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ORIGINAL REPORT

Prognostic Implications of *NOTCH1* and *FBXW7* Mutations in Adults With T-Cell Acute Lymphoblastic Leukemia Treated on the MRC UKALLXII/ECOG E2993 Protocol

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ABSTRACT

Purpose
Notch pathway activation by mutations in either *NOTCH1* and/or *FBXW7* is one of the most common molecular events in T-cell acute lymphoblastic leukemia (T-ALL) and, in pediatric disease, predicts for favorable outcome. Their prognostic significance in adult T-ALL is unclear. We sought to evaluate the outcome according to mutation status of patients with adult T-ALL treated on the United Kingdom Acute Lymphoblastic Leukaemia XII (UKALLXII)/Eastern Cooperative Oncology Group (ECOG) E2993 protocol.

Methods
NOTCH1 and *FBXW7* were screened by a combination of denaturing high-performance liquid chromatography and sequencing in 88 adult patients with T-ALL treated on the UKALLXII/ECOG E2993 protocol and compared with clinical characteristics and outcome.

Results
NOTCH1 and *FBXW7* mutations were common (60% and 18%, respectively) and were not associated with age or WBC count. *NOTCH1* heterodimerization domain mutations were associated with *FBXW7* mutations ($P = .02$), and *NOTCH1* proline, glutamic acid, serine, threonine (PEST) rich domain and *FBXW7* mutations were mutually exclusive. There were an equal number of high- and standard-risk patients in the *NOTCH1* and *FBXW7* mutated (MUT) groups. Patients wild type (WT) for both markers trended toward poorer event-free survival (EFS; MUT *v* WT, 51% *v* 27%, $P = .10$; hazard ratio, 0.6). Analysis by each marker individually was not significantly predictive of outcome (*NOTCH1* MUT *v* WT, EFS 49% *v* 34%, $P = .20$; *FBXW7* MUT *v* WT, EFS 53% *v* 41%, *P*.72).

Conclusion
NOTCH1 and *FBXW7* mutant-positive patients do not fare sufficiently well to warrant an individualized treatment approach in future studies.

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INTRODUCTION

A risk-adapted approach to the treatment of patients with acute lymphoblastic leukemia (ALL) has the potential of improving survival in high-risk patients and reducing therapy-related long-term sequelae in those at low risk. Despite stratifying risk on established criteria such as presenting blast count, age, and cytogenetics,[1-3] it remains difficult to predict patient outcome, particularly for adult T-cell ALL (T-ALL), for which cytogenetic data are less frequently informative.[3] Consequently, molecular markers that can complement or supersede current strategies are needed.

Mutations in the *NOTCH1* gene are one of the most common genetic abnormalities found in T-ALL, affecting more than 50% of patients,[4,5] and are thought to activate a broad range of anabolic routes[6] and oncogenic pathways, including those involving c-Myc,[6,7] mTOR,[8,9] and NFKB.[10] Mutations affect two hotspots—the extracellular heterodimerization domain (HD), where mutations lead to ligand-independent cleavage, and C-terminal proline, glutamic acid, serine, threonine (PEST) rich domain truncating mutations, where binding to the negative regulator *FBXW7* is disrupted, prolonging half-life of intracellular NOTCH1 (ICN1).[4,5,11] Approximately 20% of patients acquire both types of mutations in cis that synergistically activate signaling,[4] suggesting there is a selective pressure on T-ALL cells to continually increase Notch signal strength. Additionally, activating mutations in the juxtamembrane (JM) domain have

been reported in a minority of patients.[12] Recently, mutations in the E3 ubiquitin ligase *FBXW7* gene have also been described that are thought to activate Notch signaling by preventing ICN1 ubiquitination and degradation, akin to *NOTCH1* PEST domain mutations.[11,13-15]

