UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD., Petitioner,

v.

GENENTECH, INC., Patent Owner.

United States Patent No. 7,892,549
Title: Treatment with Anti-ErbB2 Antibodies

Case No.: IPR2017-01960

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,892,549

Mail Stop "PATENT BOARD"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, Virginia 22313-1450

TABLE OF CONTENTS

Page(s)

I. INTRODUCTION 1

II. MANDATORY NOTICES 2

A. 37 C.F.R. § 42.8(b)(1): Real Party-In-Interest 2

B. 37 C.F.R. § 42.8(b)(2): Related Matters 2

C. 37 C.F.R. § 42.8(b)(3) and (4): Lead and Back-Up Counsel 3

III. FEES (37 C.F.R. § 42.15(a)) 3

IV. REQUIREMENTS UNDER 37 C.F.R. § 42.104 4

A. Grounds for Standing (37 C.F.R. § 42.104(a)) 4

B. Statement of relief requested (37 C.F.R. § 42.104(b)) 4

V. THE LEVEL OF ORDINARY SKILL IN THE RELEVANT ART 7

VI. THE SCOPE AND CONTENT OF THE PRIOR ART 8

A. Chemotherapeutic Drug Combinations and Known Toxicity of Anthracyclines 8

B. Prior Art Cited in the Petition 9

1. Baselga ’97 9

2. Gelmon ’96 10

3. Drebin ’88 11

4. Presta ’97 11

5. Baselga ’96 12

6. Baselga ’94 13

VII. THE ’549 PATENT 13

VIII. CLAIM CONSTRUCTION 19

IX. DETAILED STATEMENT OF GROUNDS FOR UNPATENTABILITY 19

A. Ground 1: Claims 1-11 and 14-17 are unpatentable as obvious over Baselga '97 and Gelmon '96 25

1. Claim 1 25

a. Preamble: "A method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor, comprising" 25

b. Element [a]: "administering a combination of an antibody that binds ErbB2," 26

c. Element [b]: "a taxoid" 27

d. Element [c]: "and a further growth inhibitory agent" ... 27

e. Element [d]: "to the human patient" 29

f. Element [e]: "in an amount effective to end the time to disease progression in the human patient" 29

g. Element [f]: "wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular sequence" 31

h. Conclusion 31

2. Claim 2: "The method of claim 1 wherein the antibody is a humanized 4D5 anti-ErbB2 antibody." 32

3. Claim 3: "The method of claim 1 wherein the antibody crossblocks binding of 4D5 to the ErbB2 extracellular domain sequence." 32

4. Claim 4: "The method of claim 1 wherein the antibody binds to amino acid residues in the region from about residue 529 to about residue 625 of the ErbB2 extracellular domain sequence." 33

5. Claim 5 33

a. Preamble: "A method for the treatment of a human patient with breast cancer characterized by overexpression of ErbB2 receptor, comprising" 33

b. Element [a]: "administering an effective amount of a combination of an anti-ErbB2 antibody which binds

epitope 4D5 within the ErbB2 extracellular domain sequence,” 34

c. Element [b]: “a taxoid” 34

d. Element [c]: “and a further therapeutic agent,” 34

e. Element [d]: “to the human patient.” 35

f. Conclusion 35

6. Claim 6: “The method of claim 5 wherein the breast cancer is metastatic breast carcinoma.“ 35

7. Claim 7: “The method of claim 5 wherein the antibody is a humanized 4D5 anti-ErbB2 antibody.” 35

8. Claim 8: “The method of claim 7 wherein the antibody is administered as a 4 mg/kg dose and then weekly administration of 2 mg/kg.” 35

9. Claim 9: “The method of claim 5 wherein the taxoid is paclitaxel.” 37

10. Claim 10: “The method of claim 5 wherein efficacy is measured by determining the time to disease progression or the response rate.” 37

11. Claim 11: “The method of claim 5 wherein the further therapeutic agent is selected from the group consisting of . . . growth inhibitory agent.” 38

12. Claim 14: “The method of claim 5 wherein the further therapeutic agent is a growth inhibitory agent.” 38

13. Claim 15: “The method of claim 14 wherein the growth inhibitory agent is a DNA alkylating agent.” 38

14. Claim 16 38

a. Preamble: “A method for the treatment of a human patient with ErbB2 overexpression breast cancer, comprising” 38

b. Element [a]: "administering a combination of an antibody that binds epitope 4D5 within the ErbB2 extracellular domain sequence," 39

c. Element [b]: "a taxoid" 39

d. Element [c]: "and a further growth inhibitory agent," .. 39

e. Element [d]: "in the absence of an anthracycline derivative," 39

f. Element [e]: "to the human patient" 40

g. Element [f]: "in an amount effective to extend the time to disease progression in the human patient." 40

h. Conclusion 40

15. Claim 17: "The method of claim 16 wherein the breast cancer is metastatic breast carcinoma." 41

B. Ground 2: Claim 12 is unpatentable as obvious over Baselga '97 in view of Gelmon '96 and Drebin '88 41

C. Ground 3: Claim 13 is unpatentable as obvious over Baselga '97 in view of Gelmon '96 and Presta '97 42

D. Ground 4: Claims 1-11 and 14-17 are unpatentable as obvious over Baselga '96 in view of Baselga '94 and Gelmon '96 43

1. Claim 1 43

a. Preamble: "A method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor, comprising" 43

b. Element [a]: "administering a combination of an antibody that binds ErbB2," 44

c. Element [b]: "a taxoid" 45

d. Element [c]: "and a further growth inhibitory agent" ... 46

e. Element [d]: "to the human patient" 47

f. Element [e]: "in an amount effective to extend the time to disease progression in the human patient" 47

g. Element [f]: "wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular sequence" 48

h. Conclusion 49

2. Claim 2: "The method of claim 1 wherein the antibody is a humanized 4D5 anti-ErbB2 antibody." 50

3. Claim 3: "The method of claim 1 wherein the antibody crossblocks binding of 4D5 to the ErbB2 extracellular domain sequence." 50

4. Claim 4: "The method of claim 1 wherein the antibody binds to amino acid residues in the region from about residue 529 to about residue 625 of the ErbB2 extracellular domain sequence." 51

5. Claim 5 51

a. Preamble: "A method for the treatment of a human patient with breast cancer characterized by overexpression of ErbB2 receptor, comprising" 51

b. Element [a]: "administering an effective amount of a combination of an anti-ErbB2 antibody which binds epitope 4D5 within the ErbB2 extracellular domain sequence," 51

c. Element [b]: "a taxoid" 52

d. Element [c]: "and a further therapeutic agent," 52

e. Element [d]: "to the human patient." 52

f. Conclusion 53

6. Claim 6: "The method of claim 5 wherein the breast cancer is metastatic breast carcinoma." 53

7. Claim 7: "The method of claim 5 wherein the antibody is a humanized 4D5 anti-ErbB2 antibody." 53

8. Claim 8: "The method of claim 7 wherein the antibody is administered as a 4 mg/kg dose and then weekly administration of 2 mg/kg." 53

9. Claim 9: "The method of claim 5 wherein the taxoid is paclitaxel." 55

10. Claim 10: "The method of claim 5 wherein efficacy is measured by determining the time to disease progression or the response rate." 55

11. Claim 11: "The method of claim 5 wherein the further therapeutic agent is selected from the group consisting of . . . growth inhibitory agent." 55

