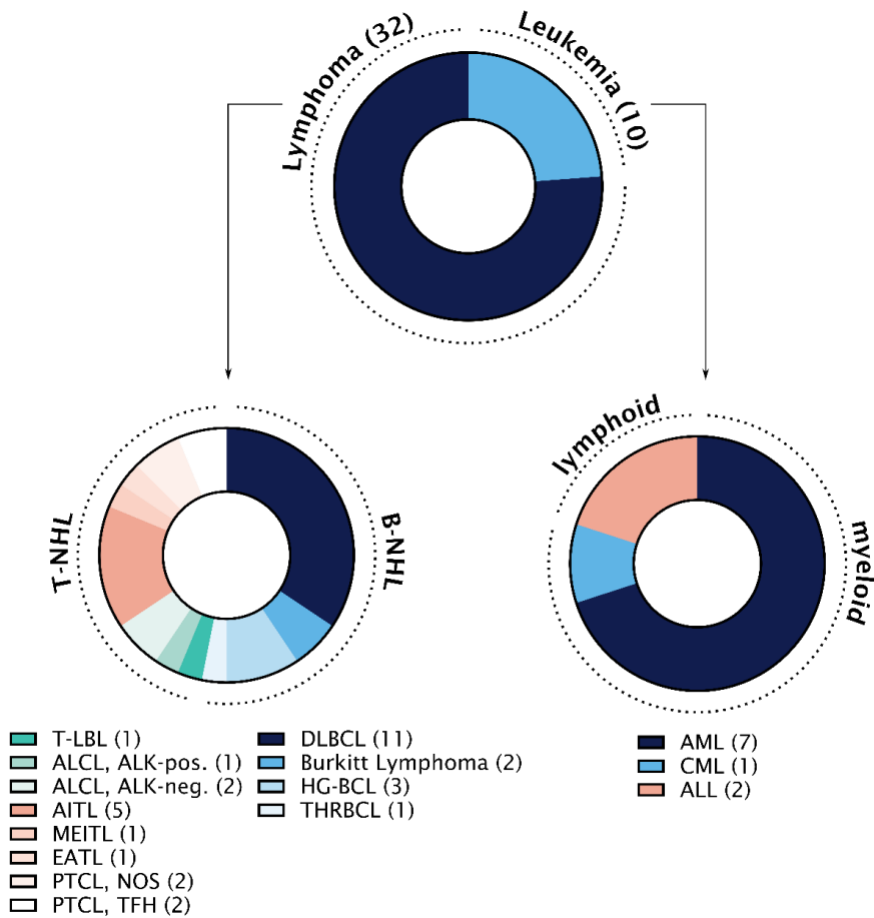


Supplementary Materials for:

Comparing Functional and Genomic-based Precision Medicine in Blood Cancer Patients

