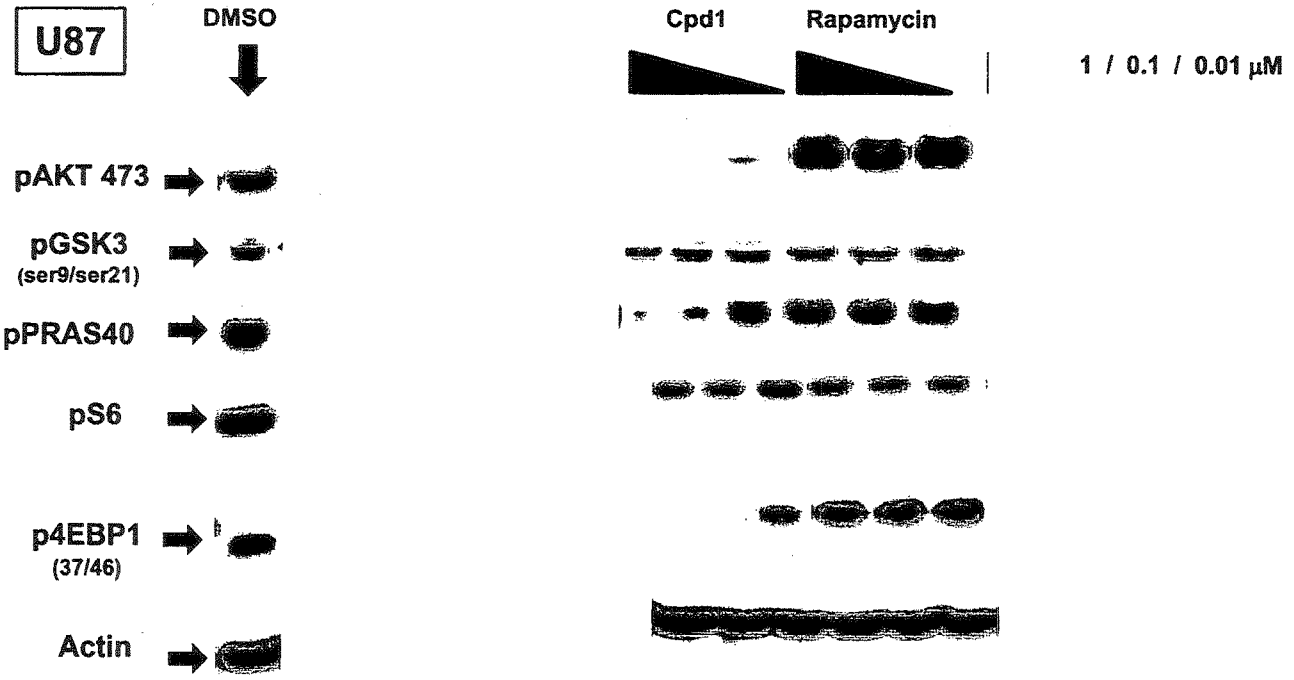
Human cancer	Cell lines	Positive drugs	IC_{50} (μ M)	
			Positive drug	Subject Compound
Fibrosarcoma	HT-1080	Doxorubicin	++++	++++
Pancreatic Cancer	MIAPACA-2	5-FU	+	+++
	Bx-PC-3		++	+++++
	PANC-1	Cisplatin	+	-
Kindney Cancer	786-O	5-FU	+++	++++
Live Cancer	Hep3B	Cisplatin	++	+++
	HepG2	5-FU	++	++
	SK-HEP-1	Doxorubicin	+++	++++
Osteosarcoma	143b		+++	++++
Melanoma	A375	Cisplatin	++	++++
	SK-MEL-5		++	++++
Nasopharyngeal	CNE2		++	++
Gastric Cancer	MCG803		++	+++
	BGC823		++	++++
Ovarian Cancer	SKOV3		+	++
	OVCAR3		+	++++
CML	K562		+	++++
Oral Cancer	KB		+	++++
Orthotopic Multiple Myeloma	RPIM-8226		+	+++++

Figure 1A

Human cancer	Cell lines	Positive drugs	IC_{50} (μ M)	
			Positive drug	Subject Compound
Breast Cancer	BT474	Doxorubicin	++	++++
	MCF-7	Cisplatin	+	+++++
	MCF-7-218	Doxorubicin	+++	++++
	MCF-7- FL		+++	+++++
	MDA-MB231	Cisplatin	+	+++++
	SKBR3		++	++++
Prostate Cancer	DU-145		++	+++
	LNCaP	Paclitaxel	+	+++
	PC-3	Irinotecon	+	+++++
Colorectal Cancer	Colo205		++	++++
	DLD-1	Cisplatin	++	+++++
	HCT-116	5-FU	+++	+++
	HT-29	Cisplatin	+	+++
	LoVo		++	++++
	SW620		+	+++++
Lung Cancer	A549		++	++++
	Calu-6		++	++++
	NCI-H226		++	+++++
	NCI-H460		++	++
	SK-MES-1		+	++++
Glioblastoma	U87MG		++	++++

Figure 1B

Figure 2



- mTORC1/2 inhibitors inhibit pAKT473 and downstream of mTor pS6 and p4EBP1
- Rapamycin activates pAKT473 by negative feedback loop.
- Rapamycin does not inhibit p4EBP1 as well as mTORC1/2 inhibitors.

