

Figures

Example	AZD7762	Imatinib	Sunitinib	Regorafenib
HTRF IC₅₀ [nM] PDGFRA-D842V KIT-D816H PDGFRA-wt KIT-wt	0.2 ± 0.1 0.3 ± 0.1 <0.1 0.9 ± 0.9	774 ± 432 331 ± 160 2.8 ± 1.5 40 ± 7	152 ± 13 52 ± 14 3.3 ± 1.1 7.9 ± 1.8	186 ± 62 220 ± 102 4.2 ± 0.4 19 ± 8
PDGFRA CTG GR₅₀ [nM] GIST48B T1-a-D842V T1-a-D842V+ G680R T1-a-D842V+ G652E/V658A	299 ± 45 6 ± 2 315 ± 62 44 ± 4	≥10000 1286 ± 254 8929 ± 1005 8800 ± 2080	2714 ± 234 1004 ± 172 5800 ± 3160 1020 ± 214	4829 ± 2507 370 ± 133 2929 ± 281 968 ± 197
c-KIT CTG GR₅₀ [nM] GIST-T1 T1-D816E T1-V654A	17 ± 0 17 ± 2 45 ± 2	39 ± 25 673 ± 63 1221 ± 244	30 ± 18 4825 ± 647 183 ± 166	69 ± 34 655 ± 117 641 ± 159
Example	AZD7762	Ripretinib	Avapritinib	Ponatinib
HTRF IC₅₀ [nM] PDGFRA-D842V KIT-D816H PDGFRA-wt KIT-wt	0.2 ± 0.1 0.3 ± 0.1 <0.1 0.9 ± 0.9	0.7 ± 0.3 1.8 ± 0.4 0.6 ± 0.2 1.7 ± 0.5	0.1 ± 0 0.2 ± 0.1 <0.1 5.8 ± 1.4	16 ± 7 13 ± 5 0.1 ± 0 1.0 ± 0.4
PDGFRA CTG GR₅₀ [nM] GIST48B T1-a-D842V T1-a-D842V+ G680R T1-a-D842V+ G652E/V658A	299 ± 45 6 ± 2 315 ± 62 44 ± 4	1432 ± 223 474 ± 30 4284 ± 237 2073 ± 416	1269 ± 166 9 ± 2 1200 ± 101 555 ± 62	293 ± 30 43 ± 8 390 ± 103 554 ± 233
c-KIT CTG GR₅₀ [nM] GIST-T1 T1-D816E T1-V654A	17 ± 0 17 ± 2 45 ± 2	6 ± 2 32 ± 6 118 ± 16	7 ± 2 131 ± 27 243 ± 125	2 ± 1 31 ± 7 134 ± 35

Figure 1

Cell line	GR50 [nM] – 72 h
GIST-T1-a-PDGFR α -D842V	9
GIST-T1-a-N659K	30
GIST-T1-a-N659K+674R	39
GIST-T1-a-842V+QGP	20
GIST-T1-a-842V+652E	20
GIST-T1-a-842V+652E+658A	20
GIST-T1-a-842V+680R	180
GIST-T1	5
GIST882	40
GIST430	3
GIST430/654	7
GIST48B (kit negative)	194
H1781 (HER2 G776del insVC)	210
H1975 (EGFR L858R+T790M)	700
A431 (EGFR-WT-OE)	90
A549 (EGFR-WT-OE)	250
JUPS	500
LPS141	500
LPS853	700
SK-LMS-1	700
LMS03	600
LMS04	800
LMS05	400

Figure 2

Driver	Cell line	Imatinib	Sunitinib	Regorafenib	Ripretinib	Avapritinib	AZD7762
KIT	T1-AYdup (e9)	115	4	164	84	88	27
	GIST-T1 (e11)	18	9	34	8	20	2
	GIST430 (e11)	11	4	23	4	27	1
	GIST882 (e13)	103	26	211	99	330	21
	T1-AY-V654A (e9+13)	>1000	21	566	106	534	30
	T1-V654A (e11+13)	747	15	314	71	77	1
	GIST430/654 (e11+13)	>1000	47	527	120	217	6
	T1-T670I (e11+14)	>1000	28	106	714	349	4
	T1-C809G (e11+17)	310	56	104	11	30	1
	T1-D816A (e11+17)	346	>1000	218	16	57	3
	T1-D816E (e11+17)	445	>1000	172	11	37	1
	T1-D820A (e11+17)	642	>1000	440	8	18	2
	T1-D820Y (e11+17)	97	160	116	7	14	1
	T1-AY-N822K (e9+17)	931	>1000	157	16	185	7
	T1-N822K (e11+17)	>1000	>1000	366	22	14	1
	T1-A829P (e11+18)	>1000	>1000	437	26	84	6
	T1-V654A-829 (e11+13+18)	>1000	82	>1000	>1000	46	1
	T1-V654A-816A (e11+13+17)	>1000	825	>1000	>1000	119	7
	T1-V654A-822 (e11+13+17)	>1000	194	>1000	>1000	75	2
PDGFRA	T1-a-D842V (e18)	>1000	>1000	673	1046	20	9
	T1-a-D842V +G680R (e18+15)	>1000	>1000	>1000	>1000	>1000	241
	T1-a-N659K (e14)	176	123	127	58	300	30
	T1-a-N659K-T674R (e14+15)	>1000	>1000	406	197	>1000	39
GIST48B (KIT-negative)		>1000	>1000	>1000	>1000	>1000	194