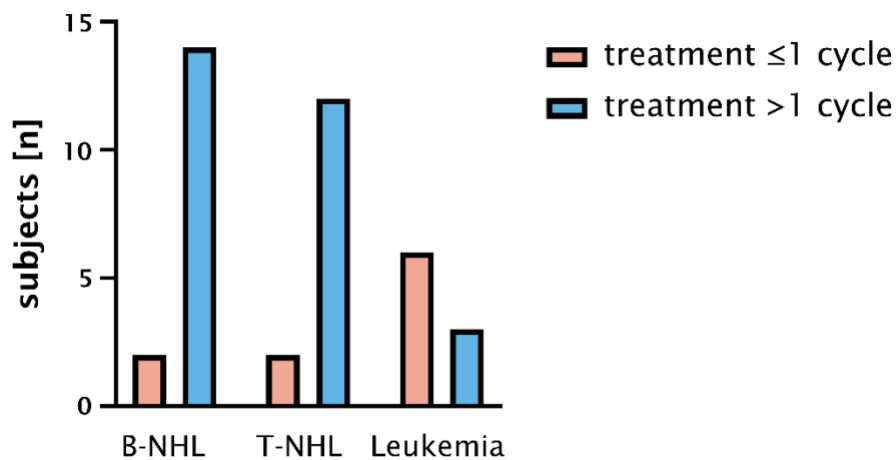
Supplementary Figures

Supplementary Figure 1

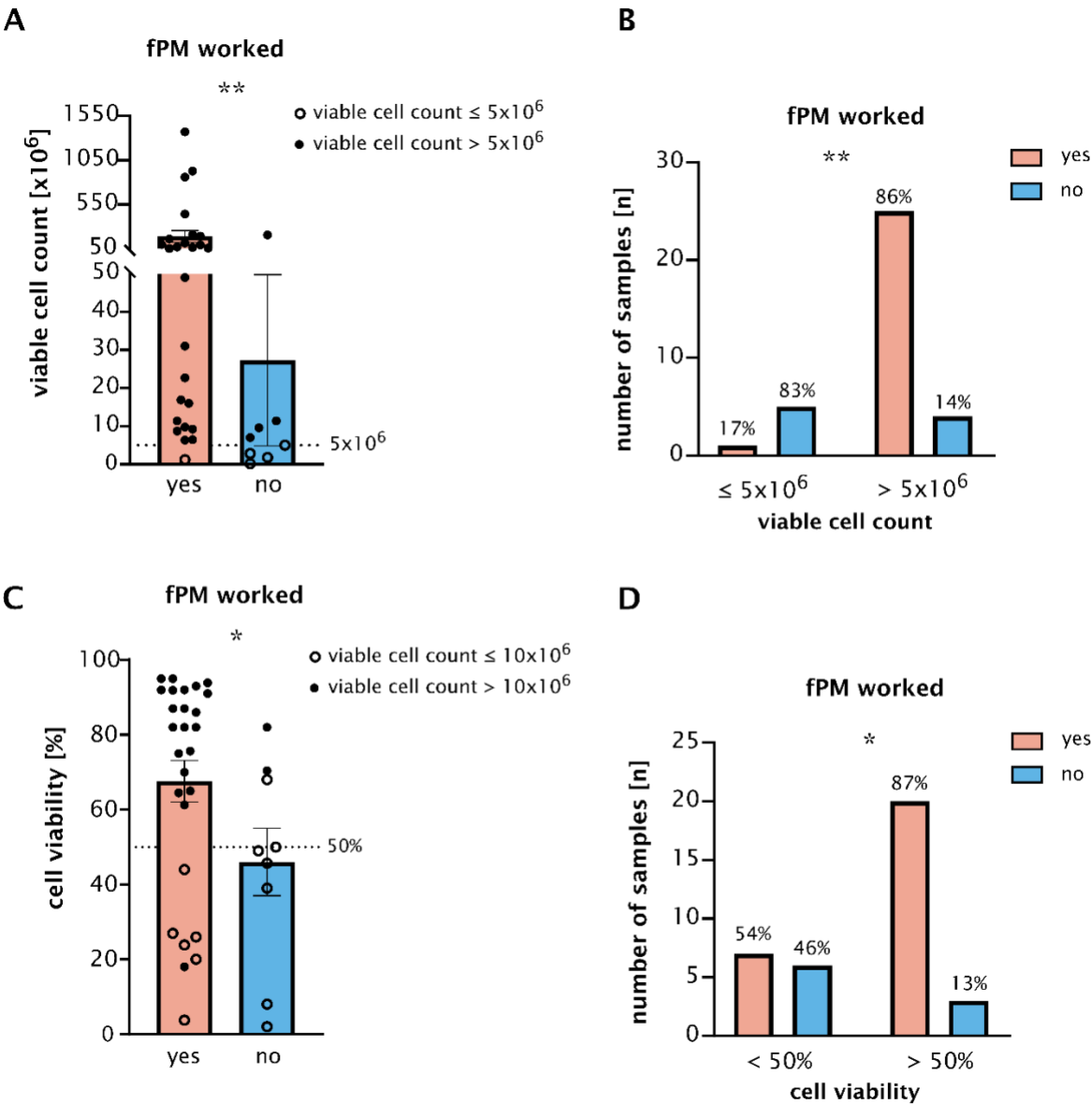


Supplementary Figure 1: Diagnoses of the 42 patients for whom a treatment recommendation was made by the EXALT-2 board. Numbers in brackets represent individual patients.

14 **Supplementary Figure 2**

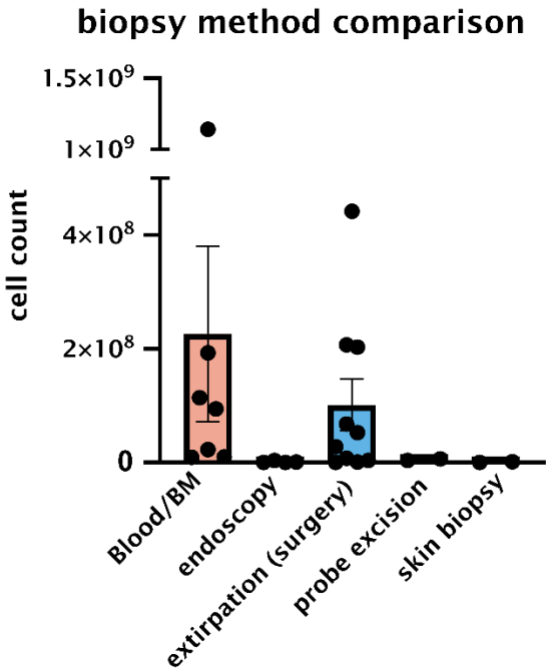


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16 **Supplementary Figure 2: EXALT-2 study treatment per disease entity.** In B-NHL, T-NHL
17 and leukemia subgroups, 2/16 (13%), 2/14 (14%) and 6/9 (67%) patients discontinued study
18 therapy before completion of the first cycle. Per definition in the study protocol these patients
19 count as early drop-out in the final efficacy analysis.



