[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 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

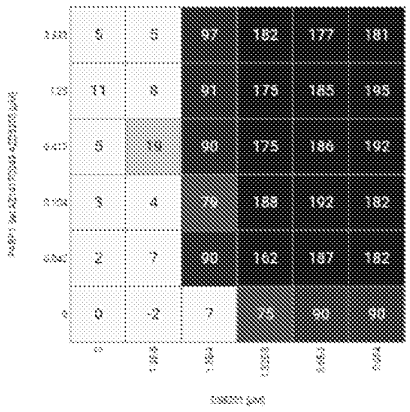
[Figure 11]

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

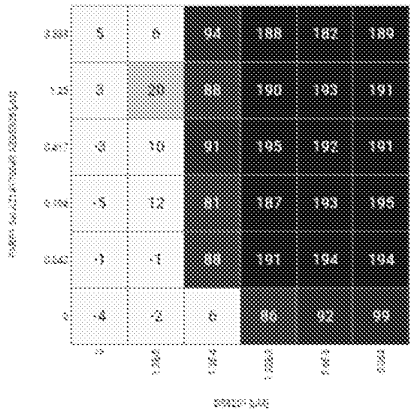
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVR
QAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSK
NTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGT
LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY
FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT
CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR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

[Figure 12A]

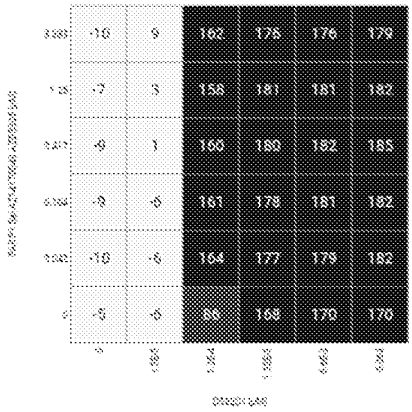
KPL4 (HER2 High)



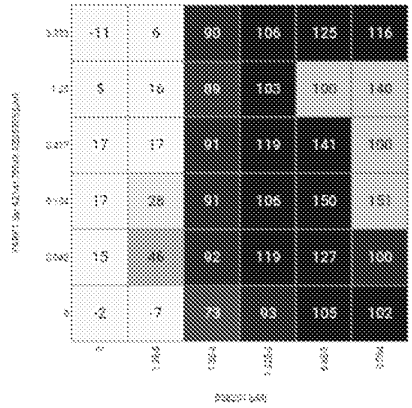
NCI-N87 (HER2 High)



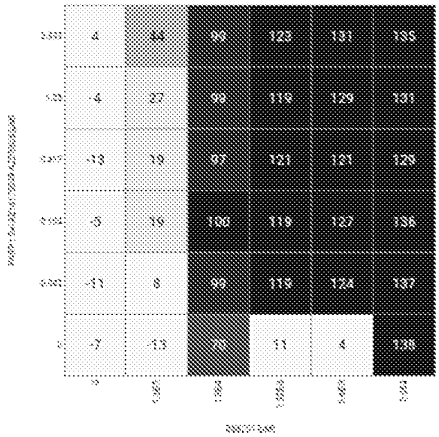
SKBR3 (HER2 High)



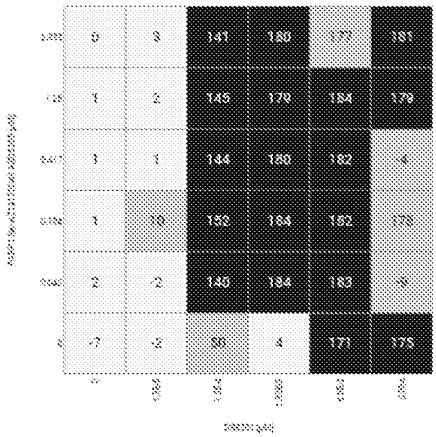
HCC1954 (HER2 High)



HCC1569 (HER2 High)

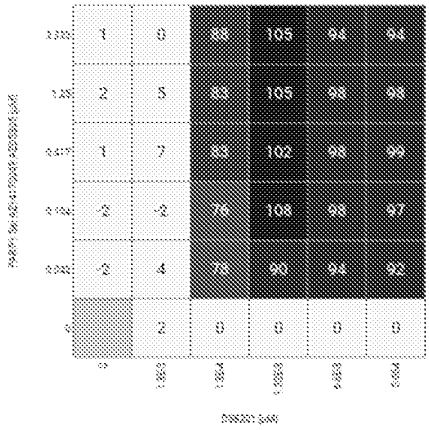


AU565 (HER2 High)

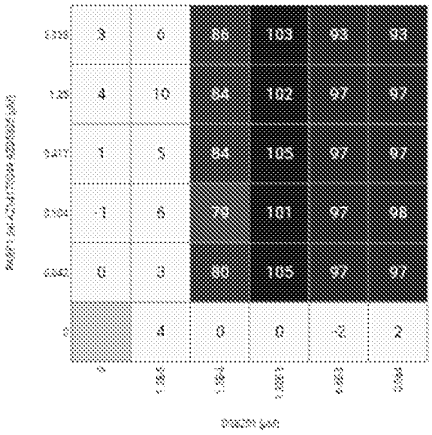


[Figure 12B]

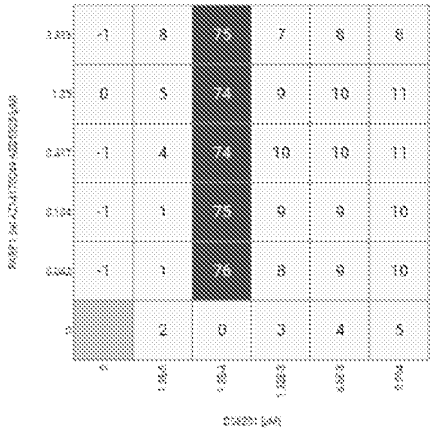
KPL4 (HER2 High)