Figure 3A

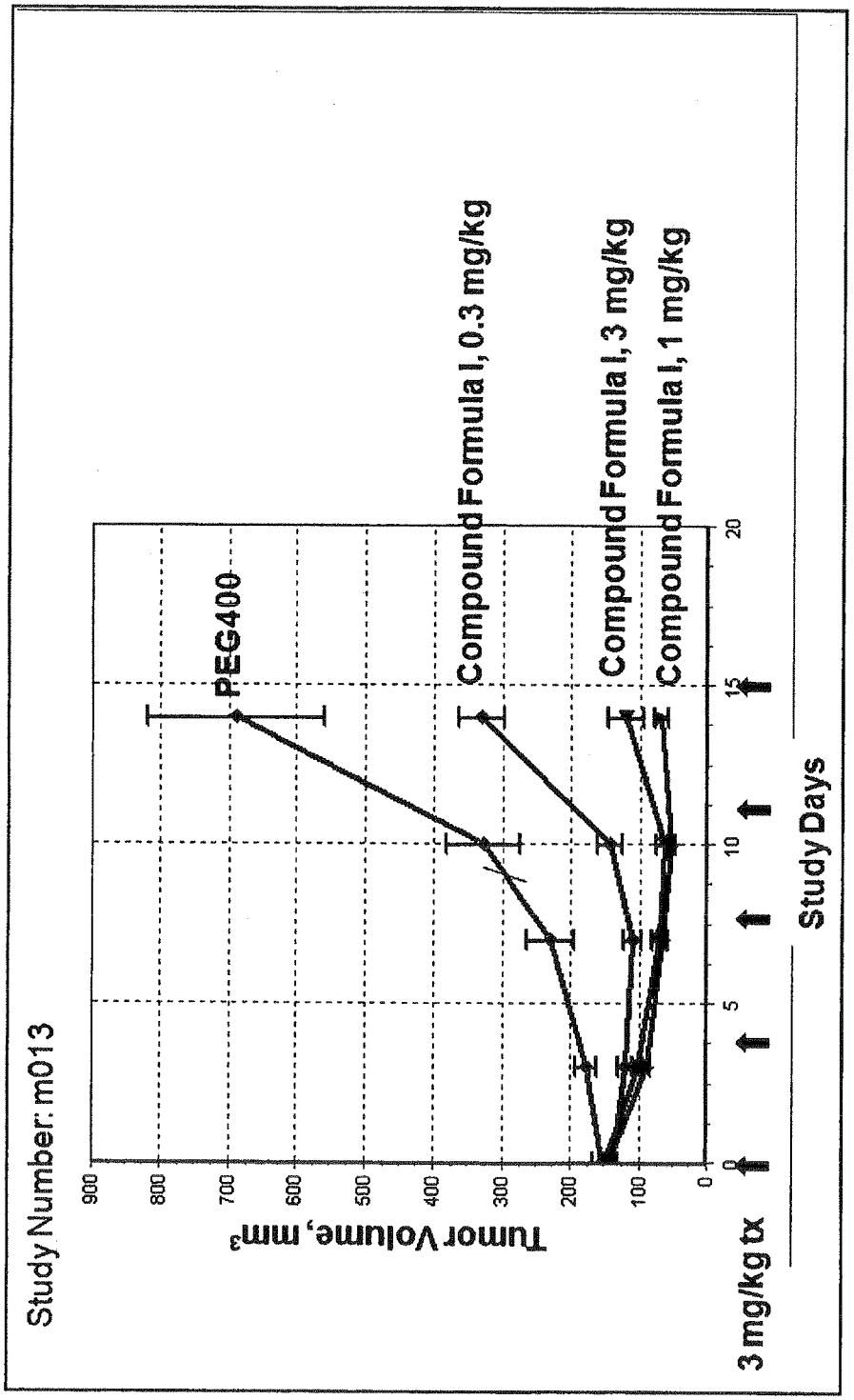

Study Number: m013
Tumor Volume, mm3
900
800
700
600
500
400
300
200
100
0
0
5
10
15
20
Study Days
3 mg/kg tx
PEG400
Compound Formula I, 0.3 mg/kg
Compound Formula I, 3 mg/kg
Compound Formula I, 1 mg/kg

Figure 3B

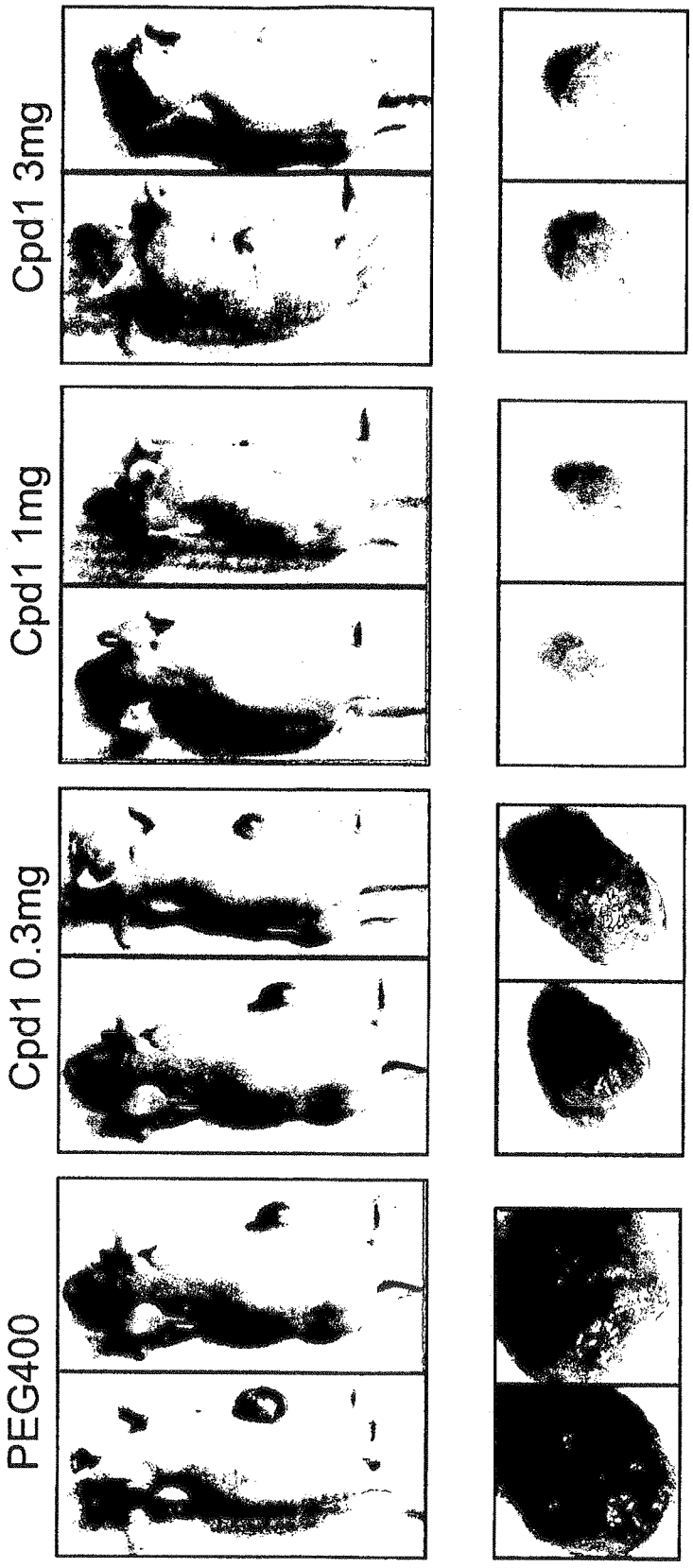


Figure 3C

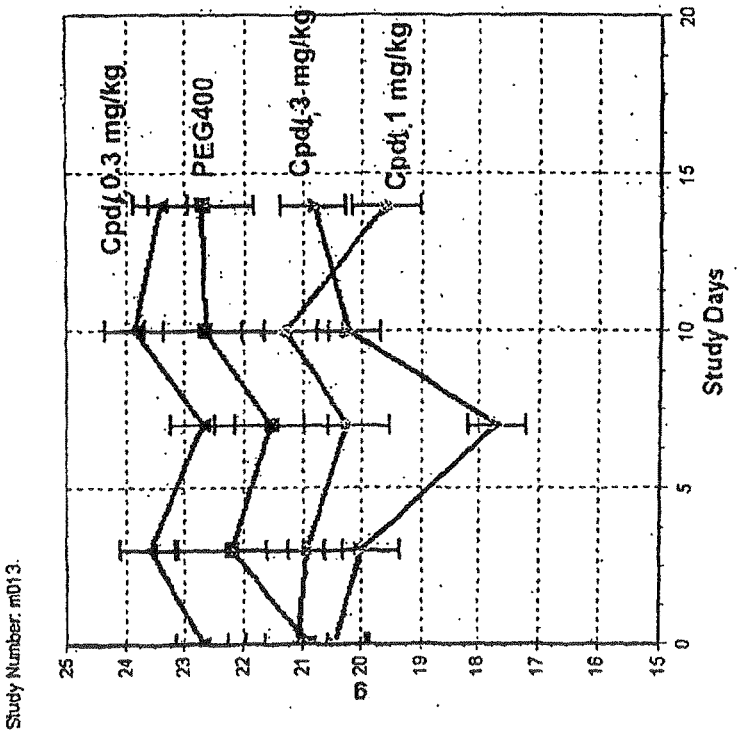

Study Number: m013.
Cpd, 0.3 mg/kg
PEG400
Cpd, 3 mg/kg
Cpd, 1 mg/kg
Study Days
25
24
23
22
21
20
19
18
17
16
15
0
5
10
15
20

