

FIG 1 GDC-0068 and GDC-0973 (2.5mg/kg) : Tumor Volumes

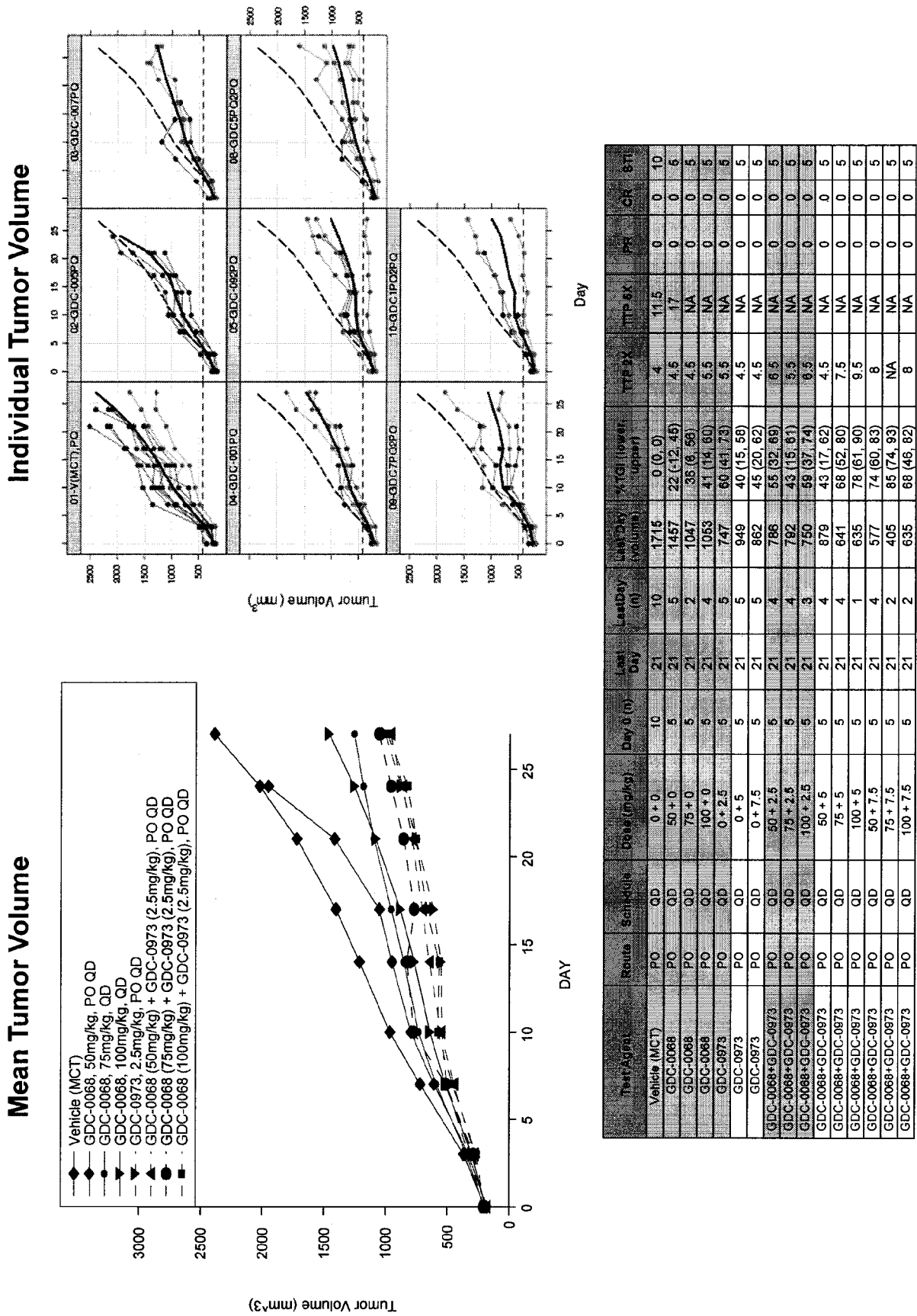
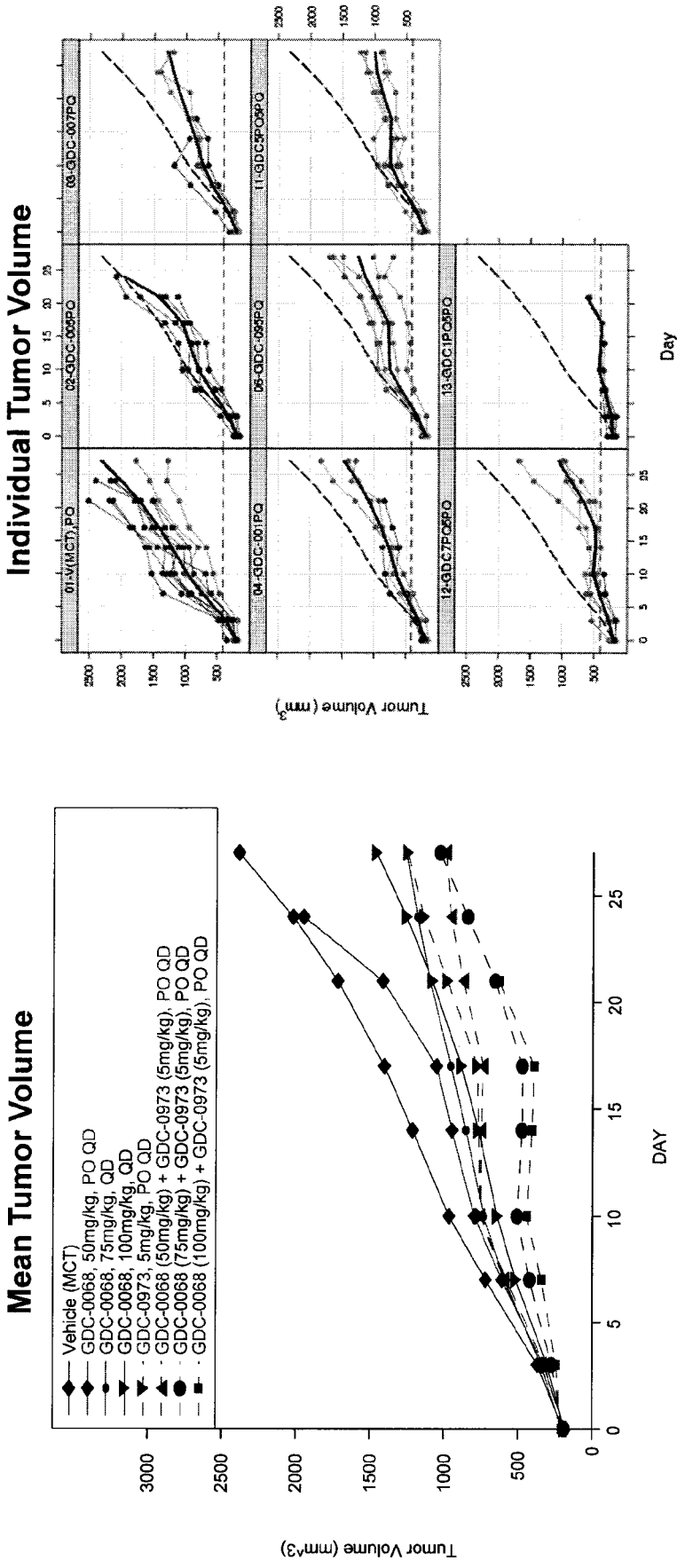


FIG 2 GDC-0068 and GDC-0973 (5mg/kg): Tumor Volumes



Treat Agent	Route	Schedule	Dose (mg/kg)	Day 0 (h)	Last Day	Last Day (n)	Log Day (volume)	%TGI (lower, upper)	TTP 32	TTP 6X	PR	CR	STI
Vehicle (MCT)	PO	QD	0 + 0	10	21	10	1715	0 (0, 0)	4	11.5	0	0	10
GDC-0068	PO	QD	50 + 0	5	21	5	1457	22 (-12, 46)	4.5	17	0	0	5
GDC-0068	PO	QD	75 + 0	5	21	2	1047	35 (6, 58)	4.5	NA	0	0	5
GDC-0068	PO	QD	100 + 0	5	21	4	1053	41 (14, 60)	5.5	NA	0	0	5
GDC-0973	PO	QD	0 + 2.5	5	21	5	747	60 (41, 73)	5.5	NA	0	0	5
GDC-0973	PO	QD	0 + 5	5	21	5	849	40 (15, 58)	4.5	NA	0	0	5
GDC-0973	PO	QD	0 + 7.5	5	21	5	862	45 (20, 62)	4.5	NA	0	0	5
GDC-0068 + GDC-0973	PO	QD	50 + 2.5	5	21	4	786	55 (32, 69)	6.5	NA	0	0	5
GDC-0068 + GDC-0973	PO	QD	75 + 2.5	5	21	4	792	43 (15, 61)	5.5	NA	0	0	5
GDC-0068 + GDC-0973	PO	QD	100 + 2.5	5	21	3	750	59 (37, 74)	6.5	NA	0	0	5
GDC-0068 + GDC-0973	PO	QD	50 + 5	5	21	4	879	43 (17, 62)	4.5	NA	0	0	5
GDC-0068 + GDC-0973	PO	QD	75 + 5	5	21	4	841	58 (52, 80)	7.5	NA	0	0	5
GDC-0068 + GDC-0973	PO	QD	100 + 5	5	21	1	635	78 (61, 90)	9.5	NA	0	0	5
GDC-0068 + GDC-0973	PO	QD	50 + 7.5	5	21	4	577	74 (60, 83)	8	NA	0	0	5
GDC-0068 + GDC-0973	PO	QD	75 + 7.5	5	21	2	405	85 (74, 93)	NA	NA	0	0	5
GDC-0068 + GDC-0973	PO	QD	100 + 7.5	5	21	2	635	88 (46, 82)	8	NA	0	0	5

