FIG. 1A

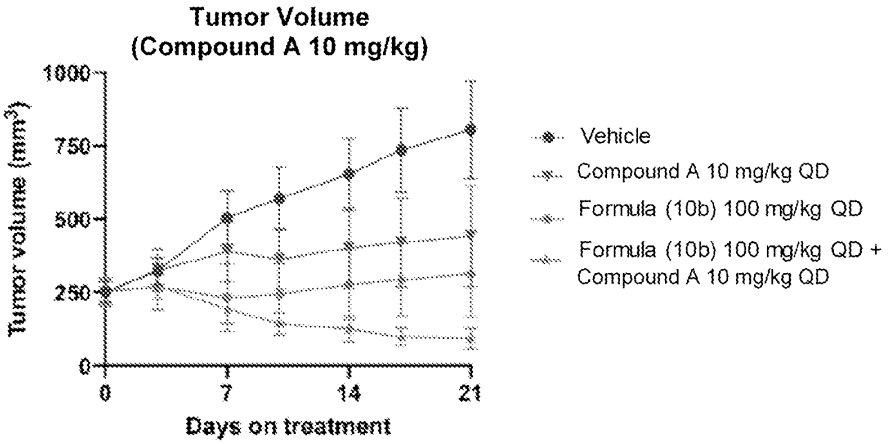

Tumor Volume
(Compound A 10 mg/kg)
Tumor volume (mm3)
1000
750
500
250
0
0
7
14
21
Days on treatment
Vehicle
Compound A 10 mg/kg QD
Formula (10b) 100 mg/kg QD
Formula (10b) 100 mg/kg QD +
Compound A 10 mg/kg QD

FIG. 1B

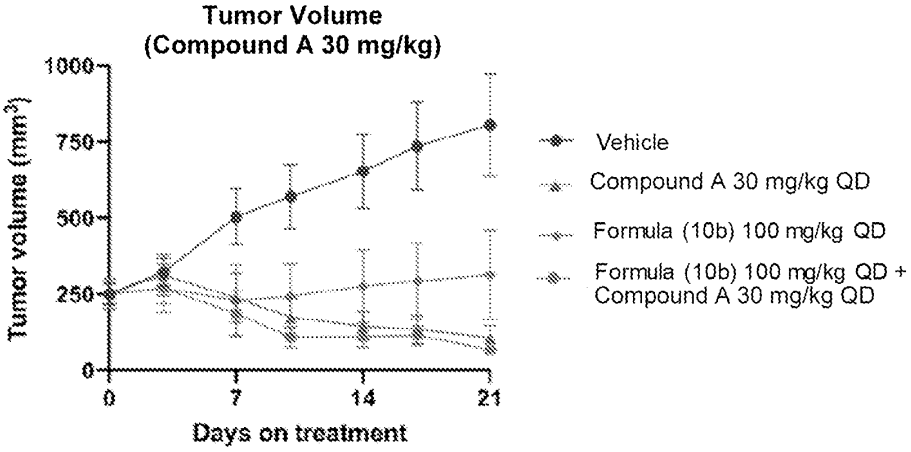

Tumor Volume
(Compound A 30 mg/kg)
Tumor volume (mm3)
1000
750
500
250
0
0
7
14
21
Days on treatment
Vehicle
Compound A 30 mg/kg QD
Formula (10b) 100 mg/kg QD
Formula (10b) 100 mg/kg QD +
Compound A 30 mg/kg QD

FIG. 1C

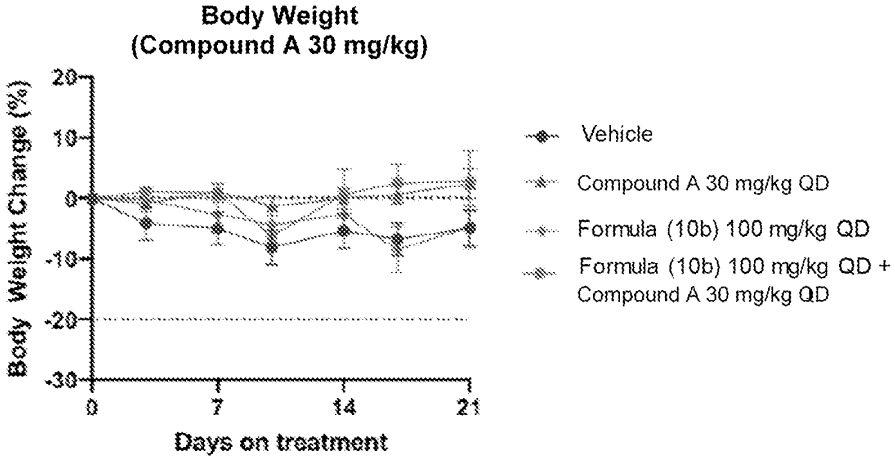

Body Weight
(Compound A 30 mg/kg)
Body Weight Change (%)
20
10
0
-10
-20
-30
0
7
14
21
Days on treatment
Vehicle
Compound A 30 mg/kg QD
Formula (10b) 100 mg/kg QD
Formula (10b) 100 mg/kg QD +
Compound A 30 mg/kg QD

FIG. 1D

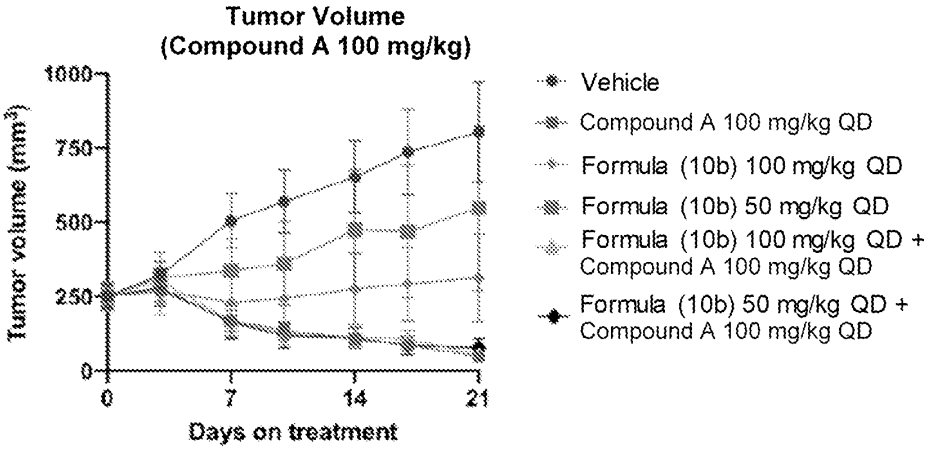

Tumor Volume
(Compound A 100 mg/kg)
Tumor volume (mm3)
1000
750
500
250
0
0
7
14
21
Days on treatment
Vehicle
Compound A 100 mg/kg QD
Formula (10b) 100 mg/kg QD
Formula (10b) 50 mg/kg QD
Formula (10b) 100 mg/kg QD +
Compound A 100 mg/kg QD
Formula (10b) 50 mg/kg QD +
Compound A 100 mg/kg QD

