Table S1. **Antibodies used for RPPA and /or Western blot**

Antibody	Source
4EBP1 pS65	Cell Signaling[1]
4EBP1 pT37/T46	Cell Signaling[1]
53BP1	Cell Signaling[1]
AKT pS473	Cell Signaling[1]
β-Actin	Sigma[2]
Bad pS112	Cell Signaling[1]
Bcl2A1	Abnova[3]
c-Raf pS338	Cell Signaling[1]
DUSP4	Cell Signaling[1]
eEF 2K	Cell Signaling[1]
MET pY1234/1235	Cell Signaling[1]
MET	Cell Signaling[1]
Flag M2	Sigma[2]
GSK-3α/β pS21/9	Cell Signaling[1]
HER3	Santa Cruz[4]
HSP27	Cell Signaling[1]
IGF1R pY1135	Cell Signaling[1]
MAPK pT202/Y204	Cell Signaling[1]
MDM2 pS166	Cell Signaling[1]
MEK1 pS217/S221	Cell Signaling[1]
NDRG1 pT346	Cell Signaling[1]
NFκB P65 pS536	Cell Signaling[1]
P21	Santa Cruz[4]
P38 pT180/Y182	Cell Signaling[1]
P70S6 pT389	Cell Signaling[1]
PDK1 pS241	Epitomics[4]
PKC β II pS660	Cell Signaling[1]
PI3K p110α	Cell Signaling[1]
PRAS40 pT246	Life Technologies[5]
Rictor pT1135	Cell Signaling[1]
S6 pS235/S436	Cell Signaling[1]
Shc pY317	Cell Signaling[1]
Smad4	Cell Signaling[1]
STAT3 pY705	Cell Signaling[1]
TAZ	Cell Signaling[1]
Tuberin pT1462	Cell Signaling[1]
V5	Invitrogen[6]
XPA	Santa Cruz[4]
YB1 pS102	Cell Signaling[1]

[1]Beverly, MA; [2] St Louis, MO; [3] Walnut, CA; [4]Santa Cruz, CA; [5]Life Technologies; Epitomics, Burlingame, CA; [6]Invitrogen, Carlsbad, CA

