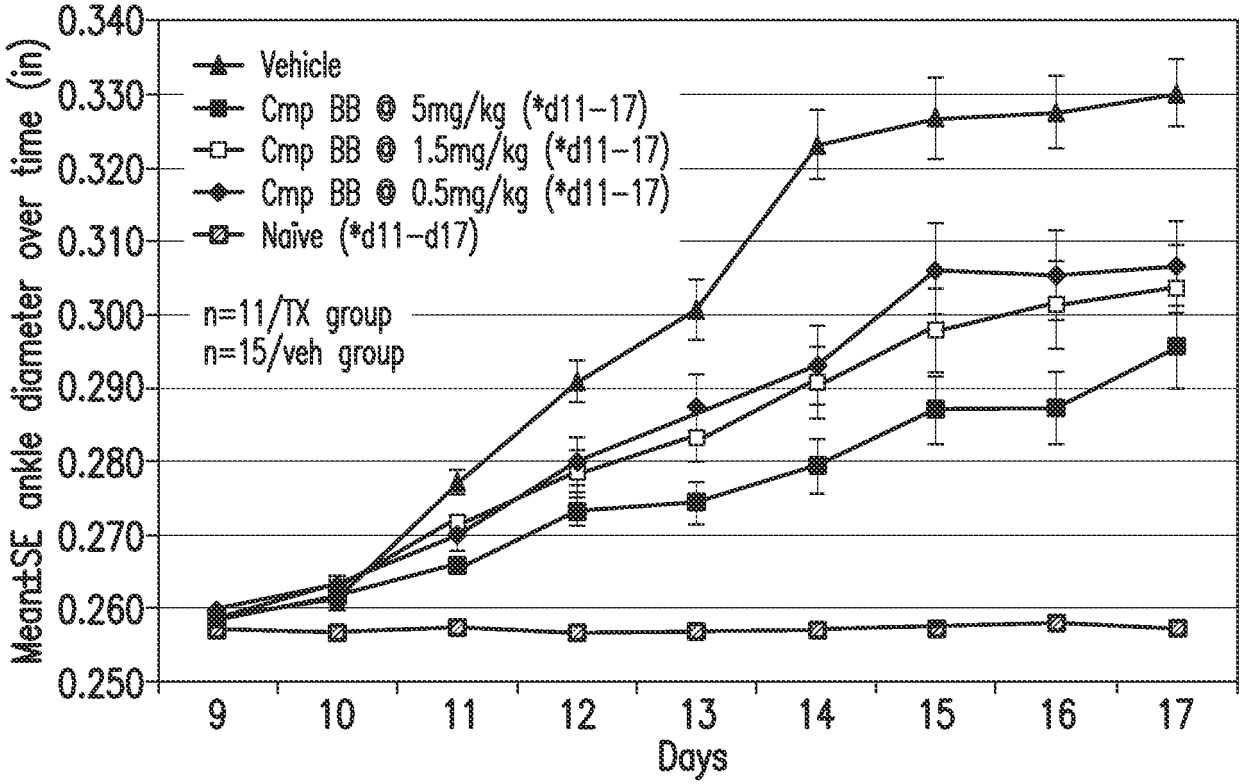

Mean±SE ankle diameter over time (in)
0.340
0.330
0.320
0.310
0.300
0.290
0.280
0.270
0.260
0.250
Vehicle
Cmp BB @ 5mg/kg (*d11-17)
Cmp BB @ 1.5mg/kg (*d11-17)
Cmp BB @ 0.5mg/kg (*d11-17)
Naive (*d11-d17)
n=11/TX group
n=15/veh group
9
10
11
12
13
14
15
16
17
Days
*p value <0.05 compared to represented vechicle

FIG. 1

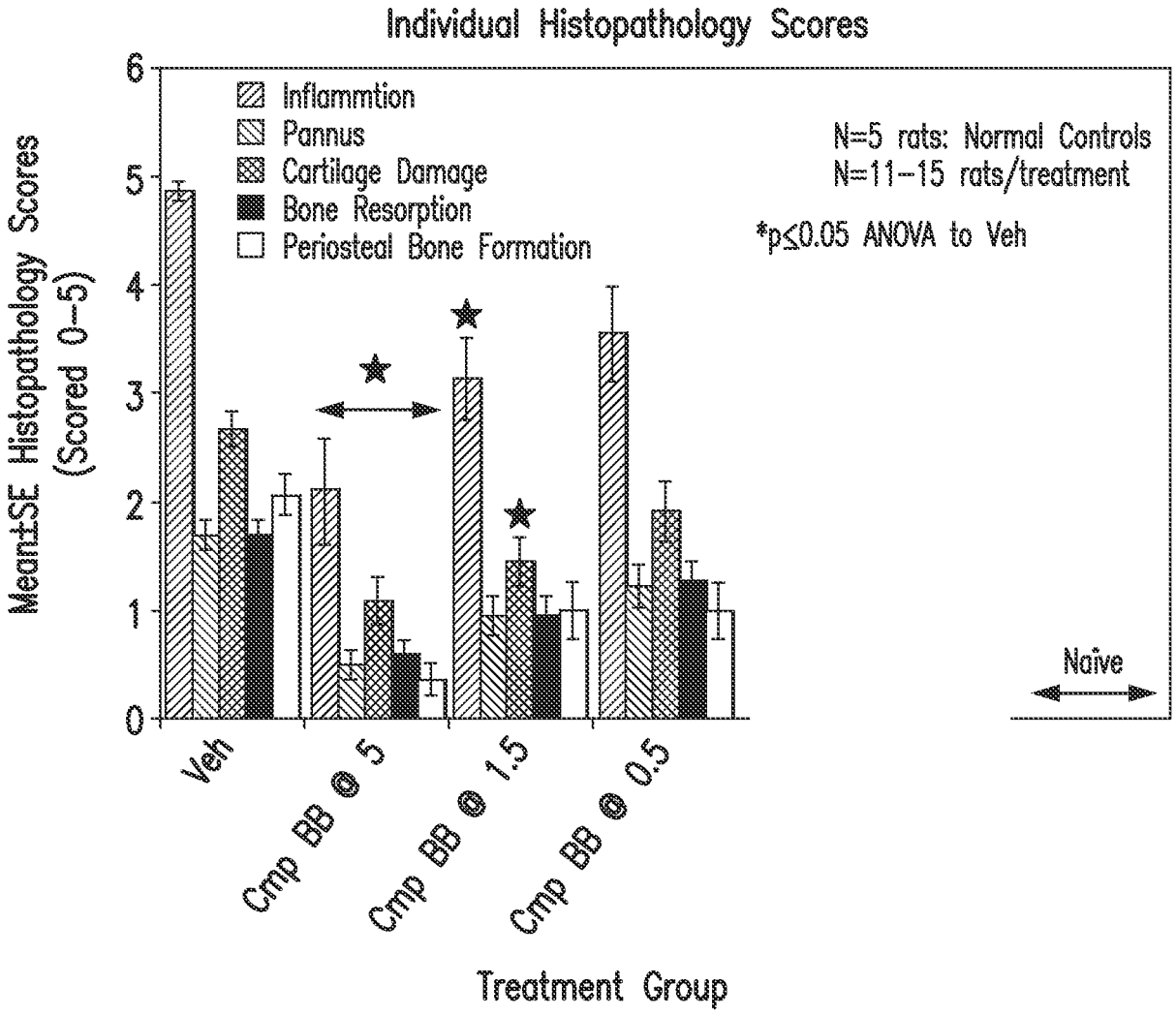

Individual Histopathology Scores
Mean±SE Histopathology Scores (Scored 0–5)
Inflammtion
Pannus
Cartilage Damage
Bone Resorption
Periosteal Bone Formation
N=5 rats: Normal Controls
N=11–15 rats/treatment
*p≤0.05 ANOVA to Veh
Naive
Veh
Cmp BB @ 5
Cmp BB @ 1.5
Cmp BB @ 0.5
Treatment Group

FIG. 2

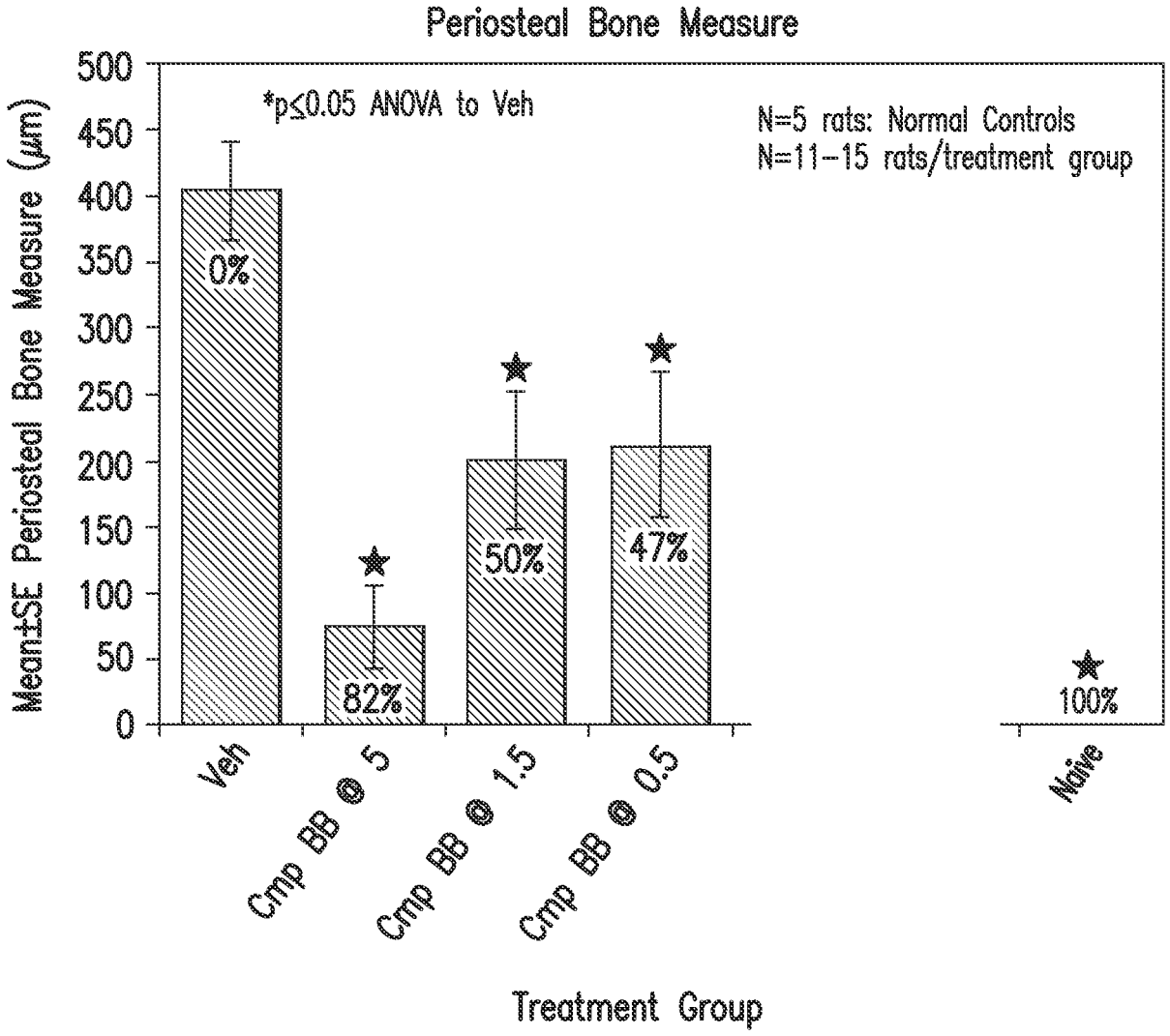

Periosteal Bone Measure
Mean±SE Periosteal Bone Measure (μm)
500
450
400
350
300
250
200
150
100
50
0
*p≤0.05 ANOVA to Veh
N=5 rats: Normal Controls
N=11-15 rats/treatment group
0%
82%
50%
47%
100%
Veh
Cmp BB @ 5
Cmp BB @ 1.5
Cmp BB @ 0.5
Naive
Treatment Group

FIG. 3

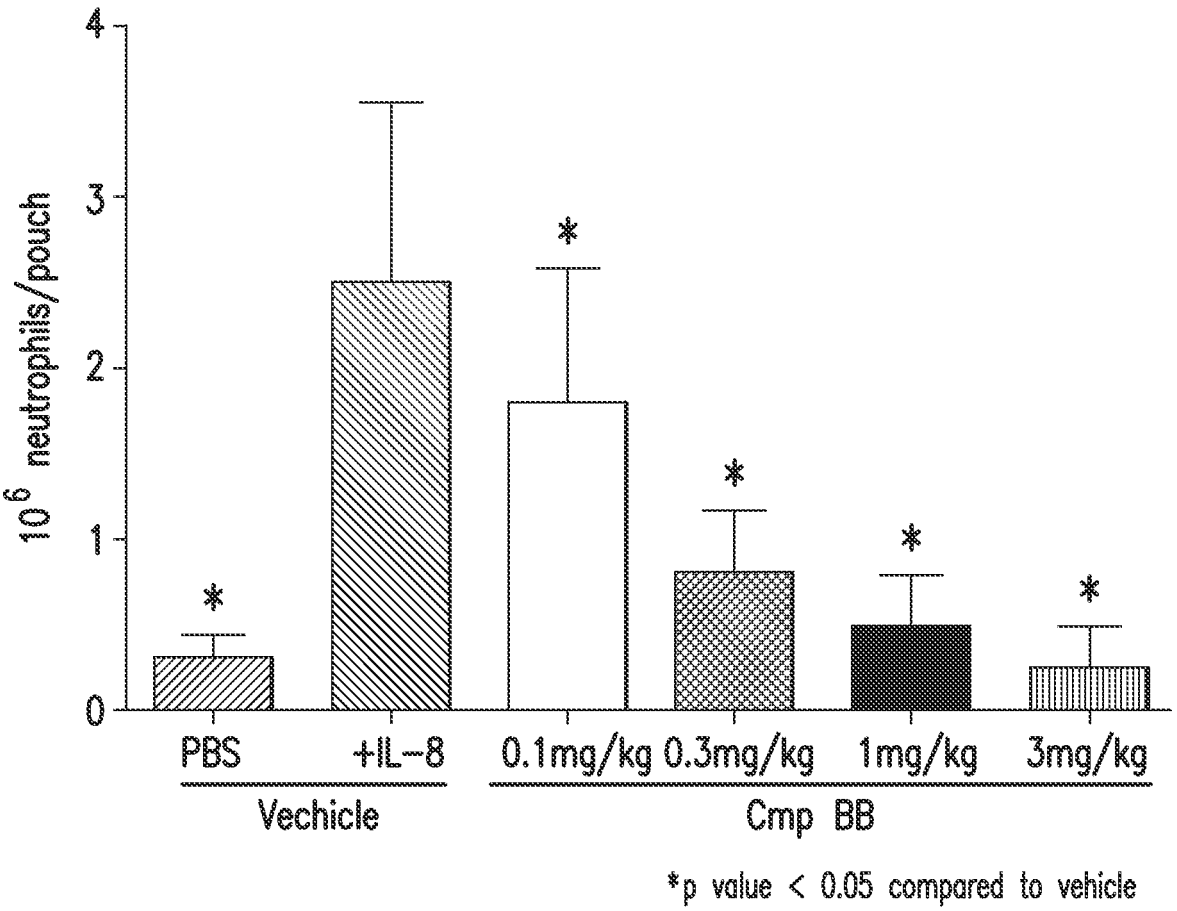

4
3
2
1
0
10^6 neutrophils/pouch
*
*
*
*
*
PBS
+IL-8
0.1mg/kg
0.3mg/kg
1mg/kg
3mg/kg
Vechicle
Cmp BB
*p value < 0.05 compared to vehicle

FIG. 4

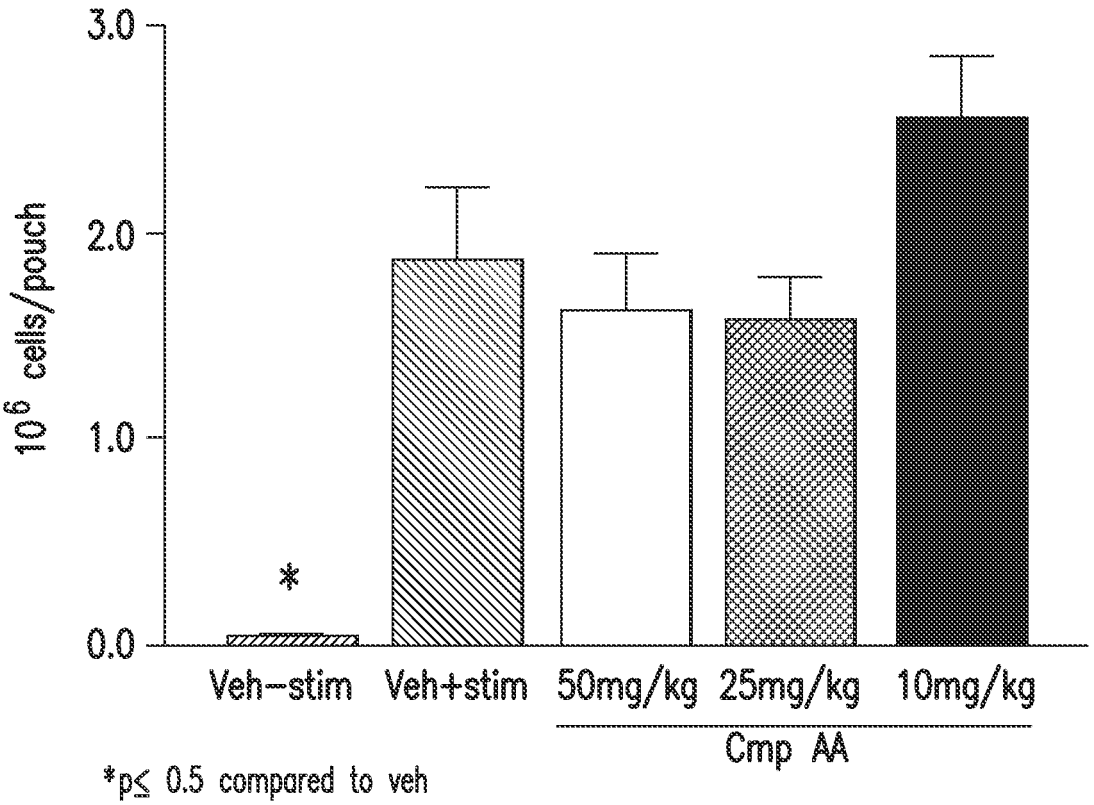

3.0
2.0
1.0
0.0
10^6 cells/pouch
*
Veh−stim
Veh+stim
50mg/kg
25mg/kg
10mg/kg
Cmp AA
*p≤ 0.5 compared to veh

FIG. 5

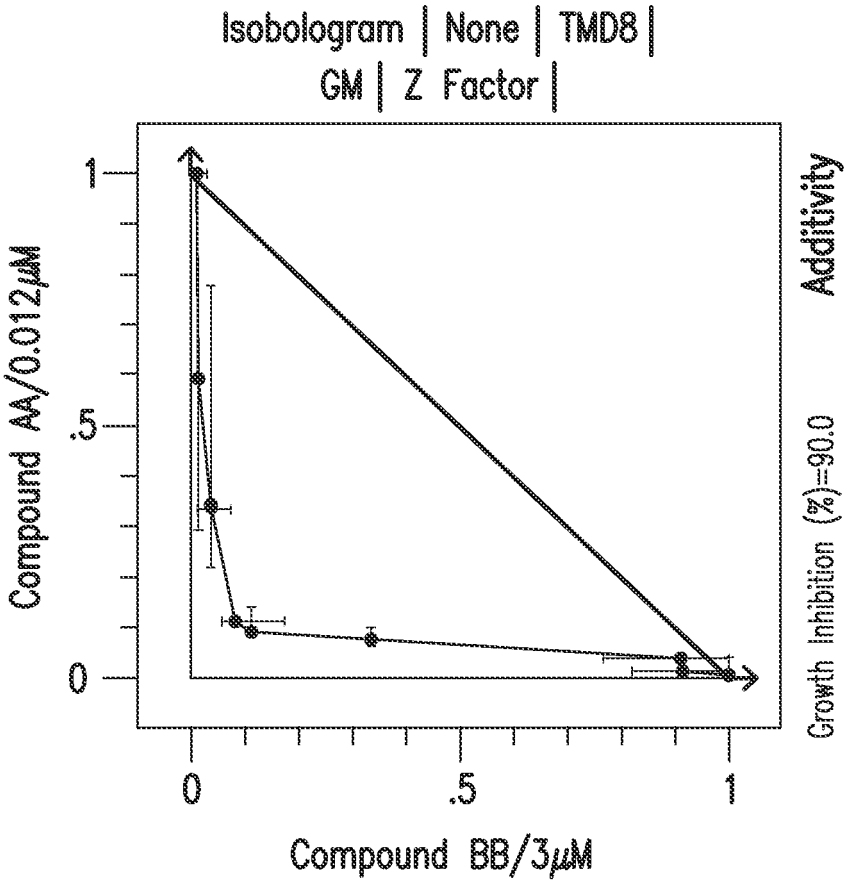

Isobologram | None | TMD8 |
GM | Z Factor |
Compound AA/0.012μM
1
.5
0
0
.5
1
Compound BB/3μM
Additivity
Growth Inhibition (%)=90.0

FIG. 6

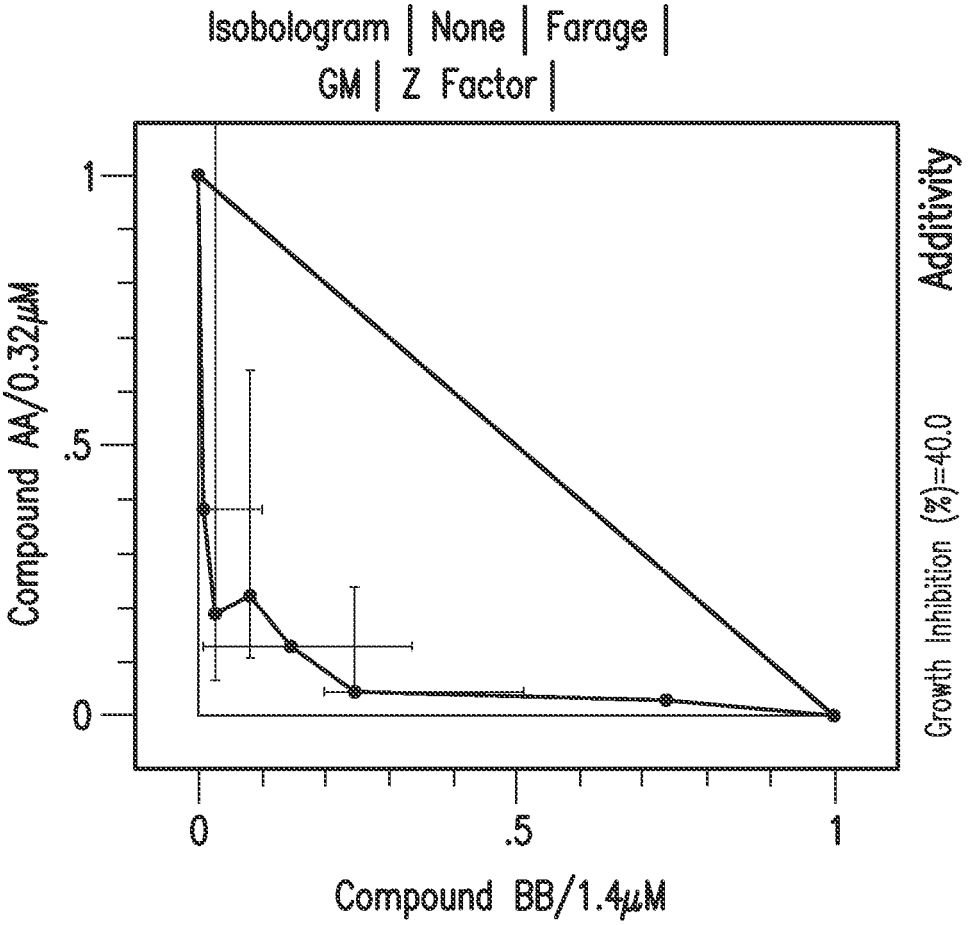

Isobologram | None | Farage |
GM | Z Factor |
Compound AA/0.32μM
1
.5
0
0
.5
1
Compound BB/1.4μM
Additivity
Growth Inhibition (%)=40.0

FIG. 7

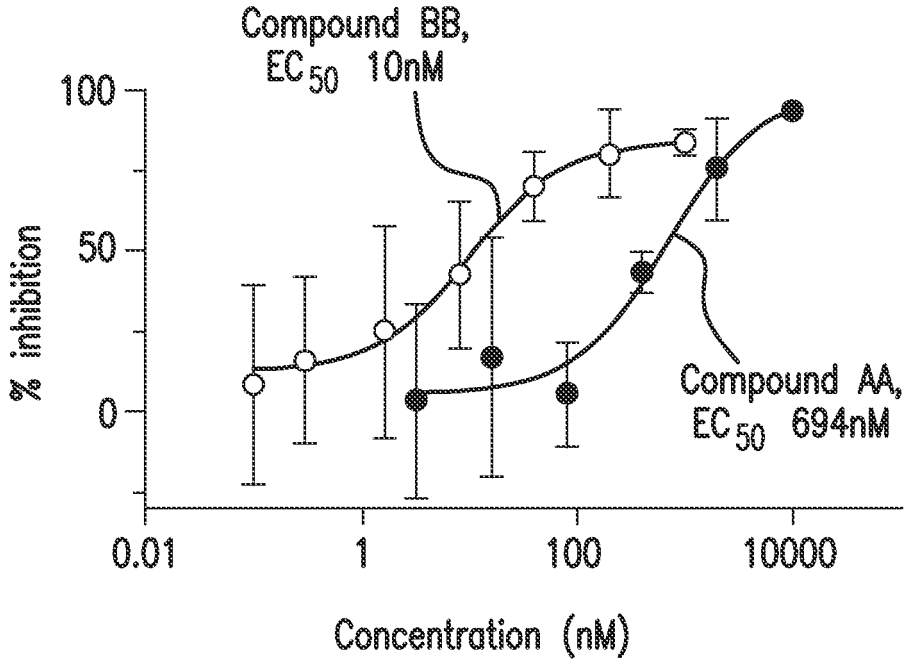

Compound BB,
EC50 10nM
100
50
0
% inhibition
Compound AA,
EC50 694nM
0.01
1
100
10000
Concentration (nM)

FIG. 8

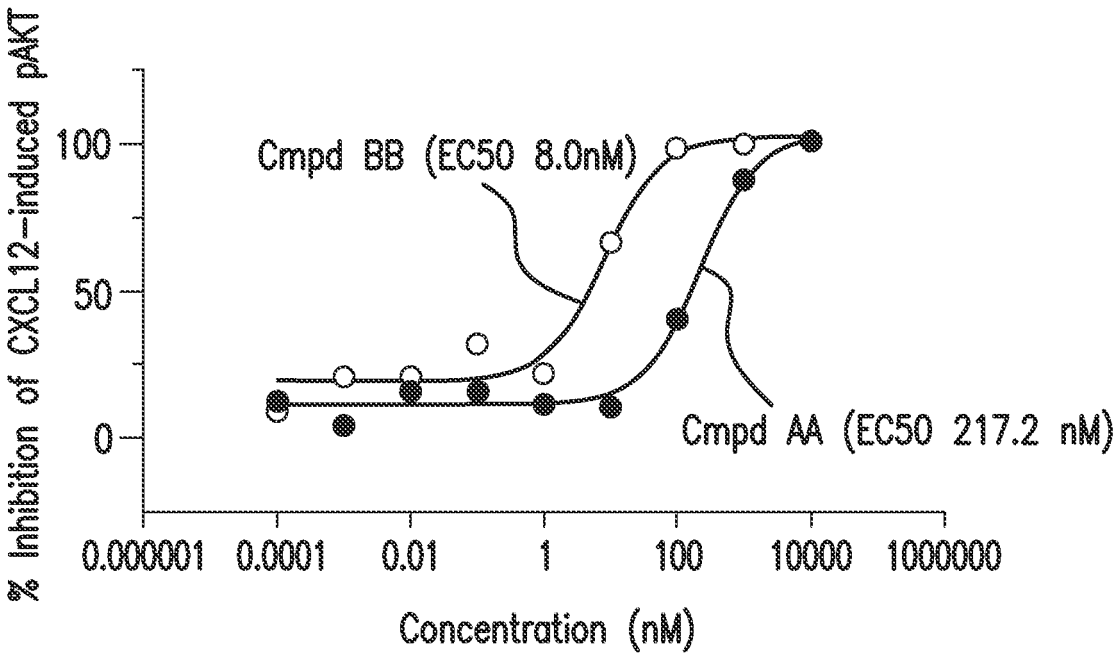

% Inhibition of CXCL12-induced pAKT
100
50
0
Cmpd BB (EC50 8.0nM)
Cmpd AA (EC50 217.2 nM)
0.000001
0.0001
0.01
1
100
10000
1000000
Concentration (nM)

FIG. 9

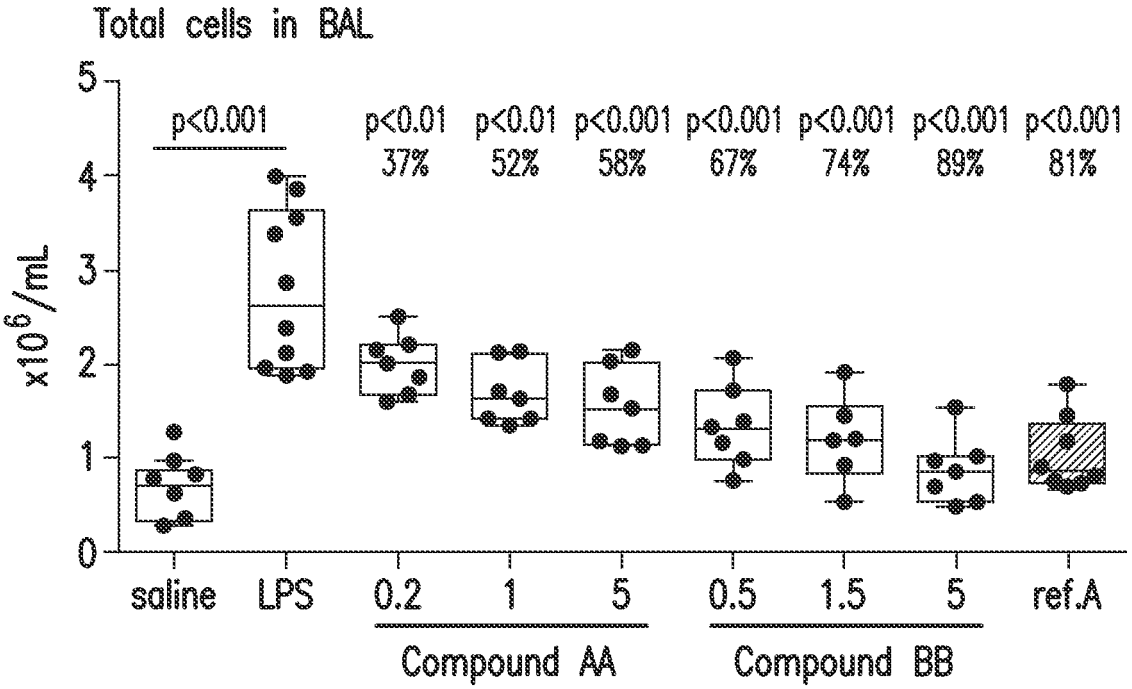

Total cells in BAL
x10^6/mL
0
1
2
3
4
5
p<0.001
p<0.01
37%
p<0.01
52%
p<0.001
58%
p<0.001
67%
p<0.001
74%
p<0.001
89%
p<0.001
81%
saline
LPS
0.2
1
5
0.5
1.5
5
ref.A
Compound AA
Compound BB

FIG. 10

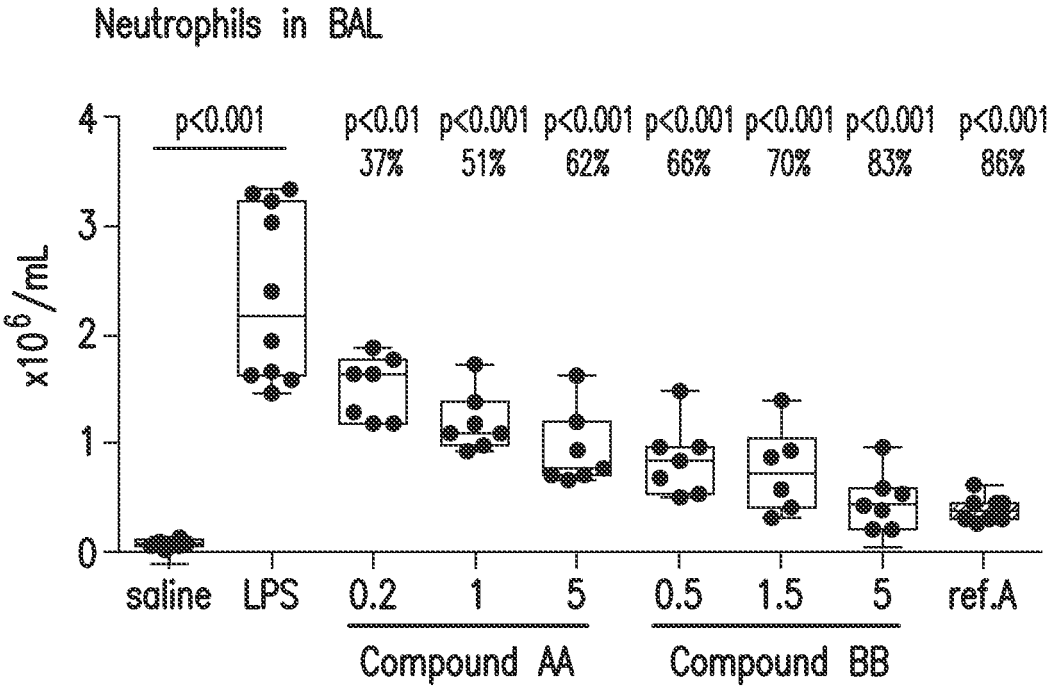

Neutrophils in BAL
p<0.001
p<0.01
37%
p<0.001
51%
p<0.001
62%
p<0.001
66%
p<0.001
70%
p<0.001
83%
p<0.001
86%
x10^6/mL
4
3
2
1
0
saline
LPS
0.2
1
5
0.5
1.5
5
ref.A
Compound AA
Compound BB

