FIGURE 1

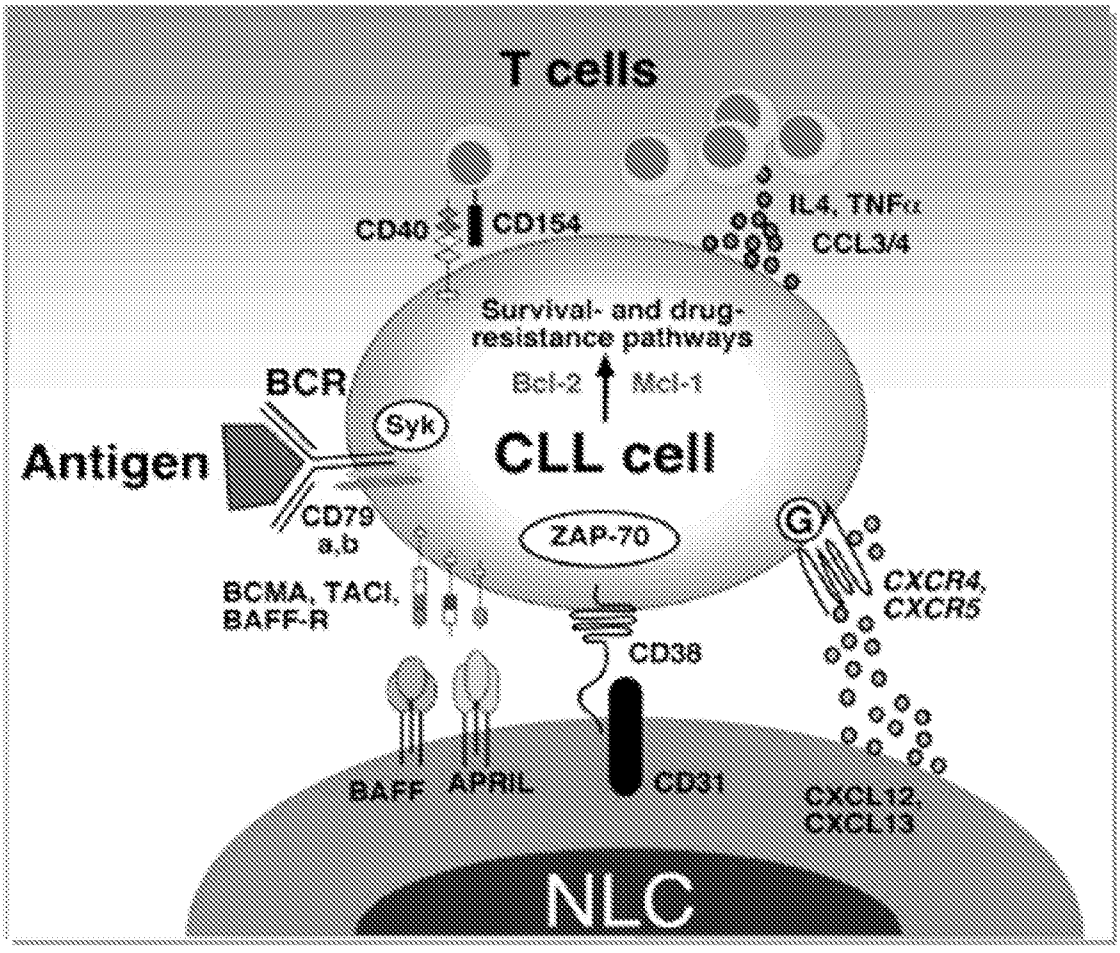

T cells
CD40
CD154
IL4, TNFα
CCL3/4
Survival- and drug-resistance pathways
Bcl-2
Mcl-1
BCR
Antigen
Syk
CLL cell
CD79 a,b
ZAP-70
BCMA, TACI, BAFF-R
CXCR4, CXCR5
CD38
BAFF
APRIL
CD31
CXCL12, CXCL13
NLC

FIGURE 2

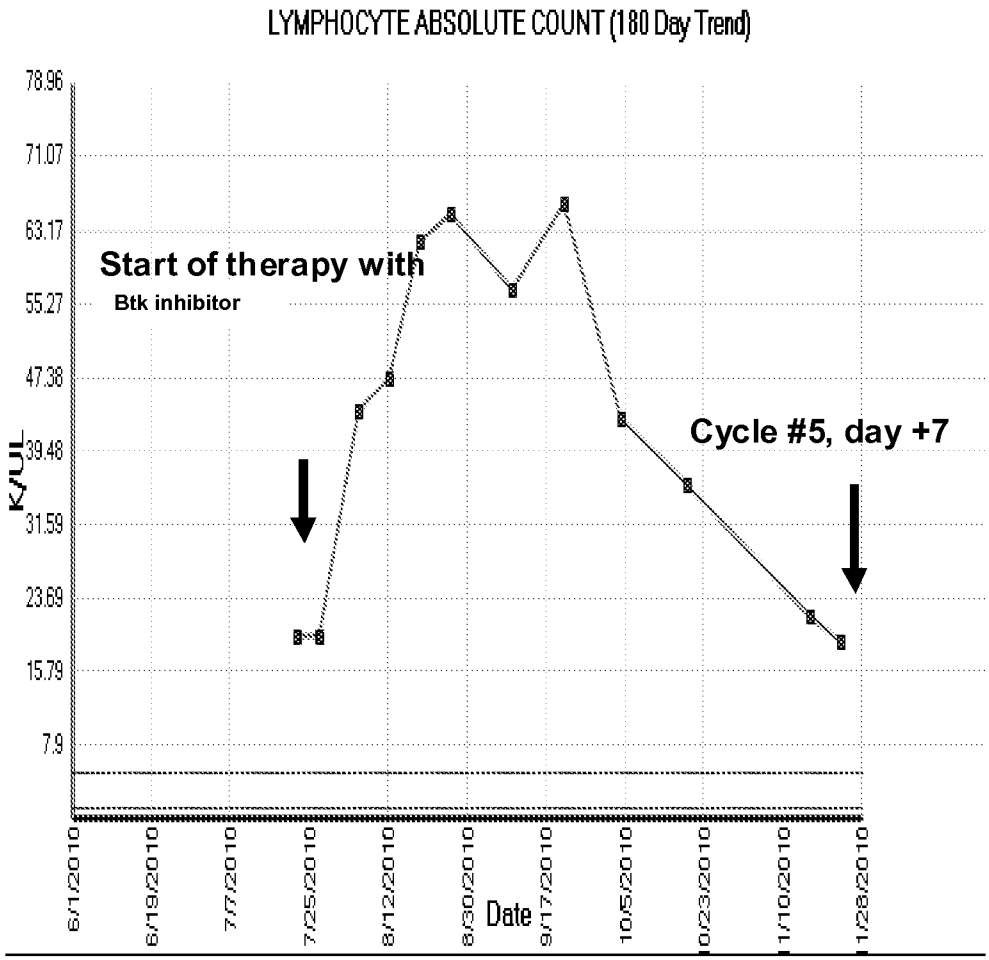

LYMPHOCYTE ABSOLUTE COUNT (180 Day Trend)
78.96
71.07
63.17
55.27
47.38
39.48
31.59
23.69
15.79
7.9
K/UL
Start of therapy with
Btk inhibitor
Cycle #5, day +7
6/1/2010
6/19/2010
7/7/2010
7/25/2010
8/12/2010
8/30/2010
9/17/2010
10/5/2010
10/23/2010
11/10/2010
11/28/2010
Date

FIGURE 3

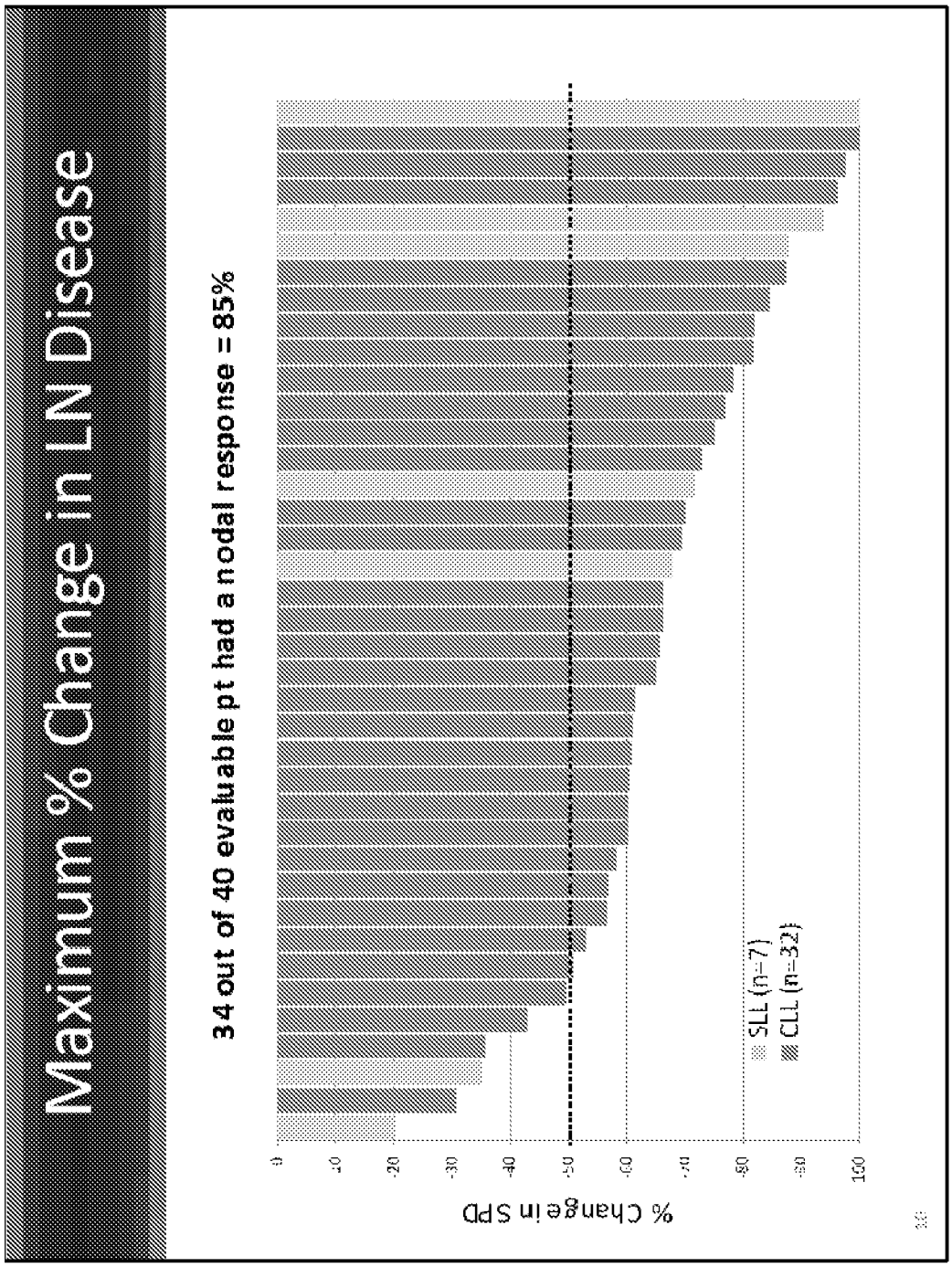

Maximum % Change in LN Disease
34 out of 40 evaluable pt had a nodal response = 85%
% Change in SPD
SLL (n=7)
CLL (n=32)

FIGURE 4



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

FIGURE 5

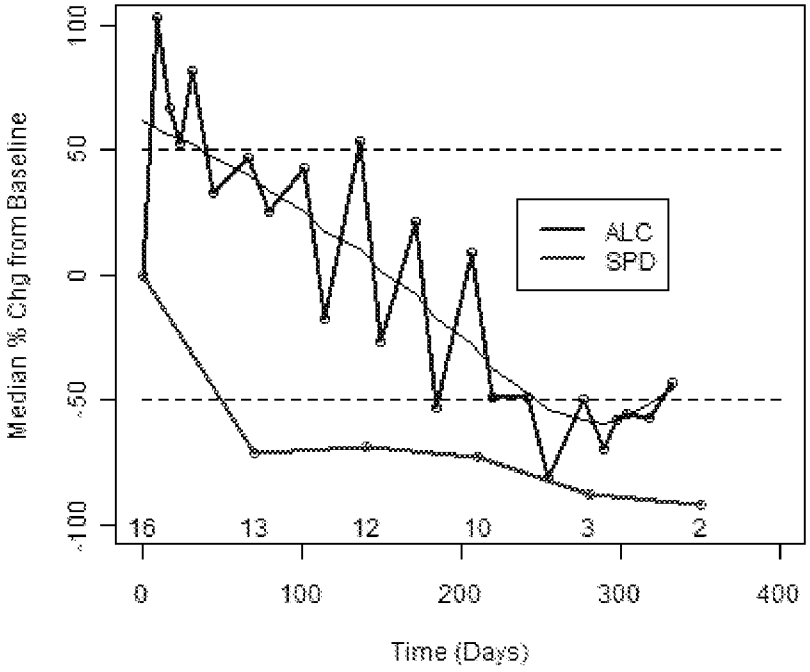

Median % Chg from Baseline
100
50
0
-50
-100
ALC
SPD
16
13
12
10
3
2
0
100
200
300
400
Time (Days)

FIGURE 6

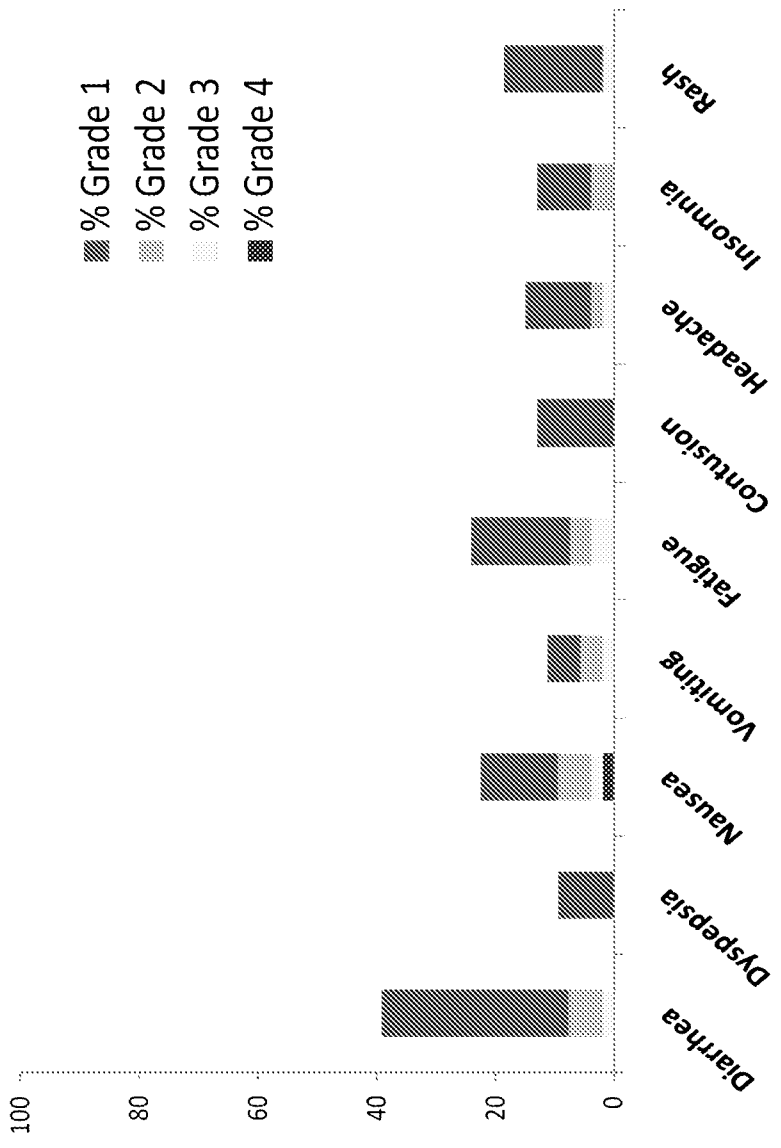

% Grade 1
% Grade 2
% Grade 3
% Grade 4
Diarrhea
Dyspepsia
Nausea
Vomiting
Fatigue
Contusion
Headache
Insomnia
Rash
0
20
40
60
80
100

