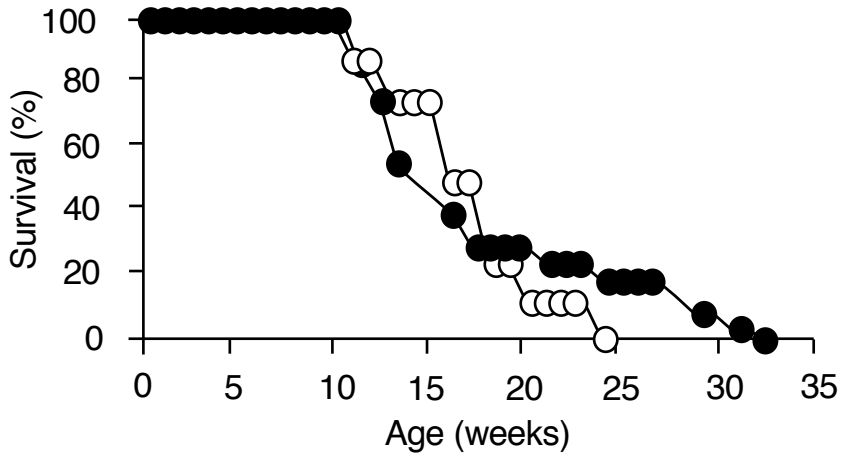
Table S1. Genes mutated in PDACs of KPeC mice analyzed by exomic NGS sequencing. Related to Figure 1.

KPeC tumour	Number of mutations	Mutated Genes
ATQ 141	4	*Lama1, Gm436, Phf20, Vmn2r45*
ATQ 270	3	*Plscr4, Chd5, Ripk2*
ATQ 274	3	*Mtap1a, Csf2ra, G2e3*
ATQ 281	15	*Zfp457* (2)*, *Grin2b, Ppp3cc, Olfr968, Trf, Sbf2, Chpt1, Enpp1, Stx4a (3), Ikzf4, Slc16a5, Fam71b*
ATQ 290	14	*Ivns1abp, Gykl1, D4Ertd22e, Tsen54, Pdia3, Tsc2, Glyr1, Trio, Skint6, Oprk1, Prrc2a, Duoxa1, 2410089E03Rik, Aim1*
ATQ 303	17	*Ret, Zfp369, Olfr1006, Trip12, Pot1a, Vmn2r51, Wdr69, Larp1b, Myh15, Serpine1, Cltc, Creld2, Olfr1462, 2610507B11Rik, Ptar1, Adamts9, Trim28*
ATQ 799	50	*Lars, Serbp1, B3gat1, Usp37, Hacl1, Apol6, Oxr1, Cpd, Zc3h12a, Flt4, Trim41, Ireb2, Pgm1, Vwa2, Bhlhe40, Fer1l4, Thpo, Ict1, Mll2, Cmpk2, Alg10b, Pik3ca, Vmn1r191, Bmp5, Dock6, Acy3, Gria4, Brip1, H2-M10.3, Lce1e, BC055004, Gpr50, Mamdc2, Reep6, Tas2r122, Hectd1, Cep164, Otop3, Olfr733, Prss54, 2410089E03Rik, Micalcl, Rrm1, Itga11, Kirrel2, Olfr617, Nras, Dpf1, Rin2, Actb*
BEH 112	2	*Dub1, Zfyve9*
BEH 280	7	*Skint6, Plxnd1, Hsp90aa1, Prcp, Cytl1, Amdhd1, Olfr1395*
BEH 420	13	*Tep1, Actc1, Psmb7, Loxl4, Krt36, Ccng1, Scarf1, Fat3, Radil, Tcfap2a, Vmn2r77* (2), *Scn1a*
BEH 461	18	*Sytl3, Pigb, Golgb1, Nipbl, Olfr895, Exosc10, Mfsd4, Igf1r, Col16a1, Trip12, Derl2, Zfp423, Rgma, Zfp759* (2), *Vmn2r67* (2), *Nbn*

A


100
80
60
40
20
0
Survival (%)
0
5
10
15
20
25
30
35
Age (weeks)

