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ORIGINAL REPORT

Early Response–Based Therapy Stratification Improves Survival in Adult Early Thymic Precursor Acute Lymphoblastic Leukemia: A Group for Research on Adult Acute Lymphoblastic Leukemia Study

Jonathan Bond, Carlos Graux, Ludovic Lhermitte, Diane Lara, Thomas Cluzeau, Thibaut Leguay, Agata Cieslak, Amélie Trinquand, Cedric Pastoret, Mohamed Belhocine, Salvatore Spicuglia, Véronique Lheritier, Stéphane Leprêtre, Xavier Thomas, Françoise Huguet, Norbert Ifrah, Hervé Dombret, Elizabeth Macintyre, Nicolas Boissel, and Vahid Asnafi

Author affiliations and support information (if applicable) appear at the end of this article.

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N.B. and V.A. contributed equally to this work.

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Corresponding author: Vahid Asnafi, MD, PhD, Hôpital Necker-Enfants Malades, Laboratoire d'onco-hématologie, 149 Rue de Sèvres, 75015 Paris, France; e-mail: vahid.asnafi@nck.aphp.fr.

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ABSTRACT

Purpose
Early thymic precursor (ETP) acute lymphoblastic leukemia (ALL) is an immunophenotypically defined subgroup of T-cell ALL (T-ALL) associated with high rates of intrinsic treatment resistance. Studies in children have shown that the negative prognostic impact of chemotherapy resistance is abrogated by the implementation of early response–based intensification strategies. Comparable data in adults are lacking.

Patients and Methods
We performed comprehensive clinicobiologic, genetic, and survival analyses of a large cohort of 213 adult patients with T-ALL, including 47 patients with ETP-ALL, treated in the GRAALL (Group for Research on Adult Acute Lymphoblastic Leukemia) -2003 and -2005 studies.

Results
Targeted next-generation sequencing revealed that the genotype of immunophenotypically defined adult T-ALL is similar to the pediatric equivalent, with high rates of mutations in factors involved in cytokine receptor and RAS signaling (62.2%), hematopoietic development (29.7%), and chemical modification of histones (48.6%). In contrast to pediatric cases, mutations in DNA methylation factor genes were also common (32.4%). We found that despite expected high levels of early bone marrow chemotherapy resistance (87%), the overall prognosis for adults with ETP-ALL treated using the GRAALL protocols was not inferior to that of the non–ETP-ALL group (5-year overall survival: ETP, 59.6%; 95% CI, 44.2% to 72.0% *v* non-ETP, 66.5%; 95% CI, 58.7% to 73.2%; $P = 0.33$) and that allogeneic stem-cell transplantation had a beneficial effect in a large proportion of patients with ETP-ALL.

Conclusion
Our results suggest that the use of response-based risk stratification and therapy intensification abrogates the poor prognosis of adult ETP-ALL.

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INTRODUCTION

T-cell acute lymphoblastic leukemias (T-ALLs) are malignant monoclonal proliferations of cells that exhibit developmental arrest at varying stages of differentiation, which partially recapitulate normal T-lymphoid ontogeny.[1,2] The immunophenotype of T-ALL ranges from cases that resemble the most immature thymic immigrants from the bone marrow (early thymic precursor [ETP]) to leukemias that express surface T-cell receptors and mature T-lymphoid antigens.[3] This phenotypic landscape is highly correlated with the transcriptional signature of the leukemic cell,[4] suggesting that the genetic and phenotypic deregulations that underpin T-ALL oncogenesis are closely coupled.

ETP-ALL is a subset of T-ALL that was originally identified in pediatric cases by transcriptional proximity to the murine ETP, although more recent gene expression analysis has revealed closer resemblance to human hematopoietic stem cells (HSCs) and immature granulocyte macrophage

ASSOCIATED CONTENT

Data Supplements
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precursors.[5,6] ETP-ALL blasts have a characteristic immunophenotype, with reduced or absent expression of T-lymphoid markers (CD1a, CD5, CD8) and positivity for at least one HSC and/or myeloid antigen (CD34, CD117, HLA antigen D related [HLA-DR], CD13, CD33, CD11b, CD65). Pediatric ETP-ALL exhibits a genetic profile distinct from other cases of childhood T-ALL, with high rates of mutations in genes coding for factors involved in cytokine receptor and RAS signaling (67.2%), hematopoietic development (57.8%), and components of the polycomb repressive complex 2 (PRC2; 42.2%).[6] The genetic landscape of adult ETP-ALL is comparatively poorly defined, although there have been reports of higher rates of *DNMT3A* and *RUNX1* mutations that are more usually seen in acute myeloid leukemia (AML) and myelodysplasia, as compared with non–ETP-ALL.[7,8]

Initial reports documented dismal outcomes for ETP-ALL that were linked to high rates of chemotherapy resistance in this cohort.[5,9,10] Recent survival data suggest that pediatric cases have a neutral prognosis in the context of minimal residual disease (MRD) response-directed protocols,[11-13] suggesting that the negative impact of early therapeutic resistance can be abrogated by timely treatment intensification. Similar data in adults are lacking, and although ETP-ALL has been reported to have a poor outcome when treated using traditional regimens, prognostic analyses are both scarce and conflicting.[14,15] We have previously shown that in the context of pediatric-inspired therapeutic strategies, the negative prognosis of adult ETP-ALL is specific to an HOXA-overexpressing subgroup.[15] In contrast, a recent study documented a poor prognosis for adults with ETP-ALL and lymphoblastic lymphoma (LBL), albeit in the context of heterogeneous treatments and a comparatively low rate (17.6%) of allogeneic stem-cell transplantation (allo-SCT).[14] The question of whether early intensification with chemotherapy and/or allo-SCT might directly affect the outcome of this intrinsically treatment-resistant cohort remains unaddressed.

We have performed comprehensive clinicobiologic, genetic, and prognostic analyses of adult patients with ETP-ALL treated during the GRAALL (Group for Research on Adult Acute Lymphoblastic Leukemia) -2003 and -2005 studies. We aimed to evaluate the outcome of adult ETP-ALL treated with the pediatric-inspired GRAALL regimen, which included further therapy intensification with allo-SCT in the case of early treatment resistance.

