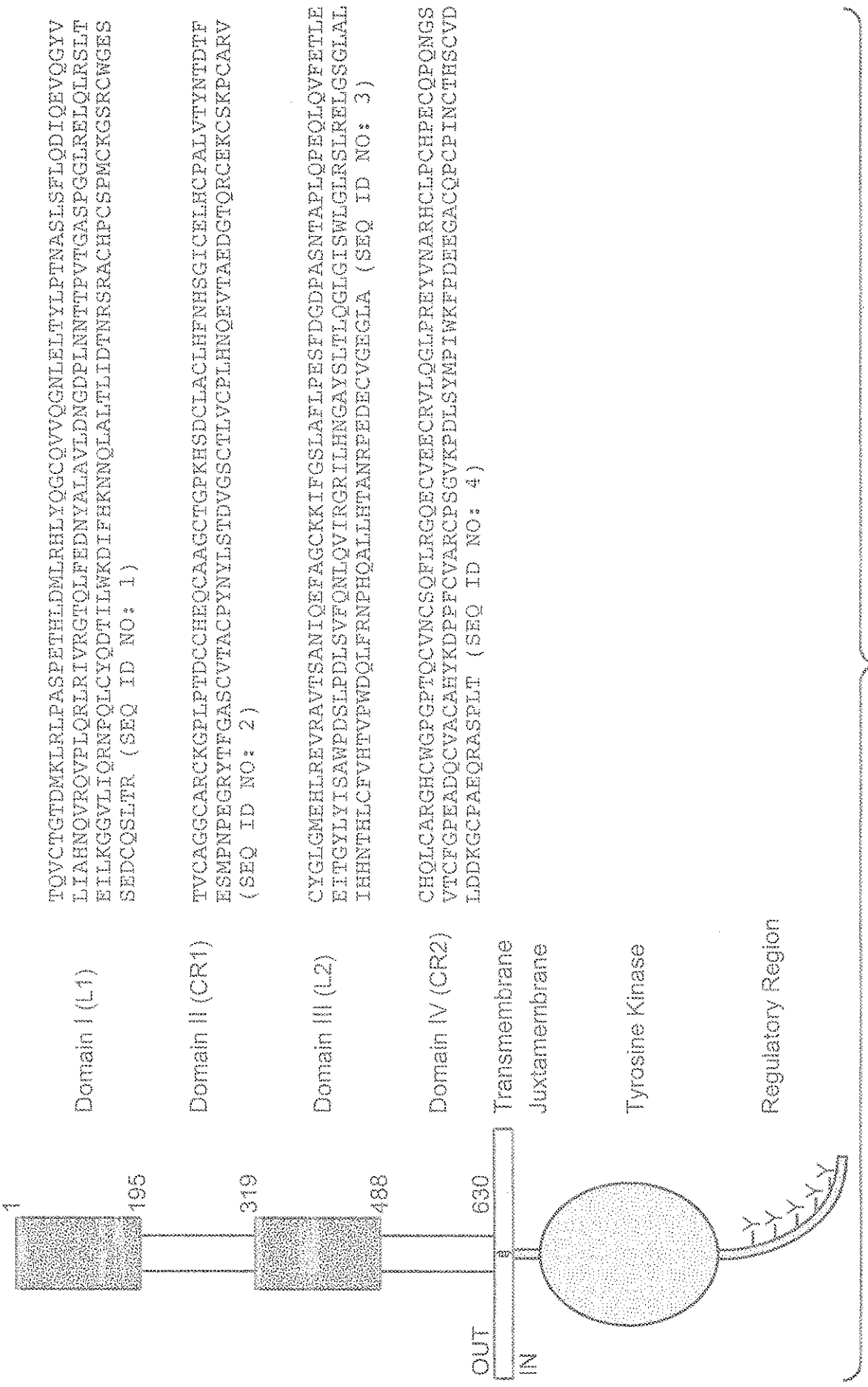

TQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNASLSFLQDIQEVQGYV
LIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLT
EILKGGVLIQRNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGES
SEDCQSLTR (SEQ ID NO: 1)
TVCAGGCARCKGPLPTDCCHEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTF
ESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCPLHNQEVTAEDGTQRCEKCSKPCARV
(SEQ ID NO: 2)
CYGLGMEHLREVRAVTSANIQEFAGCKKIFGSLAFLPESFDGDPASNTAPLQPEQLQVFETLE
EITGYLYISAWPDSLPDLSVFQNLQVIRGRILHNGAYSLTLQGLGISWLGLRSLRELGSGLAL
IHHNTHLCFVHTVPWDQLFRNPHQALLHTANRPEDECVGEGLA (SEQ ID NO: 3)
CHQLCARGHCWGPGPTQCVNCSQFLRGQECVEECRVLQGLPREYVNARHCLPCHPECQPQNGS
VTCFGPEADQCVACAHYKDPPFCVARCPSGVKPDLSYMPIWKFPDEEGACQPCPINCTHSCVD
LDDKGCPAEQRASPLT (SEQ ID NO: 4)
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

FIG. 1

Variable Light

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

                50          60          0          80
2C4     GQSPKLLIY [SASYRYT] GVPDRFTGSGSGTDFTFTISSVQA
          **                  *  *          *    * *
574     GKAPKLLIY [SASYRYT] GVPSRFSGSGSGTDFTLTISSLQP
                   * *****
hum κI  GKAPKLLIY [AASSLES] GVPSRFSGSGSGTDFTLTISSLQP

                90         100
2C4     EDLAVYYC [QQYYIYPYT] FGGGTKLEIK (SEQ ID NO:5)
           * *                 *   *
574     EDFATYYC [QQYYIYPYT] FGQGTKVEIK (SEQ ID NO:7)
                    *** *
hum κI  EDFATYYC [QQYNSLPWT] FGQGTKVEIK (SEQ ID NO:9)
```

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:6)
          ***  **                        **
574     QMNSLRAEDTAVYYCAR [NLGPSFYFDY] WGQGTLVTVSS (SEQ ID NO:8)
                           ********
hum III QMNSLRAEDTAVYYCAR [GRVGYSLYDY] WGQGTLVTVSS (SEQ ID NO:10)
```

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 (SEQ ID NO: 11)
```

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  (SEQ ID NO: 12)
```

FIG. 3B

Trastuzmab 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   (SEQ ID NO: 13)
```

FIG. 4A

Trastuzmab Heavy Chain

```
1                                                                  45
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGL
46                                                                 90
EWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAED
91                                                                135
TAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSS
136                                                               180
KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
181                                                               225
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDK
226                                                               270
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
271                                                               315
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
316                                                               360
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
361                                                               405
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
406                                                               449
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
```

(SEQ ID NO: 14)

FIG. 4B

Pertuzumab Variant Light Chain

```
1                                                                  15
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
                                                                   30                  45
46                                                                 60
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
                                                                   75                  90
91                                                                 105
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
                                                                   120                 135
136                                                                150
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
                                                                   165                 180
181                                                                195
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
                                                                   210                 217
```

(SEQ ID NO: 15)

FIG. 5A

Pertuzumab Variant 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 T F T D Y T M D W V R Q A P G K G L

46                                60                                75                                90
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                                105                               120                               135
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                               150                               165                               180
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                               195                               210                               225
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                               240                               255                               270
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                               285                               300                               315
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                               330                               345                               360
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                               375                               390                               405
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                               420                               435                               449
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
```

(SEQ ID NO: 16)

FIG. 5B

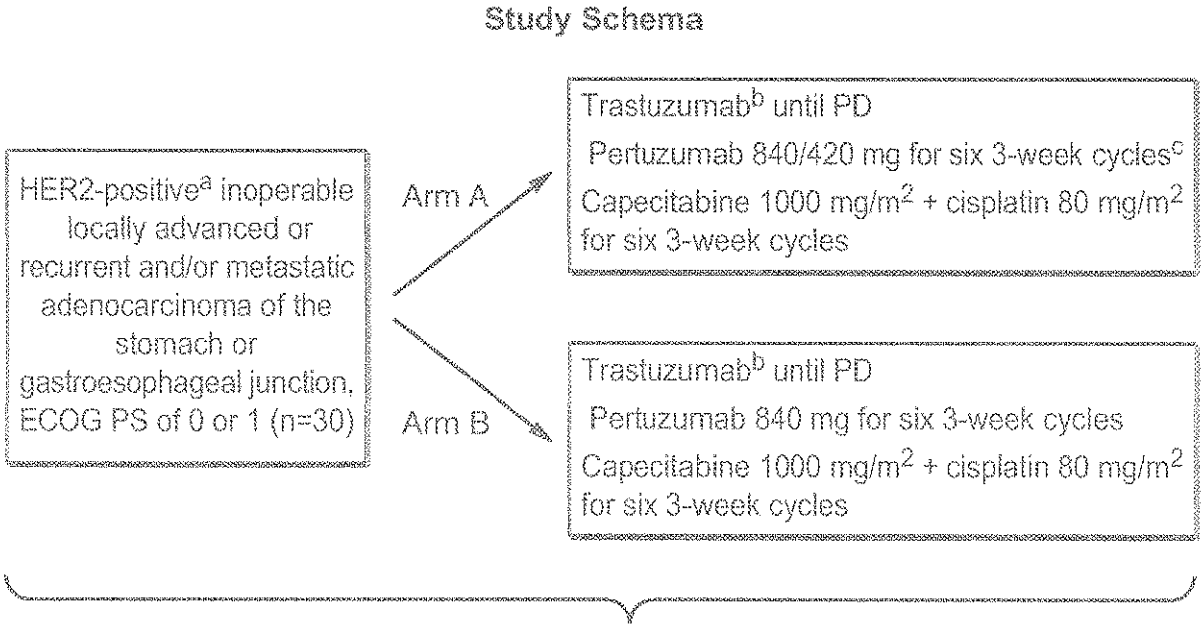

Study Schema
HER2-positive[a] inoperable locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastroesophageal junction, ECOG PS of 0 or 1 (n=30)
Arm A
Trastuzumab[b] until PD
Pertuzumab 840/420 mg for six 3-week cycles[c]
Capecitabine 1000 mg/m2 + cisplatin 80 mg/m2 for six 3-week cycles
Arm B
Trastuzumab[b] until PD
Pertuzumab 840 mg for six 3-week cycles
Capecitabine 1000 mg/m2 + cisplatin 80 mg/m2 for six 3-week cycles

FIG. 6

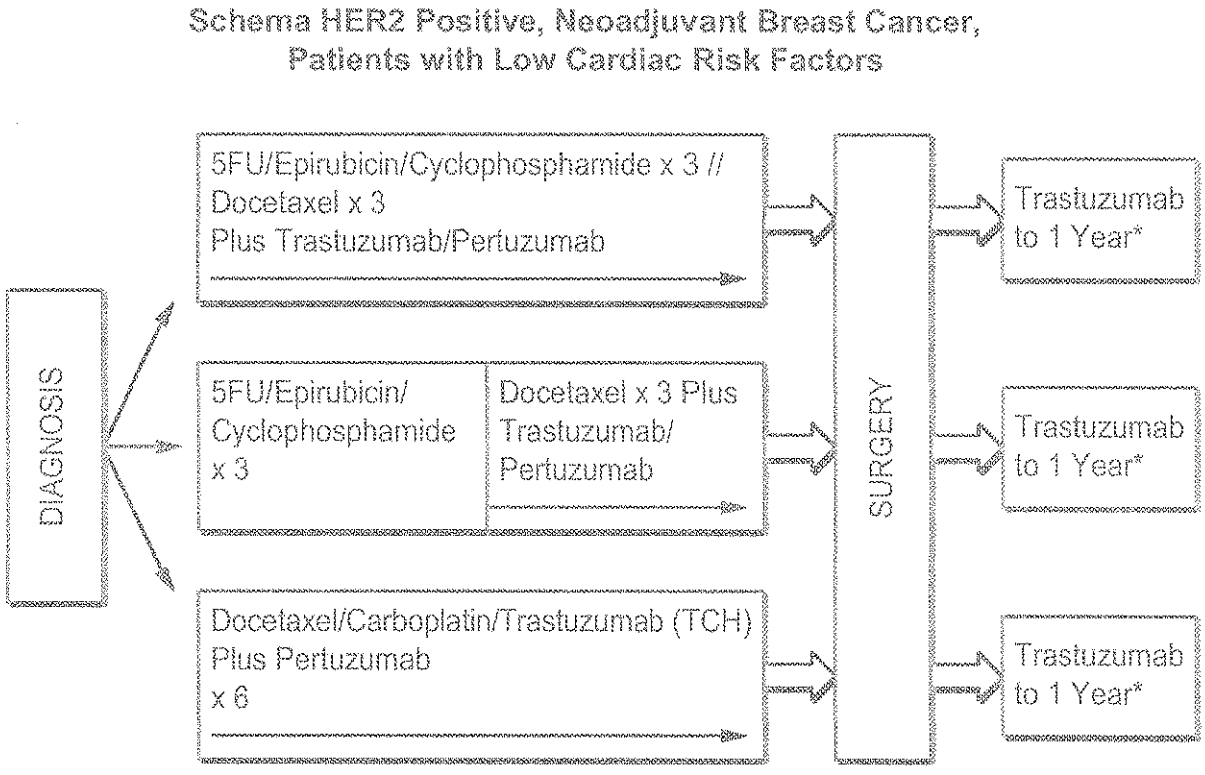

Schema HER2 Positive, Neoadjuvant Breast Cancer, Patients with Low Cardiac Risk Factors
DIAGNOSIS
5FU/Epirubicin/Cyclophospharnide x 3 // Docetaxel x 3 Plus Trastuzumab/Pertuzumab
5FU/Epirubicin/ Cyclophosphamide x 3
Docetaxel x 3 Plus Trastuzumab/ Pertuzumab
Docetaxel/Carboplatin/Trastuzumab (TCH) Plus Pertuzumab x 6
SURGERY
Trastuzumab to 1 Year*
Trastuzumab to 1 Year*
Trastuzumab to 1 Year*