B

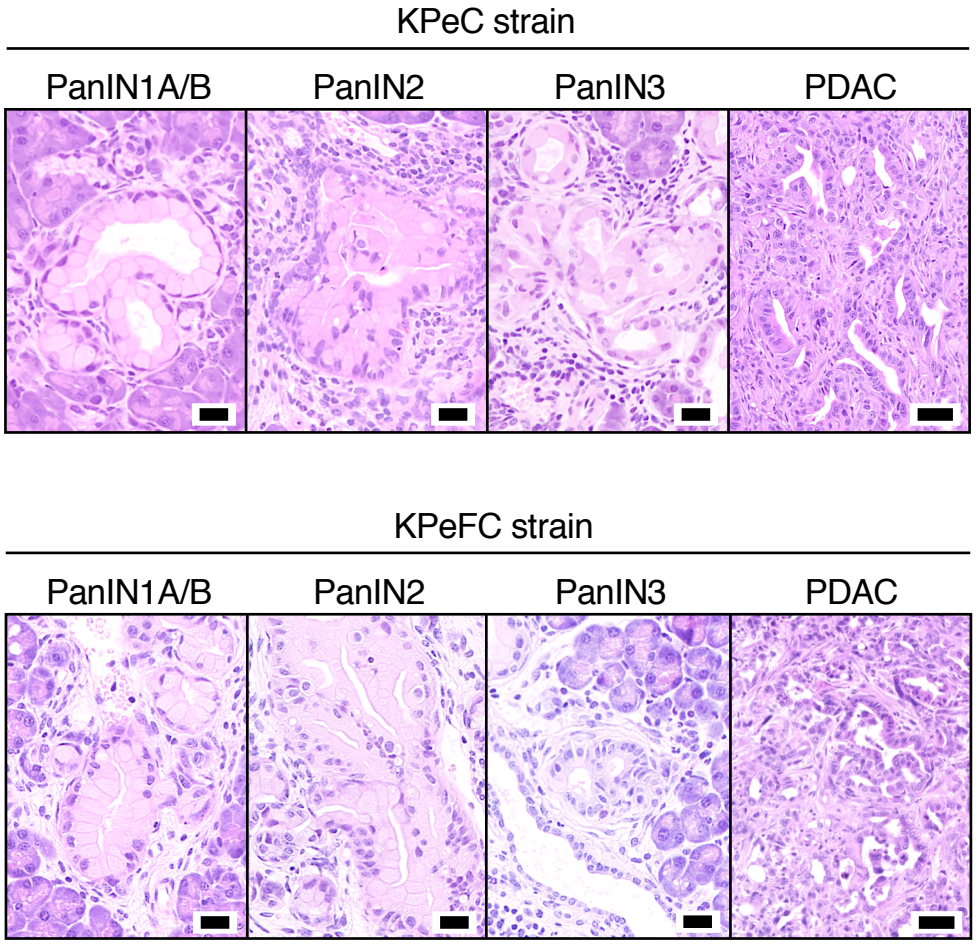
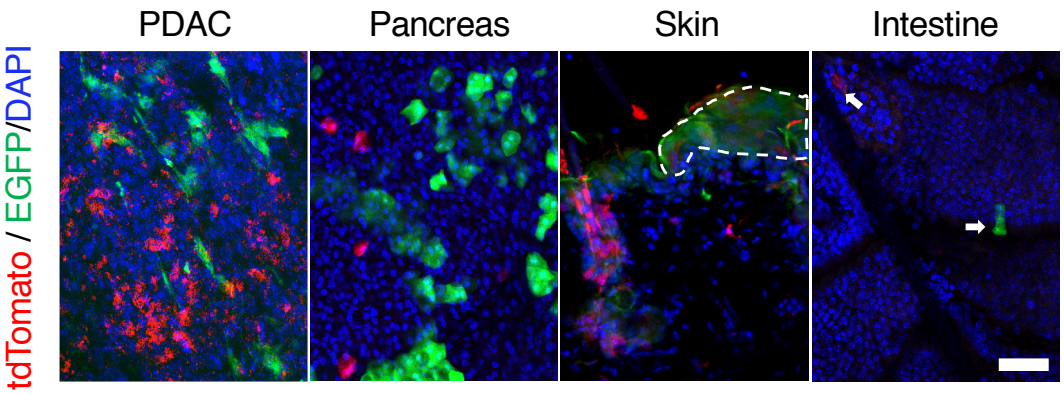

KPeC strain
PanIN1A/B
PanIN2
PanIN3
PDAC
KPeFC strain
PanIN1A/B
PanIN2
PanIN3
PDAC

Figure S1. Tumor development in the KPeC and KPeFC strains. Related to Figure 1.

