[Figure 1]

SEQ ID NO: 1 - Amino acid sequence of a heavy chain of anti-HER2 antibody

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVR
QAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSK
NTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGT
LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY
FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS
RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[Figure 2]

SEQ ID NO: 2 - Amino acid sequence of a light chain of anti-HER2 antibody

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQ
KPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTIS
SLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPS
VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN
ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK
VYACEVTHQGLSSPVTKSFNRGEC

[Figure 3]

SEQ ID NO: 3 - Amino acid sequence of heavy chain CDRH1

GFNIKDTY

[Figure 4]

SEQ ID NO: 4 - Amino acid sequence of heavy chain CDRH2

IYPTNGYT

[Figure 5]
SEQ ID NO: 5 - Amino acid sequence of heavy chain CDRH3
SRWGGDGFYAMDY

[Figure 6]
SEQ ID NO: 6 - Amino acid sequence of light chain CDRL1
QDVNTA

[Figure 7]
SEQ ID NO: 7 - Amino acid sequence comprising an amino acid sequence of light chain CDRL2 (SAS)
SASFLYS

[Figure 8]
SEQ ID NO: 8 - Amino acid sequence of light chain CDRL3
QQHYTTPPT

[Figure 9]
SEQ ID NO: 9 - Amino acid sequence of heavy chain variable region
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVR
QAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSK
NTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGT
LVTVSS

[Figure 10]
SEQ ID NO: 10 - Amino acid sequence of light chain variable region
DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQ
KPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFTLTIS
SLQPEDFATYYCQQHYTTPPTFGQGTKVEIK

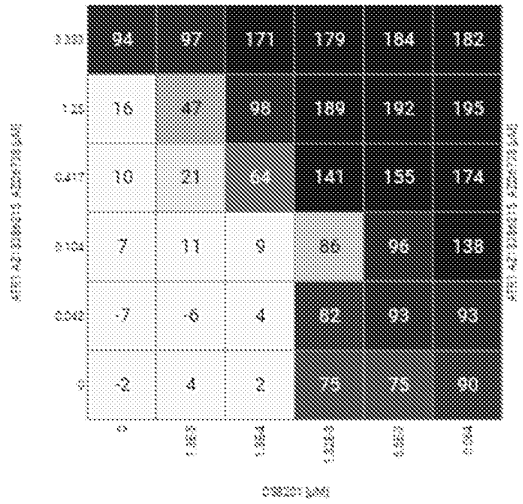
[Figure 11]

SEQ ID NO: 11 - Amino acid sequence of heavy chain

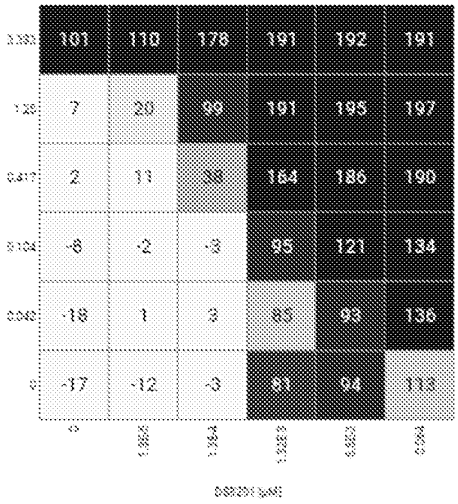
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVR
QAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSK
NTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGT
LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY
FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS
RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[Figure 12A]

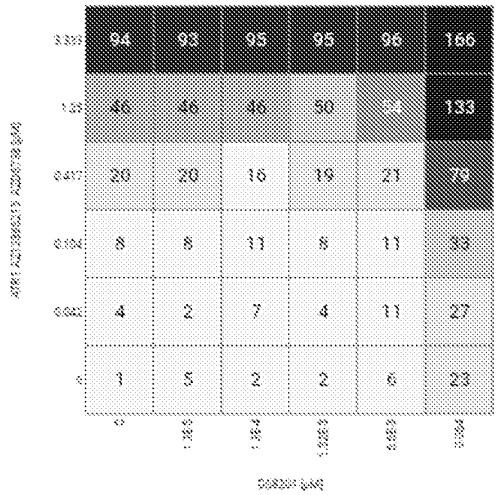
KPL4 (HER2 High)



NCI-N87 (HER2 High)

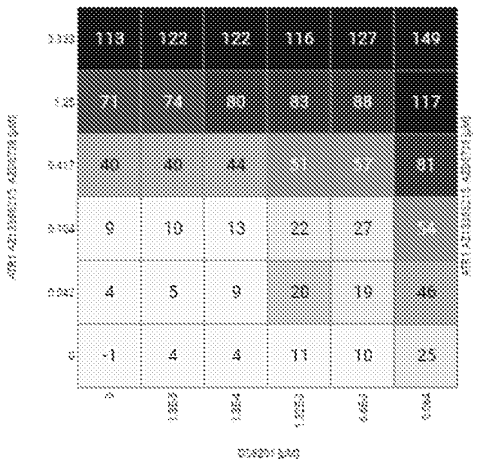


MDA-MB-468 (HER2 Low)

