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Ex vivo drug response profiling guides therapy in a case of high-risk acute undifferentiated leukemia with *PICALM::MLLT10*

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Declarations

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Data-sharing statement

Not applicable

Authors’ contributions

Conceptualization and Design: all authors; Methodology: all authors; Writing Original Draft: E.M.; L.P.; G.R.; R.L.S.; Data Curation: L.P. M.G., E.M., R.L.S., G.R.; Funding Acquisition: G.R., E.M., R.L.S.; Supervision: G.R.; R.L.S.; E.M.; L.P. All authors have read and agreed to the published version of the manuscript.

Competing Interests

The authors declare no conflict of interest.

Drug-response profiling (DRP) for high-risk, relapsed/refractory (R/R) hematological malignancies is emerging as an alternative, yet complementary, approach to genetic-based precision medicine, especially in complex situations when approved therapeutic indications are lacking [1-2]. Rare subtypes such as acute leukemia of ambiguous lineage (ALAL) are representative of this setting since no clear treatment guidelines are available.

ALAL includes cases with more than one lineage commitment, such as T/myeloid, B/myeloid, T/B/myeloid, or no clear lineage commitment. The latter is exemplified by acute undifferentiated leukemia (AUL) characterized by the lack of expression of lineage-specific markers such as myeloperoxidase, cyCD3, cyCD22, CD79a, or strong CD19 while exhibiting positivity for CD13, CD33, CD7, and/or stem cell antigens (CD34, HLA-DR, TdT) [3]. Biologically, genomic alterations typically found in acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) have been reported [4].

Due to its rarity, large case studies of AUL are precluded, resulting in a lack of unequivocal data on the most appropriate treatment and indications for allogeneic hematopoietic stem cell transplantation (allo-HSCT). Generally, ALL-oriented chemotherapy protocols have been recommended for most pediatric patients with ALAL. A large retrospective multinational study on 233 children showed that patients treated according to ALL regimens had a 5-year event-free survival (EFS) of 80 ± 4%, which is higher than those who received AML-oriented or combined treatments (36 ± 7.2% and 50 ± 12%, respectively) [5]. The outcome was even better in CD19-positive ALAL cases (5-year EFS of 83 ± 5.3%).

We report on our experience with a 6-year-old male diagnosed with AUL. Our child had the bone marrow (BM) diffusely infiltrated (80%) of medium-sized undifferentiated cells characterized by round nuclei, finely dispersed chromatin, prominent nucleoli, and basophilic agranular cytoplasm (**Figure 1A**). Multiparametric flow cytometry (MFC) could not identify a myeloid or lymphoid blast cell-specific hematopoietic lineage, according to the AIEOP-BFM Flow Network criteria. Concerning B-lineage markers, CD19 showed dim expression while CD10, cyCD79a, and cyCD22 were negative. For T-lineage, CD7 had a heterogeneous positive expression but both cyCD3 and surface CD3 were negative. Regarding

myelomonocytic markers, the leukemic cells were negative for MPO, CD33, CD13, CD64, and CD65, but showed partial expression of CD117, CD34, CD38, CD11a, and CD11b (**Figure 1B**). Besides the main clone (92%), MFC revealed a minor subclone (3.5%) that was positive for CD13, CD33, and CD117 antigens (**Table 1**).

Karyotyping and Fluorescence in situ hybridization (FISH) identified a t(10;11)(p12;q23)/*PICALM::MLLT10* (100%) plus a deletion of the long arm of chromosome 5 which was present in a subclone (24%) (**Figure 1C**). Interestingly, FISH on sorted leukemic cells confirmed that *PICALM::MLLT10* was present in both the major and minor clones, while the del(5)(q31q34) was exclusively present in the subclonal cell population expressing CD13 and CD33 (**Table 1**). Single nucleotide polymorphism array detected 8 events, including a focal monoallelic loss at 17q11.2 encompassing *NF1* and *SUZ12* (**Table 1**). Targeted NGS analysis identified four pathogenic variants in *CIITA, EZH2, NF1*, and *SETD2* (**Figure 1D; Table 1**).

