Supplemental Materials and Methods

Pathological analysis and immunohistochemistry (IHC) staining

Tissue samples harvested from PDX mice were fixed in 4% paraformaldehyde. The fixed tissues were embedded in paraffin, cut into slices, deparaffinized, and stained with hematoxylin and eosin (H&E) or optimal concentrations of mono- or poly-clonal antibodies against human CD3, CD4, CD8, CD7, CD26. For IHC, in brief, after deparaffinization, sections were soaked in target retrieval-buffered saline (Tris, pH 6.1) and soaked in a 3% H_2O_2 methanol solution. Sections were blocked with 5% BSA in Tris-buffered saline and incubated with primary antibodies for more than one hour under intermittent microwave irradiation. After washing with Tris-buffered saline containing 1% Tween 20 (TBS-T), specimens were incubated with peroxidase-conjugated (Envision System) or alkaline phosphatase-conjugated secondary antibodies (Simple Stain System) for more than 1 hour under intermittent microwave irradiation. After washing with TBS-T, sections were immersed in 3,3'-diaminobenzidine (DAB) (Vector) and washed with running water. The stained slides were evaluated by a pathologist using a light microscope.

Flow cytometry

Primary tumor cells harvested from the spleens of PDX mice were washed in PBS and resuspended in cell staining buffer (Biolegend). $1x10^5$ cells were incubated with Fc receptor blocking solution (Biolegend) for 15 minutes at 4℃. The cells were then stained with cocktails containing combinations of fluorochrome conjugated monoclonal antibodies against cell surface markers CD3, CD4, CD8, CD7, CD26 (Biolegend) in the dark for 30 minutes at 4℃. After staining, the cells were washed with PBS containing 0.2% FBS and resuspended in cell staining buffer. A BD FACS Aria 3 Cell Sorter (BD Immunocytometry Systems) was used to acquire data that were the analyzed by FlowJo software (Tree Star).

Western blotting

$1x10^6$ H9 cells were cultured at 37°C for 2 hours before stimulation and drug treatment. The cells were then stimulated with α-CD3 (1 μg/mL) and α-CD28 (0.5 μg/mL) antibody for 15

minutes before adding BKM120, at varying concentrations. After 30 minutes of drug treatment, the cells were harvested and lysed with a buffer containing 10% NP40, 10% TNE (50 mM Tris, 150 mM NaCl, 0.5 mM EDTA), dithiothreitol, cocktail protease and phosphatase inhibitors (Thermo Fisher Scientific) to generate lysates. A total amount of 60 μg protein lysates were separated using NuPAGE Novex Bis-Tris gels (Invitrogen) and then transferred to a nitrocellulose membrane using an iBlot transfer apparatus (Invitrogen). Membranes were probed with primary antibodies (Cell Signaling Technology) overnight at 4°C. Anti-pAkt (Ser473), anti-Akt, anti-p4EBP1 (Thr37/46), anti-4EBP1, anti-GAPDH were 1:1000 diluted. Protein-antibody complexes were detected using anti-rabbit IRDye 800 or anti-mouse IRDye 700 molecular probes (LI-COR Biosciences) and visualized with a LI-COR Odyssey infrared imaging system (LI-COR Biosciences). Immunoblot data were analyzed using the Odyssey application software v3.0.30.

TaqMan Gene Expression Assay

Total cellular RNA was extracted using the NucleoSpin RNA/Protein kit (Macherey-Nagel) according to the manufacturer's instruction. Complementary DNA (cDNA) for each sample was produced via reverse transcription using 2 μg of total RNA using the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems). Quantitative RealTime-PCR was performed using the TaqMan Gene Expression Assay (Applied Biosystems) with transcript-specific TaqMan primers (PIK3CA, Hs00907957_m1; PIK3CB, Hs00927728_m1; PIK3CD, Hs00192399_m1; PIK3CG, Hs00932390_m1) and endogenous control (GAPDH, Hs02786624_g1). The assays were performed according to the manufacturer's guidelines.