FIG. 11

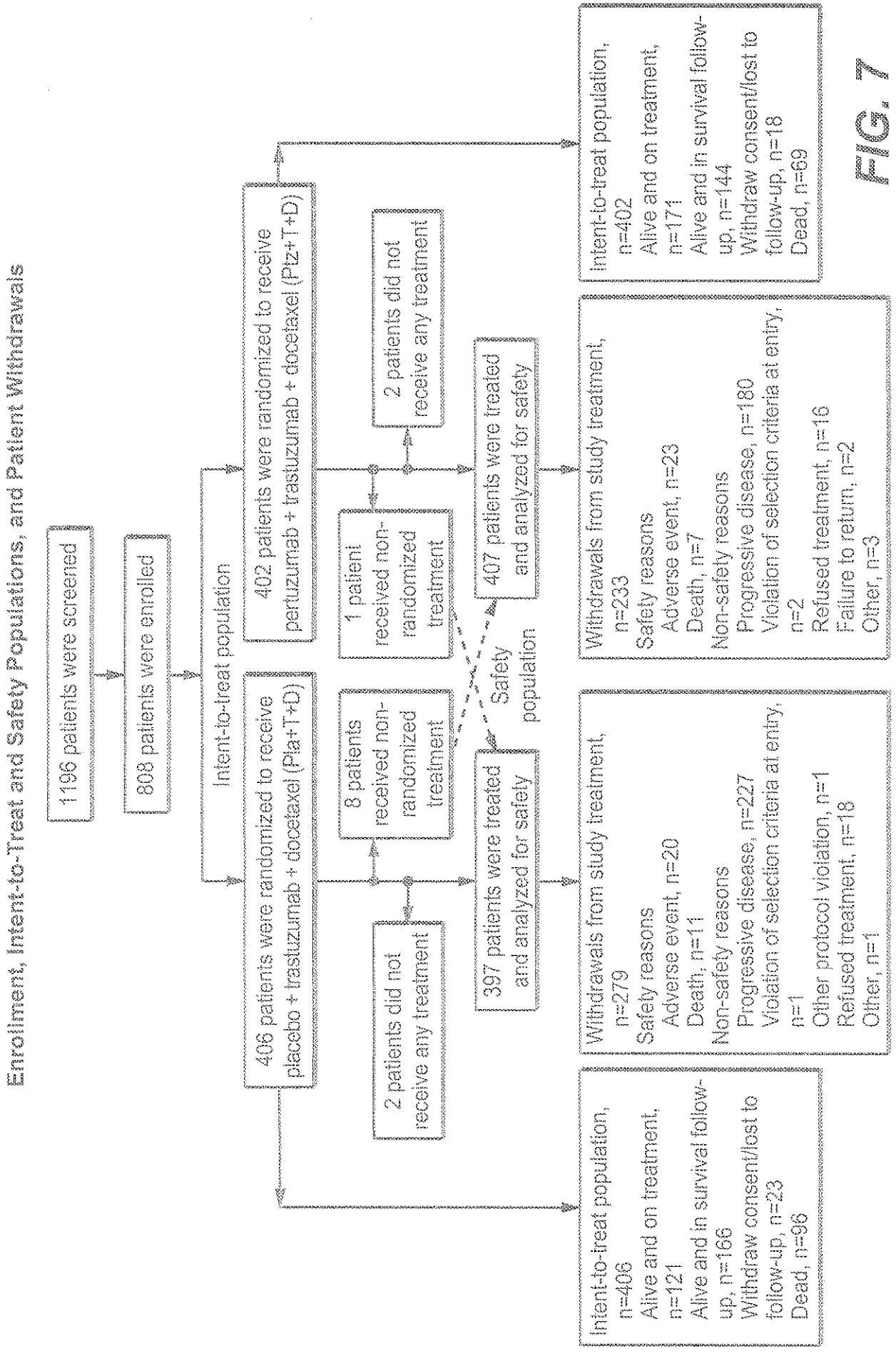

Enrollment, Intent-to-Treat and Safety Populations, and Patient Withdrawals
1196 patients were screened
808 patients were enrolled
Intent-to-treat population
406 patients were randomized to receive placebo + trastuzumab + docetaxel (Pla+T+D)
2 patients did not receive any treatment
8 patients received non-randomized treatment
397 patients were treated and analyzed for safety
Safety population
402 patients were randomized to receive pertuzumab + trastuzumab + docetaxel (Ptz+T+D)
1 patient received non-randomized treatment
2 patients did not receive any treatment
407 patients were treated and analyzed for safety
Withdrawals from study treatment, n=279
Safety reasons
Adverse event, n=20
Death, n=11
Non-safety reasons
Progressive disease, n=227
Violation of selection criteria at entry, n=1
Other protocol violation, n=1
Refused treatment, n=18
Other, n=1
Withdrawals from study treatment, n=233
Safety reasons
Adverse event, n=23
Death, n=7
Non-safety reasons
Progressive disease, n=180
Violation of selection criteria at entry, n=2
Refused treatment, n=16
Failure to return, n=2
Other, n=3
Intent-to-treat population, n=406
Alive and on treatment, n=121
Alive and in survival follow-up, n=166
Withdraw consent/lost to follow-up, n=23
Dead, n=96
Intent-to-treat population, n=402
Alive and on treatment, n=171
Alive and in survival follow-up, n=144
Withdraw consent/lost to follow-up, n=18
Dead, n=69

FIG. 7

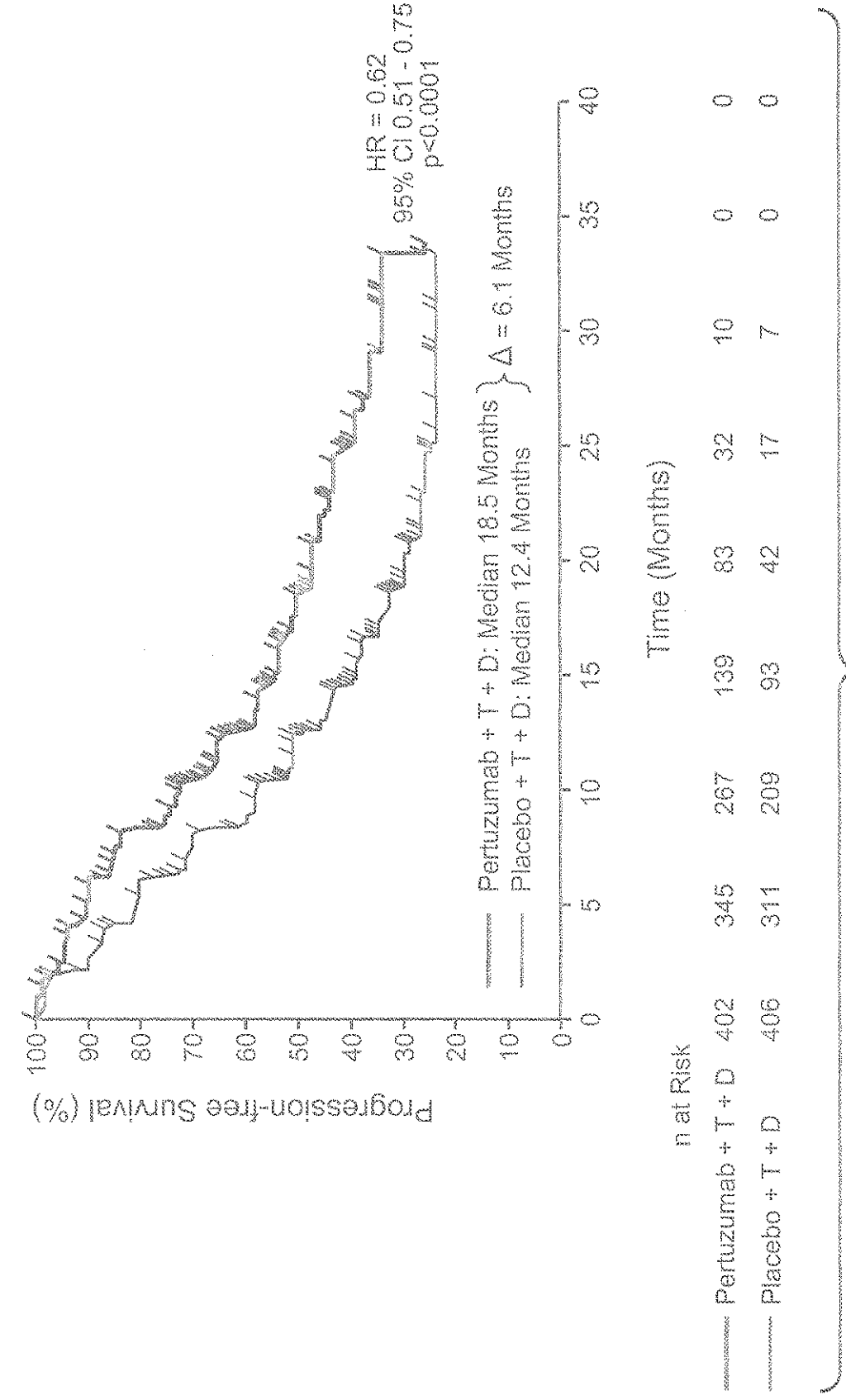

Progression-free Survival Assessed by an Independent Review Facility.
Progression-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
Time (Months)
Pertuzumab + T + D: Median 18.5 Months
Placebo + T + D: Median 12.4 Months
Δ = 6.1 Months
HR = 0.62
95% CI 0.51 - 0.75
p<0.0001
n at Risk
Pertuzumab + T + D 402 345 267 139 83 32 10 0 0
Placebo + T + D 406 311 209 93 42 17 7 0 0

FIG. 8

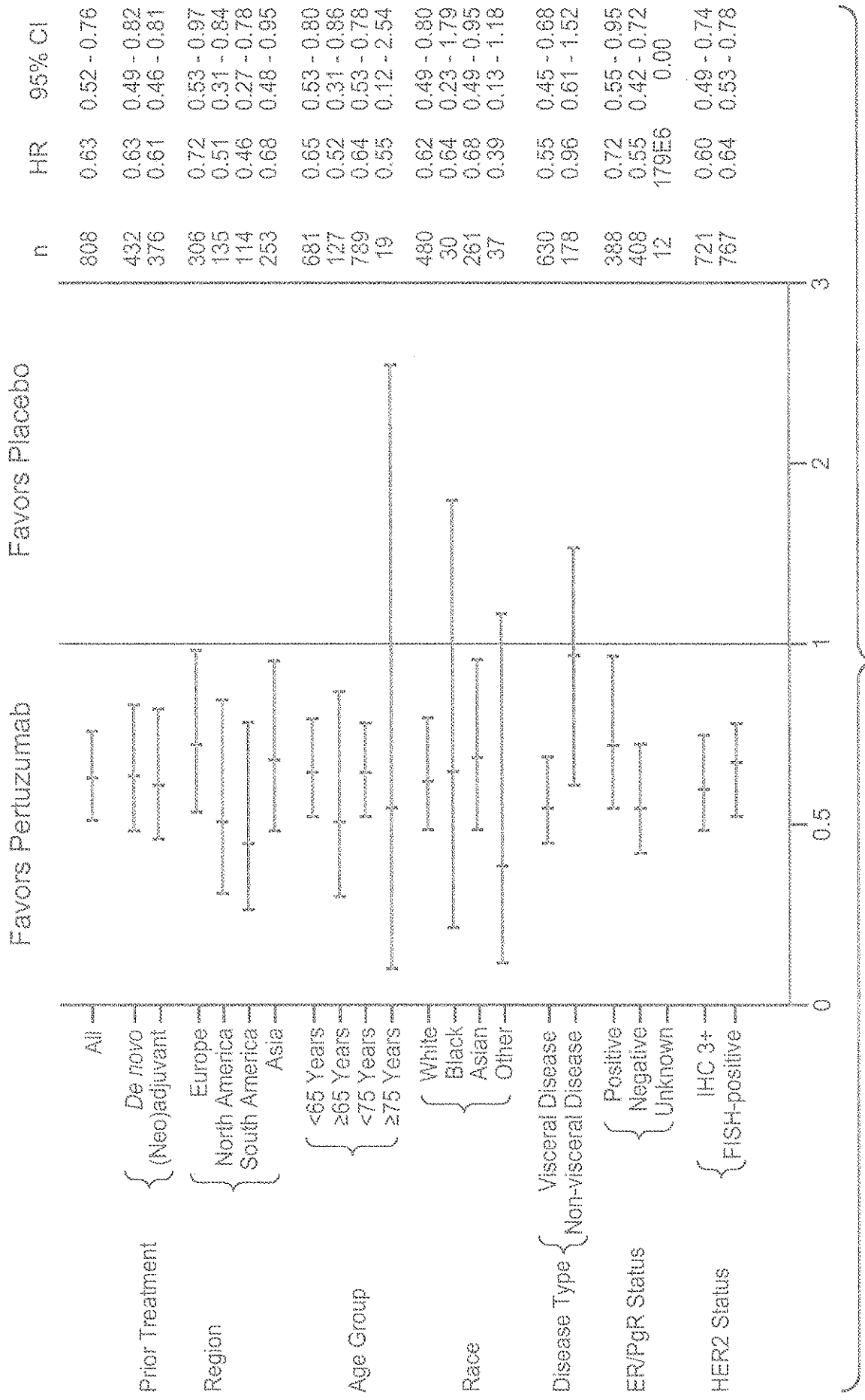

Favors Pertuzumab
Favors Placebo
0
0.5
1
2
3
n
HR
95% CI
All 808 0.63 0.52 - 0.76
Prior Treatment
De novo 432 0.63 0.49 - 0.82
(Neo)adjuvant 376 0.61 0.46 - 0.81
Region
Europe 306 0.72 0.53 - 0.97
North America 135 0.51 0.31 - 0.84
South America 114 0.46 0.27 - 0.78
Asia 253 0.68 0.48 - 0.95
Age Group
<65 Years 681 0.65 0.53 - 0.80
≥65 Years 127 0.52 0.31 - 0.86
<75 Years 789 0.64 0.53 - 0.78
≥75 Years 19 0.55 0.12 - 2.54
Race
White 480 0.62 0.49 - 0.80
Black 30 0.64 0.23 - 1.79
Asian 261 0.68 0.49 - 0.95
Other 37 0.39 0.13 - 1.18
Disease Type
Visceral Disease 630 0.55 0.45 - 0.68
Non-visceral Disease 178 0.96 0.61 - 1.52
ER/PgR Status
Positive 388 0.72 0.55 - 0.95
Negative 408 0.55 0.42 - 0.72
Unknown 12 179E6 0.00
HER2 Status
IHC 3+ 721 0.60 0.49 - 0.74
FISH-positive 767 0.64 0.53 - 0.78

