1
195
319
488
630
Domain I (L1)
Domain II (CR1)
Domain III (L2)
Domain IV (CR2)
Transmembrane
Juxtamembrane
Tyrosine Kinase
Regulatory Region
OUT
IN
Y
Y
Y
Y
Y
TQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNASLSFLQDIQEVQGYV
LIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLT
EILKGGVLIQRNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGES
SEDCQSLTR
TVCAGGCARCKGPLPTDCCHEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTF
ESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCPLHNQEVTAEDGTQRCEKCSKPCARV
CYGLGMEHLREVRAVTSANIQEFAGCKKIFGSLAFLPESFDGDPASNTAPLQPEQLQVFETLE
EITGYLYISAWPDSLPDLSVFQNLQVIRGRILHNGAYSLTLQGLGISWLGLRSLRELGSGLAL
IHHNTHLCFVHTVPWDQLFRNPHQALLHTANRPEDECVGEGLA
CHQLCARGHCWGPGPTQCVNCSQFLRGQECVEECRVLQGLPREYVNARHCLPCHPECQPQNGS
VTCFGPEADQCVACAHYKDPPFCVARCPSGVKPDLSYMPIWKFPDEEGACQPCPINCTHSCVD
LDDKGCPAEQRASPLT

FIG. 1

Variable Light

```
                10          20          30          40
2C4     DTVMTQSHKIMSTSVGDRVSITC [KASQDVSIGVA] WYQQKP
         **    **** *       *                     *
574     DIQMTQSPSSLSASVGDRVTITC [KASQDVSIGVA] WYQQKP
                                 *   ** ***
hum κI  DIQMTQSPSSLSASVGDRVTITC [RASQSISNYLA] WYQQKP

                50          60          70          80
2C4     GQSPKLLIY [SASYRYT] GVPDRFTGSGSGTDFTFTISSVQA
          **                  *  *        *    * *
574     GKAPKLLIY [SASYRYT] GVPSRFSGSGSGTDFTLTISSLQP
                   * *****
hum κI  GKAPKLLIY [AASSLES] GVPSRFSGSGSGTDFTLTISSLQP

                90          100
2C4     EDLAVYYC [QQYYIYPYT] FGGGTKLEIK (SEQ ID NO:1)
           * *                 *   *
574     EDFATYYC [QQYYIYPYT] FGQGTKVEIK (SEQ ID NO:3)
                    *** *
hum κI  EDFATYYC [QQYNSLPWT] FGQGTKVEIK (SEQ ID NO:5)
```

FIG. 2A

Variable Heavy

```
                10          20          30          40
2C4     EVQLQQSGPELVKPGTSVKISCKAS [GFTFTDYTMD] WVKQS
            **  **  *  * ***  *                   * *
574     EVQLVESGGGLVQPGGSLRLSCAAS [GFTFTDYTMD] WVRQA
                                    ** * *
hum III EVQLVESGGGLVQPGGSLRLSCAAS [GFTFSSYAMS] WVRQA

                50 a        60          70          80
2C4     HGKSLEWIG [DVNPNSGGSIYNQRFKG] KASLTVDRSSRIVYM
        *  *   **                     *** *    **** *
574     PGKGLEWVA [DVNPNSGGSIYNQRFKG] RFTLSVDRSKNTLYL
                  ****** *** ****       * * *
hum III PGKGLEWVA [VISGDGGSTYYADSVKG] RFTISRDNSKNTLYL

          abc       90         100ab        110
2C4     ELRSLTFEDTAVYYCAR [NLGPSFYFDY] WGQGTTLTVSS (SEQ ID NO:2)
        ***  **                                **
574     QMNSLRAEDTAVYYCAR [NLGPSFYFDY] WGQGTLVTVSS (SEQ ID NO:4)
                          ********
hum III QMNSLRAEDTAVYYCAR [GRVGYSLYDY] WGQGTLVTVSS (SEQ ID NO:6)
```

FIG. 2B

Amino Acid Sequence for Pertuzumab Light Chain

```
1         10        20        30        40        50        60
DIQMTQSPSSLSASVGDRVTITCKASQDVSIGVAWYQQKPGKAPKLLIYSASYRYTGVPS

          70        80        90        100       110       120
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYYIYPYTFGQGTKVEIKRTVAAPSVFIFPP

          130       140       150       160       170       180
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT

          190       200       210
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
```

FIG. 3A

Amino Acid Sequence for Pertuzumab Heavy Chain

```
1         10        20        30        40        50        60
EVQLVESGGGLVQPGGSLRLSCAASGFTFTDYTMDWVRQAPGKGLEWVADVNPNSGGSIY

          70        80        90        100       110       120
NQRFKGRFTLSVDRSKNTLYLQMNSLRAEDTAVYYCARNLGPSFYFDYWGQGTLVTVSSA

          130       140       150       160       170       180
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG

          190       200       210       220       230       240
LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP

          250       260       270       280       290       300
SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS

          310       320       330       340       350       360
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM

          370       380       390       400       410       420
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ

          430       440       448
QGNVFSCSVMHEALHNHYTQKSLSLSPG
```

FIG. 3B

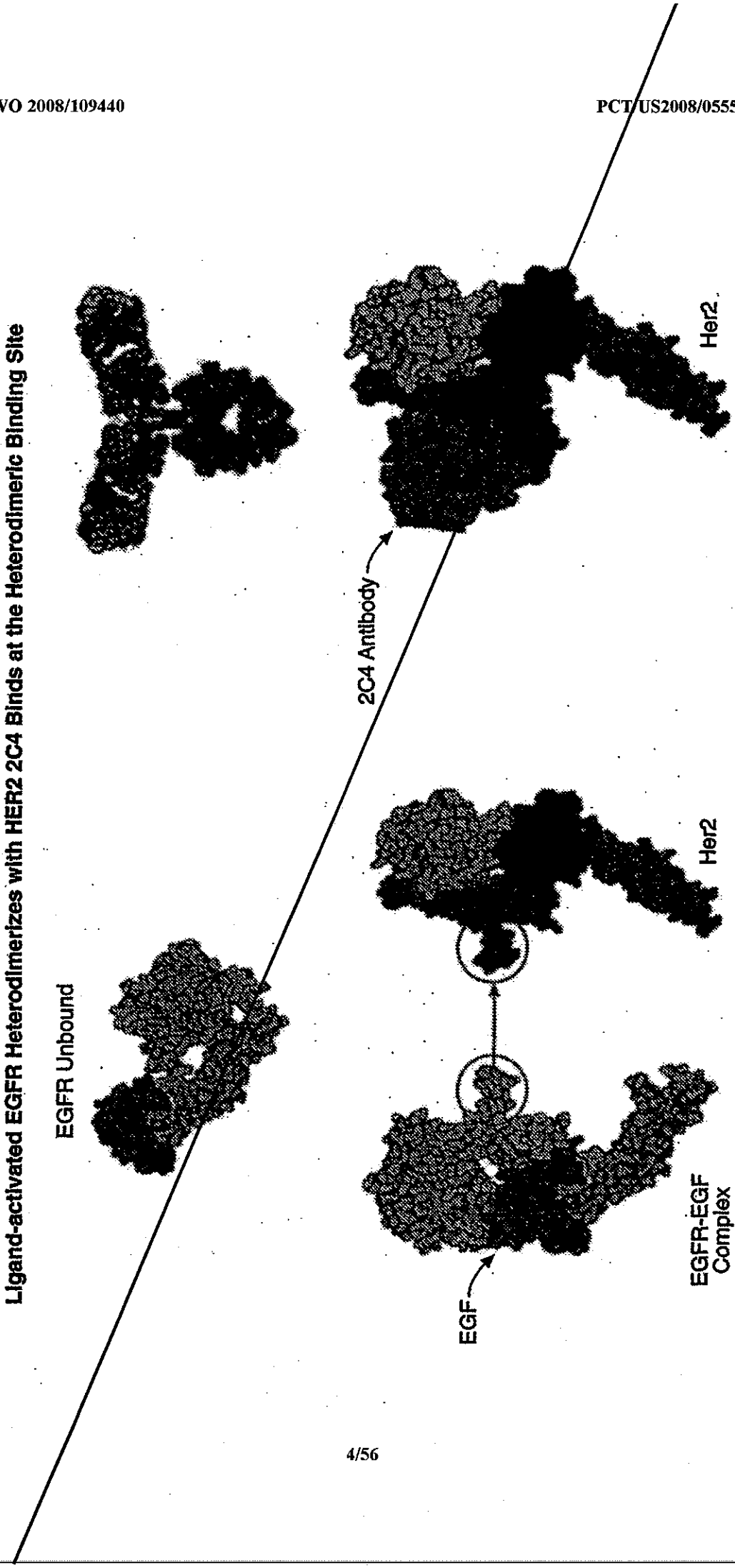

Ligand-activated EGFR Heterodimerizes with HER2 2C4 Binds at the Heterodimeric Binding Site
EGFR Unbound
2C4 Antibody
Her2
Her2
EGF
EGFR-EGF Complex

FIG. 4

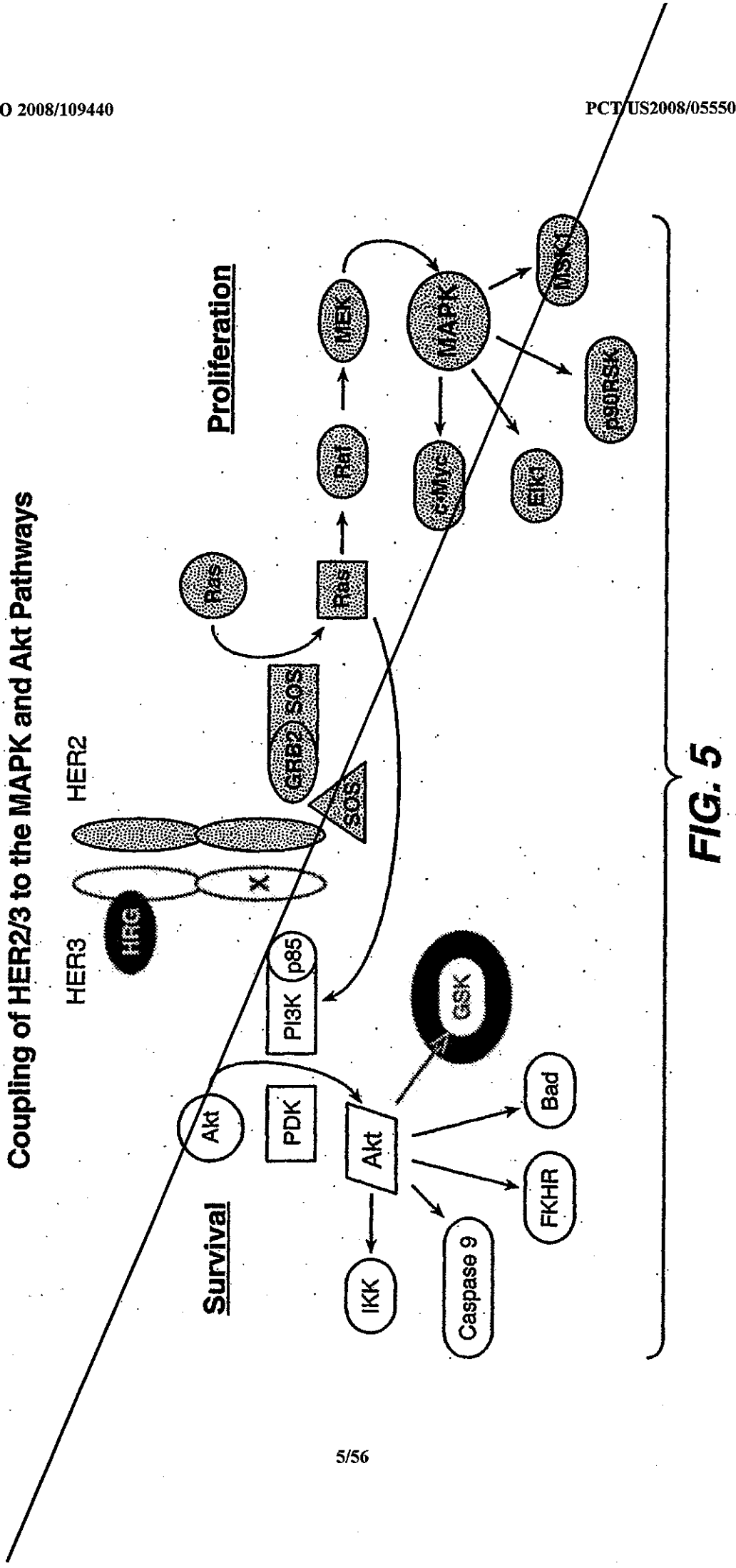
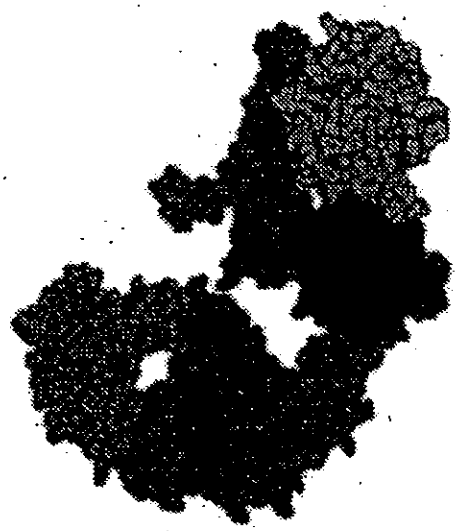

Coupling of HER2/3 to the MAPK and Akt Pathways
HER3
HER2
HRG
Ras
GRB2
SOS
SOS
Ras
Raf
MEK
MAPK
MSK1
p90RSK
c-Myc
Elk
Proliferation
PI3K
p85
PDK
Akt
Akt
GSK
Bad
FKHR
Caspase 9
IKK
Survival

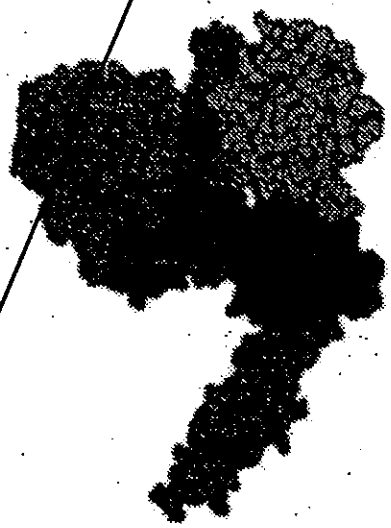
FIG. 5

Trastuzumab
Herceptin



- Binds in IV near JM.
- Protects against receptor shedding
- Moderately affects receptor down-modulation
- Slight effect on HER2's role as a coreceptor

Pertuzumab
Omnitarg



- Binds in II at dimerization interface
- Does not prevent receptor shedding
- Moderately affects receptor down-modulation
- Major effect on HER2's role as a coreceptor

FIG. 6

Light Chain

```
                                                                  45
1   DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPK
                                                                  90
46  LLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQ
                                                                 135
91  HYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL
                                                                 180
136 LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
                                                                 214
181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
```

FIG. 7A

Heavy Chain

```
1                               15                              30                              45
E V Q L V E S G G G L V Q P G G S L R L S C A A S G F N I K D T Y I H W V R Q A P G K G L

46                              60                              75                              90
E W V A R I Y P T N G Y T R Y A D S V K G R F T I S A D T S K N T A Y L Q M N S L R A E D

91                              105                             120                             135
T A V Y Y C S R W G G D G F Y A M D Y W G Q G T L V T V S S A S T K G P S V F P L A P S S

136                             150                             165                             180
K S T S G G T A A L G C L V K D Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S

181                             195                             210                             225
G L Y S L S S V V T V P S S S L G T Q T Y I C N V N H K P S N T K V D K K V E P K S C D K

226                             240                             255                             270
T H T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V V V D V S

271                             285                             300                             315
H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y R V V S V L T V L H Q D

316                             330                             345                             360
W L N G K E Y K C K V S N K A L P A P I E K T I S K A K G Q P R E P Q V Y T L P P S R E E

361                             375                             390                             405
M T K N Q V S L T C L V K G F Y P S D I A V E W E S N G Q P E N N Y K T T P P V L D S D G

406                             420                             435                             449
S F F L Y S K L T V D K S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G
```

FIG. 7B

```
1                                        15                                       30                                       45
V H S D I Q M T Q S P S S L S A S V G D R V T I T C K A S Q D V S I G V A W Y Q Q K P G K
46                                       60                                       75                                       90
A P K L L I Y S A S Y R Y T G V P S R F S G S G S G T D F T L T I S S L Q P E D F A T Y Y
91                                       105                                      120                                      135
C Q Q Y Y I Y P Y T F G Q G T K V E I K R T V A A P S V F I F P P S D E Q L K S G T A S V
136                                      150                                      165                                      180
V C L L N N F Y P R E A K V Q W K V D N A L Q S G N S Q E S V T E Q D S K D S T Y S L S S
181                                      195                                      210                  217
T L T L S K A D Y E K H K V Y A C E V T H Q G L S S P V T K S F N R G E C
```

FIG. 8A

```
1   E V Q L V E S G G G L V Q P G G S L R L S C A A S G F T F T D Y T M D W V R Q A P G K G L
46  E W V A D V N P N S G G S I Y N Q R F K G R F T L S V D R S K N T L Y L Q M N S L R A E D
91  T A V Y Y C A R N L G P S F Y F D Y W G Q G T L V T V S S A S T K G P S V F P L A P S S K
136 S T S G G T A A L G C L V K D Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G
181 L Y S L S S V V T V P S S S L G T Q T Y I C N V N H K P S N T K V D K K V E P K S C D K T
226 H T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V V V D V S H
271 E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y R V V S V L T V L H Q D W
316 L N G K E Y K C K V S N K A L P A P I E K T I S K A K G Q P R E P Q V Y T L P P S R E E M
361 T K N Q V S L T C L V K G F Y P S D I A V E W E S N G Q P E N N Y K T T P P V L D S D G S
406 F F L Y S K L T V D K S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K
```

FIG. 8B

FIG. 9

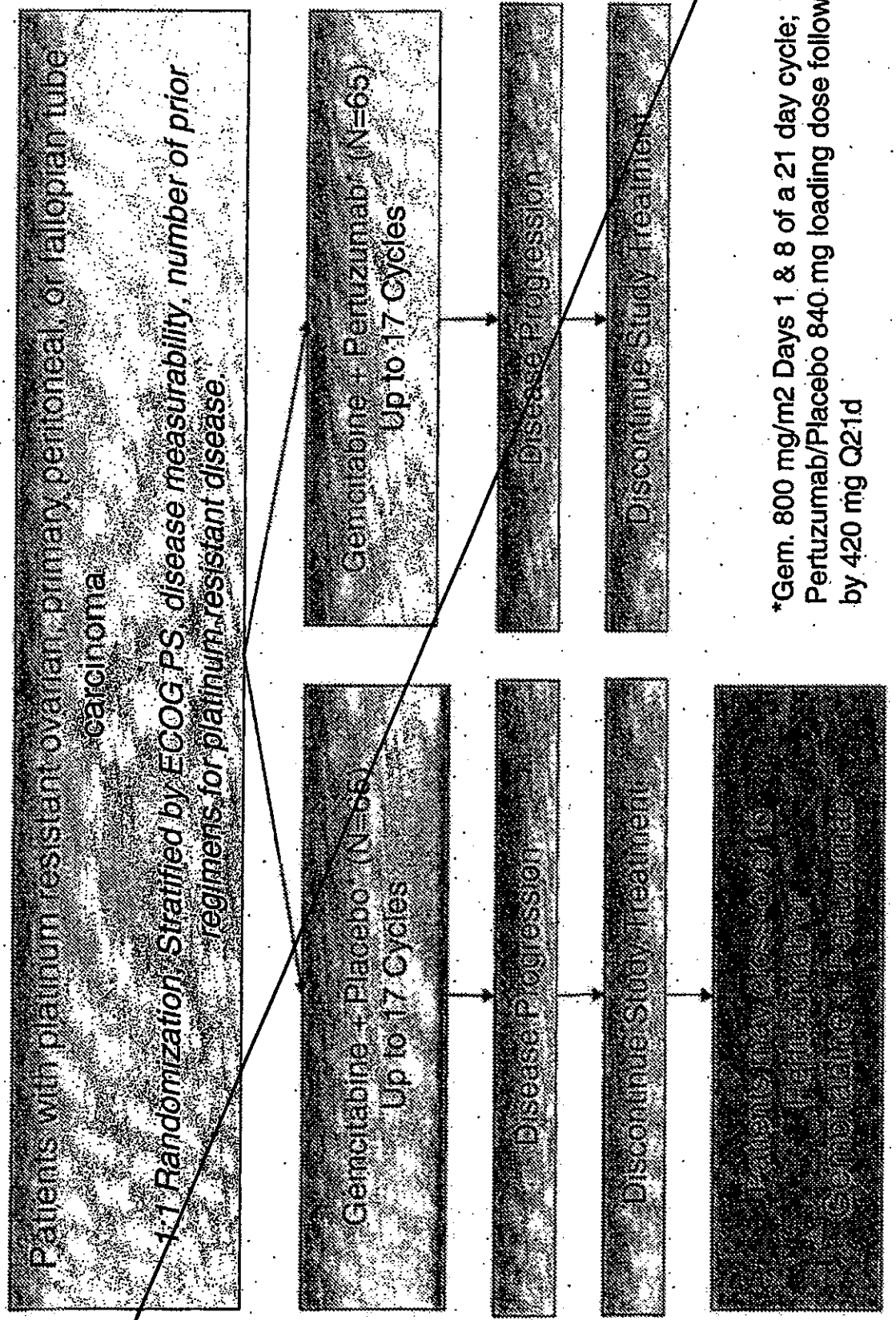

Patients with platinum resistant ovarian, primary peritoneal, or fallopian tube carcinoma
1:1 Randomization, Stratified by ECOG PS, disease measurability, number of prior regimens for platinum resistant disease.
Gemcitabine + Bevacizumab* (N=65)
Up to 17 Cycles
Gemcitabine + Placebo* (N=65)
Up to 17 Cycles
Disease Progression
Disease Progression
Discontinue Study Treatment
Discontinue Study Treatment
Patients may cross over to Pertuzumab monotherapy or Gemcitabine + Pertuzumab
*Gem. 800 mg/m2 Days 1 & 8 of a 21 day cycle; Pertuzumab/Placebo 840 mg loading dose followed by 420 mg Q21d

FIG. 10A

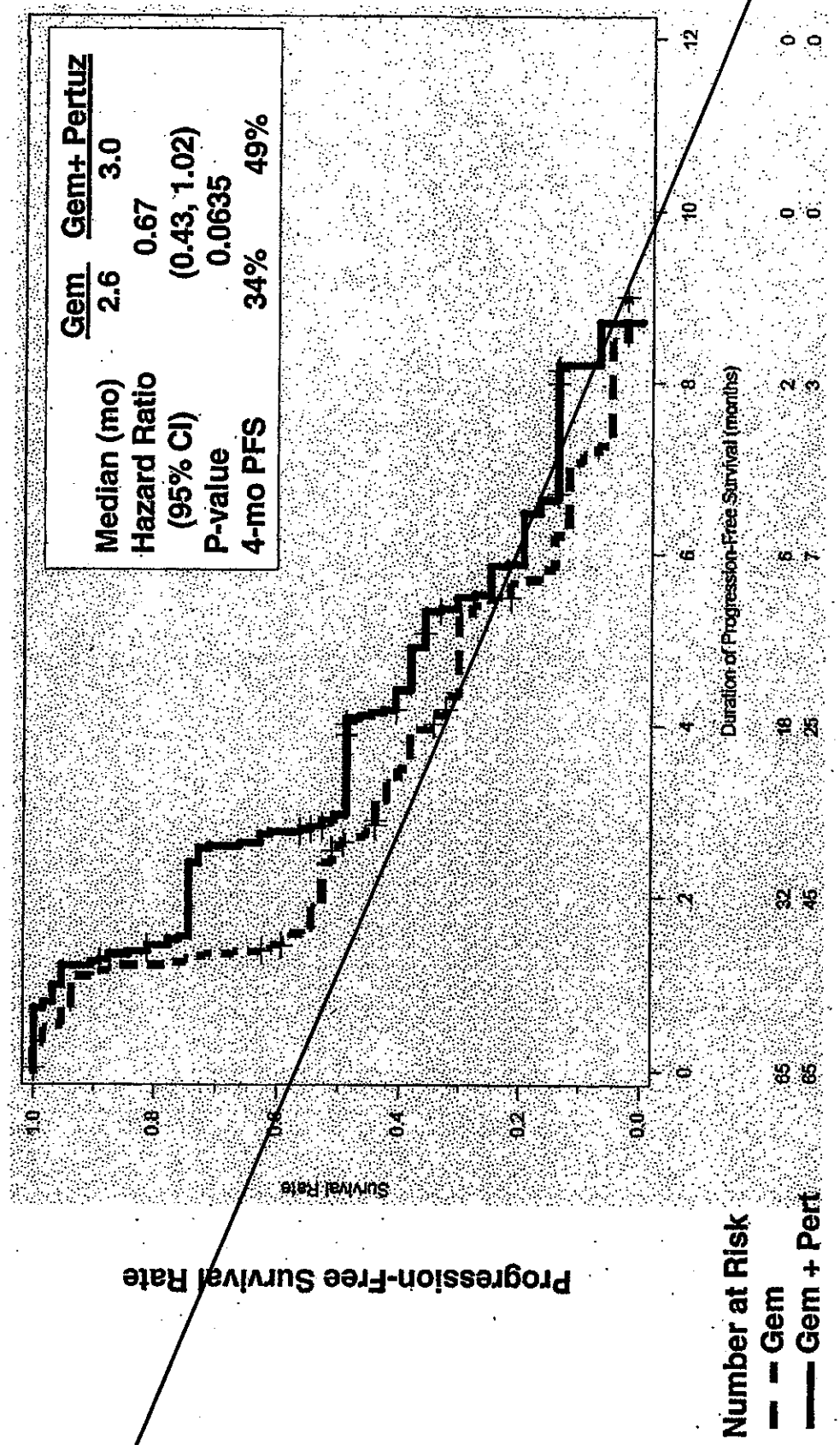

Progression-Free Survival Rate
Survival Rate
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
Duration of Progression-Free Survival (months)
Gem Gem+ Pertuz
Median (mo) 2.6 3.0
Hazard Ratio 0.67
(95% CI) (0.43, 1.02)
P-value 0.0635
4-mo PFS 34% 49%
Number at Risk
Gem
Gem + Pert
85 32 18 6 2 0 0
85 45 25 7 3 0 0

FIG. 10B

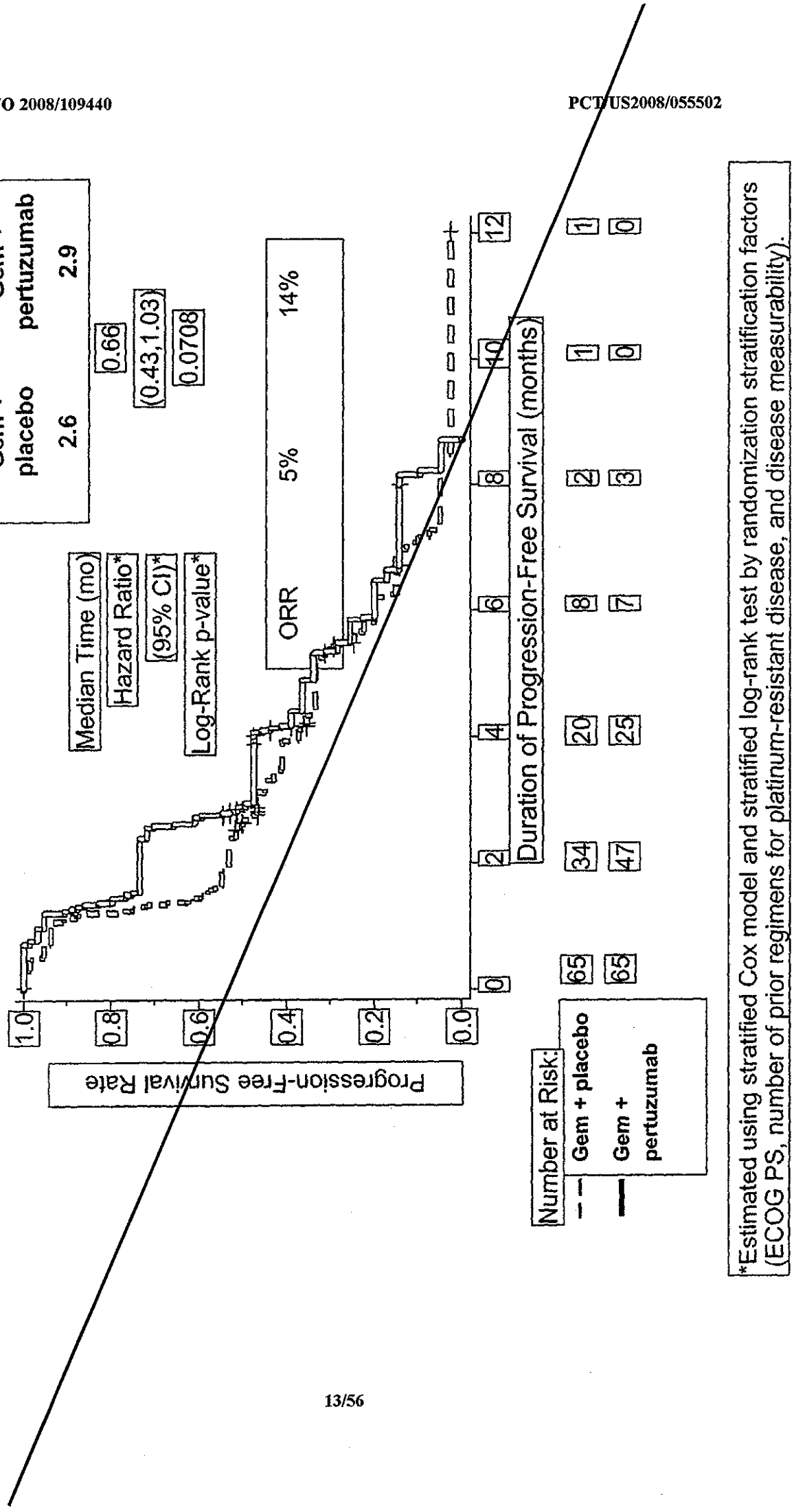

PROGRESSION-FREE SURVIVAL
Gem + placebo
Gem + pertuzumab
Median Time (mo)
2.6
2.9
Hazard Ratio*
0.66
(95% CI)*
(0.43,1.03)
Log-Rank p-value*
0.0708
ORR
5%
14%
Progression-Free Survival Rate
1.0
0.8
0.6
0.4
0.2
0.0
Duration of Progression-Free Survival (months)
0
2
4
6
8
10
12
Number at Risk:
Gem + placebo
65
34
20
8
2
1
1
Gem + pertuzumab
65
47
25
7
3
0
0
*Estimated using stratified Cox model and stratified log-rank test by randomization stratification factors (ECOG PS, number of prior regimens for platinum-resistant disease, and disease measurability).

FIG. 11A

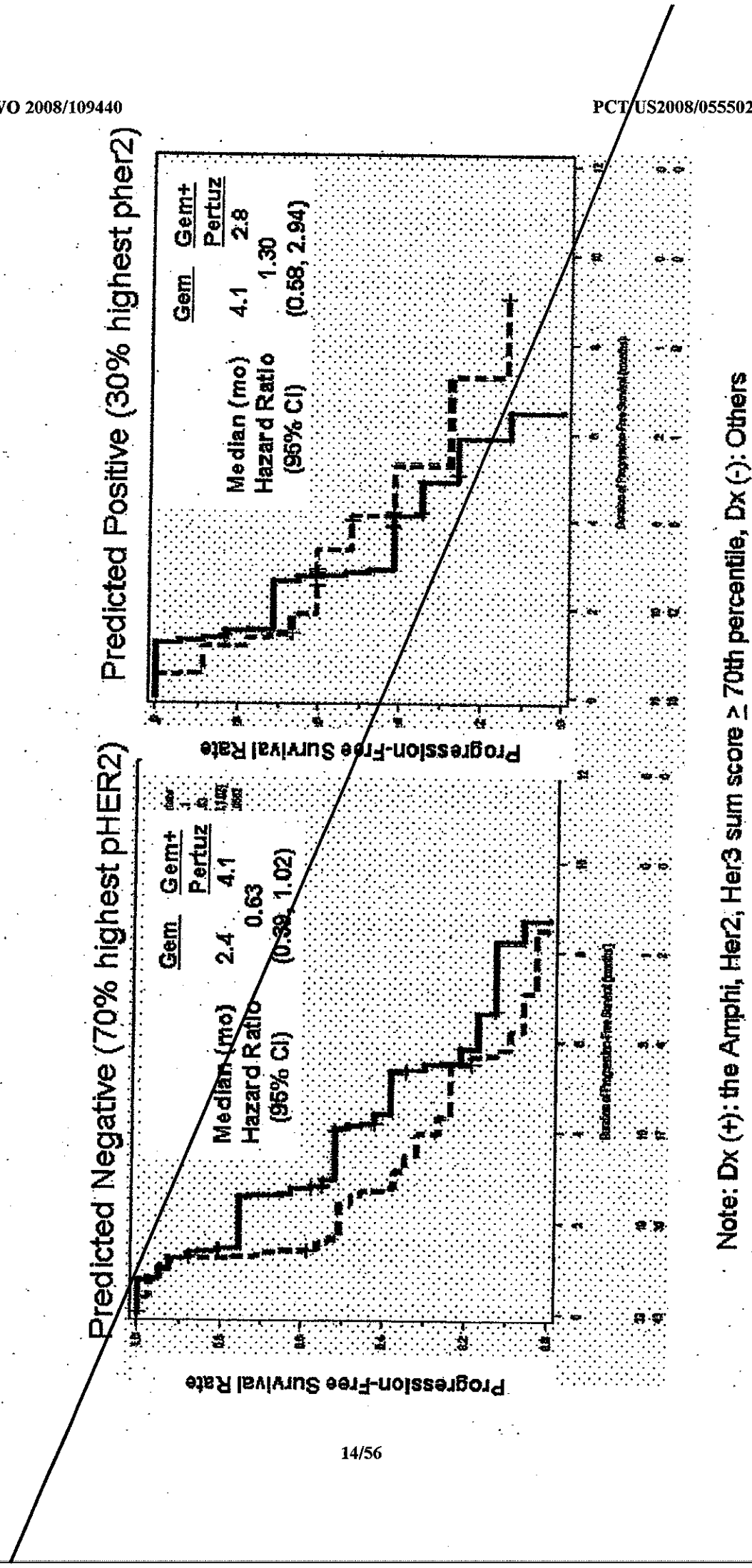
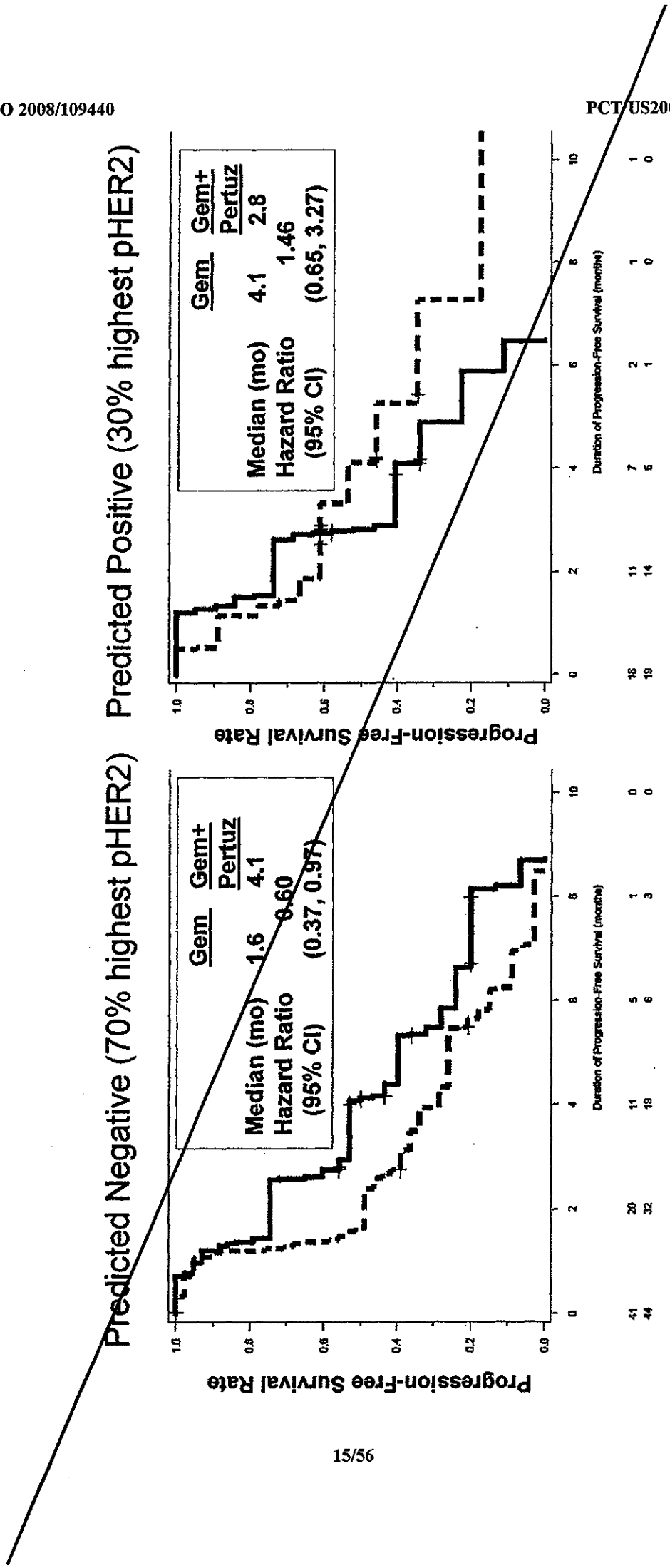

Predicted Positive (30% highest pher2)
Progression-Free Survival Rate
Gem
Gem+ Pertuz
Median (mo)
4.1
2.8
Hazard Ratio
1.30
(95% CI)
(0.58, 2.94)
Predicted Negative (70% highest pHER2)
Progression-Free Survival Rate
Gem
Gem+ Pertuz
Median (mo)
2.4
4.1
Hazard Ratio
0.63
(95% CI)
(0.38, 1.02)
Note: Dx (+): the Amphi, Her2, Her3 sum score ≥ 70th percentile, Dx (-): Others

FIG. 11B



Note: Dx (+): The Amphi, Her2, Her3 sum score ≥ 70th percentile, Dx (-): Others

FIG. 12A

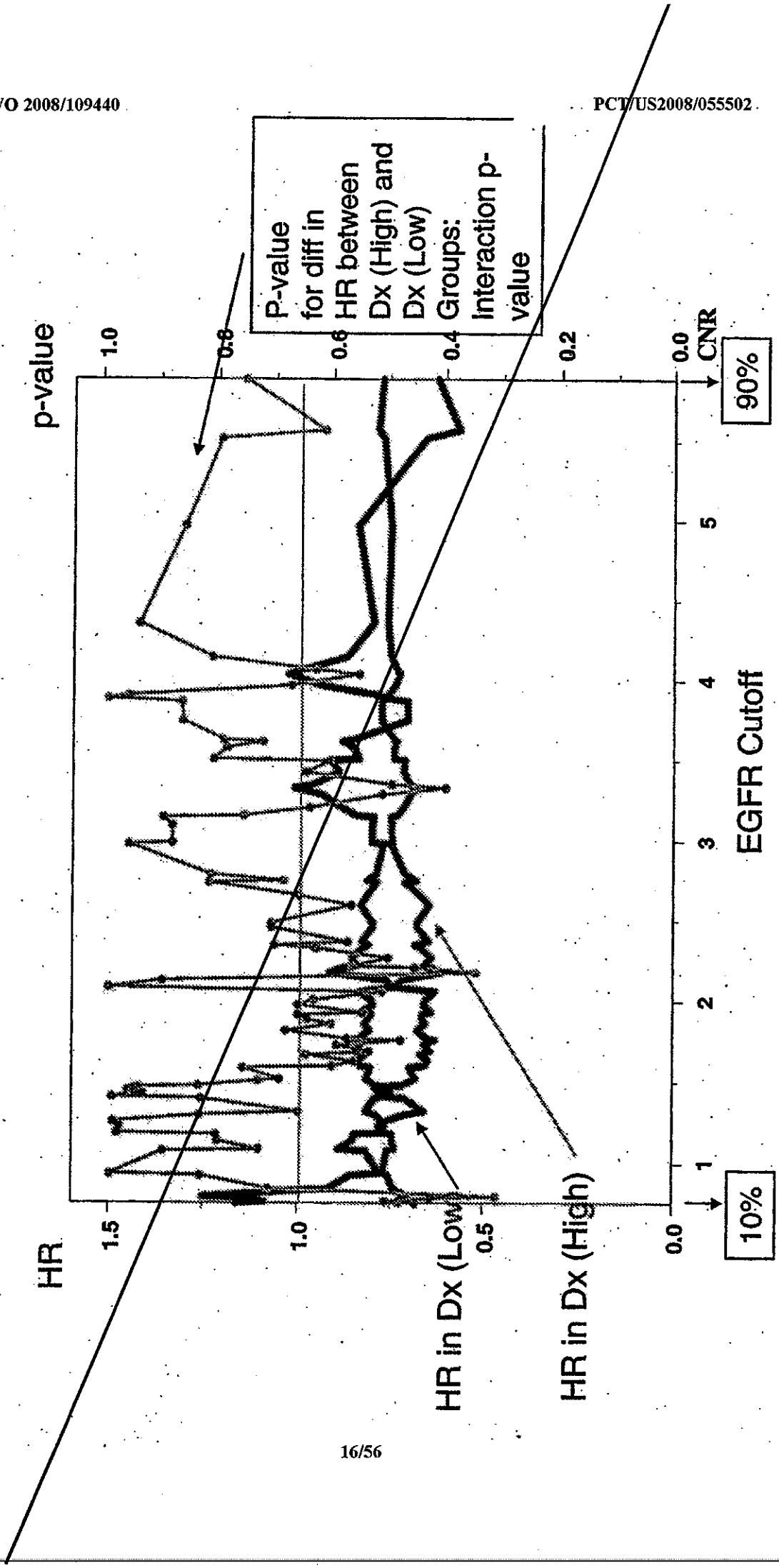
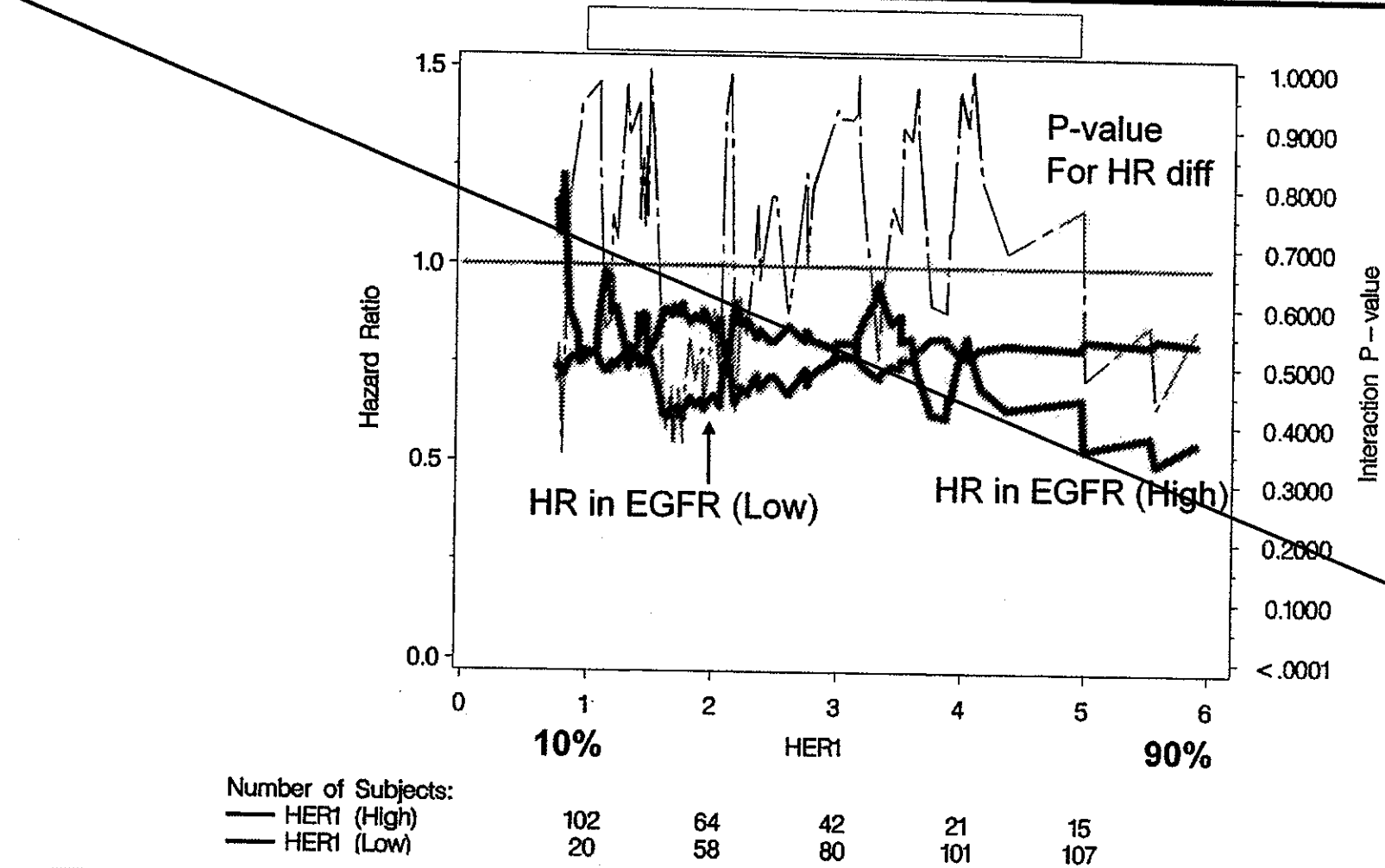

p-value
1.0
0.8
0.6
0.4
0.2
0.0
CNR
P-value for diff in HR between Dx (High) and Dx (Low) Groups: Interaction p-value
90%
HR
1.5
1.0
0.5
0.0
HR in Dx (Low)
HR in Dx (High)
1
2
3
4
5
EGFR Cutoff
10%
P-values were not adjusted for multiple comparisons.

