

Supplementary Figure1. Other inhibitors cannot block HRG1-mediated phosphorylation of HER3 and AKT

NCI-N87 and OE19 were first incubated with 1 $\mu\text{mol/L}$ lapatinib \pm 1 $\mu\text{mol/L}$ erlotinib, 300 nmol/L crizotinib, 1 $\mu\text{mol/L}$ NVP-BGJ398, 300 nmol/L AZD0530 or 1 $\mu\text{mol/L}$ PF-552281, then cultured with or without 5 ng/ml HRG1 for 2 hours. Whole cell lysates were subjected to SDS-PAGE and Western blotting with the indicated antibodies.

Supplementary Figure2. Other inhibitors cannot abrogate HRG1-mediated resistance

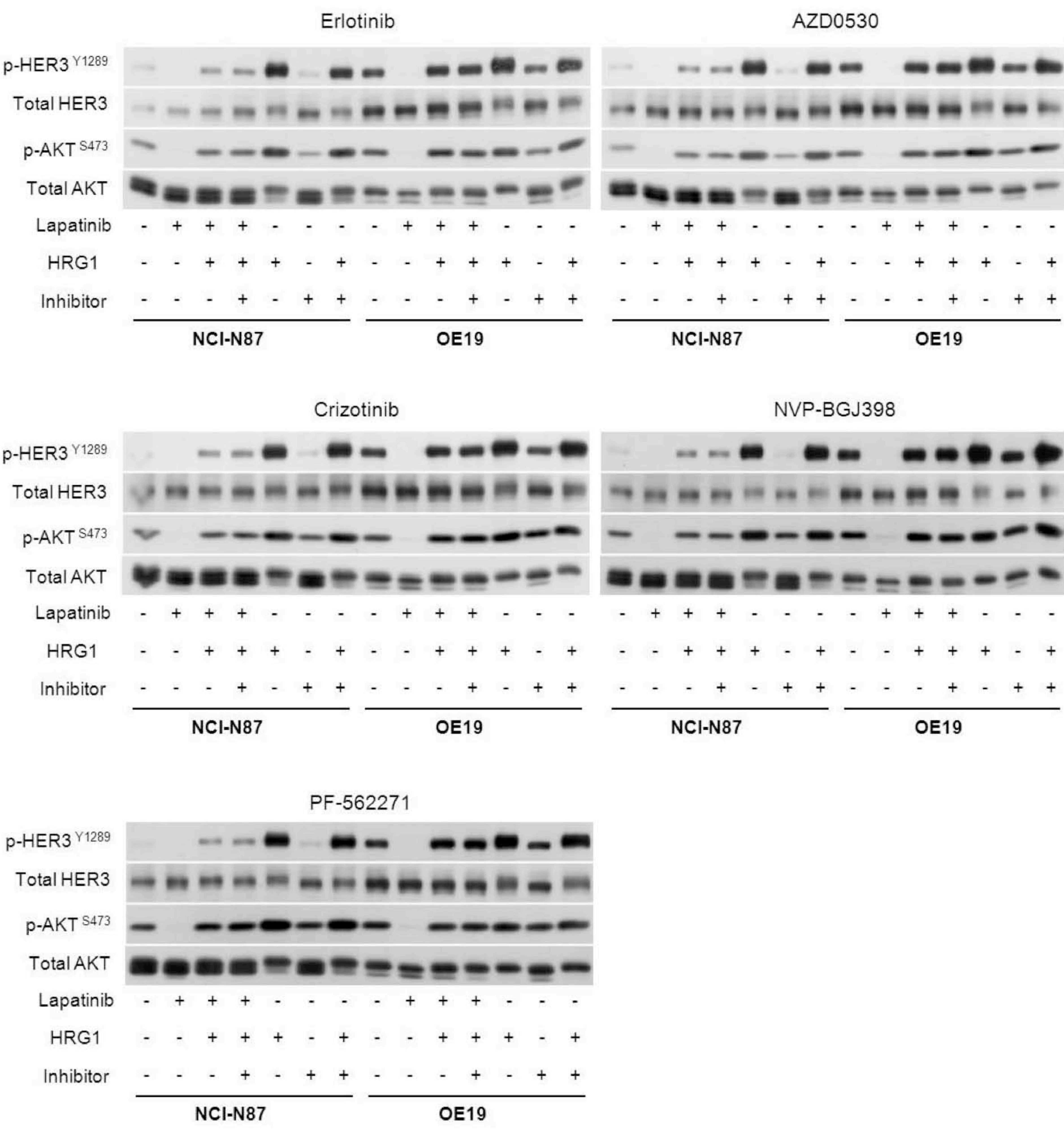
NCI-N87 and OE19 were first incubated with 1 $\mu\text{mol/L}$ lapatinib \pm 1 $\mu\text{mol/L}$ erlotinib, 300 nmol/L crizotinib, 1 $\mu\text{mol/L}$ NVP-BGJ398, 300 nmol/L AZD0530 or 1 $\mu\text{mol/L}$ PF-552281, then cultured with or without 5 ng/ml HRG1 for 72 hours. Cell proliferation was analyzed as described in Materials and Methods. All cell proliferation data are averages of quadruplicates of 3 independent experiments. bars, SD.

