FIG. 1

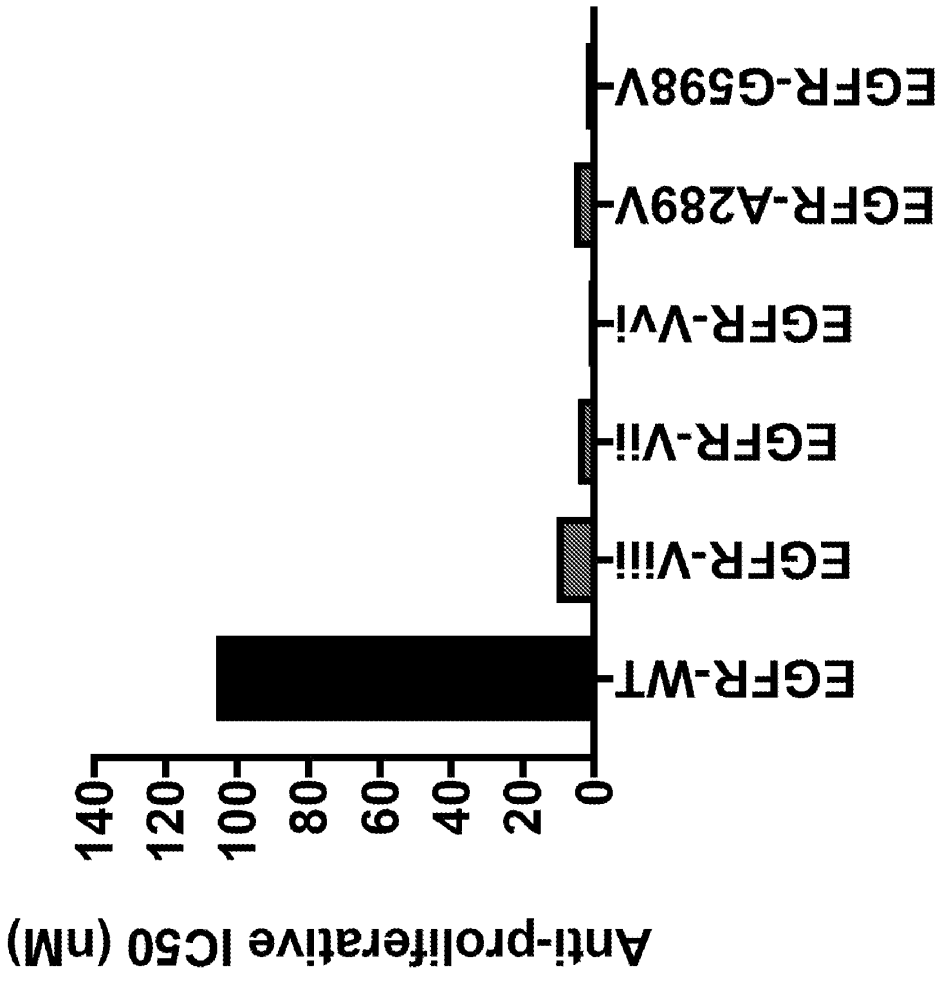

Anti-proliferative IC50 (nM)
0
20
40
60
80
100
120
140
EGFR-WT
EGFR-VIII
EGFR-VII
EGFR-VVI
EGFR-A289V
EGFR-G598V

FIG. 2

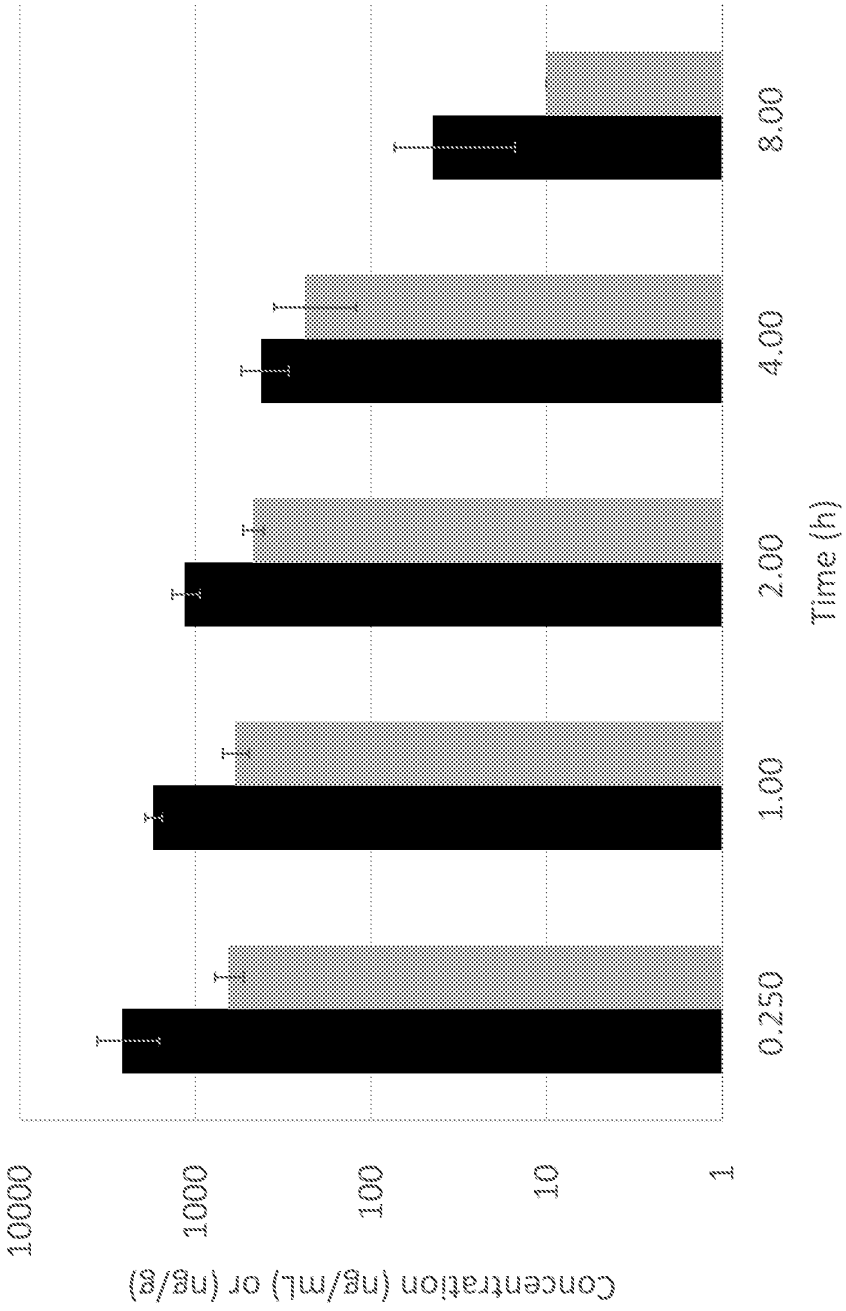

Concentration (ng/mL) or (ng/g)
10000
1000
100
10
1
0.250
1.00
2.00
4.00
8.00
Time (h)

FIG. 3

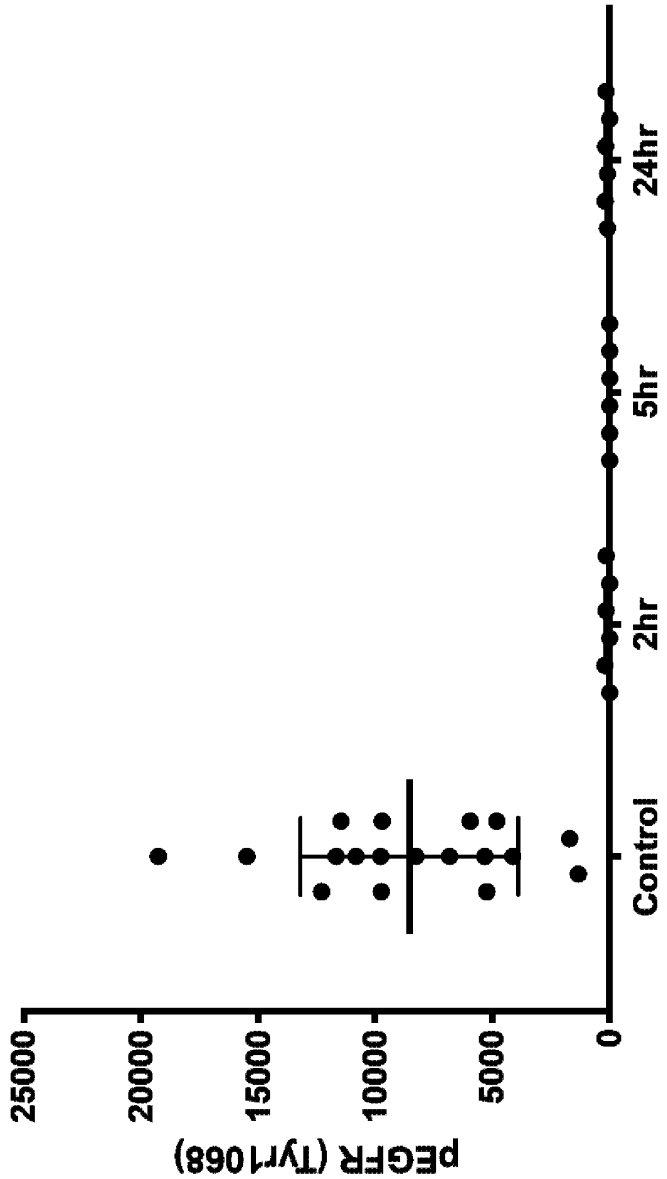

BaF3-EGFR V3 Xenografts MI4029
pEGFR (Tyr1068)
25000
20000
15000
10000
5000
0
Control
2hr
5hr
24hr

FIG. 4

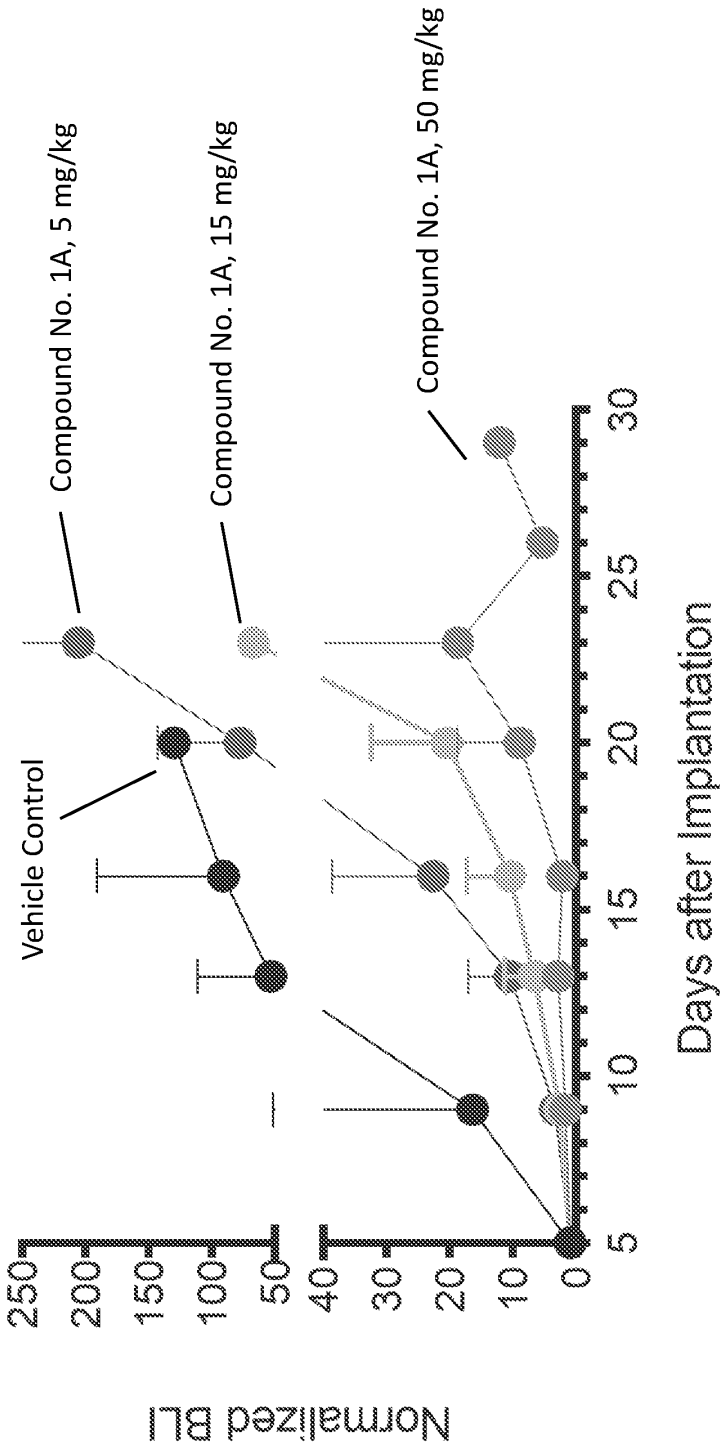

Normalized BLI
250
200
150
100
50
40
30
20
10
0
5
10
15
20
25
30
Days after Implantation
Vehicle Control
Compound No. 1A, 5 mg/kg
Compound No. 1A, 15 mg/kg
Compound No. 1A, 50 mg/kg