FIGURE 7

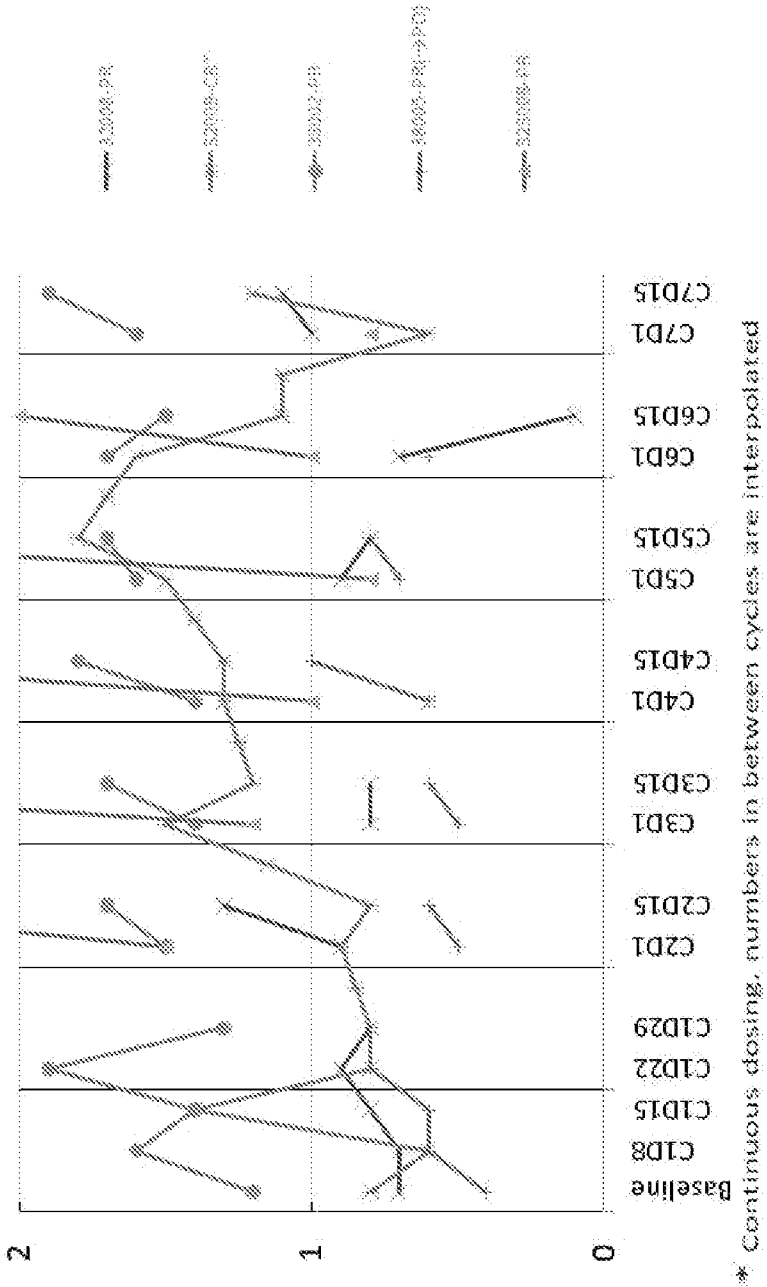

2
1
0
Baseline
C1D8
C1D15
C1D22
C1D29
C2D1
C2D15
C3D1
C3D15
C4D1
C4D15
C5D1
C5D15
C6D1
C6D15
C7D1
C7D15
* Continuous dosing, numbers in between cycles are interpolated

FIGURE 8

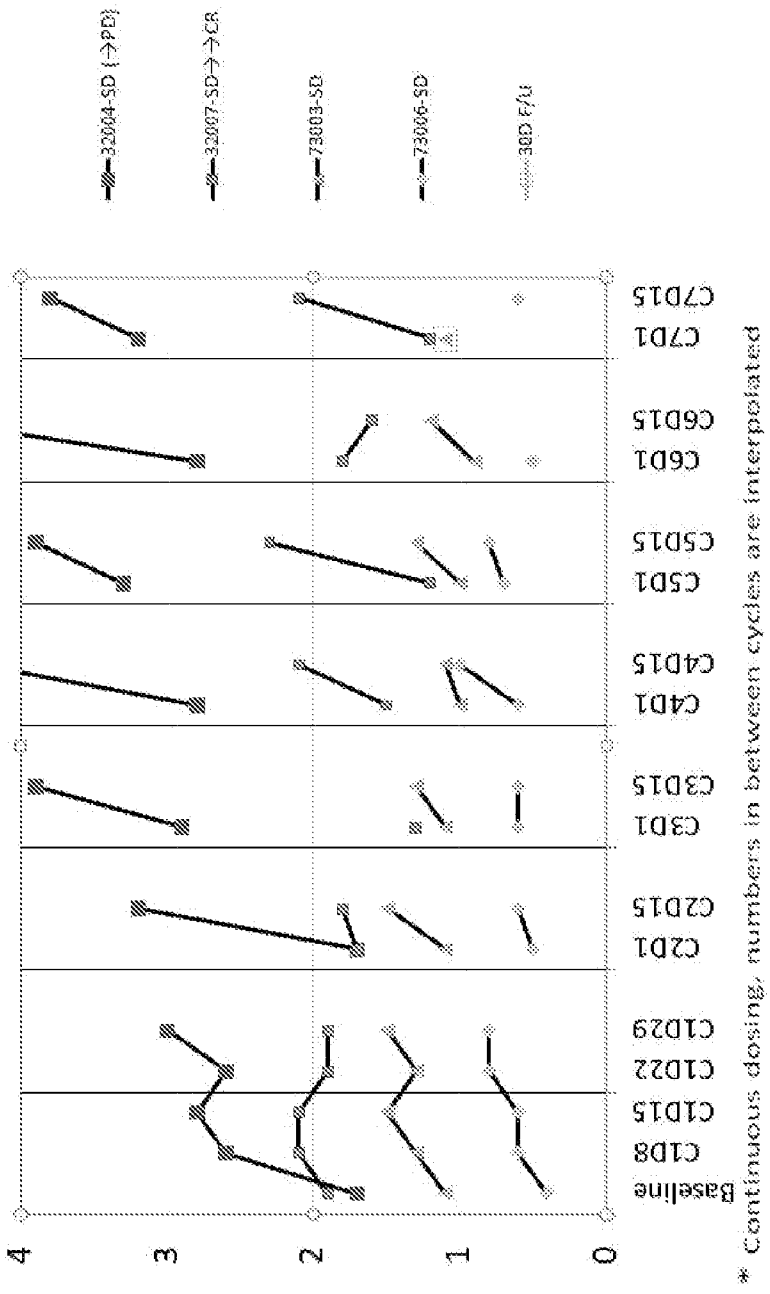

32004-SD (→PD)
32007-SD→→CR
73003-SD
73006-SD
38D F/U
4
3
2
1
0
Baseline
C1D8
C1D15
C1D22
C1D29
C2D1
C2D15
C3D1
C3D15
C4D1
C4D15
C5D1
C5D15
C6D1
C6D15
C7D1
C7D15
* Continuous dosing, numbers in between cycles are interpolated

FIGURE 9

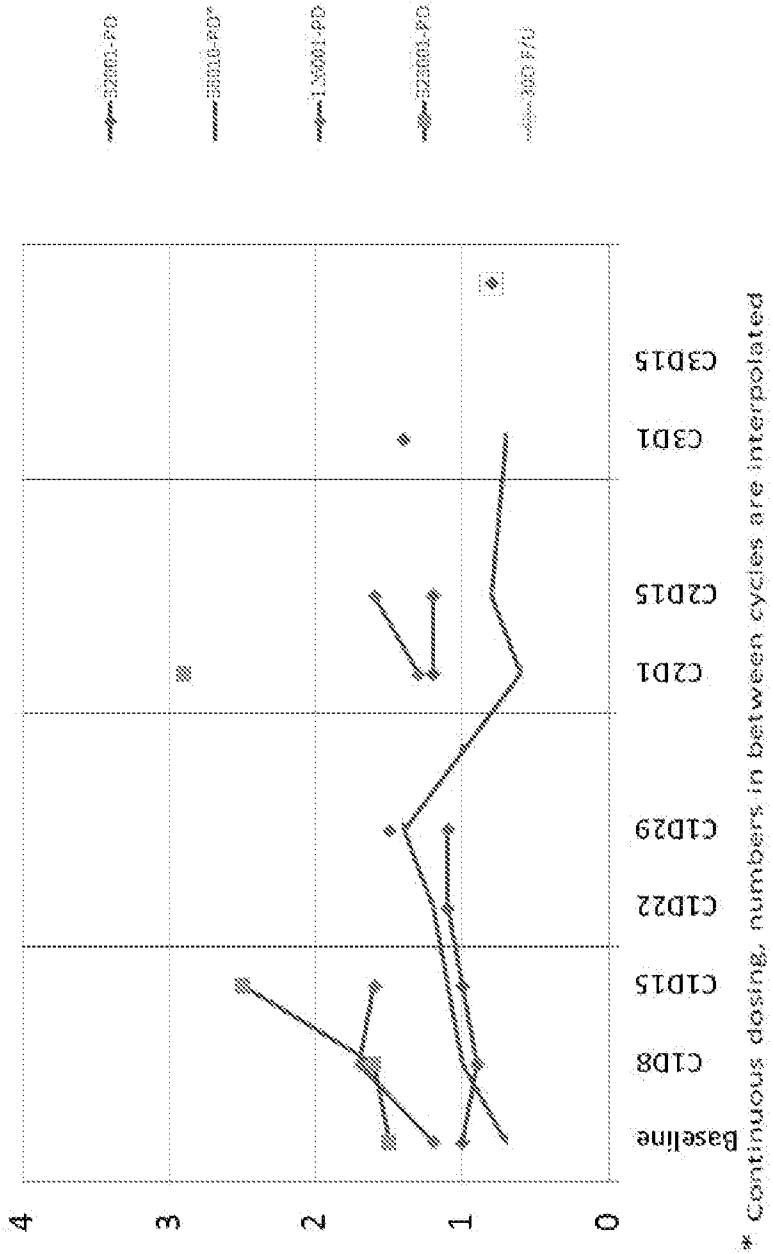
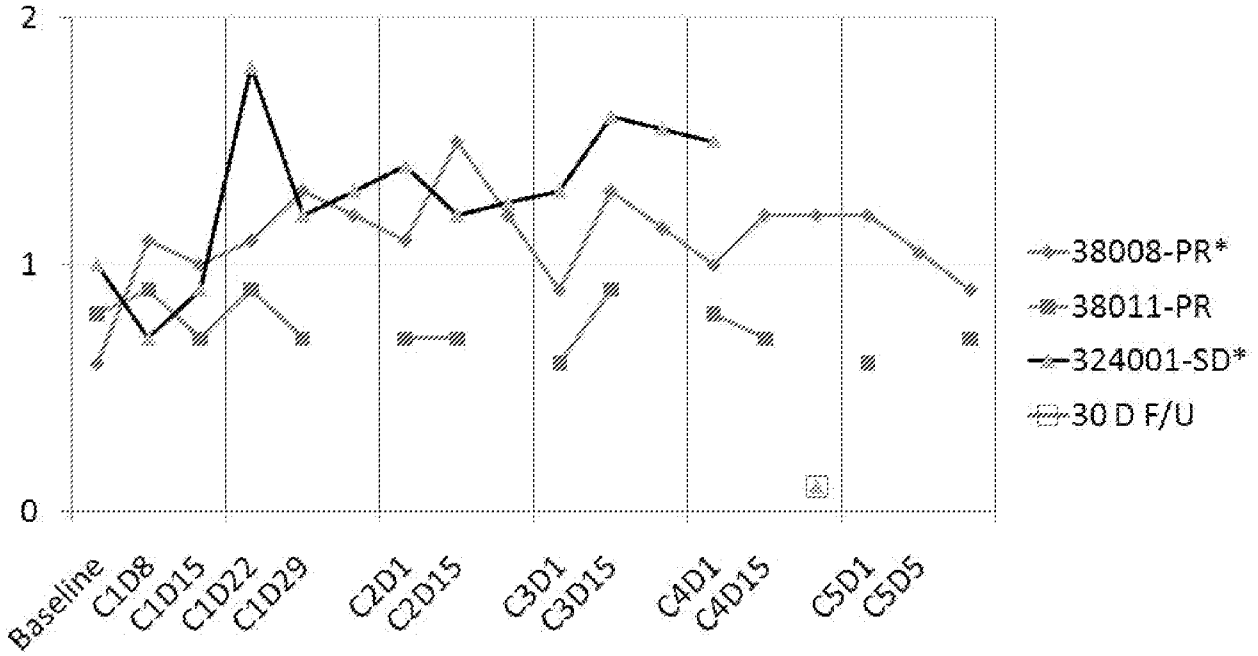

4
3
2
1
0
Baseline
C1D8
C1D15
C1D22
C1D29
C2D1
C2D15
C3D1
C3D15
* Continuous dosing, numbers in between cycles are interpolated

FIGURE 10



* Continuous dosing, numbers in between cycles are interpolated

FIGURE 11

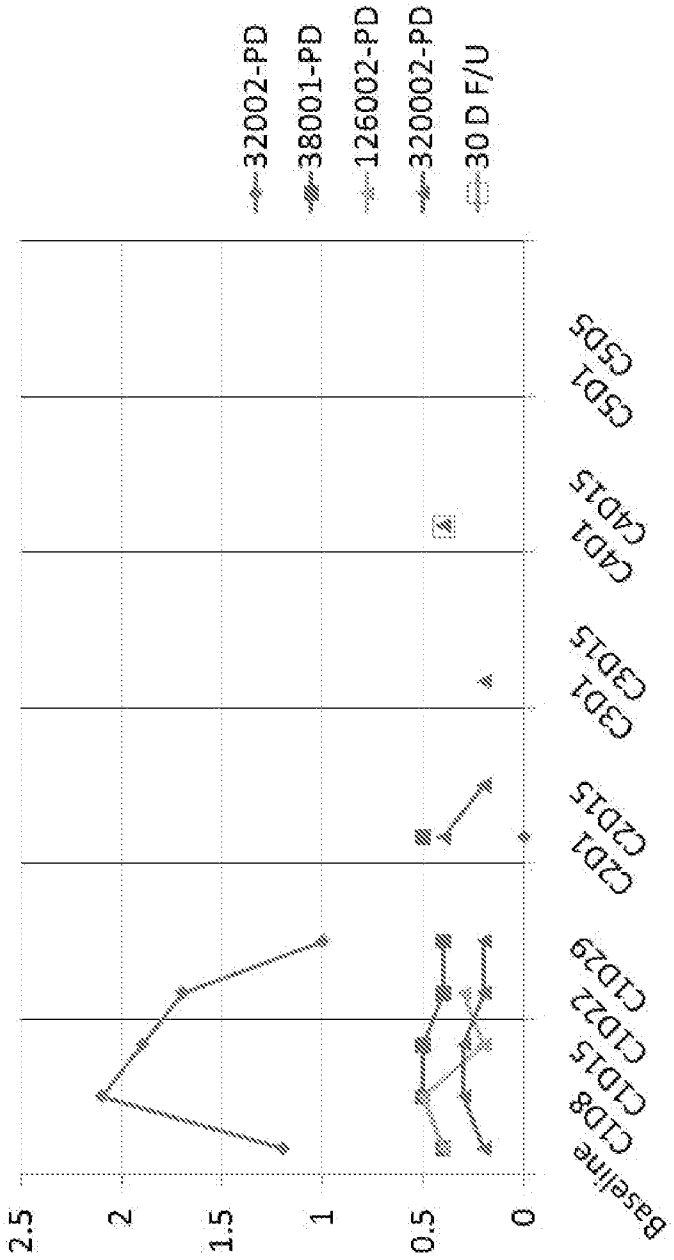
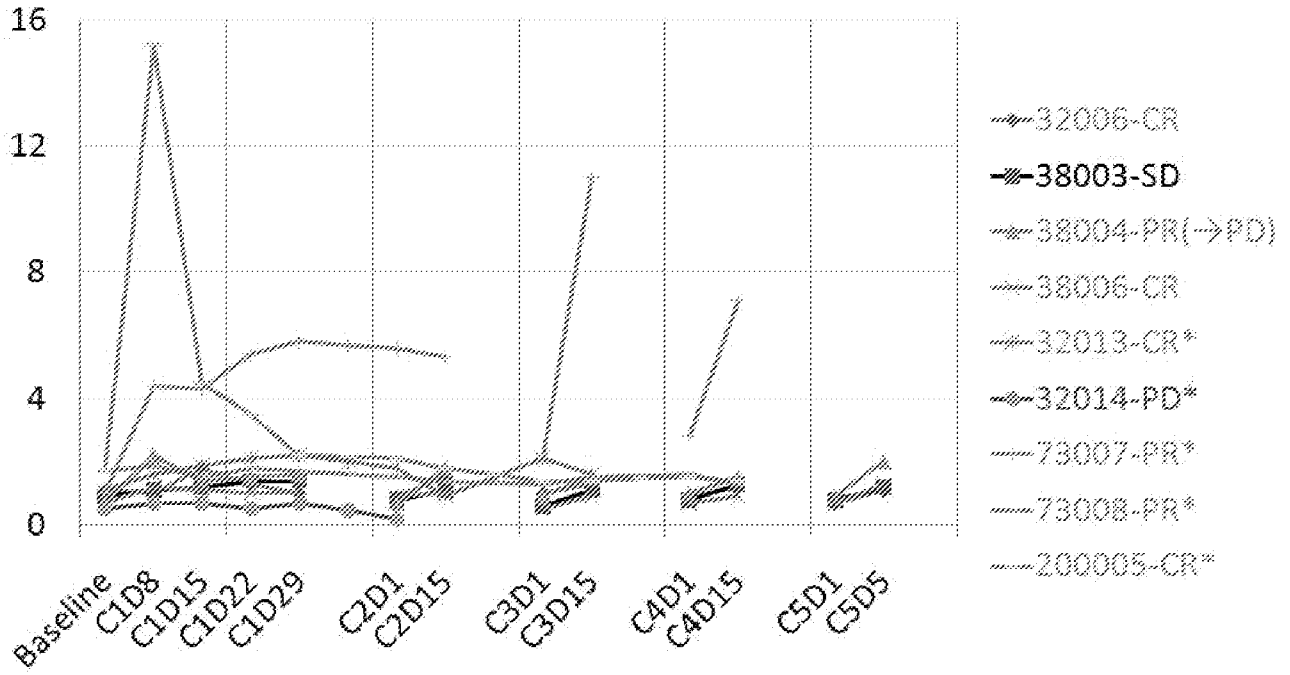

