

Supplementary table 1
Up-regulated genes expressed in resistant cells

GeneID	FC_PR1vsWT	FC_PR2vsWT	FC_PR3vsWT
ACTG2	4.551433927	4.411335526	4.057526318
CDH5	2.834495377	3.891525259	3.7988458
CPED1	2.807567467	4.289786292	3.54941775
CTTNBP2	3.280557129	3.33054698	3.228525522
CYP4F8	3.387833813	3.783098058	2.594438978
DYNLT3	3.146498872	2.557148692	2.676542776
LOC101926982	3.224415523	3.323267724	2.78837615
LOC105371930	4.438836102	4.321625326	2.571000859
MARCH11	3.015841831	3.551449322	3.078238904
MME	3.261810264	4.685406883	3.23673967
NTSR2	2.707860883	3.137797302	5.742211735
PPARG	2.661302336	3.588735952	2.910098692
RBP2	3.53308382	10.17689763	3.00718889
TAS2R14	2.654582185	3.314289531	3.572075519
TWIST2	3.782976404	6.121123854	5.573750506

Supplementary table 2

The Correlation between PPARG Expression and Clinical Characteristics of Patients

Patient Characteristics	PPARG-High		PPARG-Low		<i>p</i> values
	Num	Percentage	Num	Percentage	
Age					
≤35	0	0	6	5.1282	0.320
36-45	12	15.7895	17	14.5299	
46-55	34	44.7368	46	39.3162	
56-65	24	31.5789	41	35.0427	
≥66	6	7.8947	7	5.9829	
Local therapy					
Breast-conserving surgery	3	3.9474	8	6.8376	0.532
Mastectomy	73	96.0526	109	93.1624	
Histological grade					
II	31	40.7895	59	50.4274	0.253
II-III	7	9.2105	7	5.9829	
III	38	50.0000	48	41.0256	
Unknown	0	0	3	2.5641	
pT					
pT1	19	25.0000	27	23.0769	0.829
pT2	53	69.7368	85	72.6496	
pT3	4	5.2632	5	4.2735	
pN					
pN0	37	48.6842	59	50.4274	0.288
pN1-3	37	48.6842	58	49.5726	
Unknown	2	2.6316	0	0	
Ki-67					
≤14%	16	21.0526	23	19.6581	0.942
>14%	39	51.3158	59	50.4274	
Unknown	21	27.6316	35	29.9145	

HR status						
Negative	60	78.9474	97	82.906	0.571	
Positive	16	21.0526	20	17.094		