FIG 3 GDC-0068 and GDC-0973 (7.5mg/kg): Tumor Volumes

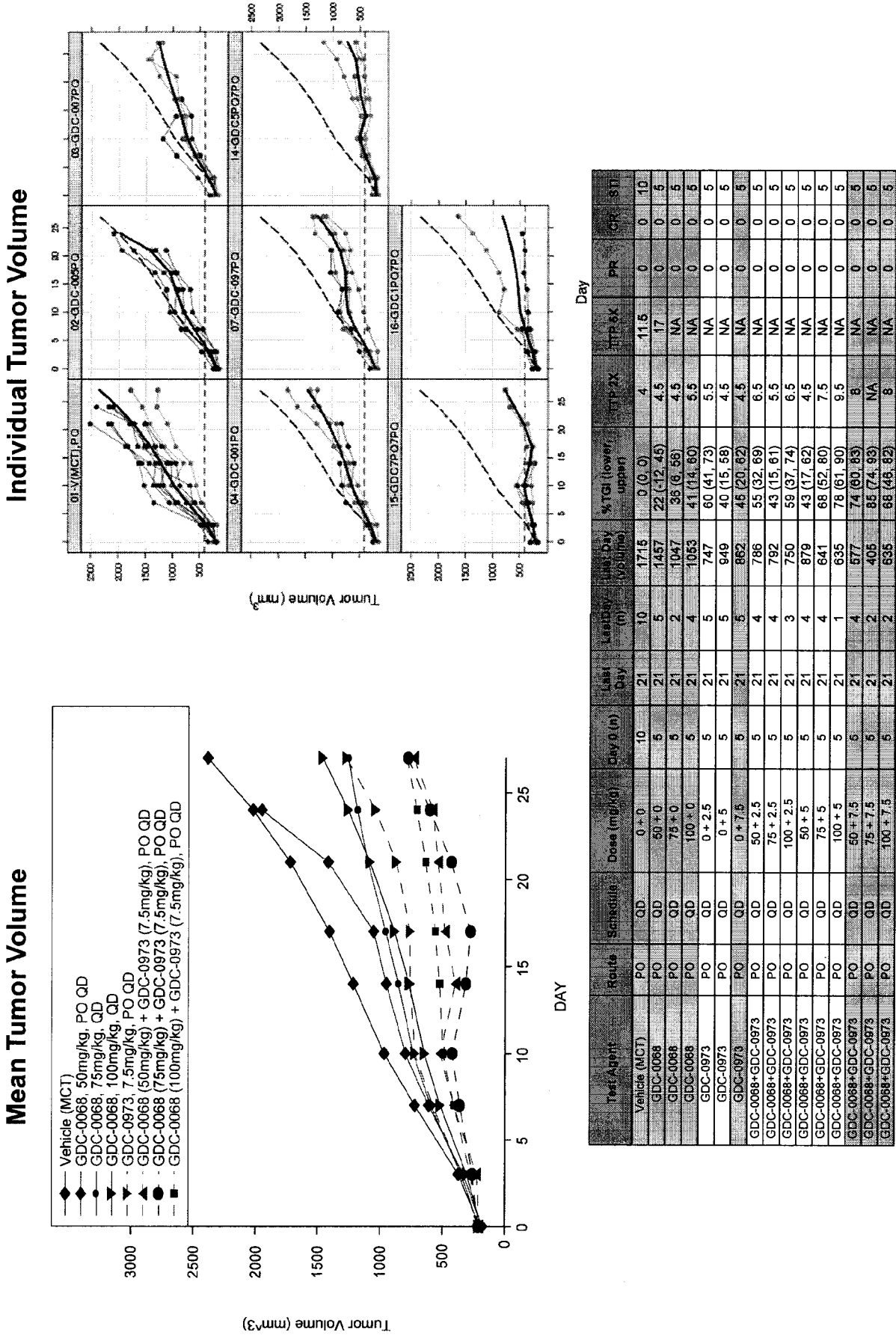


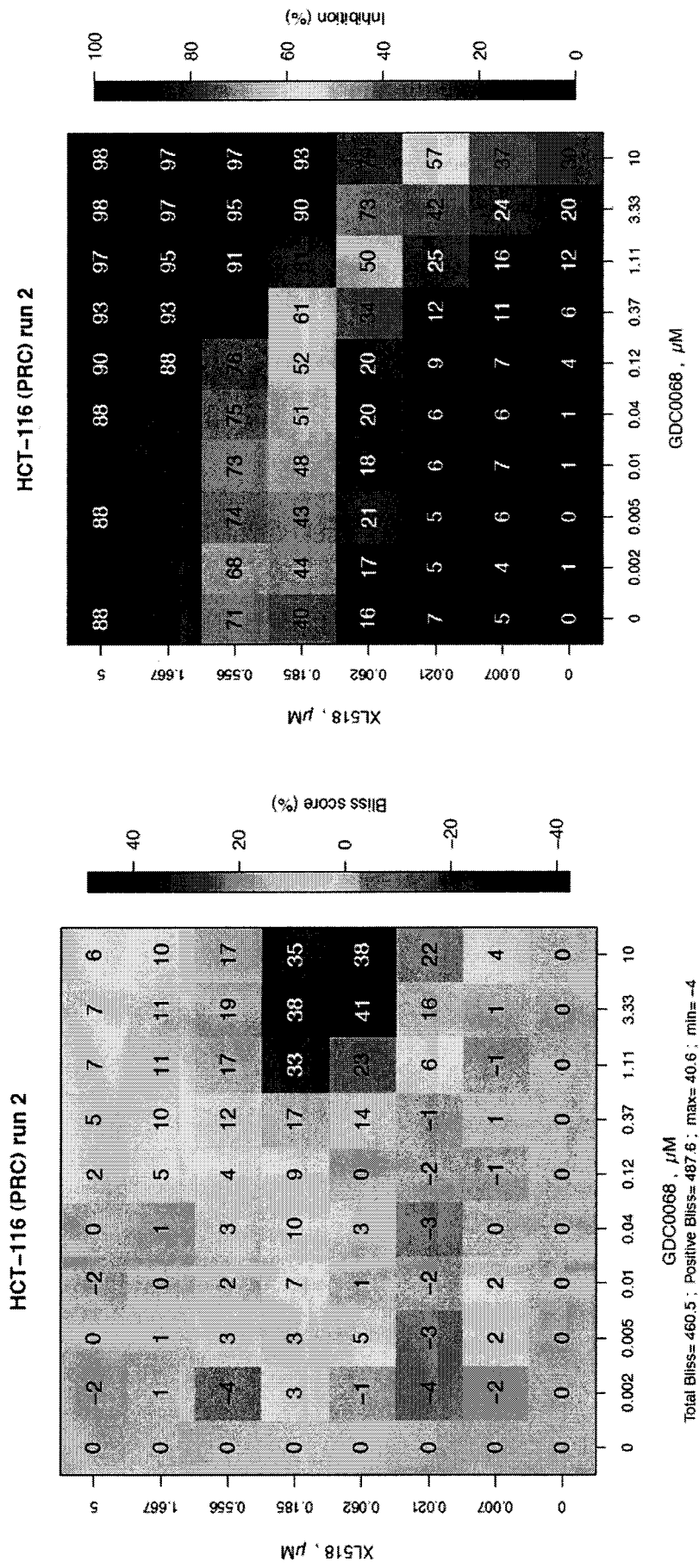
FIG 4 Colorectal Cancer in vitro

Tissue	Cell line	Akt pathway activation	Ras/Raf activation	RTK other	IC50s		Bliss Scores	
					GDC-0068	XL-518	Total Positive	Total
Colon	HCT-116 (PRC)*	PI3K H1047R	Kras G13D	E-Cad, RER+	>10	0.25	488	460
Colon	DLD-1 (PRC)*	PI3K E545K,D549N	Kras G13D	p53, RER+	>10	3.15	367	339
Colon	LS174T (PRC)*	PI3K H1047	Kras G12D	E-Cad, RER+	9.13	0.25	269	242
Colon	HM-7	PI3K H1047	Kras G12D		7.09	0.57	228	140
Colon	LS180	PI3K H1047R, P421L	Kras G12D	RER+	>10	0.08	226	173
Colon	HT-29 (PRC)*	PI3K L568F, L569F, P449T	Braf V600E	p53	>10	0.01	204	201
Colon	SW620 (PRC)*		Kras G12V	RER+	>10	0.11	199	156

XL518									
	cell line	molecular subtype	PI3K activation	MAPK activation	GDC-0068 IC50 (uM)	Run1 6/29/2009	Run2 7/10/2009	Run3 8/17/2009	
CRC	KM12		PTEN-		2.3				
CRC	Lovo		AKT2 mut	KRAS	2.25				
CRC	LS180		PI3K Mut	KRAS	max		s		
CRC	MDST8		PTEN-	BRAF	max		s		
CRC	HT-29		PI3K Mut	BRAF	max				

- High frequency of coexisting PI3K and Ras pathway mutations
- Strong synergy seen in cells with both pathway mutations

FIG 5 HCT-116 (Colon - PI3K and Kras Mutant) In Vitro Combination of Mek and Akt



Bliss Score Range: GDC-0973 0.021-0.185uM, GDC-0068 0.37-10uM

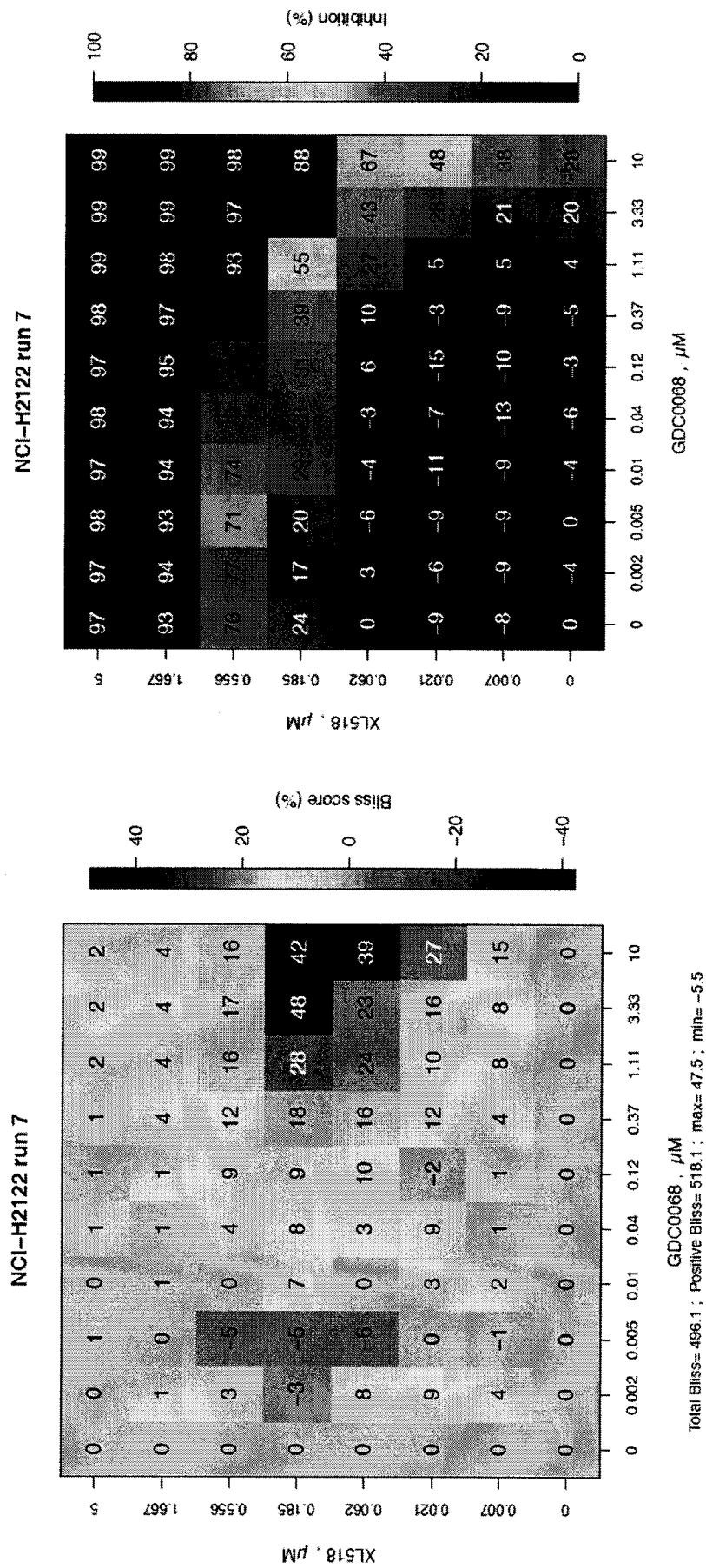
FIG 6 NSCLC

					IC50s		Bliss Scores		
Tissue	Cell line	Akt pathway activation	Ras/Raf activation	RTK	other	GDC-0068	XL-518	Total Positive	Total
Lung-NSCLC	H460 (PRC)*	PI3K E545K	Kras Q61H	EGFR L933P	LKB1	>10	>5	549	468
Lung-NSCLC	NCI-H2122		Kras G12C		p53, LKB1	>10	0.3	518	496
Lung-NSCLC	H1299 (PRC)*		Nras Q61K		p53	>10	3.01	529	384
Lung-NSCLC	SK-MES-1 (PRC)*	PI3K L997P	Kras N85K		p53	>10	0.50	426	277
Lung-NSCLC	MV522 (PRC)*		Braf V600E			>10	0.04	304	125
Lung-NSCLC	A549 (PRC)*	PI3K M772X, N996H	Kras G12S		p53, LKB1	>10	0.34	252	180
B Lymphoblast	NCI-BL2122					4.54	>5	12	-549

XL518						
cell line	molecular subtype	PI3K activation	MAPK activation	GDC-0068 IC50 (uM)	Run1	Run2
NSCLC	NCI-H2122	WT	KRAS	max	6/29/2009	7/10/2009
NSCLC	NCI-H460	PI3K mut	KRAS	max	s	s

- High frequency of coexisting PI3K and Ras pathway mutations
- Strong synergy seen in all cells tested—including cells with Ras/Raf mutations alone with no known PI3K pathway mutations

FIG 7 H2122 (NSCLC - Kras Mutant) In Vitro Combination of Mek and Akt



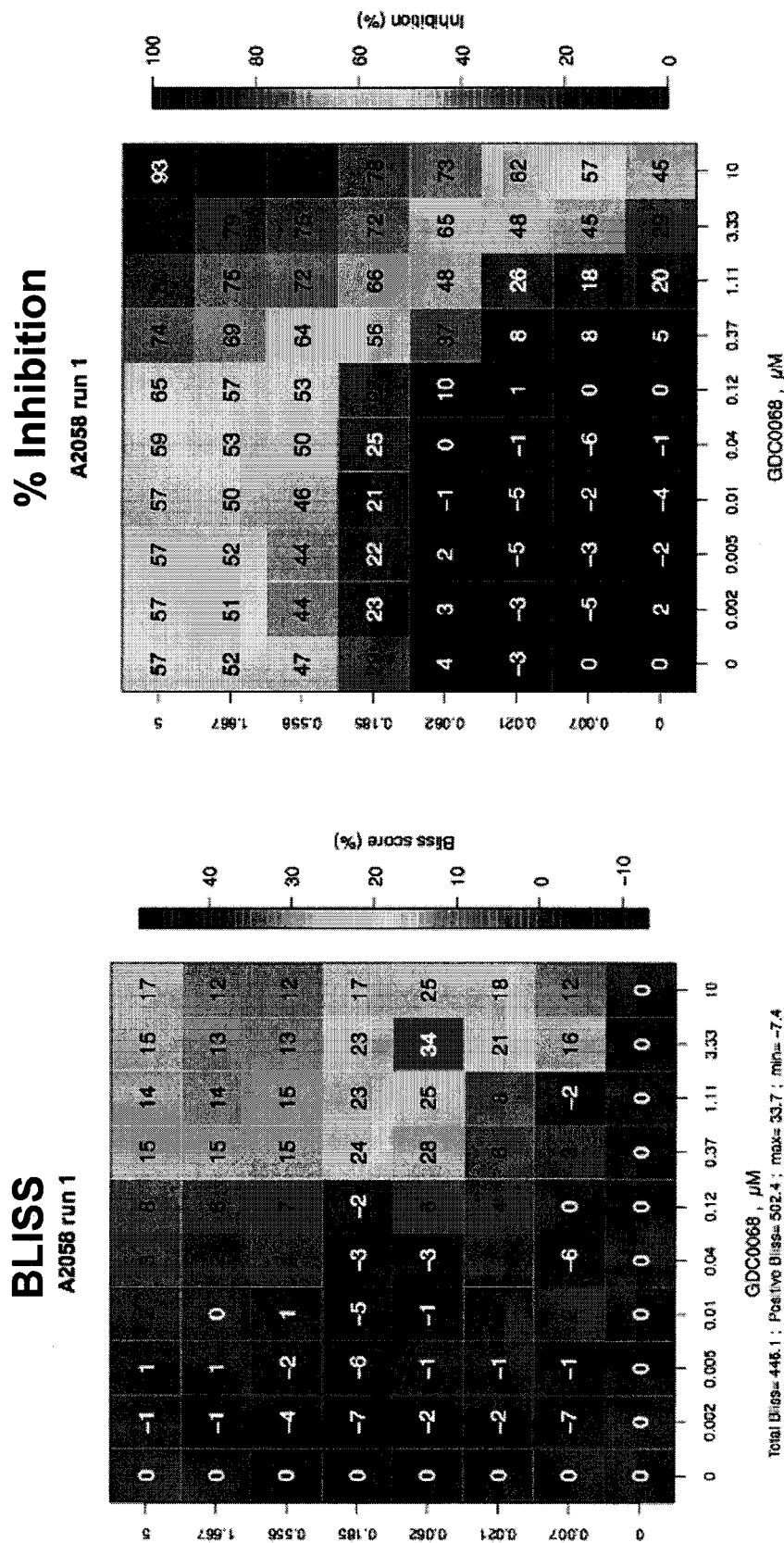
Bliss Score Range: GDC-0973 0.021-0.185uM, GDC-0068 0.37-10uM

