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

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

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Running Head: Outcome of older Ph-negative ALL patients

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Data sharing statement

Data is available upon reasonable request to the corresponding authors.

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Authors' contribution

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

Competing Interests

MC received honoraria from Novartis, Incyte, Amgen**,** Servier, Otsuka, Italfarmaco, Abbvie, Astellas, Pfizer; DL received honoraria from Amgen, Menarini, Jazz, Abbvie; EB received honoraria from Abbvie, Amgen, Incyte. ML received honoraria from Amgen, Menarini, Jazz; CP received honoraria from Novartis, GSK, Blueprint, Incyte, Amgen, Pfizer, BMS, Menarini, Astellas. FF received honoraria from Amgen, Astellas, Incyte, Sobi. PZ received honoraria from Amgen, Pfizer, Astellas, Abbvie; NF received honoraria from Abbvie, Amgen, Jazz, Pfizer; FL received honoraria from Pfizer, Abbvie, Amgen, Incyte, Clingen, BMS; SC received honoraria from Incyte, Amgen, Pfizer, Gilead, Abbvie; AC received honoraria from BMS, Astellas, Pfizer, Abbvie, Incyte, Janssen; MB received honoraria from BMS, Amgen, Incyte, Novartis, Pfizer.

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 acute lymphoblastic leukemia (Ph- 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 mandatories and asparaginase toxicity profile 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 (R/R) 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 in older Ph- BCP ALL and their cost represents a significant issue.

Currently, there is no consensus on the best front-line approach for older Ph- ALL patients, and large contemporary data sets are lacking. We therefore aimed at collecting 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 clinical trials. The study was conducted in accordance with the declaration of Helsinki and was approved by the 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, 153 (33%) with an ECOG performance status (PS) of 2 to 4 and 21 (4%) being lymphoblastic lymphoma. Patients' characteristics are summarized in **Table 1**. Eight patients (2%) received supportive care only due to advanced age and poor PS 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 reduction and adaptations: 191 (41%) according to the GIMEMA LAL1913[1], 65 (14%) to NILG10/07, 37 (8%) to the EWALL or GMALL[5] trials and 22 (5%) to other asparaginase-containing regimens. Among the 241 patients who eventually received asparaginase, 177 received peg-asparaginase, 54 native E. coli and 10 Erwinase. Conversely, 153 patients received adult-type

regimens according to the GIMEMA LAL1104 trial in 80 patients (17%), Hyper-CVAD/mini-HyperCVD in 30 (6%), or others in 43 (9%), **Supplementary Figure 1a/b**. Patients who received pediatric-like treatments were younger (mostly below 70 years) and had a better PS compared to those treated with other regimes **(Supplementary Table 1a).**

During the treatment course, 31% (147) of patients received immunotherapy, mostly for MRD persistence/relapse (N=55, 37%) or for R/R disease (N=81, 55%). Twenty-four % of patients (N=114) underwent an allogeneic hematopoietic cell transplant (allo-HCT), 64/114 (56%) in first CR, which represented 35% (64/185) of the potentially eligible patients, i.e. very high risk (VHR) and/or MRD+ up to 70 years. After induction (course I or II) the CR/CRi rate was 76% (356); 77 (16%) of 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 PCR for immunoglobulin/T-cell receptor gene rearrangements and both methods in 48% (134), 25% (70) and 25% (70) of patients, respectively [5 (2%) unknown]. Among CR/CRi patients, 35% (125) of patients achieved MRD negativity after induction, 43% (154) remained MRD+, while 22% (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 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 VHR features (39) or persistent MRD (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 BCP-ALL (**Supplementary Figure 2**). 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 associated with better outcomes (HR=0.63, P=0.009), while older age (HR=1.04, P<0.001), VHR group (HR=1.45, P=0.006) and CNS positivity (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 (**Supplementary**