Figure 3

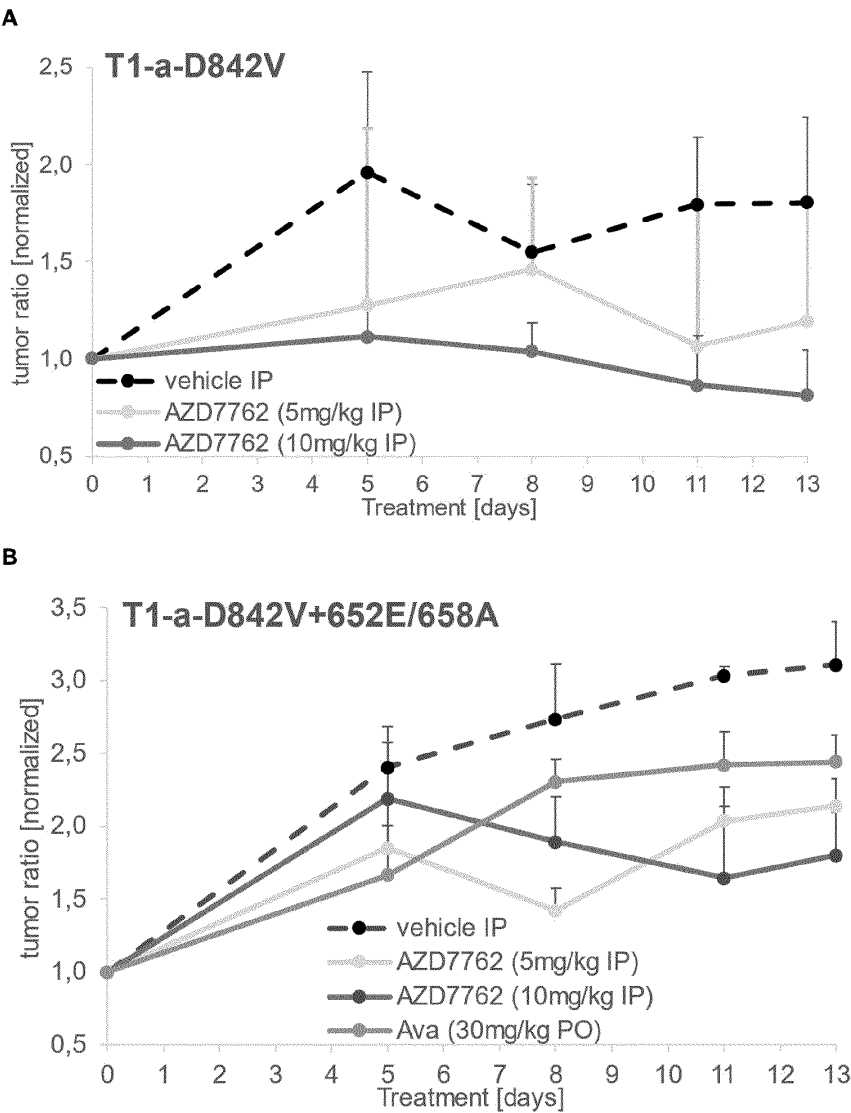


Figure 4

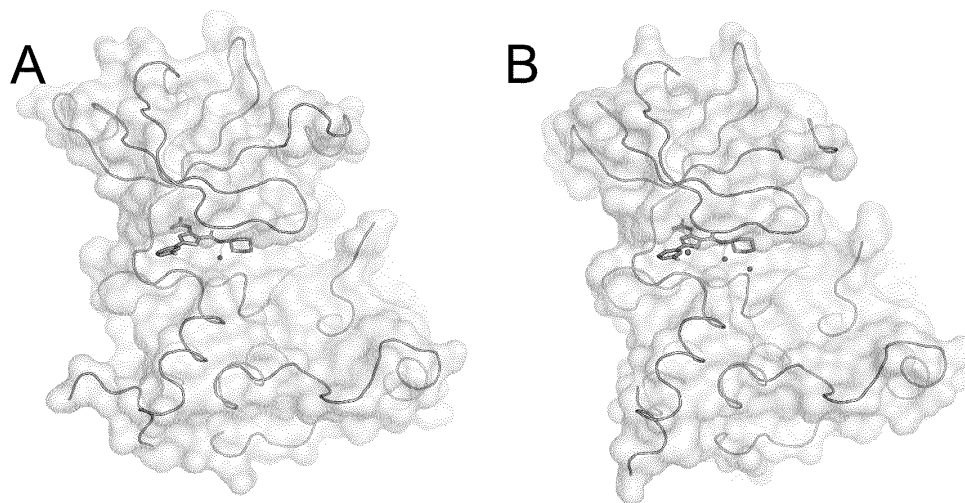


Figure 5

Example	AZD7762	3a.6	3a.7	3a.15	3a.22
HTRF IC₅₀ [nM]					
PDGFRA-D842V	0.2 ± 0.1	0.5 ± 0.7	0.9 ± 0.6	<0.1	0.8 ± 0.4
KIT-D816H	0.3 ± 0.1	0.3 ± 0.3	0.3 ± 0.2	0.3 ± 0.1	0.2 ± 0.1
PDGFRA-wt	<0.1	0.3 ± 0.2	0.4 ± 0.2	-	-
KIT-wt	0.9 ± 0.9	0.4 ± 0.3	0.3 ± 0.3	-	-
PDGFRA CTG IC₅₀ [nM]					
GIST48B	299 ± 45	827 ± 76	588 ± 157	1288 ± 173	1276 ± 45
T1-a-D842V	6 ± 2	8 ± 2	9 ± 3	14 ± 3	10 ± 3
T1-a-D842V+G680R	315 ± 62	1067 ± 52	720 ± 102	2654 ± 541	3392 ± 244
T1-a-D842V+G652E/V658A	44 ± 4	64 ± 6	65 ± 15	98 ± 32	77 ± 2
c-KIT CTG GR₅₀ [nM]					
GIST-T1	17 ± 0	14 ± 4	12 ± 4	49 ± 10	32 ± 2
T1-D816E	17 ± 2	11 ± 3	12 ± 0	20 ± 1	25 ± 5
T1-V654A	45 ± 2	19 ± 8	16 ± 6	82 ± 15	60 ± 12

Figure 6

Example	AZD7762	3a.26	3a.24	3a.25	3a.3
HTRF IC₅₀ [nM]					
PDGFRA-D842V	0.2 ± 0.1	0.1 ± 0.0	0.2 ± 0.1	0.1 ± 0.0	0.1 ± 0.1
KIT-D816H	0.3 ± 0.1	0.3 ± 0.1	0.1 ± 0.0	0.1 ± 0.0	0.3 ± 0.2
PDGFRA-wt	<0.1	0.1 ± 0.0	-	-	<0.1
KIT-wt	0.9 ± 0.9	1.1 ± 0.3	-	-	0.1 ± 0.0
PDGFRA CTG IC₅₀ [nM]					
GIST48B	299 ± 45	305 ± 125	60 ± 17	1188 ± 115	304 ± 33
T1-a-D842V	6 ± 2	3 ± 0	1 ± 0	5 ± 1	3 ± 2
T1-a-D842V+G680R	315 ± 62	247 ± 6	63 ± 19	539 ± 51	301 ± 48
T1-a-D842V+G652E/V658A	44 ± 4	23 ± 4	10 ± 1	37 ± 4	24 ± 7
c-KIT CTG GR₅₀ [nM]					
GIST-T1	17 ± 0	24 ± 2	8 ± 1	32 ± 6	-
T1-D816E	17 ± 2	20 ± 4	10 ± 2	28 ± 2	-
T1-V654A	45 ± 2	57 ± 4	23 ± 5	62 ± 19	-