The patient's parents gave informed consent for sample collection and genomic analyses, in agreement with the Declaration of Helsinki. The study was approved by the local bio-ethical committee (CER) (research project 3397/18, December 20th, 2020).

Our child was initially treated with an ALL-oriented induction regimen, including prednisone, vincristine, daunorubicin, and PEG-asparaginase (AIEOP-BFM ALL 2017 clinical trial NCT03643276) without obtaining a response (70% of leukemia cell infiltration on days 15 and 22). Thus, we employed a functional precision medicine approach through DRP in *ex vivo* assay to explore the feasibility of a "personalized" salvage treatment (**Figure 1E**). DRP was conducted on primary leukemic cells isolated from the BM aspirate using a Histopaque density gradient. The cells were cultured in RPMI 1640 medium supplemented with antibiotics and patient-derived serum and plated in 384-well plates using a peristaltic dispenser. A library of 176 compounds, including US-Food and Drugs Administration (FDA)/European Medicines Agency (EMA)-approved drugs and investigational agents such as kinase inhibitors, epigenetic modifiers, chemotherapeutics, and immunomodulatory drugs, was tested in four dilutions, ranging from 0.1 to 10,000 nM. Cell viability was measured after 72 hours using an ATP-based luminescence assay. Viability data were normalized to negative controls, and dose-response curves were generated. The compound activity was evaluated by calculating the area under the curve (AUC) and the drug sensitivity score (DSS) to identify effective treatments [6].

Drug efficacy was ranked based on DSS and viability AUC values, and only compounds with DSS ≥ 1 and AUC < 300 were considered for further evaluation (**Figure 1F**). We selected DSS cut-offs based on our experience and practices in the current literature [6]. As for AUC, we adopted a value corresponding to the first quartile of the maximum theoretical area (namely defined at 400). These combined criteria facilitate the exclusion of compounds that achieve partial growth inhibition at low doses but don't reach a robust inhibition effect at high doses or that do so only at the end of the concentration range tested.

Compounds with DSS ≥ 10 were considered to have high efficacy, 1 ≤ DSS < 10 as intermediate efficacy, and DSS < 1 as low or no efficacy. We identified 39 compounds with DSS ≥ 1 and AUC < 300, of which 36% (14/39) with intermediate efficacy and 64% (25/39) with high efficacy, mostly belonging to differentiating and epigenetic modifiers (n= 12), conventional chemotherapeutics (n= 10), kinase inhibitors (n= 8), apoptotic modulators (n= 4), glucocorticoids (n= 2), proteasome inhibitors (n = 2), and dexamethasone/SERCA inhibitor. When considering target classes with at least two representative molecules, we were able to identify 9 target class compounds, including G9a/GLP histone methyltransferase inhibitors, bromodomain/extra-terminal domain inhibitors, nucleoside analogs, cyclin-dependent kinase inhibitors, inhibitors of histone deacetylases, glucocorticoids, antiapoptotic inhibitors, proteasome inhibitors, and topoisomerase inhibitors (**Figure 1G**).

Based on the DRP, our goal was to translate assay results into clinical practice to guide the most feasible translational approach. To do so, we integrated the functional profiles with the top-scoring compounds. The selection of compounds for a translational approach considered further practical aspects such as their clinical accessibility for acute leukemia treatment, the availability of literature data on previous experience, and the off-label request processing time and regulatory procedure to enable immediate application within a time frame compatible with therapeutic decision-making. Additionally, we reviewed available data on dosing schedules and the toxicities of combination therapies, including those already approved or under investigation for each compound. We administered seven highly effective compounds in 3 consecutive cycles: new induction, consolidation, and allo-HSCT (**Figure 2A**). Initially, we selected a rescue protocol comprising vincristine, mitoxantrone, dexamethasone, and bortezomib, four compounds identified as effective against the patient's leukemic cells through *ex vivo* testing. This protocol

