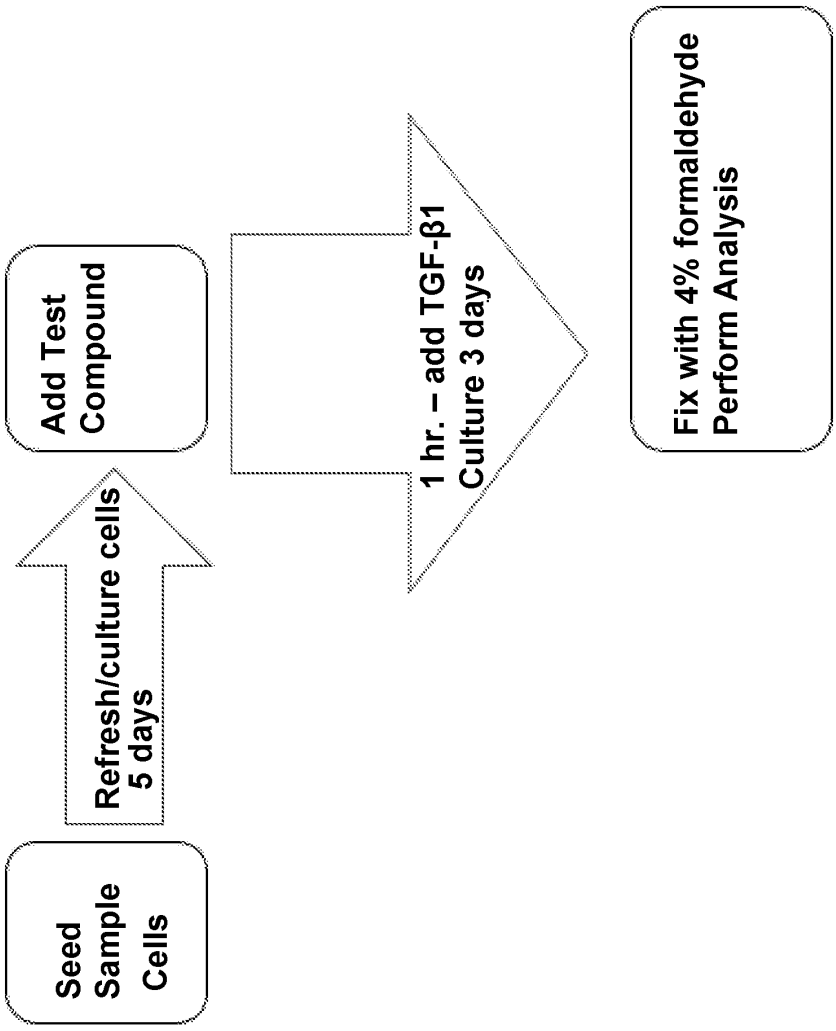

Seed Sample Cells
Refresh/culture cells 5 days
Add Test Compound
1 hr. – add TGF-β1 Culture 3 days
Fix with 4% formaldehyde Perform Analysis

FIG. 1

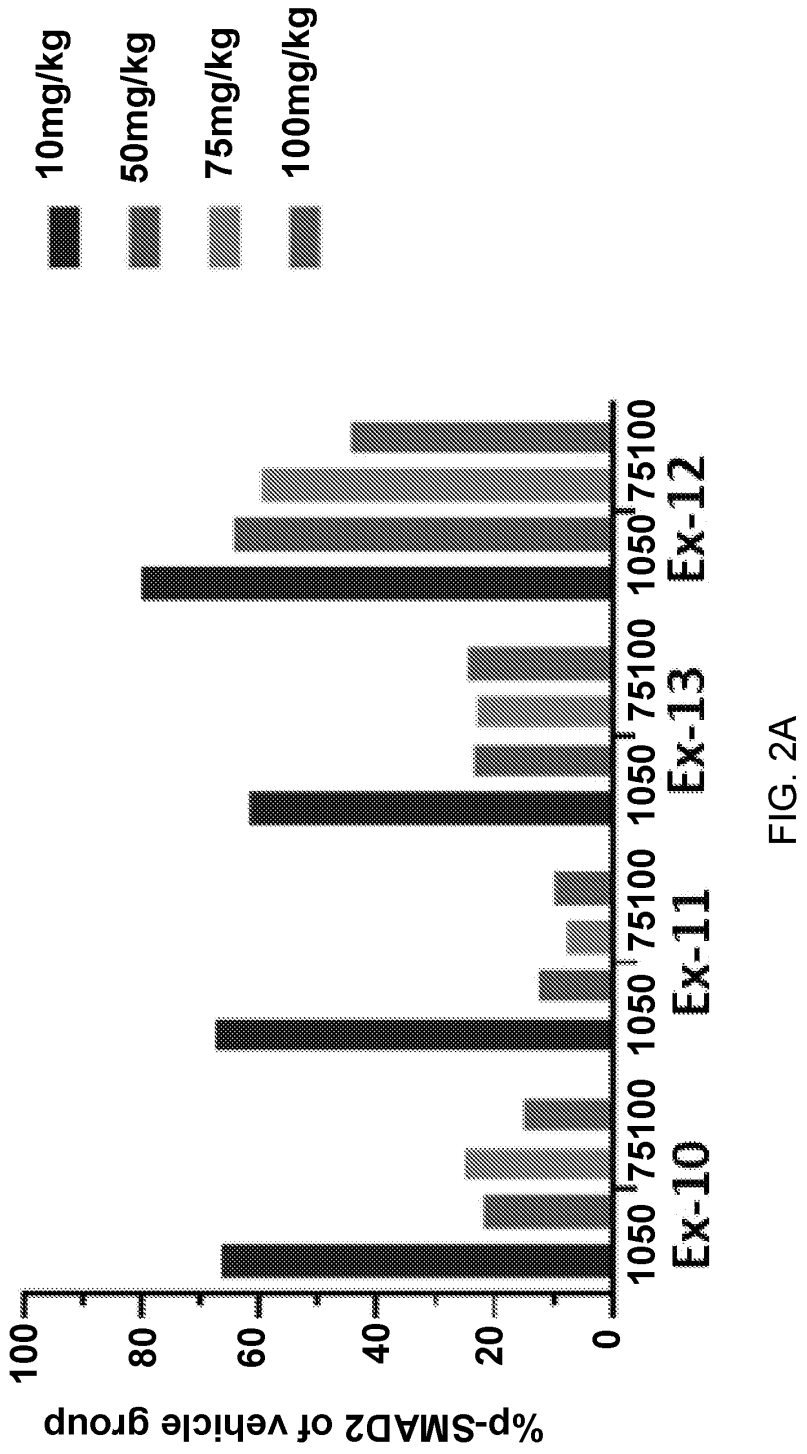

10mg/kg
50mg/kg
75mg/kg
100mg/kg
%p-SMAD2 of vehicle group
100
80
60
40
20
0
1050
75100
Ex-10
1050
75100
Ex-11
1050
75100
Ex-13
1050
75100
Ex-12

FIG. 2A

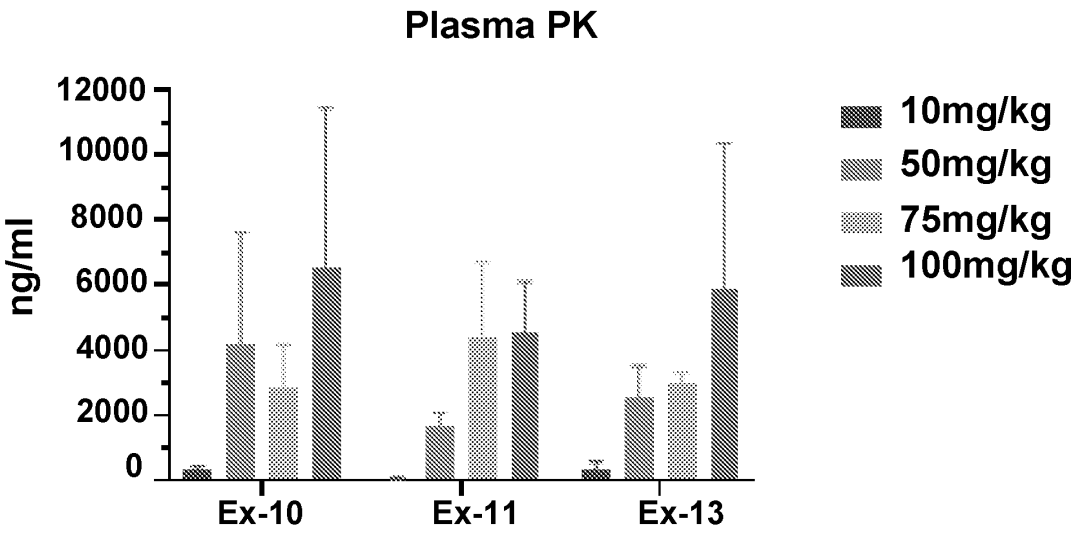

Plasma PK
12000
10000
8000
6000
4000
2000
0
ng/ml
Ex-10
Ex-11
Ex-13
10mg/kg
50mg/kg
75mg/kg
100mg/kg

FIG. 2B

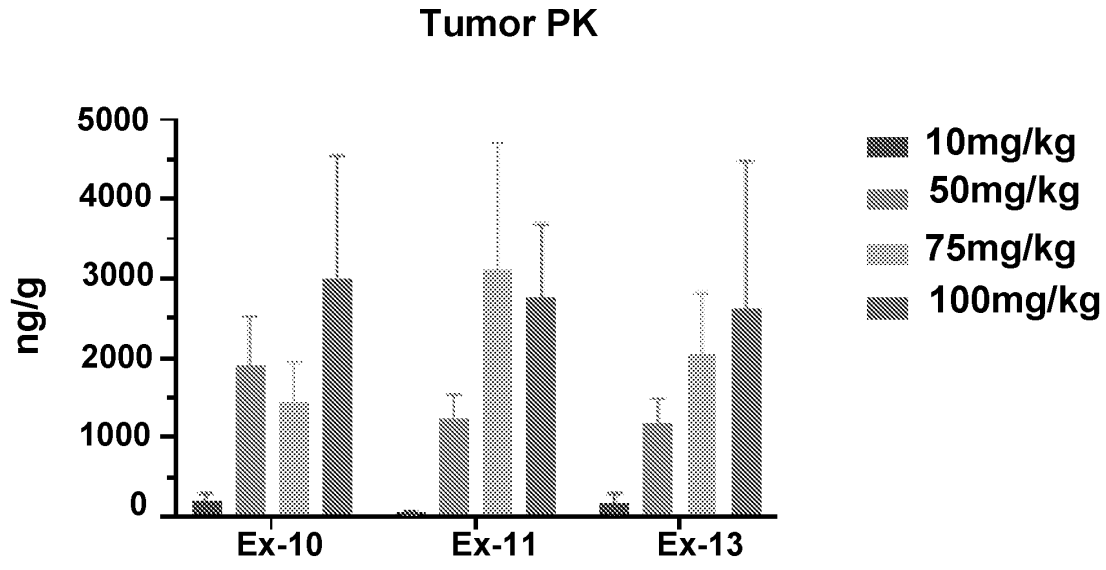

Tumor PK
5000
4000
3000
2000
1000
0
ng/g
Ex-10
Ex-11
Ex-13
10mg/kg
50mg/kg
75mg/kg
100mg/kg

FIG. 2C

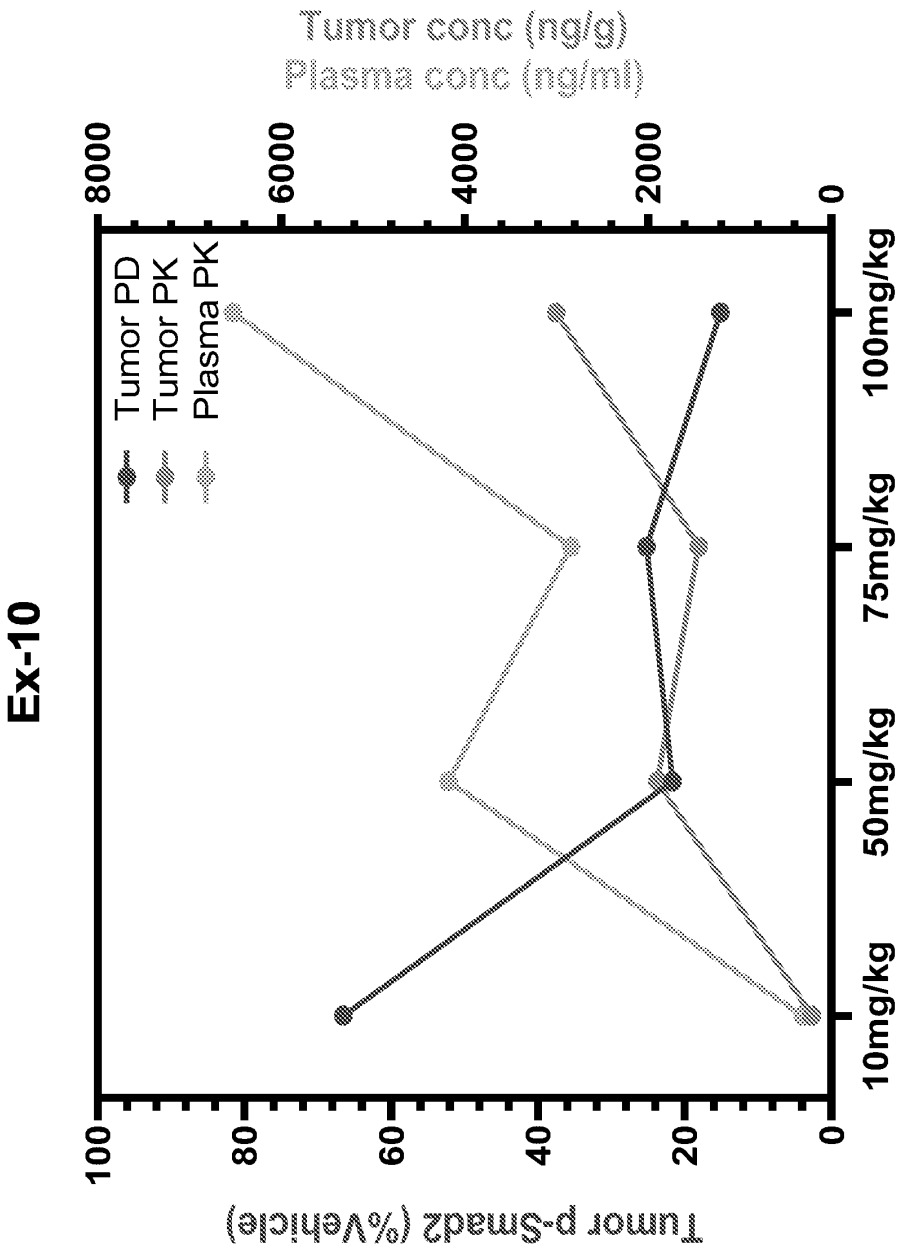

Ex-10
Tumor p-Smad2 (%Vehicle)
Tumor conc (ng/g)
Plasma conc (ng/ml)
Tumor PD
Tumor PK
Plasma PK
0
20
40
60
80
100
0
2000
4000
6000
8000
10mg/kg
50mg/kg
75mg/kg
100mg/kg

FIG. 2D

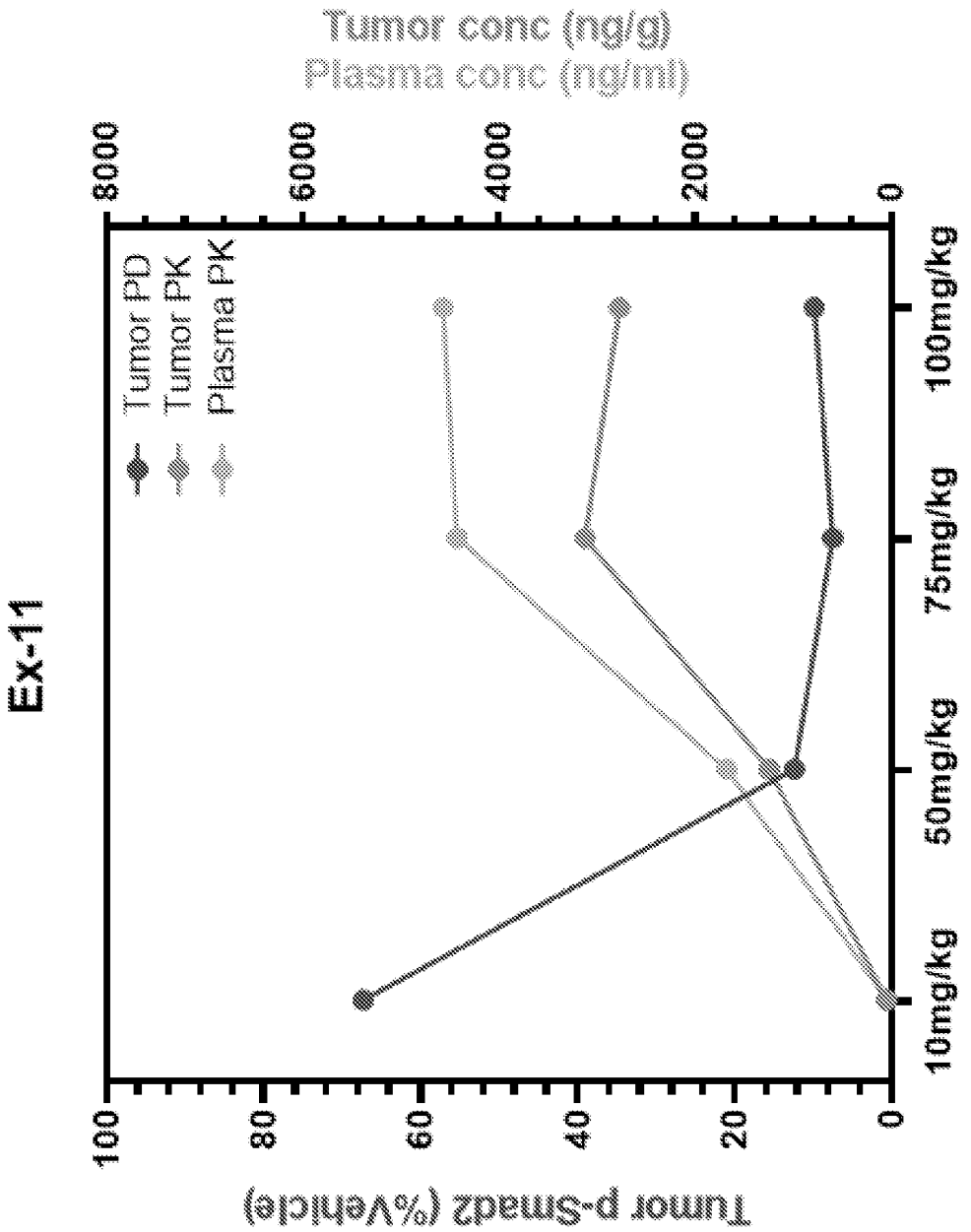

Ex-11
Tumor p-Smad2 (%Vehicle)
Tumor conc (ng/g)
Plasma conc (ng/ml)
Tumor PD
Tumor PK
Plasma PK
100
80
60
40
20
0
8000
6000
4000
2000
0
10mg/kg
50mg/kg
75mg/kg
100mg/kg

FIG. 2E

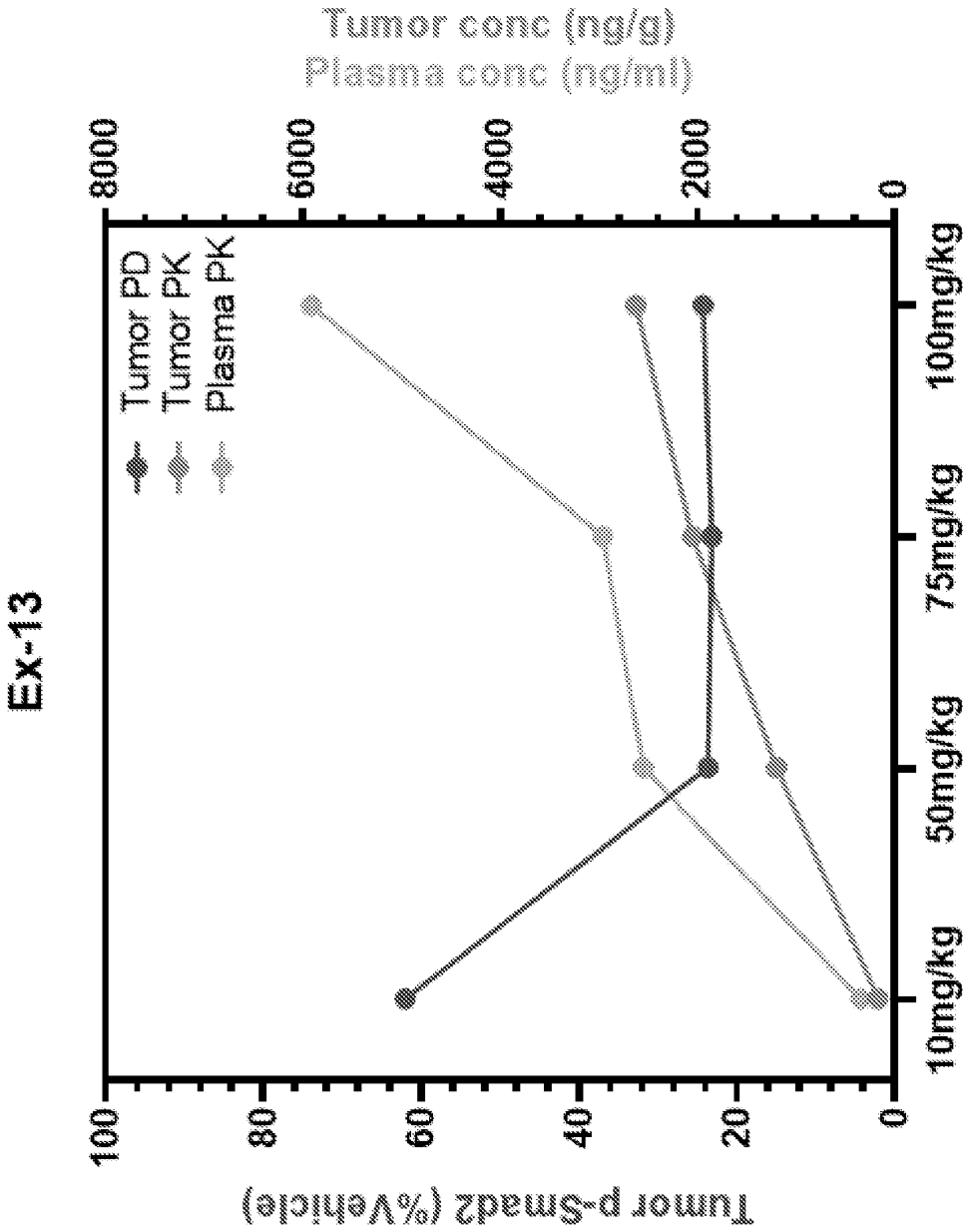

Ex-13
Tumor conc (ng/g)
Plasma conc (ng/ml)
8000
6000
4000
2000
0
Tumor PD
Tumor PK
Plasma PK
100
80
60
40
20
0
Tumor p-Smad2 (%Vehicle)
10mg/kg
50mg/kg
75mg/kg
100mg/kg