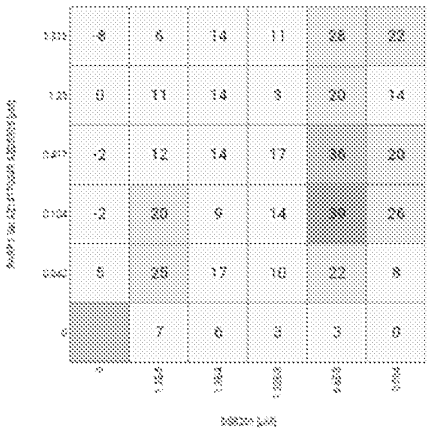
NCI-N87 (HER2 High)



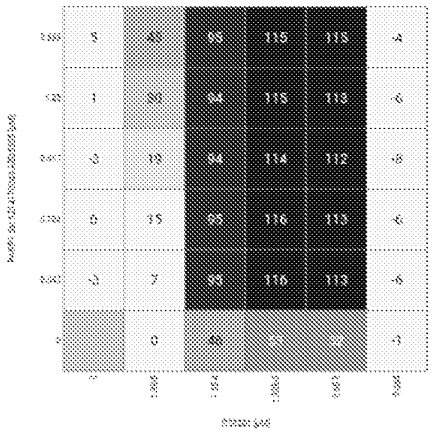
SKBR3 (HER2 High)



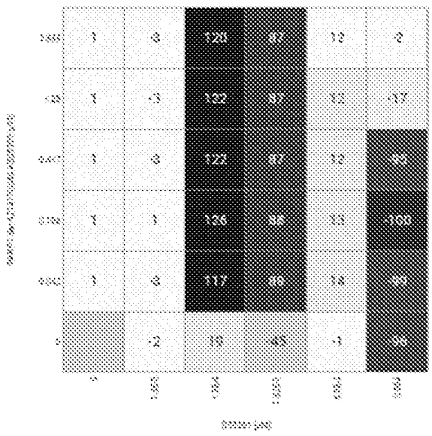
HCC1954 (HER2 High)



HCC1569 (HER2 High)

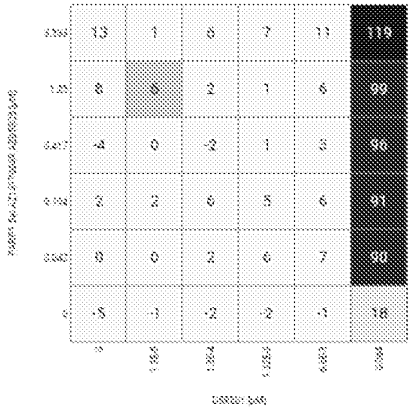


AU565 (HER2 High)

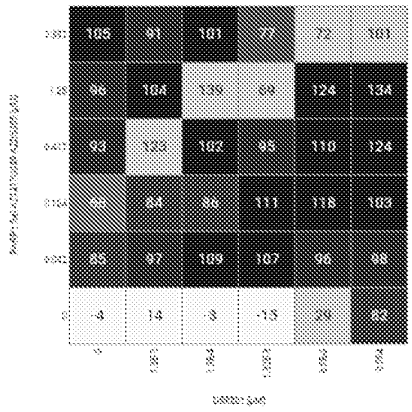


[Figure 13A]

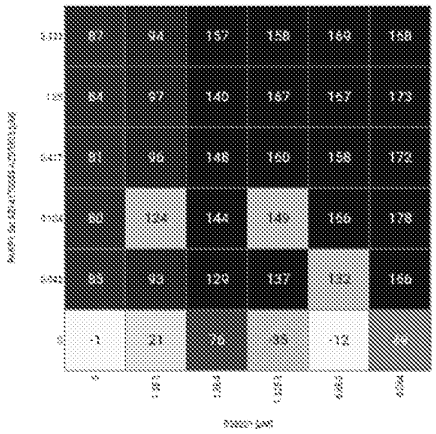
MDA-MB-468 (HER2 Low)



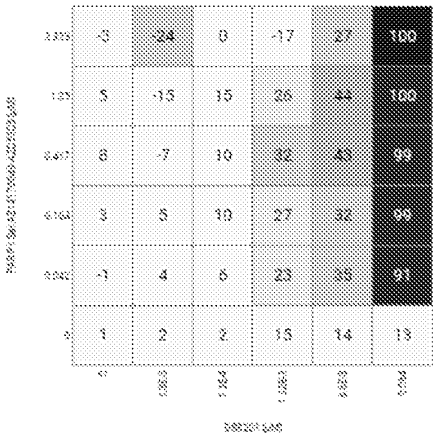
MDA-MB-157 (HER2 Low)



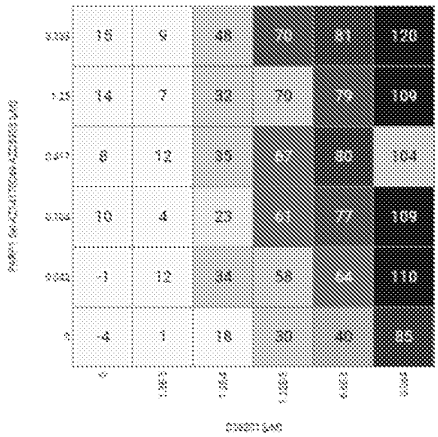
HCC1187 (HER2 Low)



T47D (HER2 Low)

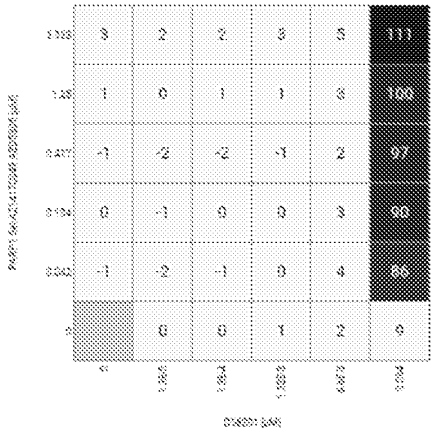


HCC38 (HER2 Low)

