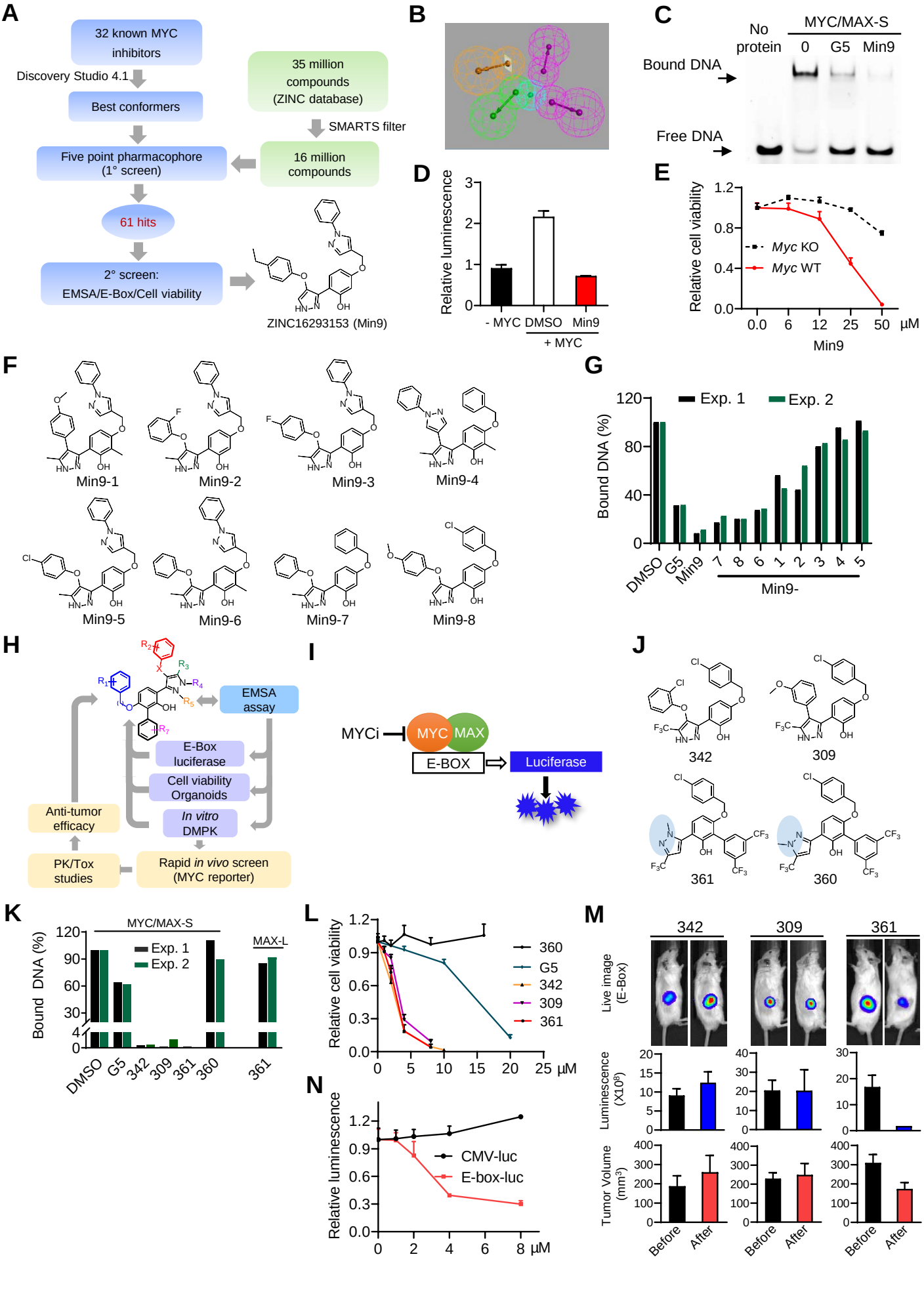

A
32 known MYC inhibitors
Discovery Studio 4.1
Best conformers
Five point pharmacophore (1° screen)
61 hits
2° screen: EMSA/E-Box/Cell viability
35 million compounds (ZINC database)
SMARTS filter
16 million compounds
ZINC16293153 (Min9)
B
C
No protein
MYC/MAX-S
0
G5
Min9
Bound DNA
Free DNA
D
Relative luminescence
- MYC
DMSO
Min9
+ MYC
E
Relative cell viability
Myc KO
Myc WT
Min9
μM
F
Min9-1
Min9-2
Min9-3
Min9-4
Min9-5
Min9-6
Min9-7
Min9-8
G
Exp. 1
Exp. 2
Bound DNA (%)
DMSO
G5
Min9
Min9-
H
EMSA assay
E-Box luciferase
Cell viability Organoids
In vitro DMPK
Anti-tumor efficacy
PK/Tox studies
Rapid in vivo screen (MYC reporter)
I
MYCi
MYC
MAX
E-BOX
Luciferase
J
342
309
361
360
K
MYC/MAX-S
MAX-L
Exp. 1
Exp. 2
Bound DNA (%)
DMSO
G5
342
309
361
360
361
L
Relative cell viability
360
G5
342
309
361
μM
N
Relative luminescence
CMV-luc
E-box-luc
μM
M
342
309
361
Live image (E-Box)
Luminescence (X10⁸)
Tumor Volume (mm³)
Before
After

Figure S1. MYC Inhibitor Screening Strategy and Lead Identification, Related to Figure 1

(A) Schematic for the approach used to identify MYC inhibitors. A pharmacophore model built from 32 compounds (reported direct MYC inhibitors and 3 decoys) was applied to screen 16 million compounds from the ZINC library. The hits identified in *in silico* screen were further evaluated with secondary screening assays.

(B) The pharmacophore model created with 5 point pharmacophoric features: one aromatic hydrophobic (ArHy), two hydrogen bond donors (HBD), one hydrogen bond acceptor (HBA) and one hydrophobic feature.

(C) EMSA for Min9 and positive control 10074-G5 (G5) at 200 μM to examine disruption of MYC/MAX binding to DNA.

(D) Min9 (25 μM) was tested for its inhibition of MYC transcriptional activity in E-box luciferase reporter assay with 293T cells after 24 hr treatment.

(E) Dose response of Min 9 anti-proliferation activity in TGR.1 (wild-type *Myc*) and HO15.19 (*Myc* knock out) cells after 7 days of treatment.

(F) Structures of Min9 analogs (Min9-1 to 8).

(G) EMSA for Min9 analogs at 200 μM. Two independent experiments are shown in the graph.

(H) Schematic for lead compound optimization strategy.

(I) Schematic for the MYC responsive reporter cell line generated from MycCaP cells, which express MYC from a probasin/androgen response element driven transgene. An E-box-luciferase reporter was introduced into the cells to monitor MYC transcriptional activity *in vitro* and *in vivo*.

(J) Structures of three representative compounds in the rapid *in vivo* screening (342, 309 and 361) and one close inactive analog (360) of 361.

(K) EMSA for the representative compounds in (J) at 100 μM. MAX-L homodimer binding to DNA was tested with the treatment of 361 (100 μM). Two independent experiments are shown in the graph.

(L) Anti-proliferation activity of compounds in (J) and positive control G5 on MycCaP cells after 48h treatment.

(M) Mice bearing established MycCaP E-box-luciferase allografts (n = 4, from 2 mice) treated with 342 (100 mg/kg), 309 (100 mg/kg) or 361 (70 mg/kg) twice daily for 2 to 3 days. Graphs show the quantification of E-box bioluminescent signal by live imaging and tumor volume by caliper measurement, respectively.

(N) Dose response effect of 361 on MycCaP cells stably expressing the E-box luciferase reporter (E-box-luc) or a CMV promoter-luciferase reporter (CMV-luc). Cells were treated with the indicated doses of 361 for 4 hr and luciferase activity was determined.

Error bars represent mean ± SEM, n= 3 to 4 replicates. Data are representative of two to three independent experiments with similar results for (C, D, E, L and N).

