# First-year results of the International Leukemia/ Lymphoma Target Board for pediatric relapsed and refractory hematological malignancies

Pediatric relapsed/refractory hematologic malignancies often lack standard-of-care options and historically show low early clinical trial enrollment[1] (approx. 6%). To improve access to targeted therapies, we established the international Leukemia/Lymphoma Target Board (iLTB, Medical Research Ethics Committee approval 21-638/C), a virtual platform providing expert multidisciplinary recommendations. In its first year, the iLTB assessed 42 cases from 18 countries. Treatment advice was provided for 41 patients, and was applied in 34 cases (81%), with 15/41 patients (36%) enrolled into clinical trials or expanded access program-named patient protocols (EAP-NP), predominantly through cross-border referrals.

Despite significant survival improvements over the past decades,[2-4] relapsed disease remains a leading cause of childhood cancer mortality. Standard options are critically lacking for subsequent relapses, necessitating innovative salvage therapies to achieve the minimal disease burden required for curative hematopoietic stem cell transplantations (HSCT). Recently, the salvage landscape has broadened with novel agents like bispecific antibodies (e.g., blinatumomab[5]), antibody-drug conjugates (e.g., inotuzumab ozogamicin[6]), and chimeric antigen receptor (CAR) T cells,[7] alongside agents targeting specific genetic abnormalities, such as menin inhibitors for *KMT2A* or *NUP98* rearrangements,[8] creating new therapeutic avenues for these high-risk patients. Expanded therapeutic options complicate treatment decisions. Previous molecular profiling programs like MAPPYACTS[9] and INFORM[10] included only a small number of hematologic cases and reported low clinical trial referral rates (4-19%). Notably, the hematology-focused LEAP consortium[1] showed that only 11% of patients received matched therapy, with just 6% in clinical trials. Optimal salvage selection is further hindered by limited drug access and prevalent off-label use, lacking centralized data collection. Consequently, we hypothesized that assembling an international expert panel, including early-phase trial investigators, would improve clinical trial enrollment and rational targeted therapy use, addressing this critical gap in structured therapeutic access.

The iLTB (ITCC-107 study, clinicaltrials.gov identifier NCT05270096) is a non-interventional, virtual platform and registry sponsored by the Princess Máxima Center in the Netherlands. The study is a multi-center discussion platform for patients under 18 years of age at initial diagnosis and under 25 years of age at relapse or refractory disease without standard-of-care options. The process starts with the initial preparation phase (Day -8 to -4), during which the treating physician notifies the iLTB, the case is registered, and essential clinical and biological data are compiled. This is followed by the pre-meeting review phase (Day -3 to -1), where actionable findings are assessed, additional information is gathered, including the latest treatments, and relevant experts are invited; at this stage, the case presentation is circulated concurrently. On Day 0, the formal iLTB meeting takes place, including presentation of the case and multidisciplinary discussion. Subsequently, a structured report is generated (Day 1-3), providing treatment recommendations to the treating physician and national coordinator. From Day 4 onward and extending up to two years, systematic follow-up is conducted to document treatment decisions, efficacy, safety, and clinical events, enabling real-world outcome capture across both clinical-trial and EAP-NP pathways in the study database. During the first year of the iLTB, patients from countries other than the sponsor were discussed as non-formal cases. For these cases, the iLTB coordinator requested data on treatment decisions from the physician at one and six months after the iLTB discussion (Figure 1). Each iLTB case was prepared by the treating physician and the iLTB coordinator. Actionable events were broadly defined as tumor characteristics (e.g., surface marker antigen expression, genetic events, drug sensitivity) for which a targeted therapy is approved or under investigation in a clinical trial for any cancer indication. Patients underwent standard diagnostic procedures, including immunophenotyping, molecular profiling (sequencing/gene panels), and in some cases, drug response profiling (DRP).[11] Biological prioritization was performed using a hematologic-specific adaptation of the INFORM algorithm,[12] which systematically scores the druggability of targets, taking the type of event, trial biomarkers, direct or indirect targeting, sensitivity in DRP, and supporting clinical evidence into account (*Online Supplementary Figure S1*). The international expert panel included (bio)medical experts in leukemia and lymphoma, genetics, HSCT, cellular immunotherapy, and clinical trials, with an average attendance of 28 experts per meeting and case-specific disease specialists invited as needed. The panel discussed the prioritized options in the context of prior therapies and drug availability. Following the discussion, a formal recommendation letter was sent to the treating physician. Follow-up data on treatment decisions and outcomes were collected at one and six months. Patients enrolled in a clinical trial or specific EAP-NP were