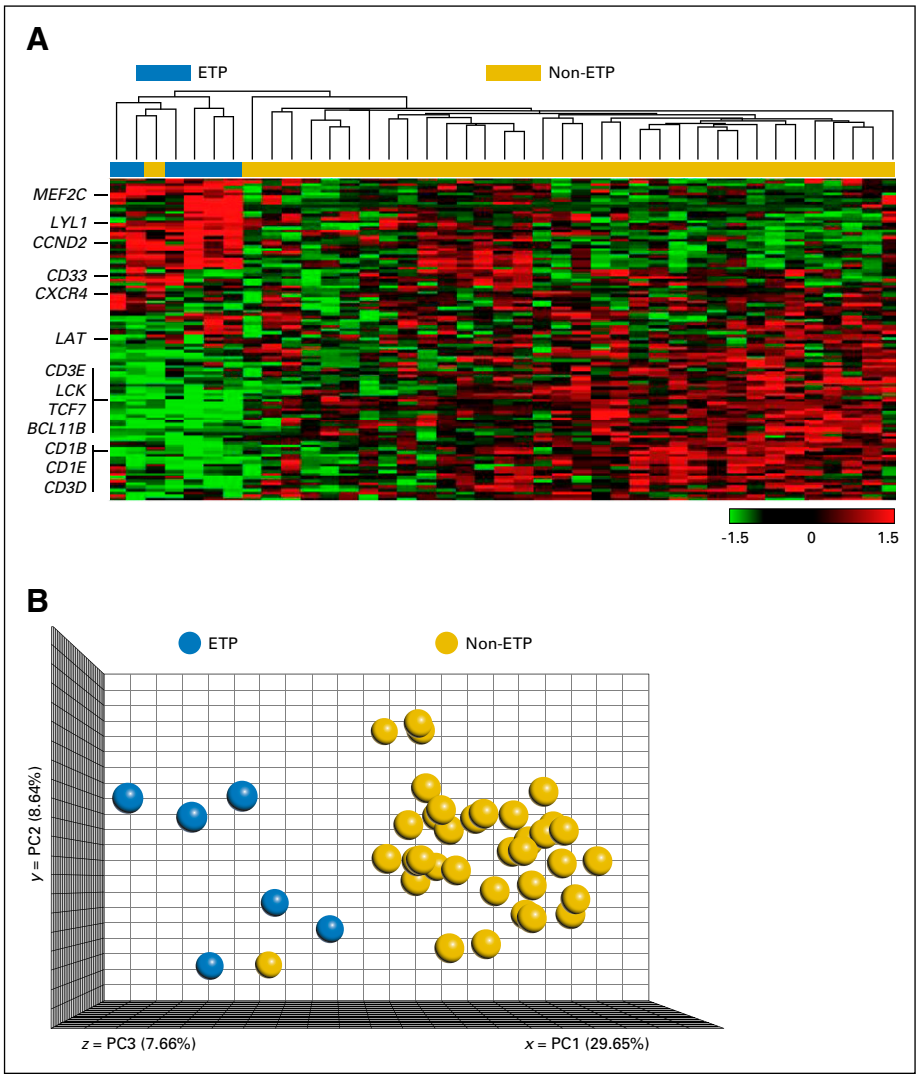

Fig 1. RNA sequencing of adult T-cell acute lymphoblastic leukemia (T-ALL). (A) Hierarchic clustering of adult cases of T-ALL using the early thymic precursor (ETP) ALL leukemic signature described in pediatric cases.[5] All ETP samples (n = 6) cluster together. The non-ETP cases (n = 35) form a separate cluster, with the exception of one sample that segregates with the ETP group. Blue bars indicate ETP, and gold bars indicate non-ETP. Rows corresponding to certain genes are annotated. The full gene list is shown in the Data Supplement. (B) Three-dimensional principal components analysis using the ETP-ALL leukemic signature. Percentage variations of the three components are indicated alongside the axes. Blue spheres indicate ETP, and gold spheres indicate non-ETP.

PATIENTS AND METHODS

GRAALL-2003 and GRAALL-2005 Studies

The GRAALL-2003 study was a multicenter phase II trial, which enrolled 76 adults with T-ALL between November 2003 and November 2005. The multicenter randomized GRAALL-2005 study was the following phase III trial, with the addition of a randomized evaluation of an intensified sequence of hyperfractionated cyclophosphamide during induction and late intensification; two hundred sixty-one adults with T-ALL were enrolled in this study between May 2006 and September 2011.

Informed consent was obtained from all patients at trial entry. Both studies were conducted in accordance with the Declaration of Helsinki and approved by local and multicenter research ethical committees. The complete study protocols are detailed in the Data Supplement. Both trials were registered at ClinicalTrials.gov. With a point date of June 2015, the median follow-up was 5.7 years (6.0 and 5.4 years for GRAALL-2003 and GRAALL-2005 patients, respectively). The data used in this project were analyzed by J.B., N.B., and V.A. All authors had access to primary clinical trial data.

The criteria for inclusion in the current study were a diagnosis of T-ALL and the availability of diagnostic material for categorization of ETP-ALL, which was defined using the classic immunophenotypic criteria of Coustan-Smith et al[5]: reduced or absent expression of CD1a, CD5, and CD8, and positivity for at least one of the following antigens: CD34, CD117, HLA-DR, CD13, CD33, CD11b, or CD65.

Survival outcomes of the 213 patients (GRAALL-2003, n = 49; GRAALL-2005, n = 164) who fulfilled these criteria did not differ from the remaining 124 patients with T-ALL in the GRAALL cohorts. The study group comprised similar proportions of GRAALL-2003 (64.5%) and GRAALL-2005 (62.8%) patients. Initial WBC was higher in the study cohort than in the nonincluded GRAALL patients, which reflects an expected bias toward inclusion of patients with available pathologic material. Study patients were less likely to obtain morphologic complete remission (CR), and there was a trend toward lower corticosteroid sensitivity rates. However, no differences in allo-SCT rate, disease-free survival, event-free survival (EFS), or overall survival (OS) were found. Full comparison of the clinical features of each group is shown in the Data Supplement. The Data Supplement also provides details of statistical analysis, RNA sequencing, next-generation sequencing (NGS), and testing for absence of biallelic deletion (ABD) of the *TRG* locus.

