FIGURE 1

FIG. 1A

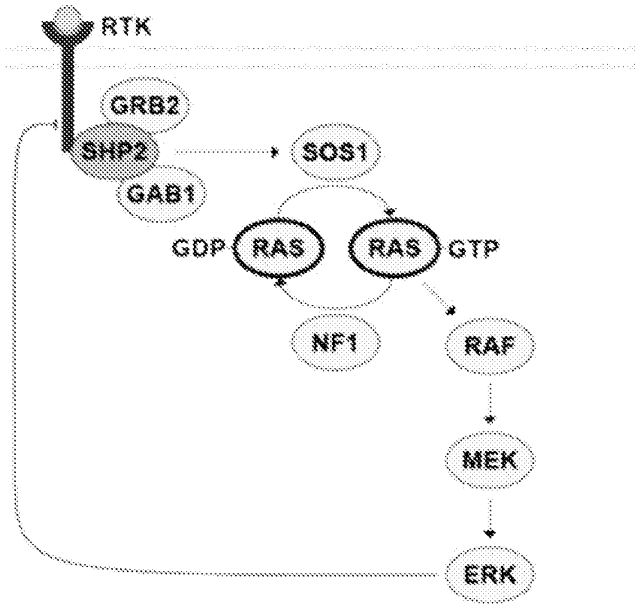


FIG. 1B

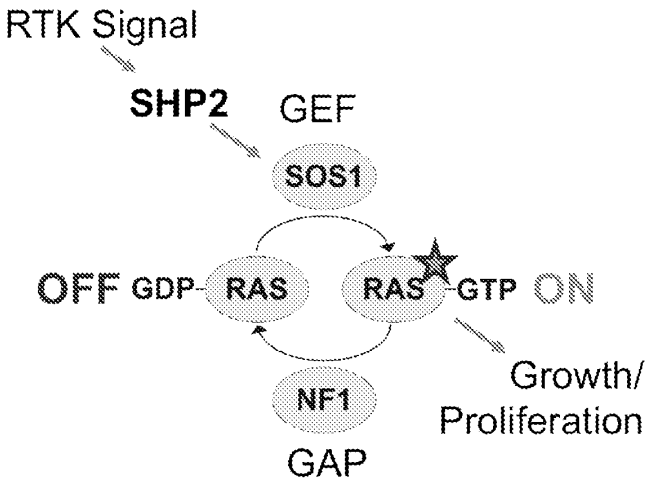


FIGURE 2

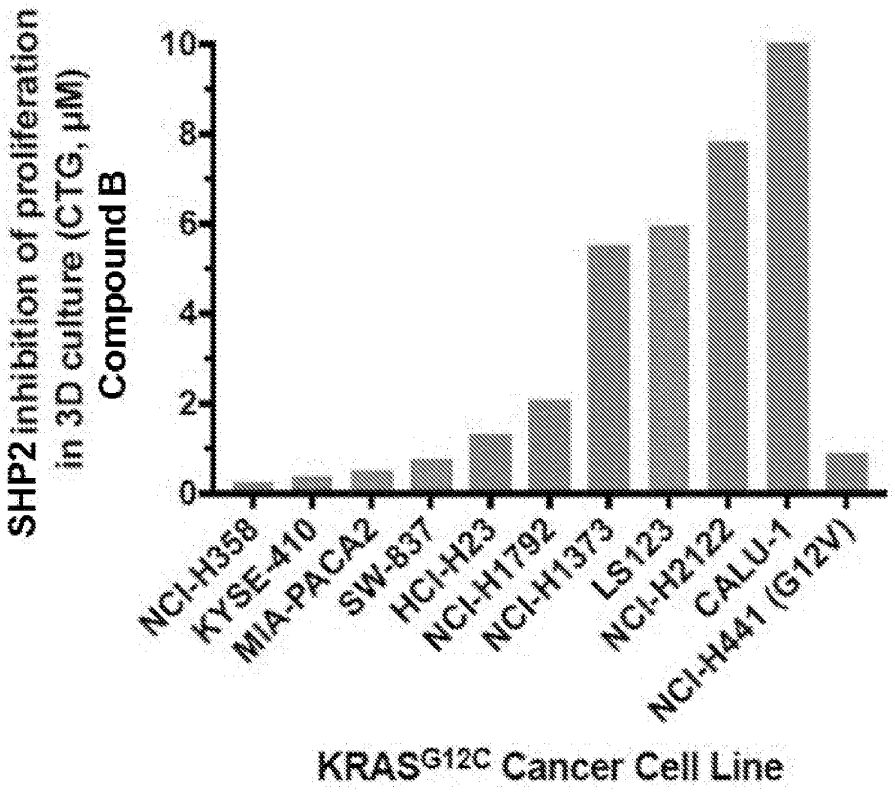

SHP2 inhibition of proliferation in 3D culture (CTG, μM)
Compound B
0
2
4
6
8
10
NCI-H358
KYSE-410
MIA-PACA2
SW-837
HCI-H23
NCI-H1792
NCI-H1373
LS123
NCI-H2122
CALU-1
NCI-H441 (G12V)
KRASG12C Cancer Cell Line

FIGURE 3

FIG. 3A

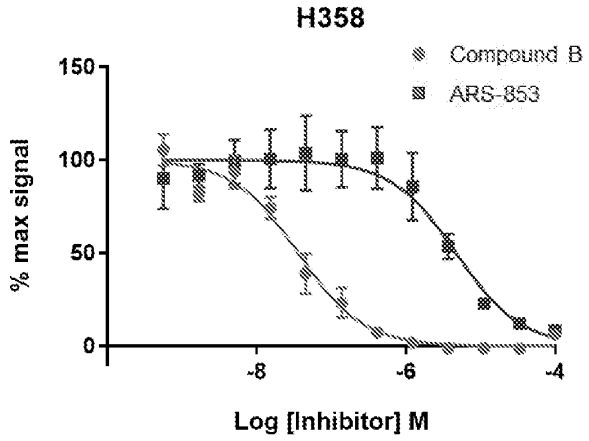


FIG. 3B

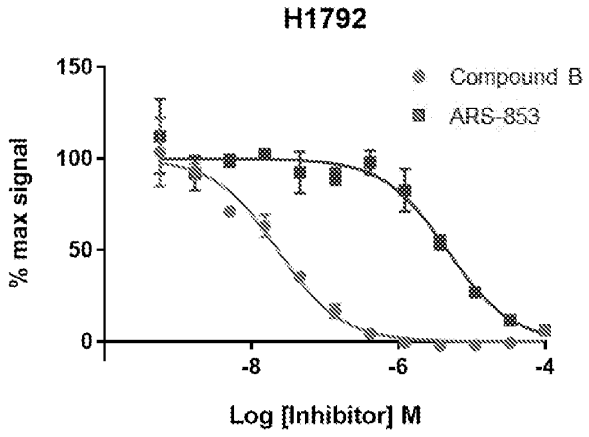


FIGURE 3 (continued)