FIG. 2F

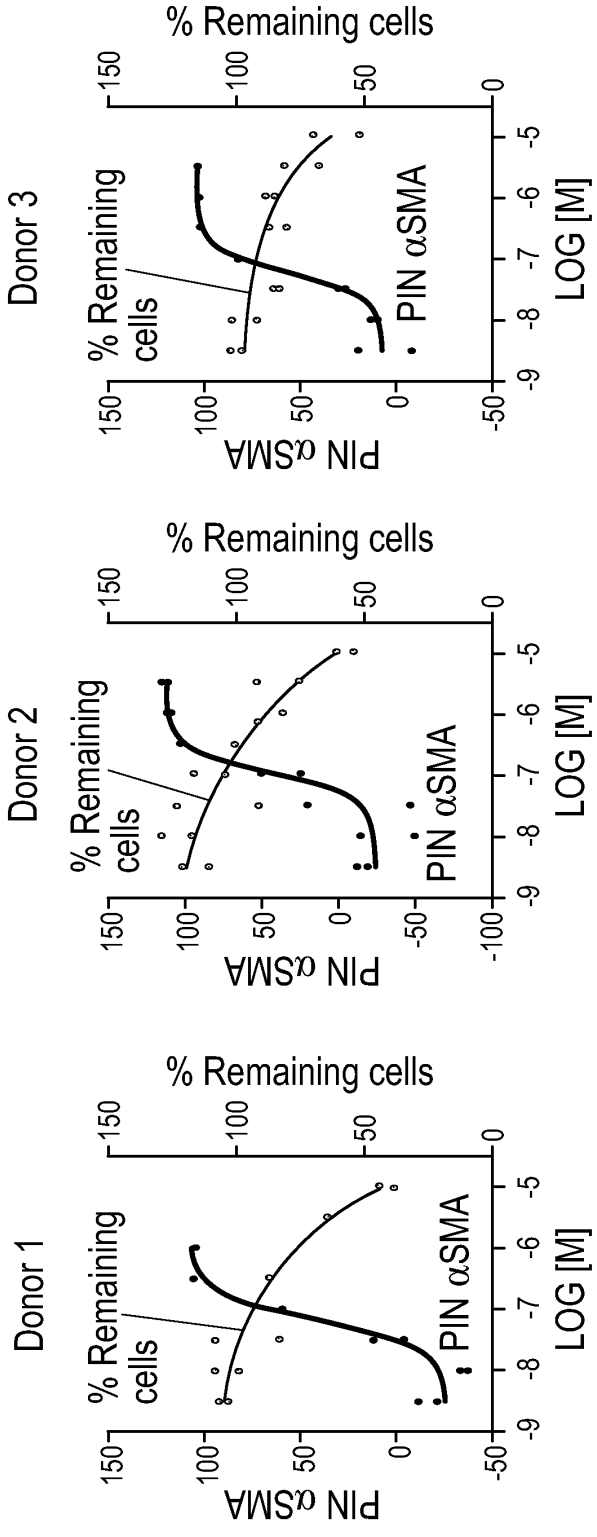

Donor 1
Donor 2
Donor 3
% Remaining cells
% Remaining cells
PIN αSMA
LOG [M]
150
100
50
0
-50
-100
-9
-8
-7
-6
-5

FIG. 3

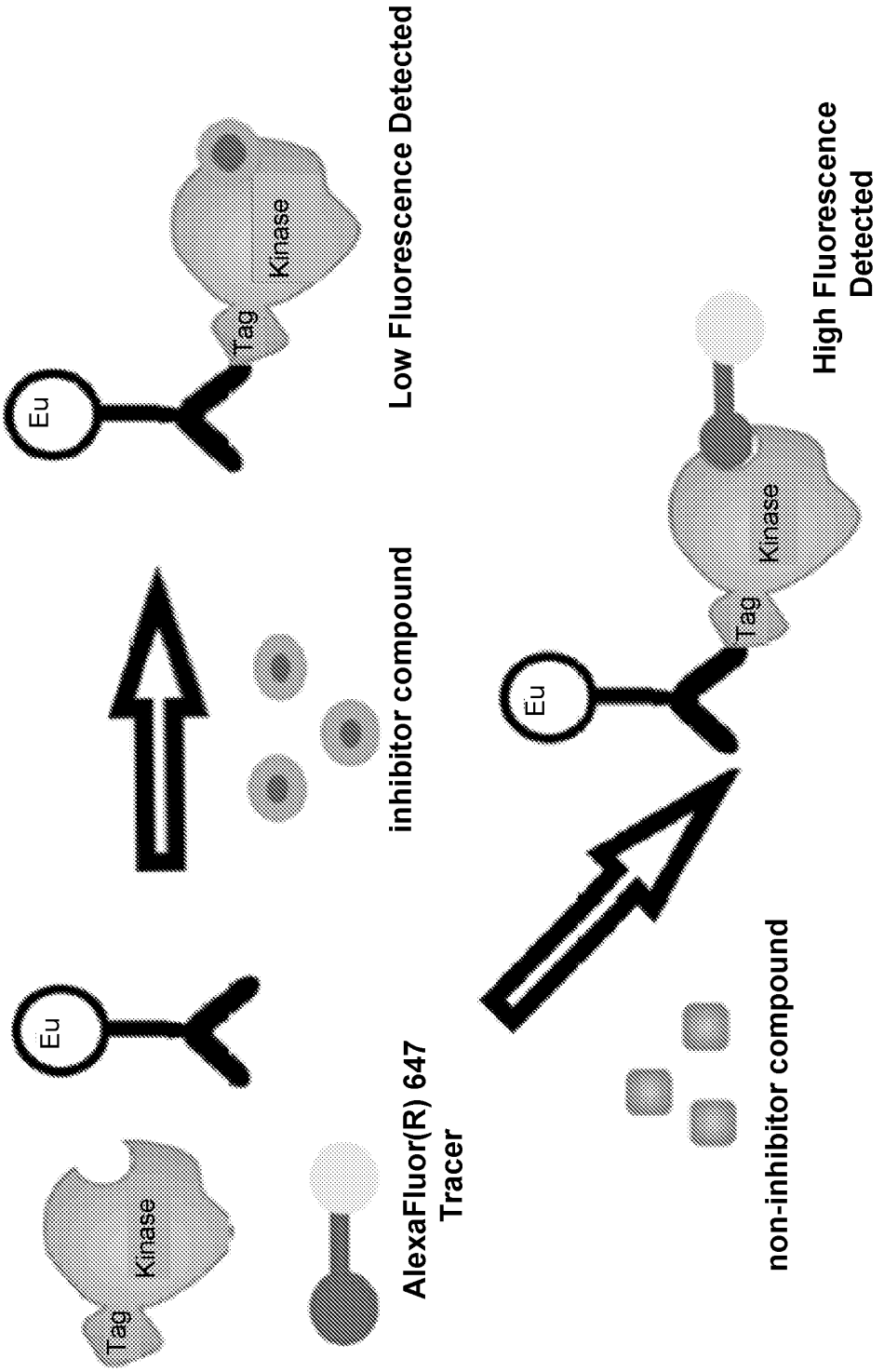

Low Fluorescence Detected
Eu
Tag
Kinase
inhibitor compound
AlexaFluor(R) 647
Tracer
Eu
Tag
Kinase
non-inhibitor compound
High Fluorescence
Detected
Eu
Tag
Kinase

FIG. 4

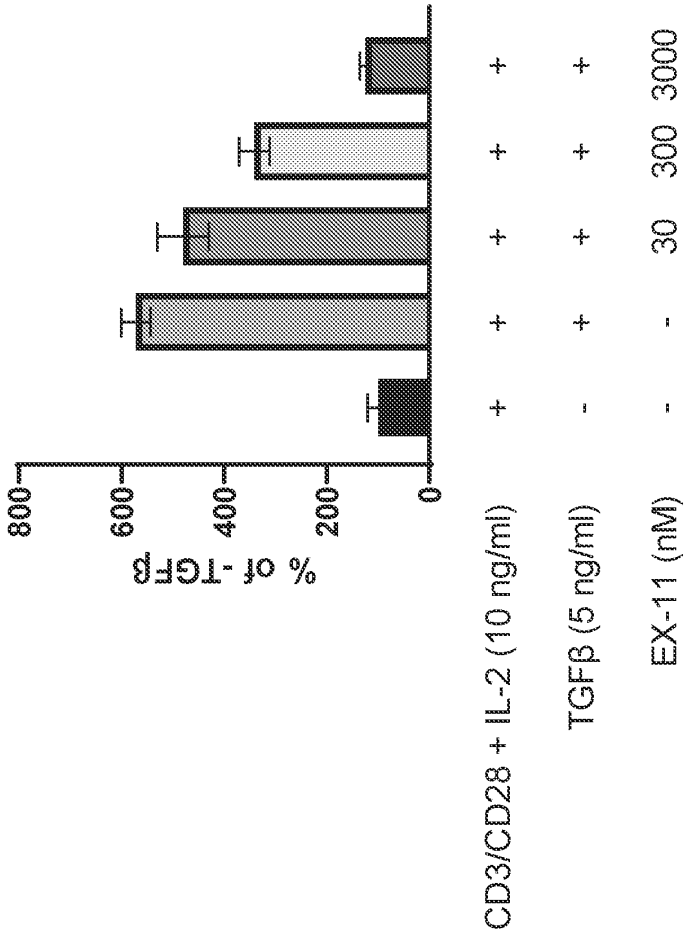

% of -TGFβ
800
600
400
200
0
CD3/CD28 + IL-2 (10 ng/ml)
TGFβ (5 ng/ml)
EX-11 (nM)
+ + + + +
- + + + +
- - 30 300 3000

FIG. 5

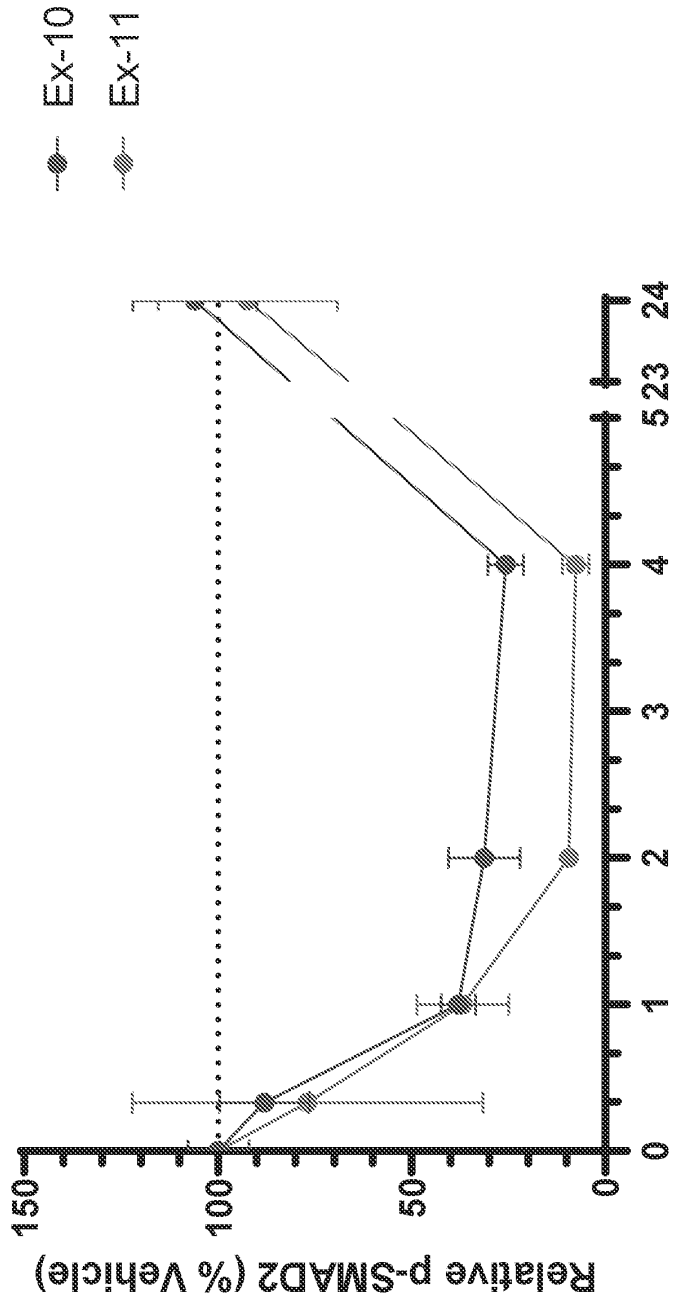

Ex-10
Ex-11
Relative p-SMAD2 (% Vehicle)
150
100
50
0
0
1
2
3
4
5
23
24
Time (h)

FIG. 6A

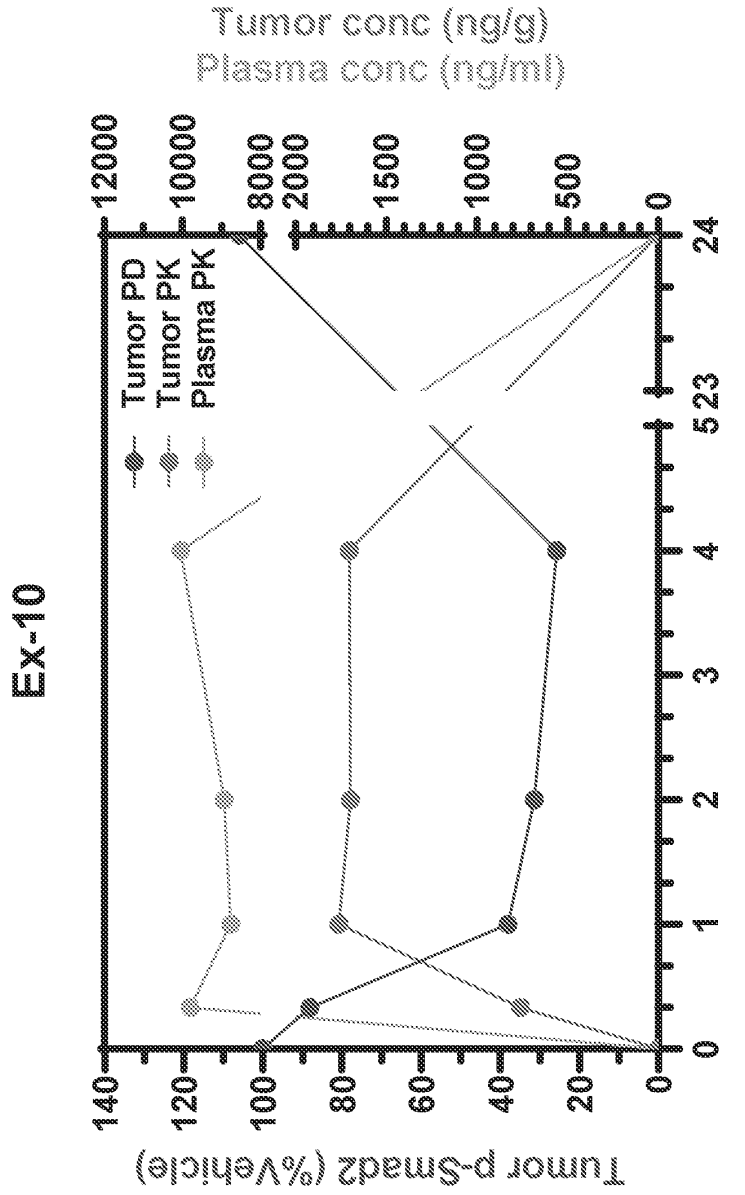

Tumor conc (ng/g)
Plasma conc (ng/ml)
12000
10000
8000
2000
1500
1000
500
0
Tumor PD
Tumor PK
Plasma PK
Ex-10
Time (h)
0
1
2
3
4
5
23
24
140
120
100
80
60
40
20
0
Tumor p-Smad2 (%Vehicle)

FIG. 6B

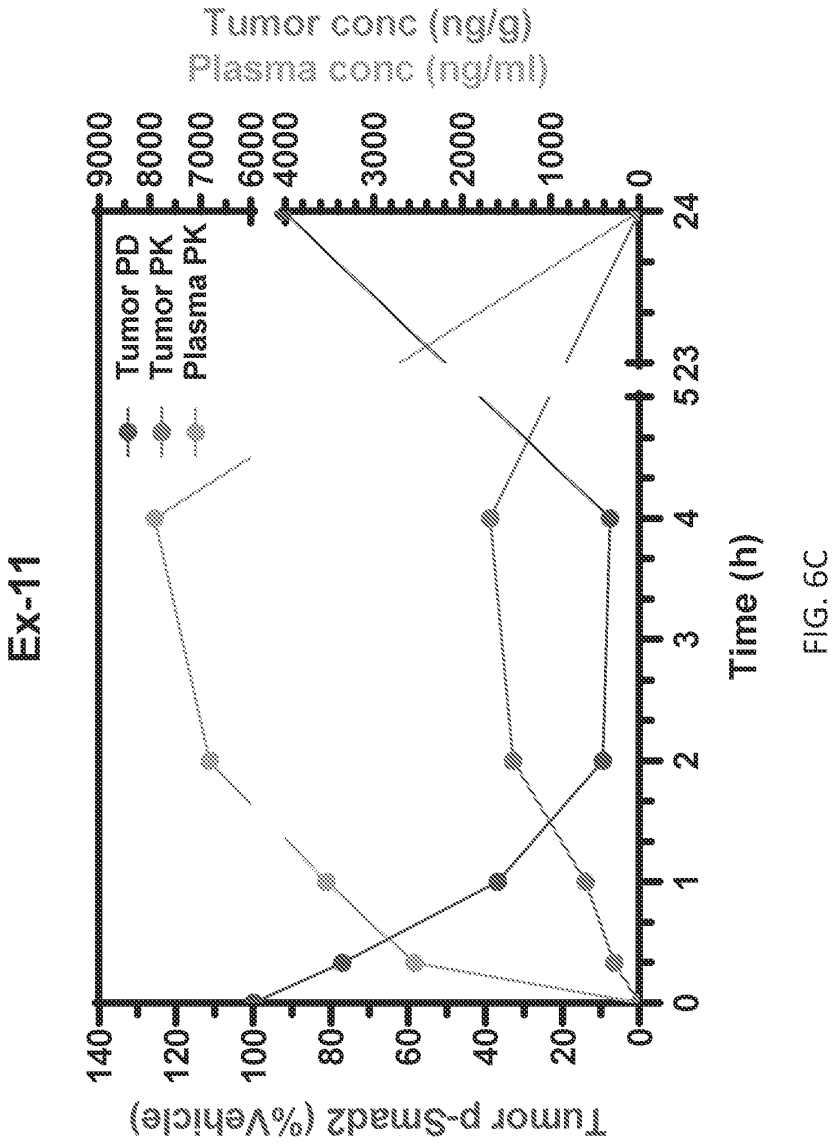

Tumor conc (ng/g)
Plasma conc (ng/ml)
9000
8000
7000
6000
4000
3000
2000
1000
0
Tumor PD
Tumor PK
Plasma PK
Ex-11
140
120
100
80
60
40
20
0
Tumor p-Smad2 (%Vehicle)
0
1
2
3
4
5
23
24
Time (h)

