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Shaping the future of older patients with Philadelphia-negative lymphoblastic leukemia

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In this issue of Haematologica Cerrano and colleagues report on the outcomes of 476 patients aged 55-91 years (median 66 years) with Philadelphia-negative acute lymphoblastic leukemia (Ph- ALL, n=455) or lymphoblastic lymphoma (n=21), who were treated between 2013-2023 with various chemotherapy regimens outside a prospective clinical trial.[1] The more frequently used protocols, totaling 256 patients, were two 'pediatric-inspired' chemotherapy programs with a minimal residual disease (MRD)-based risk stratification, that were originally applied to adults 18-65 years and differed only for a further drug dose reduction over 55 years and the use of pegaspargase in GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto) LAL1913.[1] This commendable Campus ALL study assembled a large retrospective series of real life patients with an extensive follow-up, integrating and corroborating the results of the two reference trials which included fewer patients 55-65 years and none above this range. The study provided clear evidence of the significant prognostic improvement achievable in Ph- ALL patients aged 55+ years with age-modified 'pediatric-inspired' protocols, as already demonstrated by others[2] and by population-based surveys.[3] In this real life analysis the cumulative complete remission (CR) rate was 76%, and 3 -year overall survival (OS) and relapse-free survival (RFS) were both projected at 40%. With NILG (Northern Italy Leukemia Group) 10/07- and GIMEMA 1913-type protocols OS rose to 50% and was still around 40% at 5 years (**Figure,** panel A; modified after Cerrano et al's supplementary Figure 1b[1]). These results rank among the best available for this unfavorable patient subset,[2] although it is

noted that blinatumomab (Blin) or inotuzumab ozogamicin (InO) immunotherapy was used in about one fifth of all 256 study patients because of MRD persistence or resistance/relapse. Outcome was further improved in patients 55-70 years, in MRD negative ones, and in those transplanted in CR1 because of high-risk classification. The latter experienced a remarkable 3-year OS at 64%, in line with a recent joint European analysis.[4]

Although recognizing a certain therapeutic progress, the other side of the coin is that current standards do not prevent death by disease or treatment toxicity in one half or more of these patients, particularly when considering higher ages and comorbidities. This critical issue elicited frontline immunotherapy trials with Blin and/or InO, to define new standards of care (SoC) for B-ALL. The main objective of the new immunotherapy-based trials has been to increase both CR and survival rates by lowering at one time the risk of chemotherapy-related mortality (on the average 30%, with wide ranges) through a marked downmodulation of its intensity, and that of relapse, to which most CR patients are exposed in chemotherapy only programs. The immunotherapy studies so far published including a single phase 3 trial (ECOG-ACRIN 1910) fulfilled these hopes, reporting outstanding CR and short-term survival figures compared to historical data (**Table**). Two other ongoing phase 3 trials aim to define new SoCs, comparing the efficacy of Blin alternating with low-intensity chemotherapy versus standard chemotherapy in patients aged 55+ years (NCT04994717), and of InO with low-intensity chemotherapy versus standard chemotherapy, followed by Blin and maintenance, in patients aged 50+ years (NCT05303792). Apart from stunning early results, in the two immunotherapy trials with no or very little associated chemotherapy, SWOG 1318 and Alliance A041703, the survival probability decreased steadily over time after the second year of follow-up, without any clear evidence of a long-term survival plateau. This may be a warning for an immunotherapy only post-remission approach when a prolonged survival at 3+ years is the goal. In fact, the patients of trials that combined chemo-immunotherapy consolidation (minimum of 4 Blin cycles and 2 InO cycles) and maintenance were more likely to experience long-term OS and RFS rates around 60%, as did those younger than 70 years, MRD negative, or having an allograft when suggested by their risk characteristics. And although induction toxicity was strikingly reduced in all immunotherapy trials, a high incidence of remission deaths (44%) often related to infections and secondary myeloid malignancies was reported by a MD Anderson Hospital study associating both InO and Blin plus rituximab (CD20+ ALL) with low-dose chemotherapy.

Wishing to reach the maximum therapeutic benefit in patients over 55 years, we should turn our attention to some other factors that may play a role in the process (**Figure**, panel B). First, adapting the definitions of performance status and fitness to non-intensive chemotherapy and targeting agents[5] could widen the access to age-adapted chemo-immunotherapy and allotransplantation too, increasing the transplantation rate of transplant-eligible patients, and explore in parallel other cellular therapies. Then, the sharing of an integrated risk score mainly based on post-induction MRD and ALL genetics, like the one validated across different study Groups,[6] would facilitate inter-study trials and large-scale comparative analyses on ALL subsets, risk groups and treatment elements, to better address some burning questions among which stands allotransplantation in high genetic risk ALL turning MRD negative after immunotherapy-based induction. Again, in the era of precision medicine, rapid and sensitive *ex vivo* drug response profiling (DRP) techniques can enable to determine the patterns of drug resistance or sensitivity to virtually all known antileukemic agents in both individual patients and ALL subsets, an endeavor globally referred to as pharmacotyping.[7] Pharmacotyping and DRP assays correlate with 'omics'-based ALL subtyping and MRD status, and by disclosing drug resistance or unexpected vulnerabilities unrelated to disease genetics are better than 'omics' alone when looking for a rapid prediction of drug response from ALL blast cells.[8] Because of the high risk of chemoresistance and the poor chemotherapy tolerance displayed by older patients, pharmacotyping may identify the most suitable drugs for 'low-dose' immunotherapy-based regimens, be they traditional agents repurposed through DRP or new targeting agents, also contributing to spare unnecessary drug toxicity. Finally, new more effective bispecifics, immunoconjugates and other targeting agents may become available soon, owing to the worldwide expansion of cancer immunotherapy research[9] and artificial intelligence-based accelerated on-target compound screening programs.[10]

