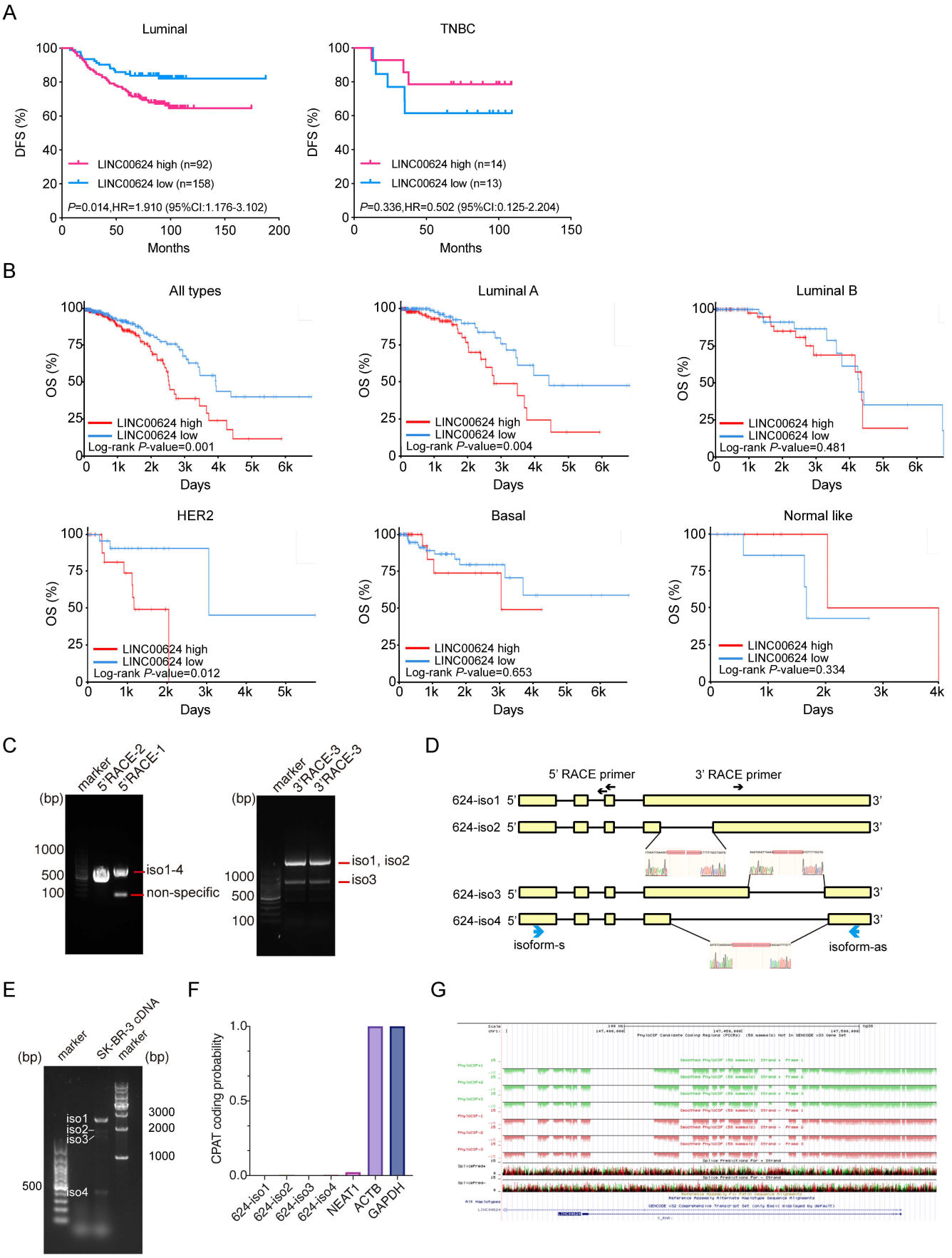
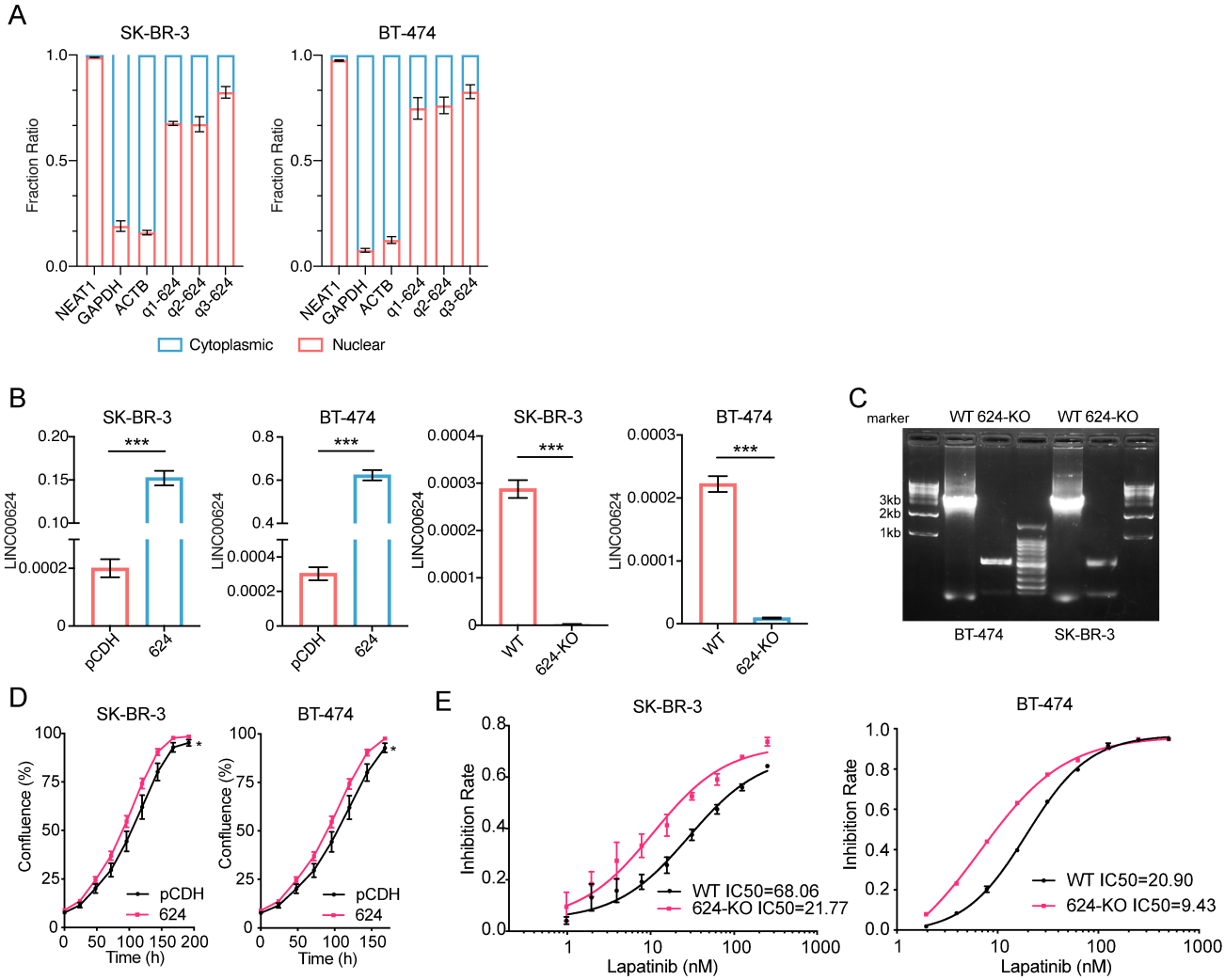
Supplementary Fig. 1



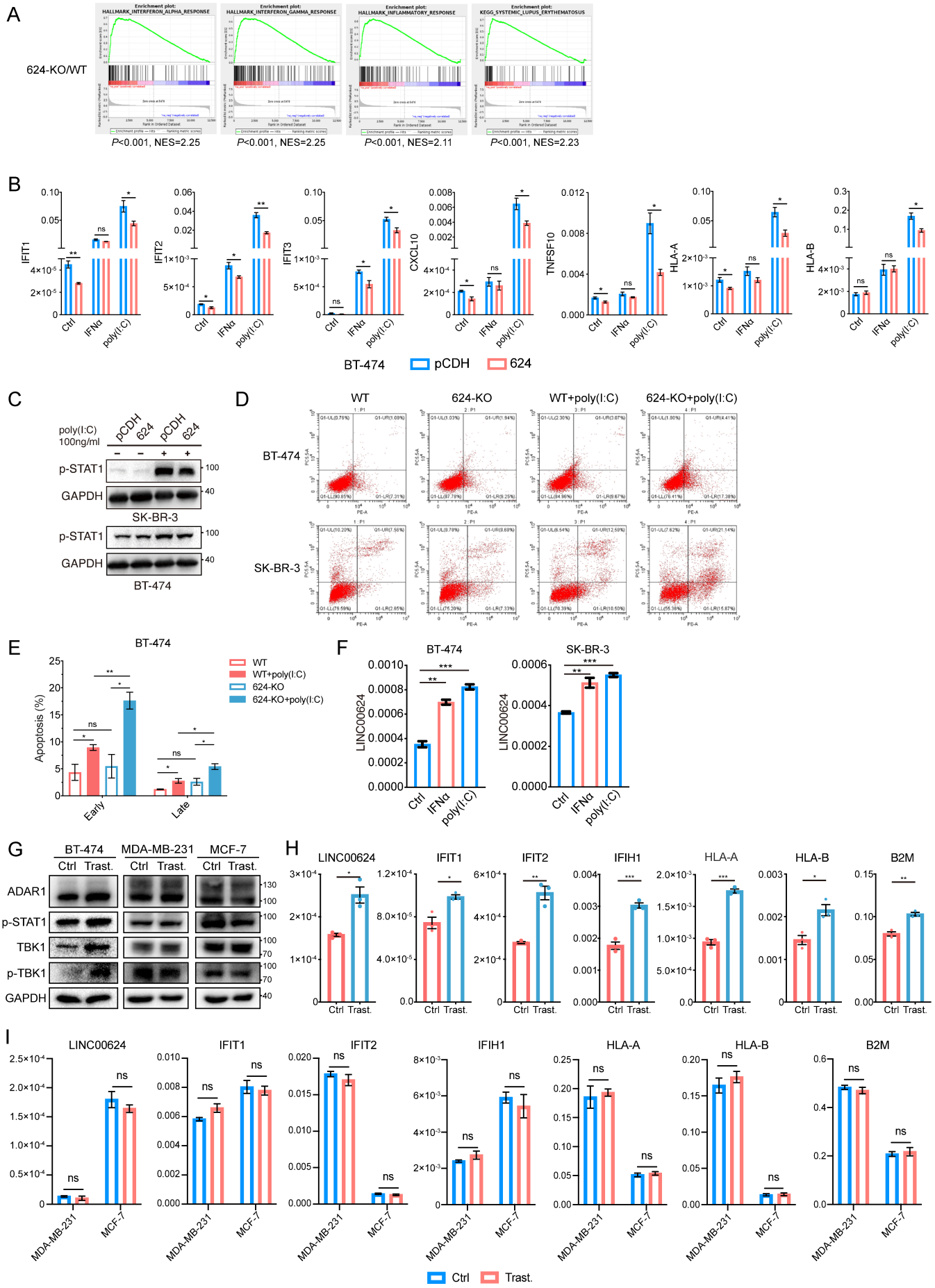
Supplementary Fig. 1 LINC00624 promotes treatment resistance in HER2+ BC. A, Disease-free survival plot (DFS) of patients in a consecutive cohort receiving adjuvant treatment. Patients were divided into high and low LINC00624 groups. Statistical analysis was performed using two-sided log-rank tests. HR, hazardous ratio. TNBC, triple negative breast cancer. CI: confidential interval. HR: hazardous ratio. **B**, TCGA-BRCA expression data were used for survival analysis. Overall survival (OS) was shown as indicated. **C-D**, RACE-PCR was performed. (**C**) Representative image of RACE-PCR electrophoresis. isoform 1-4 were verified. (**D**) Schematic view of LINC00624 isoforms and sanger sequencing at the junctions of exon 4. **E**, The abundance of LINC00624 isoforms were analyzed by PCR with SK-BR-3 cDNA. Normalized to GAPDH. Representative image was shown. **F**, CPAT coding probability of LINC00624 isoforms were shown. NEAT1, ACTB, and GAPDH were used as positive or negative control. **G**, PhyloCSF coding score were demonstrated at the LINC00624 region from UCSC genome browser. For **C-E**, the experiments were performed twice with similar results.