FIG. 3C

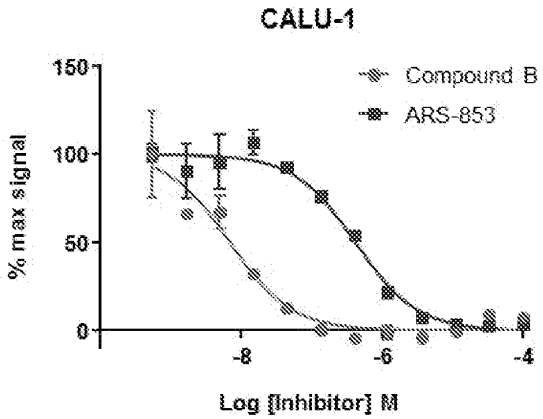


FIGURE 4

FIG. 4A

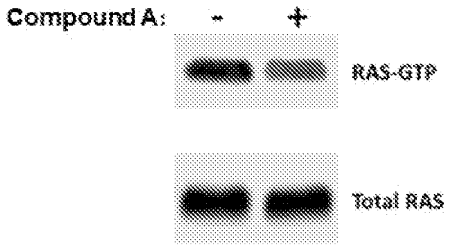


FIG. 4B

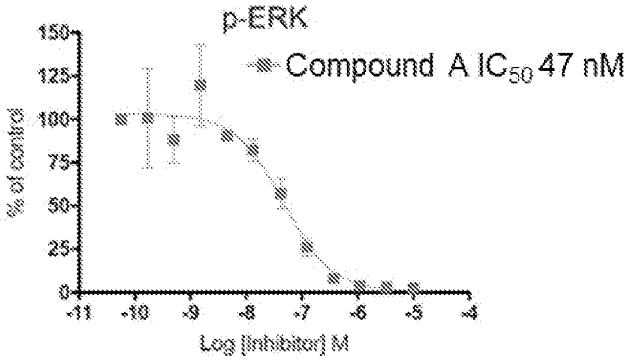


FIG. 4C

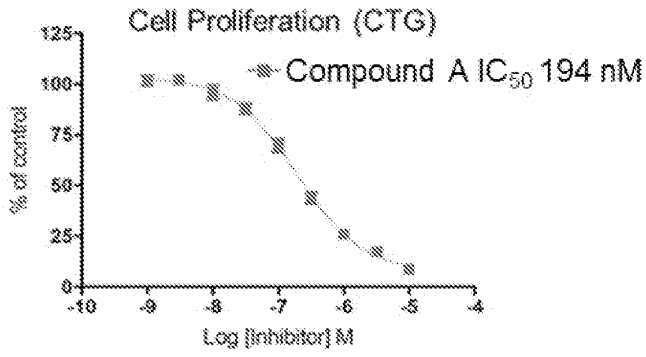


FIGURE 5

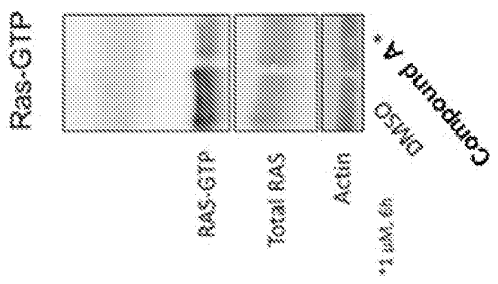


FIG. 5A

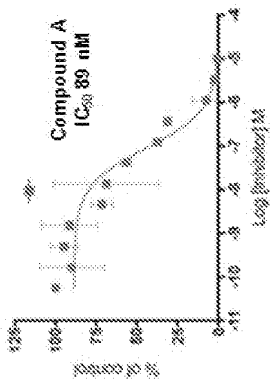


FIG. 5B

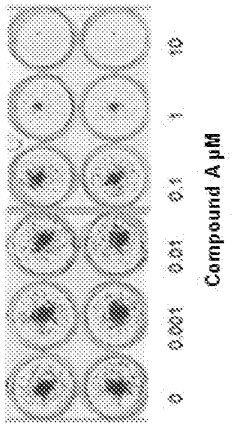


FIG. 5C

FIGURE 6

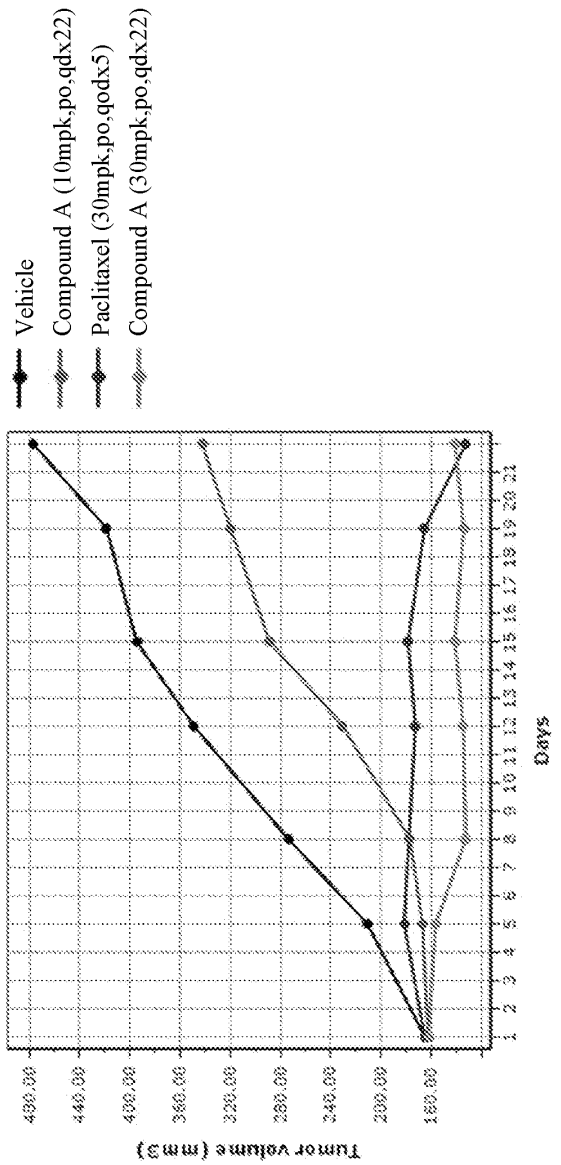

Vehicle
Compound A (10mpk,po,qdx22)
Paclitaxel (30mpk,po,qodx5)
Compound A (30mpk,po,qdx22)
Tumor volume (mm3)
480.00
440.00
400.00
360.00
320.00
280.00
240.00
200.00
160.00
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
Days

FIGURE 7

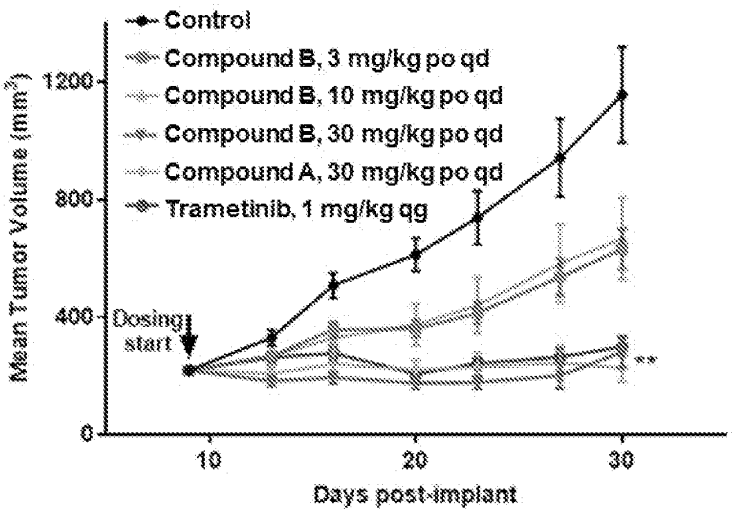

Control
Compound B, 3 mg/kg po qd
Compound B, 10 mg/kg po qd
Compound B, 30 mg/kg po qd
Compound A, 30 mg/kg po qd
Trametinib, 1 mg/kg qg
Mean Tumor Volume (mm3)
1200
800
400
0
Dosing start
**
10
20
30
Days post-implant