FIG. 5

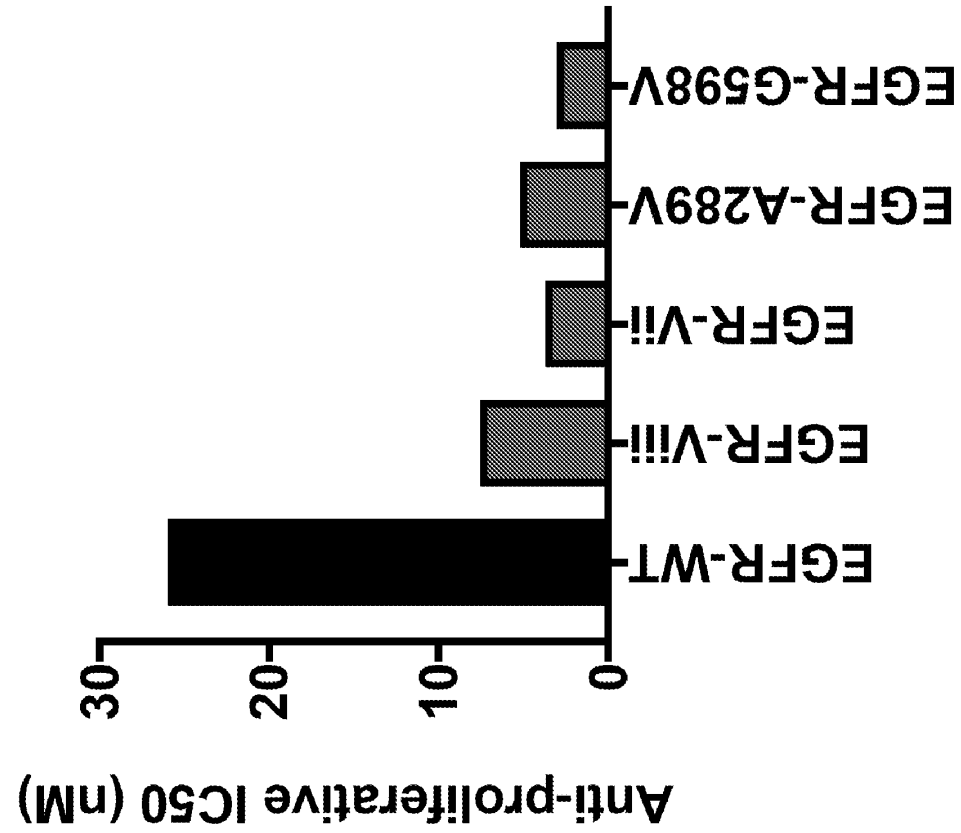

Anti-proliferative IC50 (nM)
0
10
20
30
EGFR-WT
EGFR-VIII
EGFR-VII
EGFR-A289V
EGFR-G598V

FIG. 6

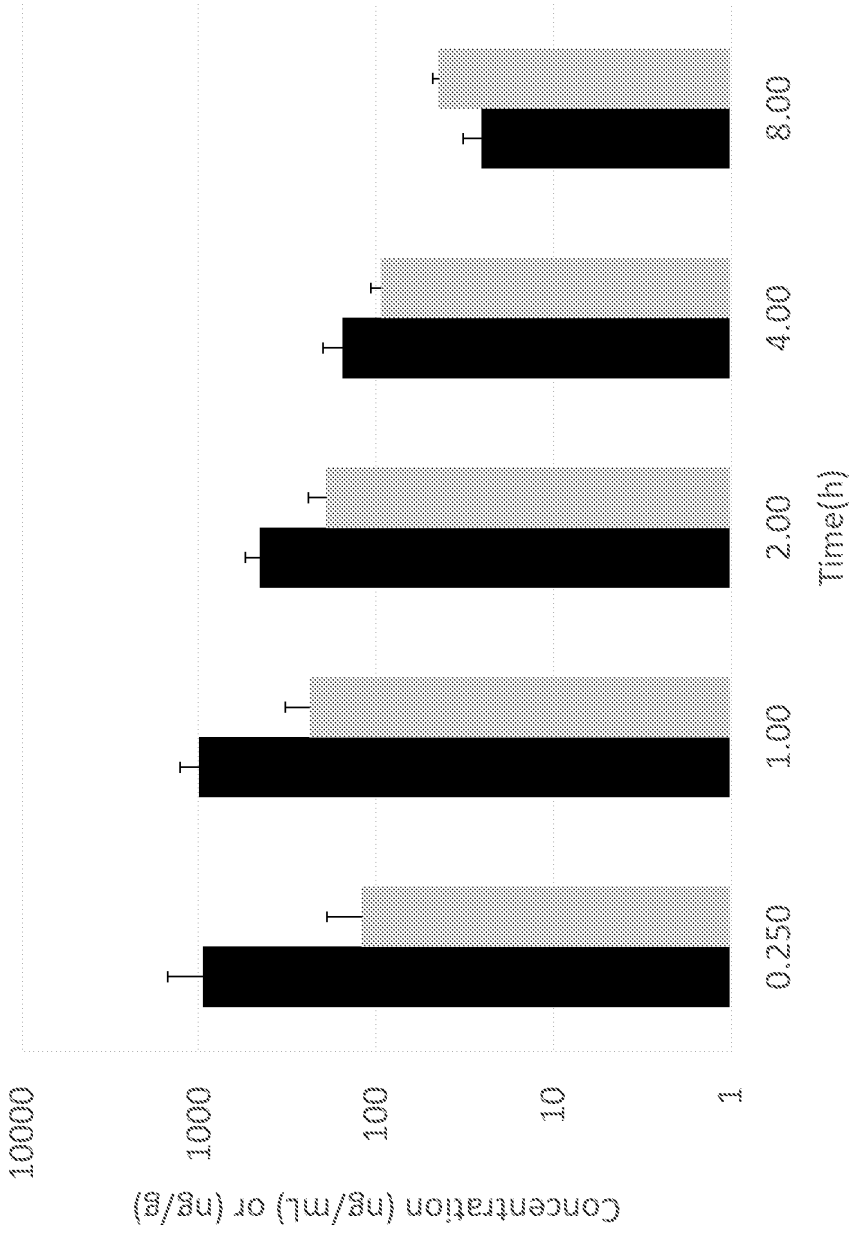

Concentration (ng/mL) or (ng/g)
10000
1000
100
10
1
0.250
1.00
2.00
4.00
8.00
Time(h)

FIG. 7

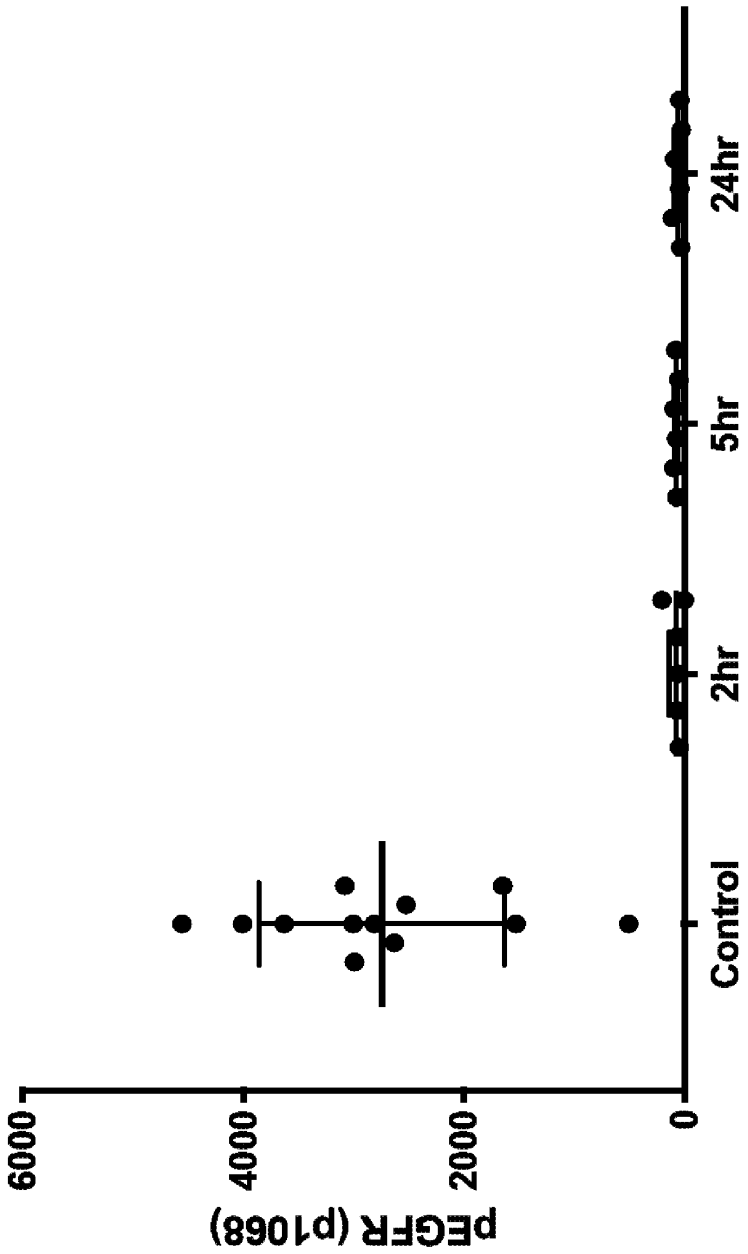

BaF3-EGFR V3 Allograft MI4415
pEGFR (p1068)
6000
4000
2000
0
Control
2hr
5hr
24hr

FIG. 8

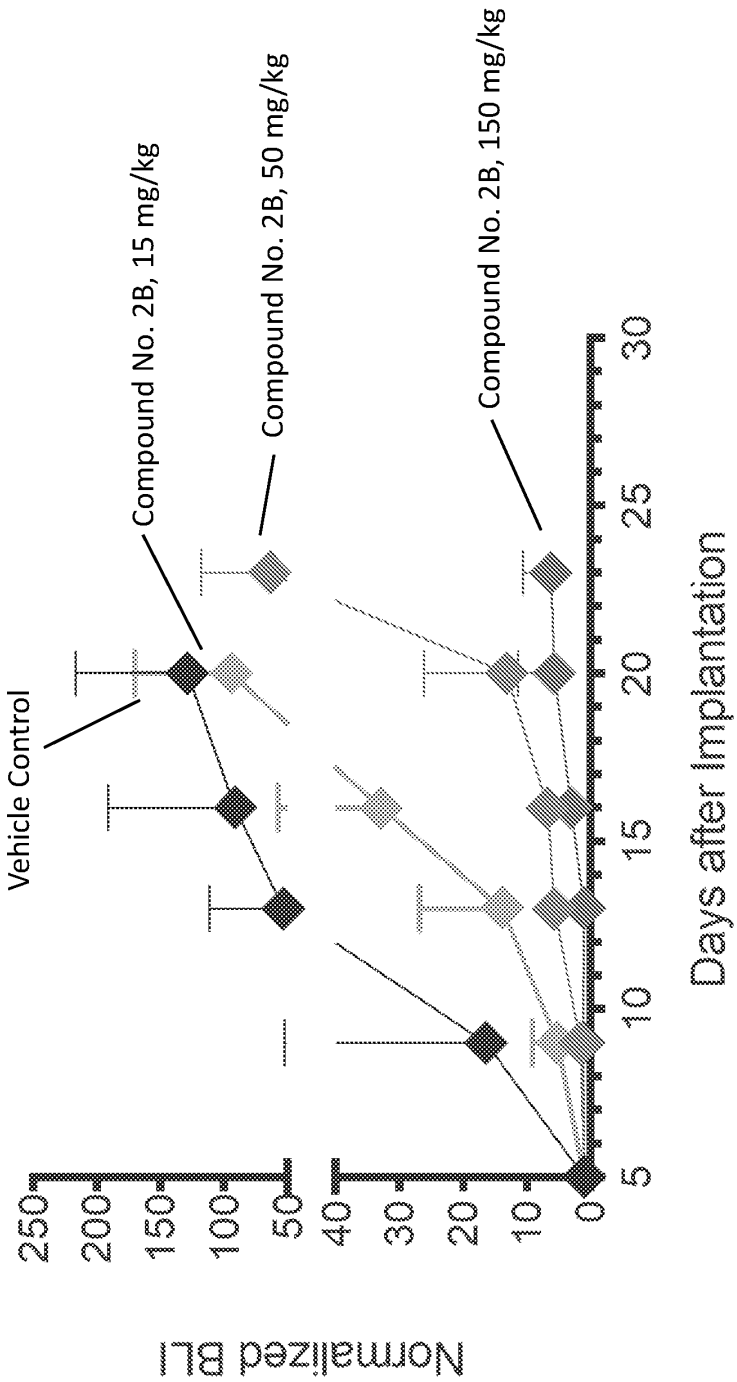

Vehicle Control
Compound No. 2B, 15 mg/kg
Compound No. 2B, 50 mg/kg
Compound No. 2B, 150 mg/kg
Normalized BLI
Days after Implantation
250
200
150
100
50
40
30
20
10
0
5
10
15
20
25
30