Supplementary Fig. 2



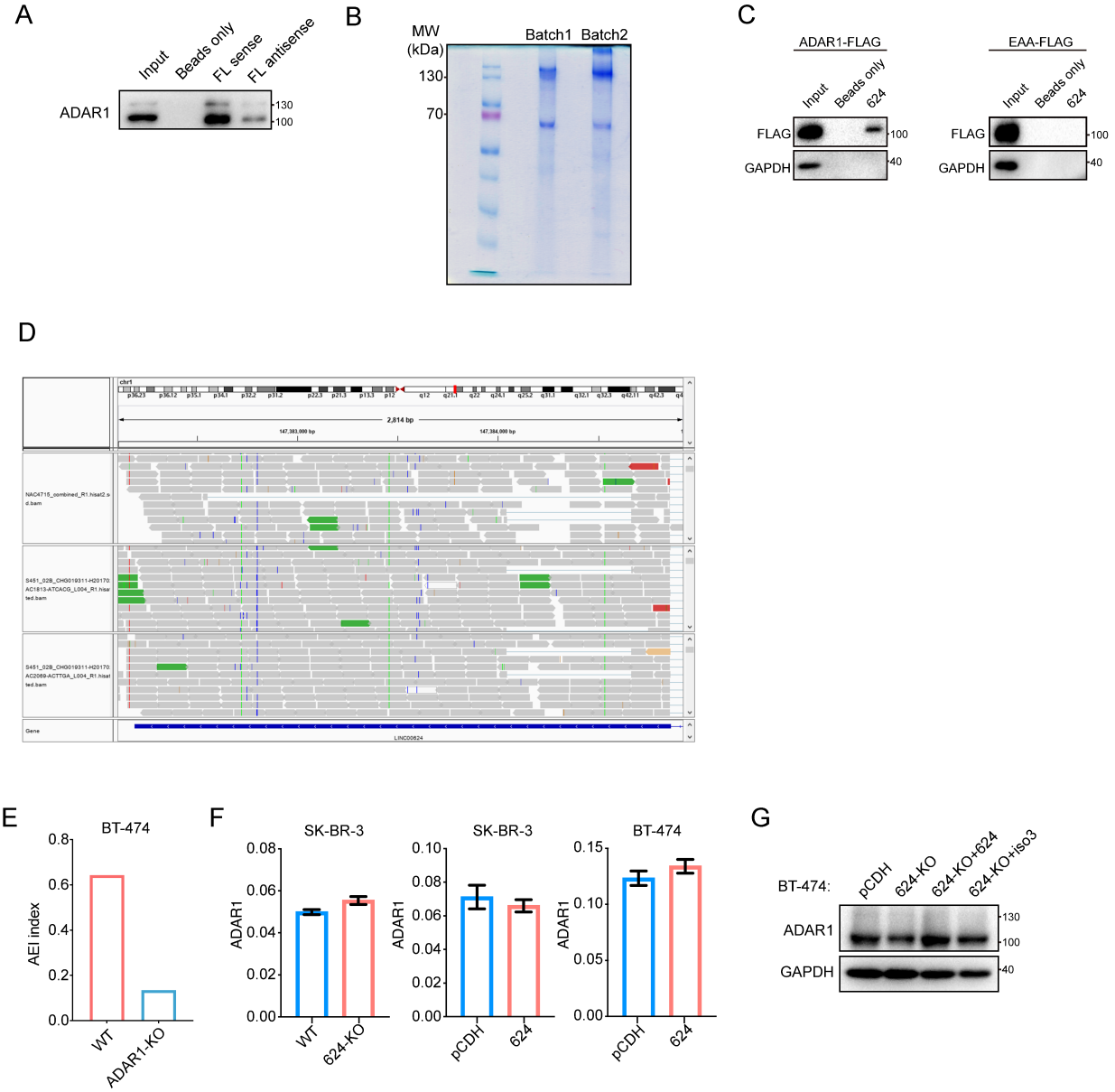
Supplementary Fig. 2 LINC00624 promotes treatment resistance in HER2+ BC. A LINC00624 mainly located in the cell nucleus of SK-BR-3 and BT-474. Cytoplasmic and nuclear fractions were extracted from SK-BR-3 and BT-474 cells. LINC00624, GAPDH and NEAT1 expression was analyzed by RT-qPCR. n=3 biological replicates. **B**, The overexpressed and KO strains of LINC00624 in SK-BR-3 and BT-474 was constructed and verified by RT-qPCR. n=3 biological replicates. **C**, LINC00624-KO strains were verified by PCR with genome DNA. Representative images were shown. The experiment was performed twice with similar results. **D**, Cell proliferation assay of pCDH and LINC00624 cells in SK-BR-3 and BT-474 cells. n=6 for each time point. Statistical analysis was performed using two-sided t-test at the end point. The experiments were performed twice with similar results. **E**, Inhibition rate of WT and LINC00624-KO SK-BR-3 and BT-474 cells in response to lapatinib. n=3 biological replicates. The experiments were performed twice with similar results. * $P<0.05$, ** $P<0.01$, *** $P<0.001$. Data are shown as mean ± s.e.m.

Supplementary Fig. 3



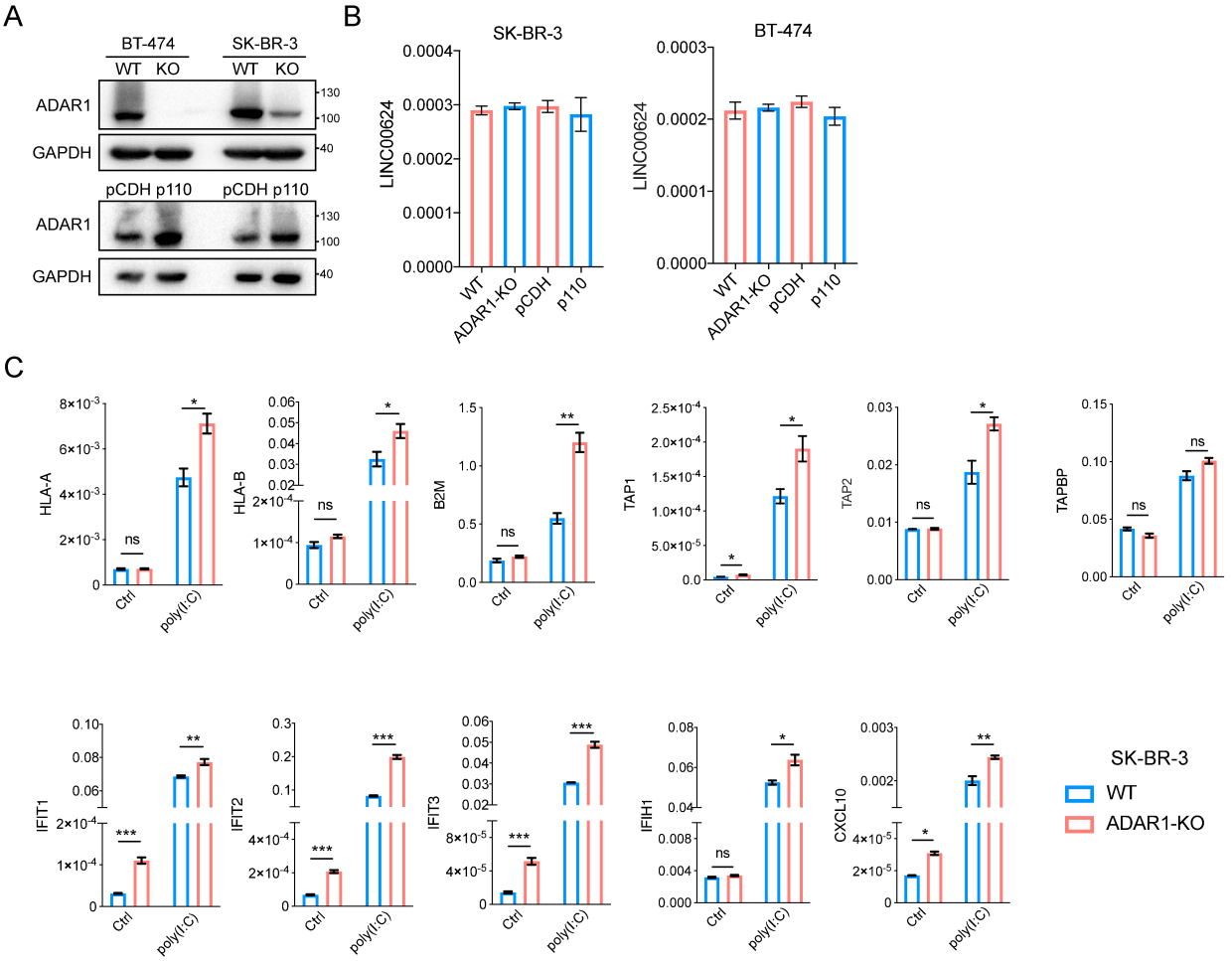
Supplementary Fig. 3 LINC00624 inhibits the innate immune response by inhibiting type I IFN signaling. A, GSEA analysis showed the indicated gene signatures comparing different LINC00624 expression SK-BR-3 cells. NES, normalized enrichment score. **B**, pCDH or LINC00624 BT-474 cells were treated with 5 ng/ml IFNα for 4 h or transfected poly(I:C) for 24h. RNA levels of ISGs and antigen presentation related genes were analyzed by RT-qPCR, normalized to GAPDH. **C**, pCDH or LINC00624 cells were treated with transfected poly(I:C) for 24h with indicated concentration. The levels of the indicated proteins were determined by immunoblot. **D**-**E**, Apoptosis of WT and LINC00624 BT-474 cells and SK-BR-3 cells were determined by flow cytometry with or without transfected poly(I:C). (**D**) Representative images of flow cytometry were shown. (**E**) The percentage of early and late apoptosis were determined after 1 μg/ml transfected poly(I:C) in BT-474 WT and LINC00624 KO cells. n=3 biological replicates. Statistical analysis was performed using two-sided t-test. **F**, RNA expression of LINC00624 in SK-BR-3 and BT-474 cells with the treatment of 5 ng/ml IFNα or 1 μg/ml poly(I:C) for 24h were analyzed by RT-qPCR, normalized to GAPDH. **G-I**, BT-474, MCF7 and MDA-MB-231 cells were treated with 20 μg/ml trastuzumab for 3 days. (**G**) The levels of the indicated proteins were determined by immunoblot. The experiment was performed twice with similar results. (**H**) RNA levels of LINC00624, ISGs and antigen presentation related genes were analyzed by RT-qPCR in BT474, (**I**) MDA-MB-231 and MCF-7 cells, normalized to GAPDH. For **B**, **E**-**F**, and **H-I**, n=3 biological replicates. Statistical analysis was performed using two-sided t-test. For **C**-**E** and **G**, the experiment was performed twice with similar results. * $P<0.05$, ** $P<0.01$, *** $P<0.001$. ns, no significance. Data are shown as mean ± s.e.m.