FIG. 12B

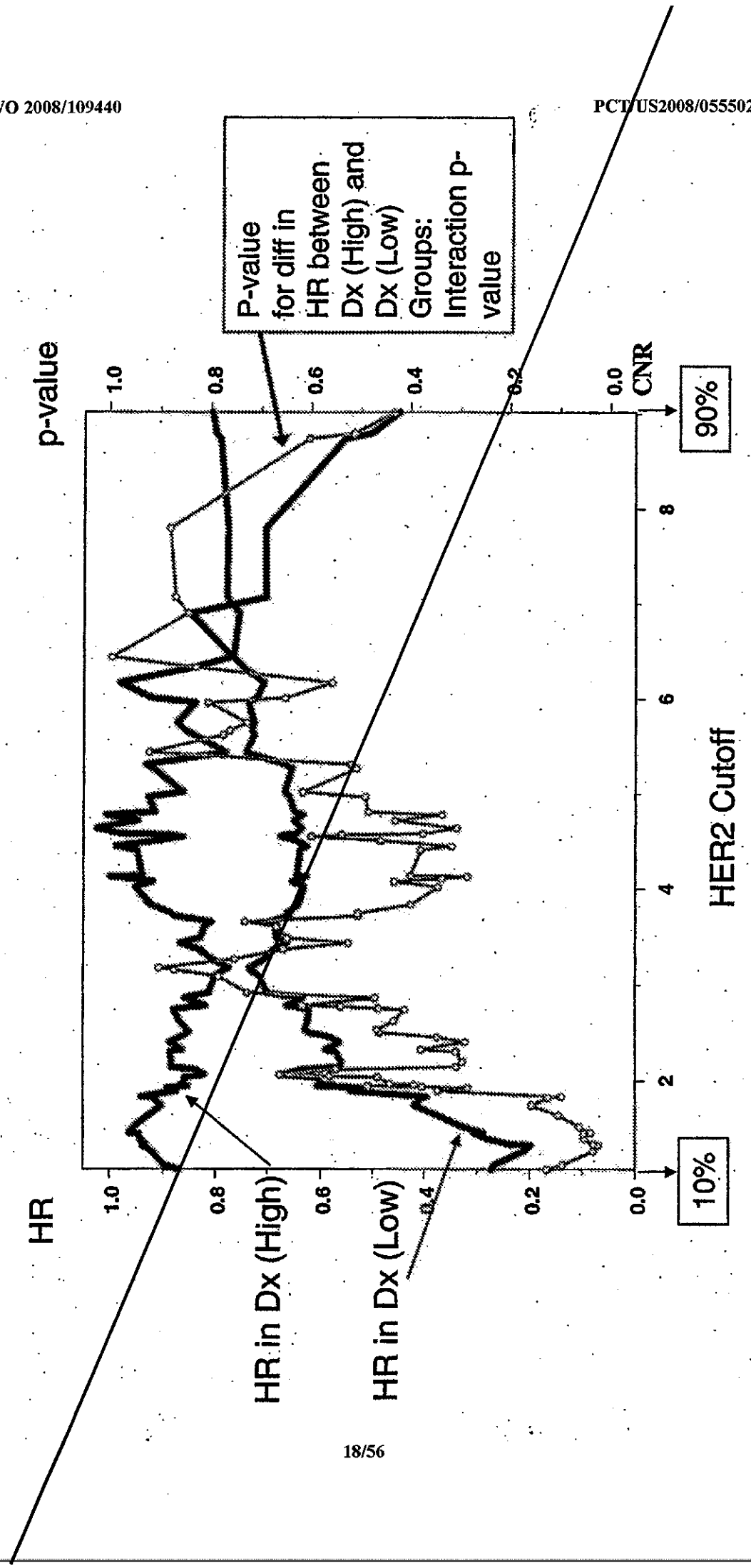
Exploratory analysis:

TOC3258g: PFS by qRT-PCR EGFR Cutoffs



P-values were not adjusted for multiple comparisons.

FIG. 13A



P-values were not adjusted for multiple comparisons.

FIG. 13B

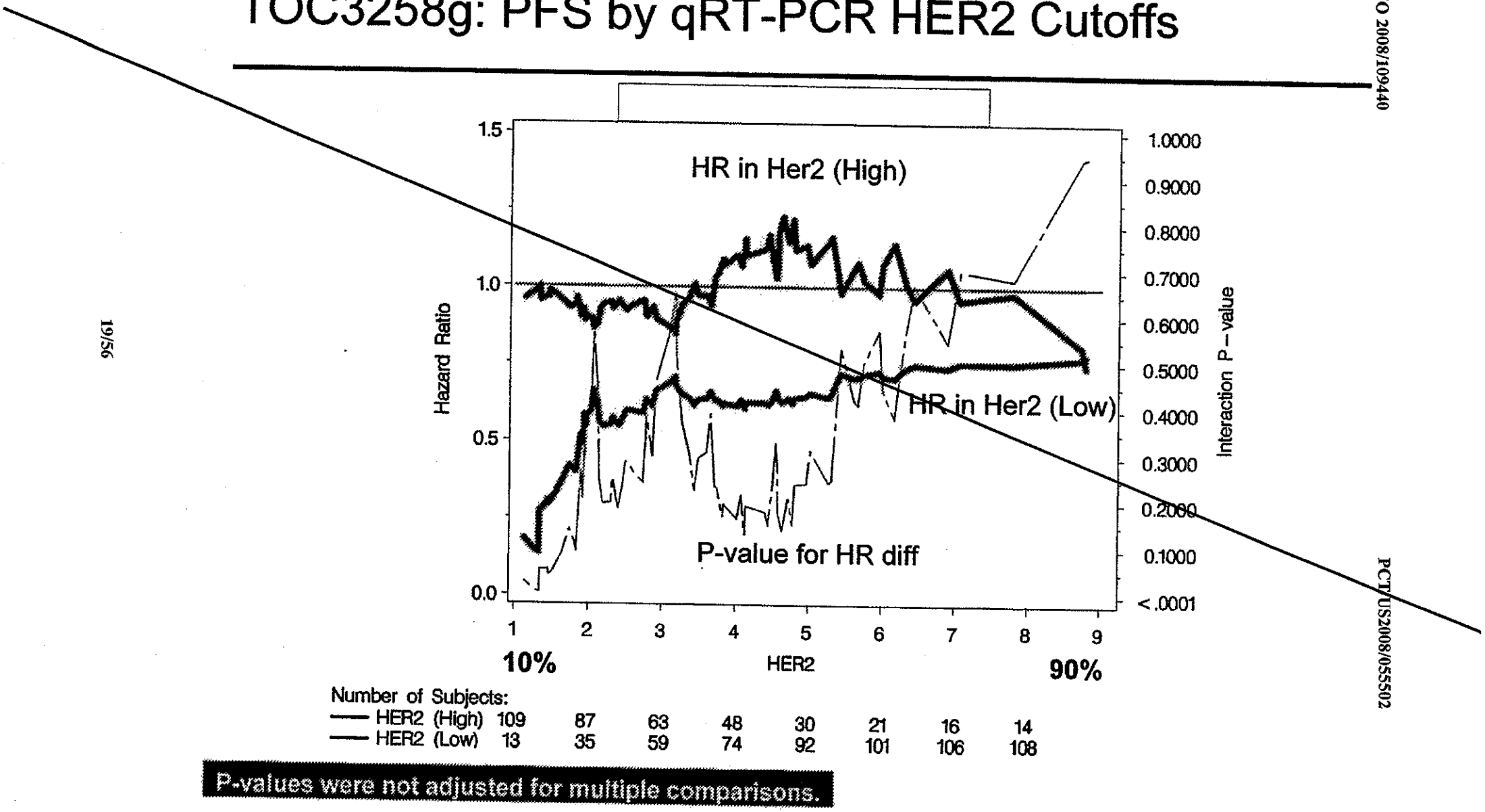

TOC3258g: PFS by qRT-PCR HER2 Cutoffs
HR in Her2 (High)
HR in Her2 (Low)
P-value for HR diff
Hazard Ratio
Interaction P−value
1.5
1.0
0.5
0.0
1.0000
0.9000
0.8000
0.7000
0.6000
0.5000
0.4000
0.3000
0.2000
0.1000
< .0001
1
2
3
4
5
6
7
8
9
10%
HER2
90%
Number of Subjects:
HER2 (High) 109 87 63 48 30 21 16 14
HER2 (Low) 13 35 59 74 92 101 106 108
P-values were not adjusted for multiple comparisons.

FIG. 14A

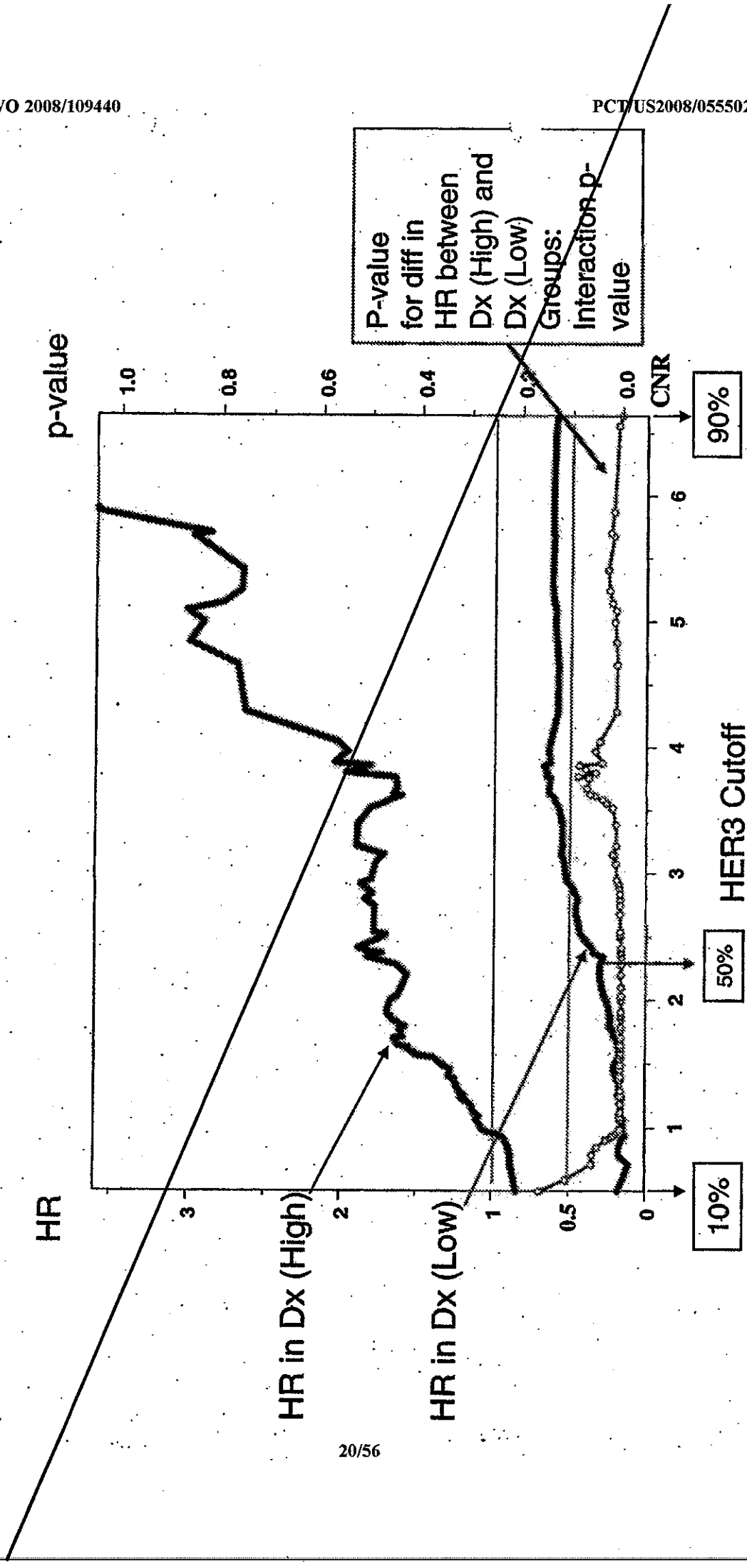
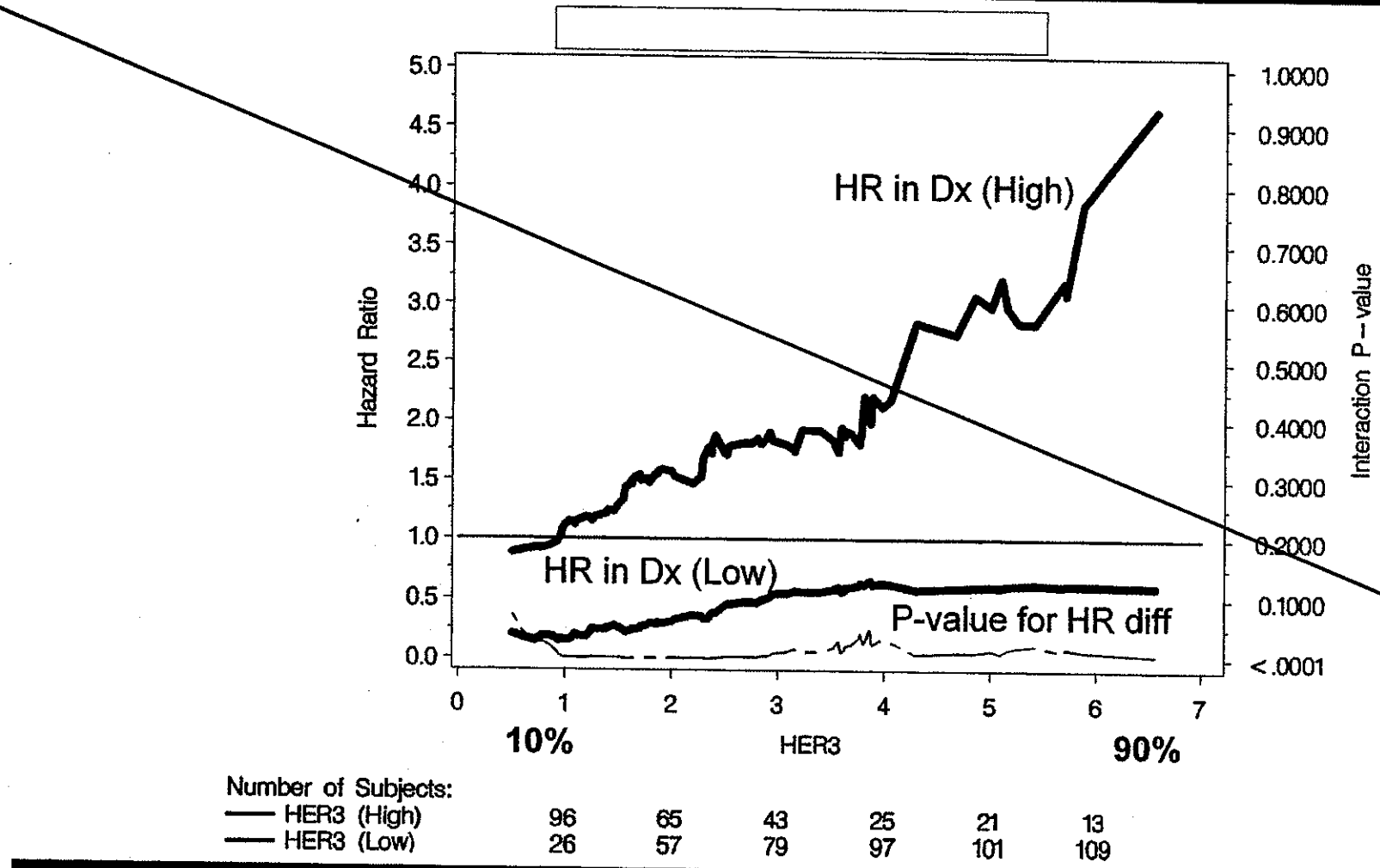

p-value
HR
CNR
P-value for diff in HR between Dx (High) and Dx (Low) Groups: Interaction p-value
HR in Dx (High)
HR in Dx (Low)
HER3 Cutoff
10%
50%
90%
P-values were not adjusted for multiple comparisons.

FIG. 14B

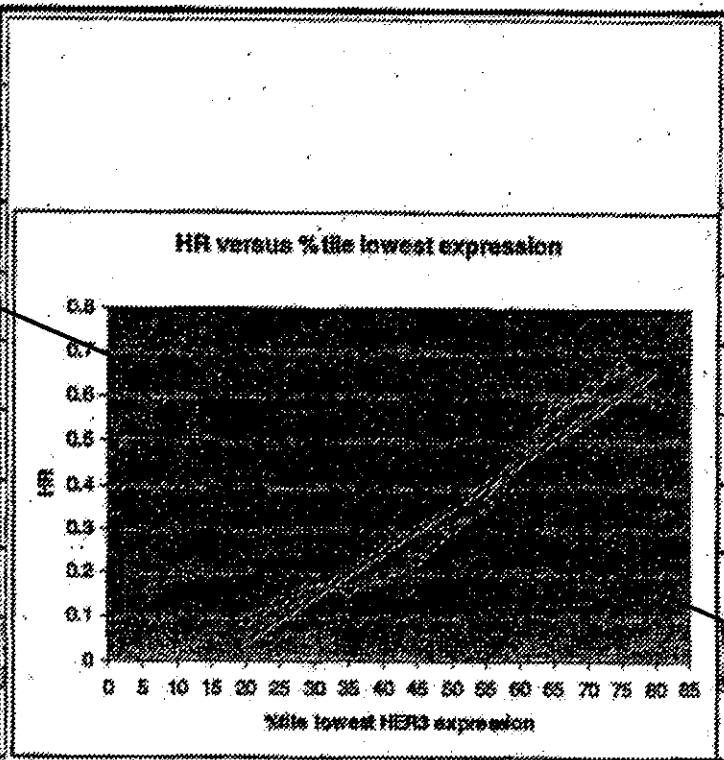
TOC3258g: PFS by qRT-PCR HER3 Cutoffs



P-values were not adjusted for multiple comparisons.

FIG. 15A

Cutoff		Low HER3 Expression			
%tile	Abs. Value	N	# Events	HR (95%CI)	Logrank P-value
20	0.99	23	16	0.09 (0.02, 0.42)	0.0002
25	1.19	28	21	0.13 (0.04, 0.45)	0.0002
30	1.4	35	28	0.18 (0.06, 0.52)	0.0004
35	1.57	41	32	0.16 (0.06, 0.43)	<.0001
40	1.71	47	36	0.19 (0.08, 0.47)	<.0001
45	1.88	53	40	0.23 (0.11, 0.50)	<.0001
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
55	2.41	65	52	0.36 (0.20, 0.65)	0.0005
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
65	3.14	77	63	0.57 (0.34, 0.95)	0.0299
70	3.59	83	69	0.62 (0.38, 1.00)	0.0488
75	3.8	89	75	0.67 (0.42, 1.06)	0.0898
80	4.29	95	78	0.59 (0.37, 0.92)	0.0196



P-values were not adjusted for multiple comparisons.

FIG. 15B

PFS by qRT-PCR HER3 Levels

Cutoff Value		Low HER3 Expression			
%tile	Abs. Value	N	# Events	HR (95%CI)	Logrank P-value
25	1.19	30	23	0.13 (0.04, 0.41)	<.0001
30	1.39	36	29	0.22 (0.09, 0.56)	0.0005
35	1.56	42	33	0.20 (0.09, 0.48)	<.0001
40	1.70	48	38	0.22 (0.10, 0.50)	<.0001
45	1.87	54	42	0.29 (0.14, 0.58)	0.0002
50	2.24	61	48	0.34 (0.18, 0.63)	0.0004
55	2.38	66	53	0.36 (0.20, 0.65)	0.0005
60	2.75	73	59	0.48 (0.28, 0.84)	0.0080
65	3.08	79	65	0.56 (0.34, 0.94)	0.0255
70	3.56	85	71	0.62 (0.38, 1.00)	0.0459
75	3.77	91	76	0.65 (0.41, 1.03)	0.0650

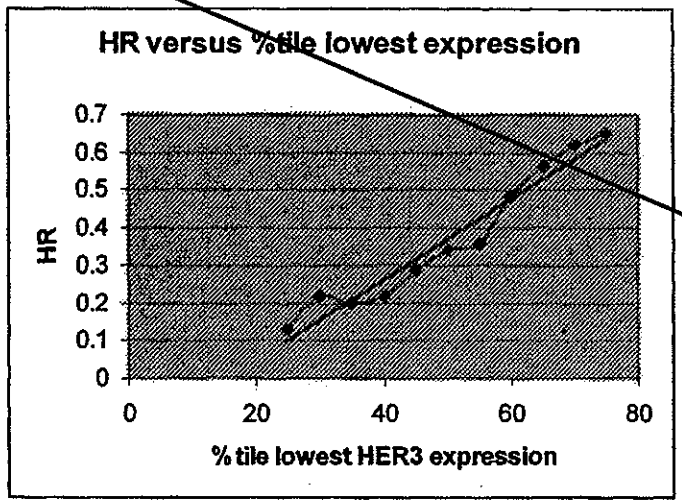
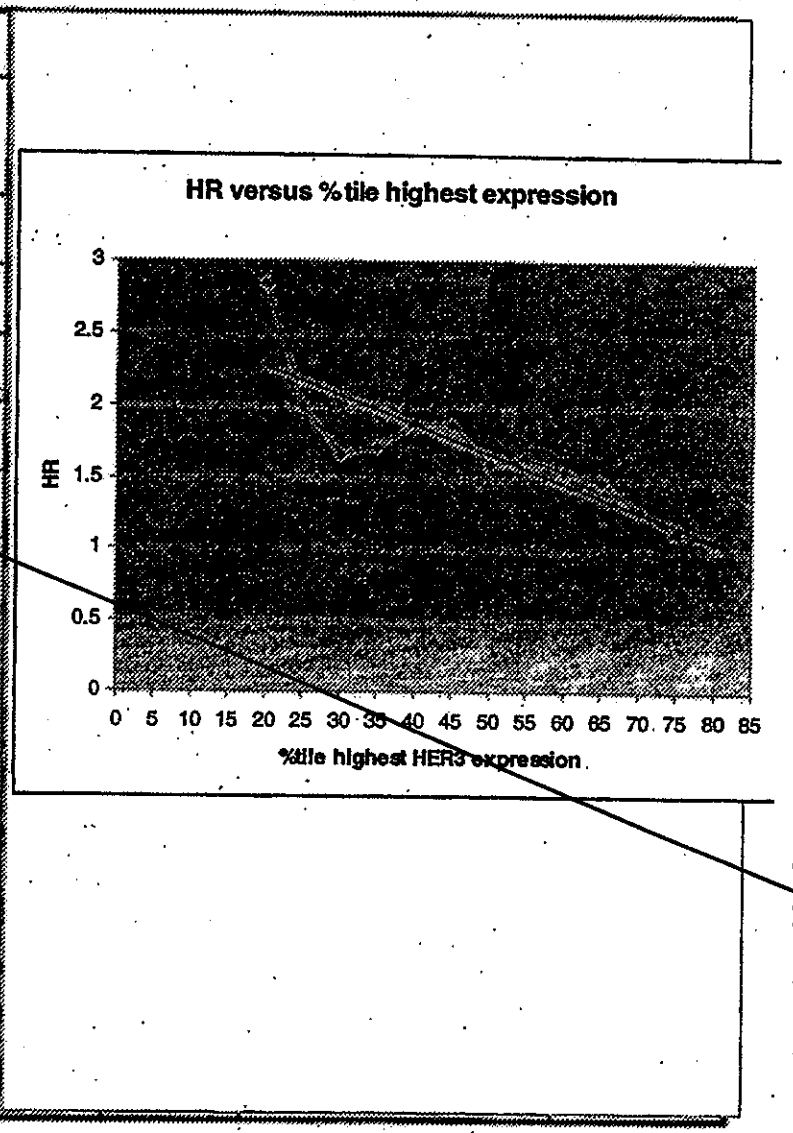


FIG. 16A

Cutoff		High HER3 Expression			
%tile	Abs. Value	N	# Events	HR (95%CI)	Logrank P-value
20	0.99	96	78	1.06 (0.67, 1.65)	0.8083
25	1.19	91	73	1.13 (0.71, 1.81)	0.5875
30	1.4	84	66	1.28 (0.77, 2.10)	0.3318
35	1.57	78	62	1.49 (0.89, 2.51)	0.1280
40	1.71	72	58	1.55 (0.90, 2.68)	0.1141
45	1.88	66	54	1.64 (0.94, 2.88)	0.0817
50	2.08	60	48	1.60 (0.89, 2.87)	0.1086
55	2.41	54	42	1.87 (0.97, 3.57)	0.0565
60	2.8	48	37	1.80 (0.89, 3.64)	0.0903
65	3.14	42	31	1.72 (0.78, 3.75)	0.1693
70	3.59	36	25	1.67 (0.72, 3.90)	0.2270
75	3.8	30	19	2.00 (0.71, 5.62)	0.1790
80	4.29	24	16	2.85 (0.89, 9.20)	0.0667



P-values were not adjusted for multiple comparisons.

FIG. 16B

PFS by qRT-PCR HER3 Levels

Cutoff Value		High HER3 Expression			
%tile	Abs. Value	N	# Events	HR (95%CI)	Logrank P-value
25	1.19	92	74	1.16 (0.73, 1.84)	0.5222
30	1.39	86	68	1.20 (0.74, 1.94)	0.4674
35	1.56	80	64	1.37 (0.83, 2.26)	0.2230
40	1.70	74	59	1.50 (0.88, 2.55)	0.1381
45	1.87	68	55	1.50 (0.87, 2.61)	0.1468
50	2.24	61	49	1.48 (0.83, 2.63)	0.1809
55	2.38	56	44	1.74 (0.93, 3.27)	0.0816
60	2.75	49	38	1.81 (0.90, 3.67)	0.0945
65	3.08	43	32	1.78 (0.82, 3.86)	0.1382
70	3.56	37	26	1.73 (0.75, 3.99)	0.1943
75	3.77	31	21	1.90 (0.73, 4.93)	0.1804

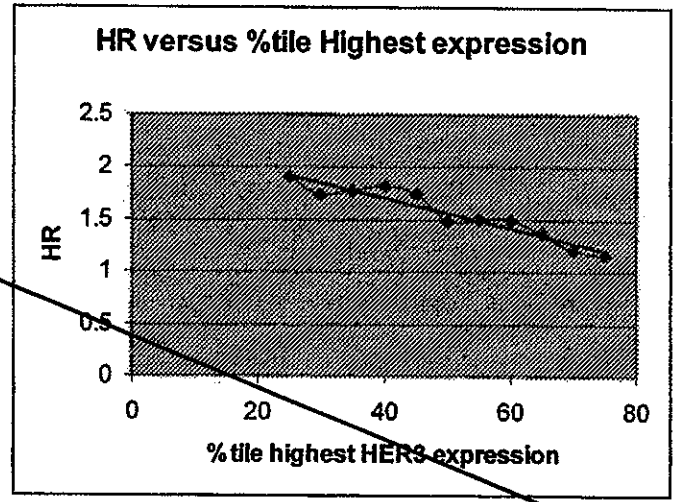


FIG. 17A

Cutoff		High HER3 Expression				Low HER3 Expression			
%tile	Abs. Value	N	# Events	HR (95%CI)	Logrank P-value	N	# Events	HR (95%CI)	Logrank P-value
20	0.99	96	78	1.06 (0.67, 1.65)	0.8083	23	16	0.09 (0.02, 0.42)	0.0002
KM→	1.19	91	73	1.13 (0.71, 1.81)	0.5875	28	21	0.13 (0.04, 0.45)	0.0002
30	1.4	84	66	1.28 (0.77, 2.10)	0.3318	35	28	0.18 (0.06, 0.52)	0.0004
35	1.57	78	62	1.49 (0.89, 2.51)	0.1280	41	32	0.16 (0.06, 0.43)	<.0001
40	1.71	72	58	1.55 (0.90, 2.68)	0.1141	47	36	0.19 (0.08, 0.47)	<.0001
45	1.88	66	54	1.64 (0.94, 2.88)	0.0817	53	40	0.23 (0.11, 0.50)	<.0001
KM→	2.28	60	48	1.60 (0.87, 2.89)	0.1161	59	46	0.30 (0.16, 0.58)	0.0002
55	2.41	54	42	1.87 (0.97, 3.57)	0.0565	65	52	0.36 (0.20, 0.65)	0.0005
60	2.55	48	35	1.53 (0.92, 3.80)	0.0960	71	57	0.42 (0.24, 0.73)	0.0020
65	3.14	42	31	1.72 (0.78, 3.75)	0.1693	77	63	0.57 (0.34, 0.95)	0.0299
70	3.59	36	25	1.67 (0.72, 3.90)	0.2270	83	69	0.62 (0.38, 1.00)	0.0488
75	3.8	30	19	2.00 (0.71, 5.62)	0.1790	89	75	0.67 (0.42, 1.06)	0.0898
80	4.29	24	16	2.85 (0.89, 9.20)	0.0667	95	78	0.59 (0.37, 0.92)	0.0196

P-values were not adjusted for multiple comparisons.

FIG. 17B

PFS by qRT-PCR HER3 Levels

Cutoff Value		High HER3 Expression				Low HER3 Expression			
%tile	Abs. Value	N	# Events	HR (95%CI)	Logrank P-value	N	# Events	HR (95%CI)	Logrank P-value
KM	1.19	92	74	1.16 (0.73, 1.84)	0.5222	30	23	0.13 (0.04, 0.41)	<.0001
30	1.39	86	68	1.20 (0.74, 1.94)	0.4674	36	29	0.22 (0.09, 0.56)	0.0005
35	1.56	80	64	1.37 (0.83, 2.26)	0.2230	42	33	0.20 (0.09, 0.48)	<.0001
40	1.70	74	59	1.50 (0.88, 2.55)	0.1381	48	38	0.22 (0.10, 0.50)	<.0001
45	1.87	68	55	1.50 (0.87, 2.61)	0.1468	54	42	0.29 (0.14, 0.58)	0.0002
KM	2.24	61	49	1.48 (0.83, 2.63)	0.1809	61	48	0.34 (0.18, 0.63)	0.0004
55	2.38	56	44	1.74 (0.93, 3.27)	0.0816	66	53	0.36 (0.20, 0.65)	0.0005
60	2.75	49	38	1.81 (0.90, 3.67)	0.0945	73	59	0.48 (0.28, 0.84)	0.0080
65	3.08	43	32	1.78 (0.82, 3.86)	0.1382	79	65	0.56 (0.34, 0.94)	0.0255
70	3.56	37	26	1.73 (0.75, 3.99)	0.1943	85	71	0.62 (0.38, 1.00)	0.0459
75	3.77	31	21	1.90 (0.73, 4.93)	0.1804	91	76	0.65 (0.41, 1.03)	0.0650

FIG. 18A

qrt-PCR HER3	n	# of Events	Treatment HR (95% CI)	Log-rank P-value
0 – < 25th percentile	28	21	0.13 (0.04, 0.45)	0.0002
25 – < 50th percentile	31	25	0.42 (0.17, 1.00)	0.0465
50 – < 75th percentile	30	29	2.11 (0.94, 4.75)	0.0631
75 – 100th percentile	30	19	2.00 (0.71, 5.62)	0.1790

P-values were not adjusted for multiple comparisons.

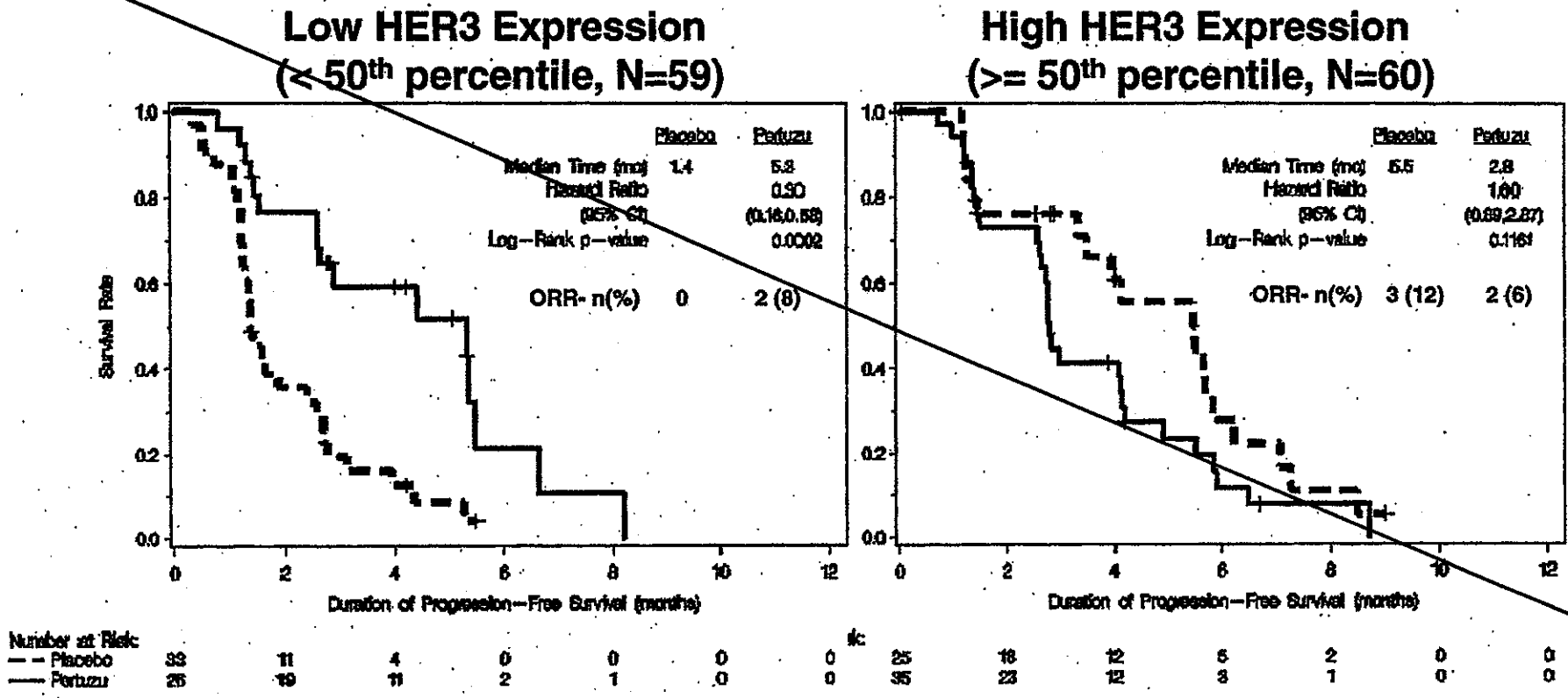
FIG. 18B

Progression-Free Survival (PFS) Analysis by HER3 Expression Quartiles

qRT-PCR HER3	N	# Events	HR (95%CI)	Logrank P-value
0 – < 25th percentile	30	23	0.13 (0.04, 0.41)	<.0001
25 – < 50th percentile	31	25	0.66 (0.29, 1.48)	0.3181
50 – < 75th percentile	30	28	1.59 (0.73, 3.44)	0.2318
75 – 100th percentile	31	21	1.90 (0.73, 4.93)	0.1804

FIG. 19A

All patients	Gem	Gem+ Pertuz
Median (mo)	2.6	3.0
Hazard Ratio*	0.67	
(95% CI)	(0.43, 1.02)	
P-value*	0.0635	
ORR-n(%)	3 (5)	5 (8)



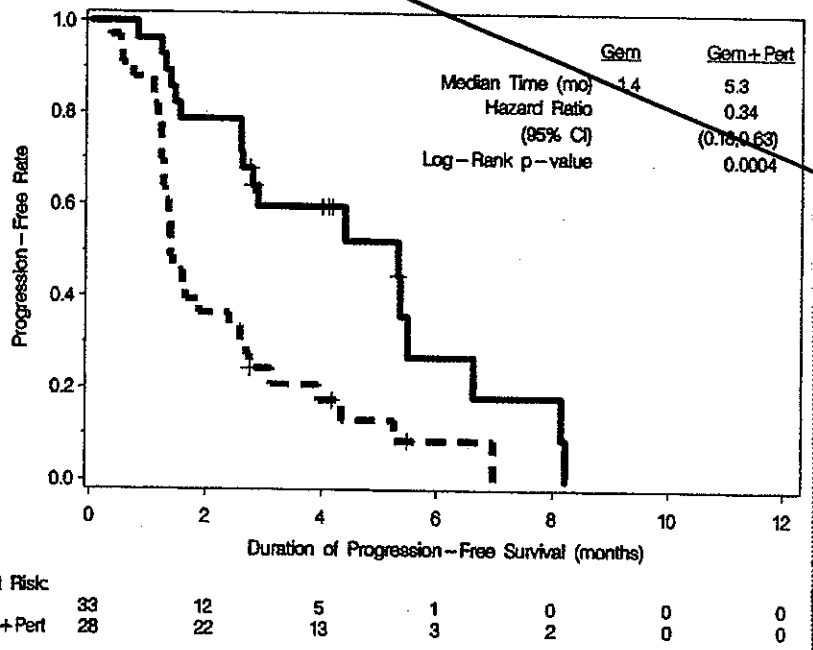
P-value for the difference in HR between two dx subgroups is 0.0001
Note: 50th percentile = 2.28 CNR.

FIG. 19B

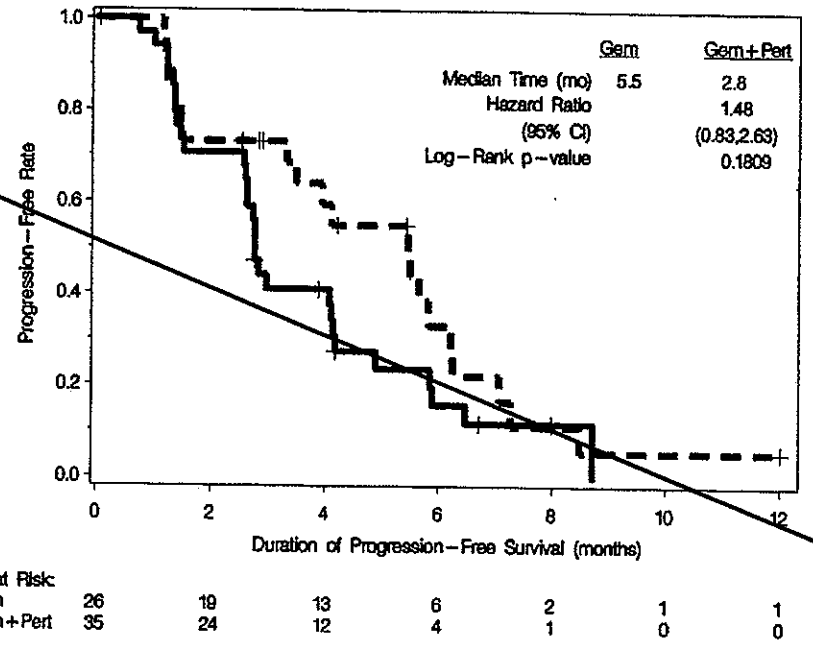
PFS by HER3 qRT-PCR 50/50 - split

All patients	Gem	Gem+Pertuz
Median (mo)	2.6	2.9
Hazard Ratio*	0.66	
(95% CI)	(0.43, 1.03)	
P-value*	0.07	

Low HER3 Expression (< 50th percentile, N=61)



High HER3 Expression (>= 50th percentile, N=61)



P-value for the difference in HR between two dx subgroups is 0.0005
Note: 50th percentile = 2.24 CNR.

FIG. 20A

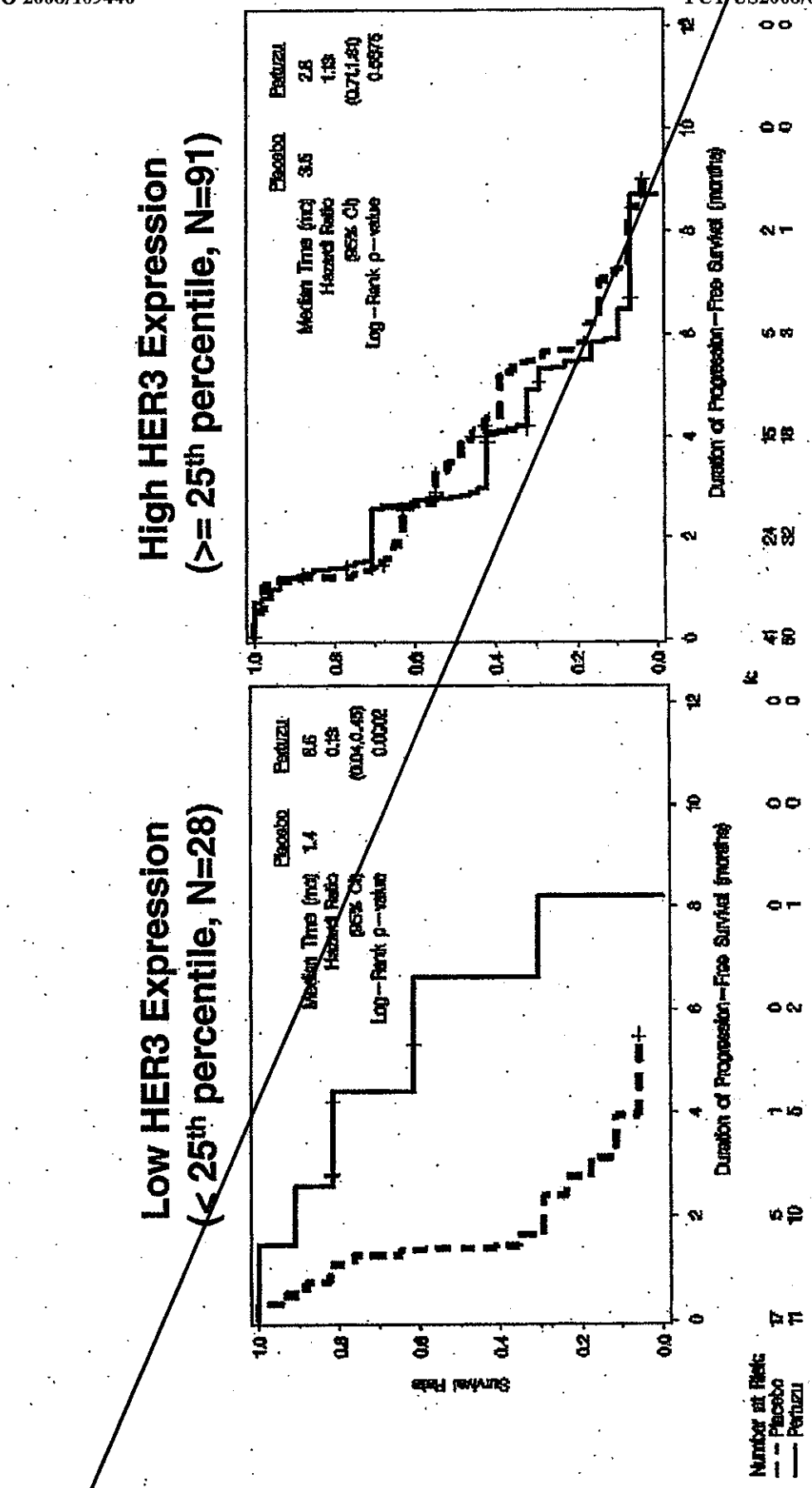
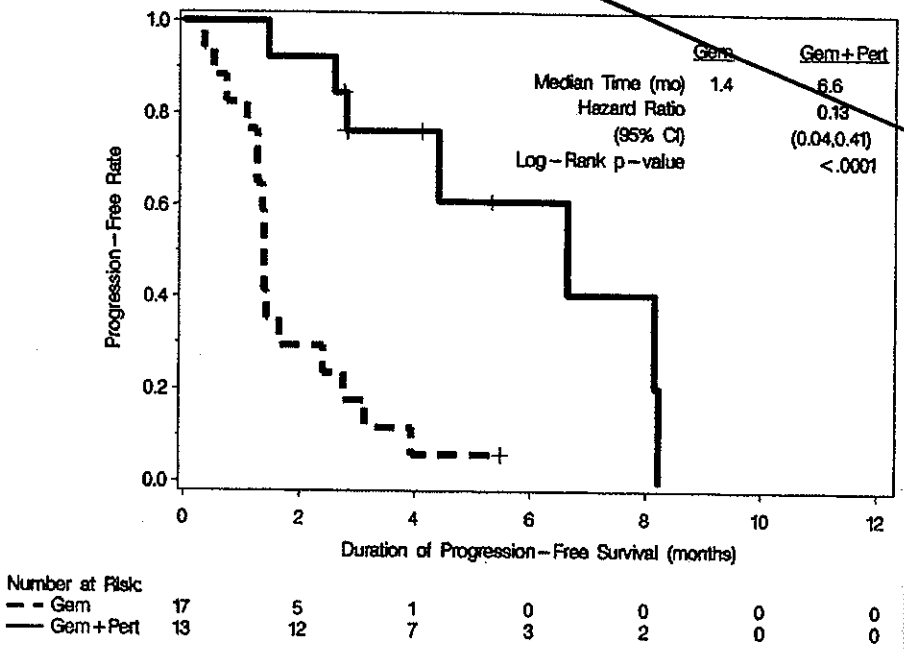

High HER3 Expression
(>= 25th percentile, N=91)
Placebo
Perjeta
Median Time (mo) 3.5 2.8
Hazard Ratio 1.19
(95% CI) (0.71,1.97)
Log-Rank p-value 0.5075
Duration of Progression-Free Survival (months)
Low HER3 Expression
(< 25th percentile, N=28)
Placebo
Perjeta
Median Time (mo) 1.4 8.5
Hazard Ratio 0.19
(95% CI) (0.04,0.49)
Log-Rank p-value 0.0002
Survival Rate
Duration of Progression-Free Survival (months)
Number at Risk:
Placebo 17 5 1 0 0 0 0
Perjeta 11 10 5 2 1 0 0

FIG. 20B

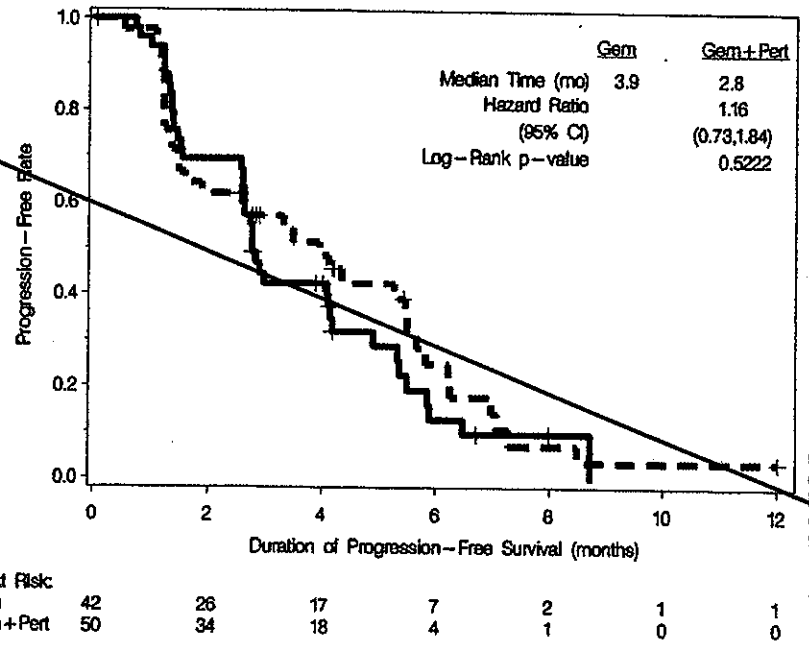
PFS by HER3 qRT-PCR 25/75 - split

All patients	Gem	Gem+Pertuz
Median (mo)	2.6	2.9
Hazard Ratio*	0.66	
(95% CI)	(0.43, 1.03)	
P-value*	0.07	

Low HER3 Expression (< 25th percentile, N=30)

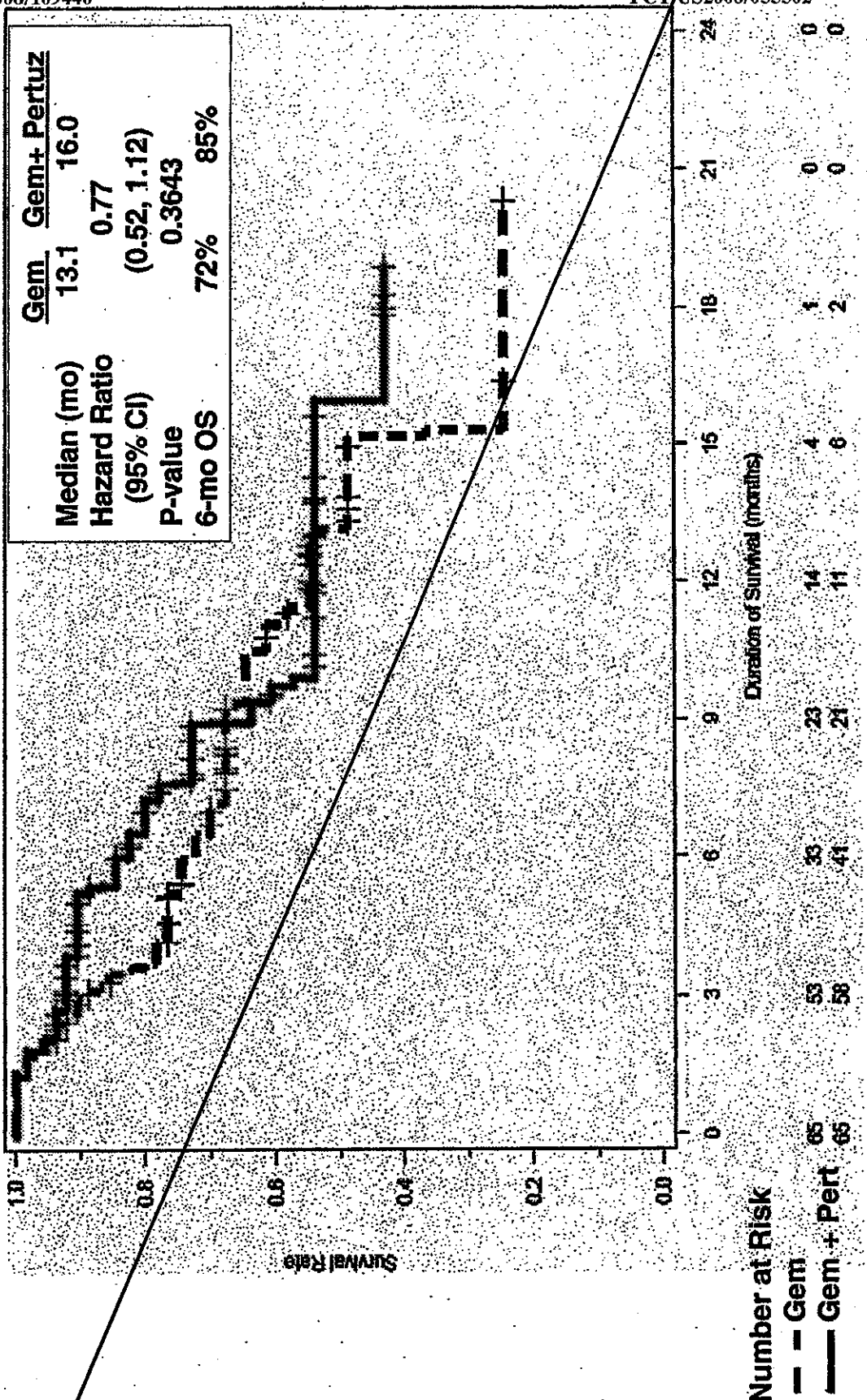


High HER3 Expression (>= 25th percentile, N=92)



P-value for the difference in HR between two dx subgroups is 0.0003
Note: 25th percentile = 1.19 CNR.