grouped due to the required structured and standardized data collection, distinguishing them from traditional compassionate or off-label use.

From January 31, 2023, to February 1, 2024, the iLTB held 26 virtual meetings, discussing a total of 42 pediatric cases originating from 18 countries (Table 1). The average patient age was 8.7 years (range: 0.7-18). The cohort included B-cell precursor acute lymphoblastic leukemia (BCP-ALL) (33%), acute myeloid leukemia (AML) (33%), T-cell acute lymphoblastic leukemia (T-ALL) (17%), T-cell lymphoblastic lymphoma (T-LBL) (7%), and rare malignancies (10%). The patient population reflected a truly high-risk, heavily pre-treated cohort: 29% (N=12) were in second or further relapse, and 24% (N=10) were discussed at first diagnosis of high-risk or refractory disease. Crucially, 38% (N=16) of patients had undergone prior HSCT, including 6 of these children having also received previous CAR T-cell therapy. The prevalence of these high-risk features underscores the complexity of treatment decisions and the lack of available therapeutic standards for the cohort.

High diagnostic coverage was achieved, with immunophenotyping conducted in 98% (N=41) of patients and molecular profiling in 88% (N=37), enabling the identification of targetable surface marker antigens and genetic abnormalities. DRP results were available only for 12% (N=5) of cases, mainly due to a lack of sufficient cells and consent-related limitations for sample shipment. Overall, 81% of patients (N=34) demonstrated actionable genetic events, 90% (N=38) of patients expressed targetable surface markers, and 5 demonstrated actionable drug sensitivities (*Online Supplementary Table S1*). These patients exhibited an average of 3.1 actionable events (range: 0-7), with the majority prioritized as 'very high' and 'high' (*Online Supplementary Figure S2A*). Reflecting this complexity, the international panel frequently provided multiple treatment recommendations, with 76% of cases receiving two or more options (*Online Supplementary Figure S2B*).

The distribution of identified targets, recommended therapies, and administered treatments is illustrated in *Online Supplementary Figure S2C*. Immunotherapies were the most common recommendations, advised in 71% of cases (N=27/38) where an immuno-target was identified, and administered to 20 patients (74% of recommendations). Frequent immunotherapies included inotuzumab ozogamicin,[6] gemtuzumab ozogamicin, and CAR T-cells.[7] Small-molecule targeted agents (SMTA) were advised in 53% of cases (N=18/34) with a relevant genetic target, with 56% (N=10) of those administered. The most frequent SMTA recommendation was a menin inhibitor.[8]

One month after the iLTB discussion, we evaluated whether the advice was followed; one patient was lost to follow-up. The treating physician's decision was in line with the iLTB panel's recommendations in 81% of cases (N=34/42) (Figure 2, *Online Supplementary Table S1*). In 38% of the discussions (N=16), the iLTB recommended a different treatment approach than that anticipated by the team presenting the case, offering new therapeutic perspectives. Three patients received DRP-guided treatment, supporting the value of integrating DRP into therapeutic decision-making. Many administered treatments were combinations (*Online Sup-*