FIG. 1E

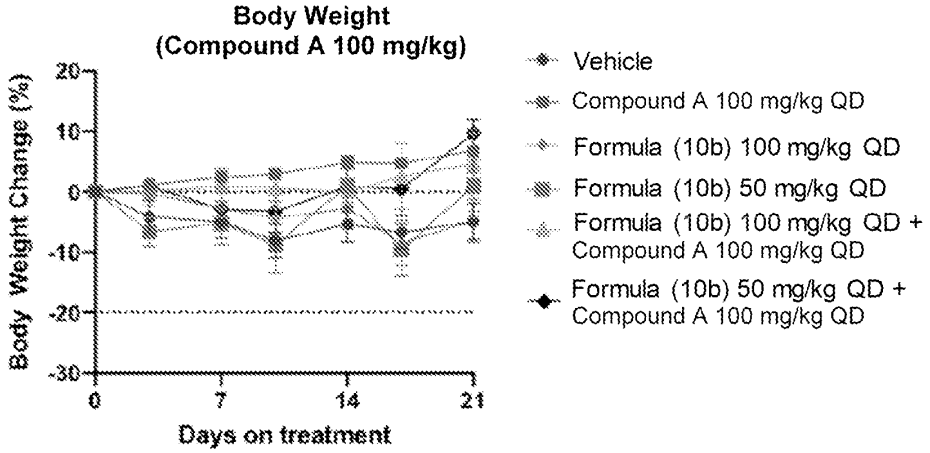
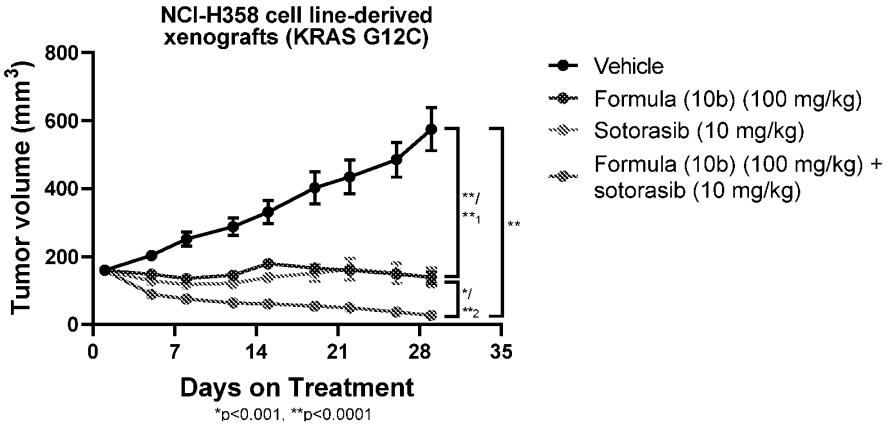