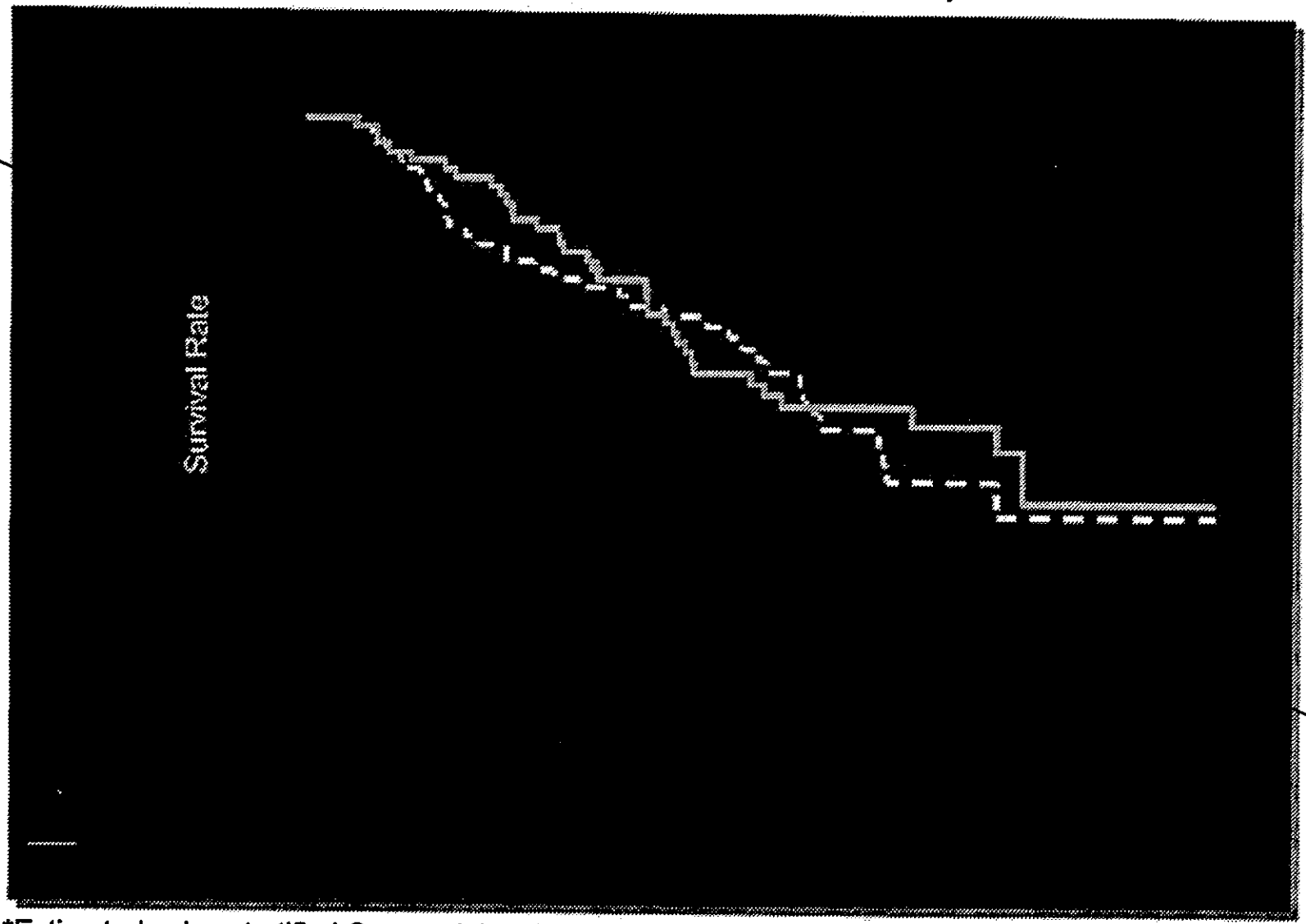
FIG. 21A


Gem
Gem+ Pertuz
Median (mo)
13.1
16.0
Hazard Ratio
0.77
(95% CI)
(0.52, 1.12)
P-value
0.3643
6-mo OS
72%
85%
Survival Rate
1.0
0.8
0.6
0.4
0.2
0.0
Duration of Survival (months)
0
3
6
9
12
15
18
21
24
Number at Risk
Gem
65
53
33
23
14
6
2
0
0
Gem + Pert
65
58
41
21
11
4
1
0
0

Preliminary Overall Survival

(71 deaths as of April 20, 2007)

FIG. 21B



*Estimated using stratified Cox model and stratified log-rank test by randomization stratification factors (ECOG PS, number of prior regimens for platinum-resistant disease, and disease measurability).

FIG. 22A

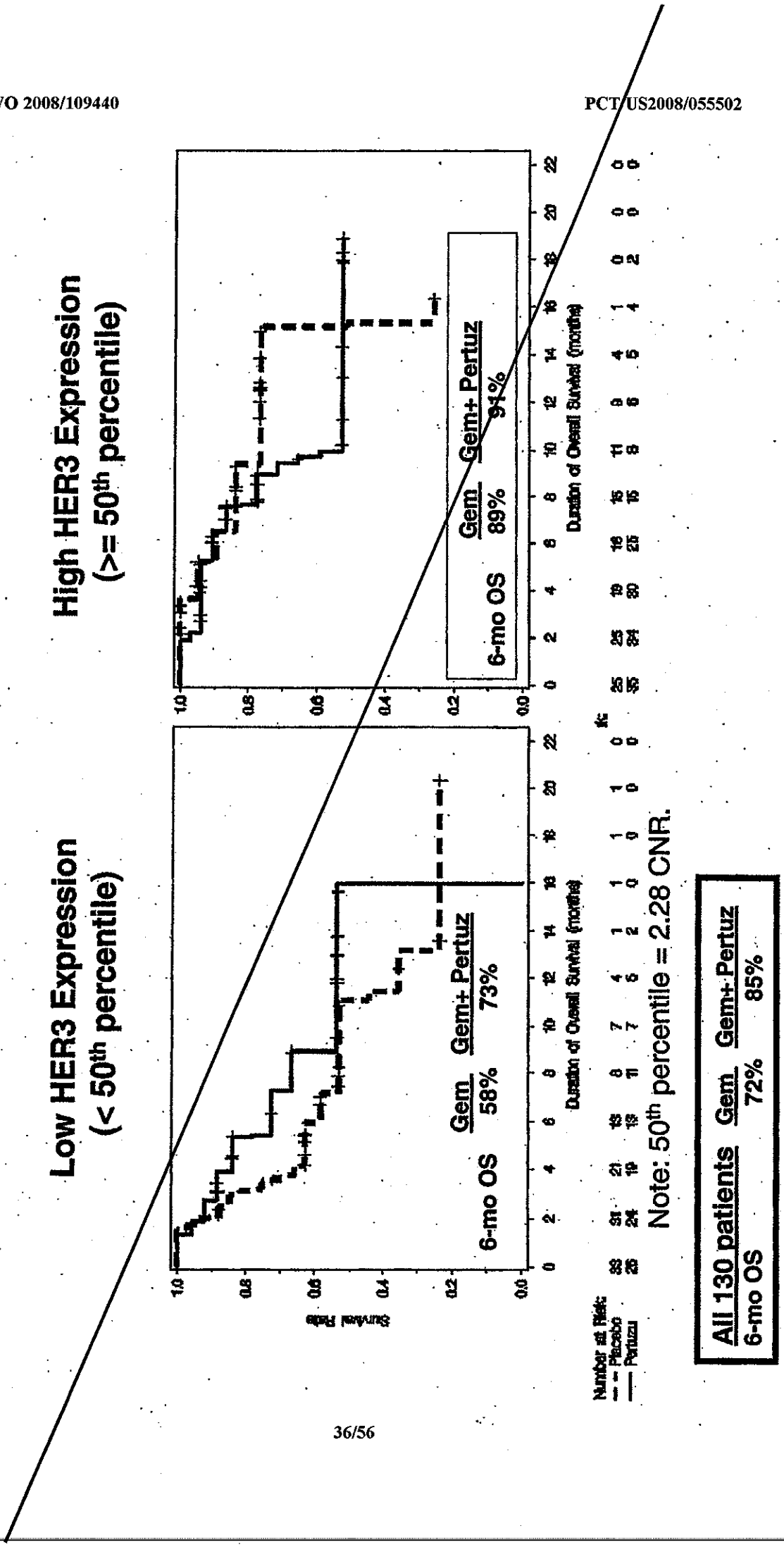
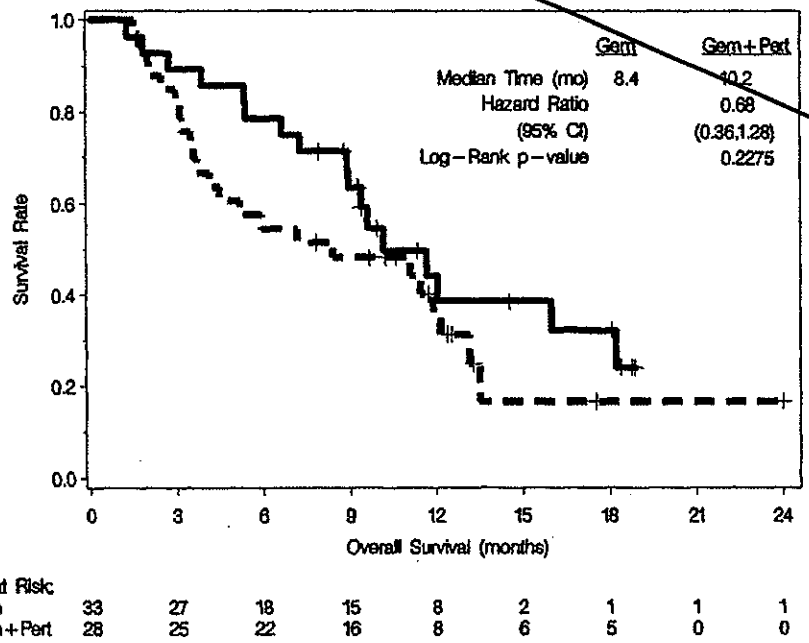

High HER3 Expression
(>= 50th percentile)
Gem Gem+ Pertuz
6-mo OS 89% 91%
Low HER3 Expression
(< 50th percentile)
Gem Gem+ Pertuz
6-mo OS 58% 73%
Duration of Overall Survival (months)
Survival Rate
Number at Risk:
Placebo
Pertuzu
All 130 patients Gem Gem+ Pertuz
6-mo OS 72% 85%
Note: 50th percentile = 2.28 CNR.

FIG. 22B

Preliminary OS by HER3 qRT-PCR 50/50 - split

Low HER3 Expression
(< 50th percentile, N=61)



High HER3 Expression
(>= 50th percentile, N=61)

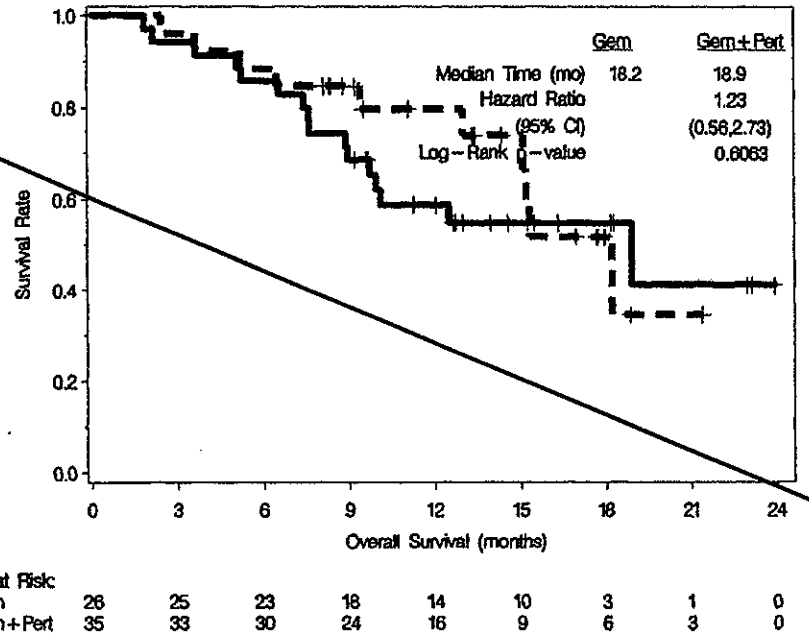


FIG. 23A

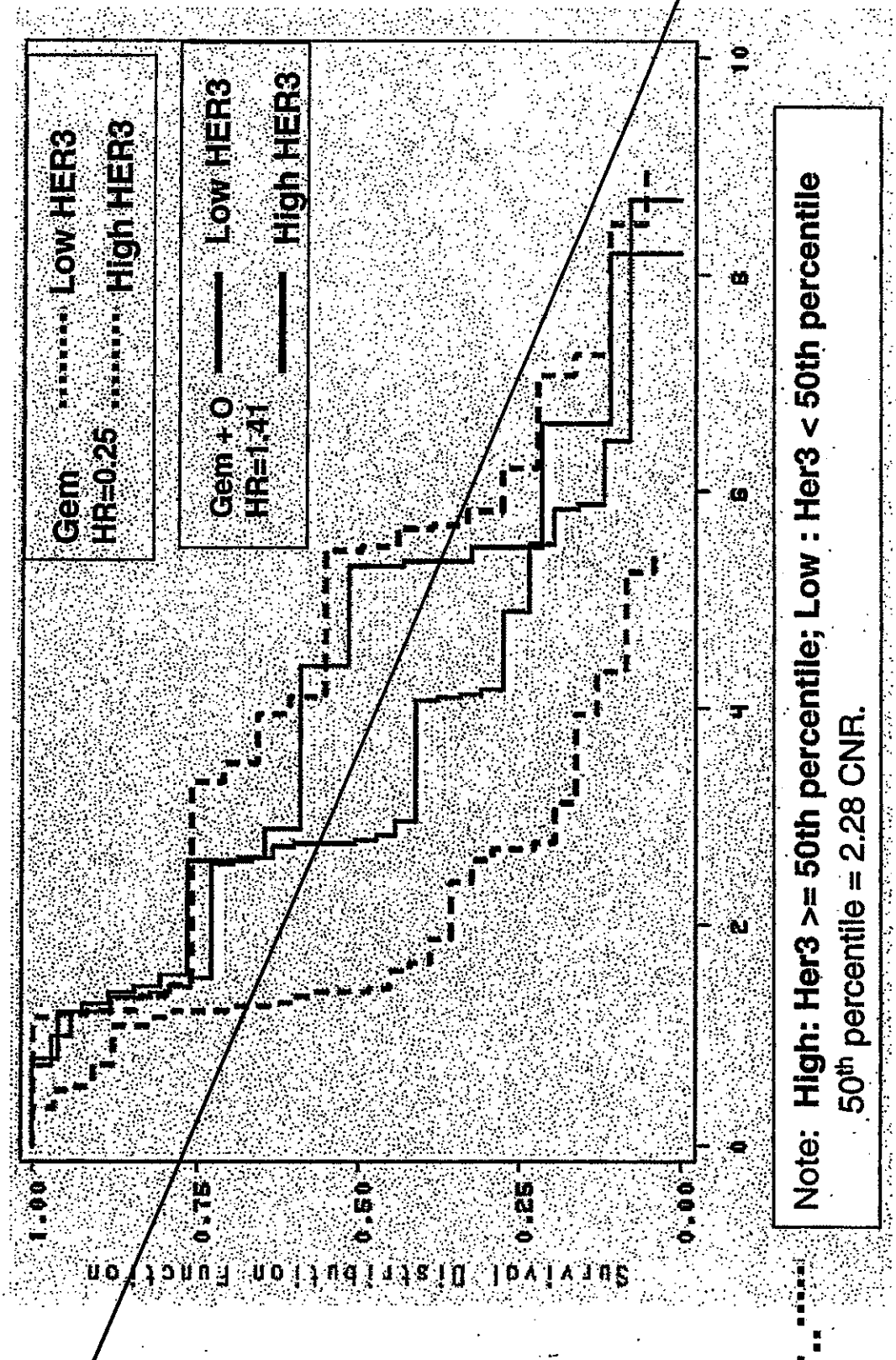

Gem
HR=0.25
Low HER3
High HER3
Gem + O
HR=1.41
Low HER3
High HER3
Survival Distribution Function
1.00
0.75
0.50
0.25
0.00
0
2
4
6
8
10
Note: High: Her3 >= 50th percentile; Low : Her3 < 50th percentile
50th percentile = 2.28 CNR.

FIG. 23B

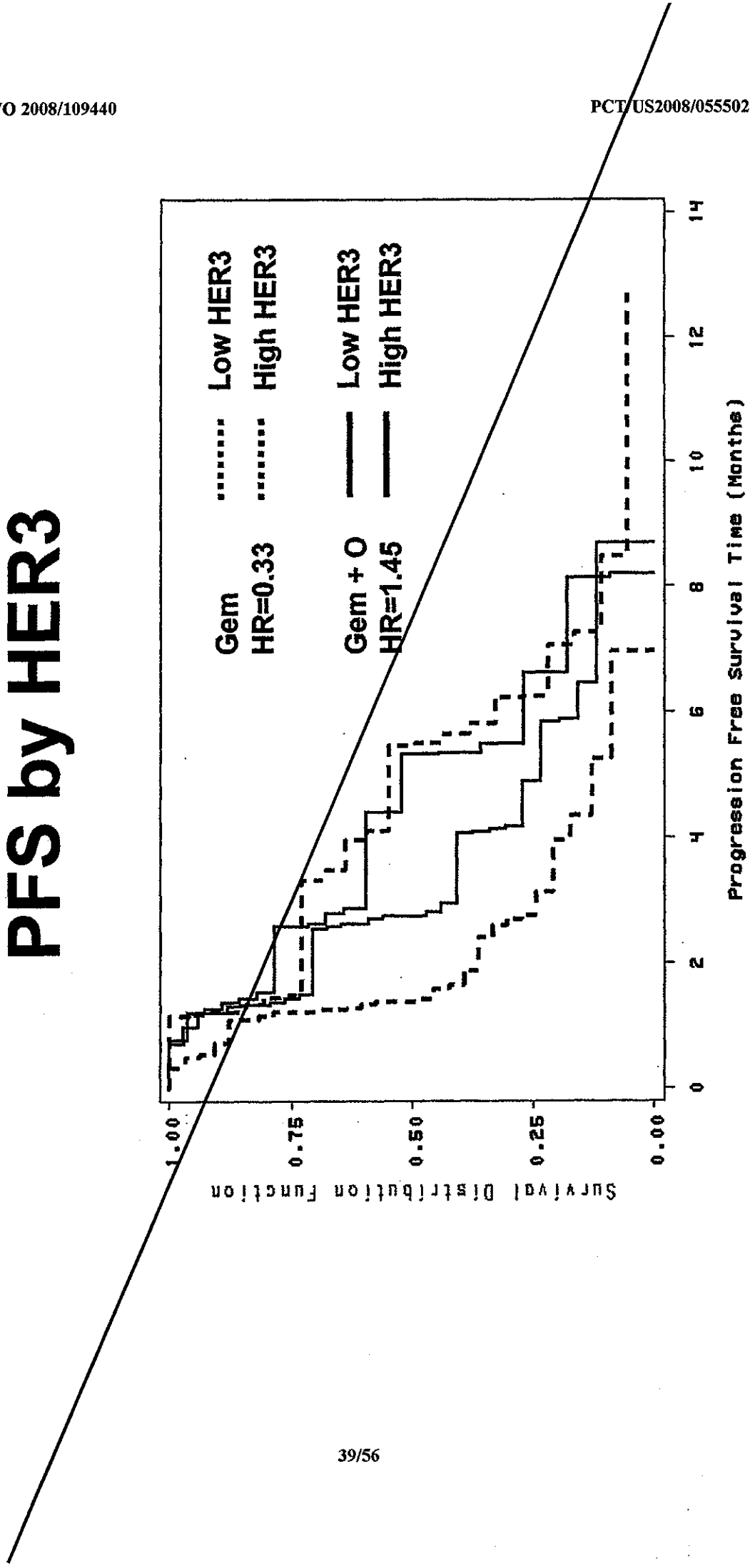
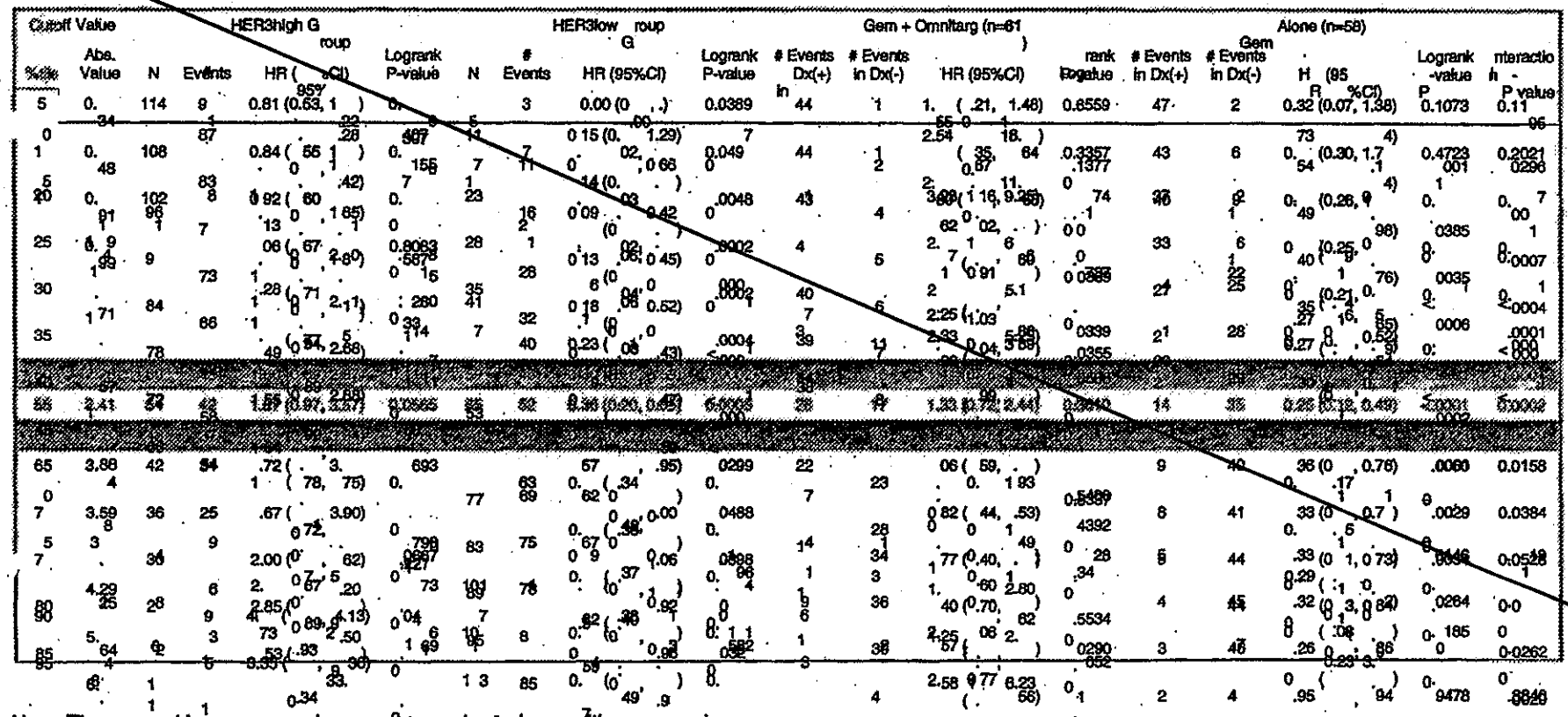

PFS by HER3
Gem
HR=0.33
Low HER3
High HER3
Gem + O
HR=1.45
Low HER3
High HER3
Survival Distribution Function
1.00
0.75
0.50
0.25
0.00
0
2
4
6
8
10
12
14
Progression Free Survival Time (Months)

FIG. 24A

Pertuzumab Platinum Resistant Ovarian Cancer. PFS by qRT-PCR HER3



Cutoff Value		HER3high Group				HER3low Group				Gem + Omnitarg (n=61)				Alone (n=58)					
%ile	Abs. Value	N	Events	HR (95% CI)	Logrank P-value	N	# Events	HR (95%CI)	Logrank P-value	# Events in Dx(+)	# Events in Dx(-)	HR (95%CI)	Logrank P-value	# Events in Dx(+)	# Events in Gem Dx(-)	HR (95% CI)	Logrank P-value	Interaction P value
5	0. 34	114	9	0.81 (0.53, 1)	0.	3	3	0.00 (0 , .)	0.0389	44	1	1. (.21, 1.48)	0.6559	47	2	0.32 (0.07, 1.38)	0.1073	0.11
0		87		.28	587	11		0 15 (0. 1.29)	7			2.54 0 18.)				73 4)		96
1	0. 48	108		0.84 (55 1)	0. 155	7	7	02, 0 66	0.049	44	1	(35, 64	.3357 .1377	43	6	0. 54 (0.30, 1.7 .1	0.4723 001	0.2021 0296
5		83		.42)	7	1		14 (0.)			2	2. 11.	0			1 4)		
20	0. 91	102 96	8 1	0 92 (60 1 65)	0. 0	23	16	03 0 42 (0 .)	0.0048	43	4	3.69 (1 16, 9.55) 62 0 02, .)	.1 0 0	74	9 1	0. 49 (0.26, 9 96)	0. 0385	0. 7 00 1
25	1. 9	9	7	06 (67 2.80)	0.9083 587	28	1	02 .	0.9002	4	5	2. 1 6 7 (66	0	33	6	0 40 (0.25 0	0. 0	0. 0.0007
30	1	73	1	0 91)	0 15	35	28	13 06 (0 0 45)	0 000			1 (0 91)	0 0389	27	22 25	1 76)	0035	1
35	1 71	84	1 66	.28 (71 2.11)	0 33	41	32	18 08 0.52)	0.0002 1	40 7	6	2 5.1 2.25 (1.03				0 35 (4 5 .27 16. 65)	0. 1	0. 0004
		78		49 0 84, 2.68)	1	7	40	0 23 (08 .43)	.0004	39	11	2.33 0 04, 3 59)	0 0355	21	28	0 0 0.52)	0006	.0001
																0 27 (. . 9)	0:	< 000
55	2.41	54	42	1.55 (0.97, 2.47)	0.0565	55	52	0.36 (0.20, 0.65)	0.0005	28	17	1.33 (0.72, 2.44)	0.3640	14	35	0.26 (0.12, 0.49)	0.0001	0.0002
65	3.88	42	34	.72 (3.	693		57	.95)	0299	22	23	06 (59,)		9	40	36 (0 , 0.76)	.0060	0.0158
0	4			1 (78, 75)	0.	63	0. (.34		0.	7		0. 1 93	0.5489			0 .17 1	0	
7	3.59 8	36	25	.67 (3.90)	0 72,	77	69	62 0 00	0488		28	0 82 (44, .53) 0 0 1	4392	8	41	33 (0 0.7) 0. 5	0029	0.0384
5	3	9		0	0	83	75	67 0 38 ( )	0.	14		49	0	5	44	0	0	
7	.	36		2.00 (0 . 62)	0667			0 9 0.06	0388	34	1	1 77 (0.40,)	0 28			33 (0 1, 0 73)	.0046	0.0528
80	4.29 25	28	6 9	2. 0 7 5 67 20 2.85 (0 4.13)	0 127 0 04	73	101 89	0. 37 (1) 0 92	0. 96 4	1 3	1	1. 0 60 2.80 40 (0.70,)	0 34	4	45	0 29 (1 0. 32 (0 3, 0 84)	0 0264	0 0
90			9	4 (0 89,	7	78	62 (36		6	1		62 .5534				0 (06)		
85	5. 64	6	3	73 (.93 2.50	1 69	10 8	0.	0 98	582	38		2. 57 ( )	0 0290	3	46	.26 0 86	0 185	0 0262
95	4	1	5	6.55 (8 36)	0	1 3	85	0. (0 49 .9	0.	4		2.58 0 77 6.23 (56)	0 652	2	4	0 23 3.)	0	0
	6	1		33.					8.				0			0 ( )	0.	0
		1	1	0.34				7								.95 , 94	9478	8849

No e Th d Log- l were n ad st d ulti p ris
H R an k p u s o J e or m e pa
e
t e on
va

FIG. 24B

Pertuzumab Platinum Resistant Ovaian Cancer: PFS by qRT-PCR HER3

Cutoff Value		Dx(High) Group				Dx(Low) Group				Gem + Pertuzumab (n=63)				Gem Alone (n=59)				
%tile	Abs. Value	N	# Events	HR (95%CI)	Logrank P-value	N	# Events	HR (95%CI)	Logrank P-value	# Events in Dx(High)	# Events in Dx(Low)	HR (95%CI)	Logrank P-value	# Events in x(High)	# Events in Dx(Low)	HR (95%CI)	Logrank P-value	Interaction P-value
20	0.99	98	80	1.09 (0.70, 1.70)	0.6973	24	17	0.08 (0.02, 0.37)	<.0001	42	5	3.20 (1.25, 8.23)	0.0109	38	12	0.47 (0.24, 0.93)	0.0272	0.0007
25	1.19	92	74	1.16 (0.73, 1.84)	0.5222	30	23	0.13 (0.04, 0.41)	<.0001	40	7	2.34 (1.03, 5.30)	0.0360	34	16	0.38 (0.20, 0.72)	0.0020	0.0003
30	1.39	86	68	1.20 (0.74, 1.94)	0.4674	36	29	0.22 (0.09, 0.56)	0.0006	39	8	2.03 (0.93, 4.39)	0.0683	29	21	0.44 (0.24, 0.79)	0.0046	0.0014
35	1.56	80	64	1.37 (0.83, 2.26)	0.2230	42	33	0.20 (0.09, 0.48)	<.0001	38	9	2.19 (1.05, 4.56)	0.0330	26	24	0.37 (0.21, 0.67)	0.0007	0.0001
40	1.70	74	59	1.50 (0.88, 2.55)	0.1381	48	38	0.22 (0.10, 0.50)	<.0001	37	10	2.14 (1.06, 4.34)	0.0312	22	28	0.35 (0.19, 0.63)	0.0004	<.0001
45	1.87	68	55	1.50 (0.87, 2.61)	0.1468	54	42	0.29 (0.14, 0.58)	0.0002	34	13	1.84 (0.97, 3.51)	0.0617	21	29	0.35 (0.19, 0.65)	0.0005	0.0002
50	2.24	61	49	1.48 (0.83, 2.63)	0.1809	61	48	0.34 (0.18, 0.63)	0.0004	29	18	1.45 (0.80, 2.62)	0.2230	20	30	0.33 (0.18, 0.62)	0.0003	0.0005
55	2.38	56	44	1.74 (0.93, 3.27)	0.0816	66	53	0.36 (0.20, 0.65)	0.0005	29	18	1.45 (0.80, 2.62)	0.2230	15	35	0.31 (0.16, 0.60)	0.0002	0.0004
60	2.75	49	38	1.81 (0.90, 3.67)	0.0945	73	59	0.48 (0.28, 0.84)	0.0080	27	20	1.33 (0.74, 2.38)	0.3459	11	39	0.37 (0.19, 0.73)	0.0030	0.0030
65	3.08	43	32	1.78 (0.82, 3.86)	0.1382	79	65	0.56 (0.34, 0.94)	0.0255	23	24	1.14 (0.64, 2.04)	0.6516	9	41	0.36 (0.18, 0.76)	0.0050	0.0112
70	3.56	37	26	1.73 (0.75, 3.99)	0.1943	85	71	0.62 (0.38, 1.00)	0.0459	18	29	0.89 (0.49, 1.62)	0.6916	8	42	0.33 (0.15, 0.71)	0.0028	0.0295
75	3.77	31	21	1.90 (0.73, 4.93)	0.1804	91	76	0.65 (0.41, 1.03)	0.0650	15	32	0.89 (0.47, 1.66)	0.6992	6	44	0.33 (0.14, 0.79)	0.0086	0.0427
80	4.05	25	18	2.33 (0.82, 6.64)	0.1053	97	79	0.64 (0.41, 1.00)	0.0493	13	34	1.04 (0.54, 2.03)	0.9069	5	45	0.32 (0.13, 0.83)	0.0136	0.0291

Note: The HRs and logrank p-values were not adjusted for multiple comparison.

FIG. 25

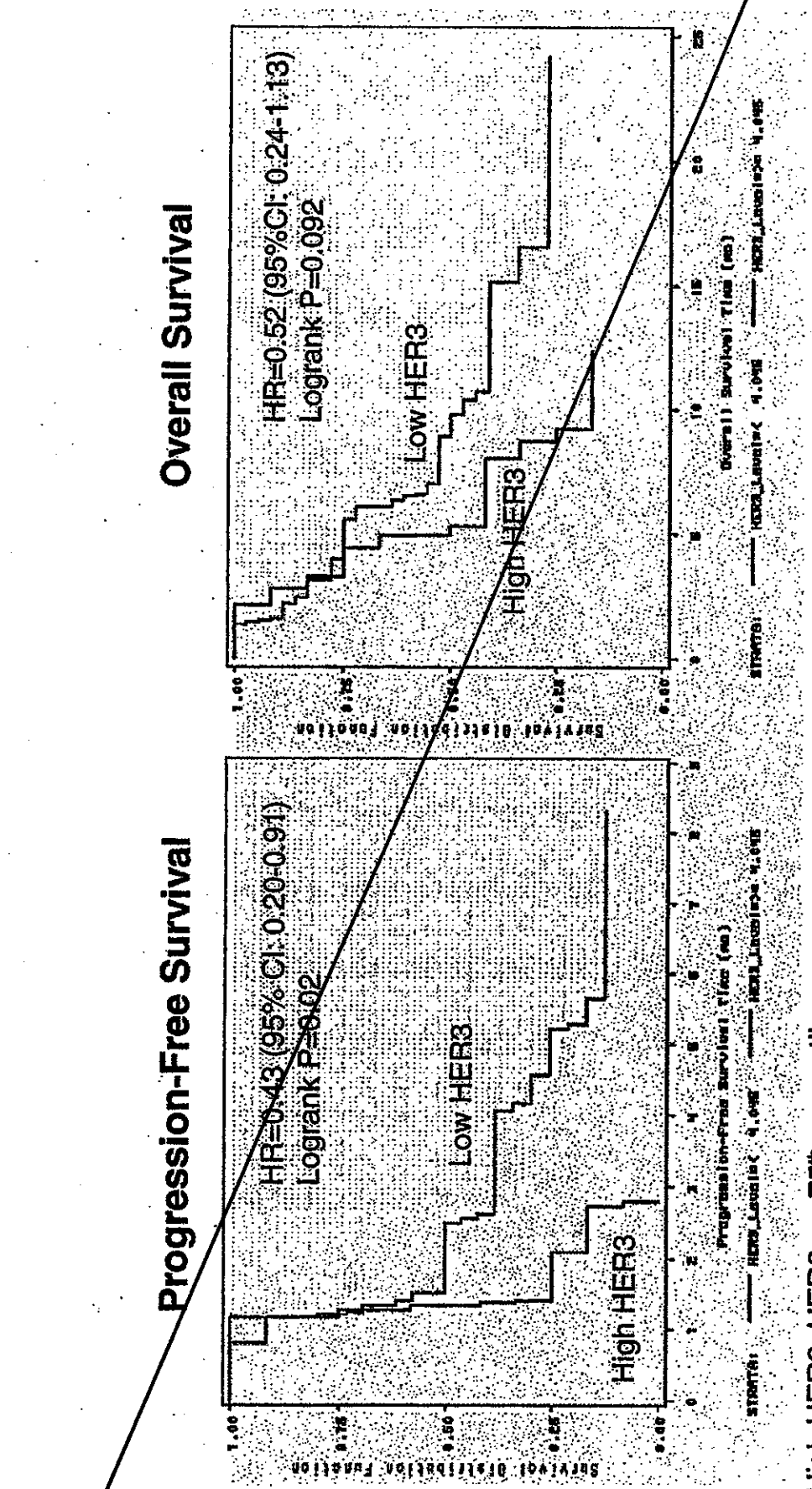
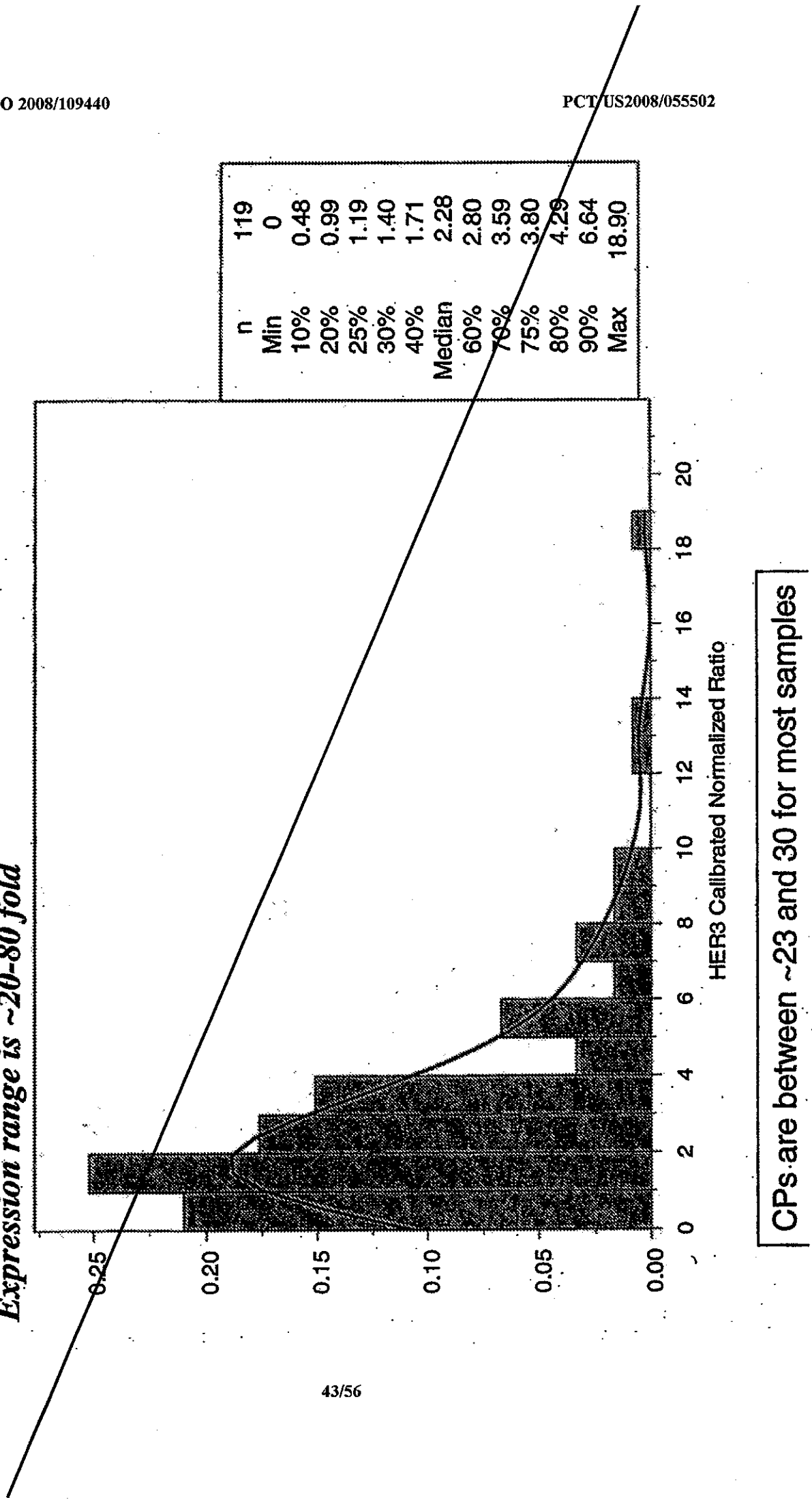
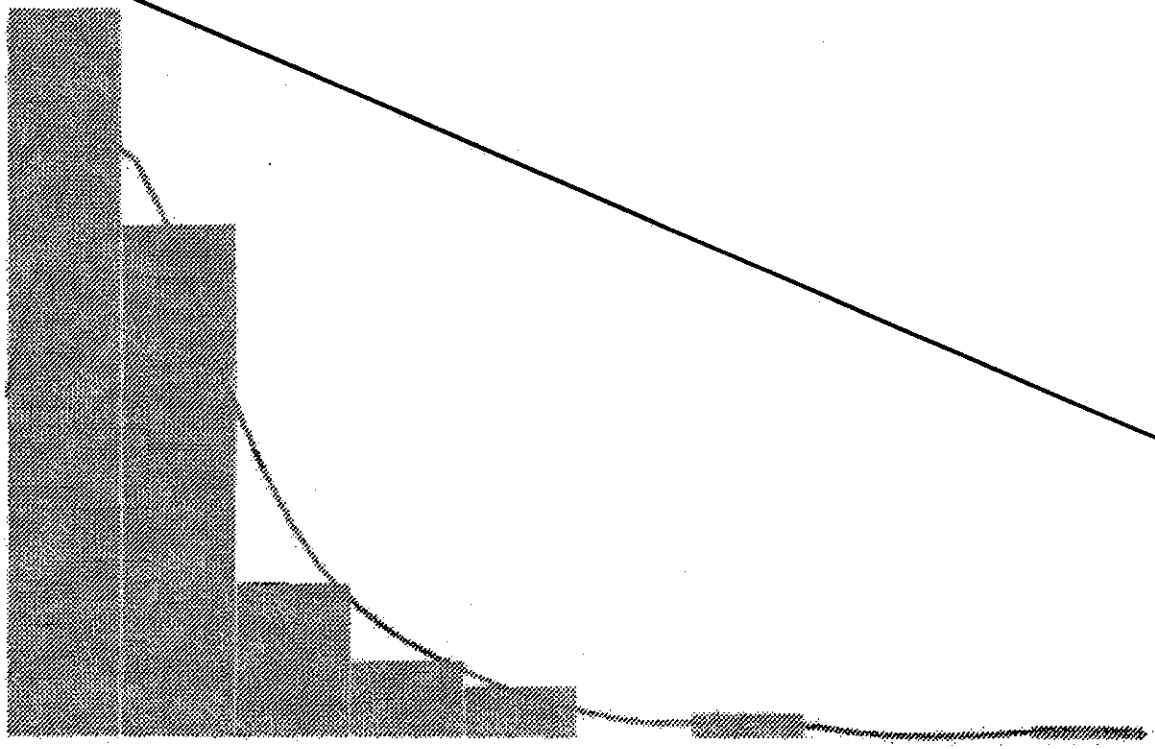