Figure S1

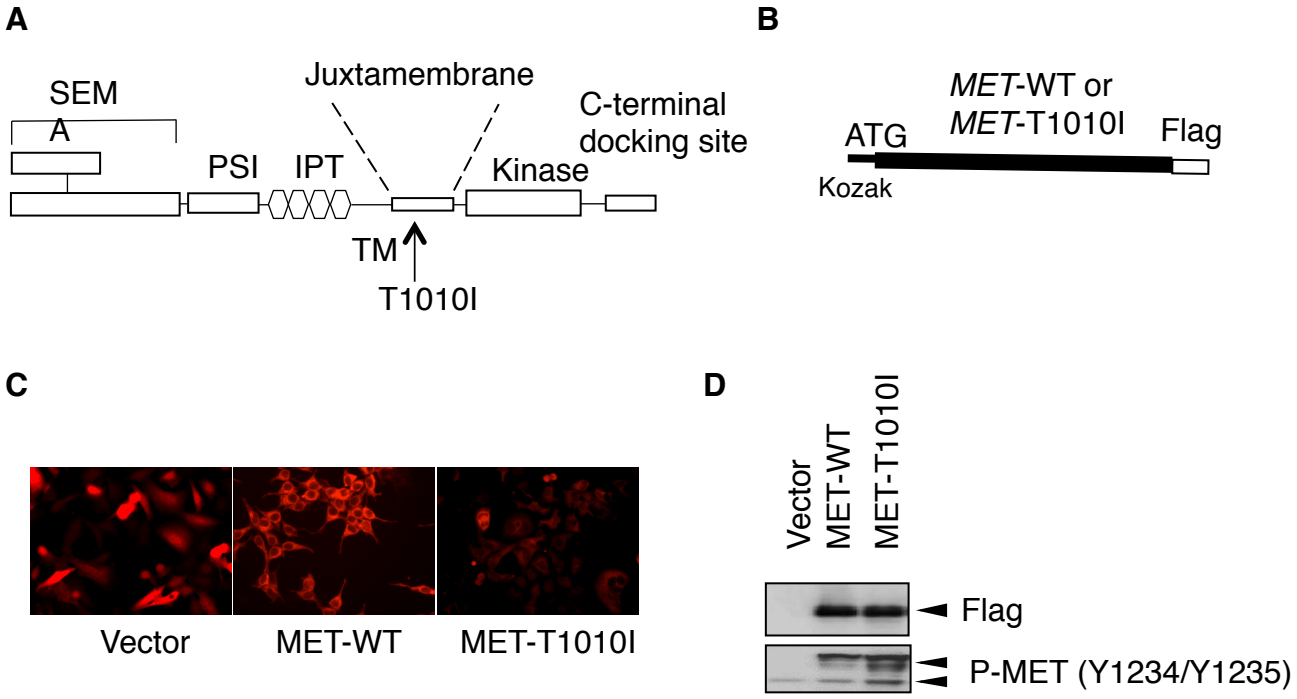


Figure S1**. Development of lentiviral constructs for expression of human wild type *MET* and *MET*—T010I genes**

A. Location of breast cancer-associated T1010I in human *MET* molecule. **B**. Human WT *MET* and *MET*-T1010I gene cassetts. The genes were synthesized by GeneART following our design. The fragments of Kozak-*MET*s-Flag were excised from pMA vector 2 with Xhol/ Xmal and inserted into pLVX-tdTomatoN1, a lentiviral vector (Clontech, Mountain View, CA). **C.