FIG. 2A



*p<0.001, **p<0.0001

1: **=(10b) **=sotorasib, 2: **=(10b) *=sotorasib

FIG. 2B

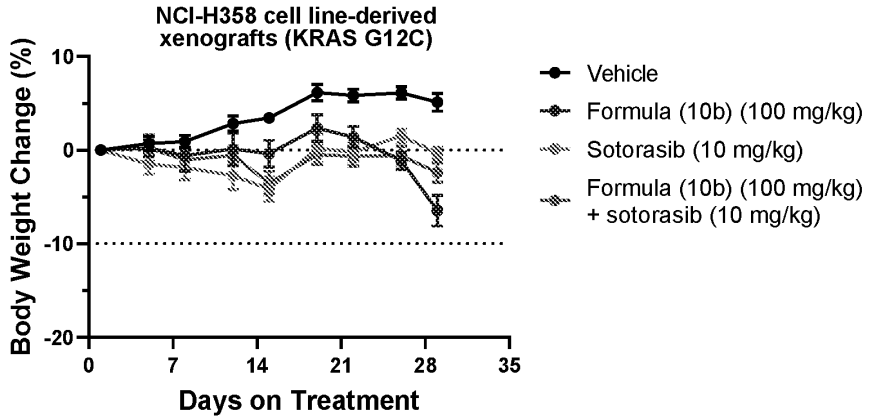


FIG. 3A

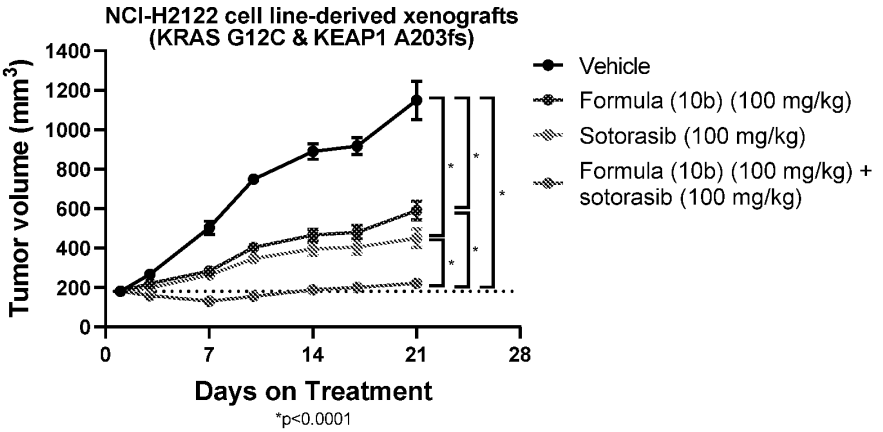


FIG. 3B

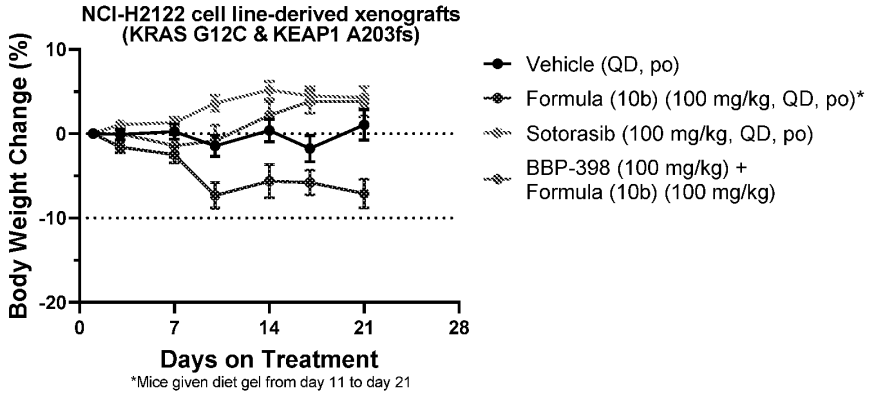


FIG. 4A

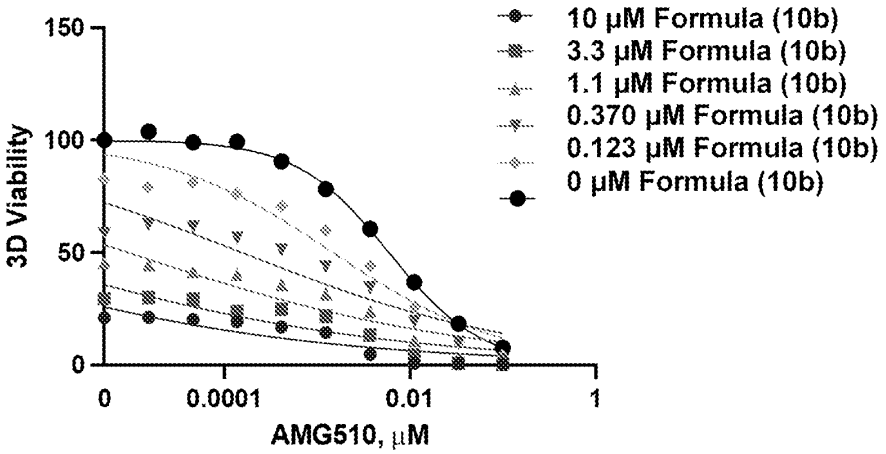

10 μM Formula (10b)
3.3 μM Formula (10b)
1.1 μM Formula (10b)
0.370 μM Formula (10b)
0.123 μM Formula (10b)
0 μM Formula (10b)
3D Viability
150
100
50
0
0
0.0001
0.01
1
AMG510, μM

FIG. 4B

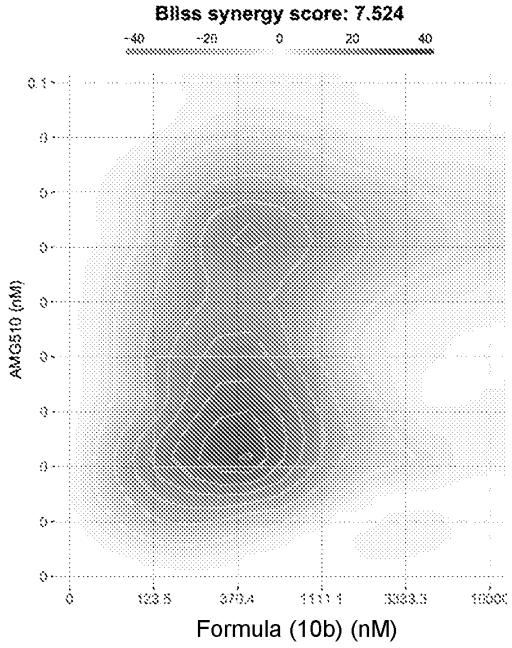

Bliss synergy score: 7.524
-40
-20
0
20
40
AMG510 (nM)
Formula (10b) (nM)

FIG. 4C

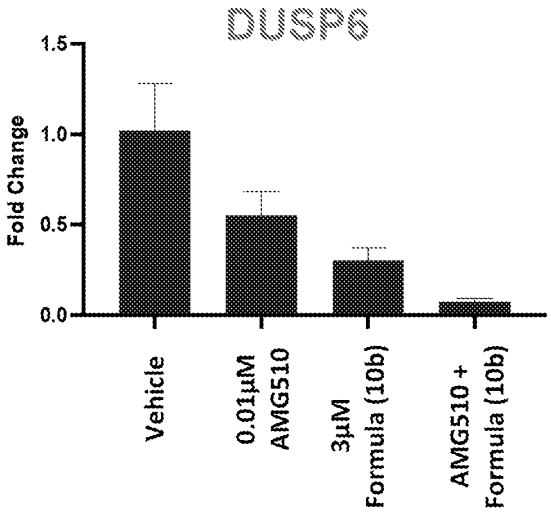

DUSP6
Fold Change
1.5
1.0
0.5
0.0
Vehicle
0.01μM AMG510
3μM Formula (10b)
AMG510 + Formula (10b)

FIG. 4D

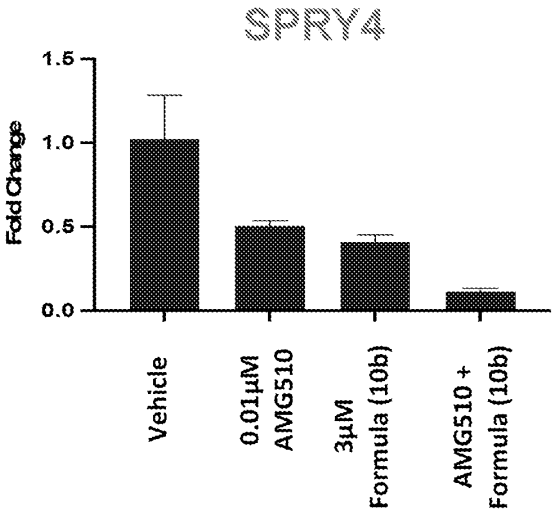

SPRY4
Fold Change
1.5
1.0
0.5
0.0
Vehicle
0.01μM AMG510
3μM Formula (10b)
AMG510 + Formula (10b)

FIG. 5A

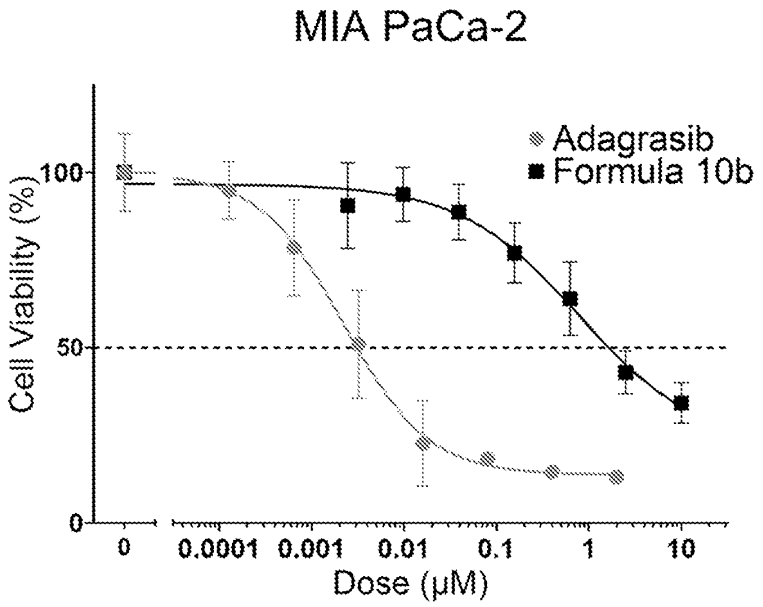

MIA PaCa-2
Adagrasib
Formula 10b
Cell Viability (%)
100
50
0
0
0.0001
0.001
0.01
0.1
1
10
Dose (μM)