Figure S1

a

Pathway	Drug
Akt	GSK690693
	MK-2206
	CCT128930
Akt/PI3K	Perifosine
ALK	SB 431542
	NVP-TAE684
ALK/c-Met	PF-2341066
ATM	KU-55933
Aurora B	AZD1152-HQPA
Aurora Kinase	VX-680
Bcl-2/Bcl-xL	ABT-263
BCR/ABL/Src	Dasatinib
BMP	LDN193189
B-Raf	PLX-4032
	PLX-4720
BTK	Ibrutinib
CDK1/2/4	Flavopiridol
CDK2/7/9	SNS-032
CDK4/6	PD0332991
Chemo	Cisplatin
	Bendabustine
	Adriamycin (Doxorubicin)
	Cytarabine
	Paclitaxel
	Gemcitabine hcl
CHK1	LY2603618
CHK1/2	AZD-7762
c-Kit/VEGFR2	OSI-930
c-Met	SU11274
	JNJ 38877605
COX-2	OSU-03012
c-Src	AZD0530
CYP17	Abiraterone
DNA-PK/PI3K/mTOR	PI-103
Farnesyltransferase	Tipifarnib
FLT3	Tandutinib
	AC-220
Gamma Secretase (GS_	RO4929097
GSK-3	SB 216763
	CHIR-99021
HDAC	Vorinostat
	Trichostatin A
	LBH589
	Romidepsin
Hedgehog	Cyclopamine
	GDC-0449
Hsp90	17-AAG
	BIIB021

Pathway	Drug
JAK	Ruxolitinib
JAK2	SAR-302503
JNK1/2/3	SP600125
KSP	SB 743921
MDM2	Nutlin-3
MEK1/2	CI-1040
	AZD6244
	PD0325901
mTORC	PP242
	Everolimus
	KU-0063794
p53	JNJ 26854165
pan-PI3K	BKM120
	LY294002
	PIK-90
	XL147
PI3K p110a	GDC-0941
	A66
	PIK-75 HCL
PI3K p110β	TGX-221
PARP1/2	ABT-888
	AZD2281
PI3K/mTOR1/2	XL765
	BEZ-235 #1
	BEZ-235 #2
Pim	SGI-1776
PKCK2	CX-4945
PKCβ	Enzastaurin
PLK1	BI 6727
	BI 2536
Proteasome	MG132
	Bortezomib
ROCK	Fasudil hcl
	GSK429286A
RTK	Imatinib
	MP-470
	Sunitinib
Smo	LDE225
STAT3	S31-201
Survivin	YM155
Syk	R935788
Tankyrase 1/2	XAV-939
TGF-BR	LY2157299
TNF-a	Pomalidomide
Topoisomerase II	Etoposide
Wee1	MK-1775

b

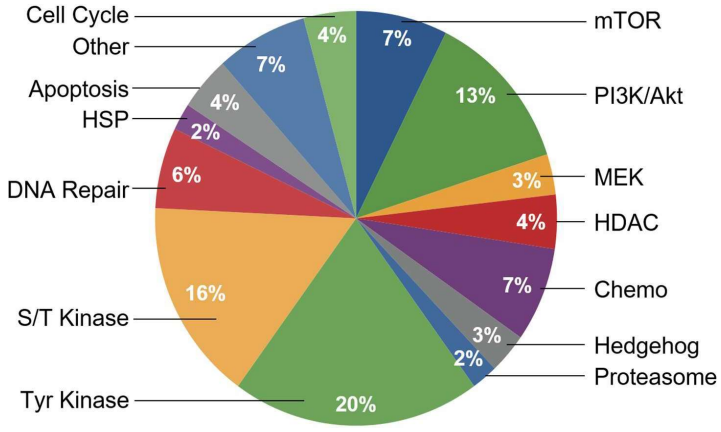
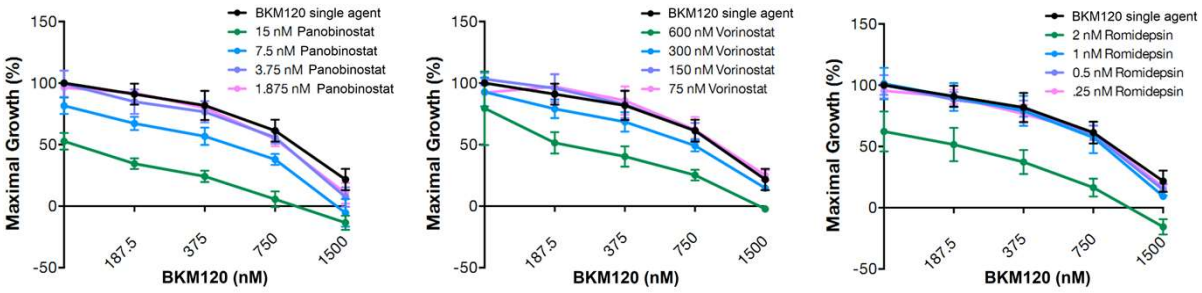


Figure S1. The agents and the targeted pathways in the drug library. List of the drug library of 94 compounds used in our high-throughput screen and its targeted molecular pathways relevant to cancer biology.