Menopause Status						
No	31	40.7895	43	36.7521	0.650	
Yes	45	59.2105	74	63.2479		

Supplementary table 3

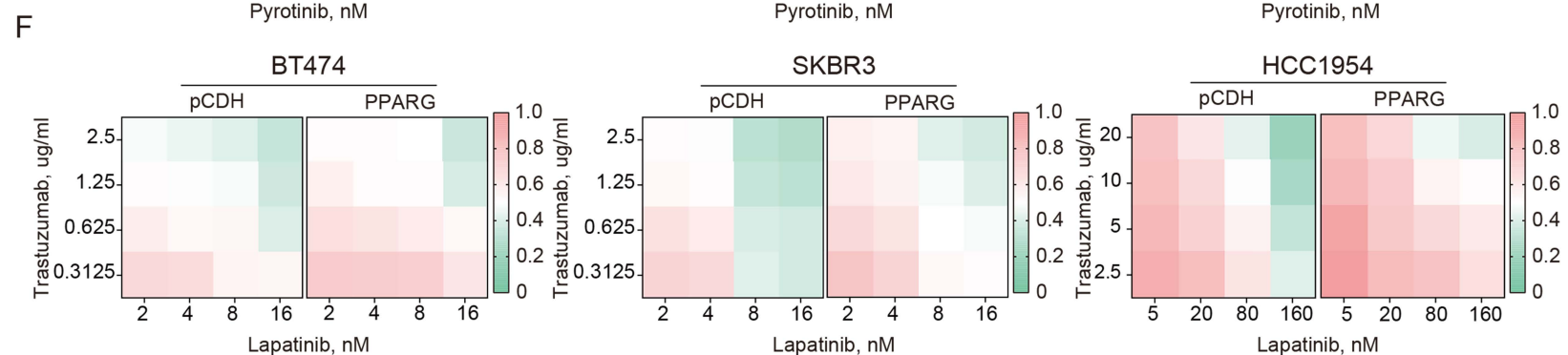
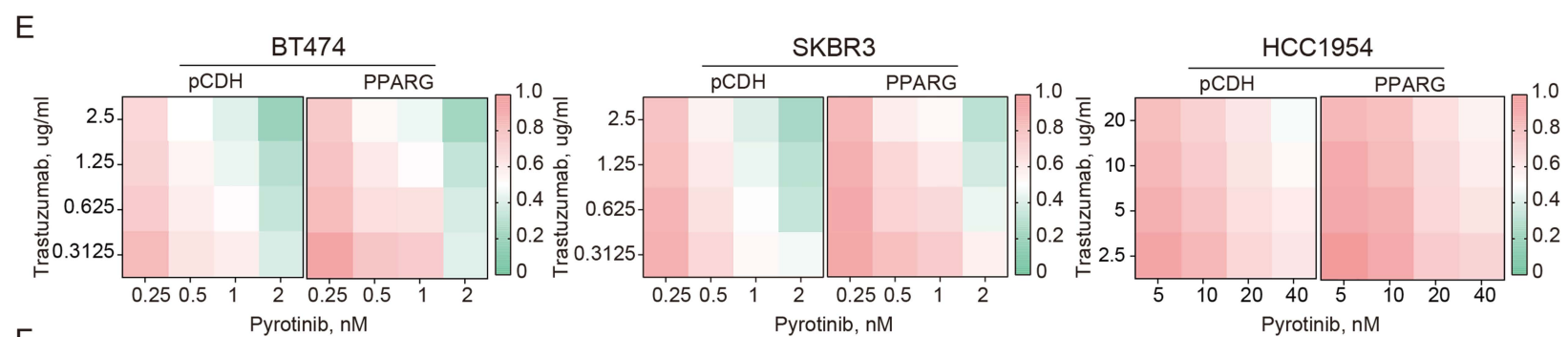
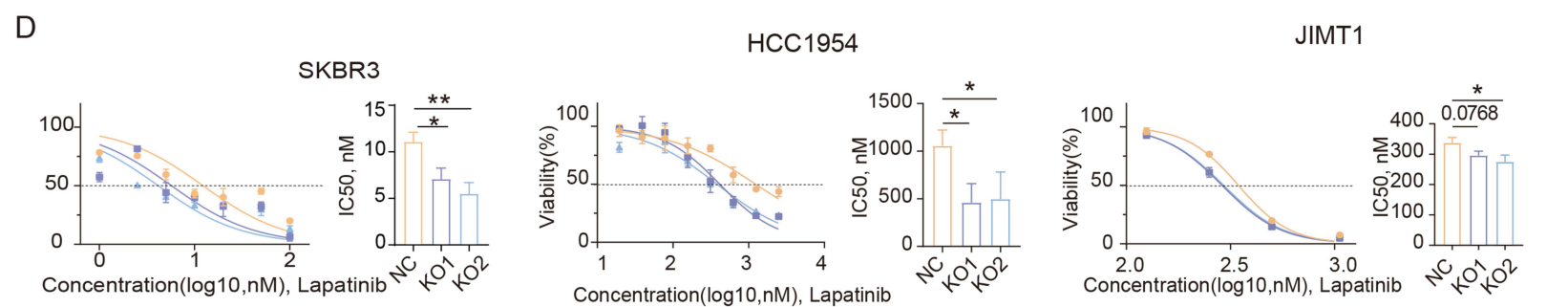
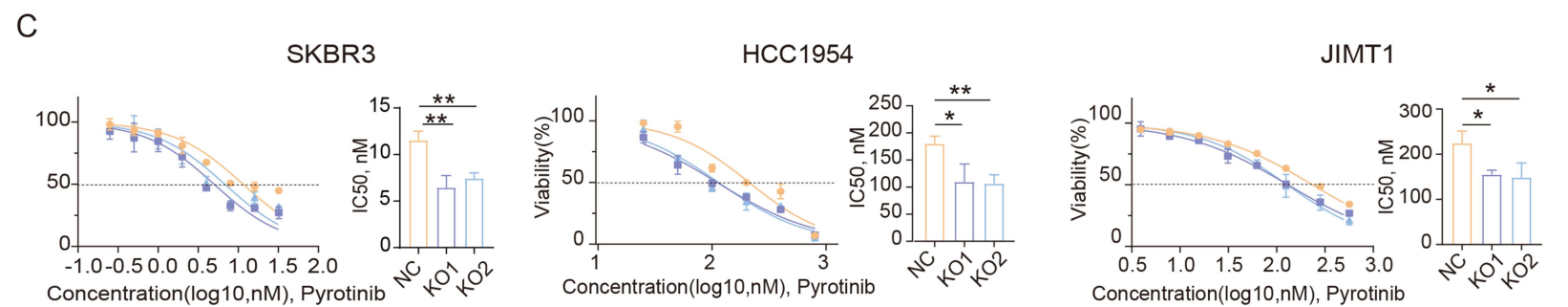
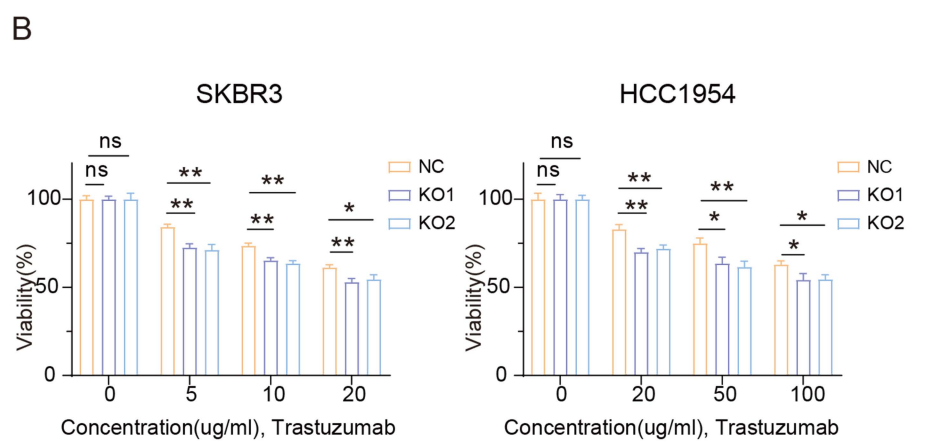
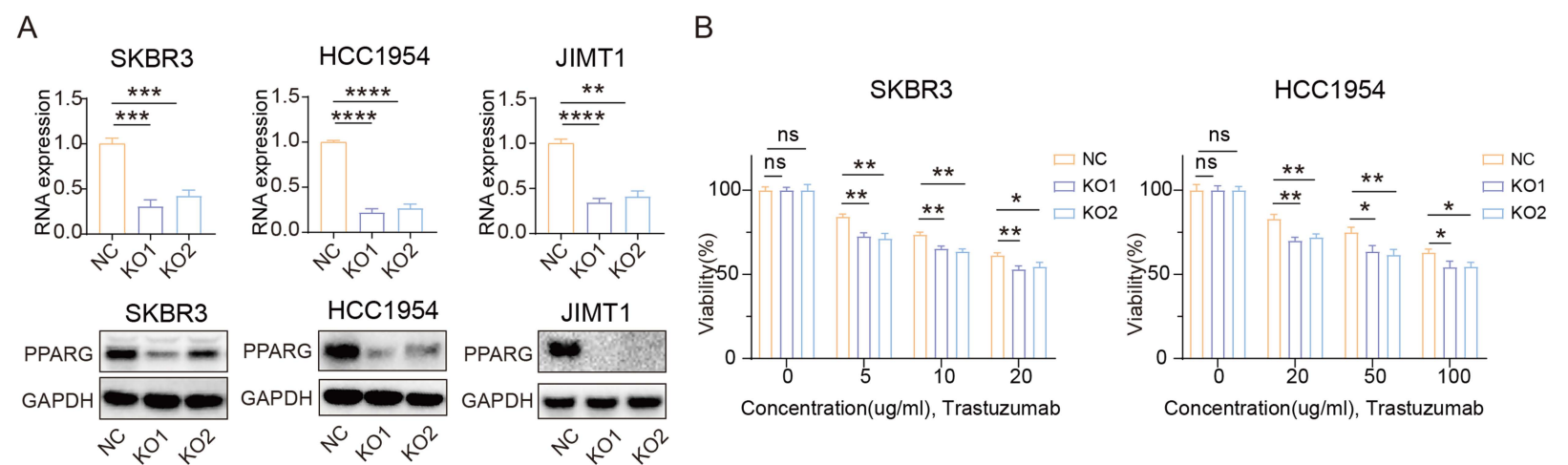
Univariate Cox Regression Analysis of OS in HER2-positive Breast Cancer

Patient Characteristics		<i>p values</i>	HR (95%)
Age	≤45		
	>45	0.339	1.799(0.540-5.994)
Local therapy	Mastectomy		
	Breast-conserving surgery	0.556	0.556(0.075-4.119)
Histological grade	II		
	II-III	0.038	4.543(1.085-19.024)
	III	0.006	4.060(1.507-10.939)
	Unknown		
pT	pT1		
	pT2	0.163	2.372(0.705-7.984)
	pT3	0.035	5.612(1.132-27.812)
pN	pN0		
	pN1-3	0.026	2.571(1.118-5.915)
	Unknown		
HR status	Negative		
	Positive	0.250	1.663(0.699-3.958)
Menopause Status	No		
	Yes	0.098	2.160(0.867-5.380)
PPARG expression	Low		
	High	0.028	2.388(1.096-5.203)

