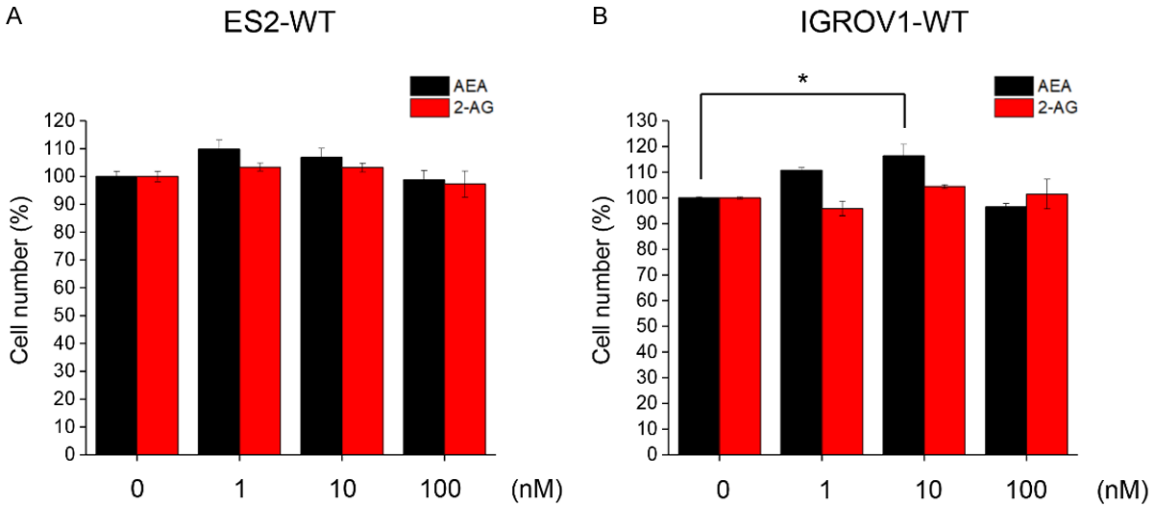
Supplementary Table 1. List of antibodies

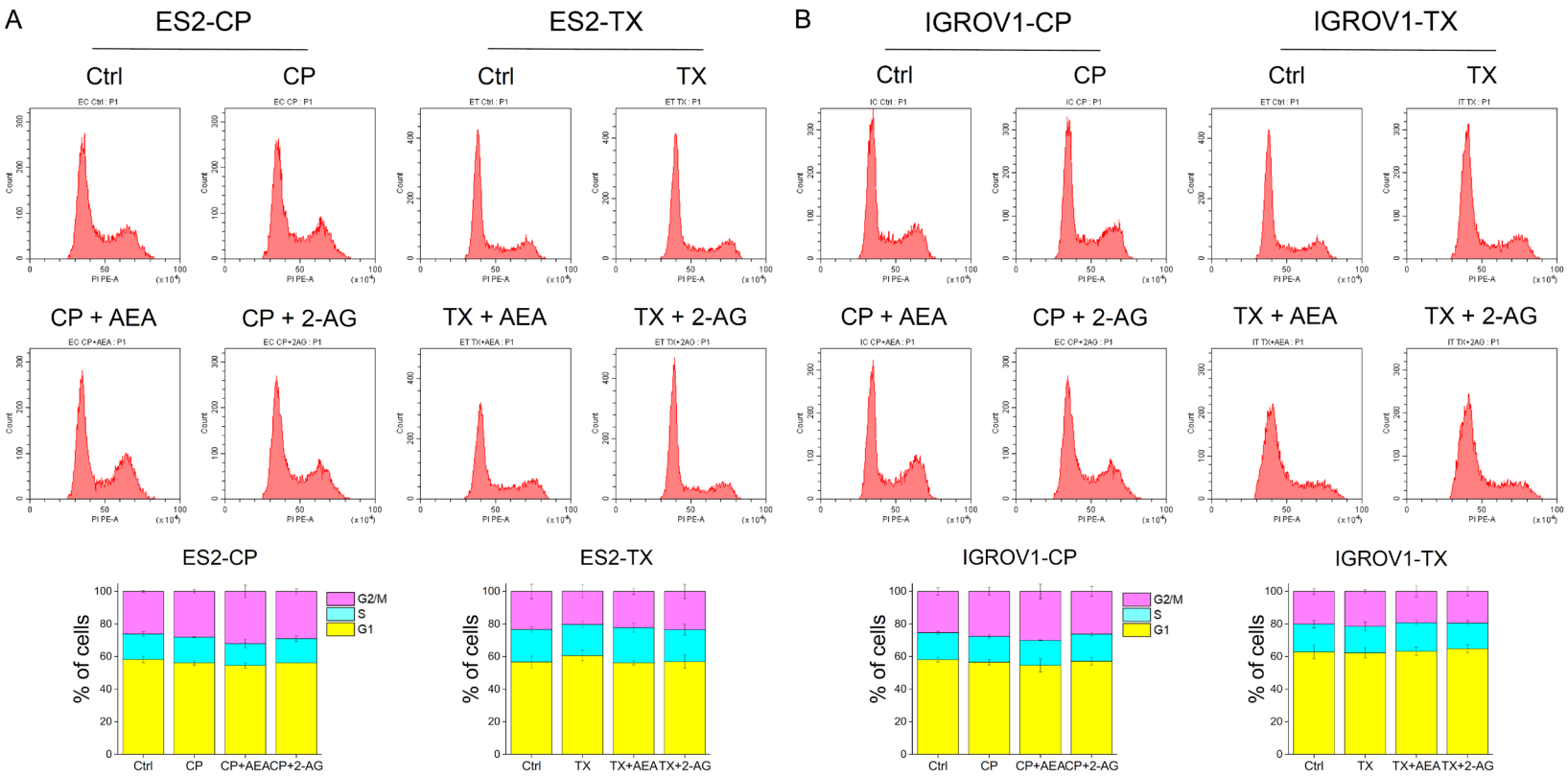
Antibody	Manufacturer	Catalog No.
CB1	Santa Cruaz	#sc-293419
CB2	Cayman	#101550
Bip/Grp78	Enzo Life Sciences	#ADI-SPA-826
CHOP	Cell Signaling Technology	#2895
ATF6α	Santa Cruz	#sc-166659
IRE1α	Abcam	#ab3707
Phospho-IRE1α	Abcam	#ab48187
eIF2α	Cell Signaling Technology	#9722
Phospho-eIF2α	Cell Signaling Technology	#9721s
LC3	Origene	#TA301542
β-actin	Sigma	#A2066
GAPDH	CROYEZ	#co6001

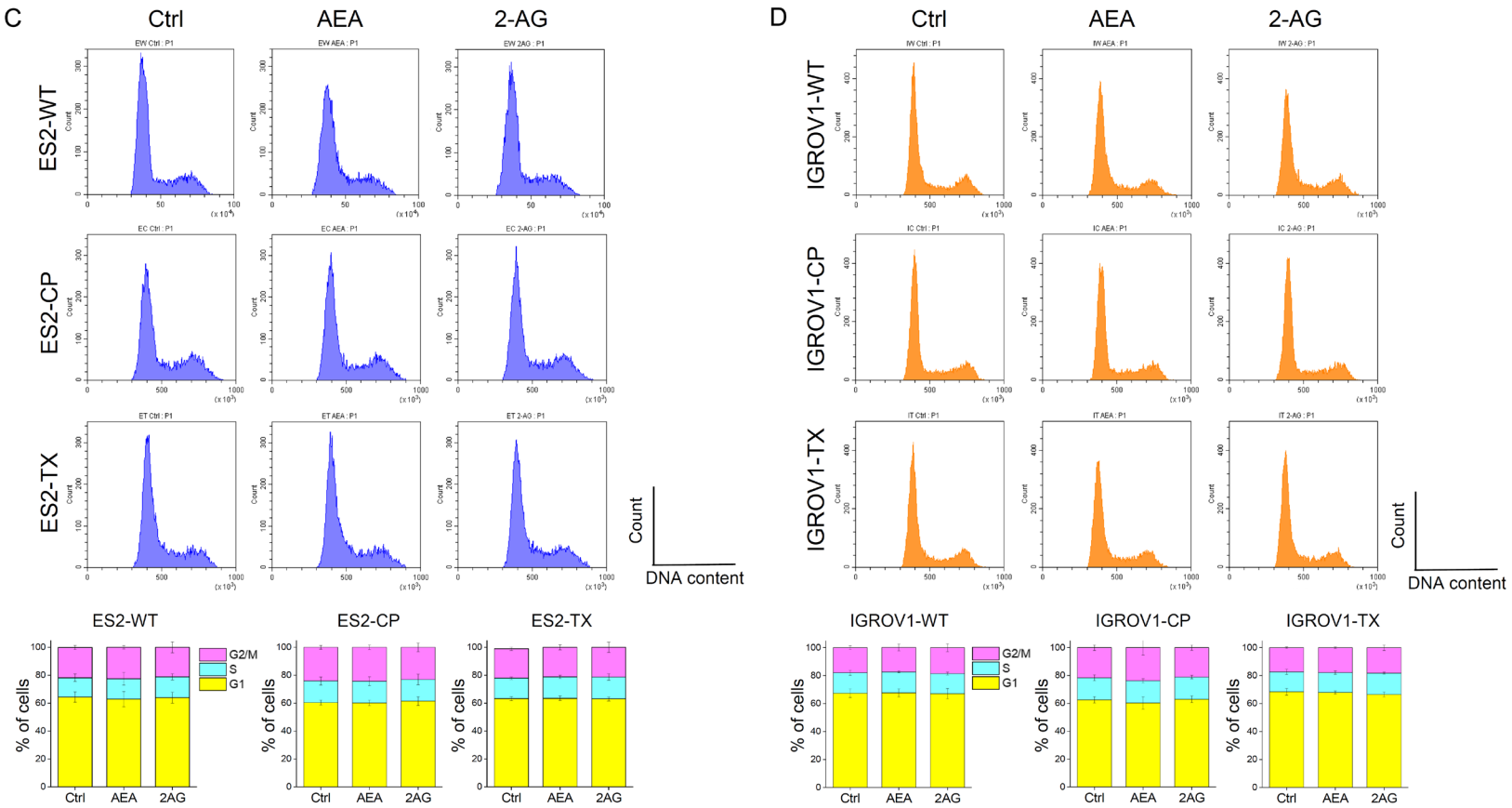
Supplementary Table 2. List of primers

Primer	Sequences (5'→3')	Manufacturer	Catalog No.	Citation