FIG. 9

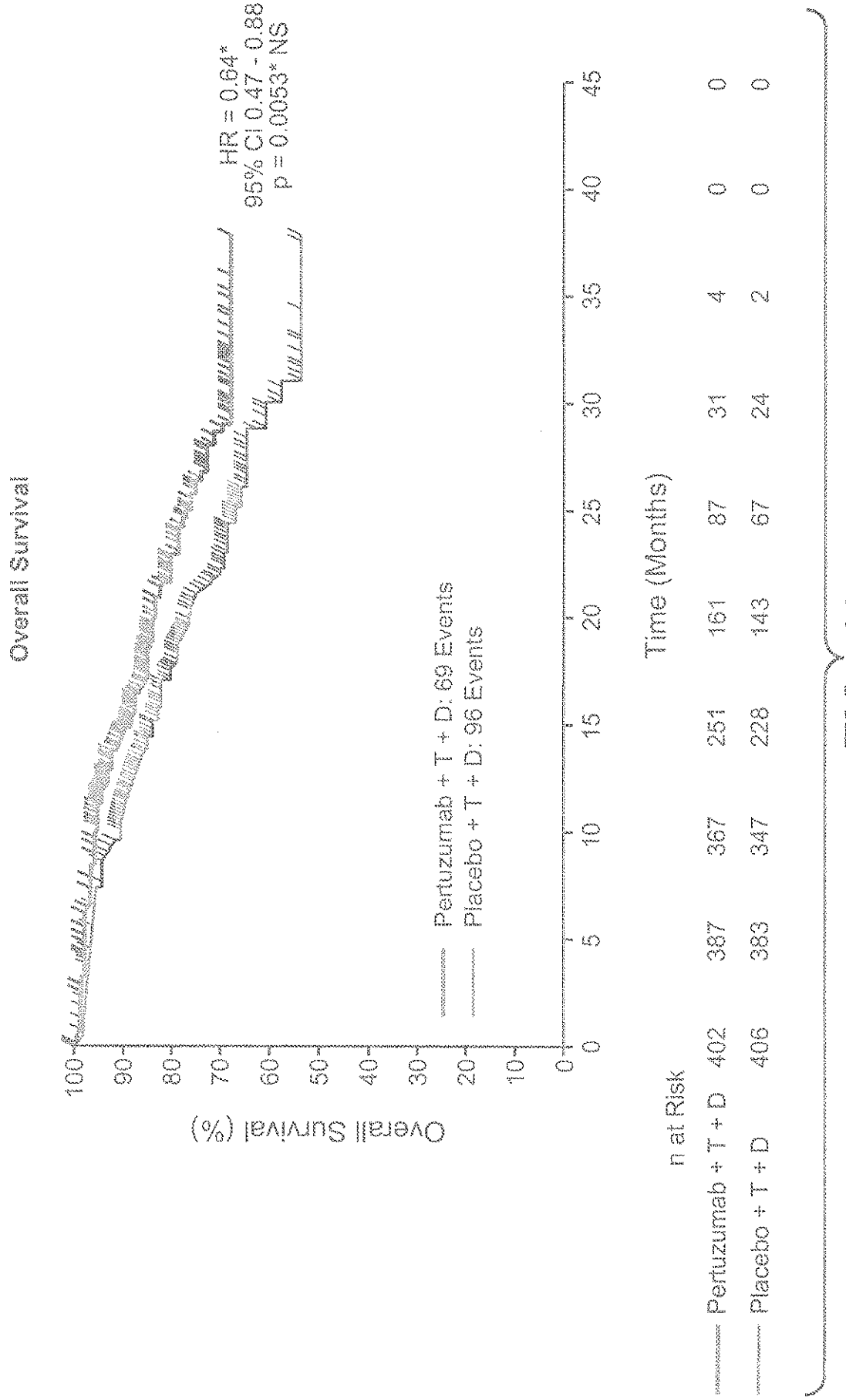

Overall Survival
HR = 0.64*
95% CI 0.47 - 0.88
p = 0.0053* NS
Overall Survival (%)
100
90
80
70
60
50
40
30
20
10
0
Pertuzumab + T + D: 69 Events
Placebo + T + D: 96 Events
0
5
10
15
20
25
30
35
40
45
Time (Months)
n at Risk
Pertuzumab + T + D 402 387 367 251 161 87 31 4 0 0
Placebo + T + D 406 383 347 228 143 67 24 2 0 0

FIG. 10

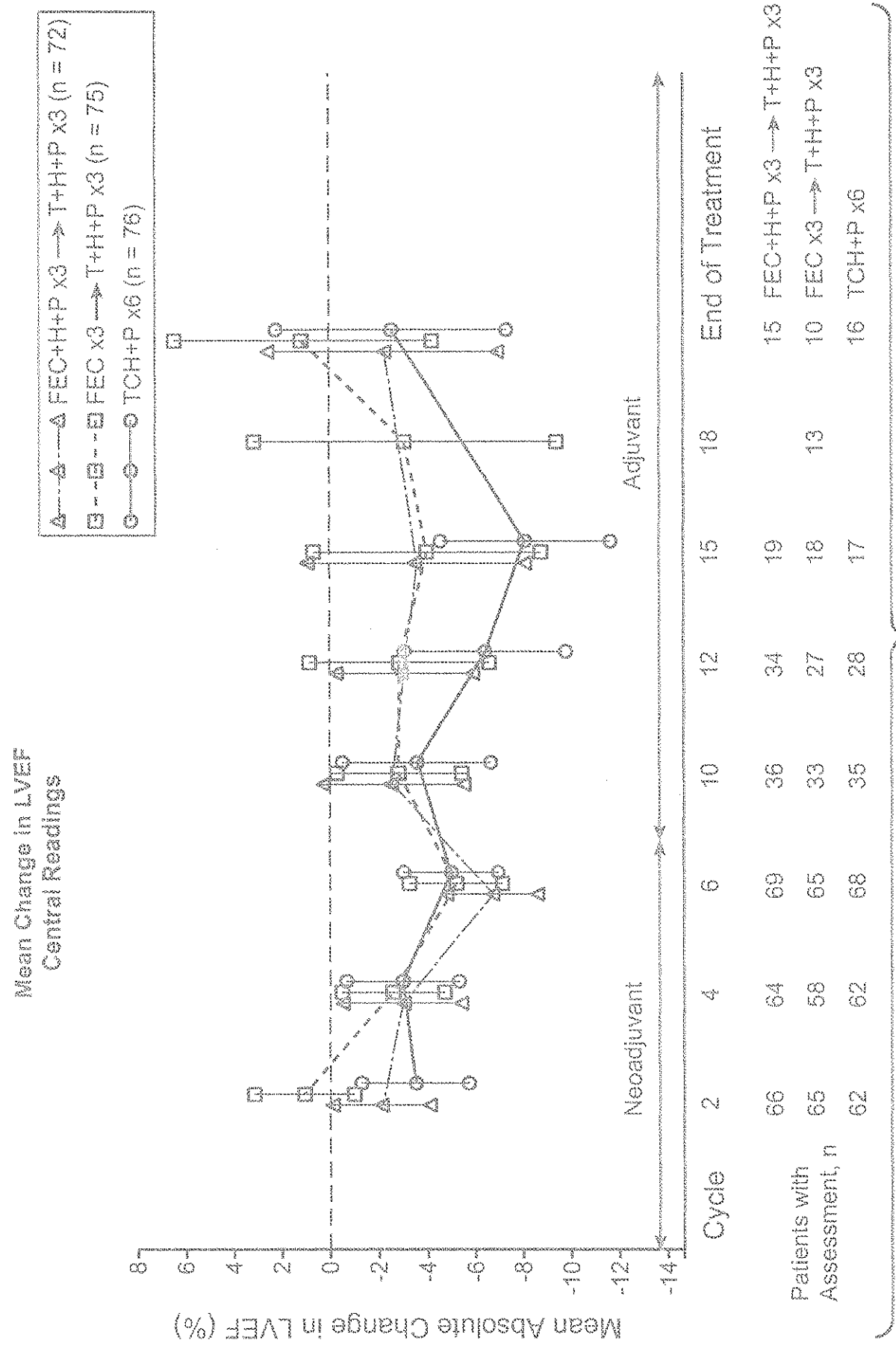

Mean Change in LVEF
Central Readings
FEC+H+P x3 → T+H+P x3 (n = 72)
FEC x3 → T+H+P x3 (n = 75)
TCH+P x6 (n = 76)
Mean Absolute Change in LVEF (%)
8
6
4
2
0
-2
-4
-6
-8
-10
-12
-14
Neoadjuvant
Adjuvant
End of Treatment
Cycle 2 4 6 10 12 15 18
Patients with Assessment, n
66 64 69 36 34 19
65 58 65 33 27 18 13
62 62 68 35 28 17
15 FEC+H+P x3 → T+H+P x3
10 FEC x3 → T+H+P x3
16 TCH+P x6

FIG. 12

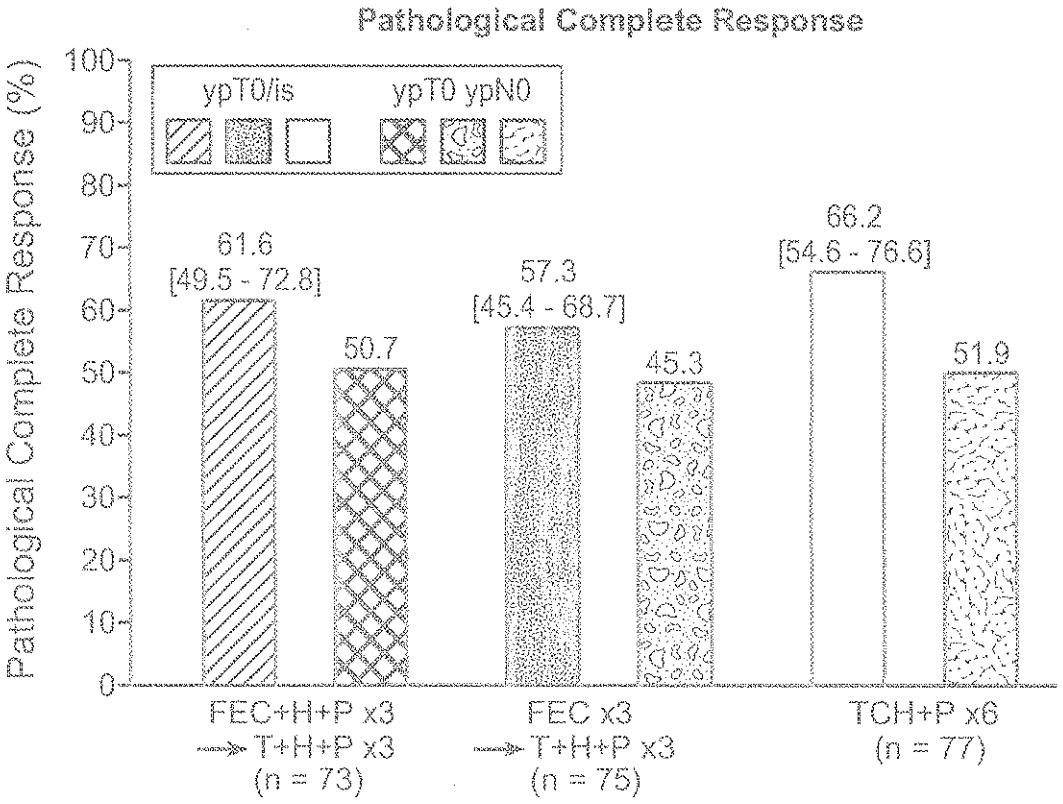

Pathological Complete Response
Pathological Complete Response (%)
ypT0/is
ypT0 ypN0
100
90
80
70
60
50
40
30
20
10
0
61.6
[49.5 - 72.8]
50.7
57.3
[45.4 - 68.7]
45.3
66.2
[54.6 - 76.6]
51.9
FEC+H+P x3
→ T+H+P x3
(n = 73)
FEC x3
→ T+H+P x3
(n = 75)
TCH+P x6
(n = 77)

FIG. 13

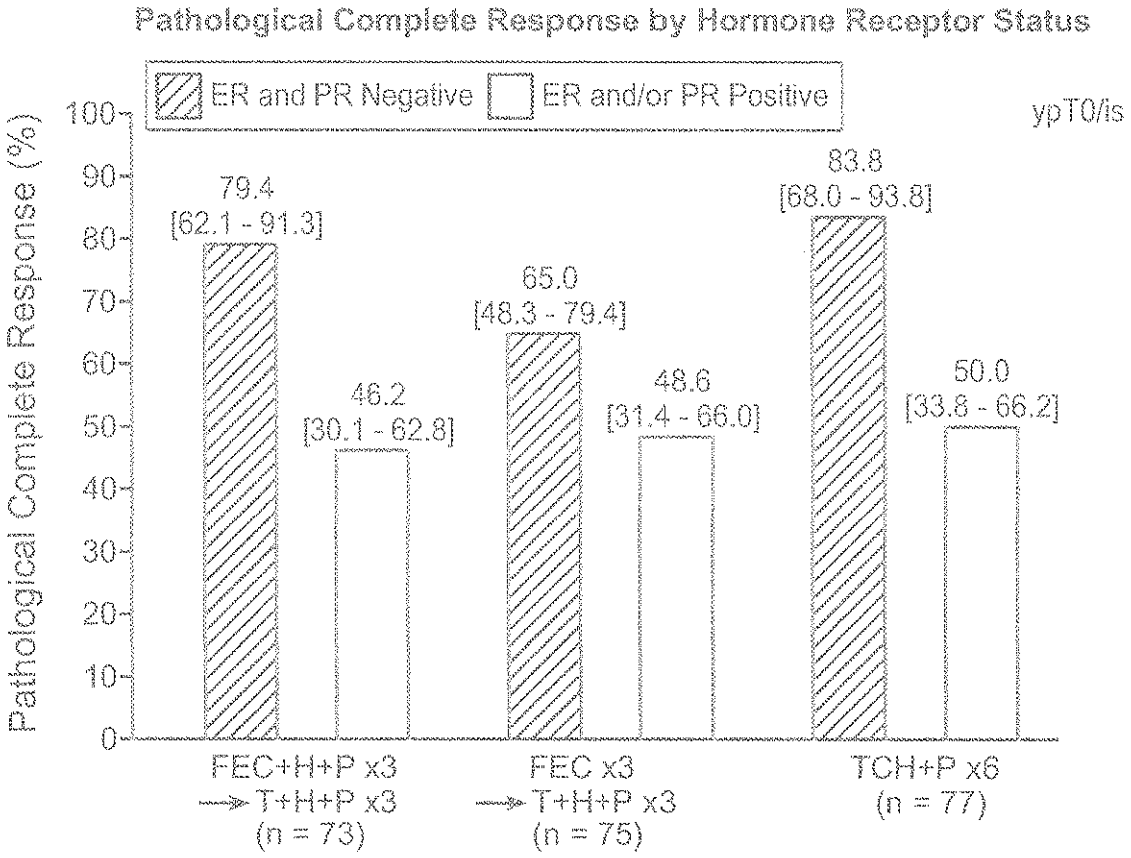

Pathological Complete Response by Hormone Receptor Status
Pathological Complete Response (%)
ER and PR Negative
ER and/or PR Positive
ypT0/is
100
90
80
70
60
50
40
30
20
10
0
79.4
[62.1 - 91.3]
46.2
[30.1 - 62.8]
65.0
[48.3 - 79.4]
48.6
[31.4 - 66.0]
83.8
[68.0 - 93.8]
50.0
[33.8 - 66.2]
FEC+H+P x3
→ T+H+P x3
(n = 73)
FEC x3
→ T+H+P x3
(n = 75)
TCH+P x6
(n = 77)

