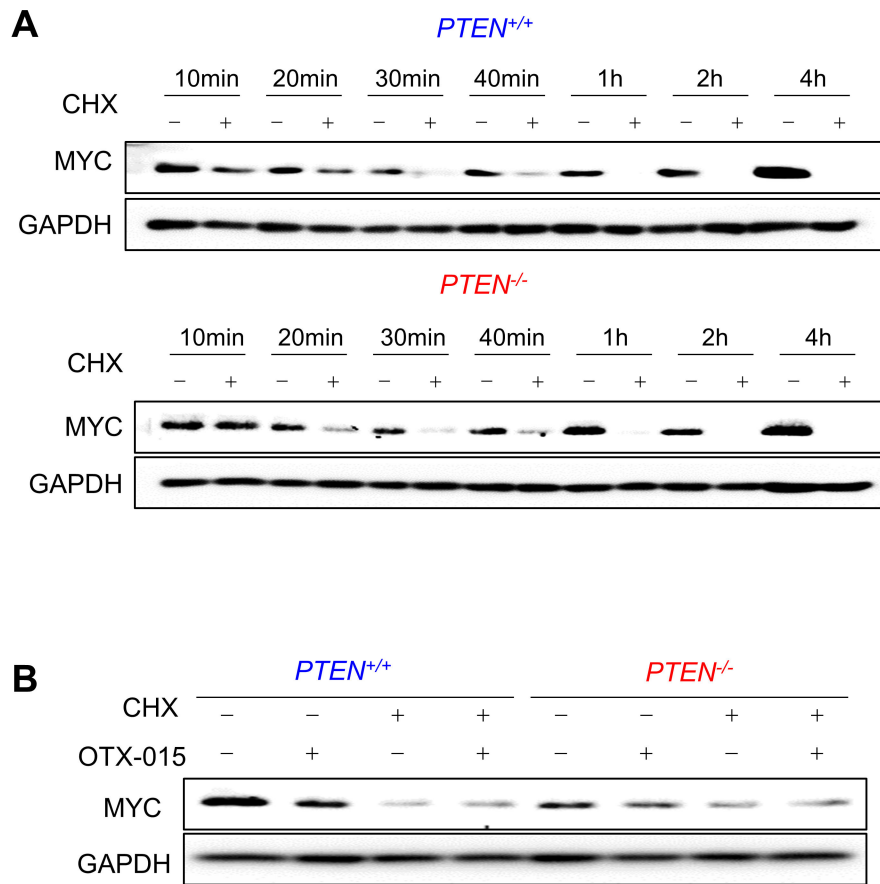
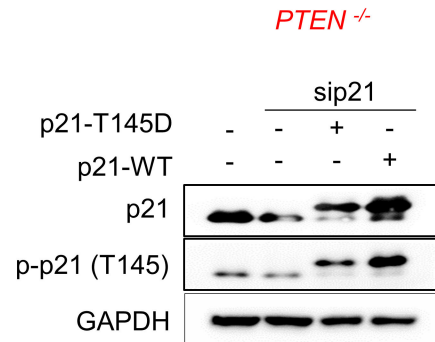