CNR1-Forward	CTGTTCCTCACAGCCATCGACA	Origene	#HP227608	
CNR1-Reverse	TGGCTATGGTCCACATCAGGCA	Origene	#HP227608	
CNR2-Forward	TATGGGCATGTTCTCTGGAA			[30]
CNR2-Reverse	GAGGAGCACAGCCAACACTA			[30]
GAPDH-Forward	GTCTCCTCTGACTTCAACAGCG	Origene	#HP205798	
GAPDH-Reverse	ACCACCCTGTTGCTGTAGCCAA	Origene	#HP205798	

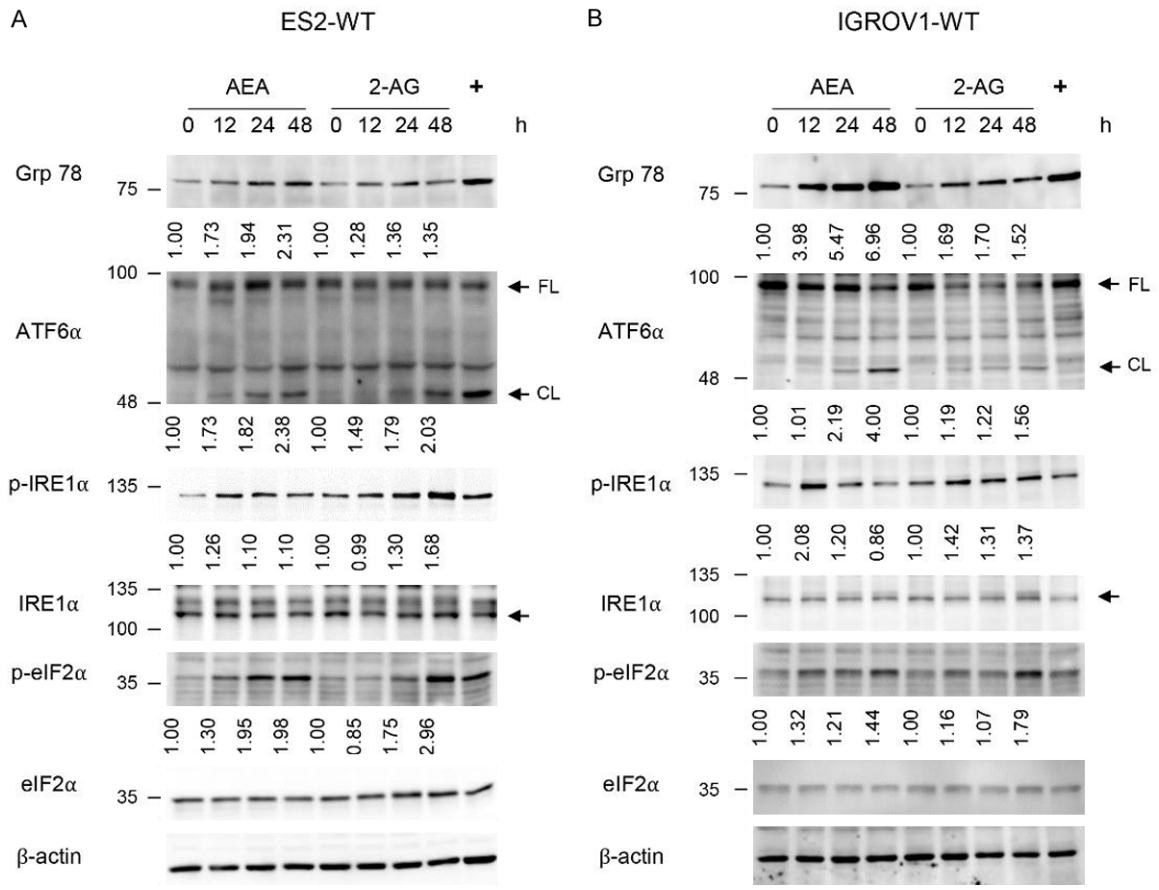


Supplementary Figure 1. Low concentration of endocannabinoid slightly promotes cancer cell proliferation. A, B. Both non-chemoresistant ES2 and IGROV1 cell lines were treated with 0-100 nM AEA or 2-AG for 48 h. The experiments were repeated for three times. Bars represent mean ± SEM. *p<0.05 by one-way ANOVA.

