**Supplementary Figure 1.**

Purity of epithelial cells isolated from PDX tumors.PDX tumor cells (n=12) were fully disaggregated and 2x105 cells stained with anti-human EpCam-AlexaFluor488 (black line) or matched isotype control (red filled) followed by flow cytometric analysis. Example data for LU12 and LU102 are shown with Marker M1 identifying the percentage of cells positive for EpCam.

**Supplementary Figure 2.**

A, Schematic of Patient Derived 3D-TGA Method. B, Full depth fluorescent deconvolution volume view of tumor (red, DiI labelled) and stromal cells (green, CFSE labelled) within a 3D TGA. C,D, brightfield images (with Hoffman modulation) of LU137 (C) and LU137 with CAF (D). E,F, in well immunofluorescence staining for E-Cadherin of LU116 (E) and LU116 with CAF (F). G, extracted cell cluster stained for DNA (DAPI, Blue), E-Cadherin (purple) and actin (phalloidin green) imaged by deconvolution microscopy. Scale bar 100m C-F, 50m G.

**Supplementary Figure 3**.

Growth of NSCLC Cells in 3D TGA (n=11). Xenograft tumors were enzymatically disaggregated and single cell suspensions entered into 3D-TGA with tumor cells only (red line) or in the presence of CAFs (green line) at a ratio of 3 epithelial to 1 stromal cell. Growth was monitored by AlamarBlue fluorescent viability assay in triplicate wells; error bars represent one standard deviation. tdTomato labelled CAFs in wells admixed with LU116 tumor cells were additionally monitored by serial fluorescent reading of the tdTomato fluorescence as an independent measure of CAF cell growth in the mixed culture (excitation 540nm/emission 586nm); results are expressed relative to the day 0 reading (black line).

**Supplementary Figure 4.**

Growth of Tumor Cells in 3D TGA (n=47).Xenograft tumors were enzymatically disaggregated and single cell suspensions entered into 3D-TGA with tumor cells only (red line) or in the presence of stromal cells (green line) at a ratio of 3 epithelial to 1 stromal cell. Growth was monitored by AlamarBlue fluorescent viability assay in triplicate wells; error bars represent one standard deviation. LU = NSCLC, CRC = Colorectal Carcinoma, CRCM=CRC metastasis to Lung (LU) or Liver (L), P= Pancreatic cancer and E = Esophageal cancer. Stromal Cells for NSCLC were NSCLC-derived CAFs; for all others MSCs were used.

**Supplementary Figure 5.**

**HGF Expression in Stromal Cells.** Level of HGF Expression in NSCLC derived CAFs (T) or normal Lung Fibroblasts (N), mesenchymal stem cells (MSC) in comparison to epithelial lung line A549, H460 and H358 measured by RT-PCR using the 2-ΔCT method.

**Supplementary Figure 6.**

Chemo-sensitivity of Tumor Cells in the Presence and Absence of CAFs. PDX tumor cells (n=30) were cultured in the 3D-TGA in the presence or absence of patient-derived CAFs and serial drug dilution applied on day 3 as single agents or combinations at fixed ratio. End point cell viability was measured at day 7 by AlamarBlue assay and IC50 curves were generated. Paired IC50 values in the presence and absence of CAFs are shown. A, all data n=30. B, data where both IC50 (+/- CAF) were accurately determined within the limits of the test, with mean and range shown by box and whiskers. Significance of difference is shown as p value calculated by ratio paired T Test. *Carbo=Carboplatin, Pacli= Paclitaxel, Gem = Gemcitabine, Cis= Cisplatin; Vin= Vinorlebine, Pem= Pemetrexed.*

**Supplementary Figure 7.**

Sensitivity of NSCLC Tumor Cells to HDAC inhibitors and SOC combinations in the Presence and Absence of CAFs.PDX tumor cells (n=29) were cultured in the 3D-TGA in the presence or absence of patient-derived CAFs and serial drug dilution applied on day 3 as single agents or combinations at fixed ratio. End point cell viability was measured at day 7 by AlamarBlue assay and IC50 curves were generated. Paired IC50 values in the presence and absence of CAFs are shown where both IC50 (+/- CAF) were accurately determined within the limits of the test, with mean and range shown by box and whiskers. Significance of difference is shown as p value calculated by ratio paired T Test. *JNJ585= JNJ-26481585,* *Gem= Gemcitabine, Cis= Cisplatin, Vin= Vinorlebine, Pem= Pemetrexed.*