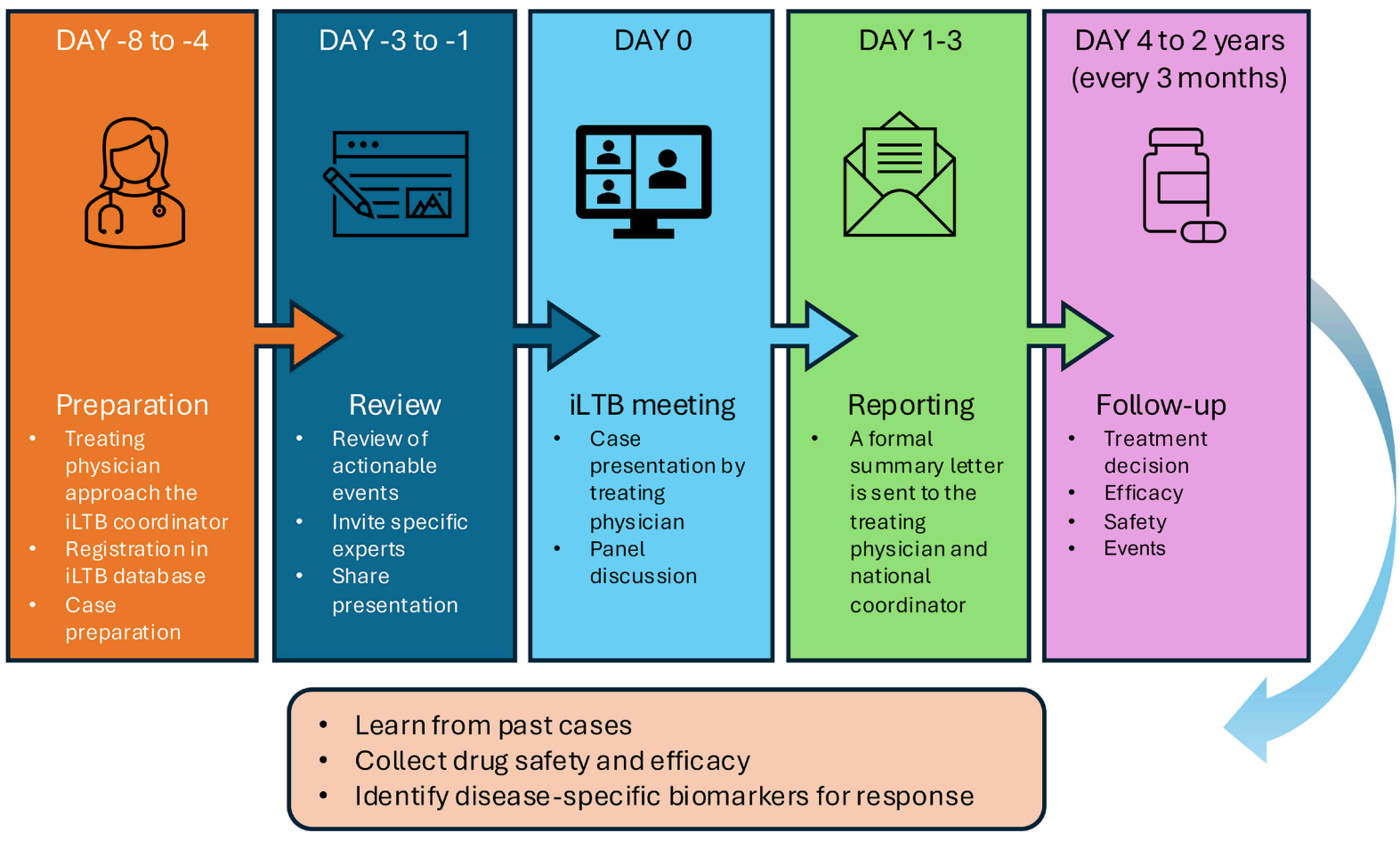



**Figure 1. Schema of the international Leukemia/Lymphoma Target Board workflow from patient enrollment to follow-up.**

*plementary Figure S2D*). Combinations of immunotherapy with untargeted therapy (e.g., daratumumab with venetoclax) were administered in 10 cases, and SMTA combined with untargeted therapy (e.g., a kinase inhibitor with chemotherapy) were used in 2 cases.