Figure S2

a



b

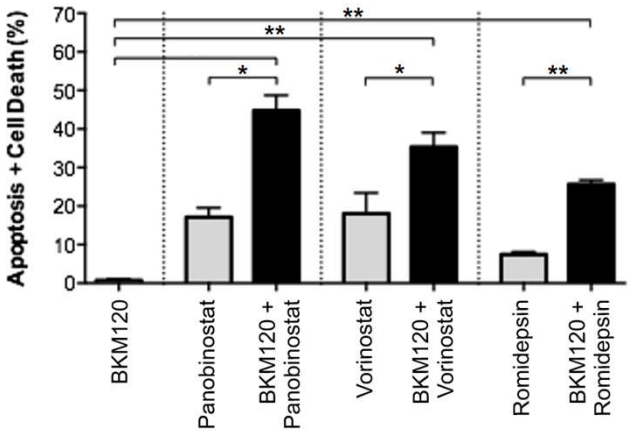


Figure S2. BKM120 (1500 nM) potentiates the (**a**) anti-proliferation and (**b**) apoptosis induction activities of three HDAC inhibitors: Panobinostat (15 nM), vorinostat (600 nM), and romidepsin (2 nM) in Hut78 cells. Data are presented as mean+/-SEM and analyzed by an unpaired *t* test with two-tailed *P* values (**P*<0.05, ***P*<0.01).

Figure S3

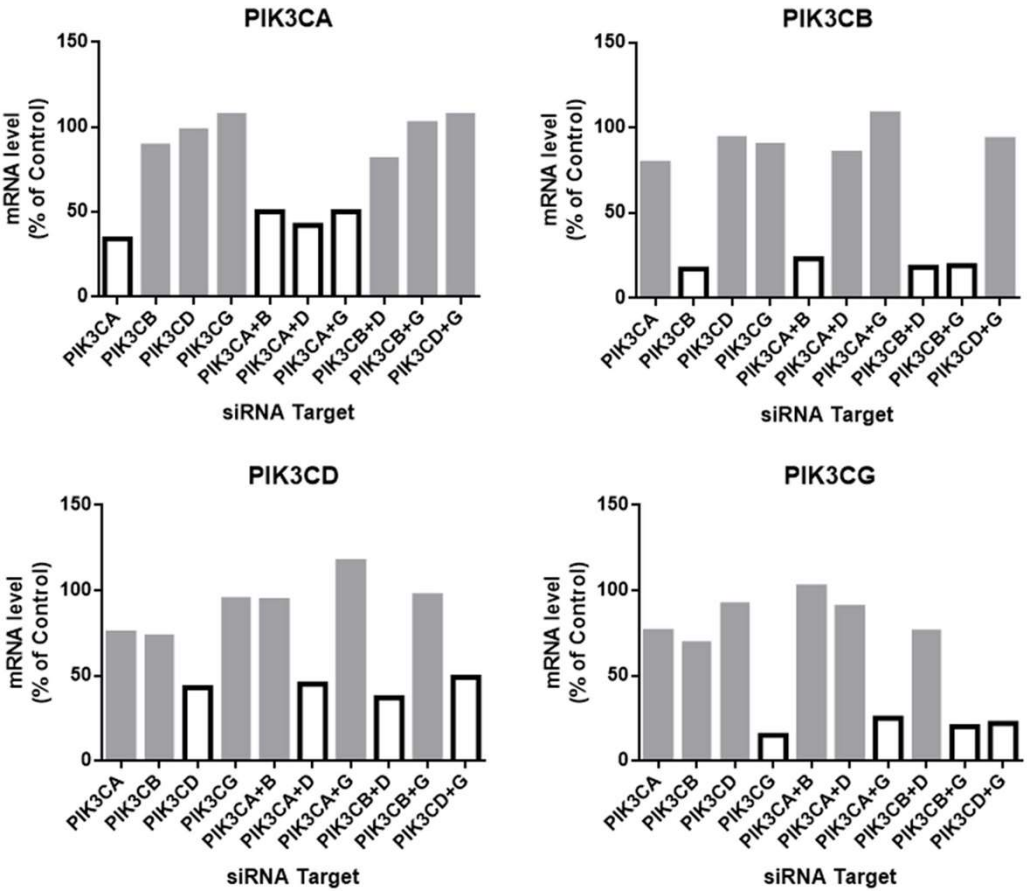


Figure S3. The specificity of isoform-specific siRNA and their knock-down efficiency in CTCL cell line. The mRNA levels of each siRNAs inhibited by its corresponding isoform alone or combination pair (open bar) and other isoforms or combination pair (grey bar).

