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

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SHORT TITLE: First year of the iLTB for pediatric leukemia and lymphoma

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

CONFLICTS OF INTEREST
BdM - Fund for Innovation and Clinical Research; KS - Speaker and/or Advisory Board Honoraria from Illumina (2021), Jazz Pharmaceuticals (2020, 2021, 2023) and Servier (2020, 2021, 2023); speaker fee from Amgen (2020, 2021) and Medscape (2020, 2021); Educational grants from Servier (2020, 2021, 2023); research grant from Novo Nordisk Foundation (2020,2022). Stocks in Novo Nordisk; JAEI - funding from Hoffman La Roche; PB - member of a Data Monitoring Committee (DMC) in a Sanofi-sponsored clinical trial, had a consulting or advisory role for Bayer, Amgen, Roche Genentech and EusaPharma, and received honoraria for speaking at symposiums from Roche Genentech and Servier (through his current affiliation at Princess Maxima) in the last 5 years. He provides consultancy services for Beigene and STRO biopharma on behalf of his current affiliation at Princess Maxima; AB - 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 - received institutional funding for clinical trials from Pfizer, Daiichi Sankyo, Jazz Pharma, Takeda, Abbvie and Kura Oncology. Holds a consultant role with Janssen, Syndax, BMS, Incyte, Sutro, Kestrel, BeiGene, and Sanofi. The other authors declare no conflicts of interest.

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

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Pediatric relapsed/refractory hematological malignancies often lack standard-of-care options and historically show low early clinical trial enrollment[1] (~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 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 hematological 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, NCT05270096) is a non-interventional, virtual, multi-center platform and registry sponsored by the Princess Máxima Center in the Netherlands (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 hematological-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 (Supplementary Figure S1). The international expert panel included (bio)medical experts in leukemia and lymphoma, genetics, hematopoietic stem cell transplant (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 BCP-ALL (33%), AML (33%), T-ALL (17%), 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 higher 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 six 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) patients expressed targetable surface markers, and five demonstrated actionable drug sensitivities (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' (Supplementary Figure 2A). Reflecting this complexity, the international panel frequently provided multiple treatment recommendations, with 76% of cases receiving two or more options (Supplementary Figure 2B).

The distribution of identified targets, recommended therapies, and administered treatments is illustrated in 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 (SMTAs) 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; Supplementary Table S1; Figure 2). In 38% of the discussions (n=16), the iLTB recommended a different treatment approach than 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 (Supplementary Figure S2D). Combinations of immunotherapy with untargeted therapy (e.g., daratumumab with venetoclax) were administered in 10 cases, and SMTAs combined with untargeted therapy (e.g., a kinase inhibitor with chemotherapy) were used in two cases.

Following the iLTB's advice, 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 (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 threefold 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 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 SACHA[15]. The iLTB functions as an academic, unbiased 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 hematological 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.

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Table:

Table 1. Summary of 42 patients discussed in the first year of the iTLB.

