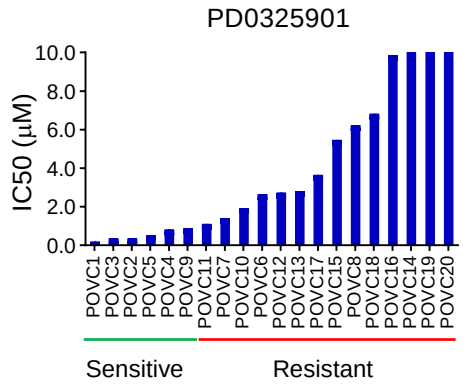
Supplemental Figure 1

A



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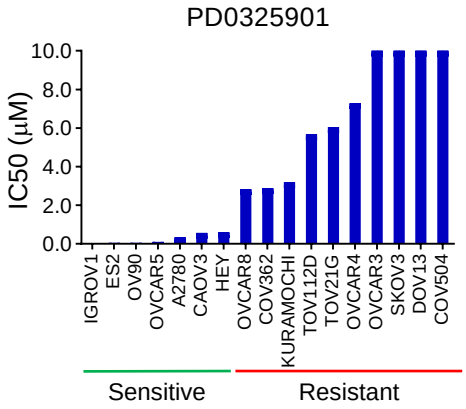

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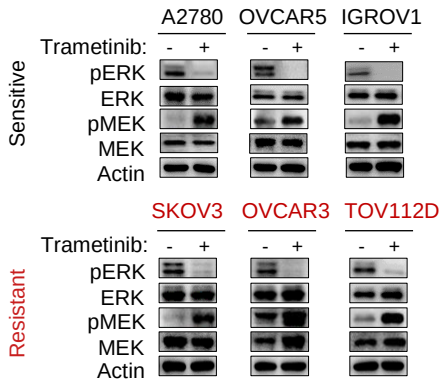

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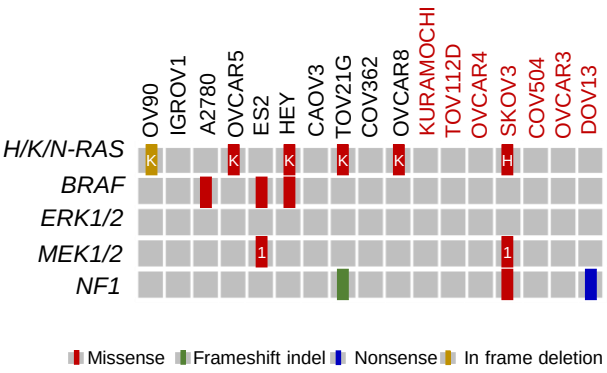
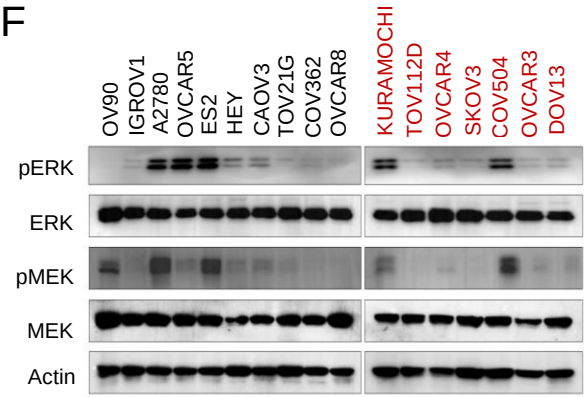


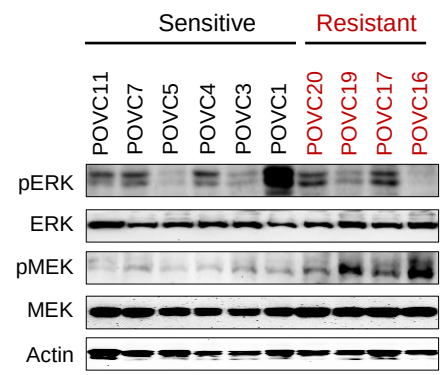
E

Genes	Sensitive (n=10)	Resistant (n=7)	P value
H/K/N-RAS			
mutation	5	1	0.3043
non-mutation	5	6	
BRAF			
mutation	3	0	0.2279
non-mutation	7	7	
ERK1/2			
mutation	0	0	1.00
non-mutation	10	7	
MEK1/2			
mutation	1	0	1.00
non-mutation	9	7	
NF1			
mutation	1	1	1.00
non-mutation	9	6	