FIGURE 8

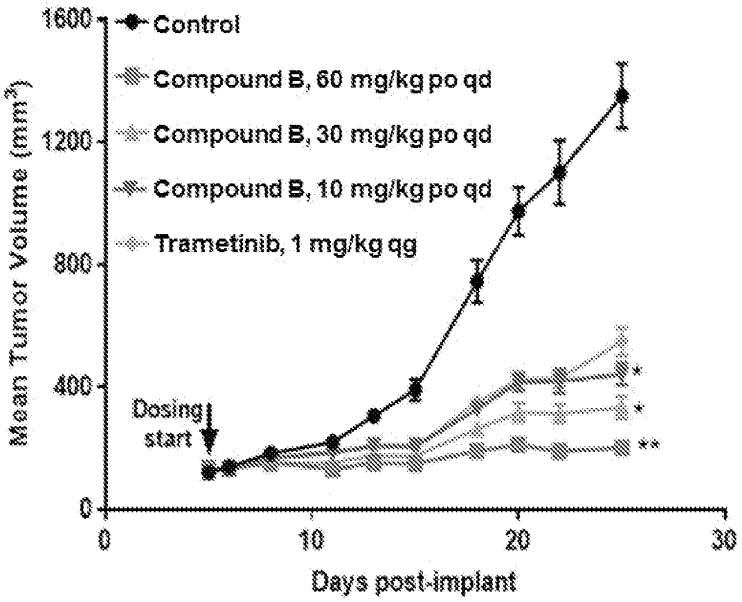

1600
1200
800
400
0
Mean Tumor Volume (mm³)
Control
Compound B, 60 mg/kg po qd
Compound B, 30 mg/kg po qd
Compound B, 10 mg/kg po qd
Trametinib, 1 mg/kg qg
Dosing start
*
*
**
0
10
20
30
Days post-implant

FIGURE 9

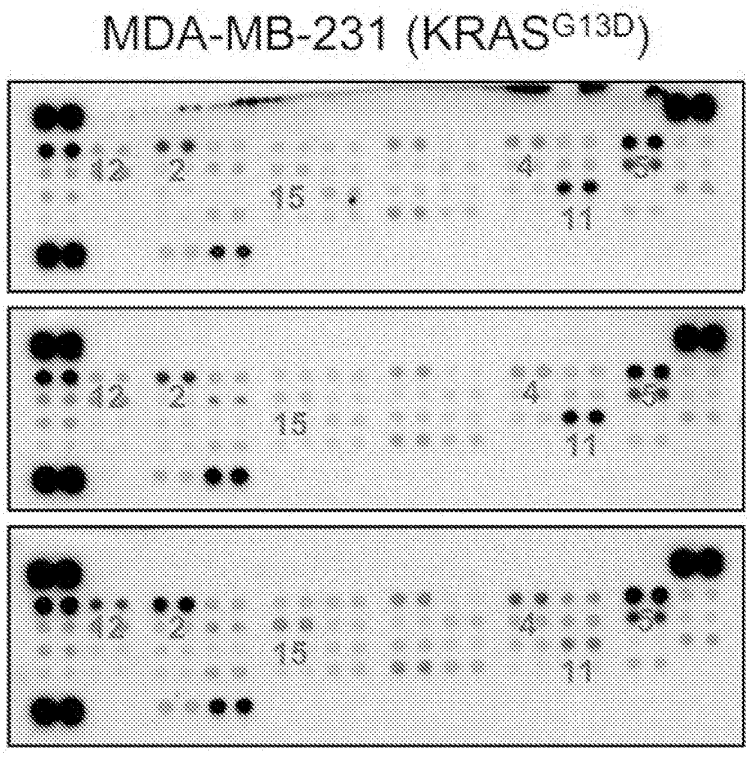

MDA-MB-231 (KRAS^{G13D})
DMSO
Compound A*
Selumetinib*
*5μM, 24 h
2. pHER3
4. pInsR
5. pAxl
11. pEphA2
12. pHER2
15. pPDGFRβ

FIGURE 10

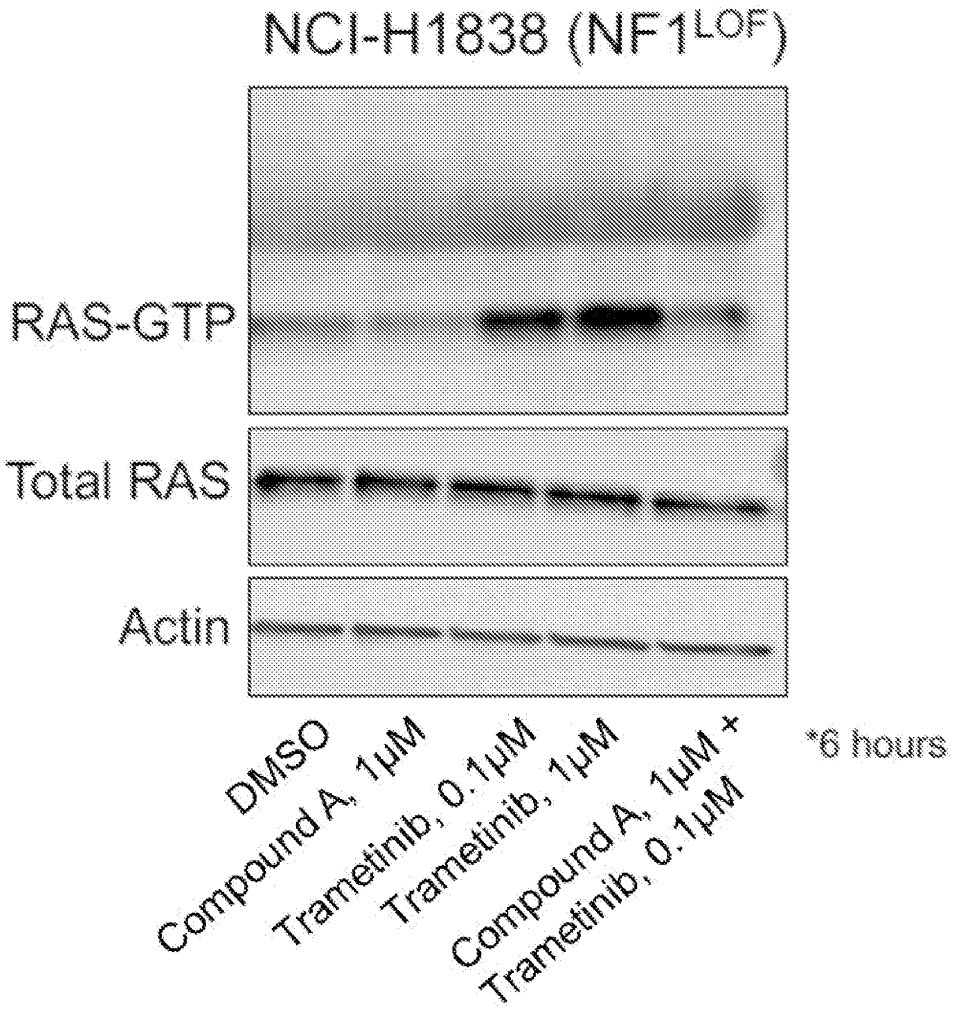

NCI-H1838 (NF1LOF)
RAS-GTP
Total RAS
Actin
DMSO
Compound A, 1μM
Trametinib, 0.1μM
Trametinib, 1μM
Compound A, 1μM + Trametinib, 0.1μM
*6 hours