Supplementary table 4

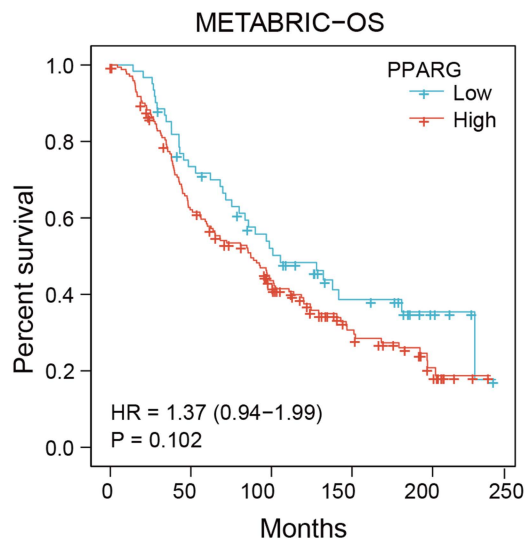
Univariate Cox Regression Analysis of DFS in HER2-positive Breast Cancer

Patient Characteristics		<i>p values</i>	HR (95%)
Age	≤45		
	>45	0.910	0.959(0.462-1.991)
Local therapy	Mastectomy		
	Breast-conserving surgery	0.474	1.457(0.520-4.083)
Histological grade	II		
	II-III	0.600	1.389(0.407-4.744)
	III	0.119	1.633(0.882-3.025)
	Unknown		
pT	pT1		
	pT2	0.334	1.463(0.676-3.168)
	pT3	0.055	3.237(0.973-10.766)
pN	pN0		
	pN1-3	0.003	2.575(1.369-4.842)
	Unknown		
HR status	Negative		
	Positive	0.099	1.745(0.900-3.382)
Menopause Status	No		
	Yes	0.360	1.336(0.719-2.484)
PPARG expression	Low		
	High	0.036	1.872(1.042-3.363)

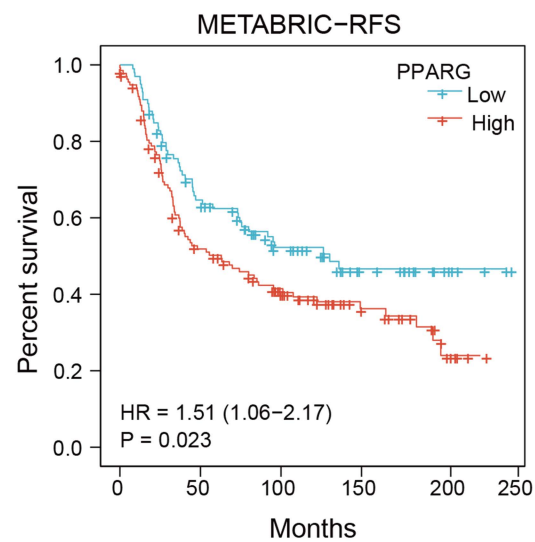


Supplementary Figure 1: (A) Expression of PPARG at the RNA and protein level in SKBR3, HCC1954, JIMT1 cells in NC and PPARG knockout groups; (B) Viability of different concentrations of trastuzumab treatment SKBR3, HCC1954 cells with PPARG knockout compared to NC groups; (C) Gradient concentrations of pyrotinib treatment SKBR3, HCC1954, JIMT1 cells with PPARG knockout compared to NC groups were plotted for IC₅₀ curves and IC₅₀ value bar graphs; (D) Gradient concentrations of lapatinib treatment SKBR3, HCC1954, JIMT1 cells with PPARG knockout compared to NC groups were plotted for IC₅₀ curves and IC₅₀ value bar graphs; (E) Heat map illustrating the survival rates of BT474, SKBR3, HCC1954 cells with PPARG overexpression and pCDH groups in combination with trastuzumab and pyrotinib treatment; (F) Heat map illustrating the survival rates of BT474, SKBR3, HCC1954 cells with PPARG overexpression and pCDH groups in combination with trastuzumab and lapatinib treatment.

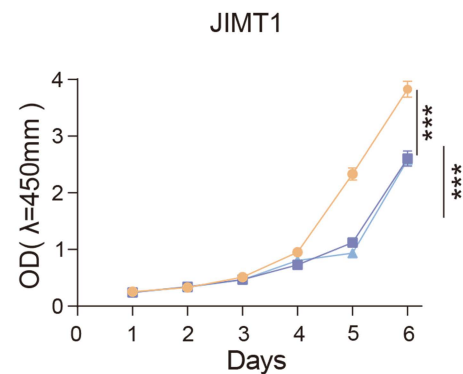
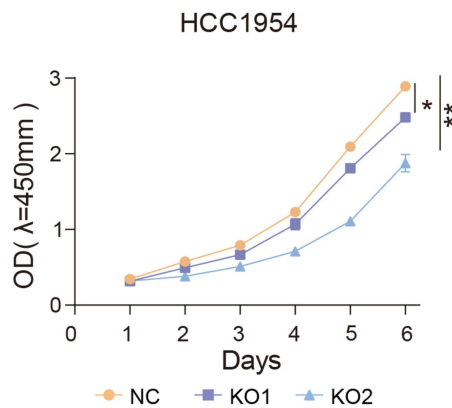
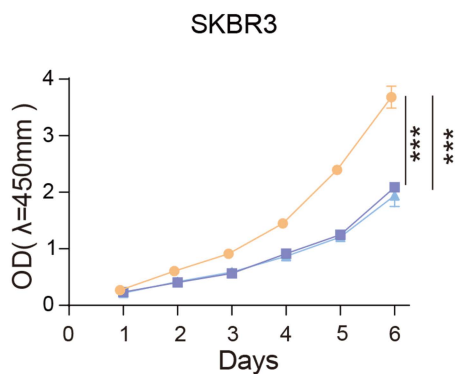
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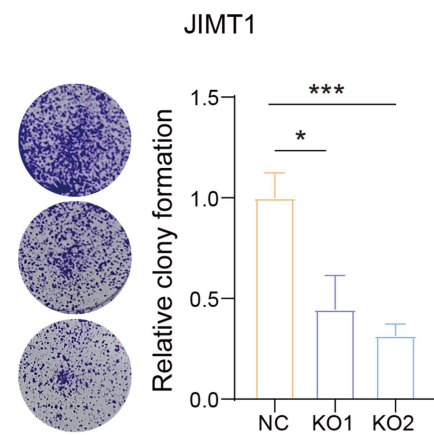
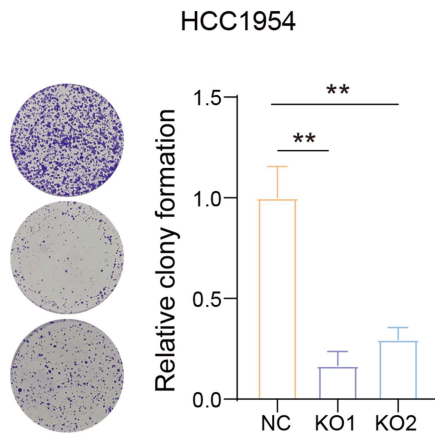
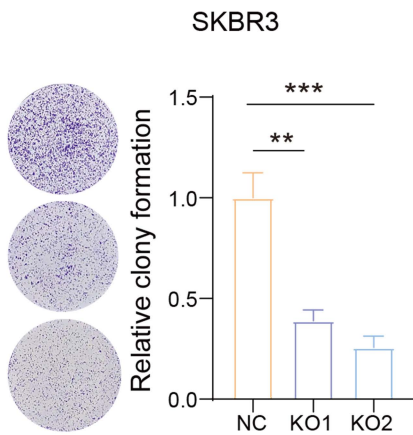
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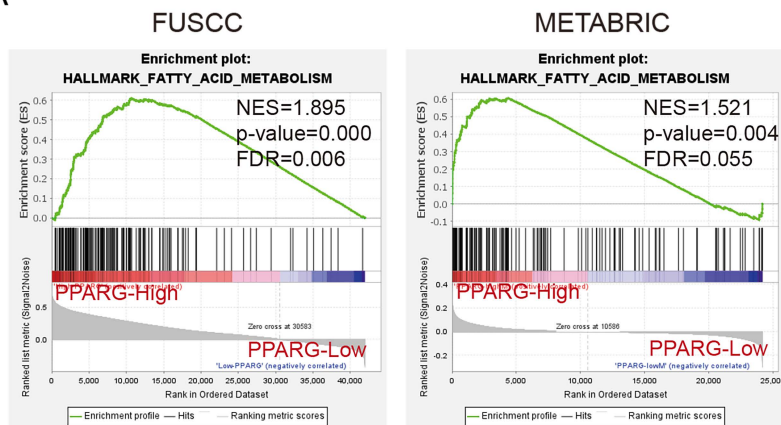