(A) Survival of KPeC (solid circles, n=20) and KPeFC (open circles, n=8) mice. All mice died of PDAC at the indicated times.

(B) Representative pancreatic lesions of KPeC and KPeFC mice stained with H&E. Scale bars represent 20 μm (PanIN1A/B, PanIN2, PanIN3) and 50 μm (PDAC).

A


PDAC
Pancreas
Skin
Intestine
tdTomato / EGFP/DAPI

B

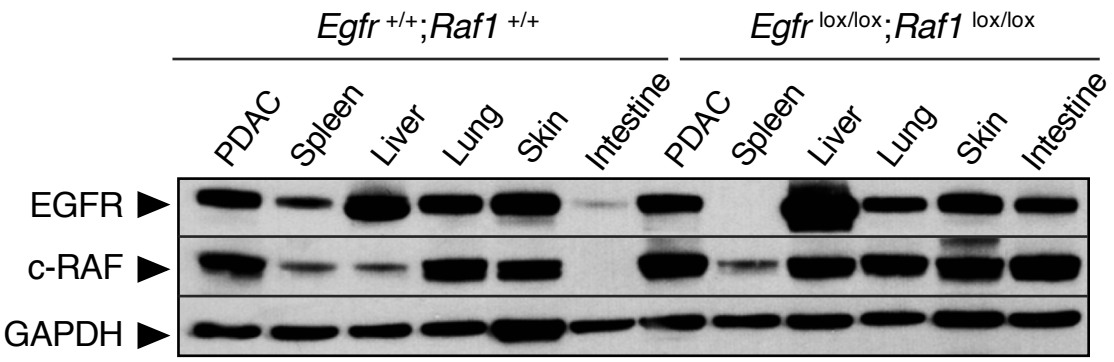
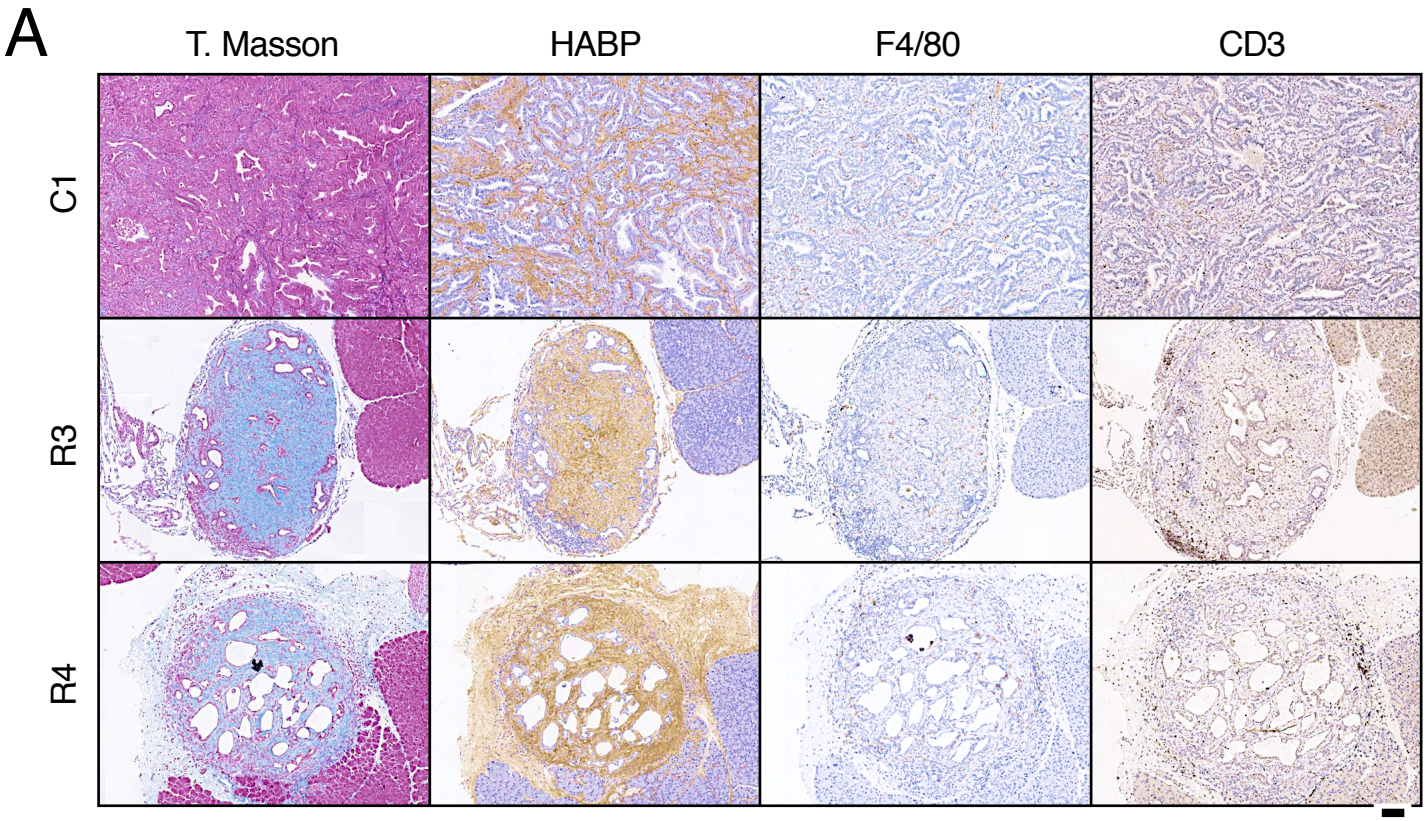
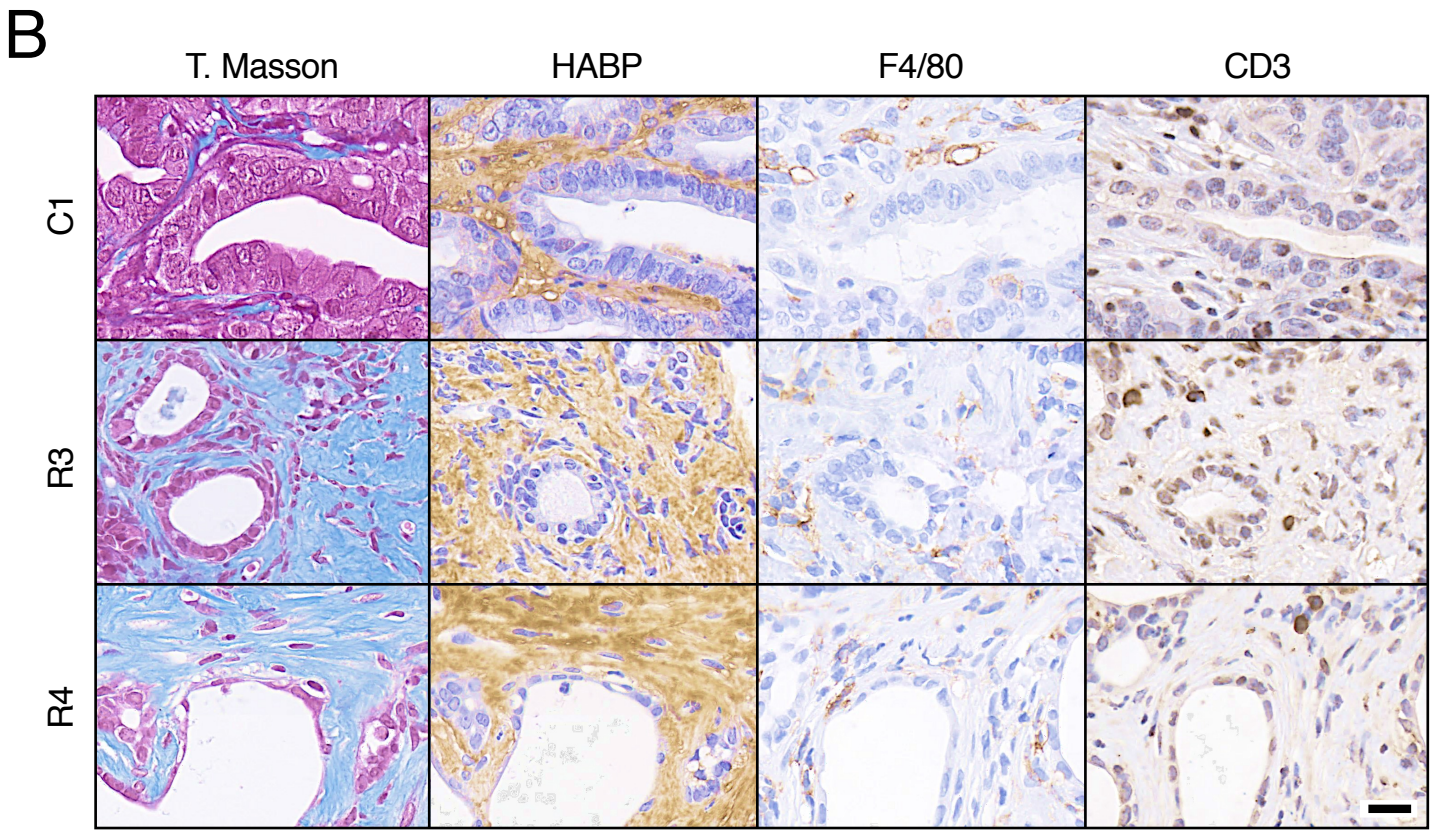

