

Supplementary Materials: Synthetic Lethality Screening Highlights Colorectal Cancer Vulnerability to Concomitant Blockade of NEDD8 and EGFR Pathways

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Supplementary Methods

Library Composition

The shRNA library targeted 200 genes (10 shRNAs per gene), which sequences were designed using a proprietary algorithm (Cellecta Inc.). shRNAs were under the control of a constitutive U6 promoter and univocally associated to a barcode cassette (BC) of 18, non-overlapping nucleotides to specifically “tag” individual constructs. The library also contained two positive (PSMA1, RPL30) and a neutral (Luciferase, LUC) controls.

shRNA Library Transduction and in vitro Screening

Concentrated lentiviral particles from the shRNAs library were produced by transfecting 293T cells, as described in the Cellecta User Manual (<https://manuals.cellecta.com/rnai-pooled-lentiviral-shrna-libraries/> accessed on 1 May 2020), and were independently added in triplicate to CRC cell lines used for the *in vitro* screening, together with 8 µg/mL polybrene (Sigma) for 24 hours and then standard growth medium was replaced. At 72h post transduction, the percentage of infected cells was determined through flow cytometry analysis and 3 µg/mL of puromycin was added before performing the experiments. Library infection was performed using a Multiplicity of Infection (MOI) of ~0.2 Transducing Unit/cell. Cells were then amplified for approximately twenty doublings in presence (+) or ten doublings in absence (–) of pevonedistat at a concentration that reduced growth rate rather than totally impair cell proliferation. Pevonedistat concentration, specifically chosen for each cell line, was 25 nM for CAR1, 100 nM for LIM2099 and SW403 and 200 nM for WIDR. Genomic DNA (gDNA) was extracted immediately from cells after complete puromycin selection as reference, and after cellular doublings +/- pevonedistat. At every passage, cells were manually counted and at least 4 million were re-plated to preserve the correct representation (1000× coverage) of the library. GDNA extraction, PCR assay and Next Generation Sequencing (NGS) were performed according to Cellecta User Manual.

Sequences and Data Analysis

BCs representation was measured by NGS on Illumina NextSeq and BCs were identified by aligning each sequencing read to the barcoded-libraries using the Bowtie aligner (2.0.2), and by considering only those BCs having, at most, three mismatches in each alignment. Upon quantification each shRNA barcode, data were normalized on library size calculating counts *per* millions (CPM). Accordingly, library constructs were represented with more than one CPM in more than 99.9% in the unselected cells supporting the complete representation and capture of the library. Each experiment included two control points: the basal, library infected unselected cells, the library infected cells after 20 cell doublings, and library infected cells selected with pevonedistat treatment. To ensure robust identification of shRNA construct depletion in pevonedistat selection, in each replicate we calculated for each construct the LOG₂ fold change of comparing pevonedistat selected cells and the minimum value of the controls. On such data, Lucif-

erase targeting shRNAs, as neutral controls, were employed as to define minimum threshold to call the depletion. To minimize false calling, each single shRNA targeting construct was then called depleted if ranked below the 33th percentile of the distribution in each replicate for CAR1, LIM2099 and SW403; WiDr required a 25th percentile threshold. Finally, to identify gene depletion we required a minimum of four shRNAs to be depleted in all the biological replicates.

Immunohistochemistry

After deparaffinization, endogenous peroxidase was blocked in 3% hydrogen peroxide and heating antigen retrieval was carried in citrate buffer (pH 6.0). Sections were stained with monoclonal mouse anti-human Ki67 (Dako), p21 and p27 (#2947 and #3686; Cell signaling Technology) antibodies. Immunoreactivities were revealed by incubation in DAB chromogen (Dako). Slides were counterstained in Mayer's hematoxylin. Images were acquired by Olympus AX70 up-right microscope (objective UPLFLN 10×) and processed by using Cell Sens Science Imaging Software (Olympus corporation, Japan). Images are presented at 10X magnification (scale bar 200 μ m). The markers' quantification (Ki67, p21 and p27) was calculated on more representative areas of the tumors for at least 15 microscopic fields in different sections and expressed as percentage (mean \pm SD).

Supplementary Figures

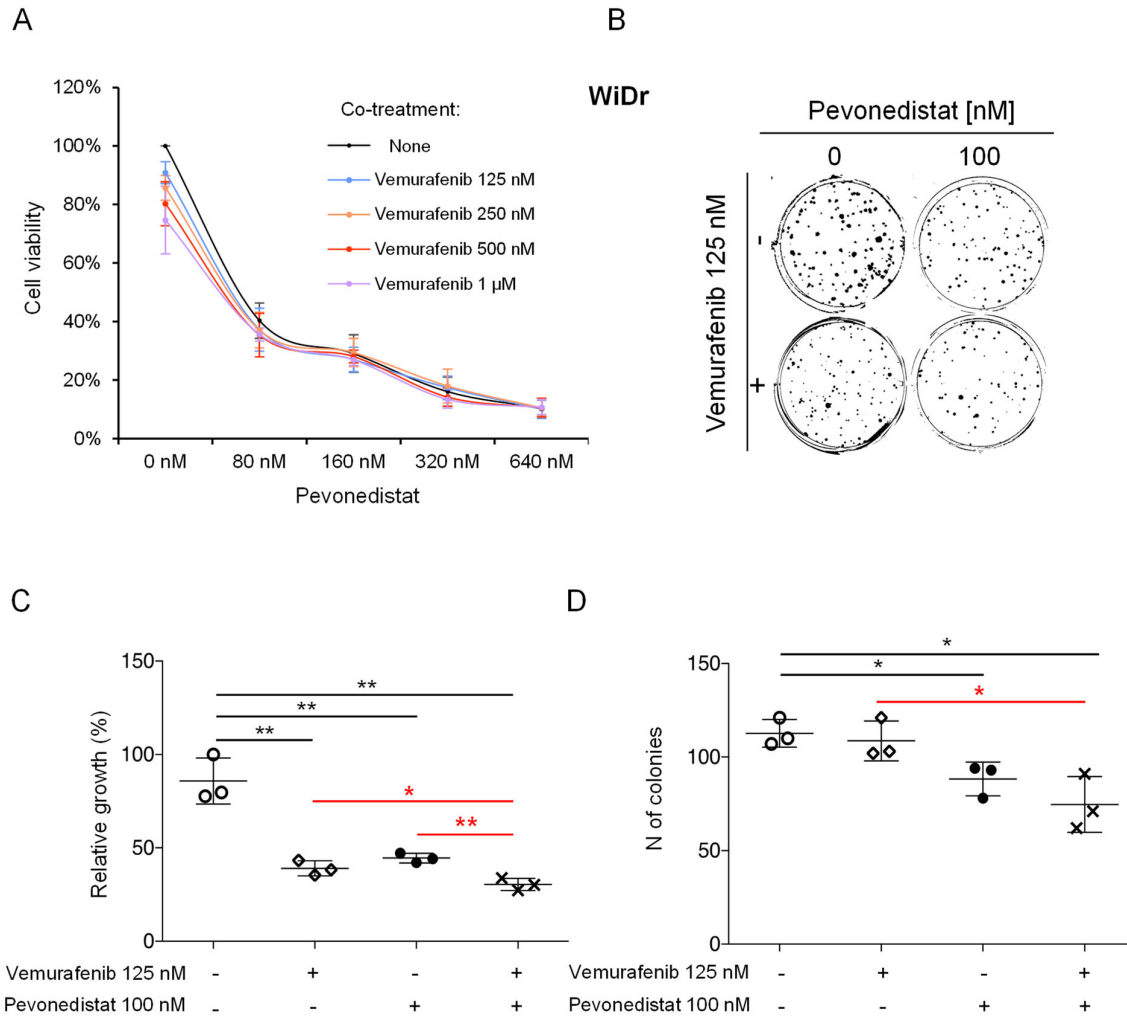


Figure S1. Evaluation of pevonedistat and vemurafenib sensitivity on *BRAF*-mutant WiDr cells. **(A)** Short-term dose-response proliferation assay on WiDr treated with increasing concentrations of pevonedistat combined with different doses of vemurafenib. At 96h the percentage of cell viability was estimated and normalized to the untreated cells. Data are expressed as average \pm SD of four technical replicates. **(B)** Colonies formation of WiDr *BRAF*-mutant cells was evaluated in response to 100 nM of pevonedistat after 17 days of treatment in presence and absence of *BRAF* inhibitor vemurafenib (125 nM). Cells were fixed by using Cristal Violet. **(C)** WiDr colonies relative growth was quantified by ImageJ analysis in triplicate and expressed as relative growth in percentage. Significant differences among groups were evaluated by Student *t* test (*: $p < 0.05$; **: $p < 0.01$). **(D)** Number of WiDr colonies was quantified by ImageJ analysis in triplicate. Significant differences among groups were evaluated by Student *t* test (*: $p < 0.05$).