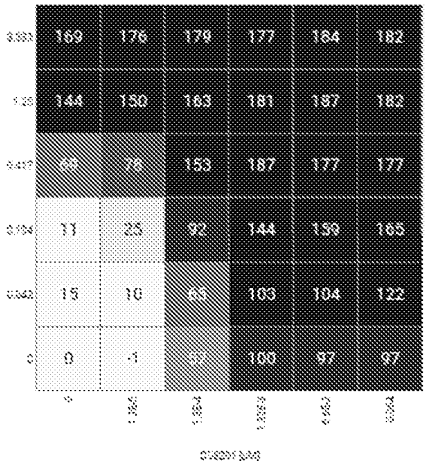


[Figure 12B]

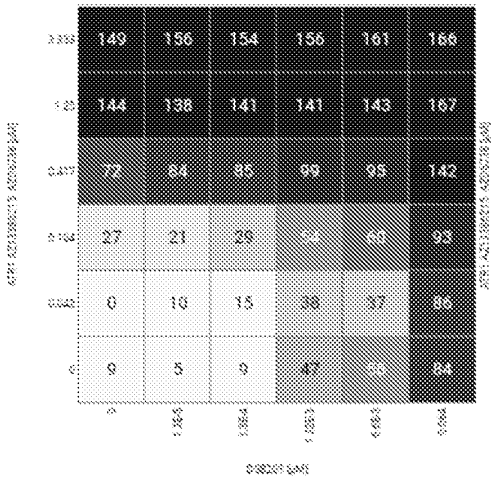
HCC1937 (HER2 Low)



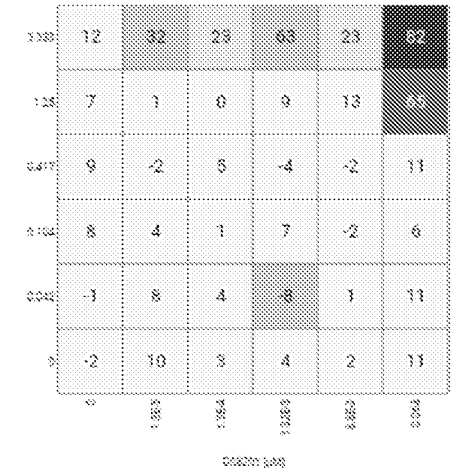
HCC1954 (HER2 High)



HCC38 (HER2 Low)

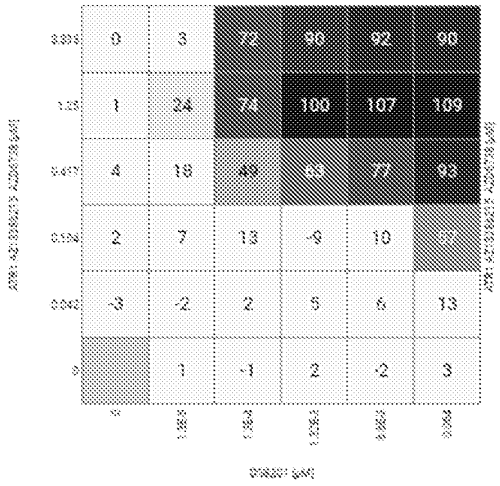


T47D (HER2 Low)

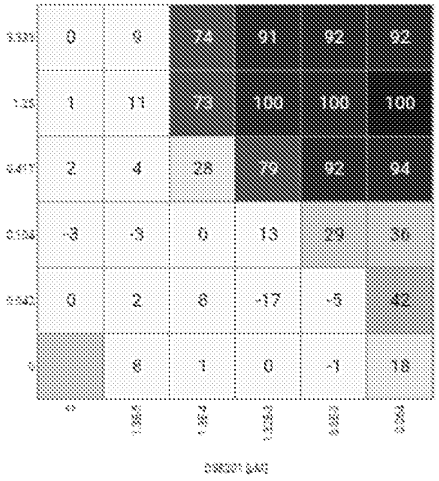


[Figure 12C]

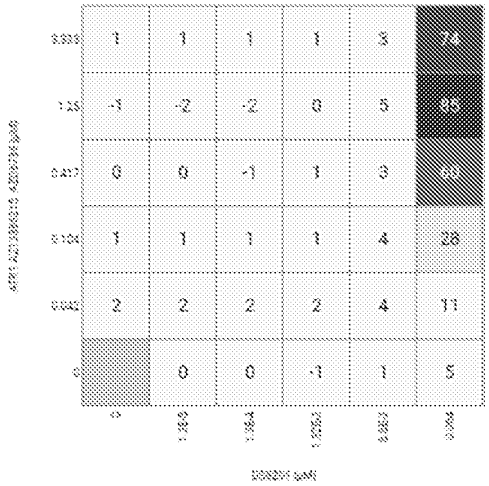
KPL4 (HER2 High)



