Figure 1

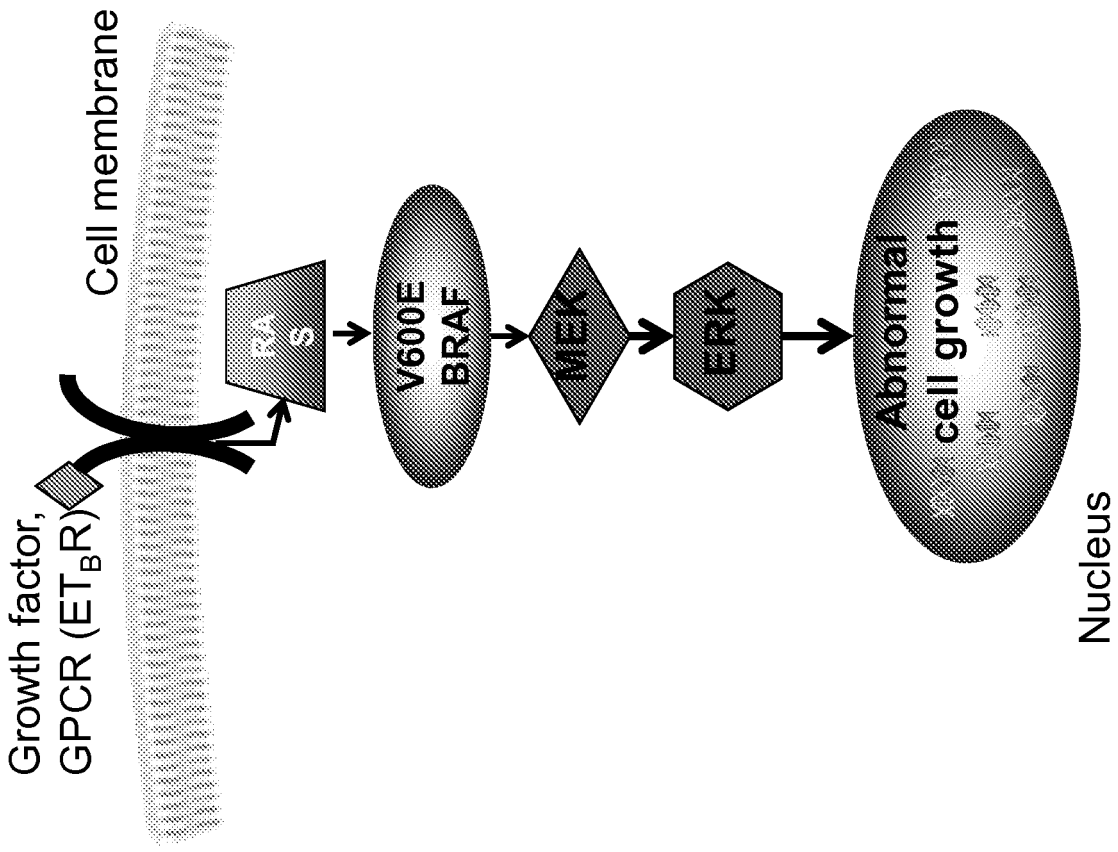

Growth factor,
GPCR (ET_BR)
Cell membrane
RAS
V600E BRAF
MEK
ERK
Abnormal cell growth
Nucleus

Figure 2

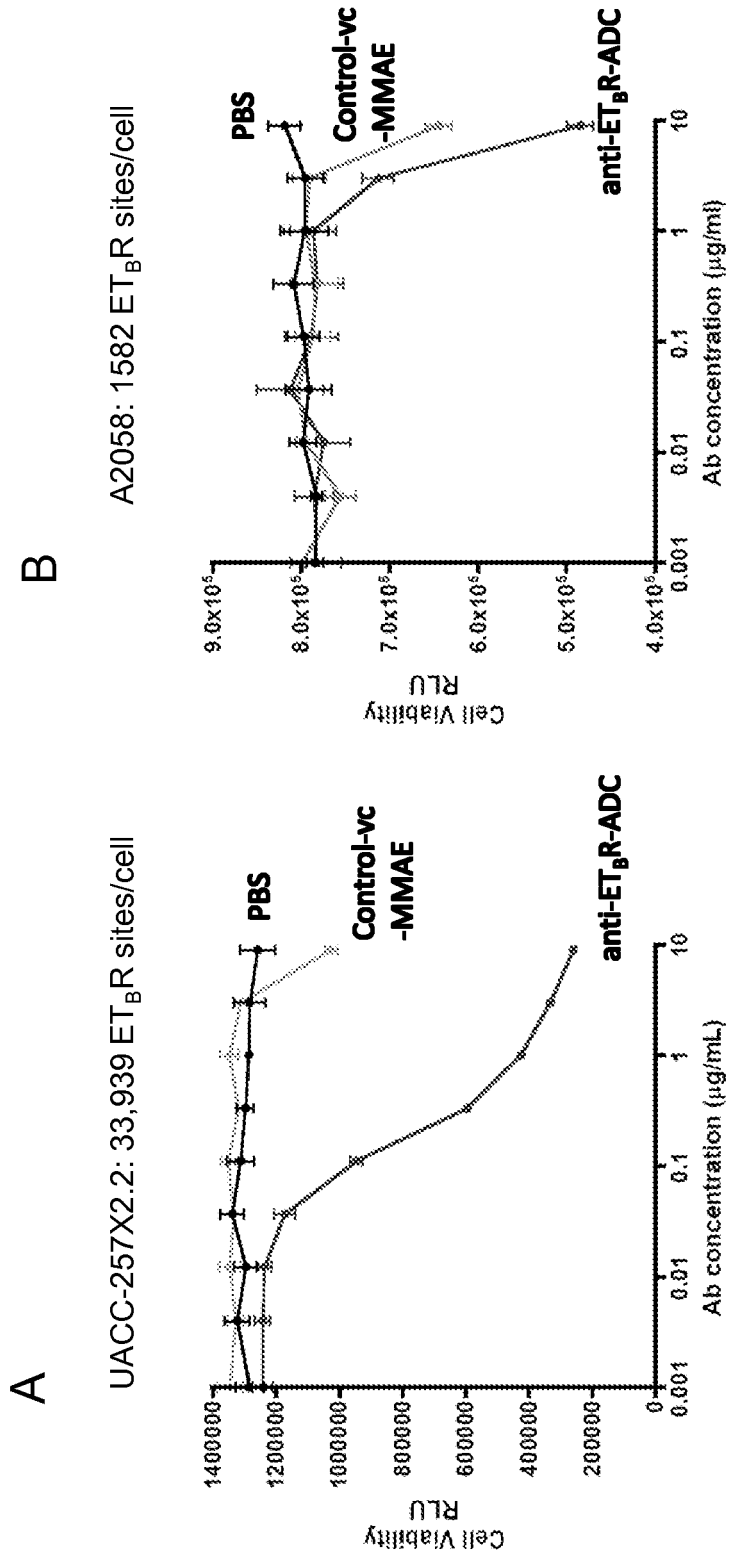

A
UACC-257X2.2: 33,939 ET$_B$R sites/cell
Cell Viability RLU
1400000
1200000
1000000
800000
600000
400000
200000
0
0.001
0.01
0.1
1
10
Ab concentration (μg/mL)
PBS
Control-vc -MMAE
anti-ET$_B$R-ADC
B
A2058: 1582 ET$_B$R sites/cell
Cell Viability RLU
9.0x10^5
8.0x10^5
7.0x10^5
6.0x10^5
5.0x10^5
4.0x10^5
0.001
0.01
0.1
1
10
Ab concentration (μg/ml)
PBS
Control-vc -MMAE
anti-ET$_B$R-ADC

Figure 3

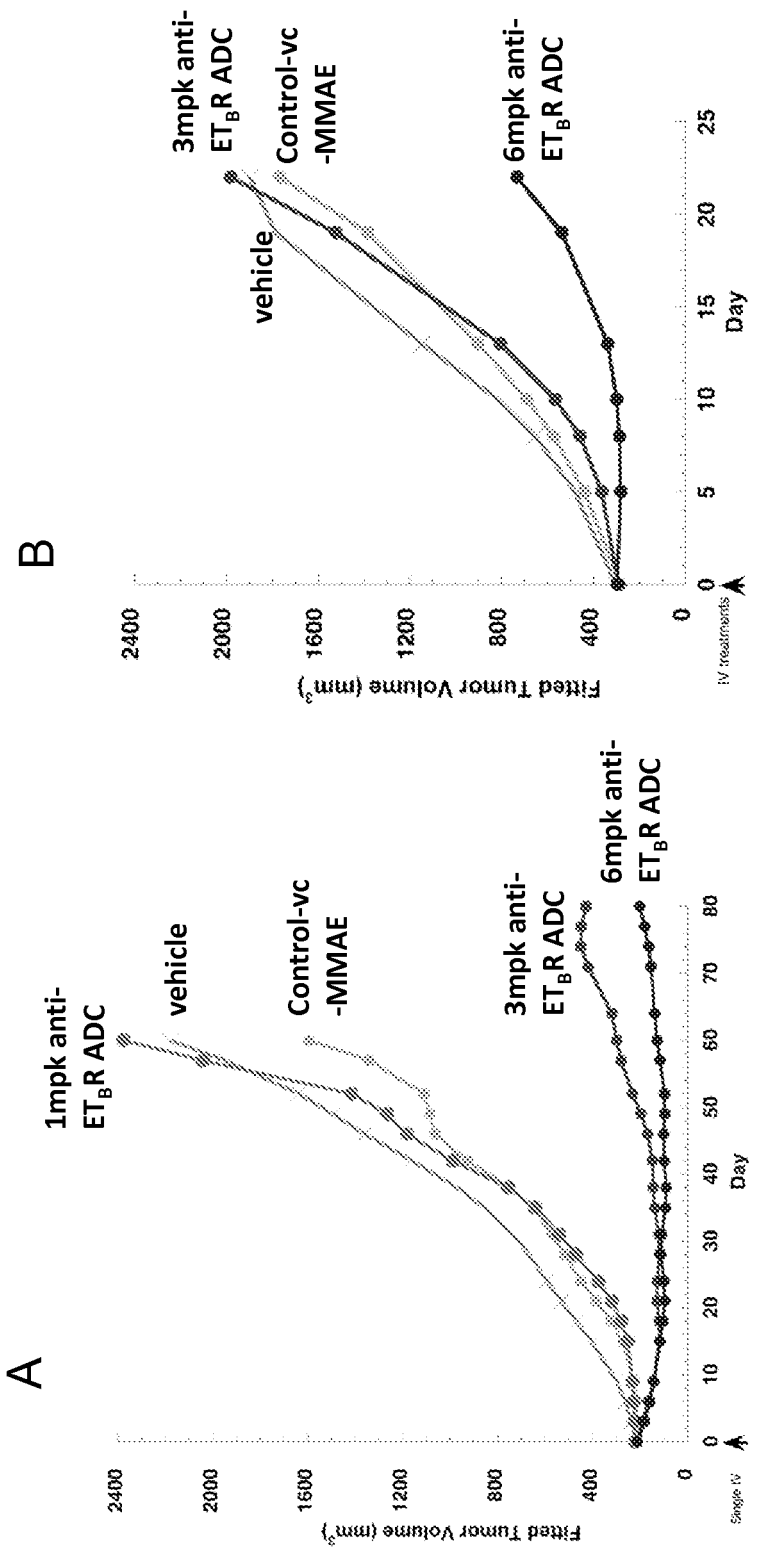
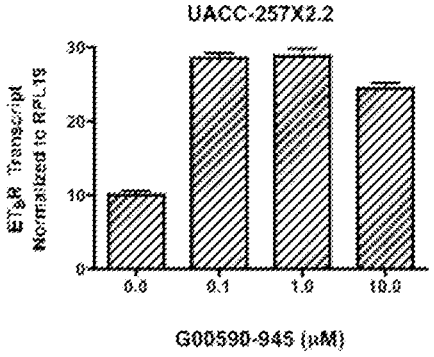

A
1mpk anti-ET$_B$R ADC
vehicle
Control-vc -MMAE
3mpk anti-ET$_B$R ADC
6mpk anti-ET$_B$R ADC
Fitted Tumor Volume (mm^3)
Day
Single IV
B
3mpk anti-ET$_B$R ADC
Control-vc -MMAE
vehicle
6mpk anti-ET$_B$R ADC
Fitted Tumor Volume (mm^3)
Day
IV treatments

Figure 4

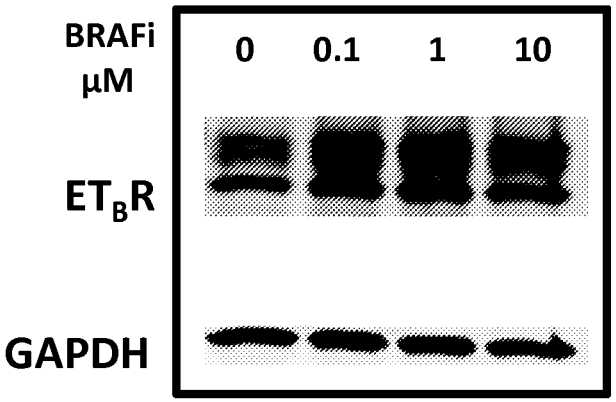
A

ET_BR Transcript
(UACC-257X2.2)



B

ET_BR Total Protein
(UACC-257X2.2)



C

ET_BR Surface Protein
(UACC-257 X2.2)

