Fig. 1

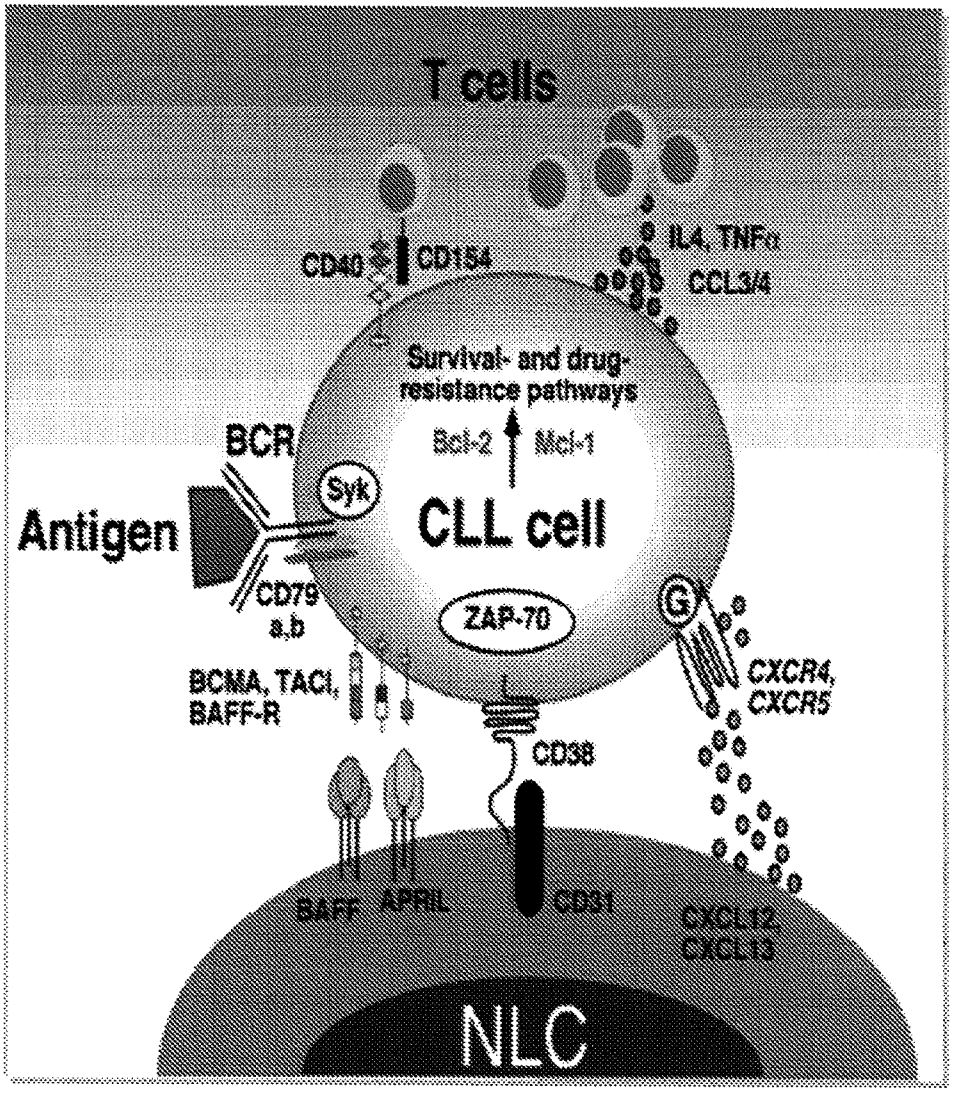
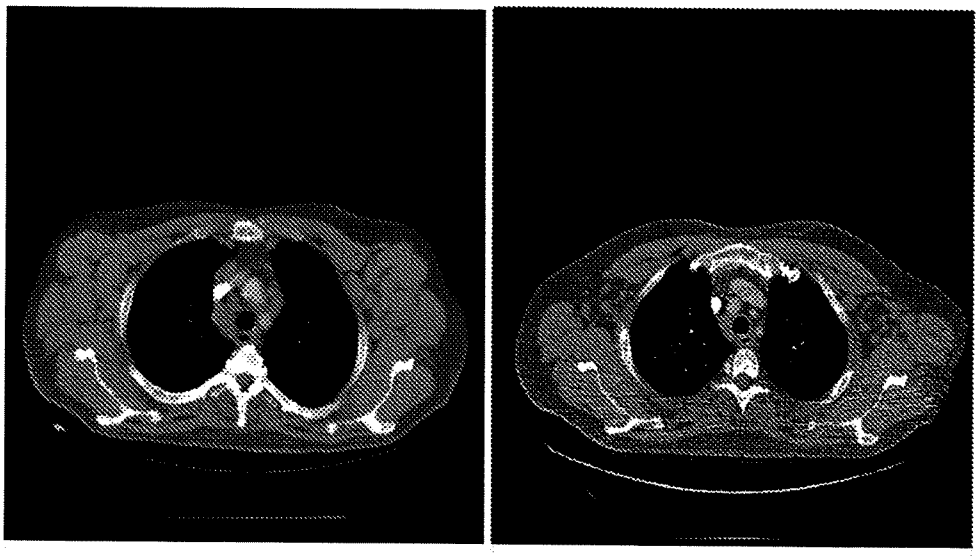

T cells
CD40
CD154
IL4, TNFα
CCL3/4
Survival- and drug-resistance pathways
Bcl-2
Mcl-1
BCR
Syk
Antigen
CLL cell
CD79 a,b
ZAP-70
G
CXCR4, CXCR5
BCMA, TACI, BAFF-R
CD38
BAFF
APRIL
CD31
CXCL12, CXCL13
NLC

Fig. 2



Pre-treatment with Btk inhibitor **Post-treatment with Btk inhibitor**

Fig. 3

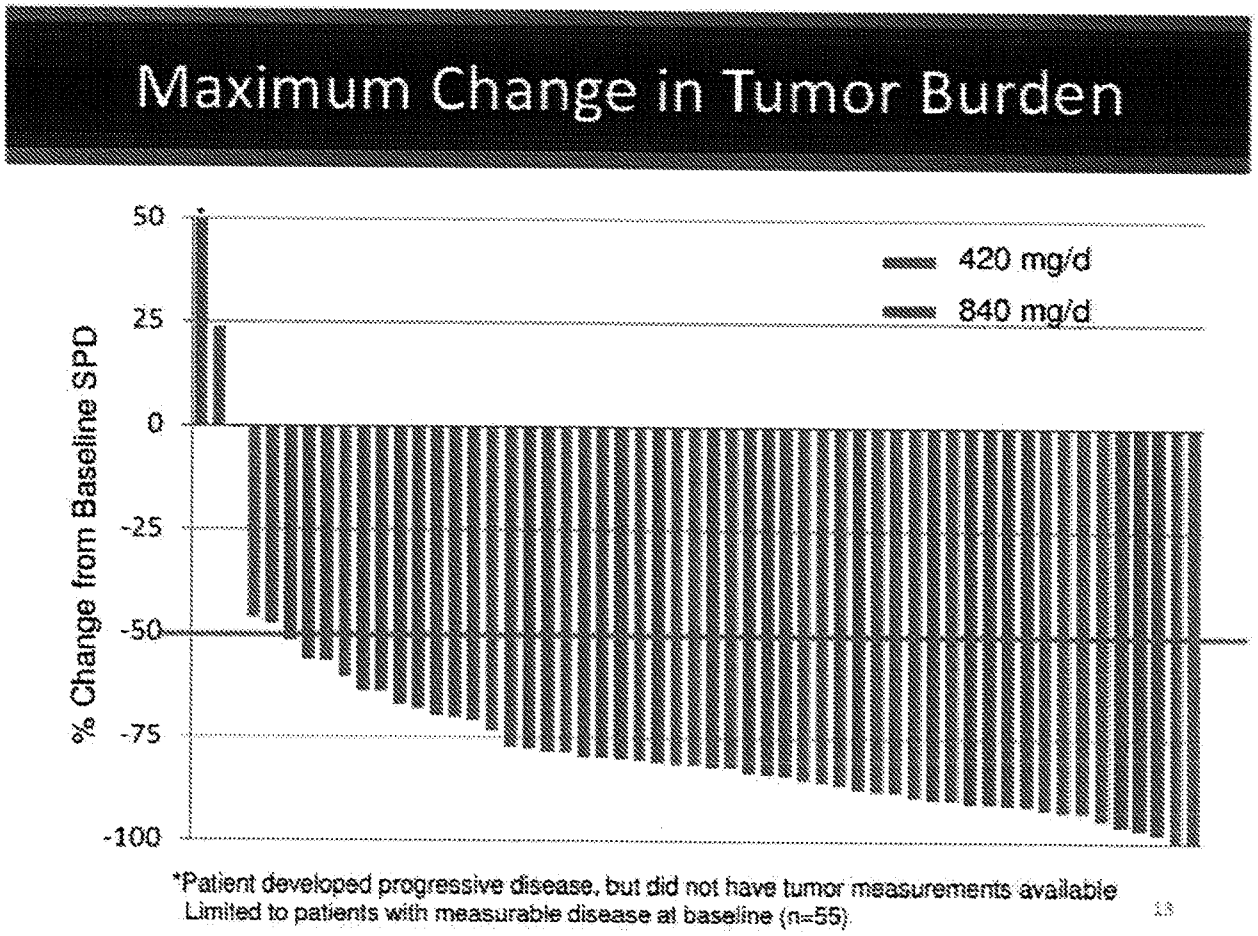
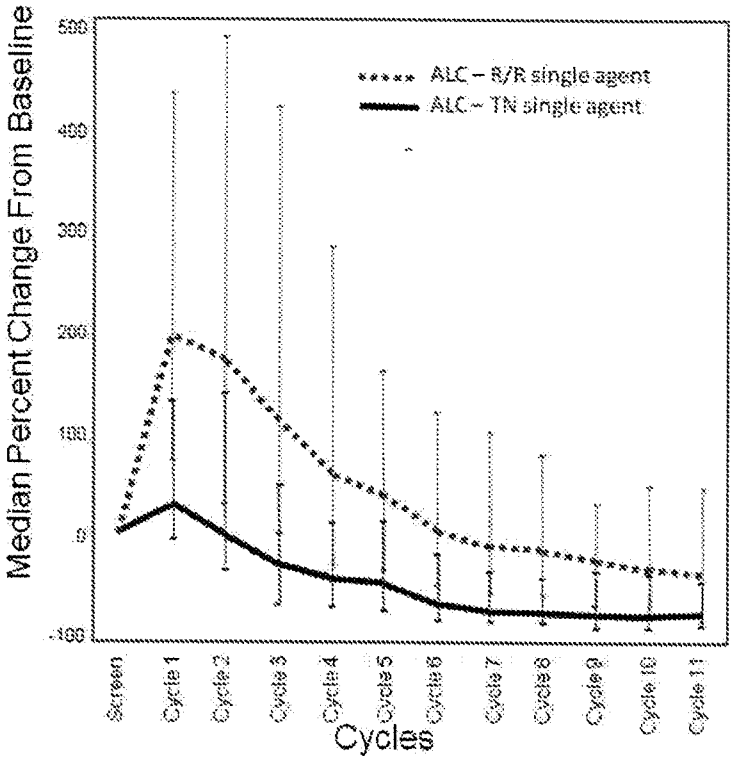

Maximum Change in Tumor Burden
50
25
0
-25
-50
-75
-100
% Change from Baseline SPD
420 mg/d
840 mg/d
*Patient developed progressive disease, but did not have tumor measurements available
Limited to patients with measurable disease at baseline (n=55)

Fig. 4


Median Percent Change From Baseline
ALC – R/R single agent
ALC – TN single agent
Screen
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
Cycle 7
Cycle 8
Cycle 9
Cycle 10
Cycle 11
Cycles

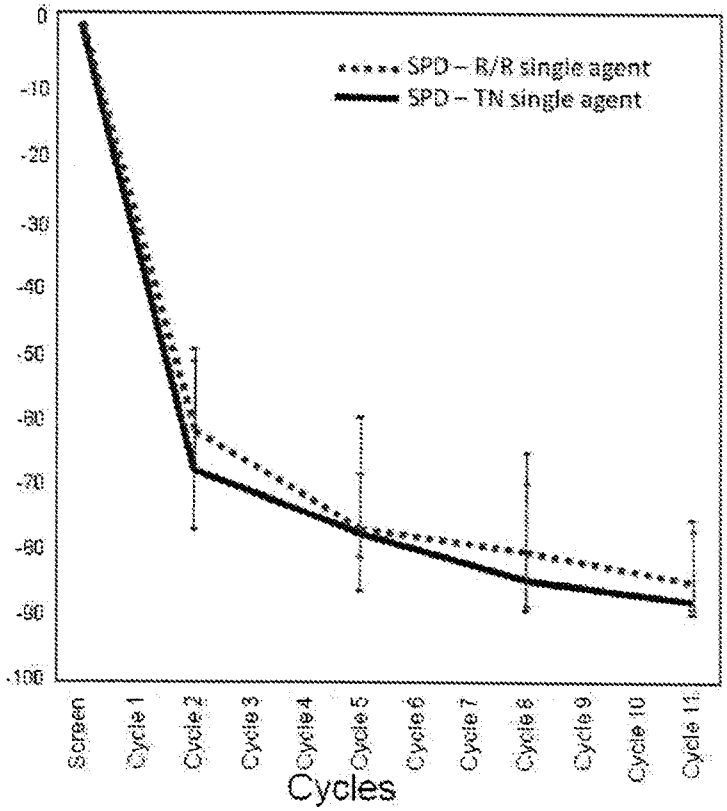

SPD – R/R single agent
SPD – TN single agent
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
Screen
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
Cycle 7
Cycle 8
Cycle 9
Cycle 10
Cycle 11
Cycles

Fig. 5

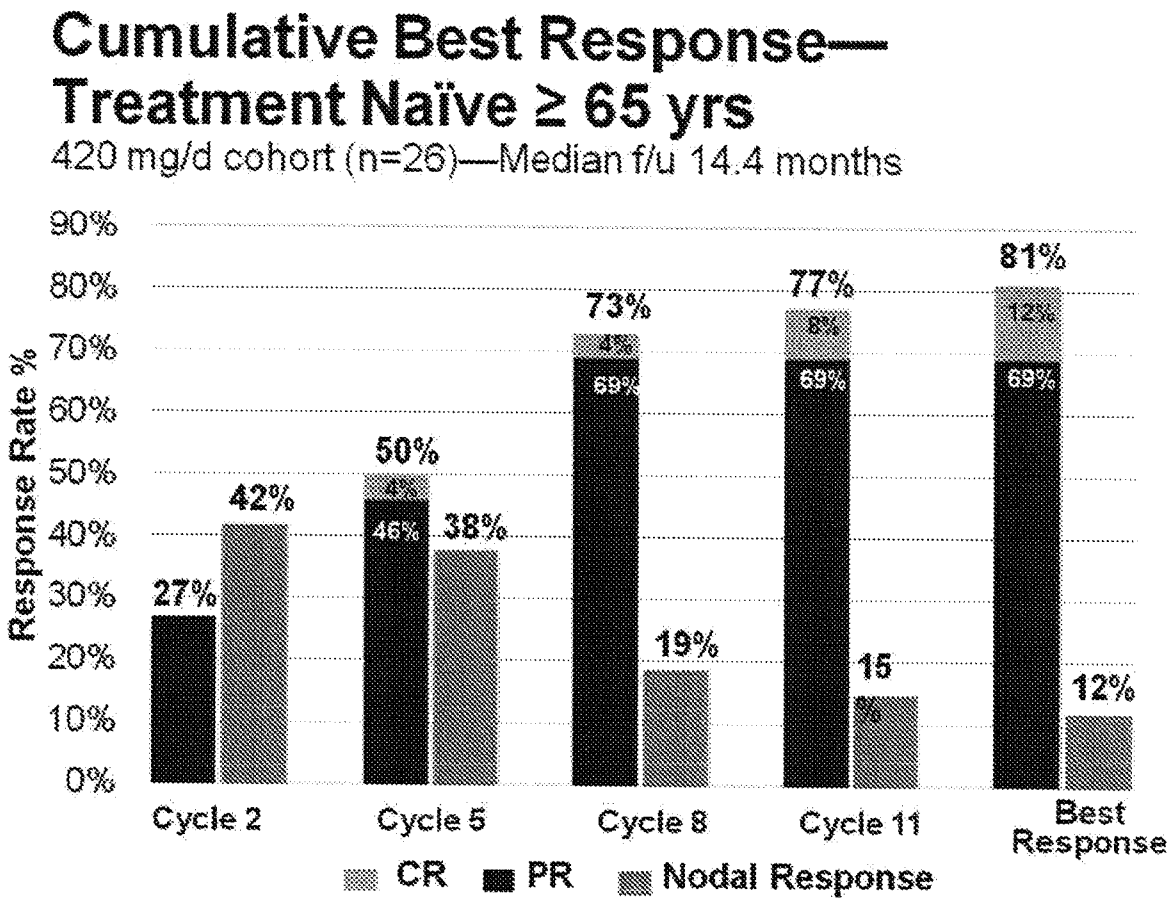

Cumulative Best Response—
Treatment Naïve ≥ 65 yrs
420 mg/d cohort (n=26)—Median f/u 14.4 months
Response Rate %
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
27%
42%
50%
4%
46%
38%
73%
4%
69%
19%
77%
8%
69%
15
%
81%
12%
69%
12%
Cycle 2
Cycle 5
Cycle 8
Cycle 11
Best Response
CR
PR
Nodal Response

