Figure S1. [Neratinib + palbociclib] interact to activate eIF2α, ATM, AMPK, ULK-1 and inactivate mTOR, ERK1/2, AKT and STAT3. A. 4T1 cells were treated with vehicle control or with [neratinib (100 nM) + palbociclib (100 nM)] for 6h. Cells were fixed in place and at least forty cells per condition were imaged in independent triplicate and the intensity ratio of phosphorylated protein levels to total protein expression plotted as a percentage of control treatment (n = 3 +/- SD). # $p < 0.05$ greater than vehicle control; * $p < 0.05$ less than vehicle control. **B.** Spiky ovarian cancer cells were treated with vehicle control, neratinib (100 nM), palbociclib (100 nM) or the drugs in combination for 6h. Cells were fixed in place and at least forty cells per condition were imaged in independent triplicate and the intensity ratio of phosphorylated protein levels to total protein expression plotted as a percentage of control treatment (n = 3 +/- SD). # $p < 0.05$ greater than vehicle control; * $p < 0.05$ less than vehicle control. **C.** Tumors cells as indicated were treated with vehicle control or treated with palbociclib (100 nM) for 4h. Cells were fixed in place and at least forty cells per condition were imaged in independent triplicate and the intensity ratio of phosphorylated AMPKα T172 levels to total AMPKα protein expression plotted as a percentage of control treatment (n = 3 +/- SD). # $p < 0.05$ greater than vehicle control.

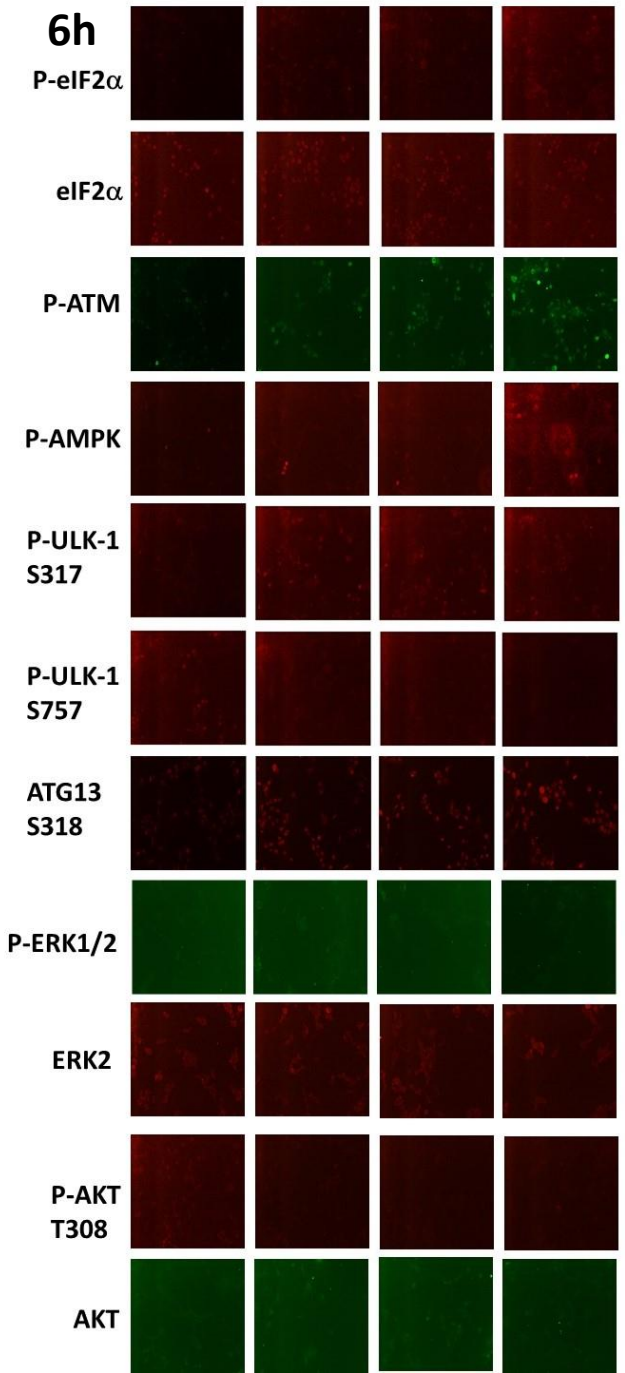
Figure S2. [Neratinib + palbociclib] enhances the expression of BIM, Beclin1 and ATG5 that is suppressed by expression of activated MEK1 or activated AKT Spiky ovarian cancer cells were transfected with empty vector (CMV) or to express the indicated “activated” proteins. Twenty-four h after transfection cells were treated with vehicle control or with [neratinib (100 nM) + palbociclib (100 nM)] for an additional 6h. Cells were fixed in place and at least forty cells per condition were imaged in independent triplicate and the intensity ratio of phosphorylated protein levels to total protein expression was determined (n = 3 +/- SD).* $p < 0.05$ less intensity in the corresponding value in vehicle control; * $p < 0.05$ greater intensity in the corresponding value in vehicle control; ¶ $p < 0.05$ greater intensity than corresponding value in CMV transfected cells; ** $p < 0.05$ lower percentage reduction in intensity than in CMV cells; ## $p < 0.05$ lower percentage increase in intensity than in CMV cells.