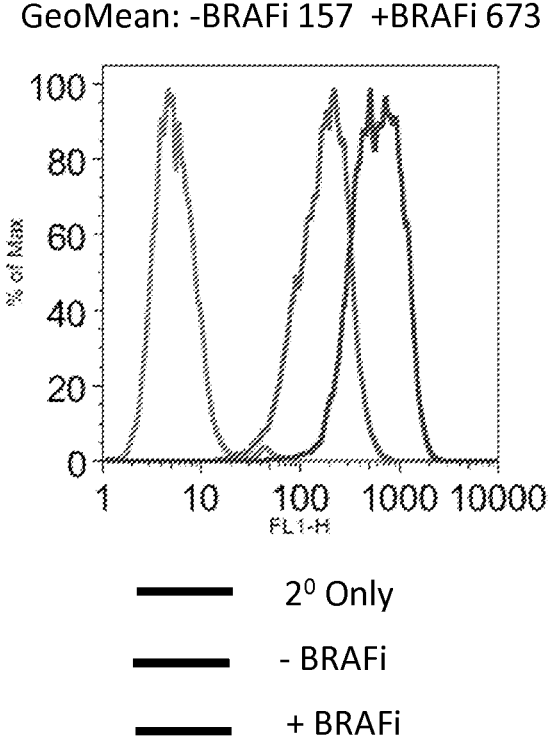


Figure 5A

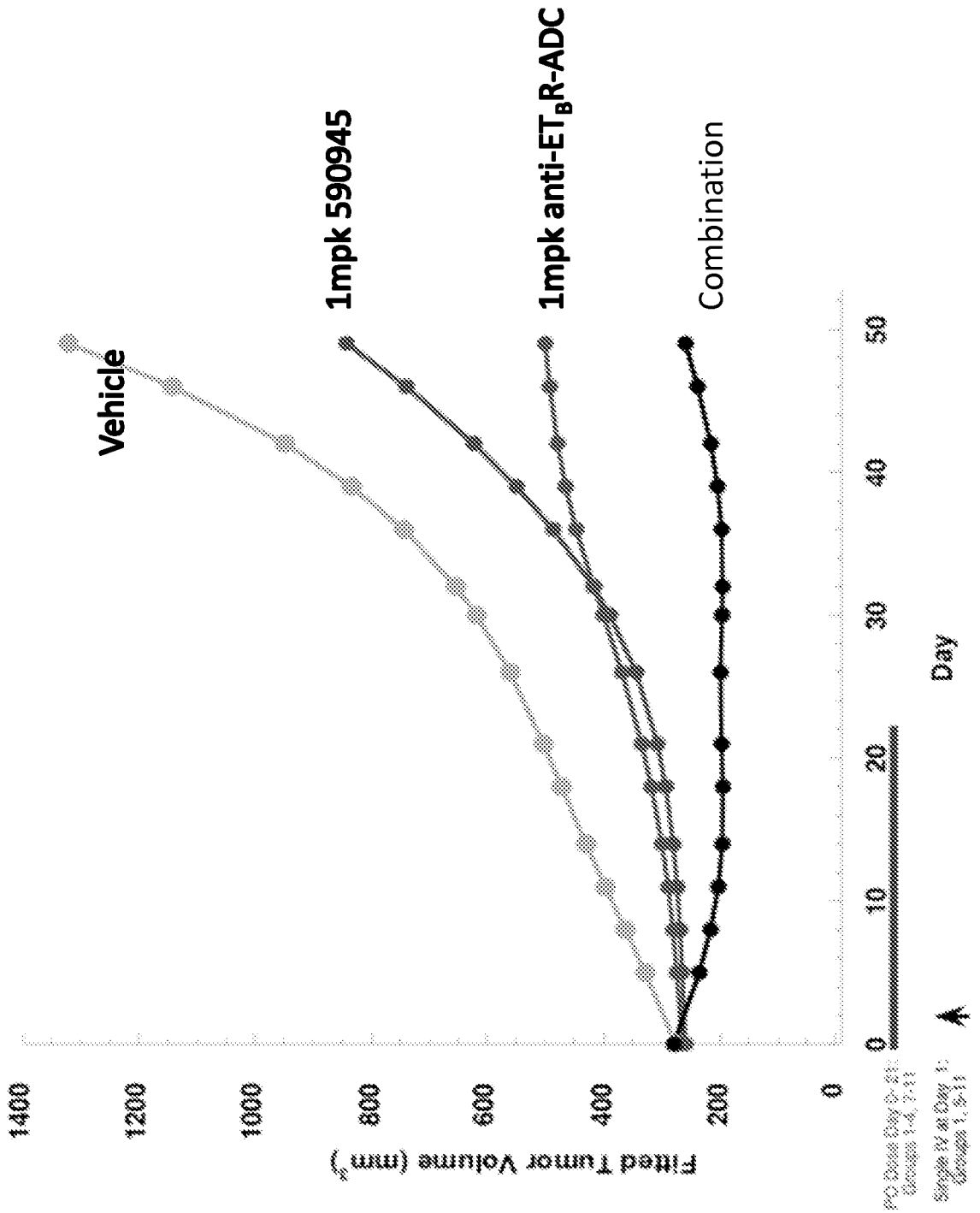

Vehicle
1mpk 590945
1mpk anti-ETBR-ADC
Combination
Fitted Tumor Volume (mm3)
1400
1200
1000
800
600
400
200
0
0
10
20
30
40
50
Day

Figure 5

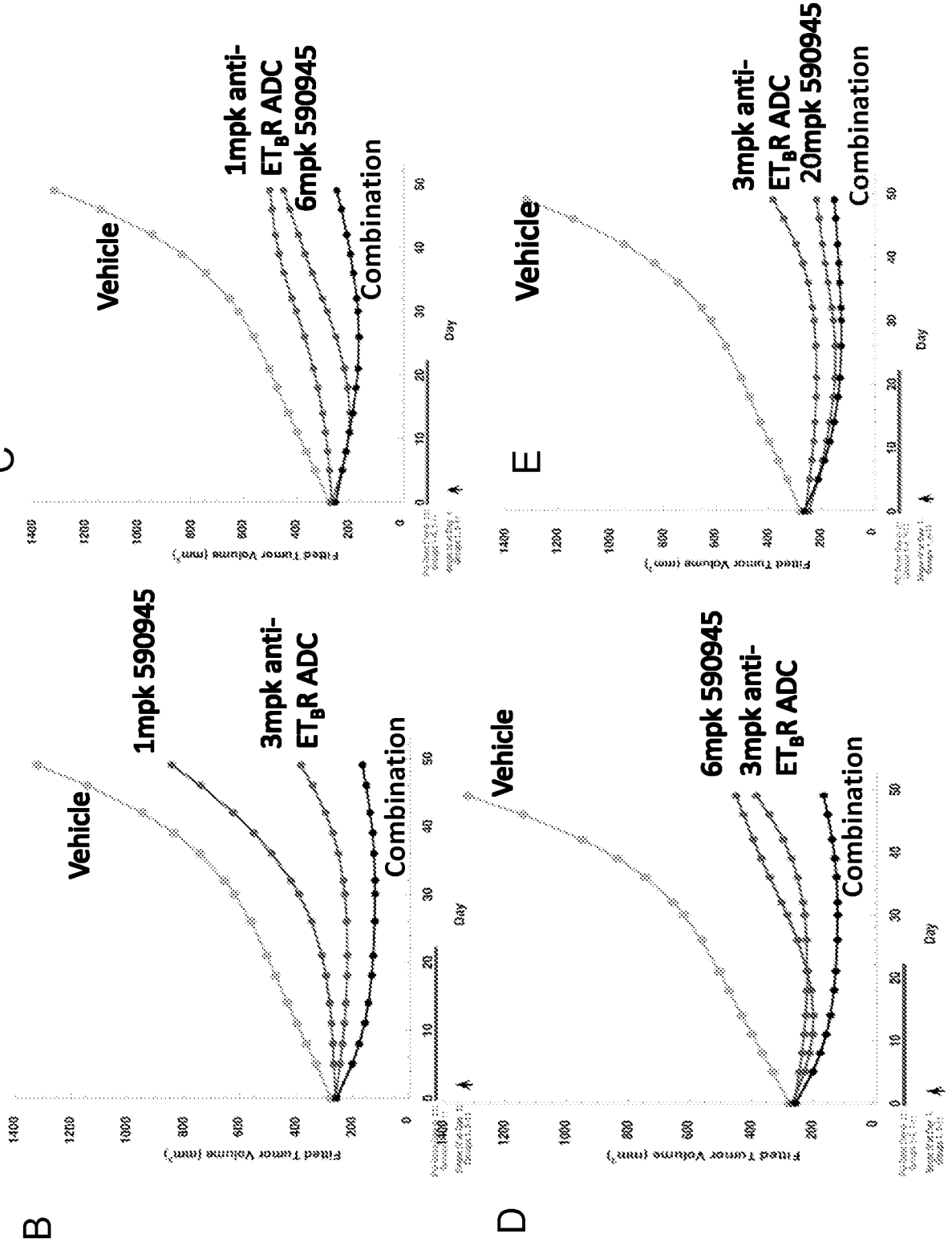
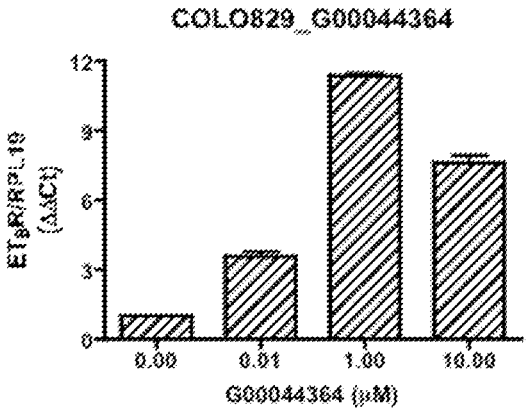

B
Vehicle
1mpk 590945
3mpk anti-ETBR ADC
Combination
C
Vehicle
1mpk anti-ETBR ADC
6mpk 590945
Combination
D
Vehicle
6mpk 590945
3mpk anti-ETBR ADC
Combination
E
Vehicle
3mpk anti-ETBR ADC
20mpk 590945
Combination
Fitted Tumor Volume (mm3)
Day

Figure 6

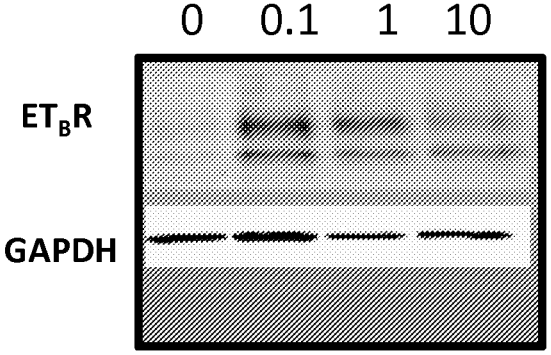
A

ET_BR Transcript
(COLO 829)



B

ET_BR Total Protein
(COLO 829)



C

ET_BR Surface Protein
(COLO 829)

1μM G00044364

GeoMean: -BRAFi 20 +BRAFi 145

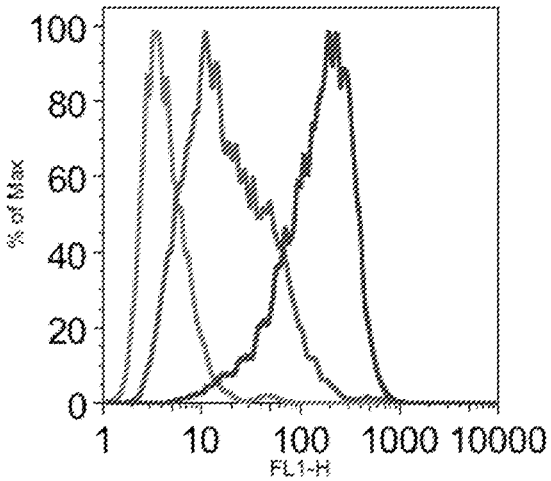


Figure 7

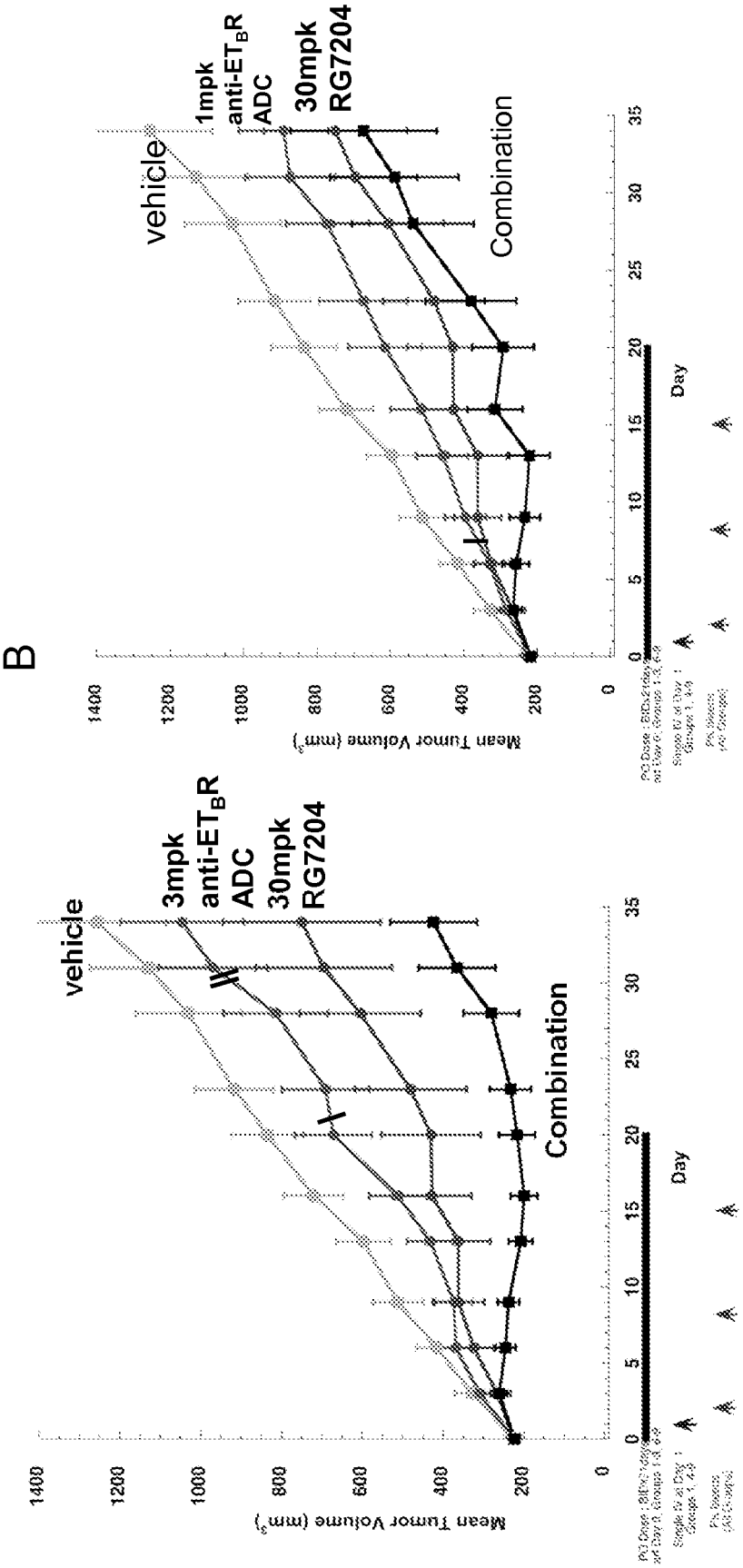
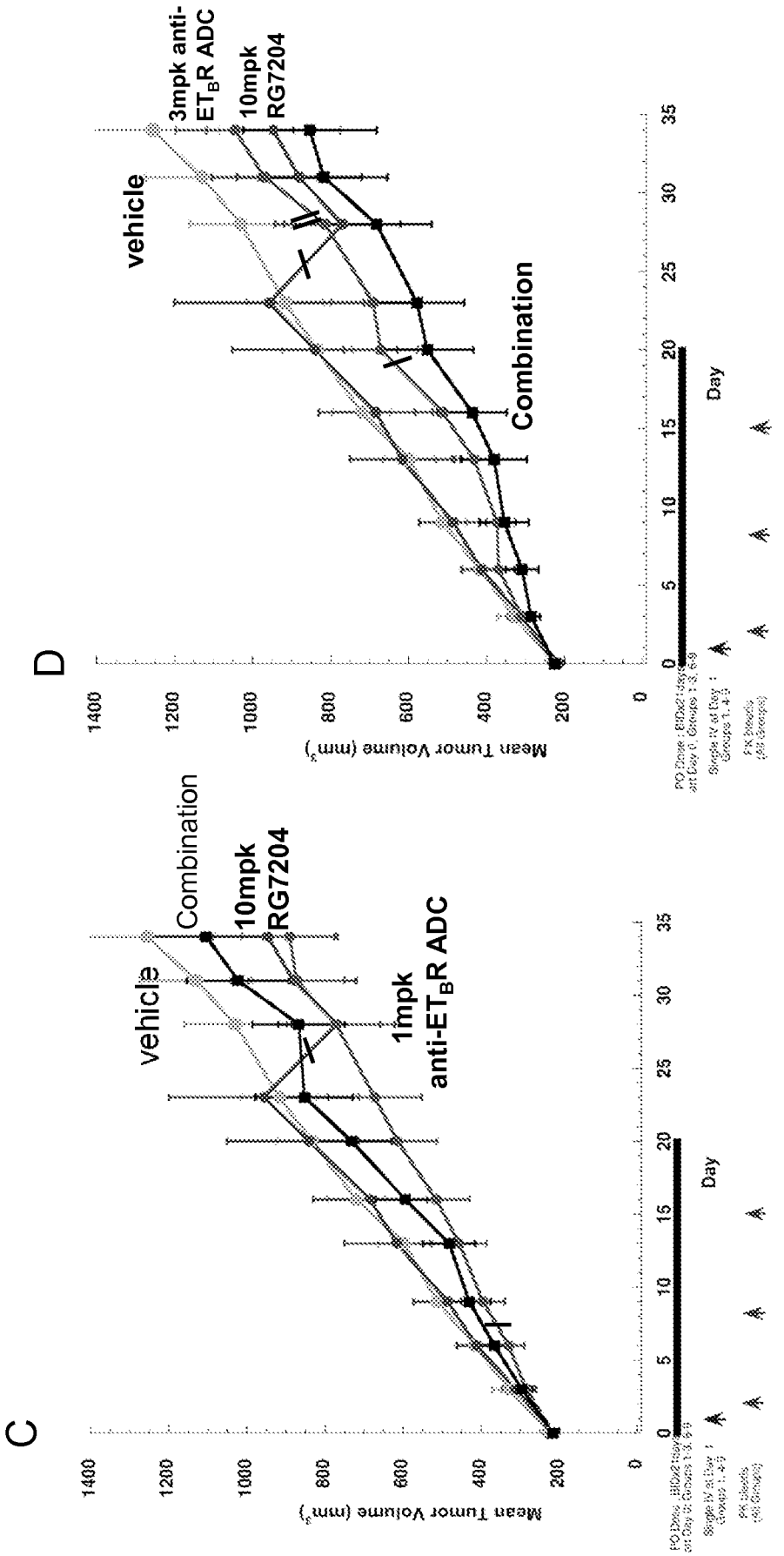