32002-PD
38001-PD
126002-PD
320002-PD
30 D F/U
2.5
2
1.5
1
0.5
0
Baseline
C1D8
C1D15
C1D22
C1D29
C2D1
C2D15
C3D1
C3D15
C4D1
C4D15
C5D1
C5D5

FIGURE 12



* Continuous dosing, numbers in between cycles are interpolated

FIGURE 13

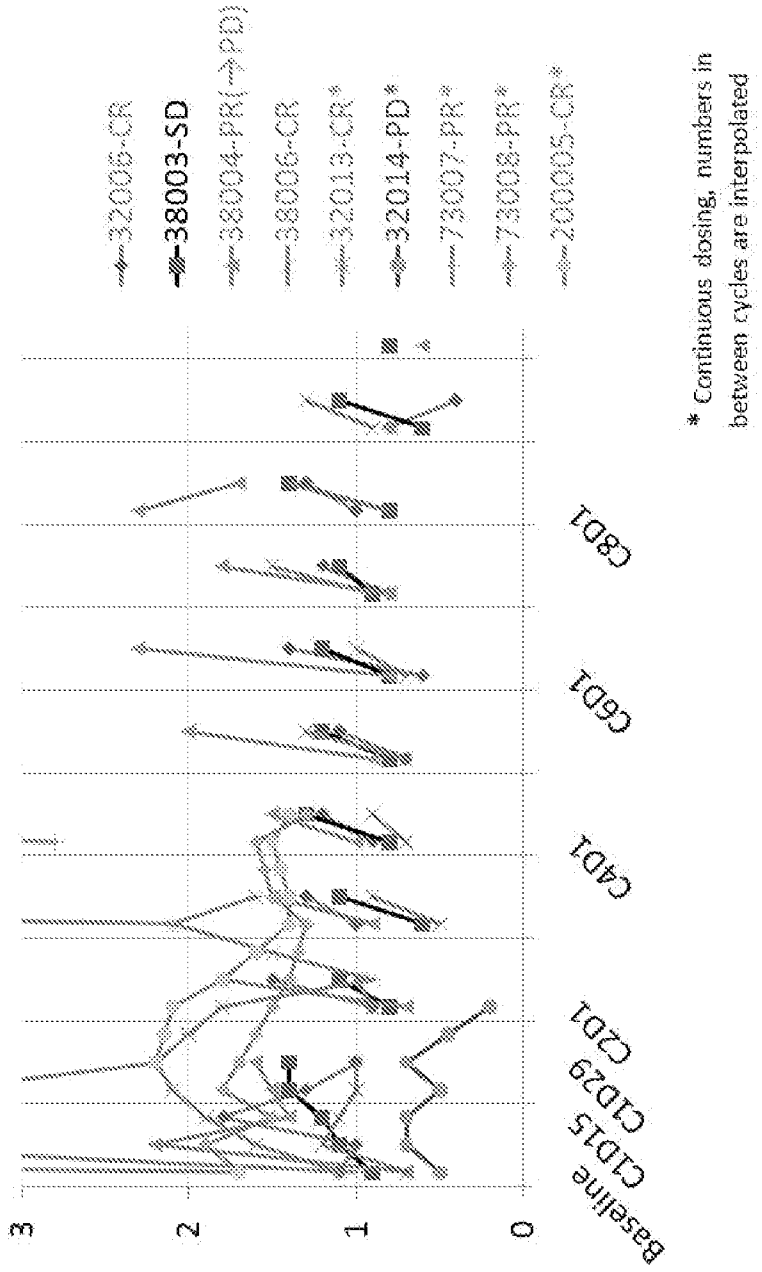

32006-CR
38003-SD
38004-PR(→PD)
38006-CR
32013-CR*
32014-PD*
73007-PR*
73008-PR*
200005-CR*
3
2
1
0
Baseline
C1D15
C1D29
C2D1
C4D1
C6D1
C8D1
* Continuous dosing, numbers in between cycles are interpolated

FIGURE 14

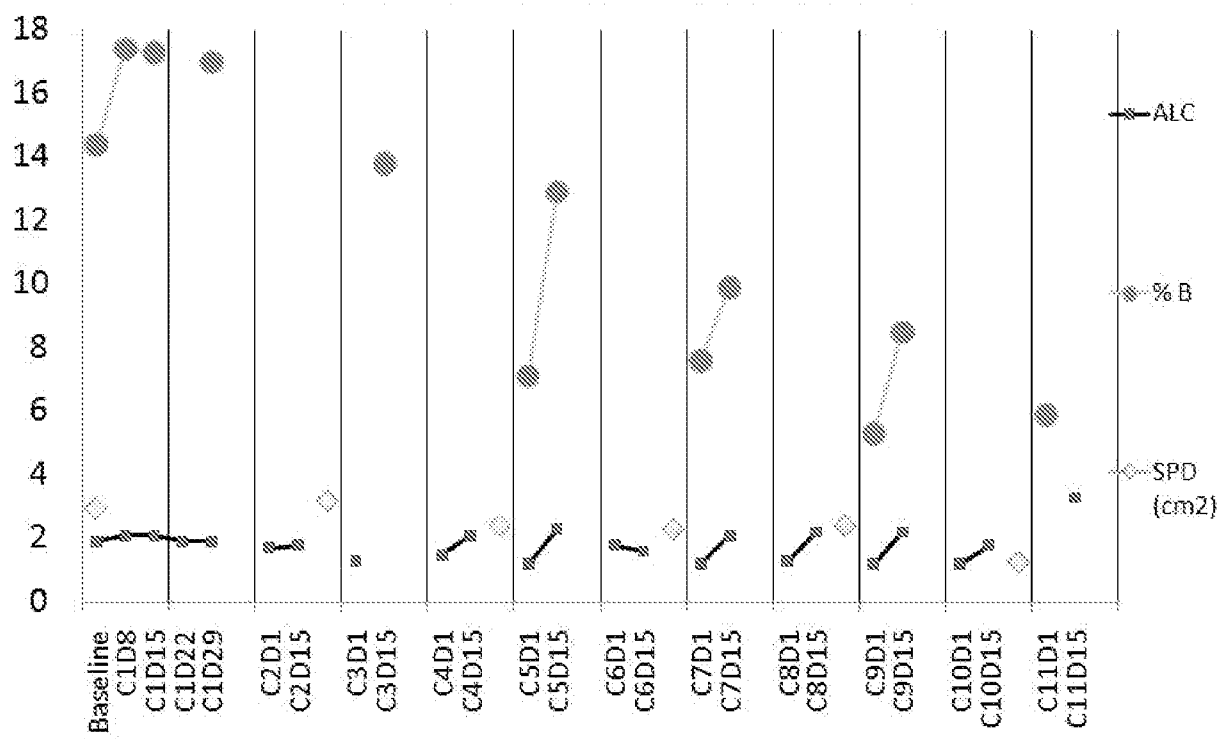

18
16
14
12
10
8
6
4
2
0
ALC
% B
SPD (cm2)
Baseline
C1D8
C1D15
C1D22
C1D29
C2D1
C2D15
C3D1
C3D15
C4D1
C4D15
C5D1
C5D15
C6D1
C6D15
C7D1
C7D15
C8D1
C8D15
C9D1
C9D15
C10D1
C10D15
C11D1
C11D15

FIGURE 15

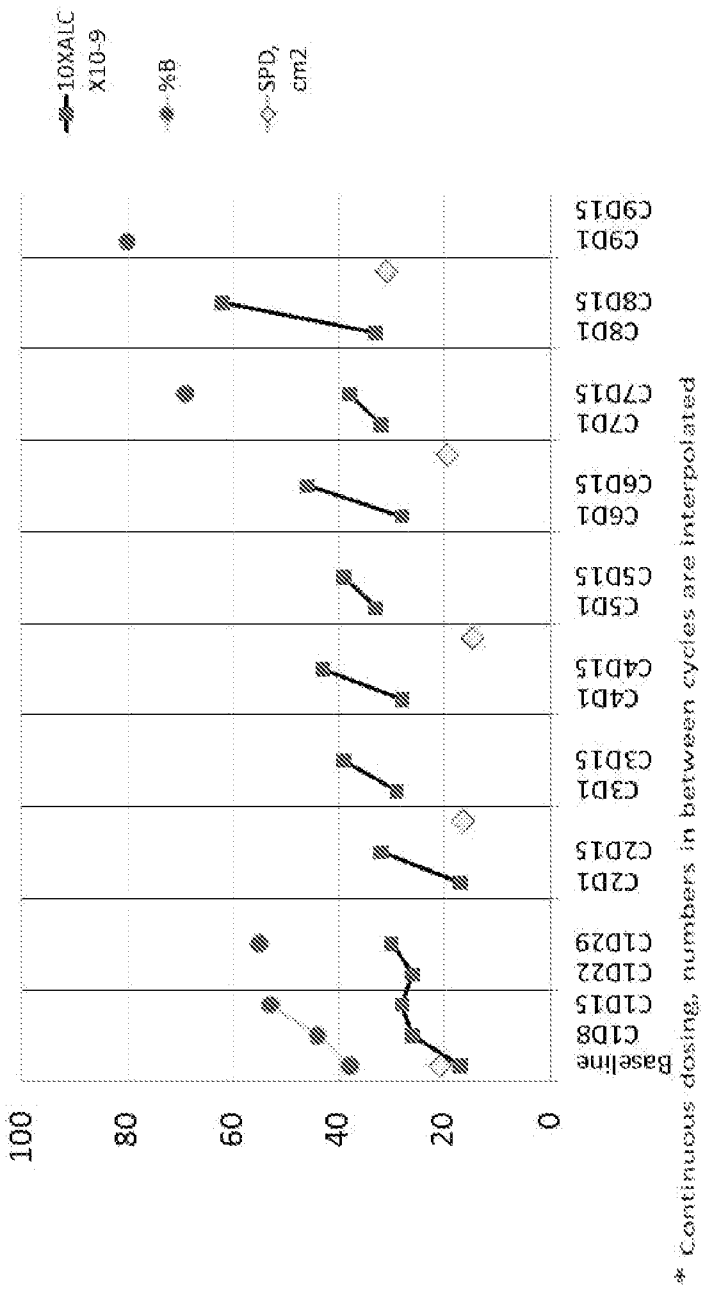

10XALC X10-9
%B
SPD, cm2
100
80
60
40
20
0
Baseline
C1D8
C1D15
C1D22
C1D29
C2D1
C2D15
C3D1
C3D15
C4D1
C4D15
C5D1
C5D15
C6D1
C6D15
C7D1
C7D15
C8D1
C8D15
C9D1
C9D15
* Continuous dosing, numbers in between cycles are interpolated

