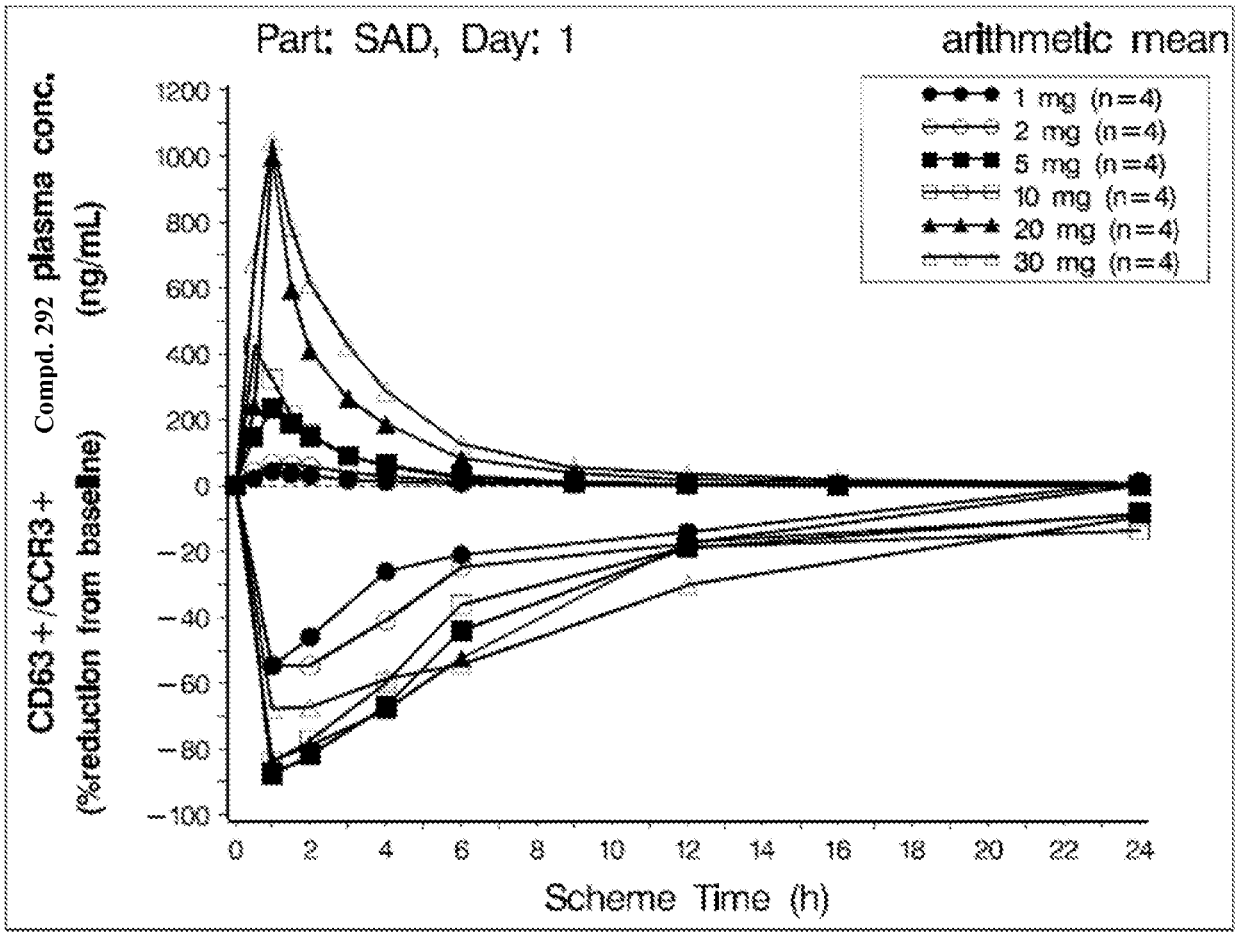
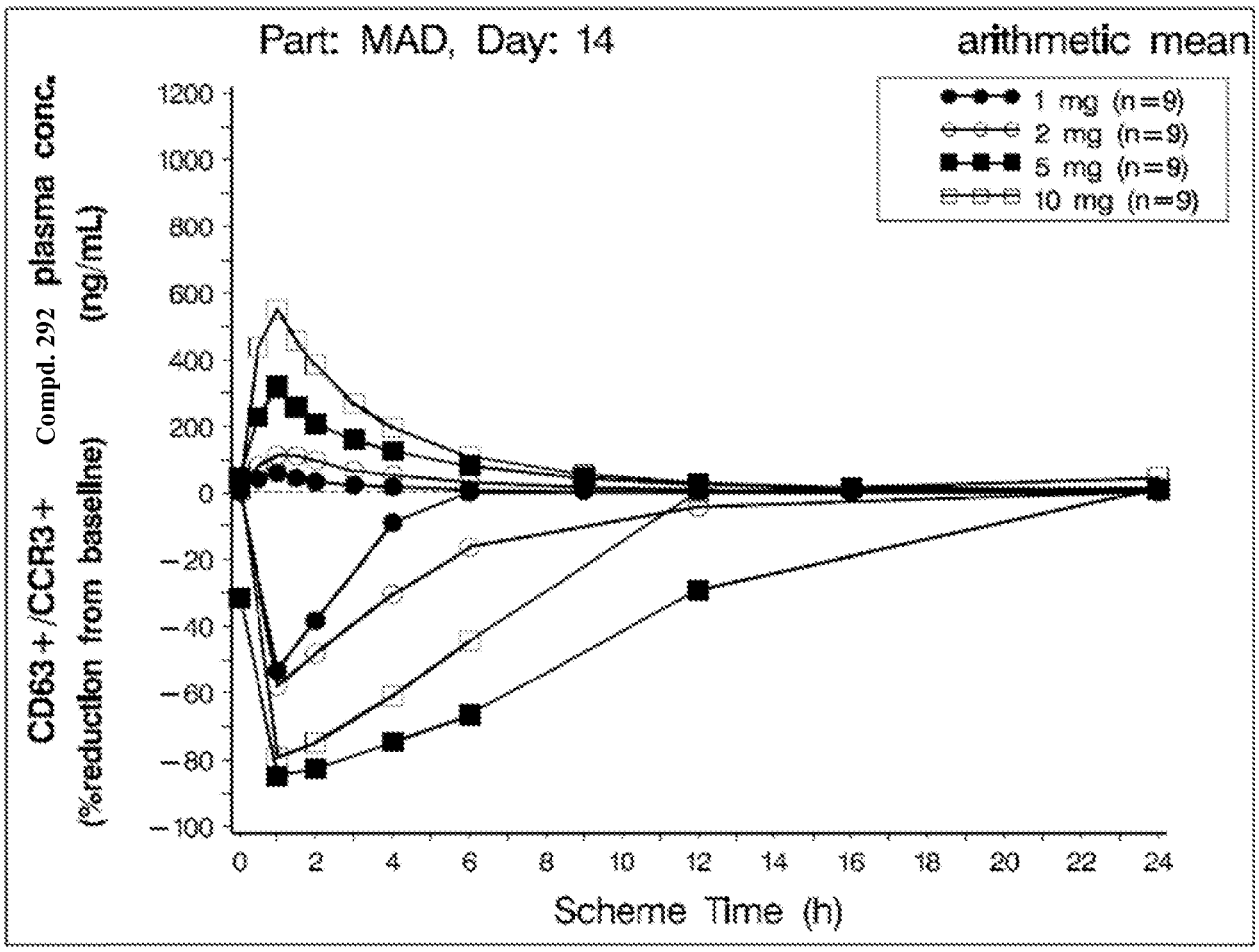
FIG. 1



SAD part, single dose QD

FIG. 2



MAD part, multiple dose, BID (1, 2, 5 mg) or QD (10 mg)

FIG. 3

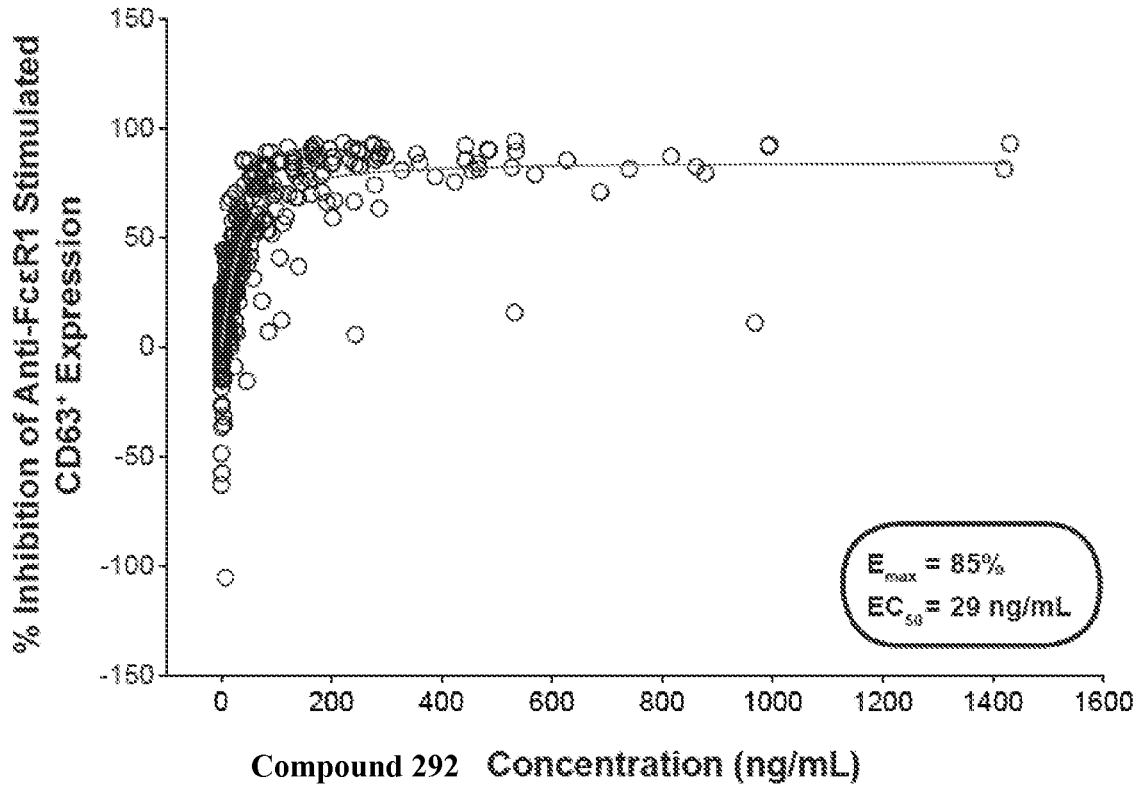

% Inhibition of Anti-FcεR1 Stimulated CD63+ Expression
150
100
50
0
-50
-100
-150
0
200
400
600
800
1000
1200
1400
1600
Emax = 85%
EC50 = 29 ng/mL
Compound 292 Concentration (ng/mL)

FIG. 4

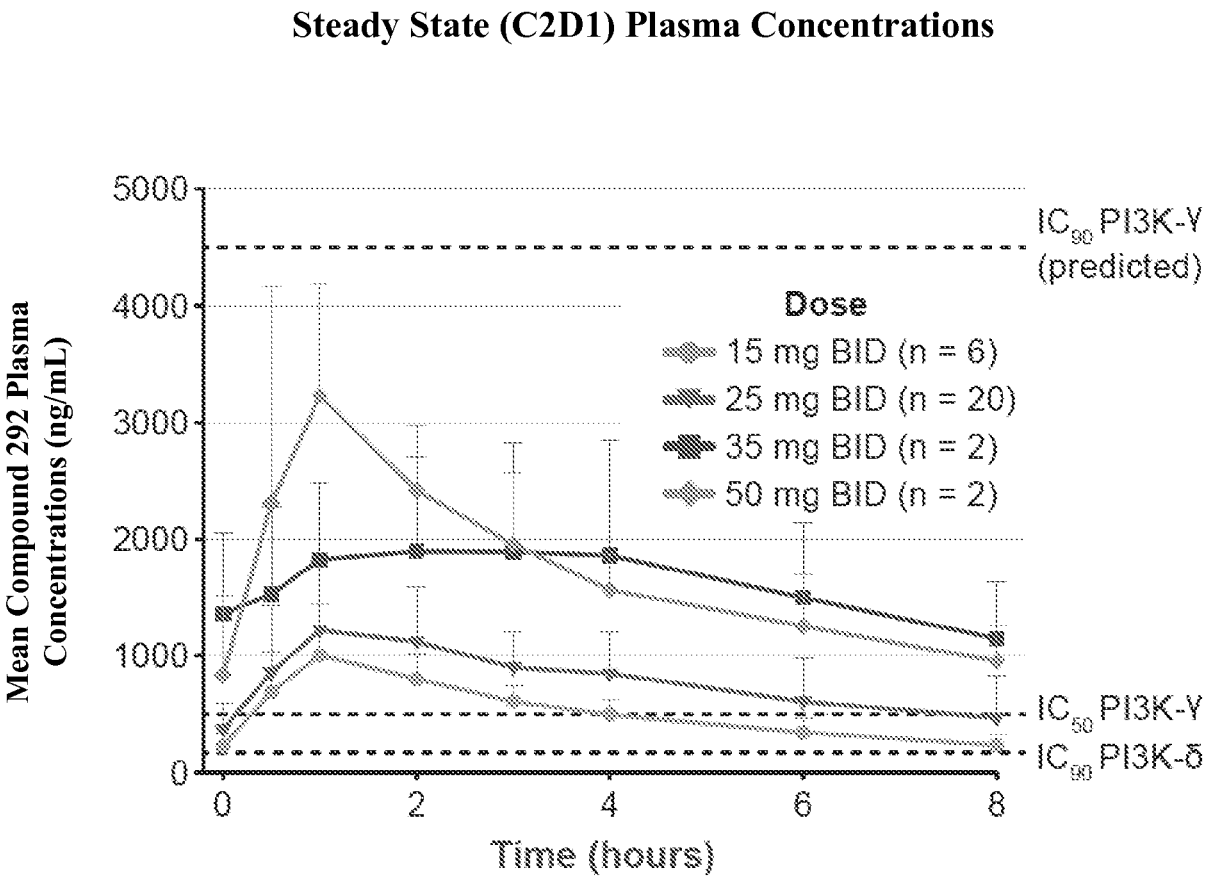
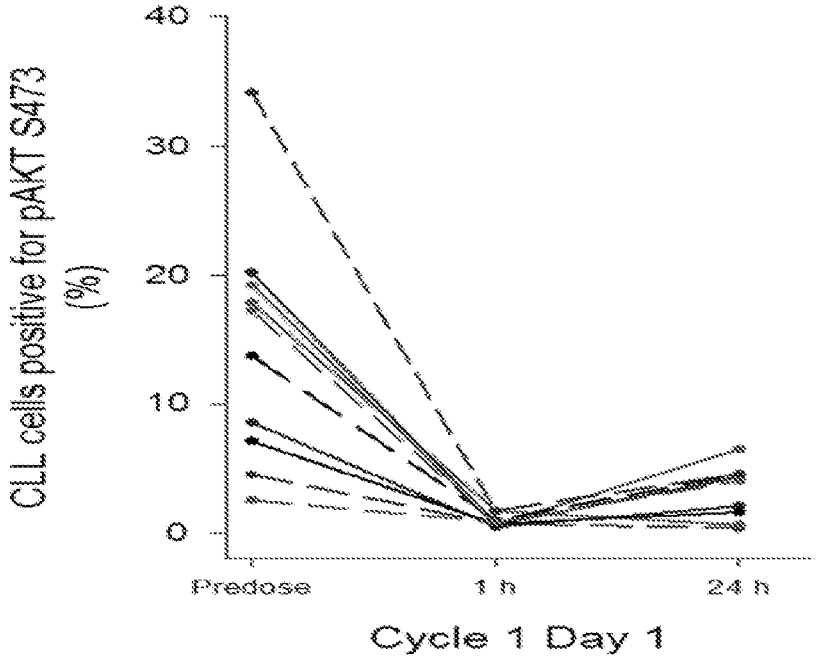

Steady State (C2D1) Plasma Concentrations
Mean Compound 292 Plasma Concentrations (ng/mL)
5000
4000
3000
2000
1000
0
0
2
4
6
8
Time (hours)
Dose
15 mg BID (n = 6)
25 mg BID (n = 20)
35 mg BID (n = 2)
50 mg BID (n = 2)
IC90 PI3K-γ (predicted)
IC50 PI3K-γ
IC90 PI3K-δ

FIG. 5

AKT Phosphorylation in CLL Cells
(individual patients at 25 mg BID)