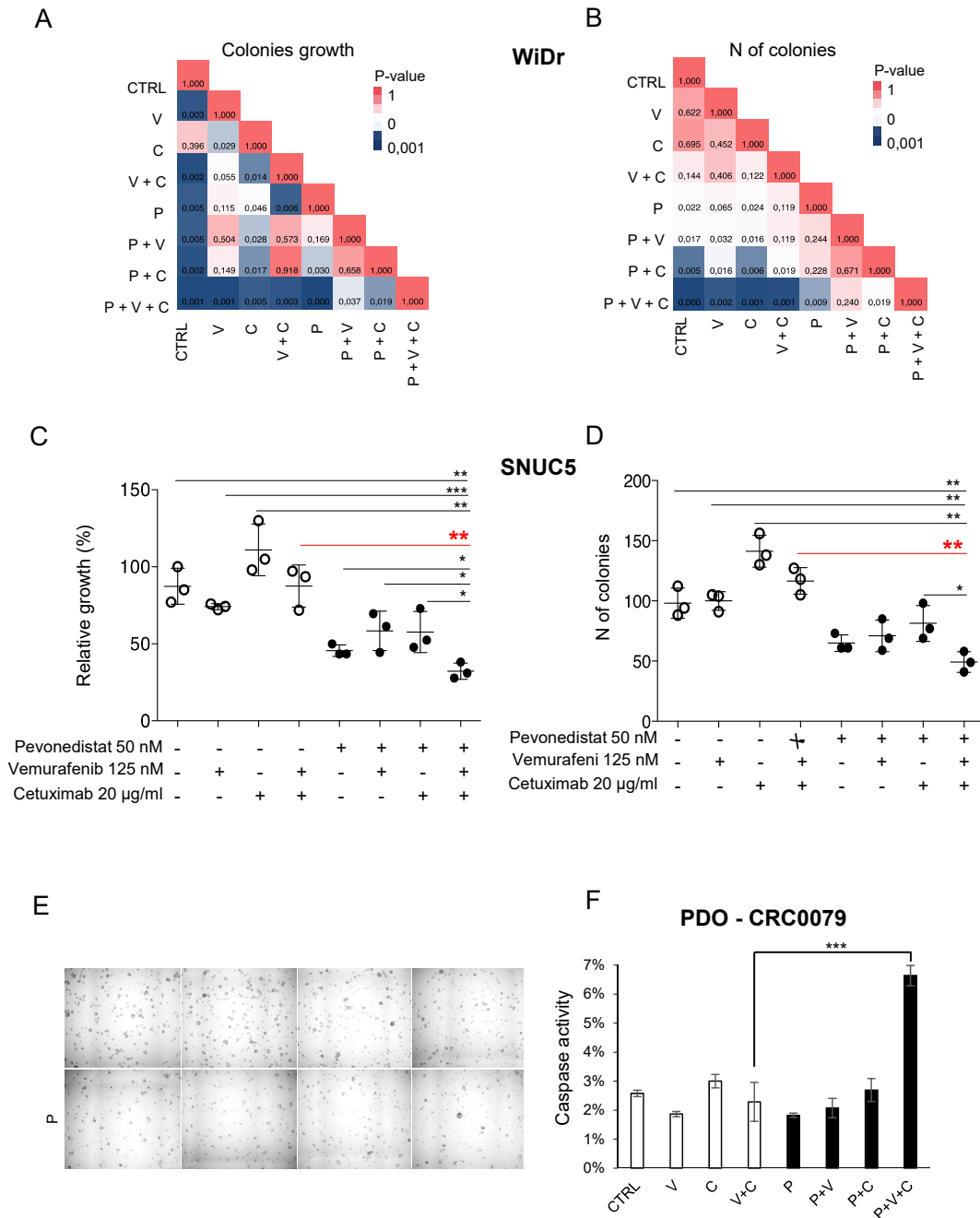


Figure S2. Effect of pevonedistat combined with EGFR inhibition on colony formation in *BRAF*-mutant CRC cell lines and organoids. A–B. WiDr cells were used to perform a colony formation assay and response to pevonedistat (100 nM), cetuximab (20 µg/ml), vemurafenib (125 nM) alone or in combination was evaluated. After 17 days cells were fixed by crystal violet. Relative growth of WiDr colonies (A) and their number (B) were quantified in triplicate and significant differences among groups (pevonedistat–P; vemurafenib–V; cetuximab–C) were analyzed by applying a Student *t* test as show in the heat maps. C–D. An additional *BRAF*-mutant CRC cell line SNUC5 was used to perform a colony formation assay and response to pevonedistat (100 nM), cetuximab (20 µg/mL), vemurafenib (125 nM) alone or in combination was evaluated. After 8 days cells were fixed by crystal violet. Relative growth of SNUC5 colonies (C) and their number (D) were quantified in triplicate and significant differences among triple combination and other treatment groups (pevonedistat–P; vemurafenib–V; cetuximab–C) were analyzed by applying a Student *t* test (*: *p* < 0.05; **: *p* < 0.01; ***: *p* < 0.001). (E) *BRAF*-mutant Patient-Derived Organoid (PDO – CRC0079) was treated for 96h with vemurafenib (125 nM), cetuximab (20 µg/ml) and increasing doses of pevonedistat (150 - 300 - 500 nM). Representative images of three technical replicates at 500 nM pevonedistat dose are reported. (F) Caspase-3/7 activity was quantified by Caspase Glo Assay after 24h treatment and expressed as ratio of proliferation. Significant differences among V+C and V+C+P groups were calculated by applying Student *t* test (***: *p* < 0.001).

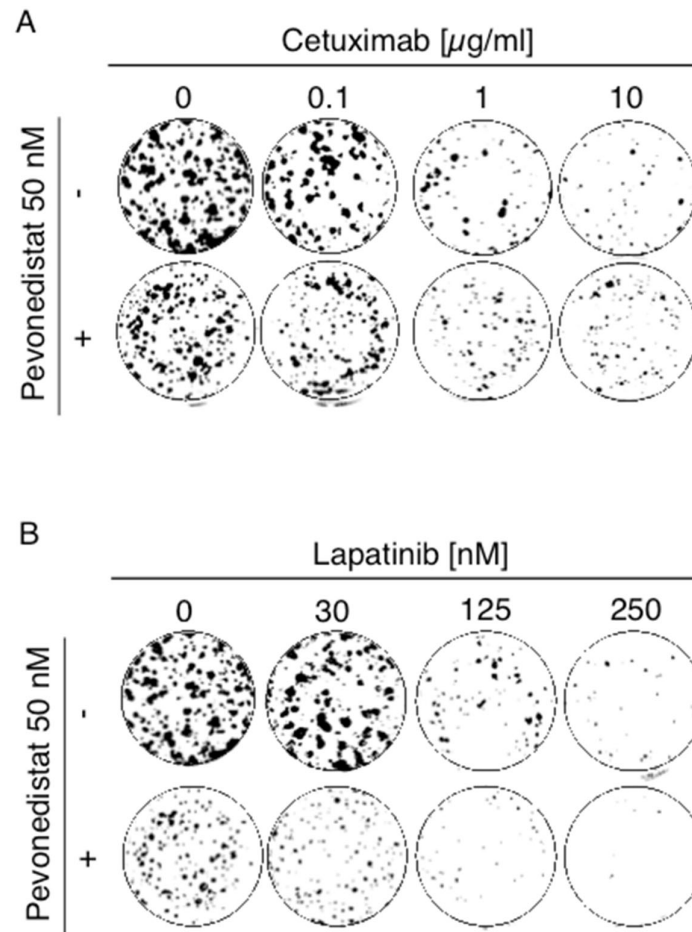


Figure S3. Evaluation of pevonedistat sensitivity combined with anti-EGFR inhibitors on *RAS/RAF* WT HCA7 cells. (**A–B**) Colony formation of HCA7 cells was evaluated in response to pevonedistat 50 nM, increasing concentrations of cetuximab (**A**) or lapatinib (**B**) and combinatorial treatments of both. After 13 days cells were fixed by crystal violet. Representative images of three technical replicates are reported.

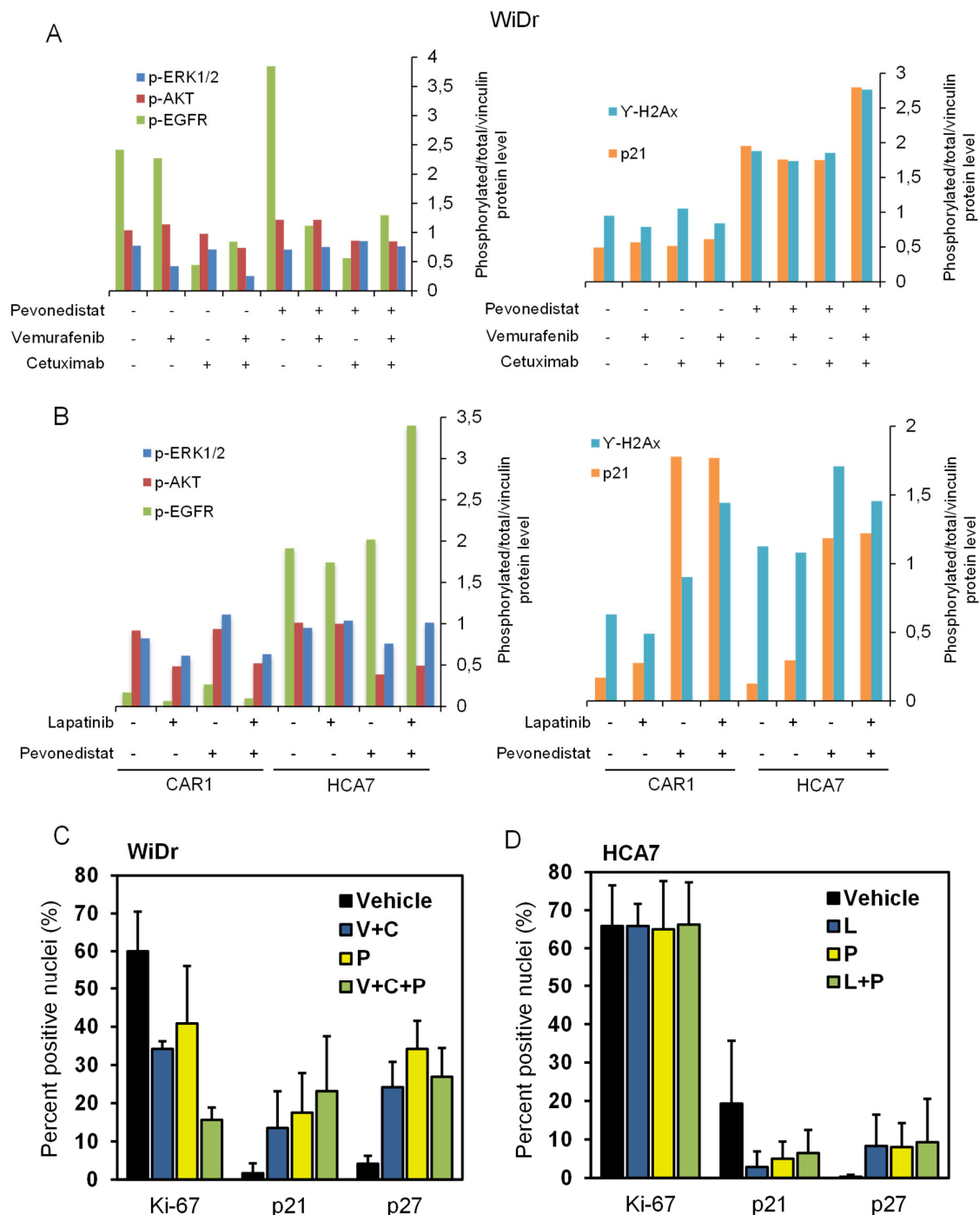
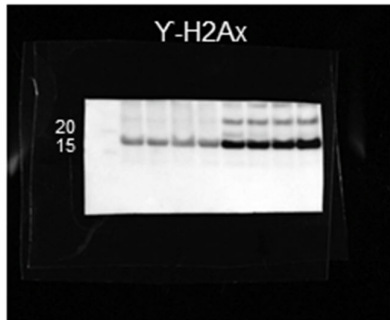
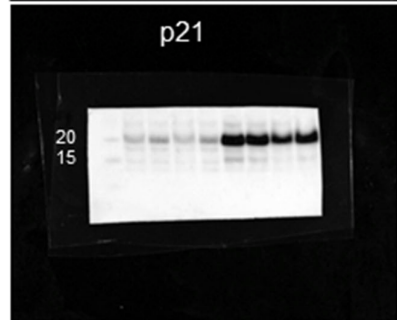
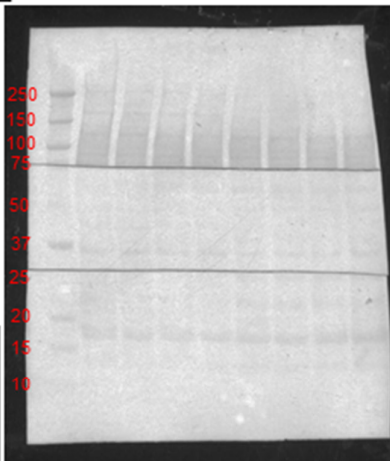
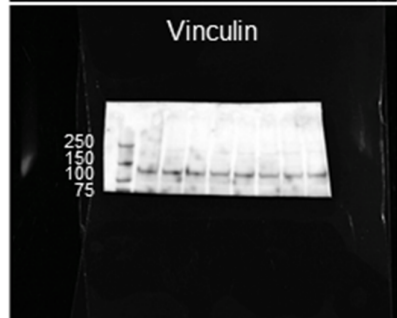
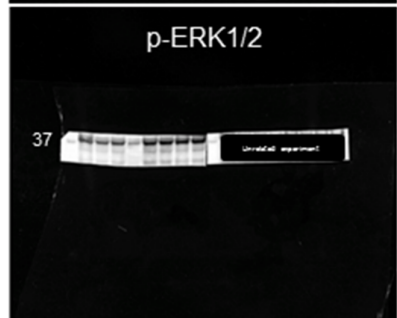
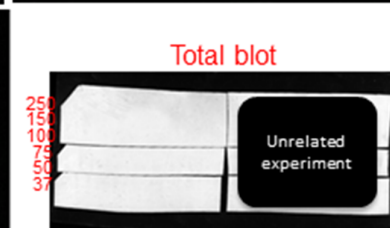
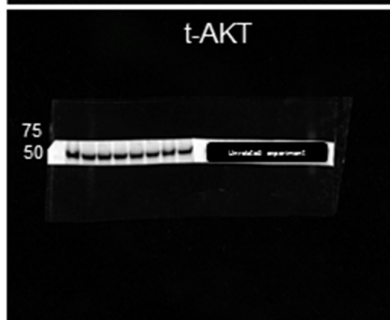
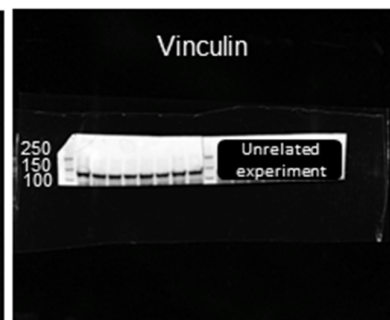
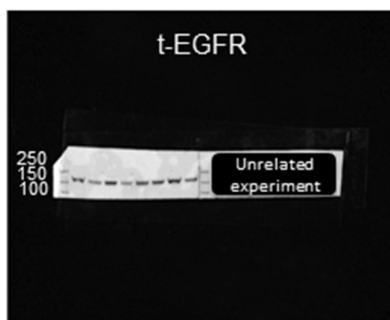
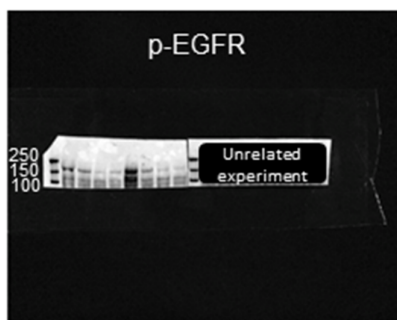


