committee (CPP Est II, Besançon, January 31st 2017, #DC2016-2791). Two cases met the criteria for a diagnosis of lymphoblastic lymphoma of T-lineage (LBL-T) while the other two were classified as T-ALL (Table 1, BM blasts ≥ 25%) with lymphoblasts (Figure 1A) and pDCs (Figure 1B) identified in the BM aspiration for all patient. No recurrent cytogenetic abnormality was detected on karyotype and no abnormalities were found by FISH if performed. Concerning disease outcomes,

three patients died, including two who had undergone allogeneic hematopoietic stem cell transplant (HSCT). (Table 1 and Figure S1 for full treatment information).

All multiparameter flow cytometry (MFC) analyses, illustrated for one patient (Figure 1C), revealed a population of pDC classically defined as $CD4^+$ $CD123^+$ HLA-DR^+, or $CD45RA^+$, $CD14^-$ $CD303/CD304^+$ cells (mean: 20.2%, range: 9-37%). In contrast to BPDCN, these pDCs did not express cTCL1, cLAMP5 or CD56 (Figure1D).[14] In some cases, they expressed myeloid or lymphoid markers such as CD13 (one case), CD33 (two cases) or CD7 (one case) that are significantly more expressed on pDCs from pDC-AML than pDCs from healthy samples.

The blast population was positive for CD7 and cCD3 for all cases and negative for CD8, CD4 and CD1a. Early-T cell precursor (ETP) criteria were met for all cases, either by a positivity of CD13 (two cases), CD33 (two cases), CD117 (one case) or HLA-DR (one case, also positive for CD117 and CD13) with the exception of the patient N128 for whom a diagnosis of near-ETP-ALL was proposed on the basis of a positivity of the CD5 marker on more than 75% of blast cells. No B-cell lineage markers or MPO positivity were identified on blast cells, ruling out the diagnosis of a mixed-phenotype acute leukemia. For all cases, the blasts did not express markers strongly associated with the pDC lineage (CD303, CD304) nor aberrant marker found in BPDCN such as CD56, cLAMP5 or cTCL1. However, we found an expression of CD123 in three cases (either moderate or strong) resembling the profile of myeloblasts in pDC-AML where around 80% of the cases are characterized by a proliferation of $CD123^+$ myeloblasts.[5,7]

In order to assess the potential link between pDC and blast populations, and to formally exclude the diagnosis of a reactive pDC expansion, cells were sorted for 3 cases (Figure 2A) for further targeted sequencing analysis (gene panel available in Table S1). Due to lack of sample material, cell sorting was not done for the latter (patient N167), for whom bulk analysis results of unsorted cells are available (Table S2). No shared mutations were found between the four cases analyzed, but all cases exhibited a classical profile for immature T-ALL, notably with epigenetic mutations (3 cases mutated for *DNMT3A*) and for Ras pathway (namely *NRAS* and *PTPN11*) (Figure 2B; Table S2). All the mutations found in lymphoblasts fraction were also detected in the pDC fraction except for *IDH1* and *NRAS* mutations for the patient N18 due to insufficient depth. The VAF between lymphoblasts and pDCs were close, with the exception of the N18 case for which the *DNTM3A* and *IKZF1* mutations were detected at a lower frequency in the pDC fraction, with VAF exceeding 50%, suggesting a loss of heterozygosity at neutral copy number for lymphoblasts, in contrast to pDCs. For the patient N128, where monocytes were also successfully sorted, mutations were also found in this population with similar VAF. All mutations were either not found, or found at a lower frequency in residual T-cells suggesting that these

cells did not develop from the clone involved in the pathogenesis of ETP-ALL and MPDCP in these cases. Interestingly, no mutations of the *RUNX1* gene were detected.