FIGURE 16

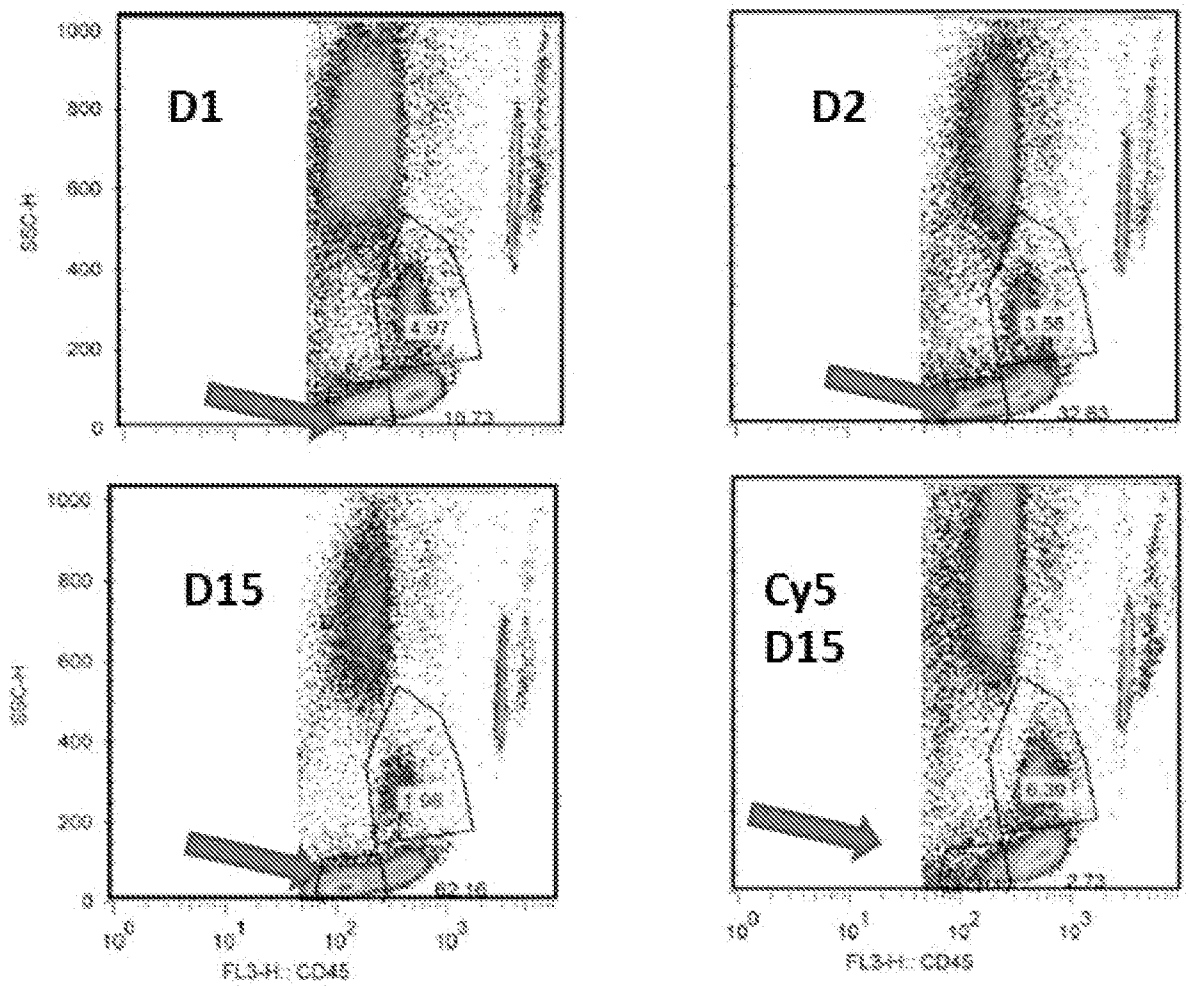


FIGURE 17

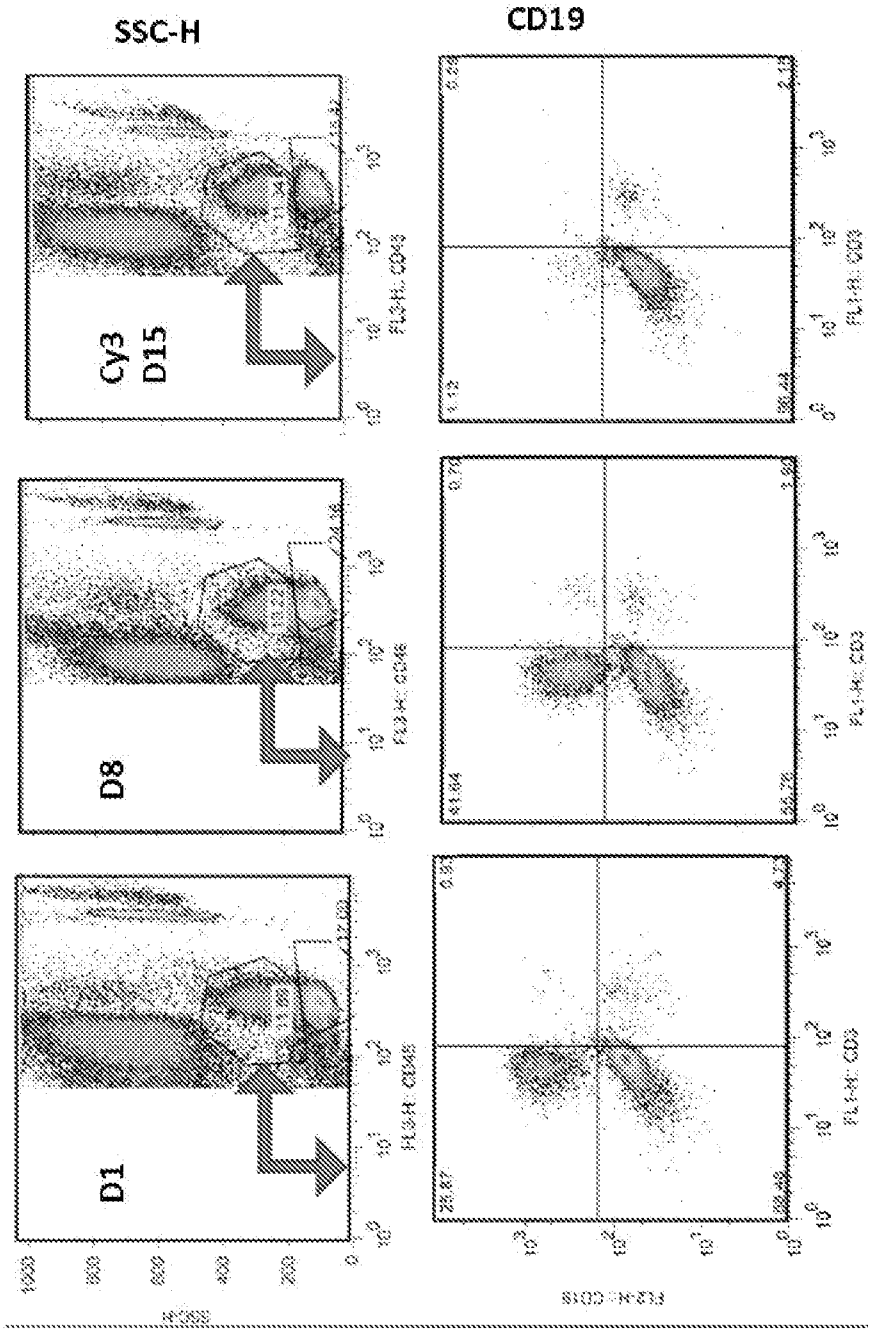


FIGURE 18

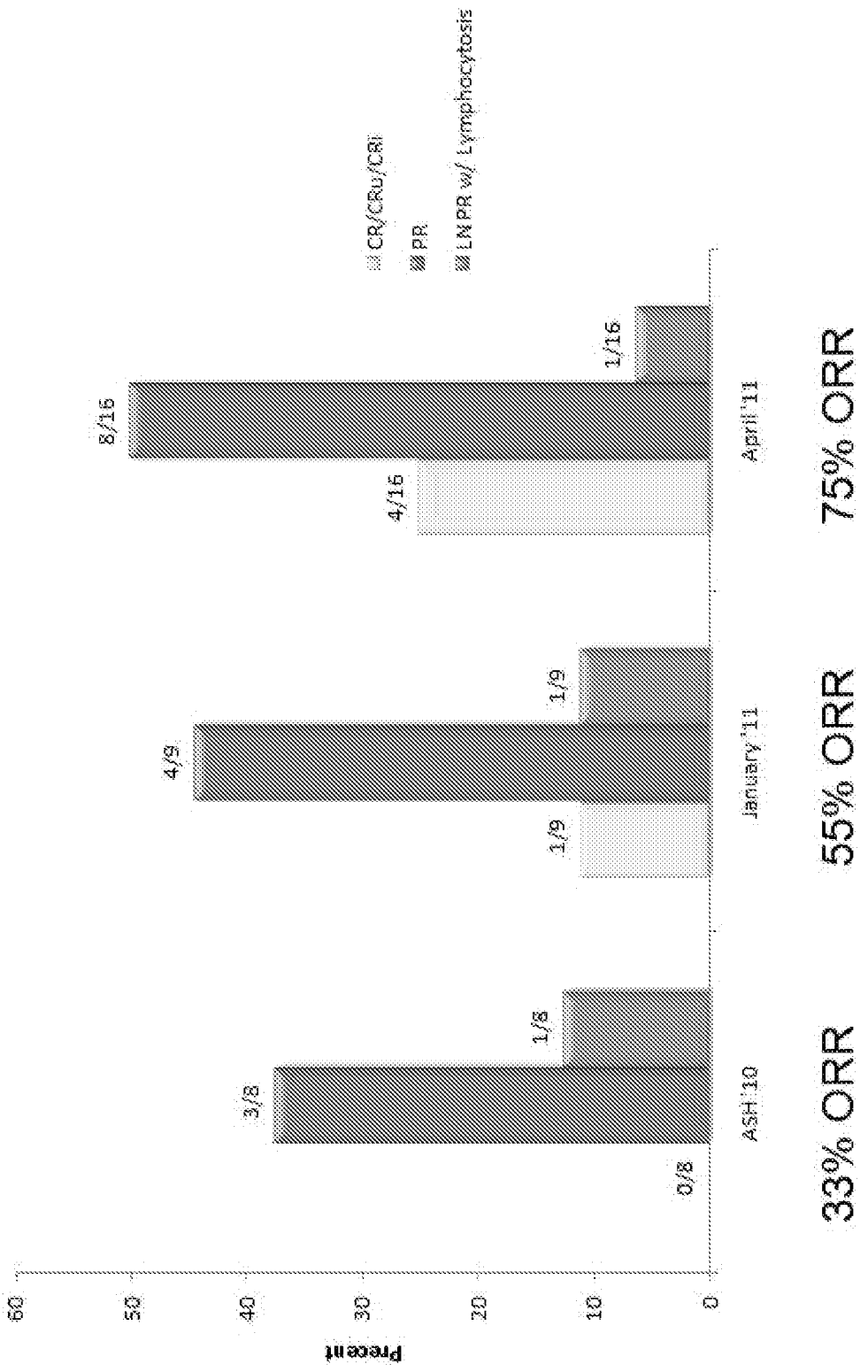

Percent
60
50
40
30
20
10
0
0/8
3/8
1/8
1/9
4/9
1/9
4/16
8/16
1/16
CR/CRu/CRi
PR
LN PR w/ Lymphocytosis
ASH '10
January '11
April '11
33% ORR
55% ORR
75% ORR

FIGURE 19

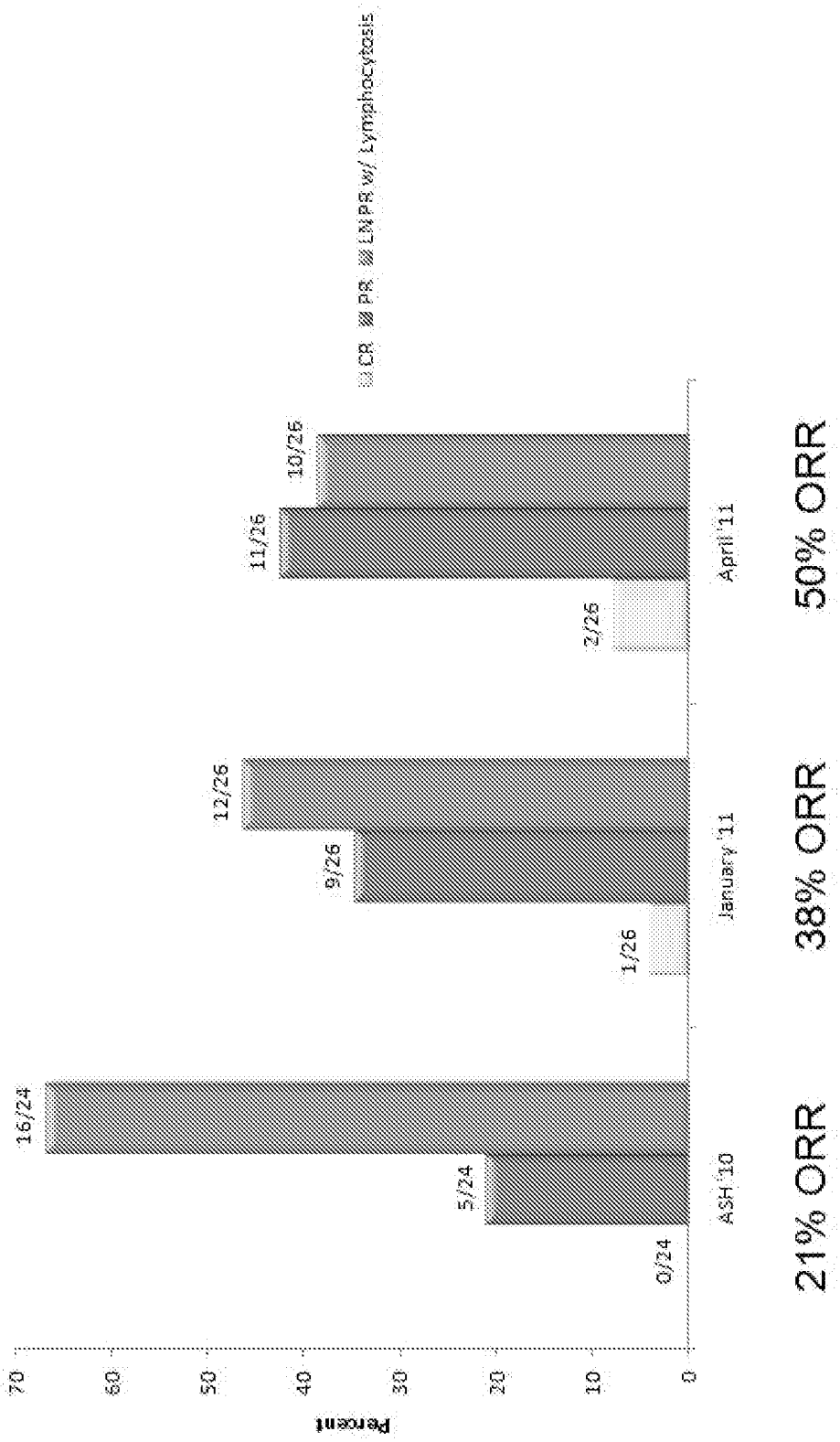

CR
PR
LN PR w/ Lymphocytosis
Percent
70
60
50
40
30
20
10
0
0/24
5/24
16/24
1/26
9/26
12/26
7/26
11/26
10/26
ASH '10
January '11
April '11
21% ORR
38% ORR
50% ORR

FIGURE 20

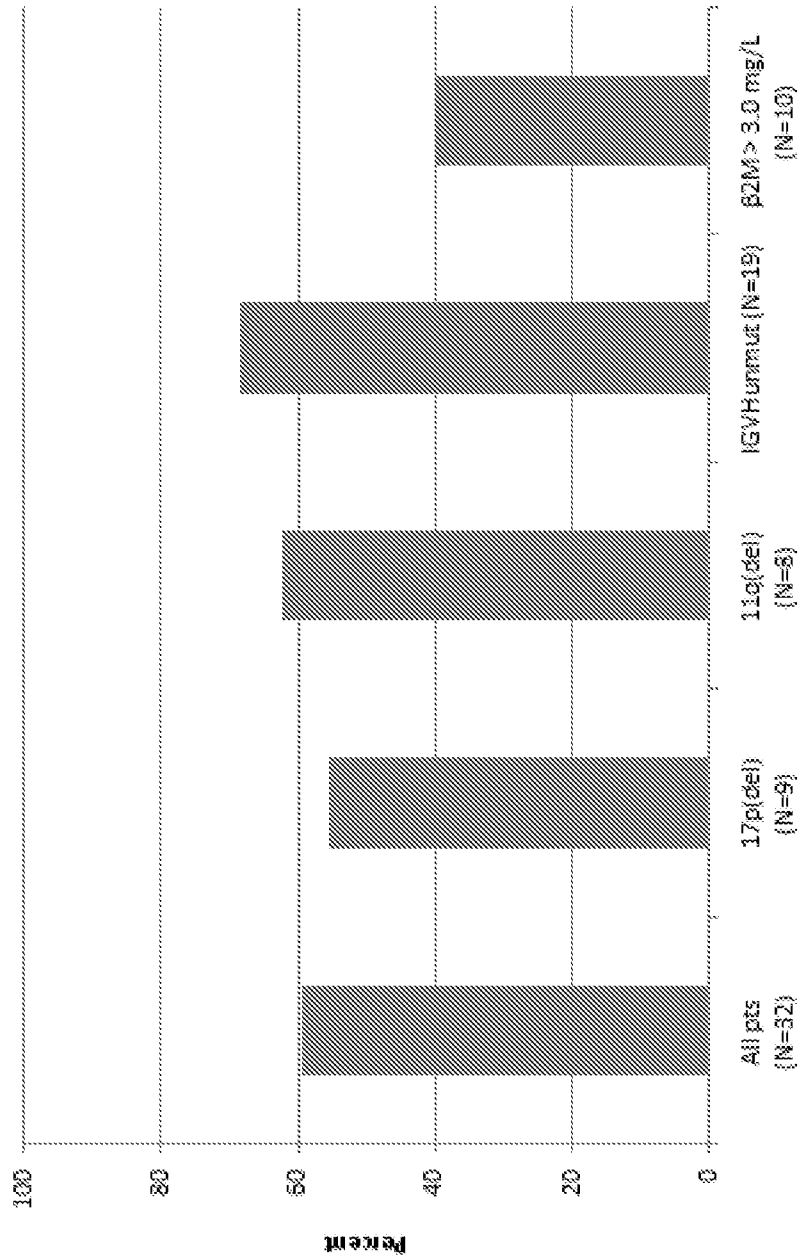

Percent
100
80
60
40
20
0
All pts (N=32)
17p(del) (N=9)
11q(del) (N=8)
IGVHunmut (N=19)
β2M > 3.0 mg/L (N=18)

