The prognosis of *CALM-AF10*-positive adult T-cell acute lymphoblastic leukemias depends on the stage of maturation arrest

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ABSTRACT

CALM-AF10 (also known as PICALM-MLLT10) is the commonest fusion protein in T-cell acute lymphoblastic leukemia, but its prognostic impact remains unclear. Molecular screening at diagnosis identified *CALM-AF10* in 30/431 (7%) patients with T-cell acute lymphoblastic leukemia aged 16 years and over and in 15/234 (6%) of those aged up to 15 years. Adult *CALM-AF10*-positive patients were predominantly (72%) negative for surface (s)CD3/T-cell receptor, whereas children were predominantly (67%) positive for T-cell receptor. Among 22 adult *CALM-AF10*-positive patients treated according to the LALA94/GRAALL03-05 protocols, the poor prognosis for event-free survival (P=0.0017) and overall survival (P=0.0014) was restricted to the 15 T-cell receptor-negative cases. Among *CALM-AF10*-positive, T-cell receptor-negative patients, 82% had an early T-cell precursor phenotype, reported to be of poor prognosis in pediatric T-cell acute lymphoblastic leukemia. Early T-cell precursor acute lymphoblastic leukemia corresponded to 22% of adult LALA94/GRAALL03-05 T-cell acute lymphoblastic leukemias, but had no prognostic impact *per se*. *CALM-AF10* fusion within early T-cell precursor acute lymphoblastic leukemia (21%) did, however, identify a group with a poor prognosis with regards to event-free survival (P=0.04). *CALM-AF10* therefore identifies a poor prognostic group within sCD3/T-cell receptor negative adult T-cell acute lymphoblastic leukemias and is over-represented within early T-cell precursor acute lymphoblastic leukemias, in which it identifies patients in whom treatment is likely to fail. Its prognosis and overlap with early T-cell precursor acute lymphoblastic leukemia in pediatric T-cell acute lymphoblastic leukemia merits analysis. *The clinical trial GRAALL was registered at Clinical Trials.gov number NCT00327678.*

Introduction

T-cell acute lymphoblastic leukemia (T-ALL) accounts for 25% of adult and 10-15% of pediatric ALL.[1,2] Although its outcome has improved significantly with current therapy, relapses are frequent and are associated with a poor prognosis[3,4] The prediction of relapsing T-ALL remains challenging and few of the classical initial prognostic factors appropriate for therapeutic stratification in B-lineage ALL apply.[5-7] Currently recognized predictors of poor outcome include the absence of *NOTCH1* and/or *FBXW7* mutation in adult T-ALL[8] and an early T-cell precursor (ETP) phenotype in pediatric T-ALL, defined as $CD1a^-$, $CD8^-$ and $CD5^{weak}$ with stem-cell or myeloid markers.[9] Debate exists regarding the prognostic impact of *NOTCH1/FBXW7* status in pediatric T-ALL[10-12] and the prognosis of ETP-ALL is increasingly controversial. Several studies show that ETP-ALL are close to acute myeloid leukemia (AML) and optimal therapy for this subgroup has not yet been defined.[9,13-15]

One classical oncogenic marker that has long been recognized to occur in both AML and T-ALL, in which it corresponds to the most frequent fusion protein, is *CALM-AF10* (also known as *PICALM-MLLT10*), resulting from the t(10;11)(p12;q14).[16,17] *(PI)CALM* is ubiquitously expressed and plays a role in clathrin-mediated endocytosis.[18] Defective CALM function alters hematopoiesis and transferrin endocytosis.[19] *AF10 (MLLT10)* encodes a protein containing an N-terminal plant homeodomain (PHD) involved in chromatin-mediated gene regulation, an extended PHD/leukemia-associated protein (LAP) domain mediating homo-oligomerization and a C' leucine-zipper domain which interacts with the histone methyltransferase hDOT1L and with Ikaros.[20,21] hDOT1L prevents nuclear export of CALM-AF10 and leads to up-regulation of the *HOXA* gene cluster by H3K79 histone methylation.[22,23] Systematic screening for *CALM–AF10* has only been performed in T-ALL, in which 20 cases were identified, predominantly in adolescents and young adults.[24] CALM-AF10 were restricted to the TCRγδ lineage with either an "ETP-like"