FIGURE 11

FIG. 11A

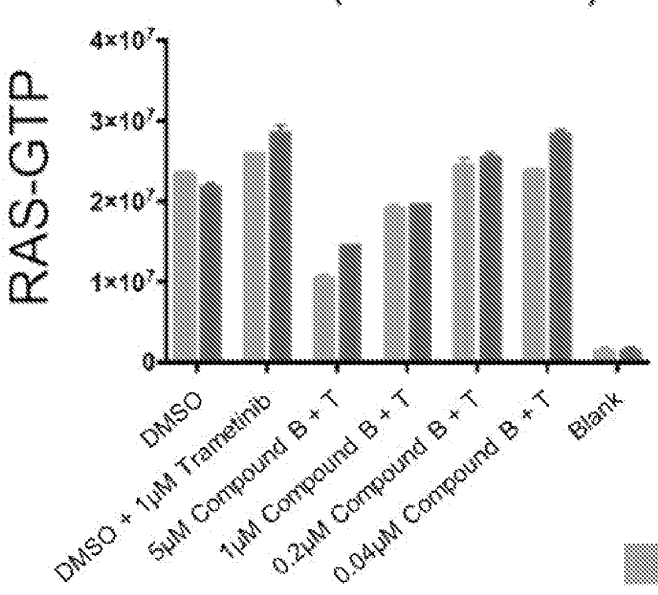


FIG. 11B

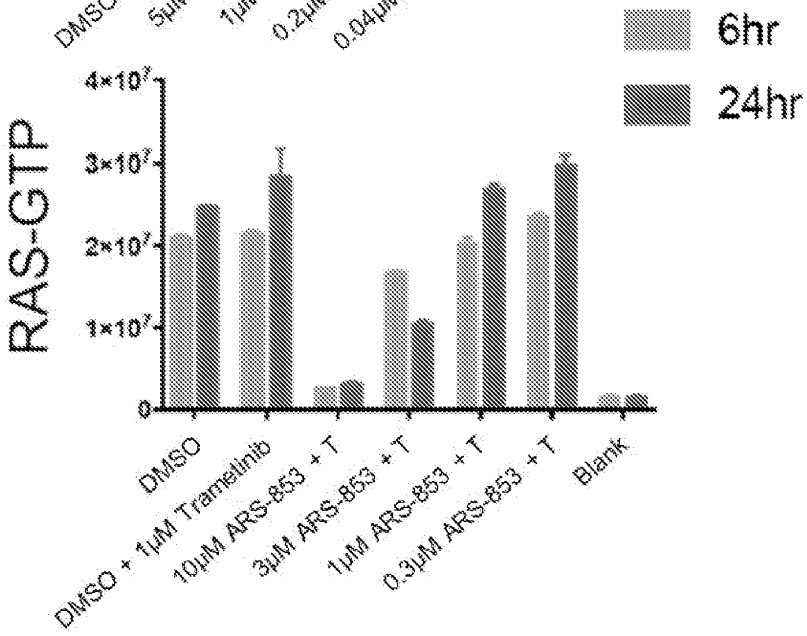


FIGURE 11 (continued)