FIG. 14

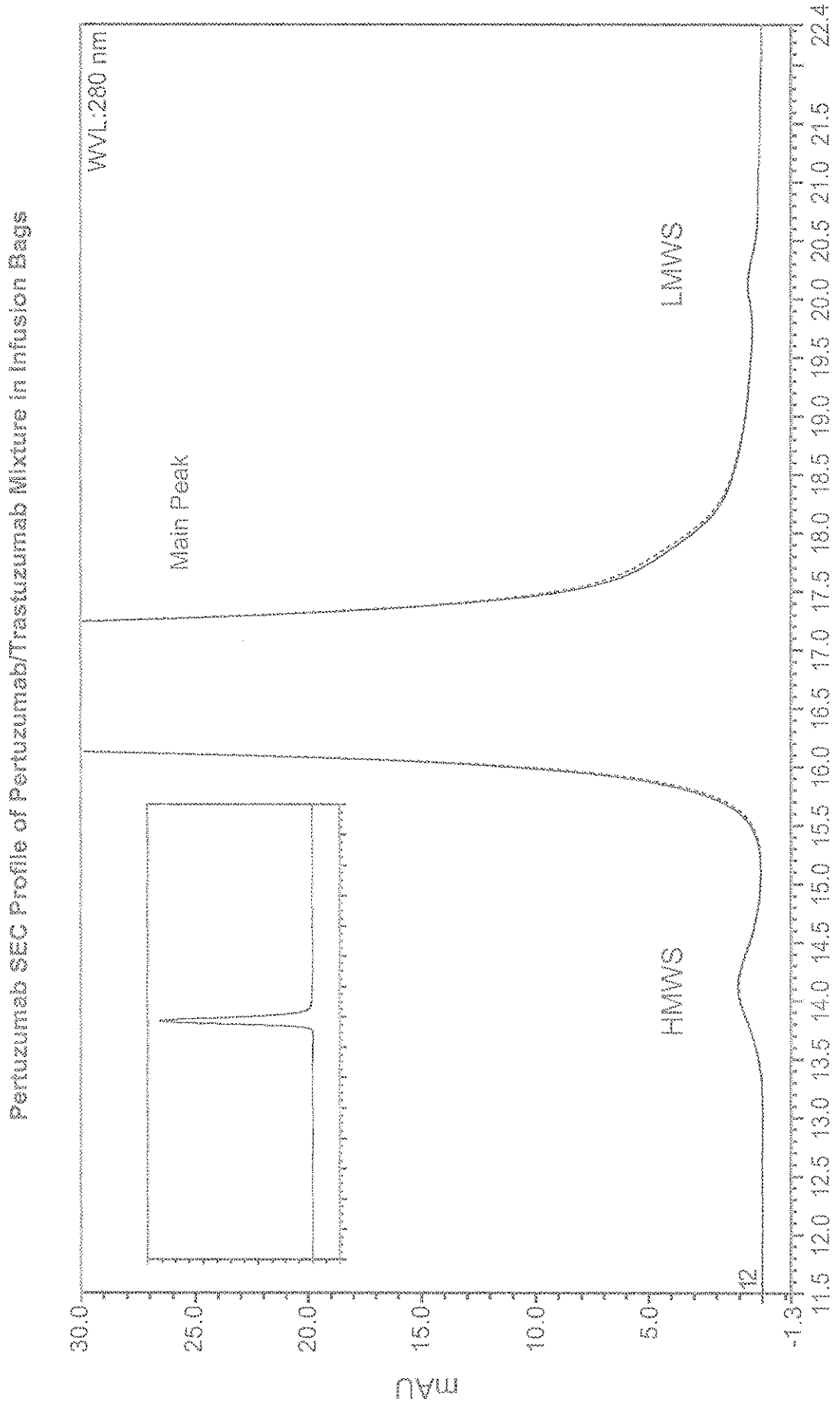

Pertuzumab SEC Profile of Pertuzumab/Trastuzumab Mixture in Infusion Bags
WVL:280 nm
Main Peak
HMWS
LMWS
mAU
Min
30.0
25.0
20.0
15.0
10.0
5.0
-1.3
11.5 12.0 12.5 13.0 13.5 14.0 14.5 15.0 15.5 16.0 16.5 17.0 17.5 18.0 18.5 19.0 19.5 20.0 20.5 21.0 21.5 22.4

FIG. 15

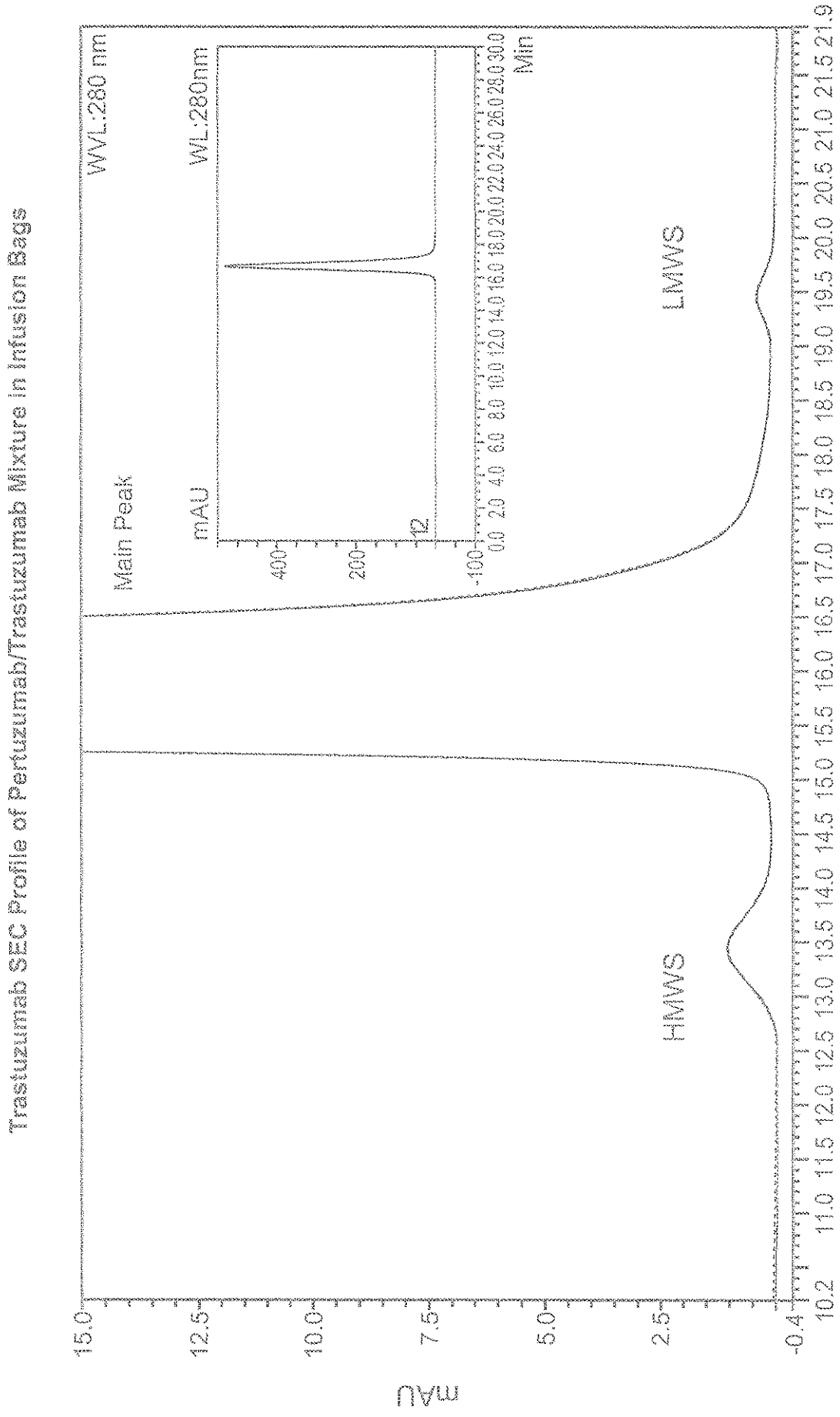

Trastuzumab SEC Profile of Pertuzumab/Trastuzumab Mixture in Infusion Bags
WVL:280 nm
Main Peak
WL:280nm
mAU
HMWS
LMWS
mAU
Min

FIG. 16

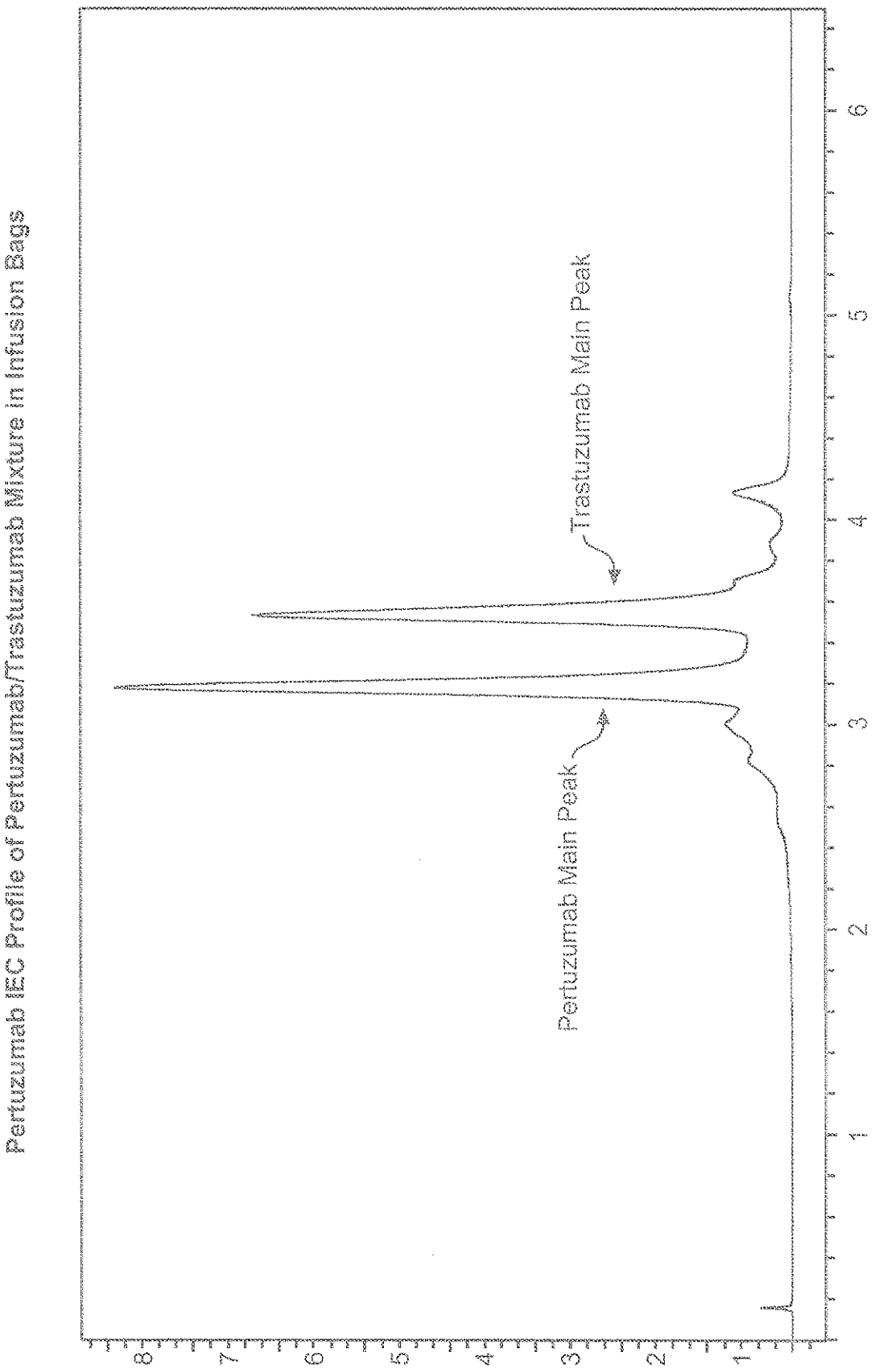

Pertuzumab IEC Profile of Pertuzumab/Trastuzumab Mixture in Infusion Bags
Pertuzumab Main Peak
Trastuzumab Main Peak
1
2
3
4
5
6
7
8

FIG. 17

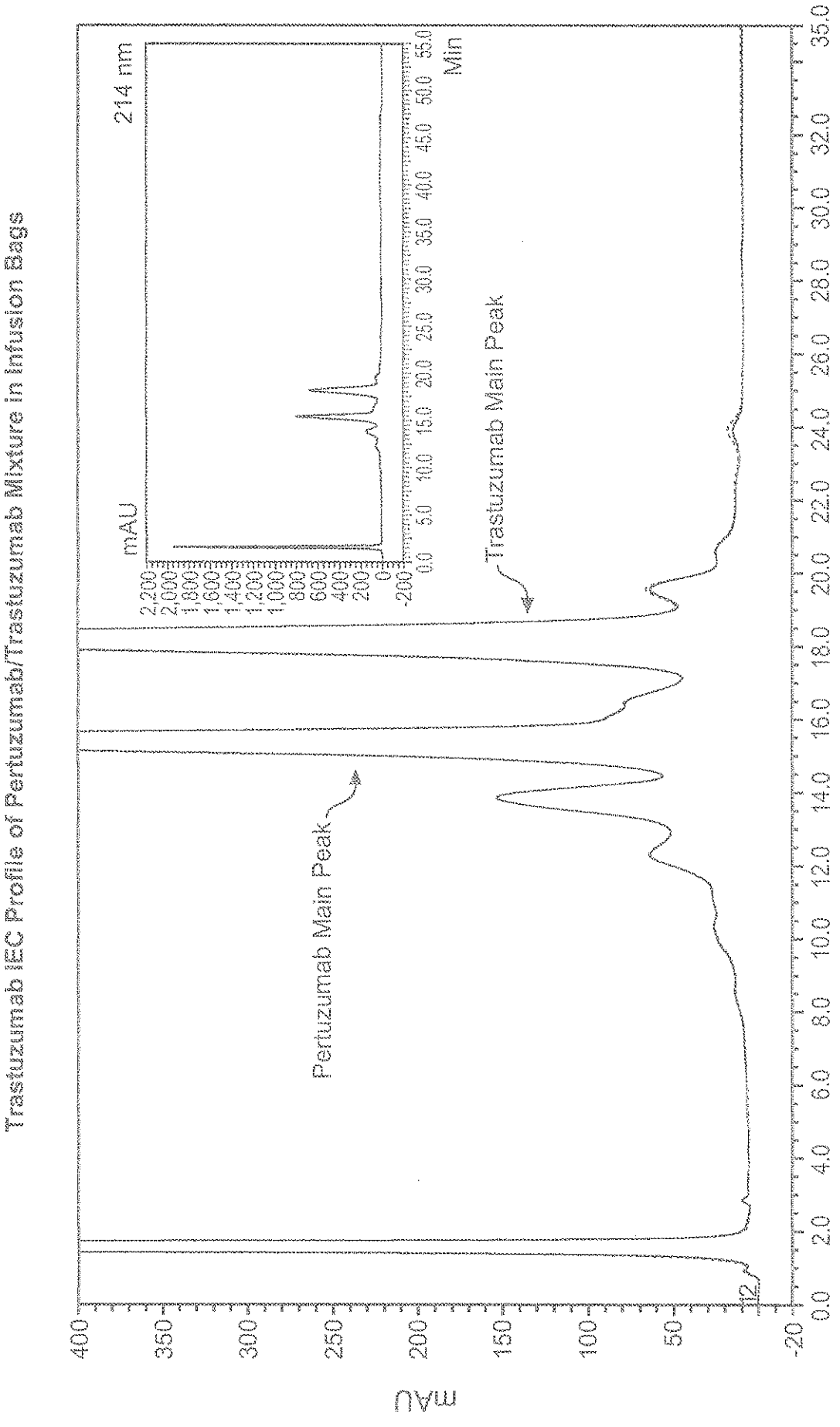

Trastuzumab IEC Profile of Pertuzumab/Trastuzumab Mixture in Infusion Bags
mAU
214 nm
Min
Pertuzumab Main Peak
Trastuzumab Main Peak
12