Figure S4. Quantification of western blot and immunohistochemistry on *BRAF*-mutant and *RAS/RAF* WT cells (see Main Figure 5). (A) Protein quantification from western blot on WiDr lysates (referred to Main Figure 5A) was performed by using ImageJ software. The level of the phosphorylated forms was expressed as ratio to the respective total form, after normalization of each sample loading by using vinculin. (B) Protein quantification from western blot on CAR1 and HCA7 lysates (referred to Main Figure 5C,D) was performed by using ImageJ software. The level of the phosphorylated forms was expressed as ratio to the respective total form, after normalization of each sample loading by using vinculin. (C) The quantification of immunohistochemistry markers Ki67, p21 and p27 on WiDr xenografts (referred to Main Figure 5B) was calculated on more representative areas of the tumors for at least 15 microscopic fields in different sections and expressed as percentage (mean \pm SD). (D) The quantification of immunohistochemistry markers Ki67, p21 and p27 on HCA7 xenografts (referred to Main Figure 5E) was calculated on more representative areas of the tumors for at least 15 microscopic fields in different sections and expressed as percentage (mean \pm SD).



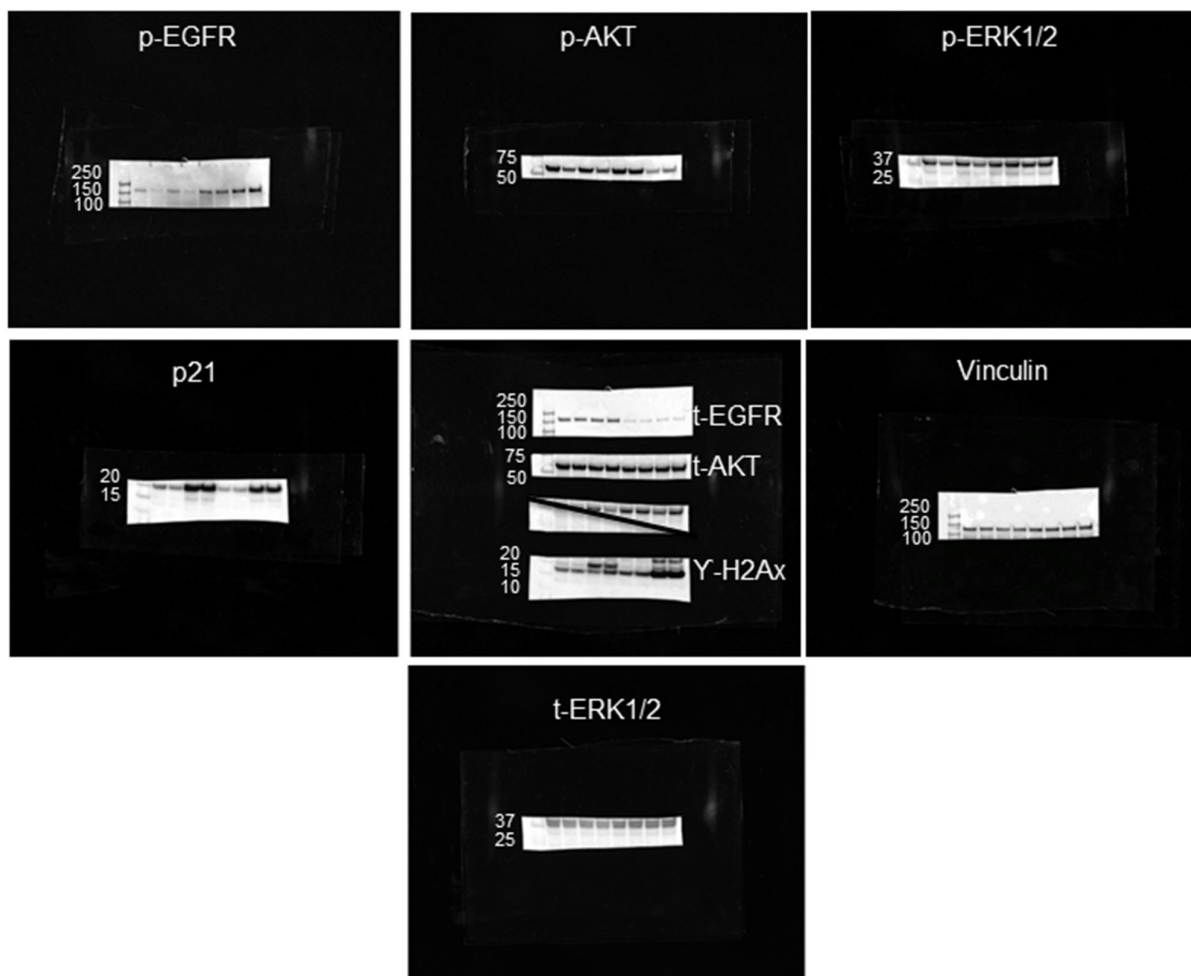


Figure S5. The uncropped Western blots.

Table S1. shRNA library details and screening candidate hit genes. (A) Genes composing the shRNA library, Ensembl annotation, drugs available targeting each gene and corresponding pathway/signaling or function are listed. (B) shRNAs targeting each gene are reported. For each cell line sequenced, LOG₂ ratio of each replicate was calculated; call for depletion in all three replicates; gene depletion call. (C) Expression levels expressed as TMM of each candidate gene hit in the CRC cell lines used for the synthetic lethal screening.

Supplementary Table S1A. Genes composing the shRNA library, Ensembl annotation, drugs available targeting each gene and corresponding pathway/signaling or function.			
Target_Gene	Ensembl Gene ID	Targeting Drug(s)	Pathway/Signaling/Function
ABL1	ENSG00000097007	adenosine-triphosphate	RAS-ERK signaling pathway
		bafetinib	
		bosutinib	
		dasatinib	
		flumatinib	
		GNF-2	
		GZD824	
		imatinib	
		KW-2449	
		LDN-212854	
		metatinib	
		nilotinib	
		ponatinib	
		PP-121	
		PP-2	
		rebastinib	
		regorafenib	
		saracatinib	
ABL2	ENSG00000143322	adenosine-triphosphate	RAS-ERK signaling pathway
		dasatinib	
AKT1	ENSG00000142208	A-674563	HGF-MET-PI3K signaling pathway
		adenosine-triphosphate	
		arsenic-trioxide	
		AT13148	
		AZD5363	
		bisindolylmaleimide-ix	
		BMS-536924	
		BMS-754807	
		CaMKII-IN-1	
		canertinib	
		enzastaurin	
		GDC-0068	
		GSK2110183	
		GSK690693	
		hexamethylenebisacetamide	
		KN-62	
		LY294002	
		MK-2206	
		PD-98059	
		perifosine	
		SB-202190	
		SB-203580	
		TIC10	

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ATM	ENSG00000149311	cafeine CGK-733 KU-55933 KU-60019 VE-822	ATM-TP53 pathway
ATR	ENSG00000175054	AZD6738 AZ20 CGK-733 NVP-BEZ235 schisandrin-b VE-821	ATR-TP53 pathway

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		alisertib	
		AMG900	
		AT-9283	
		aurora-a-inhibitor-i	
		barasertib	
		BI-847325	
		CCT129202	
		CCT137690	
		CYC116	
		danusertib	
		ENMD-2076	
AURKA	ENSG00000087586	GSK1070916	PI3K-AKT-MTOR pathway
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AURKB	ENSG00000178999	hesperadin	PI3K-AKT-MTOR pathway
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AURKC	ENSG00000105146	BI-847325	PI3K-AKT-MTOR pathway
		CCT129202	
		CCT137690	

		danusertib GSK1070916 MK-5108 PHA-680632 SNS-314 tozasertib	
AXL	ENSG00000167601	BMS-777607 LDC1267 MGCD-265 R-428 TP-0903	RAS-ERK signaling pathway
BCL2	ENSG00000171791	ABT-737 docetaxel edaravone gambogic-acid gossypol HA-14-1 HA14-1 ibuprofen-(s) navitoclax obatoclax oridonin paclitaxel rasagiline TW-37 venetoclax	BCL2 Family
BCR	ENSG00000186716	bafetinib bosutinib GNF-2 GZD824 metatinib ponatinib rebastinib	RAS-ERK signaling pathway
BIRC5	ENSG00000089685	terameproclo YM-155	Wnt signaling pathway
BLK	ENSG00000136573	dasatinib ibrutinib	SRC tyrosin kinase signaling
BMX	ENSG00000102010	ibrutinib	SRC tyrosin kinase signaling
BRAF	ENSG00000157764	AZ-628 CEP-32496 dabrafenib GDC-0879 LGX818 LY3009120 PLX-4720 PLX8394 RAF265 regorafenib Ro-5126766 SB-590885 sorafenib TAK-632	BRAF to ERK signaling pathway

		vemurafenib ZM-336372	
BRD4	ENSG00000141867	ARV-825 BI-2536 CPI-0610 CPI-203 I-BET-762 I-BET151 JQ1-(+) LY303511 OTX015 PFI-1 TG-101348	Bromodomain and extra terminal domain family
BTK	ENSG00000010671	acalabrutinib AVL-292 CNX-774 GDC-0834 ibrutinib LFM-A13 olmutinib ONO-4059 terreic-acid-(-) amygdalin AZ-10417808 DBeQ	NFKB pathway
CASP3	ENSG00000164305	minocycline NQDI-1 PAC-1 PETCM	TNF signaling pathway
CCR5	ENSG00000160791	sanguinarium-chloride adaptavir maraviroc TAK-220 vicriviroc	NFKB/PI3K/MAPK pathways
CD274	ENSG00000120217	PD1-PDL-inhibitor-1	PDL1-PD1 pathway
CDK1	ENSG00000170312	alvocidib aminopurvalanol-a AT-7519 BMS-265246 CDK1-5-inhibitor CHIR-99021 dinaciclib indirubin indirubin-3-monoxime JNJ-7706621 kenpaullone olomoucine PF-573228 PHA-767491 PHA-793887 purvalanol-a	Cell cycle regulator