Figure 4A

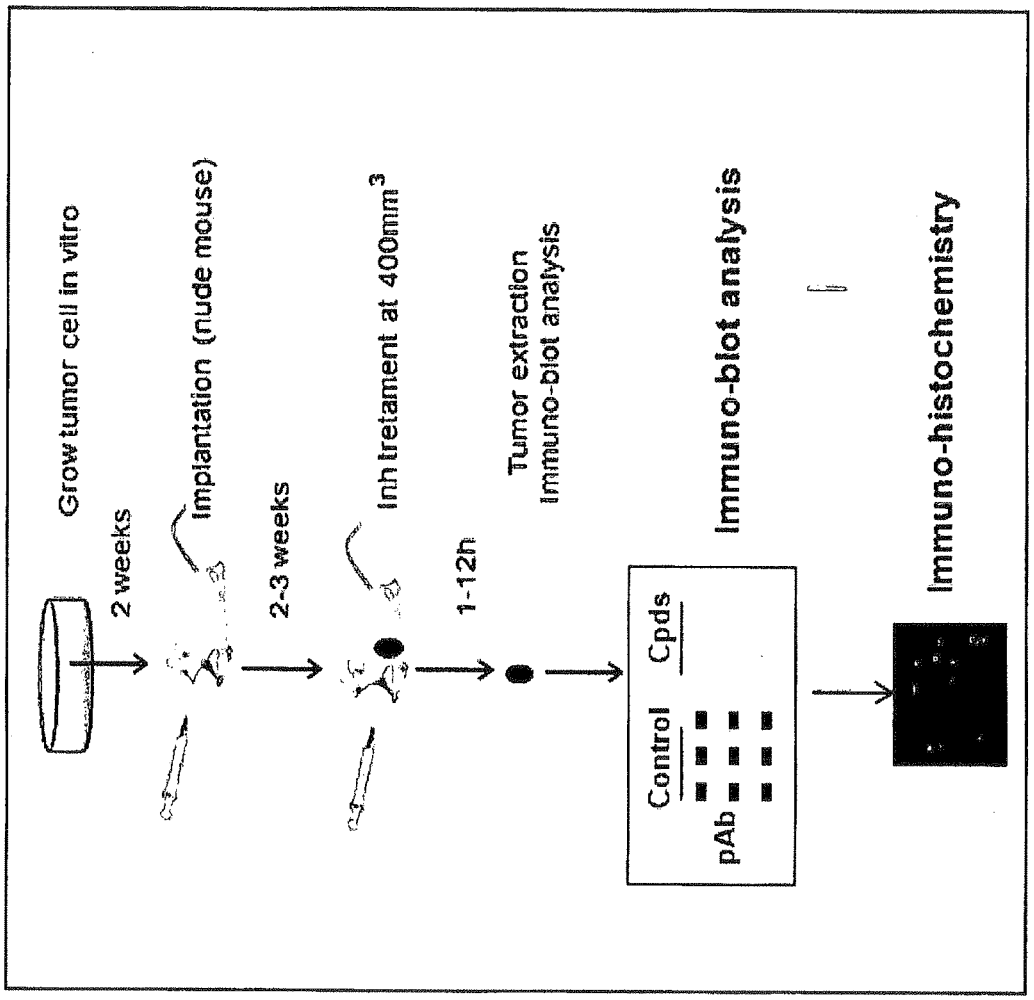

Grow tumor cell in vitro
2 weeks
Implantation (nude mouse)
2-3 weeks
Inh tretament at 400mm3
1-12h
Tumor extraction
Immuno-blot analysis
Control
Cpds
pAb
Immuno-blot analysis
Immuno-histochemistry

Figure 4B

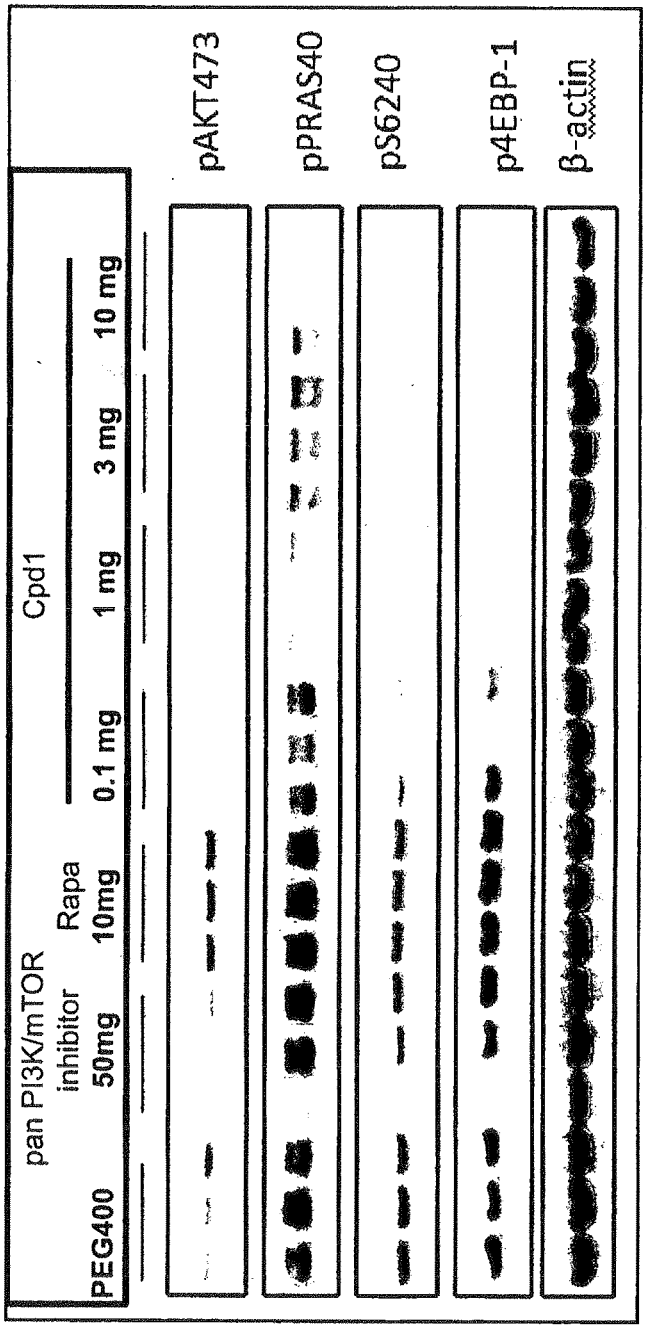

pan PI3K/mTOR inhibitor
Rapa
Cpd1
PEG400
50mg
10mg
0.1 mg
1 mg
3 mg
10 mg
pAKT473
pPRAS40
pS6240
p4EBP-1
β-actin

