New PCT Patent Application
based on EP 10 17 0004.5
F. Hoffmann-La Roche AG
Our Ref.: S1945 PCT S3

Figure 1A

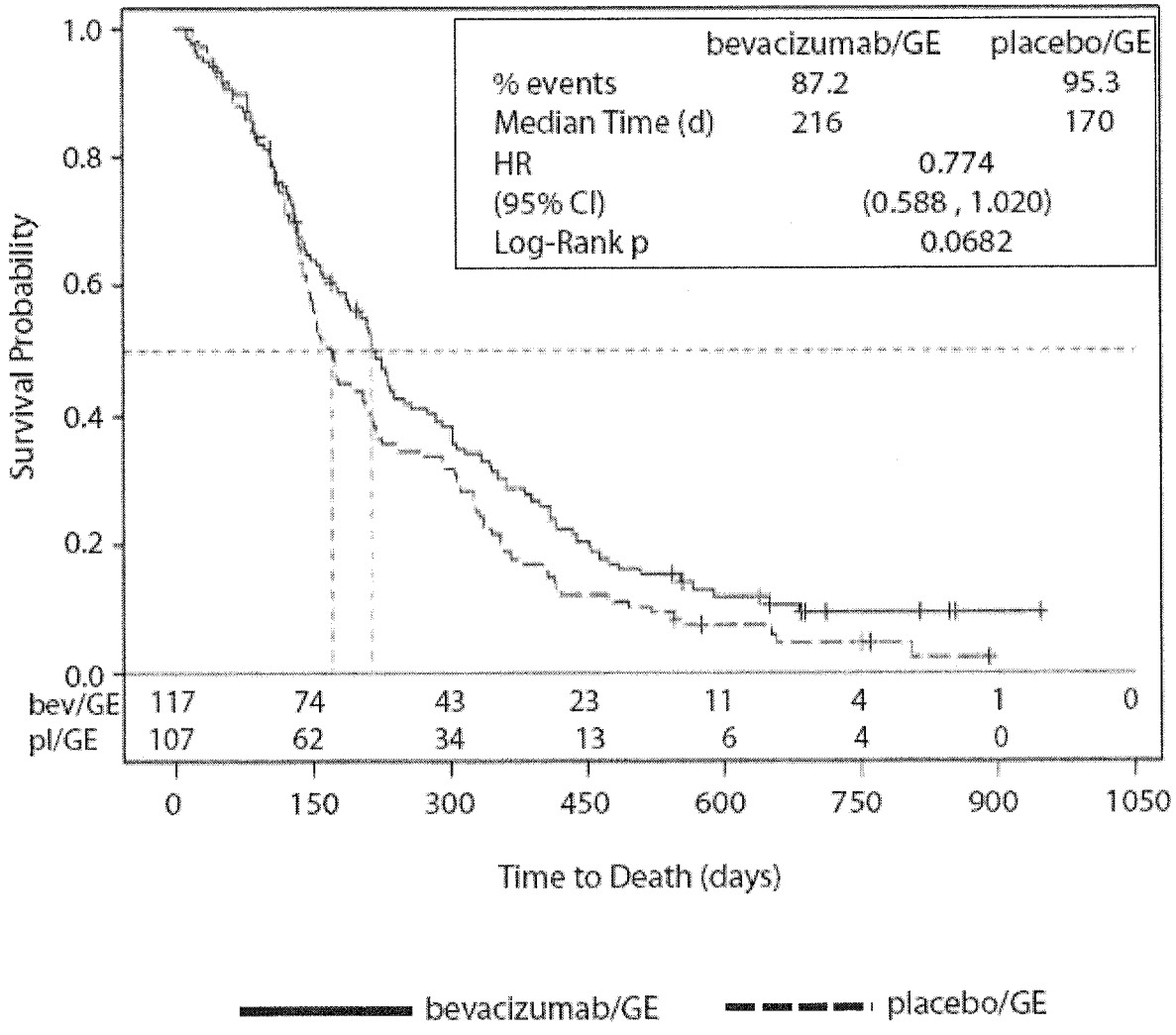


Figure 1B

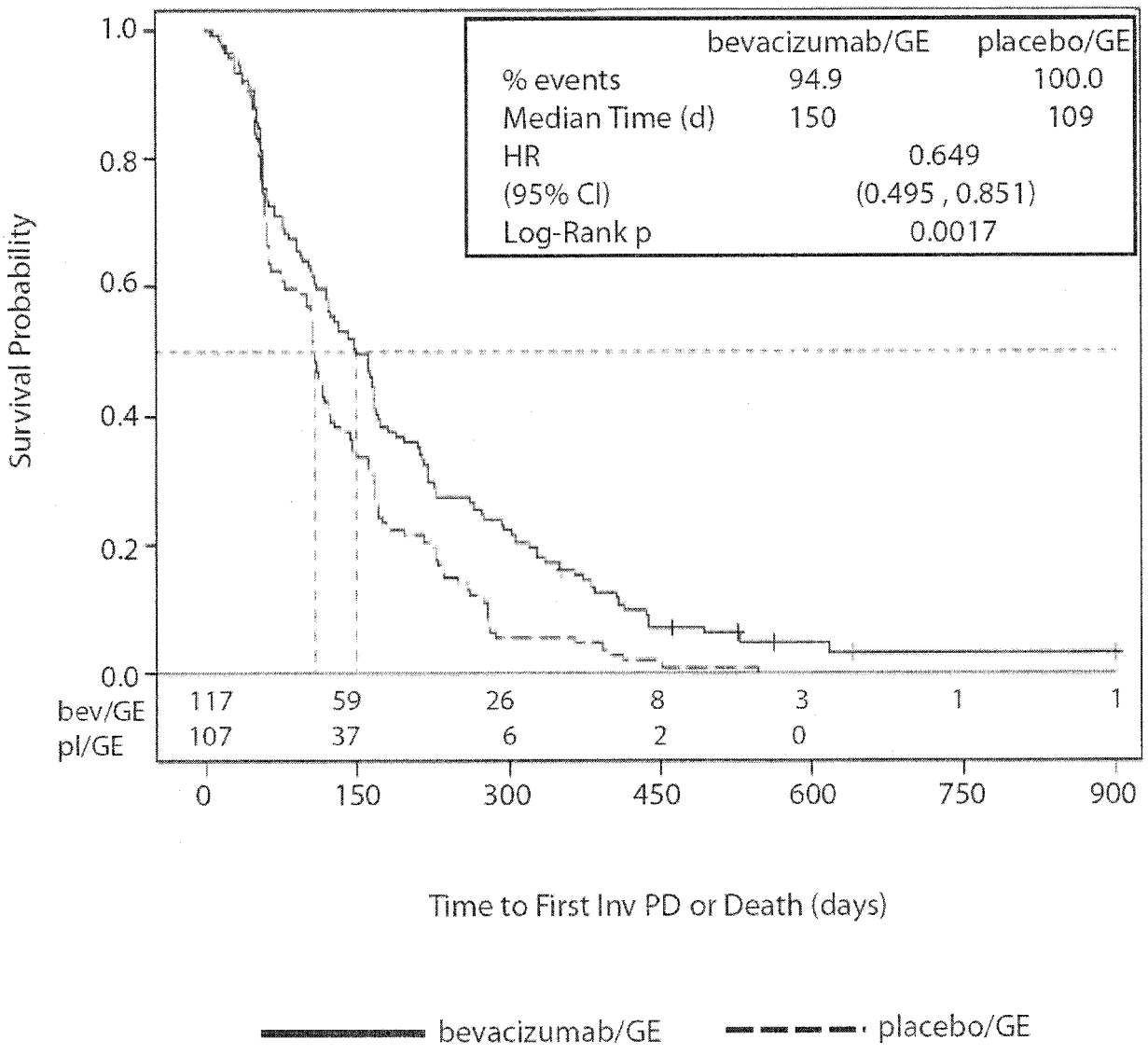
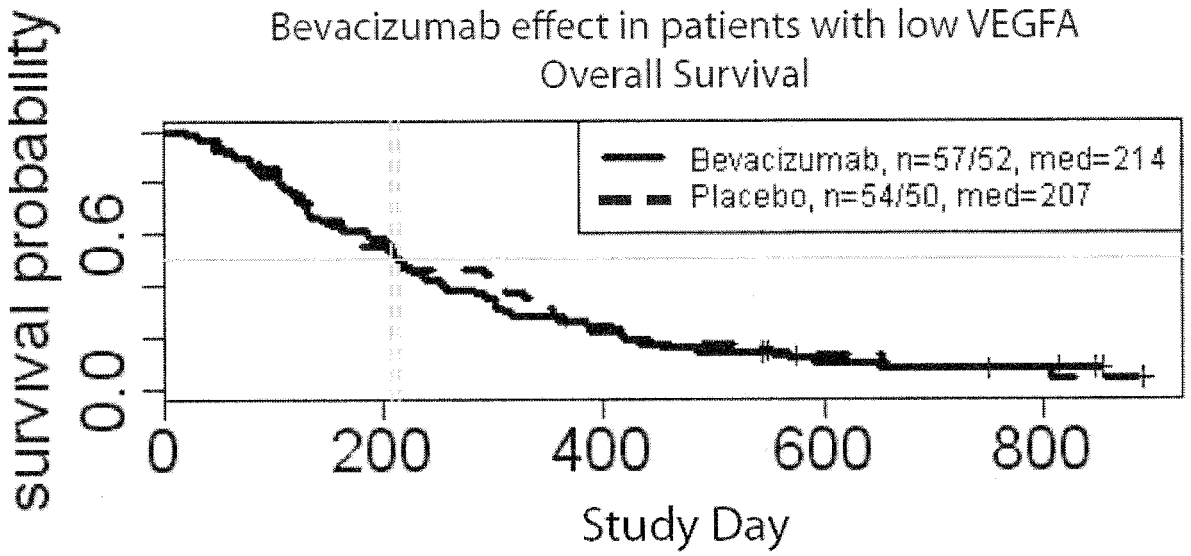

bevacizumab/GE placebo/GE
% events 94.9 100.0
Median Time (d) 150 109
HR 0.649
(95% CI) (0.495 , 0.851)
Log-Rank p 0.0017
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
bev/GE 117 59 26 8 3 1 1
pl/GE 107 37 6 2 0
0 150 300 450 600 750 900
Time to First Inv PD or Death (days)
bevacizumab/GE
placebo/GE