		P276-00 RGB-286638 R547 SU9516 terameprocol TG-02 1-azakenpaullone 8-hydroxy-DPAT	
		AG-555 alvocidib aminopurvalanol-a AT-7519 BMS-265246 BMS-387032 BMS-536924 bosutinib BX-795 BX-912 dinaciclib indirubin-3-monoxime JNJ-7706621 NSC-625987 NU6027 olomoucine PF-573228 PHA-793887 PHA-848125 purvalanol-a purvalanol-b RGB-286638 roscovitine RX-3117 ryuvidine R547 SB-216763 SCH-900776 SU9516 TG-02	
CDK2	ENSG00000123374		Cell cycle regulator
		alvocidib AMG-925 arcyriaflavin-a AT-7519 LY2835219 NSC-625987 ON123300 palbociclib PHA-793887 PHA-848125 purvalanol-a purvalanol-b P276-00 RGB-286638	
CDK4	ENSG00000135446		Cell cycle regulator

		ribociclib ryuvidine R547 SU9516	
CDK6	ENSG00000105810	alvocidib AMG-925 aminopurvalanol-a apigenin AT-7519 chrysin fisetin LY2835219 palbociclib RGB-286638 ribociclib	Cell cycle regulator
CDK7	ENSG00000134058	alvocidib BMS-387032 BS-181 PF-573228 PHA-793887 PHA-848125 RGB-286638 R547 TG-02 THZ1 THZ1-R THZ2	Cell cycle regulator
CDK9	ENSG00000136807	alvocidib AT-7519 BMS-387032 CDK9-IN-6 dinaciclib LY2857785 PHA-793887 P276-00 RGB-286638 roscovitine TG-02	Cell cycle regulator
CHEK1	ENSG00000149554	AZD7762 BX-795 BX-912 CHIR-124 KN-62 LY2603618 LY2606368 LY294002 PD-98059 PF-477736 SB-202190 SB-203580 SB-218078	ATR pathway

		SCH-900776 U-0126 7-hydroxystaurosporine 8-hydroxy-DPAT	
CHEK2	ENSG00000183765	AZD7762 PF-477736 8-hydroxy-DPAT	ATM pathway
CREBBP	ENSG00000005339	SGC-CBP30	RAS-ERK pathway
CTNNB1	ENSG00000168036	ICG-001 PNU-74654 urea	Wnt signaling pathway
DHFR	ENSG00000228716	aminopterin chlorproguanil coenzyme-i dapsone methotrexate pemetrexed pralatrexate proguanil pyrimethamine succinylsulfathiazole sulfameter trimethoprim	Reductase family
DOT1L	ENSG00000104885	EPZ-5676 EPZ004777	Histone methyltransferase
DRD2	ENSG00000149295	acepromazine acetophenazine adoprazine afalanine AJ76-(+) alizapride amantadine amisulpride amoxapine aniracetam aripiprazole asenapine azaperone benperidol blonanserin BP-897 brexpiprazole bromocriptine bromopride bromperidol buspirone butaclamol cabergoline cariprazine carmoxirole chlorpromazine	Dopamine receptor family

chlorprothixene
clebopride
clorotepine
clozapine
deoxyepinephrine
desipramine
dihydrexidine
dihydroergocristine
dihydroergotamine
domperidone
dopamine
doxepin
droperidol
ergotamine
eticlopride
flupentixol
fluphenazine
fluphenazine-decanoate
fluspirilene
haloperidol
haloperidol-decanoate
iloperidone
imipramine
itopride
JNJ-37822681
L-693403
L-745870
levodopa
levomepromazine
levosulpiride
lisuride
loxapine
lumateperone
lurasidone
maprotiline
melperone
memantine
mesoridazine
metoclopramide
mianserin
minaprine
mirtazapine
molindone
nafadotride
nemonapride
nomifensine
nortriptyline
olanzapine
paliperidone
pardoprunox
PD-128907

PD-168077
pergolide
perospirone
perphenazine
pimavanserin
pimozide
pipamperone
pipotiazine-palmitate
piribedil
pramipexole
preclamol
prochlorperazine
promazine
promethazine
quetiapine
quinagolide
quinelorane
quinpirol(-)
r(-)-apomorphine
raclopride
remoxipride
risperidone
ropinirole
rotigotine
rotundine
SCH-202676
sertindole
SNAP-94847
spiperone
sumanirole
talipexole
terguride
tetrabenazine
thiethylperazine
thiopropazine
thioridazine
thiothixene
tiapride
trifluoperazine
triflupromazine
trimethobenzamide
trimipramine
UH-232-(+)
vilazodone
yohimbine
ziprasidone
zotepine
zuclopenthixol
2-CMDO
3'-fluorobenzylspiperone
7-hydroxy-DPAT

		8-hydroxy-PIPAT		
EGFR	ENSG00000146648	AEE788	EGFR-RAS-ERK signaling pathway	
		afatinib		
		AG-490		
		alvocidib		
		AP26113		
		AST-1306		
		AV-412		
		AZD3759		
		AZD8931		
		AZ5104		
		BIBU-1361		
		BIBX-1382		
		BMS-599626		
		BMS-690514		
		brigatinib		
		canertinib		
		CGP-52411		
		CGP-53353		
		chrysophanic-acid		
		CNX-2006		
		CUDC-101		
		dacomitinib		
		dovitinib		
		EGF816		
		erbstatin-analog		
		erlotinib		
		gefitinib		
		GW-583340		
		HKI-357		
		icotinib		
		lapatinib		
		lidocaine		
		mubritinib		
		neratinib		
		olmutinib		
		orantinib		
		OSI-420		
		osimertinib		
		PD-153035		
		PD-158780		
PD-168393				
pelitinib				
PKI-166				
poziotinib				
PP-121				
rociletinib				
tyrphostin-AG-1478				
tyrphostin-AG-18				
tyrphostin-AG-494				
tyrphostin-AG-835				
tyrphostin-AG-99				
vandetanib				

		vatalanib WHI-P154 WZ-3146 WZ-4002 WZ8040 XL-647 ZM-306416	
EHMT2	ENSG00000204371	A-366 BIX-01294 BRD4770 UNC0224 UNC0321 UNC0631 UNC0638 UNC0642 UNC0646 UNC0737	Histone Lysine Methyltransferase
EIF4E	ENSG00000151247	4EGI-1 4E1RCat	RAS-ERK pathway
EPHA2	ENSG00000142627	dasatinib regorafenib vandetanib	Tyrosine-Protein Kinase Receptor family
ERBB2	ENSG00000141736	AEE788 afatinib ARRY-334543 AST-1306 AV-412 AZD8931 BIBX-1382 BMS-536924 BMS-599626 BMS-690514 canertinib CP-724714 CUDC-101 dacomitinib FERb-033 GW-583340 lapatinib mubritinib neratinib PD-168393 poziotinib TAK-285 tucatinib tyrphostin-AG-825 tyrphostin-AG-879 vandetanib WAY-200070 WZ-4002 XL-647	EGF receptor family of receptor tyrosine kinases
ESR1	ENSG00000091831	afimoxifene	Oestrogen receptor signaling

allylestrenol
AZD9496
bazedoxifene
benfluralin
bisphenol-a
bithionol
chlorotrianisene
clomifene
danazol
dehydroepiandrosterone
dehydroepiandrosterone-sulfate
desogestrel
dienestrol
diethylstilbestrol
droloxifene
endoxifen
equol
erteberel
estetrol
estradiol
estradiol-acetate
estradiol-benzoate
estradiol-cypionate
estradiol-valerate
estramustine
estramustine-phosphate
estriol
estrone
estropipate
ethinyl-estradiol
ethynodiol-diacetate
etonogestrel
flouxymesterone
fosfestrol
fulvestrant
GDC-0810
genistein
gestrinone
hexestrol
lasofoxifene
levonorgestrel
medroxyprogesterone
melatonin
mestranol
mitotane
naloxone
norgestimate
ospemifene
PPT
progesterone
promestriene

		quineestrol raloxifene SNG-1153 tamoxifen tibolone toremifene trilostane Y-134 ZK-164015 17-hydroxyprogesterone- caproate	
		afimoxifene bazedoxifene bisphenol-a bithionol chlorotrianisene C11-Acetate dehydroepiandrosterone dehydroepiandrosterone-sulfate diarylpropionitrile diethylstilbestrol equol erteberel estradiol estramustine estramustine-phosphate estriol estrone estropipate ethinyl-estradiol fosfestrol fulvestrant genistein hexestrol lasofoxifene morin naringenin ospemifene PHTPP prinaberel raloxifene tamoxifen trilostane WAY-200070 Y-134 ZK-164015 17-hydroxyprogesterone- caproate	
ESR2	ENSG00000140009		Oestrogen receptor signaling
		CPI-169 CPI-360 E11 EPZ005687	
EZH2	ENSG00000106462		Histone-lysine N-methyltransferase

		EPZ011989 GSK2816126 GSK503 tazemetostat UNC1999 3-deazaneplanocin-A	
FGFR1	ENSG00000077782	AZD4547 brivanib CH-5183284 danusertib dovitinib erdafitinib HMN-214 lucitanib LY2874455 MK-2461 nintedanib NVP-BGJ398 orantinib pazopanib PD-161570 PD-173074 ponatinib regorafenib RG1530 semaxanib sorafenib TG-100801	FGF signaling pathway
FGFR2	ENSG00000066468	AEE788 AZD4547 CH-5183284 dovitinib erdafitinib LY2874455 MK-2461 nintedanib NVP-BGJ398 orantinib PD-173074 ponatinib regorafenib RG1530 thalidomide	FGF signaling pathway
FGFR3	ENSG00000068078	AEE788 AZD4547 brivanib-alaninate CH-5183284 dovitinib erdafitinib LY2874455 masitinib MK-2461	FGF signaling pathway

		nintedanib NVP-BGJ398 pazopanib PD-173074 ponatinib	
FGFR4	ENSG00000160867	AZD4547 BLU9931 erdafitinib LY2874455 nintedanib NVP-BGJ398 PD-173074 ponatinib	FGF signaling pathway
FGR	ENSG00000000938	dasatinib GDC-0980 PRT062607 rebastinib	FGF signaling pathway
FLT1	ENSG00000102755	axitinib brivanib cediranib dovitinib foretinib HMN-214 KRN-633 linifanib lucitanib MK-2461 motesanib nintedanib pazopanib PD-173074 regorafenib semaxanib sorafenib TG-100801 tivozanib toceranib vandetanib vatalanib ZM-306416	VEGF signling
FLT3	ENSG00000122025	AMG-925 BMS-690514 cediranib ceritinib crenolanib dovitinib ENMD-2076 gilteritinib GTP-14564 HMN-214 KW-2449	VEGF signaling

		lestaurtinib linifanib midostaurin MK-2461 NMS-1286937 pacritinib pexidartinib ponatinib quizartinib rebastinib RGB-286638 SGI-1776 sorafenib tandutinib TCS-359 TG-02 toceranib tyrphostin-AG-1296 UNC2025 URMC-099	
FLT4	ENSG00000037280	axitinib cediranib dovitinib foretinib HMN-214 KRN-633 lenvatinib linifanib MK-2461 motesanib nintedanib pazopanib PD-173074 regorafenib SAR131675 sorafenib tivozanib vandetanib vatalanib XL-647 ZM-306416	VEGF signaling
FRK	ENSG00000111816	bosutinib dasatinib regorafenib	Tyrosin kinase signaling
FYN	ENSG00000010810	bosutinib dasatinib	Src Family Tyrosine Kinase
GLS	ENSG00000115419	CB-839 L-glutamic-acid	Phosphate-activated amidohydrolase
GSK3A	ENSG00000105723	AZD1080 CHIR-98014 CHIR-99021 GSK-3-inhibitor-IX	Wnt signaling pathway