12. Claim 14: "The method of claim 5 wherein the further therapeutic agent is a growth inhibitory agent." 56

13. Claim 15: "The method of claim 14 wherein the growth inhibitory agent is a DNA alkylating agent." 56

14. Claim 16 56

a. Preamble: "A method for the treatment of a human patient with ErbB2 overexpression breast cancer, comprising" 56

b. Element [a]: "administering a combination of an antibody that binds epitope 4D5 within the ErbB2 extracellular domain sequence," 57

c. Element [b]: "a taxoid" 57

d. Element [c]: "and a further growth inhibitory agent," .. 57

e. Element [d]: "in the absence of an anthracycline derivative," 57

f. Element [e]: "to the human patient" 58

g. Element [f]: "in an amount effective to extend the time to disease progression in the human patient." 58

h. Conclusion 58

15. Claim 17: "The method of claim 16 wherein the breast cancer is metastatic breast carcinoma." 59

E. Ground 5: Claim 12 is unpatentable as obvious over Baselga '96 in view of Baselga '94, Gelmon '96 and Drebin '88 59

F. Ground 6: Claim 13 is unpatentable as obvious over Baselga ’96 in view of Baselga ’94, Gelmon ’96, and Presta ’97 60

G. Secondary India do not support a finding of nonobviousness 61

X. CONCLUSION..... 65

TABLE OF AUTHORITIES

Page(s)

Cases

Hospira UK Ltd. v. Genentech Inc.,
Case No. A3 2015 3238, [2016] EWCA Civ 1185 (Nov. 30, 2016).....3

Hospira UK, Ltd. v. Genentech, Inc.,
Case No. HP-2014-000034, [2015] EWHC (HC) 1796 (Pat), (Jun. 24, 2015)
.....2

In re Woodruff,
919 F.2d 1575 (Fed. Cir. 1990) 36, 54

KSR Int'l Co. v. Teleflex, Inc.,
550 U.S. 398 (2007).....20

Pozzoli Spa v. BDMO SA & Anor.,
2007 WL 1685192, [2007] EWCA Civ. 588 (Jun. 22, 2007) 19

Rasmusson v. SmithKline Beecham Corp.,
413 F.3d 1318 (Fed. Cir. 2005) 23

Statutes

35 U.S.C. § 102.....5, 6

35 U.S.C. § 103..... 4, 5, 19

35 U.S.C. § 112.....23

35 U.S.C. § 311.....1

35 U.S.C. § 312.....1

35 U.S.C. § 313.....1

35 U.S.C. § 314.....1

35 U.S.C. § 315.....1, 4

35 U.S.C. § 316.....1

35 U.S.C. § 317 1

35 U.S.C. § 318 1

35 U.S.C. § 319 1

Rules

37 C.F.R. § 1.68 7

37 C.F.R. § 42 1

37 C.F.R. § 42.8 ..... 2, 3

37 C.F.R. § 42.10 1

37 C.F.R. § 42.15 3

37 C.F.R. § 42.100 19

37 C.F.R. § 42.104 4

MPEP 2144.06 22

MPEP 2159.01 4

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1001	U.S. Patent No. 7,892,549
1002	Assignment to Genentech, Inc. filed in U.S. Patent No. 7,846,441
1003	Eur. Patent Specification No. 1,037,926 B1
1004	*Hospira UK, Ltd. v. Genentech, Inc.*, Case No. HP-2014-000034, [2015] EWHC (CH) 1796 (Pat), (Jun. 24, 2015), Approved Judgment
1005	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*, 14(3) J. CLIN. ONCOL. 737–44 (1996) ("Baselga '96")
1006	Baselga *et al.*, *Anti-HER2 Humanized Monoclonal Antibody (MAb) Alone and in Combination with Chemotherapy Against Human Breast Carcinoma Xenografts*, 13 PROC. AM. SOC. CLIN. ONCOL. 63 (Abstract 53) (1994) ("Baselga '94")
1007	Baselga *et al.*, *HER2 Overexpression and Paclitaxel Sensitivity in Breast Cancer: Therapeutic Implications*, 11(3)(Suppl. 2) ONCOLOGY 43–48 (1997) ("Baselga '97")
1008	U.S. Patent No. 5,677,171
1009	Baselga *et al.*, *The Epidermal Growth Factor Receptor as a Target for Therapy in Breast Carcinoma*, 29(1) BREAST CANCER RESEARCH AND TREATMENT 127–38 (1994)
1010	Drebin *et. al*, *Monoclonal Antibodies Reactive with Distinct Domains of the Neu Oncogene-Encoded p185 Molecule Exert Synergistic Anti-Tumor Effects in Vivo*, 2(3) ONCOGENE 273–77 (1988) ("Drebin '88")
1011	Declaration of Allan Lipton, M.D., filed in connection with IPR 2017-00737
1012	Presta *et al.*, *Humanization of an Anti-Vascular Endothelial Growth Factor Monoclonal Antibody for the Therapy of Solid Tumors and Other Disorders*, 57(20) CANCER RESEARCH 4593–99 (1997) ("Presta '97")

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1013	Pegram *et al.*, *Phase II Study of Intra Venous Recombinant Humanized Anti-p185 HER-2 Monoclonal Antibody (rhuMAb HER-2) Plus Cisplatin in Patients with HER-2/neu Overexpressing Metastatic Breast Cancer*, 14 PROC. AM. SOC. CLIN. ONCOL. 106 (Abstract 124) (1995) ("Pegram '95")
1014	Nabholtz *et al.*, *Results of Two Open-Label Multicentre Pilot Phase II Trials with Herceptin® in Combination with Docetaxel and Platinum Salts (Cis-or Carboplatin) (TCH) as Therapy for Advanced Breast Cancer In Women with Tumors Over-Expressing HER2*, 64(1) BREAST CANCER RESEARCH AND TREATMENT 82 (Abstract 327) (2000) ("Nabholtz '00")
1015	Hudziak *et al.*, *p185^{HER2} Monoclonal Antibody has Antiproliferative Effects in Vitro and Sensitizes Human Breast Tumor Cells to Tumor Necrosis Factor*, 9(3) MOLECULAR AND CELLULAR BIOLOGY 1165–172, (1989) ("Hudziak '89")
1016	Carter *et al.*, *Humanization of an anti-p185^{HER2} antibody for human cancer therapy*, 89(10) PROC. NATL. ACAD. SCI. USA 4285–89 (1992) ("Carter '92")
1017	Phillips *et al.*, *Targeting HER2-Positive Breast Cancer with Trastuzumab-DM1, an Antibody–Cytotoxic Drug Conjugate*, 68(22) CANCER RES. 9280–90 (2008)
1018	Phillips *et al.*, *Dual Targeting of HER2-Positive Cancer with Trastuzumab Emtansine and Pertuzumab: Critical Role for Neuregulin Blockade in Antitumor Response to Combination Therapy*, 20(2) CLIN. CANCER RES. 456–68 (2014)
1019	Certified File History of U.S. Patent No. 7,892,549 (7 Volumes)
1020	U.S. Provisional Patent Application No. 60/069,346, Dec. 12, 1997
1021	U.S. Patent Application No. 09/208,649, Dec. 10, 1998
1022	Sorenson *et al.*, *Analysis of Events Associated with Cell Cycle Arrest at G2 Phase and Cell Death Induced by Cisplatin*, 82(9) J. NATL. CANCER INST. 749–55 (1990)
1023	Pietras *et al.*, *Antibody to HER-2/neu Receptor Blocks DNA Repair After Cisplatin in Human Breast and Ovarian Cancer Cells*, 9(7) ONCOGENE 1829–38 (1994)