Progression-Free Survival
HR=0.43 (95% CI: 0.20-0.91)
Logrank P=0.02
Low HER3
High HER3
Overall Survival
HR=0.52 (95%CI: 0.24-1.13)
Logrank P=0.092
Low HER3
High HER3
High HER3: HER3 >= 75th percentile
Low HER3: HER3 < 75th percentile
75th percentile = 4.045

FIG. 26A


HER3 Calibrated Normalized Ratio
Expression range is ~20-80 fold
n 119
Min 0
10% 0.48
20% 0.99
25% 1.19
30% 1.40
40% 1.71
Median 2.28
60% 2.80
70% 3.59
75% 3.80
80% 4.29
90% 6.64
Max 18.90
0.25
0.20
0.15
0.10
0.05
0.00
0
2
4
6
8
10
12
14
16
18
20
HER3 Calibrated Normalized Ratio
CPs are between ~23 and 30 for most samples

HER3 Calibrated Normalized Ratio Expression range is ~20-80 fold

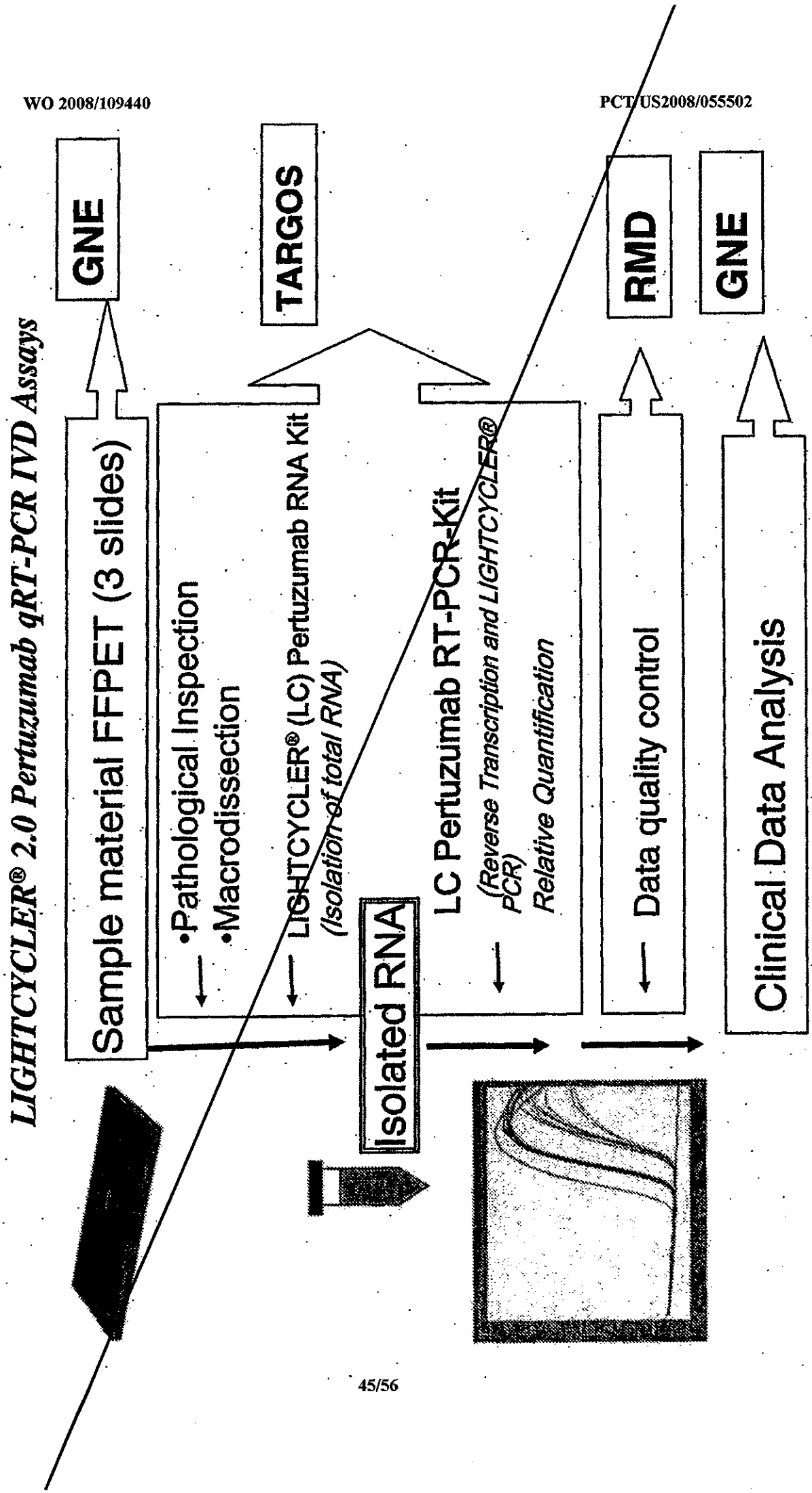


n	122
Min	0
10%	0.50
20%	0.99
25%	1.19
30%	1.39
40%	1.70
Median	2.24
60%	2.75
70%	3.56
75%	3.77
80%	4.05
90%	6.56
Max	18.90

CPs are between ~23 and 30 for most samples

FIG. 26B

FIG. 27


LIGHTCYCLER® 2.0 Pertuzumab qRT-PCR IVD Assays
GNE
TARGOS
RMD
GNE
Sample material FFPET (3 slides)
•Pathological Inspection
•Macrodissection
LIGHTCYCLER® (LC) Pertuzumab RNA Kit
(Isolation of total RNA)
Isolated RNA
LC Pertuzumab RT-PCR-Kit
(Reverse Transcription and LIGHTCYCLER® PCR)
Relative Quantification
Data quality control
Clinical Data Analysis

Pertuzumab IVD Assay
Workflow & Analysis
1 marker + reference

FIG. 28

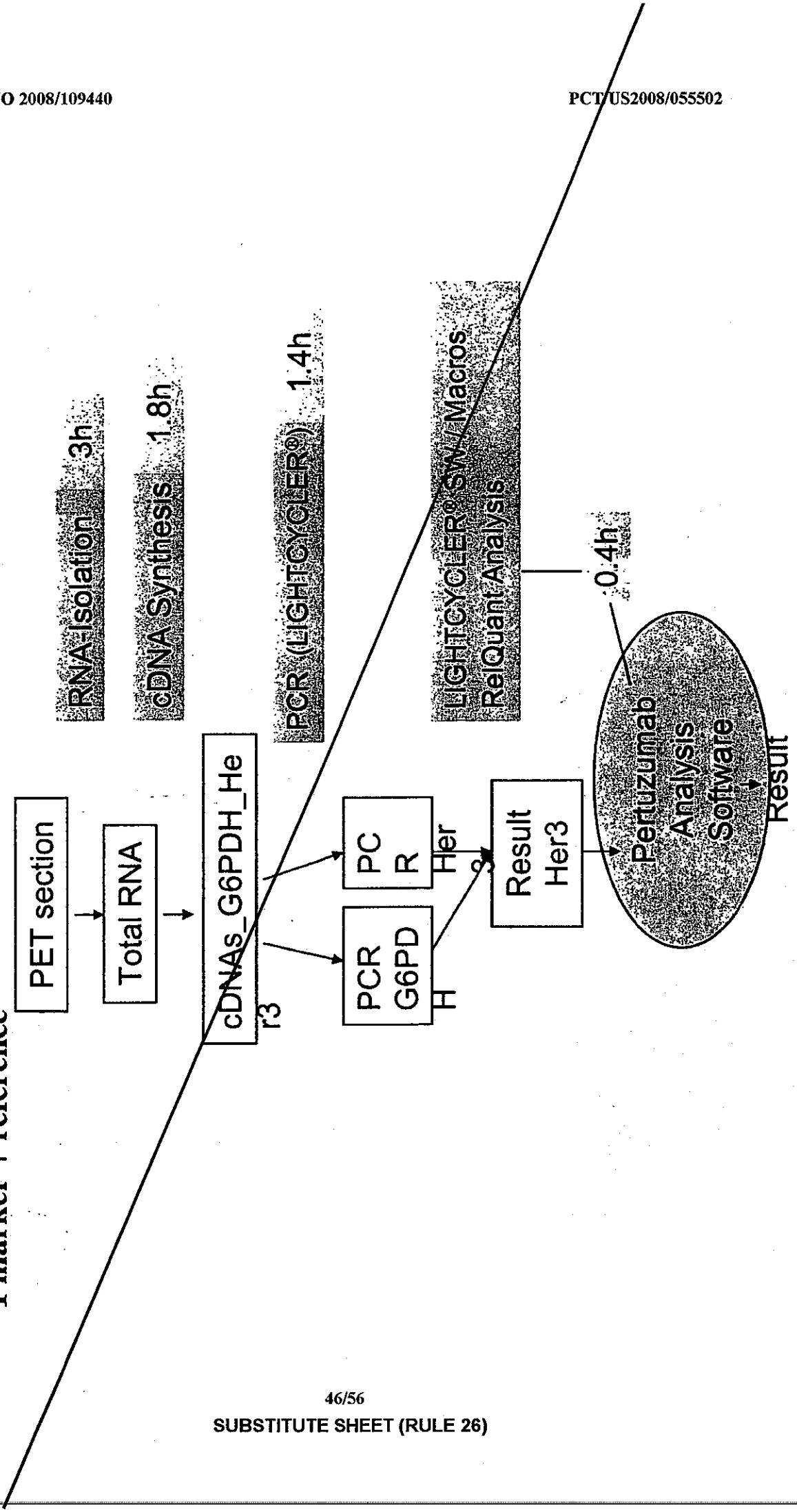


FIGURE 29A

PFS by qRT-PCR HER2/HER3 (percentiles)

Cutoff Value			Dx(High) Group			Dx(Low) Group			Gem + Omnitarg (n=60)				Gem Alone (n=58)				
%tile	Abs. Value	N	# Events	HR (95%CI)	Logrank P-value	N	# Events	HR (95%CI)	Logrank P-value	# Events in Dx(High)	# Events in Dx(Low)	HR (95%CI)	Logrank P-value	# Events in Dx(High)	# Events in Dx(Low)	HR (95%CI)	Logrank P-value	Interaction P-value
20	0.74	95	72	0.63 (0.39, 1.02)	0.0616	23	21	2.04 (0.58, 7.13)	0.2475	26	18	0.57 (0.31, 1.06)	0.0734	46	3	1.39 (0.43, 4.55)	0.5881	0.1823
25	0.82	89	67	0.46 (0.27, 0.76)	0.0021	29	26	2.85 (1.10, 7.37)	0.0249	24	20	0.53 (0.29, 0.97)	0.0370	43	6	4.07 (1.41, 11.74)	0.0055	0.0005
30	0.90	83	62	0.41 (0.24, 0.69)	0.0007	35	31	2.52 (1.13, 5.62)	0.0197	22	22	0.46 (0.25, 0.84)	0.0104	40	9	3.04 (1.33, 6.94)	0.0056	0.0002
35	1.06	77	60	0.39 (0.22, 0.68)	0.0005	41	33	2.51 (1.14, 5.54)	0.0189	20	24	0.49 (0.26, 0.90)	0.0192	40	9	3.41 (1.50, 7.73)	0.0019	0.0001
40	1.13	71	55	0.39 (0.22, 0.69)	0.0009	47	38	1.91 (0.95, 3.83)	0.0640	18	26	0.52 (0.28, 0.96)	0.0340	37	12	2.76 (1.36, 5.59)	0.0034	0.0004
45	1.26	65	50	0.31 (0.16, 0.61)	0.0003	53	43	1.93 (0.99, 3.77)	0.0492	14	30	0.54 (0.28, 1.03)	0.0584	36	13	3.21 (1.57, 6.56)	0.0007	0.0001
50	1.53	59	47	0.31 (0.15, 0.61)	0.0004	59	46	1.71 (0.91, 3.21)	0.0937	13	31	0.57 (0.30, 1.10)	0.0926	34	15	2.94 (1.50, 5.77)	0.0010	0.0003
55	1.70	54	45	0.34 (0.17, 0.68)	0.0015	64	48	1.44 (0.78, 2.65)	0.2293	13	31	0.66 (0.34, 1.28)	0.2161	32	17	2.55 (1.34, 4.83)	0.0028	0.0022
60	1.86	48	40	0.27 (0.12, 0.57)	0.0003	70	53	1.35 (0.77, 2.37)	0.2885	12	32	0.60 (0.31, 1.18)	0.1348	28	21	2.60 (1.41, 4.81)	0.0015	0.0009
65	2.15	42	34	0.27 (0.12, 0.62)	0.0010	76	59	1.10 (0.65, 1.86)	0.7119	11	33	0.56 (0.28, 1.12)	0.0974	23	26	1.81 (1.00, 3.27)	0.0447	0.0084
70	2.49	36	29	0.21 (0.08, 0.54)	0.0004	82	64	1.13 (0.69, 1.87)	0.6280	8	36	0.52 (0.24, 1.12)	0.0895	21	28	2.07 (1.14, 3.76)	0.0145	0.0032
75	2.62	30	24	0.13 (0.04, 0.46)	0.0003	88	69	1.08 (0.67, 1.75)	0.7534	6	38	0.46 (0.19, 1.10)	0.0766	18	31	2.11 (1.12, 3.96)	0.0167	0.0035
80	2.92	24	20	0.10 (0.02, 0.43)	0.0002	94	73	1.06 (0.67, 1.70)	0.7886	4	40	0.42 (0.15, 1.19)	0.0949	16	33	2.60 (1.36, 4.97)	0.0026	0.0022

FIG. 29B

Platinum Resistant Ovaian Cancer: PFS by qRT-PCR HER2/HER3 Ratio

Cutoff Value			Dx(High) Group			Dx(Low) Group				Gem + Pertuzumab (n=63)				Gem Alone (n=59)				
%tile	Abs. Value	N	# Events	HR (95%CI)	Logrank P-value	N	# Events	HR (95%CI)	Logrank P-value	# Events in Dx(High)	# Events in Dx(Low)	HR (95%CI)	Logrank P-value	# Events in x(High)	# Events in Dx(Low)	HR (95%CI)	Logrank P-value	Interaction P-value
20	0.76	97	75	0.67 (0.42, 1.06)	0.0884	24	21	1.70 (0.56, 5.19)	0.3418	29	17	0.74 (0.40, 1.37)	0.3323	46	4	1.73 (0.62, 4.87)	0.2958	0.1685
25	0.83	91	71	0.50 (0.31, 0.82)	0.0050	30	25	2.53 (0.99, 6.49)	0.0452	27	19	0.68 (0.37, 1.24)	0.2026	44	6	4.34 (1.51, 12.43)	0.0033	0.0022
30	0.91	85	66	0.48 (0.29, 0.80)	0.0042	36	30	1.98 (0.89, 4.40)	0.0876	25	21	0.65 (0.36, 1.17)	0.1529	41	9	2.92 (1.28, 6.66)	0.0075	0.0030
35	1.06	79	63	0.45 (0.26, 0.77)	0.0026	42	33	1.99 (0.94, 4.24)	0.0691	23	23	0.63 (0.35, 1.13)	0.1204	40	10	2.96 (1.37, 6.42)	0.0039	0.0015
40	1.13	73	58	0.40 (0.23, 0.71)	0.0011	48	38	1.76 (0.89, 3.47)	0.0979	21	25	0.65 (0.36, 1.17)	0.1512	37	13	2.87 (1.44, 5.71)	0.0017	0.0011
45	1.26	67	53	0.35 (0.19, 0.65)	0.0006	54	43	1.78 (0.93, 3.41)	0.0780	17	29	0.66 (0.36, 1.21)	0.1782	36	14	3.49 (1.70, 7.14)	0.0003	0.0004
50	1.54	61	49	0.32 (0.17, 0.63)	0.0005	60	47	1.63 (0.88, 3.02)	0.1154	15	31	0.64 (0.34, 1.19)	0.1566	34	16	3.15 (1.60, 6.19)	0.0005	0.0005
55	1.73	55	46	0.36 (0.18, 0.70)	0.0018	66	50	1.37 (0.77, 2.45)	0.2828	15	31	0.72 (0.39, 1.35)	0.3116	31	19	2.64 (1.41, 4.94)	0.0016	0.0033
60	2.04	49	41	0.29 (0.14, 0.60)	0.0005	72	55	1.35 (0.78, 2.34)	0.2830	13	33	0.62 (0.33, 1.20)	0.1585	28	22	2.69 (1.47, 4.93)	0.0009	0.0010
65	2.17	43	35	0.28 (0.12, 0.61)	0.0007	78	61	1.13 (0.68, 1.88)	0.6512	13	33	0.62 (0.33, 1.20)	0.1585	22	28	2.16 (1.18, 3.96)	0.0104	0.0053
70	2.50	37	30	0.19 (0.07, 0.48)	0.0001	84	66	1.16 (0.71, 1.90)	0.5512	10	36	0.58 (0.28, 1.18)	0.1290	20	30	2.64 (1.40, 4.96)	0.0018	0.0010
75	2.65	31	25	0.10 (0.03, 0.37)	<.0001	90	71	1.12 (0.70, 1.80)	0.6370	7	39	0.42 (0.18, 0.94)	0.0314	18	32	2.23 (1.19, 4.21)	0.0100	0.0010
80	2.99	25	21	0.11 (0.03, 0.40)	<.0001	96	75	1.06 (0.67, 1.67)	0.8088	6	40	0.45 (0.19, 1.08)	0.0694	15	35	2.46 (1.28, 4.74)	0.0055	0.0015

Note: The HRs and logrank p-values were not adjusted for multiple comparison.

WO 2008/109440 PCT/US2008/055502

FIGURE 30A

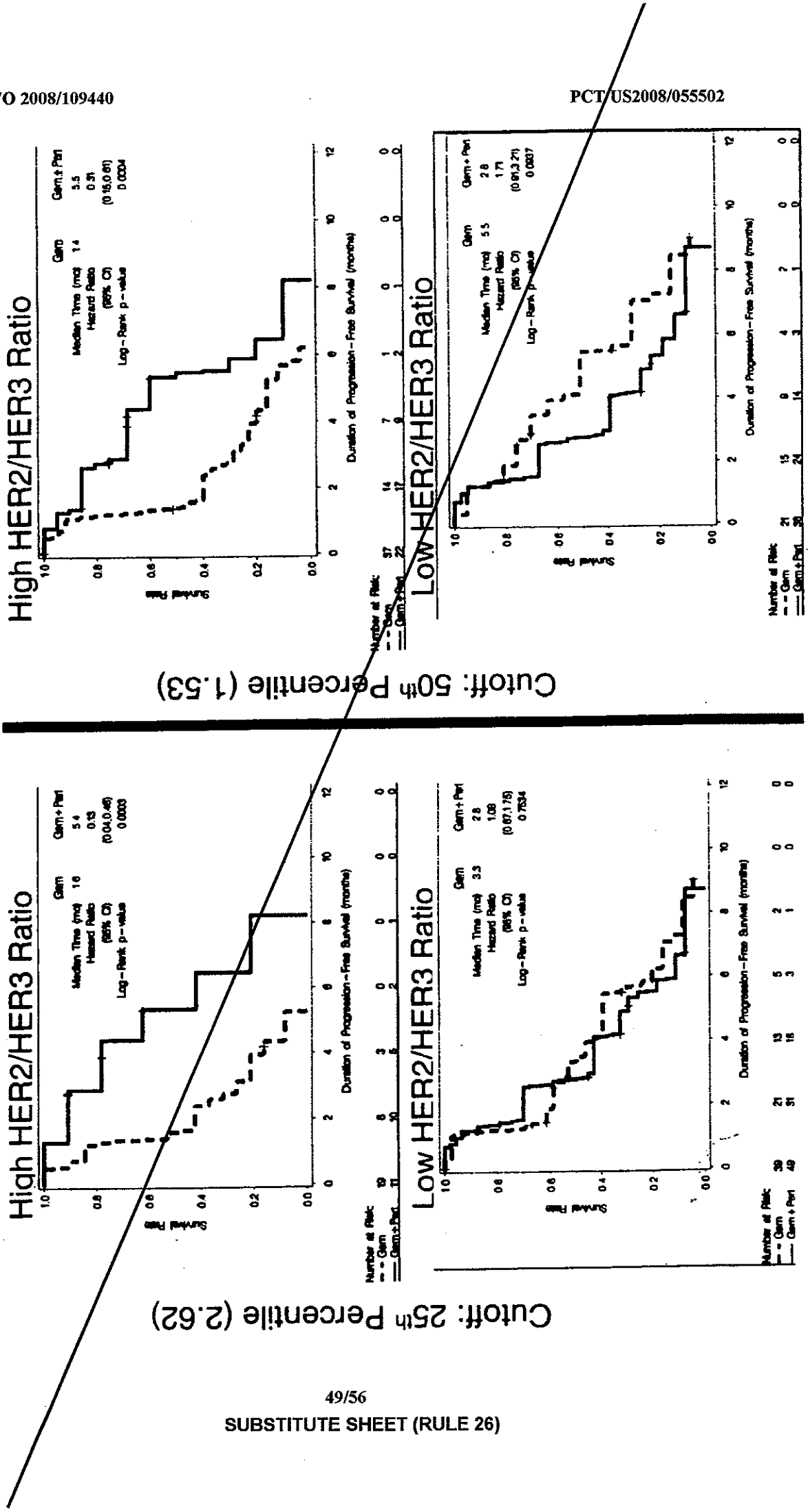

Cutoff: 50th Percentile (1.53)
High HER2/HER3 Ratio
Low HER2/HER3 Ratio
Cutoff: 25th Percentile (2.62)
High HER2/HER3 Ratio
Low HER2/HER3 Ratio

FIG. 30B

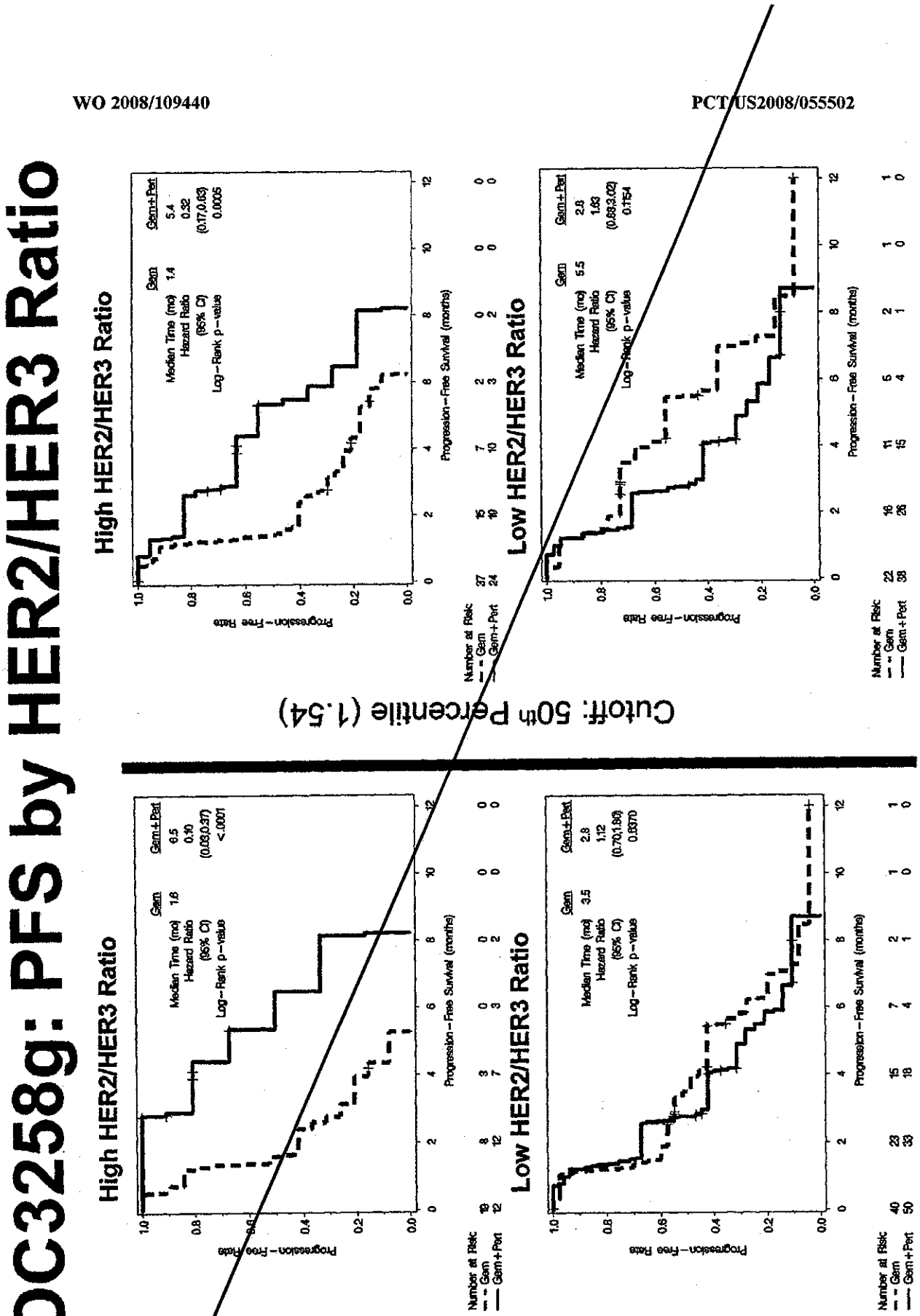

TOC3258g: PFS by HER2/HER3 Ratio
Cutoff: 25th Percentile (2.65)
High HER2/HER3 Ratio
Low HER2/HER3 Ratio
Cutoff: 50th Percentile (1.54)
High HER2/HER3 Ratio
Low HER2/HER3 Ratio
Progression-Free Rate
Progression-Free Survival (months)
Number at Risk
Gem
Gem+Pert

FIG. 31A

	Total		Gem Alone			Gem + Omnitarg				
qRT-PCR HER2/HER3 Ratio	N	# Events	N	# Events	Median (mo)	N	# Events	Median (mo)	HR (95%CI)	Logrank P-value
0 – < 25th percentile	29	26	7	6	5.5	22	20	2.6	2.85 (1.10, 7.37)	0.0249
25 – < 50th percentile	30	20	14	9	3.7	16	11	4.2	1.02 (0.41, 2.54)	0.9649
50 – < 75th percentile	29	23	18	16	1.3	11	7	5.5	0.61 (0.25, 1.52)	0.2978
75 – 100th percentile	30	24	19	18	1.6	11	6	5.4	0.13 (0.04, 0.46)	0.0003

FIG. 31B

Progression-Free Survival (PFS) Analysis by HER2/HER3 Quartiles

qRT-PCR HER2/HER3	N	# Events	HR (95%CI)	Logrank P-value
0 – < 25th percentile	30	25	2.53 (0.99, 6.49)	0.0452
25 – < 50th percentile	30	22	1.28 (0.52, 3.15)	0.5952
50 – < 75th percentile	30	24	0.76 (0.32, 1.83)	0.5618
75 – 100th percentile	31	25	0.10 (0.03, 0.37)	<.0001

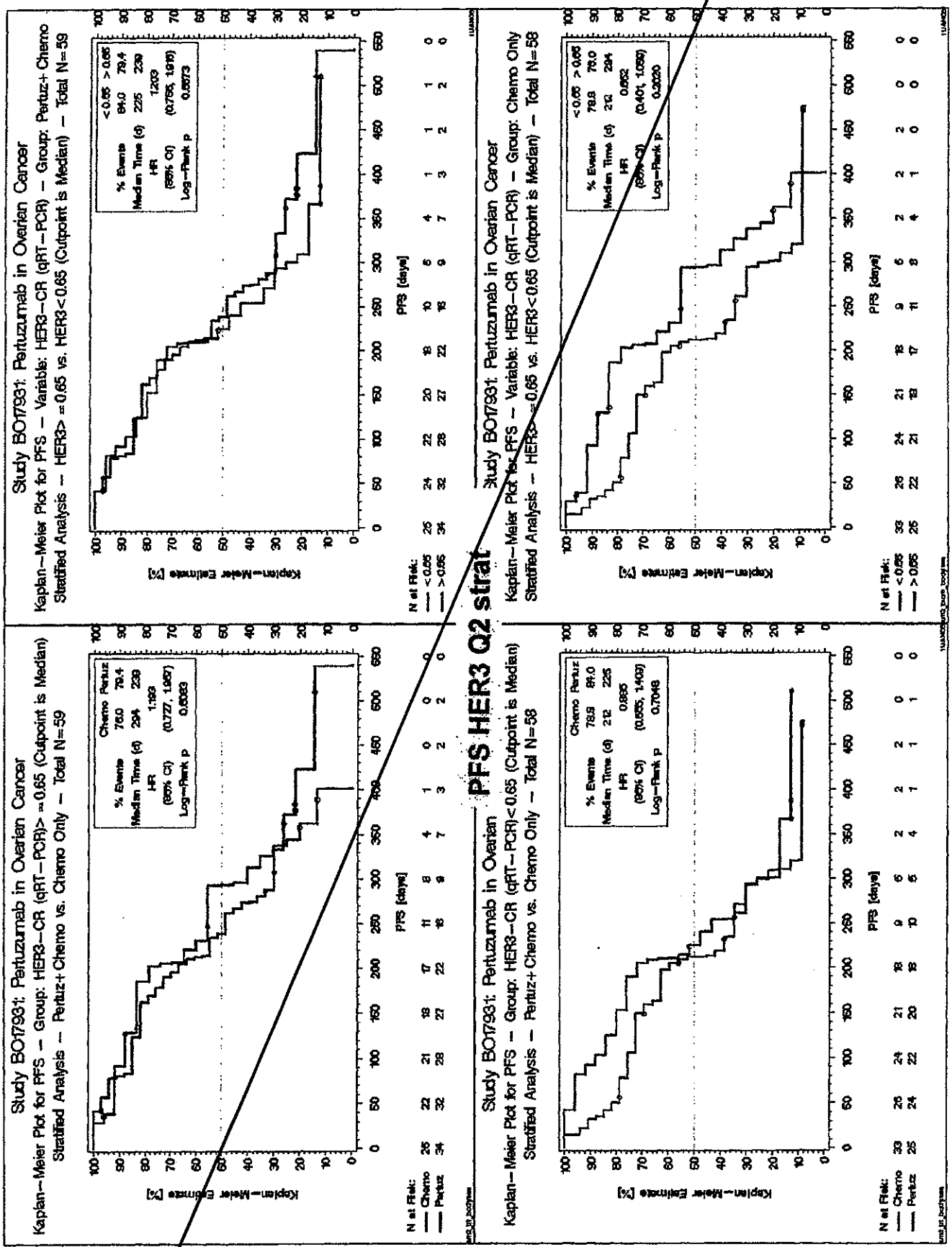
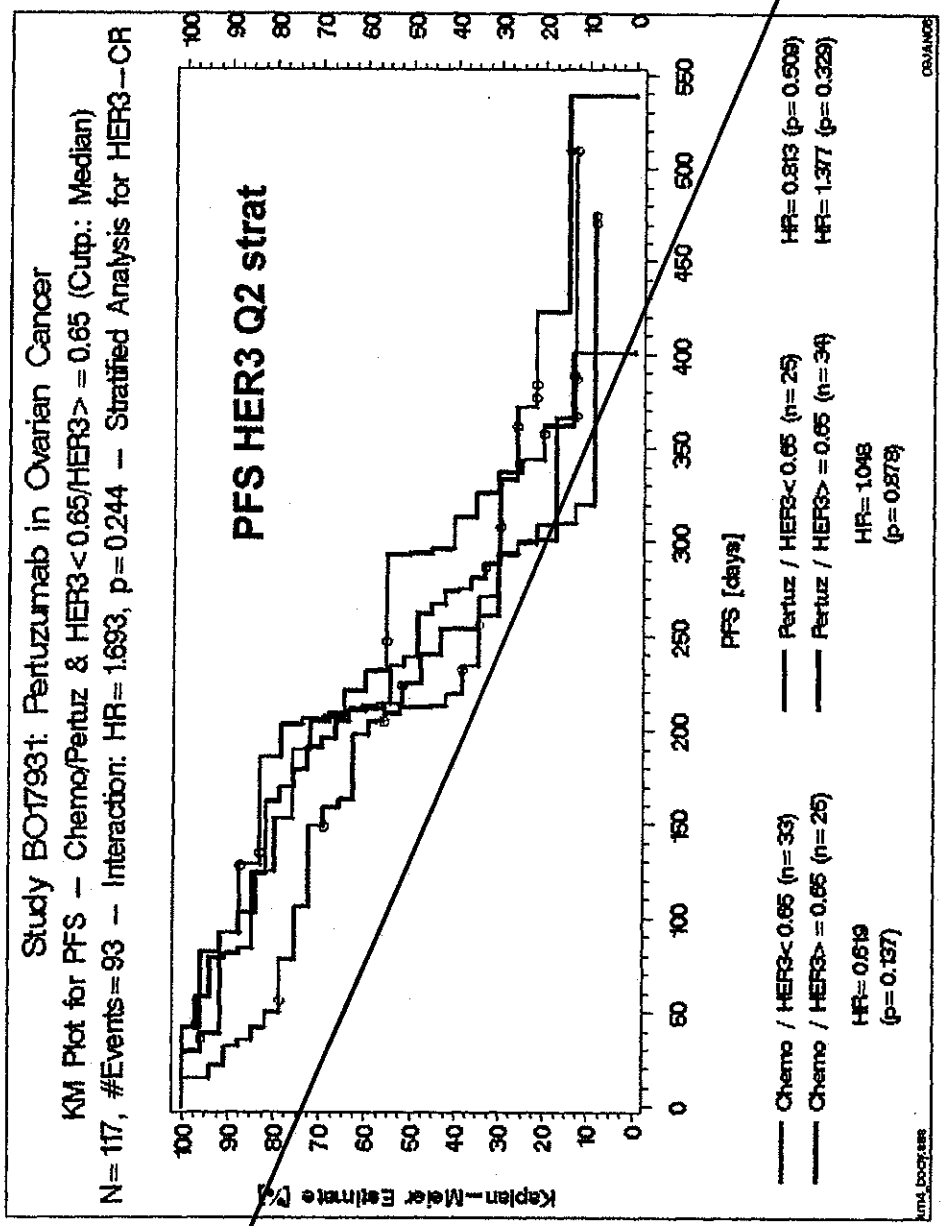

PFS HER3 Q2 strat
Study BO17931: Pertuzumab in Ovarian Cancer
Kaplan–Meier Plot for PFS – Variable: HER3–CR (qRT–PCR) – Group: Pertuz+ Chemo Only
Stratified Analysis – HER3> =0.65 vs. HER3<0.65 (Cutpoint is Median) – Total N=59
Study BO17931: Pertuzumab in Ovarian Cancer
Kaplan–Meier Plot for PFS – Variable: HER3–CR (qRT–PCR) – Group: Chemo Only
Stratified Analysis – HER3> =0.65 vs. HER3<0.65 (Cutpoint is Median) – Total N=58
Study BO17931: Pertuzumab in Ovarian Cancer
Kaplan–Meier Plot for PFS – Group: HER3–CR (qRT–PCR)> =0.65 (Cutpoint is Median)
Stratified Analysis – Pertuz+Chemo vs. Chemo Only – Total N=59
Study BO17931: Pertuzumab in Ovarian
Kaplan–Meier Plot for PFS – Group: HER3–CR (qRT–PCR)<0.65 (Cutpoint is Median)
Stratified Analysis – Pertuz+Chemo vs. Chemo Only – Total N=58
Kaplan–Meier Estimate [%]
PFS [days]
N at Risk:
Chemo
Pertuz
< 0.65
> 0.65

FIG. 33


Study BO17931: Pertuzumab in Ovarian Cancer
KM Plot for PFS – Chemo/Pertuz & HER3< 0.65/HER3> = 0.65 (Cutp.: Median)
N= 117, #Events= 93 – Interaction: HR= 1.693, p= 0.244 – Stratified Analysis for HER3–CR
PFS HER3 Q2 strat
Kaplan–Meier Estimate [%]
PFS [days]
Chemo / HER3< 0.65 (n= 33)
Chemo / HER3> = 0.65 (n= 25)
HR= 0.619
(p= 0.137)
Pertuz / HER3< 0.65 (n= 25)
Pertuz / HER3> = 0.65 (n= 34)
HR= 1.048
(p= 0.878)
HR= 0.813 (p= 0.509)
HR= 1.377 (p= 0.329)

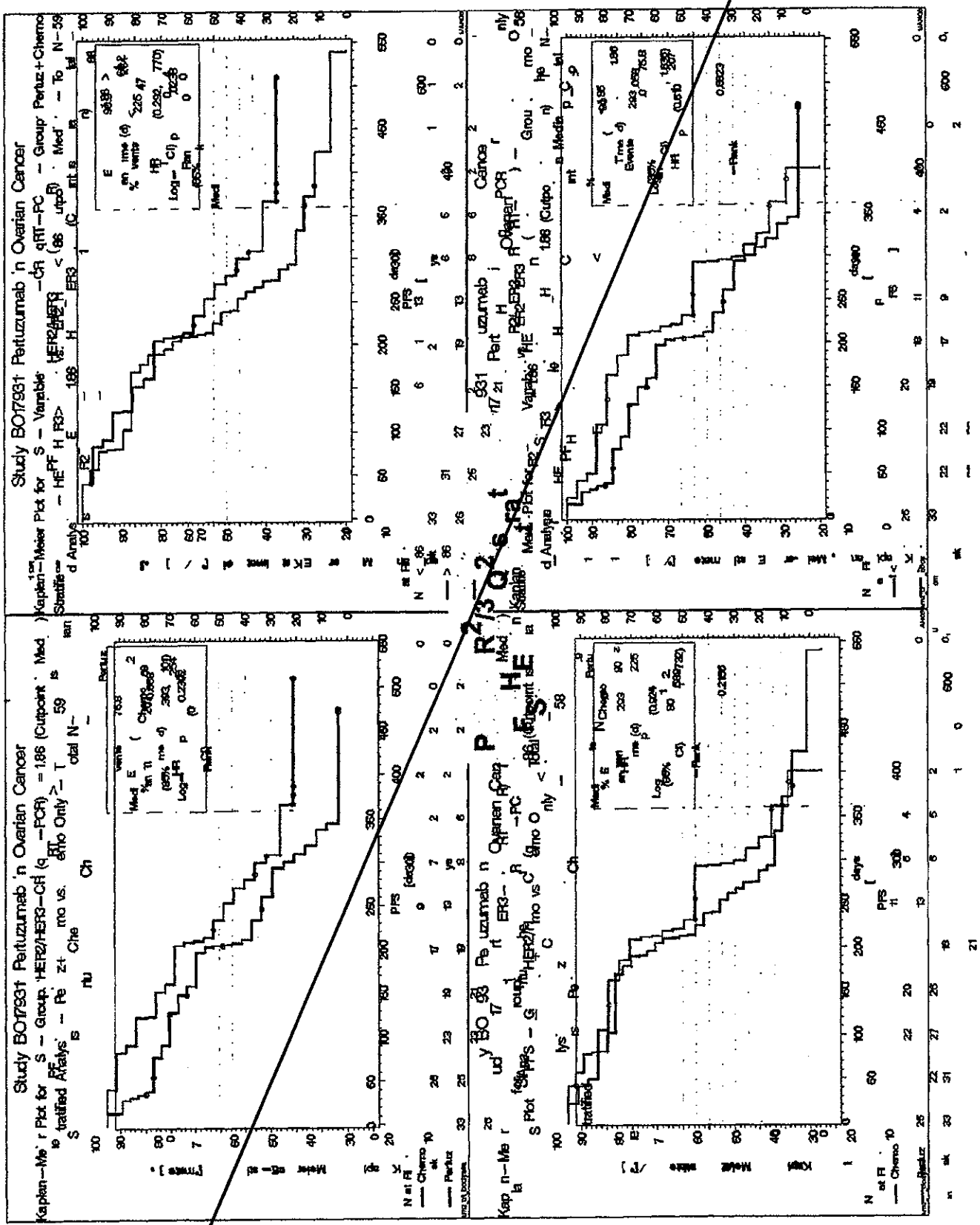
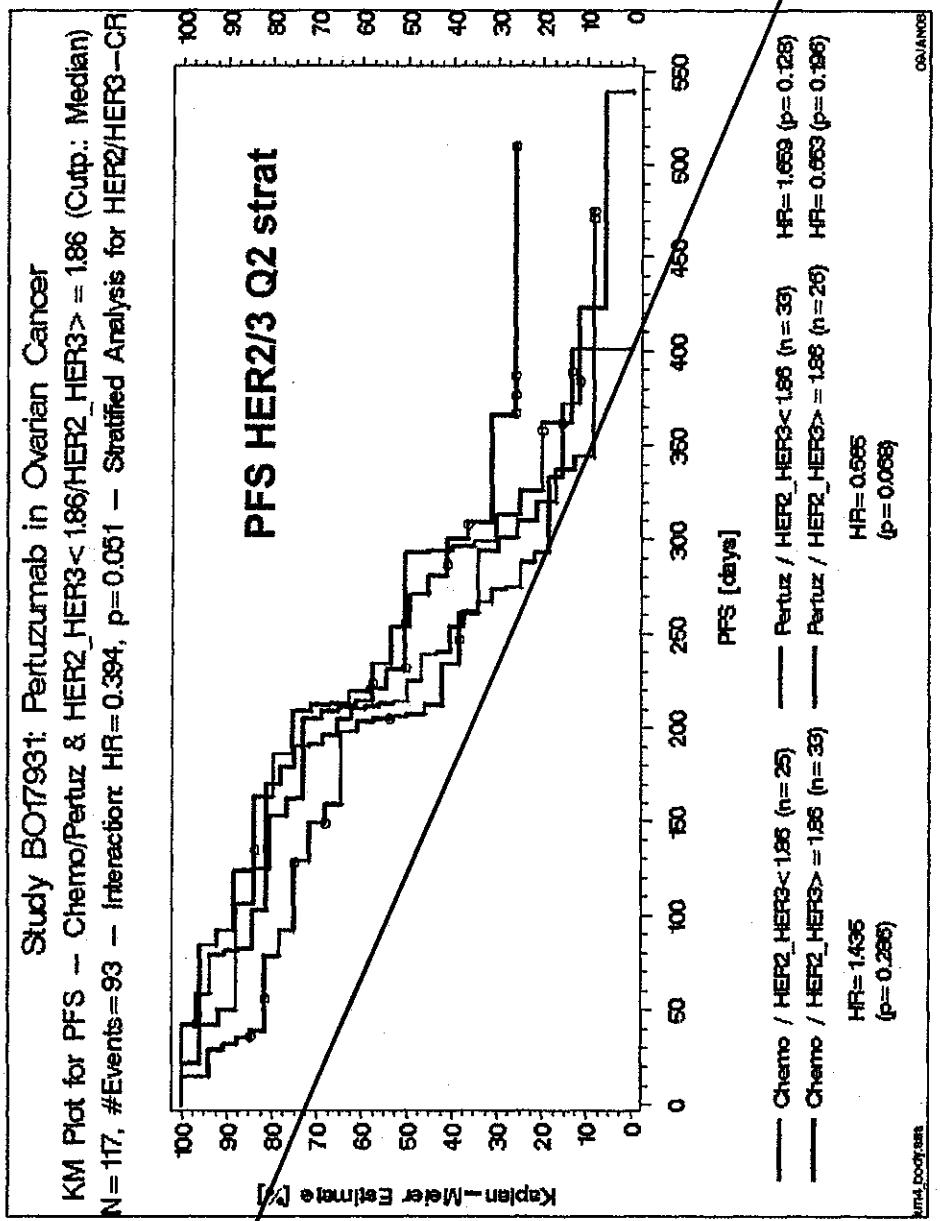


FIG. 35


Study BO17931: Pertuzumab in Ovarian Cancer
KM Plot for PFS -- Chemo/Pertuz & HER2_HER3< 1.86/HER2_HER3>= 1.86 (Cutp.: Median)
N=117, #Events=93 -- Interaction: HR=0.394, p=0.051 -- Stratified Analysis for HER2/HER3--CR
PFS HER2/3 Q2 strat
Kaplan-Meier Estimate [%]
PFS [days]
Chemo / HER2_HER3<1.86 (n=25)
Chemo / HER2_HER3>= 1.86 (n=33)
Pertuz / HER2_HER3<1.86 (n=39)
Pertuz / HER2_HER3>= 1.86 (n=26)
HR= 1.659 (p= 0.128)
HR= 0.653 (p= 0.196)
HR= 1.436
(p= 0.286)
HR= 0.585
(p= 0.068)

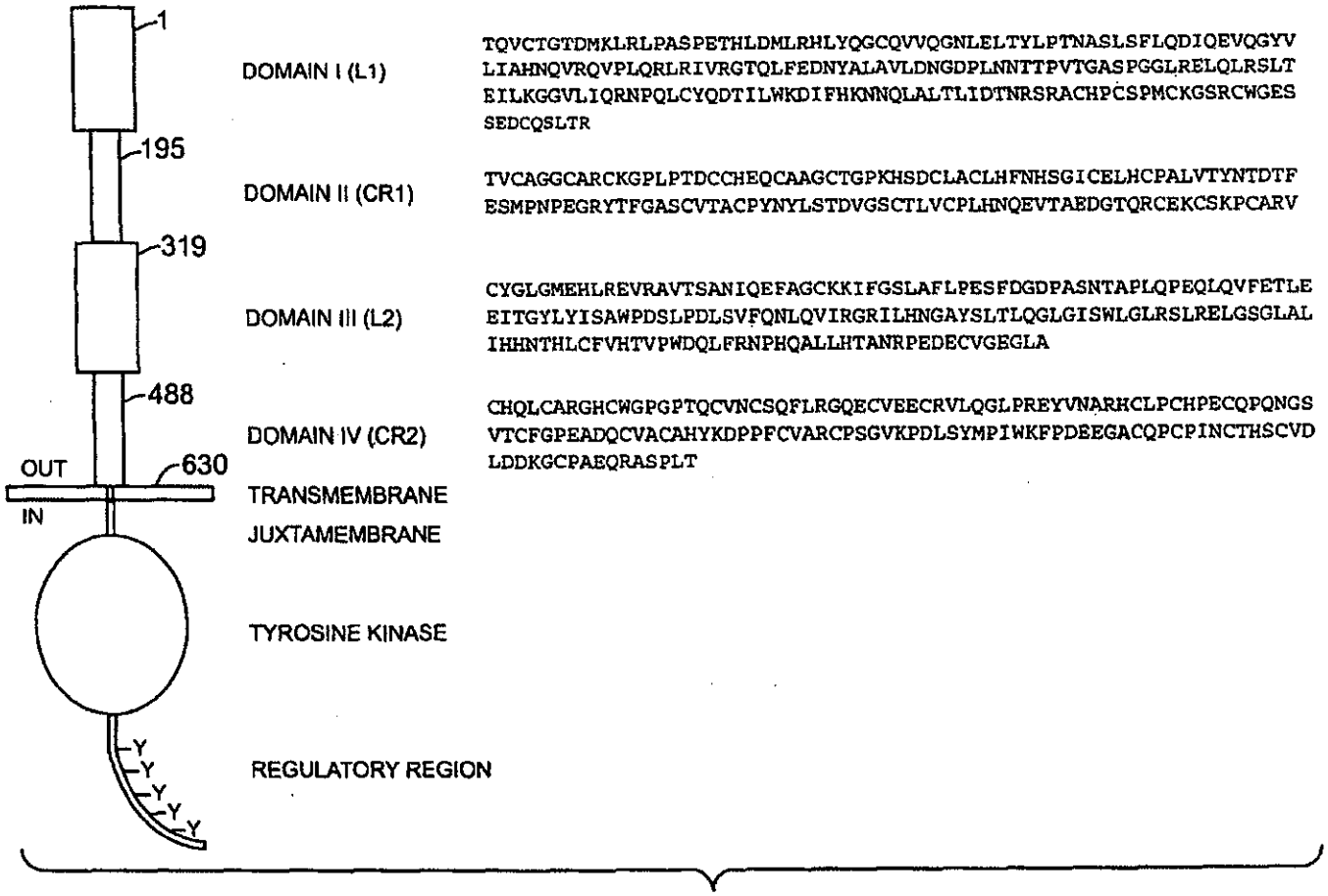

1
195
319
488
630
OUT
IN
Y
Y
Y
Y
Y
DOMAIN I (L1)
DOMAIN II (CR1)
DOMAIN III (L2)
DOMAIN IV (CR2)
TRANSMEMBRANE
JUXTAMEMBRANE
TYROSINE KINASE
REGULATORY REGION
TQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNASLSFLQDIQEVQGYV
LIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLT
EILKGGVLIQRNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGES
SEDCQSLTR
TVCAGGCARCKGPLPTDCCHEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTF
ESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCPLHNQEVTAEDGTQRCEKCSKPCARV
CYGLGMEHLREVRAVTSANIQEFAGCKKIFGSLAFLPESFDGDPASNTAPLQPEQLQVFETLE
EITGYLYISAWPDSLPDLSVFQNLQVIRGRILHNGAYSLTLQGLGISWLGLRSLRELGSGLAL
IHHNTHLCFVHTVPWDQLFRNPHQALLHTANRPEDECVGEGLA
CHQLCARGHCWGPGPTQCVNCSQFLRGQECVEECRVLQGLPREYVNARHCLPCHPECQPQNGS
VTCFGPEADQCVACAHYKDPPFCVARCPSGVKPDLSYMPIWKFPDEEGACQPCPINCTHSCVD
LDDKGCPAEQRASPLT

