

Figure S1. Transfection effect of chiMDM2 and chiMDM4. Cells were transfected with chiMDM2 or chiMDM4 at the indicated concentrations for 48 h, then analyzed for protein expression by immunoblotting. β -actin was set as the internal control. chiMDM, DNA-chimera small interfering RNA against MDM; Cont, control.










	HCT116					LoVo					SNU-1				
chiCont (nmol/l)	1	0.5		0.5		1	0.5		0.5		1	0.5		0.5	
chiMDM2 (nmol/l)		0.5	1				0.5	1				0.5	1		
chiMDM4 (nmol/l)				0.5	1				0.5	1				0.5	1
MDM2															
MDM4															
β -actin															

Figure S2. Flow cytometry plots of HCT116 (A), LoVo (B), and SNU-1 (C) of triplicate experiments. Cells transfected with chiCont (1.0 nmol/l) or chiMDM4/chiMDM2 (0.5 nmol/l each) for 24 h were exposed to trametinib (2.0 nmol/l) for 24 h and analyzed for cell cycle distribution and apoptosis by flow cytometry. chiMDM, DNA-chimera small interfering RNA against MDM; Cont, control.

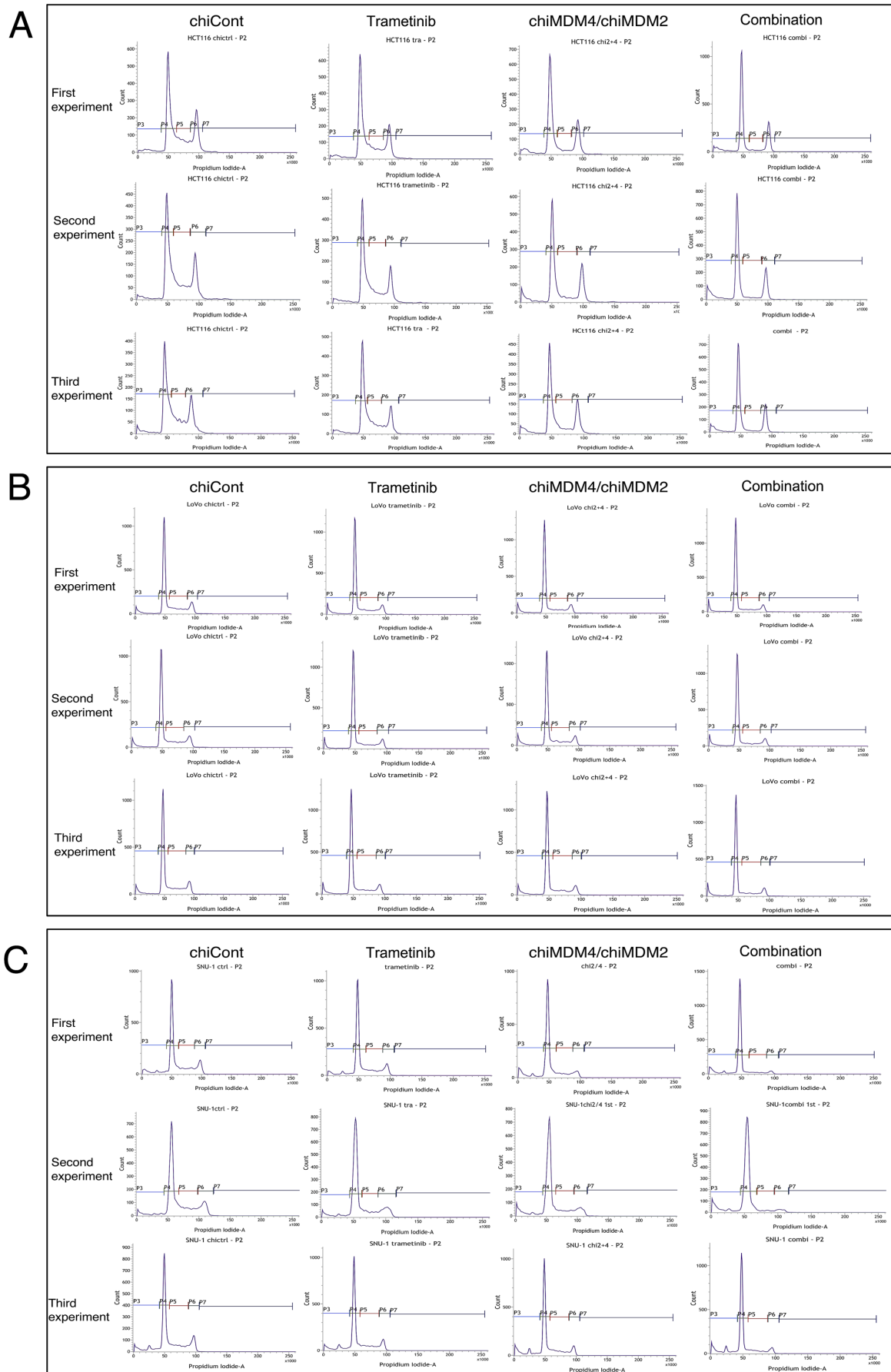