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1024	Walpole *et al*., *The weight of nations: an estimation of adult human biomass*, 12:439 BMC PUBLIC HEALTH (2012) https://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-12-439
1025	Gelmon *et al.*, *Phase I/II Trial of Biweekly Paclitaxel and Cisplatin in the Treatment of Metastatic Breast Cancer*, 14(4) J. CLIN. ONCOL. 1185–91 (1996) ("Gelmon '96")
1026	Eur. Patent File History for EP 1,037,926 B1, *Decision to Revoke European Patent EP 1,037,926 B1 in Opposition Proceedings Before the European Patent Office in Munich on 02 May 2016*, Application No. 98,963,840.8 (Jun. 13, 2016)
1027	Declaration of Scott Weingaertner
1028	Reserved
1029	Reserved
1030	Reserved
1031	Declaration of Christopher Lowden
1032	U.S. Patent Application No. 09/208,649, Declaration of Mark Sliwkowski, Ph.D, Oct. 15, 2009
1033	Slamon *et al.*, *Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/neu Oncogene*, 235(4785) SCIENCE 177–82 (1987) ("Slamon '87")
1034	Slamon *et al.*, *Studies of the HER-2/neu Proto-Oncogene in Human Breast and Ovarian Cancer*, 244(4905) SCIENCE 707–12 (1989) ("Slamon '89")
1035	HERCEPTIN® (Trastuzumab) Development Timeline, *available at* https://www.gene.com/media/product-information/herceptin-development-timeline ("March 1997" entry)
1036	Nicolaou *et al.*, *Taxoids: New Weapons against Cancer*, 274(6) SCIENTIFIC AMERICAN 94–98 (1996) ("Nicolaou '96")
1037	DeVita *et al.*, *A History of Cancer Chemotherapy*, 68(21) CANCER RES. 8643–53 (2008)
1038	Reserved

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1039	Reserved
1040	Pegram *et al.*, *Monoclonal Antibody to HER-2/neu Gene Product Potentiates Cytotoxicity of Carboplatin and Doxorubicin in Human Breast Tumor Cells*, 33 PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, 442 (Abstract 2639) (1992) ("Pegram '92")
1041	Pegram *et al.*, *The Effect of HER-2/neu Overexpression on Chemotherapeutic Drug Sensitivity in Human Breast and Ovarian Cancer Cells*, 15(5) ONCOGENE 537–47 (1997) ("Pegram '97")
1042	Shan *et al.*, *Anthracycline-Induced Cardiotoxicity*, 125(1) ANN. INTERN. MED. 47–58, (1996) ("Shan '96")
1043	Mendelsohn *et al.*, *Epidermal Growth Factor Receptor Family and Chemosensitization*, 89(5) J. NATL. CANCER INSTITUTE 341–43 (1997) ("Mendelsohn '97")
1044	U.S. Environmental Protection Agency, National Center for Environmental Assessment (NCEA), Office of Research and Development (ORD), *Exposure Factors Handbook* (1997) https://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=503445
1045	Jones *et al.*, *Replacing the Complementarity-Determining Regions in a Human Antibody With Those From a Mouse*, 321(6069) NATURE 522–25 (1986) ("Jones '86")
1046	Declaration of Simon Cohen, filed in connection with IPR 2017-00737
1047	Miller *et al.*, *Reporting Results of Cancer Treatment*, 47(1) CANCER 207–14 (1981) ("Miller '81")
1048	Johnson *et al.*, *Food and Drug Administration Requirements for Approval of New Anticancer Drugs*, 69(10) CANCER TREATMENT REPORTS 1155–57 (1985)
1049	*Hospira UK Ltd. v. Genentech Inc.*, Case No. A3 2015 3238, [2016] EWCA Civ 1185, (Nov. 30, 2016), Approved Judgment
1050	Library of Congress Copyright Record for Baselga '96
1051	Library of Congress Copyright Record for Baselga '97

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1052	Library of Congress Copyright Record for Drebin '88
1053	Library of Congress Copyright Record for Presta '97
1054	Library of Congress Copyright Record for Hudziak '89
1055	Library of Congress Copyright Record for Carter '92
1056	Library of Congress Copyright Record for Gelmon '96
1057	Reserved
1058	Library of Congress Copyright Record for Slamon '87
1059	Library of Congress Copyright Record for Slamon '89
1060	Library of Congress Copyright Record for Nicolaou '96
1061	Library of Congress Copyright Record for Pegram '92
1062	Library of Congress Copyright Record for Shan '96
1063	Library of Congress Copyright Record for Mendelsohn '97
1064	Library of Congress Copyright Record for Jones '86
1065	Library of Congress Copyright Record for Miller '81
1066	1998 FDA Approved Label for Taxol®
1067	Drugs@FDA: FDA Approved Drug Products for TAXOL, http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo= 020262
1068	Pegram *et al.*, *Phase II Study of Receptor-Enhanced Chemosensitivity Using Recombinant Humanized Anti-p185$^{HER2/neu}$ Monoclonal Antibody Plus Cisplatin in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer Refractory to Chemotherapy Treatment*, 16(8) J. CLIN. ONCOL. 2659–71 (1998) ("Pegram '98")
1069	Library of Congress Copyright Record for Pegram '98
1070	Declaration of Professor Hilary Calvert

I. INTRODUCTION

Pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42, Petitioner Samsung Bioepis Co., Ltd. ("Bioepis" or "Petitioner") respectfully requests *inter partes* review ("IPR") of claims 10-17 (the "Challenged Claims") of U.S. Patent No. 7,892,549 ("'549 patent"), which is attached to this Petition as Exhibit 1001.[1] Concurrently filed with the petition is a power of attorney pursuant to 37 C.F.R. § 42.10(b).

The Challenged Claims are directed to a method of treating human patients with breast cancer that overexpress the ErbB2 receptor by administering, a combination of an anti-ErbB2 antibody, a taxoid, and a further growth inhibitory agent. This petition shows, by a preponderance of the evidence, that the Challenged Claims are unpatentable as obvious over the prior art.

A motion for joinder with IPR2017-00737 is being filed concurrently with this petition. For the sake of completeness and efficiency, the present petition is a practical copy of the petition in IPR2017-00737, which was instituted on July 27, 2017.

USPTO assignment records indicate that the '549 patent is assigned to Genentech, Inc. ("Genentech"). (*See* Ex. 1002)

[1] All references to exhibits, *e.g.*, "Exhibit" or "Ex.," are to the table of exhibits attached hereto as Petitioner's Exhibit List.

II. MANDATORY NOTICES

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

Bioepis is the Real Party in Interest. Bioepis is a corporation organized and existing under the laws of the Republic of Korea, having its principal place of business at 107, Cheomdan-daero, Yeonsu-gu, Incheon 21987, Republic of Korea.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

Bioepis is unaware of any litigation related to the '549 patent.

Bioepis is aware of three previously filed IPR petitions related to the '549 patent. Hospira, Inc. filed IPR 2017-00737 and IPR2017-00739 on January 20, 2017. IPR2017-00737 was instituted on July 27, 2017. Celltrion, Inc. subsequently filed IPR2017-01122 on March 21, 2017, which is active and awaiting an institution decision.

EP 1,037,926 B1 (the "EP '926 patent", Ex. 1003),[2] a European patent within the same family as the '549 patent, was recently invalidated and revoked in two separate European proceedings as obvious in light of certain references asserted here. *Hospira UK, Ltd. v. Genentech, Inc.*, Case No. HP-2014-000034, [2015] EWHC (HC) 1796 (Pat), (Jun. 24, 2015), Approved Judgment (Ex. 1004); *Decision to Revoke European Patent EP 1,037,926,* Application No. 98,963,840.8

[2] The EP '926 patent and the '549 patent both claim priority to U.S. Provisional Application No. 60/069,346.