** Expression of exogenous MET fusion protein. HCC1954 cells with endogenous *PIK3CA*-H1047R were transformed with the *MET* genes. *MET*-Flag-Td Tomato fusion protein was detected with Td Tomamo fluorescence. **D.** Western blot analysis for phosphorylation of MET after stimulation with HGF (40 ng/ml for 30 minutes). The upper band shows exogenous and the lower band is endogenous.

Figure S2

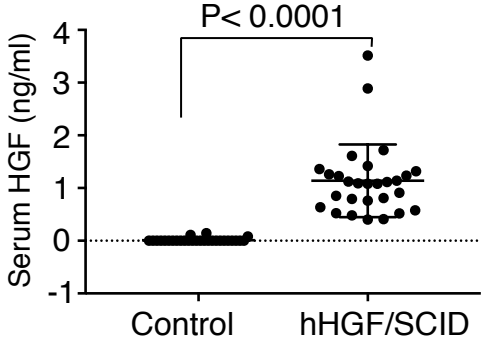
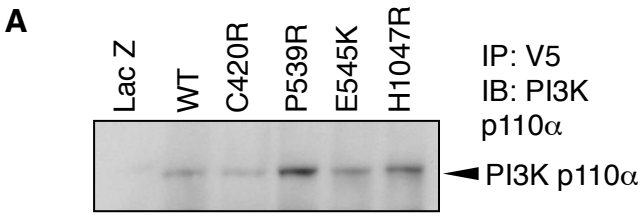
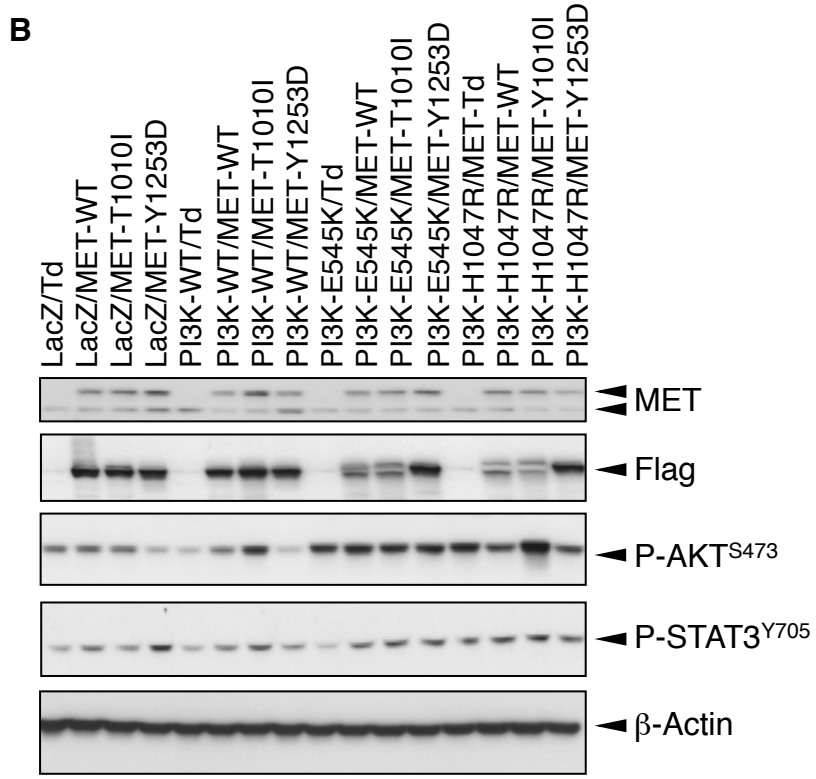


