# Real-life management of 476 older adults with Philadelphia-negative acute lymphoblastic leukemia: a Campus ALL study

The introduction of pediatric-like regimes and risk-adapted strategies mostly based on measurable residual disease (MRD) has significantly improved the prognosis of Philadelphia-negative (Ph⁻) acute lymphoblastic leukemia (ALL) in younger adults.[1-3] However, older patients still experience a poor outcome with standard chemotherapy, with a notable risk of early death, toxicities and relapse.[4] Pediatric-inspired regimens are feasible in older adults with encouraging results, but dose adaptations are mandatory and asparaginase toxicity represents a significant challenge.[4,5]

Immunotherapy has changed the treatment landscape of B-cell precursor (BCP) ALL, but long-term survival remains poor when it is employed in the relapsed/refractory setting. In recent trials, both blinatumomab and inotuzumab have been used frontline with positive results.[6,7] However, outside of clinical studies, these options are so far not widely available for older patients with Ph⁻ BCP ALL and their cost represents a significant issue.

Currently, there is no consensus on the best front-line approach for older patients with Ph⁻ ALL, and large contemporary datasets are lacking. We therefore aimed to collect a large real-life cohort to obtain a detailed picture of treatments and outcomes of patients managed outside of clinical trials.

In the context of the Campus ALL national framework in Italy, 42 centers retrospectively collected data for this study. We enrolled patients with Ph⁻ ALL aged ≥55 years, diagnosed between January 2013 and December 2023, and treated outside of clinical trials. The study was conducted in accordance with the Declaration of Helsinki and was approved by a central review board. Overall survival (OS) and relapse-free survival (RFS) were defined using the Kaplan-Meier method and competitive risk analyses were employed to estimate the cumulative incidence of relapse (CIR) and the non-relapse mortality (NRM). The cut-off date for these analyses was May 2024, and statistical analyses were performed using STATA 12.1.

We included 476 patients, with a median age of 66 years (range, 55-91), 149 (31%) being >70 years old, 153 (33%) with an Eastern Cooperative Oncology Group performance status of 2-4 and 21 (4%) having lymphoblastic lymphoma. The patients' characteristics are summarized in Table 1. Eight patients (2%) received supportive care only due to advanced age and poor performance status and were not further analyzed. Among the 468 patients who received active treatment, 315 (67%) were treated with a pediatric-like regimen, with frequent dose reductions and adaptations: 191 (41%) according to the GIMEMA LAL1913 protocol,[1] 65 (14%) according to NILG10/07, 37 (8%) according to the EWALL or GMALL[5] trials and 22 (5%) with other asparaginase-containing regimens. Among the 241 patients who eventually received asparaginase, 177 received peg-asparaginase, 54 native *E. coli* asparaginase and ten Erwinase. Conversely, 153 patients received adult-type regimens, using the GIMEMA LAL1104 trial protocol in 80 patients (17%), Hyper-CVAD/mini-HyperCVD in 30 (6%), or others in 43 (9%) (*Online Supplementary Figure S1A/B*). Patients who received pediatric-like treatments were younger (mostly below 70 years) and had a better performance status than those treated with other regimes (*Online Supplementary Table S1A*).

During the course of treatment, 31% (147) of patients received immunotherapy, mostly because of MRD persistence/relapse (N=55, 37%) or relapsed/refractory disease (N=81, 55%). Twenty-four percent of patients (N=114) underwent an allogeneic hematopoietic cell transplant (allo-HCT), 64/114 (56%) in first complete remission, which represented 35% (64/185) of the potentially eligible