Egfr +/+;Raf1 +/+
Egfr lox/lox;Raf1 lox/lox
PDAC
Spleen
Liver
Lung
Skin
Intestine
PDAC
Spleen
Liver
Lung
Skin
Intestine
EGFR
c-RAF
GAPDH

Figure S2. Mice not included in the trial. Related to Figure 3.

(A) Spurious expression of the FlpO recombinase. Fluorescent labeling in representative sections of PDAC, healthy pancreas, skin and intestine of KPeFC;*Rosa26*$^{+/CAG\text{-}tdTomato\text{-}EGFP}$ mice exposed to TMX for 4 weeks. Dotted white line indicates a small EGFP^{+} papilloma. Arrows indicate two recombinant cells in intestine. Scale bar represents 50 μm.

(B) Limited Cre-mediated cleavage of *Egfr*^{lox} and *Raf1*^{1ox} alleles, as determined by the expression of EGFR and c-RAF proteins, in representative KPeFC and KPeFC;*Egfr*$^{lox/lox}$;*Raf1*$^{1ox/lox}$ mice after TMX exposure. GAPDH served as a loading control.


A
T. Masson
HABP
F4/80
CD3
C1
R3
R4


B
T. Masson
HABP
F4/80
CD3
C1
R3
R4

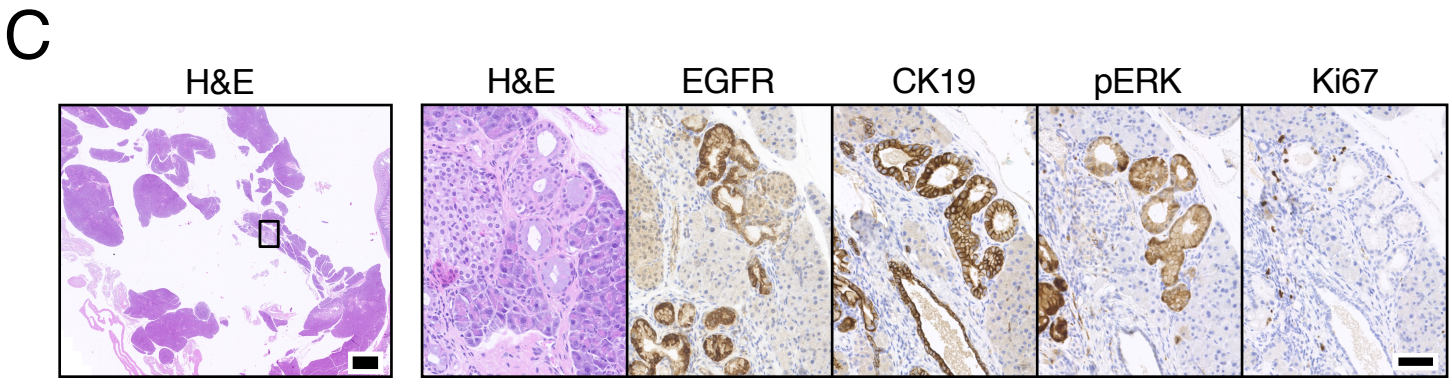

C
H&E
H&E
EGFR
CK19
pERK
Ki67

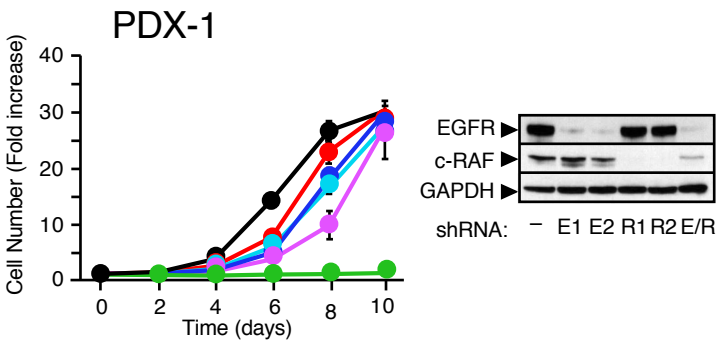
Figure S3. Histological characterization of residual scar lesions and PanINs present in "Regressor" mice after TMX exposure. Related to Figure 3.

