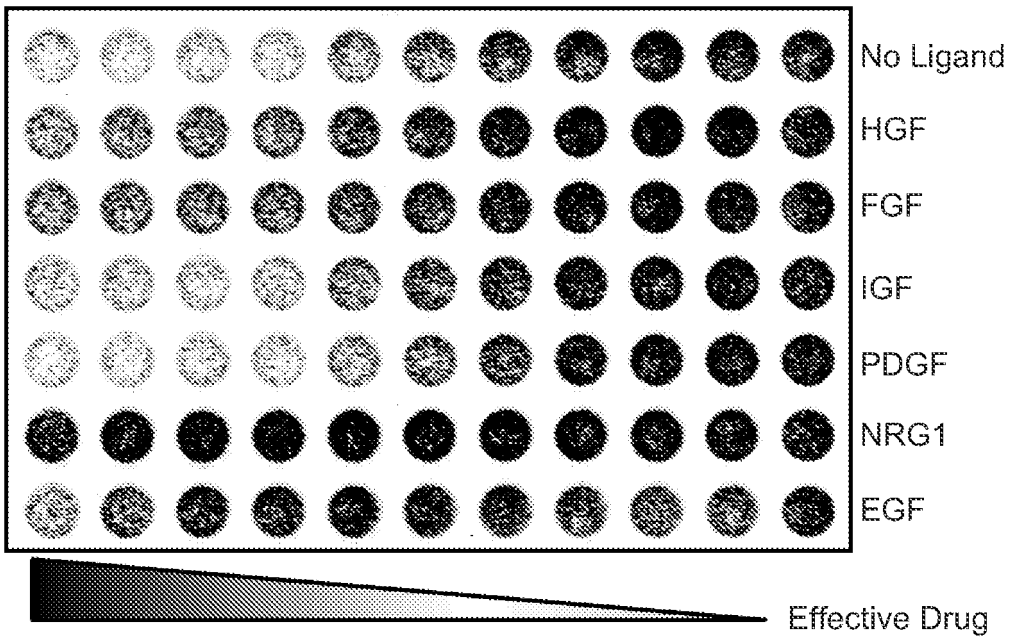


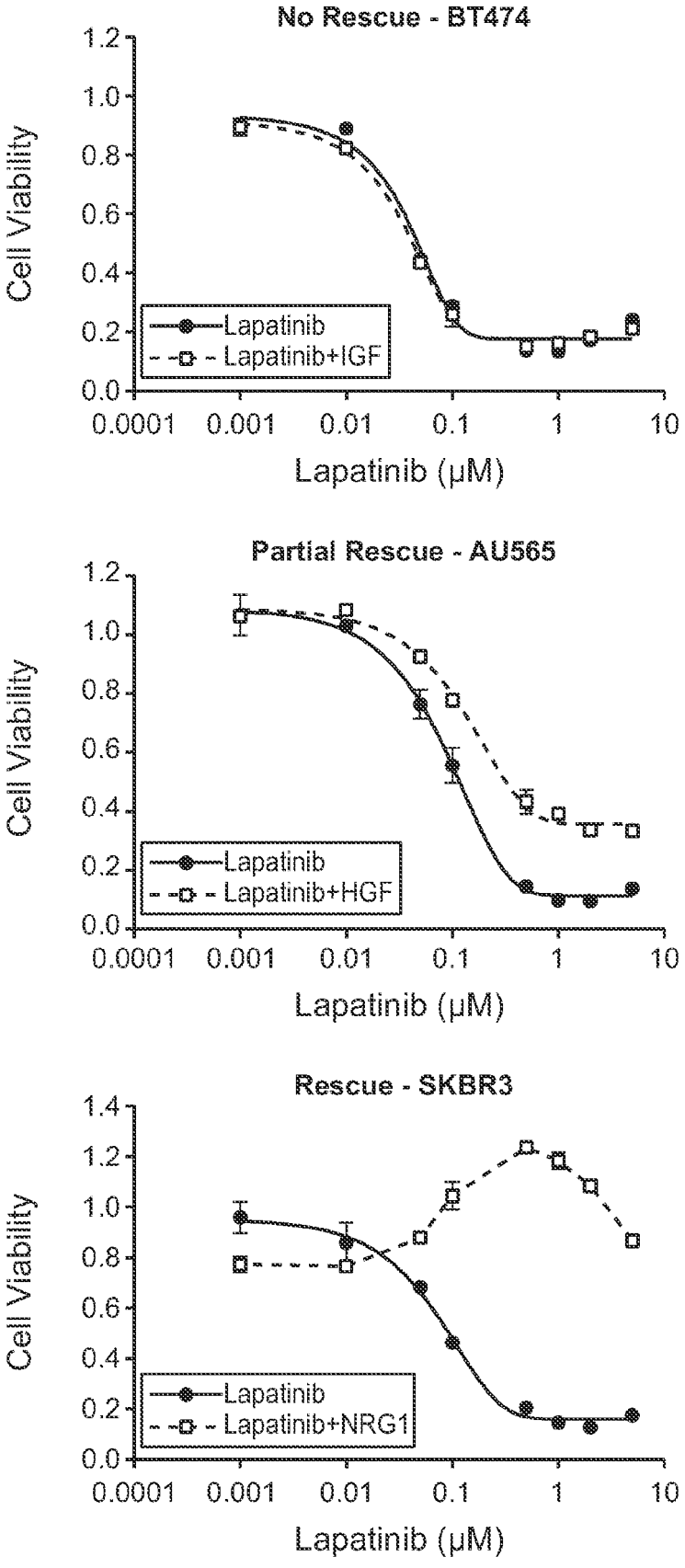
FIG. 1A

Kinase Addiction (Effective Drug)	Cell Line	HGF	FGF	IGF	PDGF	NRG1	EGF
HER2 Amplified (Lapatinib)	KPL4	P	P	NR	NR	R	NR
	EFM192A	NR	NR	NR	NR	R	NR
	SKBR3	NR	NR	NR	NR	R	R
	BT474	NR	NR	NR	NR	R	P
	AU565	P	P	NR	NR	R	P
	HCC1419	NR	NR	NR	NR	R	NR
	UACC893	NR	P	NR	NR	R	R
	HCC1954	P	NR	NR	NR	NR	P
	HCC202	NR	P	NR	NR	R	NR
NRG1 Autocrine (Lapatinib)	CHL-1	R	R	P	NR	NR	NR
	SAT	R	R	NR	NR	NR	R
	FaDu	R	R	NR	NR	NR	P
	PCI-6A	R	R	NR	NR	NR	R
EGFR Mutation (Erlotinib)	PC9	R	R	P	NR	NR	NR
	HCC827	R	P	NR	NR	NR	NR
	HCC4006	R	R	NR	NR	P	NR
	KHM-3S	R	R	P	NR	NR	NR
EGF- like Ligand Autocrine (Erlotinib)	CALU-3	P	NR	NR	NR	NR	NR
	H358	NR	NR	NR	NR	NR	NR
	H1648	NR	NR	NR	NR	NR	NR
	H1666	R	R	NR	NR	R	NR
MET Amplified (Crizotinib)	KATO II	NR	R	NR	NR	R	R
	GTL16	NR	P	NR	NR	R	R
	EBC-1	NR	NR	NR	NR	P	P
PDGFR Amplified (Sunitinib)	NCI-H1703	R	R	NR	NR	NR	R
	A-204	NR	R	NR	NR	NR	NR
FGFR Amplified (PD173074)	MFM223	NR	P	NR	NR	R	P
	Kato III	NR	NR	NR	NR	NR	NR
	RT112	R	NR	NR	NR	R	R
	RT4	NR	NR	NR	NR	R	R
ALK Translocation / Mutation (TAE684)	KELLY	NR	P	NR	NR	NR	R
	SH-SY5Y	NR	P	NR	NR	NR	NR
	NCI-H3122	R	NR	NR	NR	R	R
	NCI-H2228	NR	NR	NR	NR	NR	NR
BRAF V600E (PLX4032)	M14	NR	P	NR	NR	P	NR
	NAE	R	NR	NR	NR	R	P
	A-375	P	R	NR	NR	P	NR
	SK-MEL-28	P	NR	NR	NR	R	NR
	Malme-3M	P	P	NR	NR	NR	P
	COLO-201	P	NR	NR	NR	NR	NR
	COLO-218	P	NR	NR	NR	NR	NR

NR: No Rescue; P: Partial Rescue; R: Rescue

FIG. 1B

FIG. 1C


No Rescue - BT474
Cell Viability
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Lapatinib
Lapatinib+IGF
0.0001
0.001
0.01
0.1
1
10
Lapatinib (μM)
Partial Rescue - AU565
Cell Viability
Lapatinib
Lapatinib+HGF
Lapatinib (μM)
Rescue - SKBR3
Cell Viability
1.4
Lapatinib
Lapatinib+NRG1
Lapatinib (μM)

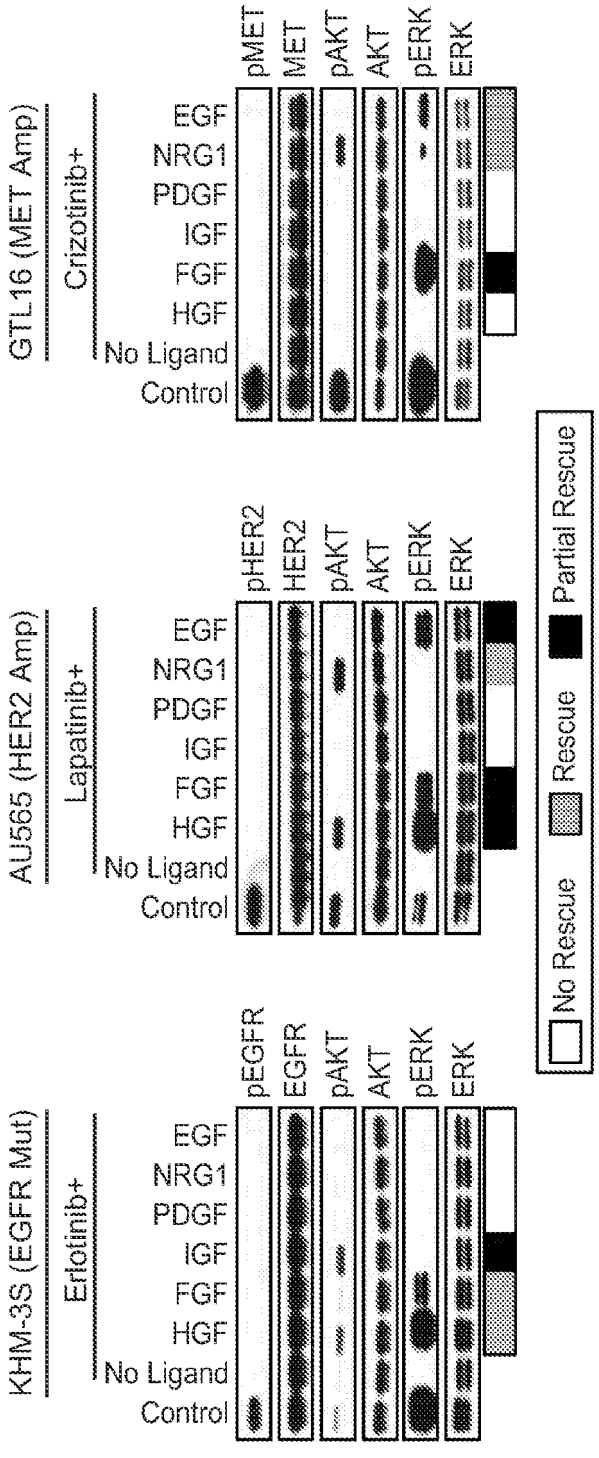

KHM-3S (EGFR Mut)
Erlotinib+
EGF
NRG1
PDGF
IGF
FGF
HGF
No Ligand
Control
pEGFR
EGFR
pAKT
AKT
pERK
ERK
AU565 (HER2 Amp)
Lapatinib+
pHER2
HER2
GTL16 (MET Amp)
Crizotinib+
pMET
MET
No Rescue
Rescue
Partial Rescue

FIG. 2A

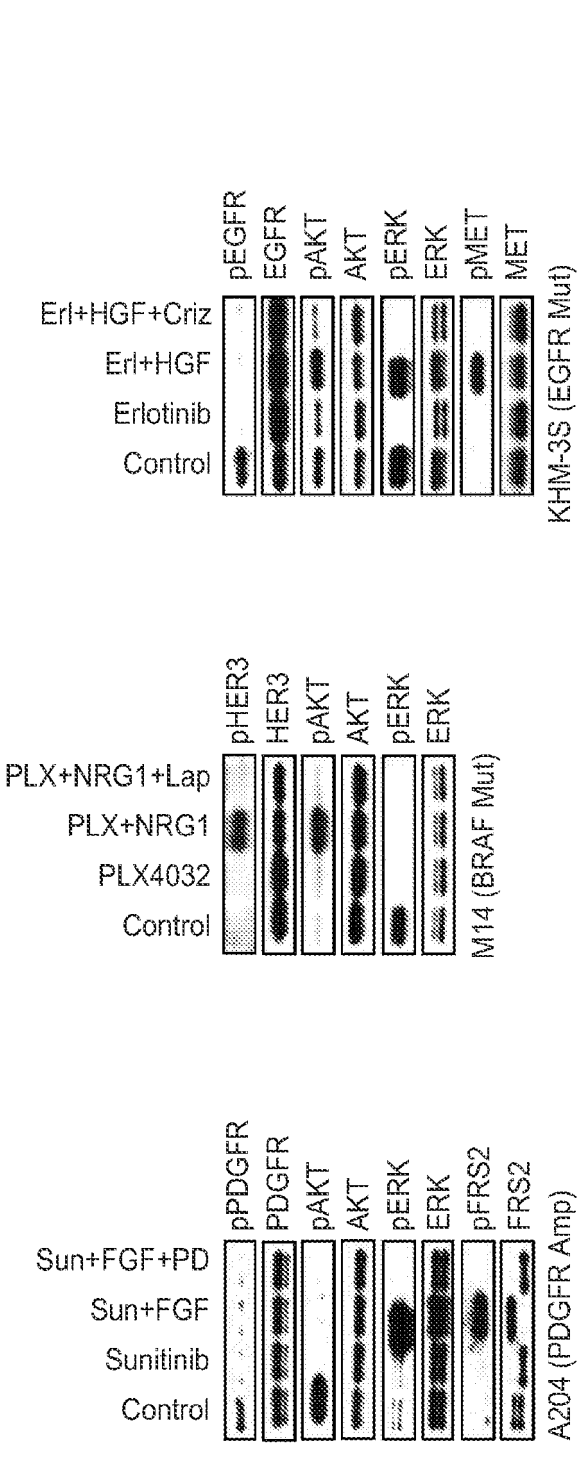

Sun+FGF+PD
Sun+FGF
Sunitinib
Control
pPDGFR
PDGFR
pFRS2
FRS2
A204 (PDGFR Amp)
PLX+NRG1+Lap
PLX+NRG1
PLX4032
pHER3
HER3
M14 (BRAF Mut)
Erl+HGF+Criz
Erl+HGF
Erlotinib
KHM-3S (EGFR Mut)

