

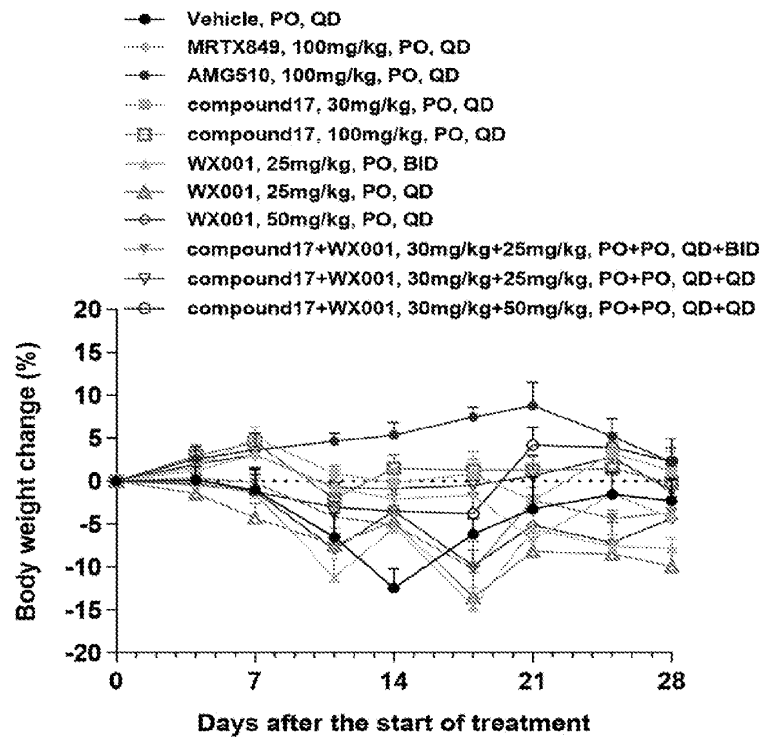


FIG. 1

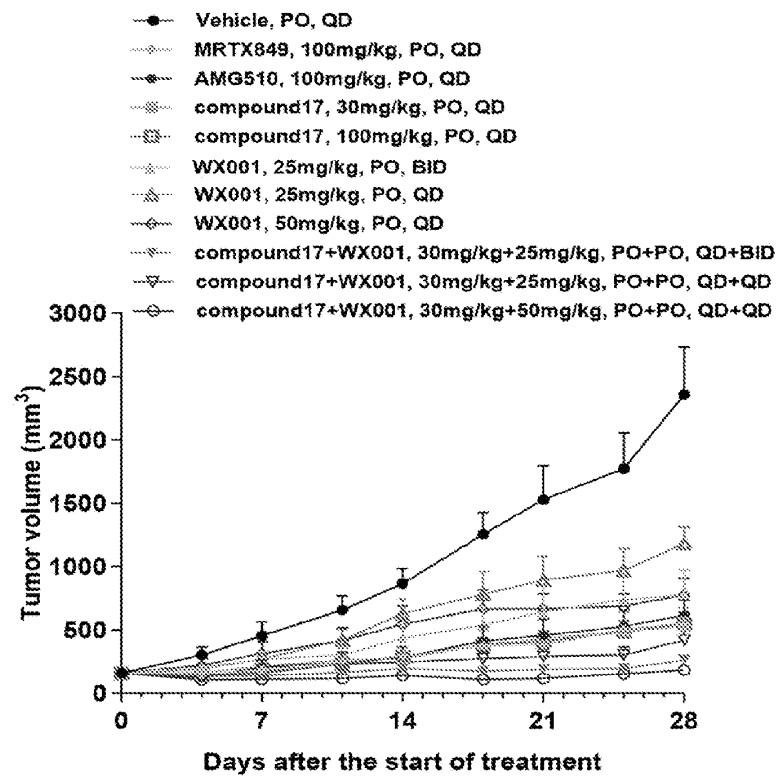


FIG. 2

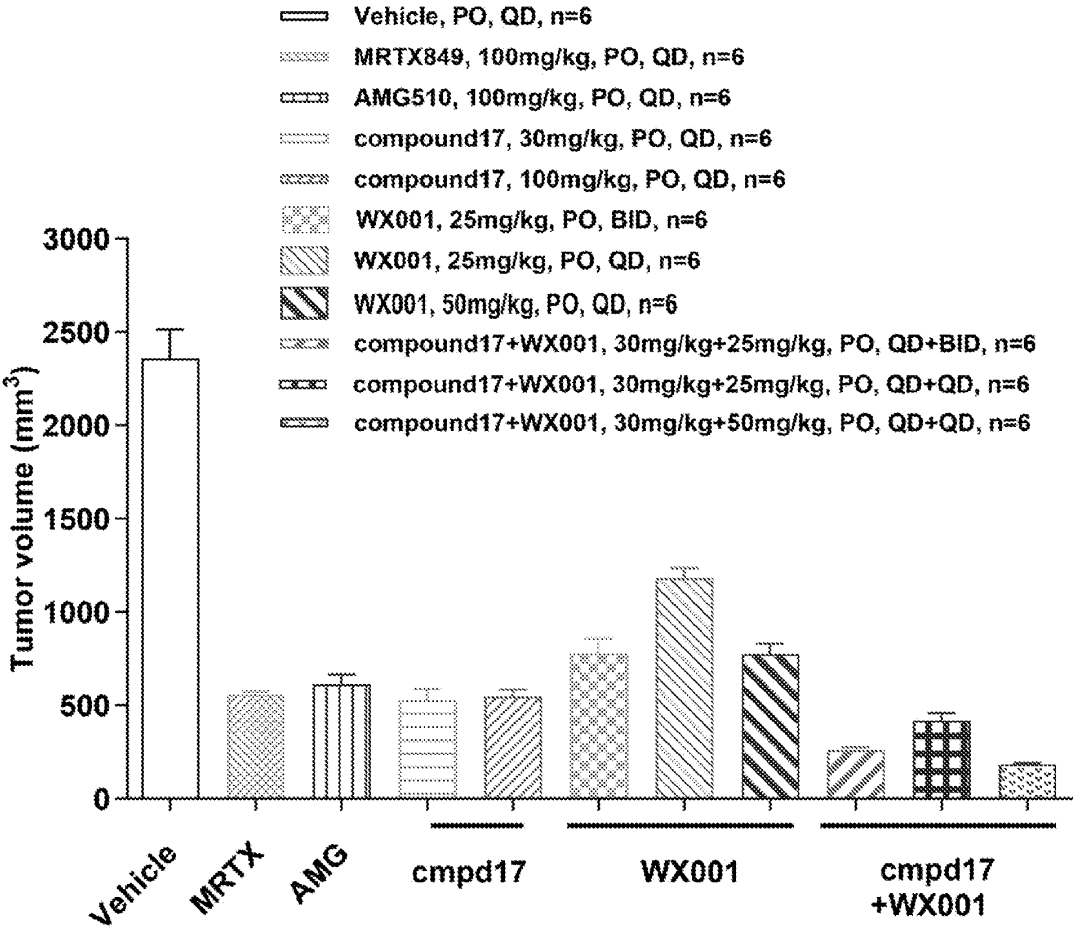


FIG. 3

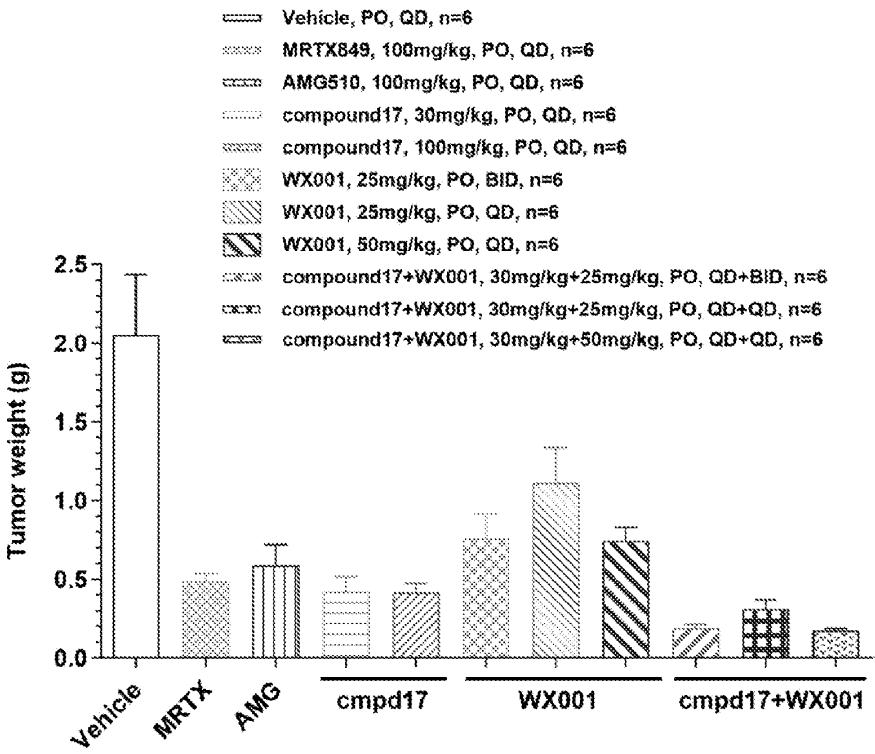