FIG. 5B

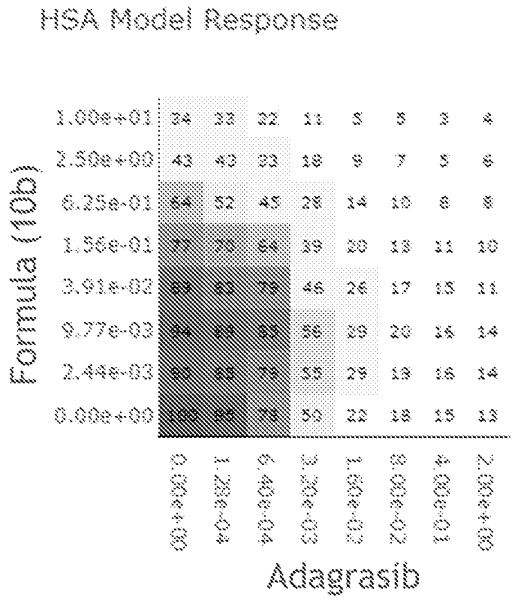

HSA Model Response
Formula (10b)
1.00e+01 34 33 22 11 5 5 3 4
2.50e+00 43 40 33 18 9 7 5 6
6.25e-01 64 52 45 28 14 10 8 8
1.56e-01 77 70 64 39 20 13 11 10
3.91e-02 84 81 73 46 26 17 15 11
9.77e-03 84 83 77 56 29 20 16 14
2.44e-03 90 85 79 55 29 19 16 14
0.00e+00 100 95 79 59 32 18 15 13
0.00e+00
1.22e-04
6.40e-04
3.20e-03
1.60e-02
8.00e-02
4.00e-01
2.00e+00
Adagrasib

FIG. 5C

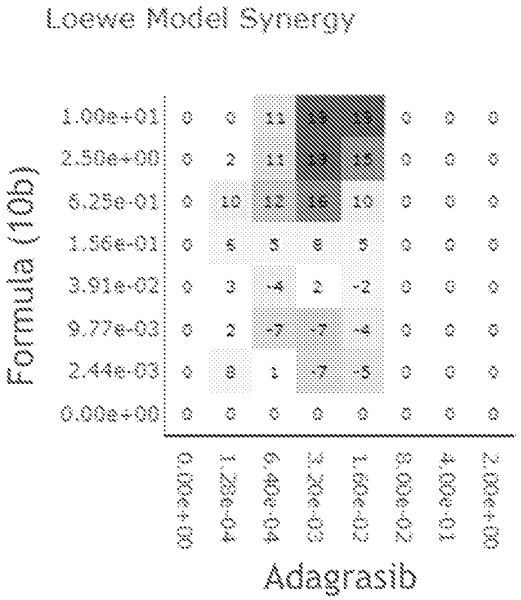

Loewe Model Synergy
Formula (10b)
1.00e+01
2.50e+00
6.25e-01
1.56e-01
3.91e-02
9.77e-03
2.44e-03
0.00e+00
Adagrasib

FIG. 5D

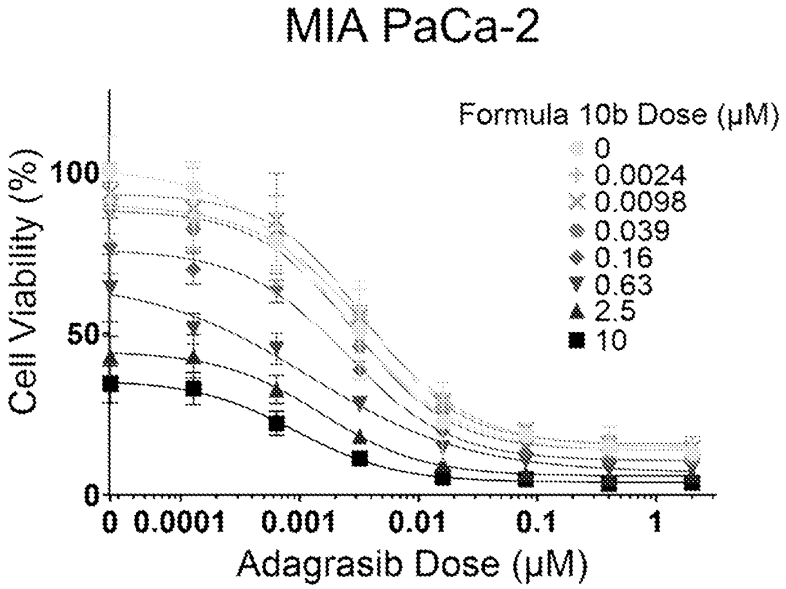

MIA PaCa-2
Formula 10b Dose (μM)
0
0.0024
0.0098
0.039
0.16
0.63
2.5
10
Cell Viability (%)
100
50
0
0 0.0001 0.001 0.01 0.1 1
Adagrasib Dose (μM)