Figure 2A


Bevacizumab effect in patients with low VEGFA
Overall Survival
survival probability
0.0
0.6
Bevacizumab, n=57/52, med=214
Placebo, n=54/50, med=207
0
200
400
600
800
Study Day

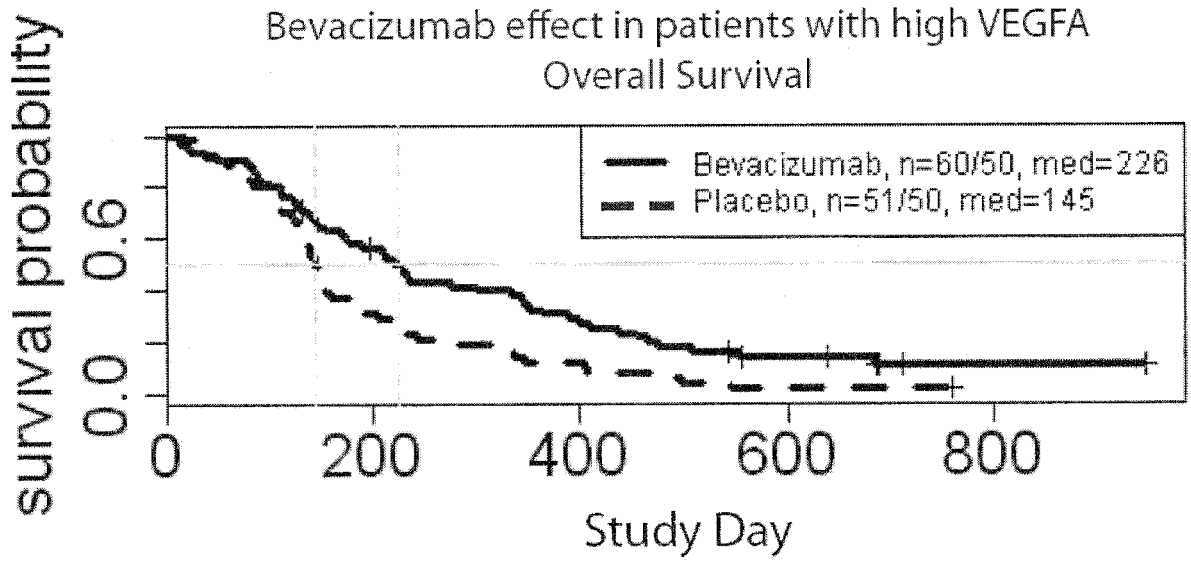
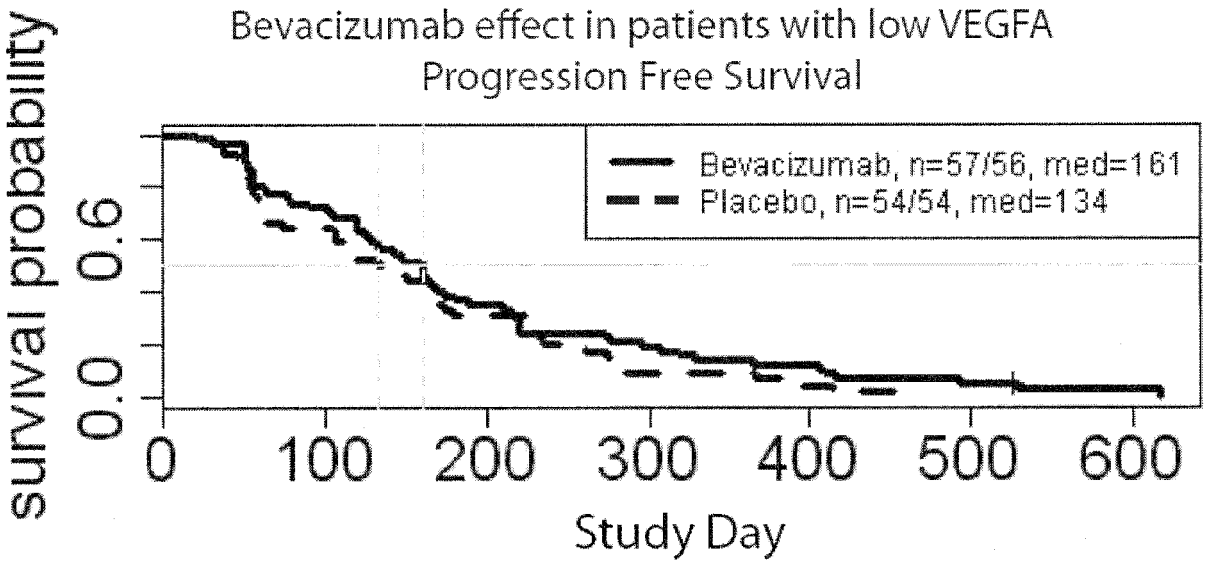

Bevacizumab effect in patients with high VEGFA
Overall Survival
survival probability
0.0
0.6
Bevacizumab, n=60/50, med=226
Placebo, n=51/50, med=145
0
200
400
600
800
Study Day

Figure 2B


Bevacizumab effect in patients with low VEGFA
Progression Free Survival
survival probability
0.0
0.6
Bevacizumab, n=57/56, med=161
Placebo, n=54/54, med=134
0
100
200
300
400
500
600
Study Day

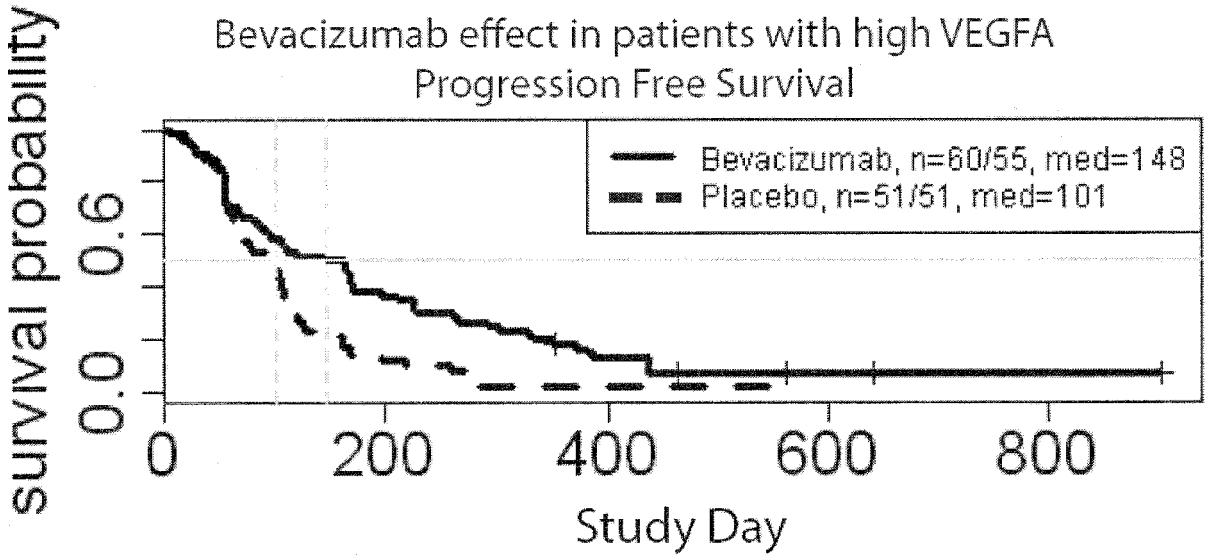
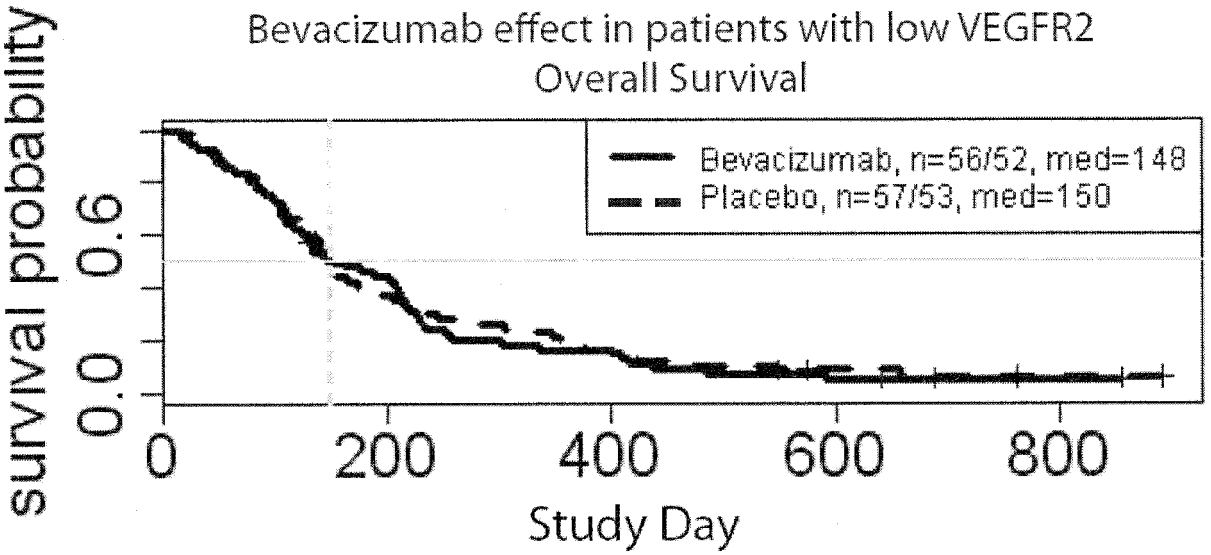

