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# Favorable outcomes after early allogeneic stem cell transplantation in adult early T-cell precursor acute lymphoblastic leukemia treated with the pediatric-inspired GIMEMA LAL1913 program. A Campus ALL study



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**To the Editor:**

Early T-cell precursor acute lymphoblastic leukemia (ETP-ALL) is a rare, biologically distinct subtype of T-lineage ALL, defined by an immature immunophenotype and specific genomic features, which is recognized as a separate entity by the 2022 WHO classification. ETP-ALL accounts for a minority of T-ALL—5–17% of pediatric and ~7% of adult cases- and has historically been considered a high-risk disease [1, 2]. ETP-ALL has been associated with lower remission rates and a markedly inferior overall survival (OS) compared to non-ETP-ALL, supporting the use of allogeneic stem cell transplant (alloHSCT) in first complete remission (CR1) [3].

The GIMEMA LAL 1913 study established a pediatric-inspired, risk-adapted, and measurable residual disease (MRD)-oriented approach that has become the standard of care for adult Philadelphia-negative ALL in Italy [4]. In the subsequent real-world Campus ALL analysis of 421 adult patients treated according to this program, clinical outcomes were comparable to those of the original trial, confirming the benefit of alloHSCT in very high-risk (VHR) patients based on the presence of clinical or molecular/cytogenetic features at diagnosis and/or MRD positivity [5, 6]. Within this real-life Campus ALL cohort, we identified 40 patients with ETP ALL, defined by absent CD8 and CD1a expression, weak/absent CD5, and the expression of at least one myeloid and/or stem cell marker, as in the WHO 2022 classification [2, 7]. In keeping with the LAL 1913 risk stratification, ETP-ALL was considered as VHR and therefore allocated to early transplant after the first three cycles of chemotherapy (week 10, MRD timepoint 2). We performed a subgroup analysis to assess the clinical outcomes of this uniformly treated, VHR T-ALL population, managed in the real-life practice with an intention-to-transplant strategy. The endpoints were OS and event-free survival (EFS, defined as non-response/disease relapse or death, whichever occurred first), while in transplanted patients non-relapse mortality (NRM) and graft-relapse-free survival (GRFS) were also evaluated. The median age was 44.5 years (range 19-65). Six out of 40 patients (15%) had a medullary blast count of less than 25%, consistent with a diagnosis of lymphoblastic lymphoma, 23 (59%) had extramedullary disease, mainly mediastinal, and 5 (13%) had a central nervous system involvement at diagnosis. The patients' characteristics are reported in Table S1 (Data Supplement). Overall, 31 of 40 patients (78%) underwent an alloHSCT. Among the 9 patients who did not proceed to transplant, the reasons included 5 deaths from NRM (3 infections, 1 cerebrovascular event, and 1 other cause), whereas 4 had refractory disease. Of these 4 patients, 3 did not respond to salvage treatments, while 1 received off-label nelarabine-decitabine-venetoclax and remains alive, without transplantation. The median number of chemotherapy cycles before alloHSCT was 4 (range 3-6). Thirty patients were transplanted in first complete remission (CR1) and 1 patient in second complete remission (CR2). Of the 30 patients transplanted in CR1, 2 received additional pre-transplant treatment for MRD positivity (1 patient received FLAG-IDA and 1 patient off-label nelarabine), both achieving MRD negativity at transplant. Overall, 22 of the 31patients (71%) were MRD-negative, while 9 (29%) were MRD-positive at transplantation. Regarding transplant characteristics, 10 patients (32%) were transplanted from an HLA-identical donor, 12 (39%) from a matched unrelated donor (MUD), 6 (19%) from a haploidentical donor, and 3 (10%) from a mismatched MUD. According to the criteria proposed by Bacigalupo et al. [8], the conditioning regimen was myeloablative (MAC) in 27 of 31 patients (87%), most commonly with a 12 Gy total body irradiation (TBI)-based regimen (23/31, 74%). The transplant characteristics and post-transplant events are reported in Table S2 (Data Supplement).