Figure S2. **Serum human HGF concentration in hHGF Tg/SCID mice.**
Serum HGF concentration of the hHGF Tg/SCID mice was measured using the Human HGF Quantikine ELISA Kit (R&D Systems, MN). The serum samples from the negative littermates were used as control.

Figure S3





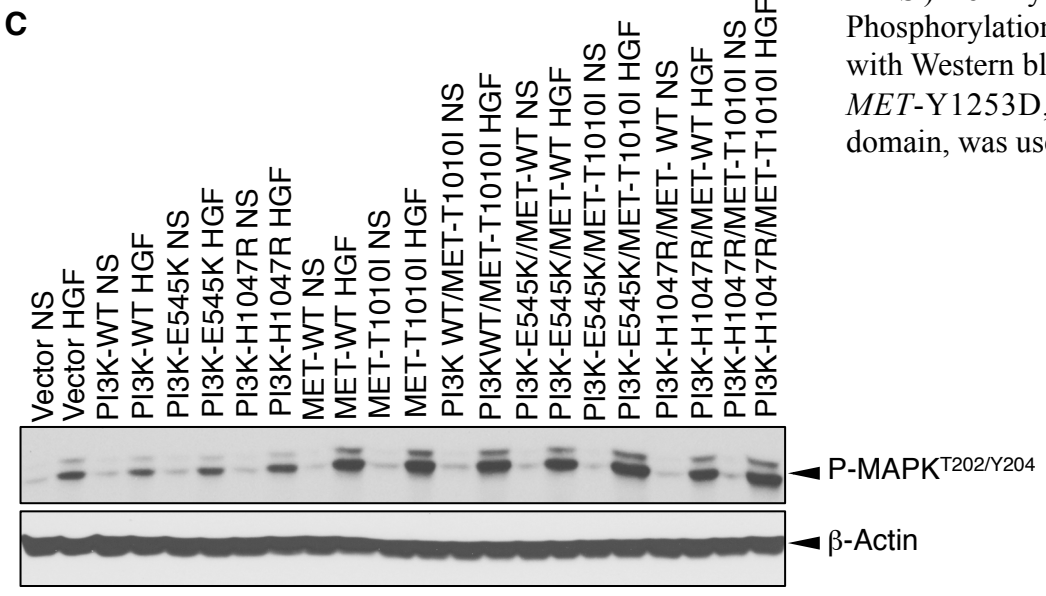


Figure S3. **Establishment of stable cells expressing breast cancer-associated mutant *PIK3CA* or *PIK3CA/MET genes* in mammary epithelial cell MCF-10A cells.**