Bevacizumab effect in patients with high VEGFA
Progression Free Survival
survival probability
0.0
0.6
Bevacizumab, n=60/55, med=148
Placebo, n=51/51, med=101
0
200
400
600
800
Study Day

Figure 3


Bevacizumab effect in patients with low VEGFR2
Overall Survival
survival probability
0.0
0.6
Bevacizumab, n=56/52, med=148
Placebo, n=57/53, med=150
0
200
400
600
800
Study Day

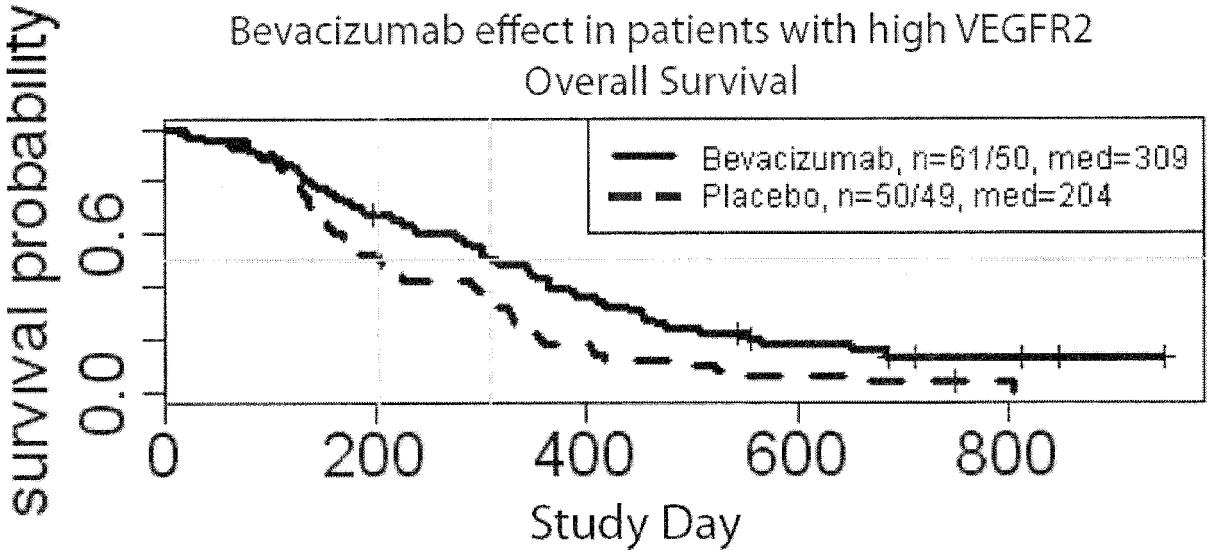
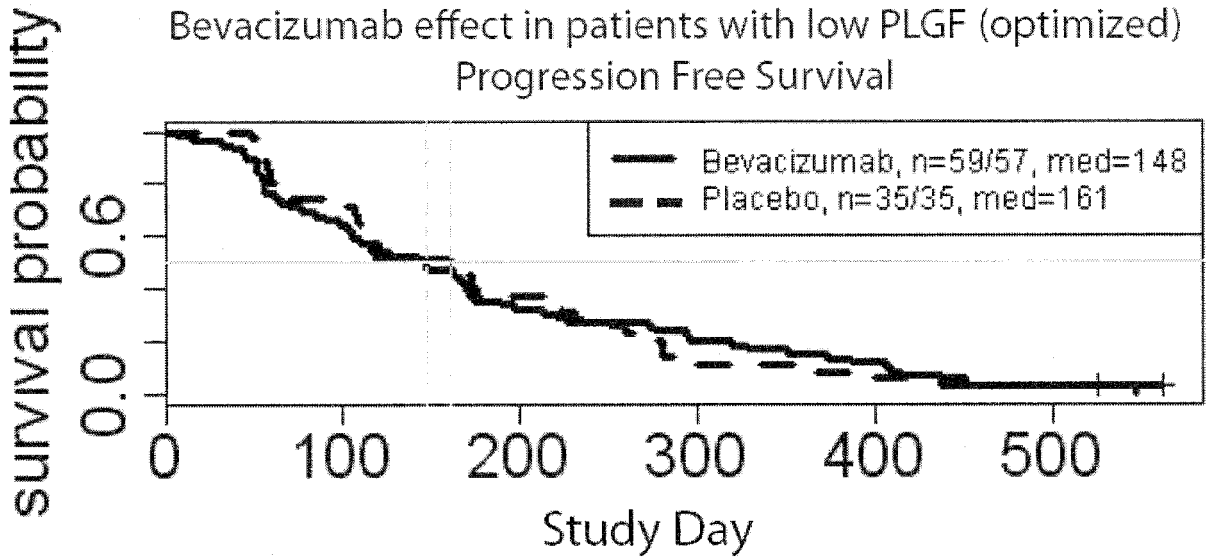

Bevacizumab effect in patients with high VEGFR2
Overall Survival
survival probability
0.0
0.6
Bevacizumab, n=61/50, med=309
Placebo, n=50/49, med=204
0
200
400
600
800
Study Day

Figure 4


Bevacizumab effect in patients with low PLGF (optimized)
Progression Free Survival
survival probability
0.0
0.6
Bevacizumab, n=59/57, med=148
Placebo, n=35/35, med=161
0
100
200
300
400
500
Study Day

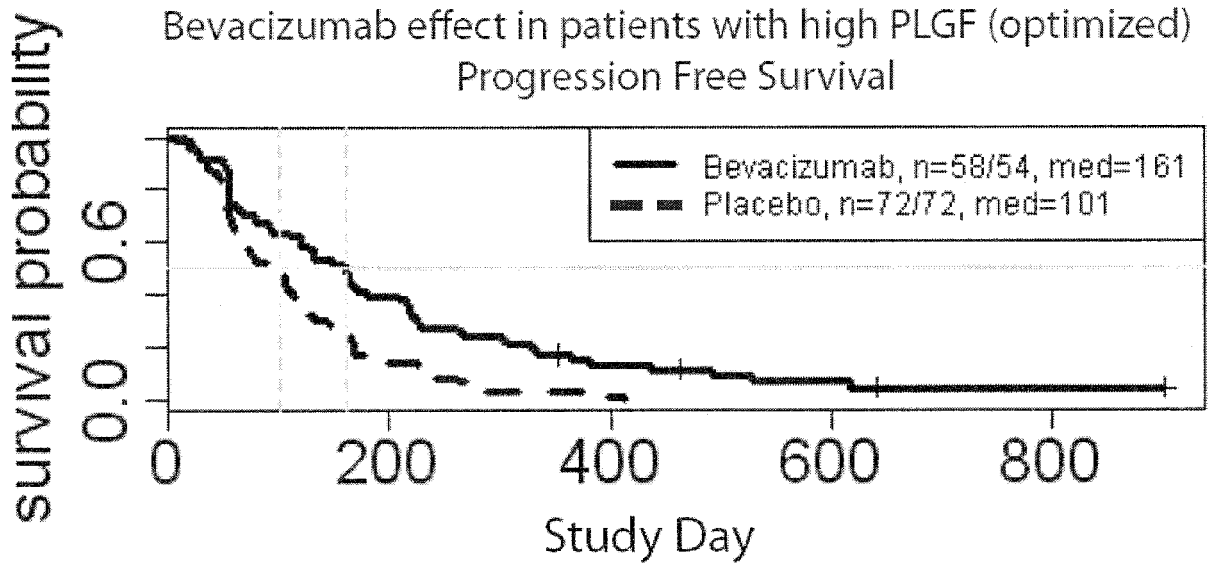

Bevacizumab effect in patients with high PLGF (optimized)
Progression Free Survival
survival probability
0.0
0.6
Bevacizumab, n=58/54, med=161
Placebo, n=72/72, med=101
0
200
400
600
800
Study Day