21
22 **Supplementary Figure 3: Thresholds for fPM feasibility.** **A)** Viable cell counts from real
23 time biopsy samples stratified whether fPM testing was technically successful and passed
24 quality control (QC) checks or not. fPM test results were only available for tests meeting
25 these criteria. A threshold of 5×10^6 cells emerged as a requirement for technically valid fPM
26 testing. Each dot represents an individual sample. Data shown as mean $\pm$ SEM, $p=0.0023$
27 (Mann-Whitney U test, two-sided). **B)** fPM success rate compared by two-sided Fisher's
28 exact test dichotomized by the suggested 5×10^6 cell threshold for fPM testing (worked:
29 technically valid test, QC passed, fPM report available; failed: assay failure, QC not passed,
30 no fPM report available; $p=0.0021$). **C)** Assessment of the impact of cell viability expressed
31 as percentages on the success rate of the fPM assays. Each dot represents an individual patient
32 sample with the distinction of samples with a viable cell count below and equal to and above
33 10×10^6 . Data shown as mean $\pm$ SEM, $p=0.0330$ (Mann-Whitney U test, two-sided). **D)** fPM
34 success rate compared by two-sided Fisher's exact test dichotomized by 50% cell viability
35 threshold, $p=0.0459$.

Supplementary Figure 4



Supplementary Figure 4: Biopsy method comparison. Cell yield for PM assays differed between biopsy methods. Blood, bone marrow (BM) samples and samples collected by surgery (mostly total LN extirpation) provided best results for downstream PM assay. Data shown as mean ± SEM.

54 **Supplementary Tables**55 **Supplementary Table 1. Screening drug collection**

COMPOUND NAME	SIMPLIFIED DRUG CLASS	MODE OF ACTION	DRUG SUBCLASS	FDA APPROVAL STATUS	SUPPLIER	SUPPLIER REG_ID	MW	MINIMUM CONC.[nM]	MAXIMUM CONC. [nM]
Venetoclax	Apoptosis modulator	BH3 mimetics	BCL2 inhibitor	Approved	Target Molecule Corp.	T2119	868.45	1	10000
Selinexor	Apoptosis modulator	CRM1 inhibitor		Approved	Adooq Bioscience	A12582	443.3	1	10000
Azathioprine	Classical chemotherapeutic	Antimetabolites		Approved	Adooq Bioscience	A10107	277.3	1	10000
Capecitabine	Classical chemotherapeutic	Antimetabolites		Approved	Sigma-Aldrich	MFCD00930626	359.4	1	10000
Cladribine	Classical chemotherapeutic	Antimetabolites		Approved	Target Molecule Corp.	T2558	285.7	1	10000
Clofarabine	Classical chemotherapeutic	Antimetabolites		Approved	Target Molecule Corp.	T0297	303.7	1	10000
Cytarabine	Classical chemotherapeutic	Antimetabolites		Approved	Sigma-Aldrich	MFCD00066487	243.2	1	10000
Decitabine	Classical chemotherapeutic	Antimetabolites		Approved	Sigma-Aldrich	MFCD00043011	228.2	1	10000
Fludarabine	Classical chemotherapeutic	Antimetabolites		Approved	Sigma-Aldrich	F2773	365.2	1	10000
5-fluorouracil	Classical chemotherapeutic	Antimetabolites		Approved	Adooq Bioscience	A10042	130.1	1	10000
Gemcitabine	Classical chemotherapeutic	Antimetabolites		Approved	Sigma-Aldrich	MFCD00869720	263.2	0.1	1000
6-mercaptopurine	Classical chemotherapeutic	Antimetabolites		Approved	Adooq Bioscience	A10568	152.2	1	10000

Methotrexate	Classical chemotherapeutic	Antimetabolites		Approved	Sigma-Aldrich	MFCD00064370	454.5	1	10000
Nelarabine	Classical chemotherapeutic	Antimetabolites		Approved	Target Molecule Corp.	T6603	297.3	1	10000
Leflunomide	Classical chemotherapeutic	Antimetabolites		Approved	Sigma-Aldrich	MFCD00867593	270.2	1	10000
Pemetrexed	Classical chemotherapeutic	Antimetabolites		Approved	Sigma-Aldrich	MFCD19105065	427.4	1	10000
5-azacitidine	Classical chemotherapeutics	Alkylating agent		Approved	Sigma-Aldrich	MFCD00006539	244.2	1	10000
Bendamustine	Classical chemotherapeutics	Alkylating agent		Approved	Angel Pharmatech Ltd.	AG309196	394.7	1	10000
Busulfan	Classical chemotherapeutics	Alkylating agent		Approved	Sigma-Aldrich	MFCD00007562	246.3	1	10000
Carboplatin	Classical chemotherapeutics	Alkylating agent		Approved	Adooq Bioscience	A10182	373.3	1	10000
Carmustine	Classical chemotherapeutics	Alkylating agent		Approved	Sigma-Aldrich	C0400	214.1	1	10000
Chlorambucil	Classical chemotherapeutics	Alkylating agent		Approved	Sigma-Aldrich	MFCD00021783	304.22	1	10000
Cisplatin	Classical chemotherapeutics	Alkylating agent		Approved	Sigma-Aldrich	P4394	300.1	1	10000
Cyclophosphamide	Classical chemotherapeutics	Alkylating agent		Approved	MedChem Express	HY-17420	261.1	1	10000
Ifosfamide	Classical chemotherapeutics	Alkylating agent		Approved	Sigma-Aldrich	MFCD00057374	261.1	1	10000
Melphalan	Classical chemotherapeutics	Alkylating agent		Approved	AvaChem Scientific	2776	305.2	1	10000

