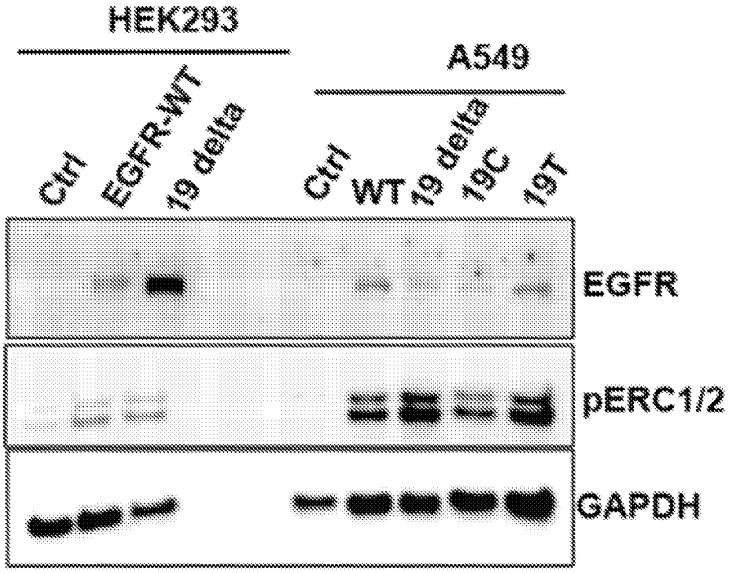

HEK293
A549
Ctrl
EGFR-WT
19 delta
Ctrl
WT
19 delta
19C
19T
EGFR
pERC1/2
GAPDH

Figure 1

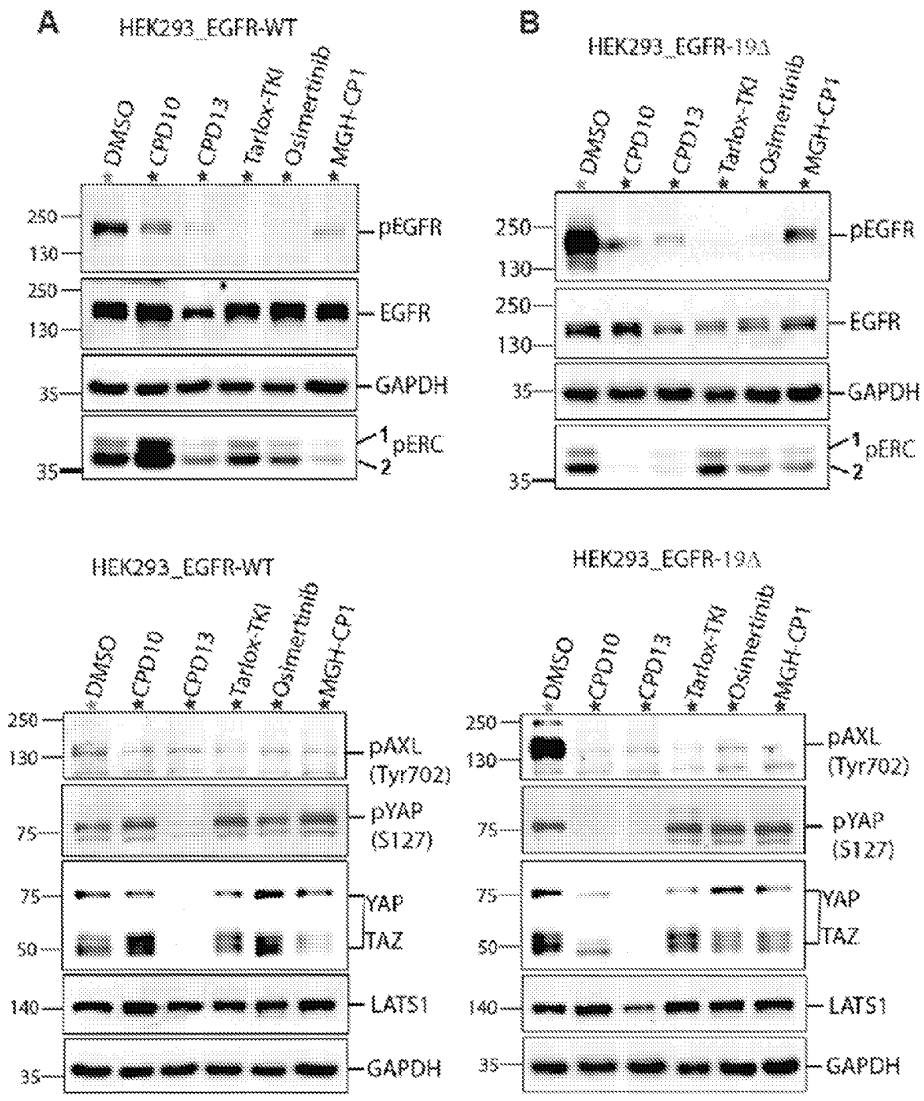

A
HEK293_EGFR-WT
DMSO
CPD10
CPD13
Tarlox-TKI
Osimertinib
MGH-CP1
250
130
pEGFR
EGFR
GAPDH
35
1
2
pERC
B
HEK293_EGFR-19Δ
HEK293_EGFR-WT
HEK293_EGFR-19Δ
75
50
pAXL (Tyr702)
pYAP (S127)
YAP
TAZ
140
LATS1