While MPDCP-MN is now much more recognized with its recent introduction in the 2022 WHO-HAEM5 classification, the data available on MPDCP-LN are scarce. Here, we report the biological description of the largest series of patients with a diagnosis of ETP-ALL/LBL associated with a MPDCP, which could be referred to as ETP-ALL-pDC. In addition to the four cases reported here, nine other cases of T-ALL and MPDCP have been reported in the literature. One of them was a non-ETP-ALL associated with MPDCP in a lymph node biopsy without BM involvement.[8] Two other cases were only described as T-ALL without further description on the phenotype of blast cells and no mention of a potential ETP phenotype.[9] Three cases were identified and classified as ETP-ALL.[10, 11, 12] Among them, single-cell RNA sequencing was performed in a 69-year-old male with a BM aspiration revealing 43% of blast cells and approximately 32% of pDC. Pseudo-time analysis suggested the presence of a transitional differentiation state between T-ALL blasts and pDC subsets with the latter originating from the former.[12] In another study, three other cases of T-ALL are reported including two for which the MFC profile matches an ETP-ALL diagnosis while not clearly mentioned by the authors.[13] Overall, despite one study suggesting a potential clonal common origin between blasts and pDC cells, no specific molecular or phenotypic profiles were described and further investigations are still needed to understand the biological mechanisms underlying the pDC expansion in the cases of ETP-ALL.

Our data, along with data reported in the literature, suggest that MPDCP-LN could occur more frequently in patients with a diagnosis of ETP-ALL. However, we were not able to assess the frequency of MPDCP in a cohort of ETP-ALL. In the largest cohort published, 95 T-ALL were screened and three patients were found to have more than 2% of pDCs in their BM, without clear mention of a potential ETP profile.[13]

As few molecular findings are available in the literature, the aim of our study was to better define the molecular relationship between cellular populations in those ETP-ALL-pDC cases. Interestingly, our results were similar to those obtained in pDC-AML in which a shared common clonal origin is described.[5] Indeed, in those cases, mutations found in blast cells are also found in pDCs, and, if applicable, in monocytes but not in lymphocytes, or at a strictly lower frequency. Despite these molecular similarities with pDC-AML, the mutational profile appears distinct with no *RUNX1* mutations, which is also confirmed by the few other cases reports available in the literature. However, our work would have benefited from the use of single cell RNA-sequencing or mitochondrial single-cell assay for transposase-accessible chromatin to fully establish clonal hierarchy between blasts and pDCs.[15]

Studies in pDC-AML suggest that the occurrence of MPDCP confers a worse prognosis in patients but without defined guidelines on how to treat these patients.[4] Unfortunately, we were not able to define the prognosis associated with this condition as only few cases were included in this study. The outcome of ETP-ALL-pDC would deserve to be clarified with a greater number of patients. Thus, we think that pDC expansion should be screened in every newly diagnosed ETP-ALL case by looking for a $CD123^{+high}$, $CD4^{+}$ and $HLA\text{-}DR^{+}$ (or $CD45RA^{+}$) population that could indicate a possible pDC excess and encourage extended screenings. Further studies are still required to assess whether the currently used threshold of 2% is biologically relevant, especially in ETP-ALL cases, and whether authentic MPDCP can be defined by fewer pDCs excess as no work focusing on such cases has been published until now.

In conclusion, this study contributes to expand the definition of MPDCP to lymphoid neoplasms, and brings further description of the biological profile of four cases of MPDCP associated with ETP-ALL/LBL. Our findings demonstrate that pDCs and lymphoblasts, as well as monocytes when present, might derive from the same clone, as they share identical molecular abnormalities. This entity displays a phenotypic and molecular profile clearly distinct from that of BPDCN and pDC-AML, and its prognosis will need to be assessed in larger cohorts.

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Table 1. Clinical and biological characteristics of the patients at diagnosis. *ALC: absolute lymphocyte count; ANC: absolute neutrophil count; ARAC: aracytine; ASNase: asparaginase, AZA: azacytidine; BM: bone marrow; BORT: bortezomib; CP: cyclophosphamide; CVAD: cyclophosphamide-vincristine-adriamycin-dexamethasone; DXM: dexamethasone; EGIL: European Group for the Immunological characterization of Leukemias; ETP-ALL/LBL: early T-precursor-acute lymphoblastic leukemia/lymphoblastic lymphoma; FISH: Fluorescent in-situ hybridization; HSCT: Hematopoietic stem cell transplant; HSM: Hepatosplenomegaly; IDA: idarubicin; M: male; ND: Not done; pDC: plasmacytoid dendritic cells; SDRPL: splenic diffuse red pulp lymphoma; VCR: vincristine; VEN: venetoclax; WBC: white blood cells; WHO: World Health Organization.*