NCI-N87 (HER2 High)

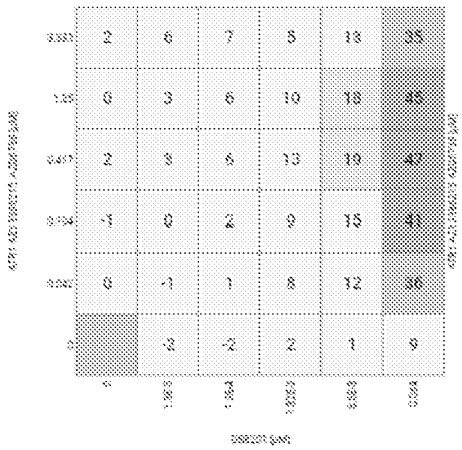


MDA-MB-468 (HER2 Low)

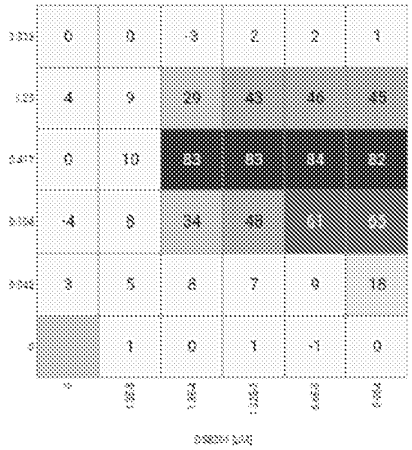


[Figure 12D]

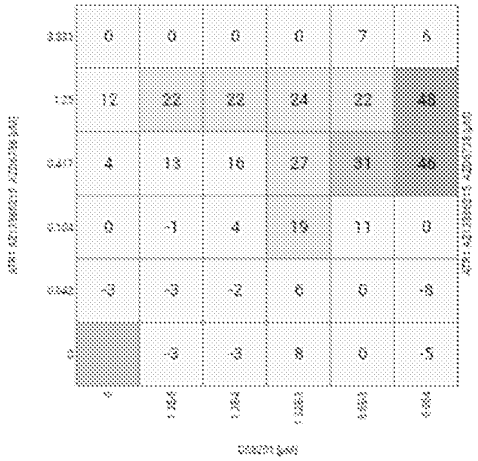
HCC1937 (HER2 Low)



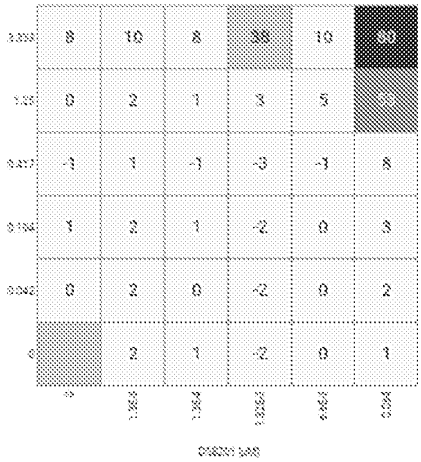
HCC1954 (HER2 High)



HCC38 (HER2 Low)

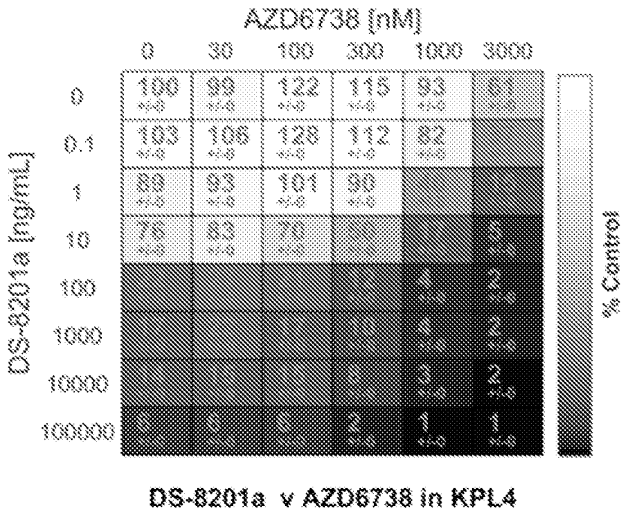


T47D (HER2 Low)