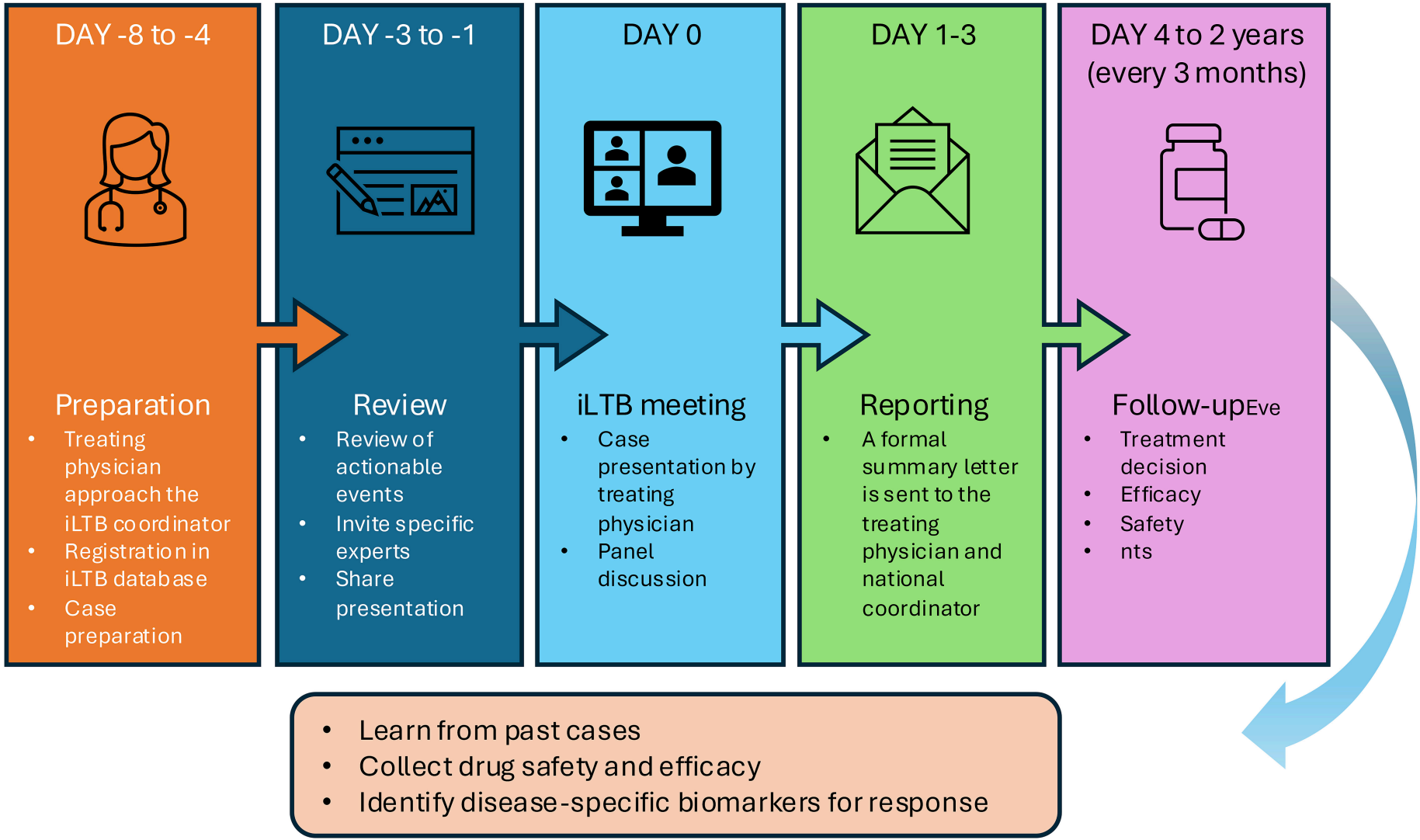
		Disease					
		BCP-ALL	AML	T-ALL	T-LBL	Other	Total
Country	Armenia			1			1
	Belgium		3			CML	4
	Bulgaria			1			1
	Czech		1				1
	Denmark		1				1
	Estonia	1					1
	Germany	1	1				2
	Greece	1	2	1		Burkitt leukemia	5
	Hungary	3				B-LBL	4
	Israel			1	1		2
	Italy		1	1			2
	Latvia	2					2
	Lithuania	1*					1
	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 type (n)	B-ALL	AML	T-ALL	T-LBL	Other	total
Disease stage	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 higher	7	4	1	0	0	12
	2nd malignancy	1	1	0	0	0	2
Previous treatment	HSCT	0	8	2	0	0	10
	HSCT+CART	6	0	0	0	0	6