Fig. 6

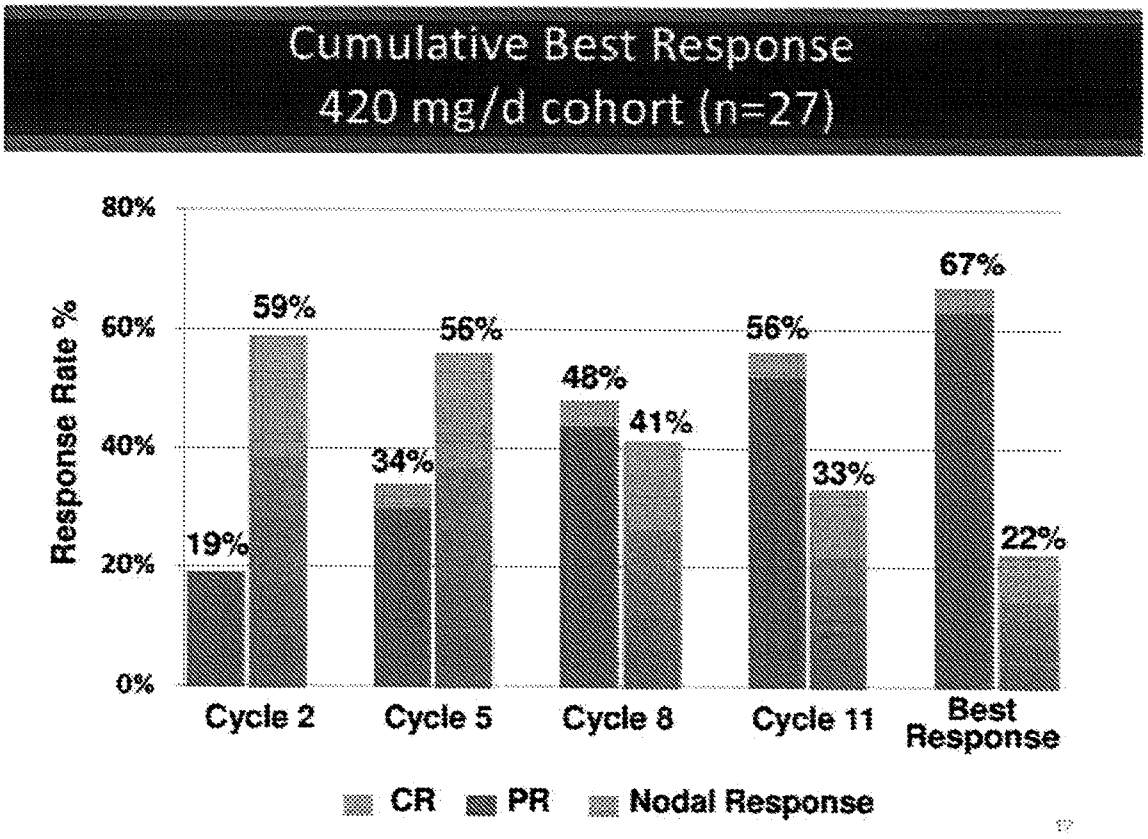

Cumulative Best Response
420 mg/d cohort (n=27)
Response Rate %
80%
60%
40%
20%
0%
19%
59%
34%
56%
48%
41%
56%
33%
67%
22%
Cycle 2
Cycle 5
Cycle 8
Cycle 11
Best Response
CR
PR
Nodal Response

Fig. 7

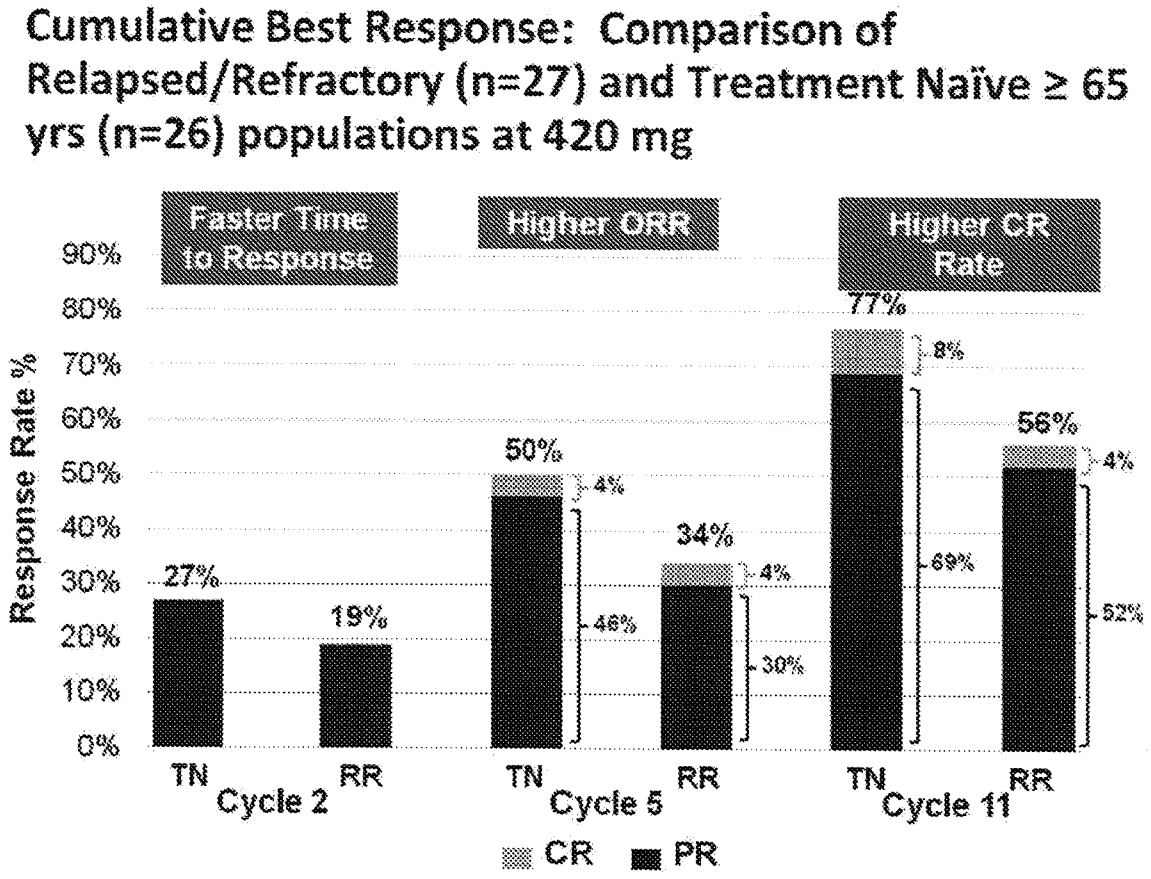
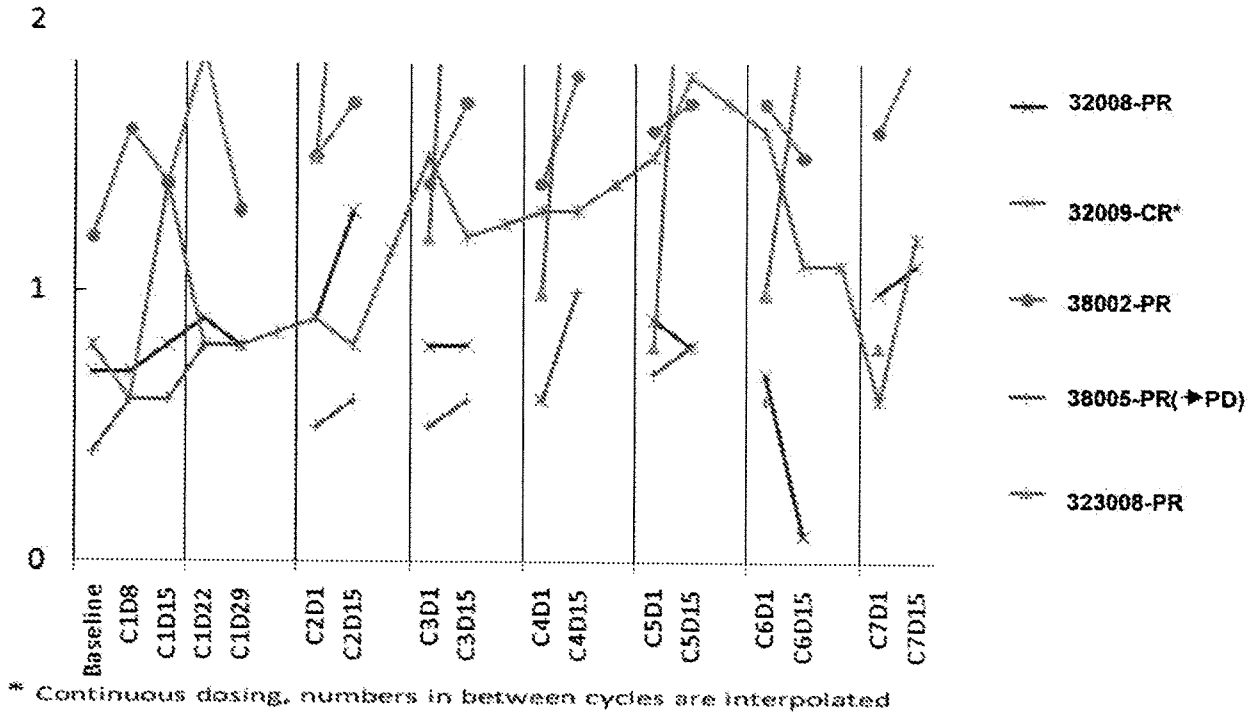
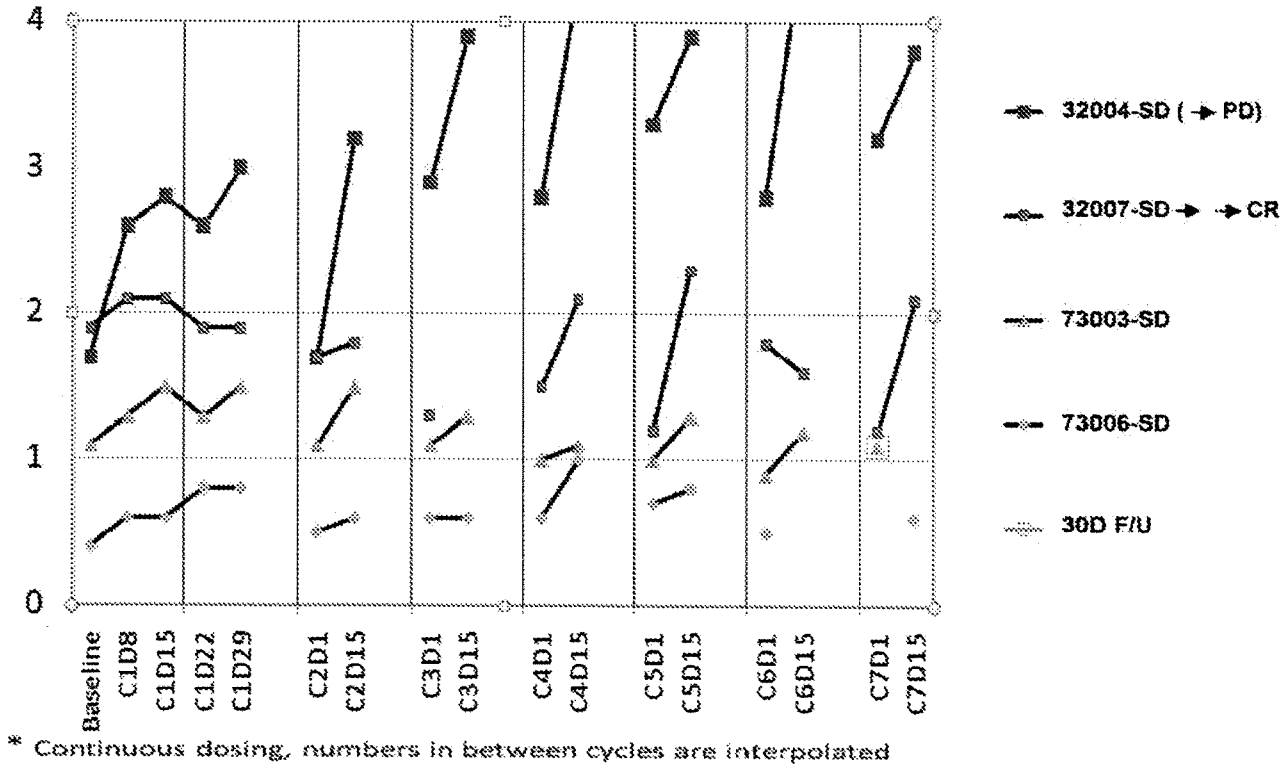

Cumulative Best Response: Comparison of Relapsed/Refractory (n=27) and Treatment Naïve ≥ 65 yrs (n=26) populations at 420 mg
Faster Time to Response
Higher ORR
Higher CR Rate
Response Rate %
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
27%
19%
50%
4%
46%
34%
4%
30%
77%
8%
69%
56%
4%
52%
TN
RR
Cycle 2
Cycle 5
Cycle 11
CR
PR

Fig. 8



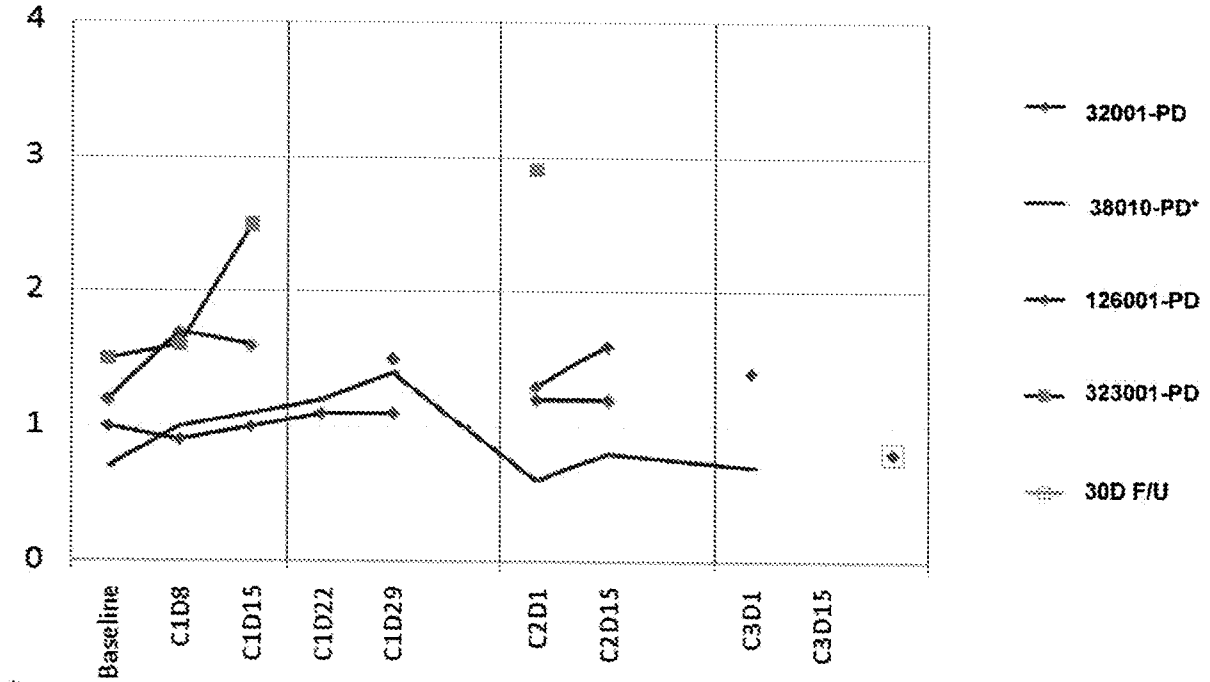
* Continuous dosing, numbers in between cycles are interpolated