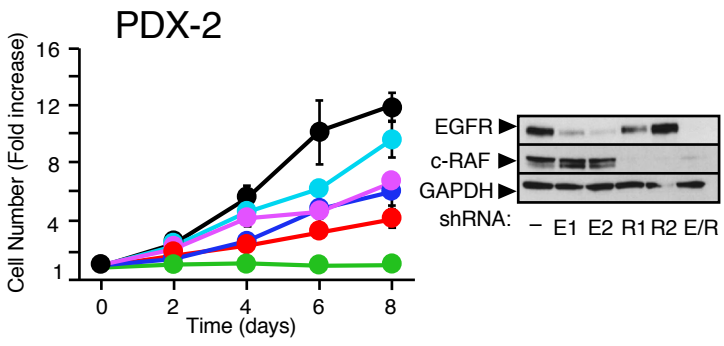
(A and B) Low (A) and high (B) magnification of representative sections of a PDAC present in control KPeFC;*Egfr*$^{+/+}$;*Raf1*$^{+/+}$ C1 mouse and in the scar lesions of KPeFC;*Egfr*$^{lox/lox}$;*Raf1*$^{lox/lox}$ R3 and R4 mice stained with Masson´s trichrome (T. Masson), Hyaluronic Acid Binding Protein (HABP), F4/80 and CD3. Scale bars represents 100 μm (A) and 20 μm (B).

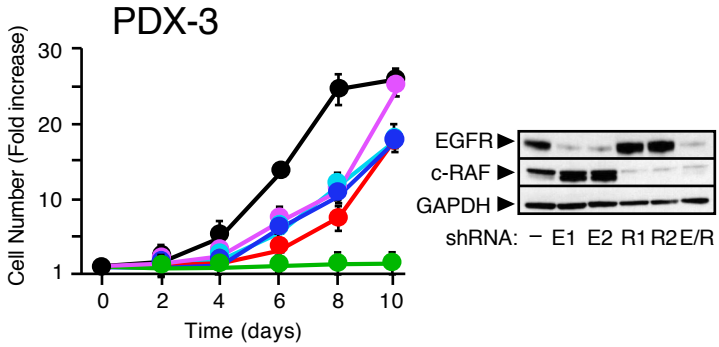
(C) Representative H&E stained paraffin sections of the pancreata of KPeFC;*Egfr*$^{lox/lox}$;*Raf1*$^{lox/lox}$ R2 mouse after six weeks of TMX exposure. Scale bar represents 1000 μm. Box inset marks the area shown at higher magnification in the adjacent images shown to the right stained for H&E, EGFR, CK19, pERK and Ki67. Scale bar represents 50 μm.

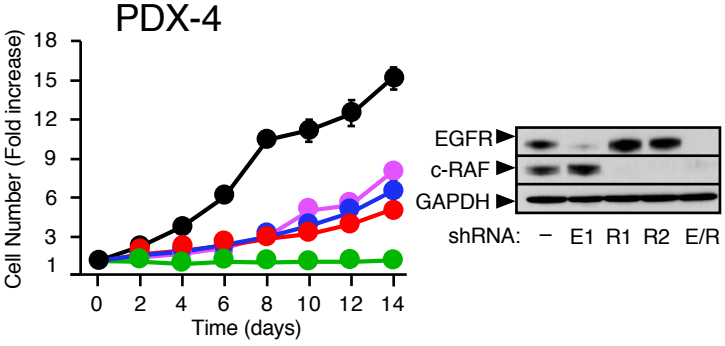
Table S3. *KRAS* and *TP53* mutations in PDX tumor models. Related to figure 7.

