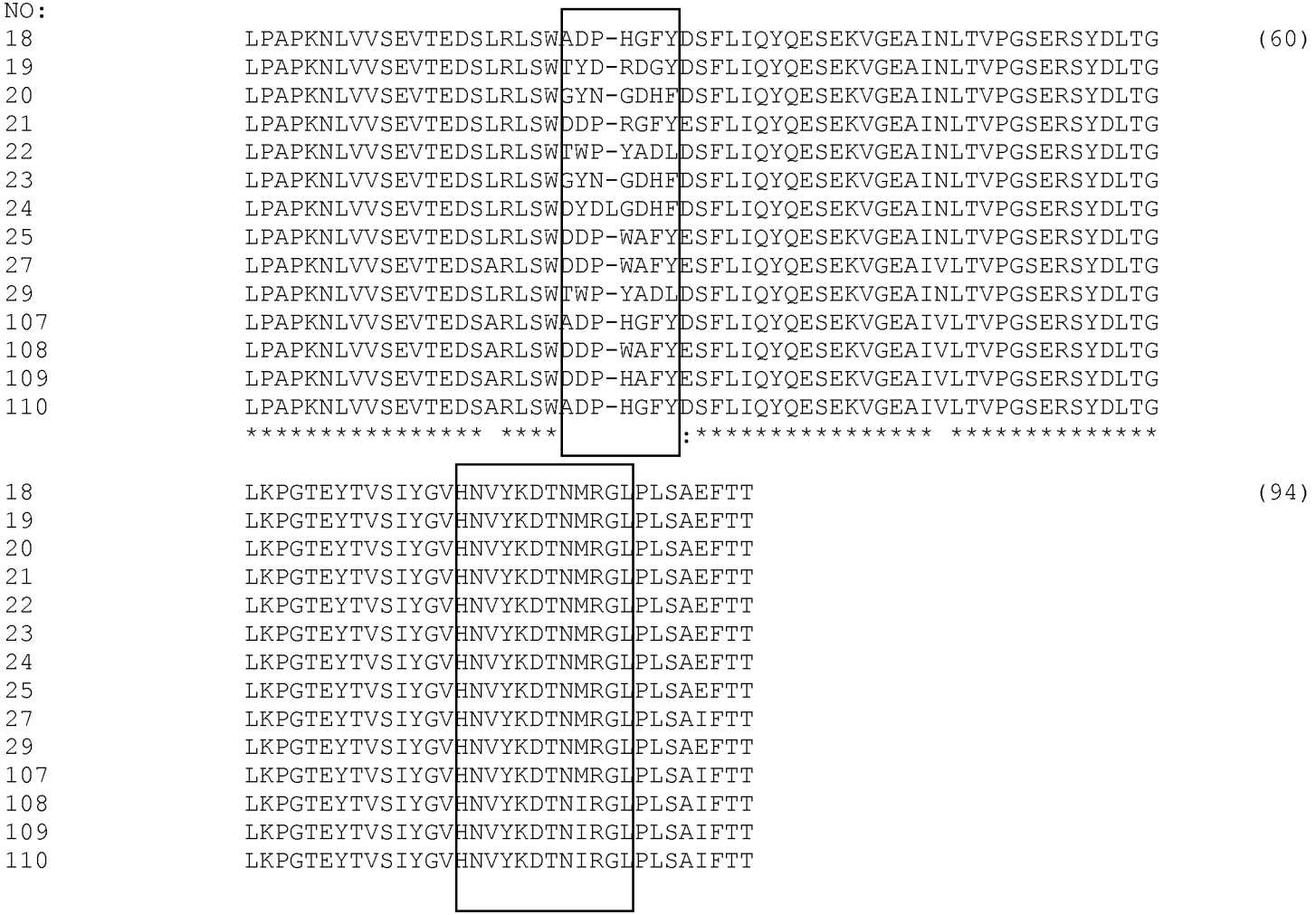
Figure 1A.


SEQ ID NO:
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19 LPAPKNLVVSEVTEDSLRLSWTYD-RDGYDSFLIQYQESEKVGEAINLTVPGSERSYDLTG
20 LPAPKNLVVSEVTEDSLRLSWGYN-GDHFDSFLIQYQESEKVGEAINLTVPGSERSYDLTG
21 LPAPKNLVVSEVTEDSLRLSWDDP-RGFYESFLIQYQESEKVGEAINLTVPGSERSYDLTG
22 LPAPKNLVVSEVTEDSLRLSWTWP-YADLDSFLIQYQESEKVGEAINLTVPGSERSYDLTG
23 LPAPKNLVVSEVTEDSLRLSWGYN-GDHFDSFLIQYQESEKVGEAINLTVPGSERSYDLTG
24 LPAPKNLVVSEVTEDSLRLSWDYDLGDHFDSFLIQYQESEKVGEAINLTVPGSERSYDLTG
25 LPAPKNLVVSEVTEDSLRLSWDDP-WAFYESFLIQYQESEKVGEAINLTVPGSERSYDLTG
27 LPAPKNLVVSEVTEDSARLSWDDP-WAFYESFLIQYQESEKVGEAIVLTVPGSERSYDLTG
29 LPAPKNLVVSEVTEDSLRLSWTWP-YADLDSFLIQYQESEKVGEAINLTVPGSERSYDLTG
107 LPAPKNLVVSEVTEDSARLSWADP-HGFYDSFLIQYQESEKVGEAIVLTVPGSERSYDLTG
108 LPAPKNLVVSEVTEDSARLSWDDP-WAFYESFLIQYQESEKVGEAIVLTVPGSERSYDLTG
109 LPAPKNLVVSEVTEDSARLSWDDP-HAFYESFLIQYQESEKVGEAIVLTVPGSERSYDLTG
110 LPAPKNLVVSEVTEDSARLSWADP-HGFYDSFLIQYQESEKVGEAIVLTVPGSERSYDLTG
18 LKPGTEYTVSIYGVHNVYKDTNMRGLPLSAEFTT (94)
19 LKPGTEYTVSIYGVHNVYKDTNMRGLPLSAEFTT
20 LKPGTEYTVSIYGVHNVYKDTNMRGLPLSAEFTT
21 LKPGTEYTVSIYGVHNVYKDTNMRGLPLSAEFTT
22 LKPGTEYTVSIYGVHNVYKDTNMRGLPLSAEFTT
23 LKPGTEYTVSIYGVHNVYKDTNMRGLPLSAEFTT
24 LKPGTEYTVSIYGVHNVYKDTNMRGLPLSAEFTT
25 LKPGTEYTVSIYGVHNVYKDTNMRGLPLSAEFTT
27 LKPGTEYTVSIYGVHNVYKDTNMRGLPLSAIFTT
29 LKPGTEYTVSIYGVHNVYKDTNMRGLPLSAEFTT
107 LKPGTEYTVSIYGVHNVYKDTNMRGLPLSAIFTT
108 LKPGTEYTVSIYGVHNVYKDTNIRGLPLSAIFTT
109 LKPGTEYTVSIYGVHNVYKDTNIRGLPLSAIFTT
110 LKPGTEYTVSIYGVHNVYKDTNIRGLPLSAIFTT

```
             ************** . *   :   ***** ***
```

Figure 1B

```
SEQ ID
NO:

26          LPAPKNLVVSEVTEDSLRLSWTAP-DAAFDSFLIQYQESEKVGEAINLTVPGSERSYDLTG     (60)
28          LPAPKNLVVSEVTEDSARLSWTAP-DAAFDSFLIQYQESEKVGEAIVLTVPGSERSYDLTG
            ***************** ***********************************************

26          LKPGTEYTVSIYGVLGSYVFEHDVMLPLSAEFTT                                (94)
28          LKPGTEYTVSIYGVLGSYVFEHDVMLPLSAIFTT
            ***************************************** ***
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Figure 2.