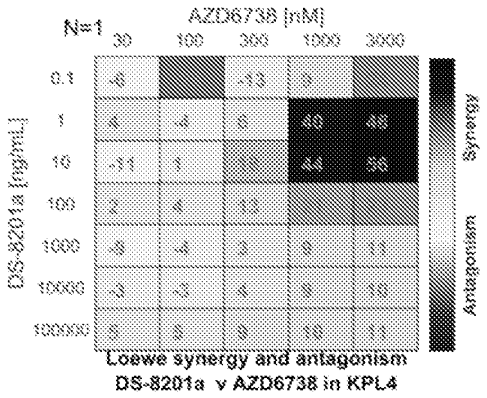
[Figure 13]

(A)

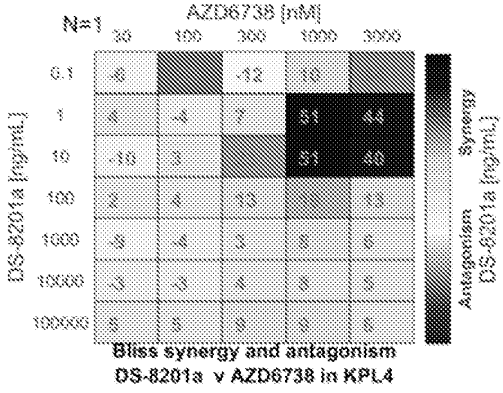


DS-8201a v AZD6738 in KPL4

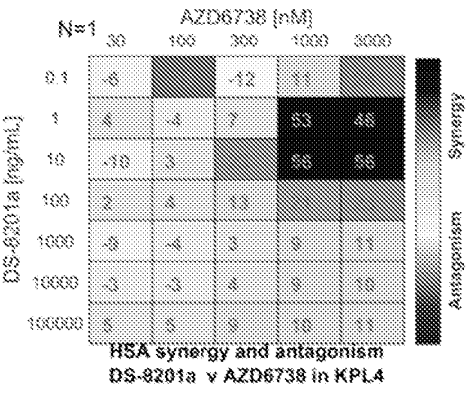
(B)



Loewe synergy and antagonism
DS-8201a v AZD6738 in KPL4



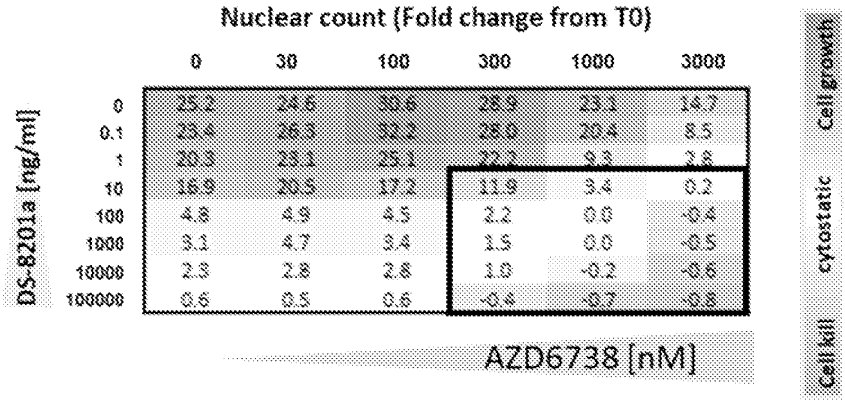
Bliss synergy and antagonism
DS-8201a v AZD6738 in KPL4



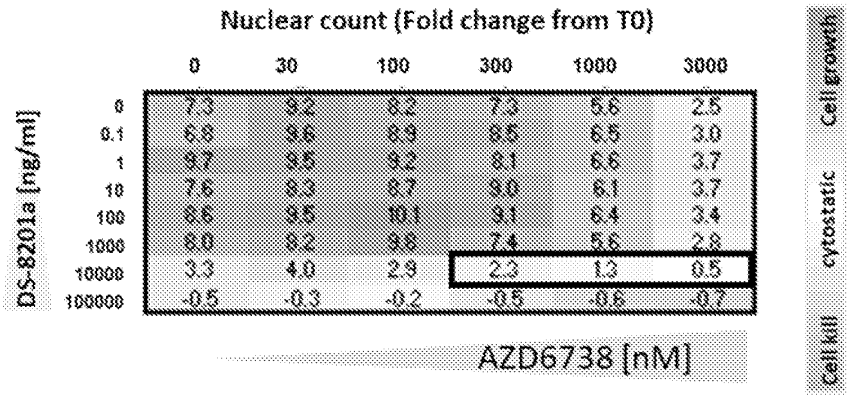
HSA synergy and antagonism
DS-8201a v AZD6738 in KPL4

[Figure 14]

(A)