Figure 5

Lipid kinase selectivity

IC_{50} (nM)										
↓	PI3K Class I*				PI3-Kinases Class II**		PI3K Class III**	PI4K**		PIKK**
mTOR	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ	PI3KC2α	PI3KC2β	VPS34	PI4Kα	PI4Kβ	DNA-PK
~1.0	>200	>5000	>200	>150	>100	>1000	>1000	>1000	>1000	10

Protein kinase selectivity

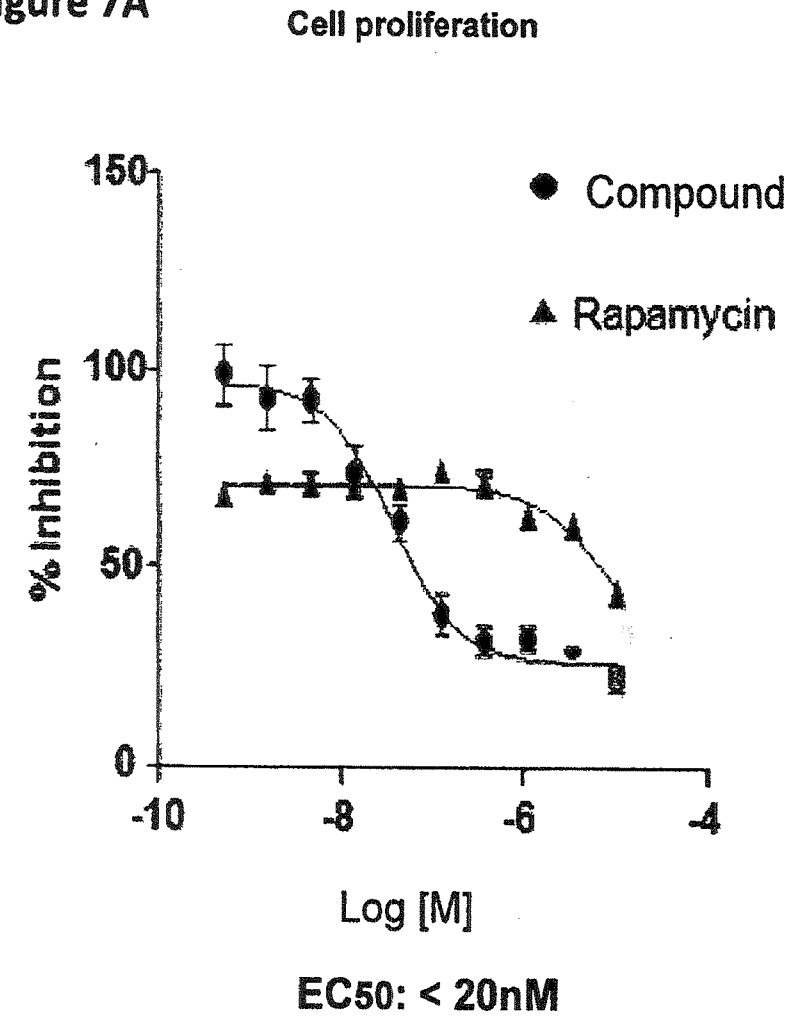
% Inhibition @ 1 μM	number of kinases (Invitrogen ~220 protein kinases)	number of kinases (Ambit ~350 protein kinases)***
> 90%	0	8
65% ~ 90%	8	15

Figure 6

Cellular Data	
PC3 Cell Proliferation (IC_{50}) *	3 nM
PC3 Cellular pAKT (IC_{50}) *	< 10nM
30 primary derived patient cell lines proliferation inhibition (average IC_{50}) **	18nM
Human Whole Blood pAKT IC_{50} shift *	< 2X

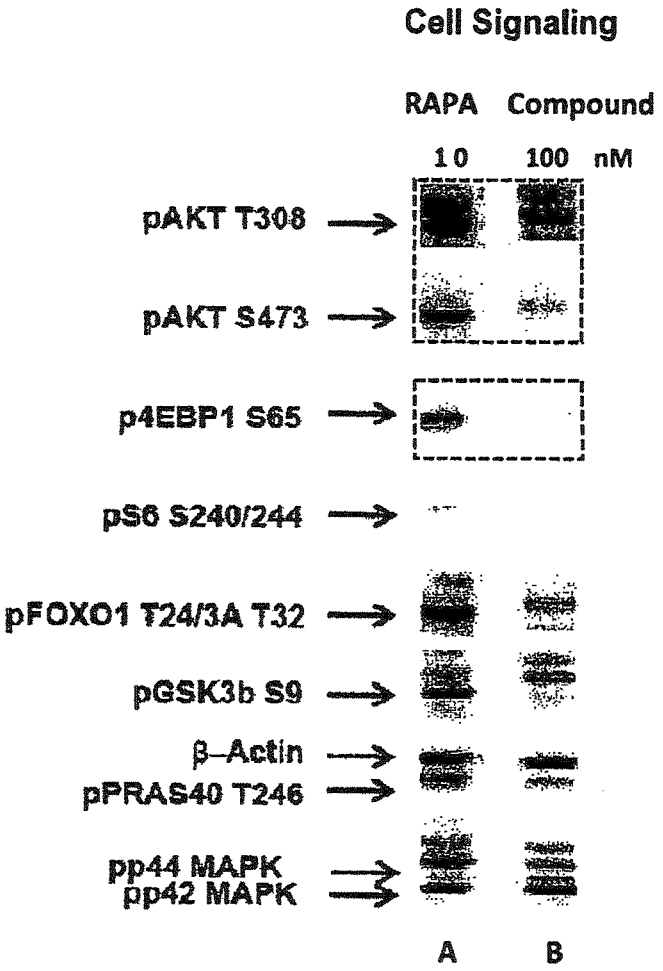
Figure 7

Figure 7A



EC50: < 20nM

Figure 7B



Akt pS473
EC50: < 10nM

Figure 8A

Tissue Type	Cell lines	Compound IC_{50} (nM)	Mutations
Colon	SW620	1	KRAS G12V
	DLD-1	1	PI3KCA E545K, KRAS G13D
	LoVo	35	KRAS G13D
	Colo205	19	BRAF V600E
	HCT-116	11	PI3KCA H1047R, KRAS G13D
	HT-29	905	PI3KCA P449T, BRAF V600E
Lung	NCI-H226	5	
	SK-MES-1	42	
	A549	8	KRAS G12S
	Calu-6	41	KRAS Q61K
	NCI-H460	310	PI3KCA E545K, KRAS Q61H