was designed to mimic the ALL R3 study protocol with Bortezomib [7]. By the end of this cycle (day +28), a significant reduction in BM blasts was observed, with only 4% of the major leukemic clone detected by MFC (cells harbored the *MLLT10* rearrangement but not the del(5)) (**Figure 2A-B**). We then devised a consolidation approach, guided by DRP results and validated through comparisons with a panel of AML and ALL human cell lines. This approach combined idarubicin and venetoclax (VEN-AML), two of the top ten compounds identified (**Figure 2B**) [8, 9]. The child achieved morphological, MFC, and cytogenetic complete remission (CR), and underwent allo-HSCT from a haplo-identical family donor (**Figure 2A-B**) [10]. He is in continuous MFC-measurable residual disease (MRD) negativity and cytogenetic remission with 100% donor chimerism at 520 days from transplant.

The challenge of selecting optimal treatments for individual cases of AUL underscores the urgent need for new compounds and strategies to improve patient outcomes in this rare and heterogeneous form of leukemia. In this regard, complementary tools integrating genomic data and DRP show significant promise for guiding personalized treatments and overcoming these limitations.

A recurring genomic alteration in AUL is the *PICALM::MLLT10* fusion, known to be associated with various types of ALs and to identify subsets of high-risk cases, particularly among T-ALL and AML cases [11-12]. Interestingly, genomic and gene expression profiling have revealed biological differences between these two leukemia subtypes, despite sharing the *PICALM::MLLT10* fusion. These differences manifest in distinct transcriptomic subgroups and markedly different spectra of co-occurring mutations [13]. Our AUL case shares genomic features with *PICALM::MLLT10*-positive T-ALL and AML, including the *EZH2* loss-of-function mutation, multi-hit *NF1* alterations, and *SUZ12* deletion. Additionally, reminiscent of AML, we identified a del(5)(q31q34) in a subclone of myeloid-oriented leukemic cells. These findings align with previously published data on *PICALM::MLLT10*-positive AUL patients, highlighting the lineage ambiguity of such cases. Gene expression analysis further supports this ambiguity, placing the AUL case between AML and T-ALL [13].

Concerning the 'druggability' of AULs, a limitation arises from the restricted number of actionable targets detectable in leukemic blasts. Similarly, challenges exist in identifying suitable cell surface markers for chimeric antigen receptor T-cell (CAR-T) therapy and immunotherapy. An effective and clinically applicable solution involves

the development of DRP approaches to identify active molecules, particularly in the context of R/R cases. While numerous experiences are emerging in the adult ALL and AML population, translating functional medicine into the pediatric clinical setting is more complex, despite new exploratory studies [2]. A recent study applied DRP in pediatric T-ALL to evaluate how primary T-lymphoblasts respond *ex vivo* to a range of compounds, pinpointing BCL2 and proteasome inhibitors as the most effective drugs in certain R/R T-ALL cases [14]. All patients who received DRP-guided therapy achieved complete or partial remission and were successfully bridged to allo-HSCT or CD7-directed CAR-T therapies.

Building on the success of venetoclax in other immature leukemia forms, our DRP assay unsurprisingly identified it as a top hit for our case. This reinforces the established role of BCL2 dependence in these leukemias [7]. Venetoclax has already been successfully used to induce remission in two young patients with AUL, one of whom harbored *PICALM::MLLT10* and multi-hit *NF1-SUZ12* alterations [8]. Furthermore, we have demonstrated the efficacy of the combination of venetoclax and bortezomib (VEBO scheme) as a chemo-free regimen to bridge-to-transplant in a case of *DDX3X::MLLT10*-positive early T-cell precursor ALL [15], underscoring the effectiveness of these drugs in a wide range of *MLLT10*-positive AL, irrespective of the translocation partner and leukemia immunophenotype.