Figure 5A

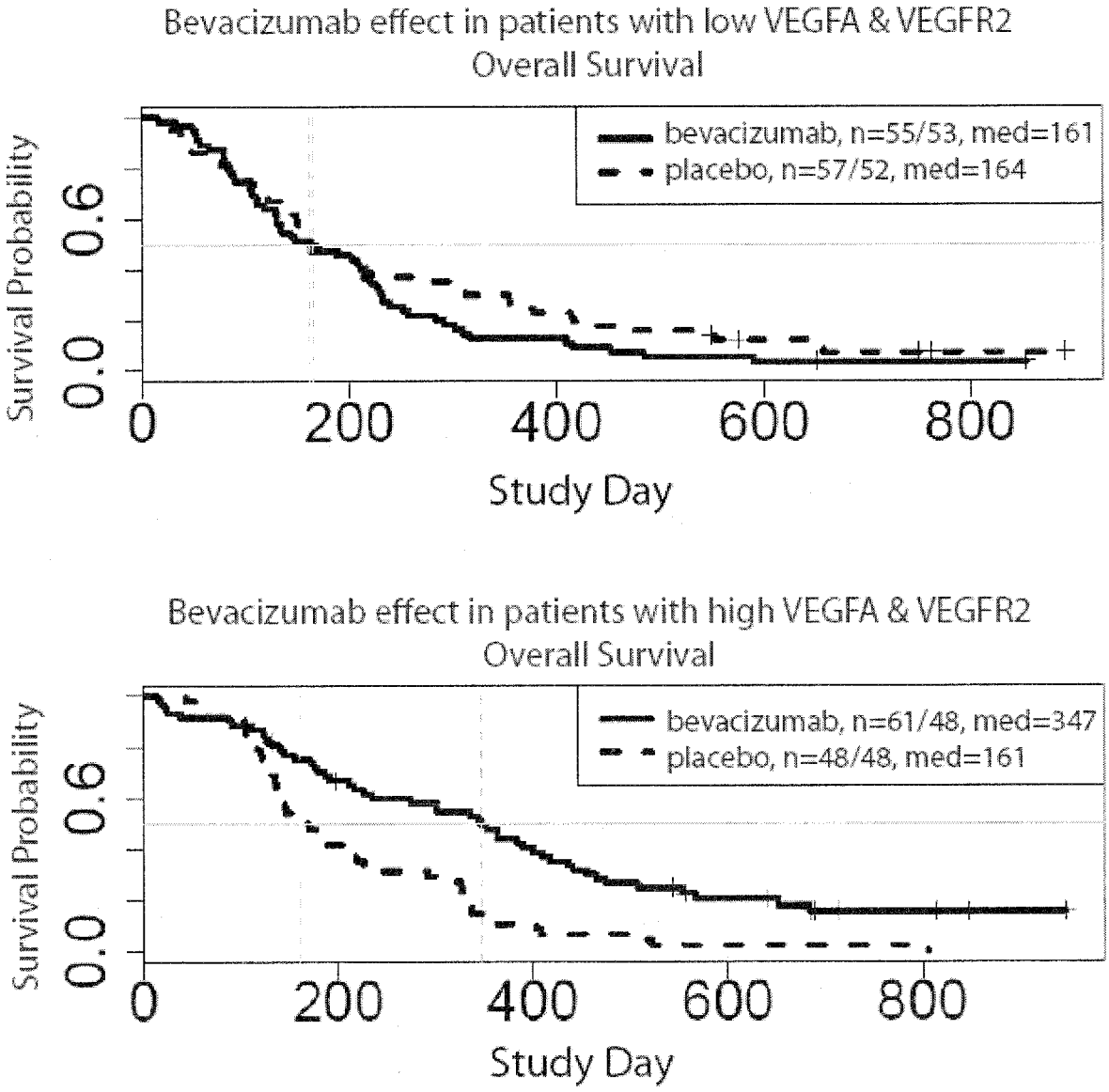

Bevacizumab effect in patients with low VEGFA & VEGFR2
Overall Survival
bevacizumab, n=55/53, med=161
placebo, n=57/52, med=164
Survival Probability
0.0
0.6
0
200
400
600
800
Study Day
Bevacizumab effect in patients with high VEGFA & VEGFR2
Overall Survival
bevacizumab, n=61/48, med=347
placebo, n=48/48, med=161
Survival Probability
0.0
0.6
0
200
400
600
800
Study Day

Figure 5B

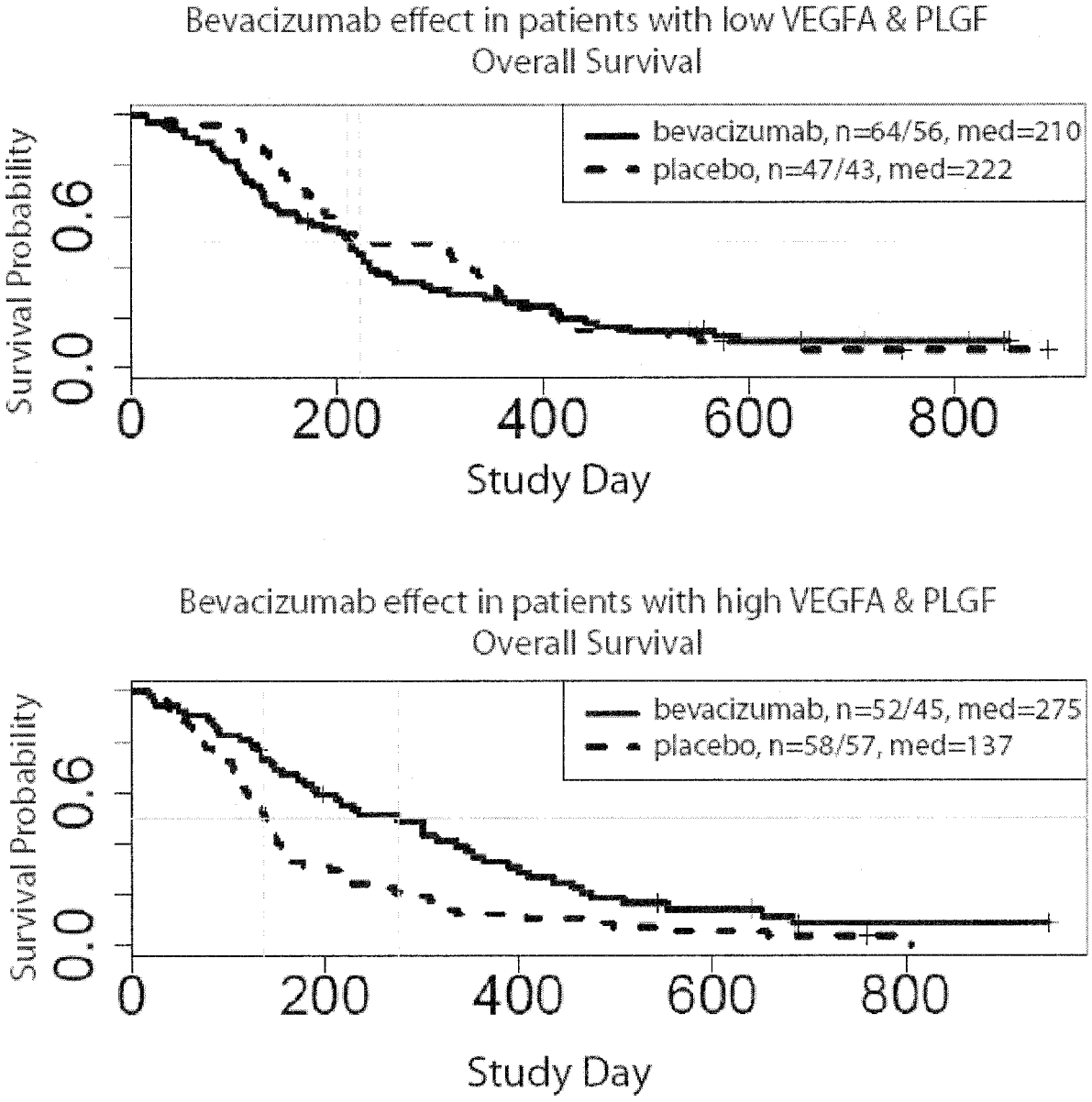

Bevacizumab effect in patients with low VEGFA & PLGF
Overall Survival
bevacizumab, n=64/56, med=210
placebo, n=47/43, med=222
Survival Probability
0.0
0.6
0
200
400
600
800
Study Day
Bevacizumab effect in patients with high VEGFA & PLGF
Overall Survival
bevacizumab, n=52/45, med=275
placebo, n=58/57, med=137
Survival Probability
0.0
0.6
0
200
400
600
800
Study Day