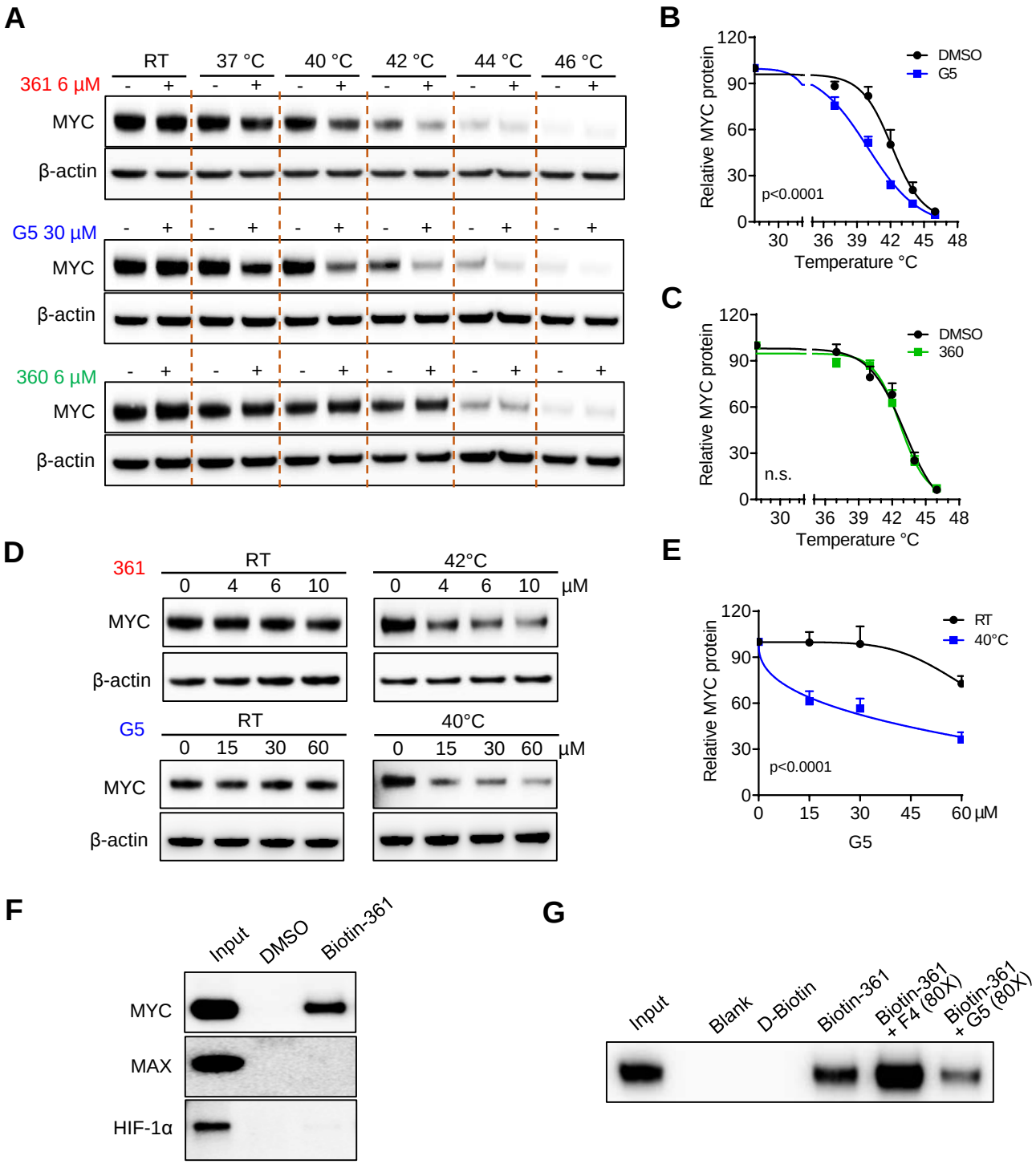

A
RT
37 °C
40 °C
42 °C
44 °C
46 °C
361 6 μM
MYC
β-actin
G5 30 μM
360 6 μM
B
Relative MYC protein
DMSO
G5
p<0.0001
Temperature °C
C
360
n.s.
D
361
G5
μM
E
RT
40°C
F
Input
DMSO
Biotin-361
MAX
HIF-1α
G
Blank
D-Biotin
Biotin-361 + F4 (80X)
Biotin-361 + G5 (80X)

Figure S2. MYC Inhibitor Lead Identification, Related to Figure 1

(A) Representative western blots for MYC and β-actin from CETSA in PC3 cells treated with 361, G5 or 360 for 30 min.

(B and C) Melt curves of MYC protein in CETSA in PC3 cells with or without the treatment of compound G5 (30 μM) (B) or 360 (6 μM) (C).

(D) Representative western blots for MYC and β-actin from isothermal CETSA analysis in 361 or G5 treated PC3 cells for 30 min.

(E) G5 in CETSA under isothermal condition. Graph shows the quantification of MYC protein at room temperature (RT, 25°C) or 40°C in PC3 cells treated with various doses of G5 for 30 min.

(F) MAX and HIF-1α were assessed by western blot after Biotin-361 (10 μM) pulldown from PC3 cell lysates.

(G) Biotin-361 (5 μM) binding to MYC was assessed in PC3 cell lysates with or without pre-treatment of 10058-F4 (80X) or G5(80X).

Error bars represent mean ± SEM, n = 3 independent experiments for (A-E), and analyzed by two-way ANOVA in Prism. Data are representative of two to three independent experiments with similar results for (F and G).

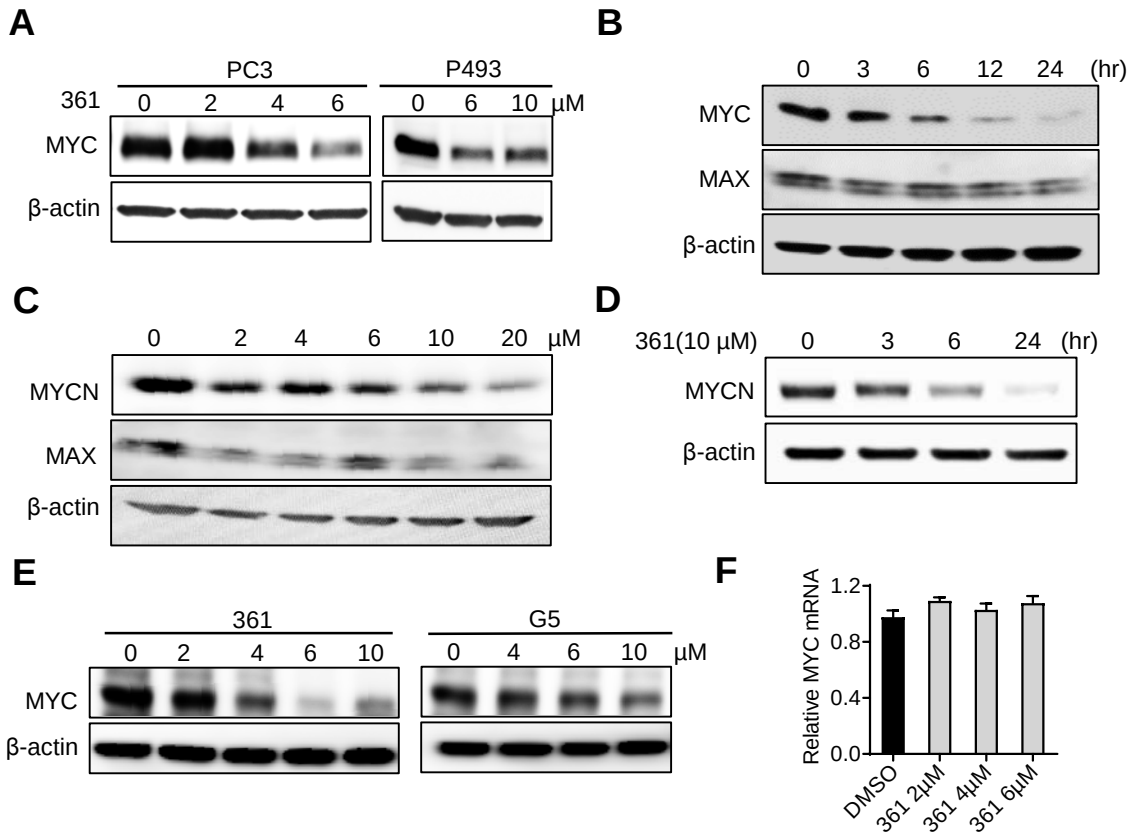


Figure S3. 361 Treatment Decreases MYC and MYCN but not MAX Protein Levels, Related to Figure 2

(A) MYC protein levels after 24 hr treatment of 361 in PC3 and P493-6 cells at the indicated concentrations, assessed by western blot.