FIG. 4

Percentage of body weight change in each treatment group in SW837 model

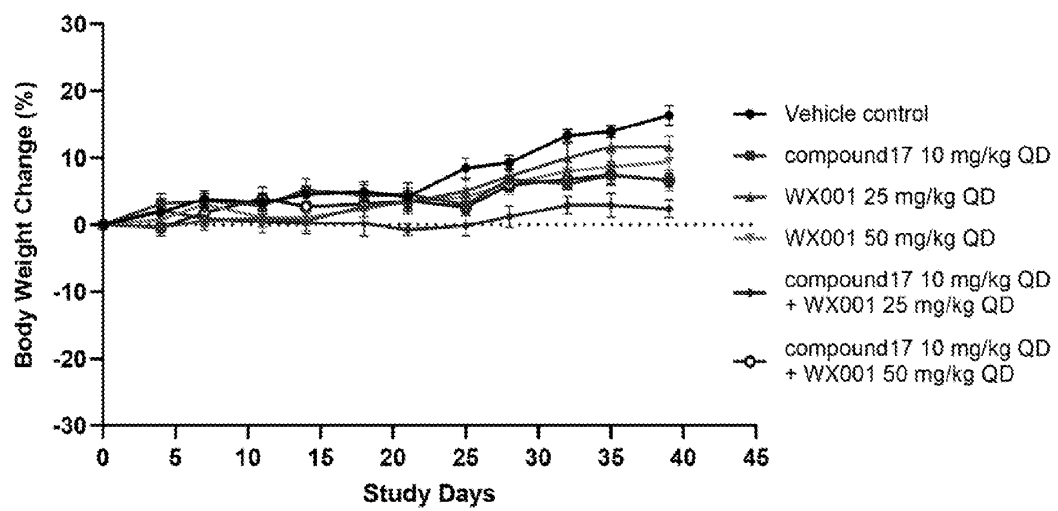


FIG. 5

Tumor growth curve of SW837 