Figure S3. [Neratinib + palbociclib + valproate] modulates protein expression and protein phosphorylation in mouse CT26 colon cancer cells. CT26 mouse colon cancer cells were treated with vehicle control, [neratinib (100 nM) + palbociclib (100 nM)], sodium valproate (250 μM) or the drugs in combination for 4h and for 8h. Cells were fixed in place and at least forty cells per condition were imaged in independent triplicate and the intensity ratio of phosphorylated protein levels to total protein expression was determined (n = 3 +/- SD).* $p < 0.05$ less intensity in the corresponding value in vehicle control; # $p < 0.05$ greater intensity in the corresponding value in vehicle control; ** $p < 0.05$ lower intensity than in individual drug-treated cells; ## $p < 0.05$ greater intensity than in individual drug-treated cells.

Figure S4. [Neratinib + palbociclib] in mouse CT26 colon cancer cells cause K-RAS to localize in punctate structures close to the plasma membrane. CT26 mouse colon cancer cells were treated with vehicle control or [neratinib (100 nM) + palbociclib (100 nM)] for 4h. Cells were fixed in place and immunostaining performed to detect total ERK2 levels and total K-RAS levels. The images were super-imposed and examined at 10X magnification.

Figure S5. [Neratinib + palbociclib] reduces the expression of PD-L1 and IDO-1, and enhances the expression of MHCA, in mammary carcinoma cells. Cells were treated with vehicle control or with [neratinib (100 nM) + palbociclib (100 nM)] for 6h. Cells were fixed in place and immune-staining performed to determine the expression levels of PD-L1, PD-L2, MHCA, IDO-1 and HMGB1. The blue arrows with HMGB1 indicate where the protein has been expelled from the cells following drug exposure.

S1A


4T1
6h
VEH
NER
PAL
N+P
P-eIF2α
eIF2α
P-ATM
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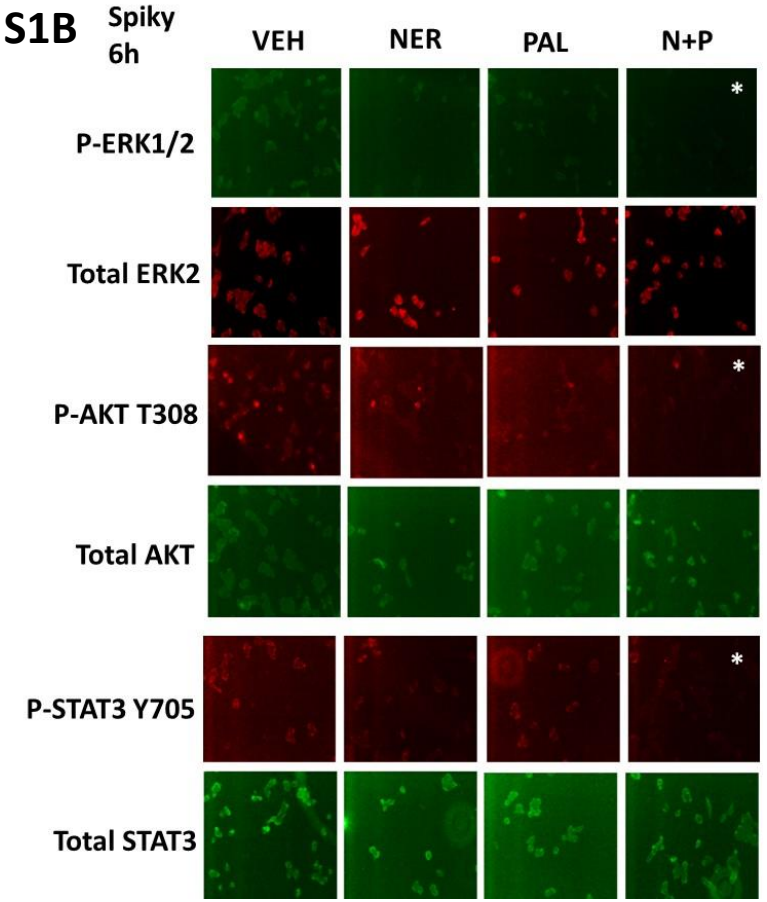
P-ULK-1 S757
ATG13 S318
P-ERK1/2
ERK2
P-AKT T308
AKT