In summary the current prospects of immunotherapy for untreated ALL may be enlarged within a context increasingly oriented to involve aspects of precision medicine, to warrant a better management of ALL patient and risk subsets, also involving T-ALL. These improvements should bring the survival of reasonably fit older patients with Ph- ALL consistently above 50% at 3+ years, with less concern for age limits, thereby gaining several life years in good health in subjects whose life expectancy without ALL diagnosis is now about 80 years and more. Make all this possible is a highly demanding task, that will require joint efforts between ALL study Groups and experts,

scientific societies, regulatory authorities, national health and funding organizations, and pharmaceutical industries.

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Study (Author, ref.)	**Patients/Age**	**Immunotherapy/ Other therapy**	**CR (%)**	**MRD- (%)**	**Outcome**	**Notes**
Blinatumomab-based (Blin)						
ECOG-ACRIN 1910 (Litzow, N Engl J Med. 2024 Jul 25;391(4):320-333)	• N 46 (MRD- CR) • Age 55-70 (N/A)	• Blin x4 cycles (CONS) • CHT (IND/CONS/Maint)	-	-	• 3-y OS 70% • 3-y RFS 69%	• Subset analysis of Phase 3 trial patients 30-70 years in MRD- CR randomized to Blin (n=112) • Outcome significantly improved vs no Blin arm • Safety: neurologic Blin toxicity grade 3+ 23% of 112 patients
GIMEMA 2317 (Bassan, Blood. 2025 May 22;145(21):2447-2459)	• N 28 • Age >55-65 (N/A)	• Blin x2 cycles (CONS) • CHT (IND/CONS/Maint)	68	92	• 3-y OS 51% • 3-y EFS 41% • 3-y RFS 51%	• Subset analysis on total study patients 18-65 years (n=149) • Safety: CHT-related IND mortality 25%; neurologic Blin toxicity grade 3+ 19% of 122 patients)
SWOG 1318 (Advani, J Clin Oncol. 2022 May 10;40(14):1574-1582)	• N 29 • Age 66-84 (75)	• Blin x1-2 cycles (IND), x3 cycles (CONS) • CHT (Maint)	66	92	• 3-y OS 37% • 3-y RFS 37%	-
GMALL BOLD (Goekbuget, Blood. 2023;142(suppl 1):964)	• N 50 • Age 56-76 (66)	• Blin x4 cycles (IND/CONS) • CHT (IND/CONS/Maint)	85	82	• 1-y OS 80% • 3-y OS 67% • 3-y EFS 60%	-
Inotuzumab ozogamicin-based (InO)						
EWALL-INO (Chevallier, J Clin Oncol. 2024 Dec 20;42(36):4327-4341)	• N 131 (CD22+) • Age 55-84 (68)	• InO x2 cycles • CHT (IND/CONS/Maint)	88.5	• 80	• 1-y OS 73% • 2-y OS 55% • 1-y EFS 64% • 2-y EFS 46% • 1-y RFS 66% • 2-y RFS 50%	• 10 patients to allograft (2-y OS 90%) • Safety: VOD/SOS 1
INITIAL-1 (Stelljes, J Clin Oncol. 2024 Jan	• N 43 (CD22+) • Age 565-80 (64)	• InO x3 cycles (IND) • Rituximab (CD20+)	100	71	• 1-y EFS 88% • 3-y EFS 55%	• Safety: VOD/SOS 1

20;42(3):273-282)		• CHT (CONS/Maint)			• 1-y OS 91% • 3-y OS 73%	
Blin- and InO-based						
M.D. Anderson Cancer Center (Jabbour, Lancet Haematol. 2023 Jul;10(7):e490)	• N 80 • Age 63-72 (68)	• InO x4 cycles (IND) • Blin x4 cycles (CONS) • Rituximab (CD20+) • Mini-hyper-CVD CHT (IND/CONS/Maint)	99	94	• 2-y OS 64% • 5-y OS 46% • 2-y PFS 58% • 5-y PFS 44%	• Blin since amendment (from patient 50), with InO reduction • CR: 7 patients with incomplete counts recovery • No outcome difference by Blin yes/no • Safety: 35 remission deaths (44%), with infection 8, MDS/AML 9, VOD/SOS 4
Alliance A041703 (Wieduwilt, J Clin Oncol. 2025 Nov 10;43(32):3526-3535)	• N 33 (CD22+) • Age 60-84 (71)	• InO x1-2 cycles (IND), • Blin x4-5 cycles (CONS)	85 (InO), 97 (InO+Blin)	91	• 1-y OS 85% • 3-y OS 60% • 1-y EFS 75% • 3-y EFS 45%	• No further therapy after CONS • Safety: VOD/SOS 1, encephalopathy 3 (1 fatal)