FIG. 5E

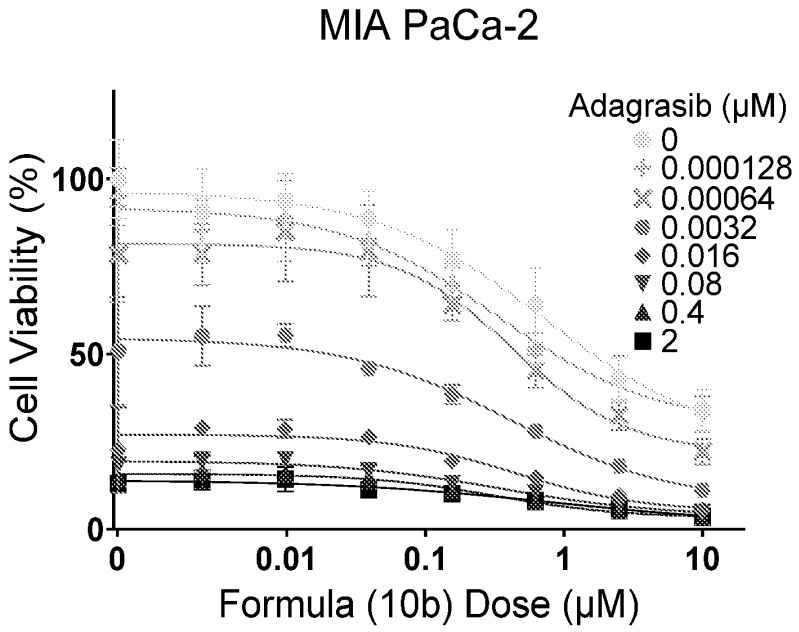

MIA PaCa-2
Adagrasib (μM)
0
0.000128
0.00064
0.0032
0.016
0.08
0.4
2
Cell Viability (%)
100
50
0
0
0.01
0.1
1
10
Formula (10b) Dose (μM)

FIG. 6A

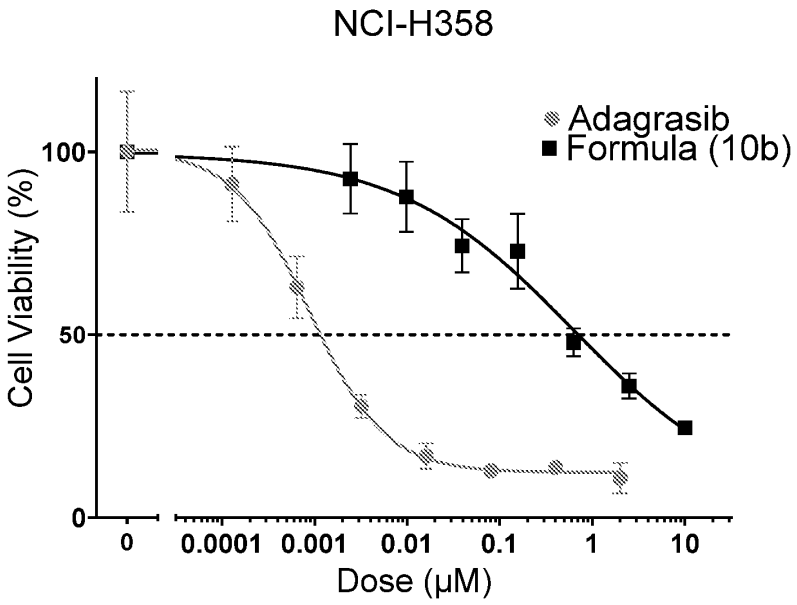

NCI-H358
Adagrasib
Formula (10b)
Cell Viability (%)
100
50
0
0
0.0001
0.001
0.01
0.1
1
10
Dose (μM)

FIG. 6B

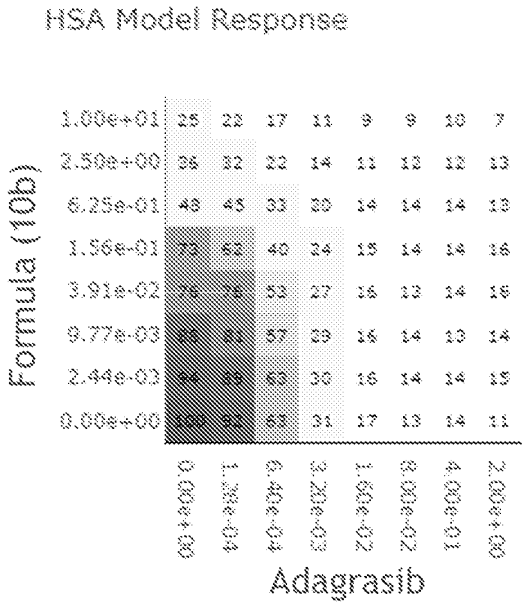

HSA Model Response
Formula (10b)
1.00e+01 25 22 17 11 9 9 10 7
2.50e+00 36 32 22 14 11 12 12 13
6.25e-01 48 45 33 20 14 14 14 13
1.56e-01 72 62 40 24 15 14 14 16
3.91e-02 76 76 52 27 16 13 14 16
9.77e-03 82 81 57 33 16 14 13 14
2.44e-03 84 79 62 30 16 14 14 15
0.00e+00 100 82 63 31 17 13 14 11
0.00e+00 1.25e-04 6.40e-04 3.20e-03 1.60e-02 8.00e-02 4.00e-01 2.00e+00
Adagrasib

FIG. 6C

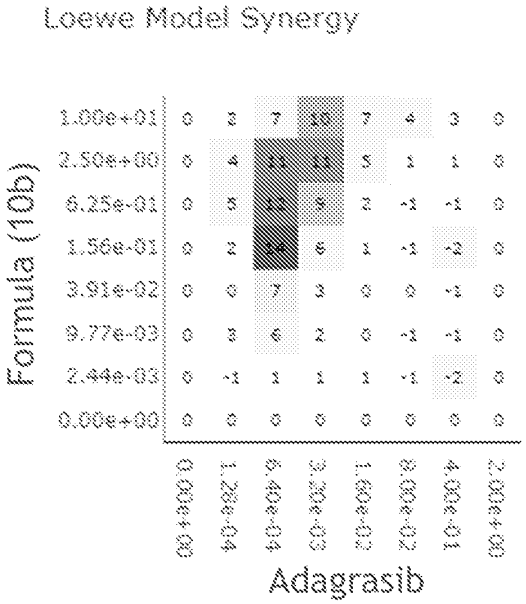

Loewe Model Synergy
Formula (10b)
1.00e+01 0 3 7 10 7 4 3 0
2.50e+00 0 4 11 11 5 1 1 0
6.25e-01 0 5 12 9 2 -1 -1 0
1.56e-01 0 2 14 6 1 -1 -2 0
3.91e-02 0 0 7 3 0 0 -1 0
9.77e-03 0 3 6 2 0 -1 -1 0
2.44e-03 0 -1 1 1 1 -1 -2 0
0.00e+00 0 0 0 0 0 0 0 0
0.00e+00 1.25e-04 6.40e-04 3.20e-03 1.60e-02 8.00e-02 4.00e-01 2.00e+00
Adagrasib