FIG. 18

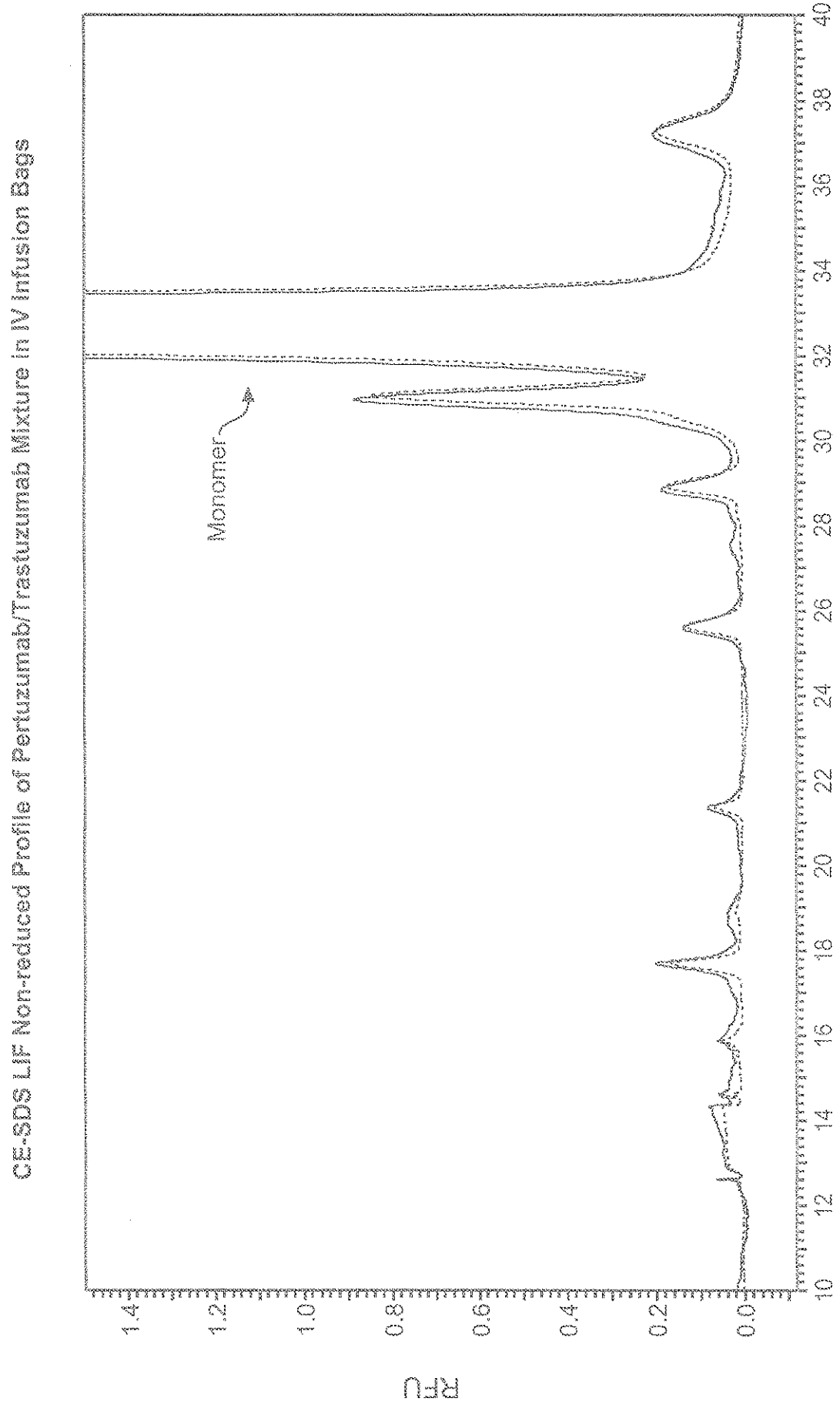

CE-SDS LIF Non-reduced Profile of Pertuzumab/Trastuzumab Mixture in IV Infusion Bags
Monomer
RFU
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
Minutes

FIG. 19

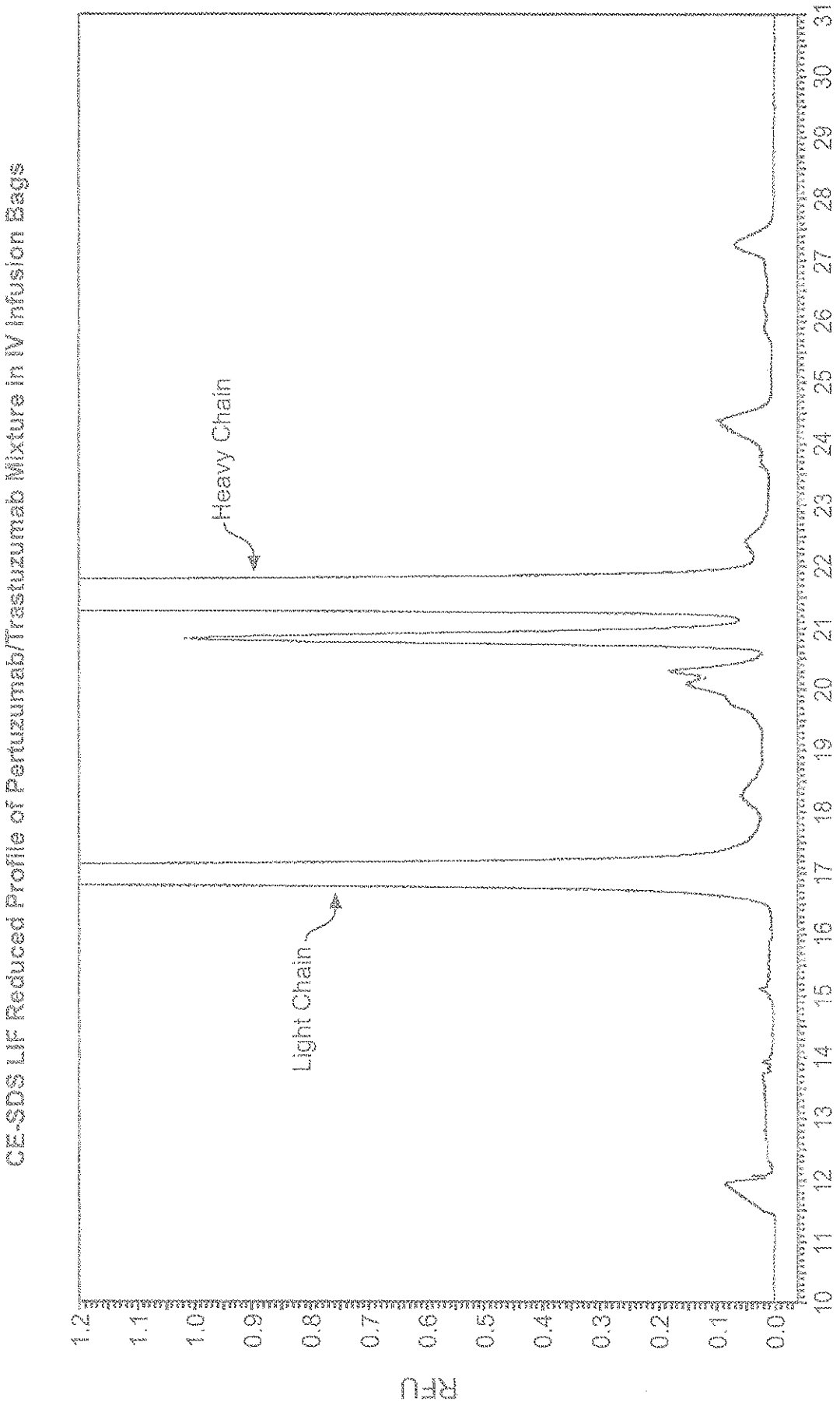

CE-SDS LIF Reduced Profile of Pertuzumab/Trastuzumab Mixture in IV Infusion Bags
Heavy Chain
Light Chain
RFU
Minutes
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31

FIG. 20

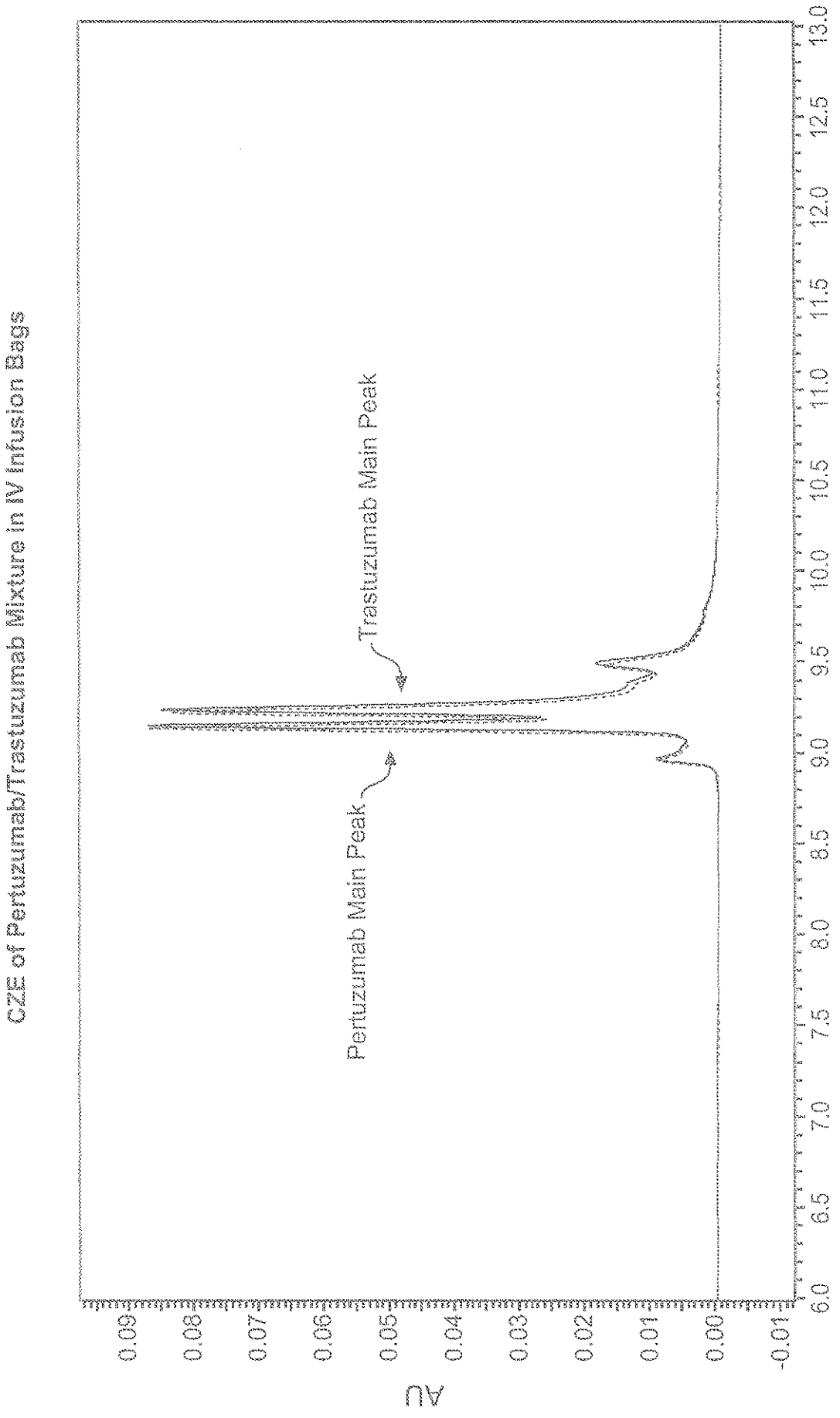

CZE of Pertuzumab/Trastuzumab Mixture in IV Infusion Bags
Trastuzumab Main Peak
Pertuzumab Main Peak
AU
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
-0.01
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
11.5
12.0
12.5
13.0
Minutes