The 3-years OS and EFS for the entire cohort were 72% and 55%, respectively (Fig. 1a, b). In transplanted patients, the 3-year OS and EFS were 80% and 77%, respectively (Fig. 1c, d), with a GRFS of 61% and a cumulative incidence of relapse (CIR) of 20% (Fig. 1e, f), and a remarkably low NRM of 3%. The cumulative incidence of acute graft-versus-host disease (GvHD) was 42%, with most cases being grade 1–2, and a single grade 3 case; the cumulative incidence of chronic GvHD was 29%, with 6 cases of moderate-severe grade GvHD. We observed 6 post-transplant deaths, 4 due to relapse and 2 due to non-relapse causes (1 secondary malignancy and 1 poor graft function). Stratification by MRD status at transplant did not show statistically significant differences in OS (90% vs 78%, $p = 0.2021$) and EFS (81% vs 67% $p = 0.3986$) between MRD-negative and MRD-positive patients.

This analysis adds clinically relevant evidence to a field still largely represented by small retrospective series and subgroup analyses. In the GRAALL study, despite very high rates of early treatment resistance and MRD positivity, adult ETP-ALL patients treated with a pediatric-inspired, response-adapted strategy achieved outcomes comparable to those of non-ETP T-ALL, and alloHSCT appeared to contribute substantially to this effect [9]. In the multicenter transplant analysis by Brammer et al., ETP-ALL patients transplanted in CR1 had a 3-year OS of 47%, and pre-transplant MRD positivity was strongly associated with disease progression, confirming the importance of the transplant timing and disease status at alloHSCT [10]. The NOPHO ALL2008 experience also showed that the ETP phenotype was associated

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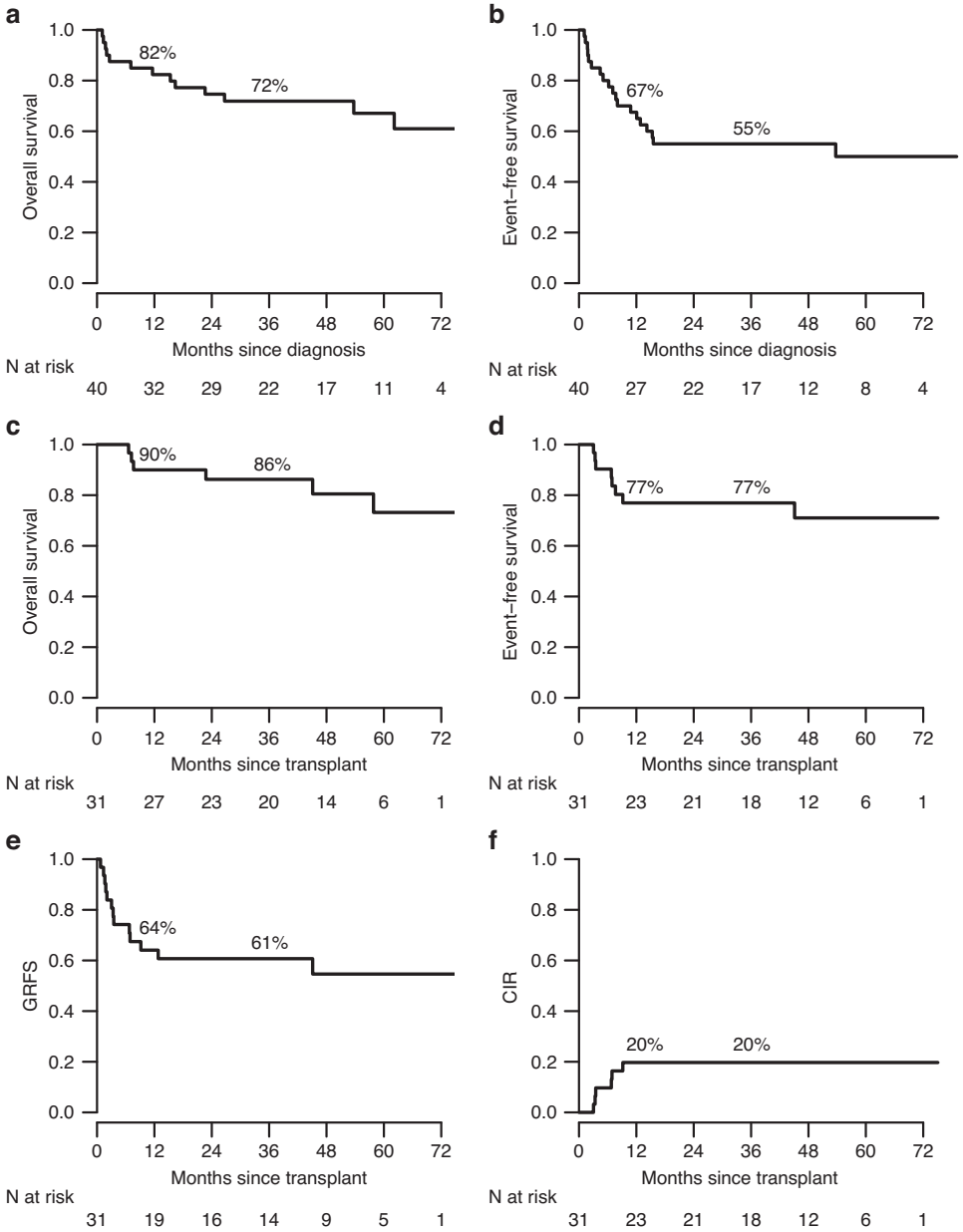