**Table 1.** Patients' characteristics.

| Characteristics | N (%) | Median (range) | N of cases with available data |
|---|---|---|---|
| Age, years | | 66 (55-91) | 476 |
| >70 years | 149 (31) | | |
| Gender | | | |
| Female | 246 (52) | - | 476 |
| ECOG PS 2-4 | 153 (33) | - | 466 |
| Lineage | | | 476 |
| B | 369 (77) | - | - |
| T | 94 (20) | - | - |
| MPAL | 13 (3) | - | - |
| Disease features | | | |
| WBC x10⁹/L | - | 7.1 (0.5-937) | 467 |
| CNS-positive | 23 (5) | - | 425 |
| Very high risk° | 171 (39) | - | 441 |
| Lymphoblastic lymphoma | 21 (4) | - | 430 |

°According to the GIMEMA LAL1913 classification. ECOG: Eastern Cooperative Oncology Group; PS: performance status; MPAL: mixed phenotype acute leukemia; WBC, white blood cells; CNS: central nervous system.

patients, i.e. very high-risk patients and/or MRD$^+$ up to 70 years old. After induction (course I or II) 76% (N=356) reached complete remission (CR) or complete remission with incomplete count recovery (CRi); 77 (16%) of the patients were refractory, while 35 (8%) died before response assessment. The 30- and 60-day mortality rates were 4% and 9%, respectively. MRD was assessed by flow cytometry, real-time quantitative polymerase chain reaction for immunoglobulin/T-cell receptor gene rearrangements and both methods in 48% (N=134), 25% (N=70) and 25% (N=70) of patients, respectively; the assessment method was unknown for five (2%) of the patients. Among patients with CR/CRi, 35% (N=125) achieved MRD negativity after induction, 43% (N=154) remained MRD$^+$, while 22% (N=77) were not evaluated.

After a median follow-up of 42.9 months, the median OS was 21.3 months, with a 3-year OS rate of 40% and a 5-year OS projected at 31%. After achieving remission, 47% of patients relapsed and 13% died in remission, with a median RFS of 17.1 months and a 3-year RFS rate of 40%. The 3-year CIR and NRM were 50% and 10%, respectively (Figure 1). In the 64 patients who received an allo-HCT in first CR (median age 59 years; range, 55-70), mostly for very high-risk features (N=39) or persistent MRD (N=12), the median OS was estimated at 105.7 months, with a 3-year OS rate of 64%; the 3-year CIR and NRM were 28% and 12%, respectively.

Patients diagnosed from 2017 onwards showed superior OS compared to those diagnosed earlier (median OS 23.1 *vs*. 18.1 months, *P*=0.045), but only for those with BCP-ALL (*Online Supplementary Figure S2*). However, after censoring at the time of immunotherapy for MRD persistence/relapse (only 4 patients treated before 2017), the statistical significance was lost (*P*=0.071). By multivariate analysis, the use of pediatric-inspired regimens appeared to be associated with better outcomes (hazard ratio [HR]=0.63, *P*=0.009), while older age (HR=1.04, *P*<0.001), very high-risk group (HR=1.45, *P*=0.006) and central nervous system invovlement (HR=3.01, *P*<0.001) were significantly associated with worse survival. In a sensitivity analysis censoring at allo-HCT in first CR/CRi, these results were confirmed (*Online Supplementary Table S1B*). Among patients who received asparaginase, the use of pegylated-asparaginase was not associated with an improved outcome compared to the outcomes with the other formulations (*P*=0.9).

Among the 279 MRD evaluable CR/CRi patients, MRD negativity after induction was associated with a reduced relapse risk (37% *vs*. 55%, *P*=0.008), reduced CIR (38% *vs*. 58% at 3 years, *P*=0.001) and improved RFS (median 40.6 *vs*. 14 months, *P*=0.001) (Figure 2), as confirmed by