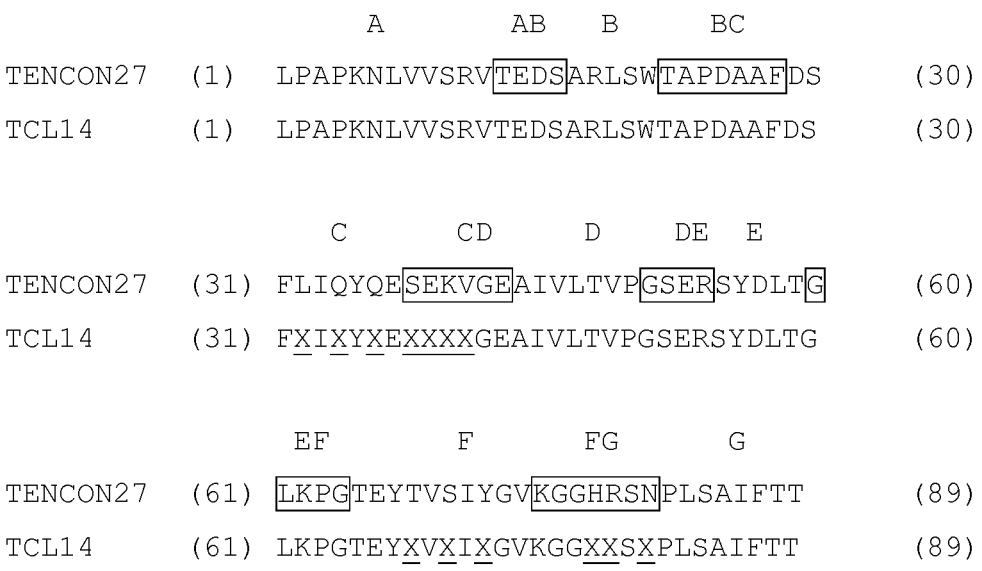

A AB B BC
TENCON27 (1) LPAPKNLVVSRVTEDSARLSWTAPDAAFDS (30)
TCL14 (1) LPAPKNLVVSRVTEDSARLSWTAPDAAFDS (30)
C CD D DE E
TENCON27 (31) FLIQYQESEKVGEAIVLTVPGSERSYDLTG (60)
TCL14 (31) FXIXYXEXXXXGEAIVLTVPGSERSYDLTG (60)
EF F FG G
TENCON27 (61) LKPGTEYTVSIYGVKGGHRSNPLSAIFTT (89)
TCL14 (61) LKPGTEYXVXIXGVKGGXXSXPLSAIFTT (89)

Figure 3.

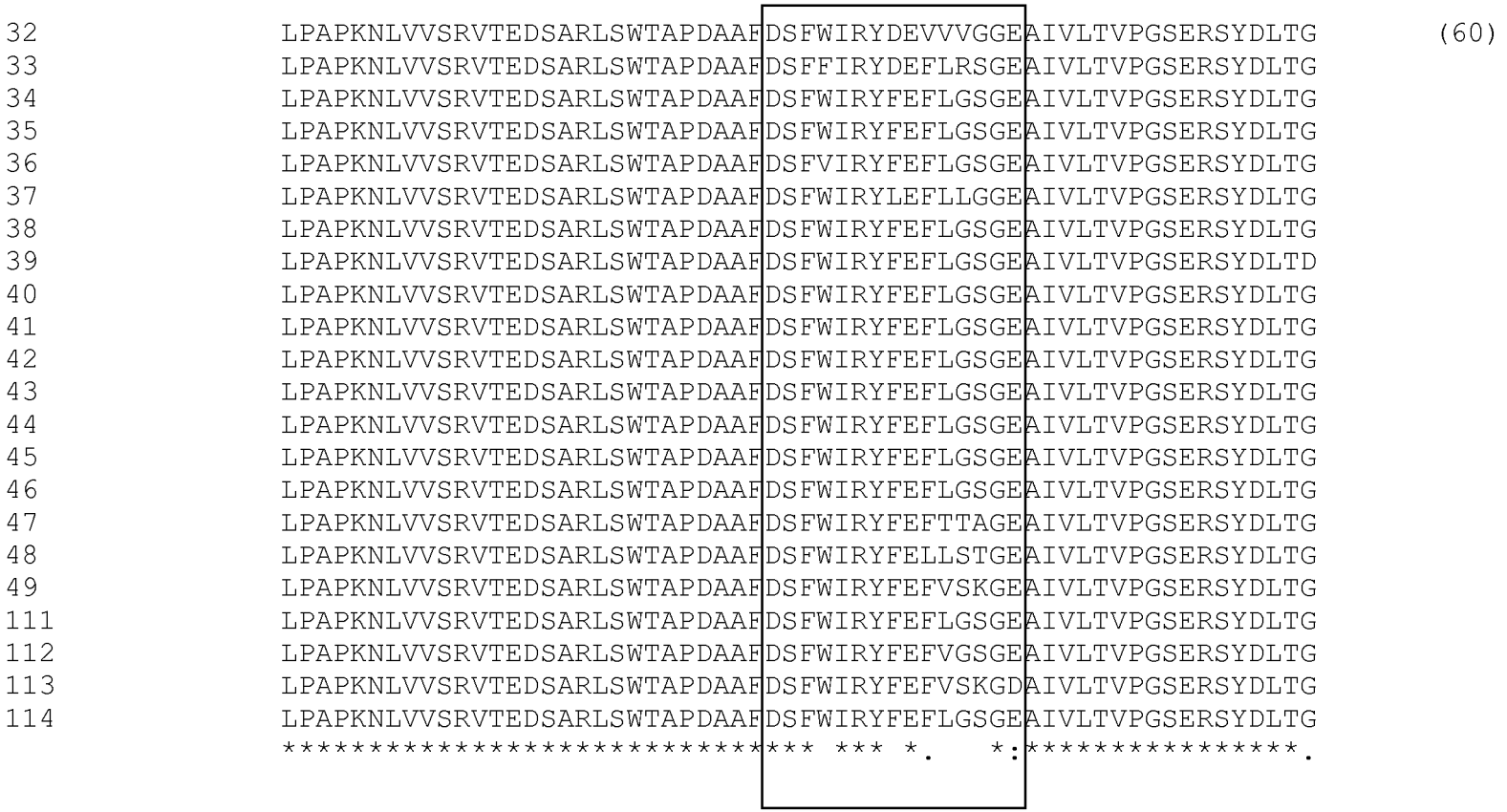
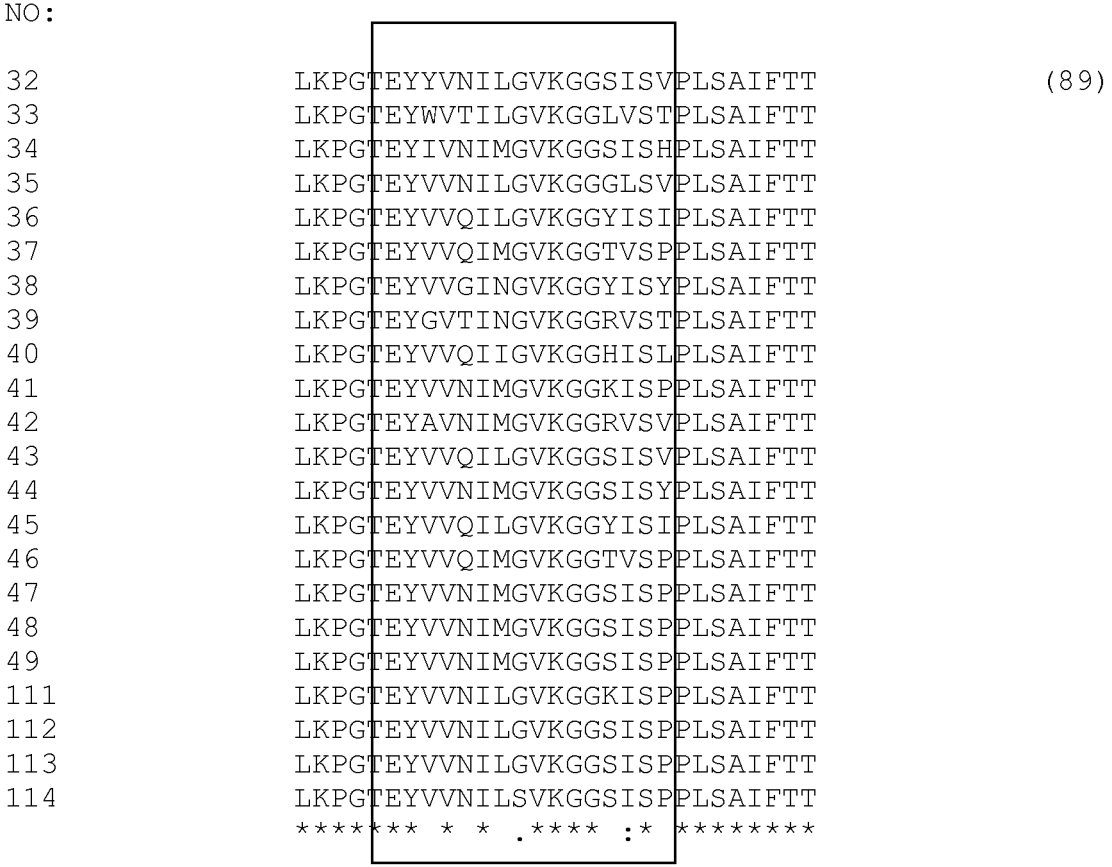

SEQ ID
NO:
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34 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTG
35 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTG
36 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFVIRYFEFLGSGEAIVLTVPGSERSYDLTG
37 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYLEFLLGGEAIVLTVPGSERSYDLTG
38 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTG
39 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTD
40 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTG
41 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTG
42 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTG
43 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTG
44 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTG
45 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTG
46 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTG
47 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFTTAGEAIVLTVPGSERSYDLTG
48 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFELLSTGEAIVLTVPGSERSYDLTG
49 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFVSKGEAIVLTVPGSERSYDLTG
111 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTG
112 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFVGSGEAIVLTVPGSERSYDLTG
113 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFVSKGDAIVLTVPGSERSYDLTG
114 LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTG

Figure 3.