F



G

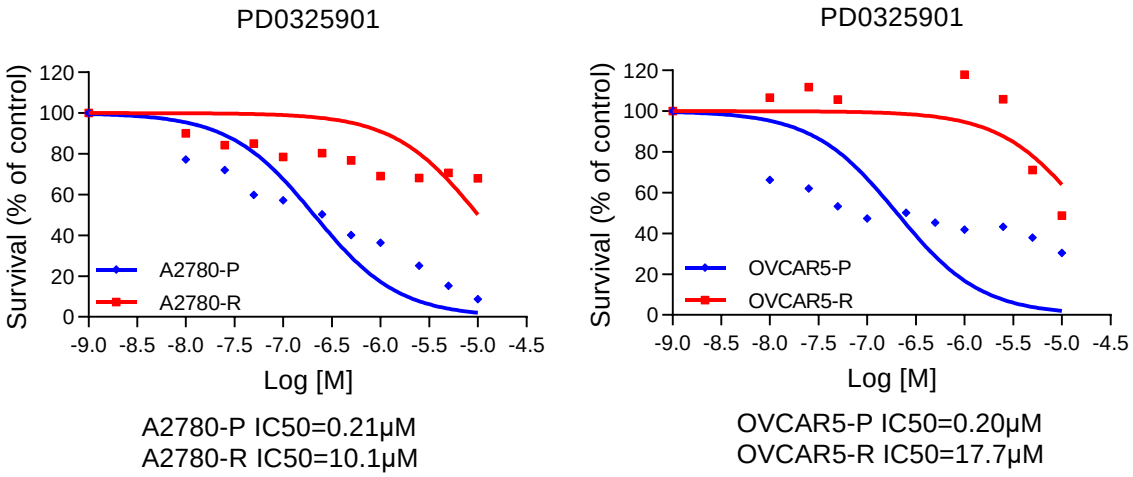


Supplemental Figure 1

Supplemental Figure 1. In vitro effect of MEK inhibitor in OV models. (**A-B**) In vitro sensitivity to PD0325901 in 20 patient-derived primary cells (**A**) and 17 commercial ovarian cell lines (**B**). The half maximal inhibitory concentration (IC50) values for PD0325901 represented on the y-axis. Data represent the mean of 3 biological replicates. The cut-off value of IC50 for sensitivity is 1.0 μM. (**C**) Immunoblot analysis of the indicated antibodies of protein lysates from different cell lines treated with 0.5 μM trametinib for 6 hr. (**D**) Sensitive (black) and resistant (red) commercial cell lines are in order of their IC50 of trametinib. Illustrated are mutation profiles *of H/K/N-RAS*, *RAF*, *MEK1/2*, *ERK1/2* and *NF1.* (**E**) Fisher exact test was used for the association between gene mutation (*H/K/N-RAS*, *RAF*, *MEK1/2*, *ERK1/2* and *NF1*) and trametinib IC50 in cell lines described in (**D**) was shown in the table. (**F-G**) Immunoblot analysis of indicated proteins in sensitive (black) and resistant (red) cells, (**F**) OV commercial cell lines; (**G**) OV patient-derived cells.

Supplemental Figure 2

A



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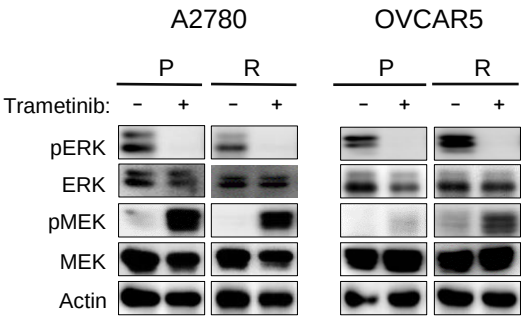
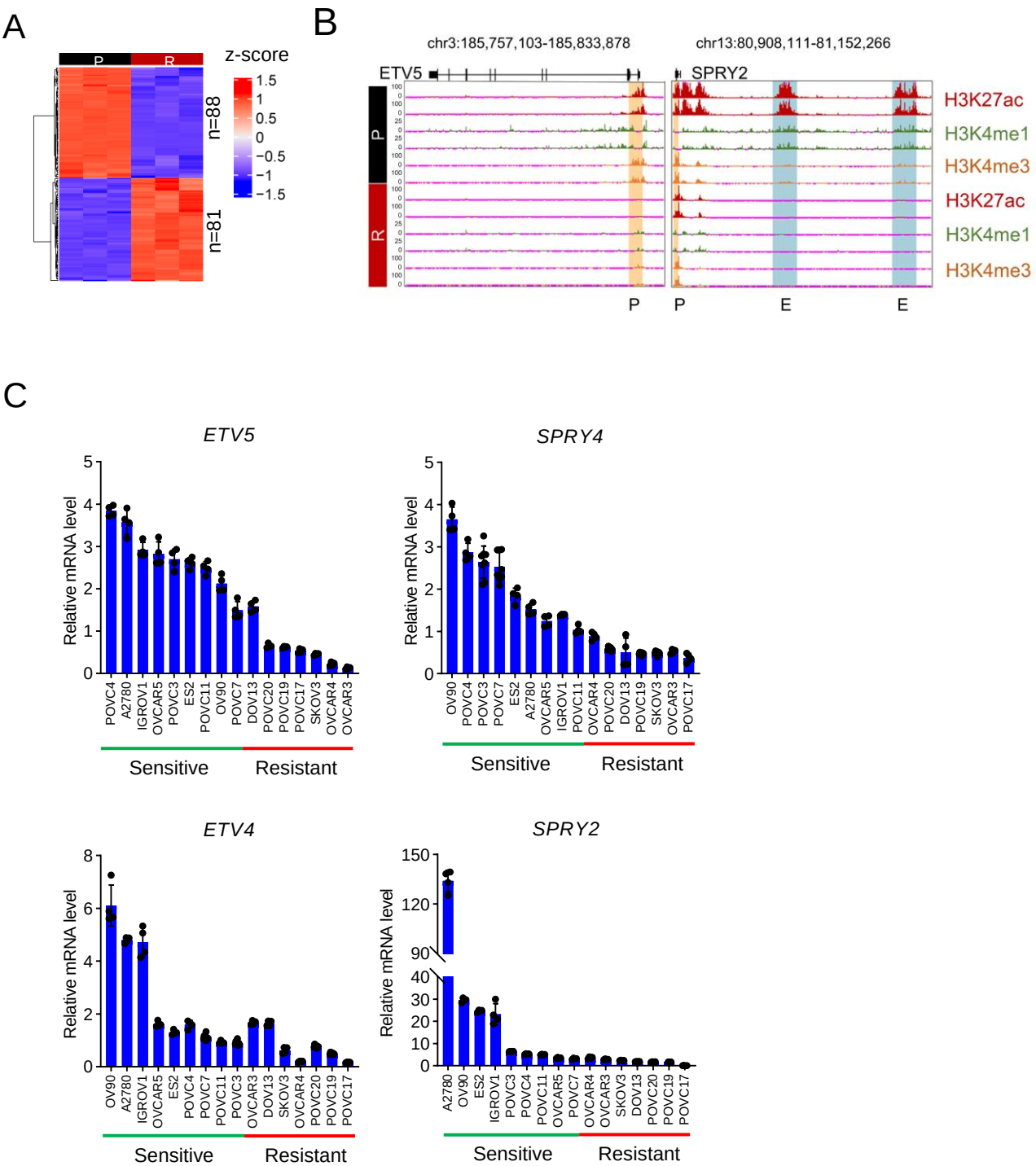