FIG. 6D

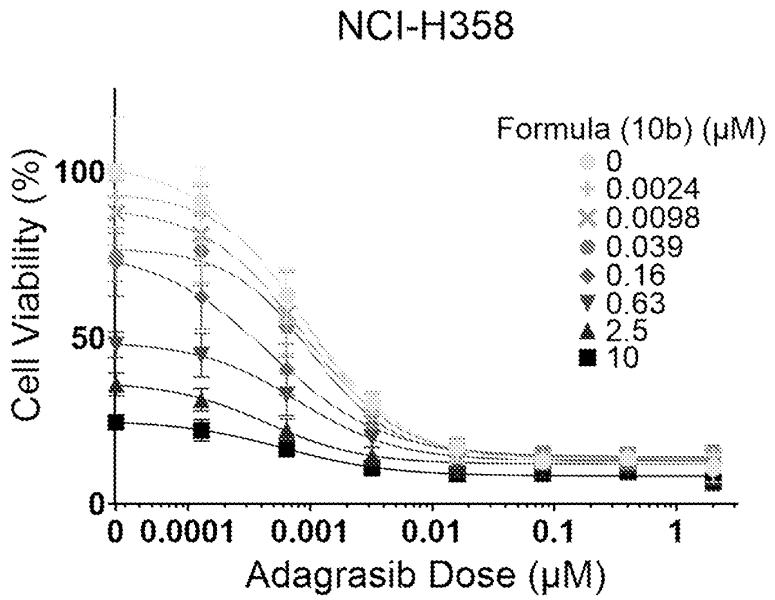

NCI-H358
Formula (10b) (μM)
0
0.0024
0.0098
0.039
0.16
0.63
2.5
10
Cell Viability (%)
100
50
0
0 0.0001 0.001 0.01 0.1 1
Adagrasib Dose (μM)

FIG. 6E

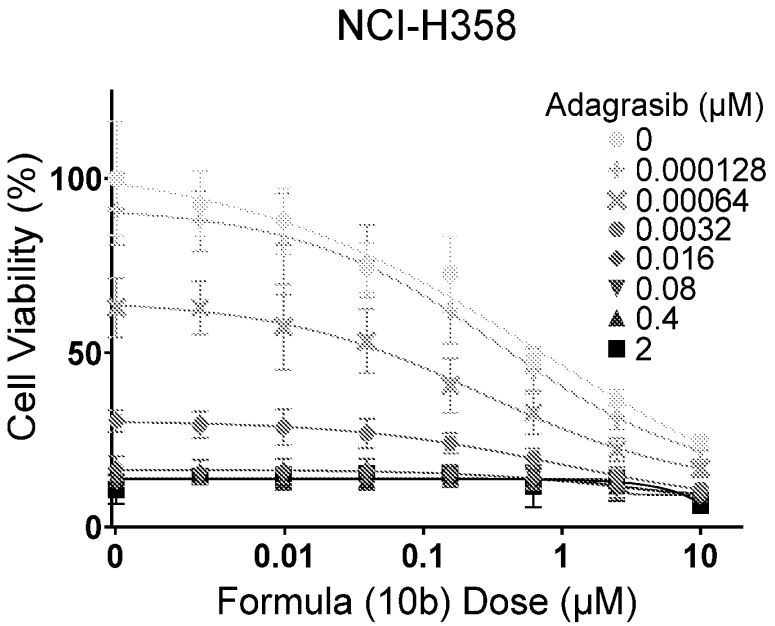

NCI-H358
Adagrasib (μM)
0
0.000128
0.00064
0.0032
0.016
0.08
0.4
2
Cell Viability (%)
100
50
0
0 0.01 0.1 1 10
Formula (10b) Dose (μM)

FIG. 7A

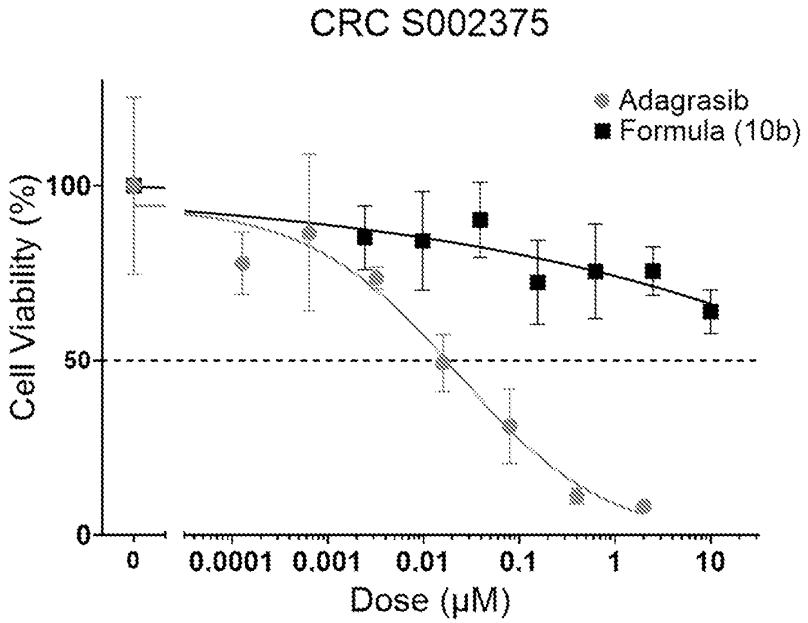

CRC S002375
Adagrasib
Formula (10b)
Cell Viability (%)
100
50
0
0
0.0001
0.001
0.01
0.1
1
10
Dose (μM)

FIG. 7B

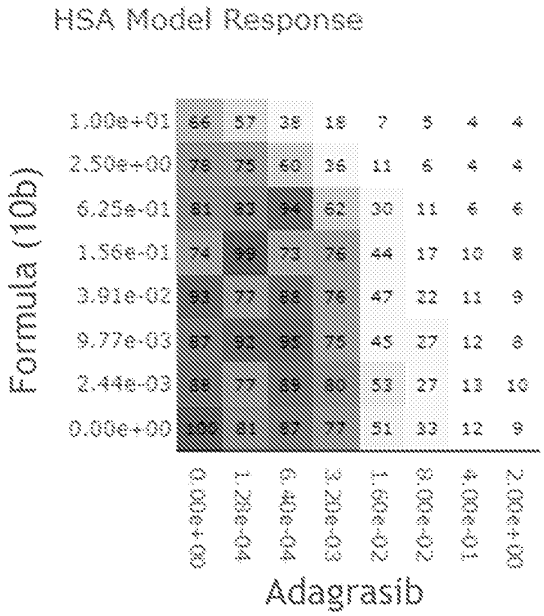

HSA Model Response
Formula (10b)
1.00e+01 66 57 38 18 7 5 4 4
2.50e+00 79 75 60 36 11 6 4 4
6.25e-01 84 84 74 62 30 11 6 6
1.56e-01 74 86 77 76 44 17 10 8
3.91e-02 82 77 86 76 47 22 11 9
9.77e-03 87 82 86 75 45 27 12 8
2.44e-03 84 77 79 80 53 27 13 10
0.00e+00 [illegible] 81 87 77 51 33 12 9
0.00e+00
1.22e-04
6.10e-04
3.20e-03
1.60e-02
8.00e-02
4.00e-01
2.00e+00
Adagrasib

