FIGURE 3

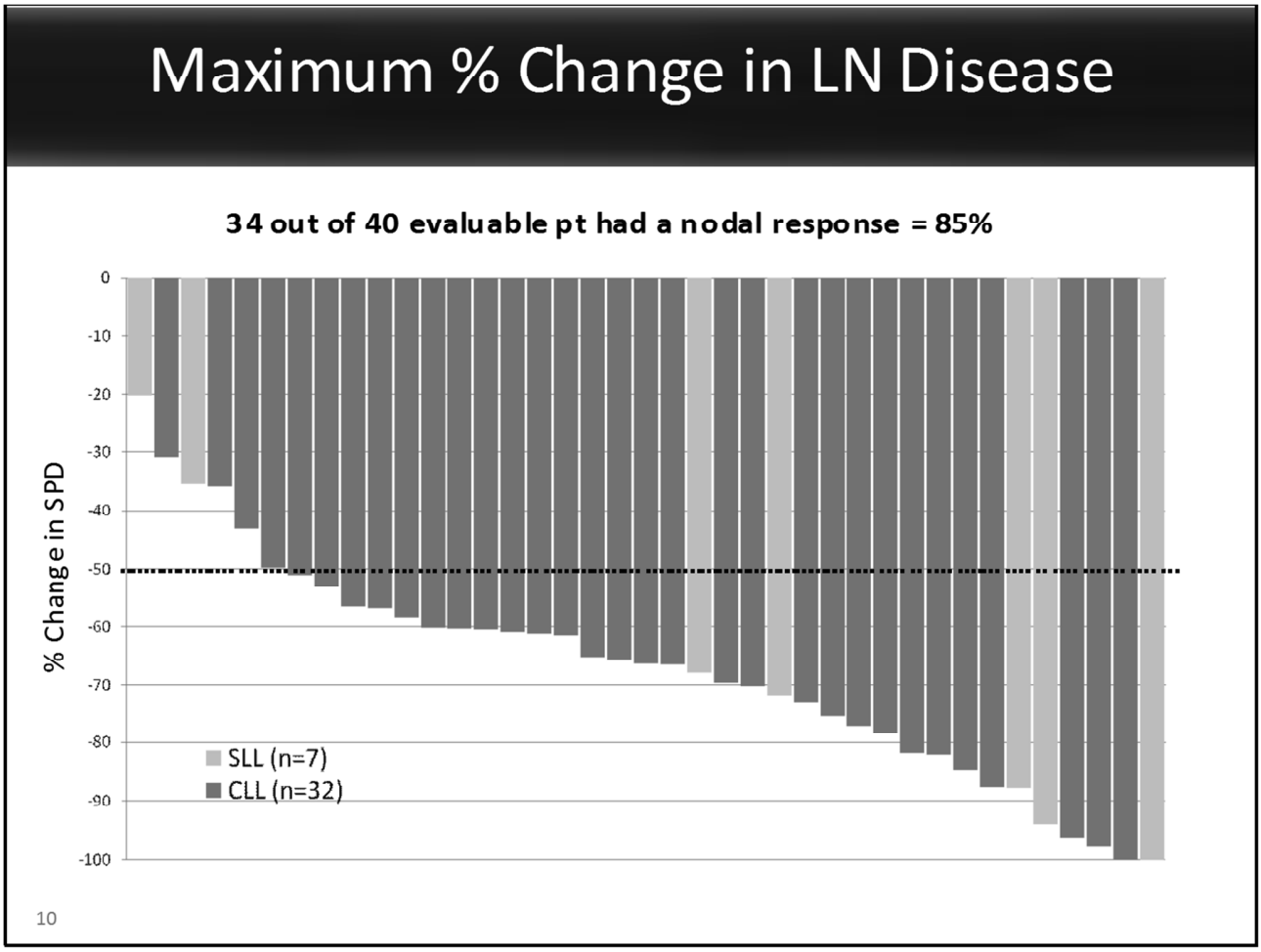

Maximum % Change in LN Disease
34 out of 40 evaluable pt had a nodal response = 85%
% Change in SPD
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
SLL (n=7)
CLL (n=32)
10

FIGURE 6

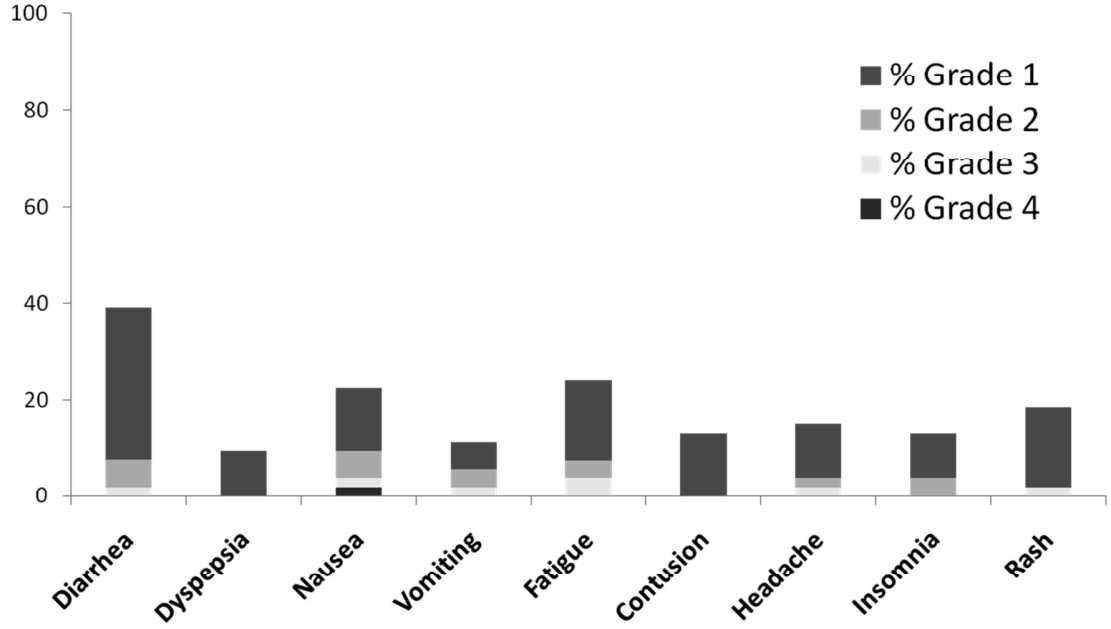

100
80
60
40
20
0
% Grade 1
% Grade 2
% Grade 3
% Grade 4
Diarrhea
Dyspepsia
Nausea
Vomiting
Fatigue
Contusion
Headache
Insomnia
Rash

FIGURE 7

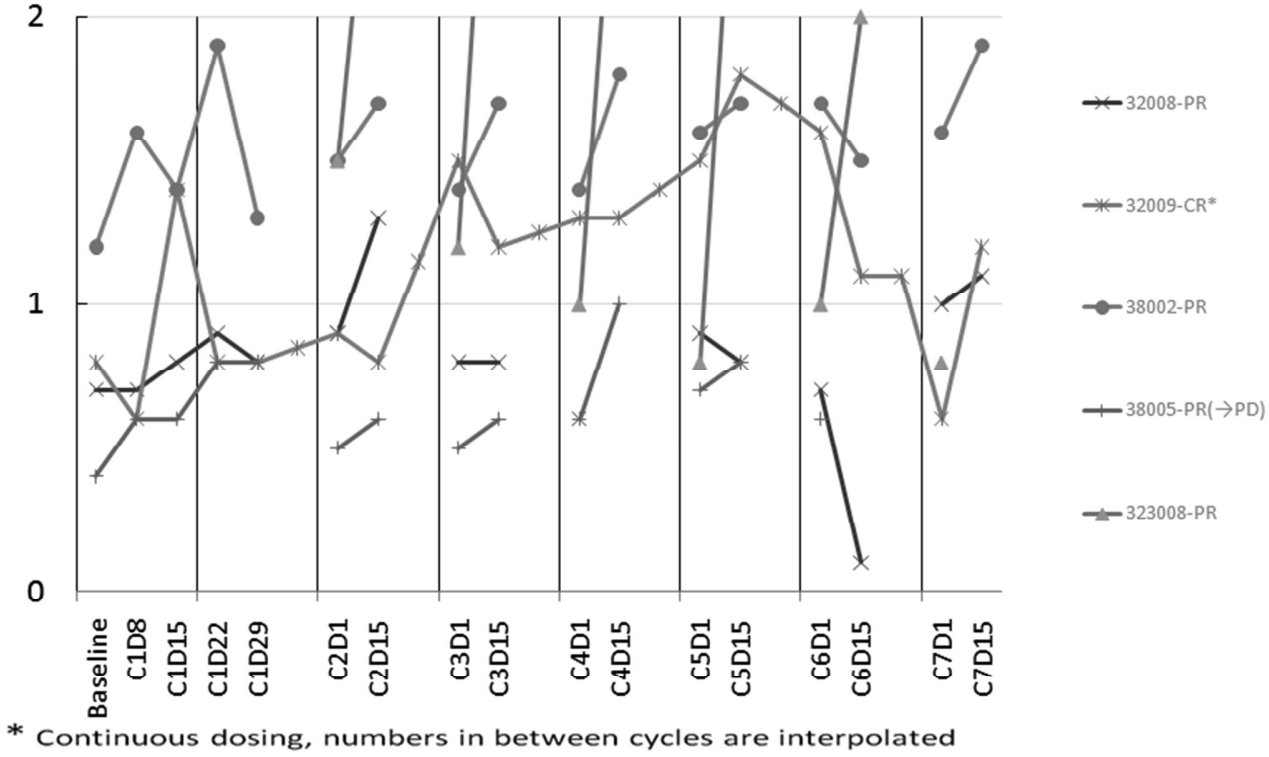

2
1
0
Baseline
C1D8
C1D15
C1D22
C1D29
C2D1
C2D15
C3D1
C3D15
C4D1
C4D15
C5D1
C5D15
C6D1
C6D15
C7D1
C7D15
32008-PR
32009-CR*
38002-PR
38005-PR(→PD)
323008-PR
* Continuous dosing, numbers in between cycles are interpolated