Figure S4

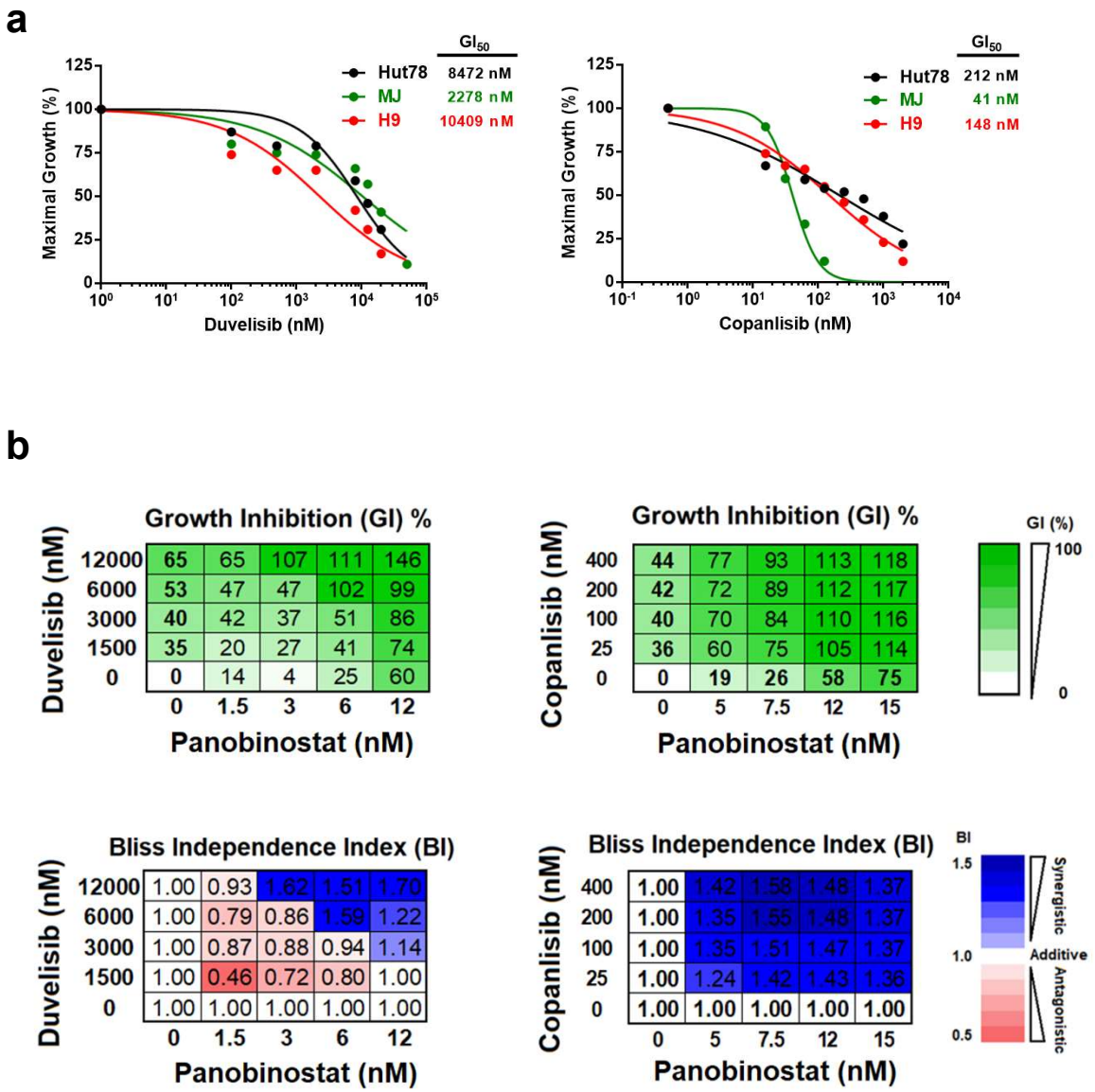


Figure S4. Growth inhibition of duvelisib and copanlisib in CTCL cell lines. (**a**) Growth inhibition of duvelisib and copanlisib in Hut78, MJ and H9 cell lines. (**b**) Growth inhibition and BI index of duvelisib and copanlisib in combination with panobinostat in Hut78 cell line.

