Venetoclax and dinaciclib elicit synergistic preclinical efficacy against hypodiploid acute lymphoblastic leukemia

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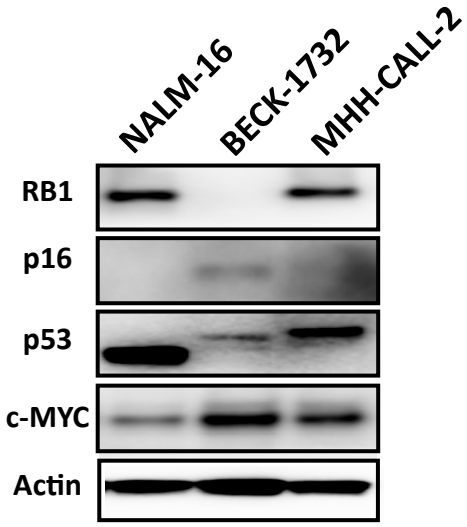
Fig. S1

A)

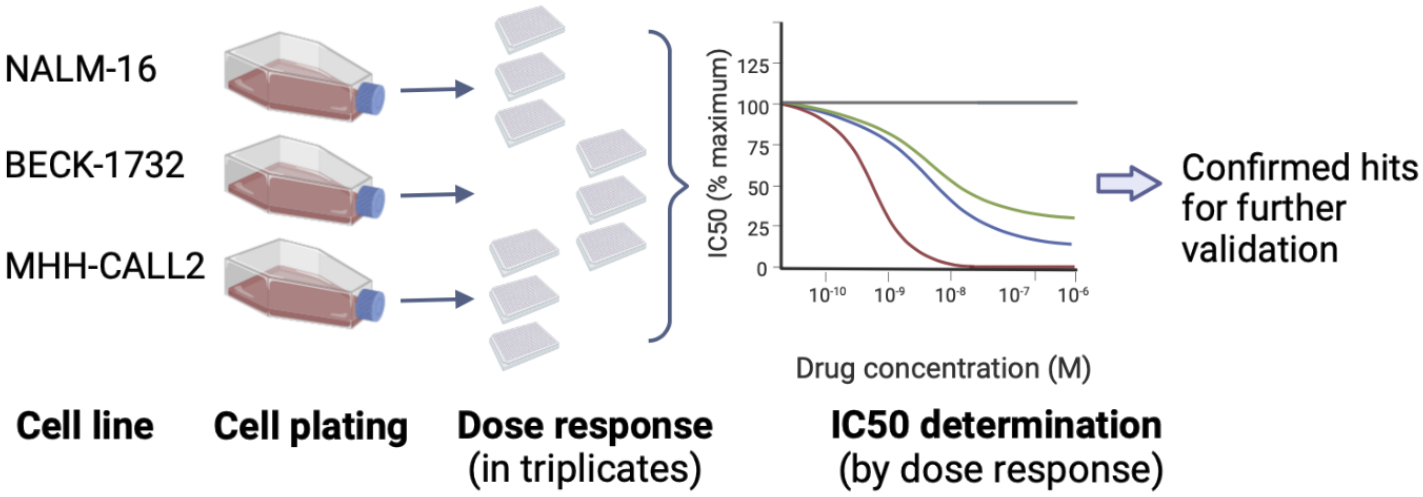
NALM-16: hypodiploid B-ALL, 27 Chr.
NF1 del, *CDKN2A/B* del, *TP53 (R290fs)*

BECK-1732: masked hypodiploid B-ALL, 25 x 2 Chr.
NRAS (G12S), *RB1* del, *CDKN2A* del

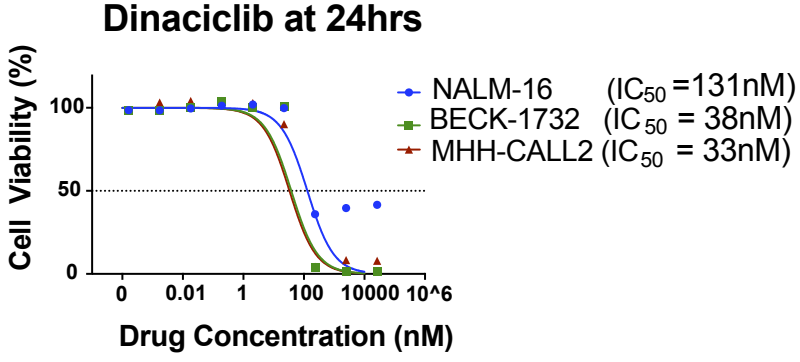
MHH-CALL-2: masked hypodiploid B-ALL, 26 x 2 Chr.
CDKN2A/B del



B)



C)



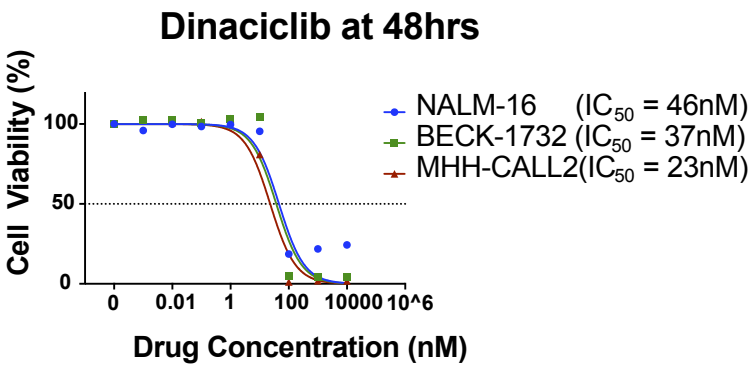
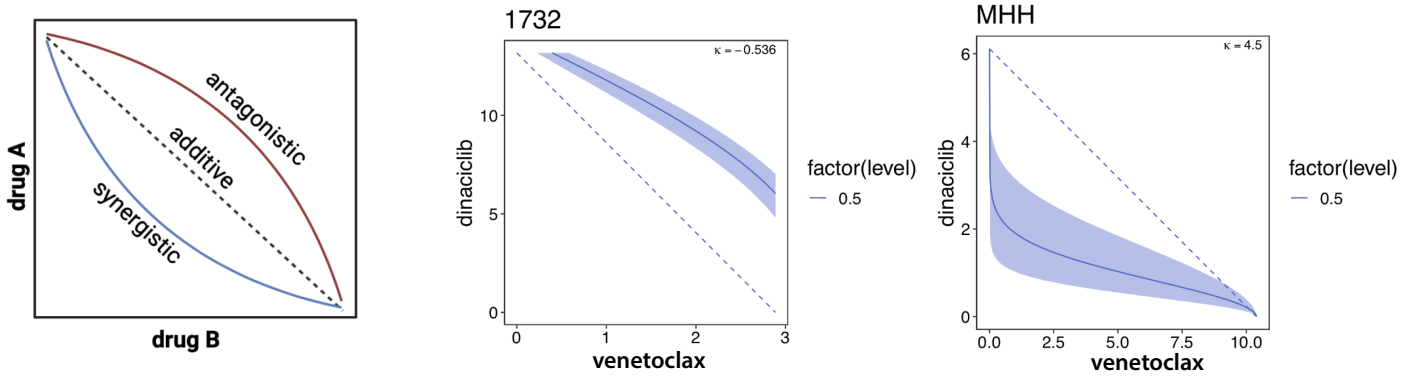


Fig. S2

A)

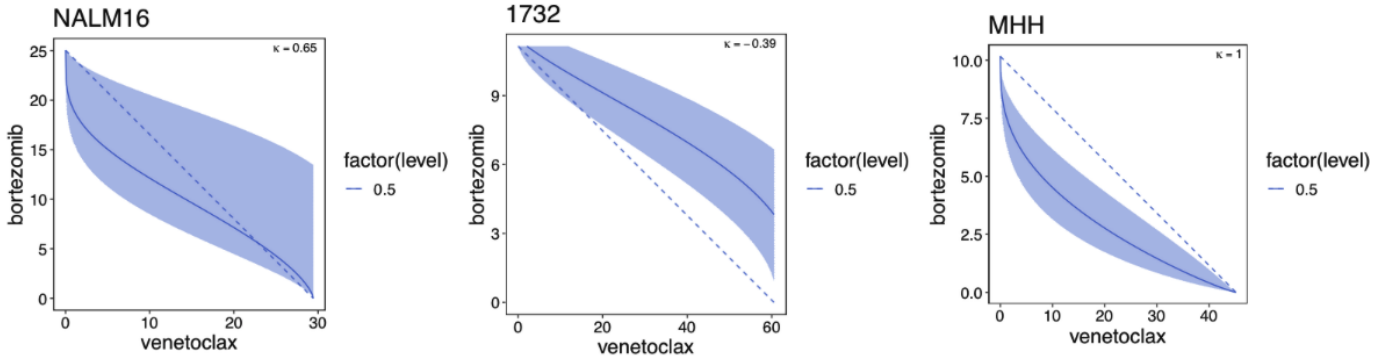


B)