Figure 2A-B

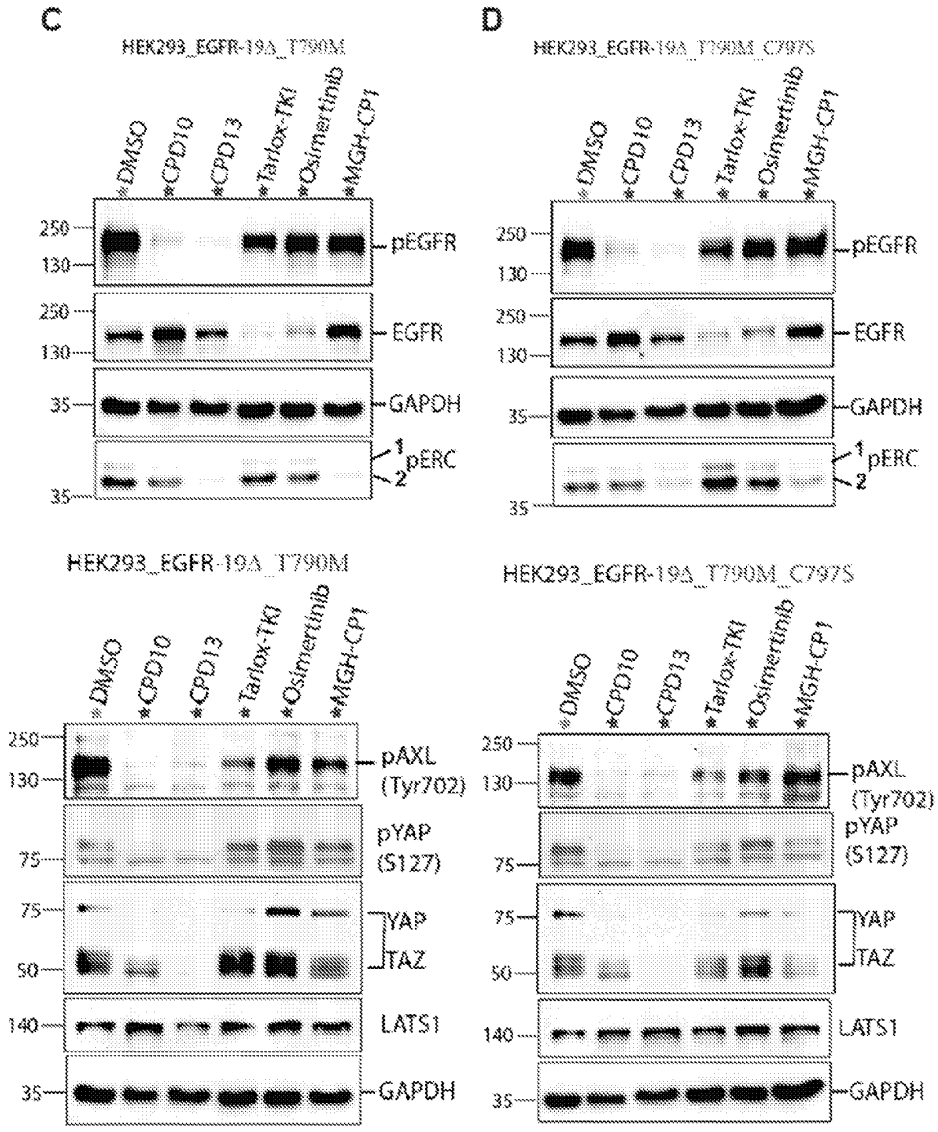

C
HEK293_EGFR-19A_T790M
*DMSO
*CPD10
*CPD13
*Tarlox-TKI
*Osimertinib
*MGH-CP1
250
130
pEGFR
250
130
EGFR
35
GAPDH
35
1
2
pERC
D
HEK293_EGFR-19A_T790M_C797S
*DMSO
*CPD10
*CPD13
*Tarlox-TKI
*Osimertinib
*MGH-CP1
250
130
pEGFR
250
130
EGFR
35
GAPDH
35
1
2
pERC
HEK293_EGFR-19A_T790M
*DMSO
*CPD10
*CPD13
*Tarlox-TKI
*Osimertinib
*MGH-CP1
250
130
pAXL
(Tyr702)
75
pYAP
(S127)
75
YAP
50
TAZ
140
LATS1
35
GAPDH
HEK293_EGFR-19A_T790M_C797S
*DMSO
*CPD10
*CPD13
*Tarlox-TKI
*Osimertinib
*MGH-CP1
250
130
pAXL
(Tyr702)
75
pYAP
(S127)
75
YAP
50
TAZ
140
LATS1
35
GAPDH

Figure 2C-D

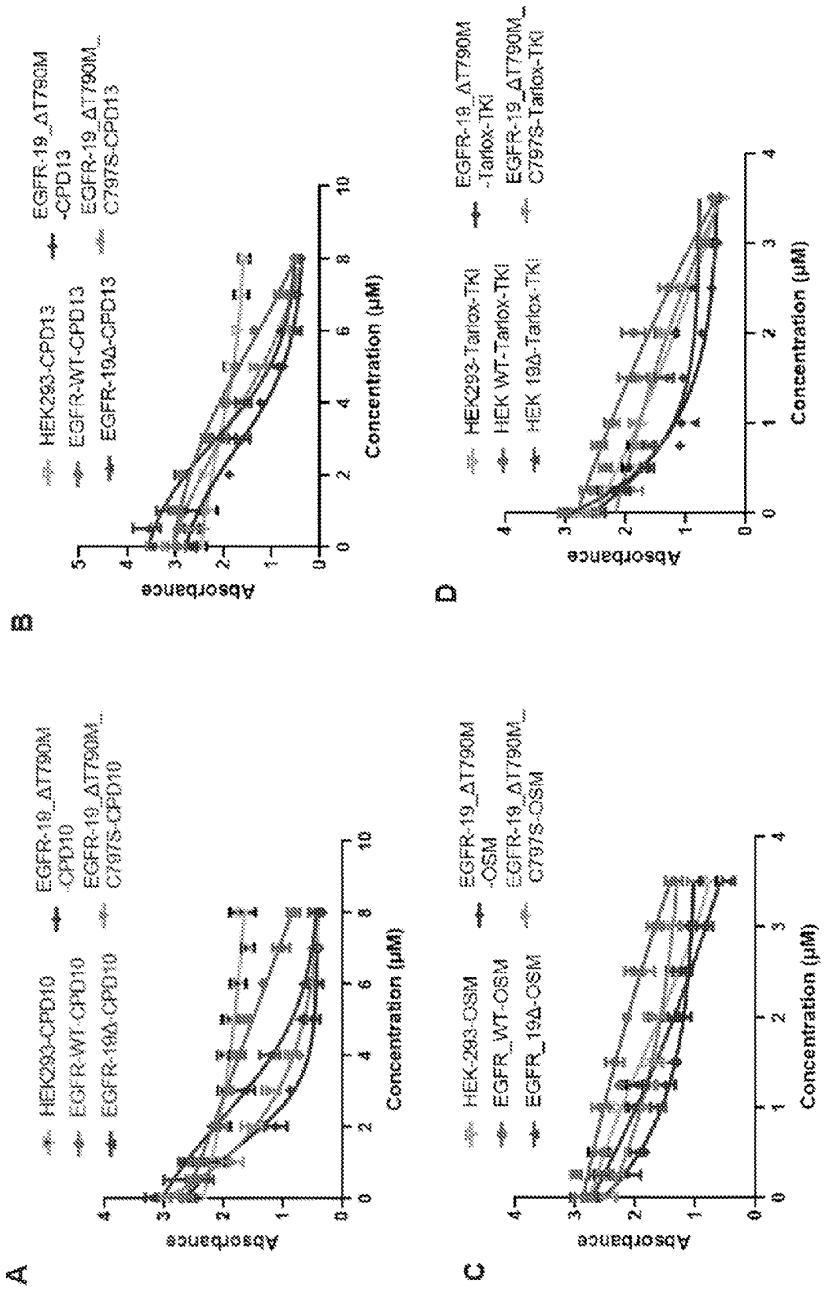

A
B
C
D
Absorbance
Concentration (μM)
HEK293-CPD10
EGFR-WT-CPD10
EGFR_19Δ-CPD10
EGFR-19_ΔT790M_C797S-CPD10
HEK293-CPD13
EGFR-WT-CPD13
EGFR-19Δ-CPD13
EGFR-19_ΔT790M_C797S-CPD13
HEK293-OSM
EGFR_WT-OSM
EGFR_19Δ-OSM
EGFR-19_ΔT790M_C797S-OSM
HEK293-Tarlox-TKI
HEK WT-Tarlox-TKI
HEK 19Δ-Tarlox-TKI
EGFR-19_ΔT790M_C797S-Tarlox-TKI