Supplementary Fig. 4



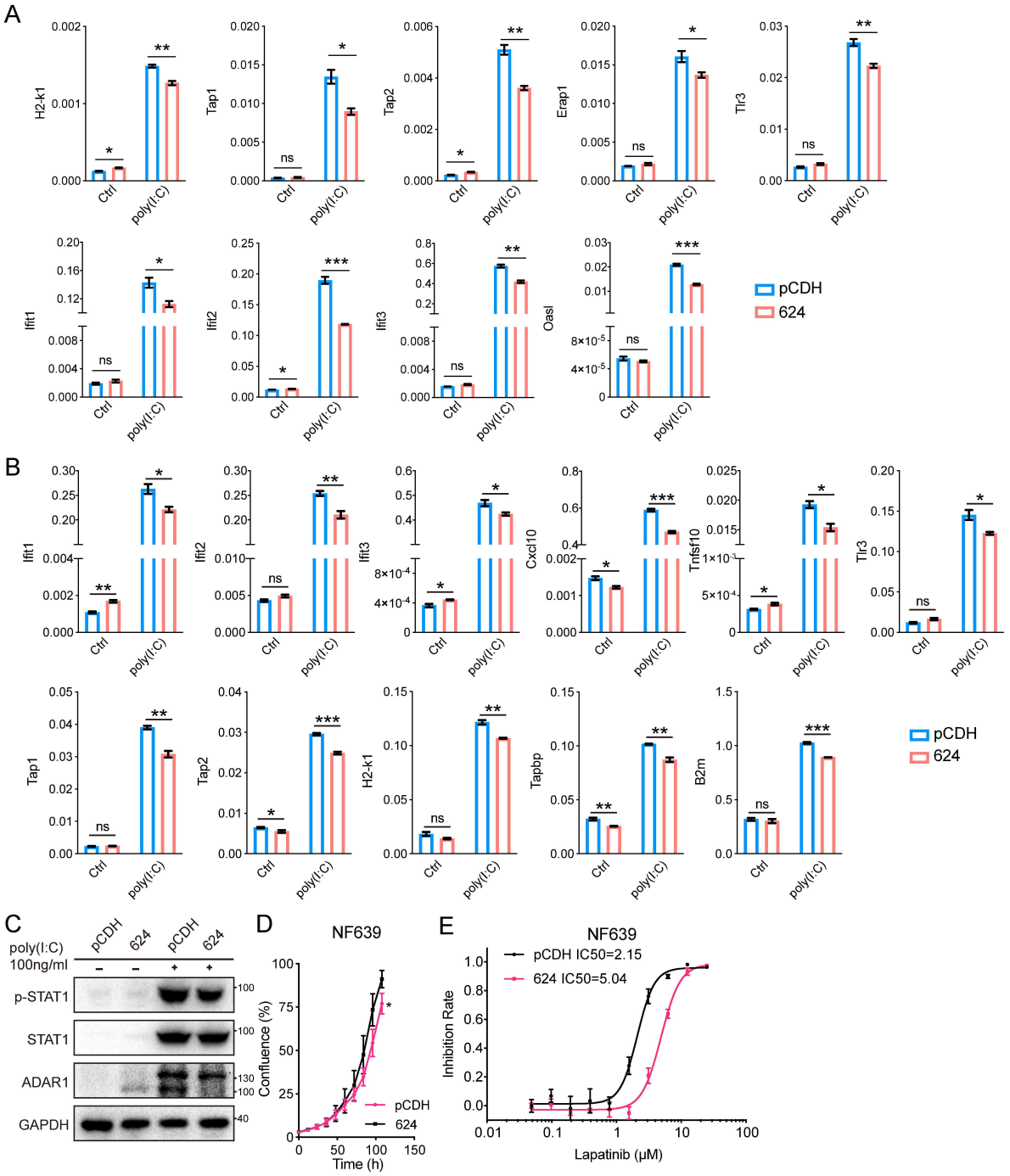
Supplementary Fig. 4 LINC00624 is bound to and edited by ADAR1. **A**, Biotin-labeled LINC00624 sense and antisense full-length (FL) RNA were incubated with SK-BR-3 whole cell lysates. ADAR1 was pull-down and verified by immunoblot. The experiment was performed twice with similar results. **B**, Recombinant ADAR1-p150 was purified and verified by SDS-PAGE and Coomassie blue staining. The Batch 1 and Batch 2 were two experiments. Batch 2 protein were used for subsequent experiments. **C**, ADAR1-FLAG or ADAR1-FLAG with EAA mutation was overexpressed in 293T cells. Cell lysates and biotin-labeled LINC00624 were used for RNA pull-down. immunoblot of FLAG and GAPDH antibodies were shown. **D**, RNA-seq results of HER2+BC core needle biopsy before neoadjuvant treatment was shown. The exon 4 of LINC00624 was illustrated. The blue dashes represent mutations where adenosines were changed to guanines. Representative images of RNA-seq results were shown. **E**, AEI score of WT or ADAR1-KO BT-474 cells were shown. **F**, The RNA expression of ADAR1 was determined by RT-qPCR in LINC00624 overexpression or KO cells, normalized to GAPDH. n=3 biological replicates. Statistical analysis was performed using two-sided t-test. There was no statistical significance found. **G**, Recovery assay of LINC00624 WT and isoform3 (iso3) in LINC00624-KO cells. The levels of the indicated proteins were determined by immunoblot. For **A**-**C,** and **F-G,** the experiment was performed twice with similar results. Data are shown as mean ± s.e.m.

Supplementary Fig. 5



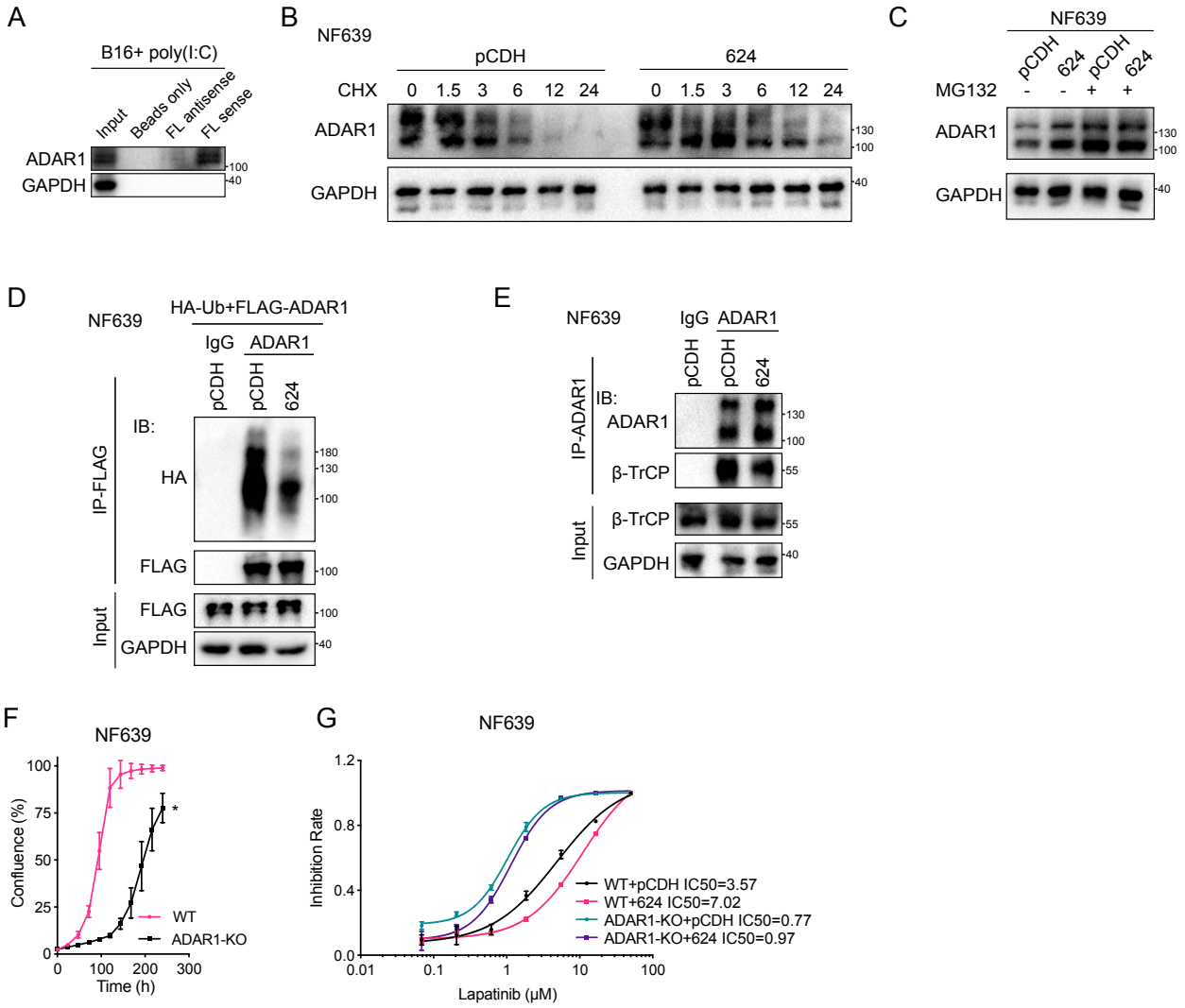
Supplementary Fig. 5 LINC00624 inhibits the immune response and promotes treatment resistance through ADAR1. A, ADAR1-KO or p110 overexpression in SK-BR-3 and BT-474 cells were verified by immunoblot. The experiment was performed twice with similar results. **B**, RNA levels of LINC00624 with ADAR1 KO or overexpression were analyzed by RT-qPCR**.** Normalized to GAPDH. **C**, RNA levels of ISGs and antigen presentation related genes were analyzed by RT-qPCR in WT and ADAR1 KO SK-BR-3 cells, normalized to GAPDH. Cells were transfected with mock or 100 ng/ml poly(I:C) for 24h before RNA extraction. For **B**-**C**, statistical analyses were performed using two-sided t-test. n=3 biological replicates. * $P<0.05$, ** $P<0.01$, *** $P<0.001$. ns, no significance. Data are shown as mean ± s.e.m.

Supplementary Fig. 6



Supplementary Fig. 6 LINC00624 inhibits tumor immunity and immunotherapy response *in vivo*. A-C, pCDH or LINC00624 were treated with transfected poly(I:C) for 24h. RNA levels of ISGs and antigen presentation related genes were analyzed by RT-qPCR in B16-OVA (**A**) and NF639 cells (**B**). Normalized to mouse GAPDH. n=3 biological replicates. (**C**) The levels of the indicated proteins were determined by immunoblot. **D**, Cell proliferation assay of pCDH and LINC00624 cells in NF639. n=6 for each time point. Statistical analysis was performed using two-sided t-test at the end point. **E**, Inhibition rate of pCDH and LINC00624 NF639 cells in response to lapatinib. For **C**-**E**, the experiments were performed twice with similar results. For **A**-**B**, statistical analyses were performed using two-sided t-test. * $P<0.05$, ** $P<0.01$, *** $P<0.001$. ns, no significance. Data are shown as mean ± s.e.m.