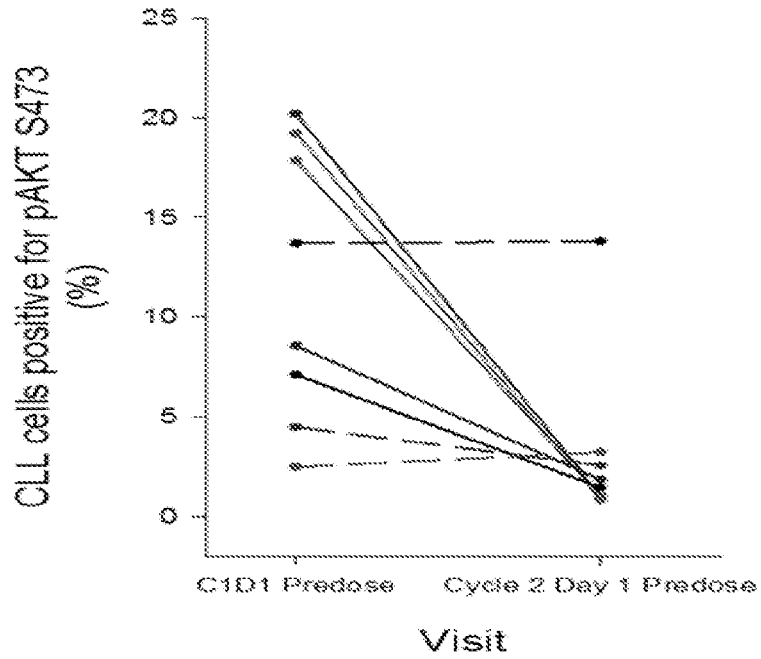


FIG. 6

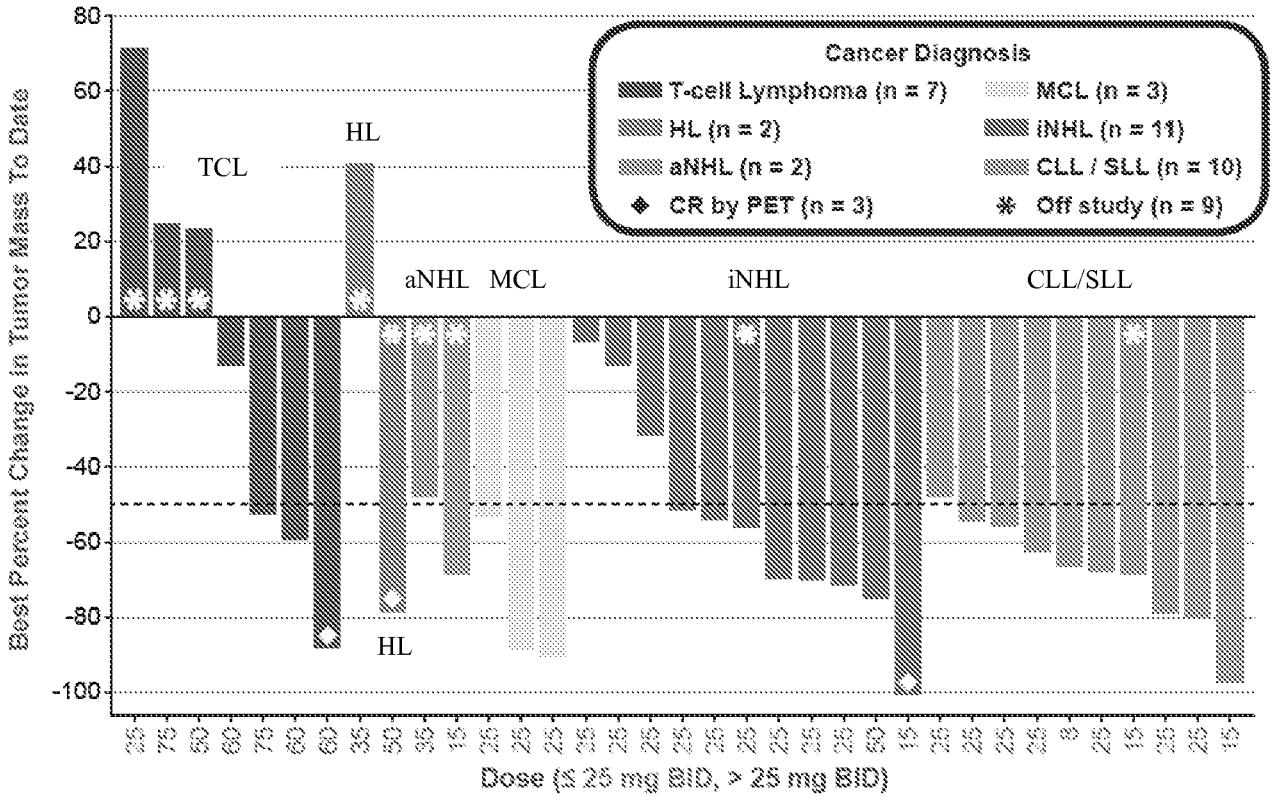

Cancer Diagnosis
T-cell Lymphoma (n = 7)
MCL (n = 3)
HL (n = 2)
iNHL (n = 11)
aNHL (n = 2)
CLL / SLL (n = 10)
CR by PET (n = 3)
Off study (n = 9)
Best Percent Change in Tumor Mass To Date
80
60
40
20
0
-20
-40
-60
-80
-100
TCL
HL
aNHL
MCL
iNHL
CLL/SLL
HL
Dose (≤ 25 mg BID, > 25 mg BID)

FIG. 7

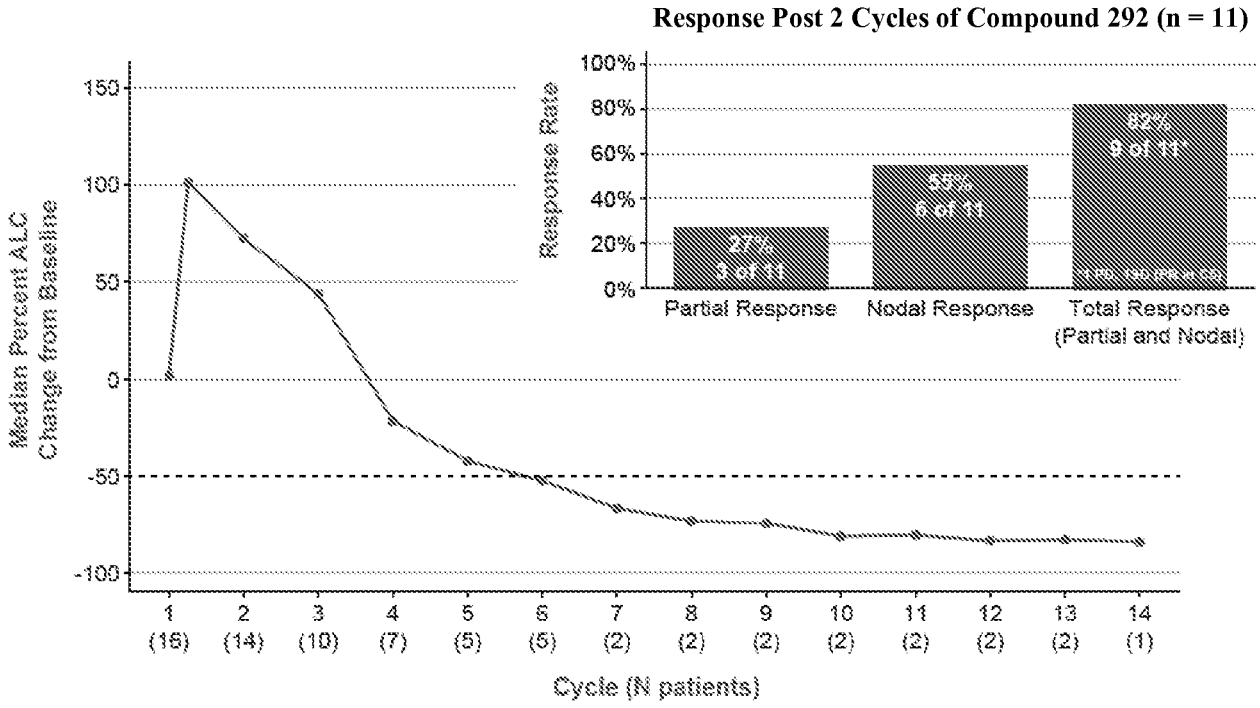

Response Post 2 Cycles of Compound 292 (n = 11)
Median Percent ALC Change from Baseline
150
100
50
0
-50
-100
1 (16)
2 (14)
3 (10)
4 (7)
5 (5)
6 (5)
7 (2)
8 (2)
9 (2)
10 (2)
11 (2)
12 (2)
13 (2)
14 (1)
Cycle (N patients)
Response Rate
100%
80%
60%
40%
20%
0%
27% 3 of 11
55% 6 of 11
82% 9 of 11*
Partial Response
Nodal Response
Total Response (Partial and Nodal)

FIG. 8

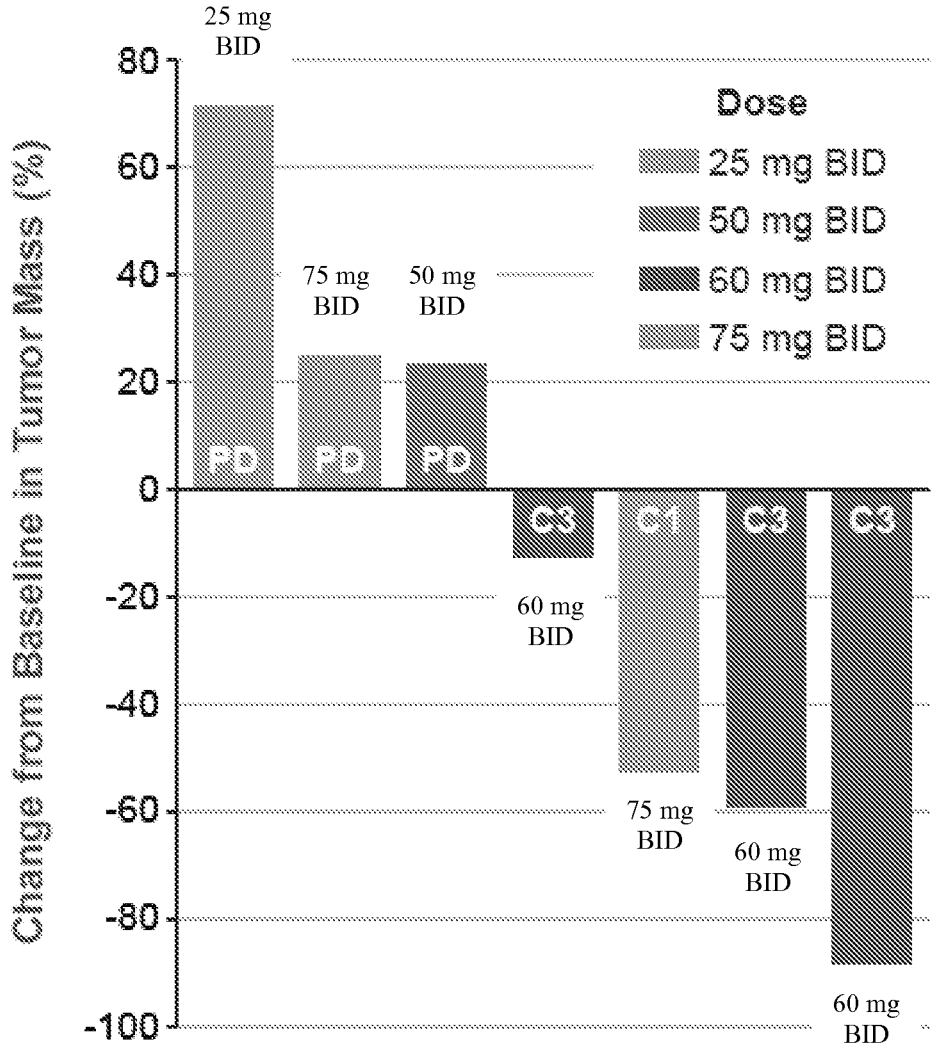
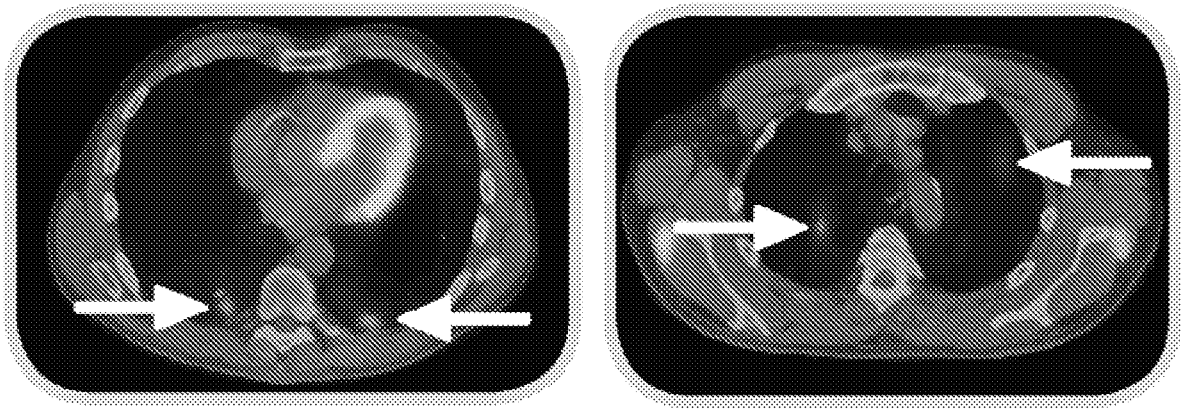
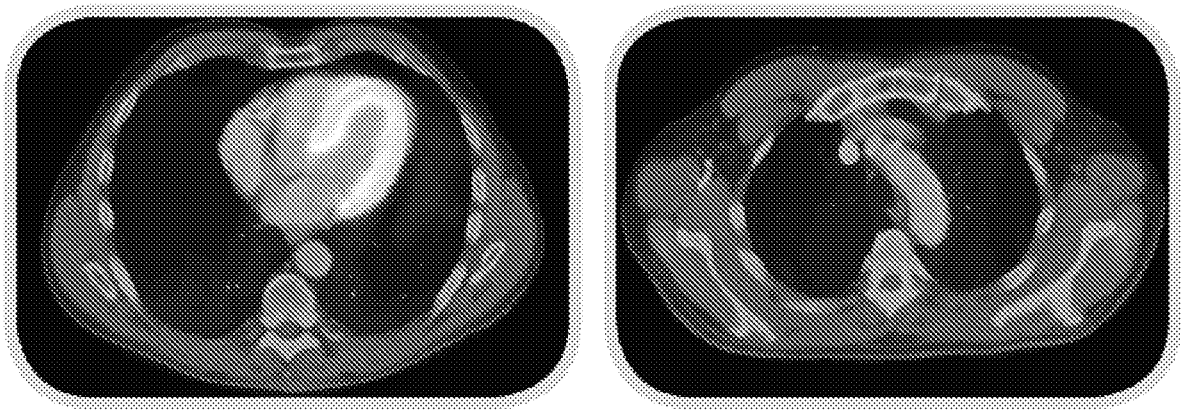

Change from Baseline in Tumor Mass (%)
80
60
40
20
0
-20
-40
-60
-80
-100
Dose
25 mg BID
50 mg BID
60 mg BID
75 mg BID
25 mg BID
75 mg BID
50 mg BID
PD
PD
PD
C3
60 mg BID
C1
75 mg BID
C3
60 mg BID
C3
60 mg BID

FIG. 9



Pre Compound 292 Therapy PET/CT



Post 2 Cycles of Compound 292 Therapy PET/CT

FIG. 10

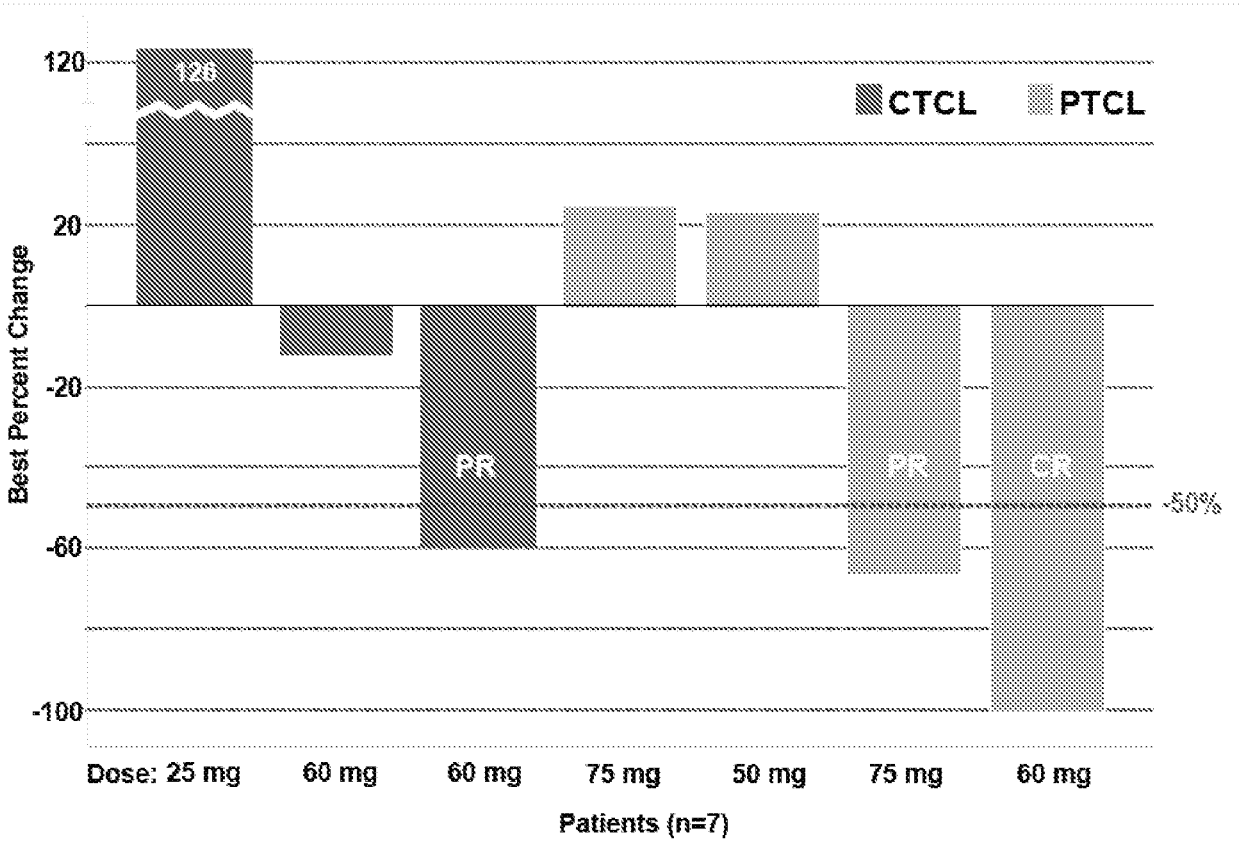

120
20
-20
-60
-100
Best Percent Change
126
CTCL
PTCL
PR
PR
CR
-50%
Dose: 25 mg
60 mg
60 mg
75 mg
50 mg
75 mg
60 mg
Patients (n=7)