FIG. 11

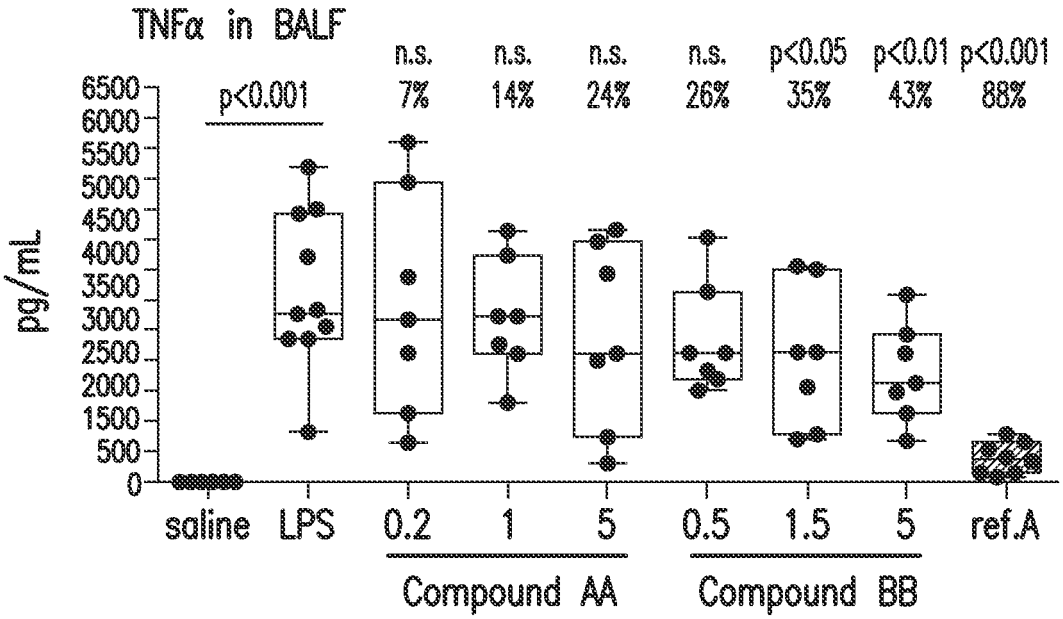

TNFα in BALF
pg/mL
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
500
0
p<0.001
n.s.
7%
n.s.
14%
n.s.
24%
n.s.
26%
p<0.05
35%
p<0.01
43%
p<0.001
88%
saline
LPS
0.2
1
5
0.5
1.5
5
ref.A
Compound AA
Compound BB

FIG. 12

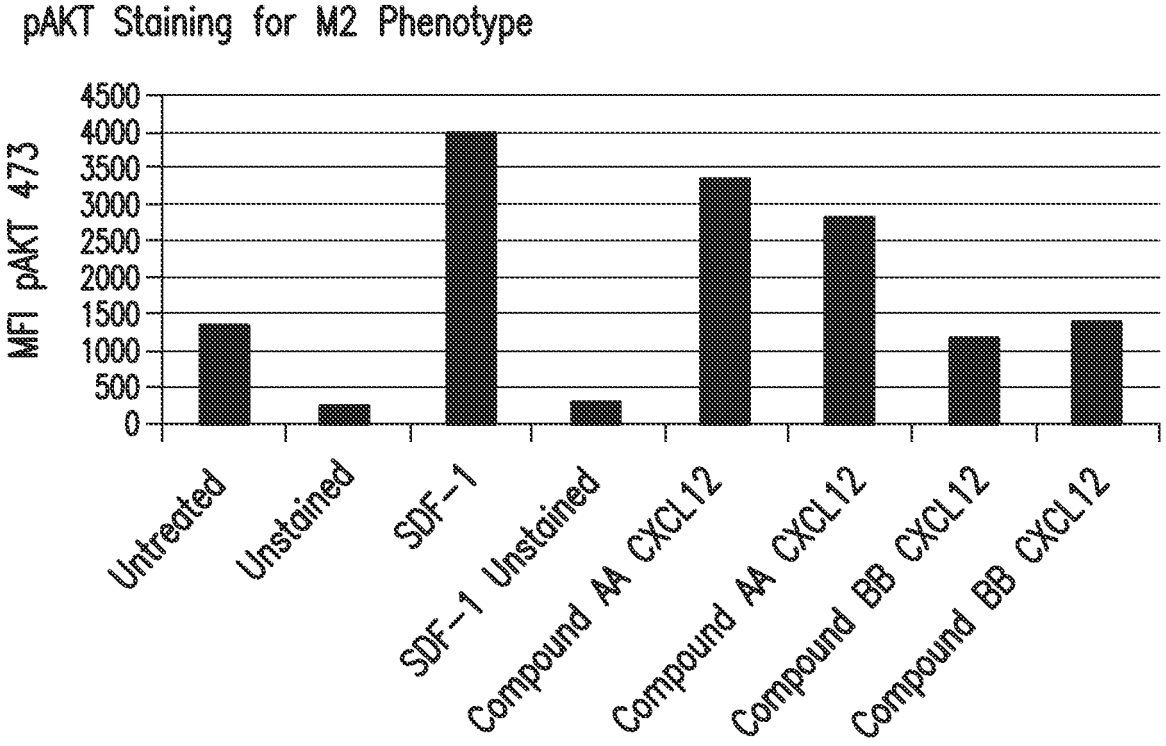

pAKT Staining for M2 Phenotype
MFI pAKT 473
4500
4000
3500
3000
2500
2000
1500
1000
500
0
Untreated
Unstained
SDF-1
SDF-1 Unstained
Compound AA CXCL12
Compound AA CXCL12
Compound BB CXCL12
Compound BB CXCL12

FIG. 13

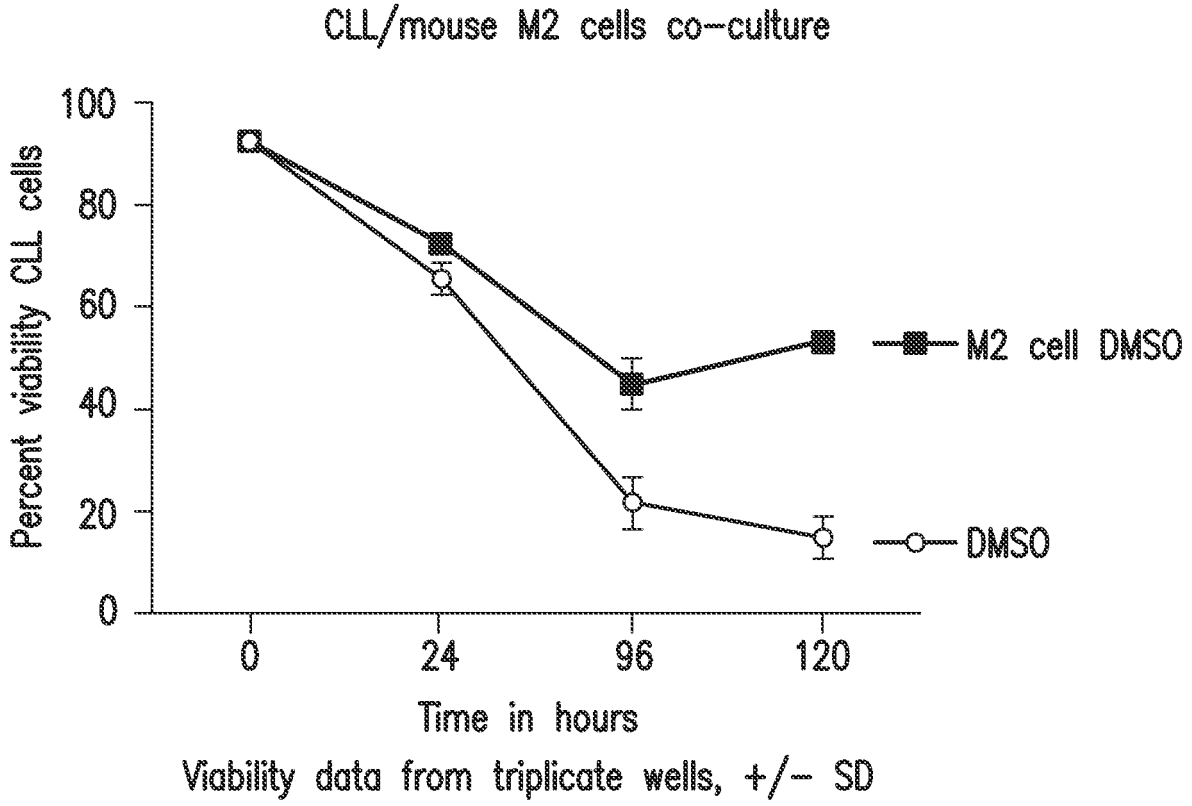

CLL/mouse M2 cells co-culture
Percent viability CLL cells
100
80
60
40
20
0
0
24
96
120
Time in hours
M2 cell DMSO
DMSO
Viability data from triplicate wells, +/- SD

FIG. 14

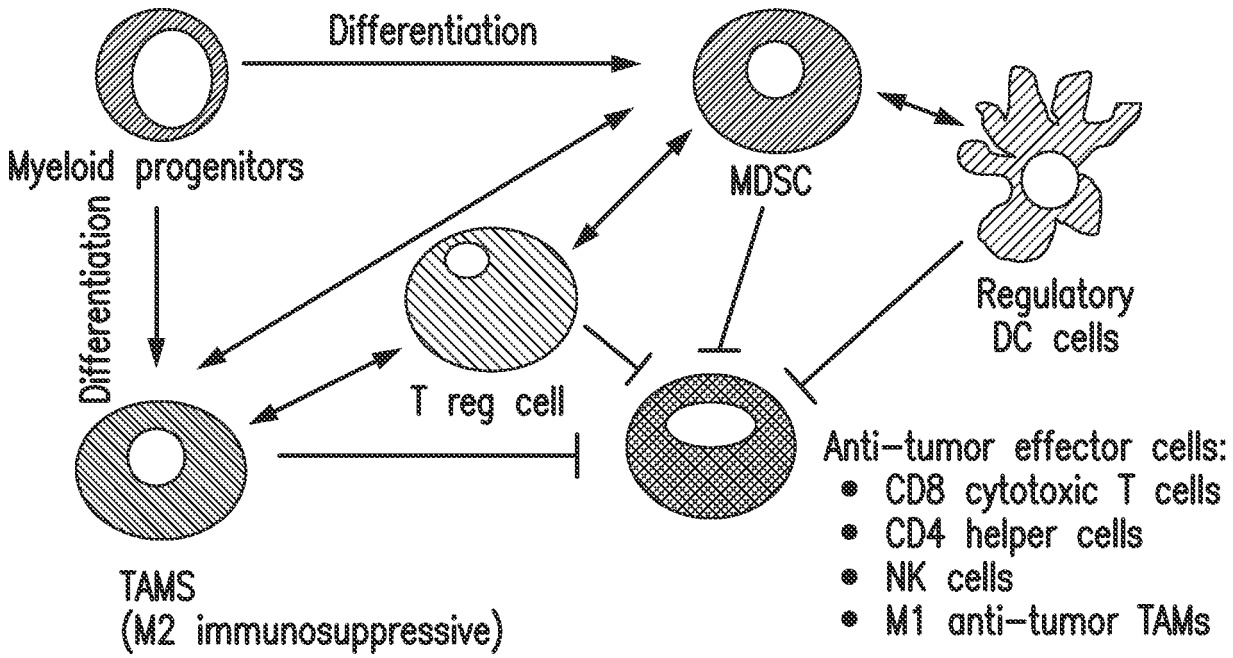

Differentiation
Myeloid progenitors
Differentiation
MDSC
Regulatory
DC cells
T reg cell
Anti-tumor effector cells:
• CD8 cytotoxic T cells
• CD4 helper cells
• NK cells
• M1 anti-tumor TAMs
TAMS
(M2 immunosuppressive)

FIG. 15

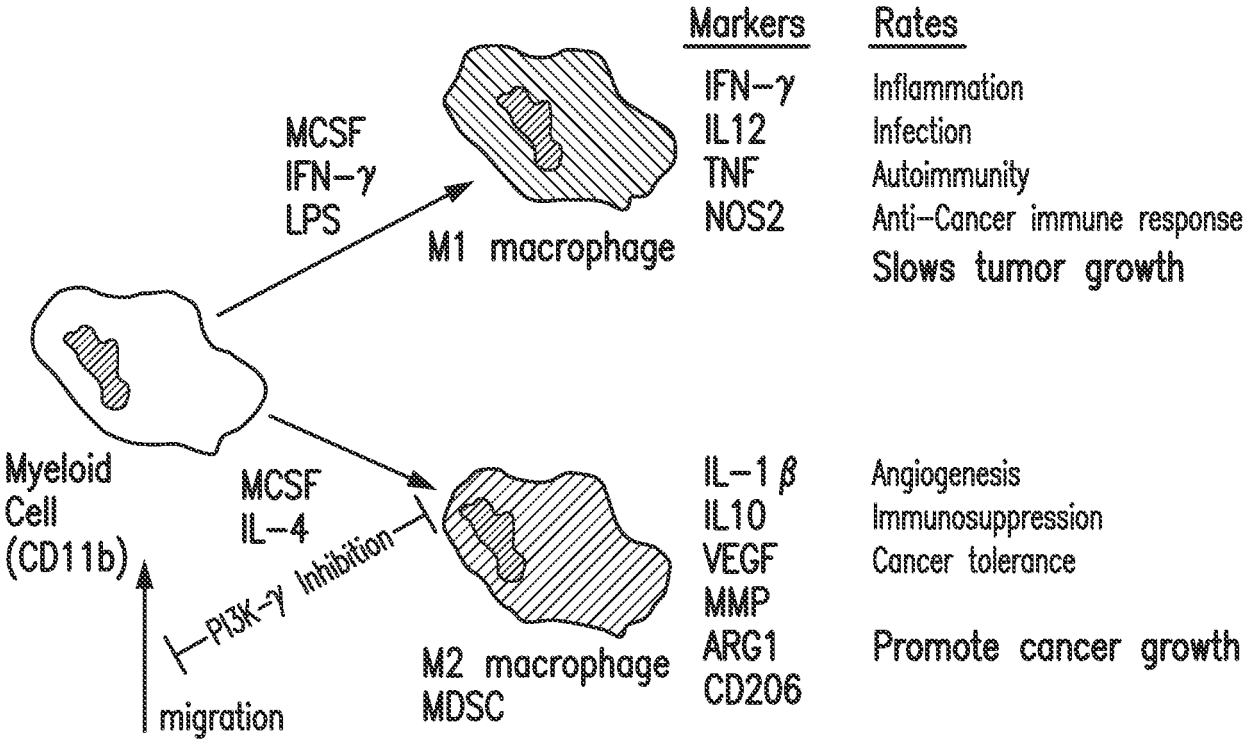

Markers
Rates
IFN-γ
IL12
TNF
NOS2
Inflammation
Infection
Autoimmunity
Anti-Cancer immune response
Slows tumor growth
MCSF
IFN-γ
LPS
M1 macrophage
Myeloid
Cell
(CD11b)
MCSF
IL-4
PI3K-γ Inhibition
migration
M2 macrophage
MDSC
IL-1β
IL10
VEGF
MMP
ARG1
CD206
Angiogenesis
Immunosuppression
Cancer tolerance
Promote cancer growth

FIG. 16

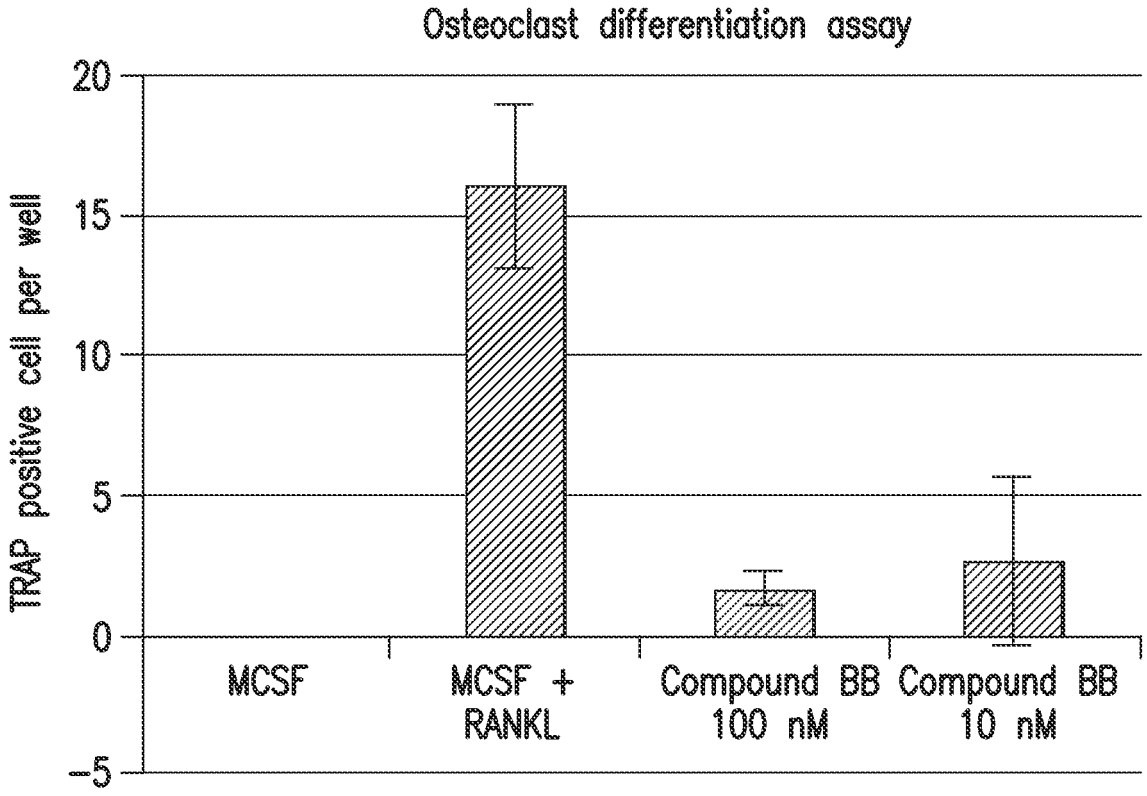

Osteoclast differentiation assay
TRAP positive cell per well
20
15
10
5
0
-5
MCSF
MCSF + RANKL
Compound BB 100 nM
Compound BB 10 nM

FIG. 17

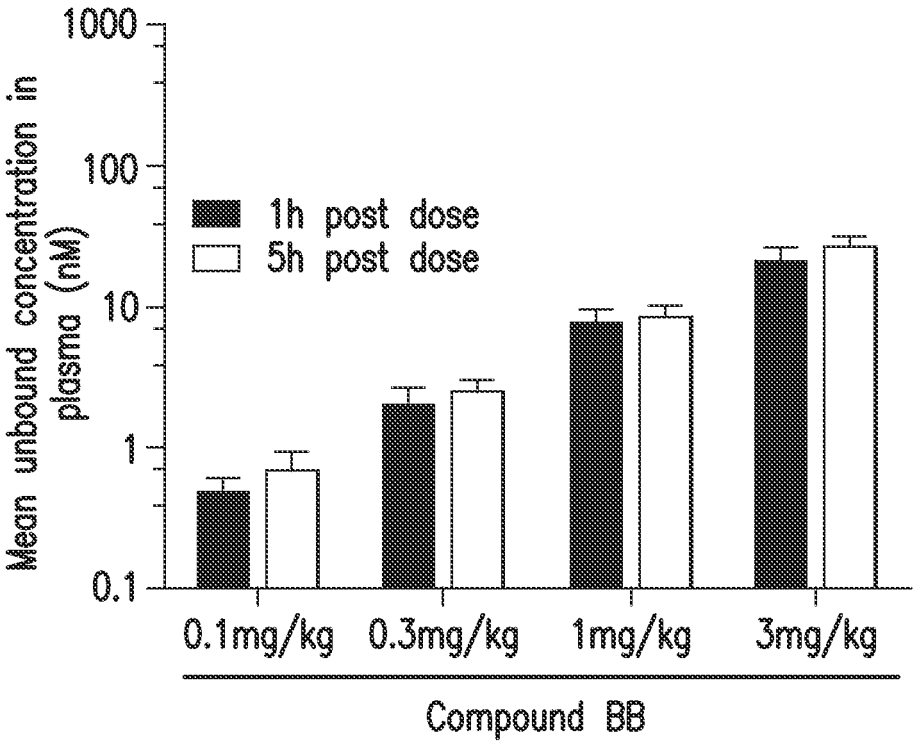

1000
100
10
1
0.1
Mean unbound concentration in plasma (nM)
1h post dose
5h post dose
0.1mg/kg
0.3mg/kg
1mg/kg
3mg/kg
Compound BB

FIG. 18

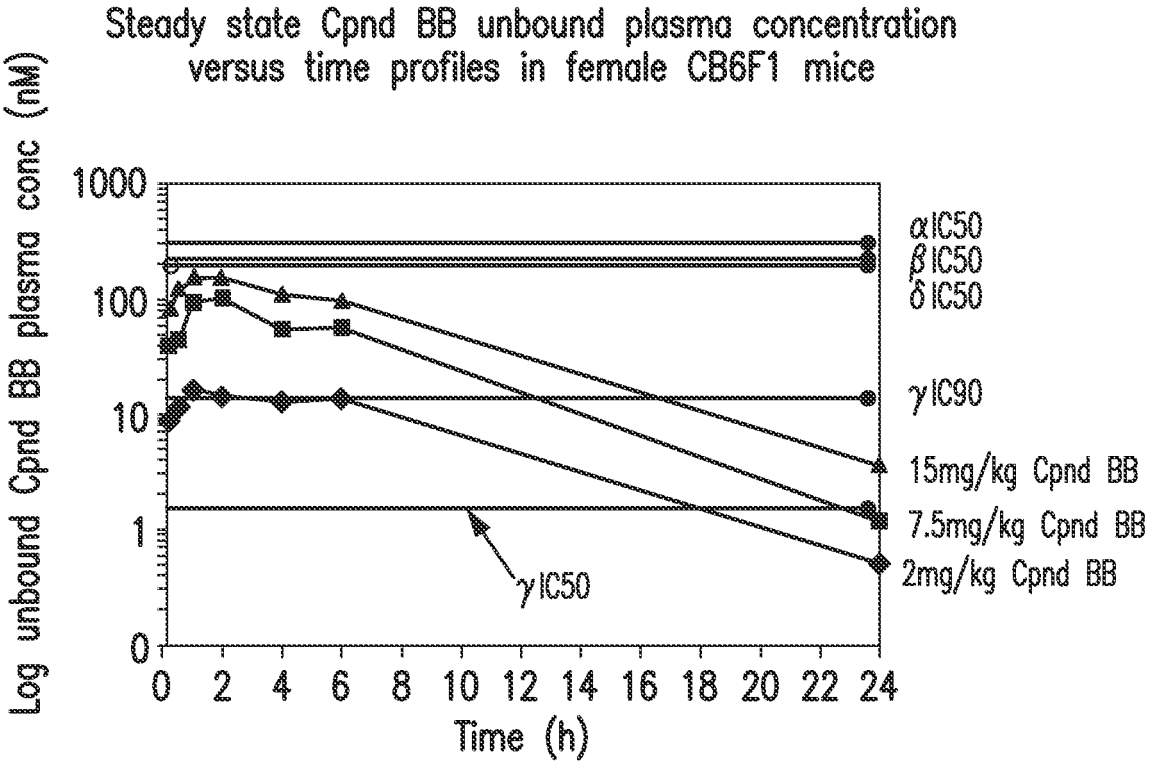

Steady state Cpnd BB unbound plasma concentration versus time profiles in female CB6F1 mice
Log unbound Cpnd BB plasma conc (nM)
1000
100
10
1
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (h)
αIC50
βIC50
δIC50
γIC90
15mg/kg Cpnd BB
7.5mg/kg Cpnd BB
2mg/kg Cpnd BB
γIC50

FIG. 19

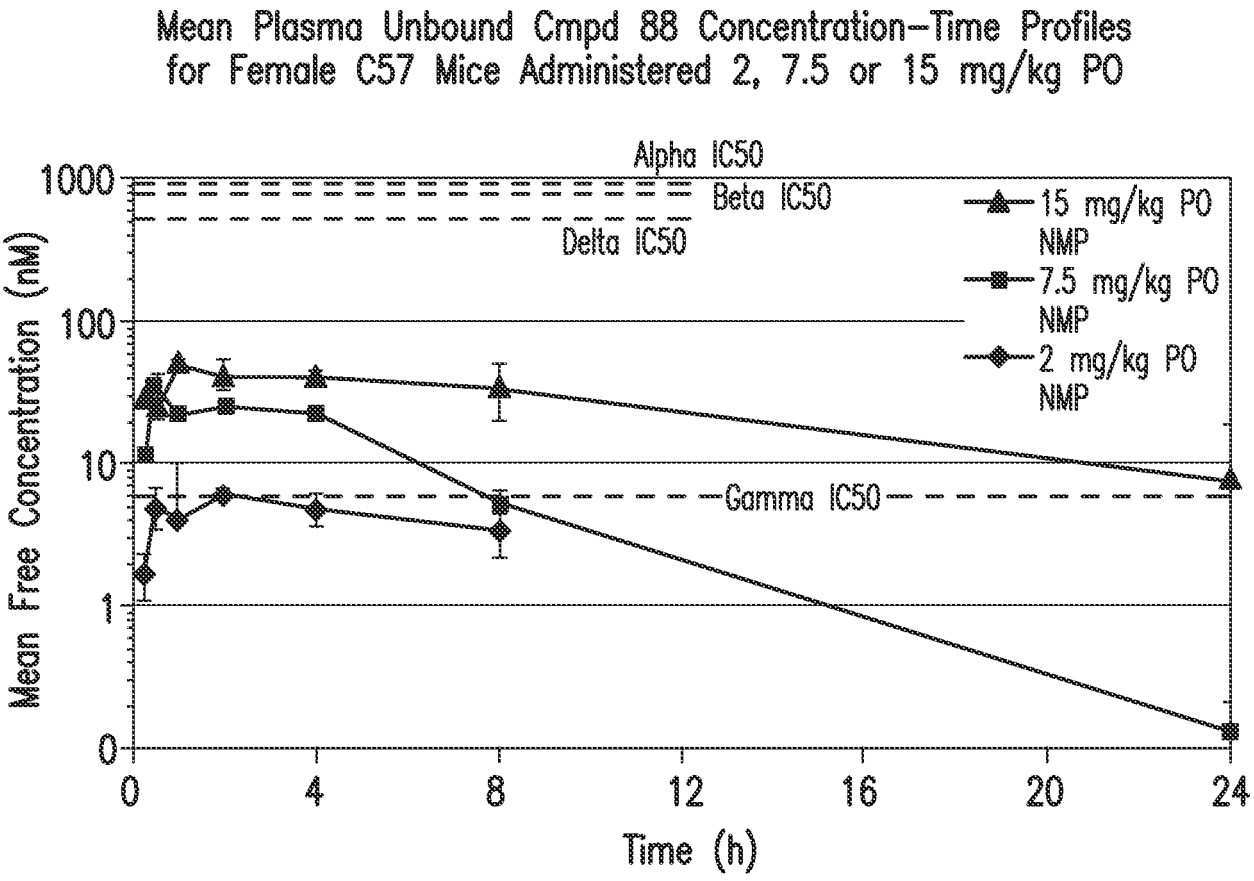

Mean Plasma Unbound Cmpd 88 Concentration–Time Profiles
for Female C57 Mice Administered 2, 7.5 or 15 mg/kg PO
Alpha IC50
Beta IC50
Delta IC50
Gamma IC50
15 mg/kg PO NMP
7.5 mg/kg PO NMP
2 mg/kg PO NMP
Mean Free Concentration (nM)
1000
100
10
1
0
0
4
8
12
16
20
24
Time (h)

FIG. 20

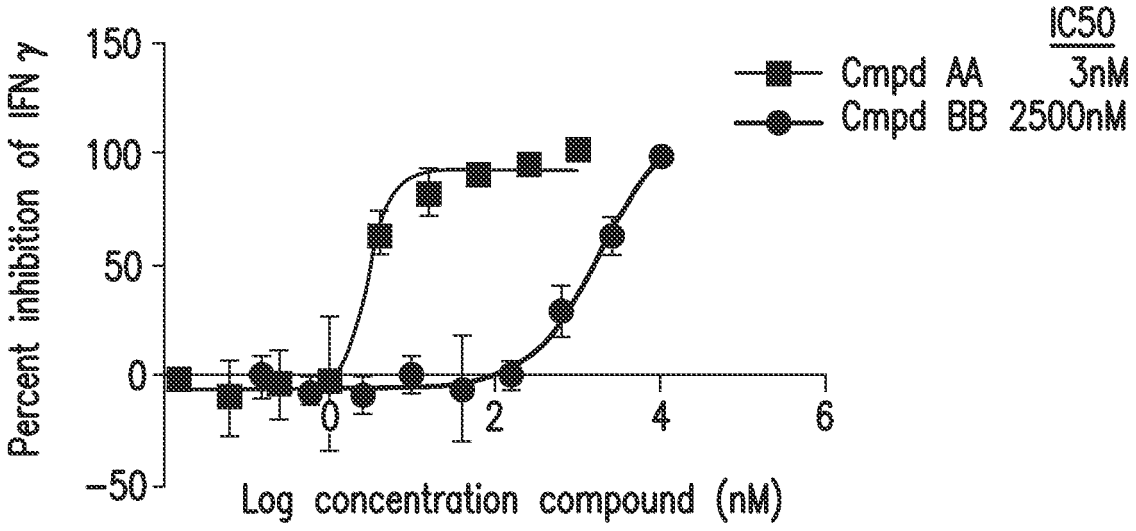

IC50
Cmpd AA 3nM
Cmpd BB 2500nM
Percent inhibition of IFN γ
150
100
50
0
-50
0
2
4
6
Log concentration compound (nM)