FIGURE 8

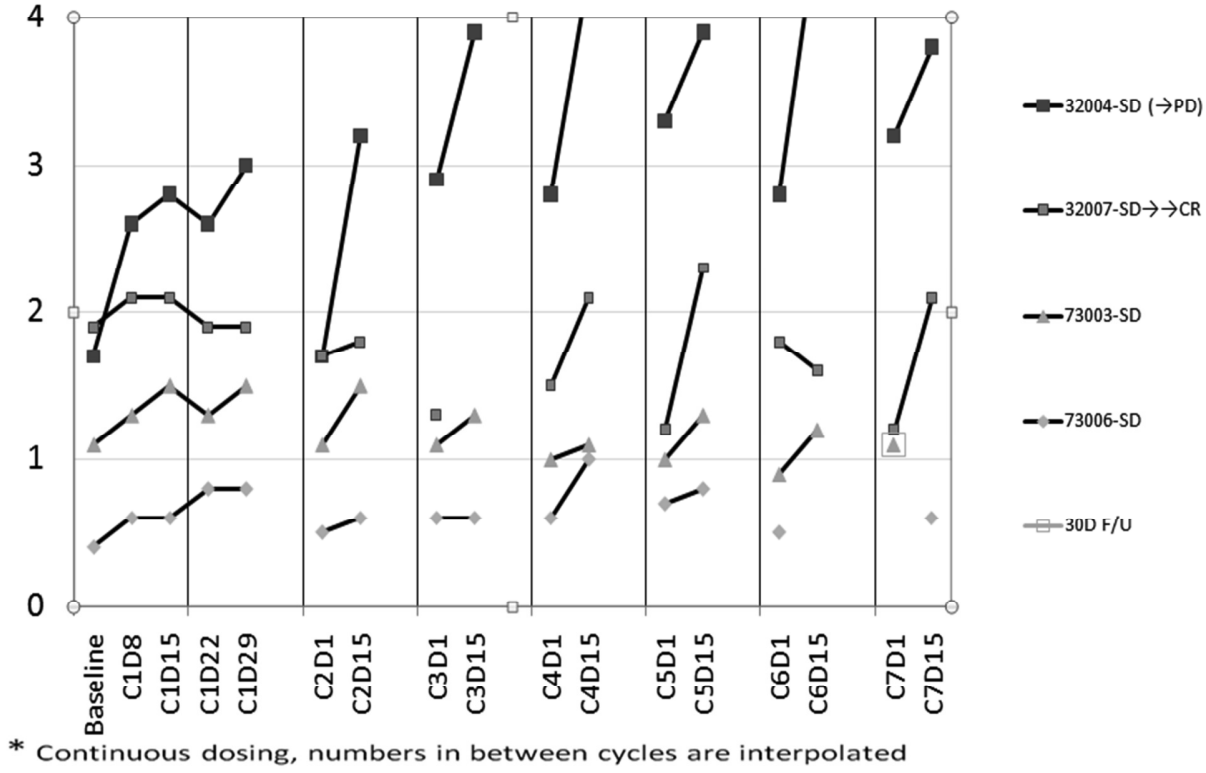

4
3
2
1
0
Baseline
C1D8
C1D15
C1D22
C1D29
C2D1
C2D15
C3D1
C3D15
C4D1
C4D15
C5D1
C5D15
C6D1
C6D15
C7D1
C7D15
32004-SD (→PD)
32007-SD→→CR
73003-SD
73006-SD
30D F/U
* Continuous dosing, numbers in between cycles are interpolated

FIGURE 9

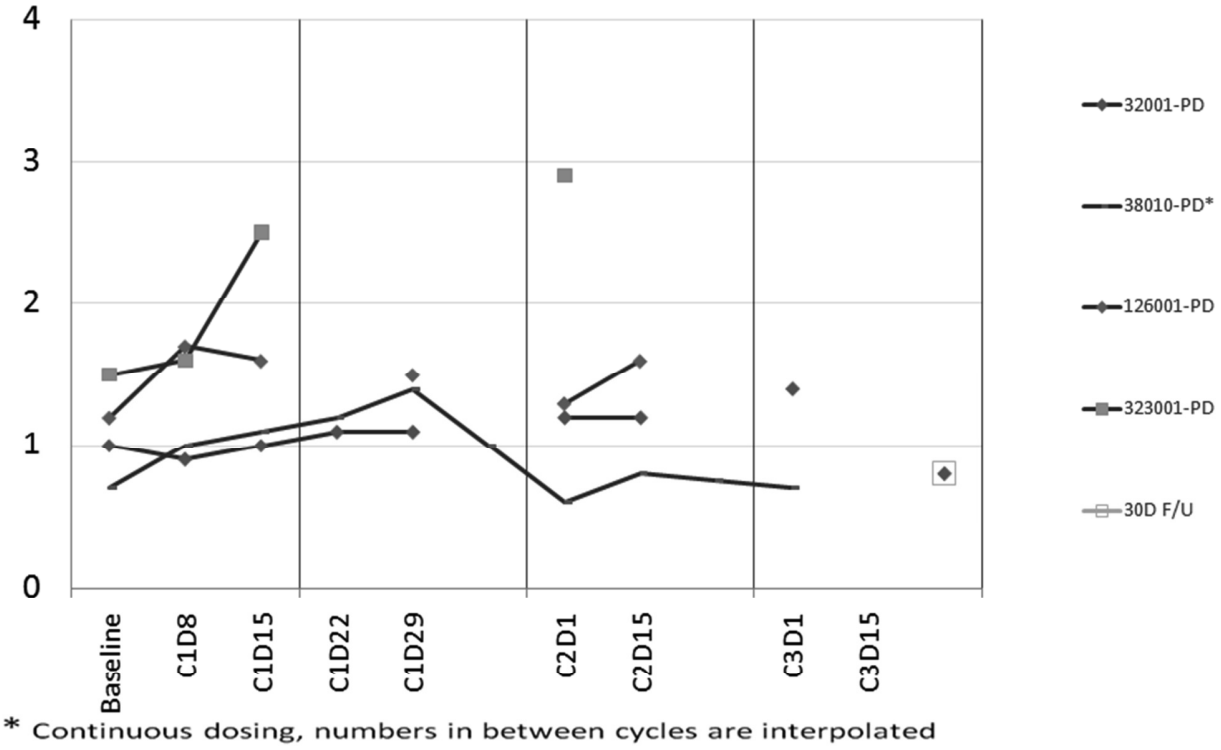
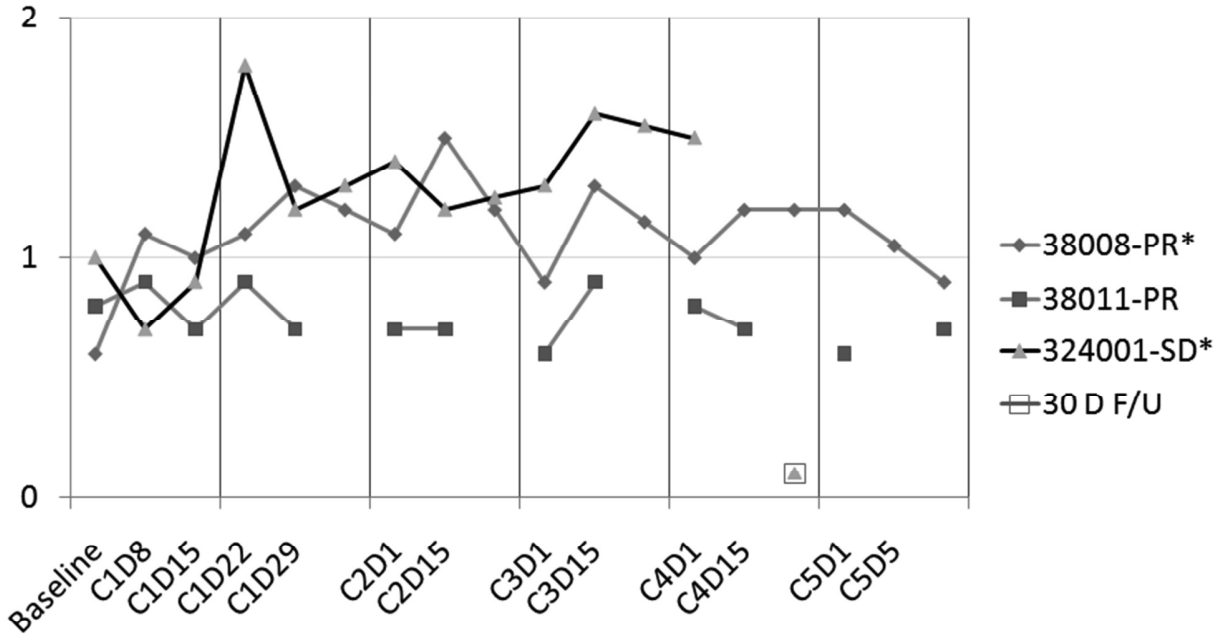

4
3
2
1
0
Baseline
C1D8
C1D15
C1D22
C1D29
C2D1
C2D15
C3D1
C3D15
32001-PD
38010-PD*
126001-PD
323001-PD
30D F/U
* Continuous dosing, numbers in between cycles are interpolated

FIGURE 10



* Continuous dosing, numbers in between cycles are interpolated

FIGURE 11

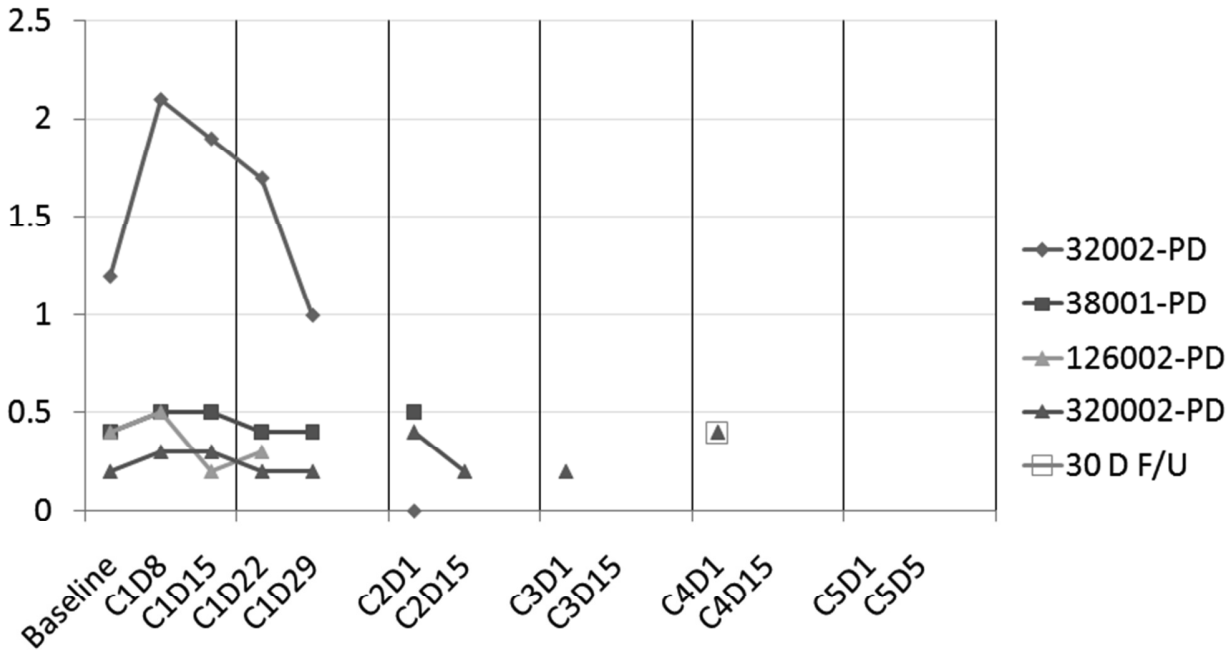

2.5
2
1.5
1
0.5
0
Baseline
C1D8
C1D15
C1D22
C1D29
C2D1
C2D15
C3D1
C3D15
C4D1
C4D15
C5D1
C5D5
32002-PD
38001-PD
126002-PD
320002-PD
30 D F/U

