Fig. 1

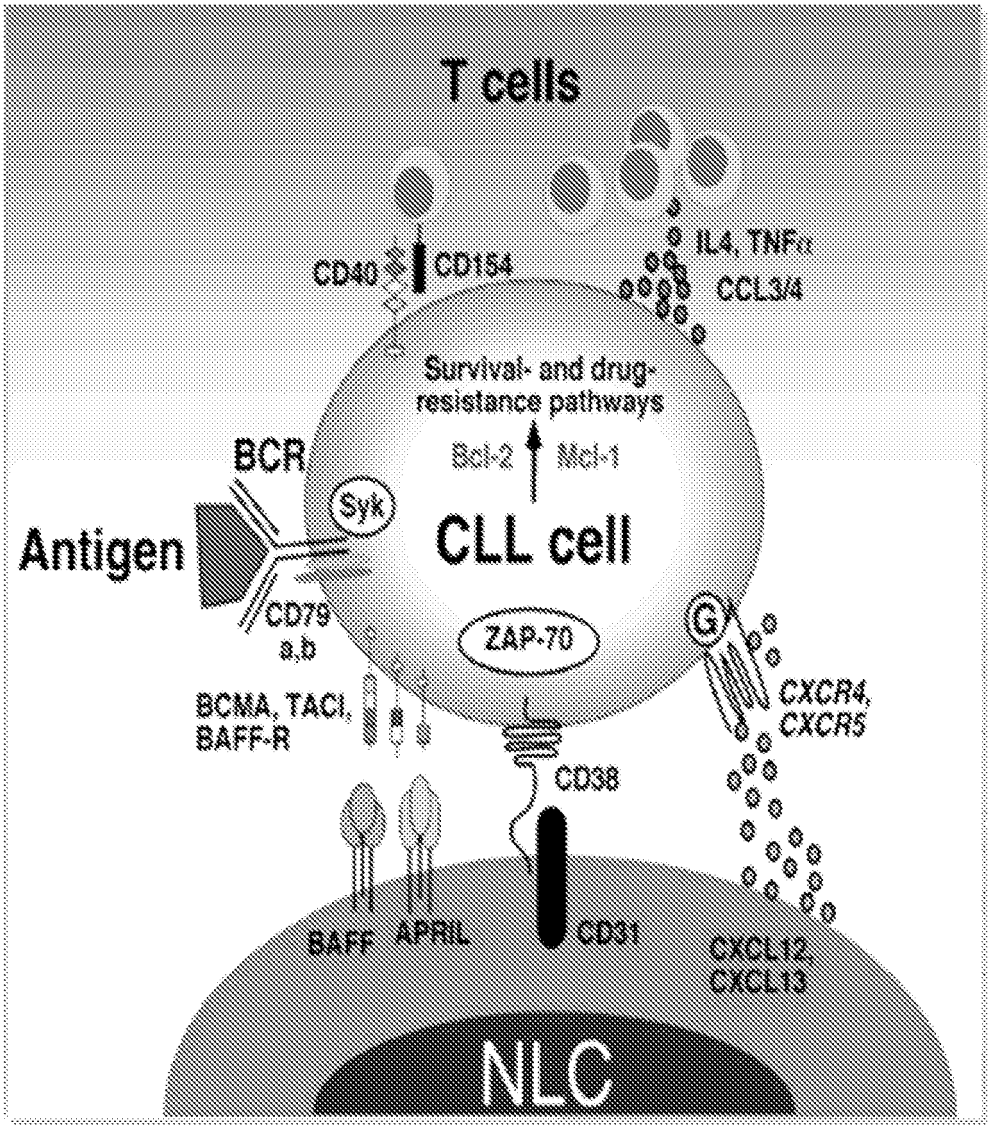

T cells
CD40
CD154
IL4, TNFα
CCL3/4
Survival- and drug-resistance pathways
Bcl-2
Mcl-1
BCR
Syk
Antigen
CLL cell
CD79 a,b
ZAP-70
G
CXCR4, CXCR5
BCMA, TACI, BAFF-R
CD38
BAFF
APRIL
CD31
CXCL12, CXCL13
NLC

Fig. 2



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

Fig. 3

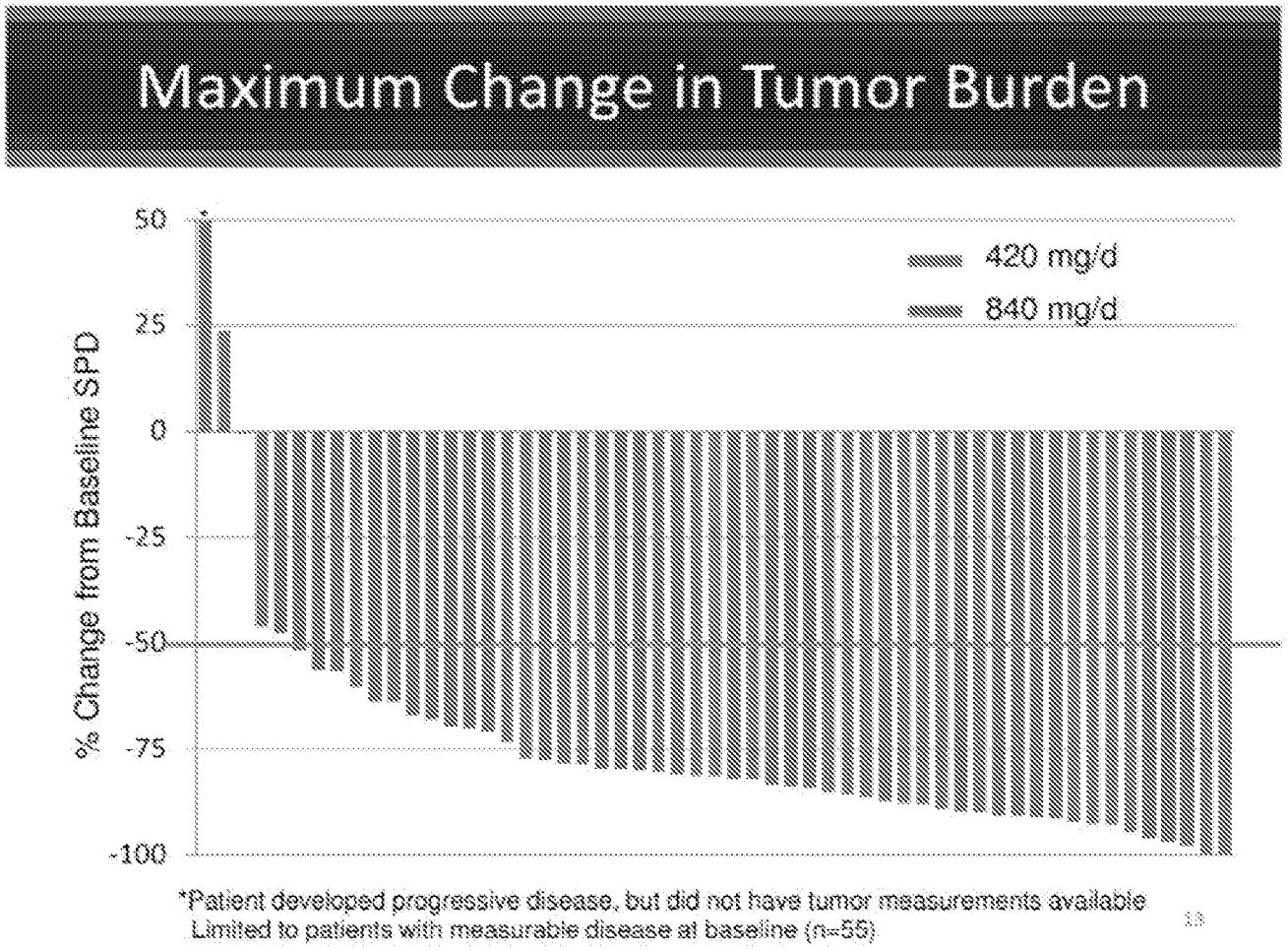
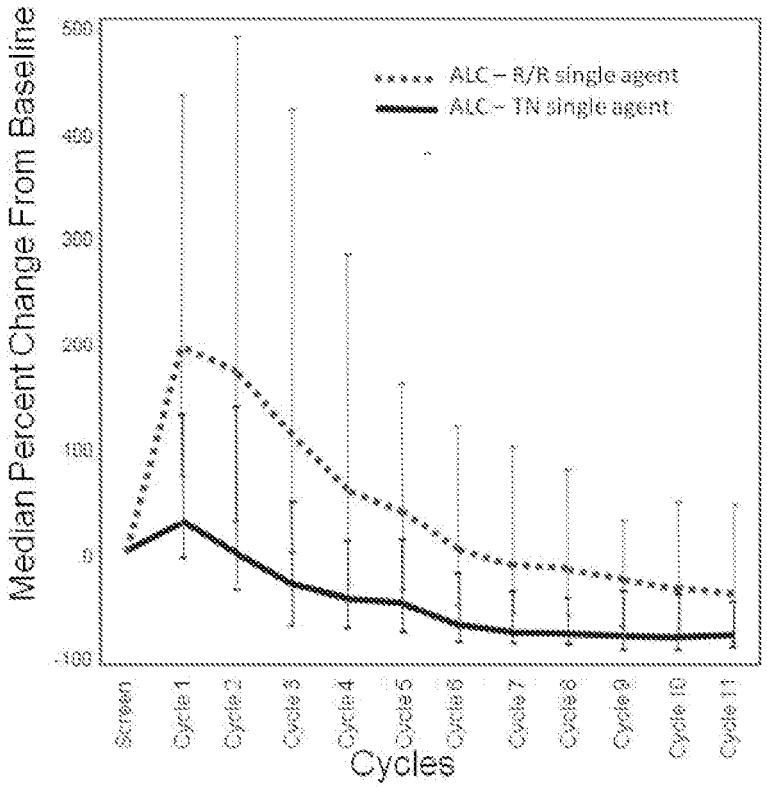

Maximum Change in Tumor Burden
50
25
0
-25
-50
-75
-100
% Change from Baseline SPD
420 mg/d
840 mg/d
*Patient developed progressive disease, but did not have tumor measurements available
Limited to patients with measurable disease at baseline (n=55)

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

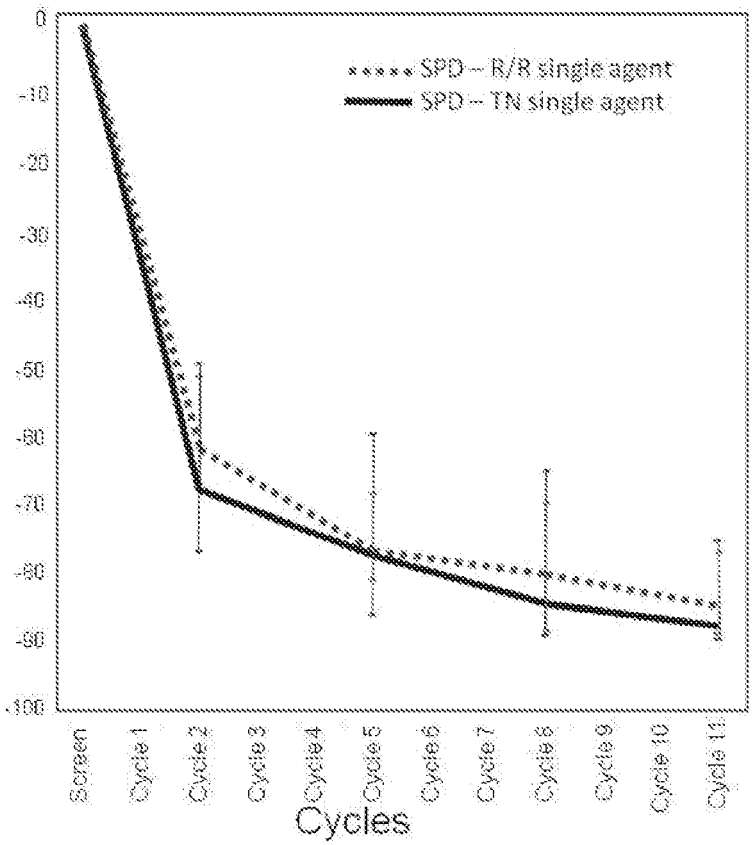

SPD – R/R single agent
SPD – TN single agent
Screen
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
Cycle 7
Cycle 8
Cycle 9
Cycle 10
Cycle 11
Cycles

Fig. 5

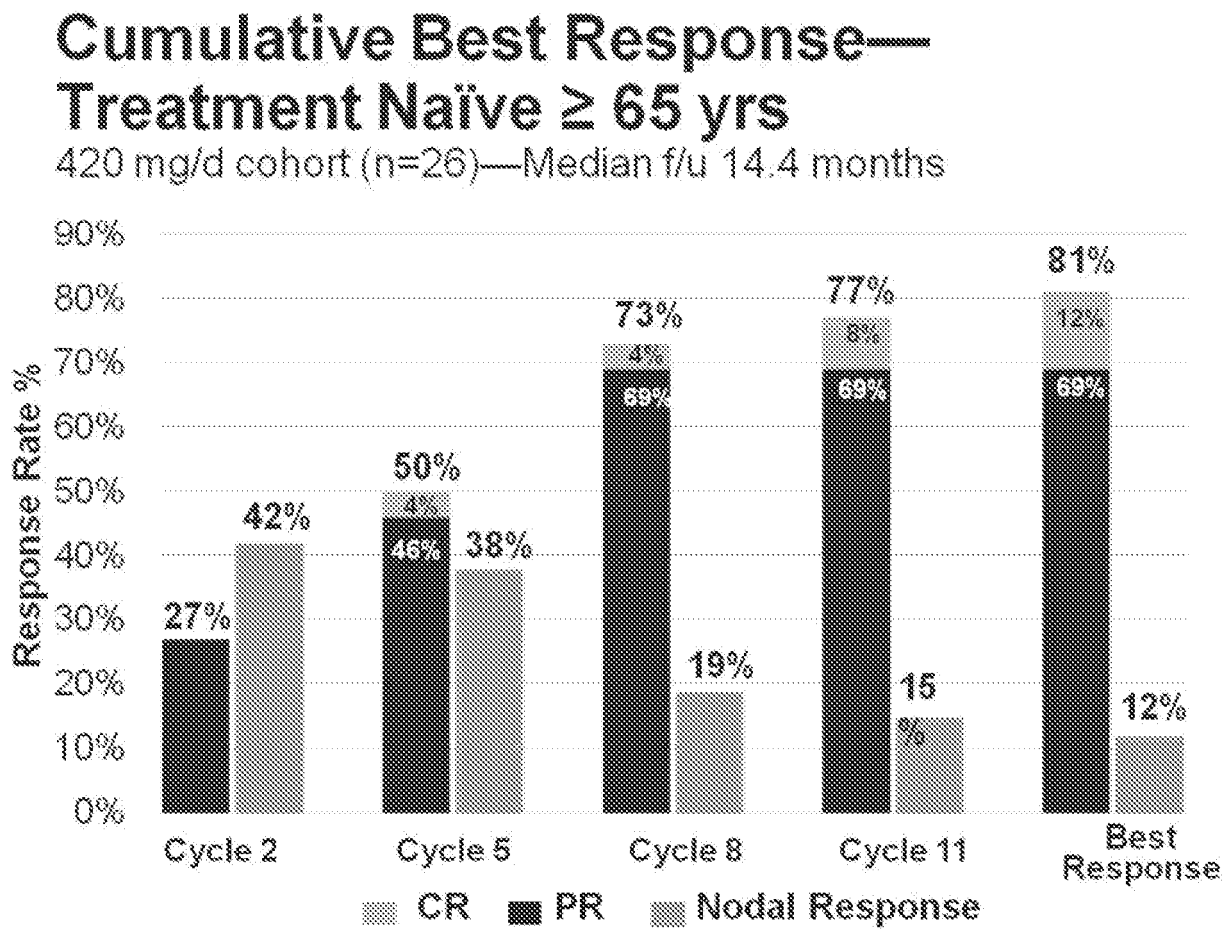

Cumulative Best Response—
Treatment Naïve ≥ 65 yrs
420 mg/d cohort (n=26)—Median f/u 14.4 months
Response Rate %
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
27%
42%
50%
4%
46%
38%
73%
4%
69%
19%
77%
8%
69%
15%
81%
12%
69%
12%
Cycle 2
Cycle 5
Cycle 8
Cycle 11
Best Response
CR
PR
Nodal Response