FIG. 21

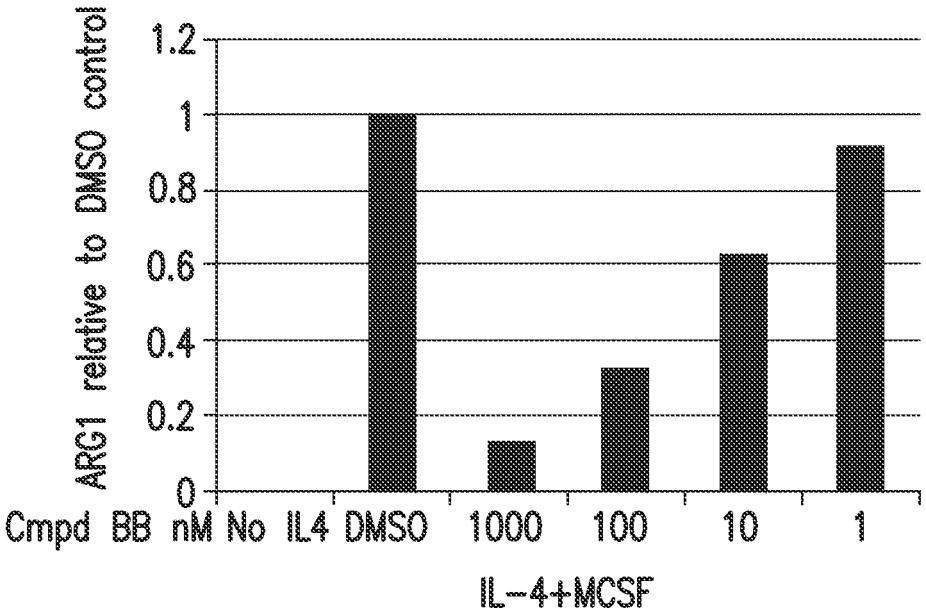


FIG. 22A

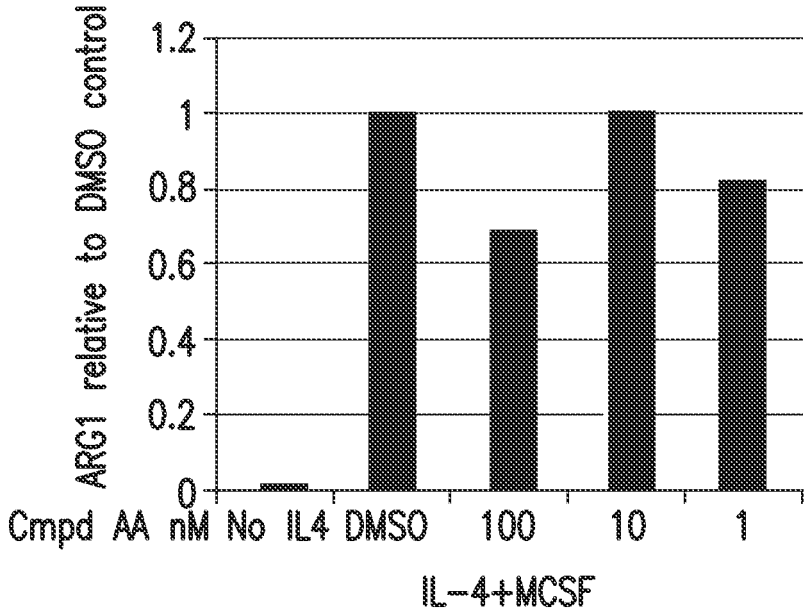


FIG. 22B

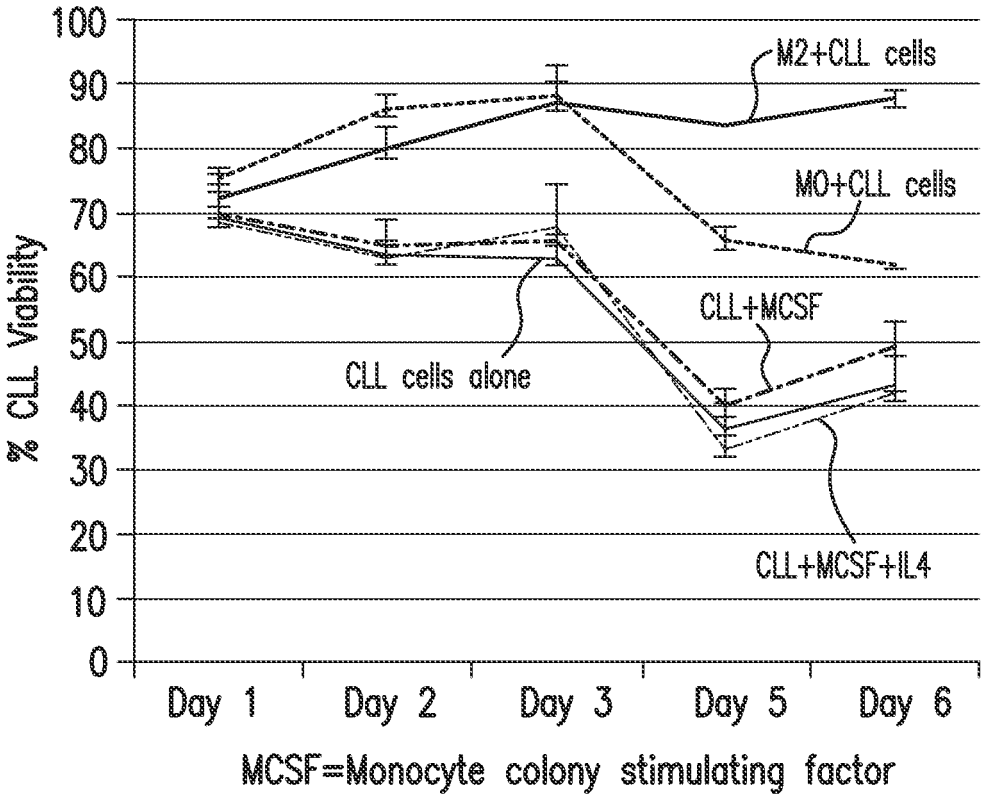

100
90
80
70
60
50
40
30
20
10
0
% CLL Viability
M2+CLL cells
MO+CLL cells
CLL+MCSF
CLL cells alone
CLL+MCSF+IL4
Day 1
Day 2
Day 3
Day 5
Day 6
MCSF=Monocyte colony stimulating factor

FIG. 23

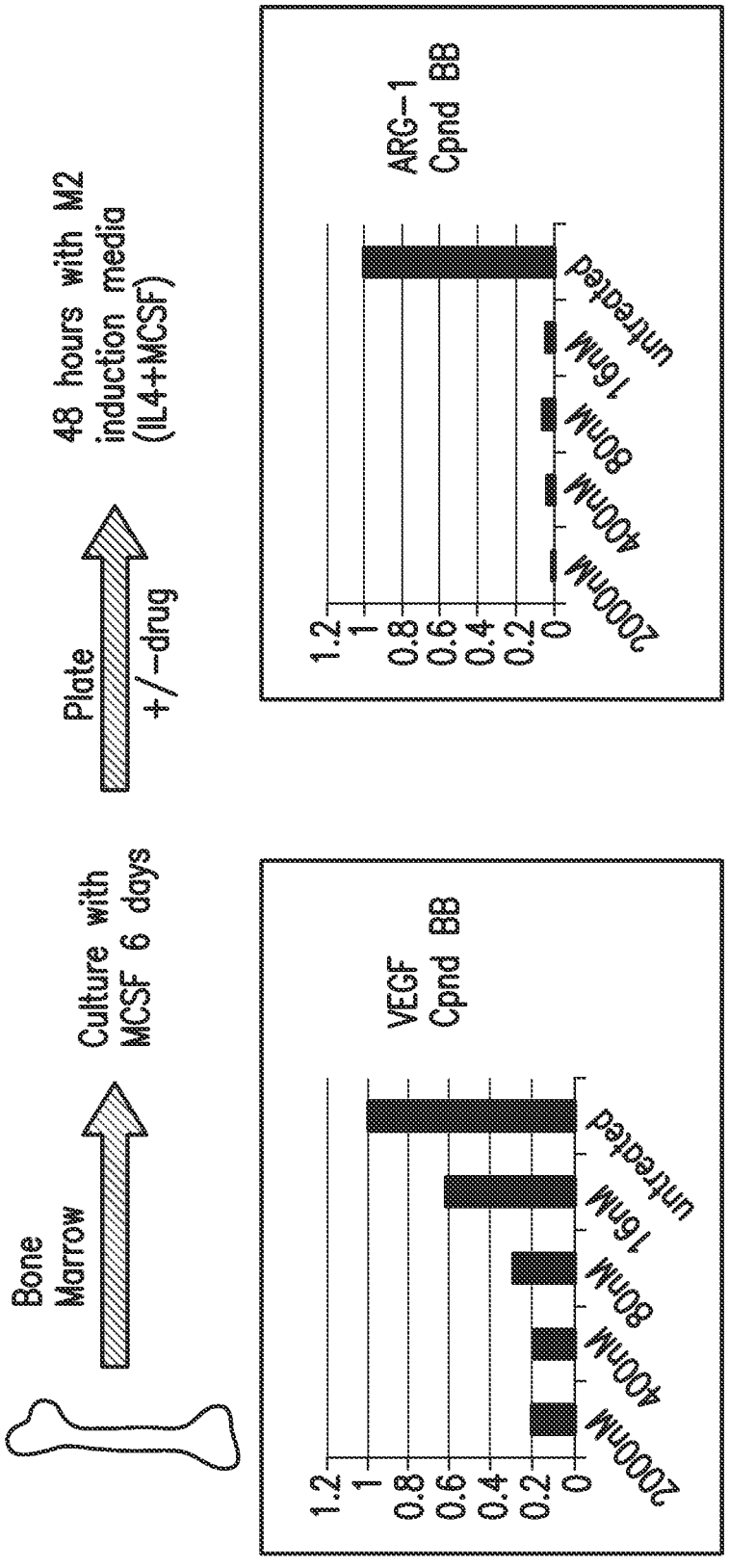
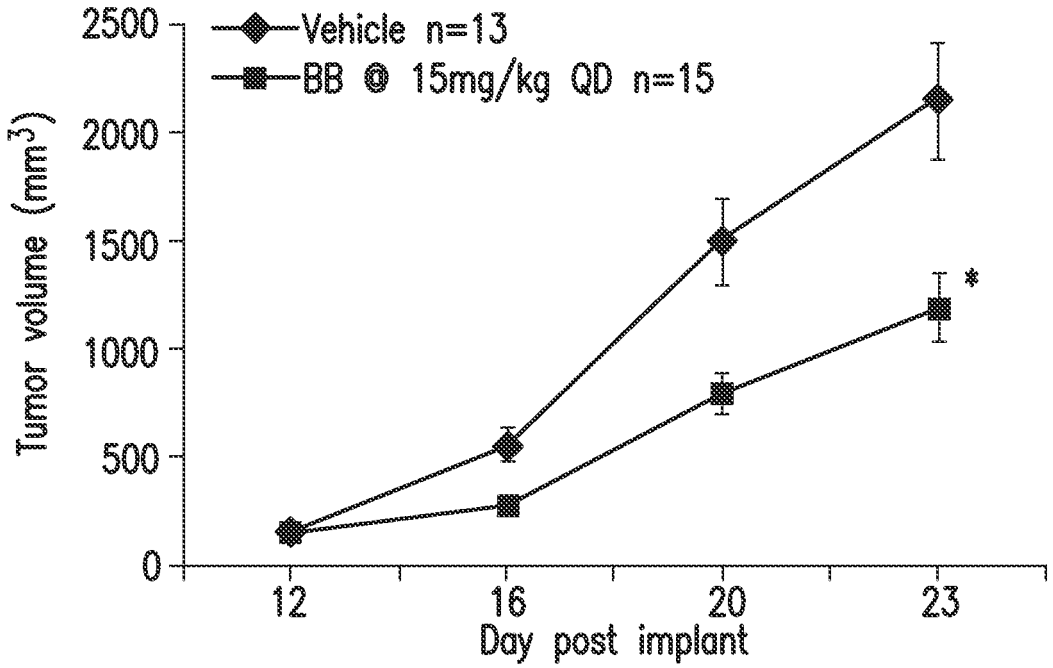


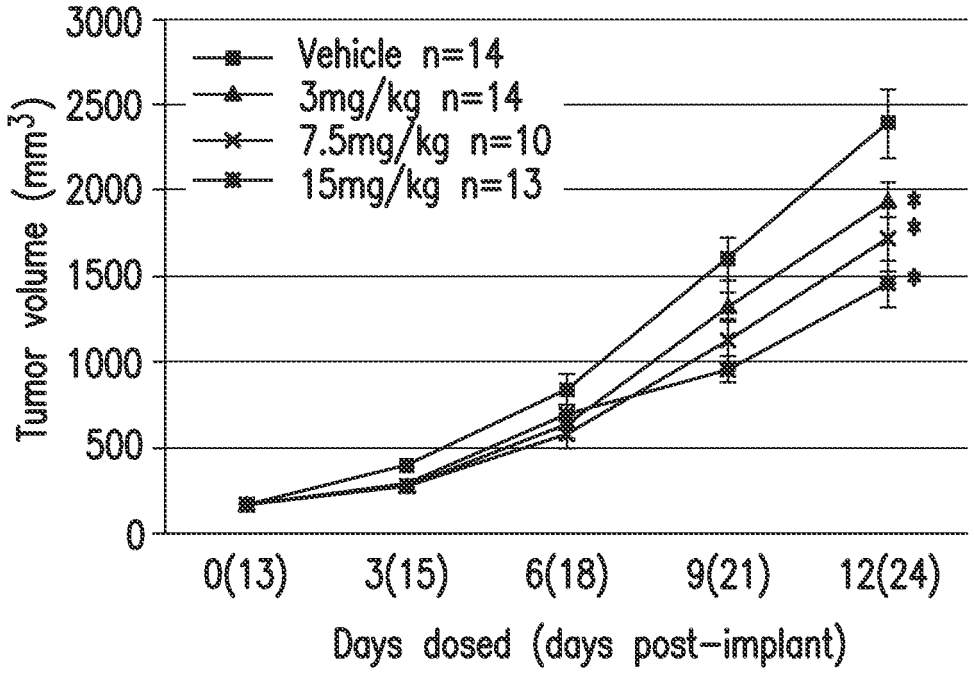
FIG. 24A

FIG. 24B



*p-value < 0.05 compared to vehicle treatment

FIG. 25A



*p-value<0.05 compared to vehicle

FIG. 25B

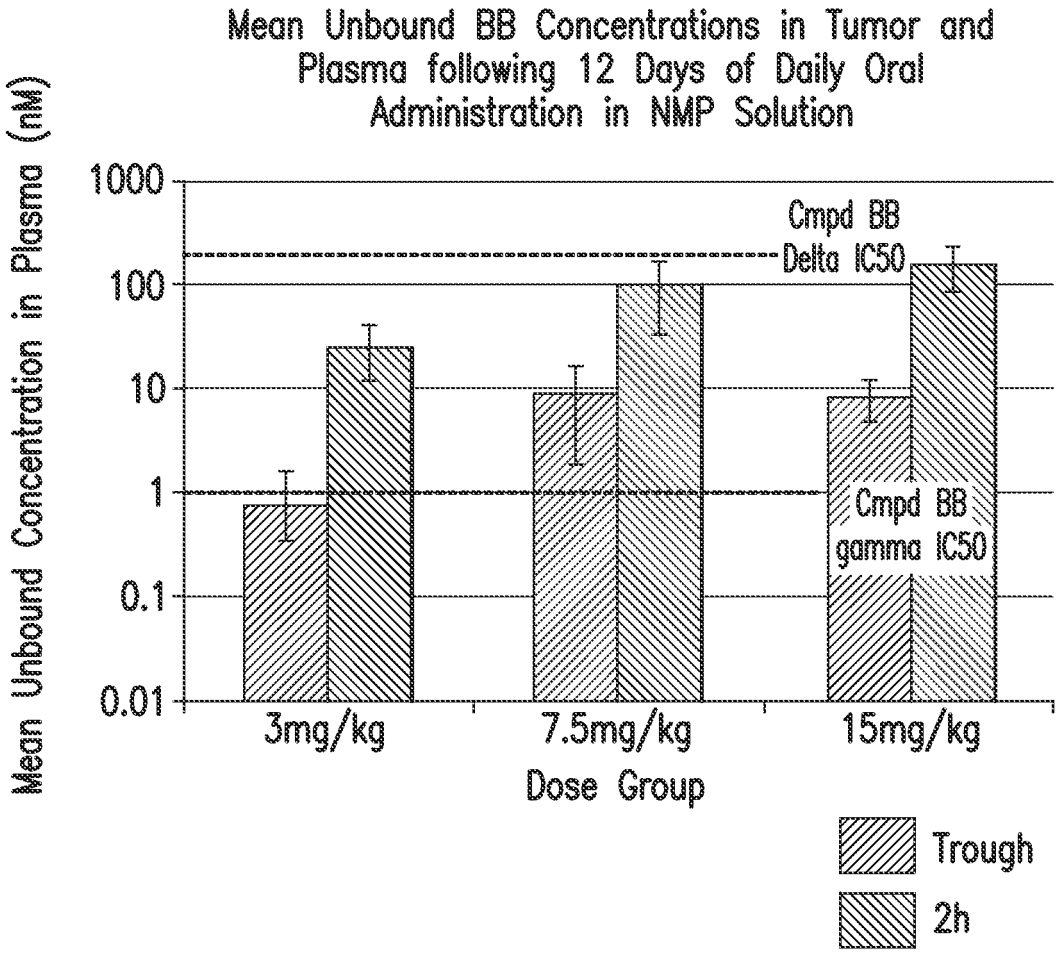

Mean Unbound BB Concentrations in Tumor and Plasma following 12 Days of Daily Oral Administration in NMP Solution
Mean Unbound Concentration in Plasma (nM)
1000
100
10
1
0.1
0.01
Cmpd BB Delta IC50
Cmpd BB gamma IC50
3mg/kg
7.5mg/kg
15mg/kg
Dose Group
Trough
2h

FIG. 26

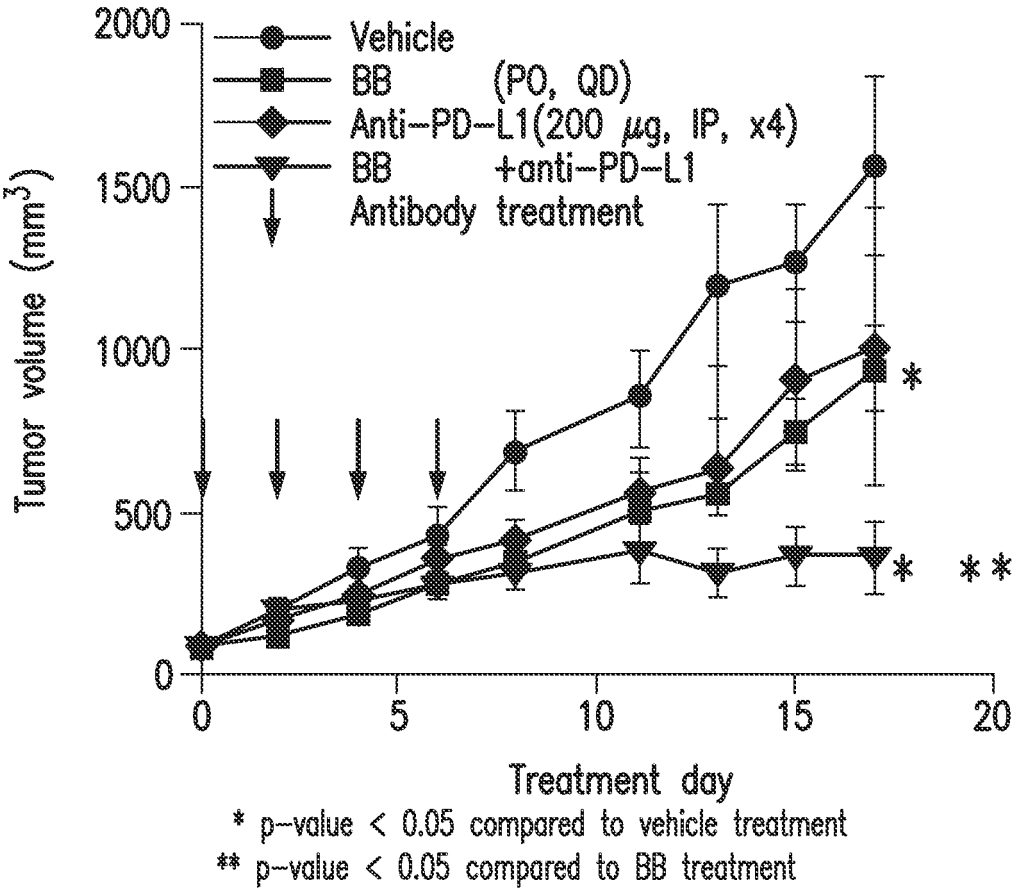


FIG. 27A

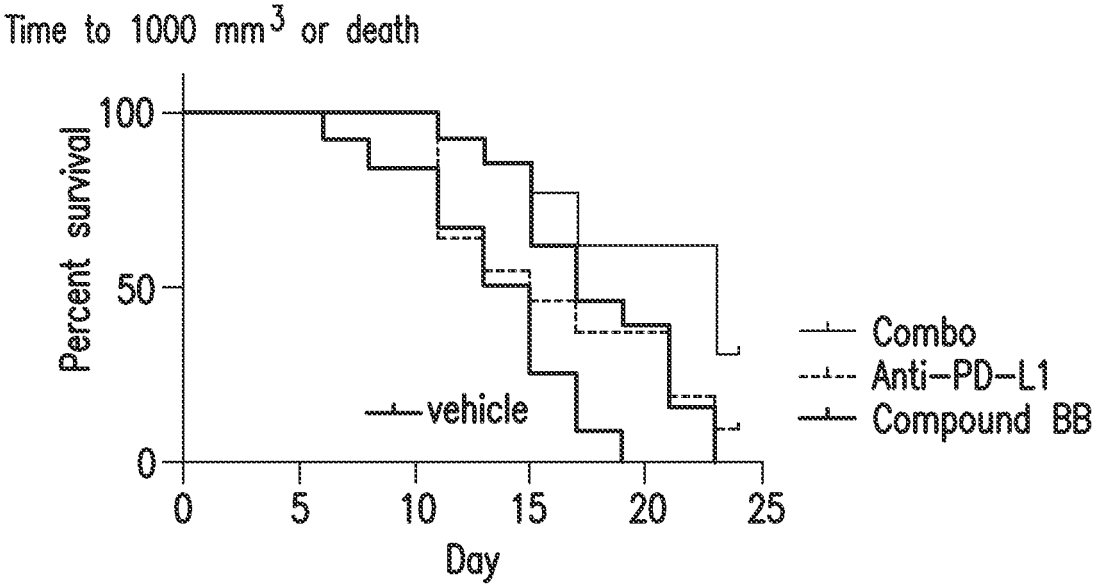


FIG. 27B

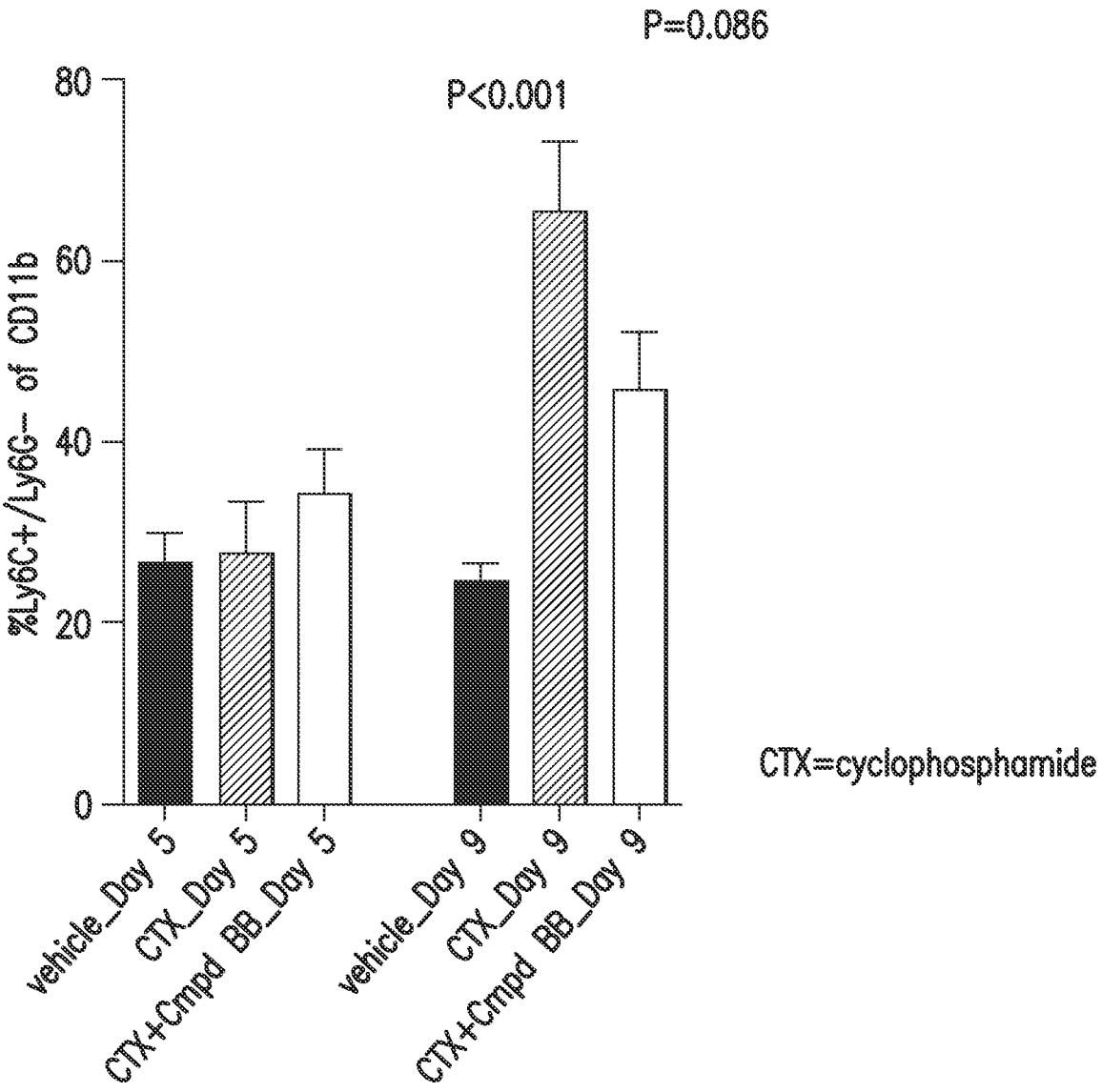

P=0.086
P<0.001
%Ly6C+/Ly6G- of CD11b
80
60
40
20
0
vehicle_Day 5
CTX_Day 5
CTX+Cmpd BB_Day 5
vehicle_Day 9
CTX_Day 9
CTX+Cmpd BB_Day 9
CTX=cyclophosphamide

FIG. 28

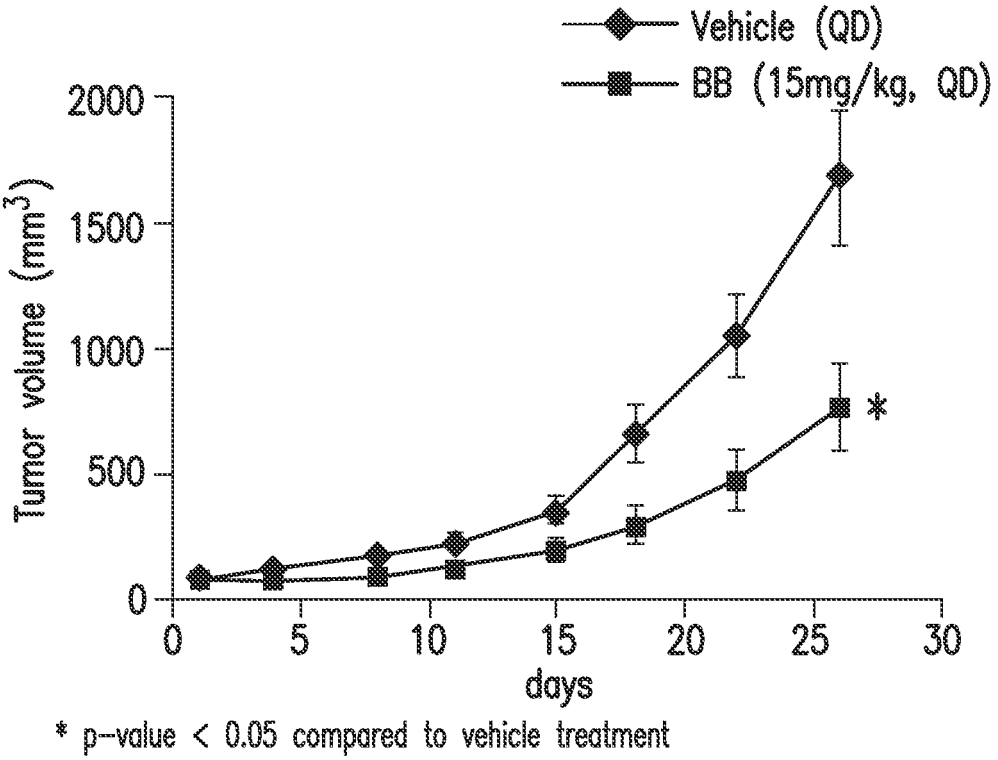


FIG. 29A

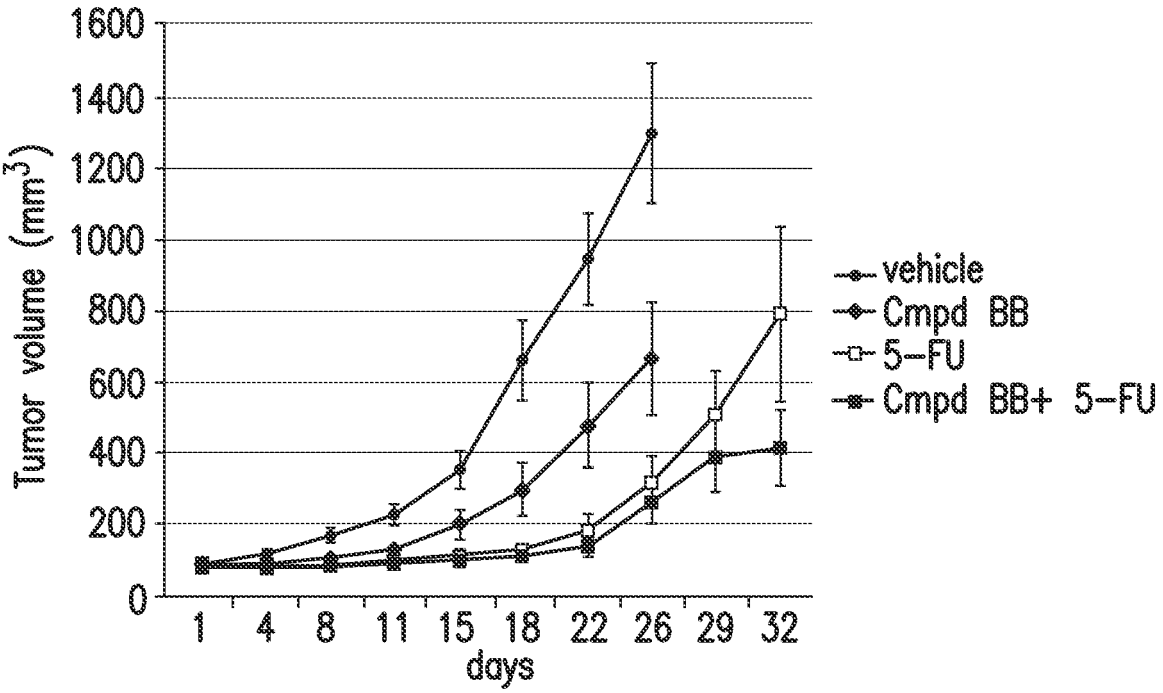


FIG. 29B

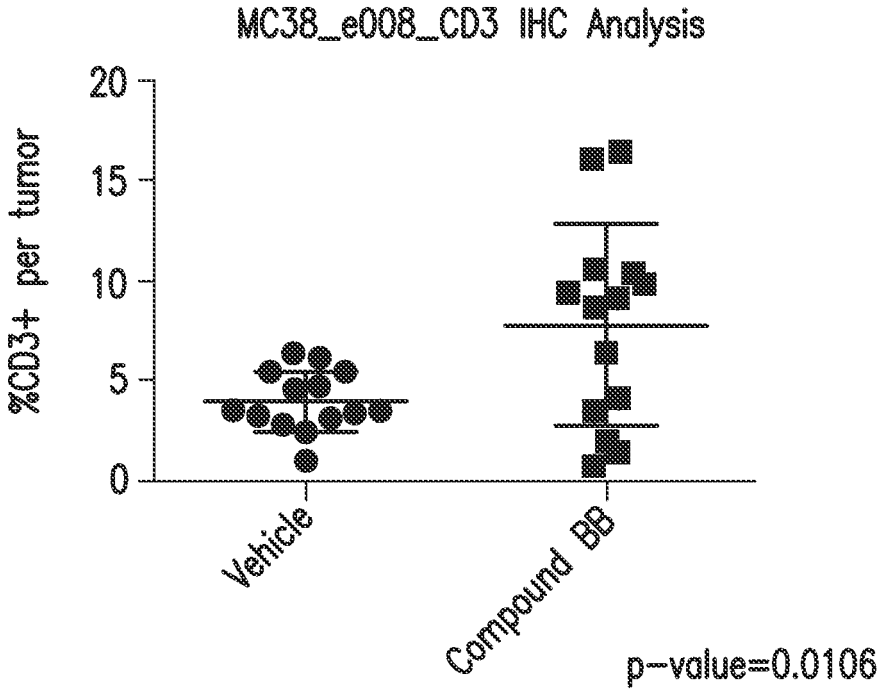

MC38_e008_CD3 IHC Analysis
%CD3+ per tumor
20
15
10
5
0
Vehicle
Compound BB
p-value=0.0106