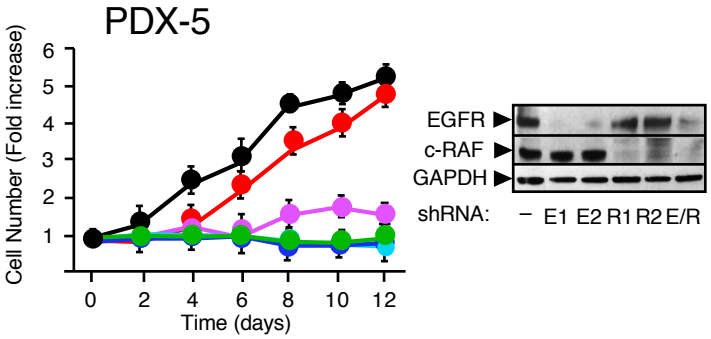
ID	PDX tumor model	*KRAS* mutation	*TP53* mutation
PDX-1	PDAC003T	G12D	Q136P
PDX-2	Panc-1	G12D	P72R, K129R
PDX-3	PDAC013T	G12D	I254T
PDX-4	Panc-4	G12D	P72R, R282W
PDX-5	Panc-198	G12D	D208V
PDX-6	Panc-2	G12D	P72R, R282W
PDX-7	Panc-185	G12D	K120R
PDX-8	H-PDAC-H-X 132	G12V	C275R
PDX-9	H-PDAC-M-X 3	Q61H	H179Y
PDX-10	H-PDAC-M-X 7	Q61H	WT

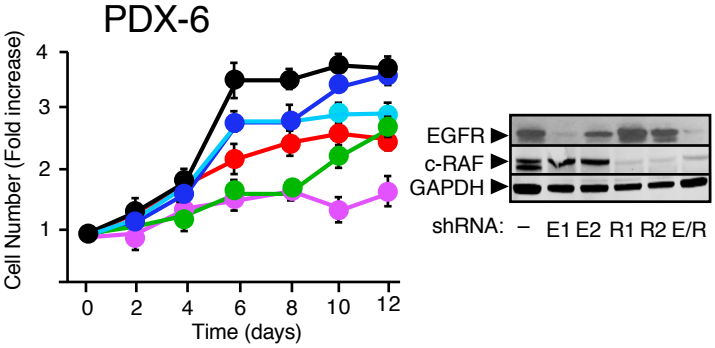

PDX-1
Cell Number (Fold increase)
Time (days)
EGFR
c-RAF
GAPDH
shRNA: – E1 E2 R1 R2 E/R

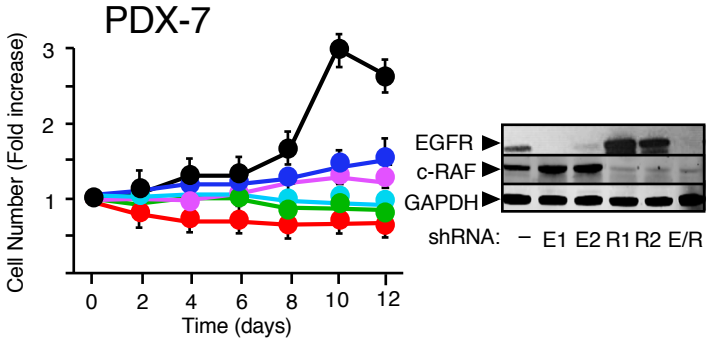

PDX-2
Cell Number (Fold increase)
Time (days)
EGFR
c-RAF
GAPDH
shRNA: – E1 E2 R1 R2 E/R

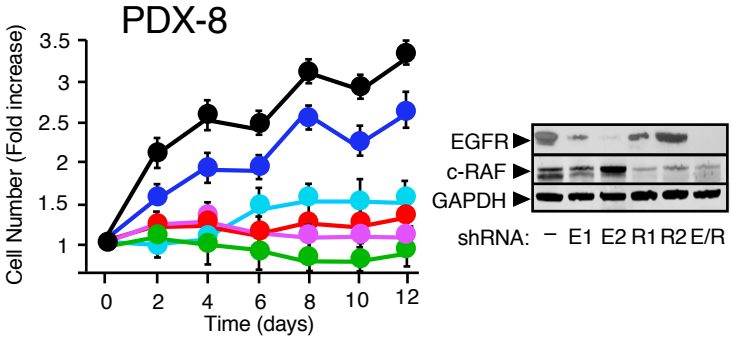

PDX-3
Cell Number (Fold increase)
Time (days)
EGFR
c-RAF
GAPDH
shRNA: – E1 E2 R1 R2 E/R

