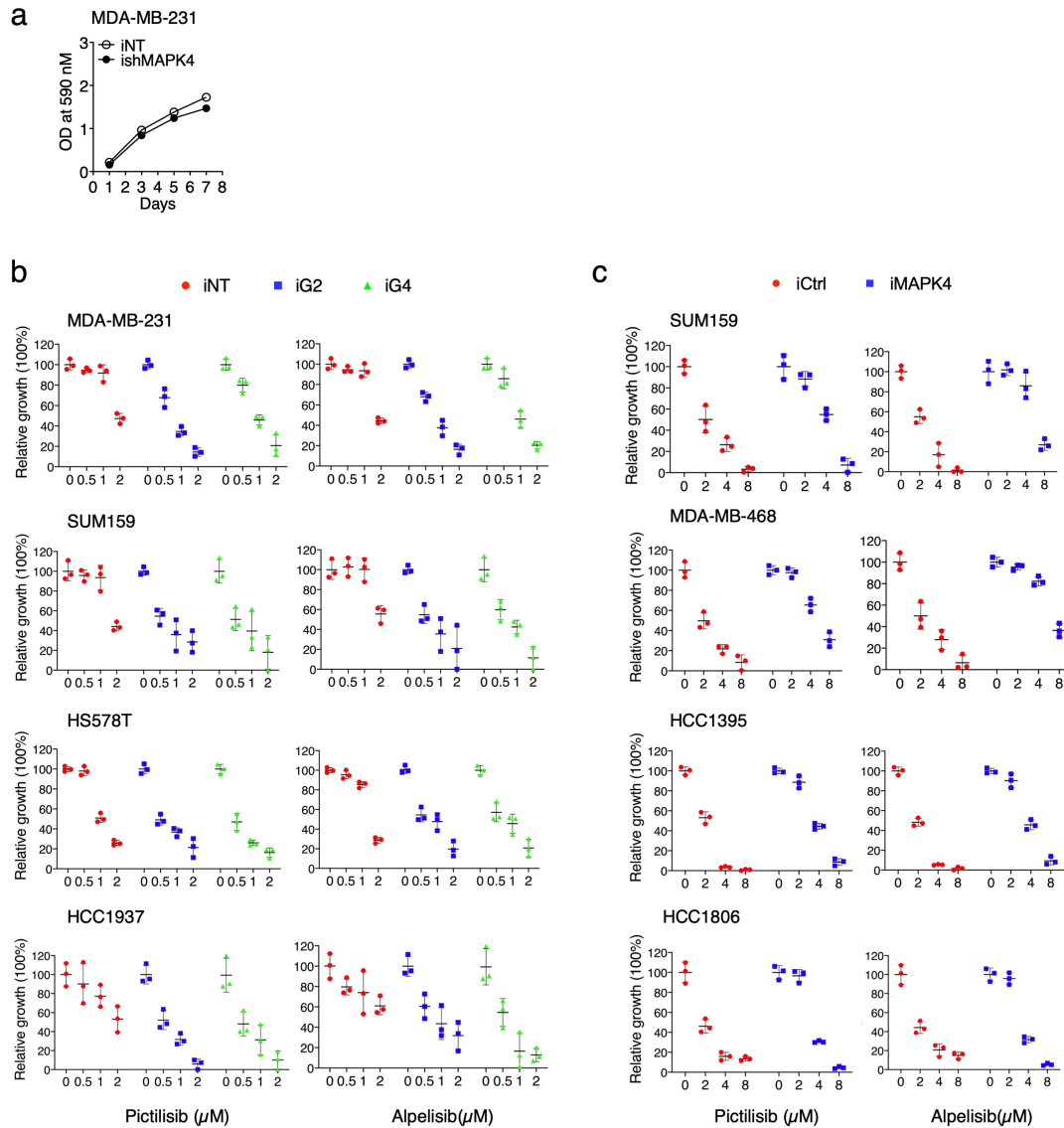