(Jun. 13, 2016) (Ex. 1026). The judgment of the UK Court was affirmed on appeal. *Hospira UK Ltd. v. Genentech Inc.*, Case No. A3 2015 3238, [2016] EWCA Civ 1185 (Nov. 30, 2016), Approved Judgment (Ex. 1049).

Bioepis is not aware of any other judicial or administrative matters that would affect, or be affected by, a decision in the proceeding.

C. Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3) and (4))

Bioepis designates the following counsel:

Lead Counsel	Backup Counsel
Dimitrios T. Drivas White & Case LLP 1221 Avenue of the Americas New York, New York 10020 Tel: (212) 819-8200 Fax: (212) 354-8113 ddrivas@whitecase.com USPTO Reg. No. 32,218	Scott T. Weingaertner White & Case LLP 1221 Avenue of the Americas New York, New York 10020 Tel: (212) 819-8200 Fax: (212) 354-8113 scott.weingaertner@whitecase.com USPTO Reg. No. 37,756

Please address all correspondence to lead and backup counsel. Bioepis consents to service by email at the following addresses: ddrivas@whitecase.com and scott.weingaertner@whitecase.com.

III. FEES (37 C.F.R. § 42.15(A))

Bioepis authorizes the United States Patent and Trademark Office to charge the fees enumerated in 37 C.F.R. § 42.15(a) regarding this Petition and any

additional fees that may be due in connection with this Petition from Deposit Account No. 50-3672.

IV. REQUIREMENTS UNDER 37 C.F.R. § 42.104

A. Grounds for Standing (37 C.F.R. § 42.104(a))

Bioepis certifies that the '549 patent is available for IPR and that Bioepis is not barred or estopped from requesting IPR on the grounds identified herein. 35 U.S.C. § 315.

B. Statement of relief requested (37 C.F.R. § 42.104(b))

The '549 patent application was filed on February 3, 2003, and therefore this Petition is governed by pre-AIA 35 U.S.C. § 103. *See* MPEP 2159.01. Pursuant to 37 C.F.R. §§ 42.104(b)(1) and (2), Petitioner requests review of the Challenged Claims on the following grounds:

Ground	Proposed Statutory Rejections for the '549 Patent
1	**Baselga '97 (Ex. 1007)** in view of **Gelmon '96 (Ex. 1025)** renders obvious claims 1–11 and 14–17 under 35 U.S.C. § 103.
2	**Baselga '97 (Ex. 1007)** in view of **Gelmon '96 (Ex. 1025)** and **Drebin '88 (Ex. 1010)** renders obvious claim 12 under 35 U.S.C. § 103.
3	**Baselga '97 (Ex. 1007)** in view of **Gelmon '96 (Ex. 1025)** and **Presta '97 (Ex. 1012)** renders obvious claim 13 under 35 U.S.C. § 103.

Ground	Proposed Statutory Rejections for the '549 Patent
4	**Baselga '96 (Ex. 1005)** in view of **Baselga '94 (Ex. 1006)** and **Gelmon '96 (Ex. 1025)** renders obvious claims 1–11 and 14–17 under 35 U.S.C. § 103.
5	**Baselga '96 (Ex. 1005)** in view of **Baselga '94 (Ex. 1006), Gelmon '96 (Ex. 1025)** and **Drebin '88 (Ex. 1010)** renders obvious claim 12 under 35 U.S.C. § 103.
6	**Baselga '96 (Ex. 1005)** in view of **Baselga '94 (Ex. 1006), Gelmon '96 (Ex. 1025)** and **Presta '97 (Ex. 1012)** renders obvious claim 13 under 35 U.S.C. § 103.

The cited prior art is as follows:[3]

- **Baselga '97.** Baselga *et al*., 11(3) (Suppl. 2) ONCOLOGY 43–48 (1997) (Ex. 1007) is prior art under 35 U.S.C. § 102(a) published March 1, 1997 bearing a Health Sciences Libraries stamp date of April 24, 1997.

[3] Additional evidence authenticating various exhibits is provided in the Declarations of Scott Weingaertner (Ex. 1027), Christopher Lowden (Ex. 1031), and Simon Cohen (Ex. 1046). The Lowden and Cohen declarations are exact copies of the documents submitted in IPR2017-00737.

- **Baselga '96.** Baselga *et al.*, 14(3) J. CLIN. ONCOL. 737–44 (1996) (Ex. 1005) is prior art under 35 U.S.C. § 102(b) published March 1996 bearing a Biomedical Library, UC San Diego, stamp date of March 13, 1996.
- **Baselga '94.** Baselga *et al.*, 13 PROC. AM. SOC. CLIN. ONCOL. 63 (Abstract 53) (1994) (Ex. 1006) is prior art under 35 U.S.C. § 102(b) published March, 1994 bearing a Health Sciences Library stamp date of September 20, 1994.
- **Gelmon '96.** Gelmon *et al.*, 14(4) J. CLIN. ONCOL. 1185–91 (1996) (Ex. 1025) is prior art under 35 U.S.C. § 102(b) published on April 1, 1996 accessible to the public more than one year prior to the earliest effective filing date of the '549 patent.
- **Drebin '88.** Drebin *et al.*, 2(3) ONCOGENE 273–77 (1988) (Ex. 1010) is prior art under 35 U.S.C. § 102(b) published March 1988 accessible to the public more than one year prior to the earliest effective filing date of the '549 patent.
- **Presta '97.** Presta *et al.*, 57(20) CANCER RES. 4593–99 (1997) (Ex. 1012) is prior art under 35 U.S.C. § 102(a) published on October 15, 1997 accessible to the public prior to the earliest effective filing date of the '549 patent.

Below is a detailed explanation of the grounds for the unpatentability of each claim. Additional evidence supporting each ground is provided in the

Declaration of Allan Lipton, M.D. (Ex. 1011),[4] the Declaration of Professor Hilary Calvert (Ex. 1070), and other supporting exhibits. 37 C.F.R. § 1.68. As detailed below, Bioepis is reasonably likely to prevail with respect to at least one claim.

V. THE LEVEL OF ORDINARY SKILL IN THE RELEVANT ART

A person of ordinary skill in the art ("POSA") is presumed to be aware of all pertinent art, think along the lines of conventional wisdom, and possess ordinary creativity in the pertinent field. A POSA at the time of the alleged invention would be a clinical or medical oncologist with experience with breast cancer research or clinical trials. (Ex. 1011 ¶¶ 15–17; Ex. 1070 ¶¶ 11-13; Ex. 1004 ¶¶ 29–31) The Challenged Claims would be obvious even if the level of ordinary skill in the art were lower.

[4] Exhibit 1011 is an exact copy of the declaration submitted by Dr. Lipton in IPR2017-00737. This declaration is cited here to avoid unnecessary cost and to advance efficiency. As mentioned above, this petition is presented along with a motion to join IPR2017-00737, and by using the same declaration, Bioepis has eliminated the need for analysis of another declaration or a new expert report. To the extent Dr. Lipton becomes unavailable in IPR2017-00737, however, Bioepis will rely upon the Declaration of Professor Hilary Calvert.