Mitomycin C	Classical chemotherapeutics	Alkylating agent		Approved	AvaChem Scientific	1996	334.3	1	10000
Temozolomide	Classical chemotherapeutics	Alkylating agent		Approved	Sigma-Aldrich	MFCD00866492	194.2	1	10000
Docetaxel	Classical chemotherapeutics	Antimitotic	Taxanes	Approved	Sigma-Aldrich	MFCD00800737	807.9	0.1	1000
Paclitaxel	Classical chemotherapeutics	Antimitotic	Taxanes	Approved	AvaChem Scientific	1364	853.9	0.1	1000
Vinblastine	Classical chemotherapeutics	Antimitotic	Vinca alkaloid	Approved	InterBioScreen Ltd.	BIO-0111	811.0	0.1	1000
Vincristine	Classical chemotherapeutics	Antimitotic	Vinca alkaloid	Approved	Adooq Bioscience	A11617	825.0	0.1	1000
Vindesine	Classical chemotherapeutics	Antimitotic	Vinca alkaloid	Approved	AvaChem Scientific	2181B	850.0	0.1	1000
Hydroxyurea	Classical chemotherapeutics	Antineoplastics		Approved	Adooq Bioscience	A10459	76.1	1	10000
Arsenic trioxide	Classical chemotherapeutics	Antineoplastics		Approved	Sigma-Aldrich	A1010	197.84	1	10000
Bortezomib	Classical chemotherapeutics	Proteasome inhibitor		Approved	Sigma-Aldrich	MFCD09056737	384.2	0.1	1000
Carfilzomib	Classical chemotherapeutics	Proteasome inhibitor		Approved	Target Molecule Corp.	T1795	719.9	0.1	1000
Ixazomib	Classical chemotherapeutics	Proteasome inhibitor		Approved	Target Molecule Corp.	T2122	361.03	0.1	1000
ATRA	Classical chemotherapeutics	Retinoid		Approved	Sigma-Aldrich	MFCD00001551	300.4	1	10000
Bexarotene	Classical chemotherapeutics	Retinoid		Approved	Target Molecule Corp.	T6410	348.5	1	10000

Etoposide	Classical chemotherapeutics	Topoisomerase I inhibitor		Approved	Sigma-Aldrich	MFCD00869325	588.6	1	10000
Mitoxantrone	Classical chemotherapeutics	Topoisomerase I inhibitor		Approved	Target Molecule Corp.	T6588	444.5	0.1	1000
Topotecan	Classical chemotherapeutics	Topoisomerase I inhibitor		Approved	Sigma-Aldrich	T2705	457.9	1	10000
Pixantrone	Classical chemotherapeutics	Topoisomerase I inhibitor		Approved	AvaChem Scientific	2637B	441.4	0.1	1000
Daunorubicin	Classical chemotherapeutics	Topoisomerase II inhibitor		Approved	AvaChem Scientific	2019B	564.0	1	10000
Doxorubicin	Classical chemotherapeutics	Topoisomerase II inhibitor		Approved	Adooq Bioscience	A14403	543.5	1	10000
Amsacrine	Classical chemotherapeutics	Topoisomerase II inhibitor		Approved	Adooq Bioscience	A13093	393.5	1	10000
Belinostat	Epigenetic modifier	HDAC inhibitor		Approved	Target Molecule Corp.	T1852	318.4	1	10000
Panobinostat	Epigenetic modifier	HDAC inhibitor		Approved	AChemBlock	L13155	349.4	0.1	1000
Romidepsin	Epigenetic modifier	HDAC inhibitor		Approved	Adooq Bioscience	A11920	540.7	0.1	1000
Vorinostat	Epigenetic modifier	HDAC inhibitor		Approved	Cayman Chemical	10009929	264.3	1	10000
Tazemetostat	Epigenetic modifier	EZH inhibitor		Approved	Adooq Bioscience	A12712	572.75	1	10000
Olaparib	Epigenetic modifier	PARP inhibitor		Approved	AvaChem Scientific	3730	434.47	1	10000
Rucaparib	Epigenetic modifier	PARP inhibitor		Approved	AChemBlock	M15391	323.37	1	10000