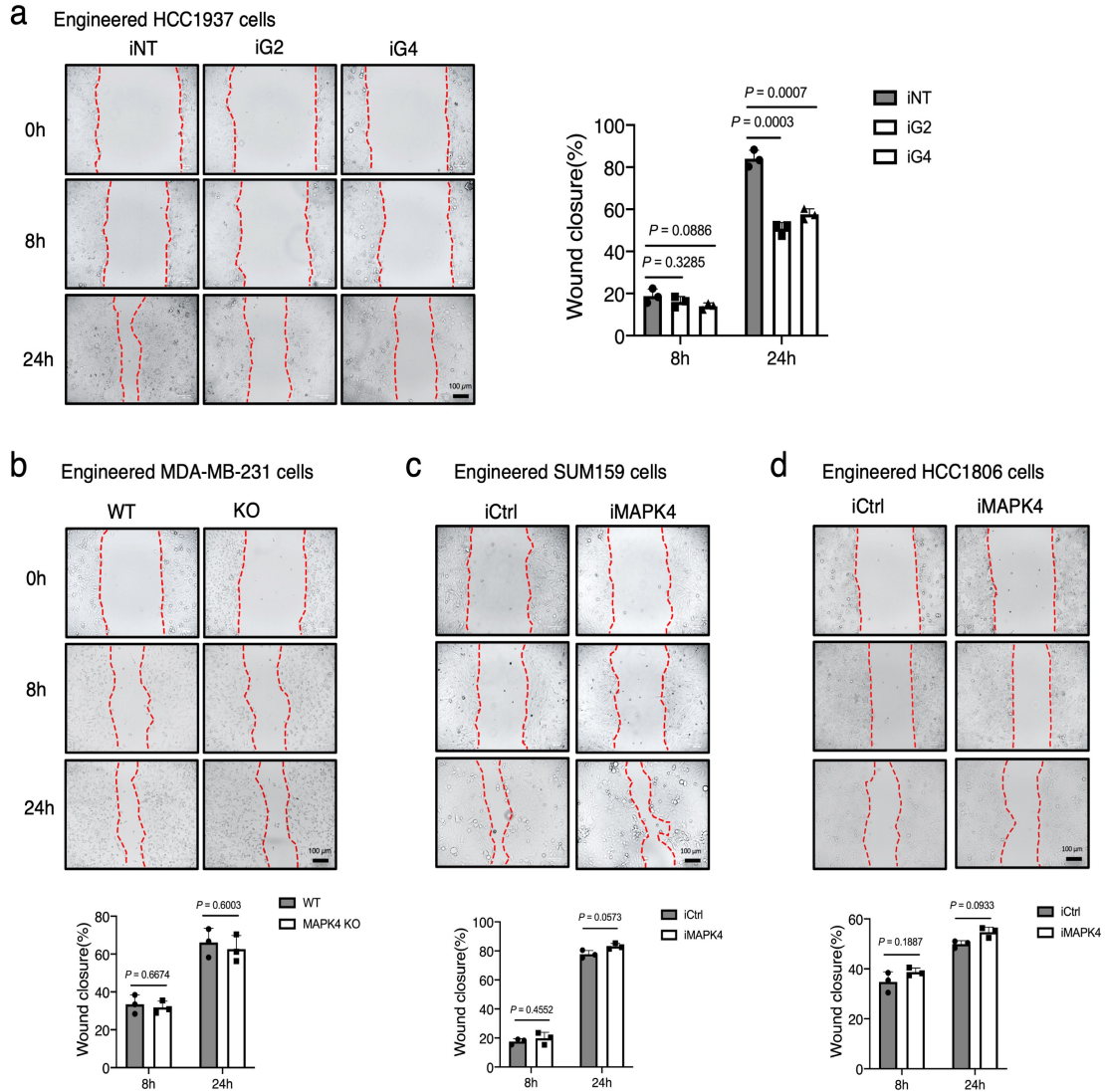