VI. THE SCOPE AND CONTENT OF THE PRIOR ART

A. Chemotherapeutic Drug Combinations and Known Toxicity of Anthracyclines

Since the 1960s, clinical oncologists used combination chemotherapies. (Ex. 1037 at 12–14; Ex. 1011 ¶¶ 28–31; Ex. 1070 ¶¶ 23-26) Higher treatment intensity (more exposure to different drugs over a shorter period of time) has resulted in greater tumor killing before cancer gains adaptive immunity. (*Id*.) In breast cancer, beginning with "CMF"—or cyclophosphamide, methotrexate, 5-fluorouracil—treatment, these combination therapies improved treatment through the 1980s. (Ex. 1037 at 14; Ex. 1011 ¶¶ 30–31; Ex. 1070 ¶¶ 25-26) When rhuMAb HER2 was created, oncologists had over 20 years of experience showing combination therapies were superior to single-agent therapies. (*See* Ex. 1011 ¶¶ 32, 43; Ex. 1070 ¶¶ 27, 38; Ex. 1015 at 8; Ex. 1040 at 5; Ex. 1041 at 6)

Anthracyclines are common first-line chemotherapeutic agents for breast cancer. (Ex. 1007 at 10; Ex. 1042 at 4, 12; Ex. 1011 ¶ 33; Ex. 1070 ¶ 28]) These drugs are effective, but cardiotoxic. By the mid-1990s, POSAs understood that cardiotoxicity was cumulative irrespective of the time between treatments. (Ex. 1042 at 5) It is unsurprising, then, that researchers were using several rhuMAb HER2 combination regimens without anthracyclines. (*See* Ex. 1013 at 5 (rhuMAb HER2 plus cisplatin); Ex. 1006 at 4 (rhuMAb HER2 plus paclitaxel); 1007 at 10 (rhuMAb HER2 plus paclitaxel); Ex. 1011 ¶ 33; Ex. 1070 ¶ 28)

B. Prior Art Cited in the Petition

1. Baselga '97

Baselga '97 teaches that 25-30% of malignant breast cancer tumors overexpress the ErbB2 receptor. (Ex. 1007 at 6) Based on this, researchers generated a monoclonal mouse antibody, 4D5, against the ErbB2 receptor, which demonstrated growth inhibition against tumor cells and in xenograft tumor models. (*Id.* at 7)

The 4D5 antibody was humanized (rhuMAb HER2) and used in phase II clinical trials. (*Id.* at 9) The overall response rate was 11.6%, and minor responses or stable disease occurred in an additional 37% of patients. (*Id.*) Baselga '97 concludes that "rhuMoAb HER2 is clinically active in patients who have metastatic breast cancers that overexpress HER2 and have received extensive prior therapy." (*Id.*)

Baselga '97 further teaches that in human breast cancer cell culture and in tumor xenografts in nude mice, the 4D5 antibody combined with paclitaxel "resulted in major antitumor activity." (*Id.*) The synergistic effect (>90% growth inhibition) was substantial as each of the 4D5 antibody and paclitaxel produced only 35% growth inhibition alone. (*Id.*) The result with paclitaxel was also "markedly better than an equipotent dose of doxorubicin…and 4D5 (70% inhibition)." (*Id.*)

Baselga ’97 teaches that the results from preclinical experiments and the phase II trials were encouraging and “led to the design of a phase III multinational study of chemotherapy in combination with rhuMoAb HER2 in patients with HER2-overexpressing breast tumors” that was underway. (*Id.* at 10) In the trial, patients received either rhuMAb HER2 plus chemotherapy, or chemotherapy alone. (*Id.*) A clinical endpoint was “to determine whether the addition of this anti-HER2 antibody increases the time to disease progression compared with the group of patients treated with [chemotherapy] alone.”[5] (*Id.*; Ex. 1011 ¶ 57; Ex. 1070 ¶ 52) Baselga ’97 notes that “[b]ecause anthracyclines are widely used in the adjuvant setting, it is likely that a significant number of patients will be treated with paclitaxel.” (Ex. 1007 at 10)

2. Gelmon ’96

Gelmon ’96 reports the results of a phase I/II clinical trial using biweekly combined treatment with paclitaxel and cisplatin in treating metastatic breast cancer. (Ex. 1025 at 9) Phase II studies of paclitaxel as a single agent had demonstrated response rates between 17–62%. (*Id.*) Gelmon ’96 states that its

[5] Figure 2 and the remainder of the article show that the control group consisted of “cytotoxic chemotherapy alone”—the statement “antibody alone” is a typographical error. (Ex. 1007 at 10, Fig. 2; Ex. 1011 ¶ 57 n.5; Ex. 1070 ¶ 52 n.4)

authors "were [ ] interested in combining [paclitaxel] with a non-cross-resistant drug with a different spectrum of toxicity[, and c]isplatin seemed to be an appropriate choice." (*Id.*) Gelmon '96 reports that 85% of the patients available for assessment showed a response. (*Id.* at 13) The median time to disease progression was 7.9 months for the responding patients. (*Id.*)

3. Drebin '88

Drebin '88 discusses experiments involving antibodies against the ErbB2 receptor. (Ex. 1010) The authors tested several antibodies in xenograft models including combinations of antibodies "reactive with two distinct regions on the p185 molecule." (*Id* at 4) Such antibody combinations "resulted in synergistic anti-tumor effects and complete eradication of tumors." (*Id.*)

4. Presta '97

Presta '97 discloses a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). (Ex. 1012 at 8) VEGF is a cytokine promoting angiogenesis (the growth of new blood vessels). (*Id.*) It is implicated in cancer and is upregulated in nearly every human tumor. (*Id.* at 13) Presta '97 teaches that antibodies capable of interfering with the action of VEGF are pursued as a strategy for mitigating uncontrolled tumor angiogenesis. (*Id.* at 8) Presta '97 reports a line of humanized murine antibodies that were tested in preclinical models—the *in vivo* preclinical testing revealed substantial tumor growth inhibition. (*Id.* at 11)

5. Baselga '96

Baselga '96 reports the results of a phase II clinical trial in patients with ErbB2-overexpressing metastatic breast cancer. (Ex. 1005 at 9)

Baselga '96 teaches that after successful experiments in mouse models, the 4D5 anti-ErbB2 antibody was humanized (rhuMAb HER2) and used in a phase II clinical trial. (*Id.* at 9–10) Baselga '96 teaches a loading dose of 250 mg followed by ten weekly 100 mg doses. *Id.* at 10. The target minimum effective concentration in blood plasma was greater than 10 μg/mL. (*Id.*) And "[s]erum levels of rhuMAb HER2 as a function of time were analyzed for each patient using a one-compartment model." (*Id.*)

Baselga '96 teaches that more than 90% of the study participants "had rhuMAb HER2 trough levels above the targeted 10 μg/mL level." (*Id.* at 11) "Toxicity [from the antibody] was minimal," and no immune response against the antibody was detected. (*Id.* at 9) Of the evaluated patients, one had complete remission and four had partial remissions. (*Id.* at 13) In addition, 14 patients had stable disease at the conclusion of the study. (*Id.* at 9) "The median time to progression for the patients with either minor or stable disease was 5.1 months." (*Id.* at 12) Baselga '96 notes that "[t]he unusually long durations of minimal responses and stable disease seen in [the] clinical trial" may be indicative of the cytostatic effects of the antibody. (*Id.* at 13) Accordingly, experimental measures

such as time to disease progression—a metric used in the clinical setting since the 1980s—are especially appropriate in assessing treatment efficacy. (*See* Ex. 1047 at 12; Ex. 1048 at 6)

Baselga '96 also teaches that "[i]n preclinical studies…rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity." Ex. 1005 at 15. As a result, "[l]aboratory studies of the mechanism of this effect and clinical trials of such combination therapy [we]re [] in progress." (*Id.*)

6. Baselga '94

Baselga '94 reports the results of experiments using a mouse xenograft tumor model. (Ex. 1006 at 4) HER2 overexpressing tumors were grown in mice followed by treatment with the 4D5-antibody in combination with paclitaxel. (*Id.*) While the antibody or paclitaxel alone produced 35% growth inhibition, the combination of the two resulted in 93% growth inhibition without increasing toxicity. (*Id.*) Baselga '94 teaches that clinical trials of this drug combination were already underway. (*Id.*)

VII. THE '549 PATENT

As the '549 patent explains, before the alleged invention, an antibody known as humanized 4D5, rhuMAb HER2, or trastuzumab, was well-known as a breast cancer treatment. (*See, e.g.* Ex. 1001 at 1:23–32 (citing Ex. 1033; Ex. 1034); Ex.