Table 1b). Among patients who received asparaginase, the use of pegylated-asparaginase was not associated with an improved outcome compared to 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 multivariate analysis (**Supplementary Table 1c**). 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 5/10 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 somehow superior compared to 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 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 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 PS were treated differently compared to frailer ones, it was challenging to perform robust prognostic analyses. Despite these limitations, by 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 received it 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 being less standardized compared to 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 the reduction of chemotherapy intensity. Indeed, recently published and ongoing trials testing this approach are showing significant improvements.[6,7,13,14]

Our study, though 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 in Ph+ ALL the role of chemotherapy is progressively reducing thanks to TKI-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. 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, aiming at partially replacing chemotherapy. New drugs and innovative approaches are urgently needed for T-ALL patients.

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Tables

Table 1. Patients' characteristics

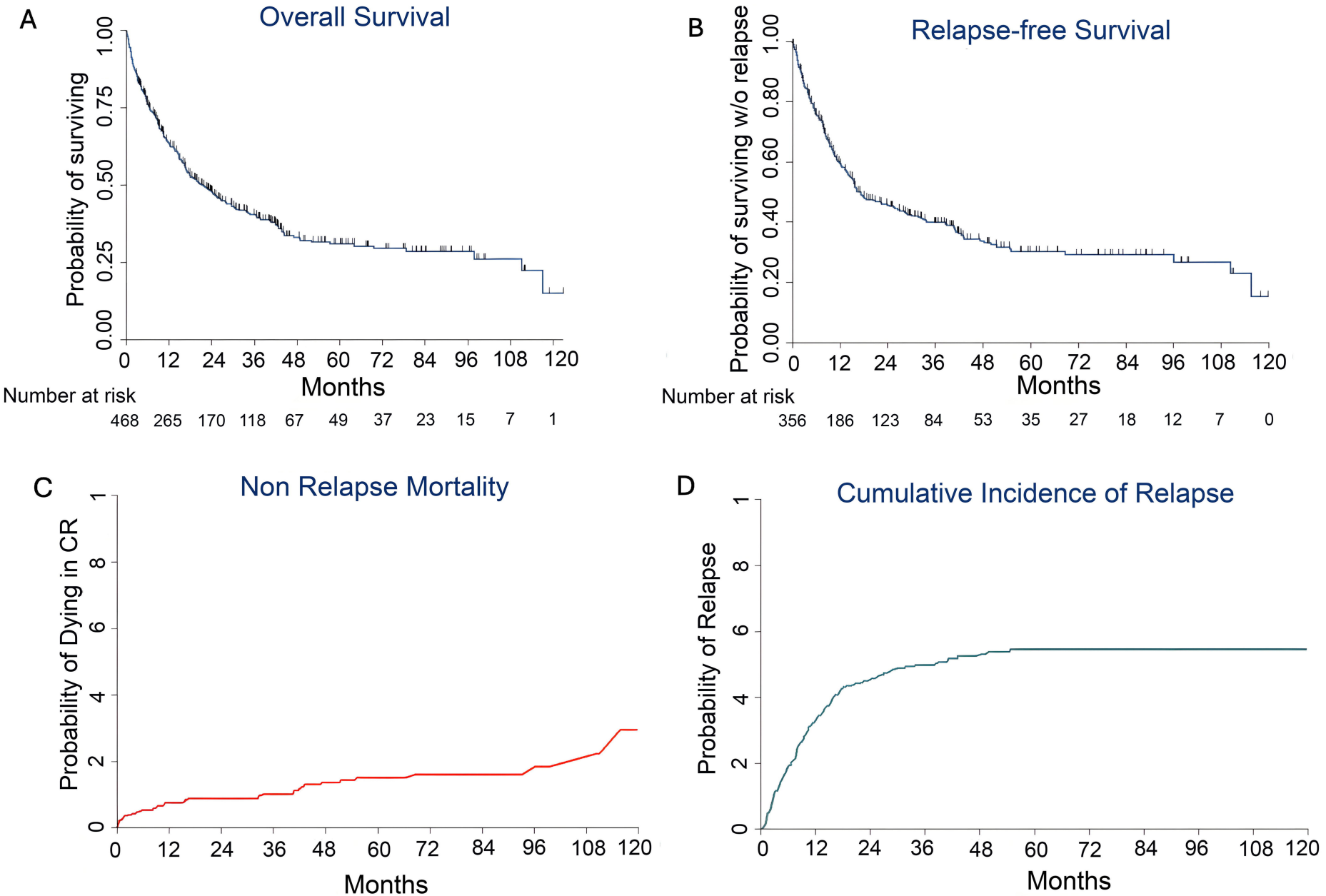
Characteristics, N=476	N (%)	Median (range)	N of cases with available data
Age, years		66 (55 – 91)	476
>70 years	149 (31)		
Gender			
Female	246 (52)		476
ECOG PS			
2-4	153 (33)		466
Lineage			476
B	369 (77)		
T	94 (20)		
MPAL	13 (3)		
Disease features			
WBC $x10^9$/L		7.1 (0.5 - 937)	467
CNS+	23 (5)		425
Very high risk°	171 (39)		441
Ly Lymphoma	21 (4)		430

