Supporting Information

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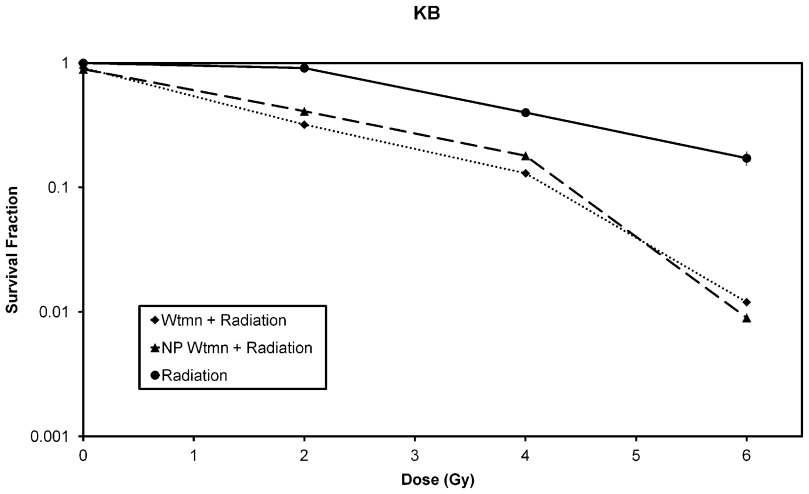

Fig. S1. In vitro efficacy of nanoparticle (NP) wortmannin (Wtmn) as a radiosensitizer. Clonogenic assay of KB cancer cells with 25 μM Wtmn or NP Wtmn (containing 25 μM Wtmn) for 1 h followed by radiation at the indicated doses. Error bars correspond to SD of repeated measurements (two NP preparations, duplicate measurements per preparation per data point).

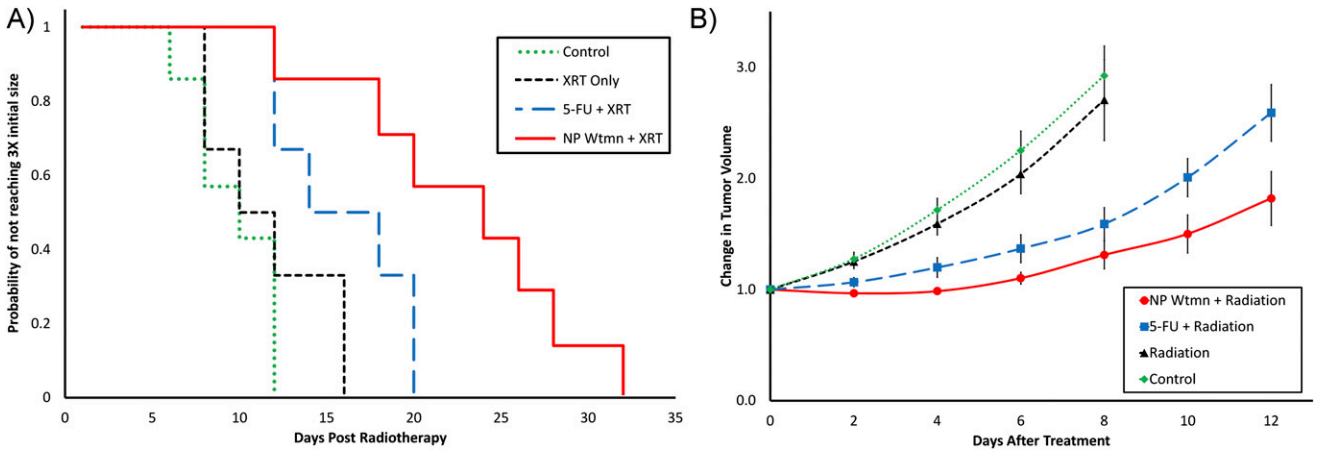

Fig. S2. In vivo efficacy of nanoparticle (NP) wortmannin (Wtmn). (*A*) Kaplan–Meier curve displaying time (in days) needed for HT-29 tumor xenografts to reach three times initial volume post treatment as the end point. Mice received single tail-vein i.v. injections of 3.5 mg/kg of NP Wtmn, 25 mg/kg 5-flurouracil (5-FU), or vehicle control. Tumors were radiated locally 3 h post injection (6 Gy). NP Wtmn-treated tumors took significantly longer to reach the end point compared with 5-FU ($P < 0.05$) or no radiosensitizer ($P < 0.01$) (*B*) Efficacy of NP Wtmn tumor growth inhibition on HT-29 s.c. tumor xenograft. The group average rate of change in tumor volume through day 12 is presented. NP Wtmn-treated tumors had significantly slower growth rates compared with 5-FU ($P < 0.02$) or no radiosensitizer ($P < 0.01$).