FIG. 11

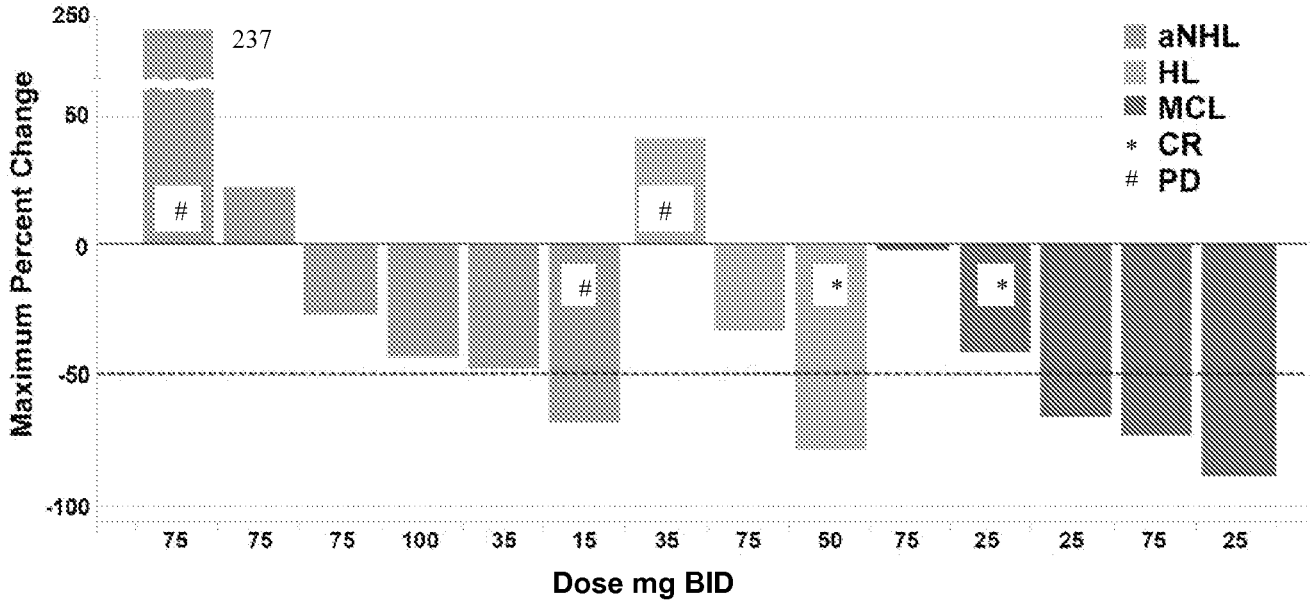

250
50
0
-50
-100
Maximum Percent Change
237
#
#
#
*
*
aNHL
HL
MCL
* CR
# PD
75
75
75
100
35
15
35
75
50
75
25
25
75
25
Dose mg BID

FIG. 12

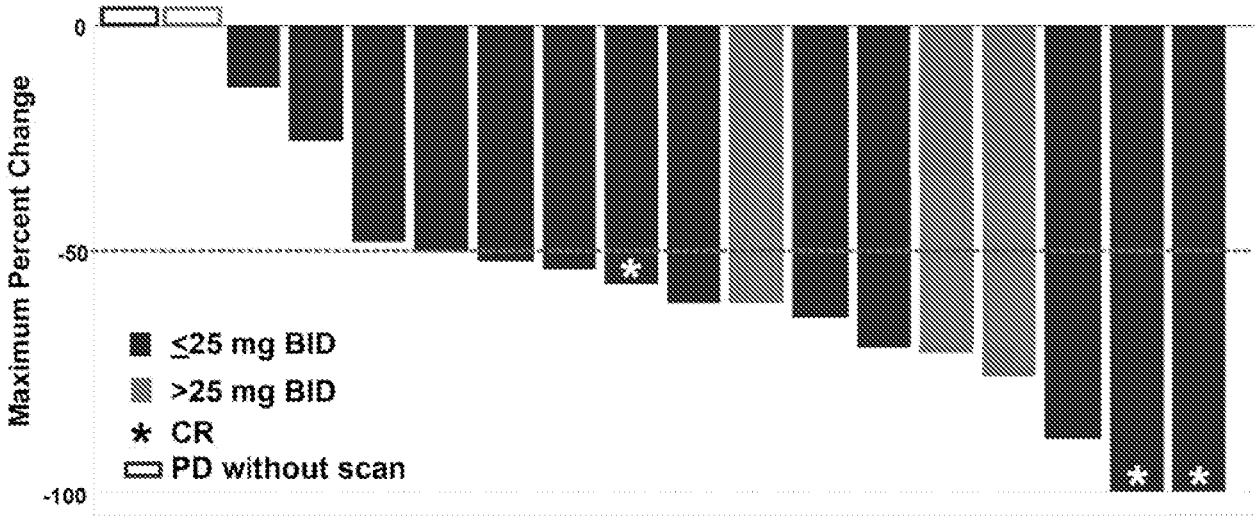

Maximum Percent Change
0
-50
-100
≤25 mg BID
>25 mg BID
CR
PD without scan

FIG. 13

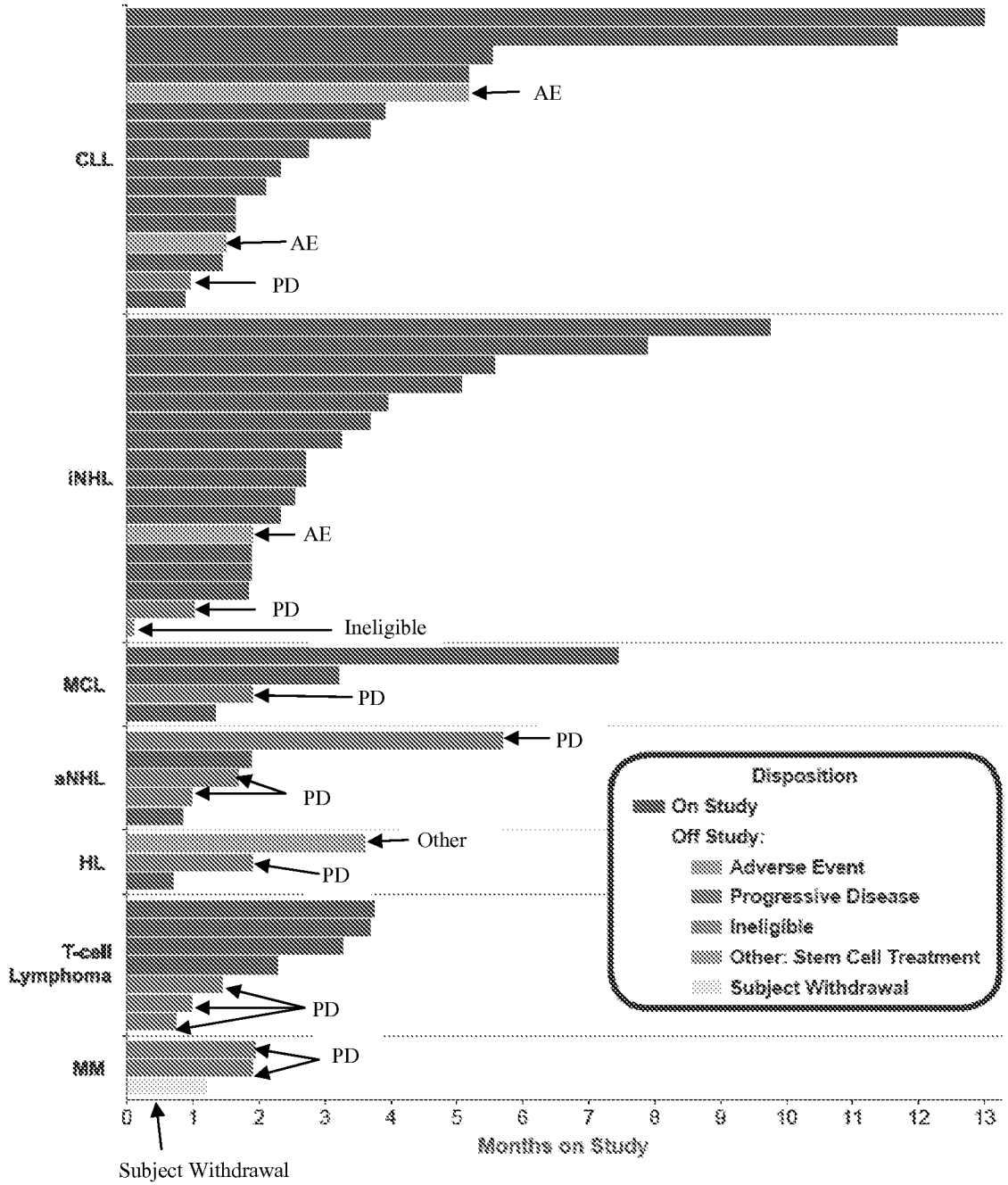

CLL
AE
AE
PD
iNHL
AE
PD
Ineligible
MCL
PD
aNHL
PD
PD
HL
Other
PD
T-cell Lymphoma
PD
MM
PD
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Months on Study
Subject Withdrawal
Disposition
On Study
Off Study:
Adverse Event
Progressive Disease
Ineligible
Other: Stem Cell Treatment
Subject Withdrawal

FIG. 14

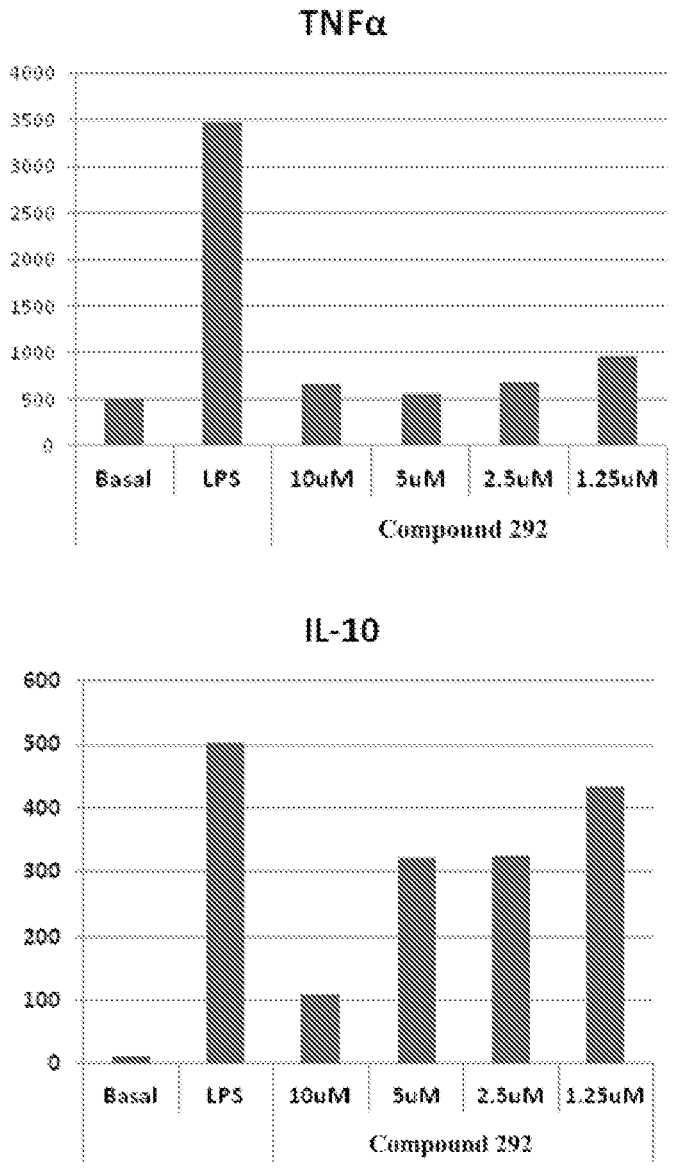

TNFα
4000
3500
3000
2500
2000
1500
1000
500
0
Basal
LPS
10uM
5uM
2.5uM
1.25uM
Compound 292
IL-10
600
500
400
300
200
100
0
Basal
LPS
10uM
5uM
2.5uM
1.25uM
Compound 292