Figure 3

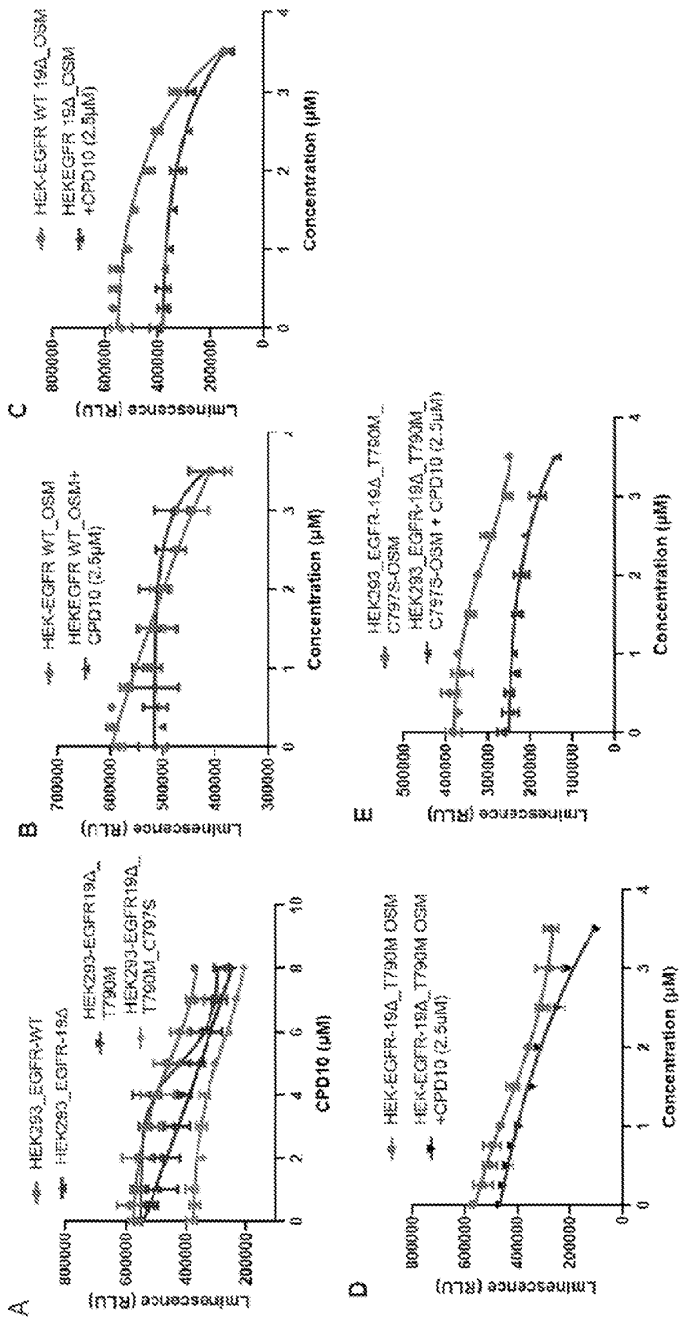

A
HEK293_EGFR-WT
HEK293_EGFR-19A
HEK293-EGFR19A_T790M
HEK293-EGFR19A_T790M_C797S
Luminescence (RLU)
CPD10 (μM)
B
HEK-EGFR WT_OSM
HEKEGFR WT_OSM+ CPD10 (2.5μM)
Luminescence (RLU)
Concentration (μM)
C
HEK-EGFR WT 19A_OSM
HEKEGFR 19A_OSM +CPD10 (2.5μM)
Luminescence (RLU)
Concentration (μM)
D
HEK-EGFR-19A_T790M OSM
HEK-EGFR-19A_T790M OSM +CPD10 (2.5uM)
Luminescence (RLU)
Concentration (μM)
E
HEK293_EGFR-19A_T790M_C797S-OSM
HEK293_EGFR-19A_T790M_C797S-OSM + CPD10 (2.5μM)
Luminescence (RLU)
Concentration (μM)

Figure 4

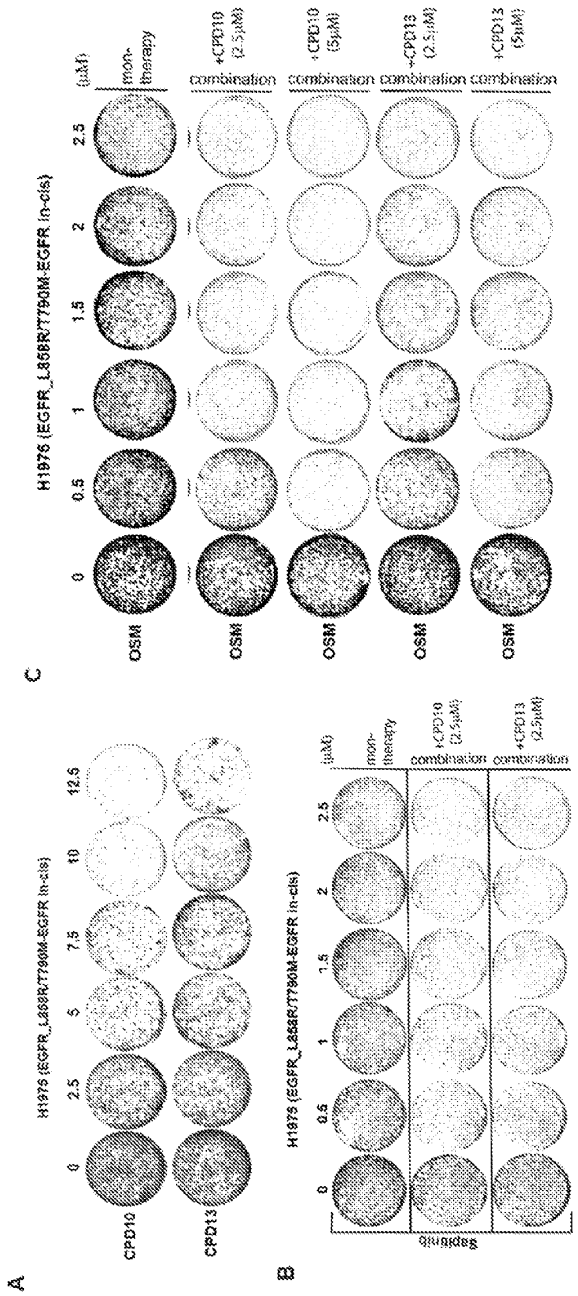

A
H1975 (EGFR_L858R/T790M-EGFR (n-cis)
0
2.5
5
7.5
10
12.5
CPD10
CPD13
B
H1975 (EGFR_L858R/T790M-EGFR (n-cis)
0
0.5
1
1.5
2
2.5
(μM)
mon-therapy
combination
+CPD10 (2.5μM)
+CPD13 (2.5μM)
Sapanisertib
C
H1975 (EGFR_L858R/T790M-EGFR (n-cis)
OSM
0
0.5
1
1.5
2
2.5
(μM)
mon-therapy
combination
+CPD10 (2.5μM)
+CPD10 (5μM)
+CPD13 (2.5μM)
+CPD13 (5μM)