Pediatric studies have shown an excellent outcome in *NOTCH1* mutated (MUT) patients[14,16]; on the Acute Lymphoblastic Leukemia-Berlin-Frankfurt-Münster (ALL-BFM) protocol, *NOTCH1* MUT patients had an event-free survival (EFS) of 90%, compared with 71% in wild-type (WT) patients.[16] The prognostic impact of *NOTCH1/FBXW7* mutation status in adult T-ALL is controversial; a Chinese study showed adult patients with MUT *NOTCH1* fared worse than WT patients,[17] whereas the converse has recently been reported on the Lymphoblastic Acute Leukemia in Adults (LALA)-94 and Group for Research on Adult Acute Lymphoblastic Leukemia 2003 (GRAALL-2003) protocol.[18] Considering the relatively small numbers of patients reported thus far and differences in treatment approach among different trials, we sought to address whether adult patients with *NOTCH1* and/or *FBXW7* mutations treated on the Medical Research Council (MRC) United Kingdom Acute Lymphoblastic Leukaemia XII (UKALLXII)/Eastern Cooperative Oncology Group (ECOG) E2993 trial also faired sufficiently well, such that they might avoid treatment intensification/transplantation in future MRC/ECOG trials.

METHODS

Patients were treated according to the MRC UKALLXII/ECOG E2993 protocol as previously reported (Fig 1).[19] Consent was obtained from all patients at trial entry according to the Declaration of Helsinki. The study was in accordance with local and multicenter research ethics committee approval. T-cell phenotype was confirmed by flow cytometry at local centers (UKALL) or centrally (ECOG).

DNA was obtained from diagnostic bone marrow samples of 88 adult patients with T-ALL (UKALLXII, n = 54; ECOG2993, n = 34) entered onto the trial between 1993 and 2005. Patients were selected according to the availability of sufficient DNA for the molecular analyses. Polymerase chain reaction products of the *NOTCH1* HD-N (exon 26), HD-C (exon 27), JM (exon 28), transactivation domain (TAD), and PEST domains (exon 34), and WD40 domain of *FBXW7* (exons 8 to 12) were screened by denaturing high-performance liquid chromatography (UKALL patients) or bidirectional sequencing (ECOG patients) as previously described.[12,20] For denaturing high-performance liquid chromatography, polymerase chain reaction products were denatured and slow cooled to encourage heteroduplex formation and were analyzed by the WAVE DNA Fragment Analysis System (Transgenomic, Elancourt, France). Abnormal chromatograms were confirmed by repeat analysis, and samples were sequenced. One low-level mutation that could not be detected by sequencing was purified using the fragment collector facility of the WAVE and sequenced.

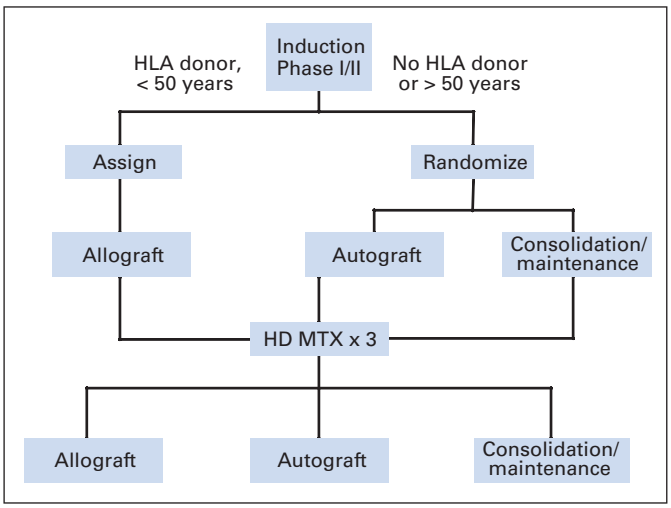

Fig 1. A simplified algorithm of the United Kingdom Acute Lymphoblastic Leukaemia XII/Eastern Cooperative Oncology Group E2993 treatment protocol. HD-MTX, high-dose methotrexate.

Statistical Analysis

The association between *NOTCH1* and *FBXW7* mutation status with age (< 35 years $v \geq 35$ years) and WBC count ($< 30 \times 10^9$/L v 30 to 99×10^9/L $v \geq 100 \times 10^9$/L) at diagnosis were investigated using Fisher's exact test in 2×2 tables and Mantel-Haenszel test for trend. Outcome was analyzed according to overall survival (OS) and EFS, the latter defined as time to relapse or death. Kaplan-Meier curves were used to assess survival, and differences between groups were compared using the log-rank test. Multivariate analyses were performed using the Cox model. All *P* values quoted are two-sided.