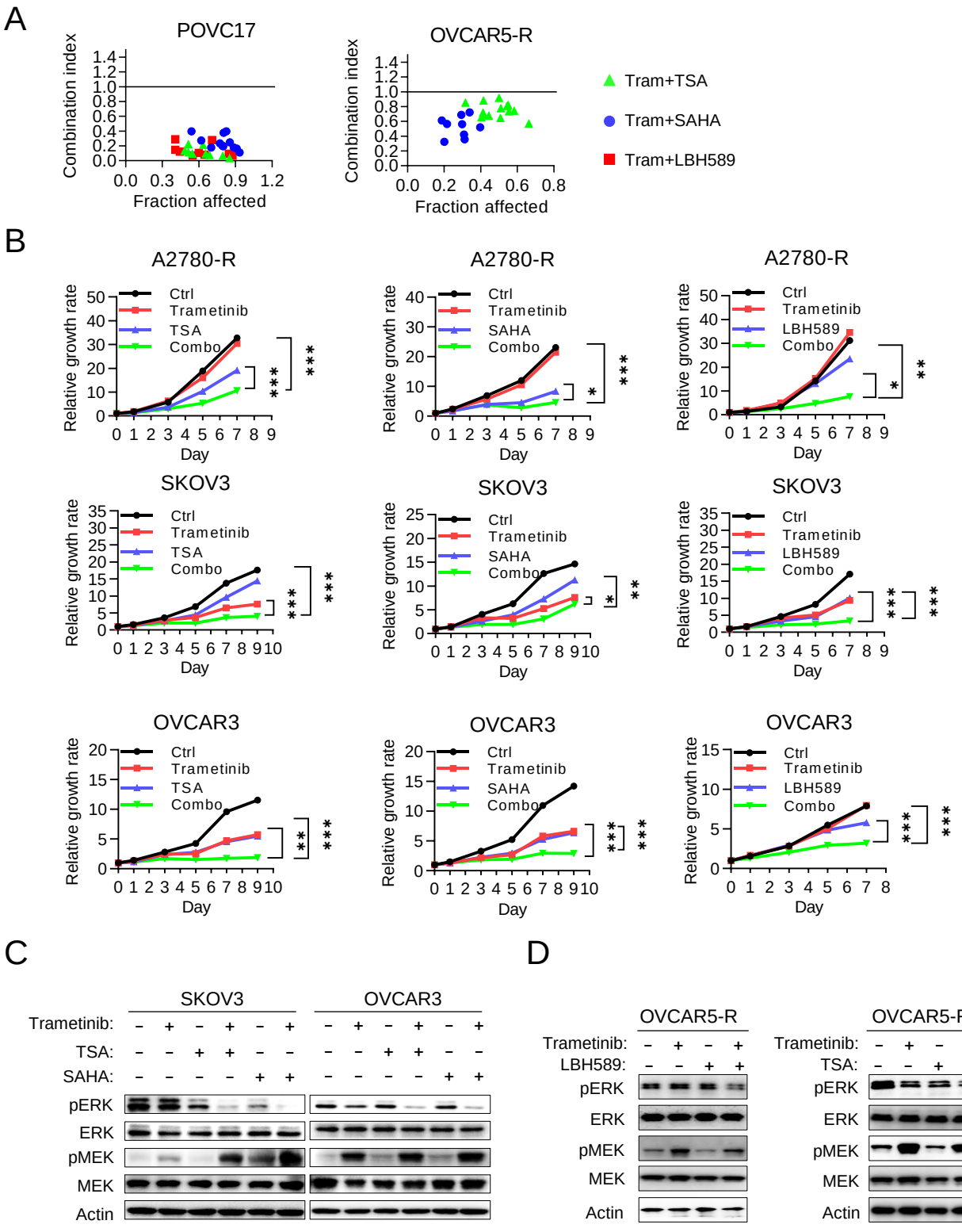
Supplemental Figure 2. Persistent ERK activation is associated with acquired resistance to MEK inhibitor in OV. (**A**) A2780-P, A2780-R, OVCAR5-P, and OVCAR5-R cells were treated with the escalating concentrations of PD0325901 for 96 hr. Viability was assessed using Cell-Titer Glo as described by the manufacturer. Data represent the mean of 3 biological replicates. (**B**) A2780-P, A2780-R, OVCAR5-P, and OVCAR5-R cells were treated with 0.5 μM trametinib for 6 hr. Cell extracts were assayed by immunoblotting to detect the indicated proteins.

Supplemental Figure 3



Supplemental Figure 3. Enhancer reprogramming accompanies acquired resistance to MEK inhibitors. (**A**) Heatmap of differentially expressed genes (DEGs) upon H3K27ac changes (by at least 50 CPM, comparing resistant and parental). DEGs are defined by the criteria: |log2 fold-change| ≥ 1 and adjusted p-value ≤ 0.05, RNA-seq was performed in biological triplicates. (**B**) ChIP-seq profiling showed the ChIP-seq signal (y-axis, reads per million [rpm]) for H3K27ac, H3K4me1 and H3K4me3 at genomic loci of *ETV5* and *SPRY2*. (**C**) Relative mRNA levels of *ETV5*, *SPRY4*, *ETV4*, and *SPRY2* in 9 sensitive and 7 resistant cells, including OV commercial cell lines and patient-derived cells. Results are represented as mean ± SD of four independent experiments.