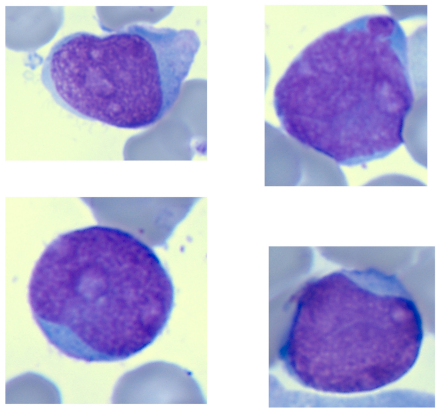
	N18	**N119**	**N128**	**N167**
Age (years)	69	71	65	44
Sex	M	M	M	M
Prior hematological neoplasm	None	SDRPL: 12 years prior to the diagnosis	None	None
Skin lesions	No	No	No	No
Lymph nodes involvement	Yes (axillary, inguinal)	No	No	No
HSM	No	No	No	No
WHO classification	ETP-ALL/LBL	ETP-ALL/LBL	Near-ETP-ALL/LBL	ETP-ALL/LBL
EGIL	Pre-T (II)	Pro-T (I)	Pre-T (II)	Pro-T (I)
Blasts (%, in BM)	16	21	49	55
pDC (%, in BM)	21	9	14	37
Hemoglobin (g/dL)	15.3	6.2	10.2	7.9
Platelets (10^9/L)	203	56	90	75
WBC count (10^9/L)	5	0.58	1.68	2.6
ANC (10^9/L)	3.75	0.34	0.74	0.43
ALC (10^9/L)	0.75	0.23	0.41	2
Karyotype	46,XY [28]	46,XY,del(20)(q11q13) [11] ; 45,X-Y [2]	45,XY,del(2)(q22q37),der(7;12)(q10;q10)[8] 46,XY(2]	47,XY,+10 [18] 46,XY [8]
FISH				
KMT2A	ND	Negative	Negative	Negative
BCR::ABL1	ND	ND	Negative	Negative
NUP98	ND	Negative	ND	ND
Treatment	Chemotherapy + allo-HSCT	Chemotherapy	Chemotherapy	Chemotherapy + allo-HSCT
Induction therapy	HyperCVAD (relapse)	IDA+VCR (progression)	FRAIL protocol (progression)	GRAALL2014 (relapse)
Response	Refractory/relapse	Refractory	Remission	Refractory
Salvage therapy	L-ASNase + IDA + BORT (relapse)	AZA+VEN (progression)	IDA+ARAC (2g/m²) (MRD+)	Nelarabine + VP16 + CP (toxicity, relapse)
	Nelarabine + Allo-HSCT (relapse)			Clofarabine + Allo-HSCT (relapse)
	VCR + CP + DXM (progression)			AZA+VEN (relapse)
Status at last follow-up	Dead (16 months)	Dead (6 months)	Alive (12 months)	Dead (20 months)

FIGURE LEGENDS

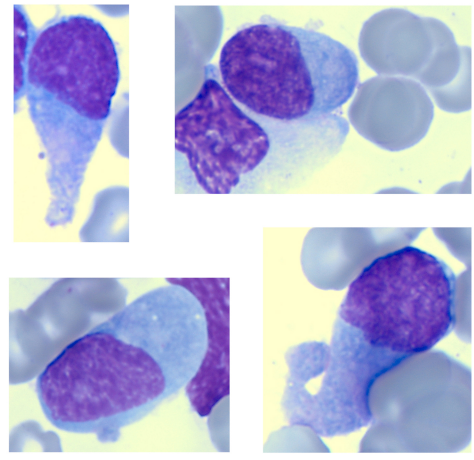
Figure 1. Cytomorphologic and flow cytometric profiles of populations of interest. Representative morphologic aspects of bone marrow sample from patient N18 (magnification 1000 X) with (A) characteristics blasts and (B) plasmacytoid dendritic cells (pDC) identified as small or medium-sized cells with lower nuclear cytoplasmic ratio, eccentric nucleus and slightly more mature chromatin. Some cells show a distinct pseudopod and small vacuoles around the nucleus. (C) Flow cytometry graphs illustrating the phenotype of lymphocytes (in blue), pDC (in pink) and lymphoblasts (in black) with all evaluated markers represented in panel (D) with markers in deep purple expressed by more than 80% of cells, in purple by 20% to 80% of cells and in light purple considered negative (<20% of positive cells). Markers in dark grey were not evaluated. Data are obtained on bone marrow leukocytes at diagnosis. Marker positivity was assessed by each laboratory and reviewed centrally by members of the French ROMI network.