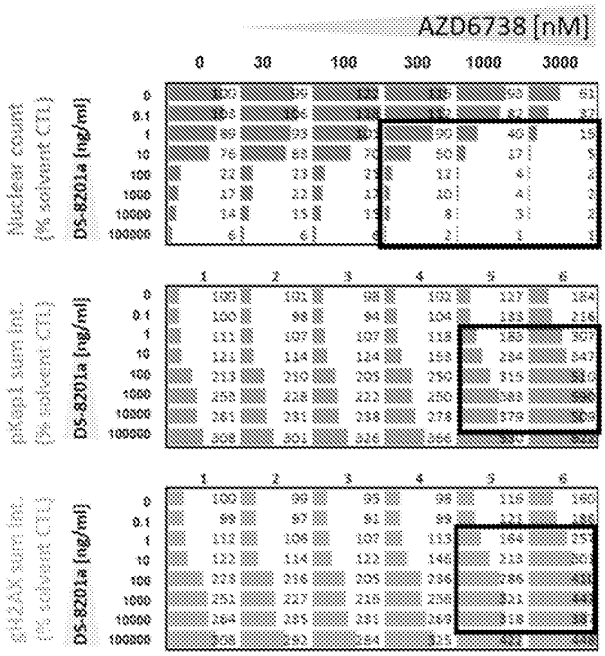

Nuclear count (Fold change from T0)
0 30 100 300 1000 3000
DS-8201a [ng/ml]
0 25.2 24.6 30.6 28.9 23.1 14.7
0.1 23.4 26.3 32.2 28.0 20.4 8.5
1 20.3 23.1 25.1 22.1 9.3 3.8
10 16.9 20.5 17.2 11.9 3.4 0.2
100 4.8 4.9 4.5 2.2 0.0 -0.4
1000 3.1 4.7 3.4 1.5 0.0 -0.5
10000 2.3 2.8 2.8 1.0 -0.2 -0.6
100000 0.6 0.5 0.6 -0.4 -0.7 -0.8
AZD6738 [nM]
Cell growth
cytostatic
Cell kill

(B)

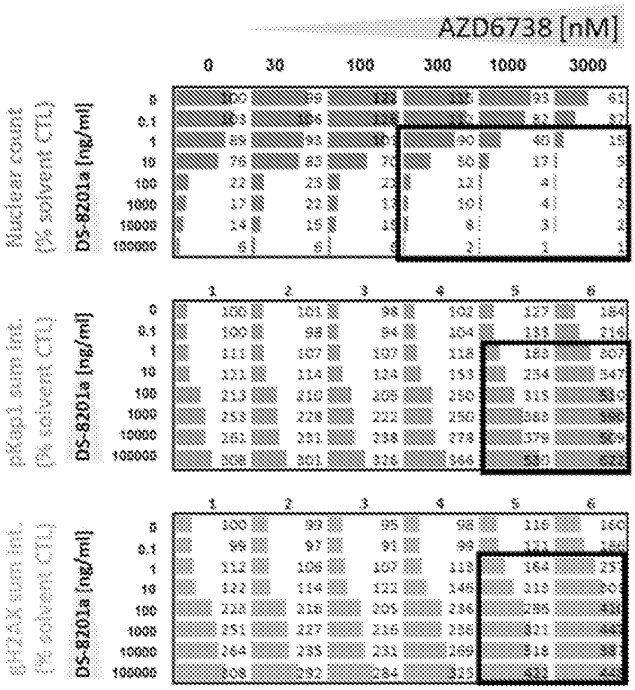

Nuclear count (Fold change from T0)
0 30 100 300 1000 3000
DS-8201a [ng/ml]
0 7.3 9.2 8.2 7.3 5.6 2.5
0.1 6.8 9.6 8.9 8.5 6.5 3.0
1 9.7 9.5 9.2 8.1 6.6 3.7
10 7.6 8.3 8.7 9.0 6.1 3.7
100 8.6 9.5 10.1 9.1 6.4 3.4
1000 8.0 9.2 9.8 7.4 5.6 2.8
10000 3.3 4.0 2.9 2.3 1.3 0.5
100000 -0.5 -0.3 -0.2 -0.5 -0.6 -0.7
AZD6738 [nM]
Cell growth
cytostatic
Cell kill

[Figure 15]