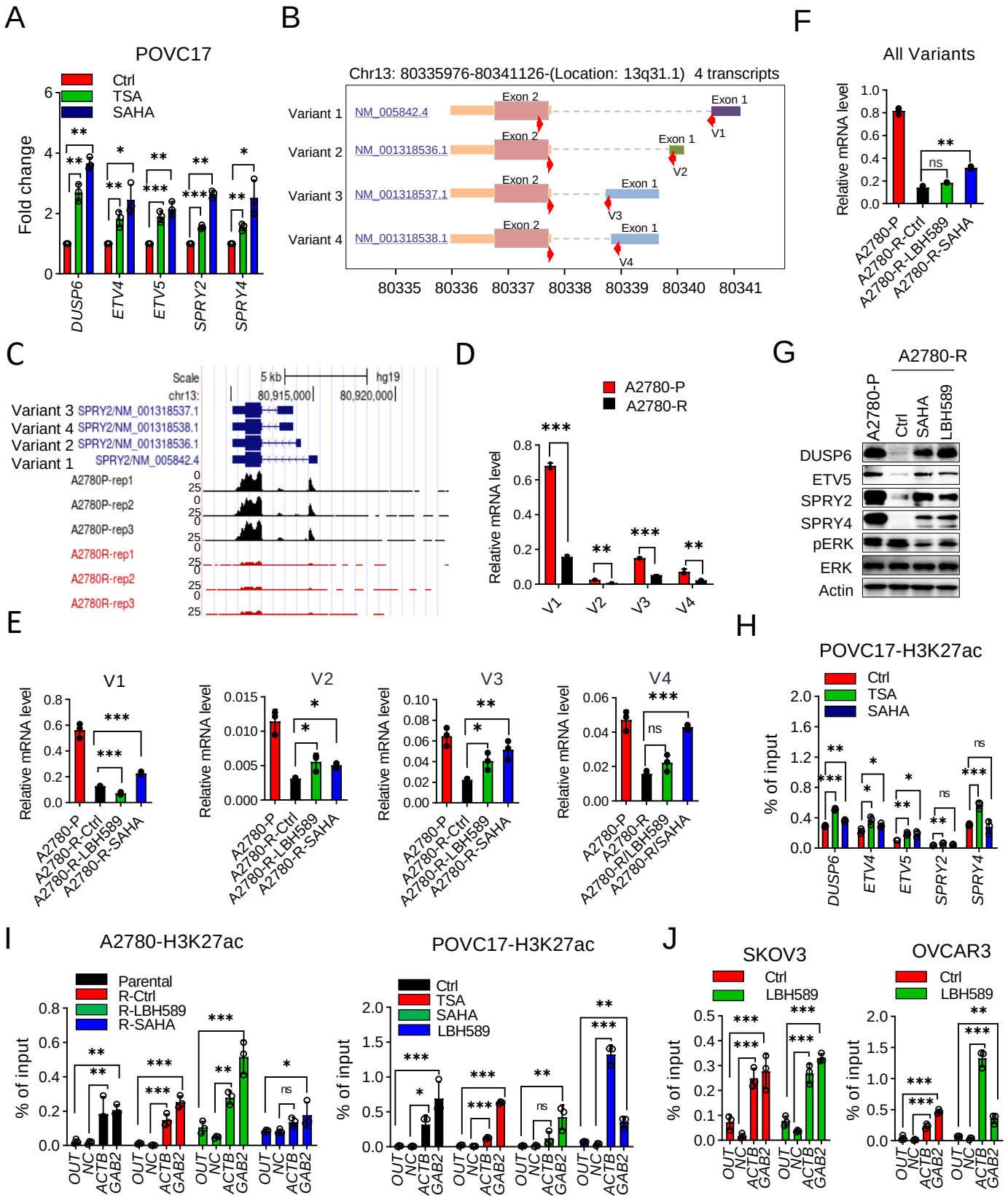
Supplemental Figure 4



Supplemental Figure 4

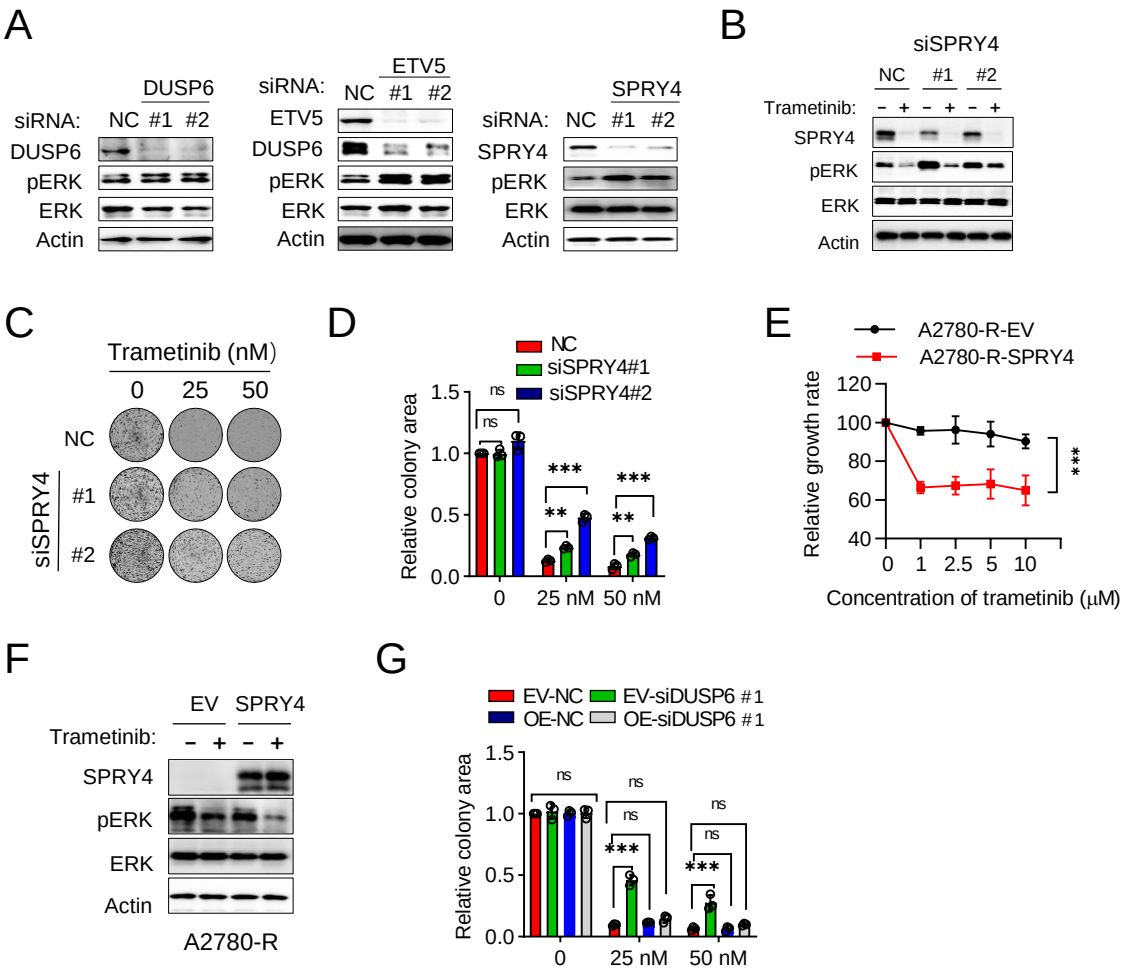
Supplemental Figure 4. HDACi inhibition sensitizers trametinib-resistant cells in vitro. (**A**) Combination index of MEK and HDAC inhibitors in patient-derived cells POVC17 (left) and acquired resistant cells OVCAR5-R (right). Combination index values were calculated using Calcusyn Software. Combination index > 1 was antagonism, combination index < 1 was defined as synergy. (**B**) Growth curves of A2780-R, SKOV3, and OVCAR3 treated with either vehicle, trametinib, HDACi or their combination. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ by 2-way ANOVA with Tukey post hoc test. (**C**) Immunoblot analysis for ERK and MEK activity for SKOV3 (left) and OVCAR3 (right) treated with either vehicle, 100 nM trametinib, HDACi (100 nM TSA or 1 μM SAHA), or their combination for 72 hr. (**D**) Immunoblot analysis of ERK and MEK activity in OVCAR5-R treated with either vehicle, 50 nM trametinib, HDACi (25 nM LBH589 or 25 nM TSA) or their combination for 48 hr.