RESULTS

Clinical Features of Patient Cohort

The cohort analyzed was representative of all the patients with T-ALL entered onto the clinical trial in terms of sex and median age, but had a higher presenting WBC count (Table 1). Median follow-up was shorter, but complete remission rates, OS, and EFS were similar. In the cohort analyzed, complete remission was achieved in 97% of patients (33 of 35 WT and 52 of 53 *NOTCH1/FBXW7* MUT patients, $P = .56$). The *NOTCH1* WT and MUT groups received similar treatment (WT v MUT, seven [20%] v 16 [30%] sibling allografts; three [9%] v seven [13%] autografts; three [9%] v three [6%] matched unrelated donor allografts; 18 [51%] v 25 [47%] chemotherapy with maintenance alone; χ^2 $P = .69$). There was no significant association with WBC count or age according to either *NOTCH1* or *FBXW7* mutational status (Mantel-Haenszel test for trend, $P > .1$ for each case).

NOTCH1/FBXW7 *Mutation Incidence and Features*

Of the 88 patients with T-ALL analyzed, 53 patients (60%) had at least one *NOTCH1* mutation, 36 patients had a mutation in the HD

Table 1. Characteristics of Patient Cohort Versus Those Not Tested

Characteristic	Patients With *Notch1/FBXW7* Mutation Data	Other UKALLXII T-Cell Patients	*P*
Total, No.	88	268	
Male sex			.8
No.	65	195	
%	74	73	
Age, years			.8
Median	30.5	28.5	
Range	16-60	15-60	
WBC, $\times 10^9$/L			.003
Median	50	31	
Range	1-653	0.6-541	
Median follow-up, years	3.6	7.9	< .0001
Achieved remission			.3
No.	85	251	
%	97	94	
Survival, %*	49.4	41.3	.98
Event-free survival, %*	42.7	44.9	.88

Abbreviation: UKALLXII, United Kingdom Acute Lymphoblastic Leukaemia XII.
*Percent at 5 years; *P* value = log-rank over all follow-up.

Table 2. Association of *NOTCH1* and *FBXW7* Mutation Status of 88 Adult Patients With T-ALL

NOTCH1	*FBXW7* WT	*FBXW7* MUT
NOTCH1 WT	30	5
NOTCH1 HD only	25	11
NOTCH1 JME	3	0
NOTCH1 PEST only	8	0
NOTCH1 HD + PEST	6	0

Abbreviations: T-ALL, T-cell acute lymphoblastic leukemia; WT, wild type; HD, heterodimerization domain; PEST, proline, glutamic acid, serine, threonine rich domain; JME, juxtamembrane expansion mutation.

only, eight patients had a mutation in the PEST domain only, six patients had mutations in both HD and PEST domains, and three patients had JM expansion mutations (Table 2). The mutation rate was similar in the UKALL and ECOG cohorts (59% *v* 62%). These results are comparable with previous studies in adult and pediatric patients.[4,5,12,16,18] Notably, all three insertions in the JM expansion contained the amino acid sequence QLHF, as has been found in the Jurkat cell line and the majority of reported primary T-ALL cases.[12]

Sixteen patients (18%) had an *FBXW7* mutation (seven with R465C, three with R505C, two with R479Q, two with R479L, one with R465H, and one with G423V), and, of note, all except one of these mutations altered conserved arginine residues in the WD40 domain thought to be responsible for binding to the *NOTCH1* PEST domain. Consistent with this finding, *FBXW7* mutations and *NOTCH1* PEST mutations were mutually exclusive (Table 2). There was a positive association between having a mutation in the *NOTCH1* HD only and an *FBXW7* mutation, the combination of which has been shown to be synergistically activating (11 of 36 patients with HD-only mutations were *FBXW7* mutant *v* five of 52 other patients; Fisher's exact test $P = .02$).[14]