FIGURE 12

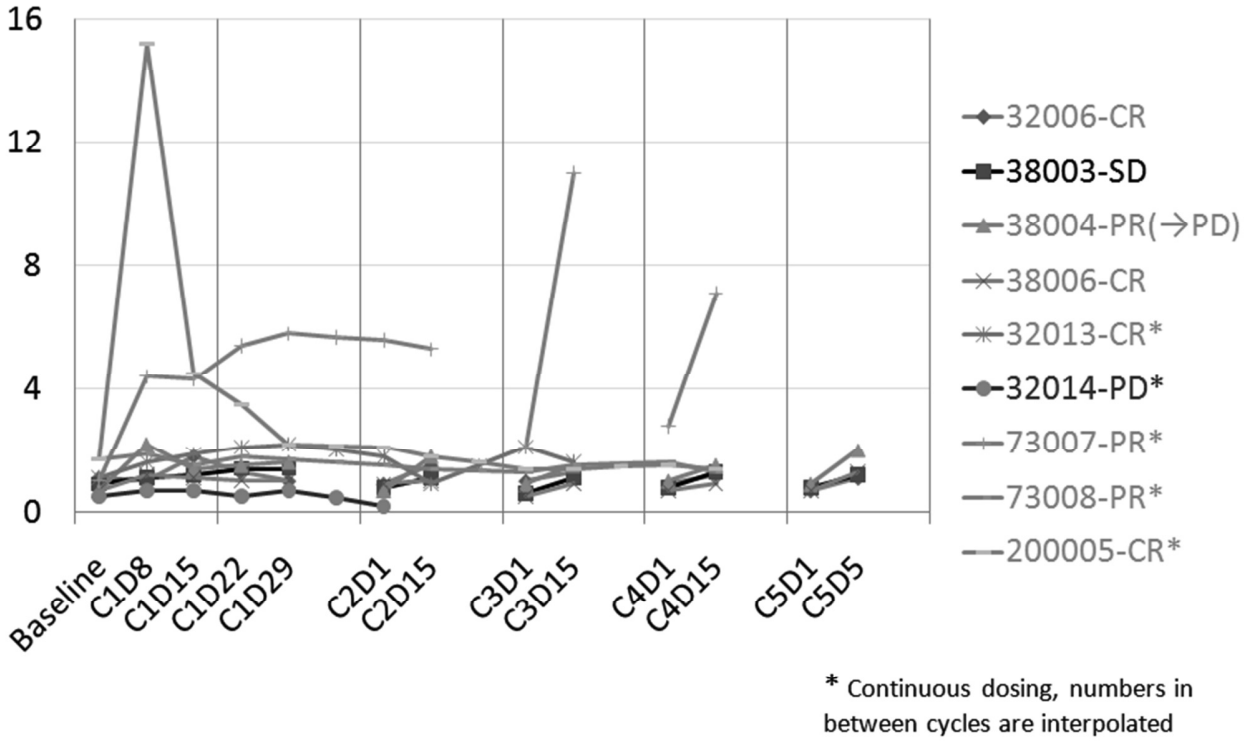

16
12
8
4
0
Baseline
C1D8
C1D15
C1D22
C1D29
C2D1
C2D15
C3D1
C3D15
C4D1
C4D15
C5D1
C5D5
32006-CR
38003-SD
38004-PR(→PD)
38006-CR
32013-CR*
32014-PD*
73007-PR*
73008-PR*
200005-CR*
* Continuous dosing, numbers in between cycles are interpolated

FIGURE 13

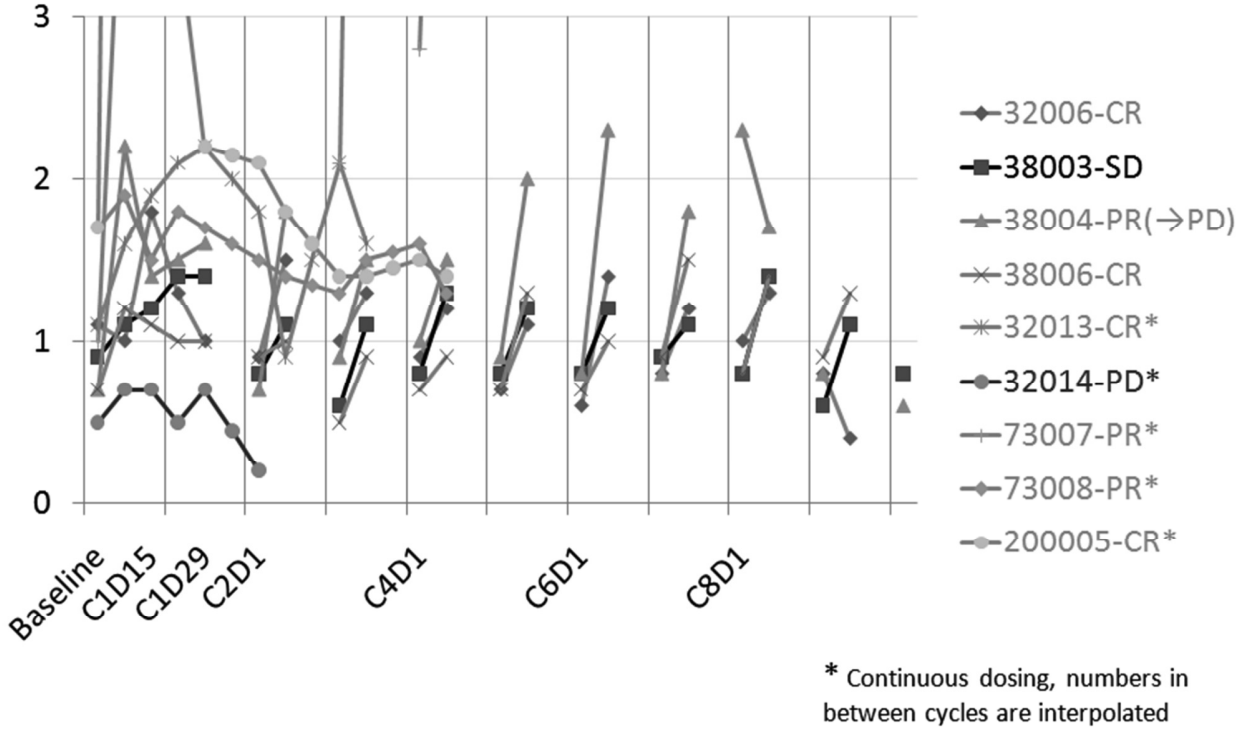

3
2
1
0
Baseline
C1D15
C1D29
C2D1
C4D1
C6D1
C8D1
32006-CR
38003-SD
38004-PR(→PD)
38006-CR
32013-CR*
32014-PD*
73007-PR*
73008-PR*
200005-CR*
* Continuous dosing, numbers in between cycles are interpolated

FIGURE 14

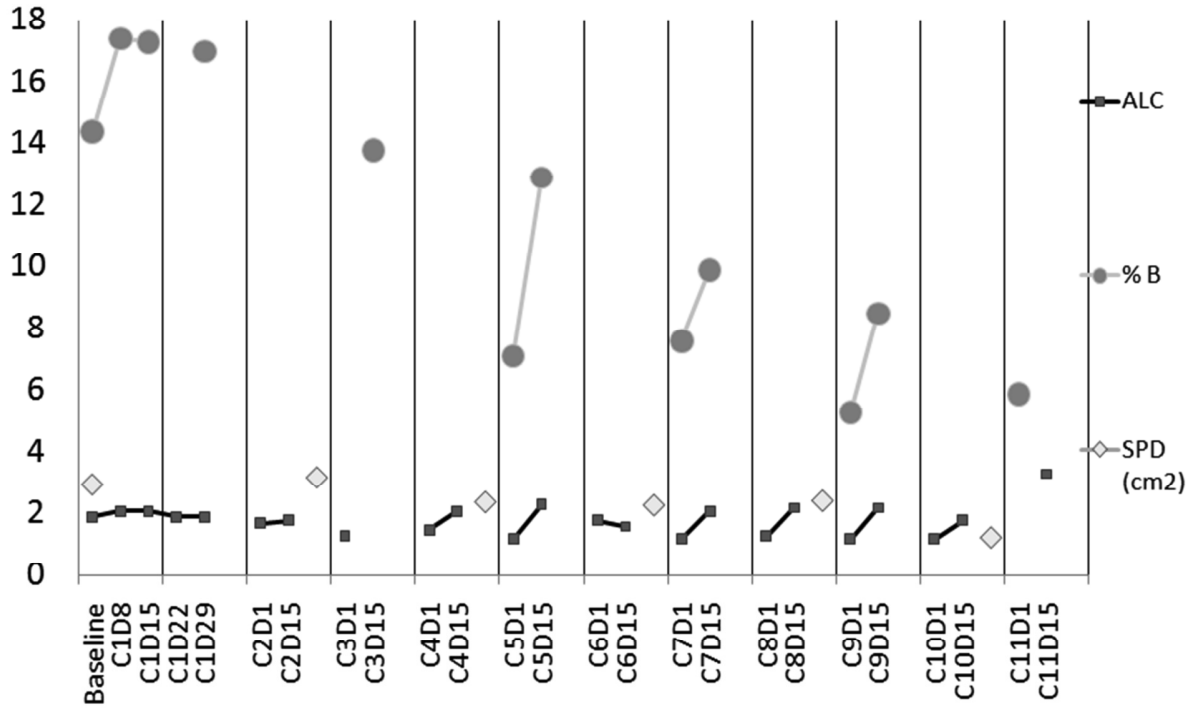

18
16
14
12
10
8
6
4
2
0
Baseline
C1D8
C1D15
C1D22
C1D29
C2D1
C2D15
C3D1
C3D15
C4D1
C4D15
C5D1
C5D15
C6D1
C6D15
C7D1
C7D15
C8D1
C8D15
C9D1
C9D15
C10D1
C10D15
C11D1
C11D15
ALC
% B
SPD
(cm2)