FIG. 9

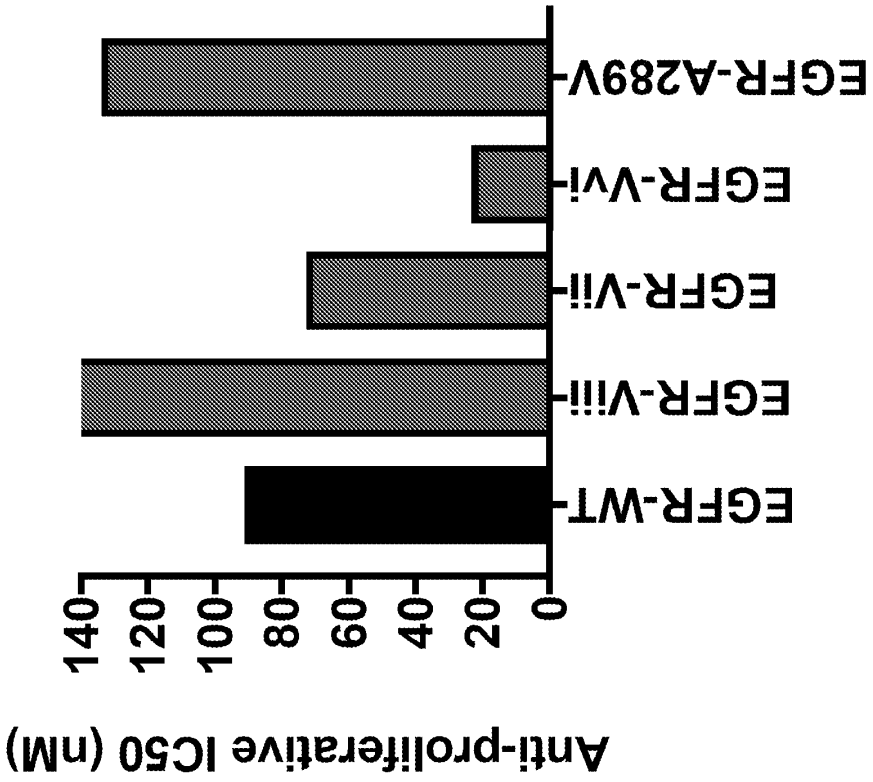

Anti-proliferative IC50 (nM)
0
20
40
60
80
100
120
140
EGFR-WT
EGFR-Viii
EGFR-Vii
EGFR-Vvi
EGFR-A289V

FIG. 10

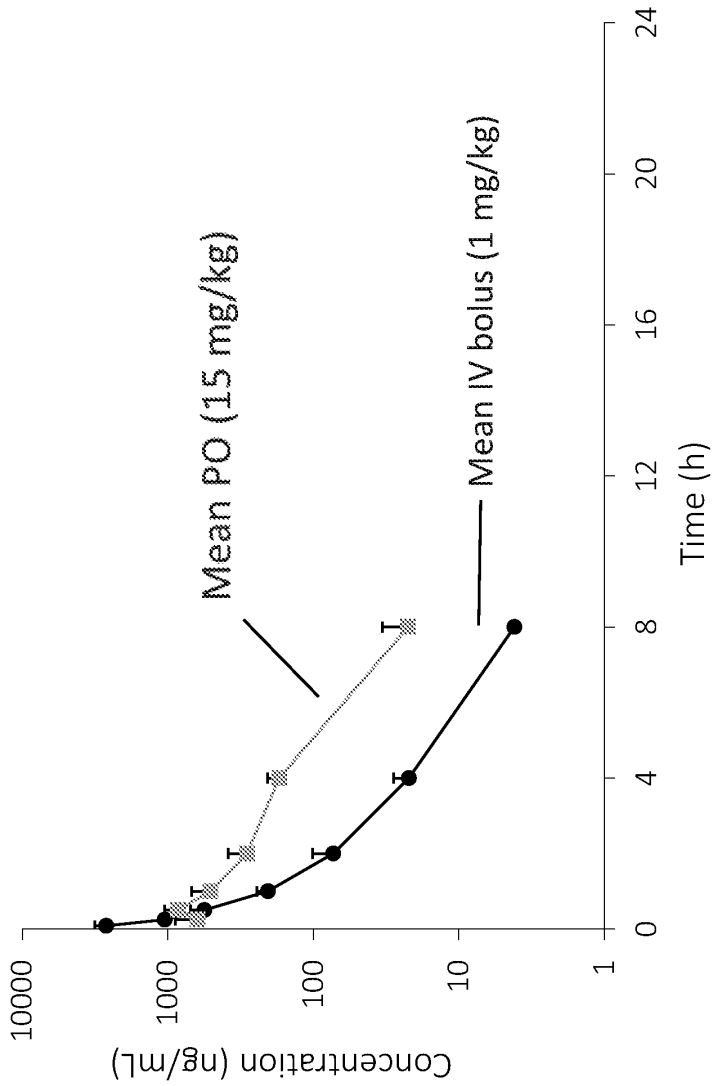

Concentration (ng/mL)
10000
1000
100
10
1
0
4
8
12
16
20
24
Time (h)
Mean PO (15 mg/kg)
Mean IV bolus (1 mg/kg)

FIG. 11

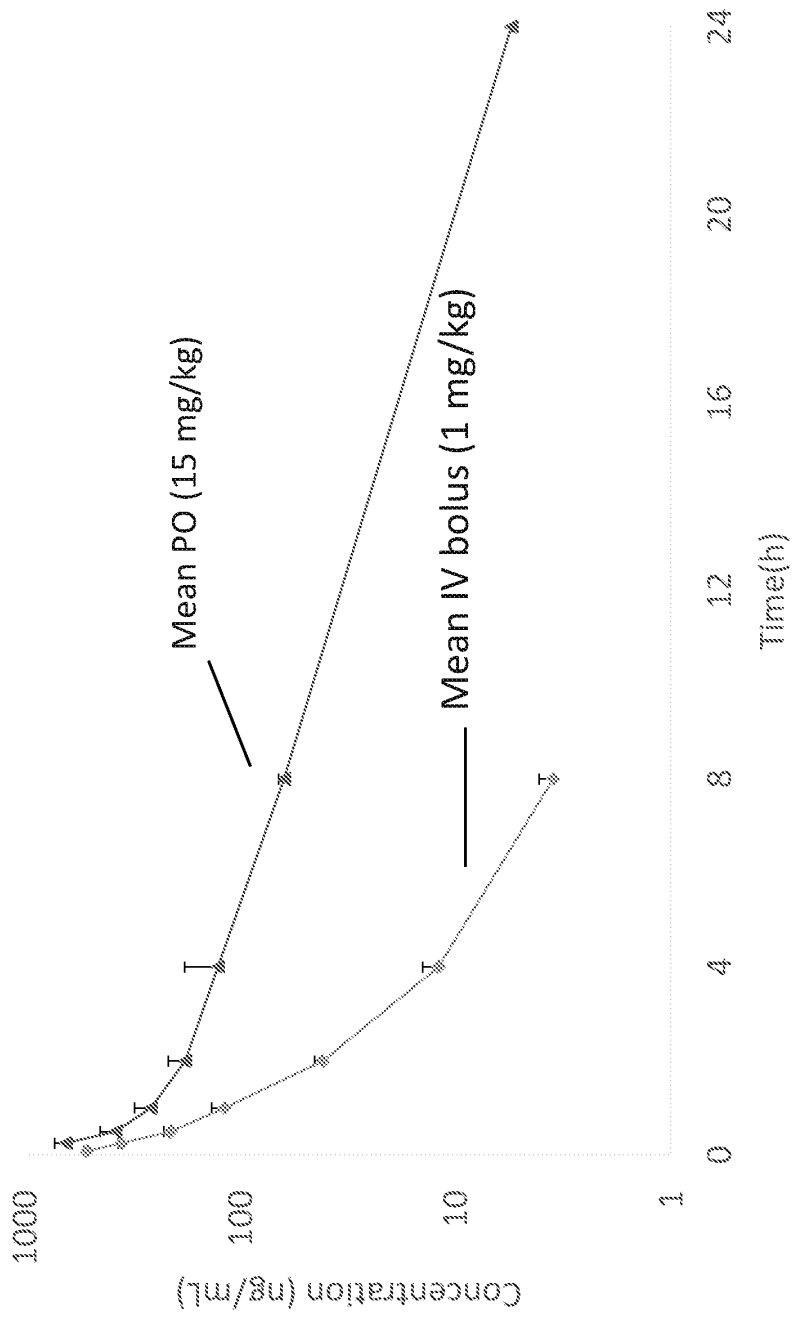

Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time(h)
Mean PO (15 mg/kg)
Mean IV bolus (1 mg/kg)

FIG. 12

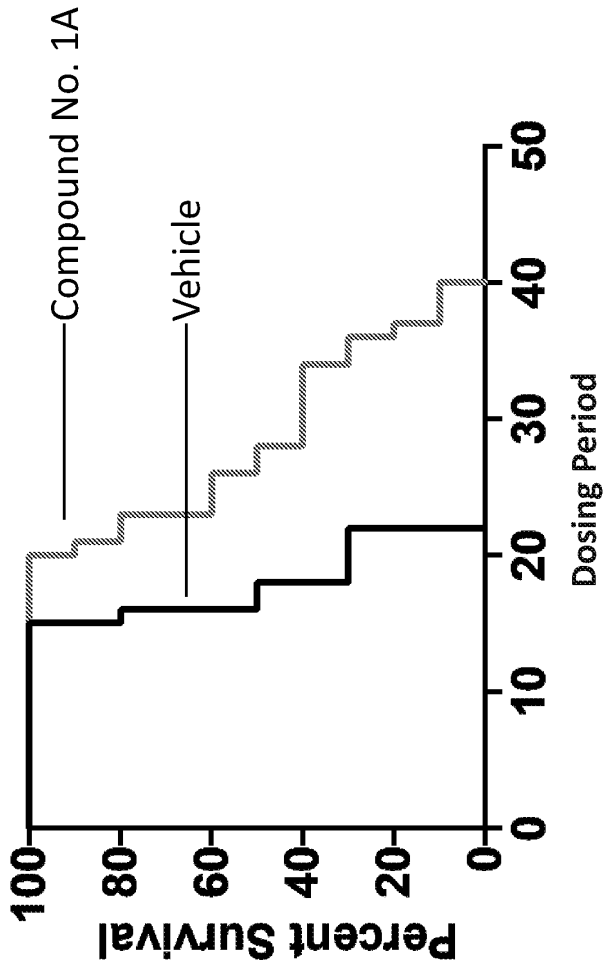

Compound No. 1A
Vehicle
Percent Survival
100
80
60
40
20
0
0
10
20
30
40
50
Dosing Period