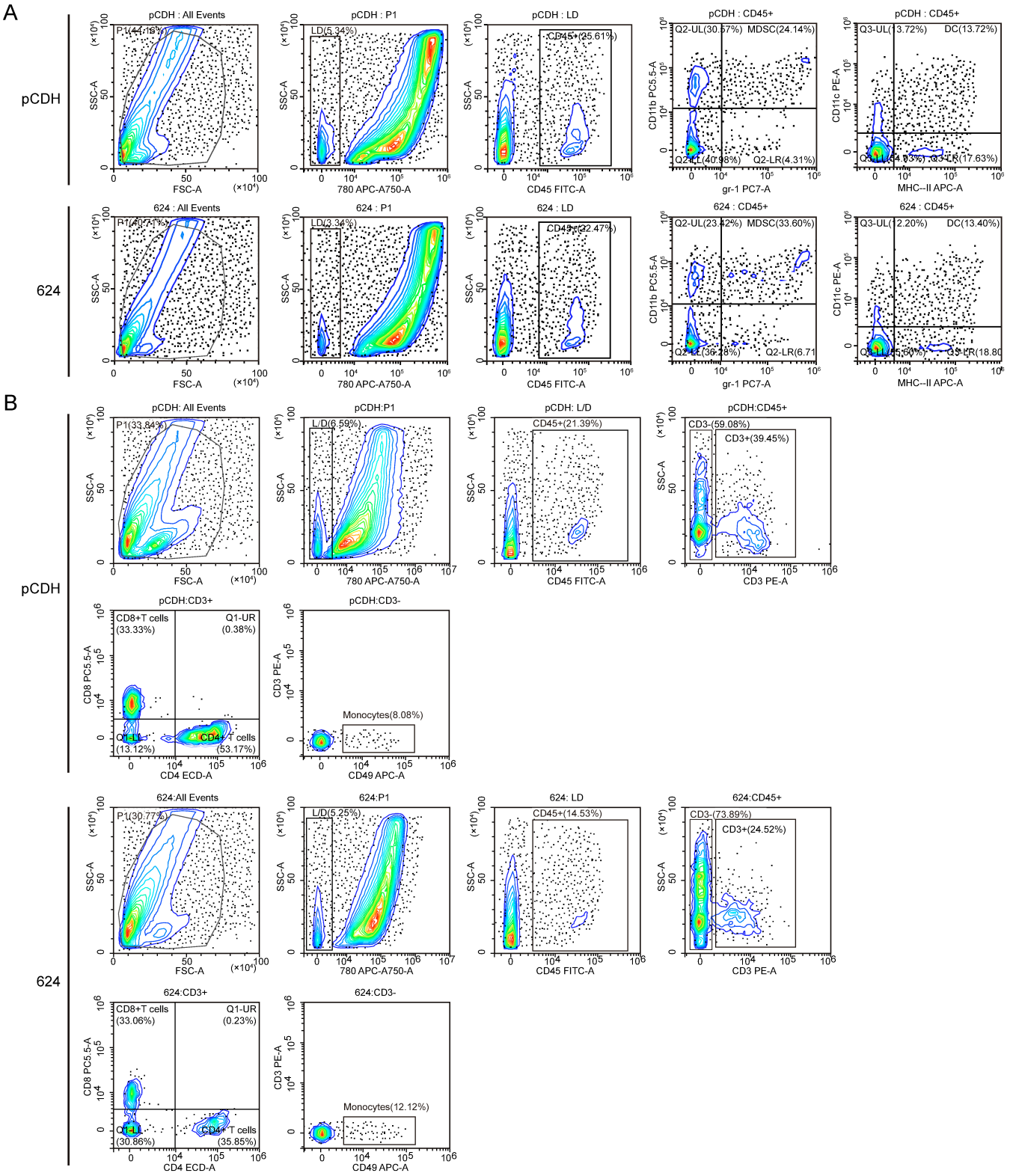
Supplementary Fig. 7



Supplementary Fig. 7

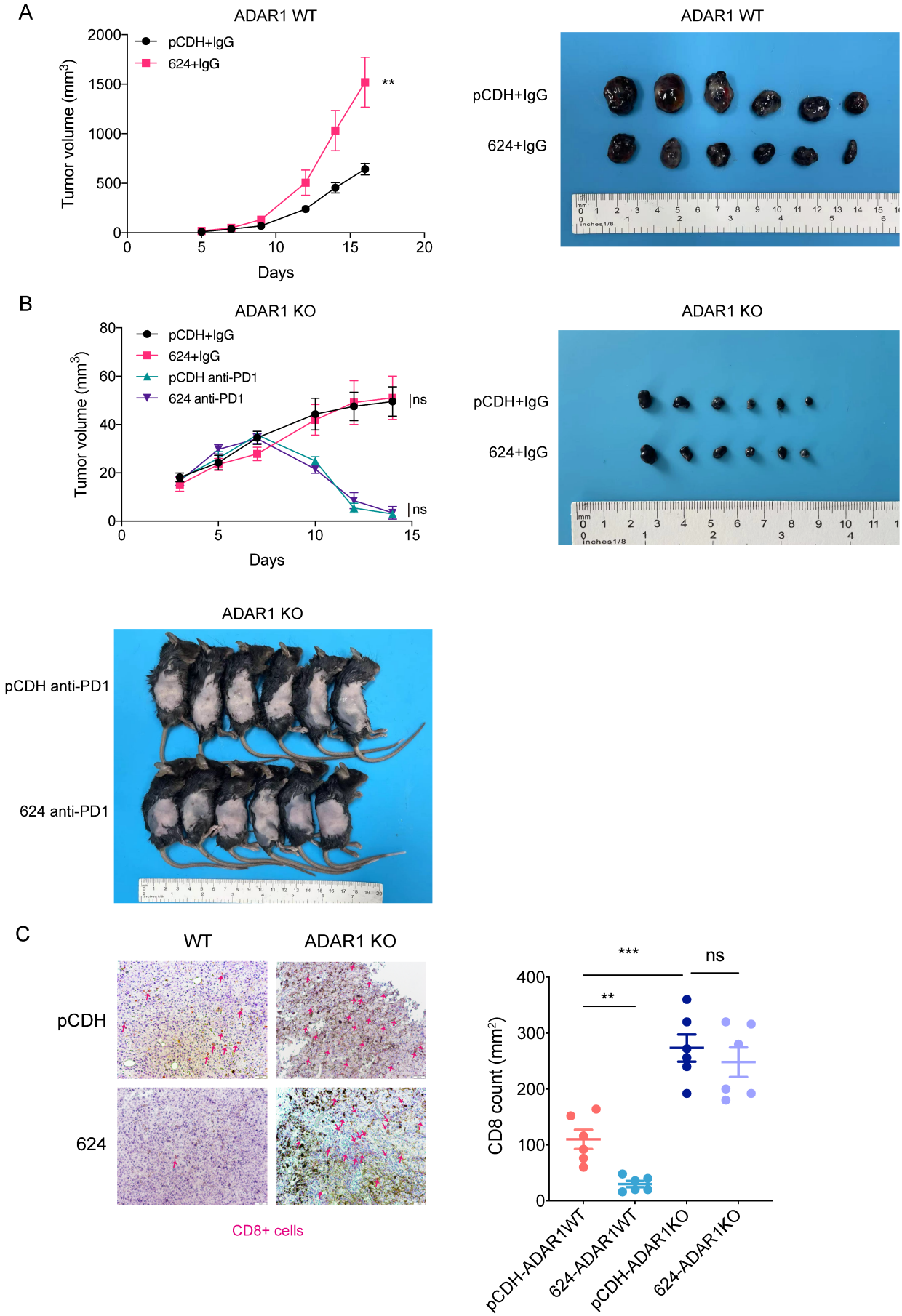
A, B16 cells were transfected with 1 μg/ml poly(I:C) for 24h. Cells were lysed and incubated with biotin-labeled in vitro transcribed RNAs. LINC00624 full-length (FL) sense or antisense RNAs were used. Beads only serving as blank control. Immunoblot of ADAR and GAPDH were shown as indicated. **B**, Expression kinetics of endogenous mouse ADAR1 in NF639 pCDH and LINC00624 overexpression cells. Cells were treated with CHX and collected at the time points as indicated. **C**, NF639 pCDH or LINC00624 cells were treated with MG132 as indicated. The expression of mouse ADAR1 was determined. **D**, pCDH and LINC00624 overexpression NF639 cells were transfected with HA-Ub and mouse ADAR1-p110-FLAG. Cells were treated with MG132 before collection. ADAR1 were immunoprecipitated (IP) with anti-FLAG antibody. IgG isotype control antibody was used. Immunoblot of the HA, FLAG and GAPDH was shown as indicated. **E**, NF639 cells with pCDH control or LINC00624 overexpression were immunoprecipitated (IP) with anti-ADAR1 (Santa Cruz) or IgG isotype control. Mouse ADAR1 and β-TrCP were detected by immunoblot (IB). **F**, Cell proliferation assay of WT and ADAR1-KO cells in NF639. n=6 for each time point. Statistical analysis was performed using two-sided t-test at the end point. **G**, Inhibition rate of WT or ADAR1 KO cells with pCDH or LINC00624 in response to lapatinib. For **A**-**G**, the experiments were performed twice with similar results.

Supplementary Fig. 8



Supplementary Fig. 8 Flow cytometry gating strategies and representative plots. A, Gating strategy and representative flow cytometry plots for the assessment of DCs and MDSCs in pCDH and LINC00624 B16-OVA tumors. **B**, Gating strategy and representative flow cytometry plots for the assessment of CD4+ T cells, CD8+ T cells and CD49f+ cells in pCDH and LINC00624 B16-OVA tumors.

Supplementary Fig. 9



Supplementary Fig. 9 LINC00624 is ADAR1-dependent in suppressing immune responses and promoting treatment resistance *in vivo*. A, Tumor growth curve (left) and tumor size (right) of B16-OVA pCDH or LINC00624 cells with wild-type ADAR1 in C57/B6J. Mice were not vaccinated. Mice were treated with IgG isotype control with 100ug/mice on day 3, 5, 7, 10. n = 6 animals in each group. **B**, Tumor growth curve and tumor size of B16-OVA pCDH or LINC00624 cells with ADAR1-KO in C57/B6J. Mice were not vaccinated. Mice were treated with anti-PD-1 or IgG isotype control as indicated with 100ug/mice on day 3, 5, 7, 10. n = 6 animals in each group. Upper right, representative image of tumor size in IgG control group. Lower left, tumors were regressed in anti-PD-1 groups. **C**, Tumor infiltrated CD8+ cells from pCDH/ADAR1-WT, pCDH/ADAR1-KO, 624/ADAR1-WT, 624 ADAR1-KO tumors with IgG treatment were determined by immunohistochemistry. AEC staining (red) was used in this assay. Left, representative images. Right, statistical analysis (n = 6 tumors each group). Statistical analyses were performed using two-sided t-test. For **A**-**B**, statistical analysis was performed using two-sided t-test for the tumor volume at the end point.

Table S1 Baseline clinicopathological characteristics of patients according to LINC00624 expression

Characteristics		Low expression	High expression	*P* value
Age at diagnosis	<40	9	10	0.565
	≥40	122	178	
BMI at diagnosis	<18.5	5	3	0.352
	18.5-24	85	117	
	>24	40	66	
Subtype	ER+/PR+	73	137	**0.005****
	HER2 positive	29	18	
	TNBC	19	21	
ER	Negative	54	38	**0.000****
	Positive	76	150	
PR	Negative	41	38	**0.007****
	Positive	77	148	
HER2	Negative	76	130	**0.041***
	Positive	46	46	
Ki-67	Low	50	67	0.389
	High	41	42	
Tumor grade	I & II	71	119	0.151
	III	52	62	
pT	pT1	52	68	0.714
	pT2	74	112	
	pT3	4	8	
pN	pN0	58	75	0.898
	pN1	37	56	
	pN2	16	26	
	pN3	20	30	
LVI	Negative	63	108	0.106
	Positive	65	76	

Abbreviations: BR: Breast Cancer; HR: hazard ratio; CI: confidence interval; BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; LVI: lymphovascular invasion. Fisher exact test was used. Statistically significant (*P<0.05 and **P<0.01).