Figure 6A

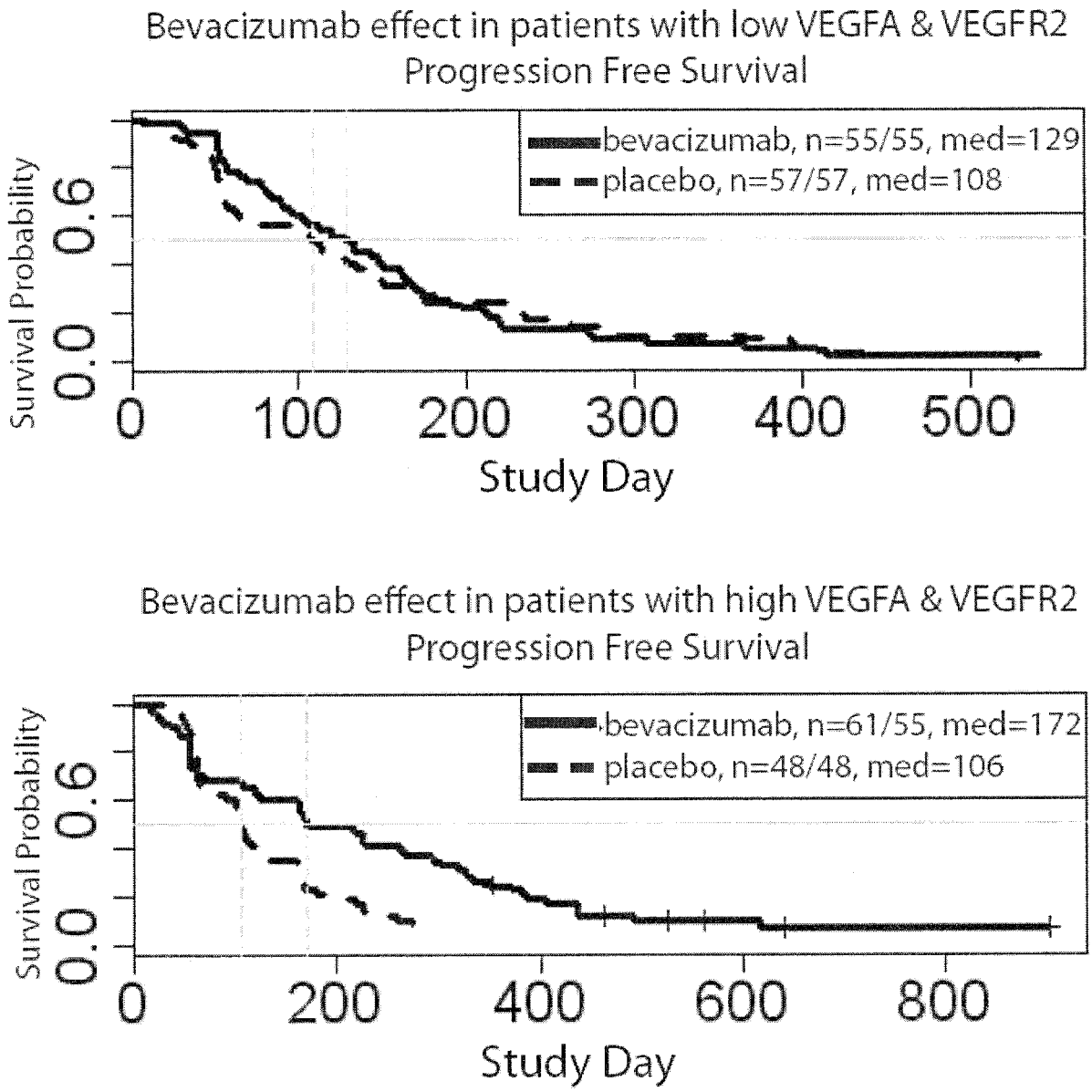

Bevacizumab effect in patients with low VEGFA & VEGFR2
Progression Free Survival
bevacizumab, n=55/55, med=129
placebo, n=57/57, med=108
Survival Probability
0.0
0.6
0
100
200
300
400
500
Study Day
Bevacizumab effect in patients with high VEGFA & VEGFR2
Progression Free Survival
bevacizumab, n=61/55, med=172
placebo, n=48/48, med=106
Survival Probability
0.0
0.6
0
200
400
600
800
Study Day

Figure 6B

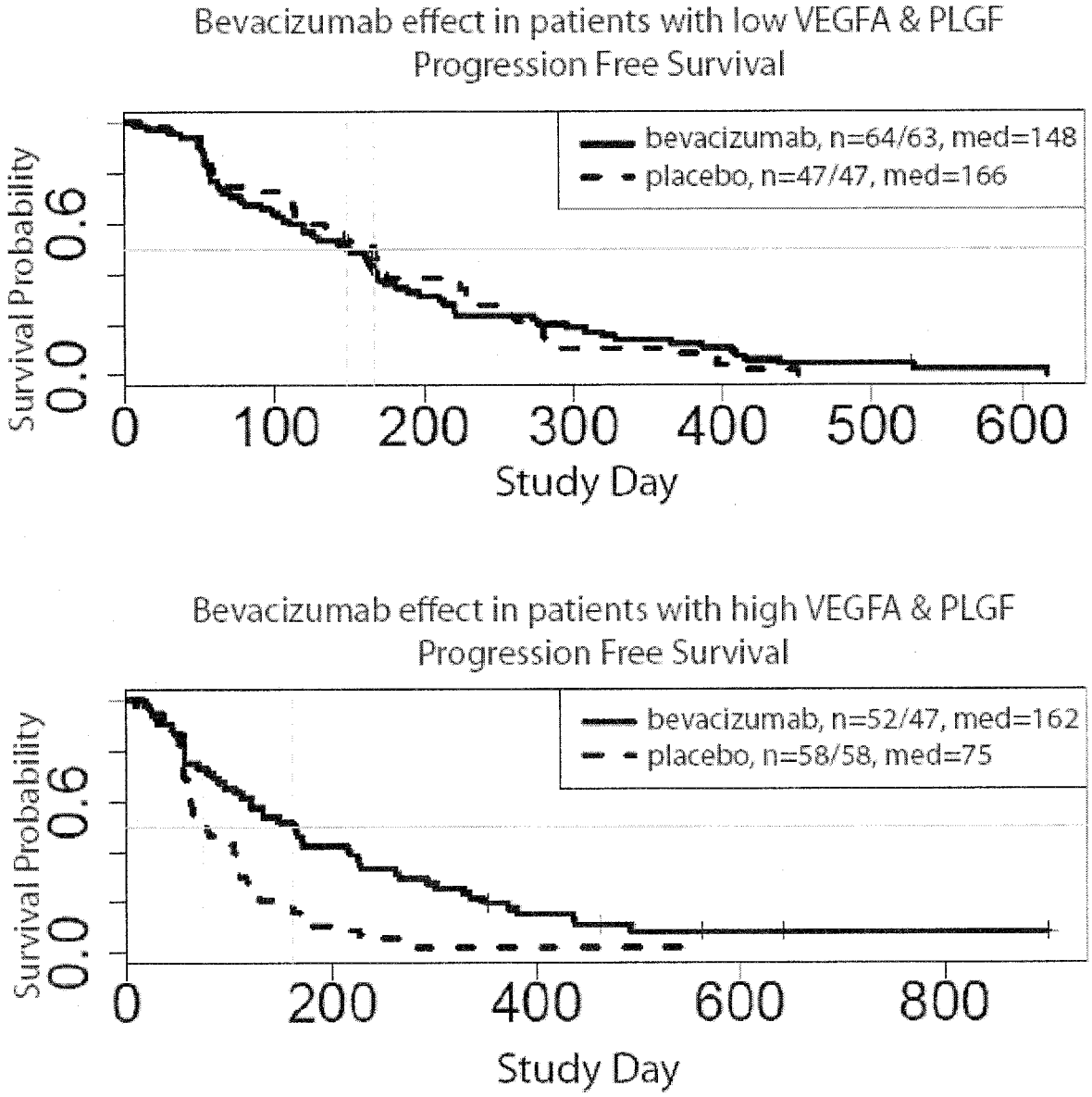

Bevacizumab effect in patients with low VEGFA & PLGF
Progression Free Survival
bevacizumab, n=64/63, med=148
placebo, n=47/47, med=166
Survival Probability
0.0
0.6
0
100
200
300
400
500
600
Study Day
Bevacizumab effect in patients with high VEGFA & PLGF
Progression Free Survival
bevacizumab, n=52/47, med=162
placebo, n=58/58, med=75
Survival Probability
0.0
0.6
0
200
400
600
800
Study Day