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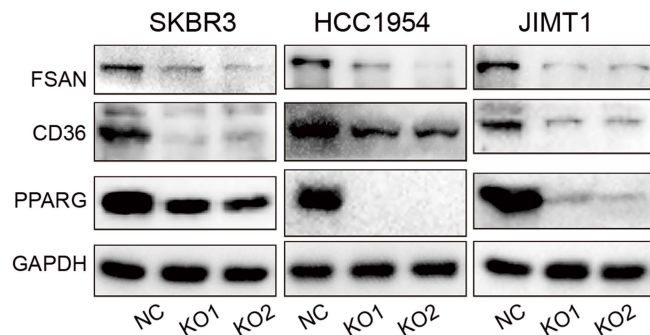


Supplementary Figure 2: Kaplan-Meier analysis of the relationship between PPARG expression levels and (A) OS and (B) DFS in HER2-positive breast cancer patients from METABRIC database; (C) Proliferation curves of SKBR3, HCC1954, and JIMT1 cells PPARG knockout compared to NC groups; (D) Plate colony formation of SKBR3, HCC1954, and JIMT1 cells PPARG knockout compared to NC groups.

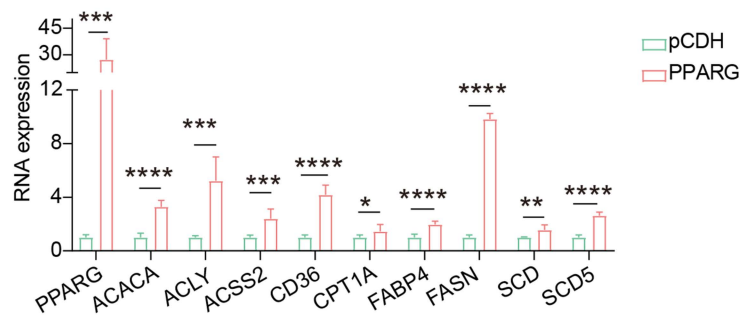
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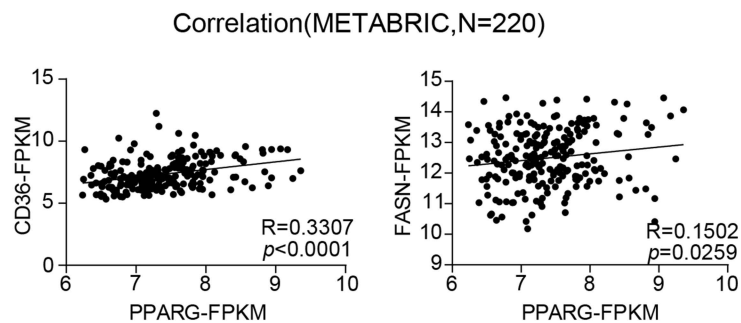
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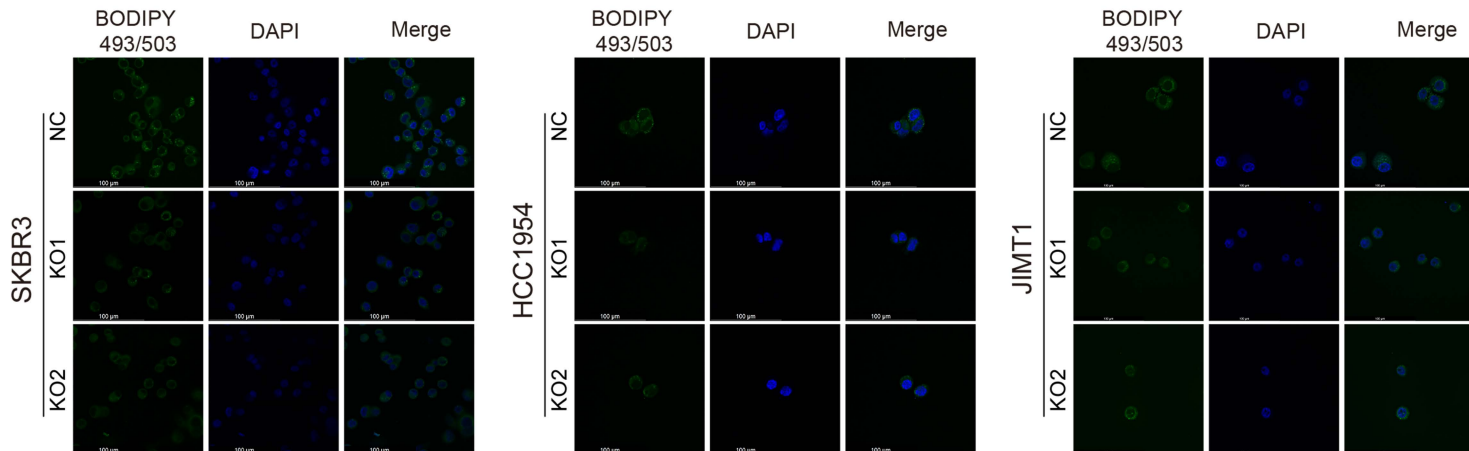
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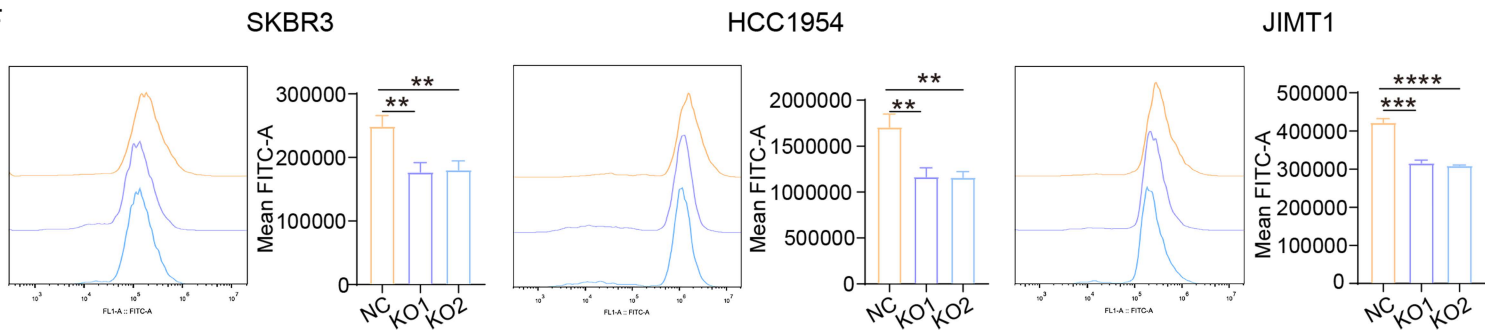
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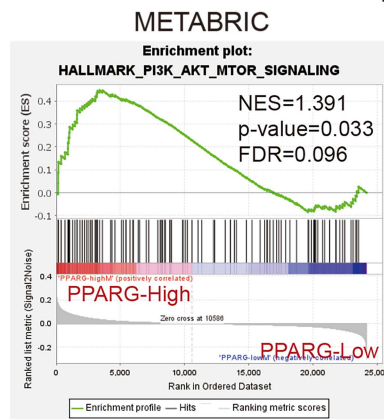
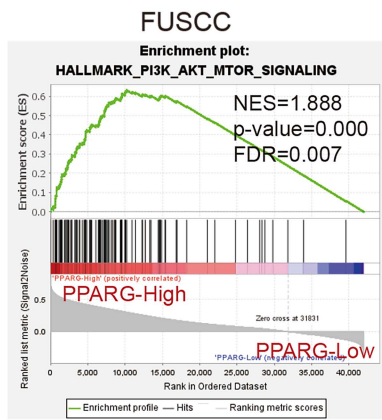