S1B


Spiky
6h
VEH
NER
PAL
N+P
P-ERK1/2
Total ERK2
P-AKT T308
Total AKT
P-STAT3 Y705
Total STAT3
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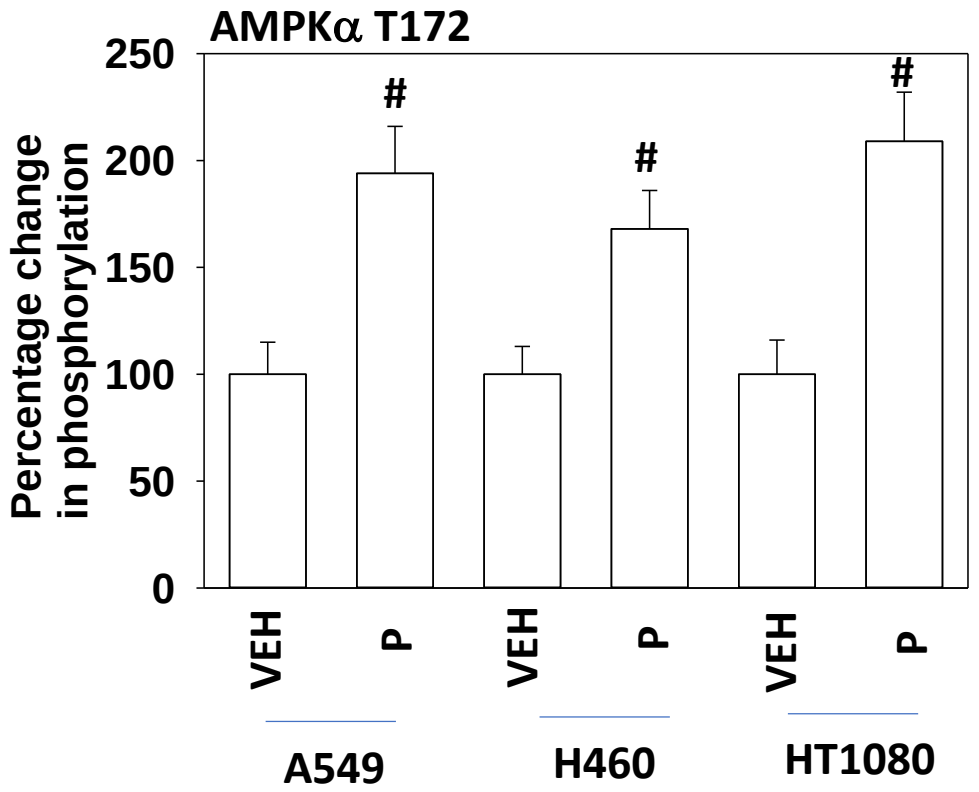
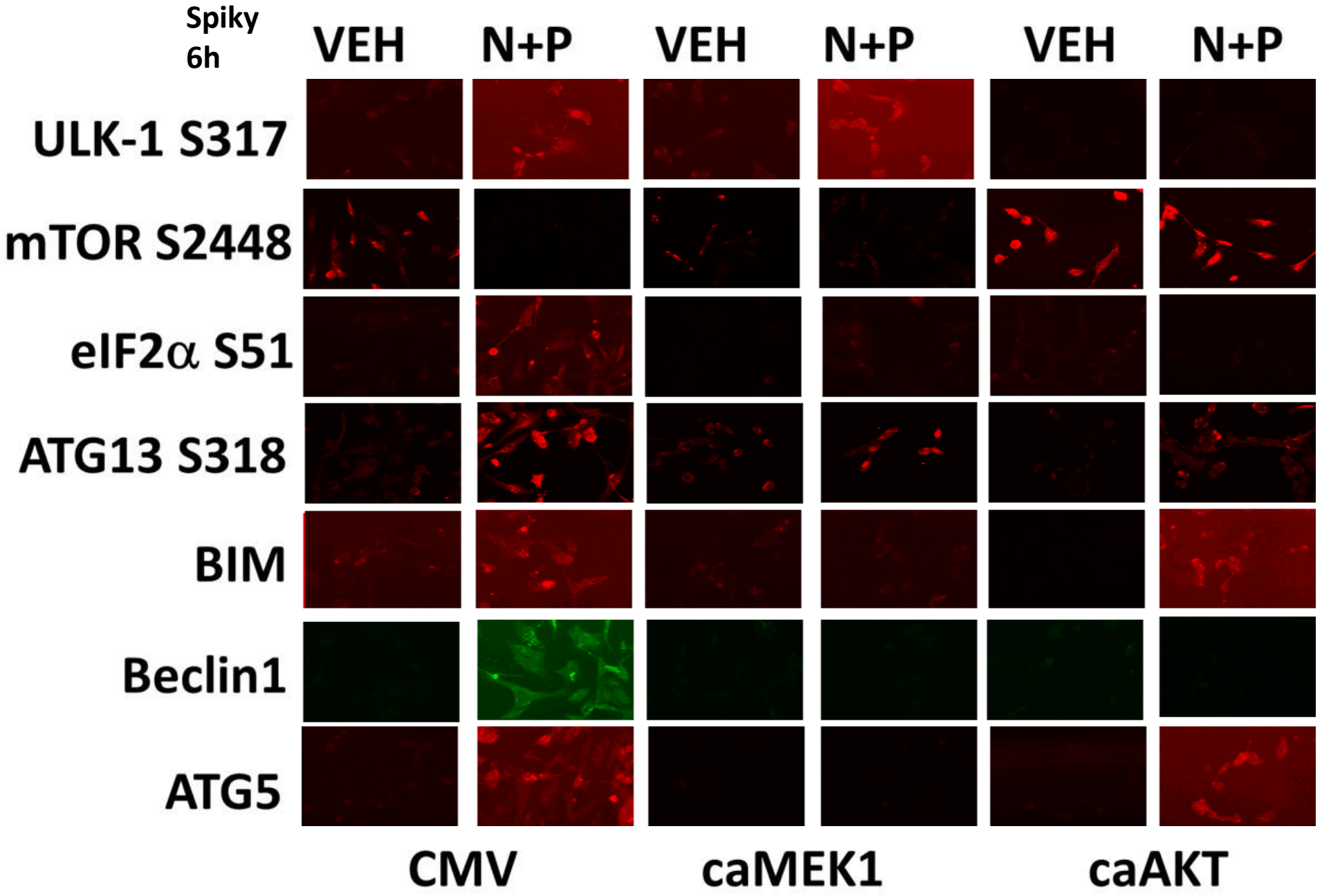
S1C