Fig.9



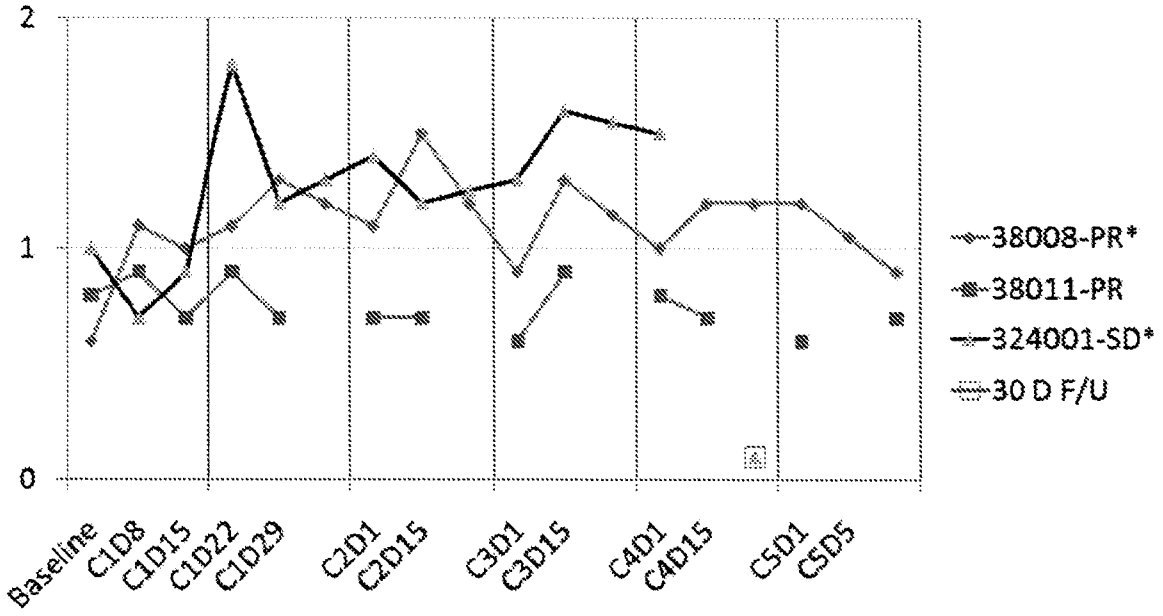
* Continuous dosing, numbers in between cycles are interpolated

Fig.10



* Continuous dosing, numbers in between cycles are interpolated

Fig.11



* Continuous dosing, numbers in between cycles are interpolated

Fig. 12

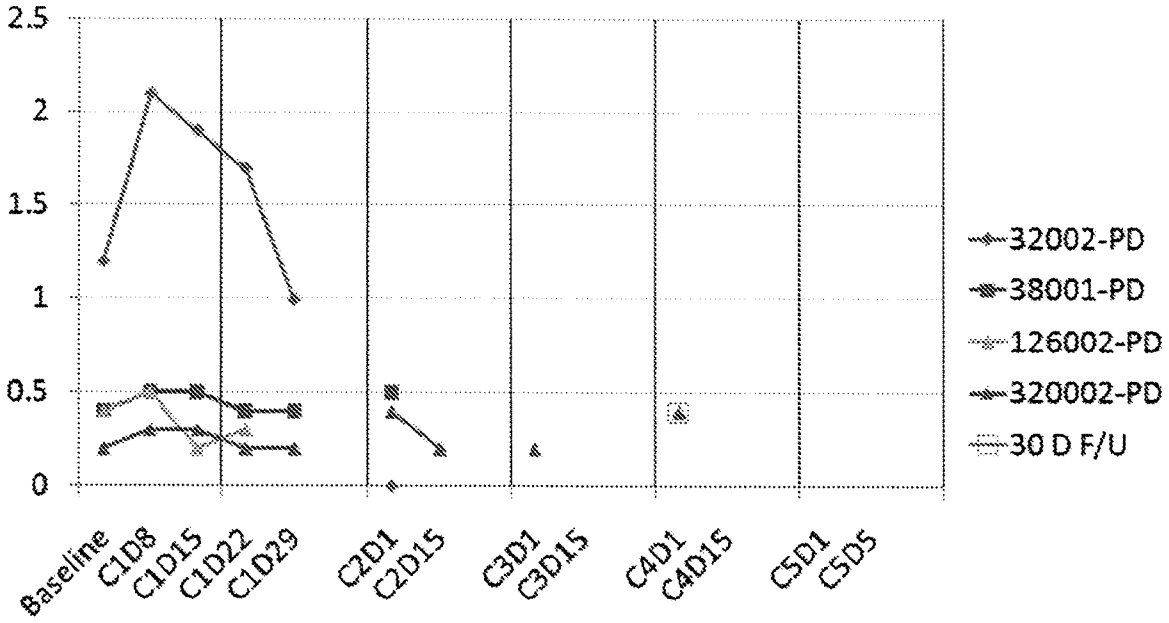
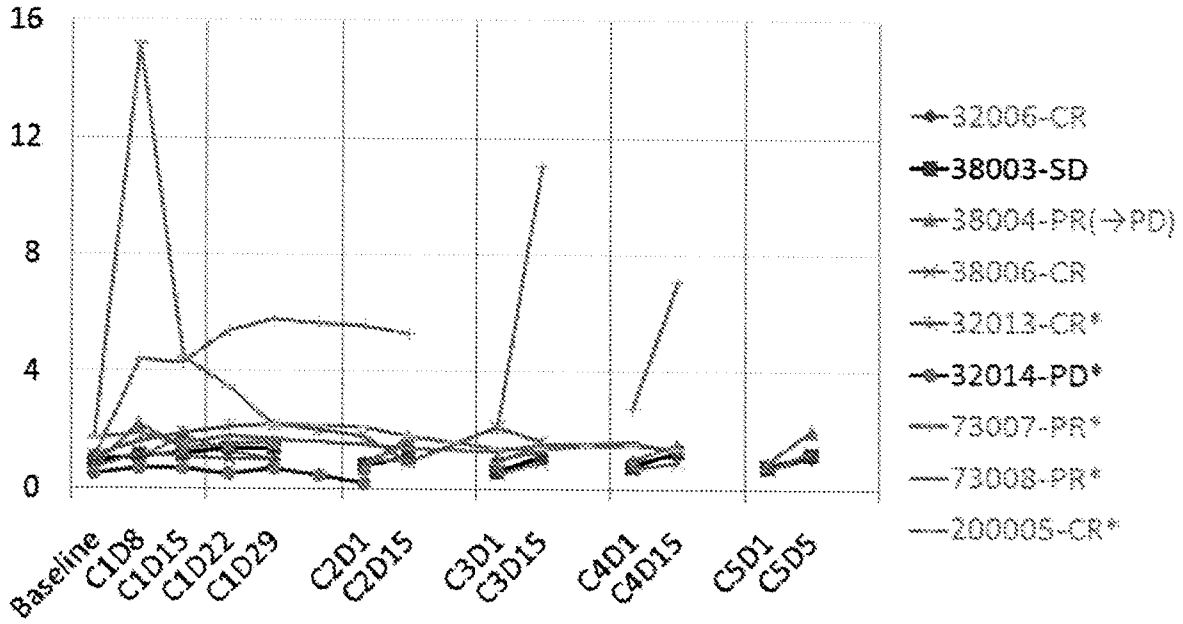
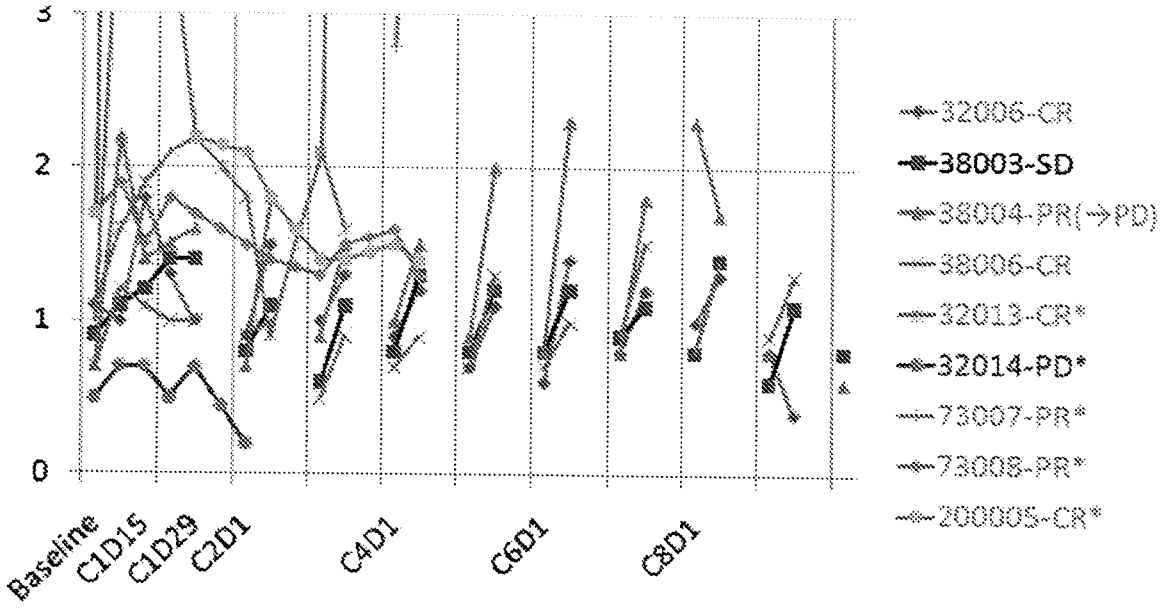

2.5
2
1.5
1
0.5
0
Baseline
C1D8
C1D15
C1D22
C1D29
C2D1
C2D15
C3D1
C3D15
C4D1
C4D15
C5D1
C5D5
32002-PD
38001-PD
126002-PD
320002-PD
30 D F/U

Fig. 13



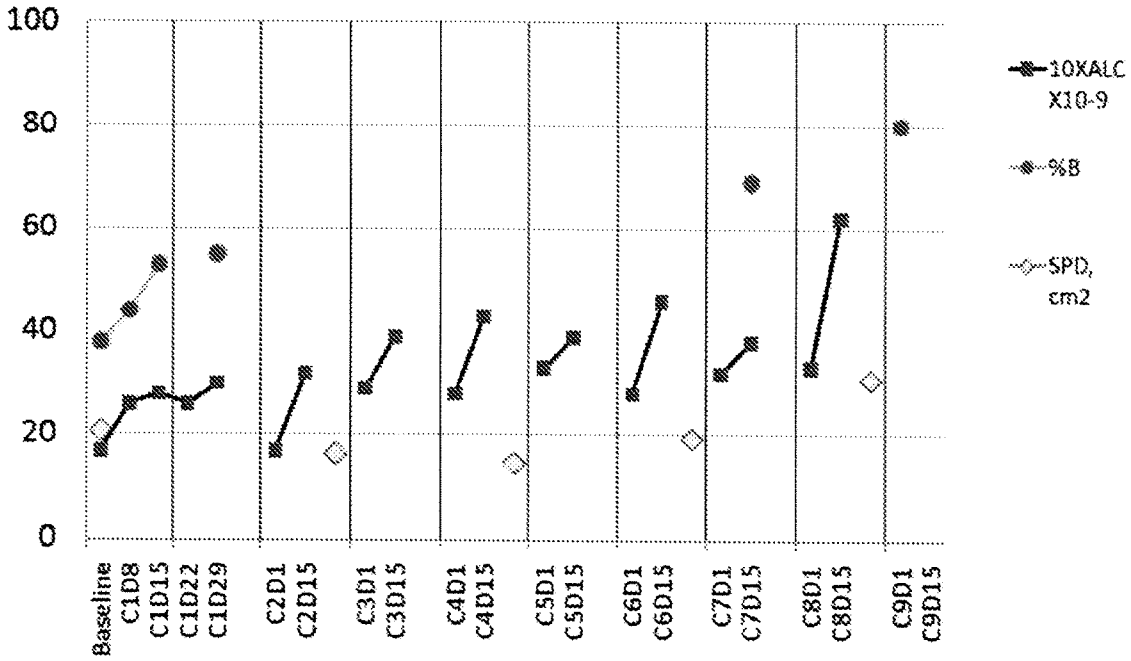
* Continuous dosing, numbers in between cycles are interpolated

Fig. 14



* Continuous dosing, numbers in between cycles are interpolated

Fig. 15



* Continuous dosing, numbers in between cycles are interpolated

Fig. 16

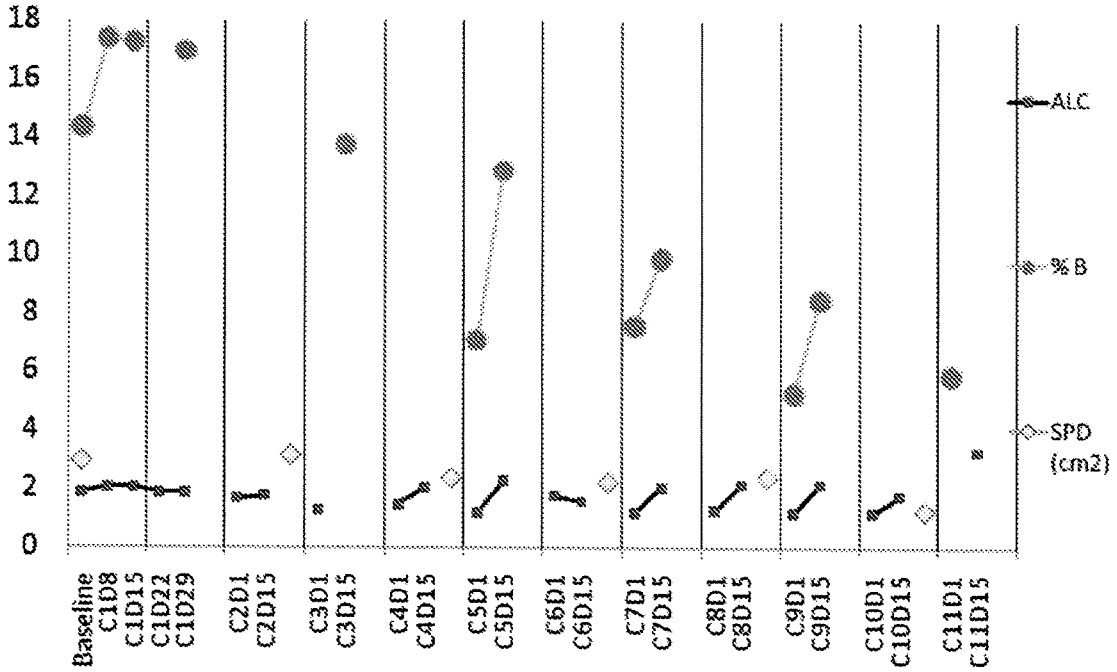

18
16
14
12
10
8
6
4
2
0
ALC
% B
SPD (cm2)
Baseline
C1D8
C1D15
C1D22
C1D29
C2D1
C2D15
C3D1
C3D15
C4D1
C4D15
C5D1
C5D15
C6D1
C6D15
C7D1
C7D15
C8D1
C8D15
C9D1
C9D15
C10D1
C10D15
C11D1
C11D15