RESULTS

Adult ETP-ALL Is Associated With Distinct Clinicobiologic Phenotype

We performed immunophenotypic assessment of 213 patients with T-ALL treated during the GRAALL-2003 and -2005 studies. All analyses were performed at a single center (Hôpital Necker-Enfants Malades, Paris, France). A total of 47 patients (22.1%) were classified as having ETP-ALL, using the phenotypic criteria previously defined in pediatric cases.[5] We complemented this phenotypic classification with RNA-sequencing profiling of 41 patients with T-ALLs for which high-quality diagnostic RNA samples were available, comprising six patients with ETP-ALLs and 35 patients with non–ETP-ALLs (henceforth ETP and non-ETP, respectively). Analysis using the gene-expression signature defined in pediatric ETP-ALL[5] showed that the ETP and non-ETP groups formed distinct transcriptional clusters (Fig 1; Data Supplement). This suggests that immunophenotypic classification of ETP-ALL identifies similar biologic entities in both adults and children.

Analysis of the clinicobiologic characteristics of patients with ETP and non-ETP revealed major differences between the two groups (Table 1). Notably, we found that the ETP cohort had a significantly lower proportion of male patients (53.2% *v* 77.7%; $P < .001$) than the non-ETP group. On average, patients with ETP were older (median age, 38.5 *v* 29.9 years; $P < .001$) and had lower WBC counts at diagnosis (median, 13.2 *v* 37.3 $\times 10^9$/L; $P = .01$). As expected in the context of phenotypic immaturity, patients with ETP were more likely to have incomplete rearrangement of T-cell receptor genes[16] (80% *v* 14.2%; $P < .001$) and had markedly elevated rates of ABD of the *TRG* locus[18] (68.9% *v* 12.9%; $P < .001$).

The results of diagnostic oncogenetic assessment showed that the ETP group had higher rates of *MLLT10* translocation (21.3% *v* 3%; $P < .001$) and lower rates of *TLX1* rearrangement (0% *v* 27.1%; $P < .001$). There were no other statistically significant differences in the frequencies of recurrent translocations, although *SIL-TAL1*–positive and *MLL*-rearranged patient cases were almost exclusively found in the non-ETP cohort. In keeping with a recent report by our group,[15] HOXA positivity was much more common in patients with ETP (50% *v* 19.6%; $P < .001$). Patients with ETP were also more frequently categorized as high risk by our previously described classifier, which integrates the prognostic impact of mutations in *NOTCH1*, *FBXW7*, *RAS*, and *PTEN*[17] (58.7% *v* 41.3%; $P = .04$).

Adult ETP-ALL Is Associated With Distinct Mutational Genotype

Pediatric ETP-ALL has been shown to present a genetic profile that differs markedly from other cases of childhood T-ALL.[6] To investigate whether the genotype of immunophenotypically

Table 1. Clinicobiologic Characteristics of Adult Patients With ETP-ALL

Characteristic	No. (%) of Patients			
	ETP	Non-ETP	Total	*P*
Total	47 (22.1)	166 (77.9)	213 (100)	
Clinical subsets analyzed				
Male sex	25 (53.2)	129 (77.7)	154 (72.3)	**< .001**
Median age, years	38.5	29.9	31.5	**< .001**
Median WBC count, $\times 10^9$/L	13.2	37.3	31.4	**.01**
CNS involvement	4 (8.5)	20 (12)	24 (11.3)	.5
T-cell receptor status				
Immature (IM0, IMD, IMG)*	36 (80)	22 (14.2)	58 (29)	**< .001**
αβ lineage	7 (15.6)	114 (73.5)	121 (60.5)	**< .001**
γδ lineage	2 (4.4)	19 (12.3)	21 (10.5)	.13
ABD (n = 184)	31 (68.9)	18 (12.9)	49 (26.6)	**< .001**
Oncogenetics				
TLX1	0 (0)	45 (27.1)	45 (21.1)	**< .001**
TLX3	5 (10.6)	20 (12)	25 (11.7)	.79
SIL-TAL1	1 (2.1)	17 (10.2)	18 (8.5)	.08
MLL rearranged	0 (0)	5 (3)	5 (2.3)	.23
MLLT10 rearranged†	10 (21.3)	5 (3)§	15 (7)	**< .001**
TCRβ-HOXA†	1 (2.1)	9 (5.4)§	10 (4.7)	.35
SET-NUP214	2 (4.3)	6 (3.6)	8 (3.8)	.84
None of the above	28 (59.6)	60 (36.1)	88 (41.3)	**.004**
HOXA positive (n = 201)*	20 (50)	29 (19.6)	49 (26.1)	**< .001**
NOTCH1/FBXW7 mutated	25 (53.2)	117 (70.5)	142 (66.7)	**.03**
Risk classifier (n = 188)*	27 (58.7)	64 (41.3)	91 (45)	**.04**

NOTE. Bold font indicates statistical significance.
Abbreviations: ABD, absence of biallelic deletion; ALL, acute lymphoblastic leukemia; ETP, early thymic precursor.
*T-cell receptor gene status, HOXA positivity, and risk classifier (based on genotype for *NOTCH1*, *FBXW7*, *PTEN*, *NRAS*, and *KRAS*) were determined as previously described.[15-17]
†One patient had both *TCRβ-HOXA* and *MLLT10* rearrangements.

