

FIG. 1A: The cDNA (SEQ ID NO:1) and amino acid sequence (SEQ ID NO:2) of 191P4D12. The start methionine is underlined. The open reading frame extends from nucleic acid 264-1796 including the stop codon.

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1  ggccgtcgttgttggccacagcgtgggaagcagctctgggggagctcggagctcccgatc
61  acggcttcttgggggtagctacggctgggtgtgtagaacggggccggggctggggctggg
121  tcccctagtggagacccaagtgcgagaggcaagaactctgcagcttccctgccttctgggt
181  cagttccttattcaagtctgcagccggctcccaggagatctcgggtggaacttcagaaac
1      M P L S L G A E M W G P E
241  gctgggcagtcctgcctttcaaccATGCCCCCTGTCCCTGGGAGCCGAGATGTGGGGCCCTG
14   A W L L L L L L L A S F T G R C P A G E
301  AGGCCTGGCTGCTGCTGCTGCTACTGCTGGCATCATTTACAGGCCGGTGCCCCGCGGGTG
34   L E T S D V V T V V L G Q D A K L P C F
361  AGCTGGAGACCTCAGACGTGGTAACTGTGGTGCTGGGCCAGGACGCAAACTGCCCTGCT
54   Y R G D S G E Q V G Q V A W A R V D A G
421  TCTACCGAGGGGACTCCGGCGAGCAAGTGGGGCAAGTGGCATGGGCTCGGGTGGACGCGG
74   E G A Q E L A L L H S K Y G L H V S P A
481  GCGAAGCGCCCCAGGAAGTAGCGCTACTGCACTCCAAATACGGGGCTTCATGTGAGCCCGG
94   Y E G R V E Q P P P P R N P L D G S V L
541  CTTACGAGGGCCGCGTGGAGCAGCCGCGCCCCACGCAACCCCTGGACGGCTCAGTGC
114  L R N A V Q A D E G E Y E C R V S T F P
601  TCCTGCGCAACGCAGTGCAGGCGGATGAGGGCGAGTACGAGTGCCGGGTCAGCACCTTCC
134  A G S F Q A R L R L R V L V P P L P S L
661  CCGCCGCGCAGCTTCCAGGCGCGGCTGCGGCTCCGAGTGCTGGTGCCTCCCCTGCCCTCAC
154  N P G P A L E E G Q G L T L A A S C T A
721  TGAATCCTGGTCCAGCACTAGAAGAGGGCCAGGGCCTGACCTGGCAGCCTCCTGCACAG
174  E G S P A P S V T W D T E V K G T T S S
781  CTGAGGGCAGCCAGCCCCAGCGTGACCTGGGACACGGAGGTCAAAGGCACAACGTCCA
194  R S F K H S R S A A V T S E F H L V P S
841  GCCGTTCCTTCAAGCACTCCCGCTCTGCTGCCGTACCTCAGAGTTCCTACTTGGTGCTTA
214  R S M N G Q P L T C V V S H P G L L Q D
901  GCCGCAGCATGAATGGGCAGCCACTGACTTGTGTGGTGTCCCATCCTGGCCTGCTCCAGG
234  Q R I T H I L H V S F L A E A S V R G L
961  ACCAAAGGATCACCCACATCTCCACGTGTCTTCCTTGCTGAGGCCTCTGTGAGGGGCC
254  E D Q N L W H I G R E G A M L K C L S E
1021 TTGAAGACCAAAATCTGTGGCACATTGGCAGAGAAGGAGCTATGCTCAAGTGCCTGAGTG
274  G Q P P P S Y N W T R L D G P L P S G V
1081 AAGGGCAGCCCCCTCCCTCATACAACGGACACGGCTGGATGGGCCTCTGCCCAGTGGGG
294  R V D G D T L G F P P L T T E H S G I Y
1141 TACGAGTGGATGGGGACACTTTGGGCTTTCCCCACTGACCACTGAGCACAGCGGCATCT
314  V C H V S N E F S S R D S Q V T V D V L
1201 ACGTCTGCCATGTGAGCAATGAGTTCTCCTCAAGGGATTCTCAGGTCACTGTGGATGTTT
      D P Q E D S G K Q V D L V S A S V V V V
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1261 TTGACCCCCAGGAAGACTCTGGGAAGCAGGTGGACCTAGTGTACAGCTCGGTGGTGGTGGT
354 G V I A A L L F C L L V V V V V L M S R