FIG. 6C

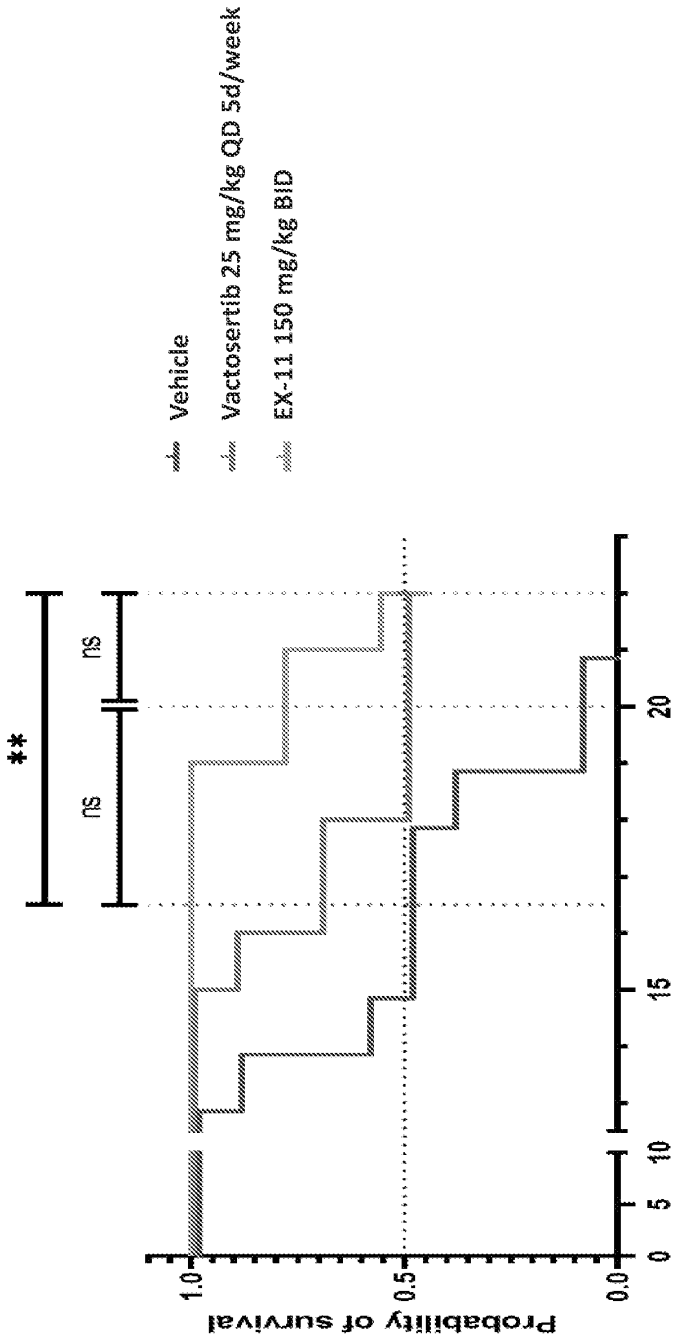

Vehicle
Vactosertib 25 mg/kg QD 5d/week
EX-11 150 mg/kg BID
**
ns
ns
Probability of survival
1.0
0.5
0.0
0
5
10
15
20
Days after dosing start

FIG. 7

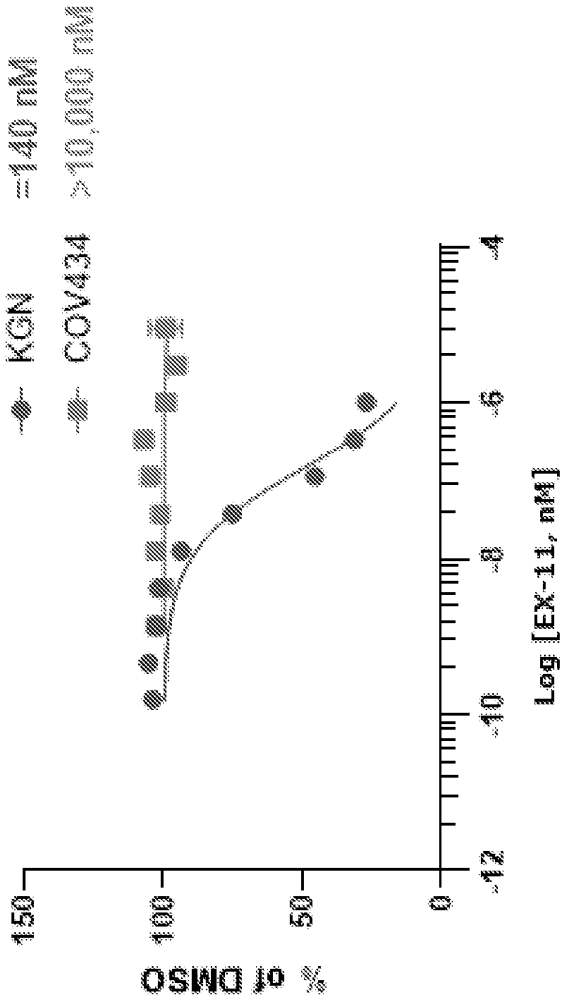

IC50
KGN =140 nM
COV434 >10,000 nM
% of DMSO
150
100
50
0
-12
-10
-8
-6
-4
Log [EX-11, nM]

FIG. 8

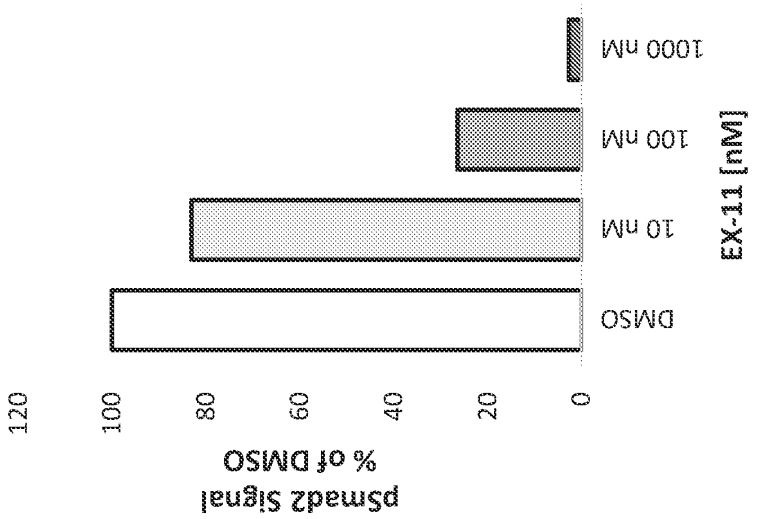

pSmad2 Signal
% of DMSO
120
100
80
60
40
20
0
DMSO
10 nM
100 nM
1000 nM
EX-11 [nM]

FIG. 9

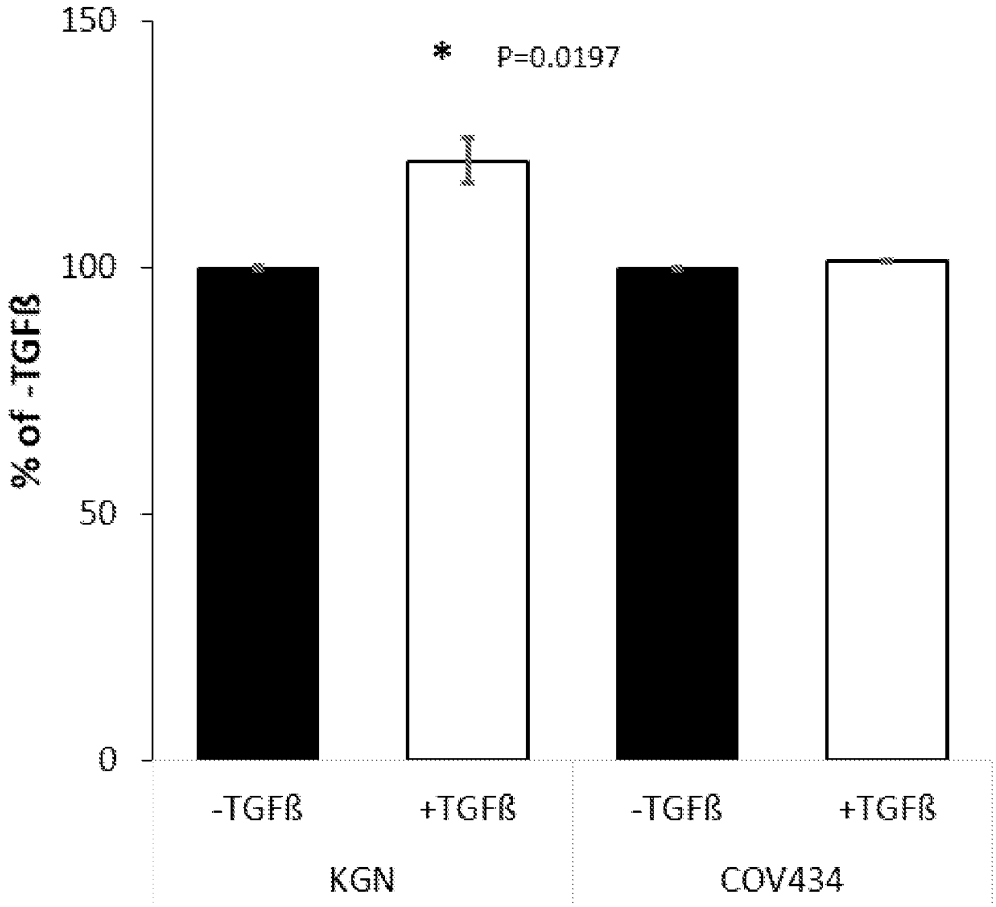


FIG. 10

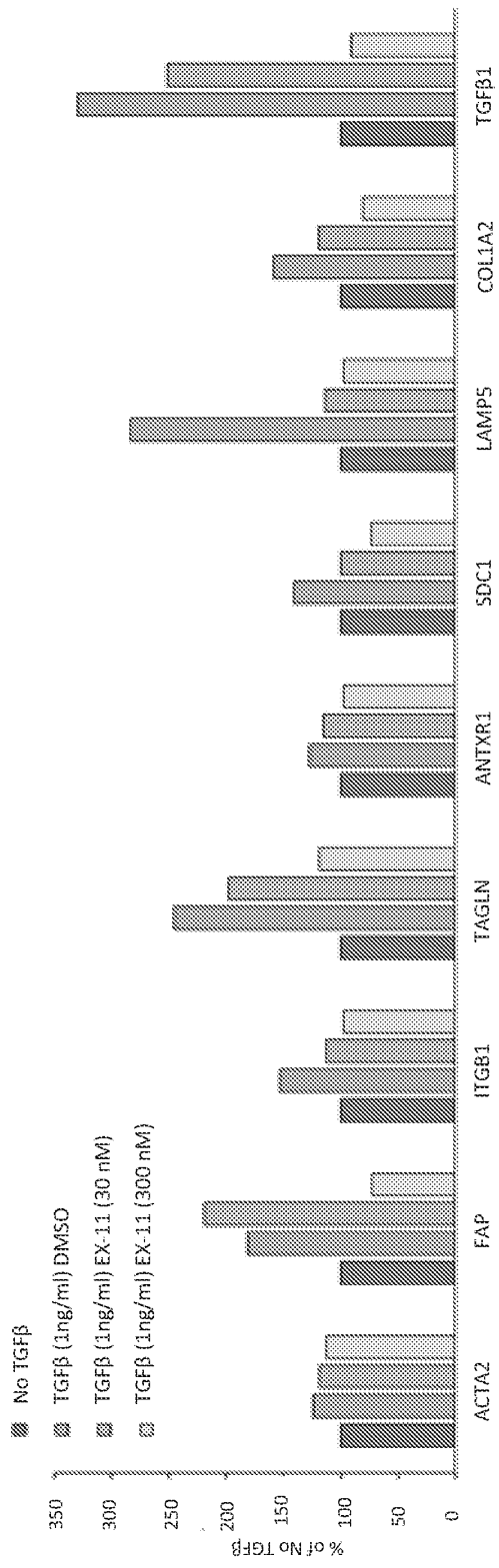

No TGFβ
TGFβ (1ng/ml) DMSO
TGFβ (1ng/ml) EX-11 (30 nM)
TGFβ (1ng/ml) EX-11 (300 nM)
% of No TGFβ
350
300
250
200
150
100
50
0
ACTA2
FAP
ITGB1
TAGLN
ANTXR1
SDC1
LAMP5
COL1A2
TGFβ1