Figure 7

Example	AZD7762	3a.19	3a.4	3a.8	3a.9
HTRF IC₅₀ [nM]					
PDGFRA-D842V	0.2 ± 0.1	0.6 ± 0.2	<0.1	2.6 ± 1.7	8.5 ± 5.0
KIT-D816H	0.3 ± 0.1	0.5 ± 0.1	0.3 ± 0.2	0.5 ± 0.2	1.2 ± 0.4
PDGFRA-wt	<0.1	-	0.1 ± 0.0	1.6 ± 0.3	5.1 ± 3.3
KIT-wt	0.9 ± 0.9	-	0.1 ± 0.1	0.9 ± 0.4	15 ± 13
PDGFRA CTG IC₅₀ [nM]					
GIST48B	299 ± 45	246 ± 58	230 ± 13	565 ± 106	1317 ± 75
T1-a-D842V	6 ± 2	9 ± 2	3 ± 1	20 ± 6	175 ± 58
T1-a-D842V+G680R	315 ± 62	256 ± 19	292 ± 8	625 ± 89	3233 ± 266
T1-a-D842V+G652E/V658A	44 ± 4	78 ± 31	21 ± 2	133 ± 23	1108 ± 199
c-KIT CTG GR₅₀ [nM]					
GIST-T1	17 ± 0	-	8 ± 3	23 ± 7	227 ± 81
T1-D816E	17 ± 2	-	7 ± 3	32 ± 13	144 ± 114
T1-V654A	45 ± 2	-	11 ± 3	28 ± 10	288 ± 129

Figure 8

Example	AZD7762	3a.11	3a.17	3a.19	3a.20
HTRF IC₅₀ [nM]					
PDGFRA-D842V	0.2 ± 0.1	12 ± 8	33 ± 19	0.6 ± 0.2	<0.1
KIT-D816H	0.3 ± 0.1	2.8 ± 0.5	3.4 ± 1.3	0.5 ± 0.1	0.1 ± 0.1
PDGFRA-wt	<0.1	8.7 ± 0.2	-	-	-
KIT-wt	0.9 ± 0.9	178 ± 77	-	-	-
PDGFRA CTG IC₅₀ [nM]					
GIST48B	299 ± 45	3550 ± 423	>10000	246 ± 58	252 ± 21
T1-a-D842V	6 ± 2	358 ± 114	3216±725	9 ± 2	3 ± 0
T1-a-D842V+G680R	315 ± 62	6400±1826	9758±297	256 ± 19	289 ± 25
T1-a-D842V+G652E/V658A	44 ± 4	1917 ± 325	8721±1783	78 ± 31	27 ± 5
c-KIT CTG GR₅₀ [nM]					
GIST-T1	17 ± 0	291 ± 100	3232 ±	-	15 ± 3
T1-D816E	17 ± 2	339 ± 153	3362864 ±	-	12 ± 3
T1-V654A	45 ± 2	495 ± 185	316 6599 ± 383	-	36 ± 18

Figure 9

Example	AZD7762	3a.21	3a.23	3a.27	3a.28
HTRF IC₅₀ [nM]					
PDGFRA-D842V	0.2 ± 0.1	<0.1	0.2 ± 0.1	0.1 ± 0.0	0.1 ± 0.0
KIT-D816H	0.3 ± 0.1	<0.1	0.1 ± 0.0	0.5 ± 0.1	0.5 ± 0.1
PDGFRA-wt	<0.1	-	-	0.1 ± 0.0	0.1 ± 0.0
KIT-wt	0.9 ± 0.9	-	-	0.8 ± 0.2	0.9 ± 0.3
PDGFRA CTG IC₅₀ [nM]					
GIST48B	299 ± 45	213 ± 6	275 ± 25	152 ± 35	1031 ± 17
T1-a-D842V	6 ± 2	3 ± 0	5 ± 1	3 ± 0	30 ± 4
T1-a-D842V+G680R	315 ± 62	213 ± 6	249 ± 16	2176 ± 38	2176 ± 38
T1-a-D842V+G652E/V658A	44 ± 4	28 ± 2	38 ± 3	247 ± 53	257 ± 53
c-KIT CTG GR₅₀ [nM]					
GIST-T1	17 ± 0	16 ± 2	17 ± 3	31 ± 2	131 ± 16
T1-D816E	17 ± 2	13 ± 2	14 ± 1	22 ± 3	66 ± 3
T1-V654A	45 ± 2	33 ± 7	42 ± 8	52 ± 8	133 ± 30

Figure 10

Example	3a.29	3a.30	4.1	4.2	4.3
HTRF IC₅₀ [nM]					
PDGFRA-D842V	0.9 ± 0.1	0.3 ± 0.1	0.2 ± 0.1	1.1 ± 0.8	0.3 ± 0.2
KIT-D816H	3.2 ± 0.3	0.4 ± 0.1	0.6 ± 0.3	0.3 ± 0.1	0.3 ± 0.3
PDGFRA-wt	0.5 ± 0.1	0.5 ± 0.1	-	-	-
KIT-wt	5.1 ± 0.8	2.2 ± 0.6	-	-	-
PDGFRA CTG IC₅₀ [nM]					
GIST48B	300 ± 54	88 ± 11	1161 ± 137	2500 ± 312	2903 ± 130
T1-a-D842V	16 ± 4	5 ± 33	31 ± 10	45 ± 2	76 ± 17
T1-a-D842V+G680R	349 ± 24	194 ± 13	1027 ± 119	1657 ± 125	3092 ± 364
T1-a-D842V+G652E/V658A	120 ± 40	58 ± 15	195 ± 34	313 ± 16	572 ± 129
c-KIT CTG GR₅₀ [nM]					
GIST-T1	78 ± 11	-	83 ± 12	197 ± 17	373 ± 43
T1-D816E	74 ± 11	-	71 ± 10	181 ± 4	204 ± 19
T1-V654A	160 ± 33	-	202 ± 14	455 ± 101	466 ± 99