Lenalidomide	Immunomodulators	IMIDS		Approved	Sigma-Aldrich	MFCD07772307	259.3	1	10000
Pomalidomide	Immunomodulators	IMIDS		Approved	Sigma-Aldrich	MFCD12756407	273.3	1	10000
Thalidomide	Immunomodulators	IMIDS		Approved	Sigma-Aldrich	MFCD00153873	258.2	1	10000
Tacrolimus	Immunomodulators	Microlides		Approved	AvaChem Scientific	1833	804.0	1	10000
Dexamethasone	Immunomodulators	Steroids		Approved	Sigma-Aldrich	MFCD00064136	392.5	1	10000
Methylprednisolone	Immunomodulators	Steroids		Approved	Sigma-Aldrich	MFCD00010591	374.5	1	10000
Prednisolone	Immunomodulators	Steroids		Approved	Sigma-Aldrich	P6004	360.5	1	10000
Palbociclib	Kinase inhibitors	CMGS inhibitors	CDK inhibitor	Approved	AvaChem Scientific	3374	447.5	1	10000
Ribociclib	Kinase inhibitors	CMGS inhibitors	CDK inhibitor	Approved	Target Molecule Corp.	T6199	434.54	1	10000
Duvelisib	Kinase inhibitors	PIKL inhibitor	Dual PI3K δ and PI3K γ inhibitor	Approved	Adooq Bioscience	A12422	416.9	0.1	1000
Idelalisib	Kinase inhibitors	PIKL inhibitor	PI3K δ inhibitor	Approved	Adooq Bioscience	A10172	415.4	1	10000
Copanlisib	Kinase inhibitors	PIKL inhibitor	pan-class I PI3K inhibitor	Approved	MedChem Express	HY-15346	480.5	0.1	1000
Everolimus	Kinase inhibitors	PIKL inhibitor	rapalog (mTOR)	Approved	Sigma-Aldrich	MFCD00929329	958.2	0.1	1000
Temsirolimus	Kinase inhibitors	PIKL inhibitor	rapalog (mTOR)	Approved	Target Molecule Corp.	T2145	1030.3	0.1	1000

Trametinib	Kinase inhibitors	STE inhibitors	MEK inhibitor	Approved	Cayman Chemical	16292	615.4	0.1	1000
Cobimetinib	Kinase inhibitors	STE inhibitors	MEK inhibitor	Approved	ACheckBlock	H-8765	531.3	0.1	1000
Selumetinib	Kinase inhibitors	STE inhibitors	MEK inhibitor	Approved	Target Molecule Corp.	T6218	457.69	1	10000
Dabrafenib	Kinase inhibitors	TKL inhibitors	BRAF inhibitor	Approved	Target Molecule Corp.	T1903	519.6	0.1	1000
Vemurafenib	Kinase inhibitors	TKL inhibitors	BRAF inhibitor	Approved	AvaChem Scientific	3087	489.93	1	10000
Bosutinib	Kinase inhibitors	Tyrosine kinase inhibitors	BCR-ABL / SRC inhibitor	Approved	Adooq Bioscience	A10161	530.5	1	10000
Dasatinib	Kinase inhibitors	Tyrosine kinase inhibitors	BCR-ABL / SRC inhibitor	Approved	Target Molecule Corp.	T1448	488.0	0.1	1000
Imatinib	Kinase inhibitors	Tyrosine kinase inhibitors	BCR-ABL / KIT / PDGFR inhibitor	Approved	Sigma-Aldrich	MFCD05662257	493.6	1	10000
Nilotinib	Kinase inhibitors	Tyrosine kinase inhibitors	BCR-ABL inhibitor	Approved	Sigma-Aldrich	MFCD09833716	529.5	1	10000
Ponatinib	Kinase inhibitors	Tyrosine kinase inhibitors	BCR-ABL / VEGFR / PDGFR inhibitor	Approved	Sigma-Aldrich	MFCD17215203	532.6	0.1	1000
Ceritinib	Kinase inhibitors	Tyrosine kinase inhibitors	ALK inhibitor	Approved	Target Molecule Corp.	T1791	558.1	0.1	1000
Crizotinib	Kinase inhibitors	Tyrosine kinase inhibitors	ALK inhibitor	Approved	Sigma-Aldrich	MFCD12407409	450.3	0.1	1000
Brigatinib	Kinase inhibitors	Tyrosine kinase inhibitors	ALK inhibitor	Approved	MedChem Express	HY-12857	584.09	0.1	1000
Ibrutinib	Kinase inhibitors	Tyrosine kinase inhibitors	BTK inhibitor	Approved	Sigma-Aldrich	MFCD20261150	440.5	0.1	1000

