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- (54) **HER2 ANTIBODY COMPOSITION**
- (75) Inventors: **Yung-Hsiang Kao**, San Mateo, CA (US); **Martin Vanderlaan**, San Francisco, CA (US)
- (73) Assignee: **Genentech, Inc.**, South San Francisco, CA (US)
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- (56) **References Cited**
U.S. PATENT DOCUMENTS
- 4,968,603 A 11/1990 Slamon et al.
- 5,183,884 A 2/1993 Kraus et al.
- 5,480,968 A 1/1996 Kraus et al.
- 5,641,869 A 6/1997 Vandlen et al.
- 5,677,171 A 10/1997 Hudziak et al.
- 5,720,937 A 2/1998 Hudziak et al.
- 5,720,954 A 2/1998 Hudziak et al.
- 5,725,856 A 3/1998 Hudziak et al.
- 5,770,195 A 6/1998 Hudziak et al.
- 5,772,997 A 6/1998 Hudziak et al.
- 5,783,186 A 7/1998 Arakawa et al.
- 5,821,337 A 10/1998 Carter et al.
- 5,824,311 A 10/1998 Greene et al.
- 6,054,297 A 4/2000 Carter et al.
- 6,165,464 A 12/2000 Hudziak et al.
- 6,267,958 B1 7/2001 Andya et al.
- 6,339,142 B1 1/2002 Basey et al.
- 6,387,371 B1 5/2002 Hudziak et al.
- 6,399,063 B1 6/2002 Hudziak et al.
- 6,407,213 B1 6/2002 Carter et al.
- 6,627,196 B1 9/2003 Baughman et al.
- 6,639,055 B1 10/2003 Carter et al.
- 6,685,940 B2 2/2004 Andya et al.
- 6,719,971 B1 4/2004 Carter et al.
- 6,800,738 B1 10/2004 Carter et al.
- 6,821,515 B1 11/2004 Cleland et al.
- 6,949,245 B1* 9/2005 Sliwkowski 424/143.1
- 7,041,292 B1 5/2006 Sliwkowski
- 7,097,840 B2 8/2006 Erickson et al.
- 7,371,376 B1 5/2008 Fendly

- 7,371,379 B2 5/2008 Baughman et al.
- 2001/0014326 A1 8/2001 Andya et al.
- 2002/0001587 A1 1/2002 Erickson et al.
- 2003/0147884 A1 8/2003 Paton et al.
- 2003/0170234 A1 9/2003 Hellmann
- 2003/0202972 A1 10/2003 Andya et al.
- 2004/0037823 A9 2/2004 Paton et al.
- 2004/0037824 A1 2/2004 Baughman et al.
- 2004/0106161 A1 6/2004 Bossenmaier et al.
- 2004/0258685 A1 12/2004 Brunetta et al.
- 2005/0002928 A1 1/2005 Hellmann
- 2005/0208043 A1 9/2005 Adams et al.
- 2005/0238640 A1 10/2005 Sliwkowski
- 2005/0244417 A1 11/2005 Ashkenazi et al.
- 2006/0013819 A1* 1/2006 Kelsey 424/155.1
- 2006/0034840 A1 2/2006 Agus
- 2006/0034842 A1 2/2006 Adams et al.
- 2006/0073143 A1 4/2006 Adams et al.
- 2006/0083739 A1 4/2006 Sliwkowski
- 2006/0088523 A1 4/2006 Andya et al.
- 2006/0121044 A1 6/2006 Amler et al.
- 2006/0165702 A1 7/2006 Allison et al.
- 2006/0188509 A1 8/2006 Derynck et al.
- 2006/0193854 A1 8/2006 Adams et al.
- 2006/0198843 A1 9/2006 Adams et al.
- 2006/0204505 A1 9/2006 Sliwkowski et al.