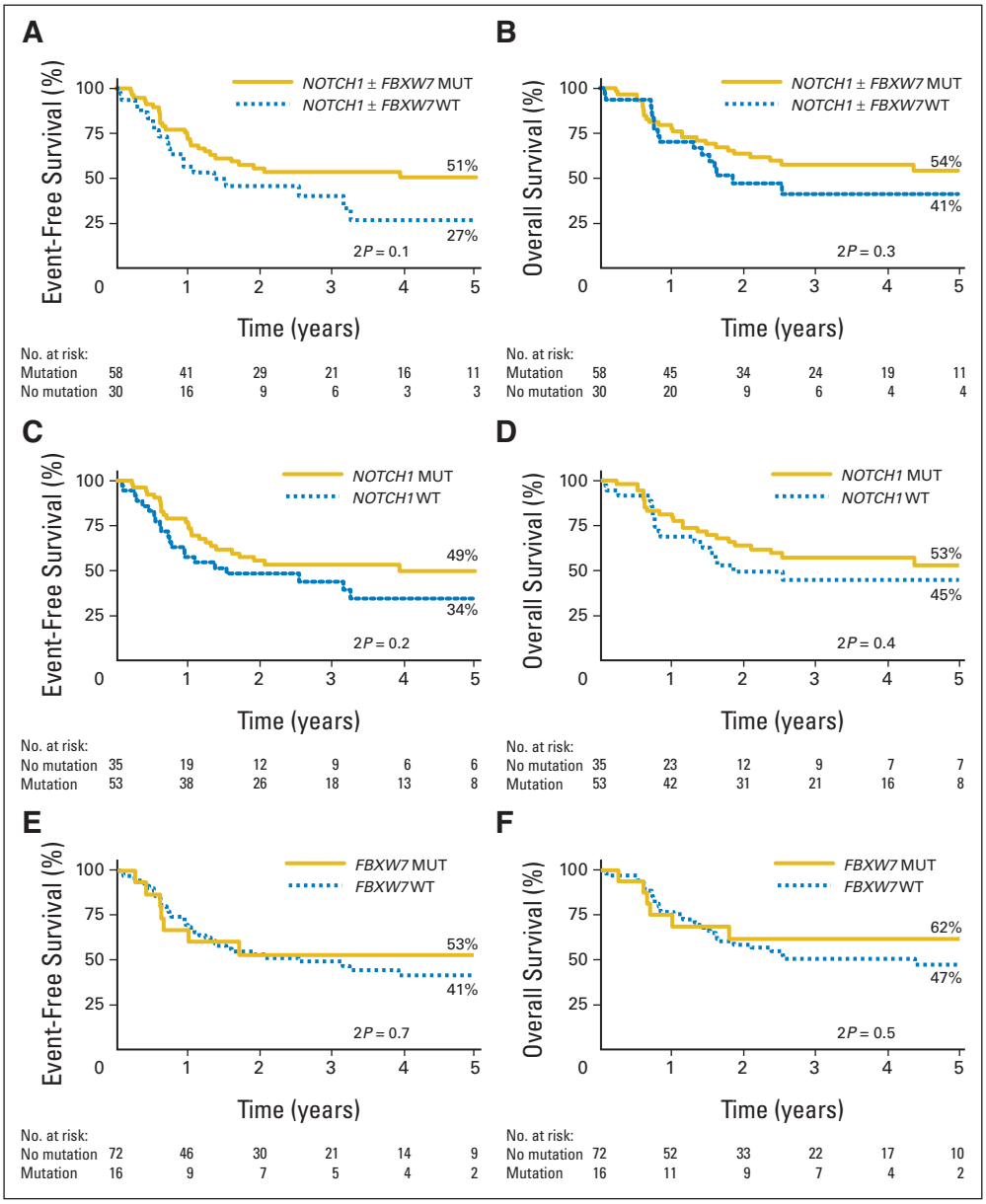

Fig 2. Outcome of adult patients with T-cell acute lymphoblastic leukemia treated on United Kingdom Acute Lymphoblastic Leukaemia XII/Eastern Cooperative Oncology Group E2993 protocol stratified by *NOTCH1* and *FBXW7* mutational status. (A) Event-free survival (EFS) by *NOTCH1* and/or *FBXW7* mutation. (B) Overall survival (OS) by *NOTCH1* and/or *FBXW7* mutation. (C) EFS by *NOTCH1* mutation. (D) OS by *NOTCH1* mutation. (E) EFS by *FBXW7* mutation. (F) OS by *FBXW7* mutation. MUT, mutated; WT, wild type.