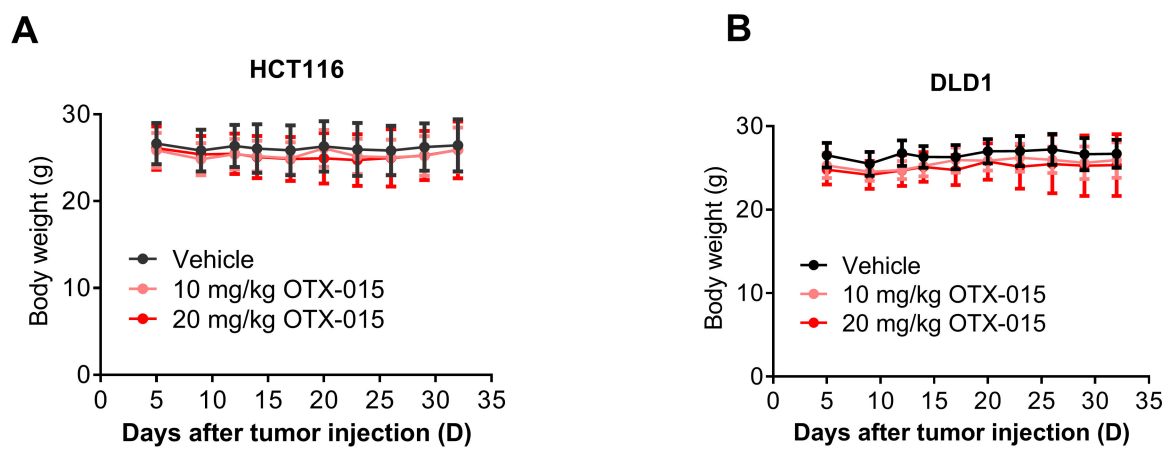
**Figure S1** BETi selectively induced apoptosis in *PTEN*-deficient cells. A. HCT116 *PTEN* isogenic cell pair were treated with 5, 10, 15  $\mu\text{M}$  OTX-015 for 72 h and the nuclei were stained with Hoechst33342. B. Active (cleaved) PARP was used as a marker of apoptosis induction.



**Figure S2** PTEN and BETi did not affect MYC protein stability. Measurement of MYC protein half-life in HCT116 *PTEN* isogenic cells. Cells were treated with or without 10  $\mu$ M cycloheximide (CHX) and analyzed MYC protein expression for the indicated time points. B. Measurement of MYC protein in *PTEN* isogenic cells with or without OTX-015 (10  $\mu$ M) treatment.



**Figure S3** Verification for p21 siRNA, p21-T145D and p21-WT plasmids transfection efficiency. Immunoblot showing p21 siRNA, p21-145A plasmid and p21-wt plasmid transfection efficiency.



**Figure S4** BETi treatment was not toxic to mice. A, B. Mice body weight curves in nude mice treated with vehicle, 10 mg/kg and 20 mg/kg of OTX-015.



Supplementary Table 1. Sequences of siRNAs used in this study

No	Target gene	Suppliers	Sequence
1	siMYC	Integrated DNA Technologies	5'-AUCAUUGAGCCAAAUCUAAAAAAAA-3'
2	siip21	Integrated DNA Technologies	5'-GCCUCUGGCAUUAGAAUUUUUAAA-3'

Supplementary Table 2. Antibodies use in this study.

No	Primary Antibodies	Suppliers	Catalog No.	Molecular weight (kDa)
1	PTEN (A2B1)	Santa Cruz Biotechnology	sc-7974	55
2	AKT (B1)	Santa Cruz Biotechnology	sc-5298	62
3	p-AKT (ser473)	Cell Signaling Technology	9271	60
4	GAPDH	Santa Cruz Biotechnology	sc-365062	37
5	PARP-1 (H-250)	Santa Cruz	Sc-7150	116
6	cMyc (9E10)	Santa Cruz	Sc-40	65
7	p21 Waf1/Cip1 (12D1)	Cell Signaling Technology	2947	21
8	Phospho-p21 (Thr145)	Thermo fisher	PA5-36677	21
9	GSK-3 $\beta$ (3D10)	Cell Signaling Technology	9832	46
10	Phospho-GSK-3 $\beta$ (Ser9) (5B3)	Cell Signaling Technology	9323	46
11	CDK4 (DCS-35)	Santa Cruz	sc-23896	34
12	Cyclin E	Cell Signaling Technology	sc-377100	53

Supplementary Table 3. Sequences of qPCR primer pairs used in this study.

No	Target gene	Suppliers	Sequence
1	MYC	BGI	Forward 5'-GGCTCCTGGCAAAGGTCA-3' Reverse 5'-CTGCGTAGTTGTGCTGATGT-3'
2	p21	BGI	Forward 5'-AATACACCAGCAAGCTAGATGC-3' Reverse 5'-AATCAGTTCCGTTCCCCAGAG-3'
3	GAPDH	BGI	Forward 5'-GTGGACCTGACCTGCCGTCT-3' Reverse 5'-GGAGGAGTGGGTGTCGCTGT-3'