(Continued)

FOREIGN PATENT DOCUMENTS

- EP 1308455 A2 5/2003

(Continued)

OTHER PUBLICATIONS

Agus et al., "Clinical Activity in a Phase I Trial of HER2-Targeted rhuMab 2C4 (pertuzumab) in Patients with Advanced Solid Malignancies" (Slides presented at the 2003 ASCO Annual Meeting) pp. 1-32 (2003).

(Continued)

Primary Examiner—Laura B Goddard
(74) *Attorney, Agent, or Firm*—Wendy M. Lee

(57) **ABSTRACT**

A composition comprising a main species HER2 antibody that binds to domain II of HER2, and an amino acid sequence variant thereof comprising an amino-terminal leader extension is disclosed. Pharmaceutical formulations comprising the composition, and therapeutic uses for the composition are also disclosed.

12 Claims, 23 Drawing Sheets

U.S. PATENT DOCUMENTS

| | | | |
|--------------|----|---------|-------------------|
| 2006/0210561 | A1 | 9/2006 | Baughman et al. |
| 2006/0216285 | A1 | 9/2006 | Adams et al. |
| 2006/0228745 | A1 | 10/2006 | Mass |
| 2006/0275305 | A1 | 12/2006 | Bryant |
| 2006/0275306 | A1 | 12/2006 | Andya et al. |
| 2007/0009976 | A1 | 1/2007 | Lenz et al. |
| 2007/0020261 | A1 | 1/2007 | Sliwkowski et al. |
| 2007/0026001 | A1 | 2/2007 | Ashkenazi et al. |
| 2007/0037228 | A1 | 2/2007 | Moecks et al. |
| 2007/0077243 | A1 | 4/2007 | Carter et al. |
| 2007/0166753 | A1 | 7/2007 | Mass |
| 2007/0184055 | A1 | 8/2007 | Sliwkowski |
| 2007/0202516 | A1 | 8/2007 | Mass |
| 2007/0224203 | A1 | 9/2007 | Friess et al. |
| 2007/0269429 | A1 | 11/2007 | Kelsey et al. |
| 2007/0292419 | A1 | 12/2007 | Hellmann |
| 2008/0038271 | A1 | 2/2008 | Amler et al. |
| 2008/0050373 | A1 | 2/2008 | Cohen |
| 2008/0050385 | A1 | 2/2008 | Friess et al. |
| 2008/0102069 | A1 | 5/2008 | Friess et al. |
| 2008/0112957 | A1 | 5/2008 | Fendly et al. |
| 2008/0112958 | A1 | 5/2008 | Mass |
| 2008/0160026 | A1 | 7/2008 | Ashkenazi et al. |

FOREIGN PATENT DOCUMENTS

| | | |
|----|--------------|------------|
| WO | WO 94/00136 | 1/1994 |
| WO | WO 94/22478 | 10/1994 |
| WO | WO 98/17797 | A1 4/1998 |
| WO | WO 00/69460 | A1 11/2000 |
| WO | WO 01/00238 | A1 1/2001 |
| WO | WO 03/087131 | A2 10/2003 |

OTHER PUBLICATIONS

Agus et al., "Efficacy and safety of single agent pertuzumab (rhuMAB 2C4), a HER dimerization inhibitor, in hormone refractory prostate cancer after failure of taxane-based therapy" *Journal of Clinical Oncology* (Abstract 4624 from the 41st Annual Meeting of ASCO) 23(16S):408s (Jun. 1, 2005).

Agus, D. et al., "Efficacy and safety of single agent pertuzumab (rhuMAB 2C4), a HER dimerization inhibitor, in hormone refractory prostate cancer after failure of taxane-based therapy" (Poster 4624 from the 41st Annual Meeting of the American Society of Clinical Oncology) (May 15, 2005).

Amler et al., "Identification of a predictive expression pattern for phosphorylated HER2 as a potential diagnostic marker for pertuzumab (Omnitarg) activity in ovarian cancer" (Poster 4497 presented at the Apr. 2006 American Association for Cancer Research Meeting) (Apr. 2006).