FIG. 7C

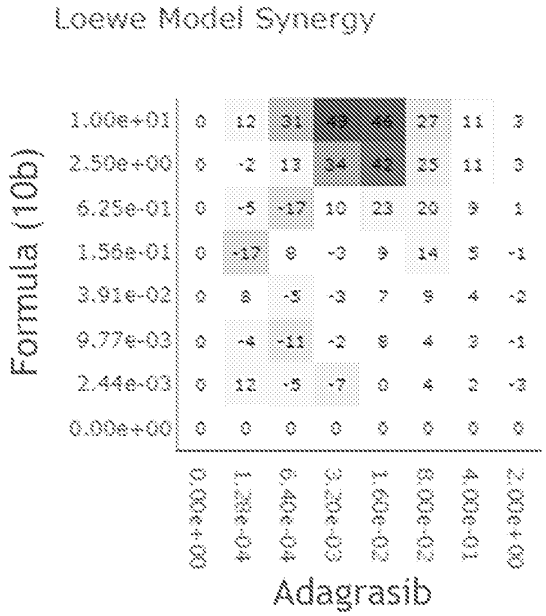

Loewe Model Synergy
Formula (10b)
1.00e+01 0 12 31 47 44 27 11 3
2.50e+00 0 -2 13 34 47 25 11 3
6.25e-01 0 -5 -17 10 23 20 9 1
1.56e-01 0 -17 0 -3 9 14 5 -1
3.91e-02 0 8 -5 -3 7 9 4 -2
9.77e-03 0 -4 -11 -2 8 4 3 -1
2.44e-03 0 12 -5 -7 0 4 2 -3
0.00e+00 0 0 0 0 0 0 0 0
0.00e+00 1.25e-03 2.50e-03 5.00e-03 1.00e-02 2.00e-02 4.00e-02 8.00e-02
Adagrasib

FIG. 7D

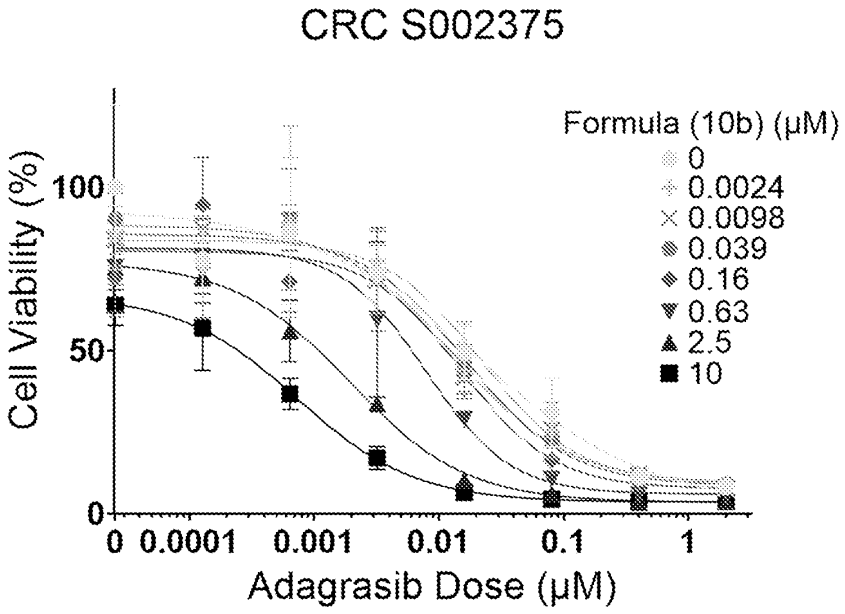
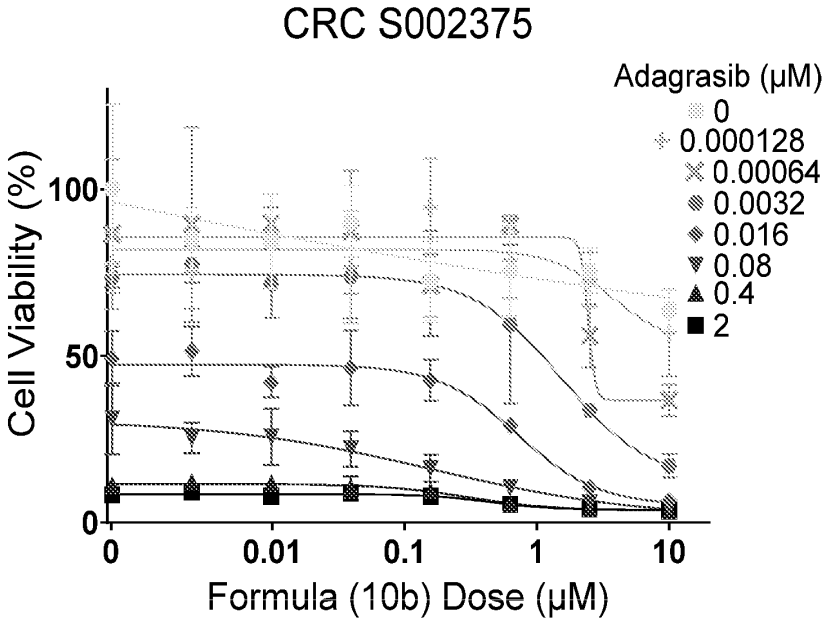

CRC S002375
Formula (10b) (μM)
0
0.0024
0.0098
0.039
0.16
0.63
2.5
10
Cell Viability (%)
100
50
0
0 0.0001 0.001 0.01 0.1 1
Adagrasib Dose (μM)

FIG. 7E


CRC S002375
Adagrasib (μM)
0
0.000128
0.00064
0.0032
0.016
0.08
0.4
2
Cell Viability (%)
100
50
0
0
0.01
0.1
1
10
Formula (10b) Dose (μM)