FIG. 2C

FIG. 2B

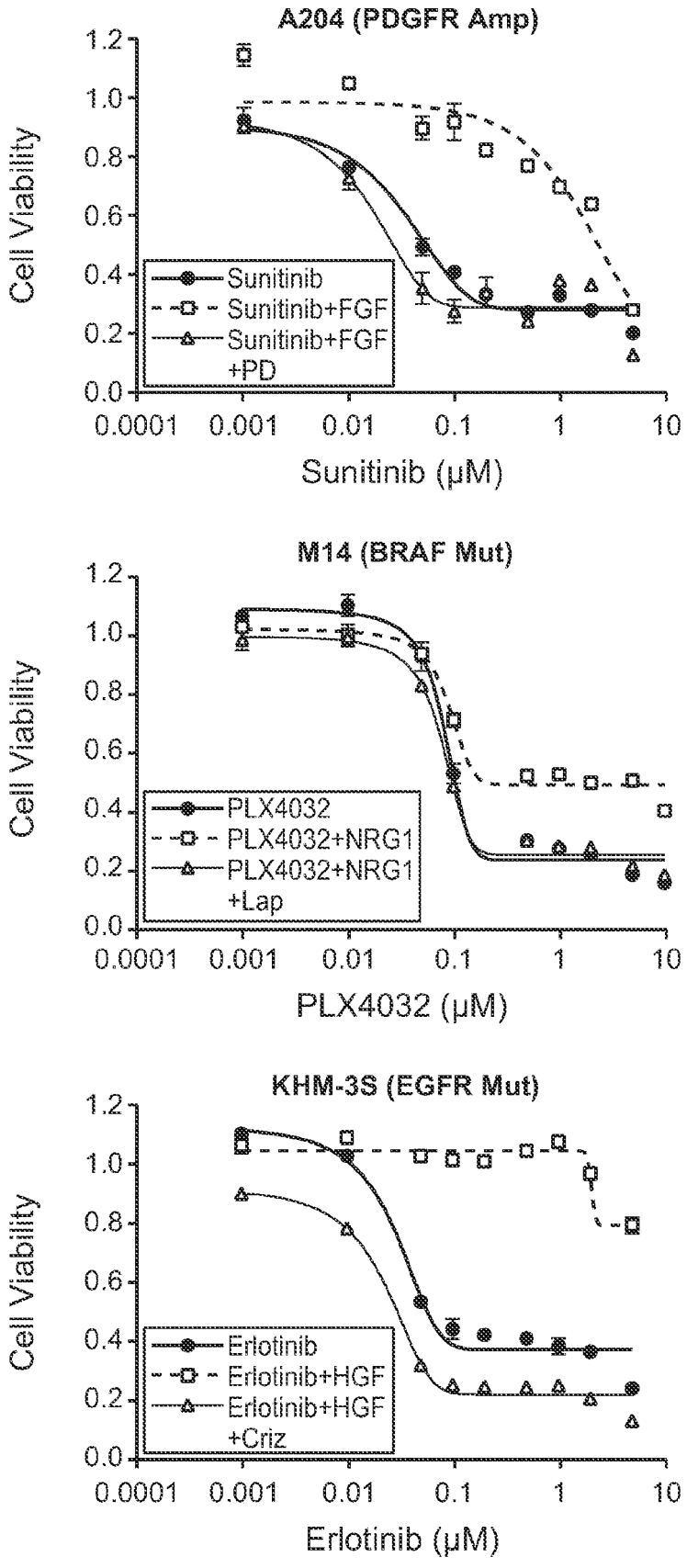

A204 (PDGFR Amp)
Cell Viability
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Sunitinib
Sunitinib+FGF
Sunitinib+FGF +PD
0.0001
0.001
0.01
0.1
1
10
Sunitinib (μM)
M14 (BRAF Mut)
Cell Viability
PLX4032
PLX4032+NRG1
PLX4032+NRG1 +Lap
PLX4032 (μM)
KHM-3S (EGFR Mut)
Cell Viability
Erlotinib
Erlotinib+HGF
Erlotinib+HGF +Criz
Erlotinib (μM)

FIG. 3A

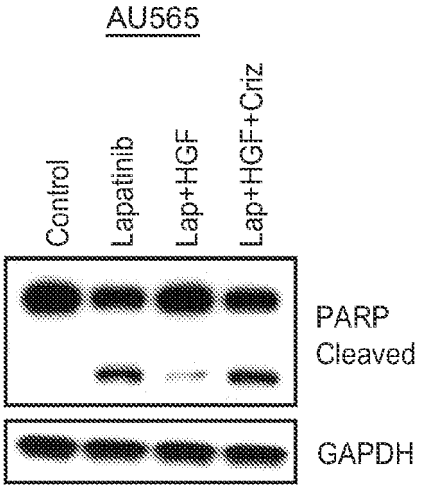


FIG. 3B

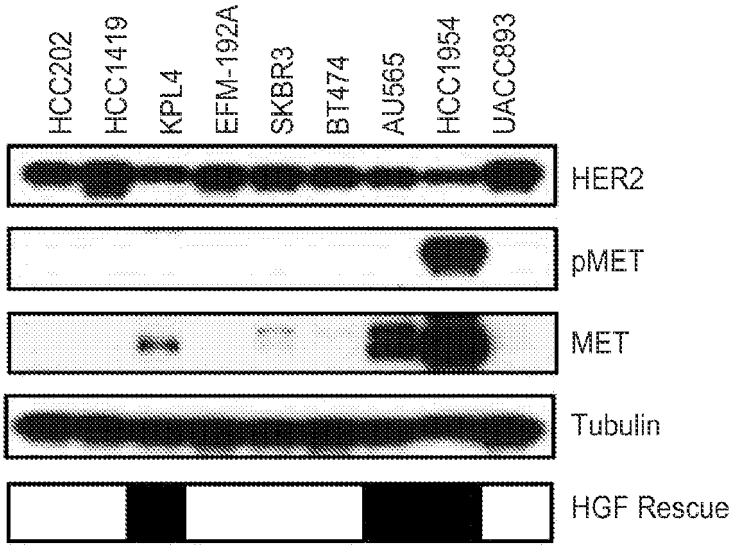


FIG. 3C

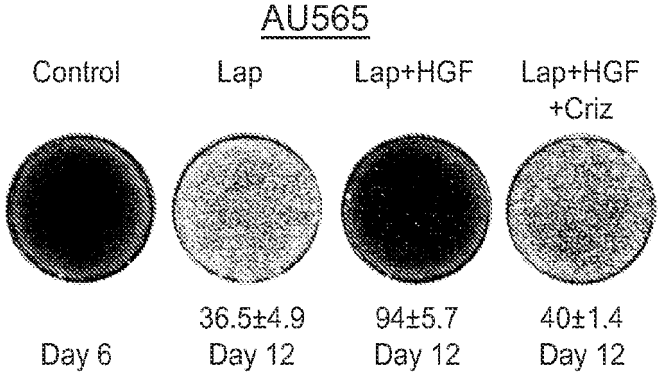


FIG. 3D

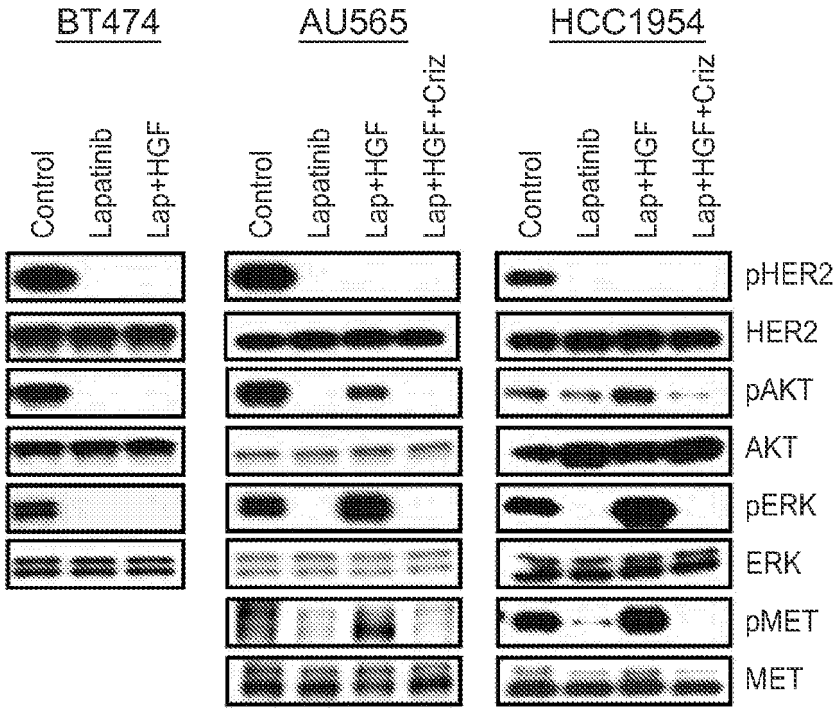


FIG. 3E

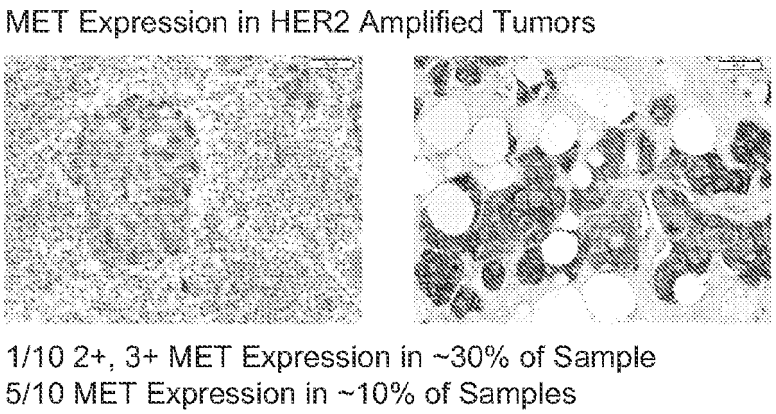


FIG. 3F

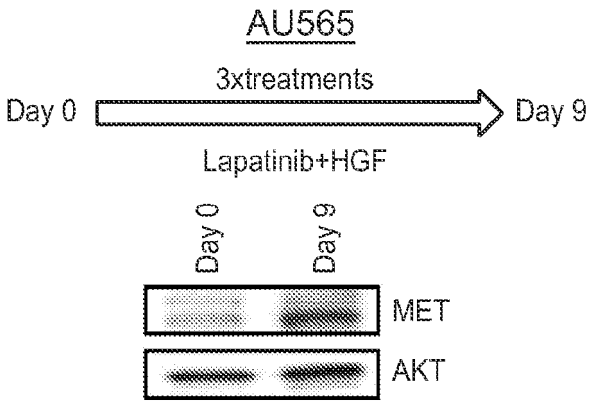
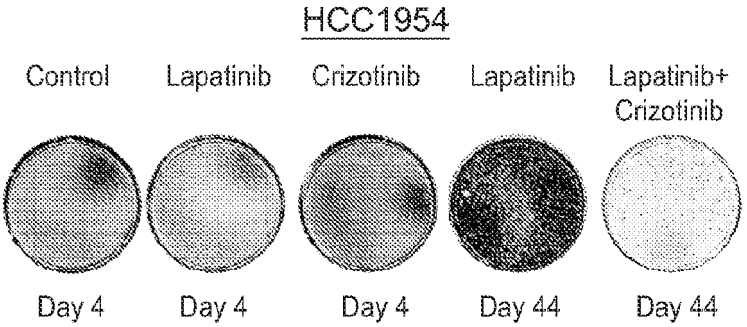
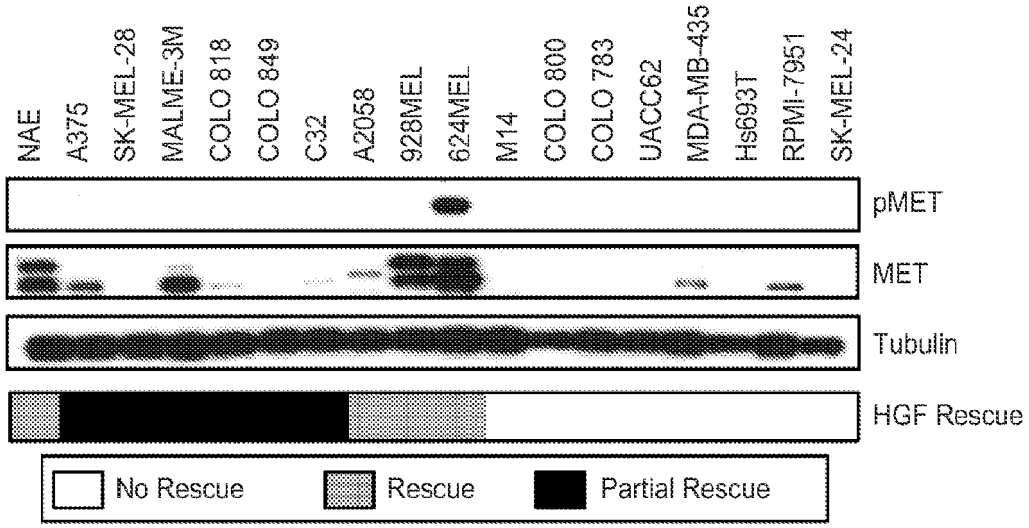


FIG. 3G


HCC1954
Control
Lapatinib
Crizotinib
Lapatinib
Lapatinib+ Crizotinib
Day 4
Day 4
Day 4
Day 44
Day 44


NAE
A375
SK-MEL-28
MALME-3M
COLO 818
COLO 849
C32
A2058
928MEL
624MEL
M14
COLO 800
COLO 783
UACC62
MDA-MB-435
Hs693T
RPMI-7951
SK-MEL-24
pMET
MET
Tubulin
HGF Rescue
No Rescue
Rescue
Partial Rescue

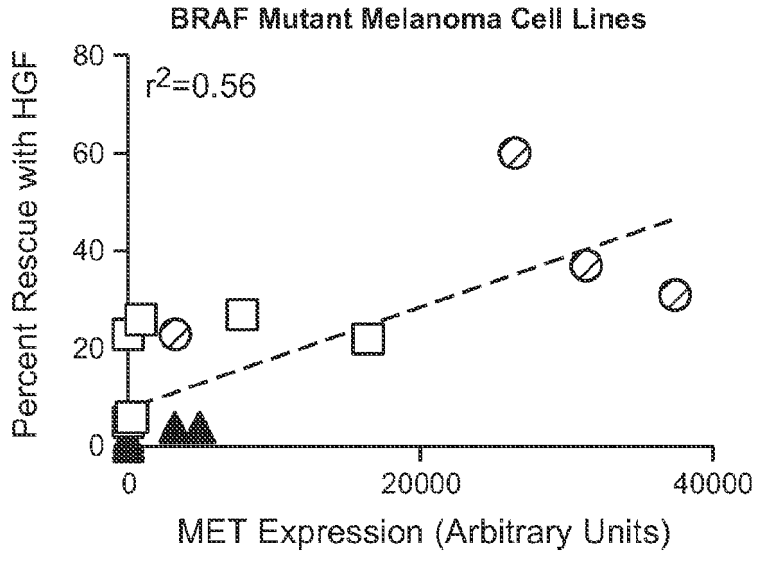

BRAF Mutant Melanoma Cell Lines
Percent Rescue with HGF
r2=0.56
80
60
40
20
0
0
20000
40000
MET Expression (Arbitrary Units)

FIG. 4A

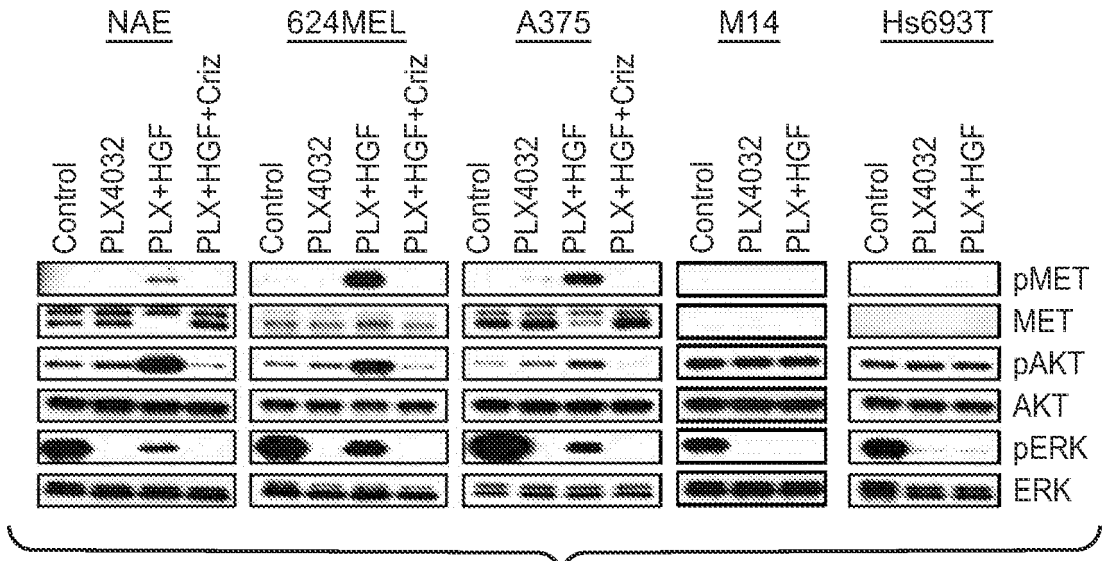
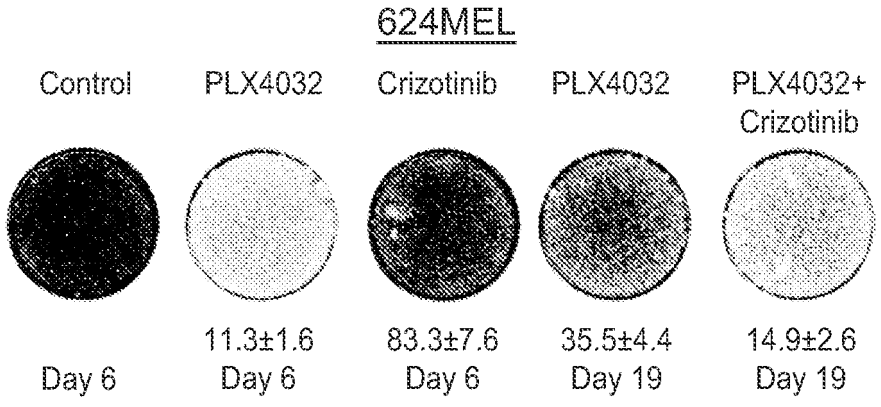