Figure 5

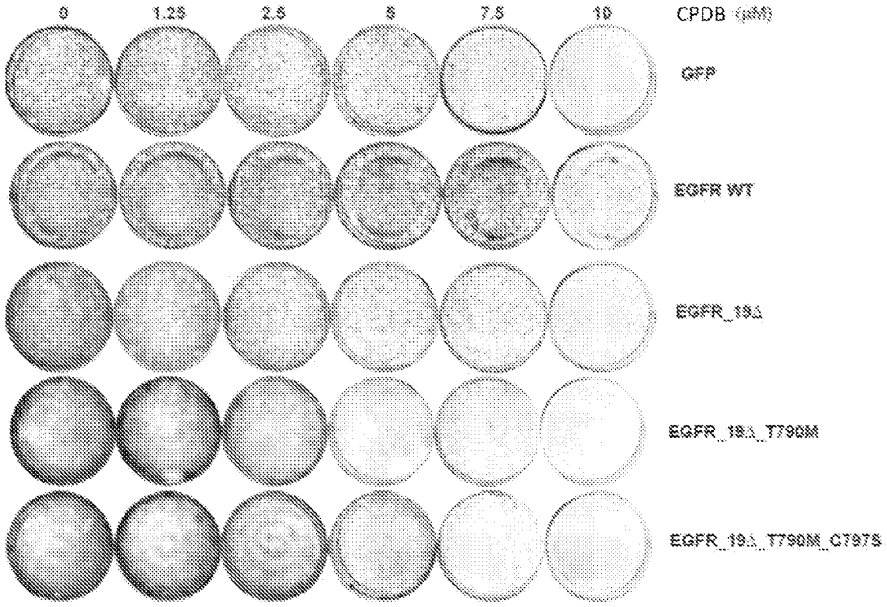


Figure 6

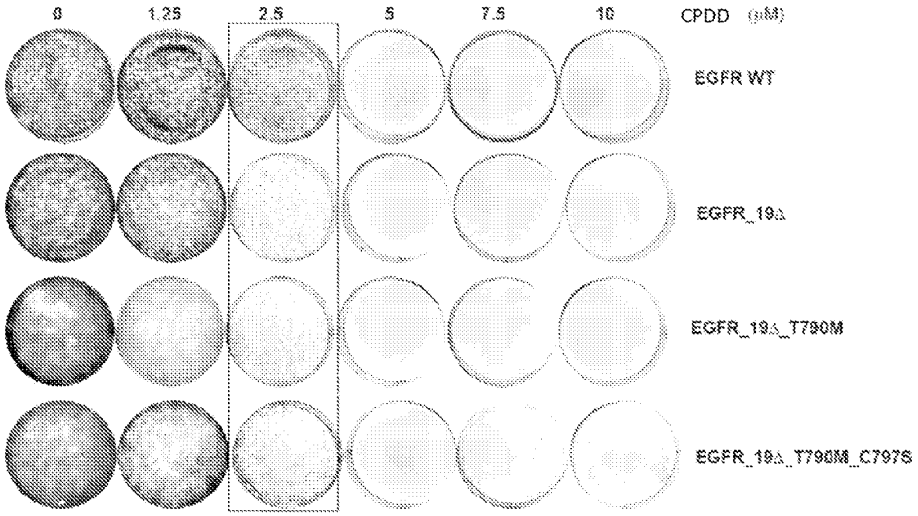


Figure 7

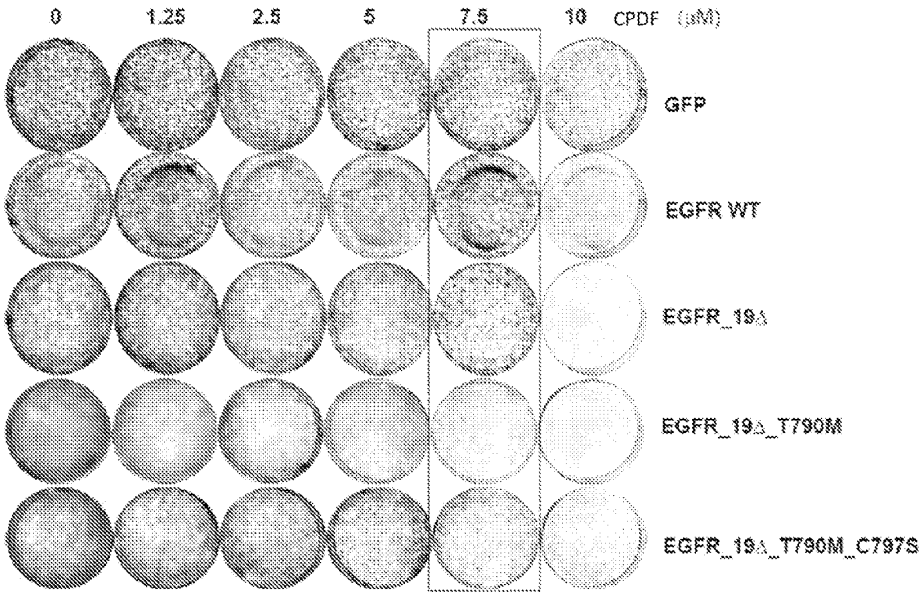


Figure 8

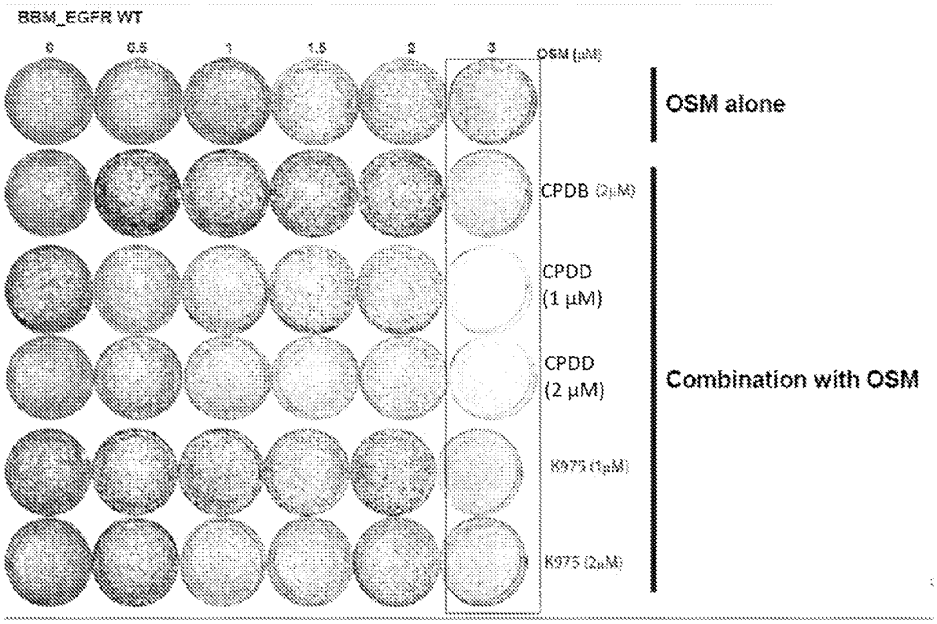


Figure 9

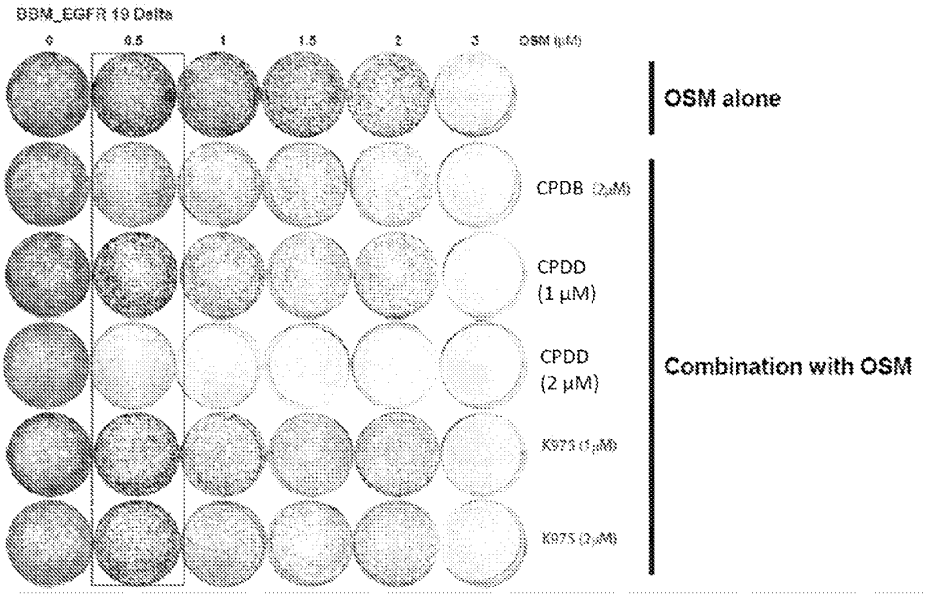


Figure 10

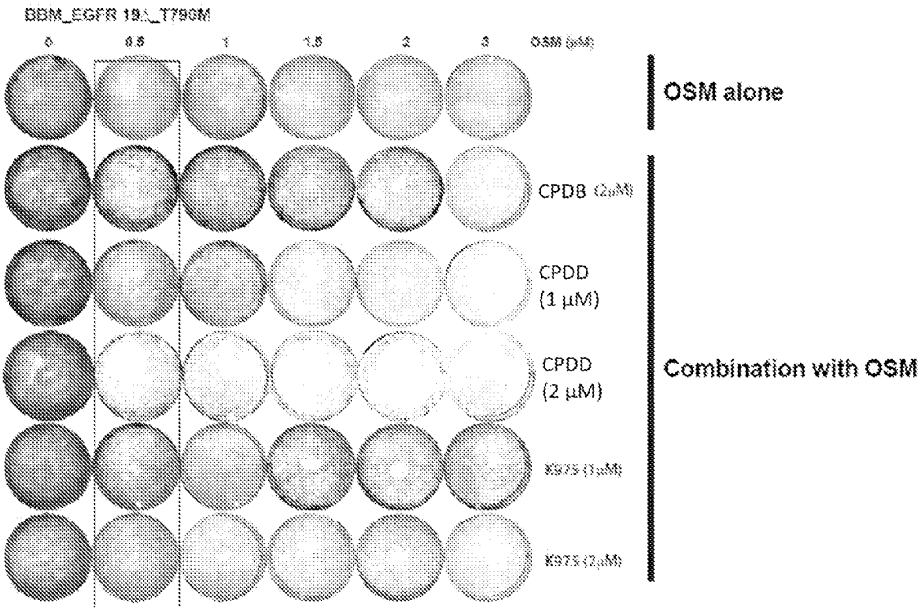


Figure 11

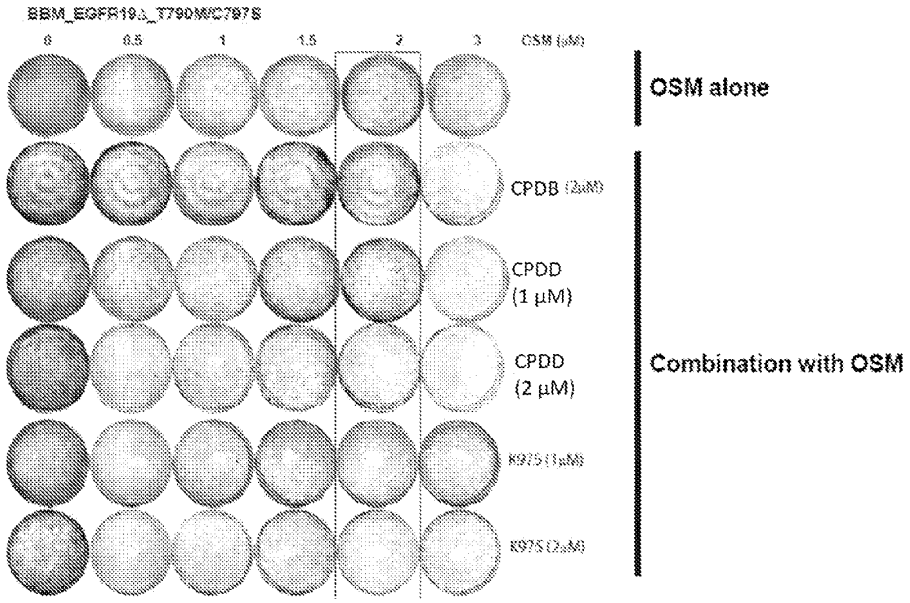

BBM_EGFR19Δ_T790MC797S
0
0.5
1
1.5
2
3
OSM (μM)
OSM alone
CPDB (2μM)
CPDD (1 μM)
CPDD (2 μM)
Combination with OSM
K975 (1μM)
K975 (2μM)

Figure 12

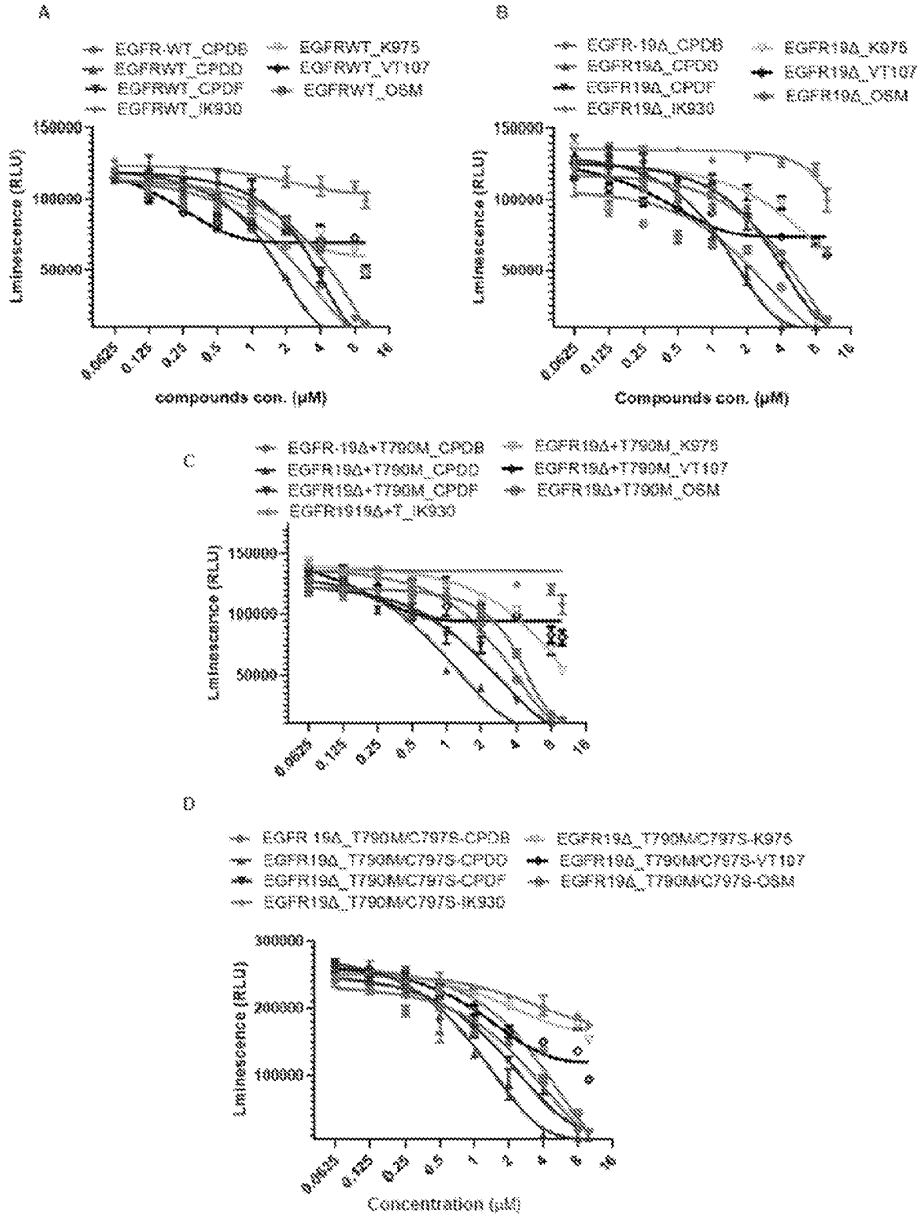

A
EGFR-WT_CPDB
EGFRWT_CPDD
EGFRWT_CPDF
EGFRWT_IK930
EGFRWT_K975
EGFRWT_VT107
EGFRWT_OSM
Luminescence (RLU)
compounds con. (μM)
B
EGFR-19A_CPDB
EGFR19Δ_CPDD
EGFR19Δ_CPDF
EGFR19Δ_IK930
EGFR19Δ_K975
EGFR19Δ_VT107
EGFR19Δ_OSM
Luminescence (RLU)
Compounds con. (μM)
C
EGFR-19Δ+T790M_CPDB
EGFR19Δ+T790M_CPDD
EGFR19Δ+T790M_CPDF
EGFR1919Δ+T_IK930
EGFR19Δ+T790M_K975
EGFR19Δ+T790M_VT107
EGFR19Δ+T790M_OSM
Luminescence (RLU)
D
EGFR 19Δ_T790M/C797S-CPDB
EGFR19Δ_T790M/C797S-CPDD
EGFR19Δ_T790M/C797S-CPDF
EGFR19Δ_T790M/C797S-IK930
EGFR19Δ_T790M/C797S-K975
EGFR19Δ_T790M/C797S-VT107
EGFR19Δ_T790M/C797S-OSM
Luminescence (RLU)
Concentration (μM)