AMPKα T172
Percentage change in phosphorylation
250
200
150
100
50
0
#
VEH
P
A549
H460
HT1080

S2


Spiky
6h
VEH
N+P
VEH
N+P
VEH
N+P
ULK-1 S317
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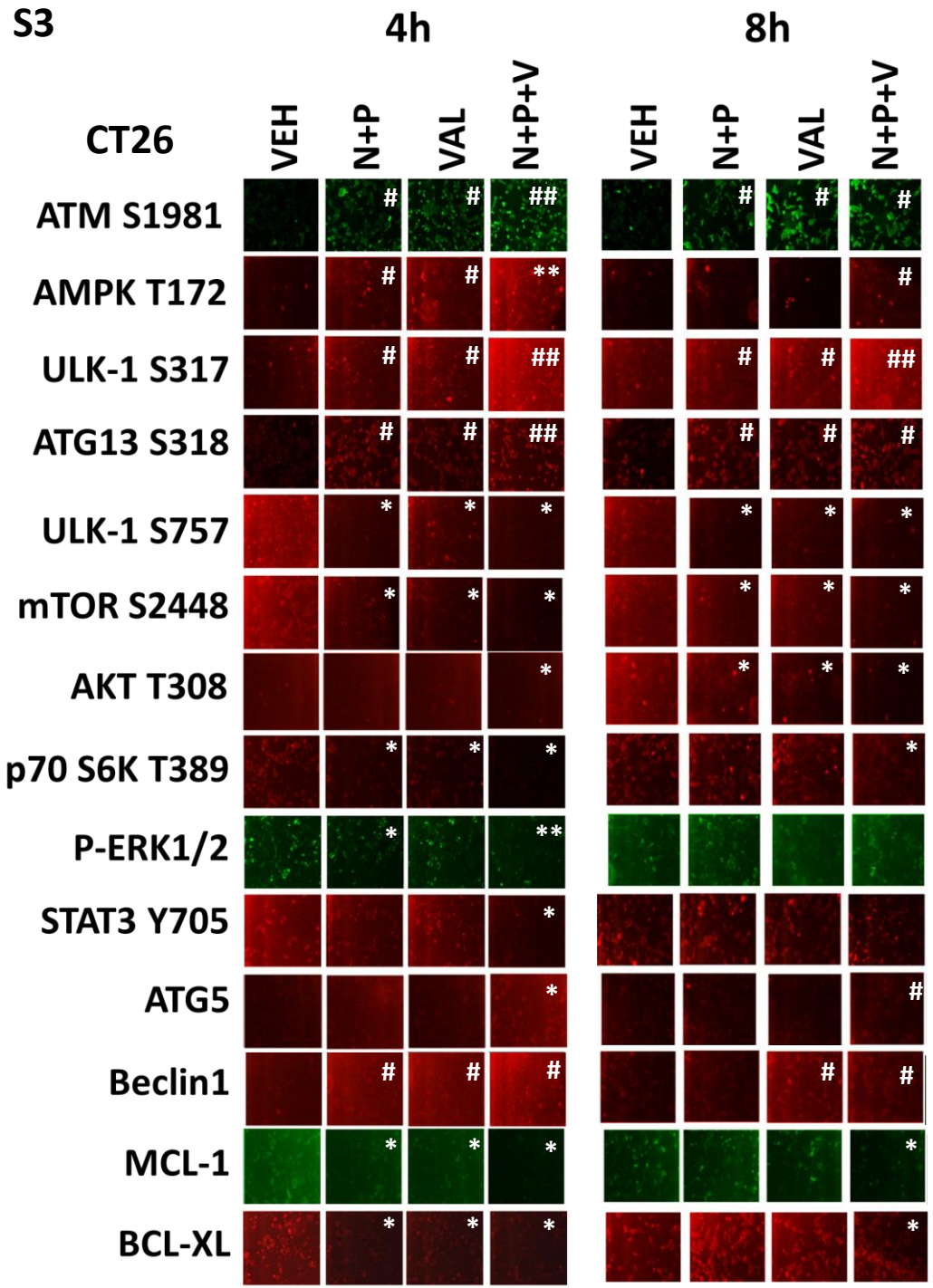
eIF2α S51
ATG13 S318
BIM
Beclin1
ATG5
CMV
caMEK1
caAKT