Fig. 6

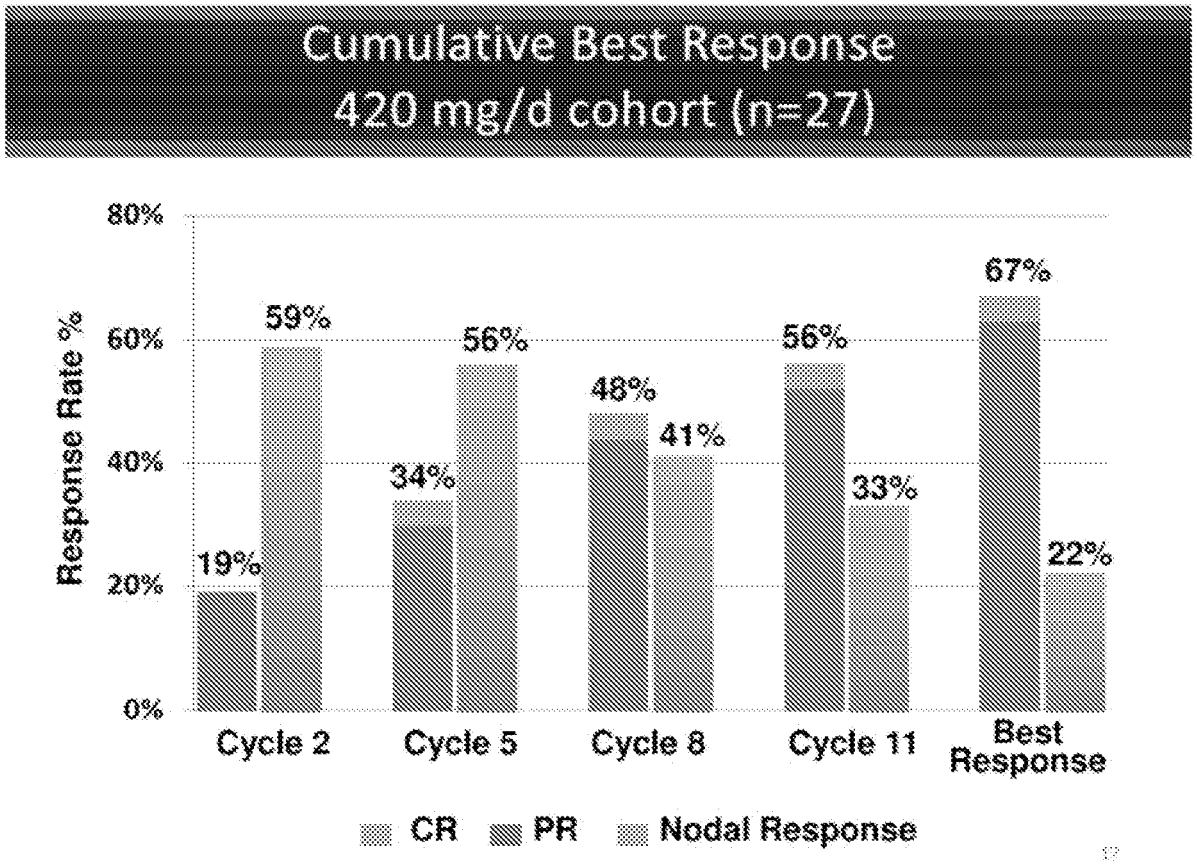

Cumulative Best Response
420 mg/d cohort (n=27)
Response Rate %
80%
60%
40%
20%
0%
19%
59%
34%
56%
48%
41%
56%
33%
67%
22%
Cycle 2
Cycle 5
Cycle 8
Cycle 11
Best Response
CR
PR
Nodal Response

Fig. 7

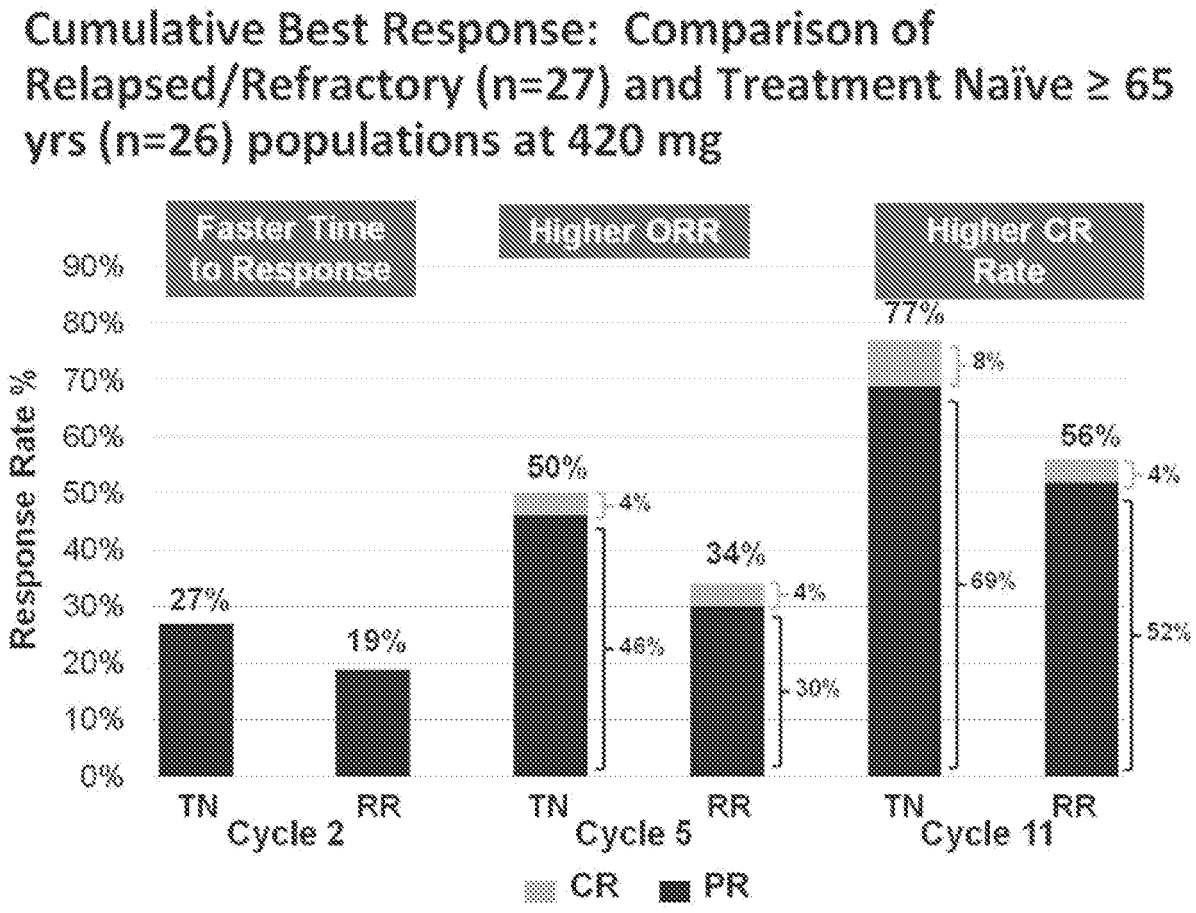
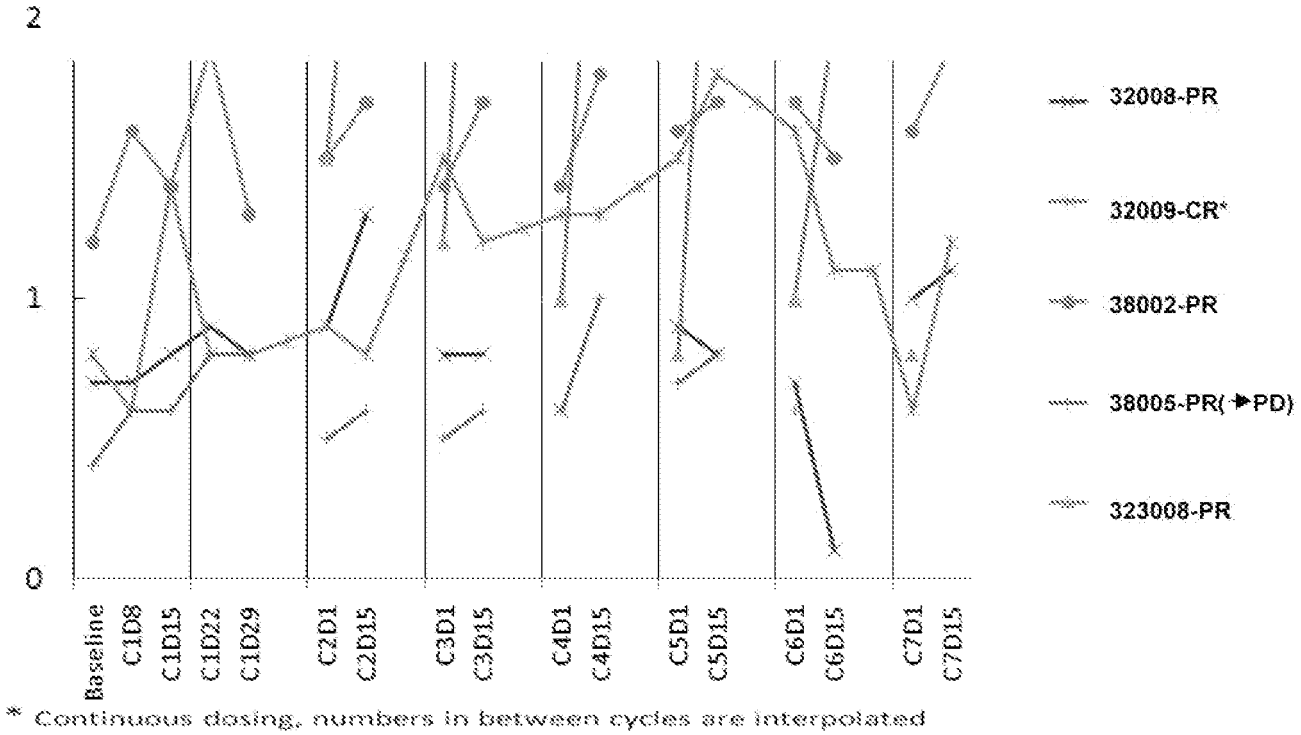

Cumulative Best Response: Comparison of Relapsed/Refractory (n=27) and Treatment Naïve ≥ 65 yrs (n=26) populations at 420 mg
Faster Time to Response
Higher ORR
Higher CR Rate
Response Rate %
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
27%
19%
50%
4%
46%
34%
4%
30%
77%
8%
69%
56%
4%
52%
TN
RR
Cycle 2
Cycle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

Fig. 8



* Continuous dosing, numbers in between cycles are interpolated

Fig.9

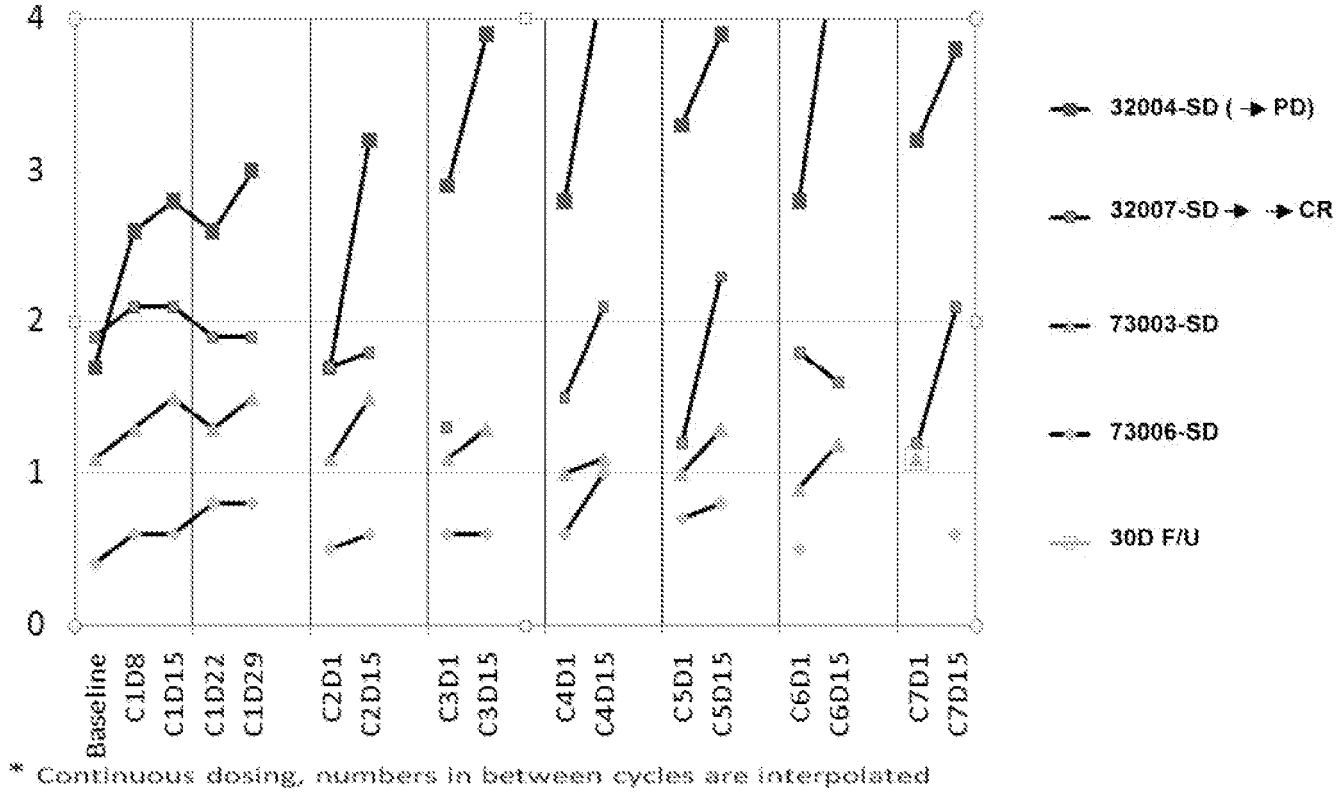

4
3
2
1
0
Baseline
C1D8
C1D15
C1D22
C1D29
C2D1
C2D15
C3D1
C3D15
C4D1
C4D15
C5D1
C5D15
C6D1
C6D15
C7D1
C7D15
32004-SD (→ PD)
32007-SD → → CR
73003-SD
73006-SD
30D F/U
* Continuous dosing, numbers in between cycles are interpolated