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surface (s)CD3⁻, immature stage of maturation arrest (IMγ > IMδ), or expression of sCD3/TCRγδ.[24] The latter were suggested to correlate with a 5' *AF10* breakpoint which retained the AF10 PHD/LAP domains.[24]

Patients with *CALM-AF10*⁺ acute leukemias are commonly considered to have a poor prognosis, but this is essentially based on sporadic reports and has not been evaluated within the context of prospective clinical trials in either ALL or AML.[16,17,25-29] Their overlap with ETP-ALL is also unknown. We, therefore, evaluated the incidence, clinical characteristics and biological features of adult and pediatric *CALM-AF10*⁺ T-ALL and, more specifically, the prognostic impact of *CALM-AF10* relative to an ETP phenotype in adult T-ALL.

Methods

Patients and treatment

Between 1993 and 2009, fresh and/or cryopreserved diagnostic bone marrow or blood samples were obtained from 811 T-ALL patients. The present study was restricted to 665 of these patients with cDNA available for *CALM-AF10* screening, including 234 pediatric (15 years or less) and 431 adult cases. The study was approved by local and multicenter research ethical committees and by the institutional review board (IRB) of the French Regulatory Agency. Consent was obtained from all patients at trial entry according to the Declaration of Helsinki.

Of the 431 adults with T-ALL, 225 were treated within the prospective multicenter LALA-94 (n=78) or GRAALL-2003/2005 (n=147) protocols by the time of the first planned interim analysis, as described elsewhere.[1,8,30] The therapeutic protocols of the remaining 206 adults with T-ALL are provided in the *Online Supplementary Appendix*. The majority (191/234) of pediatric T-ALL patients were treated on FRALLE 93 or 2000 protocols[31], including nine *CALM-AF10*⁺ cases. Remaining pediatric cases were treated with various therapeutic regimens.

Diagnostic analyses

The diagnosis of T-ALL was based on World Health Organization 2008 immunophenotypic criteria.[32] The diagnosis of ETP-ALL was defined immunophenotypically[9] (see *Online Supplementary Appendix*) and was evaluated centrally. Screening for *CALM-AF10* transcripts was performed by real-time quantitative reverse transcriptase polymerase chain reaction (RTQ-PCR), with the primers and probes listed in *Online Supplementary Table S1*. *CALM-AF10* transcript sequencing was performed as described elsewhere.[24]

Karyotypes were interpreted according to the International System for Human Cytogenetic Nomenclature.[33] Fluorescence *in situ* hybridization (FISH) using *CALM* and *AF10* probes (described by Asnafir *et al.*[24]) was performed for RTQ-PCR *CALM-AF10*⁺ patients with normal or non-informative karyotypes.

Statistical analyses

Statistical analyses are detailed in the *Online Supplementary Appendix*. Survival analyses were restricted to adult patients treated on or according to the LALA94 and GRAALL03/05 protocols. The median follow-up was 7.7 years for LALA-94 and 3.0 years for GRAALL patients. In some cases, there was insufficient material to perform all planned tests. A flow diagram of sample analyses is shown in *Online Supplementary Figure S1*. Each survival analysis was based on the entire set of available data for a given parameter (see *Online Supplementary Figure S2*).

Results

Incidence and characteristics of CALM-AF10-positive adult and pediatric T-cell acute lymphoblastic leukemias

CALM-AF10 transcripts were detected by RTQ-PCR analysis in 45 out of 665 T-ALL (7%), with a similar incidence in pediatric and adult cases (Table 1). In pediatric T-ALL, the median age of *CALM-AF10*⁺ cases was significantly higher than that of the *CALM-AF10*⁻ cases. Only four *CALM-AF10*⁺ cases were detected among the 125 children under 10 years old (3%), compared to an incidence of 10% (11/109) in those aged 10-15 years (P=0.05). In adult T-ALL, the median age of *CALM-AF10*⁺ cases was similar to that of *CALM-AF10*⁻ cases. *CALM-AF10*⁺ T-ALL patients had a lower white blood cell count at presentation but no difference in mediastinal or CNS involvement (Table 1). Karyotypic data were available for 34 *CALM-AF10*⁺ T-ALL cases; only 20 (59%) had a t(10;11) or ins(10;11) (*Online Supplementary Table S2*). FISH analyses using *CALM* and *AF10* probes confirmed the RTQ-PCR result in *CALM-AF10*⁺ cases with normal or non-informative conventional cytogenetics (*data not shown*).