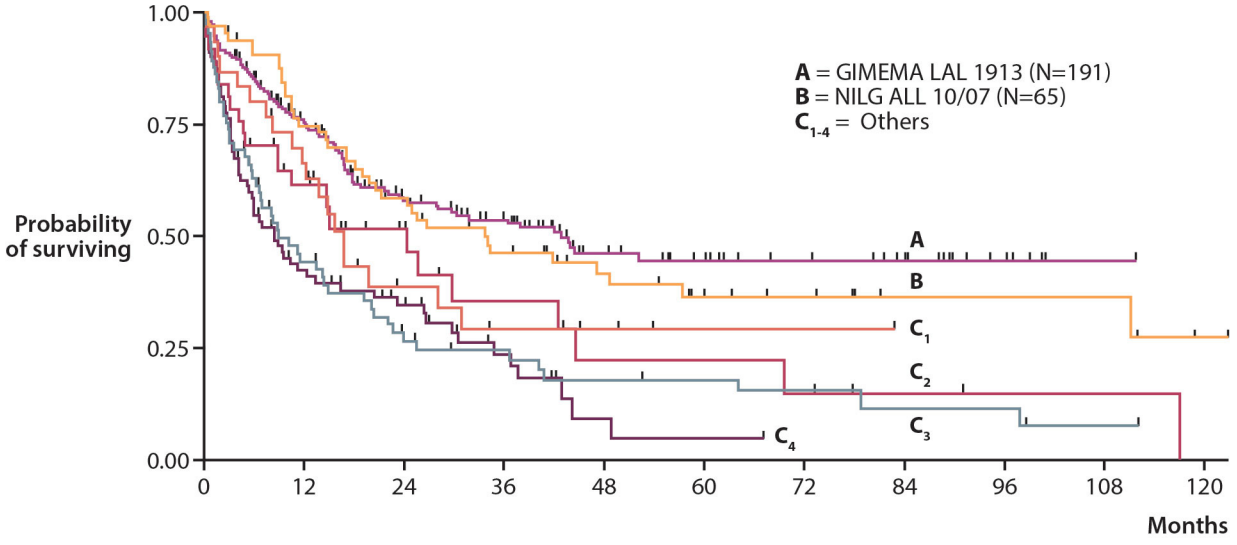
Abbreviations: N/A, not available; CR, complete remission; MRD-, minimal residual disease negative; InO, inotuzumab ozogamicin; Blin, blinatumomab; CHT, chemotherapy; IND, CR induction therapy; CONS, consolidation therapy; Maint, maintenance; OS/EFS/RFS/PFS, overall, event-free, relapse-free and progression-free survival; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; VOD/SOS, hepatic venoocclusive disease/sinusoidal obstruction syndrome

Table. Main data and results from frontline immunotherapy studies with Blin and/or InO in older adults with B-precursor ALL (median patient age, range, and outcome estimates in years, y).

Legend to the Figure

Overall survival analysis by treatment protocol in 476 older adults with Ph-negative ALL (modified after ref. 1) (**A**). Future incremental strategies for immunotherapy-based protocols in older patients with Ph- ALL (**B**).

A. Overall survival according to treatment protocol in 476 real life older patients with Ph- ALL (patient age 55-91 years; Campus ALL study 2013-2023)



B. Future incremental strategies of immunotherapy-based protocols for older patients with Ph- ALL (current/future)

Chemotherapy

- Nonintensive age-adapted *(CR induction, consolidation and maintenance)*
- IT CNS chemoprophylaxis

- Pharmacotyping/DRP *(resistance profile and repurposing of chemotherapeutic agents; chemotherapy backbone modeling)*

Immunotherapy

- InO (CD22+; x2-4 cycles), Blin (CD19+; x4-6 cycles), rituximab (CD20+)

- Best immunotherapy SoC to be defined *(trials ongoing)*
- Novel bispecifics and immunoconjugates
- Cellular therapy *(CAR-T/NK cells)*

Other targeted therapy

- Not routinely used *(experimental)*

- New clinical trials *(venetoclax, TK and menin inhibitors, etc.)*
- Pharmacotyping/ DRP *(unexpected vulnerabilities)*
- AI-accelerated discovery of new targeting agents

Risk assessment and oriented therapy

- Risk stratification *(genetics/MRD)*
- Risk-oriented allogeneic transplantation

- Integrated prognostic index *(WBC, extensive genetics, MRD; high risk index ≥ 2.50)*
- Fitness evaluation *(to nonintensive chemotherapy, targeting agents and allograft)*