		indirubin	
		SB-216763	
		SB-415286	
		AR-A014418	
		AT7867	
		AZD1080	
		AZD2858	
		bisindolylmaleimide-ix	
		BX-795	
		BX-912	
		CDK1-5-inhibitor	
		CHIR-98014	
		CHIR-99021	
		ellagic-acid	
		enzastaurin	
		GSK-3-inhibitor-IX	
		indirubin-3-monoxime	
GSK3B	ENSG00000082701	kenpaullone	Wnt signaling pathway
		LY2090314	
		LY294002	
		PD-98059	
		PF-573228	
		RGB-286638	
		SB-202190	
		SB-203580	
		SB-216763	
		SB-415286	
		TCS2002	
		tideglusib	
		TWS-119	
		U-0126	
		1-azakenpaullone	
		8-hydroxy-DPAT	
		ACY-1215	
		AR-42	
		belinostat	
		dacinostat	
		entinostat	
		givinostat	
		JNJ-26481585	
		mocetinostat	
		nexturastat-a	
HDAC1	ENSG00000116478	NSC-3852	Histone deacetylase
		panobinostat	
		parthenolide(-)	
		PCI-24781	
		PCI-34051	
		phenylbutyrate	
		pivanex	
		pyroxamide	
		resminostat	
		RG2833	

		romidepsin SB-939 scriptaid sodium-butyrate tacedinaline trichostatin-a valproic-acid vorinostat 4SC-202	
HDAC2	ENSG00000196591	ACY-1215 aminophylline belinostat CUDC-907 dacinostat entinostat givinostat JNJ-26481585 lovastatin MC1568 mocetinostat oxtriphylline panobinostat PCI-24781 pivanex romidepsin scriptaid sodium-butyrate trichostatin-a valproic-acid vorinostat	Histone deacetylase
HDAC3	ENSG00000171720	ACY-1215 belinostat chidamide dacinostat entinostat givinostat JNJ-26481585 mocetinostat panobinostat PCI-24781 pivanex resminostat RGFP966 RG2833 romidepsin SB-939 scriptaid sodium-butyrate trichostatin-a vorinostat	Histone deacetylase
HDAC6	ENSG00000094631	ACY-1215 belinostat	Histone deacetylase

		bufexamac dacinostat droxinostat givinostat JNJ-26481585 nexturastat-a panobinostat PCI-24781 PCI-34051 resminostat romidepsin scriptaid trichostatin-a tubastatin-a vorinostat	
HDAC8	ENSG00000147099	ACY-1215 belinostat dacinostat droxinostat givinostat JNJ-26481585 panobinostat PCI-34051 pivanex resminostat romidepsin scriptaid sodium-butyrate trichostatin-a vorinostat	Histone deacetylase
HSP90AA1	ENSG00000080824	alvespimycin AT13387 BIIB021 CCT018159 ganetespib gedunin geldanamycin hexylene-glycol nedocromil NVP-AUY922 NVP-HSP990 PU-H71 retaspimycin rhein rifabutin SNX-5422 tanespimycin VER-49009	Heat Shock Protein 90 Alpha Family
IDH1	ENSG00000138413	AGI-5198 enasidenib ivosidenib	Isocitrate dehydrogenase family
IDH2	ENSG00000182054	AGI-6780	Isocitrate dehydrogenase family

IGF1R	ENSG00000140443	AG-1024	Receptor tyrosine kinase family
		AZD3463	
		AZD4547	
		BMS-536924	
		BMS-754807	
		ceritinib	
		GSK1838705A	
		GSK1904529A	
		linsitinib	
		NT157	
		NVP-ADW742	
		NVP-AEW541	
		podophyllotoxin	
		PQ-401	
		XL228	
IL1B	ENSG00000125538	bergenin	Interleukin-cytokine family
		diacerein	
		glucosamine	
		hypoestoxide	
		ibudilast	
		JTE-607	
IL6	ENSG00000136244	minocycline	Interleukin-cytokine family
		tanshinone-ii-a	
		ibudilast	
INSR	ENSG00000171105	JTE-607	Receptor tyrosine kinase family
		trofinetide	
		ceritinib	
		dovitinib	
		GSK1838705A	
		GSK1904529A	
ITK	ENSG00000113263	linsitinib	Interleukin-cytokine family
		NVP-AEW541	
JAK1	ENSG00000162434	NVP-TAE684	Jak-STAT signaling pathway
		pazopanib	
		AZD1480	
		baricitinib	
		curcumol	
		cyt387	
		filgotinib	
		itacitinib	
		NS-018	
		pacritinib	
		peficitinib	
		ruxolitinib	
		ruxolitinib-(S)	
		solcitinib	
JAK2	ENSG00000096968	TG-101348	Jak-STAT signaling pathway
		tofacitinib	
		WHI-P154	
		XL019	
		ZM-39923	
		AG-490	

		AT-9283 atiprimod AZD1480 AZ960 baricitinib CEP-33779 CKD-712 curcumol cyt387 filgotinib LY2784544 NS-018 NVP-BSK805 pacritinib peficitinib RGB-286638 ruxolitinib ruxolitinib-(S) TG-02 TG-101209 TG-101348 thiram tofacitinib WHI-P154 WP1130 XL019	
JAK3	ENSG00000105639	AG-490 AT-9283 AZD1480 curcumol cyt387 decernotinib filgotinib JAK3-inhibitor-V LY2784544 NS-018 pacritinib peficitinib ruxolitinib TG-101209 TG-101348 tofacitinib WHI-P154 XL019 ZM-39923	Jak-STAT signaling pathway
KDM1A	ENSG00000004487	GSK2879552 OG-L002 ORY-1001 tranylcypromine	Histone demethylase
KDR	ENSG00000128052	ACTB-1003 AEE788	VEGF family

altiratinib
anlotinib
apatinib
axitinib
AZD4547
BMS-536924
BMS-690514
BMS-817378
brivanib
BX-795
BX-912
cabozantinib
cediranib
CYC116
dovitinib
ENMD-2076
foretinib
fruquintinib
golvatinib
HMN-214
KI-8751
KRN-633
lenvatinib
linifanib
lucitanib
LY2874455
MK-2461
motesanib
neratinib
nintedanib
NVP-BGJ398
orantinib
OSI-930
pazopanib
PD-153035
PD-173074
PLX-4720
ponatinib
PP-121
regorafenib
semaxanib
SKLB1002
sorafenib
SU-4312
SU014813
telatinib
TG-100572
TG-100801
tie2-kinase-inhibitor
tivozanib
toceranib
tyrphostin-AG-879
vandetanib

		vatalanib XL-647 ZM-306416 ZM-323881	
KIT	ENSG00000157404	amuvatinib apatinib cediranib CP-673451 crenolanib dasatinib DCC-2618 dovitinib GTP-14564 HMN-214 imatinib linifanib lucitanib masitinib motesanib nilotinib OSI-930 pazopanib pexidartinib ponatinib quizartinib regorafenib semaxanib sorafenib tandutinib tivozanib	RAS-ERK signaling pathway
LAP3	ENSG00000002549	tosedostat	Leucine Aminopeptidase
LCK	ENSG00000182866	bisindolylmaleimide-ix BMS-536924 CGP-57380 dasatinib GW-788388 KN-62 LY294002 PD-98059 ponatinib PP-2 saracatinib SB-202190 SB-203580 SRC-kinase-inhibitor-I tozasertib U-0126 ZM-336372 8-hydroxy-DPAT	Src Family Tyrosine Kinase
LDHA	ENSG00000134333	coenzyme-i nicotinamide	Lactate Dehydrogenase

LYN	ENSG00000254087	bafetinib bosutinib dasatinib ponatinib PP-2 rebastinib tolimidone	Src Family Tyrosine Kinase
MAP2	ENSG00000078018	docetaxel estramustine estramustine-phosphate paclitaxel	Microtubule Associated Protein
MAP2K1	ENSG00000169032	arctigenin AS-703026 BI-847325 bosutinib MEK162 nobiletin PD-0325901 PD-184352 PD-198306 PD-318088 PD-98059 refametinib reversine Ro-4987655 Ro-5126766 selumetinib TAK-733 trametinib U-0126	RAS-ERK signaling pathway
MAP2K2	ENSG00000126934	AS-703026 BI-847325 bosutinib MEK1-2-inhibitor MEK162 PD-198306 refametinib Ro-5126766 trametinib U-0126	RAS-ERK signaling pathway
MAP3K8	ENSG00000107968	cot-inhibitor-1 cot-inhibitor-2	RAS-ERK signaling pathway
MAP4	ENSG00000047849	docetaxel paclitaxel	Microtubule Associated Protein
MAPK1	ENSG00000100030	arsenic-trioxide bisindolylmaleimide-ix BMS-536924 CHIR-99021 FR-180204 GDC-0994 isoprenaline	RAS-ERK signaling pathway

		KN-62 LY294002 olomoucine PD-98059 purvalanol-b ravoxertinib SB-202190 SB-203580 TIC10 U-0126 VX-11e	
MAPK11	ENSG00000185386	AMG-548 bisindolylmaleimide-ix doramapimod EO-1428 KN-62 LY294002 PD-98059 PH-797804 regorafenib SB-202190 SB-203580 SB-239063 talmapimod U-0126 VX-702 VX-745	RAS-ERK signaling pathway
MAPK12	ENSG00000188130	AMG-548 bisindolylmaleimide-ix doramapimod KN-62 LY294002 PD-98059 SB-202190 SB-203580 U-0126 VX-702 VX-745	RAS-ERK signaling pathway
MAPK13	ENSG00000156711	AMG-548 doramapimod	RAS-ERK signaling pathway
MAPK14	ENSG00000112062	AMG-548 bisindolylmaleimide-ix CMPD-1 doramapimod EO-1428 GW-788388 JX-401 KN-62 losmapimod LY2228820 LY294002	RAS-ERK signaling pathway

		PD-98059 pexmetinib PH-797804 QX-314 RWJ-67657 SB-202190 SB-203580 SB-239063 SB-242235 SD-169 semapimod skeptinone-1 SKF-86002 SX-011 TA-01 TAK-715 talmapimod tie2-kinase-inhibitor tyrphostin-AG-1478 U-0126 VX-702 VX-745 ZM-336372 8-hydroxy-DPAT	
MAPK3	ENSG00000102882	arsenic-trioxide CID-5458317 FR-180204 GDC-0994 purvalanol-b ravoxertinib sulindac	RAS-ERK signaling pathway
MAPK7	ENSG00000166484	BIX-02189 ERK5-IN-1 XMD17-109 XMD8-92	RAS-ERK signaling pathway
MAPK8	ENSG00000107643	antagonist-g BI-78D3 bisindolylmaleimide-ix CC-401 KN-62 LY294002 PD-98059 PGL5001 pyrazolanthrone SB-202190 SB-203580 SR-3306 SU3327 U-0126	RAS-ERK signaling pathway
MAPK9	ENSG00000050748	PGL5001 pyrazolanthrone	RAS-ERK signaling pathway