Figure 8B

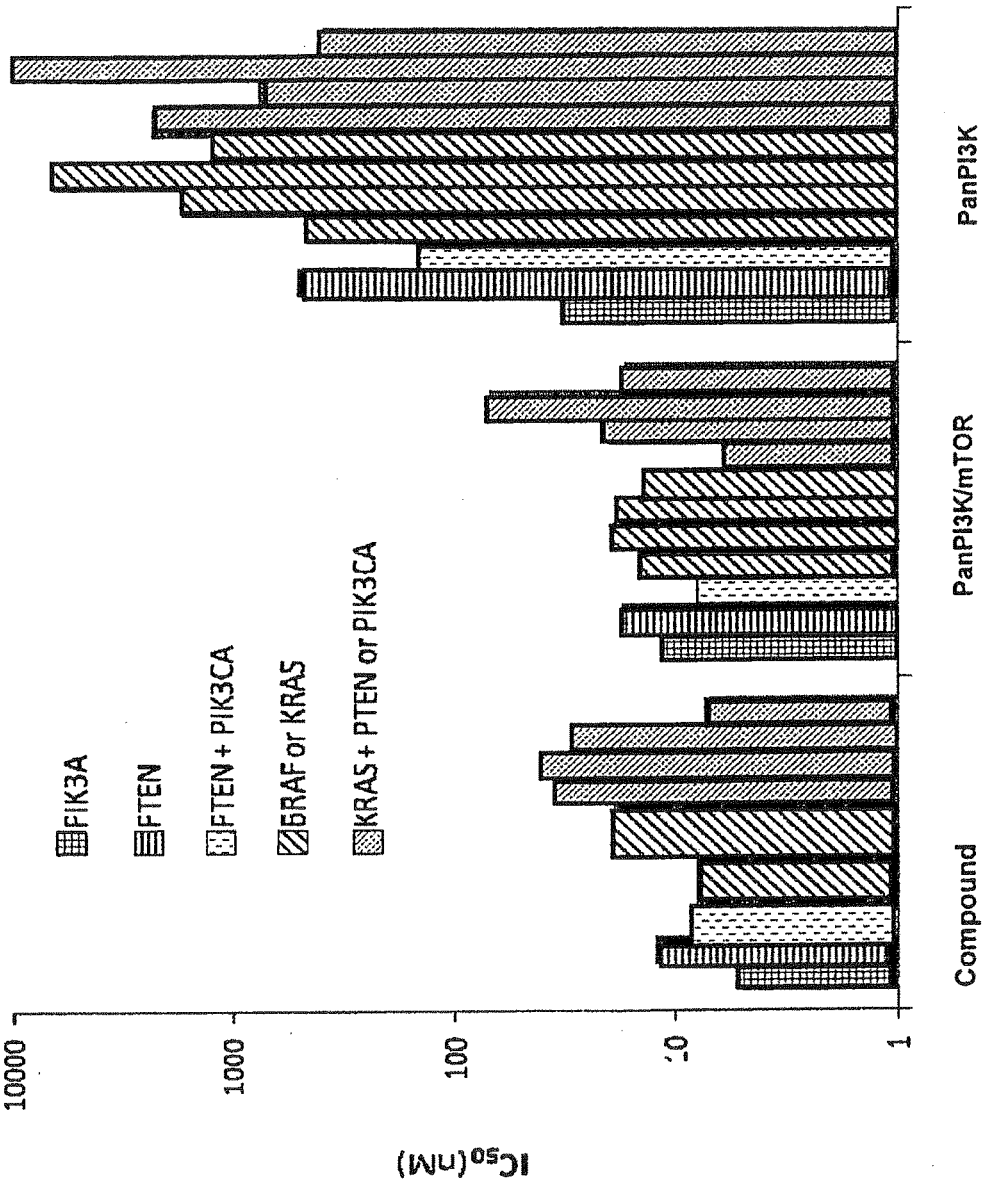

PIK3A
PTEN
PTEN + PIK3CA
BRAF or KRAS
KRAS + PTEN or PIK3CA
IC50 (nM)
10000
1000
100
10
1
Compound
PanPI3K/mTOR
PanPI3K