NAE
624MEL
A375
M14
Hs693T
Control
PLX4032
PLX+HGF
PLX+HGF+Criz
pMET
MET
pAKT
AKT
pERK
ERK

FIG. 4B

FIG. 4C


624MEL
Control
PLX4032
Crizotinib
PLX4032
PLX4032+
Crizotinib
11.3±1.6
Day 6
83.3±7.6
Day 6
35.5±4.4
Day 19
14.9±2.6
Day 19

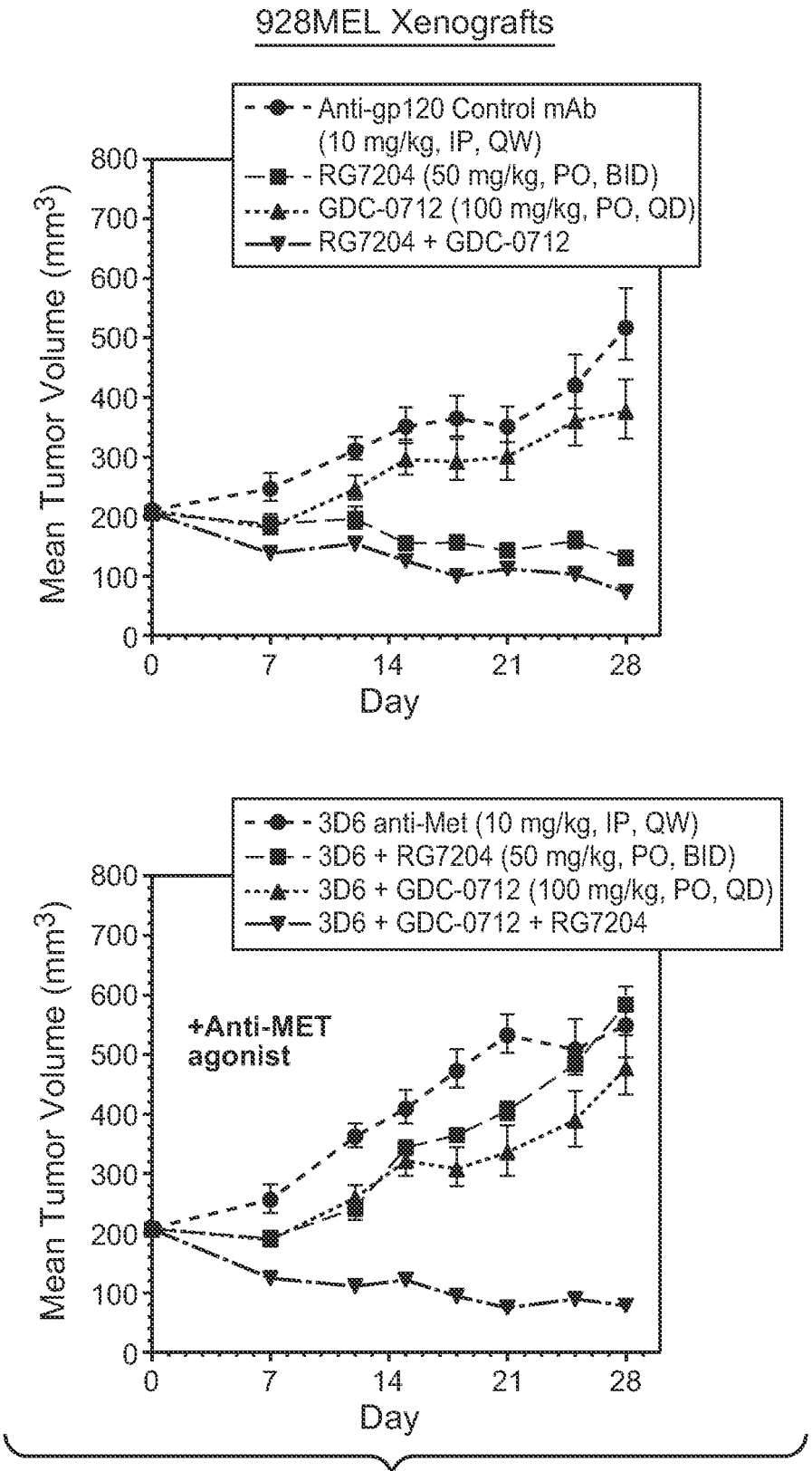

928MEL Xenografts
Anti-gp120 Control mAb (10 mg/kg, IP, QW)
RG7204 (50 mg/kg, PO, BID)
GDC-0712 (100 mg/kg, PO, QD)
RG7204 + GDC-0712
Mean Tumor Volume (mm3)
Day
3D6 anti-Met (10 mg/kg, IP, QW)
3D6 + RG7204 (50 mg/kg, PO, BID)
3D6 + GDC-0712 (100 mg/kg, PO, QD)
3D6 + GDC-0712 + RG7204
+Anti-MET agonist
Mean Tumor Volume (mm3)
Day

FIG. 4D



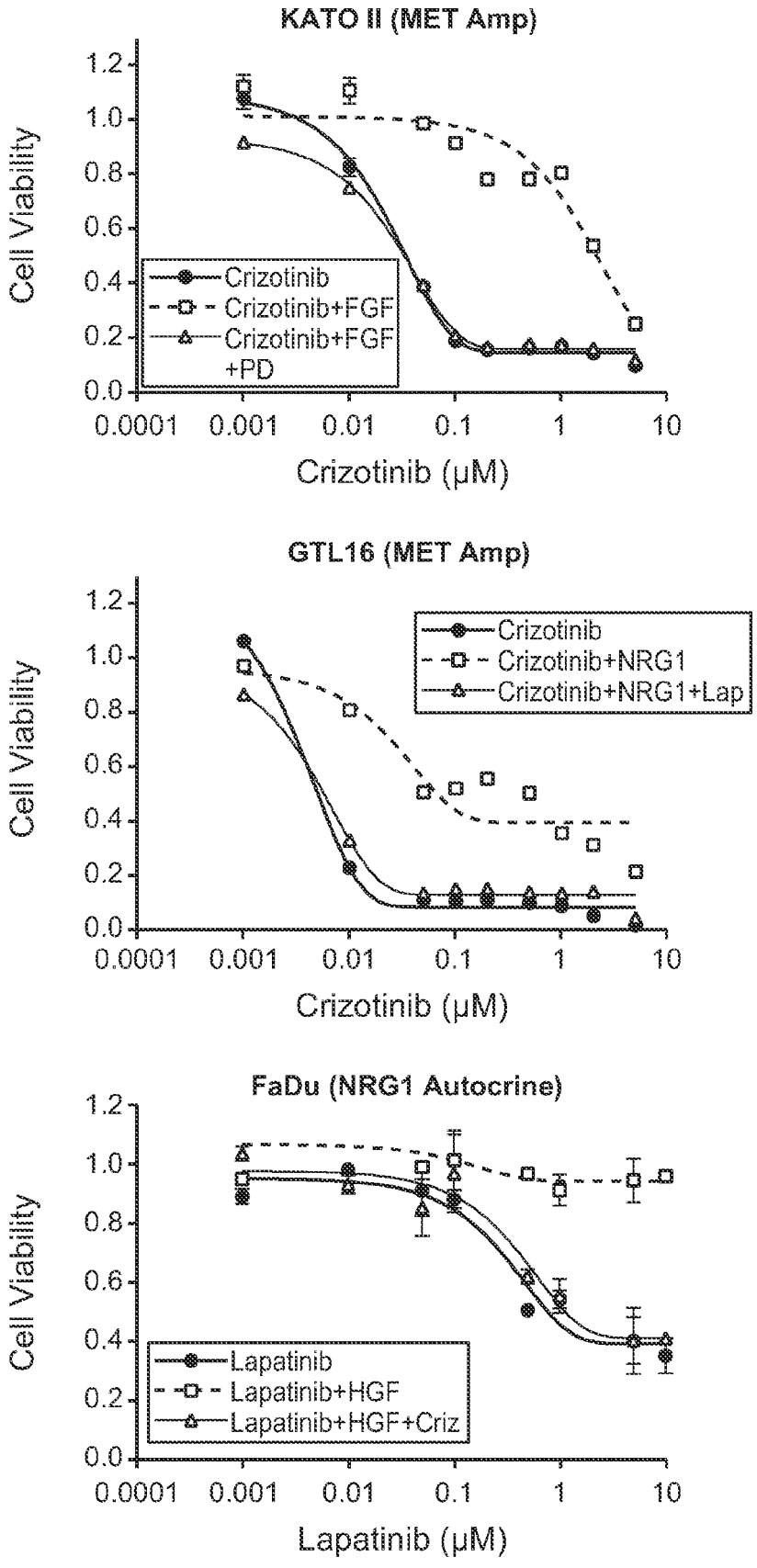
FIG. 5A

Cisplatin

Kinase Addiction	Cell Line	HGF	FGF	IGF	PDGF	NRG1	EGF
HER2 Amplified	AU565	NR	NR	NR	NR	NR	NR
MET Amplified	GTL16	NR	NR	NR	NR	NR	NR
ALK Mutation	SHSY5Y	NR	NR	NR	NR	NR	NR
NRG1 Driven	CHL-1	NR	NR	NR	NR	NR	NR
EGF-like Ligand Driven	H1648	NR	NR	NR	NR	NR	NR
BRAF Mutation	SK MEL 28	NR	NR	NR	NR	NR	NR

FIG. 5B

FIG. 5C


KATO II (MET Amp)
Cell Viability
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0001
0.001
0.01
0.1
1
10
Crizotinib (μM)
Crizotinib
Crizotinib+FGF
Crizotinib+FGF +PD
GTL16 (MET Amp)
Cell Viability
Crizotinib (μM)
Crizotinib
Crizotinib+NRG1
Crizotinib+NRG1+Lap
FaDu (NRG1 Autocrine)
Cell Viability
Lapatinib (μM)
Lapatinib
Lapatinib+HGF
Lapatinib+HGF+Criz

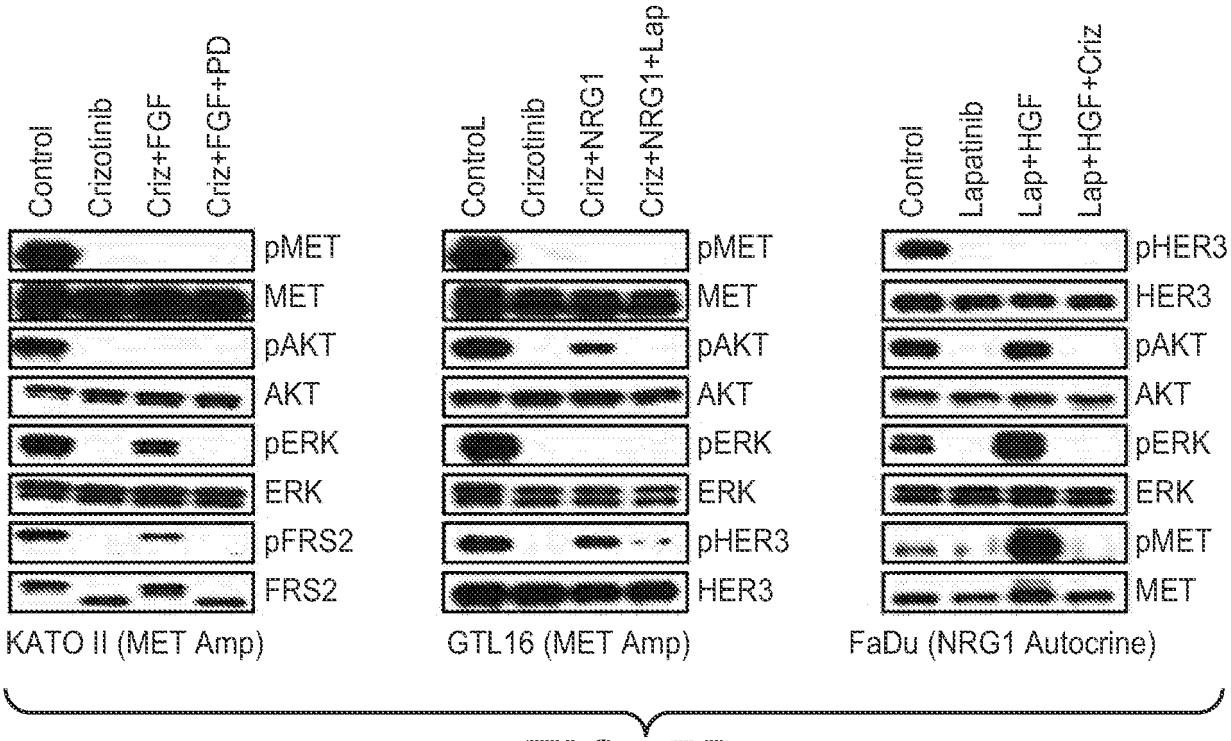

Control
Crizotinib
Criz+FGF
Criz+FGF+PD
pMET
MET
pAKT
AKT
pERK
ERK
pFRS2
FRS2
KATO II (MET Amp)
ControL
Crizotinib
Criz+NRG1
Criz+NRG1+Lap
pMET
MET
pAKT
AKT
pERK
ERK
pHER3
HER3
GTL16 (MET Amp)
Control
Lapatinib
Lap+HGF
Lap+HGF+Criz
pHER3
HER3
pAKT
AKT
pERK
ERK
pMET
MET
FaDu (NRG1 Autocrine)

