**Figure S1: Tumor growth kinetics and response to cetuximab of HNCs-PDXs, and pathological analysis of CetuximabProg-PDX, PDX #19. (A)** Tumor volume of CetuximabSen-PDXs (#01, #03, #20) and CetuximabProg-PDXs (#18, #19) in Nod. Scid mice. Mice were randomized into 2 arms (tumors, n = 6-10) and treated with vehicle or cetuximab (10 mg/kg/5d) via intraperitoneal injection for an average period of 25 days. Presented are the average tumor volumes ± SEM. Statistical significance was calculated by unpaired t-test; P values are shown. Representative images of IHC staining and analysis for **(B)** Ki67 (40X, 20 μm) and **(C)** pMAPK (40X, 20 μm) of PDX #19. The expression levels were analyzed using the 3DHISTECH software HistoQuant, comparing 10-16 different tumor regions, depending on the size of the tissue, in vehicle versus cetuximab treatment groups. Statistical significance was calculated by unpaired t-test. \*P < 0.05; \*\*P < 0.01; \*\*\*P < 0.001. Data are not shown for PDX #03, since the PDX responded strongly to the treatment.

**Figure S2: Fold-change plots of HNC-PDXs and KEGG signatures. (A)** Correlations of treatment-induced gene expression changes between patients. X and Y axes show log2 fold changes in the gene expression values between cetuximab and vehicle treatment in different patients. Only genes with |log2FC| > 0.5 are shown. Red dots denote genes with statistically significant gene expression changes (BH-corrected p-value < 0.05) in both patients. The numbers in the upper left corner of each plot represent Spearman correlations. All plots are based on human reads. **(B)** Same as A, but all plots are based on murine reads. Pearson correlation coefficients between two CetuximabSen-PDXs were 0.4 for human and 0.79 for murine, whereas for comparisons between CetuximabSen-PDXs and CetuxiambProg-PDX they were only 0.26-0.28 and 0.51-0.56, respectively**.** Number of genes with statistically significant expression changes in both patients (negative binomial test, |log2FC| > 0.5, BH-corrected p-value < 0.05) was dramatically higher for the comparison between the two CetuximabSen-PDX versus CetuximabSen-PDX/CetuxiambProg-PDX paired comparisons. **(C)** Venn diagram of KEGG pathways enriched in the murine (stroma) compartment for downregulated genes (log2FC < 0.5) of PDX #18 and upregulated genes (log2FC > 0.5) of PDX #03 and #20. **(D)** Venn diagram of KEGG pathways enriched in the human (tumor) compartment for all PDXs.

**Figure S3: Pathological analysis of CetuximabProg-PDX, PDX #19 and isolated PDX #19 CAFs. (A)** Example of stromal analysis of pSMAD2. The stromal areas within the tumor for quantifying the TGF-beta signal from the stroma were chosen. **(B)** Representative images of IHC staining and analysis for pSMAD2of PDX #19. Scale bar: (20X, 50 μm, and 82X, 10 μm). The expression levels were analyzed using the 3DHISTECH software HistoQuant, comparing 24-28 different stroma regions, depending on the size of the tissue, in vehicle versus cetuximab treatment groups. Statistical significance was calculated by unpaired t-test. \*P < 0.05; \*\*P < 0.01; \*\*\*P < 0.001. Data were not shown for PDX #03, since the PDX responded strongly to the treatment. **(C)** IF staining for pSMAD2 (Cy5 labeled) in orange, together with DAPI. 3T3 NIH cell lines and primary cultured murine normal fibroblasts (NOFs) from the lips versus CAFs (isolated from PDX #19) at baseline are compared, and after stimulation with recombinant TGF-beta1 (r-TGF-beta1), 10ng/ml, used as a positive control. Scale bar: 20X, 50 μm. **(D)** Four days proliferation assay of the Detroit562 HNC cell line with and without CM from PDX #19 CAFs (50% CM). The proliferation experiments were assessed in 3 independent experiments; one representable experiment is presented. Statistical significance was calculated using unpaired t-test (\*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001, \*\*\*\*p < 0.0001).

**Figure S4: *in vivo* experiments and analysis of CAL33-injected cells with PDX #19 isolated CAFs. (A)** The tumor volume of the CAL33 xenograft model with different amounts or without CAFs isolated from PDX #19. 0.5 x 106 cells from each cell line (CAL33 tumor cells, PDX #19 CAFs) were injected subcutaneously in Nod. Scid mice. Mice were randomized into 5 arms (tumors, n = 6-8). The actual tumor volumes ± SEM are presented. Statistical significance was calculated by unpaired t-test (\*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001, \*\*\*\*p < 0.0001). **(B)** Additional analysis of tumor volume of the CAL33 xerograph model with or without CAFs isolated from PDX #19 presented in Figure 4A. Each of the Cetuximab treatment groups was normalized to the respective Vehicle group. Statistical significance was calculated by unpaired t-test (\*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001, \*\*\*\*p < 0.0001).

**Table S1: Characteristics of patients included in the study**

**Table S2:** **Differential expression analysis of all three PDXs**. Negative binomial test, |log2FC| > 0.5, a BH-corrected p-value < 0.05). 179 genes with statistically significant expression changes between cetuximab and vehicle treatment for CetuxiambProg-PDX were detected, whereas this number was as high as 3047 and 3598 for the CetuximabSen-PDXs.

**Table S3: Complete KEGG signature**