A
B
vehicle
3mpk anti-ETBR ADC
30mpk RG7204
Combination
1mpk anti-ETBR ADC
Mean Tumor Volume (mm3)
Day
= Mouse euthanized

Figure 7

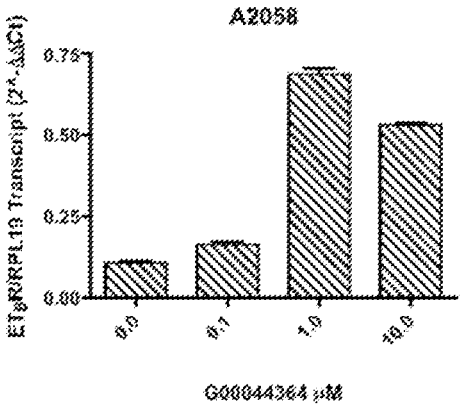


/ = Mouse euthanized

Figure 8

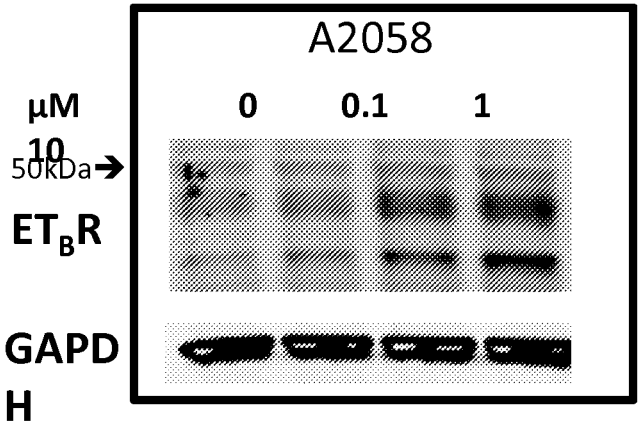
A

ET_BR Transcript
(A2058)



B

ET_BR Total Protein
(A2058)



C

ET_BR Surface Protein
(A2058)

1µM G00044364

GeoMean: -BRAFi 18 +BRAFi 40

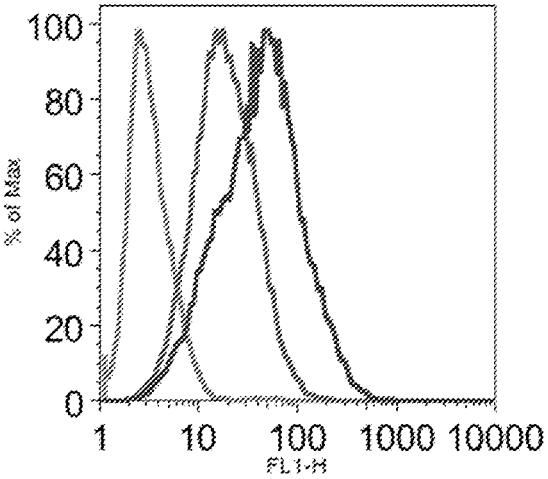


Figure 9

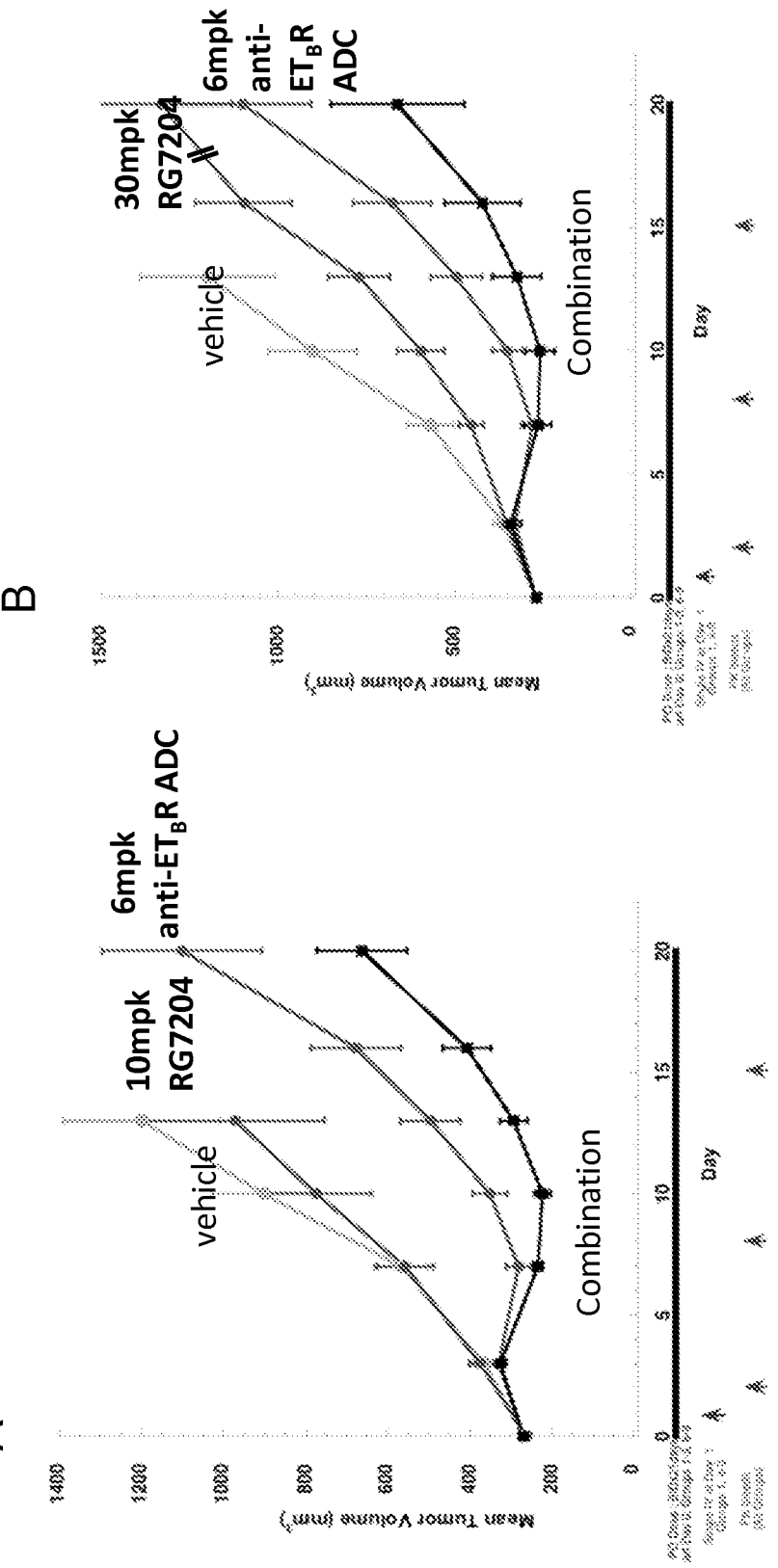

A
B
vehicle
10mpk RG7204
6mpk anti-ETBR ADC
Combination
30mpk RG7204
6mpk anti-ETBR ADC
Mean Tumor Volume (mm3)
Day
= Mouse euthanized

Figure 9

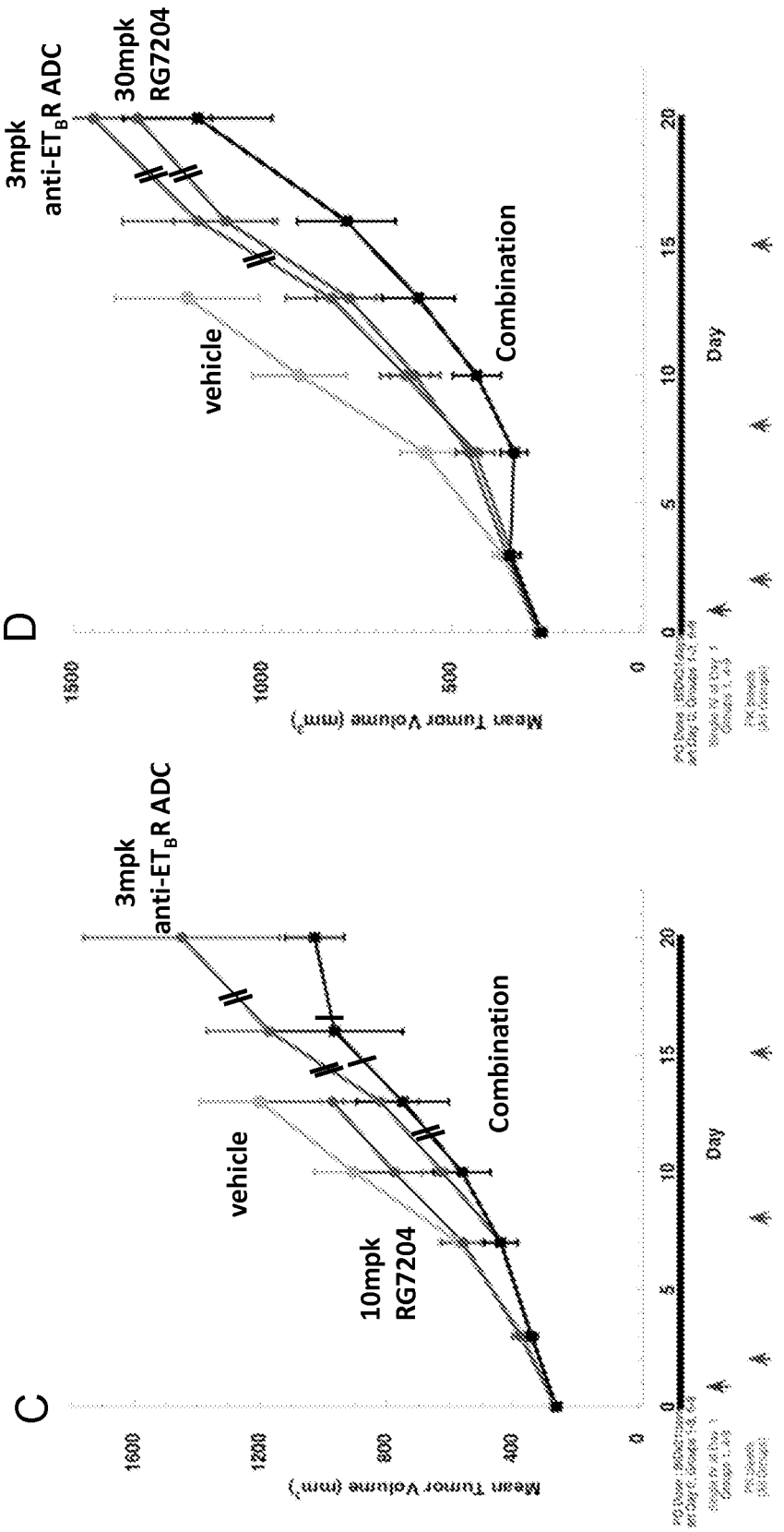

C
D
3mpk anti-ETBR ADC
10mpk RG7204
30mpk RG7204
vehicle
Combination
Mean Tumor Volume (mm³)
Day
= Mouse euthanized

FIGURE 10

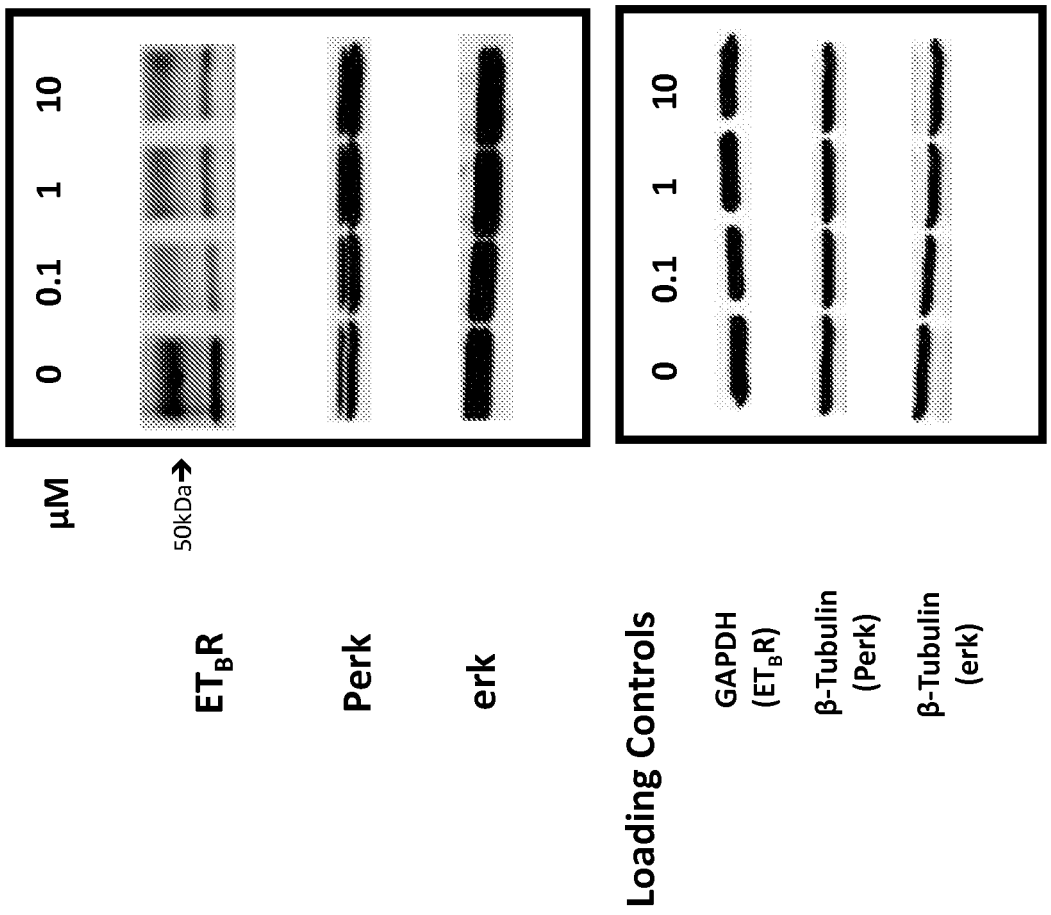

μM
0
0.1
1
10
50kDa
ET$_B$R
Perk
erk
Loading Controls
GAPDH (ET$_B$R)
β-Tubulin (Perk)
β-Tubulin (erk)