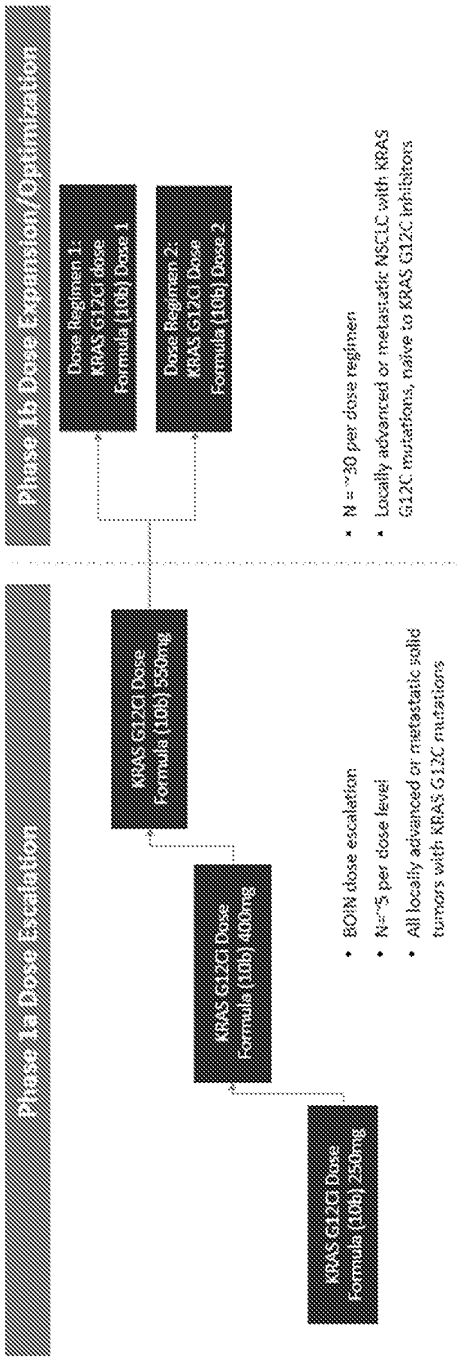
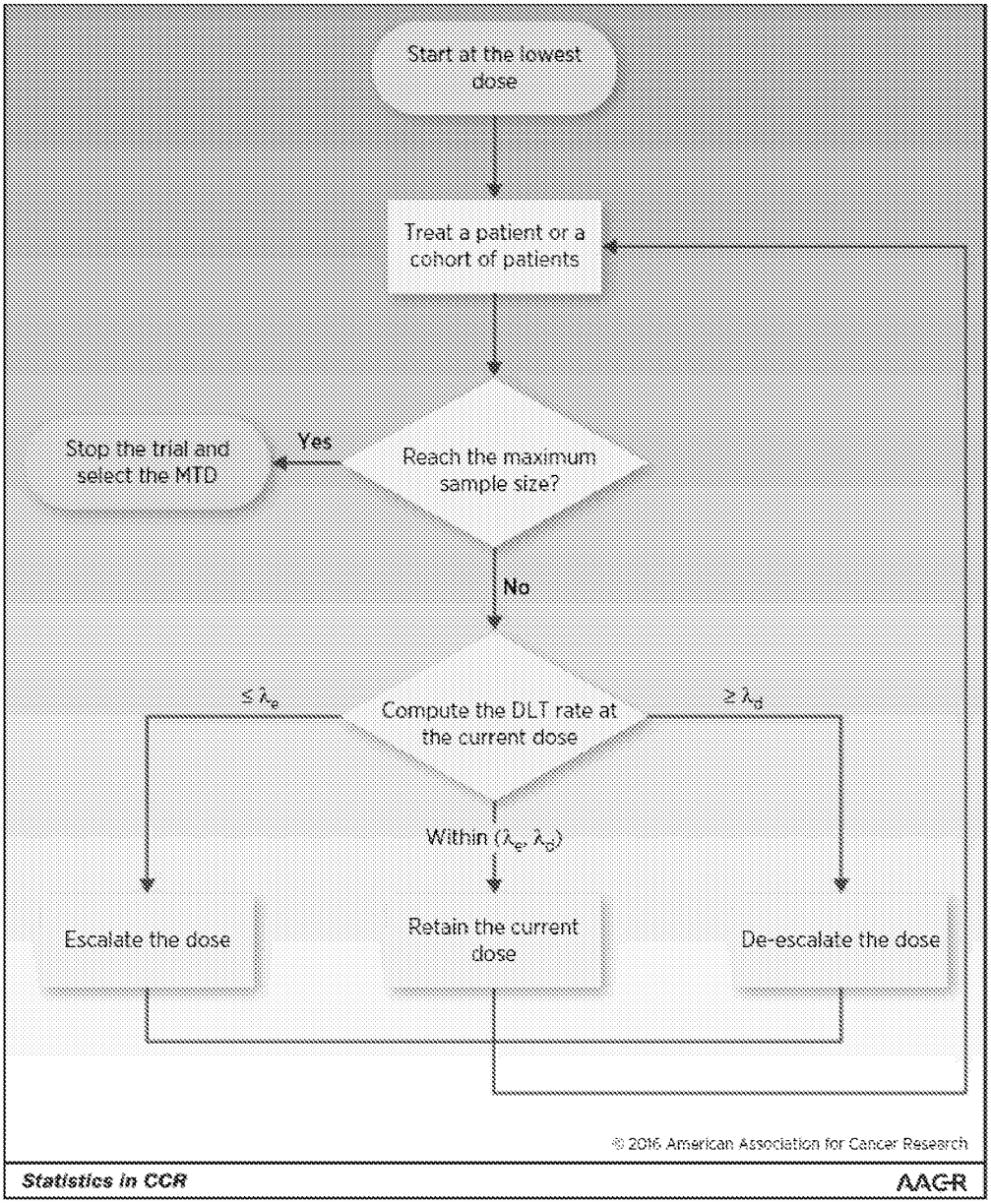

Phase 1a Dose Escalation
KRAS G12C Dose Formula (10b) 250mg
KRAS G12C Dose Formula (10b) 480mg
KRAS G12C Dose Formula (10b) 550mg
BOIN dose escalation
N=~3 per dose level
All locally advanced or metastatic solid tumors with KRAS G12C mutations
Phase 1b Dose Expansion/Optimization
Dose Regimen 1: KRAS G12C Dose Formula (10b) Dose 1
Dose Regimen 2: KRAS G12C Dose Formula (10b) Dose 2
N = ~30 per dose regimen
Locally advanced or metastatic NSCLC with KRAS G12C mutations, naive to KRAS G12C inhibitors

FIG. 8

FIG. 9


Start at the lowest dose
Treat a patient or a cohort of patients
Reach the maximum sample size?
Yes
Stop the trial and select the MTD
No
Compute the DLT rate at the current dose
≤ λe
≥ λd
Within (λe, λd)
Escalate the dose
Retain the current dose
De-escalate the dose
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Statistics in CCR
AACR