FIG. 5D

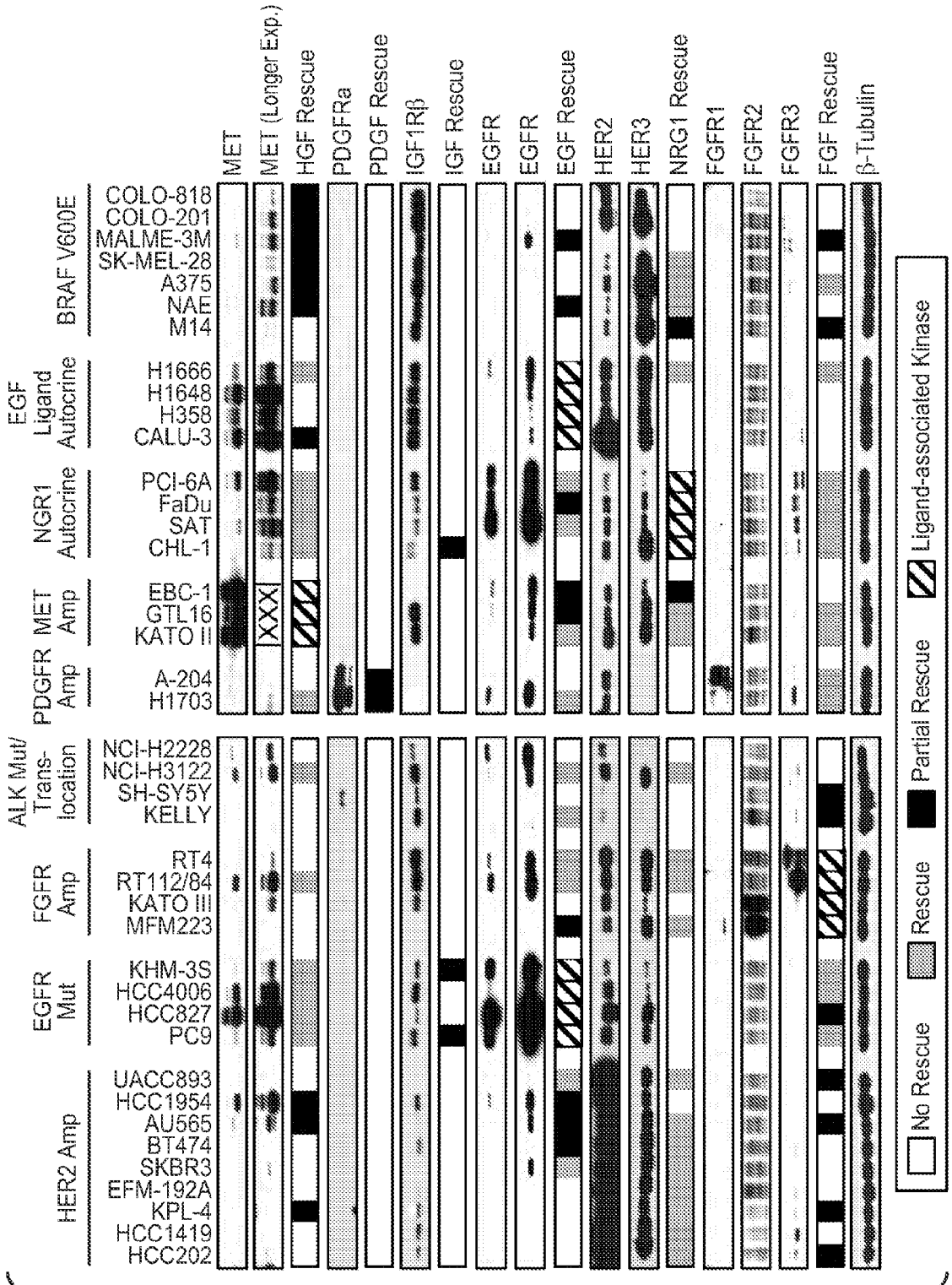

HER2 Amp
EGFR Mut
FGFR Amp
ALK Mut/ Trans-location
PDGFR Amp
MET Amp
NGR1 Autocrine
EGF Ligand Autocrine
BRAF V600E
UACC893
HCC1954
AU565
BT474
SKBR3
EFM-192A
KPL-4
HCC1419
HCC202
KHM-3S
HCC4006
HCC827
PC9
RT4
RT112/84
KATO III
MFM223
NCI-H2228
NCI-H3122
SH-SY5Y
KELLY
A-204
H1703
EBC-1
GTL16
KATO II
PCI-6A
FaDu
SAT
CHL-1
H1666
H1648
H358
CALU-3
COLO-818
COLO-201
MALME-3M
SK-MEL-28
A375
NAE
M14
MET
MET (Longer Exp.)
HGF Rescue
PDGFRa
PDGF Rescue
IGF1Rβ
IGF Rescue
EGFR
EGFR
EGF Rescue
HER2
HER3
NRG1 Rescue
FGFR1
FGFR2
FGFR3
FGF Rescue
β-Tubulin
XXX
No Rescue
Rescue
Partial Rescue
Ligand-associated Kinase

FIG. 6A

RTK/Ligand	p-value
MET\HGF	p<0.001
PDGFR\PDGF	p=1
IGF-1R\IGF	p=1
EGFR\EGF	p<0.001
HER3\NRG1	p=0.005
FGFR\FGF	p=1

FIG. 6B

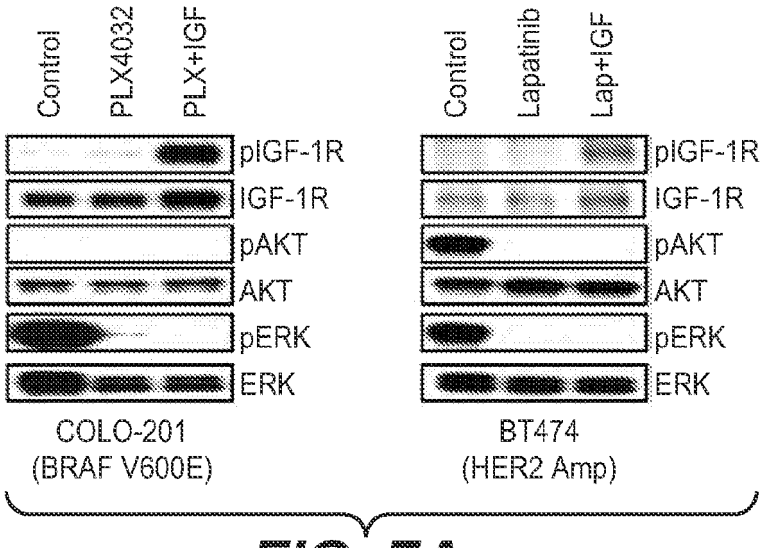


FIG. 7A

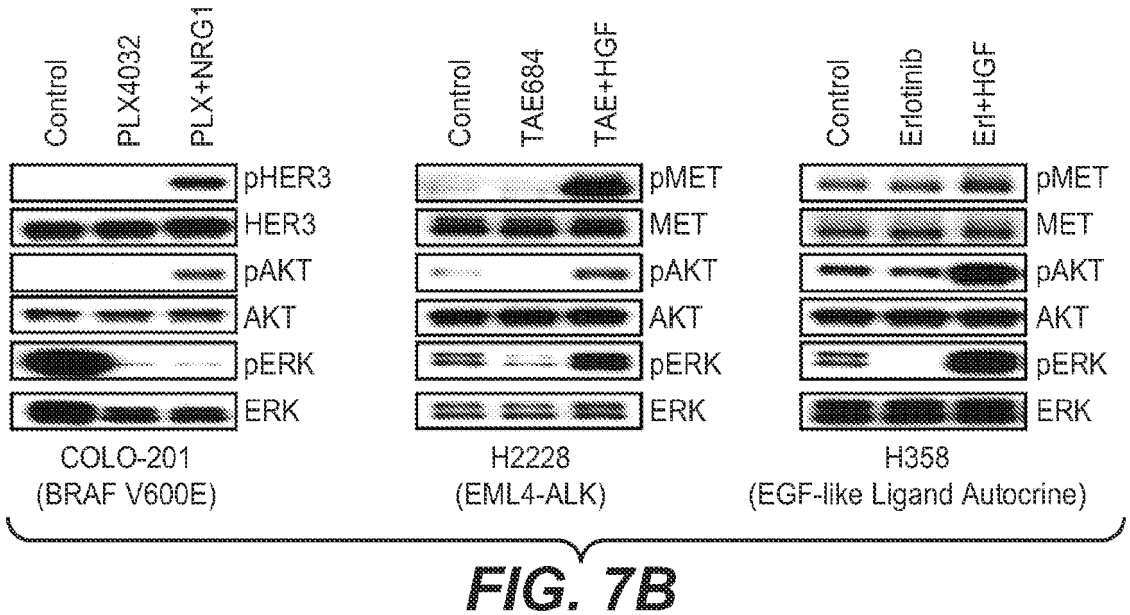


FIG. 7B

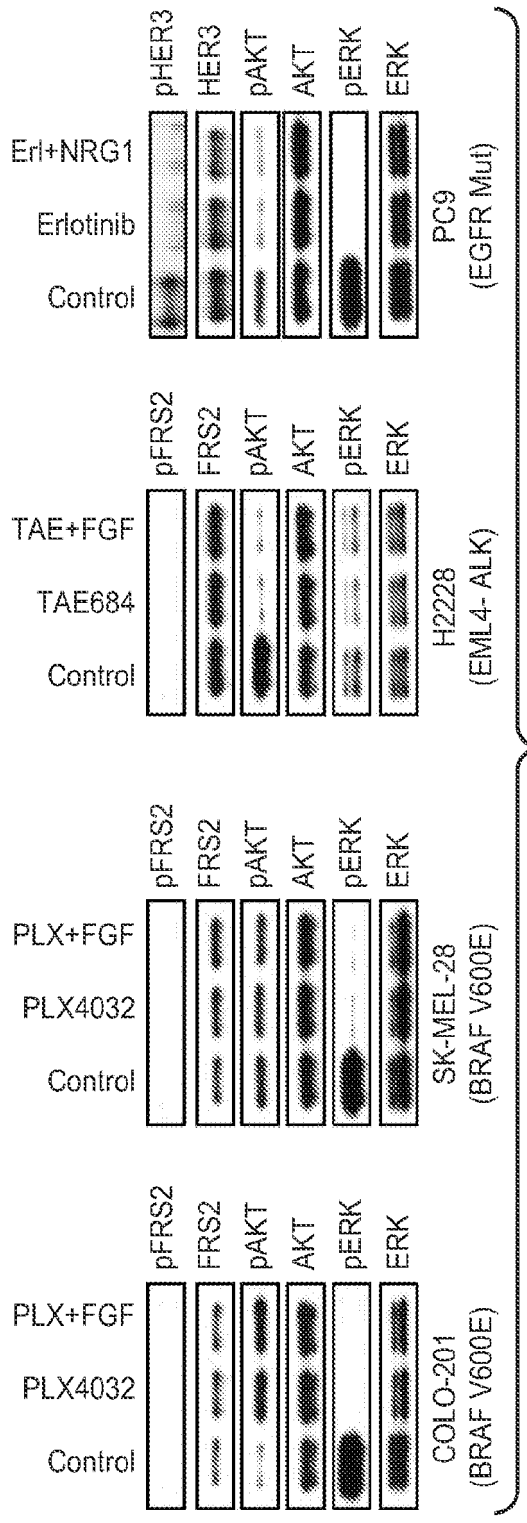

Control
Erlotinib
Erl+NRG1
pHER3
HER3
pAKT
AKT
pERK
ERK
PC9
(EGFR Mut)
Control
TAE684
TAE+FGF
pFRS2
FRS2
pAKT
AKT
pERK
ERK
H2228
(EML4- ALK)
Control
PLX4032
PLX+FGF
pFRS2
FRS2
pAKT
AKT
pERK
ERK
SK-MEL-28
(BRAF V600E)
Control
PLX4032
PLX+FGF
pFRS2
FRS2
pAKT
AKT
pERK
ERK
COLO-201
(BRAF V600E)

FIG. 7C

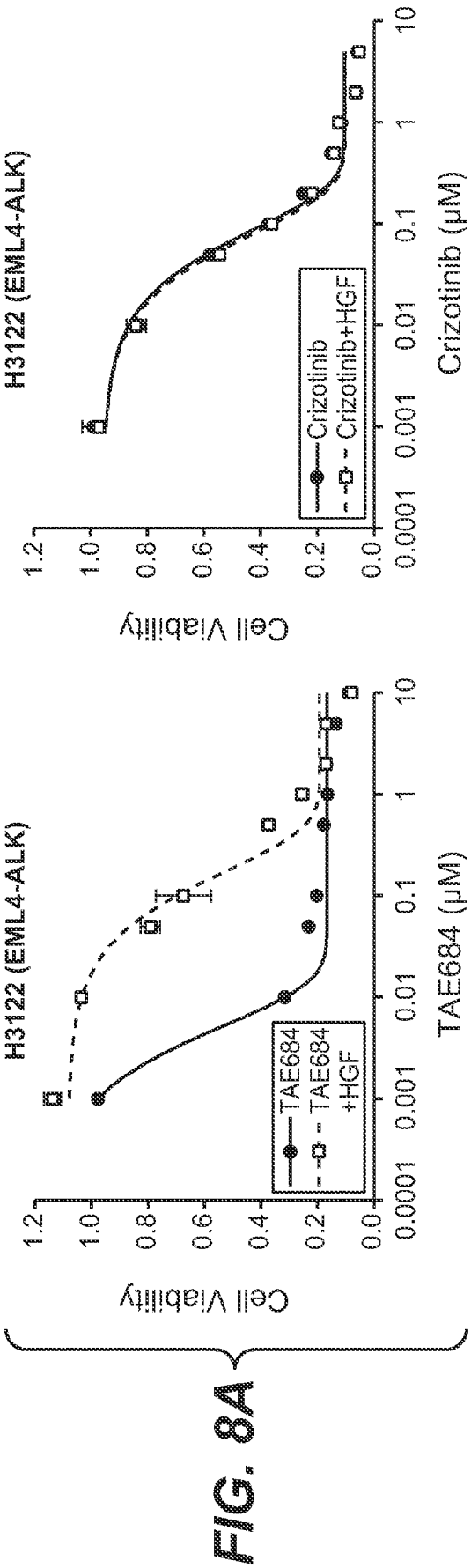

H3122 (EML4-ALK)
Cell Viability
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0001
0.001
0.01
0.1
1
10
TAE684 (μM)
TAE684
TAE684 +HGF
H3122 (EML4-ALK)
Cell Viability
Crizotinib
Crizotinib+HGF
Crizotinib (μM)