Figure 2. Mutation profile of acute T-lymphoblastic leukemia associated with pDC proliferation. (A) Workflow for mutation profile analysis on sorted cells from BM samples obtained from three patients. (B) Mutations detected by targeted sequencing with variant allele frequency (VAF) represented. *¥ PDCs were sorted using the CD123 and CD14 markers as it was verified beforehand that samples were devoid of $CD123^{+}$ $HLA\text{-}DR^{-}$ basophils; *: Insufficient depth to confirm the mutation with a reliable VAF (100x with a minimum of 15 reads); $: anomalies detected by Copy Number Variation (CNV) analysis; CNV were detected thanks to the CNV module provided by the SOPHiA Genetics bioinformatics pipeline (CNV detection configuration: CMYS_S_v1 v16.57), **: Data not available due to insufficient performances (depth, coverage, length) to assess Copy Number Variation; ^{1,2}: two different mutations were detected; icons adapted from Servier Medical Art*

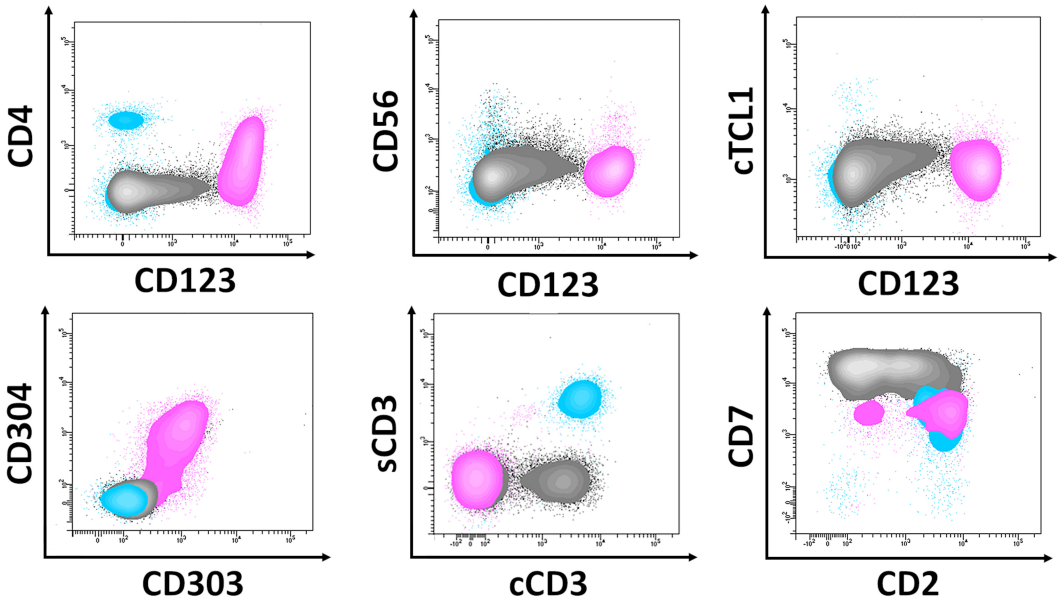
A



B

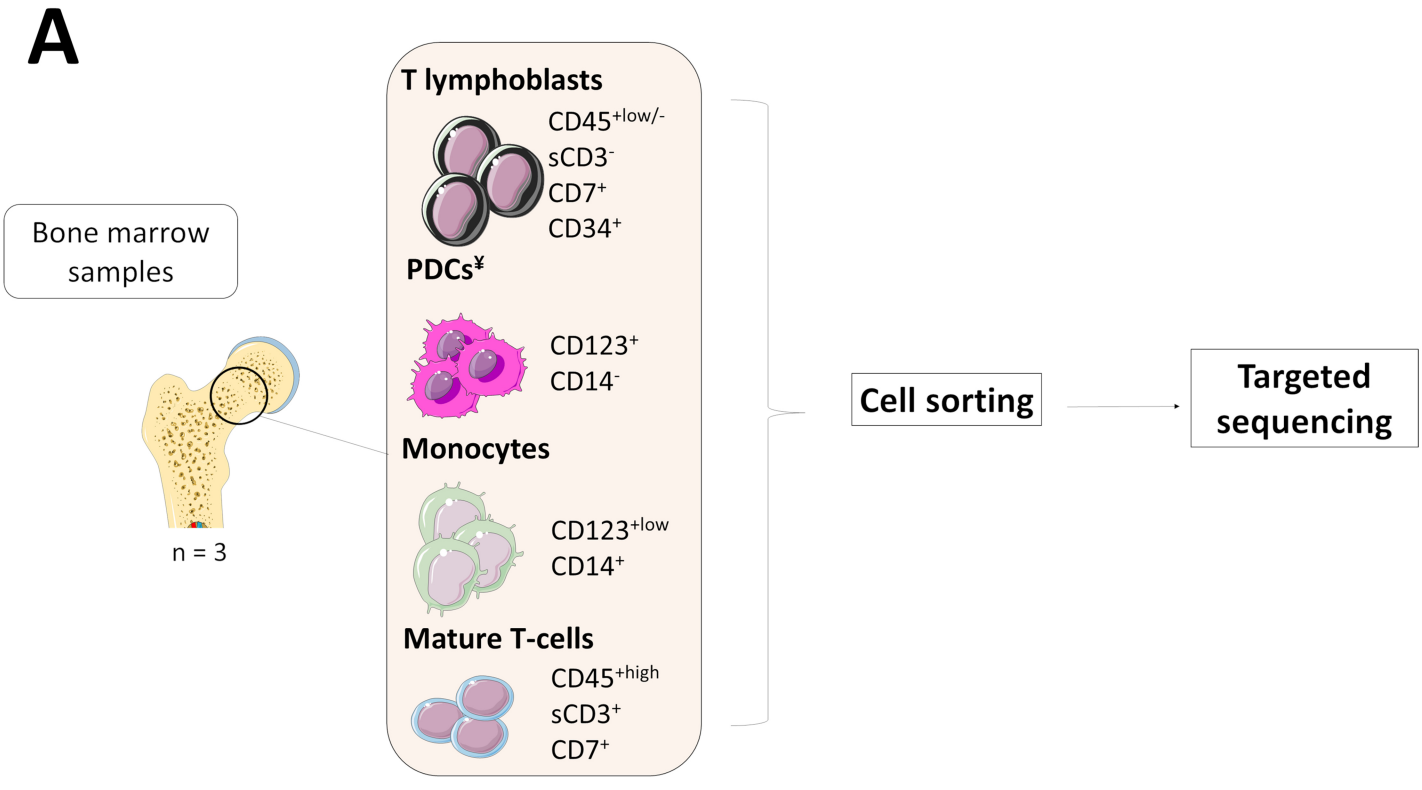


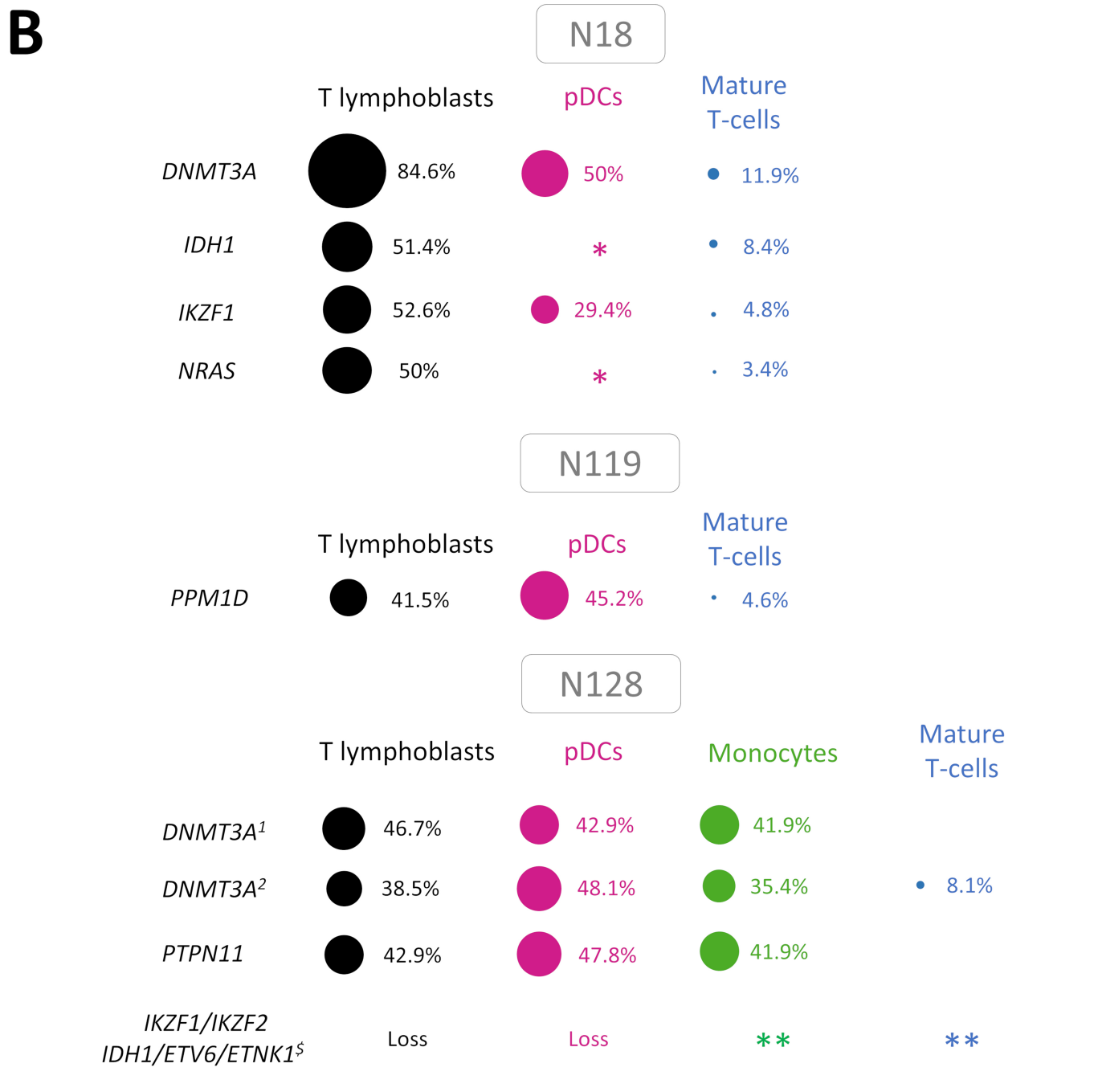
C



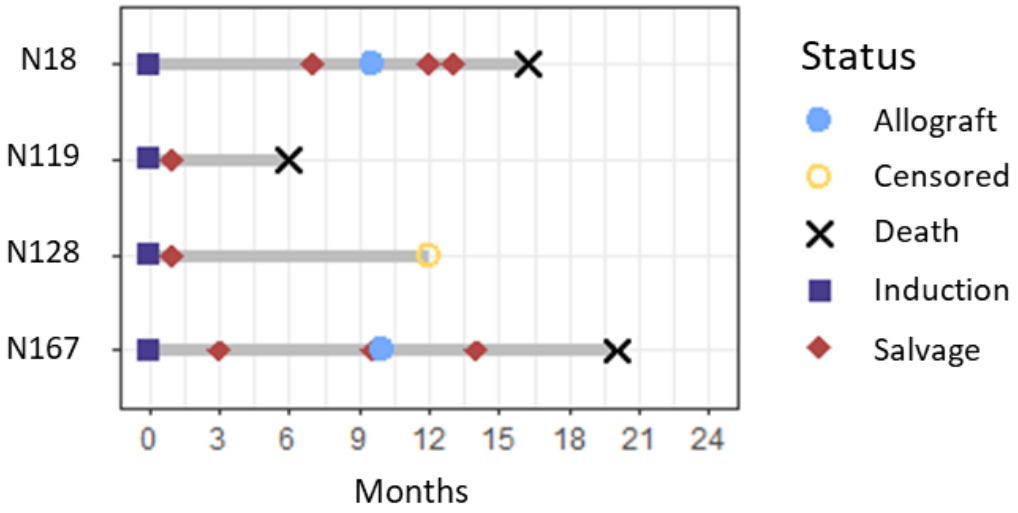
D

	N18		N119		N128		N167	
	Blasts	pDC	Blasts	pDC	Blasts	pDC	Blasts	pDC
% of cells in sample	16%	21%	21%	9%	49%	14%	55%	37%
CD7								
cCD3								
sCD3								
CD2								
CD5								
CD4								
CD8								
CD13								
CD33								
CD117								
cMPO								
HLA-DR								
TdT								
CD34								
CD123								
CD303								
CD304								
CD56								
cTCL1								
cLAMP5								


A
Bone marrow samples
n = 3
T lymphoblasts
CD45+low/-
sCD3-
CD7+
CD34+
PDCs¥
CD123+
CD14-
Monocytes
CD123+low
CD14+
Mature T-cells
CD45+high
sCD3+
CD7+
Cell sorting
Targeted sequencing


B
N18
T lymphoblasts
pDCs
Mature T-cells
DNMT3A
84.6%
50%
11.9%
IDH1
51.4%
*
8.4%
IKZF1
52.6%
29.4%
4.8%