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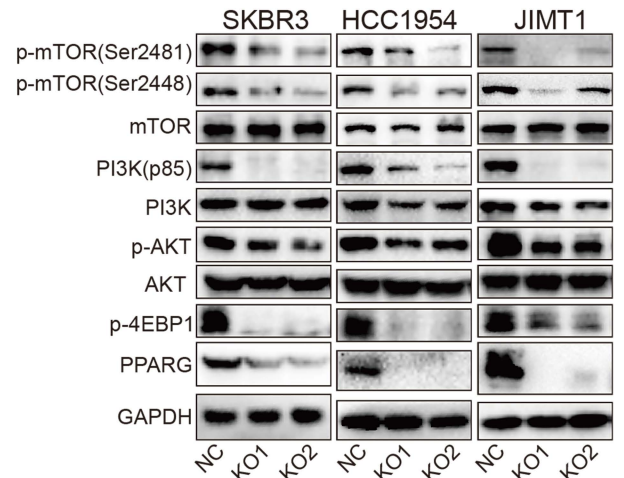


Supplementary Figure 3: (A) GSEA enrichment analysis of the fatty acid metabolism pathway with high and low expression of PPARG from FUSCC and METABRIC database; (B) Western blot of FASN and CD36 in SKBR3, HCC1954, JIMT1 cells with PPARG knockout compared to NC groups; (C) Expression levels of PPARG, ACACA, ACLY, ACSS2, CD36, CPT1A, FABP4, FASN, SCD and SCD5 in PPARG-overexpressing and pCDH group in mice with tumor formation in situ; (D) Correlation analysis between PPARG and CD36, FASN in the METABRIC database; (E) Fatty acid distribution in SKBR3, HCC1954, and JIMT1 cells PPARG knockout compared to NC groups; (F) Fatty acid distribution in SKBR3, HCC1954, and JIMT1 cells PPARG knockout compared to NC groups. ACACA: Acetyl-CoA Carboxylase Alpha; ACSS2: Acyl-CoA Synthetase Short Chain Family Member 2; FABP4: Fatty Acid-Binding Protein 4; SCD5: Stearoyl-CoA Desaturase.

A

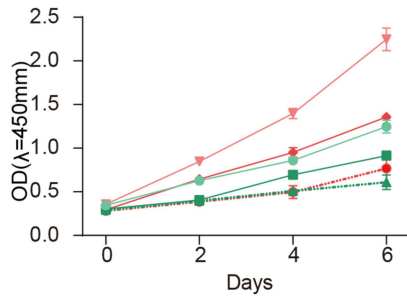


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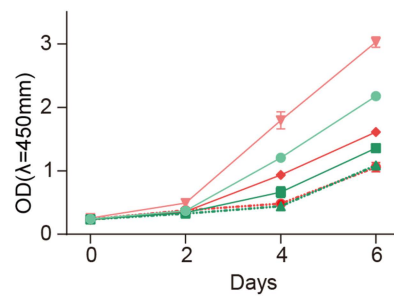


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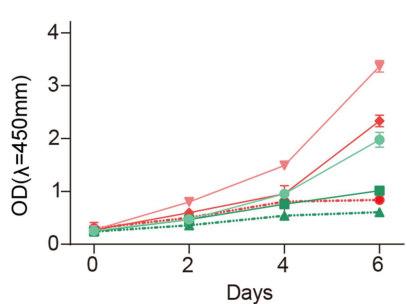
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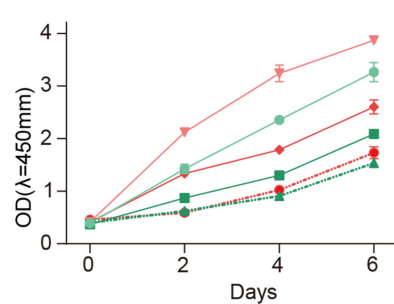
SKBR3



HCC1954

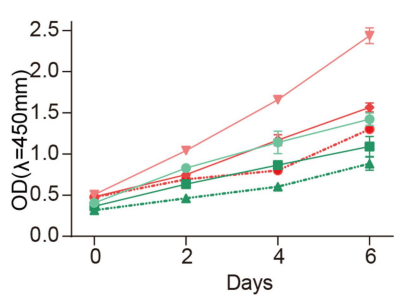


JIMT1

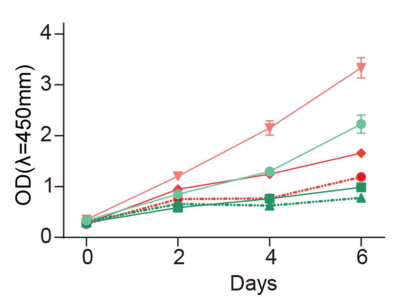


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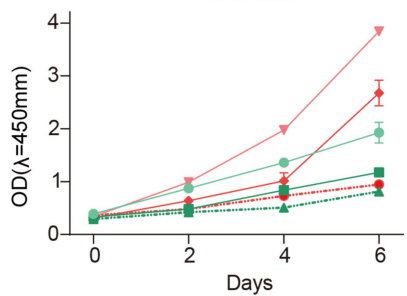
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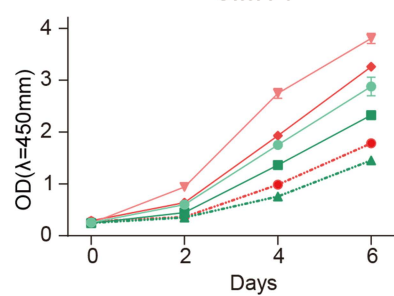
SKBR3