Fig.10

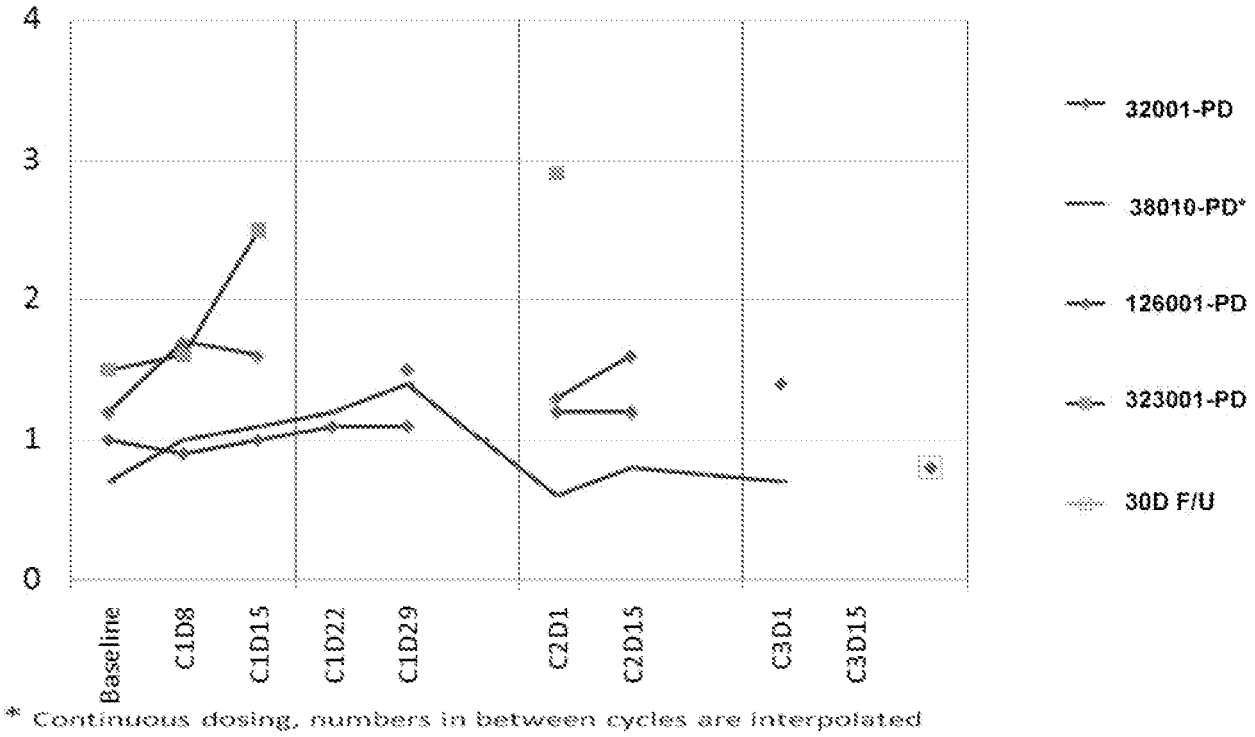
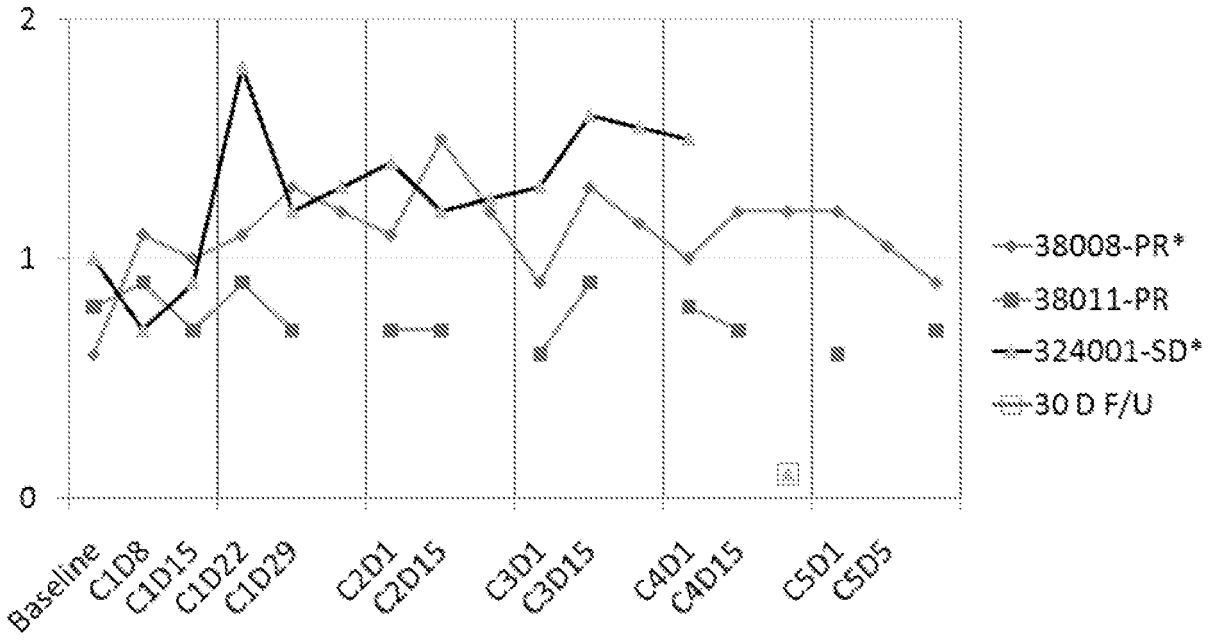

4
3
2
1
0
Baseline
C1D8
C1D15
C1D22
C1D29
C2D1
C2D15
C3D1
C3D15
32001-PD
38010-PD*
126001-PD
323001-PD
30D F/U
* Continuous dosing, numbers in between cycles are interpolated

Fig.11



* Continuous dosing, numbers in between cycles are interpolated

Fig. 12

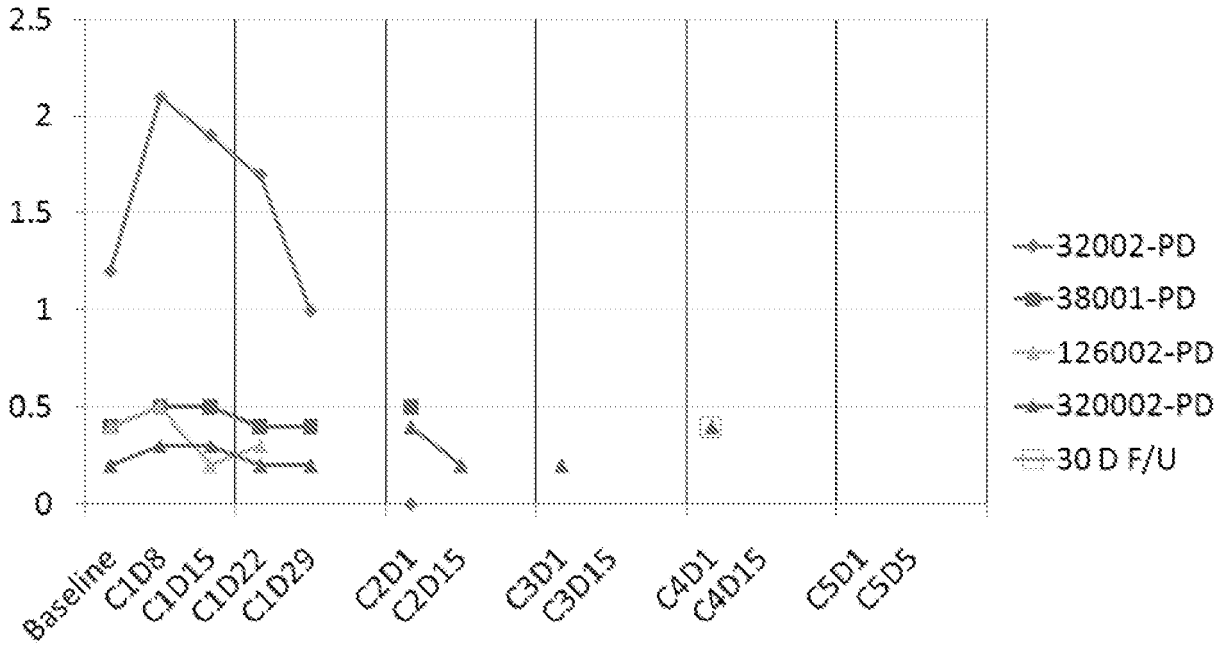
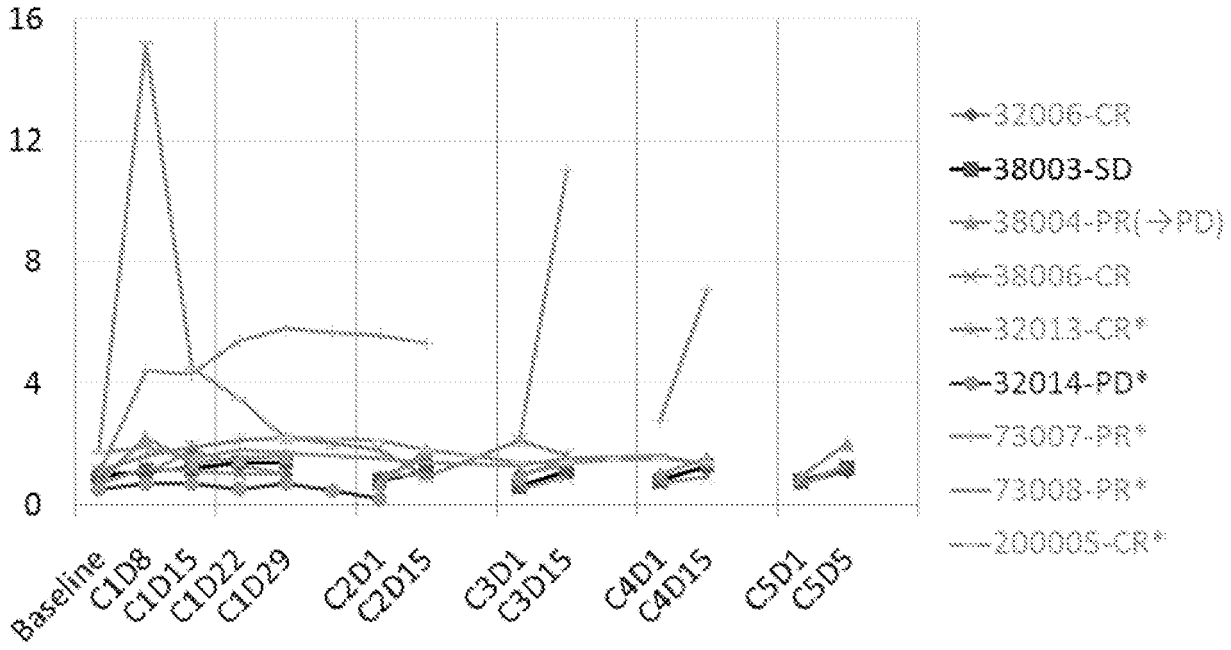
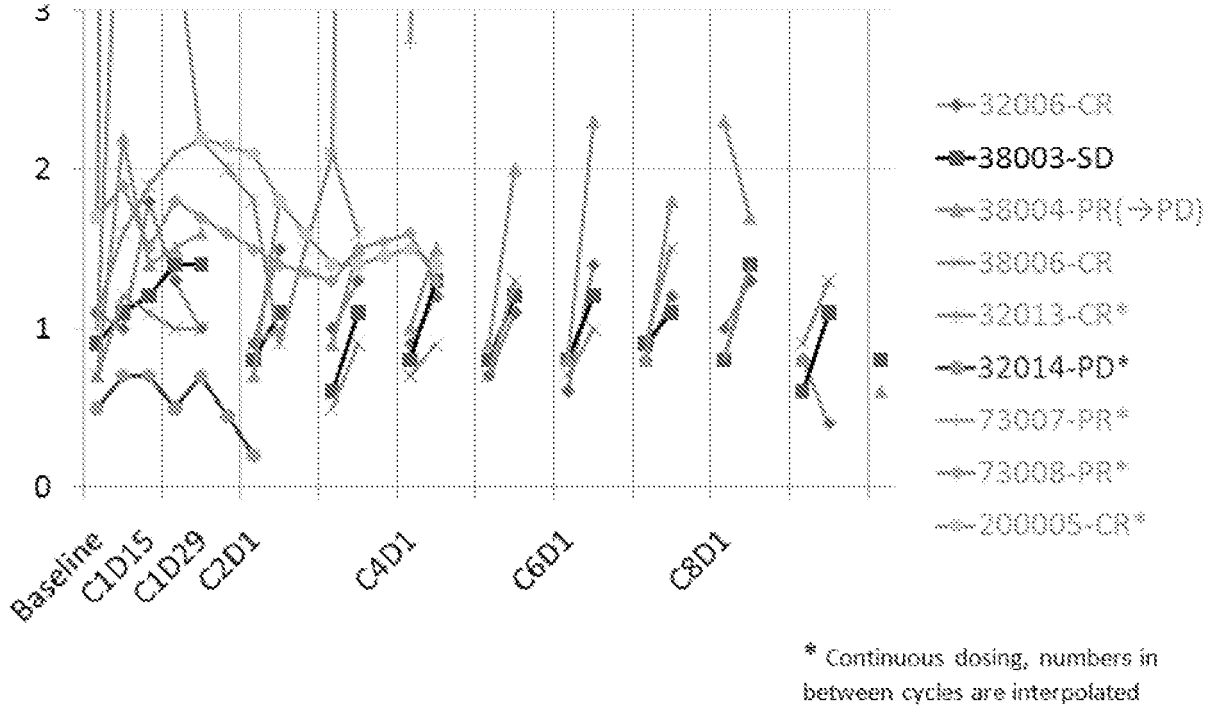

2.5
2
1.5
1
0.5
0
Baseline
C1D8
C1D15
C1D22
C1D29
C2D1
C2D15
C3D1
C3D15
C4D1
C4D15
C5D1
C5D5
32002-PD
38001-PD
126002-PD
320002-PD
30 D F/U

Fig. 13



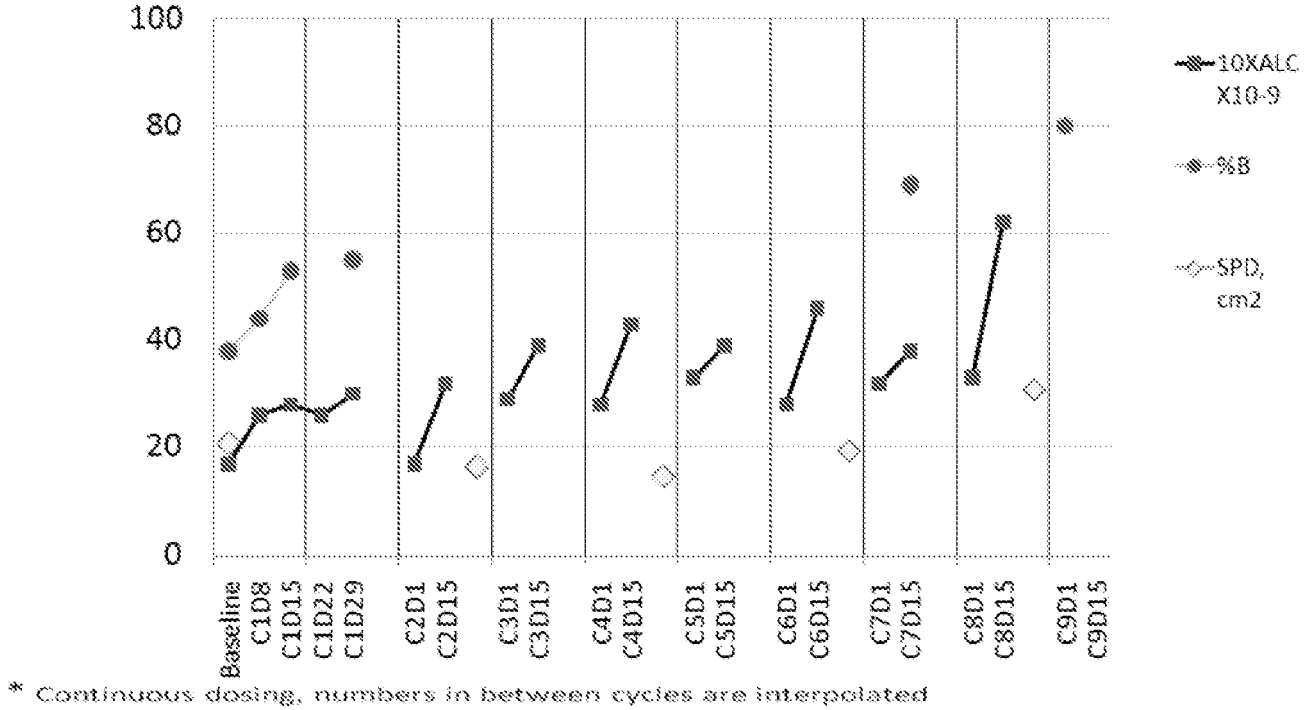
* Continuous dosing, numbers in between cycles are interpolated