Beck-1732		Dinaciclib (nM)							
		0	8	16	32	62.5	125	250	500
Venetoclax (nM)	0	100%	90%	30%	1%	1%	0%	0%	0%
	8	12%	17%	5%	0%	0%	0%	0%	0%
	16	4%	7%	1%	0%	0%	0%	0%	0%
	32	2%	3%	1%	0%	0%	0%	0%	0%
	62.5	1%	1%	0%	0%	0%	0%	0%	0%
	125	1%	1%	0%	0%	0%	0%	0%	0%
	250	0%	0%	0%	0%	0%	0%	0%	0%
	500	0%	0%	0%	0%	0%	0%	0%	0%

% Growth Inhibition
Low High

C)



D)

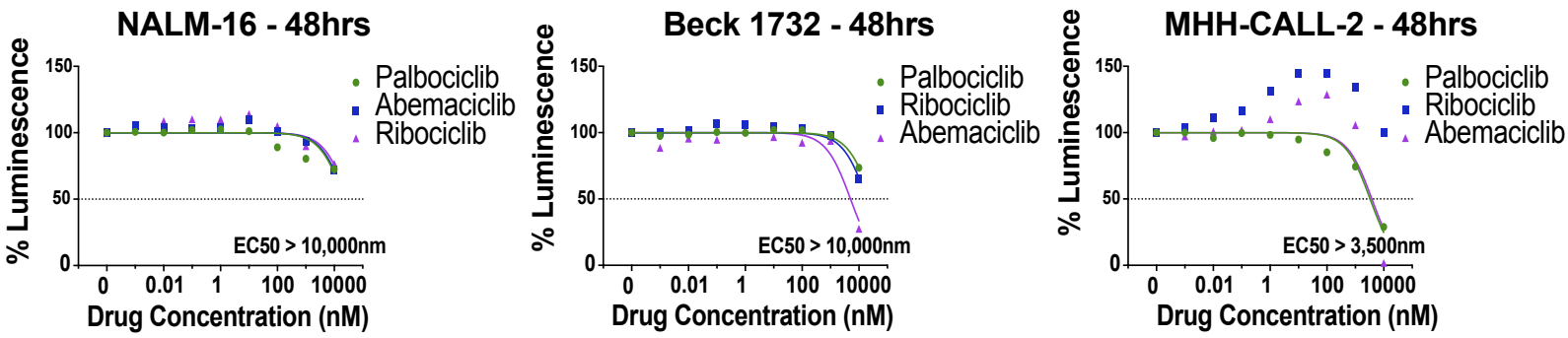


Figure S3

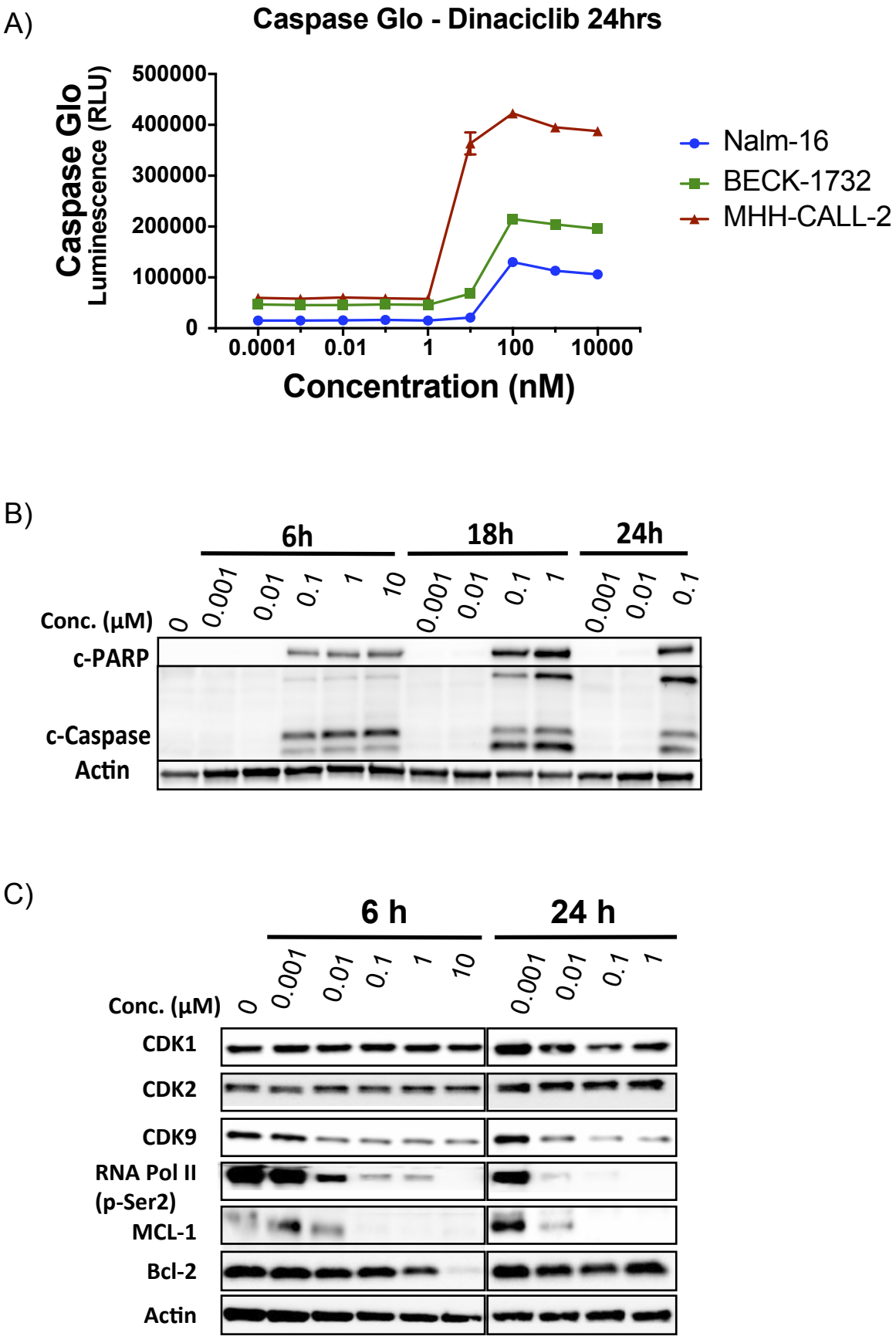

A)
Caspase Glo - Dinaciclib 24hrs
Caspase Glo
Luminescence (RLU)
500000
400000
300000
200000
100000
0
0.0001
0.01
1
100
10000
Concentration (nM)
Nalm-16
BECK-1732
MHH-CALL-2
B)
6h
18h
24h
Conc. (µM)
0
0.001
0.01
0.1
1
10
c-PARP
c-Caspase
Actin
C)
6 h
24 h
Conc. (µM)
CDK1
CDK2
CDK9
RNA Pol II
(p-Ser2)
MCL-1
Bcl-2
Actin