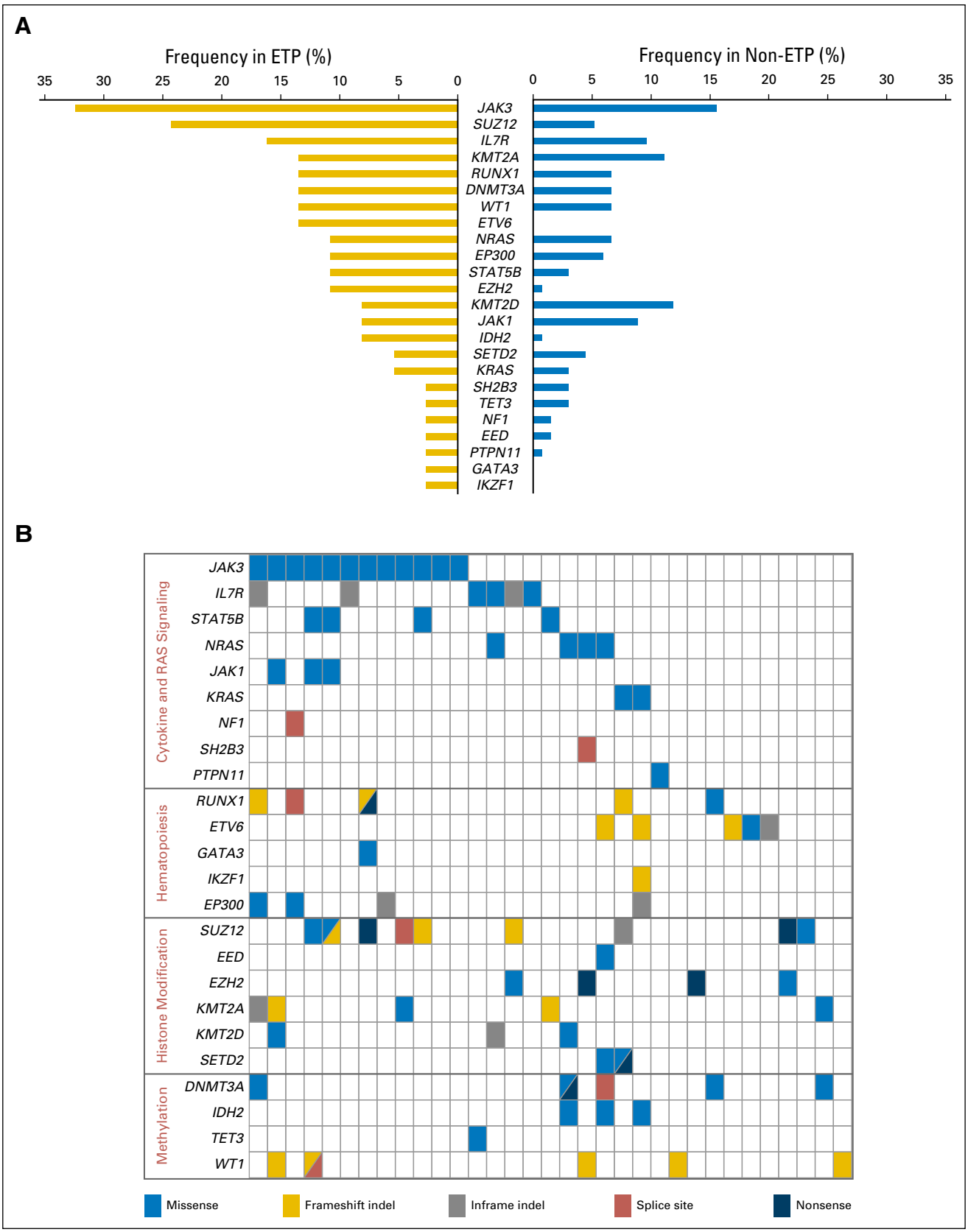

Fig 2. Genetic profile of adult early thymic precursor (ETP) acute lymphoblastic leukemia (ALL). (A) Comparison of the mutational genotypes of adult ETP-ALL (n = 37) and adult non–ETP-ALL (n = 135). Percentage frequencies in each group are depicted. (B) Details of mutations found in adult ETP-ALL. Mutations are color coded according to type, as shown. Genes are grouped by functional category, as indicated. (C) Circos plot[19] of mutations in adult ETP-ALL. Ribbons indicate associations among mutations in the genes depicted.

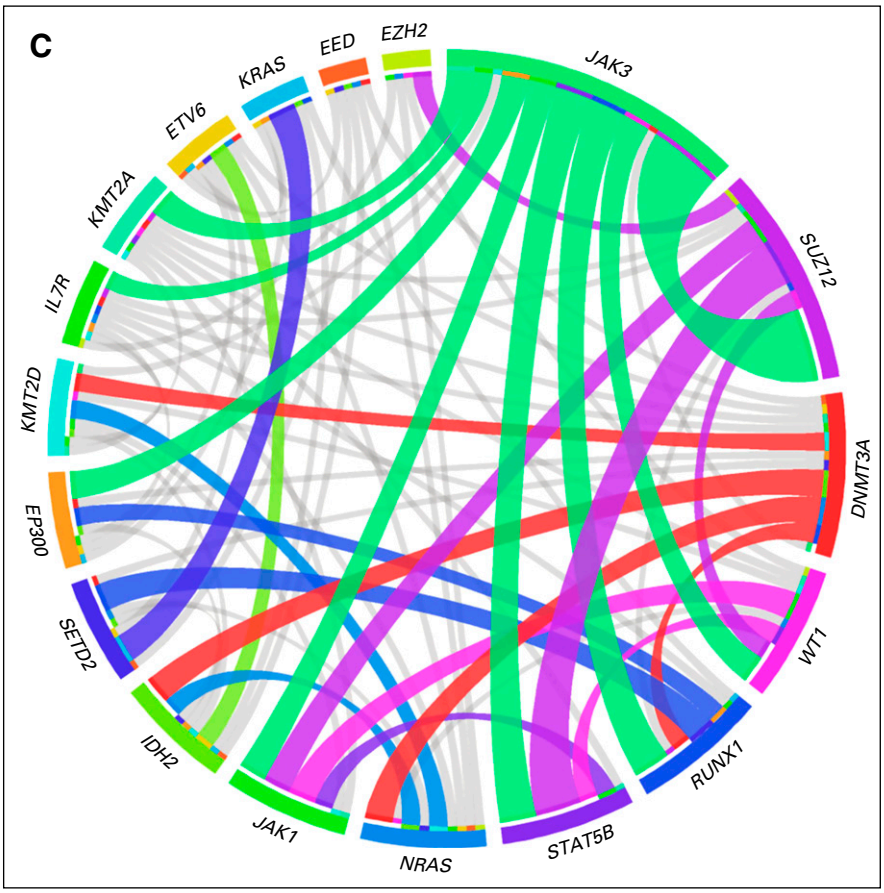

Fig 2. (Continued).

defined adult ETP-ALL has a similar mutational repertoire as pediatric cases, we performed targeted enrichment and NGS of available leukemic DNA from 172 of the 213 patients with T-ALLs in this study, comprising 37 patients with ETP and 135 with non-ETP.