S3


4h
8h
CT26
VEH
N+P
VAL
N+P+V
VEH
N+P
VAL
N+P+V
ATM S1981
AMPK T172
ULK-1 S317
ATG13 S318
ULK-1 S757
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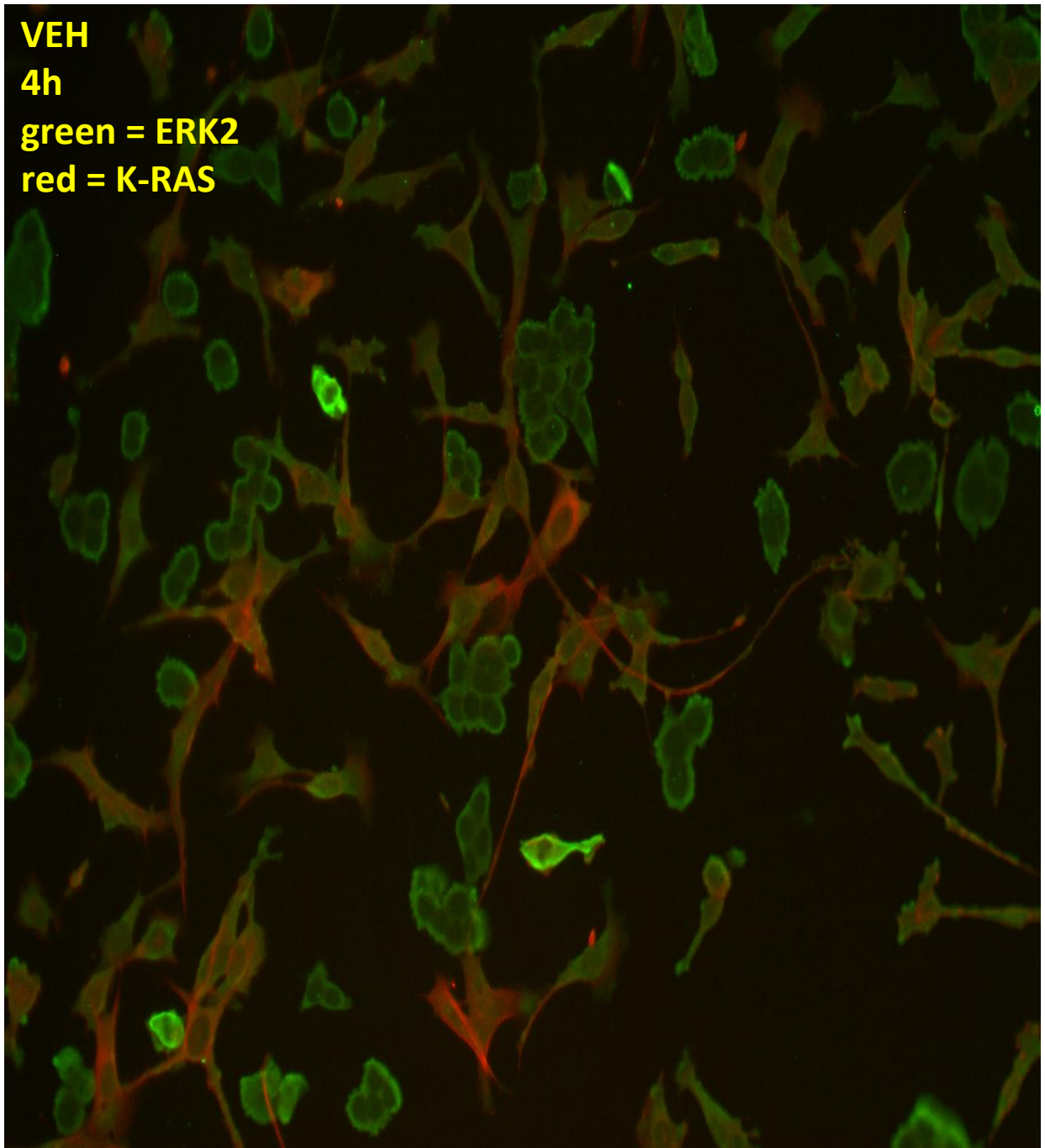
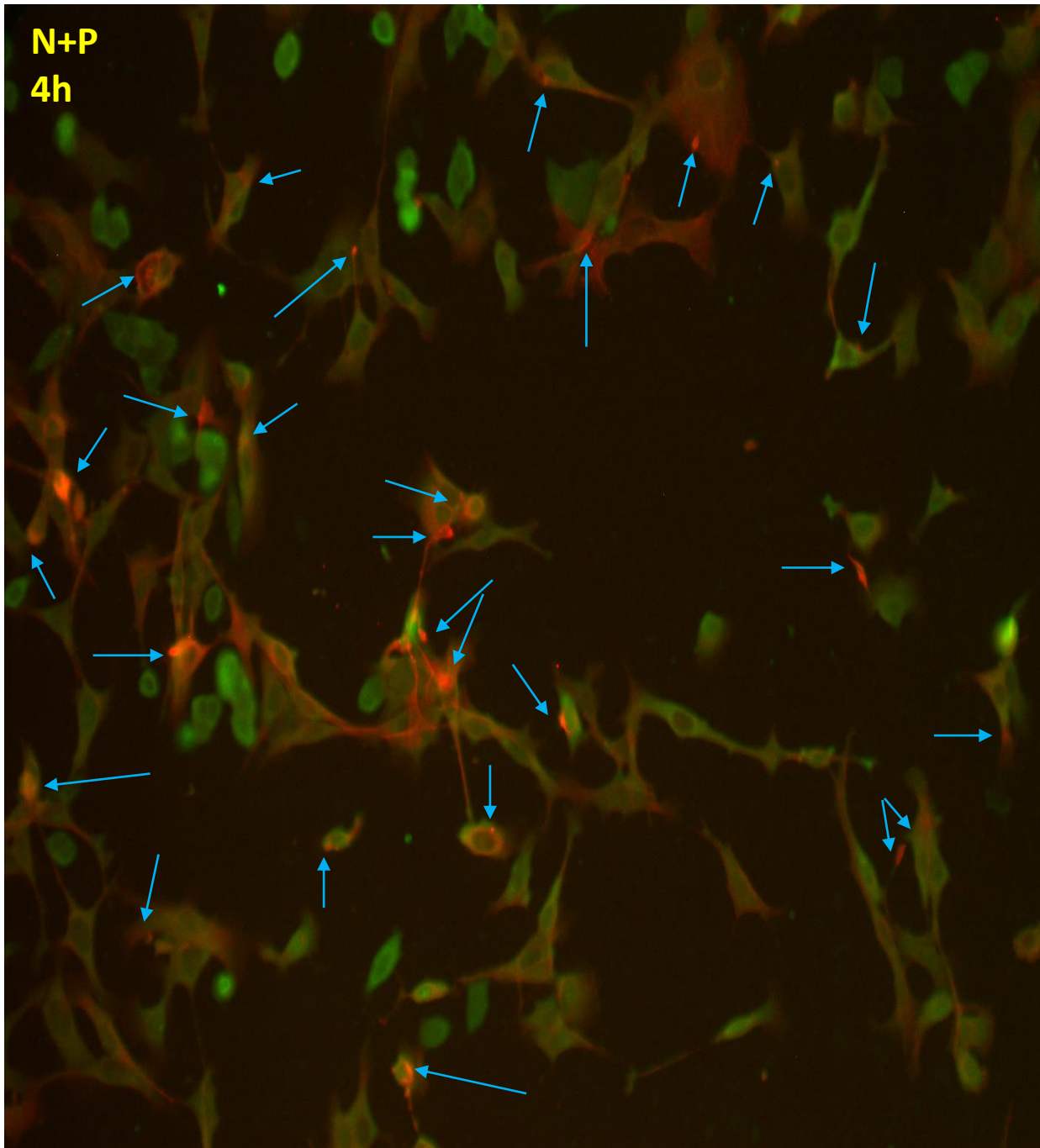