SEQ ID NO:
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33 LKPGTEYWVTILGVKGGLVSTPLSAIFTT
34 LKPGTEYIVNIMGVKGGSISHPLSAIFTT
35 LKPGTEYVVNILGVKGGGLSVPLSAIFTT
36 LKPGTEYVVQILGVKGGYISIPLSAIFTT
37 LKPGTEYVVQIMGVKGGTVSPPLSAIFTT
38 LKPGTEYVVGINGVKGGYISYPLSAIFTT
39 LKPGTEYGVTINGVKGGRVSTPLSAIFTT
40 LKPGTEYVVQIIGVKGGHISLPLSAIFTT
41 LKPGTEYVVNIMGVKGGKISPPLSAIFTT
42 LKPGTEYAVNIMGVKGGRVSVPLSAIFTT
43 LKPGTEYVVQILGVKGGSISVPLSAIFTT
44 LKPGTEYVVNIMGVKGGSISYPLSAIFTT
45 LKPGTEYVVQILGVKGGYISIPLSAIFTT
46 LKPGTEYVVQIMGVKGGTVSPPLSAIFTT
47 LKPGTEYVVNIMGVKGGSISPPLSAIFTT
48 LKPGTEYVVNIMGVKGGSISPPLSAIFTT
49 LKPGTEYVVNIMGVKGGSISPPLSAIFTT
111 LKPGTEYVVNILGVKGGKISPPLSAIFTT
112 LKPGTEYVVNILGVKGGSISPPLSAIFTT
113 LKPGTEYVVNILGVKGGSISPPLSAIFTT
114 LKPGTEYVVNILSVKGGSISPPLSAIFTT
******* * * .**** :* ********

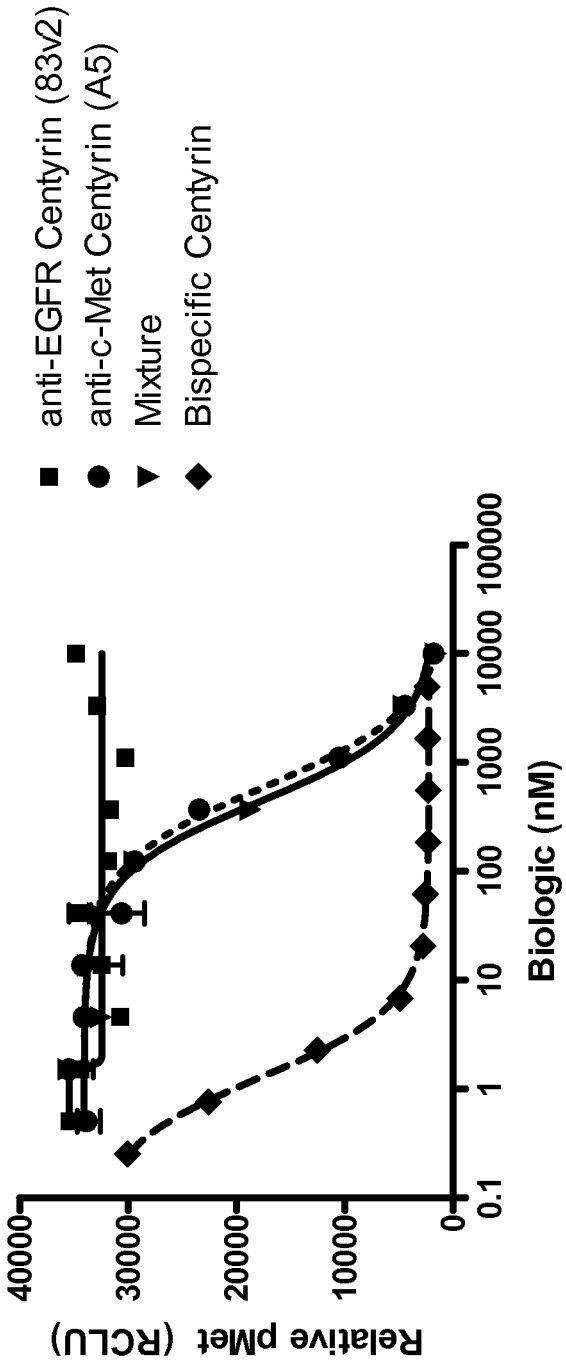
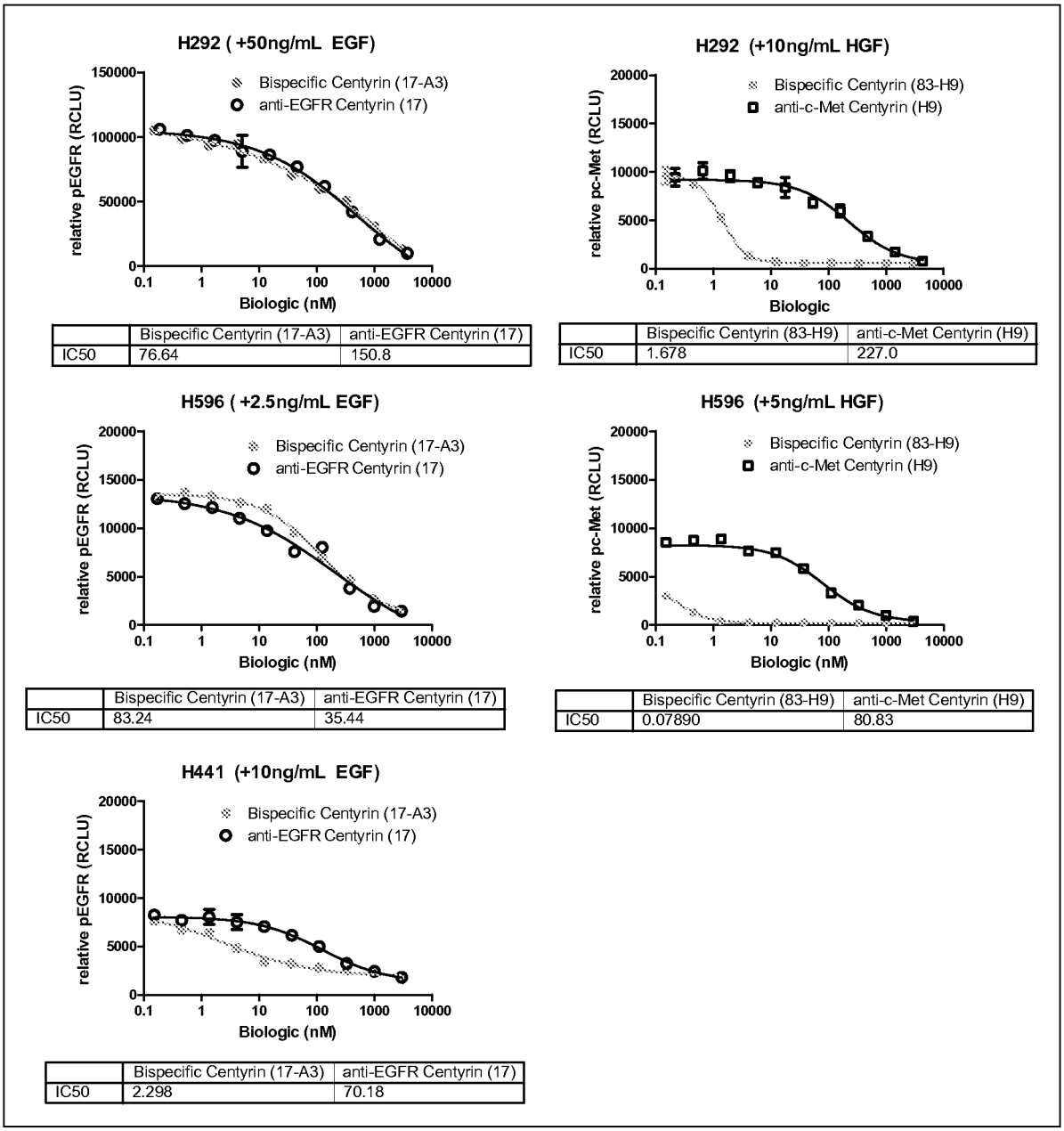

anti-EGFR Centyrin (83v2)
anti-c-Met Centyrin (A5)
Mixture
Bispecific Centyrin
Relative pMet (RCLU)
40000
30000
20000
10000
0
0.1
1
10
100
1000
10000
100000
Biologic (nM)

Figure 4.