We designed a custom NGS panel comprising genes that code for factors involved in molecular pathways known to be mutated in pediatric ETP ALL, namely cytokine receptor and RAS signaling (*NRAS*, *KRAS*, *JAK1*, *JAK3*, *STAT3*, *STAT5B*, *IL7R*, *BRAF*, *NF1*, *SH2B3*, and *PTPN11*), hematopoietic development (*RUNX1*, *ETV6*, *GATA3*, *IKZF1*, and *EP300*), and chemical modification of histones (*SUZ12*, *EED*, *EZH2*, *KMT2A*, *KMT2D*, and *SETD2*).[6]

Figure 2 shows a comparison of the mutation frequencies in the ETP and non-ETP groups (Fig 2A) and specific details of the mutations found in the ETP cohort (Fig 2B). Notably, mutations were found in 89.2% of patients with ETP, compared with only 63.7% of the non-ETP group ($P = .03$). We detected a significantly higher rate of mutations in cytokine receptor and RAS signaling pathway genes in those with ETP (ETP, 62.2% *v* non-ETP, 37.8%; $P = .008$), and mutations in hematopoietic development genes were also more common (ETP, 29.7% *v* non-ETP, 11.9%; $P = .008$). There were markedly higher rates of mutations in factors that mediate the chemical modification of histones in the ETP cohort (ETP, 48.6% *v* non-ETP, 29.6%; $P = .03$). Similar to what has been found in pediatric T-ALL,[6] mutations in PRC2 genes were significantly more common in the ETP group (ETP, 32.4% *v* non-ETP, 7.4%; $P < .001$).

We also analyzed a set of genes involved in DNA methylation, which comprised several factors previously reported to be mutated in adult ETP ALL (*DNMT3A*, *IDH1*, *IDH2*, *TET2*, *TET3*, and *WT1*).[7] We found significant numbers of mutations in these genes (Fig 2A), which were not detected at all in two large-scale studies of pediatric T-ALL.[6,20] Mutation rates were similar in patients with ETP and non-ETP (ETP, 32.4% *v* non-ETP, 23.7%; $P = .33$). Because these genes encode molecules that have divergent effects on the methylation state of DNA,[21] we tested whether any individual genotype might segregate with ETP category, but no significant differences were observed.

Associations between mutations in individual genes are shown in Figure 2C. *JAK3* mutations frequently co-occurred with mutations in most of the other analyzed genes, although rarely with *DNMT3A*. In keeping with previously published data,[22] *SUZ12* mutations were commonly associated with mutations in JAK-STAT pathway genes. Overall, these results confirm that immunophenotypically defined ETP-ALL is associated with highly similar genotypes in adults and pediatric patients, with the exception of significant rates of mutations in DNA methylation factors in adult cases.

Outcome of GRAALL-Treated Adult ETP ALL

Consistent with previous studies,[5,9-11] patients with ETP-ALL had markedly higher rates of corticosteroid resistance (63.8% *v* 36.8%; $P = .001$) and early bone marrow chemotherapy resistance (87% *v* 33.7%; $P < .001$) than those with non-ETP. Although morphologic CR was similar between the two groups (87.2% *v* 92.2%; $P = .38$), the quality of this remission differed

Table 2. Treatment Response in Adult Patients With ETP-ALL

Response	No. (%)			*P**
	ETP (n = 47)	Non-ETP (n = 166)	Total (n = 213)	
Corticosteroid resistance	30 (63.8)	61 (36.8)	91 (42.7)	**.001**
Chemotherapy resistance	40 (87.0)	55 (33.7)	95 (45.5)	**< .001**
MRD1 $\geq 10^{-4}$†	15 (71.4)	19 (20.9)	34 (30.4)	**< .001**
CR	41 (87.2)	153 (92.2)	194 (91.1)	.38
MRD2 positive	7 (50.0)	12 (14.3)	19 (19.4)	**.005**

NOTE. Bold font indicates statistical significance.
Abbreviations: ALL, acute lymphoblastic leukemia; CR, complete remission; ETP, early thymic precursor; MRD, minimal residual disease.
**P* values were calculated using Fisher's exact test.
†MRD was assessed by allele-specific oligonucleotide polymerase chain reaction.[23] MRD1 (n = 112) and MRD2 (n = 98) were measured on days 42 and 84 of treatment, respectively.

greatly, and patients with ETP were significantly more likely to have positive MRD postinduction (71.4% *v* 20.9%; $P < .001$; Table 2).

Despite these high rates of intrinsic treatment resistance, survival analyses revealed that patients with ETP had outcomes similar to those of the non-ETP cohort, with no significant differences in either 5-year OS (ETP, 59.6%; 95% CI, 44.2% to 72.0% *v* non-ETP, 66.5%; 95% CI, 58.7% to 73.2%; $P = .33$; Fig 3A) or 5-year EFS (ETP, 51.1%; 95% CI, 36.1% to 64.2% *v* non-ETP, 58.1%; 95% CI, 50.2% to 65.2%; $P = .17$; Fig 3B). Mutational genotype did not correlate with any survival differences within the ETP group (Data Supplement).