Fig. 14



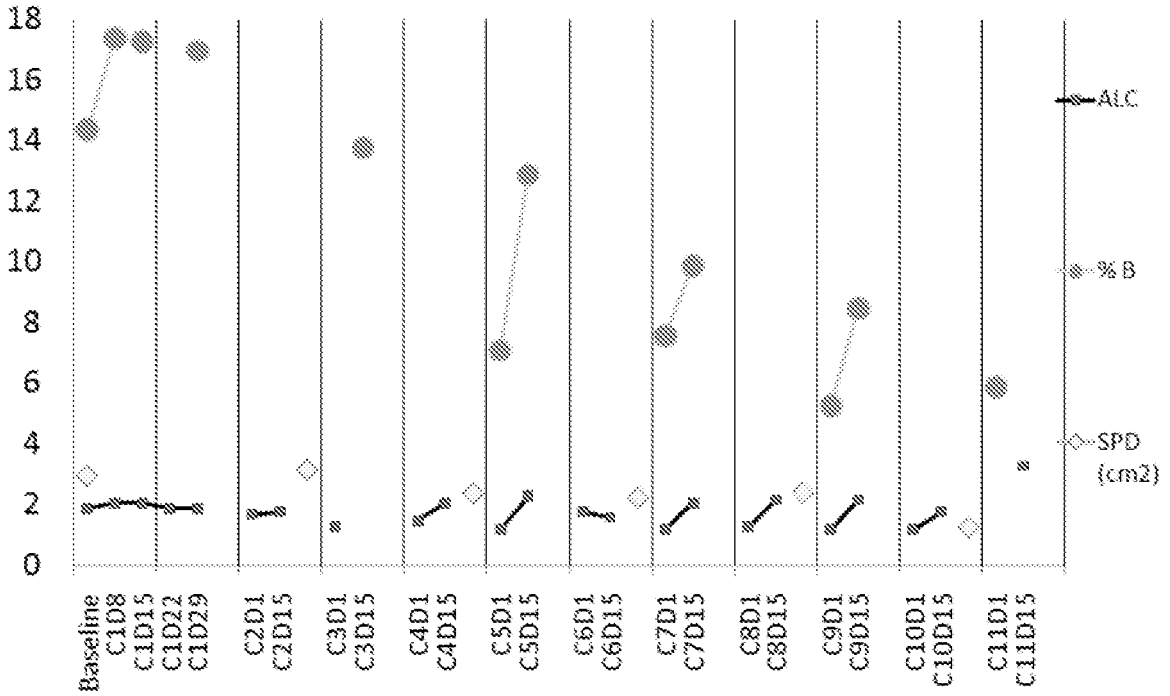
* Continuous dosing, numbers in between cycles are interpolated

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

17/39

Fig. 17

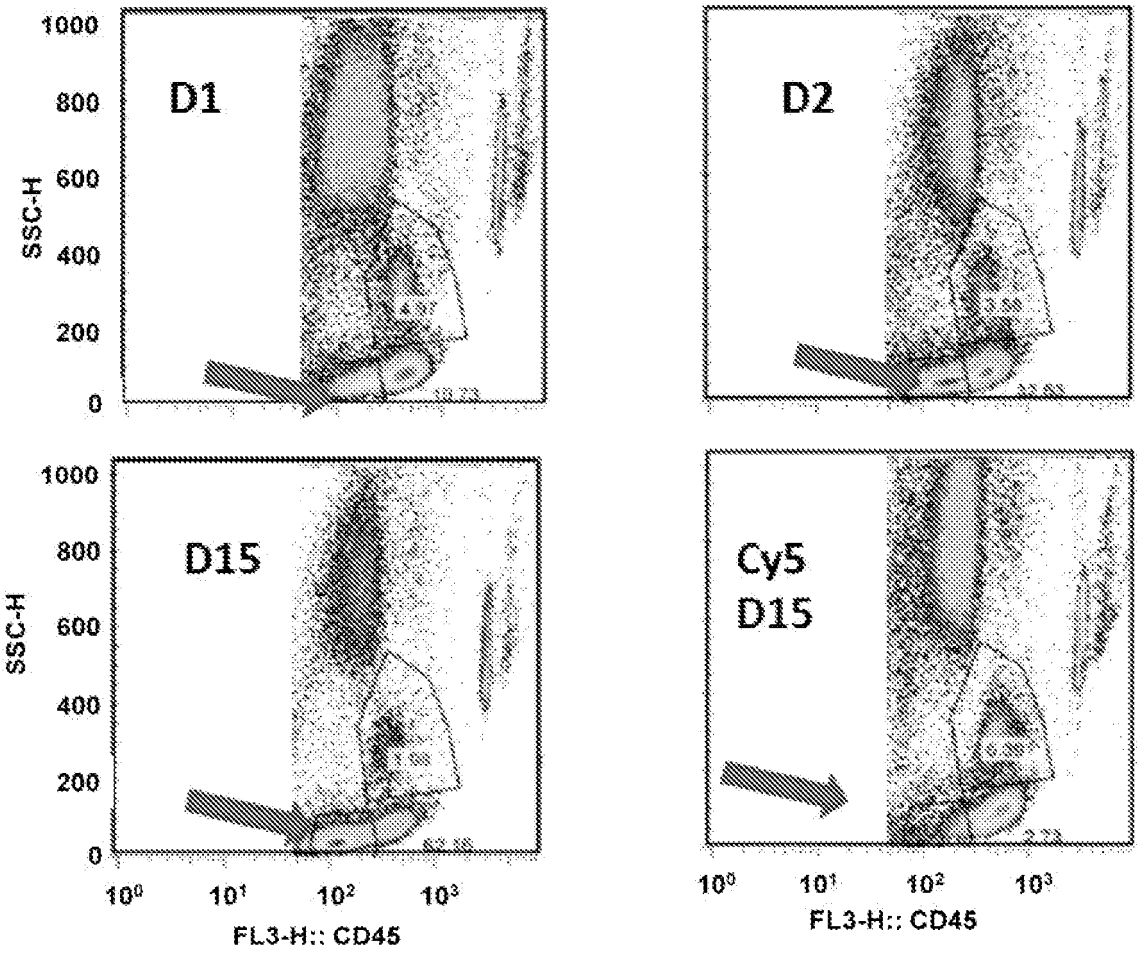

D1
D2
D15
Cy5
D15
SSC-H
1000
800
600
400
200
0
10^0
10^1
10^2
10^3
FL3-H:: CD45

Fig. 18

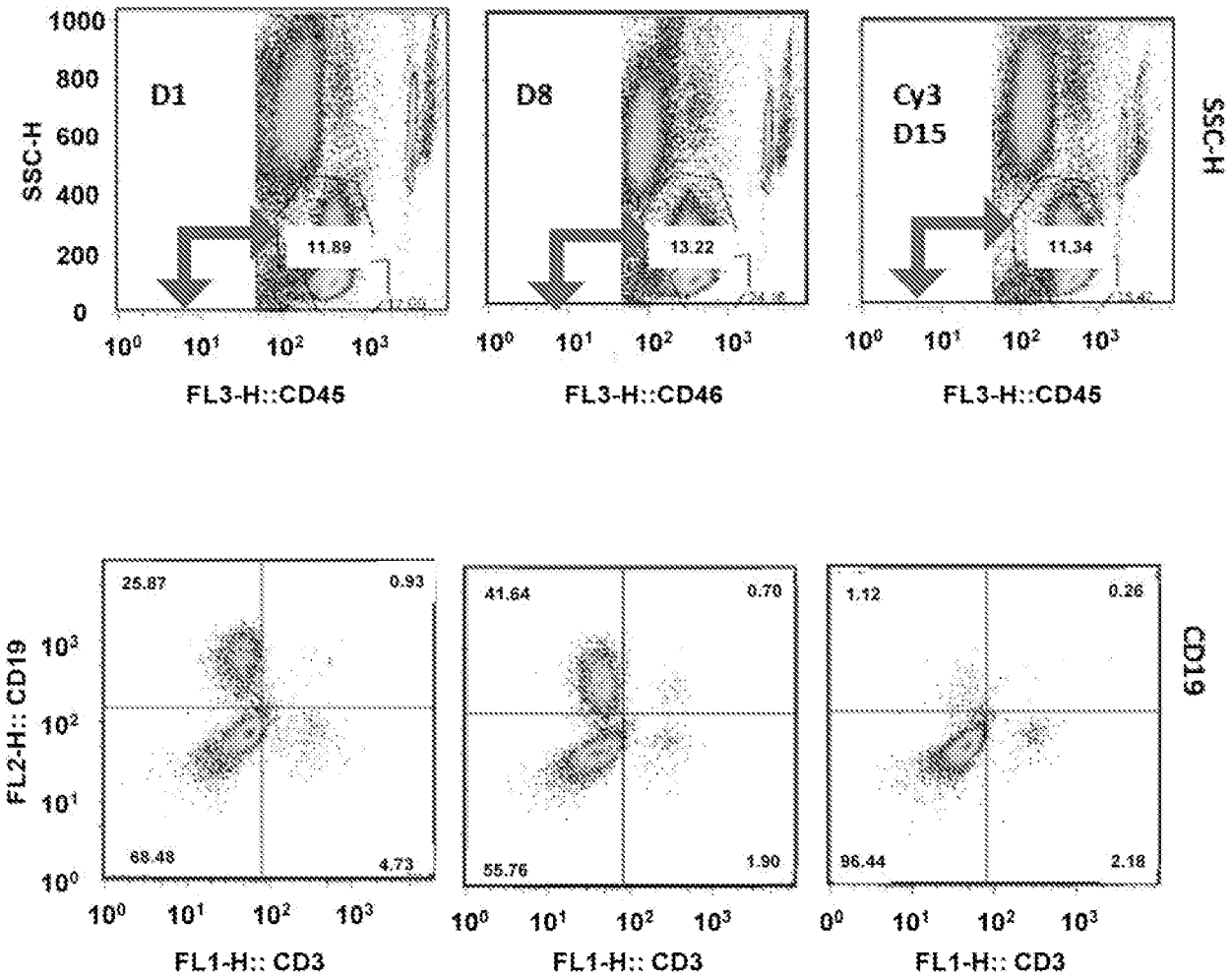

D1
D8
Cy3
D15
SSC-H
11.89
13.22
11.34
FL3-H::CD45
FL3-H::CD46
FL3-H::CD45
FL2-H:: CD19
25.87
0.93
68.48
4.73
41.64
0.70
55.76
1.90
1.12
0.26
96.44
2.18
FL1-H:: CD3
CD19

Fig. 19

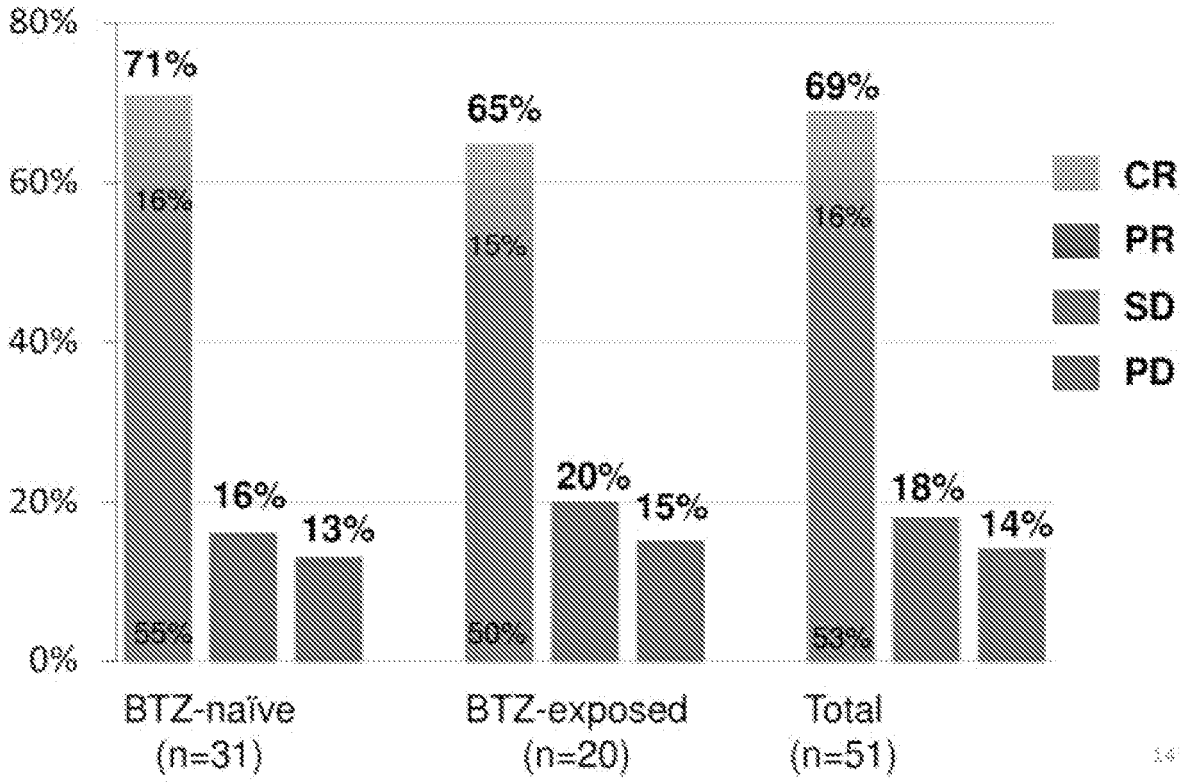

80%
60%
40%
20%
0%
71%
16%
55%
16%
13%
65%
15%
50%
20%
15%
69%
16%
53%
18%
14%
CR
PR
SD
PD
BTZ-naïve
(n=31)
BTZ-exposed
(n=20)
Total
(n=51)