1321 TGGGTGTGATCGCCGCACTCTTGTCTGCCTTCTGGTGGTGGTGGTGGTGCATGTCCC
374 Y H R R K A Q Q M T Q K Y E E E L T L T
1381 GATACCATCGGCGCAAGGCCCAGCAGATGACCCAGAAATATGAGGAGGAGCTGACCTGA
394 R E N S I R R L H S H H T D P R S Q P E
1441 CCAGGGGAGAACTCCATCCGGAGGCTGCATTCCCATCACACGGACCCAGGAGCCAGCCGG
414 E S V G L R A E G H P D S L K D N S S C
1501 AGGAGAGTGTAGGGCTGAGAGCCGAGGGCCACCCTGATAGTCTCAAGGACAACAGTAGCT
434 S V M S E E P E G R S Y S T L T T V R E
1561 GCTCTGTGATGAGTGAAGAGCCCGAGGGCCGAGTTACTCCACGCTGACCACGGTGAGGG
454 I E T Q T E L L S P G S G R A E E E E D
1621 AGATAGAAACACAGACTGAACTGCTGTCTCCAGGCTCTGGGCGGGCCGAGGAGGAGGAAG
474 Q D E G I K Q A M N H F V Q E N G T L R
1681 ATCAGGATGAAGGCATCAAACAGGCCATGAACCATTTTGTTCAGGAGAATGGGACCCCTAC
494 A K P T G N G I Y I N G R G H L V *
1741 GGGCCAAGCCCCACGGGCAATGGCATCTACATCAATGGGCGGGGACACCTGGTCTGAacca
1801 ggctgctcctccttccctagggcctggctccttctgttgacatgggagattttagctcatc
1861 ttgggggctccttaaacacccccatttcttgcggaagatgtccccatcccactgactg
1921 cttgacctttacctccaaccccttctgttcatcgggagggctccaccaattgagttctctcc
1981 caccatgcatgcaggtcactgtgtgtgtgcatgtgtgcctgtgtgagtggttgactgactg
2041 tgtgtgtgtggaggggtgactgtccgtggaggggtgactgtgtccgtggtgtgtattatg
2101 ctgtcatatcagagtcaagtgaactgtggtgtatgtgccacgggatttgagtggttgctg
2161 gggcaacactgtcagggttttggcgtgtgtgtcatgtggctgtgtgtgacctctgcctgaa
2221 aaagcaggtattttctcagaccccagagcagttaatgatgcagaggttgaggagagaga
2281 ggtggagactgtggctcagacccaggtgtgcgggcatagctggagctggaatctgcctcc
2341 ggtgtgagggaaacctgtctcctaccacttcggagccatgggggcaagtgtgaagcagcca
2401 gtccctgggtcagccagaggttgaaactgttacagaagccctctgcctctgggtggctc
2461 tgggcctgctgcatgtacatattttctgtaaatatacatgcgcgggagcttcttcagg
2521 aatactgctccgaatcacttttaattttttctttttttttcttgccctttccattagt
2581 tgtattttttattttatttttatttttatttttttttagagatggagttctcactatgttgc
2641 tcaggctggccttgaaactcctgggtcagaagaatcctcctgcctcagcctccctagtagc
2701 tgggactttaagtgtacaccactgtgcctgctttgaatcctttacgaagagaaaaaaaaa
2761 attaaagaaagcctttagatttatccaatgtttactactgggattgcttaaagtgaggcc
2821 cctccaacaccagggggttaattcctgtgattgtgaaaggggctacttccaaggcatctt
2881 catgcaggcagcccccttgggagggcacctgagagctggttagagctgtaaattagggatgt
2941 gagcctcgtggttactgagtaaggtaaaattgcataccaccattgtttgtgataccttagg
3001 gaattgcttggaacctggtgacaagggctcctgttcaatagtggtgttggggagagagaga
3061 gcagtgattatagaccgagagagtaggagttgaggtgaggtgaaggaggtgctgggggtg
3121 agaatgtcgcttccccctgggttttggatcactaattcaaggctcttctggatgttcc
3181 tctgggttggggctggagttcaatgaggtttatttttagctggcccaccagatacactc
3241 agccagaataacntagatttagtaccctaaactcttcttagtctgaaatctgctggatttct
3301 ggccaaagggagaggctcccatccttcgttcccagccagcctaggacttcgaatgtgga
cctgaagatctaagatcctaacatgtacattttatgtaaatatgtgcataattgtacat
3421 aaaatgatattctgtttttaataaacagacaaaacttgaaaaa (C