Acalabrutinib	Kinase inhibitors	Tyrosine kinase inhibitors	BTK inhibitor	Approved	MedChem Express	HY-17600	465.51	0.1	1000
Zanubrutinib	Kinase inhibitors	Tyrosine kinase inhibitors	BTK inhibitor	Approved	ACheckBlock	P50926	471.56	0.1	1000
Erlotinib	Kinase inhibitors	Tyrosine kinase inhibitors	EGFR inhibitor	Approved	Sigma-Aldrich	MFCD02089651	393.44	1	10000
Gefitinib	Kinase inhibitors	Tyrosine kinase inhibitors	EGFR inhibitor	Approved	Sigma-Aldrich	MFCD04307832	446.9	1	10000
Lapatinib	Kinase inhibitors	Tyrosine kinase inhibitors	EGFR inhibitor	Approved	Sigma-Aldrich	MFCD09264194	581.07	0.1	1000
Gilteritinib	Kinase inhibitors	Tyrosine kinase inhibitors	AXL inhibitor	Approved	ACheckBlock	L13966	552.72	0.1	1000
Lenvatinib	Kinase inhibitors	Tyrosine kinase inhibitors	FGFR1/2/3 inhibitor	Approved	ACheckBlock	M15396	426.86	0.1	1000
Nintedanib	Kinase inhibitors	Tyrosine kinase inhibitors	FGFR1/2/3 inhibitor	Approved	Angel Pharmatech Ltd.	AG-12049	539.63	1	10000
Ruxolitinib	Kinase inhibitors	Tyrosine kinase inhibitors	JAK1/2 inhibitor	Approved	ACheckBlock	G-6185	306.4	1	10000
Tofacitinib	Kinase inhibitors	Tyrosine kinase inhibitors	JAK1/2/3 inhibitor	Approved	MedChem Express	HY-40354	312.37	0.1	1000
Baricitinib	Kinase inhibitors	Tyrosine kinase inhibitors	JAK3 inhibitor	Approved	ACheckBlock	G-5743	371.42	0.1	1000
Crenolanib	Kinase inhibitors	Tyrosine kinase inhibitors	PDGFR / FLT3 inhibitor	Approved	Target Molecule Corp.	T2677	443.6	1	10000
Midostaurin	Kinase inhibitors	Tyrosine kinase inhibitors	PDGFR / FLT3 / PKC α / β / γ inhibitor	Approved	Target Molecule Corp.	T3211	570.7	1	10000
Quizartinib	Kinase inhibitors	Tyrosine kinase inhibitors	PDGFR / FLT3	Approved	Adooq Bioscience	A10027	560.7	0.1	1000

Entrectinib	Kinase inhibitors	Tyrosine kinase inhibitors	TRKA	Approved	Adooq Bioscience	A15801	560.65	0.1	1000
Larotrectinib	Kinase inhibitors	Tyrosine kinase inhibitors	TRKA	Approved	ACheckBlock	H-8992	428.44	1	10000
Cabozantinib	Kinase inhibitors	Tyrosine kinase inhibitors	VEGFR inhibitor	Approved	Target Molecule Corp.	T2586	501.5	0.1	1000
Pazopanib	Kinase inhibitors	Tyrosine kinase inhibitors	VEGFR inhibitor	Approved	Sigma-Aldrich	MFCD11616589	437.5	1	10000
Axitinib	Kinase inhibitors	Tyrosine kinase inhibitors	VEGFR	Approved	Sigma-Aldrich	MFCD09837898	386.48	1	10000
Sorafenib	Kinase inhibitors	Tyrosine kinase inhibitors	VEGFR inhibitor	Approved	Target Molecule Corp.	T0093L	464.8	0.1	1000
Sunitinib	Kinase inhibitors	Tyrosine kinase inhibitors	VEGFR inhibitor	Approved	Sigma-Aldrich	MFCD09260778	398.5	0.1	1000
Regorafenib	Kinase inhibitors	Tyrosine kinase inhibitors	VEGFR inhibitor	Approved	Target Molecule Corp.	T1792	482.82	1	10000
Vandetanib	Kinase inhibitors	Tyrosine kinase inhibitors	VEGFR / EGFR / RET inhibitor	Approved	Sigma-Aldrich.	MFCD07772346	475.4	0.1	1000
Tivozanib	Kinase inhibitors	Tyrosine kinase inhibitors	VEGFR inhibitor	Approved	MedChem Express	HY-10977	454.86	1	10000
Anagrelide	Other	Phosphodiesterase inhibitors		Approved	Target Molecule Corp.	T0160	256.1	1	10000
Erismodegib	Other	Hedgehog pathway	Smoothened inhibitor	Approved	Target Molecule Corp.	T1926	485.5	1	10000
Vismodegib	Other	Hedgehog pathway	Smoothened inhibitor	Approved	Sigma-Aldrich	MFCD12407408	421.3	1	10000
Glasdegib	Other	Hedgehog pathway	Smoothened inhibitor	Approved	Cayman Chemical	9002936	374.45	1	10000

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Ivosidenib	Other	Metabolic modifier	IDH1 inhibitor	Approved	Target Molecule Corp.	T3617	582.97	1	10000
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Supplementary Table 2. Study Arm Changes

#	sex	Age [years]	diagnosis	Randomized arm	Treatment arm	Reason for fPM failure	Reason for gPM failure
1	male	61.6	HG-BCL	fPM	gPM	not enough viable cells for fPM	-
2	female	57.5	MEITL	fPM	gPM	not enough viable cells for fPM	-
3	female	74.8	Burkitt lymphoma	fPM	PC	not enough viable cells for fPM	gPM without actionable target
4	male	63.9	Burkitt lymphoma	fPM	PC	not enough viable cells for fPM	gPM without actionable target
5	female	80.7	DLBCL	fPM	PC	QC for image-bassed fPM assay not passed	QC for gPM assay not passed
6	female	67.8	AITL	fPM	PC	not enough viable cells for fPM	gPM without actionable target
7	male	72	DLBCL	fPM	PC	insufficient biopsy quality	insufficient biopsy quality
8	male	62.3	T-LBL	fPM	PC	not enough viable cells for fPM	gPM without actionable target
9	female	69.7	AML	gPM	fPM	-	Time limit exceeded
10	male	21.9	ALL	gPM	fPM	-	QC for gPM assay not passed
11	female	64.3	AITL	gPM	fPM	-	Prior exposure to gPM-suggested therapy
12	male	43.6	CML	gPM	fPM	-	Prior exposure to gPM-suggested therapy
13	female	81.2	AITL	gPM	PC	QC for image-bassed fPM assay not passed	gPM without actionable target
14	female	66.8	DLBCL	gPM	PC	QC for image-bassed fPM assay not passed	QC for gPM assay not passed