Supplementary Information



Supplementary Fig. S1 MAPK4 regulation of TNBC cells. **a** Proliferation assays comparing the growth of engineered MDA-MB-231 cells with 4 μ g/ml Dox-induced knockdown of MAPK4 (ishMAPK4) or control (iNT). **b** The relative growth of MAPK4-knockdown TNBC cells as described in Fig. 7a-d. **c** The relative growth of MAPK4-overexpressing TNBC cells as described in Fig. 8a-d. All vehicle treated arms were set at 100% to provide relative growth inhibition by PI3K inhibitors in these differentially engineered TNBC cells.



Supplementary Fig. S2 MAPK4 regulation of TNBC cell migration. Wound healing assays on the engineered **a** H1937 cells with 4 $\mu\text{g/ml}$ Dox induced knockdown of MAPK4 (iG2, iG4) or control (iNT), **b** wild type (WT) and *MAPK4*-knockout (KO, clone #3) MDA-MB-231 cells, and **c,d** SUM159 and HCC1806 cells with 0.5 $\mu\text{g/ml}$ Dox induced overexpression of MAPK4 (iMAPK4) or control (iCtrl). Representative images of cells after 0, 8h, and 24h after the initial scratch were shown. Bar: 100 μm . Also shown are the quantification (mean \pm SD) of percentage of wound closure at 8h and 24h after scratch. *P* values determined by unpaired 2-tailed Student's *t* test. Data are representative of at least 2-3 independent experiments.

Source Data for supplementary Fig. 1a

Day	iNT			ishMAPK4 (G4)		
1	0.226	0.211	0.21	0.172	0.163	0.14
3	0.925	0.99	0.973	0.897	0.851	0.773
5	1.42	1.366	1.358	1.301	1.196	1.23
7	1.762	1.693	1.721	1.417	1.469	1.522

Source Data for supplementary Fig. 1b

MDA-MB-231

Pictilisib	iNT			iG2			iG4		
	0	105.7	99	95.38	104.5	96.3	99.18	107	97.19
0.5	93.92	92.4	96.94	68.74	76.3	58.04	84.2	72.01	83.4
1	93.97	82.8	98.61	39.49	30.8	33.27	48.4	48.88	40.1
2	47.54	42.1	52.18	10.33	14.1	18.83	12.1	32.93	17.2
Alpelisib	iNT			iG2			iG4		
	0	105.7	99	95.38	104.5	96.3	99.18	107	97.19
0.5	92.86	92.7	98.05	63.25	68.7	72.3	81.5	96.96	79
1	92.2	101	87.77	44.88	29.7	38.21	38.6	44.66	55
2	42.09	44	47.49	20.66	17.7	10.88	23	16.07	22.1

SUM159

Pictilisib	iNT			iG2			iG4		
	0	111	92.5	96.51	104.5	96.9	98.62	95.3	113.6
0.5	96.51	101	89.68	45.58	57.4	60.71	64.3	46.2	43.6
1	104	97.2	79.64	50.88	19.3	37.52	23.4	61.68	33.4
2	48.95	40.3	43.1	18.07	27.3	39.88	20.6	33.6	0
Alpelisib	iNT			iG2			iG4		
	0	111	92.5	96.51	104.5	96.9	98.62	95.3	113.6
0.5	93.03	112	103.6	65.03	50.9	48.53	68.5	62.34	48.4
1	87.73	103	110.3	50.88	17.9	37.52	44.4	34.93	48
2	59.55	61.2	45.75	0	18.5	44.2	0	11.94	22.3

HS578T

Pictilisib	iNT			iG2			iG4		
	0	102.8	99.6	97.52	105.2	95.4	99.38	105	95.24
0.5	97.22	103	93.85	44.74	47.7	54.81	47.4	55.19	38.4
1	47.15	56	49.42	32.15	40.4	37.94	29.2	25.1	23.8
2	28.8	23.7	25.19	11.25	22.3	30.3	19	18.91	10.8

Alpelisib		iNT		iG2			iG4		
0	102.8	99.6	97.52	105.2	97.7	99.38	105	95.24	100
0.5	100.2	94.5	91.57	62.53	49.7	51.12	50.8	52.35	68.2
1	81.92	88	86.41	54.81	49.6	38.44	34.5	50.63	51.7
2	31.4	25.5	29.34	18.55	27.9	12.67	19.7	30.26	12.5