FIG. 11C

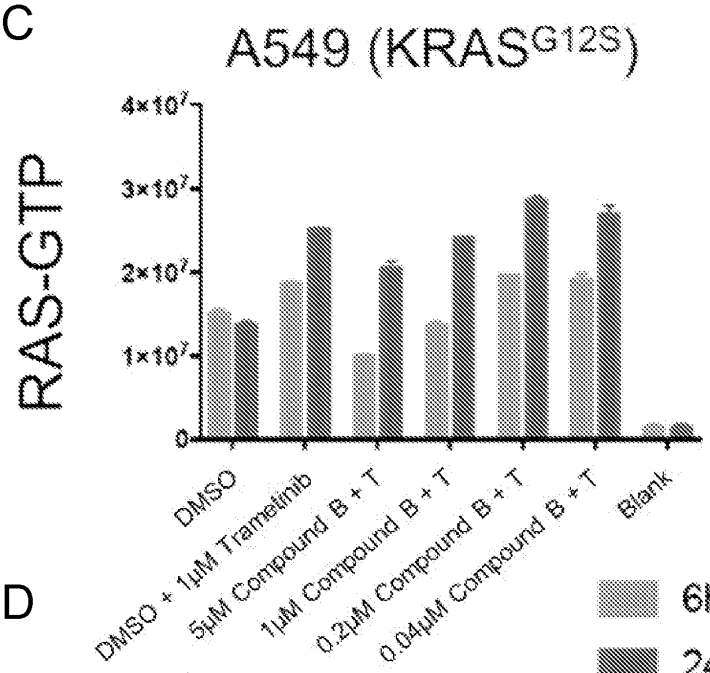


FIG. 11D

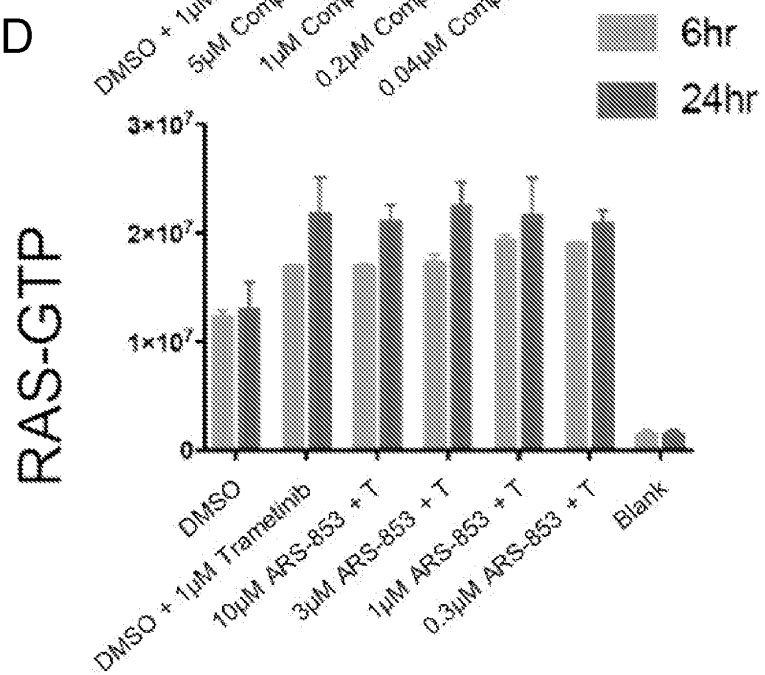


FIGURE 12

FIG. 12A

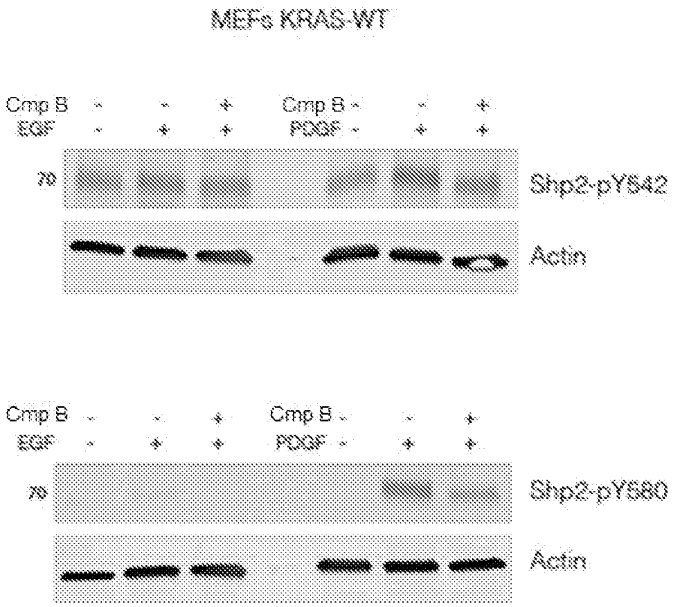


FIGURE 12 (continued)

FIG. 12B

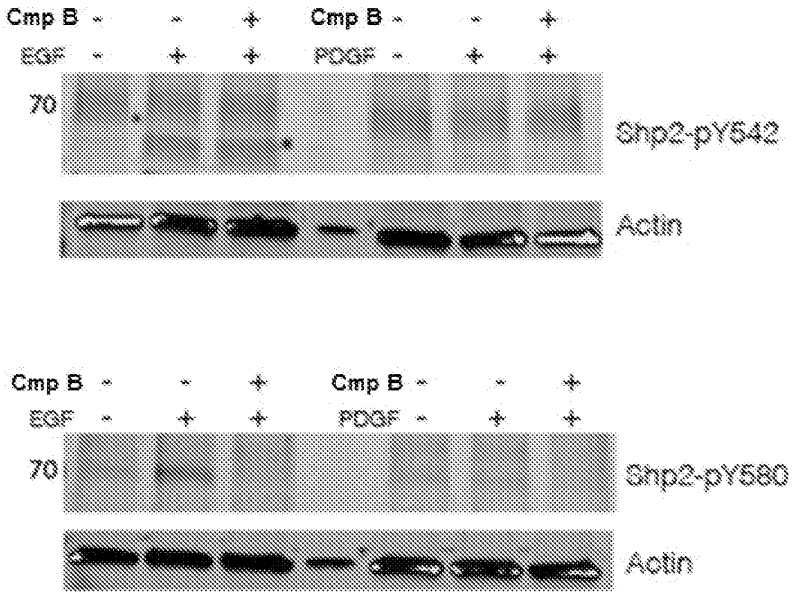


FIGURE 12 (continued)

FIG. 12C

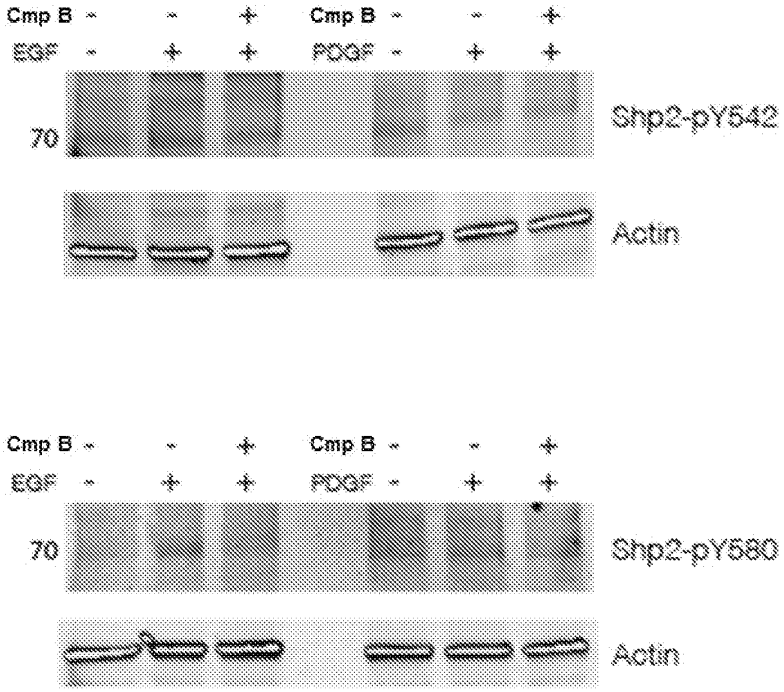


FIGURE 13

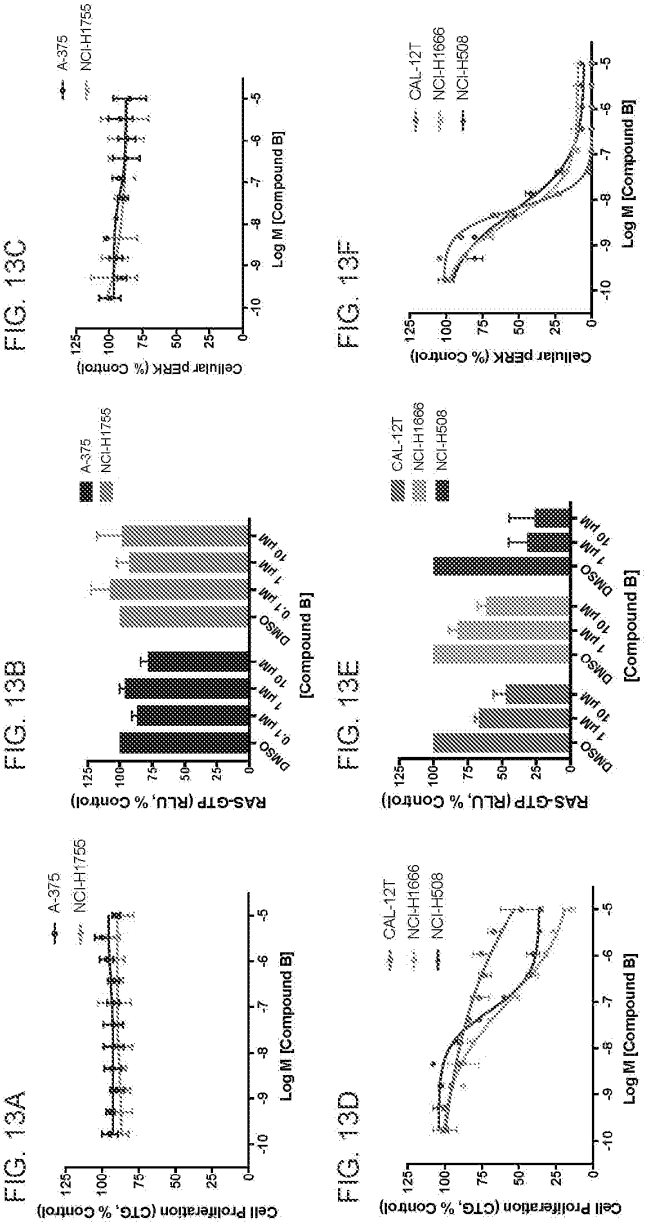

FIG. 13A
A-375
NCI-H1755
Cell Proliferation (CTG, % Control)
Log M [Compound B]
FIG. 13B
A-375
NCI-H1755
RAS-GTP (RLU, % Control)
DMSO
0.1 μM
1 μM
10 μM
0.1 μM
1 μM
10 μM
[Compound B]
FIG. 13C
A-375
NCI-H1755
Cellular pERK (% Control)
Log M [Compound B]
FIG. 13D
CAL-12T
NCI-H1666
NCI-H508
Cell Proliferation (CTG, % Control)
Log M [Compound B]
FIG. 13E
CAL-12T
NCI-H1666
NCI-H508
RAS-GTP (RLU, % Control)
DMSO
0.1 μM
1 μM
10 μM
0.1 μM
1 μM
10 μM
[Compound B]
FIG. 13F
CAL-12T
NCI-H1666
NCI-H508
Cellular pERK (% Control)
Log M [Compound B]