Supplemental Figure 5



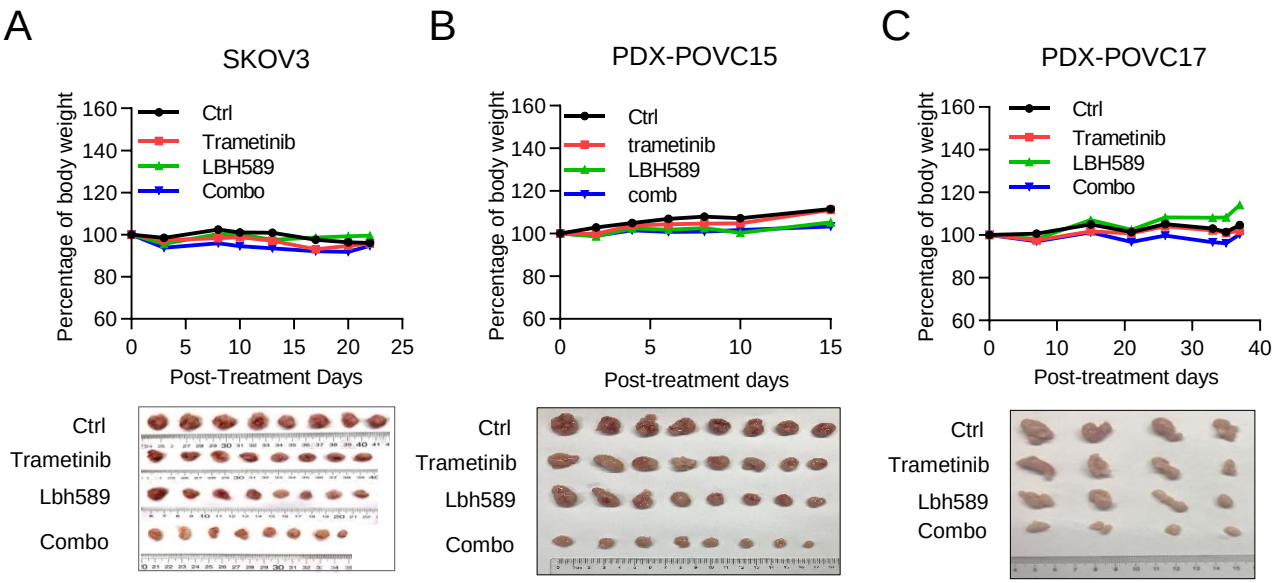
Supplemental Figure 5. HDAC inhibitors reactivate repressive enhancers in Ovarian cancer-resistant cells. qRT-PCR analysis (**A**) and ChIP-qPCR of H3K27ac binding (**H**) of MAPK negative regulators in patient-derived cells POVC17 treated with either vehicle, TSA (25 nM) or SAHA (1 μM) for 72 hr. (**B**) The schematic of transcript variants and primers designed in the human *SPRY2* gene. There are four transcript variants encoding the same protein in *SPRY2* gene. The accession numbers are NM_005842.3 (variant 1), NM_001318536.1 (variant 2), NM_001318537.1 (variant 3) and NM_001318538.1 (variant 4). All these SPRY2 transcript variants consist of two exons. *SPRY2* primers (named V1) only detect SPRY2 transcript 1. The additional 3 pairs of primers named V2, V3 or V4 specifically amplify SPRY2 transcript 2, 3 or 4, respectively. (**C**) RNA-seq profiles show the RNA-seq signal (y-axis, reads per million [rpm]) for different variants of *SPRY2* in A2780-P and A2780-R cells. (**D**) Relative mRNA levels of different variants of *SPRY2* in A2780-P and A2780-R cells. (**E**) qRT-PCR analysis of different variants of *SPRY2* in A2780-P and A2780-R cells treated with vehicle, SAHA (1 μM) or LBH589 (100 nM) for 24 hr. (**F**) qRT-PCR analysis using the All Variants primers which covered all variants of *SPRY2* in A2780-P and A2780-R cells treated with vehicle, SAHA (1 μM) or LBH589 (100 nM) for 24 hr. (**G**) Immunoblot analysis of indicated proteins in A2780-P cells and A2780-R cells treated with vehicle, SAHA (1 μM) or LBH589 (100 nM) for 24 hr. (**H, I**) ChIP-qPCR of H3K27Ac binding in OUT, NC (negative control) and ACTB, GAB2 (positive control) for the experiment described in (**Figure 5, C and D, and Supplemental Figure 5H**). (**A, D-F, H-J**) Results expressed as mean ± SD of three biological replicates. ns, not significant; *p < 0.05, **p < 0.01, ***p < 0.001; (**A, E, F, H-J**) 1-way ANOVA with Bonferroni's post hoc test; (**D**) unpaired Student's t-test.

Supplemental Figure 6



Supplemental Figure 6. Effects of gain- and loss-of-function of MAPK negative regulators on trametinib resistance. (**A**) Immunoblot analysis of indicated proteins in A2780-P cells transfected with either siNC, siDUSP6 (left), or siETV5 (medium) or siSPRY4 (right), respectively. (**B**) Immunoblot analysis of indicated proteins in A2780-P cells treated with trametinib after transfection with either siNC or siSPRY4. Representative images (**C**) and quantification (**D**) of colony formation assay in A2780-P cells treated with trametinib after transfection with either siNC or siSPRY4. (**E**) Cell viability assay of *SPRY4* re-expression in A2780-R cells on trametinib sensitivity. (**F**) Immunoblot analysis of indicated proteins in A2780-R cells with *SPRY4* re-expression and subsequently treated with vehicle or trametinib (25 nM 48 hr). (**G**) Quantification of colony formation assay described in (**Figure 5, J and K**). (**D, E, G**) Results expressed as mean ± SD of three biological replicates. ns, not significant; **p < 0.01, ***p < 0.001; (**D, G**) 1-way ANOVA with Bonferroni's post hoc test; (**E**) 2-way ANOVA with Bonferroni's post hoc test.

Supplemental Figure 7



Supplemental Figure 7. HDACi inhibition sensitizes trametinib-resistant cells in vivo. (**A-C**) Relative weight measurements of mice (upper) and the excised tumors at the termination day (lower) from the experiment described in (**Figure 6, A-C**), respectively.