FIG. 1A
(Continued)

FIG. 1B: The cDNA (SEQ ID NO:3) and amino acid sequence (SEQ ID NO:4) of Ha22-2(2,4)6.1 heavy chain. Double-underlined is the leader sequence, underlined is the heavy chain variable region, and underlined with a dashed line is the human IgG1 constant region.

M E L G L C W V F L V A I L E

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1  GGTGATCAGCACTGAACACAGAGGACTCACCATGGAGTTGGGGCTGTGCTGGGTTTTCCTTGTGTGCTATTTTAGA
   · G V Q C E V Q L V E S G G G L V Q P G G S L R L S
76  AGGTGTCCAGTGTGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGTCCTCTGAGACTCTC
   · C A A S G F T F S S Y N M N W V R Q A P G K G L E
151 CTGTGCAGCCTCTGGATTACCTTCAGTAGCTATAACATGAAGTGGTCCGCCAGGCTCCAGGGAAGGGCTGGA
   · W V S Y I S S S S S S T I Y Y A D S V K G R F T I S
226 GTGGGTTTCATACATTAGTAGTAGTAGTAGTACCATACTACGCAGACTCTGTGAAGGGCCGATTACCATCTC
   · R D N A K N S L S L Q M N S L R D E D T A V Y Y C
301 CAGAGACAATGCCAAGAACTCACTGTCTCTGCAATGAACAGCCTGAGAGACGAGGACACGGCTGTGTATTACTG
   · A R A Y Y Y G M D V W G Q G T T V T V S S A S T K
376 TGCCGAGACATACTACTACCGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTCCACCAA
   · G P S V F P L A P S S K S T S G G T A A L G C L V
451 GGGCCCCATCGSTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGGT
   · 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
526 CAAGGACTACTTCCCGAACCCTGACCGTGTCTGGAACTCAGGCGCCCTGACCAGCGCGTGCACACCTTCCC
   · A V L Q S S G L Y S L S S V V T V P S S S L G T Q
601 GGCTGTCTACAGTCTCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCTCCAGCAGCTTGGGCACCCA
   · T Y T C N V N H K P S N T K V D K R V E P K S C D
676 GACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAATCTTGTGA
   · K T H T C P P C P A P E L L G G P S V F L F P P K
751 CAAACTCACACATGCCACCGTGGCCAGCACCTGAATCTCTGGGGGACCGTCAGTCTTCTCTTCCCGCCAAA
   · P K D T L M I S R T P E V T C V V V D V S H E D P
826 ACCAAGGACACCTCATGATCTCCCGGACCCCTGAGGTTCAGATGCGTGGTGGTGGACGTGAGCCACGAAGCCC
   · 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
901 TGAGGTCAAGTCAACTGGTACGTGGACGCGTGGAGGTGCATAATGCCAAGACAAGCCGCGGGAGGAGCAGTA
   · N S T Y R V V S V L T V L H Q D W L N G K E Y K C
976 CAACAGCAGCTACCGTGTGGTTCAGCGCTCCTCACCGTCCCTGCCACGAGACTGGCTGAATGCCAAGGAGTACAAGTG
   · 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
1051 CAAGGTCTCCAAACAAGCCCTCCCGAGCCCATCGAGAAAACCATCTCCAAAGCCAAAGGCGAGCCCGGACAC
   · Q V Y T L P P S R E E M T K N Q V S L T C L V K G
1126 ACAGGTGTACACCTGCCCGCATCCCGGAGGAGATGACCAAGAACCAGGTACGCTGACCTGCCTGGTCAAGG
   · 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
1201 CTTCTATCCCGGACATCCCGCTGGAGTGGCAGCAATGGGCGAGCGAGAACAACTACAAGACCAAGCCCTCC
   · V L D S D G S F F L Y S K L T V D K S R W Q Q G N
1276 CGTGCTGAGCTCCGAGGCTCCTTCTCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAA
   · 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
1351 CGTCTTCTCATGCTCCGTGATGCAATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCCCGGG
   · K *
1426 TAAATGA