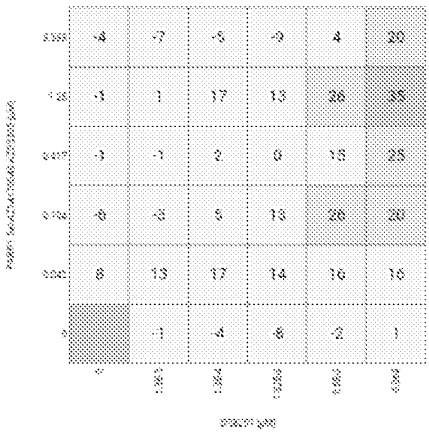


[Figure 13B]

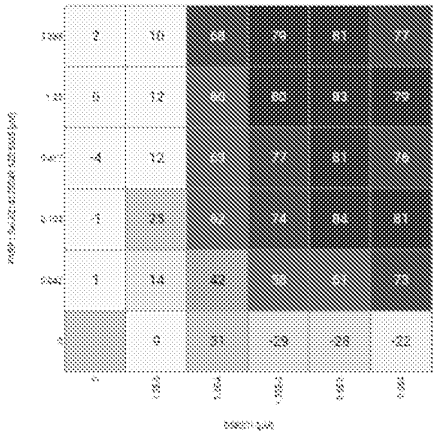
MDA-MB-468 (HER2 Low)



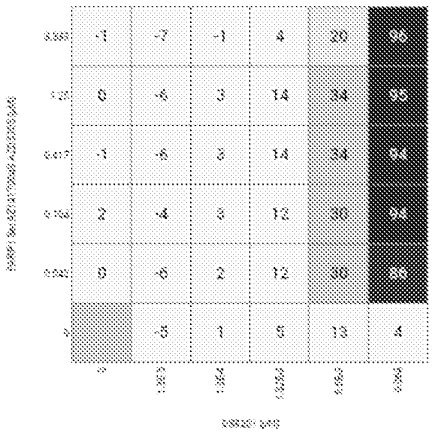
MDA-MB-157 (HER2 Low)



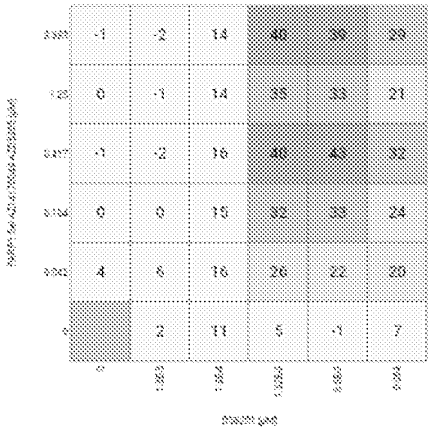
HCC1187 (HER2 Low)



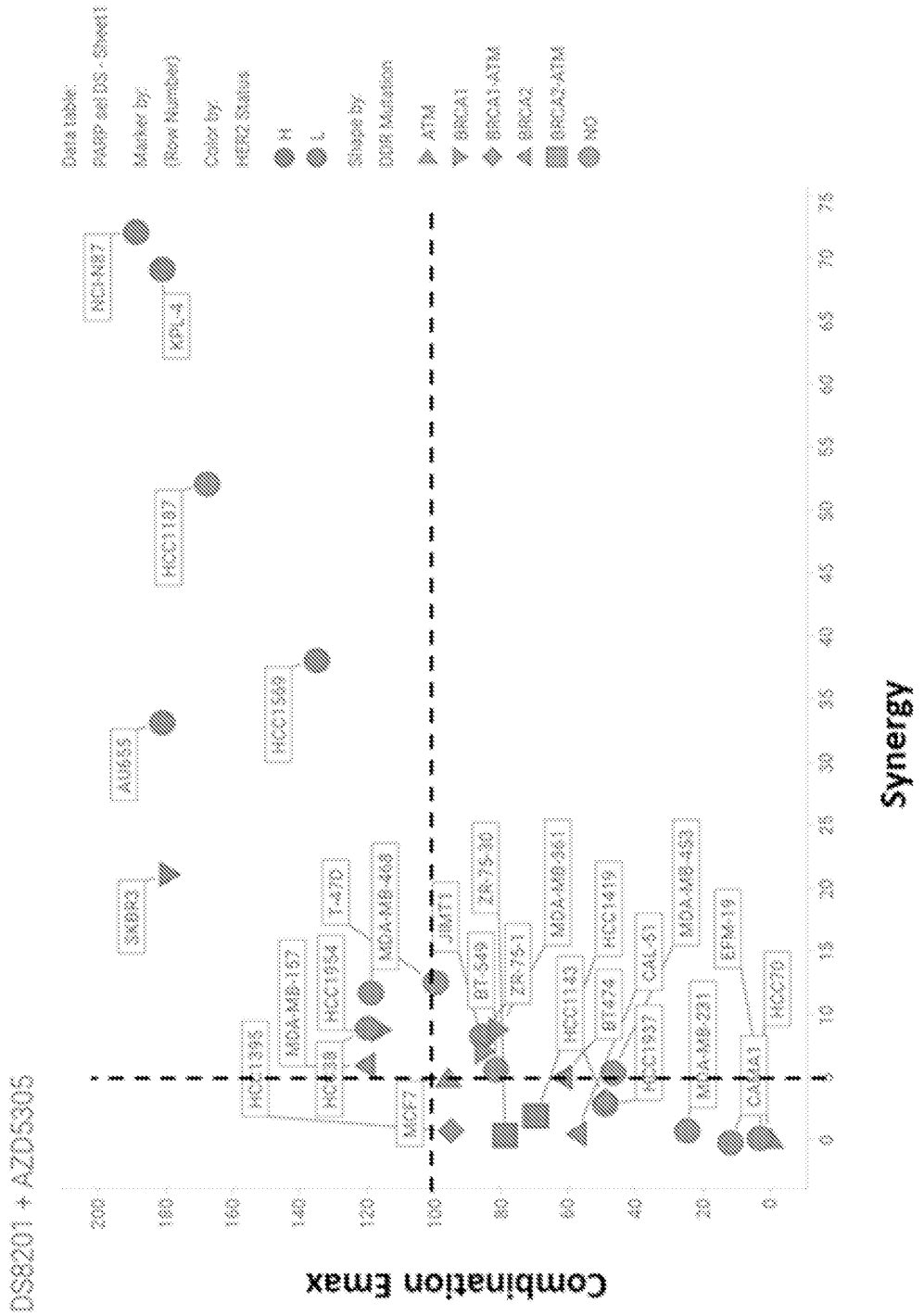
T47D (HER2 Low)