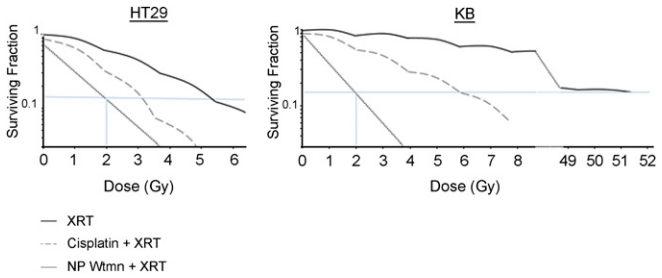

Fig. S3. Potential impact of NP wortmannin (Wtmn) on clinical radiotherapy. Using data from both a radiosensitive (HT-29) and a radioresistant (KB) cancer cell line, we have projected how the cell lines would respond to clinical radiotherapy of 2 Gy delivered daily. Because 2 Gy falls within the "shoulder" region, the shoulder cell killing is propagated for cells treated with no radiosensitizer or cisplatin, thus resulting in an overall higher amount of Gy needed for treatment. nanoparticle (NP) Wtmn eliminates the shoulder, resulting in significantly less Gy needed for effective treatment.

Table S1. Full toxicity profile of Wtmn formulations in CD1 mice post i.v. injection

	Normal range	Wtmn	NP Wtmn
1/5th of the MTD dose (0.14 mg/kg)			
Hematologic toxicity			
WBC	3.5–10 (10^3/μL)	2.8 ± 0.28	5.1 ± 0.42
Granulocytes	1.2–8 (10^3/μL)	0.8 ± 0.14	2.9 ± 0.07
Lymphocytes	0.5–5 (10^3/μL)	0.4 ± 0.42	3.56 ± 0.21
Monocytes	0.1–1.5 (10^3/μL)	0.55 ± 0.07	0.7 ± 0.14
LYMF (%)	15.0–50.0	13.05 ± 14.07	59.35 ± 18.88
GRAN (%)	35.0–80.0	78.35 ± 3.32	38.7 ± 32.95
MONO (%)	2.0–15.0	14.15 ± 2.9	12.55 ± 0.92
HCT (%)	30.0–50.0	40.515 ± 1.01	47.01 ± 2.53
MCV (fl)	75.0–100.0	54.3 ± 11.03	57.25 ± 4.17
RBC (*n*)	3.50–5.50 (10^6/μL)	7.85 ± 1.02	7.295 ± 2.37
HGB (g/dL)	11.5–16.5	13.85 ± 0.35	14.5 ± 0.57
MCH (pg)	25.0–35.0	18.8 ± 3.39	19.5 ± 3.96
MCHC (g/dL)	31.0–38.0	33.95 ± 1.91	31.25 ± 0.78
RDW (%)	11.0–16.0	16 ± 4.24	17.5 ± 0.71
Hepatotoxicity			
ALT U/L	40–50 U/L	134 ± 17	82 ± 12
AST U/L	40–50 U/L	44 ± 3	46 ± 7
1/10th of the MTD dose (0.07 mg/kg)			
Hematologic toxicity			
WBC	3.5–10 (10^3/μL)	4.3 ± 0.13	4.9 ± 0.20
Granulocytes	1.2–8 (10^3/μL)	2.4 ± 0.11	3.7 ± 0.12
Lymphocytes	0.5–5 (10^3/μL)	0.9 ± 0.28	1.05 ± 0.21
Monocytes	0.1–1.5 (10^3/μL)	0.8 ± 0.42	0.5 ± 0.14
LYMF (%)	15.0–50.0	21.5 ± 2.12	37 ± 8.49
GRAN (%)	35.0–80.0	66 ± 4.24	62.5 ± 13.43
MONO (%)	2.0–15.0	12.5 ± 0.71	10.5 ± 0.71
HCT (%)	30.0–50.0	32.5 ± 0.71	45.5 ± 3.53
MCV (fl)	75.0–100.0	73 ± 12.72	81.5 ± 2.12
RBC (*n*)	3.50–5.50 (10^6/μL)	6.1 ± 1.41	5.75 ± 0.78
HGB (g/dL)	11.5–16.5	12.95 ± 1.76	14.1 ± 2.83
MCH (pg)	25.0–35.0	19.4 ± 2.26	21.35 ± 1.34
MCHC (g/dL)	31.0–38.0	32.6 ± 0.57	40.5 ± 0.71
RDW (%)	11.0–16.0	15.5 ± 0.71	15 ± 1.41
Hepatotoxicity			
ALT U/L	40–50 U/L	64 ± 11	60 ± 9
AST U/L	40–50 U/L	40 ± 7	42 ± 10

Mice were treated with indicated doses of wortmannin (Wtmn) or nanoparticle (NP) Wtmn containing an equivalent dose of Wtmn (2% wt/wt) Single tail-vein i.v. injection was given, and a toxicity profile was taken 24 h post injection. NP, nanoparticle; MTD, maximum tolerated dose. ALT, alanine transaminase; AST, aspartate aminotransferase; fl, femtoliters; GRAN, granulocyte; HCT, hematocrit; HGB, hemoglobin; LYMF, lymphocyte; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MONO, monocyte; RDW, red cell distribution width.

Table S2. Sensitizer enhancement ratio of Wtmn, NP Wtmn (2% wt/wt Wtmn), or cisplatin formulations for different cancer cell lines at 10% survival

	SER at 10% surviving fraction		
	Wtmn	NP Wtmn	Cisplatin
KB	3.51	3.68	1.42
PC-3	2.52	2.71	1.33
HT-29	3.33	2.72	1.68

NP, nanoparticle; SER, sensitizer enhancement ratio; Wtmn, Wortmannin.