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FIG. 1C: The cDNA (SEQ ID NO:5) and amino acid sequence (SEQ ID NO:6) of Ha22-2(2,4)6.1 light chain. Double-underlined is the leader sequence, underlined is the light chain variable region, and underlined with a dashed line is the human kappa constant region.

M D M R V P A Q L L G L L L L W F

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1  AGTCAGACCCAGTCAGGACACAGCATGGACATGAGGGTCCCCGCTCAGCTCCTGGGGCTCCTGCTGCTGTGGTTC
   P G S R C D I Q M T Q S P S S V S A S V G D R V T
76  CCAGGTTCAGATGCGACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTGGAGACAGAGTCACC
   I T C R A S Q G I S G W L A W Y Q Q K P G K A P K
151 ATCACTTGTCTGGGCGAGTCAGGGTATTAGCGGCTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAGCCCTAAG
   F L I Y A A S T L Q S G V P S R F S G S G S G T D
226 TTCTTGATCTATGCTGCATCCACTTTGCAAGTGGGGTCCCATCAAGGTTACGCGGAGTGGATCTGGGACAGAT
   F T L T I S S L Q P E D F A T Y Y C Q Q A N S F P
301 TTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTATGTCAACAGGCTAACAGTTTCCTT
   P T F G G G T K V E I K R T V A A P S V F I F P P
376 CCCATTTCCGGGAGGAGGACCAAGGTGGAGATCAACGAAGTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCA
   S D E Q L K S G T A S V V C L L N N F Y P R E A K
451 TCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTGTGTGCTGCTGAATTAACCTCTATCCAGAGAGGCCAAA
   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
526 GTACAGTGAAGGTGGATAACGCCCTCCAAATCGGGTAACCTCCAGGAGAGTGTACAGAGCAGGACGACGAGAC
   S T Y S L S S T L T L S K A D Y E K H K V Y A C E
601 ACCACTCAGACCTCAGCAGCACCCCTGACGCTGAGCAAGCAGACTACGAGAAACACAAAGTCTACGCTGCGGAA
   H Q G L S S P V T K S F N R G E C *
-----CCATCAGGGCCTGAGCTCGCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTAG

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FIG. 1D: The amino acid sequence (SEQ ID NO:7) of Ha22-2(2,4)6.1 heavy chain. Double-underlined is the leader sequence, underlined is the heavy chain variable region, (SEQ ID NO:22, which is the sequence ranging from the 20th to the 136th amino acid of SEQ ID NO:7) and underlined with a dashed line is the human IgG1 constant region.

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1  MELGLCWVFLVAILEGVOCEVOLVESGGGLVQPGGSLRLSCAASGFTFSS
51 YNMNVWRQAPGKGLEWVSYISSSSSTIYYADSVKGRFTISRDNAKNSLSL
101 QMNSLRDEDTAVYYCARAYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPS
151 SKSTSGGTAALGCLVKDYFPEPVTSWNSGALTSGVHTFPAVLQSSGLYS
201 LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPA
251 PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
301 VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
351 IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW
401 ESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEA
451 LHNHYTQKSLSLSPGK

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FIG. 1E: The amino acid sequence (SEQ ID NO:8) of Ha22-2(2,4)6.1 light chain. Double-underlined is the leader sequence, underlined is the light chain variable region (SEQ ID NO:23, which is the sequence ranging from the 23rd to the 130th amino acid of SEQ ID NO:8), and underlined with a dashed line is the human kappa constant region.