A. Expression of PIK3CA-V5. V5 antibody was used for IP and anti-PI3K P110α antibody was used for immunoblot (IB). **B.** Effect of expression of *PIK3CA* and/or *MET* genes on PI3K-AKT pathway (Western blot). The cells indicated were cultured in growth medium, without starvation and stimulation. Exogenous MET-Flag-Tdtomato fusion protein (upper band) and endogenous MET (lower band) were detected with cMET antibody. **C.** Effect of expression of *PIK3CA* and/or *MET* genes on MAPK pathway (Western blot). The cells indicated received starvation for over night, followed by stimulation with HGF (40 ng/ml) for 10 minutes (HGF), while the cells were treated with the vehicle (0.1% BSA in PBS) only as control (NS). Phosphorylation of MAPK was detected with Western blot.

MET-Y1253D, a mutation in kinase domain, was used as positive control.

Figure S4

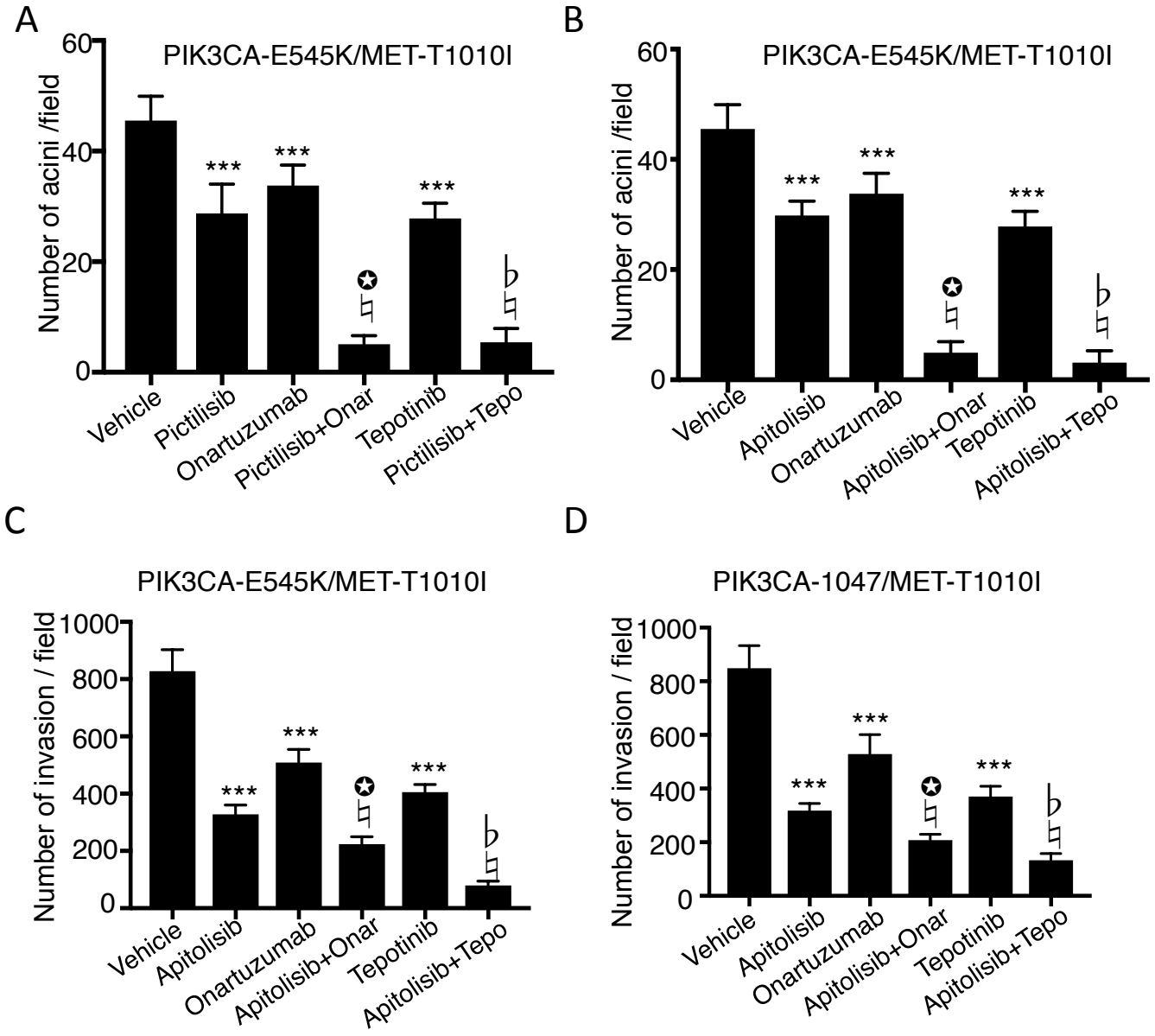


Figure S4. Effects of combined targeting PI3K and MET on acini formation or cell invasion MCF-10A derived cells. A total of 4 x10^3 MCF-10A derived cells with expression of *MET*-T1010I/ *PIK3CA*-E545K genes were resuspended in modified growth medium (2.5 % horse serum, 5 ng/mL EGF), supplemented HGF 40 ng/ml and 2% growth factor decreased matrigel, and treated with onnartuzumab (Onar) or Tepotinib (Tepo) alone or combined with Pictilisib (**A**) or apitolisib (**B**). The acini were accounted (detain in Supplementary Methods). The MCF-10A-derived cells with expression of PIK3CA-E545K/MET-T1010I (**C**) or PIK3CA-1047/MET-T1010I (**D**) were starved for 20 hours in serum-free DMEM F12 lacking EGF, insulin, and hydrocortisone. A total of 1x10^5 cells were inoculated into the upper chamber. apitolisib, onartuzumab (Onar) or Tepotinib (Tepo) alone or different combinations as indicated were added into both the upper and lower chambers. HGF and fibronectin were added in the lower chamber as the inducer. Invasive cells were photographed (not shown) and counted in 10 random fields. The data are mean ± standard deviation of triplicates, representative of two independent experiments (*, $P < 0.01$; **, $P < 0.001$; ***, $P < 0.0001$ versus vehicle; ♮, $P < 0.0001$ versus Pictilisib; ✪, $P < 0.0001$ versus Onartuzumab; ♭, $P < 0.0001$ versus Tepotinib, ANOVA).