FIGURE 15

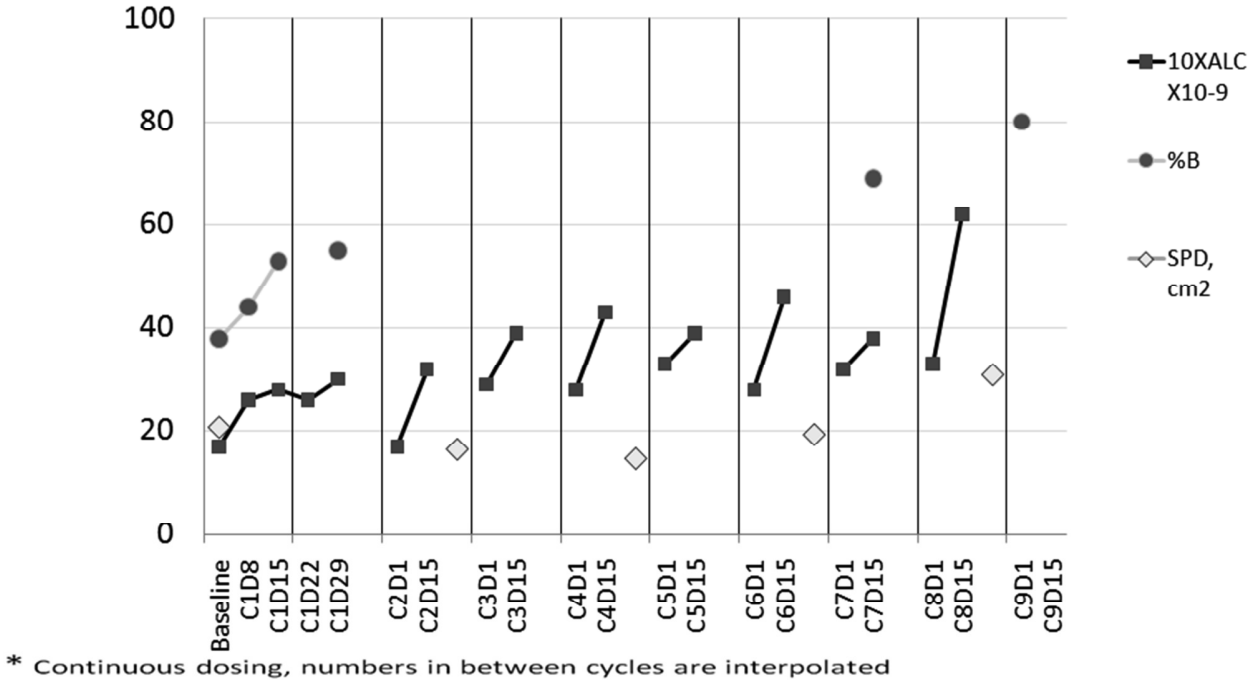

100
80
60
40
20
0
Baseline
C1D8
C1D15
C1D22
C1D29
C2D1
C2D15
C3D1
C3D15
C4D1
C4D15
C5D1
C5D15
C6D1
C6D15
C7D1
C7D15
C8D1
C8D15
C9D1
C9D15
10XALC X10-9
%B
SPD, cm2
* Continuous dosing, numbers in between cycles are interpolated

FIGURE 16

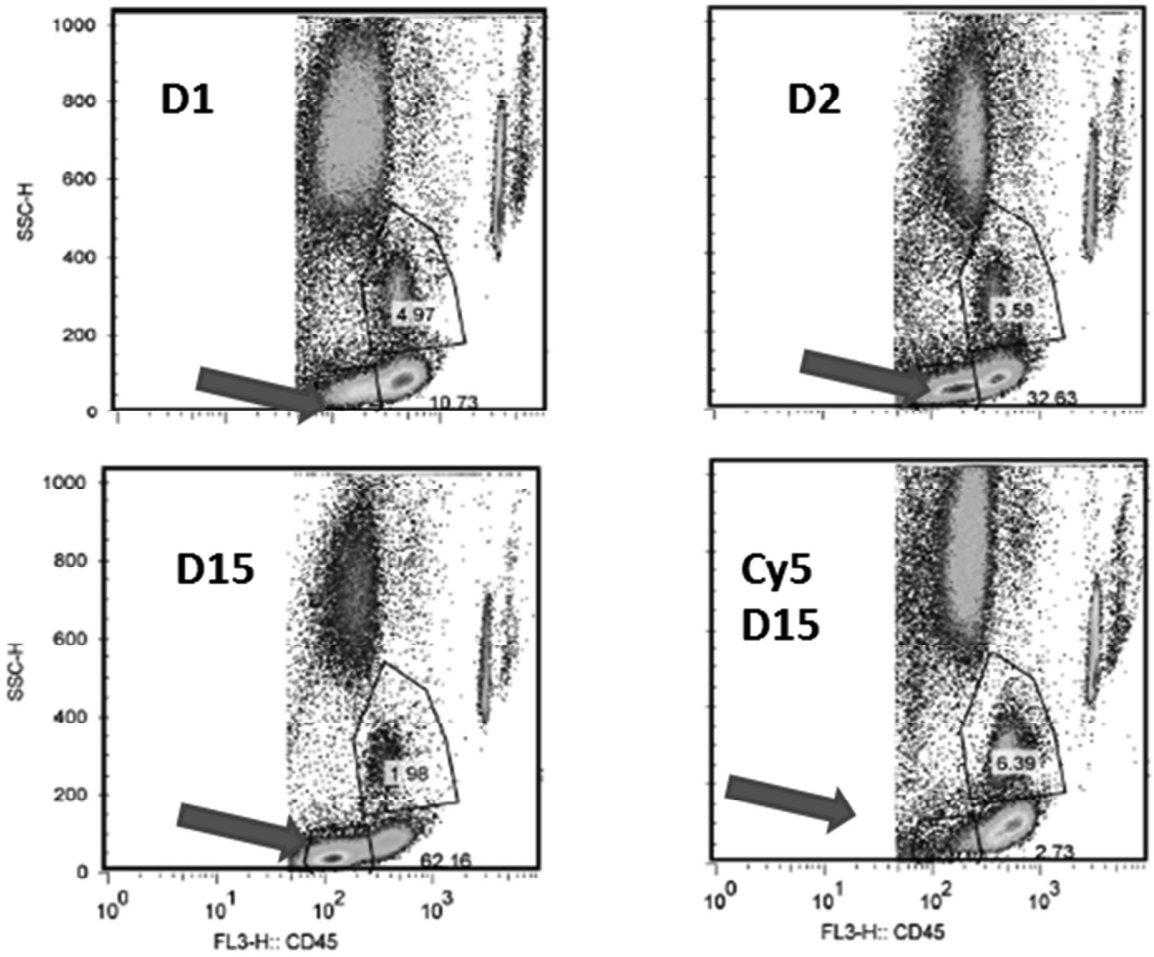

D1
4.97
10.73
D2
3.58
32.63
D15
1.98
62.16
Cy5
D15
6.39
2.73
SSC-H
FL3-H:: CD45
0
200
400
600
800
1000
10^0
10^1
10^2
10^3

FIGURE 17

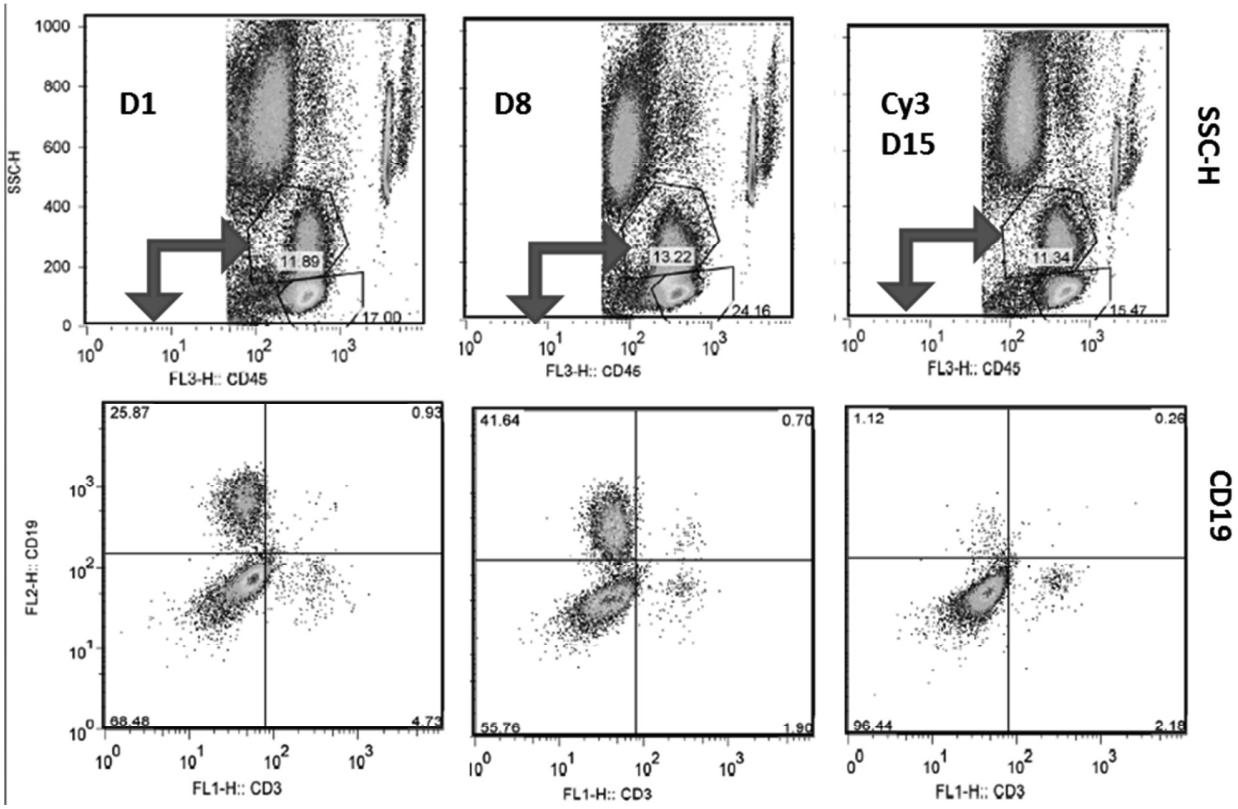

D1
D8
Cy3
D15
SSC-H
SSC-H
FL3-H:: CD45
11.89
17.00
13.22
24.16
11.34
15.47
FL2-H:: CD19
FL1-H:: CD3
25.87
0.93
68.48
4.73
41.64
0.70
55.76
1.90
1.12
0.26
96.44
2.18
CD19