FIGURE 14

FIG. 14A

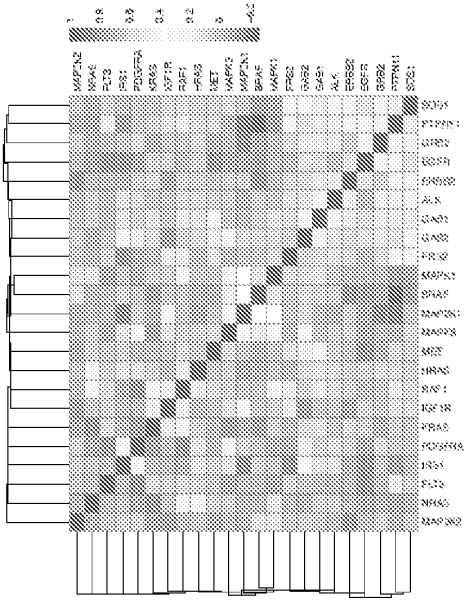


FIG. 14B

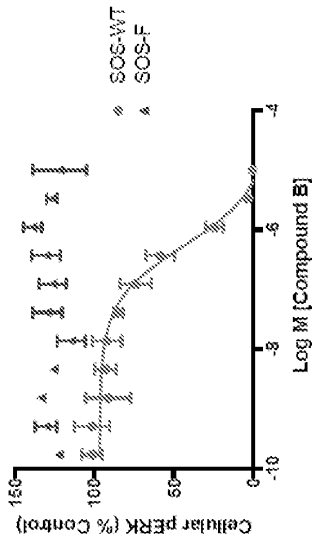


FIGURE 14 (continued)

FIG. 14C

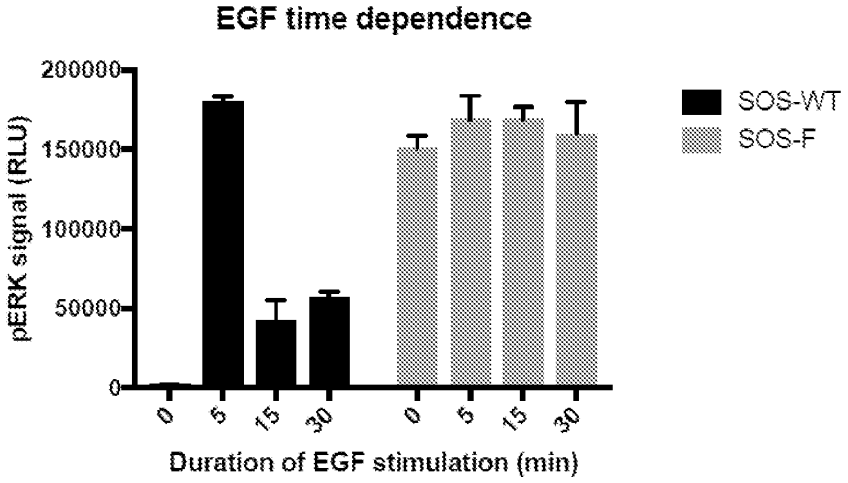


FIGURE 15

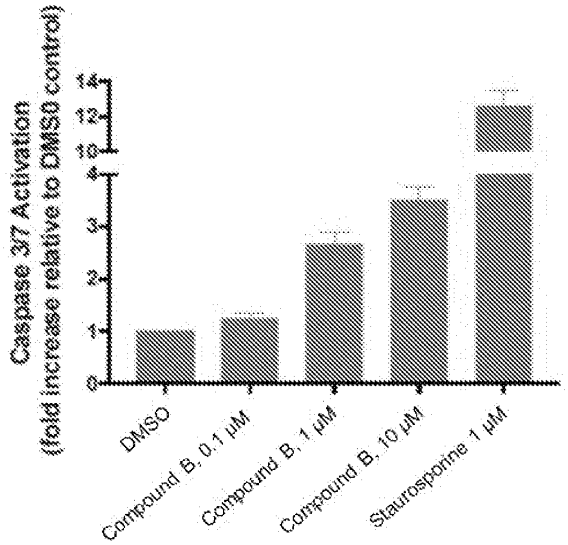
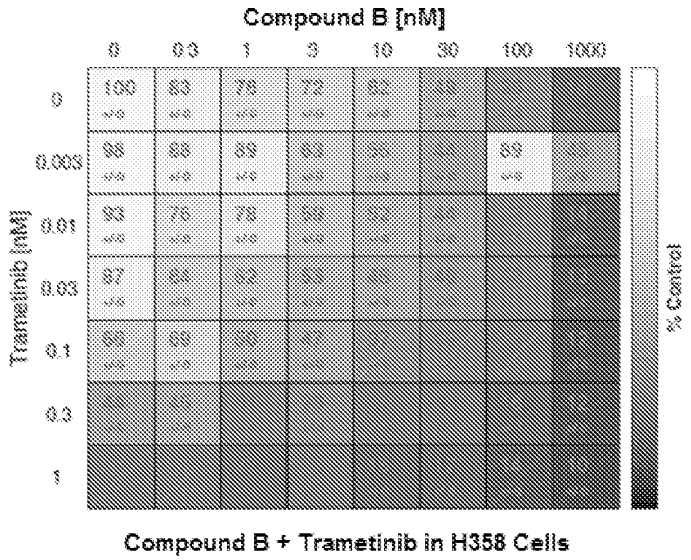


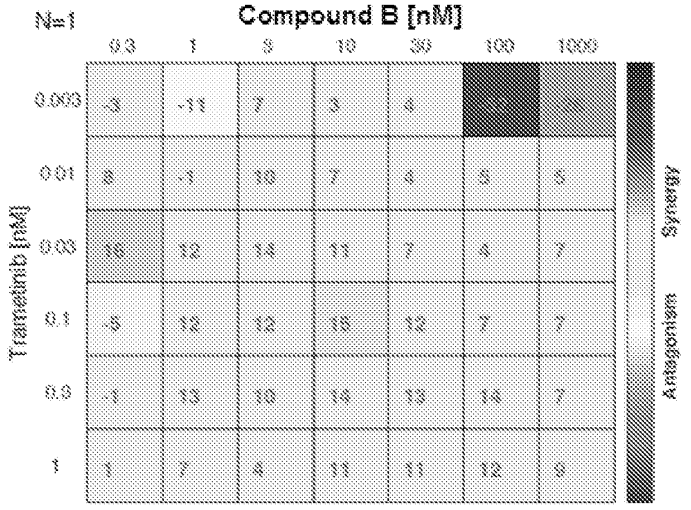
FIGURE 16

FIG. 16A



Compound B + Trametinib in H358 Cells

FIG. 16B



Loewe synergy and antagonism
Compound B + Trametinib in H358 Cells

FIGURE 16 (continued)

