Table S1. A significant correlation for two different genetic scores identified PDAC cells with KRAS dependency. Cells with high L- and S-scores and dependent to K-RAS (HPAF-II, PA-TU-8902, and CAPAN-1) were used for these studies and referred to as dep-PDACs, whereas cells with low S- and L-scores (PA-TU-8988T and KP4), although carrying K-RAS mutations, were considered K-RAS independent and referred to as indep-PDACs.

Figure S1. A. Schematic representation of built K-RAS-net by MANTRA 2.0 and used in this study. Each node of the net (circle) represents a prototyped-ranked list of genes derived by the indicated experimental studies (see **MATERIALS AND METHODS**) and relative to forward or reverse (REV) K-RAS-dependent signature. Edge (gray line) among nodes indicates connections in the MANTRA network. The number close to the edge is the MANTRA distance; distances lower than 0.85 are significant for similarity among gene signatures. The K-RAS-specific gene signatures generated by using different experimental models (**MATERIALS AND METHODS**) are close to the MANTRA network, indicating robust signatures. Moreover, K-RAS-REV nodes are significantly close to the node generated by the prototyped-ranked list of cells treated with simvastatin, a known inhibitor of K-RAS-dependent signaling pathway. DEC node is significantly close to the K-RAS-REV nodes (red edge), thus representing a potential inhibitor able to revert K-RAS-dependent gene signatures. **B.** Chemical structure of 5-aza-2'-deoxycytidine (DEC). **C.** DEC-regulated oncogenic KRAS-dependent gene expression. Total RNA was harvested from HPDE wild-type or an isogenic clone carrying a K-RAS^{G12V} mutation after treatment with DMSO or DEC (100 nM) for 6 hours. The most differentially expressed genes were predicted and selected as described in **MATERIALS AND METHODS**. The expression of genes upregulated by oncogenic KRAS (*API5, PRR16, RBM12,* and *TRIO*) and downregulated by oncogenic KRAS (*ALG12* and *DOK4*) was analyzed by qRT-PCR. Data indicate absolute values ± standard deviation and are the average of at least three independent experiments (n = 3). Statistical significance was calculated by two-tailed *t*-test (** $P \leq 0.01$; * $P \leq 0.05$; NS: not significant). **D.** The indicate cell lines were grown for 7 days with different doses of DEC ranging from 0.001 μM to 20 μM. Cell viability was then assayed by the ATP-based Celltiter-Glo assay. Graphs report the percentage of inhibition compared to DMSO-treated cells (n = 4). **E.** DEC induced cellular senescence in HPDE-KRAS (G12V) but not in HPDE-WT. Quantification of β-gal staining after 6 days of treatment with vehicle (DMSO) or DEC. Histograms show mean ± standard deviation. Statistical significance was calculated by two-tailed *t*-test (*** $P \leq 0.001$; NS: not significant).

Figure S2. **A.** Scatter plot comparing L-scores and DEC EC_{50} (μM) values in 13 pancreatic cell lines from the Cancer Therapeutics Response Portal (CTRP). **B.** DEC did inhibit clonogenic growth of dep-PDAC cells. Colonies-forming assay of dep-PDAC PA-TU-8902 and indep-PDAC PA-TU-8988T cell lines treated with 1.25 μM DEC for 6 days. The quantification of results from three independent experiments is provided in the histograms. **C.** Decitabine induced a robust cell cycle block at G2/M phases in KRAS dep CAPAN-1 cells. CAPAN-1 were treated with high doses (1.25 μM) of DEC or DMSO for 3 days, then assayed by fluorescence-activated cell sorting (FACS) analysis of Propidium Iodide (PI) stained cells. Histograms show mean ± standard deviation (n=4). Statistical significance was calculated by two tails t-test (*** $p \leq 0.001$, **: $p \leq 0.01$, *: $p \leq 0.05$, NS: not significant). **D.** DEC induced a robust cell cycle block at G2/M phases in dep-PDAC but not in indep-PDAC. Representative image of FACS analysis of propidium iodide-stained cells treated with DEC (1.25 μM) or DMSO. **E.** Cellular size was quantified by FACS analysis. Representative plot of size analysis (n = 3) of dep-PDAC and indep-PDAC cells, treated for 3 days with DMSO (black line) or DEC (red line). **F**. DEC induced an irreversible proliferation arrest. Colonies-forming assay of dep-PDAC PA-TU-8902 cell lines was performed in the presence or not of 1.25 μM DEC (upper panel); after 5 days, DEC-treated colonies were either refreshed with DEC (DEC) or grown in the absence of DEC (DEC + washout) to induce cell proliferation rescue. After an additional 12 days, cells were collected and analyzed for colonies formation (lower panel). **G.** DEC induced DNA damage in dep-PDACs. Immunofluorescence analysis quantification of cells treated with DMSO or DEC (1.25 μM) and stained with anti-phospho-H2AX antibody, a molecular marker of DNA damage, as reported in Figure 1F. For each experimental replicate (n = 4), cells were counted (n = 100), and the percentage of positive stained cells was reported (right panel). Histograms show mean ± standard deviation. Statistical significance was calculated by two-tailed *t*-test (*** $P \leq 0.001$; NS: not significant). **H.** DNA-damage agents do not differently affect the viability of dep-PDACs versus indep-PDACs. The indicated cell lines were grown for 3 days with the indicated doses of DNA damage-inducing chemicals. Cell viability was assayed by ATP-based Celltiter-GLO assay and plotted as a percentage of inhibition compared to DMSO-treated cells (n = 3).