Table S2 Univariate COX regression analyses of DFS in BC patients

Characteristics		No of Patients	No of Events	*P* value	HR (95%CI)
Age at diagnosis	<40	19	6		
	≥40	300	84	0.888	0.942 (0.412-2.157)
BMI at diagnosis	<18.5	8	3		
	18.5-24	202	56	0.519	0.682 (0.214-2.179)
	>24	106	30	0.594	0.724 (0.221-2.373)
Subtype	ER+/PR+	250	67		
	HER2 positive	92	11	0.748	0.901 (0.476-1.705)
	TNBC	27	10	0.437	1.302 (0.67-2.531)
ER	Negative	92	25		
	Positive	226	64	0.842	1.049 (0.656-1.677)
PR	Negative	79	23		
	Positive	225	67	0.842	1.049 (0.656-1.677)
HER2	Negative	206	50		
	Positive	92	28	0.217	1.339 (0.842-2.131)
Ki-67	<14%	117	31		
	≥14%	83	29	0.135	1.472 (0.887-2.443)
Tumor grade	I & II	190	47		
	III	114	36	0.139	1.388 (0.899-2.144)
pT	pT1	120	29		
	pT2	186	57	0.18	1.357 (0.868-2.123)
	pT3	12	4	0.406	1.558 (0.548-4.432)
pN	pN0	133	21		
	pN1	93	28	**0.013***	2.053 (1.166-3.615)
	pN2	42	14	**0.015***	2.321 (1.18-4.566)
	pN3	50	26	**0.000****	4.355 (2.447-7.75)
LVI	Negative	171	40		
	Positive	141	45	0.079	1.465 (0.957-2.244)
LINC00624	Low	131	28		
	High	188	62	**0.037***	1.602 (1.025-2.503)

Abbreviations: BR: Breast Cancer; HR: hazard ratio; CI: confidence interval;BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; LVI: lymphovascular invasion. Statistically significant (*P<0.05 and **P<0.01).

Table S3 MS result of LINC00624 RNA pull down

gene name	protein score	MW	Cover (%)
NONO	2570	54311	56.3
PTBP1	2158	57357	60.6
PTBP3	1630	59937	50.9
ALB	1574	71317	53.2
TUBA1B	455	50804	34.6
TUBA1C	439	50548	34.7
HNRNPL	433	64720	34.6
FUBP3	415	61944	27.6
MCCC2	376	61808	33.6
ADAR	372	137178	15.6
STAU1	288	63428	22.9
SFPQ	267	76216	11.2
CPNE3	246	60947	19.7
HNRNPM	242	77749	15.1
PTBP2	240	57569	6.2
MCCC1	236	80935	13.2
ILF3	221	95678	8.5
CCT2	206	57794	22.6
DDX5	192	69618	14.8
SERBP1	189	44995	13.5
YBX3	183	40066	25.8
CCT4	172	58401	23.6
HNRNPU	171	91269	6.3
HRNR	168	283140	0.8
EIF2AK2	167	62512	10.7
ACTC1	163	42334	26.5
ACTA1	163	42366	26.5
STAU2	161	62829	17.7
G6PD	154	59675	14
HIST2H2BF	140	13912	24.6

Abbreviations: MS: mass spectrometry; MW: molecular weight;

Table S4 Primers and sequences

Primers for RT-qPCR	
LINC00624-F	CCAGGTTTGCCTTCCTGTTGA
LINC00624-R	GATGCTCCTGTGATGTGCCTC
q2-624-F	CTGTGGCGATGAGAGAGAGAGG
q2-624-R	ACCCAGTACAGTGAAGACAAACC
q3-624-F	GAATACCTACCTTGGGCACAGAA
q3-624-R	CACATTGTCTCTCTAGGTTGCCT
h-NEAT1-F	CTTCCTCCCTTTAACTTATCCATTCAC
h-NEAT1-R	CTCTTCCTCCACCATTACCAACAATAC
h-GAPDH-F	AACGGGAAGCTTGTCATCAA
h-GAPDH-R	TGGACTCCACGACGTACTCA
h-ACTB-F	GCCAACCGCGAGAAGATGA
h-ACTB-R	CATCACGATGCCAGTGGTA
h-IFIT1-F	CGCTATAGAATGGAGTGTCCA
h-IFIT1-R	TTTCCTCCACACTTCAGCA
h-IFIT2-F	CTAAAGCACCTCAAAGGGCA
h-IFIT2-R	GCATAGTTTCCCCAGGTGAC
h-IFIT3-F	AGTCTAGTCACTTGGGGAAAC
h-IFIT3-R	ATAAATCTGAGCATCTGAGAGTC
h-CXCL10-F	TGACTCTAAGTGGCATTCAAGGAG
h-CXCL10-R	TTTTTCTAAAGACCTTGGATTAACAGG
h-B2M-F	AGCAGCATCATGGAGGTTTG
h-B2M-R	TCAAACATGGAGACAGCACTCAA
h-TAPBP-F	CCTGGAGGTAGCAGGTCTTTC
h-TAPBP-R	ATCCTTGCAGGTGGACAGGTA
h-TAP1-F	TGCCCCGCATATTCTCCCT
h-TAP1-R	CACCTGCGTTTTCGCTCTTG
h-TAP2-F	AATCCCTCACTATTCTGGTCGT
h-TAP2-R	TCGAGACATGGTGTAGGTGAAG
h-ERAP1-F	AGAGCACTGAAGCATCTCCAA
h-ERAP1-R	AACTGGGATGACGTACTCAGG
h-NLRC5-F	AACGAGACCTTGGACCCTGAA
h-NLRC5-R	GCTGGTGAACCCATCATCATAG
m-H-2K1-k-F	GAGACACAGGTCGCCAAGAAC
m-H-2K1-k-R	CGCTGGTAAGTGTGAGAGCC
m-OASL-F	CAGGAGCTGTACGGCTTCC
m-OASL-R	CCTACCTTGAGTACCTTGAGCAC
m-TLR3-F	GTGAGATACAACGTAGCTGACTG
m-TLR3-R	TCCTGCATCCAAGATAGCAAGT
m-B2M-F	TTCTGGTGCTTGTCTCACTGA
m-B2M-R	CAGTATGTTCGGCTTCCCATTC
m-ACTB-F	GTGACGTTGACATCCGTAAAGA
m-ACTB-R	GCCGGACTCATCGTACTCC
m-TNFSF10-F	GCTTGCAGGTTAAGAGGCAAC
m-TNFSF10-R	GCTTCTCCGAGTGATCCCAG
m-CXCL10-F	CCAAGTGCTGCCGTCATTTTC
m-CXCL10-R	GGCTCGCAGGGATGATTTCAA

m-IFIT1-F	CTGAGATGTCACTTCACATGGAA
m-IFIT1-R	GTGCATCCCCAATGGGTTCT
m-IFIT2-F	AGTACAACGAGTAAGGAGTCACT
m-IFIT2-R	AGGCCAGTATGTTGCACATGG
m-IFIT3-F	GCCGTTACAGGGAAATACTGGA
m-IFIT3-R	TAGGAGTTCAAAGGACTTCGCC
m-Adar-F	TGAGCATAGCAAGTGGAGATACC
m-Adar-R	GCCGCCCTTTGAGAAACTCT
m-Tap1-F	GGACTTGCCTTGTTCCGAGAG
m-Tap1-R	GCTGCCACATAACTGATAGCGA
m-Tap2-F	CTGGCGGACATGGCTTTACTT
m-Tap2-R	CTCCCACTTTTAGCAGTCCCC
m-Tapbp-F	GGCCTGTCTAAGAAACCTGCC
m-Tapbp-R	CCACCTTGAAGTATAGCTTTGGG
m-Erap1-F	TAATGGAGACTCATTCCCTTGGA
m-Erap1-R	AAAGTCAGAGTGCTGAGGTTTG

Primers for RACE

5'624-1	GTAAGCCCCCACTGACTAAGGTAGC
5'624-2	CTTTCATGCATCAGGTGGCAGTGTT
3'624-1	TAATGTCTCTCTTCTCTGGGGTGTC
isoform-F	CTGCTGTGGGAGCTTTGTTCTTTC
isoform-R	TATGCGTGCTGTAACAAGGTGC

Primers for CRISPR verification

624-KO-F	TTCAGAAGATTCATGGTGCTCTGGG
624-KO-R	GAGTGACCTCCAAGGATTATTCAGGG
h-ADARKO-F	AGCAACTCCACATCTGCCTTGG
h-ADARKO-R	TGTTCGTATTTCTCTTGATTTGCATCC
m-ADARKO-F	AGCTTCAGCAGATAGAGTTTCTCAAAGGG
m-ADARKO-R	GCAGTCTCATTGGTCCTGGTCTGG

Primers for IVT

T7-624/SEG1-F	TAATACGACTCACTATAGGGAGAAGCTGCTGCAACCCG
624/SEG1-R	GTTAATTATTTTATTGATACATAATAGATGTACATATTTTGAGGG
T7-SEG2-F	TAATACGACTCACTATAGGGATTCATCAGAATTGCTGGAGAGTCC
SEG2-R	TAAAATCAGTATCTTTGGATACTCGTGTAATTATTC
T7-SEG3-F	TAATACGACTCACTATAGGGATACTGATTTTAGGAGAACAAGGTTGTTGG
SEG3-R	CATTTCTAGTTTCAGGAAAACAAAATTGTTGGG
T7-Alu-PHACTR4-F	TAATACGACTCACTATAGGGATGTGGACTTGCTGAAGAAACAGAATATC

Alu-PHACTR4-R	TTGTCACTTCTCTTCCCTCAGTTATCCC

ASOs	
ASO-LINC00624-1	GCCTATTTATTCACACCAAG
ASO-LINC00624-2	TGTTTCCTGCAGTATGCACC
ASO-LINC00624-3	GCAGAAGTAGGCCACATCTT
ASO-LINC00624-4	GAATACCTACCTTGGGCACA
ASO-LINC00624-5	CAACTTGCCTGGTACGGAGG

CRISPR Target sequence	
624-F1	GGGTATAAAAGCTGGCCACG
624-F2	GGAGGACACATGATAAGGAG
624-R1	GCAGAACTTTGTGCAGTACT
624-R2	GACCTGCTGCTCCTTGAAGG
h-ADAR-1	CTGCAGGGGTATTCCCTCAG
h-ADAR-2	TTAGAACCACCACCTTCAAC
m-ADAR-1	TTCCAAGTCAATCAGCACTG
m-ADAR-2	TGTGACTCTCAGAAATCAG

Table S5 Conservation Analaysis of LINC00624 by PLAR database

Symbol	Transcripts With Conservation	Non-redundant Exons	Species With Seq Orthologs	Species With BLAST	Species With WGA	Species With Synteny	Species With Sequence And Synteny	Mouse BLAST	Mouse WGA	Mouse Synteny	Mouse Sequence+Synteny
NEAT1	ENST00000499732.3_2, ENST00000501122.2_1, ENST00000601801.3_2, ENST00000612303.2_2, ENST00000616315.2_2, ENST00000642367.1_1, ENST00000645023.1_1, ENST00000646243.1_1	1	Mouse, Dog, Ferret, Marmoset, Opossum, Rabbit	Mouse, Dog, Ferret, Marmoset, Opossum, Rabbit	Mouse, Dog, Ferret, Marmoset	Mouse, Dog, Ferret, Gar, Lizard, Marmoset, Opossum	Mouse, Dog, Ferret, Marmoset, Opossum	ENSMUST000000173672.1, ENSMUST000000174287.1, ENSMUST000000174829.1, ENSMUST000000232969.1	ENSMUST000000173672.1, ENSMUST000000174287.1, ENSMUST000000174829.1	ENSMUST000000172812.2, ENSMUST000000173314.1, ENSMUST000000173499.1, ENSMUST000000173672.1, ENSMUST000000174287.1, ENSMUST000000174808.1, ENSMUST000000174829.1, ENSMUST000000232969.1	ENSMUST000000173672.1, ENSMUST000000174287.1, ENSMUST000000174829.1, ENSMUST000000232969.1
LINC00624	ENST00000619867.4_1, ENST00000621316.1_1	7	Dog, Rhesus	Rhesus	Dog, Rhesus	Mouse, Dog, Gar, Rabbit, Rhesus	Dog, Rhesus	-	-	ENSMUST000000198613.1, ENSMUST000000199972.1	-

Data were extracted from PLAR database. BLAST: Basic Local Alignment Search Tool. WGA: Whole-Genome Amplification. NEAT1 were shown as control.