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1  MDMRVPAQLLGLLLWFPGSRCDIQMTQSPSSVSASVGDRVTITCRASQG
51 ISGWLAWYQQKPGKAPKFLIYAASTLQSGVPSRFGSGSGTDFTLTISL
101 QPEDFATYYCQQANSFPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSG
151 TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST
201 LTLTKADYEKKHKVYACEVTHQGLSSPVTKSFNRGEC

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FIG. 2: Efficacy of Ha22-2(2,4)6.1-vcMMAE in subcutaneous established human lung cancer xenograft AG-L4 in SCID mice

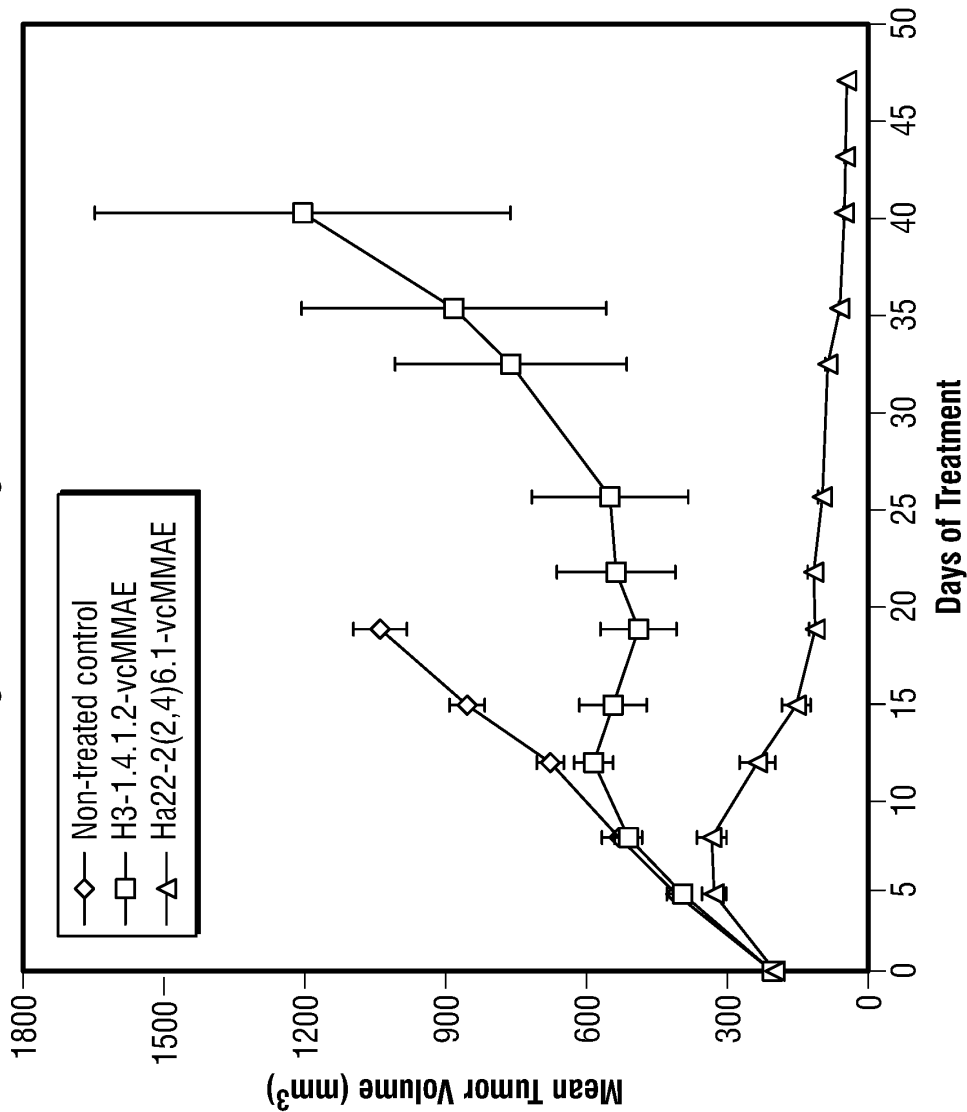
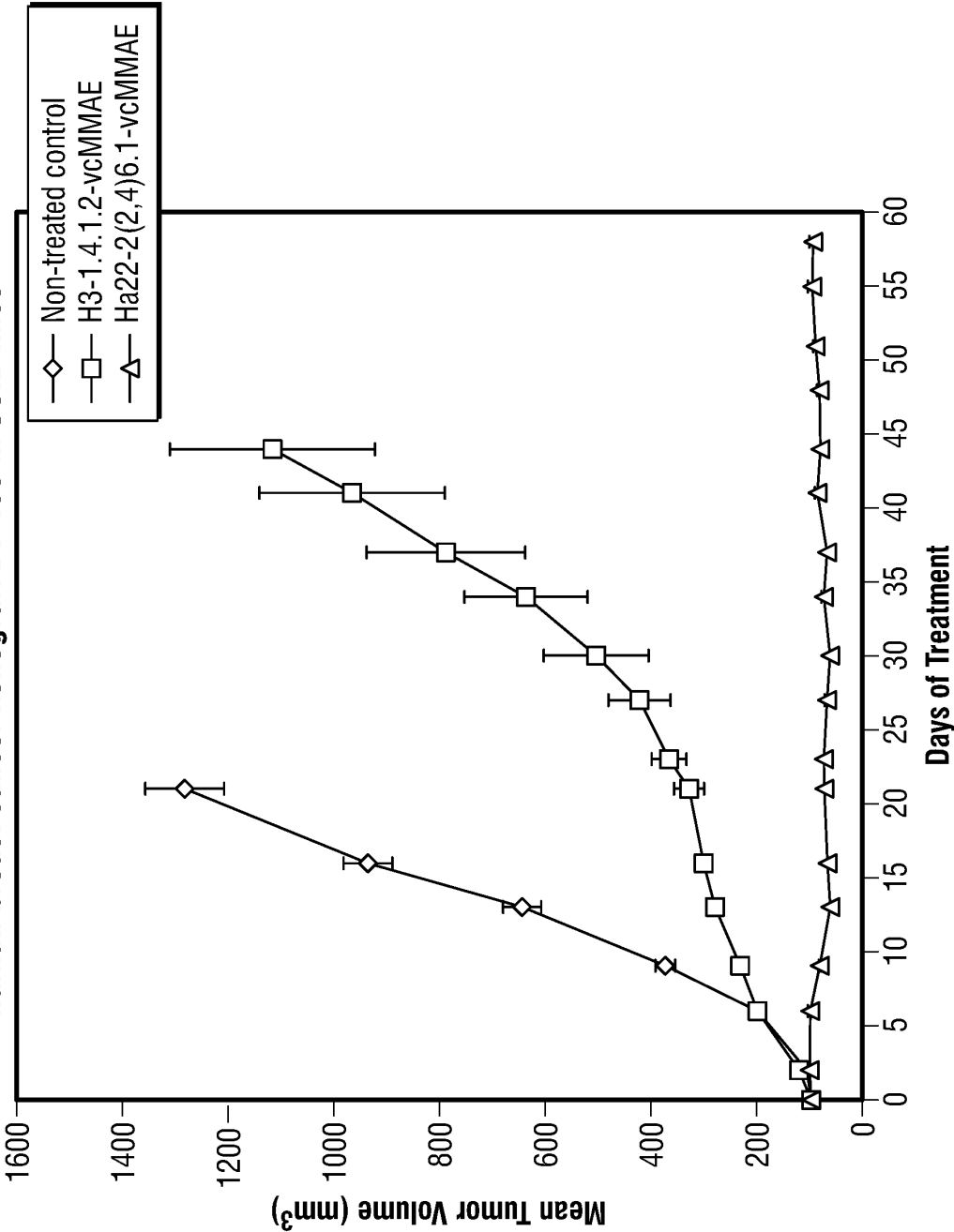