FIG. 30

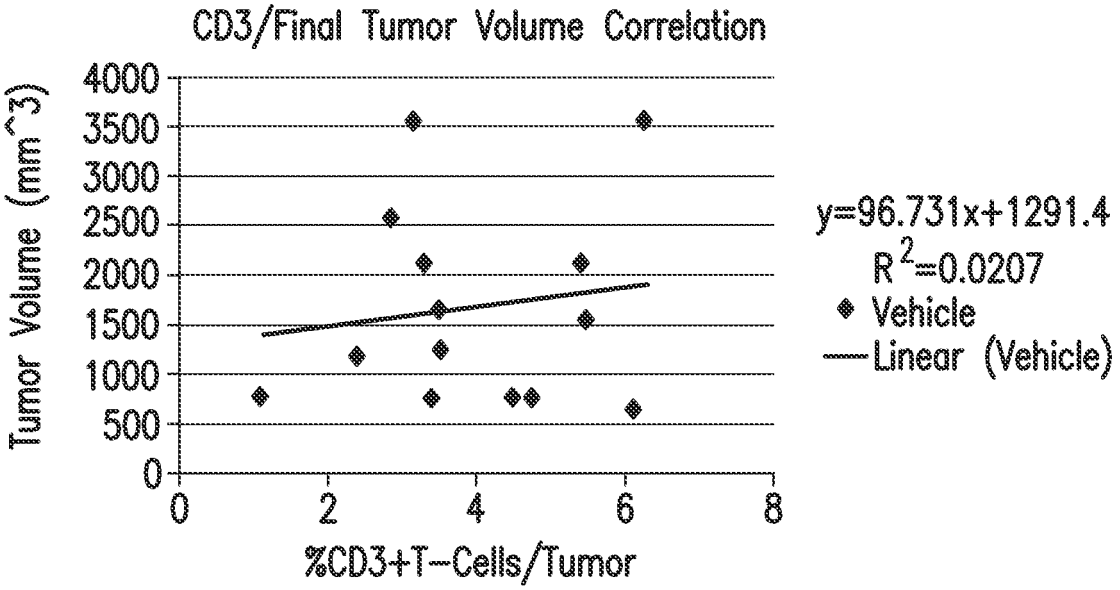


FIG. 31A

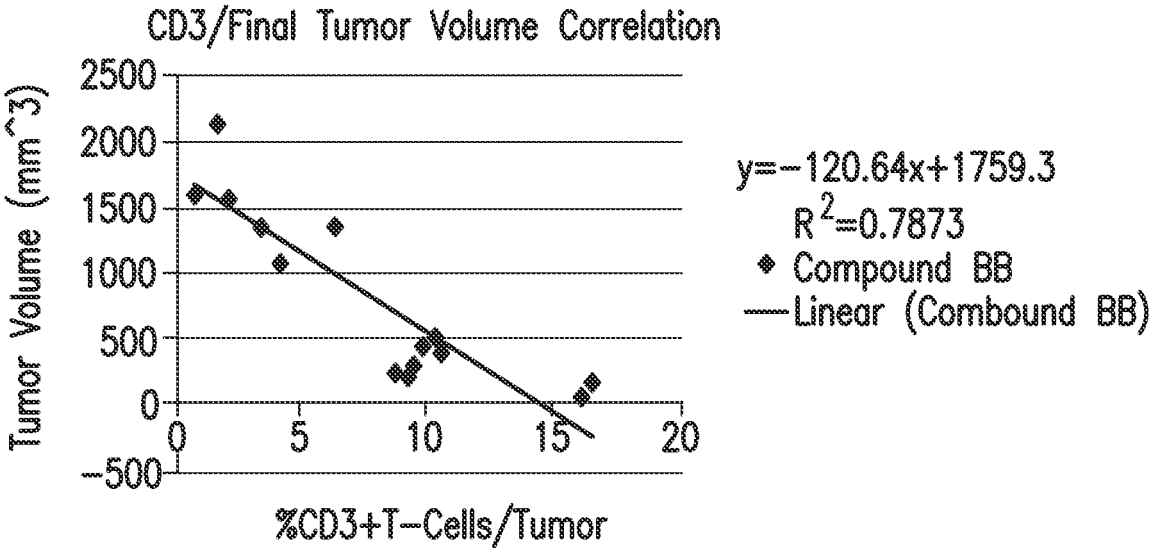


FIG. 31B

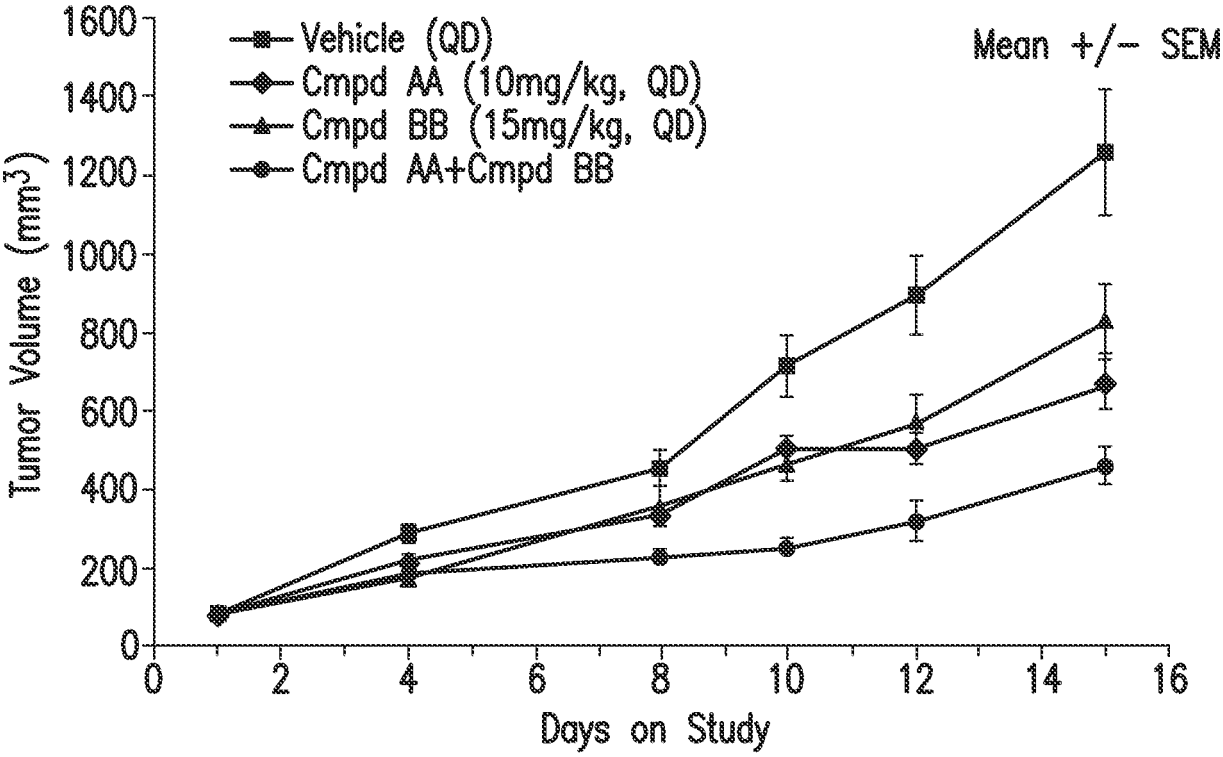


FIG. 32A

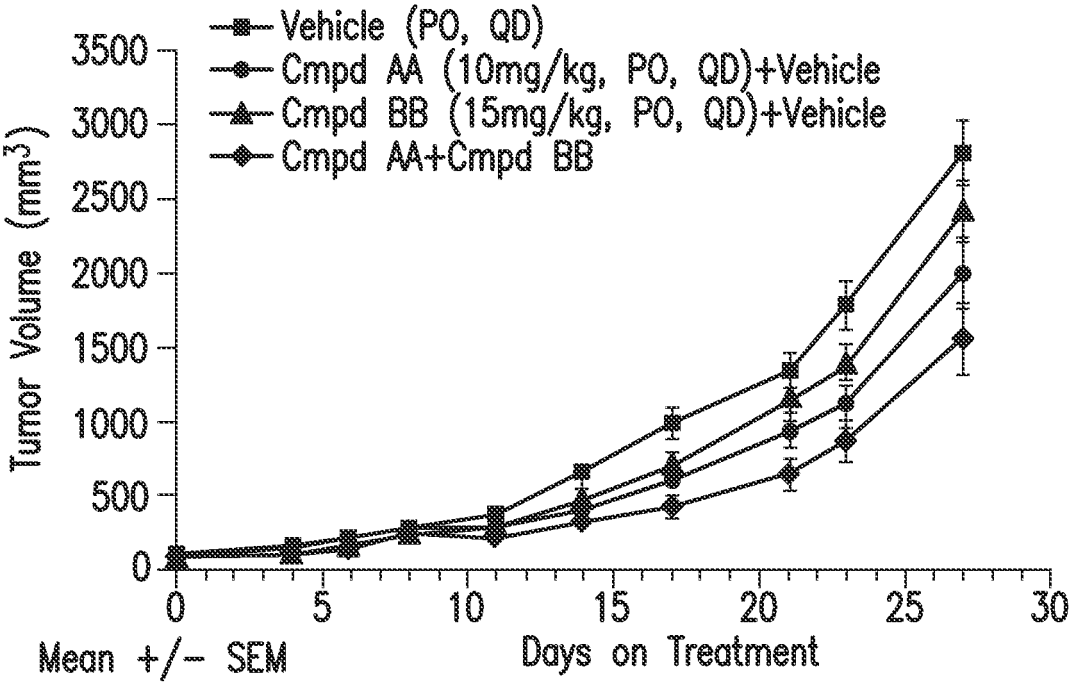


FIG. 32B

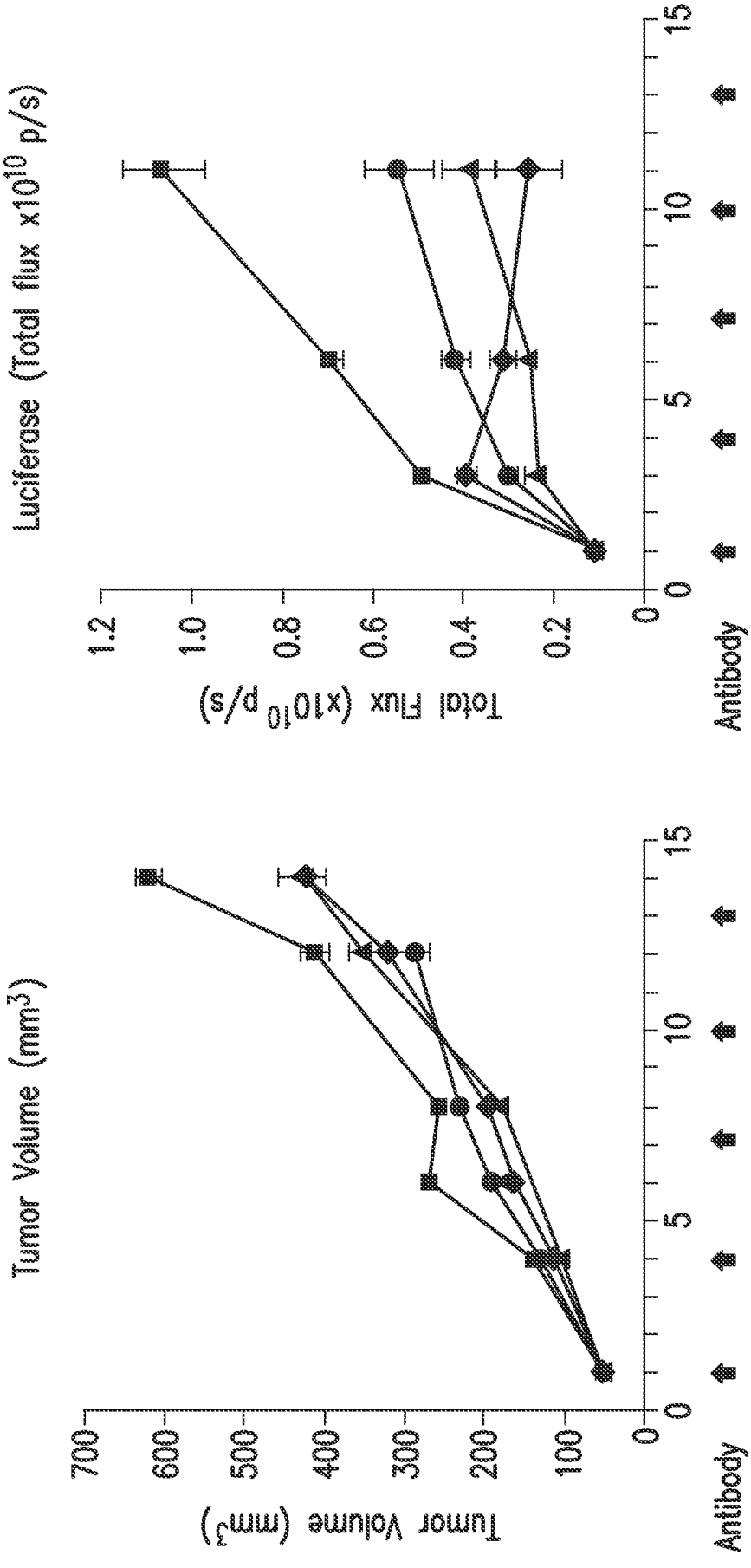


FIG. 33A

FIG. 33B

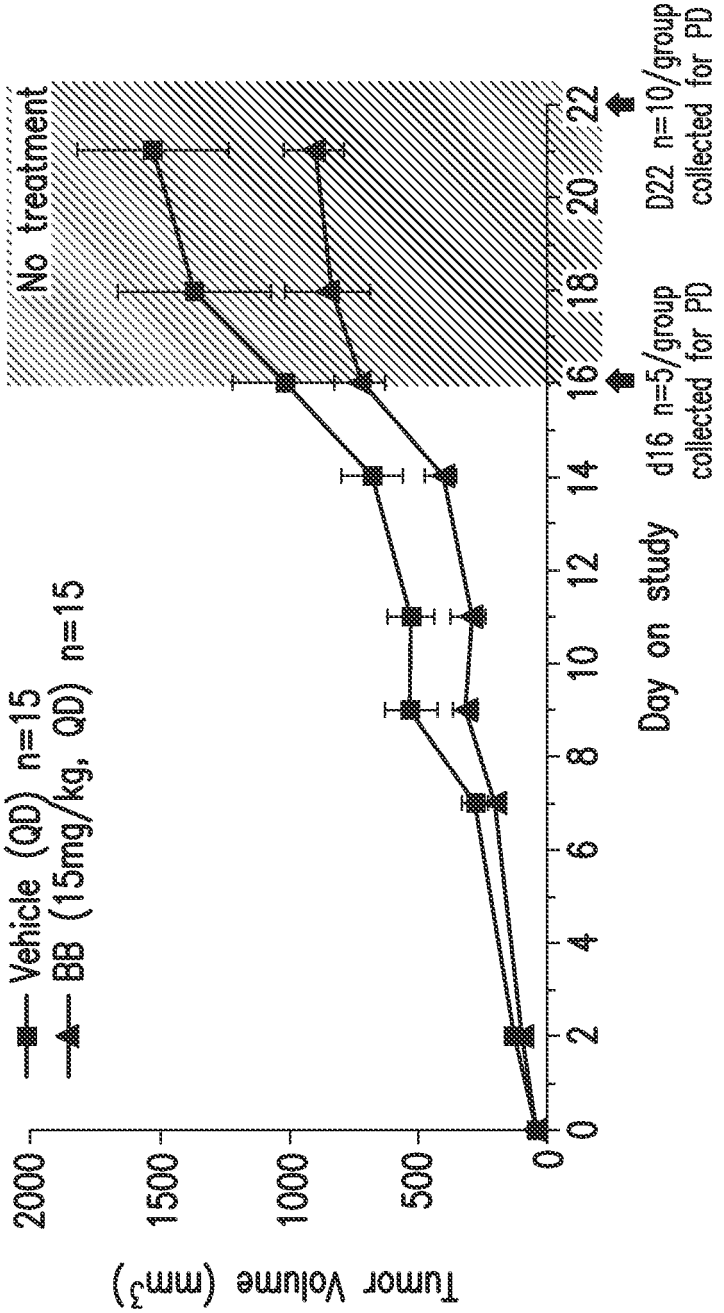

Tumor Volume (mm3)
2000
1500
1000
500
0
0 2 4 6 8 10 12 14 16 18 20 22
Day on study
Vehicle (QD) n=15
BB (15mg/kg, QD) n=15
No treatment
d16 n=5/group collected for PD
D22 n=10/group collected for PD
* p-value <0.05 compared to vehicle treatment

FIG. 34

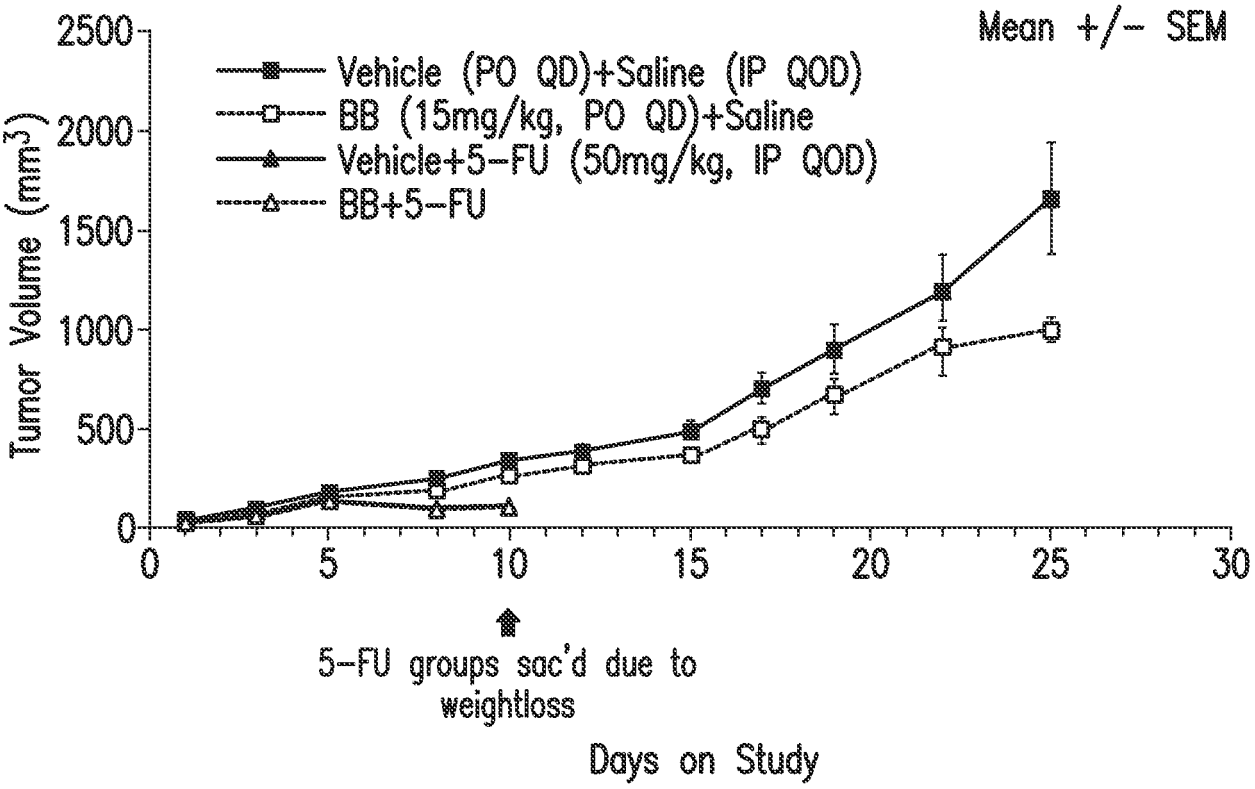

Mean +/- SEM
Vehicle (PO QD)+Saline (IP QOD)
BB (15mg/kg, PO QD)+Saline
Vehicle+5-FU (50mg/kg, IP QOD)
BB+5-FU
Tumor Volume (mm3)
2500
2000
1500
1000
500
0
0
5
10
15
20
25
30
5-FU groups sac'd due to weightloss
Days on Study

FIG. 35

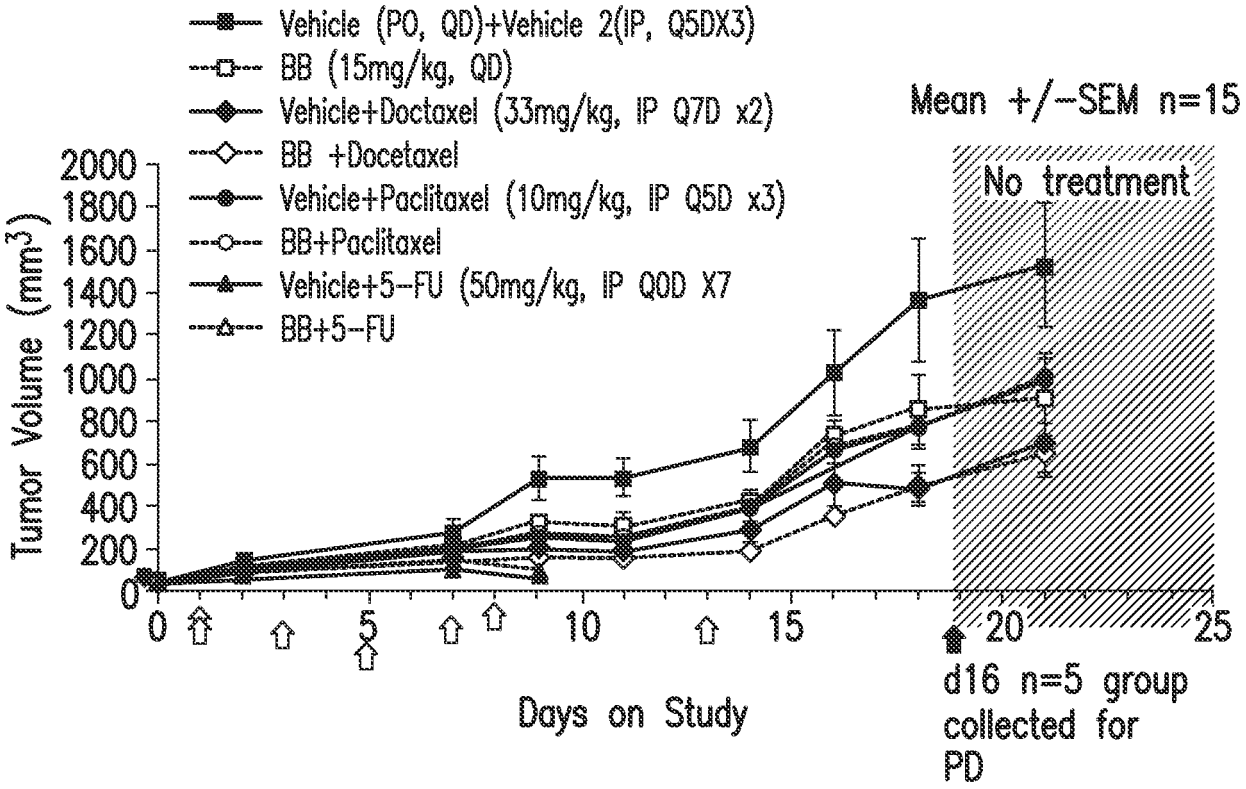

Vehicle (PO, QD)+Vehicle 2(IP, Q5DX3)
BB (15mg/kg, QD)
Vehicle+Doctaxel (33mg/kg, IP Q7D x2)
BB +Docetaxel
Vehicle+Paclitaxel (10mg/kg, IP Q5D x3)
BB+Paclitaxel
Vehicle+5-FU (50mg/kg, IP QOD X7
BB+5-FU
Mean +/-SEM n=15
No treatment
Tumor Volume (mm3)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0
5
10
15
20
25
Days on Study
d16 n=5 group collected for PD

FIG. 36

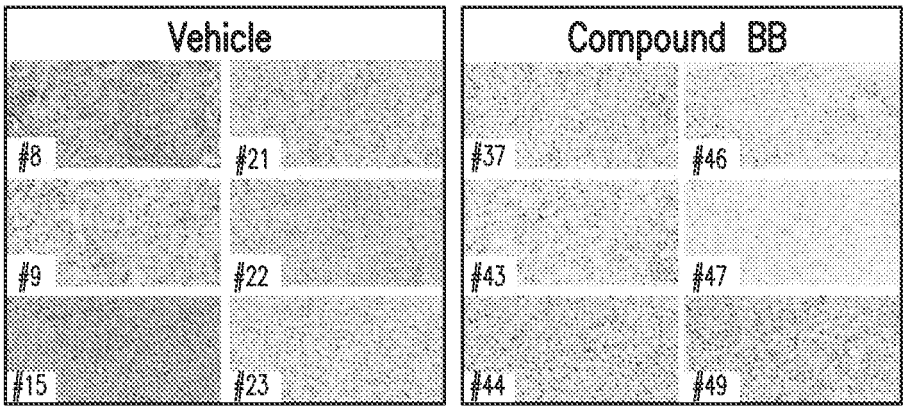


FIG. 37A

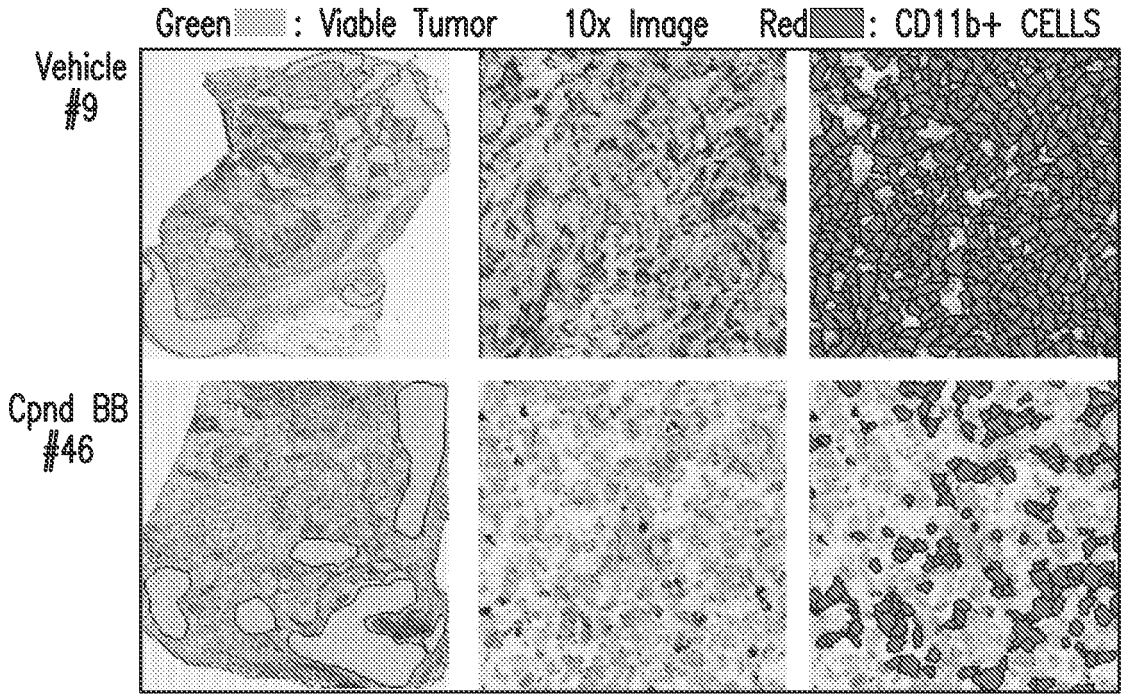
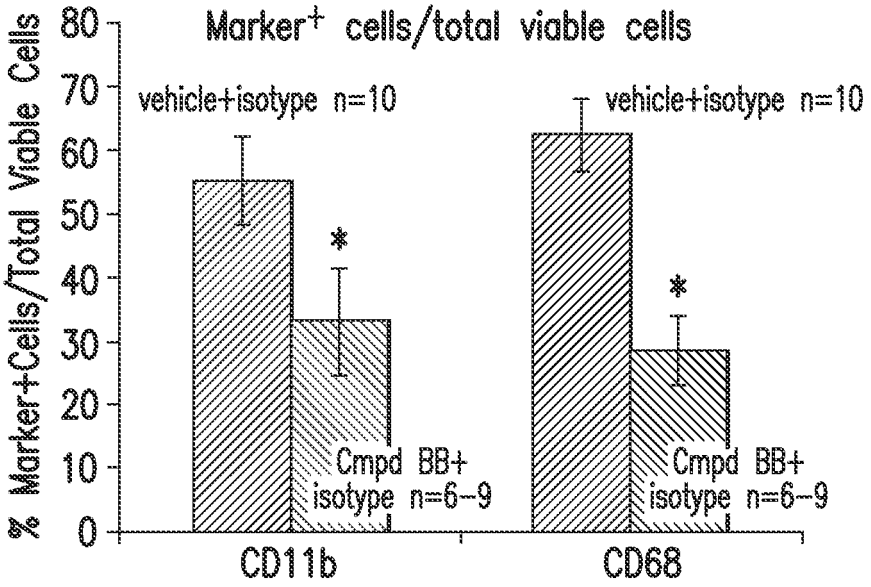