FIGURE 21

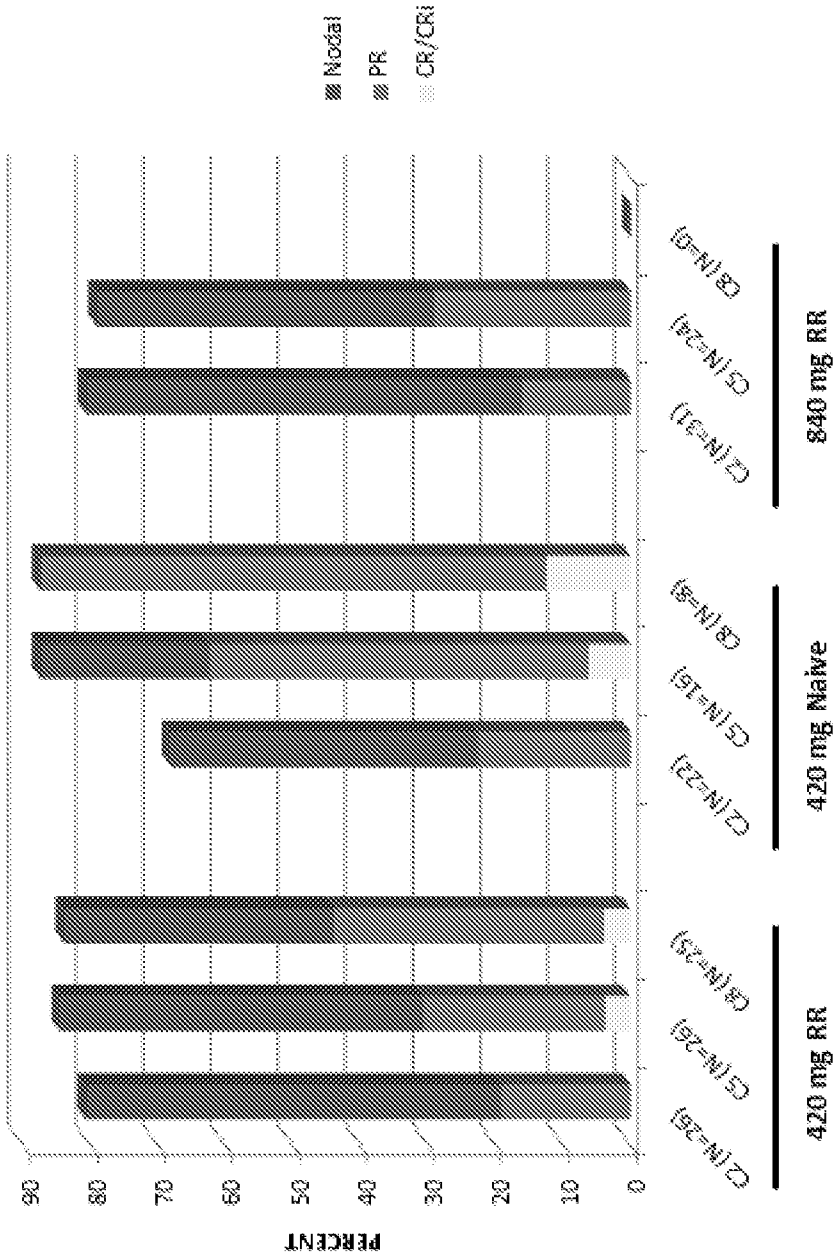

Nozal
PR
CR/CRi
PERCENT
90
80
70
60
50
40
30
20
10
0
C2 (N=25)
C3 (N=26)
C4 (N=25)
420 mg RR
C2 (N=23)
C3 (N=15)
C4 (N=20)
420 mg Naive
C2 (N=21)
C3 (N=24)
C4 (N=20)
840 mg RR

FIGURE 22

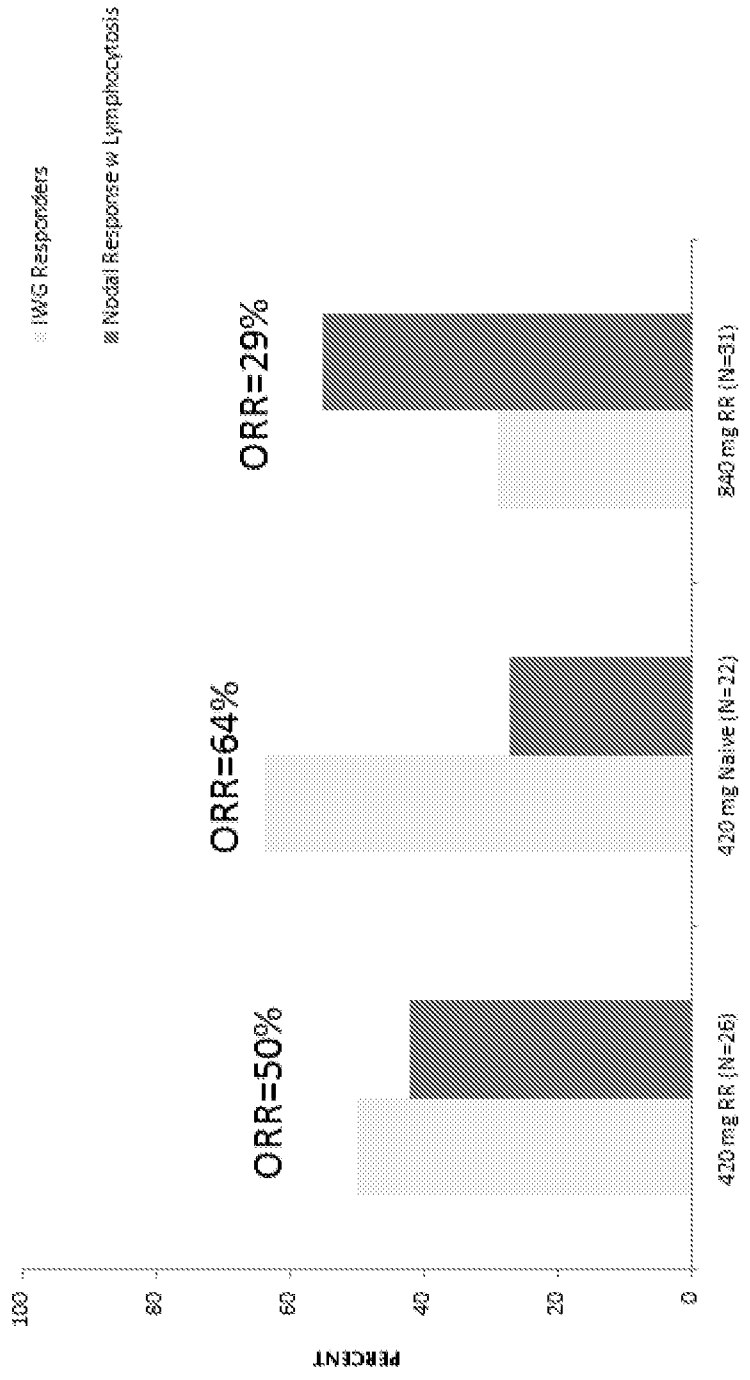

IWG Responders
Nodal Response w Lymphocytosis
ORR=50%
ORR=64%
ORR=29%
PERCENT
100
80
60
40
20
0
420 mg RR (N=26)
420 mg Naive (N=22)
840 mg RR (N=31)

FIGURE 23

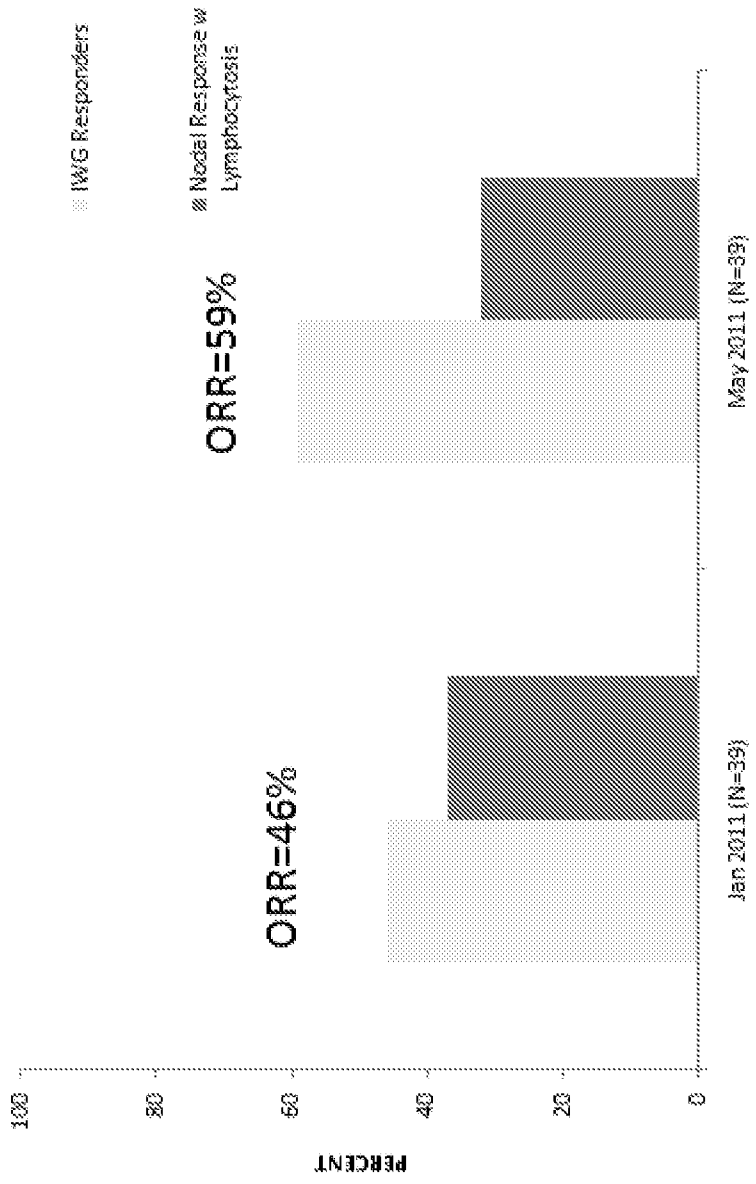

IWG Responders
% Nodal Response w Lymphocytosis
ORR=59%
ORR=46%
PERCENT
100
80
60
40
20
0
Jan 2011 (N=39)
May 2011 (N=39)

FIGURE 24

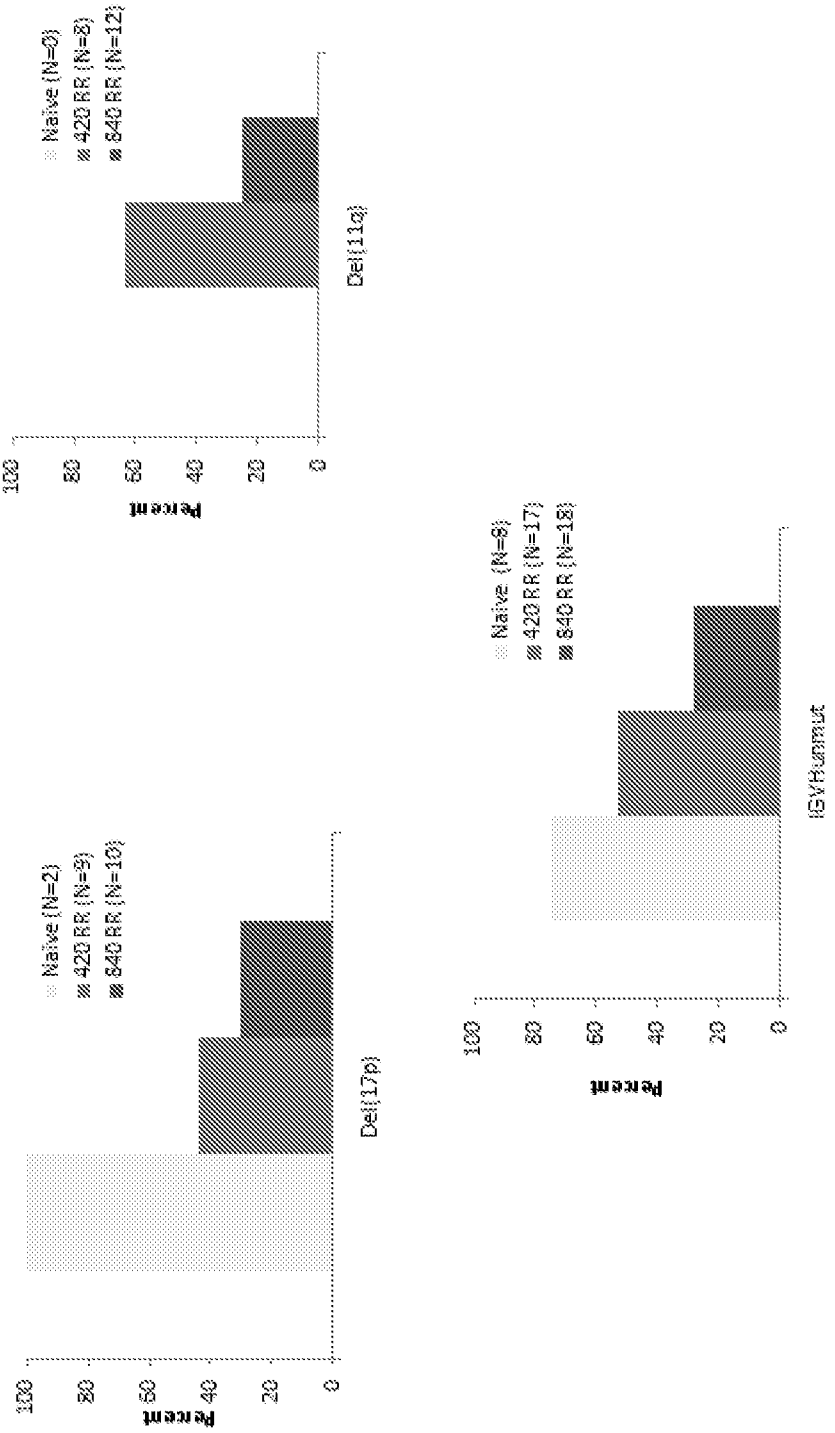

Naive (N=2)
420 RR (N=9)
840 RR (N=10)
Del(17p)
Percent
100
80
60
40
20
0
Naive (N=0)
420 RR (N=8)
840 RR (N=12)
Del(11q)
Percent
100
80
60
40
20
0
Naive (N=6)
420 RR (N=17)
840 RR (N=18)
IGVH Mutat
Percent
100
80
60
40
20
0

FIGURE 25

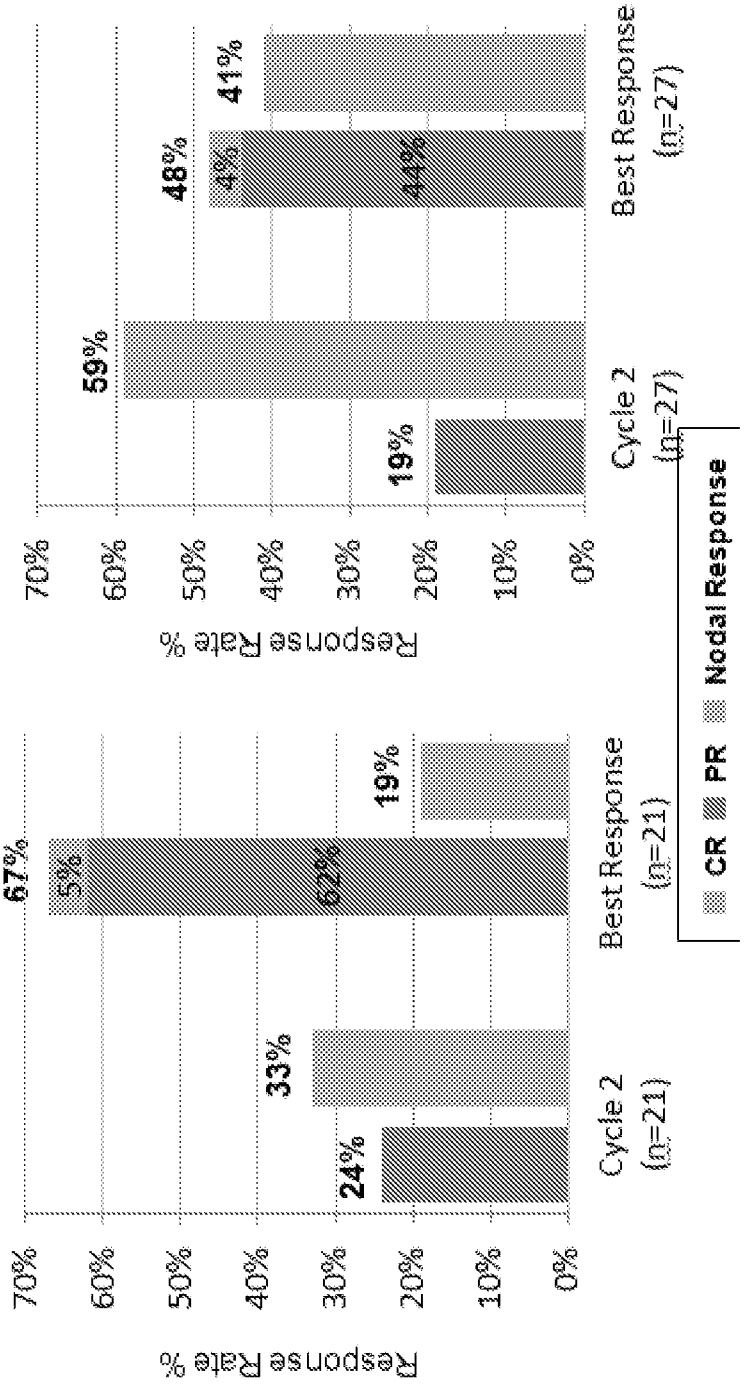

Treatment-Naïve (420mg)
Relapsed/Refractory (420mg)
Response Rate %
70%
60%
50%
40%
30%
20%
10%
0%
67%
5%
62%
19%
33%
24%
59%
48%
4%
44%
41%
19%
Cycle 2 (n=21)
Best Response (n=21)
Cycle 2 (n=27)
Best Response (n=27)
CR
PR
Nodal Response