Supplementary Table 1. Summary of the clinical and pathlogical characteristics for OV patient-derived cells

ID	Clinical Attributes		Pathlogical Characteristics				IC50	
	Age	Histopathlogical diagnosis	P53	PAX8	WT1	ki67	Trametinib	PD0325901
POVC1	37	HGSOC	-	+	+	NA	0.03982	0.1969
POVC2	60	HGSOC	+	+	+	10+	0.04906	0.3615
POVC3	40	HGSOC	70%+	+	+	30+	0.12	0.3531
POVC4	48	HGSOC	15%+	+	+	30+	0.1228	0.8215
POVC5	44	HGSOC	+	+	+	75+	0.1453	0.5254
POVC6	56	HGSOC	-	NA	partially+	NA	0.1517	2.648
POVC7	47	HGSOC	+	+/-	NA	NA	0.224	1.403
POVC8	60	HGSOC	NA	NA	NA	NA	0.2302	6.223
POVC9	57	HGSOC	NA	+	+	NA	0.3213	0.8891
POVC10	37	HGSOC	-	+	+	30+	0.5582	1.925
POVC11	45	HGSOC	+	+	+	15+	0.5886	1.113
POVC12	46	HGSOC	80%+	+	+	40-80%+	2.369	2.726
POVC13	46	HGSOC	90%+	+	+	10-20%+	3.127	2.809
POVC14	35	HGSOC	70%+	+	+	60+	6.491	11.27
POVC15	52	HGSOC	70%+	NA	+	60%+	6.55	5.469
POVC16	59	HGSOC	5%+	partially+	partially+	30+	8.788	9.886
POVC17	52	HGSOC	-	+	+	40%+	9.91	3.653
POVC18	82	HGSOC	+	+	+	NA	9.986	6.83
POVC19	56	HGSOC	+	+	+	30+	10	28.46
POVC20	44	HGSOC	70%+	diffuse+	+	70+	10.51	100

NA:not avaliable

Supplementary Table 2： Epigenetic Drug screen in A2780-R

NO.	Drugs	Target	Single Survival rate(%)	Combination Survival rate (%)	S/C score	ln(S/C score)
1	Trichostatin A (TSA)	HDAC	0.9230	0.0978	9.4380	2.2447
2	JIB-04	Histone Demethylase	9.7453	1.9674	4.9533	1.6001
3	Panobinostat (LBH589)	HDAC	3.3087	1.2800	2.5850	0.9497
4	Pracinostat (SB939)	HDAC	30.6843	13.7936	2.2245	0.7995
5	(+)-JQ1	Epigenetic Reader Domain	42.9168	22.6734	1.8928	0.6381
6	Belinostat (PXD101)	HDAC	36.4702	19.6522	1.8558	0.6183
7	OTX015	Epigenetic Reader Domain	49.3701	29.0618	1.6988	0.5299
8	PFI-1 (PF-6405761)	Epigenetic Reader Domain	107.1497	65.5921	1.6336	0.4908
9	Entinostat (MS-275)	HDAC	67.3340	41.7697	1.6120	0.4775
10	OF-1	Epigenetic Reader Domain	125.6962	78.4739	1.6018	0.4711
11	Vorinostat (SAHA, MK0683)	Autophagy,HDAC	85.1040	53.6983	1.5849	0.4605
12	GSK591	Histone Methyltransferase	46.4104	30.8970	1.5021	0.4069
13	GSK2879552 2HCl	Histone Demethylase	108.3068	72.8011	1.4877	0.3972

14	MS023	Histone Methyltransferase	81.8492	55.8344	1.4659	0.3825
15	UNC0631	Histone Methyltransferase	106.1669	72.7207	1.4599	0.3784
16	I-BRD9	Epigenetic Reader Domain	130.5817	90.2462	1.4469	0.3695
17	GSK J4 HCl	Histone Demethylase	114.5674	80.5922	1.4216	0.3518
18	Resveratrol	Autophagy,Sirtuin	79.9374	56.3653	1.4182	0.3494
19	CPI-360	Histone Methyltransferase	132.1917	94.1165	1.4046	0.3397
20	EI1	Histone Methyltransferase	134.8450	96.8045	1.3930	0.3314
21	Resminostat	HDAC	116.9897	84.7045	1.3812	0.3229
22	Azacitidine	DNA Methyltransferase	76.8131	55.7507	1.3778	0.3205
23	Anacardic Acid	Histone Acetyltransferase	126.3835	93.9094	1.3458	0.2970
24	Pinometostat (EPZ5676)	Histone Methyltransferase	128.1045	95.6640	1.3391	0.2920
25	IOX1	Histone Demethylase	136.9123	102.4457	1.3364	0.2900
26	MM-102	Histone Methyltransferase	130.9758	98.3044	1.3323	0.2869
27	3-deazaneplanocin A (DZNeP) HCl	Histone Methyltransferase	44.2137	33.3853	1.3243	0.2809
28	SGC-CBP30	Epigenetic Reader Domain	105.1739	79.4922	1.3231	0.2800
29	Sirtinol	Sirtuin	121.7589	92.8411	1.3115	0.2712

30	RVX-208	Epigenetic Reader Domain	115.3171	88.0289	1.3100	0.2700
31	A-366	Histone Methyltransferase	113.6294	87.6080	1.2970	0.2601
32	HLCL-61 HCL	Histone Methyltransferase	118.3686	91.4414	1.2945	0.2581
33	Entacapone	Histone Methyltransferase	114.6231	89.3578	1.2827	0.2490
34	PF-CBP1 HCl	Epigenetic Reader Domain	131.3057	102.9337	1.2756	0.2434
35	Selisistat (EX 527)	Sirtuin	122.0661	96.2081	1.2688	0.2380
36	SGC 0946	Histone Methyltransferase	124.2929	101.3269	1.2267	0.2043
37	MS436	Epigenetic Reader Domain	131.4084	107.2657	1.2251	0.2030
38	EPZ015666(GSK 3235025)	Histone Methyltransferase	63.6935	52.5473	1.2121	0.1924
39	OG-L002	Histone Demethylase	119.7010	99.1064	1.2078	0.1888
40	SP2509	Histone Demethylase	108.1256	89.7539	1.2047	0.1862
41	GSK1324726A (I-BET726)	Epigenetic Reader Domain	34.2109	28.6211	1.1953	0.1784
42	C646	Histone Acetyltransferase	109.6700	93.2274	1.1764	0.1624
43	Tazemetostat (EPZ-6438)	Histone Methyltransferase	108.2600	92.4028	1.1716	0.1584
44	UNC0379	Histone Methyltransferase	124.0722	107.2664	1.1567	0.1455
45	CPI-169	Histone Methyltransferase	113.6439	99.0954	1.1468	0.1370