Figure S3. DEC inhibited xenograft tumours growth and the development of lung metastases. **A.** Weight of tumours at the end of the experiments shown in Figure 2A-D. Data are means ± standard deviation of volumes. Differences in tumour weight were evaluated using a two-tailed t-test analysis (*** $P \leq 0.001$, ** $P \leq 0.01$, NS: not significant). **B.** Representative images of haematoxylin and eosin (H&E) stained lungs sections showing the occurrence of spontaneous metastases. Scale bar: 100µm; image magnification: X100.

Figure S4. The TRAM and DEC drug combination is synergic in dep-PDAC PA-TU-8902 and HPAF-II cells. Combination index (CI) values are plotted as a function of the fractional inhibition (Fa) from 0.10 to 0.97 (upper panels). The CI values of < 0.9 (below the lower dashed line), 0.9-1.1, and > 1.1 (above the upper dashed line) represent synergism, additivity, and antagonism, respectively. Lower panels show the dose effects relationship of IC parameters and the CI value. Data are representative of three independent experiments with equivalent results.

Figure S5. Metabolite Set Enrichment Analysis (MSEA) results adapted from MetaboAnalyst software package. Identified metabolites and their relative fold change over DMSO-treated cells were used to calculate the enrichment and statistical significance of metabolites in PA-TU-8988T cells. Top 50 perturbed pathways are shown. Color intensity (yellow to red) reflects increasing statistical significance as reported (P Value (pV) < 0.05).

Figure S6. A-B. DEC induces senescence in K-RAS-dep PDX-PDACs model. **A.** Cellular senescence was scored by β-gal staining of indicated cells after 3 days of treatment. Scale bar: 100 μm; image magnification: 20X. **B.** Box plots represent the percentage of β-gal-positive cells from **A**. Statistical significance was calculated by two-tailed *t*-test (*** P ≤ 0.001; ** P ≤ 0.01; * P ≤ 0.05). **C.** Cell cycle analysis in a selected K-RAS-dependent PDX-PDAC model. Cells were treated with high doses (1.25 μM) of DEC or vehicle (DMSO) for 3 days, and analysis was performed as described in Figure 1. Statistical significance was calculated by two-tailed *t*-test (*** P ≤ 0.001; **P ≤ 0.01; * P ≤ 0.05). **D**. Box plots represent the percentage of phospho-H2AX-positive cells from Figure 5C. Statistical significance was calculated by two-tailed *t*-test (**** P ≤ 0.0001; *** P ≤ 0.001). **E-F.** Box plots represent the percentage of phospho-H2AX- (**E**) and Ki67- (**F**) positive cells in tumors collected from mice injected with one dep-PDAC (PATX53) and one indep-PDAC (PATX153) and treated with DMSO or DEC (Figure 5H-I). (**P < 0.01; NS: not significant). **G.** Heat map describing four properties of PDX models. The leftmost matrix defines the mutation status of four genes commonly mutated in PDAC (K-RAS, TP53, CDKN2A, and SMAD4). Green boxes represent missense mutation; black box represents truncating mutation; and gray boxes constitute PDXs that were not profiled. The second two-column matrix represents the L-score and S-score of the PDX models from the RNA sequencing. The third heat map represents the normalized expression (log10 ratio of the mean expression) of genes associated with the basal-like (orange gene labels) and classical (blue gene labels) subtypes. This matrix was used to cluster PDX samples into putative basal-like (orange PDX labels) and classical (blue PDX labels) subtypes. **H.** Box plots comparing L-scores and S-scores in PDAC-PDX sample groups predicted to be basal-like or classical according to Moffit classification**.**