Fig. S4

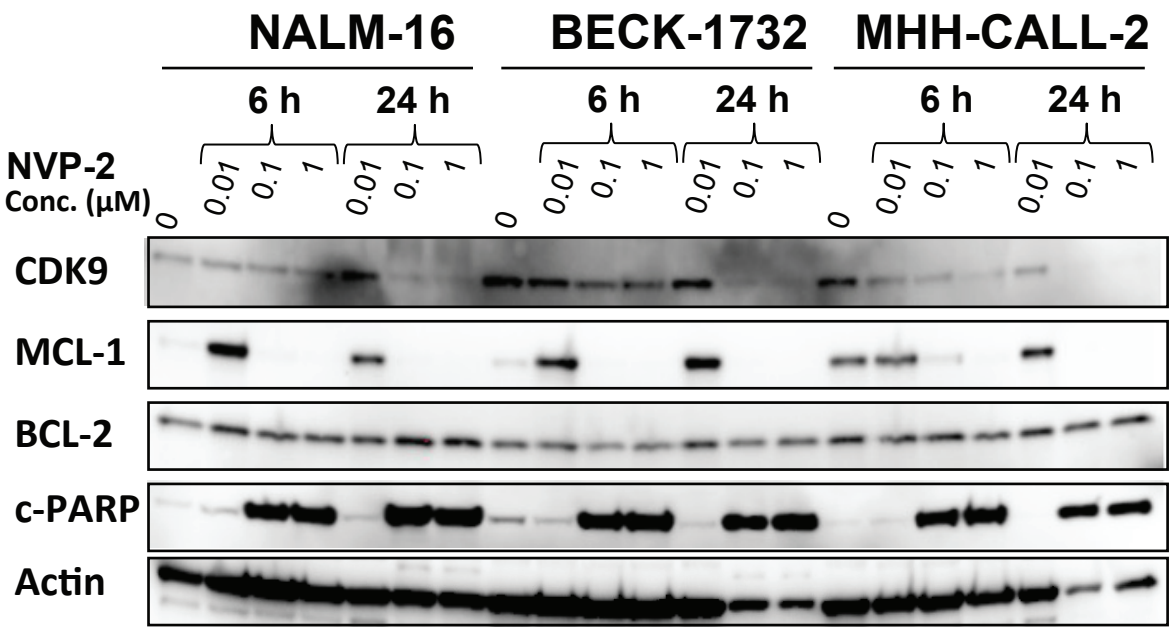

NALM-16
BECK-1732
MHH-CALL-2
6 h
24 h
6 h
24 h
6 h
24 h
NVP-2
Conc. (μM)
0
0.01
0.1
1
0.01
0.1
1
0
0.01
0.1
1
0.01
0.1
1
0
0.01
0.1
1
0.01
0.1
1
CDK9
MCL-1
BCL-2
c-PARP
Actin

Fig. S5

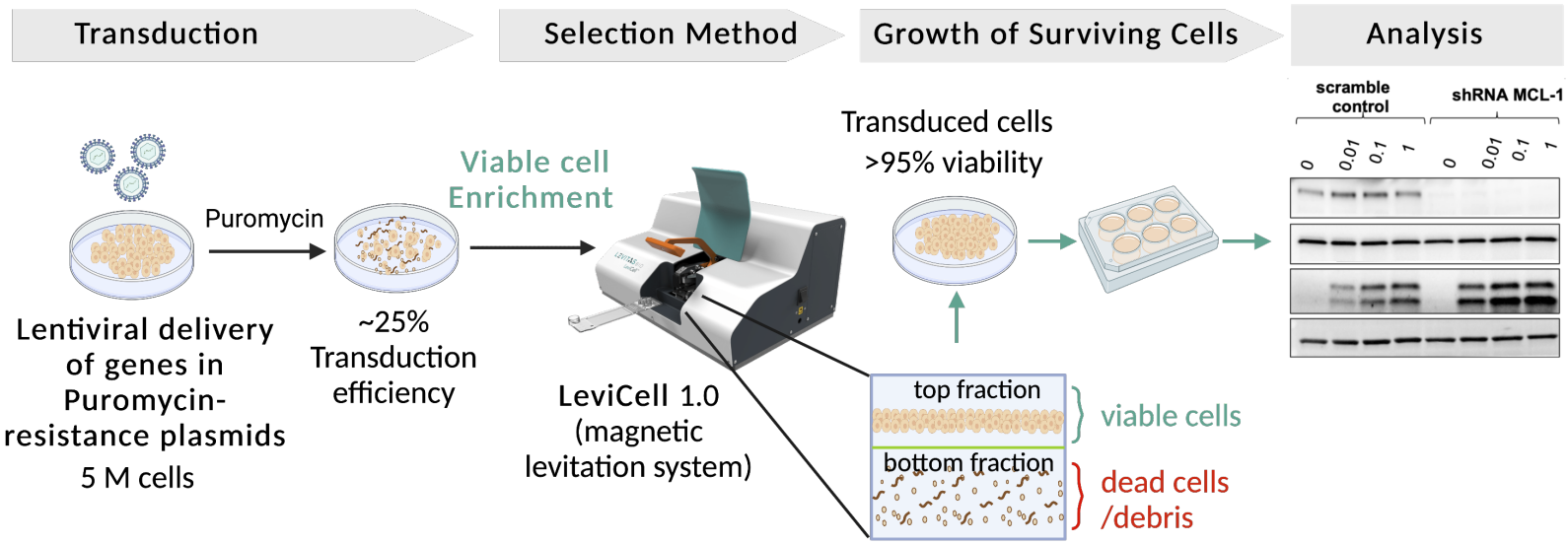

Transduction
Selection Method
Growth of Surviving Cells
Analysis
Puromycin
Lentiviral delivery of genes in Puromycin-resistance plasmids
5 M cells
~25% Transduction efficiency
Viable cell Enrichment
LeviCell 1.0 (magnetic levitation system)
Transduced cells >95% viability
top fraction
bottom fraction
viable cells
dead cells /debris
scramble control
shRNA MCL-1
0
0.01
0.1
1
0
0.01
0.1
1