Figure 9 A

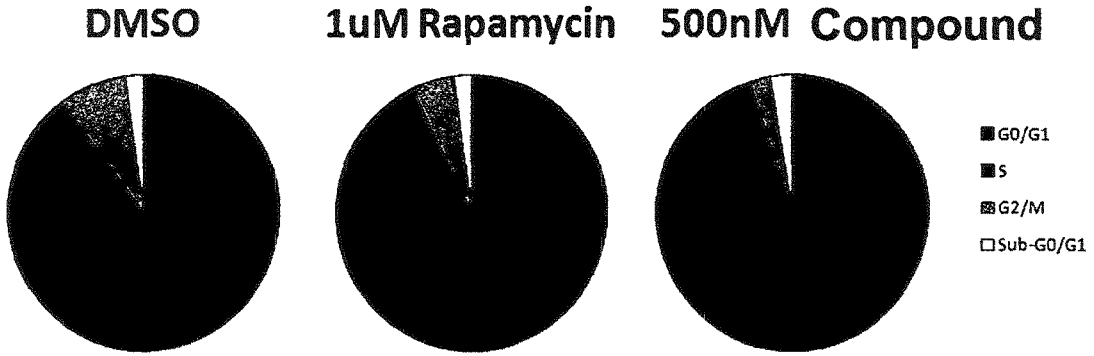


Figure 9 B

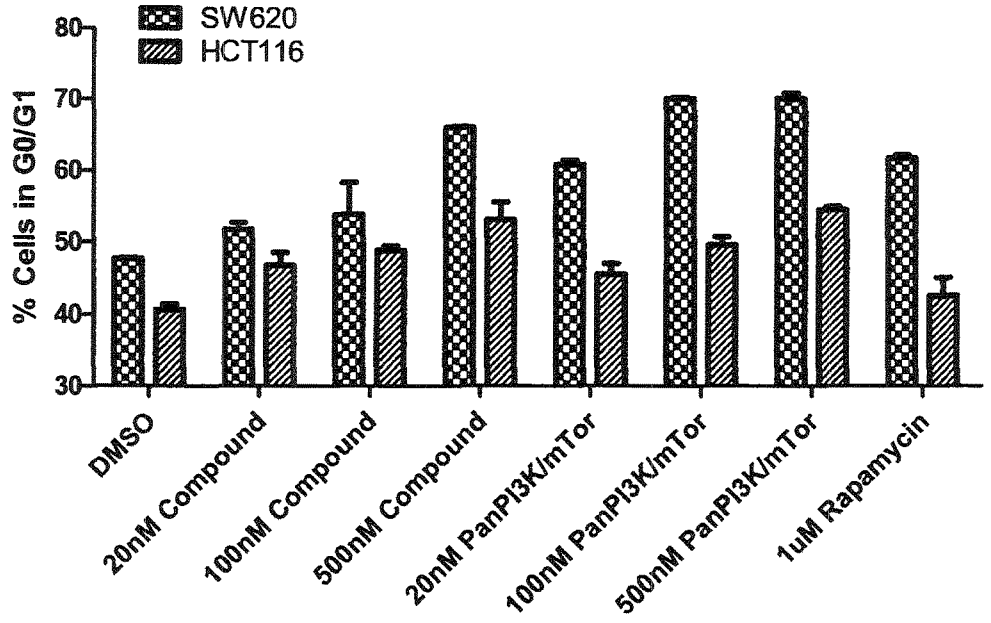
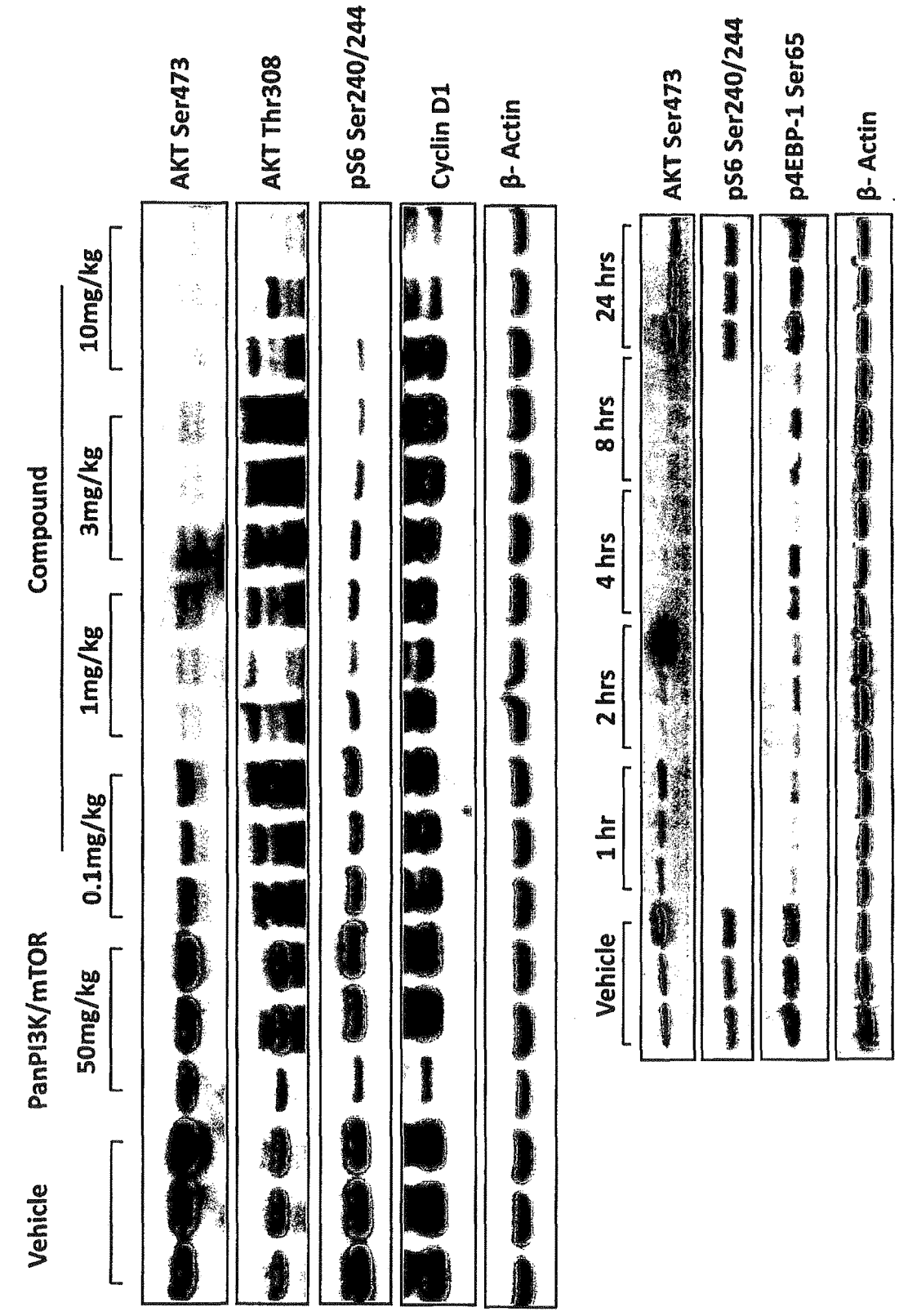


Figure 10


Vehicle
PanPI3K/mTOR
Compound
50mg/kg
0.1mg/kg
1mg/kg
3mg/kg
10mg/kg
AKT Ser473
AKT Thr308
pS6 Ser240/244
Cyclin D1
β- Actin
Vehicle
1 hr
2 hrs
4 hrs
8 hrs
24 hrs
AKT Ser473
pS6 Ser240/244
p4EBP-1 Ser65
β- Actin

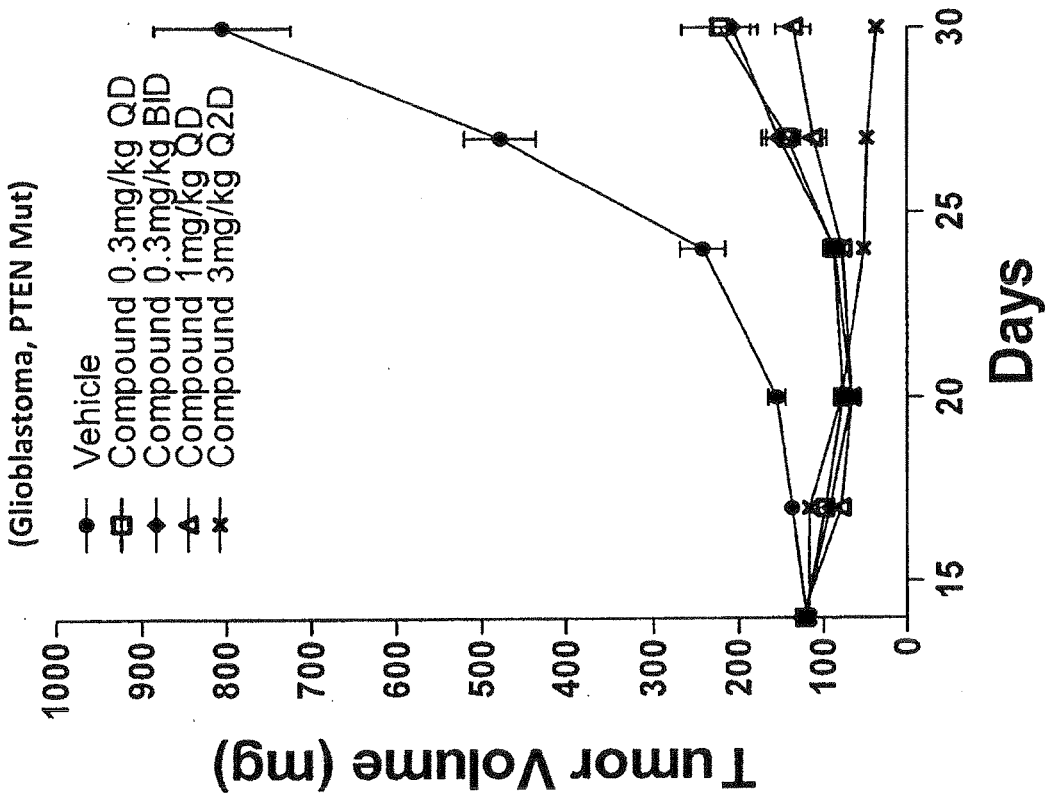

U87-MG
(Glioblastoma, PTEN Mut)
Vehicle
Compound 0.3mg/kg QD
Compound 0.3mg/kg BID
Compound 1mg/kg QD
Compound 3mg/kg Q2D
Tumor Volume (mg)
1000
900
800
700
600
500
400
300
200
100
0
15
20
25
30
Days

