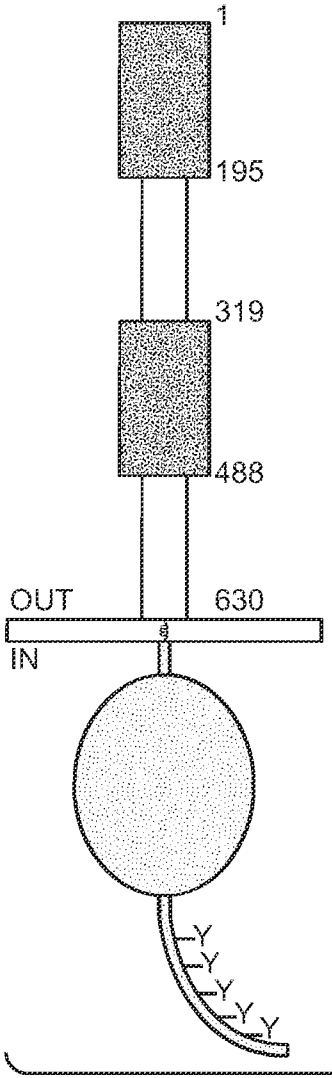


Domain I (L1)

TQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNASLSFLQDIQEVQGYV
LIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLT
EILKGGVLIQRNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGES
SEDCQSLTR (SEQ ID NO: 1)

Domain II (CR1)

TVCAGGCARCKGPLPTDCCHEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTF
ESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCPLHNQEVTAEDGTQRCEKCSKPCARV
(SEQ ID NO: 2)

Domain III (L2)

CYGLGMEHLREVRAVTSANIQEFAGCKKIFGSLAFLPESFDGDPASNTAPLQPEQLQVFETLE
EITGYLYISAWPDSLPDLSVFQNLQVIRGRILHNGAYSLTLQGLGISWLGLRSLRELGSGLAL
IHHNTHLCFVHTVPWDQLFRNPHQALLHTANRPEDECVGEGLA (SEQ ID NO: 3)

Domain IV (CR2)

CHQLCARGHCWGPGPTQCVNCSQFLRGQECVEECRVLQGLPREYVNARHCLPCHPECQPQNGS
VTCFGPEADQCVACAHYKDPPFCVARCPSGVKPDLSYMPIWKFPDEEGACQPCPINCTHSCVD
LDDKGCPAEQRASPLT (SEQ ID NO: 4)

Transmembrane

Juxtamembrane

Tyrosine Kinase

Regulatory Region

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
DIQMTQSPSSLSASVGDRVTITC KASQDVSIGVA WYQQKPGKAPKLLIYS ASYRYT GVPS

          70         80         90         100        110        120
RFSGSGSGTDFTLTISSLQPEDFATYYC QQYYIYPYT FGQGTKVEIKRTVAAPSVFIFPP

          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
EVQLVESGGGLVQPGGSLRLSCAAS GFTFTDYTMD WVRQAPGKGLEWVA DVNPNSGGSIY

          70         80         90         100        110        120
NQRFK GRFTLSVDRSKNTLYLQMNSLRAEDTAVYYCARN LGPSFYFDY WGQGTLVTVSSA

          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                               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
```

(SEQ ID NO: 14)

FIG. 4B

Pertuzumab Variant Light Chain

```
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  (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