46	BRD4770	Histone Methyltransferase	104.3161	91.3310	1.1422	0.1329
47	I-BET-762	Epigenetic Reader Domain	98.5199	86.4777	1.1393	0.1304
48	EPZ011989	Histone Methyltransferase	110.9441	98.2842	1.1288	0.1212
49	GSK503	Histone Methyltransferase	111.6068	100.5174	1.1103	0.1047
50	GSK J1	Histone Demethylase	114.5153	103.2326	1.1093	0.1037
51	MI-2 (Menin-MLL Inhibitor)	Histone Methyltransferase	106.1766	95.7684	1.1087	0.1032
52	Ricolinostat (ACY-1215)	HDAC	123.7827	112.4686	1.1006	0.0959
53	PFI-3	Epigenetic Reader Domain	109.6727	99.7899	1.0990	0.0944
54	CUDC-101	EGFR,HDAC,HER2	108.1309	98.6469	1.0961	0.0918
55	ORY-1001 (RG-6016) 2HCl	Histone Demethylase	97.3309	89.8649	1.0831	0.0798
56	Decitabine	DNA Methyltransferase	69.4644	64.3326	1.0798	0.0767
57	BIX 01294	Histone Methyltransferase	96.3844	89.4609	1.0774	0.0745
58	MG149	Histone Acetyltransferase	99.5402	92.9287	1.0711	0.0687
59	EPZ004777	Histone Methyltransferase	124.2779	116.1957	1.0696	0.0672
60	Zebularine	DNA Methyltransferase	88.9890	84.0514	1.0587	0.0571
61	SGC707	Histone Methyltransferase	109.1321	103.8989	1.0504	0.0491

62	GSK-LSD1 2HCl	Histone Demethylase	112.4758	111.1408	1.0120	0.0119
63	ML324	Histone Demethylase	105.4068	104.7124	1.0066	0.0066
64	SRT1720 HCl	Sirtuin	103.9234	103.2587	1.0064	0.0064
65	Tranylcypromine (2-PCPA) HCl	MAO	93.4334	97.8887	0.9545	-0.0466
66	PFI-2 HCl	Histone Methyltransferase	102.0973	110.9315	0.9204	-0.0830
67	CPI-203	Epigenetic Reader Domain	26.1302	29.1574	0.8962	-0.1096

Supplementary Table 2: Epigenetic Drug screen in SKOV3

NO.	Drugs	Target	Single Survival rate(%)	Combination Survival rate (%)	S/C score	ln(S/C score)
1	Trichostatin A (TSA)	HDAC	20.5482	7.9253	2.5927	0.9527
2	Belinostat (PXD101)	HDAC	117.0505	68.8072	1.7011	0.5313
3	Panobinostat (LBH589)	HDAC	62.6669	37.0716	1.6904	0.5250
4	SGC707	Histone Methyltransferase	108.1856	67.1334	1.6115	0.4772
5	Entinostat (MS-275)	HDAC	105.7573	65.8123	1.6070	0.4743
6	Pracinostat (SB939)	HDAC	115.4338	72.6133	1.5897	0.4635
7	Decitabine	DNA Methyltransferase	109.6138	69.3466	1.5807	0.4578
8	MG149	Histone Acetyltransferase	111.0907	72.0101	1.5427	0.4335
9	MS023	Histone Methyltransferase	100.5443	65.2291	1.5414	0.4327
10	SRT1720 HCl	Sirtuin	112.3432	73.4215	1.5301	0.4253
11	EPZ011989	Histone Methyltransferase	108.2717	71.0259	1.5244	0.4216
12	Sirtinol	Sirtuin	107.1955	71.5905	1.4973	0.4037
13	Selisistat (EX 527)	Sirtuin	108.4862	72.8909	1.4883	0.3977
14	I-BRD9	Epigenetic Reader Domain	115.4864	77.8278	1.4839	0.3947

15	EI1	Histone Methyltransferase	108.1101	73.4723	1.4714	0.3862
16	C646	Histone Acetyltransferase	109.3530	74.3815	1.4702	0.3854
17	Vorinostat (SAHA, MK0683)	HDAC	108.3341	73.7851	1.4682	0.3841
18	Entacapone	Histone Methyltransferase	109.2628	74.4822	1.4670	0.3832
19	GSK503	Histone Methyltransferase	101.6588	70.5007	1.4420	0.3660
20	Azacitidine	DNA Methyltransferase	97.9930	67.9717	1.4417	0.3658
21	GSK591	Histone Methyltransferase	97.9775	68.2039	1.4365	0.3622
22	ORY-1001 (RG-6016) 2HCl	Histone Demethylase	108.2746	75.5895	1.4324	0.3594
23	GSK1324726A (I-BET726)	Epigenetic Reader Domain	59.6592	41.6556	1.4322	0.3592
24	I-BET-762	Epigenetic Reader Domain	92.2519	64.5080	1.4301	0.3577
25	Ricolinostat (ACY-1215)	HDAC	114.3610	80.0679	1.4283	0.3565
26	PFI-1 (PF-6405761)	Epigenetic Reader Domain	86.1297	60.4274	1.4253	0.3544
27	EPZ015666(GSK3235025)	Histone Methyltransferase	105.3885	74.8088	1.4088	0.3427
28	Zebularine	DNA Methyltransferase	106.4758	75.6744	1.4070	0.3415
29	UNC0379	Histone Methyltransferase	101.1044	71.9395	1.4054	0.3403
30	OTX015	Epigenetic Reader Domain	69.7096	49.6353	1.4044	0.3396