Figure S3. ChiMDM4/chiMDM2 and trametinib induced weak cleavage of caspase-8 in SNU-1 cells. Cells were transfected with chiCont (1.0 nmol/l) or chiMDM4/chiMDM2 (0.5 nmol/l each) overnight, followed by exposure to trametinib (2.0 nmol/l) for 24 h, and then analyzed for protein expression by immunoblotting. The volume of proteins used for immunoblotting was 40 μ g/lane. β -actin was set as the internal control. chiMDM, DNA-chimera small interfering RNA against MDM; Cont, control.



cell line	SNU-1			
chiCont	+	+	-	-
chiMDM2 +chiMDM4	-	-	+	+
trametinib	-	+	-	+
cleaved-CASP8				
β -actin				

Figure S4. Flow cytometry plots of *EGFP*- and *BCL2*-transduced HCT116 and LoVo. Cells were transfected with chiCont (1.0 nmol/l) or chiMDM4/chiMDM2 (0.5 nmol/l each) for 24 h, followed by exposure to trametinib (2.0 nmol/l) for 24 h, and the cell cycle distribution and apoptosis were analyzed by flow cytometry. chiMDM, DNA-chimera small interfering RNA against MDM; Cont, control; EGFP, enhanced green fluorescent protein.

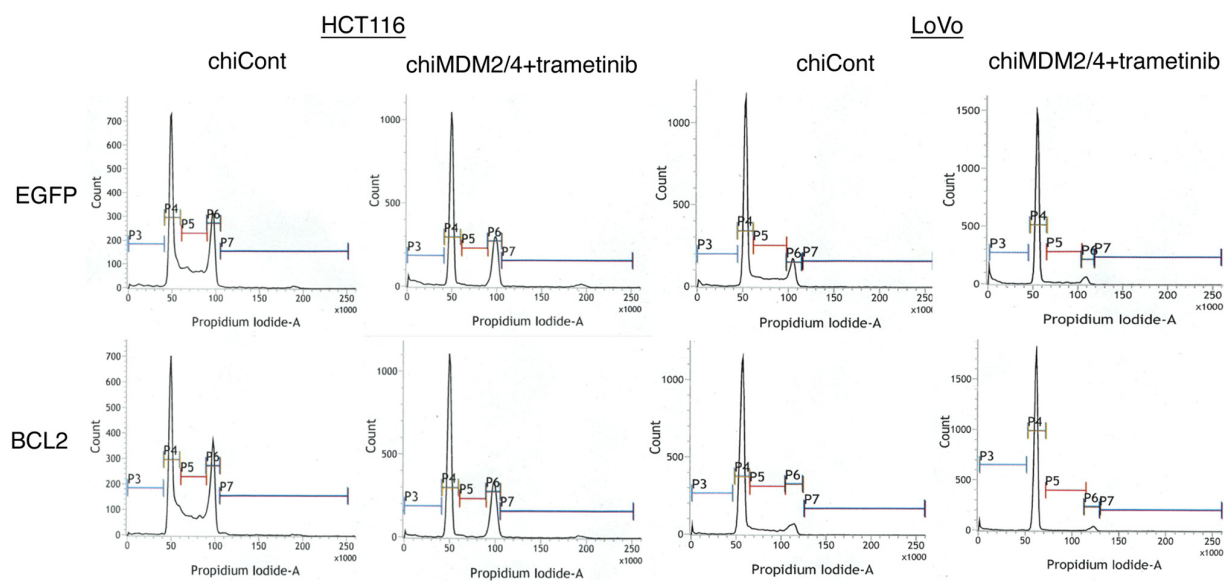


Table SI. Primary antibody list.