FIG. 1

Variable Light

```
                  10          20          30          40
2C4       DIVMTQSHKIMSTSVGDRVSITC [KASQDVSIGVA] WYQQRP
           **    **** *       *                    *
574       DIQMTQSPSSLSASVGDRVTITC [KASQDVSIGVA] WYQQKP
                                   *   ** ***
hum kI    DIQMTQSPSSLSASVGDRVTITC [RASQSISNYLA] WYQQKP

                 50          60          70          80
2C4       GQSPKLLIY [SASYRYT] GVPDRFTGSGSGTDFTFTISSVQA
           **                  *  *          *    * *
574       GKAPKLLIY [SASYRYT] GVPSRFSGSGSGTDFTLTISSLQP
                    * *****
hum kI    GKAPKLLIY [AASSLES] GVPSRFSGSGSGTDFTLTISSLQP

                 90          100
2C4       EDLAVYYC [QQYYIYPYT] FGGGTKLEIK (SEQ ID NO:1)
            * *                 *   *
574       EDFATYYC [QQYYIYPYT] FGQGTKVEIK (SEQ ID NO:3
                     *** *
hum kI    EDFATYYC [QQYNSLPWT] FGQGTKVEIK (SEQ ID NO:5)
```

FIG. 2A

Variable Heavy

```
                  10          20          30          40
2C4       EVQLQQSGPELVKPGTSVKISCKAS [GFTFTDYTMD] WVKQS
              **  **  *  * ***  *                   * *
574       EVQLVESGGGLVQPGGSLRLSCAAS [GFTFTDYTMS] WVRQA
                                     ** * *
hum III   EVQLVESGGGLVQPGGSLRLSCAAS [GFTFSSYAMS] WVRQA

                 50 a        60          70          80
2C4       HGKSLEWIF [DVNPNSGGSIYNQRFKG] KASLTVDRSSRIVYM
          *  *   **                     *** *    **** *
574       PGKGLEWVA [DVNPNSGGSIYNQRFKG] RFTLSVDRSKNTLYL
                     ****** *** ****       * * *
hum III   PGKGLEWVA [VISGDGGSTYYADSVKG] RFTISRDNSKNTLYL

            abc       90          100ab         110
2C4       ELRSLTFEDTAVYYCAR [NLGPSFYFDY] WGQGTTLTVSS (SEQ ID NO:2)
          ***  **                                **
574       QMNSLRAEDTAVYYCAR [NLGPSFYFDY] WGQGTLVTVSS (SEQ ID NO:4)
                             ********
hum III   QMNSLRAEDTAVYYCAR [GRVGYSLYDY] WGQGTLVTVSS (SEQ ID NO:6)
```

FIG. 2B

Amino Acid Sequence for Pertuzumab Light Chain

```
1          10         20         30         40         50         60
|          |          |          |          |          |          |
DIQMTQSPSSLSASVGDRVTITCKASQDVSIGVAWYQQKPGKAPKLLIYSASYRYTGVPS

          70         80         90         100        110        120
          |          |          |          |          |          |
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYYIYPYTFGQGTKVEIKRTVAAPSVFIFPP

          130        140        150        160        170        180
          |          |          |          |          |          |
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT

          190        200        210
          |          |          |
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
```

FIG. 3A

Amino Acid Sequence for Pertuzumab Heavy Chain

```
1          10         20         30         40         50         60
|          |          |          |          |          |          |
EVQLVESGGGLVQPGGSLRLSCAASGFTFTDYTMDWVRQAPGKGLEWVADVNPNSGGSIY

          70         80         90         100        110        120
          |          |          |          |          |          |
NQRFKGRFTLSVDRSKNTLYLQMNSLRAEDTAVYYCARNLGPSFYFDYWGQGTLVTVSSA

          130        140        150        160        170        180
          |          |          |          |          |          |
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG

          190        200        210        220        230        240
          |          |          |          |          |          |
LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP

          250        260        270        280        290        300
          |          |          |          |          |          *|
SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS

          310        320        330        340        350        360
          |          |          |          |          |          |
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM

          370        380        390        400        410        420
          |          |          |          |          |          |
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ

          430        440        448
          |          |          |
QGNVFSCSVMHEALHNHYTQKSLSLSPG
```

FIG. 3B

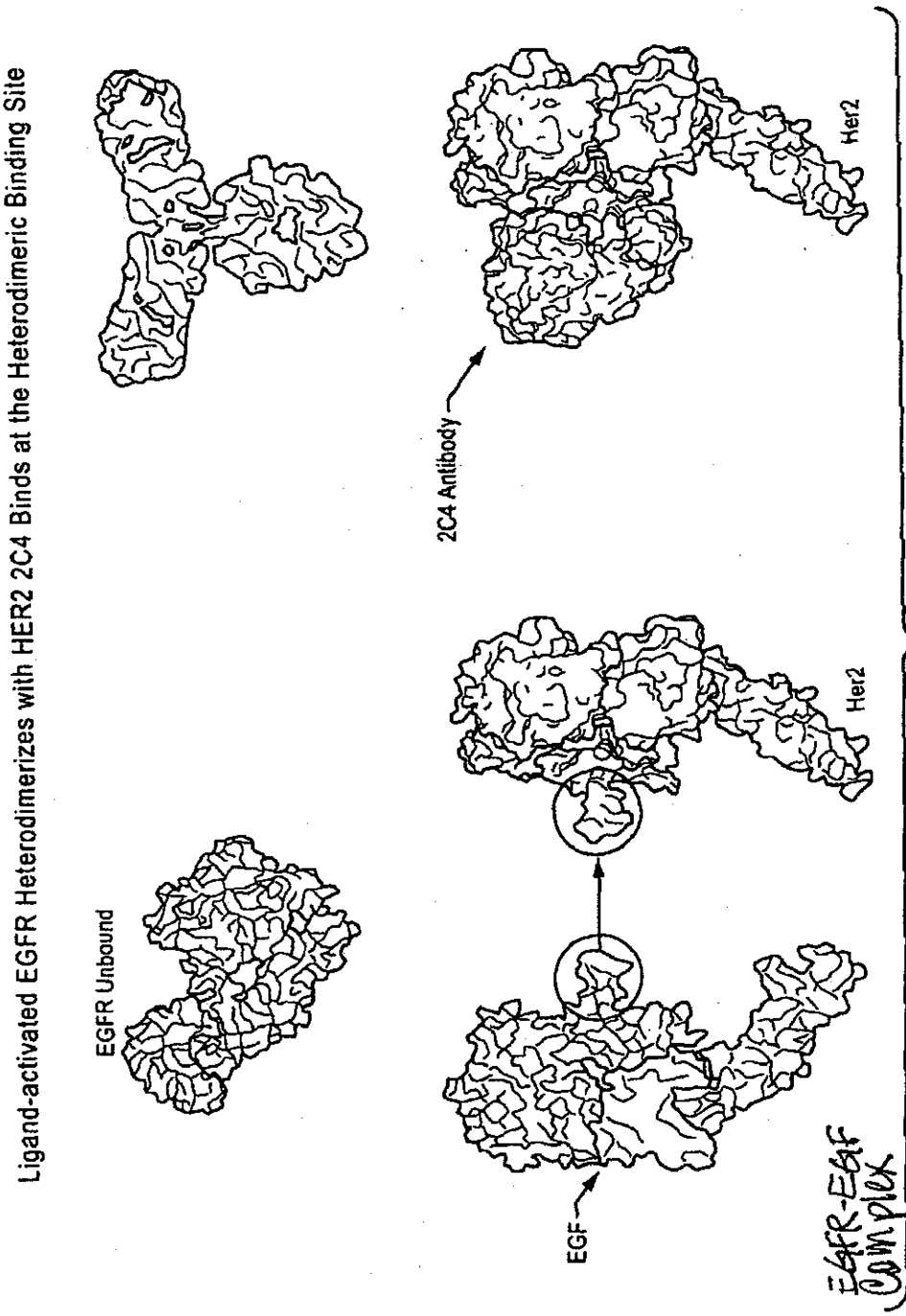

Ligand-activated EGFR Heterodimerizes with HER2 2C4 Binds at the Heterodimeric Binding Site
EGFR Unbound
2C4 Antibody
Her2
Her2
EGF
EGFR-EGF Complex

FIG. 4

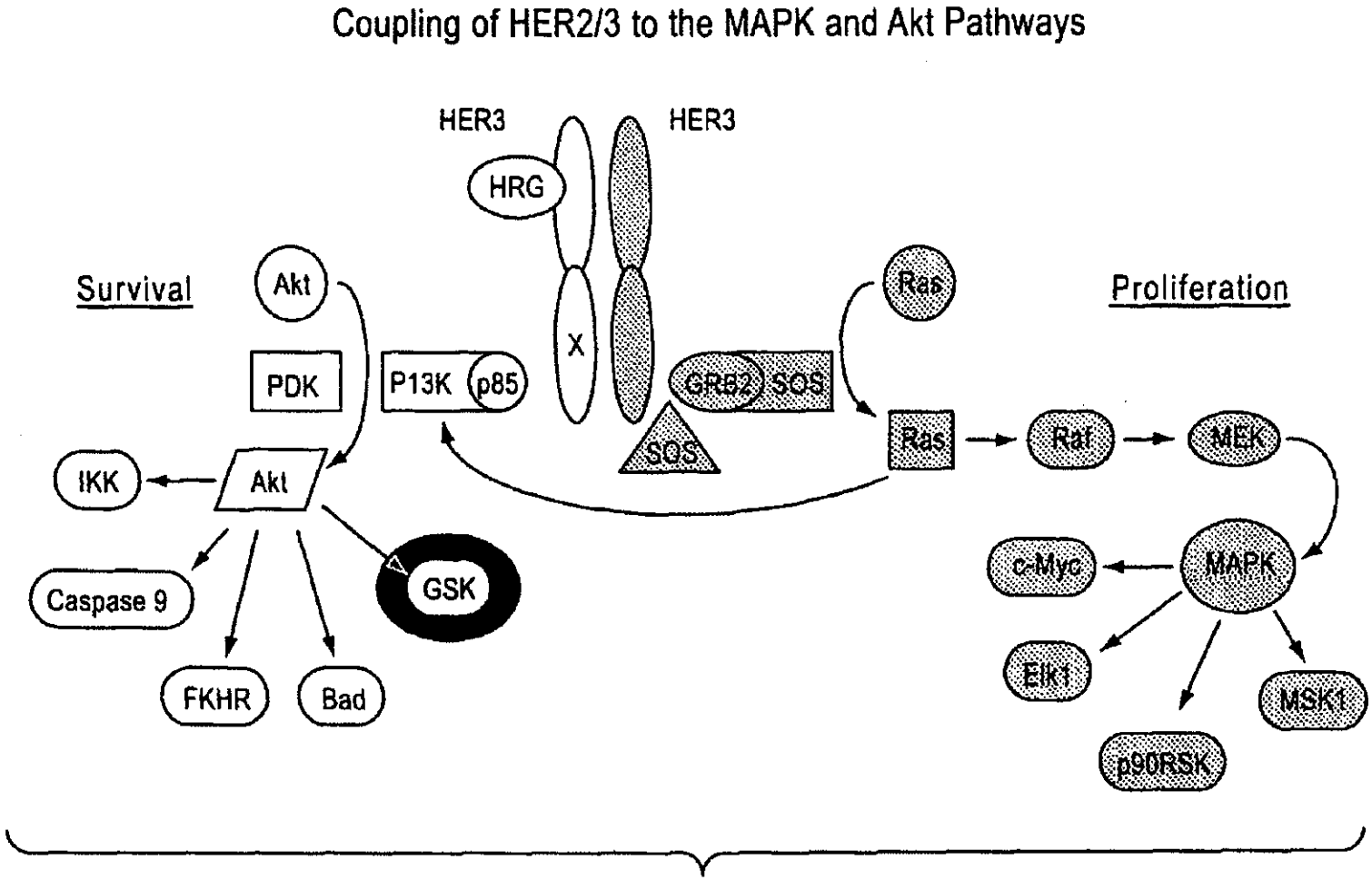

Coupling of HER2/3 to the MAPK and Akt Pathways
HER3
HER3
HRG
X
SOS
GRB2
SOS
Ras
Survival
Akt
PDK
P13K
p85
IKK
Akt
Caspase 9
GSK
FKHR
Bad
Ras
Raf
MEK
Proliferation
c-Myc
MAPK
Elk1
MSK1
p90RSK

FIG. 5

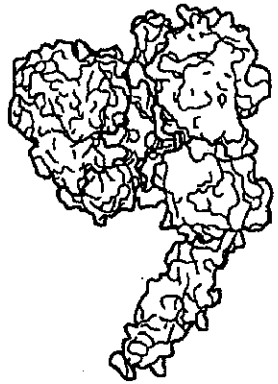
TRASTUZUMAB HERCEPTIN	PERTUZUMAB OMNITARG
	
• Binds in IV near JM • Protects against receptor shedding • Moderately affects receptor down-modulation • Slight effect on HER2's role as a coreceptor	• Binds in II at dimerization interface • Does not prevent receptor shedding • Moderately affects receptor down-modulation • Major effect on HER2's role as a coreceptor

FIG. 6

LIGHT CHAIN

```
1                               15                              30                              45
D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q D V N T A V A W Y Q Q K P G K A P K

46                              60                              75                              90
L L I Y S A S F L Y S G V P S R F S G S R S G T D F T L T I S S L Q P E D F A T Y Y C Q Q

91                              105                             120                             135
H Y T T P P T F G Q G T K V E I K R T V A A P S V F I F P P S D E Q L K S G T A S V V C L

136                             150                             165                             180
L N N F Y P R E A K V Q W K V D N A L Q S G N S Q E S V T E Q D S K D S T Y S L S S T L T

181                             195                             210    214
L S K A D Y E K H K V Y A C E V T H Q G L S S P V T K S F N R G E C
```

FIG. 7A

HEAVY CHAIN

```
1                   15                  30                  45
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGL

46                  60                  75                  90
EWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAED

91                  105                 120                 135
TAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSS

136                 150                 165                 180
KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS

181                 195                 210                 225
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDK

226                 240                 255                 270
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS

271                 285                 300                 315
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD

316                 330                 345                 360
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE

361                 375                 390                 405
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG

406                 420                 435                 449
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
```

FIG. 7B

```
1                   15                  30                  45
VHSDIQMTQSPSSLSASVGDRVTITCKASQDVSIGVAWYQQKPGK

46                  60                  75                  90
APKLLIYSASYRYTGVPSRFSGSGSGTDFTLTISSLQPEDFATYY

91                  105                 120                 135
CQQYYIYPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV

136                 150                 165                 180
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSS

181                 195                 210         217
TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
```

FIG. 8A

```
1                 15                  30                  45
EVQLVESGGGLVQPGGSLRLSCAASGFTFTDYTMDWVRQAPGKGL

46                60                  75                  90
EWVADVNPNSGGSIYNQRFKGRFTLSVDRSKNTLYLQMNSLRAED

91                105                 120                 135
TAVYYCARNLGPSFYFDYWGQGTLVTVSSASTKGPSVFPLAPSSK

136               150                 165                 180
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG

181               195                 210                 225
LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT

226               240                 255                 270
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH

271               285                 300                 315
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW

316               330                 345                 360
LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM

361               375                 390                 405
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS

406               420                 435                 449
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
```

FIG. 8B

FIG. 9

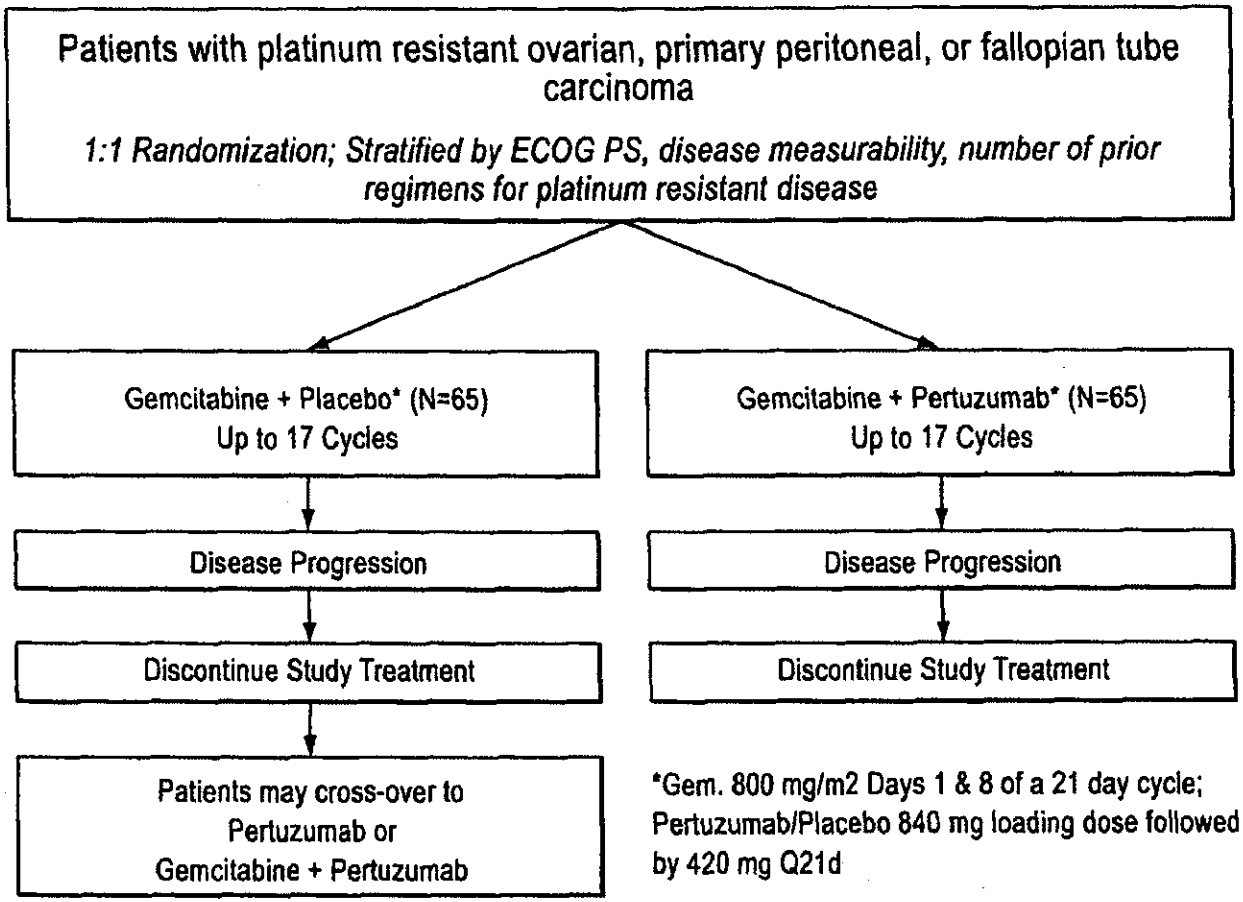

Patients with platinum resistant ovarian, primary peritoneal, or fallopian tube carcinoma
1:1 Randomization; Stratified by ECOG PS, disease measurability, number of prior regimens for platinum resistant disease
Gemcitabine + Placebo* (N=65)
Up to 17 Cycles
Gemcitabine + Pertuzumab* (N=65)
Up to 17 Cycles
Disease Progression
Disease Progression
Discontinue Study Treatment
Discontinue Study Treatment
Patients may cross-over to
Pertuzumab or
Gemcitabine + Pertuzumab
*Gem. 800 mg/m2 Days 1 & 8 of a 21 day cycle;
Pertuzumab/Placebo 840 mg loading dose followed
by 420 mg Q21d

FIG. 10A

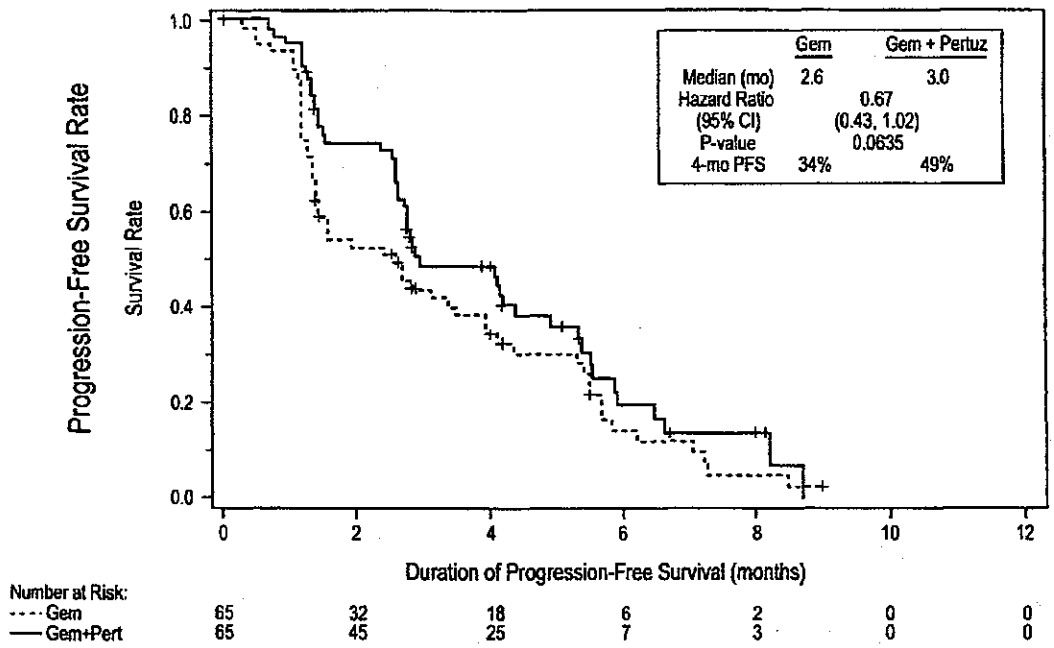

Progression-Free Survival Rate
Survival Rate
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
Duration of Progression-Free Survival (months)
Gem
Gem + Pertuz
Median (mo) 2.6 3.0
Hazard Ratio 0.67
(95% CI) (0.43, 1.02)
P-value 0.0635
4-mo PFS 34% 49%
Number at Risk:
Gem 65 32 18 6 2 0 0
Gem+Pert 65 45 25 7 3 0 0

FIG. 10B

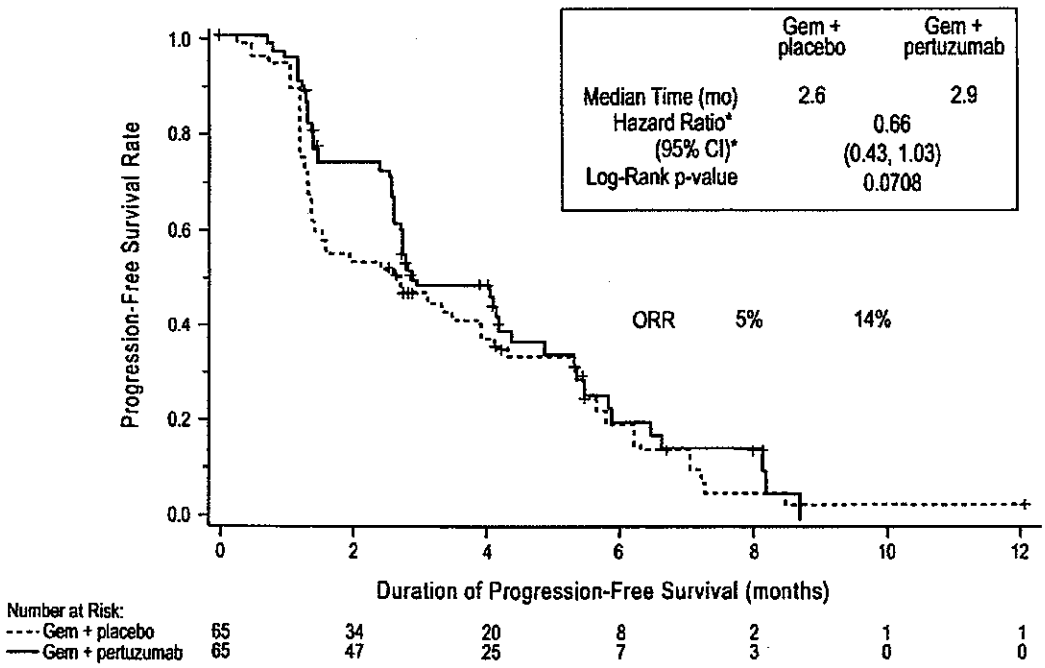
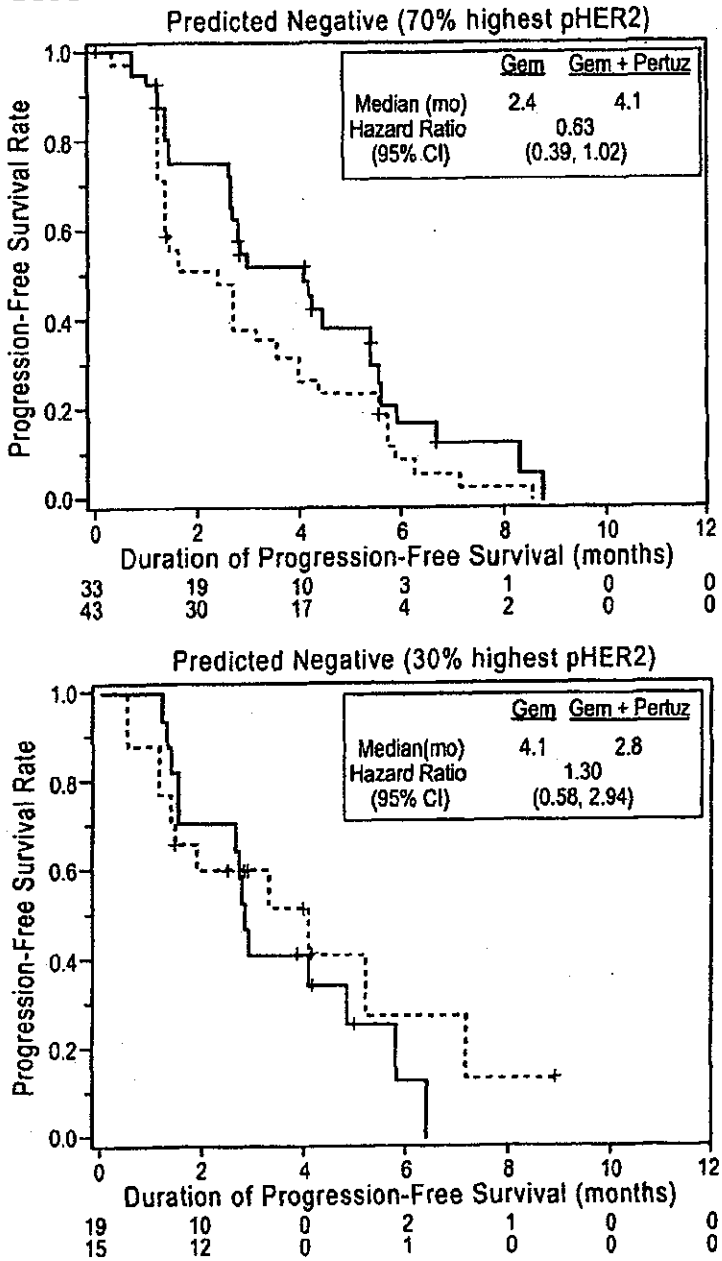
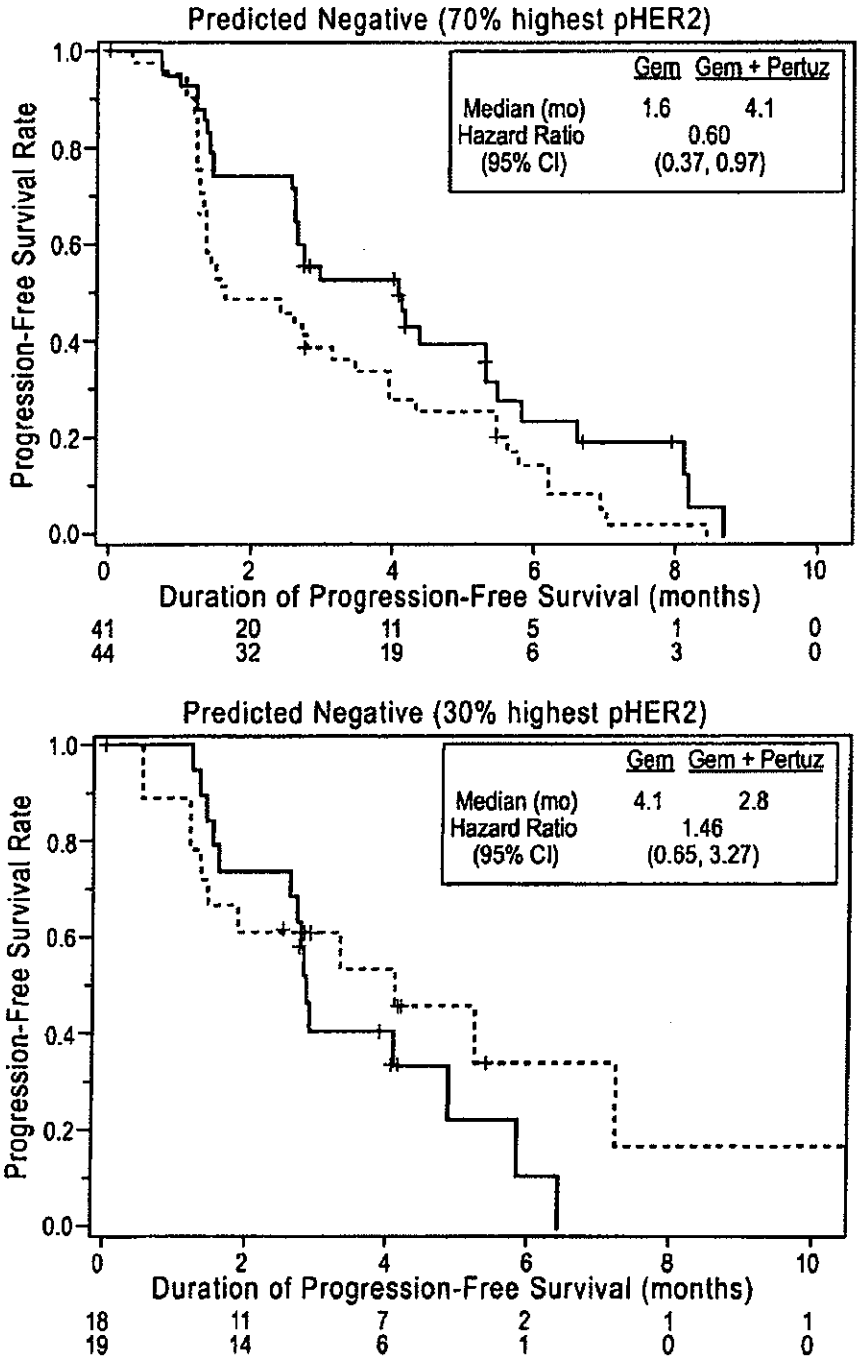

Gem + placebo
Gem + pertuzumab
Median Time (mo) 2.6 2.9
Hazard Ratio* 0.66
(95% CI)* (0.43, 1.03)
Log-Rank p-value 0.0708
ORR 5% 14%
Progression-Free Survival Rate
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
Duration of Progression-Free Survival (months)
Number at Risk:
---- Gem + placebo 65 34 20 8 2 1 1
—— Gem + pertuzumab 65 47 25 7 3 0 0

FIG. 11A



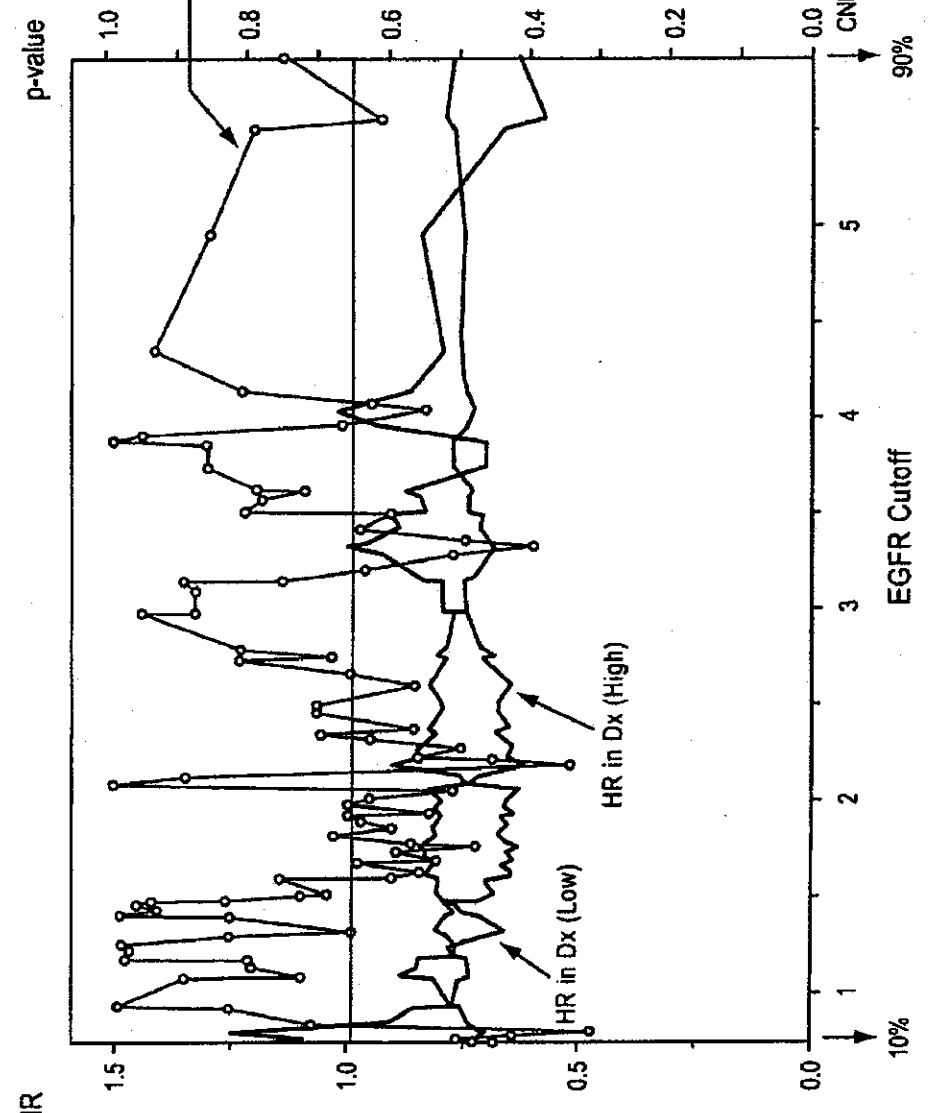
Note: Dx (+): the Amphi, Her2, Her3 sum score ≥ 70th percentile, Dx (-): Others

FIG. 11B



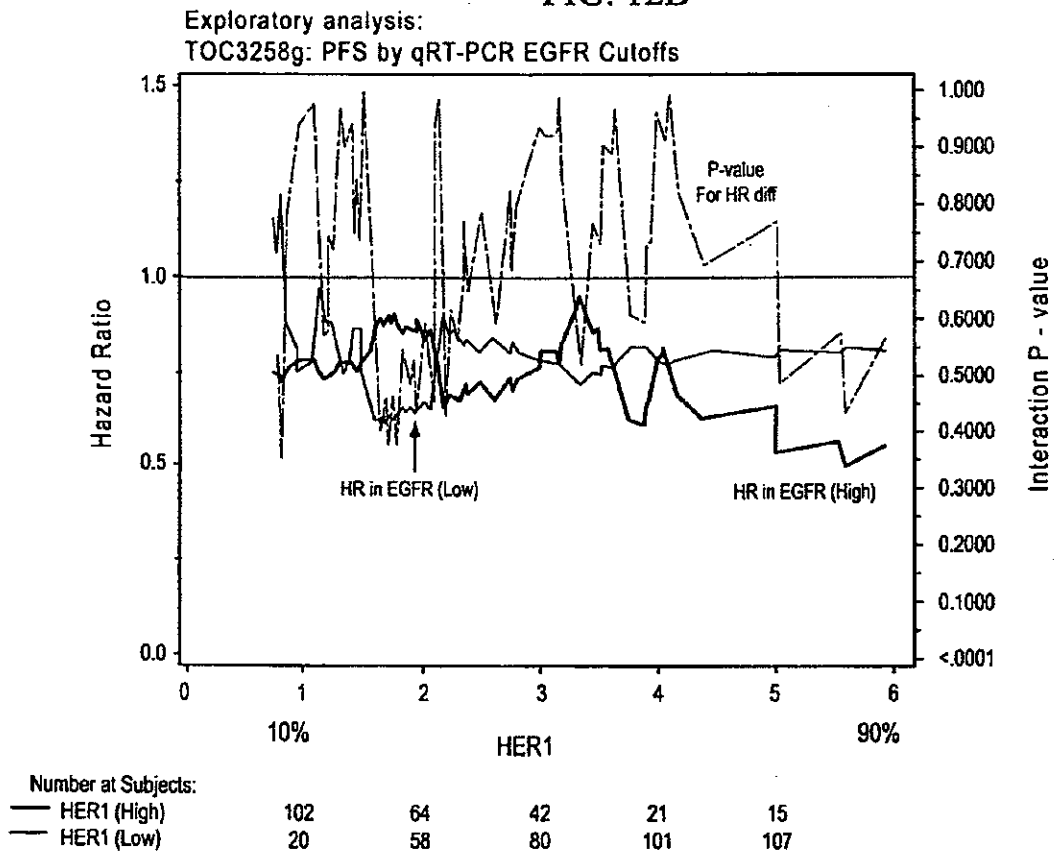
Note: Dx (+): the Amphi, Her2, Her3 sum score ≥ 70th percentile, Dx (-): Others

FIG. 12A



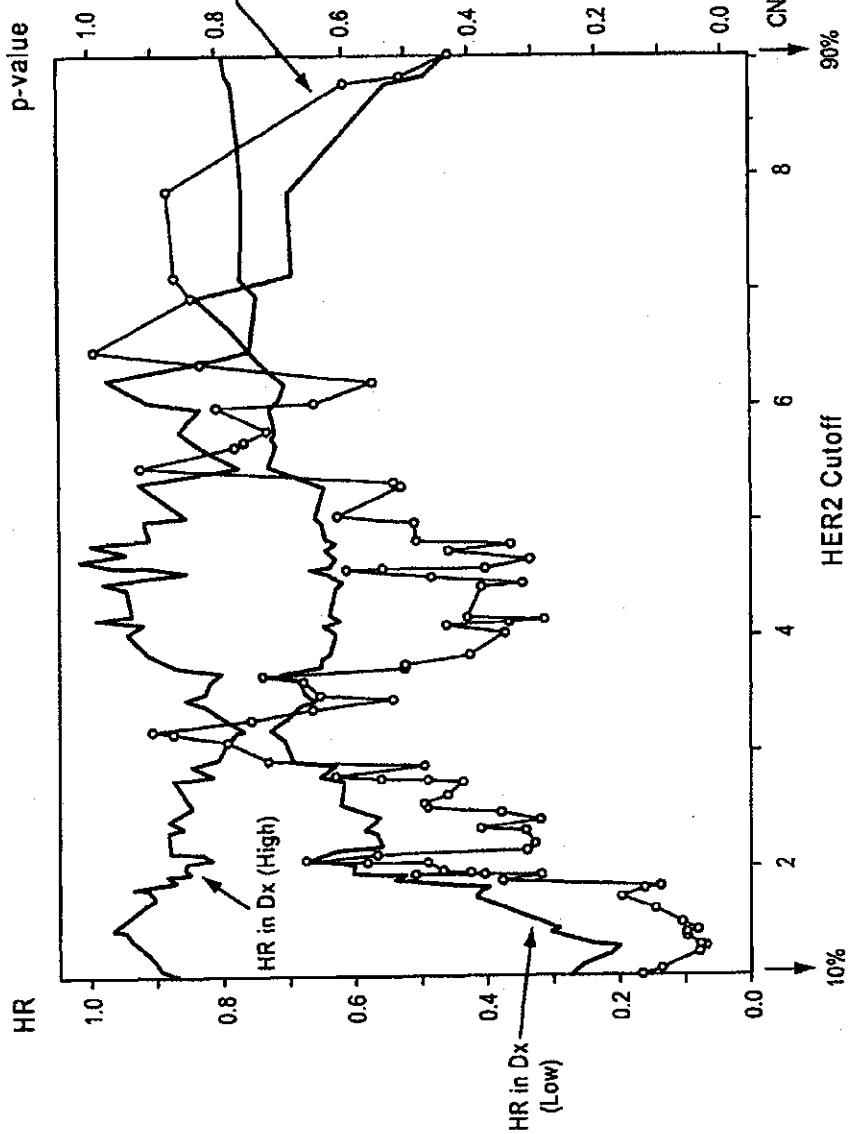
P-values were not adjusted for multiple comparisons

FIG. 12B



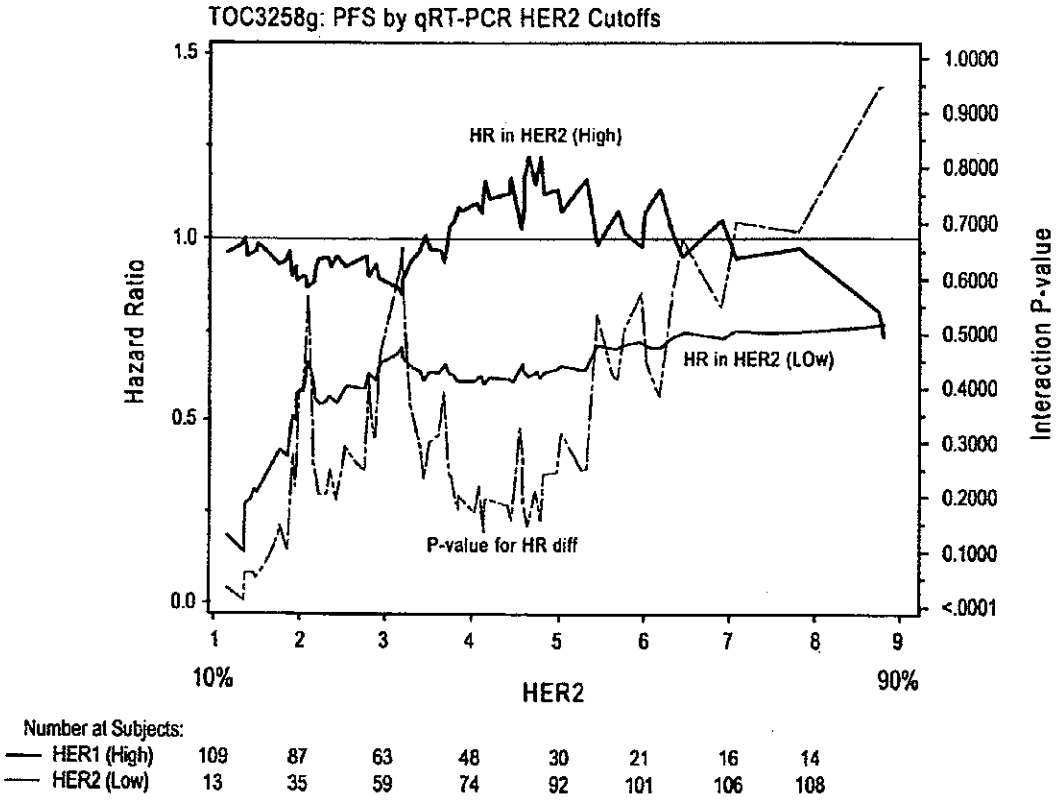
P-values were not adjusted for multiple comparisons