FIG. 11

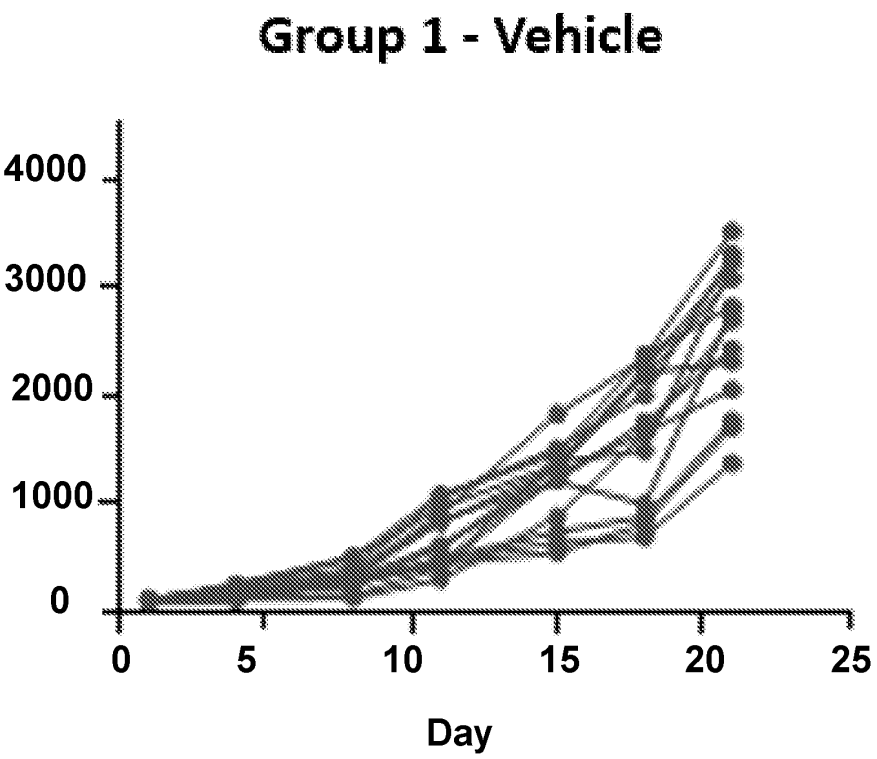


FIG. 12A

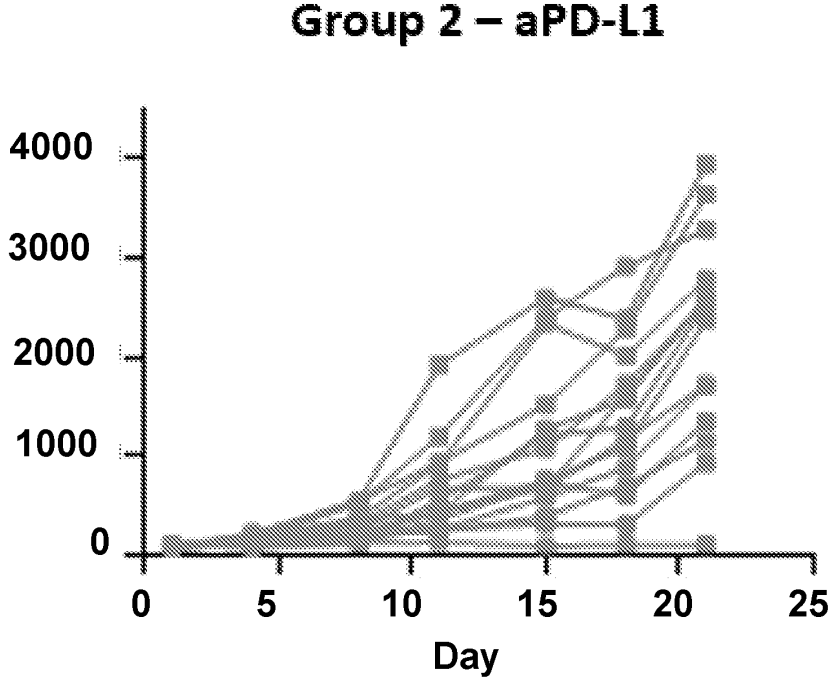


FIG. 12B

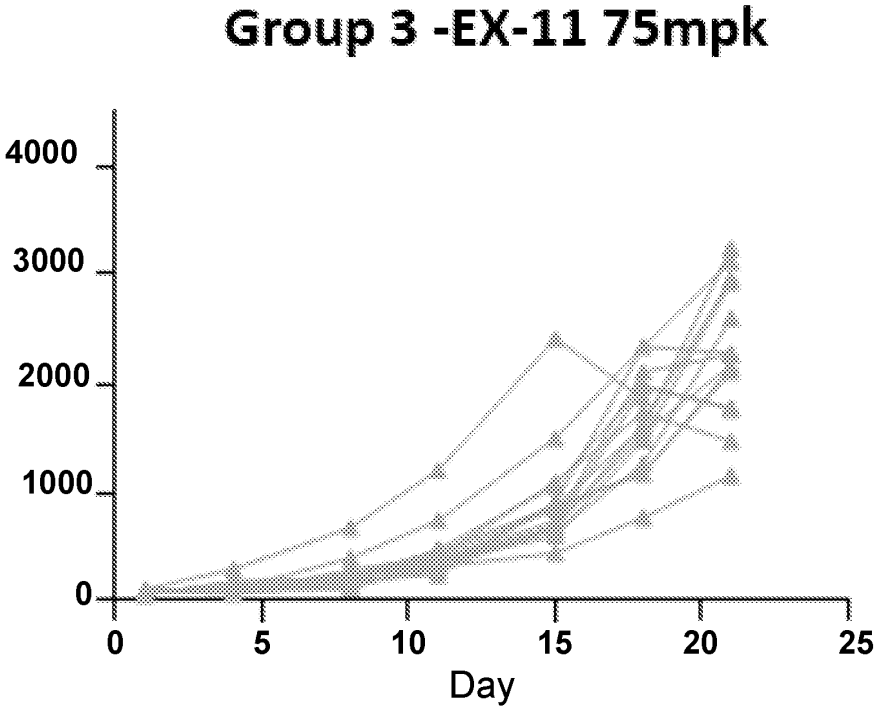


FIG. 12C

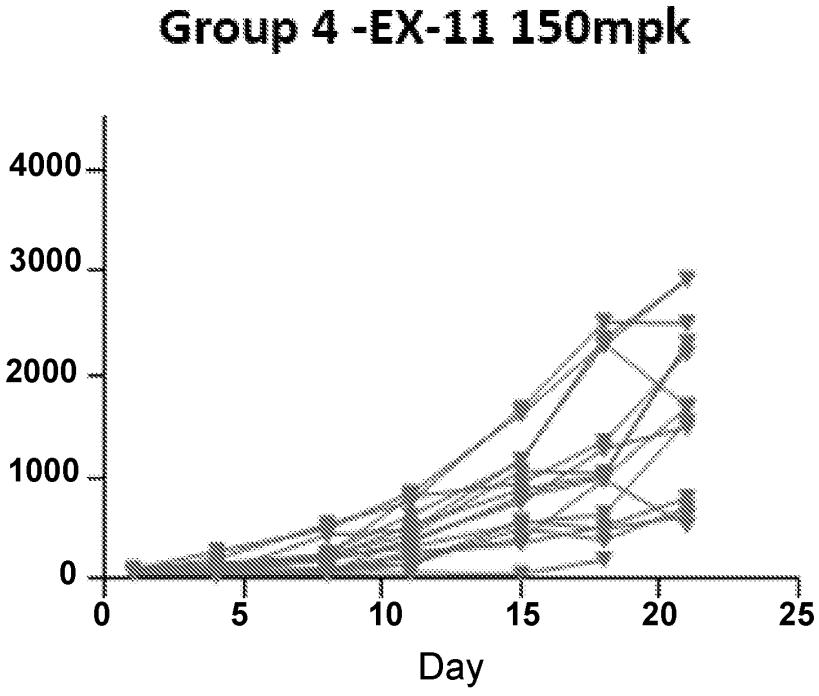


FIG. 12D

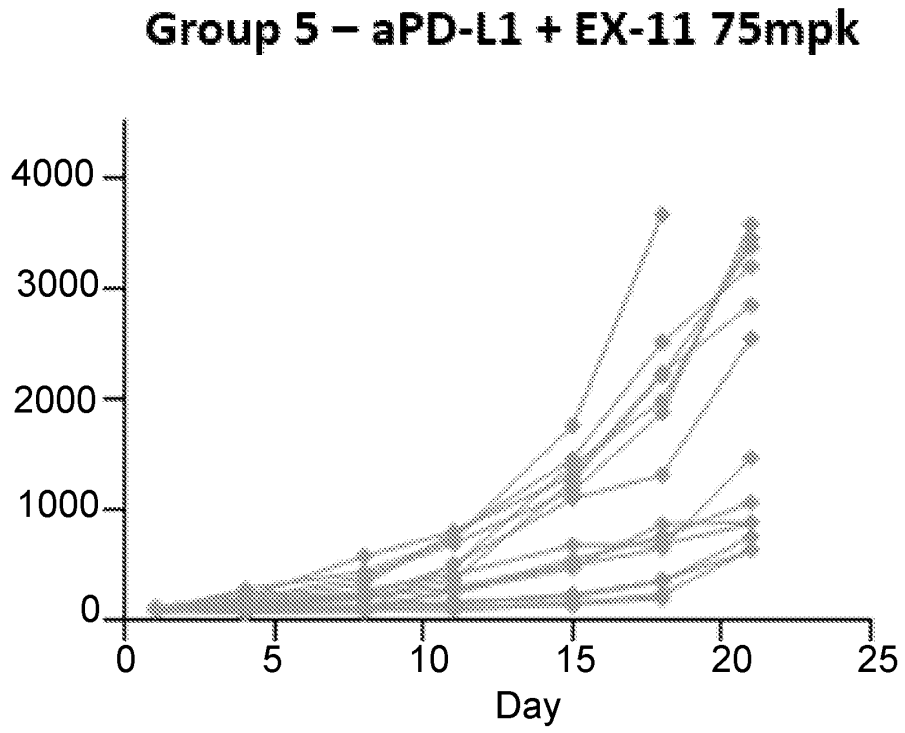


FIG. 12E

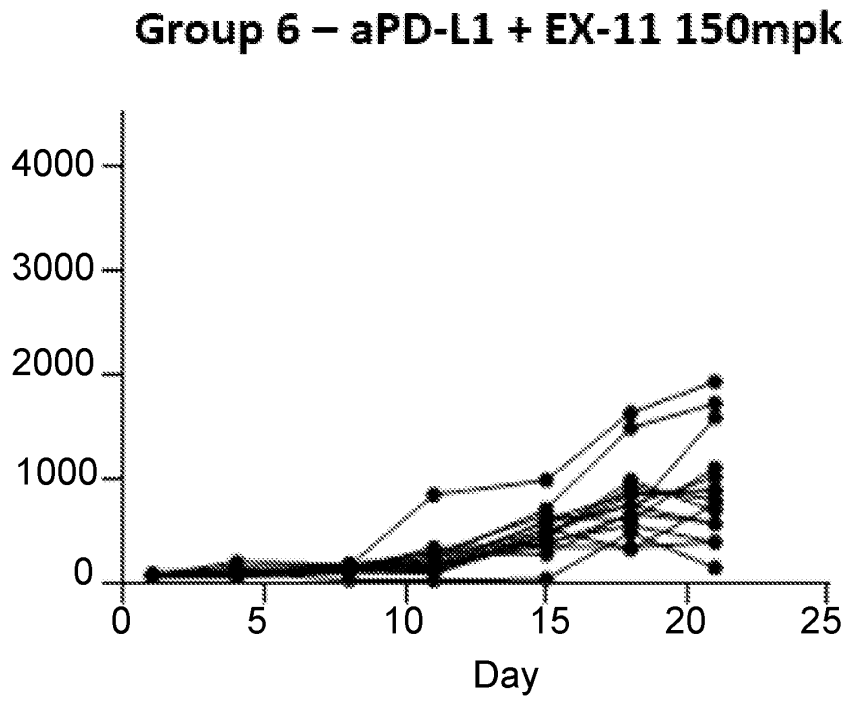


FIG. 12F

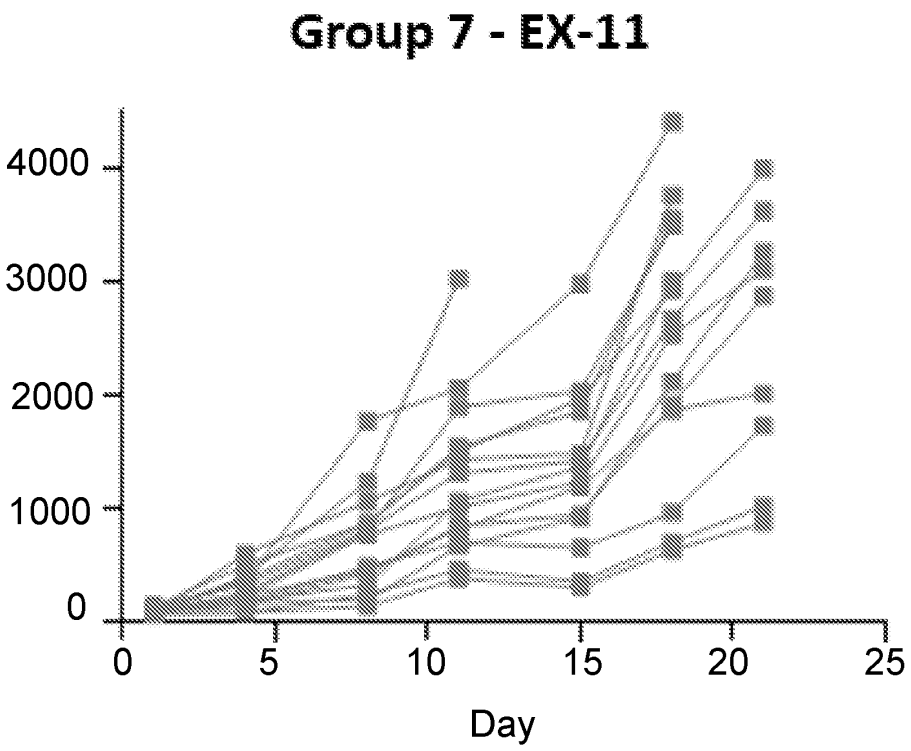


FIG. 12G

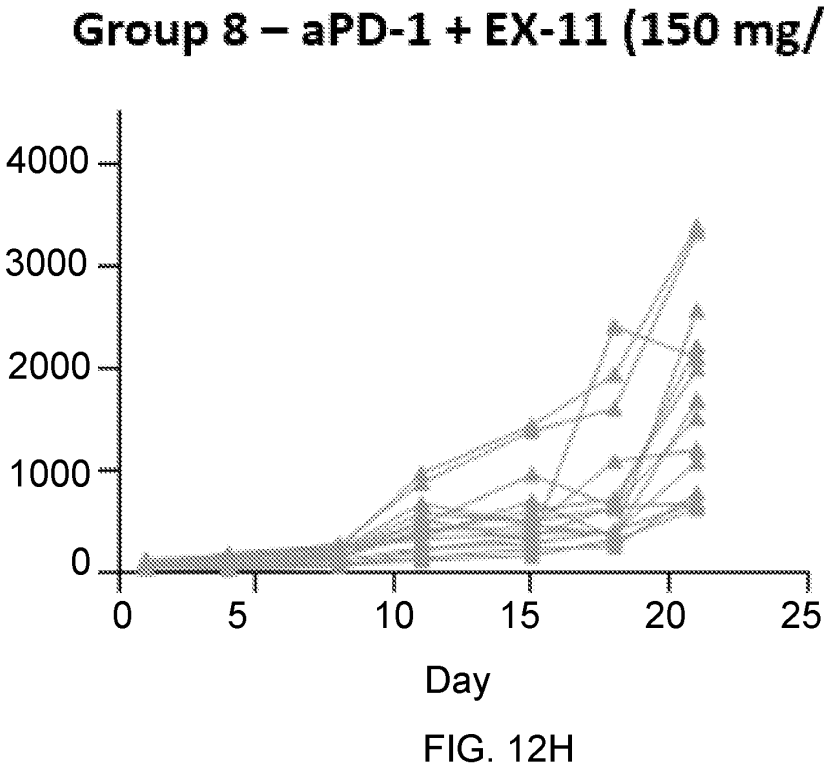


FIG. 12H

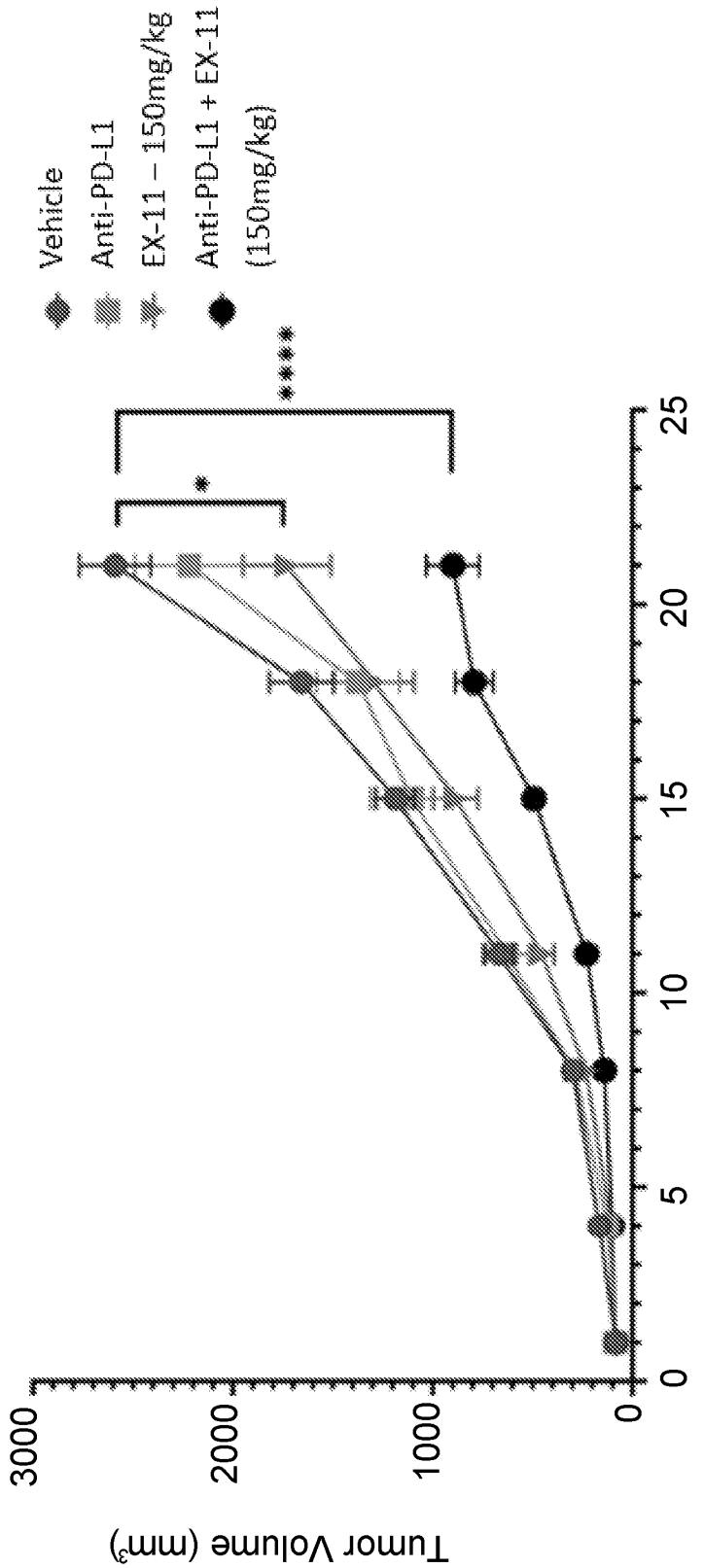

Vehicle
Anti-PD-L1
EX-11 – 150mg/kg
Anti-PD-L1 + EX-11
(150mg/kg)
****
*
Tumor Volume (mm³)
3000
2000
1000
0
0
5
10
15
20
25
Day

FIG. 12I

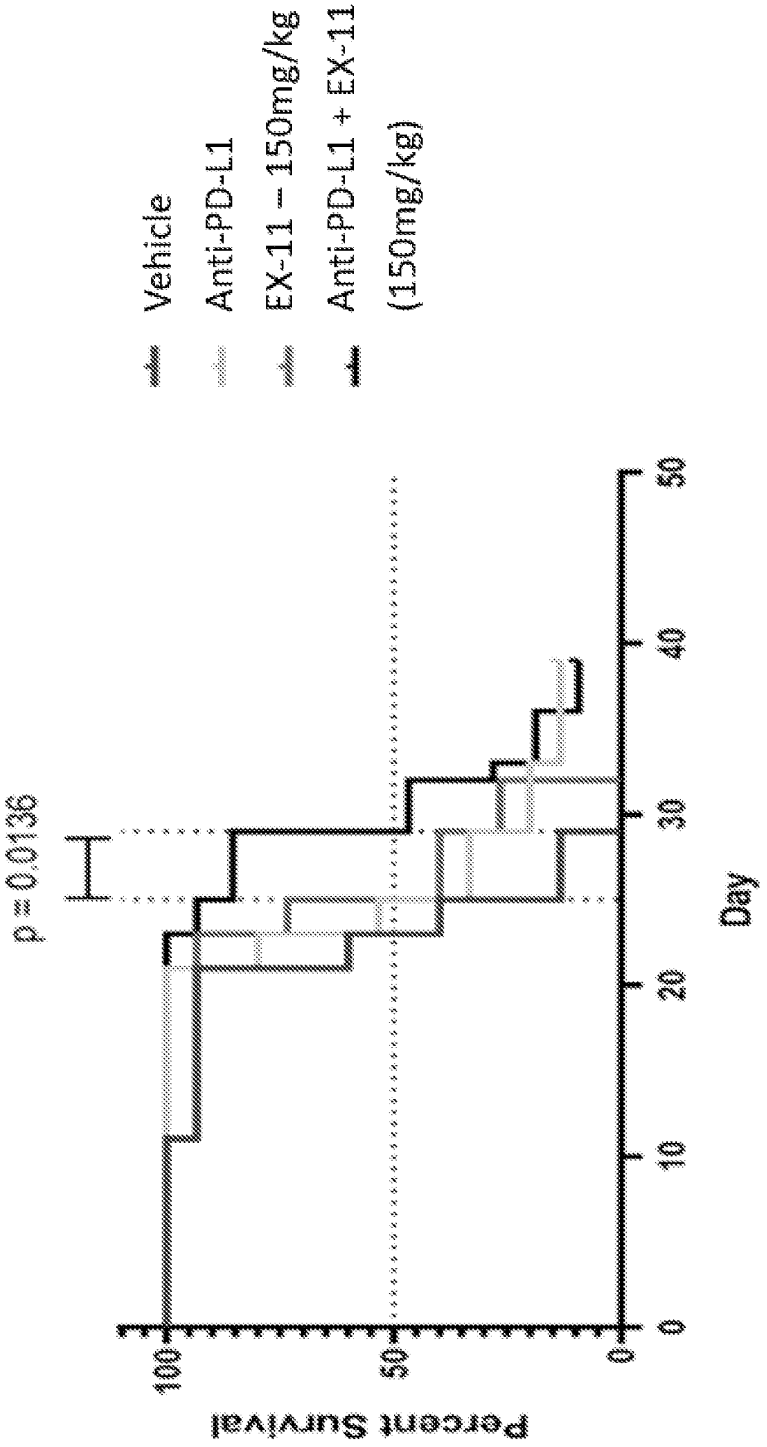

Vehicle
Anti-PD-L1
EX-11 – 150mg/kg
Anti-PD-L1 + EX-11
(150mg/kg)
p = 0.0136
Percent Survival
100
50
0
0
10
20
30
40
50
Day

FIG. 12J

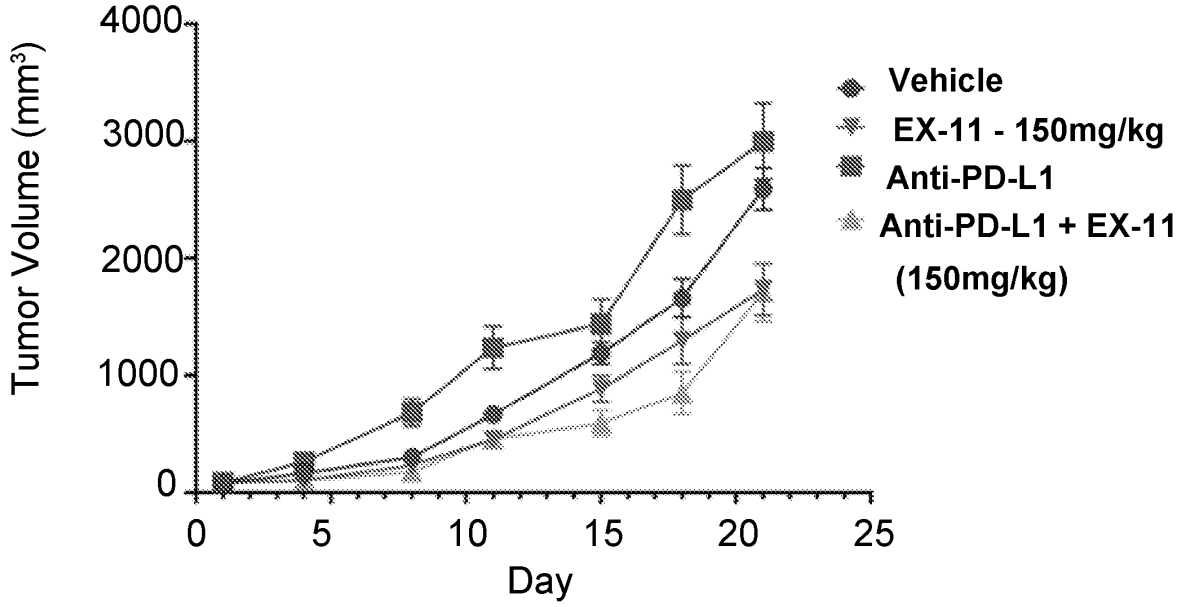


FIG. 12K

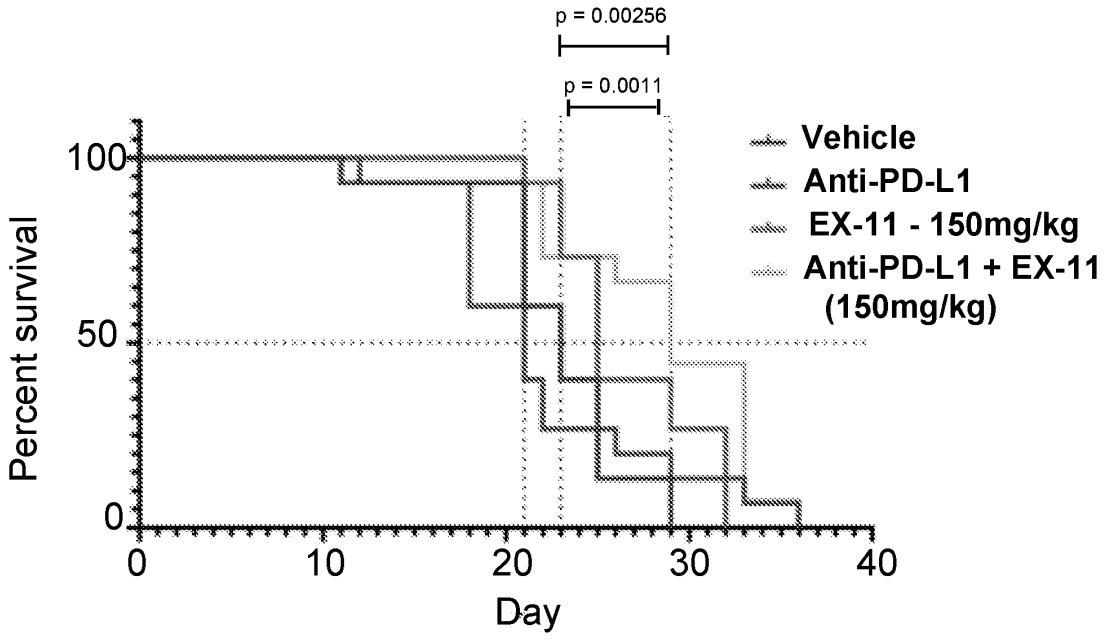


FIG. 12L

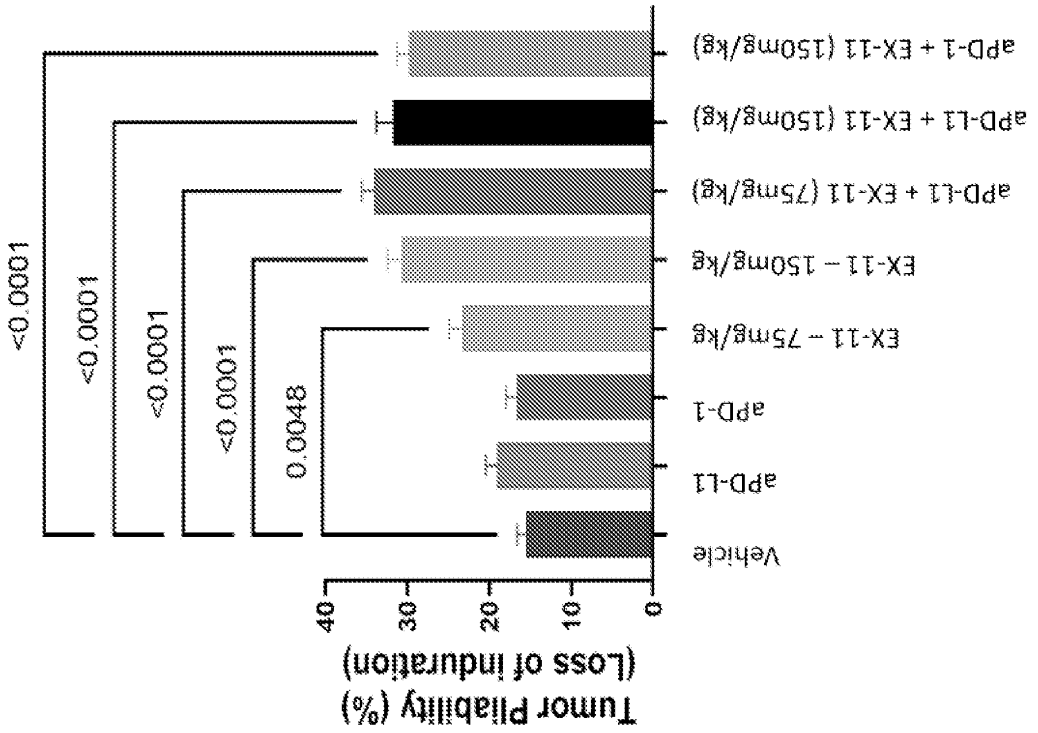

Tumor Pliability (%)
(Loss of induration)
40
30
20
10
0
Vehicle
aPD-L1
aPD-1
EX-11 – 75mg/kg
EX-11 – 150mg/kg
aPD-L1 + EX-11 (75mg/kg)
aPD-L1 + EX-11 (150mg/kg)
aPD-1 + EX-11 (150mg/kg)
0.0048
<0.0001
<0.0001
<0.0001
<0.0001