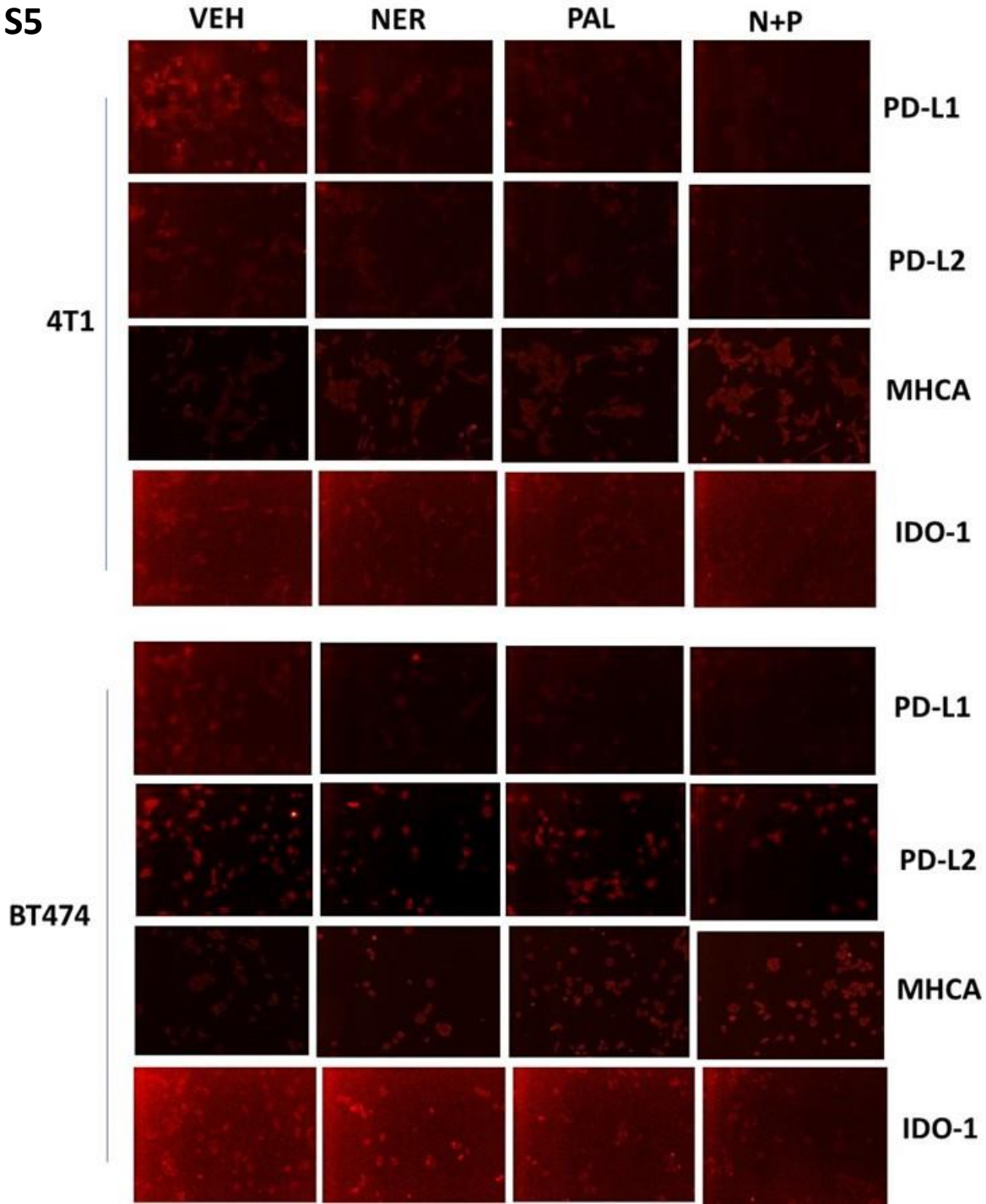
p70 S6K T389
P-ERK1/2
STAT3 Y705
ATG5
Beclin1
MCL-1
BCL-XL