(B) MYC and MAX protein levels in PC3 cells treated with 6 μM 361 at the indicated time points, assessed by western blot.

(C and D) MYCN and MAX protein levels in SK-N-BE (2) cells treated with 361 at the indicated doses for 24 hr (C) or time points (D), assessed by western blot.

(E) MycCaP cells were treated with the indicated concentrations of 361 or G5 for 24 hr, MYC levels were assessed by western blot.

(F) MYC transcript levels after 24 hr treatment of 361 in PC3 cells by RT-PCR.

Error bars represent mean ± SEM, n= 3 replicates for (F). Data are representative of two to three independent experiments with similar results.

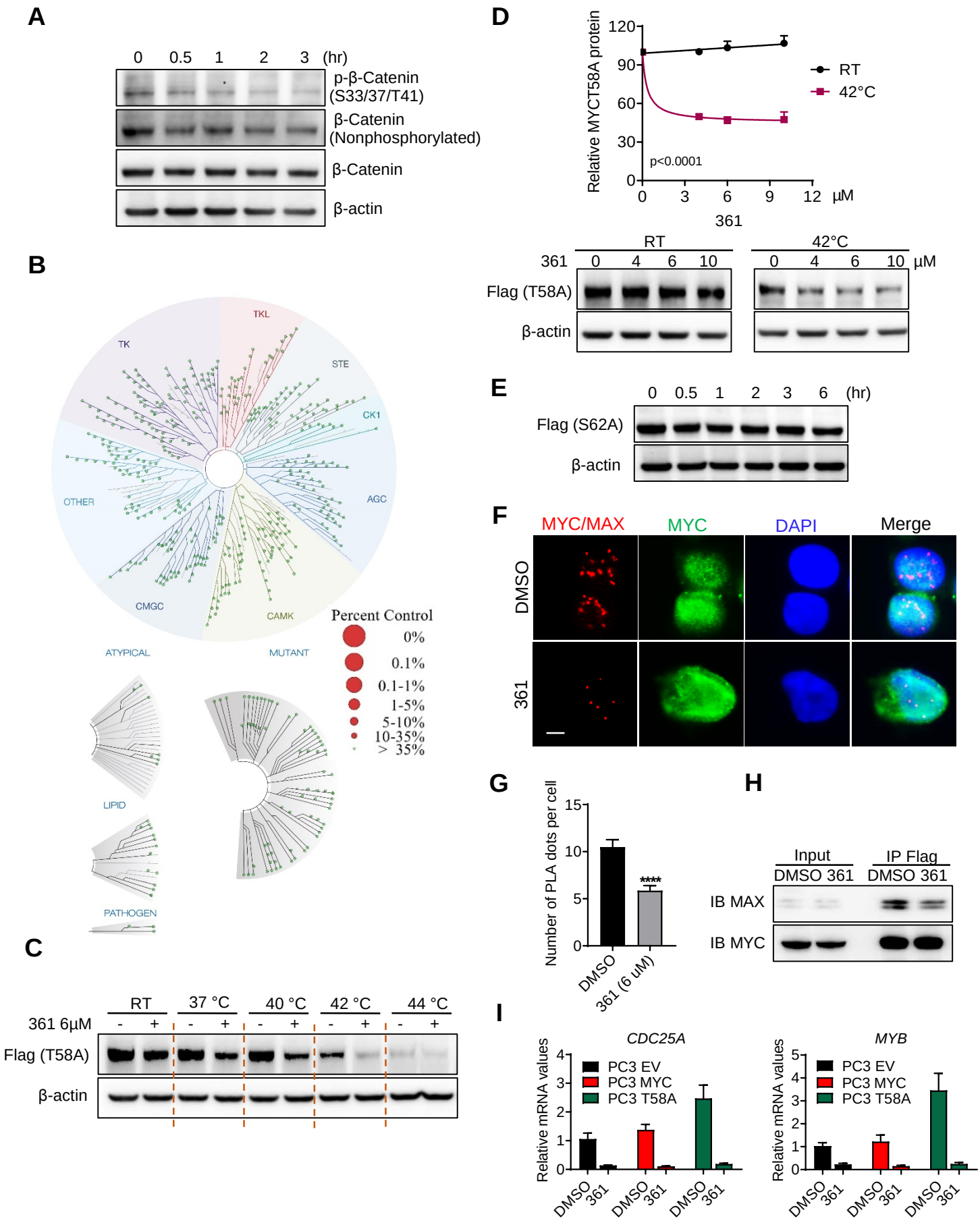

A
0 0.5 1 2 3 (hr)
p-β-Catenin (S33/37/T41)
β-Catenin (Nonphosphorylated)
β-Catenin
β-actin
B
TKL
TK
STE
CK1
OTHER
AGC
CMGC
CAMK
ATYPICAL
MUTANT
LIPID
PATHOGEN
Percent Control
0%
0.1%
0.1-1%
1-5%
5-10%
10-35%
> 35%
C
RT
37 °C
40 °C
42 °C
44 °C
361 6μM
Flag (T58A)
β-actin
D
Relative MYCT58A protein
RT
42°C
p<0.0001
361
μM
Flag (T58A)
β-actin
E
0 0.5 1 2 3 6 (hr)
Flag (S62A)
β-actin
F
MYC/MAX
MYC
DAPI
Merge
DMSO
361
G
Number of PLA dots per cell
****
DMSO
361 (6 uM)
H
Input
IP Flag
DMSO 361
IB MAX
IB MYC
I
CDC25A
MYB
Relative mRNA values
PC3 EV
PC3 MYC
PC3 T58A
DMSO
361

Figure S4. 361 promotes MYC Protein Degradation through MYC-threonine 58 Phosphorylation and Engages MYCT58A, Related to Figure 2

(A) Western blot analysis on β-Catenin phosphorylation status in 361 (6 μM) treated PC3 cells at the indicated time points.

(B) TREEspot Interaction Maps of Kinase (Kinome) inhibition screen (468 kinases tested) for 361 at 6 μM.

(C) Representative CETSA western blot analysis on MYC mutant T58A in Figure 2I.

(D) Isothermal CETSA analysis of MYCT58A mutant in MYCT58A-expressing PC3 cells following 361 treatment.

(E) Western blot analysis of MYCS62A in MYCS62A-expressing PC3 cells after 361 (6 μM) treatment at the indicated time points.

(F and G) Representative IF images (F) and quantification (G) of PLA for MYC/MAX interaction in MYCT58A-expressing PC3 cells after 2 hr treatment of 361 (scale bar, 5 μm).

(H) Co-IP of MYC/MAX complex in MYCT58A-expressing PC3 cells after 2 hr treatment with 361 (6 μM) by western blot analysis.

(I) RT-PCR analysis of MYC target genes CDC25A and MYB in wild-type MYC and MYCT58A-expressing PC3 cells after 24 hr treatment with 6 μM 361.

Error bars represent mean ± SEM, n = 3 independent experiments for (D), n = 80 to 110 cells/group counted for (G), n = 4 replicates for (I), and analyzed by two-way ANOVA for (E), and unpaired t test for (G) in Prism. ****p < 0.0001.