Figure 11A

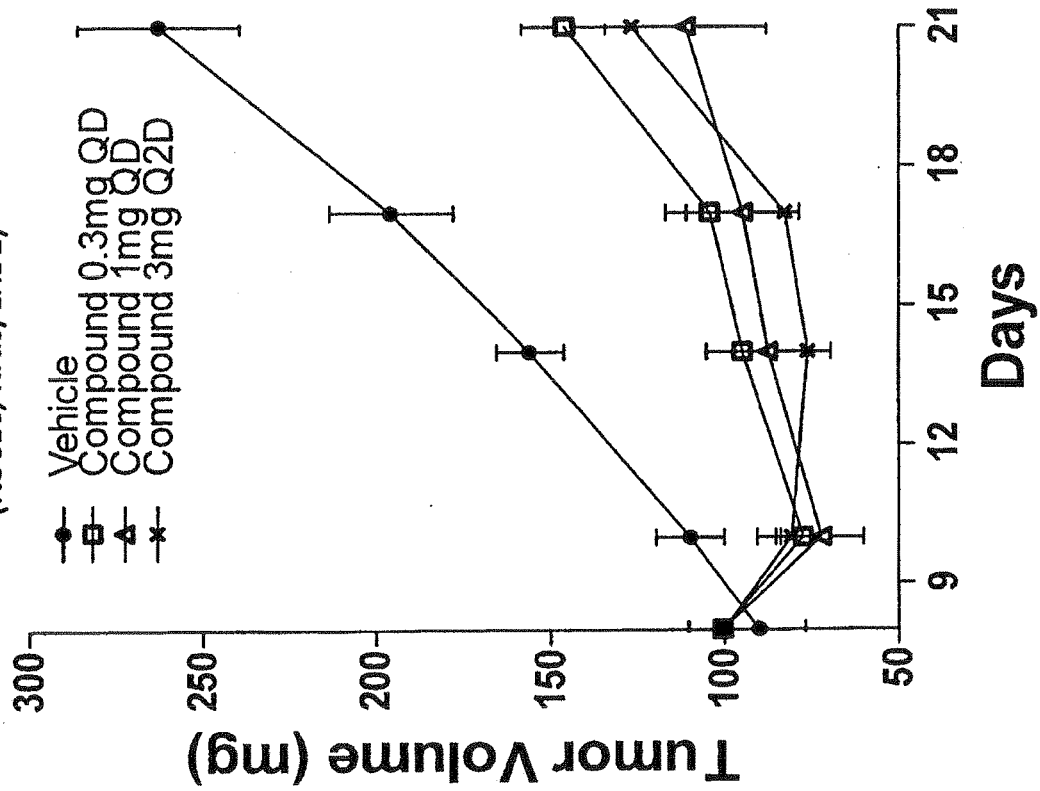

A549
(NSCLC, Kras/LKB1)
Vehicle
Compound 0.3mg QD
Compound 1mg QD
Compound 3mg Q2D
Tumor Volume (mg)
300
250
200
150
100
50
9
12
15
18
21
Days

Figure 11B

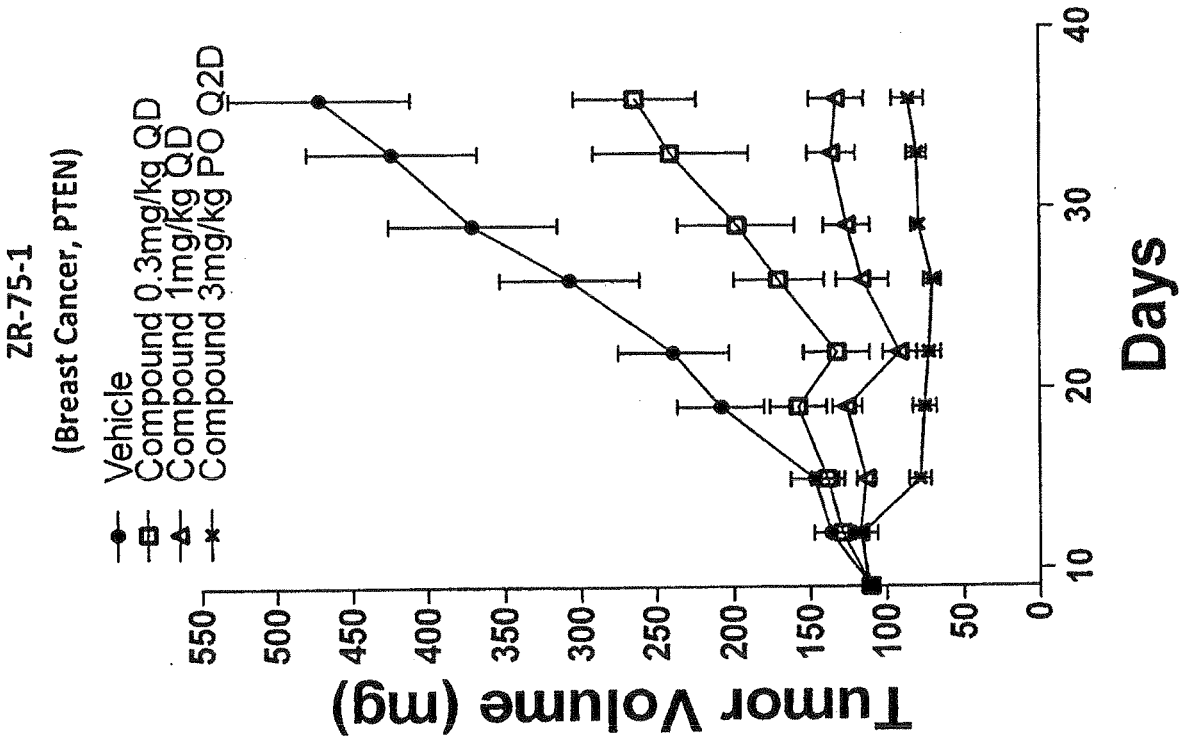

ZR-75-1
(Breast Cancer, PTEN)
Vehicle
Compound 0.3mg/kg QD
Compound 1mg/kg QD
Compound 3mg/kg PO Q2D
Tumor Volume (mg)
550
500
450
400
350
300
250
200
150
100
50
0
10
20
30
40
Days