Fig. 17

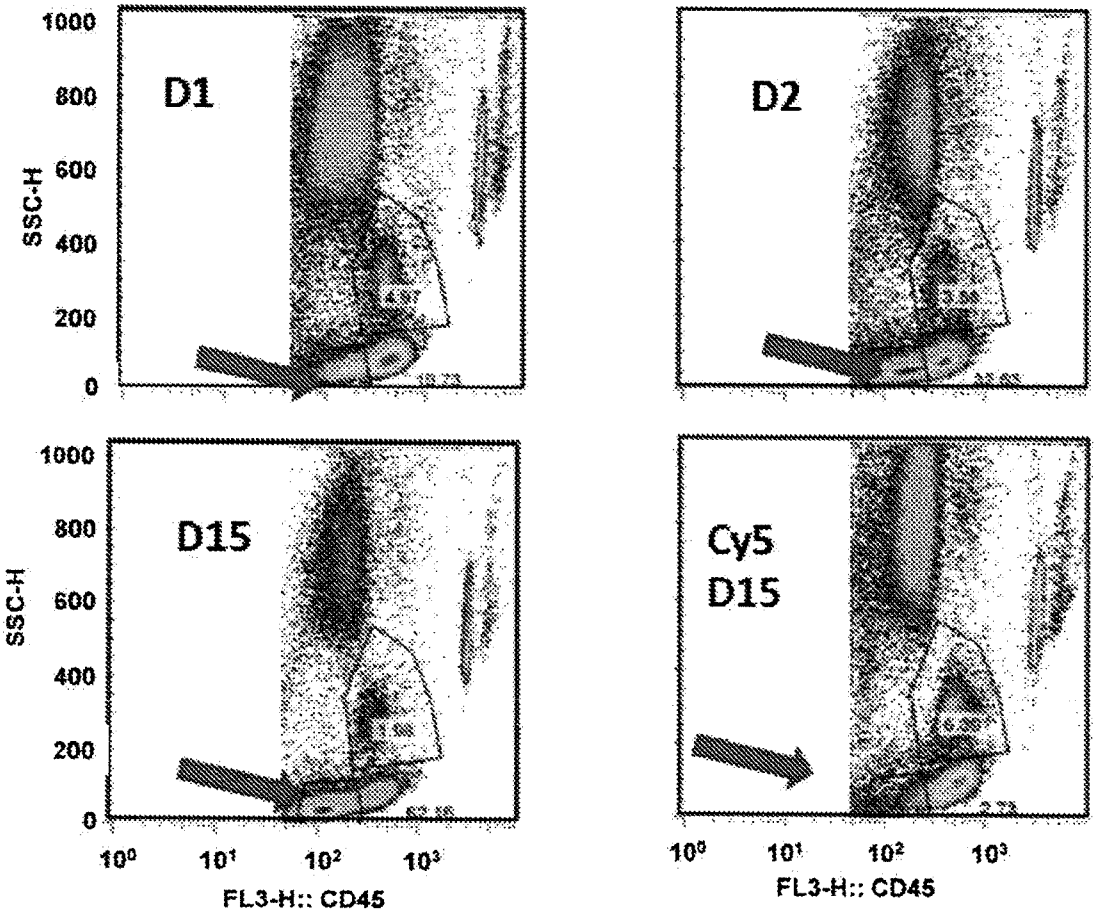

D1
D2
D15
Cy5
D15
SSC-H
1000
800
600
400
200
0
10^0
10^1
10^2
10^3
FL3-H:: CD45

Fig. 18

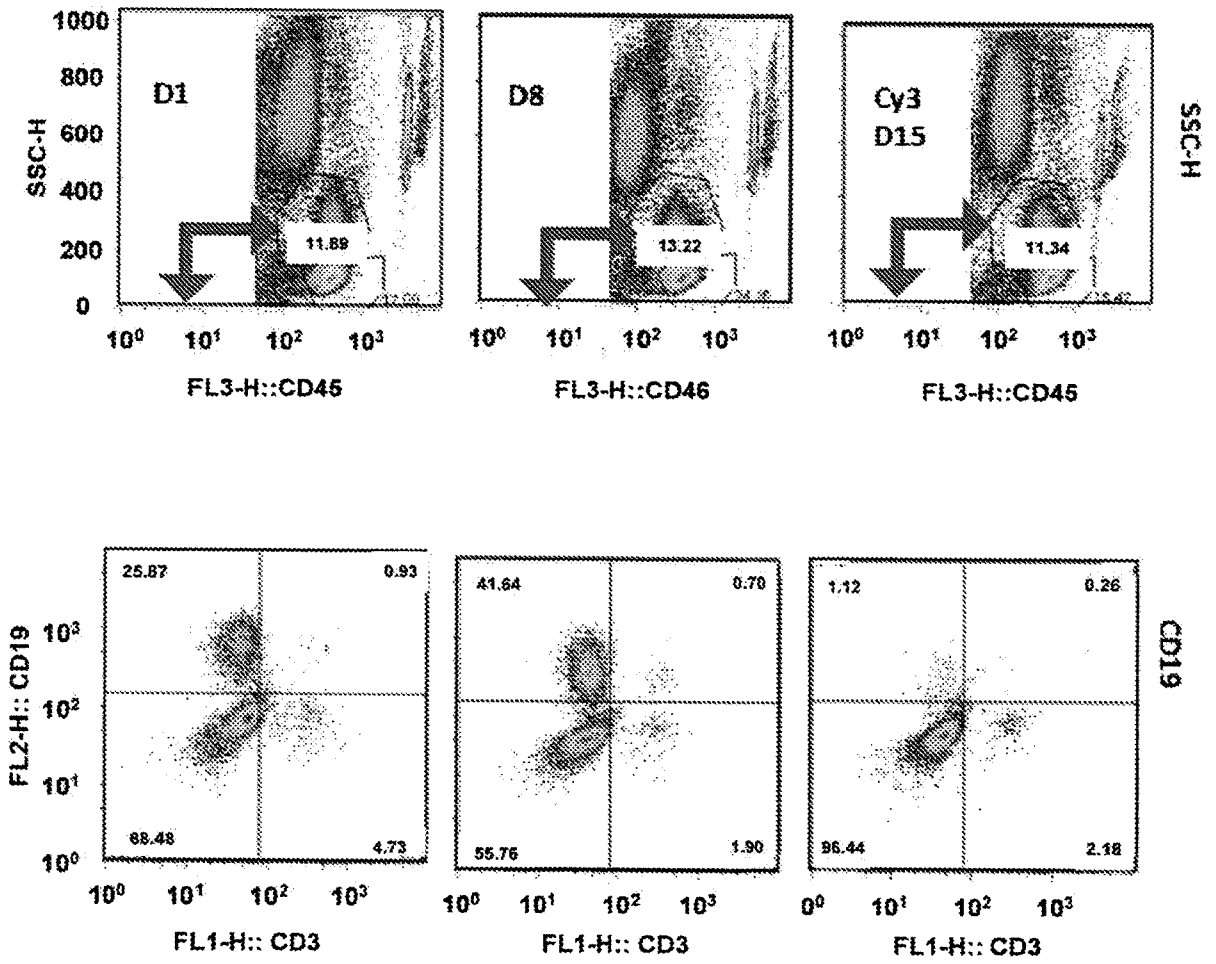

D1
D8
Cy3
D15
SSC-H
11.89
13.22
11.34
FL3-H::CD45
FL3-H::CD46
FL3-H::CD45
25.87
0.93
68.48
4.73
41.64
0.70
55.76
1.90
1.12
0.26
96.44
2.18
FL2-H:: CD19
FL1-H:: CD3
CD19

Fig. 19

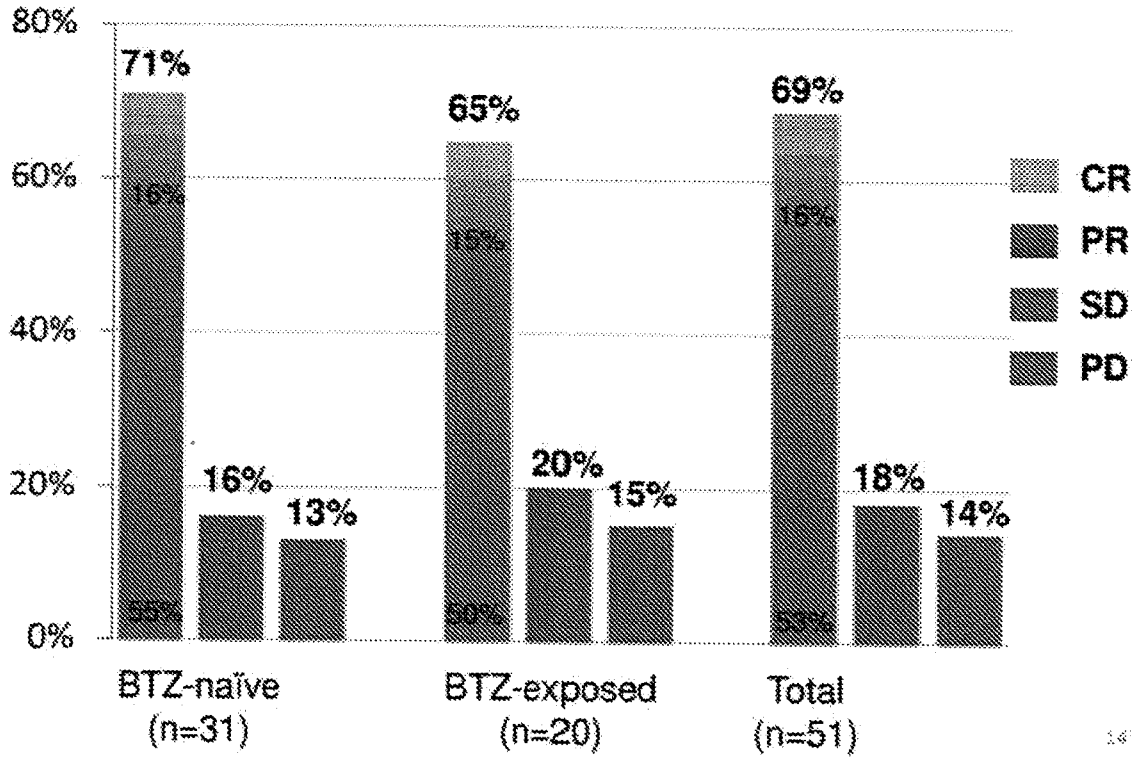
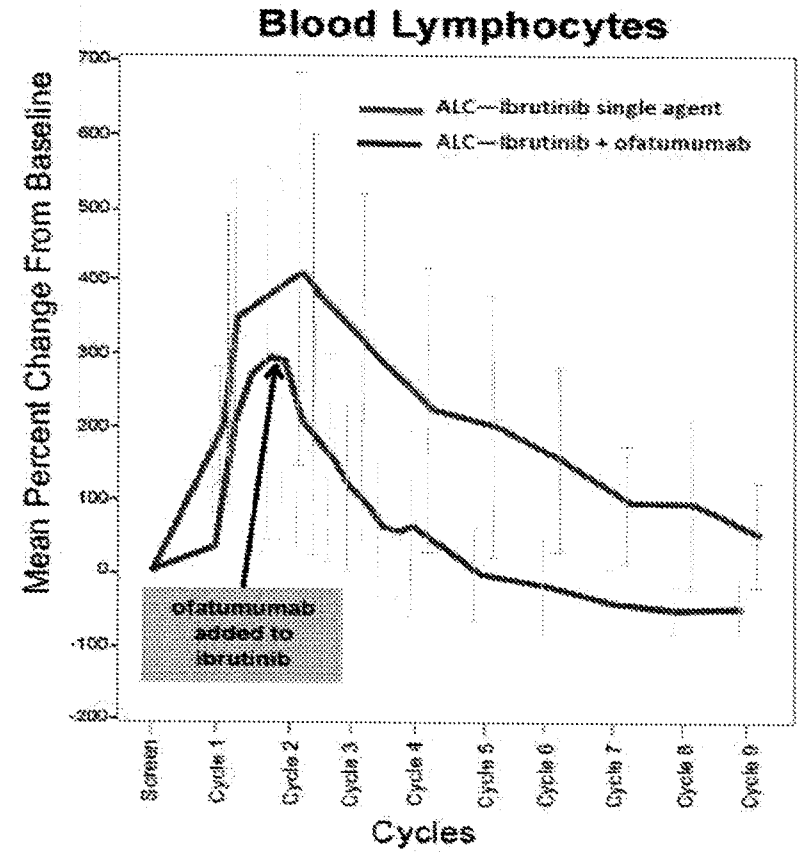

80%
60%
40%
20%
0%
71%
16%
55%
16%
13%
65%
15%
50%
20%
15%
69%
16%
53%
18%
14%
CR
PR
SD
PD
BTZ-naïve
(n=31)
BTZ-exposed
(n=20)
Total
(n=51)

Fig. 20


Blood Lymphocytes
Mean Percent Change From Baseline
ALC—ibrutinib single agent
ALC—ibrutinib + ofatumumab
ofatumumab added to ibrutinib
Screen
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
Cycle 7
Cycle 8
Cycle 9
Cycles

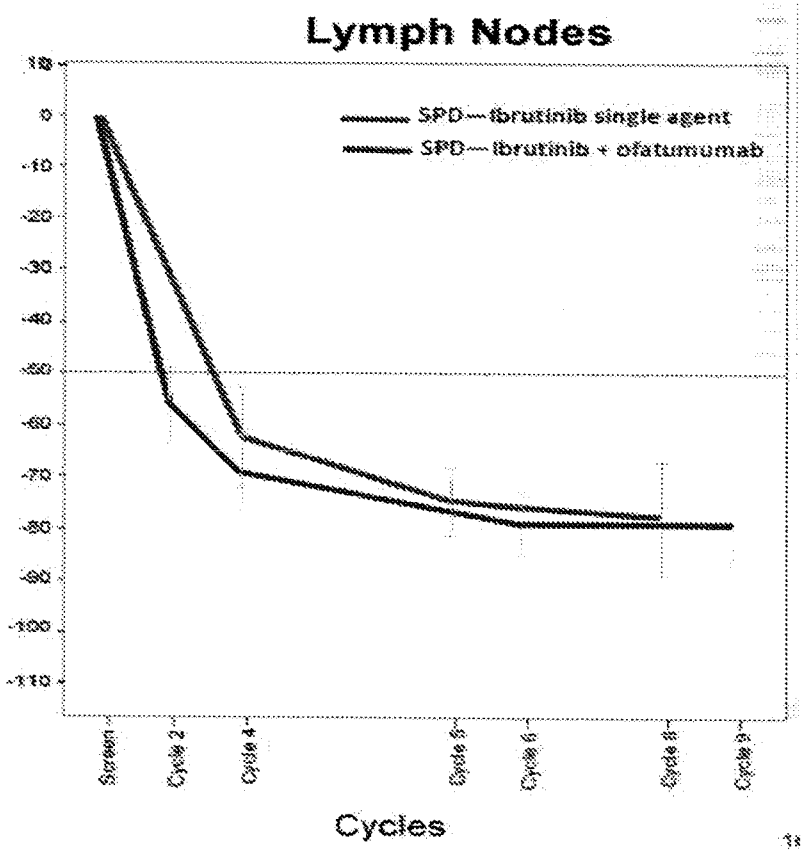
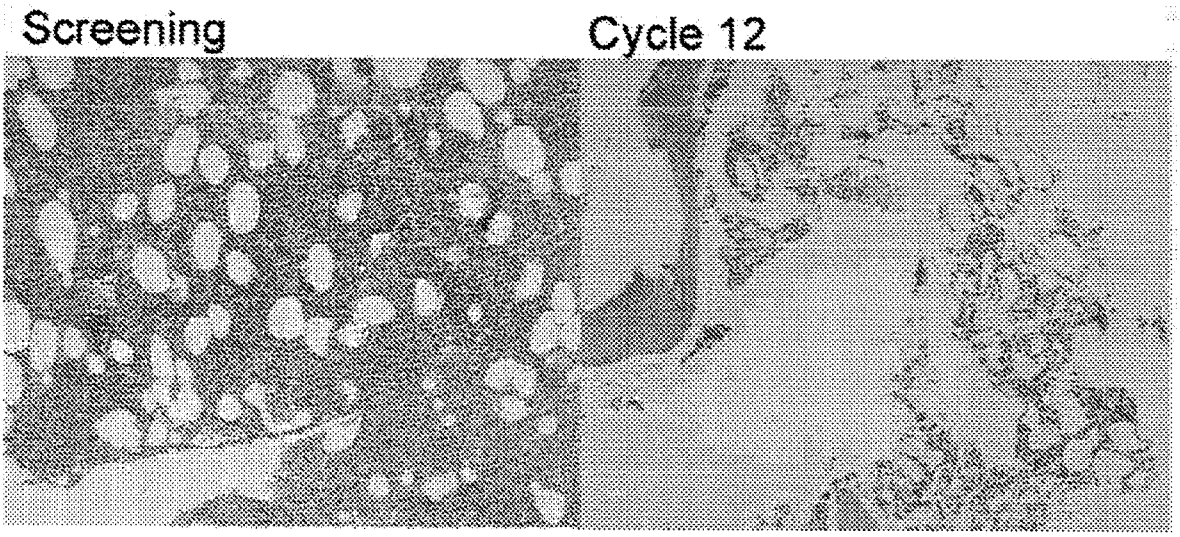
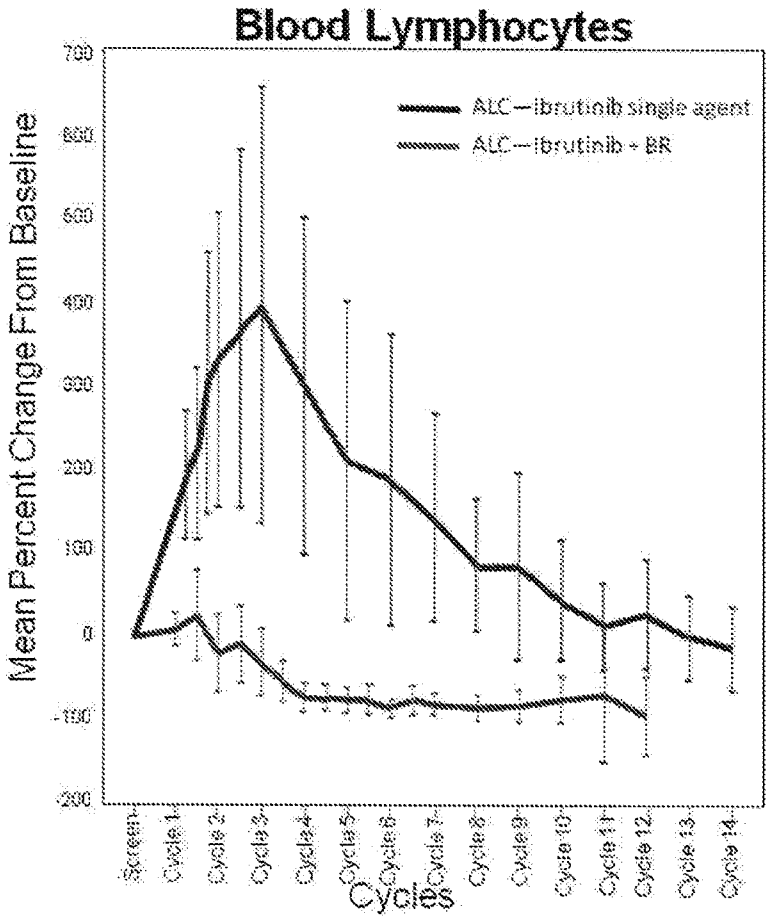