Table S1. Kinase and phosphatase inhibition screen on 361, Related to Figure 2

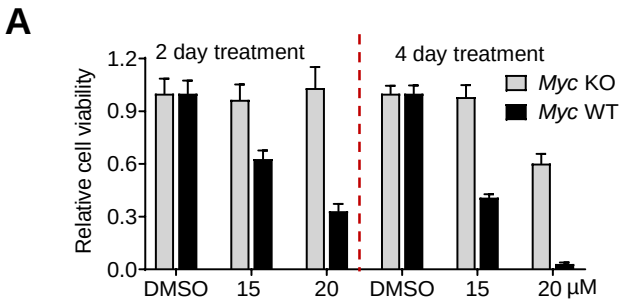
Kinase inhibition screen 361 (6 μM)

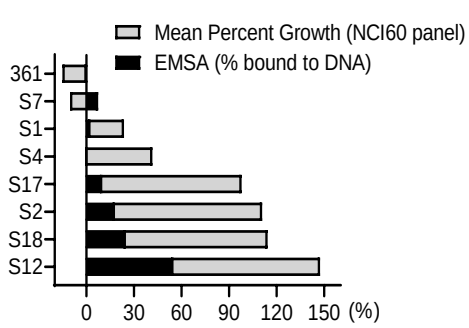
Selectivity Score Type	Number of Hits	Number of Kinases	Selectivity Score
S(35)	0	468	0
S(10)	0	468	0
S(1)	0	468	0

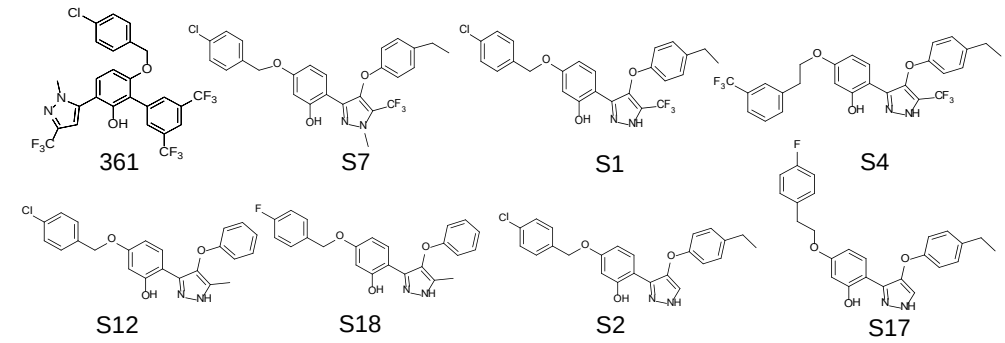
Phosphatase inhibition screen 361*

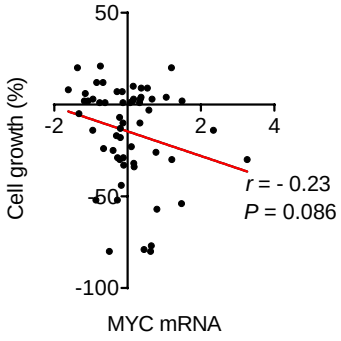
	Compound IC_{50} (μM)	Control IC_{50} (μM)
Phosphatase:	**361**	**PTP1B Inhibitor**
DUSP22/MKPX	>100	5.2
PP1A	N/A	11.7
PP1B	N/A	7.8
PP2A alpha	N/A	9.0
PTPN1/PTP1B	76.4	3.3
PTPN2/TC-PTP	98.9	8.8
PTPN6/SHP1	N/A	4.8
PTPN7/LC-PTP	17.2	5.8
PTPN11/SHP2	41.7	4.4
PTPN12/PTP-PEST	63.8	1.1

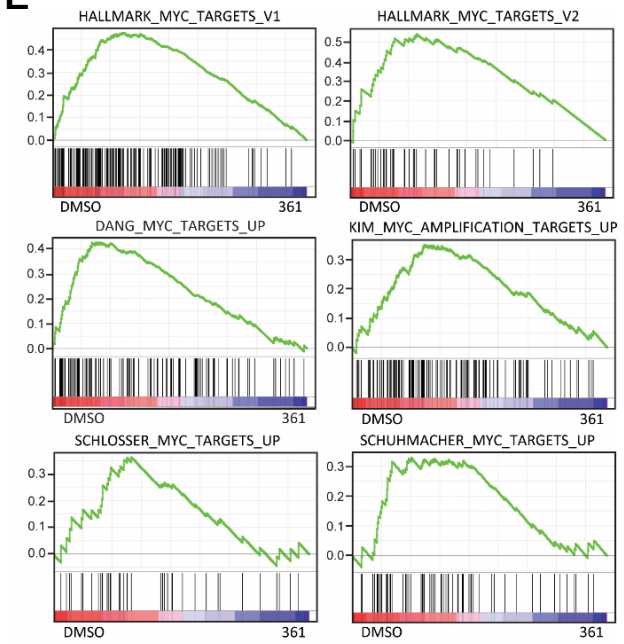
N/A indicates no inhibition or compound activity not fit to an IC_{50}
*361 treatment: 10-dose IC_{50} mode with 3-fold serial dilution starting at 100 μM



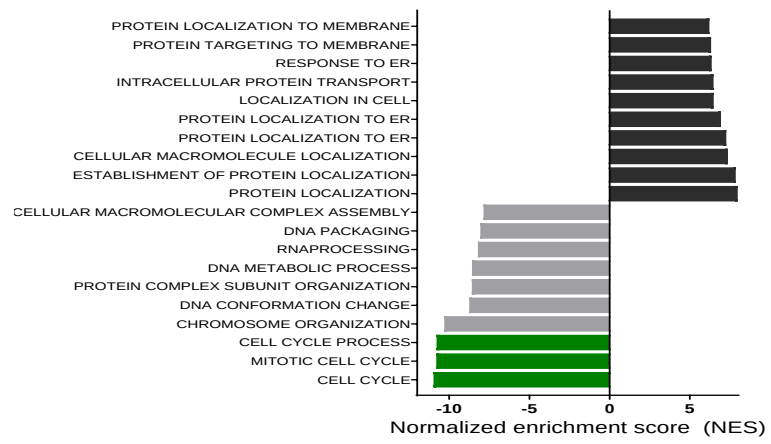


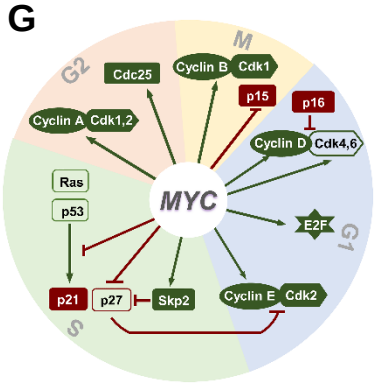


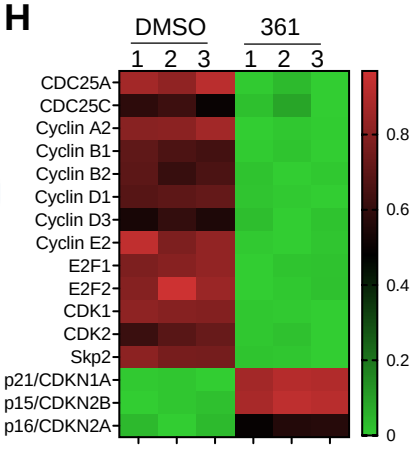




Gene set	SIZE	NES	FDR q-val
HALLMARK_MYC_TARGETS_V1	173	2.7	0
HALLMARK_MYC_TARGETS_V2	46	2.3	0
DANG_MYC_TARGETS	111	2.2	0
KIM_MYC_AMPLIFICATION_TARGETS	130	1.9	0.0016
SCHUHMACHER_MYC_TARGETS	68	1.6	0.0194
SCHLOSSER_MYC_TARGETS	39	1.5	0.0259







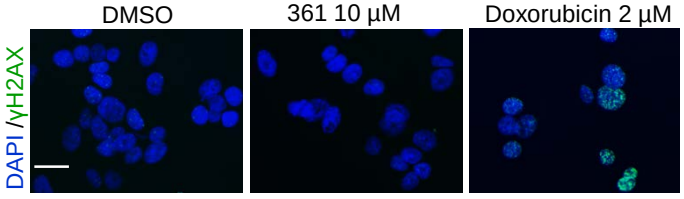


Figure S5. 361 Inhibits Cancer Cell Proliferation in a MYC-dependent manner, and Suppresses MYC Target Gene expression, Related to Figure 3

(A) Relative cell growth of TGR.1 (wild-type *Myc*) and HO15.19 (*Myc* knockout) cell lines after treatment with 361 for 2 or 4 days, assessed by viable cell counting. Error bars represent mean ± SEM, n = 3 replicates. Data are representative of two independent experiments with similar results.