Figure 11C

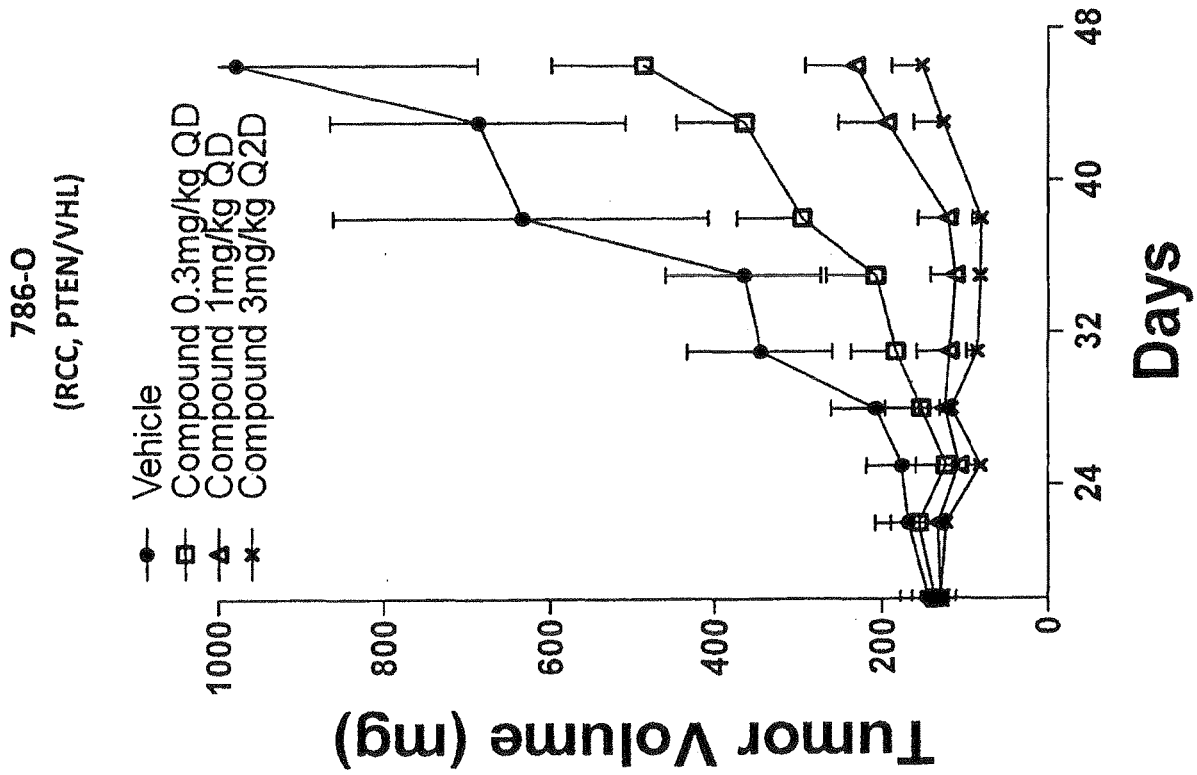
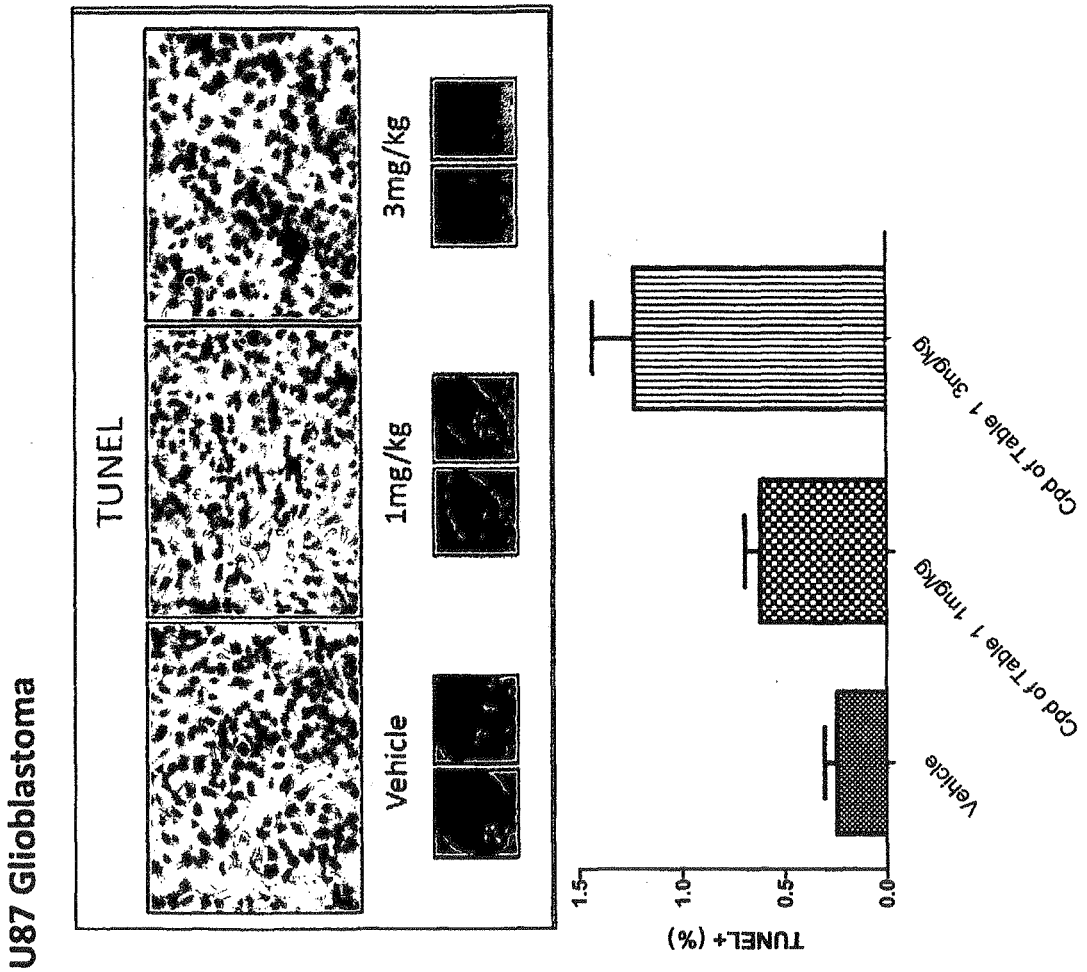

786-O
(RCC, PTEN/VHL)
Vehicle
Compound 0.3mg/kg QD
Compound 1mg/kg QD
Compound 3mg/kg Q2D
Tumor Volume (mg)
1000
800
600
400
200
0
24
32
40
48
Days

Figure 11D

Figure 12


U87 Glioblastoma
TUNEL
Vehicle
1mg/kg
3mg/kg
TUNEL+ (%)
1.5
1.0
0.5
0.0
Vehicle
Cpd of Table 1 1mg/kg
Cpd of Table 1 3mg/kg