Figure S6

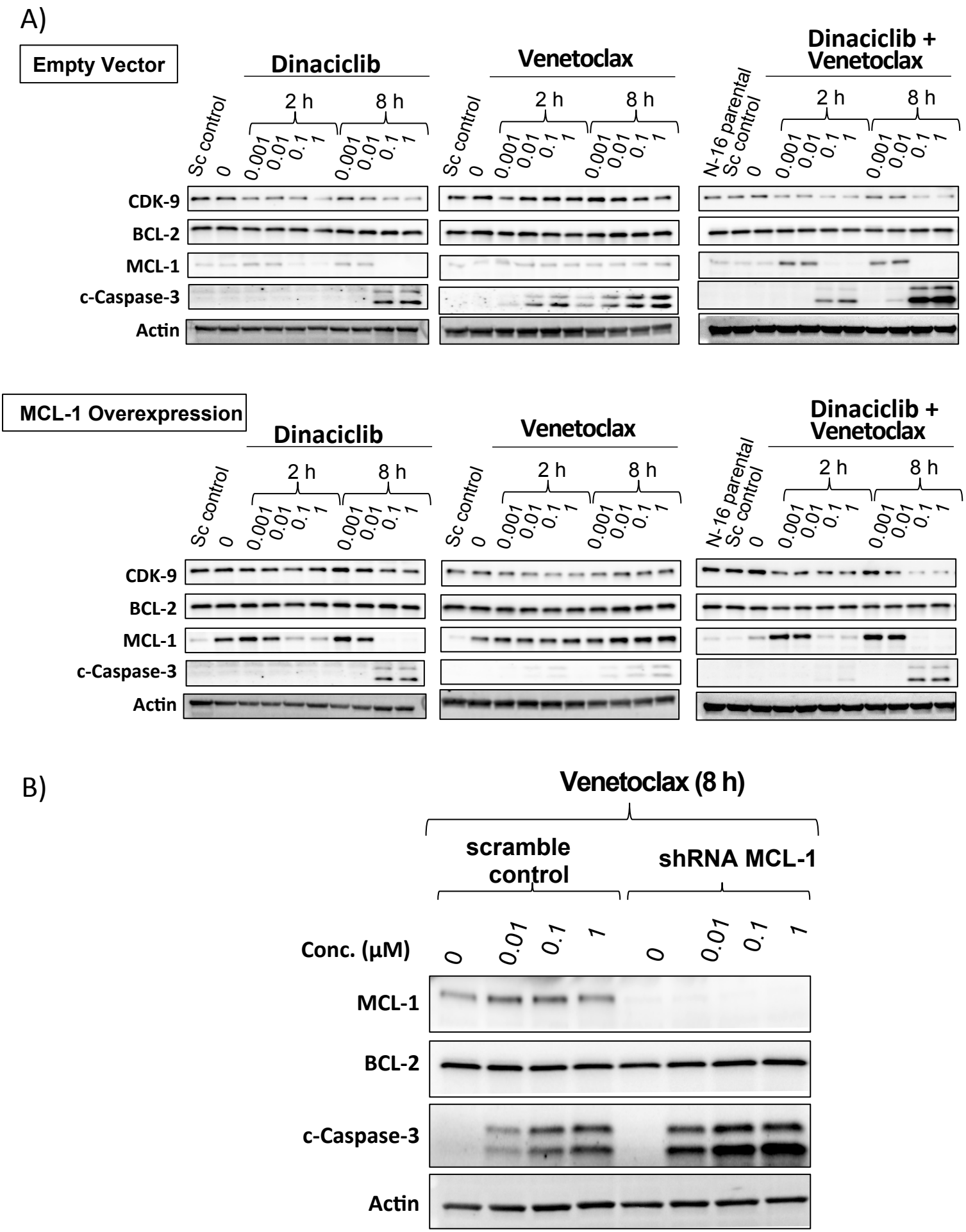
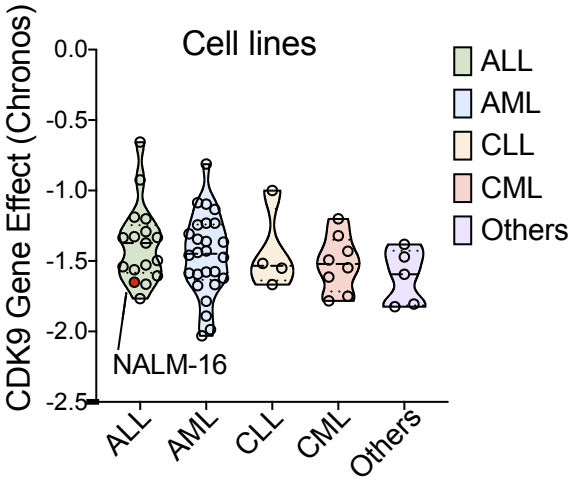
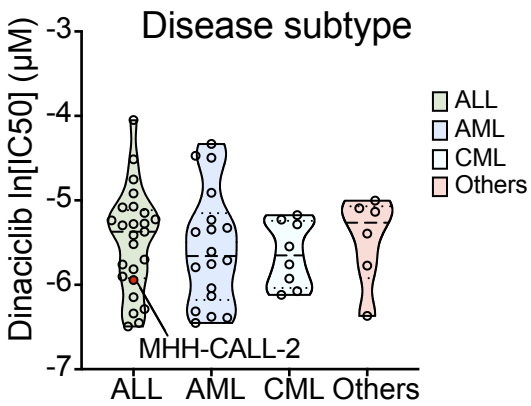

A)
Empty Vector
Dinaciclib
Venetoclax
Dinaciclib + Venetoclax
2 h
8 h
Sc control
N-16 parental
0
0.001
0.01
0.1
1
CDK-9
BCL-2
MCL-1
c-Caspase-3
Actin
MCL-1 Overexpression
B)
Venetoclax (8 h)
scramble control
shRNA MCL-1
Conc. (µM)

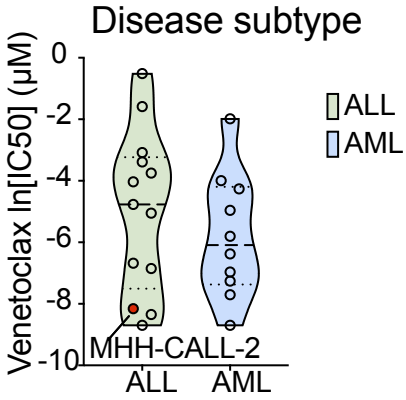
Fig. S7

A)


Cell lines
CDK9 Gene Effect (Chronos)
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
NALM-16
ALL
AML
CLL
CML
Others
ALL
AML
CLL
CML
Others

B)


Disease subtype
Dinaciclib ln[IC50] (μM)
-3
-4
-5
-6
-7
MHH-CALL-2
ALL
AML
CML
Others
ALL
AML
CML
Others


Disease subtype
Venetoclax ln[IC50] (μM)
0
-2
-4
-6
-8
-10
MHH-CALL-2
ALL
AML
ALL
AML

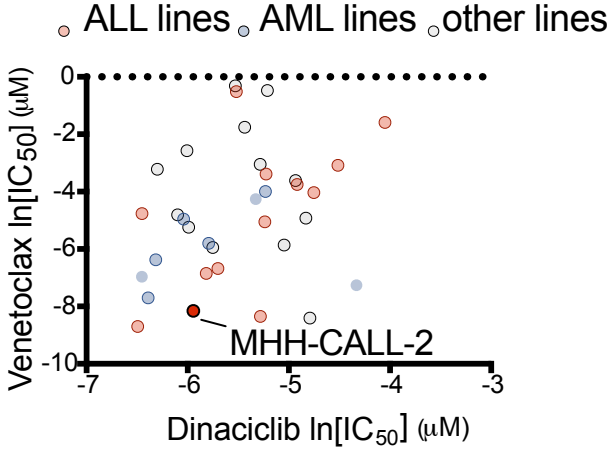
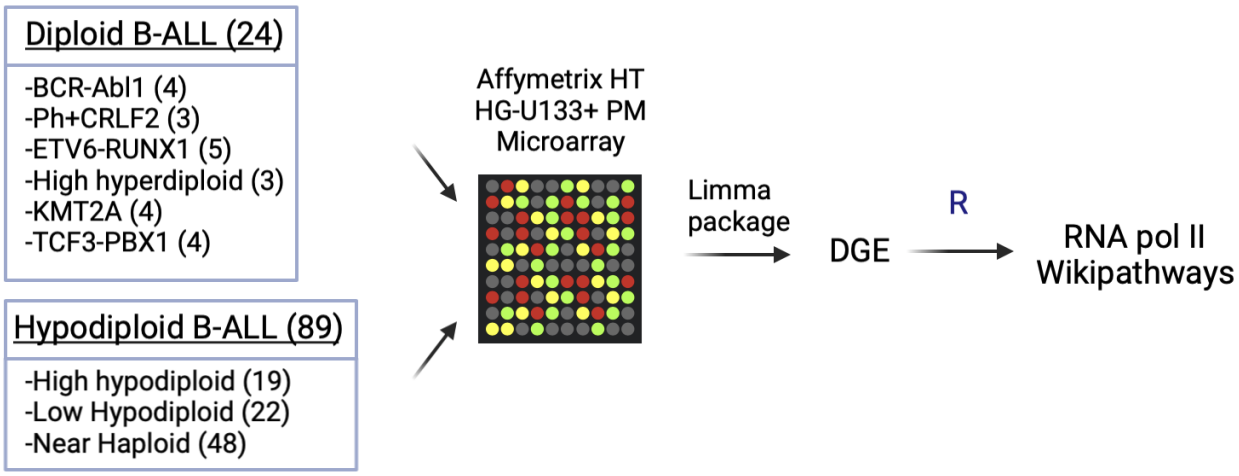

ALL lines
AML lines
other lines
Venetoclax ln[IC50] (μM)
0
-2
-4
-6
-8
-10
MHH-CALL-2
-7
-6
-5
-4
-3
Dinaciclib ln[IC50] (μM)

Fig. S8

A)



B)