Supplementary File 1

Sequences

1.LINC00624-isoform1 full-length (FL, 3372nt)

AGCTGCTGCAACCCGCTGCCCTCTGGTGTCCTGCTGTGGGAGCTTTGTTCTTTCAC
TCTCGTAATAAGTCTTGCTGCTGCTCACTCTTTGGGTCCGCACTGTCTCTGTGAGCT
GTAACACTCACCGCGAGGTTCTGTGCCTTCGTTCTTTAAGTCAGGGAGACCACGAAC
CCACCGGGAGGAACAAACAACTGTGATGCGCCATCTTTAAGAGCTGTAACATTCACC
GCCGGGGTCTGCGGCTTCATTCCTGGAGTGAGTGAGACCACGAACCCACCAGAAG
GAAGAAACTCTGGACCCATCTGAACAGCTGAAGGAACAAACTCCGGACACACCATC
TTTAAGAACTGTAACACTCACCGGGAGTCTCCGTGGCTTCATTCTTGAAGACAGCGA
GACCAAGAACCCACCAGAAGGAATGAATTCCGCACACAGCAACAGCACAAAGTTAAA
CCAGGAAGTCCCTCTGCCTTGCTAGGGATCCAGGTTTGCCTTCCTGTTGAGGTATCC
CATTTCATTACAGTTGACCTAAGTTTGAACAAACACTGCCACCTGATGCATGAAAGCT
CTACTGTGACCTACGTTAAAAGGAGCTGACACTCCCTCAGGCTACCTTAGTCAGTGG
GGGCTTACTGCAGCATACCTGTGGCGATGAGAGAGAGAGGCACATCACAGGAGCAT
CTGGCACCAGTGGCATCCTGAATTTAAGATGAAACAATAGAGAAAGAACCAAGAAGT
TACATACATTCATCAGAATTGCTGGAGAGTCCTGACCTCTGGCCATCGATCAAAGGGA
AGCGTTCACTACTGAAGGTTTGTCTTCACTGTACTGGGTATTCAACTTCCTTGAAATT
AAAAGGAAGAAGGATAAAAAGTGGTATGCTGAATGGATTAAAGGTAATATTTTGATTAT
ATCAATAGTTTTCAAACTTTTATAACTCATGAGCTGTTTGGGAATATTTGAGCATATGGT
CAATCCACATCTGAATTATCCTGCCCACAAAAATGTCAAGGAAATACTTCTACTGCCC
CTTCTGAAGCCATCTTAATTCCAGGAGTTGAATCAATTTCAAAGTCATTGATAACTGCA
TCAGCCAAAATTTGTCCAAATGTTTTGAAATGCATTTCTATTTCCTGTCACACCTACCT
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TTTAAAGTTGTTGAATAAGCAAATCTCTGTTCACTTTATTTGTACTATTTATGGTTATATA
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CAGAGATATACCAGTATAAAGCTTGCTTTCCAGTATAGTCCTTAATGATTTTCTTCATTT
TCTAGGTCTTTTTGCCTGATGCAGAATATTGGTACATATGCTGGGGTCAACATTTAATG
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TTTAGATTACTCATAAATTCATTACTTTTTCCTCACACACATTATAACATCTCTTAAGGCT
CTGCCCATTGACACGAATCTCAGGATTATTCTATAATGTCTCTCTTCTCTGGGGTGTCT
TCTTTCTGGGGAGATTTGTATATCTTGGAGTCTGAGACTTCACTATGTACTCCTTCCTT
ATCATCATTTATAAACCTATTCAACAGACTCTGCCCCAGAATGGATTCTTGAGCAATCT
TGAATAATTACACGAGTATCCAAAGATACTGATTTTAGGAGAACAAGGTTGTTGGGTAC
AGGTAGTTAATTATTCCTAAAACTGAATATGTCCAATACCTATGTCTTGAGAAGCTCTAA
GAGAGTAACAGAAGAGCAACAATGGAATGTGACAATTGCCTGCACTGTCTTTCTAGG
TTGAAAATCCAAGAAATTTACATGCACTGAATTTTATTTCCTTTATTTGCCTATTTATTCA
CACCAAGAATTCAGGGTCCATGTTGCTGTAGTGGAAATTGGTTATTTCTGTTTTAGTC
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GCCACATCTTCCATTTTCATCCTTGGATTCCTGTGGAATTTACAGATGCACAGATAGAA

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TATTCAGTGTGCTTTCTTGAATACCAGCCTTGTTTCAACTCTTTAATGAGTGGACTATT
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CACATGCACGTAACAGGAGCACTTTTCCGAGAATTGTAAAGGAGCCACGGTGCAAA
GCCTTCTGGACCTGGGTCTCATGTGAAAACTCAGCAATGAGCCTCCTGGCCTGAGA
TGAGCCTGCGGAGCACCTTGTTACAGCACGCATATGATGTATATAAAAAATGAACACA
TGTATTCCAATTACACTGATTTGATCTTTACAAACTATATGGATGTATTAAATTGTCACAT
GTACCCTCAAAATATGTACATCTATTATGTATCAATAAAATAATTAACA

* Segment 1 Uncolored; Segment 2 Green ; Segment 3 Yellow

2. LINC00624-isoform2 (2754nt)

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TCTCGTAATAAGTCTTGCTGCTGCTCACTCTTTGGGTCCGCACTGTCTCTGTGAGCT
GTAACACTCACCGCGAGGTTCTGTGCCTTCGTTCTTTAAGTCAGGGAGACCACGAAC
CCACCGGGAGGAACAAACAACTGTGATGCGCCATCTTTAAGAGCTGTAACATTCACC
GCCGGGGTCTGCGGCTTCATTCCTGGAGTGAGTGAGACCACGAACCCACCAGAAG
GAAGAAACTCTGGACCCATCTGAACAGCTGAAGGAACAAACTCCGGACACACCATC
TTTAAGAACTGTAACACTCACCGGGAGTCTCCGTGGCTTCATTCTTGAAGACAGCGA
GACCAAGAACCCACCAGAAGGAATGAATTCCGCACACAGCAACAGCACAAAGTTAAA
CCAGGAAGTCCCTCTGCCTTGCTAGGGATCCAGGTTTGCCTTCCTGTTGAGGTATCC
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GGGCTTACTGCAGCATACCTGTGGCGATGAGAGAGAGAGGCACATCACAGGAGCAT
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GCAGAATCTAAGGGATAGTCTTTCATTTTATAGATGTGTTTTAGATTACTCATAAATTCA
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GTCACATCTGTAATTCTCTGATCTCGTGATGCAGAAGTAGGCCACATCTTCCATTTTC
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GATACCTTCATCTGCTTTGTCAATTGATGATGAATAAGACTGAGTTGAATGTATTTAGA
ATGTCTTGGCTATAAATTCCTCCATATAGCTTAACCCACTGTTTCCTGCAGTATGCACC
CCTTTACCAAGAGAGAGAAAGAGAGAAAGAATTTCATGTTTCTGTGGGTTTTAGAAG
GCTATAGGAAGGGATTTTTGTTTGCTCATTTTCAGAACTTATTAATAGACAGTTATTGAA
TACCTACCTTGGGCACAGAAATAATCACATTCTCTCCTGAGAATTTTCAACCCACAGC
CAAGTACAGGTGTGGAAATTTGATGATAGAATTAATACCAATGGAAAAAGGGGCCCAC
AGAACTGAAAAAGTGGCCACTGGTGATGACAGTGACCTGGGAGGGAGCGAGGCAA
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CTTGGAGCTTCTCAAGCCACAGGTGTCAGTCATATTGGTTTTAGAGATTATTAGTAACT
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3. LINC00624-isoform3 (2363nt)

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CCACCGGGAGGAACAAACAACTGTGATGCGCCATCTTTAAGAGCTGTAACATTCACC
GCCGGGGTCTGCGGCTTCATTCCTGGAGTGAGTGAGACCACGAACCCACCAGAAG
GAAGAAACTCTGGACCCATCTGAACAGCTGAAGGAACAAACTCCGGACACACCATG
TTTAAGAACTGTAACACTCACCGGGAGTCTCCGTGGCTTCATTCTTGAAGACAGCGA
GACCAAGAACCCACCAGAAGGAATGAATTCCGCACACAGCAACAGCACAAAGTTAAA
CCAGGAAGTCCCTCTGCCTTGCTAGGGATCCAGGTTTGCCTTCCTGTTGAGGTATCC
CATTTCATTACAGTTGACCTAAGTTTGAACAAACACTGCCACCTGATGCATGAAAGCT
CTACTGTGACCTACGTTAAAAGGAGCTGACACTCCCTCAGGCTACCTTAGTCAGTGG
GGGCTTACTGCAGCATACCTGTGGCGATGAGAGAGAGAGGCACATCACAGGAGCAT
CTGGCACCAGTGGCATCCTGAATTTAAGATGAAACAATAGAGAAAGAACCAAGAAGT
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CTCATGTGAAAACTCAGCAATGAGCCTCCTGGCCTGAGATGAGCCTGCGGAGCACC
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ATCTATTATGTATCAATAAAATAATTAACA

4.LINC00624-isoform4 (1745nt)

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CCACCGGGAGGAACAAACAACTGTGATGCGCCATCTTTAAGAGCTGTAACATTCACC
GCCGGGGTCTGCGGCTTCATTCCTGGAGTGAGTGAGACCACGAACCCACCAGAAG
GAAGAAACTCTGGACCCATCTGAACAGCTGAAGGAACAAACTCCGGACACACCATC
TTTAAGAACTGTAACACTCACCGGGAGTCTCCGTGGCTTCATTCTTGAAGACAGCGA
GACCAAGAACCCACCAGAAGGAATGAATTCCGCACACAGCAACAGCACAAAGTTAAA
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CTACTGTGACCTACGTTAAAAGGAGCTGACACTCCCTCAGGCTACCTTAGTCAGTGG
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AATGAGCCTCCTGGCCTGAGATGAGCCTGCGGAGCACCTTGTTACAGCACGCATAT
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AATAATTAACA

5.LINC00624-Segment 3 (S3)

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TTGCCTGGTACGGAGGGGAGATTCACCAGTGGGCCTCACCTGTAAGTGAGGGTCAC
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CCCAACAATTTTGTTTTCCTGAAACTAGAAATG

* AER was highlighted

6.LINC00624 S3-AER

GAAAATCCAAGAAATTTACATGCACTGAATTTTATTTCCTTTATTTGCCTATTTATTCACA
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GGGAGCGAGGC

7.LINC00624 A-to-C

AGCTGCTGCAACCCGCTGCCCTCTGGTGTCCTGCTGTGGGAGCTTTGTTCTTTCAC
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GTAACACTCACCGCGAGGTTCTGTGCCTTCGTTCTTTAAGTCAGGGAGACCACGAAC
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7.LINC00624 A-to-G

AGCTGCTGCAACCCGCTGCCCTCTGGTGTCCTGCTGTGGGAGCTTTGTTCTTTCAC
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GCCGGGGTCTGCGGCTTCATTCCTGGAGTGAGTGAGACCACGAACCCACCAGAAG
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Supplementary Methods

Patients and tumor samples

Core needle biopsy samples were collected before treatment from 20 patients diagnosed with HER2+ invasive breast carcinoma, receiving paclitaxel + carboplatin + trastuzumab neoadjuvant chemotherapy followed by surgical resection at Fudan University Shanghai Cancer Center (FUSCC). The 100 tumor tissue cohort is built from another HER2+ breast cancer project in our lab, and used for verification. Patients received chemotherapy + trastuzumab with or without pyrotinib. Samples were collected before treatment. RNA-seq data of LINC00624 were extracted from this cohort. The prognosis cohort samples were collected from 319 patients with early breast cancer receiving surgical resection and adjuvant treatment from 2010 to 2011. The clinical data were collected, and the patients were followed as shown in the Figures. Tumor samples were collected and stored in the liquid nitrogen. The survival analysis was performed by using Kaplan-Meier methods. Patients were analyzed (*All types*) or divided into subgroups according to ER, PR and HER2 expression. *HER2* were defined as IHC HER2 3+ or HER2 2+ with HER2 FISH amplification with ER and PR negative. TNBC were defined as IHC ER, PR and HER2 negative. *Luminal* were defined as IHC ER+ or PR+. This study was approved by the ethics committee of FUSCC and informed consent for the use of sample for research purposes was obtained by participants. TCGA data were extracted and analyzed by GEPIA[1].