FIGURE 26

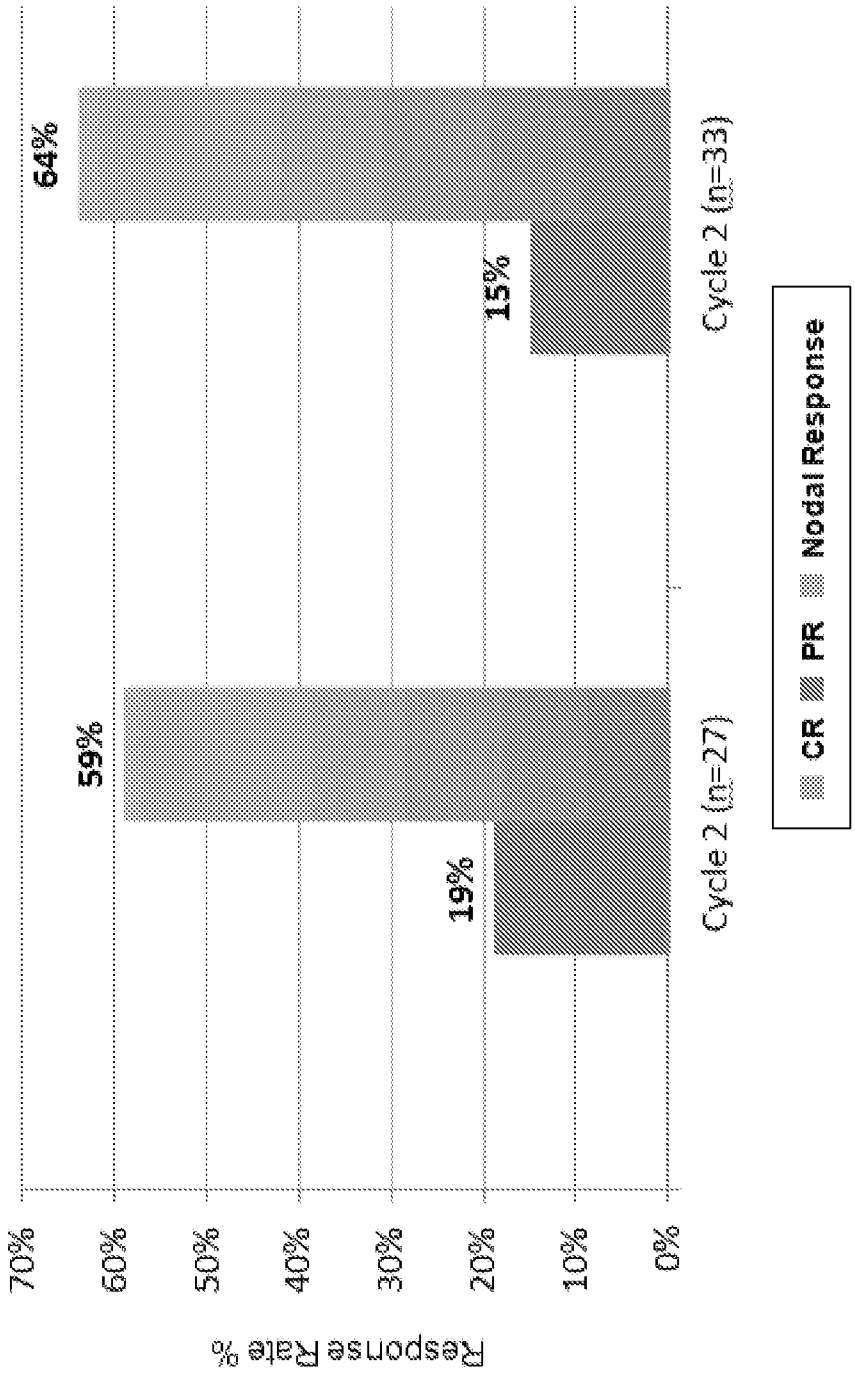

420mg qD
840mg qD
59%
19%
64%
15%
Cycle 2 (n=27)
Cycle 2 (n=33)
Response Rate %
70%
60%
50%
40%
30%
20%
10%
0%
CR
PR
Nodal Response

FIGURE 27

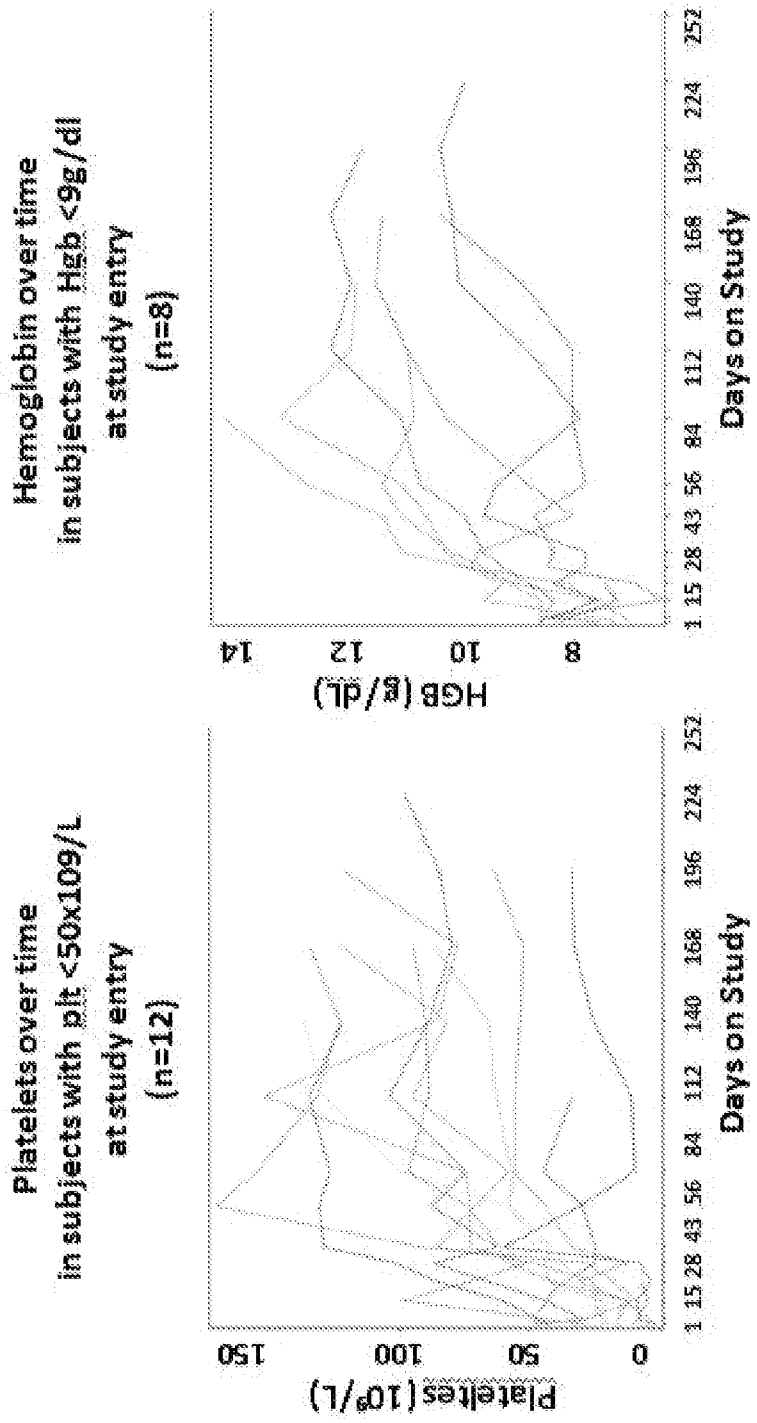
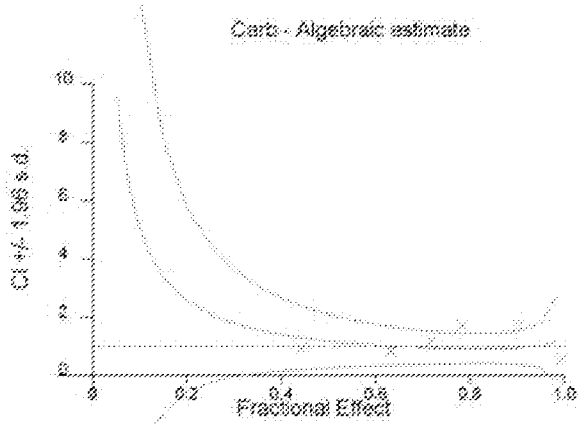

Platelets over time
in subjects with plt <50x109/L
at study entry
(n=12)
Platelets (10⁹/L)
0
50
100
150
1 15 28 43 56 84 112 140 168 196 224 252
Days on Study
Hemoglobin over time
in subjects with Hgb <9g/dl
at study entry
(n=8)
HGB (g/dL)
8
10
12
14
1 15 28 43 56 84 112 140 168 196 224 252
Days on Study

FIGURE 28

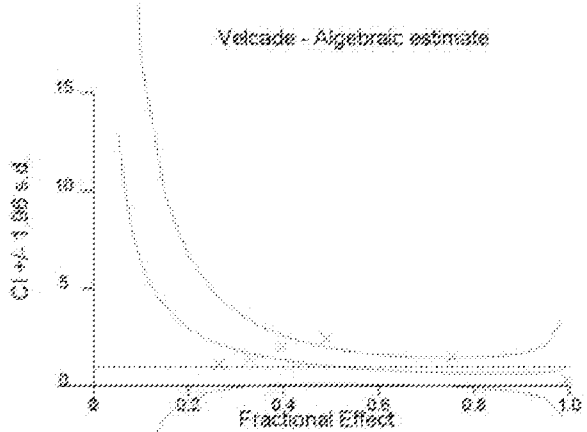
	Btk inhibitor (uM)	Carb(uM)
GI50	0.096	15.382
r:	0.994	0.990

	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	0.783398	1.718
0.5	100	0.899868	1.74
1	200	0.993211	0.564

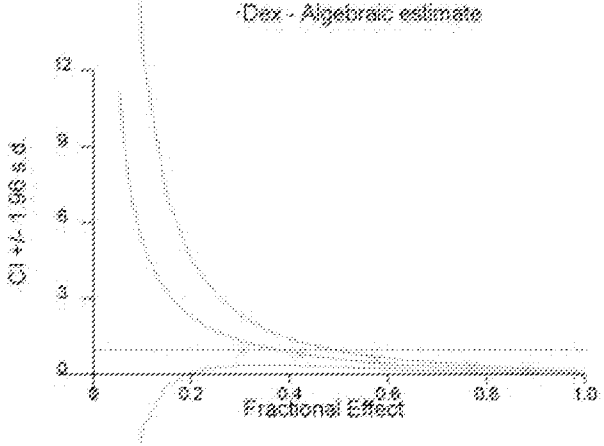


CI For experimental values

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

FIGURE 29

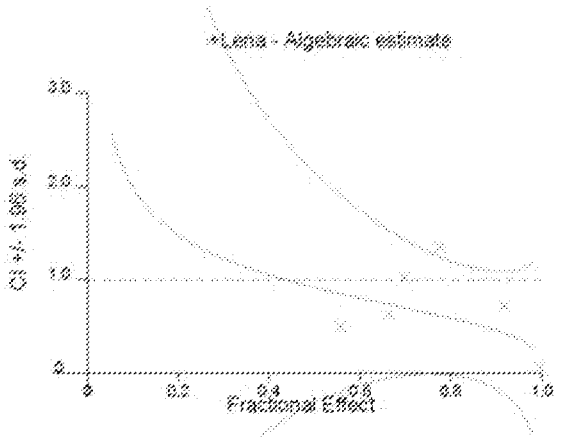
	Btk Inhibitor (uM)	Dex(uM)
GI50	0.177	45.850
r:	0.964	0.991



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

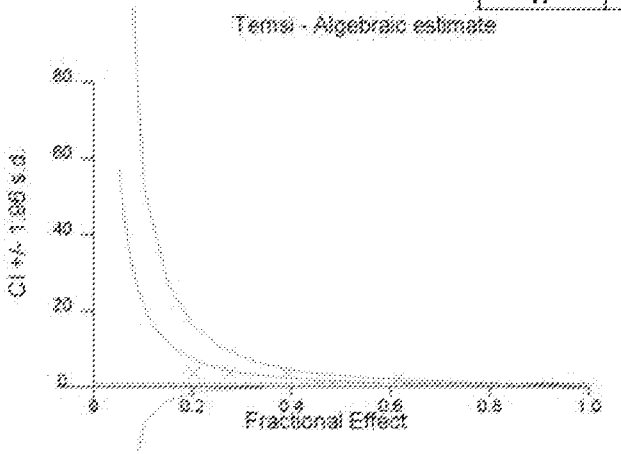


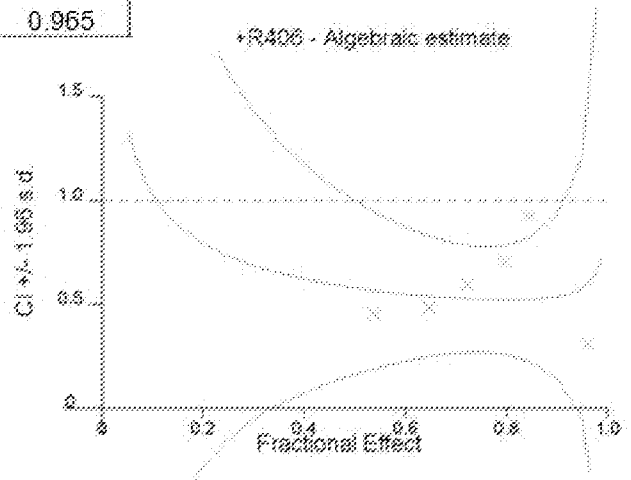
CI For experimental values

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

FIGURE 30

	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

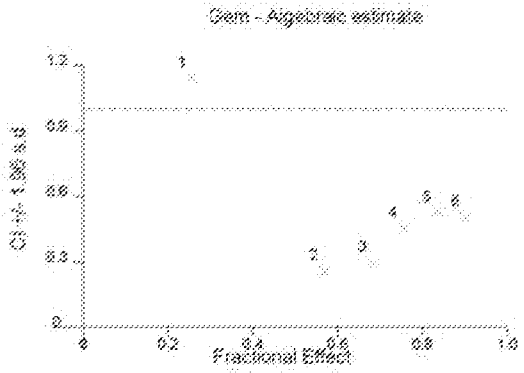
Btk inhibitor (uM)	Temsi (uM)	Fa	CI
0.03125	0.3125	0.200943	3.779
0.0625	0.625	0.275482	3.93
0.125	1.25	0.394234	3.529
0.25	2.5	0.614251	2.244
0.5	5	0.91765	0.907
1	10	0.99999	0.016