FIG. 15

Serum CXCL13

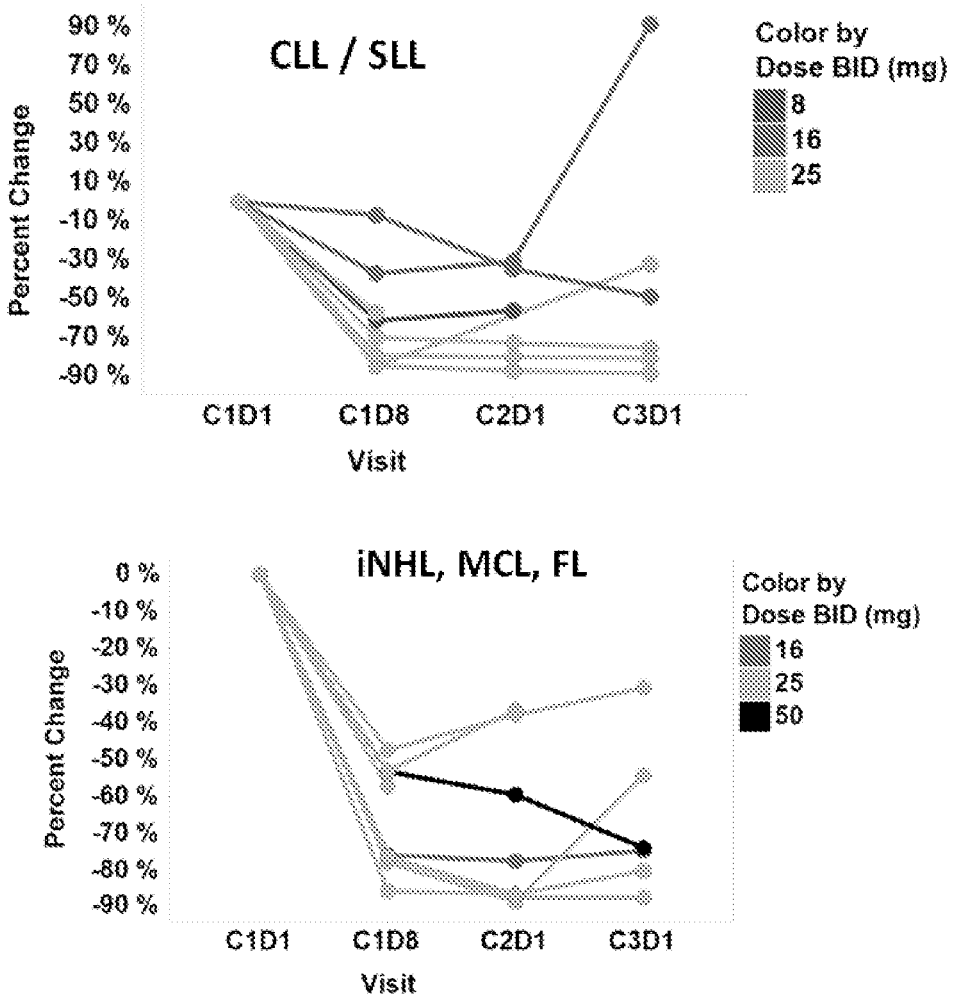


FIG. 16

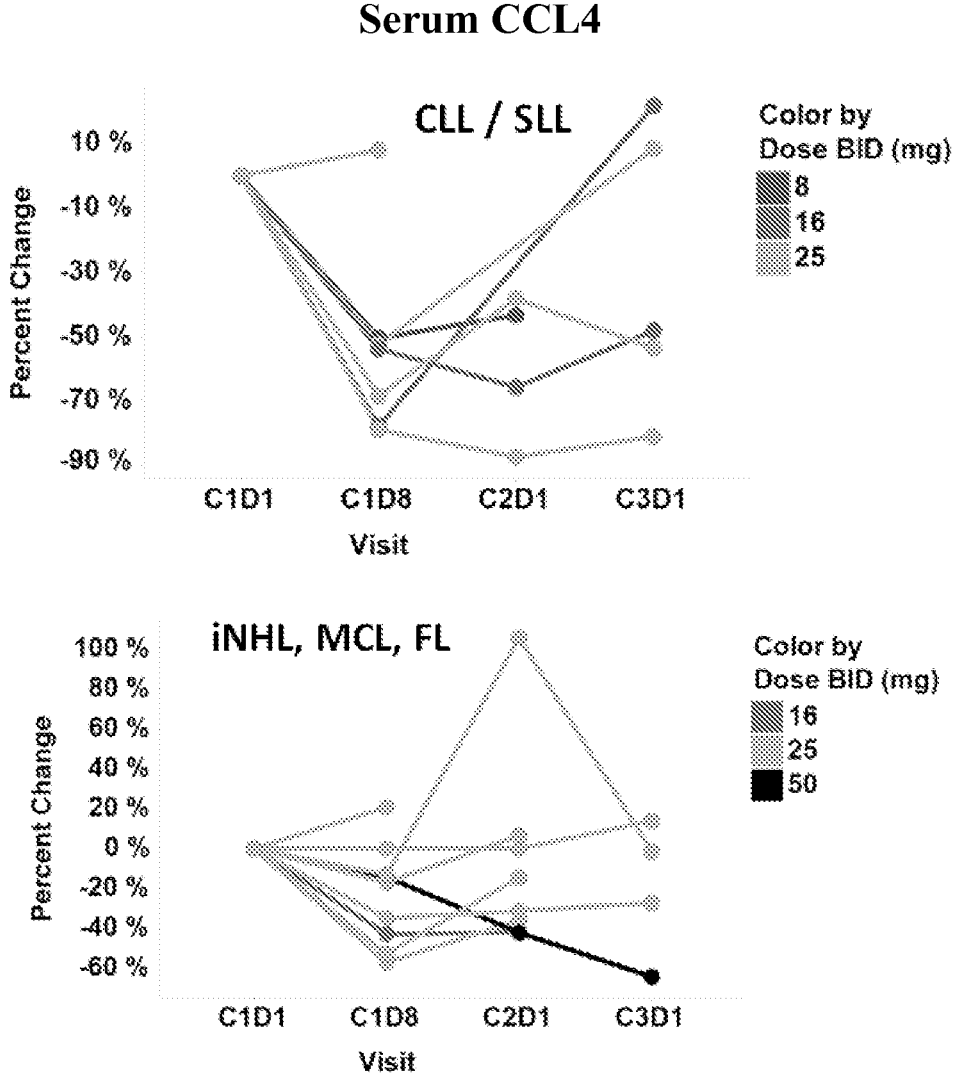

Serum CCL4
CLL / SLL
Percent Change
10 %
-10 %
-30 %
-50 %
-70 %
-90 %
C1D1
C1D8
C2D1
C3D1
Visit
Color by
Dose BID (mg)
8
16
25
iNHL, MCL, FL
Percent Change
100 %
80 %
60 %
40 %
20 %
0 %
-20 %
-40 %
-60 %
C1D1
C1D8
C2D1
C3D1
Visit
Color by
Dose BID (mg)
16
25
50

FIG. 17

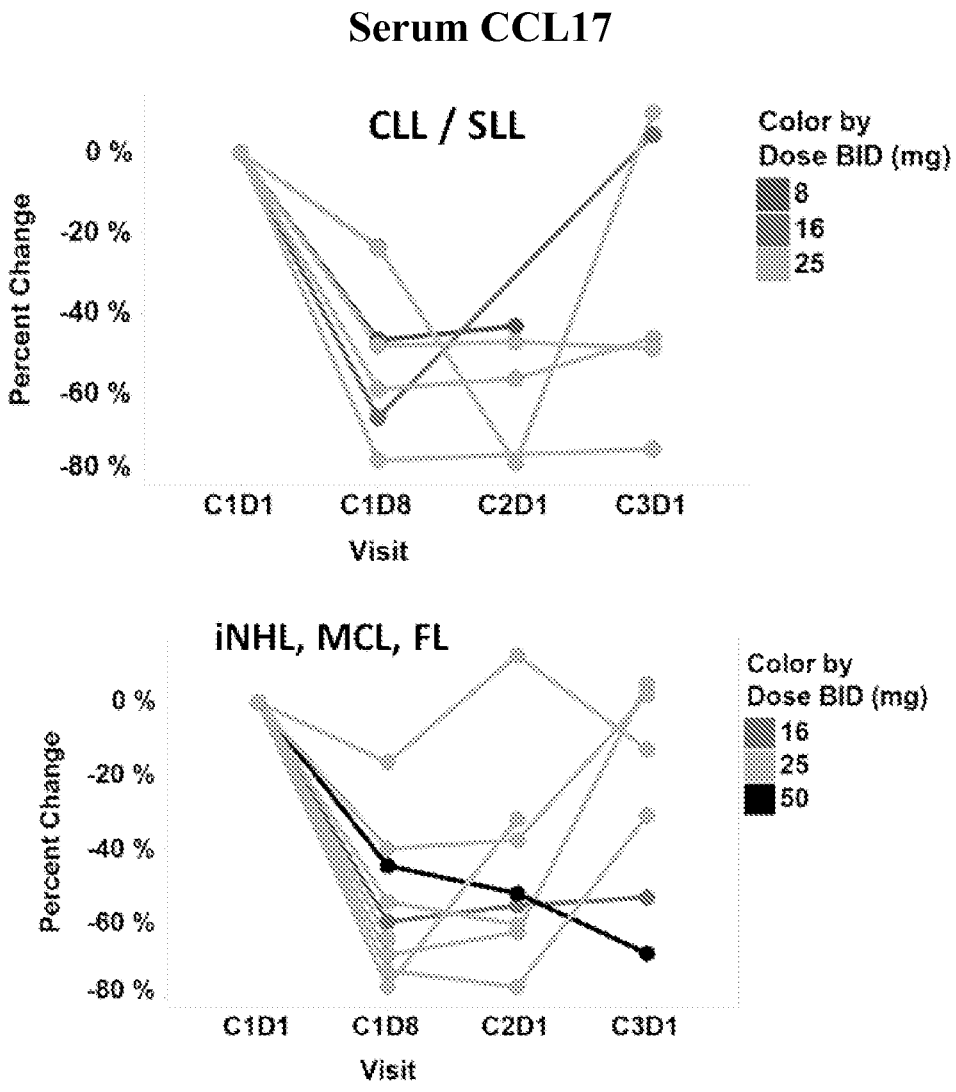

Serum CCL17
CLL / SLL
Percent Change
0 %
-20 %
-40 %
-60 %
-80 %
C1D1
C1D8
C2D1
C3D1
Visit
Color by
Dose BID (mg)
8
16
25
iNHL, MCL, FL
Percent Change
0 %
-20 %
-40 %
-60 %
-80 %
C1D1
C1D8
C2D1
C3D1
Visit
Color by
Dose BID (mg)
16
25
50

FIG. 18

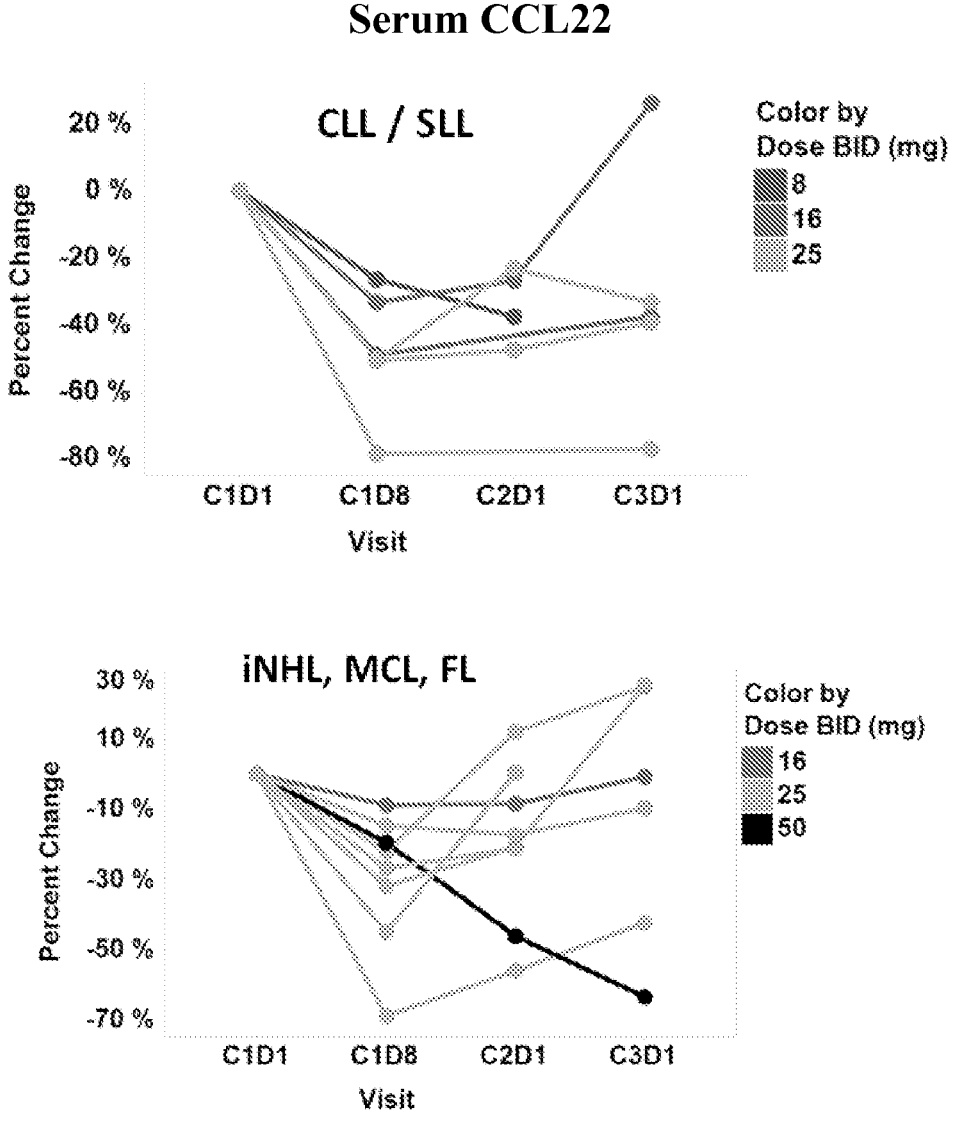

Serum CCL22
CLL / SLL
20 %
0 %
-20 %
-40 %
-60 %
-80 %
Percent Change
C1D1
C1D8
C2D1
C3D1
Visit
Color by
Dose BID (mg)
8
16
25
iNHL, MCL, FL
30 %
10 %
-10 %
-30 %
-50 %
-70 %
Percent Change
C1D1
C1D8
C2D1
C3D1
Visit
Color by
Dose BID (mg)
16
25
50

FIG. 19

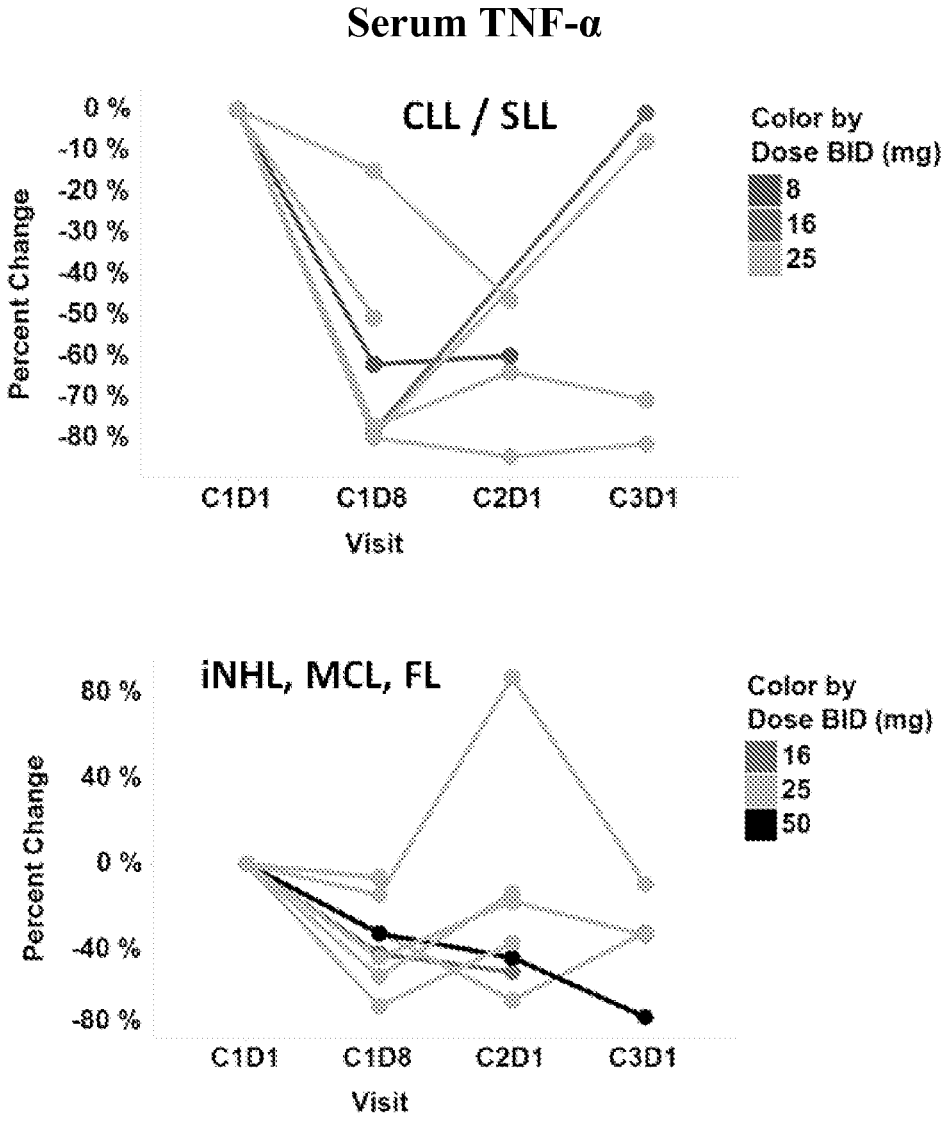

Serum TNF-α
CLL / SLL
0 %
-10 %
-20 %
-30 %
-40 %
-50 %
-60 %
-70 %
-80 %
Percent Change
C1D1
C1D8
C2D1
C3D1
Visit
Color by
Dose BID (mg)
8
16
25
iNHL, MCL, FL
80 %
40 %
0 %
-40 %
-80 %
Percent Change
C1D1
C1D8
C2D1
C3D1
Visit
Color by
Dose BID (mg)
16
25
50

FIG. 20

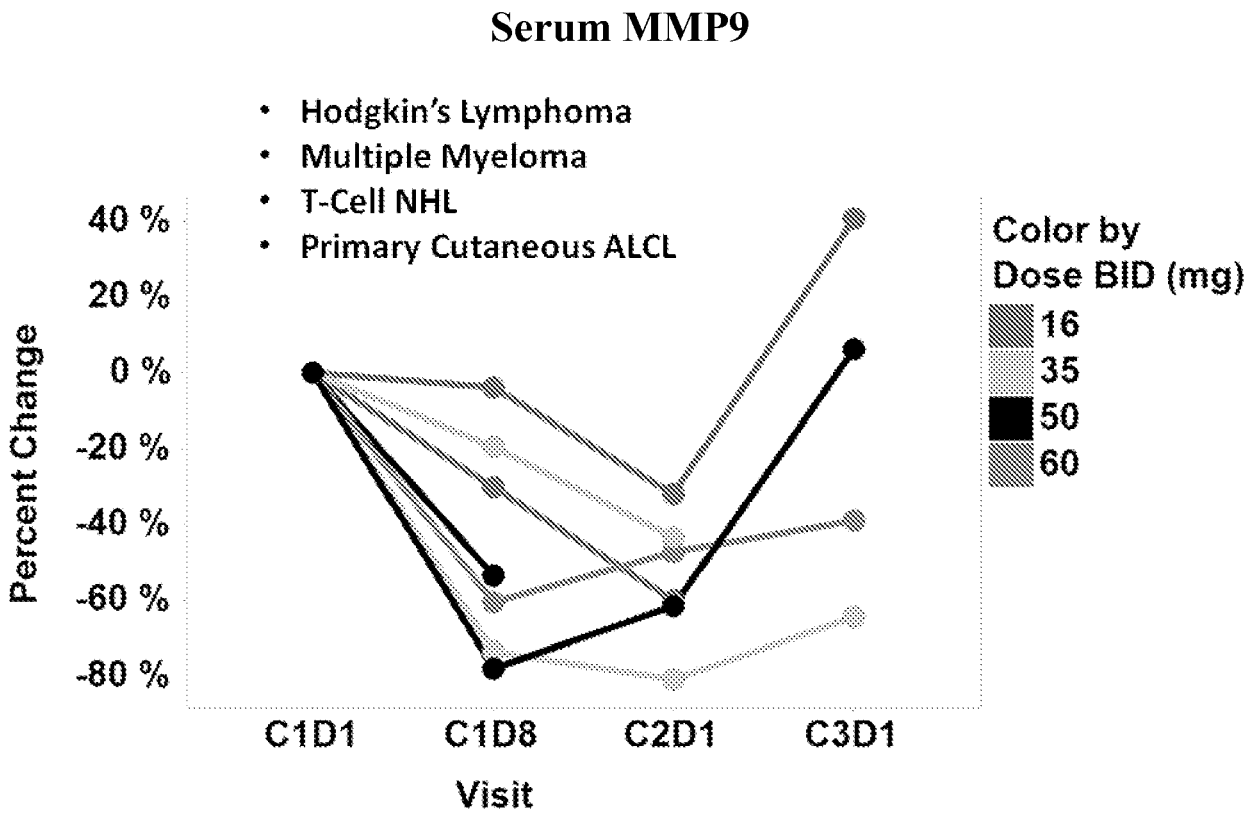

Serum MMP9
Hodgkin's Lymphoma
Multiple Myeloma
T-Cell NHL
Primary Cutaneous ALCL
Percent Change
40 %
20 %
0 %
-20 %
-40 %
-60 %
-80 %
C1D1
C1D8
C2D1
C3D1
Visit
Color by
Dose BID (mg)
16
35
50
60