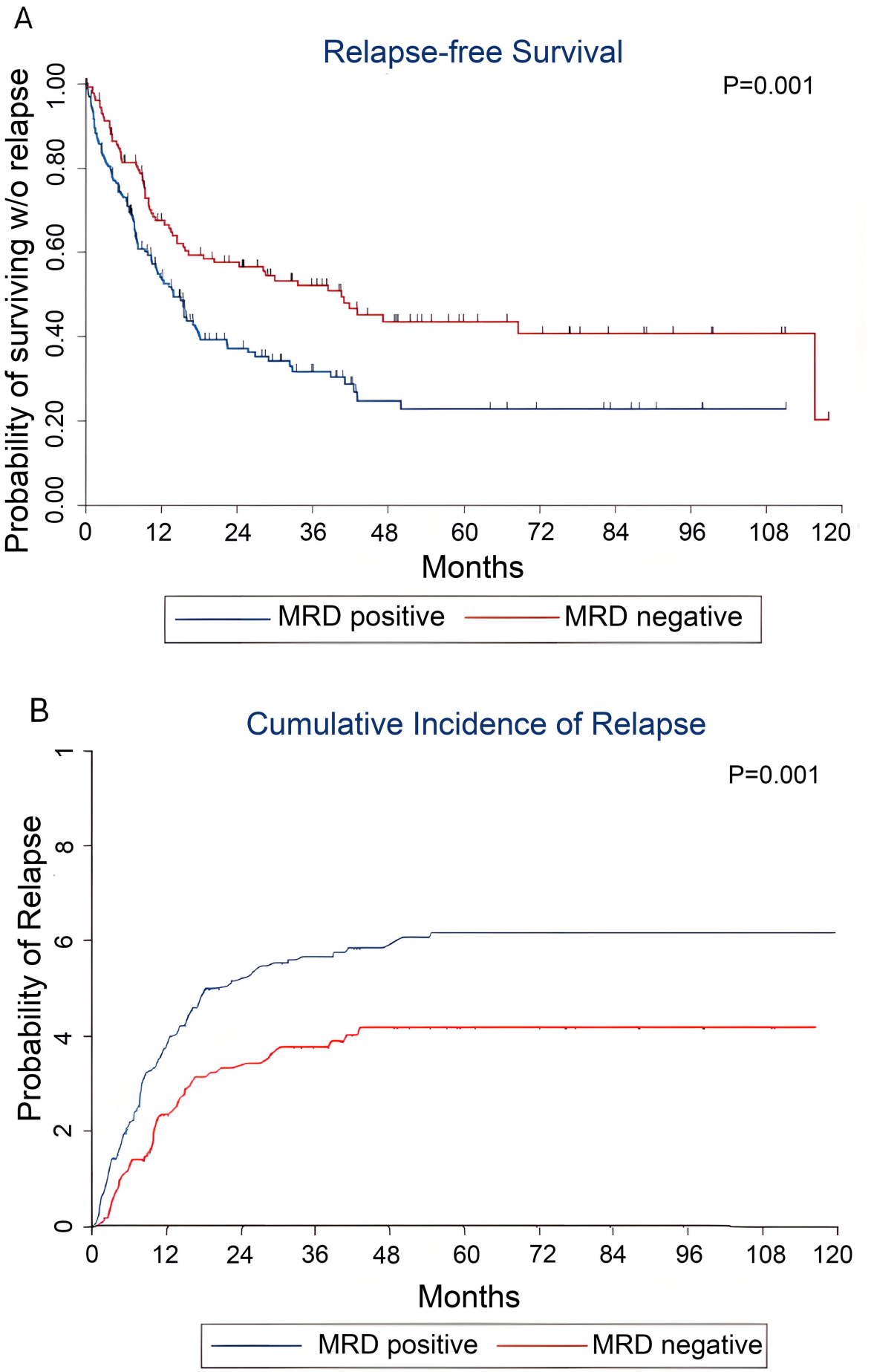
°According to the GIMEMA LAL1913 classification
CNS, central nervous system; Ly, lymphoblastic; N, number; PS, performance status; WBC, white blood cells