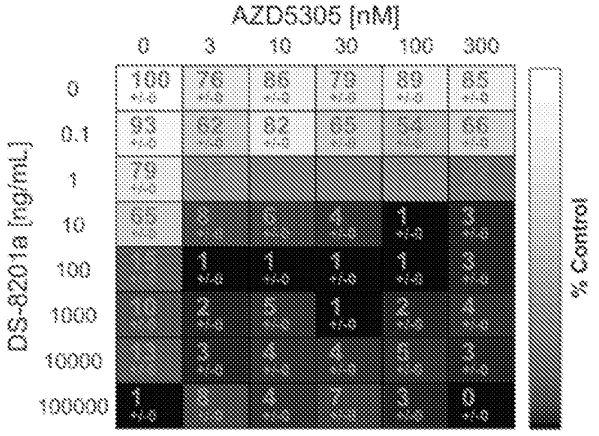
HCC38 (HER2 Low)



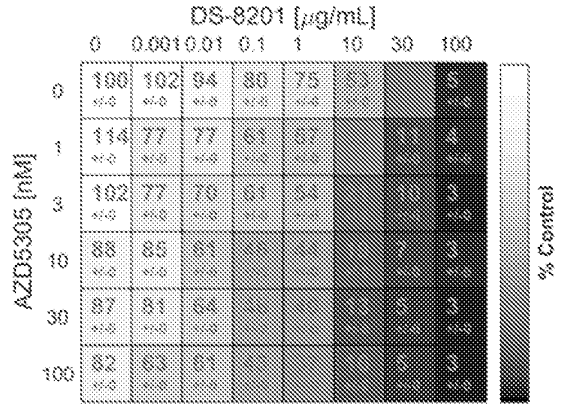
[Figure 14]


DS8201 + AZD5305
Combination Emax
Synergy
Data table:
PARP and DS - Sheet1
Marker by:
(Row Number)
Color by:
HER2 Status
H
L
Shape by:
DDR Mutation
ATM
BRCA1
BRCA1-ATM
BRCA2
BRCA2-ATM
NO
NCI-N87
KPL-4
HCC1187
HCC1569
AU565
SKBR3
HCC1395
MDA-MB-157
HCC1954
T-47D
MDA-MB-468
JIMT1
ZR-75-30
BT-549
ZR-75-1
MDA-MB-361
HCC1419
HCC1143
BT474
CAL-51
MDA-MB-453
EFM-19
HCC70
MDA-MB-231
CAMA1
MCF7

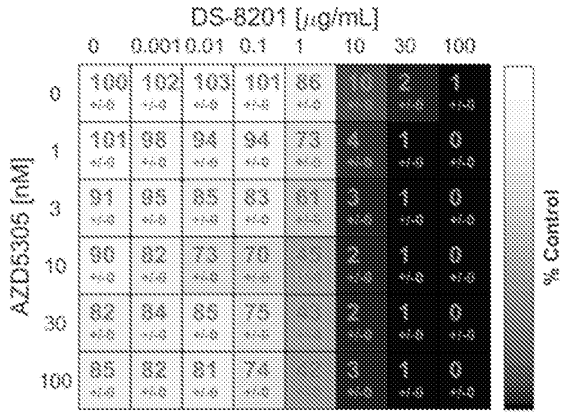
[Figure 15A]