NRAS
50%
*
3.4%
N119
T lymphoblasts
pDCs
Mature T-cells
PPM1D
41.5%
45.2%
4.6%
N128
T lymphoblasts
pDCs
Monocytes
Mature T-cells
DNMT3A1
46.7%
42.9%
41.9%
DNMT3A2
38.5%
48.1%
35.4%
8.1%
PTPN11
42.9%
47.8%
41.9%
IKZF1/IKZF2
IDH1/ETV6/ETNK1$
Loss
Loss
**
**

Supplementary data



Supplementary Figure 1. Swimmer plot displaying type of treatment and therapy response in ETP-ALL patients.

Representation of the type of treatment received by the four ETP-ALL patients from time to diagnosis.

Supplementary Table S1. Targeted sequencing panel used for the molecular profile analysis of sorted fractions.

Gene	Targeted region	Transcript
ABL1	exons 4-9	NM_005157.5
ANKRD26	exons 1, 2	NM_014915.2
ARID1A	exons 1-20	NM_006015.6
ASXL1	exons 10,12,13	NM_015338.5
ASXL2	exons 12-13	NM_018263.6
ATRX	exons 1-35	NM_000489.4
BAX	full gene	NM_138761.3
BCOR	full gene	NM_001123385.1
BCORL1	full gene	NM_021946
BRAF	exons 11-15	NM_004333.4