Figure 5.



	Bispecific Centyrin (17-A3)	anti-EGFR Centyrin (17)
IC50	76.64	150.8

	Bispecific Centyrin (83-H9)	anti-c-Met Centyrin (H9)
IC50	1.678	227.0

	Bispecific Centyrin (17-A3)	anti-EGFR Centyrin (17)
IC50	83.24	35.44

	Bispecific Centyrin (83-H9)	anti-c-Met Centyrin (H9)
IC50	0.07890	80.83

	Bispecific Centyrin (17-A3)	anti-EGFR Centyrin (17)
IC50	2.298	70.18

Figure 6.

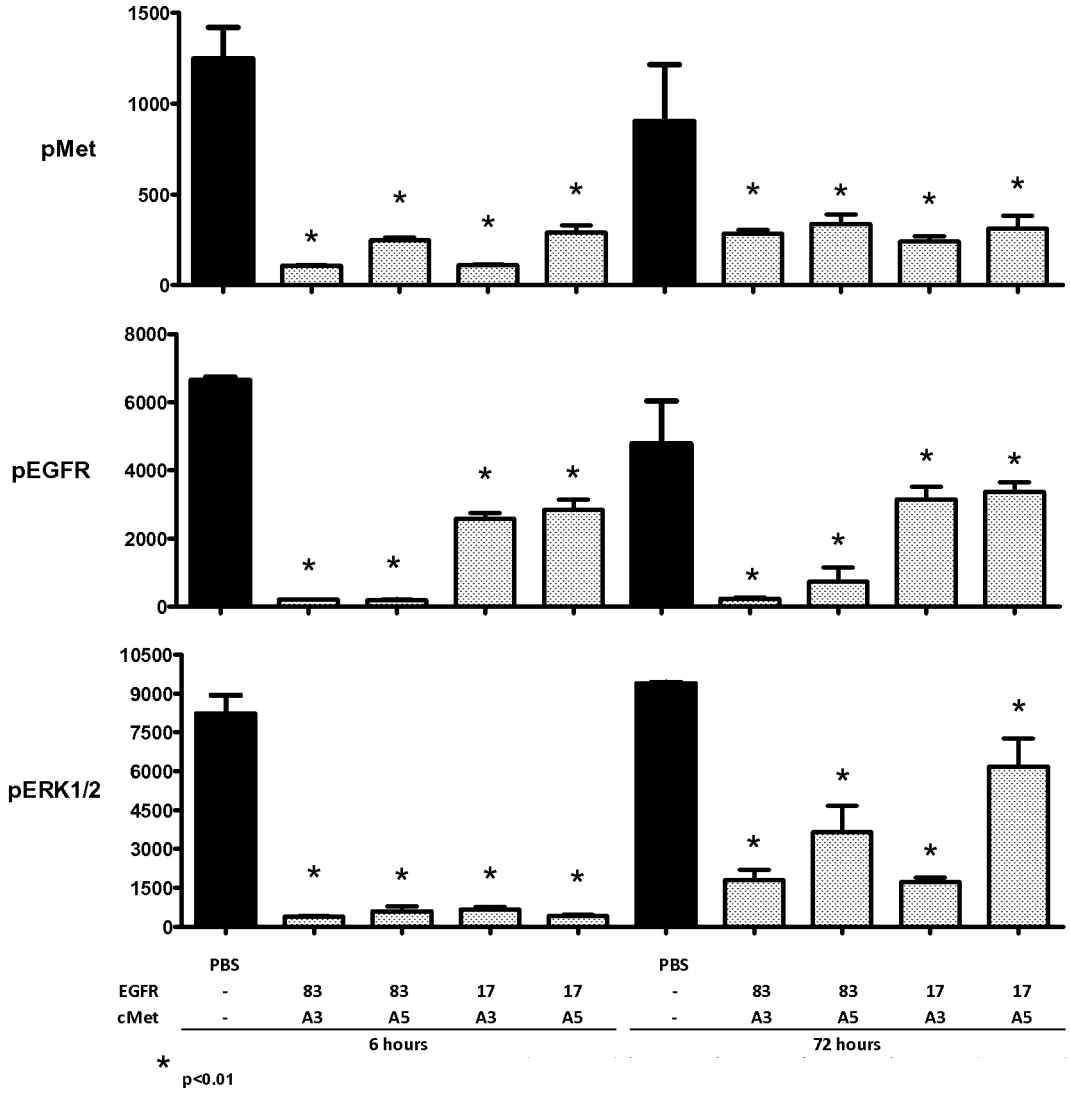
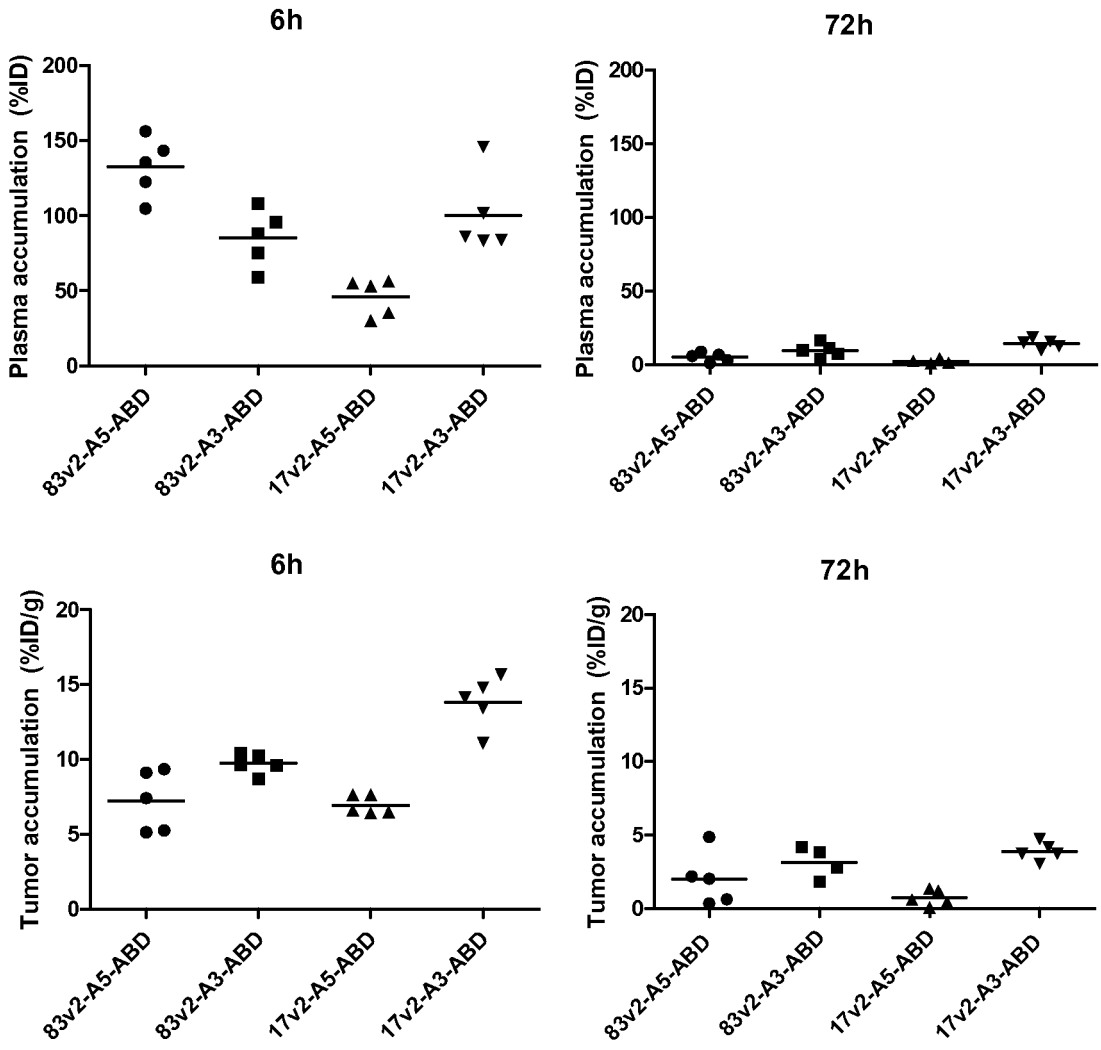

pMet
pEGFR
pERK1/2
1500
1000
500
0
8000
6000
4000
2000
0
10500
9000
7500
6000
4500
3000
1500
0
PBS
EGFR - 83 83 17 17 - 83 83 17 17
cMet - A3 A5 A3 A5 - A3 A5 A3 A5
6 hours
72 hours
* p<0.01

Figure 7.