Figure 11

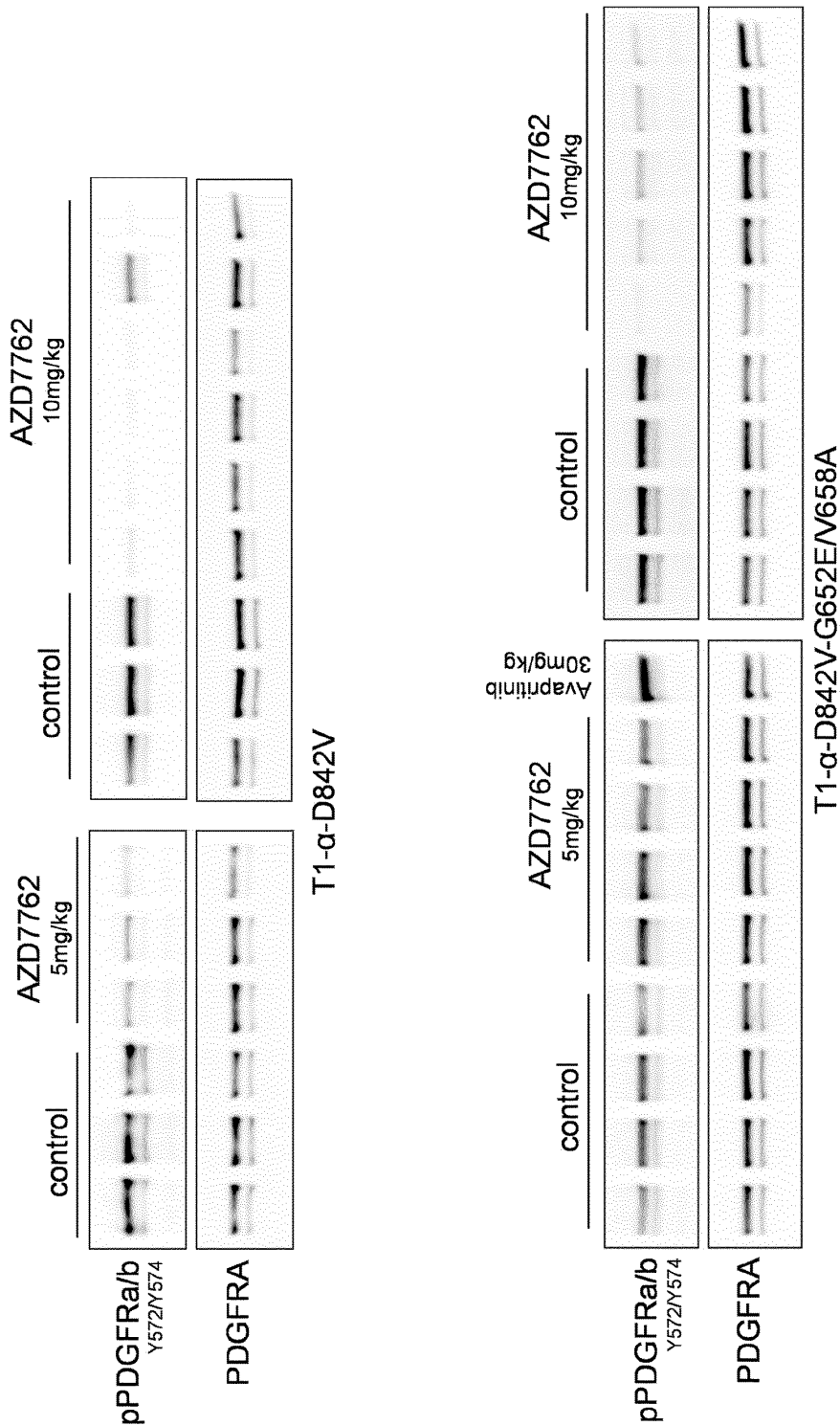


Figure 12

10/18

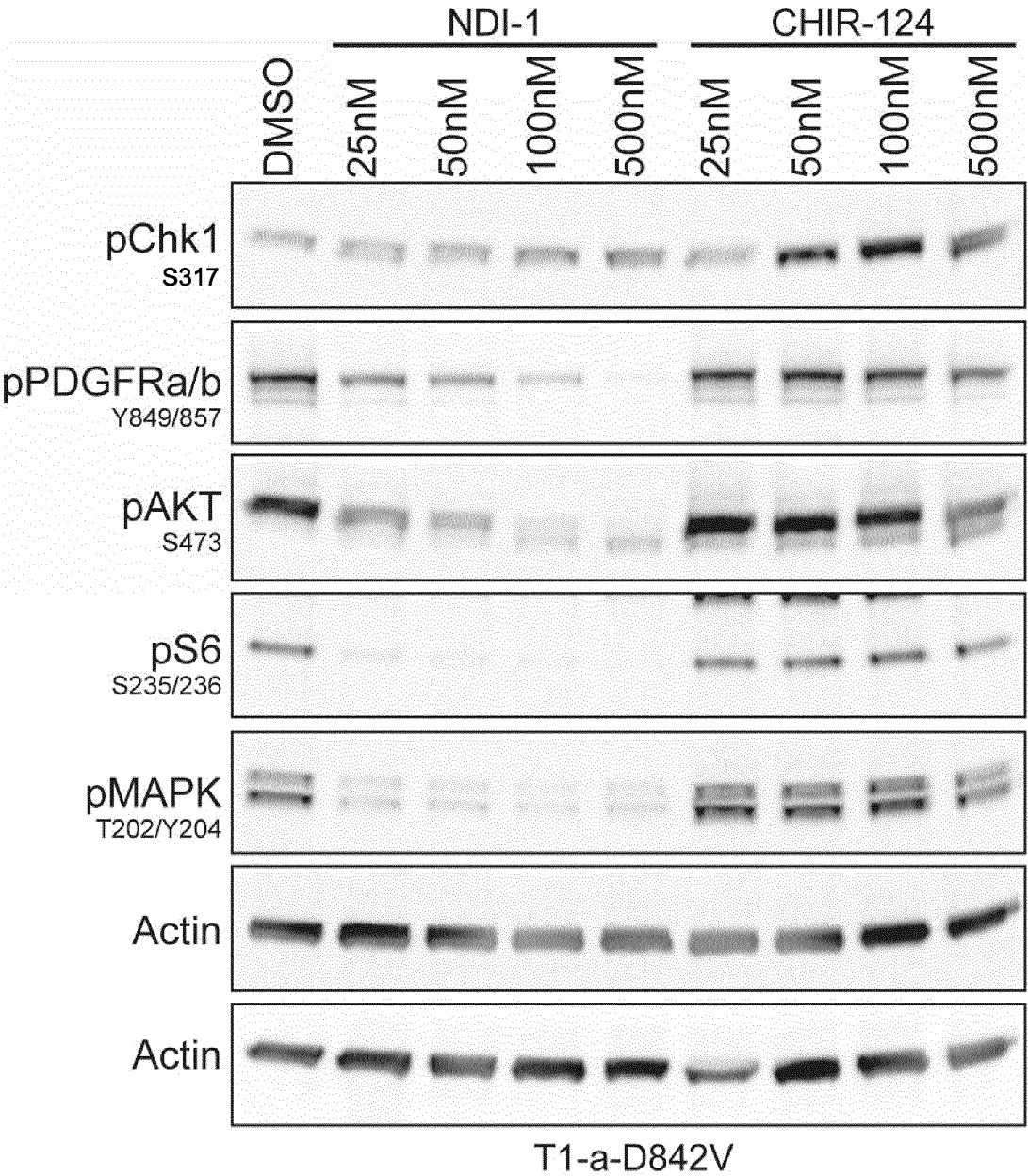