FIG. 13

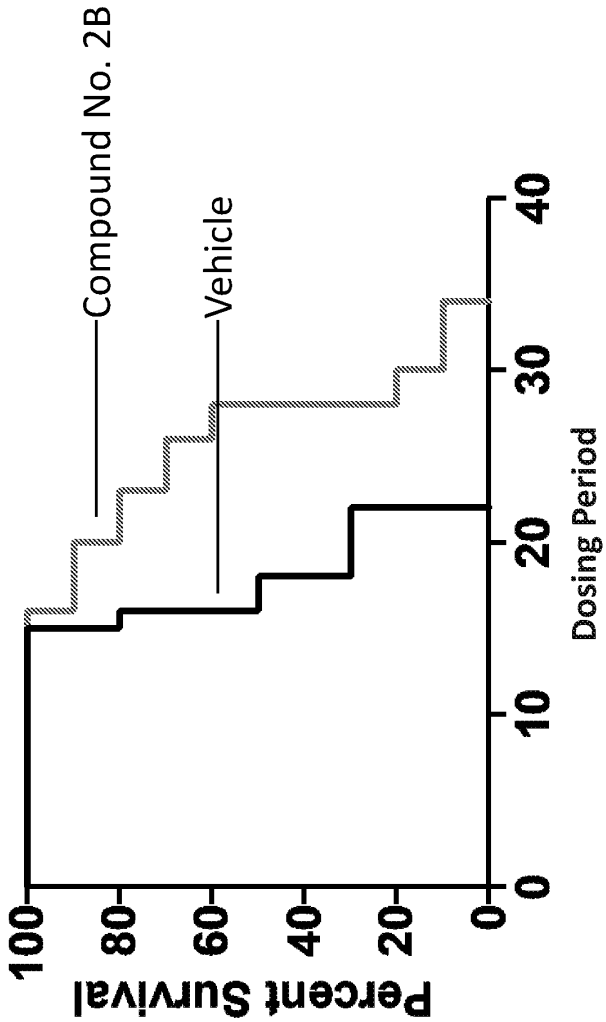

Compound No. 2B
Vehicle
Percent Survival
100
80
60
40
20
0
0
10
20
30
40
Dosing Period

FIG. 14A

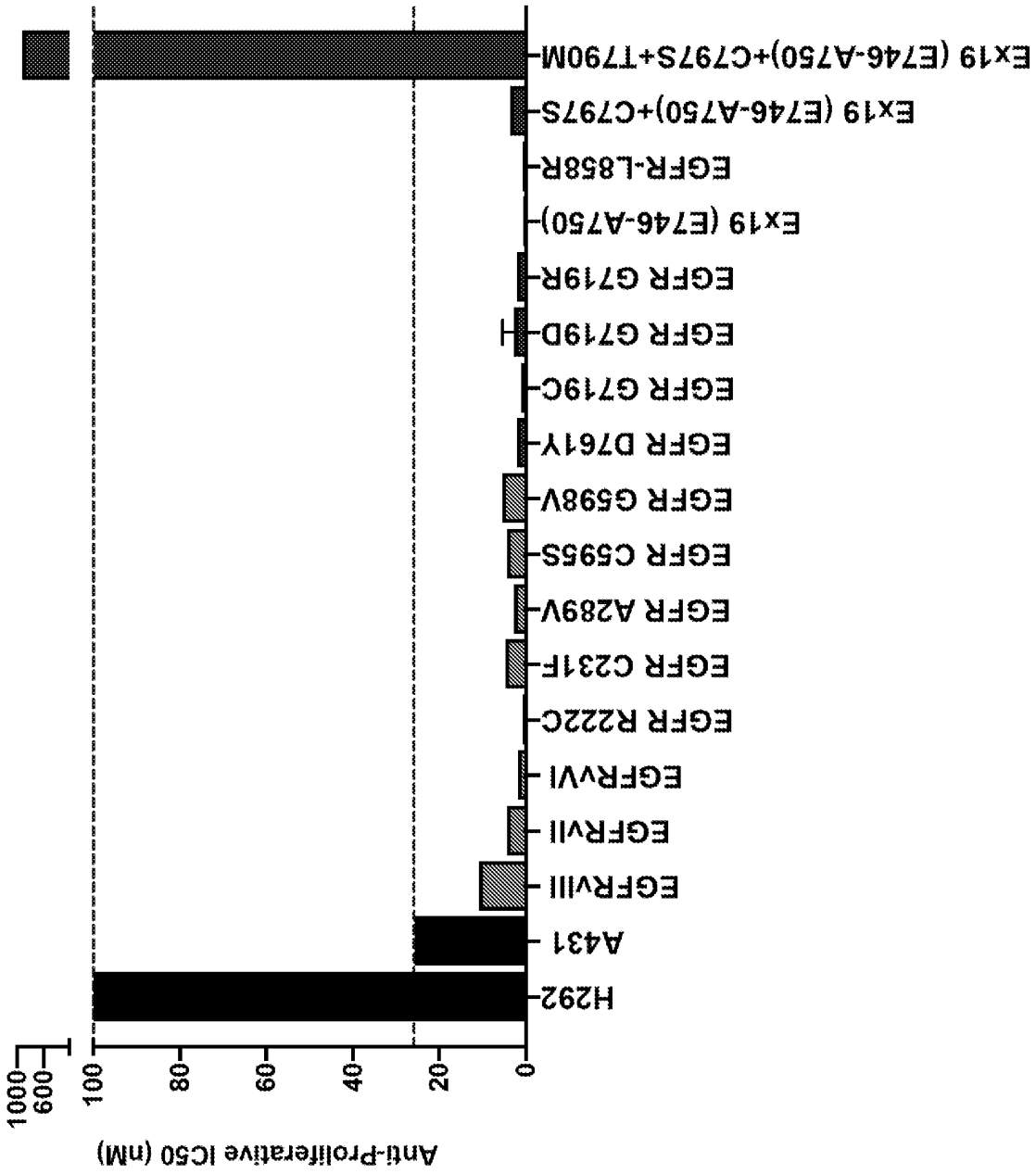

Anti-Proliferative IC50 (nM)
1000
600
100
80
60
40
20
0
H292
A431
EGFRvIII
EGFRvII
EGFRvVI
EGFR R222C
EGFR C231F
EGFR A289V
EGFR C595S
EGFR G598V
EGFR D761Y
EGFR G719C
EGFR G719D
EGFR G719R
Ex19 (E746-A750)
EGFR-L858R
Ex19 (E746-A750)+C797S
Ex19 (E746-A750)+C797S+T790M

FIG. 14B

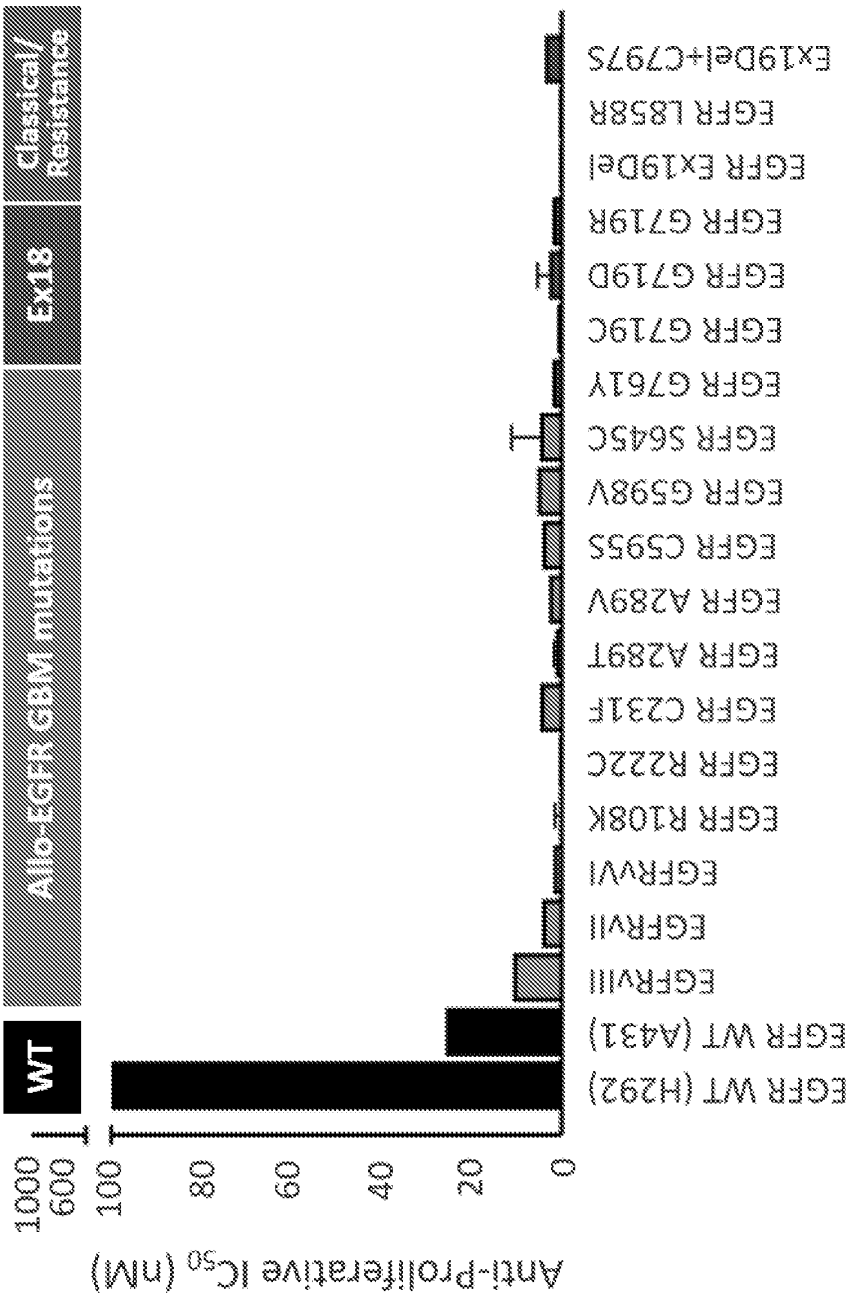

Classical/ Resistance
Ex18
Allo-EGFR GBM mutations
WT
Anti-Proliferative IC50 (nM)
1000
600
100
80
60
40
20
0
EGFR WT (H292)
EGFR WT (A431)
EGFRvIII
EGFRvII
EGFRvVI
EGFR R108K
EGFR R222C
EGFR C231F
EGFR A289T
EGFR A289V
EGFR C595S
EGFR G598V
EGFR S645C
EGFR G761Y
EGFR G719C
EGFR G719D
EGFR G719R
EGFR Ex19Del
EGFR L858R
Ex19Del+C797S

FIG. 14C

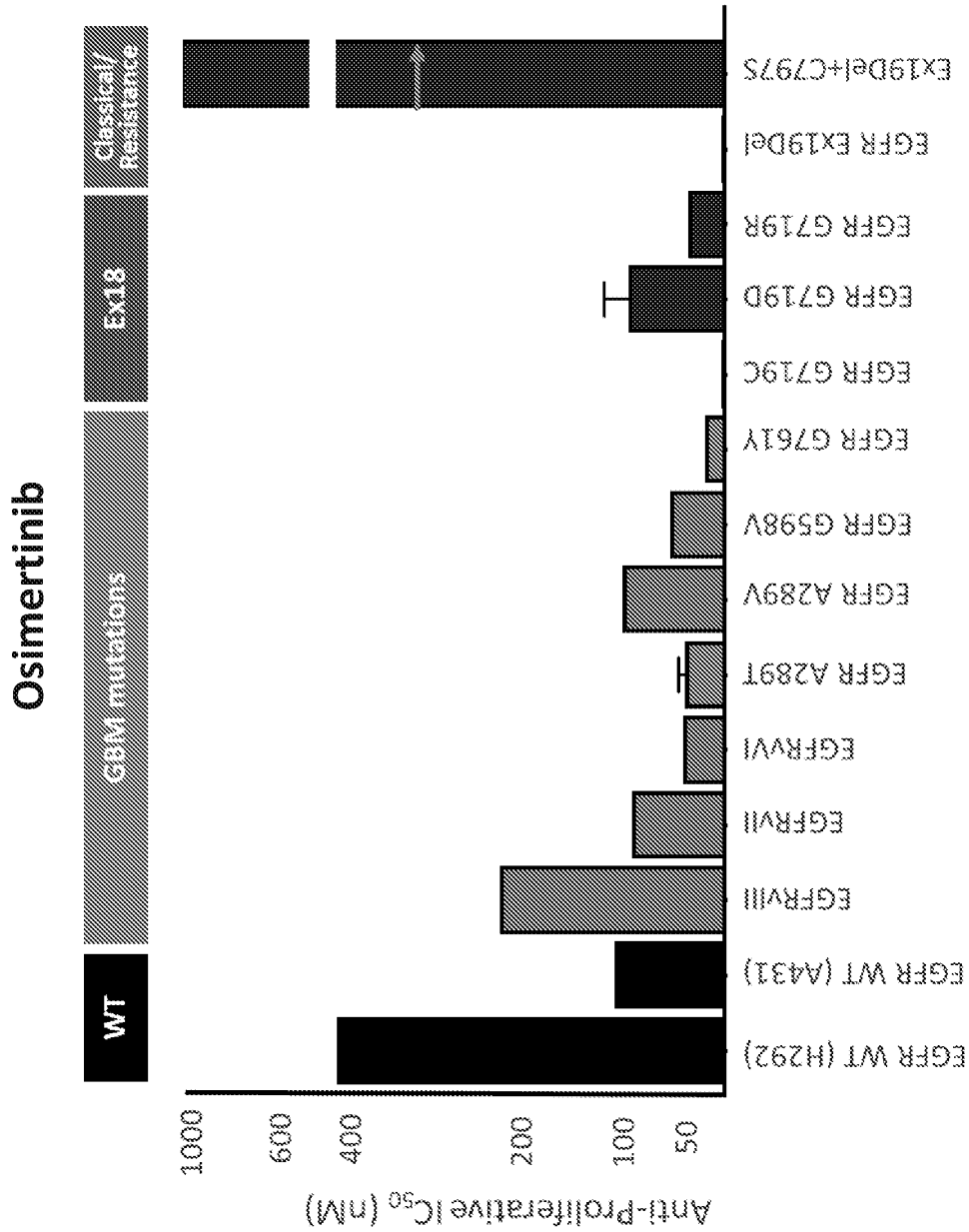

Osimertinib
WT
CBM mutations
Ex18
Classical/ Resistance
Anti-Proliferative IC50 (nM)
1000
600
400
200
100
50
EGFR WT (H292)
EGFR WT (A431)
EGFRvIII
EGFRvII
EGFRvVI
EGFR A289T
EGFR A289V
EGFR G598V
EGFR G761Y
EGFR G719C
EGFR G719D
EGFR G719R
EGFR Ex19Del
Ex19Del+C797S