In contrast to past reports in pediatric and adult T-ALL,[18,24,25] we found that ABD of the *TRG* locus conferred no differences in prognosis in this study, with highly similar OS (69.3% *v* 64.3%; $P = .48$) at 5 years in those with ABD and those without (Data Supplement).

Allo-SCT Improves Survival in Adult ETP-ALL

The discordance between the high rates of intrinsic treatment resistance and neutral prognosis led us to question whether additional factors might modulate the outcome of the ETP cohort. For patients with T-ALL treated during the GRAALL studies, allo-SCT eligibility required the presence of at least one of four criteria: CNS involvement at diagnosis, corticosteroid resistance, early bone marrow chemotherapy resistance, and failure of remission induction (Data Supplement). Because of frequent poor initial treatment response, patients with ETP were more likely to be treated with transplantation in first CR (allo-SCT rates: ETP, 23 [48.9%] of 47 *v* 47 [28.3%] of 165; $P = .008$). Notably, only one of 23 patients with ETP underwent allo-SCT because of CNS involvement, which means that those with ETP received an allograft almost exclusively because of early treatment resistance. We therefore examined whether SCT influenced the prognosis of adult ETP-ALL.

Initial analysis of survival data censored at allo-SCT revealed that the ETP group had significantly reduced 5-year OS (ETP, 49.2%; 95% CI, 27.8% to 67.5% *v* non-ETP, 67.4%; 95% CI, 58.2% to 75.0%; $P = .02$), with only a trend in 5-year EFS (ETP, 49.9%; 95% CI, 28.3% to 68.2% *v* non-ETP, 59.2%; 95% CI, 49.8% to 67.4%; $P = .08$; Figs 4A and 4B). This suggests

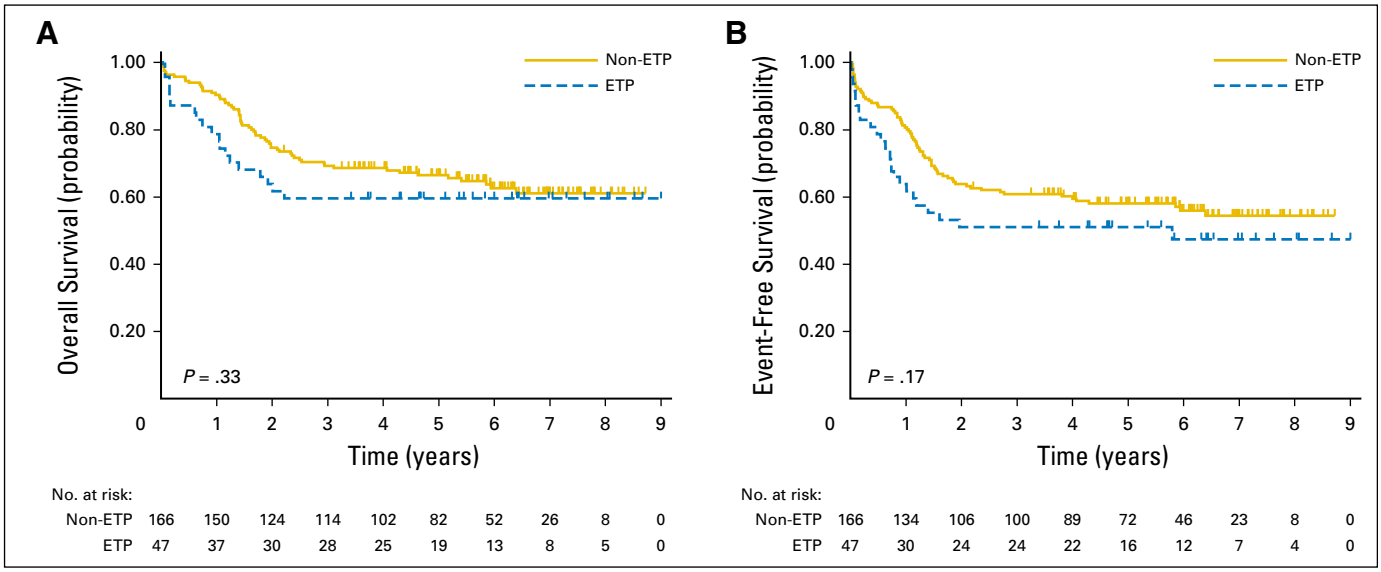

Fig 3. Adult early thymic precursor (ETP) acute lymphoblastic leukemia is associated with a neutral prognosis. (A) Overall survival. The 5-year survival figures were 59.6% (95% CI, 44.2% to 72.0%) for the ETP group and 66.5% (95% CI, 58.7% to 73.2%) for the non-ETP group. (B) Event-free survival. The 5-year survival figures were 51.1% (95% CI, 36.1% to 64.2%) for the ETP group and 58.1% (95% CI, 50.2% to 65.2%) for the non-ETP group. *P* values are indicated.