DS-8201a v AZD5305 in KPL4

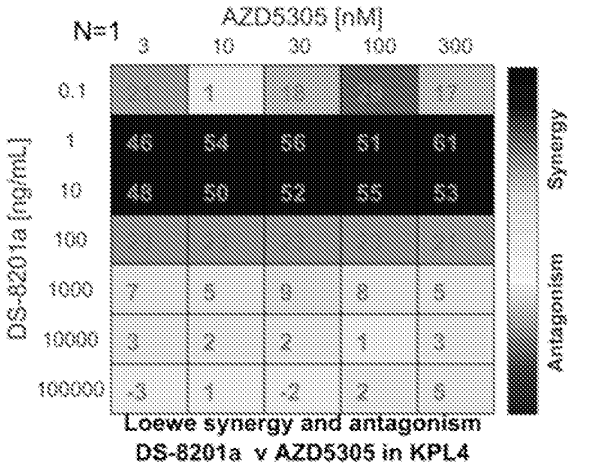


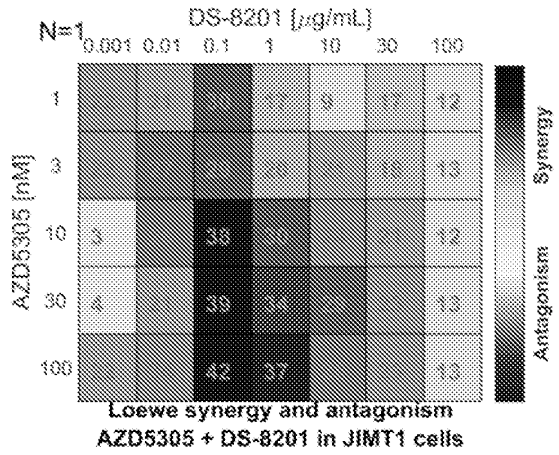
AZD5305 + DS-8201 in JIMT1 cells

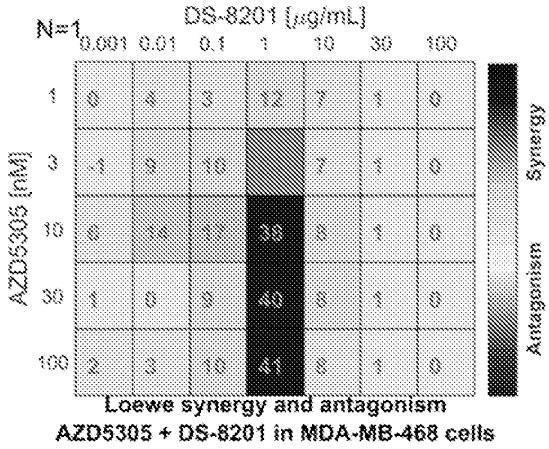


AZD5305 + DS-8201 in MDA-MB-468 cells

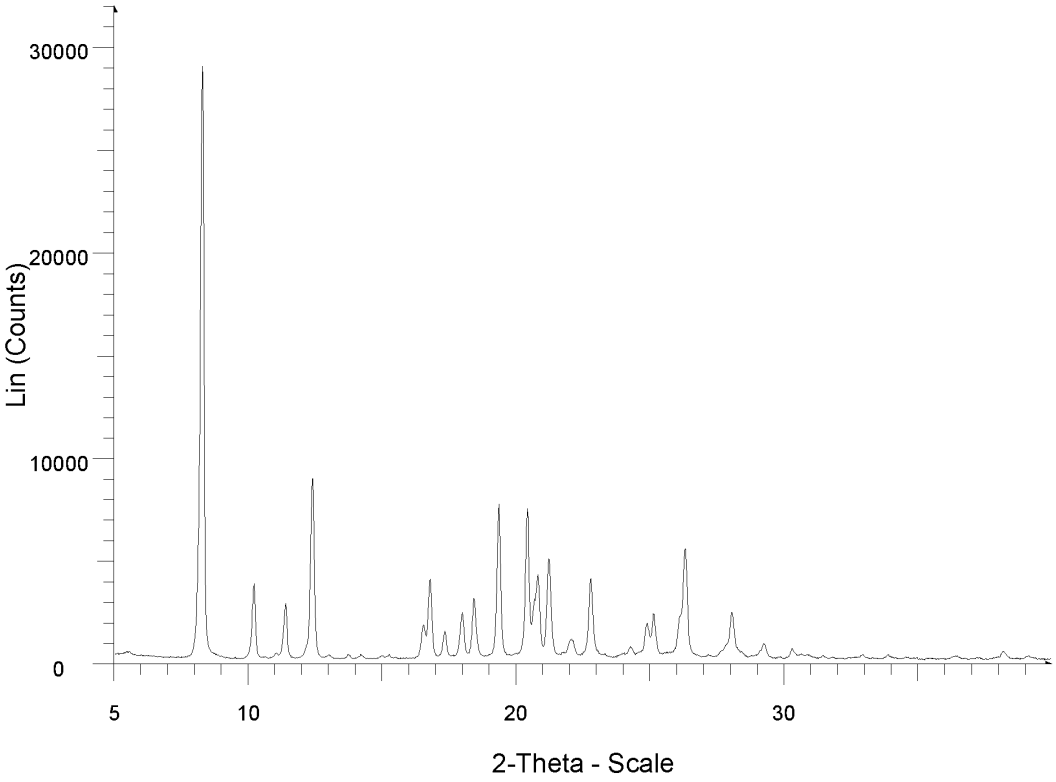
[Figure 15B]


N=1
AZD5305 [nM]
3
10
30
100
300
DS-8201a [ng/mL]
0.1
1
10
100
1000
10000
100000
46
54
56
51
61
48
50
52
55
53
7
5
8
8
8
3
2
2
1
3
-3
1
-2
2
8
Synergy
Antagonism
Loewe synergy and antagonism
DS-8201a v AZD5305 in KPL4

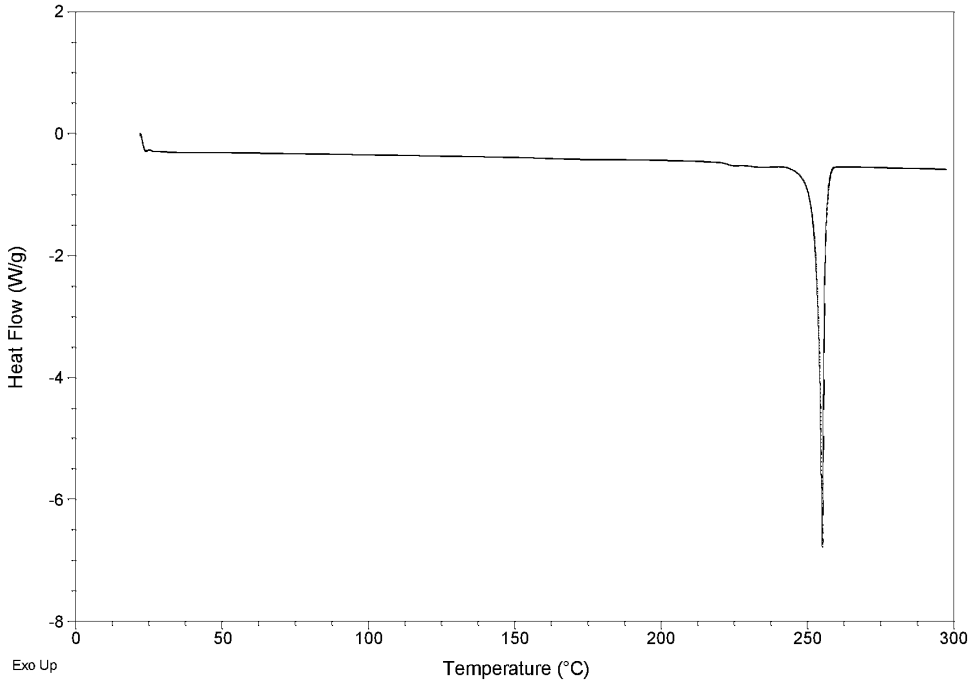

N=1
DS-8201 [µg/mL]
0.001
0.01
0.1
1
10
30
100
AZD5305 [nM]
1
3
10
30
100
3
33
4
35
42
37
Synergy
Antagonism
Loewe synergy and antagonism
AZD5305 + DS-8201 in JIMT1 cells