CALM-AF10-positive TCR-negative T-cell acute lymphoblastic leukemias have an early T-cell immuno-genotype

Genetic, immunophenotypic and clinical data of *CALM-AF10*⁺ T-ALL are shown in *Online Supplementary Table S3*. Most (59%) *CALM-AF10*⁺ T-ALL were immature (IM) sCD3⁻, sTCR⁻, cTCRβ⁻ with *TCRδ* (IMδ) and/or *TCRγ* (IMγ) rearrangements but no or incomplete *TCRβ* DJ by genomic PCR (referred to here as TCR⁻ T-ALL). The remaining 18 adequately phenotyped cases expressed a sCD3/TCR and cortical/pre-αβ T-ALL were strikingly absent. Sixteen expressed a TCRγδ, but two adult T-ALL

Table 1. Clinical characteristics of *CALM-AF10*⁺ and *CALM-AF10*⁻ pediatric and adult T-ALL patients.

	Pediatric (0-15 years)			Adult (16 years or over)		
	CALM-AF10 positive	*CALM-AF10* negative	*P*	*CALM-AF10* positive	*CALM-AF10* negative	*P*
Incidence	6% (n= 15)	94% (n= 219)		7% (n= 30)	93% (n= 401)	
Sex ratio (male/female)	2.75	3.14	ns	2	3.8	ns
Median age in years. (range)	14 (3-15)	9 (1 month-15)	**0.01**	29 (17-46)	32 (16-78)	ns
Median WBC (x10⁹/L)	68.5	122.7	**0.03**	11.2	48	**0.02**
Mediastinal involvement	66%	70%	ns	33%	45%	ns
CNS involvement	7%	7%	ns	12%	9%	ns

WBC: white blood count; CNS: central nervous system.

expressed an atypical CD2$^-$/CD4$^-$/CD8$^-$/TCRαβ phenotype, one in conjuction with a Vα29/Vδ5-Jδ1 rearrangement, and as such was compatible with a hybrid β/δ receptor.[34] *CALM-AF10*$^+$ TCR$^-$ predominated in adults and TCR$^+$ forms in children (P=0.02; Table 2). Importantly, 82% of *CALM-AF10*$^+$ TCR$^-$ T-ALL had an ETP phenotype compared to none of the *CALM-AF10*$^+$ TCR$^+$ T-ALL (P<10^{-7}).

Prognosis associated with CALM-AF10 *in adult T-cell acute lymphoblastic leukemia*

CALM-AF10 was detected in 16/225 (7%) patients treated within LALA/GRAALL protocols (indicated by asterisks in *Online Supplementary Table S3*). All, apart from one who died early, obtained complete remission (CR). The characteristics of the 16 *CALM-AF10*$^+$ *versus* 209 *CALM-AF10*$^-$ T-ALL are shown in Table 3. *CALM-AF10*$^+$ patients differed once again by a lower presenting leukocytosis (P=0.02) and more frequent ETP phenotype (P=0.002).

No differences were found between the overall *CALM-AF10*$^+$ and *CALM-AF10*$^-$ group regarding 3-year event-free survival (EFS) (P=0.57) and overall survival (OS) (P=0.53) (*Online Supplementary Figure S3A,B*). However, when clinical outcome was assessed according to the TCR subset, it was strikingly different in TCR$^-$ and TCR$^+$ *CALM-AF10*$^+$ T-ALL. Kaplan-Meier analyses showed a significantly higher risk of events (P=0.028) and death (P=0.014) at 3 years for *CALM-AF10*$^+$ TCR$^-$ patients, when compared to *CALM-AF10*$^+$ TCR$^+$ or *CALM-AF10*$^-$ patients (Figure 1A,B).

Since the number of *CALM-AF10*$^+$ protocol patients was limited (n=16), clinical follow-up of an additional six *CALM-AF10*$^+$ patients treated according to LALA/GRAALL but off protocol, were included in outcome analyses of *CALM-AF10*$^+$ T-ALL. This confirmed and reinforced the strikingly inferior outcome of TCR$^-$ compared to TCR$^+$ *CALM-AF10*$^+$ T-ALL treated on adult ALL protocols (P=0.0017 for EFS and P=0.0014 for OS; *Online Supplementary Figure S4A,B*). A comparison of patients with a *CALM-AF10* 5'FT which retains the *AF10* PHD/LAP and 3'FT cases having lost this domain showed no difference in EFS or OS (*data not shown*).