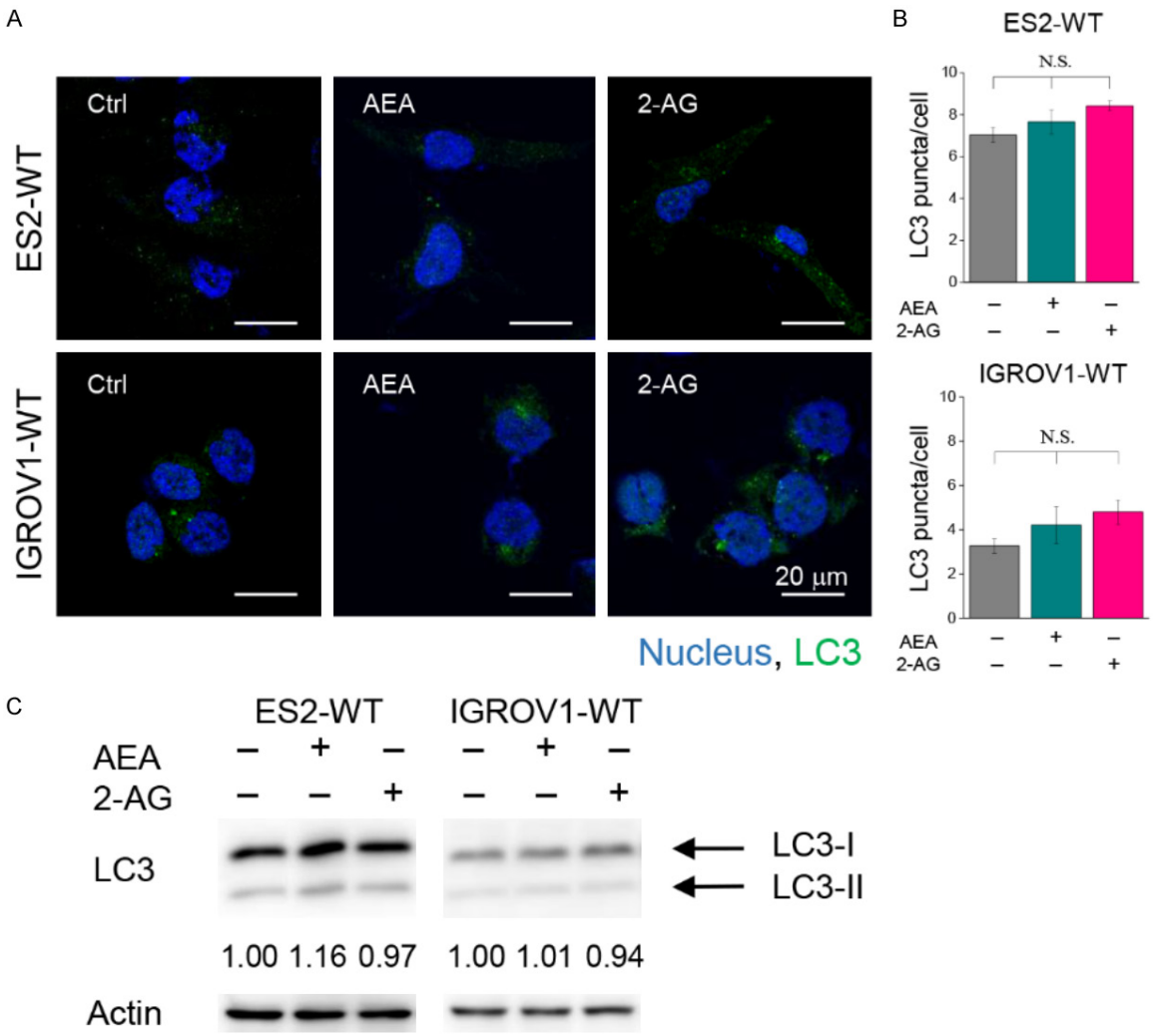

A
ES2-CP
ES2-TX
B
IGROV1-CP
IGROV1-TX
Ctrl
CP
TX
CP + AEA
CP + 2-AG
TX + AEA
TX + 2-AG
Count
PI PE-A
% of cells
G2/M
S
G1
Ctrl
CP
CP+AEA
CP+2-AG
TX
TX+AEA
TX+2-AG



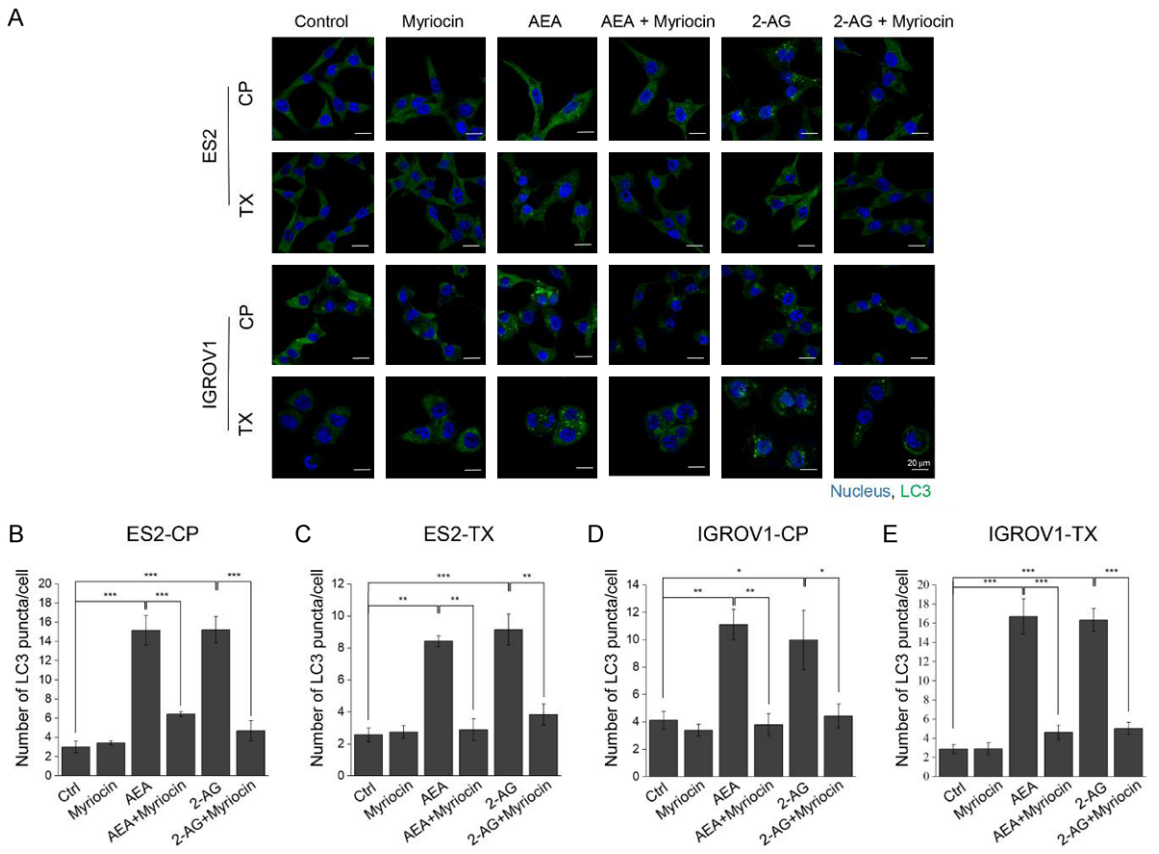
Supplementary Figure 2. Combined treatments or endocannabinoids alone do not arrest cell cycle in chemoresistant cancer cells. A, B. Upper panel: Representative images of cell cycle was shown. Cell cycle was examined by flow cytometry after 1 μM cisplatin, 0.01 μg/mL (for ES2-TX) or 0.1 μg/mL (for IGROV1-TX) paclitaxel and IC_{30} of AEA and 2-AG treatments. Cells were incubated with