Fig. 20

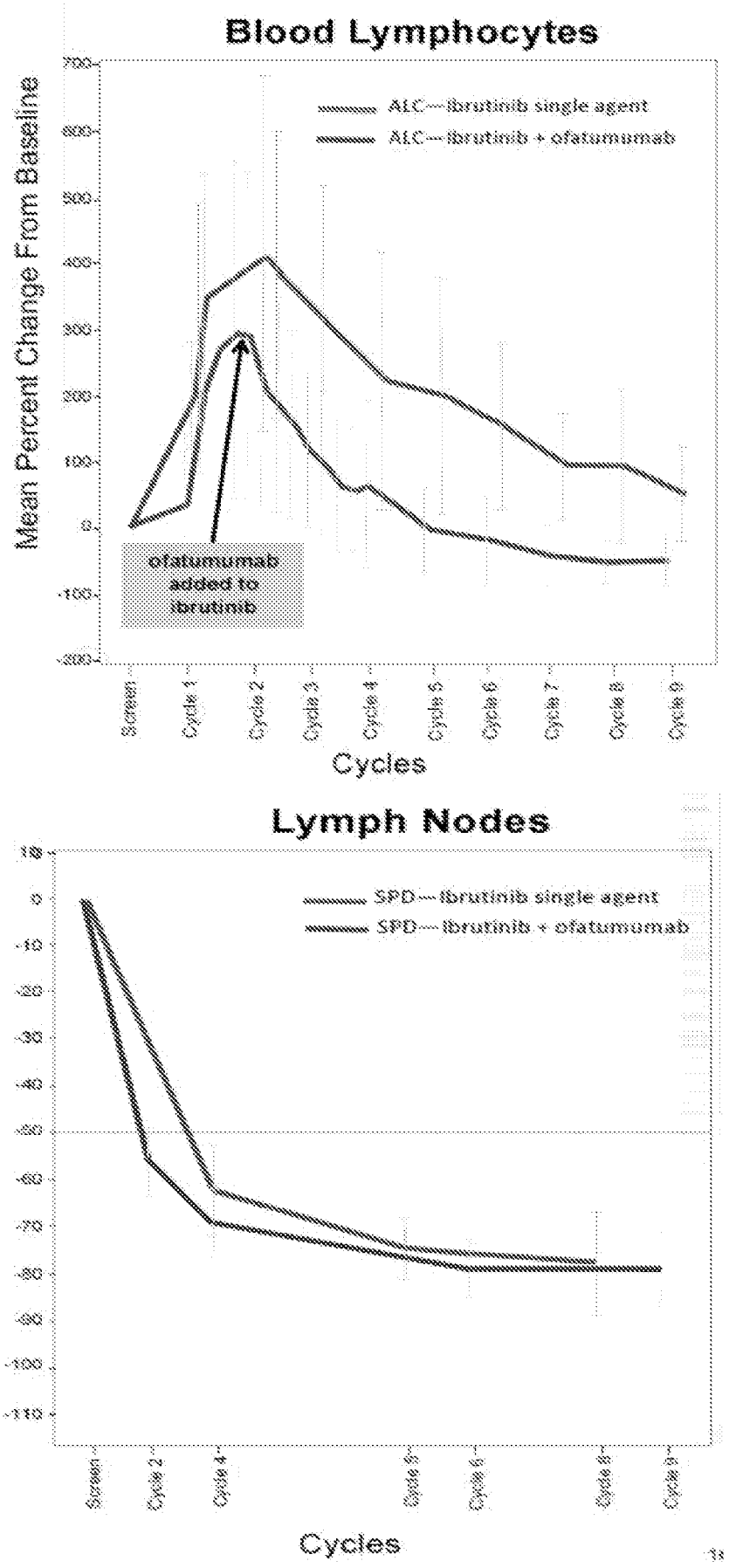
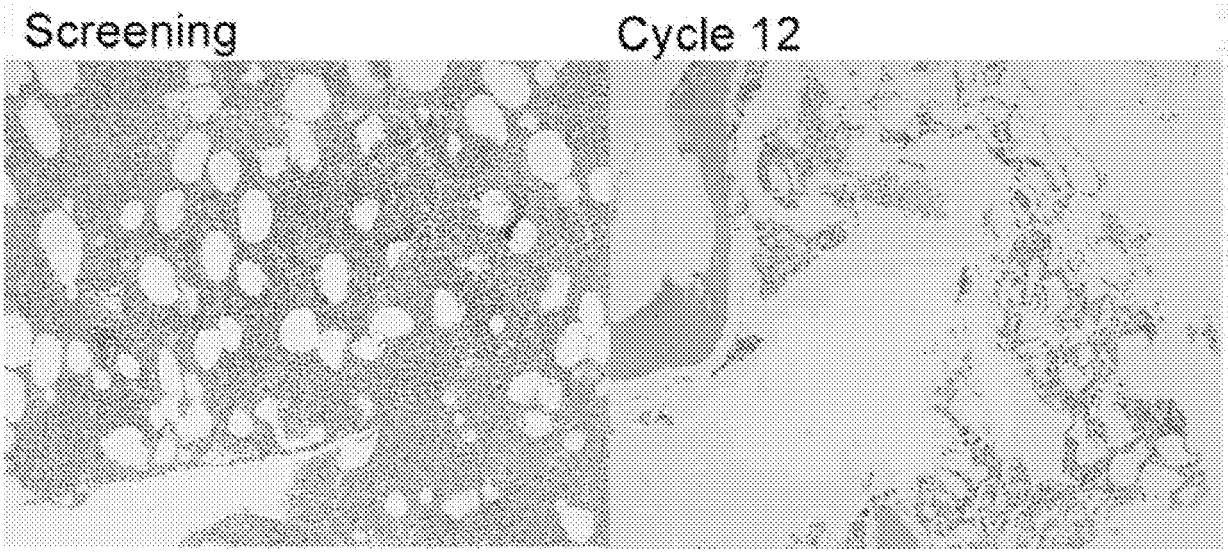
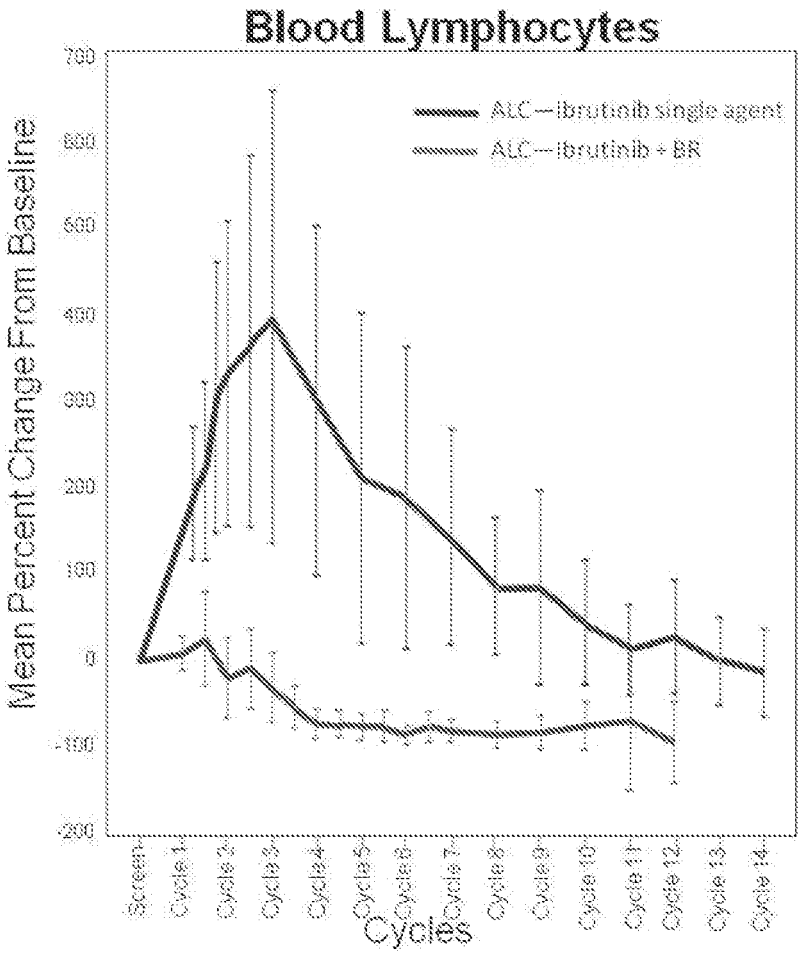

Blood Lymphocytes
Mean Percent Change From Baseline
ALC—Ibrutinib single agent
ALC—Ibrutinib + ofatumumab
ofatumumab added to Ibrutinib
Screen
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
Cycle 7
Cycle 8
Cycle 9
Cycles
Lymph Nodes
SPD—Ibrutinib single agent
SPD—Ibrutinib + ofatumumab
Screen
Cycle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

Fig. 21



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

Fig. 22


Blood Lymphocytes
ALC—ibrutinib single agent
ALC—ibrutinib + BR
Mean Percent Change From Baseline
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

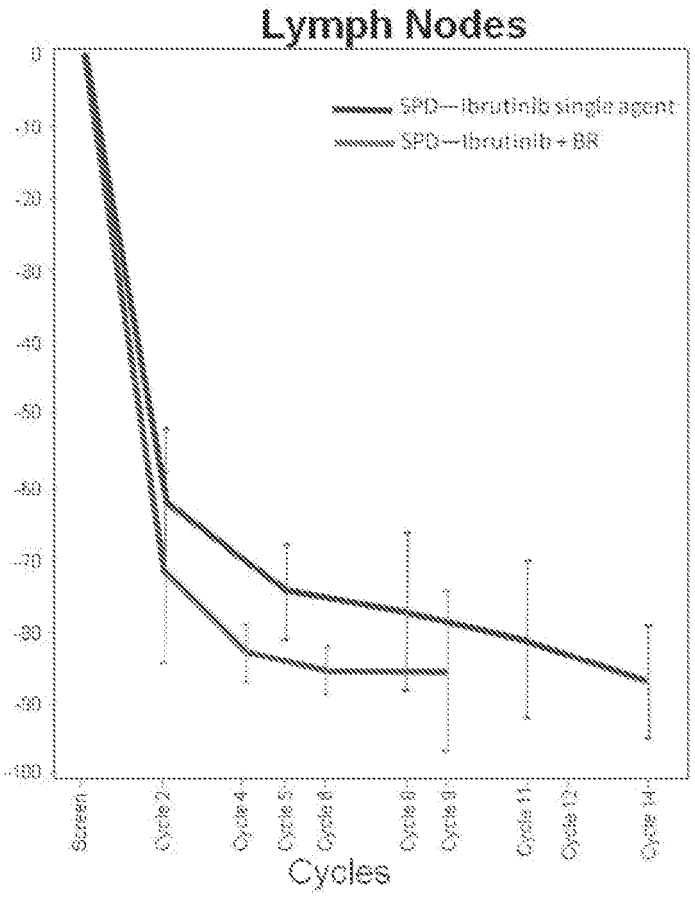
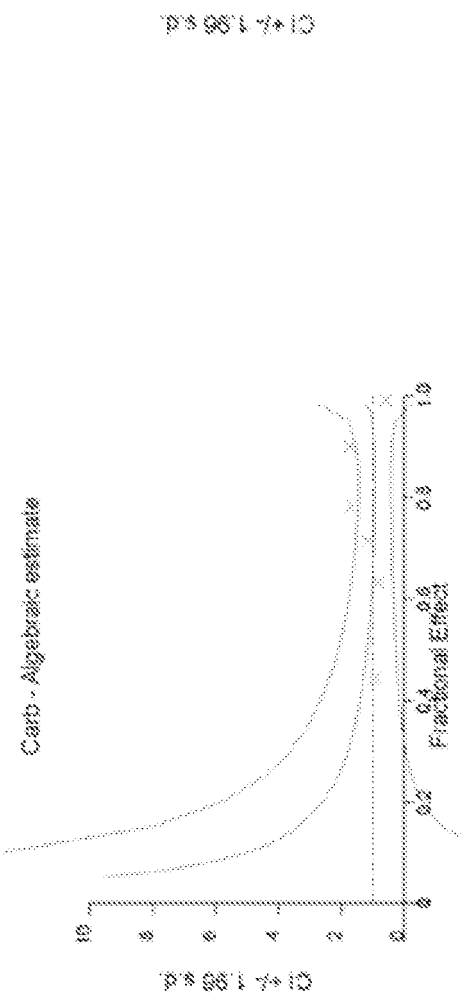
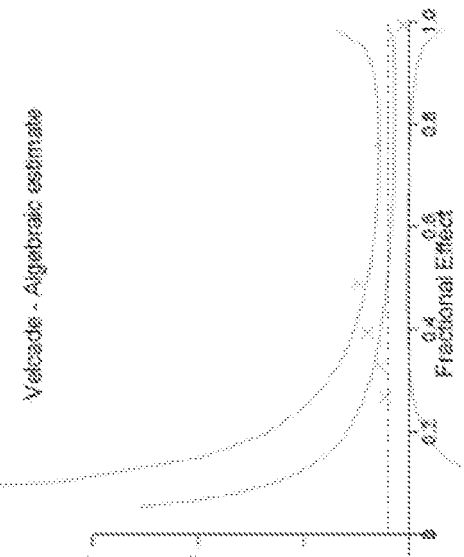

Lymph Nodes
SPD—ibrutinib single agent
SPD—ibrutinib + BR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
Screen
Cycle 2
Cycle 4
Cycle 5
Cycle 6
Cycle 8
Cycle 9
Cycle 11
Cycle 13
Cycles

Fig. 23

	Btk inhibitor (uM)	Carb(uM)
G150	0.096	15.382
r.	0.994	0.990

	Btk inhibitor (uM)	Velcade(uM)
G150	0.176	6.434
r.	0.986	0.850





CI For experimental values

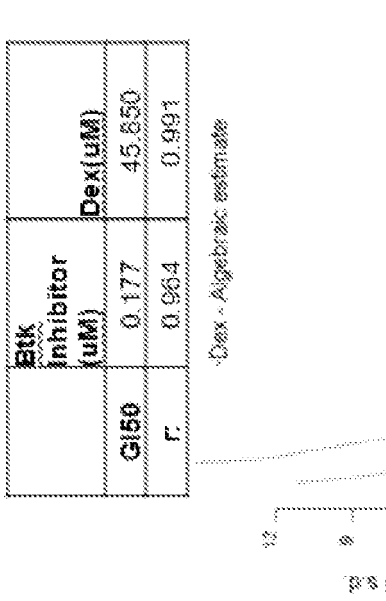
Btk inhibitor	Carb	Fa	CI
(uM)	(uM)		
0.03125	6.25	0.443223	0.954
0.0625	12.5	0.632339	0.828
0.125	25	0.715772	1.165
0.25	50	0.763398	1.718
0.5	100	0.899868	1.74
1	200	0.993211	0.564

CI For experimental values

Btk inhibitor	Velcade	Fa	CI
(uM)	(nM)		
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

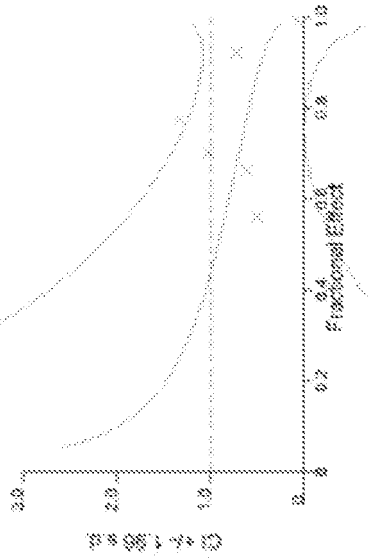
	Btk Inhibitor (uM)	Dex(uM)
GI50	0.177	45.850
r	0.964	0.991



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	0.760886	0.337
0.5	50	0.879476	0.249
1	100	0.968855	0.035

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

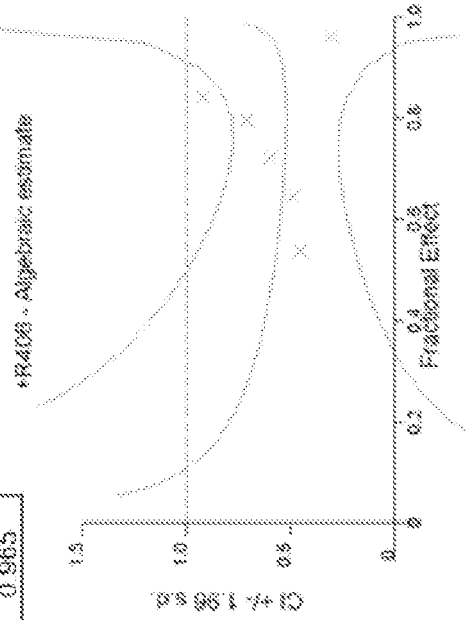


CI For experimental values

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	0.997	0.836	0.965



CI For experimental values

Btk inhibitor	Temsi	Fa	CI
(uM)	(uM)		
0.03125	0.3125	0.200943	3.779
0.0625	0.625	0.275482	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	0.99399	0.016

CI For experimental values

Btk inhibitor	R406	Fa	CI
(uM)	(uM)		
0.03125	3.125	0.33672	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)
G150	0.247	0.005	0.006
r	0.996	0.897	0.892

CI For experimental values

Btk inhibitor (uM)	Dox (uM)	Fa	CI
0.03125	0.0032	0.339005	1.356
0.0625	0.016	0.674194	1.256
0.125	0.08	0.899547	0.673
0.25	0.4	0.99899	0
0.5	2	0.99899	0.001
1	10	0.997236	2.032

CI For experimental values

Btk inhibitor (uM)	Gem (uM)	Fa	CI
0.03125	0.000192	0.238111	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