FIG. 8A

FIG. 8B

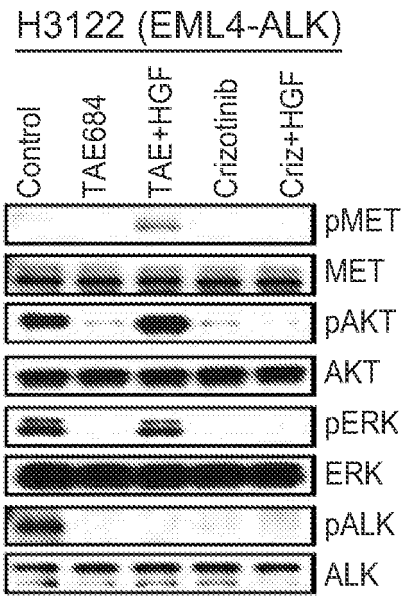


FIG. 8C

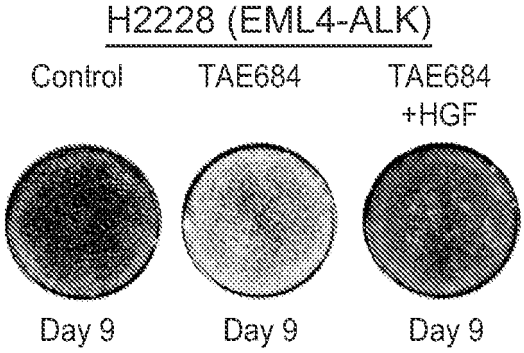


FIG. 8D

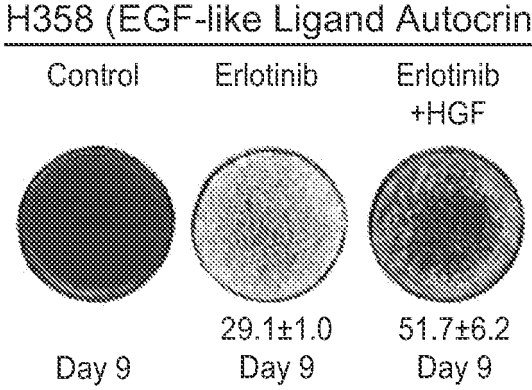


FIG. 9A

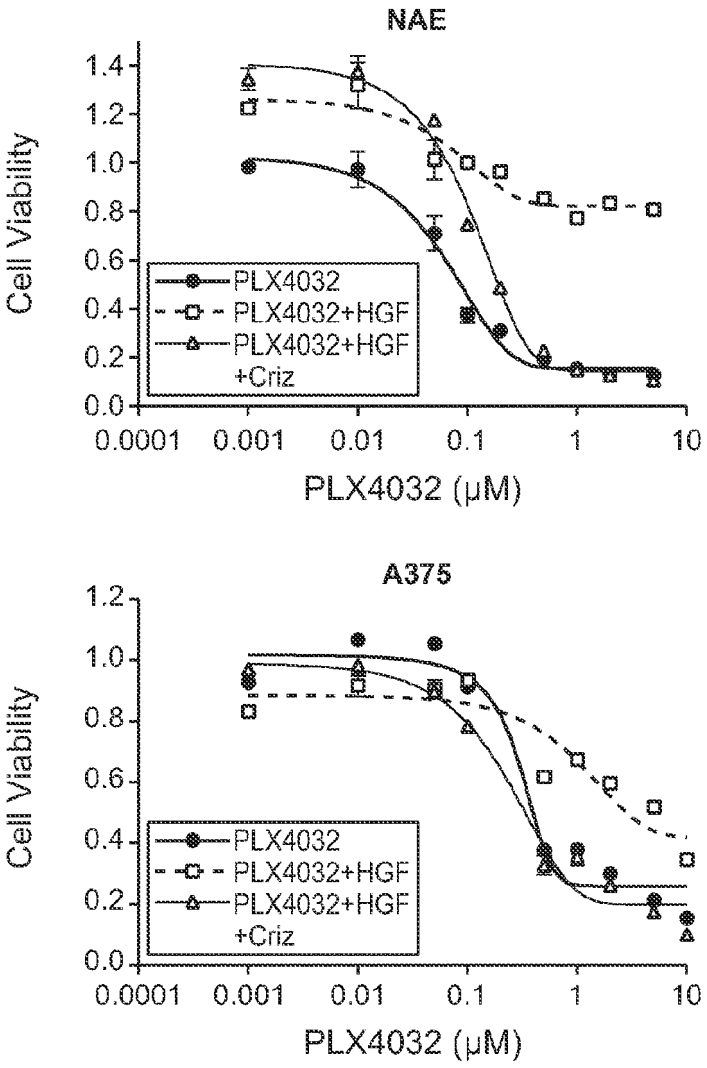
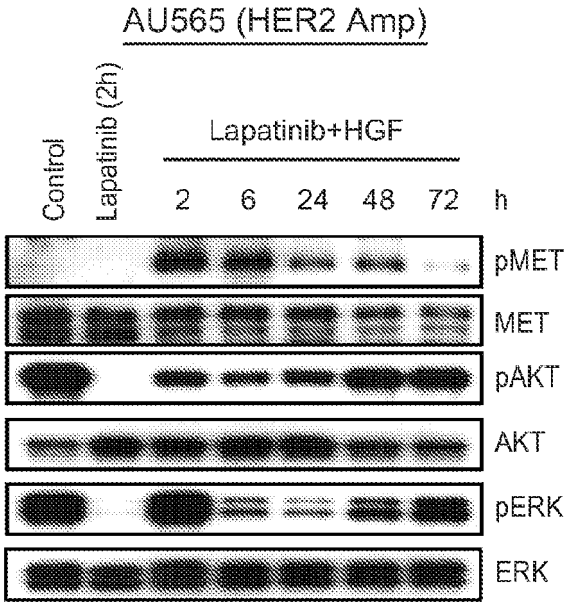

NAE
Cell Viability
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
PLX4032
PLX4032+HGF
PLX4032+HGF
+Criz
0.0001
0.001
0.01
0.1
1
10
PLX4032 (μM)
A375
Cell Viability
1.2
1.0
0.8
0.6
0.4
0.2
0.0
PLX4032
PLX4032+HGF
PLX4032+HGF
+Criz
0.0001
0.001
0.01
0.1
1
10
PLX4032 (μM)

FIG. 9B

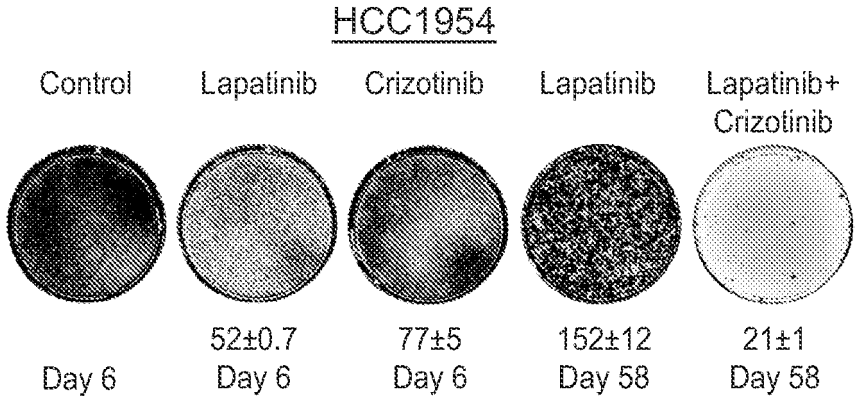

AU565 (HER2 Amp)
Control
Lapatinib (2h)
Lapatinib+HGF
2
6
24
48
72
h
pMET
MET
pAKT
AKT
pERK
ERK

Kinase Addiction (Effective Drug)	Cell Line	HGF	FGF	IGF	PDGF	NRG1	EGF
BRAF V600E (PLX4032)	M14	NR	P	NR	NR	P	NR
	NAE	R	NR	NR	NR	R	P
	A-375	P	R	NR	NR	P	NR
	SK-MEL-28	P	NR	NR	NR	R	NR
	Malme-3M	P	R	NR	NR	NR	P
	COLO-201	P	NR	NR	NR	NR	NR
	COLO-818	P	NR	NR	NR	NR	NR

NR: No Rescue; P: Partial Rescue; R: Rescue

FIG. 10

FIG. 11



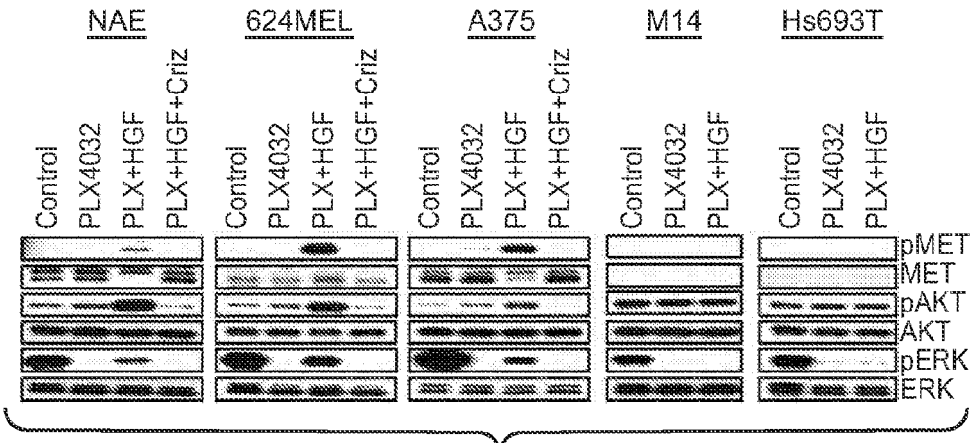


FIG. 12A

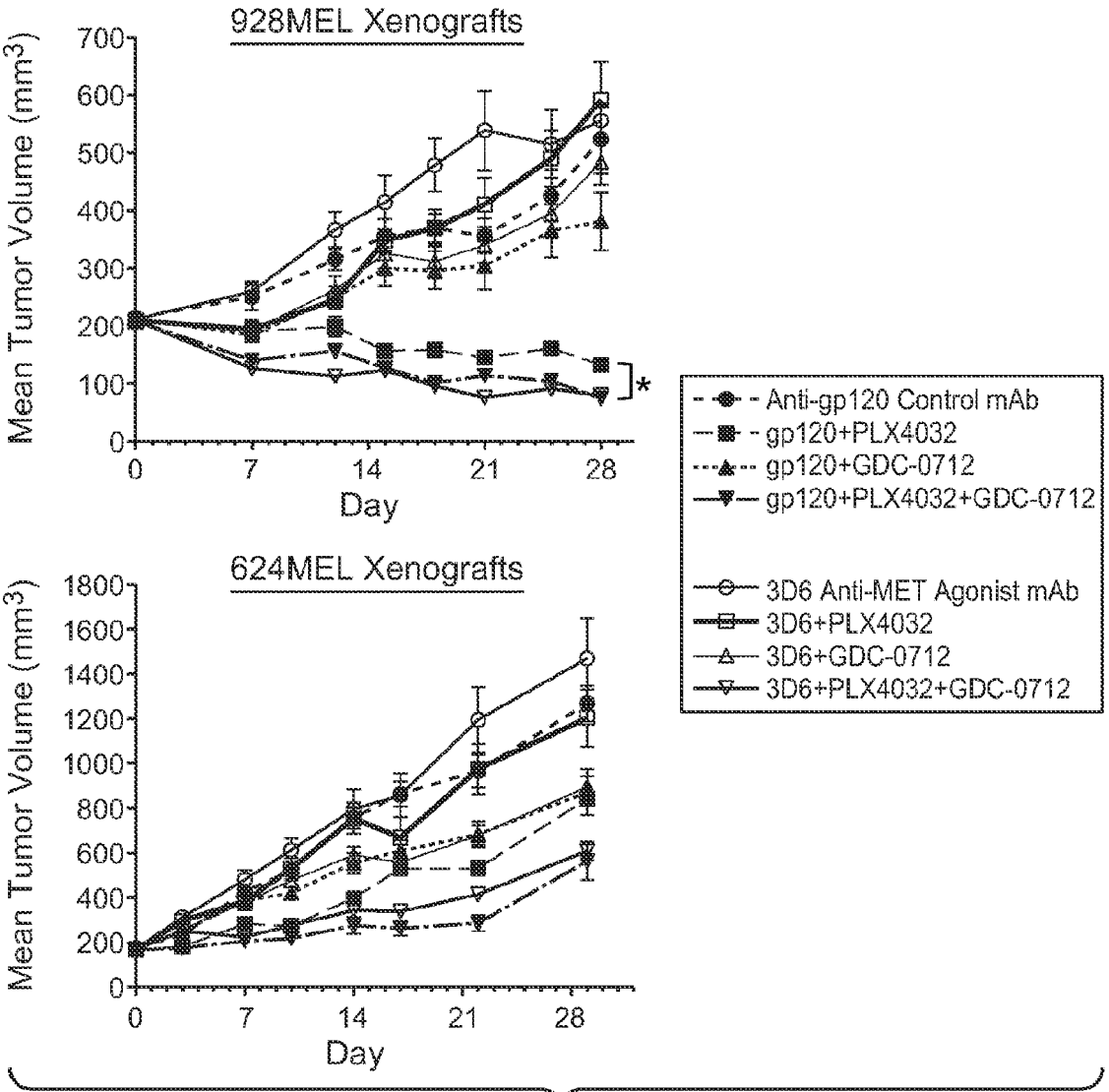


FIG. 12B

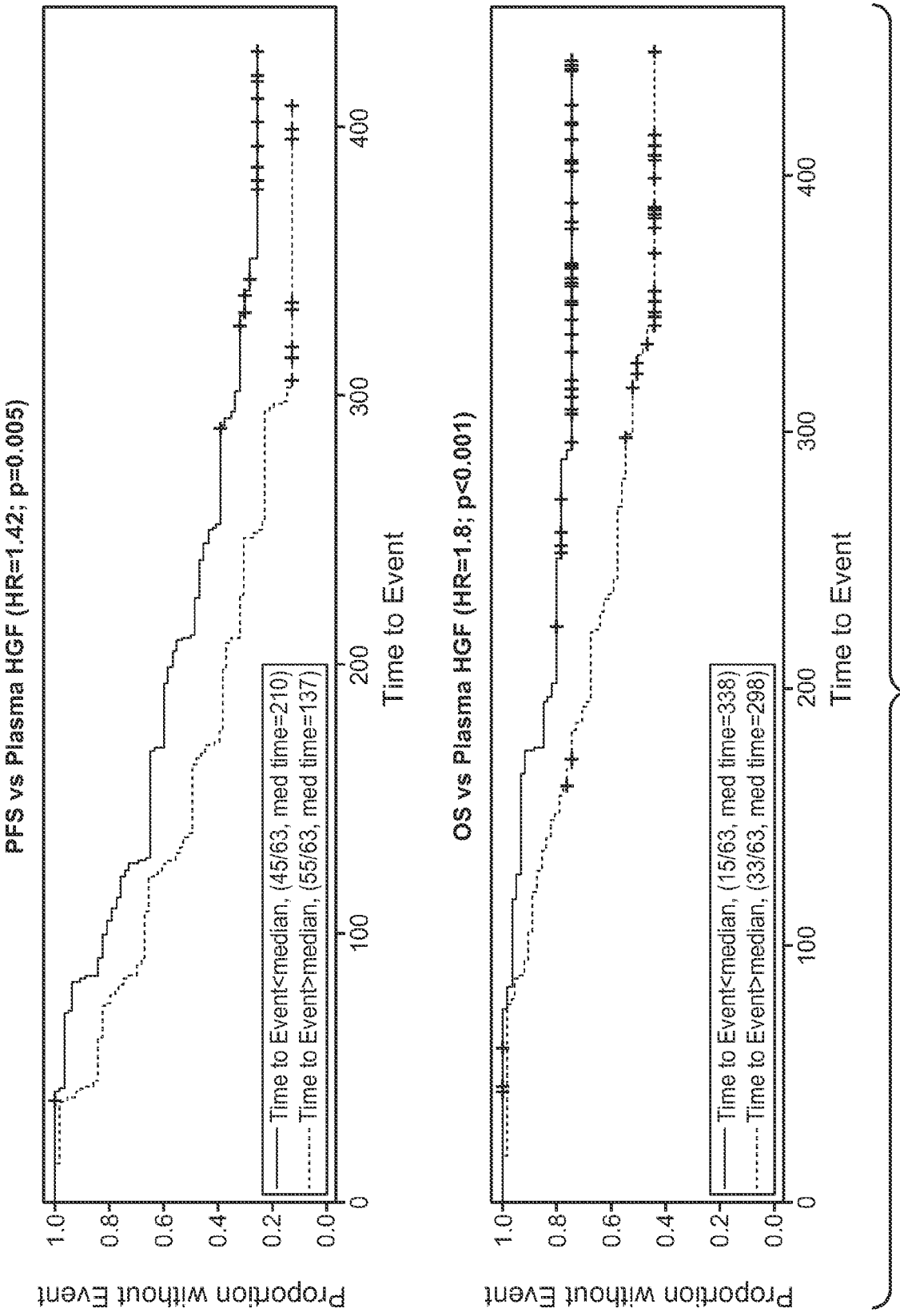

PFS vs Plasma HGF (HR=1.42; p=0.005)
Proportion without Event
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
Time to Event
Time to Event<median, (45/63, med time=210)
Time to Event>median, (55/63, med time=137)
OS vs Plasma HGF (HR=1.8; p<0.001)
Proportion without Event
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
Time to Event
Time to Event<median, (15/63, med time=338)
Time to Event>median, (33/63, med time=298)