Figure 13

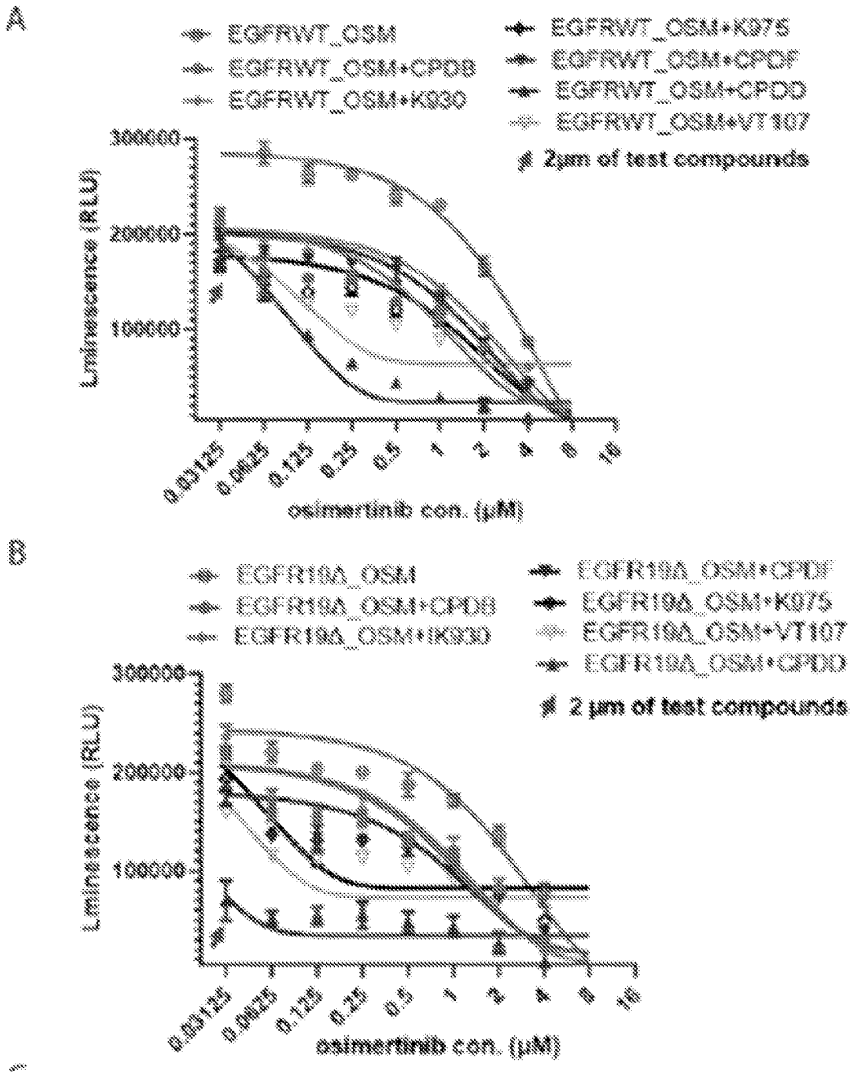

A
EGFRWT_OSM
EGFRWT_OSM+CPDB
EGFRWT_OSM+K930
EGFRWT_OSM+K975
EGFRWT_OSM+CPDF
EGFRWT_OSM+CPDD
EGFRWT_OSM+VT107
2μm of test compounds
Luminescence (RLU)
300000
200000
100000
0.03125
0.0625
0.125
0.25
0.5
1
2
4
8
16
osimertinib con. (μM)
B
EGFR19A_OSM
EGFR19A_OSM+CPDB
EGFR19A_OSM+K930
EGFR19A_OSM+CPDF
EGFR19A_OSM+K975
EGFR19A_OSM+VT107
EGFR19A_OSM+CPDD
2 μm of test compounds
Luminescence (RLU)
300000
200000
100000
0.03125
0.0625
0.125
0.25
0.5
1
2
4
8
16
osimertinib con. (μM)

Figure 14A-B

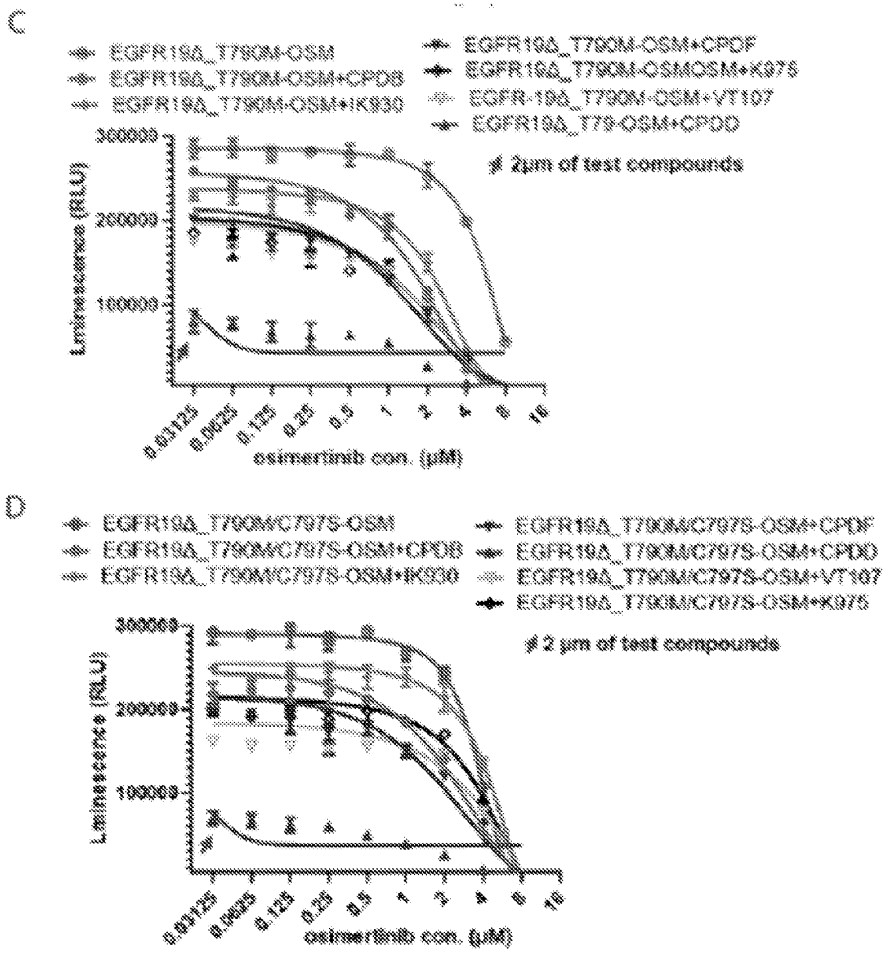

C
EGFR19Δ_T790M-OSM
EGFR19Δ_T790M-OSM+CPDB
EGFR19Δ_T790M-OSM+IK930
EGFR19Δ_T790M-OSM+CPDF
EGFR19Δ_T790M-OSMOSM+K975
EGFR-19Δ_T790M-OSM+VT107
EGFR19Δ_T79-OSM+CPDD
2μm of test compounds
Luminescence (RLU)
300000
200000
100000
0.03125
0.0625
0.125
0.25
0.5
1
2
4
8
10
osimertinib con. (μM)
D
EGFR19Δ_T790M/C797S-OSM
EGFR19Δ_T790M/C797S-OSM+CPDB
EGFR19Δ_T790M/C797S-OSM+IK930
EGFR19Δ_T790M/C797S-OSM+CPDF
EGFR19Δ_T790M/C797S-OSM+CPDD
EGFR19Δ_T790M/C797S-OSM+VT107
EGFR19Δ_T790M/C797S-OSM+K975
2 μm of test compounds
Luminescence (RLU)
300000
200000
100000
0.03125
0.0625
0.125
0.25
0.5
1
2
4
8
10
osimertinib con. (μM)