Figure 7A

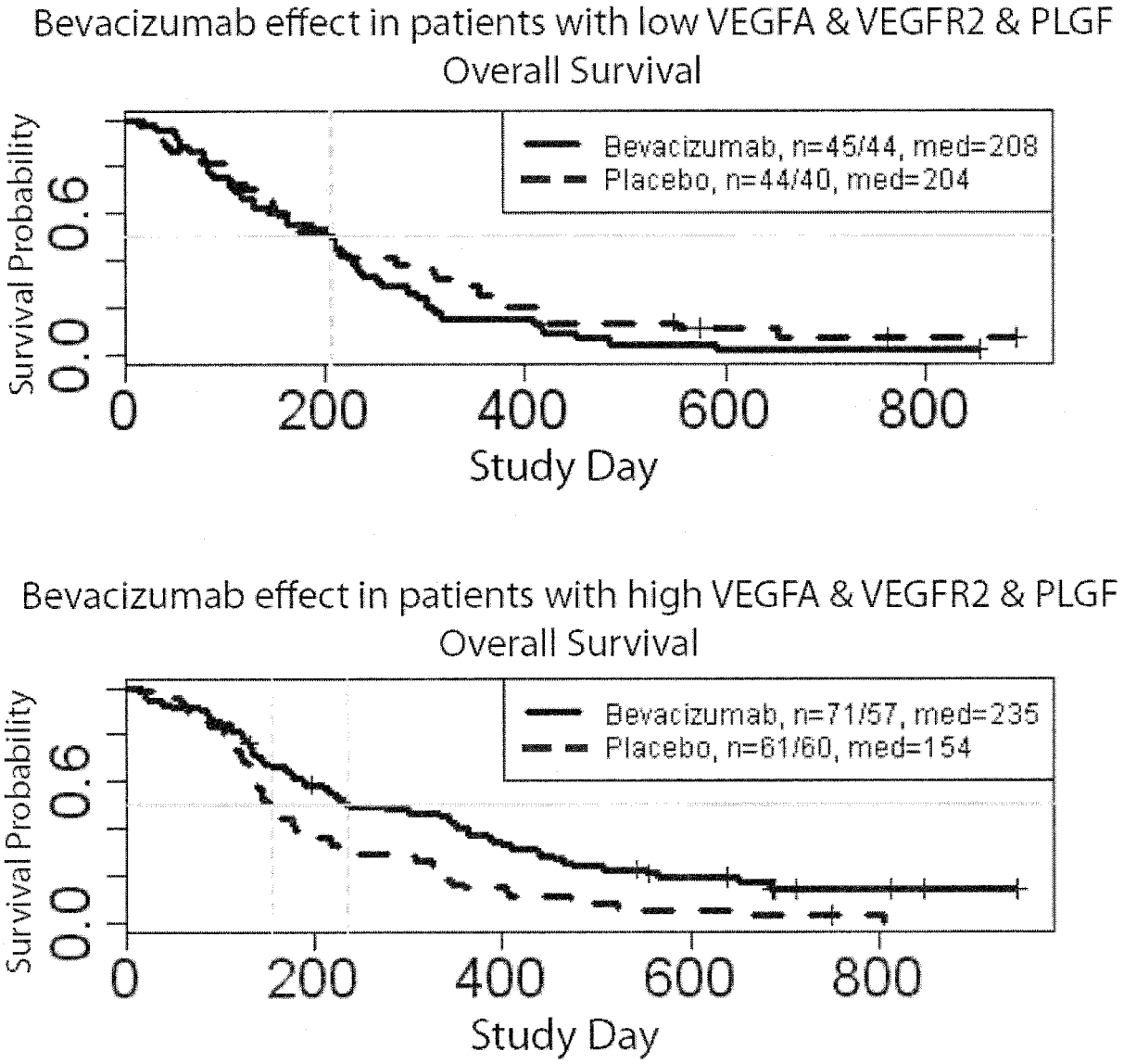

Bevacizumab effect in patients with low VEGFA & VEGFR2 & PLGF
Overall Survival
Survival Probability
0.0
0.6
Bevacizumab, n=45/44, med=208
Placebo, n=44/40, med=204
0
200
400
600
800
Study Day
Bevacizumab effect in patients with high VEGFA & VEGFR2 & PLGF
Overall Survival
Survival Probability
0.0
0.6
Bevacizumab, n=71/57, med=235
Placebo, n=61/60, med=154
0
200
400
600
800
Study Day

Figure 7B

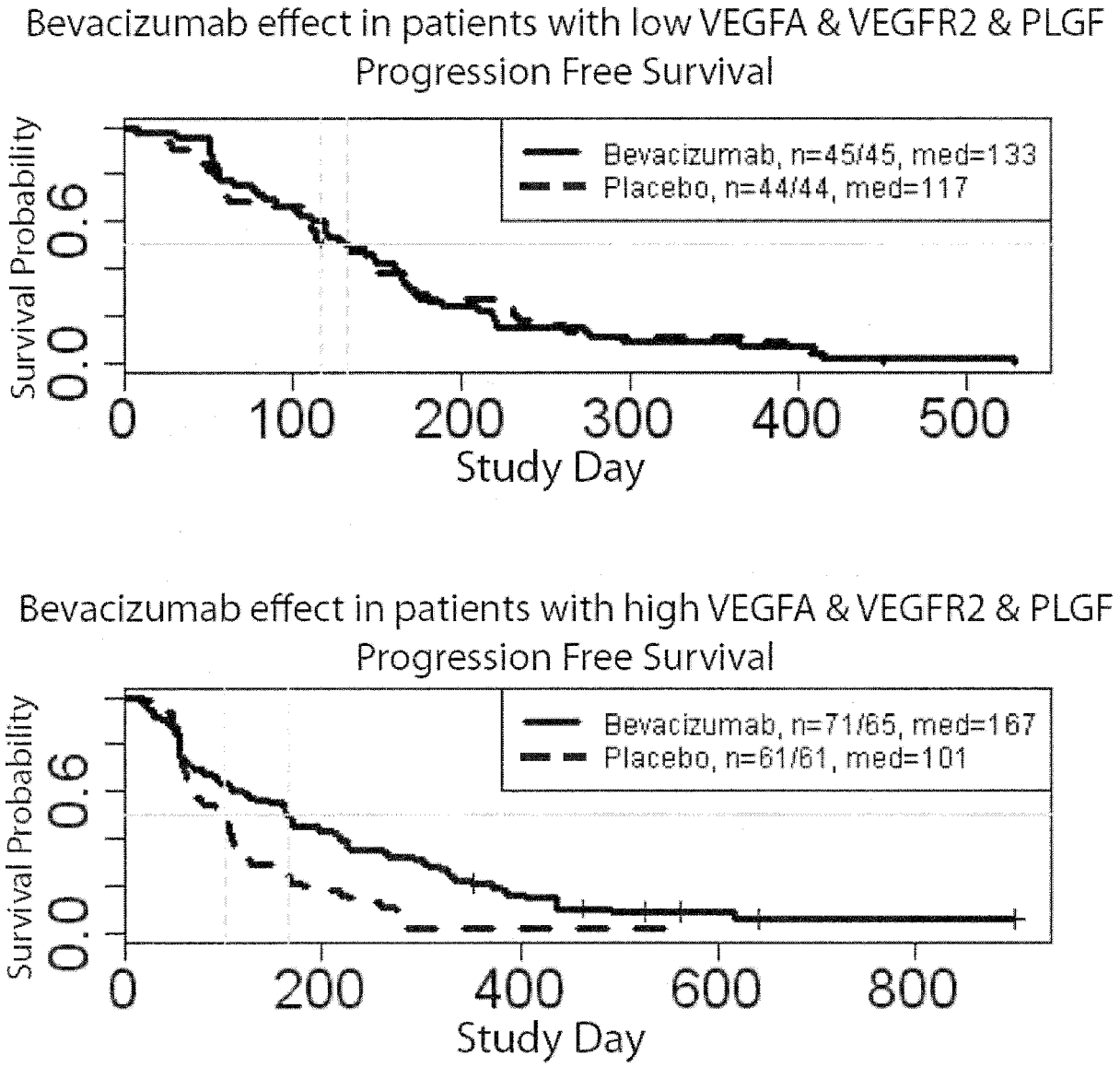

Bevacizumab effect in patients with low VEGFA & VEGFR2 & PLGF
Progression Free Survival
Survival Probability
0.0
0.6
Bevacizumab, n=45/45, med=133
Placebo, n=44/44, med=117
0
100
200
300
400
500
Study Day
Bevacizumab effect in patients with high VEGFA & VEGFR2 & PLGF
Progression Free Survival
Survival Probability
0.0
0.6
Bevacizumab, n=71/65, med=167
Placebo, n=61/61, med=101
0
200
400
600
800
Study Day

Figure 8: SEQ ID NO:1, Exemplary amino acid sequence of VEGFA.

```
        10         20         30         40         50         60
MNFLLSWVHW SLALLLYLHH AKWSQAAPMA EGGGQNHHEV VKFMDVYQRS YCHPIETLVD

        70         80         90        100        110        120
IFQEYPDEIE YIFKPSCVPL MRCGGCCNDE GLECVPTEES NITMQIMRIK PHQGQHIGEM

       130        140        150        160        170        180
SFLQHNKCEC RPKKDRARQE KKSVRGKGKG QKRKRKKSRY KSWSVYVGAR CCLMPWSLPG

       190        200        210        220        230
PHPCGPCSER RKHLFVQDPQ TCKCSCKNTD SRCKARQLEL NERTCRCDKP RR
```

Figure 9: SEQ ID NO:2, Exemplary amino acid sequence of VEGFR2.

```
      10         20         30         40         50         60
MQSKVLLAVA LWLCVETRAA SVGLPSVSLD LPRLSIQKDI LTIKANTTLQ ITCRGQRDLD

      70         80         90        100        110        120
WLWPNNQSGS EQRVEVTECS DGLFCKTLTI PKVIGNDTGA YKCFYRETDL ASVIYVYVQD

     130        140        150        160        170        180
YRSPFIASVS DQHGVVYITE NKNKTVVIPC LGSISNLNVS LCARYPEKRF VPDGNRISWD

     190        200        210        220        230        240
SKKGFTIPSY MISYAGMVFC EAKINDESYQ SIMYIVVVVG YRIYDVVLSP SHGIELSVGE

     250        260        270        280        290        300
KLVLNCTART ELNVGIDFNW EYPSSKHQHK KLVNRDLKTQ SGSEMKKFLS TLTIDGVTRS

     310        320        330        340        350        360
DQGLYTCAAS SGLMTKKNST FVRVHEKPFV AFGSGMESLV EATVGERVRI PAKYLGYPPP

     370        380        390        400        410        420
EIKWYKNGIP LESNHTIKAG HVLTIMEVSE RDTGNYTVIL TNPISKEKQS HVVSLVVYVP

     430        440        450        460        470        480
PQIGEKSLIS PVDSYQYGTT QTLTCTVYAI PPPHHIHWYW QLEEECANEP SQAVSVTNPY

     490        500        510        520        530        540
PCEEWRSVED FQGGNKIEVN KNQFALIEGK NKTVSTLVIQ AANVSALYKC EAVNKVGRGE

     550        560        570        580        590        600
RVISFHVTRG PEITLQPDMQ PTEQESVSLW CTADRSTFEN LTWYKLGPQP LPIHVGELPT

     610        620        630        640        650        660
PVCKNLDTLW KLNATMFSNS TNDILIMELK NASLQDQGDY VCLAQDRKTK KRHCVVRQLT

     670        680        690        700        710        720
VLERVAPTIT GNLENQTTSI GESIEVSCTA SGNPPPQIMW FKDNETLVED SGIVLKDGNR
```