Figure S5

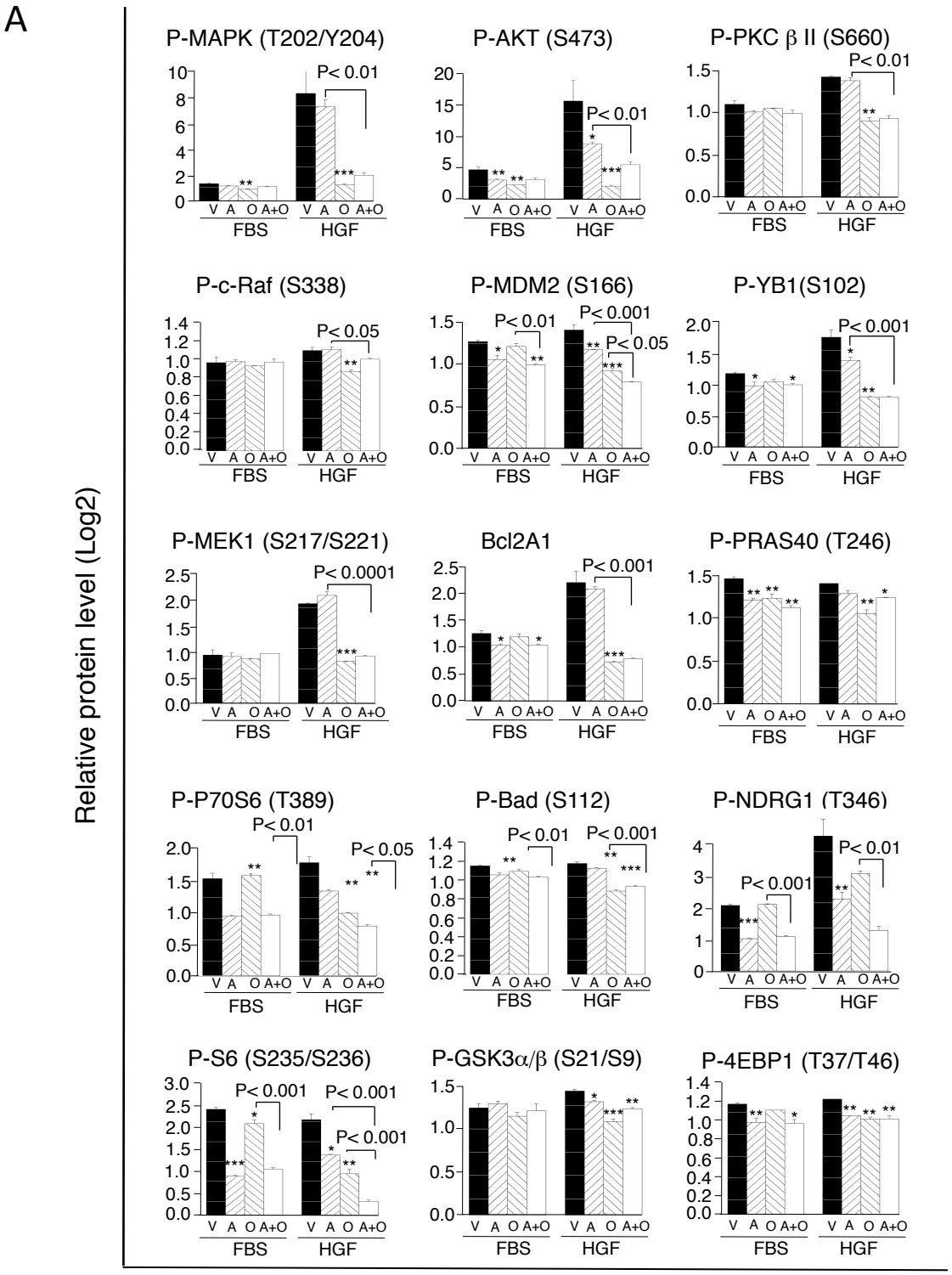

A
Relative protein level (Log2)
P-MAPK (T202/Y204)
P-AKT (S473)
P-PKC β II (S660)
P-c-Raf (S338)
P-MDM2 (S166)
P-YB1(S102)
P-MEK1 (S217/S221)
Bcl2A1
P-PRAS40 (T246)
P-P70S6 (T389)
P-Bad (S112)
P-NDRG1 (T346)
P-S6 (S235/S236)
P-GSK3α/β (S21/S9)
P-4EBP1 (T37/T46)
V A O A+O
FBS
HGF