FIGURE 24

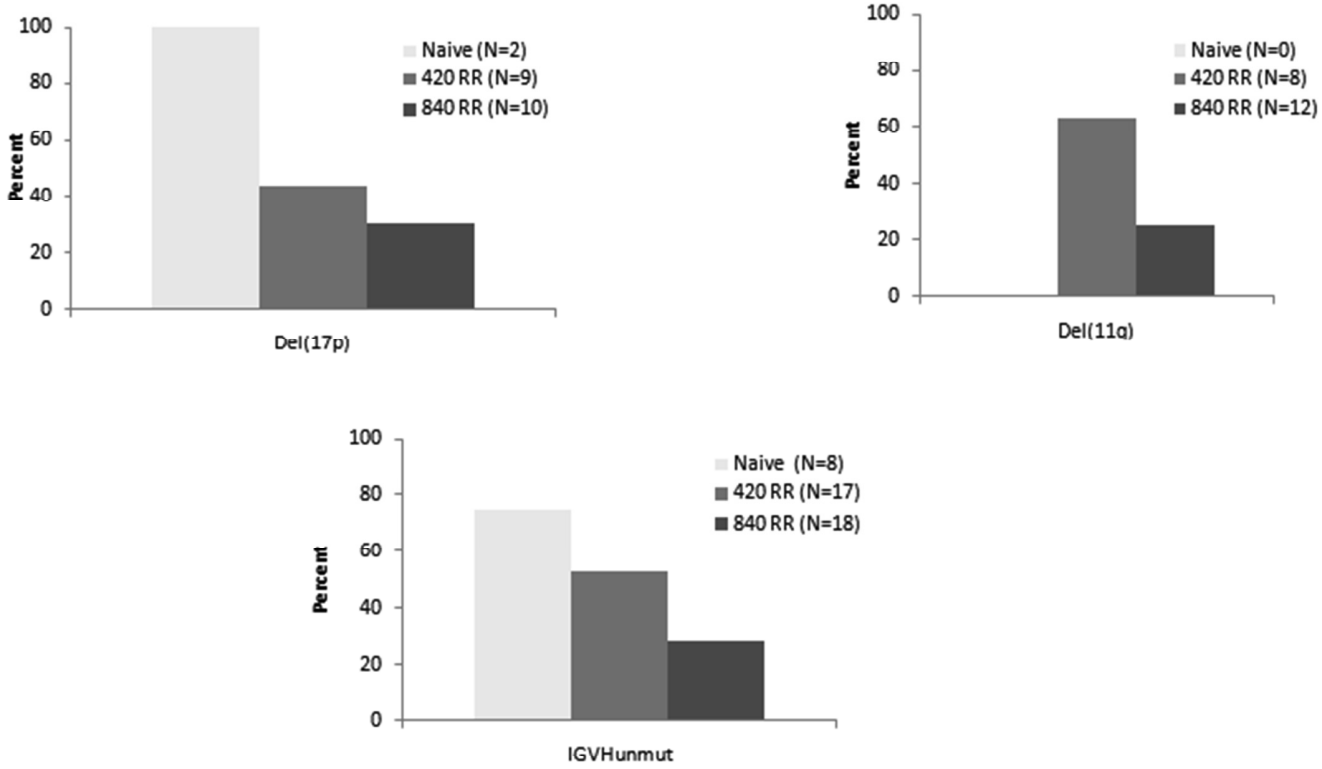

100
80
60
40
20
0
Percent
Naive (N=2)
420 RR (N=9)
840 RR (N=10)
Del(17p)
100
80
60
40
20
0
Percent
Naive (N=0)
420 RR (N=8)
840 RR (N=12)
Del(11q)
100
80
60
40
20
0
Percent
Naive (N=8)
420 RR (N=17)
840 RR (N=18)
IGVHunmut

FIGURE 27

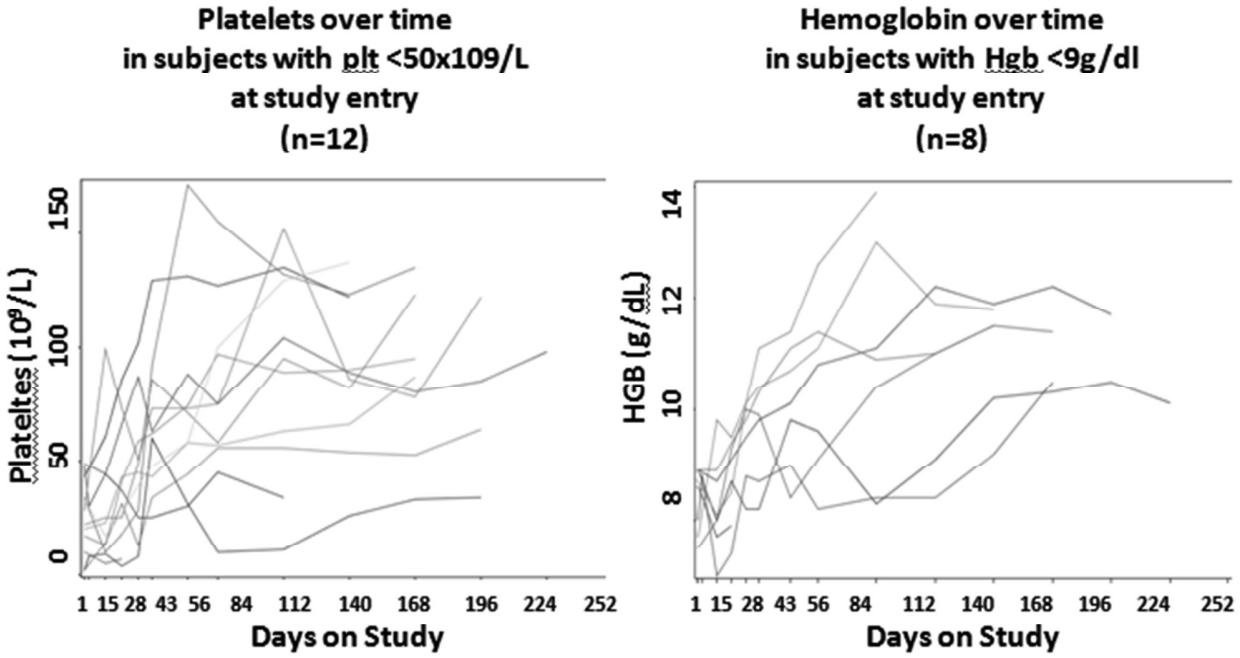
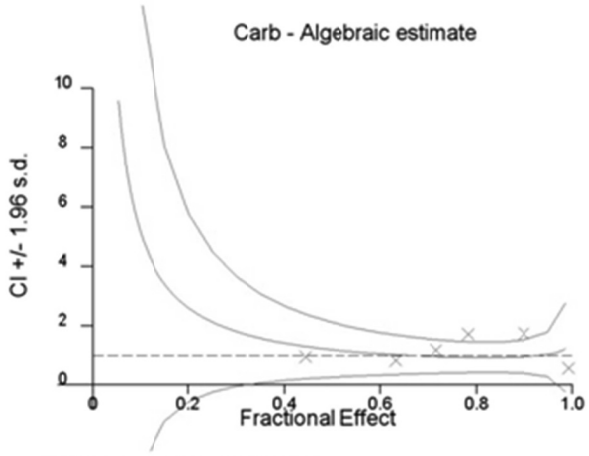

Platelets over time
in subjects with plt <50x109/L
at study entry
(n=12)
Platelets (10⁹/L)
0
50
100
150
1 15 28 43 56 84 112 140 168 196 224 252
Days on Study
Hemoglobin over time
in subjects with Hgb <9g/dl
at study entry
(n=8)
HGB (g/dL)
8
10
12
14
1 15 28 43 56 84 112 140 168 196 224 252
Days on Study

FIGURE 28

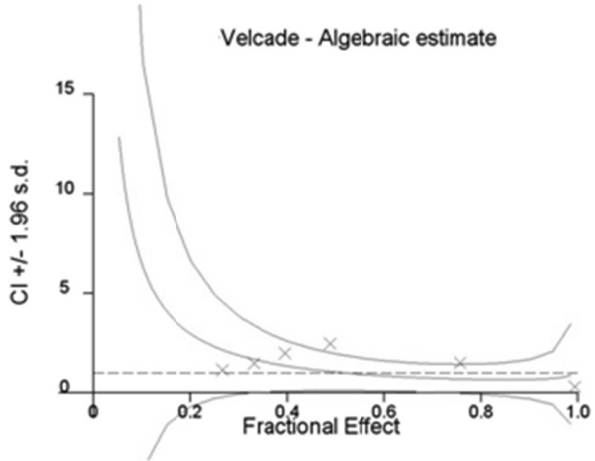
	Btk inhibitor (uM)	Carb(uM)
GI50	0.096	15.382
r:	0.994	0.990

	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

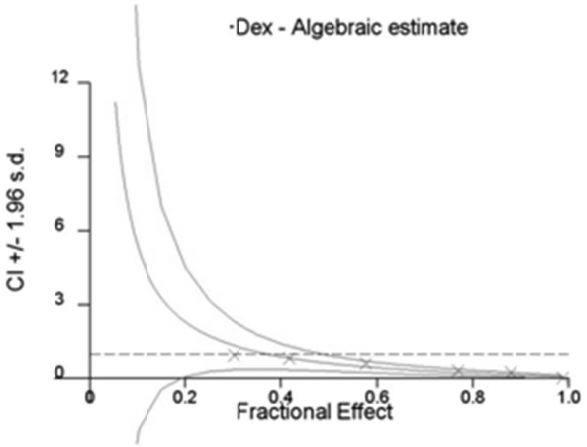


CI For experimental values

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

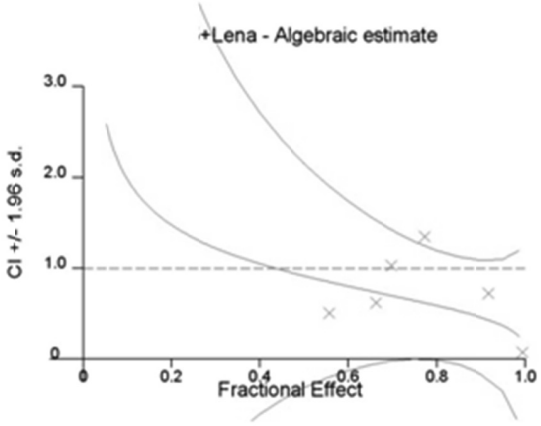
	Btk Inhibitor (uM)	Dex(uM)
GI50	0.177	45.850
r:	0.964	0.991



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

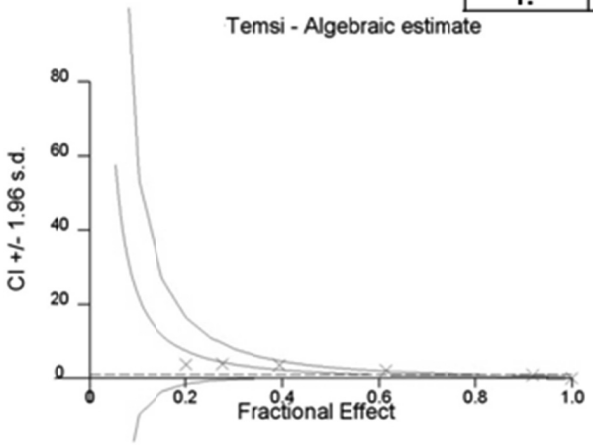


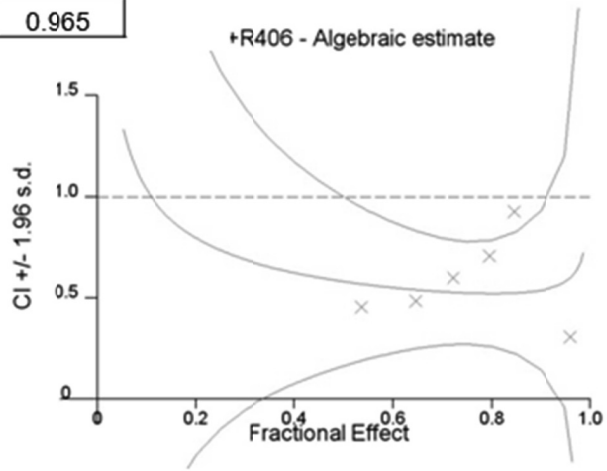
CI For experimental values

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

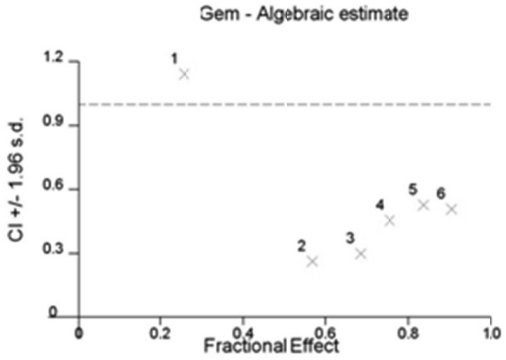
Btk inhibitor (uM)	Temsi (uM)	Fa	CI
0.03125	**0.3125**	0.200943	3.779
0.0625	**0.625**	0.275482	3.93
0.125	**1.25**	0.394234	3.529
0.25	**2.5**	0.614251	2.244
0.5	**5**	0.91765	0.907
1	**10**	0.99999	0.016