N=1
DS-8201 [µg/mL]
0.001
0.01
0.1
1
10
30
100
AZD5305 [nM]
1
3
10
30
100
0
4
3
12
7
1
0
-1
3
10
7
1
0
0
14
17
56
8
1
0
1
0
3
40
8
1
0
2
3
10
41
8
1
0
Synergy
Antagonism
Loewe synergy and antagonism
AZD5305 + DS-8201 in MDA-MB-468 cells

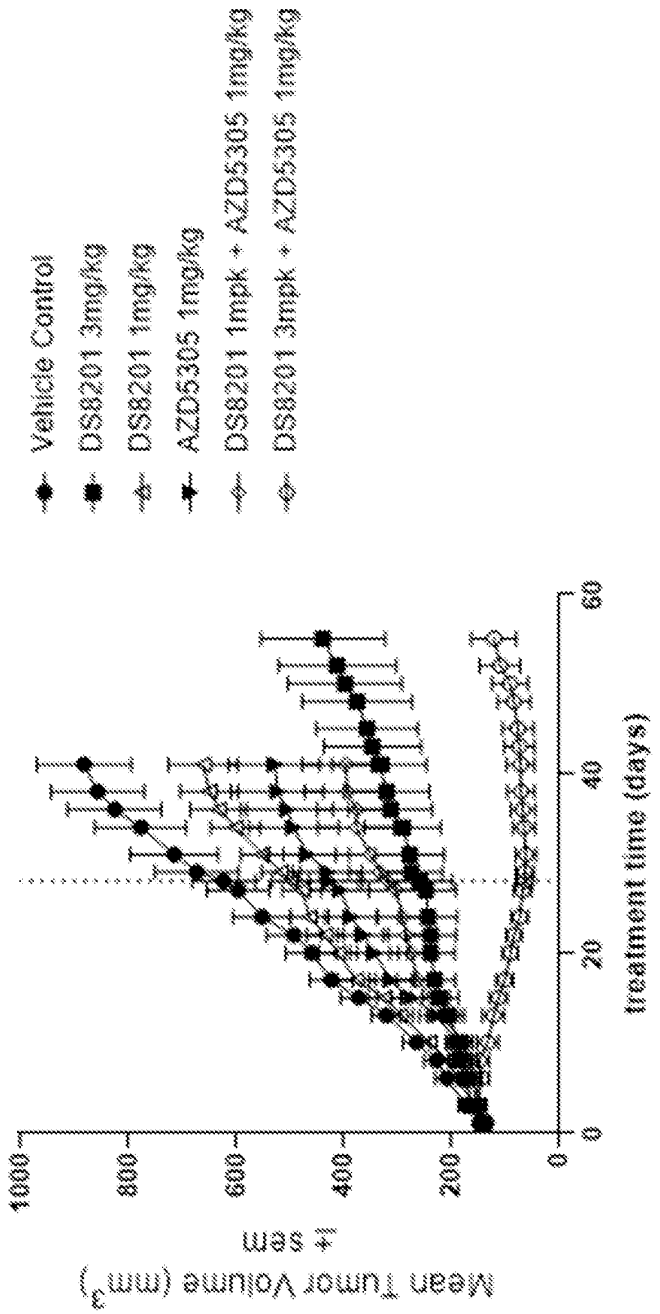
[Figure 16A]



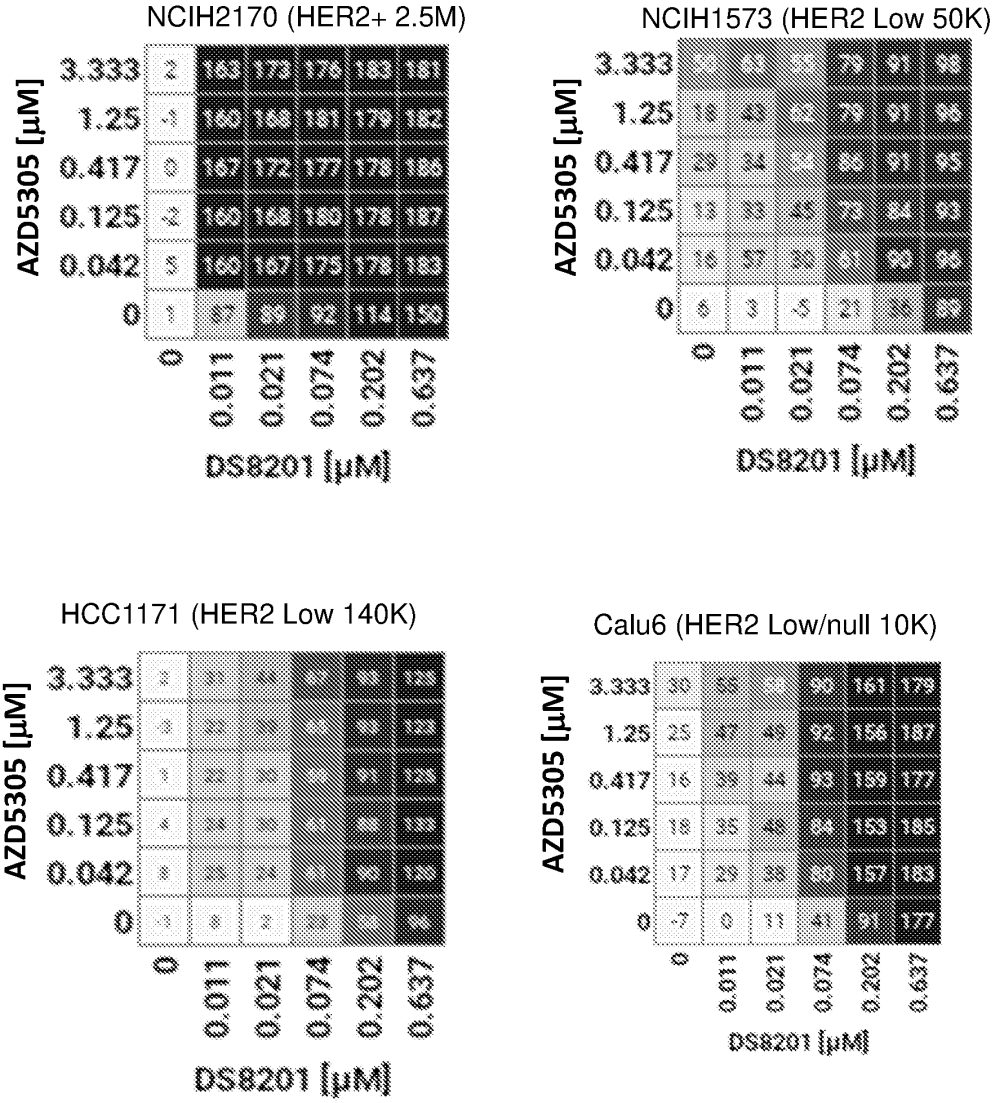
[Figure 16B]