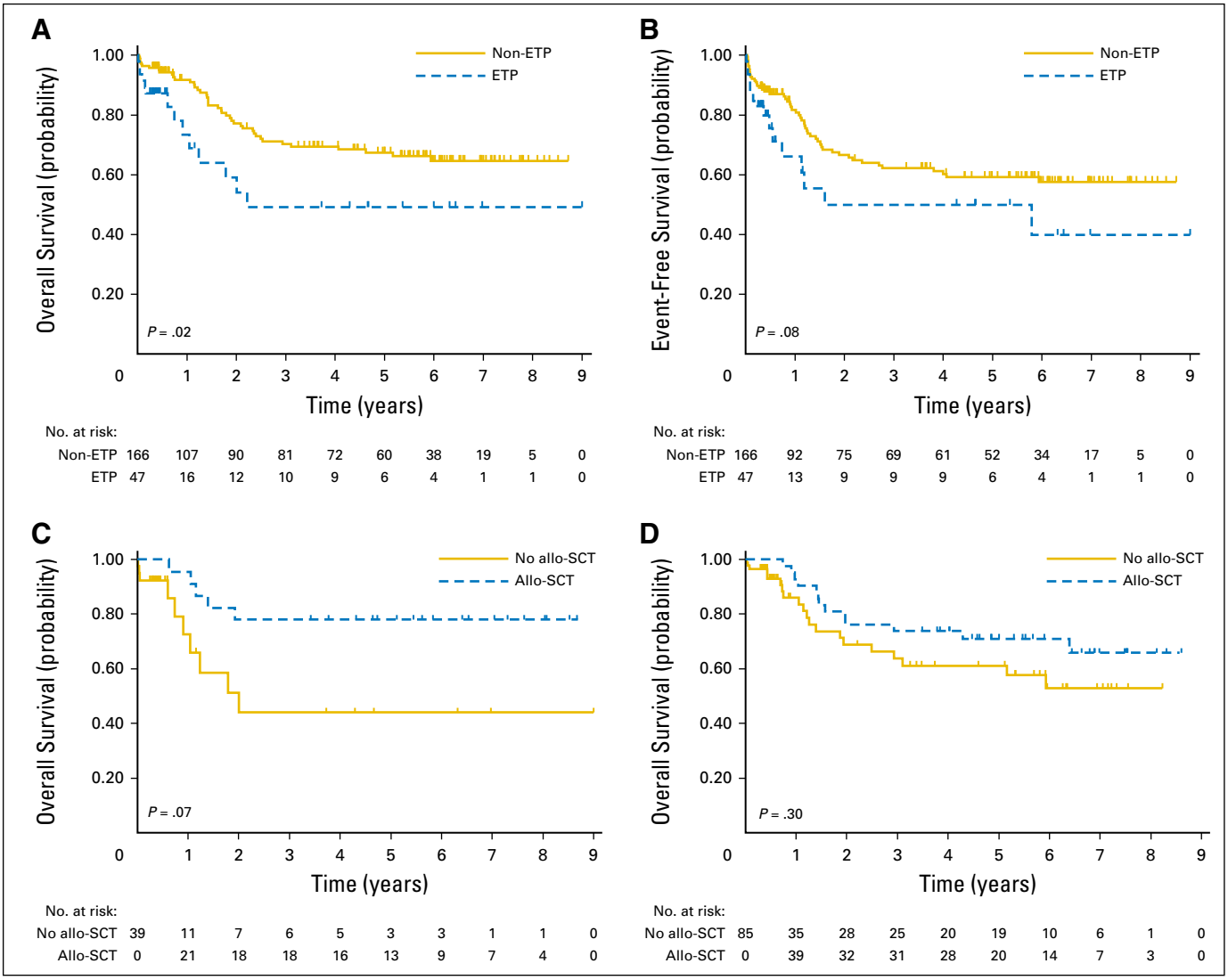

Fig 4. Allogeneic stem-cell transplantation (allo-SCT) confers survival benefit in adult early thymic precursor (ETP) acute lymphoblastic leukemia. (A) Overall survival censored at allo-SCT. The 5-year survival figures were 49.2% (95% CI, 27.8% to 67.5%) for the ETP group and 67.4% (95% CI, 58.2% to 75.0%) for the non-ETP group. (B) Event-free survival censored at allo-SCT. The 5-year survival figures were 49.9% (95% CI, 28.3% to 68.2%) for the ETP group and 59.2% (95% CI, 49.8% to 67.4%) for the non-ETP group. Simon-Makuch plots for overall survival of patients (C) with and (D) without ETP in the presence or absence of allo-SCT. *P* values are indicated. Per protocol, a vast majority of patients underwent transplantation after a myeloablative conditioning regimen and with a sibling or a 10/10 matched unrelated donor (additional details are provided in the Data Supplement).

that performance of allo-SCT directly affected the outcome of the ETP cohort.

To investigate this further, we analyzed allo-SCT as a time-dependent covariate using the Mantel-Byar approach. This analysis was confined to the 124 patients who were eligible for allo-SCT according to the protocol criteria, comprising 39 patients with ETP and 85 with non-ETP. We found that allo-SCT correlated with a trend toward better OS in those with ETP (hazard ratio, 0.36; $P = .07$; Fig 4C) but not in the non-ETP group (hazard ratio, 0.70; $P = .30$; Fig 4D). Moreover, multivariable analysis (Data Supplement) revealed a significant interaction between ETP status and allo-SCT ($P = .034$), suggesting a correlation between ETP status and benefit from allo-SCT. Taken together, these results suggest that the implementation of allo-SCT in first CR confers a survival benefit that abrogates the negative effects of intrinsic therapeutic resistance in ETP-ALL.

DISCUSSION

We have provided a comprehensive analysis of clinicobiology, mutational genotype, and outcome in adult patients with ETP-ALL treated in the GRAALL-2003 and -2005 studies. To our knowledge, this is the largest uniformly treated cohort of adult patients with ETP-ALL yet reported.

ETP-ALL has been thought to be much more common in adults than in children, in part because of the high proportions of immature cases detected in expression microarray studies. The proportion of patients with ETP-ALL found in our cohort is indeed higher than the range of 12.0% to 16.2% previously reported in immunophenotypically categorized ETP-ALL in children,[5,9-11,26] but markedly lower than the approximately 50% incidence suggested by transcriptional

profiling in adults.[25,27] A recent single-center report found that 17.1% of adult patients with T-ALL/LBL expressed an ETP phenotype,[14] and the similar 22.1% incidence found in our study, which also benefited from uniform phenotypic analysis at a single institution, suggests that this range is the current best estimation of the proportion of pediatric-type ETP-ALL in adults.

As might be predicted from reports in children, patients with ETP were on average older than their non-ETP counterparts. In contrast to pediatric disease, we found that the ETP group comprised a significantly lower proportion of male patients than the rest of the cohort. To our knowledge, this abrogation of the normally male-biased sex ratio has not previously been noted in either pediatric or adult T-ALL.[5,9-11,14,26] We think it likely that the large size and unselected composition of the GRAALL cohorts allowed detection of this novel finding in adult cases. This observation suggests that sex-related genetic factors (eg, X-linked tumor suppressor genes[28,29]) that contribute to the higher frequency of T-ALL in males are not significantly associated with ETP-ALL in adults.