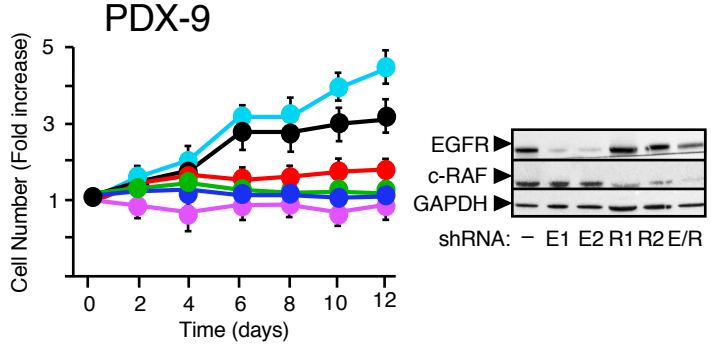

PDX-4
Cell Number (Fold increase)
Time (days)
EGFR
c-RAF
GAPDH
shRNA: – E1 R1 R2 E/R


PDX-5
Cell Number (Fold increase)
Time (days)
EGFR
c-RAF
GAPDH
shRNA: – E1 E2 R1 R2 E/R


PDX-6
Cell Number (Fold increase)
Time (days)
EGFR
c-RAF
GAPDH
shRNA: – E1 E2 R1 R2 E/R


PDX-7
Cell Number (Fold increase)
Time (days)
EGFR
c-RAF
GAPDH
shRNA: – E1 E2 R1 R2 E/R


PDX-8
Cell Number (Fold increase)
Time (days)
EGFR
c-RAF
GAPDH
shRNA: – E1 E2 R1 R2 E/R


PDX-9
Cell Number (Fold increase)
Time (days)
EGFR
c-RAF
GAPDH
shRNA: – E1 E2 R1 R2 E/R

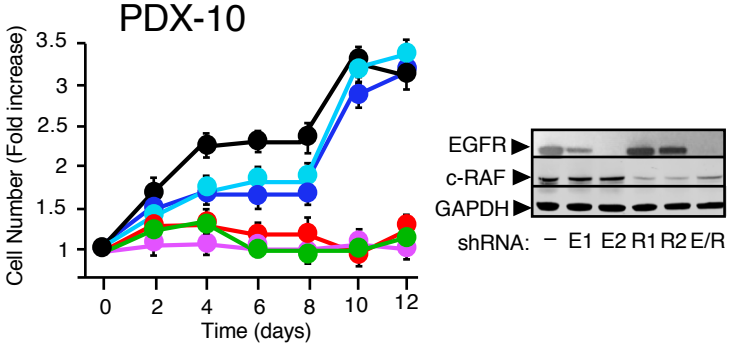

PDX-10
Cell Number (Fold increase)
Time (days)
EGFR
c-RAF
GAPDH
shRNA: – E1 E2 R1 R2 E/R

Figure S4. EGFR and c-RAF expression is essential for *in vitro* proliferation of PDAC cells-derived from PDX tumor models. Related to Figure 7.

(Left) Cell proliferation of the indicated PDX-derived cells infected with a scramble shRNA (black) or with shRNAs against *EGFR* (light and dark blue), *RAF1* (red and pink) and *EGFR* plus *RAF1* (green). (Right) Western blot analysis of EGFR and c-RAF expression in whole cell extracts obtained from the indicated PDX-derived cells using either a scramble shRNA (–), shRNAs against *EGFR* (E1, E2), *RAF1* (R1, R2) and *EGFR* plus *RAF1* (E1/R1) (right). Proliferation was determined by MTT and expressed as fold increase in the number of cells determined at each of the indicated days. Error bars indicate mean ± SD. GAPDH served as loading control.

Table S4. IC_{50} of Gefitinib and Erlotinib for each of the PDX-derived cells. Related to Figure 8.

ID	PDX tumor model	IC_{50} (μM)	
		Gefitinib	Erlotinib
PDX-1	PDAC003T	13.2	11.7
PDX-2	Panc-1	11.3	6.1
PDX-3	PDAC013T	3.3	2.05
PDX-4	Panc-4	2.8	2.82
PDX-5	Panc-198	14.9	32.8
PDX-6	Panc-2	18.7	>100
PDX-7	Panc-185	16.8	10.1
PDX-8	H-PDAC-H-X 132	15.2	>100
PDX-9	H-PDAC-M-X 3	5.4	24.5
PDX-10	H-PDAC-M-X 7	15.8	74.3