FIG. 15

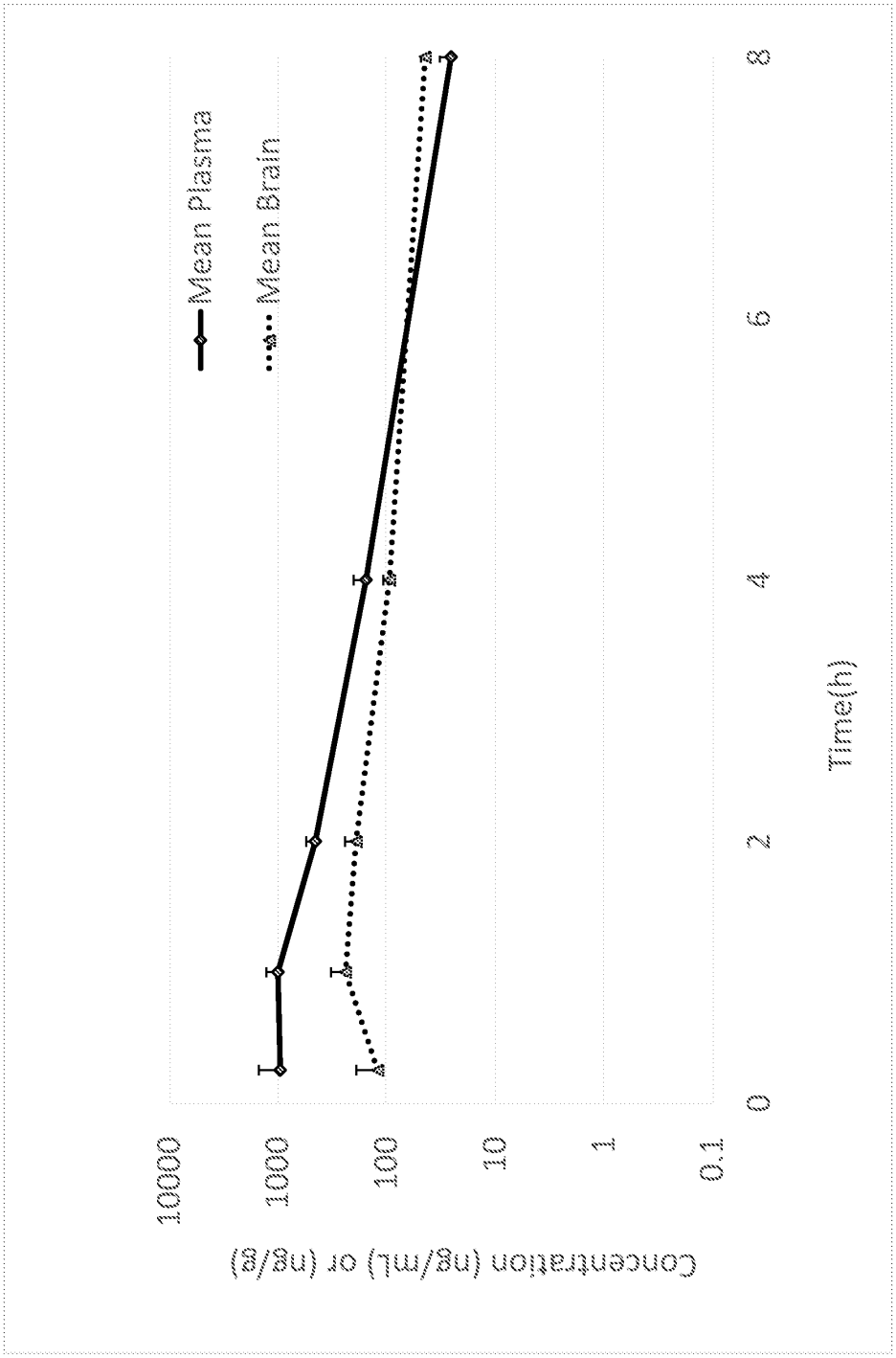

Mean Plasma
Mean Brain
Concentration (ng/mL) or (ng/g)
10000
1000
100
10
1
0.1
0
2
4
6
8
Time(h)

FIG. 16

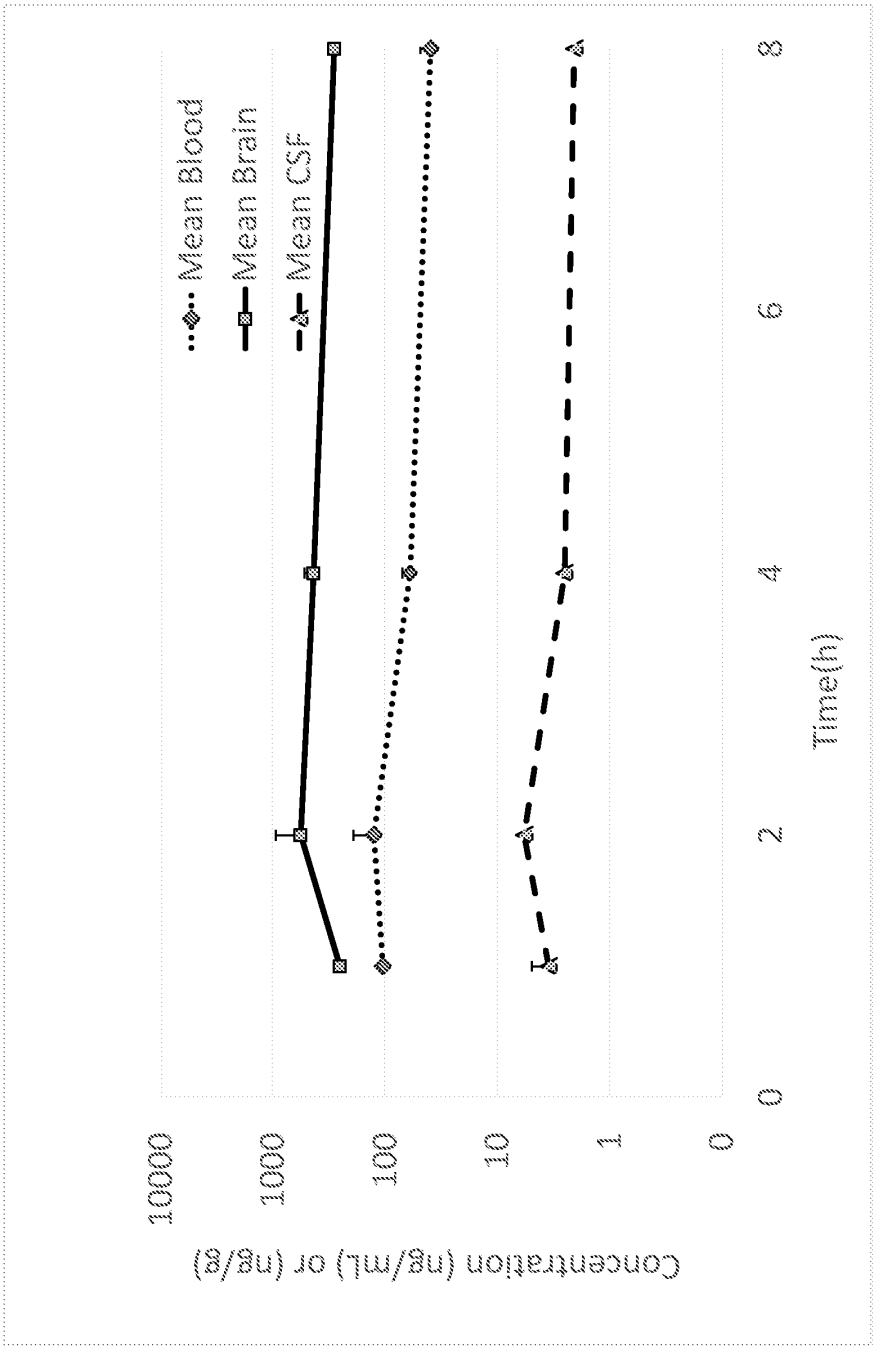

Mean Blood
Mean Brain
Mean CSF
Concentration (ng/mL) or (ng/g)
10000
1000
100
10
1
0
0
2
4
6
8
Time(h)

FIG. 17

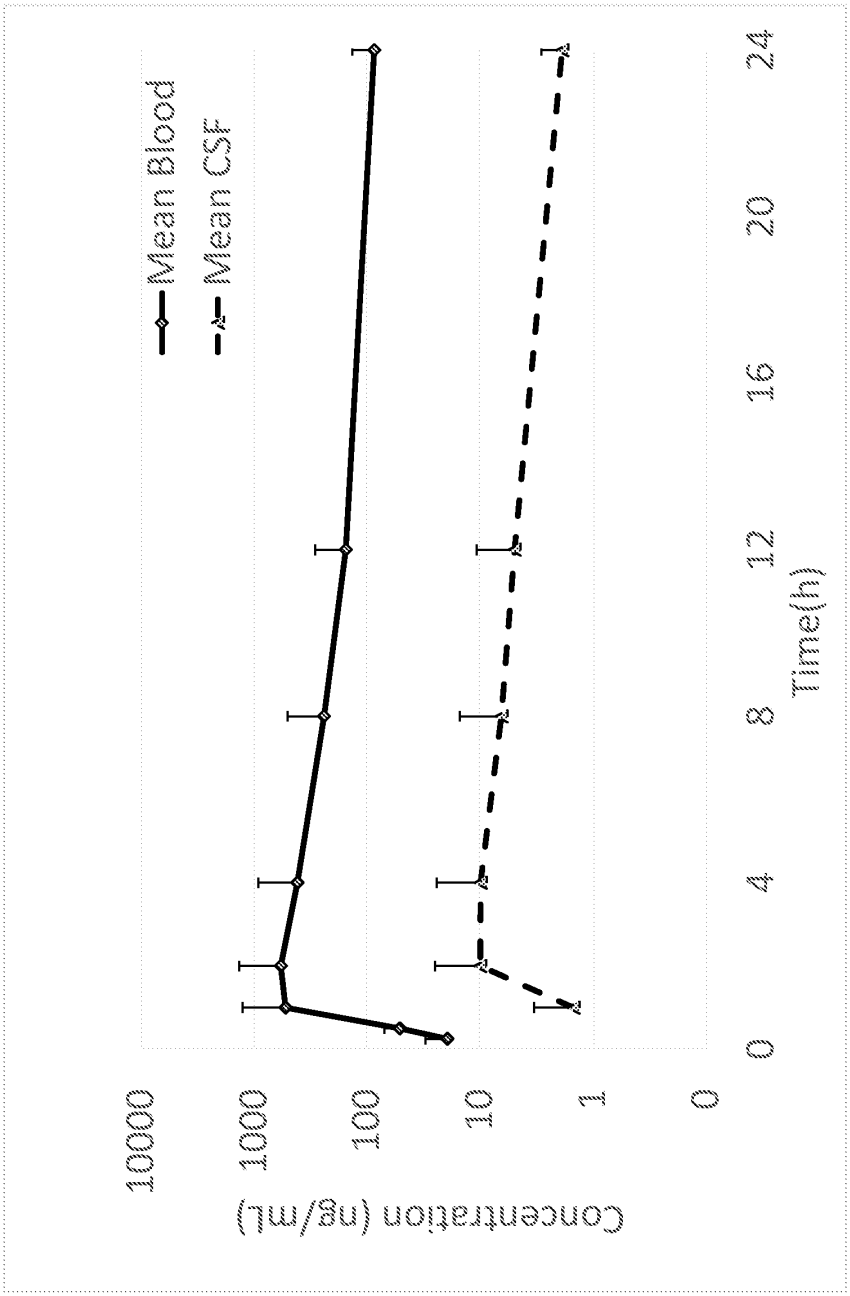

Mean Blood
Mean CSF
Concentration (ng/mL)
10000
1000
100
10
1
0
0
4
8
12
16
20
24
Time(h)