Prognosis associated with CALM-AF10 *in pediatric T-cell acute lymphoblastic leukemia*

Of the ten pediatric *CALM-AF10*$^+$ TCR$^+$ patients, all but two (one early death at induction and one death from graft-*versus*-host disease) are in continuous CR at 6 to 115 months after induction (median 69 months), whereas three

Table 2. Age, transcript type and ETP phenotype of *CALM-AF10* positive T-ALL according to TCR status.

	TCR negative	TCR positive	*P*	Unknown TCR status	All patients
	26	18		1	45
Median age (range)	25 (12-46)	15 (3-45)	0.03	29	24 (3-46)
Adult	21 (72%)	8 (28%)	0.02	1	30
Pediatric	5 (33%)	10 (67%)			15
<10 years	0 (0%)	4 (100%)			4
10-15 years	5 (45%)	6 (55%)			11
CA transcript type					
5'	9 (41%)	10 (62%)	0.32		19
3'	13 (59%)	6 (38%)			19
not available	4	2		1	7
ETP phenotype					
yes	18 (82%)	0 (0%)	P<10^{-7}		18
no	4 (18%)	18 (100%)			22
not available	4	0		1	5

CA: CALM-AF10; *TCR: T-cell receptor; ETP: early T-cell precursor.*

Table 3. Characteristics of *CALM-AF10*$^+$ and *CALM-AF10*$^-$ adult T-ALL patients treated in LALA/GRAALL protocols.

	Total 225	CALM-AF10 positive 16 (7%)	CALM-AF10 negative 209 (93%)	*P*
TCR subsets (n=204)				
TCR$^-$	160 (78%)	11(69%)	149 (79%)	ns
TCR$^+$	44 (22%)	5 (31%)	39 (21%)	
Not available	21	0	21	
ETP phenotype (n=190)				
yes	42 (22%)	9 (56%)	33 (19%)	**0.002**
no	148 (78%)	7 (44%)	141 (81%)	
not available	35	0	35	
NOTCH1/FBXW7 mutations (n=214)				
yes	144 (67%)	6 (46%)	138 (69%)	ns
no	70 (33%)	7 (54%)	63 (31%)	
not available	11	3	8	
Clinical subsets analyzed (n=225)				
sex(male/female)	175/50	11/5	164/45	ns
age median years (range)	30 (16-59)	32 (23-46)	30 (16-59)	ns
age>35 years	79 (35%)	6 (37%)	73 (35%)	ns
WBC median (10^9/L)	42	7,75	48	**0.02**
WBC>100x10^9/L	67 (30%)	1 (6%)	66 (32%)	**0.04**
mediastinal involvement	99 (44%)	5 (31%)	94 (45%)	ns
CNS involvement	20 (9%)	2 (12%)	18 (9%)	ns
complete remission rate	92%	94%	92%	ns
relapse	43%	56%	42%	ns
stem cell transplant rate	24%	44%	22%	ns

TCR: T-cell receptor; ETP: early T-cell precursor; WBC: white blood cell; CNS: central nervous system; ns: non-significant.

of the five pediatric cases with *CALM-AF10*$^+$ TCR$^-$ T-ALL have relapsed (P=0.03 for relapse rate) and two have died (*Online Supplementary Table S3*). It is noteworthy that both fully documented *CALM-AF10*$^+$ TCR$^-$ survivors benefited from stem cell allograft (one each in first and second CR). The third *CALM-AF10*$^+$ TCR$^-$ patient was lost to follow-up in CR at 60 months from diagnosis.