WP4933

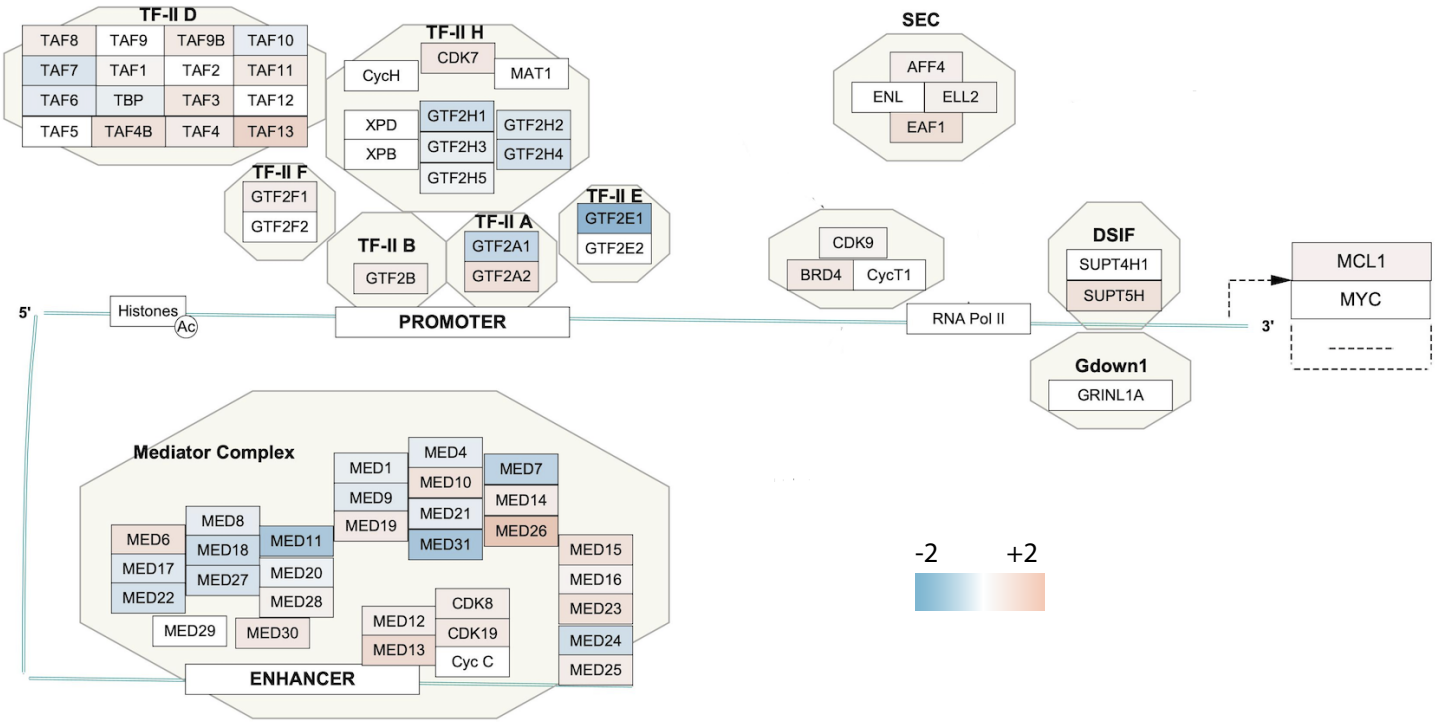


Fig. S9

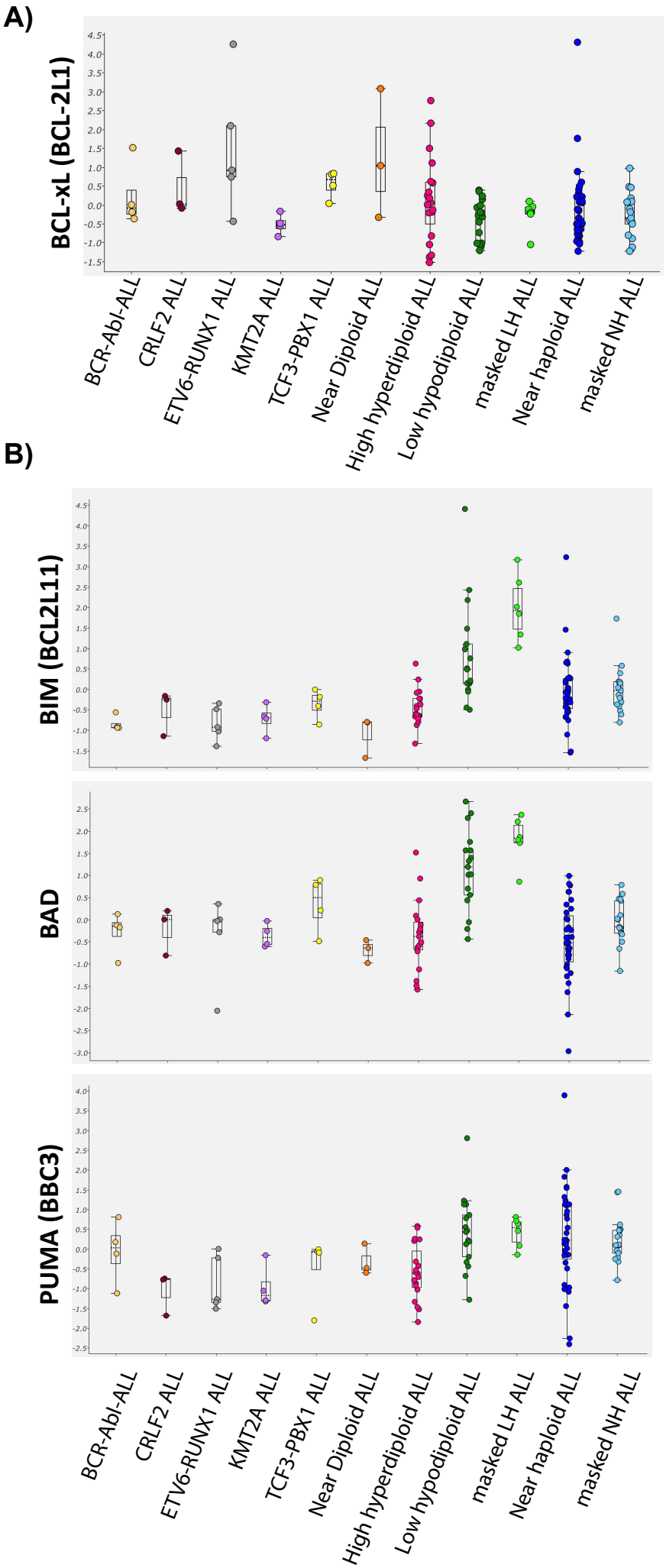

A)
BCL-xL (BCL-2L1)
B)
BIM (BCL2L11)
BAD
PUMA (BBC3)
BCR-Abl-ALL
CRLF2 ALL
ETV6-RUNX1 ALL
KMT2A ALL
TCF3-PBX1 ALL
Near Diploid ALL
High hyperdiploid ALL
Low hypodiploid ALL
masked LH ALL
Near haploid ALL
masked NH ALL