Figure 13

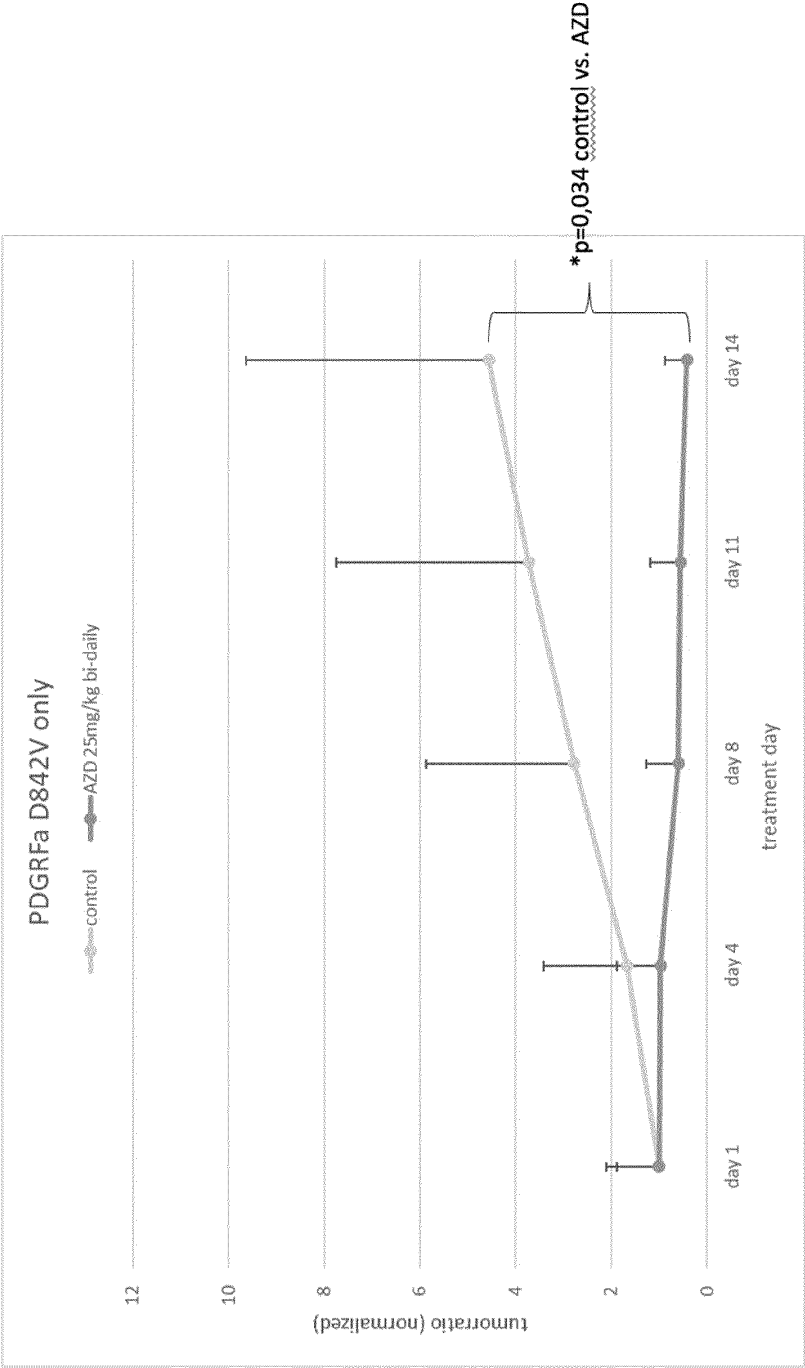


Figure 14A

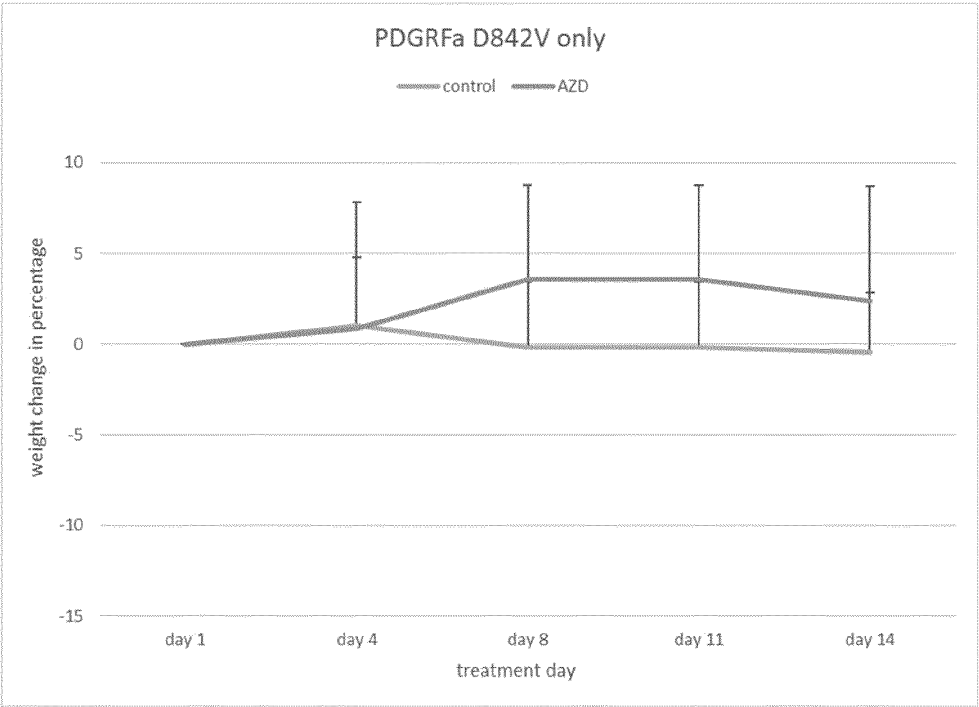