FIG. 13

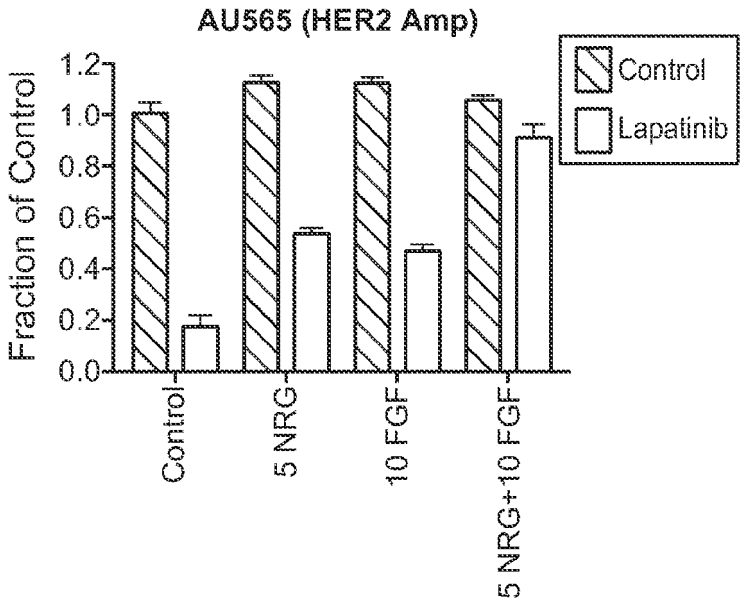


FIG. 14A

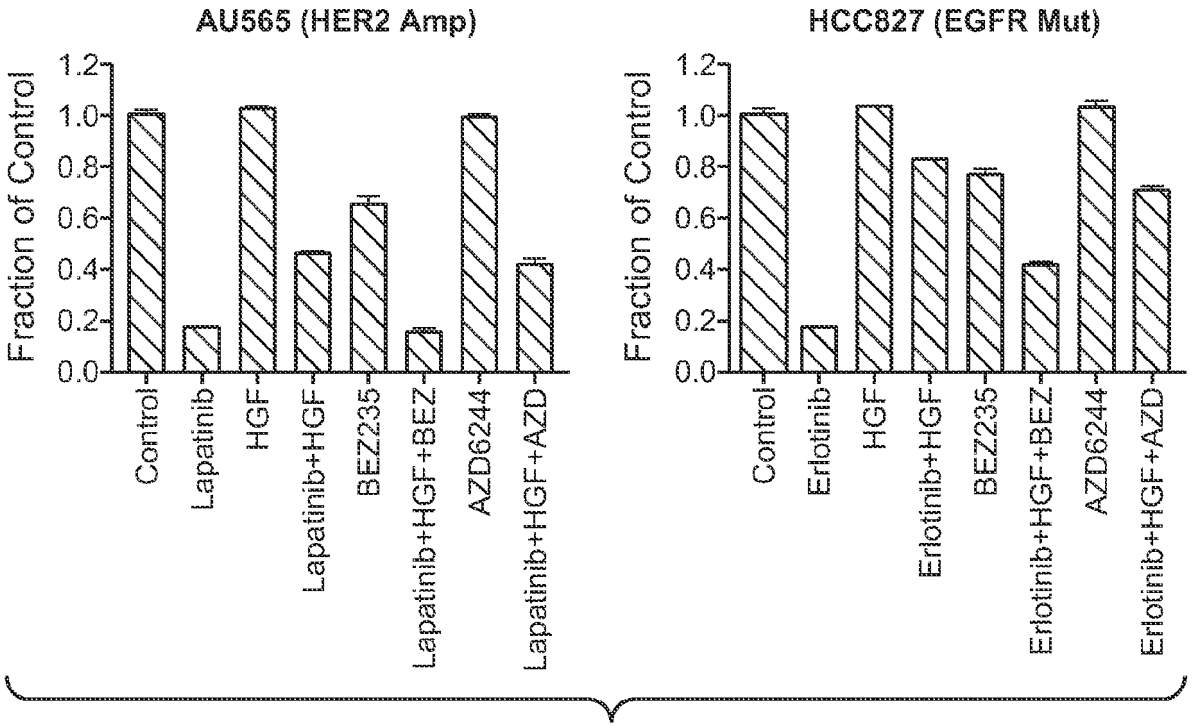


FIG. 14B

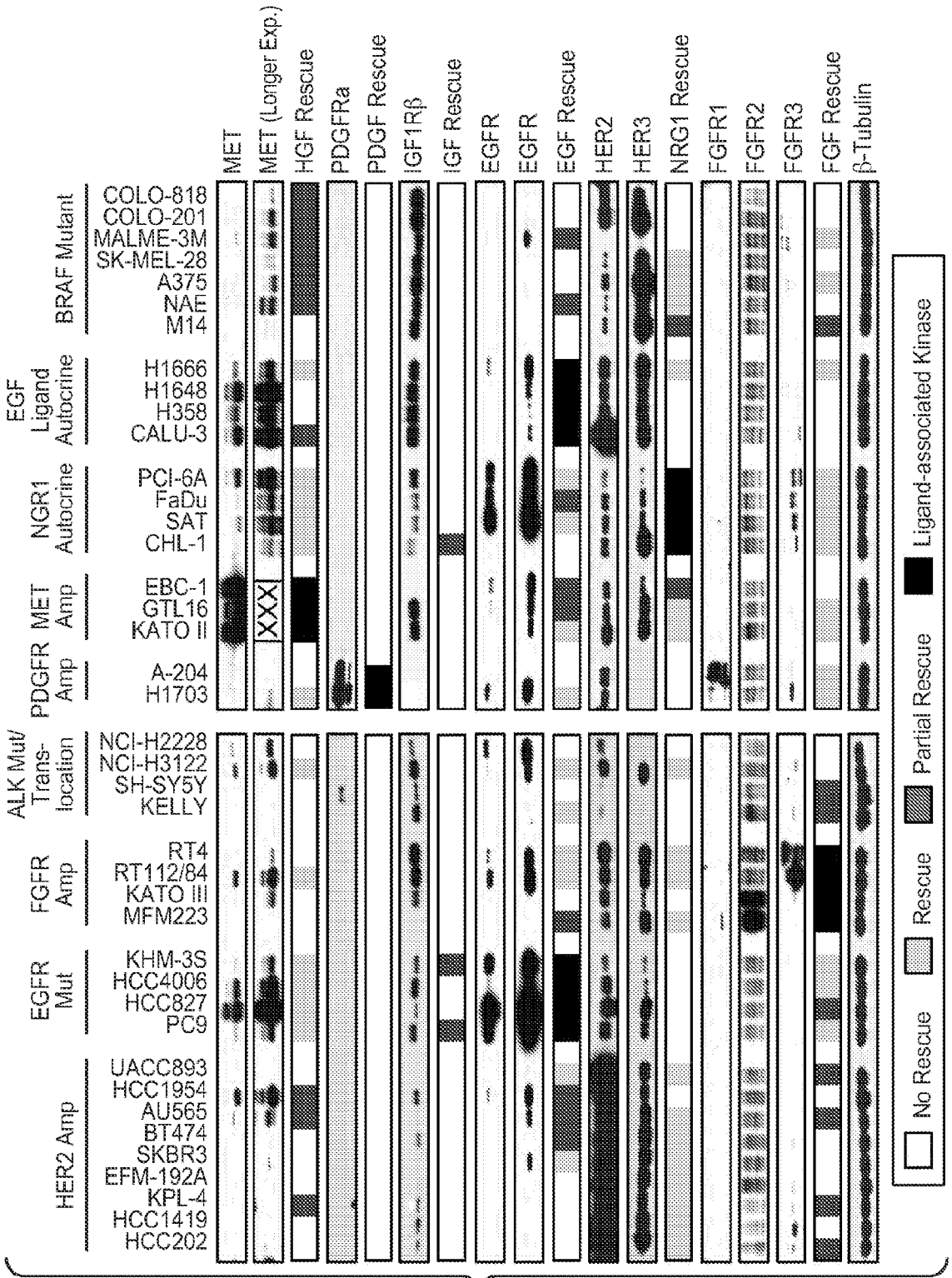

HER2 Amp
UACC893
HCC1954
AU565
BT474
SKBR3
EFM-192A
KPL-4
HCC1419
HCC202
EGFR Mut
KHM-3S
HCC4006
HCC827
PC9
FGFR Amp
RT4
RT112/84
KATO III
MFM223
ALK Mut/ Trans-location
NCI-H2228
NCI-H3122
SH-SY5Y
KELLY
PDGFR Amp
A-204
H1703
MET Amp
EBC-1
GTL16
KATO II
NGR1 Autocrine
PCI-6A
FaDu
SAT
CHL-1
EGF Ligand Autocrine
H1666
H1648
H358
CALU-3
BRAF Mutant
COLO-818
COLO-201
MALME-3M
SK-MEL-28
A375
NAE
M14
MET
MET (Longer Exp.)
HGF Rescue
PDGFRa
PDGF Rescue
IGF1Rβ
IGF Rescue
EGFR
EGFR
EGF Rescue
HER2
HER3
NRG1 Rescue
FGFR1
FGFR2
FGFR3
FGF Rescue
β-Tubulin
XXX
No Rescue
Rescue
Partial Rescue
Ligand-associated Kinase

FIG. 15

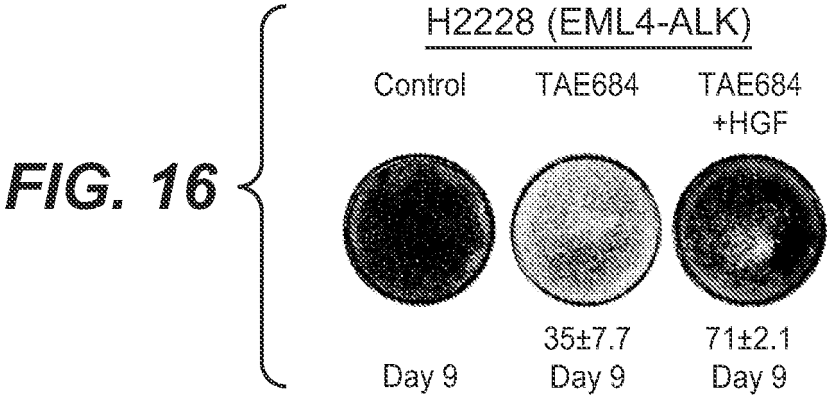


FIG. 16

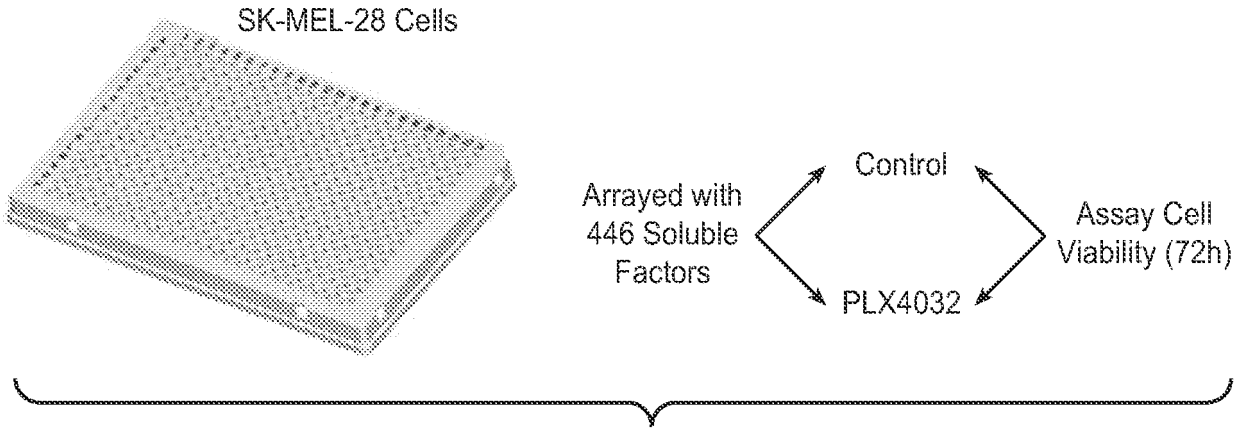
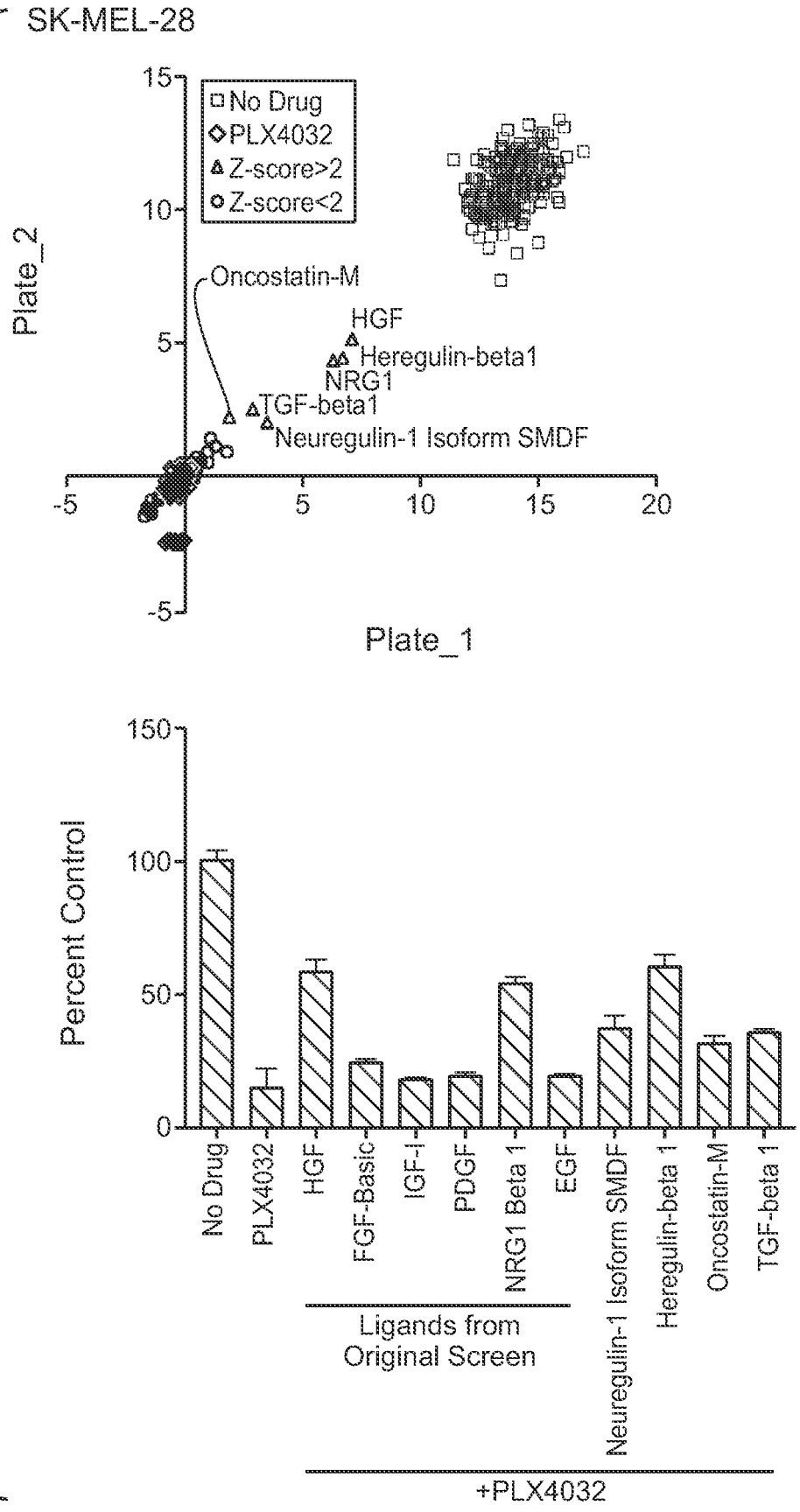


FIG. 17A

FIG. 17B


SK-MEL-28
No Drug
PLX4032
Z-score>2
Z-score<2
Oncostatin-M
HGF
Heregulin-beta1
NRG1
TGF-beta1
Neuregulin-1 Isoform SMDF
Plate_2
Plate_1
Percent Control
No Drug
PLX4032
HGF
FGF-Basic
IGF-I
PDGF
NRG1 Beta 1
EGF
Neuregulin-1 Isoform SMDF
Heregulin-beta 1
Oncostatin-M
TGF-beta 1
Ligands from Original Screen
+PLX4032