FIG 8 Melanoma

Tissue	Cell line	Akt pathway activation	Ras/Raf activation	RTK	other	IC50s		Bliss Scores	
						GDC-0068	XL-518	Total Positive	Total
Melanoma	MALME3M		Braf V600E			>10	0.07	719	684
Melanoma	A375	Akt3 hi	Braf V600E			>10	0.01	55	548
Melanoma	A2058	PTEN-	Braf V600E		p53	>10	0.6	502	446
Melanoma	537MEL	PTEN-	Braf del,amp			2.33	0.02	434	428
Normal fibroblast	MALME3					5.02	>5	42	-142

- Predominantly Braf mut, often coexist with PTEN-, sometimes with PI3K mut or Akt3 overexpression
- Strong synergy seen in all melanoma cells tested—including cells with BRAF mutation alone with no known PI3K pathway mutations

FIG 9 A2058 (Melanoma - PTEN -/- and Braf Mutant) In Vitro Combination of Mek and Akt Minimal In Vitro Single Agent Activity



Cell Line	Tissue	PTEN	PI3K	Kras	Braf	Other	IC50s		Bliss Scores				Max % Inhibition		
							GDC-0068	GDC-0973	# Combo	[GDC-0068]	[GDC-0973]	GDC-0068	GDC-0973		
A2058	Tissue														
	Melanoma	N			V600F		>10	>5		12	34	3.33	0.062	93	45
									502	Total	BS>15	Max @	Max @	Combo	only
															57

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Bliss Score Range: GDC-0973 0.21uM-0.185uM, GDC-0068 0.37-10uM

FIG 10 Enhanced knockdown of both pathway activity compared to single agents alone

BT474M1 (ER+ breast, PI3K K111N, Her2+, Braf G534D?)

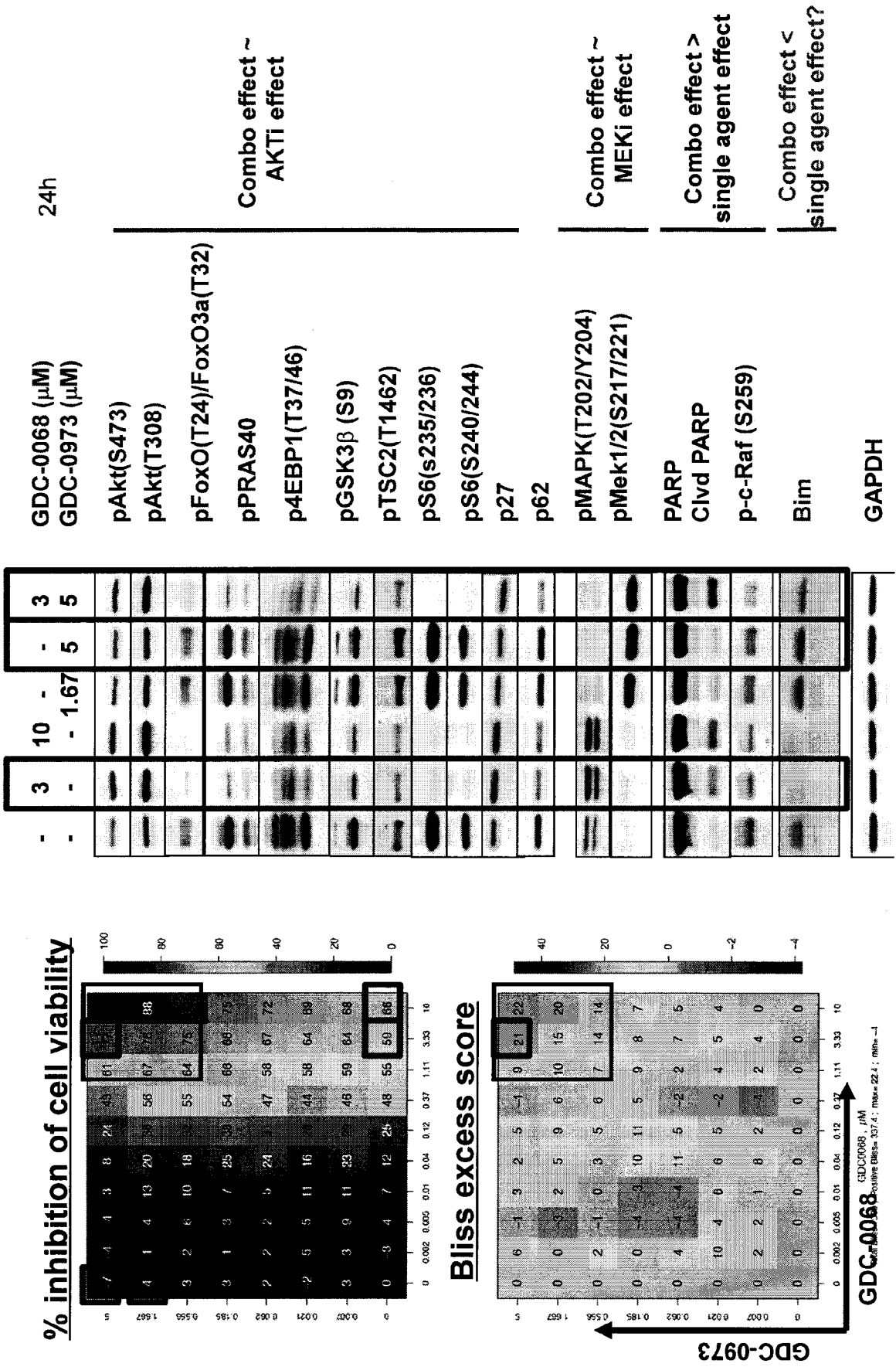


FIG 11 XL518 x GDC0068 combo – MDA-MB-468

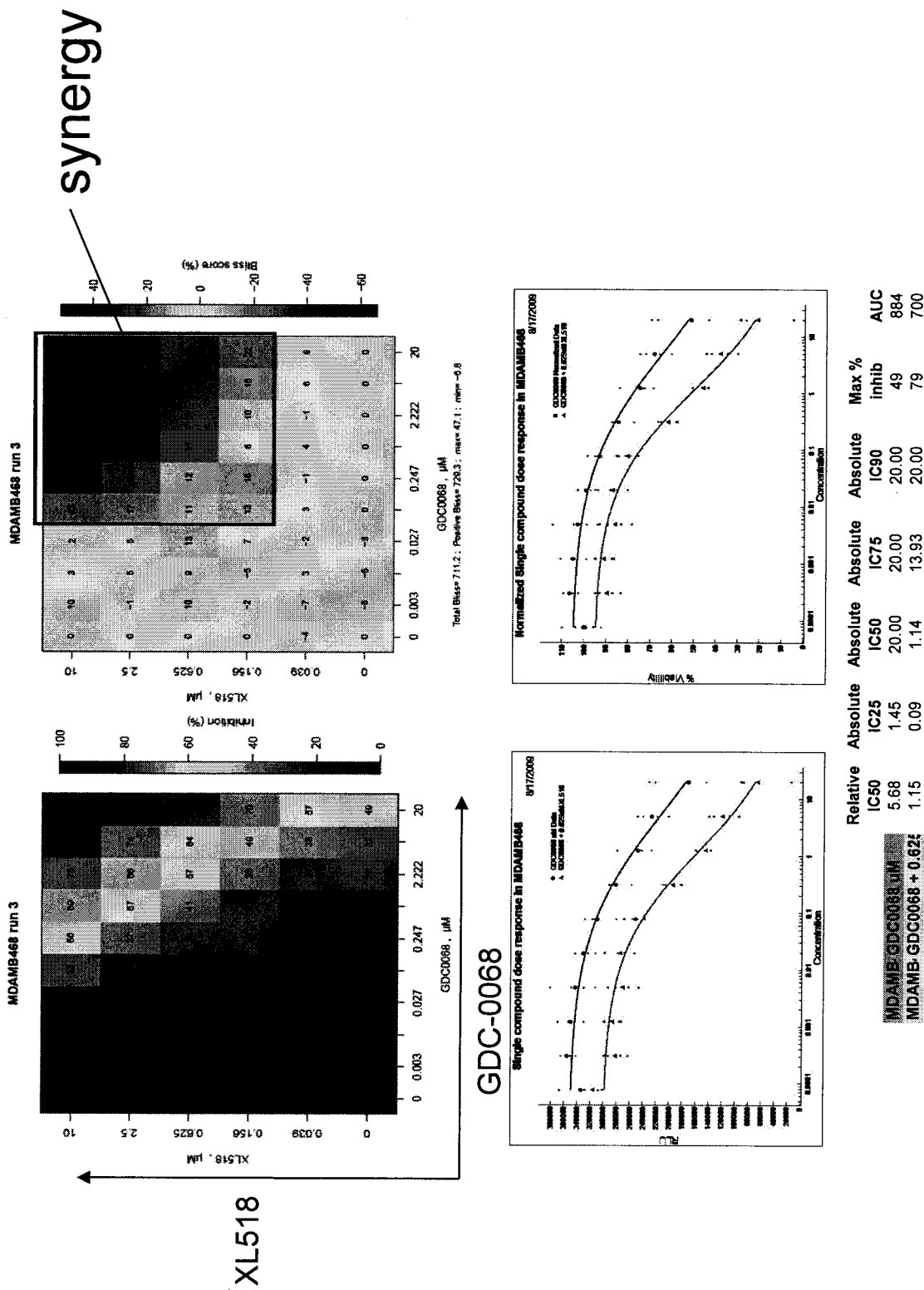


FIG 12 GDC-0973 (MEKi) + GDC0068 combination

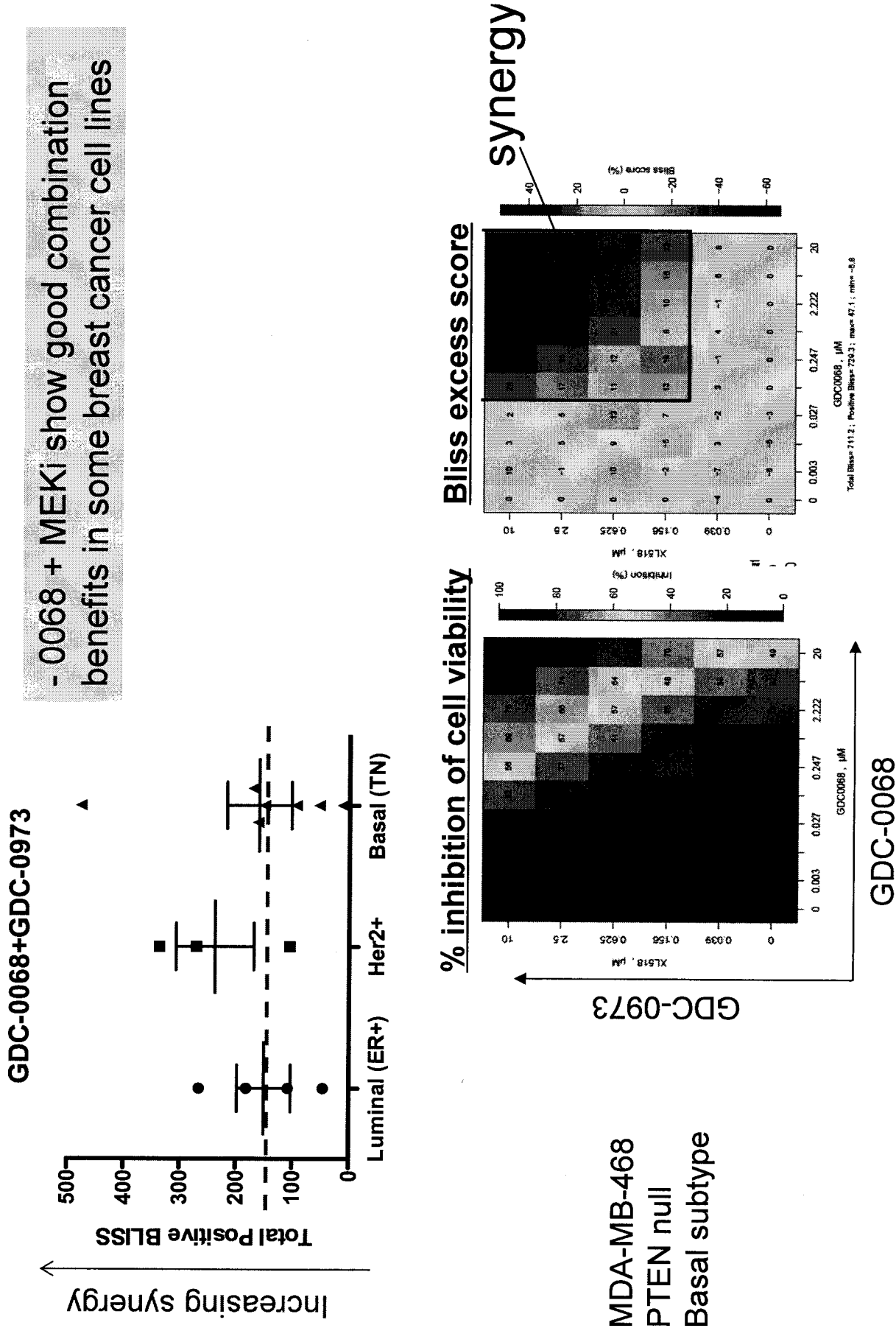


FIG 13 Ovarian

Tissue	Cell line	Akt pathway activation	Ras/Raf activation	RTK	other	IC50s		Bliss Scores	
						GDC-0068	XL-518	Total Positive	Total
Ovarian	OVCAR-3	PI3Kp110amp, p85mut, Akt2amp			p53	9.04	>5	5.75	573
Ovarian	PEO1	ND	ND	ND	ND	>10	1.81	2.44	334
Ovarian	TOV-21G	PTEN-, PI3K H1047Y	Kras G13C			0.67	2.48	2.98	282
Ovarian	SK-OV-3 (PRC)*	PI3K H1047R				>10	>5	2.91	239
Ovarian	JGROV1	PI3K O1069W			p53	0.66	0.39	237	211
Ovarian	A2780 (PRC)*	PTEN mut				>10	0.98	131	43
Ovarian	OV-90		Braf del		p53,p16	9.19	0.39	107	47