FIG. 12M

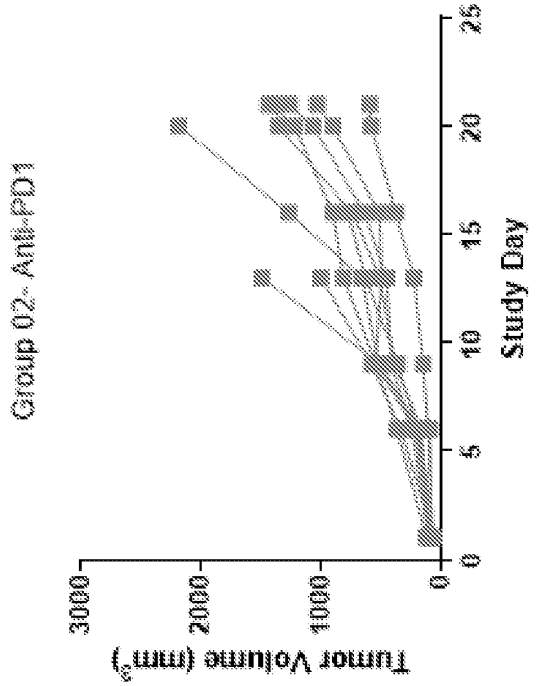


FIG. 13B

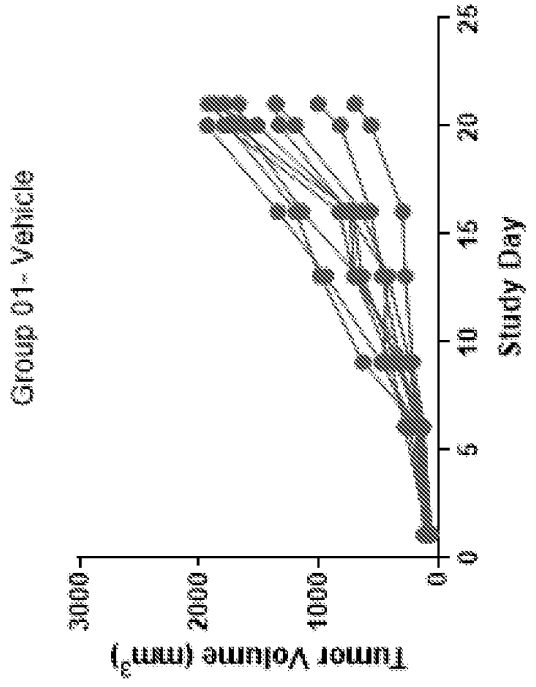


FIG. 13A

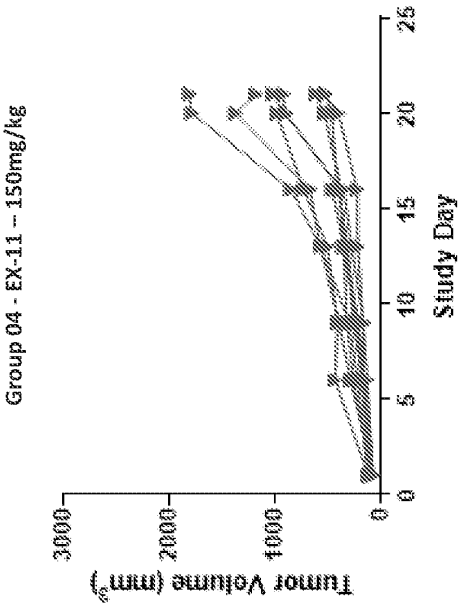


FIG. 13D

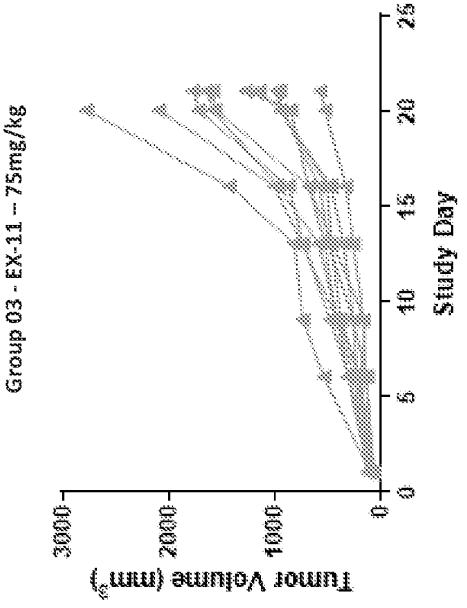


FIG. 13C

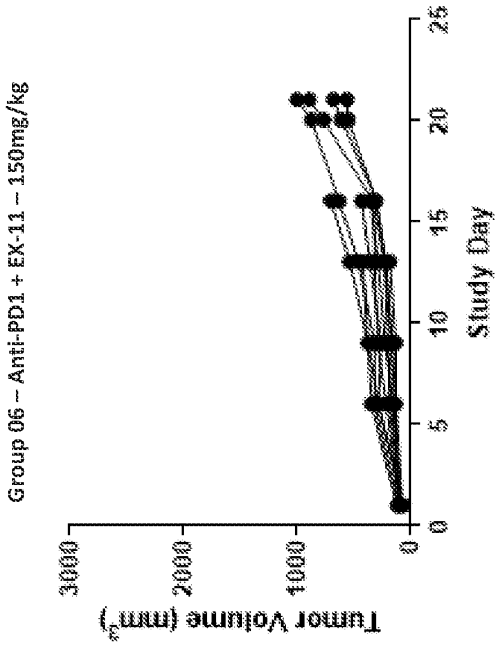


FIG. 13F

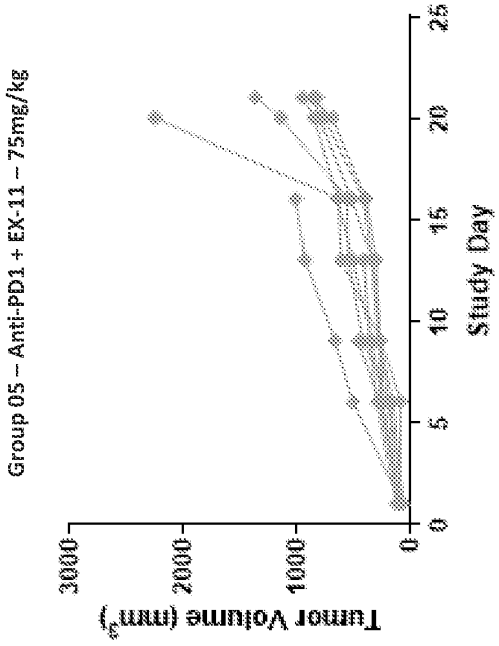


FIG. 13E

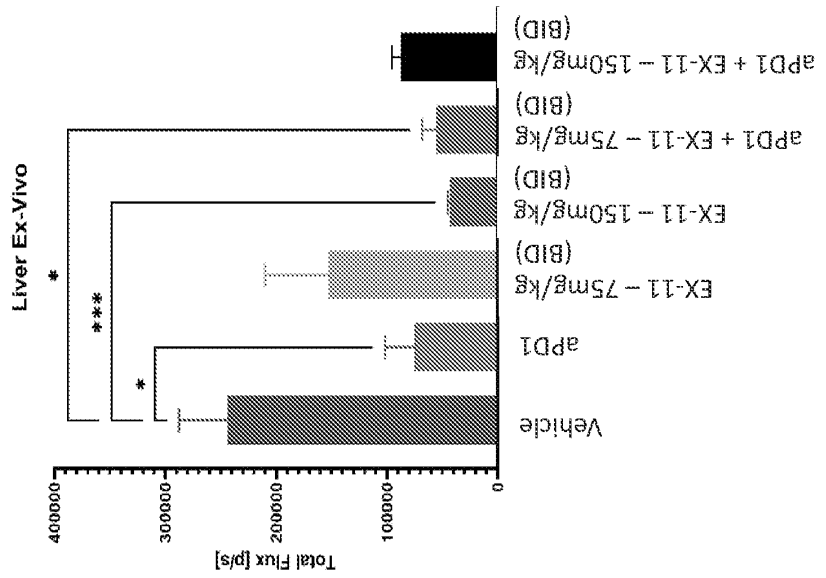

Liver Ex-Vivo
Total Flux [p/s]
400000
300000
200000
100000
0
*
***
*
Vehicle
aPD1
EX-11 – 75mg/kg (BID)
EX-11 – 150mg/kg (BID)
aPD1 + EX-11 – 75mg/kg (BID)
aPD1 + EX-11 – 150mg/kg (BID)

FIG. 13G

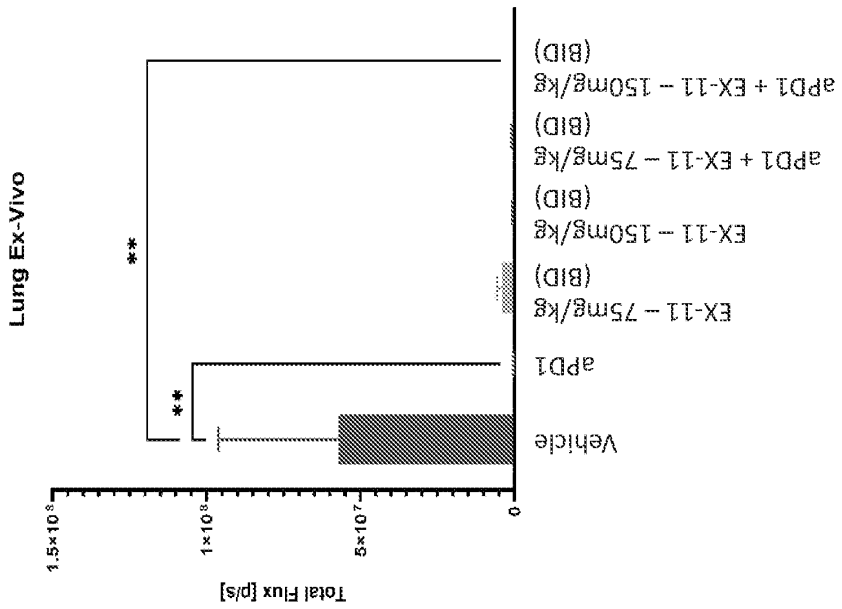

Lung Ex-Vivo
Total Flux [p/s]
1.5×10⁸
1×10⁸
5×10⁷
0
**
**
Vehicle
aPD1
EX-11 – 75mg/kg (BID)
EX-11 – 150mg/kg (BID)
aPD1 + EX-11 – 75mg/kg (BID)
aPD1 + EX-11 – 150mg/kg (BID)

FIG. 13H

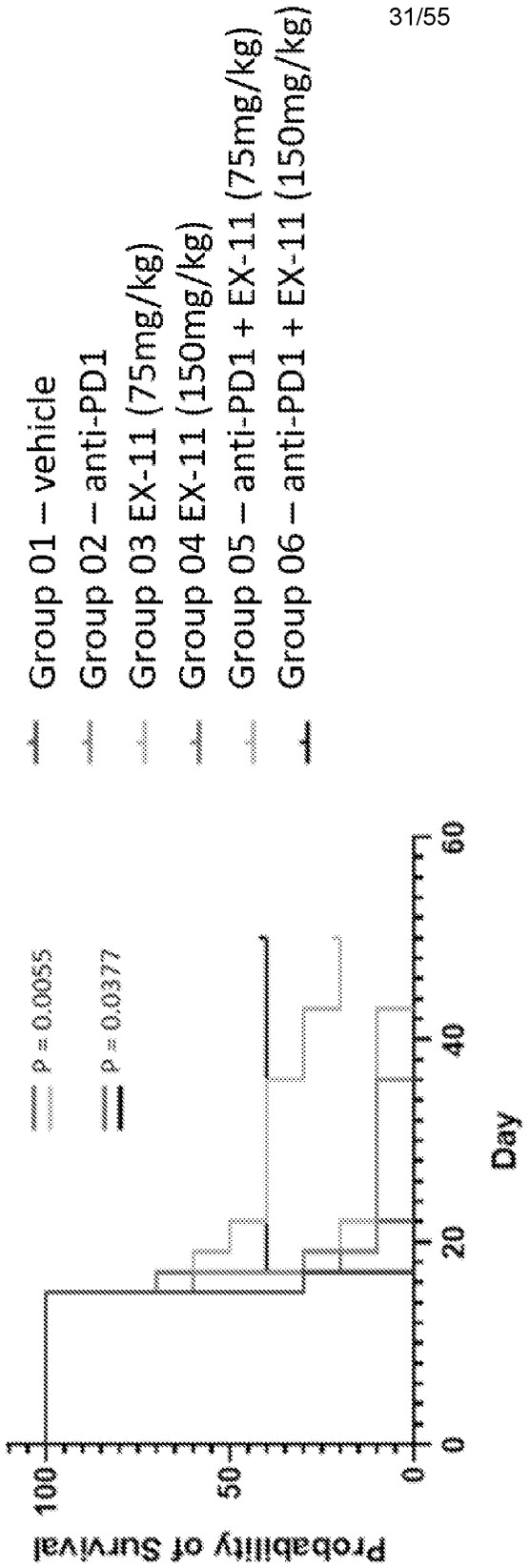

Group 01 – vehicle
Group 02 – anti-PD1
Group 03 EX-11 (75mg/kg)
Group 04 EX-11 (150mg/kg)
Group 05 – anti-PD1 + EX-11 (75mg/kg)
Group 06 – anti-PD1 + EX-11 (150mg/kg)
p = 0.0055
p = 0.0377
Probability of Survival
100
50
0
0
20
40
60
Day