FIG. 21

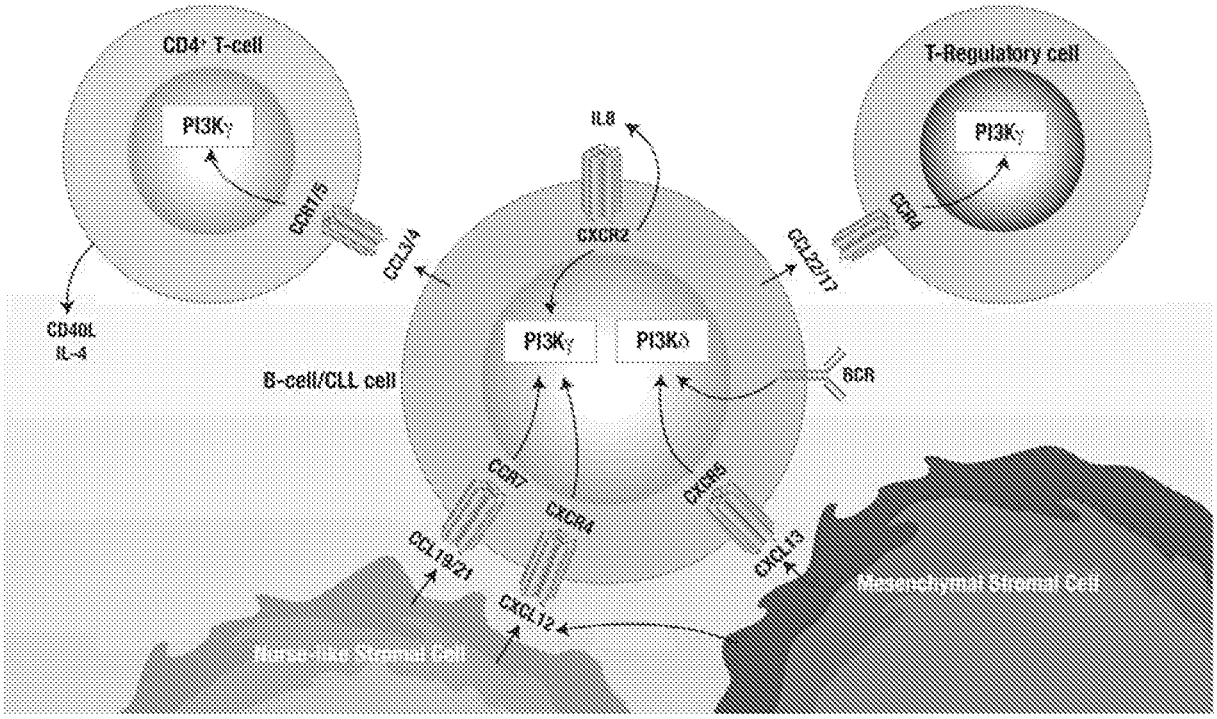

CD4+ T-cell
PI3Kγ
CCR1/5
CCL3/4
CD40L
IL-4
IL8
CXCR2
PI3Kγ
PI3Kδ
B-cell/CLL cell
BCR
CCR7
CXCR4
CXCR5
CCL19/21
CXCL12
CXCL13
Mesenchymal Stromal Cell
T-Regulatory cell
PI3Kγ
CCR4
CCL22/17

FIG. 22

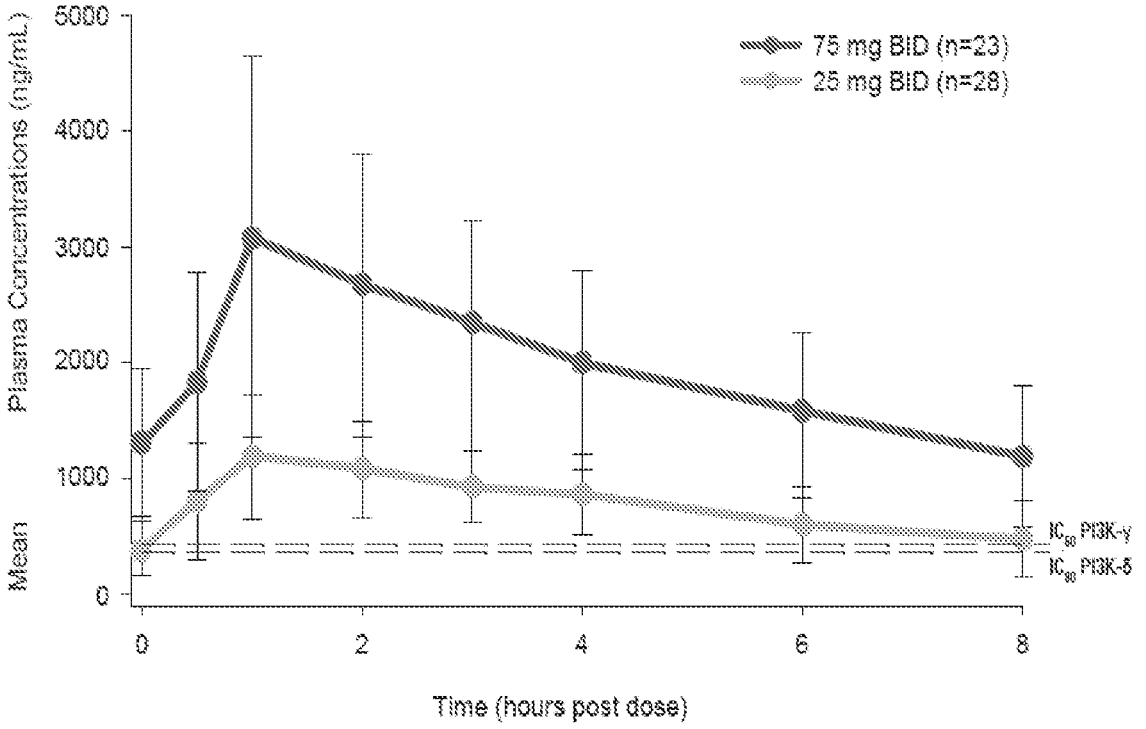

Mean Plasma Concentrations (ng/mL)
5000
4000
3000
2000
1000
0
0
2
4
6
8
Time (hours post dose)
75 mg BID (n=23)
25 mg BID (n=28)
IC90 PI3K-γ
IC90 PI3K-δ

FIG. 23

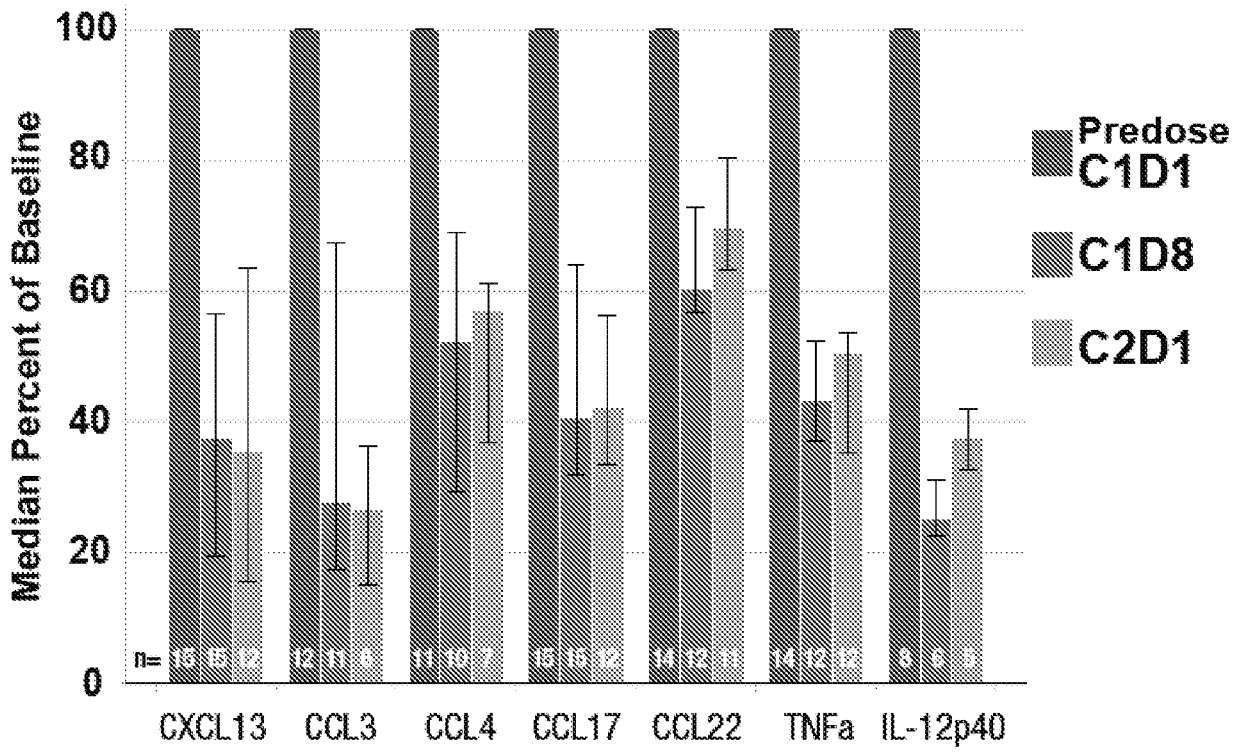

Median Percent of Baseline
100
80
60
40
20
0
n=
15 15 12
12 11 5
11 10 7
15 15 12
14 12 11
14 12 12
5 5 5
CXCL13
CCL3
CCL4
CCL17
CCL22
TNFa
IL-12p40
Predose
C1D1
C1D8
C2D1

FIG. 24

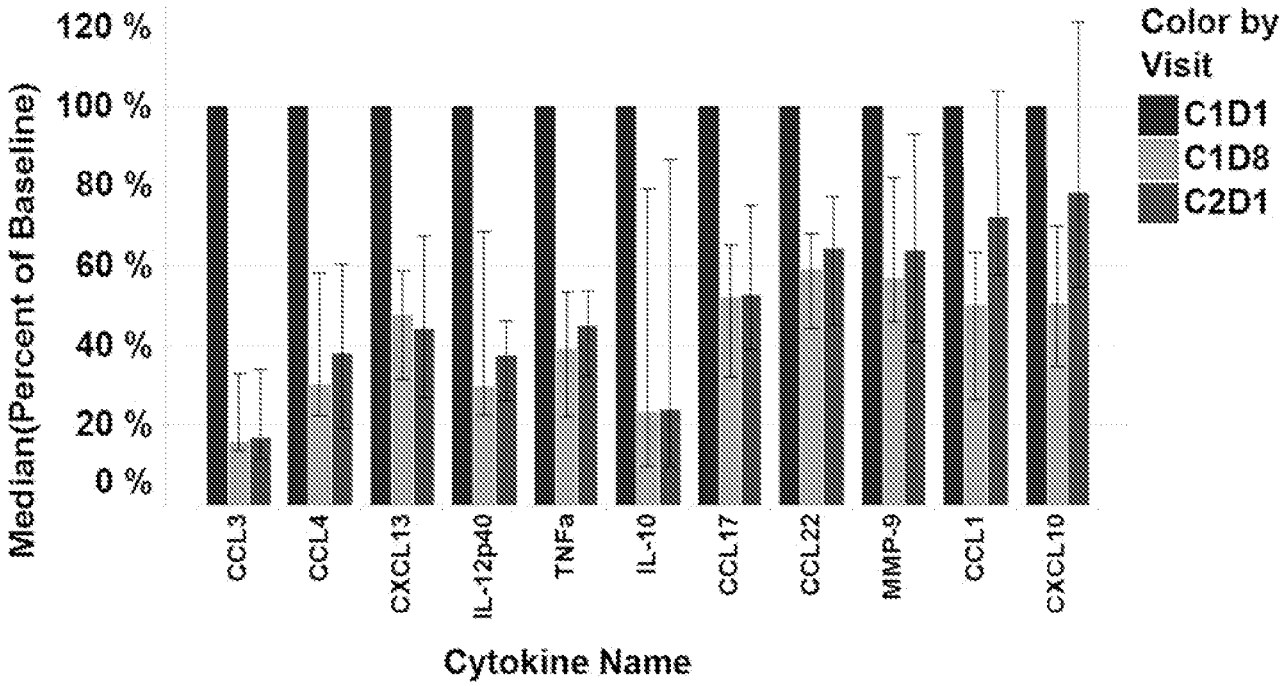

120 %
100 %
80 %
60 %
40 %
20 %
0 %
Median(Percent of Baseline)
CCL3
CCL4
CXCL13
IL-12p40
TNFa
IL-10
CCL17
CCL22
MMP-9
CCL1
CXCL10
Cytokine Name
Color by Visit
C1D1
C1D8
C2D1