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

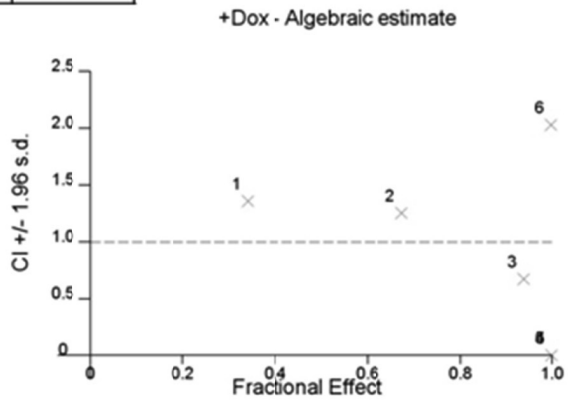
FIGURE 31

	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	0.339005	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

FIGURE 32

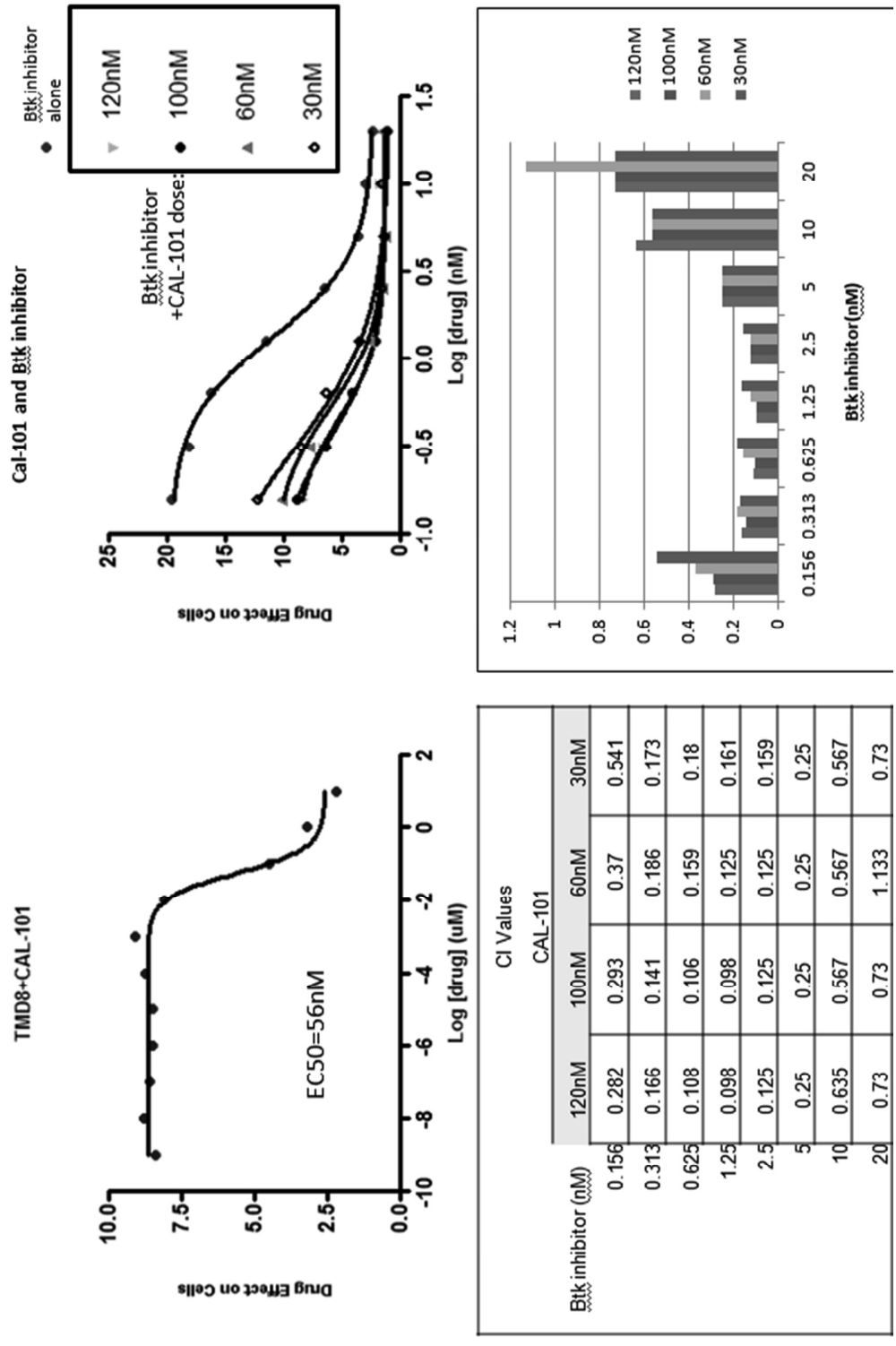
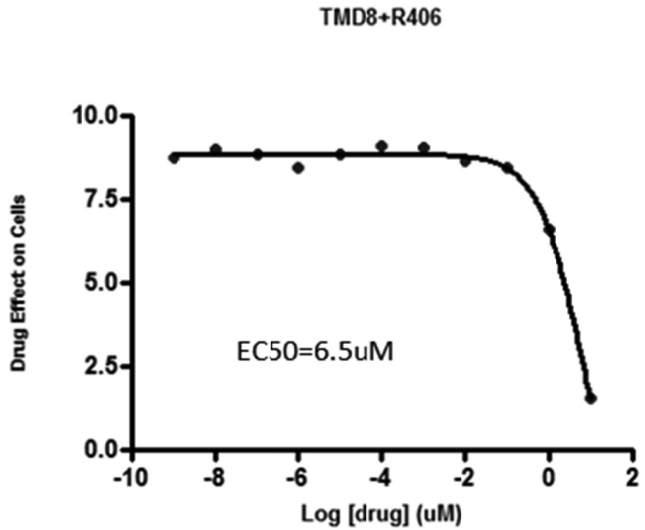
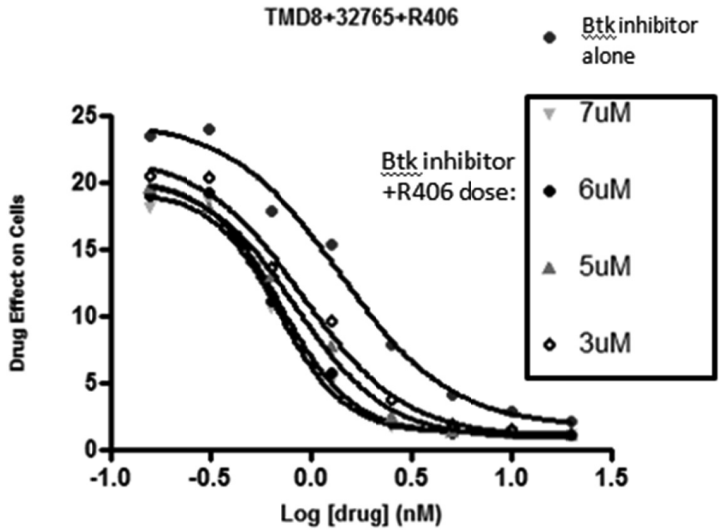

TMD8+CAL-101
Drug Effect on Cells
Log [drug] (uM)
EC50=56nM
Cal-101 and Btk inhibitor
Btk inhibitor alone
Btk inhibitor +CAL-101 dose:
120nM
100nM
60nM
30nM
Drug Effect on Cells
Log [drug] (nM)
Btk inhibitor(nM)
CI Values
CAL-101
Btk inhibitor (nM)
120nM 100nM 60nM 30nM
0.156 0.282 0.293 0.37 0.541
0.313 0.166 0.141 0.186 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

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

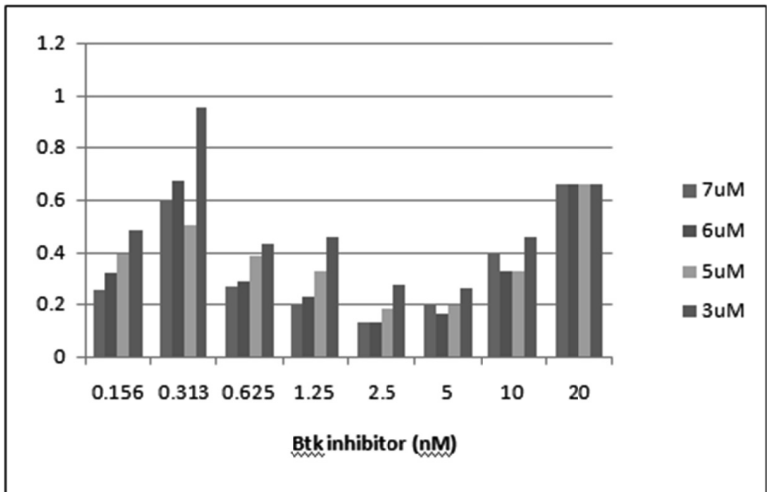
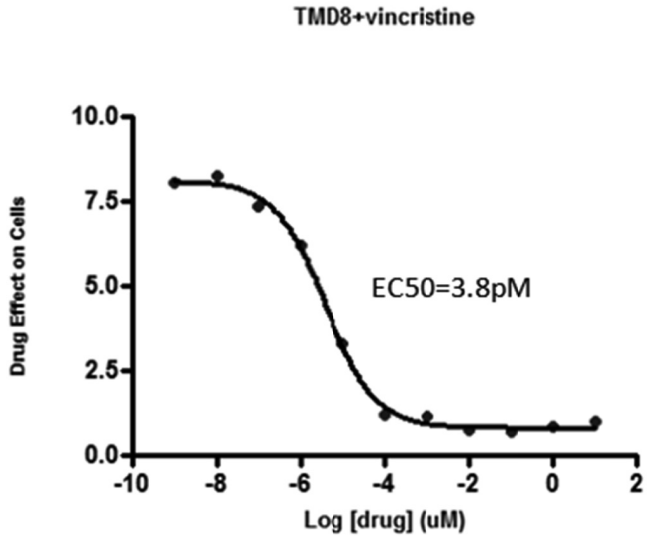
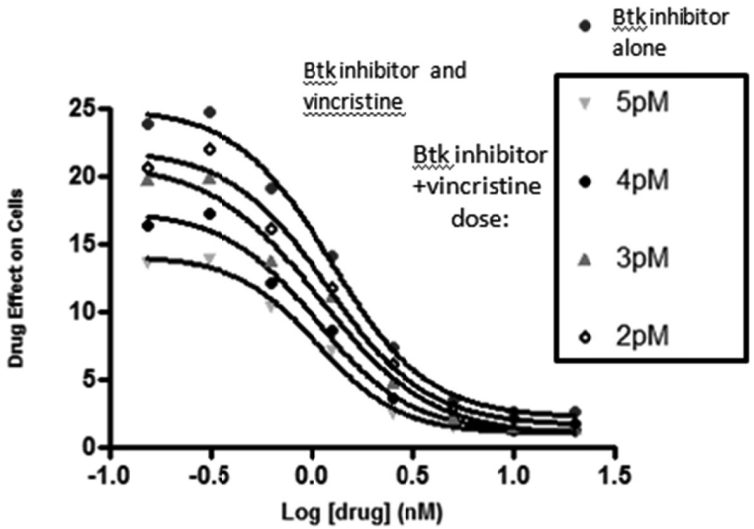