CALR	exon 9	NM_004343.3
CBL	exons 1-9	NM_005188
CEBPA	full gene	NM_004364.3
CSF3R	full gene	NM_000760.3
CSNK1A1	exons 2-4	NM_001892.5
CTCF	full gene	NM_006565.4
CTNNB1	exon 3	NM_001098209
CUX1	full gene	NM_181552.3
DDX41	full gene	NM_016222.3
DNMT3A	full gene	NM_022552.4
ETNK1	exon 3	NM_018638
ETV6	full gene	NM_001987.4
EZH2	full gene	NM_004456.4
FLT3	full gene	NM_004119.2
GATA2	full gene	NM_0320638.4
GNAS	full gene	NM_000516.5
GNB1	exons 5,6	NM_002074.4
IDH1	full gene	NM_005896.2
IDH2	full gene	NM_002168.2
IKZF1	exons 2-8	NM_006060.5
IKZF2	exons 2-9	NM_001387220.1
JAK2	full gene	NM_004972.4
KDM6A	full gene	NM_021140.2
KIT	full gene	NM_000222.2
KMT2A	full gene	NM_005933.3
KRAS	exons 1-4	NM_033360.4
LUC7L2	full gene	NM_016019.5
MPL	full gene	NM_005373.2
MYC	exons 1-3	NM_002467.6
MYD88	exons 2-5	NM_002468.4
NF1	full gene	NM_001042492.2
NPM1	full gene	NM_002520.6
NRAS	exons 1-4	NM_002524.4