Bossenmaier et al., "Presence of HER2/HER3 heterodimers predicts antitumor effects of pertuzumab (Omnitarg) in different human xenograft models" *Proc Am Assoc Cancer Res.* (Abstract 5342) 45:1232 (Mar. 2004).

Cortes et al., "Open label, randomized, phase II study of pertuzumab (Omnitarg) in patients with metastatic breast cancer (MBC) with low expression of HER2" (Poster 3068 from the 41st Annual Meeting of the American Society of Clinical Oncology (ASCO)) (May 15, 2005).

Cortes et al., "Open label, randomized phase II study of pertuzumab (P) in patients (pts) with metastatic breast cancer (MBC) with low expression of HER2" *Journal of Clinical Oncology* (Abstract 3068 from the 41st Annual Meeting of ASCO) 23(16s):208s (Jun. 1, 2005).

de Bono et al., "An open label, phase II, multicenter study to evaluate the efficacy and safety of pertuzumab in chemotherapy-naive patients with Hormone-Refractory Prostate Cancer (HRPC)" (Poster 4609 from the 41st Annual Meeting of the American Society of Clinical Oncology (ASCO)) (May 15, 2005).

de Bono et al., "An open label, phase II, multicenter, study to evaluate

Journal of Clinical Oncology (Abstract 4609; 41st Annual Meeting of ASCO) 23(16S):405s (Jun. 1, 2005).

Friess et al., "Combination treatment with erlotinib and pertuzumab against human tumor xenografts is superior to monotherapy" *Clinical Cancer Research* 11(14):5300-5309 (Jul. 15, 2005).

Friess et al., "In vivo activity of recombinant humanized monoclonal antibody 2C4 in xenografts is independent of tumor type and degree of HER2 overexpression" *European Journal of Cancer* (Abstract 496 from the EORTC-NCI-AACR conference in Frankfurt, Germany Nov. 19-22, 2002.) 38(Suppl. 7):S149 (2002).

Gordon et al., "Clinical activity of pertuzumab (rhuMab 2C4) in advanced, refractory or recurrent ovarian cancer (OC), and the role of HER2 activation status" *Journal of Clinical Oncology* (Abstract #5051 from the 41st Annual Meeting of ASCO) 23(16S):467s (Jun. 1, 2005).

Gordon et al., "Clinical activity of pertuzumab (rhuMab 2C4) in advanced, refractory or recurrent ovarian cancer and the role of HER2 activation status" (Poster #5051 from the 41st Annual Meeting of the American Society of Clinical Oncology (ASCO)) (May 15, 2005).

Hasmann et al., "Pertuzumab (Omnitarg) Potentiates Antitumor Effects on NSCLS Xenografts without Increasing Toxicity when Combined with Cytotoxic Chemotherapeutic Agents" *American Association for Cancer Research* (Abstract #B213; supplement to *Clinical Cancer Research*) 9(16) (Dec. 1, 2003).

Nahta et al., "The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells" *Cancer Research* 64(7):2343-2346 (Apr. 1, 2004).

Spiridon et al., "Targeting multiple Her-2 epitopes with monoclonal antibodies results in improved antigrowth activity of a human breast cancer cell line in vitro and in vivo" *Clinical Cancer Research* 8(6):1720-1730 (Jun. 2002).

Vajdos et al., "Comprehensive functional maps of the antigen-binding site of an anti-ErbB2 antibody obtained with shotgun scanning mutagenesis" *Journal of Molecular Biology* 320(2):415-428 (Jul. 5, 2002).

Aasland et al., "Expression of Oncogenes in Thyroid Tumours: Coexpression of c-erbB2/neu and c-erbB" *British Journal of Cancer* 57(4):358-363 (Apr. 1988).

Agus et al., "Clinical Activity in a Phase I Trial of HER-2-Targeted rhuMAB 2C4 (pertuzumab) in Patients with Advanced Solid Malignancies (AST)" *Proceedings of the American Association for Cancer Research* (Abstract No. 771) 22:192 (2003).