Following the advice of the iLTB, 15 patients (36%) were enrolled in a clinical trial or EAP-NP (Figure 2). The remaining patients received compassionate use/off-label treatments (31%) or approved (as standard of care) pediatric treatments (12%). Notably, 12 of the 15 patients (80%) enrolled in a trial or EAP-NP did so in a country other than their home country (Figure 2), highlighting the platform's role as a facilitator of cross-border access. Full follow-up data at six months post discussion were reported back for 23 patients (*Online Supplementary Figure S2E*). Twelve of these patients (52%) were alive, and 10 were successfully bridged to HSCT following the iLTB-recommended therapy. The 36% clinical trial/EAP-NP enrollment rate is approximately a 3-fold increase compared to previous cohorts,[9,10] validating the iLTB's core strategy of prioritizing trial-specific biomarkers and facilitating direct communication between treating physicians and principal investigators. The structured, consensus-driven approach enables the systematic identification and prioritization of early-phase therapeutic opportunities. When benchmarked against other academic cohorts, such as MAPPYACTS,[9] it shows the effectiveness of a harmonized approach to connecting patients with novel agents, even those who have failed prior CAR T-cell therapies. The finding that 80% of trial patients accessed treatment outside their home country underscores the platform's critical role as a facilitator of cross-border access for rare patient populations, as establishing trial sites in every country may be unfeasible due to financial and/or expertise-related constraints. Inclusion of international patients accelerates trial accrual, facilitating earlier acquisition of safety and efficacy data, and advancing broader drug availability. Furthermore, in some cases, formal iLTB recommendations have supported healthcare cost reimbursement.

While long-term survival conclusions are limited by the

**Table 1.** Summary of 42 patients discussed in the first year of the international Leukemia/Lymphoma Target Board.

| | Disease | | | | | |
|---|---|---|---|---|---|---|
| | **BCP-ALL** | **AML** | **T-ALL** | **T-LBL** | **Other** | **Total** |
| Country, N | | | | | | |
| Armenia | - | - | 1 | - | - | 1 |
| Belgium | - | 3 | - | - | CML | 4 |
| Bulgaria | - | - | 1 | - | - | 1 |
| Czech Republic | - | 1 | - | - | - | 1 |
| Denmark | - | 1 | - | - | - | 1 |
| Estonia | 1 | - | - | - | - | 1 |
| Germany | 1 | 1 | - | - | - | 2 |
| Greece | 1 | 2 | 1 | - | Burkitt leukemia | 5 |
| Hungary | 3 | - | - | - | B-LBL | 4 |
| Israel | - | - | 1 | 1 | - | 2 |
| Italy | - | 1 | 1 | - | - | 2 |
| Latvia | 2 | - | - | - | - | 2 |
| Lithuania | 1* | - | - | - | - | 1 |
| the Netherlands | - | 1 | 1 | 2 | BPDCN | 5 |
| Poland | - | 1 | - | - | - | 1 |
| Spain | 5 | 1 | - | - | - | 6 |
| Turkey | - | - | 1 | - | - | 1 |
| UK | - | 2 | - | - | - | 2 |
| Total | 14 | 14 | 7 | 3 | 4 | 42 |
| Average age, years | 8.4 | 5.3 | 14.6 | 11.7 | 9.0 | 8.7 |
| Disease stage, N | | | | | | |
| 1st diagnosis | 2 | 2 | 2 | 1 | 3 (CML, BPDCN, B-LBL) | 10 |
| 1st relapse | 4 | 7 | 4 | 2 | 1 (Burkitt leukemia) | 18 |
| 2nd relapse or further | 7 | 4 | 1 | 0 | 0 | 12 |
| 2nd malignancy | 1 | 1 | 0 | 0 | 0 | 2 |
| Previous treatment, N | | | | | | |
| HSCT | 0 | 8 | 2 | 0 | 0 | 10 |
| HSCT+CAR-T | 6 | 0 | 0 | 0 | 0 | 6 |