FIGURE 11

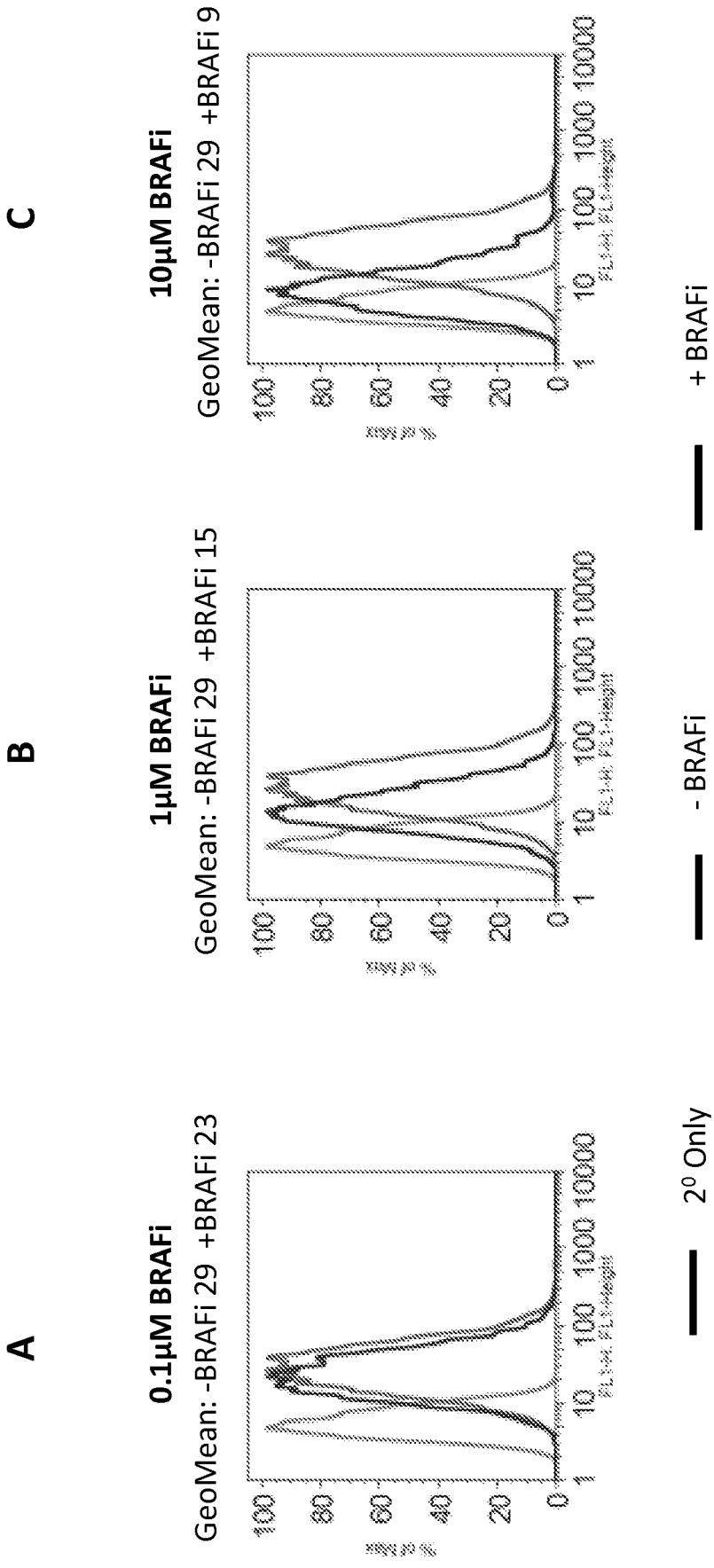

A
0.1µM BRAFi
GeoMean: -BRAFi 29 +BRAFi 23
B
1µM BRAFi
GeoMean: -BRAFi 29 +BRAFi 15
C
10µM BRAFi
GeoMean: -BRAFi 29 +BRAFi 9
Max %
100
80
60
40
20
0
1
10
100
1000
10000
2° Only
- BRAFi
+ BRAFi

FIGURE 12

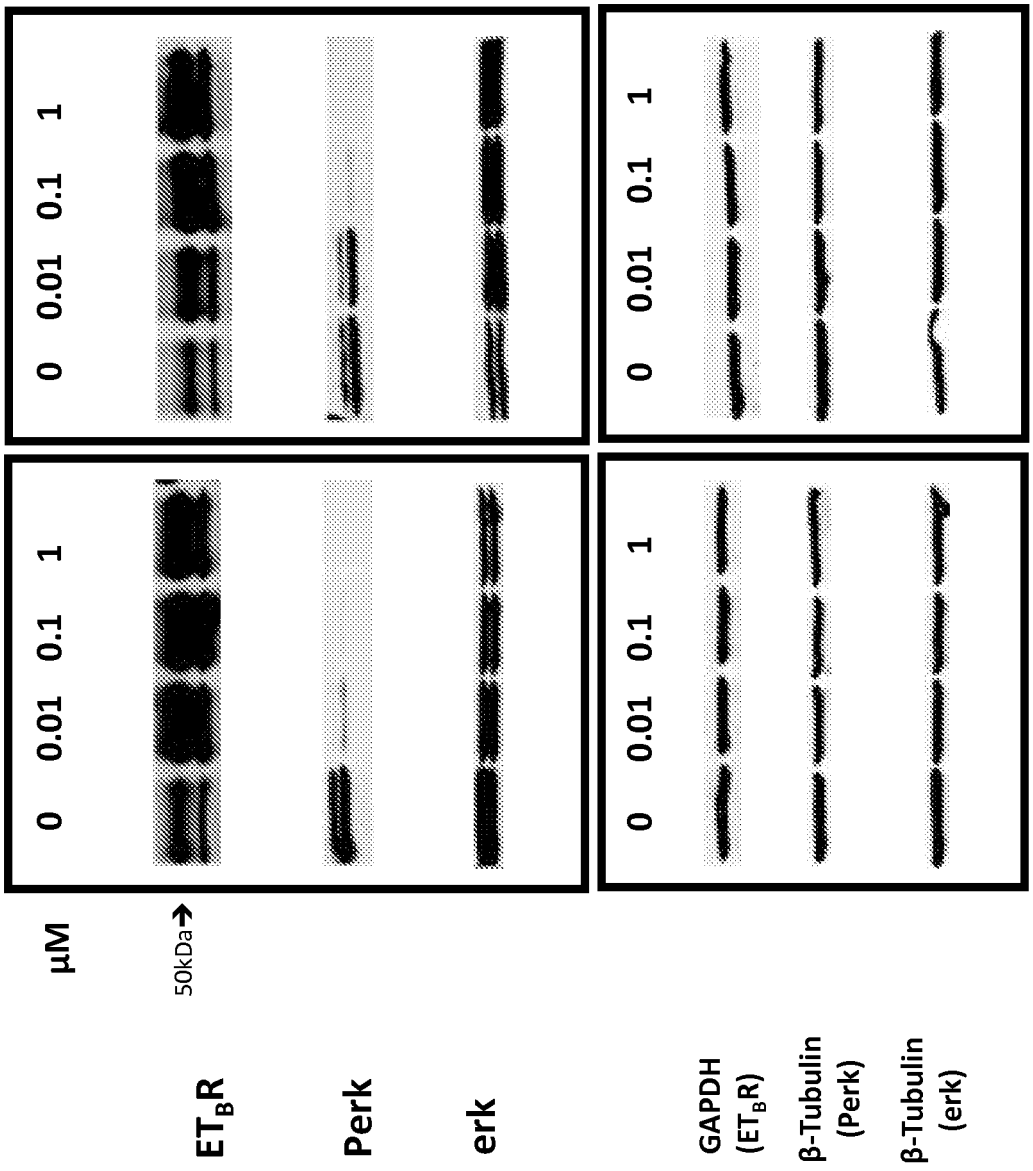

A
MEKi-0623
B
MEKi-0973
0 0.01 0.1 1
0 0.01 0.1 1
µM
50kDa
ET$_B$R
Perk
erk
GAPDH (ET$_B$R)
β-Tubulin (Perk)
β-Tubulin (erk)

FIGURE 13

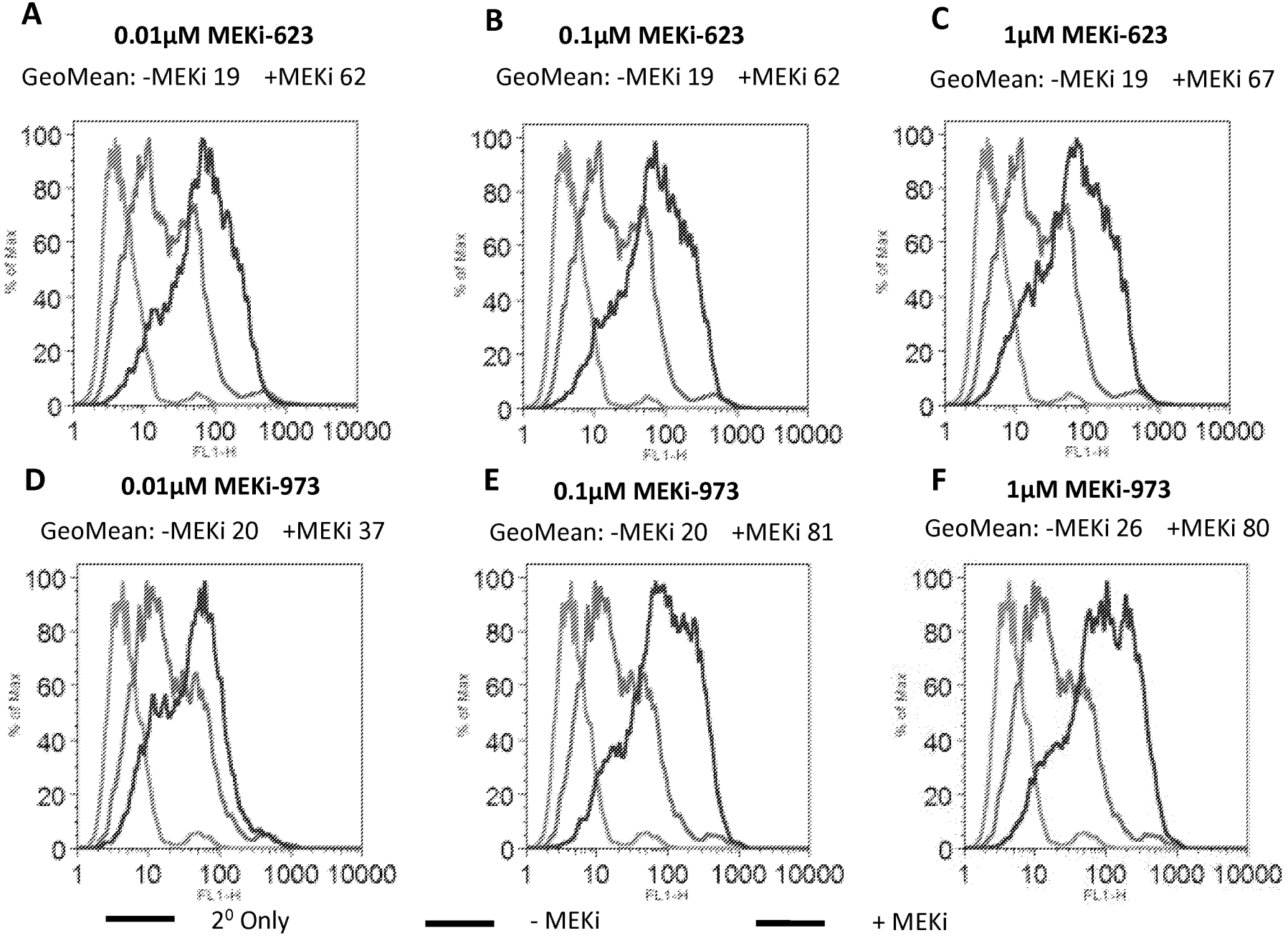

A
0.01µM MEKi-623
GeoMean: -MEKi 19 +MEKi 62
B
0.1µM MEKi-623
GeoMean: -MEKi 19 +MEKi 62
C
1µM MEKi-623
GeoMean: -MEKi 19 +MEKi 67
D
0.01µM MEKi-973
GeoMean: -MEKi 20 +MEKi 37
E
0.1µM MEKi-973
GeoMean: -MEKi 20 +MEKi 81
F
1µM MEKi-973
GeoMean: -MEKi 26 +MEKi 80
% of Max
FL1-H
1 10 100 1000 10000
0 20 40 60 80 100
2⁰ Only
- MEKi
+ MEKi