Figure S5

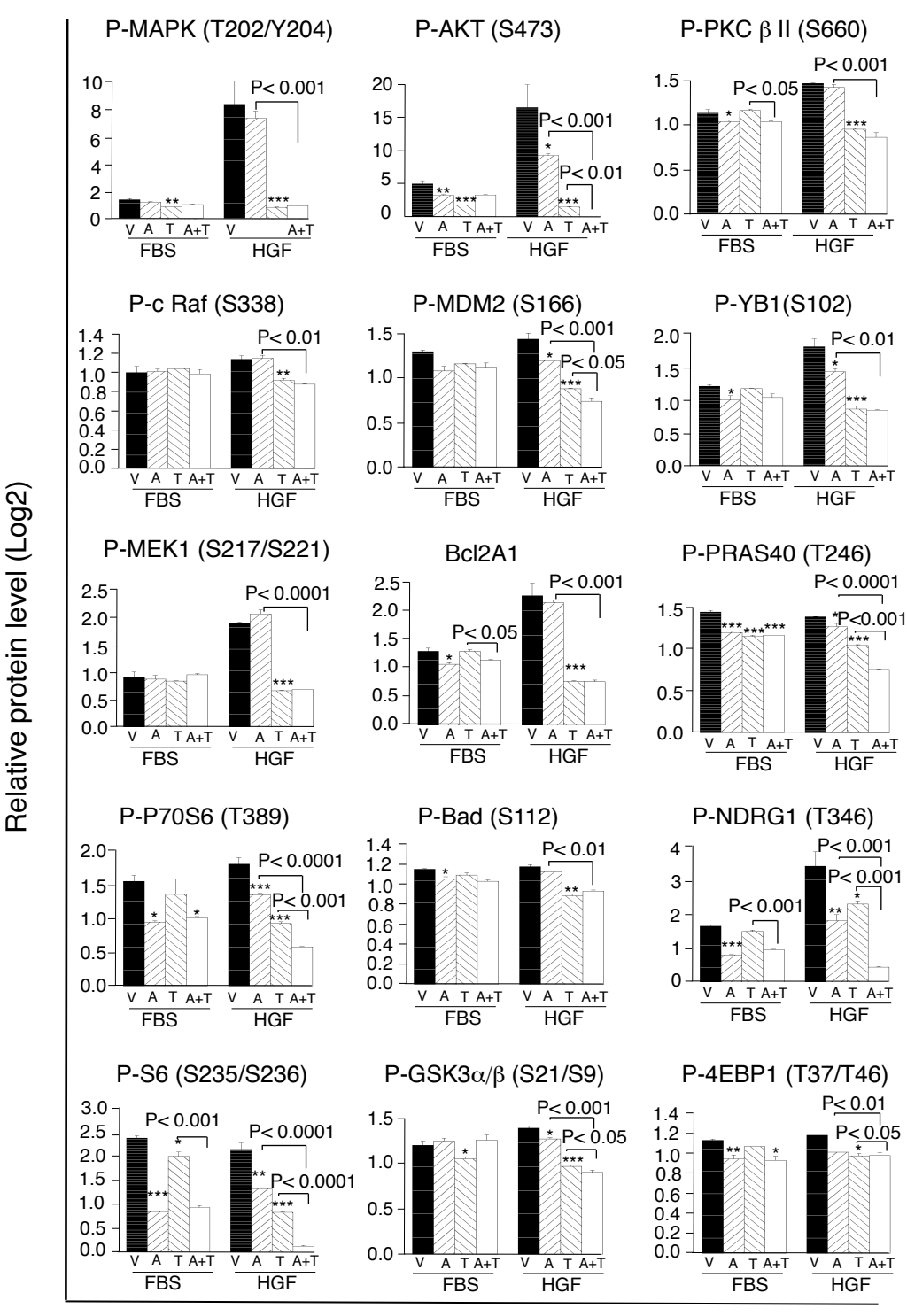


Figure S5. **Effect of HGF on cellular signaling response to targeted therapies in oncogenic MET-T1010I and PIK3CA-H1047R gene transformed cells. A.** MCF-10A derived cells with expression of *MET*-T1010I /*PIK3CA*-H1047R genes received starvation for overnight, followed by treatment with apitolisib (A), onartuzumab (O) alone or their combination (A+O), and stimulation with HGF or FBS. **B**. Using Tepotinib (T) instead of Onatuzumab. The RPPA data were analyzed (as described in Materials and Methods (mean ± SD; the *P*-value based on the log2 data).