		RGB-286638 SB-203580 SR-3306	
MAPT	ENSG00000186868	docetaxel leucomethylene-blue paclitaxel	Microtubule Associated Protein
MCL1	ENSG00000143384	bithionol morin rosmarinic-acid TW-37	BCL2 Family Member
MDM2	ENSG00000135679	AMG-232 CGM097 idasanutlin JNJ-26481585 nutlin-3 RG7112 RITA SAR405838 serdemetan	TP53-MDM2 pathway
MET	ENSG00000105976	alectinib altiratinib AMG-208 AMG-337 AMG458 amuvatinib BMS-536924 BMS-777607 BMS-817378 cabozantinib crizotinib EMD-1214063 foretinib golvatinib INC-280 JNJ-38877605 LY2801653 MGCD-265 MK-2461 MK-8033 NVP-BVU972 PF-04217903 PHA-665752 savolitinib SGX523 SU-11274 tivantinib	RAS-ERK signaling pathway
MKNK1	ENSG00000079277	CGP-57380	
MTOR	ENSG00000198793	AZD2014 AZD8055 AZ20 beta-hydroxy-beta-	HGF-MET-PI3K signaling pathway

		methylbutyrate BGT226 CC-115 CC-223 chrysophanic-acid CH5132799 compound-401 deforolimus everolimus GDC-0980 GSK2126458 ku-0063794 LY294002 LY3023414 MLN0128 NVP-BEZ235 OSI-027 palomid-529 PF-04691502 PF-05212384 PI-103 pimecrolimus PKI-179 PP-121 PP242 SAR-245409 SB-2343 sirolimus temsirolimus torin-1 torin-2 VE-822 voxtalisib WAY-600 WYE-125132 WYE-354 XL388	
MYC	ENSG00000136997	TWS-119	MYC family
NAMPT	ENSG00000105835	FK-866 GMX1778 STF-118804	Nicotinamide Phosphoribosyltransferase
NFKB1	ENSG00000109320	andrographolide arglabin aspirin pranlukast thalidomide triflusal	NFKB pathway
NR2C2	ENSG00000177463	retinol tretinoin	Hormone receptor family
NTRK1	ENSG00000198400	amitriptyline danusertib	Tyrosine kinase receptor family

		entrectinib GW-441756 GW-5074 imatinib lestaurtinib LOXO-101 MK-2461 PHA-848125 regorafenib tyrphostin-AG-879	
NUDT1	ENSG00000106268	crizotinib-(S) TH588	Hydrolase family
P4HB	ENSG00000185624	ribostamycin-sulfate	Hydroxylase famliy
PAK1	ENSG00000149269	FRAX486 IPA-3 RKI-1447	PAK family - P21 activated kinase
PAK4	ENSG00000130669	FRAX486 GSK690693 PF-03758309	PAK family - P21 activated kinase
PARP1	ENSG00000143799	AG-14361 BYK-204165 DR-2313 E7449 iniparib inosine nicotinamide niraparib NU-1025 olaparib PJ-34 rucaparib S-111 veliparib 3-amino-benzamide 4-HQN	TP53-MDM2 pathway
PARP2	ENSG00000129484	AC-55541 E7449 olaparib rucaparib talazoparib UPF-1069 veliparib	TP53-MDM2 pathway
PARP3	ENSG00000041880	DR-2313 ME0328 PJ-34	TP53-MDM2 pathway
PDGFRA	ENSG00000134853	BMS-536924 cediranib CP-673451 crenolanib DCC-2618 dovitinib ENMD-2076	PDGF-PDGFR-RAS-ERK signaling pathway

		HMN-214 imatinib lucitanib masitinib nintedanib orantinib pazopanib PD-173074 ponatinib PP-121 quizartinib regorafenib semaxanib TAK-593 tivozanib toceranib trapidil	
		anlotinib BMS-536924 cediranib CP-673451 crenolanib dasatinib dovitinib flumatinib GTP-14564 HMN-214 imatinib linifanib lucitanib masitinib MK-2461 nintedanib ON123300 orantinib pazopanib PD-173074 quizartinib regorafenib semaxanib sorafenib SU-4312 tandutinib tivozanib toceranib vatalanib	
PDGFRB	ENSG00000113721		PDGF-PDGFR-RAS-ERK signaling pathway
		AZD7545 BX-795 BX-912 dichloroacetate	PI3K signaling pathway
PDK1	ENSG00000152256		
PGD	ENSG00000142657	dacarbazine	Phosphogluconate Dehydrogenase

		ketotifen	
		pentetic-acid	
		alpelisib	
		AS-604850	
		AZD6482	
		AZD8835	
		A66	
		BGT226	
		buparlisib	
		caffeine	
		CH5132799	
		copanlisib	
		GDC-0349	
		GDC-0941	
		GDC-0980	
		GSK2126458	
		idelalisib	
PIK3CA	ENSG00000121879	IPI-145	HGF-MET-PI3K signaling pathway
		LY294002	
		MLN0128	
		MLN1117	
		NVP-BEZ235	
		PF-04691502	
		PF-05212384	
		PI-103	
		PIK-293	
		PIK-75	
		PP-121	
		SB-2343	
		taselisib	
		TG100-115	
		voxtalisib	
		wortmannin	
		XL-147	
		acalisib	
		alpelisib	
		AZD6482	
		AZD8186	
		BGT226	
		caffeine	
		CH5132799	
		copanlisib	
PIK3CB	ENSG00000051382	GDC-0941	HGF-MET-PI3K signaling pathway
		GDC-0980	
		GSK2126458	
		GSK2636771	
		idelalisib	
		IPI-145	
		LY294002	
		PI-103	
		PIK-293	
		PIK-294	

		PIK-75 PP-121 SB-2343 TGX-221 TG100-115 ZSTK-474	
		acalisib alpelisib AMG-319 AMG319 AZD6482 AZD8186 AZD8835 caffeine CH5132799 copanlisib GDC-0941 GDC-0980 GSK2126458 idelalisib IPI-145 LY294002 MLN0128 NVP-BEZ235 PI-103 PIK-293 PIK-294 PIK-75 PP-121 SB-2343 TGX-221 TG100-115 wortmannin XL-147 ZSTK-474	
PIK3CD	ENSG00000171608		HGF-MET-PI3K signaling pathway
		alpelisib AS-252424 AS-604850 AZD6482 BGT226 buparlisib CAY10505 CH5132799 copanlisib CZC24832 GDC-0941 GDC-0980 GSK1059615 GSK2126458 idelalisib IPI-145 LY294002	
PIK3CG	ENSG00000105851		HGF-MET-PI3K signaling pathway

		MLN0128 myricetin NVP-BEZ235 PI-103 PIK-293 PIK-294 PIK-75 PIK-93 PP-121 quercetin SAR-245409 SB-2343 TG100-115 VE-822 wortmannin XL-147 ZSTK-474	
PIM1	ENSG00000137193	adenosine-phosphate ammonium-perfluorocaprylate AZD1208 BMS-863233 dexfosfoserine GF109203X PIM-1-Inhibitor-2 quercetin SGI-1776 SMI-4a 10-DEBC	Serine/Threonine Kinase family
PIM2	ENSG00000102096	AZD1208 SGI-1776	Serine/Threonine Kinase family
PIM3	ENSG00000198355	AZD1208 SGI-1776	Serine/Threonine Kinase family
PLK1	ENSG00000166851	BI-2536 GSK461364 GW-843682X LY294002 NMS-1286937 rigosertib TAK-960 volasertib wortmannin	Serine/threonine kinase family
PORCN	ENSG00000102312	ETC-159 IWP-L6 LGK-974 wnt-c59	WNT signaling pathway
PPM1D	ENSG00000170836	GSK2830371	Serine/threonine kinase family
PRKAA1	ENSG00000132356	adenosine-phosphate adenosine-triphosphate aspirin phenformin	Serine/threonine kinase family
PRKCA	ENSG00000154229	bisindolylmaleimide-ix	Serine/threonine kinase family

		C-1 ellagic-acid enzastaurin go-6983 ingenol-mebutate KN-62 LY294002 myricitrin PD-98059 SB-202190 SB-203580 SC-10 SC-9 sotrastaurin tamoxifen U-0126 vitamin-E 8-hydroxy-DPAT	
PRKCB	ENSG00000166501	CGP-53353 ellagic-acid enzastaurin go-6983 ingenol-mebutate sotrastaurin tamoxifen vitamin-E 8-hydroxy-DPAT	Serine/threonine kinase family
PRKCD	ENSG00000163932	afimoxifene enzastaurin go-6983 ingenol-mebutate sotrastaurin tamoxifen 8-hydroxy-DPAT	Serine/threonine kinase family
PRKCE	ENSG00000171132	afimoxifene BMY-45618 ingenol-mebutate sotrastaurin tamoxifen Y-27632 8-hydroxy-DPAT	Serine/threonine kinase family
PRKCG	ENSG00000126583	enzastaurin go-6983 ingenol-mebutate midostaurin tamoxifen 8-hydroxy-DPAT	Serine/threonine kinase family
PRKCH	ENSG00000027075	sotrastaurin	Serine/threonine kinase family
PRKCI	ENSG00000163558	aurothioglucose GF109203X tamoxifen	Serine/threonine kinase family

PRKCQ	ENSG00000065675	afimoxifene dexfosfoserine GSK690693 sotrastaurin tamoxifen	Serine/threonine kinase family
PRKCZ	ENSG00000067606	afimoxifene arachidonic-acid GF109203X go-6983 tamoxifen	Serine/threonine kinase family
PRKDC	ENSG00000253729	caffeine compound-401 KU-55933 LY294002 NU-7026 NU-7441 PI-103 PIK-75 PP-121 wortmannin	Serine/threonine kinase family
PSMB1	ENSG0000008018	bortezomib carfilzomib MG-132	Multicatalytic proteinase complex
PSMD1	ENSG00000173692	bortezomib	Multicatalytic proteinase complex
PTGS2	ENSG00000073756	aceclofenac acemetacin alpha-linolenic-acid amfenac aminosalicylate amproxicam amtolmetin-guacil arundic-acid asaraldehyde aspirin azapropazone balsalazide bendazac bromfenac carprofen celecoxib cicloprofen curcumin deracoxib diclofenac diflunisal dihomo-gamma-linolenic-acid doconexent DUP-697 epirizole etodolac etofenamate	Prostaglandin-endoperoxide synthase family

etoricoxib
felbinac-ethyl
fenbufen
fenoprofen
fentiazac
firocoxib
FK-3311
floctafenine
flufenamic-acid
flurbiprofen-(+/-)
flurbiprofen-(S)-(+)
fosfosal
gamma-linolenic-acid
ginsenoside-c-k
honokiol
ibuprofen
ibuprofen-(s)
ibuprofen-lysine
ibuprofen-piconol
icosapent
iguratimod
indobufen
indomethacin
indoprofen
isoxicam
ketoprofen
ketorolac
lenalidomide
licofelone
lornoxicam
loxoprofen
lumiracoxib
meclofenamic-acid
mefenamic-acid
meloxicam
mesalazine
metoxibutropate
nabumetone
naproxen
nepafenac
niflumic-acid
nimesulide
NO-ASA
oxaprozin
oxyphenbutazone
paracetamol
phenazone
phenylbutazone
piroxicam
pomalidomide
proglumetacin

		propacetamol proquazone pterostilbene resveratrol rofecoxib rutaecarpine RWJ-67657 salicylic-acid sasapyrine SB-239063 sodium-salicylate sulfasalazine sulindac suprofen tenoxicam thalidomide thioctic-acid tiaprofenic-acid tolmetin tropesin ufenamate valdecoxib	
PTK2	ENSG00000169398	defactinib ENMD-2076 NVP-TAE226 PF-562271	Serine/threonine kinase family
PTPN11	ENSG00000179295	BVT-948	Protein tyrosine phosphatase (PTP) family
PTPN6	ENSG00000111679	sodium-stibogluconate	Protein tyrosine phosphatase (PTP) family
RAC1	ENSG00000136238	dextromethorphan EHop-016	RAS superfamily
RAF1	ENSG00000132155	AZ-628 CEP-32496 dabrafenib GW-5074 LY3009120 PD-98059 regorafenib Ro-5126766 SB-203580 sorafenib U-0126 vemurafenib ZM-336372	EGFR-RAS-ERK signaling pathway
RARA	ENSG00000131759	AC-55649 acitretin adapalene AGN-195183 AM-580 CH55 EC-23 etretinate	Retinoic acid signaling pathway

		fenretinide isotretinoin tamibarotene tazarotene tretinoin TTNPB	
RARB	ENSG00000077092	AC-55649 acitretin adapalene adarotene CH55 EC-23 etretinate isotretinoin LE-135 tamibarotene tazarotene tretinoin TTNPB	Retinoic acid signaling pathway
RARG	ENSG00000172819	acitretin adapalene adarotene CD-1530 CD-437 EC-23 etretinate isotretinoin palovarotene tazarotene tretinoin TTNPB	Retinoic acid signaling pathway
RET	ENSG00000165731	apatinib danusertib fostamatinib HMN-214 imatinib linifanib lucitanib ponatinib PP-1 quizartinib regorafenib semaxanib sorafenib vandetanib	RAS-ERK signaling pathway
ROCK1	ENSG00000067900	AT13148 bisindolylmaleimide-ix fasudil GSK429286A hydroxyfasudil KN-62 LX7101	RhoGEF pathway