Fig. S10

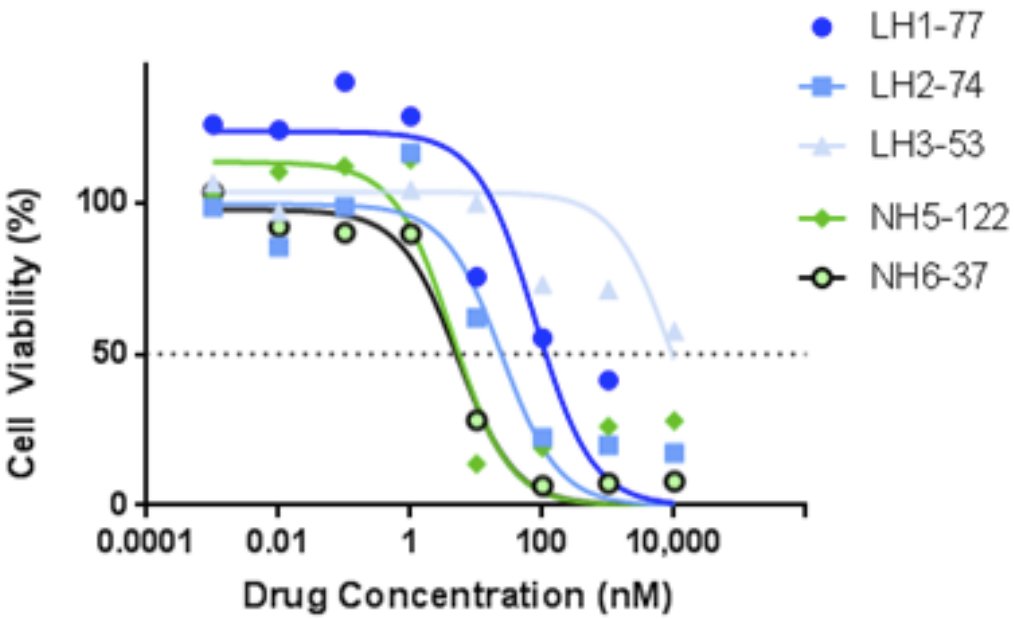
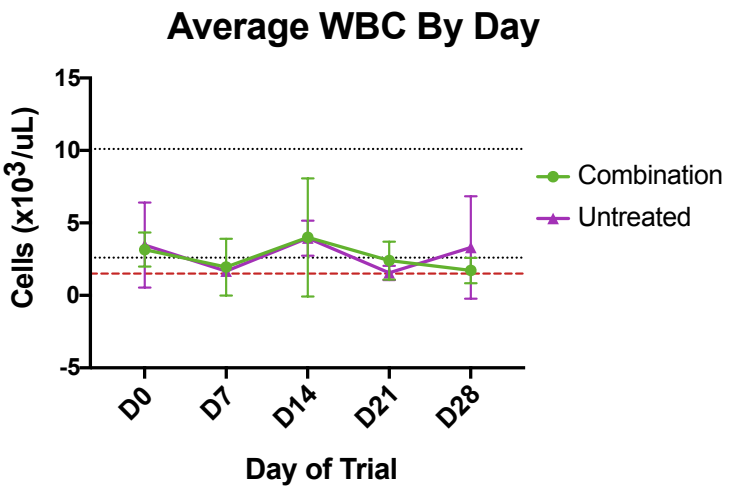
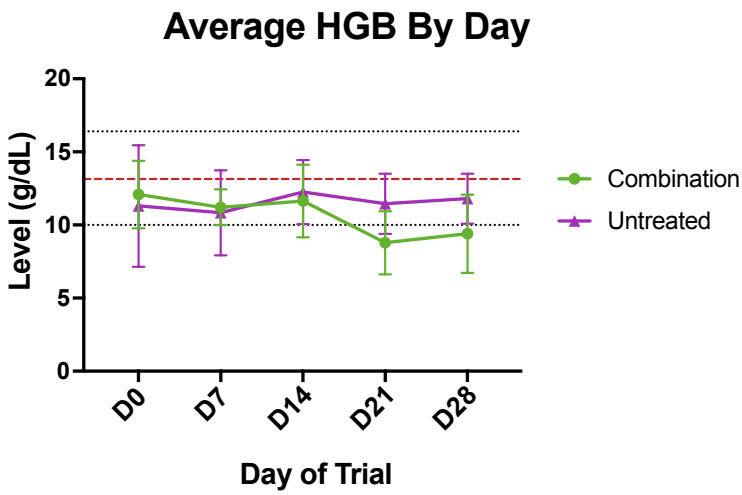
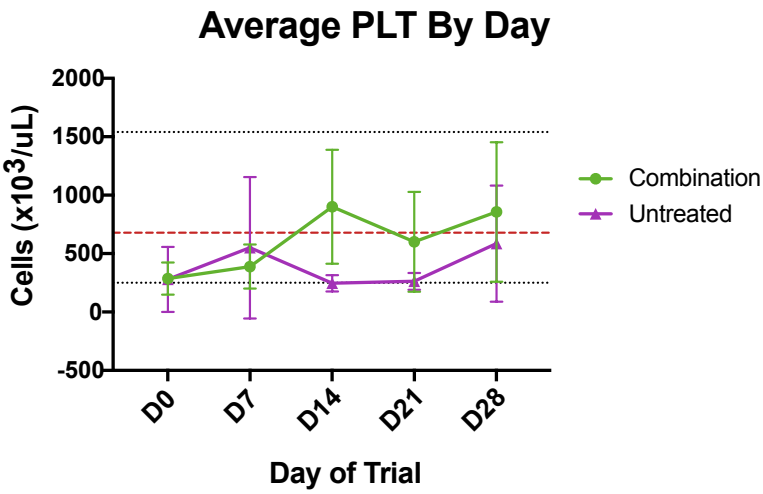
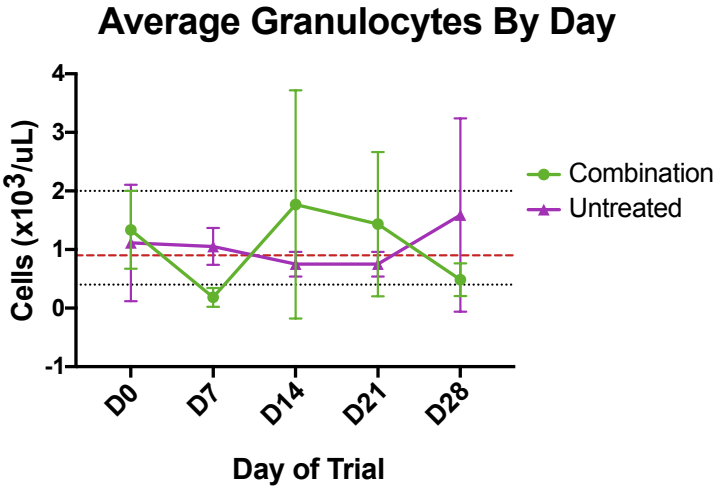

LH1-77
LH2-74
LH3-53
NH5-122
NH6-37
Cell Viability (%)
100
50
0
0.0001
0.01
1
100
10,000
Drug Concentration (nM)

Fig. S11


Average WBC By Day
Cells (x10^3/uL)
15
10
5
0
-5
D0
D7
D14
D21
D28
Day of Trial
Combination
Untreated


Average HGB By Day
Level (g/dL)
20
15
10
5
0
D0
D7
D14
D21
D28
Day of Trial
Combination
Untreated


Average PLT By Day
Cells (x10^3/uL)
2000
1500
1000
500
0
-500
D0
D7
D14
D21
D28
Day of Trial
Combination
Untreated


Average Granulocytes By Day
Cells (x10^3/uL)
4
3
2
1
0
-1
D0
D7
D14
D21
D28
Day of Trial
Combination
Untreated

Supplemental Material:

Supplementary Table 1

COMPOUND	MECHANISM OF ACTION	NALM16 %inhibition
Sepantronium Bromide (YM155)	Survivin expression inhibitor	**90**
Bortezomib	Proteosome Inhibitor	**90**
Elesclomol	Small-molecule that induces oxidative stress,	**89**
Carfilzomib	Proteosome Inhibitor	**89**
Panobinostat	HDAC Inhibitor	**88**
Givinostat	HDAC Inhibitor	85
Pralatrexate	A folate analogue inhibitor of dihydrofolate reductase (DHFR)	**84**
Delanzomib	Proteosome Inhibitor	**84**
Pracinostat	HDAC Inhibitor	83
Belinostat	HDAC Inhibitor	83
Quisinostat	HDAC inhibitor	**81**
Trichostatin A	HDAC Inhibitor	78
Mocetinostat	HDAC Inhibitor	77
Quisinostat	HDAC Inhibitor	77
Dacinostat	HDAC Inhibitor	75
Panobinostat	HDAC Inhibitor	75
Triptolide	Inhibits heat shock protein 70 (HSP70) and prevents HSP70-mediated inhibition of apoptosis	**74**
Dacinostat	HDAC inhibitor	**73**
Dinaciclib	Inhibitor of cyclin-dependent kinases CDK1, CDK2, CDK5, and CDK9	**72**
Abexinostat	HDAC Inhibitor	72
Vorinostat	HDAC Inhibitor	66
Ixazomib	Proteosome Inhibitor	**66**
Nocodazole	Antimicrotubular agent	**66**
Volasertib	PLK1 (polo-like kinase 1) protein inhibitor	**65**
Cabazitaxel	Antimicrotubular agent	**65**
Vincristine	Antimicrotubular agent	**64**
Taxol, Paclitaxel	Antimicrotubular agent	**63**
2-Methoxyestradiol	Angiogenesis inhibitor	63
Ispinesib	Inhibitor of mitotic spindle assembly	**63**
Epothilone A	Antimicrotubular agent	**63**
Docetaxel	Antimicrotubular agent	**62**
Ibrutinib	Bruton's tyrosine kinase (BTK) inhibitor	61
Cephalomannine	Antimicrotubular agent; Inhibition of mitosis	61