Our clinical case provides new insights for applying individualized treatment based on *ex vivo* drug testing. Specifically, our functional approach has been invaluable in guiding the sequential use of a series of DRP-based agents, administered in different combinations and phases, induction, consolidation, and allo-HSCT, to induce MFC-MRD negativity and cytogenetic remission. By identifying several active compounds, this approach offers the opportunity to design and implement new patient-specific therapeutic combinations to achieve synergistic effects, thereby enhancing anti-leukemic activity for patients with high-risk leukemias.

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Table 1. Clinical, and genomic characteristics of the patient at baseline

WBC	3130/mmc
CNS	no involvement
Multiparametric flow cytometry	- major clone (92%): CD7+HET, CD22PP1, CD99+, CD117+HET, CD38+, CD11b+HET, CD19PP1, CLL-1+HET, CD45+MEDIUM, CD11a+, CD34+HET, cyCD3 NEG - minor clone (3.5%): CD33+, CD13+, CD7+, HLADR+, CD38+, CLL1+,CD117+
Karyotype	46,XY,t(10;11)(p12;q23)[19] 46,idem,del(5)(q31q34)[6]
FISH	*PICALM::MLLT10* fusion: 80% *EGR1-CSF1R*/5q31-q32 deletion: 5% *NF1-SUZ12* deletion: 80%
FISH on sorted cells	major clone (CD33-, CD13-): *PICALM::MLLT10*: 100% fusion; *EGR1*/5q31: normal minor clone (CD33+, CD13+): *PICALM::MLLT10*: 100% fusion; *EGR1*/5q31: 35% deletion
SNPa	LOSS: 6p25.3p22.3, 17q11.2, 18q22.2q23 GAIN: 17q21.33q25.3 cnLOH: 11p15.5p11.2, 19p13.3p13.11
NGS	*CIITA*(NM_000246)c.2342_2345delinsTGGC p.(Ser781_Val782delinsLeuAla) VAF 50% *EZH2* (NM_004456) c.301_302del p.(Leu101Glufs*24) VAF 2.1% *NF1* (NM_001042492) c.823delinsTAG p.(Ile275*) VAF 67.6% *SETD2* (NM_014159) c.913dup p.(Thr305Asnfs*4) VAF 40.8%

Legend: WBC, white blood cell; cnLOH, copy number loss of heterozygosity; CNS, central nervous system; FISH, fluorescence in situ hybridization; PP1, partial positive 1; HET, heterogeneous; SNPa, single nucleotide polymorphism array; NGS, next-generation sequencing; VAF, variant allele fraction.

Legends to the Figures

Figure 1. Chemogenomic profiling identifies effective compounds for a translational purpose.

A) Light microscopy image of a bone marrow blood smear at diagnosis showing medium-sized undifferentiated blasts with prominent nucleoli and agranular basophilic cytoplasm. Scale bars, 10 μm.

B) Immunophenotype assessment at diagnosis showing a prevalent population of undifferentiated blasts. See the text for details.

C) Cytogenetic assessment of the major clone. Top: karyotype of the major clone: 46,XY,t(10;11)(p12;q23)[19]. Bottom: FISH analysis of the major clone: *PICALM* (RP11-12D16/RP11-90K17, green) plus *MLLT10* (RP11-249M6/RP11-418C1, orange).

D) Lollipop graphs showing sequenced mutations in the exonic region of *CIITA*, *EZH2*, *NF1*, and *SETD2* genes. Allelic variants are depicted with a circle (red, frameshift; blue, missense; orange, nonsense) relative to their amino acid position and their protein domains (color-coded). AWS: associated with SET; CSR: cysteine- and serine-rich; GR: GAP-related; LRR: Leucine-rich repeats; SRI: Set2-Rpb1 interacting; RI: ribonuclease inhibitor-like.

E) Outline of the drug response profiling (DRP) platform.

F) Radar plot with a color indication from the drug class group showing the drug sensitivity scores (DSS) of each compound tested. DSS values (white and red dots) range from zero (center) to the maximum value (outside border). Red dots identify compounds with DSS ≥ 1 and AUC < 300.