Expression plasmids, reagents

LINC00624 full length cDNA were synthesized (Genewiz) according to 5' and 3' RACE results and cloned into pCDH-CMV-Puro vector. Isoforms with A-to-C or A-to-G mutations were synthesized according to the editing results from Sanger sequencing of LINC00624 in ADAR1 overexpressed SK-BR-3 cells. Isoform3 and S1, S2, S3 segments were cloned from the full length LINC00624. The full sequences of isoforms were listed in Supplementary file 1. The ORF of human ADAR1-p110, ADAR1-p150 were cloned from SK-BR-3 cDNA and inserted into pCDH-CMV-Puro with N-terminus 3×FLAG tag. ADAR1-p110 was used for overexpression experiments unless noted otherwise. Serial mutations of ADAR1-p110 were subcloned and constructed with N-terminus 3×FLAG tag. The ORF of mouse ADAR1-p110 was cloned from NF639 cell and inserted into pCDH-CMV-Puro with N-terminus 3×FLAG tag. The plasmids used in this study are available upon request.

The pharmacological reagents lapatinib (S2111, Selleck), trastuzumab (A2007, Selleck), MG132 (C2211, Sigma), Cycloheximide (C7698, Sigma), DMSO (D8418, Sigma), poly(I:C)(HMW) (tlrl-pic, InvivoGen), human IFN-α (C006, Novoprotein), human IFN-γ (300-2, Peprotech), murine IFN-α (CK83, Novoprotein), murine IFN-γ (315-05, Peprotech), 8-azaadenosine (HY-115686, MCE) purchased and used according to the manufacturer's instructions.

ASOs for LINC00624 *in vitro* use were synthesized from Ribobio. ASOs with 5'cholesterol modification for *in vivo* use were synthesized from Hippobio, sequences were listed in Supplementary Table 4.

Cell culture, transfections, and infections

HEK293T, SK-BR-3, BT-474, MCF-7, MDA-MB-231, NF639, and B16 cells were obtained from the ATCC. The cell lines were tested for mycoplasma contamination every month. Human cell lines were authenticated by STR determination. BT-474, NF639, and B16 were cultured in RPMI-1640 medium (L210KJ, BasalMedia) supplemented with 10% FBS (10099141, Gibco). SK-BR-3 which were cultured in McCOY's 5A (L630KJ, BasalMedia) + 10% FBS. HEK293T, MCF-7 and MDA-MB-231 cells were cultured in DMEM (L110KJ, BasalMedia) + 10% FBS. All cells were maintained at 37 °C under 5% CO_2. LINC00624 was deleted in BT-474 and SK-BR-3 cells using transient transfection of GFP and mCherry tagged Cas9 sgRNA plasmids (derived from pX459, Addgene) with the lipofectamine 3000 transfection reagent (L3000150, Invitrogen). Two sgRNAs were transfected at the same time targeting the promoter of LINC00624. Transfected cells were sorted by flow cytometry with GFP and mCherry. For monoclonal selection, sorted cells were plated in 96-well plates with an average of 1-3 cells in a well. Clones were expanded and verified by PCR. Human and mouse ADAR1 were deleted with transfection of GFP tagged Cas9 sgRNA plasmids as described above. Clones were expanded and verified.

For poly(I:C) transfection assays, 1×10^6 cells were plated 24h before transfection. 1 μg/ml poly(I:C) (HMW) (tlrl-pic, InvivoGen) were transfected with Lipofectamine 2000 (11668500, Invitrogen). Cells were harvested or used for downstream analysis after 24h. ASOs and siRNAs for in vitro use were synthesized by RiboBio as listed in Supplementary Table 5. Cells were plated 24h before transfection. 0.1 nmol siRNA or ASO were transfected with RNAiMAX (13778150, Invitrogen) and harvested 72h after transfection.

For overexpression cell lines, lentivirus was produced by co-transfecting HEK293T

cells with desired plasmids together with psPAX2 and pMD2.G (Addgene). After 72 h, virus was harvested by passing through a 0.45 mm filter. Collected lentivirus was used directly to infect cells with the addition of 8 mg/ml polybrene (H9268, Sigma) or stored in -80℃. Infected cells were selected with puromycin (ant-pr-1, InvivoGen) at 2 μg/ml.

Immunoblot

Cells were lysed and homogenized by RIPA (89901, Thermo) containing Protease Inhibitor cocktail (B14001, Bimake) and phosphatase inhibitor cocktail. and Pierce BCA Protein Assay kit (23225, Thermo) was used for protein quantification. Cell lysates were separated by 10% SDS–PAGE and fractionated proteins were transferred to PVDF membranes (ISEQ00010, Millipore). After blocking with TBS, 0.1% Tween-20 and 5% skim milk, the membranes were probed with antibodies signals were enhanced by secondary antibodies (anti-mouse, 111-035-144, Jackson; anti-rabbit, 111-035-046, Jackson). Chemiluminescent detection (180-5001, Tanon) was used. The monoclonal anti-β-TrCP (4394S; 1:1,000 dilution), anti-ADAR1(81284S; 1:1,000 dilution), anti-STAT1 (9172S; 1:1,000 dilution), anti-pSTAT1(T701) (9167S; 1:1,000 dilution), anti-IRF3 (11904S; 1:1,000 dilution), anti-pIRF3(S396) (29047S; 1:1,000 dilution), anti-TBK1 (3504S; 1:1,000 dilution), anti-pTBK1(S172) (5483S; 1:1,000 dilution), and anti-HA (3724S; 1:1,000 dilution) antibodies were purchased from Cell Signaling Technology. The monoclonal HRP-anti-GAPDH (60004-1-Ig; 1;10,000 dilution) were purchased from Proteintech. The mouse monoclonal anti-ADAR1 (sc-73408; 1:1,000) were purchased from Santa Cruz Biotechnology (used in immunoblot of mouse cell lines).

RNA isolation, RT-PCR and RT-qPCR

Total RNAs from cultured cells were extracted with TRIzol (15596026, Invitrogen) according to the manufacturer's protocol. Clinical samples were stored in RNAlater (AM7024, Invitrogen) and extracted with TRIzol with the facilitation of rotor-stator homogenizer. cDNAs were reverse transcribed with Hiscript III Reverse Transcriptase (R312, Vazyme) with oligo (dT) and random hexamers followed by qRT-PCR analysis and applied for PCR/qPCR analysis. Real time quantitative PCR was performed with ChamQ SYBR qPCR Master Mix (Q311, Vazyme) and QuantStudio 7 (4485701, Applied Biosystems). The relative expression of different sets of genes was quantified to GAPDH or ACTB mRNA. Primer sequences for RT-qPCR and RT-PCR used were listed in

Supplementary Table 4.

Cell proliferation and viability assay

For proliferation assay, cells were seeded in 96-well flat-bottomed plates with each well containing 3000 cells in 200 µl of culture medium and cultured in ambient environment described above. Plates were imaged by using IncuCyte ZOOM System (Essen Bioscience) at 12-hour interval. The growth rate was measured according to confluence change analyzed by IncuCyte software.

For cell viability studies, 3500 of SK-BR-3 or BT-474 cells were plated in each well of 96 well plates and treated with the indicated agents 24 hours later at the concentrations shown. For viability assays assessing the effect of lapatinib and trastuzumab, cells were treated for 120 hours before measuring viability. Cell viability was measured using the Cell Counting Kit 8 (CK04, Dojindo) according to manufacturer's instructions. Plates were read at 450nM absorbance. Technical replicates were performed 3 times for each condition, and biological replicates were performed 2-3 times per experiment.

Cell death assays

SK-BR-3 or BT-474 were plated in 6-well plates at a concentration of 1 million cells per well 24 h before poly(I:C) transfection. Cells were transfected with 1 µg/ml poly(I:C) and incubated for 24h with ambient culture environment. Following trypsinization and washes in PBS + 2% FBS, cells were stained for 30 min on ice using the manufacturer's recommended concentrations of Annexin-V PE and 7-AAD from the PE Annexin V Apoptosis Detection Kit 1(559763, BD Pharmingen). Staining of cell surface markers was then analyzed using an Accuri C6 flow cytometry system. Analysis was carried out using CytoExpert 2.3 software.

RNA-seq and AEI score calculation

For clinical sample analysis, the core needle biopsy specimens were immediately stored into RNAlater according to the manufacturer's instruction. Samples were extracted with RNAeasy mini kit (74106, Qiagen) according to the manufacturer's instruction. The RiboMinus Eukaryote Kit (A1083708, Invitrogen) was used to eliminate rRNAs. Libraries were prepared using NEBNext Ultra Directional RNA Library Prep Kit (E7775, NEB). Transcript expression was analyzed using StringTie (version 1.2.3) and quantified by

FPKM (fragments per kilobase of exon per million fragments mapped).

For AEI score analysis or GSEA analysis, the total RNA samples of cell lines were treated with VAHTS mRNA Capture Beads (Vazyme) to enrich polyA+ RNA before constructing the RNA-seq libraries. RNA-seq libraries were prepared using VAHTS mRNA-seq v3 Library Prep Kit for Illumina (NR611, Vazyme) following the manufacturer's instructions. Sequencing reads from RNA-seq data were aligned using the spliced read aligner HISAT2, which was supplied with the Ensembl human genome assembly (Genome Reference Consortium GRCh38) as the reference genome. Gene annotation and analysis was conducted by metascape (http://metascape.org/). Gene expression levels were calculated by the FPKM. Gene Set Enrichment Analysis (GSEA) was conducted according to the instructions from the Broad Institute using the pre-ranked method. After gene expression was quantified by FPKM, log2 scaled fold change of all expressed genes was calculated. Graphic representations of results were generated using the cluster Profiler package in R (https://www.r-project.org/).

The analysis of Alu Editing Index (AEI) was following the protocol detailed in Roth et al. with default parameters[2].

Rapid Amplification of Cloned cDNA Ends (RACE)

The 3' and 5' RACE was performed using the RLM-RACE kit (AM1700, Invitrogen) following the manufacturer's instruction. RNA was extracted from SK-BR-3 cells. Primers used for 3' and 5' RACE were listed in Supplementary Table 4.

RNA fluorescence in situ hybridization (FISH) and Subcellular Location

LINC00624 RNA FISH was performed using Ribo FISH Kit (C10910, Ribobio) according to the manufacturer's protocol. FISH probes were synthesized by Ribobio (18S, lnc110102; LINC00624, lnc1CM001). Briefly, cells were grown on coverslips in a 24-well culture plate. Cells were fixed with 4% (w/v) paraformaldehyde in 1×PBS for 10 min. Fixed cells were permeabilized for 5 min at 4℃. The coverslips were washed three time with PBS for 5 min at room temperature and then blocked with pre-hybridization Buffer at 37℃ for 30 min. Cy3 labeled-LINC00624 or 18S RNA probes were hybridized at 37℃ overnight. The coverslips were then washed three times with Wash Buffer I, once with Wash Buffer II and once with Wash Buffer III. Cover slides were stained with DAPI and then mounted. Images were acquired with Leica confocal microscope.

For nuclear and cytoplasmic RNA separation, 1×10^6 cells were collected and extracted using PARIS™ kit according to the manufacturer's instructions (AM1921, Invitrogen). RNAs were reverse transcribed and analyzed with quantitative PCR. The proportion of genes expressed in nuclear and cytoplasmic fraction was calculated.