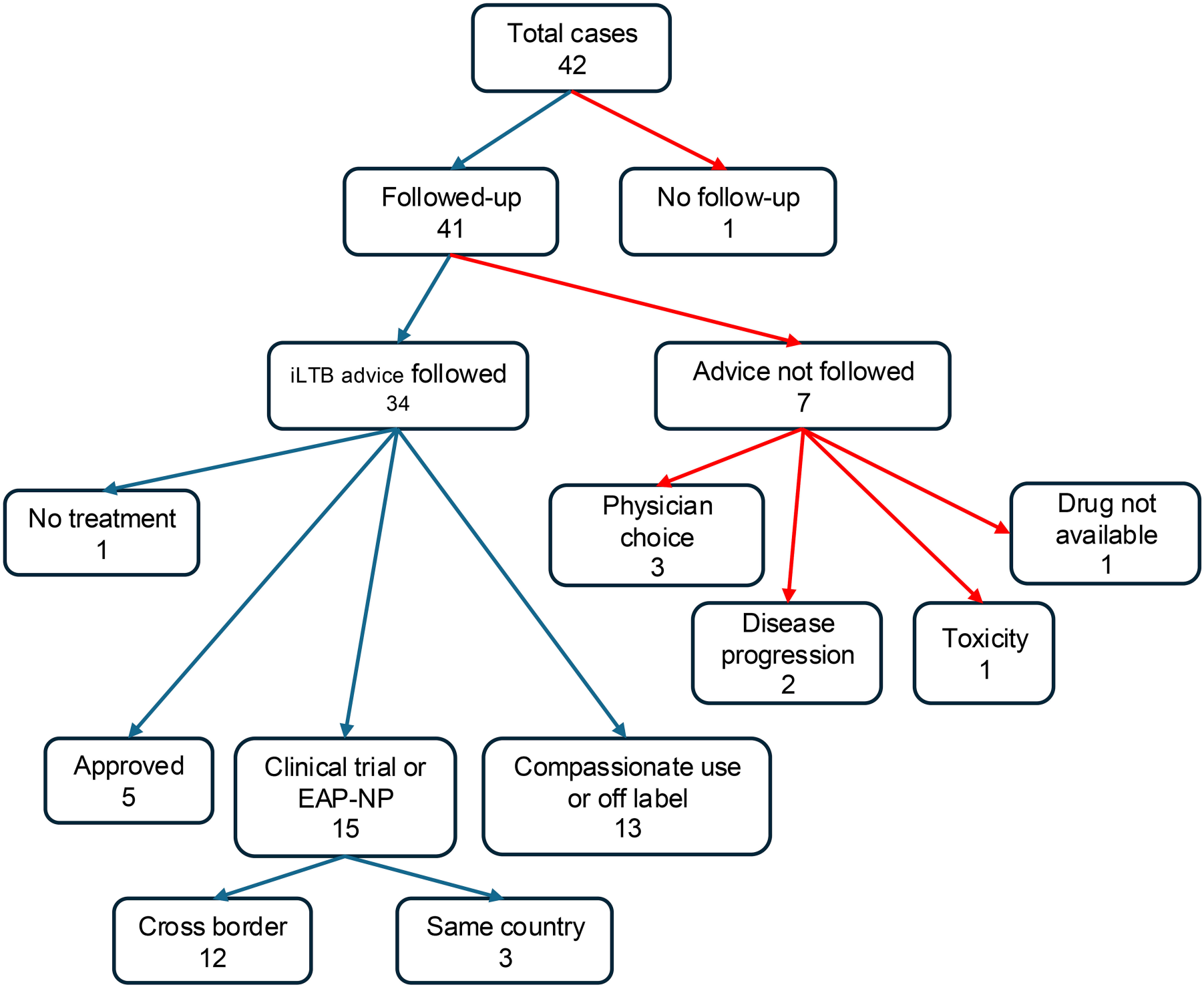
*The case was discussed twice. BCP-ALL: B-cell precursor acute lymphoblastic leukemia; AML: acute myeloid leukemia; T-ALL: T-cell acute lymphoblastic leukemia; T-LBL: T-cell lymphoblastic lymphoma; BPDCN: blastic plasmacytoid dendritic cell neoplasm; B-LBL: B-cell lymphoblastic lymphoma; CML: chronic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

Figure 1: **Schema of the iLTB workflow from patient enrollment to follow-up.**

The iLTB (ITCC-107 study, NCT05270096) is a non-interventional, multi-center discussion platform for patients <18 years at initial diagnosis and <25 years at relapse or refractory disease without standard-of-care options. As outlined in Figure 1, the process starts with the initial preparation phase (Day -7 to -3), 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 0), 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 3 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 2: **Flow diagram of iLTB-enrolled patients:**
Flow diagram of iLTB-enrolled patients. Illustrating adherence to advice and subsequent treatment modality. Clinical trial or EAP-NP 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 of 15 cases). EAP-NP: Expanded Access Program–Named Patient protocols 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.