FIGURE 14

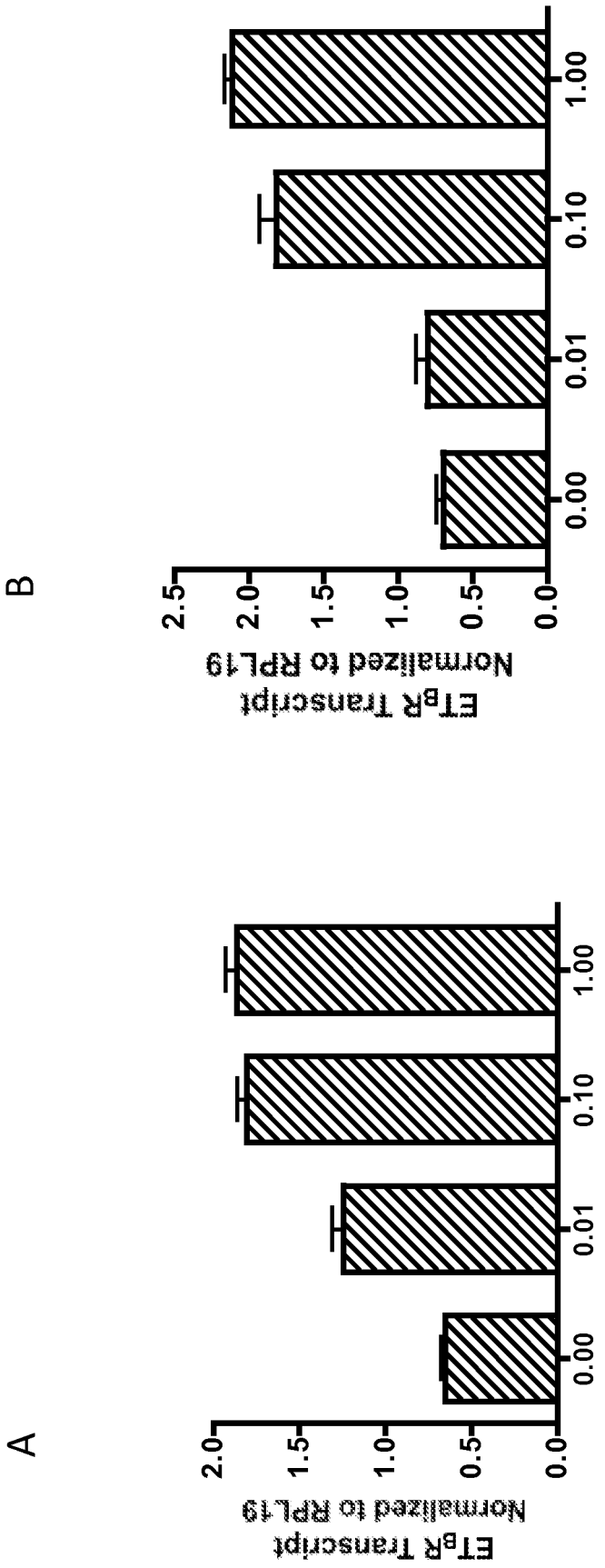

A
ETBR Transcript
Normalized to RPL19
2.0
1.5
1.0
0.5
0.0
0.00
0.01
0.10
1.00
B
ETBR Transcript
Normalized to RPL19
2.5
2.0
1.5
1.0
0.5
0.0
0.00
0.01
0.10
1.00

FIGURE 15

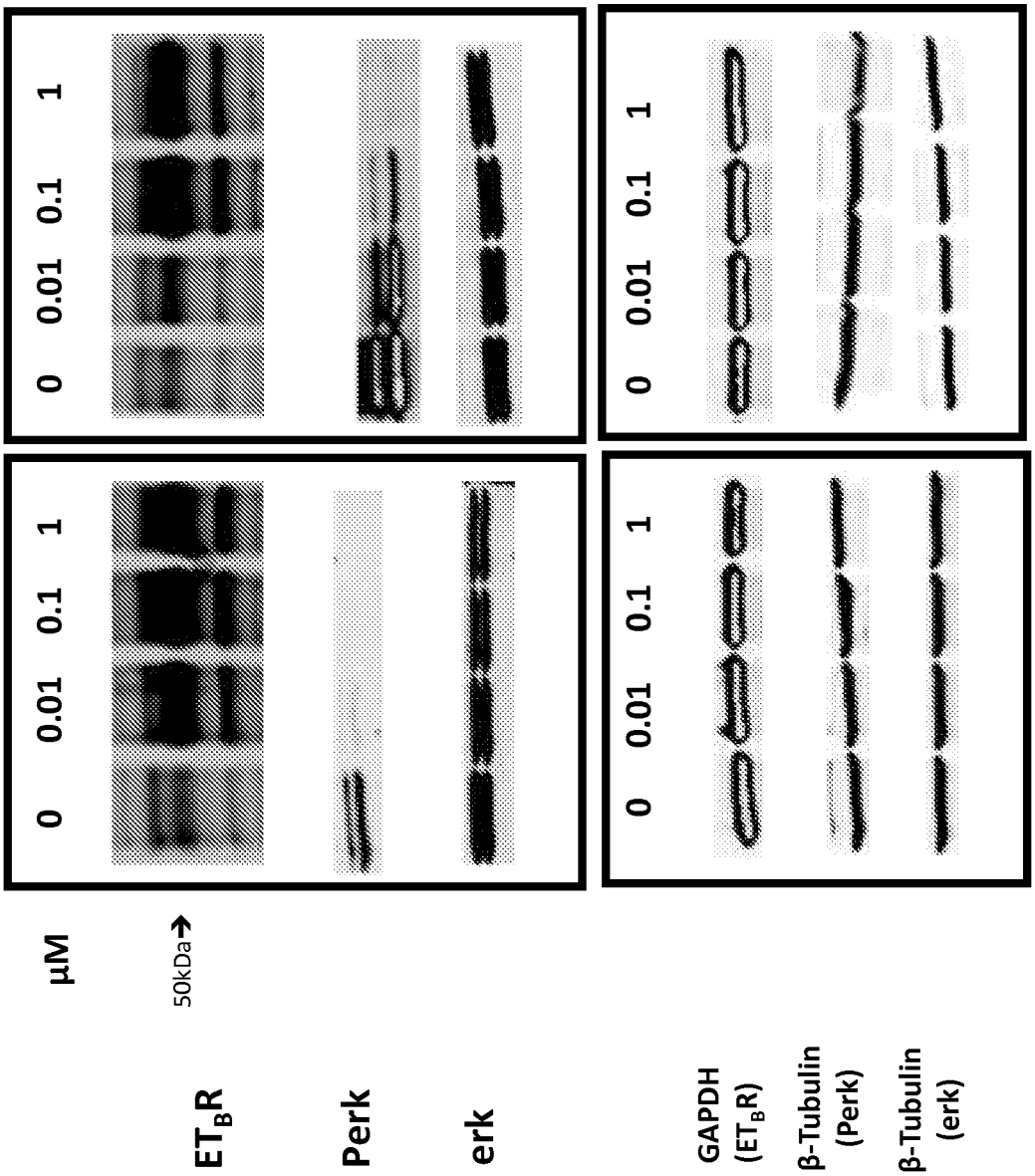
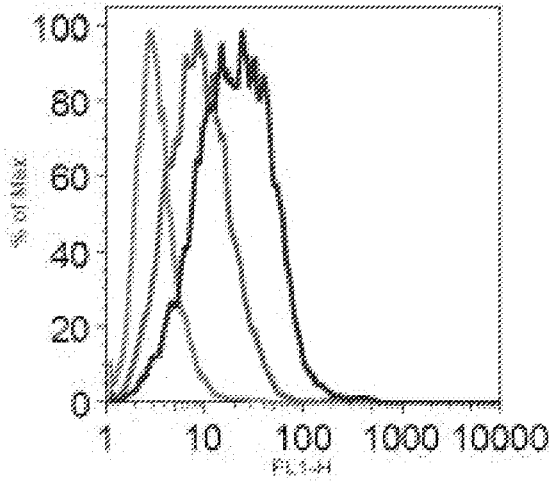

A
B
MEKi-623
MEKi-973
μM
0 0.01 0.1 1
50kDa
ET$_B$R
Perk
erk
GAPDH (ET$_B$R)
β-Tubulin (Perk)
β-Tubulin (erk)

FIGURE 16

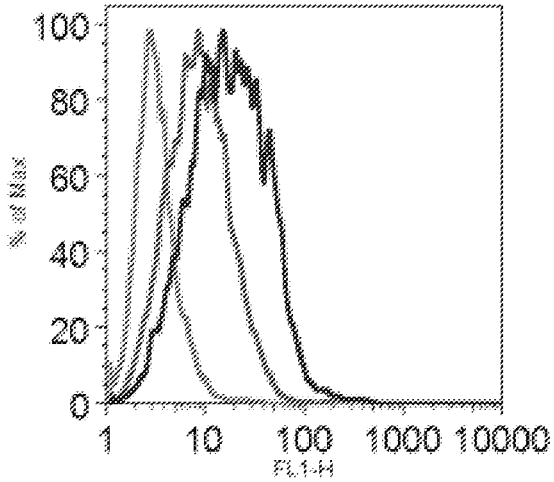
A **0.01µM MEKi-623**

GeoMean: -MEKi 8.4 +MEKi 18.4



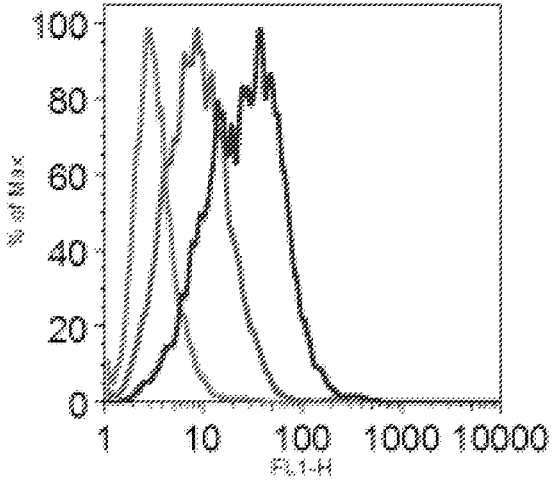
B **0.1µM MEKi-623**

GeoMean: -MEKi 8.4 +MEKi 15



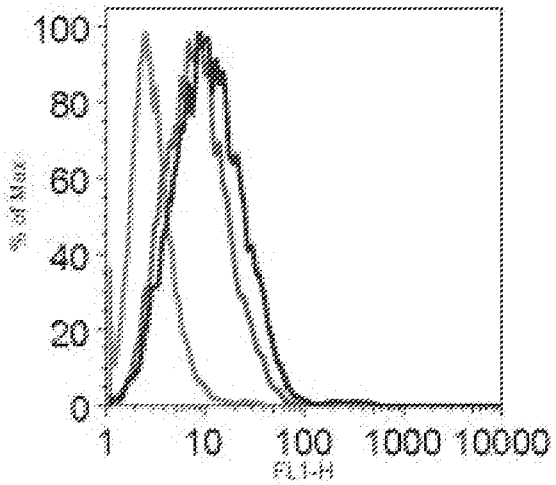
C **1µM MEKi-623**

GeoMean: -MEKi 8.4 +MEKi 23.4



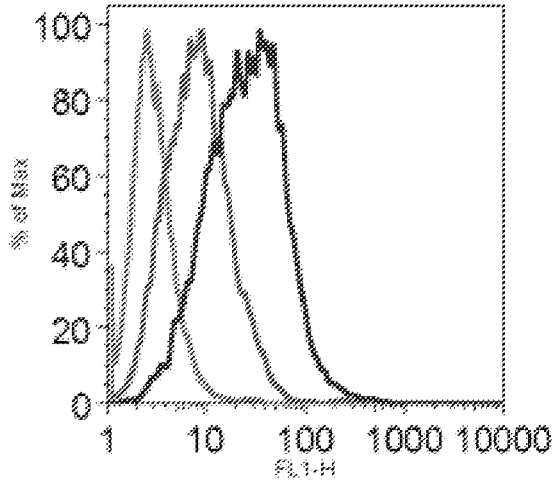
D **0.01µM MEKi-973**

GeoMean: -MEKi 7.7 +MEKi 10



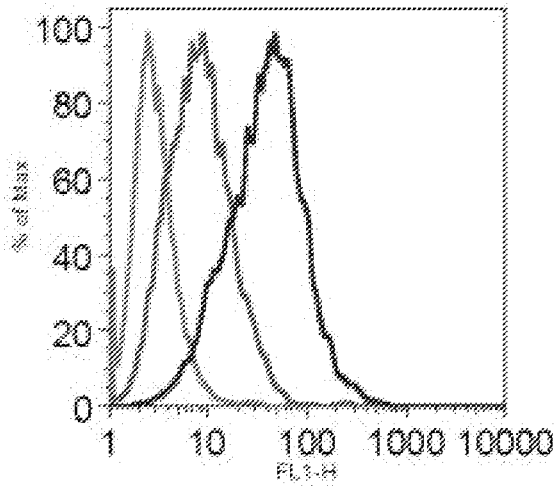
E **0.1µM MEKi-973**

GeoMean: -MEKi 7.7 +MEKi 23.4



F **1µM MEKi-973**

GeoMean: -MEKi 15 +MEKi 36.4



2^0 Only — - MEKi — + MEKi

FIGURE 17

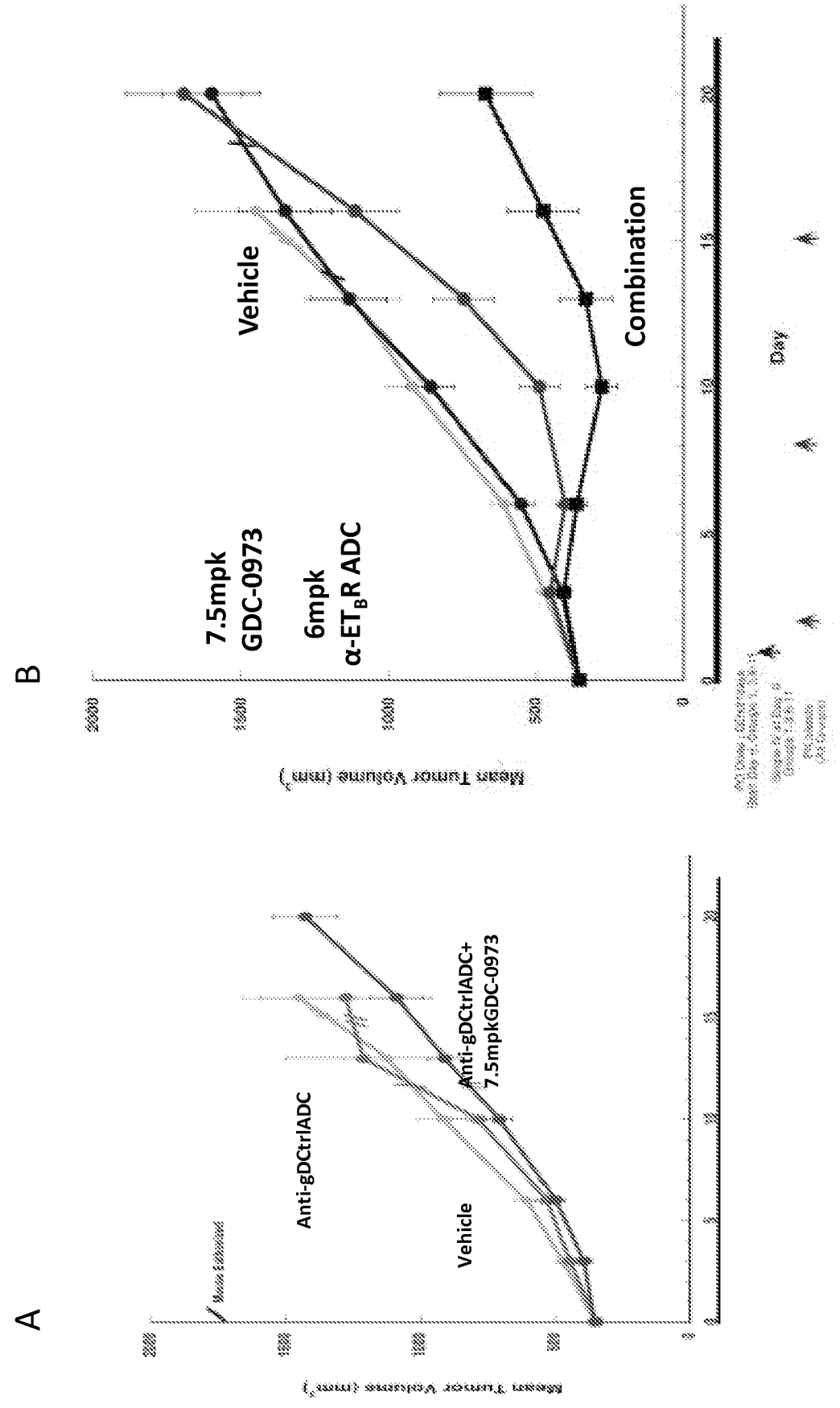

A
Anti-gDCtrlADC
Vehicle
Anti-gDCtrlADC+
7.5mpkGDC-0973
B
Vehicle
7.5mpk
GDC-0973
6mpk
α-ETBR ADC
Combination
Day