colorectal cancer model after treatment

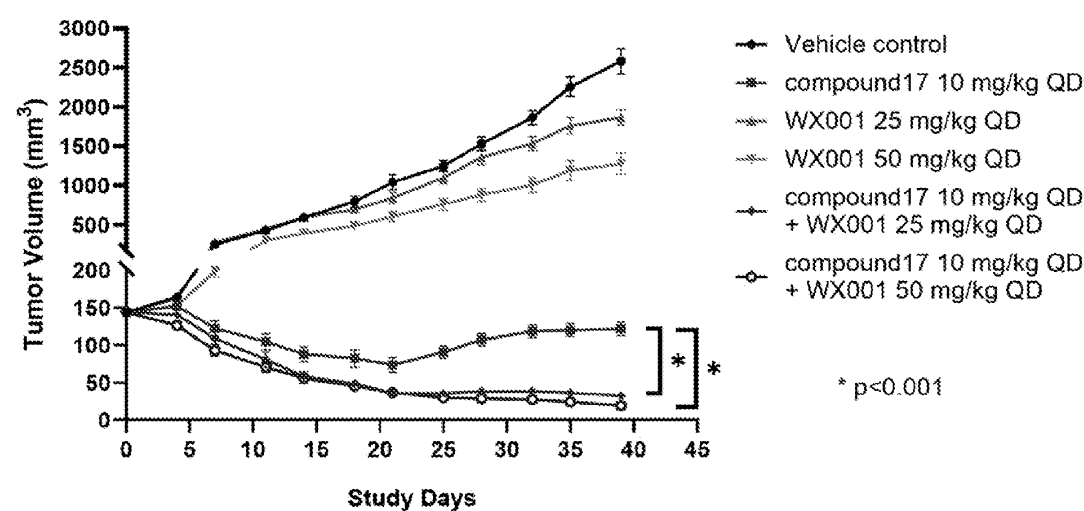


FIG. 6A

FIG. 6B

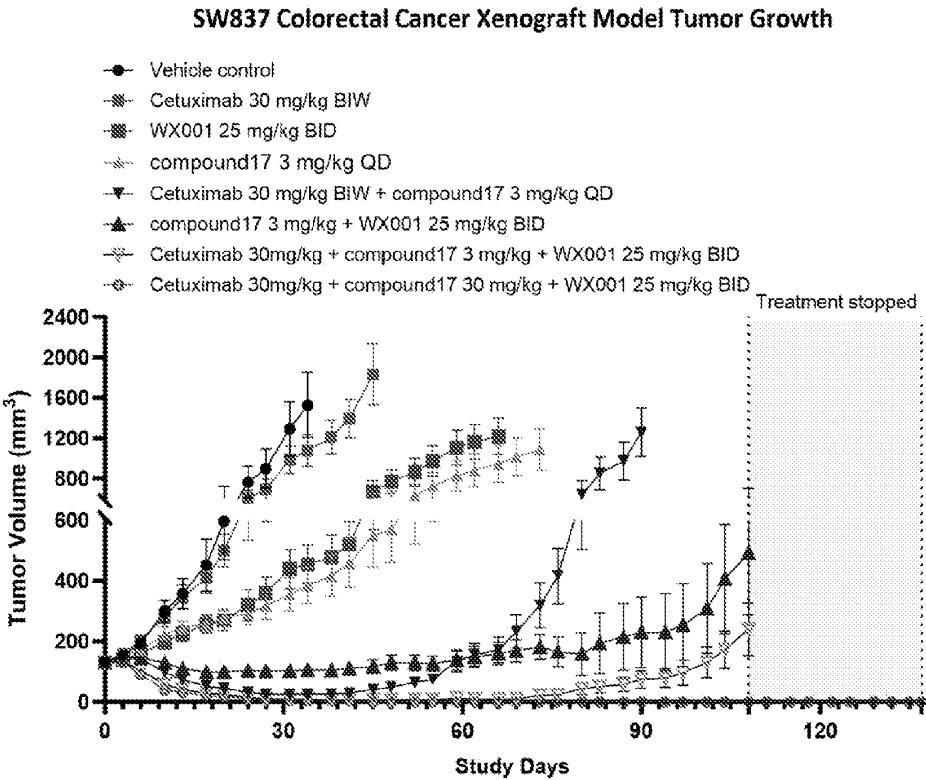
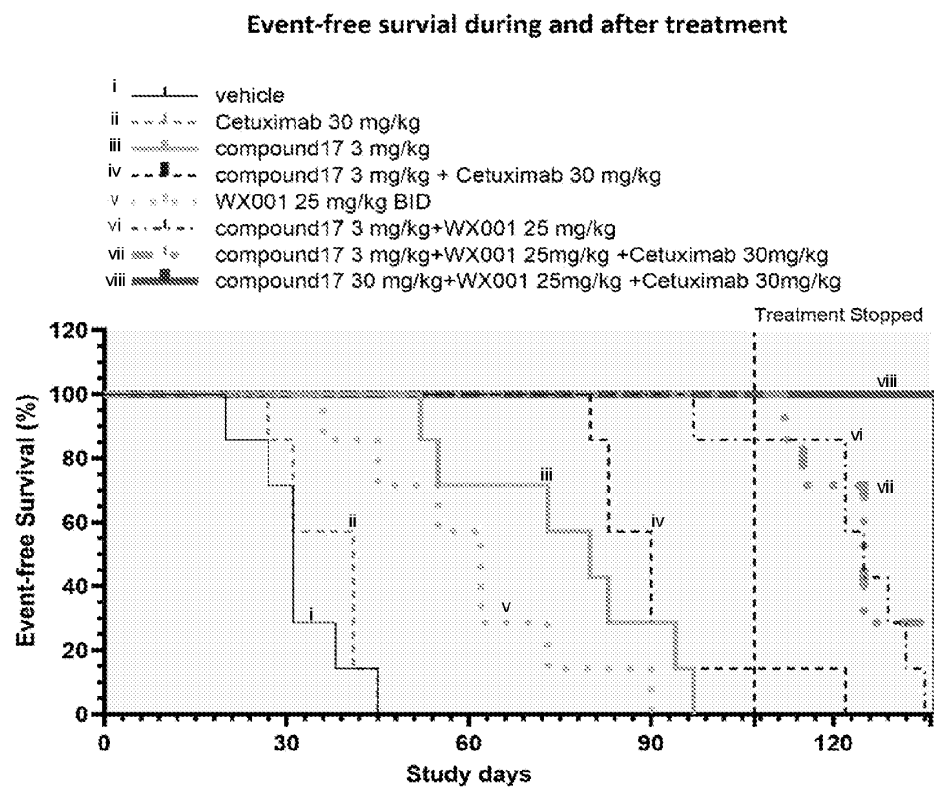