Supplementary Figure3. Trastuzumab cannot inhibit HRG1-mediated phosphorylation of HER3 and AKT and HRG1-mediated resistance to lapatinib

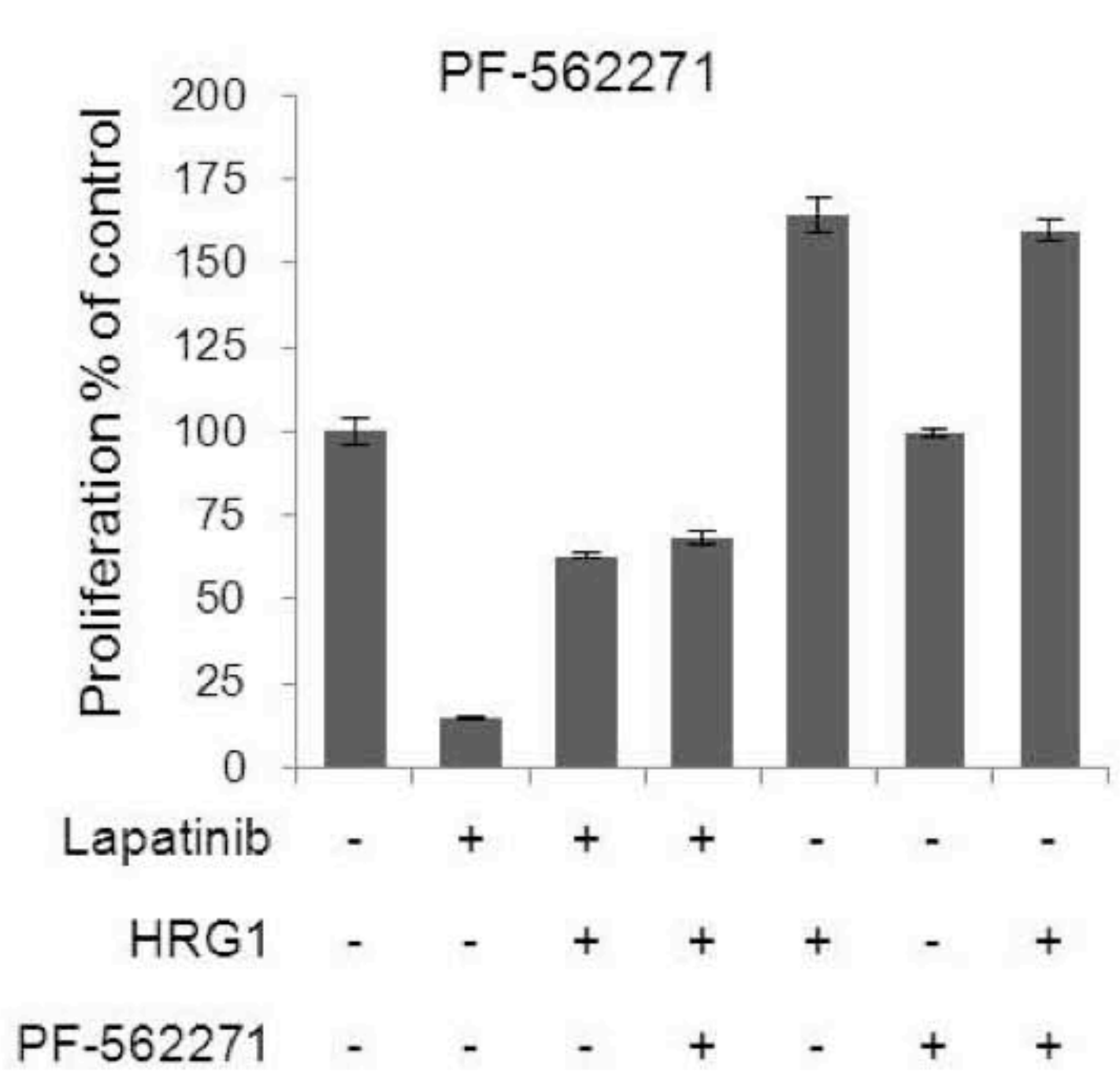
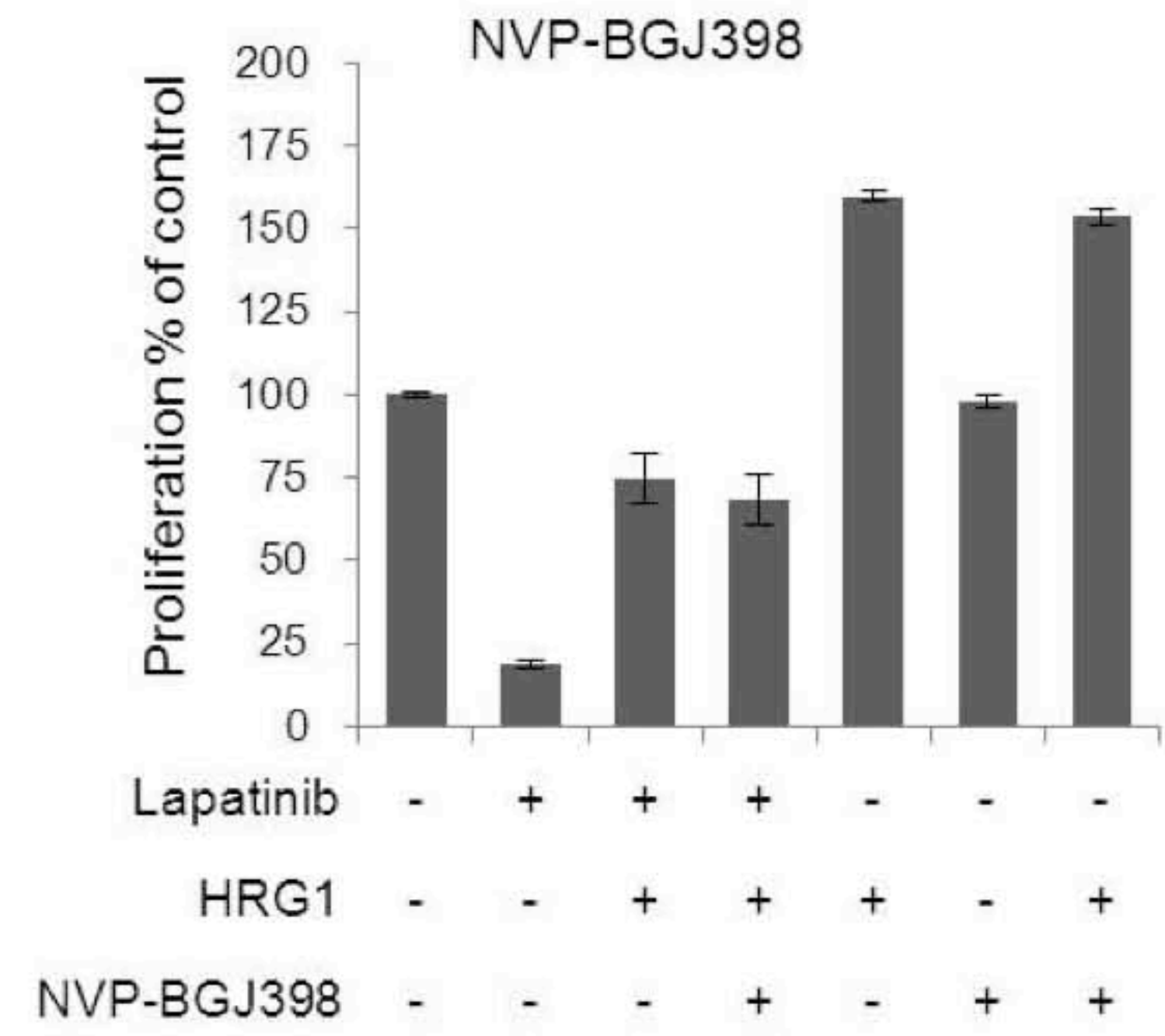