Antigen	Catalogue number	Clonality (clone)	Manufacturer
Apaf-1	8,969	Rabbit monoclonal (D5C3)	Cell Signaling Technology, Inc.
β -actin	PM053	Rabbit polyclonal	MBL International Co.
BAX	M010-3	Mouse monoclonal (4F11)	MBL International Co.
BCL2	2,872	Rabbit polyclonal	Cell Signaling Technology, Inc.
MYC	5,605	Rabbit monoclonal (D84C12)	Cell Signaling Technology, Inc.
Cleaved caspase-8	9,496	Rabbit monoclonal (18C8)	Cell Signaling Technology, Inc.
Caspase-9	M054-3	Mouse monoclonal (5B4)	MBL International Co.
CDC2	MT-19-3	Mouse monoclonal (5F6)	MBL International Co.
CDC25A	K0072-3	Mouse monoclonal (DCS-121)	MBL International Co.
CDK2	2,546	Rabbit monoclonal (78B2)	Cell Signaling Technology, Inc.
CDK4	12,790	Rabbit monoclonal (D9G3E)	Cell Signaling Technology, Inc.
Cyclin A	K0162-3	Mouse monoclonal (E23.1)	MBL International Co.
Cyclin B1	K0128-3	Mouse monoclonal (V152)	MBL International Co.
Cyclin D1	2,978	Rabbit monoclonal (92G2)	Cell Signaling Technology, Inc.
Cyclin D3	2,936	Mouse monoclonal (DCS22)	Cell Signaling Technology, Inc.
Cyclin E2	4,132	Rabbit polyclonal	Cell Signaling Technology, Inc.
DNA polymerase δ (p125)	K0160-3	Rat monoclonal (5G1)	MBL International Co.
DR4	42,533	Rabbit monoclonal (D9S1R)	Cell Signaling Technology, Inc.
DR5	3,696	Rabbit polyclonal	Cell Signaling Technology, Inc.
E2F1	05-379	Mouse monoclonal (KH20 & KH95)	Upstate Biotechnology, Inc.
ERK1/2	AM2189b	Mouse monoclonal (784CT7.6.3)	Abgent Biotec Co., Ltd.
Phospho-ERK1/2 (Thr202/Tyr204)	AP3906a	Rabbit polyclonal	Abgent Biotec Co., Ltd.
Fas	4,233	Rabbit monoclonal (C18C12)	Cell Signaling Technology, Inc.
14-3-3 σ	GTX100289	Rabbit polyclonal	GeneTex, Inc.
MDM2	ab16895	Mouse monoclonal (2A10)	Abcam
MDM4	sc-14738	Goat polyclonal (D-19)	Santa Cruz Biotechnology, Inc.
p15INK4b	M124-3	Mouse monoclonal (1F6)	MBL International Co.
p21CIP1	2,946	Mouse monoclonal (DCS60)	Cell Signaling Technology, Inc.
p27KIP1	3,686	Rabbit monoclonal (D69C12)	Cell Signaling Technology, Inc.
p53	MON 7051	Mouse monoclonal (BP53-12)	Cell Sciences, Inc.
PCNA	MH-12-3	Mouse monoclonal (5A10)	MBL International Co.
PolA2	A302-477A-T	Rabbit polyclonal	Bethyl Laboratories, Inc.
PUMA	4,976	Rabbit polyclonal	Cell Signaling Technology, Inc.
RB	554,136	Mouse monoclonal (G3-245)	BD Biosciences
RRM1	GTX100758	Rabbit polyclonal	GeneTex, Inc.
Thymidylate synthase	9,045	Rabbit monoclonal (D5B3)	Cell Signaling Technology, Inc.