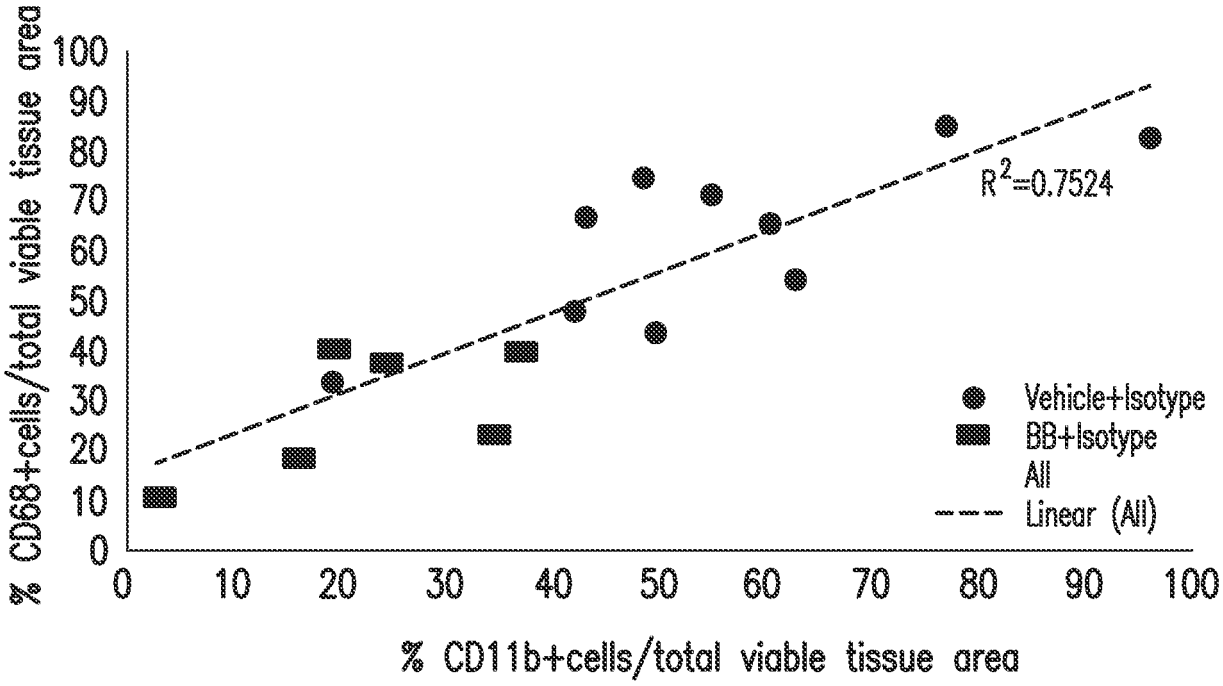
FIG. 37B



*p-value<0.05 compared to vehicle treatment

Isotype = Antibody control

FIG. 37C



Isotype=Antibody control

FIG. 37D

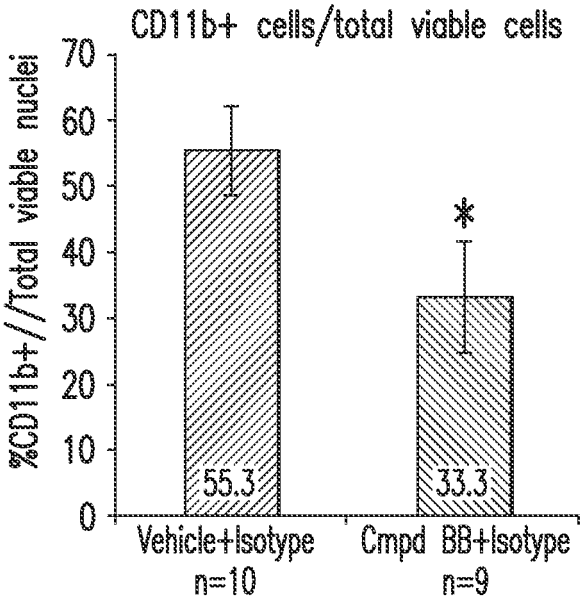


FIG. 37E

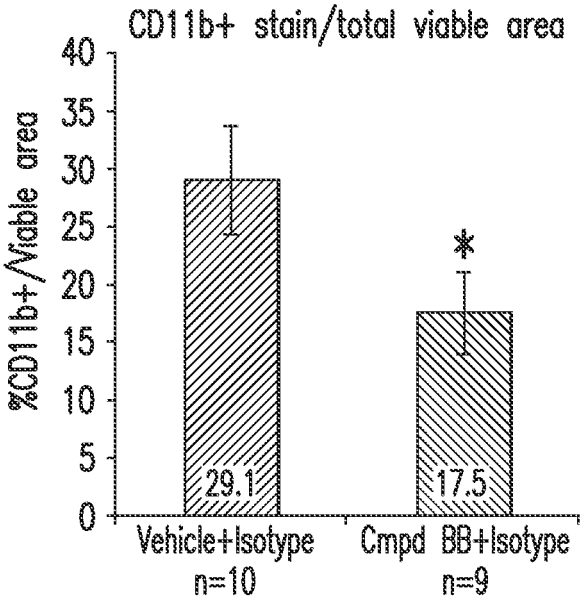


FIG. 37F

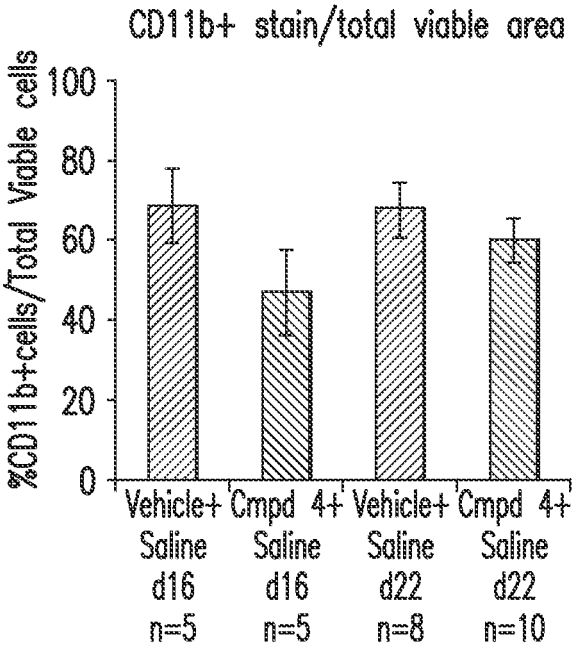


FIG. 37G

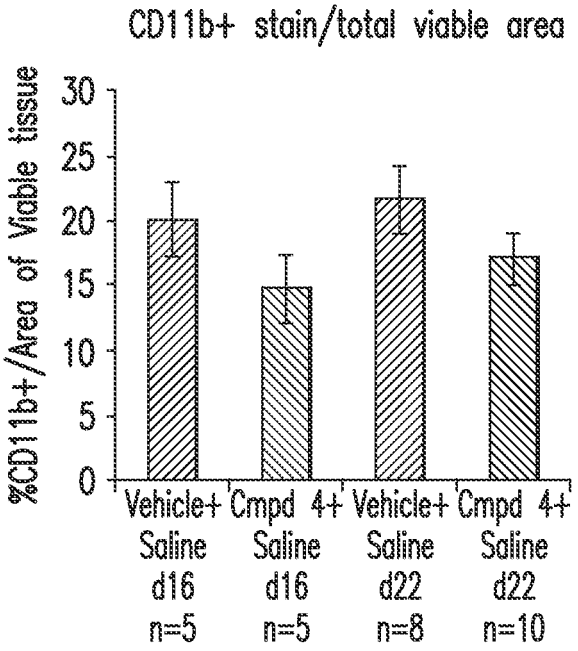


FIG. 37H

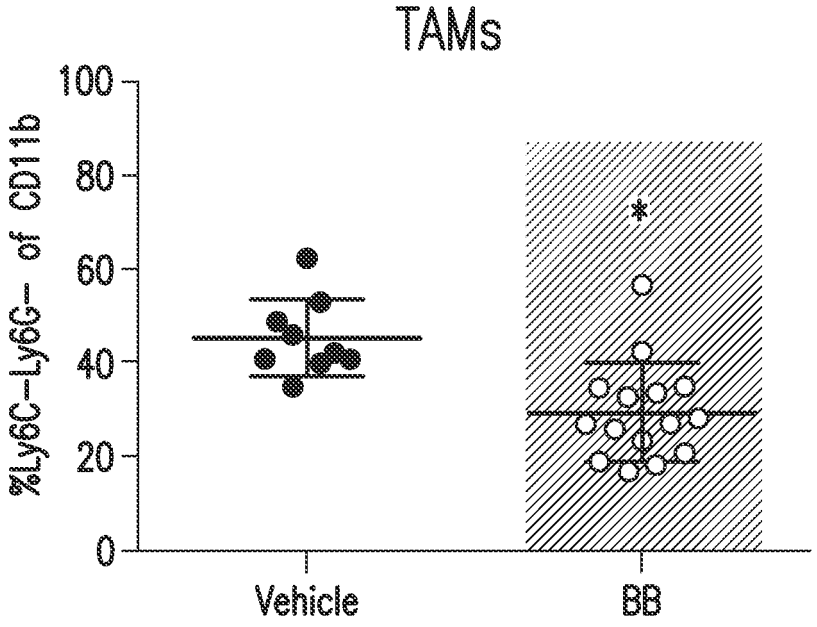


FIG. 38A

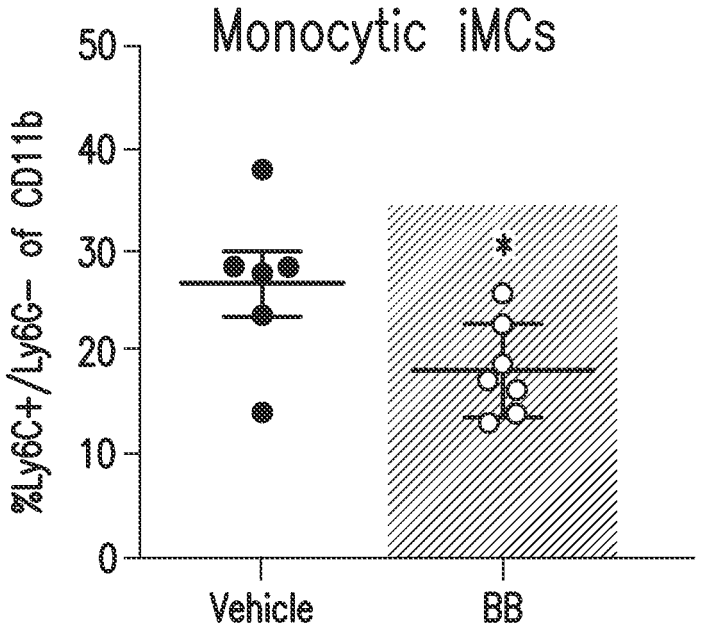


FIG. 38B

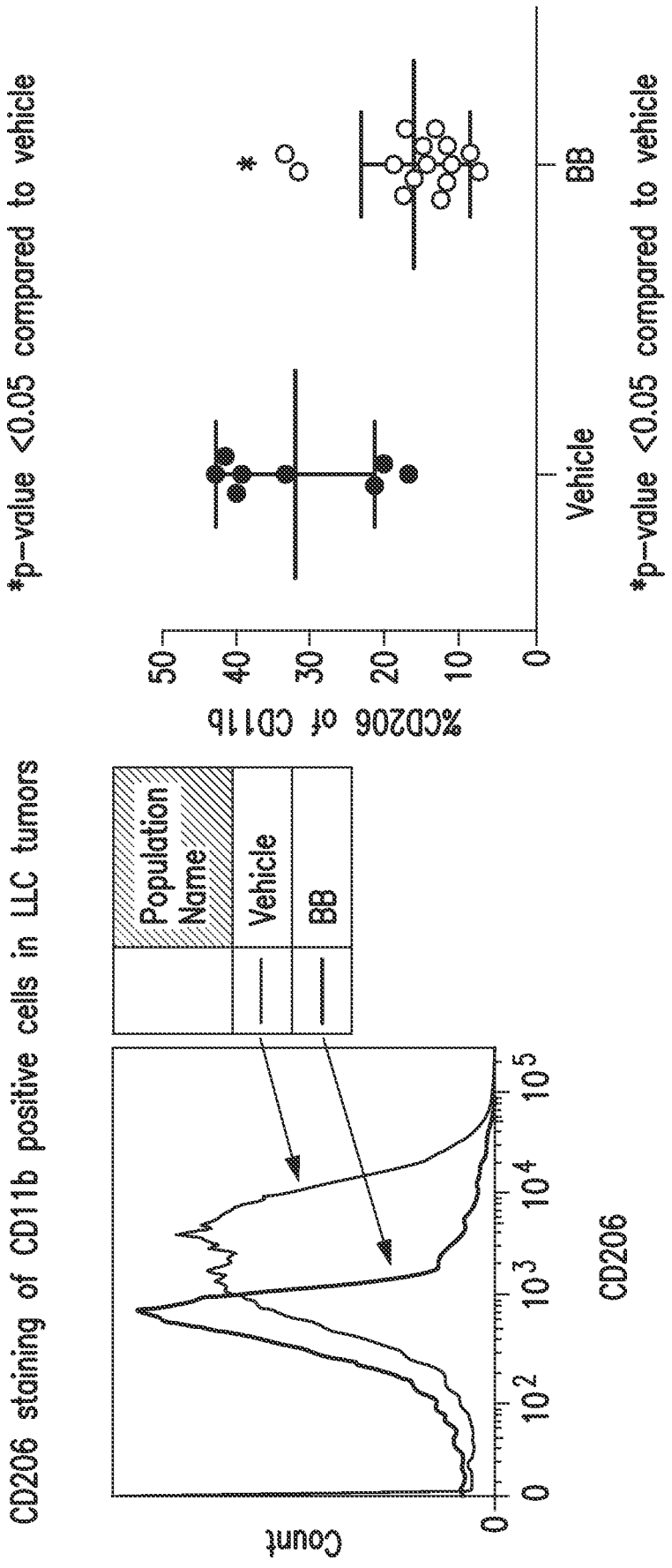
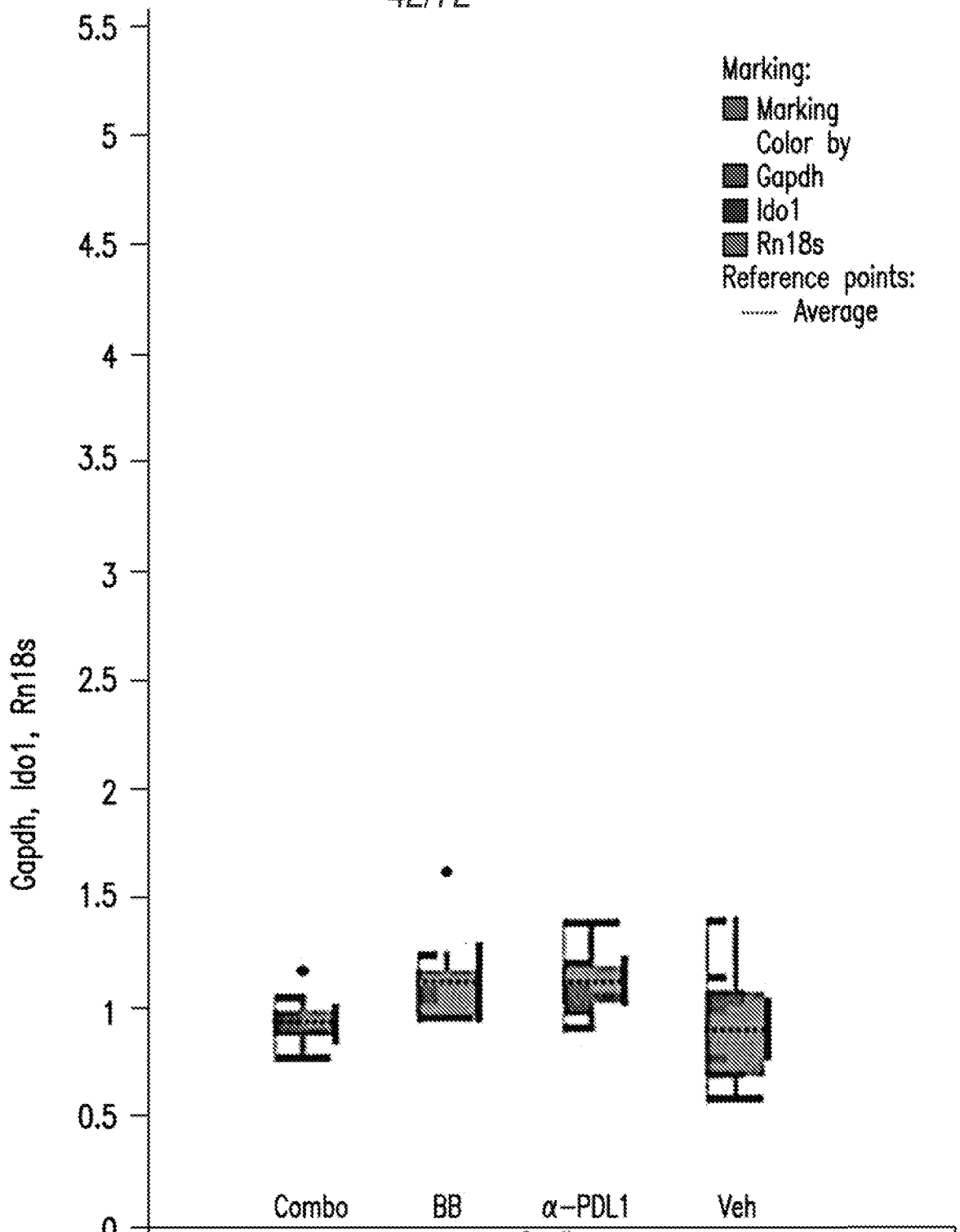
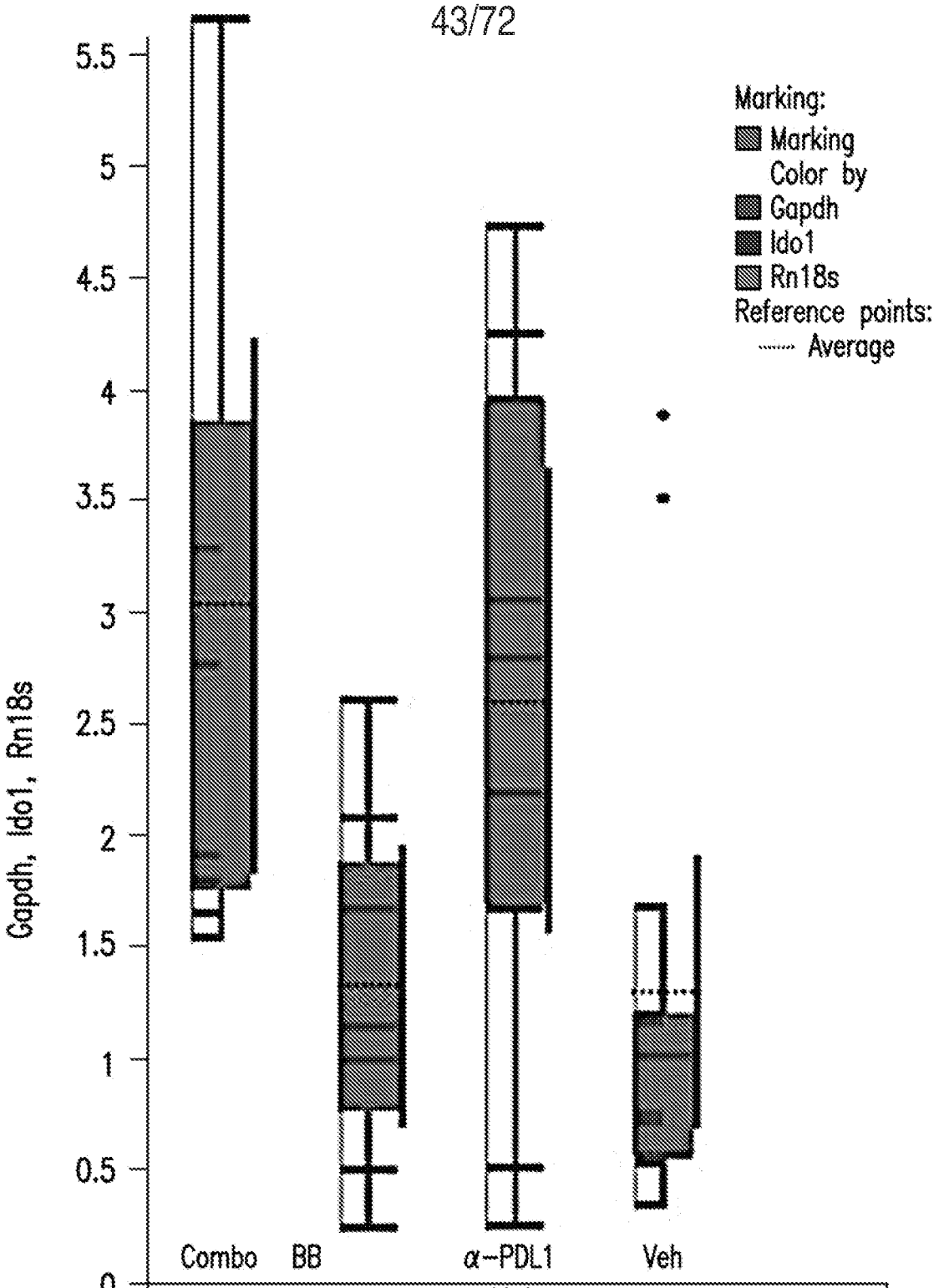

CD206 staining of CD11b positive cells in LLC tumors
Count
CD206
Population Name
Vehicle
BB
%CD206 of CD11b
Vehicle
BB
*p-value <0.05 compared to vehicle
*p-value <0.05 compared to vehicle

FIG. 39



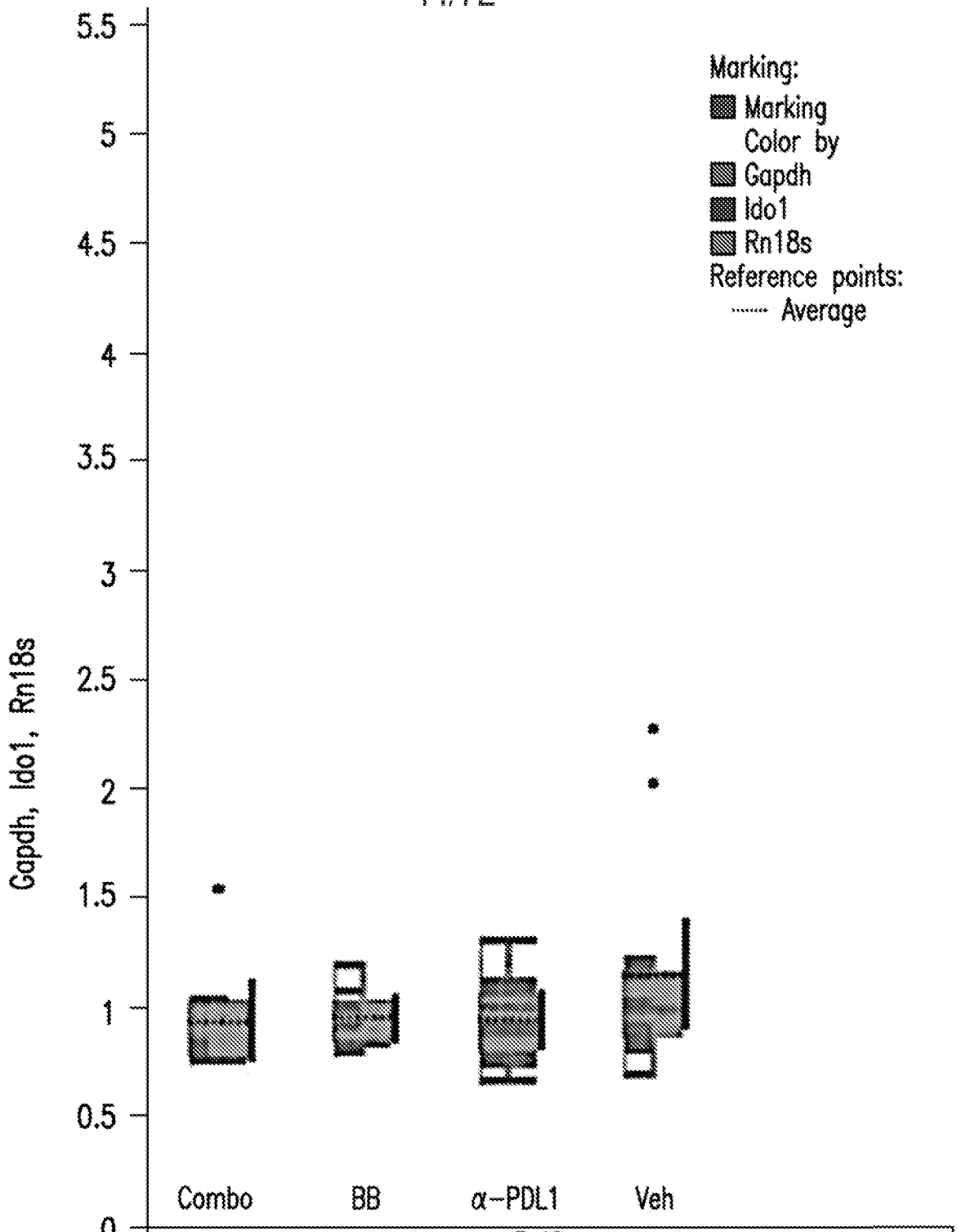
	Gapdh				
	Com	IPI	PDL	Veh	(Empty)
Count	8	7	9	13	0
Median	0.916142	1.01621	1.06387	1	(Empty)
Outliers	1	1	0	0	(Empty)

FIG. 40



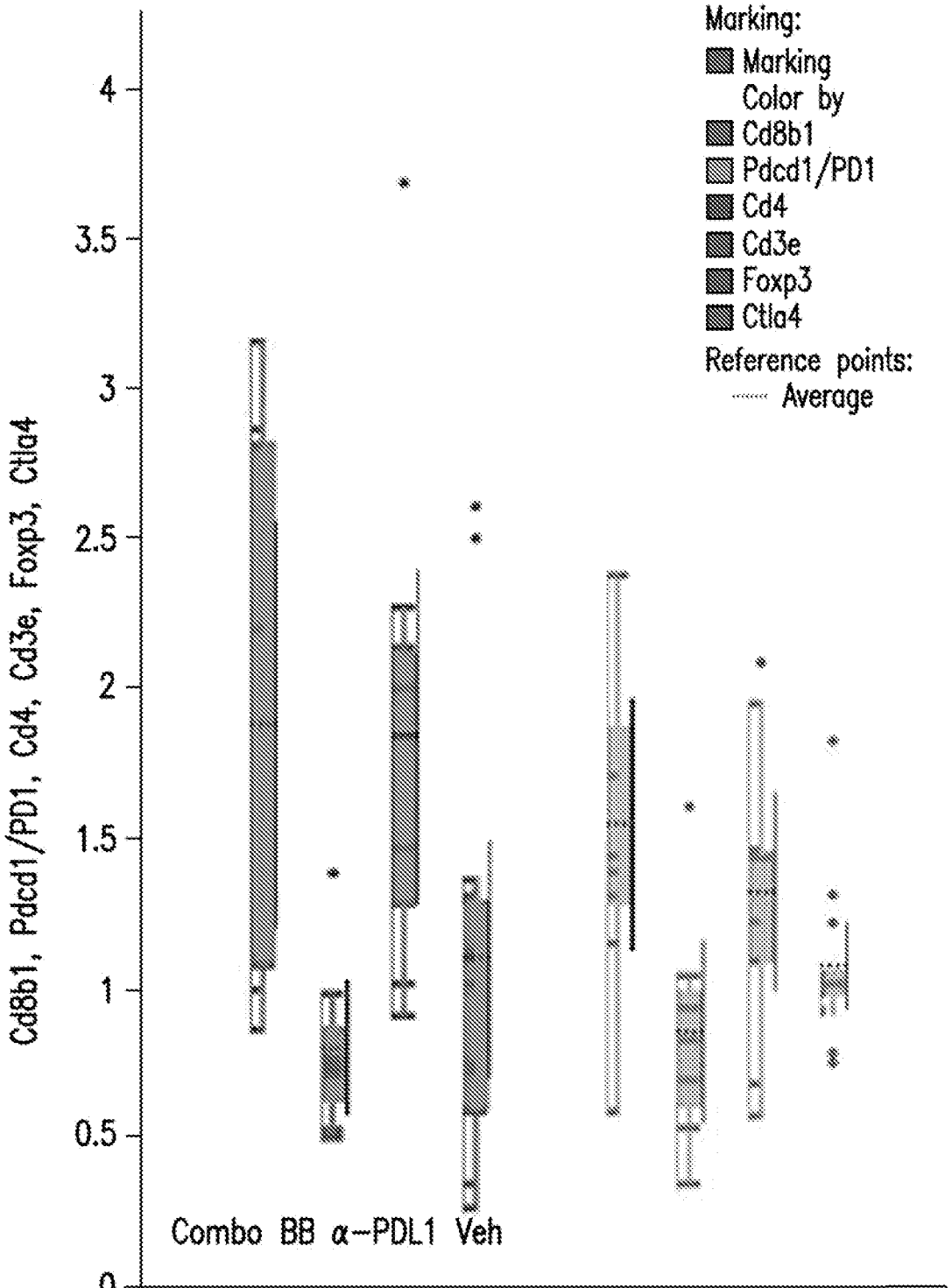
	Ido1				
	Com	IPI	PDL	Veh	(Empty)
Count	8	7	9	13	0
Median	2.33528	1.12757	2.77892	1	(Empty)
Outliers	0	0	0	2	(Empty)

FIG. 40 (cont.)



	Rn18s				
	Com	IPI	PDL	Veh	(Empty)
Count	8	7	9	13	0
Median	0.806881	0.916437	0.927663	1	(Empty)
Outliers	1	0	0	2	(Empty)

FIG. 40 (cont.)



	Cd8b1					Pdcd1/PD1				
	Com	IPI	PDL	Veh	(Em...	Com	IPI	PDL	Veh	(Em...
Count	8	7	9	13	0	8	7	9	13	0
Medium	1.62105	0.6...	1.81...	1	(Em...	1.3...	0.8	1.40...	1	(Em...
Outliers	0	1	1	2	(Em...	0	1	1	5	(Em...

Treatment Group

Cd8b1 Pdcd1/PD1

FIG. 41

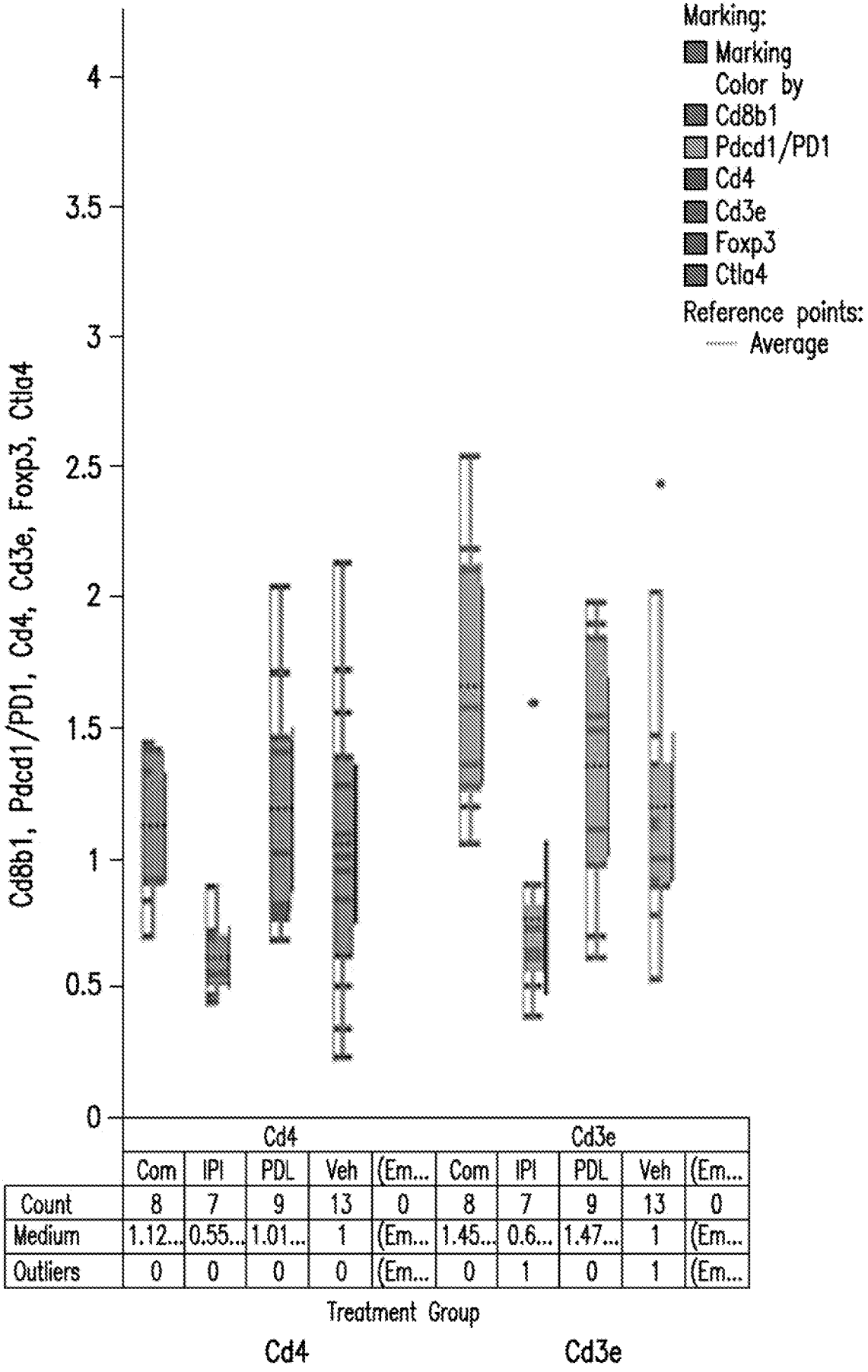
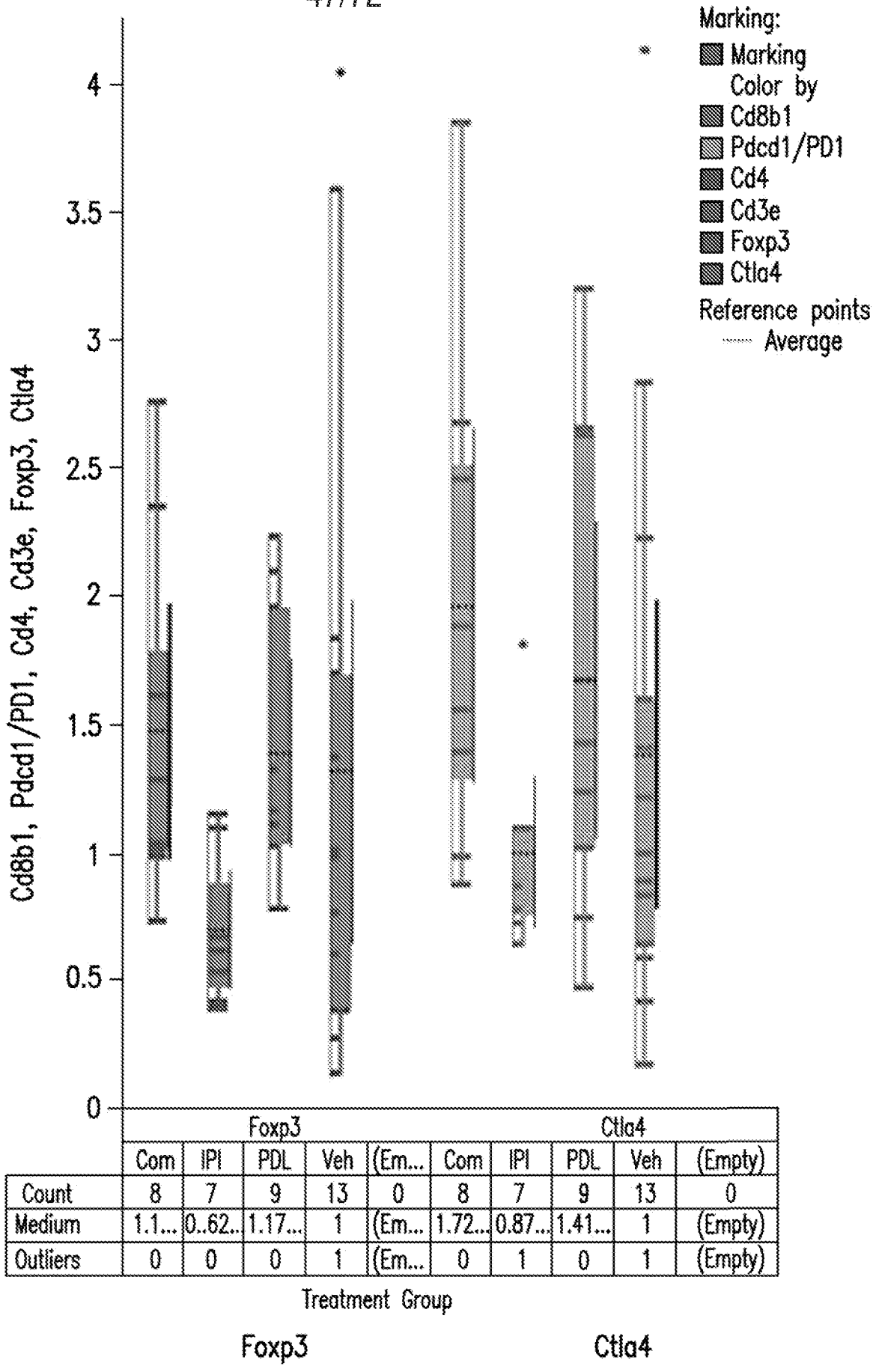

Marking:
Marking Color by
Cd8b1
Pdcd1/PD1
Cd4
Cd3e
Foxp3
Ctla4
Reference points:
Average
Cd8b1, Pdcd1/PD1, Cd4, Cd3e, Foxp3, Ctla4
0
0.5
1
1.5
2
2.5
3
3.5
4
Cd4
Cd3e
Com IPI PDL Veh (Em... Com IPI PDL Veh (Em...
Count 8 7 9 13 0 8 7 9 13 0
Medium 1.12... 0.55... 1.01... 1 (Em... 1.45... 0.6... 1.47... 1 (Em...
Outliers 0 0 0 0 (Em... 0 1 0 1 (Em...
Treatment Group
Cd4
Cd3e

FIG. 41 (cont.)



	Foxp3					Ctla4				
	Com	IPI	PDL	Veh	(Em...	Com	IPI	PDL	Veh	(Empty)
Count	8	7	9	13	0	8	7	9	13	0
Medium	1.1...	0..62..	1.17...	1	(Em...	1.72...	0.87...	1.41...	1	(Empty)
Outliers	0	0	0	1	(Em...	0	1	0	1	(Empty)

Treatment Group

Foxp3 Ctla4

FIG. 41 (cont.)