*The case was discussed twice. AML: acute myeloid leukemia; BCP-ALL: B-cell precursor acute lymphoblastic leukemia; B-LBL: B-cell lymphoblastic lymphoma; BPDCN: blastic plasmacytoid dendritic cell neoplasm; CAR-T: chimeric antigen receptor T-cell immunotherapy; CML: chronic myeloid leukemia; HSCT: hematopoietic stem cell transplant; N: number; T-ALL: T-cell acute lymphoblastic leukemia; T-LBL: T-cell lymphoblastic lymphoma.

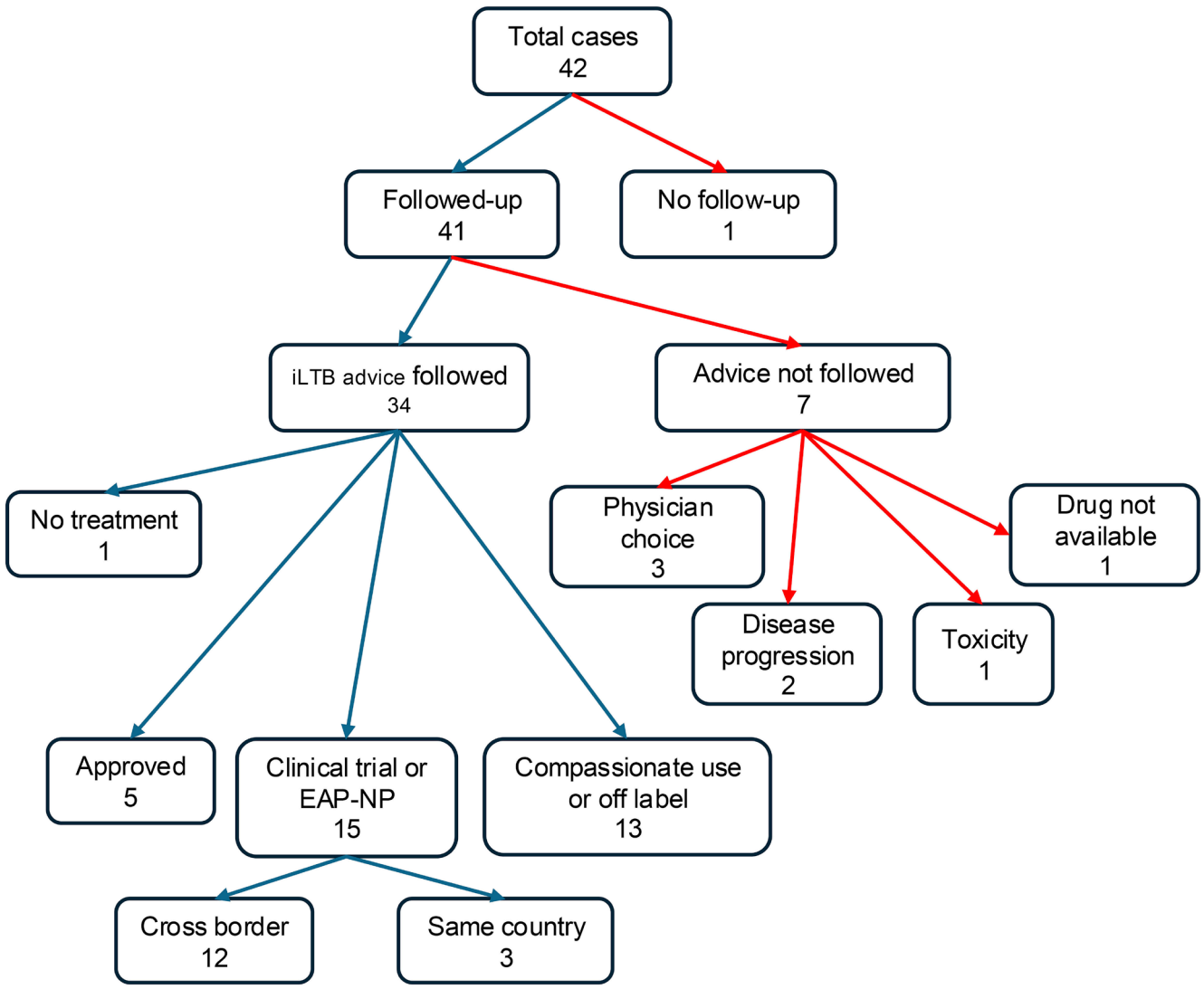



**Figure 2. Flow diagram of international Leukemia/Lymphoma Target Board-enrolled patients.** Flow diagram of international Leukemia/Lymphoma Target Board (iLTB)-enrolled patients. Illustrating adherence to advice and subsequent treatment modality. Clinical trial or expanded access program–named patient (EAP-NP) protocol enrollment accounted for 36% of patients (15/42). Cross-border refers to patients enrolled in a clinical study or EAP-NP outside their home country (12/15 cases). EAP-NP followed the same systematic follow-up standards as clinical trials. Approved treatments refer to therapies that can be administered as standard of care in the respective country.

considerable heterogeneity of this high-risk population, the 52% survival at six months is comparable to data reported by a national tumor board.[13] The majority of patients received targeted therapies for high-priority events, which is consistent with evidence from other registries (INFORM,[10] ZERO[14]) suggesting potential therapeutic benefits when adhering to tumor board recommendations.