FIG. 14A

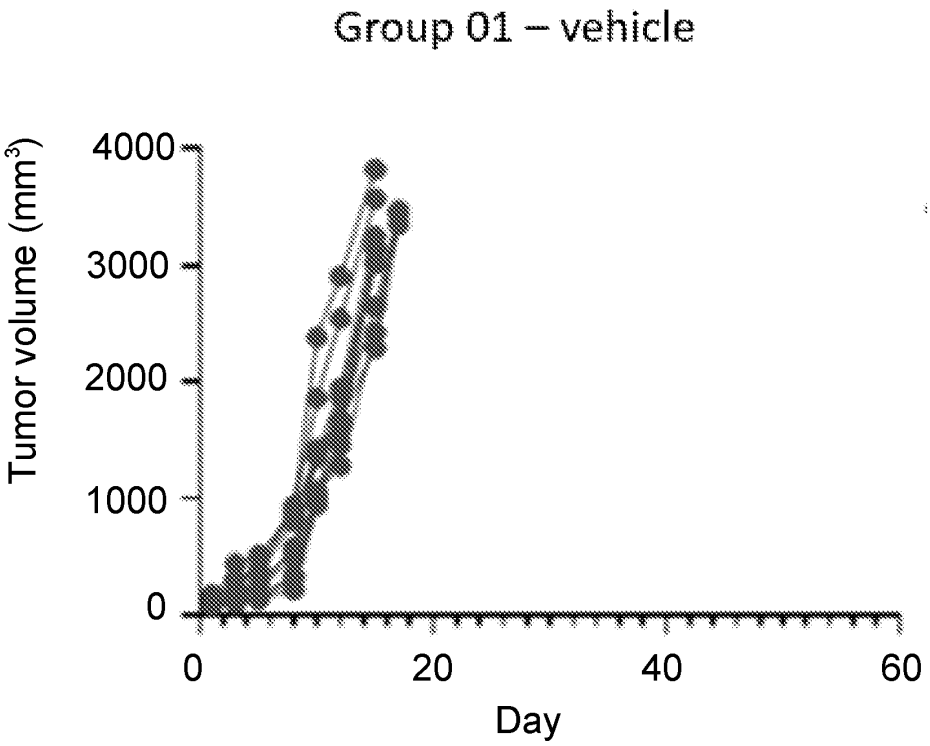


FIG. 14B

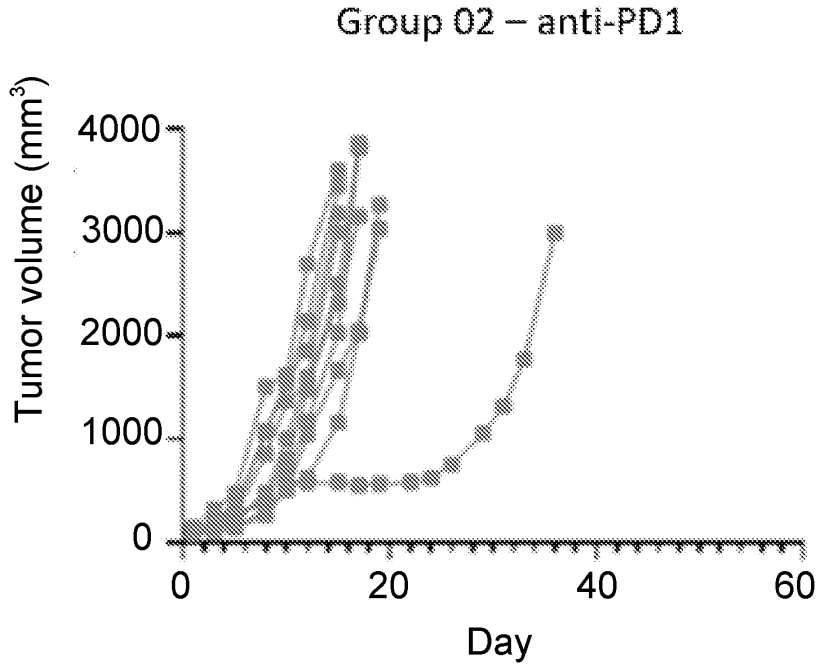


FIG. 14C

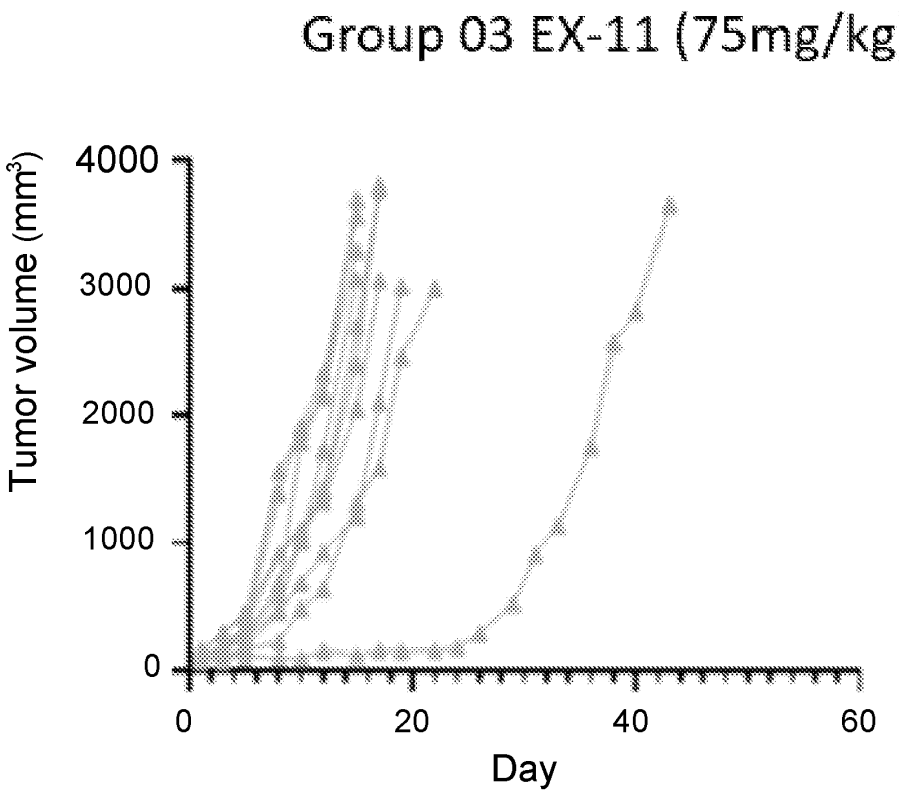


FIG. 14D

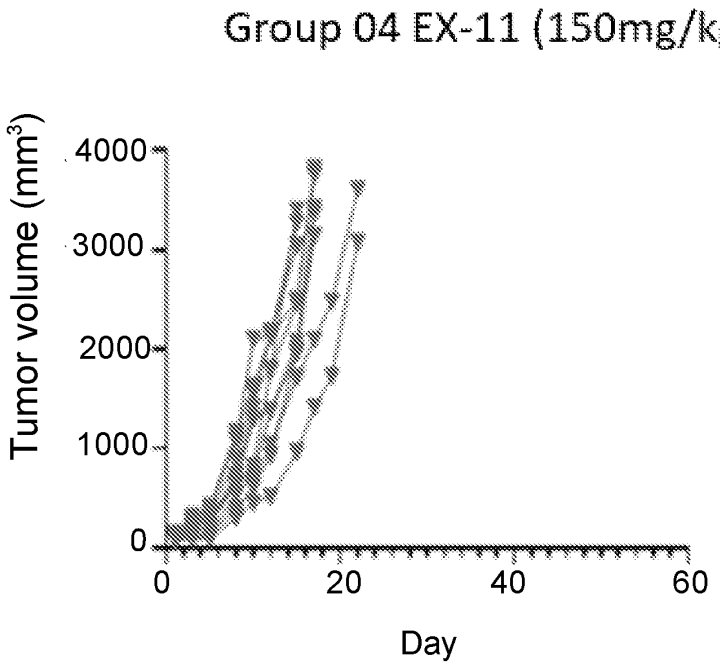


FIG. 14E

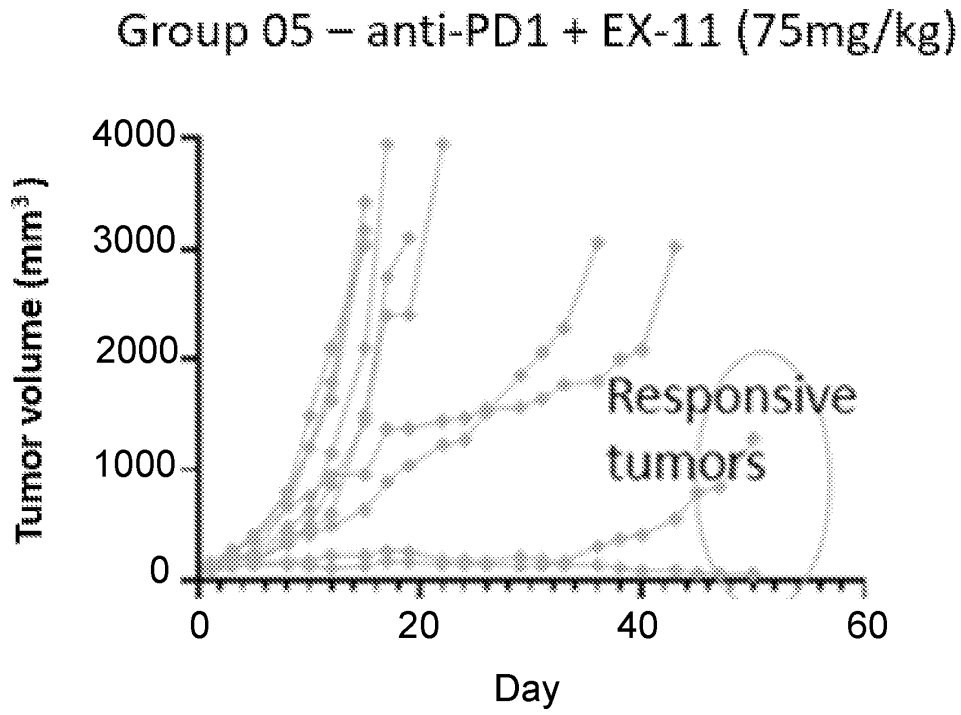


FIG. 14F

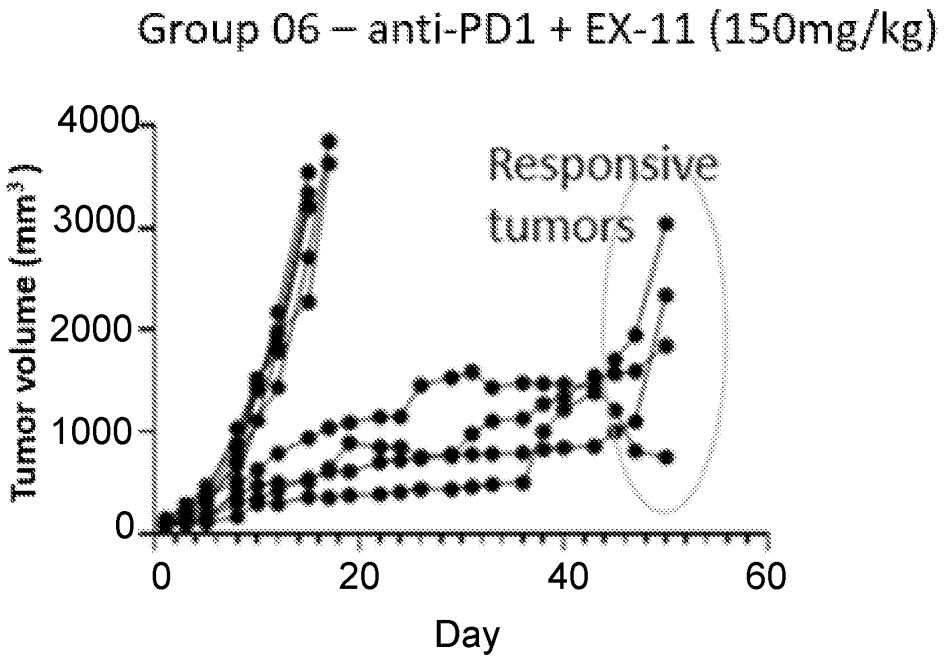


FIG. 14G

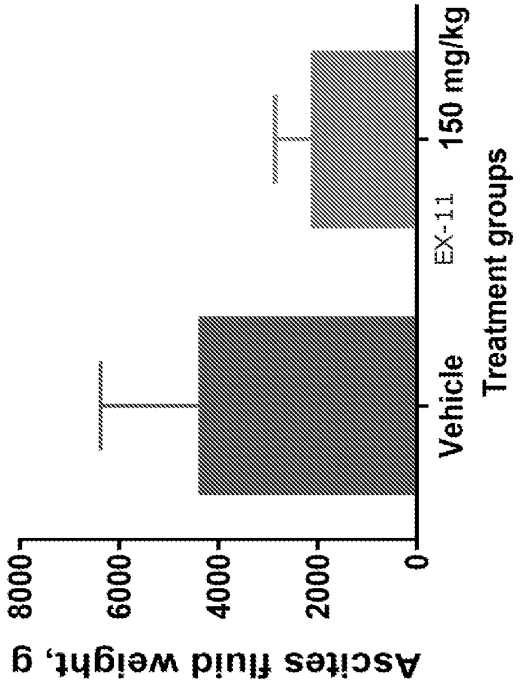

Ascites fluid weight, g
8000
6000
4000
2000
0
Vehicle
EX-11
150 mg/kg
Treatment groups

FIG. 15A

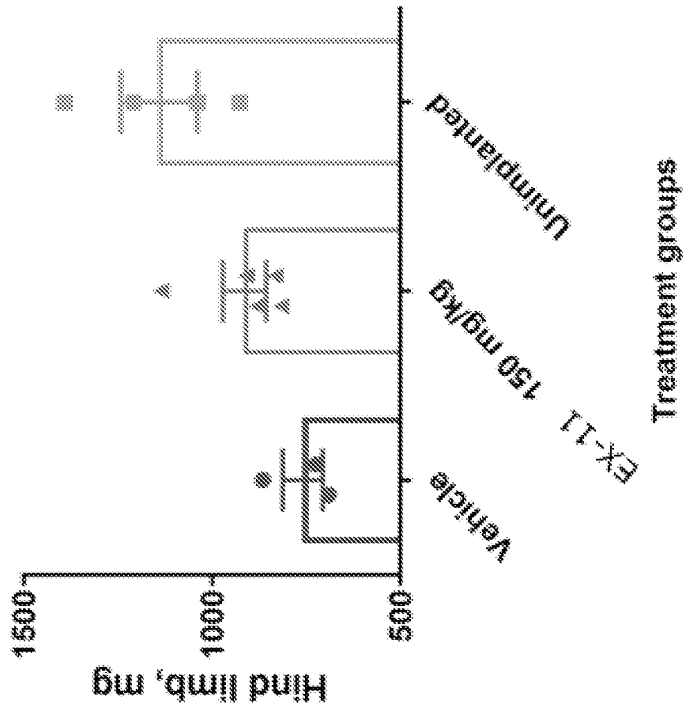

Hind limb, mg
1500
1000
500
Vehicle
Ex-11 150 mg/kg
Unimplanted
Treatment groups

FIG. 15B

FIG. 16

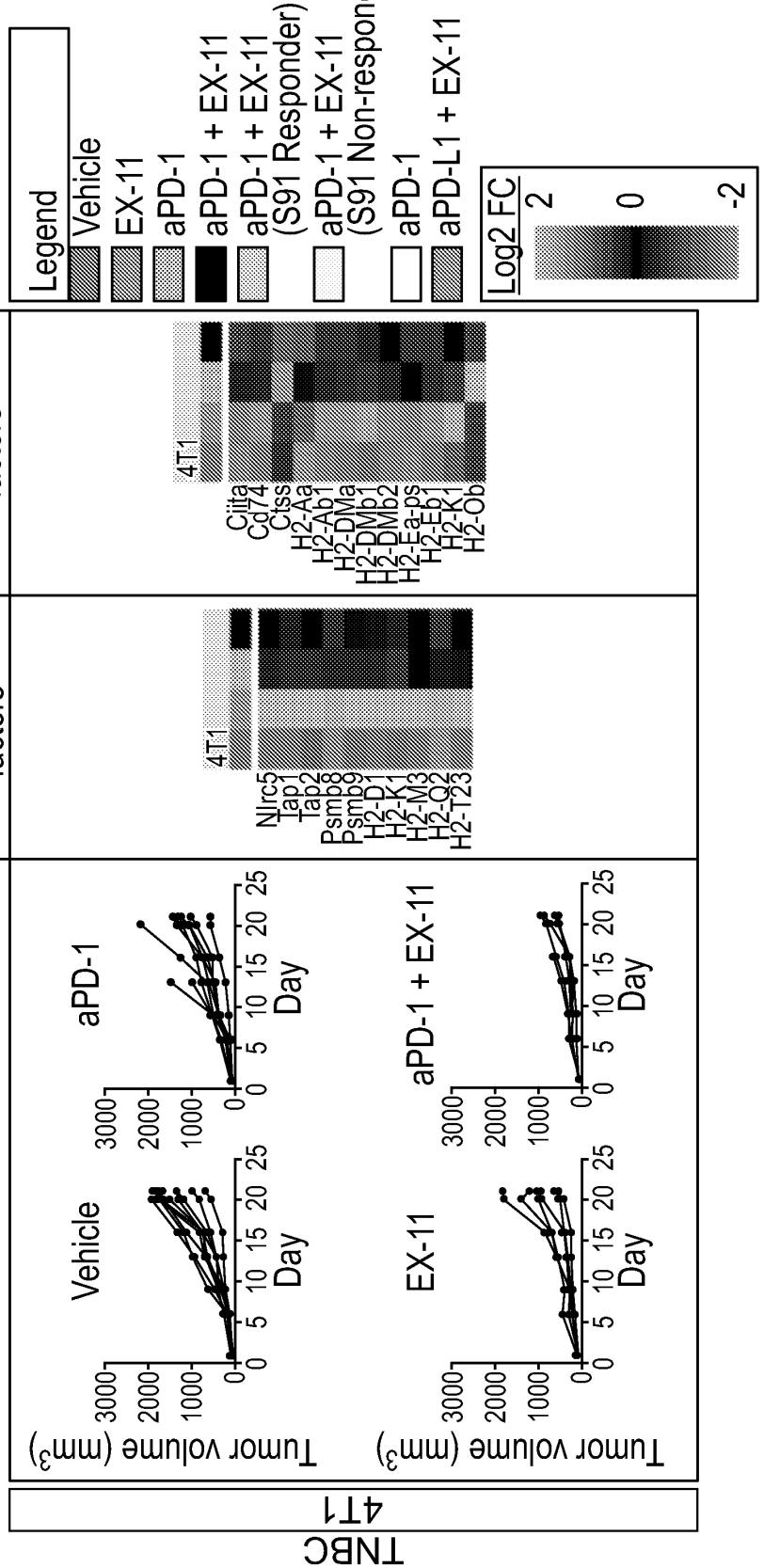

TNBC
4T1
Tumor volume (mm3)
Vehicle
EX-11
aPD-1
aPD-1 + EX-11
Day
MHC class I factors
MHC class II factors
4T1
Nlrc5
Tap1
Tap2
Psmb8
Psmb9
H2-D1
H2-K1
H2-M3
H2-Q2
H2-T23
Ciita
Cd74
Ctss
H2-Aa
H2-Ab1
H2-DMa
H2-DMb1
H2-DMb2
H2-Ea-ps
H2-Eb1
H2-K1
H2-Ob
Legend
Vehicle
EX-11
aPD-1
aPD-1 + EX-11
aPD-1 + EX-11 (S91 Responder)
aPD-1 + EX-11 (S91 Non-responder)
aPD-1
aPD-L1 + EX-11
Log2 FC
2
0
-2

FIG. 16 (cont.)

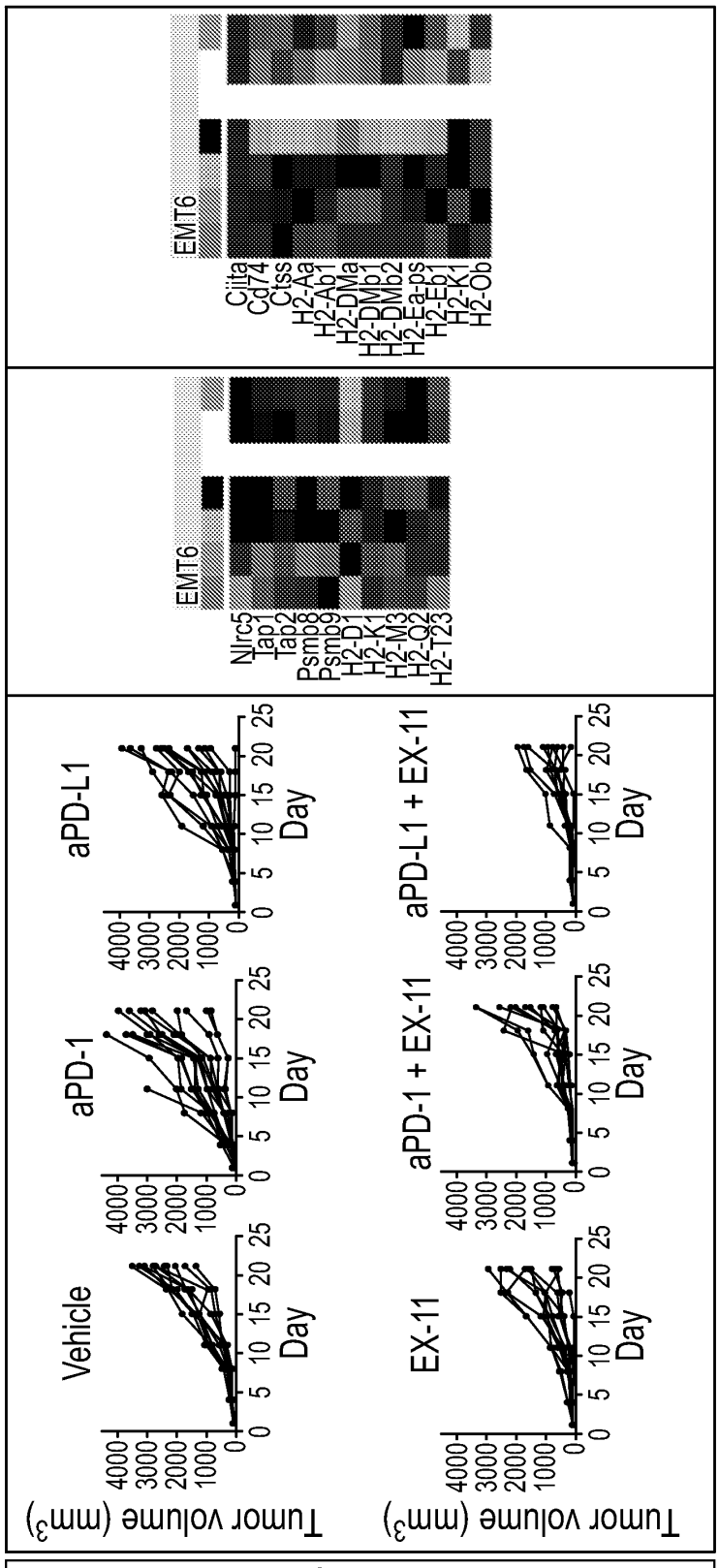
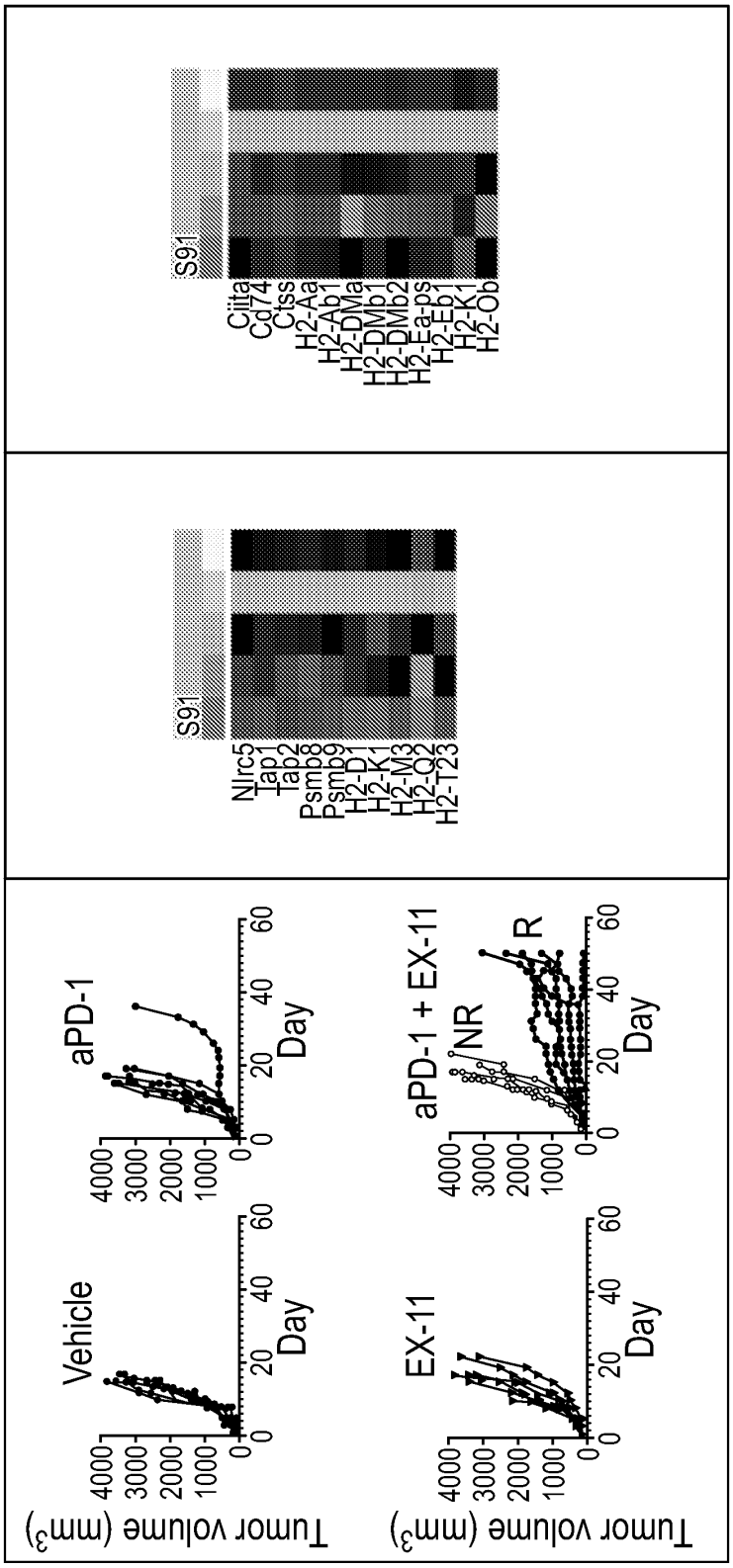

TNBC
EMT6
Tumor volume (mm3)
Vehicle
aPD-1
aPD-L1
EX-11
aPD-1 + EX-11
aPD-L1 + EX-11
Day
0 5 10 15 20 25
1000 2000 3000 4000
EMT6
Nlrc5
Tap1
Tap2
Psmb8
Psmb9
H2-D1
H2-K1
H2-M3
H2-Q2
H2-T23
Ciita
Cd74
Ctss
H2-Aa
H2-Ab1
H2-DMa
H2-DMb1
H2-DMb2
H2-Ea-ps
H2-Eb1
H2-K1
H2-Ob

FIG. 16 (cont.)