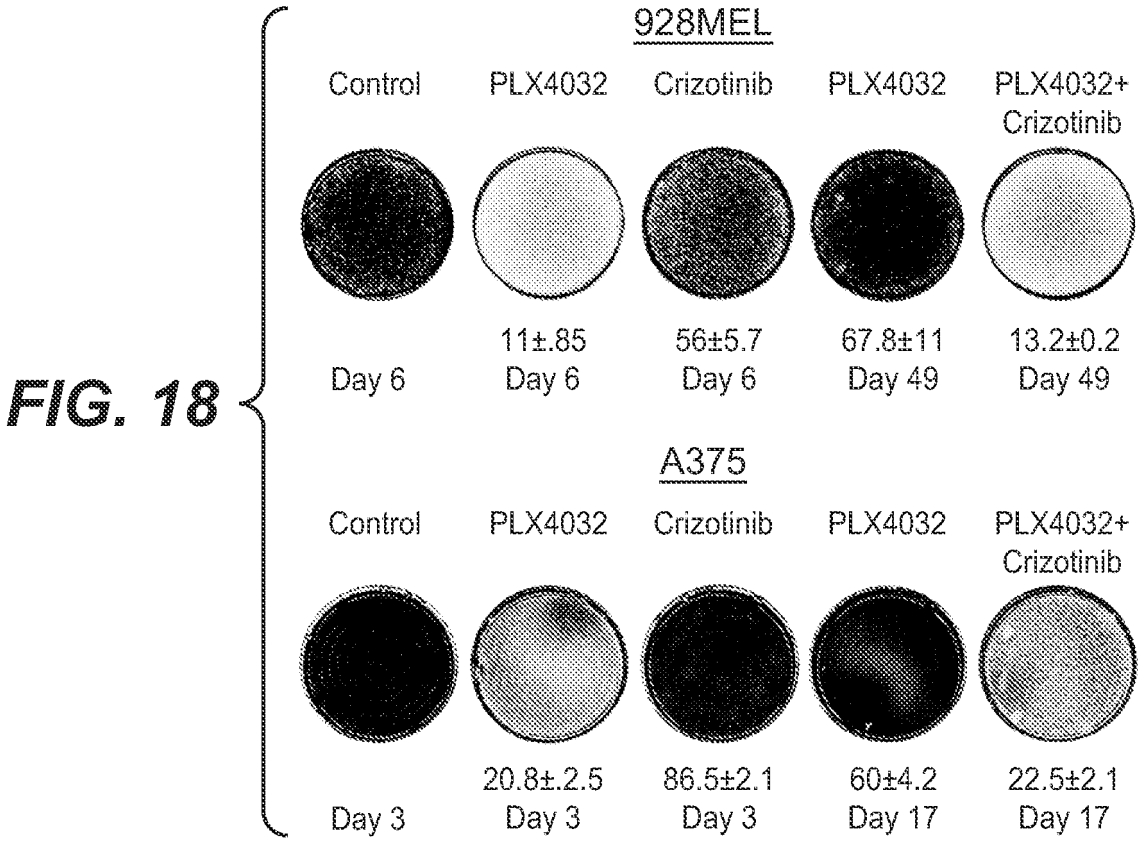

928MEL
Control
PLX4032
Crizotinib
PLX4032
PLX4032+ Crizotinib
11±.85 Day 6
56±5.7 Day 6
67.8±11 Day 49
13.2±0.2 Day 49
Day 6
A375
Control
PLX4032
Crizotinib
PLX4032
PLX4032+ Crizotinib
20.8±.2.5 Day 3
86.5±2.1 Day 3
60±4.2 Day 17
22.5±2.1 Day 17
Day 3

FIG. 18

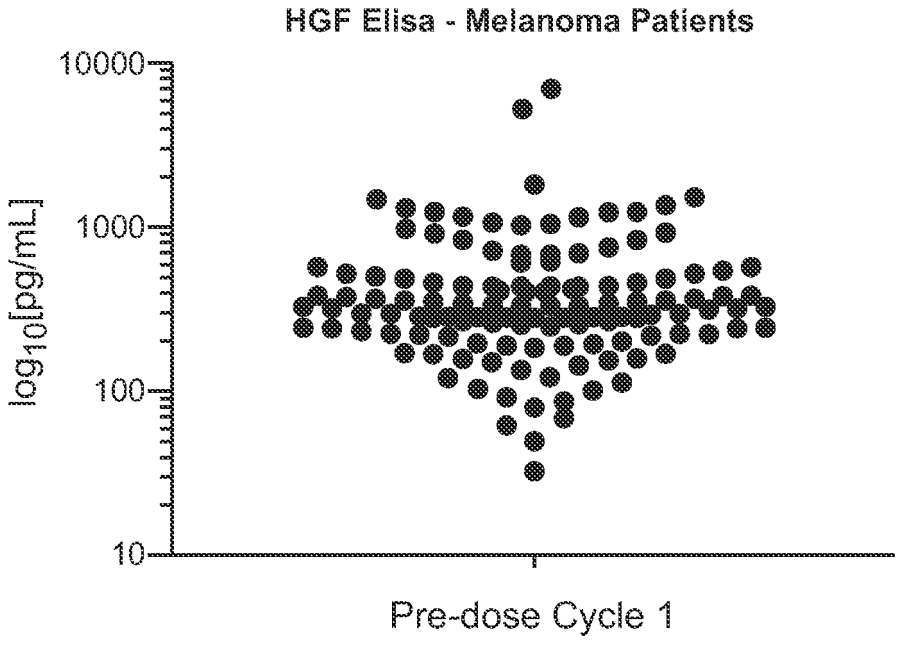

HGF Elisa - Melanoma Patients
10000
1000
100
10
log10[pg/mL]
Pre-dose Cycle 1

FIG. 20

928MEL

Study Data with Control Antibody

Group #	Antibody Treatment	SMI Treatment	Dose (mg/kg)	Regimen	%TGI Days	%TGI (AUC/ Day)	Lower CI	Upper CI	PR	CR	Max %BW
1	Anti-gp120 Isotype Control Ab (10 mg/kg, IP, QW)	-	10	QW	28	0	0	0	0	0	-13.2
2	Anti-gp120 Isotype Control Ab (10 mg/kg, IP, QW)	PLX4032 (50 mg/kg, PO, BID)	10 + 50	QW, BID	28	131	103	172	1	0	-5.48
3	Anti-gp120 Isotype Control Ab (10 mg/kg, IP, QW)	GDC-0712 (100 mg/kg, PO, QD)	10 + 100	QW, QD	28	53	-3	92	0	0	-8.36
4	Anti-gp120 Isotype Control Ab (10 mg/kg, IP, QW)	PLX4032 (50 mg/kg, PO, BID) + GDC-0712 (100 mg/kg, PO, QD)	10 + 50 + 100	QW, BID, QD	28	164	132	216	8	0	-5.36

Study Data with Anti-MET Agonist Antibody

Group #	Antibody Treatment	SMI Treatment	Dose (mg/kg)	Regimen	%TGI Days	%TGI (AUC/ Day)	Lower CI	Upper CI	PR	CR	Max %BW
5	3D6.16.6 (MET:1580) (10 mg/kg, IP, QW)	-	10 + 50	QD	28	0	0	0	0	0	-16
6	3D6.16.6 (MET:1580) (10 mg/kg, IP, QW)	PLX4032 (50 mg/kg, PO, BID)	10 + 100	QD	28	39	-14	70	0	0	-14.9
7	3D6.16.6 (MET:1580) (10 mg/kg, IP, QW)	GDC-0712 (100 mg/kg, PO, QD)	10 + 50 + 100	BID, QD	28	56	13	82	0	0	-12.5
8	3D6.16.6 (MET:1580) (10 mg/kg, IP, QW)	PLX4032 (50 mg/kg, PO, BID) + GDC-0712 (100 mg/kg, PO, QD)	10 + 50	BID, QD	28	147	129	178	10	0	-10.6

FIG. 19A

624MEL

Study Data with Control Antibody

Group #	Antibody Treatment	SMI Treatment	Dose (mg/kg)	Regimen	%TGI Days	%TGI (AUC/ Day)	Lower CI	Upper CI	PR	CR	Max %BW
1	Anti-gp120 Isotype Control Ab (10 mg/kg, IP, QW)	-	10	QW	29	0	0	0	0	0	-12.4
2	Anti-gp120 Isotype Control Ab (10 mg/kg, IP, QW)	PLX4032 (50 mg/kg, PO, BID)	10 + 50	QW, BID	29	51	29	67	0	0	-4.05
3	Anti-gp120 Isotype Control Ab (10 mg/kg, IP, QW)	GDC-0712 (100 mg/kg, PO, QD)	10 + 100	QW, QD	29	37	10	57	0	0	-11.6
4	Anti-gp120 Isotype Control Ab (10 mg/kg, IP, QW)	PLX4032 (50 mg/kg, PO, BID) + GDC-0712 (100 mg/kg, PO, QD)	10 + 50 + 100	QW, BID, QD	29	81	72	89	0	0	-3.34

Study Data with Anti-MET Agonist Antibody

Group #	Antibody Treatment	SMI Treatment	Dose (mg/kg)	Regimen	%TGI Days	%TGI (AUC/ Day)	Lower CI	Upper CI	PR	CR	Max %BW
5	3D6.16.6 (MET:1580) (10 mg/kg, IP, QW)	-	10 + 50	QD	29	0	0	0	0	0	-9.14
6	3D6.16.6 (MET:1580) (10 mg/kg, IP, QW)	PLX4032 (50 mg/kg, PO, BID)	10 + 100	QD	29	27	-7	50	0	0	-8.99
7	3D6.16.6 (MET:1580) (10 mg/kg, IP, QW)	GDC-0712 (100 mg/kg, PO, QD)	10 + 50 + 100	BID, QD	29	38	10	56	0	0	-10.4
8	3D6.16.6 (MET:1580) (10 mg/kg, IP, QW)	PLX4032 (50 mg/kg, PO, BID) + GDC-0712 (100 mg/kg, PO, QD)	10 + 50	BID, QD	29	73	58	83	0	0	-5.5