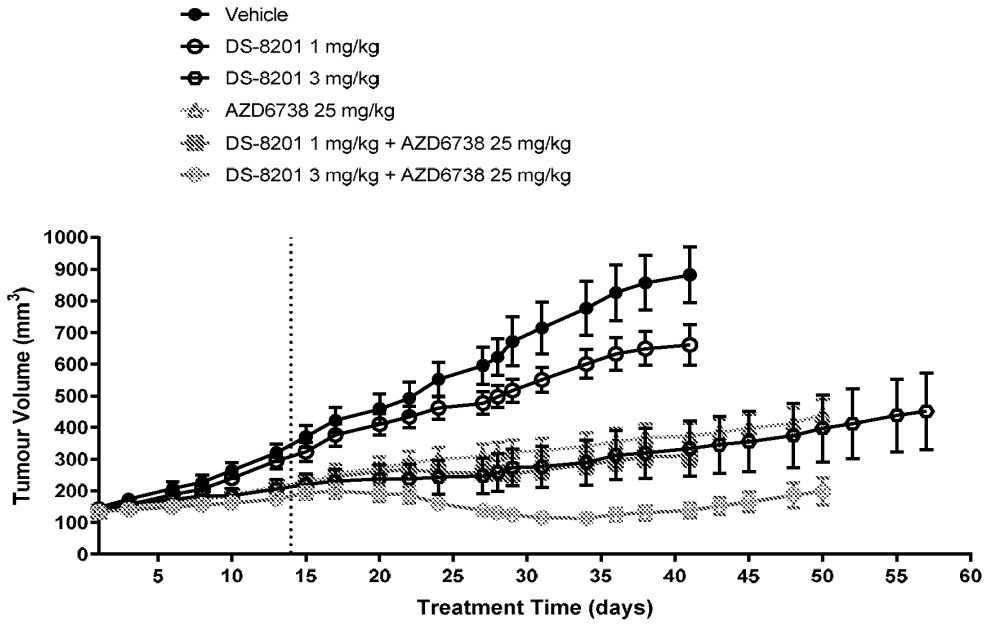
(A)


AZD6738 [nM]
0
30
100
300
1000
3000
Nuclear count (% solvent CTL)
pKap1 sum int. (% solvent CTL)
gH2AX sum int. (% solvent CTL)
DS-8201a [ng/ml]

(B)

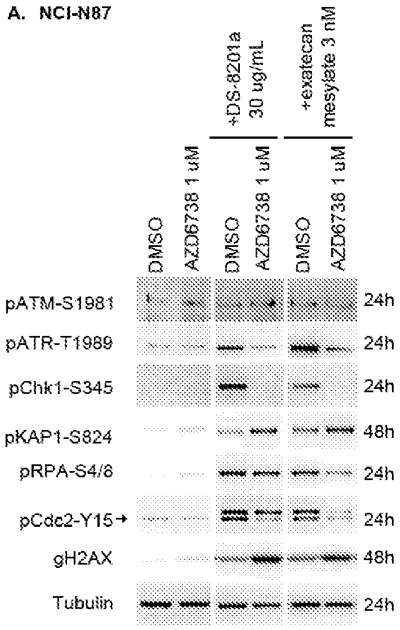

AZD6738 [nM]
0
30
100
300
1000
3000
Nuclear count (% solvent CTL)
pKap1 sum int. (% solvent CTL)
gH2AX sum int. (% solvent CTL)
DS-8201a [ng/ml]

[Figure 16]

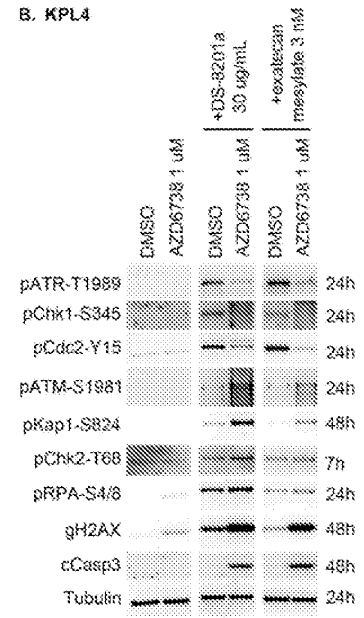

Vehicle
DS-8201 1 mg/kg
DS-8201 3 mg/kg
AZD6738 25 mg/kg
DS-8201 1 mg/kg + AZD6738 25 mg/kg
DS-8201 3 mg/kg + AZD6738 25 mg/kg
Tumour Volume (mm3)
1000
900
800
700
600
500
400
300
200
100
0
5
10
15
20
25
30
35
40
45
50
55
60
Treatment Time (days)

[Figure 17]