Melanoma
S91
Tumor volume (mm3)
Vehicle
aPD-1
EX-11
aPD-1 + EX-11
NR
R
Day
0
20
40
60
1000
2000
3000
4000
S91
Nlrc5
Tap1
Tap2
Psmb8
Psmb9
H2-D1
H2-K1
H2-M3
H2-Q2
H2-T23
S91
Ciita
Cd74
Ctss
H2-Aa
H2-Ab1
H2-DMa
H2-DMb1
H2-DMb2
H2-Ea-ps
H2-Eb1
H2-K1
H2-Ob

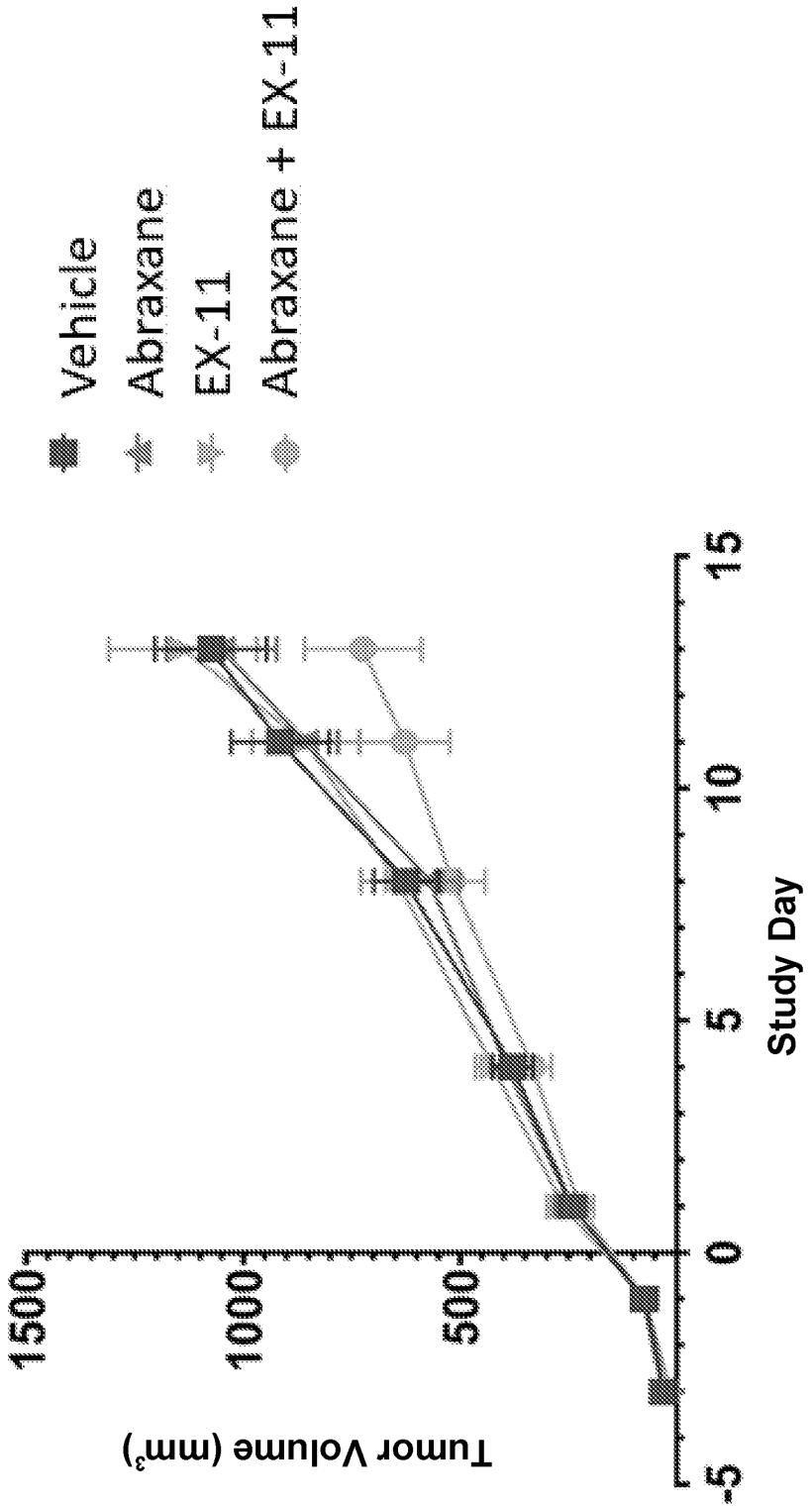

Vehicle
Abraxane
EX-11
Abraxane + EX-11
Tumor Volume (mm³)
1500
1000
500
0
-5
5
10
15
Study Day

FIG. 17A

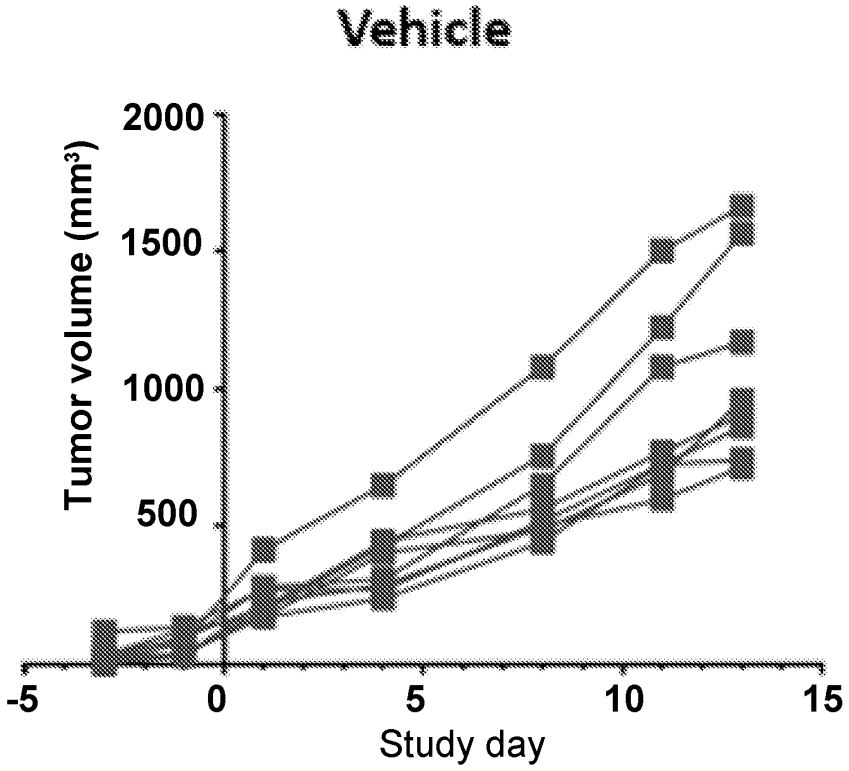


FIG. 17B

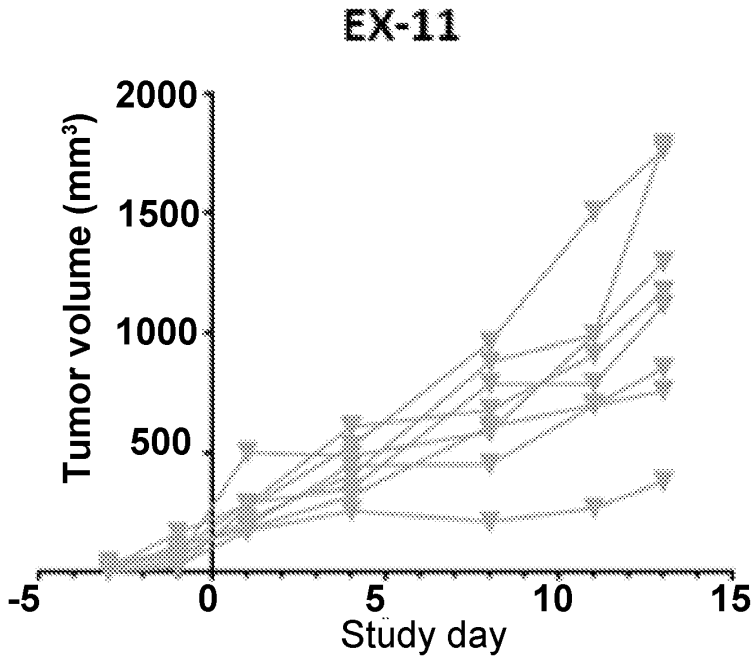


FIG. 17C

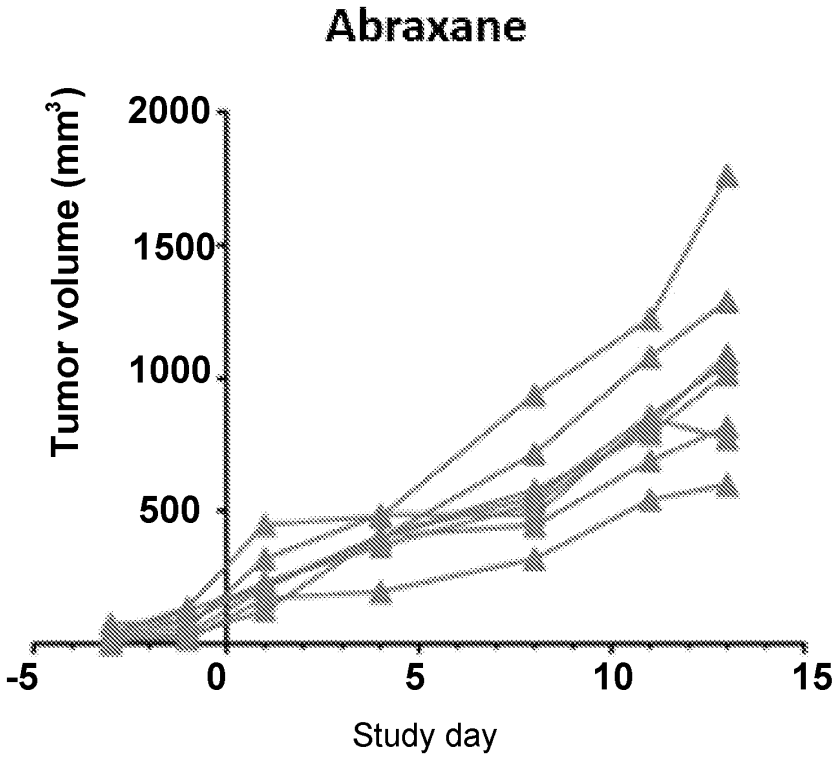


FIG. 17D

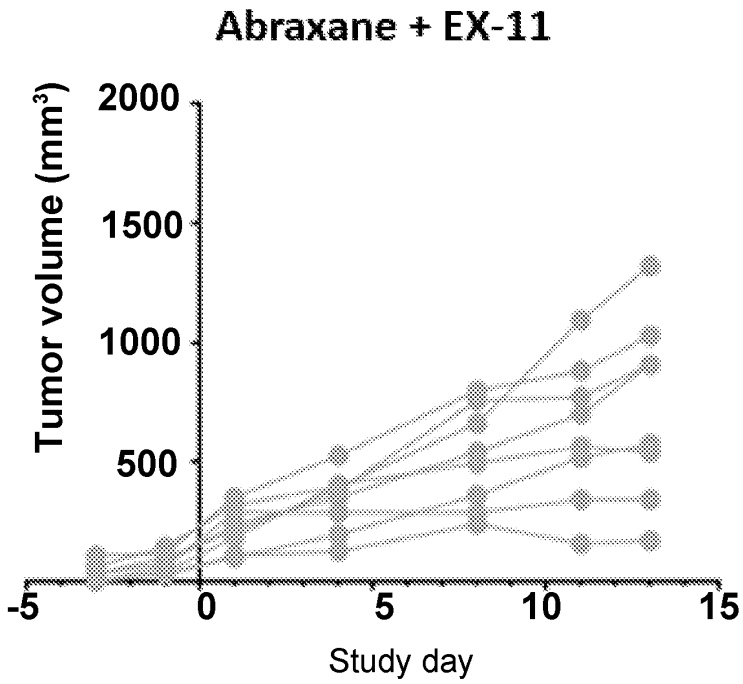


FIG. 17E

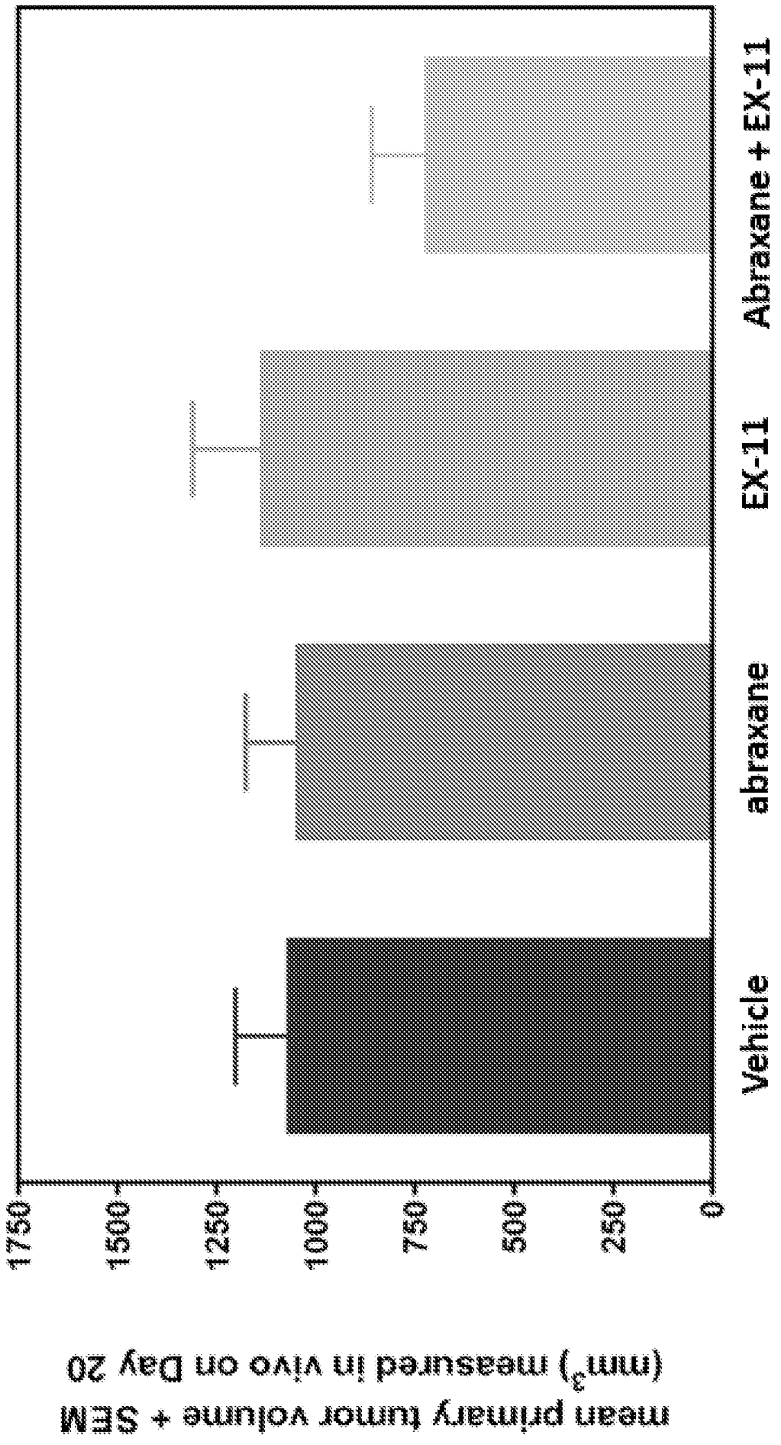

mean primary tumor volume + SEM
(mm3) measured in vivo on Day 20
1750
1500
1250
1000
750
500
250
0
Vehicle
abraxane
EX-11
Abraxane + EX-11

FIG. 17F

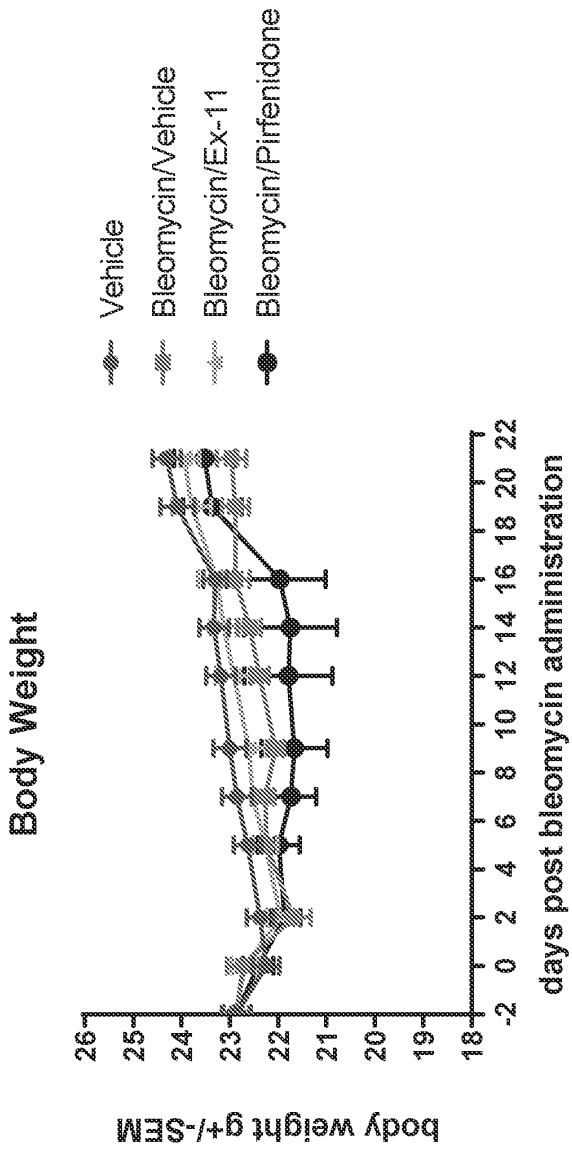

Body Weight
Vehicle
Bleomycin/Vehicle
Bleomycin/Ex-11
Bleomycin/Pirfenidone
body weight g+/-SEM
26
25
24
23
22
21
20
19
18
-2 0 2 4 6 8 10 12 14 16 18 20 22
days post bleomycin administration

FIG. 18A

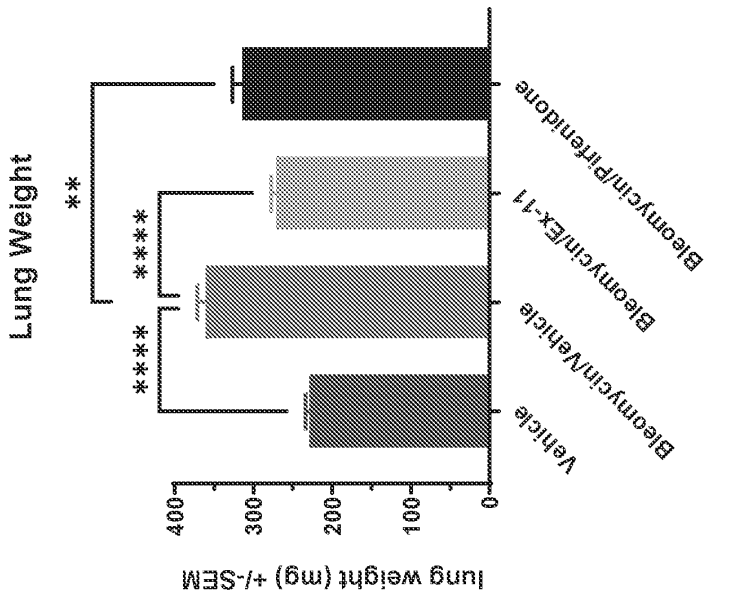

Lung Weight
**
****
****
lung weight (mg) +/-SEM
400
300
200
100
0
Vehicle
Bleomycin/Vehicle
Bleomycin/Ex-1
Bleomycin/Pirfenidone

FIG. 18B

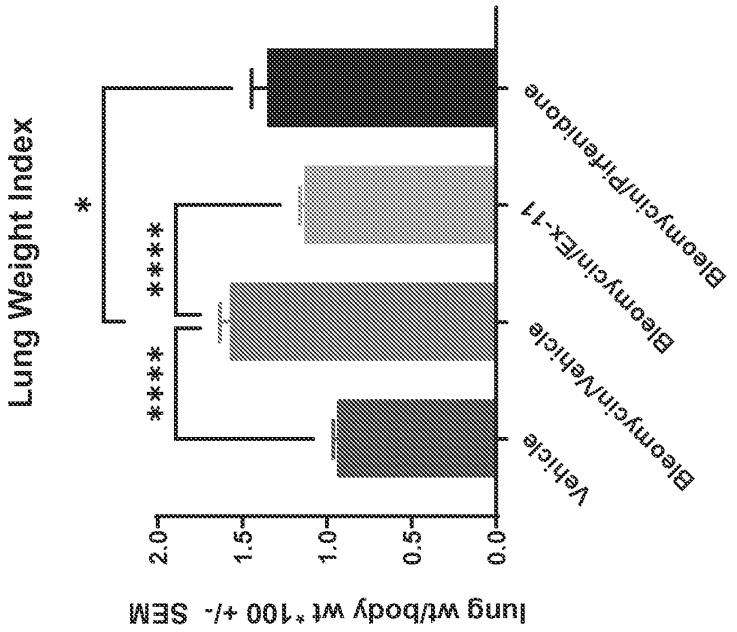

Lung Weight Index
lung wt/body wt *100 +/- SEM
2.0
1.5
1.0
0.5
0.0
Vehicle
Bleomycin/Vehicle
Bleomycin/EX-1
Bleomycin/Pirfenidone
*
****
****

