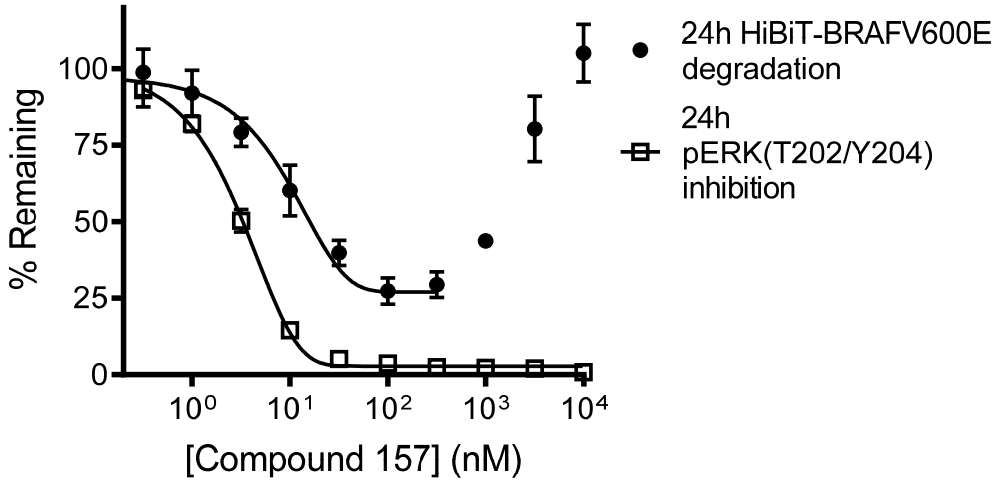

24h HiBiT-BRAFV600E degradation
24h pERK(T202/Y204) inhibition
% Remaining
100
75
50
25
0
10^0
10^1
10^2
10^3
10^4
[Compound 157] (nM)

FIG. 1

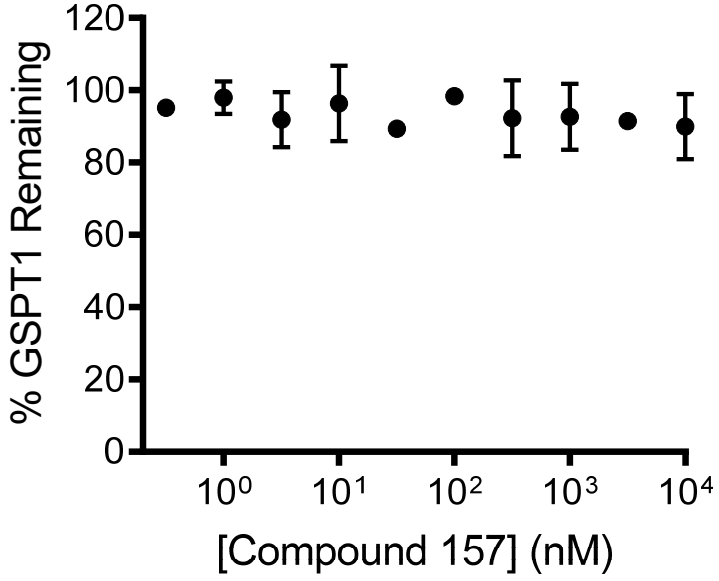

% GSPT1 Remaining
120
100
80
60
40
20
0
10^0
10^1
10^2
10^3
10^4
[Compound 157] (nM)

FIG. 2

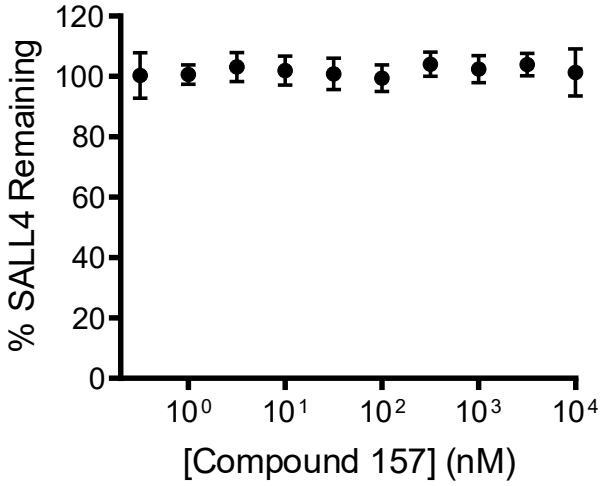

120
100
80
60
40
20
0
% SALL4 Remaining
10^0
10^1
10^2
10^3
10^4
[Compound 157] (nM)

FIG. 3

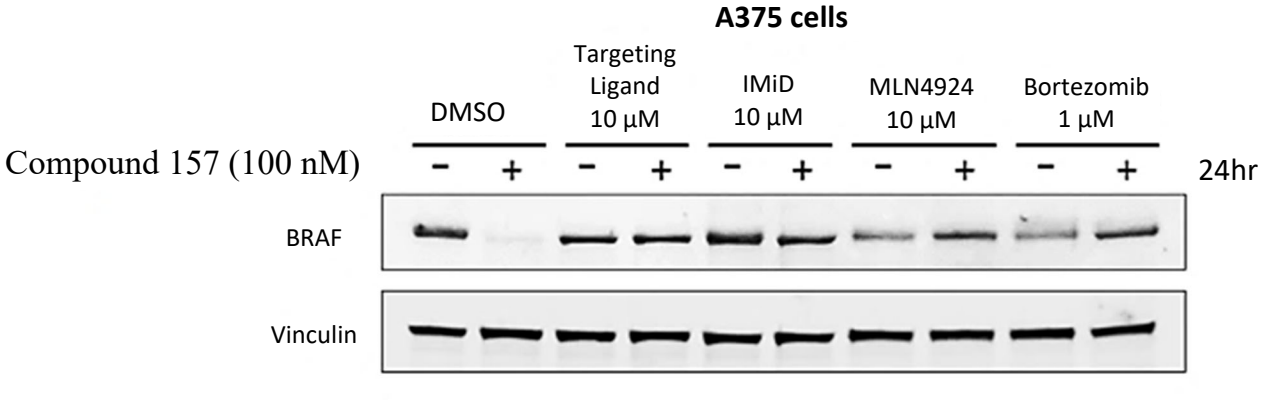

A375 cells
DMSO
Targeting Ligand 10 µM
IMiD 10 µM
MLN4924 10 µM
Bortezomib 1 µM
Compound 157 (100 nM)
- + - + - + - + - +
24hr
BRAF
Vinculin

FIG. 4

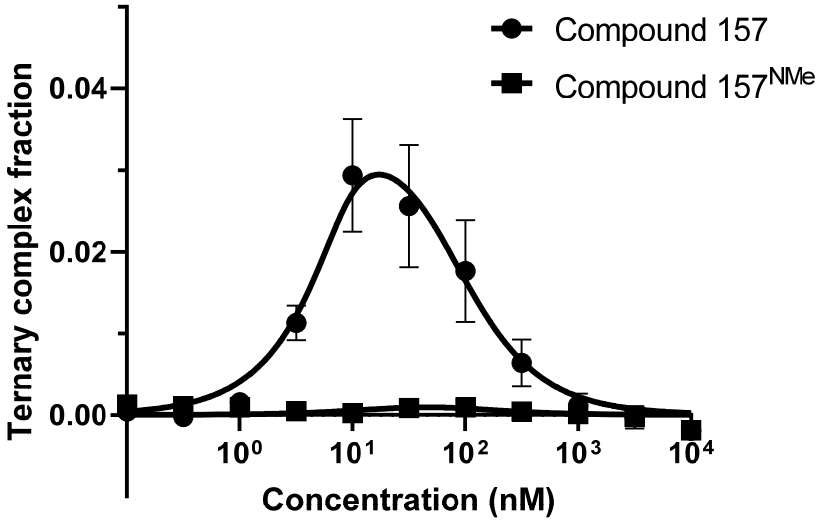

Compound 157
Compound 157NMe
Ternary complex fraction
0.04
0.02
0.00
10^0
10^1
10^2
10^3
10^4
Concentration (nM)