FIG. 13A



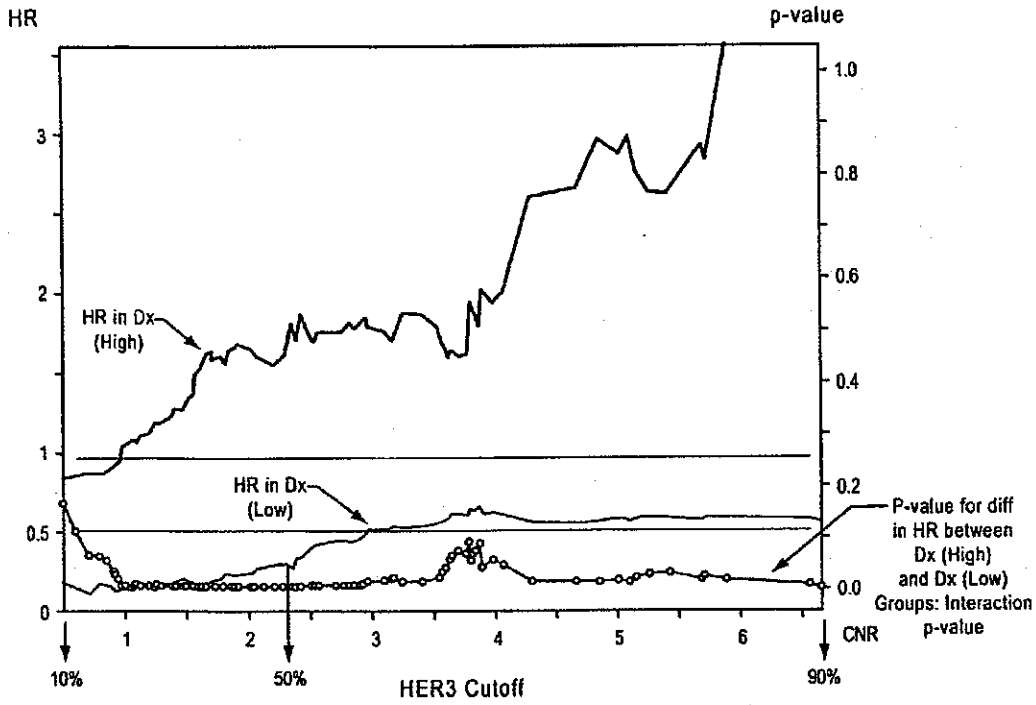
P-values were not adjusted for multiple comparisons

FIG. 13B



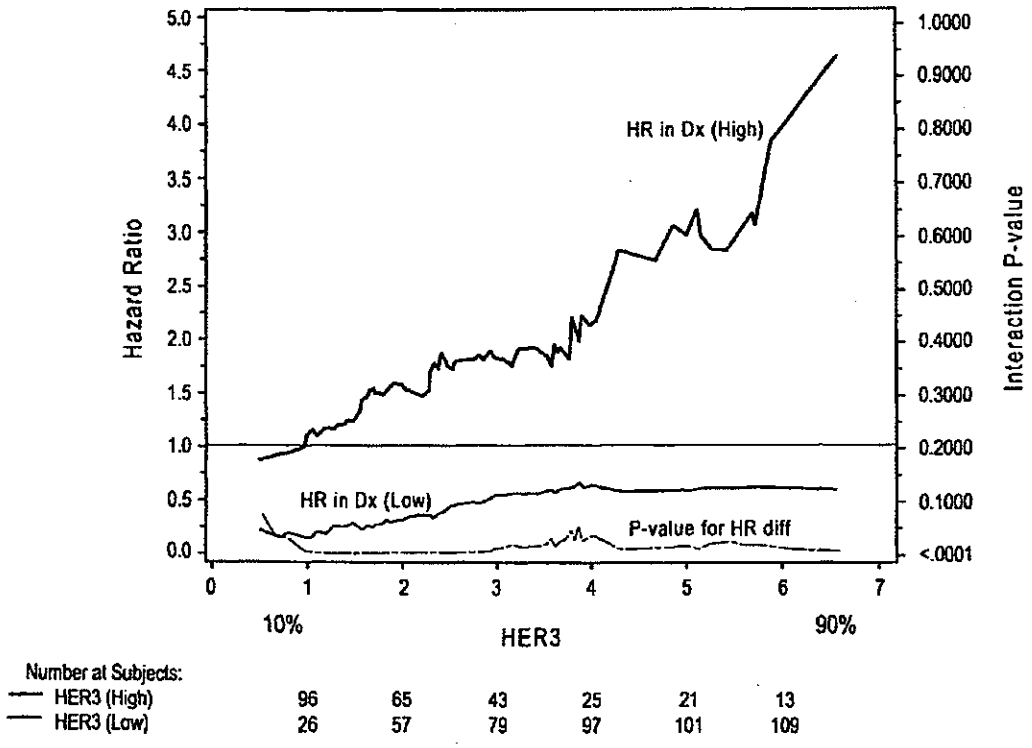
P-values were not adjusted for multiple comparisons

FIG. 14A



P-values were not adjusted for multiple comparisons

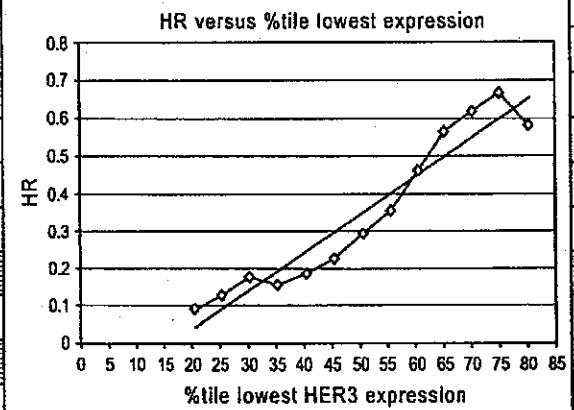
FIG. 14B



P-values were not adjusted for multiple comparisons

FIG. 15A

Cutoff		Low HER3 Expression			
%tile	Abs. Value	N	# Events	HR (96%CI)	Logrank P-value
20	0.99	20	16	0.09 (0.02, 0.42)	0.0002
25	1.19	28	21	0.13 (0.04, 0.45)	0.0002
30	1.4	35	28	0.18 (0.06, 0.52)	0.0004
35	1.57	41	32	0.16 (0.06, 0.43)	<.0001
40	1.71	47	36	0.19 (0.08, 0.47)	<.0001
45	1.88	53	40	0.23 (0.11, 0.50)	<.0001
50	2.26	59	46	0.30 (0.16, 0.58)	0.0002
55	2.41	65	52	0.36 (0.20, 0.65)	0.0005
60	2.8	71	57	0.47 (0.27, 0.81)	0.0060
65	3.14	77	63	0.57 (0.34 0.95)	0.0299
70	3.59	83	69	0.62 (0.38, 1.00)	0.0488
75	3.8	89	75	0.67 (0.42, 1.06)	0.0898
80	4.29	95	78	0.59 (0.37, 0.92)	0.0196



P-values were not adjusted for multiple comparisons

Cutoff Value		Low HER3 Expression			
%tile	Abs. Value	N	# Events	HR (96%CI)	Logrank P-value
25	1.19	30	23	0.13 (0.04, 0.41)	<.0001
30	1.39	36	29	0.22 (0.09, 0.56)	0.0005
35	1.56	42	33	0.20 (0.09, 0.48)	<.0001
40	1.70	48	38	0.22 (0.10, 0.50)	<.0001
45	1.87	54	42	0.29 (0.14, 0.58)	0.0002
50	2.24	61	48	0.34 (0.18, 0.63)	0.0004
55	2.38	66	53	0.36 (0.20, 0.65)	0.0005
60	2.75	73	59	0.48 (0.28, 0.84)	0.0080
65	3.08	79	65	0.56 (0.34, 0.94)	0.0255
70	3.56	85	71	0.62 (0.38, 1.00)	0.0459
75	3.77	91	76	0.65 (0.41, 1.03)	0.0650

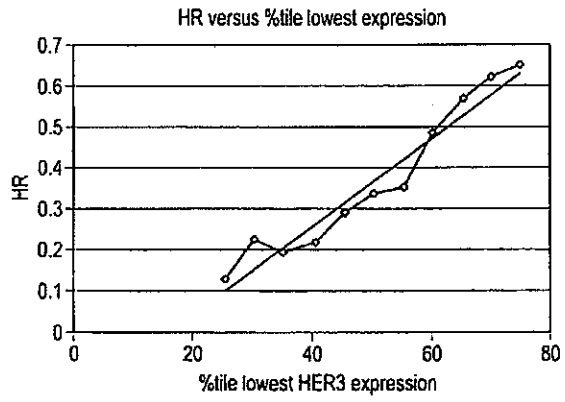


FIG. 15B

FIG. 16A

Cutoff		High HER3 Expression			
%tile	Abs. Value	N	# Events	HR (96%CI)	Logrank P-value
20	0.99	96	78	1.06 (0.67, 1.65)	0.8083
25	1.19	91	73	1.13 (0.71, 1.81)	0.5875
30	1.4	84	66	1.28 (0.77, 2.10)	0.3318
35	1.57	78	62	1.49 (0.89, 2.51)	0.1280
40	1.71	72	58	1.55 (0.90, 2.68)	0.1141
45	1.88	66	54	1.64 (0.94, 2.88)	0.0817
50	2.28	60	48	1.60 (0.89, 2.87)	0.1161
55	2.41	54	42	1.87 (0.97, 3.57)	0.0565
60	2.8	48	37	1.88 (0.92, 3.84)	0.0766
65	3.14	42	31	1.72 (0.78, 3.75)	0.1693
70	3.59	36	25	1.67 (0.72, 3.90)	0.2270
75	3.8	30	19	2.00 (0.71, 5.62)	0.1790
80	4.29	24	16	2.85 (0.89, 9.20)	0.0667

P-values were not adjusted for multiple comparisons

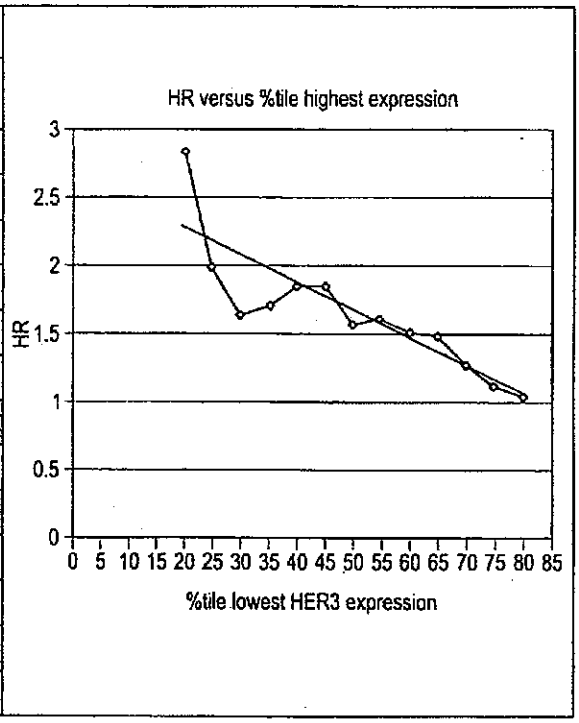


FIG. 16B

Cutoff Value		High HER3 Expression			
%tile	Abs. Value	N	# Events	HR (96%CI)	Logrank P-value
25	1.19	92	74	1.16 (0.73, 1.84)	0.5222
30	1.39	86	68	1.20 (0.74, 1.94)	0.4674
35	1.56	80	64	1.37 (0.83, 2.26)	0.2230
40	1.70	74	59	1.50 (0.88, 2.55)	0.1381
45	1.87	68	55	1.50 (0.87, 2.61)	0.1468
50	2.24	61	49	1.48 (0.83, 2.63)	0.1809
55	2.38	56	44	1.74 (0.93, 3.27)	0.0816
60	2.75	49	38	1.81 (0.90, 3.67)	0.0945
65	3.08	43	32	1.78 (0.82, 3.86)	0.1382
70	3.56	37	26	1.73 (0.75, 3.99)	0.1943
75	3.77	31	21	1.90 (0.73, 4.93)	0.1804

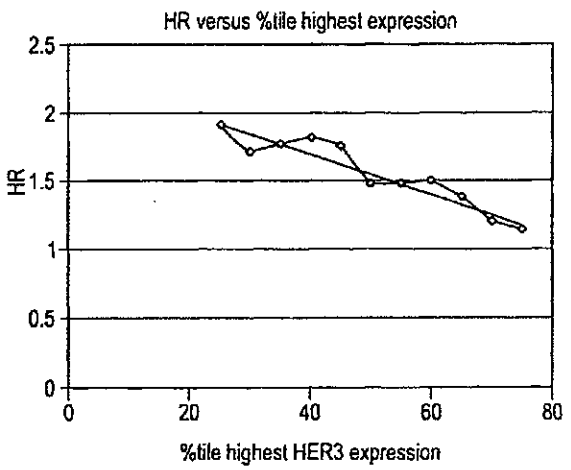


FIG. 17A

Cutoff		High HER3 Expression				Low HER3 Expression			
%tile	Abs. Value	N	# Events	HR (95%CI)	Logrank P-value	N	# Events	HR (95%CI)	Logrank P-value
20	0.99	96	78	1.06 (0.67, 1.65)	0.8083	23	16	0.09 (0.02, 0.42)	0.0002
KM	1.19	91	73	1.13 (0.71, 1.81)	0.5875	28	21	0.13 (0.04, 0.45)	0.0002
30	1.4	84	66	1.28 (0.77, 2.10)	0.3318	35	28	0.18 (0.06, 0.52)	0.0004
35	1.57	78	62	1.49 (0.89, 2.51)	0.1280	41	32	0.16 (0.06, 0.43)	<.0001
40	1.71	72	58	1.55 (0.90, 2.68)	0.1141	47	36	0.19 (0.08, 0.47)	<.0001
45	1.88	66	54	1.64 (0.94, 2.88)	0.0817	53	40	0.23 (0.11, 0.50)	<.0001
KM	2.28	60	48	1.60 (0.89, 2.87)	0.1161	59	46	0.30 (0.16, 0.58)	0.0002
55	2.41	54	42	1.87 (0.97, 3.57)	0.0565	65	52	0.36 (0.20, 0.65)	0.0005
60	2.8	48	37	1.88 (0.92, 3.84)	0.0766	71	57	0.47 (0.27,0.81)	0.0060
65	3.14	42	31	1.72 (0.78, 3.75)	0.1693	77	63	0.57 (0.34, 0.95)	0.0299
70	3.59	36	25	1.67 (0.72, 3.90)	0.2270	83	69	0.62 (0.38, 1.00)	0.0488
75	3.8	30	19	2.00 (0.71, 5.62)	0.1790	89	75	0.67 (0.42, 1.06)	0.0898
80	4.29	24	16	2.85 (0.89, 9.20)	0.0667	95	78	0.59 (0.37, 0.92)	0.0196

FIG. 17B

Cutoff Value		High HER3 Expression				Low HER3 Expression			
%tile	Abs. Value	N	# Events	HR (95%CI)	Logrank P-value	N	# Events	HR (95%CI)	Logrank P-value
KM	1.19	92	74	1.16 (0.73, 1.84)	0.5222	30	23	0.13 (0.04, 0.41)	<.0001
30	1.39	86	68	1.20 (0.74, 1.94)	0.4674	36	29	0.22 (0.09, 0.56)	0.0005
35	1.56	80	64	1.37 (0.83, 2.26)	0.2230	42	33	0.20 (0.09, 0.48)	<.0001
40	1.70	74	59	1.50 (0.88, 2.55)	0.1381	48	38	0.22 (0.10, 0.50)	<.0001
45	1.87	68	55	1.50 (0.87, 2.61)	0.1468	54	42	0.29 (0.14, 0.58)	0.0002
KM	2.24	61	49	1.48 (0.83, 2.63)	0.1809	61	48	0.34 (0.18, 0.63)	0.0004
55	2.38	56	44	1.74 (0.93, 3.27)	0.0816	66	53	0.36 (0.20, 0.65)	0.0005
60	2.75	49	38	1.81 (0.90, 3.67)	0.0945	73	59	0.48 (0.28, 0.84)	0.0080
65	3.08	43	32	1.78 (0.82, 3.86)	0.1382	79	65	0.56 (0.34, 0.94)	0.0255
70	3.56	37	26	1.73 (0.75, 3.99)	0.1943	85	71	0.62 (0.38, 1.00)	0.0459
75	3.77	31	21	1.90 (0.73, 4.93)	0.1804	91	76	0.65 (0.41, 1.03)	0.0650

FIG. 18A

qrt-PCR HER3	n	# of Events	Treatment HR (95% CI)	Log-rank P-value
0 - < 25th percentile	28	21	0.13 (0.04, 0.45)	0.0002
25 - < 50th percentile	31	25	0.42 (0.17, 1.00)	0.0465
50 - < 75th percentile	30	29	2.11 (0.94, 4.75)	0.0631
75 - 100th percentile	30	19	2.00 (0.71, 5.62)	0.1790

P-values were not adjusted for multiple comparisons

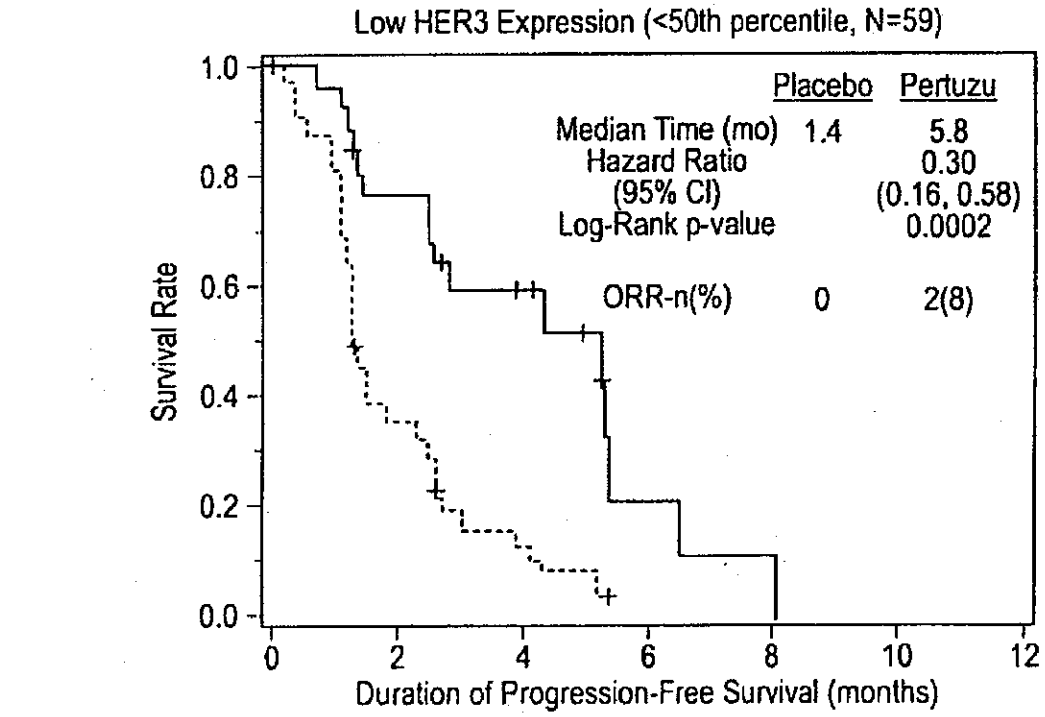
FIG. 18B

Progression-Free Survival (PFS) Analysis
by HER3 Expression Quartiles

qRT-PCR HER3	N	# of Events	Treatment HR (95% CI)	Log-rank P-value
0 - < 25th percentile	30	23	0.13 (0.04, 0.41)	<.0001
25 - < 50th percentile	31	25	0.66 (0.29, 1.48)	0.3181
50 - < 75th percentile	30	28	1.59 (0.73, 3.44)	0.2318
75 - 100th percentile	31	21	1.90 (0.73, 4.93)	0.1804

FIG. 19A (Part 1)

All patients	Gem	Gem + Pertuz
Median (mo)	2.6	3.0
Hazard Ratio*	0.67	
(95% CI)	(0.43, 1.02)	
P-value*	0.0635	
ORR-n(%)	3 (5)	5 (8)

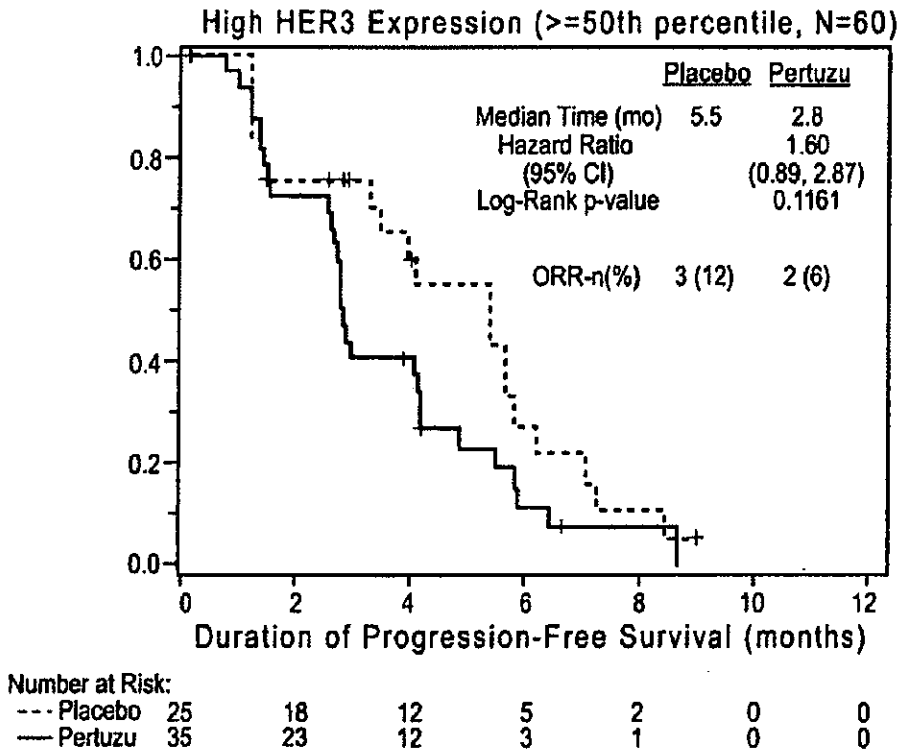


Number at Risk:

------ Placebo	33	11	4	0	0	0	0
—— Pertuzu	26	19	11	2	1	0	0

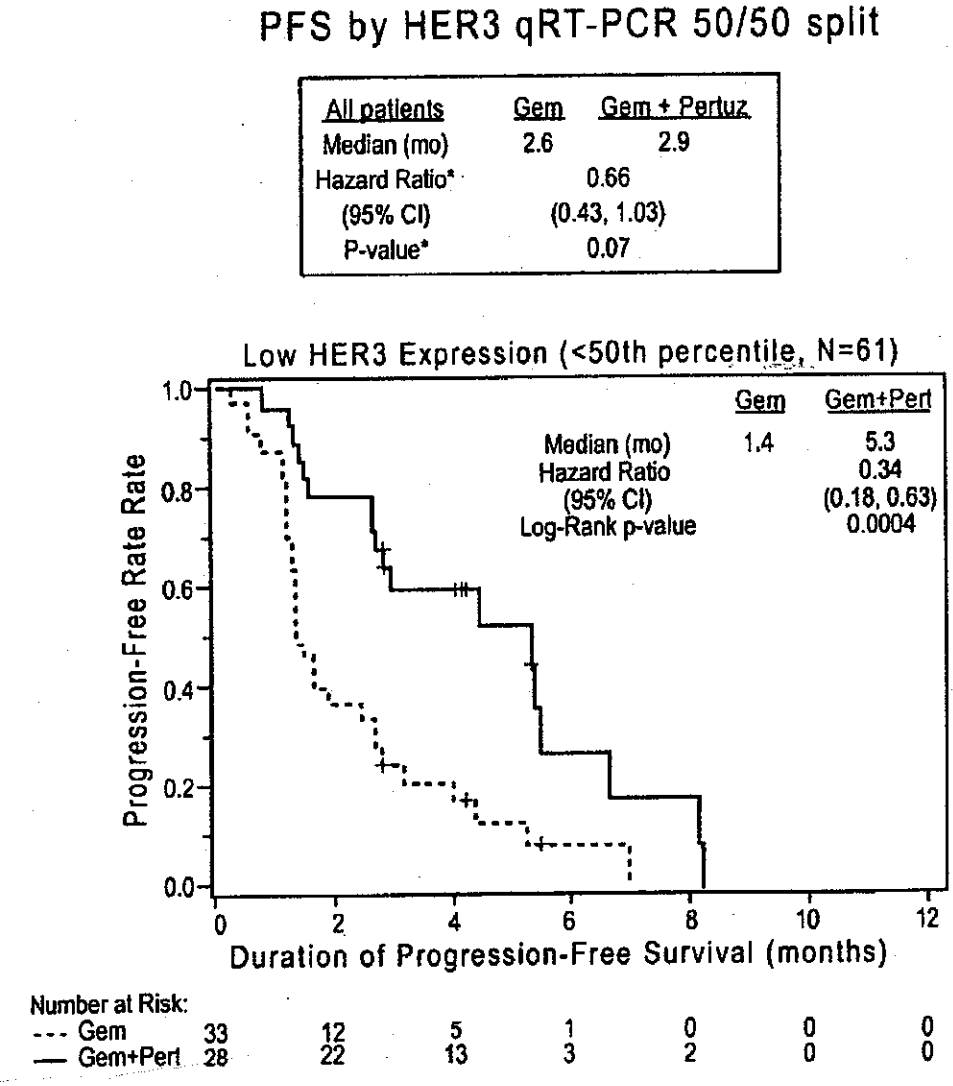
P-value for the difference.....

FIG. 19A (Part 2)



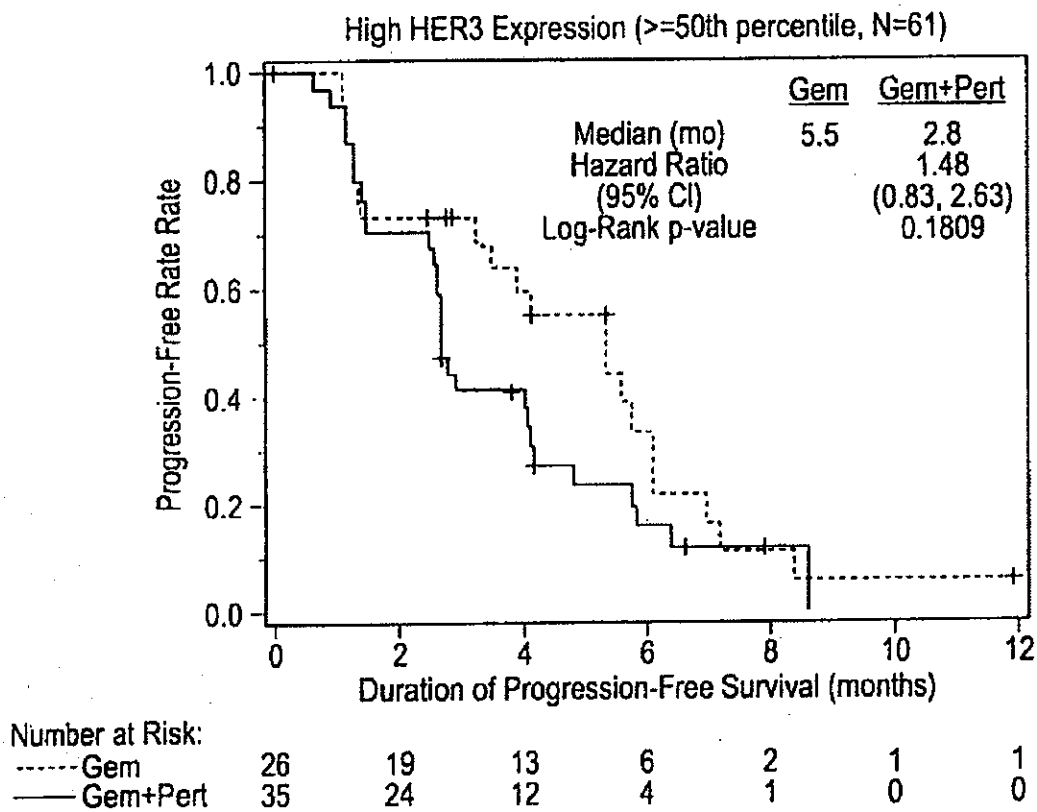
P-value for the difference in HR between two dx subgroups is 0.0001
Note: 50th percentile = 2.28 CNR

FIG. 19B (Part 1)



P-value for the difference in HR between two dx subgroups is 0.0005
Note: 50th percentile = 2.24 CNR

FIG. 19B (Part 2)



P-value for the difference.....

FIG. 20A

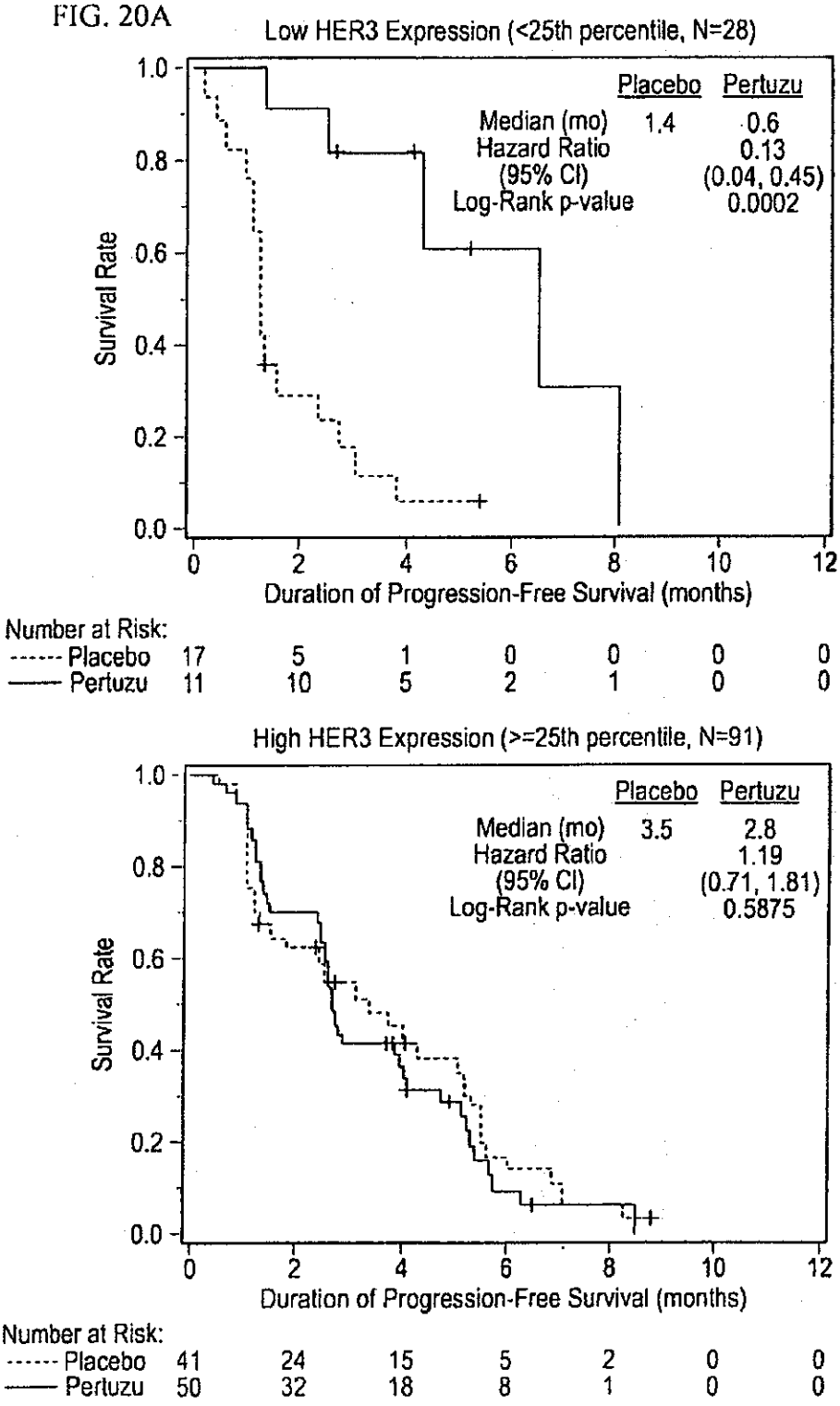
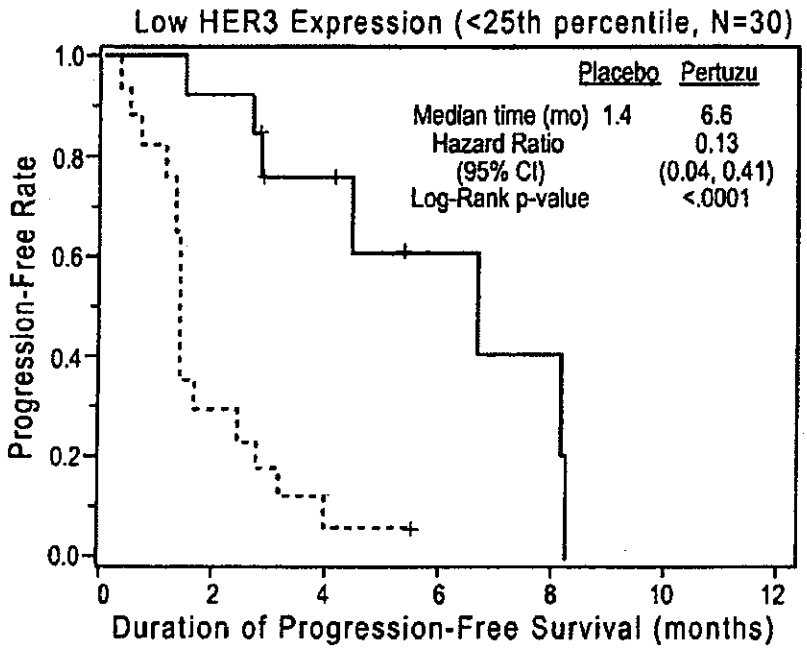

Low HER3 Expression (<25th percentile, N=28)
Placebo Pertuzu
Median (mo) 1.4 0.6
Hazard Ratio 0.13
(95% CI) (0.04, 0.45)
Log-Rank p-value 0.0002
Survival Rate
1.0
0.8
0.6
0.4
0.2
0.0
0 2 4 6 8 10 12
Duration of Progression-Free Survival (months)
Number at Risk:
------ Placebo 17 5 1 0 0 0 0
—— Pertuzu 11 10 5 2 1 0 0
High HER3 Expression (>=25th percentile, N=91)
Placebo Pertuzu
Median (mo) 3.5 2.8
Hazard Ratio 1.19
(95% CI) (0.71, 1.81)
Log-Rank p-value 0.5875
Survival Rate
1.0
0.8
0.6
0.4
0.2
0.0
0 2 4 6 8 10 12
Duration of Progression-Free Survival (months)
Number at Risk:
------ Placebo 41 24 15 5 2 0 0
—— Pertuzu 50 32 18 8 1 0 0

FIG. 20B (Part 1)

All patients	Gem	Gem + Pertuz
Median (mo)	2.6	2.9
Hazard Ratio*	0.66	
(95% CI)	(0.43, 1.03)	
P-value*	0.07	

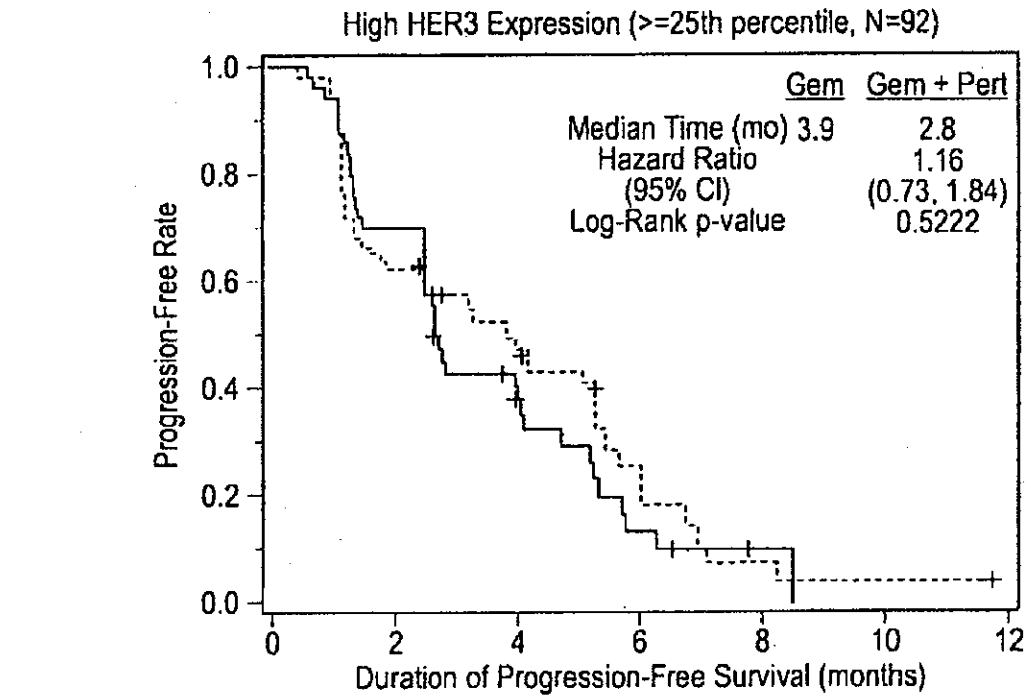


Number at Risk:

--- Gem	17	5	1	0	0	0	0
— Gem+ Pert	13	12	7	3	2	0	0

P-value for the difference in HR between two dx subgroups is 0.0003
Note: 25th percentile = 1.19 CNR

FIG. 20B (Part 2)



Number at Risk:

------ Gem	42	26	17	7	2	1	1
—— Gem + Pert	50	34	18	4	1	0	0

P-value for the difference.....

FIG. 21A

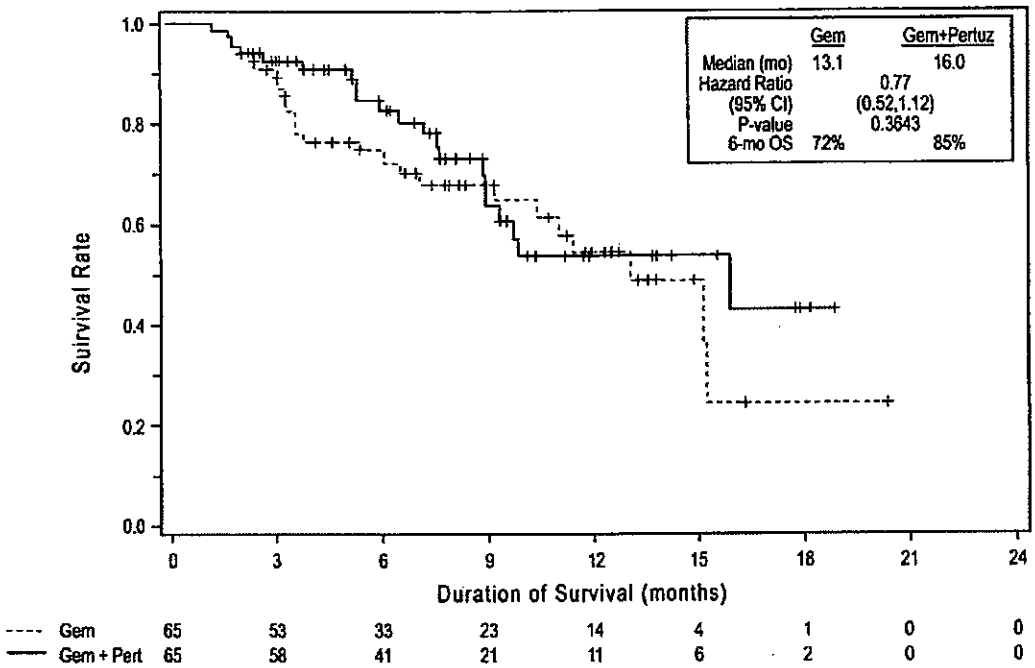
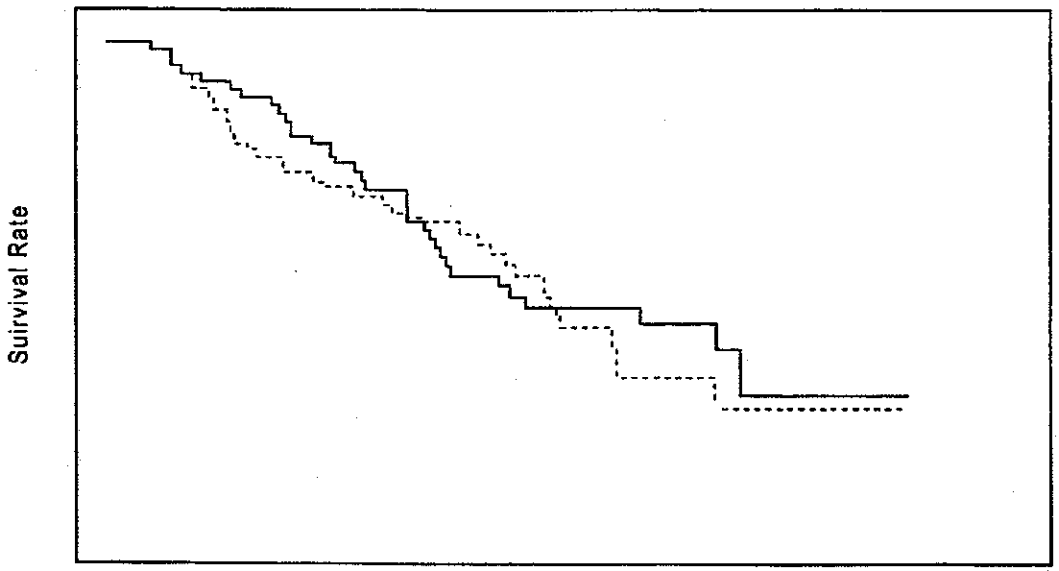

Gem
Gem+Pertuz
Median (mo) 13.1 16.0
Hazard Ratio 0.77
(95% CI) (0.52,1.12)
P-value 0.3643
6-mo OS 72% 85%
Suirvival Rate
1.0
0.8
0.6
0.4
0.2
0.0
0 3 6 9 12 15 18 21 24
Duration of Survival (months)
Gem 65 53 33 23 14 4 1 0 0
Gem + Pert 65 58 41 21 11 6 2 0 0

FIG. 21B

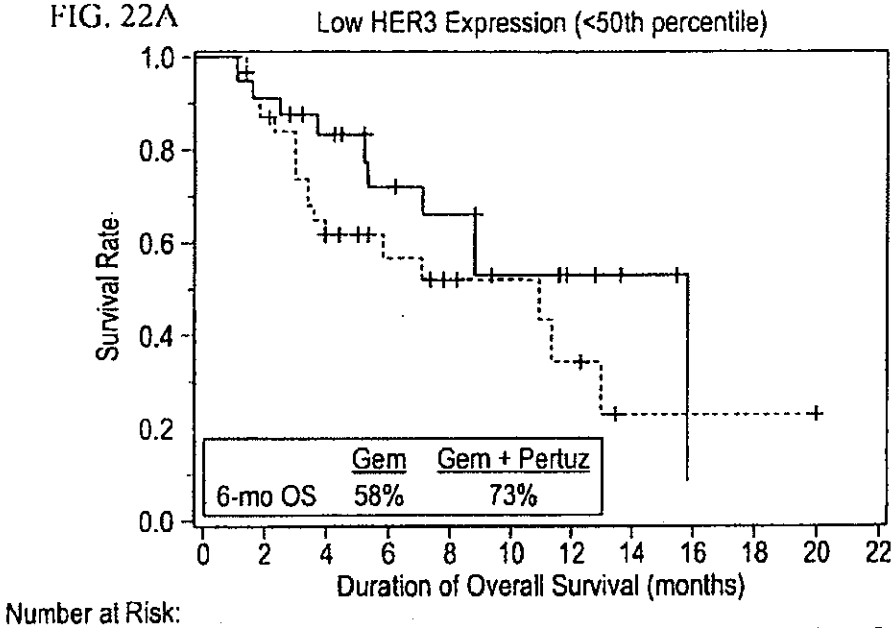
Preliminary Overall Survival

(71 deaths as of April 20, 2007



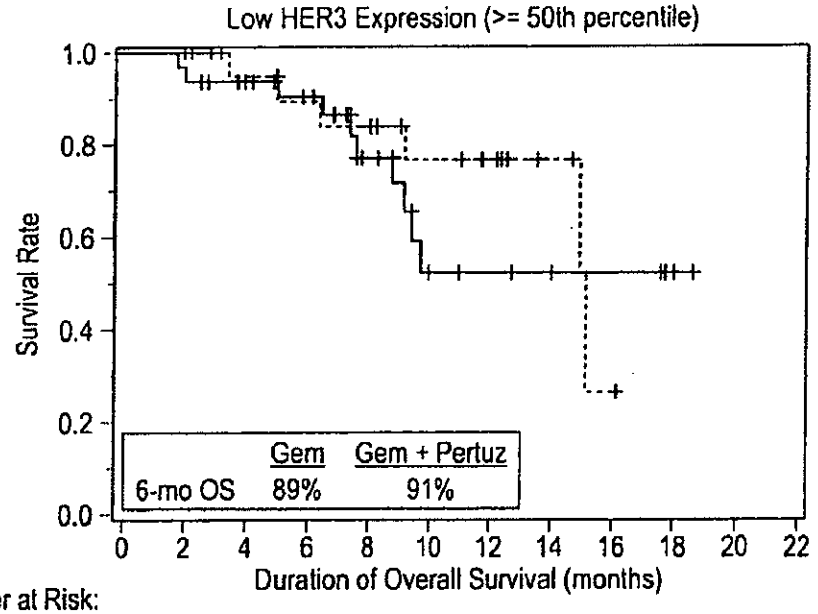
*Estimated using stratified Cox model and stratified log-rank test by randomization stratification factors (ECOG PS, number of prior regimens for platinum-resistant disease, and disease measurability)

FIG. 22A



Number at Risk:

------ Placebo	33	31	21	13	8	7	4	1	1	1	1	0
—— Pertuzu	26	24	19	13	11	7	5	2	0	0	0	0



Number at Risk:

------ Placebo	25	25	19	16	15	11	9	4	1	0	0	0
—— Pertuzu	35	34	30	25	15	8	6	5	4	2	0	0