XL518									
	cell line	molecular subtype	PI3K activation	MAPK activation	GDC-0068 IC50 (uM)	Run1 6/29/2009	Run2 7/10/2009	Run3 8/17/2009	
ovarian	TOV21G		PTEN/PI3K	KRAS	0.558	s			
ovarian	CAOV3		PIK3CA 4 copies		max				
ovarian	EFO27		PTEN		0.55				
ovarian	OVCAR3		AKT2 amp		1.44				
ovarian	SKOV3		PI3K		max			s	

- Low frequency of coexisting PI3K and Ras pathway mutations
- Raf-1 and A-Raf but not Braf activation have been implicated in ovarian cancers
- synergy seen in cells with no known Ras/Raf mutations, including cells resistant to GDC-0068 alone or both agents

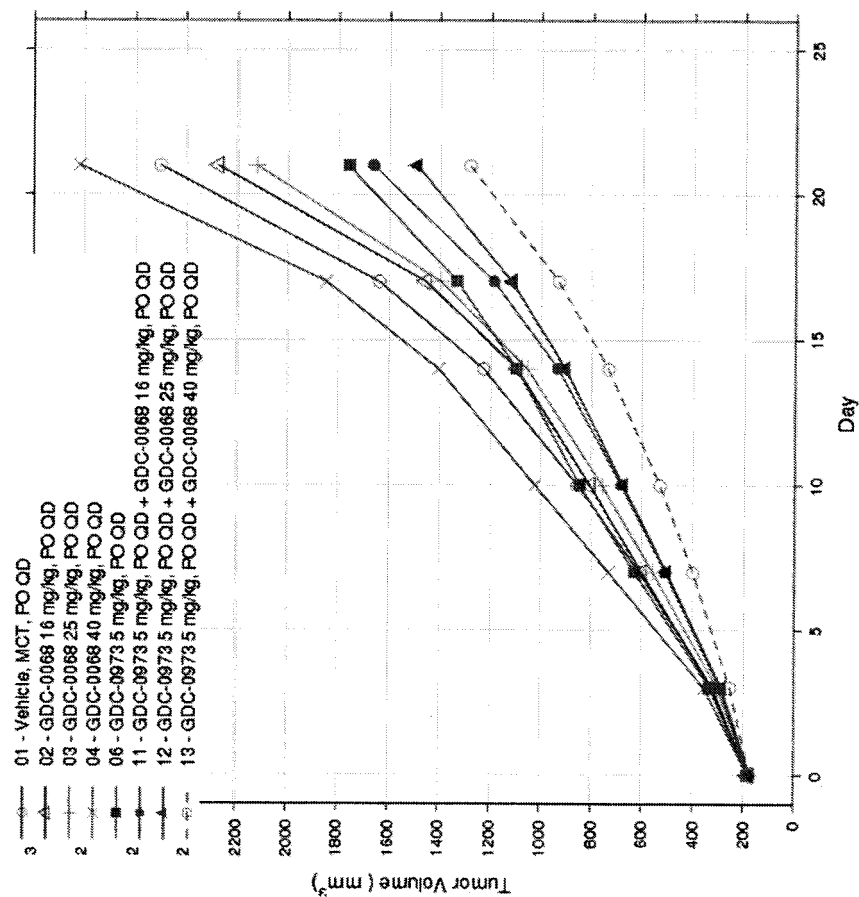
FIG 14 Prostate

		XL518				
	cell line	molecular subtype	PI3K activation	MAPK activation	GDC-0068 IC50 (uM)	Run1 Run2 Run3
prostate	22RV1		PI3K Mut	BRAF	9.09	6/29/2009 7/10/2009 8/17/2009
prostate	DU145		WT		max	s
prostate	PC3		PTEN-		2.26	
prostate	PC3MLN4		PTEN-		11.03	
					IC50>5	

- Low frequency of coexisting PI3K and Ras pathway mutations
- Synergy seen with a line with both PI3K and Braf mutations.

FIG 15 GDC-0068 Dosed PO + GDC-0973 (MEK inhibitor) in MX-1 Breast Tumors

GDC-0973 5mg/kg QD



GDC-0973 15mg/kg Q3D

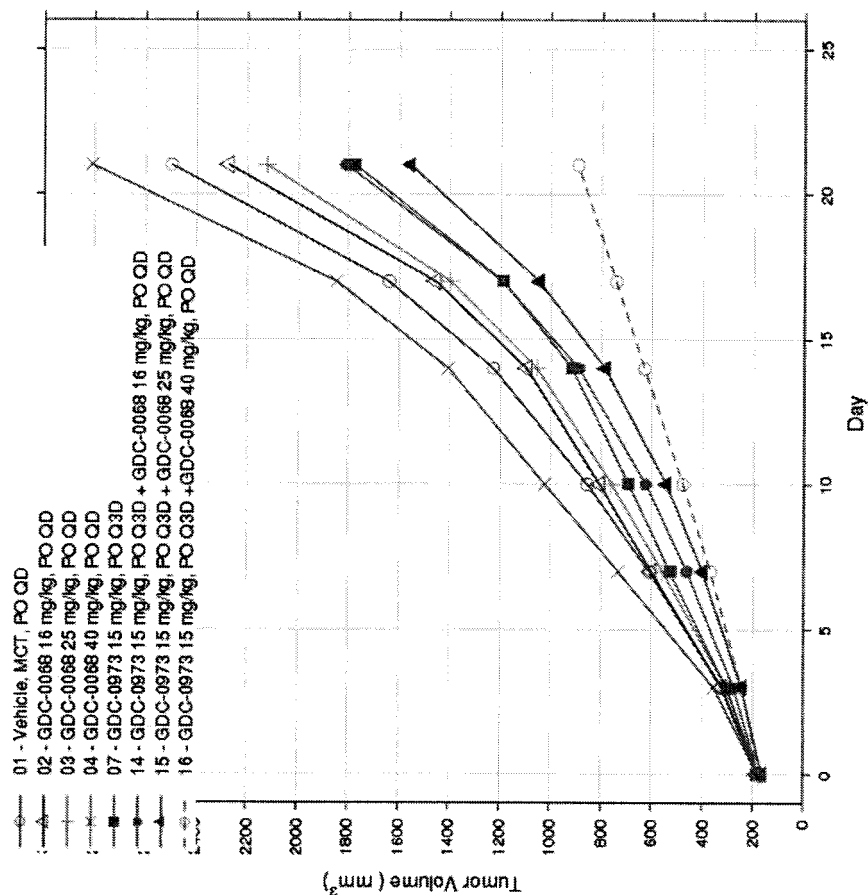


FIG 16 GDC-0068 Dosed PO + GDC-0973 (MEK inhibitor) in H2122 NSCLC Tumors

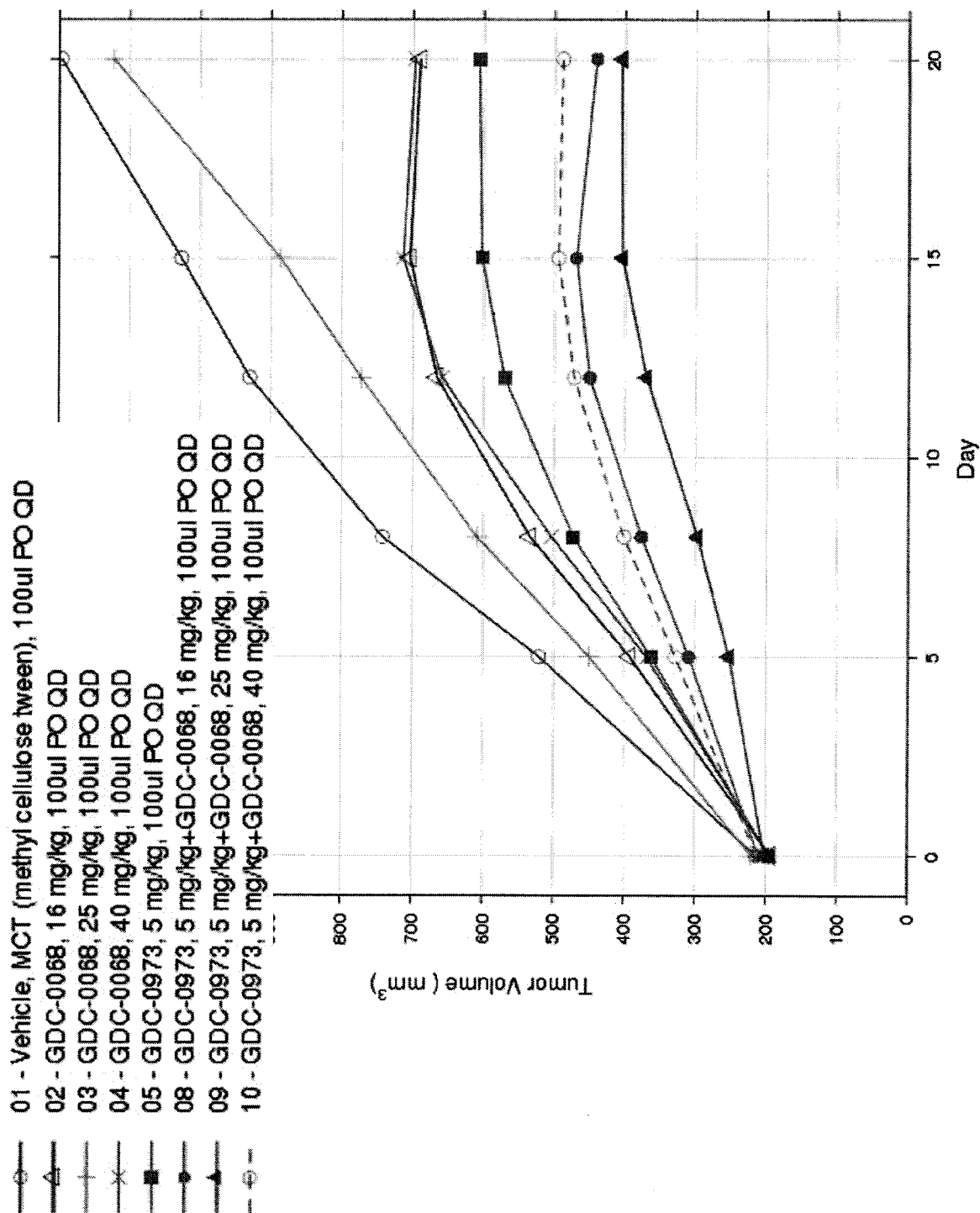


FIG 17 GDC-0068 Dosed PO + GDC-0973 (MEK inhibitor) in SW1990 Pancreatic Tumors

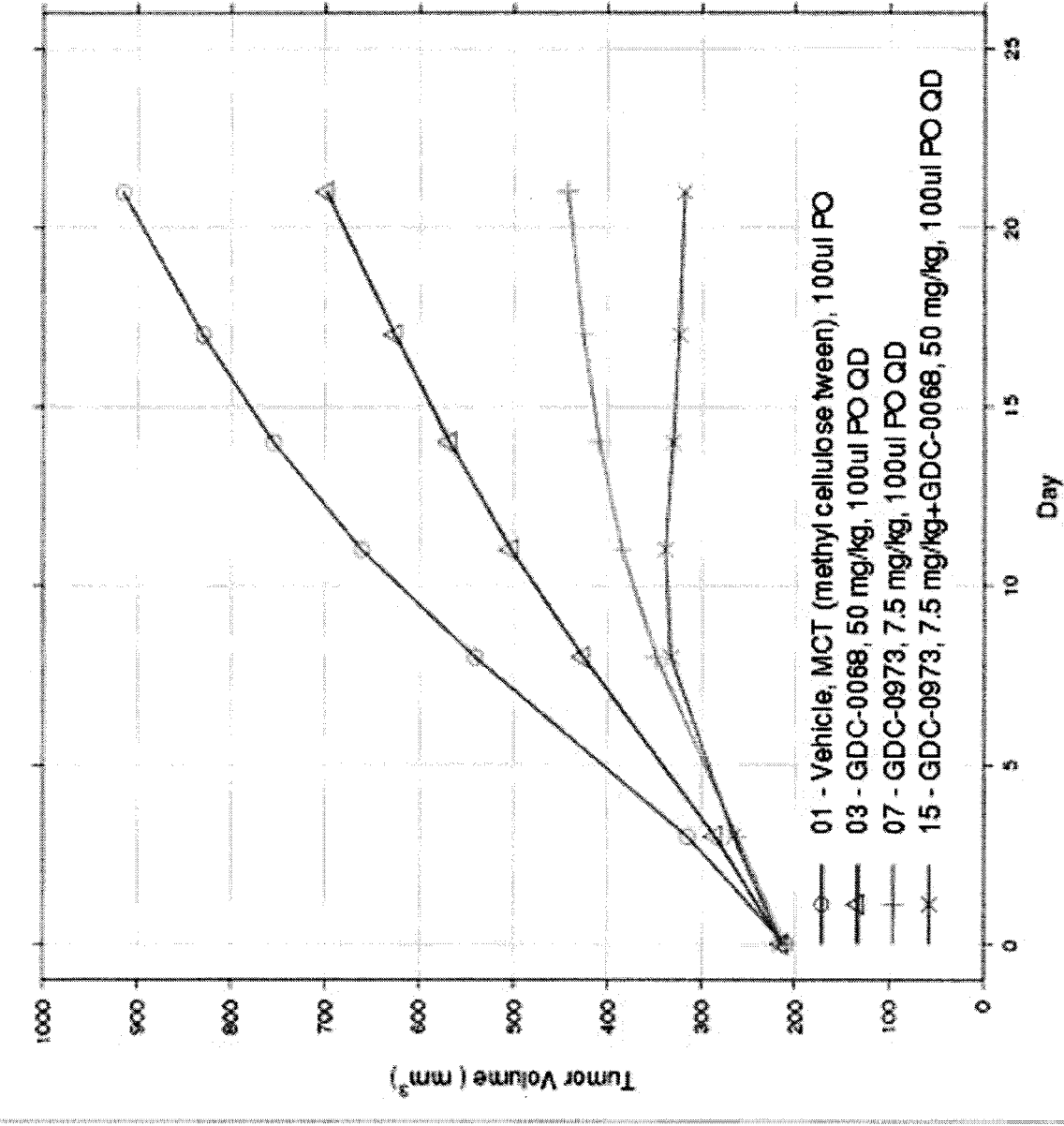


FIG 18 GDC-0068 Dosed PO + GDC-0973 (MEK inhibitor) in Pa_Tu-8902 Pancreatic Tumors