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64 **Supplementary Table 3. Response Evaluation Schedule**

PERIODS	Name	SCREENING	TREATMENT							FOLLOW-UP	
	Duration		9 months								
VISITS	Number	1	2	3	4	5	6	7	8	9	10
	Name	Screening/ Randomization/ Board	Treatment Start	Control 1	Control 2	Control 3	Control 4	Control 5	Control 6	Follow-up 1	Follow-up 2
	Time	Days/Weeks	Day 0	Month 1 (± 10 days)	Month 2 (± 10 days)	Month 3 (± 10 days)	Month 4 (± 10 days)	Month 6 (± 10 days)	Month 9 (± 10 days)	Month 12 (± 10 days)	Month 16 (± 10 days)
			VISIT SCHEDULE								
Informed Consent		x									
Inclusion / Exclusion Criteria		x									
Medical History		x		x	x	x	x	x	x	x	x
Concomitant/change in medication		x		x	x	x	x	x	x	x	x
Physical Examination		x		x	x	x	x	x	x	x	x
Body weight and height		x		x	x	x	x	x	x	x	x
Vital Signs (BP, PR)		x		x	x	x	x	x	x	x	x
12-lead ECG		x		x					x		x
Laboratory Tests		x		x	x	x	x	x	x	x	x
Pregnancy Test		x									
EORTC QLQ-C30		x		x	x		x	x	x	x	x
Real-Time Biopsy		x									
fPM (image- or flow-based)		x									
gPM		x									
Adverse Events		x		x	x	x	x	x	x	x	x
			DISEASE ASSESSMENT SCHEDULE								
Cross-sectional imaging for lymphoma		x			x		x	x	x	x	x
Bone marrow examination for leukemia		x		x*	x*		x*	x*	x*	x*	x*

¹Long-term Follow-up as clinically indicated

¹ Long-term Follow Up: every 6 Months (to detect PFS/OS events: date of relapse/death, or date of visit)

* to establish a response in patients without circulation blast cells

Supplementary Table 4. Hit overlap between the two fPM platforms

Sample_ID	Top 10 hits overall overlap %	Flow cytometry-based fPM matching image-based fPM top hits	Image-based fPM matching flow cytometry-based fPM hits
25	70	8/10 (80%)	7/10 (70%)
30	50	6/10 (60%)	6/10 (60%)
31	50	6/8 (75%)	7/13 (54%)
32	30	4/10 (40%)	3/10 (30%)
36	30	4/10 (40%)	3/10 (30%)
42	50	6/10 (60%)	5/10 (50%)
52	60	6/9 (66.7%)	6/10 (60%)

79 **Supplementary Table 5. fPM and gPM assay overlaps**

#	diagnosis	Actionable genetic alteration	gPM treatment suggestion	fPM drug hit (among top 10 drugs)	fPM rank	fPM assay type
1	AML	FLT3, CCND3	midostaurin, gilteritinib, sunitinib, sorafenib, ponatinib	ponatinib	4	flow-based
2	AML	FLT3, TET2, BCR-ABL, KMT2A, NF1	decitabine, azacitidine, gilteritinib, midostaurin, pexidartinib, BCR-ABL inhibitors	ponatinib	6	flow-based
3	AML	IDH1, KMT2A	azacitidine, decitabine, ivosidenib, venetoclax	venetoclax	3 (image-based) 7 (flow-based)	both
4	AML	NRAS	cobimetinib, selumetinib, trametinib	trametinib	3	flow-based
5	sAML	IDH2, JAK2	azacitidine, decitabine, enasidenib, ruxolitinib, venetoclax	venetoclax	10	image-based
6	CML	BCR-ABL	BCR-ABL inhibitors	dasatinib	4	flow-based
7	DLBCL	BRAF	selumetinib, trametinib	trametinib, selumetinib	5 (trametinib), 9 (selumetinib)	image-based
8	DLBCL	CDK6, MEF2B, MYC	palbociclib, ribociclib, ademaciclib, romidepsin, tazemetostat, belinostat	belinostat	1	flow-based
9	DLBCL	IGH-BCL2	venetoclax	venetoclax	2 (image-based) 2 (flow-based)	both
10	DLBCL	IGH-BCL2	venetoclax	venetoclax	1	flow-based
11	DLBCL	KRAS, IGH-BCL6	selumetinib, trametinib	selumetinib	6	flow-based
12	DLBCL	PTEN	copanlisib	copanlisib	8	image-based

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82 **Supplementary Table 6. Comparison of EXALT-2 Board Treatment Recommendations for the Three Most Frequent Entities.**