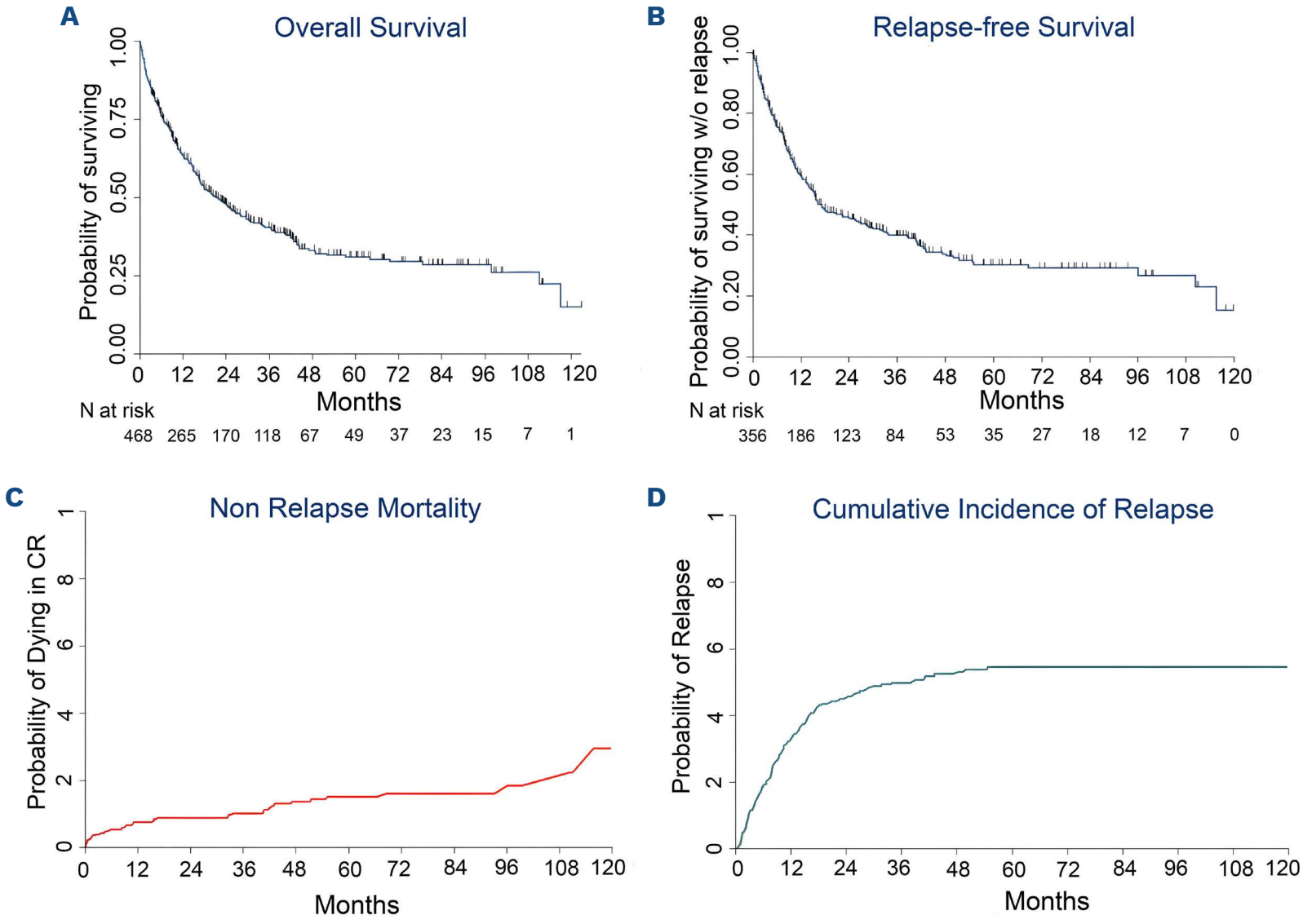



**Figure 1. Survival outcomes.** (A) Overall survival. (B) Relapse-free survival. (C) Non-relapse mortality. (D) Cumulative incidence of relapse. CR: complete remission.