FIG. 25

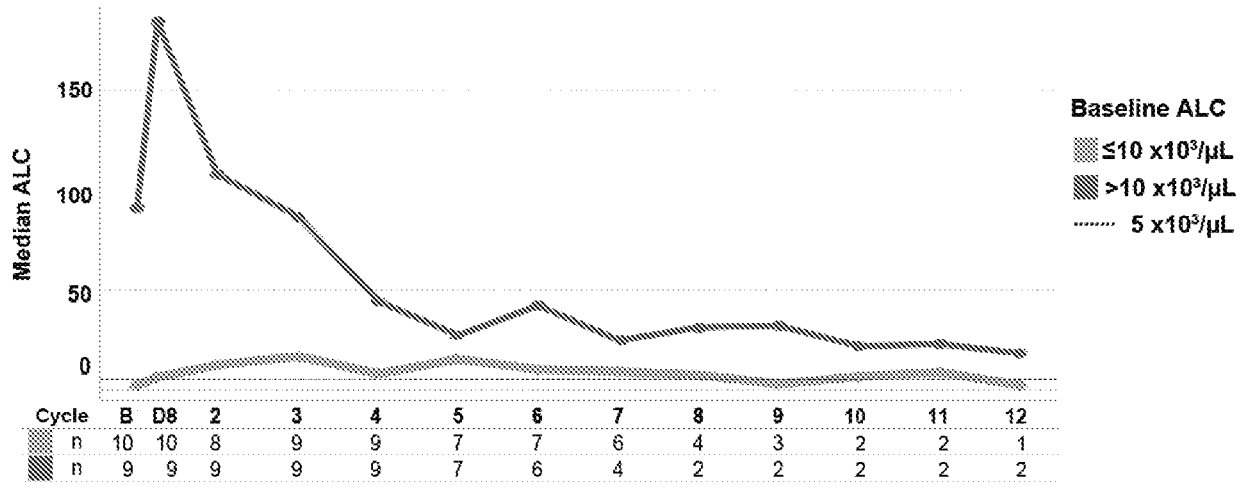
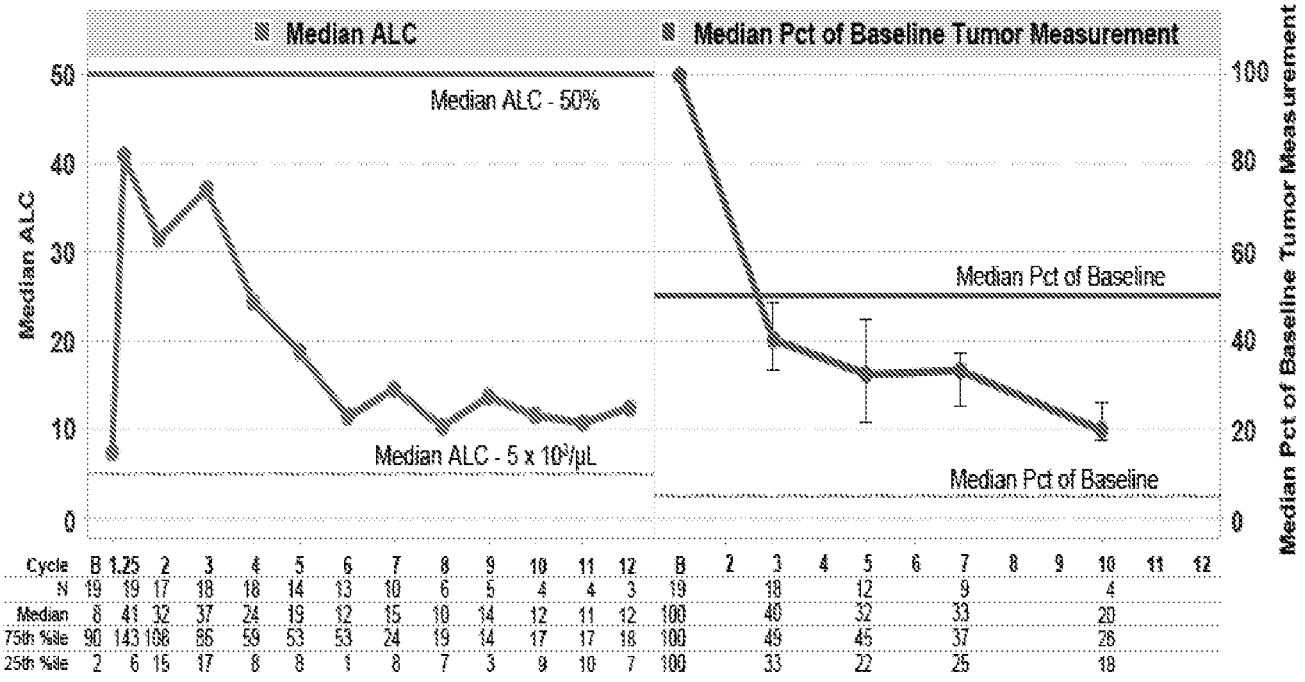
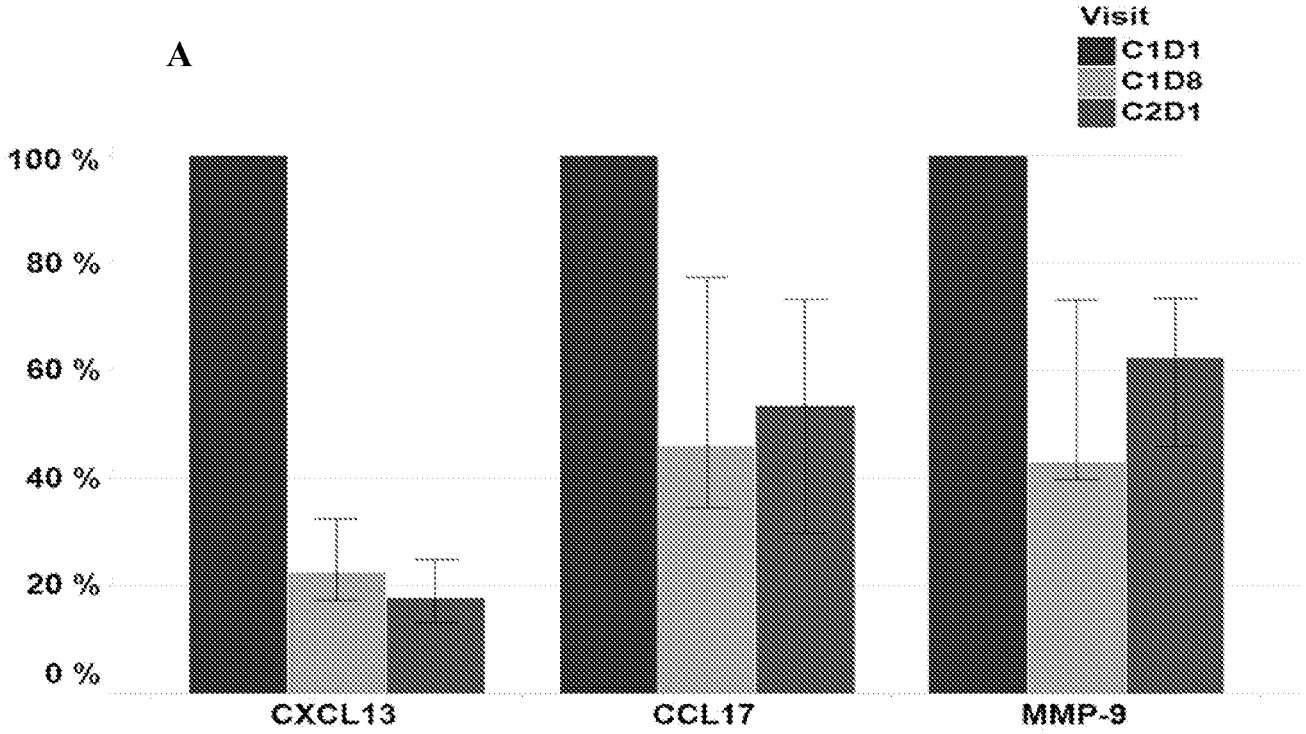

Median ALC
150
100
50
0
Baseline ALC
≤10 x10³/µL
>10 x10³/µL
5 x10³/µL
Cycle B D8 2 3 4 5 6 7 8 9 10 11 12
n 10 10 8 9 9 7 7 6 4 3 2 2 1
n 9 9 9 9 9 7 6 4 2 2 2 2 2

FIG. 26



Cycle	B	1.25	2	3	4	5	6	7	8	9	10	11	12	B	2	3	4	5	6	7	8	9	10	11	12
N	19	19	17	18	18	14	13	10	6	5	4	4	3	19		18		12		9			4		
Median	8	41	32	37	24	19	12	15	10	14	12	11	12	100		40		32		33			20		
75th %ile	90	143	108	86	59	53	53	24	19	14	17	17	18	100		49		46		37			26		
25th %ile	2	6	15	17	8	8	1	8	7	3	9	10	7	100		33		22		25			18		

FIG. 27


A
Visit
C1D1
C1D8
C2D1
100 %
80 %
60 %
40 %
20 %
0 %
CXCL13
CCL17
MMP-9

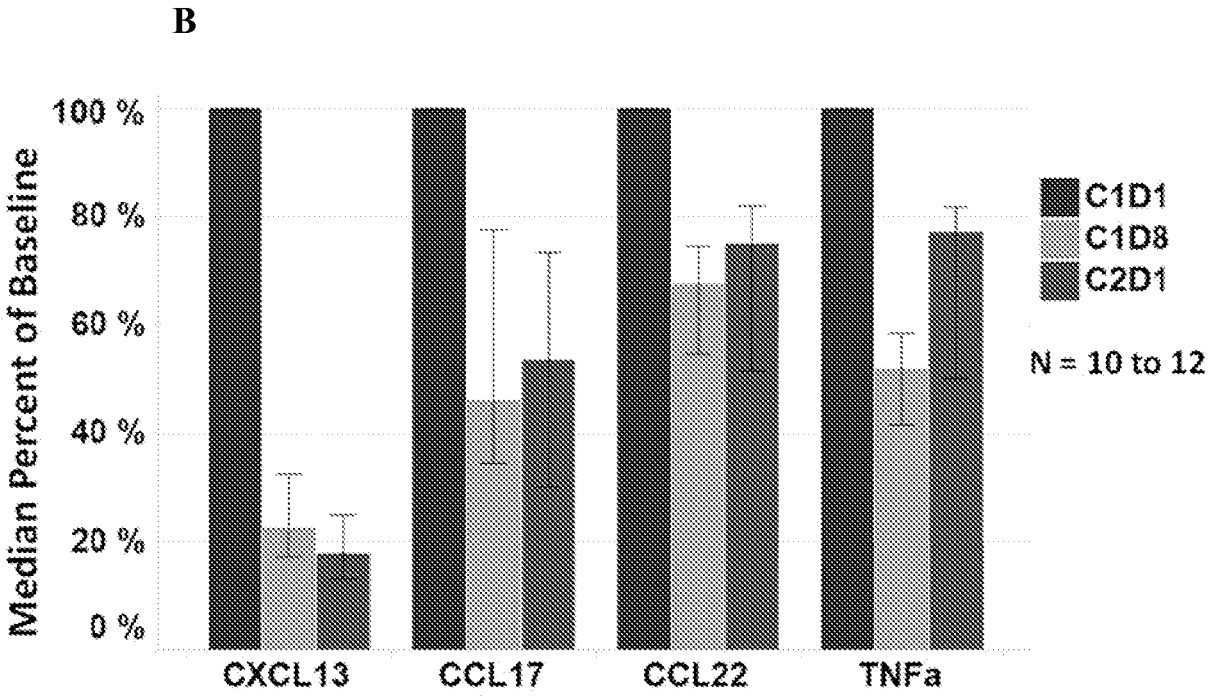

B
Median Percent of Baseline
100 %
80 %
60 %
40 %
20 %
0 %
CXCL13
CCL17
CCL22
TNFa
C1D1
C1D8
C2D1
N = 10 to 12

FIG. 28

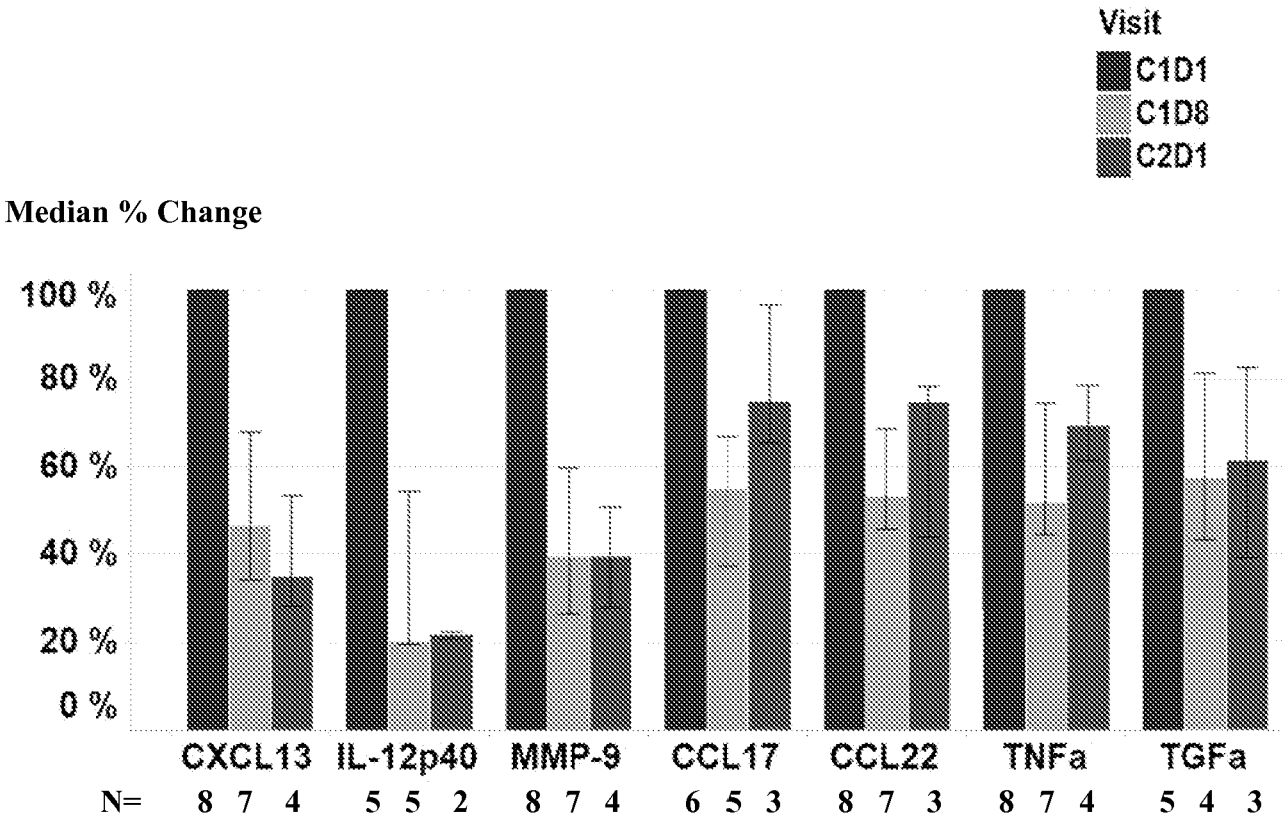

Visit
C1D1
C1D8
C2D1
Median % Change
100 %
80 %
60 %
40 %
20 %
0 %
CXCL13
IL-12p40
MMP-9
CCL17
CCL22
TNFa
TGFa
N= 8 7 4 5 5 2 8 7 4 6 5 3 8 7 3 8 7 4 5 4 3

FIG. 29

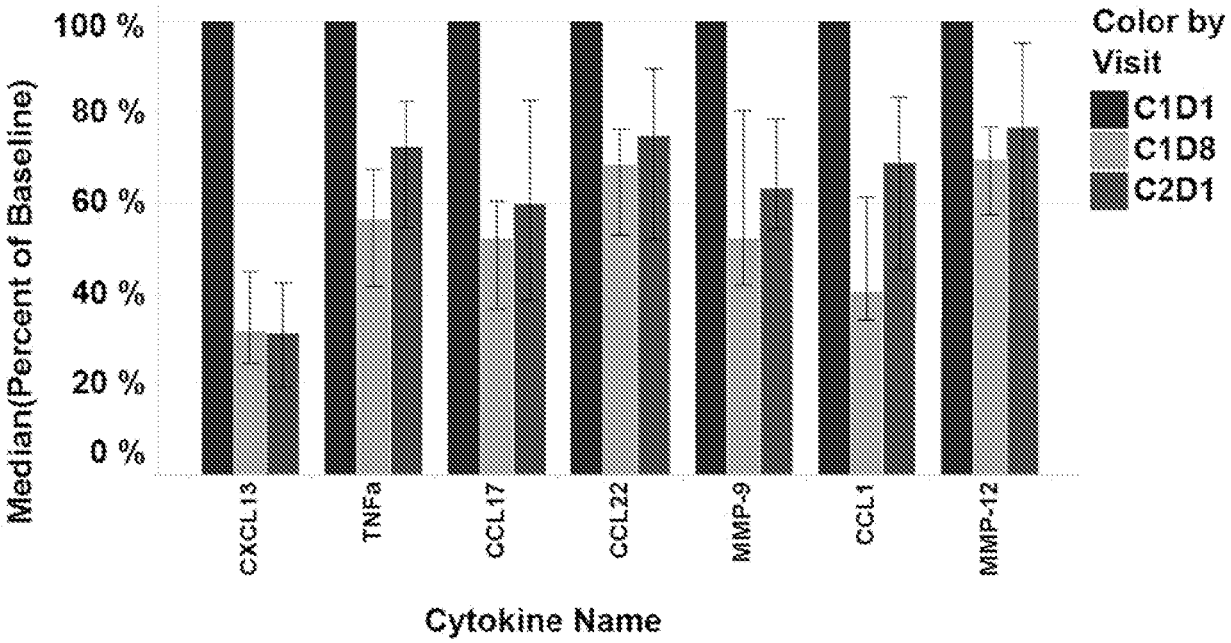

Median(Percent of Baseline)
100 %
80 %
60 %
40 %
20 %
0 %
CXCL13
TNFa
CCL17
CCL22
MMP-9
CCL1
MMP-12
Cytokine Name
Color by Visit
C1D1
C1D8
C2D1