FIGURE 18

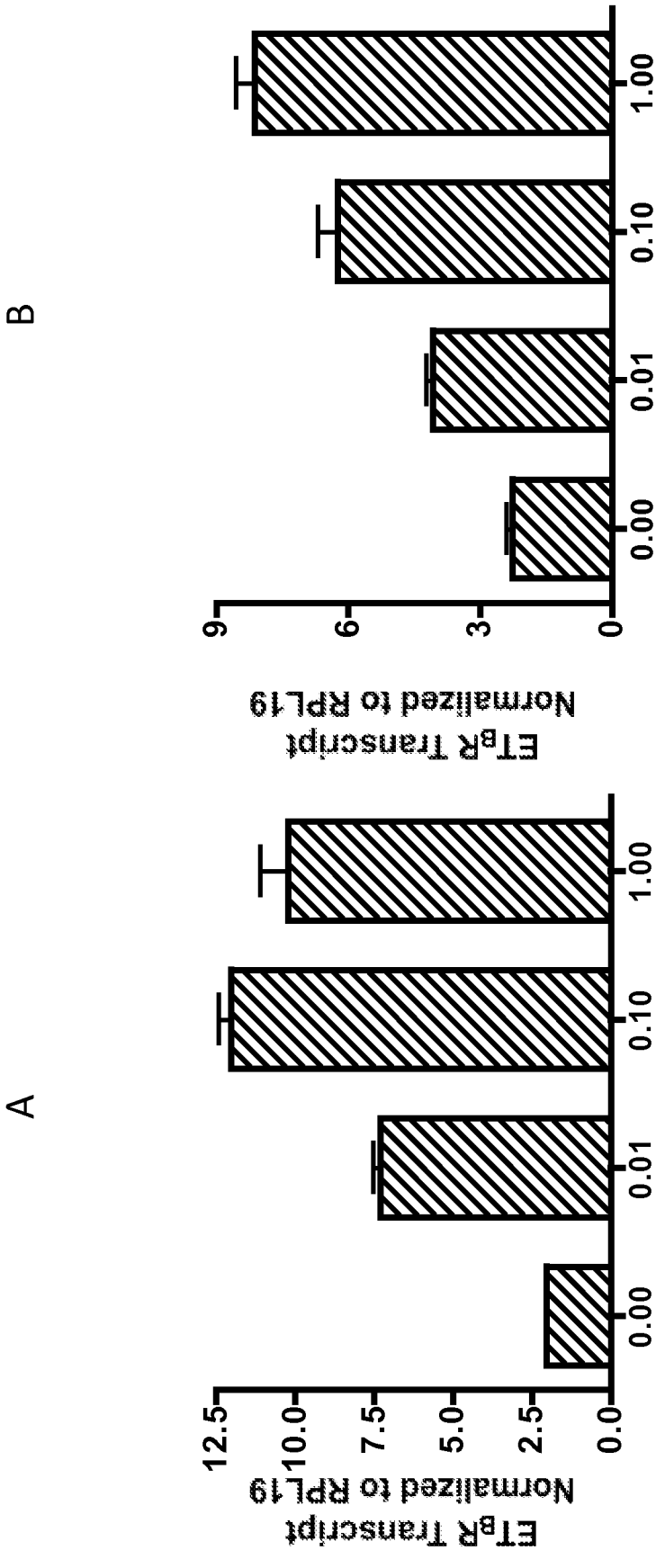

A
ETBR Transcript
Normalized to RPL19
12.5
10.0
7.5
5.0
2.5
0.0
0.00
0.01
0.10
1.00
B
ETBR Transcript
Normalized to RPL19
9
6
3
0
0.00
0.01
0.10
1.00

FIGURE 19

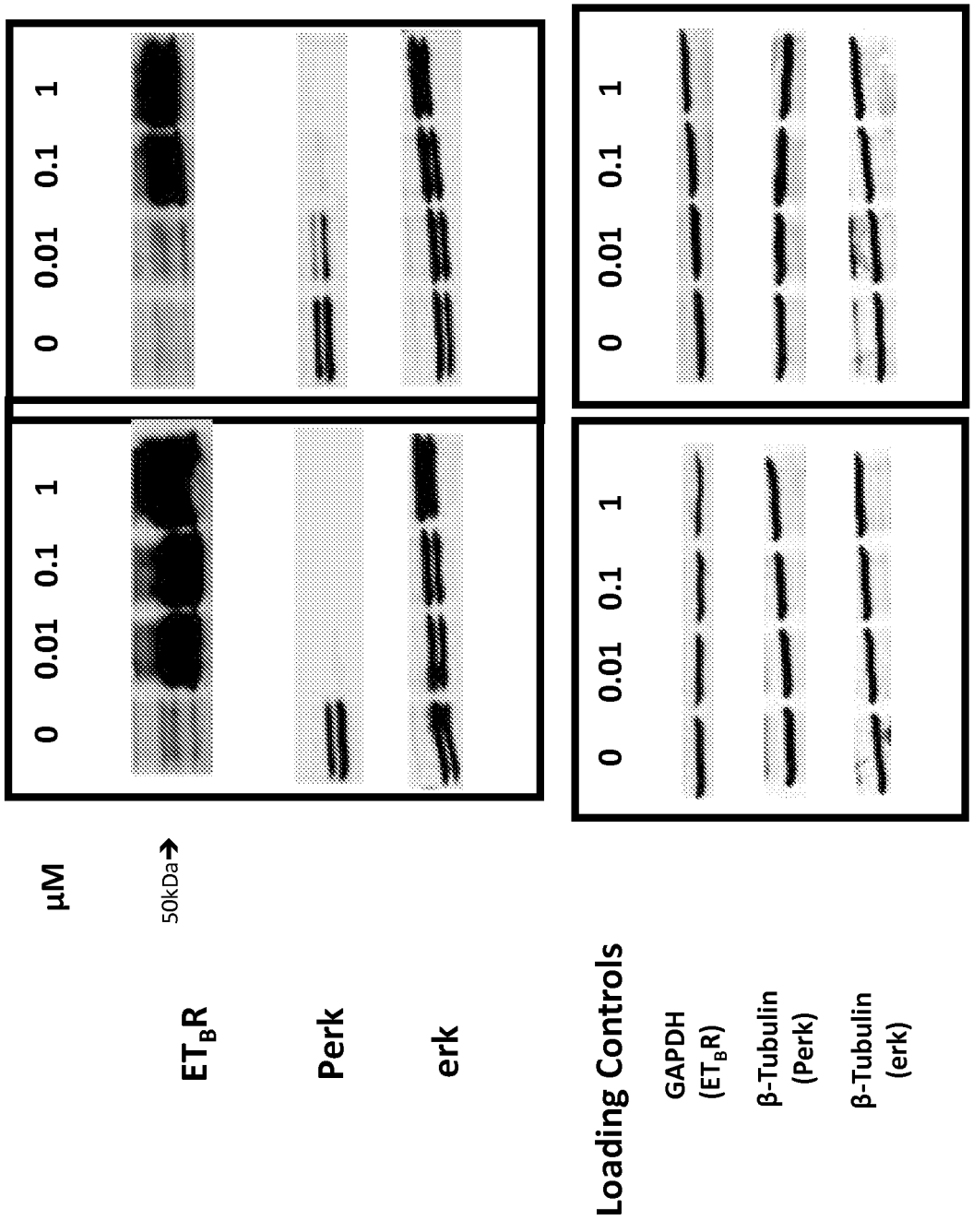

A
MEKi-623
B
MEKi-973
μM
0 0.01 0.1 1
0 0.01 0.1 1
50kDa→
ETBR
Perk
erk
Loading Controls
GAPDH (ETBR)
β-Tubulin (Perk)
β-Tubulin (erk)

FIGURE 20

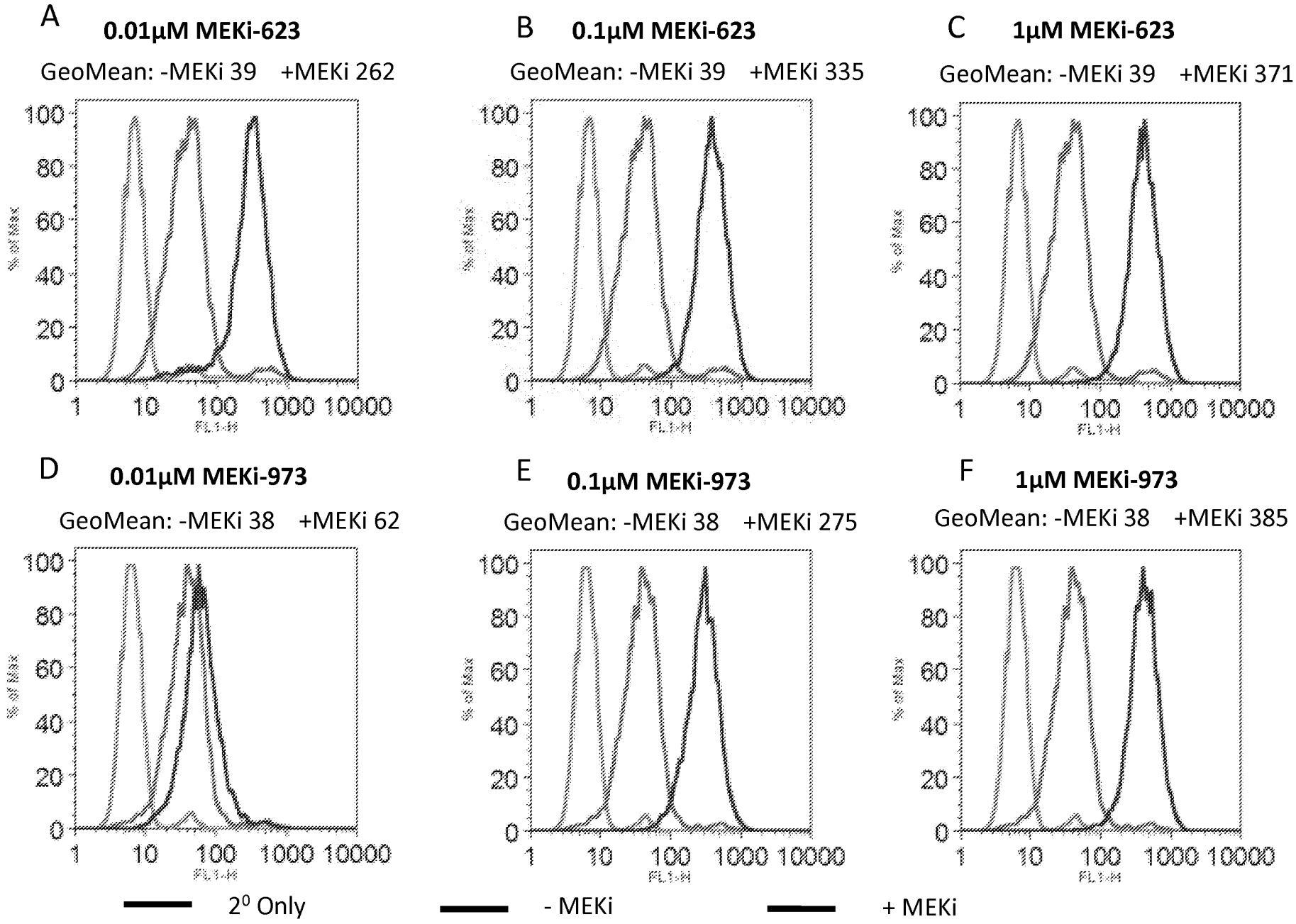

A
0.01µM MEKi-623
GeoMean: -MEKi 39 +MEKi 262
B
0.1µM MEKi-623
GeoMean: -MEKi 39 +MEKi 335
C
1µM MEKi-623
GeoMean: -MEKi 39 +MEKi 371
D
0.01µM MEKi-973
GeoMean: -MEKi 38 +MEKi 62
E
0.1µM MEKi-973
GeoMean: -MEKi 38 +MEKi 275
F
1µM MEKi-973
GeoMean: -MEKi 38 +MEKi 385
% of Max
FL1-H
1 10 100 1000 10000
0 20 40 60 80 100
2⁰ Only
- MEKi
+ MEKi