DAY -8 to -4
Preparation
• Treating physician approach the iLTB coordinator
• Registration in iLTB database
• Case preparation
DAY -3 to -1
Review
• Review of actionable events
• Invite specific experts
• Share presentation
DAY 0
iLTB meeting
• Case presentation by treating physician
• Panel discussion
DAY 1-3
Reporting
• A formal summary letter is sent to the treating physician and national coordinator
DAY 4 to 2 years (every 3 months)
Follow-upEve
• Treatment decision
• Efficacy
• Safety
• nts
• Learn from past cases
• Collect drug safety and efficacy
• Identify disease-specific biomarkers for response


Total cases
42
Followed-up
41
No follow-up
1
iLTB advice followed
34
Advice not followed
7
No treatment
1
Physician
choice
3
Drug not
available
1
Disease
progression
2
Toxicity
1
Approved
5
Clinical trial or
EAP-NP
15
Compassionate use
or off label
13
Cross border
12
Same country
3

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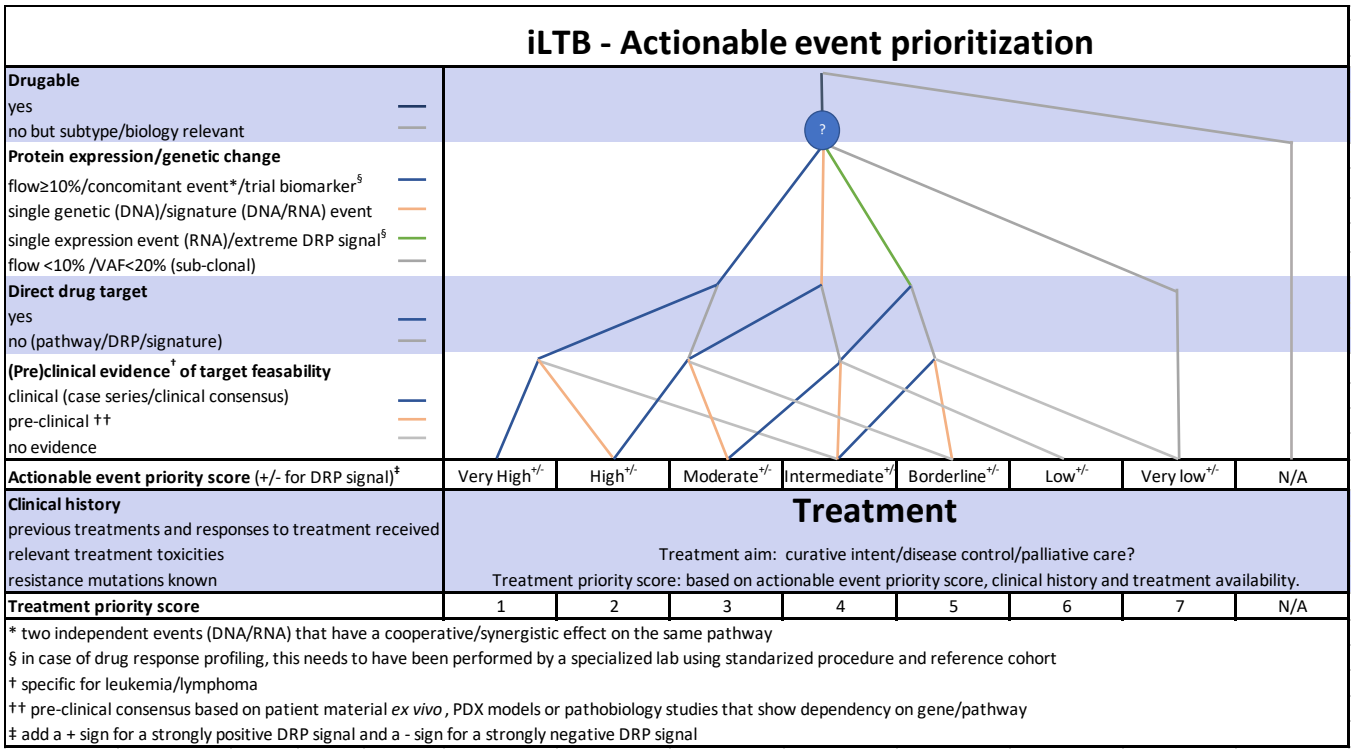
Uri Ilan*[1,2] Judith M. Boer*[1], *et al.*