(B) Graph shows the activities of compounds in disrupting MYC/MAX binding to DNA by EMSA and their growth inhibitory effects (mean percent growth) on NCI-60 tumor cell lines after treatment with 10 μM concentration for 48 hr.

(C) Chemical structures of compounds tested in NCI-60 panel screen.

(D) Correlation between growth percent of 361 and the MYC mRNA Z scores in NCI-60 tumor cell line panel, analyzed by Pearson's correlation coefficient (r) in Prism.

(E) Gene set enrichment analysis (GSEA) of six MYC-target gene signature sets for RNA-seq data from PC3 cells treated with 361 (6 μM) or DMSO for 24 hr in triplicates. NES, negative enrichment score.

(F) GO biological processes analysis of differentially expressed genes from the RNA-seq data shows the top 10 down- and up-regulated pathways based on NES.

(G) Schematic of MYC regulated genes involved in cell cycle phases.

(H) Heatmap of down- and up-regulated genes involved in cell cycle network controlled by MYC from the RNA-seq data (> 2 fold change; FDR < 0.01).

(I) γH2AX staining of PC3 cells after 24h treatment with 10 μM 361 or 2 μM Doxorubicin (scale bar, 20 μm).

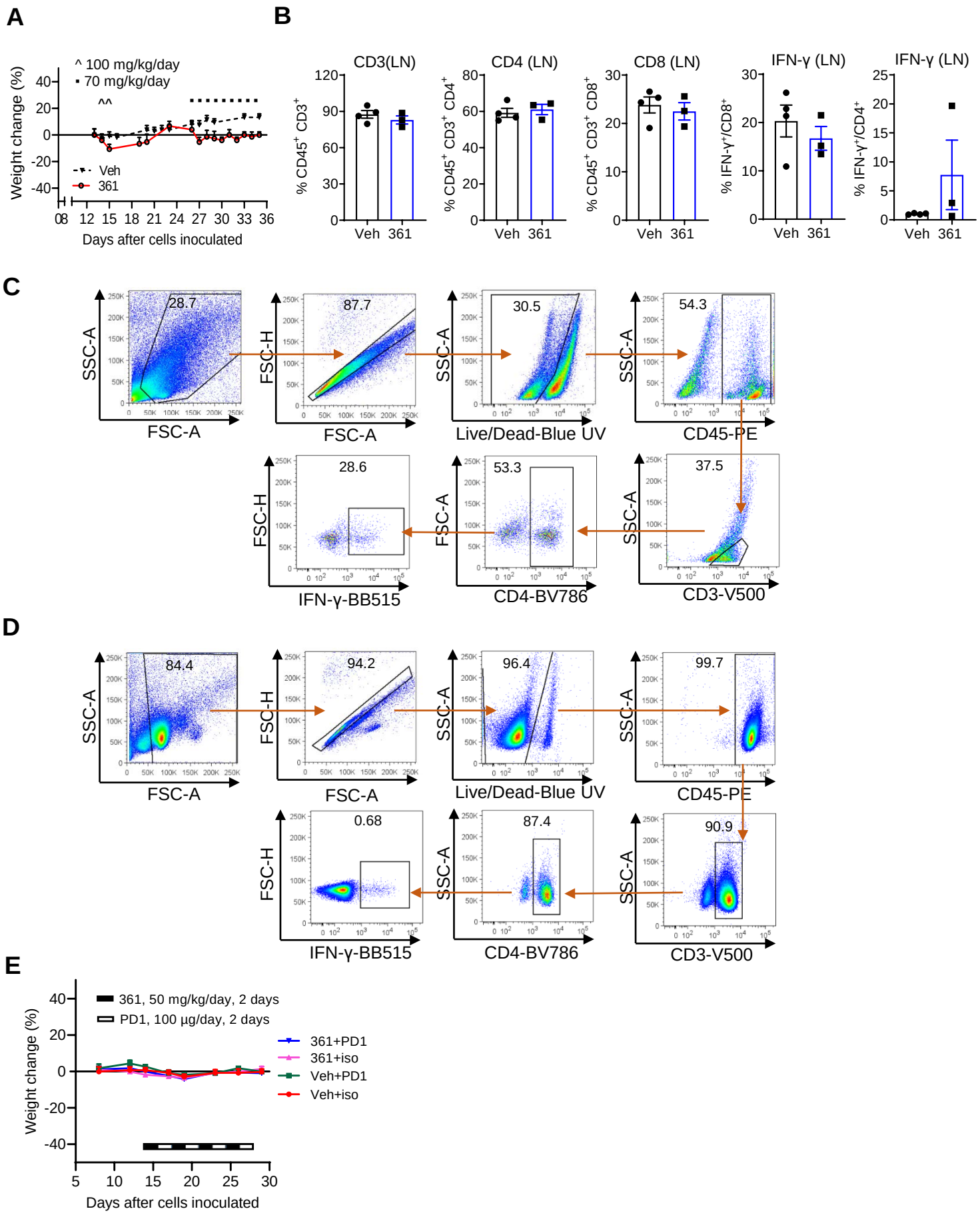

A
^ 100 mg/kg/day
▪ 70 mg/kg/day
Weight change (%)
Veh
361
Days after cells inoculated
B
CD3(LN)
CD4 (LN)
CD8 (LN)
IFN-γ (LN)
IFN-γ (LN)
Veh 361
C
28.7
87.7
30.5
54.3
28.6
53.3
37.5
SSC-A
FSC-A
FSC-H
Live/Dead-Blue UV
CD45-PE
IFN-γ-BB515
CD4-BV786
CD3-V500
D
84.4
94.2
96.4
99.7
0.68
87.4
90.9
E
361, 50 mg/kg/day, 2 days
PD1, 100 µg/day, 2 days
361+PD1
361+iso
Veh+PD1
Veh+iso
Weight change (%)
Days after cells inoculated

Figure S6. 361 Inhibits MYC-dependent Tumor Growth *in Vivo*, and Potentiates Anti-PD1 Immunotherapy, Related to Figure 4 and Figure 5

(A) Mice average body weight (% of initial weight) from the study described in Figure 4B.

(B) Flow cytometry analysis of immune cells on peripheral LNs from FVB mice bearing MycCaP allografts treated with 361 (related to the studies in Figure 5C and 5D).

(C and D) Gating strategy of flow cytometry analysis on immune cells from tumors (D) or LNs (E) in the study described in Figure 5D and S6B. For all the analysis, the initial gating was performed on overall morphology, singlets, live cells, and $CD45^+$ cells, followed by antigens of interest, SSC-A = Side Scatter-Area, FSC-A = Forward Scatter-Area, FSC-H = Forward Scatter-Height.

(E) Mice average body weight (% of initial weight) from the study described in Figure 5H.

Error bars represent mean ± SEM, n = 3- 4 mice/group in (A) and (B), n = 4-6 mice/group in (E).