FIGURE 34





	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

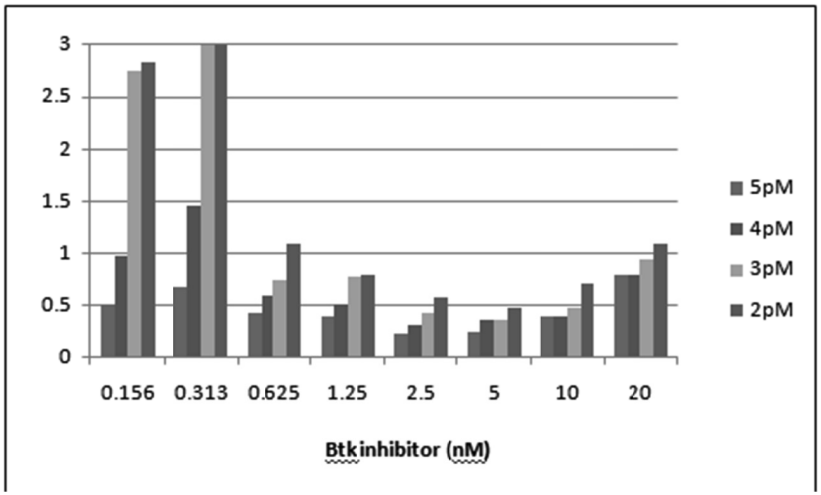
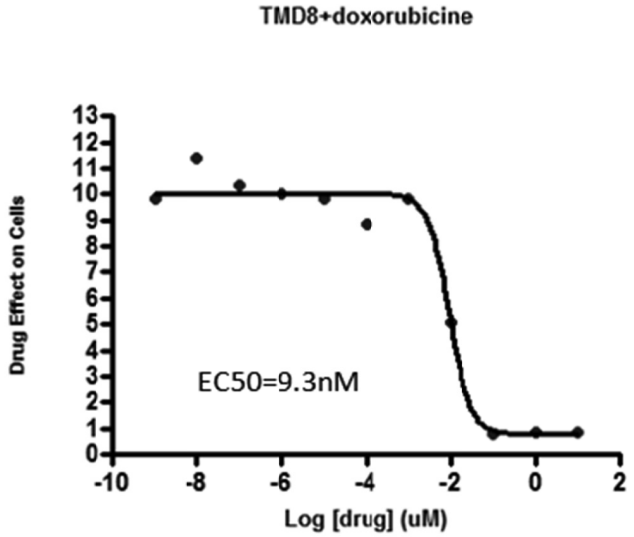
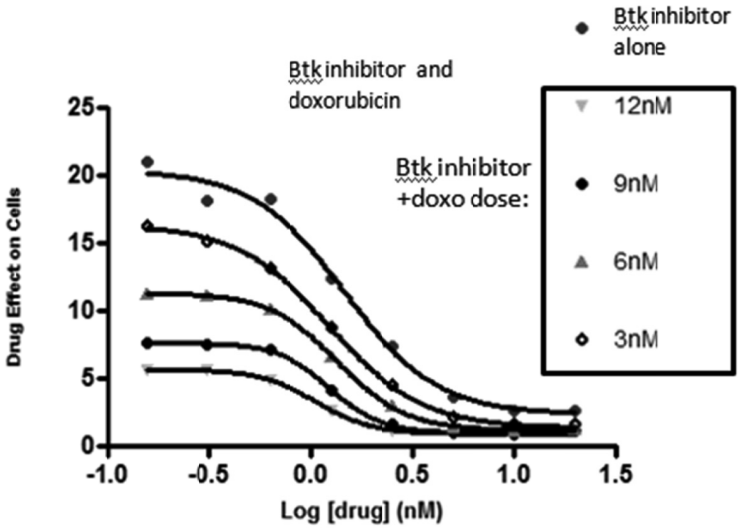


FIGURE 35





	CI Values Doxorubicin			
Btk inhibitor (nM)	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

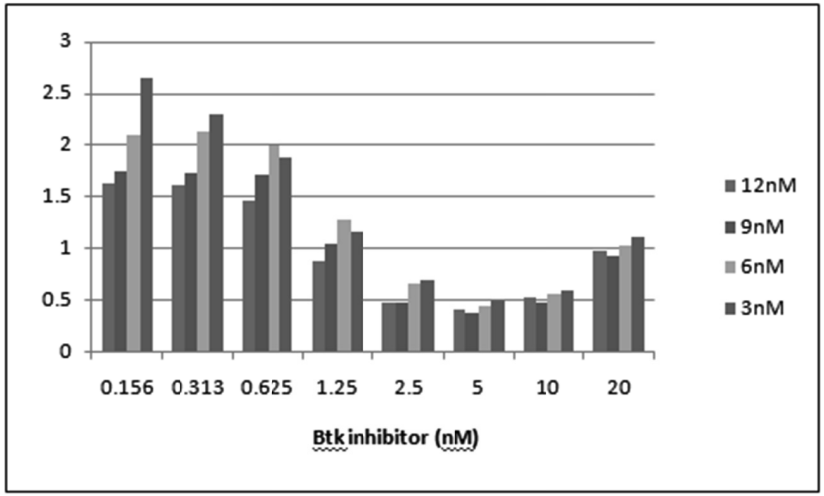
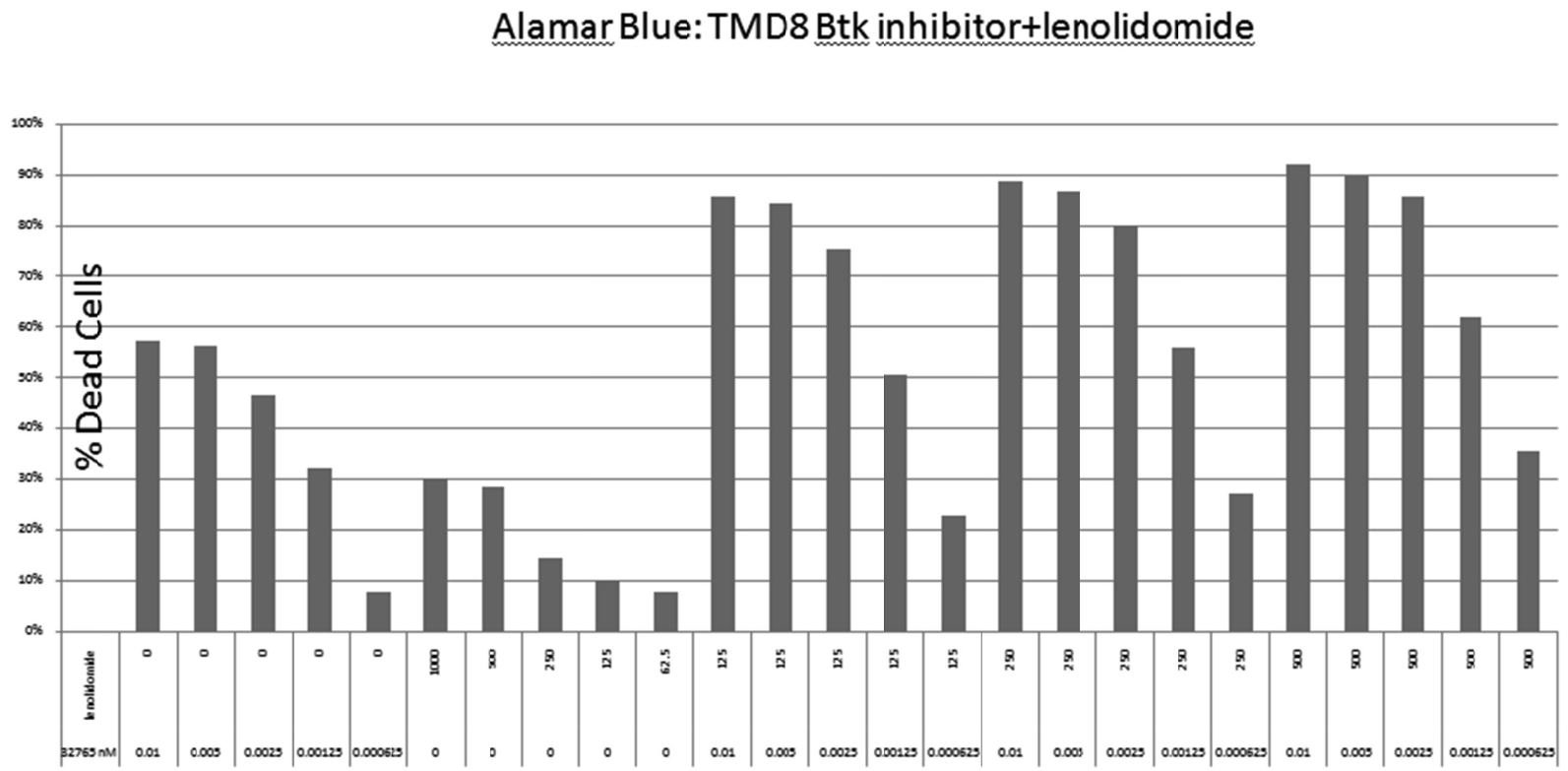