FIG. 21

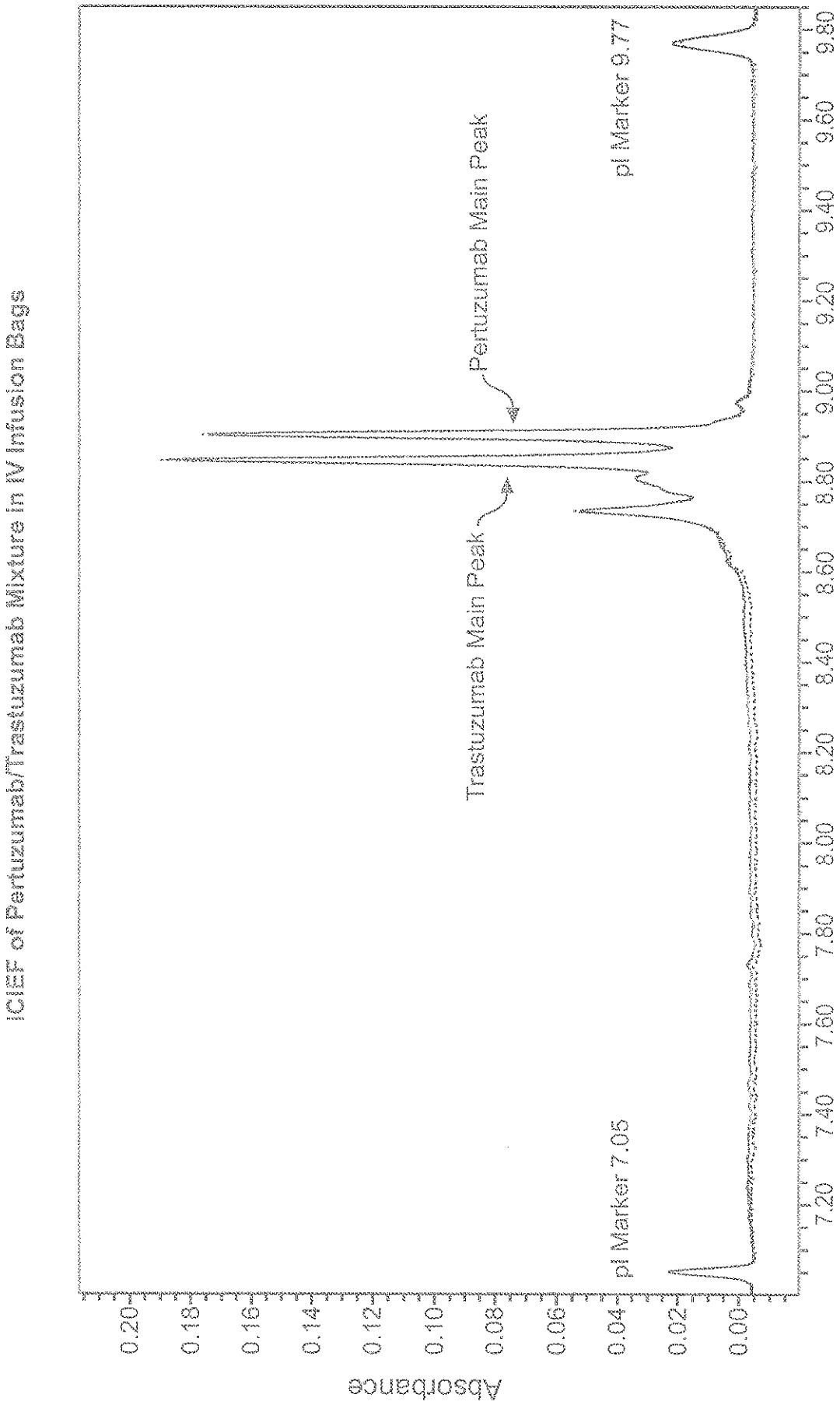

iCIEF of Pertuzumab/Trastuzumab Mixture in IV Infusion Bags
Absorbance
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
pI Marker 7.05
Trastuzumab Main Peak
Pertuzumab Main Peak
pI Marker 9.77
7.20
7.40
7.60
7.80
8.00
8.20
8.40
8.60
8.80
9.00
9.20
9.40
9.60
9.80
pI

FIG. 22

Potency Dose Response Curves of Pertuzumab/Trastuzumab Mixture, Pertuzumab Alone, and Trastuzumab Alone in Infusion Bags

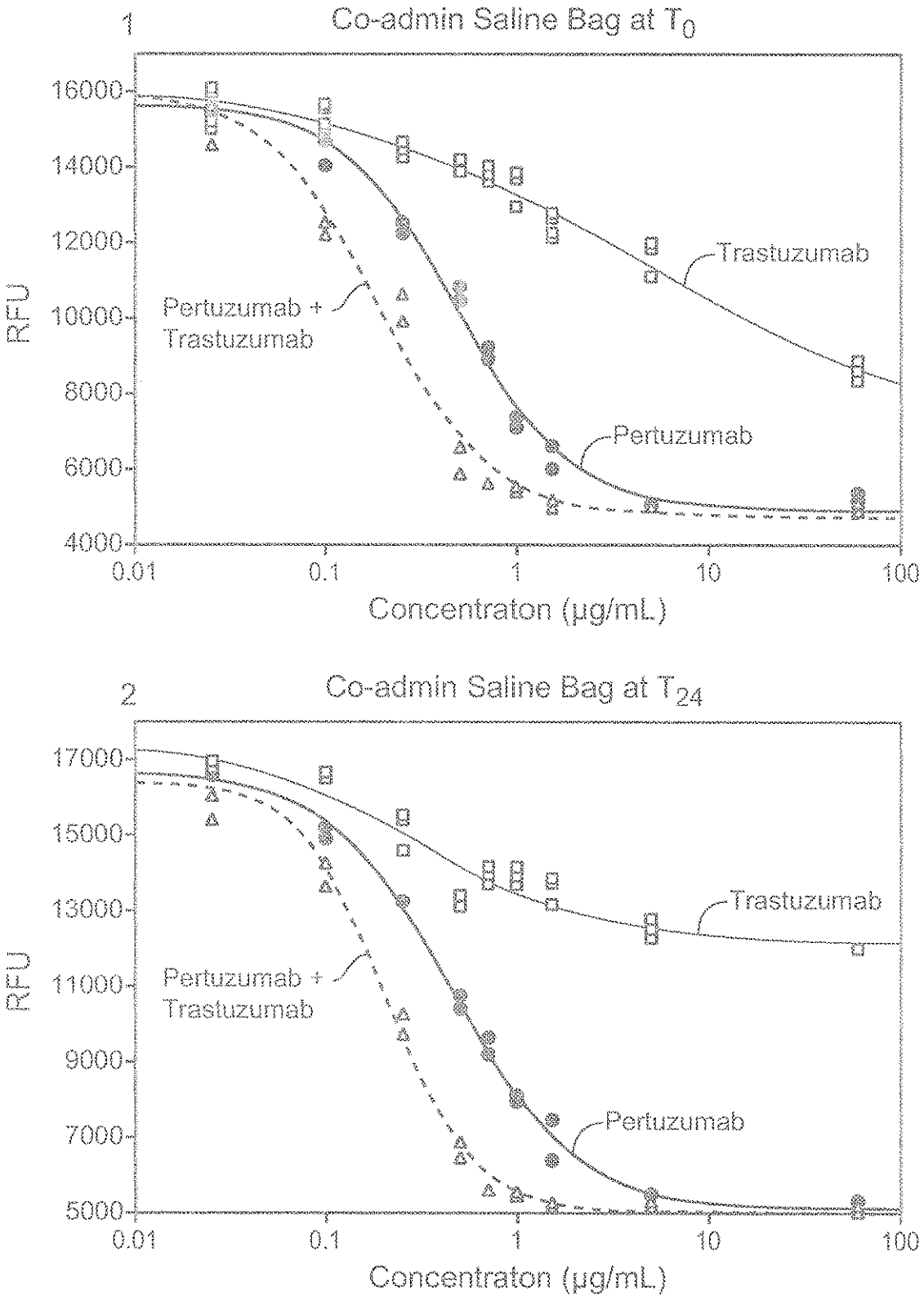


FIG. 23

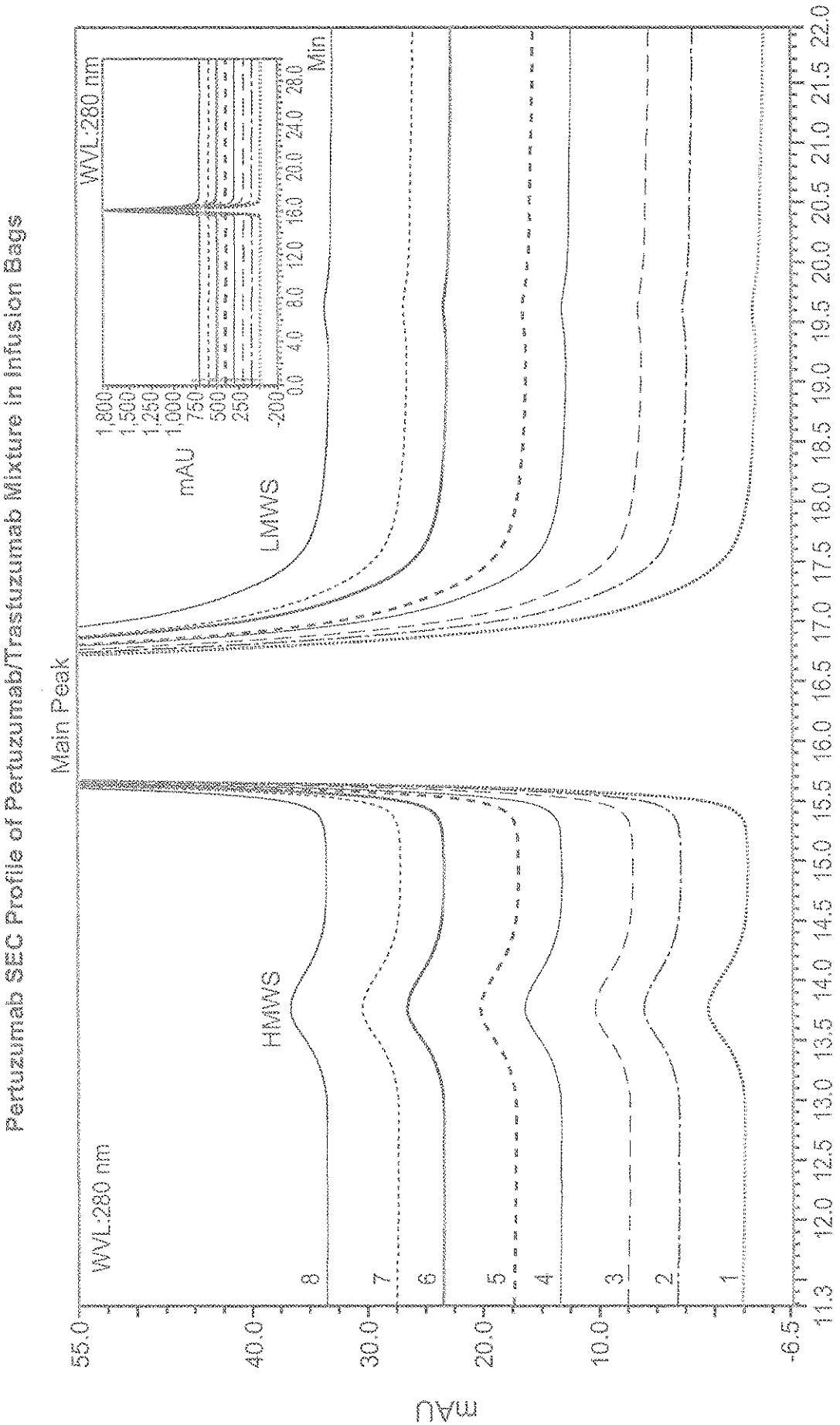

Pertuzumab SEC Profile of Pertuzumab/Trastuzumab Mixture in Infusion Bags
WVL:280 nm
Main Peak
HMWS
LMWS
mAU
Min
1
2
3
4
5
6
7
8

FIG. 24

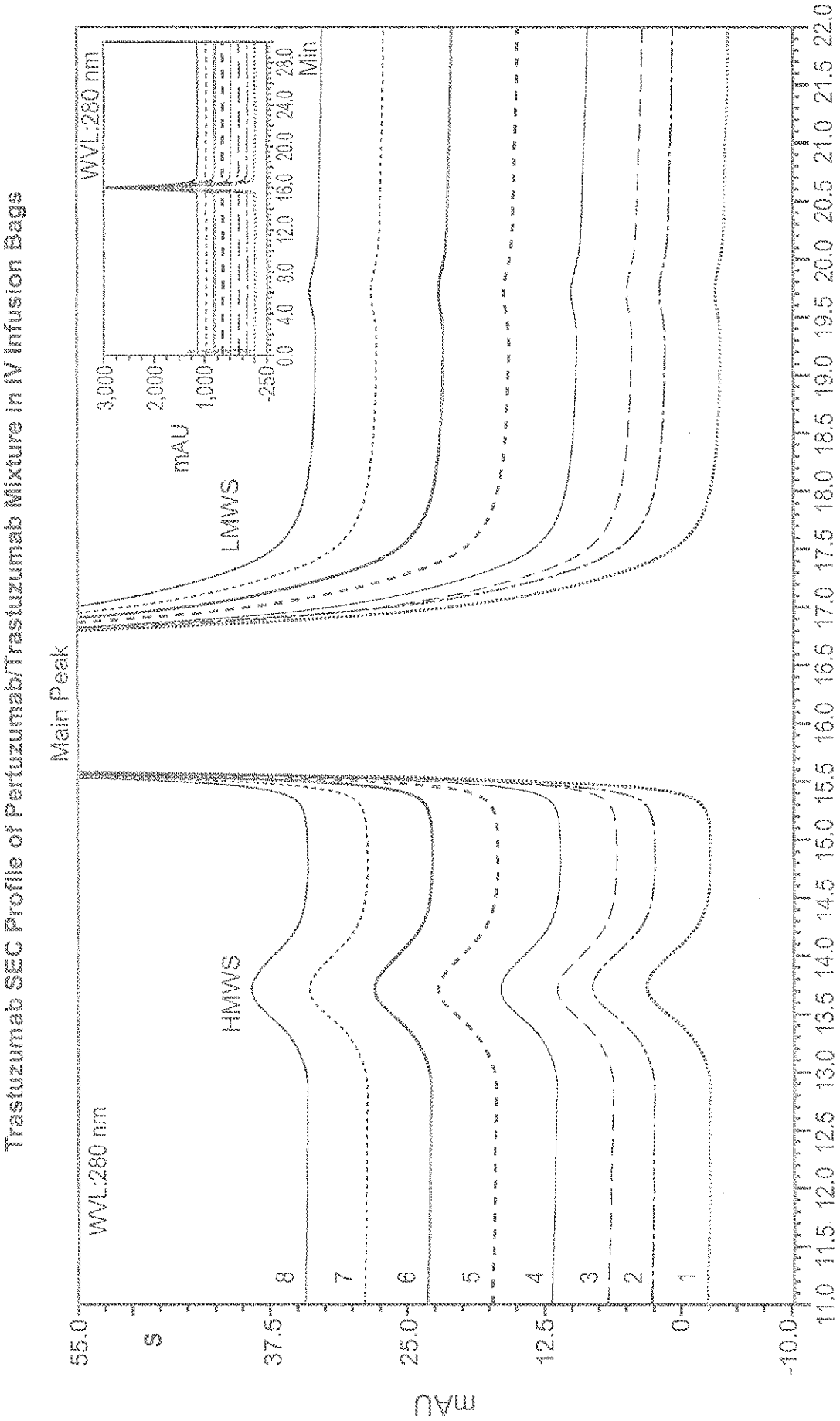

Trastuzumab SEC Profile of Pertuzumab/Trastuzumab Mixture in IV Infusion Bags
WVL:280 nm
HMWS
Main Peak
LMWS
mAU
Min
8
7
6
5
4
3
2
1