HCC1954

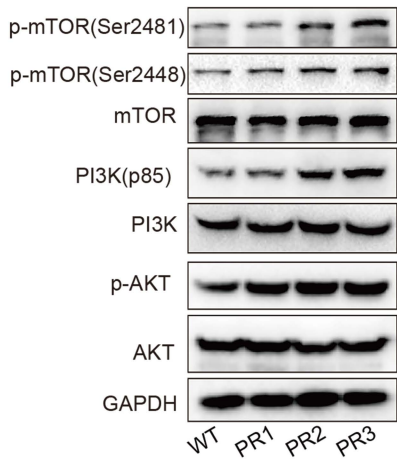


JIMT1



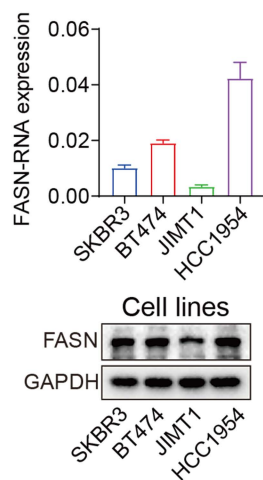
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BT474



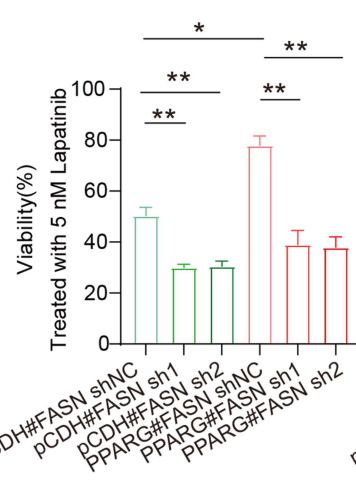
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Cell lines