6h
72h
Plasma accumulation (%ID)
Tumor accumulation (%ID/g)
200
150
100
50
0
20
15
10
5
0
83v2-A5-ABD
83v2-A3-ABD
17v2-A5-ABD
17v2-A3-ABD

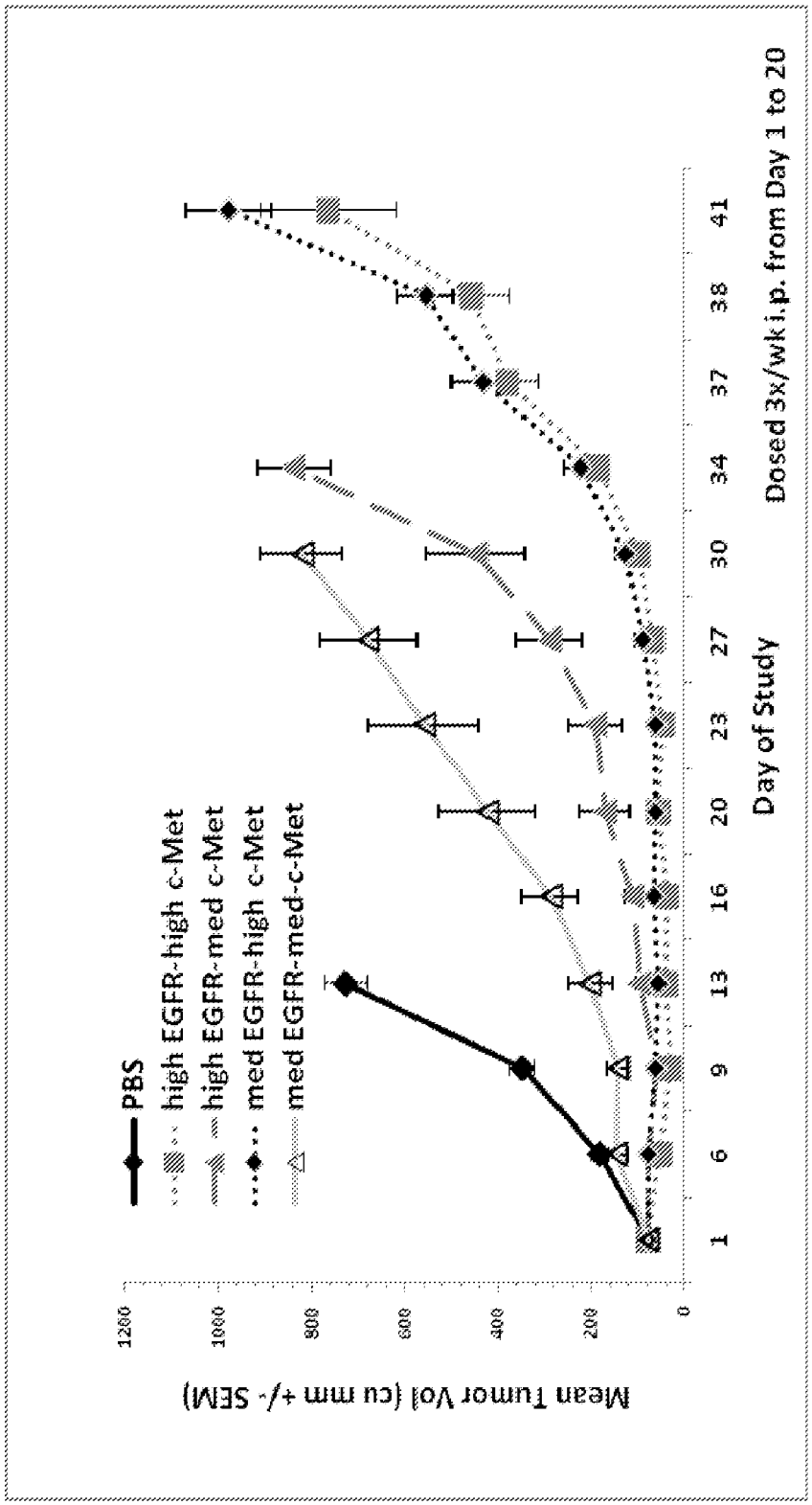

Mean Tumor Vol (cu mm +/- SEM)
1200
1000
800
600
400
200
0
1
6
9
13
16
20
23
27
30
34
37
38
41
Day of Study
Dosed 3x/wk i.p. from Day 1 to 20
PBS
high EGFR-high c-Met
high EGFR-med c-Met
med EGFR-high c-Met
med EGFR-med-c-Met

Figure 8.

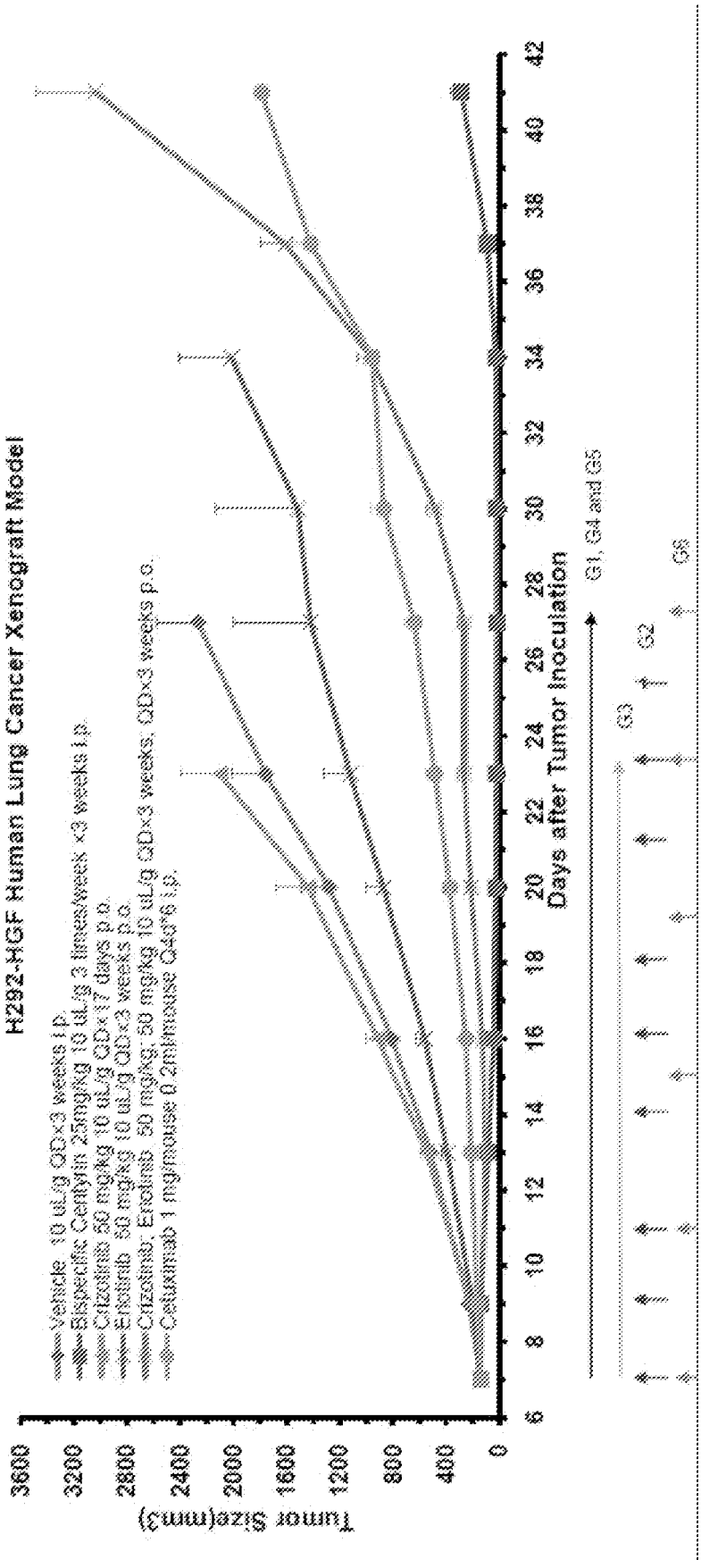

H292-HGF Human Lung Cancer Xenograft Model
Vehicle 10 uL/g QDx3 weeks i.p.
Bispecific Centyrin 25mg/kg 10 uL/g 3 times/week x3 weeks i.p.
Crizotinib 50 mg/kg 10 uL/g QDx17 days p.o.
Erlotinib 50 mg/kg 10 uL/g QDx3 weeks p.o.
Crizotinib; Erlotinib 50 mg/kg; 50 mg/kg 10 uL/g QDx3 weeks, QDx3 weeks p.o.
Cetuximab 1 mg/mouse 0.2ml/mouse Q4d*6 i.p.