FIG. 16C

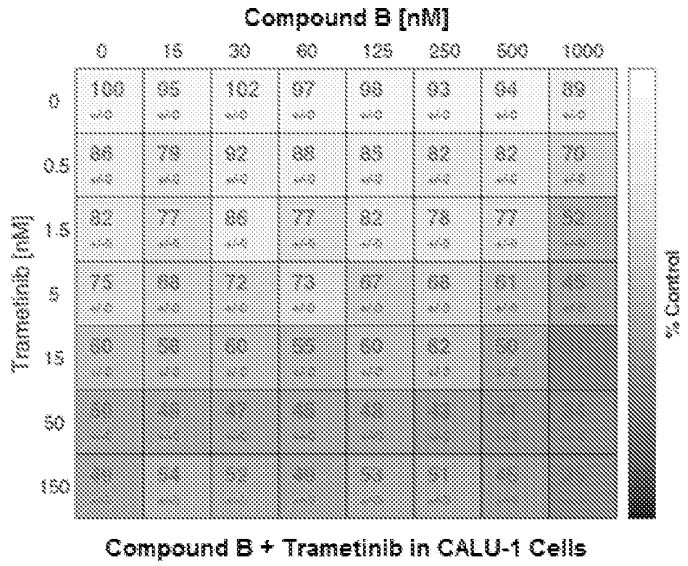


FIG. 16D

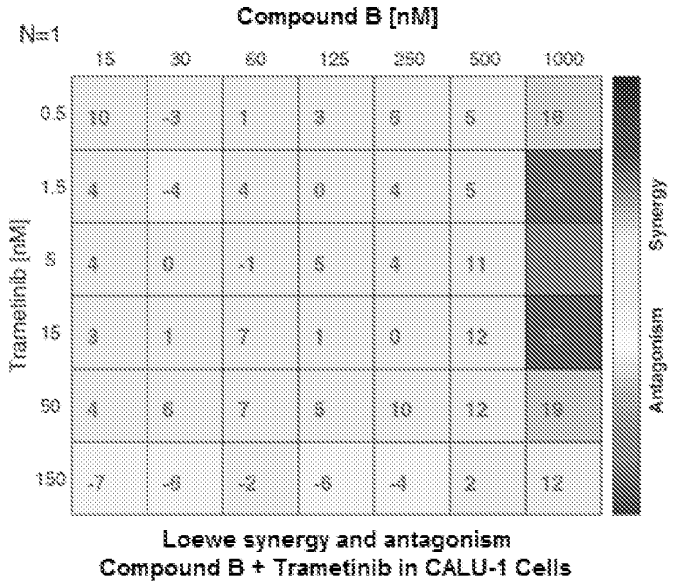


FIGURE 17

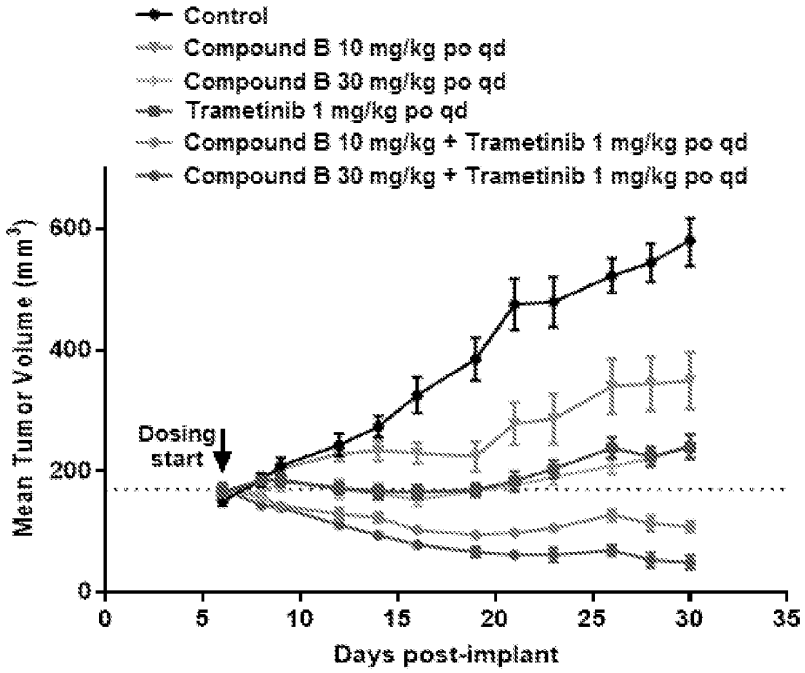


FIGURE 18

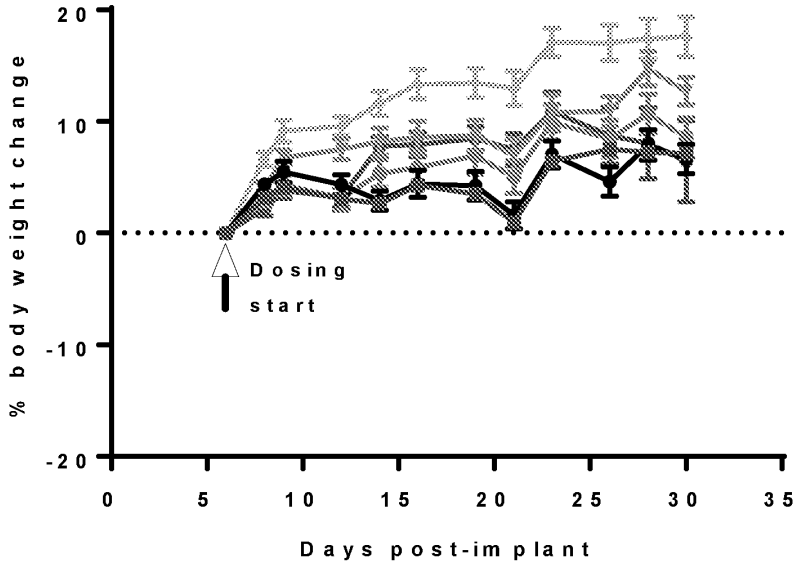


FIGURE 19

FIG. 19A

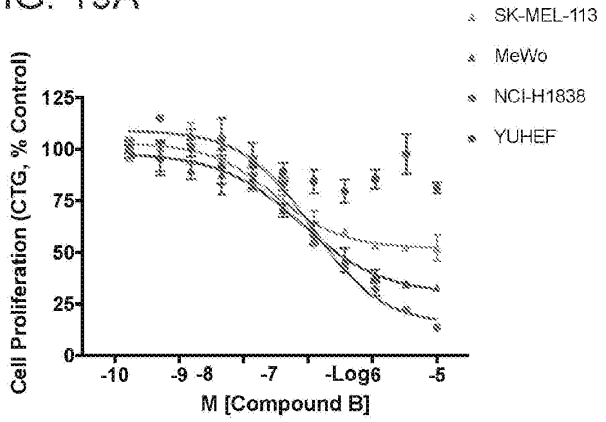


FIG. 19B

Cell Line	Compound B IC_{50} (μM)	NF1 mutation
SK-MEL-113	0.04	L161*/Q282*
MeWo	0.05	Q1336*
NCI-H1838	0.20	N184fs
YUHEF	>10	Q853*/FS-indel