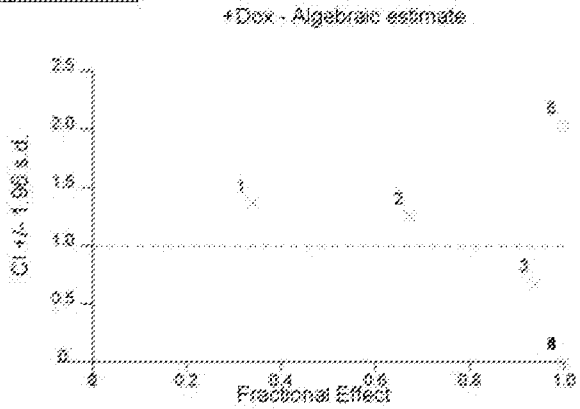
CI For experimental values

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

FIGURE 31

	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	0.339085	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

FIGURE 32

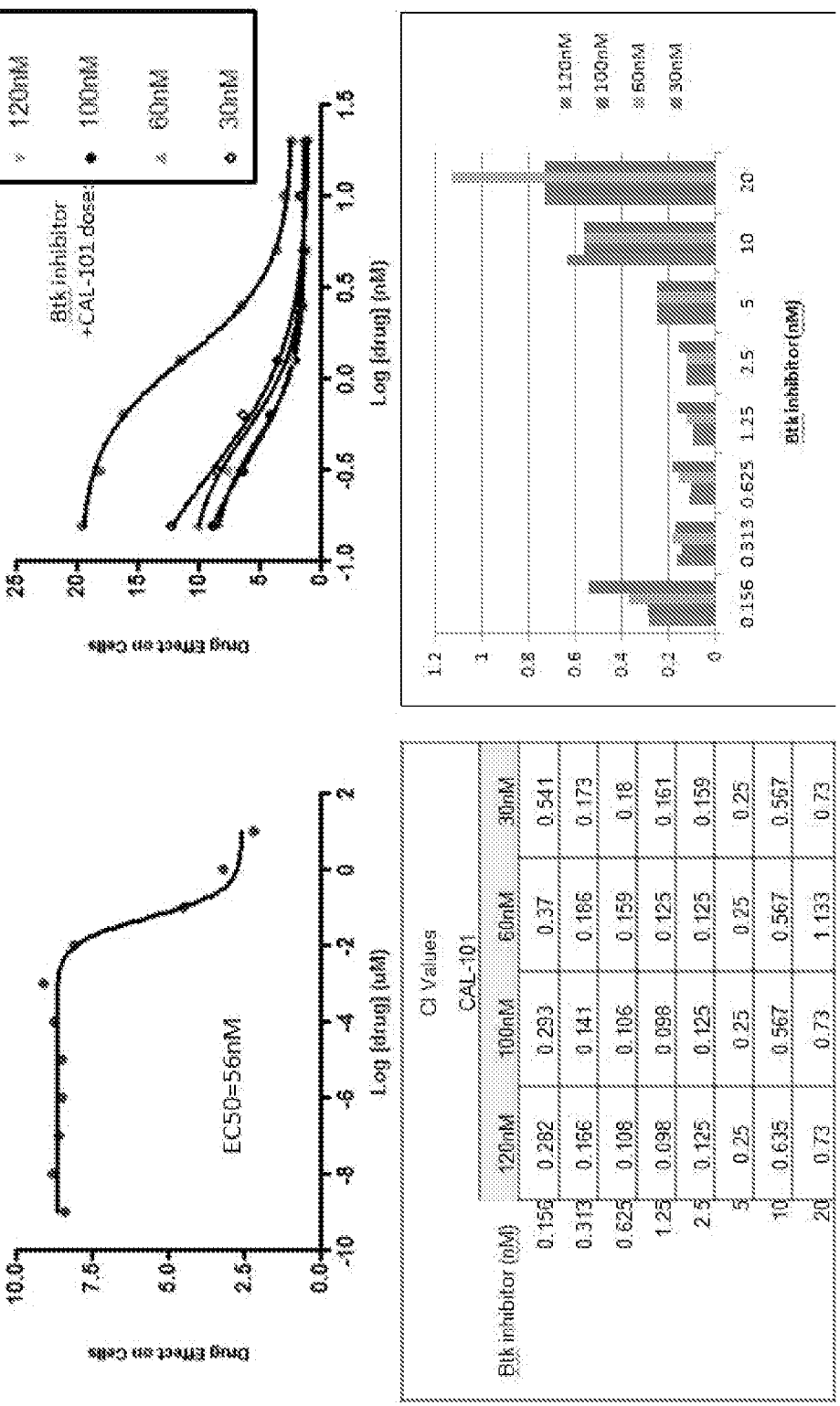
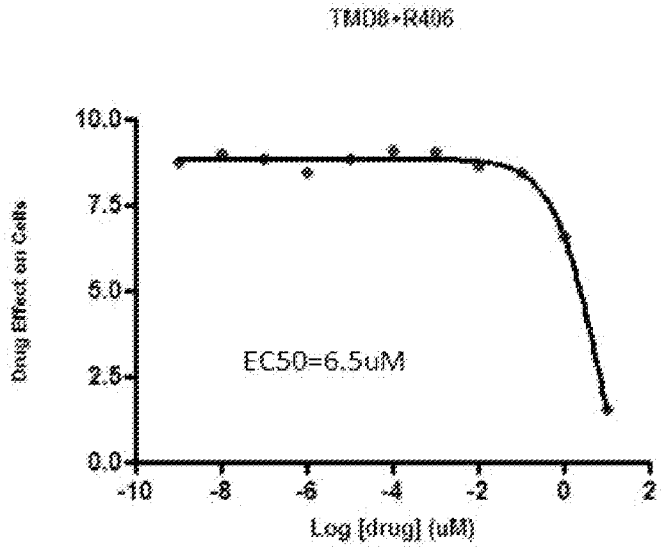
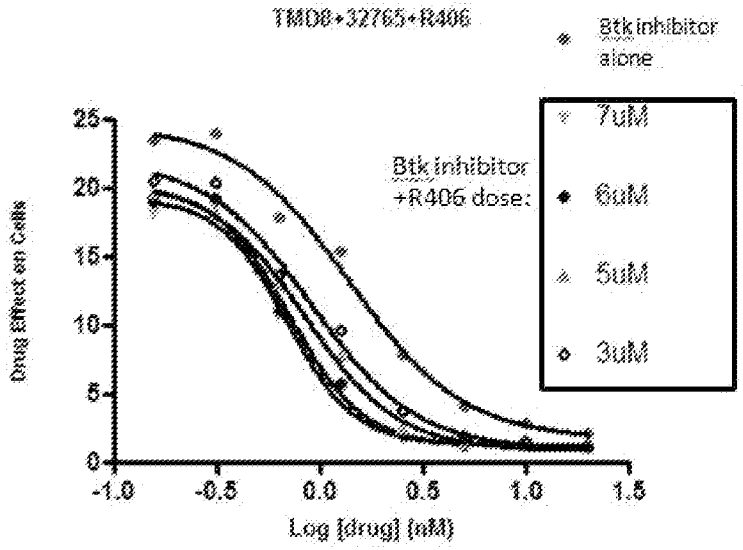

TMD8+CAL-101
Drug Effect on Cells
Log [drug] (uM)
EC50=56nM
Cal-101 and Btk inhibitor
Btk inhibitor alone
120nM
100nM
60nM
30nM
Btk inhibitor +CAL-101 dose
Drug Effect on Cells
Log [drug] (nM)
CI Values
CAL-101
Btk inhibitor (nM)
120nM
100nM
60nM
30nM
0.156 0.282 0.293 0.37 0.541
0.313 0.166 0.141 0.166 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
120nM
100nM
60nM
30nM
Btk inhibitor(nM)

FIGURE 33





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

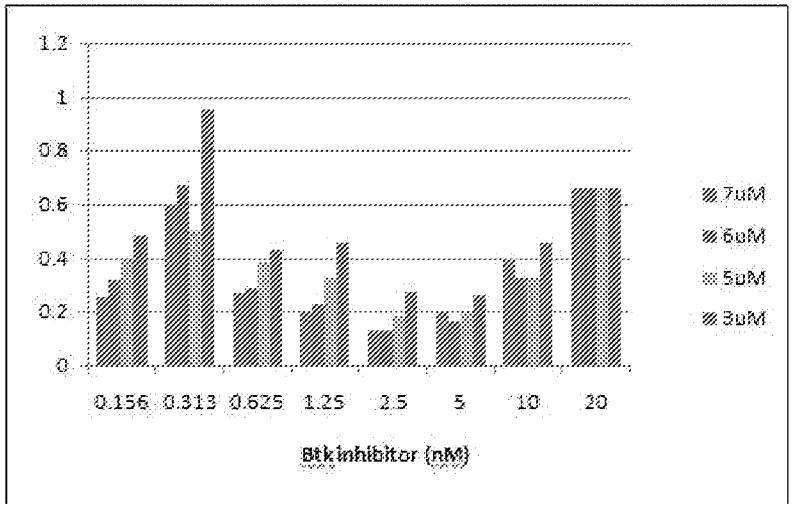


FIGURE 34

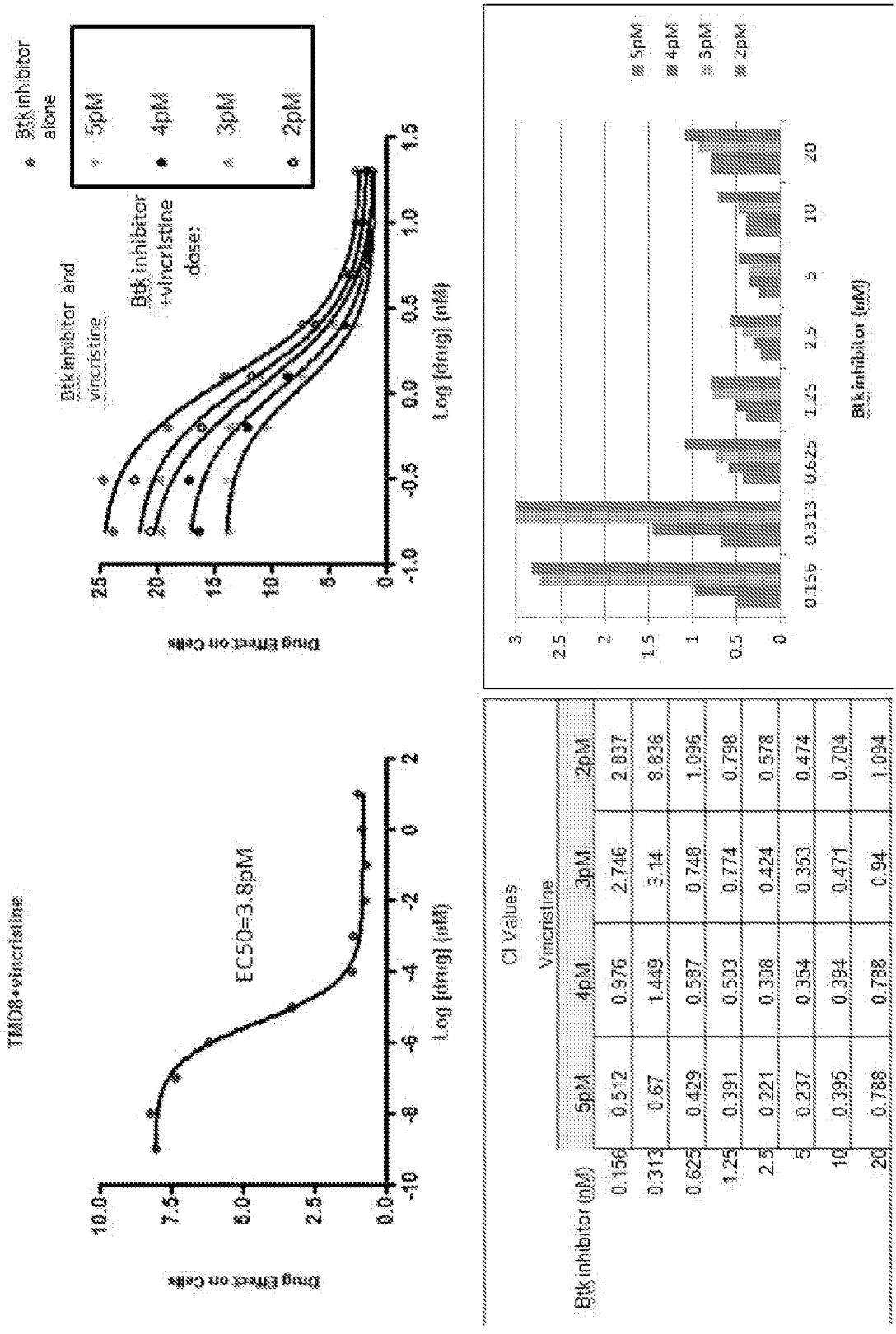
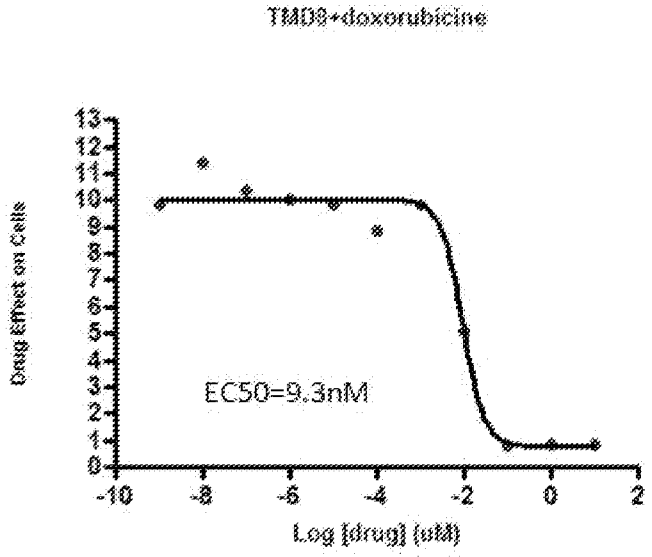
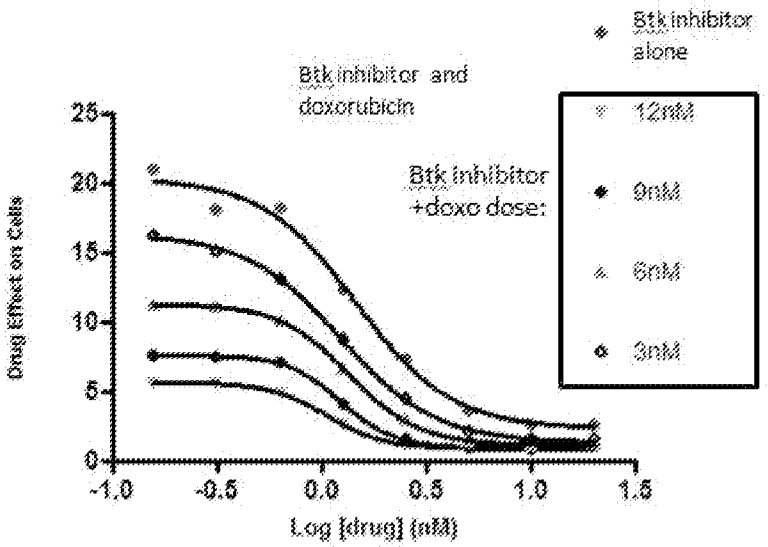

TMD8+vincristine
EC50=3.8pM
Drug Effect on cells
Log [drug] (nM)
Btk inhibitor and vincristine
Btk inhibitor alone
Btk inhibitor +vincristine dose:
5pM
4pM
3pM
2pM
Drug Effect on cells
Log [drug] (nM)
CI Values
Vincristine
Btk inhibitor (nM)
5pM 4pM 3pM 2pM
0.156 0.512 0.976 2.746 2.837
0.313 0.67 1.449 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 0.308 0.424 0.578
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
5pM
4pM
3pM
2pM
0.156 0.313 0.625 1.25 2.5 5 10 20
Btk inhibitor (nM)