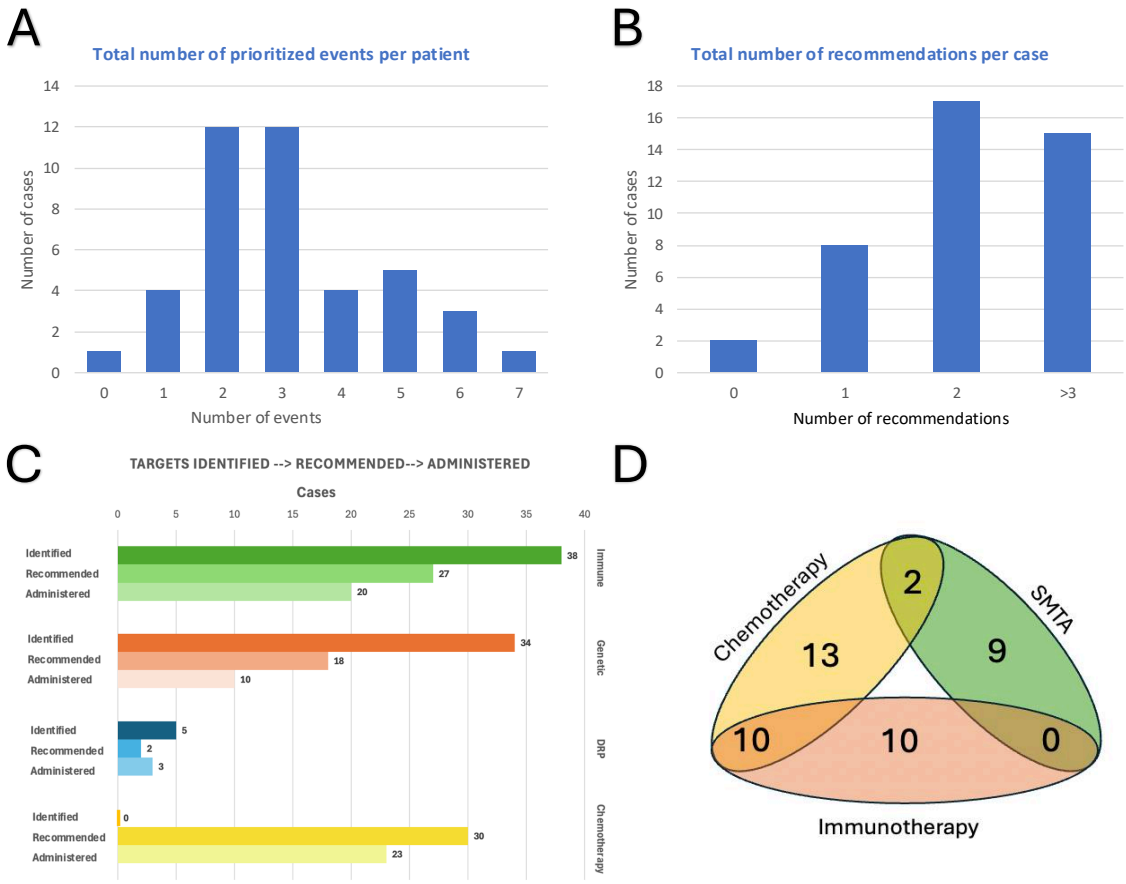
Supplementary Table S1: Summary of reported actionable events and the respective prioritization discussed in the iLTB