31	Tranylcypromine (2-PCPA) HCl	MAO	96.4289	68.7438	1.4027	0.3384
32	SGC-CBP30	Epigenetic Reader Domain	86.8187	62.1441	1.3971	0.3344
33	RVX-208	Epigenetic Reader Domain	104.4566	75.0283	1.3922	0.3309
34	MM-102	Histone Methyltransferase	101.9356	73.8881	1.3796	0.3218
35	ML324	Histone Demethylase	106.9088	77.8146	1.3739	0.3176
36	OF-1	Epigenetic Reader Domain	99.4895	72.9435	1.3639	0.3104
37	PF-CBP1 HCl	Epigenetic Reader Domain	109.1044	80.1819	1.3607	0.3080
38	Pinometostat (EPZ5676)	Histone Methyltransferase	110.5526	81.3915	1.3583	0.3062
39	Tazemetostat (EPZ-6438)	Histone Methyltransferase	107.9590	79.7153	1.3543	0.3033
40	CPI-203	Epigenetic Reader Domain	51.7473	38.2144	1.3541	0.3032
41	PFI-3	Epigenetic Reader Domain	106.0540	78.5358	1.3504	0.3004
42	CUDC-101	EGFR,HDAC,HER2	77.2812	57.3037	1.3486	0.2991
43	GSK J4 HCl	Histone Demethylase	108.8677	80.8863	1.3459	0.2971
44	BRD4770	Histone Methyltransferase	113.5446	84.5996	1.3421	0.2943
45	CPI-360	Histone Methyltransferase	102.8241	77.0596	1.3343	0.2884
46	OG-L002	Histone Demethylase	105.4126	79.0021	1.3343	0.2884

47	A-366	Histone Methyltransferase	110.3449	83.0747	1.3283	0.2839
48	JIB-04	Histone Demethylase	74.4364	56.6495	1.3140	0.2731
49	Resminostat	HDAC	95.0351	72.4838	1.3111	0.2709
50	(+)-JQ1	Epigenetic Reader Domain	54.2927	41.7098	1.3017	0.2637
51	Resveratrol	Autophagy,Sirtuin	105.0395	81.3833	1.2907	0.2552
52	GSK J1	Histone Demethylase	99.4753	77.5943	1.2820	0.2484
53	UNC0631	Histone Methyltransferase	104.7027	82.0249	1.2765	0.2441
54	CPI-169	Histone Methyltransferase	107.9718	84.6150	1.2760	0.2438
55	SGC 0946	Histone Methyltransferase	110.2350	86.5344	1.2739	0.2421
56	IOX1	Histone Demethylase	103.4030	81.7943	1.2642	0.2344
57	MI-2 (Menin-MLL Inhibitor)	Histone Methyltransferase	101.5644	80.6548	1.2592	0.2305
58	Anacardic Acid	Histone Acetyltransferase	96.3488	76.9819	1.2516	0.2244
59	PFI-2 HCl	Histone Methyltransferase	97.2941	79.0216	1.2312	0.2080
60	MS436	Epigenetic Reader Domain	101.0908	82.3187	1.2280	0.2054
61	EPZ004777	Histone Methyltransferase	101.9790	83.5759	1.2202	0.1990
62	SP2509	Histone Demethylase	37.5530	30.8832	1.2160	0.1955

63	BIX 01294	Histone Methyltransferase	108.5704	92.1021	1.1788	0.1645
64	GSK-LSD1 2HCl	Histone Demethylase	104.1881	88.7964	1.1733	0.1599
65	GSK2879552 2HCl	Histone Demethylase	99.8545	86.1814	1.1587	0.1473
66	HLCL-61 HCL	Histone Methyltransferase	90.4383	79.9542	1.1311	0.1232
67	3-deazaneplanocin A (DZNeP) HCl	Histone Methyltransferase	66.4298	65.7871	1.0098	0.0097

Supplementary Table 3 qRT-PCR primer, CHIP-qPCR primer, and siRNA sequence

1.qRT-PCR primer		
Genes		Oligonucleotide (5'–3')
DUSP6	Forward	GTTCTACCTGGAAGATGAA
	Reverse	ATAAGGTAAGCCACAGTC
ETV4	Forward	TGGAAATCAGGAACAAACTGC
	Reverse	GCCCCTCGACTCTGAAGAT
ETV5	Forward	GGATCTCAGTCAACTTCAAG
	Reverse	AAGCACCAGGTTATCAGA
SPRY2-V1	Forward	CATTCGCTCATCTGCCAGGA
	Reverse	CACATCTGAACTCCGTGATCG
SPRY2-V2	Forward	CTCTCTTCCGTTCTTCGTGG
	Reverse	TCACTCCAGCAGGCTTAGAA
SPRY2-V3	Forward	CGTTTGTCACCTGCCTTGTT
	Reverse	GTCACTCCAGCAGGCTTAGA
SPRY2-V4	Forward	CAGTCCGCCTGGAGAAACTC
	Reverse	GAAGTGTGGTCACTCCAGCA
SPRY2-All variants	Forward	CCTACTGTCGTCCCAAGACCT
	Reverse	GGGGCTCGTGCAGAAGAAT
SPRY4	Forward	CTCCTCAAAGGCCCCTAG
	Reverse	GGTTGTCTATGTAGTCATTCTC
18S	Forward	GTAACCCGTTGAACCCCATT
	Reverse	CCATCCAATCGGTAGTAGCG

2.CHIP-qPCR primer		
Genes		Oligonucleotide (5'–3')
DUSP6	Forward	CTTTAGTGACCGATGAGGTGTT
	Reverse	TTCTGCACAACCAGACGTT
ETV4	Forward	CGGTTTGTCTCTCTTGCTCTT
	Reverse	CCCGCTTCTCGCAGAAAT
ETV5	Forward	TTCTGTAGTCGAGGTGAGACA
	Reverse	CCCGTTTCGGAGGGATTTAG
SPRY2	Forward	TTACAAGTATCCGCCACCAAG
	Reverse	TTGAGGTCAGGAGTTCGAGA
SPRY4	Forward	GGTGAGGATTGGTGAGTGAAT
	Reverse	CTGGCTGAGTTGCCAGAAT
NC	Forward	CGGTATGGAGCCCTGAAGACT
	Reverse	AGGTGAGGGAGGTGGCTTAGA
OUT	Forward	GAGCAGCTCCTGGATCACACT
	Reverse	GCCAGTTAACTCTGGAAGCATGT
ACTB	Forward	AAGCCGGCCTTGCACAT
	Reverse	GCTATTCTCGCAGCTCACCAT
GAB2	Forward	CTCGGTCGTCGATCGATTTT
	Reverse	GAACCTGACCCGCAGAATGT

3.siRNA sequence	
siRNAs	Oligonucleotide （5'-3'）
NC	UUCUCCGAACGUGUCACGUTT
siDUSP6#1	CGGACACUAUUAUCACUAATT
siDUSP6#2	CCGGCAUCAAGUACAUCUUGAATT
siETV5#1	CAGGGAAAUCUCGAUCUGATT
siETV5#2	GCUCUCUCCGCUAUUACUATT
siSPRY4#1	GACCAGCCAUGUGGAGAAUdTdT
siSPRY4#2	UCAACUAUGGCACGUGCAUdTdT