FIG. 18

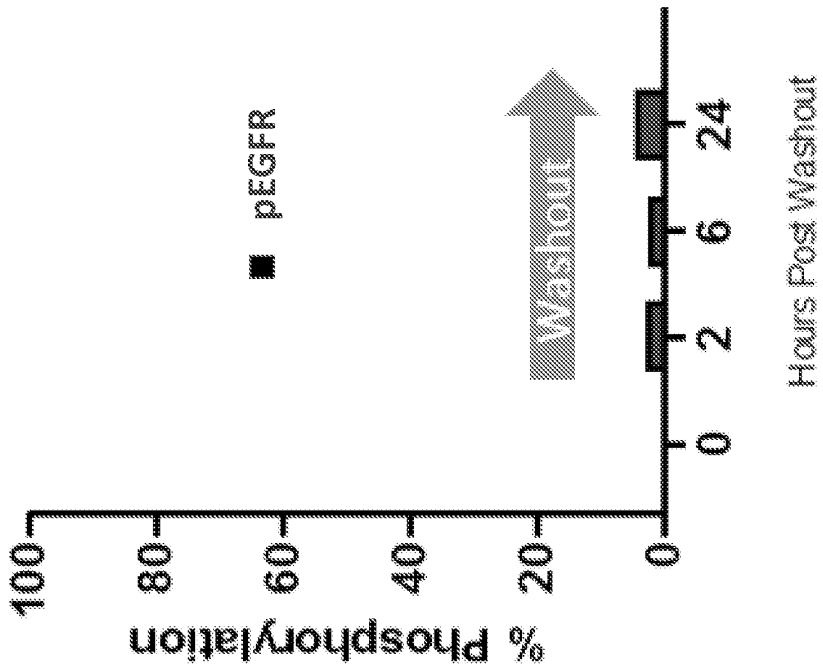

% Phosphorylation
100
80
60
40
20
0
pEGFR
Washout
0
2
6
24
Hours Post Washout

FIG. 19A

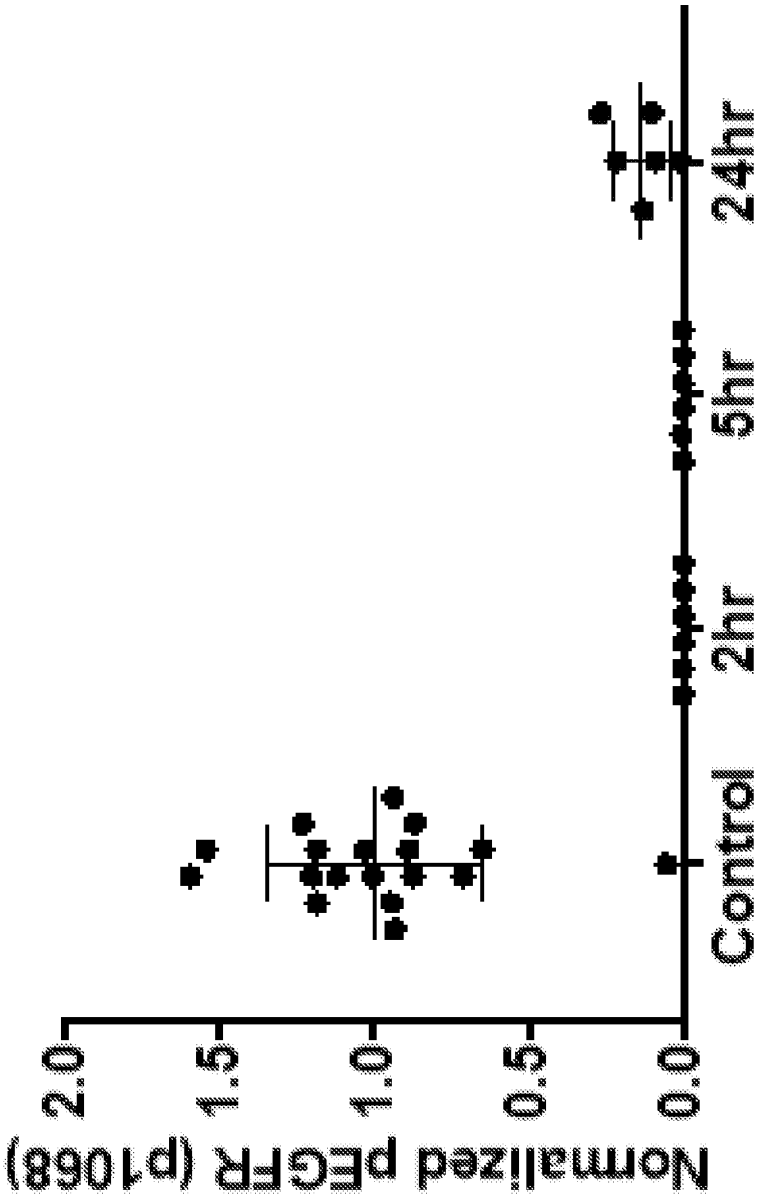


FIG. 19B

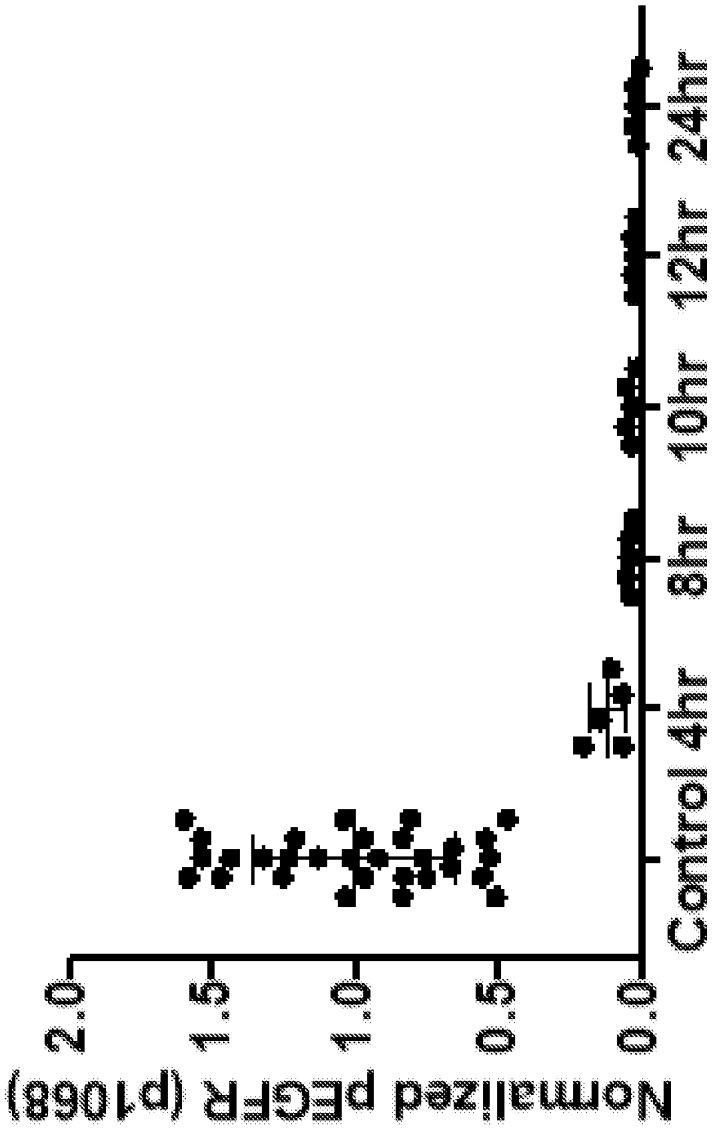

Normalized pEGFR (p1068)
2.0
1.5
1.0
0.5
0.0
Control
4hr
8hr
10hr
12hr
24hr

FIG. 19C

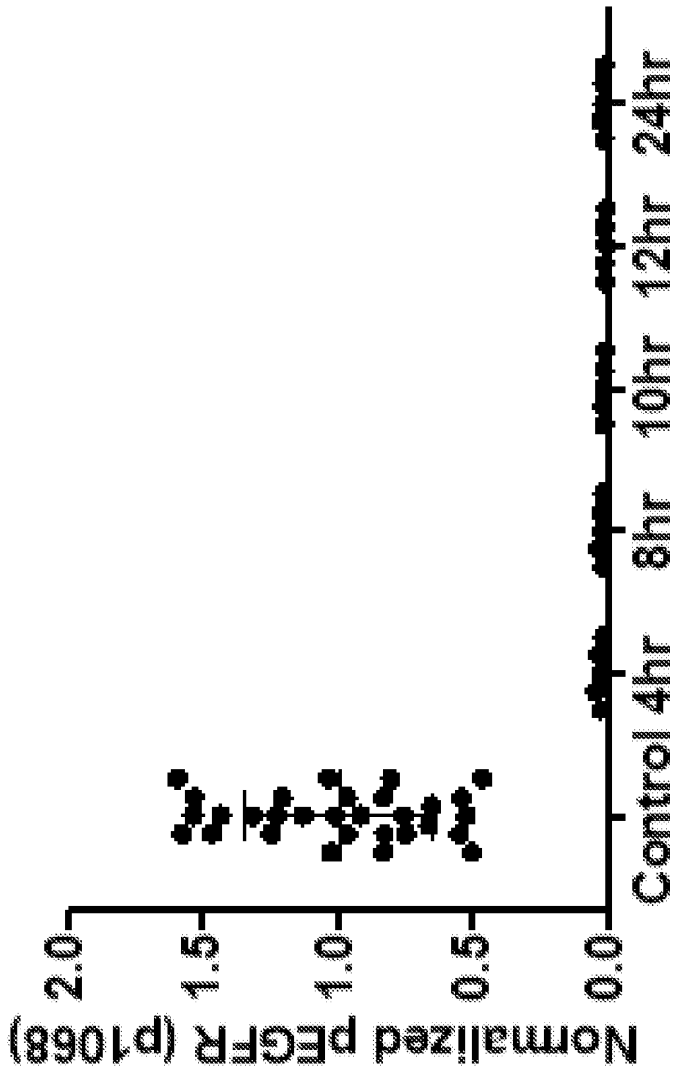

Normalized pEGFR (p1068)
2.0
1.5
1.0
0.5
0.0
Control
4hr
8hr
10hr
12hr
24hr

FIG. 20

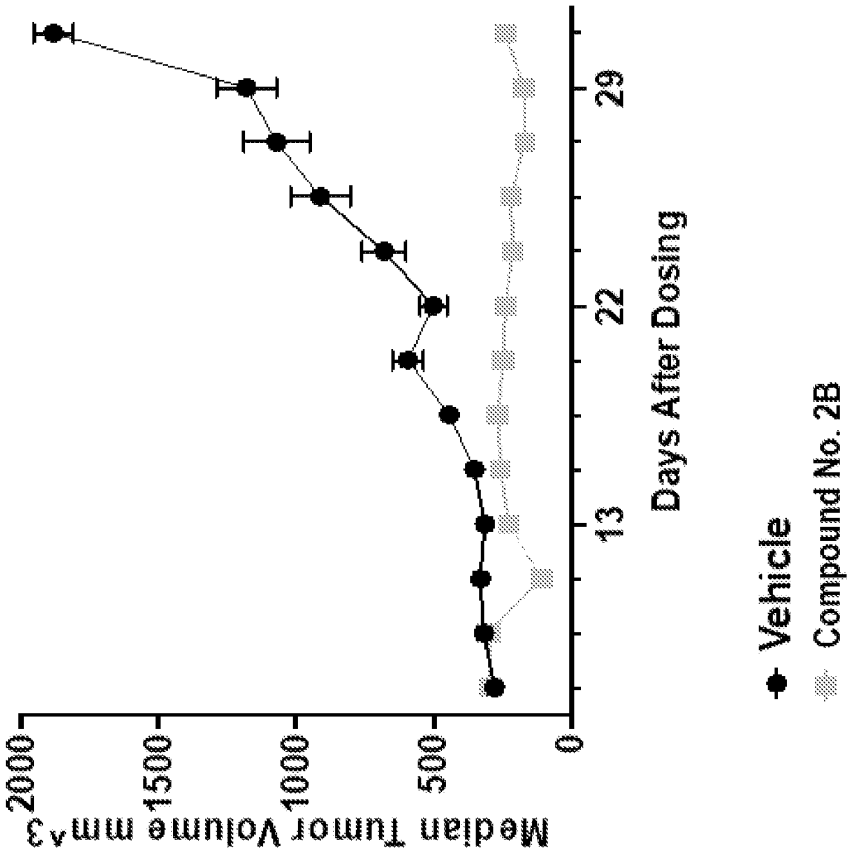

Median Tumor Volume mm^3
2000
1500
1000
500
0
13
22
29
Days After Dosing
Vehicle
Compound No. 2B