FIG. 18C

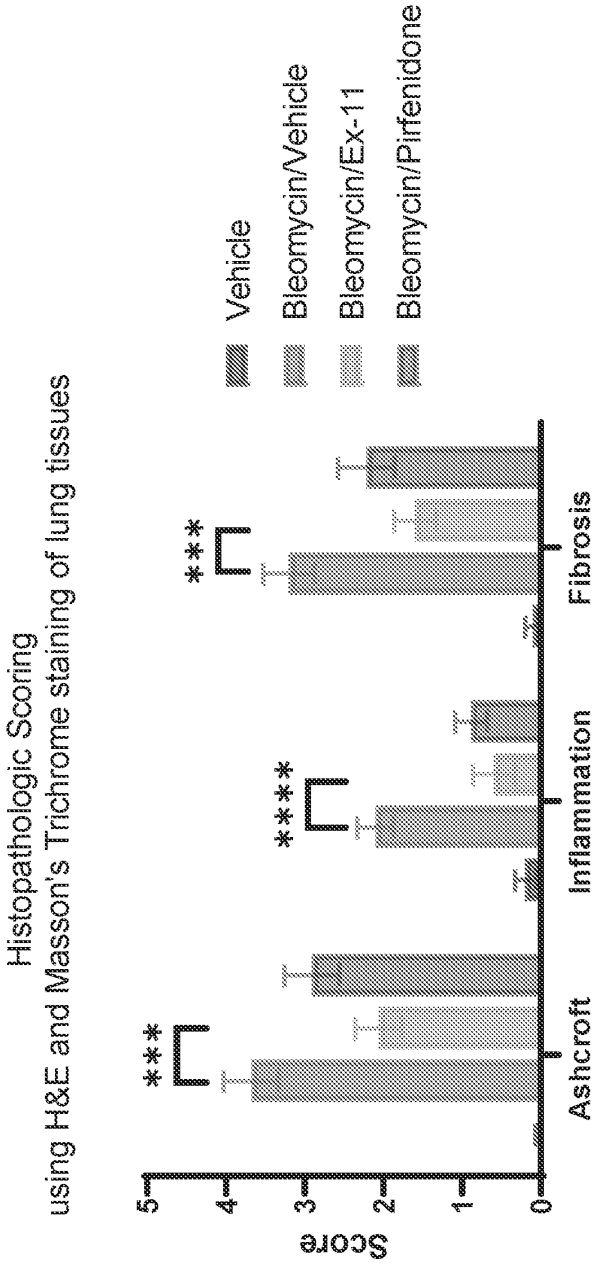

Histopathologic Scoring
using H&E and Masson's Trichrome staining of lung tissues
Vehicle
Bleomycin/Vehicle
Bleomycin/Ex-11
Bleomycin/Pirfenidone
***
****
***
Score
0
1
2
3
4
5
Ashcroft
Inflammation
Fibrosis

FIG. 18D

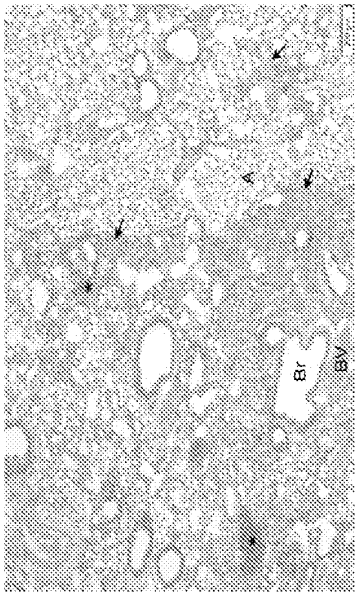


FIG. 18F

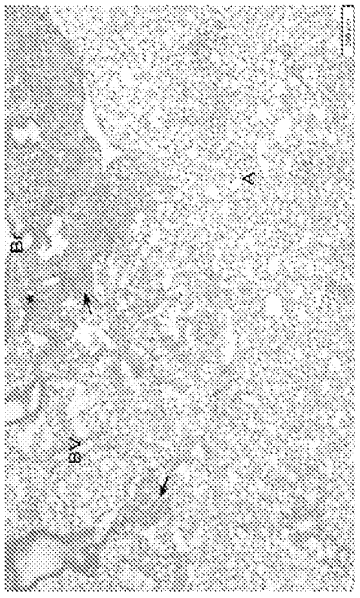


FIG. 18H

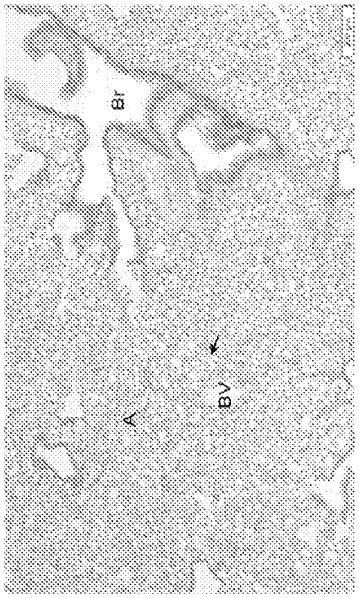


FIG. 18E

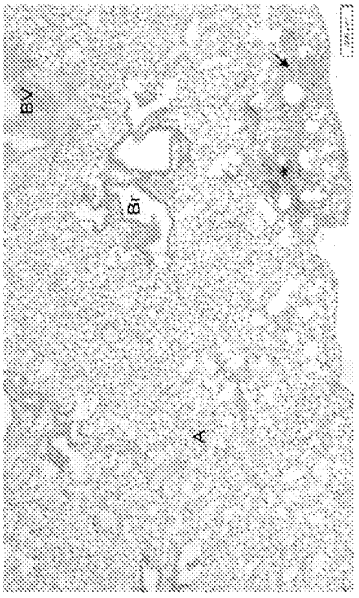


FIG. 18G

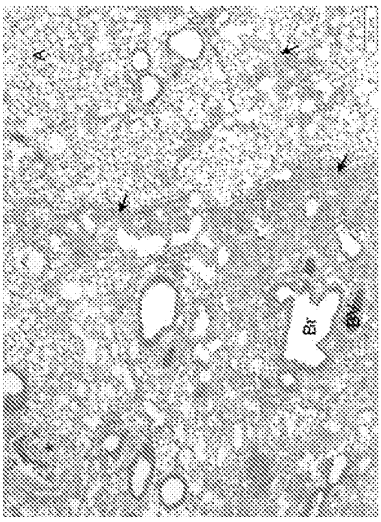


FIG. 18J

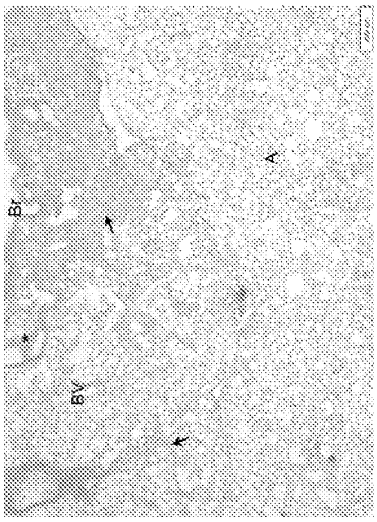


FIG. 18L

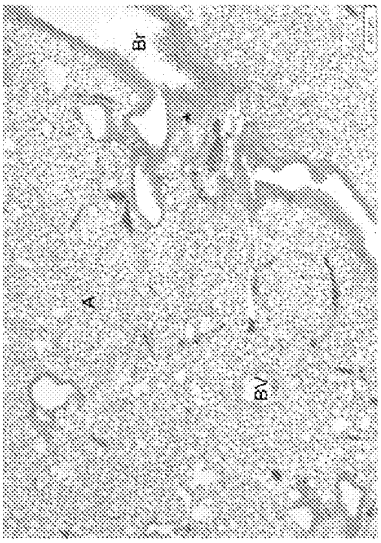


FIG. 18I

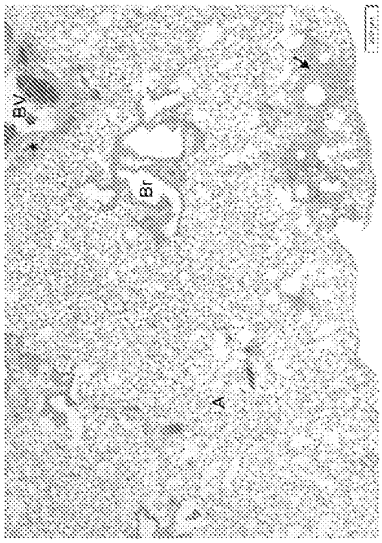


FIG. 18K

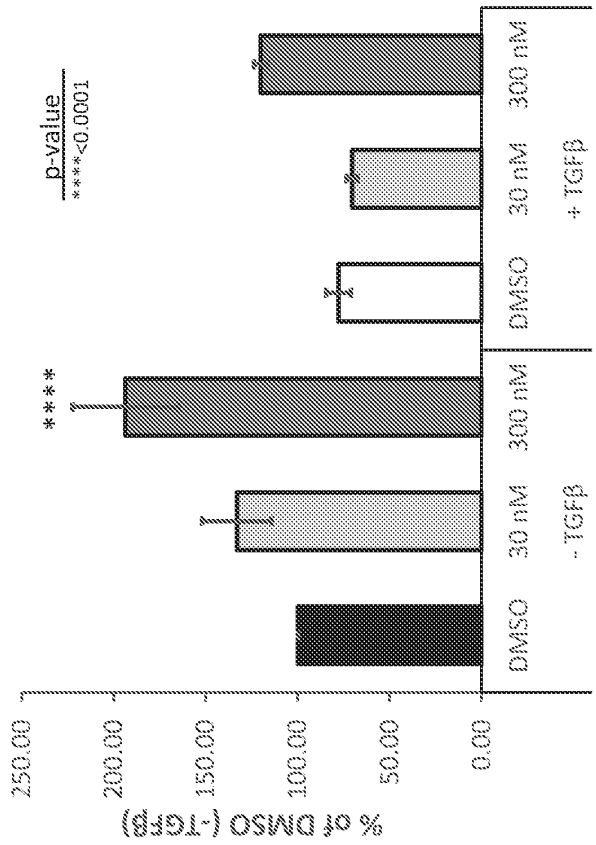

p-value
****<0.0001
****
% of DMSO (-TGFβ)
250.00
200.00
150.00
100.00
50.00
0.00
DMSO
30 nM
300 nM
- TGFβ
DMSO
30 nM
300 nM
+ TGFβ

FIG. 19

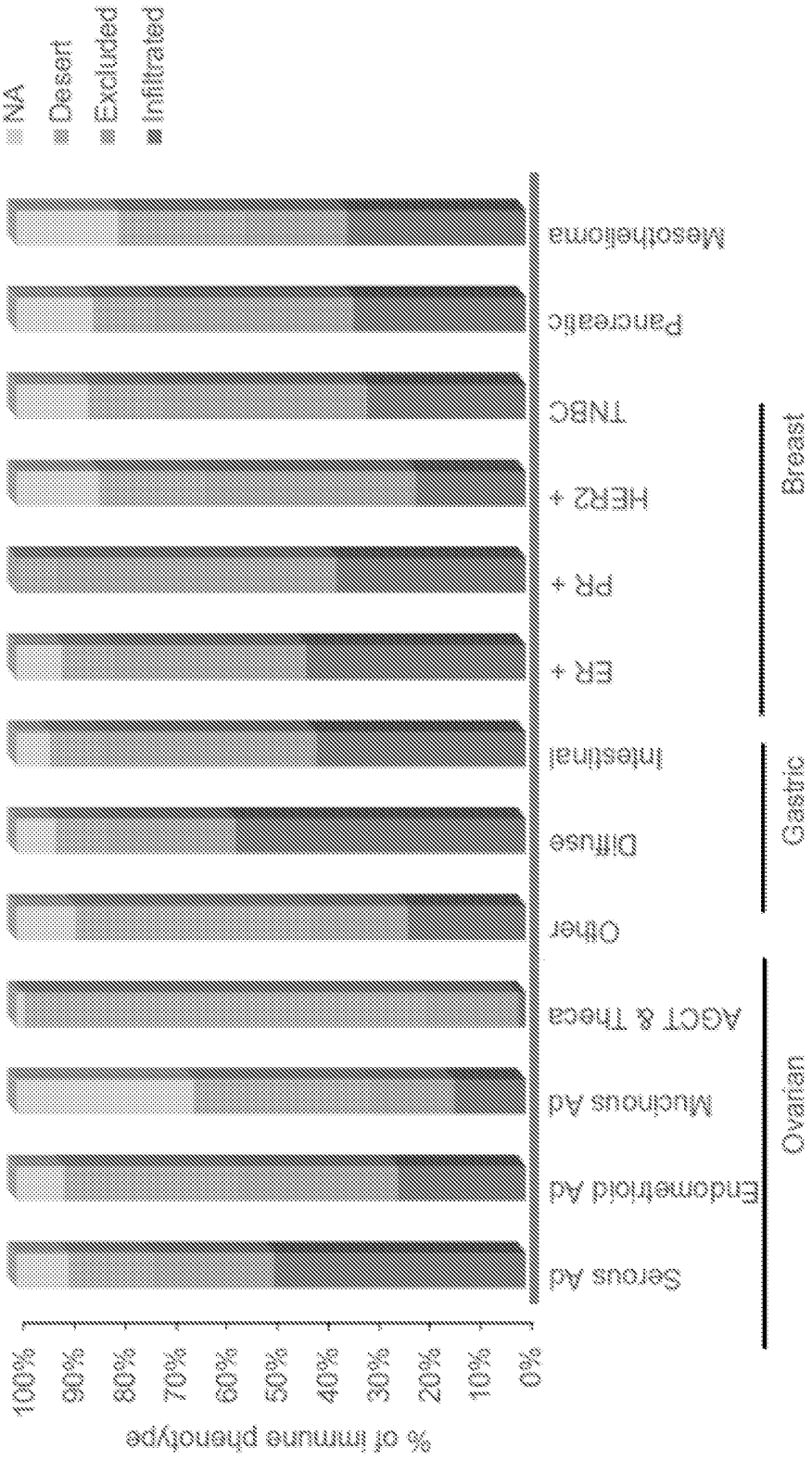

NA
Desert
Excluded
Infiltrated
Mesothelioma
Pancreatic
TNBC
HER2 +
PR +
ER +
Intestinal
Diffuse
Other
AGCT & Theca
Mucinous Ad
Endometrioid Ad
Serous Ad
Breast
Gastric
Ovarian
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
% of immune phenotype

FIG. 20

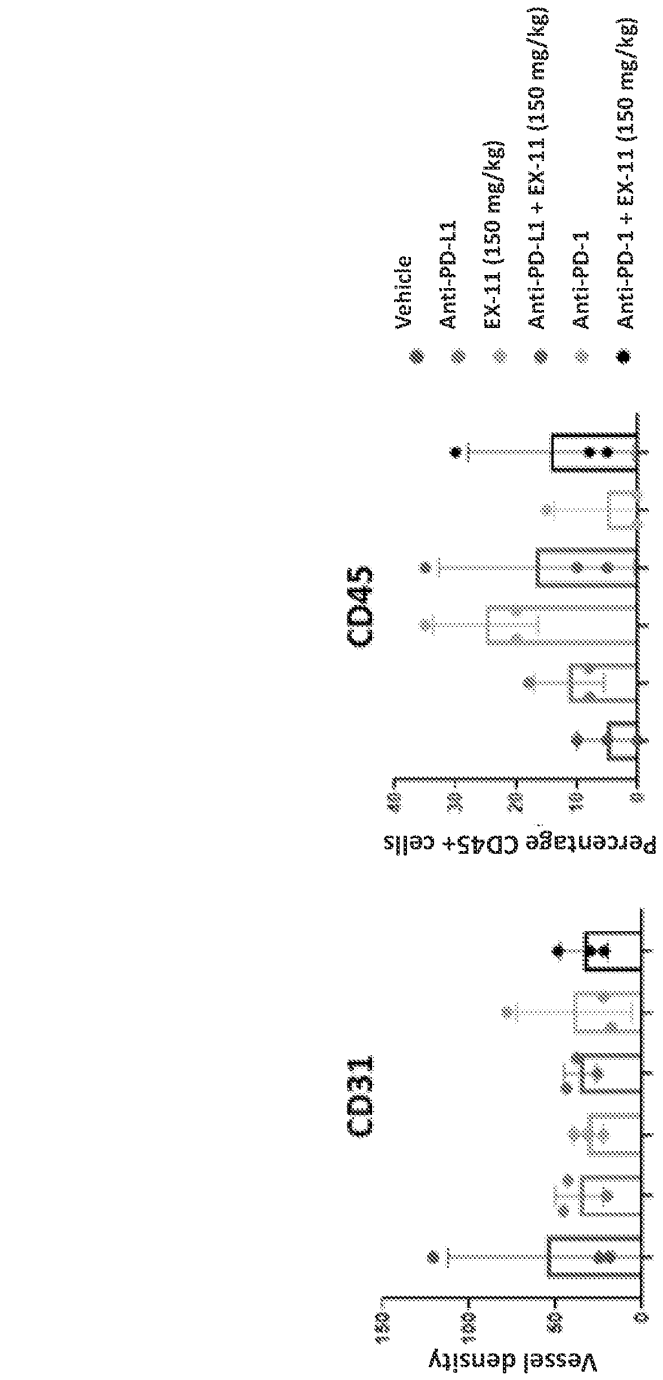

CD31
Vessel density
0
60
100
150
CD45
Percentage CD45+ cells
0
10
20
30
40
Vehicle
Anti-PD-L1
EX-11 (150 mg/kg)
Anti-PD-L1 + EX-11 (150 mg/kg)
Anti-PD-1
Anti-PD-1 + EX-11 (150 mg/kg)

FIG. 21A

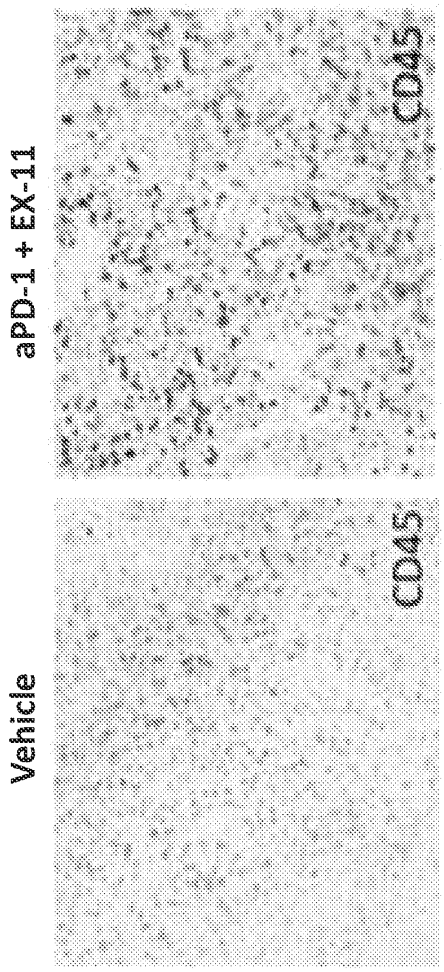


FIG. 21B

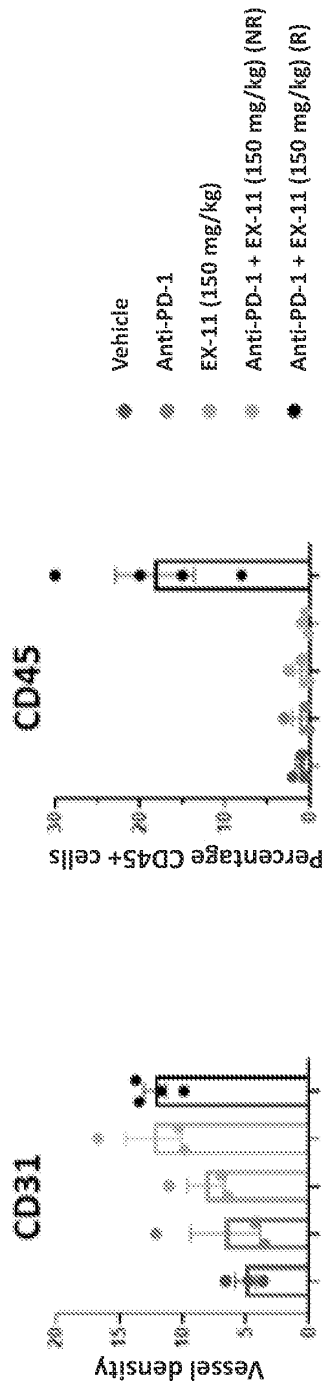

Vessel density
CD31
Percentage CD45+ cells
CD45
Vehicle
Anti-PD-1
EX-11 (150 mg/kg)
Anti-PD-1 + EX-11 (150 mg/kg) (NR)
Anti-PD-1 + EX-11 (150 mg/kg) (R)

FIG. 21C

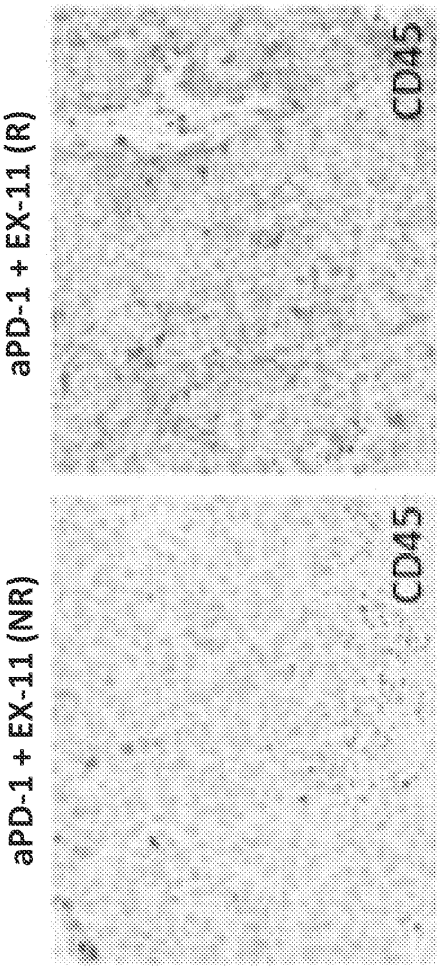


FIG. 21D