FIG. 30

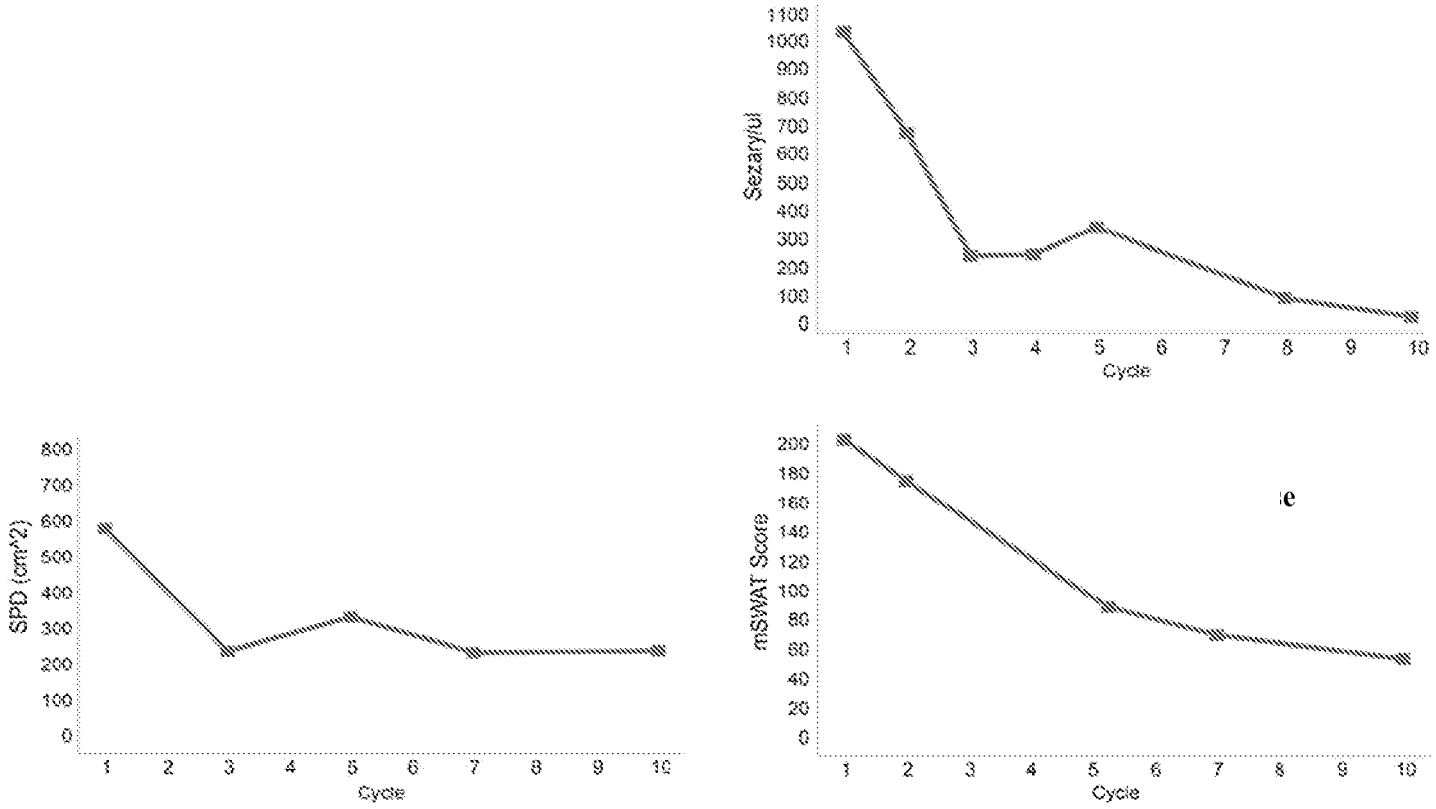


FIG. 31

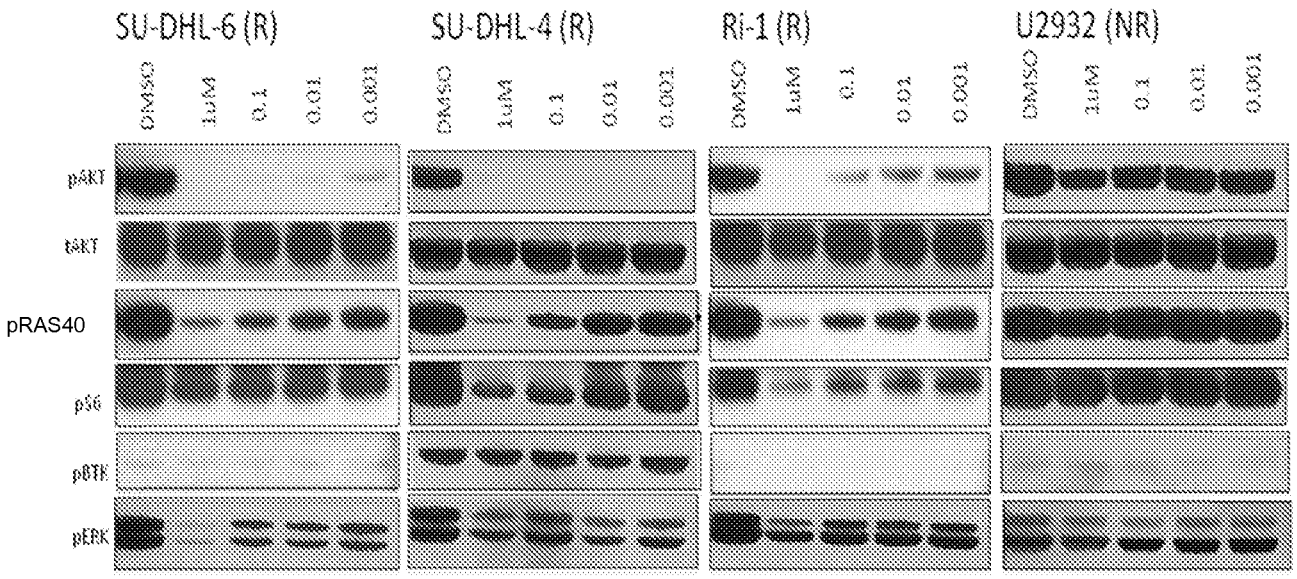
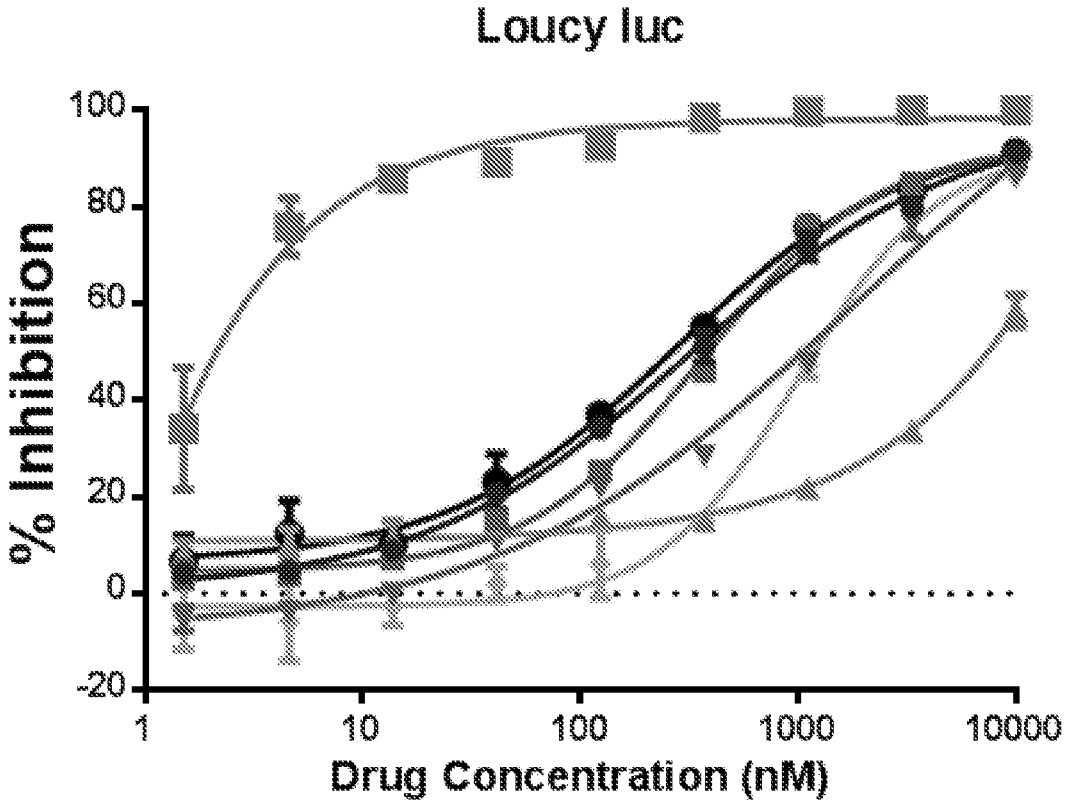

SU-DHL-6 (R)
SU-DHL-4 (R)
Ri-1 (R)
U2932 (NR)
DMSO
1uM
0.1
0.01
0.001
pAKT
tAKT
pRAS40
pS6
pBTK
pERK

FIG. 32



	IC_{50}
Compound 292	311 nM
δ/γ Selective inhibitor	366 nM
B selective Inhibitor	
γ Selective Inhibitor	1877 nM
δ Selective Inhibitor	1013 nM
δ/γ Selective Inhibitor	272 nM
Doxorubicin	

FIG. 33

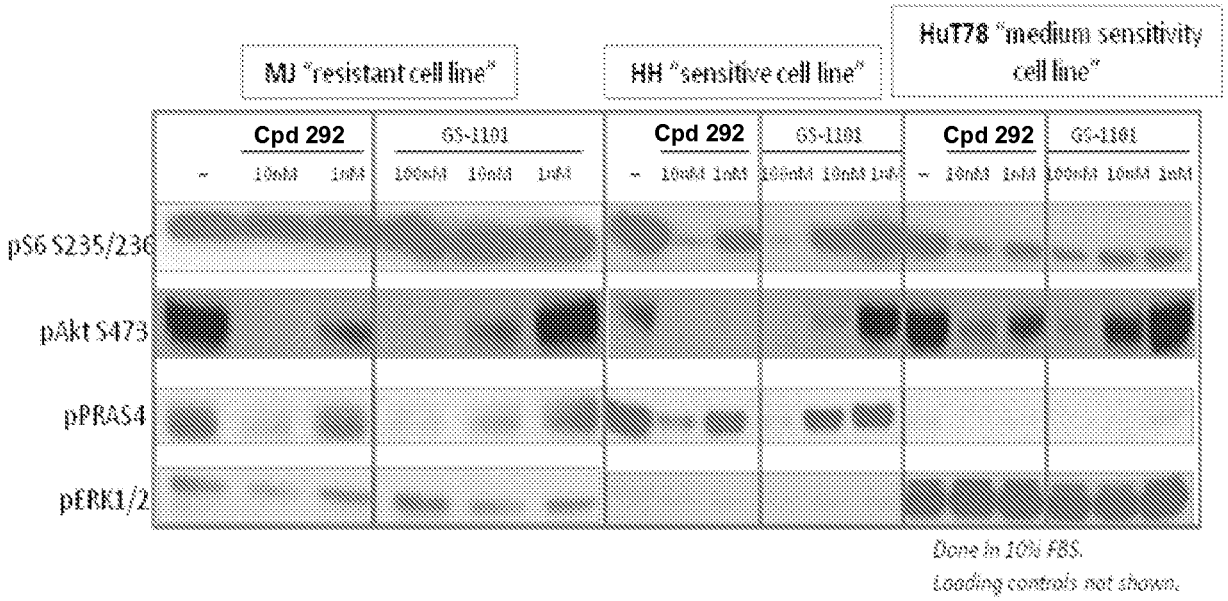

MJ "resistant cell line"
HH "sensitive cell line"
HuT78 "medium sensitivity cell line"
Cpd 292
GS-1101
pS6 S235/236
pAkt S473
pPRAS4
pERK1/2
Done in 10% FBS.
Loading controls not shown.

FIG. 34

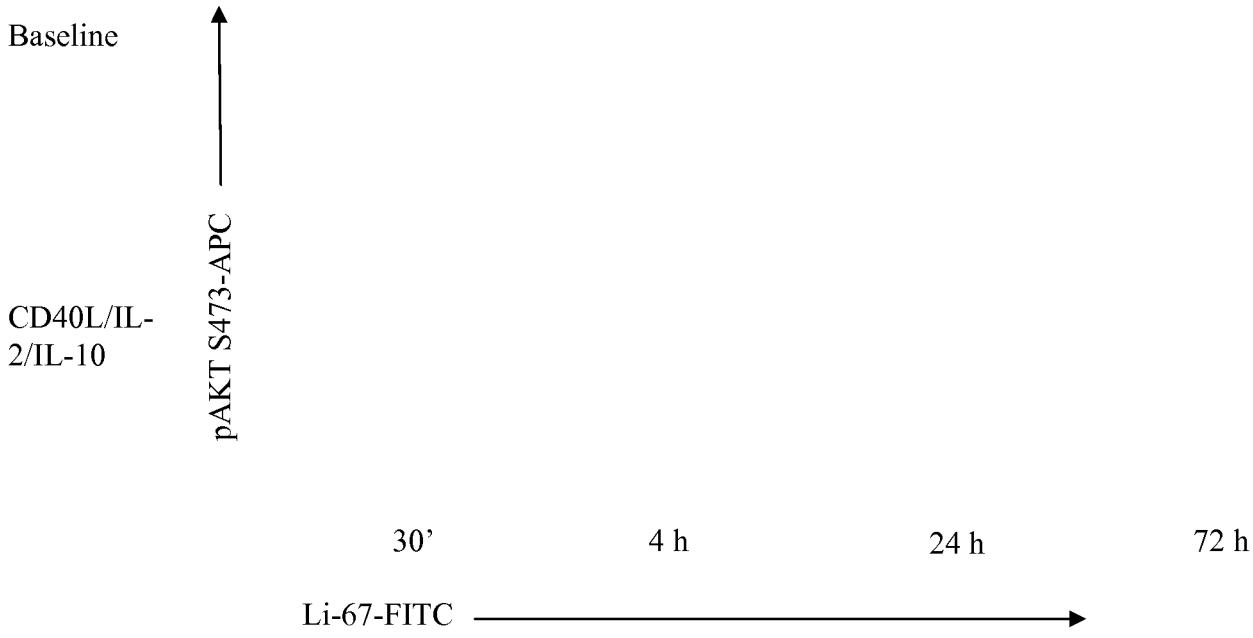


FIG. 35

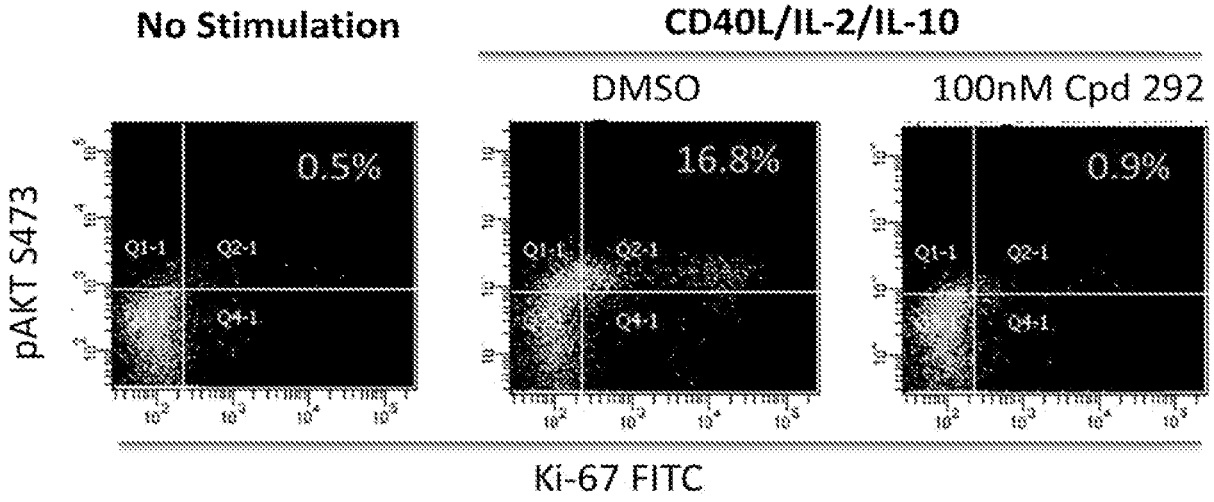

No Stimulation
CD40L/IL-2/IL-10
DMSO
100nM Cpd 292
0.5%
16.8%
0.9%
Q1-1
Q2-1
Q4-1
pAKT S473
Ki-67 FITC

FIG. 36

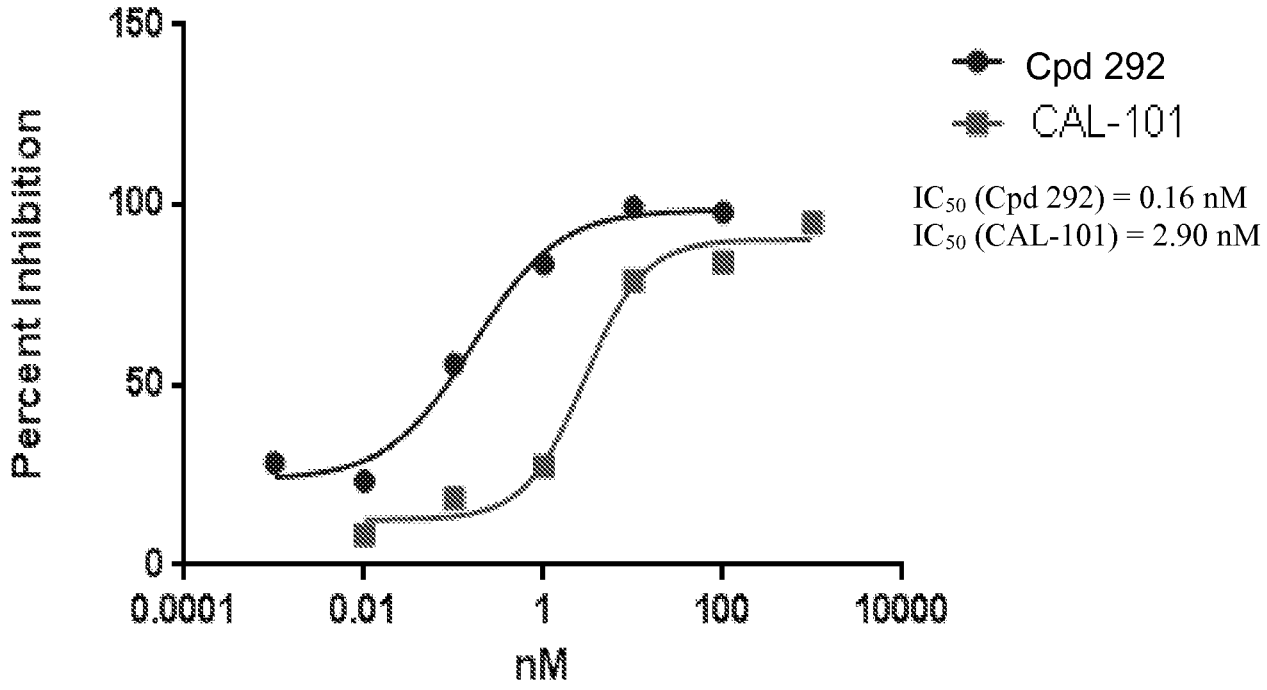
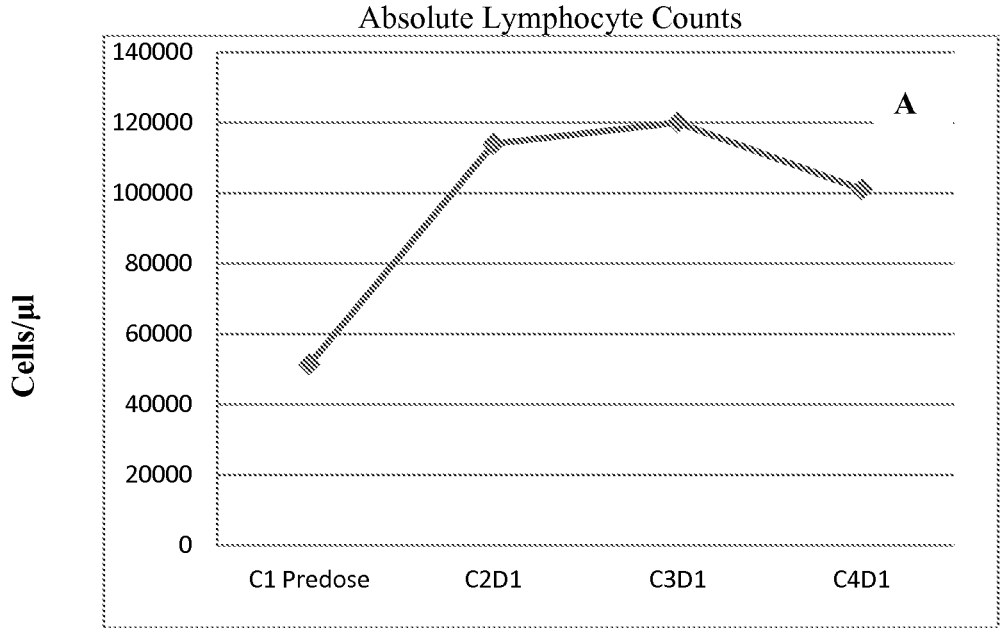