The high rate of patients receiving therapies through compassionate use (31%) emphasizes the necessity of systematically recording clinical histories, treatments, and outcomes, a critical objective demonstrated by studies like the Secured Access to Innovative Medicines for Children with Cancer (SACHA) study.[15] The iLTB functions as an unbiased, academic platform to prospectively collect this real-world evidence in a registry. This information is invaluable to the clinical research community, providing preliminary evidence of efficacy to guide the design of future biomarker-driven platform trials. Furthermore, the iLTB provides an important educational benefit, exposing early-career pediatric hemato-oncologists to the consensus-building process and the application of precision medicine principles in rare and complex cases, thereby enhancing their understanding of how to interpret high-level diagnostic data.

In conclusion, the iLTB's first year achieved its primary objectives, significantly increasing access to innovative treatments for children with relapsed/refractory hematologic malignancies. The high compliance rate (81%) and the introduction of new therapeutic strategies in nearly 40% of cases confirm the utility of a multidisciplinary, international expert consensus approach for this rare and high-risk pediatric patient population.

## Authors

Uri Ilan,[1*] Judith M. Boer,[1*] Maaike Luesink,[1] Francisco Bautista,[1] Mattias Hofmans,[2] Aditi Vedi,[3] Bálint Egyed,[4] Birgit Geoerger,[5] Ruta Tuckuviene,[6] Bodil Als-Nielsen,[7] Pablo Velasco,[8] Jose Luis Fuster,[9] Alba Rubio,[10] Sarah K. Tasian,[1,11,12] Frederik van Delft,[13] Julie A.E. Irving,[14] Dániel J. Erdély,[4] Kjeld Schmiegelow,[15] Barbara De Moerloose,[16] André Baruchel,[17] Monique L. den Boer[1,18#] and C. Michel Zwaan[1,19#]

[1]Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands; [2]Department of Laboratory Medicine, Ghent University