Lymph Nodes
SPD—ibrutinib single agent
SPD—ibrutinib + ofatumumab
Screen
Cycle 2
Cycle 4
Cycle 6
Cycle 8
Cycle 9
Cycles

Fig. 21



77-yo man with del17p, C1D1 ALC 145; C12D1 ALC 5

Fig. 22


Blood Lymphocytes
Mean Percent Change From Baseline
ALC—ibrutinib single agent
ALC—ibrutinib + BR
700
600
500
400
300
200
100
0
-100
-200
Screen
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
Cycle 7
Cycle 8
Cycle 9
Cycle 10
Cycle 11
Cycle 12
Cycle 13
Cycle 14
Cycles

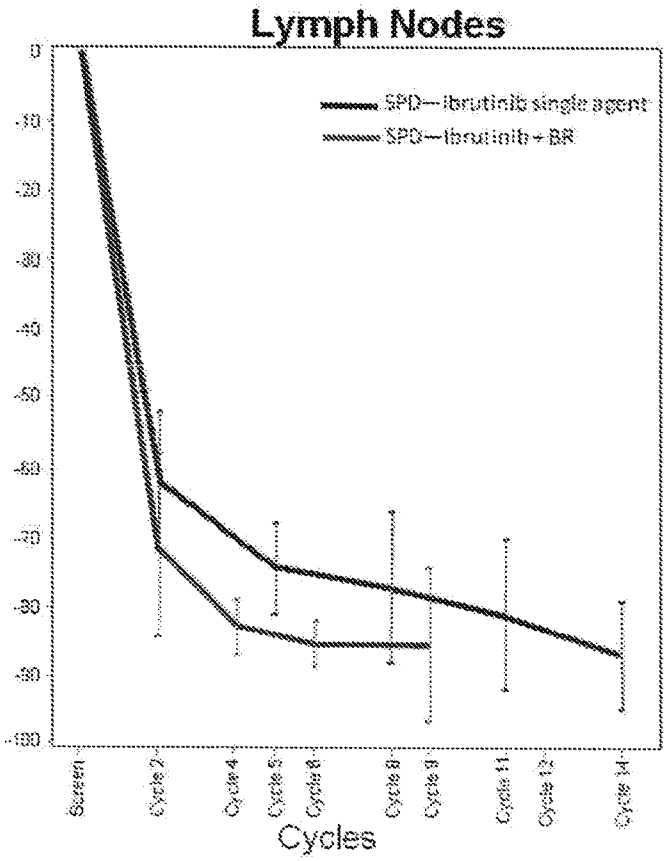
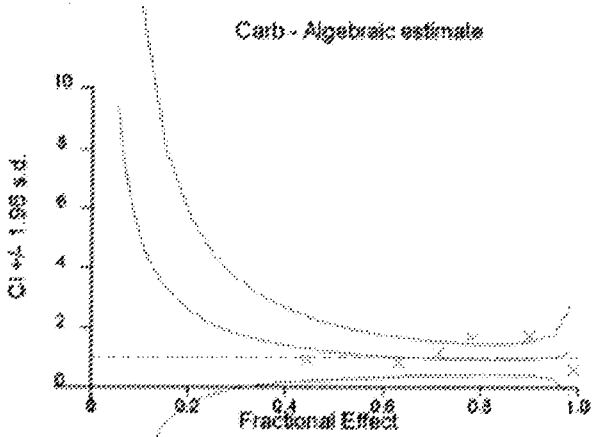

Lymph Nodes
SPD—ibrutinib single agent
SPD—ibrutinib + BR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
Screen
Cycle 2
Cycle 4
Cycle 5
Cycle 6
Cycle 8
Cycle 9
Cycle 11
Cycle 12
Cycle 14
Cycles

Fig. 23

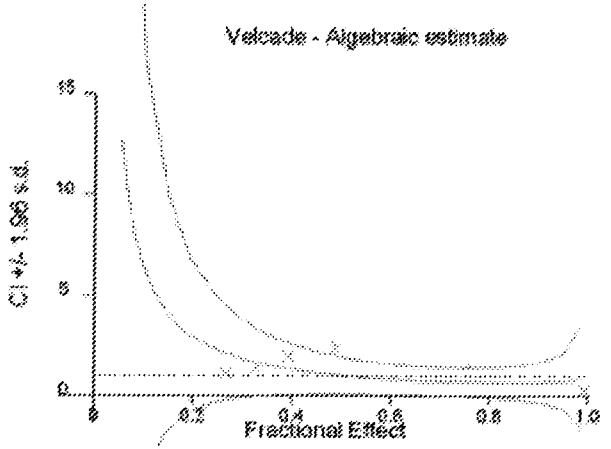
	Btk inhibitor (uM)	Carb(uM)
GI50	0.096	15.382
r:	0.994	0.990

	Btk inhibitor (uM)	Velcade(uM)
GI50	0.176	5.434
r:	0.986	0.850



CI For experimental values

Btk inhibitor (uM)	Carb (uM)	Fa	CI
0.03125	6.25	0.443223	0.954
0.0625	12.5	0.632339	0.828
0.125	25	0.715772	1.165
0.25	50	0.763398	1.718
0.5	100	0.899868	1.74
1	200	0.993211	0.564

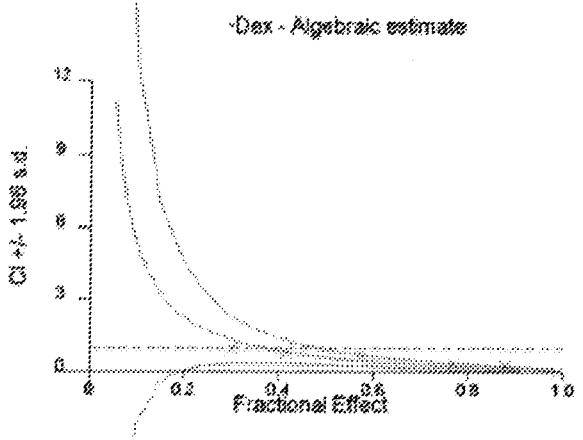


CI For experimental values

Btk inhibitor (uM)	Velcade (nM)	Fa	CI
0.03125	0.625	0.265657	1.16
0.0625	1.25	0.329518	1.487
0.125	2.5	0.394877	2.011
0.25	5	0.48706	2.488
0.5	10	0.756802	1.505
1	20	0.99494	0.314

Fig. 24

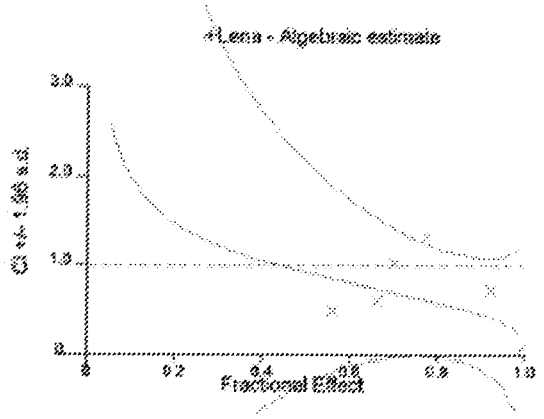
	Btk Inhibitor (uM)	Dex(uM)
GI50	0.177	45.850
r:	0.964	0.991



CI For experimental values

Btk Inhibitor (uM)	Dex (uM)	Fa	CI
0.03125	3.125	0.300998	0.953
0.0625	6.25	0.41699	0.83
0.125	12.5	0.577051	0.606
0.25	25	0.769886	0.337
0.5	50	0.879476	0.249
1	100	0.988855	0.035

	Btk Inhibitor (uM)	Lena(uM)
GI50	0.183	12.653
r:	0.980	0.795

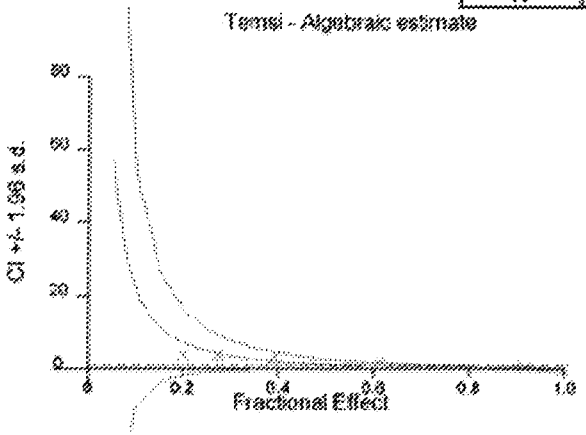


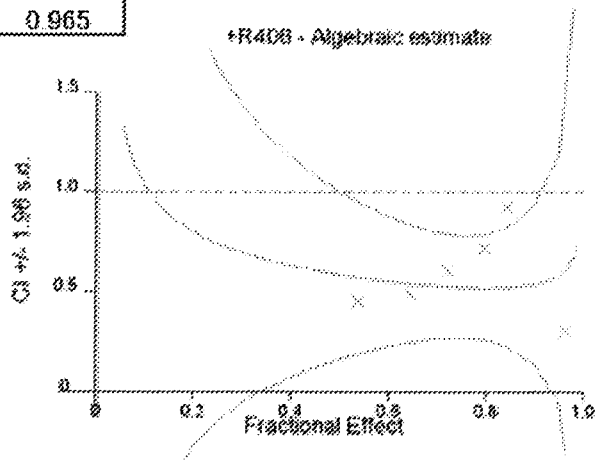
CI For experimental values

Btk Inhibitor (uM)	Lena (uM)	Fa	CI
0.03125	6.25	0.558238	0.511
0.0625	12.5	0.663338	0.621
0.125	25	0.698831	1.034
0.25	50	0.773021	1.349
0.5	100	0.918456	0.722
1	200	0.994404	0.073

Fig. 25

	Btk inhibitor (uM)	Temsi(uM)	R406(uM)
GI50	0.099	1.774	12.750
r:	0.987	0.836	0.965





CI For experimental values

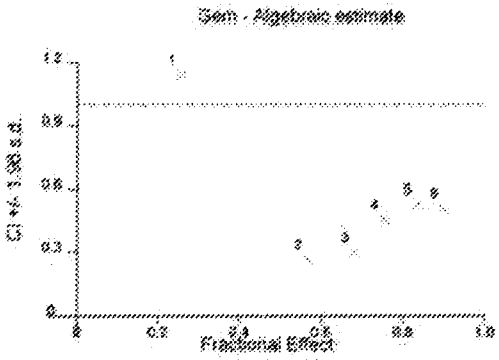
Btk inhibitor (uM)	Temsi (uM)	Fa	CI
0.03125	0.3125	0.200943	3.779
0.0625	0.625	0.275462	3.93
0.125	1.25	0.394234	3.529
0.25	2.5	0.614251	2.244
0.5	5	0.91765	0.907
1	10	0.99999	0.016

CI For experimental values

Btk inhibitor (uM)	R406 (uM)	Fa	CI
0.03125	3.125	0.53672	0.455
0.0625	6.25	0.64571	0.484
0.125	12.5	0.722258	0.6
0.25	25	0.795651	0.709
0.5	50	0.844892	0.927
1	100	0.960979	0.307

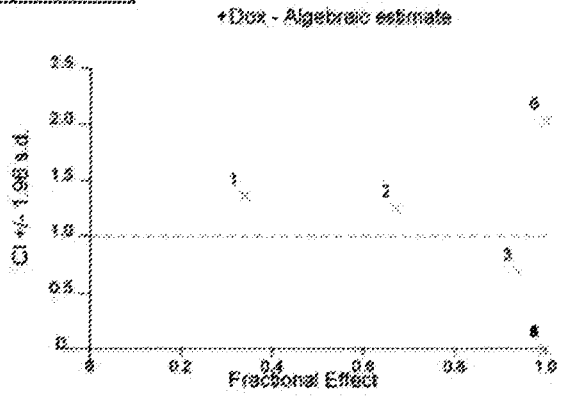
Fig. 26

	Btk inhibitor (uM)	Gem(uM)	Dox(uM)
GI50	0.247	0.005	0.006
r:	0.996	0.897	0.892



CI For experimental values

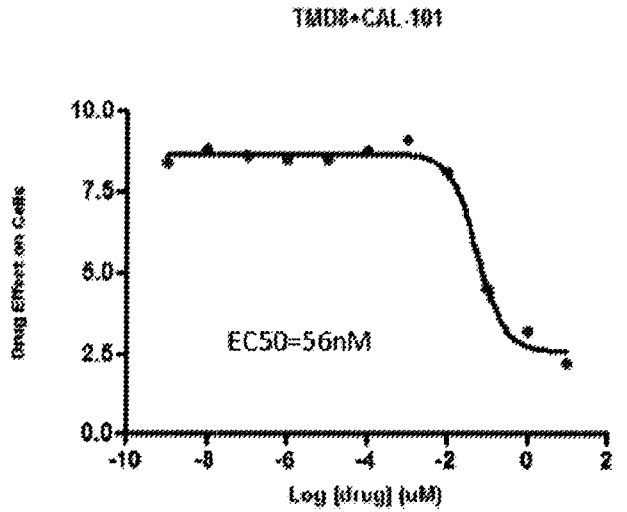
Btk inhibitor (uM)	Gem (uM)	Fa	CI
0.03125	0.000192	0.258111	1.144
0.0625	0.00096	0.569329	0.262
0.125	0.0048	0.683823	0.299
0.25	0.024	0.754917	0.456
0.5	0.12	0.836676	0.527
1	0.6	0.903074	0.51

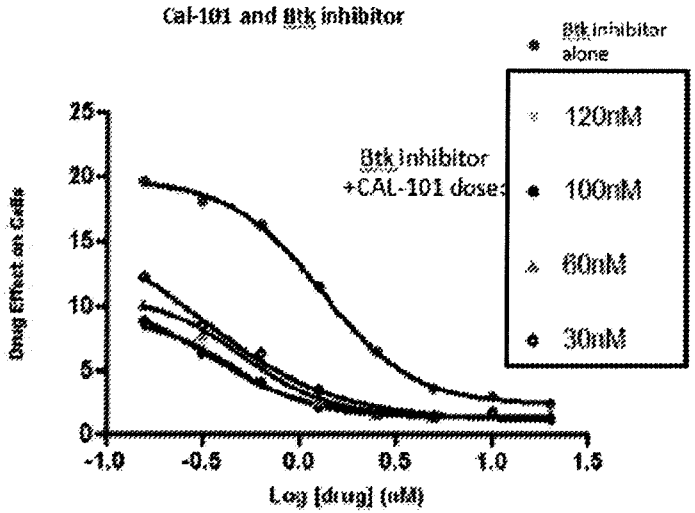


CI For experimental values

Btk inhibitor (uM)	Dox (uM)	Fa	CI
0.03125	0.0032	0.339005	1.358
0.0625	0.016	0.674194	1.256
0.125	0.08	0.939547	0.673
0.25	0.4	0.99999	0
0.5	2	0.99999	0.001
1	10	0.997935	2.032