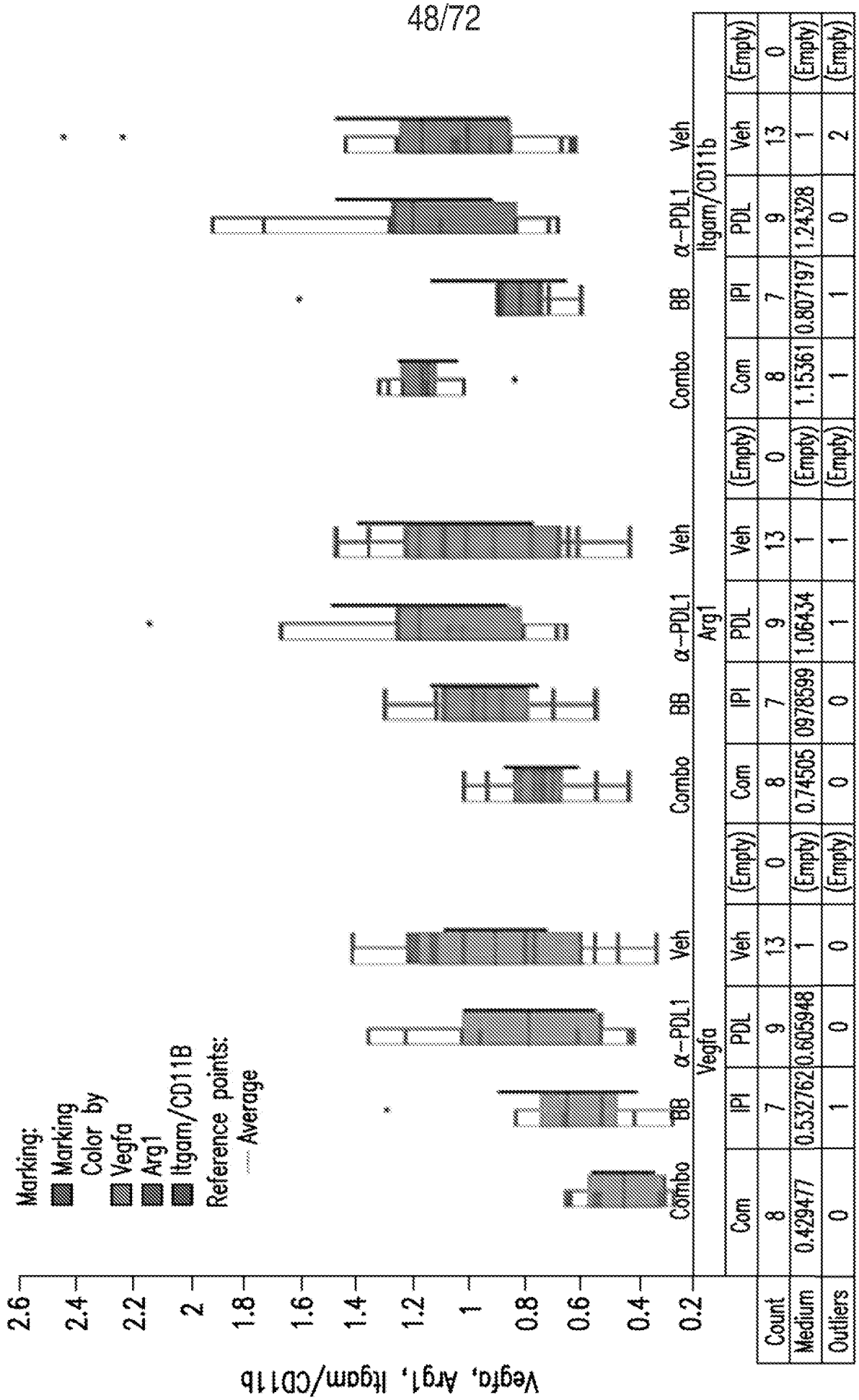

Marking:
Marking
Color by
Vegfa
Arg1
Itgam/CD11B
Reference points:
Average
Vegfa, Arg1, Itgam/CD11b
2.6
2.4
2.2
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
Vegfa
Arg1
Itgam/CD11b
Treatment Group
Combo BB α-PDL1 Veh Combo BB α-PDL1 Veh Combo BB α-PDL1 Veh
Count 8 7 9 13 0 8 7 9 13 0 8 7 9 13 0
Medium 0.429477 0.532762 0.605948 1 (Empty) 0.74505 0.978599 1.06434 1 (Empty) 1.15361 0.807197 1.24328 1 (Empty)
Outliers 0 1 0 0 (Empty) 0 0 1 1 (Empty) 1 1 0 2 (Empty)

FIG. 42A

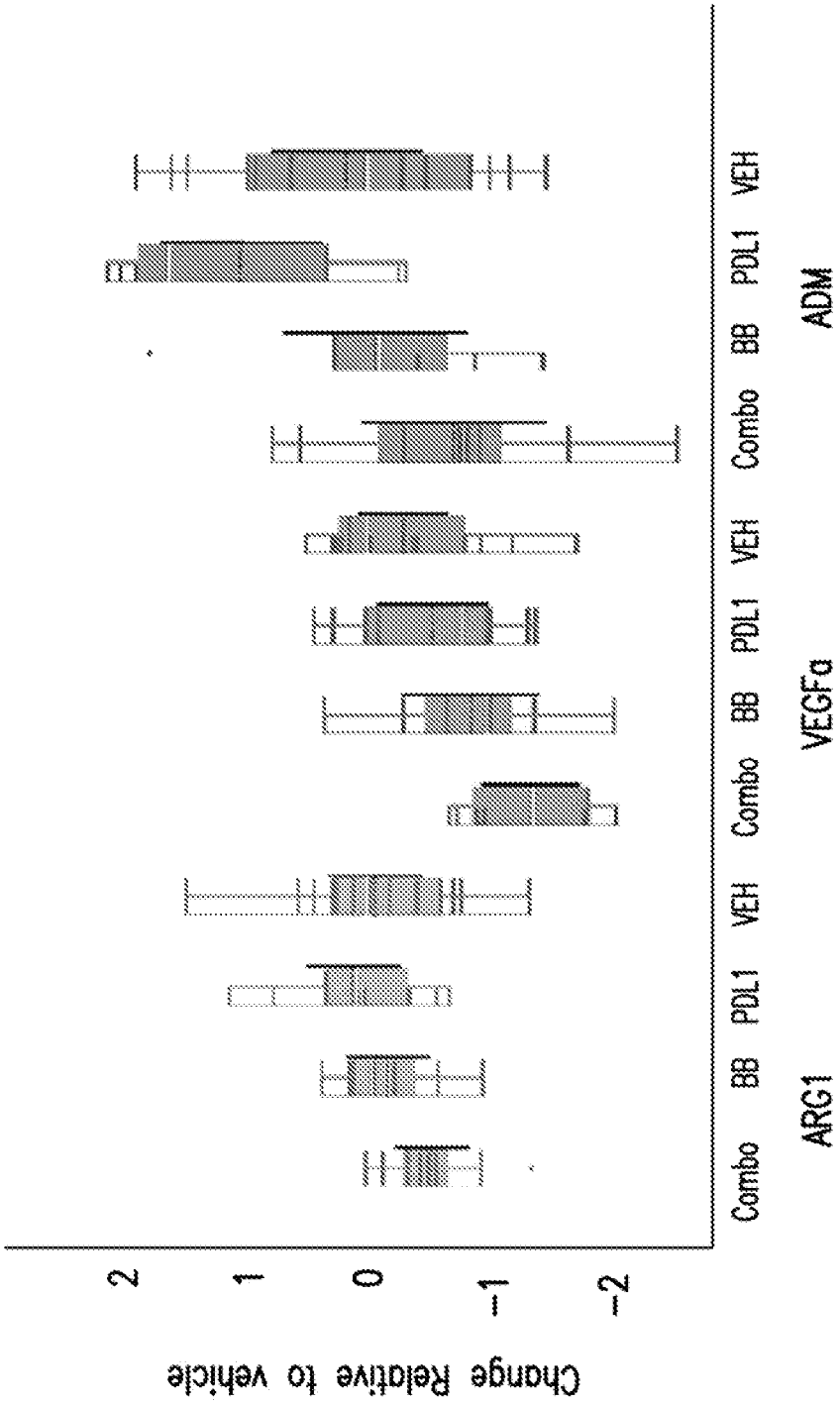

Change Relative to vehicle
2
1
0
-1
-2
Combo
BB
PDL1
VEH
ARG1
Combo
BB
PDL1
VEH
VEGFa
Combo
BB
PDL1
VEH
ADM

FIG. 42B

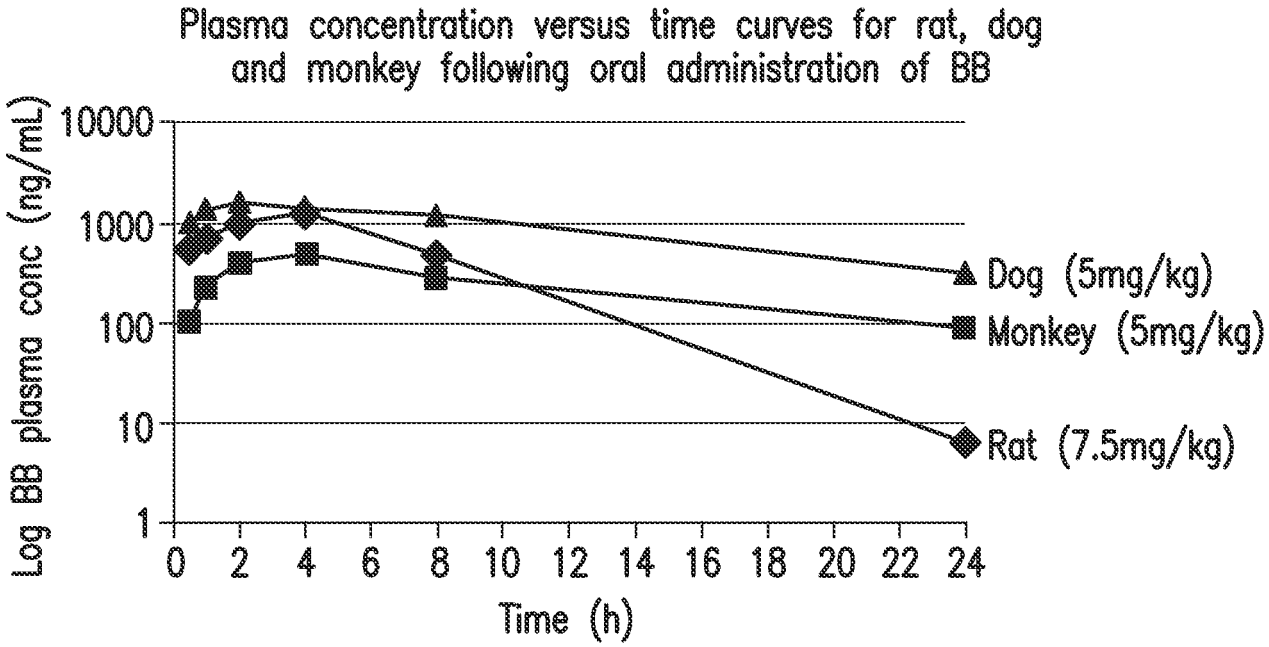

Plasma concentration versus time curves for rat, dog and monkey following oral administration of BB
Log BB plasma conc (ng/mL)
10000
1000
100
10
1
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (h)
Dog (5mg/kg)
Monkey (5mg/kg)
Rat (7.5mg/kg)

FIG. 43

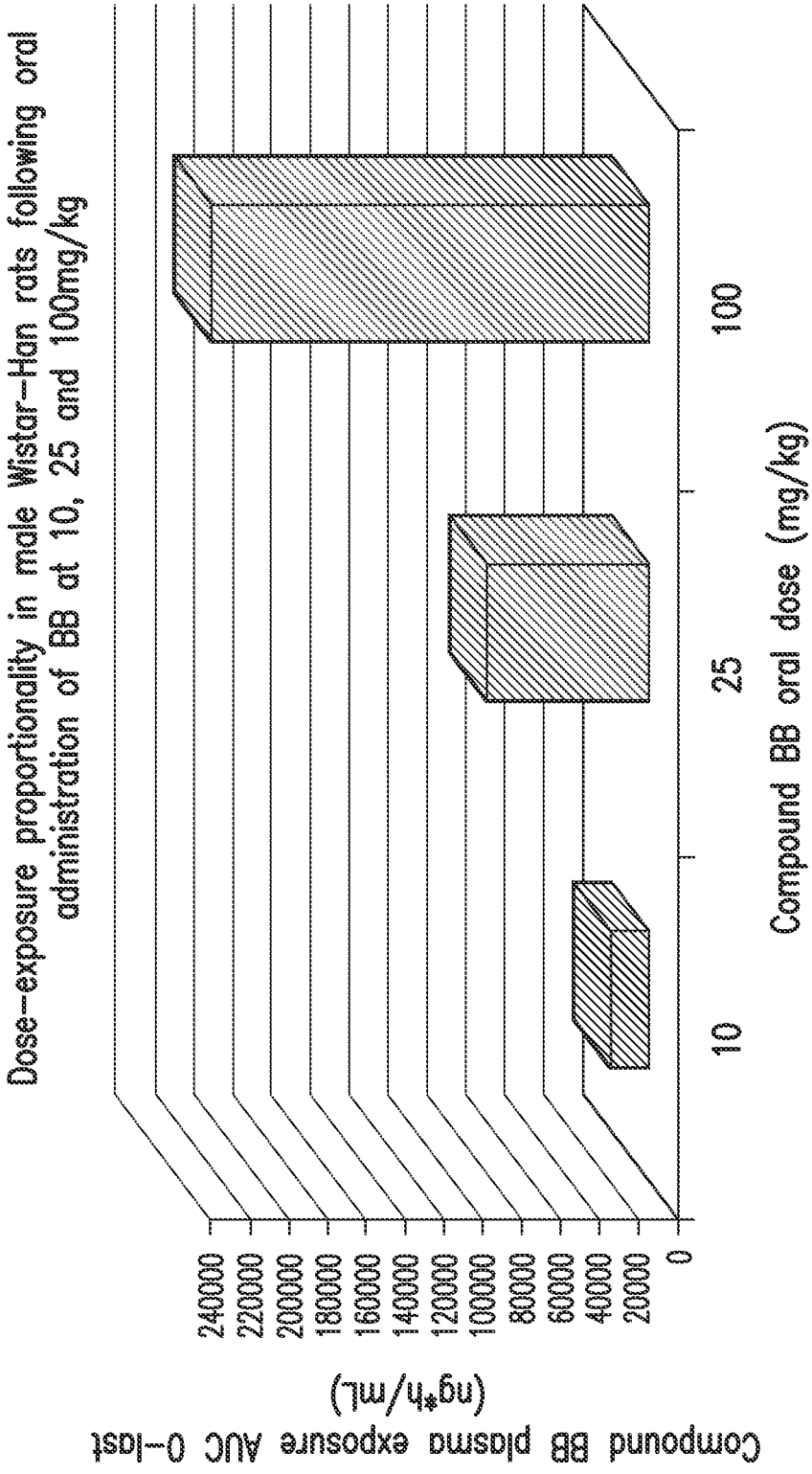

Dose-exposure proportionality in male Wistar-Han rats following oral administration of BB at 10, 25 and 100mg/kg
Compound BB plasma exposure AUC 0-last (ng*h/mL)
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
10
25
100
Compound BB oral dose (mg/kg)

FIG. 44

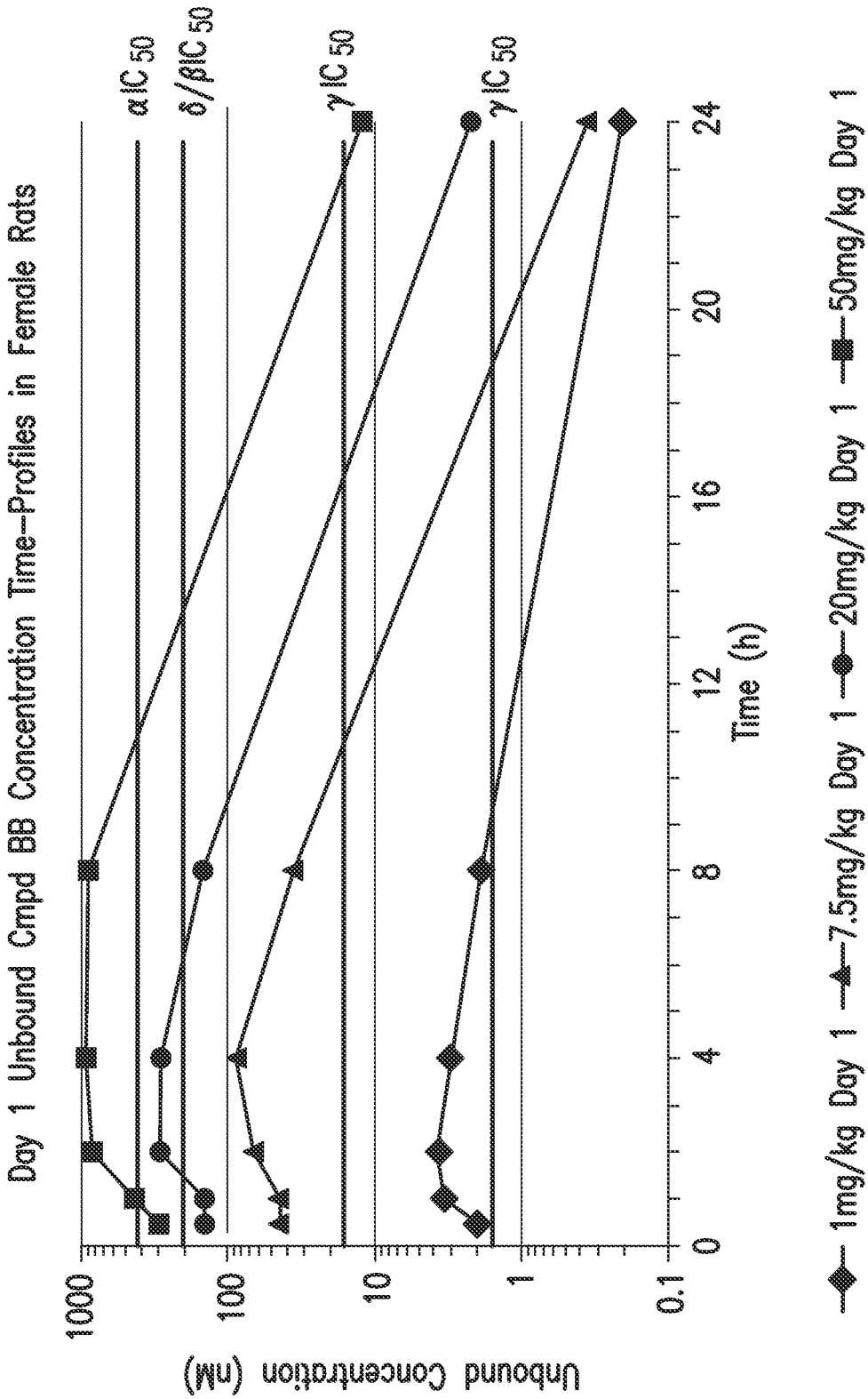

Day 1 Unbound Cmpd BB Concentration Time-Profiles in Female Rats
αIC 50
δ/βIC 50
γIC 50
γIC 50
Unbound Concentration (nM)
1000
100
10
1
0.1
0
4
8
12
16
20
24
Time (h)
1mg/kg Day 1
7.5mg/kg Day 1
20mg/kg Day 1
50mg/kg Day 1

FIG. 45

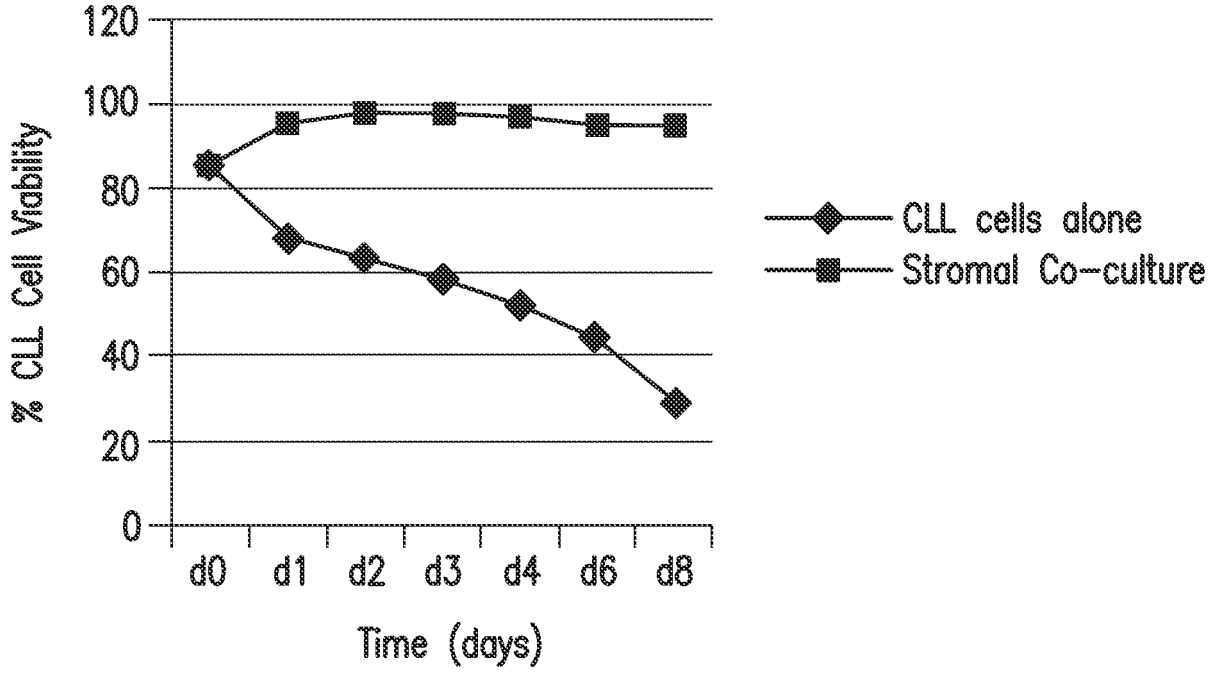

120
100
80
60
40
20
0
% CLL Cell Viability
d0
d1
d2
d3
d4
d6
d8
Time (days)
CLL cells alone
Stromal Co-culture

FIG. 46

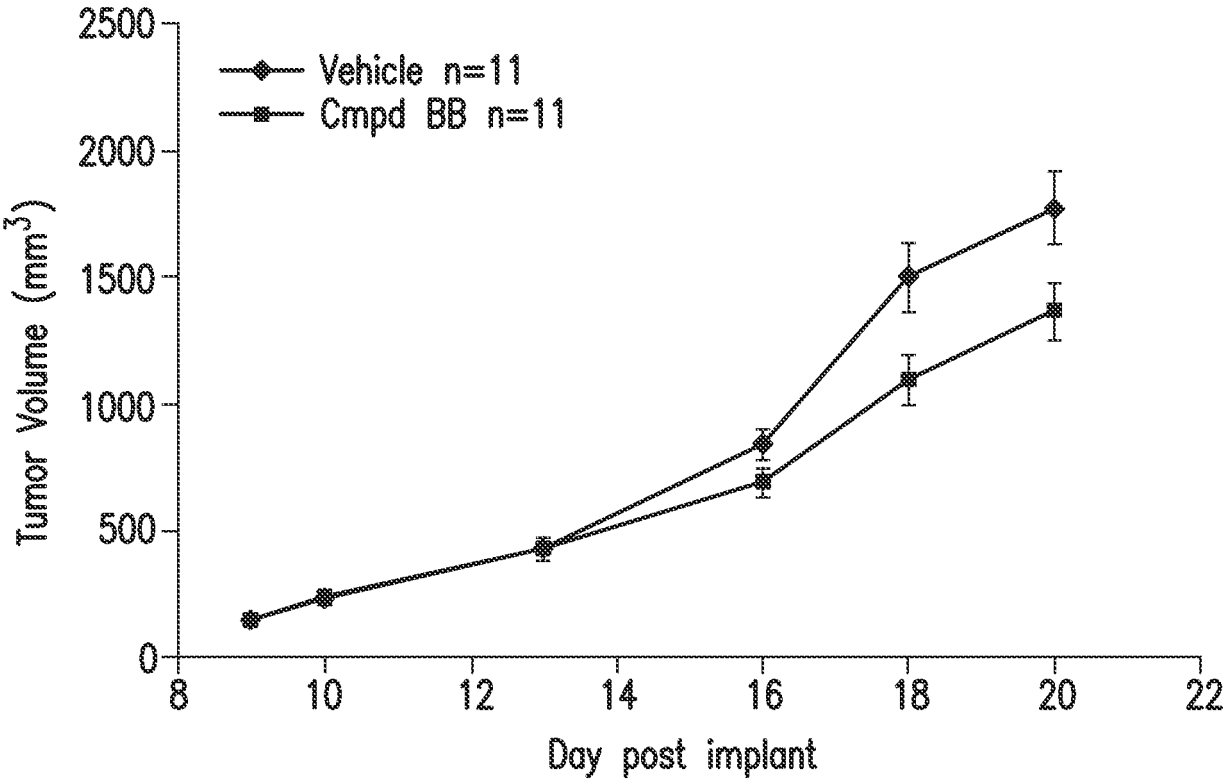


FIG. 47A

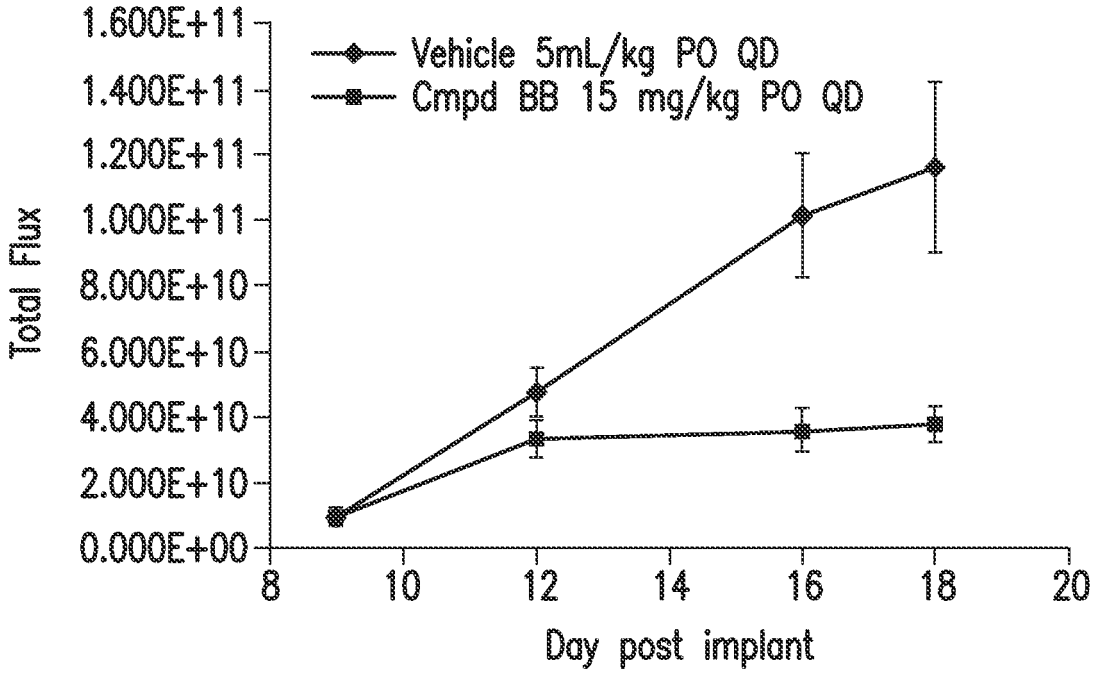


FIG. 47B

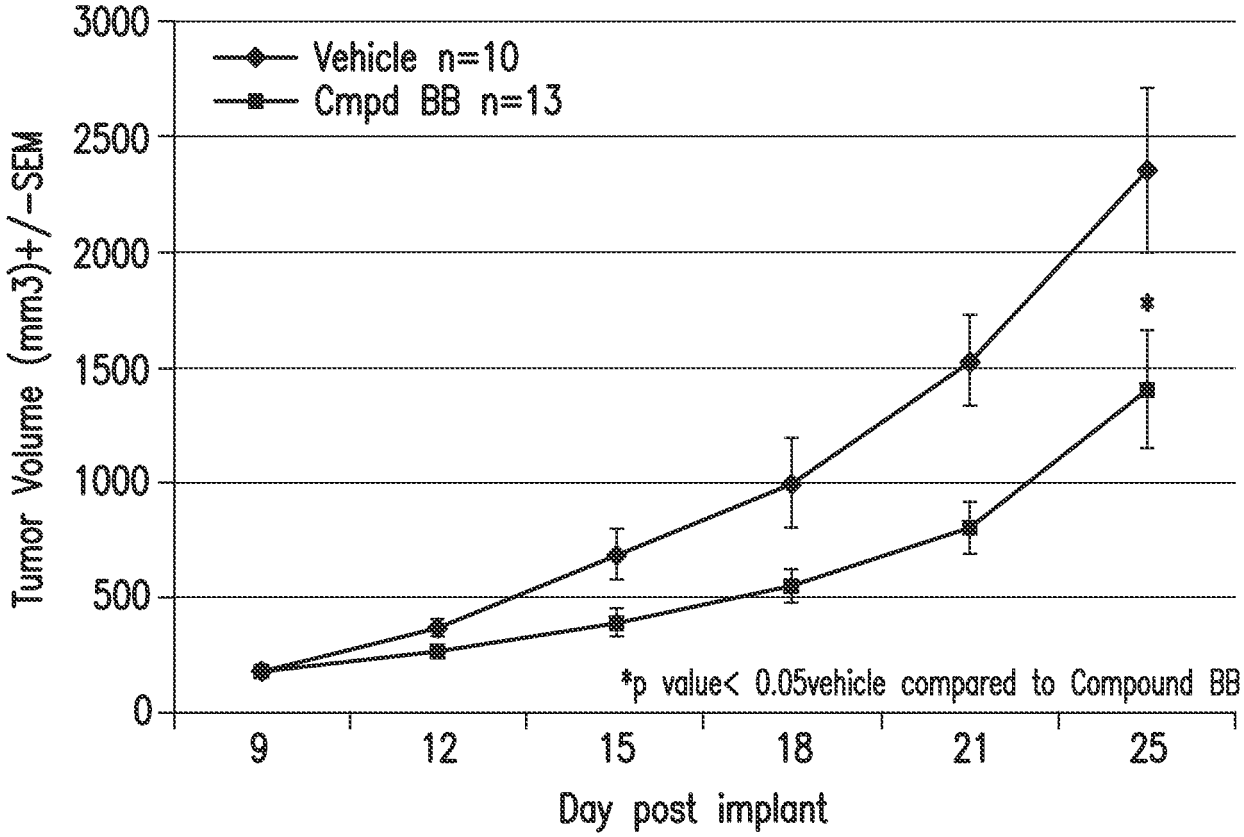

3000
2500
2000
1500
1000
500
0
Tumor Volume (mm3)+/-SEM
Vehicle n=10
Cmpd BB n=13
*
*p value< 0.05vehicle compared to Compound BB
9
12
15
18
21
25
Day post implant

FIG. 47C

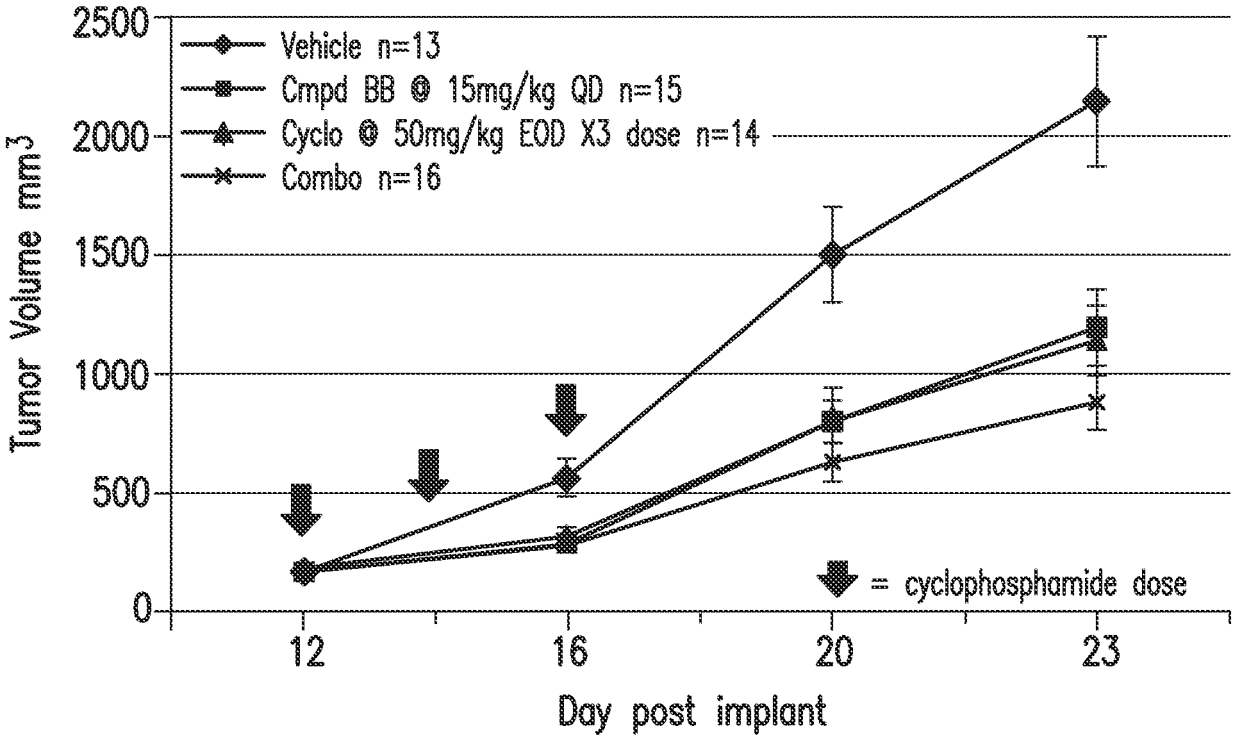

2500
2000
1500
1000
500
0
Tumor Volume mm3
Vehicle n=13
Cmpd BB @ 15mg/kg QD n=15
Cyclo @ 50mg/kg EOD X3 dose n=14
Combo n=16
= cyclophosphamide dose
12
16
20
23
Day post implant