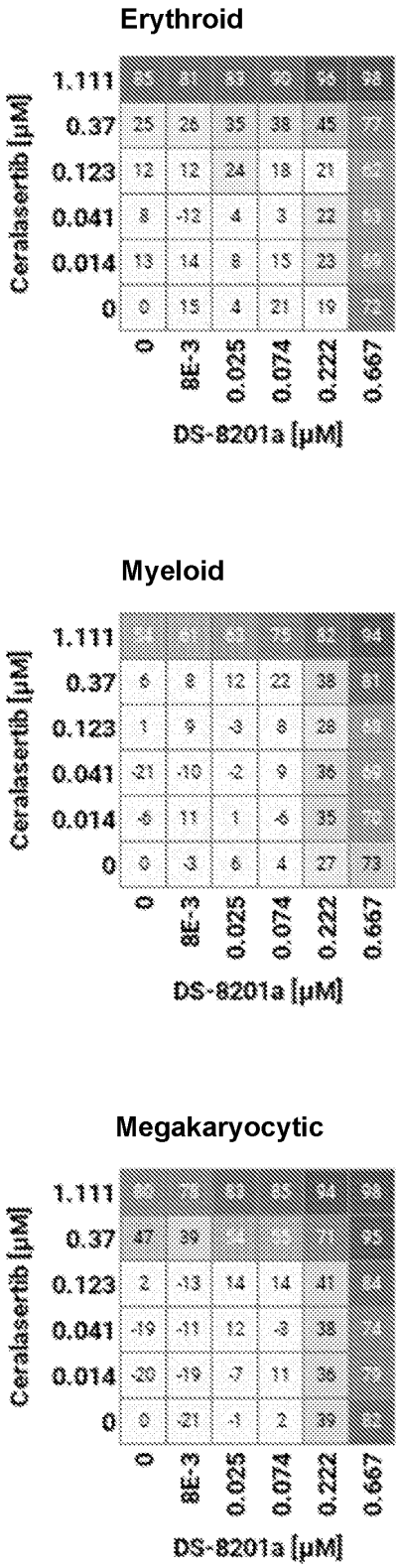
(A)


A. NCI-N87
DMSO
AZD6738 1 uM
+DS-8201a 30 ug/mL
DMSO
AZD6738 1 uM
+exatecan mesylate 3 nM
DMSO
AZD6738 1 uM
pATM-S1981
pATR-T1989
pChk1-S345
pKAP1-S824
pRPA-S4/8
pCdc2-Y15
gH2AX
Tubulin
24h
24h
24h
48h
24h
24h
48h
24h

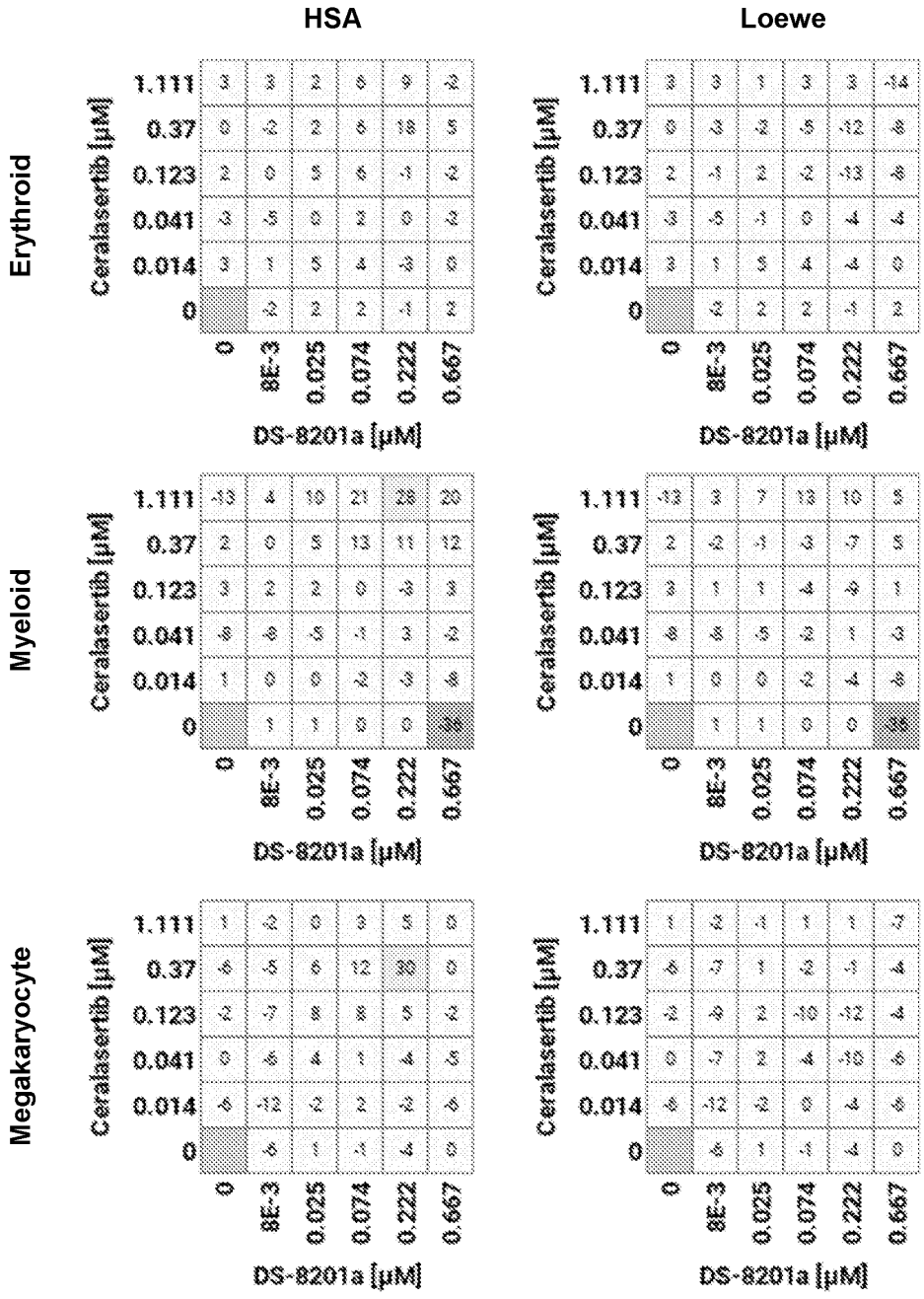
(B)