Hospital, Ghent, Belgium; [3]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; [4]Department of Pediatrics, Semmelweis University, Budapest, Hungary; [5]Gustave Roussy Cancer Center, Department of Pediatric and Adolescent Oncology, INSERM U1015, Université Paris-Saclay, Villejuif, France; [6]Department of Pediatrics, Aalborg University Hospital, Aalborg, Denmark; [7]Department of Pediatrics and Adolescent Medicine, University Hospital Rigshospitalet, Copenhagen, Denmark; [8]Pediatric Oncology and Hematology Department, Hospital Vall d'Hebrón, Barcelona, Spain; [9]Sección de Oncohematología Pediátrica, Hospital Virgen de Arrixaca, Murcia, Spain; [10]Pediatric Oncology and Hematology Department, Hospital Infantil Universitario Niño Jesús, Madrid, Spain; [11]Children's Hospital of Philadelphia, Division of Oncology and Center for Childhood Cancer Research, Philadelphia, PA, USA; [12]University of Pennsylvania School of Medicine, Department of Pediatrics, Philadelphia, PA, USA; [13]Wolfson Childhood Cancer Research Centre, Newcastle University Centre for Cancer, Newcastle upon Tyne, UK; [14]Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, UK; [15]Department of Pediatrics and Adolescent Medicine, University Hospital Rigshospitalet, Copenhagen, Denmark; [16]Department of Pediatric Hematology-Oncology and Stem Cell Transplantation, Ghent University Hospital, Ghent, Belgium; [17]University Hospital Robert Debré (APHP) and Université de Paris, Paris, France; [18]Center for Translational Immunology, University Medical Center Utrecht, Utrecht, the Netherlands and [19]Department of Pediatric Oncology, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands

**UI and JMB contributed equally as first authors.*
*[#]MLdB and CMZ contributed equally as senior authors.*

Correspondence:
C.M. ZWAAN - c.m.zwaan-2@prinsesmaximacentrum.nl
M.L. DEN BOER - m.l.denboer@prinsesmaximacentrum.nl

https://doi.org/10.3324/haematol.2025.300154

Received: November 4, 2025.
Accepted: March 25, 2026.
Early view: April 2, 2026.

©2026 Ferrata Storti Foundation
Published under a CC BY-NC license

**Disclosures**

BdM reports Fund for Innovation and Clinical Research. KS reports speaker and/or advisory board honoraria from Illumina, Jazz Pharmaceuticals and Servier, speaker fee from Amgen and Medscape, educational grants from Servier, research grant from Novo Nordisk Foundation, and stocks in Novo Nordisk. JAEI reports funding from Hoffman La Roche. PB is a member of a data monitoring committee (DMC) in a Sanofi-sponsored clinical trial, held a consulting or advisory role for Bayer, Amgen, Roche Genentech, and EusaPharma, has received honoraria for speaking at symposiums from Roche Genentech and Servier (through his current affiliation at Princess Maxima) in the last 5 years, and provides consultancy services for Beigene and STRO biopharma on behalf of his current affiliation at Princess Maxima. AB has served on advisory boards for and received honoraria and/or travel support from Amgen, Astra-Zeneca, Janssen, Jazz Pharmaceuticals, Novartis, Sanofi, Servier, and Wugen, and received research funding from Shire/Sevier. MZ has received institutional funding for clinical trials from Pfizer, Daiichi Sankyo, Jazz Pharma, Takeda, Abbvie, and Kura Oncology, and holds a consultant role with Janssen, Syndax, BMS, Incyte, Sutro, Kestrel, BeiGene, and Sanofi. All other authors have no conflicts of interest to disclose.

**Contributions**

UI and JMB conceptualized and designed the study, analyzed and interpreted data, and wrote the manuscript. MLdB and CMZ conceptualized and designed the study, and wrote the manuscript. FB, BG, PV, JLF, FvD, JAEI, DJE, KS, BdM and AB provided recommendations to further improve the design of the study. ML, MH, AV, PE, SKT, RT, BAN and AR provided patients' data and discussion input. All authors approved the final version of the manuscript for publication.