Agus et al., "Targeting ligand-activated ErbB2 signaling inhibits breast and prostate tumor growth" *Cancer Cell* 2(2):127-137 (Aug. 2002).

Arteaga et al., "p185^{c-erbB-2} Signaling Enhances Cisplatin-induced Cytotoxicity in Human Breast Carcinoma Cells: Association Between an Oncogenic Receptor Tyrosine Kinase and Drug-induced DNA Repair" *Cancer Research* 54(14):3758-3765 (Jul. 15, 1994).

Bacus et al., "Differentiation of Cultured Human Breast Cancer Cells (AU-565 and MCF-7) Associated With Loss of Cell Surface HER-2/neu Antigen" *Molecular Carcinogenesis* 3(6):350-362 (1990).

Bacus et al., "Tumor-inhibitory Monoclonal Antibodies to the HER-2/Neu Receptor Induce Differentiation of Human Breast Cancer Cells" *Cancer Research* 52(9):2580-2589 (May 1, 1992).

Baselga and Mendelsohn, "Receptor Blockade With Monoclonal Antibodies As Anti-Cancer Therapy" *Pharmac. Ther.* 64:127-154 (1994).

Baselga et al., "Phase II Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients With HER2/neu-Overexpressing Metastatic Breast Cancer" *J. Clin. Oncol.* 14(3):737-744 (Mar. 1996).

Borst et al., "Oncogene Alterations in Endometrial Carcinoma" *Gynecologic Oncology* 38(3):364-366 (Sep. 1990).

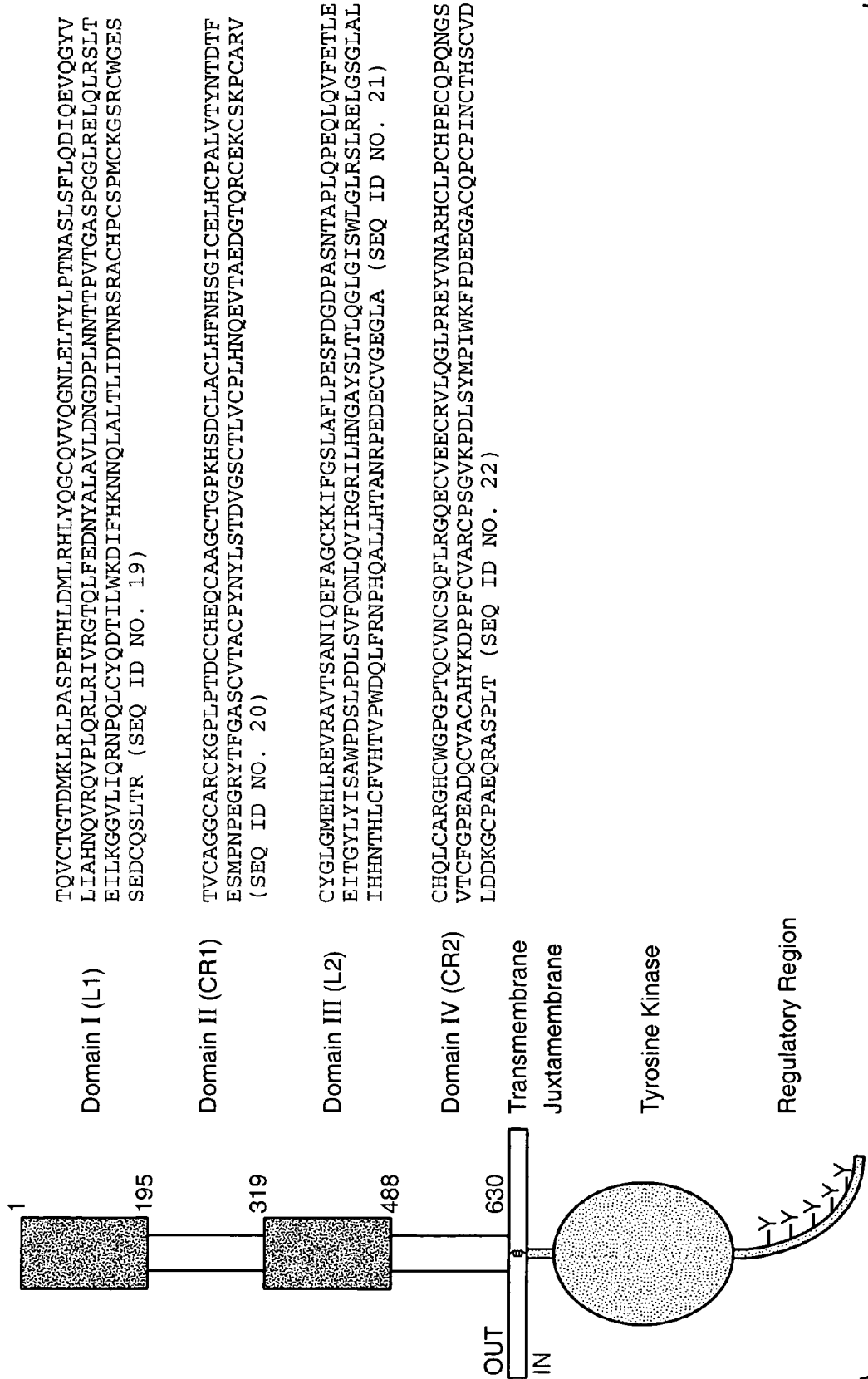
Carraway and Cantley, "A Neu Acquaintance for ErbB3 and ErbB4: A Role for Receptor Heterodimerization in Growth Signaling" *Cell* 78:5-8 (Jul. 15, 1994).