Legend to figures

Figure 1. Survival outcomes. Overall survival (A), relapse-free survival (B), non-relapse mortality (C) and cumulative incidence of relapse (D)

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


A
Overall Survival
Probability of surviving
0.00
0.25
0.50
0.75
1.00
0 12 24 36 48 60 72 84 96 108 120
Months
Number at risk
468 265 170 118 67 49 37 23 15 7 1
B
Relapse-free Survival
Probability of surviving w/o relapse
0.00
0.20
0.40
0.60
0.80
1.00
0 12 24 36 48 60 72 84 96 108 120
Months
Number at risk
356 186 123 84 53 35 27 18 12 7 0
C
Non Relapse Mortality
Probability of Dying in CR
0
2
4
6
8
1
0 12 24 36 48 60 72 84 96 108 120
Months
D
Cumulative Incidence of Relapse
Probability of Relapse
0
2
4
6
8
1
0 12 24 36 48 60 72 84 96 108 120
Months


A
Relapse-free Survival
P=0.001
Probability of surviving w/o relapse
0.00
0.20
0.40
0.60
0.80
1.00
0
12
24
36
48
60
72
84
96
108
120
Months
MRD positive
MRD negative
B
Cumulative Incidence of Relapse
P=0.001
Probability of Relapse
0
2
4
6
8
1
0
12
24
36
48
60
72
84
96
108
120
Months
MRD positive
MRD negative

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Supplementary appendix

Supplementary Table 1. Pediatric-inspired regimens vs other approaches

Supplementary Tables 1a. Patients' characteristics according to the treatment strategy (pediatric-inspired vs other regimens)

Characteristics	**N (%) or median (range)**	**N (%) or median (range)**	**N (%) or Median (range)**	**P°**
	Whole cohort	**Pediatric-inspired regimens***	**Other regimens***	
Age years	66 (55-91)	62 (55-83)	73 (56-91)	<0.001
Gender, female	246 (52)	165 (52)	76 (50)	0.62
ECOG PS, 2-4	153 (33)	80 (26)	65 (45)	<0.001
B-lineage	369 (77)	233 (74)	130 (85)	0.009
Disease features				
WB, x10^9/L	7.1 (0.5-937)	7.1 (0.4-937)	6.5 (0.6-373)	0.76
CNS +	23 (5)	15 (5)	8 (6)	0.65
Very High Risk (GIMEMA)	171 (39)	123 (41)	46 (34)	0.17