150
100
50
0
Percent Inhibition
0.0001
0.01
1
100
10000
nM
Cpd 292
CAL-101
IC50 (Cpd 292) = 0.16 nM
IC50 (CAL-101) = 2.90 nM

FIG. 37


Absolute Lymphocyte Counts
Cells/µl
140000
120000
100000
80000
60000
40000
20000
0
A
C1 Predose
C2D1
C3D1
C4D1

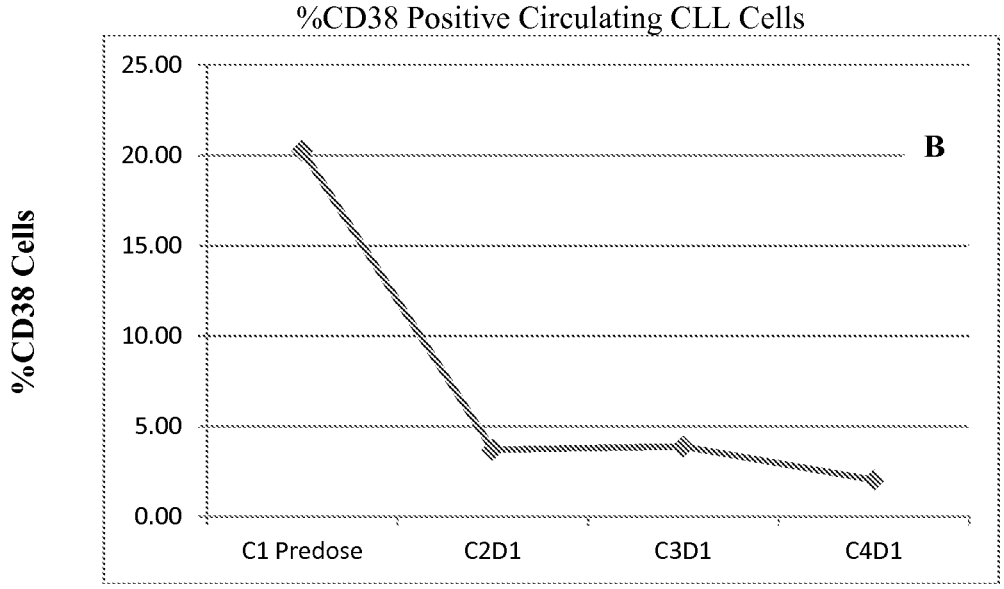
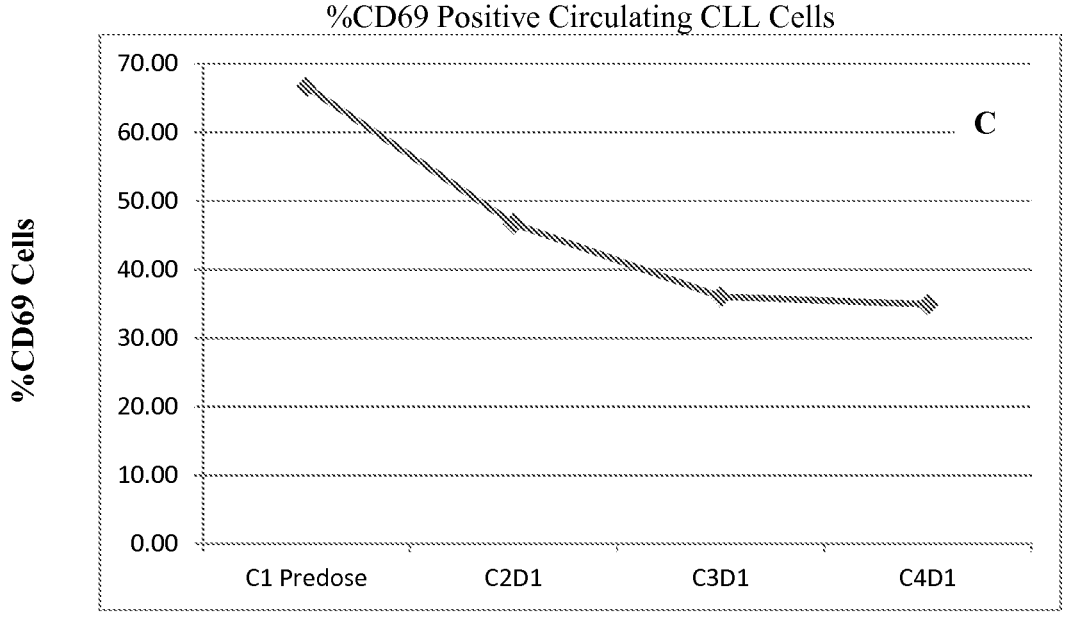

%CD38 Positive Circulating CLL Cells
%CD38 Cells
25.00
20.00
15.00
10.00
5.00
0.00
B
C1 Predose
C2D1
C3D1
C4D1

FIG. 37 (Cont'd)


%CD69 Positive Circulating CLL Cells
%CD69 Cells
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
C
C1 Predose
C2D1
C3D1
C4D1

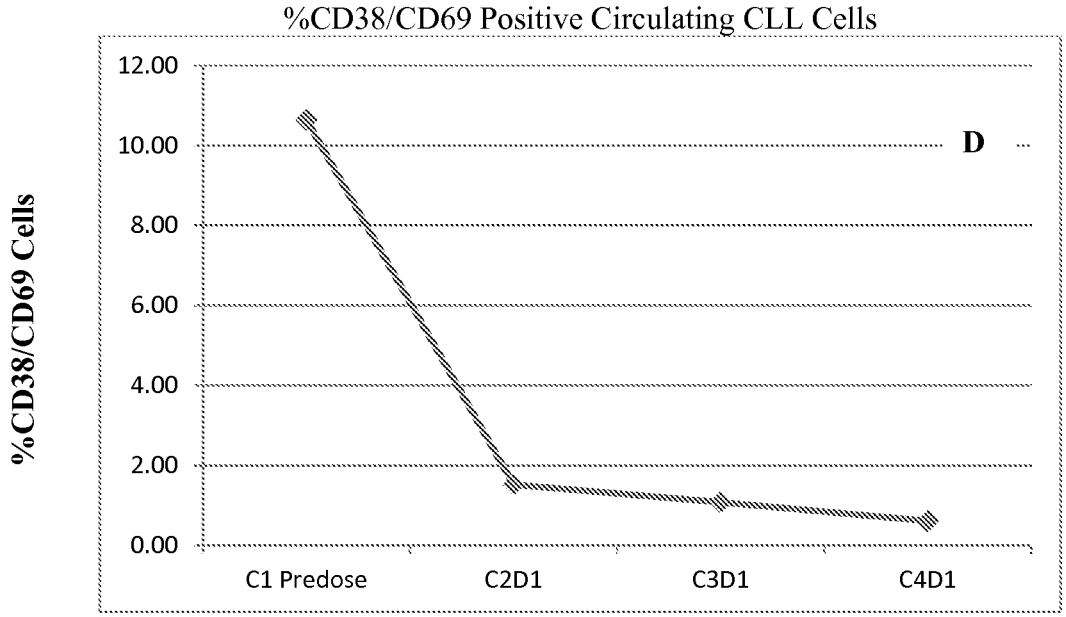

%CD38/CD69 Positive Circulating CLL Cells
%CD38/CD69 Cells
12.00
10.00
8.00
6.00
4.00
2.00
0.00
D
C1 Predose
C2D1
C3D1
C4D1

FIG. 38

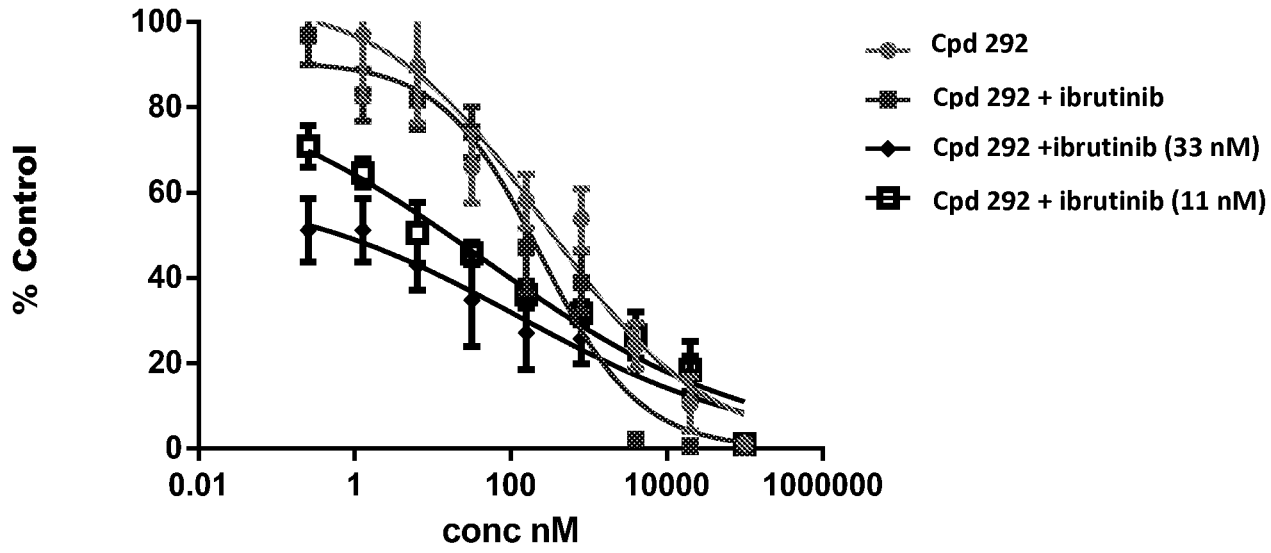

100
80
60
40
20
0
% Control
0.01
1
100
10000
1000000
conc nM
Cpd 292
Cpd 292 + ibrutinib
Cpd 292 +ibrutinib (33 nM)
Cpd 292 + ibrutinib (11 nM)

FIG. 39

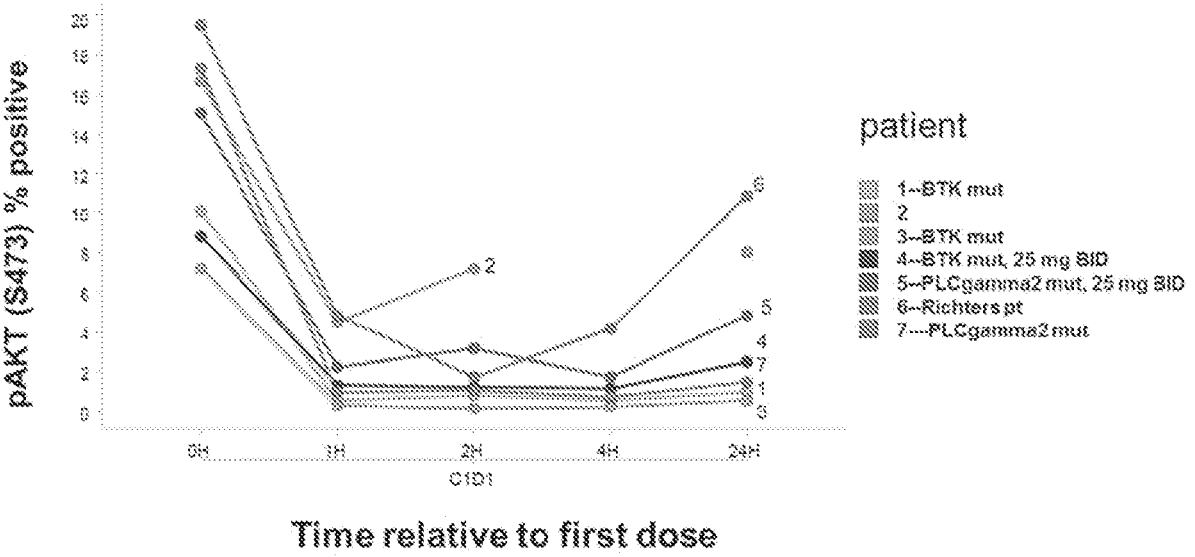

pAKT (S473) % positive
0H
1H
2H
4H
24H
C1D1
Time relative to first dose
patient
1--BTK mut
2
3--BTK mut
4--BTK mut, 25 mg BID
5--PLCgamma2 mut, 25 mg BID
6--Richters pt
7---PLCgamma2 mut

FIG. 40

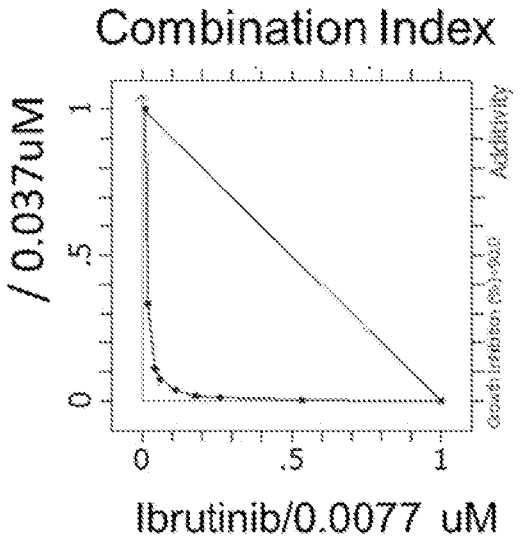

Combination Index
/ 0.037uM
0
.5
1
0
.5
1
Ibrutinib/0.0077 uM
Additivity

FIG. 41

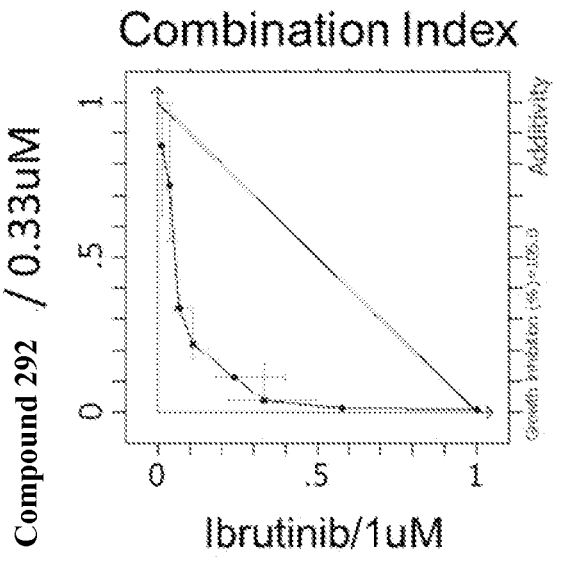
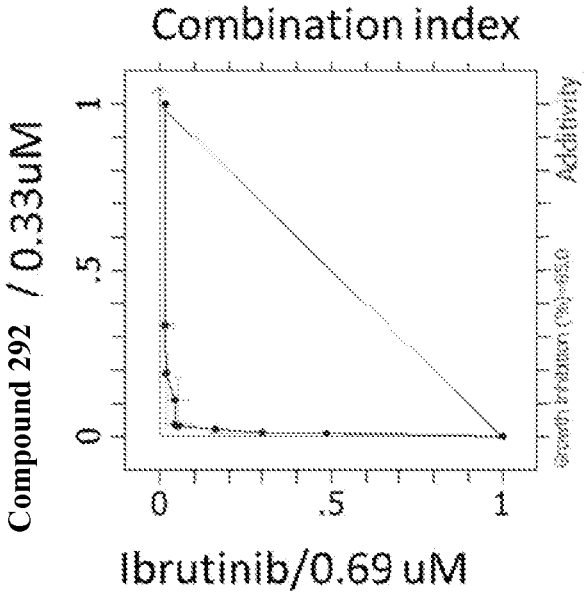

Combination Index
Compound 292 / 0.33uM
Ibrutinib/1uM
0
.5
1
Additivity

FIG. 42


Combination index
Compound 292 / 0.33uM
Ibrutinib/0.69 uM
0
.5
1
Additivity