FIG. 6C



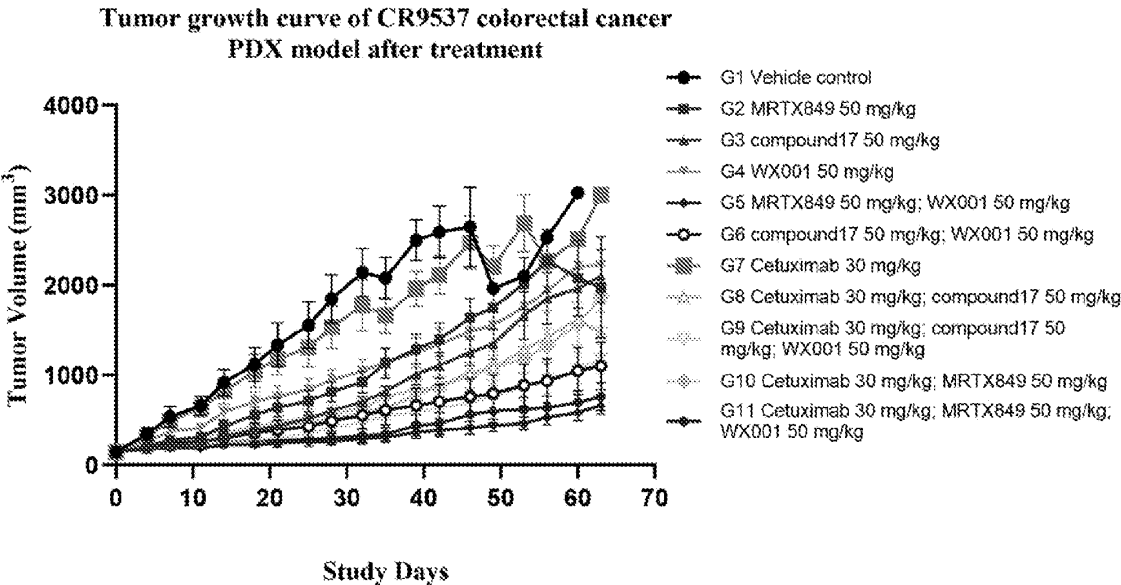


FIG. 7

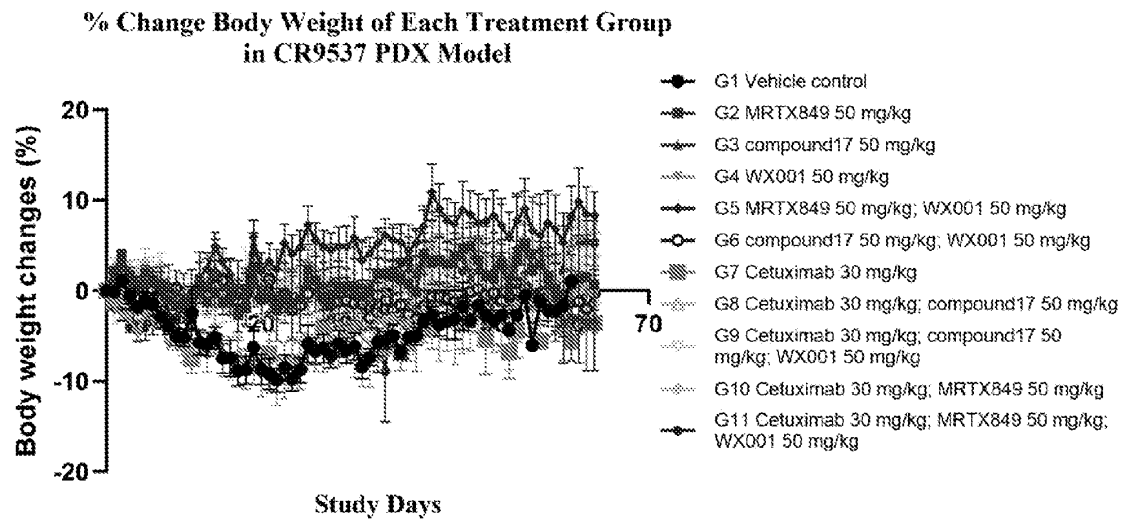


FIG. 8

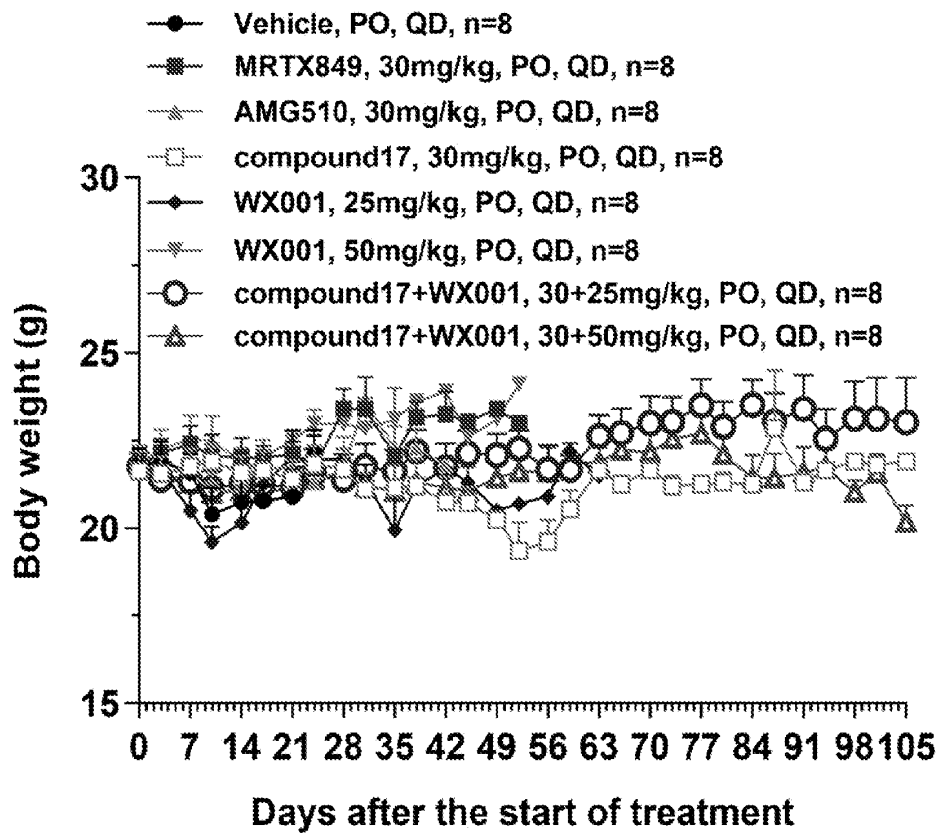


FIG. 9

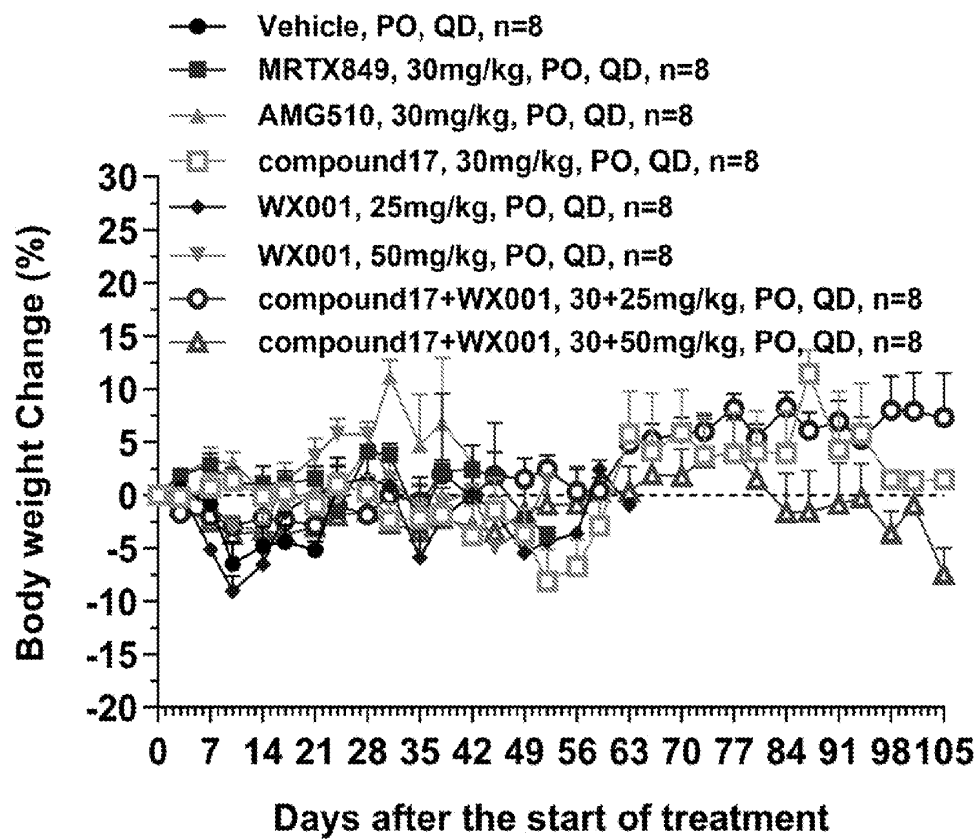


FIG. 10

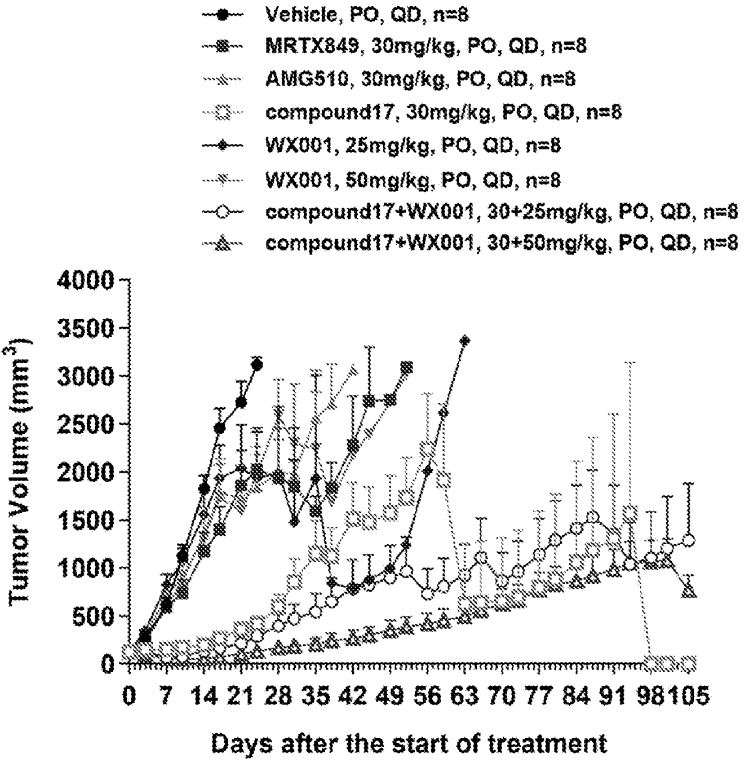


FIG. 11

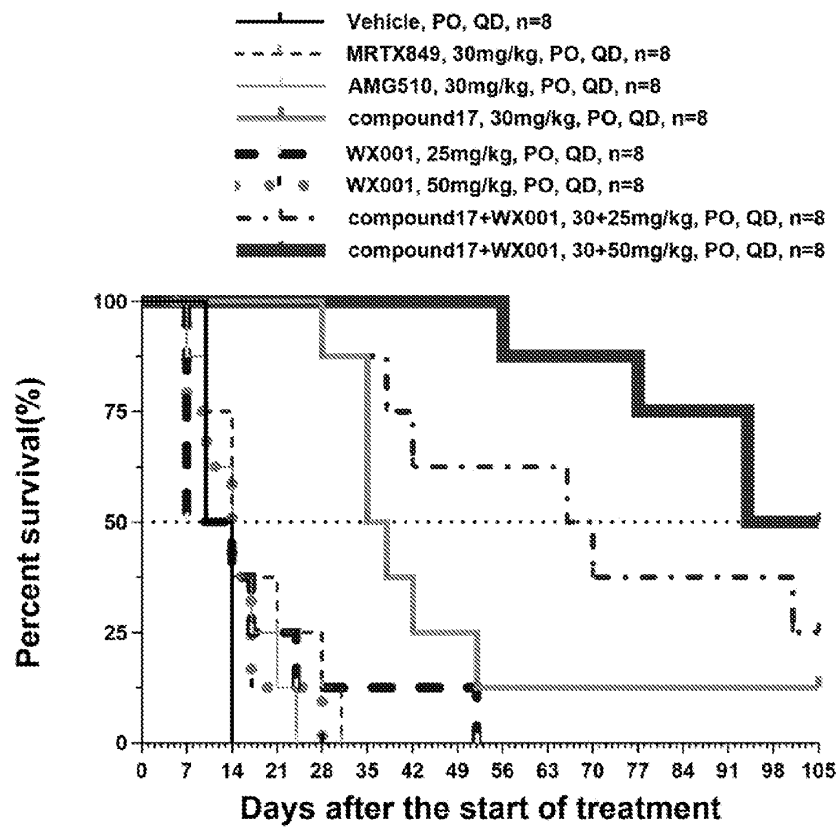


FIG. 12

FIG. 13

Overall properties of WX001

Properties	WX001
MW, PSA, LogD	474.5, 106.6, 2.6
Kinetic solubility (µg/mL) (pH = 2.0, 6.5, 7.4)	94.7, 1.4, 1.3
pKa	1.9, 4.1
PPB% (h, m, r, d, c)	84.1, 88.3, 91.6, 85.7, 85.8
P _{app} (10 ⁻⁶ cm/s) (A to B, B to A, ER)	5.2, 43.6, 8.4
MMS (h, m, r, d, c) (% remaining, 60 min)	65.4, 25.6, 61.0, 46.1, 31.1
HMS (h, m, r, d, c) CL _{int} (mL/min/kg)	41, 106, 70, <44, 58
ERK1/2@1mM ATP IC ₅₀ (nM)	1.9/0.6
A375 pRSK IC ₅₀ (nM)	16.8
NCI-H358 pRSK IC ₅₀ (nM)	14.2
A375 (BRAF ^{V600E}) IC ₅₀ (nM)	115.3
HCT116 (KRAS ^{G13D}) IC ₅₀ (nM)	69.6
NCI-H358 (KRAS ^{G12C}) IC ₅₀ (nM)	82.5
SW837 (KRAS ^{G12C}) IC ₅₀ (nM)	101.2
MIA PaCa2 (KRAS ^{G12C}) IC ₅₀ (nM)	99.4
HEK293 human embryonic kidney cells IC ₅₀ (nM)	>20,000
CYP inhibition (µM) 1A2, 2C9, 2C19, 2D6, 3A4	>50, >50, >50, >50, 26.8
hERG (µM)	>40
Oral bioavailability (m, r, d, c)	>100%, 49%, 60%, 50%