Fig. 27

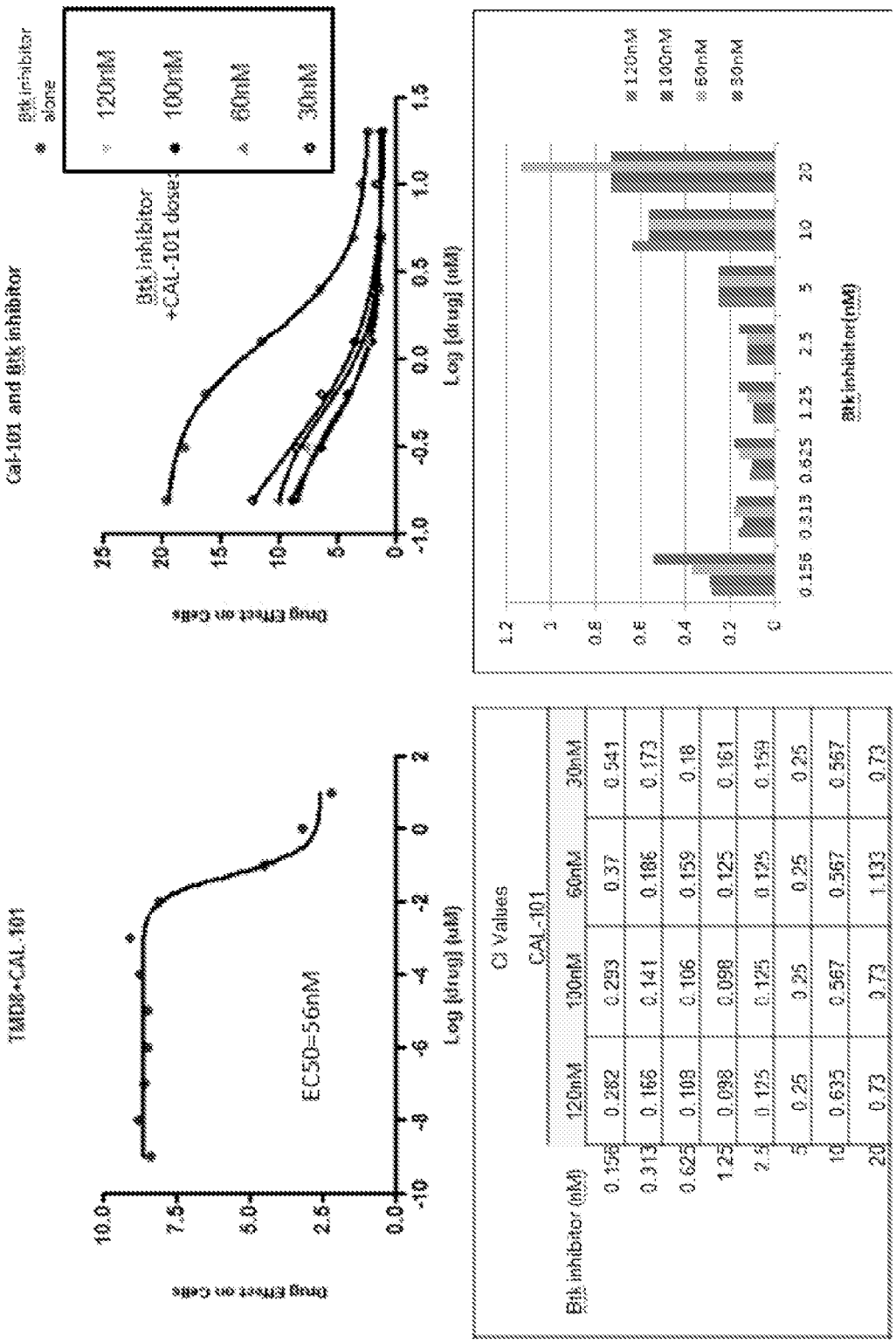

Cal-101 and Btk inhibitor
Btk inhibitor alone
120nM
100nM
60nM
30nM
Btk inhibitor +CAL-101 dose
Drug Effect on Cells
Log [drug] (nM)
TMD8+CAL-101
EC50=56nM
CI Values
CAL-101
Btk inhibitor (nM)
120nM
100nM
60nM
30nM
0.156 0.282 0.293 0.37 0.541
0.313 0.166 0.141 0.186 0.173
0.625 0.103 0.106 0.159 0.18
1.25 0.098 0.098 0.125 0.161
2.5 0.125 0.125 0.125 0.193
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

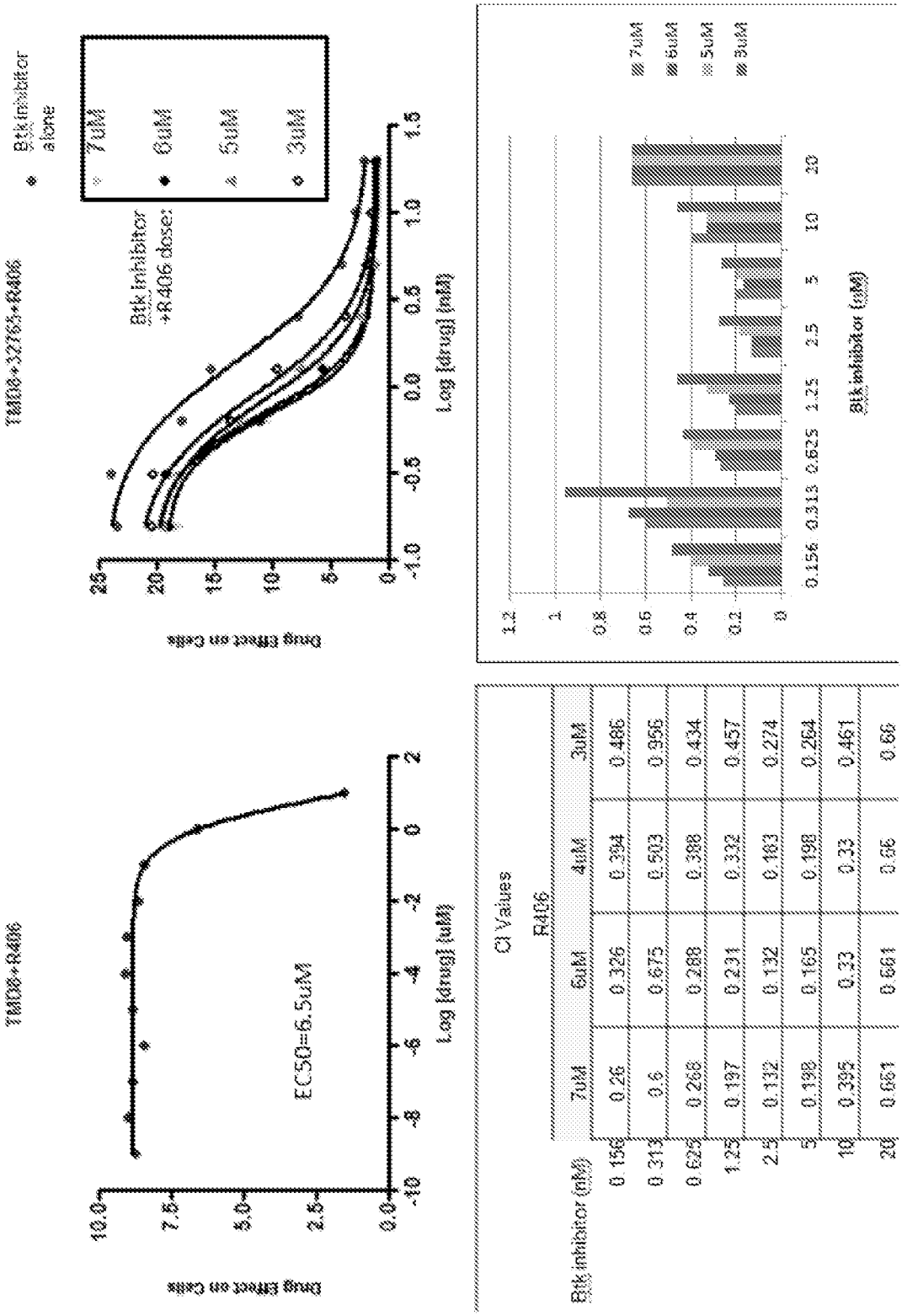
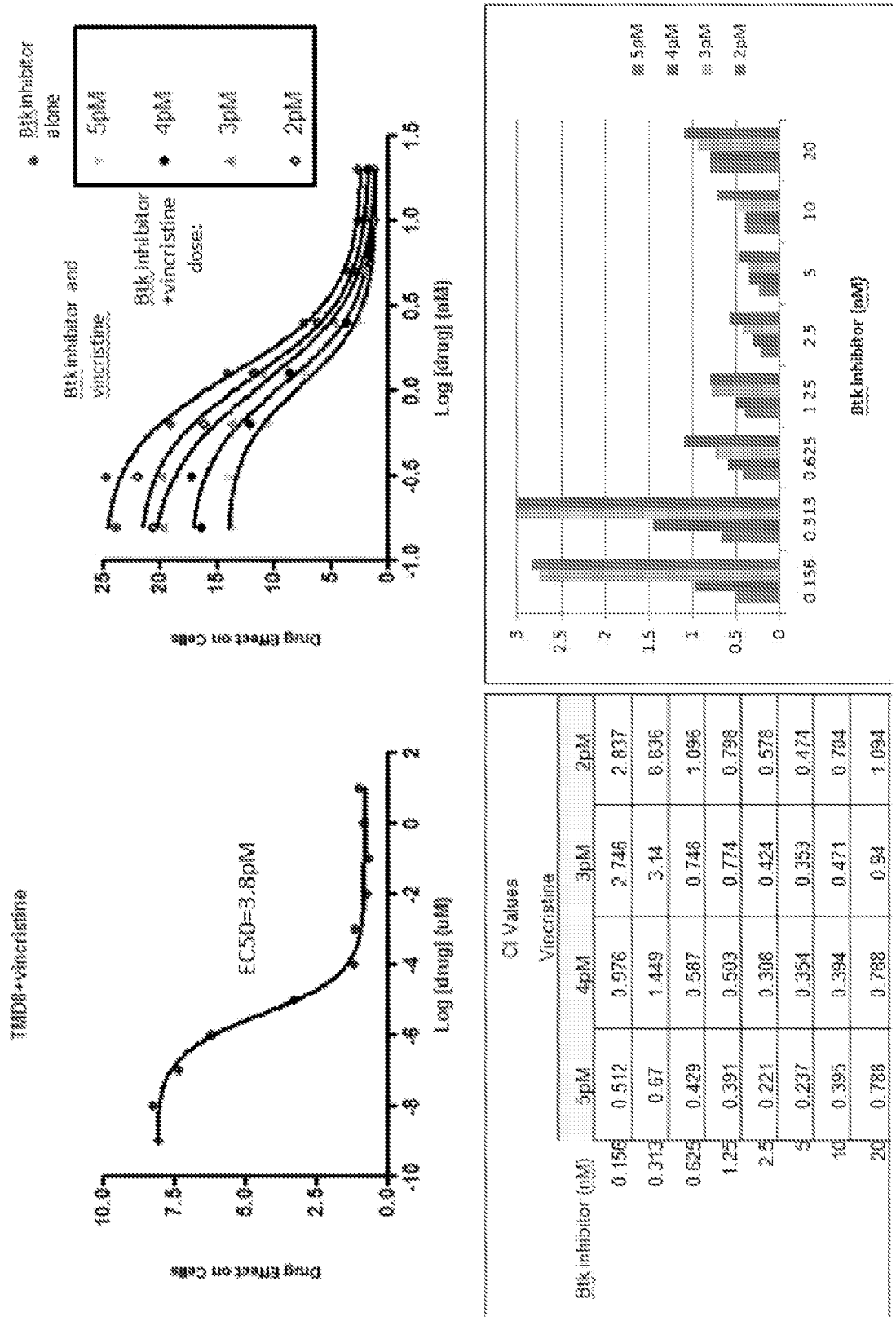
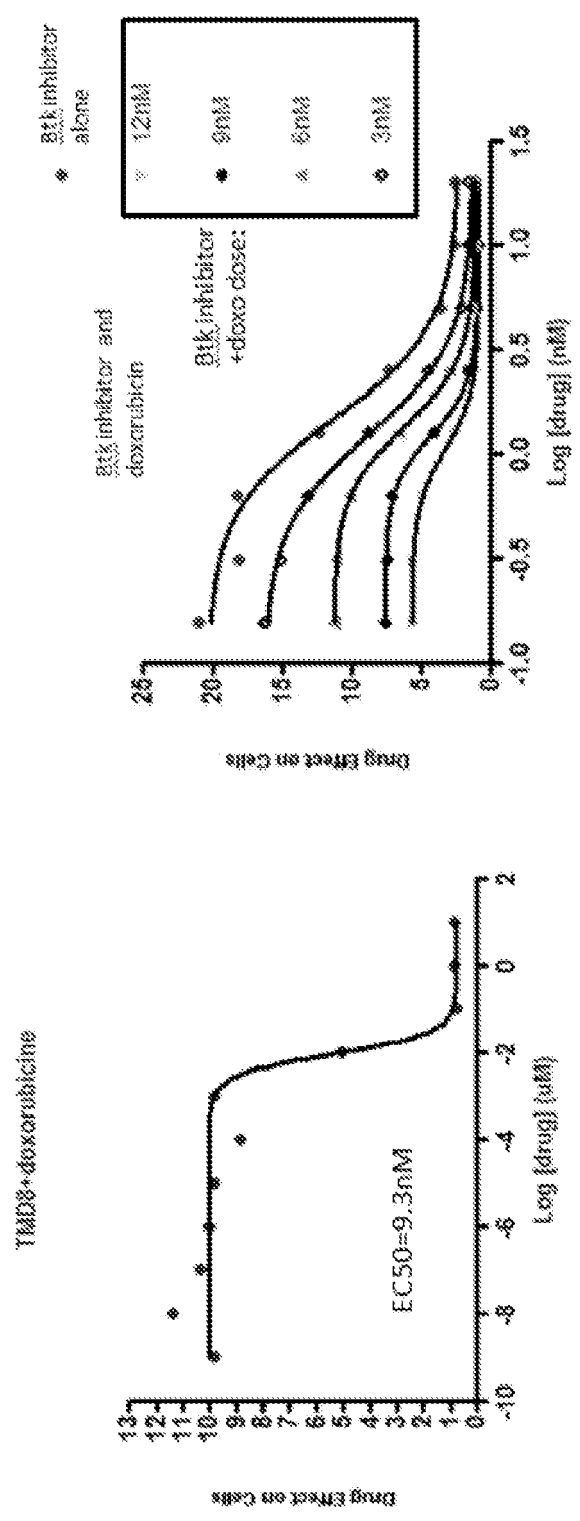

TM08+32765+R406
Btk inhibitor alone
Btk inhibitor +R406 dose:
7uM
6uM
5uM
3uM
Drug Effect on Cells
Log [drug] (uM)
TM08+R406
EC50=6.5uM
CI Values
R406
Btk inhibitor (nM)
7uM
6uM
4uM
3uM
0.156 0.26 0.326 0.394 0.486
0.313 0.6 0.675 0.503 0.356
0.625 0.268 0.268 0.388 0.434
1.25 0.197 0.231 0.332 0.457
2.5 0.132 0.132 0.163 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
Btk inhibitor (uM)

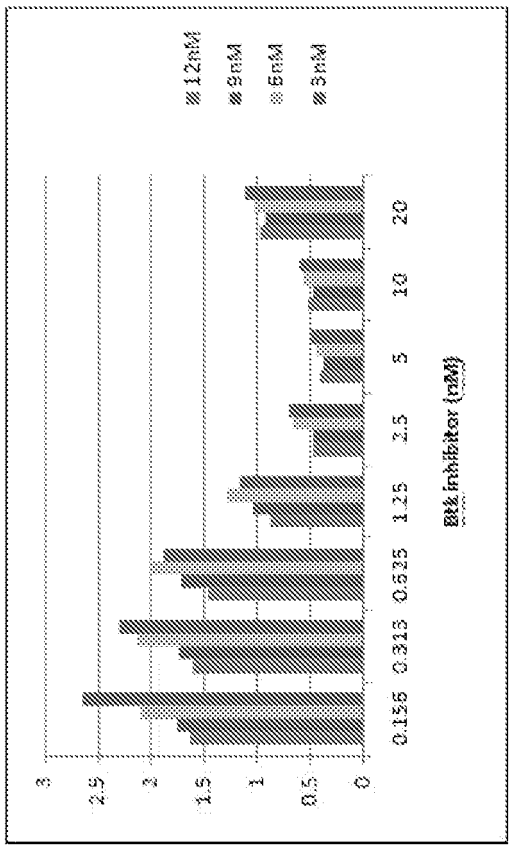
Fig. 29



Btk inhibitor (nM)	5pM	4pM	3pM	2pM
0.156	0.512	0.976	2.746	2.637
0.313	0.67	1.449	3.14	8.836
0.625	0.429	0.587	0.748	1.096
1.25	0.391	0.503	0.774	0.798
2.5	0.221	0.386	0.424	0.578
5	0.237	0.354	0.353	0.474
10	0.395	0.394	0.471	0.734
20	0.788	0.788	0.94	1.094