FIGURE 21

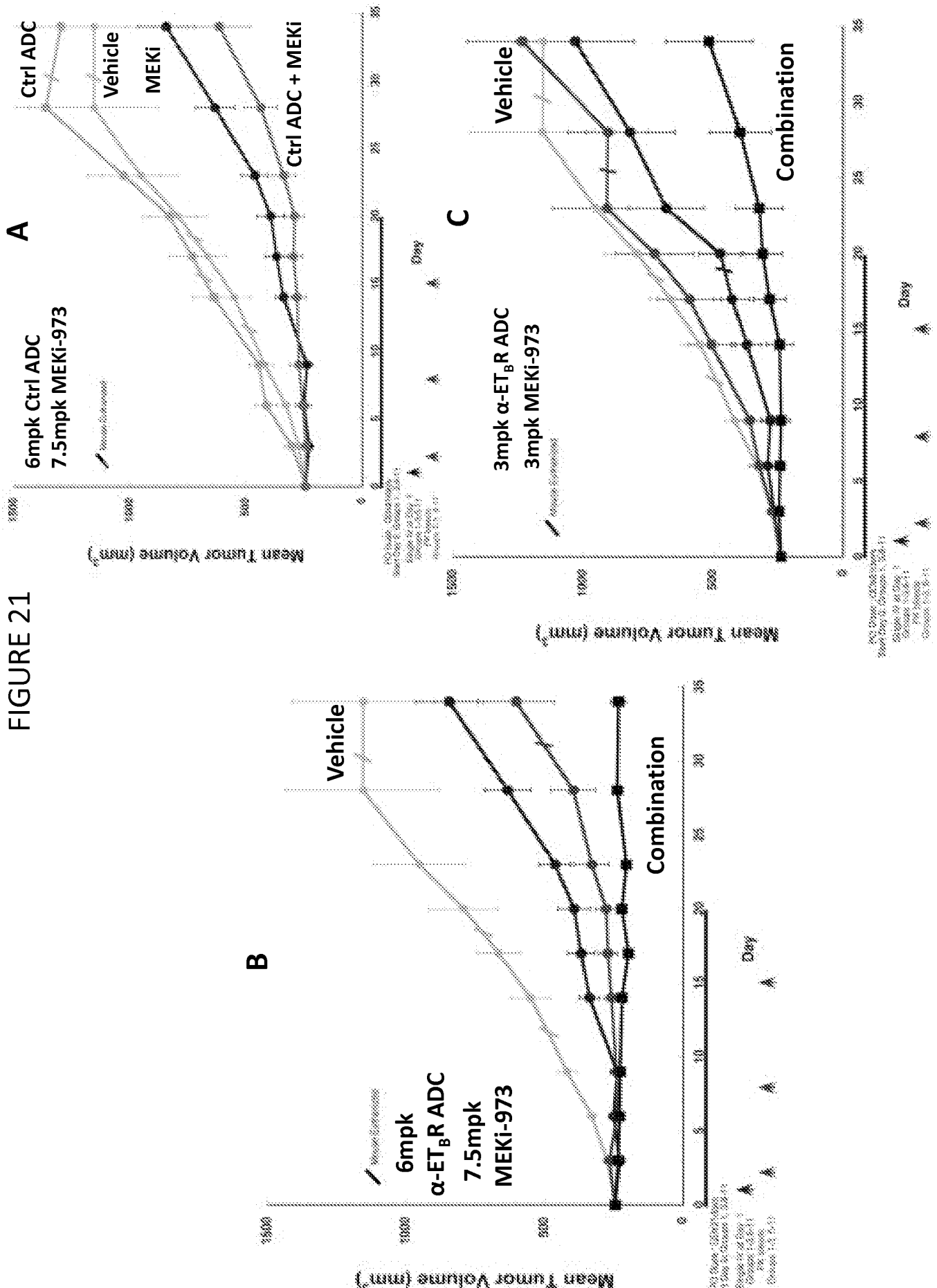

A
6mpk Ctrl ADC
7.5mpk MEKi-973
Ctrl ADC
Vehicle
MEKi
Ctrl ADC + MEKi
Mean Tumor Volume (mm³)
Day
B
6mpk
α-ET$_B$R ADC
7.5mpk
MEKi-973
Vehicle
Combination
Mean Tumor Volume (mm³)
Day
C
3mpk α-ET$_B$R ADC
3mpk MEKi-973
Vehicle
Combination
Mean Tumor Volume (mm³)
Day

FIGURE 21

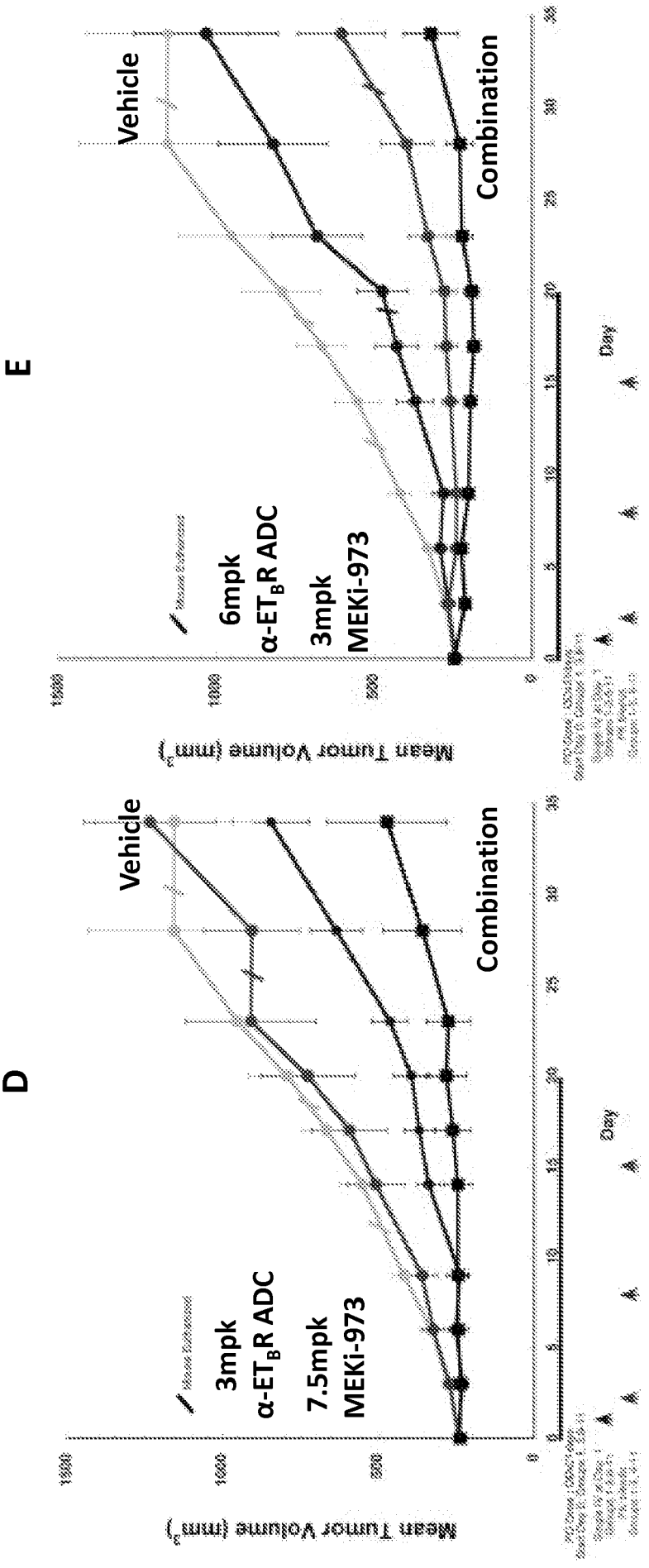

D
Vehicle
3mpk
α-ETBR ADC
7.5mpk
MEKi-973
Combination
Mean Tumor Volume (mm3)
Day
E
Vehicle
6mpk
α-ETBR ADC
3mpk
MEKi-973
Combination
Mean Tumor Volume (mm3)
Day

FIGURE 22

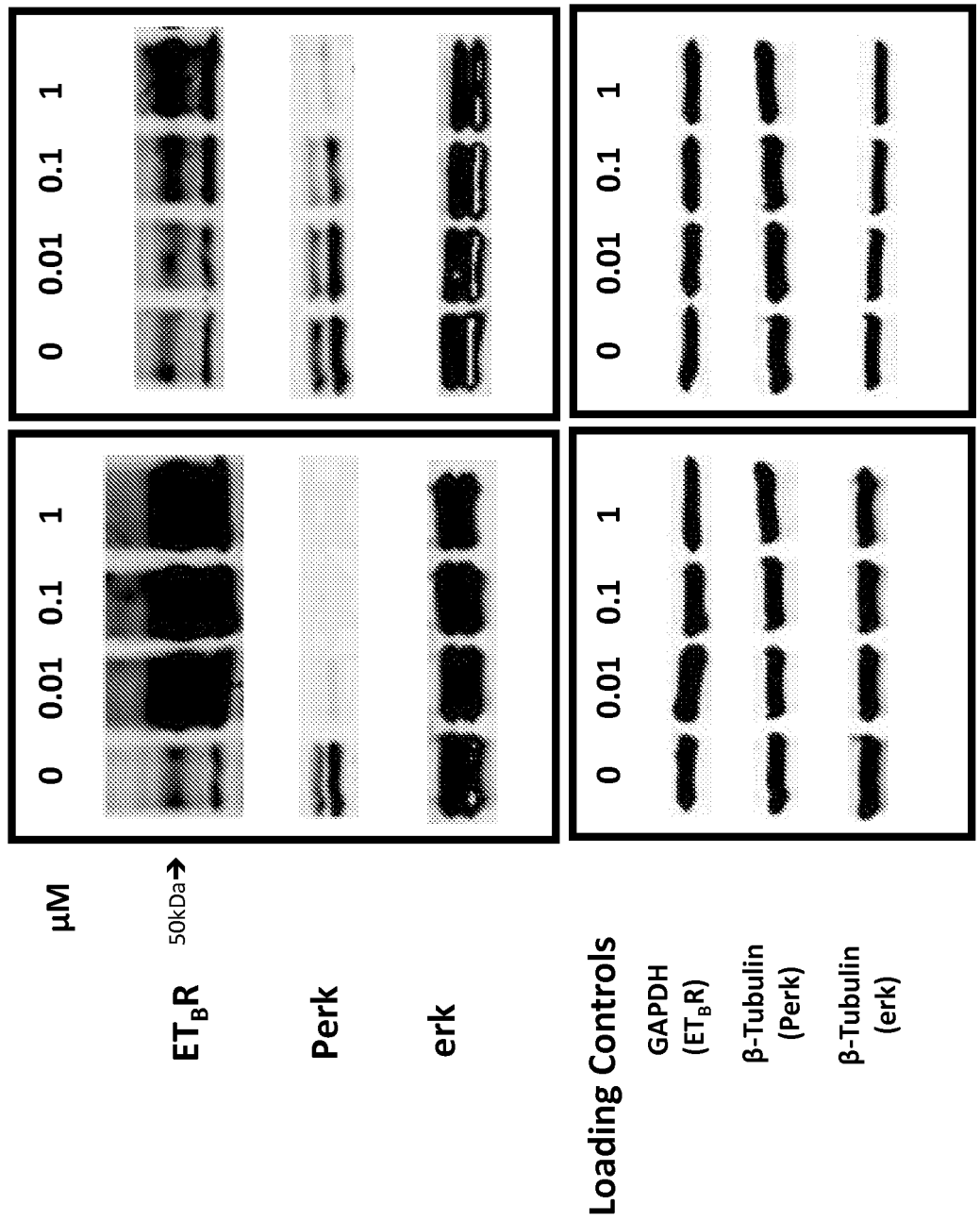
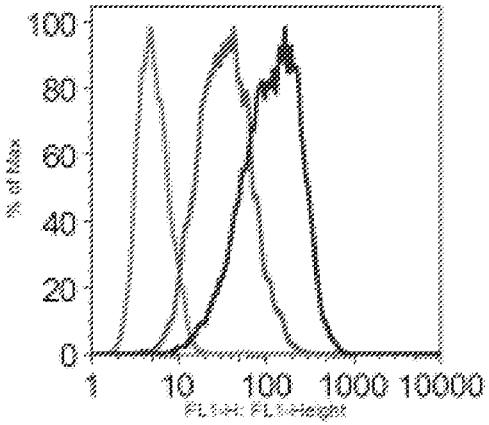

A
MEKi-623
B
MEKi-973
0 0.01 0.1 1
0 0.01 0.1 1
μM
50kDa
ETBR
Perk
erk
Loading Controls
GAPDH (ETBR)
β-Tubulin (Perk)
β-Tubulin (erk)