Supplementary Table 2

		48 hour			96 hr
MECHANISM OF ACTION	Compound	NALM-16 EC50 (nM)	BECK-1732 EC50 (nM)	MHH-CALL-2 EC50 (nM)	NALM-16 EC50 (nM)
HDAC Inhibitors					
1	Mocetinostat	100	1	100	3
2	Trichostatin A	5000	4	4000	1000
3	Vorinostat	2000	1	3000	200
4	Panobinostat	0.2	0.2	0.2	0.2
5	Dacinostat	0.2	0.2	0.4	0.2
6	Quisinostat	0.2	0.2	0,2	0,2
Antimicrotubular Agents					
7	Epothilone A	0.2	0.2	0.2	0.2
8	Vincristine	0.2	0.2	0.2	0.2
9	Taxol, Paclitaxel	0.2	0.2	0.2	0.2
10	Vinblastine	70	60	200	10
11	Cabazitaxel	0.2	0.2	0.2	0.2
12	Ispinesib	0.2	0.2	0.2	0.2
CDK Inhibitors					
13	Dinaciclib	0.2	0.2	0.2	0.2
14	Milciclib	4000	1000	4000	200
Proteosome Inhibitors					
15	Bortezomib	0.2	0.2	0.2	0.2
16	Ixazomib	100	30	200	50
17	Carfilzomib	8	0,2	10	2
Aurora Kinase Inhibitors					
18	Alisertib	>4000	500	>4000	10
19	VX-680	>4000	4000	>4000	4000
Pyrimidine Analogue Inhibitor					
20	Cytarabine	2000	2000	4000	0,2
21	Gemcitabine	0.2	0.2	0.2	0.2
HSP90 Inhibitor					
22	Geldanamycin	70	0,2	1000	0,2
23	Ganetespib	90	0,2	900	0,2
Other					
24	Sepantronium Bromide	0.2	0.2	0.2	0.2
25	Topotecan HCl	200	5	300	10
26	Pralatrexate	0,2	>4000	0,2	0,2
27	Volasertib	0,2	>4000	0,2	0,2
28	LE-SN38	10	0,2	20	0,2
29	Birinapant	4000	20	4000	400
30	Clofarabine	100	10	90	3

Supplementary Table 3

Sample ID	Sub-type	Chr #	DNA Index	Cytogenetics	*TP53*	*CDKN2A/B*	*RB*	*IKZF*	*NRAS*	*NF1*	Full annotation
LH-77	LH	36	0,833	36,X,+Y,+1,+5,+6,+8,+9,+10,+11,+14,+18,+19,+21,+22[8]/72,idemx2[1]/62,idemx2,-X,-Y,-5,-6,-8,-9,-10,-11,-14,-22[4]	mutant		deleted	*IKZF2* del			*TP53_Y163N, RB1 del, IKZF2 del, GAB2*
LH-74	LH	35	0,801	35,X+X,+1,+5,+6,+8,+10,+11,+14,+18,+19,+21,+22[11]/46,XX[18]	mutant			*IKZF2* del			*TP53_R273C, IKZF2 del*
LH-53	mLH	31/62	0.694 in 47%; 37% hyperdiploid peak	31,X,+Y,+5,+9,add(9)(p13),der(10)t(9;10)(p13;p15),+11,+14,+19,+21[6]/62,idemx2,-5,-add(9)(p13),-add(9)(p13),+der(9)t(9;13)(p13;q22)inv(9)(q13q34)x2,+10,+10,-der(10)t(9;10),-der(10)t(9;10),-11,-14,+18[5]/72,(33,X,+Y,+5,+8,+9,der(9)t(9;13)(p13;q22)inv(9)(q…	mutant	deleted		*IKZF3* del			*TP53_PinsR282, CDKN2A/B het del, IKZF3 hom del*
NH5-122	NH					deleted	deleted			deleted	*NF1 del, CDKN2A/B hom del, RB1 del*
NH6-37	NH	25	0,577	25,X,+18,+21,add(21)(p11.2)[11]/50,idemx2[3]/46,XX[7]		deleted			mutant		*NRAS_G12S, CDKN2A/B del*
NH1	NH	28								deleted	*NF1 del*
NH2	NH	27	0,55	27,X,+Y,+13,+18,+21[cp8]/34,idem,+1,+2,+3,+5,+7,+15,+16[cp6]/46,XY[9]						deleted	*NF1 del, Histone 6p22 del*
NH3	NH	26		26,X,+10,+18,+21[8]/26,idem,-10,+r(10)[3]/46,XY[7]				*IKZF3* del		deleted	*NF1, IKZF3*

Supplementary Table 4

CD45 in Peripheral Blood

Vehicle	D0	D7	D14	D21	D28
NH1-821-5V	0,49	0,17	0,11	1,38	Died
NH2-839-2V	0,84	3,35	2	10	14,32
NH3-849-3V	0,84	3,35	2	10	18,75
NH3-851-2D	2,31	Died			
NH1-822-1C	0,23	Died			

Venetoclax	D0	D7	D14	D21	D28
NH1-821-1A	20,75	N/A	0,11	0,02	0,02
NH1-827-2A	0,43	0,33	0,06	0,33	0
NH2-841-3A	7,35	0,17	0	0	0
NH2-844-1A	0,59	0	0	0	0
NH3-847-4A	1,17	0,14	0,17	0,7	1,81
NH1-850-1A	0,45	0	0,02	0,21	0,17

Dinaciclib	D0	D7	D14	D21	D28
NH1-821-2D	5,51	0,56	2,18	2,82	1,36
NH1-826-1D	3,26	0,26	0,39	0,85	0,86
NH2-837-2D	2,85	3,99	2,94	19,92	54,23
NH2-841-1D	0,29	4,39	0,75	0,57	0,16
NH2-842-2D	0,13	13,21	0,55	0,46	3,93
NH3-848-2D	15,25	0,49	2,13	3,36	Died

Combo	D0	D7	D14	D21	D28
NH1-825-1C	1,23	0,7	0,24	Died	
NH2-838-1C	0,35	0	0	0	0,48
NH2-841-2C	1,17	0,23	0,07	0	0
NH2-843-1C	3	0	0	0	0
NH3-851-3C	1,03	0	0	0,32	0,29
NH3-851-4C	4,6	0	0,17	2,61	0

	Median %hCD45 Over Trial in Peripheral Blood				
	D0	D7	D14	D21	D28
Vehicle	0,84	3,35	2,00	10,00	16,54
Venetoclax	0,88	0,14	0,04	0,12	0,01
Dinaciclib	3,06	2,28	1,44	1,84	1,36
Combination	1,20	0,00	0,04	0,00	0,00

Supplementary Materials and Methods

Cell Lines: CCRF- CEM and Reh (ATCC), NALM-16 and RCH-ACV (DSMZ (Leibniz, GE)). MHH-CALL-2 was obtained from Dr. Mullighan (SJCRH).

Inhibitors: Abemaciclib (S7158), Bortezomib (S1013), Dinaciclib (S2768), Flavopiridol (S1230), Palbociclib (S1116), Panobinostat (S1030), Quisinostat (S1096), Ribociclib (S7440), Roscovitine (S1153) and SNS-032 (S1145) were from SelleckChem. NVP-2 (1263373-43-8 from MedChem Express). Venetoclax (ABT-199) was kindly provided by ABBVIE.

Intracellular Antibodies: Actin-HRP (5125), CDK1 (91165;), CDK2 (2546S;), CDK9 (2316T), Cyclin B1 (12231S), Cyclin E1 (4129T), Cyclin E2 (4132T), Cleaved Caspase-3 (9664L), MYC (5605S) and RB1 (9309S) were from Cell Signaling. Bcl-2 (ab32124), Bcl-XL (ab32370), Cleaved-PARP (ab110315), Cyclin A1/2 (ab185619), MCL-1 (ab32087), RNA polymerase II (ab193468). p16 (BioLegend; 675602), p53 (Bio-Rad; MCA1701), HRP-Anti-Mouse 2° (Dako; P0447), HRP-Anti-Rabbit 2° (Dako; P0448).