FIG. 25

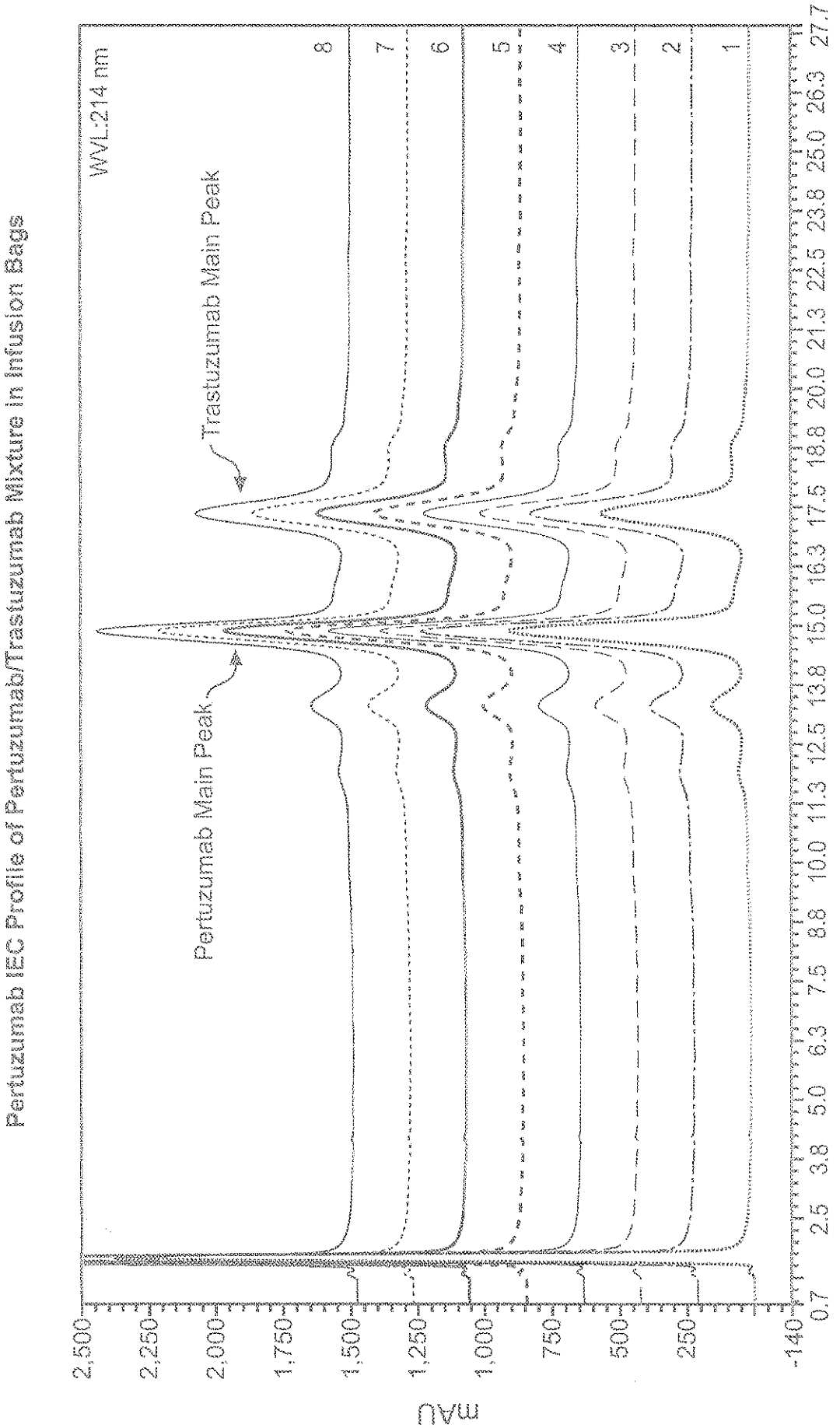

Pertuzumab IEC Profile of Pertuzumab/Trastuzumab Mixture in Infusion Bags
WVL:214 nm
Trastuzumab Main Peak
Pertuzumab Main Peak
8
7
6
5
4
3
2
1
mAU
2,500
2,250
2,000
1,750
1,500
1,250
1,000
750
500
250
-140
0.7
2.5
3.8
5.0
6.3
7.5
8.8
10.0
11.3
12.5
13.8
15.0
16.3
17.5
18.8
20.0
21.3
22.5
23.8
25.0
26.3
27.7
Min

FIG. 26

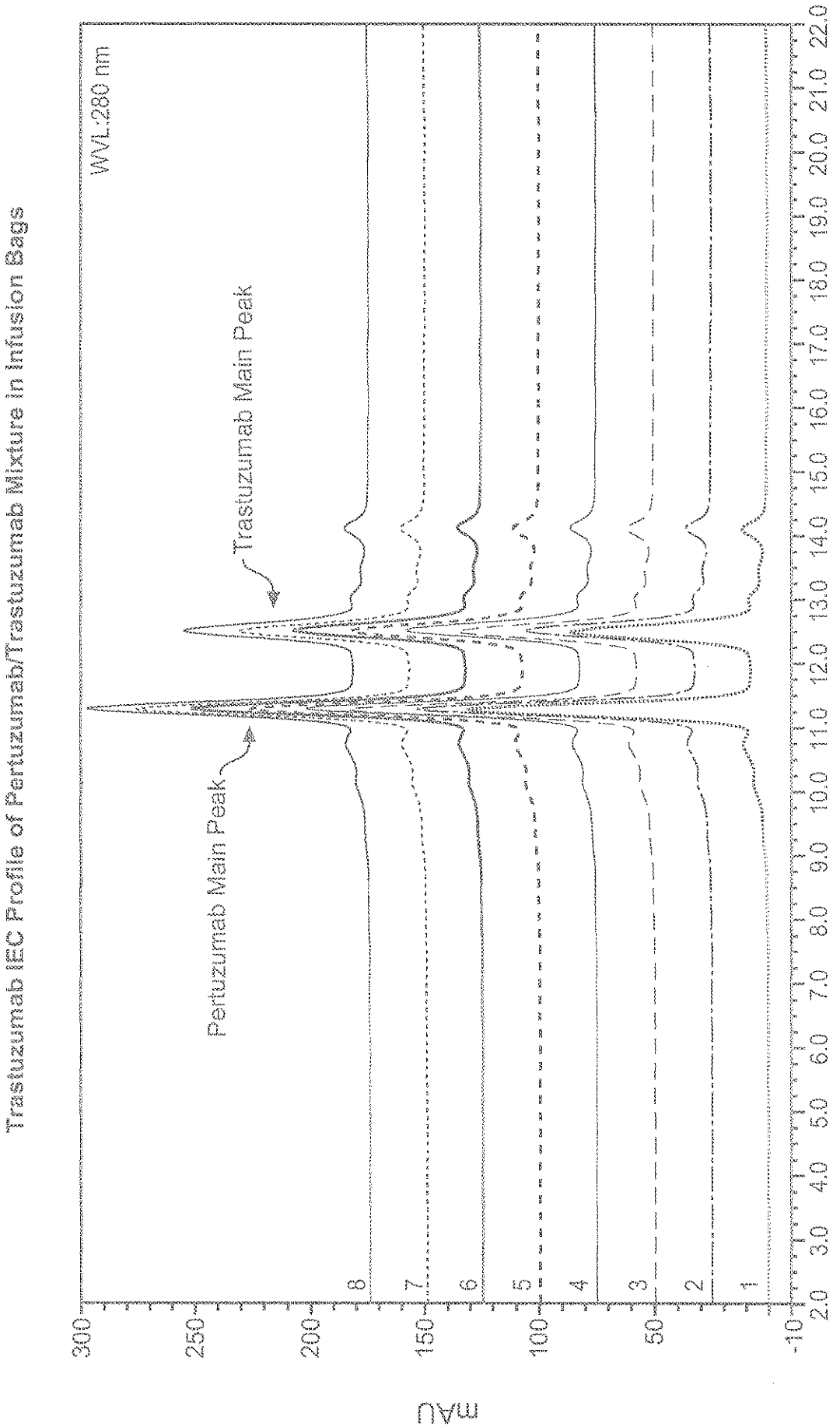

Trastuzumab IEC Profile of Pertuzumab/Trastuzumab Mixture in Infusion Bags
WVL:280 nm
Trastuzumab Main Peak
Pertuzumab Main Peak
mAU
Min
300
250
200
150
100
50
-10
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
14.0
15.0
16.0
17.0
18.0
19.0
20.0
21.0
22.0
1
2
3
4
5
6
7
8

FIG. 27

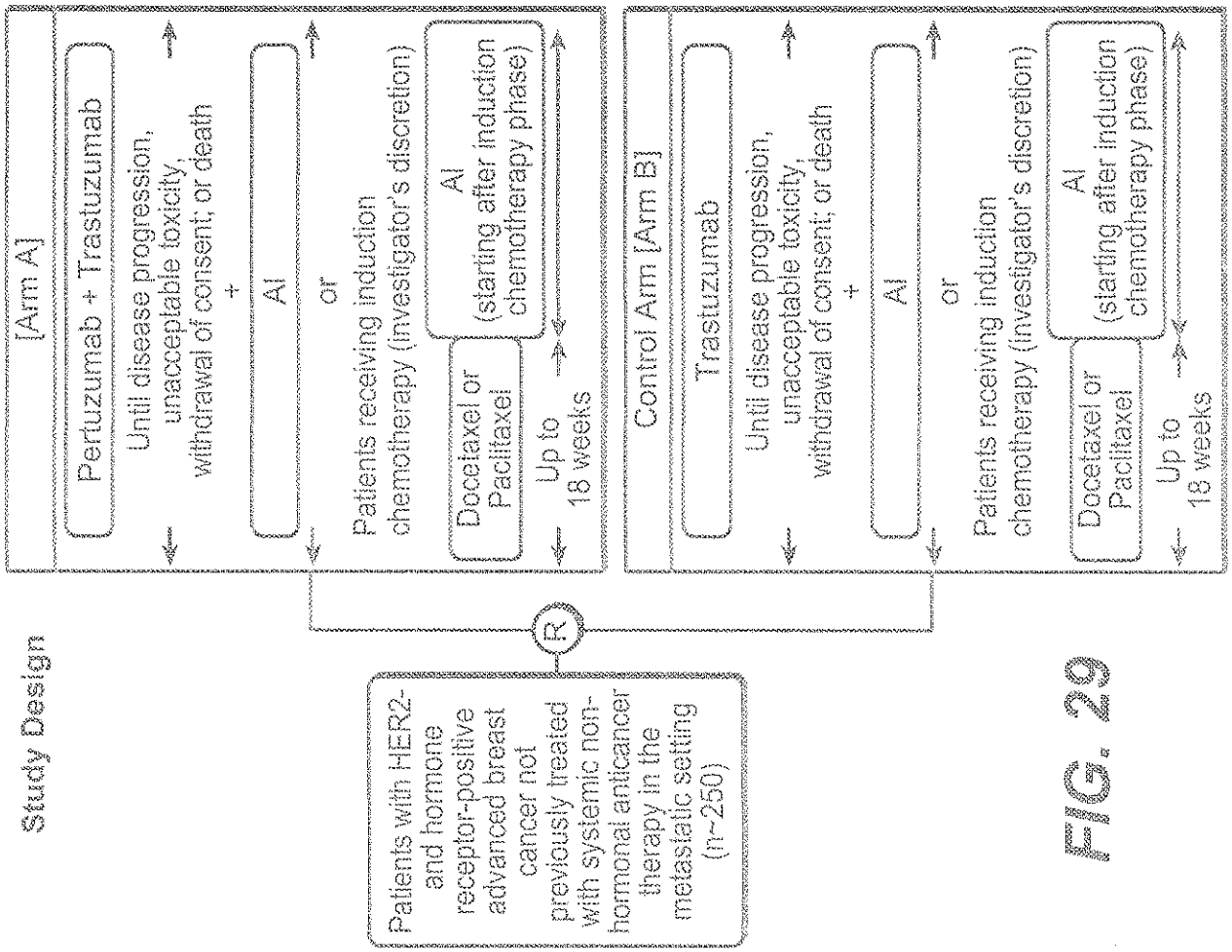

Study Design
Patients with HER2- and hormone receptor-positive advanced breast cancer not previously treated with systemic non-hormonal anticancer therapy in the metastatic setting (n~250)
R
[Arm A]
Pertuzumab + Trastuzumab
Until disease progression, unacceptable toxicity, withdrawal of consent; or death
+
AI
or
Patients receiving induction chemotherapy (investigator's discretion)
Docetaxel or Paclitaxel
Up to 18 weeks
AI (starting after induction chemotherapy phase)
Control Arm [Arm B]
Trastuzumab
Until disease progression, unacceptable toxicity, withdrawal of consent; or death
+
AI
or
Patients receiving induction chemotherapy (investigator's discretion)
Docetaxel or Paclitaxel
Up to 18 weeks
AI (starting after induction chemotherapy phase)

FIG. 29

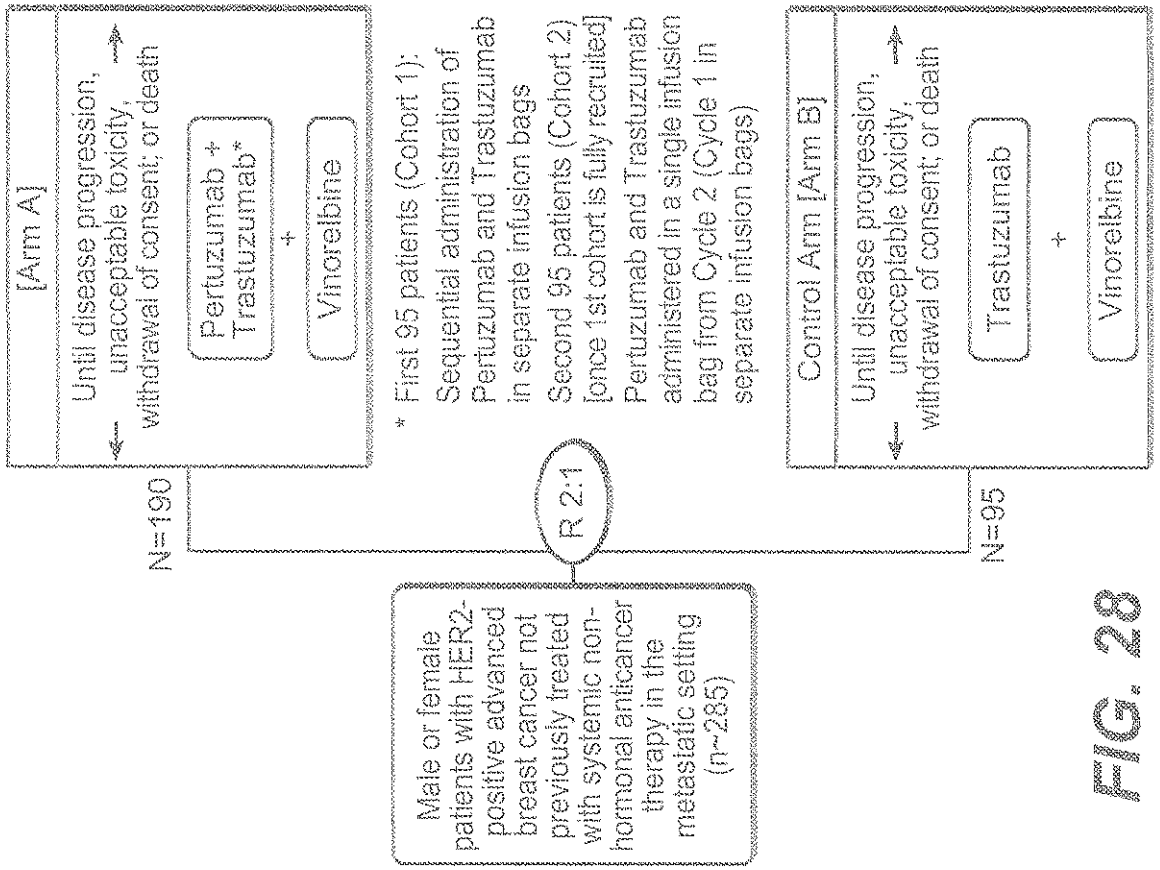

Male or female patients with HER2-positive advanced breast cancer not previously treated with systemic non-hormonal anticancer therapy in the metastatic setting (n~285)
R 2:1
N=190
[Arm A]
Until disease progression, unacceptable toxicity, withdrawal of consent; or death
Pertuzumab + Trastuzumab*
+
Vinorelbine
N=95
Control Arm [Arm B]
Until disease progression, unacceptable toxicity, withdrawal of consent; or death
Trastuzumab
+
Vinorelbine
* First 95 patients (Cohort 1): Sequential administration of Pertuzumab and Trastuzumab in separate infusion bags
Second 95 patients (Cohort 2) [once 1st cohort is fully recruited] Pertuzumab and Trastuzumab administered in a single infusion bag from Cycle 2 (Cycle 1 in separate infusion bags)