**Acknowledgments**

We thank the clinicians and research nurses involved in the iLTB and the various studies, the diagnostic laboratory personnel involved in sample processing and data analysis, and the patients for consenting to use their data for research.

**Data-sharing statement**

For original data, please contact the corresponding author at c.m.zwaan-2@prinsesmaximacentrum.nl.

# References

1. Pikman Y, Tasian SK, Sulis ML, et al. Matched targeted therapy for pediatric patients with relapsed, refractory, or high-risk leukemias: a report from the LEAP consortium. Cancer Discov. 2021;11(6):1424-1439.
2. Kaspers GJ, Zimmermann M, Reinhardt D, et al. Improved outcome in pediatric relapsed acute myeloid leukemia: results of a randomized trial on liposomal daunorubicin by the International BFM Study Group. J Clin Oncol. 2013;31(5):599-607.
3. Moricke A, Zimmermann M, Valsecchi MG, et al. Dexamethasone vs prednisone in induction treatment of pediatric ALL: results of the randomized trial AIEOP-BFM ALL 2000. Blood. 2016;127(17):2101-2112.
4. Tallen G, Ratei R, Mann G, et al. Long-term outcome in children with relapsed acute lymphoblastic leukemia after time-point and site-of-relapse stratification and intensified short-course multidrug chemotherapy: results of trial ALL-REZ BFM 90.

J Clin Oncol. 2010;28(14):2339-2347.
5. von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol. 2016;34(36):4381-4389.
6. Brivio E, Locatelli F, Lopez-Yurda M, et al. A phase 1 study of inotuzumab ozogamicin in pediatric relapsed/refractory acute lymphoblastic leukemia (ITCC-059 study). Blood. 2021;137(12):1582-1590.
7. Laetsch TW, Maude SL, Rives S, et al. Three-year update of tisagenlecleucel in pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia in the ELIANA trial. J Clin Oncol. 2023;41(9):1664-1669.
8. Issa GC, Aldoss I, DiPersio J, et al. The menin inhibitor revumenib in KMT2A-rearranged or NPM1-mutant leukaemia. Nature. 2023;615(7954):920-924.
9. Berlanga P, Pierron G, Lacroix L, et al. The European MAPPYACTS trial: precision medicine program in pediatric and adolescent patients with recurrent malignancies. Cancer Discov. 2022;12(5):1266-1281.
10. van Tilburg CM, Pfaff E, Pajtler KW, et al. The pediatric precision oncology INFORM registry: clinical outcome and benefit for patients with very high-evidence targets. Cancer Discov. 2021;11(11):2764-2779.
11. Frismantas V, Dobay MP, Rinaldi A, et al. Ex vivo drug response profiling detects recurrent sensitivity patterns in drug-resistant acute lymphoblastic leukemia. Blood. 2017;129(11):e26-e37.
12. Worst BC, van Tilburg CM, Balasubramanian GP, et al. Next-generation personalised medicine for high-risk paediatric cancer patients - the INFORM pilot study. Eur J Cancer. 2016;65:91-101.
13. Boer JM, Ilan U, Boeree A, et al. Oncogenic and immunological targets for matched therapy of pediatric blood cancer patients: Dutch iTHER study experience. Hemasphere. 2024;8(7):e122.
14. Lau LMS, Khuong-Quang DA, Mayoh C, et al. Precision-guided treatment in high-risk pediatric cancers. Nat Med. 2024;30(7):1913-1922.
15. Berlanga P, Ndounga-Diakou LA, Aerts I, et al. Measuring safety and outcomes for the use of compassionate and off-label therapies for children, adolescents, and young adults with cancer in the SACHA-France study. JAMA Netw Open. 2023;6(7):e2321568.