Targeted NGS analysis revealed that adult ETP-ALL presents a similar profile of mutations in factors implicated in signaling, hematopoietic development, and histone modification as its pediatric equivalent.[6] Taken together with the evident transcriptional heterogeneity between ETP and non-ETP groups found by RNA-sequencing profiling, this suggests that immunophenotypic definition of ETP-ALL identifies a biologic entity that is underpinned by similar genetic dysregulation in adults and children. We did, however, find that adult patients had frequent mutations in DNA methylation factor genes, which have never been found in pediatric patients.[6,20] These results are in keeping with reports in smaller adult T-ALL cohorts[7,8,25] and suggest that compared with pediatric disease, adult ETP-ALL might be more genetically proximate to AML. This may reflect an increased probability of age-related mutations and/or biologic differences in the original hematopoietic precursor that undergoes oncogenic transformation in adults. These findings also suggest potential avenues of investigation for novel targeted therapies in adult ETP-ALL, because hypomethylating agents have demonstrated promising efficacy in *DNMT3A*-mutated AML.[30] This idea is supported by recent data showing that decitabine increases ETP-ALL blast chemotherapy sensitivity.[31]

We found that the overall prognosis of patients with ETP-ALL was similar to that of the rest of the T-ALL cohort, which differs from recent data reporting inferior survival in adult ETP ALL/LBL.[14] An important difference between that study and ours was the rate of SCT. Because allo-SCT was not routinely performed in first CR, only 17.6% of patients with ETP underwent transplantation in the previous study.[14] In contrast, allo-SCT in first CR was recommended for patients in the GRAALL studies with high-risk features, including corticosteroid resistance and early bone marrow chemotherapy resistance, which were extremely frequent in patients with ETP, resulting in an allo-SCT rate of 48.9%. Importantly, the fact that transplantation conferred survival benefit in high-risk patients with ETP-ALL who had already received augmented induction regimens suggests that allo-SCT is a key component of therapy escalation and that chemotherapeutic intensification alone is inadequate for this group. Of note, we found a significant interaction between ETP and allo-SCT in multivariable analysis, suggesting that ETP immunophenotype is a specific predictor of allo-SCT benefit in the cohort of patients with T-ALL. In a manner analogous to the positive impact of MRD-directed chemotherapeutic intensification in treatment-resistant pediatric cases,[11-13] our results strongly suggest that risk stratification and therapy intensification based on early treatment response abrogate the unfavorable prognosis of ETP-ALL biology in the adult T-ALL population. Because MRD data were incomplete in this study, we were unable to test whether allo-SCT was beneficial for patients with ETP achieving molecular remission, and we hope to address this in future analyses. Additional studies should also determine whether outcomes may be further improved by treatments targeting pathways that are preferentially mutated in ETP-ALL (eg, JAK-STAT inhibition) or by the addition of nelarabine, which is being evaluated in our current study GRAALL-2014/T (ClinicalTrials.gov identifier 02619630).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Jonathan Bond, Nicolas Boissel, Vahid Asnafi
Collection and assembly of data: All authors
Data analysis and interpretation: Jonathan Bond, Ludovic Lhermitte, Agata Cieslak, Amélie Trinquand, Mohamed Belhocine, Salvatore Spicuglia, Véronique Lheritier, Hervé Dombret, Elizabeth Macintyre, Nicolas Boissel, Vahid Asnafi
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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leukemia: Mutations in RUNX1 and DNMT3A are associated with poor prognosis in T-ALL. Genes Chromosomes Cancer 52:410-422, 2013

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Affiliations

Jonathan Bond, **Ludovic Lhermitte**, **Agata Cieslak**, **Amélie Trinquand**, **Elizabeth Macintyre**, and **Vahid Asnafi**, Hôpital Necker-Enfants Malades; **Jonathan Bond**, **Ludovic Lhermitte**, **Agata Cieslak**, **Amélie Trinquand**, **Elizabeth Macintyre**, and **Vahid Asnafi**, Institut National de la santé et de la recherche médicale (INSERM) U1151; **Hervé Dombret** and **Nicolas Boissel**, University Hospital Saint-Louis, Paris; **Diane Lara**, Hospitalier de Versailles, Le Chesnay; **Thomas Cluzeau**, Centre Hospitalier Universitaire (CHU) de Nice, Nice; **Thibaut Leguay**, CHU de Bordeaux, Bordeaux; **Cedric Pastoret**, CHU de Rennes, Rennes; **Mohamed Belhocine** and **Salvatore Spicuglia**, Aix-Marseille University, Marseille; **Véronique Lheritier**, Centre Hospitalier Lyon Sud; **Xavier Thomas**, CHU de Lyon, Lyon; **Stéphane Leprêtre**, Centre Henri Becquerel and Université de Rouen Normandie, Rouen; **Françoise Huguet**, CHU de Toulouse, Toulouse; **Norbert Ifrah**, CHU d'Angers, Angers, France; and **Carlos Graux**, Godinne University Hospital, Yvoir, Belgium.

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Jonathan Bond
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Carlos Graux
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Ludovic Lhermitte
No relationship to disclose

Diane Lara
No relationship to disclose

Thomas Cluzeau
No relationship to disclose

Thibaut Leguay
No relationship to disclose

Agata Cieslak
No relationship to disclose

Amélie Trinquand
No relationship to disclose

Cedric Pastoret
No relationship to disclose

Mohamed Belhocine
No relationship to disclose

Salvatore Spicuglia
No relationship to disclose

Véronique Lheritier
No relationship to disclose

Stéphane Leprêtre
No relationship to disclose

Xavier Thomas
No relationship to disclose

Françoise Huguet
Honoraria: Amgen, Bristol-Myers Squibb, Incyte, Jazz Pharmaceuticals, Novartis, Pfizer
Consulting or Advisory Role: Bristol-Myers Squibb, Novartis, Jazz Pharmaceuticals

Norbert Ifrah
No relationship to disclose

Hervé Dombret
No relationship to disclose

Elizabeth Macintyre
Honoraria: Amgen
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Vahid Asnafi
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