FIG. 48

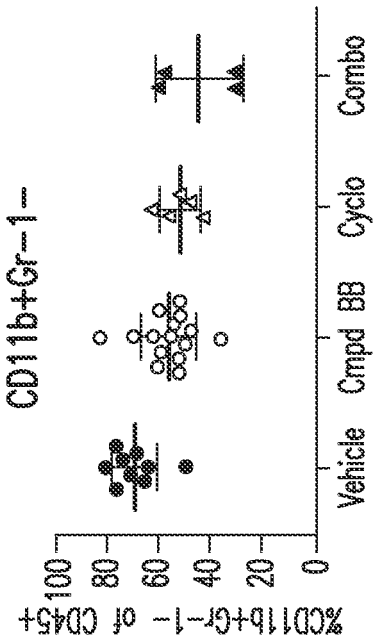


FIG. 49B

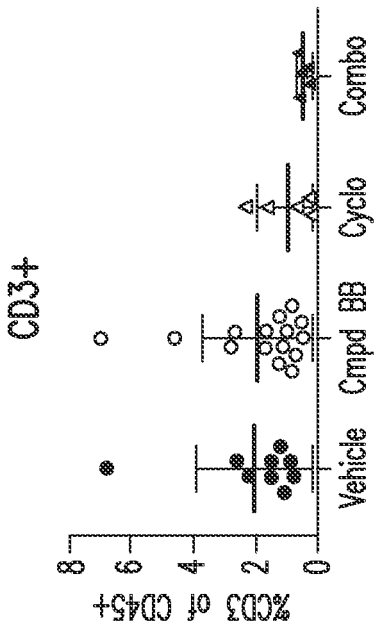


FIG. 49A

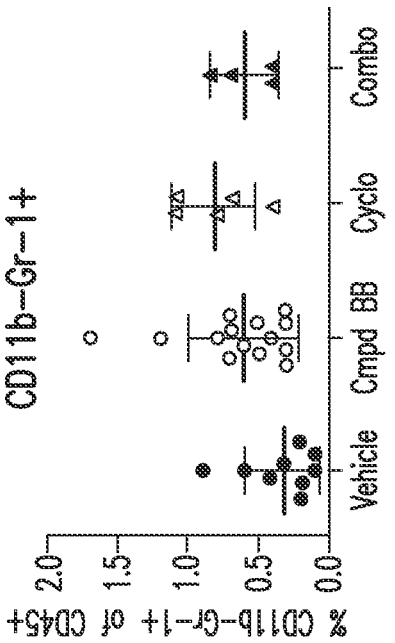


FIG. 49E

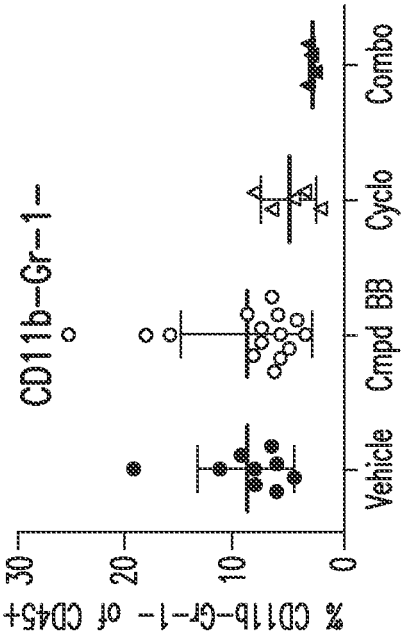


FIG. 49D

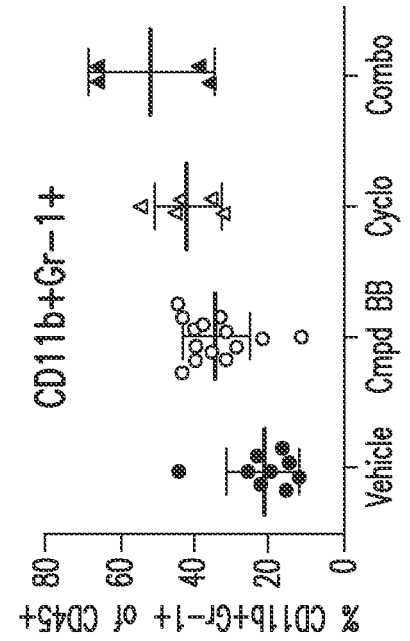


FIG. 49C

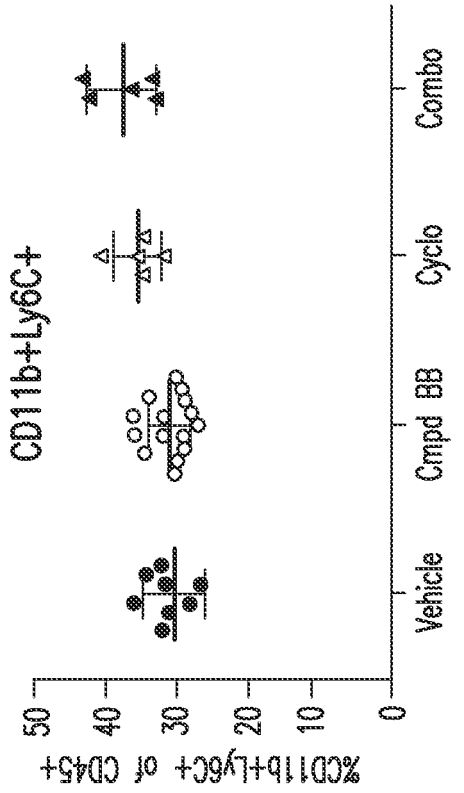


FIG. 50B

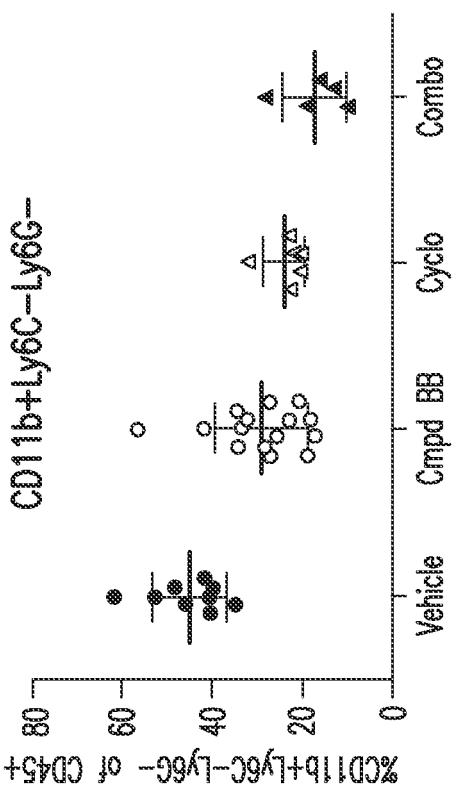


FIG. 50D

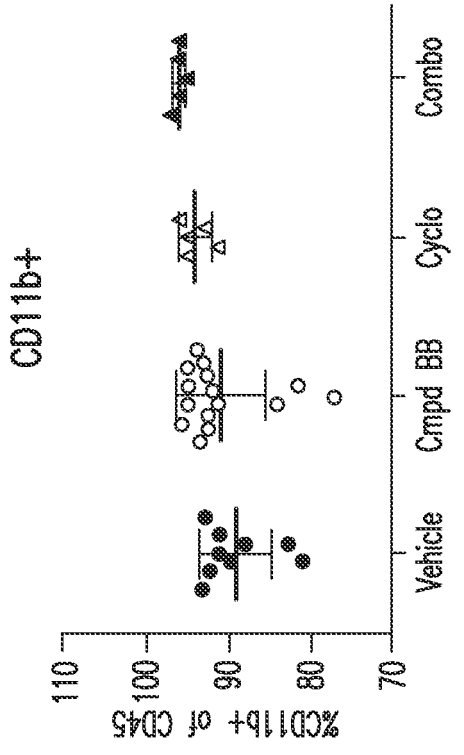


FIG. 50A

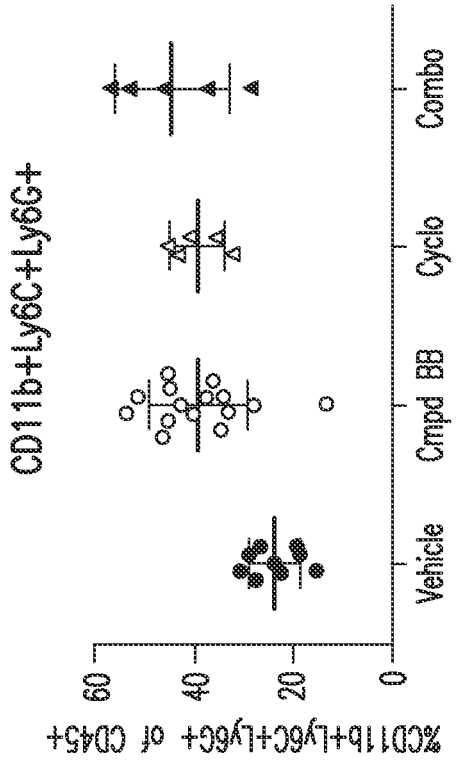


FIG. 50C

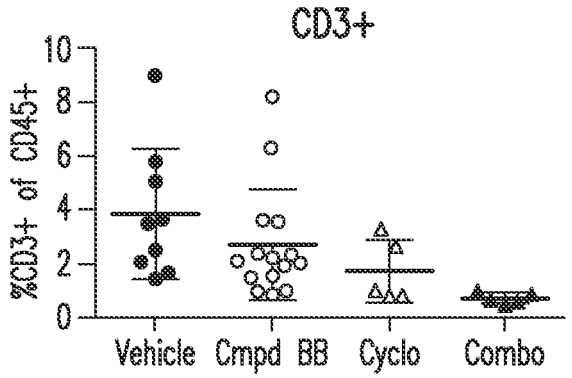


FIG. 51A

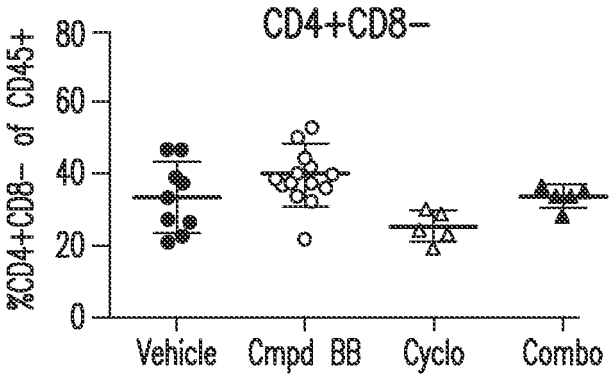


FIG. 51B

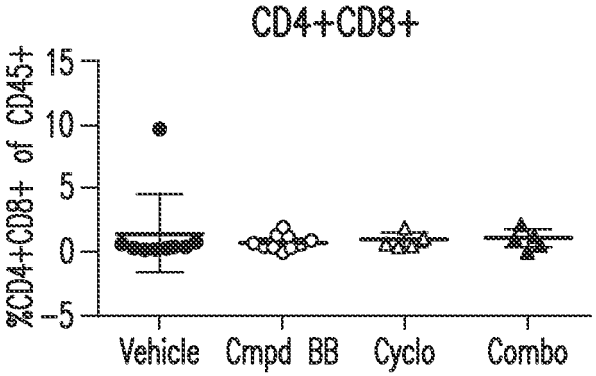


FIG. 51C

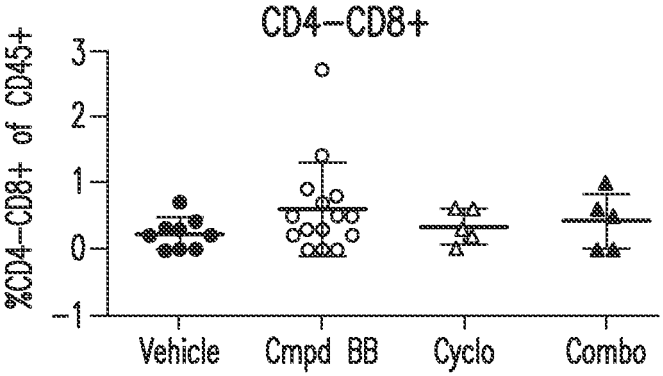


FIG. 51D

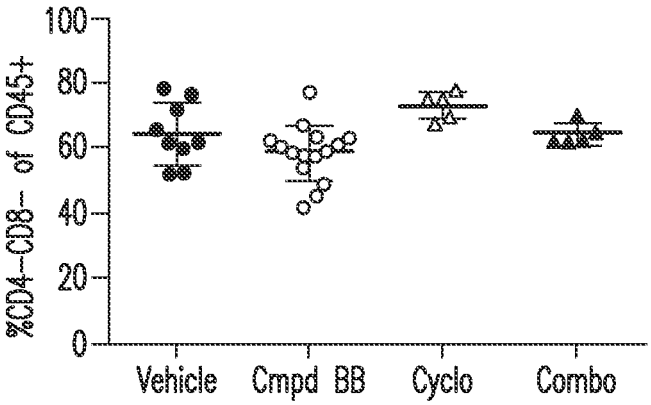


FIG. 51E

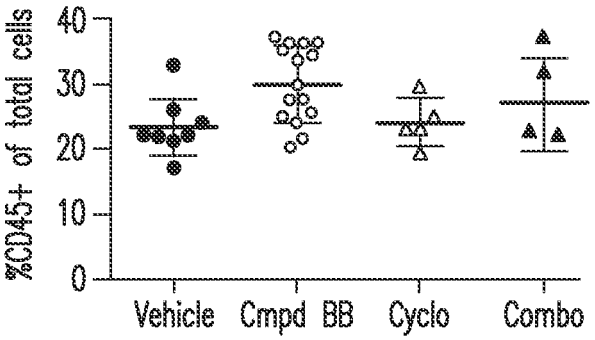


FIG. 52A

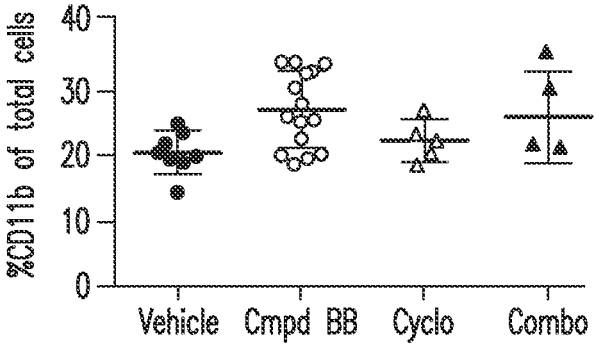


FIG. 52B

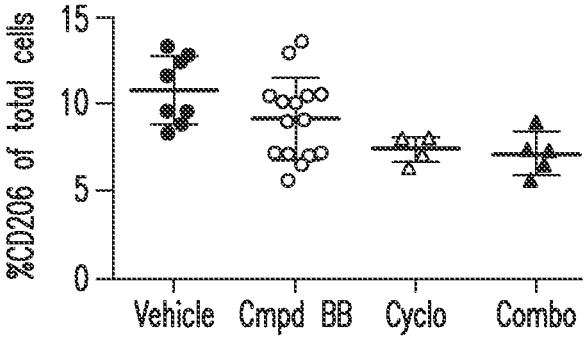


FIG. 52C

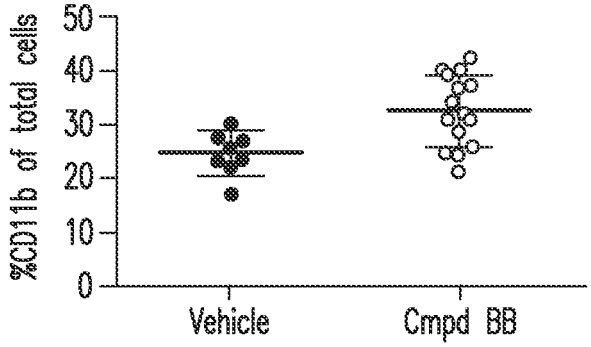


FIG. 52D

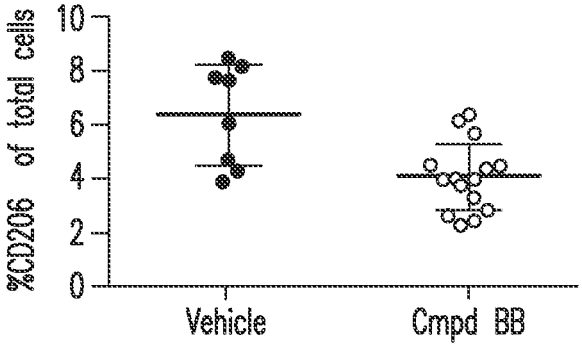


FIG. 52E

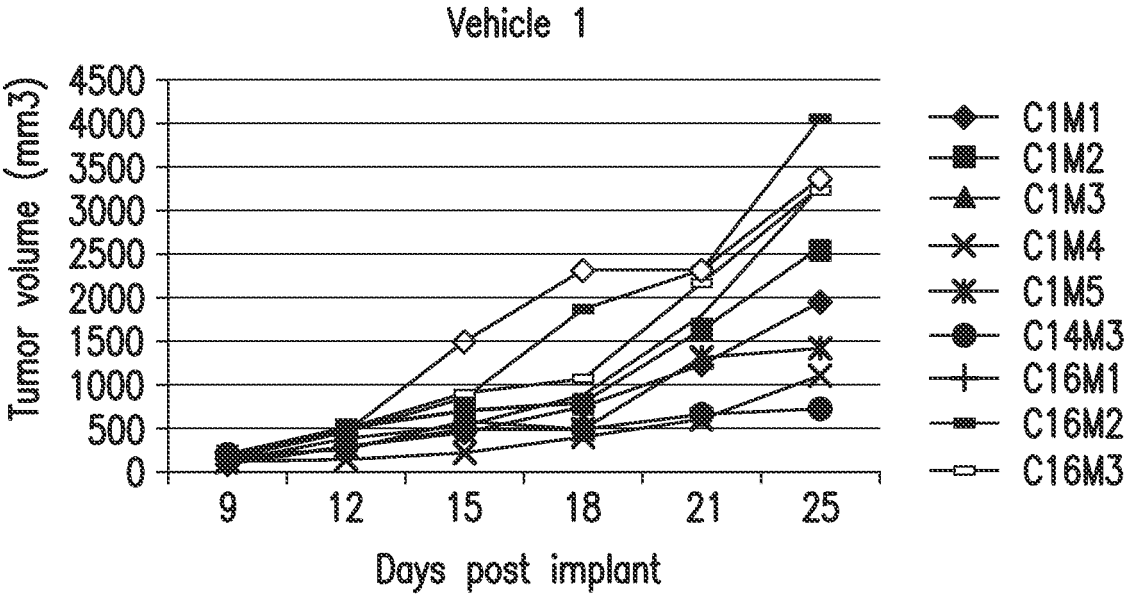


FIG. 53A

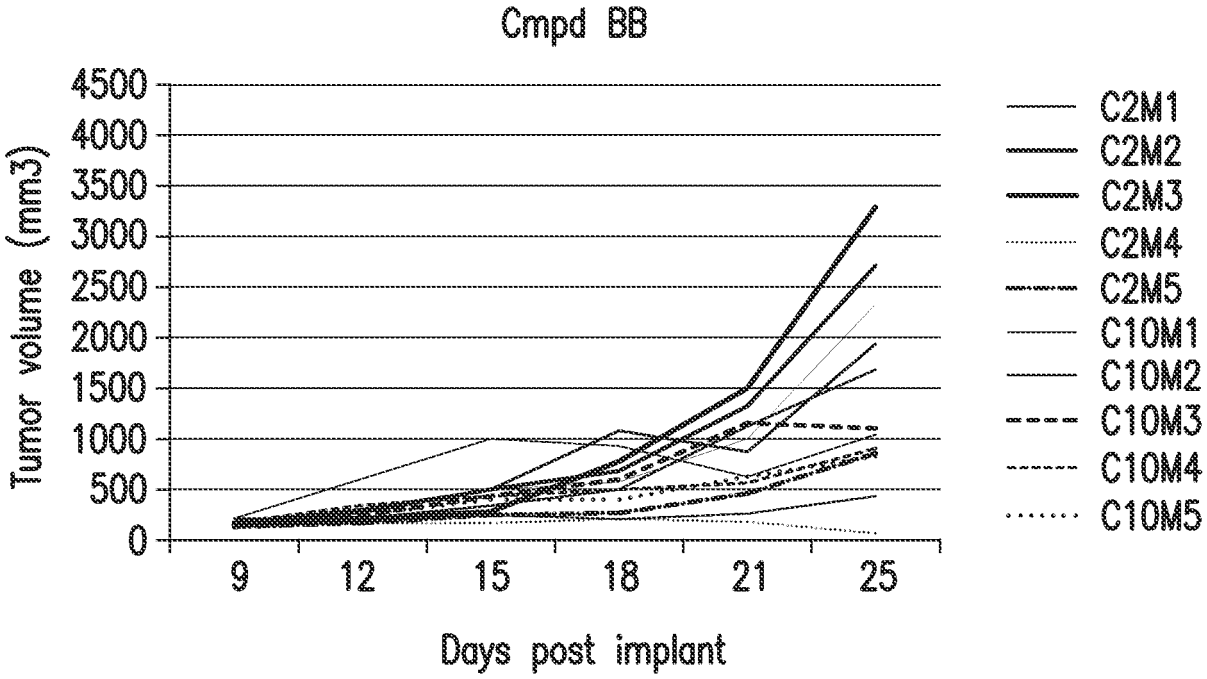


FIG. 53B

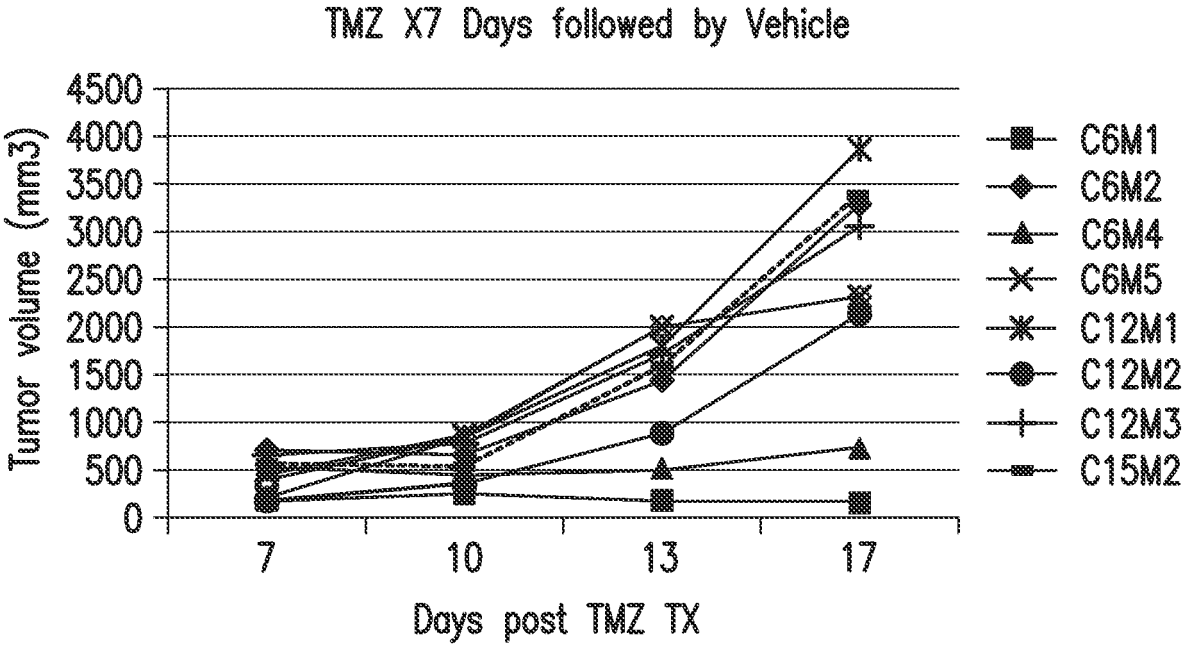


FIG. 53C

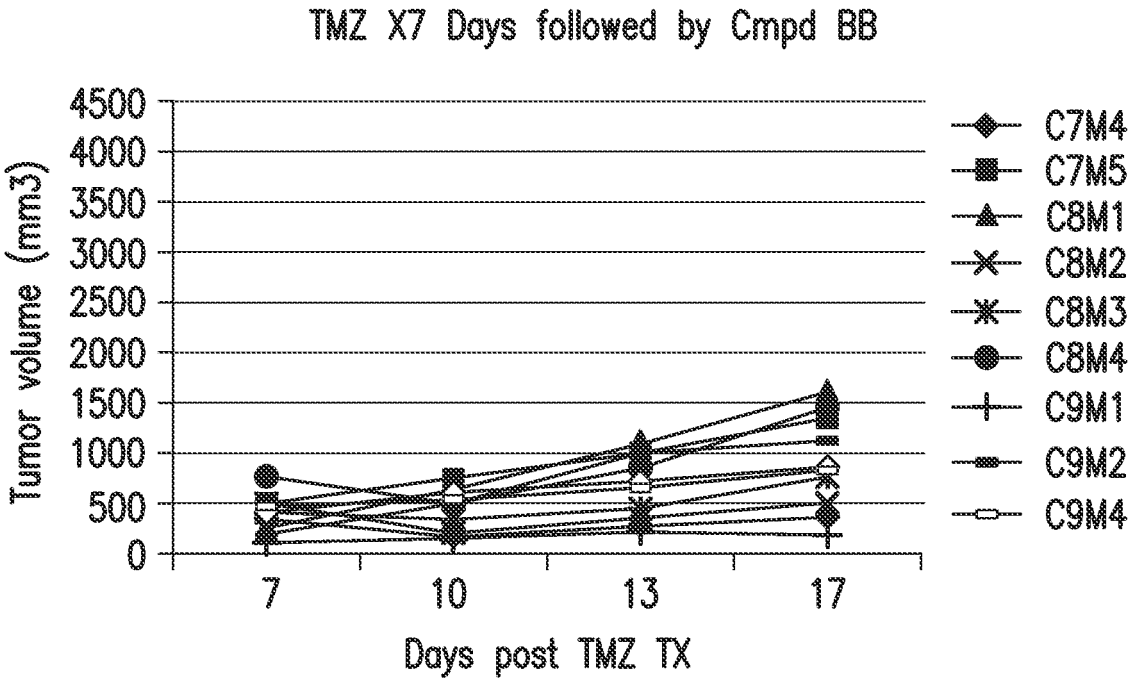


FIG. 53D

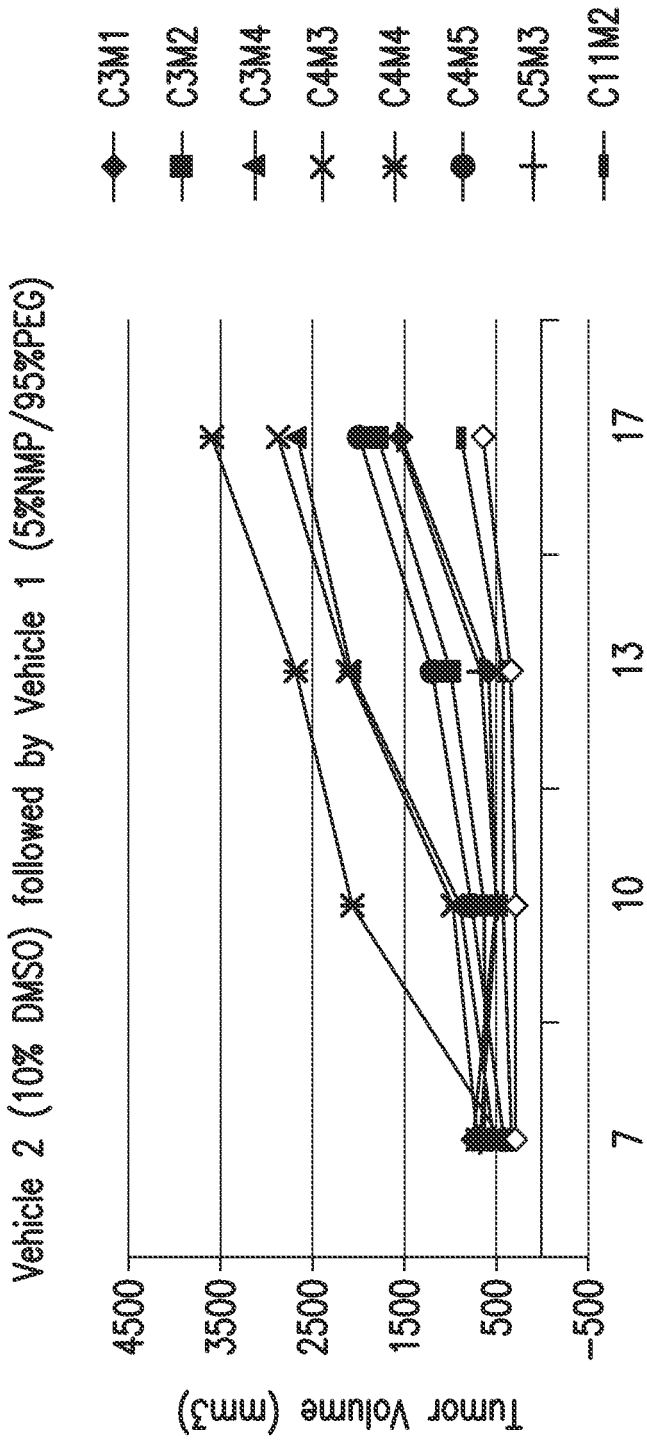

C3M1
C3M2
C3M4
C4M3
C4M4
C4M5
C5M3
C11M2
Vehicle 2 (10% DMSO) followed by Vehicle 1 (5%NMP/95%PEG)
Tumor Volume (mm3)
4500
3500
2500
1500
500
-500
7
10
13
17
Days on Veh 1