Fig. 30

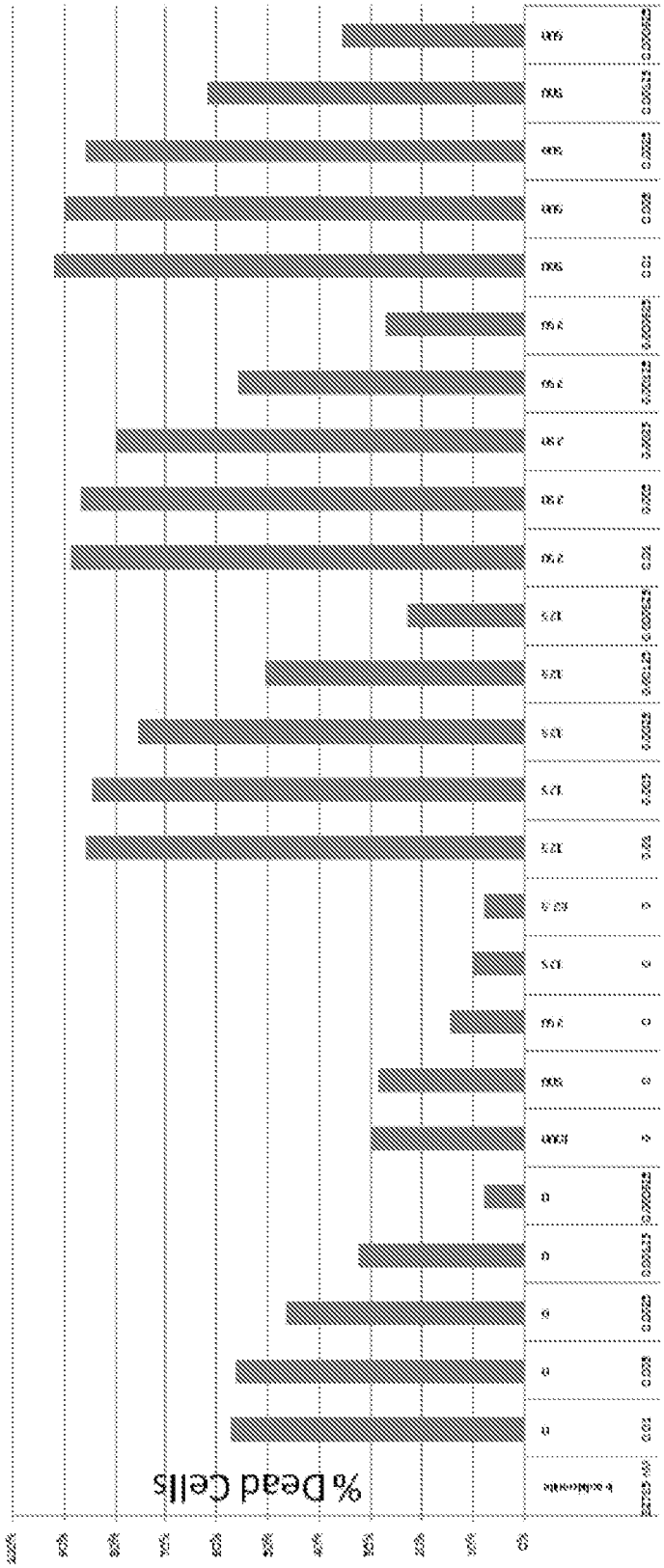




CI Values

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	1.45	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	0.469
10	0.534	0.464	0.559	0.602
20	0.987	0.936	1.034	1.105

Fig. 31

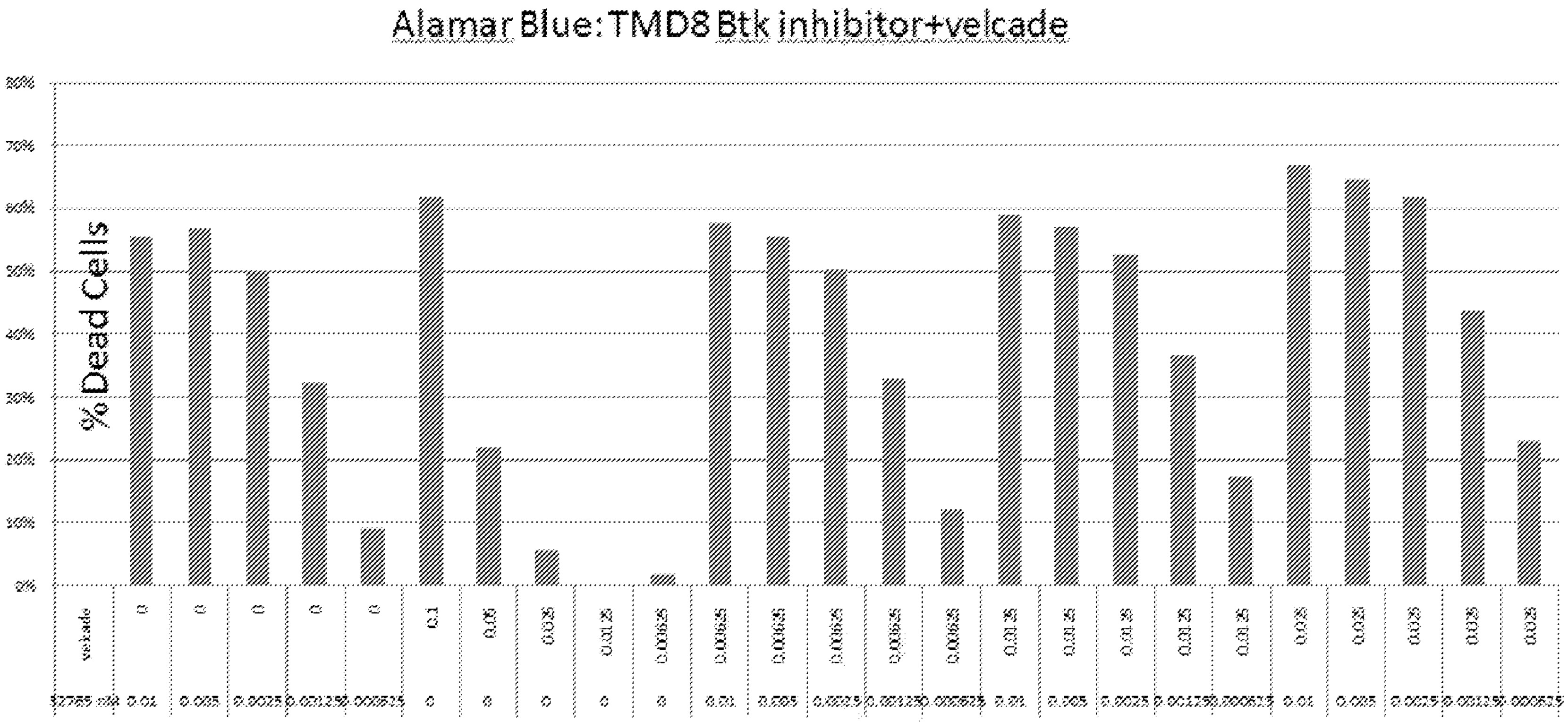


Btk inhibitor nM	lenolidomide nM	CI
0.000625	125	0.77
0.00125	125	0.311
0.0025	125	0.175
0.005	125	0.188
0.01	125	0.332

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	0.656
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	1.615

Btk inhibitor nM	velcade nM	CI
0.000625	0.0125	1.083
0.00125	0.0125	0.656
0.0025	0.0125	0.582
0.005	0.0125	0.868
0.01	0.0125	1.839

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	1.129

Fig. 33

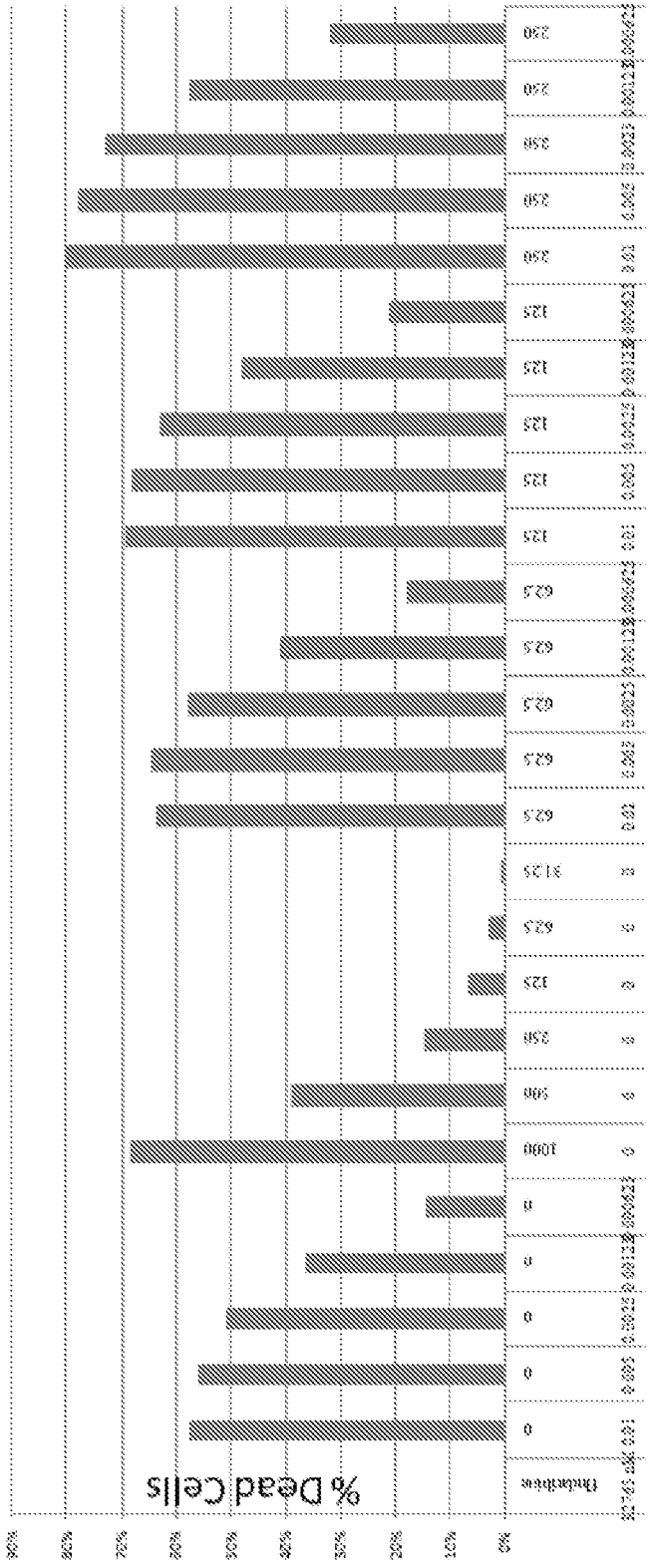
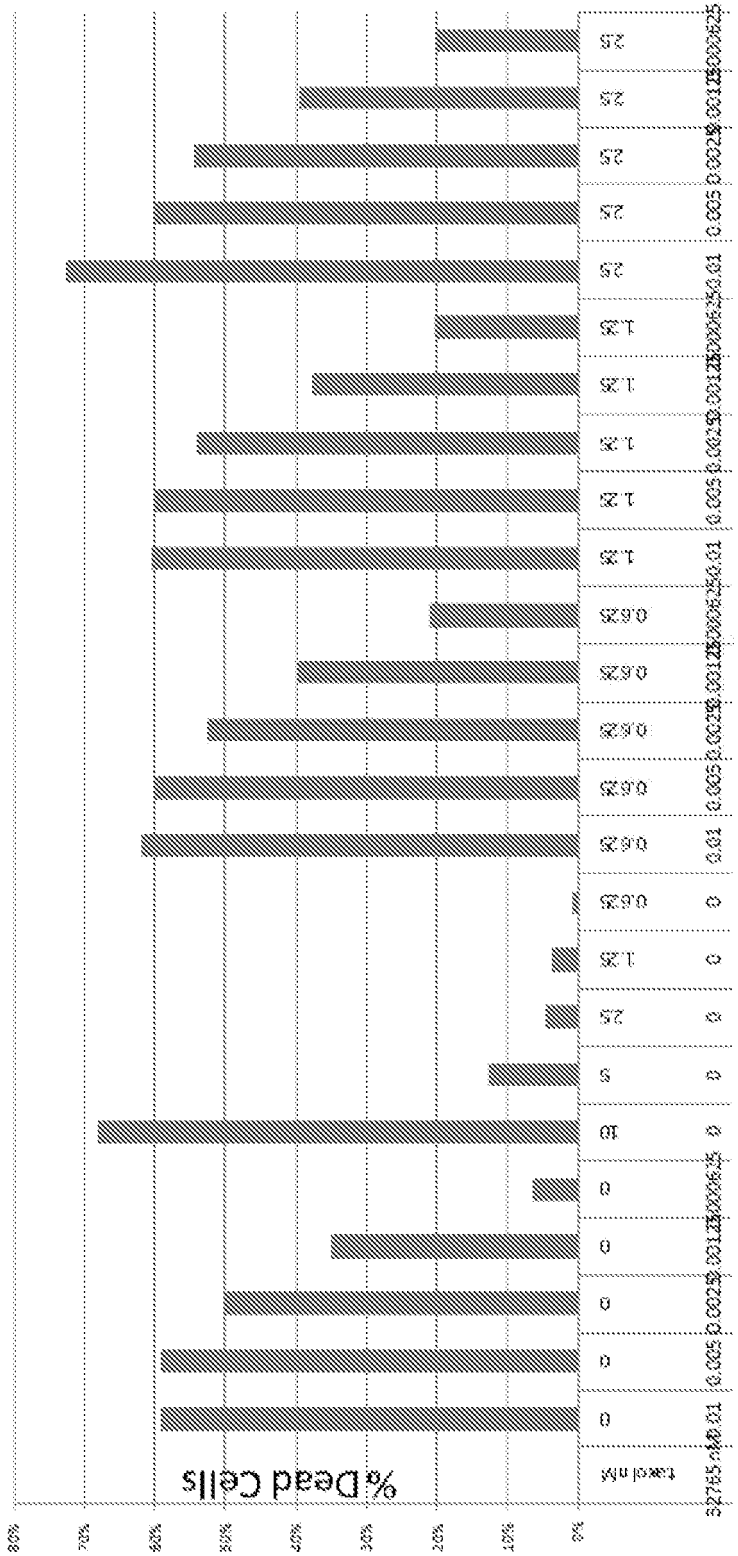

Alamar Blue: TMD8 Btk inhibitor+Fludarabine
% Dead Cells
Btk inhibitor nM
fludarabine nM
CI
0.00125
62.5
0.636
0.0025
62.5
0.474
0.005
62.5
0.598
0.01
125
0.548
0.0025
125
0.427
0.005
125
0.542
0.01
125
0.689
0.00125
250
0.518
0.0025
250
0.356
0.005
250
0.383
0.01
250
0.518

Fig. 34



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	1.106

Btk inhibitor nM	taxol nM	CI
0.000625	1.25	0.85
0.00125	1.25	0.864
0.0025	1.25	0.634
0.005	1.25	0.918
0.01	1.25	1.203