Tumor Size(mm3)
3600
3200
2800
2400
2000
1600
1200
800
400
0
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
Days after Tumor Inoculation
G1, G4 and G5
G3
G2
G6

Figure 9.

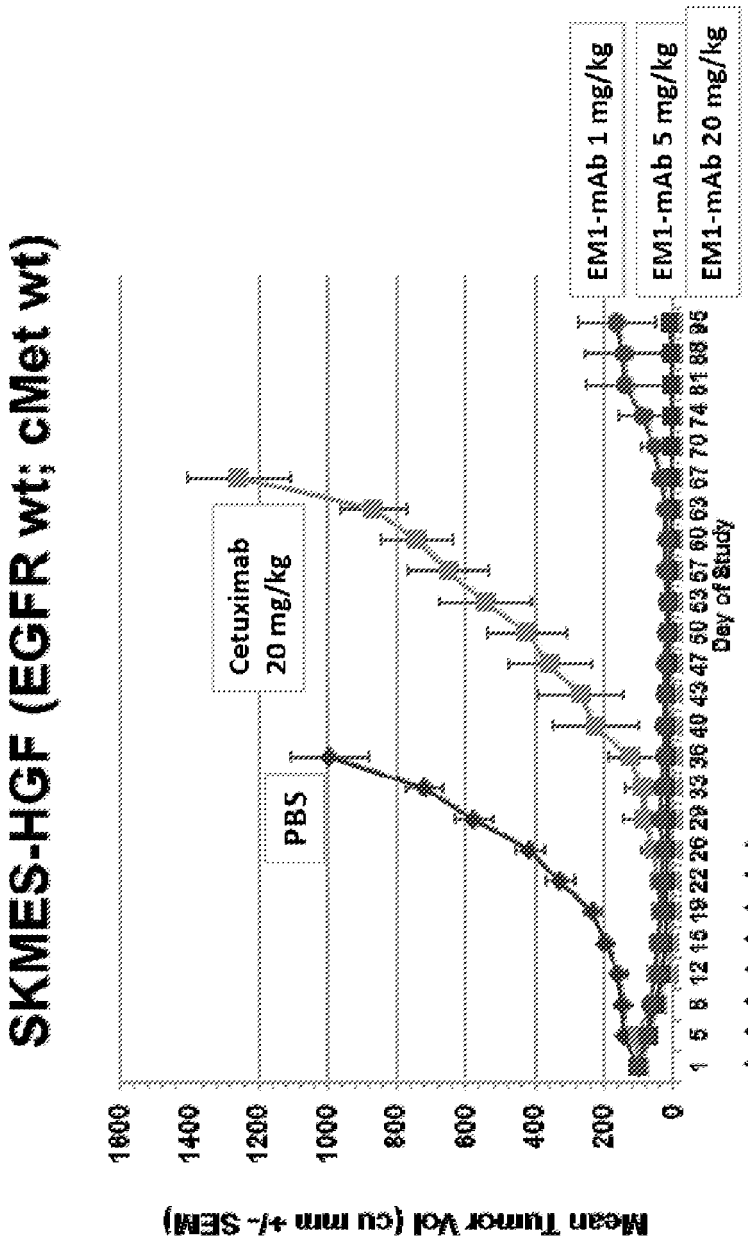

SKMES-HGF (EGFR wt; cMet wt)
Mean Tumor Vol (cu mm +/- SEM)
1800
1400
1200
1000
800
600
400
200
0
Cetuximab 20 mg/kg
PBS
EM1-mAb 1 mg/kg
EM1-mAb 5 mg/kg
EM1-mAb 20 mg/kg
1 5 8 12 15 19 22 26 29 33 36 40 43 47 50 53 57 60 63 67 70 74 81 88 95
Day of Study
Dosing:

Figure 10.

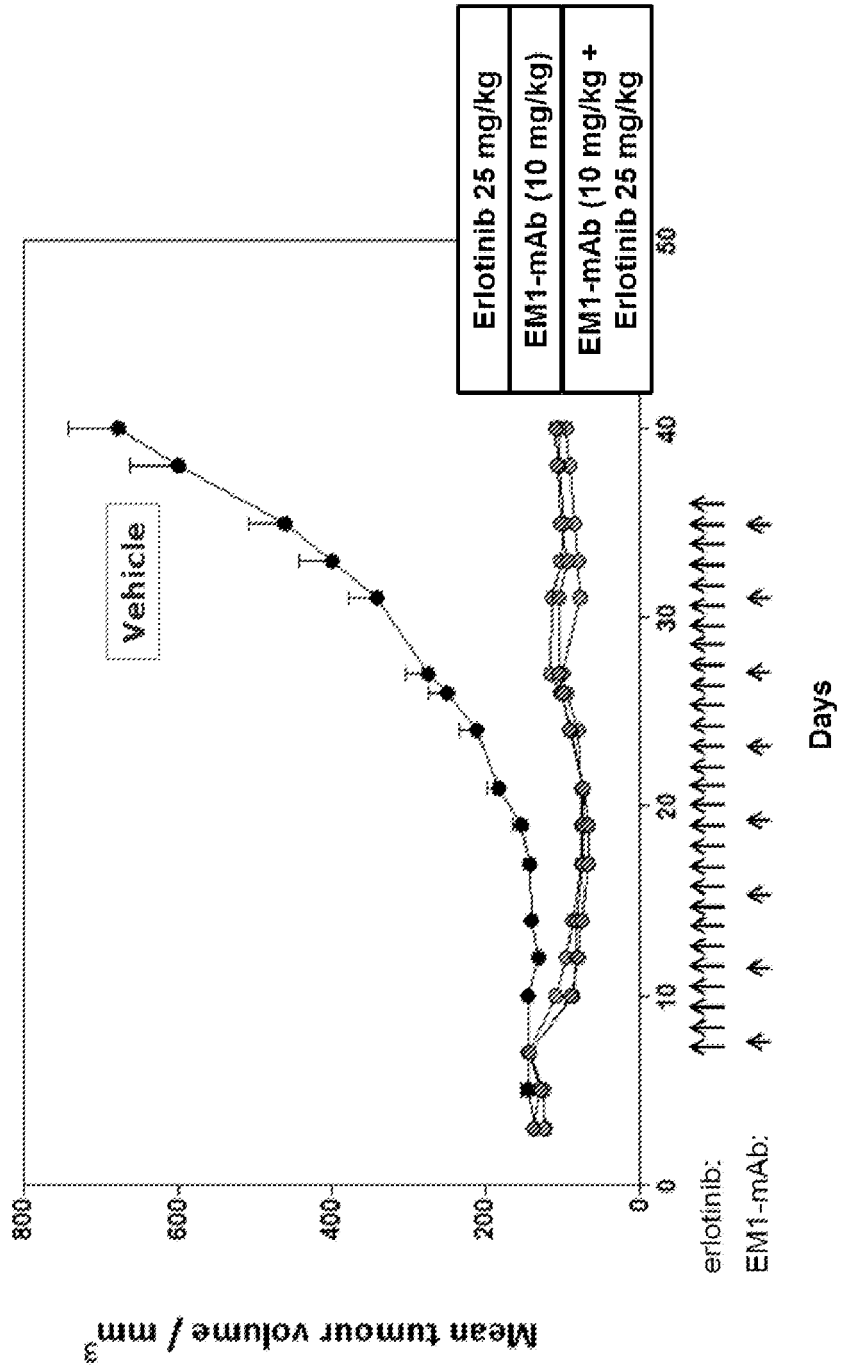

HCC827 (EGFR del (E746, A750))
Mean tumour volume / mm3
800
600
400
200
0
0
10
20
30
40
50
Days
erlotinib:
EM1-mAb:
Vehicle
Erlotinib 25 mg/kg
EM1-mAb (10 mg/kg)
EM1-mAb (10 mg/kg + Erlotinib 25 mg/kg

Figure 11.