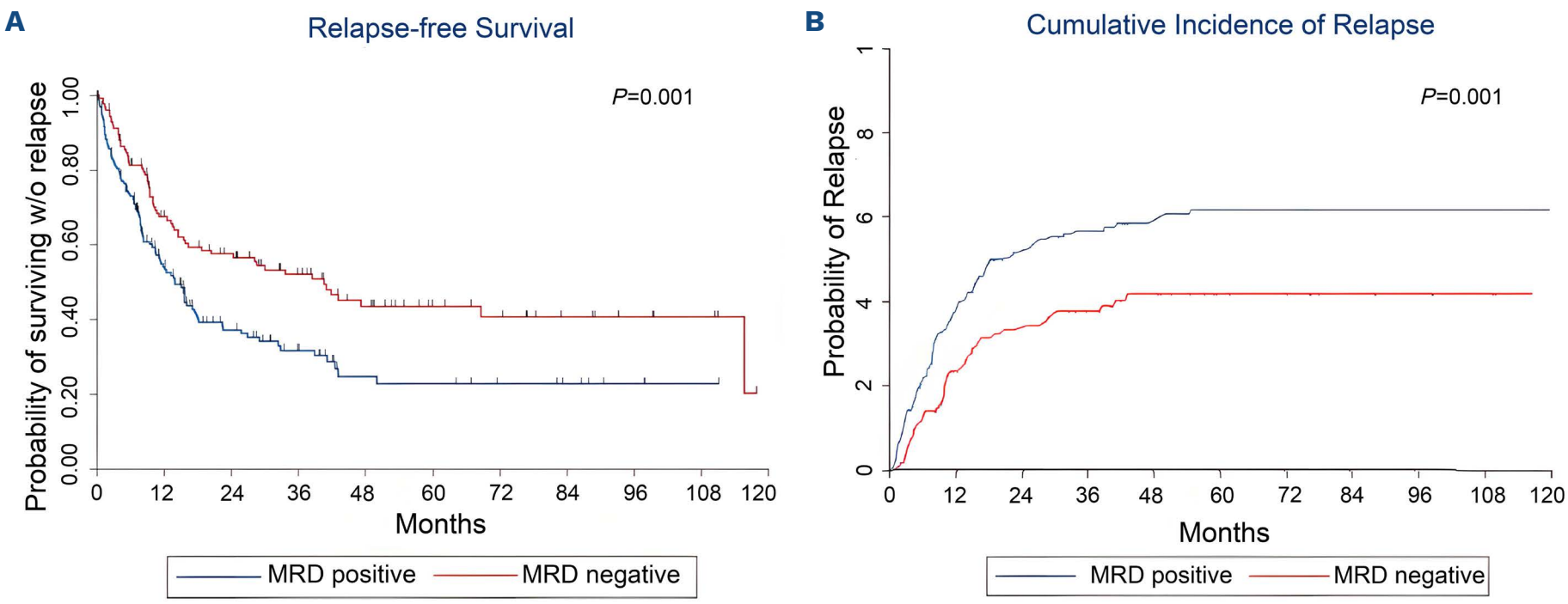



**Figure 2. Impact of measurable residual disease.** (A, B) Relapse-free survival (A) and cumulative incidence of relapse (B) according to measurable residual disease (MRD) status.

multivariate analysis (*Online Supplementary Table S1C*). Among patients with MRD persistence, 31 received blinatumomab, with a MRD negativity rate of 71% (22/31). Ultimately, 77% (17/22) of responding patients remained in persistent MRD$^-$ remission with or without further consolidation. Twelve patients received blinatumomab for MRD recurrence, and 83% (10/12) responded, with five of these ten responders remaining in long-lasting MRD$^-$ CR/CRi. Twelve patients were treated with inotuzumab for MRD positivity, either off-label (4 cases, 3 achieving MRD negativity) or in the context of an ongoing clinical trial (response data not available).