FIG. 5

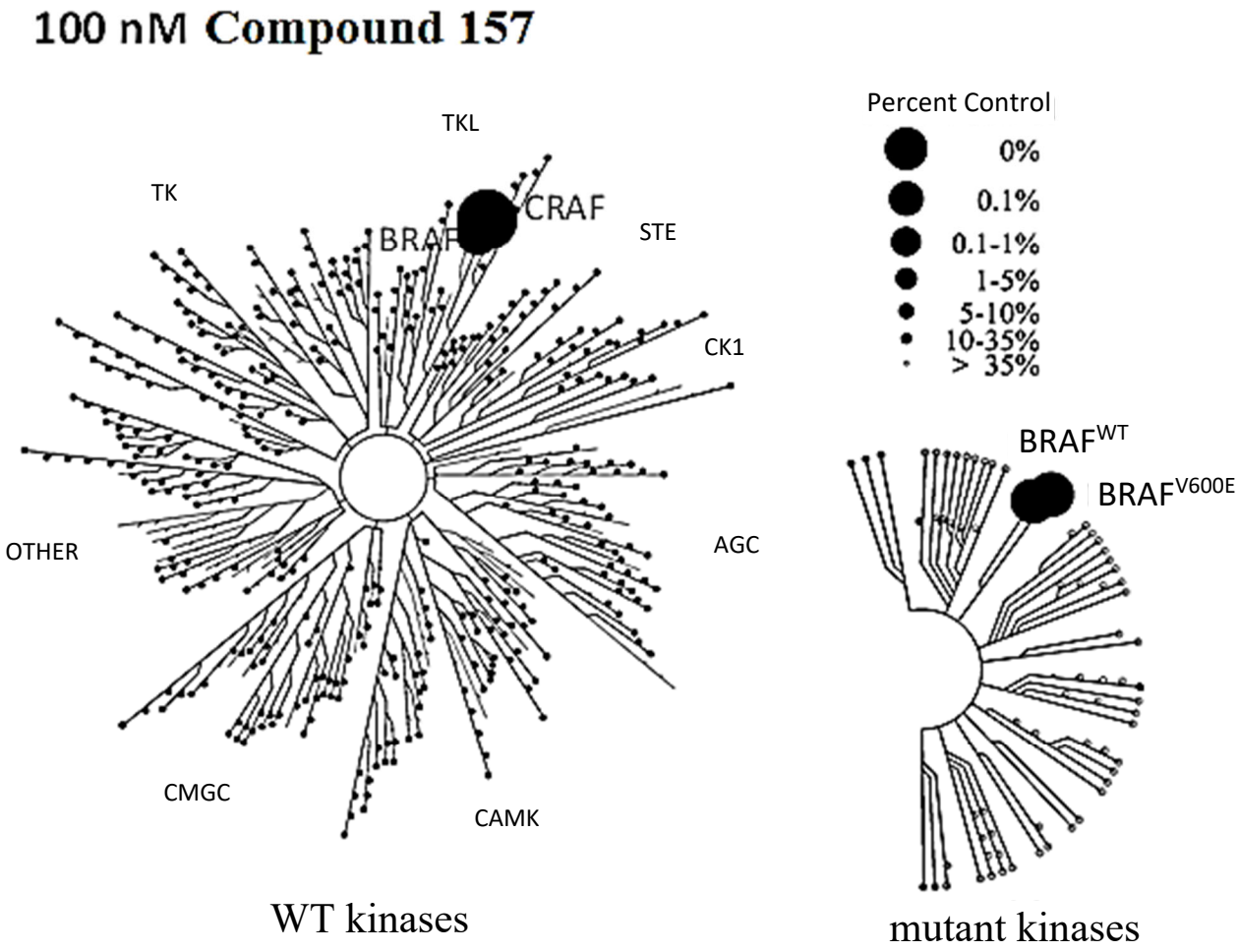

100 nM Compound 157
TKL
TK
CRAF
BRAF
STE
CK1
OTHER
AGC
CMGC
CAMK
WT kinases
Percent Control
0%
0.1%
0.1-1%
1-5%
5-10%
10-35%
> 35%
BRAF^WT
BRAF^V600E
mutant kinases

FIG. 6

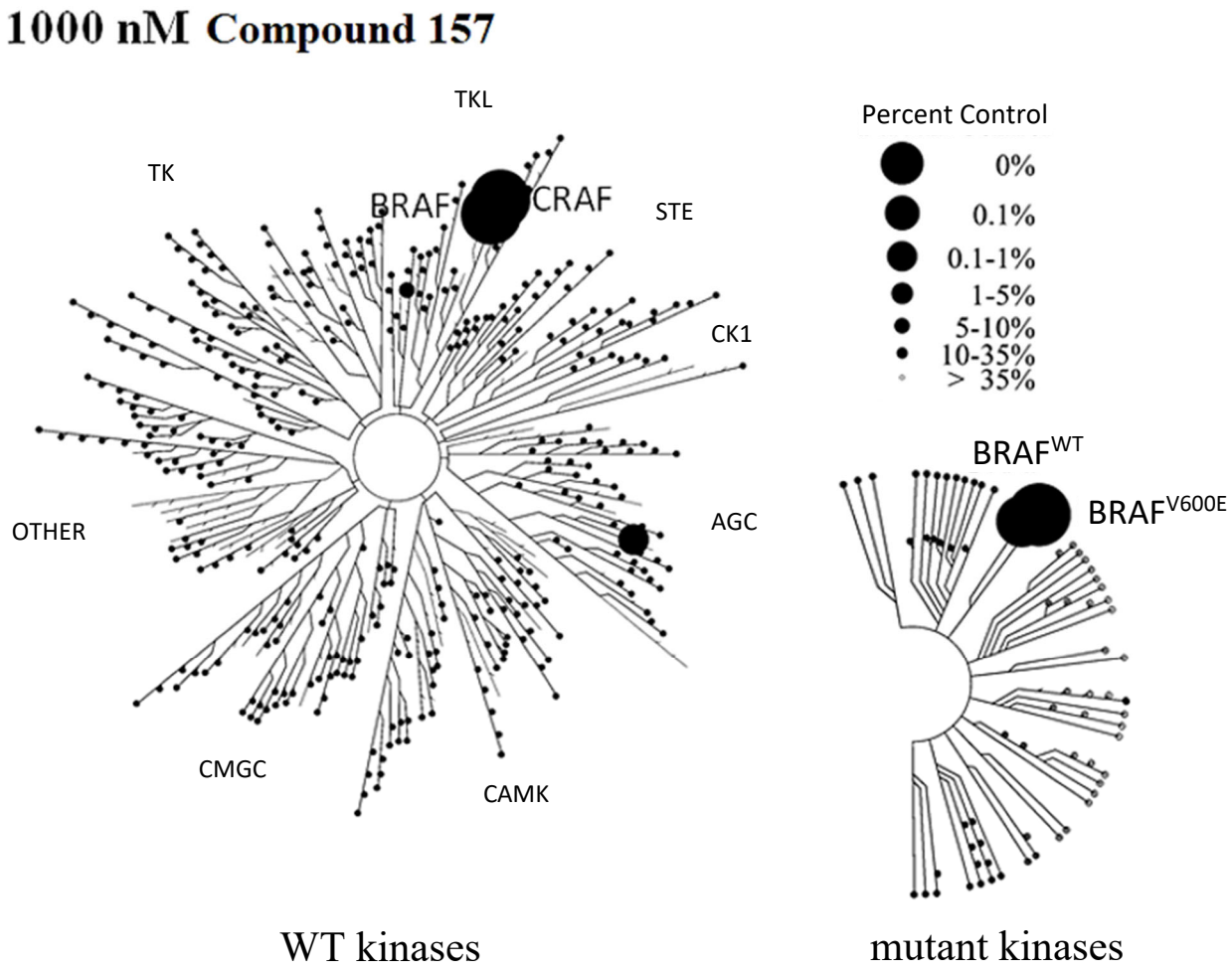

1000 nM Compound 157
TKL
TK
BRAF
CRAF
STE
CK1
OTHER
AGC
CMGC
CAMK
Percent Control
0%
0.1%
0.1-1%
1-5%
5-10%
10-35%
> 35%
BRAF^WT
BRAF^V600E
WT kinases
mutant kinases