Relative prognostic impact of CALM-AF10 and early T-cell phenotype in adult T-cell acute lymphoblastic leukemia

Since 82% of *CALM-AF10*$^+$ TCR$^-$ T-ALL had an ETP phenotype, reported to identify a very poor prognostic subset of pediatric T-ALL, we evaluated the relative prognostic impact of *CALM-AF10* and ETP phenotype in the LALA/GRAALL protocol cohort. Sufficient immunophenotypic data were available to classify 190 patients into 42 ETP-ALL and 148 non-ETP-ALL (Table 3). The 42 cases of ETP-ALL included nine *CALM-AF10*$^+$ (all TCR$^-$) while the 148 non-ETP-ALL included seven *CALM-AF10*$^+$ cases (5 TCR$^+$ and 2 TCR$^-$). It is noteworthy that *CALM-AF10* was the most frequent genetic aberration in ETP-ALL (9 *CALM-AF10*$^+$, 6 *TLX3*$^+$ and 1 *SIL-TAL*$^+$). Surprisingly, no significant differences were found between ETP-ALL and non-ETP-

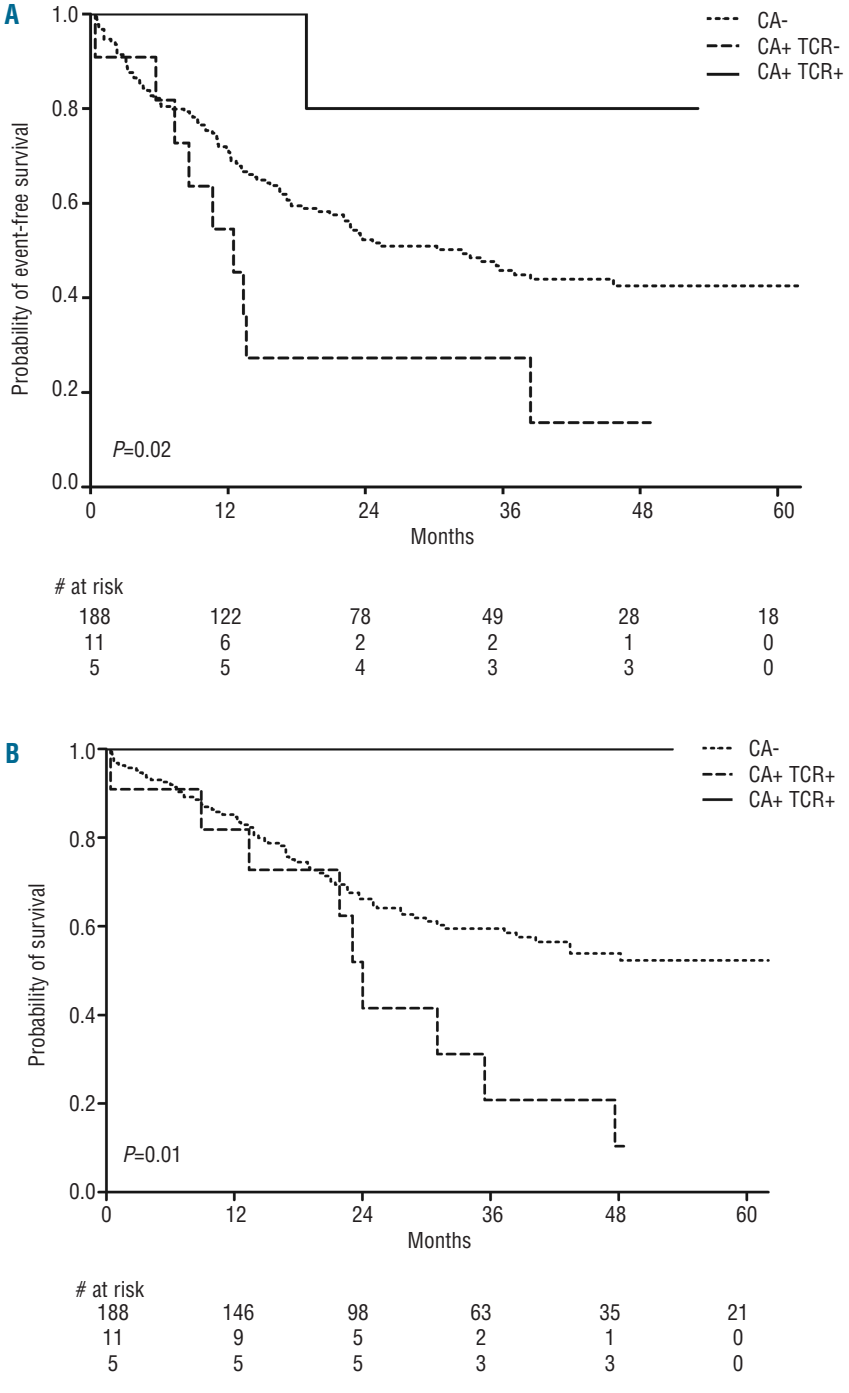
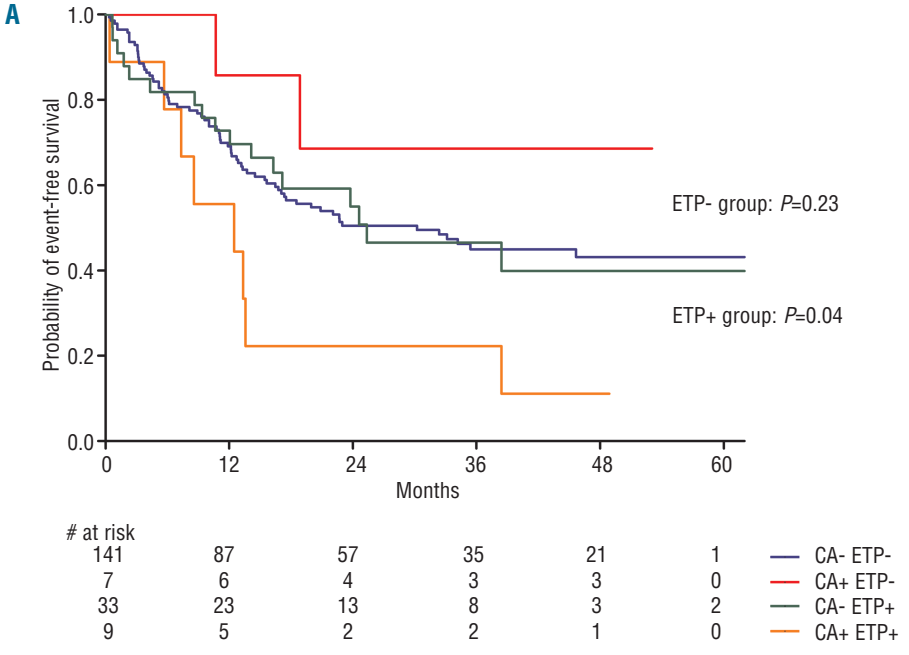