FIGURE 36

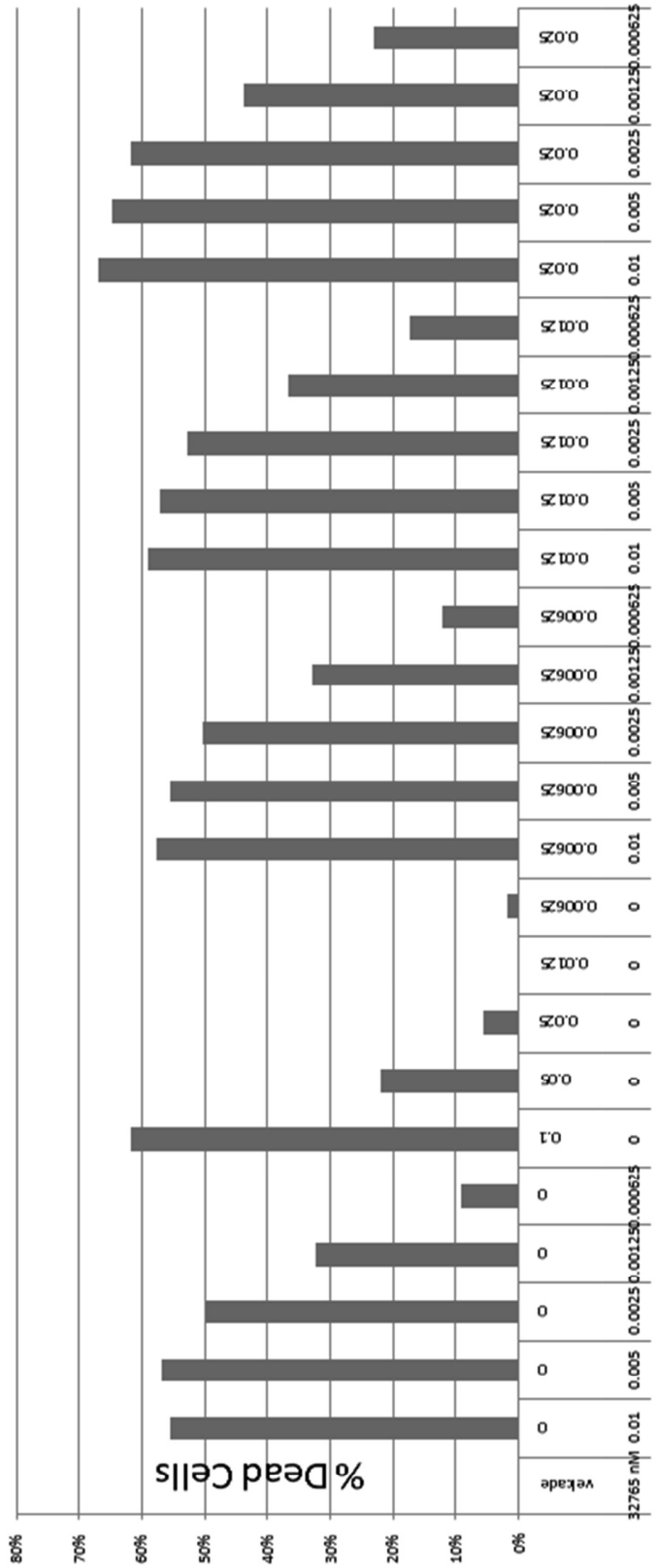


Btk inhibitor nM	lenolidomide nM	CI
0.000625	125	0.77
0.00125	125	0.311
0.0025	125	0.175
0.005	125	0.188
0.01	125	0.332

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

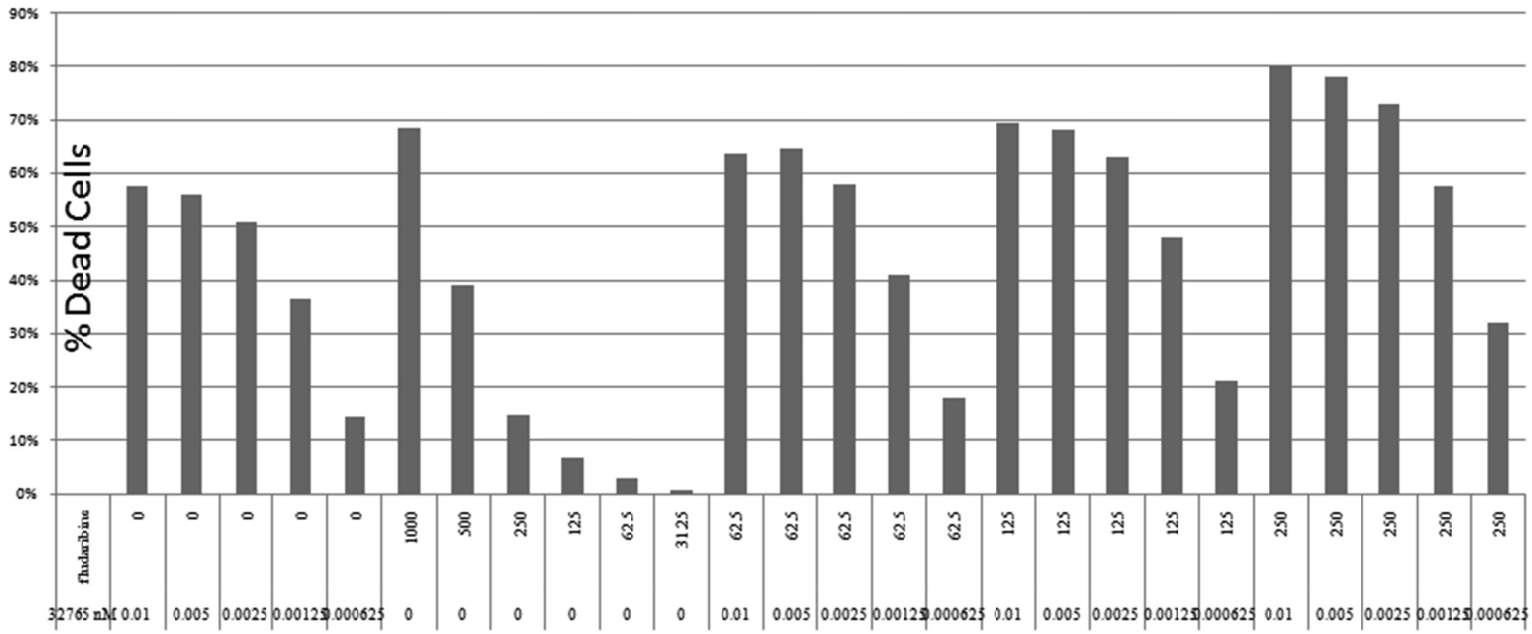


Btk inhibitor nM	velcade nM	CI
0.000625	0.00625	1.486
0.00125	0.00625	0.701
0.0025	0.00625	0.601
0.005	0.00625	0.91
0.01	0.00625	1.615

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	0.888
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

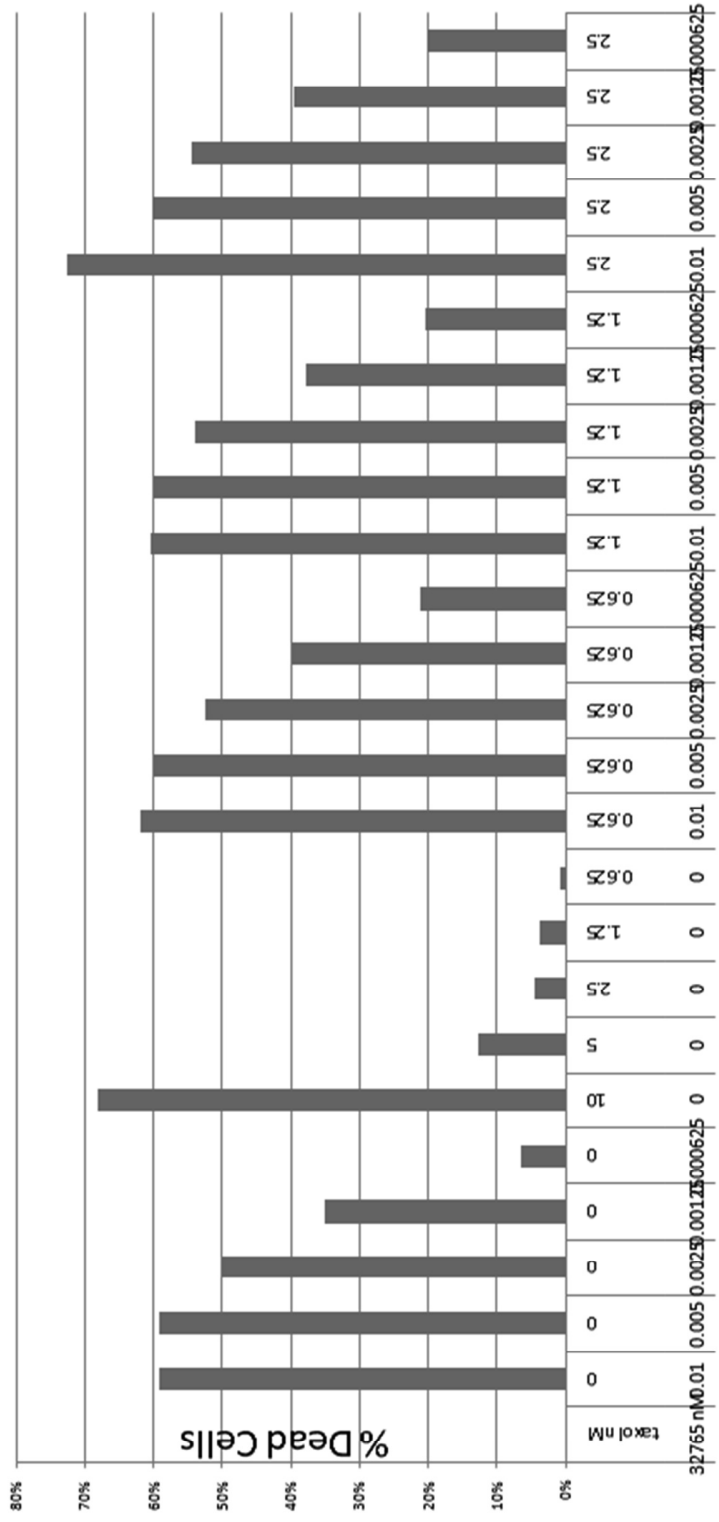


Btk inhibitor nM	fludarabine nM	CI
0.000625	62.5	1.551
0.00125	62.5	0.636
0.0025	62.5	0.474
0.005	62.5	0.598
0.01	62.5	1.196

Btk inhibitor nM	fludarabine nM	CI
0.000625	125	1.389
0.00125	125	0.548
0.0025	125	0.427
0.005	125	0.542
0.01	125	0.889

Btk inhibitor nM	fludarabine nM	CI
0.000625	250	1.055
0.00125	250	0.518
0.0025	250	0.356
0.005	250	0.383
0.01	250	0.518

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	1.556

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	1.703

Btk inhibitor nM	taxol nM	CI
0.000625	2.5	1.13
0.00125	2.5	0.784
0.0025	2.5	0.735
0.005	2.5	1.007
0.01	2.5	1.084