We hereby report one of the largest real-life cohorts of older Ph$^-$ ALL patients, showing a median OS of 21.3 months, a result somewhat superior compared to that in older reports and more in line with recent ones.[5,8] The CR/CRi rate of 75% and early death rate below 10% suggest that dose adaptations and better supportive care have led to improved early outcomes compared to those in the past. However, roughly half of the patients eventually relapsed, and long-term survivals are projected only at around 30%. We observed a moderate survival improvement in recent years in patients with BCP-ALL, likely due to the availability of immunotherapy, while patients with T-ALL did not show any improvement over time.

Patients in our cohort underwent heterogeneous chemotherapy regimens, in contrast to younger patients who are uniformly treated according to the national programs in Italy.[9] Thus, also considering that younger patients with better performance status were treated differently compared to frailer ones, it was challenging to perform robust prognostic analyses. Despite these limitations, through multivariate analyses we observed a significant survival advantage with pediatric-inspired regimens, confirming the effectiveness of this strategy in selected older patients. The role of allo-HCT is less established in this setting[10] and, as expected, only a limited number of patients underwent transplantation in first CR. However, results were encouraging, with lower-than-expected NRM and prolonged remissions, suggesting that allo-HCT should be considered in selected cases with high-risk disease. Despite MRD evaluation being less standardized compared to that in children and younger adults, MRD was assessed in 78% of CR/CRi patients after induction and confirmed its strong association with prognosis. Unfortunately, only a minority of cases with MRD persistence or recurrence received immunotherapy, but those who did showed rather high rates of long-lasting remissions. The outcome of patients who achieved early MRD negativity was encouraging, but relapses remained rather frequent also in this setting. Following the E1910 trial results, blinatumomab has been approved for MRD$^-$ Ph$^-$ ALL patients and, although not yet available in many countries, it represents an important tool to reduce the risk of relapse and toxicities.[11] However, given the lower benefit observed with blinatumomab consolidation in patients aged 55-70 years compared to younger ones, and the lower remission rate and higher early death probability with standard induction,[11,12] earlier incorporation of immunotherapy is advisable, together with reduction of chemotherapy intensity. Indeed, recently published and ongoing trials testing this approach are showing significant improvements.[6,7,13,14]

Our study, although limited by its retrospective nature, offers a valuable picture of the current real-life treatment landscape of Ph$^-$ ALL in older patients managed in Italy outside of clinical trials. While the role of chemotherapy in Ph$^+$ ALL is progressively reducing thanks to tyrosine kinase inhibitor-immunotherapy combinations,[15] chemotherapy still plays a role in Ph$^-$ cases, and a positive impact of

pediatric-inspired approaches is observed at least up to the age of 70 years. Treatment of BCP-ALL patients should be tailored according to age and comorbidities, and integrated with an early use of immunotherapy, already in induction and/or early consolidation even in MRD⁻ cases, with the aim of partially replacing chemotherapy. New drugs and innovative approaches are urgently needed for T-ALL patients.

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MCe has received honoraria from Novartis, Incyte, Amgen, Servier, Otsuka, Italfarmaco, Abbvie, Astellas and Pfizer. DL has received honoraria from Amgen, Menarini, Jazz and Abbvie. EBor has received honoraria from Novartis, Incyte, Amgen, Servier, Otsuka, Italfarmaco, AbbVie, Astellas and Pfizer. DL has received honoraria from Amgen, Menarini, Jazz and AbbVie. MLu has received honoraria from Amgen, Menarini and Jazz. CPap has received honoraria from Novartis, GSK, Blueprint, Incyte, Amgen, Pfizer, BMS, Menarini and Astellas. FFo has received honoraria from Amgen, Astellas, Incyte and Sobi. PZ has received honoraria from Amgen, Pfizer, Astellas and AbbVie. NF has

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**Contributions**

MCe, MB and RF designed the study. MCe, EBos and DL assembled and analyzed the data. MCe, MB, SC and RF drafted the manuscript. All authors contributed to data collection, revised the manuscript, and accepted its final version.

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**Data-sharing statement**

Data is available upon reasonable request to the corresponding authors.

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