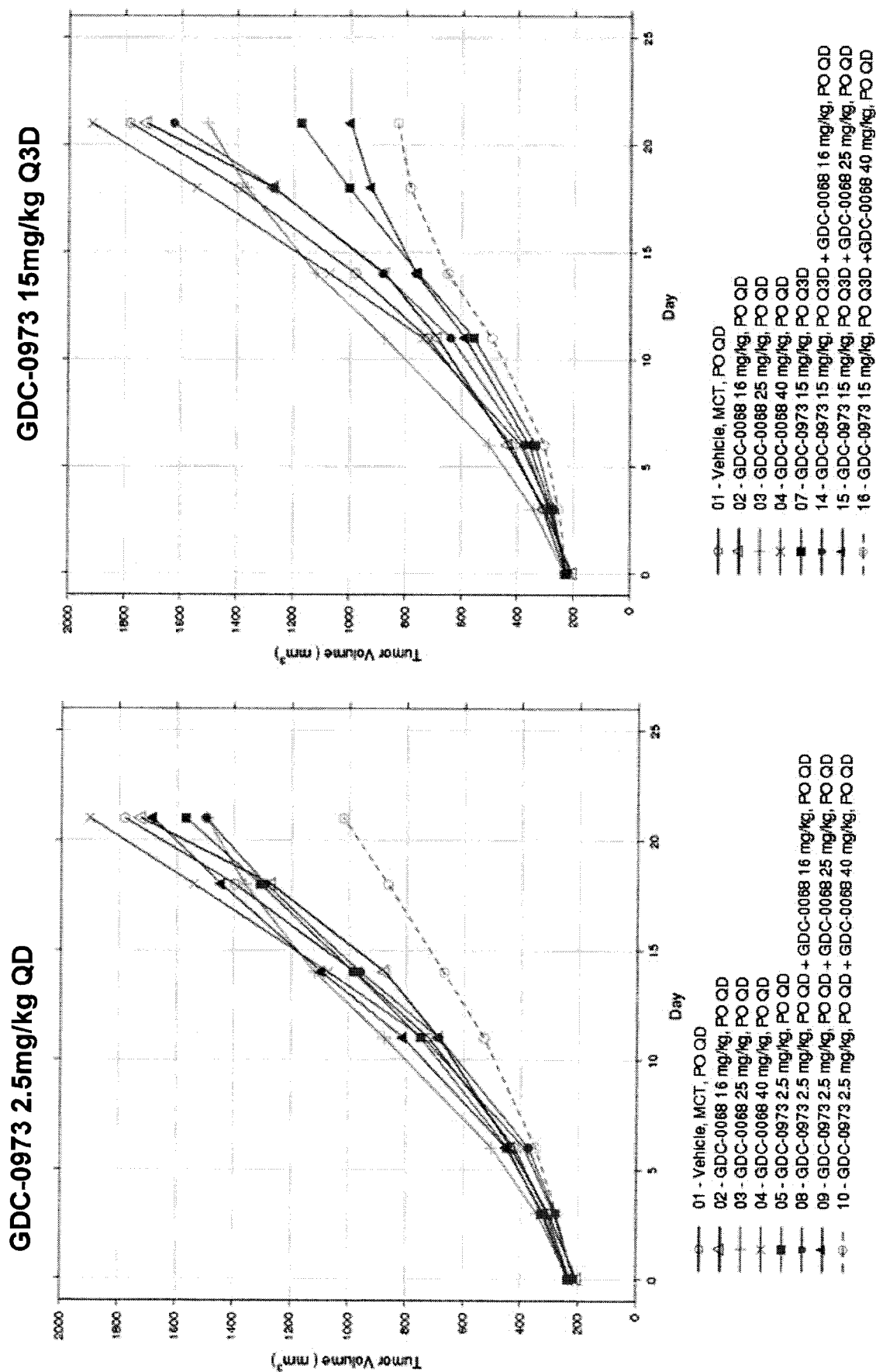


FIG 19 GDC-0068 Dosed PO + GDC-0973 (MEK inhibitor) in 537Mel Melanoma Tumors

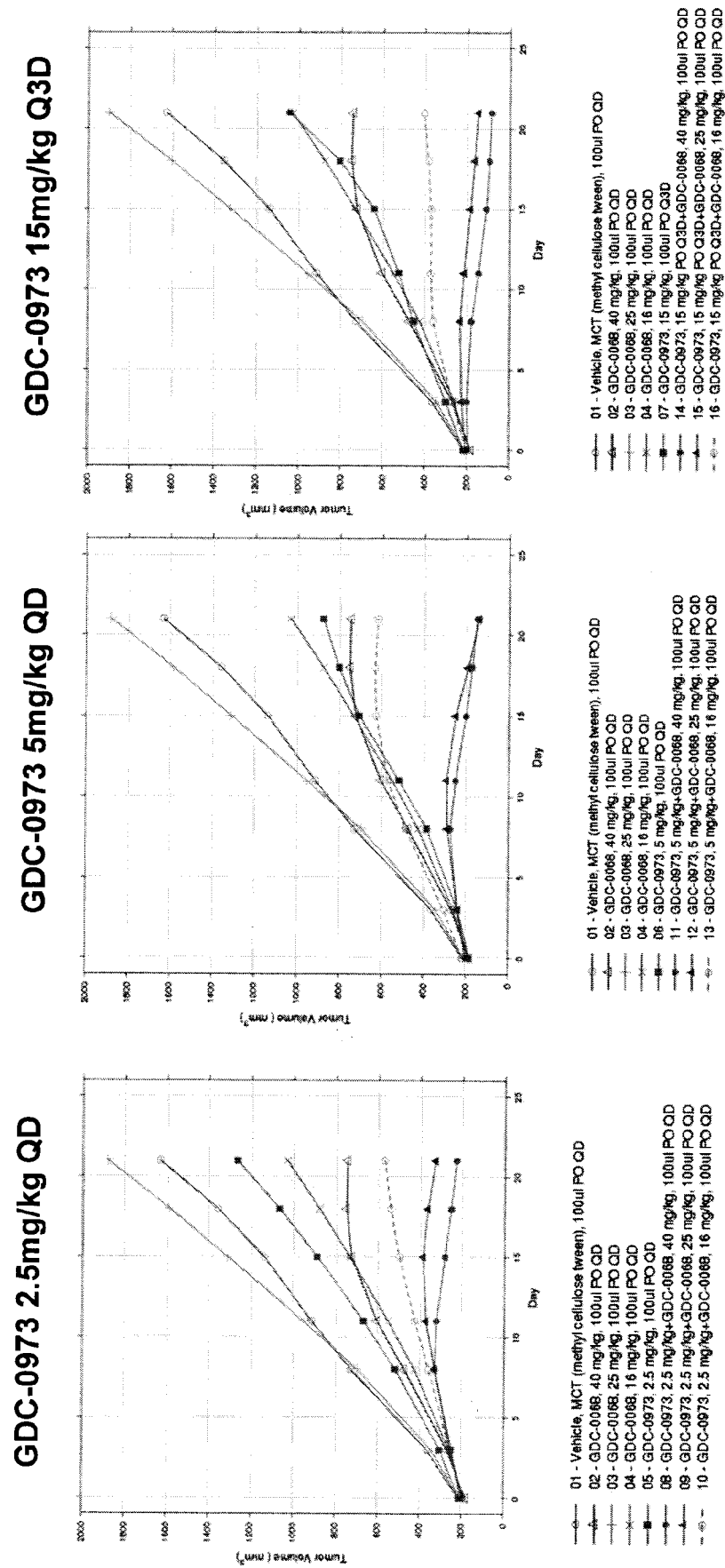


FIG 20 GDC-0068 Dosed PO + GDC-0973 (MEK inhibitor) in A2058 Melanoma Tumors

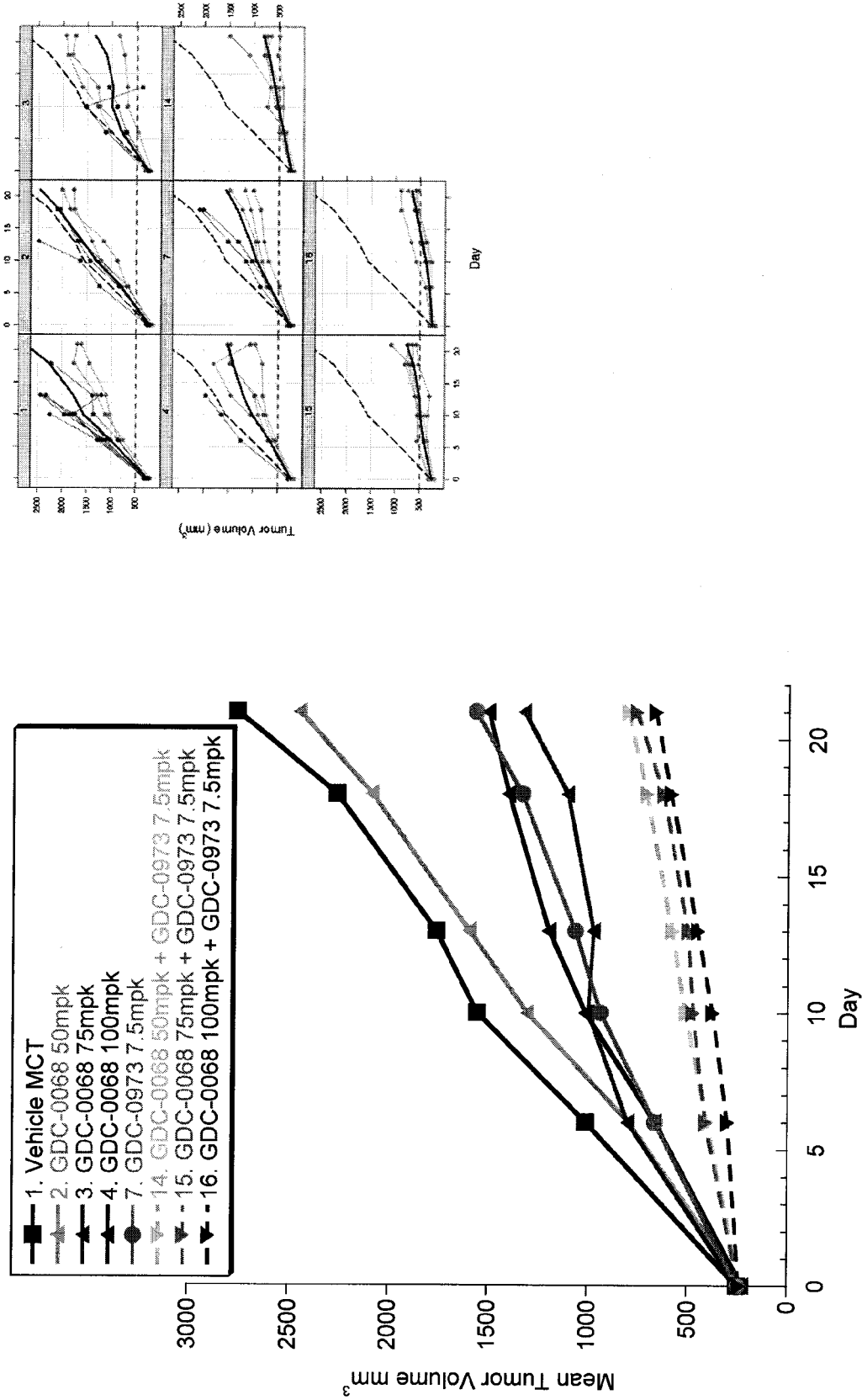


FIG 21 GDC-0068 Dosed PO + GDC-0973 (MEK inhibitor) in HCT-116 Colorectal Tumors