2
0
-2
-4
-6
-8
Heat Flow (W/g)
Exo Up
0
50
100
150
200
250
300
Temperature (°C)

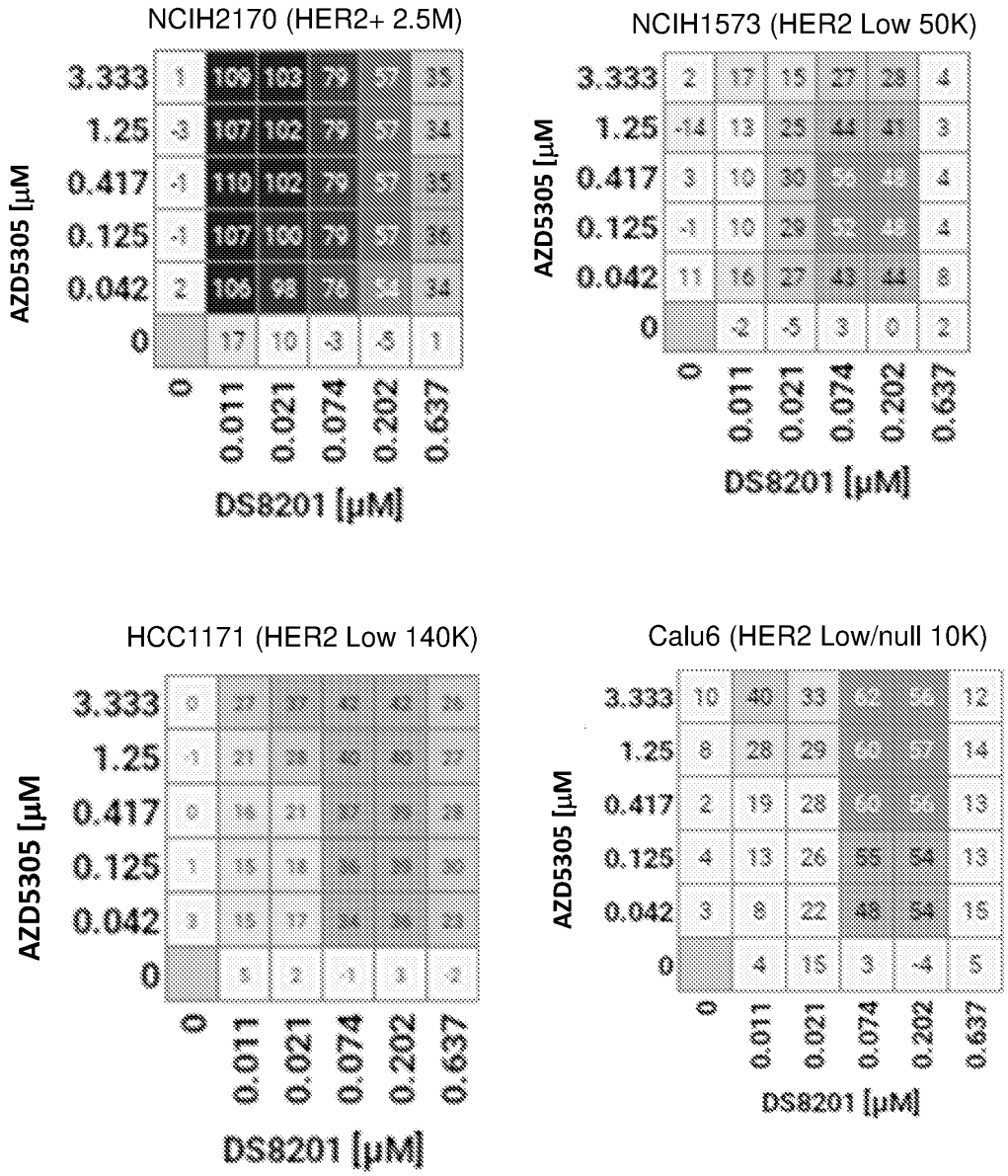
[Figure 17]


Vehicle Control
DS8201 3mg/kg
DS8201 1mg/kg
AZD5305 1mg/kg
DS8201 1mpk + AZD5305 1mg/kg
DS8201 3mpk + AZD5305 1mg/kg
Mean Tumor Volume (mm³) ± sem
1000
800
600
400
200
0
0
20
40
60
treatment time (days)