Patient Outcome According to Mutation Status

Importantly, standard- and high-risk patients were evenly distributed between the MUT and WT groups (by WBCs, 61% of patients with WBCs $< 100 \times 10^9$/L were *NOTCH1* MUT *v* 62% patients with WBCs $\geq 100 \times 10^9$/L, Fisher's exact test $P = 1.0$; by age, 55% of patients ≤ 35 years of age were *NOTCH1* MUT *v* 69% of patients > 35 years of age, $P = .37$). The overall outcome of all patients on the trial has recently been reported.[21] Comparison of outcome in patients with a mutation in the Notch pathway (*NOTCH1* and/or *FBXW7*) with those without showed a trend toward improved outcome in those with a mutation. At 5 years, EFS and 95% CIs were 51% ± 14% versus 27% ± 19% ($P = .10$) in MUT and WT patients, respectively (Fig 2A; hazard ratio, 0.6; 95% CI, 0.3 to 1.1). The OS rates at 5 years were 54% ± 14% and 41% ± 20%, respectively ($P = .30$; Fig 2B). Analysis of patients with or without a *NOTCH1* mutation revealed a 5-year EFS of 49% ± 15% versus 34% ± 18% ($P = .2$; Fig 2C) and OS of 53% ± 15% versus 45% ± 17% ($P = .41$; Fig 2D), respectively. Comparison of patients with or without an *FBXW7* mutation showed a 5-year EFS at 53% ± 26% versus 41% ± 13% ($P = .72$; Fig 2E) and OS of 62% ± 24% versus 47% ± 12% ($P = .51$; Fig 2F). On the trial as a whole, treatment, age, and WBCs significantly influenced outcome.[19,21] Of these, only treatment received was significant in the Cox model ($P = .03$) in this smaller cohort of patients with T-ALL, and inclusion of these variables did not materially effect EFS (Table 3). There were insufficient data to test the effect of transplantation by means of a donor versus no donor comparison. Standard-risk patients with a *NOTCH1/FBXW7* mutation did not fair significantly differently from standard-risk WT patients (EFS = 47.7% for WBCs $< 100 \times 10^9$/L *v* 30.3%, $P = .5$; 45.5% for age < 35 years *v* 39.3%, $P = .6$), and there was no interaction between effects of mutation and risk group.

Considering the marked in vitro synergistic activation of the Notch pathway by dual HD and PEST mutations or dual HD and *FBXW7* mutations,[4,14] we analyzed the outcome of this synergistic subgroup versus the WT patients. The EFS was 62% versus 30%, respectively, but this did not reach statistical significance ($P = .17$). Overall, our data show a trend toward improved EFS in patients with a Notch pathway mutation, but did not identify a subgroup of patients with a significantly favorable outcome to warrant treatment reduction on future trials.

Table 3. Multivariate Analyses of Event-Free Survival

Model	Hazard Ratio for Variable Shown in Italics	95% CI
NOTCH1/FBXW7	0.62	0.34 to 1.11
NOTCH1/FBXW7, age, log(WBC+1)	0.66	0.34 to 1.29
NOTCH1/FBXW7, age, log(WBC+1), treatment*	0.73	0.37 to 1.44
NOTCH1	0.70	0.39 to 1.24
NOTCH1, age, log(WBC+1)	0.77	0.42 to 1.42
NOTCH1, age, log(WBC+1), treatment*	0.85	0.45 to 1.61
FBXW7	0.85	0.38 to 1.91
FBXW7, age, log(WBC+1)	0.91	0.40 to 2.08
FBXW7, age, log(WBC+1), treatment*	0.87	0.36 to 2.13

*First remission transplantation or chemotherapy (n = 84).