RNA pull-down assay and mass spectrometry

RNA pull-down was performed as previously described[3]. Briefly, LINC00624 isoforms were in vitro transcribed (E2040S, NEB) and labeled with Biotin-16-UTP (11388908910, Roche). SK-BR-3 cells were used for RNA pull-down/MS analysis. HEK293T cells transfected with ADAR1 truncation plasmids were used for binding analysis. Cells lysates were prepared with modified RIPA (50mM Tris-HCl pH 7.4, 150mM NaCl, 1% Igepal 630, 0.5% sodium deoxycholate). For each sample, 3 μg RNA was mixed with 1×10^7 cell extract and incubated at 4℃ for 4h, followed by incubating with Dynabeads C1 (65002, Invitrogen) at 4℃ for 1h. After elution, the samples were detected by immunoblot or proceed to mass spectrometry. For MS, samples were separated by SDS-PAGE and stained with Fast Silver Stain Kit (P0017S, Beyotime) according to the manufacturer's instructions. Specific bands were cut and analyzed by LC-MS/MS (Shanghai Applied Protein Technology, Shanghai, China). Protein identification was retrieved in the human RefSeq protein database (National Center for Biotechnology Information), using Mascot version 2.4.01 (Matrix Science, London, UK).

In vitro RNA editing assay

Editing of a synthetic Glut-B B11 RNA was assayed in vitro with purified ADAR1 proteins. The standard editing reaction mixture contained 0.2 ng of ADAR1 protein, 0.02 M HEPES (pH 7.0), 0.1 M NaCl, 10% glycerol, 5 mM EDTA, 1 mM DTT, and 4 U of RiboLock RNase inhibitor (EO0384, Thermo) in a 20 μl reaction volume. The synthetic LINC00624 or Alu from 3'UTR of PHACTR4 RNA (Alu-PHAC) was added into the mixtures and pre-incubated at 30℃ for 15 minutes. Then, 50 ng of a synthetic Glut-B11 RNA substrate was added and incubated for 5 or 15 minutes. The reaction was terminated by 70℃ 5min. 6 μl of reaction was reverse transcribed with specific primer and HiScript III (Vazyme) at 37℃ 15min, 45℃ 15min, and then 50℃ 15min. PCR and sanger sequencing of Glut-B11, LINC00624, and Alu-PHAC template was performed and quantified with Snapgene.

Recombinant ADAR1 Expression

ADAR1 was codon optimized, synthesized, and then subcloned into target vector for insect cell expression. DH10Bac strain was used for the recombinant bacmid (rbacmid) generation. The positive rbacmid containing ADAR sequence gene was confirmed by PCR. Sf9 cells were grown in Sf-900 II SFM Expression Medium (10902-088, Life Technologies). The cells were maintained in Erlenmeyer Flasks at 27 °C in an orbital shaker. One day before transfection, the cells were seeded at an appropriate density in 6 wells. On the day of transfection, DNA and Transfection Reagent (E2691, Promega) were mixed at an optimal ratio and then added into the plate with cells ready for transfection. Cells were incubated in Sf-900 II SFM for 5-7 days at 27 °C before harvest. The supernatant was collected after centrifugation and designated as P1 viral stock. P2 was amplified for later infection. The expression was analyzed by Western blot. The 0.1 L SF9 cell culture were infected by P2 virus. Cells were incubated in Sf-900II SFM(1X) for 3 days at 27 °C before harvest. The expression was analyzed by Western blot. Cell pellets were harvested and lysed by proper cell lysis buffer. The cell lysate supernatant was incubated with Anti-Flag column to capture the target protein. Higher purity fractions were pooled and followed by 0.22 μm filter sterilization. The purified protein was dialyzed and stored in 50 mM Tris-HCl, 500 mM NaCl, 20% Glycerol, pH 7.5. Proteins were analyzed by SDS-PAGE by using standard protocols for molecular weight and purity measurements. The concentration was determined by Bradford protein assay with BSA as a standard.

RNA EMSA

The AER region was cloned, in vitro transcribed, and labeled with biotin-16-UTP (11388908910, Roche). Recombinant ADAR1 and AER was incubated in a 10μl reaction volume with editing buffer (0.02 M HEPES (pH 7.0), 0.1 M NaCl, 10% glycerol, 5 mM EDTA, 1 mM DTT, and 4 U of RiboLock RNase inhibitor (EO0384, Thermo)) at 30℃ for 15min. Native PAGE was performed for separating components followed by transferring to Nylon membrane (AM10102, Invitrogen). After ultraviolet cross-linking, HRP-conjugated streptavidin was added according to manufacturer's instruction with LightShift® Chemiluminescent RNA EMSA Kit (20158, Thermo).

OT-I cells isolation and co-culture with B16-OVA cells

C57BL/6-Tg(TcraTcrb)1100Mjb/J (OT-I) mice (JAX stock, 003831) were purchased

from the Jackson Laboratory. The spleen was homogenized, and single cells were suspended in 3 ml ACK buffer (0.15M NH_4Cl, 1mM $KHCO_3$, 0.1mM EDTA, pH 7.4) for 1 min. Cells were pelleted and washed with Wash Buffer (PBS+0.5%BSA+2mM EDTA). CD8+ cells were negatively selected with CD8a+ T cell Isolation Kit, mouse (130-104-075, Miltenyi) as manufacturer's instruction. Purified cells were washed, stained with anti-CD3e and anti-CD8a, and analyzed with flow cytometry for verification.

B16-OVA-pCDH and B16-OVA-LINC00624 cells were pre-incubated with 40 μg/mL of anti-H-2Kb-SIINFEKL (130-096-810, Miltenyi) or isotype control (130-106-545, Miltenyi) for 1 h at 37°C. CD8+ T cells were washed with T cell culture media (RPMI 1640+5%FBS+55 μM 2-Mercaptoethanol (21985023, Gibco)). 1.6×10^5 $CD8^+$ T cells were co-cultured with 2×10^4 tumor cells in a final concentration of 10 μg/mL of the anti-H-2Kb-SIINFEKL or isotype control with 2.5 ng/mL IL-7 (217-17-2, Peprotech), 50 ng/mL IL-15 (210-15-2, Peprotech), and 2 ng/mL IL-2 (212-12-5, Peprotech) for 72 h at 37°C in the dark. At the experimental endpoint, cytokines in conditioned media were analyzed by ELISA with Mouse Interferon-gamma ELISA kit (BE45201, IBL) according to the manufacturer's instruction. Three technical replicates were used for analysis each time.

Tumor immune cell profiling

Tumors were dissected from the surrounding fascia, weighed, mechanically minced, and treated with collagenase I (1 mg/ml, LS004197, Worthington) and DNase I (1 mg/ml, 11284932001, Roche) for 30 min at 37 °C. Cells were passed through a 70μm filter to remove clumps, washed in D-PBS. Live or dead staining were performed with Fixable Viability Stain 780 (565388, BD Biosciences) at 4℃ for 30 min. After washing twice with Stain Buffer FBS (554656, BD Biosciences), blocked with CD16/CD32 (1 μg per 1 million cells in 100 ul, 553141, BD biosciences), antibodies for surface staining were added. Cells were stained for 30 min at 4℃. Cells were washed twice with Stain Buffer and then resuspended in 1 ml of freshly prepared Fix/Perm solution (554714, BD biosciences) for intracellular staining. After fixation and washes, antibodies for intracellular staining were added. Cells were stained for 30 min at 4℃. After washes, analysis was performed using an Accuri C6 flow cytometry system. CytoExpert 2.3 software was used for data analysis. Gating strategy was indicated in Supplementary Fig 8. Antibodies used were listed as below.

Antigen presentation analysis

1×10^6 B16-OVA pCDH or LINC00624 cells were seeded per well in 6-well plate 24 h before stimulation. Murine IFN-α (5 ng/ml) or IFN-γ (10 ng/ml) were added to the culture media. Following trypsinization and washes in PBS + 2% FBS, cells were stained for 30 min on ice with anti-SIINFEKL-H2K^b (1:100, 141605, Biolegend). For *in vivo* analysis, digested tumor cells were stained with Live/Dead first as described above. Then cells were stained with anti-SIINFEKL-H2K^b for 30 min on ice. The analysis was using an Accuri C6 flow cytometry system and CytoExpert 2.3 software.

Immunohistochemistry

Tissue or tumors were fixed in 4% paraformaldehyde overnight. Dehydration and embedding in paraffin were performed following routine methods. These paraffin blocks were cut into 5 mm slides and adhered on the slides glass. Paraffin sections were deparaffinized in xylene and then rehydrated in 100%, 95%, 75% alcohol successively. Antigen was retrieved by critic acid buffer (pH 6.0) in the 100℃ water bath for 15 min. Endogenous peroxidase was inactivated by incubation in 3% H_2O_2 for 15 min. Following a preincubation with 10% normal goat serum to block nonspecific sites for 30 min, the sections were incubated with primary antibodies in a humidified chamber at 4℃ overnight. After the sections were washed with PBS three times, HRP-conjugated secondary antibodies were applied. Staining was performed with DAB or AEC system as indicated. anti-CD8α (1:400, 98941S, CST), anti-ADAR1 (1:400, 81284S, CST), anti-mouse secondary antibody (1:1000, 111-035-144, Jackson), anti-rabbit secondary antibody (1:1000, 111-035-046, Jackson).

Animal treatment

The designs of animal studies and procedures were approved by the Fudan University Shanghai Cancer Center (FUSCC) IACUC committees. Ethical compliance with IACUC protocols and institute standards was maintained. All mice were maintained under pathogen-free conditions. The animal room has a controlled temperature (18-23°C), humidity (40–60%) and a 12 h-12 h light-dark cycle. In each experiment, animals were randomly assigned into each group. No blind was used in this study.

For B16-OVA xenograft model, six-week-old wild-type female C57BL/6J mice were used. 1×10^5 B16-OVA-pCDH or B16-OVA-LINC00624 were subcutaneously injected on

the flank. For ADAR1 KO B16 tumors, 5×10^5 cells were injected. For BT-474 xenograft model, 17b-estradiol pellet 0.72mg (SE-121, IRA) was implanted subcutaneously into 6-week-old nude mice one week before inoculation. 2.5×10^6 BT-474 pCDH or LINC00624 cells were resuspended in D-PBS solution (Gibco), mixed 1:1 by volume with BME (3632-010-02, Cultrex) and subcutaneously injected into the fourth mammary fat pat. 100μg anti-HER2/neu (BE0277, BioXcell) or isotype control (BE0085, BioXcell) was intraperitoneally injected as indicated. For ASO treatment assay, 17b-estradiol pellet 0.72mg (SE-121, IRA) was implanted subcutaneously into 6-week-old nude mice one week before inoculation. 2.5×10^6 BT-474 pCDH or LINC00624 cells were resuspended in D-PBS solution (Gibco), mixed 1:1 by volume with BME (3632-010-02, Cultrex) and subcutaneously injected into the fourth mammary fat pat. ASO2 and ASO3 were mixed 1:1. 10nmol ASO 2 & 3 mixture (5 nmol each) or ASO control were intravenously injected each time for each mouse as indicated. For PD-1 treatment assay, six-week-old wild-type female C57BL/6J mice were obtained from Jackson laboratories. B16-OVA cells were transfected with poly(I:C) at 1 μg/ml for 4 hr and irradiated by a UVC500 UV crosslinker at 120 mJ/cm^2 followed by 24 h incubation. For anti-tumor effects, mice were injected intraperitoneally (I.P.) with UV irradiated B16 OVA cells (1 x 10^6 cells / mouse) 7 days before inoculation. 1×10^5 B16-OVA-pCDH or B16-OVA-LINC00624 were subcutaneously injected on the flank. At 0 and 6 days, mice were I.P. with UV irradiated B16 OVA cells again. Antibodies were administered subcutaneously at day 5, 8, and 12 at 100 μg/mouse using isotype control IgG (BE0089, BioXcell) or anti PD-1 (BE0146, BioXcell).

The tumor volume was measured using calipers and calculated with the formula Volume=(length×width×width)/2. Animals were randomized before treatment and no blinding was performed.

Statistics and Reproducibility

Statistical analyses were performed using SPSS v.23.0 (SPSS) or Prism GraphPad 9.0. For most of the experiments, independent sample t-tests were used to calculate the *P* values. Survival curves were plotted using the Kaplan–Meier method and compared using log-rank tests. All statistical analyses were performed using two-tailed *P* values. Statistical details and methods used are indicated in the Figure legends, text or methods.

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