FIG. 14A

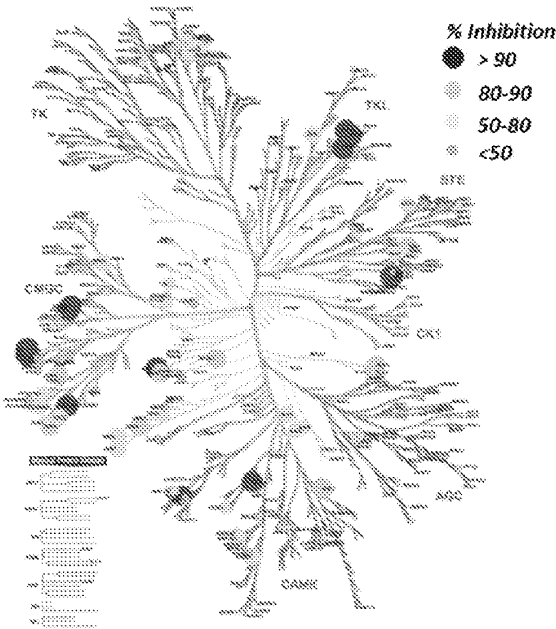


FIG. 14B

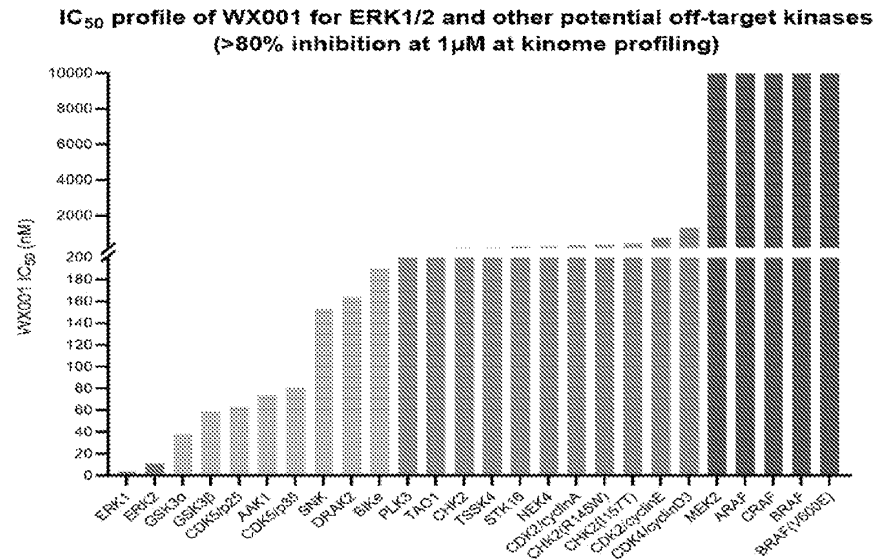


FIG. 14C

Kinase	IC ₅₀ (nM)	Kinase	IC ₅₀ (nM)
ERK1	4	TSSK4	230
ERK2	11	STK16	267
GSK3α	38	NEK4	273
GSK3β	59	CDK2/cyclin A	316
CDK5/p25	63	CHK2(R145W)	369
AAK1	74	CHK2(I157T)	406
CDK5/p35	81	CDK2/cyclin E	742
SNK	153	CDK4/cyclinD3	1291
DRAK2	164	MEK2	>10000
BIKe	190	ARAF	>10000
PLK3	210	CRAF	>10000
TAO1	222	BRAF	>10000
CHK2	226	BRAF(V600E)	>10000

FIG. 15A

The inhibitory effect of WX001 on pRSK1 in A375 cells

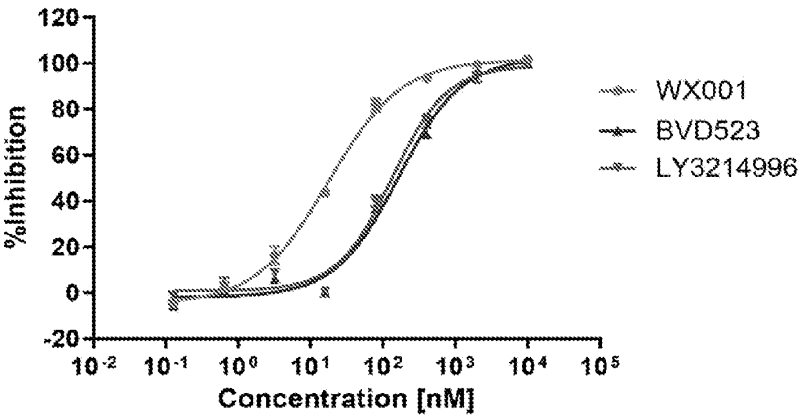


FIG. 15B

Cellular PD IC ₅₀ (nM)	BVD523	LY3214996	WX001
p-RSK in A375 (BRAFV600E) cells	131.6	150.0	16.8
p-RSK in NCI-H358 (KRAS G12C) cells	159.3	175.6	14.2
Anti-proliferation IC ₅₀ (nM)	BVD523	LY3214996	WX001
A375 (BRAFV600E)	350.9	447.1	115.3
HCT116 (KRASG13D)	319.3	437.3	69.6
NCI-H358 (KRASG12C)	386.1	505.2	82.5
SW837 (KRASG12C)	501.1	654.6	101.2
MIA PaCa2 (KRASG12C)	587.8	459.6	99.4