***** 8 palliative patients are excluded

° By Fisher exact test or Mann-Whitney U test

Supplementary Table 1b. Multivariate analysis for overall survival (main and censored at allo-HCT)

	Main analysis			**Analysis censored at allo-HCT**		
Variable	**HR**	**95% CI**	**P**	**HR**	**95%CI**	**P**
Age	1.04	1.02-1.06	0.001	1.03	1.01 – 1.05	0.009
ECOG PS				1.4	1.04 - 1.89	0.026
VHR	1.45	1.11-1.89	0.006	1.53	1.15 – 2.04	0.004
CNS+	3.01	1.83-4.93	<0.001	2.78	1.69 – 4.58	<0.001
Pediatric-inspired regimens	0.63	0.45-0.89	0.009	0.67	0.47 - 0.94	0.022

°VHR**,** very high risk According to the GIMEMA LAL1913 classification

ASP, asparaginase; CNS, central nervous system; HR, hazard ratio; PS, performance status

***** Potential prognostic variable considered were age (continuous), sex, PS (0-1 vs 2-4), CNS positivity, treatment (pediatric-inspired vs other regimens), lineage (BCP vs others), VHR. Cox proportional hazards models were followed by backward stepwise selection. The impact of treatment regimens on outcomes was analyzed by intention to treat, i.e. according to the schema that was chosen for each patient even if it was interrupted or modified prematurely.

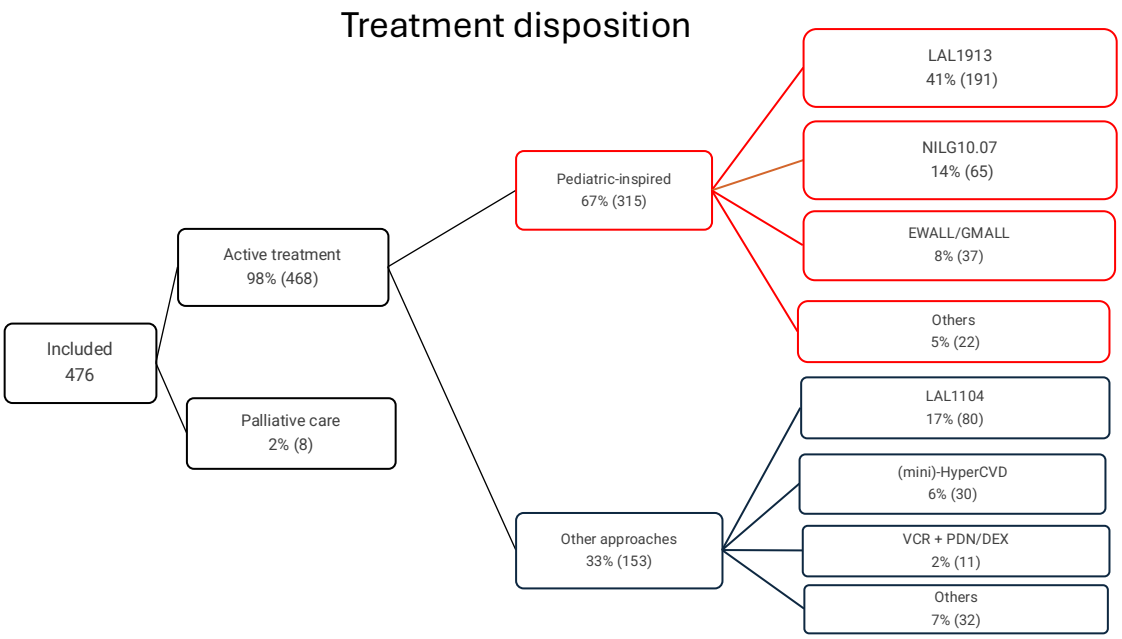
Supplementary Table 1c. Multivariate analyses for RFS and CIR