FIG. 3: Efficacy of Ha22-2(2,4)6.1-vcMMAE in subcutaneous established human breast cancer xenograft BT-483 in SCID mice



Breast cancer specimen

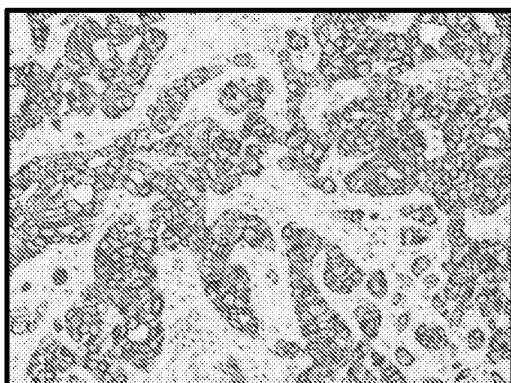


FIG. 4A

Breast cancer specimen



FIG. 4B

Lung cancer specimen

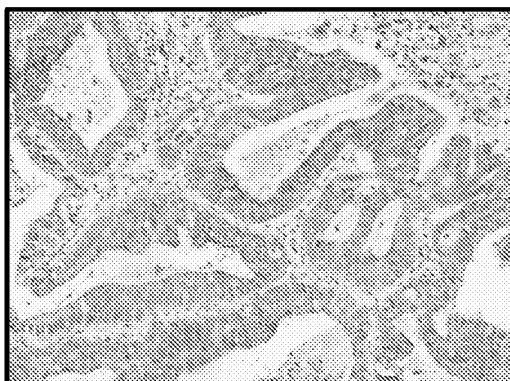


FIG. 4C

Lung cancer specimen

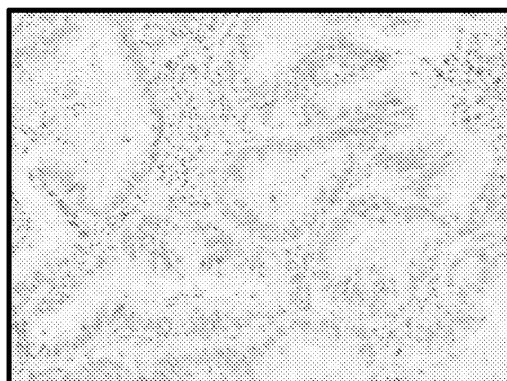


FIG. 4D

Esophageal cancer specimens

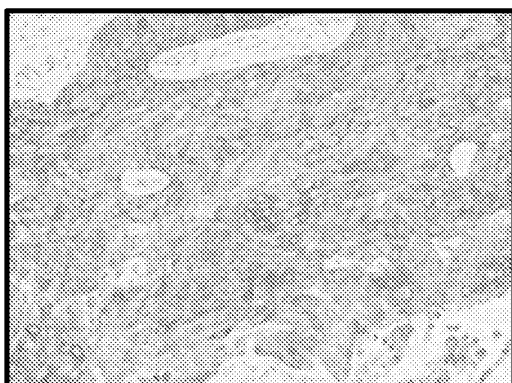


FIG. 4E

Esophageal cancer specimens



FIG. 4F

Head and neck cancer specimens

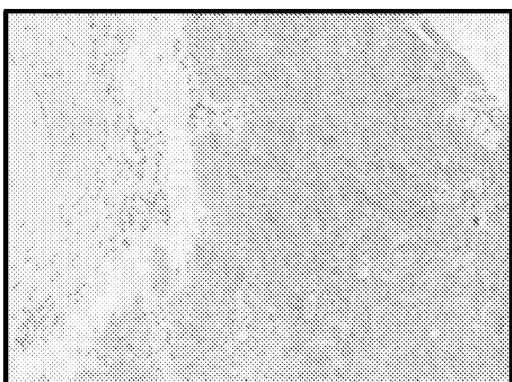


FIG. 4G

Head and neck cancer specimens

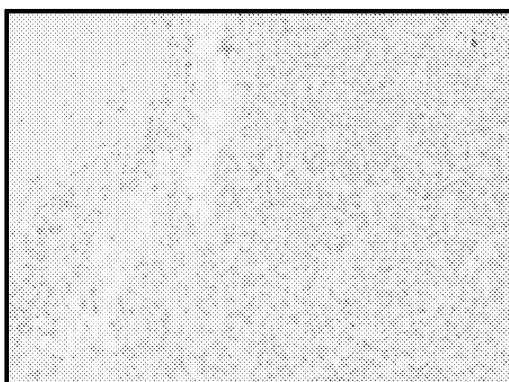


FIG. 4H