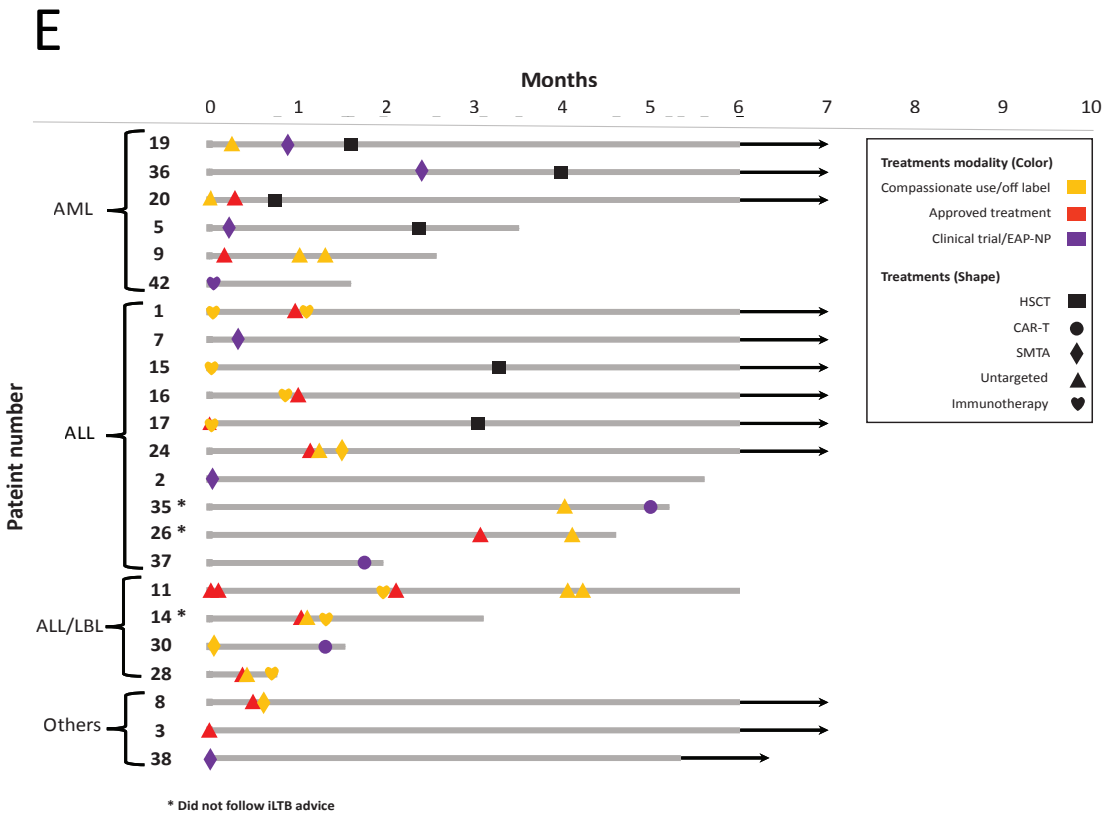
Bold - Highest recommendation by the panel *Italic* **- administered**					**Treatment priority score**					**New insigt**	**Recommandation followed**
Case number	**Disease type**	**Flow**	**NGS**	**DRP**	very high	high	moderate	intermediate	borderline/low/very low		
Case 1	BCP-ALL	*	*		***CD19*** ; CD22; CRLF2 high expression and JAK2 mutation	CD20; CD38				yes	yes
Case 2	BCP-ALL	*	*		CD19; **KMT2Ar**	CD38				same	yes
Case 3	BPDCN	*	*		**CD123**	CD38; CDKN2A deletion and CCNE1 overexpression		NRAS mutation		same	yes
Case 4	BCP-ALL	*	*	*	CD22; *KMT2Ar*				***panabinostat sensitivity***	yes	yes
Case 5	AML	*	*		CD33; CD123; ***NUP98r***	CD38		NRAS mutation	EVI1 overexpression	same	yes
Case 6	AML	*	*		***CD33*** ; KMT2Ar					same	yes
Case 7	BCP-ALL	*	*		**CD19**; CD22; ***BCR::ABL1***					same	yes
Case 8	B-LBL	*	*		CD19; ***BCR::ABL1***					same	yes
Case 9	AML	*			**CD33**; CD123					yes	yes
Case 10	Burkitt leukemia	*			CD19; ***CD20***					same	yes
Case 11	T-LBL	*	*		CD7; ***CD38***	JAK3 mutation				yes	yes
Case 12	BCP-ALL	*	*		CD19; CD22	CD20	PTPN11 mutation			same	yes
Case 13	T-ALL		*							yes	no
Case 14	T-ALL	*	*					CDKN2A/B deletion	*CD38 weak*	yes	no
Case 15	BCP-ALL	*	*		***CD19*** ; CD22	KRAS mutation				same	yes
Case 16	BCP-ALL	*	*		***CD19*** ; CD22; KMT2Ar	CD38				same	yes
Case 17	BCP-ALL	*	*		**CD19**; CD22	CD20 partial; CD38	IL7R mutation and overexpression			same	yes
Case 18	AML	*	*		**CD33**; KMT2Ar	CD38				same	yes
Case 19	AML	*	*		CD33; ***KMT2Ar***	CD38				same	yes
Case 20	AML	*	*		**KMT2Ar**	CD38				same	yes
Case 21	AML	*	*		CD33		BCL2 high expression			yes	yes
Case 22	AML	*	*		*CD33* ; KMT2Ar	CD38				yes	yes
Case 23	AML	*	*					**CBFA2T3::GLIS2**		same	no
Case 24	BCP-ALL	*	*	*	CD19; **CD22**		*FLT3 mutation*		venetoclax sensitivity, bortezomib sensitivity	yes	yes
Case 25	AML	*	*		CD33; ***KMT2Ar***					same	yes
Case 26	BCP-ALL	*	*	*	CD22; **CD19**				fludarabine sensitivity, ruxolitinib sensitivity	same	no
Case 27	AML	*	*		***KMT2Ar***					same	yes
Case 28	T-LBL	*	*		CD7; ***CD38***	IKZF1::NOTCH1 fusion; CDKN2A/B deletion and PTEN deletion; CDKN2A/B deletion and CCNE1 overexpression		CDKN2A/B deletion		yes	yes
Case 29	T-LBL	*	*		***CD7*** ; CD38	IKZF2::NOTCH1; CDKN2A/B deletion and PIK3R1 mutation		CDKN2A/B deletion		same	yes
Case 30	T-ALL	*			***CD7*** ; CD38					same	yes
Case 31	T-ALL	*	*		CD7; **KMT2Ar**					same	NA
Case 32	T-ALL	*			**CD7**					same	yes
Case 33	BCP-ALL	*	*	*	**CD19**; *CD22*	KRAS mutation		CDKN2A/B deletion	venetoclax sensitivity, MEK inhibitor sensitivity, induction chemotherapy sensitivity	yes	yes
Case 34	BCP-ALL	*	*		*CD19* ; **CD22**	CD20; NRAS mutation		CDKN2A/B deletion		yes	yes
Case 35	BCP-ALL	*	*		**CD22**	CD20		CDKN2A/B deletion		yes	no
Case 36	AML	*	*		CD33; CD123; ***KMT2Ar***					same	yes
Case 37	BCP-ALL	*	*		***CD19*** ; CD22; KMT2Ar					same	yes
Case 38	CML	*	*		***BCR::ABL1***					yes	yes
Case 39	AML	*	*		CD33; **KMT2Ar**	CD38				same	no
Case 40	T-ALL	*	*		**CD7**; CD38					yes	no
Case 41	T-ALL	*			CD7; *CD38*					yes	yes
Case 42	AML	*	*	*	CD33; ***CD123*** ; KMT2Ar; FLT3-ITD	CD38			selinexor sensitivity, venetoclax sensitivity	same	yes

