**Supplementary Methods**

**Cell lines**

RT112 and T24 cells were grown in RPMI medium (Sigma) and CAL29 in Dulbecco’s modified Eagle medium (DMEM, Invitrogen). Media were supplemented with 10% foetal bovine serum (FBS, Invitrogen).

**Panobinostat concentration levels in plasma, xenografts, bladder and intestines**

CD1-nude mice bearing 100 mm3 RT112 xenografts were injected with 10 mg/kg PAN IP or intravenously (IV, tail vein), and culled 6 h later. Blood was immediately taken from the right heart using heparin-rinsed needles and placed in sodium citrate vials (Sarstedt Ltd, UK). Tumour, bladder, sections of small and large intestine and heart were excised and frozen in liquid nitrogen. Plasma was extracted from blood held at room temperature for 10 min, by centrifuging 1500 g for 10 min and supernatant was snap frozen on dry ice. Panobinostat concentrations were determined by HPLC-MS/MS after addition of internal standard (carbamazepine) and extraction with acetonitrile. Gradient HPLC was carried out on an Alliance 2695 HPLC system (Waters) using 10 mM formic acid as solvent A and acetonitrile as solvent B. Gradient was run over 5 min starting with solvent B at 20% and increasing to 70% under the flow rate of 0.25 mL/min. The column was an ACE C18, 3 μm, 150 x 2.1 mm (Hichrom), and detection was done by tandem MS (Micromass Quattro Micro), panobinostat transition 349.9-158, carbamazepine 236.9-194.1.

**Normal tissue response models**

***Drug treatment alone***

Small intestine was divided into three pieces of equal length to make “Swiss rolls”(17). The samples were formalin-fixed overnight in 10% neutral buffered formalin and stored in 70% ethanol prior to paraffin-embedding. Four micrometre sections were cut and stained for haematoxylin and eosin (H&E), BrdU and cleaved caspase 3. Rat monoclonal antibody to BrdU (1 mg/mL, Abcam, ab6326) and rabbit monoclonal antibody to cleaved caspase 3 (5A1E, Cell Signalling, 9664) were diluted 200 times as the primary antibodies. Alexa Fluo 488 goat anti-rat (IgG, 2 mg/mL, Invitrogen) and Alexa Fluo 568 goat-anti rabbit (IgG, 2 mg/mL, Invitrogen) were diluted 1000 times as the secondary antibodies. Nuclei were stained with DAPI.

***Drug/irradiation combinations***

In acute effects experiments, Swiss rolls were made from large (one length) and small intestines (three consecutive lengths). Samples were stored in 10% neutral buffered formalin overnight, and then in 70% ethanol until further processing. Following embedding in paraffin, 4-5 µm sections were cut and stained with haematoxylin & eosin (H&E).

**Crypt assay**

H&E-stained Swiss roll slides were grouped per mouse, anonymised, and scanned using an Aperio CS2 digital pathology scanner (Leica). As only part of the abdomen had been irradiated, two independent observers selected the most affected areas in each Swiss roll and reached consensus. No crypt loss was observed for mice treated with only panobinostat or gemcitabine. Irradiated mouse samples were excluded if there was less than 3 mm of intestinal damage. One observer counted regenerating crypts (the presence of >10 cells arranged in a distinct shape with no sign of apoptosis). The control number of crypts per length of small intestine, for each of the three small intestinal lengths (si1, si2, si3), was determined from the mean of two mock and one panobinostat-treated mice (Figure 3C) or two mock, one panobinostat-treated and one gemcitabine-treated mice (Figure 3D). The percentage of surviving crypts was calculated as:

Number of regenerating crypts per mm x 100

Number of control crypts per mm

To compare effects of panobinostat and gemcitabine with 12 Gy IR, one gemcitabine pilot and three further independent experiments were done. Two mice from the 12 Gy only group showing no damage to the small intestine were excluded from the final data. One 12 Gy only and one PAN+12 Gy mouse were also excluded due to total damage of less than 3 mm.

**Real-time quantitative polymerase chain reaction (qPCR)**

Real-time qPCR was performed by ∆∆Ct method, using SYBR® Green PCR Mastermix (Applied Biosystems). Relative quantitation of HDACs was measured using *HDAC1-11* primers (Supplementary Table 1) and results normalised to *GAPDH* levels. Samples were run on an Applied Biosystems 7500 Fast Real-Time PCR system (ThermoFisher): 20 s at 50oC, 10 min at 95oC, then 40 cycles of 1 min at 60oC, 15 s at 95oC, 1 min at 60oC, 1 min at 95oC.

**Western blots**

Western blot samples were prepared as previously described (15,16) with antibodies detailed in Supplementary Table 2. Protein visualisation and quantification was performed using an infrared LiCor Odyssey imaging system (LiCor Biosciences). All western blots were performed twice independently.

**Homologous recombination (HR) assays**

For the I-SceI assay, RT112 cells with stable integration of the HR Pem1-GFP reporter construct were seeded at 1 x105 cells per 5 cm dish and transiently transfected with 4 μg pCBASceI expression plasmid (#26477, Addgene) using FugeneHD (Promega) at a 1:3 ratio. Panobinostat or vehicle was added 6 h post-transfection. Cells were trypsinised and resuspended in PBS 48 h post transfection and analysed for GFP positivity using a FACSCalibur flow cytometer (Beckton Dickinson).

A PCR-based method (Norgen Biotek Corp) was performed to test the HR functionality following different drug treatments. RT112 cells (1\*105/well) were plated in 24-well dishes and transfected with two HR dl plasmids (dl-1 and dl-2). Six hours after transfection, panobinostat (final concentration: 10, 25, 50 nM), mocetinostat (final concentration: 1, 1.5, 2 µM), and TMP-195 (final concentration: 1.25, 2.5, 5 µM) were added to the medium. Twenty-four hours later, total DNA was extracted by QIAamp DNA Mini Kit (Qiagen) as per manufacturer’s instructions. HR activity was quantified by qPCR using supplied primers and normalised to the dl plasmid in each sample.