Figure 14C-D

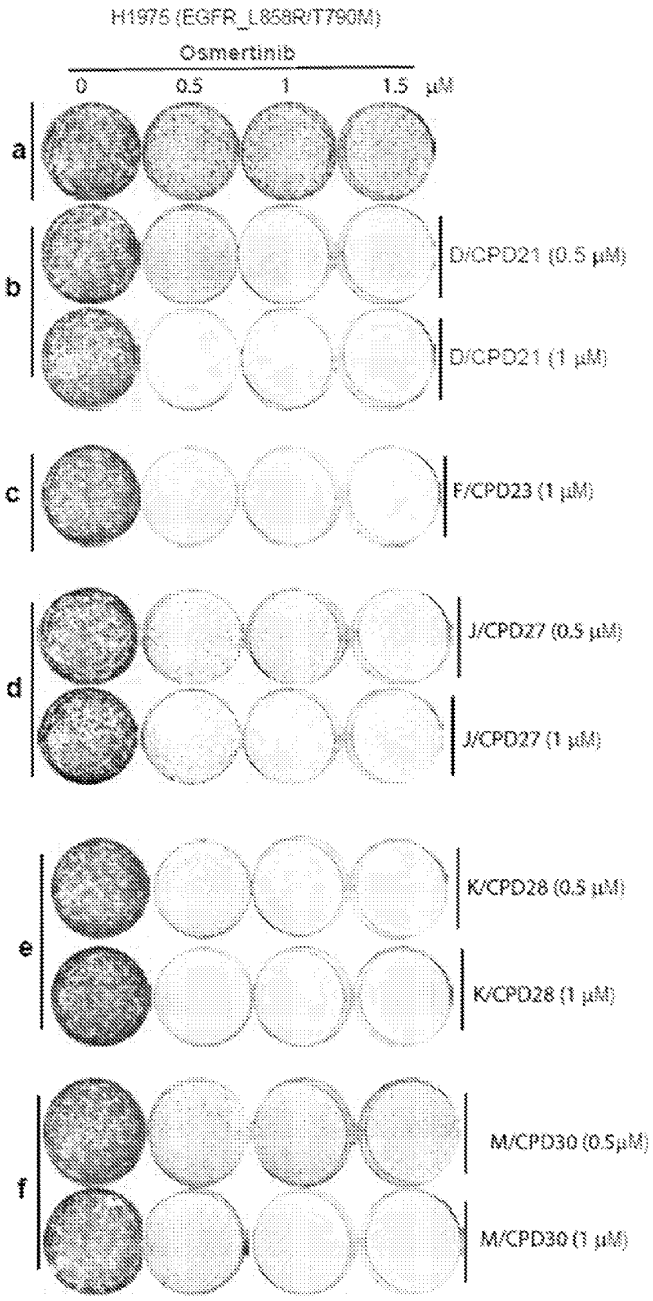

H1975 (EGFR_L858R/T790M)
Osmertinib
0
0.5
1
1.5 μM
a
b
D/CPD21 (0.5 μM)
D/CPD21 (1 μM)
c
F/CPD23 (1 μM)
d
J/CPD27 (0.5 μM)
J/CPD27 (1 μM)
e
K/CPD28 (0.5 μM)
K/CPD28 (1 μM)
f
M/CPD30 (0.5μM)
M/CPD30 (1 μM)

Figure 15

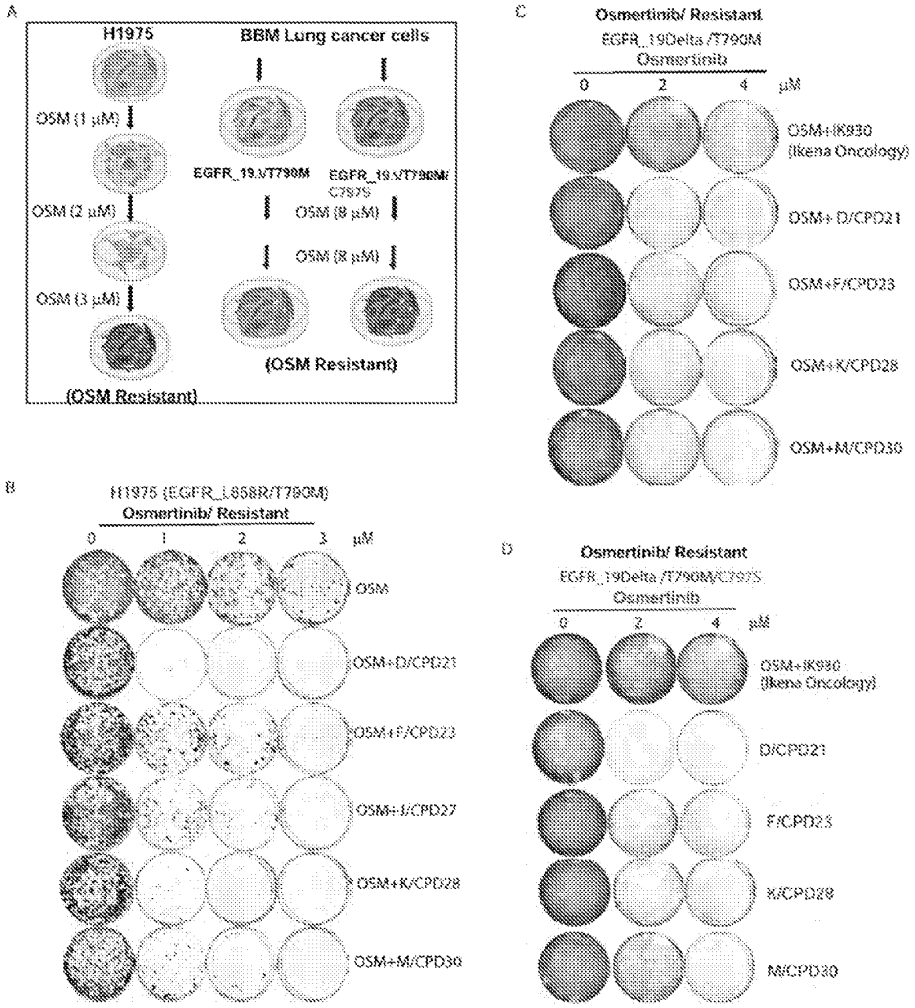

A
H1975
BBM Lung cancer cells
OSM (1 μM)
EGFR_19.V/T790M
EGFR_19.V/T790M/C797S
OSM (2 μM)
OSM (8 μM)
OSM (8 μM)
OSM (3 μM)
(OSM Resistant)
(OSM Resistant)
B
H1975 (EGFR_L858R/T790M)
Osmertinib/ Resistant
0 1 2 3 μM
OSM
OSM+D/CPD21
OSM+F/CPD23
OSM+I/CPD27
OSM+K/CPD28
OSM+M/CPD30
C
Osmertinib/ Resistant
EGFR_19Delta /T790M
Osmertinib
0 2 4 μM
OSM+IK930
(Ikena Oncology)
OSM+ D/CPD21
OSM+F/CPD23
OSM+K/CPD28
OSM+M/CPD30
D
Osmertinib/ Resistant
EGFR_19Delta /T790M/C797S
Osmertinib
0 2 4 μM
OSM+IK930
(Ikena Oncology)
D/CPD21
F/CPD23
K/CPD28
M/CPD30

Figure 16

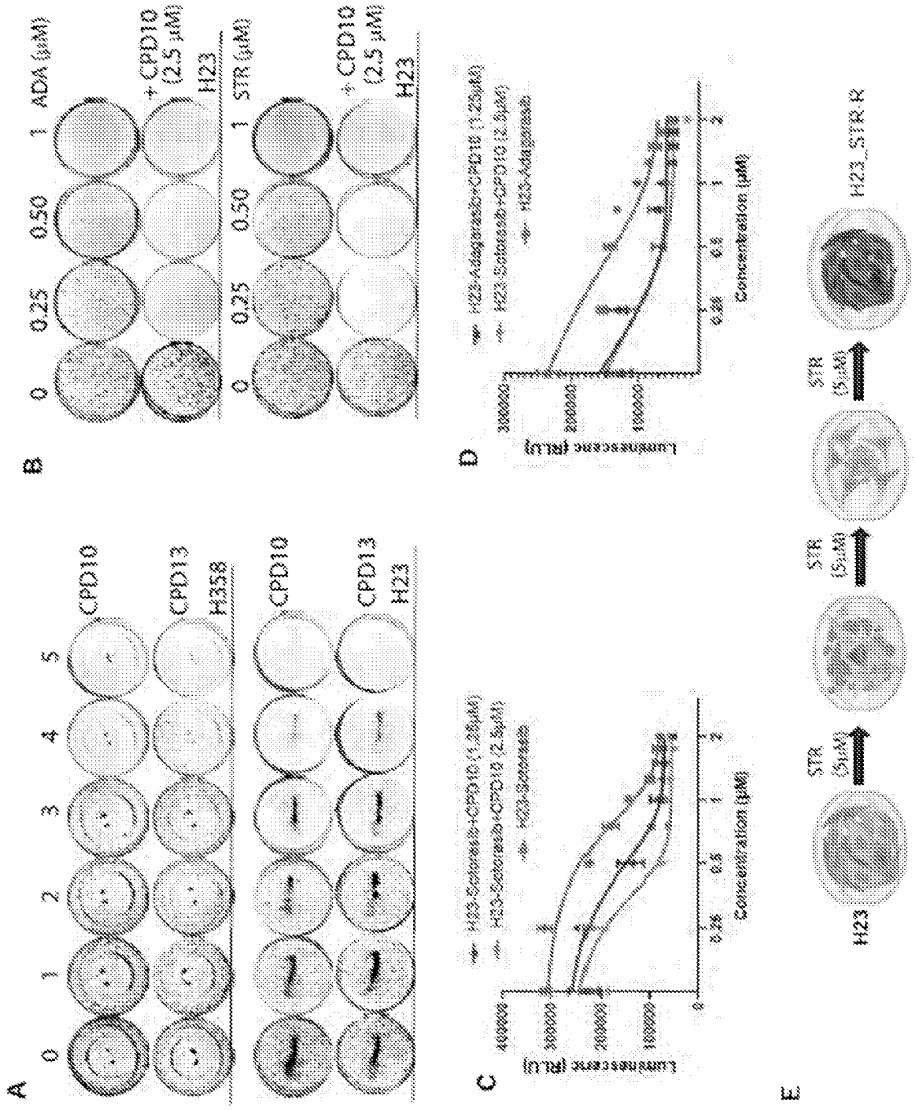

A
0
1
2
3
4
5
CPD10
CPD13
H358
CPD10
CPD13
H23
B
0
0.25
0.50
1
ADA (μM)
+ CPD10 (2.5 μM)
H23
STR (μM)
C
H23-Sotorasib+CPD10 (1.25μM)
H23-Sotorasib+CPD10 (2.5μM)
H23-Sotorasib
Luminescence (RLU)
Concentration (μM)
D
H23-Adagrasib+CPD10 (1.25μM)
H23-Sotorasib+CPD10 (2.5μM)
H23-Adagrasib
E
H23
STR (5μM)
H23_STR R