FIGURE 23

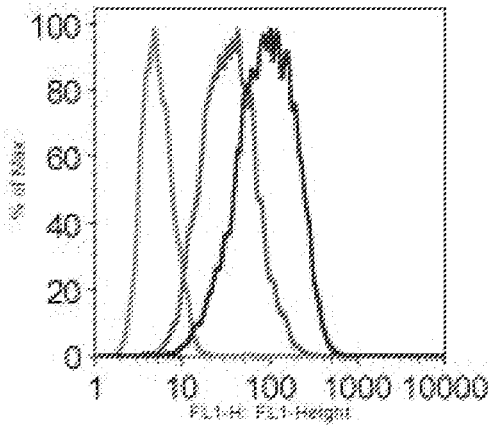
A **0.01µM MEKi-623**

GeoMean: -MEKi 33 +MEKi 105



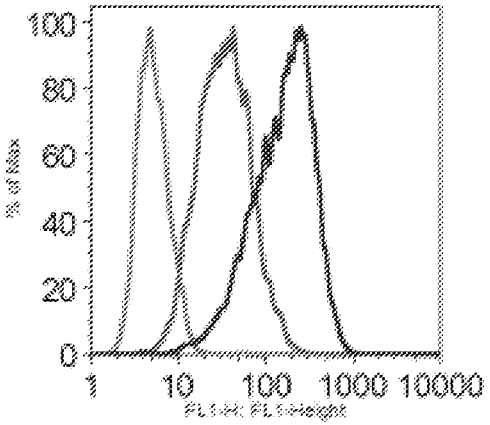
B **0.1µM MEKi-623**

GeoMean: -MEKi 33 +MEKi 85



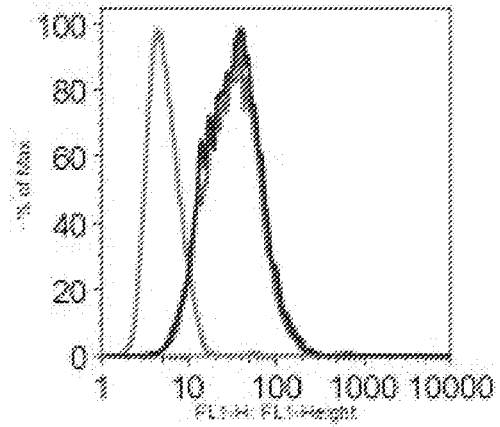
C **1µM MEKi-623**

GeoMean: -MEKi 33 +MEKi 142



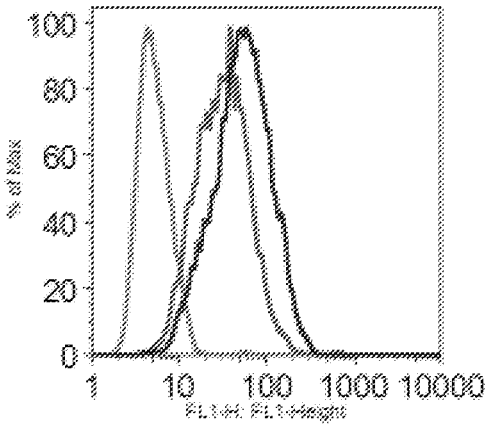
D **0.01µM MEKi-973**

GeoMean: -MEKi 31 +MEKi 31



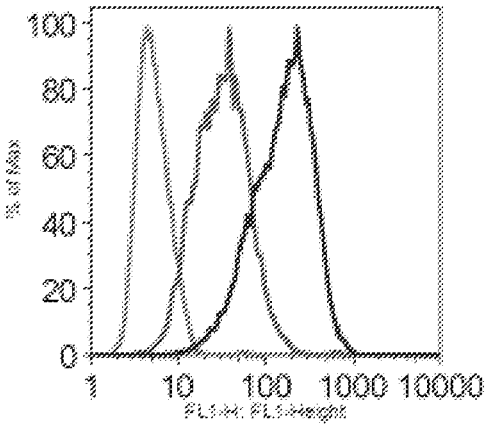
E **0.1µM MEKi-973**

GeoMean: -MEKi 31 +MEKi 50



F **1µM MEKi-973**

GeoMean: -MEKi 31 +MEKi 142



2^0 Only — - MEKi — + MEKi

FIGURE 24

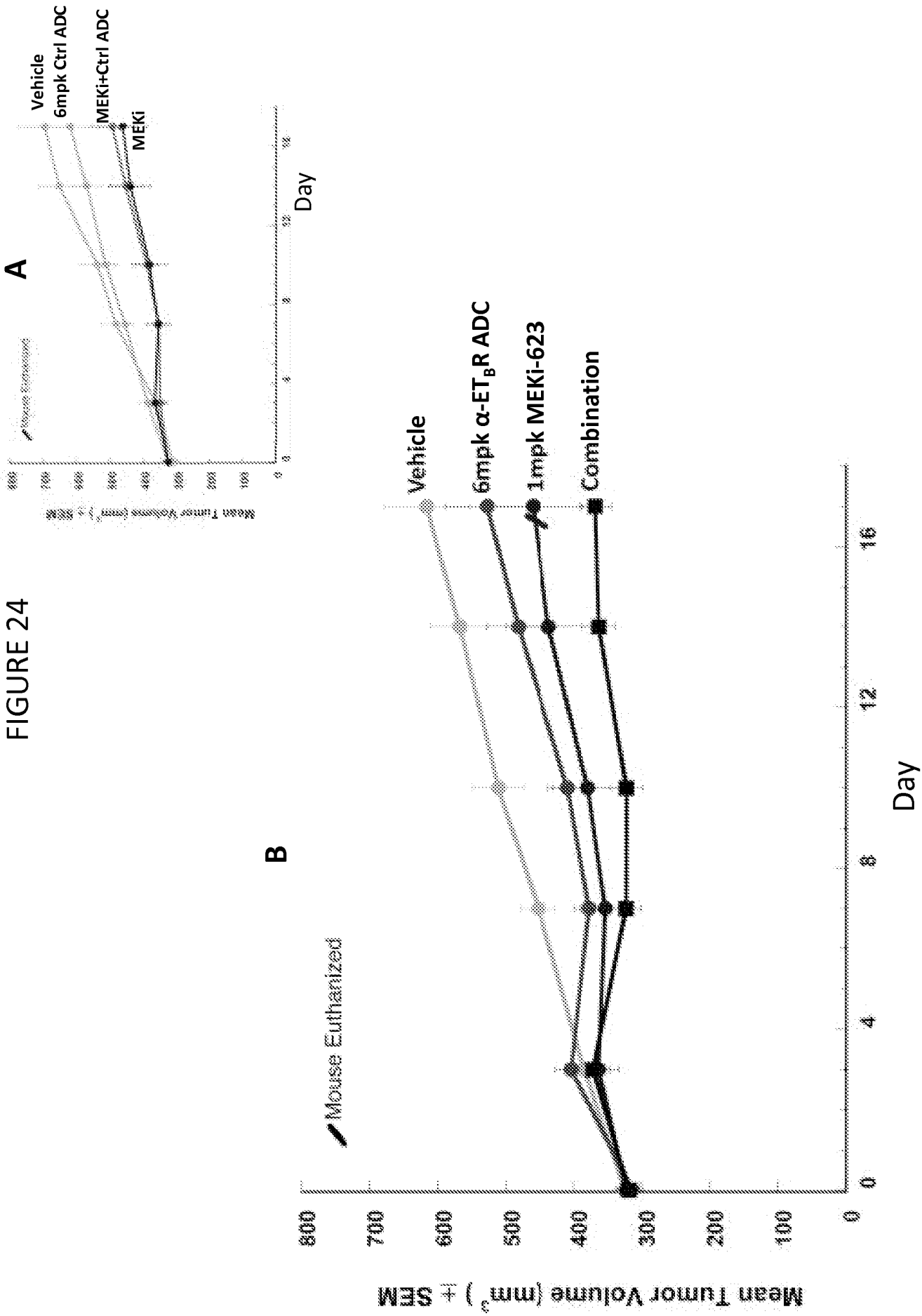

A
Vehicle
6mpk Ctrl ADC
MEKi+Ctrl ADC
MEKi
Day
B
Mouse Euthanized
Vehicle
6mpk α-ETBR ADC
1mpk MEKi-623
Combination
Mean Tumor Volume (mm3) ± SEM
800
700
600
500
400
300
200
100
0
4
8
12
16
Day

FIGURE 25

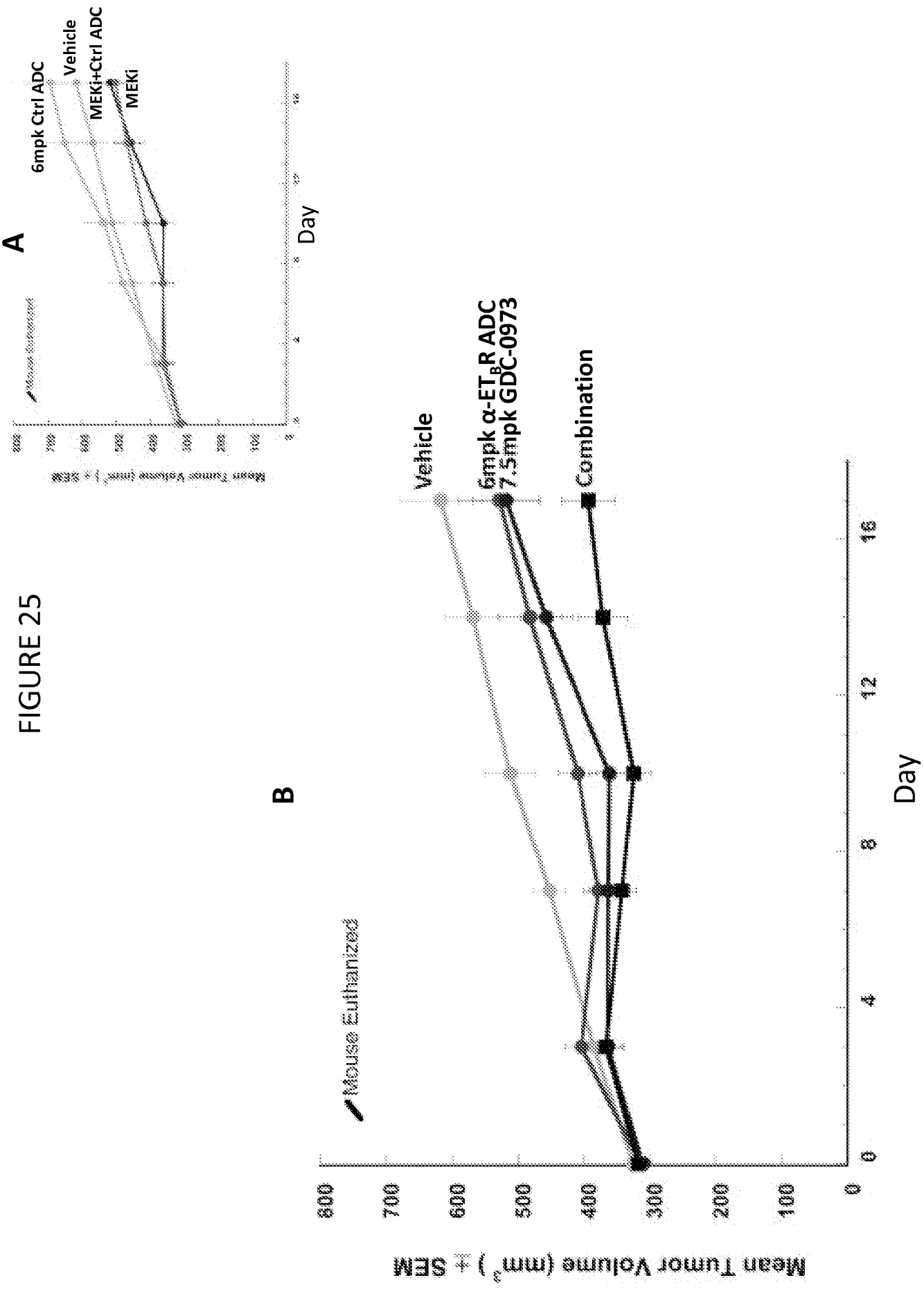

A
6mpk Ctrl ADC
Vehicle
MEKi+Ctrl ADC
MEKi
Day
B
Vehicle
6mpk α-ETBR ADC
7.5mpk GDC-0973
Combination
Mouse Euthanized
Mean Tumor Volume (mm3) ± SEM
Day
800
700
600
500
400
300
200
100
0
4
8
12
16

FIGURE 26

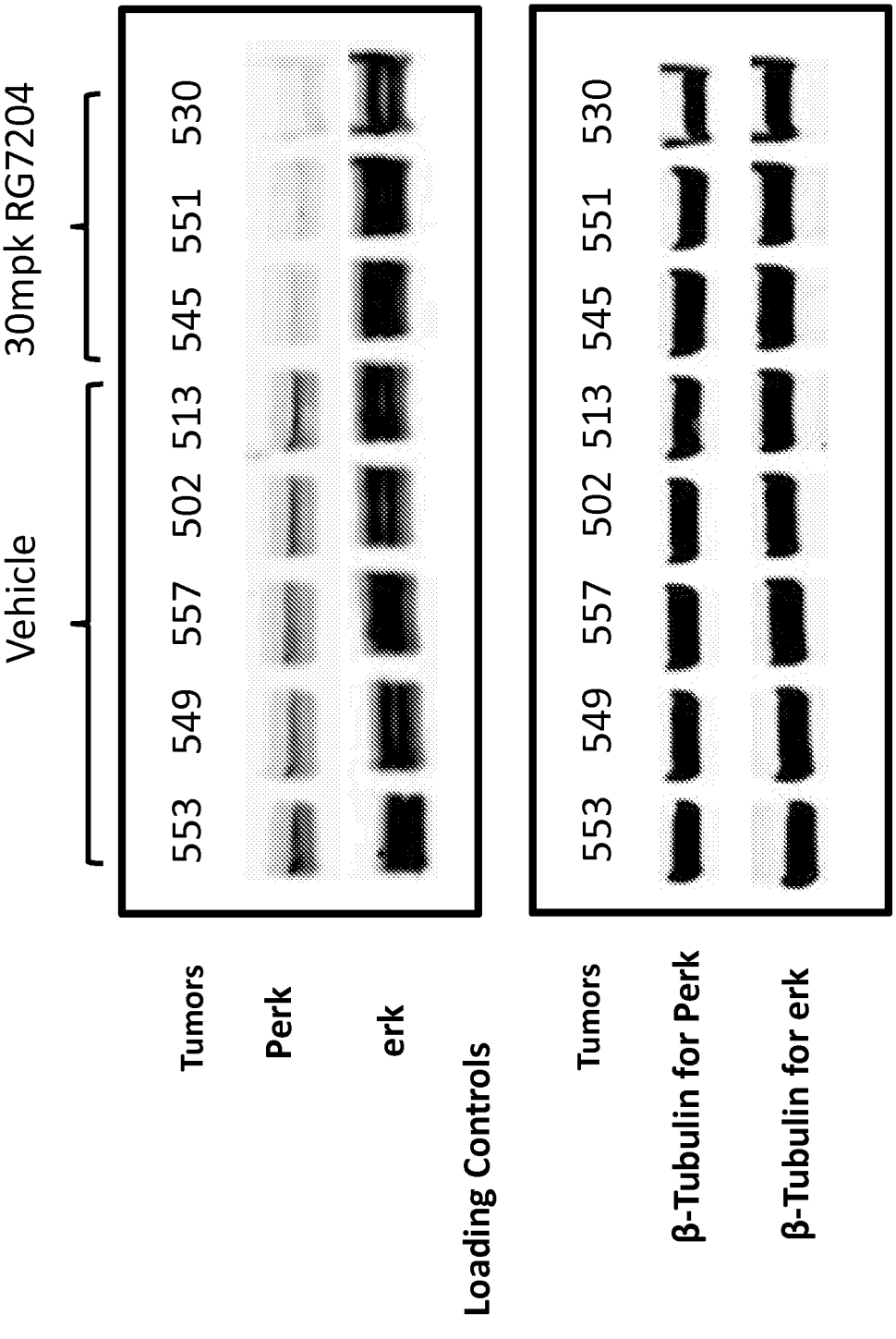
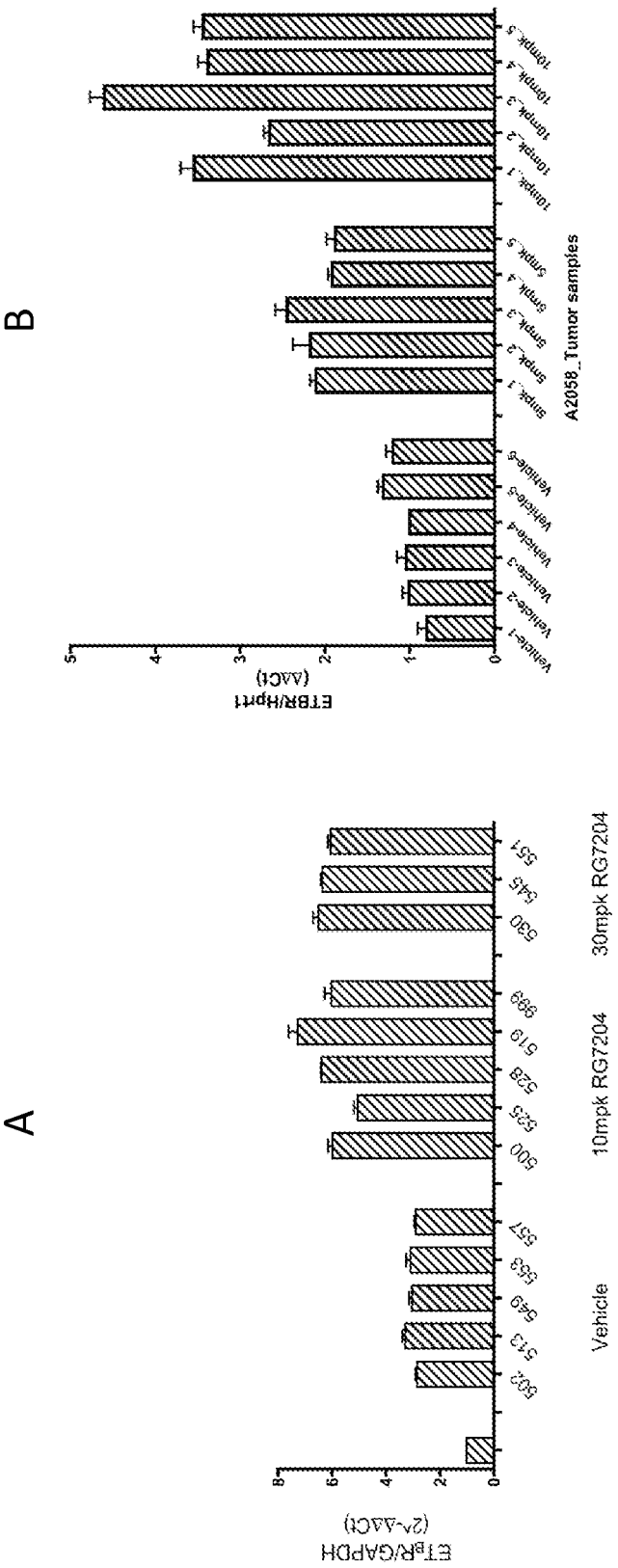

Vehicle
30mpk RG7204
553 549 557 502 513 545 551 530
Tumors
Perk
erk
Loading Controls
Tumors
β-Tubulin for Perk
β-Tubulin for erk

FIGURE 27


A
B
ETBR/GAPDH
(2^-ΔΔCt)
Vehicle
10mpk RG7204
30mpk RG7204
ETBR/Hprt1
(ΔΔCt)
A2058_Tumor samples