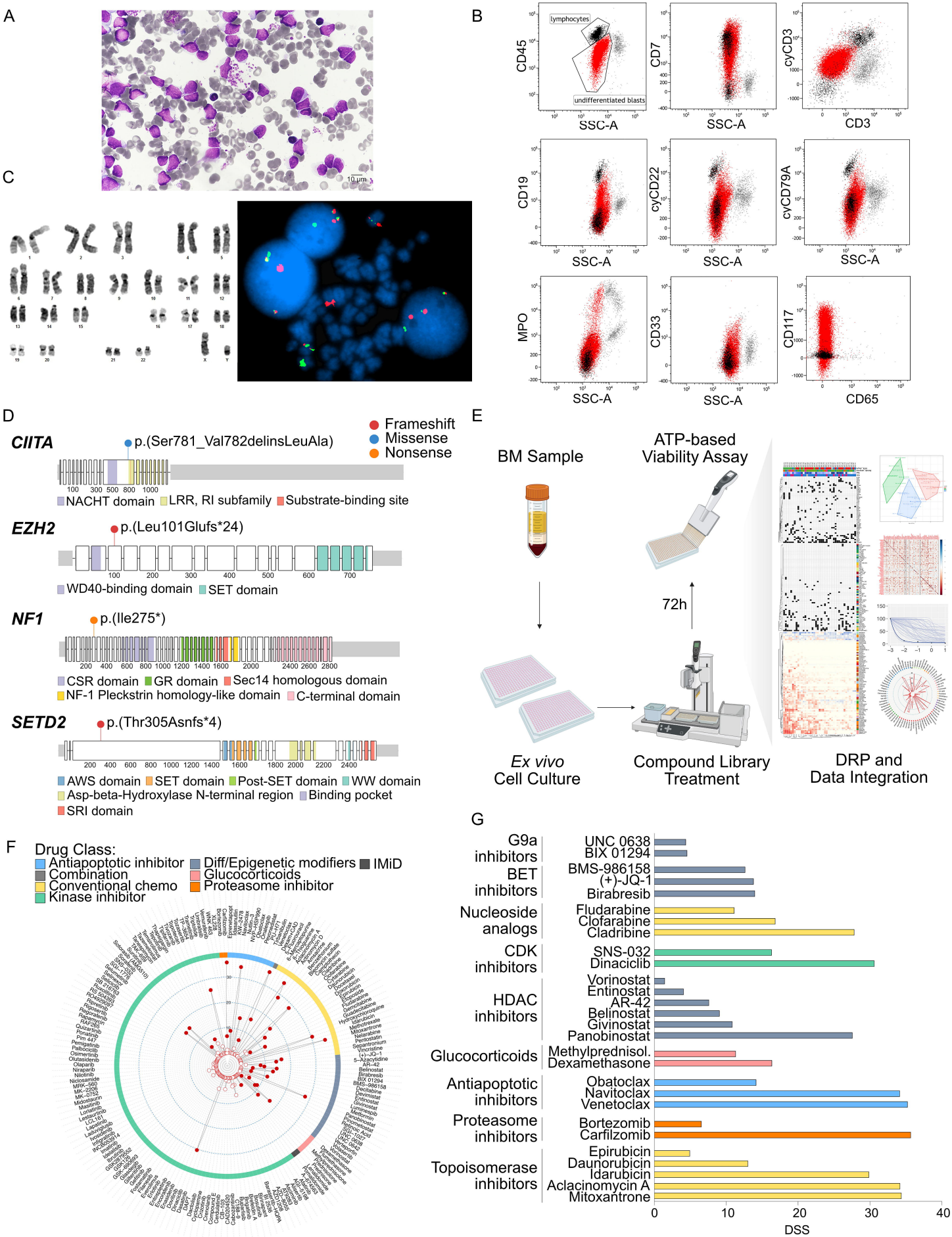
G) DSS values of compound classes by target identification with at least two representative compounds for each class. Bar colors identify the main compound class as in (F).