Figure 1. Prognostic impact of *CALM-AF10* according to TCR status in adult LALA/GRAALL T-ALL. (A) Event-free survival and (B) overall survival. Significant differences in 3-year EFS (P=0.028) and OS (P=0.014) were found between *CALM-AF10*$^+$ TCR$^-$ (dashed line) (27% [95%CI, 7-54] for EFS and 21% [95%CI, 3-49] for OS), *CALM-AF10*$^-$ (dotted line) (45% [95%CI, 38-53] for EFS and 59% [95%CI, 51-66] for OS) and *CALM-AF10*$^+$ TCR$^+$ (full line) (80% [95%CI, 20-97] for EFS and 100% for OS) groups.

ALL patients regarding 3-year EFS (P=0.42) and OS (P=0.24) (*Online Supplementary Figure S5A,B*). We then combined ETP phenotype and *CALM-AF10* status, and compared 3-year EFS (Figure 2A) and OS (Figure 2B). Interestingly, this showed a significantly higher risk of events (P=0.04) and a trend towards lower OS (P=0.07) for *CALM-AF10*$^+$ ETP-ALL patients when compared to *CALM-AF10*$^-$ ETP-ALL patients. Furthermore, the outcome of *CALM-AF10*$^-$ ETP-ALL patients did not differ from that of *CALM-AF10*$^-$ non-ETP-ALL patients (P=0.94 and P=0.86 for EFS and OS, respectively).