HCC1937

Pictilisib		iNT		iG2			iG4		
0	87.51	101	111.7	111.5	95.4	93.16	90.4	121.9	87.7
0.5	69.75	87.7	112.9	63.47	48.3	44.53	41.3	62.57	40.1
1	66.2	89.1	76.37	26.84	38.2	30	30.2	47.6	15.9
2	39.24	53.6	66.52	7.263	0	10.11	0	11.08	19.2
Alpelisib		iNT		iG2			iG4		
0	87.51	101	112.2	111.5	95.4	93.16	90.4	120.7	87.7
0.5	73.79	76.4	88.64	48.63	72.6	60.32	58.1	39.52	66.2
1	53.12	73.1	95.59	31.89	61.3	37.58	12.6	35.63	1.5
2	54.57	57.5	70.88	33.79	44.8	16.74	20.1	7.186	11.4

Source Data for supplementary Fig. 1c

SUM159

Pictilisib		iCtrl		iMAPK4		
0	101	93.2	105.9	101.8	87.8	110
0.5	39	63.8	47.68	92.3	80.1	92.5
1	33.5	24.8	20.87	55.14	49.3	60.2
2	3.91	5.22	0.435	8.569	12.8	0.28
Alpelisib		iCtrl		iMAPK4		
0	101	93.2	105.9	101.8	87.8	110
0.5	53.5	62.5	48.99	107.9	96.5	101
1	4.93	17.1	28.55	74.05	83.1	100
2	0	0	4.058	21.98	33.1	25.8

MDA-MB-468

Pictilisib		iCtrl		iMAPK4		
0	98.4	93	108.6	99.98	104	95.5
2	47.1	58.7	43.24	101.8	92.4	98.5
4	24.4	24.2	16.87	65.64	72	58.6
8	10.1	14.9	0.331	38.63	24	30

Alpelisib		iCtrl		iMAPK4		
0	98.5	93	108.6	99.98	104	95.5
2	63.4	47	39.37	97.05	96.7	92.3
4	36	18.1	29.67	86.95	81.1	78.7
8	14.4	2.1	2.757	30.62	43.1	35.8

HCC1395

Pictilisib		iCtrl		iMAPK4		
0	104	101	95.69	97.98	98.8	103
2	46.8	58.5	53.85	88.18	95	82.9
4	3.15	4.41	3.09	41.43	44.6	47.4
8	0.92	0	1.374	9.159	4.93	11.8

Alpelisib		iCtrl		iMAPK4		
0	104	101	95.69	97.98	98.8	103
2	47.1	44.8	52.71	83.14	97	90.6
4	4.86	5.84	5.265	44.83	51	41.1
8	1.66	0	3.205	5.964	8.06	13.9

HCC1806

Pictilisib		iCtrl		iMAPK4		
0	89	101	109.8	106	101	92.5
2	44.3	53.7	40.41	99.61	89.3	101
4	15.9	20	11.93	30.26	31.8	29.9
8	11.4	13.3	15.94	5.815	3.54	4.42

Alpelisib		iCtrl		iMAPK4		
0	89	101	109.8	106	101	92.5
2	42.8	38.8	51.24	101.9	95.8	89.4
4	25.4	23.2	13.27	34.63	32	28.1
8	11	16.4	17.4	4.285	6.82	5.03

Source Data for supplementary Fig. 2a

	iNT			iG2			iG4		
8h	15.6	22.34	18.57	16.35	13.72	18.43	14.38	12.79	15.95
24h	80.2	88.32	83.41	52.56	52.34	47.42	57.46	60.68	55.77

Source Data for supplementary Fig. 2b

	WT			MAPK4 KO		
8h	33.42	38.42	28.45	35.52	30.92	29.04
24h	66.76	73.24	58.19	61.23	56.37	70.43

Source Data for supplementary Fig. 2c

	iCtrl			iMAPK4		
8h	18.32	15.34	19.04	20.41	23.57	15.32
24h	80.43	77.74	75.82	85.32	88.58	81.34

Source Data for supplementary Fig. 2d

	iCtrl			iMAPK4		
8h	35.17	30.45	38.82	40.58	37.28	38.37
24h	50.42	51.07	48.38	55.57	52.41	56.91