Figure 2. The functional precision medicine approach induced measurable residual disease negativity (MRD) and cytogenetic remission in a refractory acute undifferentiated leukemia (AUL) patient.

A) Timeline depicting the course of disease and treatment choice coupled with measurable residual disease assessment. Colored lines correspond to the

percentage of blasts at morphology (pink), flow cytometry (green), and percentage of nuclei at fluorescence in situ hybridization (FISH) analysis for del(5q) (blue), and t(10;11) *PICALM::MLLT10* (cyan).

B) Top: The color boxes show the therapy schedules of the relative DRP-driven treatments depicted in (A); VEN-AML, venetoclax was administered orally (360 mg/m^2 daily) from days 1 to 28, idarubicin (12 mg/m^2) on day 13, cytarabine (1000 mg/m^2) twice daily from days 13 to 16. Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) conditioning regimen consisted of total body irradiation, thiotepa (5 mg/kg) for 2 days, cyclophosphamide (15 mg/kg) 2 days), and fludarabine (40 mg/m2) 4 days; T-reg, T-regulatory cell infusion was performed as prophylaxis against graft versus host disease. Bottom: Effect of the selected compounds on cell viability after 72 h of treatments in the AUL patient's sample (dark blue line) and a panel of acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) cell lines (light blue lines). Cell lines: ALL/SIL, DND41, HSB-2, HNT-34, Jurkat, Loucy, MOLM-1, PF-382, SUPT-1, UCSD-AML1.