Table S1 Patient characteristics

Patient	PDX	Diagnosis	Stage	Prior treatment	Specimen collection
Patient-1	PRS-1	Mycosis fungoides	Stage IIB	chlorambucil	Lymph node FNA
Patient-2	PRS-2	Sezary syndrome	Stage IVA	none	Blood
Patient-3	PRS-3	Sezary syndrome	Stage IVB	none	Blood

Table S2 Somatic mutations of genes in PRS-1, PRS-2, and PRS-3 identified in MF/SS patients.

PRS-1	Variant_Classification	Single Nucleotide Variation (SNV)-encoded variations	Alteration_Frequency
ALPK2	Silent	p.G1696=	0.552
CACNA1H	Missense_Mutation	p.E45K	0.625
CNTRL	Missense_Mutation	p.S21C	0.333
CPQ	Silent	p.G249=	0.435
DENND1A	Missense_Mutation	p.S554F	0.497
DMXL1	Missense_Mutation	p.I72F	0.800
FAT4	Missense_Mutation	p.S4865F	0.440
HHIPL2	Silent	p.Y117=	0.516
JAKMIP3	Missense_Mutation	p.R356C	0.536
KCNT2	Missense_Mutation	p.D396N	0.333
LAMC3	Silent	p.D615=	0.429
MPDZ	Missense_Mutation	p.P1565L	0.313
NPHS1	Missense_Mutation	p.G269E	0.986
NRAS	Missense_Mutation	p.G13D	0.500
PCDH15	Silent	p.P1141=	0.463
PCDHB10	Missense_Mutation	p.A515T	0.309
PCLO	Splice_Region		0.306
PLCG1	Missense_Mutation	p.R48W	0.424
RARA	Missense_Mutation	p.R394Q	0.200
ROS1	Silent	p.L1947=	0.531
SCN5A	Silent	p.Y1409=	0.412
TP53BP1	Missense_Mutation	p.R1463H	0.371
UNC80	Missense_Mutation	p.S73F	0.632

Table S2 Somatic mutations of genes in PRS-1, PRS-2, and PRS-3 identified in MF/SS patients. (Continue)

PRS-2	Variant_Classification	Single Nucleotide Variation (SNV)-encoded variations	Alteration_Frequency
CTXN3	Missense_Mutation	p.L44F	0.444
DNER	Missense_Mutation	p.S638F	0.379
DSG1	Missense_Mutation	p.G817V	0.386
EDN3	Silent	p.T98=	0.481
EPG5	Missense_Mutation	p.V790L	0.667
FTMT	Missense_Mutation	p.G209S	0.462
KL	Missense_Mutation	p.T686M	0.517
KMT2D	Silent	p.E1904=	0.346
L3MBTL4	Missense_Mutation	p.P44L	0.583
LRRN4CL	Missense_Mutation	p.P178S	0.374
PRDM16	Splice_Region		0.425
PRMT8	Missense_Mutation	p.V339I	0.380
ROBO1	Missense_Mutation	p.S836F	0.273
SFTPA2	Silent	p.V164=	0.350
SPHKAP	Missense_Mutation	p.L1037P	0.341
STAB1	Missense_Mutation	p.P538S	0.416
STAT5A	Missense_Mutation	p.A497V	0.021
STK19	Missense_Mutation	p.T183I	0.338
TP53	Splice_Region		0.976
TTBK1	Missense_Mutation	p.R407Q	0.372
ZDBF2	Missense_Mutation	p.S1787F	0.429

Table S2 Somatic mutations of genes in PRS-1, PRS-2, and PRS-3 identified in MF/SS patients. (Continue)

PRS-3	Variant_Classification	Single Nucleotide Variation (SNV)-encoded variations	Alteration_Frequency
ARHGEF17	Missense_Mutation	p.P713S	0.366
BNC2	Missense_Mutation	p.R444H, p.R391H, p.R486H	0.335
BRCA2	Missense_Mutation	p.D420N	0.438
CD3E	Missense_Mutation	p.S39C	0.426
FAT3	Missense_Mutation	p.L783F	0.524
FAT4	Missense_Mutation	p.V1670I, p.V1670I, p.V1670I	0.461
HMCN1	Missense_Mutation	p.S3257T	0.501
PXDNL	Missense_Mutation	p.A863V	0.327
RARA	Missense_Mutation	p.R179Q, p.R271Q, p.R276Q, p.R276Q	0.119
TACC2	Missense_Mutation	p.G1422R, p.G1422R, p.G1422R	0.700
ZNF608	Missense_Mutation	p.M1306T	0.304