PDGFRA	exon 18	NM_006206.6
PHF6	full gene	NM_001015877.1
PPM1D	exon 6	NM_003620.3
PRPF8	full gene	NM_006445.3
PTPN11	full gene	NM_002834.3
RAD21	full gene	NM_006265.2
RB1	exons 1-27	NM_000321.3
RHOA	exon 2	NM_001664.2
RIT1	exons 4-5	NM_006912.5
RUNX1	full gene	NM_001754.4
RUNX2	exons 1-9	NM_001024630.4
SAMD9	full gene	NM_017654.3
SAMD9L	full gene	NM_152703.2
SETBP1	exons 4, 5	NM_015559.2
SF3B1	full gene	NM_012433.2
SH2B3	full gene	NM_005475.2
SMC1A	full gene	NM_006306.3
SMC3	full gene	NM_005445.3
SRSF2	exons 1, 2	NM_003016.4
STAG2	full gene	NM_001042749.1
STAT3	exons 10, 16, 19 - 21	NM_139276.2
SUZ12	exons 1-16	NM_015355.4
TET2	full gene	NM_001127208.2
TP53	full gene	NM_000546.5
U2AF1	exons 2, 6	NM_006758.2
UBA1	full gene	NM_003334.3
UBTF	exons 10-15	NM_014233.4
WT1	full gene	NM_024426.4
ZEB2	exon 2-10	NM_014795.4
ZRSR2	full gene	NM_005089.3

Supplementary Table S2. Mutation profile of each ETP-ALL patient with MPDCP detected by targeted sequencing. Only mutations with a VAF ≥ 2% are represented. *NA: Not Available (due to the absence of monocytes in these samples); ND: Not Detected; * Data not available due to insufficient depth of analysis;* ¥ *Targeted sequencing was performed on bulk cells as cell sorting was not feasible due to the lack of biological samples left for cell sorting.*

Patient	Mutations	VAF in Blasts	VAF in pDC	VAF in Monocytes	VAF in T-cells
N18	***DNMT3A*** exon 8, p.(Gly298Glu), c.893G>A	84.6	50	NA	11.9
	IDH1 exon 4, p.(Arg132Ser), c.394C>A	51.4	*		8.4
	IKZF1 exon 4, p.(Pro113Trpfs*3), c.336_337insTGGC	52.6	29.4		4.8
	NRAS exon 2, p.(Gly13Val), c.38G>T	50	*		3.4
N119	***PPM1D*** exon 6, p.(Cys478*), c.1434C>A	41.1	45.2	NA	4.6
N128	***DNMT3A*** exon 23, p.(Arg885Ser), c.2655G>T	46.7	42.9	41.9	ND
	DNMT3A exon 13, p.(Cys497Gly), c.1489T>G	38.5	48.1	35.4	8.1
	PTPN11 exon 7, p.(Arg265Gln), c.794G>A	42.9	47.8	45.8	ND
N167¥	***DNMT3A*** exon 17 c.2057A>T : p.D686V	87			
	IDH2 exon 4 c.419G>A : p.R140Q	41			
	IKZF1 exon 4 c.421+1dup	41			
	IKZF1 exon 4 c.172_173insTC : p.K58IfsX3	5			
	NOTCH1 exon 26 c.4727T>A : p.V1576E	28			
	NOTCH1 exon 27 c.5020T>C : p.S1674P	14			
	NRAS exon 2 c.35G>A : p.G12D	27			
	NRAS exon 3 c.182A>C : p.Q61P	15			