#	Treatment arm	EXALT-2 Board Recommendation	fPM type	top 5 fPM hits	gPM results
DLBCL					
1	PC	methotrexate, ibrutinib, pembrolizumab, dexamethasone	image	failed	KRAS, IGH, DNMT3A
2	PC	tafasitamab, lenalidomide	image	failed	failed
3	PC	radiotherapy, anti-CD20 treatment	image	failed	no actionable aberration
4	PC	rituximab, polatuzumab	image	dexamethasone, methylprednisolone, vinblastine, idelalisib, midostaurin	no actionable aberration
5	PC	tafasitamab, lenalidomide	image	failed	failed
6	PC	glofitamab, azacytidine, paclitaxel	flow	sunitinib, temsirolimus, bendamustine, busulfan, selumetinib	KRAS, IGH
7	PC	gemcitabine, oxaliplatin	flow	failed	failed
8	fPM	olaparib, polatuzumab	image	olaparib, romidepsin, zanubrutinib, clofarabine, duvelisib	no actionable aberration
9	gPM	rituximab, venetoclax, ibrutinib	image	failed	IGH, SMARCB1, MYD88
10	gPM	rituximab, copanlisib	both	vincristine, venetoclax, romidepsin, topotecan, clofarabine	PTEN
11	gPM	venetoclax, HDAC inhibitor	flow	belinostat, lenvatinib, imatinib, panobinostat, amsacrine	CDK6, MYC, MEF2B
AML					
1	PC	low-dose cytarabine, glasdegib	image	romidepsin, carfilzomib, panobinostat, bortezomib, ponatinib	IDH2, JAK2
2	PC	low-dose cytarabine, glasdegib	image	panobinostat, romidepsin, belinostat, flavopiridol, venetoclax	failed
3	fPM	romidepsin, venetoclax, azacytidine	image	carfilzomib, panobinostat, romidepsin, flavopiridol, bortezomib	FLT3, TET2, BCR-ABL, KMT2A, NF1
4	fPM	cladribine, bortezomib	both	rigosertib, cladribine, vincristine, panobinostat, venetoclax	IDH1, KMT2A
5	fPM	azacytidine, venetoclax	both	venetoclax, azacytidine, axitinib, carfilzomib, romidepsin	Failed

6	fPM	erismodegib, ponatinib, azacytidine	flow	clofarabine, venetoclax, erismodegib, bortezomib, azacytidine	FLT3, CCND3
7	gPM	cobimetinib, azacytidine, venetoclax	flow	axitinib, carfilzomib, mitoxantrone, cyclophosphamide, belinostat	NRAS
AITL					
1	PC	romidepsin, dexamethasone	image	failed	no actionable target
2	PC	brentuximab	image	carfilzomib, bortezomib*	IDH2, TET2
3	PC	azacytidine	image	failed	TET2
4	fPM	romidepsin, venetoclax	flow	rucaparib, venetoclax, romidepsin, clofarabine, ixazomib	TET2
5	fPM	romidepsin, carfilzomib	both	carfilzomib, romidepsin, Panobinostat, cladribine, dexamethasone	TET2

* Only two hits available

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List of abbreviations:

abbreviation		abbreviation		Abbreviation	
AITL	Angioimmunoblastic T-cell lymphoma	ECG	Electrocardiography	OS	Overall survival
ALCL	Anaplastic large cell lymphoma	EDTA	Ethylenediaminetetraacetic acid	PC	Physicians' choice
ALK	Anaplastic lymphoma kinase	EMA	European Medicines Agency	PD	Progressive disease
ALL	Acute lymphoblastic leukemia	EORTC	European Organisation for Research and Treatment	PFS	Progression-free survival
AML	Acute myeloid leukemia	FDA	Food and Drug Administration	PM	Precision medicine
ANOVA	Analysis of variance	FFPE	formaldehyde-fixed paraffin- embedded	PP	Per protocol
AUC	Area under the curve	fPM	functional precision medicine	PR	Partial response

B-NHL	B Non-Hodgkin Lymphoma	gPM	Genomic-based precision medicine	PTCL	Peripheral T-cell lymphoma
BM	Bone marrow	HG-BCL	High.grade B-cell lymphoma	QC	Quality control
BP	Blood pressure	HT	high-throughput	RNA	Ribonucleic acid
CML	Chronic myeloid leuemia	ITT	intention to treat	r/r	Relapsed/refractory
Conc.	Concentration	LN	Lymph node	SD	Stable disease
CR	Complete remission	MEITL	Monomorphic epitheliotrophic intestinal T-cell lymphoma	SEM	Standard error of the mean
DAPI	4',6-Diamidino-2-phenylindol	MR	Mixed response	TFH	T follicular helper
DMSO	Dimethyl sulfoxide	MW	Molar weight	THRBCL	T-cell and histiocyte rich B-cell lymphoma
DNA	Deoxyribonucleic acid	NCCN	National Comprehensive Cancer Network	T-LBL	T-lymphoblastic lymphoma

EATL	Enteropathy-associated T-cell lymphoma	NOS	Not otherwise specified	T-NHL	T Non-Hodgkin lymphoma
ECOG	Eastern Cooperative Oncology Group	ORR	Overall response rate	WHO	World Health Organization

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