Discussion

CALM-AF10 is a rare fusion transcript and the present series represents by far the largest published. We show that *CALM-AF10* is found in 3% of T-ALL in younger children, in 10% of 10- to 15-year olds and in 7% of older cases. Sporadic reports of *CALM-AF10* in AML and T-ALL tended to suggest that this anomaly is associated with a poor prognosis.[16,17,25-29] Overall, this fusion transcript had no prognostic impact in LALA/GRAALL-treated patients, in keeping with data showing no difference in EFS and OS of six



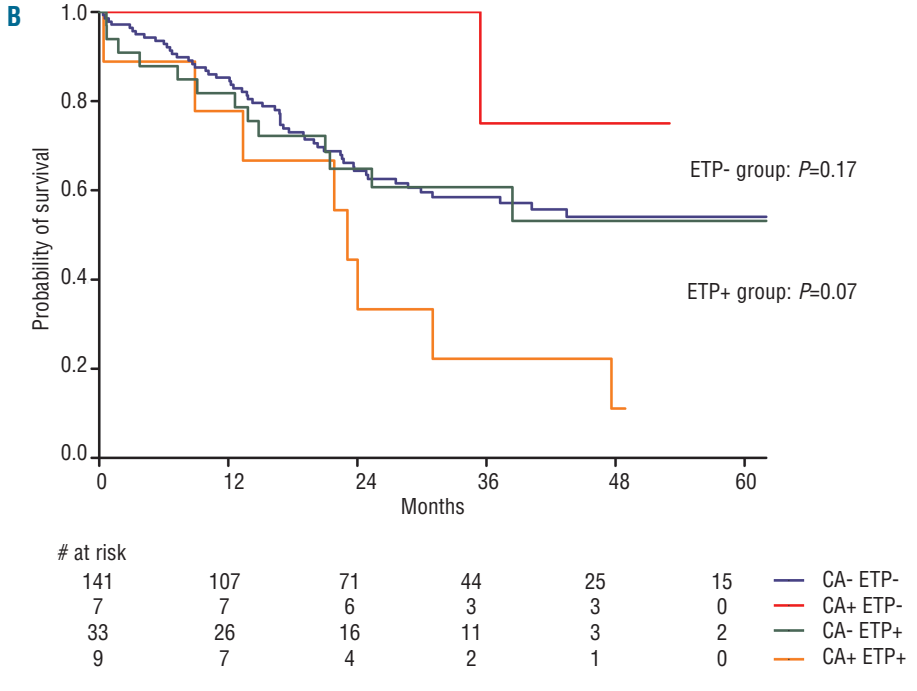


Figure 2. Prognostic impact of *CALM-AF10* according to ETP phenotype in adult LALA/GRAALL T-ALL. (A) Event-free survival (EFS) and (B) overall survival (OS). ETP-ALL and non-ETP-ALL are referred to as ETP$^+$ and ETP$^-$, respectively. We compared 3-year EFS and OS of *CALM-AF10*$^+$ ETP$^+$ (orange line) *versus* *CALM-AF10*$^-$ ETP$^+$ (green line): 22% [95%CI, 3-51] *versus* 47% [95%CI, 28-64], P=0.04 for EFS and 22% [95%CI, 3-51] *versus* 61% [95%CI, 41-76], P=0.07 for OS. We also compared *CALM-AF10*$^+$ ETP$^-$ (red line) *versus* *CALM-AF10*$^-$ ETP$^-$ (blue line) outcomes: 69% [95%CI, 21-91] *versus* 44% [95%CI, 35-52], P=0.23 for EFS and 75% [95%CI, 13-96] *versus* 57% [95%CI, 48-65]; P=0.17 for OS.

CALM-AF10$^+$ individuals among 214 adults with T-ALL treated on UKALLXII/ECOG2993 protocols.[7] *CALM-AF10*$^+$ T-ALL do, however, include two very distinct subsets with respect to response to T-ALL therapy. In adults, mature TCRγδ$^+$ *CALM-AF10*$^+$ T-ALL respond well to treatment, whereas TCR$^-$ *CALM-AF10*$^+$ T-ALL have a strikingly inferior outcome. Our data on an albeit limited number of pediatric *CALM-AF10*$^+$ T-ALL suggest that this may also be the case in children, although the very low incidence of TCR$^-$cases and their marked correlation with adolescent T-ALL will make screening of very large series of homogeneously treated patients necessary to address this issue definitively.