Surface Marker Antibodies (all preconjugated): CD10 (312203; PE), CD19 (302212; APC), Human CD45 (B368517; APC/Fire 750), Mouse CD45 (103133; BV421) were from BioLegend.

Overexpression plasmids: 1) empty vector: pLV[Exp]-EGFP/Puro-EF1A>ORF_stuffer (VB010000-9389rbj) and 2) MCL-1 overexpression plasmid: pLV[Exp]-EGFP:T2A:Puro EF1A>hMCL1[NM_021960.5] (VB900003-6631wfp) were from VectorBuilder.

shRNA plasmids: 1) plasmid targeting MCL-1: pLV[shRNA]-EGFP:T2A:Puro-U6>hMCL1 [shRNA#1] (VB900051-0516gwp), 2) scrambled control [shRNA]-EGFP/Puro-U6>Scramble_ shRNA (VB010000-0009mxc) (from VectorBuilder).

Supplementary legends

Supplementary Table 1: Results of the initial HTS. A summary of compounds that demonstrated inhibitory efficacy greater than 60% in NALM-16 cells at 48 hours identified by the HTS of the SelleckChem Bioactive Compound Library.

Supplementary Table 2: Secondary drug screen in all NH pre-B ALL cell lines. Summary of EC50s of the top 30 compounds identified in the initial HTS. Compounds were tested in NALM-16, BECK-1732 and MHH-CALL-2 at 48 and 96 h. Those with IC50 at or below the limit of detection of 0.2 nM are shown in red.

Supplementary Table 3: Molecular and cytogenetical features of patient samples. Description of molecular and cytogenetic features in the 3 LH and 5 NH samples used in this study.

Supplementary Table 4: Leukemic burden in mice throughout the trial. % hCD45 in peripheral blood collected weekly from individual mice throughout the trial. Bottom table indicates the median expression per treatment arm.

Figure S1: Dinaciclib is efficacious across molecularly distinct NH pre-B ALL cell lines. **A)** Three cytogenetically distinct hypodiploid B-ALL cell lines used throughout this manuscript are described here. Western blots measuring RB1, p16, p53 and c-MYC in NALM-16, BECK-1732 and MHH-CALL-2 cells are shown **B)** Schema of secondary drug screen in NH pre-B ALL cell lines. Cells were treated with top 30 compounds in a 10-fold serial dilution with doses up to 10 μM at 48 and 96 hours **C)** Growth inhibition measured at 24 and 48h using a luminescent cell viability assay in all three hypodiploid ALL cells treated with Dinaciclib are shown. 10-fold serial dilutions were used with concentrations up to 10 μM.

Figure S2: CDK expression and sensitivity to CDK inhibitors in hypodiploid B-ALL cells. **A)** Synergy measured using an isobologram model. BECK-1732 and MHH-CALL-2 cells were treated with a combination of dinaciclib and venetoclax at two-fold serial dilution doses ranging from 8-500 nM for 24h using a luminescent cell viability assay. **B)** Growth inhibition measured at 24h using a luminescent cell viability assay in BECK-1732 cells treated with a combination of Dinaciclib and venetoclax at two-fold serial dilution doses ranging from 8-500 nM. **C)** Synergy measured using an isobologram model. NALM-16, BECK-1732 and MHH-CALL-2 cells were treated with a combination of bortezomib and venetoclax at two-fold serial dilution doses ranging from 8-500 nM for 24h. **C)** Growth inhibition measured at 48h using a luminescent cell viability assay in three hypodiploid cell lines treated with CDK4/6 inhibitors, Palbociclib, Ribociclib and Abemaciclib.

Figure S3: Time course of Dinaciclib and Venetoclax -induced protein modulation and cell death. A) Induction of apoptosis in NALM-16, BECK-1732 and MHH-CALL-2 cells, measured using a caspase activity assay following 24h treatment with dinaciclib. **B)** Western blot measuring cleaved PARP and cleaved caspase-3 in NALM-16 cells treated with dinaciclib for 6,18 and 24h. **C)** Western blot data shows levels of CDK1, 2, 9; RNA polymerase II phosphorylation on Ser 2, and prosurvival proteins BCL-2, and MCL-1 in NALM-16 cells treated with dinaciclib for 6, and 24h.

Figure S4: Apoptosis induction by NVP-2 in hypodiploid lines. B) NALM-16, BECK-1732 and MHH-CALL-2 cells were treated with NVP-2, for 6h and 24h. Levels of CDK9, prosurvival proteins MCL-1 and BCL-2, and the apoptosis marker cleaved PARP are shown via WB.

Figure S5: Enrichment of lentivirally transduced viable cells using magnetic levitation. Cells were lentivirally transduced with scramble or MCL-1 expressing plasmids containing puromycin-selection gene. After 24h, cells were subjected to puromycin to select for transduced cells. To remove the excess of dead untransduced cells we used a Levicell system (LevitasBio). As per the manufacturer's protocol, cells are resuspended in a magnetic levitation buffer, loaded on a cartridge and introduced in the LeviCell sorter. Upon subjected to a magnetic field viable cells levitate (5-20 min) above dead cells, the top fraction is then sorted (5 min). Output cells showed >95% viability and were plated and subjected to Venetoclax and analyzed by WB.

Figure S6: Apoptosis induction by dinaciclib, venetoclax and the combination in isogenic lines. A) NALM-16 cells were transduced with empty vector (control) or MCL-1 overexpression plasmid plasmid. Each isogenic cell was exposed to dinaciclib, venetoclax or the combination for 2 and 8h. Protein levels were measured by WB. **B)** NALM-16 cells were transduced with a plasmid containing either empty vector or shRNA against MCL1. Upon selection of transduced cells and validated for MCL-1 silencing, each isogenic cell line was subjected to increasing concentrations of venetoclax for 8h. Levels of MCL-1, BCL-2, cleaved-Caspase and Actin were measured.

Figure S7: Hypodiploid ALL cell lines are genetically dependent on CDK9 and pharmacologically sensitive to dinaciclib and venetoclax. A) Violin plot representing genetic dependency scores (CRISPR DepMap 22Q2 Public dataset) of ALL and other blood cancer cell lines; highlighted the hypodiploid line NALM-16 **B)** Pharmacologic sensitivity (Sanger GDSC2 dataset) of blood cancer cell lines to dinaciclib and venetoclax; data expressed as $\ln(IC_{50})$; highlighted MHH-CALL-2 cell line. **C)** Dual pharmacologic sensitivity of MHH-CALL-2 cell line to dinaciclib and venetoclax; data expressed as $\ln(IC_{50})$; highlighted MHH-CALL-2 cell line.

Figure S8: Transcript level of the CDK9/RNApol/Mediator pathway in hypodiploid patient samples. A) Illustration of a 124 patients microarray RNA database[1] (GSE27237) comparing 89 (LH- and NH-) hypodiploid B-ALL versus 24 diploid B-ALL. **B)** Gene expression levels from the microarray were analyzed and plotted against a Wikipathway (WP4933) representing the RNA pol II transcription complex as previously reported[2,3]. Red represents over expression, blue downregulation.

Figure S9: Prosurvival and proapoptotic levels in B-ALL leukemia patients. Comparison of BCL-xL (A) and BIM, BAD and PUMA (B) gene expression in hypodiploid B-ALL sutbypes (LH, mLH, NH and mNH) vs. diploid B-ALL of different genotypes obtained from microarray data (GSE23237).

Figure S10: Primary samples validation. A) Five hypodiploid ALL xenografted patient samples were thawed and treated *ex vivo* with increasing concentrations of dinaciclib for 24h. Growth inhibition was measured using a luminescent cell viability assay.

Figure S11: Minimal hematotoxicity seen at end of 28-days of treatment with combination therapy. Complete blood counts including total white blood cell, hemoglobin, platelet and granulocyte counts were measured weekly starting at day 0 prior to treatment randomization in mice. Untreated and combination therapy arms are shown. Black dashed lines represent normal range for healthy mice per HemaTrue guidelines. Red dashed line represents median normal for 10 non-engrafted, untreated NSG mice.