1007 at 6; Ex. 1005 at 9; Ex. 1008 at 20:15–20) The antibody, commercially known as Herceptin®, had been characterized and used in humans with breast cancer overexpressing the ErbB2 receptor. (Ex. 1001 at 2:20–31, 3:36–42 (citing Ex. 1005 as showing "HERCEPTIN®" to be "clinically active in patients with ErbB2-overexpressing metastatic breast cancers" including prior paclitaxel treatment); *see also* Ex. 1016 at 10; Ex. 1005 at 9–10) Paclitaxel was also a well-known treatment for breast cancer. (*See* Ex. 1066 at 10; Ex. 1067)

Genentech Never Performed the Subject Matter Claimed in the '549 Patent

The '549 patent concerns "the treatment of disorders characterized by the overexpression of ErbB2," including "cancer" with "a combination of an anti-ErbB2 antibody and a chemotherapeutic agent other than an anthracycline." Other than claims 16–17, the claims do not exclude anthracycline derivatives. The claims require an anti-ErbB2 antibody, a taxoid, and either "a further growth inhibitory agent" or a "further therapeutic agent" administered "in an amount effective to extend the time to disease progression in [a] human patient." (Ex. 1001 at claims 1, 5, 16)

There is no data in the '549 patent showing the inventors attempted the claimed three-drug combination before filing their application and thus no data disclosing what "an amount effective" means. The sole Example uses an anti-

ErbB2 antibody in combination with a taxoid as one of the two tested combinations with no third agent administered. (*See id.* at 28:17–23)

Prosecution of the '549 patent

There are two significant events in the '549 patent's prosecution:

(1) Genentech argued for an earlier priority of its parent application to antedate the Nabholtz reference discussed below, and

(2) Genentech submitted a declaration from Mark Sliwkowski, arguing that the combination of rhuMAb HER2 plus a taxoid demonstrated unexpected results.

The '549 patent issued from U.S. Patent Application No. 10/356,824 (the "'824 application"). (*See* Ex. 1019–1:2[6]) The '824 application claims priority to U.S. Patent Application No. 09/208,649 (the "'649 application") (Ex. 1021) which itself claims priority to U.S. Provisional Patent Application No. 60/069,346 (the "'346 application") (Ex. 1020), filed on December 12, 1997. (Ex. 1019–1:7)

The '549 patent began as a continuation of the '649 application. The originally filed claims recited both two-and three-drug combinations involving anti-ErbB2 antibodies and chemotherapeutic agents including taxoids. (*Id.* at 1:51–53) Genentech dropped the claims to two-drug combinations in response to a

[6] Citations to Ex. 1019 are in the format: volume:page.

restriction requirement. (*Id.* at 5:19–23) Between that time and 2011, when the '549 patent issued, the claims of the '824 application were rejected six times.

The Examiner's initial Office Action provided five grounds for rejection, including one over Nabholtz *et al.* (64(1) BREAST CANCER RESEARCH AND TREATMENT 82 (Abstract 327) (2000) ("Nabholtz")) (Ex. 1014). *Id.* at 5:36–43. The Examiner reasoned that Nabholtz was prior art because the remaining claims of the '824 application were not entitled to the earlier priority date of the '346 application. (*Id.* at 5:41–42)

In an attempt to overcome this rejection, Genentech pointed to the following places in its '649 application purportedly disclosing the claimed elements of the three-drug combination:

- The reference to plural "chemotherapeutic regimens" and "agents";
- A statement that "[t]he formulation herein may also contain more than one active compound…preferably those with complementary activities that do not adversely affect each other";
- A statement that "[i]t may be desirable to also administer antibodies against other tumor associated antigens…one or more cytokines…[or, preferably,] a growth inhibitory agent";
- "The present invention…is based on the recognition that while treatment with anti-ErbB2 antibodies markedly enhances the clinical

> benefit of the use of chemotherapeutic agents in general, a syndrome of myocardial dysfunction that has been observed as a side-effect of anthracycline derivatives is increased by the administration of anti-ErbB2 antibodies."

(*See id.* at 5:179–81 (citing Ex. 1021 at 20 (16:11–24), at 39 (35:6–14), at 41 (37:9–18), at 9 (5:14–17))) Relying on these "disclosures," Genentech argued a POSA "would understand that the presently claimed combinations…were clearly contemplated and described therein." (*Id.* at 5:181) Genentech further cited an article by Drs. Daniel and Roger Herzig for the notion that "combinations of two or more chemotherapeutic agents were well known in the art at the time the above application was filed in 1997." (*Id.* at 5:180, 5:228–38)

The Examiner maintained the rejection over Nabholtz and additionally issued obviousness rejections over a series of references including Baselga '96 and '94 for the remaining claims. (*Id.* at 5:265–69) In response, Genentech argued, based on a declaration by inventor Dr. Susan Hellmann, that mouse models are not predictive of clinical results in breast cancer, and the combination of paclitaxel and rhuMAb HER2 was "surprisingly synergistic" in humans. (*Id.* at 5:308–13)

On June 26, 2008, the Examiner withdrew the rejection based on Nabholtz, finding that "the claims have priority to parent application 60/069,346 (filed 12/12/1997)." (*Id.* at 6:245) The Examiner continued to reject the claims as

obvious over a number of references, including Baselga '96 and on other grounds. Genentech had a call with the Examiner on August 25, 2009 and followed this call by filing Dr. Sliwkowski's Declaration. (*Id.* at 6:329–7:38) This Declaration did not differ in substance from the Declaration by Dr. Sliwkowski filed in the '649 application. (Ex. 1032) His Declaration argued that:

(1) a POSA would not have had a reasonable expectation of success combining anti-ErbB2 antibodies with taxoids because the two treatments result in cell cycle arrest at different and incompatible points in the cell cycle, and

(2) data based on xenograft mouse models is not sufficiently predictable to provide a POSA with a reasonable expectation of success.