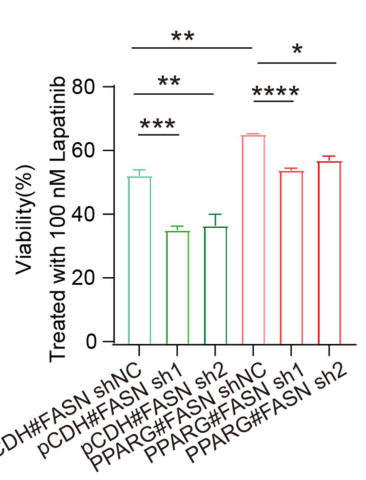


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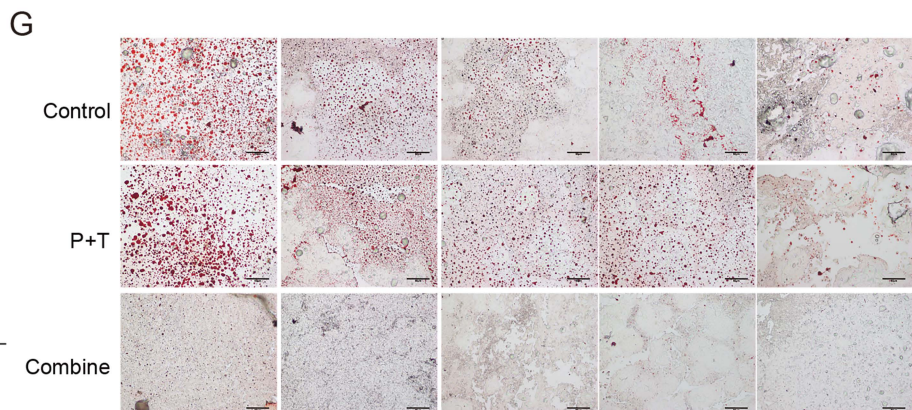
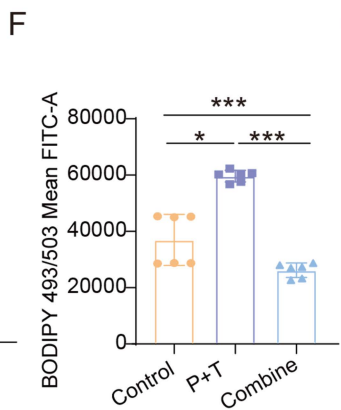
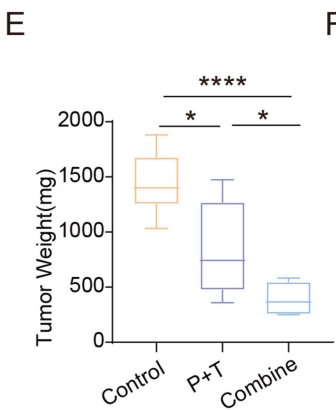
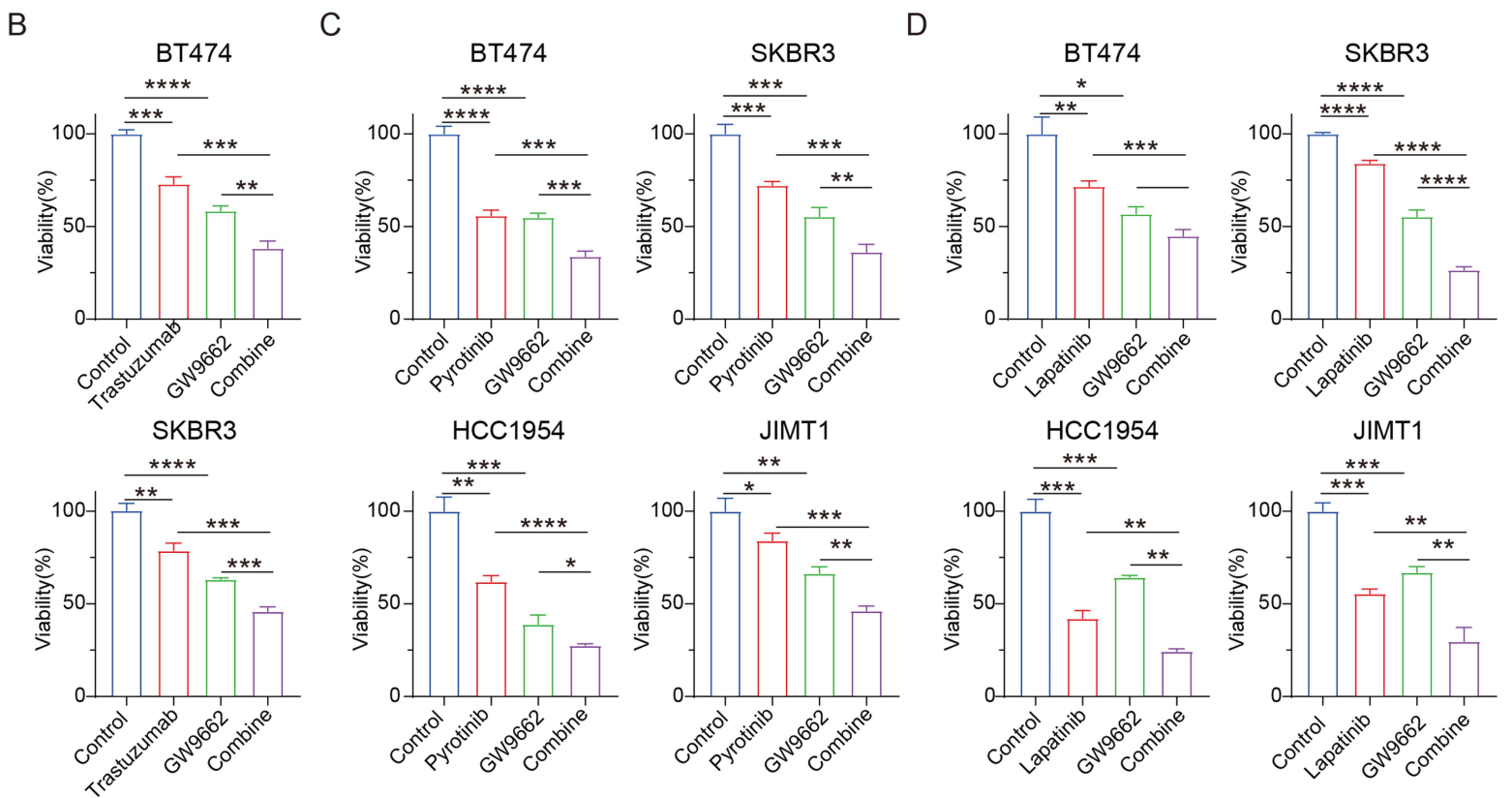
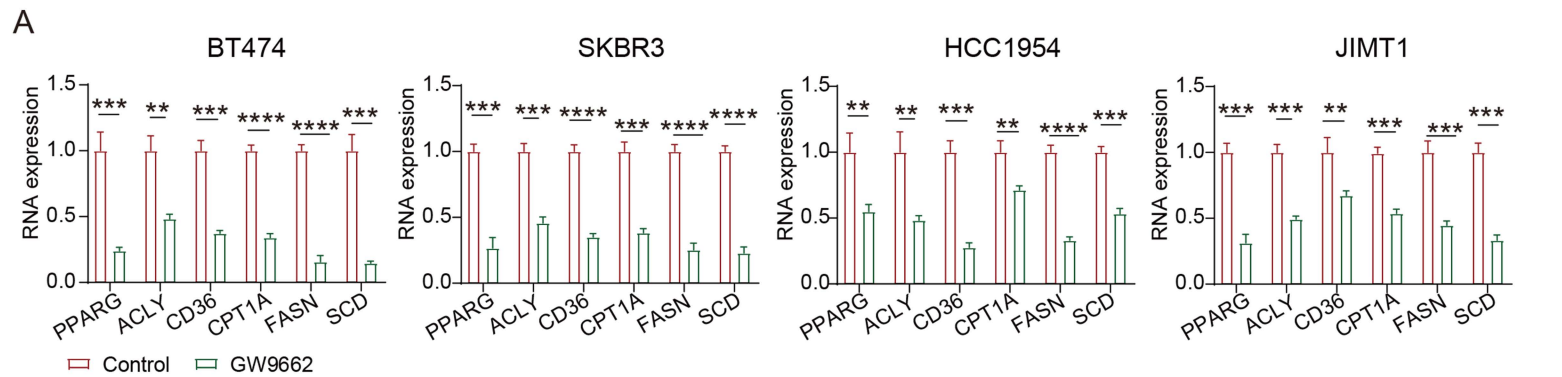
SKBR3



HCC1954



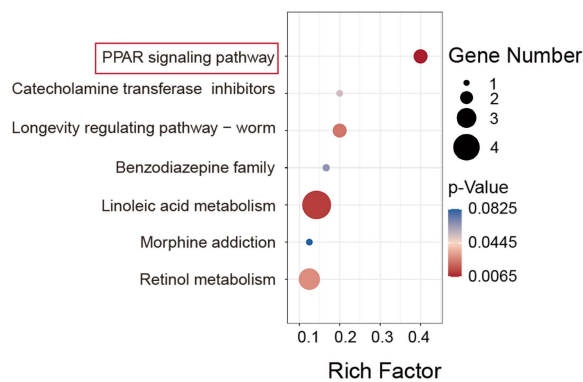
Supplementary Figure 4: (A) GSEA analysis of the PI3K/Akt/mTOR signaling pathway in FUSCC and METABRIC databases (PPARG-high vs PPARG-low); (B) Expression levels of PI3K/Akt/mTOR signaling pathway proteins in SKBR3, HCC1954 and JIMT1 cells with PPARG knockout compared to NC groups; (C) Proliferation curves of BT474, SKBR3, HCC1954 and JIMT1 cells PPARG-overexpressing group and pCDH group treated with or without Pyrotinib/ everolimus; (D) Proliferation curves of BT474, SKBR3, HCC1954 and JIMT1 cells PPARG-overexpressing group and pCDH group treated with or without Lapatinib/ everolimus; (E) Expression levels of PI3K/Akt/mTOR signaling pathway proteins in BT474 WT and PR cells; (F) Expression of FASN at the RNA and protein level in four HER2-positive breast cancer cell lines (SKBR3, BT474, JIMT1, HCC1954 cells); (G) Viability of SKBR3 and HCC1954 cells treated with lapatinib.