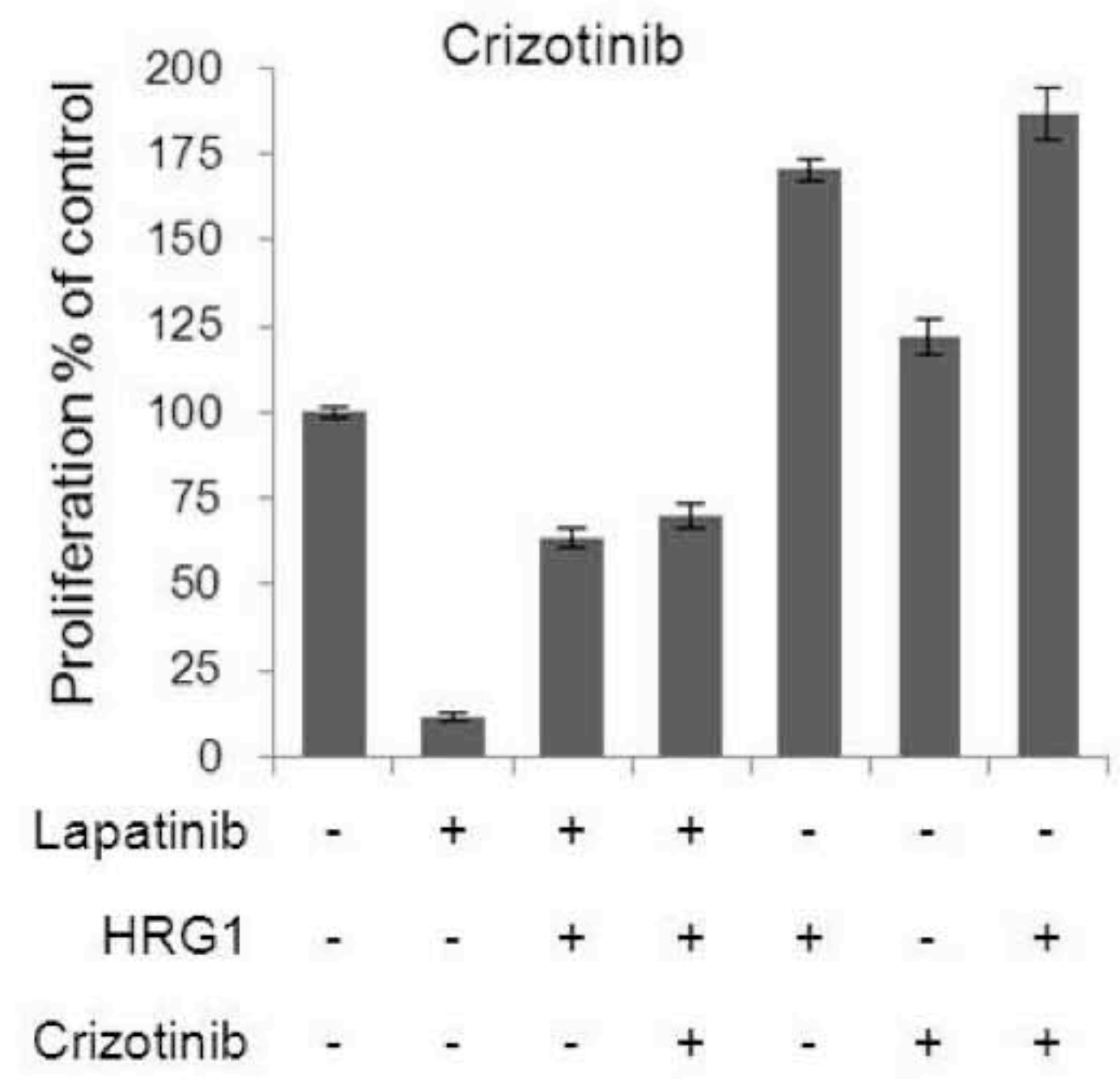
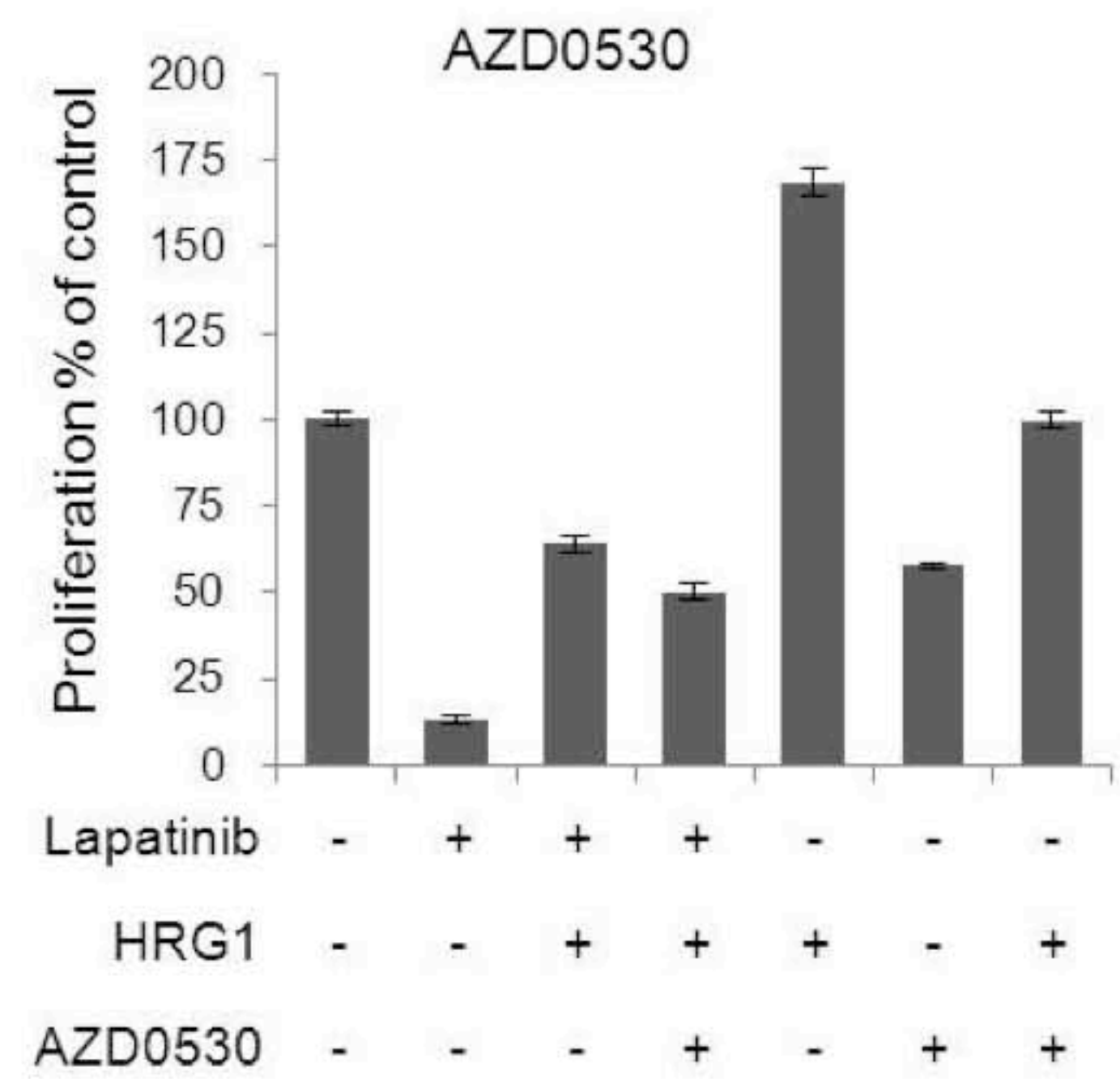
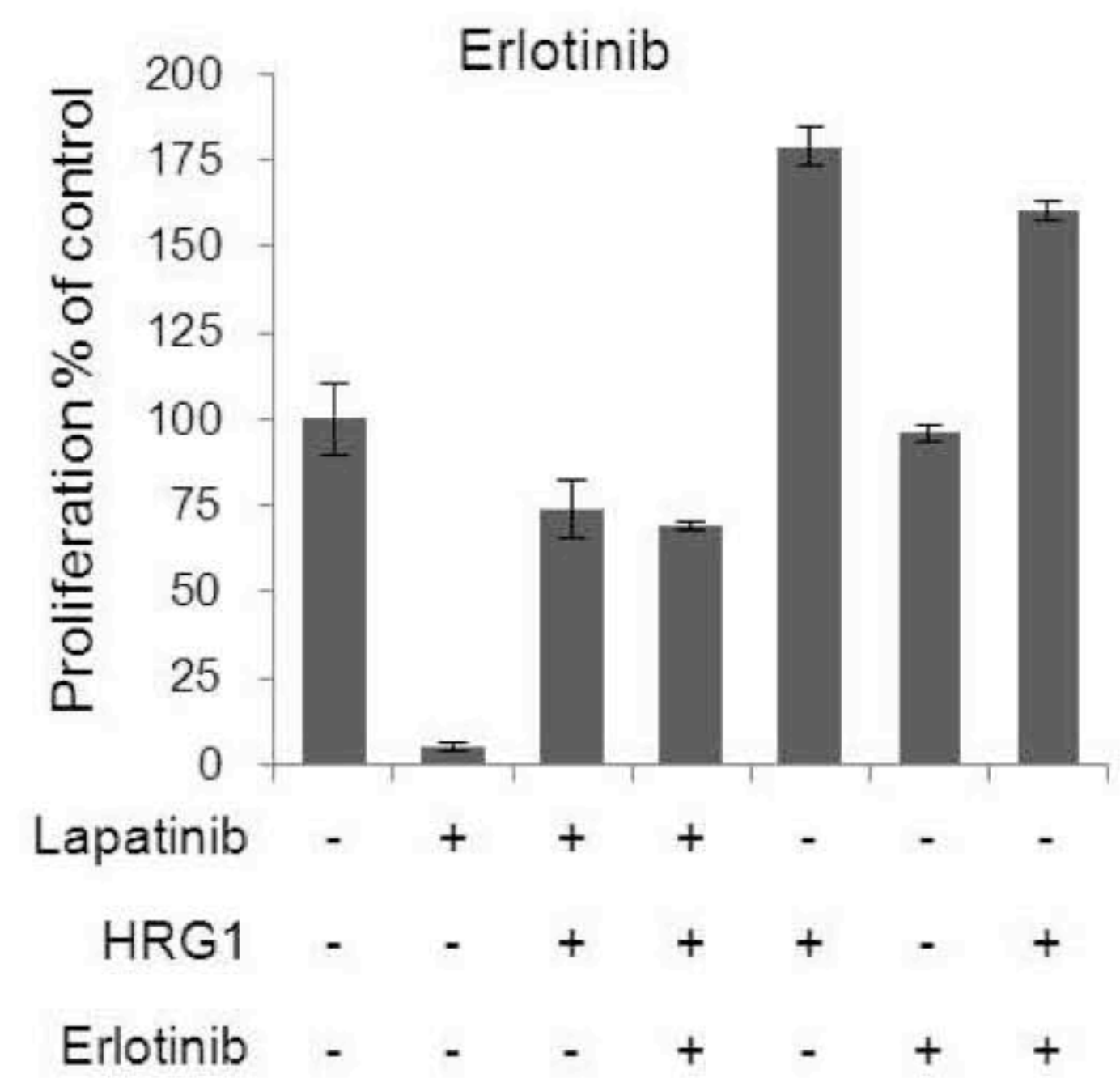
(A) NCI-N87 and OE19 were treated with 1 $\mu\text{mol/L}$ lapatinib \pm 20 $\mu\text{g/ml}$ trastuzumab for 30 minutes, then cultured with or without 5 ng/ml HRG1 for 2 hours. Whole cell lysates were