Table S2. PK study and toxicity evaluation on 361, Related to Figure 4

PK Parameters: 361 in Plasma

PK Parameters	i.p.	p.o.
Rsq_adj	0.582	0.904
No. points used for $T_{1/2}$	4.00	4.00
C_{max} (ng/mL)	27200	13867
$C_{24\ h}$ (ng/mL)	12733	5283
T_{max} (hr)	1.00	1.00
$T_{1/2}$ (hr)	44	20
T_{last} (hr)	24.0	24.0
$AUC_{0\text{-}last}$ (ng.hr/mL)	388109	179783
$AUC_{0\text{-}inf}$ (ng.hr/mL)	1193406	336395
$MRT_{0\text{-}last}$ (hr)	11.1	10.5
$MRT_{0\text{-}inf}$ (hr)	62.5	30.6
AUC_{Extra} (%)	67.5	46.6
$AUMC_{Extra}$ (%)	94.2	81.6

Clinical signs of the animals in acute toxicity analysis of 361 (p.o., single dose)

Treatment group (mg/kg, n=3 mice)	General appearance and condition	Behavioral activity	Posture	Respiration	Skin and hair coat
50 mg/kg	Normal	Normal	No change	Normal	No change
200 mg/kg	Normal	Normal	No change	Normal	No change
220 mg/kg	Normal	Normal	No change	Normal	No change
240 mg/kg	Normal	Normal	No change	Normal	No change
250 mg/kg	15 min after dosing animals got immobile /stayed in one corner for 10 min.	It took several min after 'immobile stage' before they started to groom.	No change	Breathing pattern labored	No change

Histopathology report and diagnosis for 361

Treatment	361 (240 mg/kg, p.o., single dose)		
Mice ID	**M1**	**M2**	**M3**
Spleen	A	A	A
Reduced cellularity, periarteriolar lymphocytic sheaths, white pulp	2	2	N/A
Lung	N	N	N
Liver	A	A	A
Hypertrophy, hepatocellular, zones 2 & 3	2	2	1
Kidney	N	N	N
Heart	N	N	N
Vacuolar artefacts			3
Brain	N	N	N
Vacuolar artefacts	3	3	

KEY: N = No significant lesion; A = Lesion observed; 0 = No tissue; Grade 1 = modest, rare<10%; Grade 2 = mild, infrequent 10-20%; Grade 3 = moderate, frequent 20-50%; N/A = not available

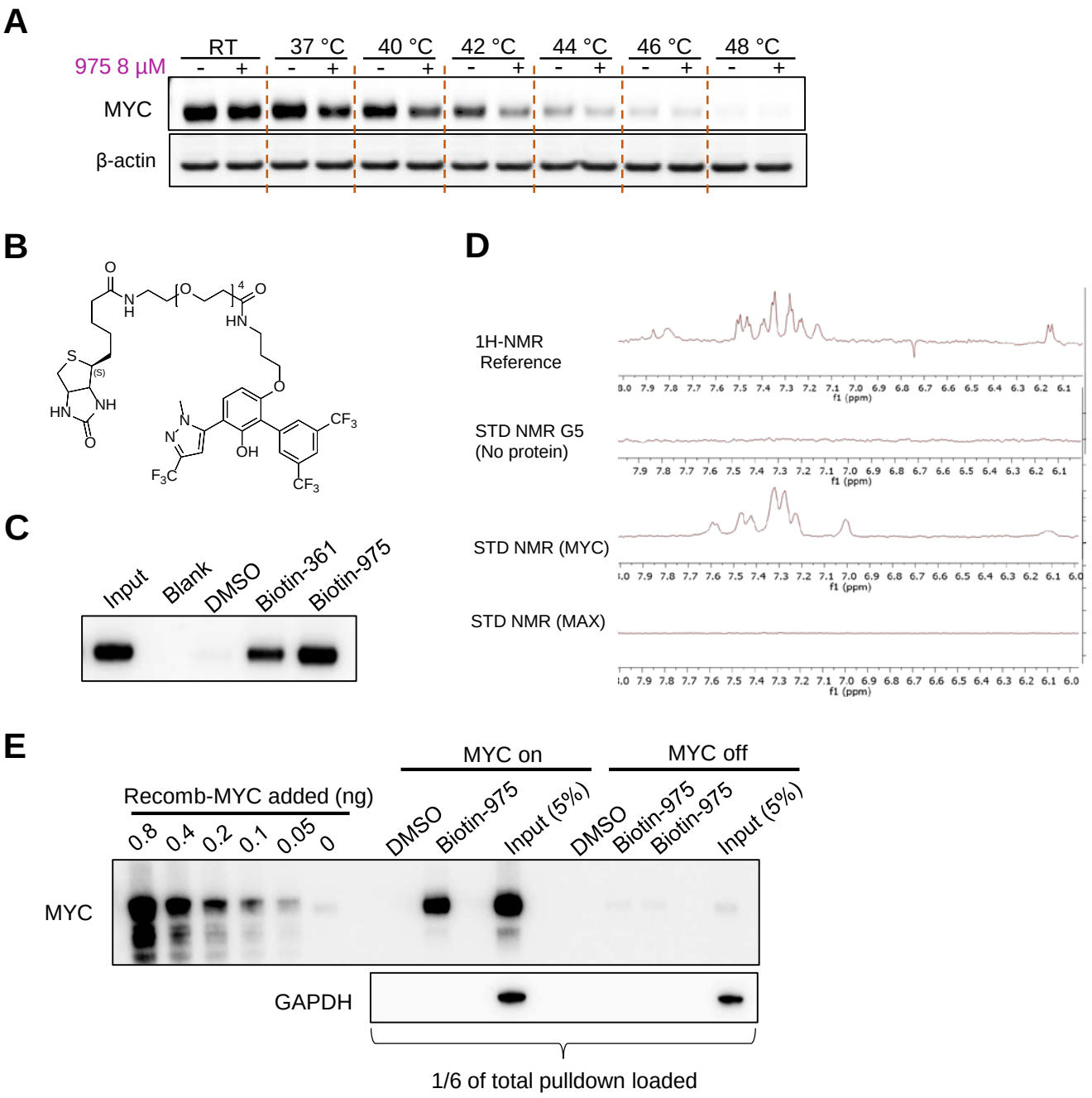


Figure S7. 975 Binds MYC and Engages MYC in Cells, Related to Figure 6

(A) A representative CETSA western blot analysis for MYC in PC3 cells after 975 (8 µM) treatment, related to the study in Figure 6B.

(B) Structure of Biotin-975.

(C) Western blot analysis on MYC protein after Biotin-975 or Biotin-361 pulldown in PC3 lysates .

(D) STD NMR analysis of control compound G5 (200 µM) with MYC or MAX proteins.

(E) Biotin-975 pulldown experiments in P493-6 cell lysates under MYC-on and MYC-off (0.1 µg/ml tetracycline treated for 3 days) conditions. 1/6 of total pulldown was used for WB analysis, with the rest of the sample sent for Mass Spec analysis. One of duplicate samples in the MYC-off condition was used as spike-in control. Recombinant MYC protein was titrated in MYC-off cell lysates to create a standard curve for quantifying the amount of MYC pulled down in MYC-on condition.

Table S3. GO analysis on 975/361 overlap genes in PC3, Related to Figure 7

GO terms enriched (Top 5 representatives, FDR<0.05)	-Log(p value)
Upregulated genes (n = 1071)	
response to organic substance	12.5
regulation of cell death	8.7
cellular response to nutrient levels	8.7
cellular response to unfolded protein	8.6
response to endoplasmic reticulum stress	8.6
Downregulated genes (n = 984)	
cell cycle process	66.8
mitotic cell cycle process	61.5
chromosome organization	59.4
cell division	43.4
DNA replication	37.6

Table S4. GSEA analysis on 361 uniquely regulated genes in PC3, Related to Figure 7

Gene set	NES	FDR q-val
***KEGG_SYSTEMIC_LUPUS_ERYTHEMATOSUS**	-4.3	0
*RNA_POL_I_TRANSCRIPTION	-4.2	0
*RNA_POL_I_PROMOTER_OPENING	-4.1	0
*MEIOSIS	-4.0	0
*MEIOTIC_RECOMBINATION	-4.0	0
*AMYLOIDS	-4.0	0
*RNA_POL_I_RNA_POL_III_AND_MITOCHONDRIAL_TRANSCRIPTION	-4.0	0
*TRANSCRIPTION	-3.9	0
*CHROMOSOME_MAINTENANCE	-3.7	0
*DEPOSITION_OF_NEW_CENPA_CONTAINING_NUCLEOSOMES_ AT_THE_CENTROMERE	-3.7	0
*MEIOTIC_SYNAPSIS	-3.7	0
*TELOMERE_MAINTENANCE	-3.6	0
*CELL_CYCLE	-3.6	0
TCA_CYCLE_AND_RESPIRATORY_ELECTRON_TRANSPORT	-2.4	7E-04
*MEGAKARYOCYTE_DEVELOPMENT_AND_PLATELET_PRODUCTION	-2.3	1E-03