FIG. 53E

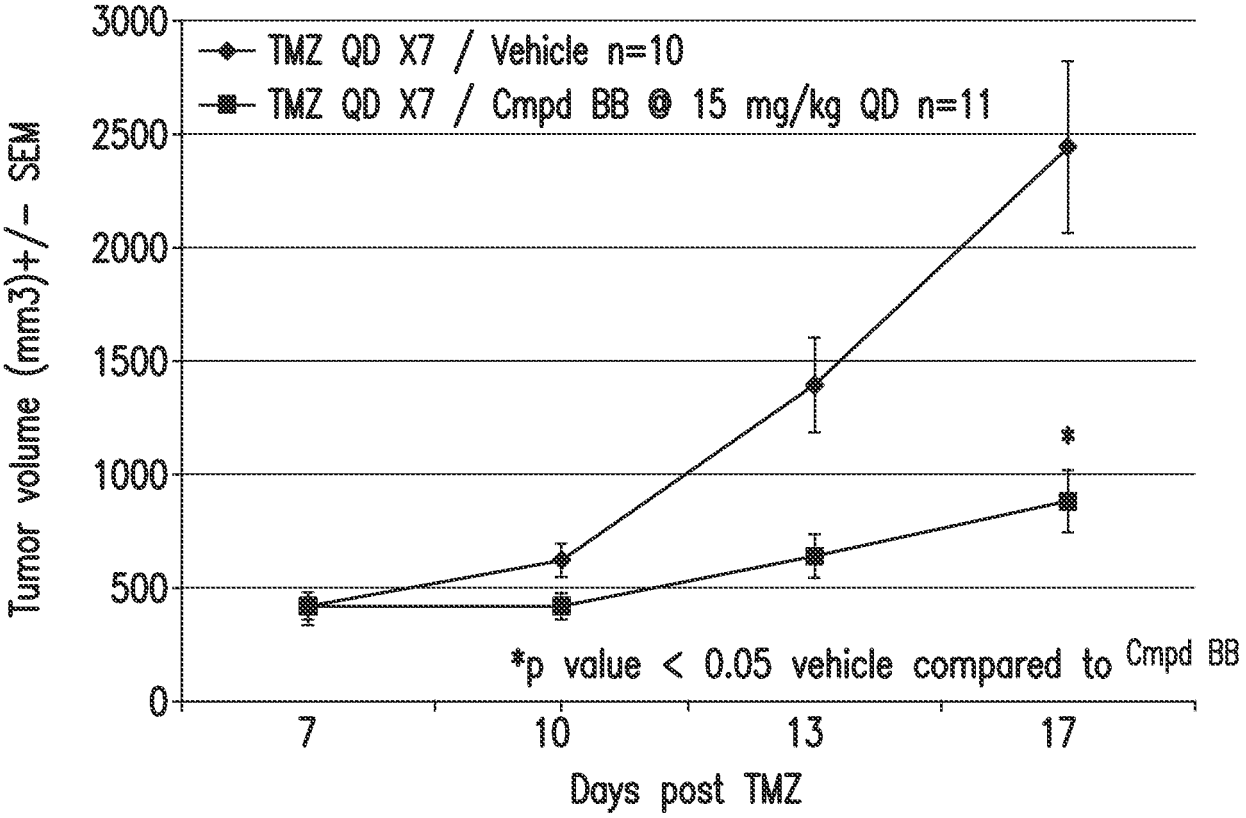


FIG. 54A

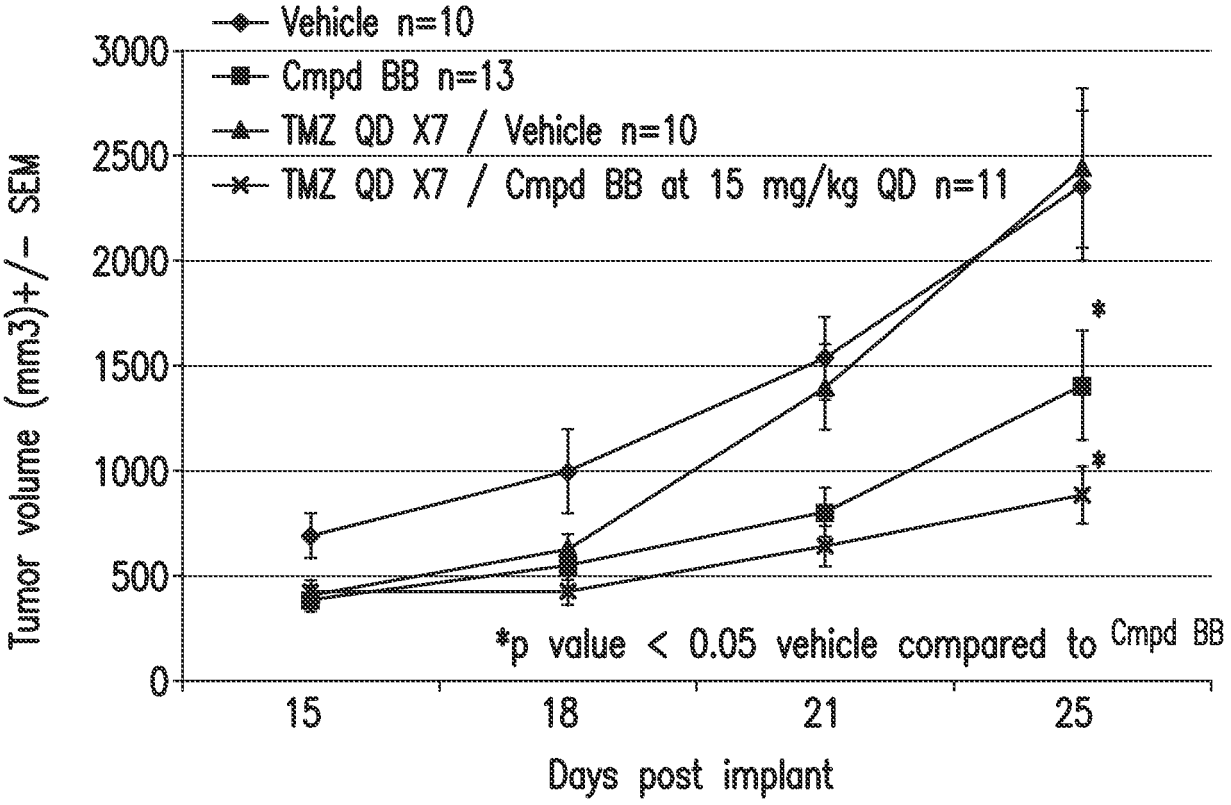


FIG. 54B

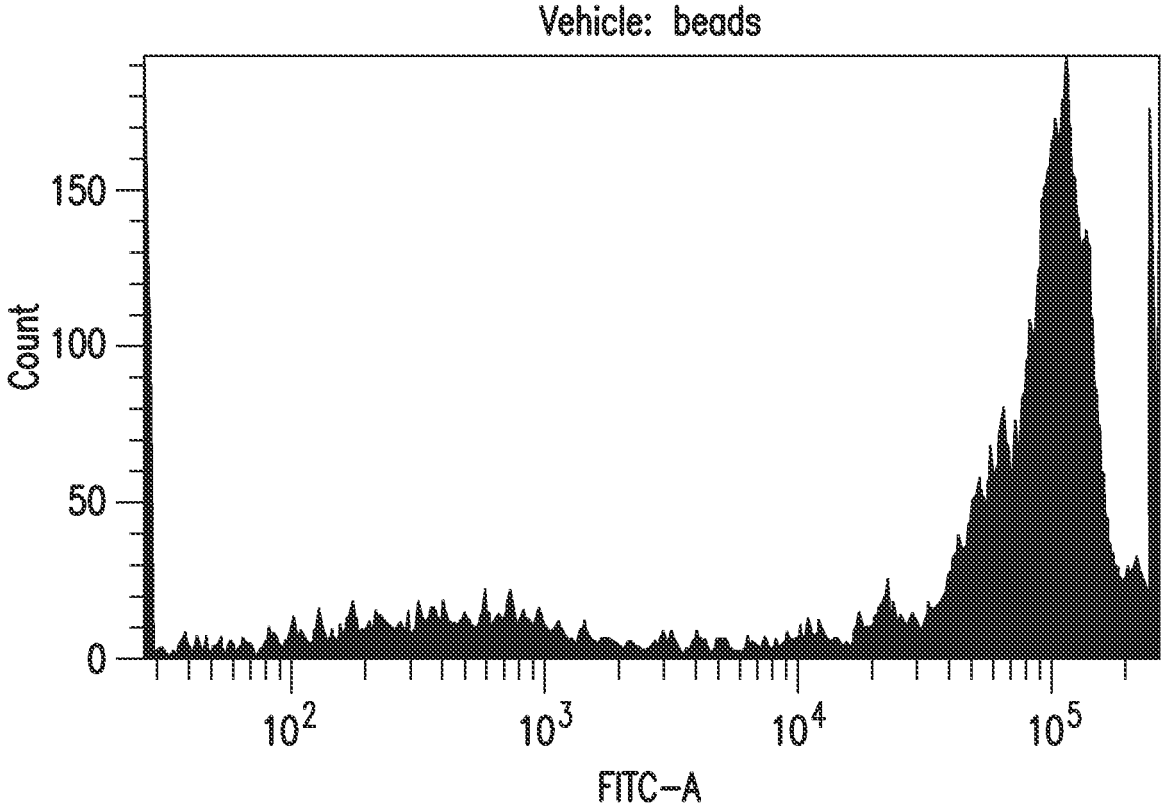


FIG. 55A

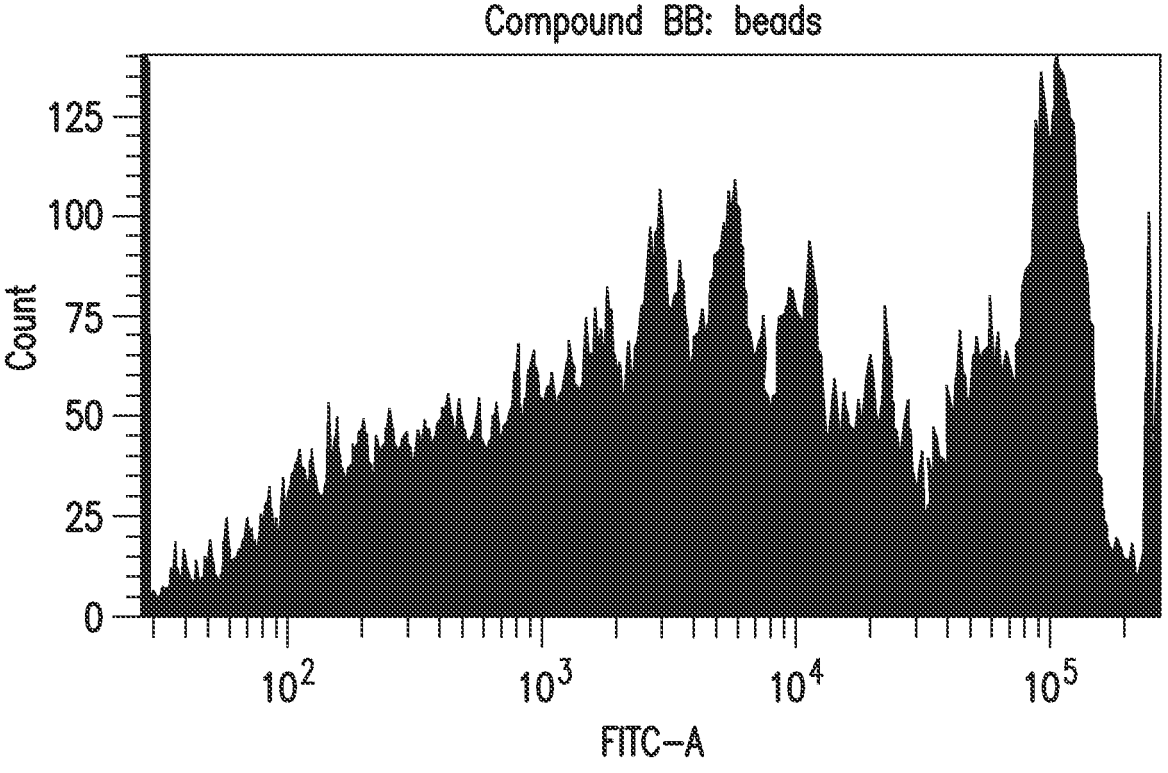


FIG. 55B

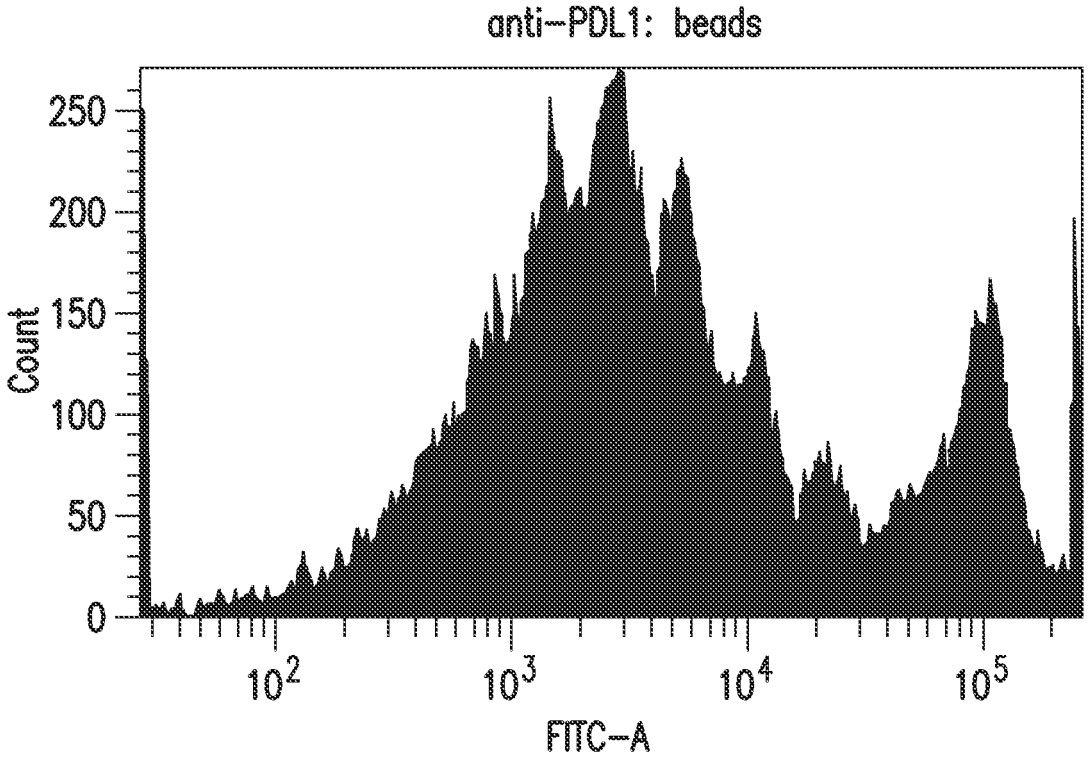
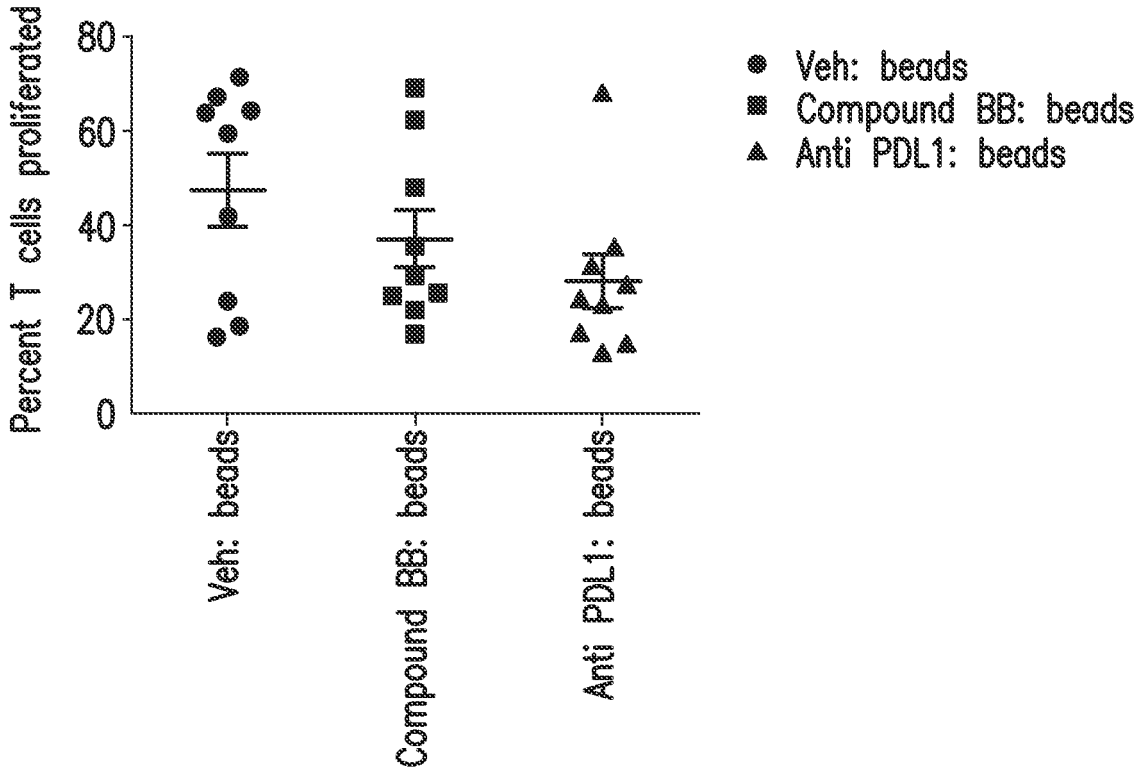

anti-PDL1: beads
250
200
150
100
50
0
Count
10^2
10^3
10^4
10^5
FITC-A

FIG. 55C



* Denotes significance vs vehicle by T test, Compound BB p=0.08

FIG. 56A

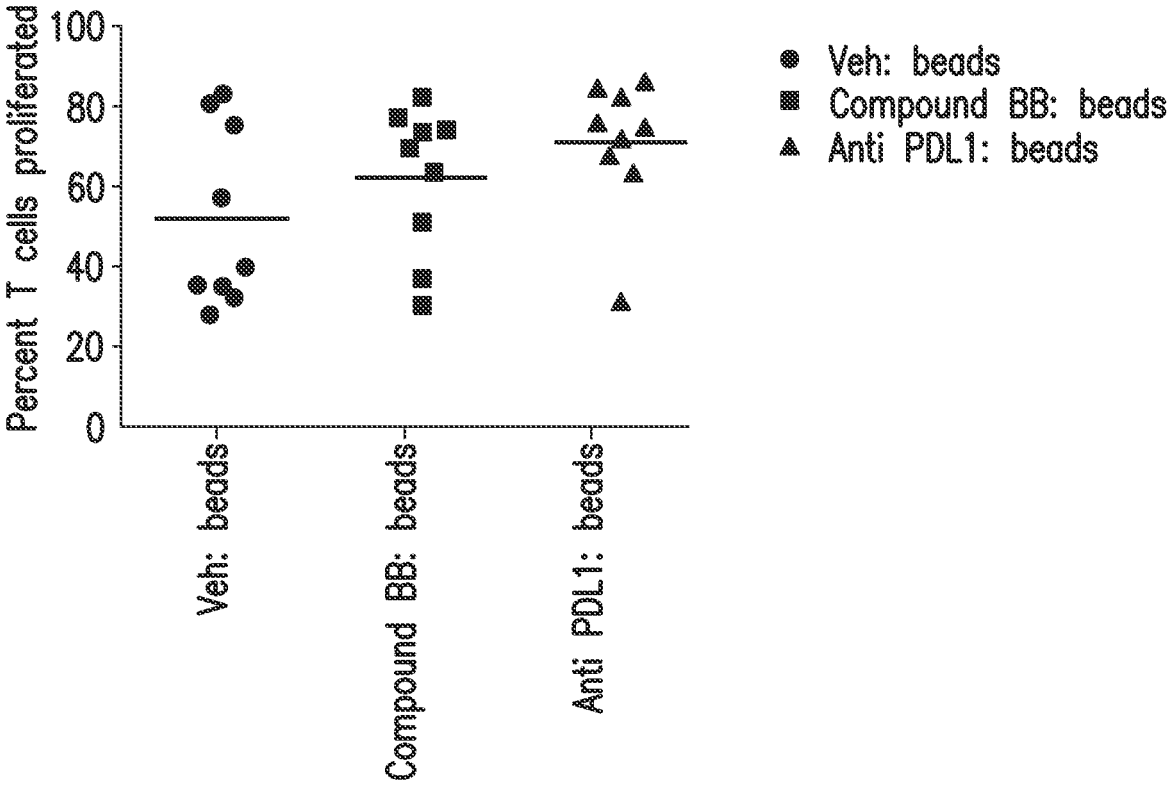


FIG. 56B

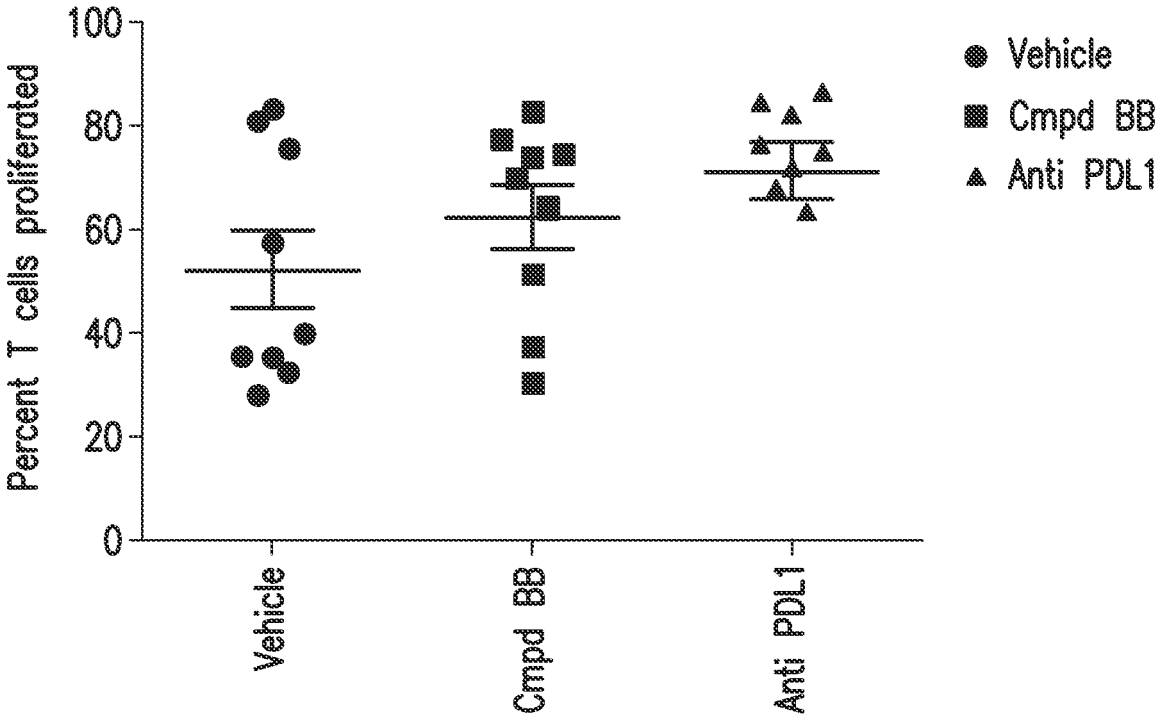

Percent T cells proliferated
100
80
60
40
20
0
Vehicle
Cmpd BB
Anti PDL1
Vehicle
Cmpd BB
Anti PDL1
* P value <0.05 vs Vehicle. Compound BB is 0.08

FIG. 57

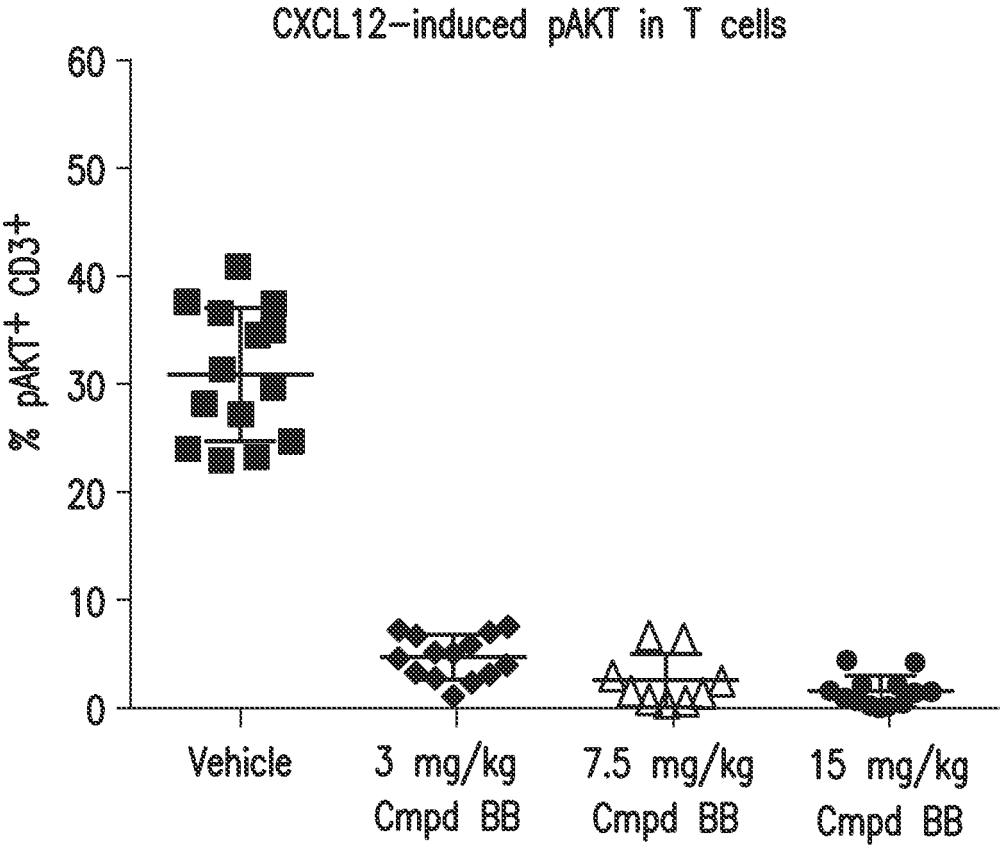

CXCL12-induced pAKT in T cells
% pAKT+ CD3+
60
50
40
30
20
10
0
Vehicle
3 mg/kg Cmpd BB
7.5 mg/kg Cmpd BB
15 mg/kg Cmpd BB

FIG. 58

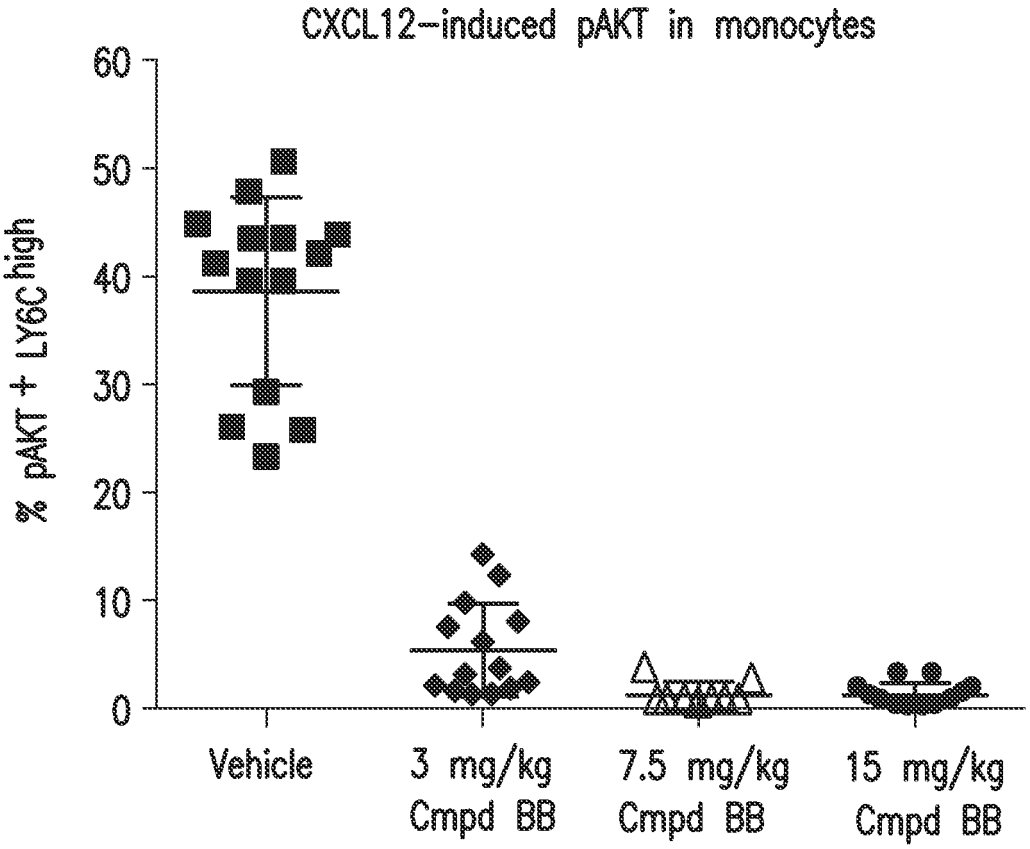

CXCL12-induced pAKT in monocytes
% pAKT + LY6C high
60
50
40
30
20
10
0
Vehicle
3 mg/kg Cmpd BB
7.5 mg/kg Cmpd BB
15 mg/kg Cmpd BB

FIG. 59

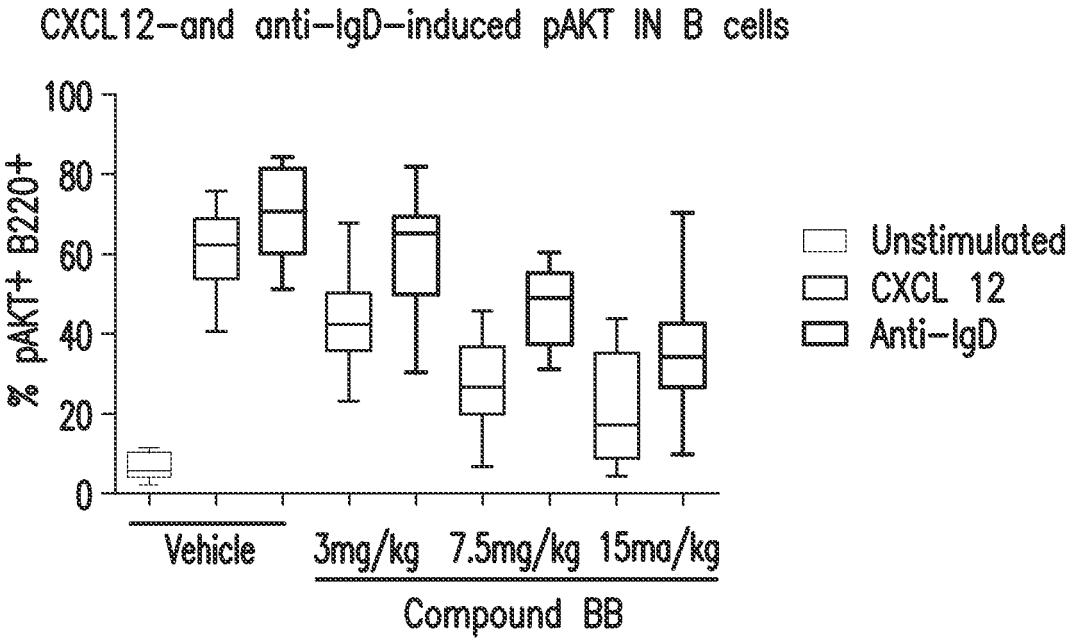

CXCL12-and anti-IgD-induced pAKT IN B cells
% pAKT+ B220+
100
80
60
40
20
0
Vehicle
3mg/kg
7.5mg/kg
15mg/kg
Compound BB
Unstimulated
CXCL 12
Anti-IgD

FIG. 60

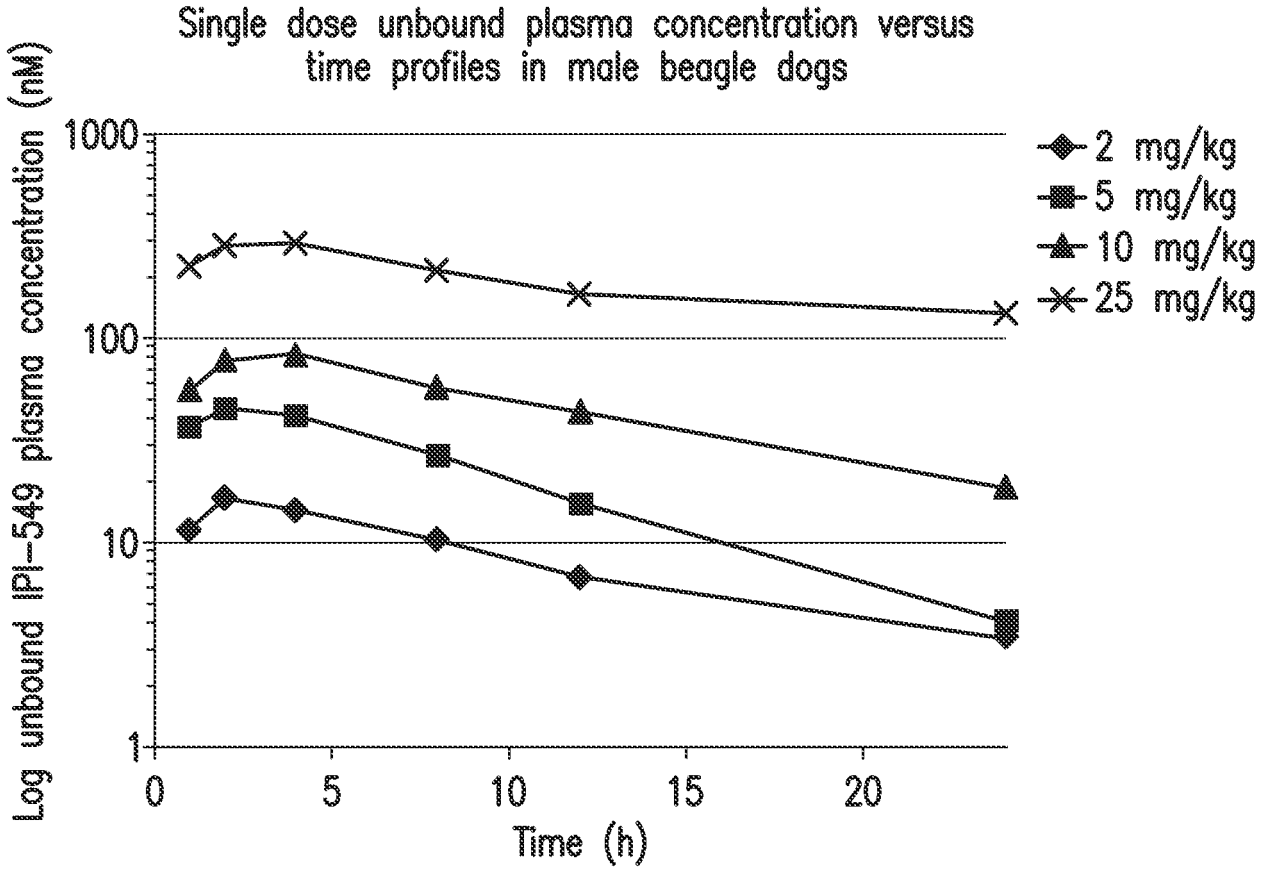

Single dose unbound plasma concentration versus time profiles in male beagle dogs
Log unbound IPI-549 plasma concentration (nM)
1000
100
10
1
0
5
10
15
20
Time (h)
2 mg/kg
5 mg/kg
10 mg/kg
25 mg/kg

FIG. 61