FIGURE 35





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

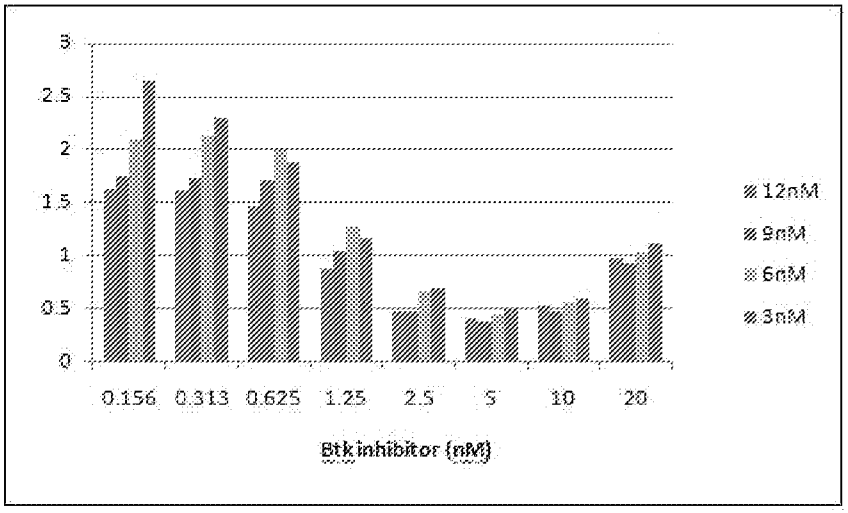
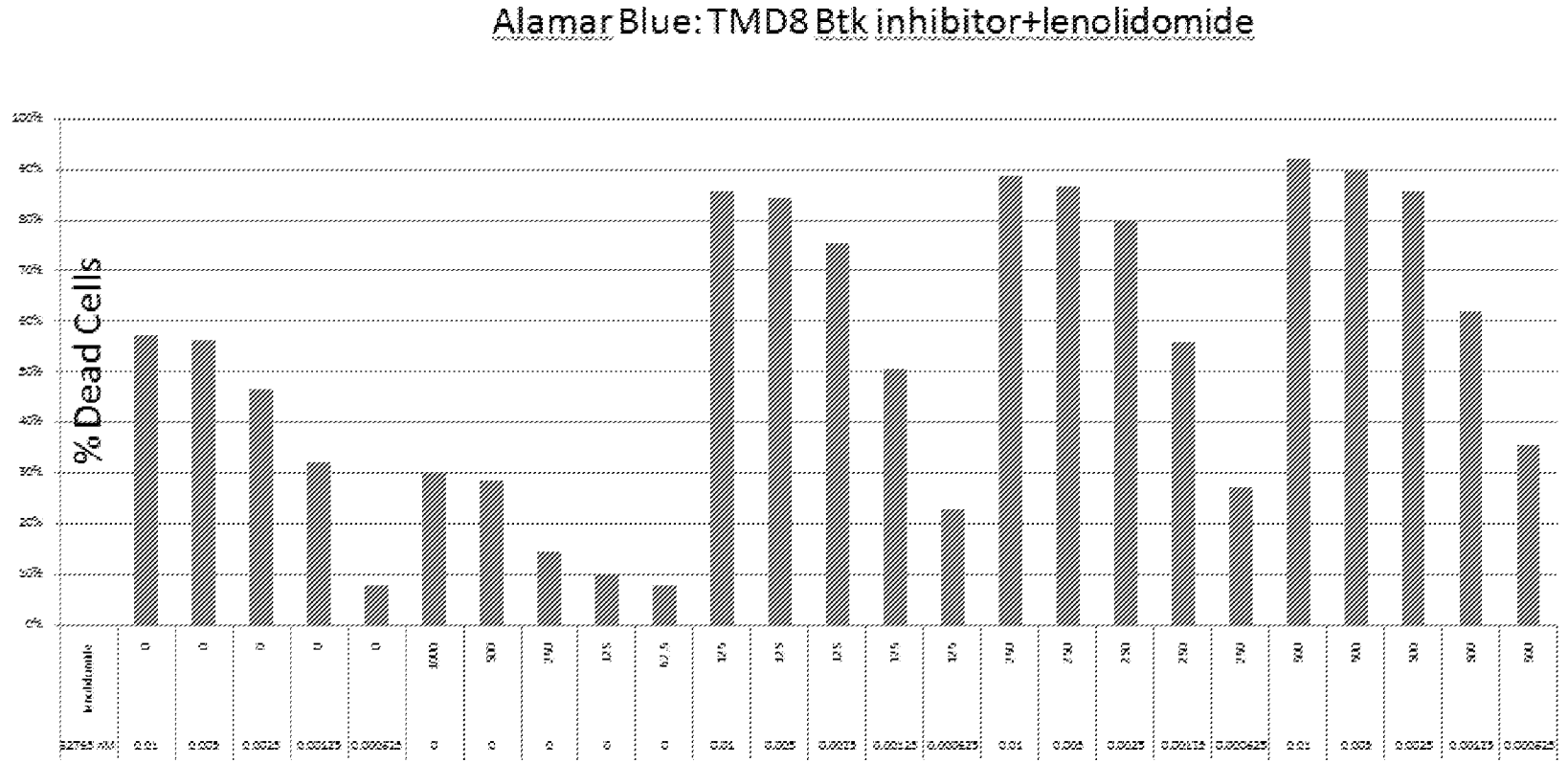


FIGURE 36

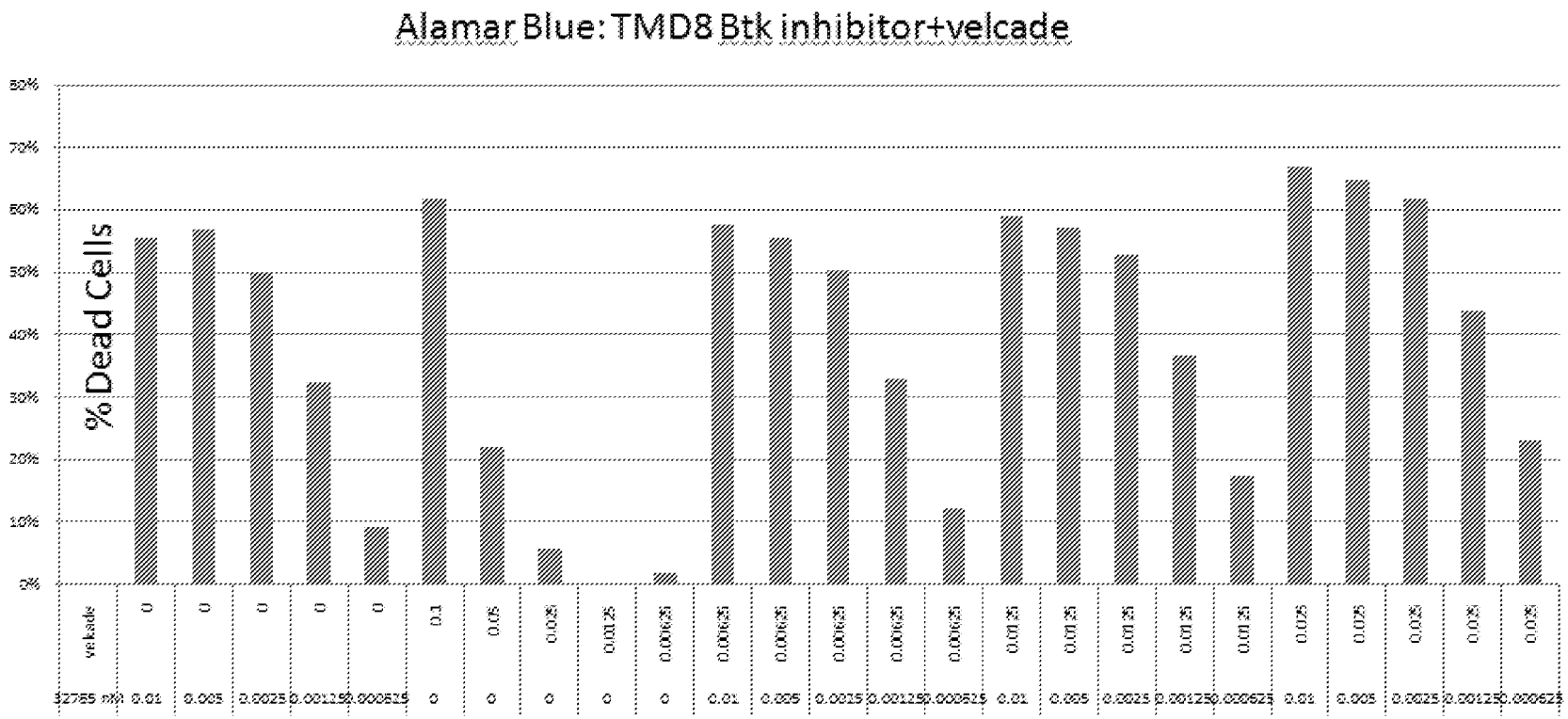


Btk inhibitor nM	lenolidomide nM	CI
0.000625	125	0.77
0.00125	125	0.311
0.0025	125	0.175
0.005	125	0.188
0.01	125	0.332

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

FIGURE 37



Btk inhibitor nM	velcade nM	CI
0.000625	0.00625	1.466
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	0.888
0.01	0.0125	1.539

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

FIGURE 38

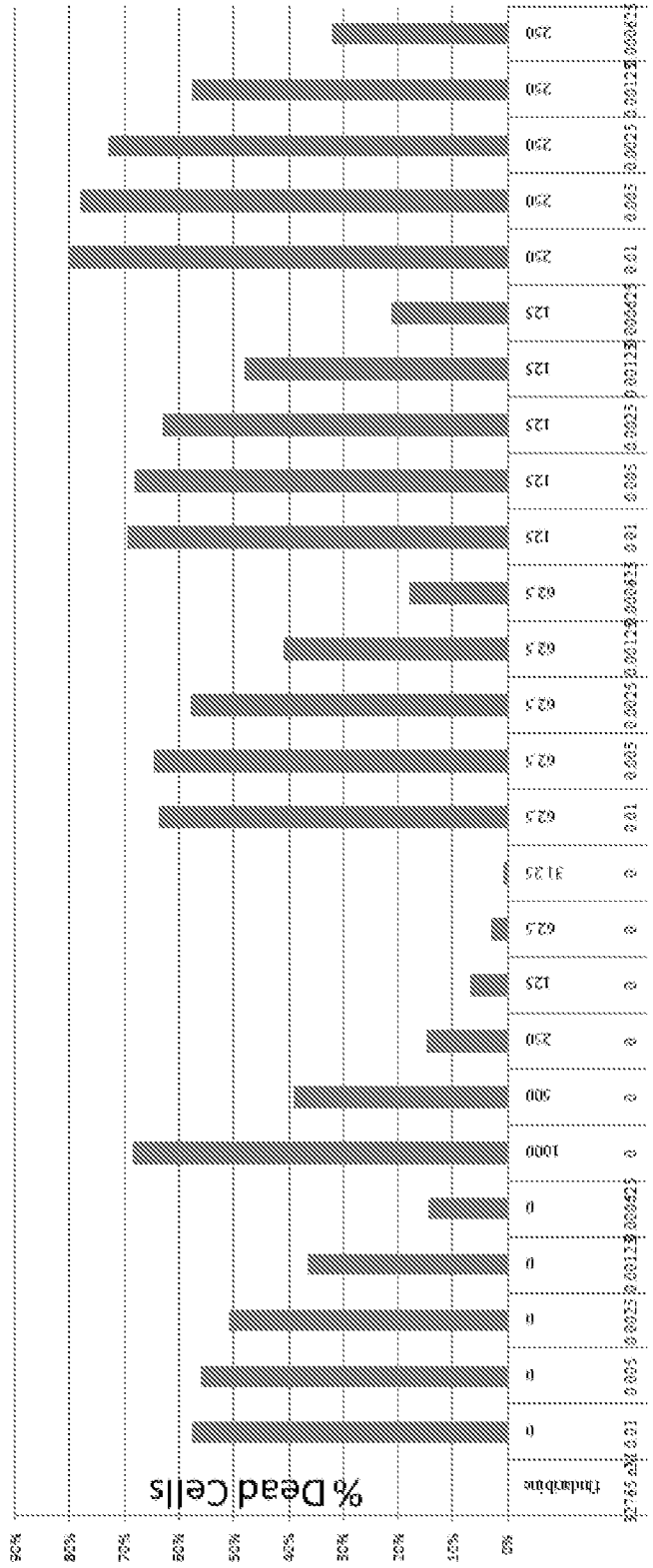
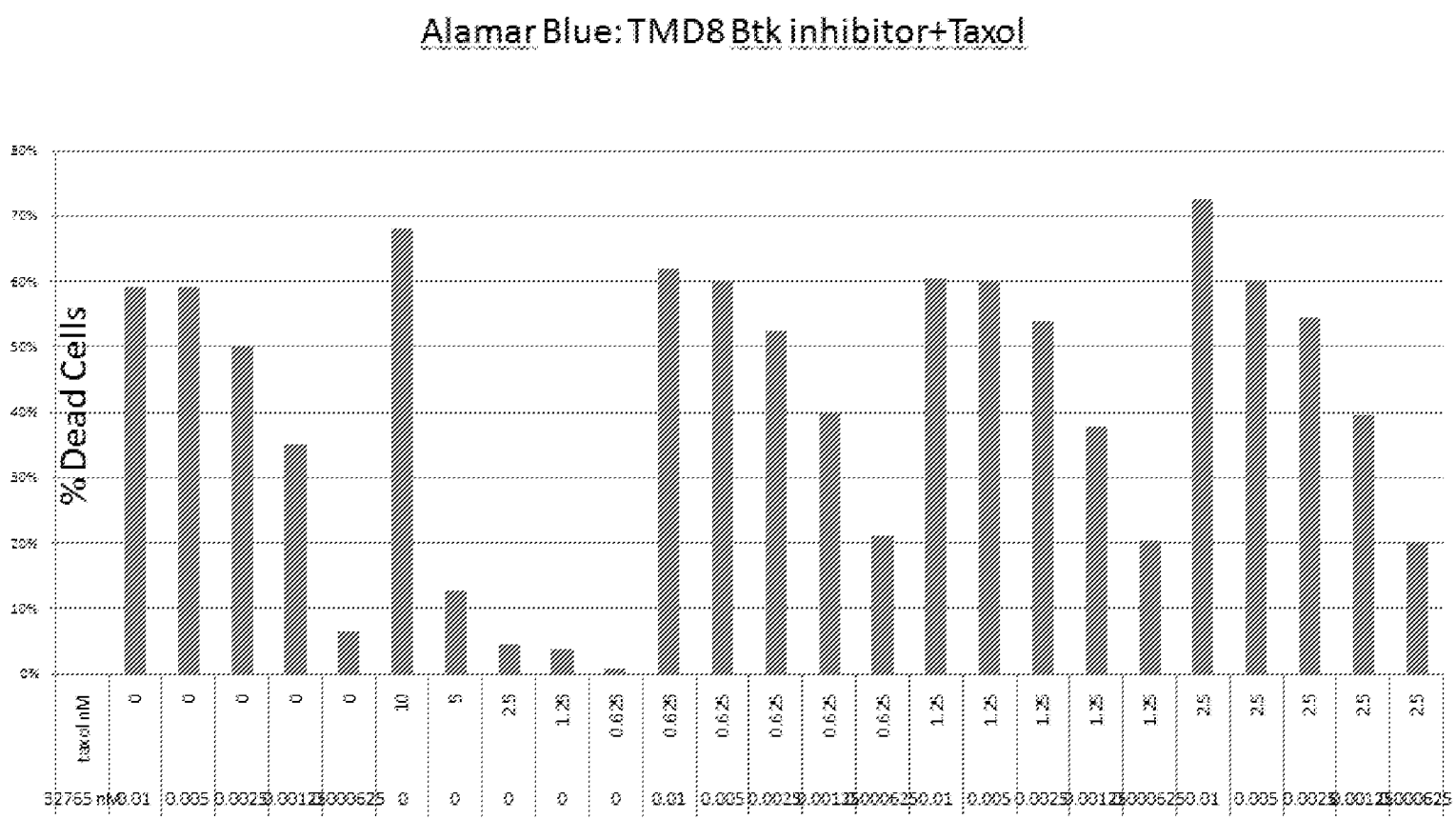

Alamar Blue: TMD8 Btk inhibitor+Fludarabine
% Dead Cells
95%
85%
75%
65%
55%
45%
35%
25%
15%
5%
Thalidomide
0
0
0

FIGURE 39



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	1.536

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	1.784

Btk inhibitor nM	taxol nM	CI
0.000625	2.5	1.12
0.00125	2.5	0.784
0.0025	2.5	0.735
0.005	2.5	1.007
0.01	2.5	1.984