Carraway et al., "Neuregulin-2, A New Ligand of ErbB3/ErbB4-Receptor Tyrosine Kinases" *Nature* 387:512-516 (May 1997).

- Cohen et al., "Expression Pattern of the neu (NGL) Gene-Encoded Growth Factor Receptor Protein (p185^{neu}) in Normal and Transformed Epithelial Tissues of the Digestive Tract" *Oncogene* 4(1):81-88 (Jan. 1989).
- D'Souza and Taylor-Papadimitriou., "Overexpression of ERBB2 in Human Mammary Epithelial Cells Signals Inhibition of Transcription of the E-Cadherin Gene" *Proc. Natl. Acad. Sci. USA* 91(15):7202-7206 (Jul. 19, 1994).
- Drebin et al., "Down-Modulation of an Oncogene Protein Product and Reversion of the Transformed Phenotype by Monoclonal Antibodies" *Cell* 41(3):695-706 (Jul. 1985).
- Drebin et al., "Monoclonal Antibodies Reactive With Distinct Domains of the neu Oncogene-Encoded p185 Molecule Exert Synergistic Anti-Tumor Effects In Vivo" *Oncogene* 2:273-277 (1988).
- Earp et al., "Heterodimerization and Functional Interaction Between EGF Receptor Family Members: A New Signaling Paradigm With Implications For Breast Cancer Research" *Breast Cancer Res and Treatment* 35:115-132 (1995).
- Fendly, B.M. et al., "Characterization of Murine Monoclonal Antibodies Reactive to Either the Human Epidermal Growth Factor Receptor or HER2/neu Gene Product" *Cancer Research* 50:1550-1558 (Mar. 1, 1990).
- Fukushige et al., "Localization of a Novel v-erbB-Related Gene, c-erbB2, on Human Chromosome 17 and Its Amplification in a Gastric Cancer Cell Line" *Molecular & Cellular Biology* 6(3):955-958 (Mar. 1986).
- Groenen et al., "Structure-Function Relationships for the EGF/TGF- α Family of Mitogens" *Growth Factors* 11:235-257 (1994).
- Gu et al., "Overexpression of her-2/neu Human Prostate Cancer and Benign Hyperplasia" *Cancer Letters* 99:185-189 (1996).
- Guerin et al., "Overexpression of Either c-myc or c-erbB-2/neu Proto-Oncogenes in Human Breast Carcinomas: Correlation with Poor Prognosis" *Oncogene Res.* 3:21-31 (1988).
- Hancock et al., "A Monoclonal Antibody Against the c-erbB-2 Protein Enhances the Cytotoxicity of cis-Diamminedichloroplatinum Against Human Breast and Ovarian Tumor Cell Lines" *Cancer Research* 51:4575-4580 (Sep. 1, 1991).
- Harari et al., "Neuregulin-4: A Novel Growth Factor That Acts Through the ErbB-4 Receptor Tyrosine Kinase" *Oncogene* 18:2681-2689 (1999).
- Harris, Reed, "The Ideal Chromatographic Antibody Characterization Method" (Slides 1-36, IBC Antibody Production Conference, Feb. 13, 2002).
- Harwerth et al., "Monoclonal Antibodies Against the Extracellular Domain of the erbB-2 Receptor Function as Partial Ligand Agonists" *Journal of Biological Chemistry* 267(21):15160-15167 (Jul. 25, 1992).