Figure 14B

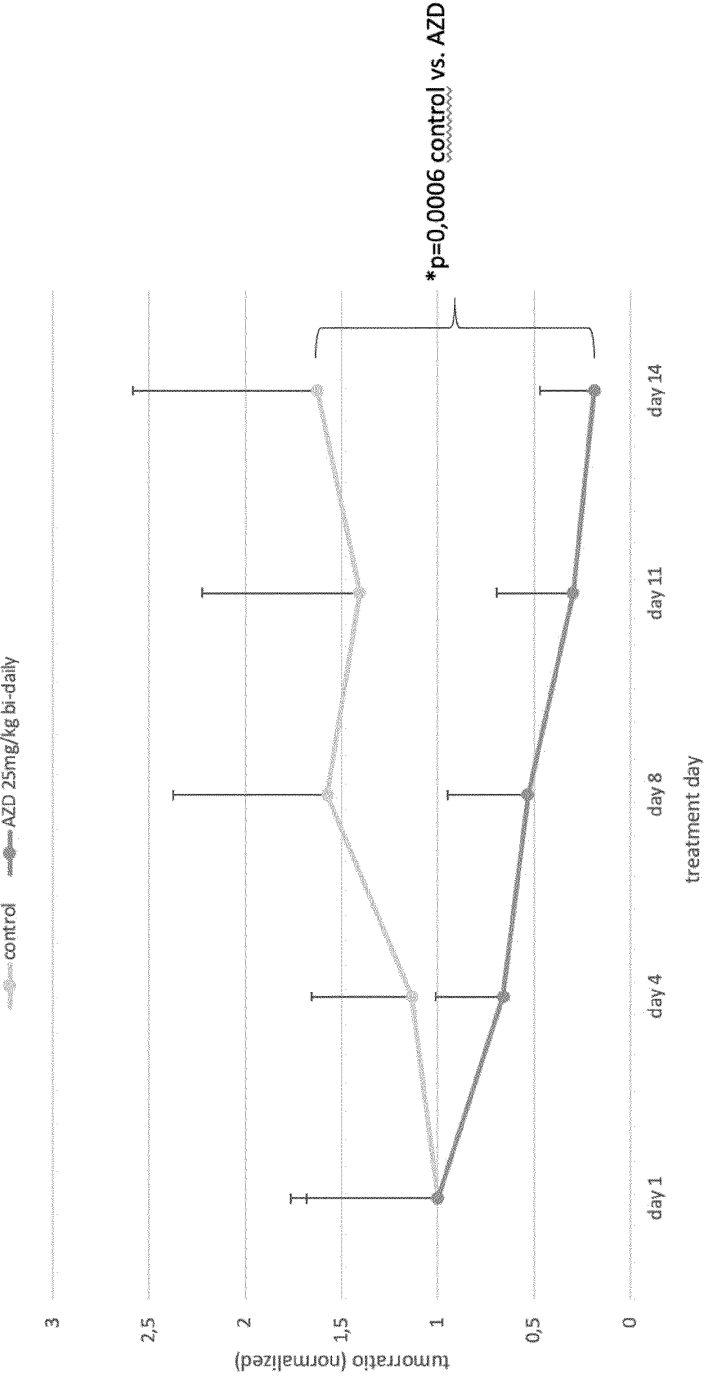


Figure 15A

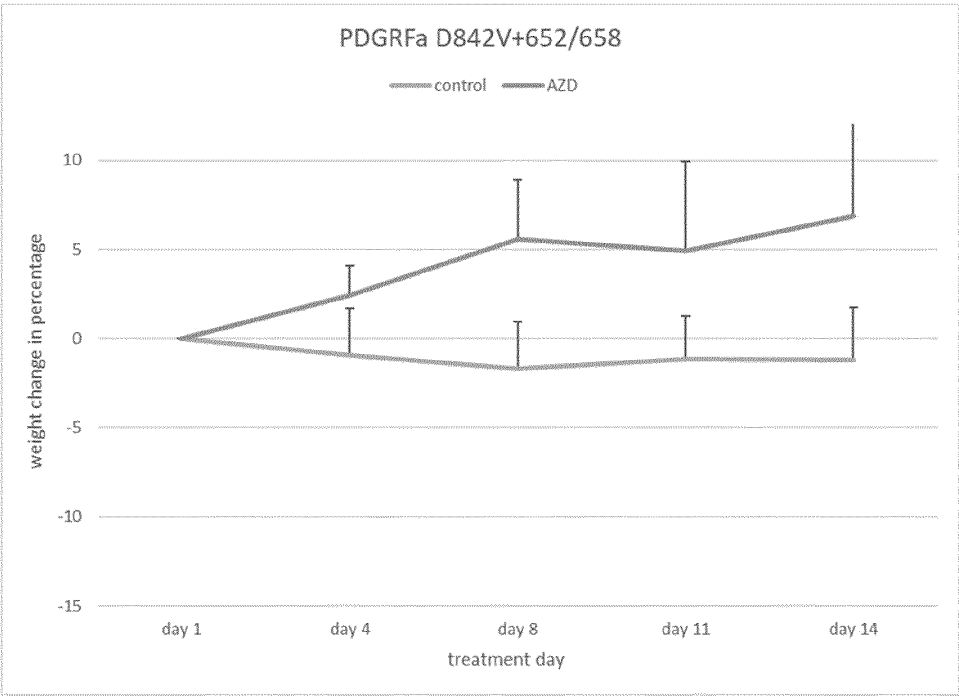