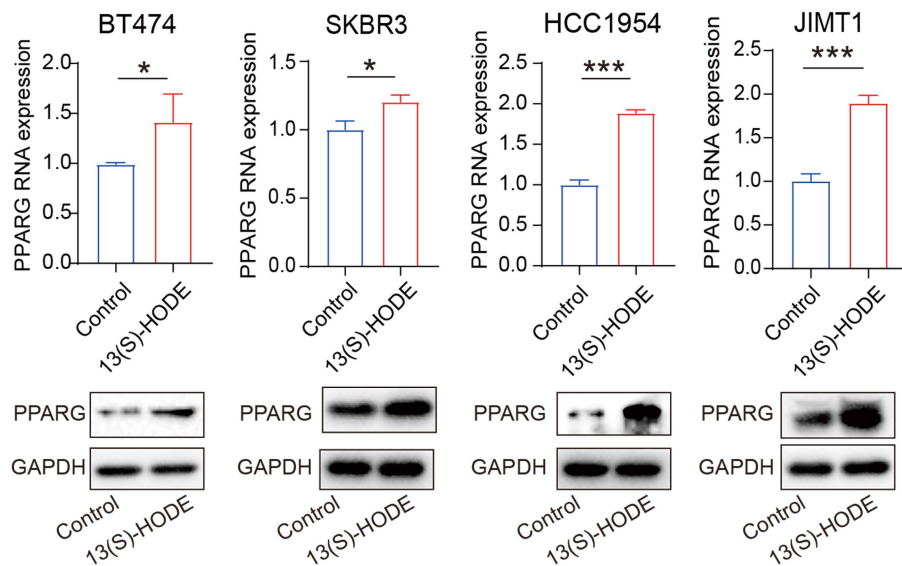
Supplementary Figure 5: (A) GW9662 treatment effects on the expression of PPARG, ACLY, CD36, CPT1A, FASN, and SCD in BT474, SKBR3, HCC1954, and JIMT1 cells; (B) Cell viability when BT474 and SKBR3 cells were treated with GW9662 and trastuzumab alone or in combination; (C) Cell viability when BT474, SKBR3, HCC1954, JIMT1 cells were treated with GW9662 and pyrotinib alone or in combination; (D) Cell viability when BT474, SKBR3, HCC1954, JIMT1 cells were treated with GW9662 and lapatinib alone or in combination; (E) Mass box diagram of in situ tumors in Control, P+T, and Combine groups; (F) Lipid fluorescence values of in situ tumors in Control, P+T, and Combine groups; (G) Oil Red staining images of in situ tumors in Control, P+T, and Combine group mice.

A

KEGG Enrichment Scatter Plot

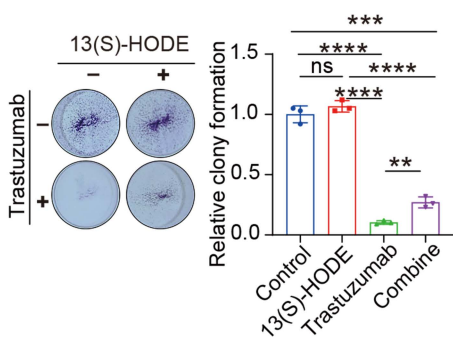


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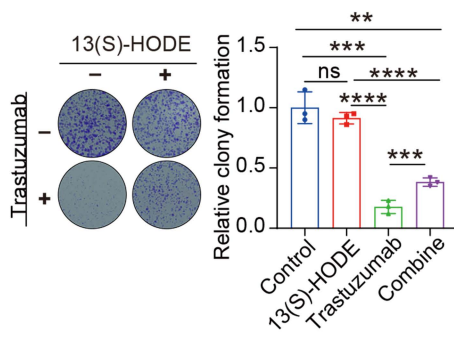


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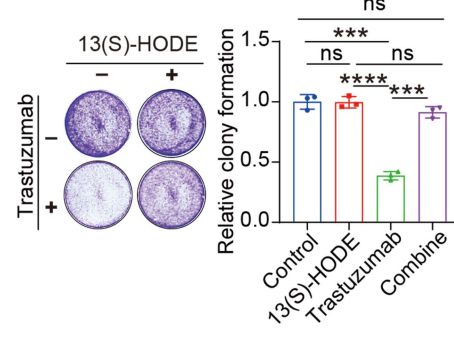
BT474



SKBR3

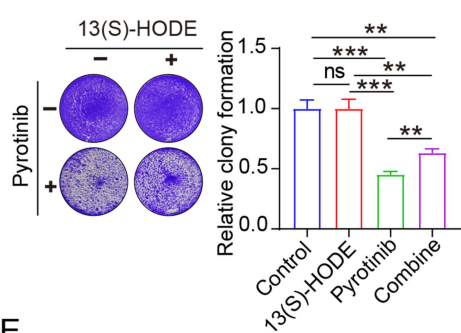


HCC1954

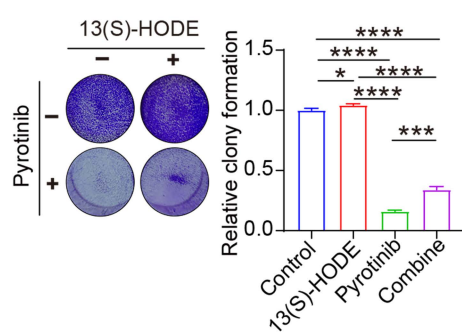


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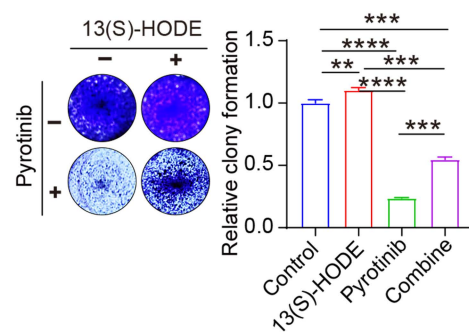
SKBR3



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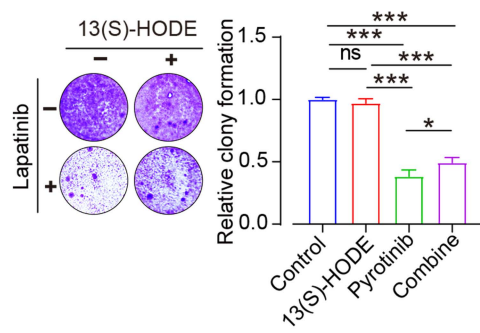


JIMT1

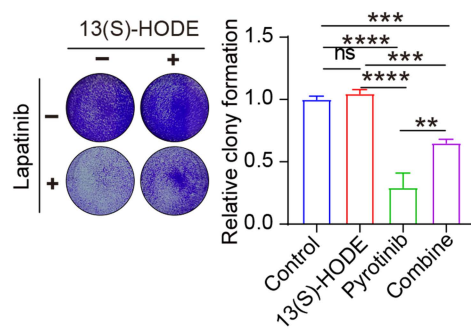


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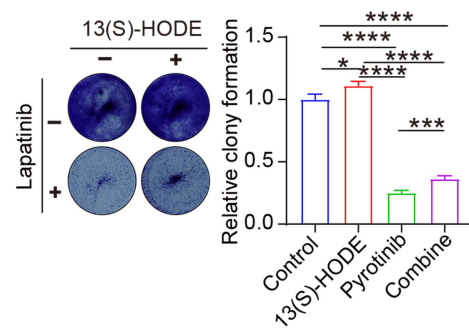
SKBR3



HCC1954



JIMT1



Supplementary Figure 6: (A) Enrichment of the PPAR signaling pathway in the non-pCR group; (B) RNA and protein expression of PPARG after treatment with 13(S)-HODE in BT474, SKBR3, HCC1954, JIMT1 cells; (C) Plate clone formation of BT474, SKBR3, and HCC1954 cells with or without 13(S)-HODE and trastuzumab treatment; (D) Plate clone formation of SKBR3, HCC1954 and JIMT1 cells with or without 13(S)-HODE and pyrotinib treatment; (E) Plate clone formation of SKBR3, HCC1954 and JIMT1 cells with or without 13(S)-HODE and lapatinib treatment.