FIG. 21

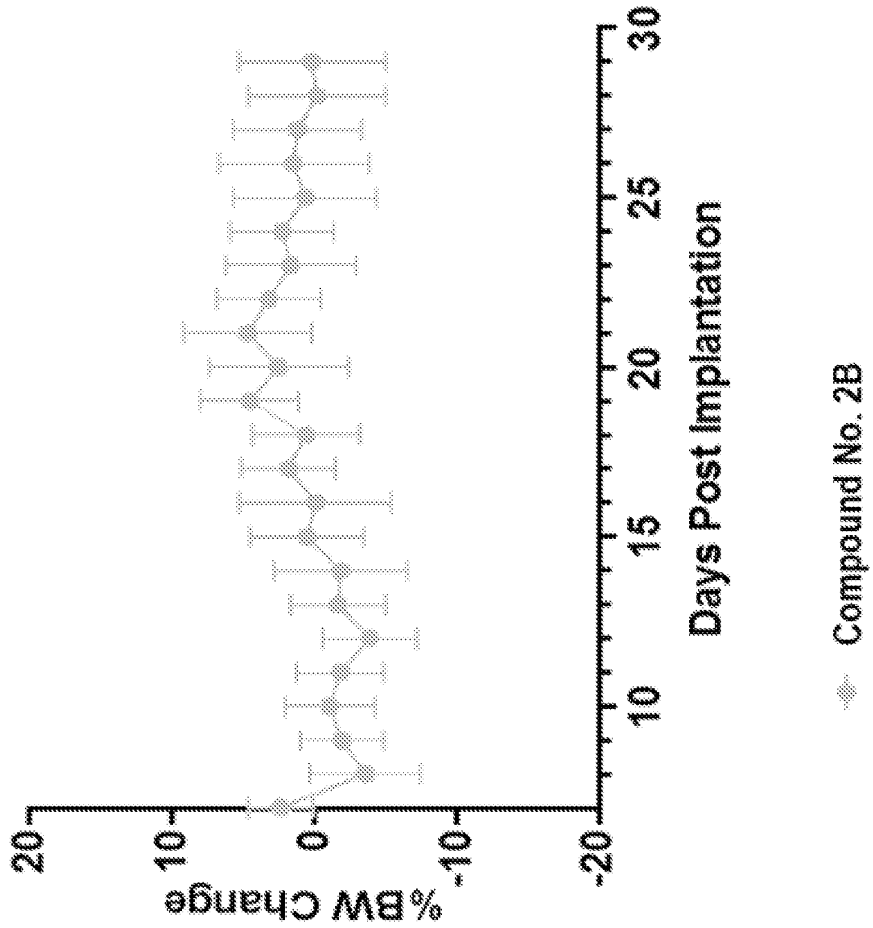

20
10
0
-10
-20
% BW Change
10
15
20
25
30
Days Post Implantation
Compound No. 2B

FIG. 22

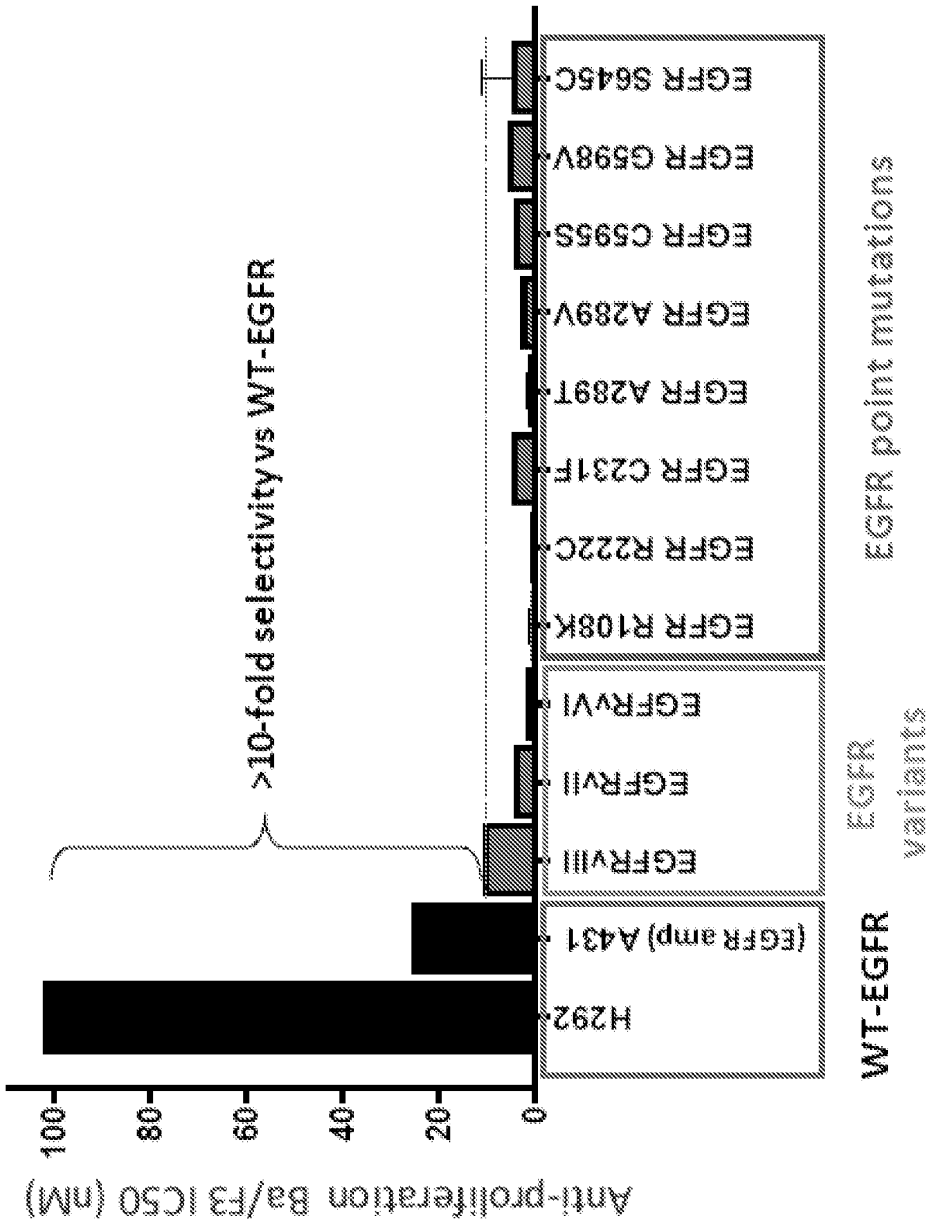

Anti-proliferation Ba/F3 IC50 (nM)
100
80
60
40
20
0
>10-fold selectivity vs WT-EGFR
H292
(EGFR amp) A431
EGFRvIII
EGFRvII
EGFRvVI
EGFR R108K
EGFR R222C
EGFR C231F
EGFR A289T
EGFR A289V
EGFR C595S
EGFR G598V
EGFR S645C
WT-EGFR
EGFR variants
EGFR point mutations

FIG. 23

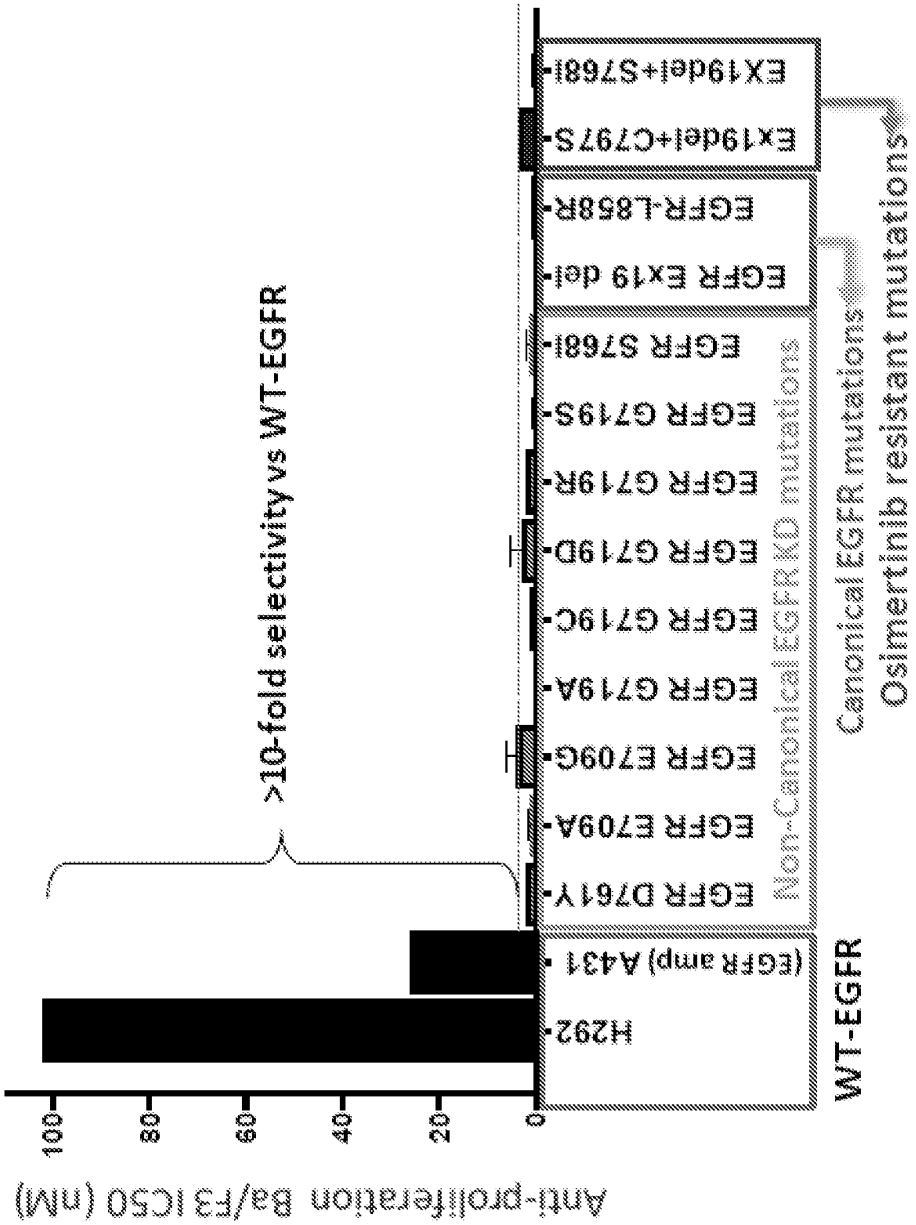

Anti-proliferation Ba/F3 IC50 (nM)
100
80
60
40
20
0
>10-fold selectivity vs WT-EGFR
H292
(EGFR amp) A431
EGFR D761Y
EGFR E709A
EGFR E709G
EGFR G719A
EGFR G719C
EGFR G719D
EGFR G719R
EGFR G719S
EGFR S768I
EGFR Ex19 del
EGFR-L858R
Ex19del+C797S
EX19del+S768I
WT-EGFR
Non-Canonical EGFR KD mutations
Canonical EGFR mutations
Osimertinib resistant mutations