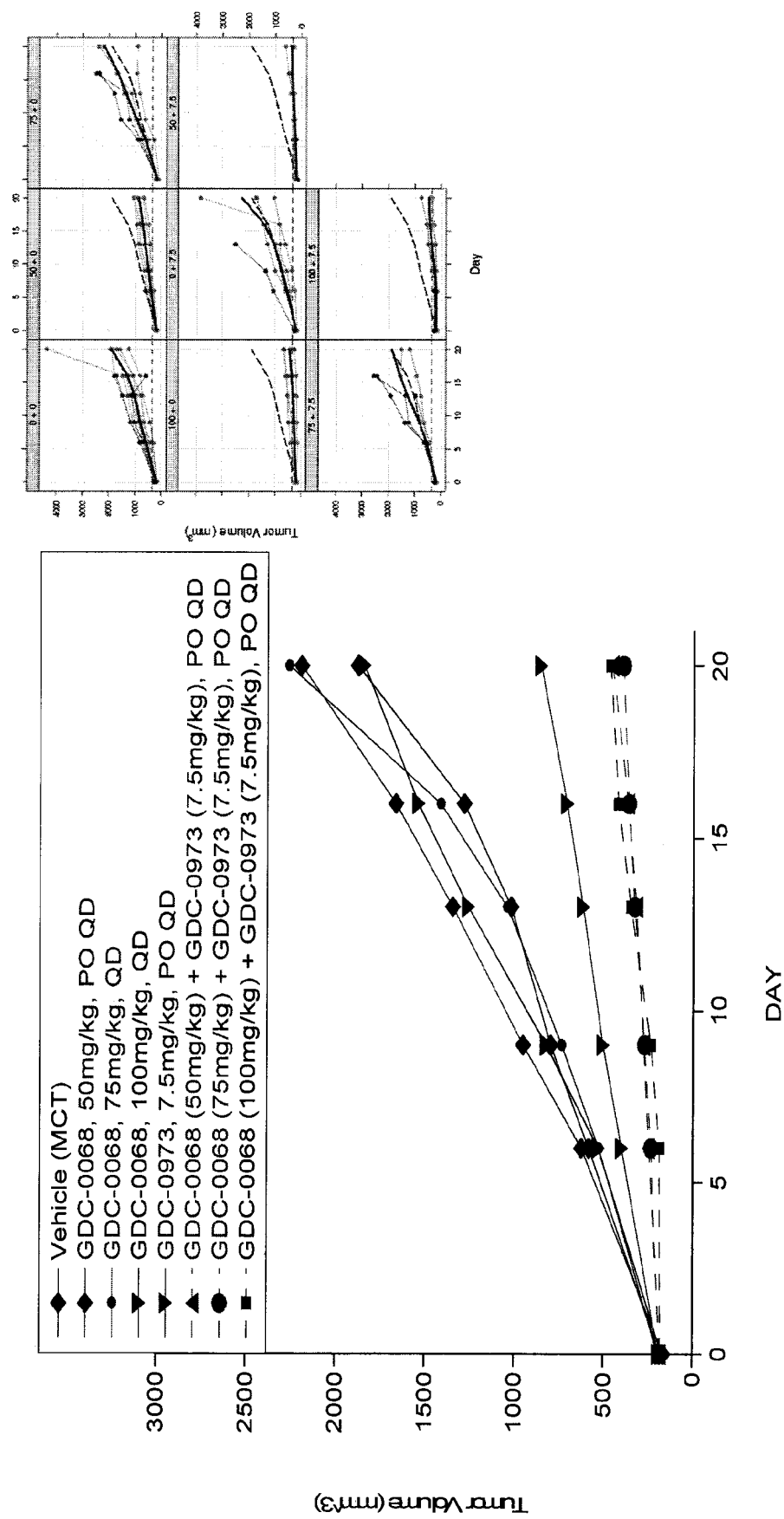


FIG 22a GDC-0068 and GDC-0973 Combination Synergy in Multiple Cell Lines

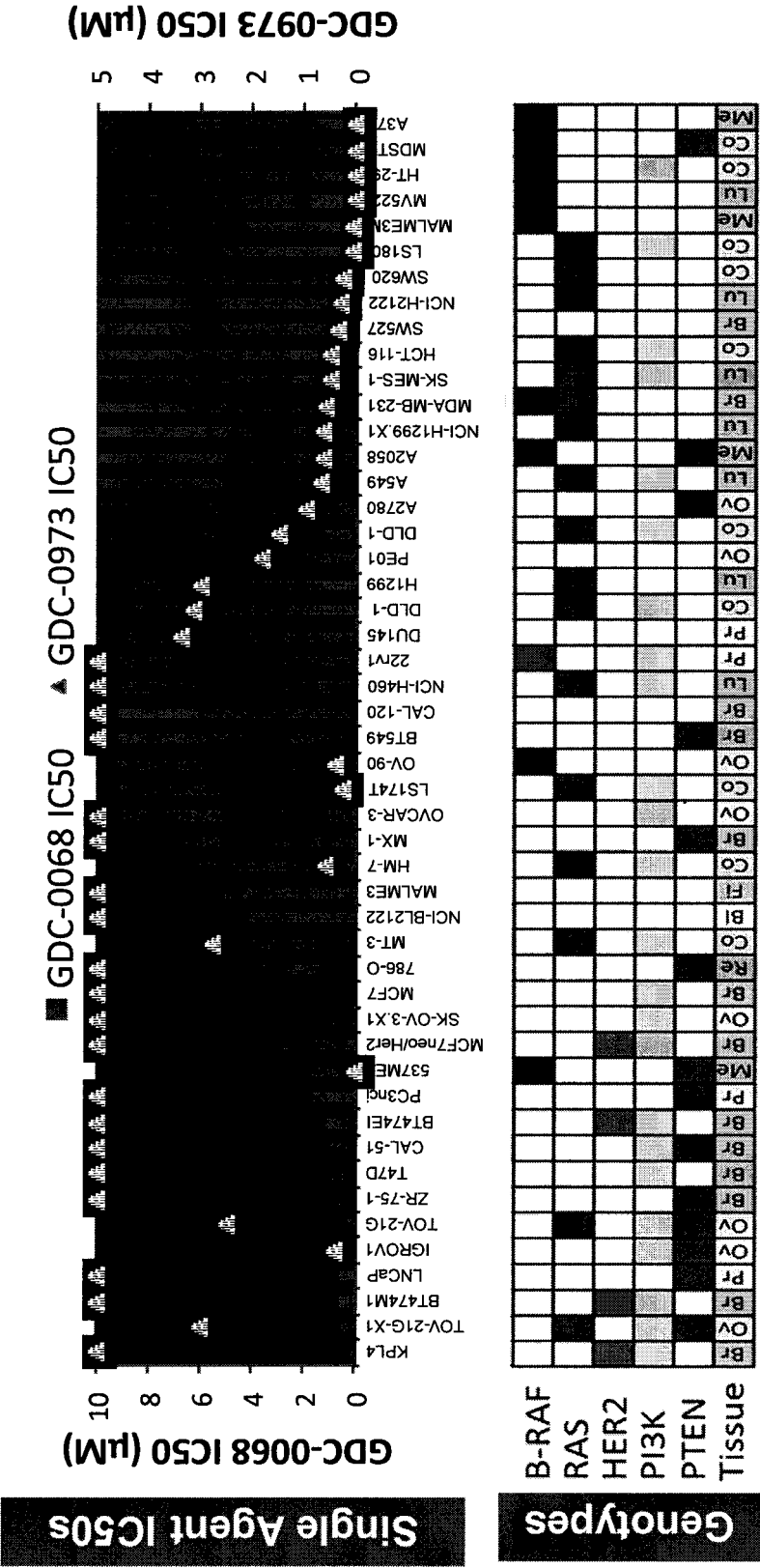


FIG 22b GDC-0068 and GDC-0973 Combination Synergy in Multiple Cell Lines

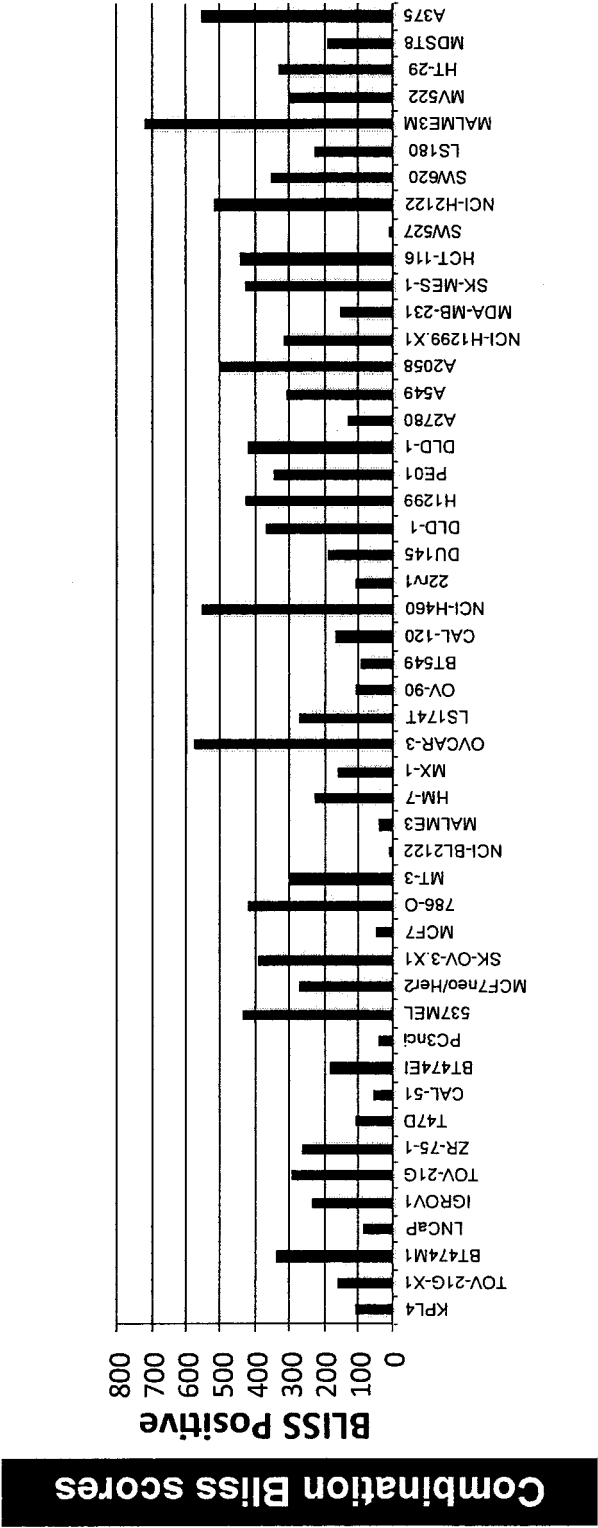


FIG 23

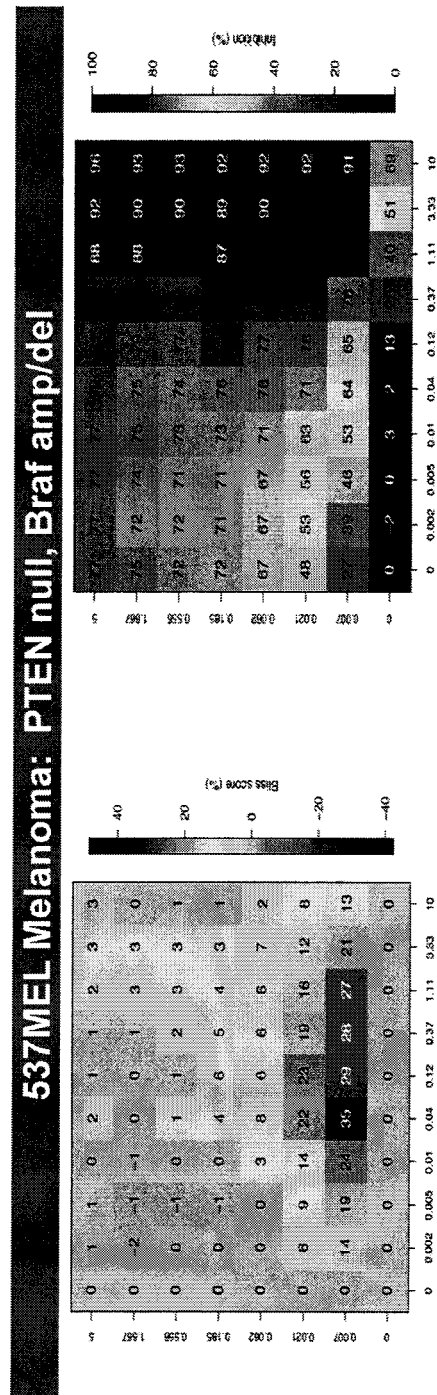


FIG 24

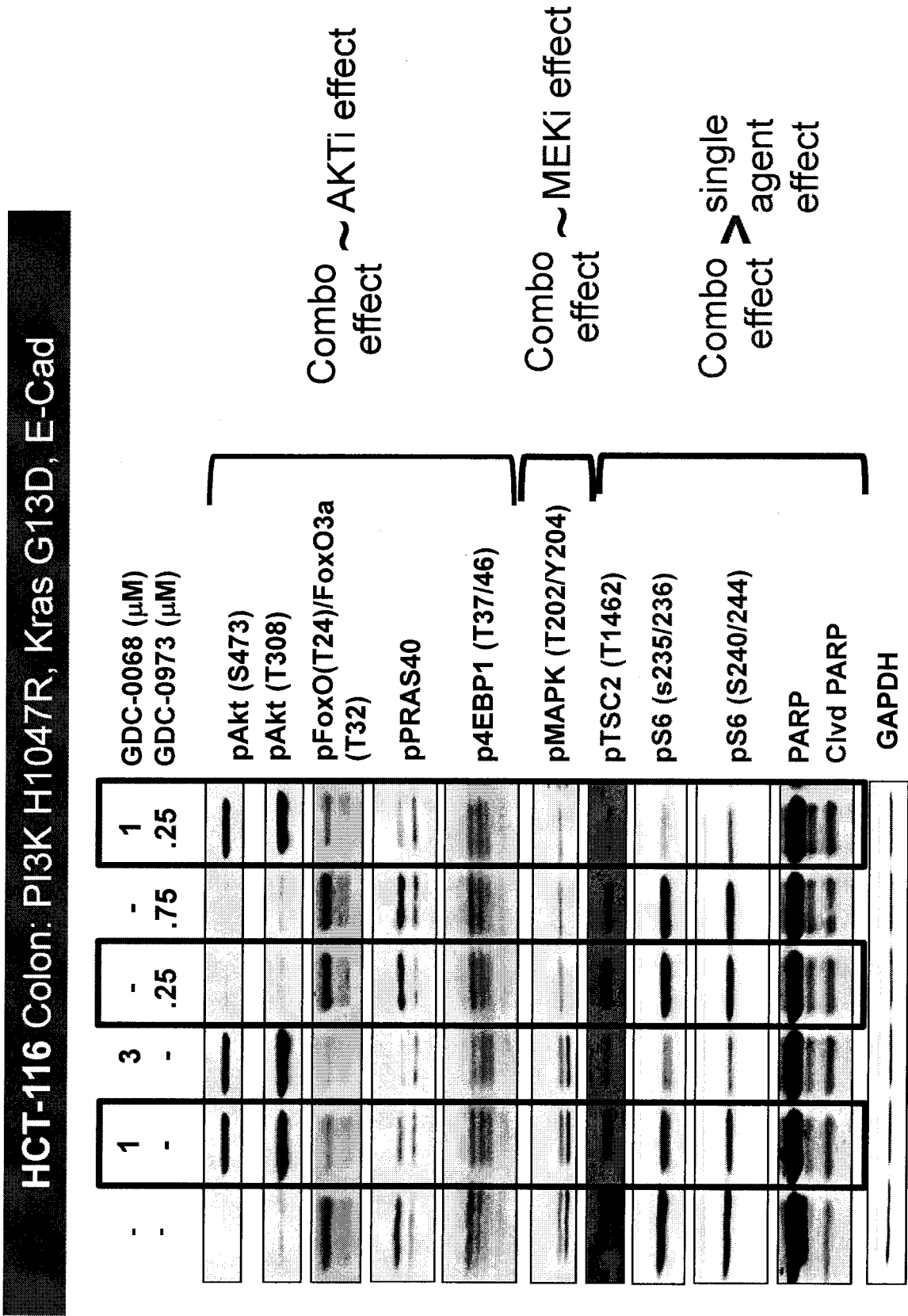
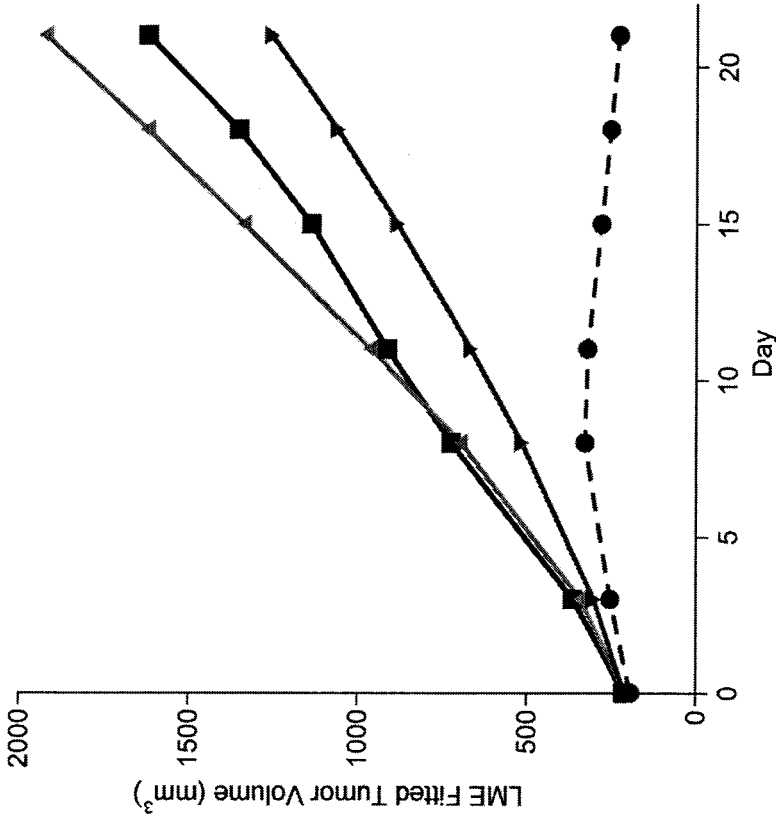