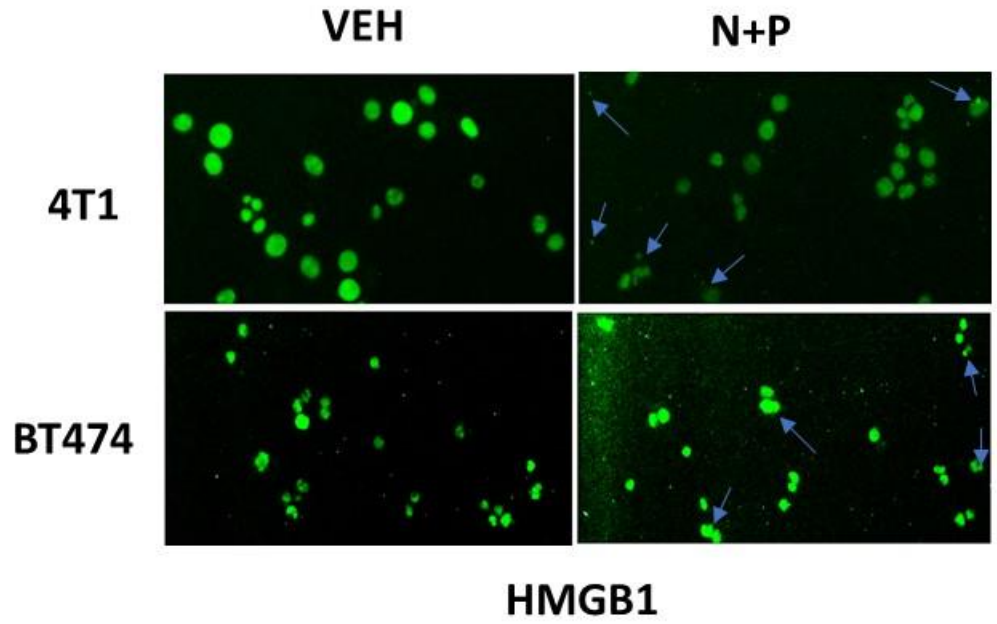
S4





S5


VEH
NER
PAL
N+P
PD-L1
PD-L2
MHCA
IDO-1
4T1
BT474


VEH
N+P
4T1
BT474
HMGB1