*Gene set contains Histone leading edge genes

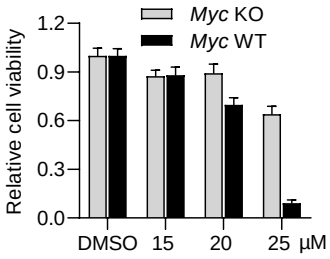
Leading edge genes of two major pathways

***KEGG_SYSTEMIC_LUPUS_ ERYTHEMATOSUS**	**TCA_CYCLE_AND_RESPIRATORY_ ELECTRON_TRANSPORT**
C1R	SDHD
SSB	NDUFA5
SNRPB	NDUFS5
FCGR2A	CYCS
SNRPD3	IDH3B
HIST1H3E	SUCLG1
HIST1H4E	NDUFB1
HIST1H4K	OGDH
HIST1H2AK	ATP5F1
HIST1H3F	LDHB
HIST1H2AE	PDHB
HIST1H4B	NDUFA12
HIST1H2BG	COX7B
HIST1H4A	NDUFA9
HIST1H2AM	ATP5G1
HIST1H3A	ATP5A1
HIST1H3H	UQCRHL
HIST1H3B	NNT
HIST1H2BH	ATP5C1
HIST1H2BF	CS
HIST1H2BO	FH
HIST1H2AJ	ETFDH
HIST1H2BB	DLD
HIST1H2AH	NDUFB6
HIST1H3C	DLAT
HIST1H2AB	NDUFC2
HIST1H2AL	L2HGDH
HIST1H2BM	ATP5J2
	NDUFB3
	PDK1
	NDUFV2
	PDK3
	SDHA

A

Cell viability assay	Cell line	IC_{50} (μM) (3 day)
975	P493-6	3.7
	MV411	3.9
	SK-N-B2	6.4
Colony forming assay		**IC_{50} (μM) (8 day)**
361	PC3	1.9
975	PC3	2.2

B



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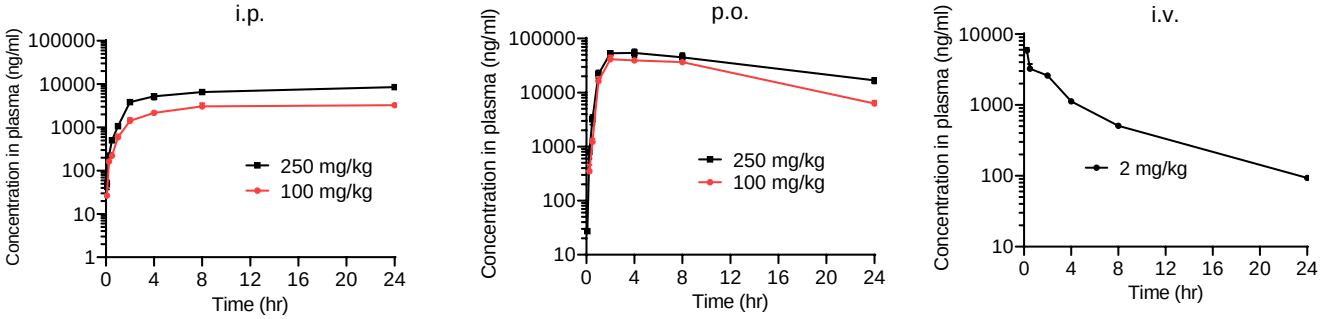


D

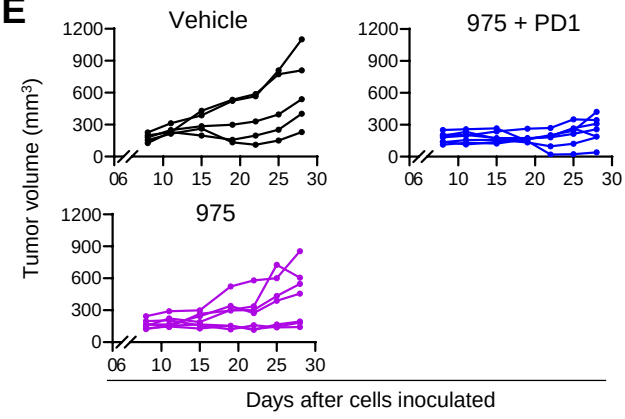
PK parameters of 975 in plasma (i.p. and p.o. dosing)

PK Parameters	i.p. (mg/kg)		p.o. (mg/kg)	
	100	250	100	250
No. points used for $T_{1/2}$	n.a.	n.a.	3	3
C_{max} (ng/mL)	3267	8470	41533	54000
T_{max} (hr)	24.0	24.0	2.0	4.0
$T_{1/2}$ (hr)	n.a.	n.a.	7	12
T_{last} (hr)	24	24	24	24
$AUC_{0\text{-}last}$ (ng.hr/mL)	65792	170240	608726	838188
$AUC_{0\text{-}inf}$ (ng.hr/mL)	n.a.	n.a.	673339	1121583
$MRT_{0\text{-}inf}$ (hr)	n.a.	n.a.	10.3	17.1
AUC_{Extra} (%)	n.a.	n.a.	10.6	33.8

PK parameters of 975 in plasma (i.v. dosing)

PK Parameters	IV (2 mg/kg)
No. points used for $T_{1/2}$	5
C_0 (ng/mL)	47528
$T_{1/2}$ (hr)	5.4
Vd_{ss} (L/kg)	0.50
Cl (mL/min/kg)	1.6
T_{last} (hr)	24
$AUC_{0\text{-}last}$ (ng.hr/mL)	19531
$AUC_{0\text{-}inf}$ (ng.hr/mL)	20236
$MRT_{0\text{-}inf}$ (hr)	5.0
AUC_{Extra} (%)	3.6

E



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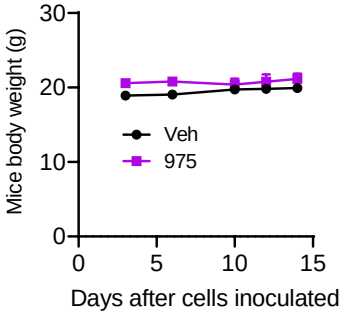

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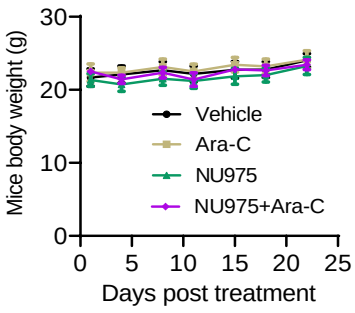


H

Treatment group (mg/kg, n=3 mice, p.o.)	General appearance and condition	Behavioral activity	Posture	Respiration	Skin and hair coat
50 mg/kg	Normal	Normal	No change	Normal	No change
100 mg/kg	Normal	Normal	No change	Normal	No change
250 mg/kg	Normal	Normal	No change	Normal	No change
500 mg/kg	Normal	Normal	No change	Normal	No change
1000 mg/kg	Normal	Normal	No change	Normal	No change

Figure S8. Additional 975 Anti-tumor Efficacy, PK, and Toxicity Studies, Related to Figure 7 and 8

(A) IC_{50}s of 975 on tested cell lines in proliferation assay with 3 day treatment, and IC_{50}s of 975 and 361 in colony forming assay in PC3 cells. Data are representative of two to three independent experiments with similar results.

(B) Relative cell growth of TGR.1 (*Myc* WT) and HO15.19 (*Myc* KO) cell lines after treatment with 975 for 2 days, assessed by viable cell counting. Error bars represent mean ± SEM, n = 3 replicates.