Fig. 27





CI Values

Btk inhibitor (nM)	CAL-101 120nM	CAL-101 100nM	CAL-101 60nM	CAL-101 30nM
0.156	0.282	0.293	0.37	0.541
0.313	0.166	0.141	0.186	0.173
0.625	0.108	0.106	0.159	0.18
1.25	0.098	0.098	0.125	0.161
2.5	0.125	0.125	0.125	0.159
5	0.25	0.25	0.25	0.25
10	0.635	0.567	0.567	0.567
20	0.73	0.73	1.133	0.73

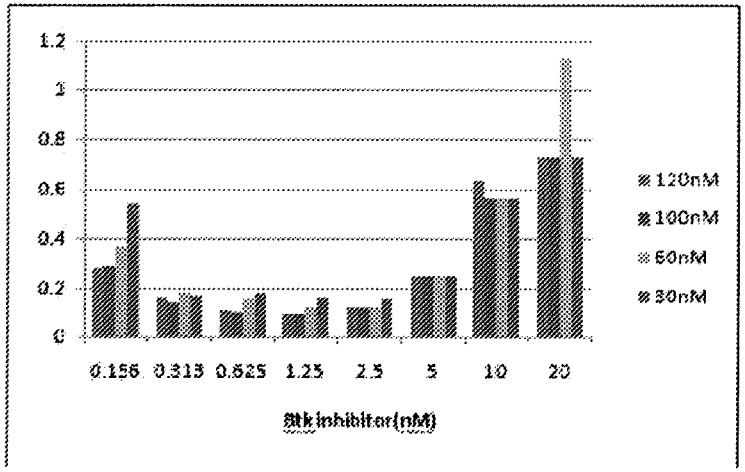
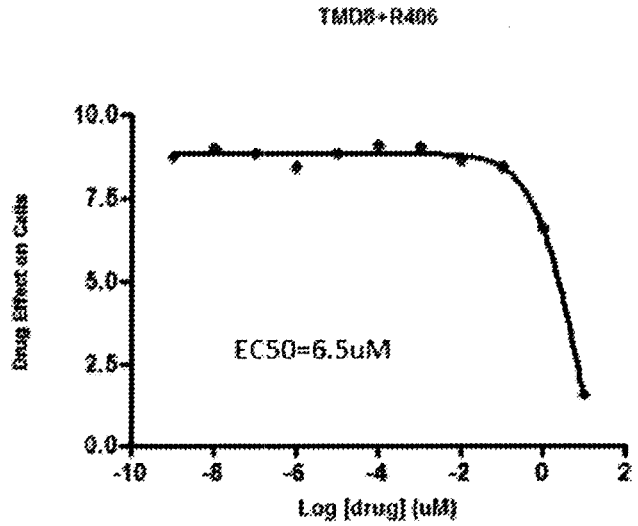
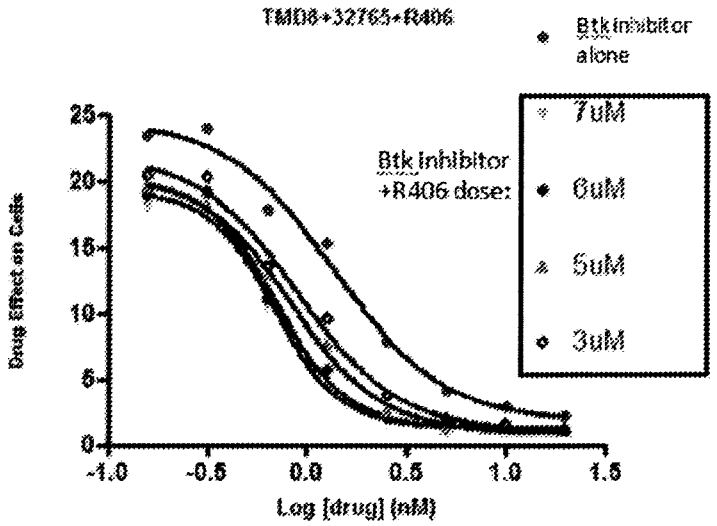


Fig. 28





CI Values

Btk inhibitor (nM)	R406 7uM	6uM	4uM	3uM
0.156	0.26	0.326	0.394	0.486
0.313	0.6	0.675	0.503	0.956
0.625	0.268	0.288	0.388	0.434
1.25	0.197	0.231	0.332	0.457
2.5	0.132	0.132	0.183	0.274
5	0.198	0.165	0.198	0.264
10	0.395	0.33	0.33	0.461
20	0.661	0.661	0.66	0.66

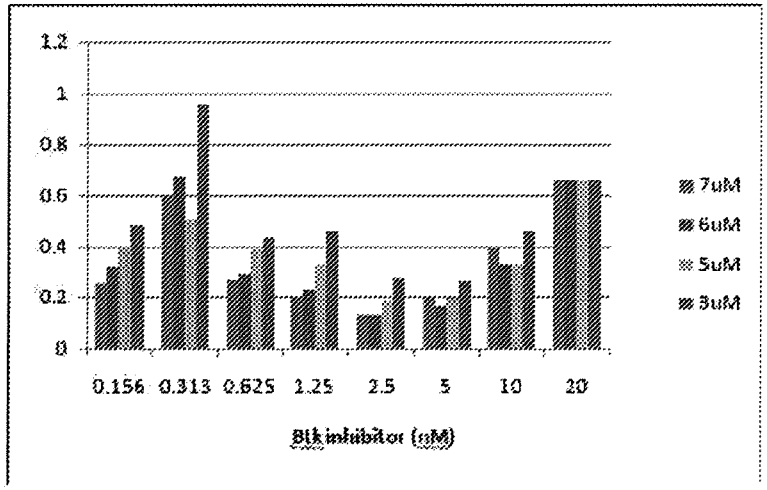
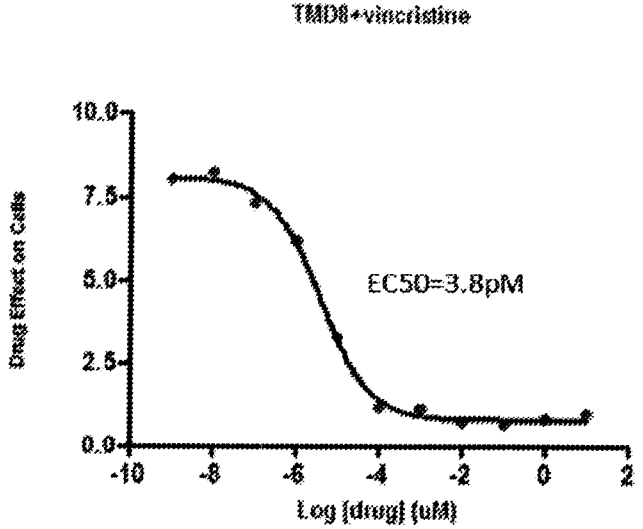
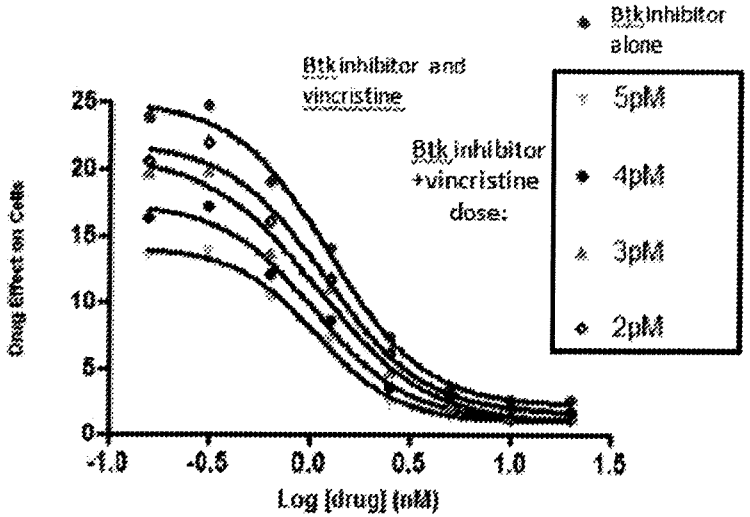


Fig. 29





CI Values

Btk inhibitor (nM)	Vincristine 5pM	4pM	3pM	2pM
0.156	0.512	0.976	2.746	2.837
0.313	0.67	1.449	3.14	8.636
0.625	0.429	0.587	0.748	1.096
1.25	0.391	0.503	0.774	0.798
2.5	0.221	0.308	0.424	0.678
5	0.237	0.354	0.353	0.474
10	0.395	0.394	0.471	0.704
20	0.788	0.788	0.94	1.094

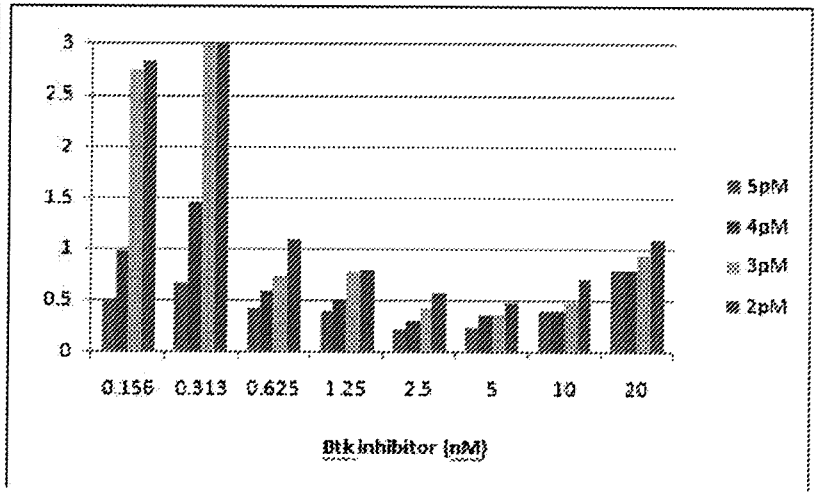
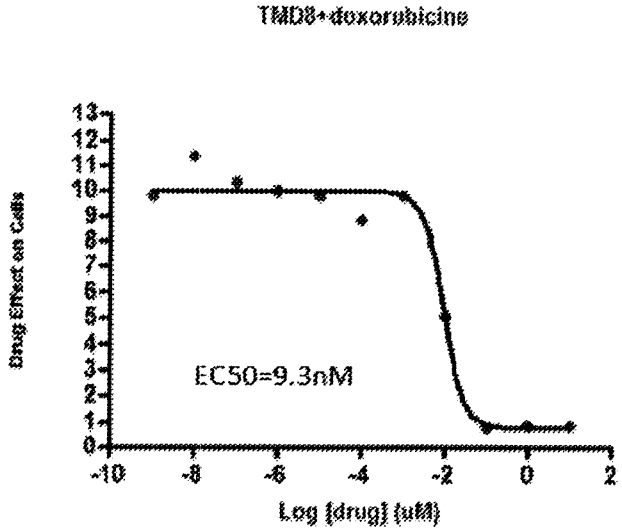
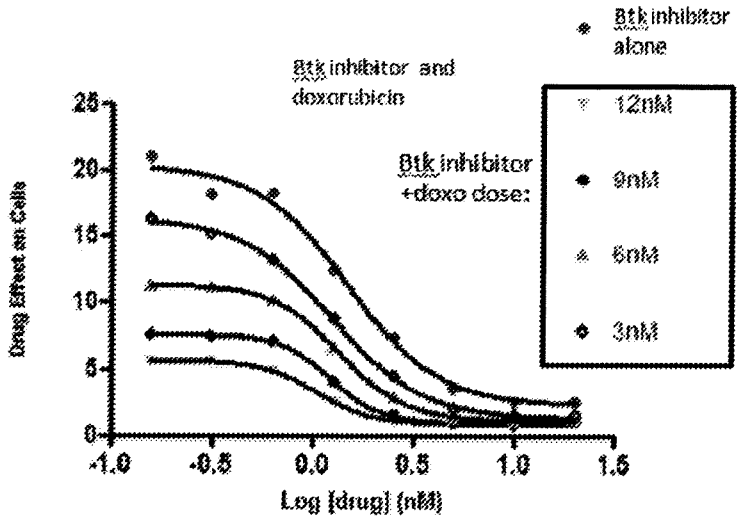


Fig. 30





CI Values

Btk inhibitor (nM)	Doxorubicin 12nM	9nM	6nM	3nM
0.156	1.633	1.745	2.102	2.659
0.313	1.622	1.738	2.138	2.302
0.625	1.46	1.709	2.004	1.877
1.25	0.873	1.05	1.283	1.157
2.5	0.474	0.481	0.654	0.699
5	0.418	0.374	0.436	0.489
10	0.534	0.484	0.559	0.602
20	0.987	0.936	1.034	1.105

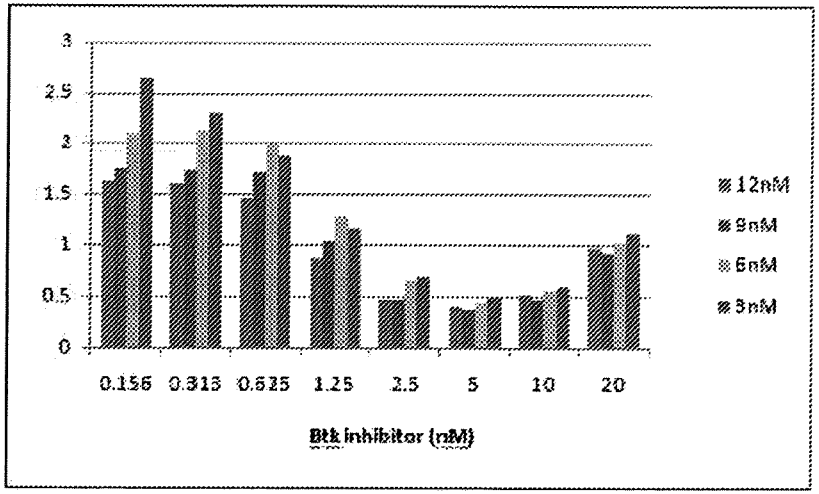
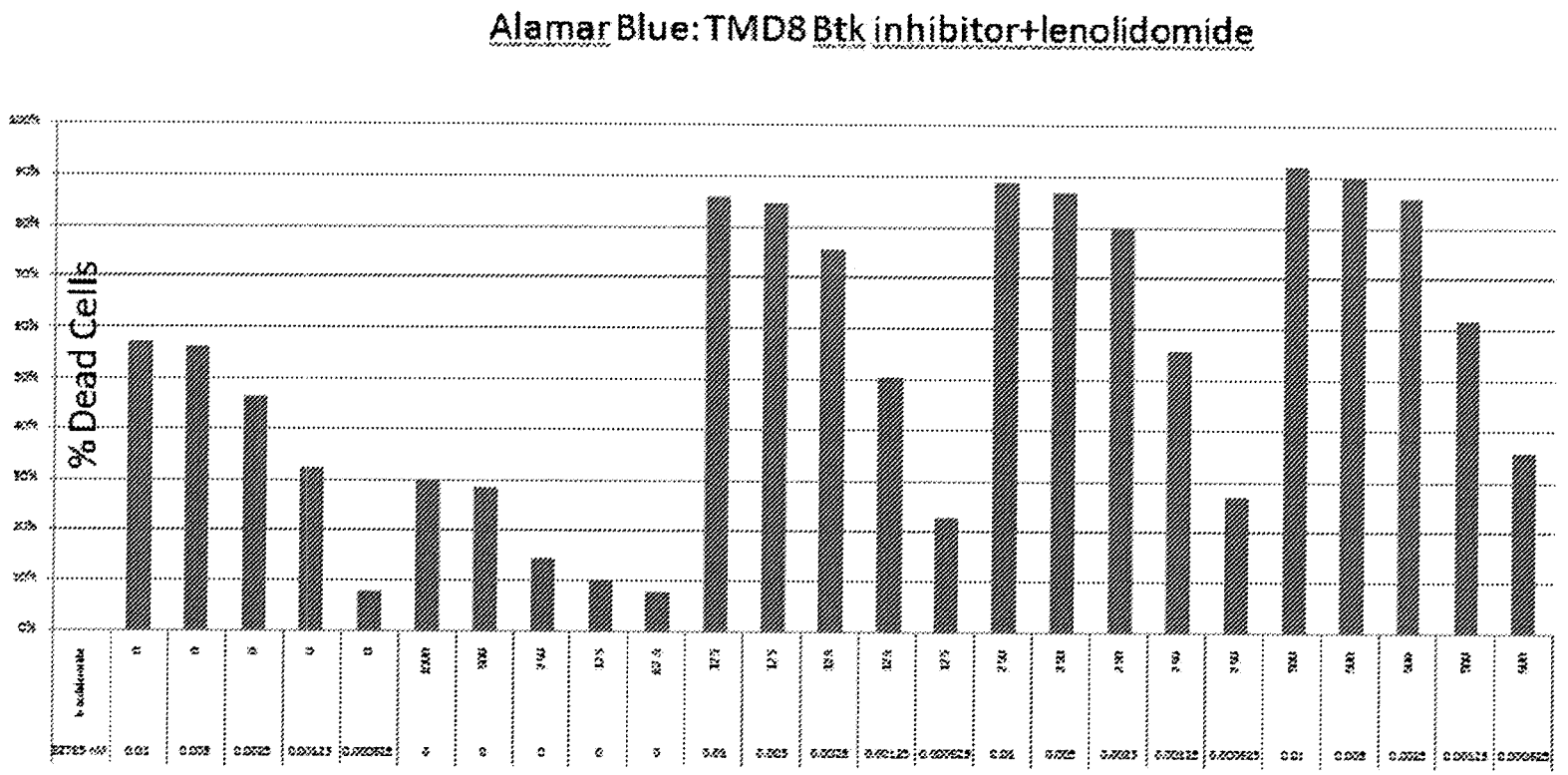