FIG. 24

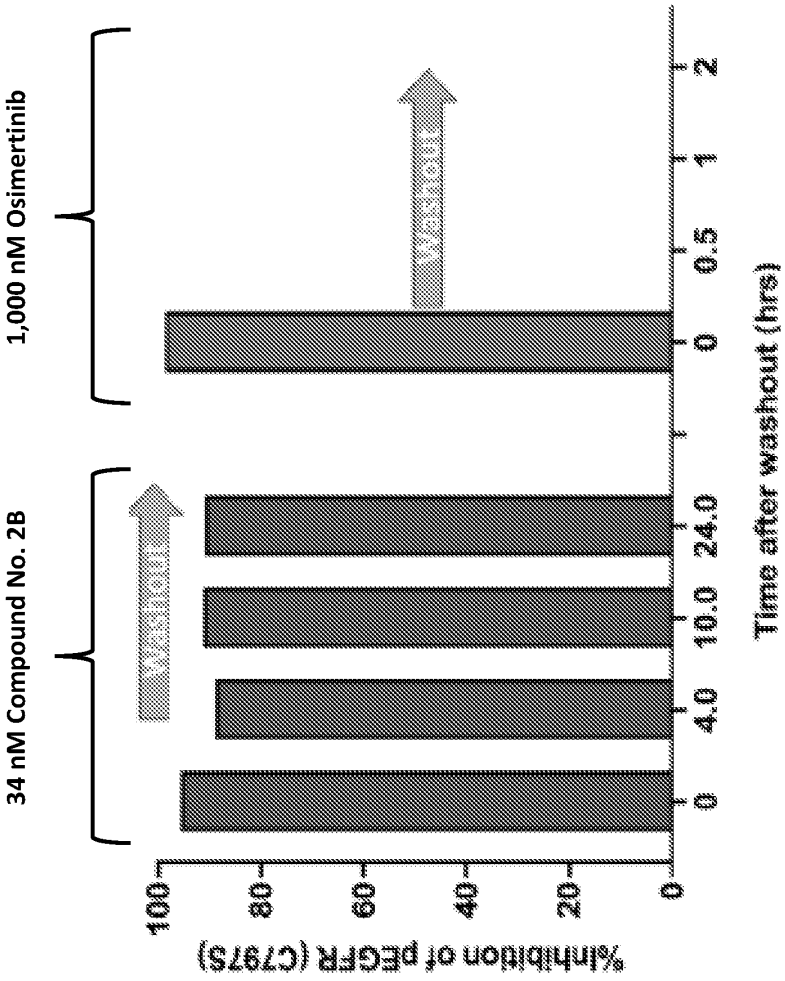

%Inhibition of pEGFR (C797S)
100
80
60
40
20
0
34 nM Compound No. 2B
1,000 nM Osimertinib
Washout
Washout
0
4.0
10.0
24.0
0
0.5
1
2
Time after washout (hrs)

FIG. 25

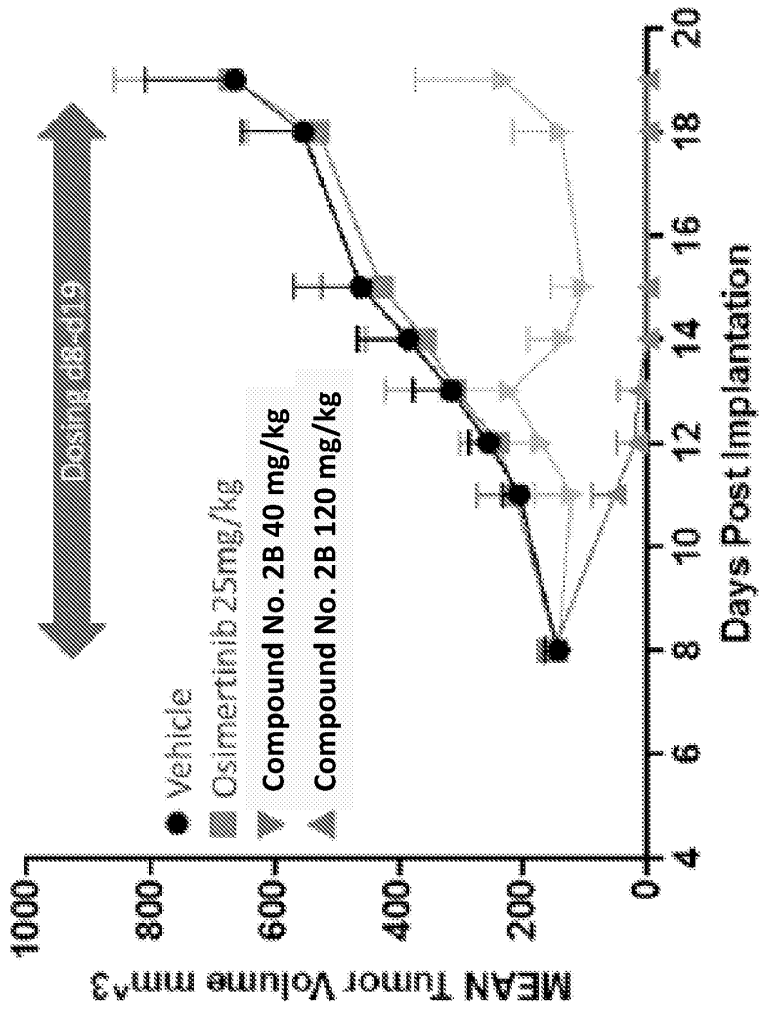

Dosing duration
Vehicle
Osimertinib 25mg/kg
Compound No. 2B 40 mg/kg
Compound No. 2B 120 mg/kg
MEAN Tumor Volume mm^3
1000
800
600
400
200
0
4
6
8
10
12
14
16
18
20
Days Post Implantation

FIG. 26

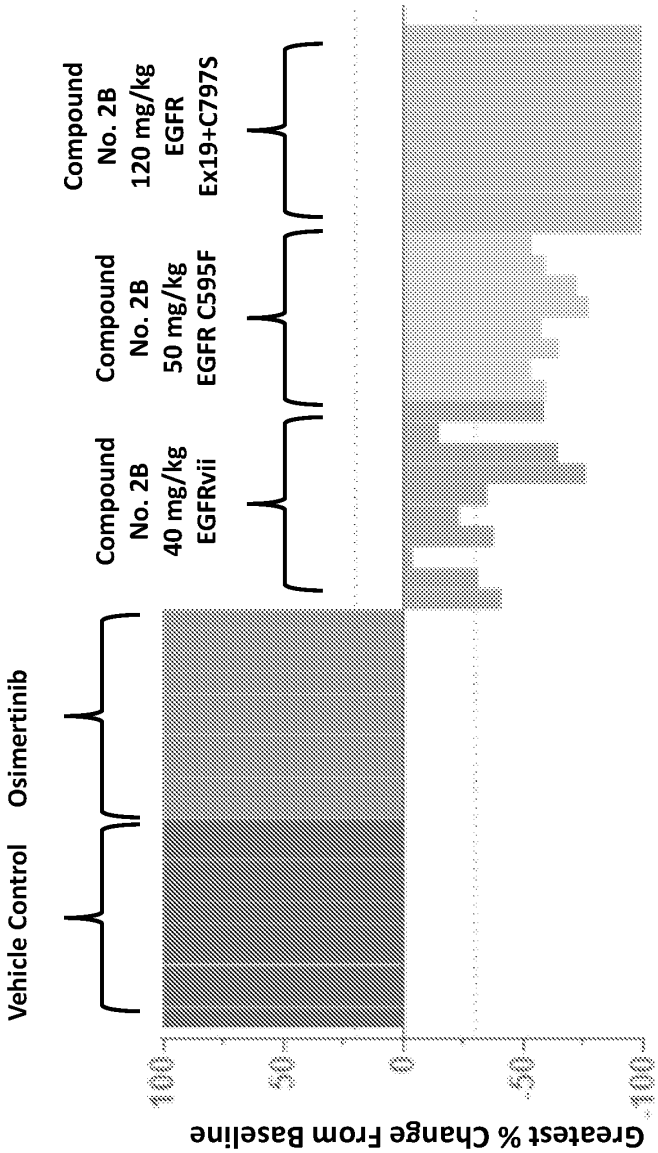
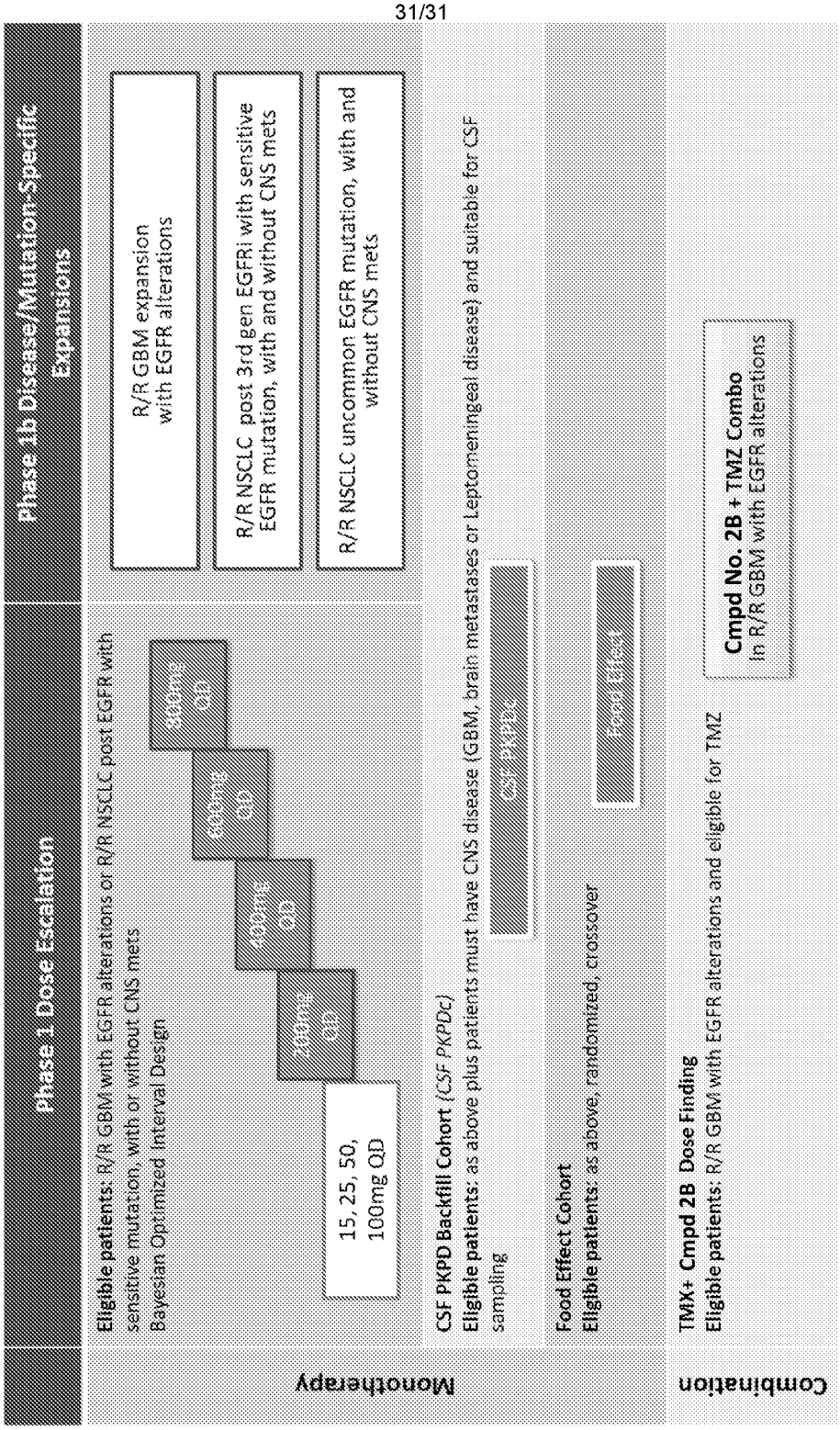

Greatest % Change From Baseline
100
50
0
-50
-100
Vehicle Control
Osimertinib
Compound No. 2B 40 mg/kg EGFRvii
Compound No. 2B 50 mg/kg EGFR C595F
Compound No. 2B 120 mg/kg EGFR Ex19+C797S

FIG. 27


Phase 1 Dose Escalation
Phase 1b Disease/Mutation-Specific Expansions
Monotherapy
Eligible patients: R/R GBM with EGFR alterations or R/R NSCLC post EGFR with sensitive mutation, with or without CNS mets
Bayesian Optimized Interval Design
15, 25, 50, 100mg QD
CSF PKPD Backfill Cohort (CSF PKPDc)
Eligible patients: as above plus patients must have CNS disease (GBM, brain metastases or Leptomeningeal disease) and suitable for CSF sampling
CSF PKPDc
Food Effect Cohort
Eligible patients: as above, randomized, crossover
Food Effect
R/R GBM expansion with EGFR alterations
R/R NSCLC post 3rd gen EGFRi with sensitive EGFR mutation, with and without CNS mets
R/R NSCLC uncommon EGFR mutation, with and without CNS mets
Combination
TMX+ Cmpd 2B Dose Finding
Eligible patients: R/R GBM with EGFR alterations and eligible for TMZ
Cmpd No. 2B + TMZ Combo
In R/R GBM with EGFR alterations