(C and D) Plasma concentration of 975 at indicated time points up to 24 hr (C) and PK parameters of 975 in plasma (D) after a single dose administration through i.p., p.o., or i.v route.

(E) Individual tumor growth trajectories of study in Figure 8G.

(F and G) Mice average body weight in LLC1 allografts study shown in Figure 8I (F) and in MV4 xenograft study shown in Figure 8J (G) for 975. Error bars represent mean ± SEM, n = 7 mice/group in (F), n = 4 mice/group in (G).

(H) Clinical evaluation of acute toxicity in CD-1 mice treated with increasing doses of 975.

Table S5. 975 systematic toxicity evaluation, Related to Figure 8

Mice body weight (g)

Days after cell inoculated	Vehicle (n=5 mice)	975 (n=5 mice)
0	27.7 ± 1.4	27.6 ± 1.1
3	27.2 ± 1.7	27.3 ± 1.6
6	27.6 ± 1.4	27.9 ± 1.2
10	26.8 ± 1.4	27.8 ± 1.2
13	28.1 ± 0.9	29.1 ± 1.2
20	28.4 ± 1.1	29.2 ± 0.8

Hematology

	Vehicle	975	Normal range
Leukocytes:			
WBC (k/µL)	3.80 ± 1.21	6.63 ± 2.1	1.8 - 10.7
NE (k/uL)	0.40 ± 0.05	0.62 ± 0.19	0.1 - 2.4
LY (k/uL)	3.36 ± 1.21	5.87 ± 1.90	0.9 - 9.3
MO (k/uL)	0.03 ±0.02	0.03 ± 0.45	0.0- 0.4
EO (k/uL)	0.01 ± 0.02	0.12 ± 0.09	0.0 - 0.2
BA (k/uL)	0.00 ± 0	0.00 ± 0	0.0 - 0.2
% NE	11.25 ± 3.5	9.40 ± 2.07	6.6 - 38.9
% LY	87.50 ± 4.2	88.40 ± 0.55	55.8 – 91.6
% MO	1.00 ± 0.82	0.40 ± 0.55	0.0 – 7.5
% EO	0.25 ± 0.5	1.80 ± 1.48	0.0 – 3.9
% BA	0.00 ± 0	0.00 ± 0	0.0 – 2.0
Erythrocytes:			
RBC (M/µL)	9.89 ± 0.45	10.04 ± 0.73	6.36 – 9.42
HGB (g/dL)	14.65 ± 0.88	15.38 ± 0.69	11.0 – 15.1
HCT (%)	49.73 ± 2.94	48.84 ± 3.94	35.1 – 45.4
MCV (fL)	50.30 ± 1.08	48.64 ± 0.96	45.4 – 60.3
MCH (pg)	14.85 ± 0.26	15.34 ± 0.49	14.1 – 19.3
MCHC (g/dL)	29.53 ± 0.17	31.56 ± 1.30	30.2 – 34.2
RDW (%)	13.13 ± 0.12	13.32 ± 0.90	12.4 – 27.0
Thrombocytes			
PLT (k/uL)	1094 ± 253	1247 ± 234	592 - 2972
MPV (fL)	7.35 ± 0.68	8.36 ± 2.65	5.0 – 20.0

Blood chemistry

	Vehicle	975	Normal range
ALT (U/L)	58.80 ± 24.16	53.00 ± 19.81	17 - 77
AST (U/L)	130.40 ± 92.57	147.00 ± 64.93	54 - 298
ALP (U/L)	68.80 ± 4.27	76.80 ± 9.76	35 - 96
TP (g/dL)	4.98 ± 0.13	5.47 ± 0.31	3.5 - 7.2
ALB (g/dL)	2.80 ± 0.12	3.20 ± 0.26	2.5 - 3
GLOB (g/dL)	2.18 ± 0.15	2.27 ± 0.15	1.0 - 4.2
BUN (mg/dL)	20.20 ± 2.17	18.33 ± 0.58	8 - 33
CREAT (mg/dL)	0.10 ± 0.00	0.13 ± 0.06	0.2 - 0..9
TBIL (mg/dL)	0.35 ± 0.08	0.42 ± 0.09	0 - 0.9

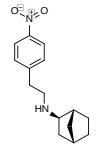
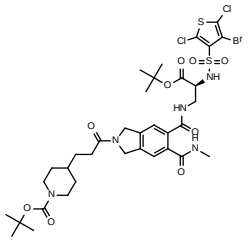
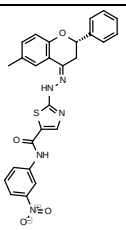
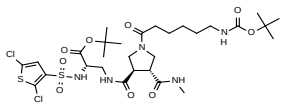
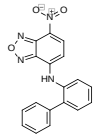
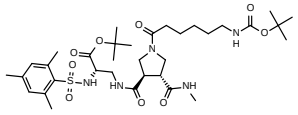
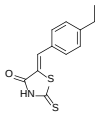
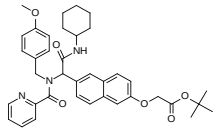
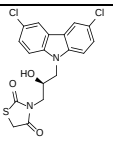
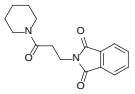
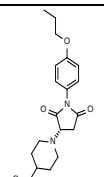
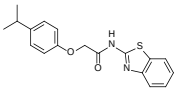
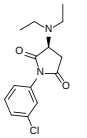
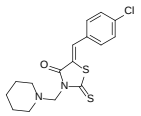
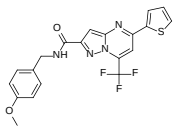
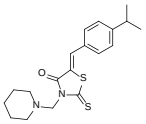
Histopathology report and diagnosis

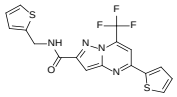
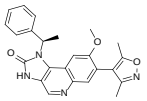
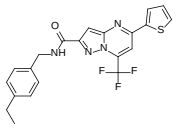
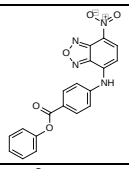
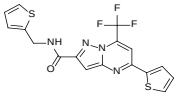
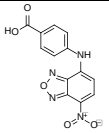
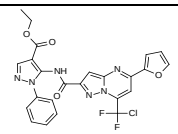
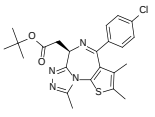
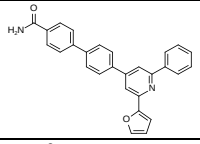
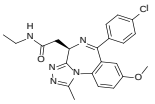
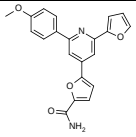
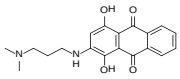
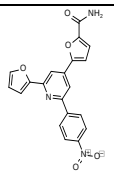
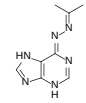
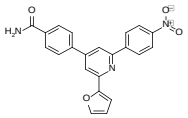
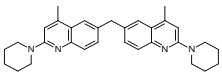
	Vehicle	975
Spleen	N	N
Skin	N	N
Lung		

Hemorrhage, alveolar, peracute (terminal), multifocal	0	1
Liver		
Hypertrophy, hepatocyte, zones 2 & 3	1	1
Kidney	N	N
Intestine	N	N
Heart	N	N
Brain	N	N

KEY: N = No significant lesion; A = Lesion observed; 0 = No tissue; Grade 1 = modest, rare<10%; Grade 2 = mild, infrequent 10-20%; Grade 3 = moderate, frequent 20-50%

Table S7. 32 known compounds for building the pharmacophore, Related to STAR Methods

Structure	References	Structure	References
	(Yin et al., 2003)		(Berg et al., 2002)
			(Shi et al., 2009)
			
			(Xu et al., 2006)
			(Mustata et al., 2009)
			
			(Wang et al., 2007)
			

	(Kiessling et al., 2006)		* (Seal et al., 2012)
			(Yap et al., 2013)
			
			*(Filippakopoulos et al., 2010)
	(Hart et al., 2014)		
			(Mo and Henriksson, 2006)
			
			(Jiang et al., 2009)

*BET bromodomain inhibitors as decoys