Fig. 31

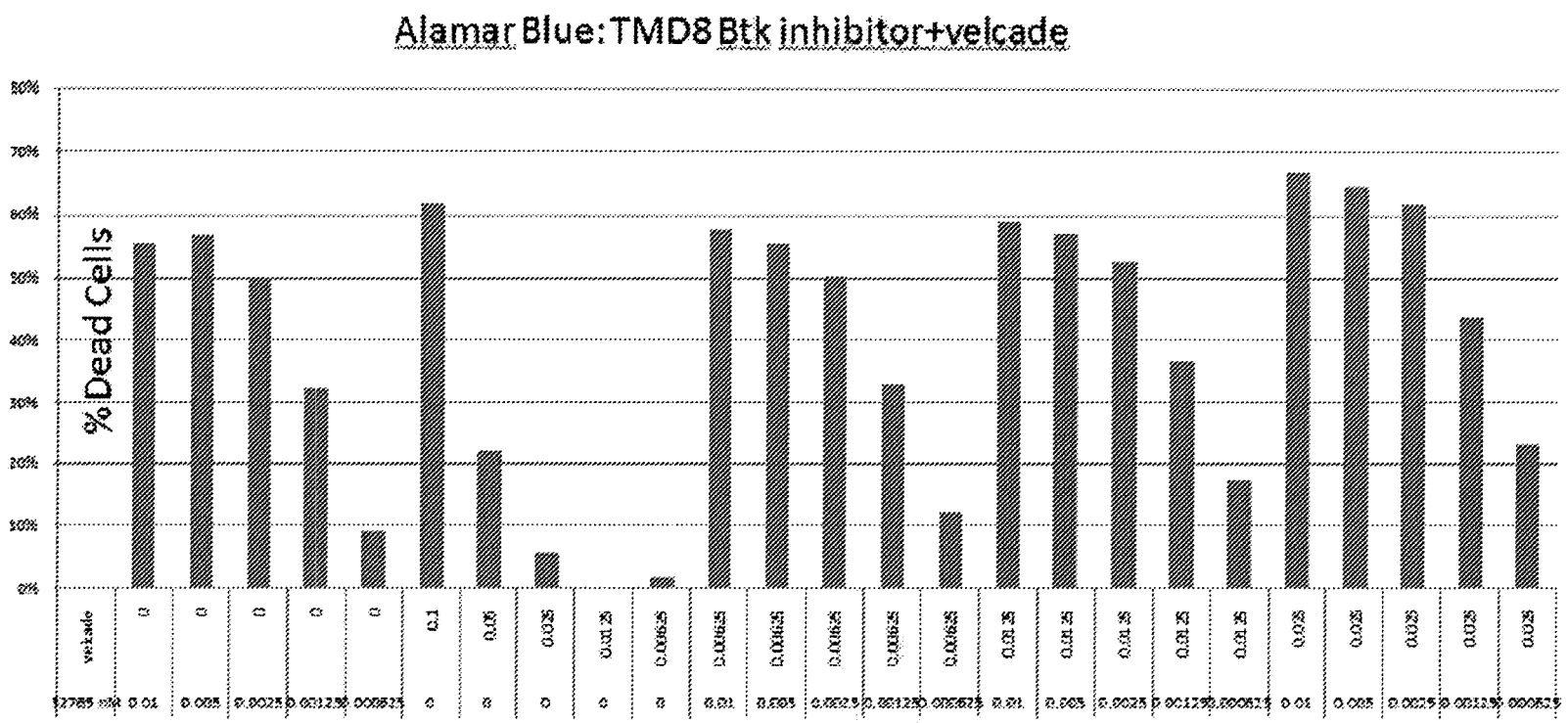


Btk inhibitor nM	lenolidomide nM	CI
0.000625	125	0.77
0.00125	125	0.311
0.0025	125	0.175
0.005	125	0.188
0.01	125	0.332

Btk inhibitor nM	lenolidomide nM	CI
0.000625	250	0.773
0.00125	250	0.271
0.0025	250	0.136
0.005	250	0.154
0.01	250	0.25

Btk inhibitor nM	lenolidomide nM	CI
0.000625	500	0.668
0.00125	500	0.244
0.0025	500	0.093
0.005	500	0.119
0.01	500	0.163

Fig. 32

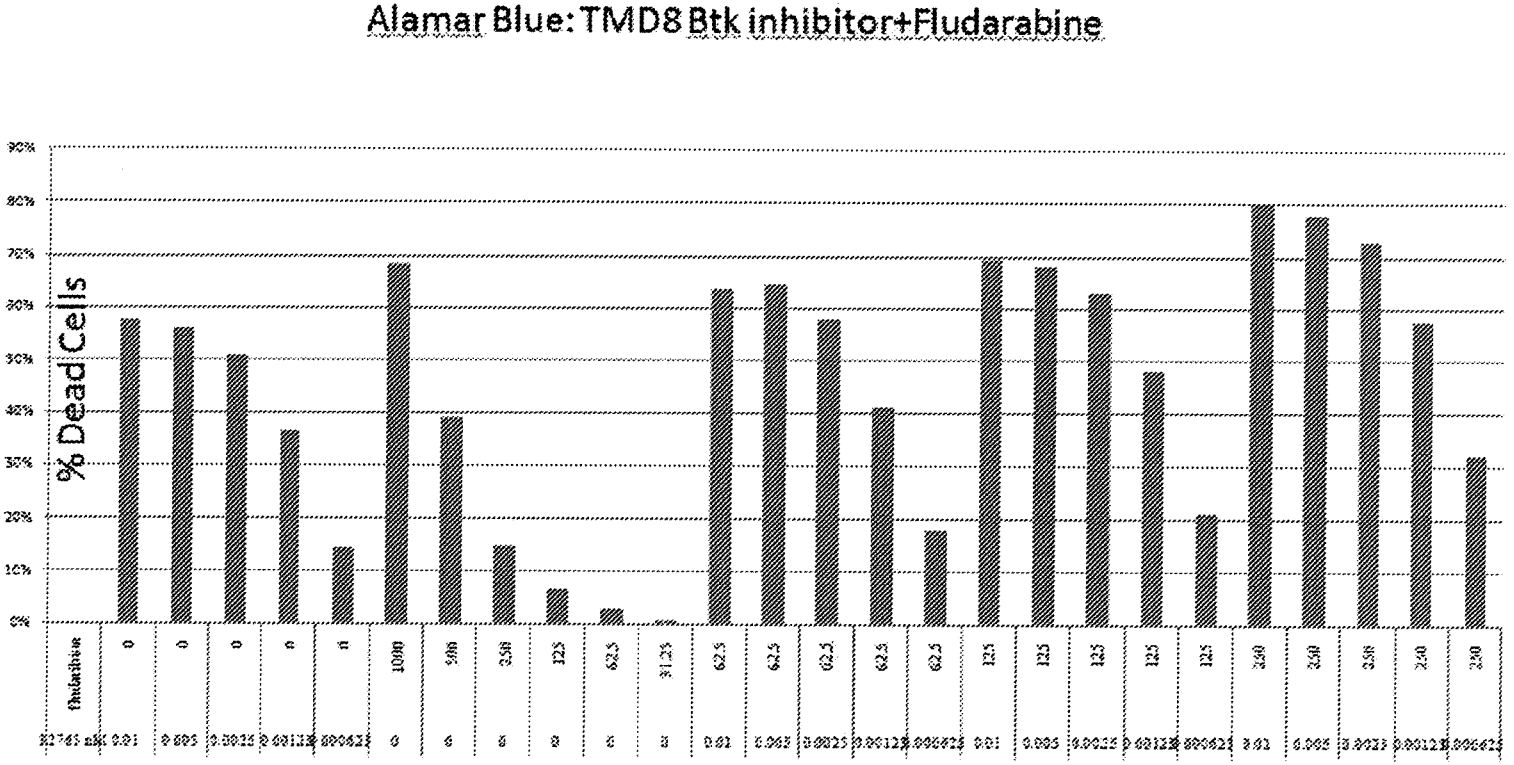


Btk inhibitor nM	velcade nM	CI
0.000625	0.00625	1.486
0.00125	0.00625	0.701
0.0025	0.00625	0.601
0.005	0.00625	0.91
0.01	0.00625	1.015

Btk inhibitor nM	velcade nM	CI
0.000625	0.0125	1.003
0.00125	0.0125	0.656
0.0025	0.0125	0.582
0.005	0.0125	0.868
0.01	0.0125	1.036

Btk inhibitor nM	velcade nM	CI
0.000625	0.025	0.942
0.00125	0.025	0.596
0.0025	0.025	0.472
0.005	0.025	0.691
0.01	0.025	1.124

Fig. 33



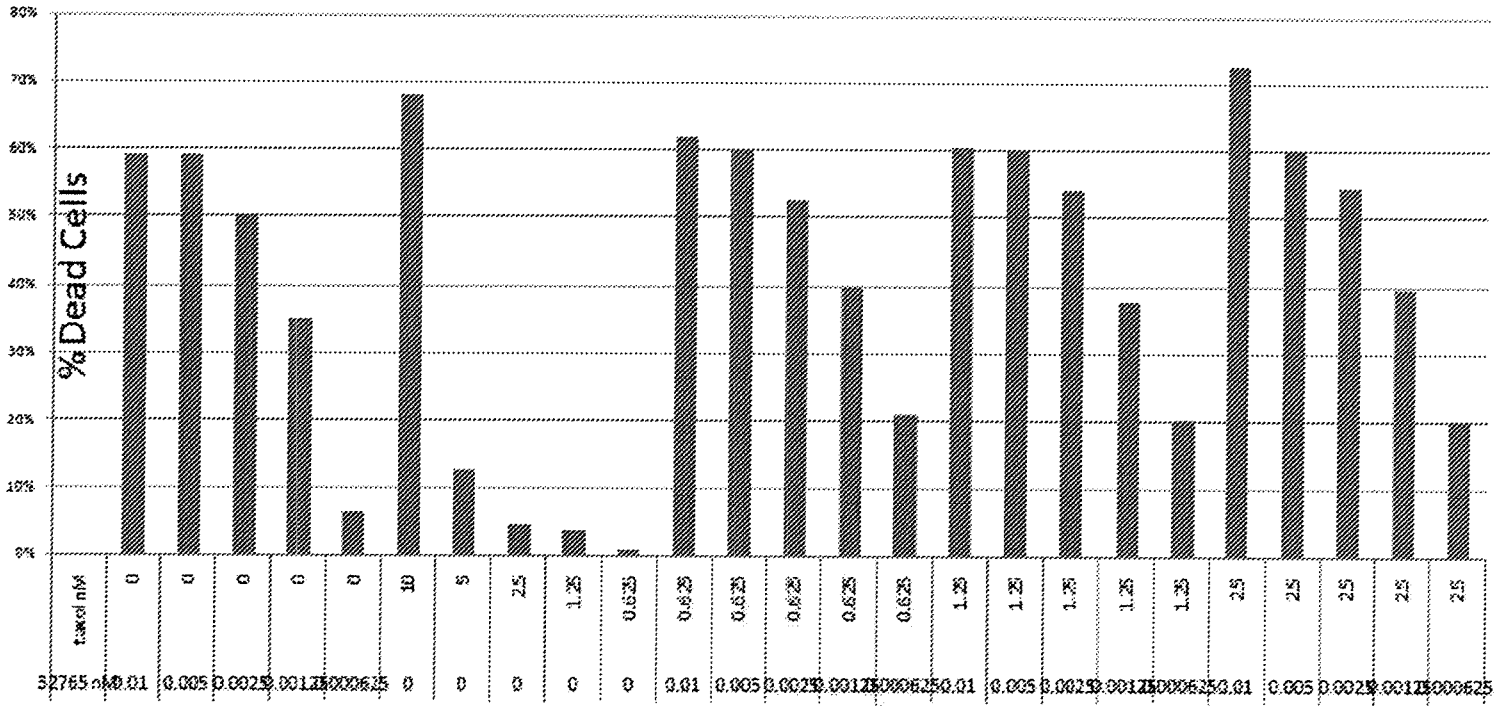
Btk inhibitor nM	fludarabine nM	CI
0.00125	62.5	0.636
0.0025	62.5	0.474
0.005	62.5	0.598

Btk inhibitor nM	fludarabine nM	CI
0.00125	125	0.548
0.0025	125	0.427
0.005	125	0.542
0.01	125	0.689

Btk inhibitor nM	fludarabine nM	CI
0.00125	250	0.518
0.0025	250	0.356
0.005	250	0.383
0.01	250	0.518

Fig. 34

Alamar Blue: TMD8 Btk inhibitor+Taxol



Btk inhibitor nM	taxol nM	CI
0.000625	0.625	0.683
0.00125	0.625	0.535
0.0025	0.625	0.612
0.005	0.625	0.865
0.01	0.625	1.036

Btk inhibitor nM	taxol nM	CI
0.000625	1.25	0.85
0.00125	1.25	0.664
0.0025	1.25	0.634
0.005	1.25	0.918
0.01	1.25	1.178

Btk inhibitor nM	taxol nM	CI
0.000625	2.5	1.19
0.00125	2.5	0.784
0.0025	2.5	0.735
0.005	2.5	1.047
0.01	2.5	1.284