FIG. 16A

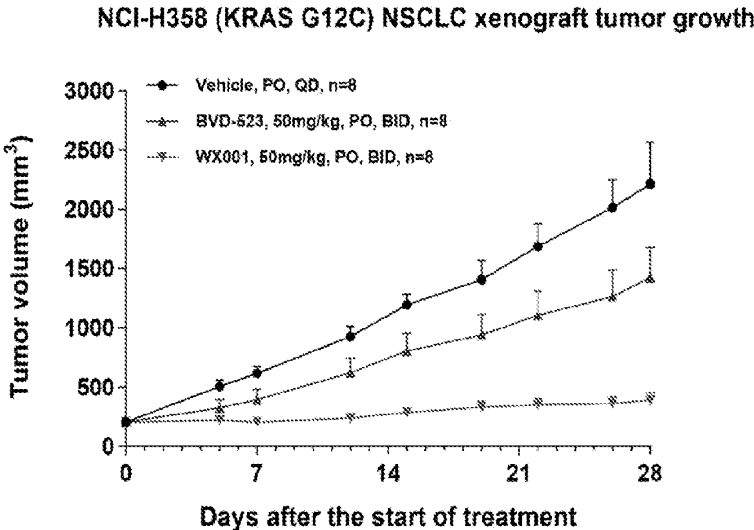


FIG. 16B

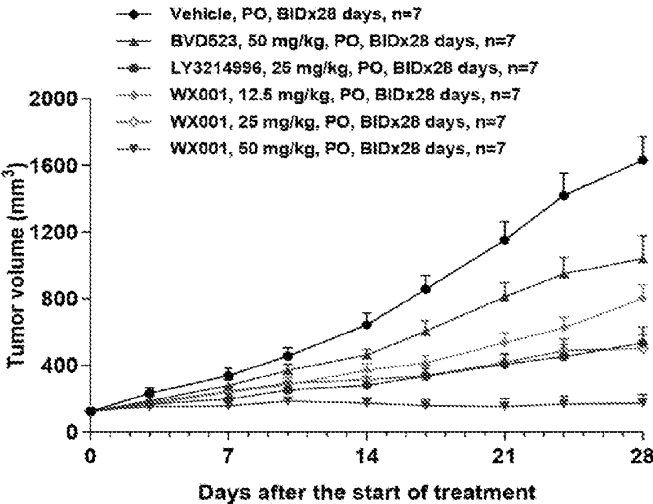


FIG. 17A

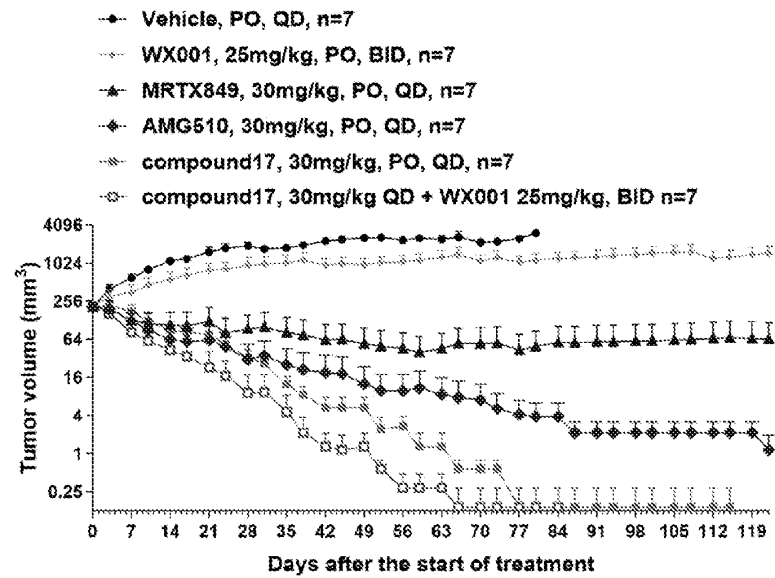


FIG. 17B

Complete remission rate	Day 87	Day 119
WX001 (ERK1/2i)	0/7 (0%)	0/7 (0%)
MRTX849 (KRAS G12Ci)	2/7 (29%)	2/7 (29%)
AMG510 (KRAS G12Ci)	2/7 (29%)	4/7 (57%)
compound17 (KRAS G12Ci)	6/7 (86%)	7/7 (100%)
compound17 + WX001	7/7 (100%)	7/7 (100%)