FIG 25

537MEL Melanoma: PTEN null Braf amp/del



Improved TGI seen in combination groups

- **TGI of combination is 81%**
- TGI of single agent GDC-0068 activity <0%
- TGI of single agent GDC-0973 is 30%

FIG 26

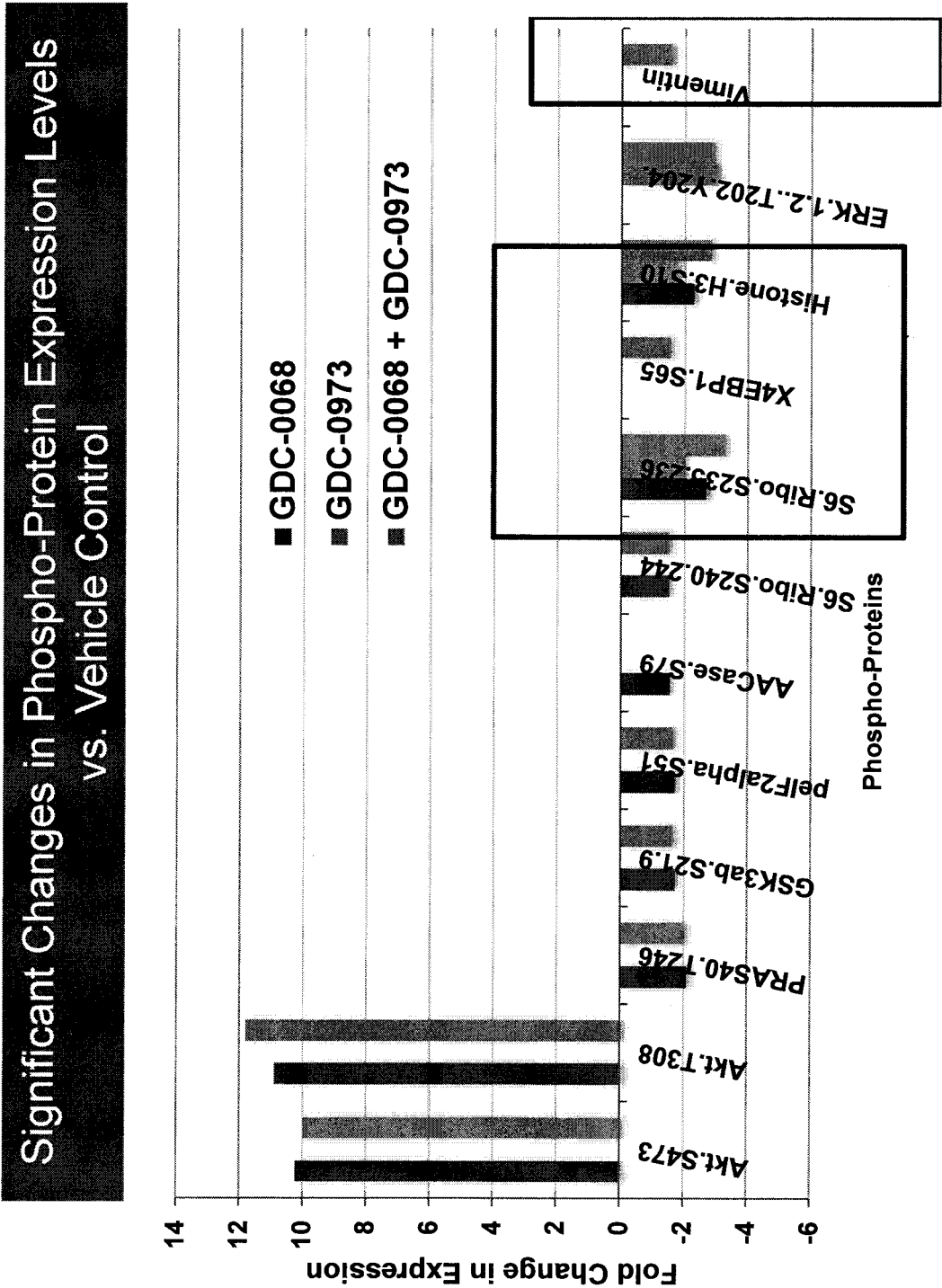


FIG 27

Significant Changes in Phospho-Protein Expression Levels in the Combination vs. Either Single Agent