Fig. 35

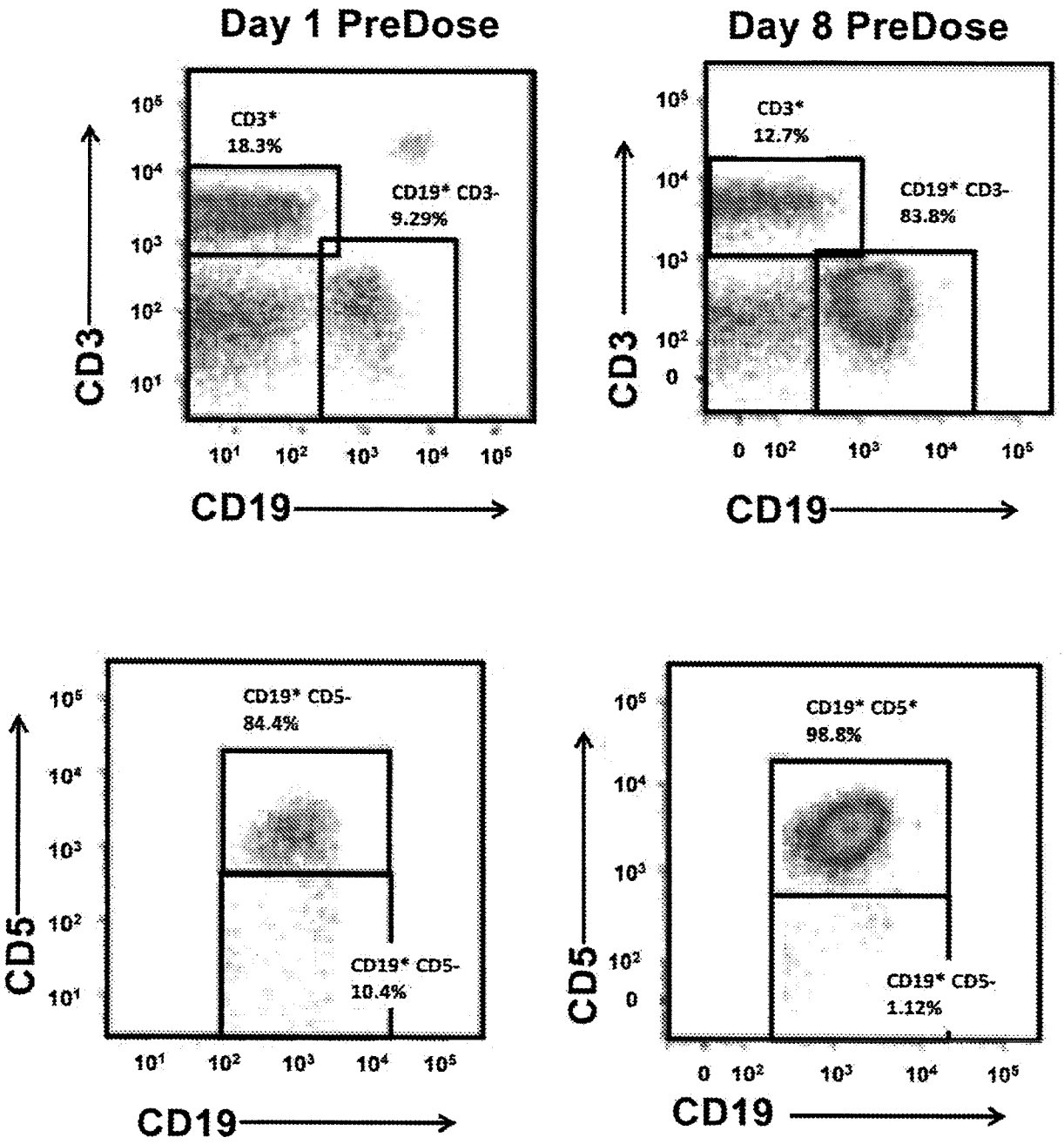
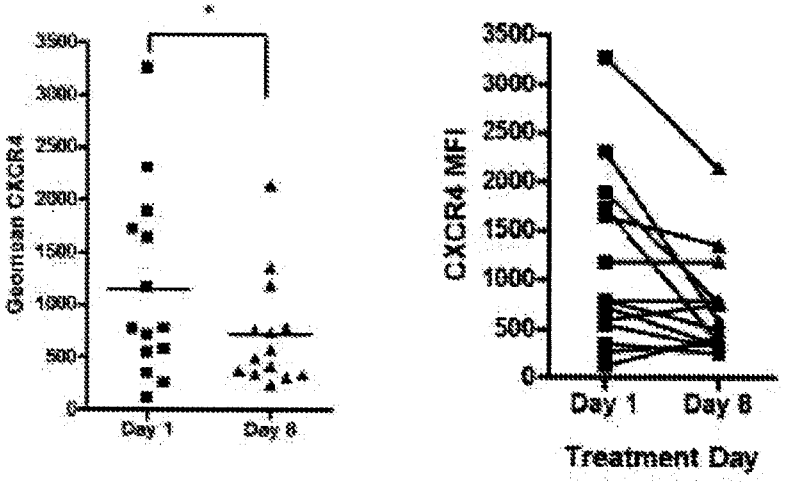

Day 1 PreDose
CD3*
18.3%
CD19* CD3-
9.29%
CD3
CD19
Day 8 PreDose
CD3*
12.7%
CD19* CD3-
83.8%
CD3
CD19
CD19* CD5-
84.4%
CD19* CD5-
10.4%
CD5
CD19
CD19* CD5*
98.8%
CD19* CD5-
1.12%
CD5
CD19

Fig. 36

A.


*
Geomean CXCR4
3500
3000
2500
2000
1500
1000
500
0
Day 1
Day 8
CXCR4 MFI
Day 1
Day 8
Treatment Day

B.

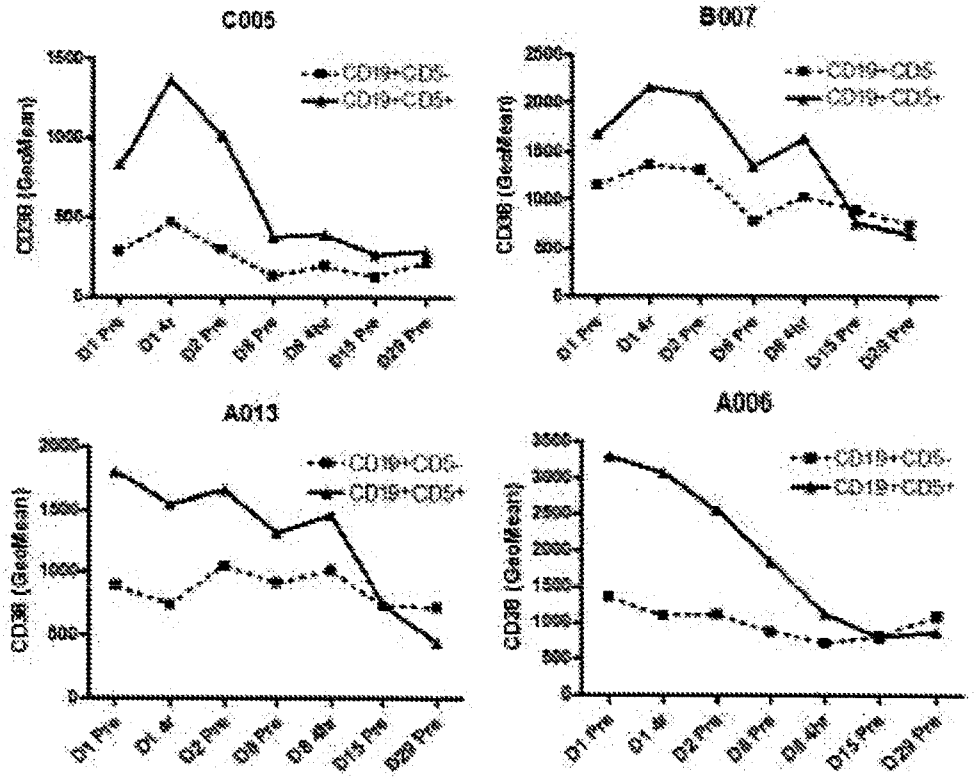
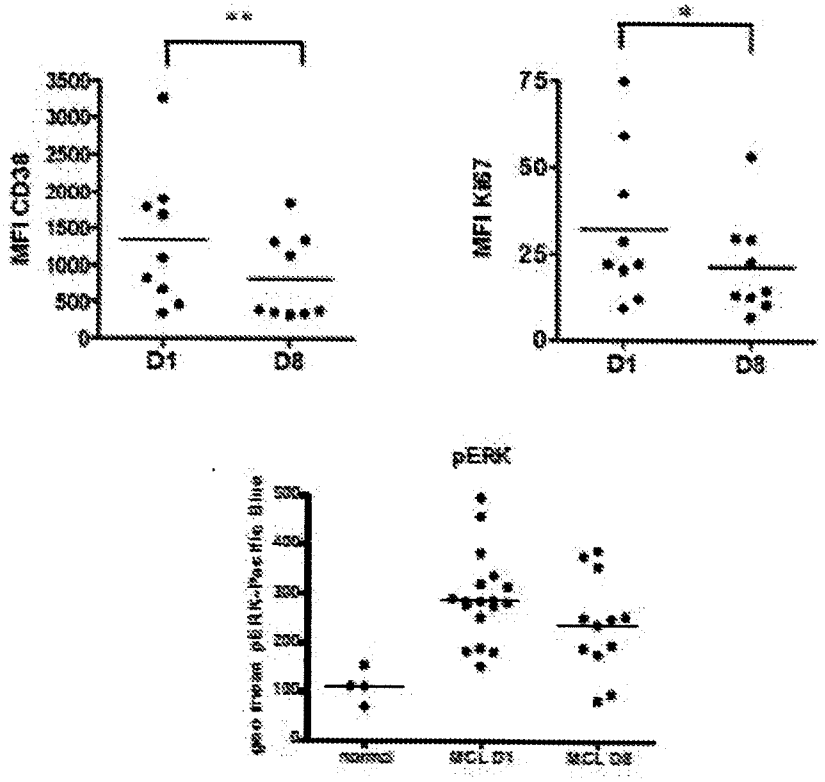

C005
B007
A013
A006
CD19+CD5-
CD19+CD5+
CD38 (GeoMean)

Fig. 36 (cont'd)

C.



D.

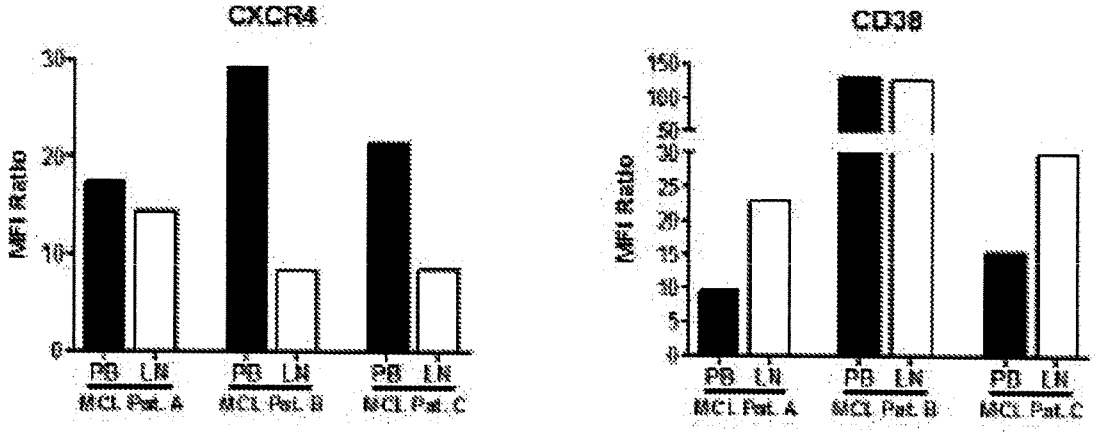


Fig. 36 (cont'd)

E.

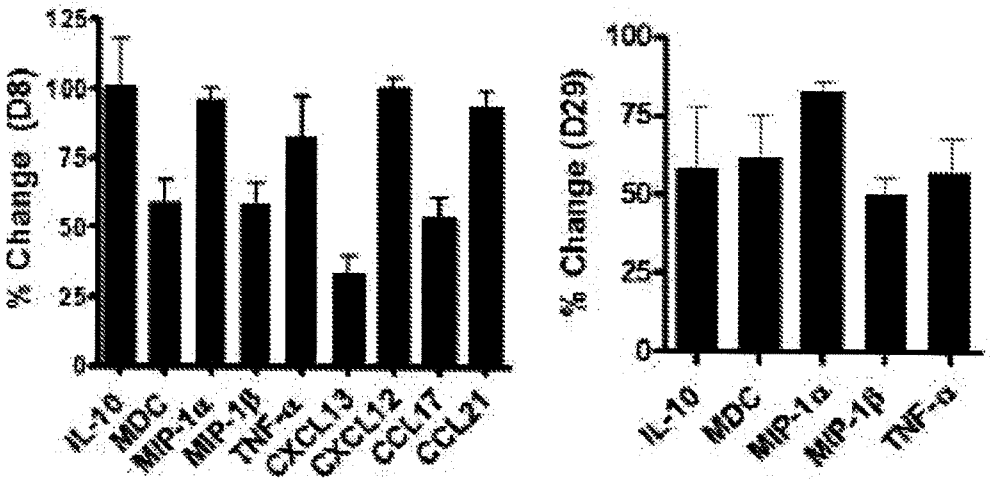
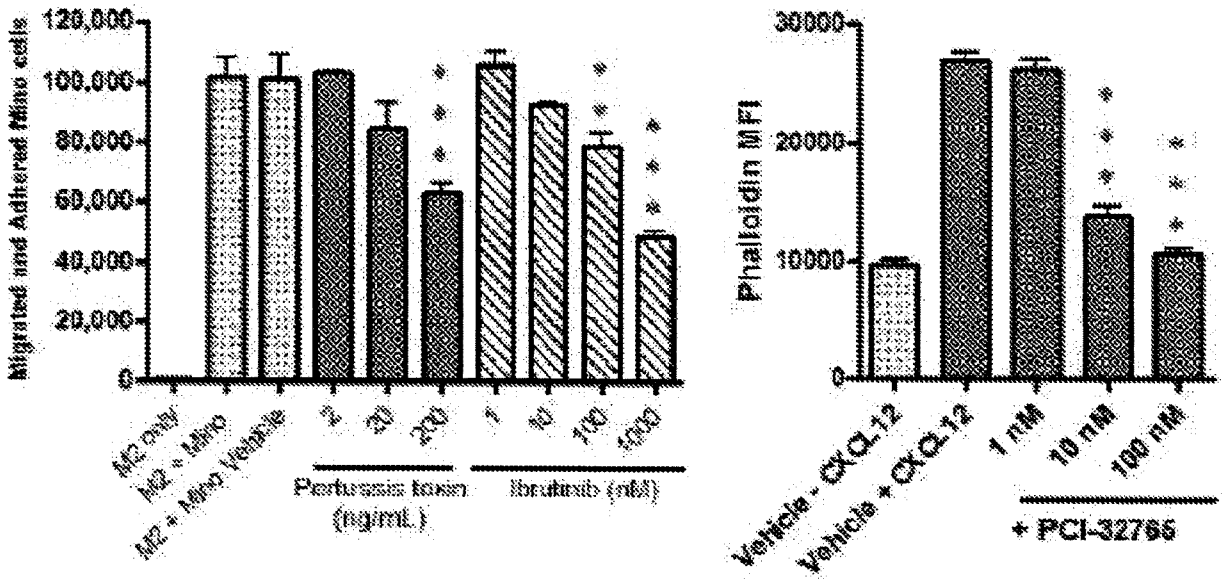
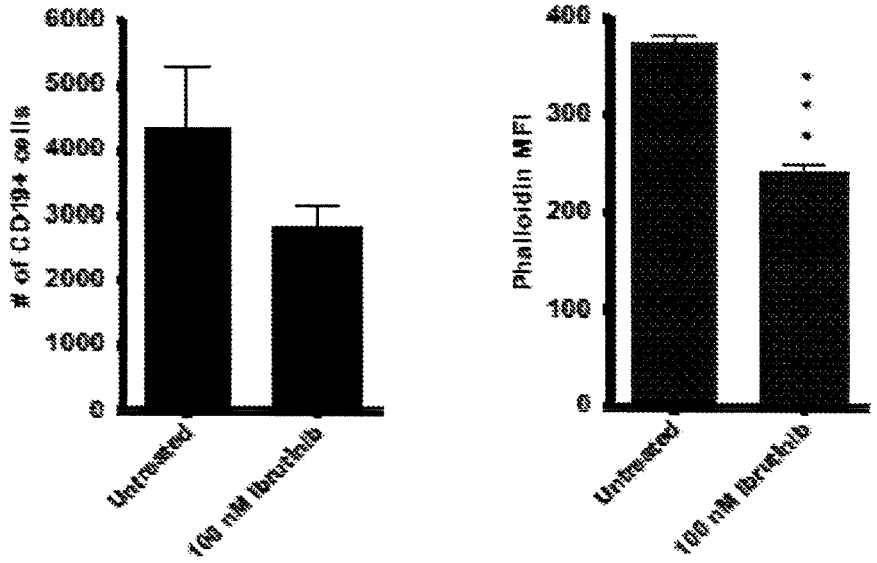


Fig. 37

A


Migrated and Adhered Mino cells
120,000
100,000
80,000
60,000
40,000
20,000
0
MC only
M2 + Mino
M2 + Mino Vehicle
Pertussis toxin (ng/mL)
Ibrutinib (nM)
Phalloidin MFI
30000
20000
10000
Vehicle - CXCL12
Vehicle + CXCL12
1 nM
10 nM
100 nM
+ PCI-32765

B


# of CD19+ cells
6000
5000
4000
3000
2000
1000
0
Untreated
100 nM Ibrutinib
Phalloidin MFI
400
300
200
100
0
Untreated
100 nM Ibrutinib