- Holmes et al., "Identification of Heregulin, A Specific Activator of p185^{erbB2}" *Science* 256:1205-1210 (May 22, 1992).
- Hudziak et al., "p185^{HER2} Monoclonal Antibody Has Antiproliferative Effects In Vitro and Sensitizes Human Breast Tumor Cells to Tumor Necrosis Factor" *Molecular & Cellular Biology* 9(3):1165-1172 (Mar. 1989).
- Kasprzyk et al., "Therapy of an Animal Model of Human Gastric Cancer Using a Combination of Anti-erbB-2 Monoclonal Antibodies" *Cancer Research* 52(10):2771-2776 (May 15, 1992).
- Kern et al., "p185^{neu} Expression in Human Lung Adenocarcinomas Predicts Shortened Survival" *Cancer Research* 50(16):5184-5191 (Aug. 15, 1990).
- King et al., "Amplification of a Novel v-erbB-Related Gene in a Human Mammary Carcinoma" *Science* 229:974-976 (Sep. 1985).
- Klapper et al., "A Subclass of Tumor-Inhibitory Monoclonal Antibodies to ErbB-2/HER2 Blocks Crosstalk With Growth Factor Receptors" *Oncogene* 14:2099-2109 (1997).
- Kotts et al., "Differential Growth Inhibition of Human Carcinoma Cells Exposed to Monoclonal Antibodies Directed against the Extracellular Domain of the HER2/ERBB2 Protooncogene" In Vitro (Abstract #176) 26(3):59A (1990).
- Kraus et al., "Isolation and Characterization of ERBB3, A Third Member of the ERBB/Epidermal Growth Factor Receptor Family: Kumar et al., "Regulation of Phosphorylation of the c-erbB-2/HER2 Gene Product by a Monoclonal Antibody and Serum Growth Factor(s) in Human Mammary Carcinoma Cells" *Molecular & Cellular Biology* 11(2):979-986 (Feb. 1991).
- Lee, "Transforming growth factor alpha: expression, regulation, and biological activities" *Pharm. Rev.* 47(1):S1-85 (Mar. 1995).
- Lemke, G., "Neuregulins in Development" *Molecular and Cellular Neurosciences* 7:247-262 (1996).
- Levi et al., "The Influence of Heregulins on Human Schwann Cell Proliferation" *J. Neuroscience* 15(2):1329-1340 (Feb. 1995).
- Lewis et al., "Differential Responses of Human Tumor Cell Lines to Anti-p185^{HER2} Monoclonal Antibodies" *Cancer Immunol. Immunother.* 37:255-263 (1993).
- Lewis et al., "Growth Regulation of Human Breast and Ovarian Tumor Cells by Heregulin: Evidence for the Requirement of ErbB2 as a Critical Component in Mediating Heregulin Responsiveness" *Cancer Research* 56:1457-1465 (Mar. 15, 1996).
- Maier et al., "Requirements for the Internalization of a Murine Monoclonal Antibody Directed against the Her-2/neu Gene Product c-erbB-2" *Cancer Research* 51(19):5361-5369 (Oct. 1, 1991).
- Masui et al., "Growth Inhibition of Human Tumor Cells in Athymic Mice by Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies" *Cancer Research* 44(3):1002-1007 (Mar. 1984).