**Fig. 1 Clinical outcomes for the intention-to-transplant population and for the transplanted patients. a** Overall survival (OS) in the intention-to-transplant population; **b** Event-free survival (EFS) in the intention-to-transplant population; **c** Overall survival (OS) in the transplanted patients. **d** Event-free survival (EFS) in the transplanted patients. **e** Graft-relapse-free survival (GRFS) in the transplanted patients. **f** Cumulative incidence of relapse (CIR) in the transplanted patients.

with an inferior early MRD response but not with a worse long-term survival when treated within a pediatric protocol [11].

The main originality of our study is that it specifically documents, in the routine clinical practice and within a homogeneous national treatment protocol, the feasibility and efficacy of an early intention-to-transplant strategy for adult ETP-ALL. To the best of our knowledge, this is one of the largest reported adult ETP-ALL cohorts uniformly managed according to a pre-defined pediatric-inspired, MRD-oriented, intention-to-transplant strategy. Notably, the favorable results reported were achieved in a relatively older adult population, including patients up to the age of 65, with a high proportion of patients ultimately undergoing an alloHSCT according to the intention-to-treat strategy (78%), almost always in CR1. The very low NRM observed in our cohort (3%) is particularly noteworthy given the age distribution and the predominance of myeloablative, frequently TBI-based conditioning. This finding supports that early HSCT allocation in ETP-ALL, by limiting pre-transplant chemotherapy exposure, may allow patients to reach the alloHSCT in better clinical conditions, thereby reducing NRM. The lack of a significant survival disadvantage in MRD-positive patients at the time of transplant should be interpreted with caution, as it likely reflects the limited sample size rather than a true lack of prognostic impact. In the broader Campus ALL transplant series, including both B- and T-lineage ALL, MRD positivity was associated with markedly inferior outcomes, while Brammer et al. likewise identified pre-transplant MRD positivity as a strong predictor of progression in T-ALL [6, 10]. By contrast, the recent report from the pediatric FORUM trial did not show a detrimental effect of pre-transplant MRD positivity in transplanted T-ALL, probably reflecting a stronger graft-versus-leukemia effect in this setting [12].

Our data support early alloHSCT in CR1 as an effective strategy for adult ETP-ALL within the GIMEMA LAL1913 framework, while the major unmet need remains improving the proportion of patients who successfully reach transplant by overcoming primary refractory disease. In this regard, a phase II GIMEMA study (NCT06253637) evaluating the addition of daratumumab to the LAL 1913 treatment protocol for high-risk T-ALL patients is ongoing and has recently completed accrual.

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## DATA AVAILABILITY

Data are available upon reasonable request to the corresponding Author

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## AUTHOR CONTRIBUTIONS

GC and FL designed the study, collected data, collaborated in data interpretation, wrote the manuscript, and gave final approval before manuscript submission. CP performed statistical analysis, collaborated in data interpretation, revised the manuscript, and gave the final approval before manuscript submission. DL, FV, AG, MC, MD, ML, FG, SI, GL, AM, PS, PZ, MB, PC, MD, ME, CM, CS, SC, AC collaborated in data collection and interpretation, revised the manuscript, and gave the final approval before manuscript submission. AR, SC, RF and AC designed the study, provided major intellectual contributions to the manuscript, and gave the final approval before manuscript submission.

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## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

**Supplementary information** The online version contains supplementary material available at https://doi.org/10.1038/s41409-026-02975-1.

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