Note: 50th percentile = 2.28 CNR

All 130 patients	Gem	Gem+Pertuz
6-mo OS	72%	85%

FIG. 22B

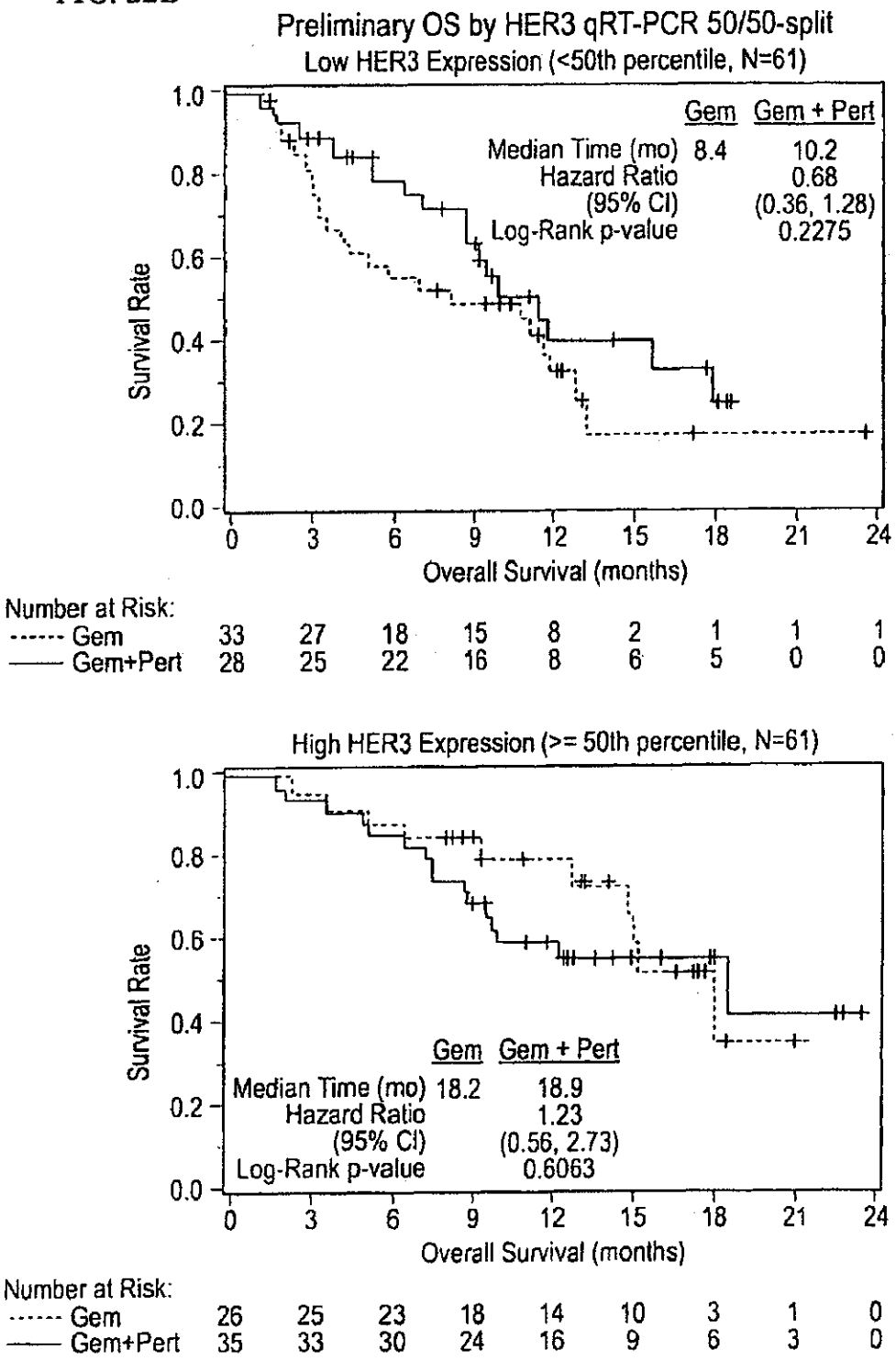

Preliminary OS by HER3 qRT-PCR 50/50-split
Low HER3 Expression (<50th percentile, N=61)
Gem
Gem + Pert
Median Time (mo) 8.4
10.2
Hazard Ratio
0.68
(95% CI)
(0.36, 1.28)
Log-Rank p-value
0.2275
Survival Rate
1.0
0.8
0.6
0.4
0.2
0.0
0
3
6
9
12
15
18
21
24
Overall Survival (months)
Number at Risk:
Gem 33 27 18 15 8 2 1 1 1
Gem+Pert 28 25 22 16 8 6 5 0 0
High HER3 Expression (>= 50th percentile, N=61)
Gem
Gem + Pert
Median Time (mo) 18.2
18.9
Hazard Ratio
1.23
(95% CI)
(0.56, 2.73)
Log-Rank p-value
0.6063
Survival Rate
Overall Survival (months)
Number at Risk:
Gem 26 25 23 18 14 10 3 1 0
Gem+Pert 35 33 30 24 16 9 6 3 0

FIG. 23A

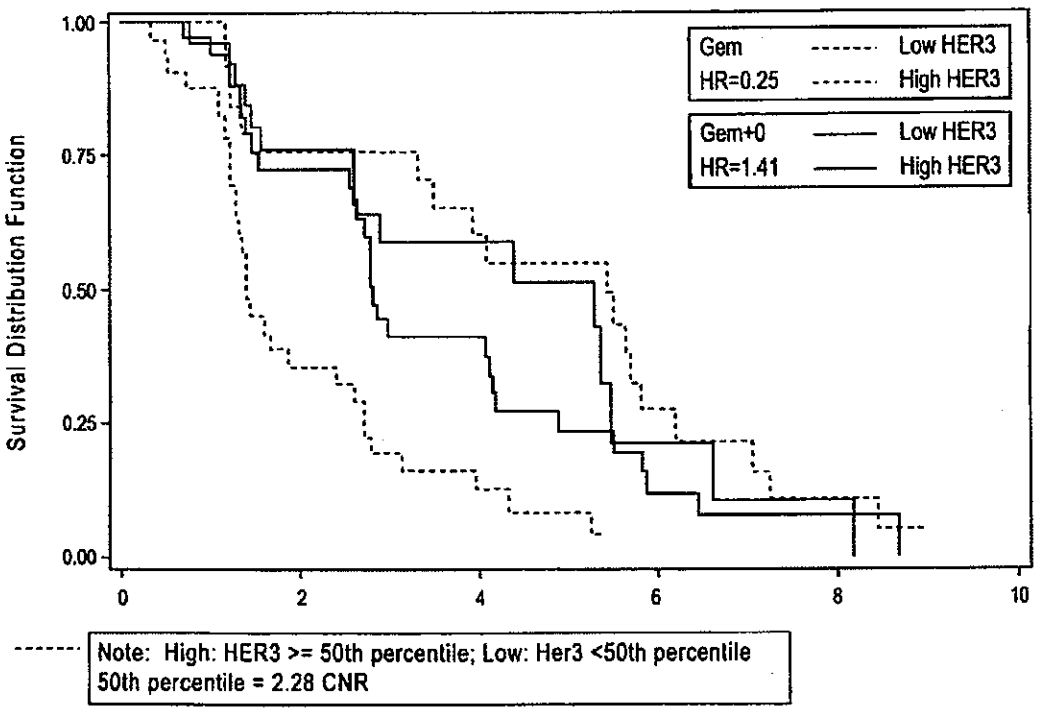

Survival Distribution Function
1.00
0.75
0.50
0.25
0.00
0
2
4
6
8
10
Gem
HR=0.25
Low HER3
High HER3
Gem+0
HR=1.41
Low HER3
High HER3
Note: High: HER3 >= 50th percentile; Low: Her3 <50th percentile
50th percentile = 2.28 CNR

FIG. 23B

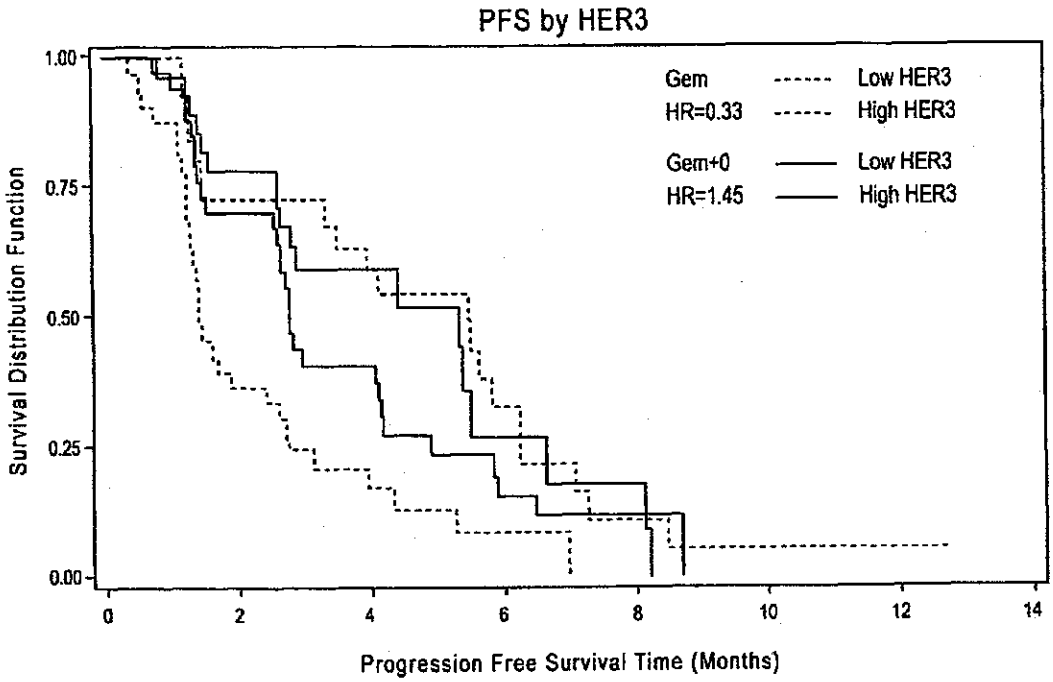

PFS by HER3
Gem
HR=0.33
Low HER3
High HER3
Gem+0
HR=1.45
Low HER3
High HER3
Survival Distribution Function
1.00
0.75
0.50
0.25
0.00
0
2
4
6
8
10
12
14
Progression Free Survival Time (Months)

FIG. 24A (Part 1)

Pertuzumab Platinum Resistant Ovarian Cancer: PFS by qRT-PCR HER3

Cutoff Value		HER3high Group				HER3low Group				
%tile	Abs. Value	N	# Events	HR (95%CI)	Logrank P-value	N	# Events	HR (95%CI)	Logrank P-value	# Events In Dx(+)
5	0.34	114	91	0.81 (0.53, 1.22)	0.3076	5	3	0.00 (0.00,.)	0.0389	44
10	0.48	108	87	0.84 (0.55, 1.28)	0.4076	11	7	0.15 (0.02, 1.29)	0.0497	44
15	0.91	102	83	0.92 (0.60, 1.42)	0.7155	17	11	0.14 (0.03, 0.66)	0.0048	43
20	0.99	96	78	1.06 (0.67, 1.65)	0.8083	23	16	0.09 (0.02, 0.42)	0.0002	41
25	1.19	91	73	1.13 (0.71, 1.81)	0.5875	28	21	0.13 (0.04, 0.45)	0.0002	40
30	1.4	84	66	1.28 (0.77, 2.10)	0.3318	35	28	0.18 (0.06, 0.52)	0.0004	39
35	1.57	78	62	1.49 (0.89, 2.51)	0.1280	41	32	0.16 (0.06, 0.43)	<.0001	38
40	1.71	72	58	1.55 (0.90, 2.68)	0.1141	47	36	0.19 (0.08, 0.47)	<.0001	37
45	1.88	66	54	1.64 (0.94, 2.88)	0.0817	53	40	0.23 (0.11, 0.50)	<.0001	34
50	2.26	60	48	1.60 (0.89, 2.87)	0.1161	59	46	0.30 (0.16, 0.58)	0.0002	29
55	2.41	54	42	1.87 (0.97, 3.57)	0.0565	65	52	0.36 (0.20, 0.65)	0.0005	28
60	2.8	48	37	1.88 (0.92, 3.84)	0.0766	71	57	0.47 (0.27, 0.81)	0.0060	26
65	3.14	42	31	1.72 (0.78, 3.75)	0.1693	77	63	0.57 (0.34, 0.95)	0.0299	22
70	3.59	36	25	1.67 (0.72, 3.90)	0.2270	83	69	0.62 (0.38, 1.00)	0.0488	17
75	3.8	30	19	2.00 (0.71, 5.62)	0.1790	89	75	0.67 (0.42,1.06)	0.0898	14
80	4.29	24	16	2.85 (0.89, 9.20)	0.0667	95	78	0.59 (0.37, 0.92)	0.0196	11
85	5.25	18	13	2.53 (0.67, 9.50)	0.1473	101	81	0.62 (0.40, 0.96)	0.0324	9
90	6.64	12	9	4.73 (0.93, 24.13)	0.0416	107	85	0.59 (0.38, 0.91)	0.0151	6
95	8.4	6	5	3.35 (0.34, 33.36)	0.2769	113	89	0.74 (0.49,1.13)	0.1582	3

Note: The HR and Log-rank p-values were not adjusted for multiple comparison

FIG. 24A (Part 2)

Gem+Omnitarg (n=61)			Gem Alone (n=58)				
# Events In Dx(-)	HR (95%CI)	Logrank P-value	# Events In Dx(+)	# Events In Dx(-)	HR (95%CI)	Logrank P-value	Interaction n P-value
1	1.55 (0.21, 11.48)	0.6559	47	2	0.32 (0.07, 1.38)	0.1073	0.1195
1	2.54 (0.35, 18.64)	0.3357	43	6	0.73 (0.30, 1.74)	0.4723	0.2021
2	2.80 (0.67, 11.68)	0.1377	40	9	0.54 (0.26, 1.14)	0.1001	0.0296
4	3.28 (1.16, 9.25)	0.0174	37	12	0.49 (0.25, 0.98)	0.0385	0.0017
5	2.62 (1.02, 6.69)	0.0369	33	16	0.40 (0.21, 0.76)	0.0035	0.0007
6	2.17 (0.91, 5.16)	0.0737	27	22	0.35 (0.19, 0.65)	0.0006	0.0004
7	2.33 (1.03, 5.25)	0.0355	24	25	0.27 (0.14, 0.52)	<.0001	<.0001
8	2.55 (1.04, 4.86)	0.0339	21	28	0.30 (0.16, 0.59)	0.0002	<.0001
11	1.96 (0.99, 3.89)	0.0508	20	29	0.27 (0.14, 0.54)	<.0001	<.0001
16	1.41 (0.76, 2.62)	0.2700	19	30	0.25 (0.13, 1.51)	<.0001	0.0001
17	1.33 (0.72, 2.44)	0.3610	14	35	0.25 (0.12, 0.49)	<.0001	0.0002
19	1.38 (0.76, 2.50)	0.2943	11	38	0.36 (0.18, 0.71)	0.0023	0.0020
23	1.06 (0.59, 1.93)	0.8337	9	40	0.36 (0.17, 0.76)	0.0050	0.0158
28	0.82 (0.44, 1.53)	0.5400	8	41	0.33 (0.15, 0.71)	0.0029	0.0384
31	0.77 (0.40, 1.49)	0.4392	5	44	0.29 (0.11, 0.73)	0.0054	0.0528
34	1.40 (0.70, 2.80)	0.3428	5	44	0.33 (0.13, 0.84)	0.0146	0.0119
36	1.25 (0.60, 2.62)	0.5534	4	45	0.32 (0.11, 0.92)	0.0264	0.0262
39	2.58 (1.06, 6.23)	0.0290	3	46	0.26 (0.08, 0.86)	0.0185	0.0020
42	2.57 (0.77, 8.56)	0.1052	2	47	0.95 (0.23, 3.94)	0.9478	0.3840

FIG. 24B (Part 1)

Pertuzumab Platinum Resistant Ovarian Cancer: PFS by qRT-PCR HER3

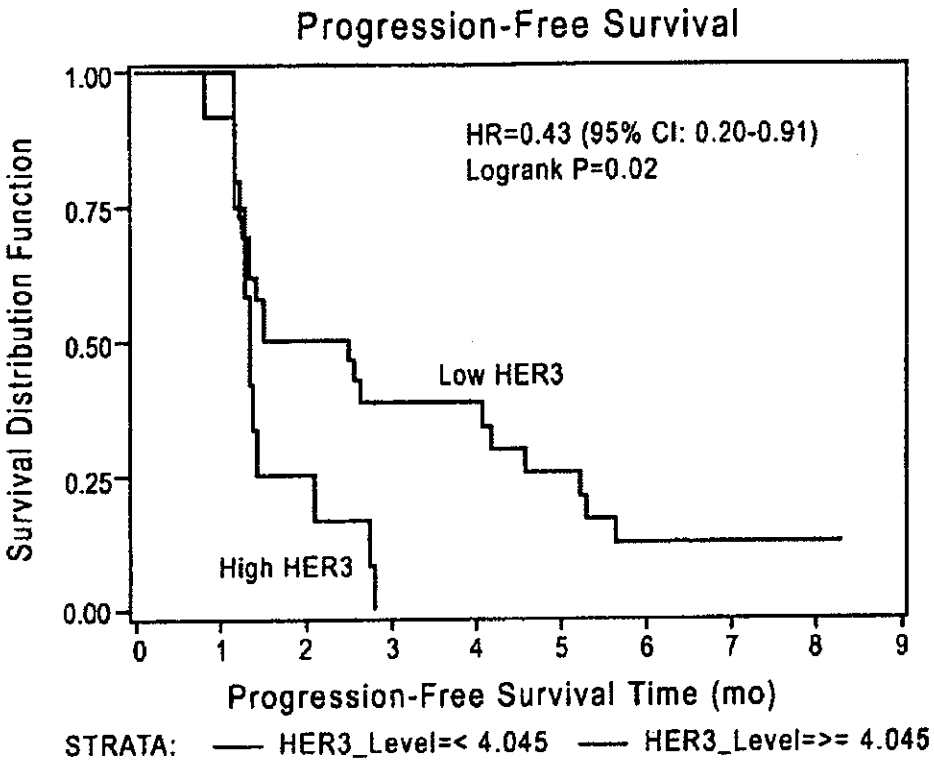
Cutoff Value		Dx(High) Group				Dx(Low) Group				
%tile	Abs. Value	N	# Events	HR (95%CI)	Logrank P-value	N	# Events	HR (95%CI)	Logrank P-value	# Events In Dx(High)
20	0.99	98	80	1.09 (0.70, 1.70)	0.6973	24	17	0.08 (0.02, 0.37)	<.0001	42
25	1.19	92	74	1.16 (0.73, 1.84)	0.5222	30	23	0.13 (0.04, 0.41)	<.0001	40
30	1.39	86	68	1.20 (0.74, 1.94)	0.4674	36	29	0.22 (0.09, 0.56)	0.0005	39
35	1.56	80	64	1.37 (0.83, 2.26)	0.2230	42	33	0.20 (0.09, 0.48)	<.0001	38
40	1.70	74	59	1.50 (0.88, 2.55)	0.1381	48	38	0.22 (0.10, 0.50)	<.0001	37
45	1.87	68	55	1.50 (0.87, 2.61)	0.1468	54	42	0.29 (0.14, 0.58)	0.0002	34
50	2.24	61	49	1.48 (0.83, 2.63)	0.1809	61	48	0.34 (0.18, 0.63)	0.0004	29
55	2.38	56	44	1.74 (0.93, 3.27)	0.0816	66	53	0.36 (0.20, 0.65)	0.0005	29
60	2.75	49	38	1.81 (0.90, 3.67)	0.0945	73	59	0.48 (0.28, 0.84)	0.0080	27
65	3.08	43	32	1.78 (0.82, 3.86)	0.1382	79	65	0.56 (0.34, 0.94)	0.0255	23
70	3.56	37	26	1.73 (0.75, 3.99)	0.1943	85	71	0.62 (0.38, 1.00)	0.0459	18
75	3.77	31	21	1.90 (0.73, 4.93)	0.1804	91	76	0.65 (0.41, 1.03)	0.0650	15
80	4.05	25	18	2.33 (0.82, 6.64)	0.1053	97	79	0.64 (0.41, 1.00)	0.0493	13

Note: The HR and Log-rank p-values were not adjusted for multiple comparison

FIG. 24B (Part 2)

Gem + Pertuzumab (n=63)			Gem Alone (n=59)				
# Events In Dx(Low)	HR (95%CI)	Logrank P-value	# Events In Dx(High)	# Events In Dx(Low)	HR (95%CI)	Logrank P-value	Interaction n P-value
5	3.20 (1.25, 8.23)	0.0109	38	12	0.47 (0.24, 0.93)	0.0272	0.0007
7	2.34 (1.03, 5.30)	0.0360	34	16	0.38 (0.20, 0.72)	0.0020	0.0003
8	2.03 (0.93, 4.39)	0.0683	29	21	0.44 (0.24, 0.79)	0.0046	0.0014
9	2.19 (1.05, 4.56)	0.0330	26	24	0.37 (0.21, 0.67)	0.0007	0.0001
10	2.14 (1.06, 4.34)	0.0312	22	28	0.35 (0.19, 0.63)	0.0004	<.0001
13	1.84 (0.97, 3.51)	0.0617	21	29	0.35 (0.19, 0.65)	0.0005	0.0002
18	1.45 (0.80, 2.62)	0.2230	20	30	0.33 (0.18, 0.62)	0.0003	0.0005
18	1.45 (0.80, 2.62)	0.2230	15	35	0.31 (0.16, 0.60)	0.0002	0.0004
20	1.33 (0.74, 2.38)	0.3459	11	39	0.37 (0.19, 0.73)	0.0030	0.0030
24	1.14 (0.64, 2.04)	0.6516	9	41	0.36 (0.18, 0.76)	0.0050	0.0112
29	0.89 (0.49, 1.62)	0.6916	8	42	0.33 (0.15, 0.71)	0.0028	0.0295
32	0.89 (0.47, 1.66)	0.6992	6	44	0.33 (0.14, 0.79)	0.0086	0.0427
34	1.04 (0.54, 2.03)	0.9069	5	45	0.32 (0.13, 0.83)	0.0136	0.0291

FIG. 25 (Part 1)



High HER3: HER3 >= 75th percentile
Low HER3: HER3 < 75th percentile
75th percentile = 4.045

FIG. 25 (Part 2)

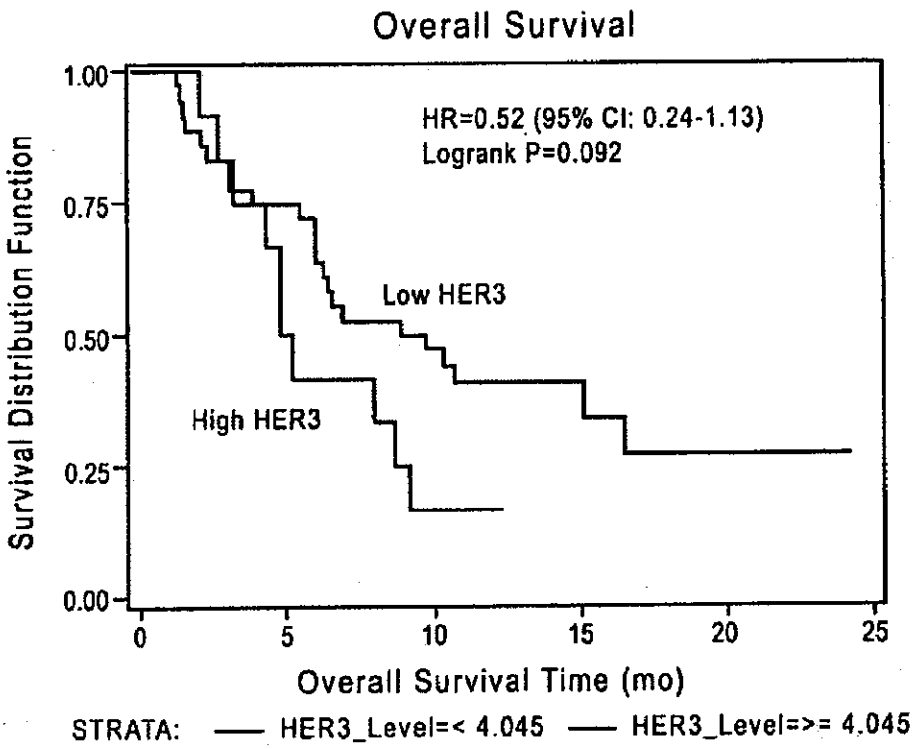

Overall Survival
HR=0.52 (95% CI: 0.24-1.13)
Logrank P=0.092
Low HER3
High HER3
Survival Distribution Function
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
25
Overall Survival Time (mo)
STRATA: HER3_Level=< 4.045 HER3_Level=>= 4.045

FIG. 26A

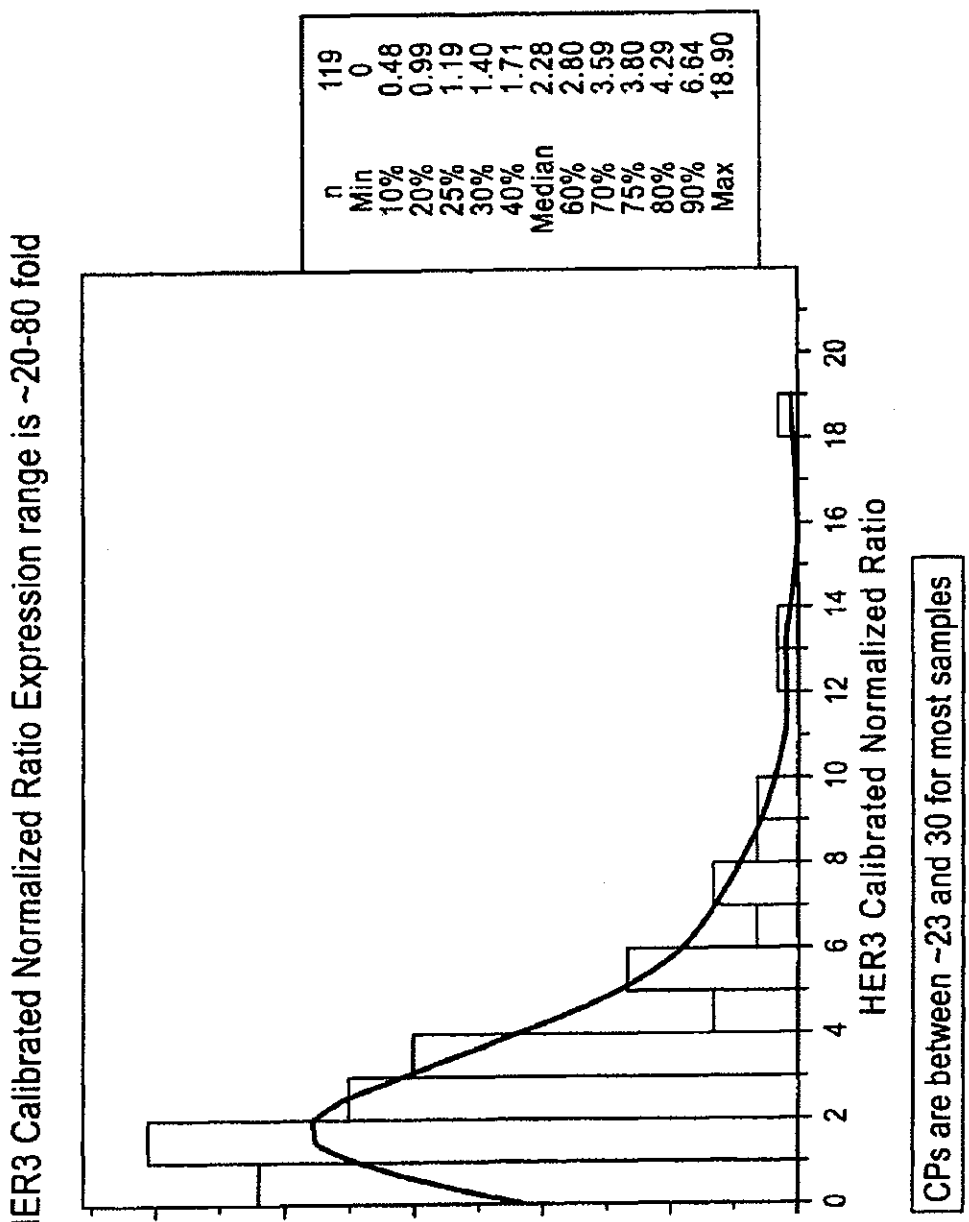

HER3 Calibrated Normalized Ratio Expression range is ~20-80 fold
n 119
Min 0
10% 0.48
20% 0.99
25% 1.19
30% 1.40
40% 1.71
Median 2.28
60% 2.80
70% 3.59
75% 3.80
80% 4.29
90% 6.64
Max 18.90
0.25
0.20
0.15
0.10
0.05
0.00
0
2
4
6
8
10
12
14
16
18
20
HER3 Calibrated Normalized Ratio
CPs are between ~23 and 30 for most samples

FIG. 26B

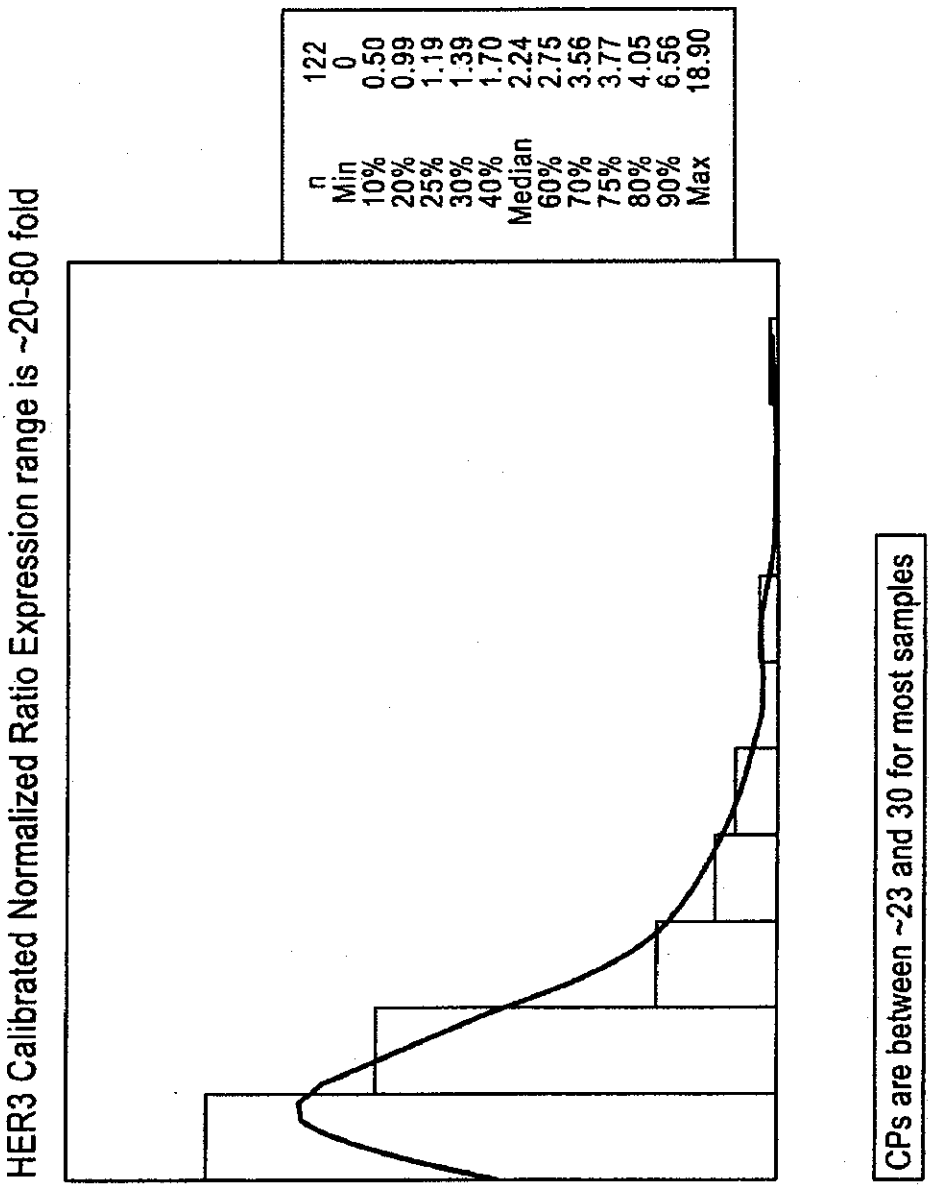
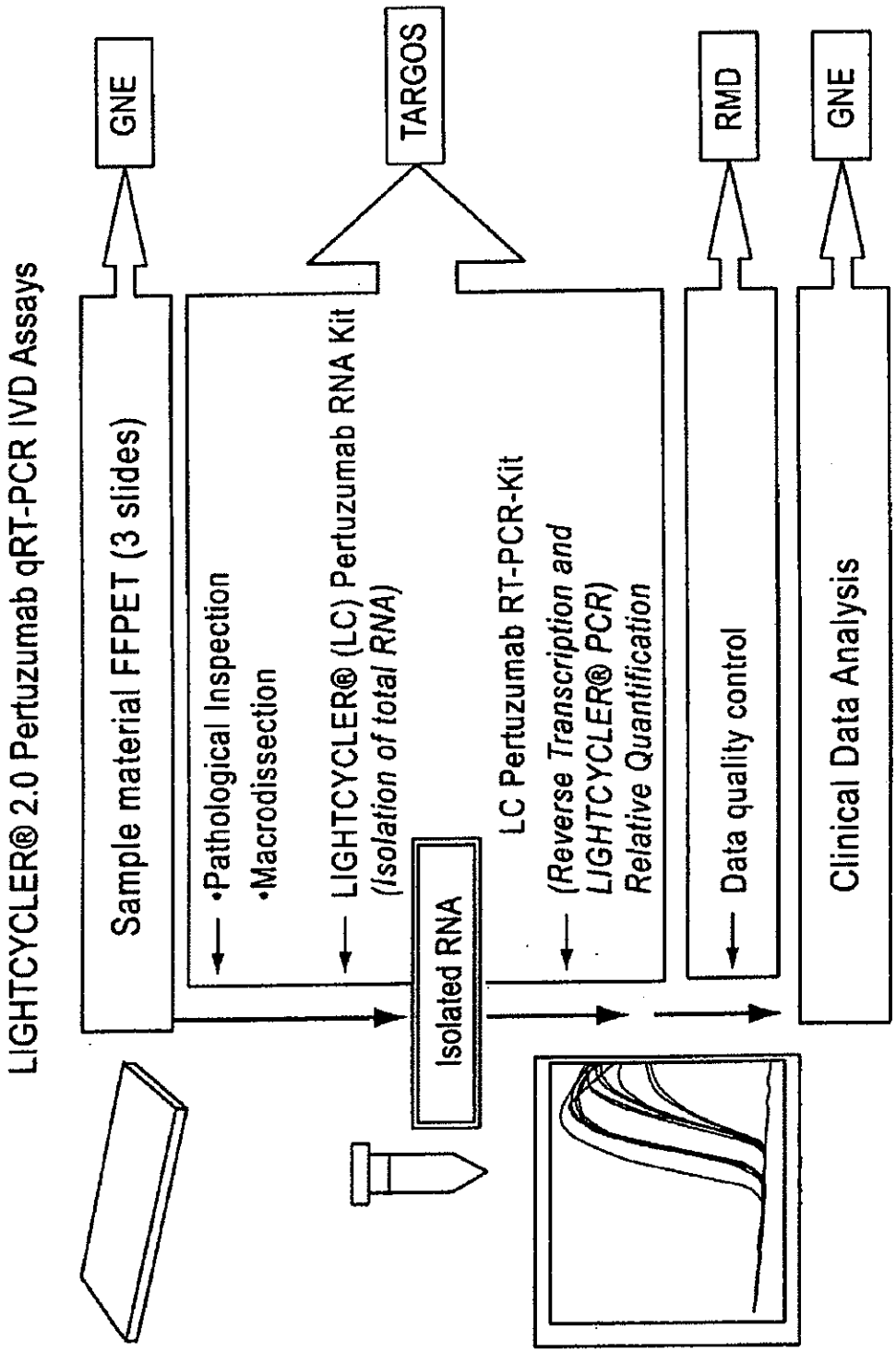

HER3 Calibrated Normalized Ratio Expression range is ~20-80 fold
n 122
Min 0
10% 0.50
20% 0.99
25% 1.19
30% 1.39
40% 1.70
Median 2.24
60% 2.75
70% 3.56
75% 3.77
80% 4.05
90% 6.56
Max 18.90
CPs are between ~23 and 30 for most samples

FIG. 27


LIGHTCYCLER® 2.0 Pertuzumab qRT-PCR IVD Assays
Sample material FFPET (3 slides)
GNE
•Pathological Inspection
•Macrodissection
LIGHTCYCLER® (LC) Pertuzumab RNA Kit
(Isolation of total RNA)
TARGOS
Isolated RNA
LC Pertuzumab RT-PCR-Kit
(Reverse Transcription and
LIGHTCYCLER® PCR)
Relative Quantification
Data quality control
RMD
Clinical Data Analysis
GNE

Pertuzimab IVD Assay
Workflow & Analysis
1 marker + reference

FIG. 28

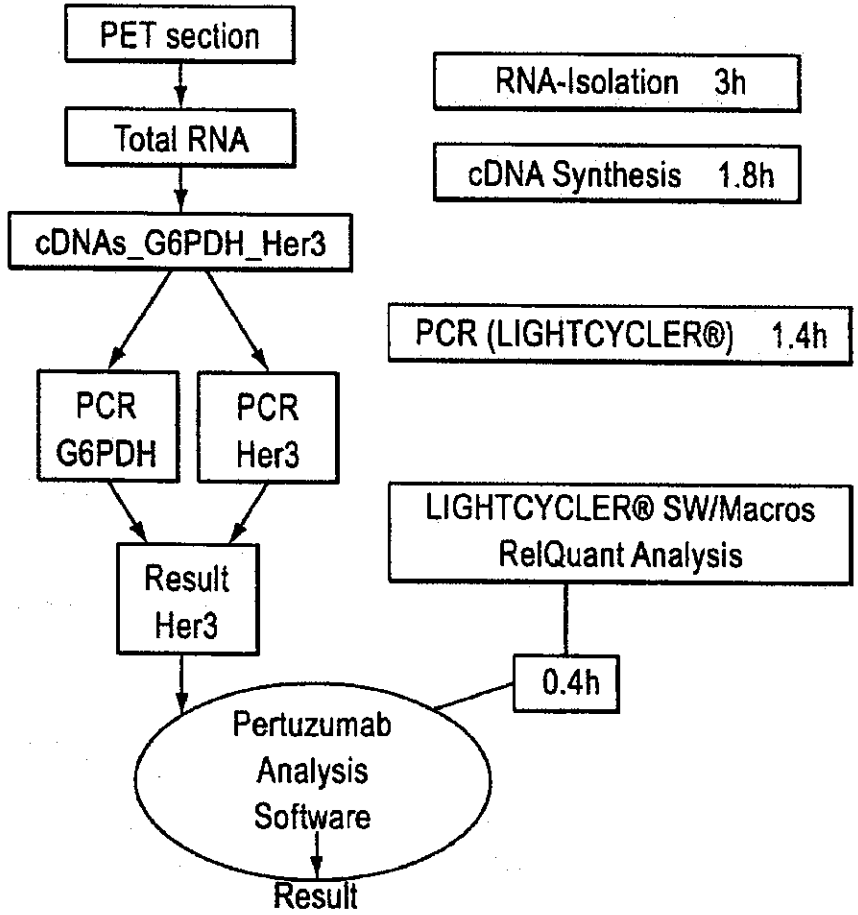


FIG. 29A (Part 1)

PFS by qRT-PCR HER2/HER3 (percentiles)

Cutoff Value		Dx (High) Group				Dx (Low) Group				
%tile	Abs. Value	N	# Events	HR (95%CI)	Logrank P-value	N	# Events	HR (95%CI)	Logrank P-value	# Events In Dx(High)
20	0.74	95	72	0.63 (0.39, 1.02)	0.0616	23	21	2.04 (0.58, 7.13)	0.2475	26
25	0.82	89	67	0.46 (0.27, 0.76)	0.0021	29	26	2.85 (1.10, 7.37)	0.0249	24
30	0.90	83	62	0.41 (0.24, 0.69)	0.0007	35	31	2.52 (1.13, 5.62)	0.0197	22
35	1.06	77	60	0.39 (0.22, 0.68)	0.0005	41	33	2.51 (1.14, 5.54)	0.0189	20
40	1.13	71	55	0.39 (0.22, 0.69)	0.0009	47	38	1.91 (0.95, 3.83)	0.0640	18
45	1.26	65	50	0.31 (0.16, 0.61)	0.0003	53	43	1.93 (0.99, 3.77)	0.0492	14
50	1.53	59	47	0.31 (0.15, 0.61)	0.0004	59	46	1.71 (0.91, 3.21)	0.0937	13
55	1.70	54	45	0.34 (0.17, 0.68)	0.0015	64	48	1.44 (0.78, 2.65)	0.2293	13
60	1.86	48	40	0.27 (0.12, 0.57)	0.0003	70	53	1.35 (0.77, 2.37)	0.2885	12
65	2.15	42	34	0.27 (0.12, 0.62)	0.0010	76	59	1.10 (0.65, 1.86)	0.7119	11
70	2.49	36	29	0.21 (0.08, 0.54)	0.0004	82	64	1.13 (0.69, 1.87)	0.6280	8
75	2.62	30	24	0.13 (0.04, 0.46)	0.0003	88	69	1.08 (0.67, 1.75)	0.7534	6
80	2.92	24	20	0.10 (0.02, 0.43)	0.0002	94	73	1.06 (0.67, 1.70)	0.7886	4

FIG. 29A (Part 2)

Gem+Omnitarg (n=60)			Gem Alone (n=58)				
# Events In Dx(Low)	HR (95%CI)	Logrank P-value	# Events In Dx(High)	# Events In Dx(Low)	HR (95%CI)	Logrank P-value	Interaction n P-value
17	0.57 (0.31, 1.06)	0.0734	46	3	1.39 (0.43, 4.55)	0.5881	0.1823
20	0.53 (0.29, 0.97)	0.0370	43	6	4.07 (1.41, 11.74)	0.0055	0.0005
22	0.46 (0.25, 0.84)	0.0104	40	9	3.04 (1.33, 6.94)	0.0056	0.0002
24	0.49 (0.26, 0.90)	0.0192	40	9	3.41 (1.50, 7.73)	0.0019	0.0001
26	0.52 (0.28, 0.96)	0.0340	37	12	2.76 (1.36, 5.59)	0.0034	0.0004
30	0.54 (0.28, 1.03)	0.0584	36	13	3.21 (1.57, 6.56)	0.0007	0.0001
31	0.57 (0.30, 1.10)	0.0926	34	15	2.94 (1.50, 5.77)	0.0010	0.0003
31	0.66 (0.34, 1.28)	0.2161	32	17	2.55 (1.34, 4.83)	0.0028	0.0022
32	0.60 (0.31, 1.18)	0.1348	28	21	2.60 (1.41, 4.81)	0.0015	0.0009
33	0.56 (0.28, 1.12)	0.0974	23	26	1.81 (1.00, 3.27)	0.0447	0.0084
36	0.52 (0.24, 1.12)	0.0895	21	28	2.07 (1.14, 3.76)	0.0145	0.0032
38	0.46 (0.19, 1.10)	0.0766	18	31	2.11 (1.12, 3.96)	0.0167	0.0035
40	0.42 (0.15, 1.19)	0.0949	16	33	2.60 (1.36, 4.97)	0.0026	0.0022

FIG. 29B (Part 1)

Platinum Resistant Ovarian Canver:
PFS by qRT-PCR HER2/HER3 Ratio

Cutoff Value		Dx (High) Group				Dx (Low) Group				
%tile	Abs. Value	N	# Events	HR (95%CI)	Logrank P-value	N	# Events	HR (95%CI)	Logrank P-value	# Events In Dx(High)
20	0.76	97	75	0.67 (0.42, 1.06)	0.0884	24	21	1.70 (0.56, 5.19)	0.3418	29
25	0.83	91	71	0.50 (0.31, 0.82)	0.0050	30	25	2.53 (0.99, 6.49)	0.0452	27
30	0.91	85	66	0.48 (0.29, 0.80)	0.0042	36	30	1.98 (0.89, 4.40)	0.0876	25
35	1.06	79	63	0.45 (0.26, 0.77)	0.0026	42	33	1.99 (0.94, 4.24)	0.0691	23
40	1.13	73	58	0.40 (0.23, 0.71)	0.0011	48	38	1.76 (0.89, 3.47)	0.0979	21
45	1.26	67	53	0.35 (0.19, 0.65)	0.0006	54	43	1.78 (0.93, 3.41)	0.0780	17
50	1.54	61	49	0.32 (0.17, 0.63)	0.0005	60	47	1.63 (0.88, 3.02)	0.1154	15
55	1.73	55	46	0.36 (0.18, 0.70)	0.0018	66	50	1.37 (0.77, 2.45)	0.2828	15
60	2.04	49	41	0.29 (0.14, 0.60)	0.0005	72	55	1.35 (0.78, 2.34)	0.2830	13
65	2.17	43	35	0.28 (0.12, 0.61)	0.0007	78	61	1.13 (0.68, 1.88)	0.6512	13
70	2.50	37	30	0.19 (0.07, 0.48)	0.0001	84	66	1.16 (0.71, 1.90)	0.5512	10
75	2.65	31	25	0.10 (0.03, 0.37)	<.0001	90	71	1.12 (0.70, 1.80)	0.6370	7
80	2.99	25	21	0.11 (0.03, 0.40)	<.0001	96	75	1.06 (0.67, 1.67)	0.8088	6

Note: The HR and Log-rank p-values were not adjusted for multiple comparison

FIG. 29B (Part 2)

Gem+Pertuzimab (n=63)			Gem Alone (n=59)				
# Events In Dx(Low)	HR (95%CI)	Logrank P-value	# Events In Dx(High)	# Events In Dx(Low)	HR (95%CI)	Logrank P-value	Interaction P-value
17	0.74 (0.40, 1.37)	0.3323	46	4	1.73 (0.62, 4.87)	0.2958	0.1685
19	0.68 (0.37, 1.24)	0.2026	44	6	4.34 (1.51, 12.43)	0.0033	0.0022
21	0.65 (0.36, 1.17)	0.1529	41	9	2.92 (1.28, 6.66)	0.0075	0.0030
23	0.63 (0.35, 1.13)	0.1204	40	10	2.96 (1.37, 6.42)	0.0039	0.0015
25	0.65 (0.36, 1.17)	0.1512	37	13	2.87 (1.44, 5.71)	0.0017	0.0011
29	0.66 (0.36, 1.21)	0.1782	36	14	3.49 (1.70, 7.14)	0.0003	0.0004
31	0.64 (0.34, 1.19)	0.1566	34	16	3.15 (1.60, 6.19)	0.0005	0.0005
31	0.72 (0.39, 1.35)	0.3116	31	19	2.64 (1.41, 4.94)	0.0016	0.0033
33	0.62 (0.33, 1.20)	0.1585	28	22	2.69 (1.47, 4.93)	0.0009	0.0010
33	0.62 (0.33, 1.20)	0.1585	22	28	2.16 (1.18, 3.96)	0.0104	0.0053
36	0.58 (0.28, 1.18)	0.1290	20	30	2.64 (1.40, 4.96)	0.0018	0.0010
39	0.42 (0.18, 0.94)	0.0314	18	32	2.23 (1.19, 4.21)	0.0100	0.0010
40	0.45 (0.19, 1.08)	0.0694	15	35	2.46 (1.28, 4.74)	0.0055	0.0015