- McCann et al., "c-erbB-2 Oncoprotein Expression in Primary Human Tumors" *Cancer* 65(1):88-92 (Jan. 1, 1990).
- McKenzie et al., "Generation and Characterization of Monoclonal Antibodies Specific for the Human neu Oncogene Product, p185" *Oncogene* 4:543-548 (1989).
- Morrissey et al., "Axon-Induced Mitogenesis of Human Schwann Cells Involves Heregulin and p185^{erbB2}" *Proc. Natl. Acad. Sci. USA* 92:1431-1435 (Feb. 1995).
- Myers et al., "Biological Effects of Monoclonal Antireceptor Antibodies Reactive with neu Oncogene Product, p185^{neu}" *Methods in Enzymology* 198:277-290 (1991).
- Park et al., "Amplification, Overexpression, and Rearrangement of the erbB-2 Protooncogene in Primary Human Stomach Carcinomas" *Cancer Research* 49(23):6605-6609 (Dec. 1, 1989).
- Pietras et al., "Antibody to HER-2/neu Receptor Blocks DNA Repair After Cisplatin in Human Breast and Ovarian Cancer Cells" *Oncogene* 9:1829-1838 (1994).
- Plowman et al., "Heregulin Induces Tyrosine Phosphorylation of HER4/p180^{erbB4}" *Nature (Letters to Nature)* 366:473-475 (Dec. 2, 1993).
- Plowman et al., "Ligand-Specific Activation of HER4/p180^{erbB4}, A Fourth Member of the Epidermal Growth Factor Receptor Family" *Proc. Natl. Acad. Sci. USA* 90:1746-1750 (Mar. 1993).
- Porter, Jill, "The role of Analytical Comparability in the Global Approval of Zenapax" *Case Studies—Biotech Manufacturing Changes* (Slides 1-18, The 3rd International Conference: Strategic Use of Comparability Studies and Assays for Well Characterized Biologicals), Washington, D.C., Sep. 18-21, 2000.
- Reid et al., "Effects of Cell Culture Process Change on Humanized Characteristics" (Poster presented at WCBP 2003 conference in San Francisco, Jan. 7-10, 2003, p. 1).
- Ross et al., "HER-2/neu Gene Amplification Status in Prostate Cancer by Fluorescence in Situ Hybridization" *Hum. Pathol.* 28(7):827-833 (Jul. 1997).
- Ross et al., "Prognostic Significance of HER-2/neu Gene Amplification Status by Fluorescence In Situ Hybridization of Prostate Carcinoma" *Cancer* 79(11):2162-2170 (Jun. 1, 1997).
- Rouse et al., "Top Down Glycoprotein Characterization by High Resolution Mass Spectrometry and Its Application to Biopharmaceutical Development" (Slides 1-27, WCBP 2004 meeting, Washington DC, Jan. 6-9, 2004).
- Sadasivan et al., "Overexpression of Her-2/Neu May Be An Indicator of Poor Prognosis in Prostate Cancer" *J. Urol.* 150:126-131 (Jul. 1993).
- Sarup et al., "Characterization of an Anti-P185^{HER2} Monoclonal Antibody that Stimulates Receptor Function and Inhibits Tumor Cell Growth" *Growth Regulation* 1:72-82 (1991).
- Schaefer et al., "γ-Heregulin: A Novel Heregulin Isoform That is an