Abbreviations: BCP-ALL, B-cell precursor acute lymphoblastic leukemia; AML, acute myeloid leukemia; T-ALL, T-cell acute lymphoblastic leukemia; T-LBL, T lymphoblastic lymphoma; NGS, Next generation sequencing; DRP, Drug response profiling; HSCT, hematopoietic stem-cell transplant; CAR-T, chimeric antigen receptor T-cell immunotherapy. BPDCN: blastic plasmacytoid dendritic cell neoplasm.



Supplementary Figure S1: iLTB actionable event prioritization algorithm.
iLTB actionable event prioritization algorithm. Each actionable event was prioritized using an established algorithm that considered target druggability, somatic genetic alterations, gene overexpression levels, direct drug-target interactions, and supporting clinical evidence. Following this prioritization, a multidisciplinary discussion was conducted, incorporating prior treatment history, observed toxicities, treatment response, and known resistance patterns.


A
Total number of prioritized events per patient
Number of cases
Number of events
B
Total number of recommendations per case
Number of cases
Number of recommendations
C
TARGETS IDENTIFIED --> RECOMMENDED--> ADMINISTERED
Cases
Identified
Recommended
Administered
Immune
Genetic
DRP
Chemotherapy
D
Chemotherapy
SMTA
Immunotherapy
13
2
9
10
10
0


E
Months
Pateint number
AML
ALL
ALL/LBL
Others
Treatments modality (Color)
Compassionate use/off label
Approved treatment
Clinical trial/EAP-NP
Treatments (Shape)
HSCT
CAR-T
SMTA
Untargeted
Immunotherapy
* Did not follow iLTB advice

Supplementary Figure S2: **Identified events, treatment recommendations, and treatments administered in patients after discussion in the iLTB.**
(A) Bar graph representing the number of prioritized events per patient discussed in the iLTB.
(B) Bar graph representing the total number of recommendations per discussed case.
(C) Bar graph representing the identified actionable events, the iLTB panel treatment recommendations, and the administered therapy.
(D) Venn diagram illustrating the treatments and combinations administered. Patients may appear in more than one category if they received multiple treatments. DRP: drug response profile sensitivities.
(E) A swimmer plot of iLTB-enrolled patients with indicated treatment modalities and clinical follow-up. The length of the line represents the time of follow-up after iLTB. An arrow represents that the patient is alive at the last follow-up available at the time of analysis. Symbols represent treatments (shape) and treatment modality (color). Approved treatments refer to therapies that can be administered as standard of care in the respective country.