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	1.084

Fig. 35

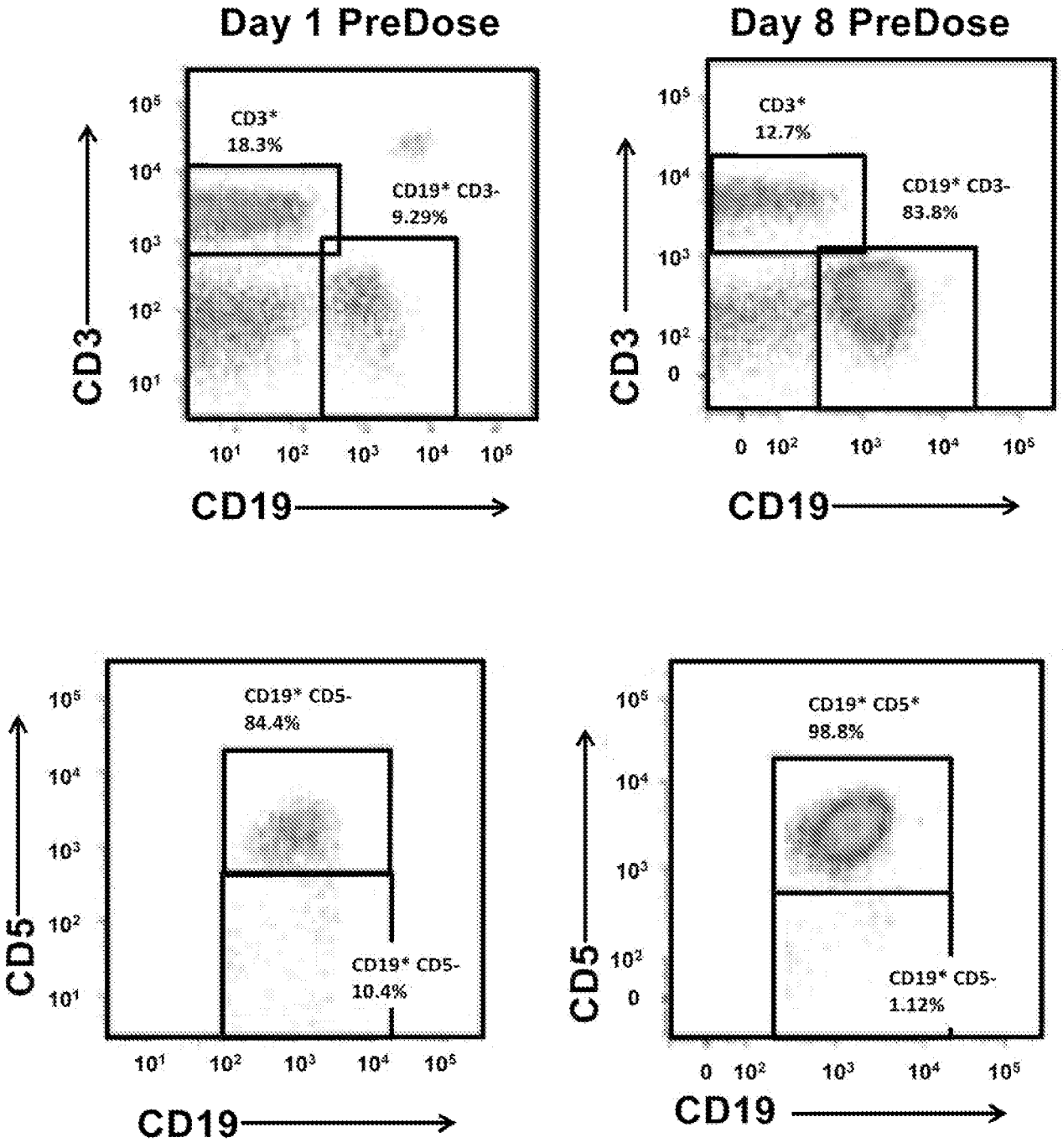
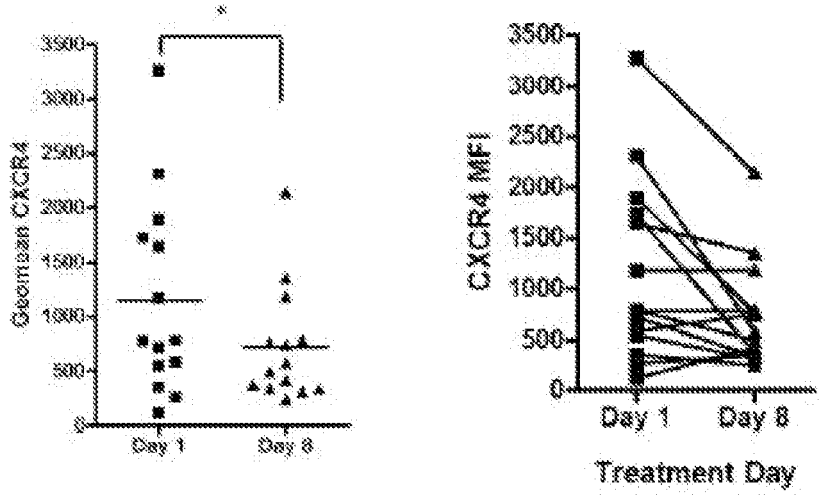

Day 1 PreDose
CD3*
18.3%
CD19* CD3-
9.29%
CD3
CD19
Day 8 PreDose
CD3*
12.7%
CD19* CD3-
83.8%
CD3
CD19
CD19* CD5-
84.4%
CD19* CD5-
10.4%
CD5
CD19
CD19* CD5*
98.8%
CD19* CD5-
1.12%
CD5
CD19

Fig. 36

A.


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

B.

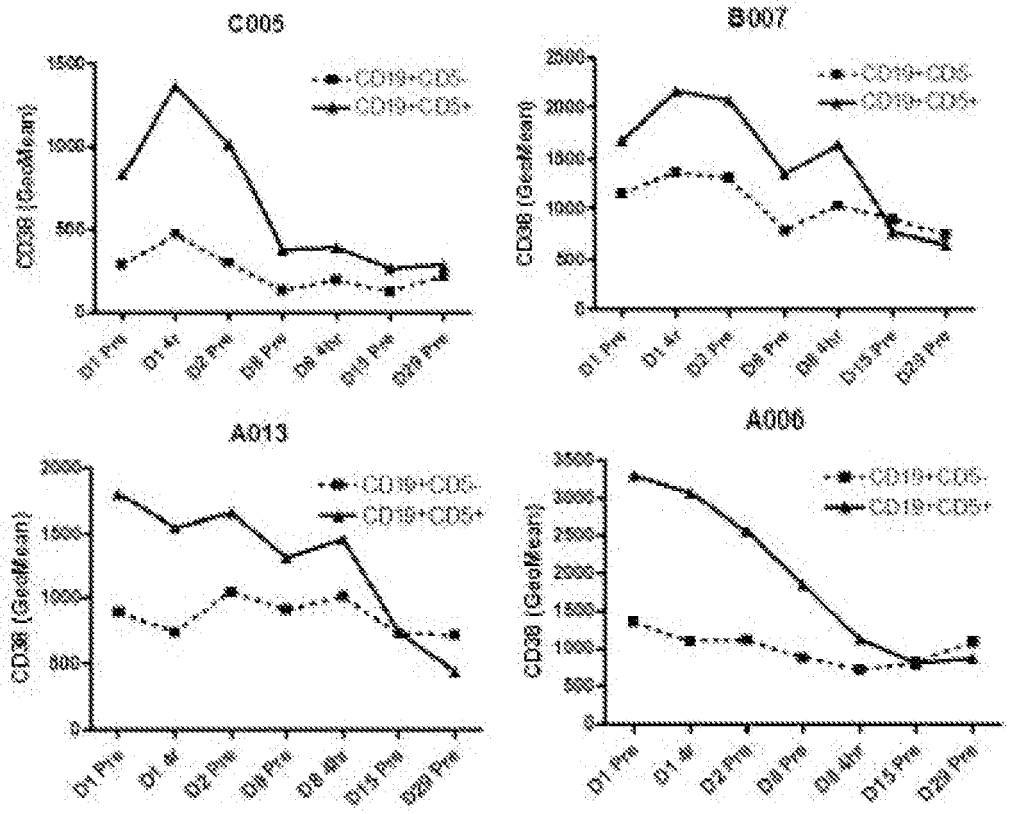
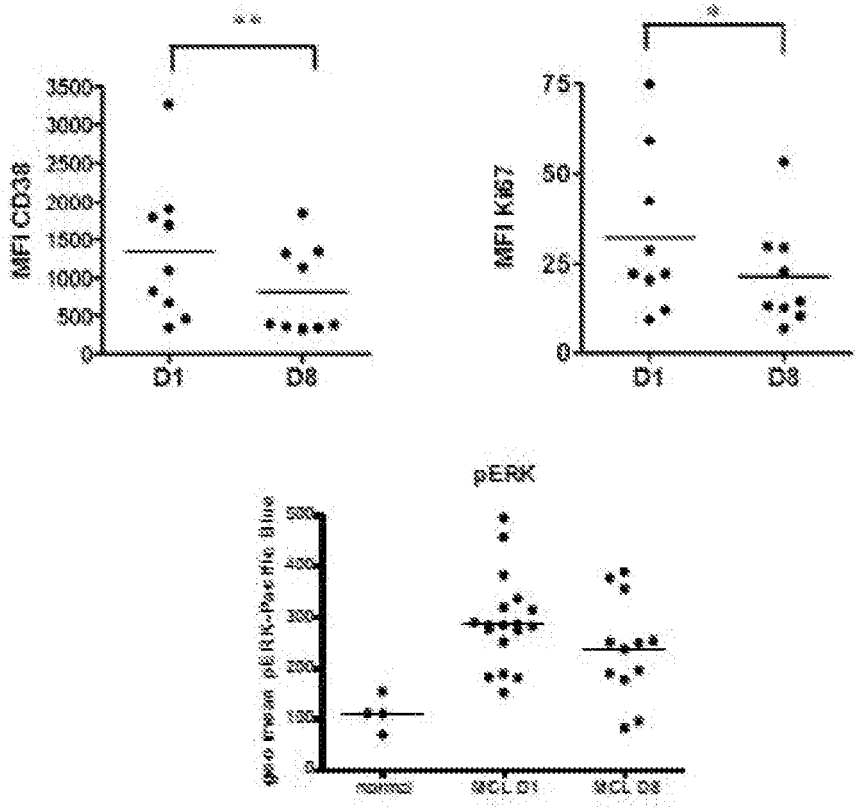

C005
B007
A013
A006
CD38 (GeoMean)
CD19+CD5-
CD19+CD5+

Fig. 36 (cont'd)

C.



D.

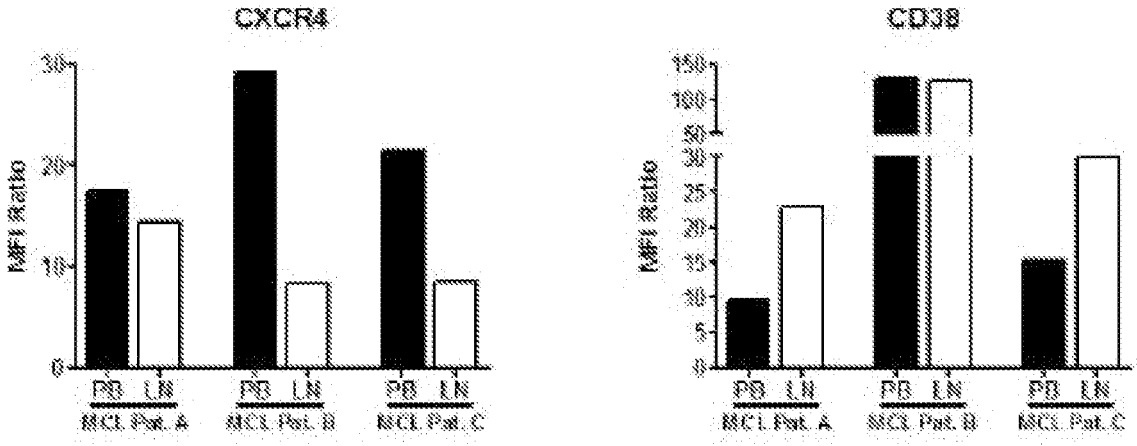


Fig. 36 (cont'd)

E.

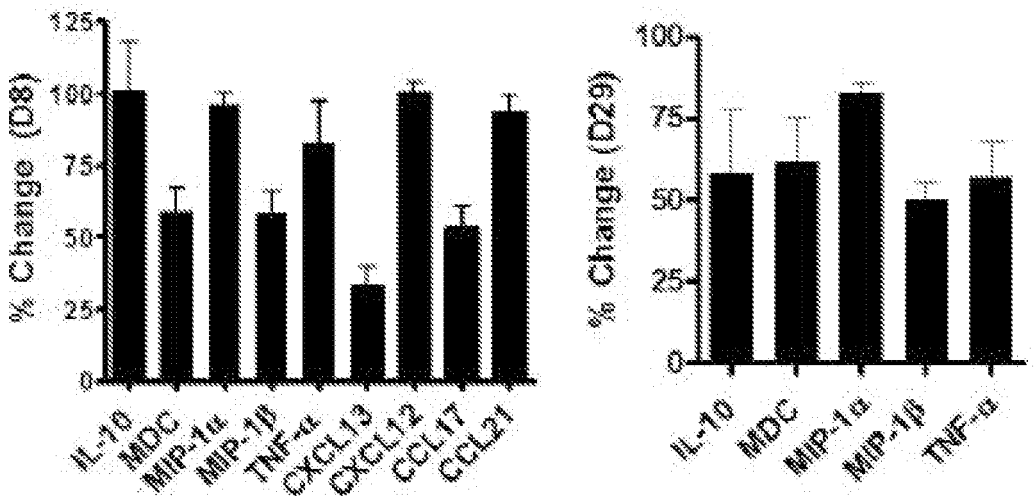
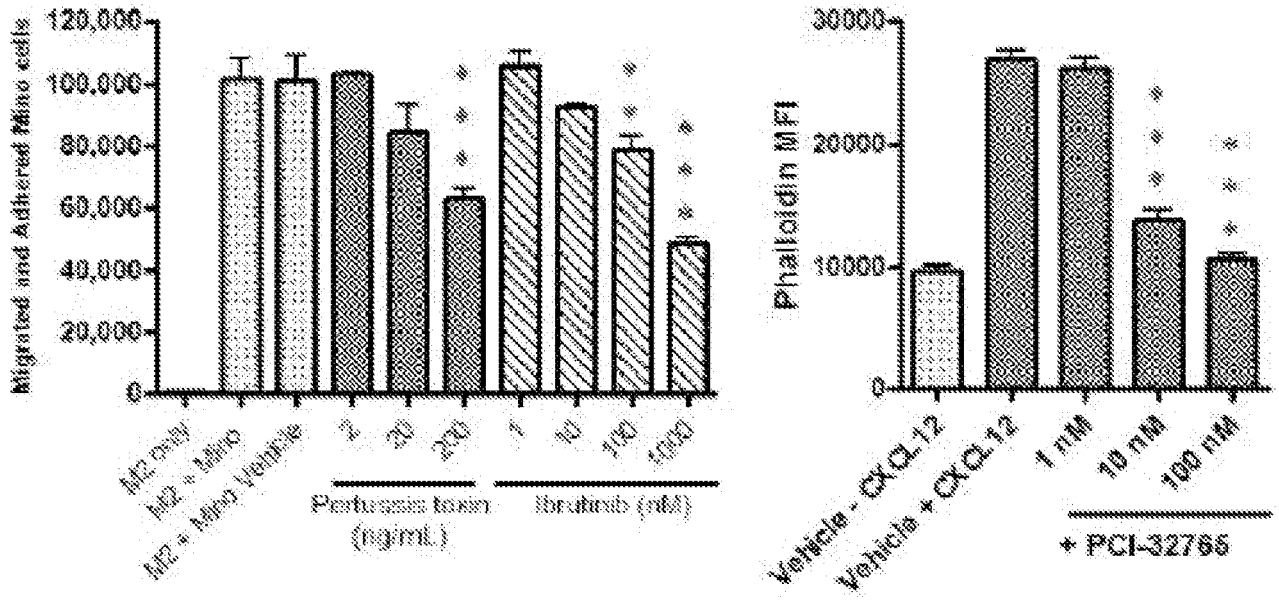
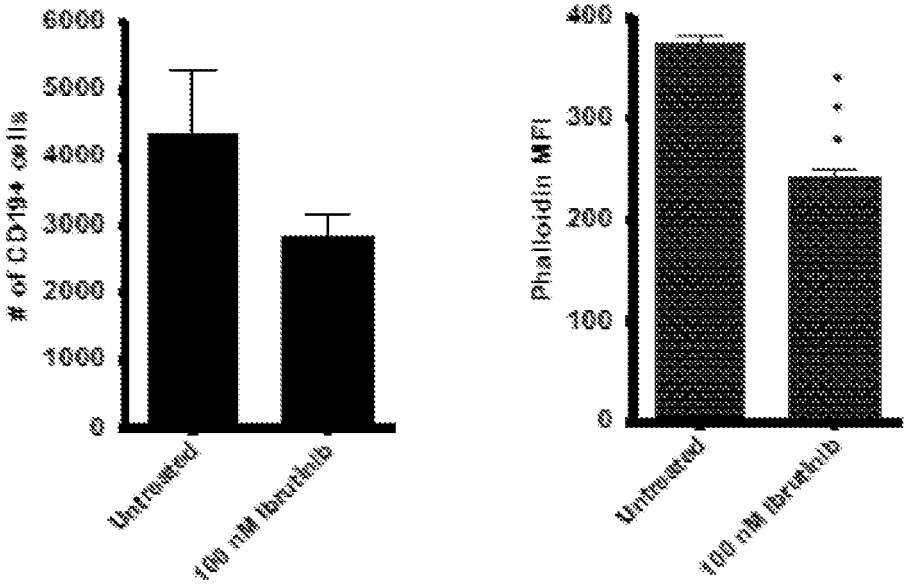


Fig. 37

A


Migrated and Adhered Mino cells
120,000
100,000
80,000
60,000
40,000
20,000
0
MZ only
MZ + Mino
MZ + Mino Vehicle
Pertussis toxin (ng/mL)
Ibrutinib (nM)
Phalloidin MFI
30000
20000
10000
0
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