- Scott et al., "p185^{HER2} Signal Transduction in Breast Cancer Cells" *Journal of Biological Chemistry* 266(22):14300-14305 (Aug. 5, 1991).
- Shawver et al., "Ligand-Like Effects Induced by Anti-c-erbB-2 Antibodies Do Not Correlate with and Are Not Required for Growth Inhibition of Human Carcinoma Cells" *Cancer Research* 54(5):1367-1373 (Mar. 1, 1994).
- Shepard et al., "Monoclonal Antibody Therapy of Human Cancer: Taking the HER2 Protooncogene to the Clinic" *J. Clin. Immunol.* 11(3):117-127 (1991).
- Shields et al., "High Resolution Mapping of the Binding Site on Human IgG1 for C γ RI, Fc γ RII, Fc γ RIII, and FcRn and Design of IgG1 Variants with Improved Binding to the Fc γ R*" *Journal of Biological Chemistry* 276(9):6591-6604 (2001).
- Slamon et al., "Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/neu Oncogene" *Science* 235:177-182 (Jan. 9, 1987).
- Slamon et al., "Studies of the HER-2/neu Proto-Oncogene in Human Breast and Ovarian Cancer" *Science* 244:707-712 (May 12, 1989).
- Sliwkowski et al., "Coexpression of erbB2 and erbB3 Proteins Reconstitutes a High Affinity Receptor for Heregulin" *Journal of Biological Chemistry* 269(20):14661-14665 (May 20, 1994).
- Stancovski et al., "Mechanistic Aspects of the Opposing Effects of Monoclonal Antibodies to the ERBB2 Receptor on Tumor Growth" *Proc. Natl. Acad. Sci. USA* 88(19):8691-8695 (Oct. 1, 1991).
- Tagliabue et al., "Selection of Monoclonal Antibodies Which Induce Internalization and Phosphorylation of p185^{HER2} and Growth Inhibition of Cells With HER2/NEU Gene Amplification" *International Journal of Cancer* 47(6):933-937 (Apr. 1, 1991).
- Vitetta and Uhr, "Monoclonal Antibodies as Agonists: An Expanded Role for Their Use in Cancer Therapy" *Cancer Research* 54(20):5301-5309 (Oct. 15, 1994).
- Weiner et al., "Expression of the neu Gene-encoded Protein (P185^{neu}) in Human Non-Small Cell Carcinomas of the Lung" *Cancer Research* 50(2):421-425 (Jan. 15, 1990).
- Williams et al., "Expression of c-erbB-2 in Human Pancreatic Adenocarcinomas" *Pathobiology* 59(1):46-52 (1991).
- Wu et al., "Apoptosis Induced By an Anti-Epidermal Growth Factor Receptor Monoclonal Antibody in a Human Colorectal Carcinoma Cell Line and Its Delay By Insulin" *Journal of Clinical Investigation* 95(4):1897-1905 (Apr. 1995).
- Xu et al., "Antibody-Induced Growth Inhibition is Mediated Through Immunochemically and Functionally Distinct Epitopes on the Extracellular Domain of the c-erbB-2 (HER-2/neu) Gene Product p185" *International Journal of Cancer* 53(3):401-408 (Feb. 1, 1993).
- Yokota et al., "Amplification of c-erbB-2 Oncogene in Human Adenocarcinomas in Vivo" *Lancet* 1(8484):765-767 (Apr. 5, 1986).
- Yonemura et al., "Evaluation of Immunoreactivity for erbB-2 Protein as a Marker of Poor Short Term Prognosis in Gastric Cancer" *Cancer Research* 51(3):1034-1038 (Feb. 1, 1991).
- Zhang et al., "Neuregulin-3 (NRG3): A novel neural tissue-enriched protein that binds and activates ErbB4" *Proc. Natl. Acad. Sci. USA* 94:9562-9567 (Sep. 22, 1997).
- Zhou et al., "Amplification and Expression of the c0erb B-2/neu Proto-Oncogene in Human Bladder Cancer" *Molecular Carcinogenesis* 3(5):254-257 (1990).

* cited by examiner



TQVCTGTDMLRLPASPETHLDMRLHLYQGCQVQGNLELTYLPTNASLSFLQDIQEVQGYV
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FIG. 1

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