	RFS			CIR		
Variable*	**HR**	**95%CI**	**P**	**sHR**	**95%CI**	**P**
CNS+	3.05	1.66-5.60	<0.001			
Pediatric-inspired regimens	0.49	0.33-0.73	<0.001			
MRD negativity	0.46	0.32-0.67	<0.001	0.51	0.34-0.75	0.001

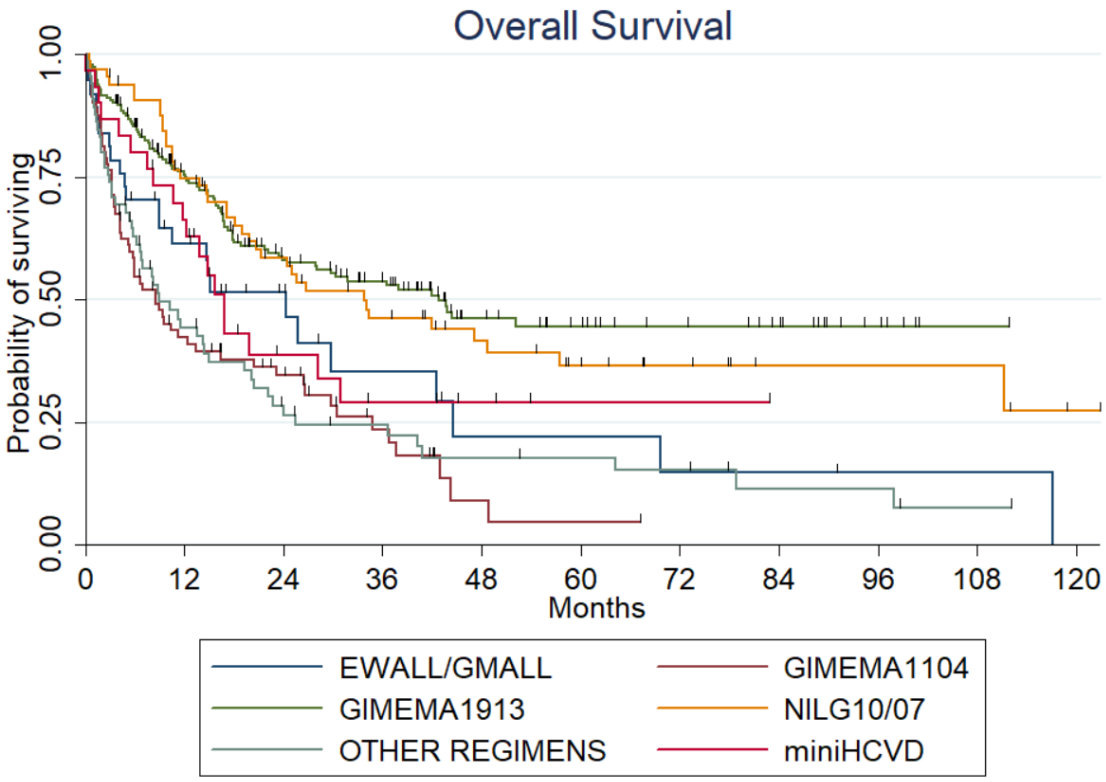
ASP, asparaginase; CIR, cumulative incidence of relapse; CNS, central nervous system; HR, hazard ratio; MRD, measurable residual disease; RFS, relapse-free survival; sHR, sub-hazard ratio
***** Potential prognostic variable considered were age (continuous), sex, PS (0-1 vs 2-4), CNS positivity, treatment (pediatric-inspired vs other regimens), lineage (BCP vs others), VHR, MRD. Cox proportional hazards models and competitive risk models were followed by backward stepwise selection.

Supplementary Figure 1. Treatments and outcomes

Supplementary Figure 1a. Treatment disposition



Supplementary Figure 1b. Overall survival according to the different treatment regimens



Supplementary Figure 2. Outcome of Ph- B-ALL and T-ALL according to the year of diagnosis**.**