FIG. 7

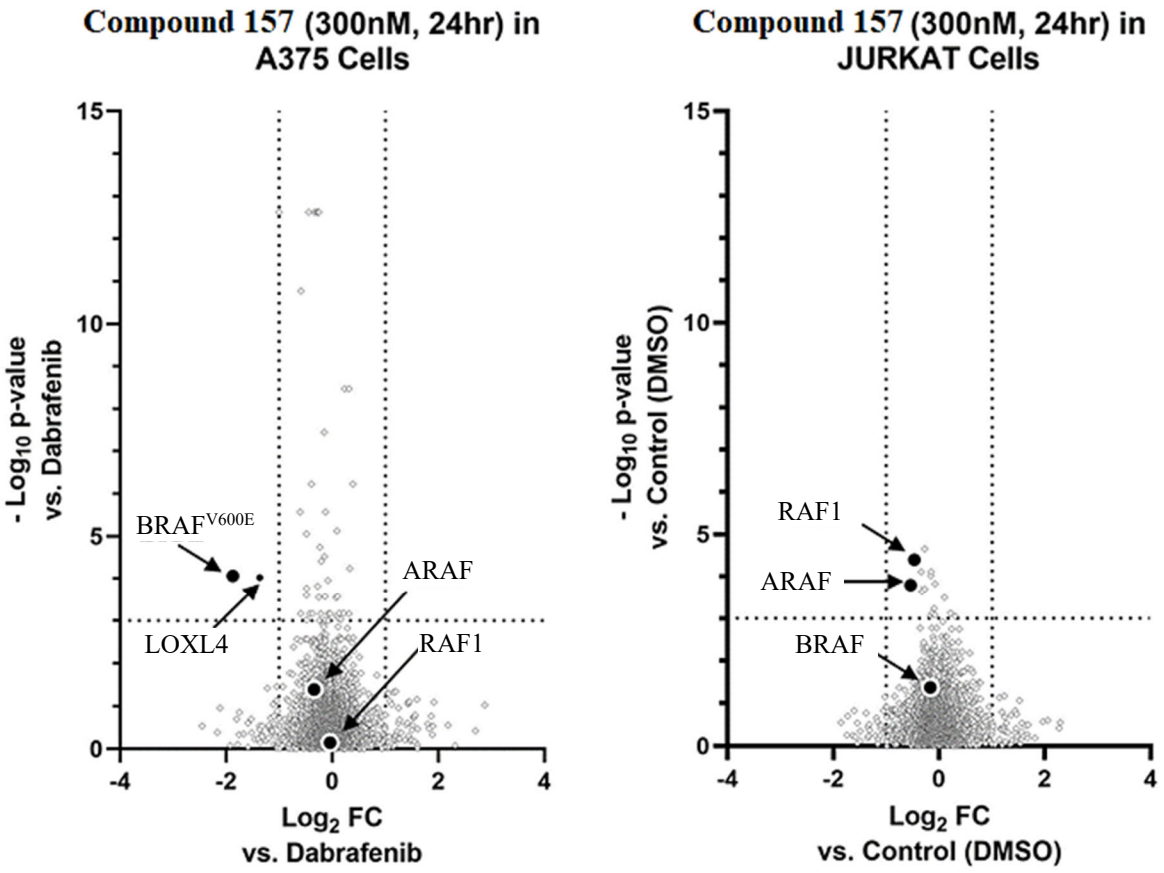

Compound 157 (300nM, 24hr) in A375 Cells
- Log10 p-value vs. Dabrafenib
Log2 FC vs. Dabrafenib
BRAFV600E
LOXL4
ARAF
RAF1
Compound 157 (300nM, 24hr) in JURKAT Cells
- Log10 p-value vs. Control (DMSO)
Log2 FC vs. Control (DMSO)
RAF1
ARAF
BRAF

FIG. 8

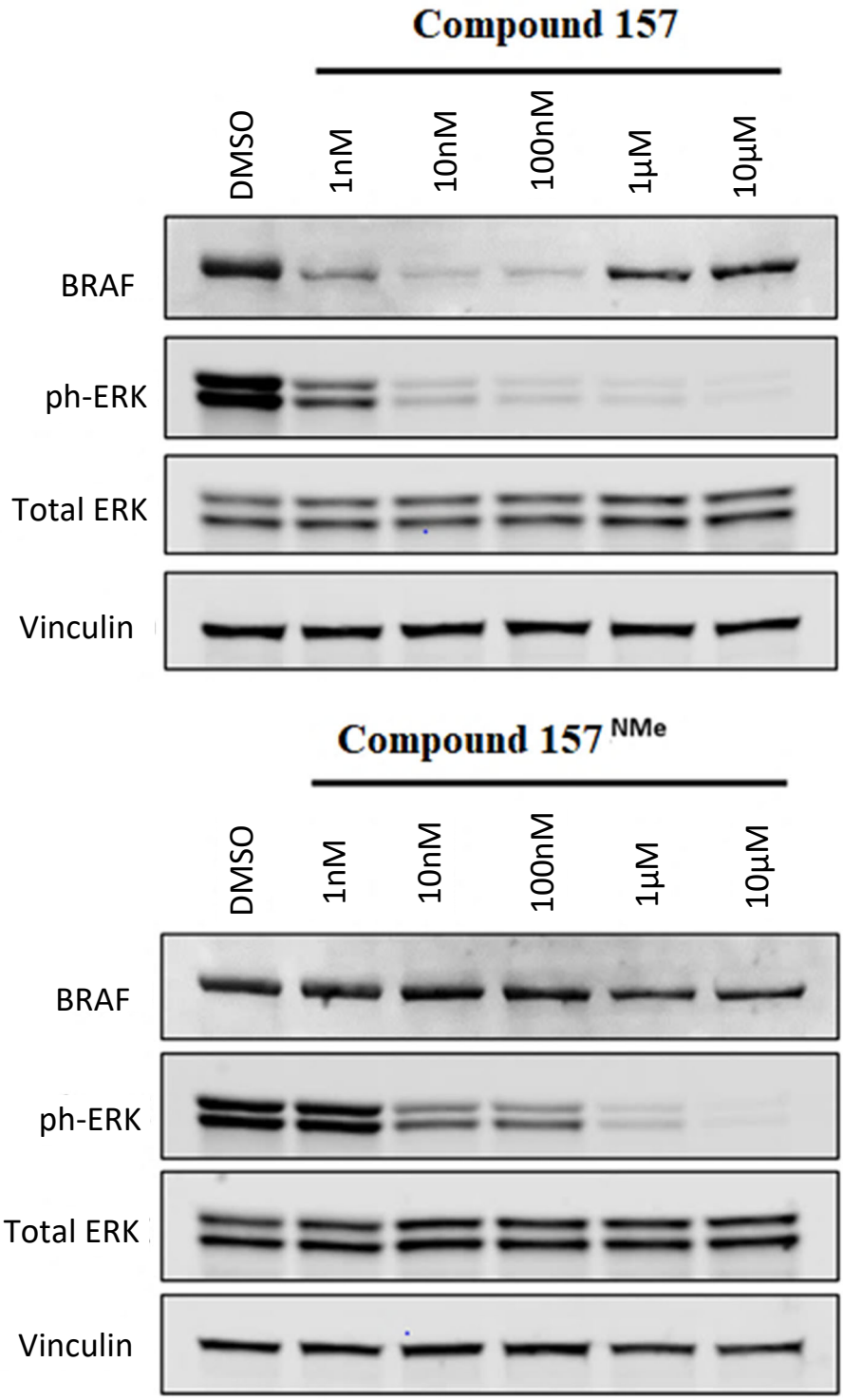

Compound 157
DMSO
1nM
10nM
100nM
1μM
10μM
BRAF
ph-ERK
Total ERK
Vinculin
Compound 157 NMe
DMSO
1nM
10nM
100nM
1μM
10μM
BRAF
ph-ERK
Total ERK
Vinculin

FIG. 9

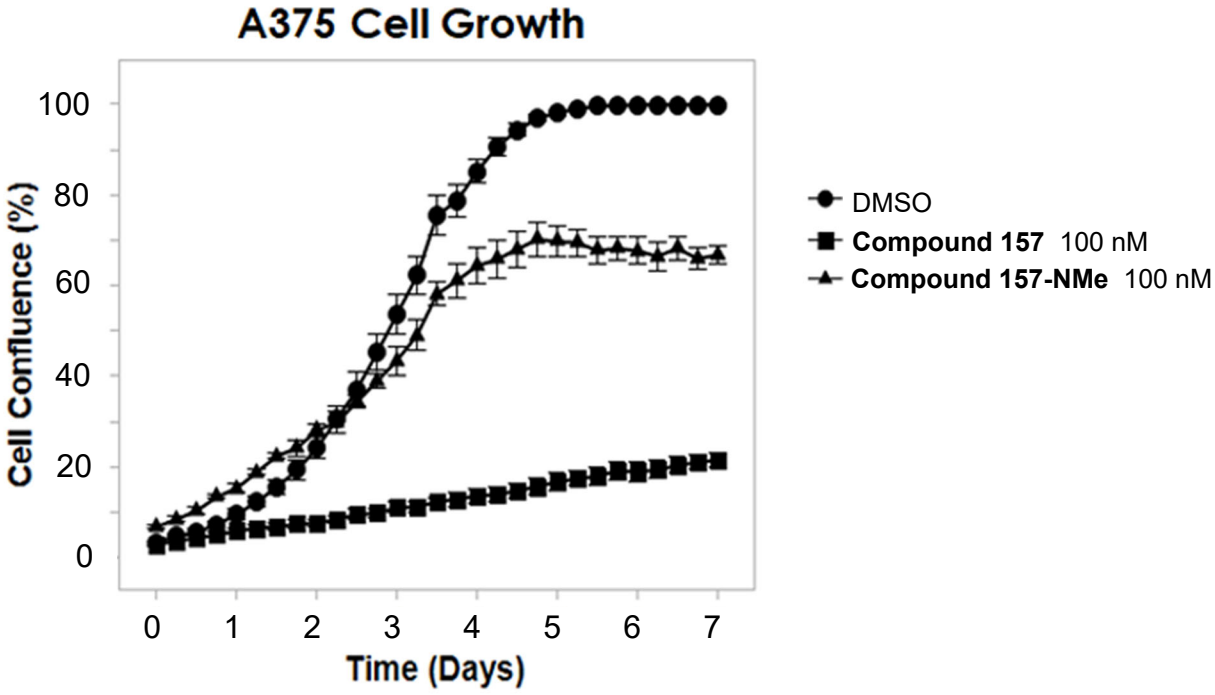

A375 Cell Growth
Cell Confluence (%)
100
80
60
40
20
0
0
1
2
3
4
5
6
7
Time (Days)
DMSO
Compound 157 100 nM
Compound 157-NMe 100 nM