subjected to SDS-PAGE and Western blotting with the indicated antibodies. (B) NCI-N87 and OE19 were treated with 1 $\mu\text{mol/L}$ lapatinib \pm 20 $\mu\text{g/ml}$ trastuzumab for 30 minutes, then cultured with or without 5 ng/ml HRG1 for 72 hours. Cell proliferation was analyzed as described in Materials and Methods. All cell proliferation data are averages of quadruplicates of 3 independent experiments. bars, SD. *t-test, $p < 0.001$

Supplementary figure 1

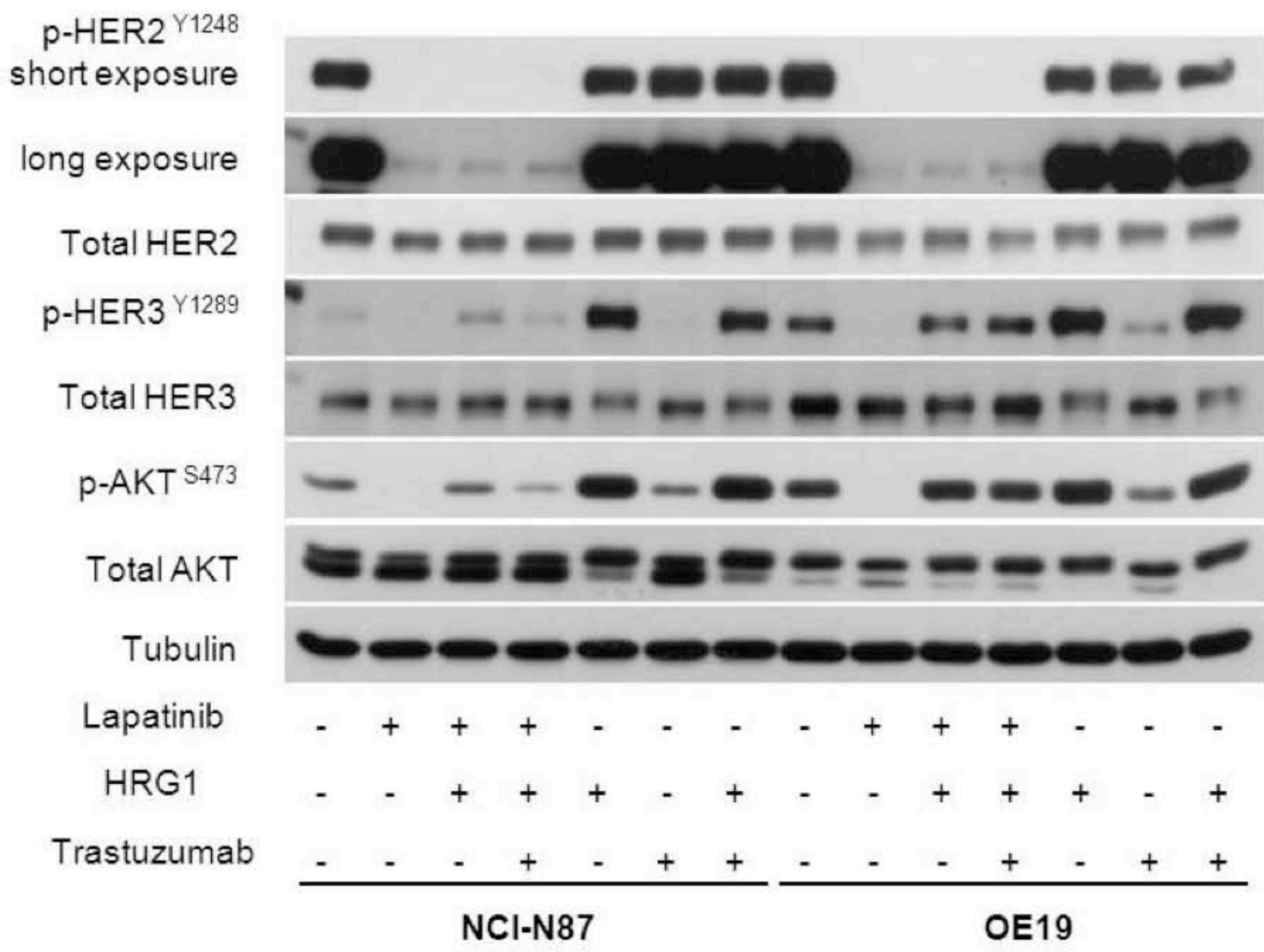


Supplementary figure 2



Supplementary figure 3

A



B