FIG. 19C

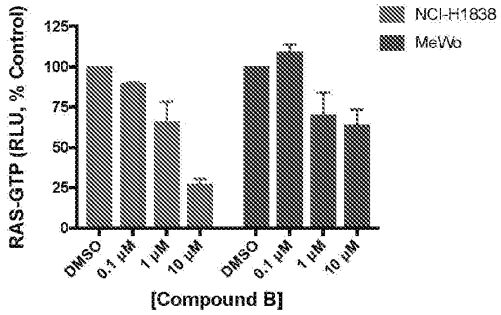


FIG. 19D

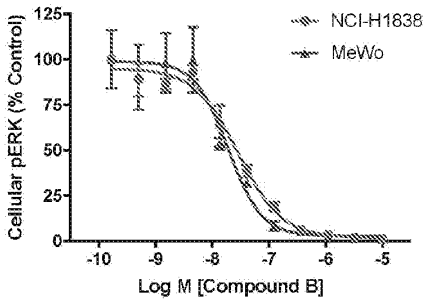


FIGURE 20

FIG. 20A LUN023 $BRAF^{D594N}$

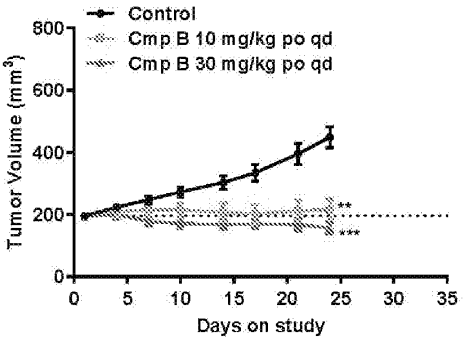


FIG. 20B LUN037 $BRAF^{N581D}$

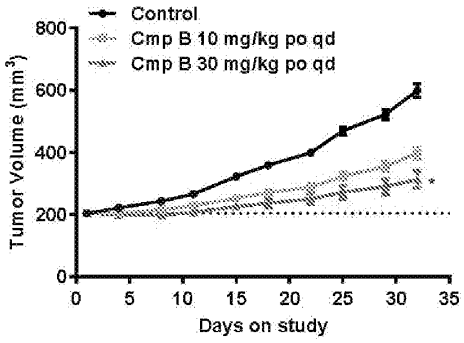


FIG. 20C LUN092 $KRAS^{G12C}$

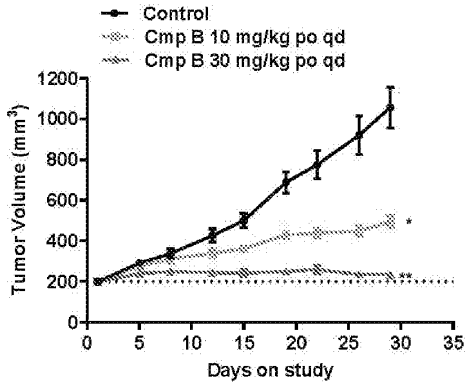


FIG. 20D LUN156 $KRAS^{G12C}$

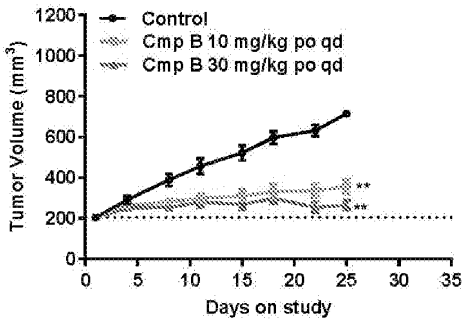


FIGURE 21

FIG. 21A

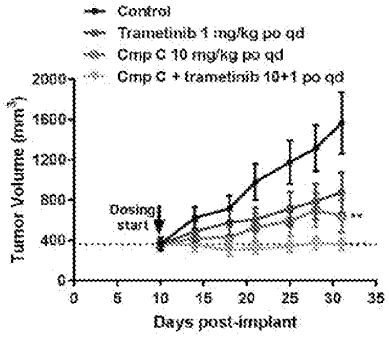


FIG. 21B

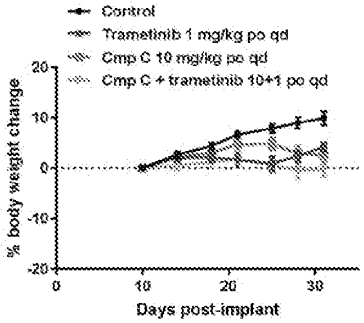


FIG. 21C

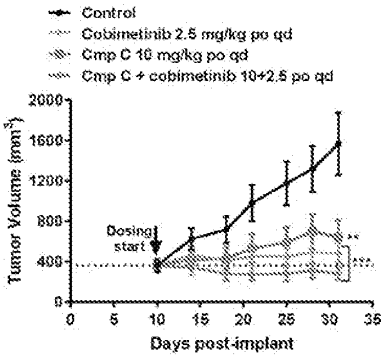


FIG. 21D

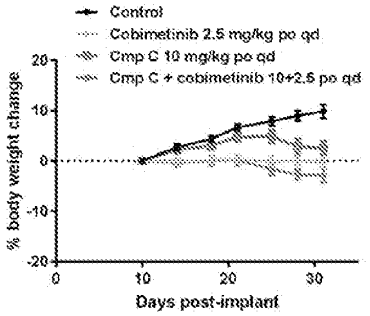


FIG. 21E

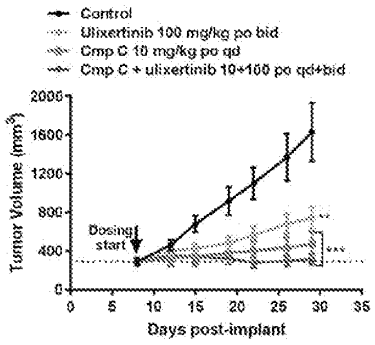


FIG. 21F

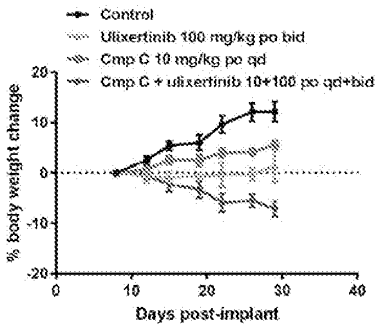


FIGURE 22

FIG. 22A

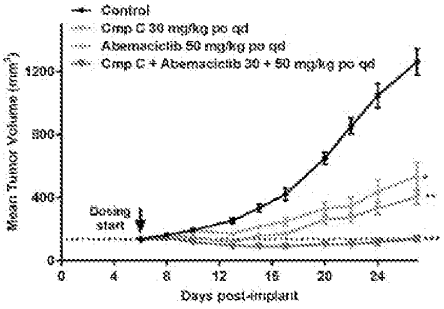


FIG. 22B