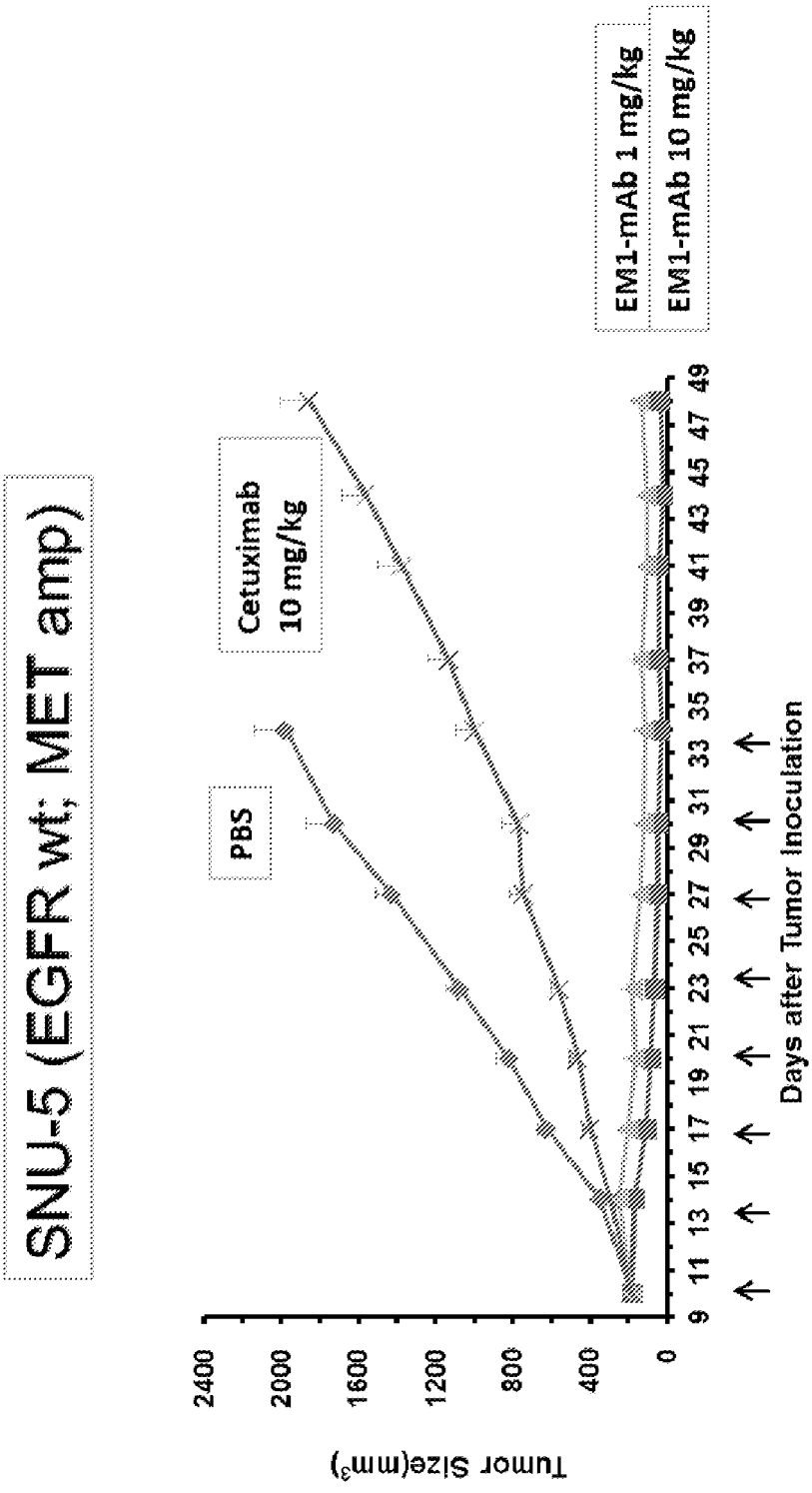

SNU-5 (EGFR wt; MET amp)
PBS
Cetuximab 10 mg/kg
EM1-mAb 1 mg/kg
EM1-mAb 10 mg/kg
Tumor Size(mm³)
2400
2000
1600
1200
800
400
0
9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49
Days after Tumor Inoculation

Figure 12.

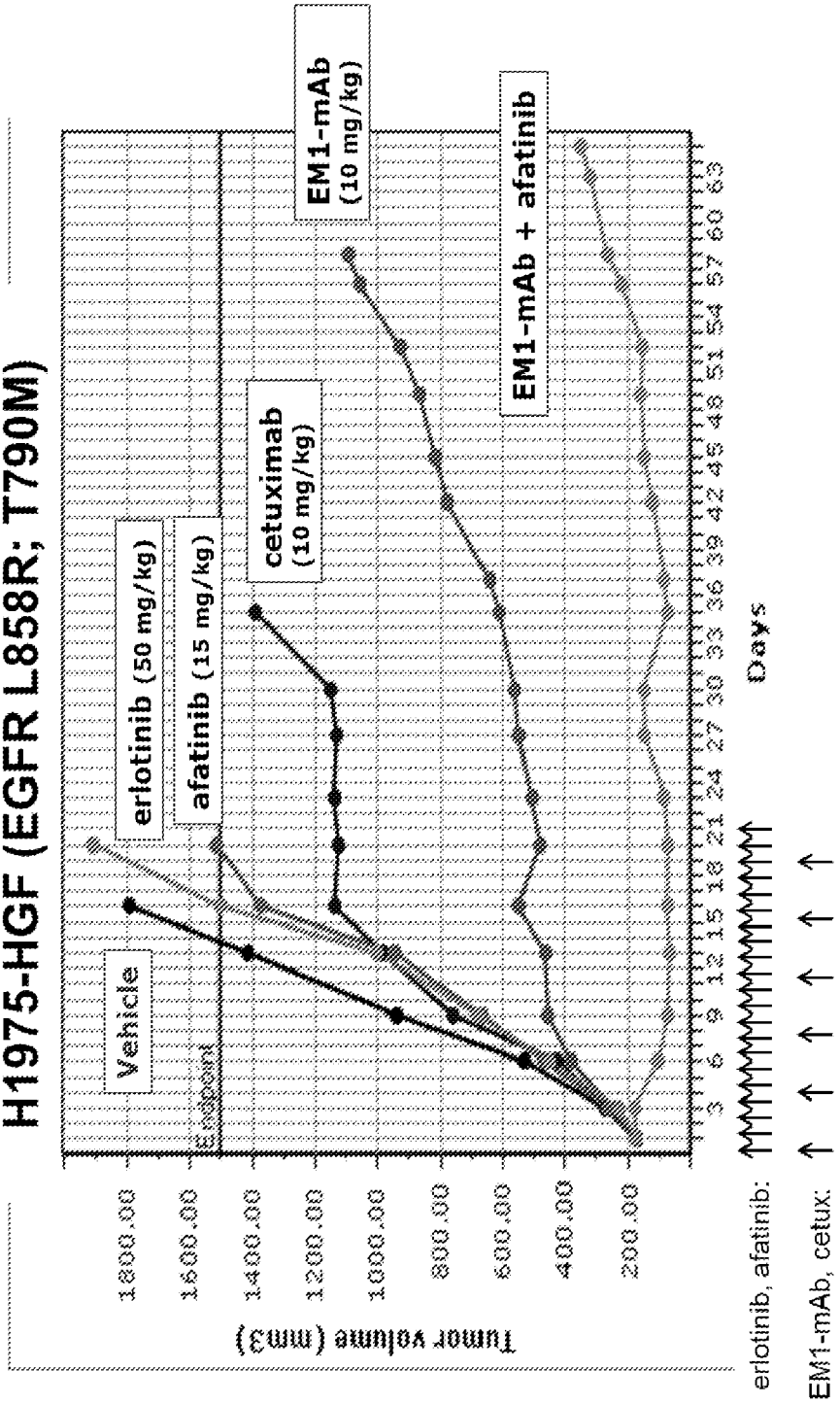

H1975-HGF (EGFR L858R; T790M)
Vehicle
erlotinib (50 mg/kg)
afatinib (15 mg/kg)
cetuximab (10 mg/kg)
EM1-mAb (10 mg/kg)
EM1-mAb + afatinib
Enrolment
Tumor volume (mm3)
1800.00
1600.00
1400.00
1200.00
1000.00
800.00
600.00
400.00
200.00
3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60 63
Days
erlotinib, afatinib:
EM1-mAb, cetux:

Figure 13.