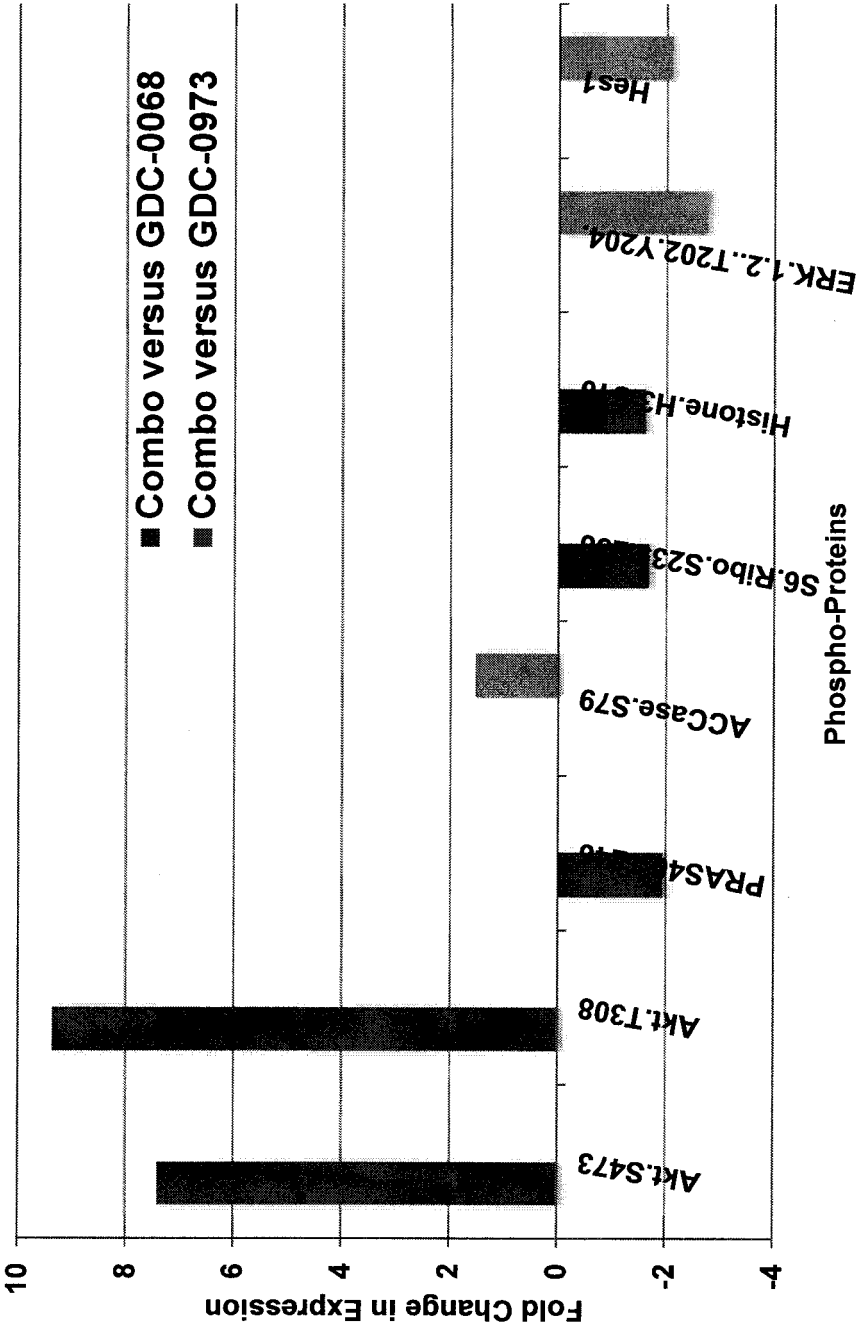


FIG 28

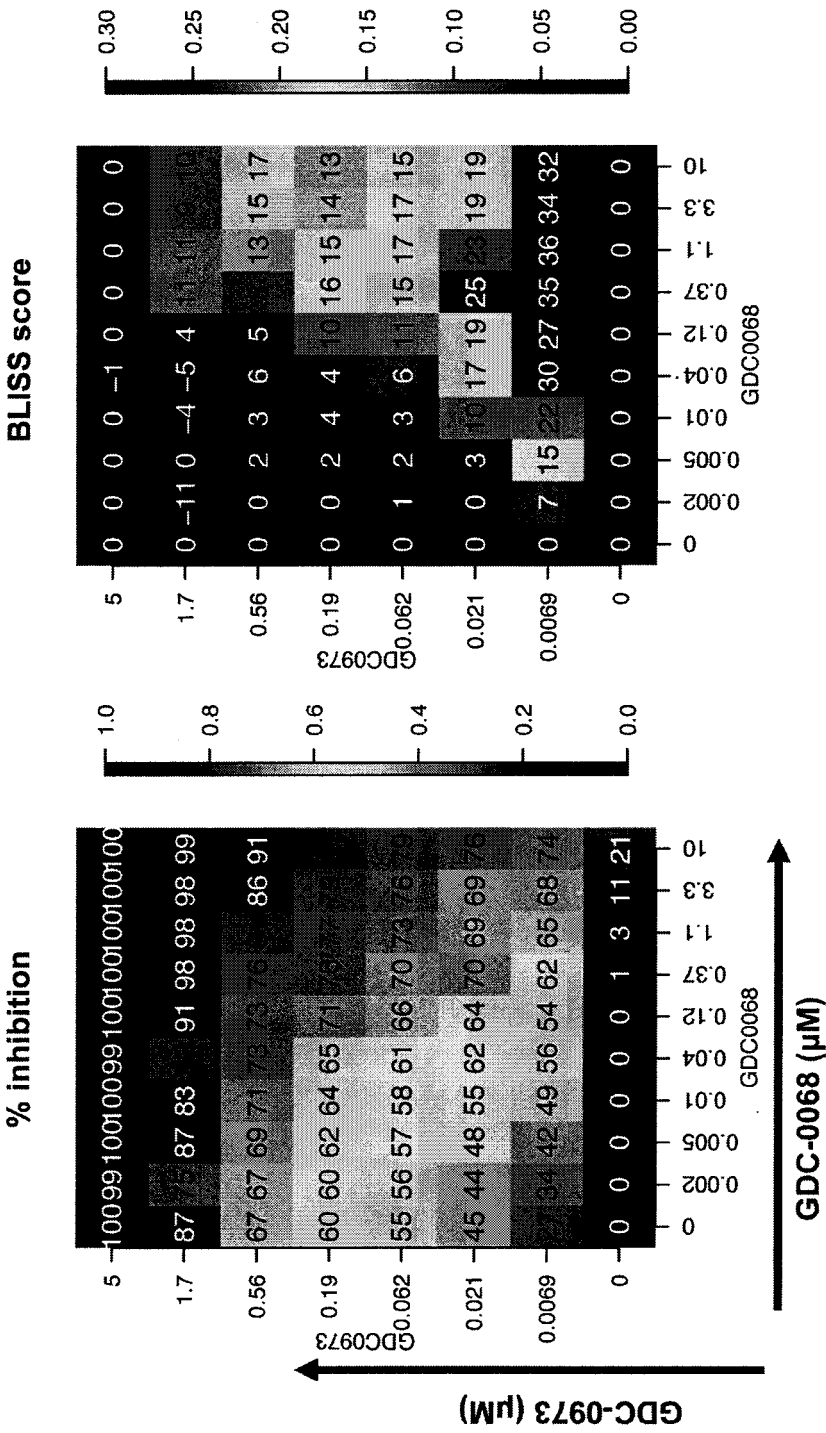


FIG 29

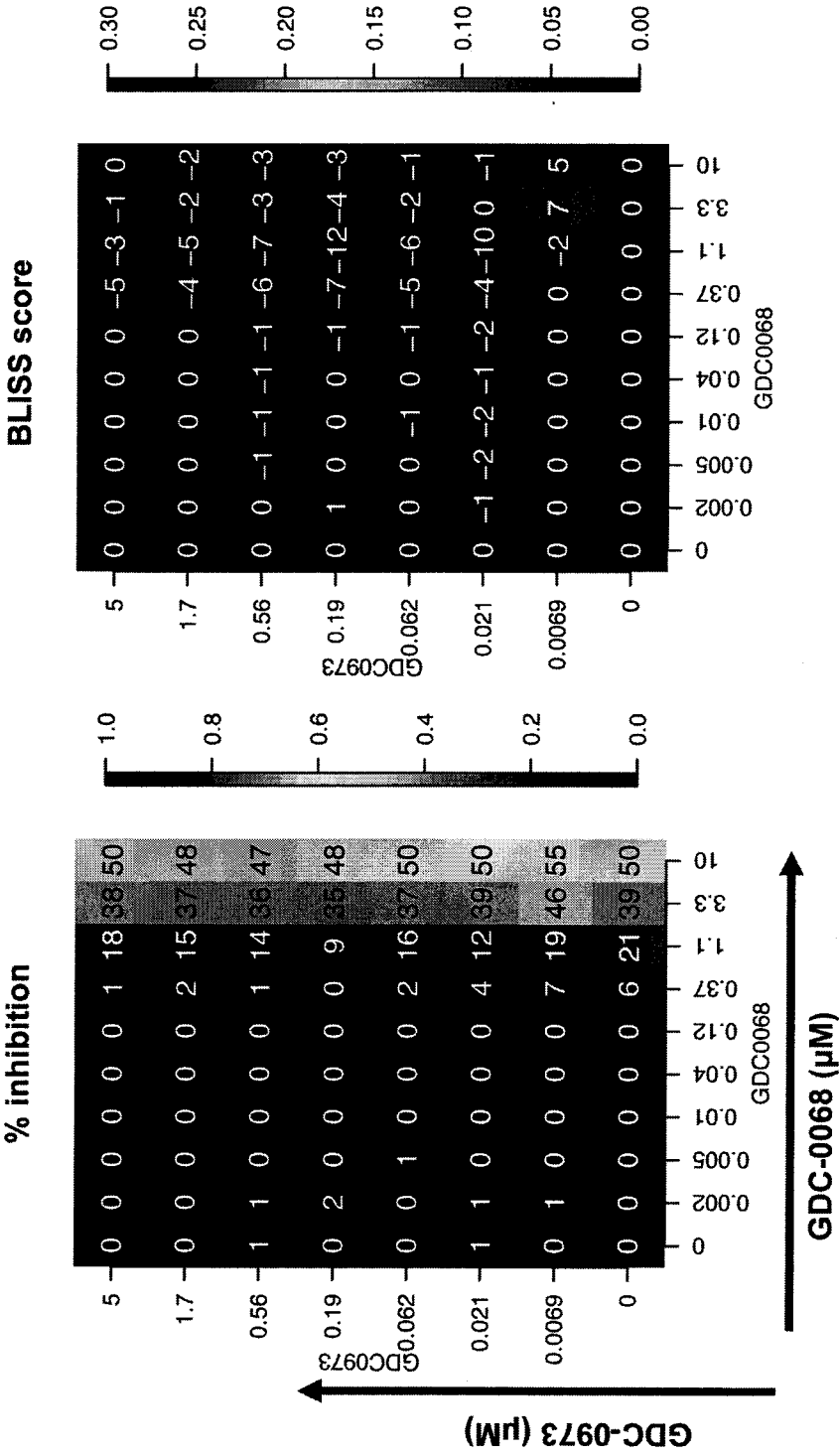
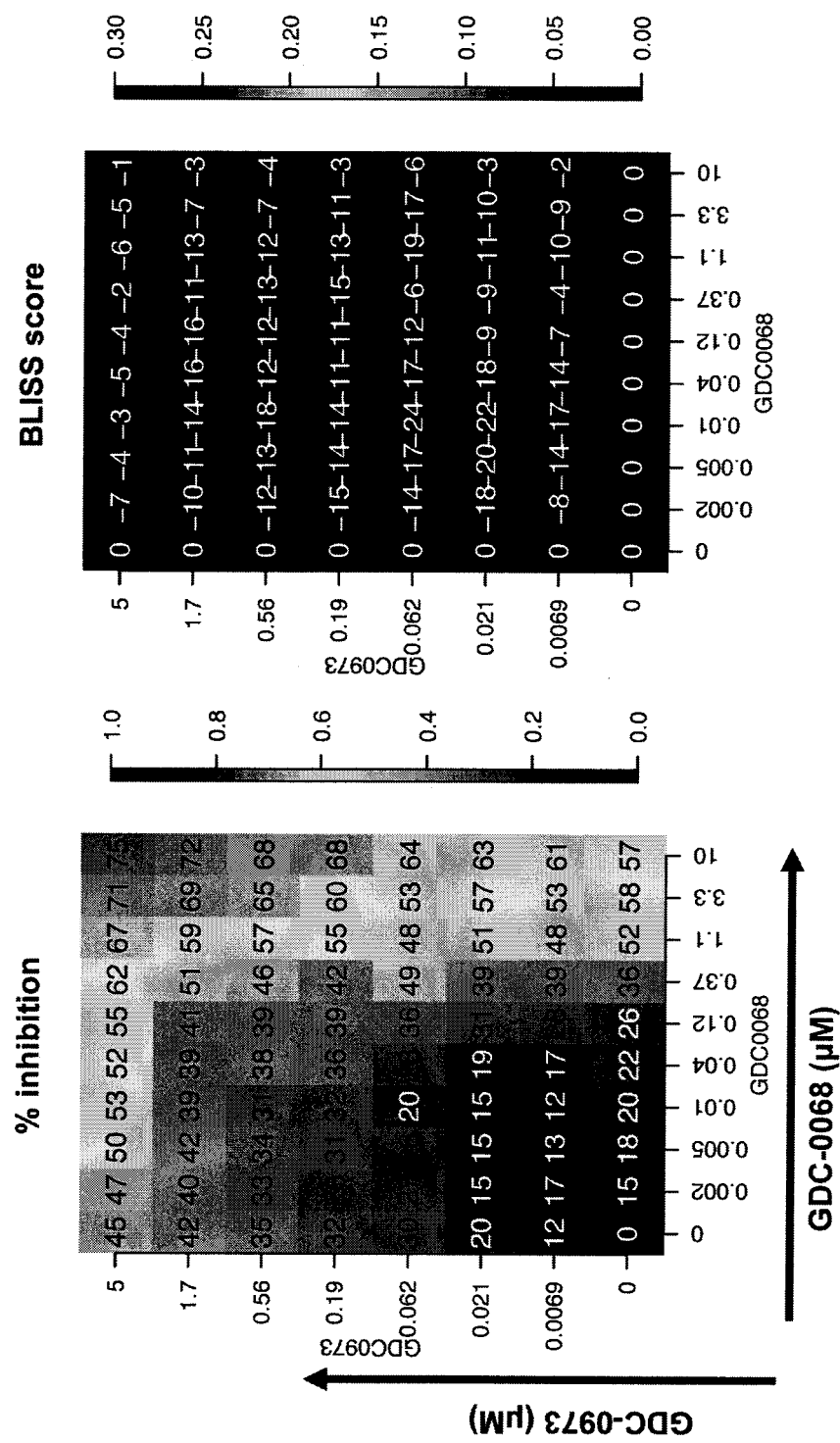


FIG 30



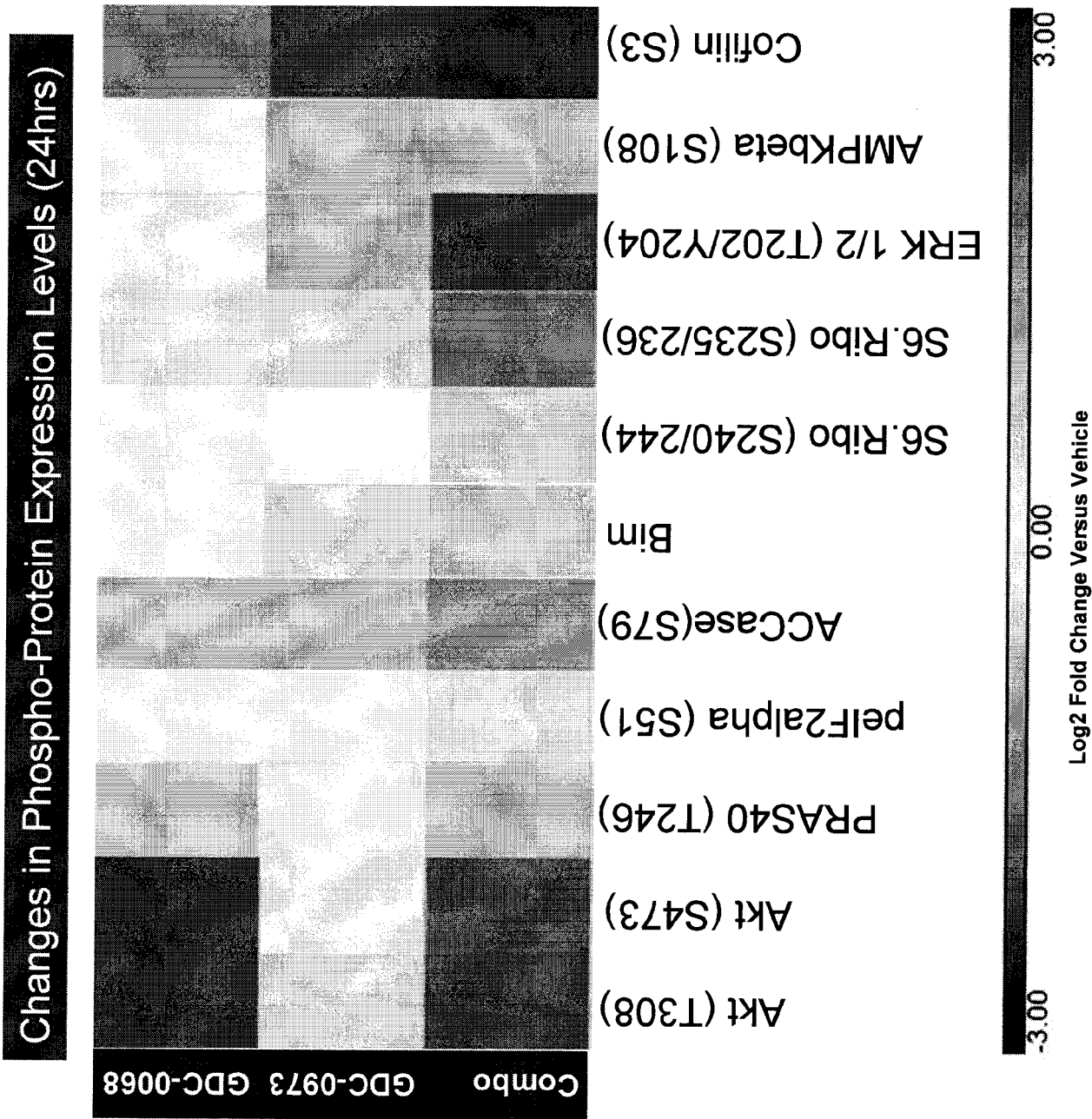


FIG 31