Figure15B

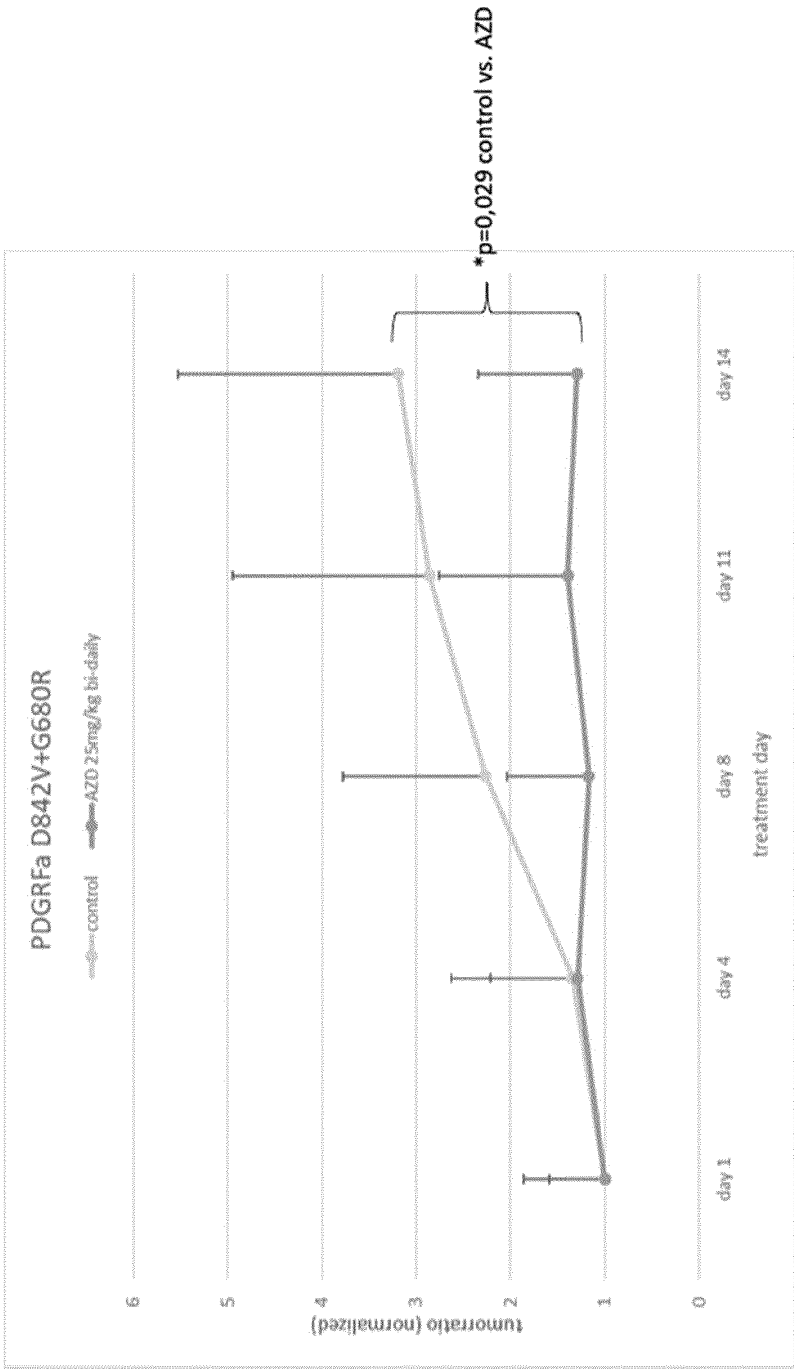


Figure 16A

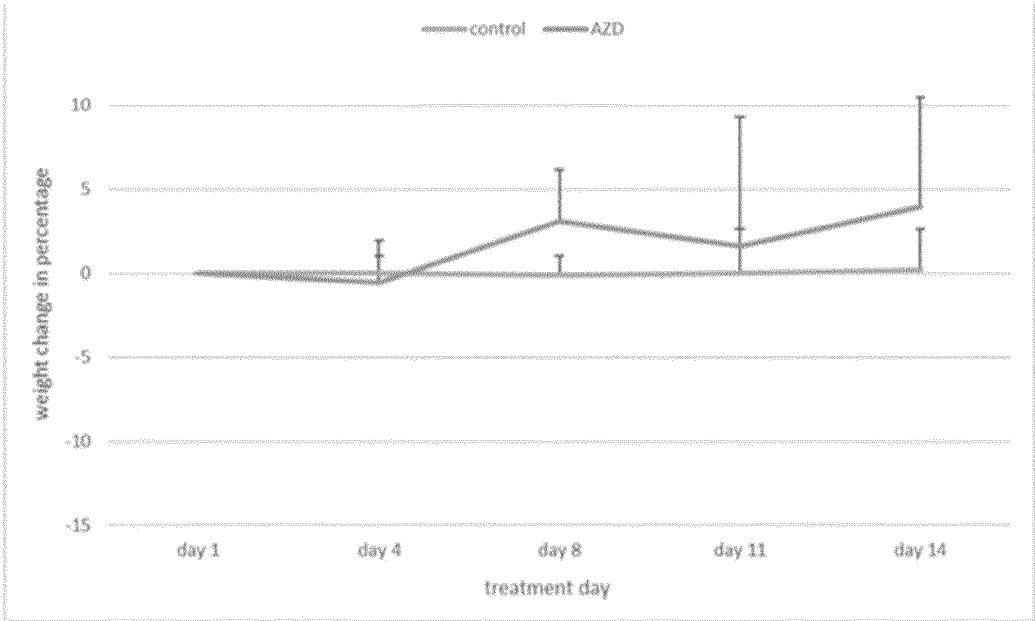


Figure 16B