FIG. 30A-1

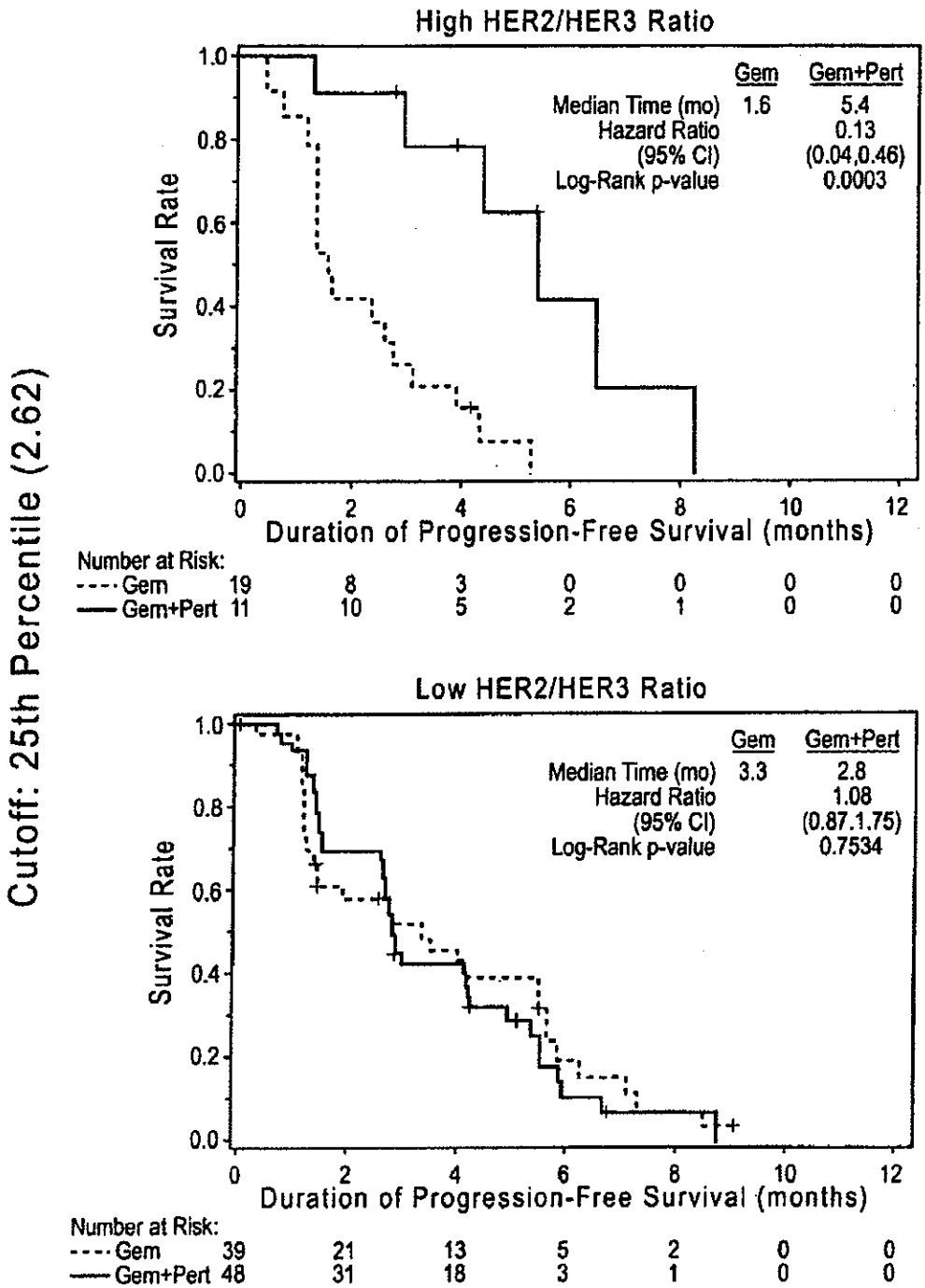

Cutoff: 25th Percentile (2.62)
High HER2/HER3 Ratio
Survival Rate
1.0
0.8
0.6
0.4
0.2
0.0
Gem
Gem+Pert
Median Time (mo) 1.6 5.4
Hazard Ratio 0.13
(95% CI) (0.04,0.46)
Log-Rank p-value 0.0003
0 2 4 6 8 10 12
Duration of Progression-Free Survival (months)
Number at Risk:
Gem 19 8 3 0 0 0 0
Gem+Pert 11 10 5 2 1 0 0
Low HER2/HER3 Ratio
Survival Rate
1.0
0.8
0.6
0.4
0.2
0.0
Gem
Gem+Pert
Median Time (mo) 3.3 2.8
Hazard Ratio 1.08
(95% CI) (0.87.1.75)
Log-Rank p-value 0.7534
0 2 4 6 8 10 12
Duration of Progression-Free Survival (months)
Number at Risk:
Gem 39 21 13 5 2 0 0
Gem+Pert 48 31 18 3 1 0 0

FIG. 30A-2

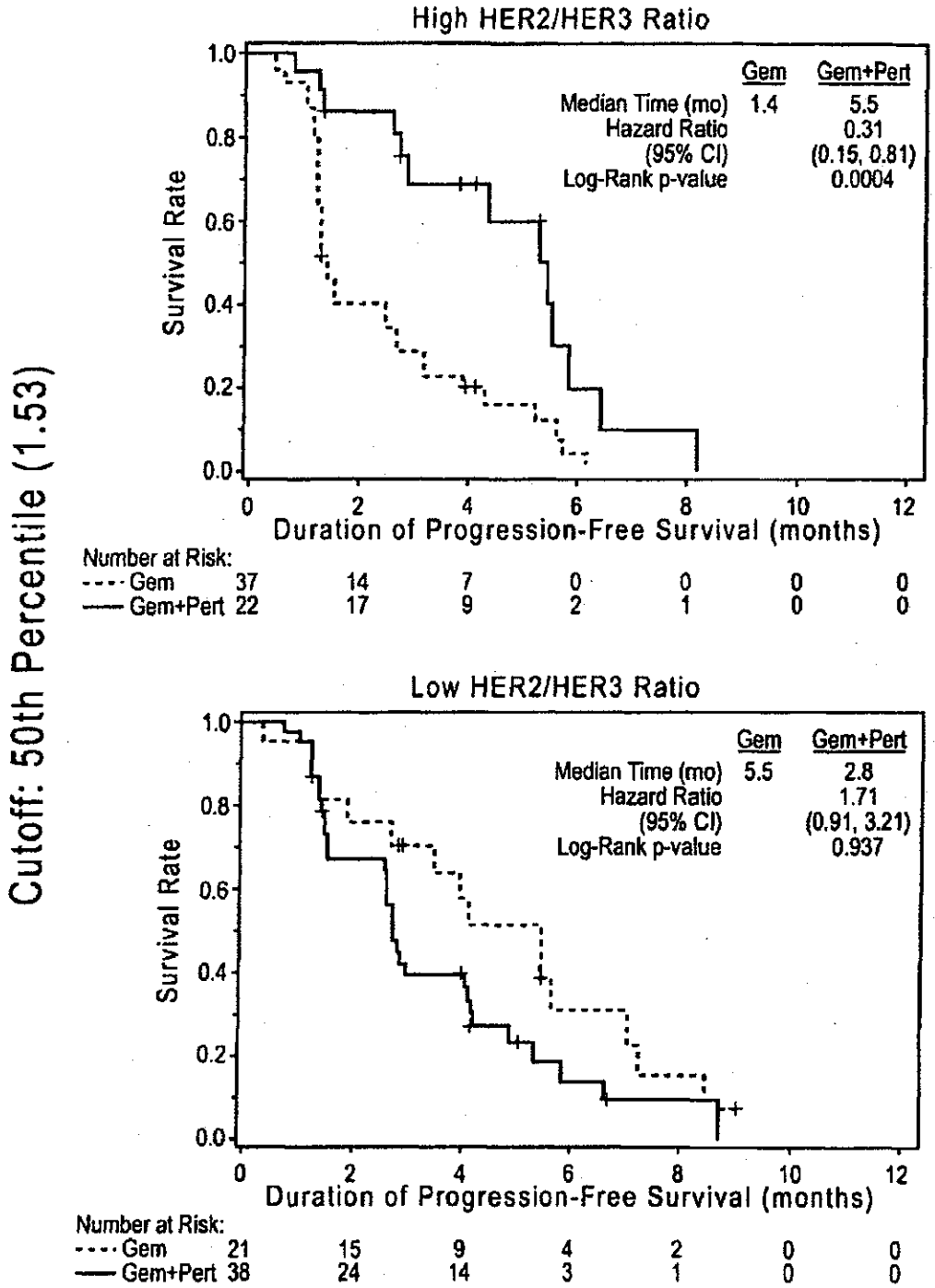

Cutoff: 50th Percentile (1.53)
High HER2/HER3 Ratio
Survival Rate
1.0
0.8
0.6
0.4
0.2
0.0
Gem
Gem+Pert
Median Time (mo) 1.4 5.5
Hazard Ratio 0.31
(95% CI) (0.15, 0.81)
Log-Rank p-value 0.0004
0 2 4 6 8 10 12
Duration of Progression-Free Survival (months)
Number at Risk:
Gem 37 14 7 0 0 0 0
Gem+Pert 22 17 9 2 1 0 0
Low HER2/HER3 Ratio
Survival Rate
1.0
0.8
0.6
0.4
0.2
0.0
Gem
Gem+Pert
Median Time (mo) 5.5 2.8
Hazard Ratio 1.71
(95% CI) (0.91, 3.21)
Log-Rank p-value 0.937
0 2 4 6 8 10 12
Duration of Progression-Free Survival (months)
Number at Risk:
Gem 21 15 9 4 2 0 0
Gem+Pert 38 24 14 3 1 0 0

FIG. 30B-1

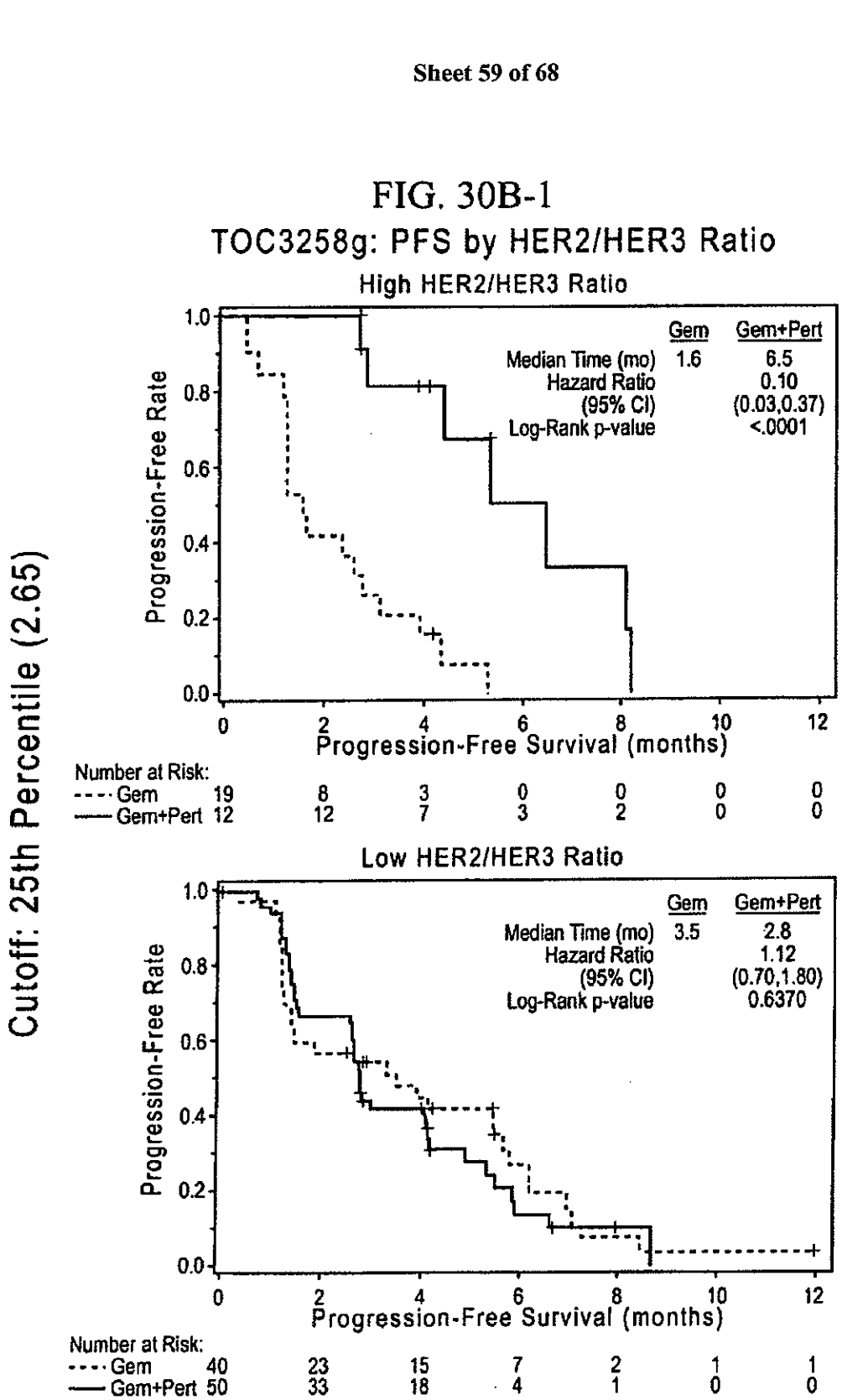

TOC3258g: PFS by HER2/HER3 Ratio
Cutoff: 25th Percentile (2.65)
High HER2/HER3 Ratio
Gem
Gem+Pert
Median Time (mo) 1.6 6.5
Hazard Ratio 0.10
(95% CI) (0.03,0.37)
Log-Rank p-value <.0001
Progression-Free Rate
Progression-Free Survival (months)
Number at Risk:
Gem 19 8 3 0 0 0 0
Gem+Pert 12 12 7 3 2 0 0
Low HER2/HER3 Ratio
Gem
Gem+Pert
Median Time (mo) 3.5 2.8
Hazard Ratio 1.12
(95% CI) (0.70,1.80)
Log-Rank p-value 0.6370
Progression-Free Rate
Progression-Free Survival (months)
Number at Risk:
Gem 40 23 15 7 2 1 1
Gem+Pert 50 33 18 4 1 0 0

FIG. 30B-2

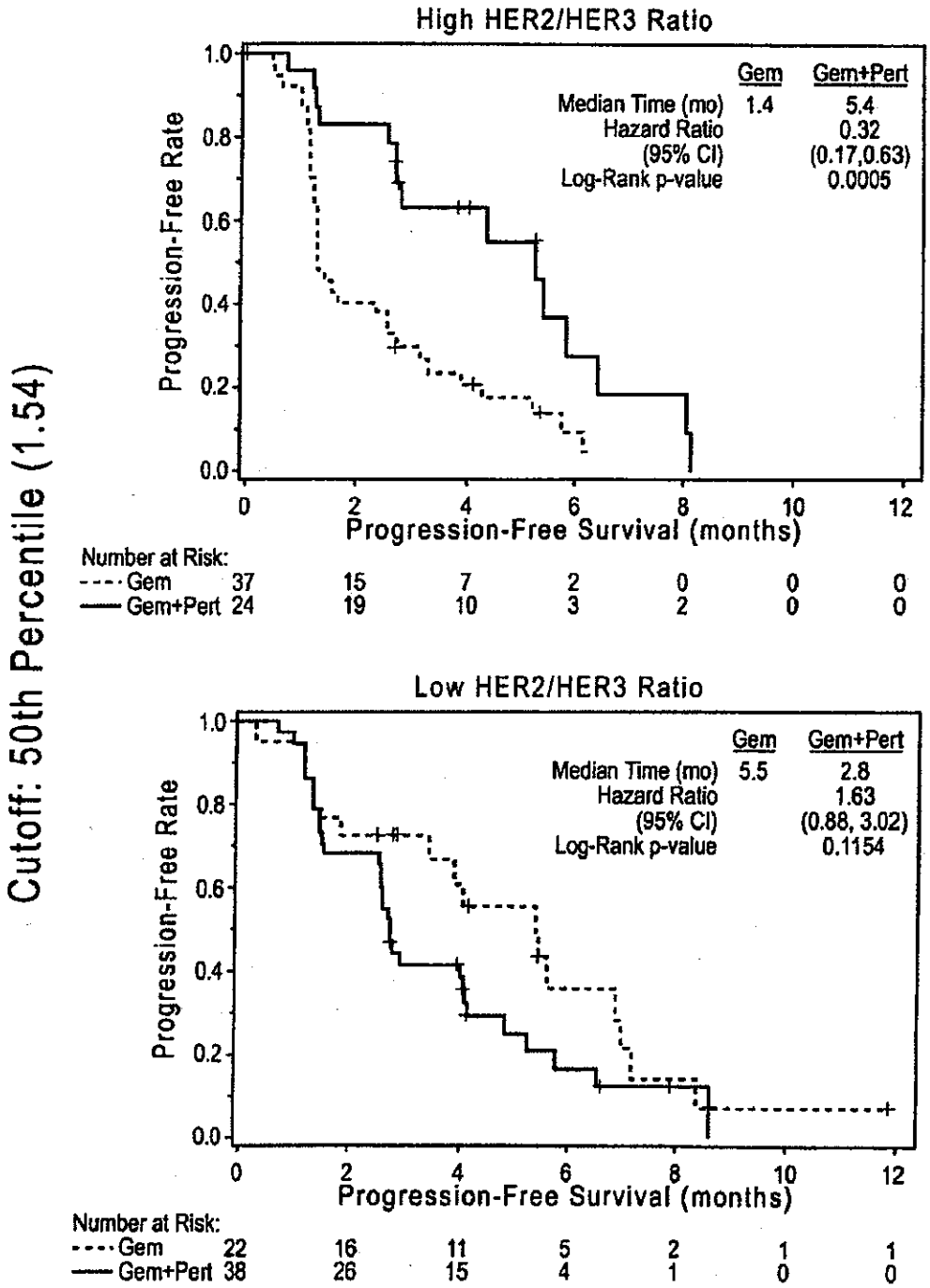

Cutoff: 50th Percentile (1.54)
High HER2/HER3 Ratio
Progression-Free Rate
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
Progression-Free Survival (months)
Gem
Gem+Pert
Median Time (mo) 1.4 5.4
Hazard Ratio 0.32
(95% CI) (0.17,0.63)
Log-Rank p-value 0.0005
Number at Risk:
Gem 37 15 7 2 0 0 0
Gem+Pert 24 19 10 3 2 0 0
Low HER2/HER3 Ratio
Progression-Free Rate
Progression-Free Survival (months)
Gem
Gem+Pert
Median Time (mo) 5.5 2.8
Hazard Ratio 1.63
(95% CI) (0.88, 3.02)
Log-Rank p-value 0.1154
Number at Risk:
Gem 22 16 11 5 2 1 1
Gem+Pert 38 26 15 4 1 0 0

FIG. 31A

		Total	Gem Alone			Gem + Omnitarg				
qRT-PCR HER2/HER3 Ratio	N	# Events	N	# Events	Medium (mo)	N	# Events	Medium (mo)	HR (95%CI)	Logrank P-value
0 - < 25th percentile	29	26	7	6	5.5	22	20	2.6	2.85 (1.10, 7.37)	0.0249
25 - < 50th percentile	30	20	14	9	3.7	16	11	4.2	1.02 (0.41, 2.54)	0.9649
50 - < 75th percentile	29	23	18	16	1.3	11	7	5.5	0.61 (0.25, 1.52)	0.2978
75 - 100th percentile	30	24	19	18	1.6	11	6	5.4	0.13 (0.04, 0.46)	0.0003

FIG. 31B

Progression-Free Survival (PFS) Analysis by HER2/HER3 Quartiles

qRT-PCR HER2/HER3	N	# Events	HR (95%CI)	Logrank P-value
0 - < 25th percentile	30	25	2.53 (0.99, 6.49)	0.0452
25 - <50th percentile	30	22	1.28 (0.52, 3.15)	0.5952
50 - < 75th percentile	30	24	0.76 (0.32, 1.83)	0.5618
75 - 100th percentile	31	25	0.10 (0.03, 0.37)	<.0001

FIG. 32-1

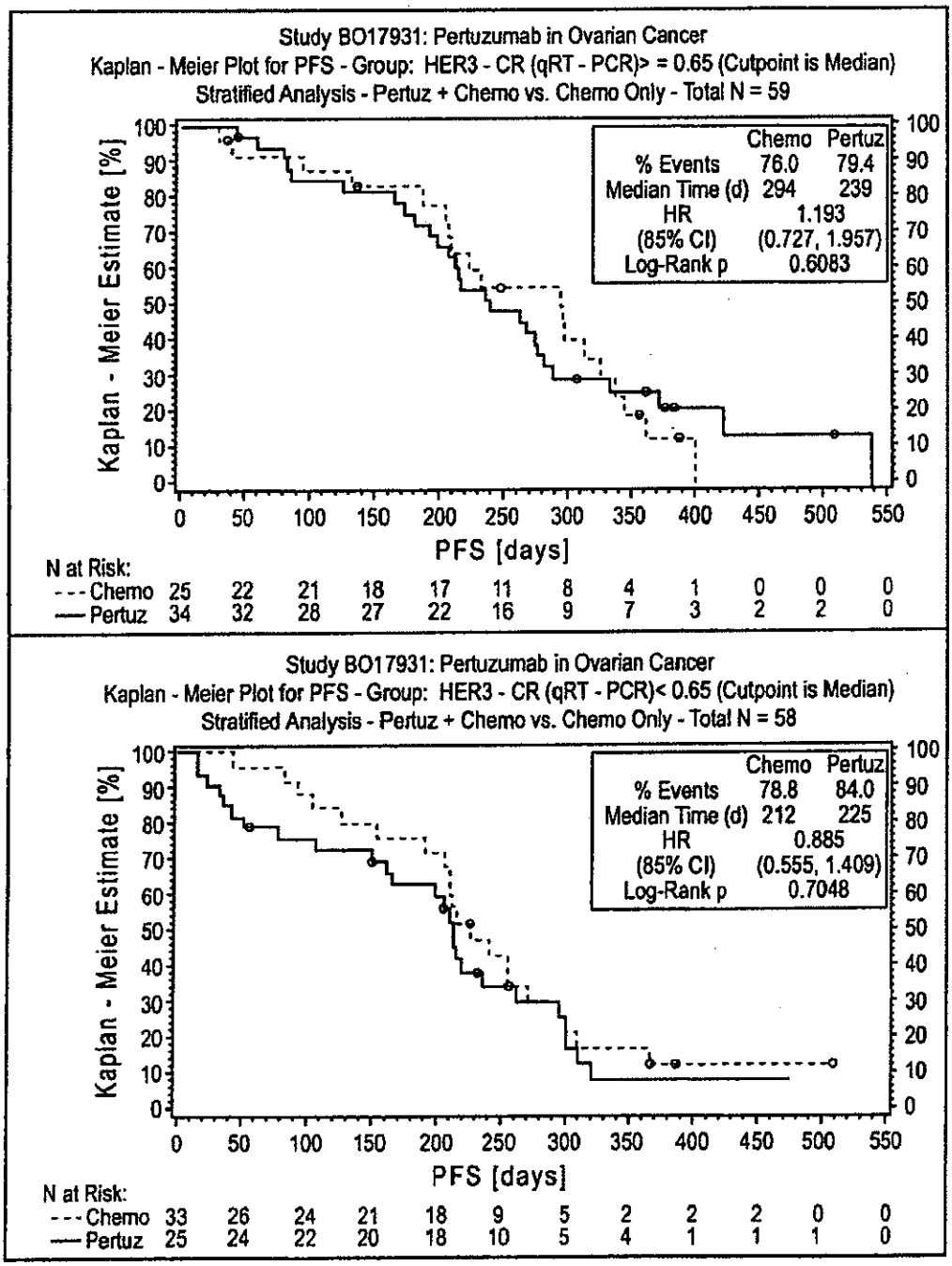

Study BO17931: Pertuzumab in Ovarian Cancer
Kaplan - Meier Plot for PFS - Group: HER3 - CR (qRT - PCR)> = 0.65 (Cutpoint is Median)
Stratified Analysis - Pertuz + Chemo vs. Chemo Only - Total N = 59
Kaplan - Meier Estimate [%]
PFS [days]
Chemo Pertuz
% Events 76.0 79.4
Median Time (d) 294 239
HR 1.193
(85% CI) (0.727, 1.957)
Log-Rank p 0.6083
N at Risk:
Chemo 25 22 21 18 17 11 8 4 1 0 0 0
Pertuz 34 32 28 27 22 16 9 7 3 2 2 0
Study BO17931: Pertuzumab in Ovarian Cancer
Kaplan - Meier Plot for PFS - Group: HER3 - CR (qRT - PCR)< 0.65 (Cutpoint is Median)
Stratified Analysis - Pertuz + Chemo vs. Chemo Only - Total N = 58
Kaplan - Meier Estimate [%]
PFS [days]
Chemo Pertuz
% Events 78.8 84.0
Median Time (d) 212 225
HR 0.885
(85% CI) (0.555, 1.409)
Log-Rank p 0.7048
N at Risk:
Chemo 33 26 24 21 18 9 5 2 2 2 0 0
Pertuz 25 24 22 20 18 10 5 4 1 1 1 0

FIG. 32-2

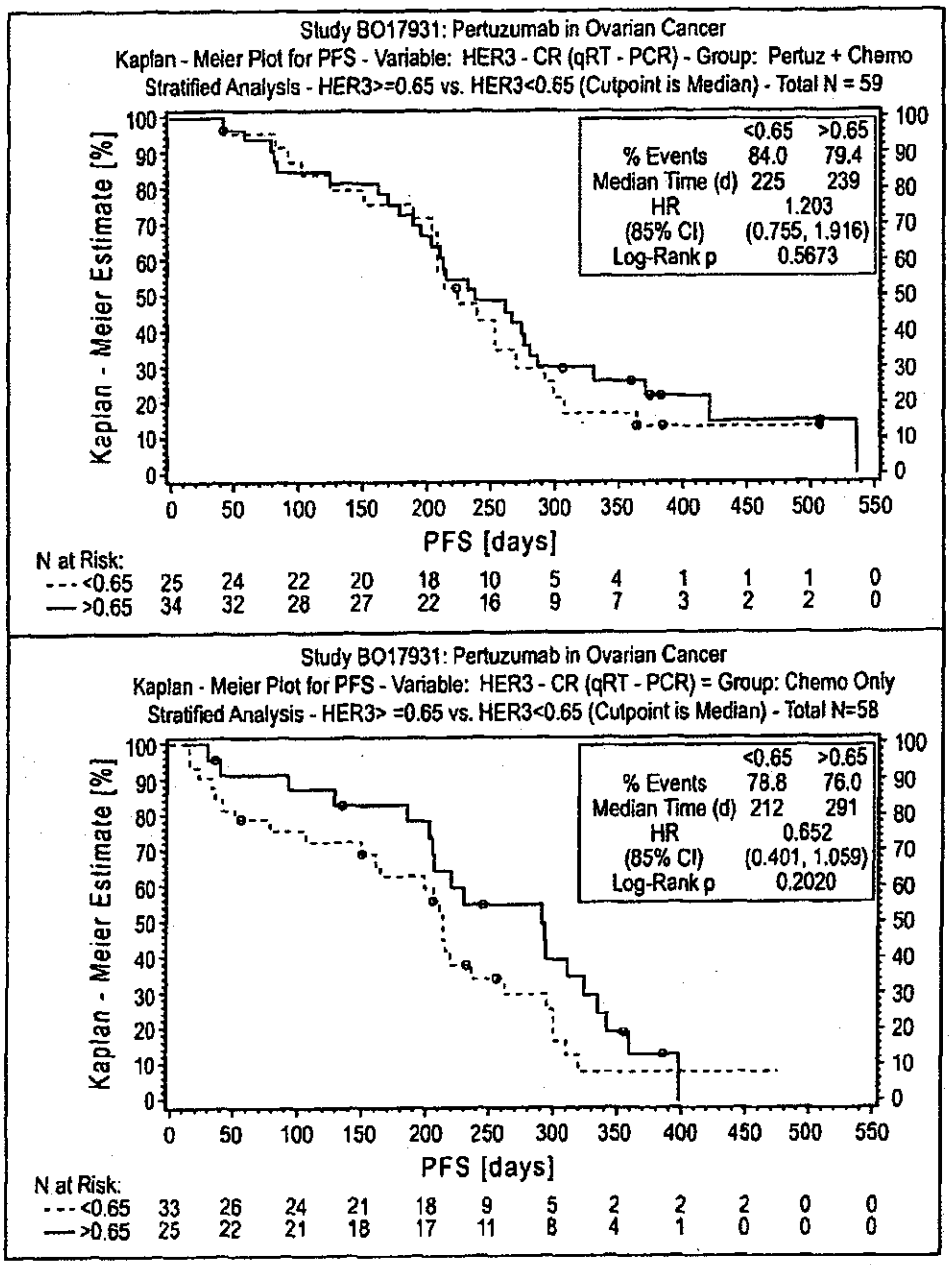

Study BO17931: Pertuzumab in Ovarian Cancer
Kaplan - Meier Plot for PFS - Variable: HER3 - CR (qRT - PCR) - Group: Pertuz + Chemo
Stratified Analysis - HER3>=0.65 vs. HER3<0.65 (Cutpoint is Median) - Total N = 59
Kaplan - Meier Estimate [%]
PFS [days]
<0.65 >0.65
% Events 84.0 79.4
Median Time (d) 225 239
HR 1.203
(85% CI) (0.755, 1.916)
Log-Rank p 0.5673
N at Risk:
---<0.65 25 24 22 20 18 10 5 4 1 1 1 0
—>0.65 34 32 28 27 22 16 9 7 3 2 2 0
Study BO17931: Pertuzumab in Ovarian Cancer
Kaplan - Meier Plot for PFS - Variable: HER3 - CR (qRT - PCR) = Group: Chemo Only
Stratified Analysis - HER3> =0.65 vs. HER3<0.65 (Cutpoint is Median) - Total N=58
Kaplan - Meier Estimate [%]
PFS [days]
<0.65 >0.65
% Events 78.8 76.0
Median Time (d) 212 291
HR 0.652
(85% CI) (0.401, 1.059)
Log-Rank p 0.2020
N at Risk:
---<0.65 33 26 24 21 18 9 5 2 2 2 0 0
—>0.65 25 22 21 18 17 11 8 4 1 0 0 0

FIG. 33

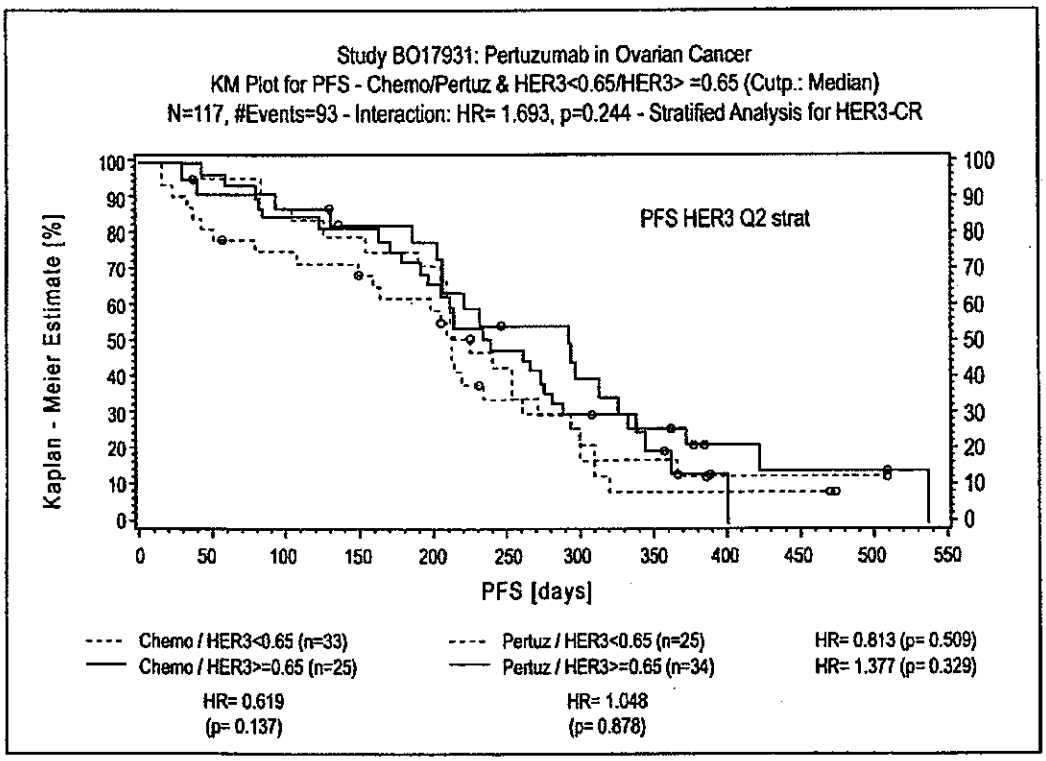

Study BO17931: Pertuzumab in Ovarian Cancer
KM Plot for PFS - Chemo/Pertuz & HER3<0.65/HER3> =0.65 (Cutp.: Median)
N=117, #Events=93 - Interaction: HR= 1.693, p=0.244 - Stratified Analysis for HER3-CR
PFS HER3 Q2 strat
Kaplan - Meier Estimate [%]
PFS [days]
Chemo / HER3<0.65 (n=33)
Chemo / HER3>=0.65 (n=25)
HR= 0.619
(p= 0.137)
Pertuz / HER3<0.65 (n=25)
Pertuz / HER3>=0.65 (n=34)
HR= 1.048
(p= 0.878)
HR= 0.813 (p= 0.509)
HR= 1.377 (p= 0.329)

FIG. 34-1

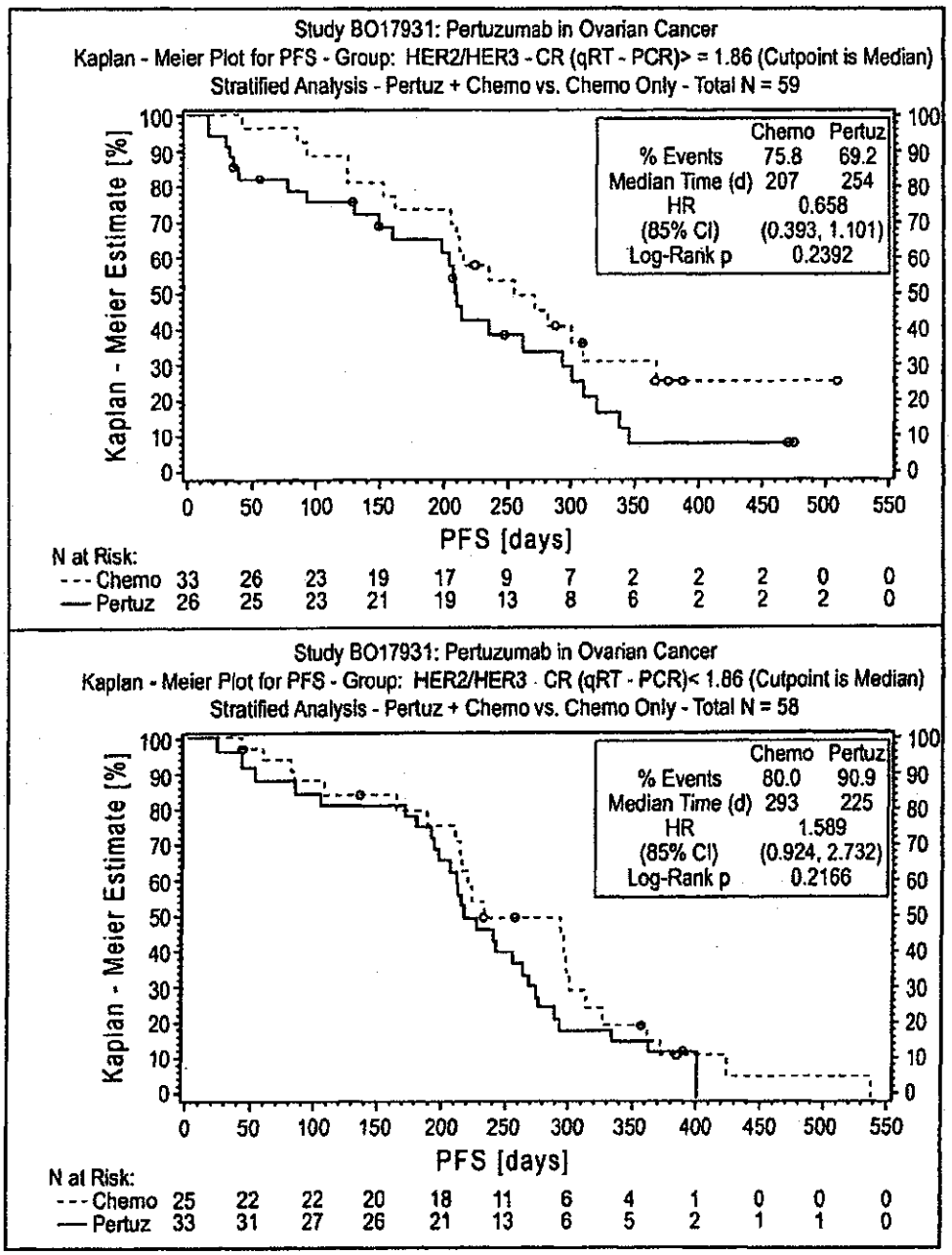

Study BO17931: Pertuzumab in Ovarian Cancer
Kaplan - Meier Plot for PFS - Group: HER2/HER3 - CR (qRT - PCR)> = 1.86 (Cutpoint is Median)
Stratified Analysis - Pertuz + Chemo vs. Chemo Only - Total N = 59
Kaplan - Meier Estimate [%]
PFS [days]
Chemo Pertuz
% Events 75.8 69.2
Median Time (d) 207 254
HR 0.658
(85% CI) (0.393, 1.101)
Log-Rank p 0.2392
N at Risk:
--- Chemo 33 26 23 19 17 9 7 2 2 2 0 0
— Pertuz 26 25 23 21 19 13 8 6 2 2 2 0
Study BO17931: Pertuzumab in Ovarian Cancer
Kaplan - Meier Plot for PFS - Group: HER2/HER3 - CR (qRT - PCR)< 1.86 (Cutpoint is Median)
Stratified Analysis - Pertuz + Chemo vs. Chemo Only - Total N = 58
Kaplan - Meier Estimate [%]
PFS [days]
Chemo Pertuz
% Events 80.0 90.9
Median Time (d) 293 225
HR 1.589
(85% CI) (0.924, 2.732)
Log-Rank p 0.2166
N at Risk:
--- Chemo 25 22 22 20 18 11 6 4 1 0 0 0
— Pertuz 33 31 27 26 21 13 6 5 2 1 1 0

FIG. 34-2

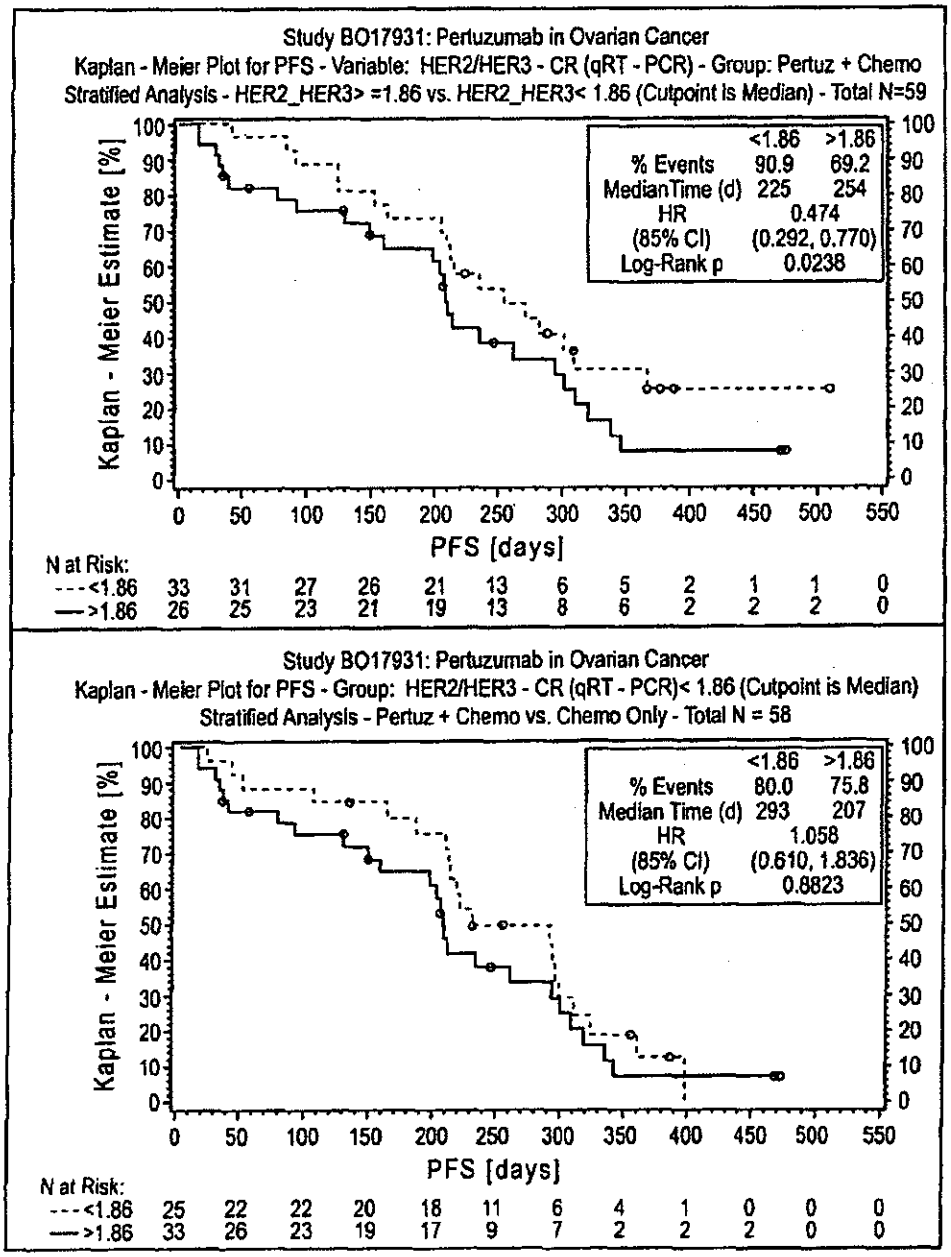
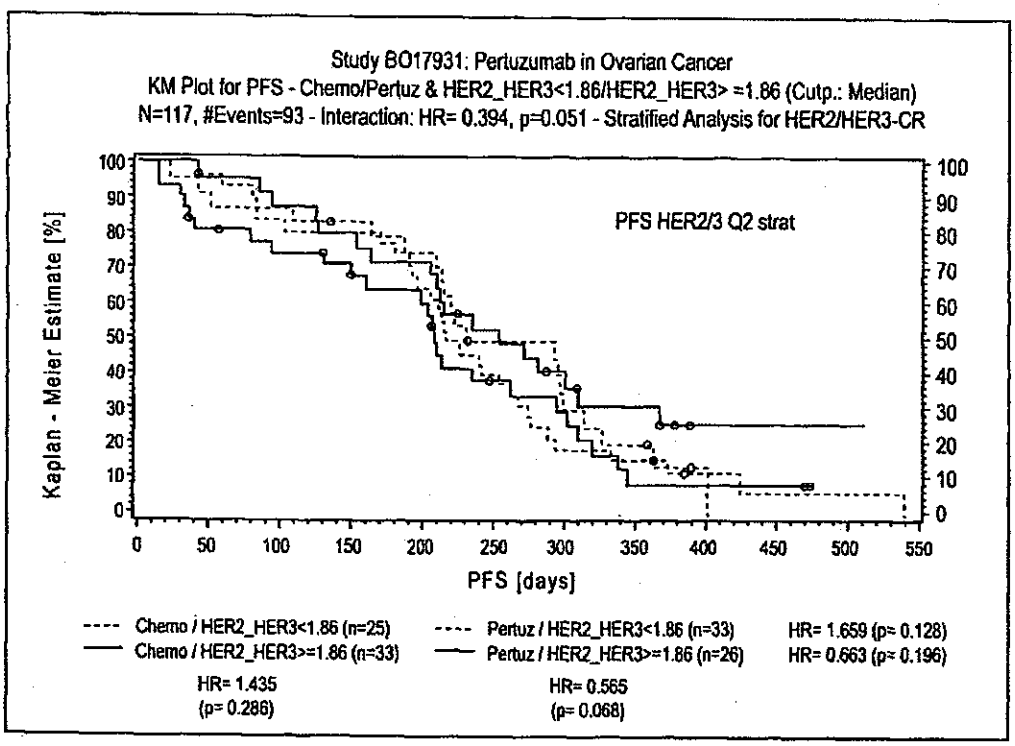

Study BO17931: Pertuzumab in Ovarian Cancer
Kaplan - Meier Plot for PFS - Variable: HER2/HER3 - CR (qRT - PCR) - Group: Pertuz + Chemo
Stratified Analysis - HER2_HER3> =1.86 vs. HER2_HER3< 1.86 (Cutpoint is Median) - Total N=59
Kaplan - Meier Estimate [%]
PFS [days]
<1.86 >1.86
% Events 90.9 69.2
MedianTime (d) 225 254
HR 0.474
(85% CI) (0.292, 0.770)
Log-Rank p 0.0238
N at Risk:
---<1.86 33 31 27 26 21 13 6 5 2 1 1 0
—>1.86 26 25 23 21 19 13 8 6 2 2 2 0
Study BO17931: Pertuzumab in Ovarian Cancer
Kaplan - Meier Plot for PFS - Group: HER2/HER3 - CR (qRT - PCR)< 1.86 (Cutpoint is Median)
Stratified Analysis - Pertuz + Chemo vs. Chemo Only - Total N = 58
Kaplan - Meier Estimate [%]
PFS [days]
<1.86 >1.86
% Events 80.0 75.8
Median Time (d) 293 207
HR 1.058
(85% CI) (0.610, 1.836)
Log-Rank p 0.8823
N at Risk:
---<1.86 25 22 22 20 18 11 6 4 1 0 0 0
—>1.86 33 26 23 19 17 9 7 2 2 2 0 0

FIG. 35


Study BO17931: Pertuzumab in Ovarian Cancer
KM Plot for PFS - Chemo/Pertuz & HER2_HER3<1.86/HER2_HER3> =1.86 (Cutp.: Median)
N=117, #Events=93 - Interaction: HR= 0.394, p=0.051 - Stratified Analysis for HER2/HER3-CR
PFS HER2/3 Q2 strat
Kaplan - Meier Estimate [%]
PFS [days]
Chemo / HER2_HER3<1.86 (n=25)
Chemo / HER2_HER3>=1.86 (n=33)
HR= 1.435
(p= 0.286)
Pertuz / HER2_HER3<1.86 (n=33)
Pertuz / HER2_HER3>=1.86 (n=26)
HR= 0.565
(p= 0.068)
HR= 1.659 (p= 0.128)
HR= 0.663 (p= 0.196)