drugs for 24 h. Lower panel: The percentage of cells in each cell cycle phase (G1, S and G2/M phases) was analyzed from three independent experiments. The bars represent mean ± SEM. C, D. Upper panel: 50 μM AEA and-2-AG were treated to ES2 and IGROV1 cell lines for 24 h. Representative images from flow cytometry were shown. Lower panel: Quantification of the percentage of cells in each cell cycle was analyzed from three independent experiments. The bars represent mean ± SEM.



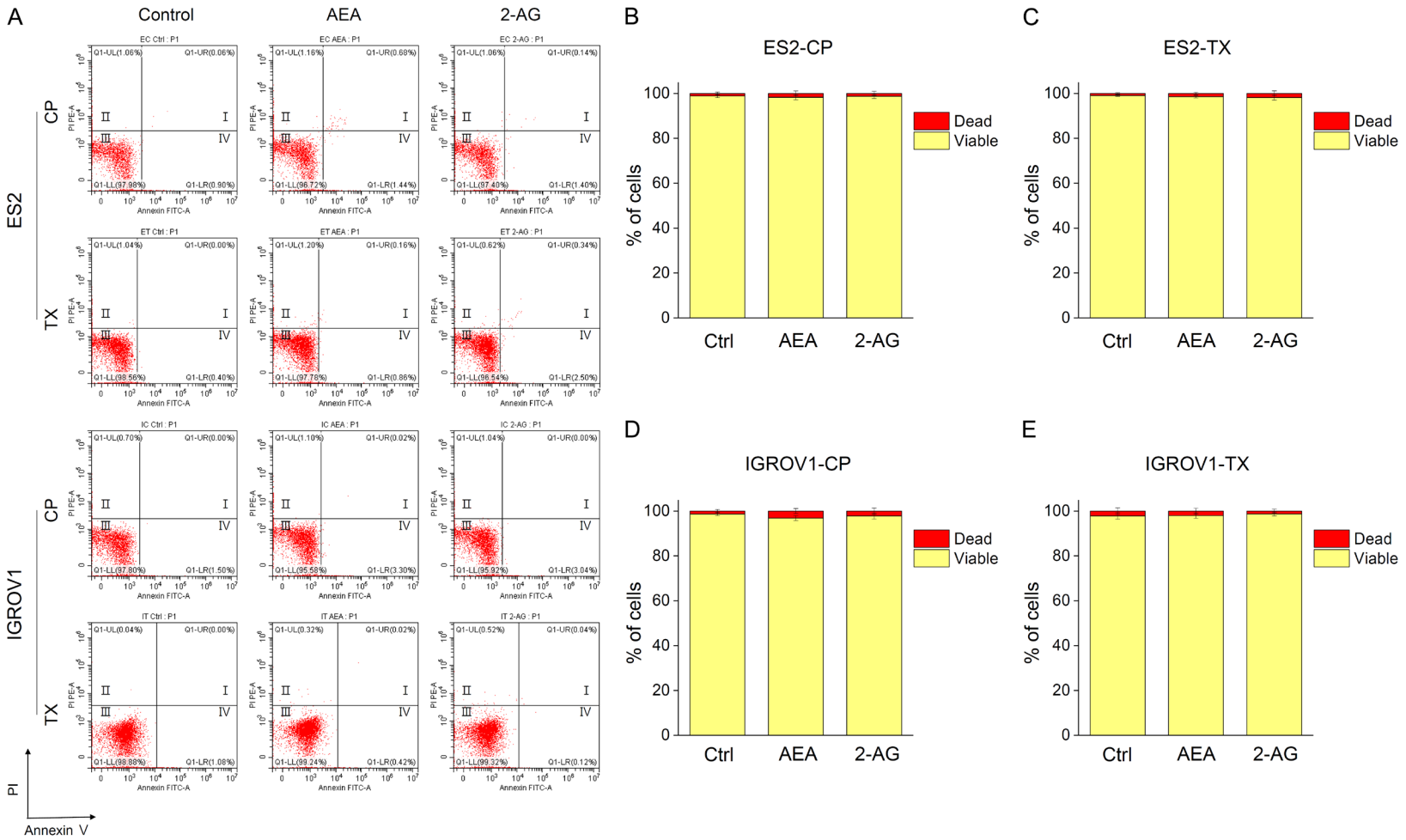
Supplementary Figure 3. Activation of ER stress in wild-type cancer cells under endocannabinoid treatments. A, B. Wild-type ES2 