FIG. 28

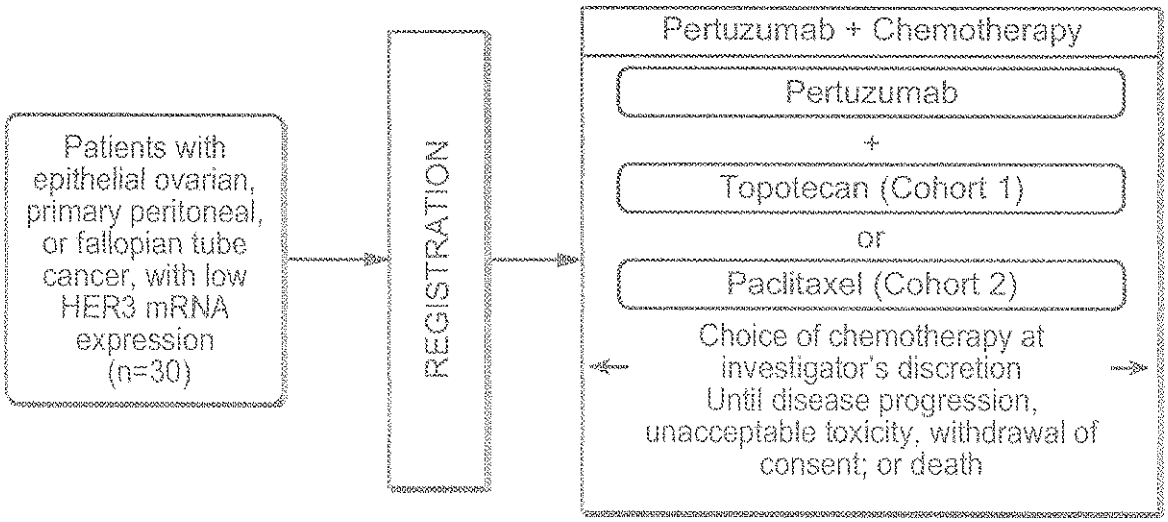

Patients with epithelial ovarian, primary peritoneal, or fallopian tube cancer, with low HER3 mRNA expression (n=30)
REGISTRATION
Pertuzumab + Chemotherapy
Pertuzumab
+
Topotecan (Cohort 1)
or
Paclitaxel (Cohort 2)
Choice of chemotherapy at investigator's discretion
Until disease progression, unacceptable toxicity, withdrawal of consent; or death

FIG. 30

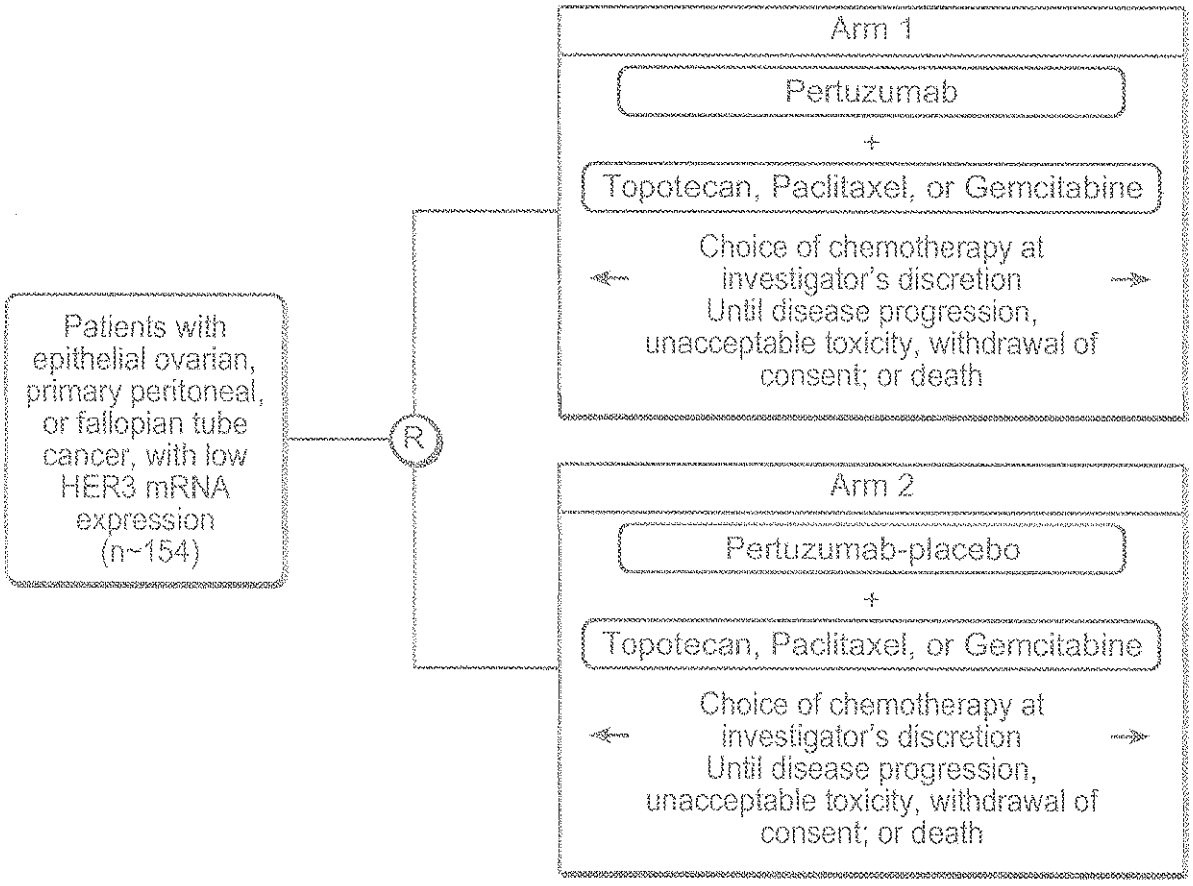

Patients with epithelial ovarian, primary peritoneal, or fallopian tube cancer, with low HER3 mRNA expression (n~154)
R
Arm 1
Pertuzumab
+
Topotecan, Paclitaxel, or Gemcitabine
Choice of chemotherapy at investigator's discretion
Until disease progression, unacceptable toxicity, withdrawal of consent; or death
Arm 2
Pertuzumab-placebo
+
Topotecan, Paclitaxel, or Gemcitabine
Choice of chemotherapy at investigator's discretion
Until disease progression, unacceptable toxicity, withdrawal of consent; or death

FIG. 31

Samples Taken and Time Points

	Treatment Period													
Cycle	1				2				3		4		6	
Day of cycle	1		8	15	1		8	15	1		1		1	
Study Day	1		8	15	22		29	36	43		64		106	
	PRE[a]	EOI[b]			PRE[a]	EOI[b]			PRE[a]	EOI[b]	PRE[a]	EOI[b]	PRE[a]	EOI[b]
Trastuzumab	X	X							X	X			X	X
Pertuzumab	X	X	X[c]	X[c]	X	X	X[c]	X[c]	X[d]	X	X	X	X	X
HER2 ECD	X													

EOI = end of infusion; PRE = pre-dose.

Note: Each blood sample will be 5 mL in volume. Separate PK samples will be collected for each drug (i.e., Trastuzumab & Pertuzumab)

a. Sample can be collected up to 6 hours prior to administration of the specified drug (i.e., Trastuzumab or Pertuzumab).

b. Sample can be collected up to 30 minutes after the end of infusion of the specified drug (i.e., Trastuzumab or Pertuzumab).

c. Sample can be collected within ±6 hours (relative to the start of infusion of the specified drug).

d. Cycle 2 trough level = primary study endpoint - must be drawn on Study Day 43 (22 days after Cycle 2 dose) regardless of whether Cycle 3 dose is delayed or not given.

FIG. 32

Demographics

	Arm A 420mg (N=15)	Arm B 840mg (N=15)
Age (yr)		
Mean (SD)	60.6 (14.7)	57.3 (11.5)
Median	67.0	59.0
Min-Max	29-76	27-72
<65 (%)	6 (40.0)	10 (66.7)
≥65 (%)	9 (60.0)	5 (33.3)
Sex		
Male (%)	14 (93.3)	10 (66.7)
Female (%)	1 (6.7)	5 (33.3)
Race		
Asian (%)	9 (60.0)	8 (53.5)
White (%)	6 (40.0)	7 (46.7)
Weight (kg) at baseline		
Mean (SD)	67.55 (8.64)	67.69 (11.68)
Median	67.00	66.80
ECOG		
0	10 (66.7)	6 (40.0)
1	5 (33.3)	9 (60.0)

FIG. 33

Gastric Cancer History

	Pertuzumab 420mg (N=15)	Pertuzumab 840mg (N=15)
Extent of Disease on Entry		
n	15	15
Metastatic disease	13 (86.7%)	12 (80.0%)
Unresectable locally advanced disease	2 (13.3%)	3 (20.0%)
Primary Site		
n	15	15
Stomach	12 (80.0%)	13 (86.7%)
Gastroesophageal junction	3 (20.0%)	2 (13.3%)
Measurability		
n	15	15
Measurable disease	11 (73.3%)	13 (86.7%)
Non-measurable evaluable disease only	4 (26.7%)	2 (13.3%)
Histological Subtypes		
n	15	15
Intestinal	6 (40.0%)	5 (33.3%)
Diffuse	1 (6.7%)	3 (20.0%)
Not known	8 (53.3%)	7 (46.7%)

FIG. 34

Patient Disposition

	Arm A Pertuzumab 840mg (N=15)	Arm B Pertuzumab 840mg (N=15)
Completed six cycles of pertuzumab (%)	5 (33.3)	5 (33.3)
Discontinued treatment (%)	1 (6.7)	3 (20.0)
Safety (%)	0	2 (13.3)
Adverse event (%)	0	1 (6.7)
Death (%)	0	1 (6.7)
Non-safety (%)	1 (6.7)	1 (6.7)
Physician decision (%)	0	1 (6.7)
Progression of disease (%)	1 (6.7)	0

FIG. 35

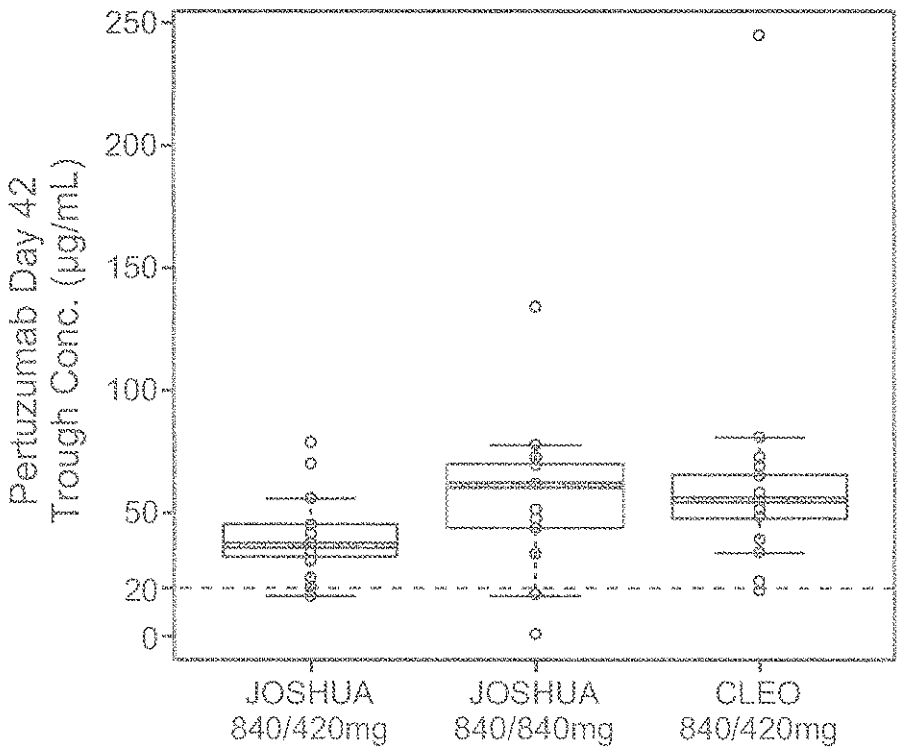
Overall Response Rate

	Arm A Pertuzumab 420mg (N=15)	Arm B Pertuzumab 840mg (N=15)
Total number of patients with tumor assessment at baseline	15	15
End of Cycle 3		
n	12	8
Partial response (%)	8 (66.7)	5 (62.5)
Stable disease (%)	2 (16.7)	2 (25.0)
Non-complete response/ non-progressive disease (%) [a]	1 (8.3)	1 (12.5)
Progressive disease (%)	1 (8.3)	0
End of Cycle 6		
n	4	4
Partial response (%)	3 (75.0)	3 (75.0)
Stable disease (%)	1 (25.0)	1 (25.0)

[a] Non-complete response/non-progressive disease is stable disease in patients with non-measurable disease.

FIG. 36

FIG. 37



Pertuzumab - Day 42 C_{trough} (µg/mL)

	JOSHUA 840/420mg	JOSHUA 840/840mg[a]	CLEO 840/420mg
N	15	12	19
Mean (SD)	40.0 (17.3)	62.7 (29.1)	63.7 (46.8)
Median	36.7	65.9	56.0
Range	(15.8-78.7)	(17.1-135)	(19.3-245)
Geometric Mean	36.8	56.4	54.9
Estimated % of Patients ≥20 µg/mL[b] (95% CI)	91.6% (79.6-99.1)	98.6% (92.2-99.97)	94.1%[c]

[a] Patient 8100 Day 42 concentration considered abnormally low (0.66ug/mL) and was excluded from summary statistics

[b] Estimated using Bootstrap analysis, assuming log-normal distribution

[c] Based on observed concentrations