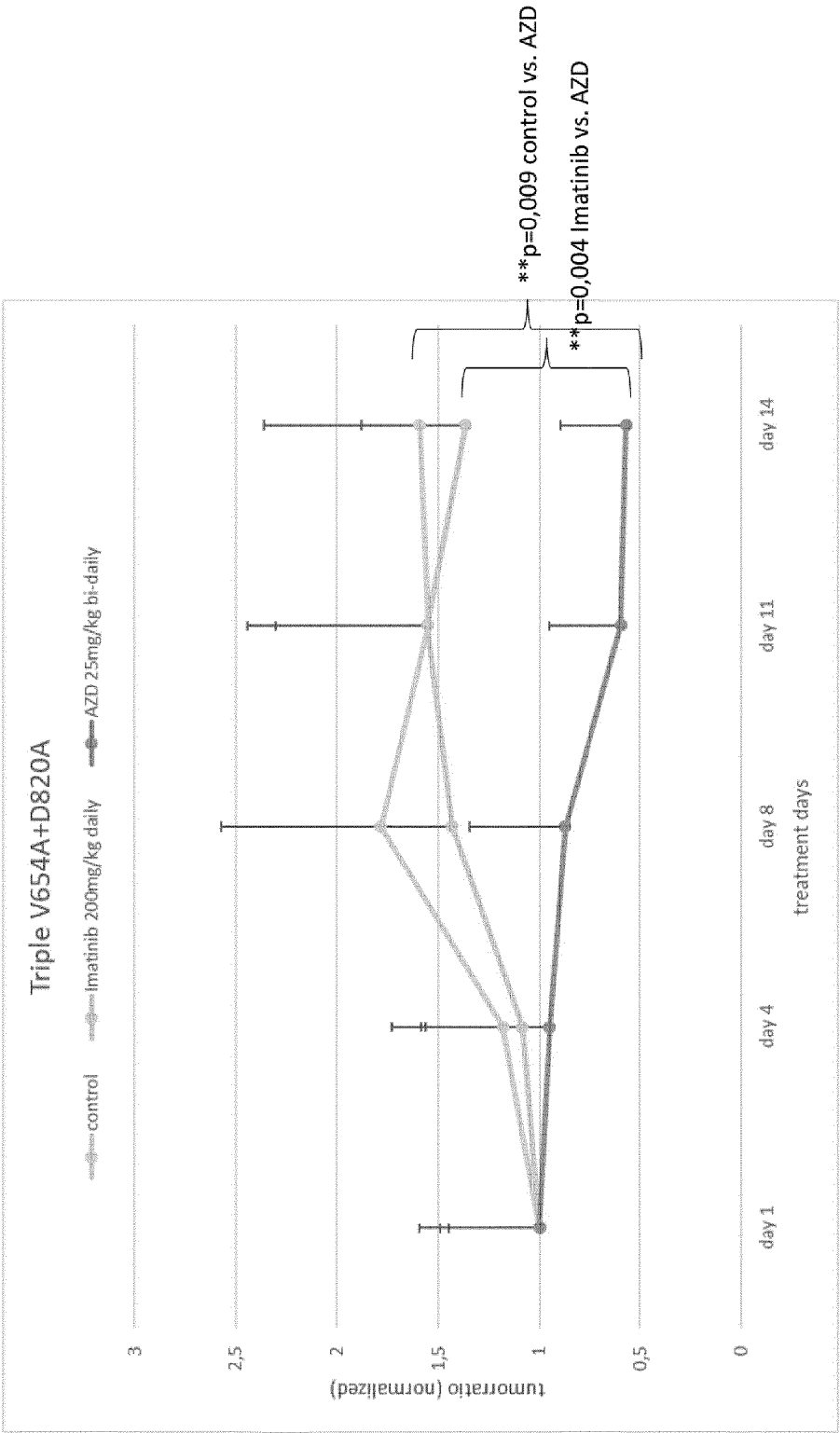
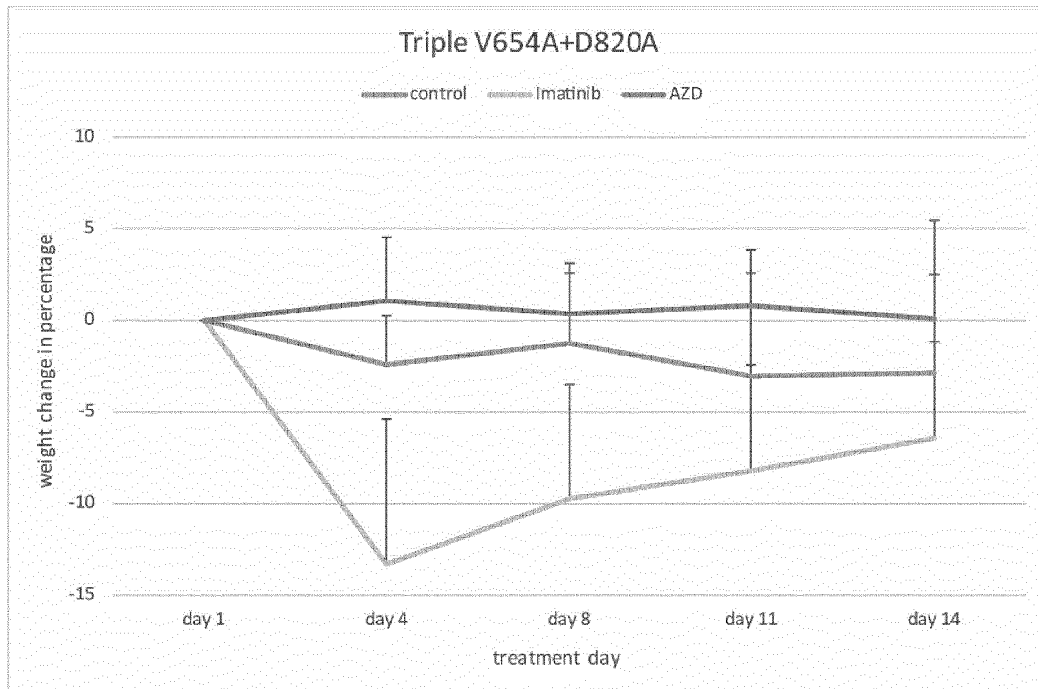


Figure 17A

**Figure 17B**