FIG. 10

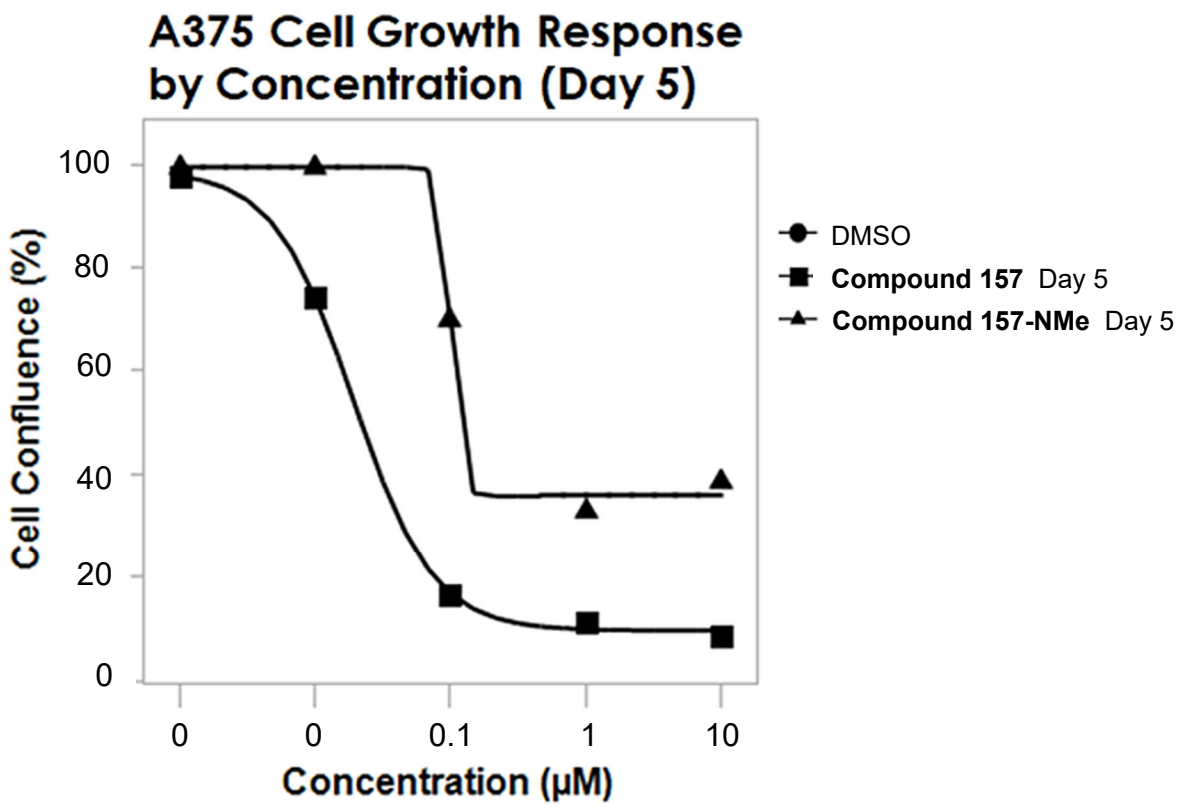

A375 Cell Growth Response by Concentration (Day 5)
Cell Confluence (%)
100
80
60
40
20
0
0
0
0.1
1
10
Concentration (μM)
DMSO
Compound 157 Day 5
Compound 157-NMe Day 5

FIG. 11

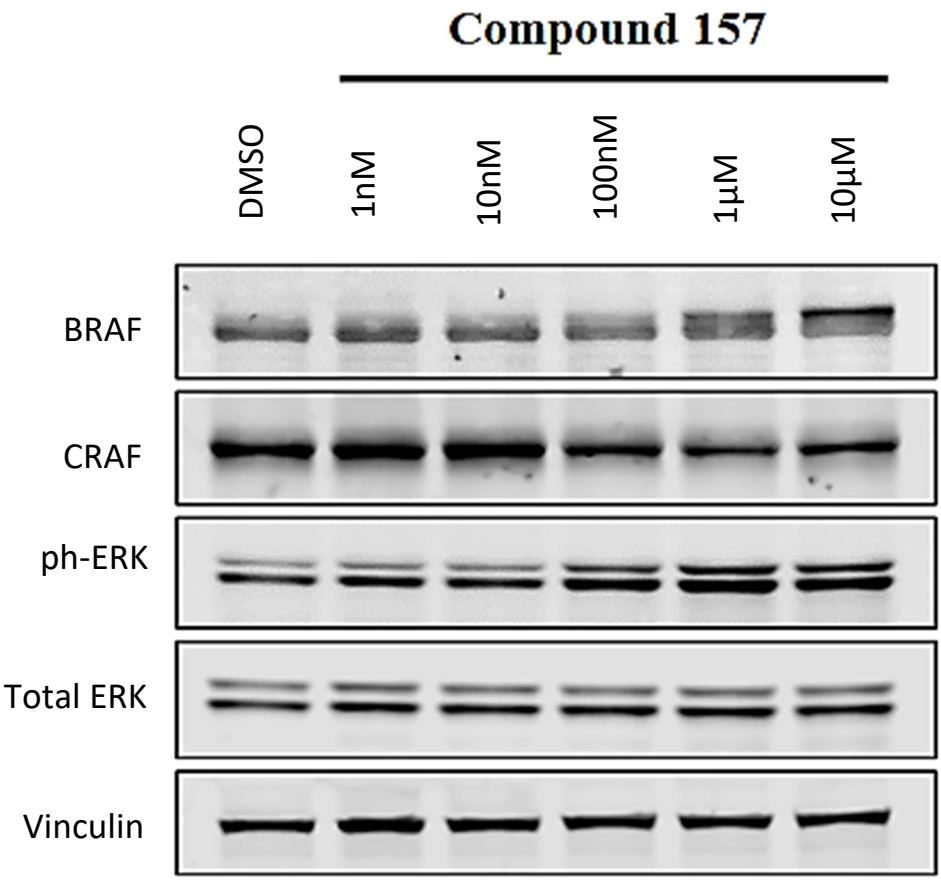

Compound 157
DMSO
1nM
10nM
100nM
1μM
10μM
BRAF
CRAF
ph-ERK
Total ERK
Vinculin

FIG. 12

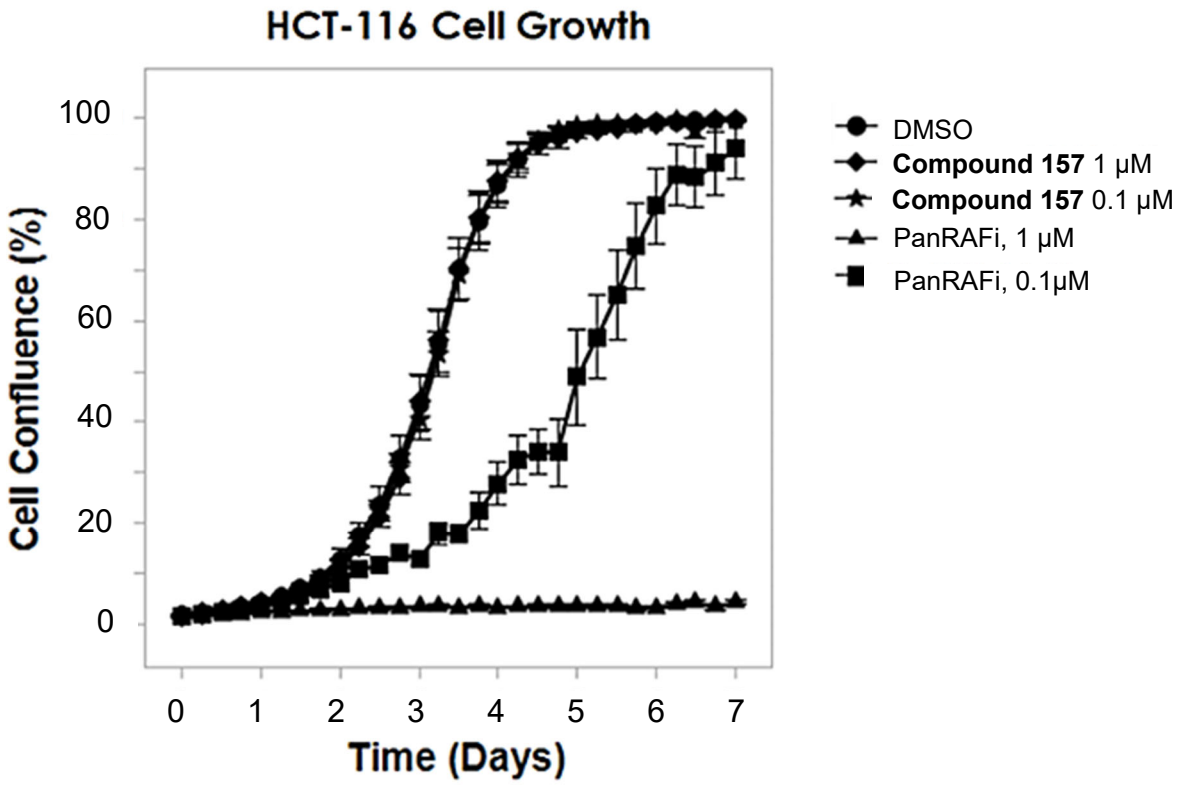

HCT-116 Cell Growth
Cell Confluence (%)
100
80
60
40
20
0
0
1
2
3
4
5
6
7
Time (Days)
DMSO
Compound 157 1 μM
Compound 157 0.1 μM
PanRAFi, 1 μM
PanRAFi, 0.1μM