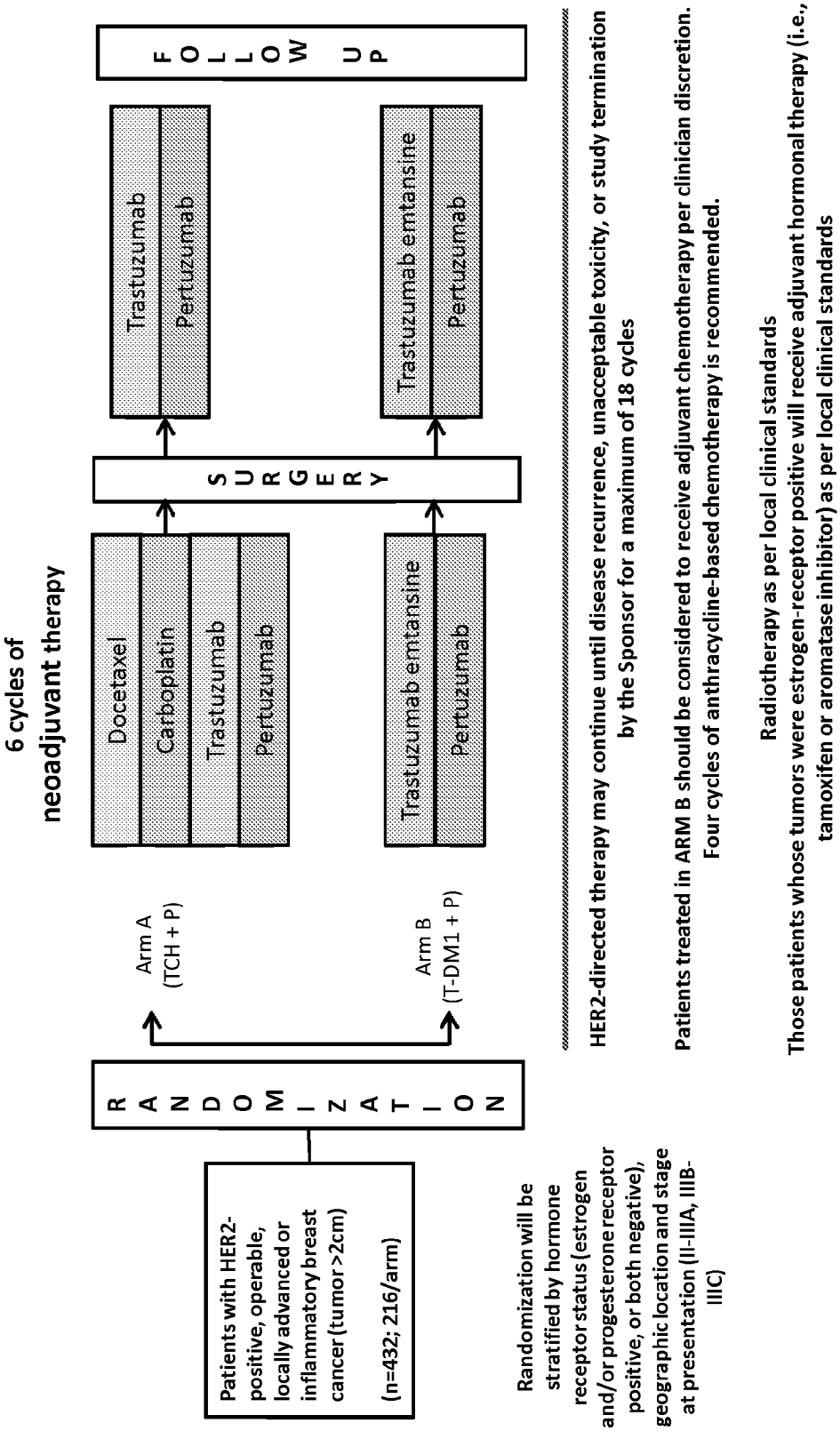

Patients with HER2-positive, operable, locally advanced or inflammatory breast cancer (tumor >2cm)
(n=432; 216/arm)
RANDOMIZATION
Randomization will be stratified by hormone receptor status (estrogen and/or progesterone receptor positive, or both negative), geographic location and stage at presentation (II-IIIA, IIIB-IIIC)
Arm A (TCH + P)
Arm B (T-DM1 + P)
6 cycles of neoadjuvant therapy
Docetaxel
Carboplatin
Trastuzumab
Pertuzumab
Trastuzumab emtansine
Pertuzumab
SURGERY
Trastuzumab
Pertuzumab
Trastuzumab emtansine
Pertuzumab
FOLLOW UP
HER2-directed therapy may continue until disease recurrence, unacceptable toxicity, or study termination by the Sponsor for a maximum of 18 cycles
Patients treated in ARM B should be considered to receive adjuvant chemotherapy per clinician discretion. Four cycles of anthracycline-based chemotherapy is recommended.
Radiotherapy as per local clinical standards
Those patients whose tumors were estrogen-receptor positive will receive adjuvant hormonal therapy (i.e., tamoxifen or aromatase inhibitor) as per local clinical standards

FIG. 6