Why the stage of maturation arrest should have such an impact on outcome is not yet clear. It is possible that TCR$^-$ *CALM-AF10* cases, but not TCR$^+$ ones, are associated with other somatic gene abnormalities which render TCR$^-$ cases resistant to treatment, possibly in conjunction with *CALM-AF10*. One candidate would be *EZH2*, which is mutated relatively frequently in *CALM-AF10*$^+$ acute leukemias[35] (see below). The presence of the *AF10* PHD/LAP domains are unlikely to explain the improved response to treatment in TCR$^+$ *CALM-AF10*$^+$ T-ALL, since the AF10 breakpoint no longer correlates significantly with maturation arrest, as initially suspected.[24] Alternatively, we have recently shown that TCR restitution can lead to leukemic cell death in *TLX1*$^+$ T-ALL,[36] suggesting that appropriate TCR expression in a relevant cellular context can contribute to chemosensitivity. Since TCR$^+$ T-ALL are relatively frequent, it is clear that expression of a TCR alone is not sufficient to induce leukemic cell death. These hypotheses obviously need to be tested.

TCR$^-$, but not TCR$^+$, *CALM-AF10*$^+$ T-ALL demonstrated a major overlap with ETP-ALL. Early T-cell precursors represent recent thymic immigrants from the bone marrow, which retain multi-lineage differentiation potential, including for the myeloid lineage, which is a possible explanation of the poor response of ETP-ALL to ALL chemotherapy in children.[9,13] *CALM-AF10* status in ETP-ALL was not reported by Coustan-Smith *et al.*[9], but it is worth noting that 13/17 cases were aged over 10 years and 7/17 cases demonstrated chromosomal abnormalities at 10p or 11q. It is tempting to speculate that *CALM-AF10*$^+$ may represent a significant genetic identifier of ETP-ALL, as defined by Coustan-Smith *et al.*[9]

One surprising finding of the present study was that the overall outcome of ETP-ALL in adults from the LALA and GRAALL trials was not significantly different from that of non-ETP-ALL. The incidence of ETP-ALL in LALA/GRAALL patients was 22%, which is higher than the 13% incidence reported in pediatric T-ALL, and reflects the fact that immature T-ALL are more frequent in adults. Indeed, when defined by the absence of complete TCRβ VDJ rearrangement and a sCD3/TCR$^-$ phenotype, immature T-ALL accounted for 8% of cases in children under 10 years old, 22% of cases in adolescents (11-20 years) and 38% of cases in adults over 20 years old.[37] The present incidence of ETP-ALL was also higher than the 7% reported for adult GMALL 1993-2003 T-ALL.[38] In the latter study, the prognosis of phenotypically defined ETP-ALL was the same as that of non-ETP immature T-ALL, but was not compared to the overall T-ALL outcome. It would be interesting to determine what proportion of *CALM-AF10*$^+$ T-ALL co-segregates with the recently identified early immature cluster of adult T-ALL.[14] It should, however, be noted that the immunophenotypic definition of ETP is not easy to standardize, being partially based on qualitative assessment of intensity of antigen expression. Despite the fact that the majority of phenotypes in the present series were evaluated centrally, we emphasize that it will be necessary to improve the reproducibility of the definition of ETP if it is to be used for stratification of patients. Our data and those from the GMALL study group would, however, suggest that immunophenotypic identification of ETP status *per se* may be less important in adults than in children.

In our LALA/GRAALL cohort, 21% of ETP-ALL were *CALM-AF10*$^+$ and the poor prognosis was restricted to this subgroup, although it is possible that other poor prognostic subgroups exist within adult ETP-ALL. The corollary of this is that ETP is a heterogeneous group in adult T-ALL, and could also include patients who respond well to T-ALL therapy. The recent demonstration that adult T-ALL and pediatric ETP-ALL are commonly associated with loss-of-function mutations in *EZH2* and *SUZ12*, involved in histone modification[15,39] and that *EZH2* may be relatively frequent in *CALM-AF10*$^+$ acute leukemia[35], suggest that cases with such modifications may identify poor prognosis ETP-ALL in adults and children, along with *CALM-AF10*.

Taken together, these data demonstrate that *CALM-AF10* identifies a poor prognostic group only in sCD3/TCR$^-$ T-ALL and is over-represented within adults with ETP-ALL, in whom it identifies those in whom treatment is most likely to fail. ETP alone has no prognostic impact in LALA/GRAALL adult T-ALL, particularly relative to data in pediatric ETP-ALL.[9] In practice, *CALM-AF10* status needs to be interpreted in conjunction with immunophenotype since it has no prognostic value taken in isolation. Its overlap with T-ALL demonstrating histone-modifying mutations requires further analysis.

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Authorship and Disclosures

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