FIG. 13

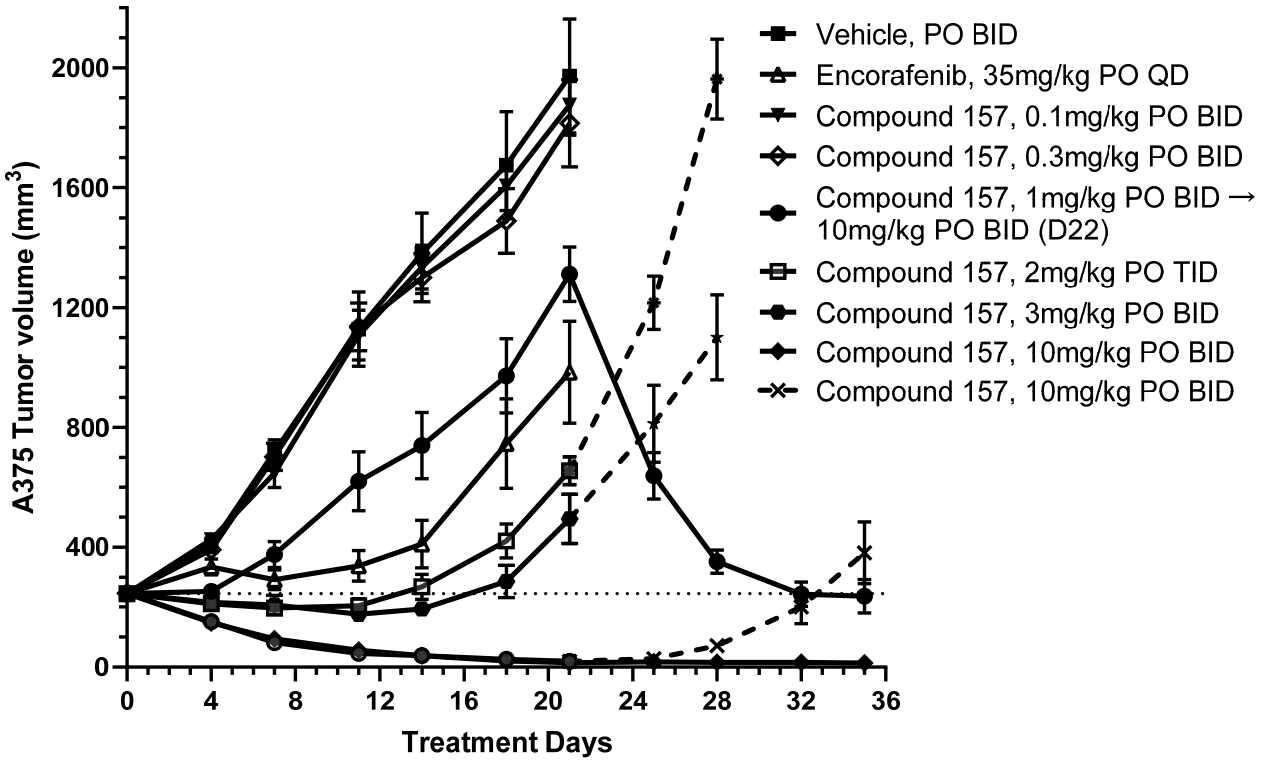

A375 Tumor volume (mm3)
2000
1600
1200
800
400
0
0
4
8
12
16
20
24
28
32
36
Treatment Days
Vehicle, PO BID
Encorafenib, 35mg/kg PO QD
Compound 157, 0.1mg/kg PO BID
Compound 157, 0.3mg/kg PO BID
Compound 157, 1mg/kg PO BID → 10mg/kg PO BID (D22)
Compound 157, 2mg/kg PO TID
Compound 157, 3mg/kg PO BID
Compound 157, 10mg/kg PO BID
Compound 157, 10mg/kg PO BID

FIG. 14

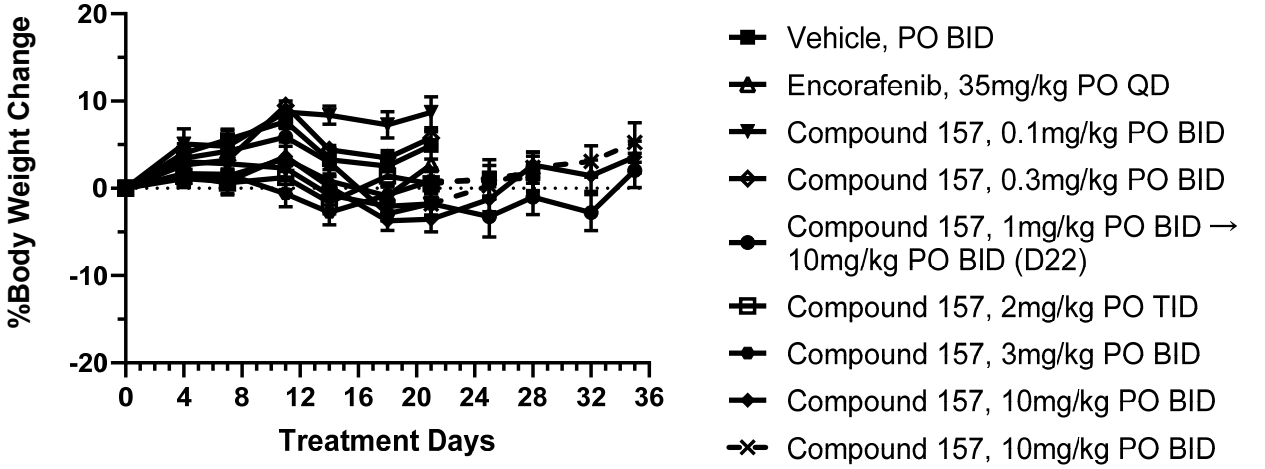

%Body Weight Change
20
10
0
-10
-20
0
4
8
12
16
20
24
28
32
36
Treatment Days
Vehicle, PO BID
Encorafenib, 35mg/kg PO QD
Compound 157, 0.1mg/kg PO BID
Compound 157, 0.3mg/kg PO BID
Compound 157, 1mg/kg PO BID → 10mg/kg PO BID (D22)
Compound 157, 2mg/kg PO TID
Compound 157, 3mg/kg PO BID
Compound 157, 10mg/kg PO BID
Compound 157, 10mg/kg PO BID

FIG. 15

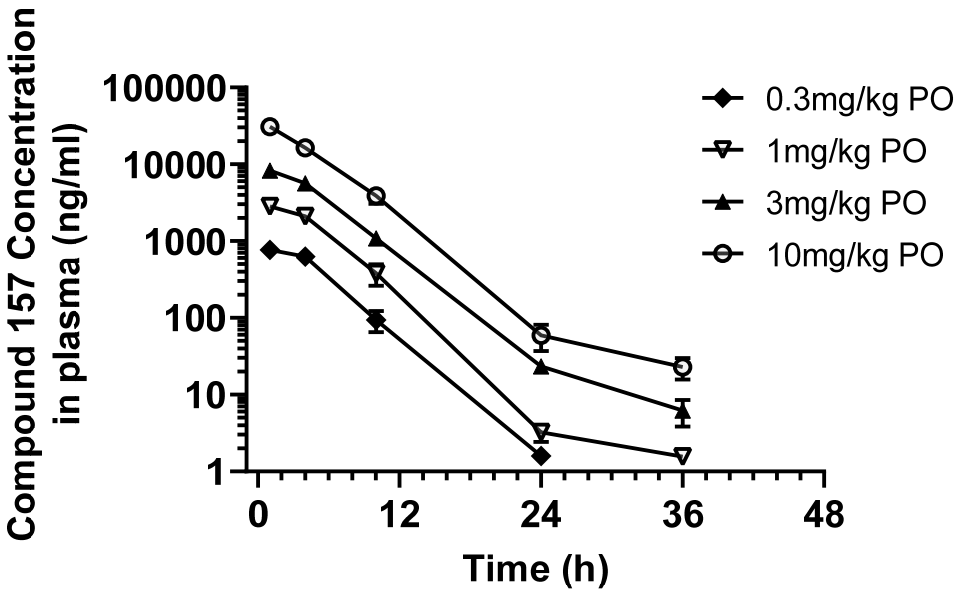

Compound 157 Concentration in plasma (ng/ml)
100000
10000
1000
100
10
1
0
12
24
36
48
Time (h)
0.3mg/kg PO
1mg/kg PO
3mg/kg PO
10mg/kg PO