		LY294002 PD-98059 ripasudil RKI-1447 SAR407899 SB-202190 SB-203580 U-0126 Y-27632 Y-39983	
ROCK2	ENSG00000134318	AT13148 fasudil KD025 LX7101 ripasudil RKI-1447 Y-27632 Y-39983	RhoGEF pathway
RPS6KB1	ENSG00000108443	bisindolylmaleimide-ix KN-62 LY2584702 LY294002 PD-98059 PF-4708671 PHA-767491 SB-202190 SB-203580 SB-415286 U-0126	PI3K-AKT-MTOR pathway
RRM1	ENSG00000167325	caracemide cladribine clofarabine didox enocitabine fludarabine fludarabine-phosphate gemcitabine gemcitabine-elaidate hydroxyurea imexon triapine	RAS-ERK signaling pathway
RXRA	ENSG00000186350	acitretin adapalene AGN-194310 bexarotene BMS-649 etodolac etretinate GW-9662 peretinoin retinol	Retinoic acid signaling pathway

RXRB	ENSG00000204231	acitretin adapalene AGN-194310 bexarotene etretinate retinol T-0901317 tazarotene tretinoin	Retinoic acid signaling pathway
SGK3	ENSG00000104205	AT13148	PI3K-AKT-MTOR pathway
SMO	ENSG00000128602	BMS-833923 CUR-61414 fluocinonide glasdegib PF-5274857 purmorphamine SANT-1 SANT-2 sonidegib taladegib vismodegib	Hedgehog signaling pathway
SRC	ENSG00000197122	bosutinib citric-acid dasatinib ENMD-2076 KX2-391 PD-168393 ponatinib PP-121 PP-2 purvalanol-a rebastinib saracatinib SB-203580 TG-100572 TG-100801 tolimidone vandetanib XL228 1-naphthyl-PP1	SRC pathway
STAT3	ENSG00000168610	acitretin atiprimod bardoxolone-methyl cryptotanshinone meisoindigo napabucasin niclosamide ochromycinone STAT3-inhibitor-VI WP1066	Jak-STAT signaling pathway
SYK	ENSG00000165025	BAY-61-3606 ellagic-acid	TLR signaling

		ER-27319 fostamatinib GDC-0980 GS-9973 PRT062070 PRT062607 R112	
TEK	ENSG00000120156	ACTB-1003 altiratinib linifanib pexmetinib ponatinib regorafenib vandetanib	Tie2 family
TNF	ENSG00000232810	amrinone baicalein bergenin chloroquine clenbuterol CPI-1189 epinephrine ethyl-pyruvate glucosamine glycitein hypoestoxide JTE-607 lenalidomide ligustilide pentoxifylline pirfenidone pomalidomide pranlukast SB-203580 tanshinone-ii-a thalidomide trofinetide	TNF signaling pathway
TNFSF11	ENSG00000120659	lenalidomide	TNF signaling pathway
TNFSF13B	ENSG00000102524	citric-acid	TNF signaling pathway
TOP1	ENSG00000198900	aclarubicin beta-lapachone camptothecin exatecan-mesylate genz-644282 irinotecan luteolin nemorubicin pyrazoloacridine rubitecan SN-38 sodium-stibogluconate TAS-103	Topoisomerase family

		topotecan 10-hydroxycamptothecin 9-aminocamptothecin	
		aclarubicin aldoxorubicin amonafide amrubicin amsacrine ciprofloxacin daunorubicin dexrazoxane doxorubicin enoxacin epirubicin etoposide etoposide-phosphate garenoxacin genistein idarubicin levofloxacin lomefloxacin merbarone mitoxantrone moxifloxacin nemorubicin norfloxacin ofloxacin pefloxacin pirarubicin pixantrone podophyllotoxin pyrazoloacridine sparfloxacin teniposide trovafloxacin valrubicin voreloxin	
TOP2A	ENSG00000131747		Topoisomerase family
		amonafide amrubicin daunorubicin dexrazoxane etoposide teniposide	
TOP2B	ENSG00000077097		Topoisomerase family
		allicin alpha-linolenic-acid AM-404 AMG-517 AMG-9810 anandamide aspartame camphor-(+)	
TRPV1	ENSG00000196689		TRP family of ion channels

		capsaicin capsazepine evodiamine icosapent JNJ-17203212 MK-2295 nonivamide olvanil paracetamol piperine SB-366791 SB-705498 2-APB 6-iodo-nordihydrocapsaicin	
TUBB	ENSG00000196230	ABT-751 albendazole cabazitaxel carbendazim cevipabulin colchicine CYT-997 D-64131 docetaxel dolastatin-10 epothilone-b epothilone-d fenbendazole flubendazole ixabepilone mebendazole oxibendazole paclitaxel parbendazole podophyllotoxin verubulin vinblastine vincristine vindesine vinorelbine 2-methoxyestradiol	Microtubule Associated Protein
TXN	ENSG00000136810	C11-Acetate PX-12	Redox signaling
TYMS	ENSG00000176890	capecitabine carmofur doxifluridine enocitabine floxuridine ftorafur gemcitabine gemcitabine-elaidate leucovorin nolatrexed	Thymidylate synthase

		pemetrexed pralatrexate raltitrexed trifluridine trimethoprim WR99210 5-fluorouracil 5-FP	
TYRO3	ENSG00000092445	BMS-777607 LDC1267	Protein Tyrosine Kinase family
VEGFA	ENSG00000112715	carvedilol glucicazide minocycline pidolic-acid trometamol vandetanib	VEGF family
WEE1	ENSG00000166483	MK-1775 PD-407824	Serine/Threonine Kinase family
XIAP	ENSG00000101966	AZD5582 birinapant cisplatin CUDC-427 embelin GDC-0152 LCL-161 SM-164	BCL2 signaling
XPO1	ENSG00000082898	elactocin KPT-185 KPT-276 selinexor	Cell cycle regulator

Supplementary Table S1B. shRNAs targeting each candidate gene are reported. For each cell line sequenced, LOG₂ ratio of each replica calculated; call for depletion in all tree replicates; gene depletion call.

Cell line	shRNAs	LOG2R(1)	LOG2R(2)	LOG2R(3)	Triplicate shRNA Hit
CAR1	BIRC5_1908	-5,85	-7,39	-4,04	0
	BIRC5_1909	-6,21	-6,91	-7,64	1
	BIRC5_1910	-8,56	-7,15	-6,91	1
	BIRC5_1911	1,15	-1,89	-0,95	0
	BIRC5_1912	-0,96	-7,14	-5,28	0
	BIRC5_1913	-0,68	-2,55	-2,59	0
	BIRC5_599	-8,87	-7,51	-8,20	1
	BIRC5_600	-7,96	-7,55	-7,42	1
	BIRC5_601	-7,39	-7,82	-4,23	0
	BIRC5_602	-10,89	1,81	-9,36	0
CAR1	EGFR_1660	-3,43	-2,36	-11,33	0
	EGFR_1701	-9,64	-7,98	-9,40	1
	EGFR_1753	-10,06	-8,28	-9,61	1
	EGFR_716	3,74	-7,11	-3,36	0
	EGFR_717	-10,14	-7,83	-7,25	1
	EGFR_718	-1,22	-9,98	-4,53	0
	EGFR_719	-0,22	-8,64	-10,63	0
	EGFR_720	-10,92	-10,02	-7,31	1
	EGFR_721	-3,38	-5,43	-5,25	0
	EGFR_722	-5,05	-4,10	-4,77	0
CAR1	LAP3_2092	-4,25	-1,21	-5,51	0
	LAP3_2093	-2,38	-2,40	-1,41	0
	LAP3_2094	-11,38	-9,06	-9,13	1
	LAP3_2095	-4,07	-3,46	-12,70	0
	LAP3_2096	-10,42	-8,18	-8,59	1
	LAP3_947	-5,02	-3,89	-2,28	0
	LAP3_948	-6,16	-9,58	-10,06	1
	LAP3_949	-3,21	-3,77	-1,94	0
	LAP3_950	-11,14	-6,28	-7,04	1
	LAP3_951	-4,64	-11,95	-2,35	0
WIDR	BRAF_1610	1,08	-1,00	-0,63	0
	BRAF_1795	-2,17	-1,26	-1,27	1
	BRAF_613	-1,52	-1,35	-3,85	1
	BRAF_614	-0,37	-3,56	-0,33	0
	BRAF_615	-5,58	-1,01	1,24	0
	BRAF_616	-1,93	-1,96	-1,75	1
	BRAF_617	-2,46	-0,72	-0,83	0
	BRAF_618	-6,94	-3,61	0,35	0
	BRAF_619	-1,34	-1,58	-1,53	1
	BRAF_620	-1,84	-7,33	-3,94	1
WIDR	GLS_2030	0,64	0,00	0,21	0
	GLS_2031	-0,52	0,13	-0,61	0
	GLS_2032	0,40	0,61	-0,91	0
	GLS_2033	-1,08	-1,54	-1,12	1
	GLS_2034	-0,68	-0,55	-1,01	0
	GLS_807	-2,54	-3,38	-2,13	1
	GLS_808	1,06	1,06	0,64	0