Figure 9 (continued): SEQ ID NO:2, Exemplary amino acid sequence of VEGFR2.

```
       730        740        750        760        770        780
NLTIRRVRKE DEGLYTCQAC SVLGCAKVEA FFIIEGAQEK TNLEIIILVG TAVIAMFFWL

       790        800        810        820        830        840
LLVIILRTVK RANGGELKTG YLSIVMDPDE LPLDEHCERL PYDASKWEFP RDRLKLGKPL

       850        860        870        880        890        900
GRGAFGQVIE ADAFGIDKTA TCRTVAVKML KEGATHSEHR ALMSELKILI HIGHHLNVVN

       910        920        930        940        950        960
LLGACTKPGG PLMVIVEFCK FGNLSTYLRS KRNEFVPYKT KGARFRQGKD YVGAIPVDLK

       970        980        990       1000       1010       1020
RRLDSITSSQ SSASSGFVEE KSLSDVEEEE APEDLYKDFL TLEHLICYSF QVAKGMEFLA

      1030       1040       1050       1060       1070       1080
SRKCIHRDLA ARNILLSEKN VVKICDFGLA RDIYKDPDYV RKGDARLPLK WMAPETIFDR

      1090       1100       1110       1120       1130       1140
VYTIQSDVWS FGVLLWEIFS LGASPYPGVK IDEEFCRRLK EGTRMRAPDY TTPEMYQTML

      1150       1160       1170       1180       1190       1200
DCWHGEPSQR PTFSELVEHL GNLLQANAQQ DGKDYIVLPI SETLSMEEDS GLSLPTSPVS

      1210       1220       1230       1240       1250       1260
CMEEEEVCDP KFHYDNTAGI SQYLQNSKRK SRPVSVKTFE DIPLEEPEVK VIPDDNQTDS

      1270       1280       1290       1300       1310       1320
GMVLASEELK TLEDRTKLSP SFGGMVPSKS RESVASEGSN QTSGYQSGYH SDDTDTTVYS

      1330       1340       1350
SEEAELLKLI EIGVQTGSTA QILQPDSGTT LSSPPV
```

Figure 10: SEQ ID NO:3, Exemplary amino acid sequence of PLGF.

```
        10         20         30         40         50         60
MPVMRLFPCF LQLLAGLALP AVPPQQWALS AGNGSSEVEV VPFQEVWGRS YCRALERLVD

        70         80         90        100        110        120
VVSEYPSEVE HMFSPSCVSL LRCTGCCGDE NLHCVPVETA NVTMQLLKIR SGDRPSYVEL

       130        140        150        160        170        180
TFSQHVRCEC RHSPGRQSPD MPGDFRADAP SFLPPRRSLP MLFRMEWGCA LTGSQSAVWP

       190        200        210        220
SSPVPEEIPR MHPGRNGKKQ QRKPLREKMK PERCGDAVPR R
```

Figure 11:

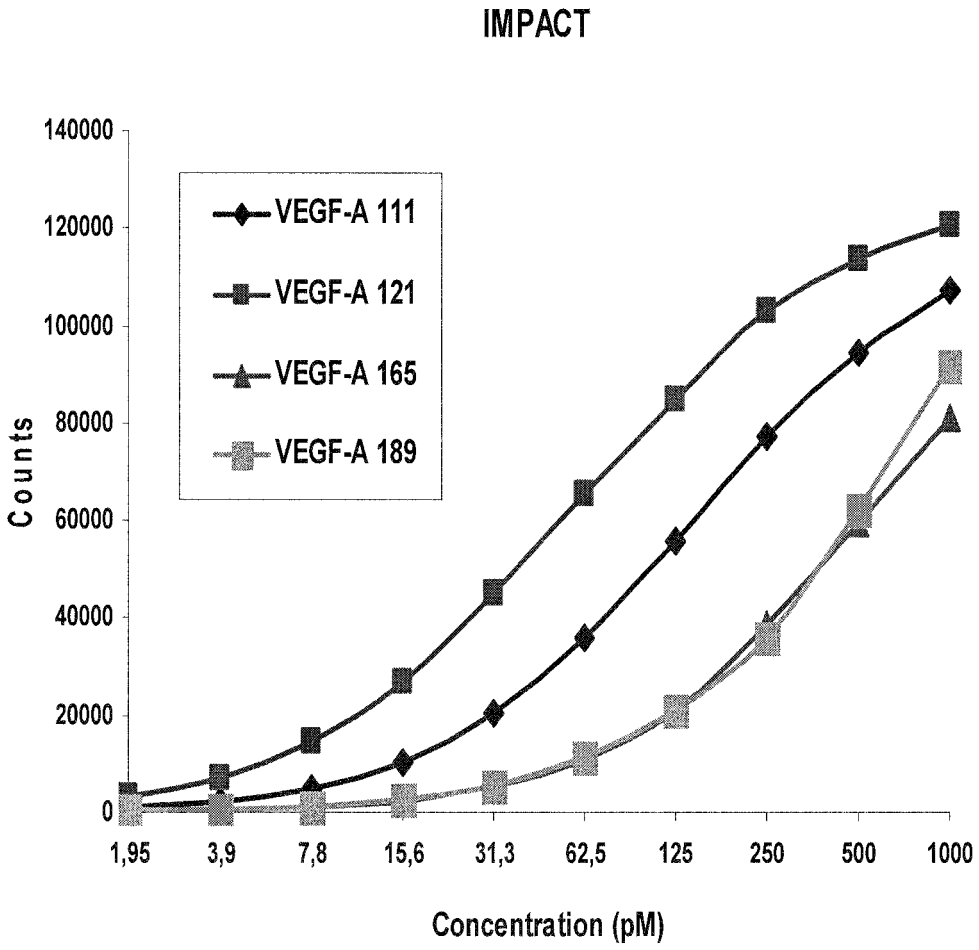

IMPACT
140000
120000
100000
80000
60000
40000
20000
0
Counts
VEGF-A 111
VEGF-A 121
VEGF-A 165
VEGF-A 189
1,95
3,9
7,8
15,6
31,3
62,5
125
250
500
1000
Concentration (pM)

Figure 12:

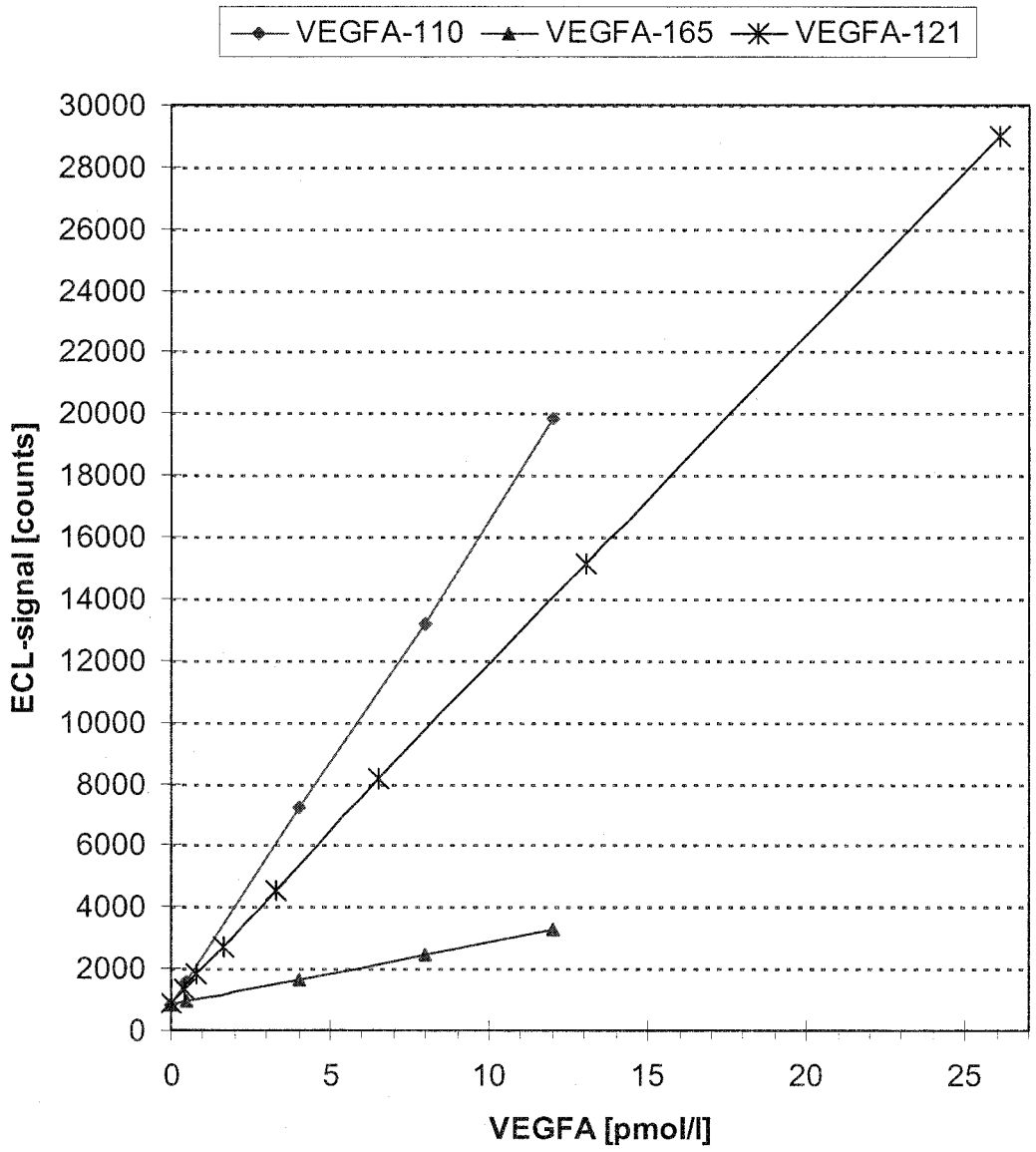

VEGFA-110
VEGFA-165
VEGFA-121
ECL-signal [counts]
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
0
5
10
15
20
25
VEGFA [pmol/l]

Figure 13:

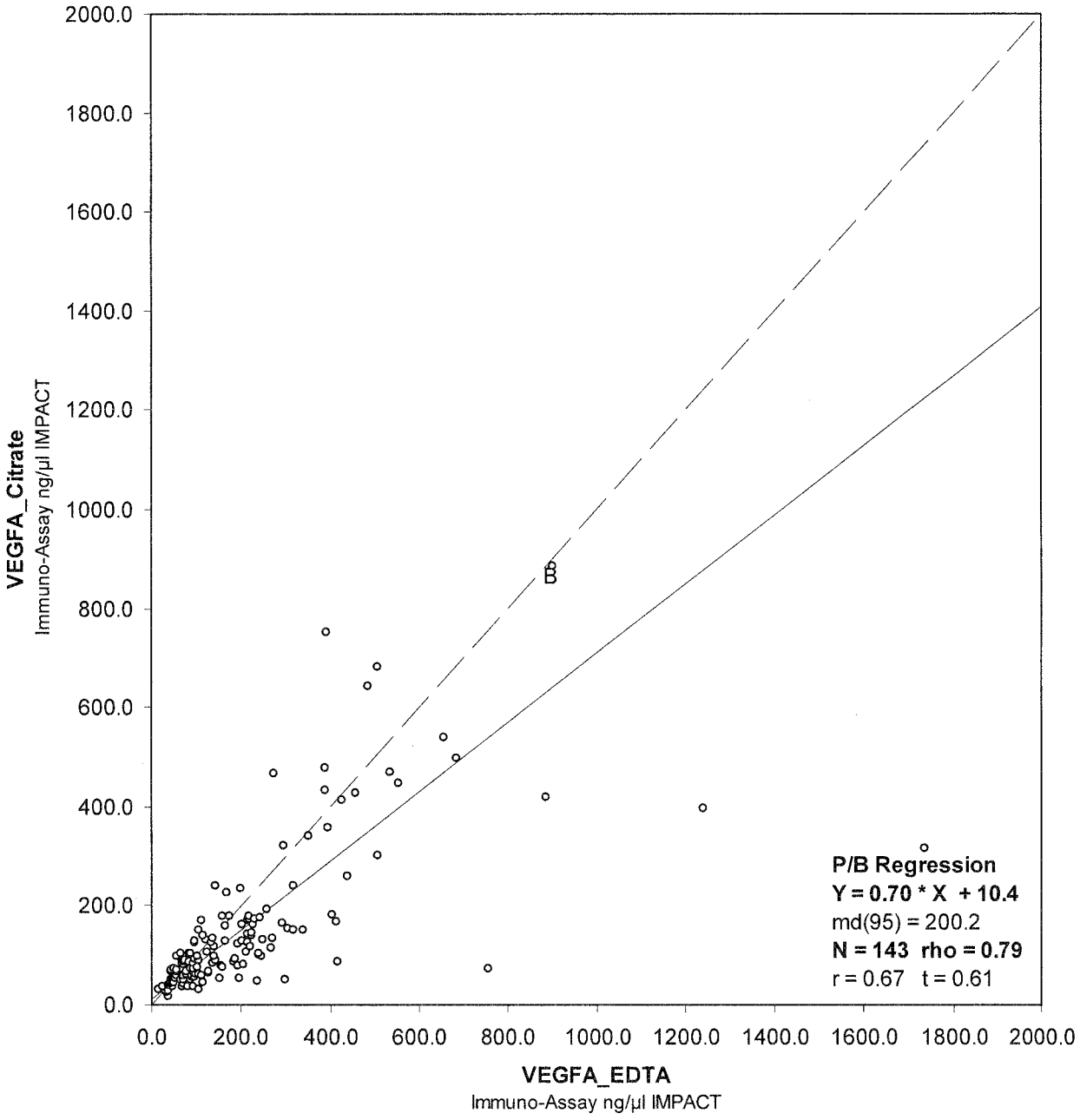
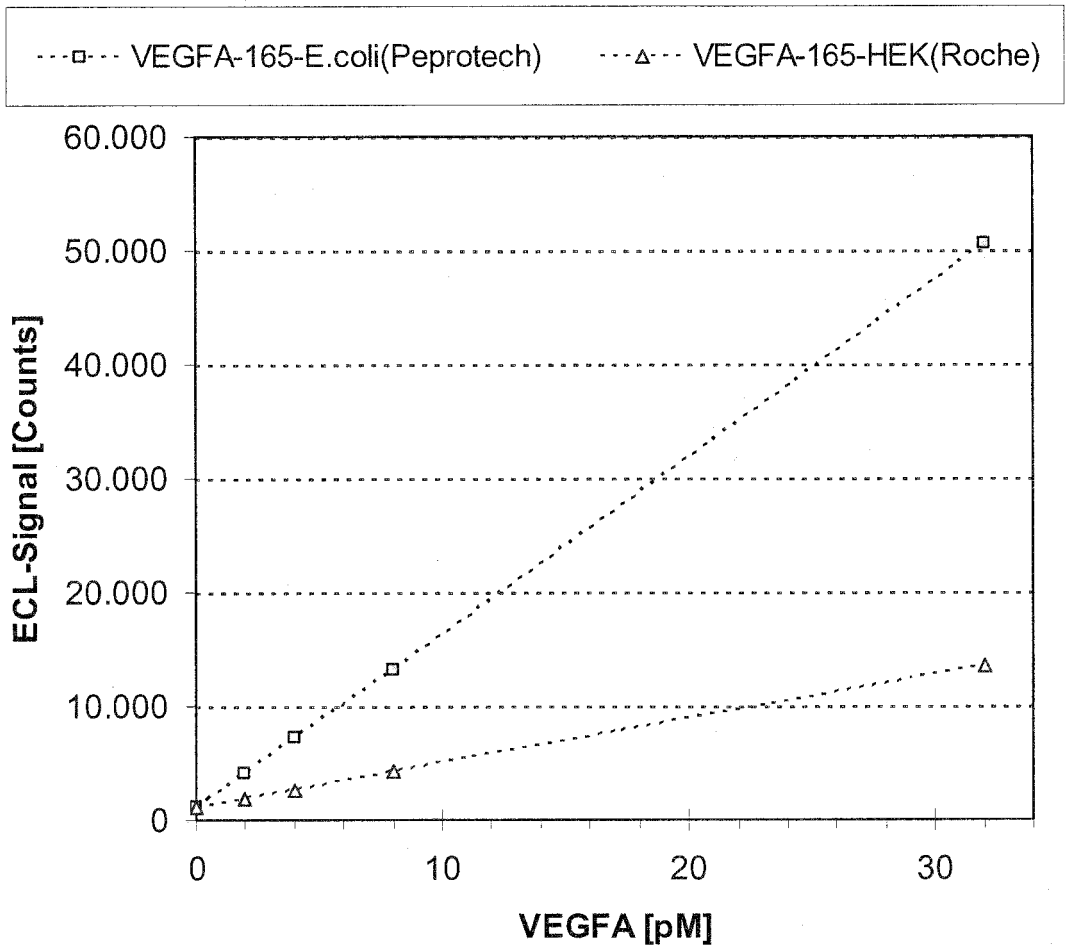

2000.0
1800.0
1600.0
1400.0
1200.0
1000.0
800.0
600.0
400.0
200.0
0.0
VEGFA_Citrate
Immuno-Assay ng/µl IMPACT
0.0
200.0
400.0
600.0
800.0
1000.0
1200.0
1400.0
1600.0
1800.0
2000.0
VEGFA_EDTA
Immuno-Assay ng/µl IMPACT
B
P/B Regression
Y = 0.70 * X + 10.4
md(95) = 200.2
N = 143 rho = 0.79
r = 0.67 t = 0.61

Figure 14:


VEGFA-165-E.coli(Peprotech)
VEGFA-165-HEK(Roche)
60.000
50.000
40.000
30.000
20.000
10.000
0
ECL-Signal [Counts]
0
10
20
30
VEGFA [pM]