FIG. 16

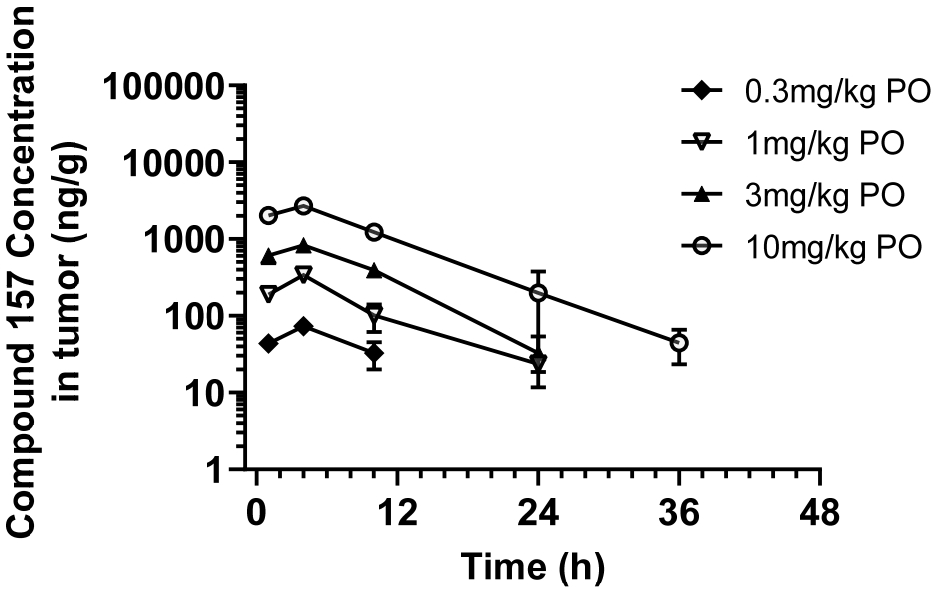

Compound 157 Concentration in tumor (ng/g)
100000
10000
1000
100
10
1
0
12
24
36
48
Time (h)
0.3mg/kg PO
1mg/kg PO
3mg/kg PO
10mg/kg PO

FIG. 17

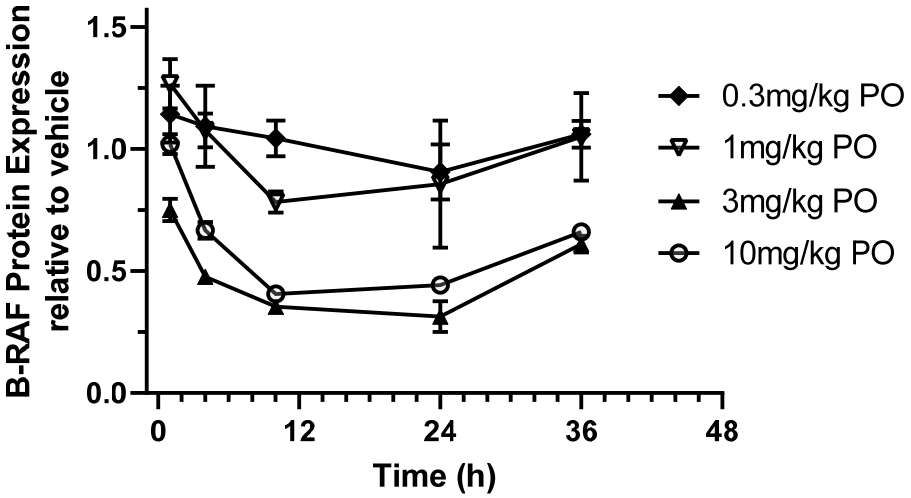

B-RAF Protein Expression
relative to vehicle
1.5
1.0
0.5
0.0
0
12
24
36
48
Time (h)
0.3mg/kg PO
1mg/kg PO
3mg/kg PO
10mg/kg PO

FIG. 18

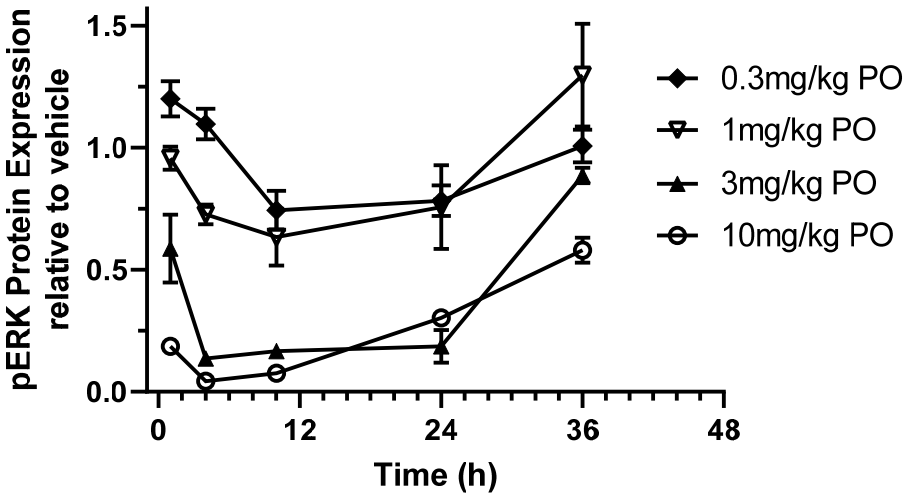

pERK Protein Expression
relative to vehicle
1.5
1.0
0.5
0.0
0
12
24
36
48
Time (h)
0.3mg/kg PO
1mg/kg PO
3mg/kg PO
10mg/kg PO

FIG. 19

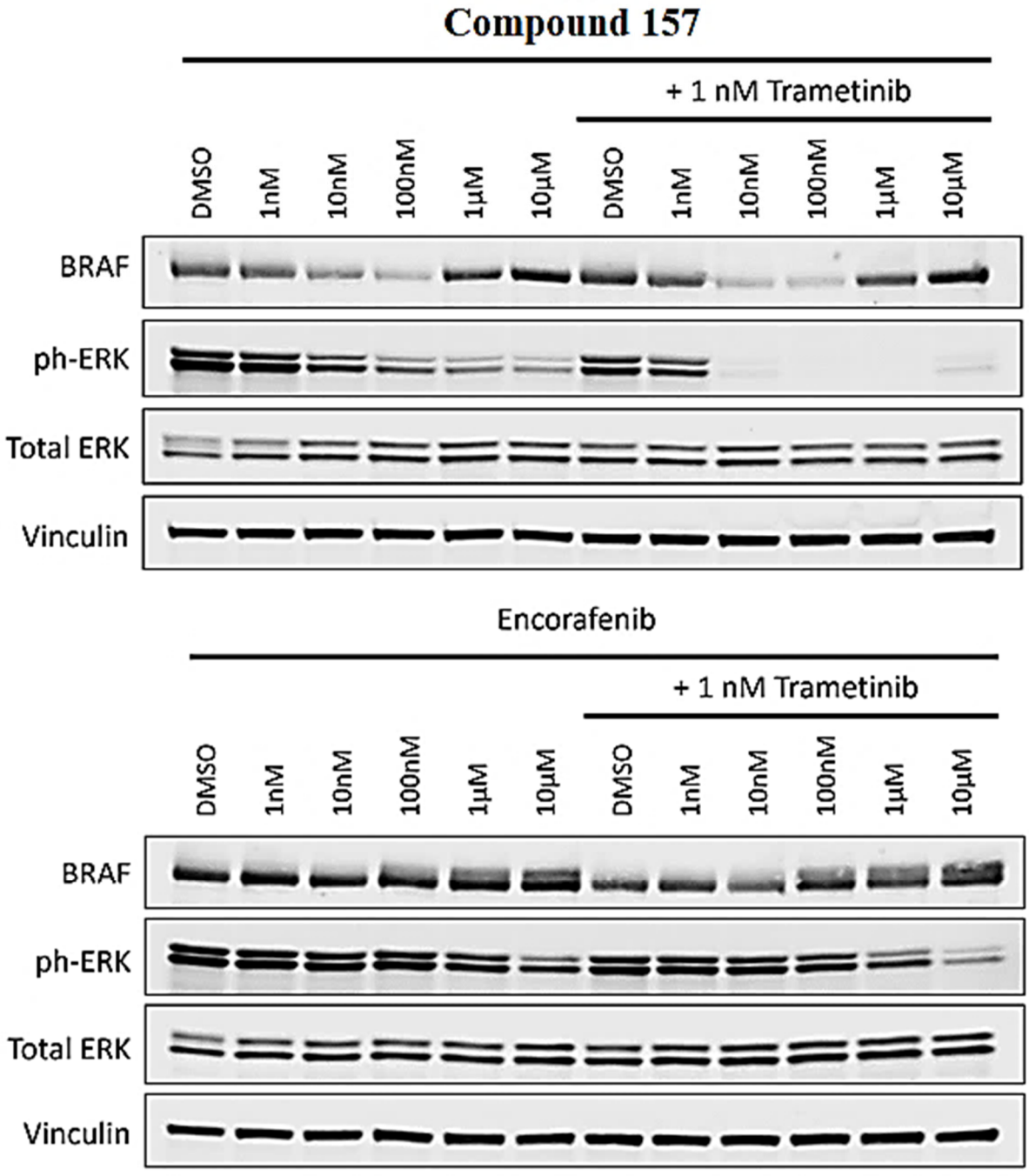

Compound 157
+ 1 nM Trametinib
DMSO
1nM
10nM
100nM
1μM
10μM
DMSO
1nM
10nM
100nM
1μM
10μM
BRAF
ph-ERK
Total ERK
Vinculin
Encorafenib
+ 1 nM Trametinib
DMSO
1nM
10nM
100nM
1μM
10μM
DMSO
1nM
10nM
100nM
1μM
10μM
BRAF
ph-ERK
Total ERK
Vinculin