Figure S6

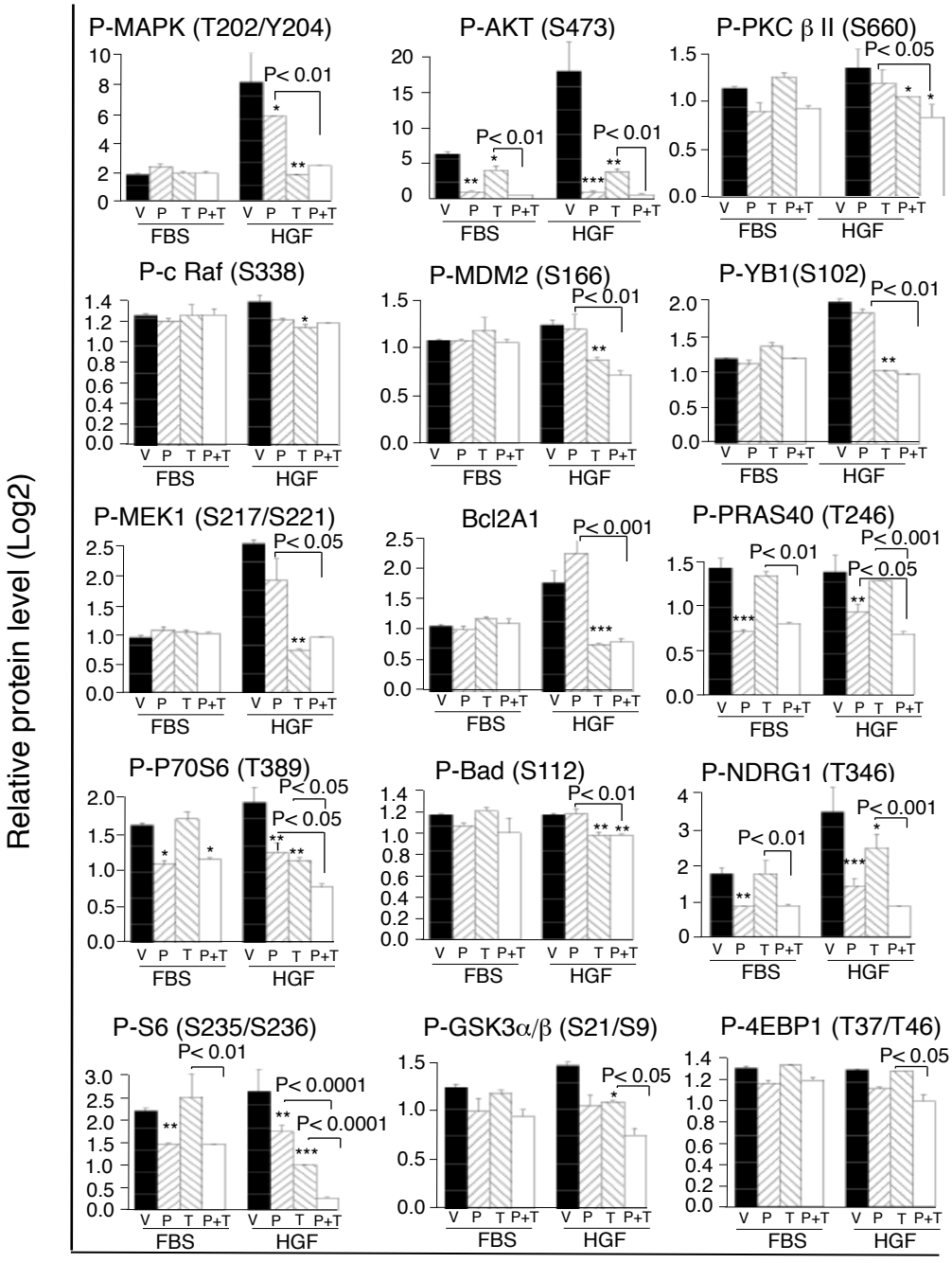


Figure S6. **Effect of HGF on cellular signaling response to targeted therapies in oncogenic MET-Y1253D and PIK3CA-H1047R gene transformed cells.** MCF-10A derived cells with expression of *MET*-Y1253D/*PIK3CA*-H1047R genes received starvation for overnight, followed by treatment with pictilisib (P) or tepotinib (T)) alone or their combination (P+T), and stimulation with HGF or FBS.