A
10 µm
B
lymphocytes
undifferentiated blasts
CD45
SSC-A
CD7
cyCD3
CD3
CD19
cyCD22
cyCD79A
MPO
CD33
CD117
CD65
C
D
CIITA
p.(Ser781_Val782delinsLeuAla)
Frameshift
Missense
Nonsense
NACHT domain
LRR, RI subfamily
Substrate-binding site
EZH2
p.(Leu101Glufs*24)
WD40-binding domain
SET domain
NF1
p.(Ile275*)
CSR domain
GR domain
Sec14 homologous domain
NF-1 Pleckstrin homology-like domain
C-terminal domain
SETD2
p.(Thr305Asnfs*4)
AWS domain
SET domain
Post-SET domain
WW domain
Asp-beta-Hydroxylase N-terminal region
Binding pocket
SRI domain
E
BM Sample
ATP-based Viability Assay
72h
Ex vivo Cell Culture
Compound Library Treatment
DRP and Data Integration
F
Drug Class:
Antiapoptotic inhibitor
Diff/Epigenetic modifiers
IMiD
Combination
Glucocorticoids
Conventional chemo
Proteasome inhibitor
Kinase inhibitor
G
G9a inhibitors
UNC 0638
BIX 01294
BET inhibitors
BMS-986158
(+)-JQ-1
Birabresib
Nucleoside analogs
Fludarabine
Clofarabine
Cladribine
CDK inhibitors
SNS-032
Dinaciclib
HDAC inhibitors
Vorinostat
Entinostat
AR-42
Belinostat
Givinostat
Panobinostat
Glucocorticoids
Methylprednisol.
Dexamethasone
Antiapoptotic inhibitors
Obatoclax
Navitoclax
Venetoclax
Proteasome inhibitors
Bortezomib
Carfilzomib
Topoisomerase inhibitors
Epirubicin
Daunorubicin
Idarubicin
Aclacinomycin A
Mitoxantrone
0
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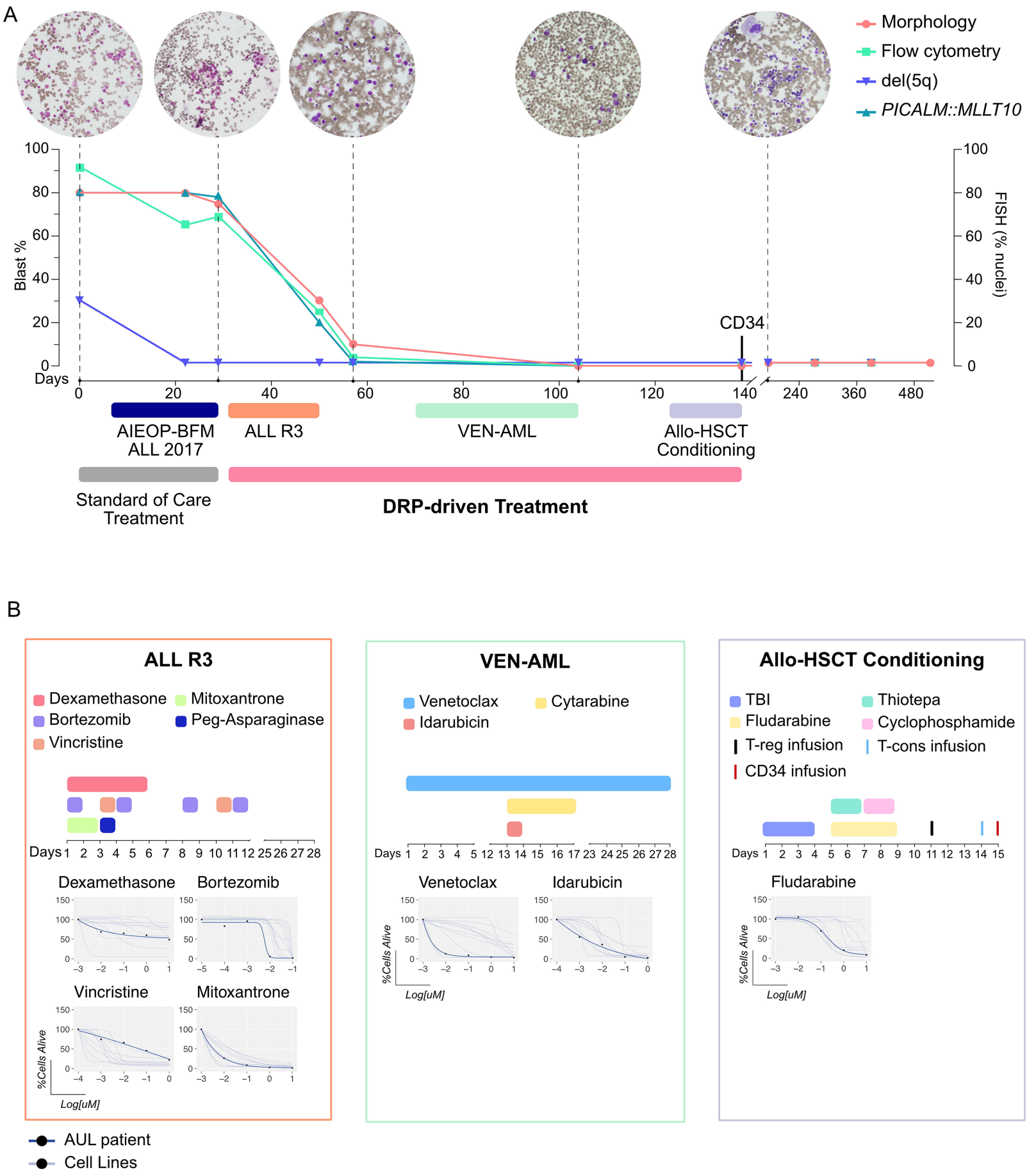
A
Morphology
Flow cytometry
del(5q)
PICALM::MLLT10
Blast %
FISH (% nuclei)
Days
CD34
AIEOP-BFM ALL 2017
ALL R3
VEN-AML
Allo-HSCT Conditioning
Standard of Care Treatment
DRP-driven Treatment
B
ALL R3
Dexamethasone
Mitoxantrone
Bortezomib
Peg-Asparaginase
Vincristine
Venetoclax
Cytarabine
Idarubicin
TBI
Thiotepa
Fludarabine
Cyclophosphamide
T-reg infusion
T-cons infusion
CD34 infusion
%Cells Alive
Log[uM]
AUL patient
Cell Lines