FIG. 20

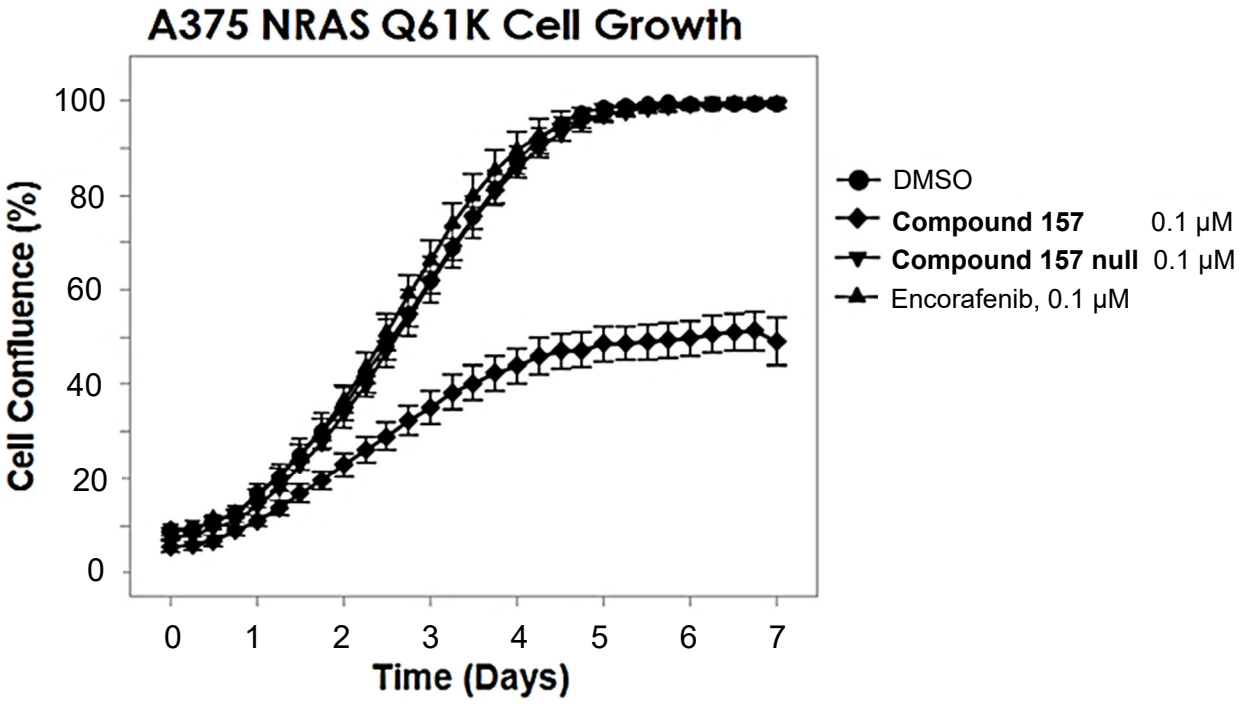

A375 NRAS Q61K Cell Growth
Cell Confluence (%)
100
80
60
40
20
0
0
1
2
3
4
5
6
7
Time (Days)
DMSO
Compound 157 0.1 µM
Compound 157 null 0.1 µM
Encorafenib, 0.1 µM

FIG. 21

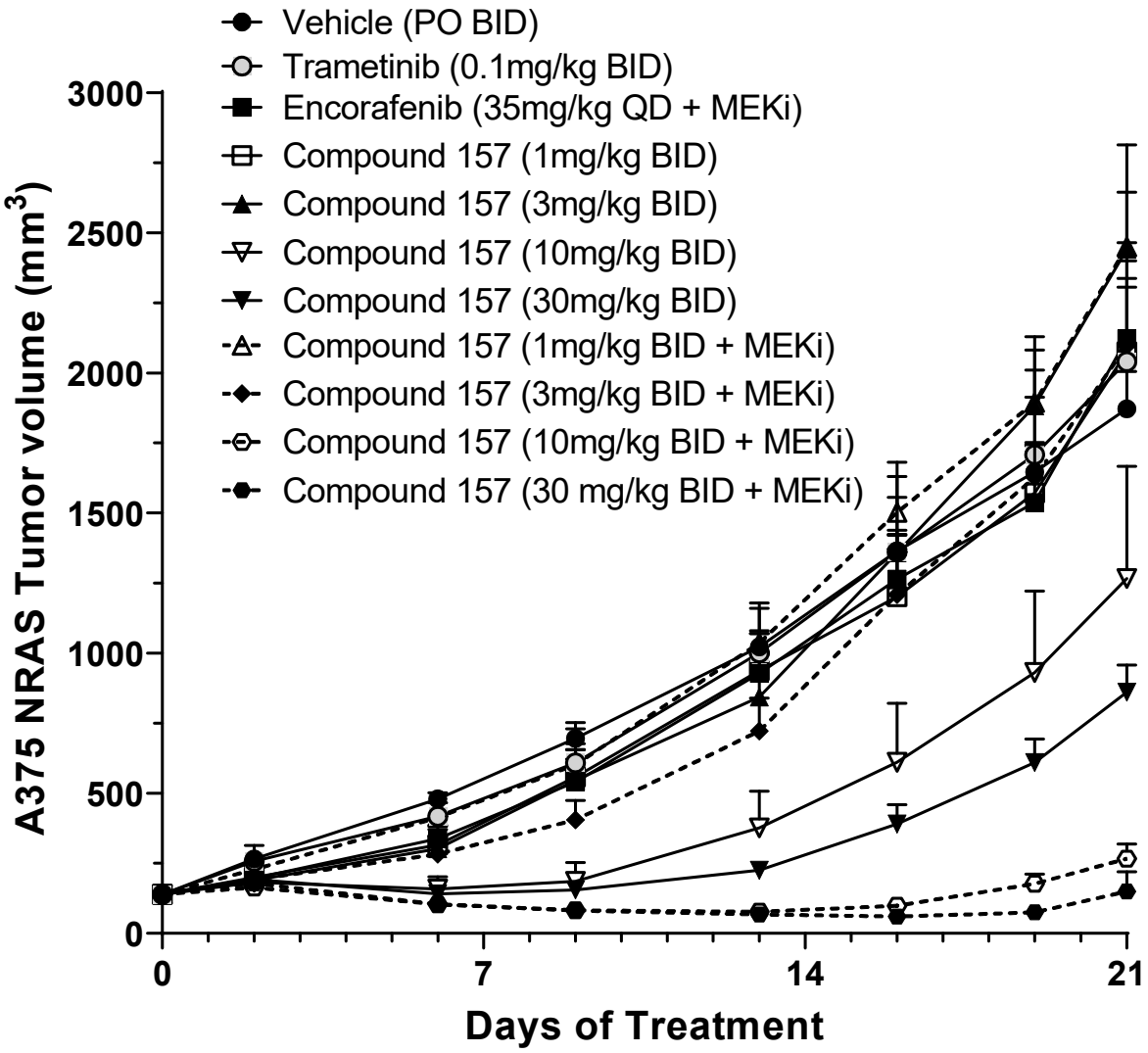

Vehicle (PO BID)
Trametinib (0.1mg/kg BID)
Encorafenib (35mg/kg QD + MEKi)
Compound 157 (1mg/kg BID)
Compound 157 (3mg/kg BID)
Compound 157 (10mg/kg BID)
Compound 157 (30mg/kg BID)
Compound 157 (1mg/kg BID + MEKi)
Compound 157 (3mg/kg BID + MEKi)
Compound 157 (10mg/kg BID + MEKi)
Compound 157 (30 mg/kg BID + MEKi)
A375 NRAS Tumor volume (mm3)
3000
2500
2000
1500
1000
500
0
0
7
14
21
Days of Treatment