(Ex. 1019–6:343–44) Genentech's arguments reiterated and cited to the statements in Dr. Sliwkowski's Declaration. (*Id.* at 6:333–40) In light of the Declaration, the Examiner withdrew all obviousness rejections to the '824 application. (*Id.* at 7:45)

After the filing of a terminal disclaimer with the patent that issued from the '649 application, the Examiner allowed the claims. (*Id.* at 7:90–96)

Related European Proceedings

The EP '926 patent claimed a method of using an anti-ErbB2 antibody to treat breast cancer patients overexpressing ErbB2 receptor in combination with a taxoid, in the absence of an anthracycline, where the combined administration has

clinical efficacy as measured by time to disease progression. (Ex. 1003 at 23 (claim 1)) The specification reported the same experimental data as the '549 patent. (*See id.* at 20 ¶¶ 0148–51) Citing Baselga '97 and '96, the Patents Court invalidated the EP '926 patent as lacking an "inventive step," (Ex. 1004 ¶¶ 118–34[7]), and was then affirmed. (*See* Ex. 1049)

On May 2, 2016, in a separate proceeding, the European Patent Office also revoked EP '926 as obvious. (Ex. 1026 ¶¶ 50-59)

VIII. CLAIM CONSTRUCTION

In an IPR, claims receive their reasonable interpretation ("BRI") in light of the specification. 37 C.F.R. § 42.100(b). For purposes of resolving this IPR, Bioepis does not believe construction of claim terms is required.

IX. DETAILED STATEMENT OF GROUNDS FOR UNPATENTABILITY

Analysis under Section 103 requires several steps: "[T]he scope and content

[7] In the U.K., the standard for lack of inventive step is "obvious[ness] to a person skilled in the art." Patents Act, 37§ 3 (U.K.) ("An invention shall be taken to involve an inventive step if it is not obvious to a person skilled in the art.") A similar analysis to the *Graham* factors considered by U.S. Courts is performed. *See Pozzoli Spa v. BDMO SA & Anor.*, 2007 WL 1685192, [2007] EWCA Civ. 588 (Jun. 22, 2007) ¶ 23.

of the prior art are . . . determined; differences between the prior art and the claims at issue are . . . ascertained; and the level of ordinary skill in the pertinent art [is] resolved." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007). Then, "[a]gainst this background, the obviousness or nonobviousness of the subject matter is determined." *Id.* Additionally, "secondary considerations [such] as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Id.*

A patent claim is unpatentable as obvious if the differences between the patented subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the pertinent art. *Id*. In addition, "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *See id*. at 421.

Claims 1-17 are obvious. The '549 patent claims nothing inventive. The prior art disclosed every component of the claimed three-drug combination. 4D5-binding, anti-ErbB2 antibodies were known to treat ErbB2-overexpressing breast

cancer since 1996, (*see* Ex. 1001 at 1:23–32, 2:20–31, 3:36–42; Ex. 1033 at 4; Ex. 1034 at 4; Ex. 1007 at 6; Ex. 1005 at 9; *see also* Ex. 1016 at 10; Ex. 1005 at 9–10; Ex. 1035; Ex. 1043 at 6), and paclitaxel and platinum drugs were known to treat breast cancer. (Ex. 1036 at 5; Ex. 1037 at 14) Combining these known treatments was nothing more than routine skill.

Combinations of an anti-ErbB2 antibody with chemotherapeutic agents were known since the early 1990s. (*E.g.*, Ex. 1006 at 4; Ex. 1013 at 5; Ex. 1009 at 14–15; Ex. 1017 at 7; Ex. 1011 ¶ 41; Ex. 1070 ¶ 36; Ex. 1043 at 6) Scientists had already demonstrated that combined treatment with an anti-ErbB2 antibody and paclitaxel resulted in a synergistic increase in tumor-killing power. (*See* Ex. 1001 at 3:56–61; Ex. 1005 at 15; Ex. 1006 at 4; Ex. 1007 at 9–10) Published studies demonstrated that breast cancer patients treated with anti-ErbB2 antibodies plus cisplatin had improved outcomes over cisplatin alone. (Ex. 1007 at 9–10; Ex. 1013 at 5) The combination of paclitaxel with cisplatin was also known to be synergistic. (*See e.g.*, Ex. 1025 at 9)

Therefore, a POSA reviewing the prior art before the earliest claimed filing date at minimum would know:

1) anti-ErbB2 antibody + paclitaxel (a taxoid) ➔ synergistic;

2) anti-ErbB2 antibody + cisplatin (a growth inhibitory agent) ➔ synergistic;

3) paclitaxel (a taxoid) + cisplatin (a growth inhibitory agent) ➔ synergistic;

The next logical step was to combine all three of the above. MPEP 2144.06 ("It is *prima facie* obvious to combine two compositions . . . taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose . . . [T]he idea of combining them flows logically from their having been individually taught in the prior art.").

There was motivation to try the claimed combination therapies and reason to expect they would be successful before the '549 patent. Breast cancer had not been eradicated. Anti-ErbB2 antibodies, paclitaxel, and cisplatin had all been used in human patients in the prior art, and two-drug combinations of each of them were shown to be synergistic. Drug combinations generally, including two-and three-agent combinations, were routinely used to fight cancer, including breast cancer. (*See, e.g.*, Ex. 1037 at 11–15; Ex. 1025 at 9–10; Ex. 1011 ¶¶ 28–31; Ex. 1070 ¶¶ 23-26) And it was well-known that combination chemotherapies were superior to single agent therapies. (Ex. 1011 ¶ 31; Ex. 1070 ¶ 26) Combinations, like anti-ErbB2 antibodies, paclitaxel, and cisplatin, acting on different and complementary pathways were known to have a greater probability of exhibiting synergy without resulting in drug resistance or enhanced toxicity. (Ex. 1025 at 9–10; Ex. ¶¶ 30, 41–43)

The ’549 patent specification itself contains no suggestion to combine a known growth inhibitory agent with the known combination of an anti-ErbB2 antibody and paclitaxel. And, as discussed above, the ’549 patent does not include any data showing that the named inventors had tried a combination of an anti-ErbB2 antibody, a taxoid, and a further growth inhibitory agent in a patient before purporting (through their claims) to know it would be an amount effective to extend the time to disease progression in a human.

Indeed, if the prior art does not teach the claimed inventions (it does), the ’549 patent would fail to meet the requirements of 35 U.S.C. § 112 ¶ 1. As explained in *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323–25 (Fed. Cir. 2005), the standard for satisfying the enablement requirement of 35 U.S.C. § 112 is higher than that for what constitutes proper enablement of a prior-art reference. For example, to obtain an earlier priority date for claims directed to an “effective” cancer treatment, the Federal Circuit has held an inventor “need[s] to provide experimental proof that his invention could be effective in treating cancer,” whereas “proof of efficacy is not required . . . for a reference to be enabled for purposes of anticipation.” *Id.* at 1326.

In fact, the prior art discloses *more* than what Genentech argued was sufficient to establish an earlier priority date. *Id.* A POSA reading Baselga ’94 (rhuMAb HER2 + paclitaxel), Baselga ’96 (rhuMAb HER2 + chemotherapy),

Baselga ’97 (rhuMAb HER2 + paclitaxel), Pegram ’95 (rhuMAb HER2 + cisplatin), or Gelmon ’96 (cisplatin + paclitaxel) would not merely see a recitation of an idea or “desir[e]” to use a treatment that “may [] contain more than one active compound . . . preferably those with complementary activities that do not adversely affect each other.” (Ex. 1001 at 23:60–63; Ex. 1019–5:179–81) A POSA would know that such combinations (including rhuMAb HER2 plus paclitaxel or cisplatin) *had actually been tried*, both in mice and in humans, *and experimental data* showed they worked better than rhuMAb HER2 alone. (Ex. 1005 at 15; Ex. 1006 at 4; Ex. 1007 at 9–10; Ex. 1013 at 5)

During prosecution, Genentech’s main criticism of the prior art was that “data from clinical trials of the *combination* are needed to demonstrate that they can be usefully combined.” (Ex. 1019–5:308–09) But the Examiner seemingly overlooked that Genentech’s patent specification contains no such data from clinical trials—or any other testing—of the claimed three-drug combination. (*See* Ex. 1011 ¶¶ 51–52; Ex. 1070 ¶¶ 46-47)