DISCUSSION

Despite risk-stratification in adult ALL by WBC count, age, and neurologic involvement, there remains marked heterogeneity in outcome among standard- and high-risk patients. Although minimal residual disease kinetics using T-cell receptor rearrangements are likely to contribute significantly toward stratification protocols in the future,[22,23] minimal residual disease in adult T-ALL is less robust at predicting prognosis and identifying early relapse than it is in adult B-ALL, or pediatric B- or T-ALL.[24-26] Subsequently, simple mutation screening strategies that predict outcome could prove invaluable in clinical decision making in adult T-ALL, particularly in evaluation of patients for allogeneic hematopoietic stem-cell transplantation.

Here we show a high incidence of activating mutations in the *NOTCH1* (60%) and *FBXW7* genes (18%) in adult T-ALL, similar to that seen in pediatric T-ALL cohorts,[7,16] and this indicates that the presence of these mutations, in themselves, is unlikely to explain the disparity in outcome seen between these age groups. There was a significant positive association between having a *NOTCH1* mutation in the HD domain only and an *FBXW7* mutation and a strong negative association between having a *NOTCH1* PEST mutation and *FBXW7* mutation. This observation is consistent with the hypothesis that *NOTCH1* HD and *FBXW7* mutations act in concert, similar to dual HD and PEST mutations.[11,14] Although FBXW7 also targets c-Myc for degradation,[11,27] the association described here favors the concept that *FBXW7* mutations are acquired by T-ALL cells primarily as a means of increasing *NOTCH1* signal strength. If *FBXW7* mutations were acquired by tumor cells predominantly to upregulate c-Myc, they would likely be found in conjunction with PEST mutations in some cases.

Although our data did not show a significantly improved outcome in those patients with mutations in the Notch pathway, the trend is in accord with data previously presented in pediatric patients treated on the ALL-BFM protocol[16] and, more recently, in adults on the French LALA-94 and GRAALL-2003 trials,[18] and in contrast to the association with poor prognosis reported in adults by Zhu et al.[17] Other molecular markers have been reported to have some impact on prognostic outcome in adult T-ALL. For example, *TLX1* mRNA upregulation has been shown to be associated with an improved prognosis.[28] It was not possible to evaluate this in our cohort because of lack of RNA samples from all patients. However, patients with *TLX1* upregulation constitute a minority of patients and are strongly associated with *NOTCH1* mutations (20 of 21 patients with *TLX1* upregulation were *NOTCH1* MUT in the French study).[18] *NOTCH1/FBXW7* has also been shown to be prognostically important independently of *TLX1*.[18] Together, these data suggest it is valid to evaluate patient outcome according to *NOTCH1/FBXW7* status alone. Furthermore, when the three most robust prognostic factors on the overall UKALLXII/ECOG trial were taken into account (age, WBCs, and treatment arm), the differences in EFS and OS were unaffected, and the *NOTCH1/FBXW7* MUT and WT groups were equally balanced in regard to the percentages of standard- and high-risk patients.

Although we found no significant difference in outcome in *NOTCH1* or *FBXW7* MUT patients when analyzed individually, the combined *NOTCH1/FBXW7* MUT group showed a trend toward improved outcome ($P = .1$), highlighting the importance of the addition of *FBXW7* status to that of *NOTCH1*. Thus unlike the situation of *FLT3* mutations in acute myeloid leukemia, where activating the same receptor by either point mutation or internal tandem duplication is

associated with a diametric prognostic outcome,[29] the suggestion in T-ALL may be that it is Notch pathway activation itself that is important in determining treatment response.

To date, this is the largest adult cohort of T-ALL patients treated on a single trial addressing outcome by *NOTCH1/FBXW7* mutation status. Although the data show a nonsignificant difference between the MUT and WT groups, it is compatible with the MUT group having a better prognosis, as shown by Asnafi et al,[18] and much larger studies of adult patients will be required to demonstrate this unequivocally. The current study has 80% power to detect a 30% increase in EFS. The data on this adult cohort do show that, even if there is a better outcome in those with a Notch pathway mutation, the magnitude of the improvement in EFS is likely to be too low to consider de-intensification of therapy in this group of patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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