B. KPL4
DMSO
AZD6738 1 uM
+DS-8201a 30 ug/mL
DMSO
AZD6738 1 uM
+exatecan mesylate 3 nM
DMSO
AZD6738 1 uM
pATR-T1989
pChk1-S345
pCdc2-Y15
pATM-S1981
pKap1-S824
pChk2-T68
pRPA-S4/8
gH2AX
cCasp3
Tubulin
24h
24h
24h
24h
48h
7h
24h
48h
48h
24h

[Figure 18A]

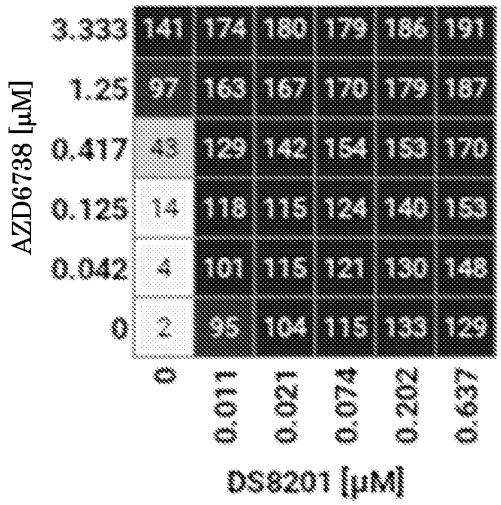

Erythroid
Ceralasertib [µM]
1.111
0.37
0.123
0.041
0.014
0
25 26 35 38 45
12 12 24 18 21
8 -12 4 3 22
13 14 8 15 23
0 15 4 21 19
0
8E-3
0.025
0.074
0.222
0.667
DS-8201a [µM]
Myeloid
Ceralasertib [µM]
1.111
0.37
0.123
0.041
0.014
0
6 8 12 22 38
1 9 -3 8 28
-21 -10 -2 9 36
-6 11 1 -6 35
0 -3 6 4 27
0
8E-3
0.025
0.074
0.222
0.667
DS-8201a [µM]
Megakaryocytic
Ceralasertib [µM]
1.111
0.37
0.123
0.041
0.014
0
47 39
2 -13 14 14 41
-19 -11 12 -3 38
-20 -19 -7 11 36
0 -21 -1 2 39
0
8E-3
0.025
0.074
0.222
0.667
DS-8201a [µM]

[Figure 18B]

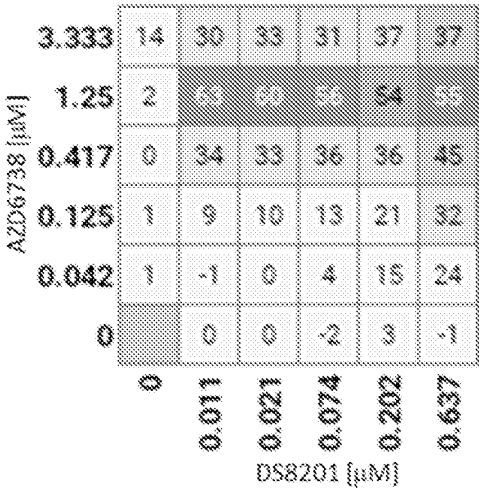

HSA
Loewe
Erythroid
Myeloid
Megakaryocyte
Ceralasertib [μM]
1.111
0.37
0.123
0.041
0.014
0
DS-8201a [μM]
0
8E-3
0.025
0.074
0.222
0.667

[Figure 19]

(A)


AZD6738 [μM]
3.333
1.25
0.417
0.125
0.042
0
141 174 180 179 186 191
97 163 167 170 179 187
43 129 142 154 153 170
14 118 115 124 140 153
4 101 115 121 130 148
2 95 104 115 133 129
0
0.011
0.021
0.074
0.202
0.637
DS8201 [μM]

(B)


AZD6738 [μM]
3.333
1.25
0.417
0.125
0.042
0
14 30 33 31 37 37
2 54 54
0 34 33 36 36 45
1 9 10 13 21 32
1 -1 0 4 15 24
0 0 -2 3 -1
0
0,011
0,021
0,074
0,202
0,637
DS8201 [μM]