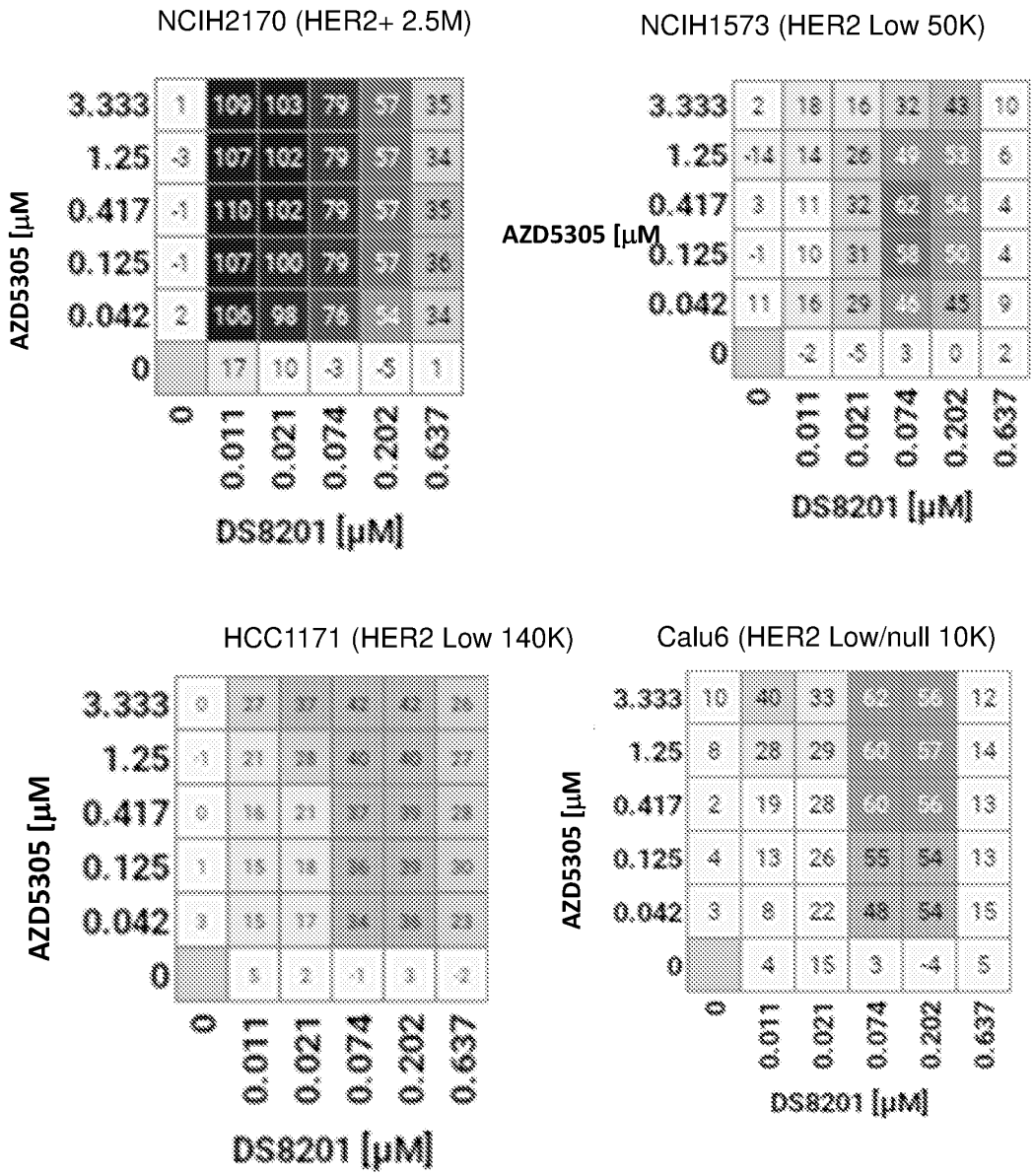
[Figure 18A]


NCIH2170 (HER2+ 2.5M)
AZD5305 [μM]
3.333
1.25
0.417
0.125
0.042
0
DS8201 [μM]
0
0.011
0.021
0.074
0.202
0.637
NCIH1573 (HER2 Low 50K)
HCC1171 (HER2 Low 140K)
Calu6 (HER2 Low/null 10K)

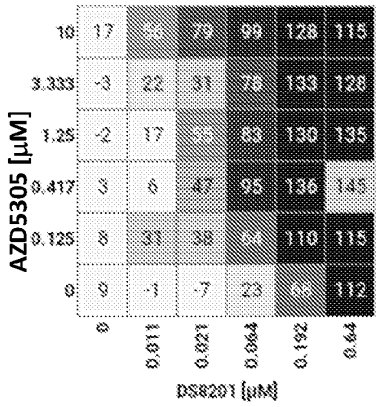
[Figure 18B]


NCIH2170 (HER2+ 2.5M)
NCIH1573 (HER2 Low 50K)
HCC1171 (HER2 Low 140K)
Calu6 (HER2 Low/null 10K)
AZD5305 [µM
DS8201 [µM]
3.333
1.25
0.417
0.125
0.042
0
0.011
0.021
0.074
0.202
0.637

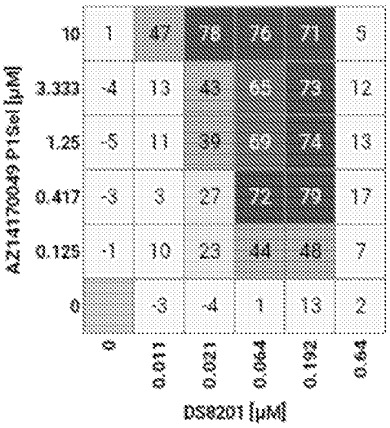
[Figure 18C]


NCIH2170 (HER2+ 2.5M)
NCIH1573 (HER2 Low 50K)
HCC1171 (HER2 Low 140K)
Calu6 (HER2 Low/null 10K)
AZD5305 [µM]
DS8201 [µM]
3.333
1.25
0.417
0.125
0.042
0
0.011
0.021
0.074
0.202
0.637

[Figure 19A]



[Figure 19B]



[Figure 19C]