FIG. 19B

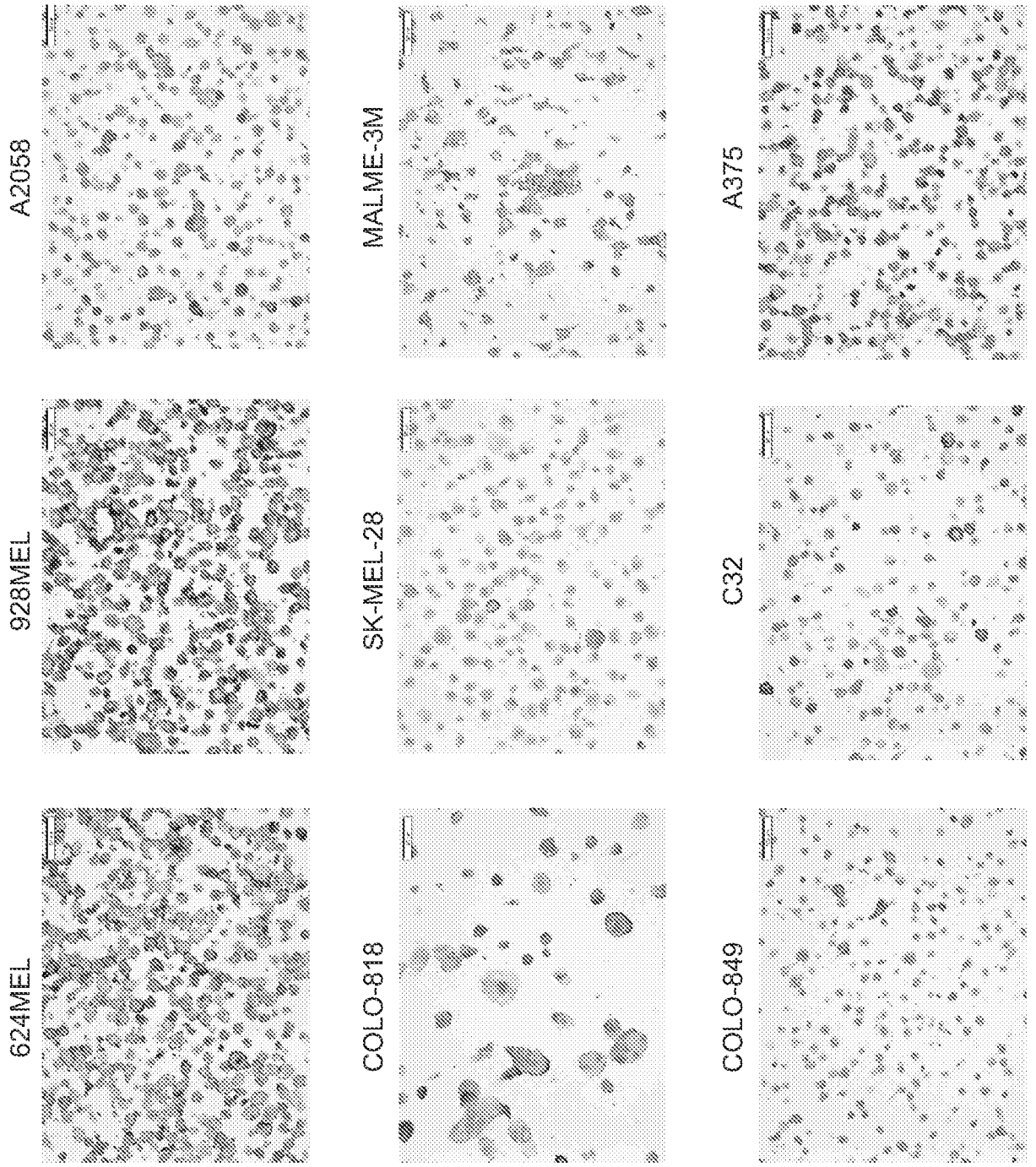

A2058
MALME-3M
A375
928MEL
SK-MEL-28
C32
624MEL
COLO-818
COLO-849

FIG. 21

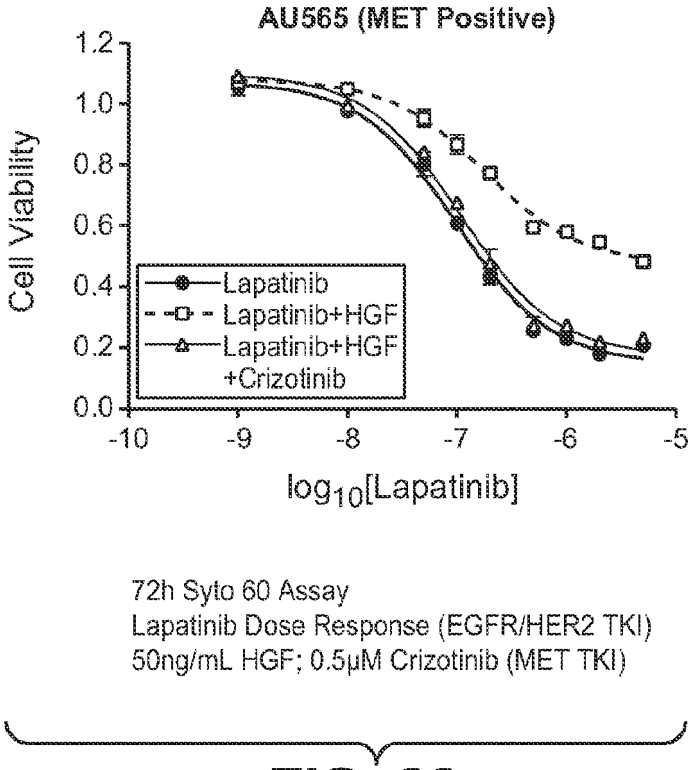


FIG. 22

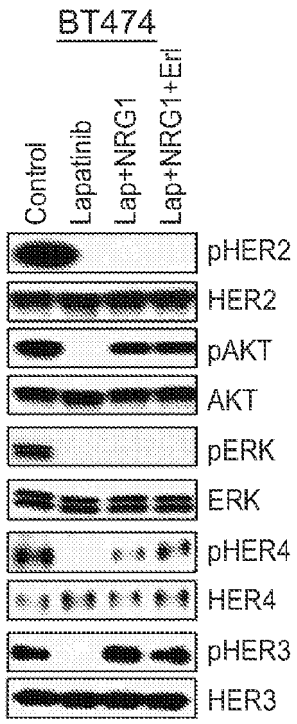


FIG. 23

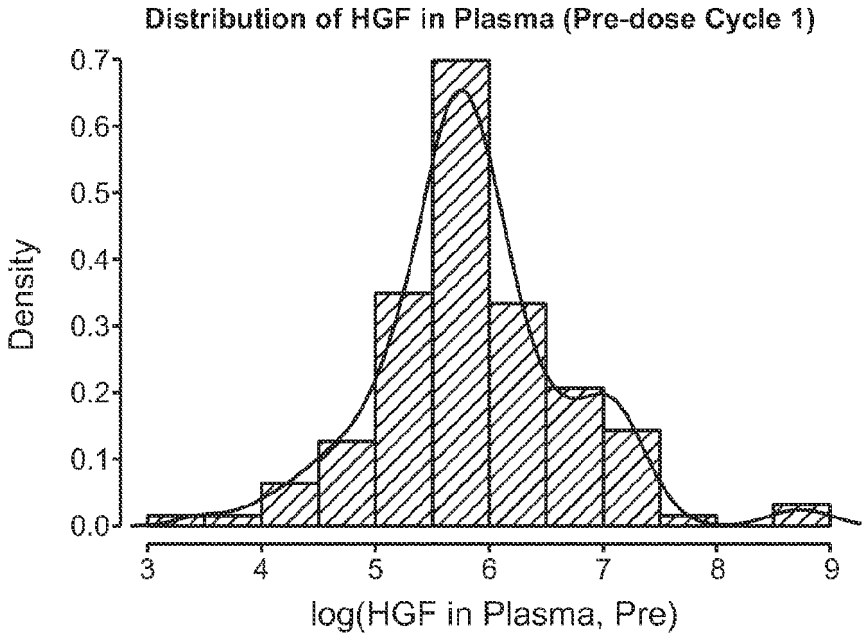
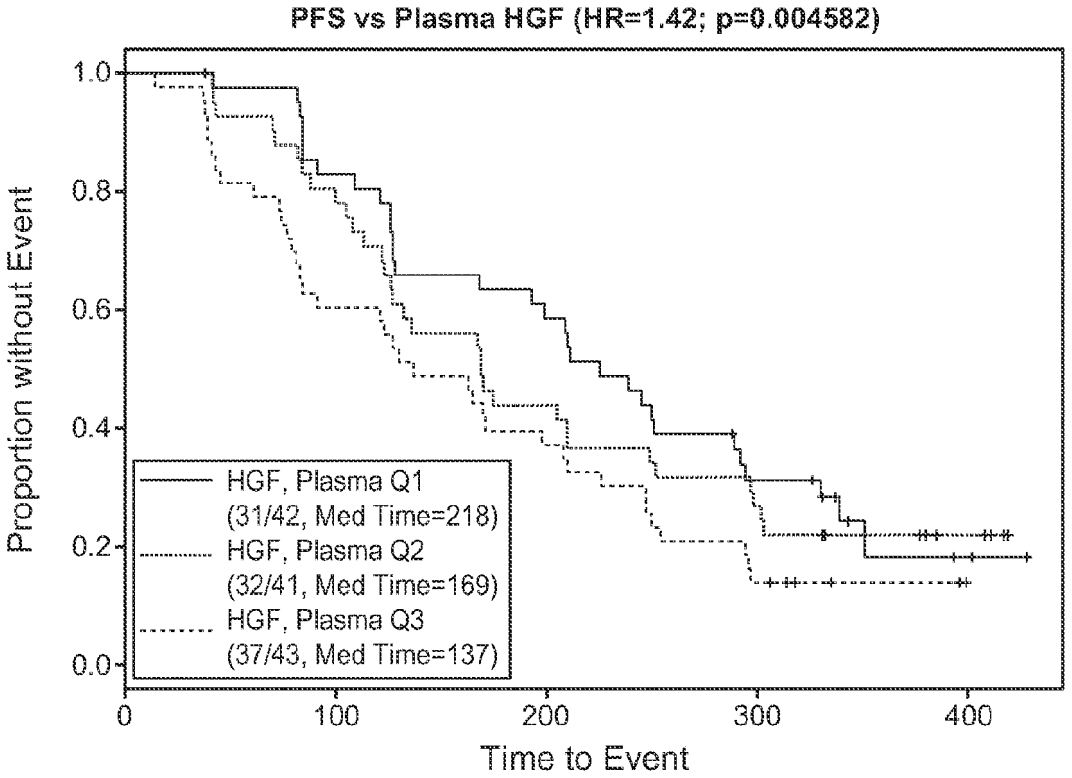


FIG. 24A


PFS vs Plasma HGF (HR=1.42; p=0.004582)
Proportion without Event
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
Time to Event
HGF, Plasma Q1
(31/42, Med Time=218)
HGF, Plasma Q2
(32/41, Med Time=169)
HGF, Plasma Q3
(37/43, Med Time=137)

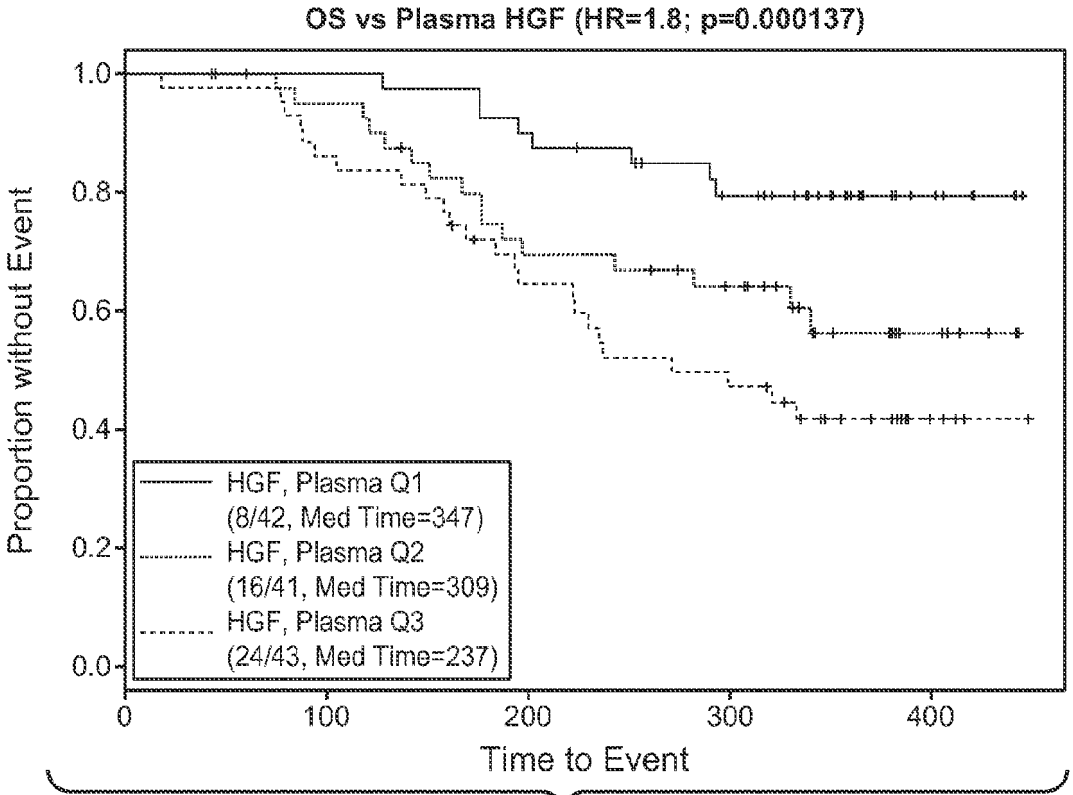
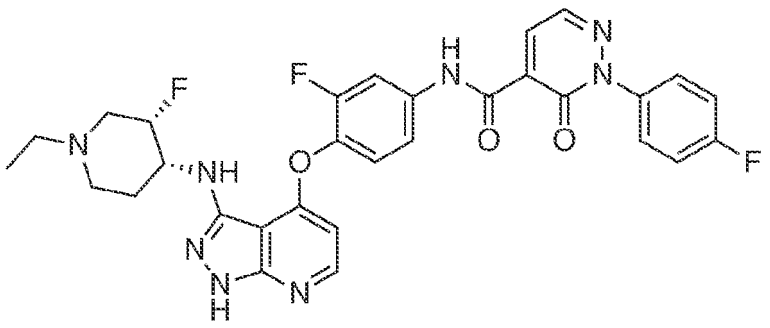

OS vs Plasma HGF (HR=1.8; p=0.000137)
Proportion without Event
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
Time to Event
HGF, Plasma Q1
(8/42, Med Time=347)
HGF, Plasma Q2
(16/41, Med Time=309)
HGF, Plasma Q3
(24/43, Med Time=237)

FIG. 24B

FIG. 25A



Enzyme Assay	
Kinase	IC_{50} (μM)
cMet	0.005
Mer	0.004
HIPK4	0.005
Rse	0.017
MuSK	0.036

FIG. 25B

Cell Assay		
Kinase	Assay (Cell Line)	IC_{50} (μM)
cMet	Autophos ELISA (MKN45)	0.014
KDR	Autophos ELISA (CHO-KDR)	0.43
Axl	Autophos MSD (A172)	0.0017
TrkA	Autophos MSD (CHO-TrkA)	0.034
TrkB	Autophos ELISA (CHO-TrkB)	0.07

FIG. 25C

Selectivity Profiling	
Kinase	Percent Inhibition @ 0.1 μM
Mer	96
HIPK4	93
Met	92.75
Axl	90
Flt3	88
Ros	82
TrkC	80
TrkA	71.75
Rse	70
Lck	66
Met(1250T)	66
MuSK	65
TrkB	64
Ron	56
B-Raf	52.5

FIG. 25D

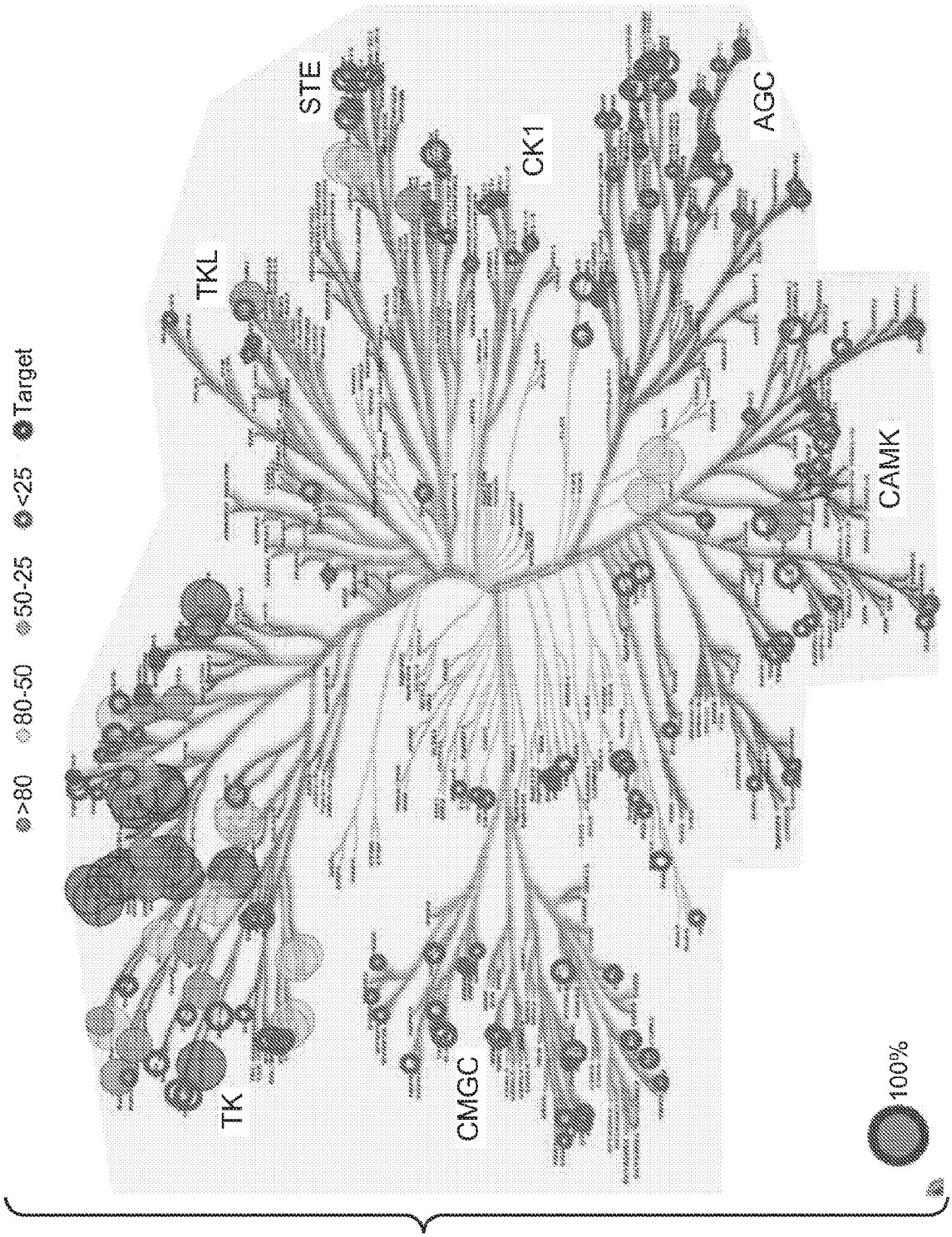


FIG. 25E

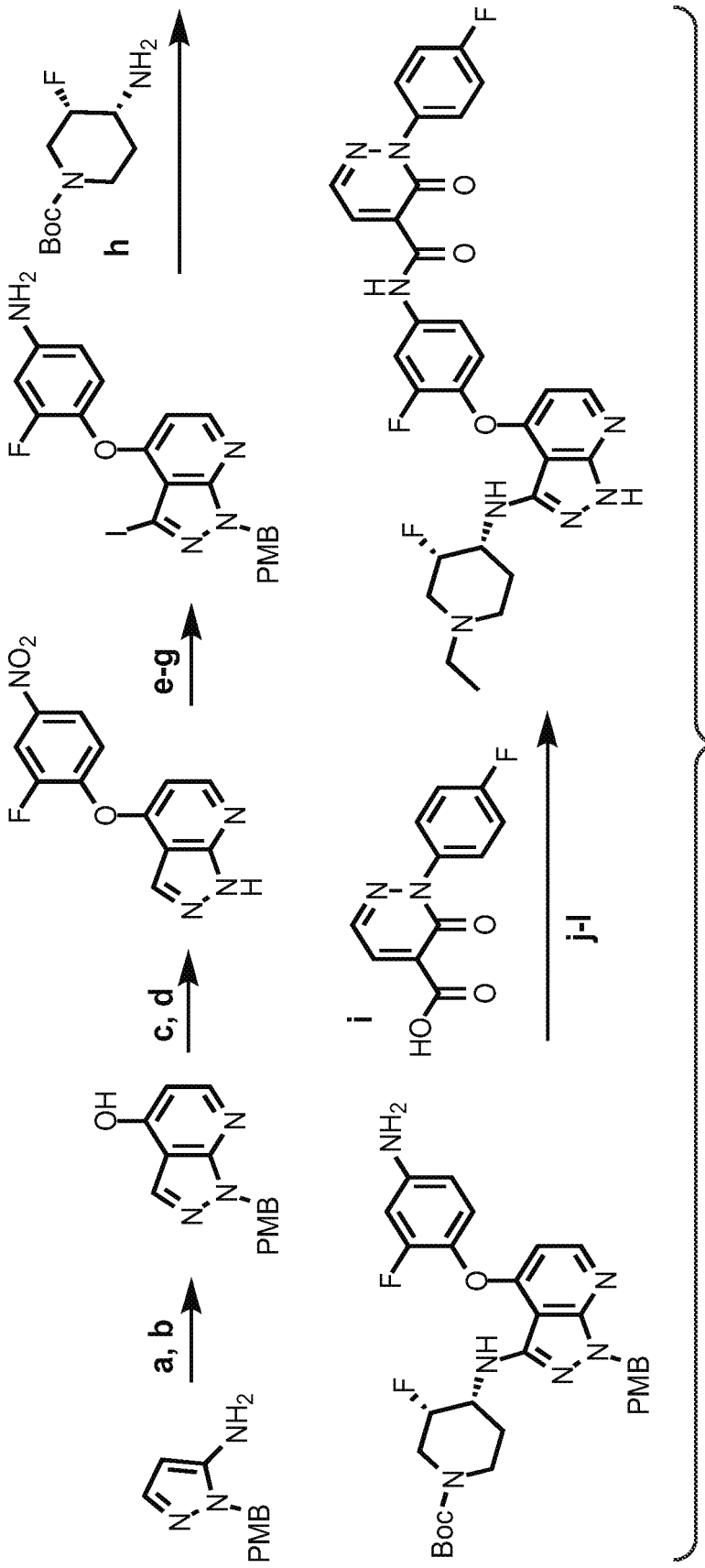


FIG. 26