Figure 17A-E

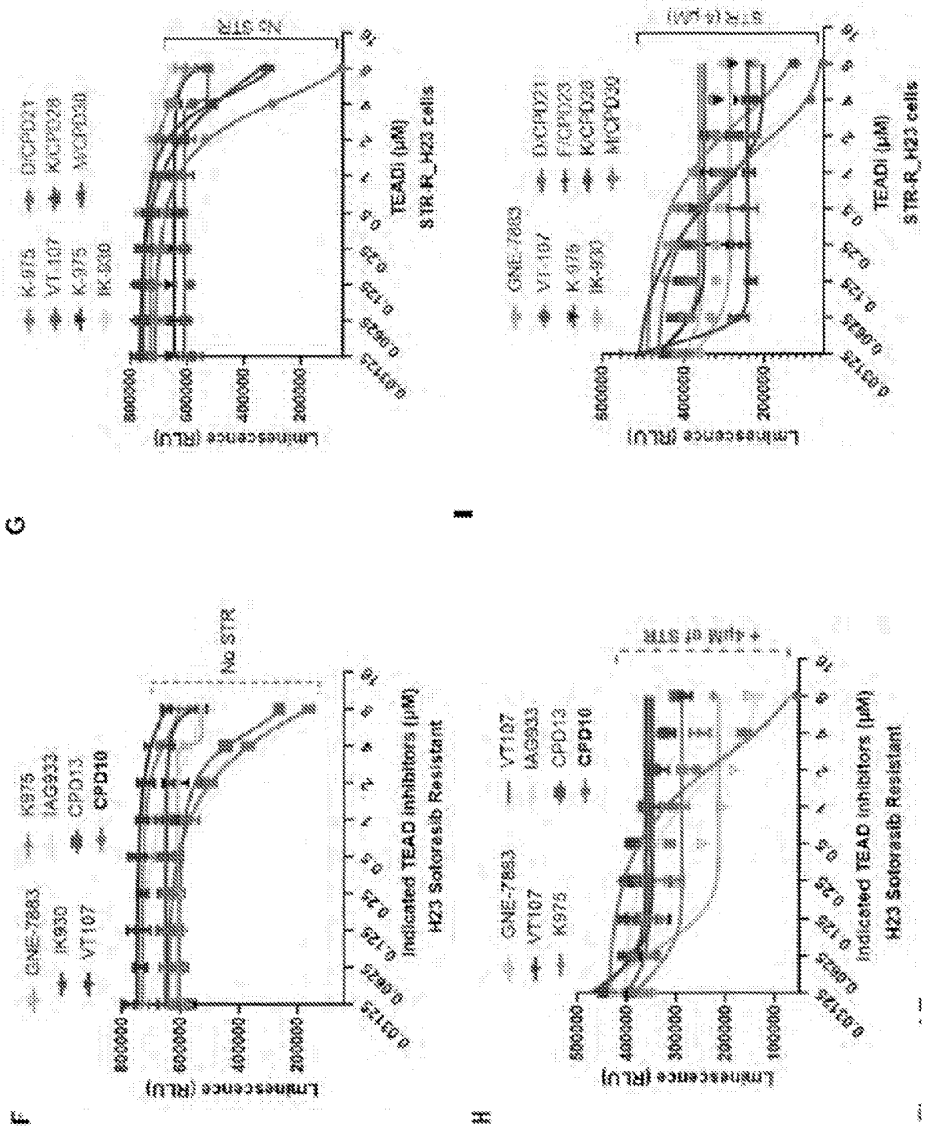

G
No STR
K-975
VT-107
K-975
IK-930
DICPD21
KICPD28
MICPD30
TEADi (μM)
STR-R_H23 cells
Luminescence (RLU)
I
STR (μM)
GNE-7883
VT-107
K-975
IK-930
DICPD21
FICPD23
KICPD28
MICPD30
TEADi (μM)
STR-R_H23 cells
Luminescence (RLU)
F
No STR
GNE-7883
IK930
VT107
K975
IAG933
CPD13
CPD16
Indicated TEAD inhibitors (μM)
H23 Sotorasib Resistant
Luminescence (RLU)
H
+ 4μM of STR
GNE-7883
VT107
K975
VT107
IAG933
CPD13
CPD16
Indicated TEAD inhibitors (μM)
H23 Sotorasib Resistant
Luminescence (RLU)

Figure 17F–I

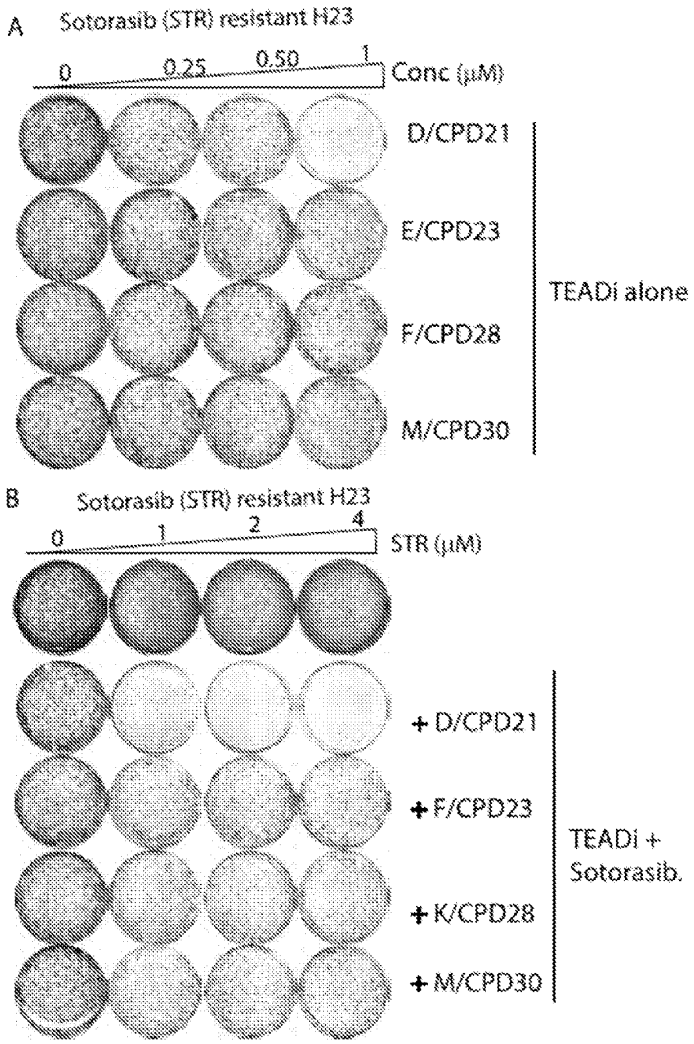

A
Sotorasib (STR) resistant H23
0
0.25
0.50
1
Conc (μM)
D/CPD21
E/CPD23
F/CPD28
M/CPD30
TEADi alone
B
Sotorasib (STR) resistant H23
0
1
2
4
STR (μM)
+ D/CPD21
+ F/CPD23
+ K/CPD28
+ M/CPD30
TEADi + Sotorasib.

Figure 18