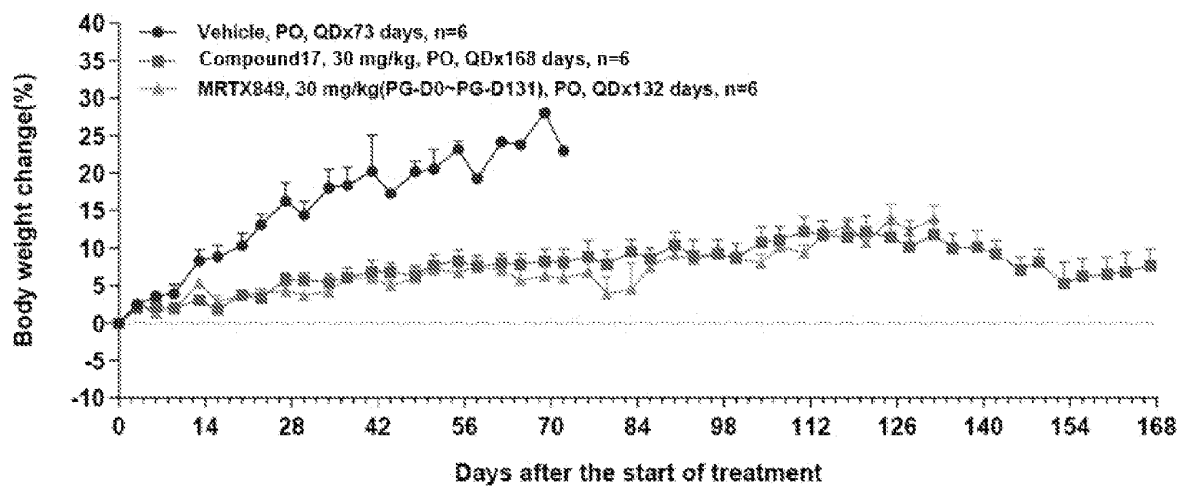


FIG. 18

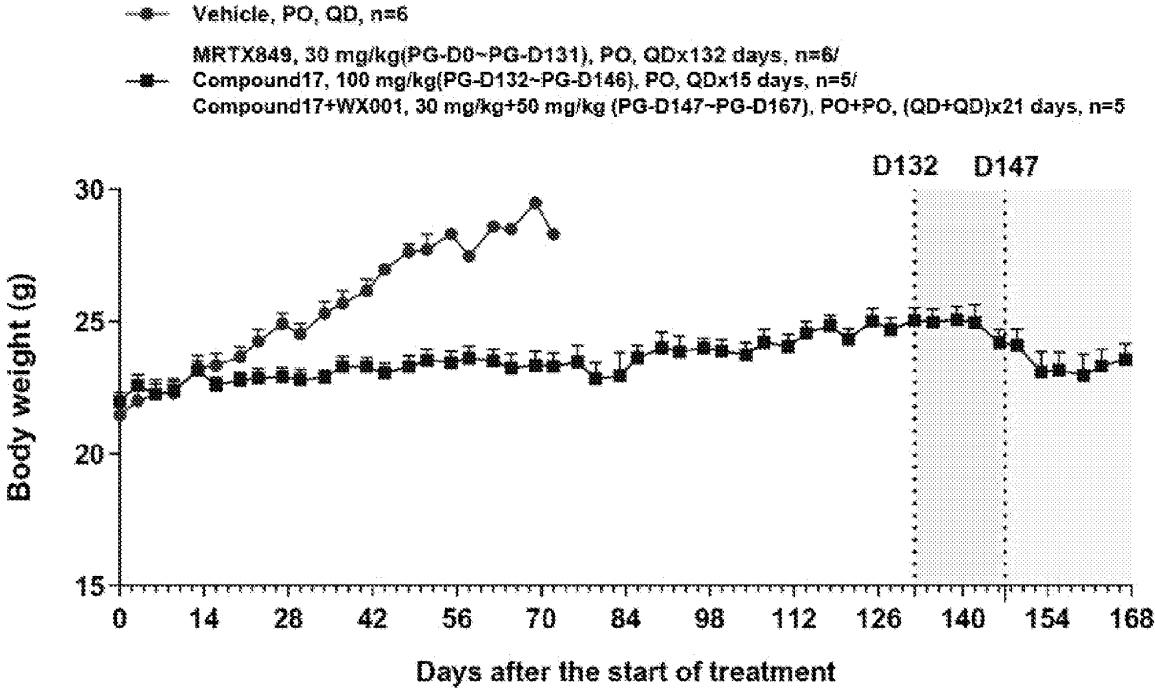


FIG. 19

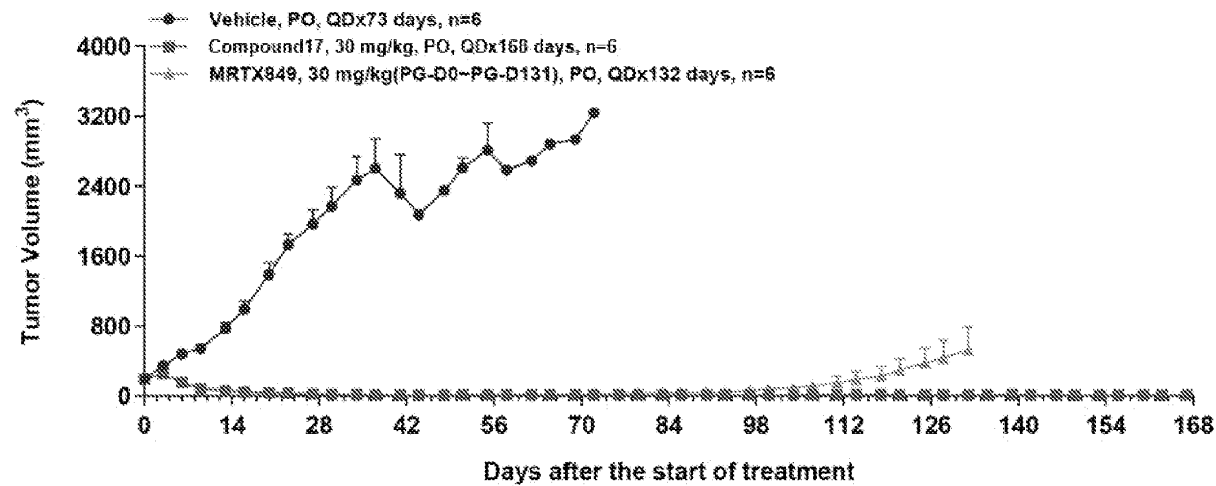


FIG. 20

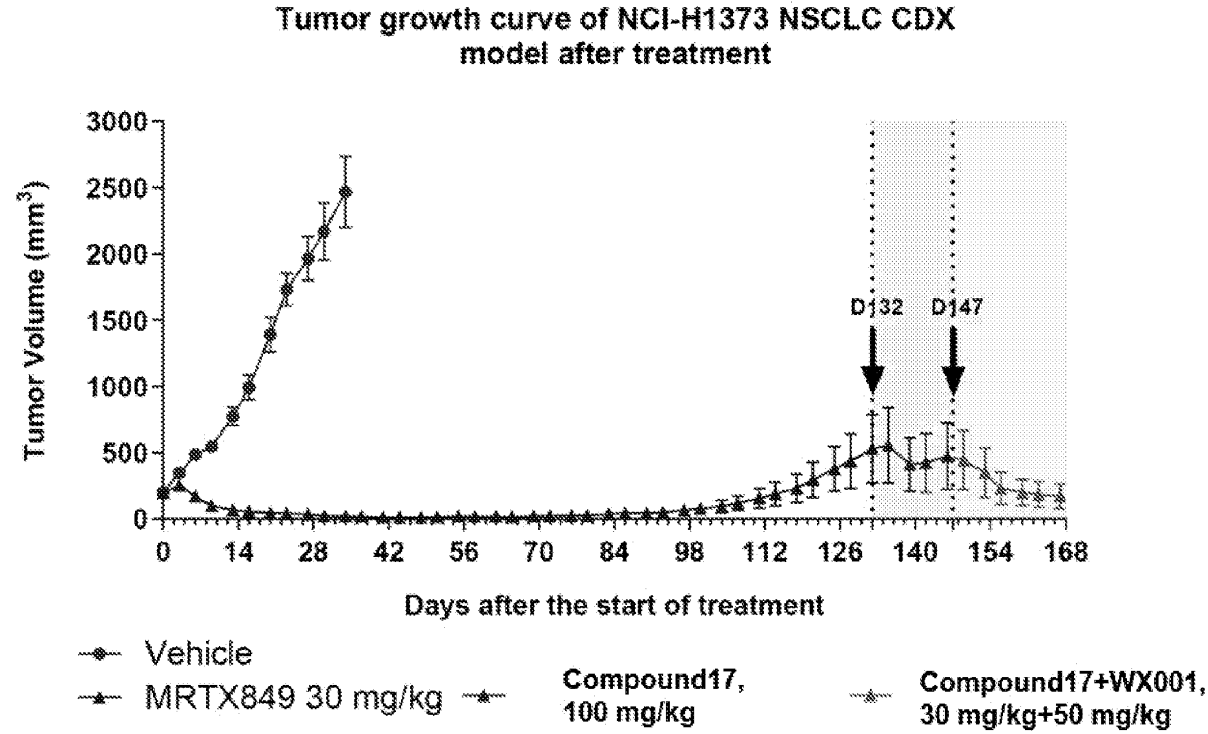


FIG. 21