FIG. 22

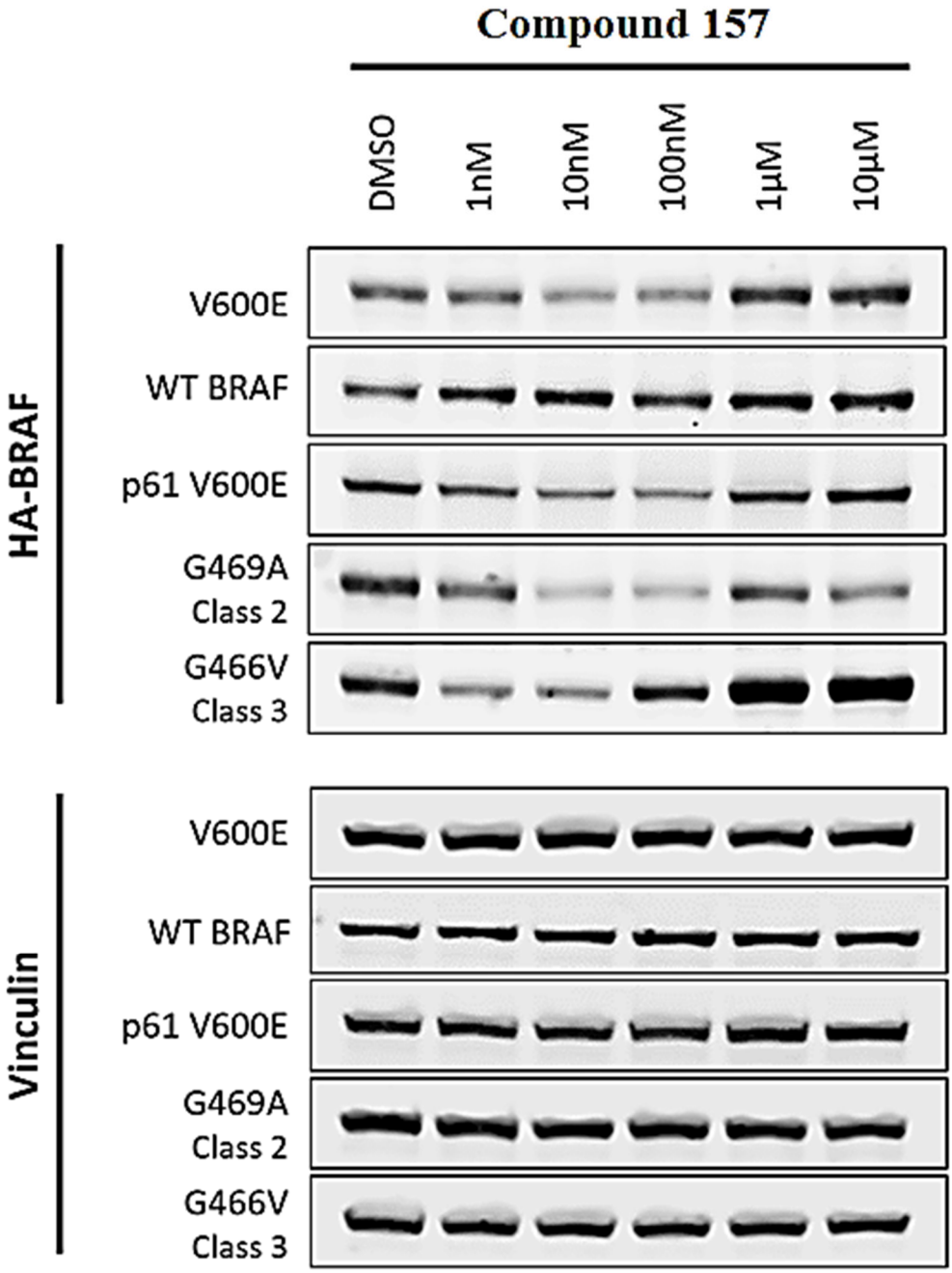

Compound 157
DMSO
1nM
10nM
100nM
1µM
10µM
HA-BRAF
V600E
WT BRAF
p61 V600E
G469A
Class 2
G466V
Class 3
Vinculin
V600E
WT BRAF
p61 V600E
G469A
Class 2
G466V
Class 3

FIG. 23

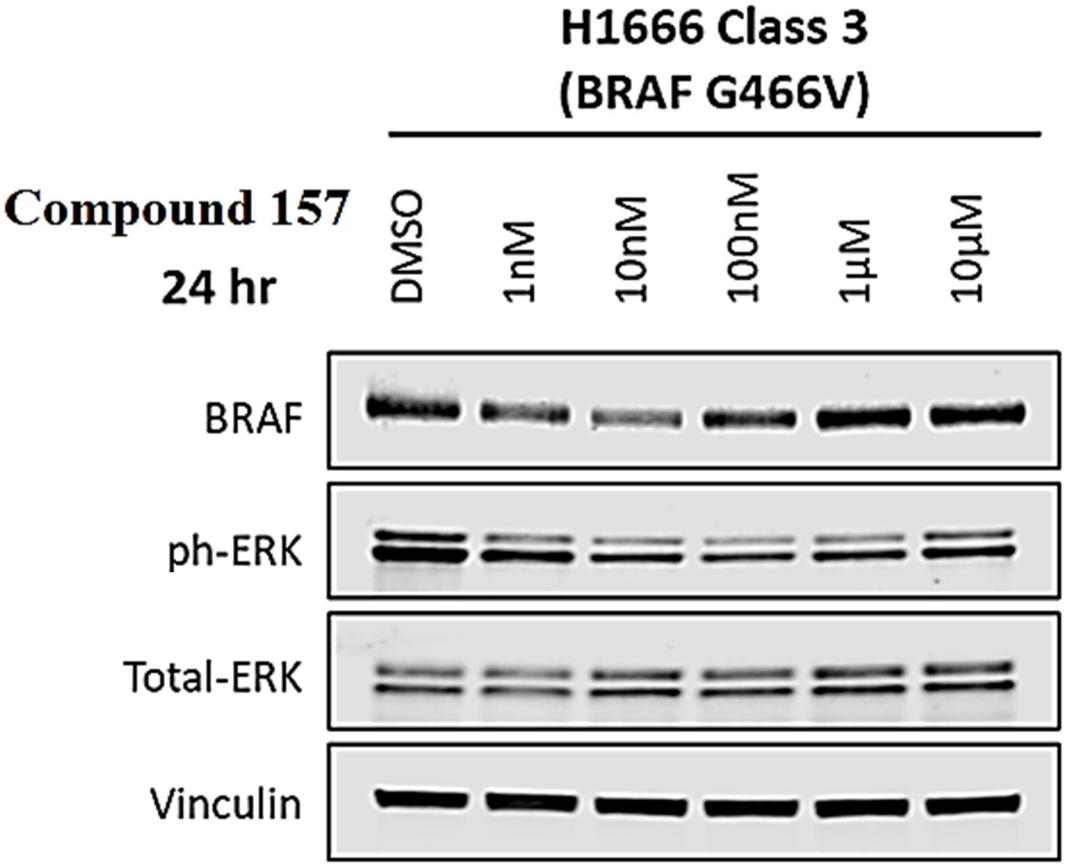

H1666 Class 3
(BRAF G466V)
Compound 157
24 hr
DMSO
1nM
10nM
100nM
1µM
10µM
BRAF
ph-ERK
Total-ERK
Vinculin

FIG. 24

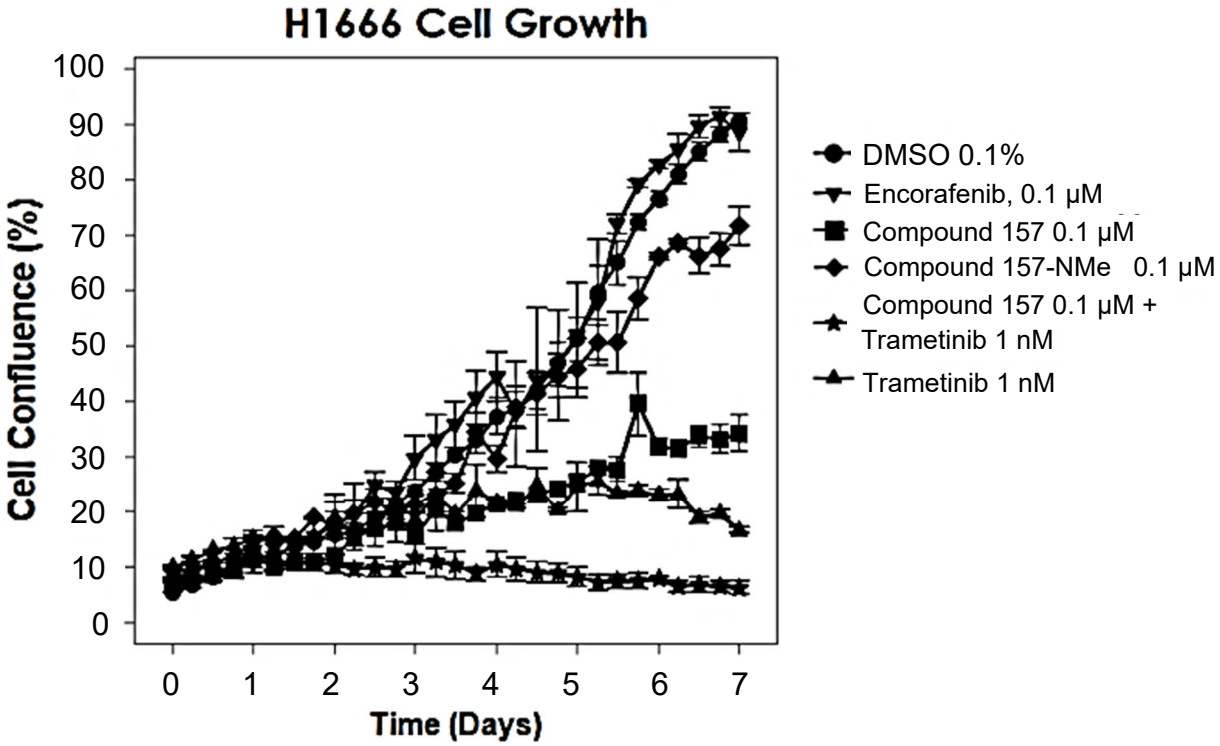

H1666 Cell Growth
Cell Confluence (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
Time (Days)
DMSO 0.1%
Encorafenib, 0.1 μM
Compound 157 0.1 μM
Compound 157-NMe 0.1 μM
Compound 157 0.1 μM + Trametinib 1 nM
Trametinib 1 nM

FIG. 25