and IGROV1 cells were treated with IC_{30} of AEA and 2-AG for 12, 24 and 48 h. Antibodies against ER stress-related proteins, including Grp78, ATF6α, p-IRE1α, IRE1α, p-eIF2α and eIF2α were used in the immunoblotting analysis. 10 μg/mL tunicamycin was served as positive control (+) of ER stress. β-actin was served as the internal control. FL: full-length form, CL: cleaved form.



Supplementary Figure 4. Endocannabinoids do not enhance autophagy in non-chemoresistant wild-type cancer cells. A. IC_{30} of AEA and 2-AG were treated to ES2 and IGROV1 cell lines for 48 h. Autophagy was detected by LC3 antibody (green) and the nucleus was stained with Hoechst dye (blue). The images were taken by confocal microscopy. B. Quantification of LC3 puncta per cell from panel A was analyzed. The experiments were repeated for 3 times. Bars represent mean ± SEM. C. Antibody against LC3 was used to detect autophagy under IC_{30} of AEA or 2-AG treatments in wild-type cell lines. Actin was served as internal control.



Supplementary Figure 5. Myriocin decreased LC3 expression in chemoresistant OVC. A. Representative images of LC3 expression in chemoresistant cancer cells treated with IC_{30} of AEA or 2-AG for 24 h. 2 μM myriocin was pre-treated for 1 h. B-E. Quantification of the number of LC3 puncta per cell from panel A. The results were obtained from three independent experiments. The bars represent mean ± SEM. *p<0.05, **p<0.05, ***p<0.001 by one-way ANOVA.



Supplementary Figure 6. Endocannabinoids alone do not induce cell apoptosis in chemoresistant cancer cells. A. Chemoresistant cancer cells were treated with IC_{30} of AEA or 2-AG for 48 h. Annexin V and propidium iodide were used to quantify apoptosis. Representative images of flow cytometry were shown. B-E. Quantification of the percentage of dead cells, including necrotic and apoptotic cells, was analyzed from three independent experiments. The bars represent mean ± SEM.