	GLS_809	-3,07	-3,22	-3,34	1
	GLS_810	-5,07	-1,95	-2,15	1
	GLS_811	-0,33	-1,25	-0,89	0
WIDR	HDAC8_1830	-3,21	-4,17	-1,24	1
	HDAC8_2042	1,55	1,40	1,52	0
	HDAC8_2043	-0,37	-2,47	-1,62	0
	HDAC8_2044	-2,99	-1,64	-2,51	1
	HDAC8_2045	-0,84	-0,18	-0,45	0
	HDAC8_856	1,11	0,82	0,28	0
	HDAC8_857	-2,04	-3,05	-1,12	1
	HDAC8_858	1,07	1,58	0,89	0
	HDAC8_859	-0,97	-0,87	-0,70	0
	HDAC8_860	-2,92	-1,50	-3,42	1
WIDR	MAPK1_1004	-1,02	-0,45	-1,17	0
	MAPK1_1005	-1,09	-1,07	-0,85	1
	MAPK1_1006	-1,53	-2,61	-1,32	1
	MAPK1_1007	-0,80	-0,46	-0,40	0
	MAPK1_1008	-2,47	-1,45	-1,84	1
	MAPK1_1009	-1,88	-2,19	0,18	0
	MAPK1_1010	-1,54	0,44	-0,01	0
	MAPK1_1717	-0,21	-0,13	0,02	0
	MAPK1_2122	-0,03	-4,17	-3,95	0
	MAPK1_2123	-1,70	-1,73	-2,51	1
WIDR	PRKAA1_1238	-1,10	-2,56	-2,27	1
	PRKAA1_1239	-1,43	1,40	-1,58	0
	PRKAA1_1240	-2,00	-1,11	-1,04	1
	PRKAA1_1241	-1,37	-1,70	-1,46	1
	PRKAA1_1539	0,90	0,80	0,79	0
	PRKAA1_1540	0,20	-1,47	-1,33	0
	PRKAA1_1541	-1,72	-2,43	-1,33	1
	PRKAA1_1789	2,69	2,75	2,51	0
	PRKAA1_1790	-0,57	-1,43	-2,07	0
	PRKAA1_1791	1,63	1,12	1,14	0
WIDR	PRKCI_1267	-1,39	-0,53	-1,91	0
	PRKCI_1268	-0,37	0,23	-0,04	0
	PRKCI_1269	-2,58	-1,78	-2,55	1
	PRKCI_1270	-1,46	-1,81	-1,87	1
	PRKCI_1271	-1,15	-1,69	-0,89	1
	PRKCI_1272	-1,03	-1,50	0,99	0
	PRKCI_1604	3,37	4,24	4,31	0
	PRKCI_1605	-0,71	1,25	0,42	0
	PRKCI_1787	1,53	0,83	1,12	0
	PRKCI_2255	-3,26	-1,26	-2,01	1
LIM2099	CDK1_1944	2,92	2,57	0,93	0
	CDK1_1945	0,96	0,30	0,14	0
	CDK1_1946	-5,39	-1,58	-3,55	1
	CDK1_1947	-3,06	0,55	-0,84	1
	CDK1_1948	-7,33	6,56	-1,14	0
	CDK1_1949	0,20	0,62	-0,21	0
	CDK1_1950	-0,02	2,77	1,88	0
	CDK1_641	-2,44	-2,94	-1,81	1

	CDK1_642	-4,85	-5,44	-4,28	1
	CDK1_643	0,57	0,55	0,21	0
LIM2099	FYN_1575	0,05	5,10	3,93	0
	FYN_1576	-2,57	-1,69	-5,52	1
	FYN_1833	0,82	-0,60	-0,34	0
	FYN_1834	2,43	2,00	2,29	0
	FYN_801	1,28	2,27	1,21	0
	FYN_802	-2,56	0,64	-3,90	1
	FYN_803	-1,29	2,82	1,94	0
	FYN_804	-0,79	5,71	0,82	0
	FYN_805	-1,54	-1,40	-1,40	1
	FYN_806	-5,47	-1,46	-1,66	1
SW403	CDK1_1944	0,01	-0,11	0,53	0
	CDK1_1945	1,14	1,38	0,84	0
	CDK1_1946	-3,15	-0,13	-2,52	0
	CDK1_1947	-0,65	0,81	-1,54	0
	CDK1_1948	-9,31	-8,88	-8,54	1
	CDK1_1949	-5,06	-3,30	0,84	0
	CDK1_1950	-1,50	-3,18	-8,13	1
	CDK1_641	-2,91	-2,39	-1,08	1
	CDK1_642	-1,95	3,30	-8,36	0
	CDK1_643	-1,21	-3,64	-2,06	1
SW403	CDK4_1508	3,24	-0,19	-2,38	0
	CDK4_1734	4,76	-9,70	-0,59	0
	CDK4_652	-5,72	-2,68	-1,88	1
	CDK4_653	-0,90	-5,22	-3,27	1
	CDK4_654	6,32	-0,71	-6,10	0
	CDK4_655	-9,62	-9,52	-1,49	1
	CDK4_656	-0,20	-0,06	0,99	0
	CDK4_657	-0,57	-2,75	-1,23	0
	CDK4_658	0,88	1,40	-7,44	0
	CDK4_659	-1,90	-2,03	-1,80	1
SW403	HDAC6_2039	-1,24	-2,50	-5,23	1
	HDAC6_2040	-2,08	-1,63	0,49	0
	HDAC6_2041	-0,81	-6,58	-4,91	1
	HDAC6_849	-2,00	-2,47	-2,55	1
	HDAC6_850	3,30	2,74	0,83	0
	HDAC6_851	1,99	0,04	-0,27	0
	HDAC6_852	-0,39	-0,95	0,53	0
	HDAC6_853	-0,59	2,01	1,46	0
	HDAC6_854	-2,72	-5,76	-1,64	1
	HDAC6_855	-1,45	0,28	-0,97	0
SW403	PARP1_1147	2,73	-0,23	-2,52	0
	PARP1_1148	-0,95	-2,11	-4,38	1
	PARP1_1149	-1,82	-1,54	-1,95	1
	PARP1_1150	-2,18	1,64	5,08	0
	PARP1_1151	0,07	-1,81	-0,35	0
	PARP1_1152	-2,67	-2,63	-1,70	1
	PARP1_1622	0,39	0,60	1,54	0
	PARP1_2191	3,91	0,53	1,53	0
	PARP1_2192	-5,79	-2,66	-2,95	1

	PARP1_2193	1,76	-2,56	-0,14	0
SW403	PGD_1173	-7,43	-0,27	-2,38	0
	PGD_1174	0,22	-3,31	-1,77	0
	PGD_1175	-8,08	0,81	-5,96	0
	PGD_1176	-5,45	-5,28	-1,29	1
	PGD_1647	0,47	-4,68	-8,65	0
	PGD_1648	-2,76	-3,28	-2,80	1
	PGD_1649	-1,91	-1,62	-4,91	1
	PGD_1819	0,49	0,49	1,09	0
	PGD_1820	-6,62	-3,40	-4,60	1
	PGD_2208	-0,40	0,26	-2,22	0
SW403	PRKCH_1265	2,57	-0,92	-0,75	0
	PRKCH_1266	1,22	0,72	0,34	0
	PRKCH_1611	-0,14	1,27	4,70	0
	PRKCH_1612	-4,34	-0,77	-0,88	0
	PRKCH_2249	-4,00	-3,36	-1,50	1
	PRKCH_2250	4,60	1,36	2,84	0
	PRKCH_2251	-1,55	-1,58	-1,49	1
	PRKCH_2252	-3,27	-2,44	-2,48	1
	PRKCH_2253	-2,14	-0,94	-1,03	1
	PRKCH_2254	8,42	-9,58	-9,63	0
SW403	TUBB_1459	2,75	-2,68	-7,62	0
	TUBB_1460	-10,65	-0,60	-2,37	0
	TUBB_1461	-9,44	-11,47	-2,11	1
	TUBB_2394	-5,05	-3,57	-8,12	1
	TUBB_2395	-3,02	-5,05	-7,67	1
	TUBB_2396	-2,35	-2,50	-2,26	1
	TUBB_2397	0,46	-0,52	-0,38	0
	TUBB_2398	-4,44	-2,47	1,70	0
	TUBB_2399	-2,65	-1,68	-0,69	0
	TUBB_2400	-0,92	-7,40	-1,45	1

Supplementary Table S1C. Expression levels expressed as TMM of each candidate hit in the CRC cell lines used for the synthetic lethal screening.

Gene	CAR1	LIM2099	SW403	WIDR
TUBB	4076.296	10098.391	4903.074	2268.020
EGFR	711.560	387.6250	31.195	280.3801
PGD	2564.576	1263.310	2009.560	1563.810
LAP3	752.781	1085.649	612.888	2131.641
CDK1	302.359	478.156	1635.901	603.011
CDK4	994.588	1089.631	1342.928	895.392
PARP1	968.608	1244.899	926.659	340.057
BIRC5	432.197	1177.517	945.513	245.406
GLS	324.003	955.374	267.322	174.226
PRKAA1	272.887	187.631	214.635	772.220
PRKCI	231.198	147.509	170.540	569.553
MAPK1	192.555	286.090	139.834	190.285
FYN	58.214	334.174	59.743	317.741
HDAC6	225.543	185.989	159.662	296.634
BRAF	74.448	25.649	19.513	187.492
PRKCH	100.0732	12.522	36.291	122.889
HDAC8	51.831	61.586	76.324	60.069

Table S2. Gene Ontology (GO) analysis on candidate hits from the pevonedistat synthetic lethality screening in four CRC cell lines. 17 candidate hits were used to perform a Gene Ontology (GO) analysis. GO biological processes, number of genes, P-values associated to the functional enrichment and gene belonging to each category are reported.

GO Biological Process Term	N. of hits	Hit Gene Count	Genes	Percent of hits that are members of the gene set	Fold Enrichment	p-Value
GO:0006468~protein phosphorylation	17	8	MAPK1, BRAF, FYN, PRKCI, PRKCH, PRKAA1, BIRC5, CDK4	47.059	17.329	0.00000010
GO:0043066~negative regulation of apoptotic process	17	6	EGFR, CDK1, BRAF, PRKCI, PRKAA1, BIRC5	35.294	13.025	0.00004874
GO:0008284~positive regulation of cell proliferation	17	5	EGFR, MAPK1, PRKAA1, BIRC5, CDK4	29.412	10.598	0.00081719
GO:0007165~signal transduction	17	5	EGFR, MAPK1, PRKCH, PRKAA1, CDK4	29.412	4.254	0.02115887
GO:0009636~response to toxic substance	17	4	MAPK1, CDK1, CDK4, HDAC6	23.529	46.483	0.00006684
GO:0018105~peptidyl-serine phosphorylation	17	4	MAPK1, CDK1, PRKCI, PRKCH	23.529	31.608	0.00021009
GO:0043524~negative regulation of neuron apoptotic process	17	4	BRAF, FYN, PRKCI, BIRC5	23.529	29.932	0.00024671
GO:0000165~MAPK cascade	17	4	EGFR, MAPK1, BRAF, FYN	23.529	15.080	0.00180911
GO:0051301~cell division	17	4	CDK1, TUBB, BIRC5, CDK4	23.529	11.289	0.00410933
GO:0035556~intracellular signal transduction	17	4	FYN, PRKCI, PRKCH, PRKAA1	23.529	9.804	0.00608930
GO:0070301~cellular response to hydrogen peroxide	17	3	CDK1, PRKAA1, HDAC6	17.647	51.988	0.00131763
GO:0031647~regulation of protein stability	17	3	MAPK1, HDAC8, HDAC6	17.647	42.333	0.00197944
GO:0014066~regulation of phosphatidylinositol 3-kinase signaling	17	3	EGFR, MAPK1, FYN	17.647	37.991	0.00245049
GO:0000187~activation of MAPK activity	17	3	MAPK1, CDK1, PRKAA1	17.647	27.694	0.00455375
GO:0030168~platelet activation	17	3	MAPK1, FYN, PRKCH	17.647	25.768	0.00524030
GO:0000086~G2/M transition of mitotic cell cycle	17	3	CDK1, TUBB, BIRC5	17.647	21.630	0.00735728
GO:0016477~cell migration	17	3	CDK1, FYN, PRKCI	17.647	17.228	0.01139106
GO:0010628~positive regulation of gene expression	17	3	CDK1, BRAF, PRKAA1	17.647	11.310	0.02519840
GO:0042493~response to drug	17	3	CDK1, FYN, CDK4	17.647	9.748	0.03316525