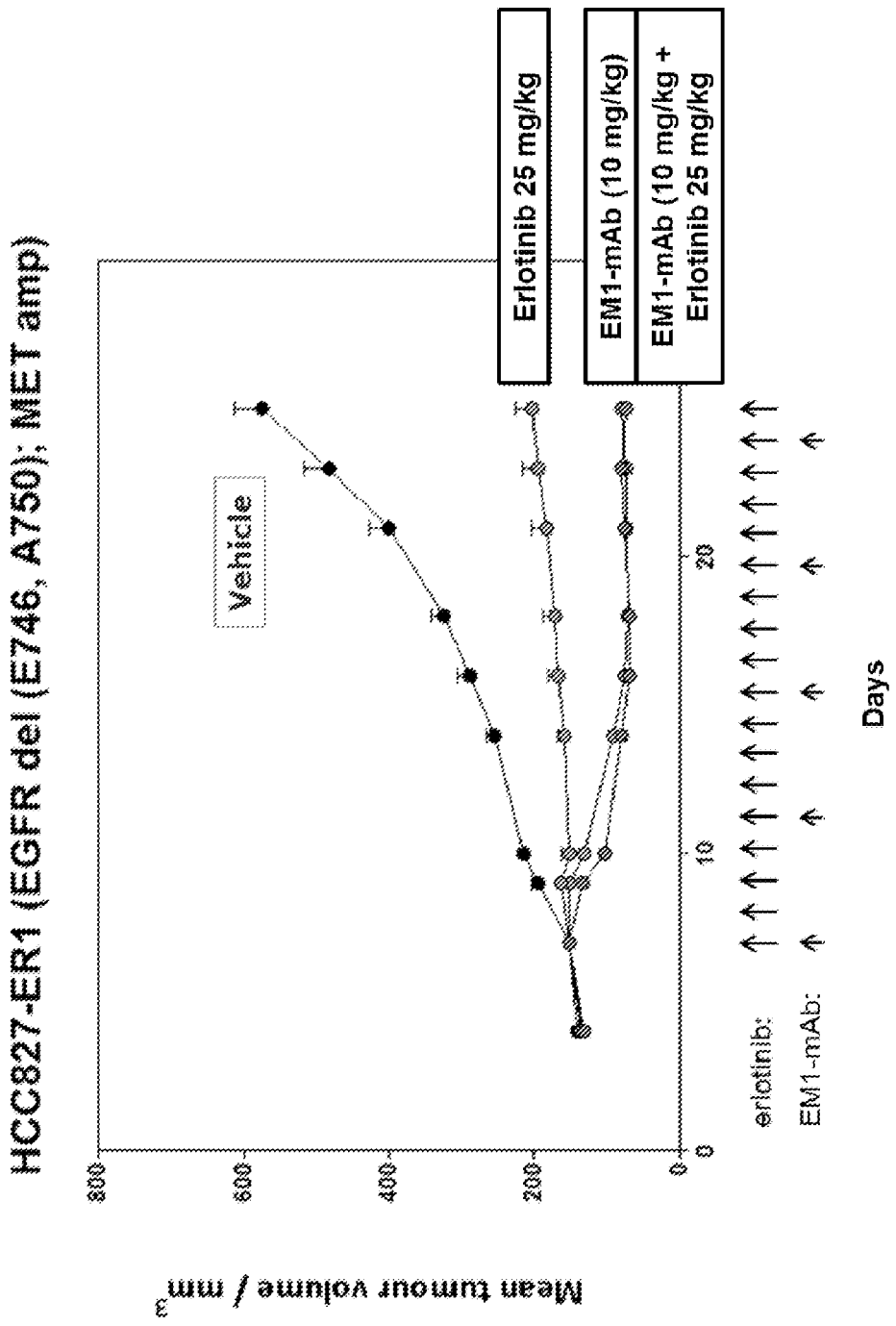

HCC827-ER1 (EGFR del (E746, A750); MET amp)
Mean tumour volume / mm3
800
600
400
200
0
0
10
20
Days
Vehicle
Erlotinib 25 mg/kg
EM1-mAb (10 mg/kg)
EM1-mAb (10 mg/kg + Erlotinib 25 mg/kg
erlotinib:
EM1-mAb:

Figure 14.

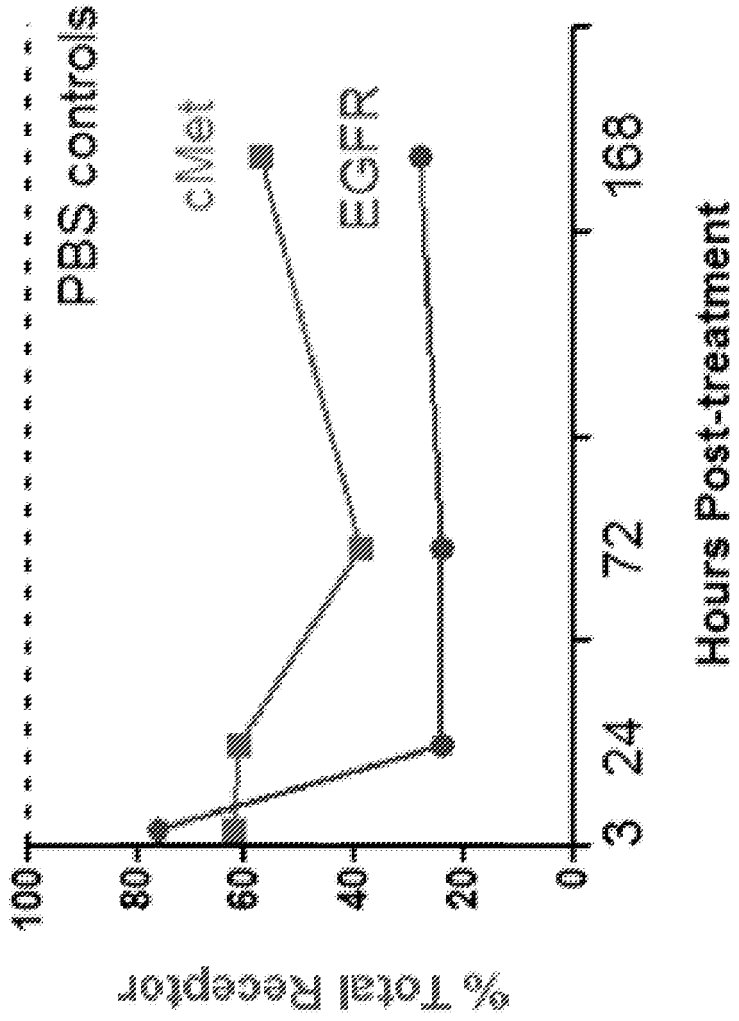

% Total Receptor
100
80
60
40
20
0
3
24
72
168
Hours Post-treatment
PBS controls
cMet
EGFR

Figure 15.

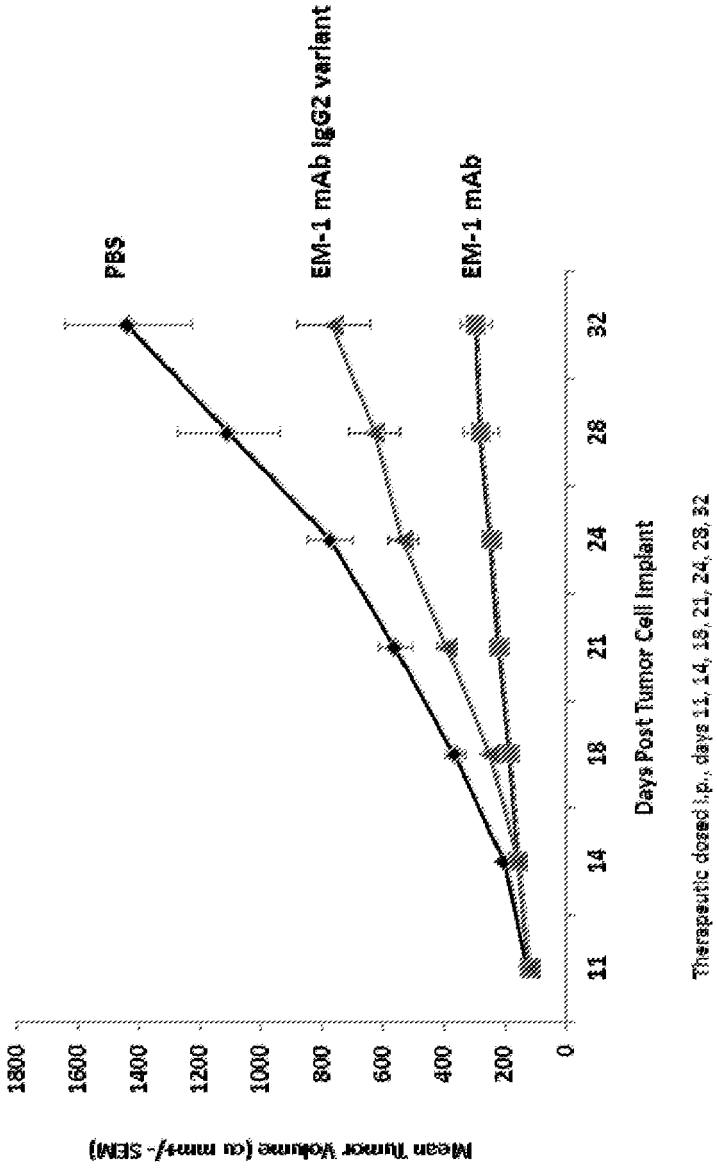

PBS
EM-1 mAb IgG2 variant
EM-1 mAb
Mean Tumor Volume (cu mm+/- SEM)
1800
1600
1400
1200
1000
800
600
400
200
0
11
14
18
21
24
28
32
Days Post Tumor Cell Implant
Therapeutic dosed i.p., days 11, 14, 18, 21, 24, 28, 32

Figure 16.