And yet Genentech affirmatively argued that same specification sufficed to “clearly . . . describe[]” the claimed invention by its use of plural words (“agents”) and generic disclosures about combining chemotherapeutic agents. (Ex. 1019–5:179–81.) To declare Genentech’s patent claims patentable would be to unfairly

reward it with exclusionary rights for contributing *less* to the public about the claimed invention than the prior art. (*See* Ex. 1011 ¶ 53; Ex. 1070 ¶ 48)

Finally, none of the dependent claims adds anything inventive. Genentech did not argue that any of the dependent claims of the '549 patent added anything over and above what had already been disclosed by the prior art at any time during the prosecution history of the '549 patent. (*See generally* Ex. 1019)

A. Ground 1: Claims 1-11 and 14-17 are unpatentable as obvious over Baselga '97 and Gelmon '96

1. Claim 1

a. Preamble: "A method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor, comprising"

Baselga '97 in view of Gelmon '96 discloses "[a] method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor." Baselga '97 teaches that rhuMAb HER2 was used in "patients with metastatic breast carcinomas overexpressing HER2." (Ex. 1007 at 9) Metastatic breast carcinoma is a malignant breast cancer that has spread to another area. (Ex. 1011 ¶ 75; Ex. 1070 ¶ 70) Baselga '97 further teaches that "[t]he HER2 gene (also known as *neu* and as *c-erb*B-2) encodes a…glycoprotein receptor ($p185^{HER2}$)." (Ex. 1007 at 6) Thus the c-erbB-2 gene is also known as the HER2 gene—and a POSA would know that the ErbB2 receptor protein is also known as the HER2 receptor protein. (Ex. 1011 ¶ 76; Ex. 1070 ¶ 71)

Baselga ’97 teaches that positive results with single-therapy and mouse models “led to the design of a phase III multinational study of chemotherapy in combination with rhuMoAb HER2 in patients with HER2-overexpressing breast tumors.” (Ex. 1007 at 10)

b. Element [a]: “administering a combination of an antibody that binds ErbB2,”

Baselga ’97 in view of Gelmon ’96 discloses “administering a combination of an antibody that binds ErbB2.” The phase III trial reported in Baselga ’97 involved administering “rhuMoAb HER2 in combination with cytotoxic chemotherapy.” (*Id.*)

Baselga ’97 confirms that “[t]he murine monoclonal antibody (MoAb) 4D5 [is] directed against the extracellular domain of $p185^{HER2}$.” (*Id.* at 7; *see also* Ex. 1001 at 5:26–37) MAb 4D5 was then humanized by combining “the antigen-binding portions of murine MoAb 4D5…and a human immunoglobulin variable region framework” to produce “rhuMoAb HER2 IgG1.” (Ex. 1007 at 9) The antigen-binding portions of an antibody are the portions of the antibody that determine what protein and where on that protein (the epitope) the antibody binds. (Ex. 1011 ¶ 77; Ex. 1070 ¶ 72) A POSA would understand that, because rhuMAb HER2 contains the antigen-binding portions of MAb 4D5, it binds to the same epitope as MAb 4D5 and therefore rhuMAb HER2 binds to epitope 4D5 within the

ErbB2 extracellular domain sequence of ErbB2. (Ex. 1007 at 9; Ex. 1011 ¶ 77; Ex. 1070 ¶ 72)

c. Element [b]: "a taxoid"

Baselga '97 in view of Gelmon '96 teaches a combination of an antibody and "a taxoid." Baselga '97 teaches that "[t]he treatment with paclitaxel plus 4D5 [in preclinical xenograft models] resulted in major antitumor activity." (Ex. 1007 at 9) It also describes "a phase III multinational study of chemotherapy in combination with rhuMoAb HER2 in patients with HER2-overexpressing breast tumors" was underway. (*Id.* at 10) The experimental group included patients receiving "paclitaxel, if patients have received anthracycline therapy in the adjuvant setting." (*Id.*; Ex. 1001 at 4:23–25 (paclitaxel is a taxoid); *see also* Ex. 1007 at 7–8, 10 (discussing "encouraging" "[r]esults from the phase II studies and the activity of rhuMoAb HER2 against xenografts when given in combination with doxorubicin and paclitaxel"); Ex. 1011 ¶ 78; Ex. 1070 ¶ 73)

d. Element [c]: "and a further growth inhibitory agent"

Baselga '97 in view of Gelmon '96 discloses "a further growth inhibitory agent." Baselga '97 discusses the results of a phase II clinical trial of rhuMAb HER2 with cisplatin "in patients with breast carcinomas that overexpress $p185^{HER2}$." (Ex. 1007 at 9) Baselga '97 reports an overall response rate of 25% "suggesting that the synergy observed in the laboratory was reproducible in the

clinic. In addition, the combined therapy was no more toxic than cisplatin alone." *Id.* Thus, Baselga '97 teaches that the combination of rhuMAb HER2 with paclitaxel or cisplatin results in synergistic effects over single therapies without increasing toxicity. (Ex. 1011 ¶ 79; Ex. 1070 ¶ 74)

Gelmon '96 teaches a synergistic effect of paclitaxel and cisplatin in patients with metastatic breast cancer. (Ex. 1025 at 9) Gelmon '96 explains the motivation to combine paclitaxel and cisplatin: "We were also interested in combining [paclitaxel] with a non-cross-resistant drug with a different spectrum of toxicity. Cisplatin seemed to be an appropriate choice." (*Id.*) In particular, "[t]he mechanisms of resistance for cisplatin and paclitaxel differ . . . [and], except for neurotoxicity, the toxicities associated with [the two drugs] do not overlap." (*Id.* at 9–10; *see also* Ex. 1011 ¶ 80; Ex. 1070 ¶ 75)

Both Baselga '97 and Gelmon '96 are directed to finding therapies for breast cancer. A POSA reading Gelmon '96 would understand that HER2 positive breast cancer patients are resistant to paclitaxel and cisplatin therapies, but looking to Baselga '97 would know that rhuMAb HER2 sensitizes HER2 positive tumors to both therapies. Thus, a POSA would combine the teachings of Baselga '97 and Gelmon '96 with a reasonable expectation of success. (*See id.* ¶ 84)

e. Element [d]: "to the human patient"

Baselga '97 in view of Gelmon '96 discloses administration in human patients. (Ex. 1007 at 10)

f. Element [e]: "in an amount effective to end the time to disease progression in the human patient"

Baselga '97 in view of Gelmon '96 discloses "in an amount effective to extend the time to disease progression in the human patient." First, the claim itself purports to capture *any* "amount effective to extend the time to disease progression" even though the '549 patent describes no such effective amounts for the claimed three-drug combination. (*See* Ex. 1011 ¶ 83; Ex. 1070 ¶ 78) Thus, the patent itself relies on the fact that a POSA would have known how to conduct the necessary experimentation to determine an appropriate dose of the combined treatment to extend the time to disease progression. (*Id.*)

Second, Baselga '97 discloses that a loading dose of 250 mg followed by weekly doses of 100 mg of rhuMAb HER2 as a single therapy results in an increase in time to disease progression. Ex. 1007 at 9. Specifically, the responses "lasted for a median of 5.1 months." (*Id.*; *see also* Ex. 1011 ¶ 84; Ex. 1070 ¶ 79) Baselga '97 additionally reports that "[a]dequate serum levels of rhuMoAb HER2 were obtained in 90% of the patients" with a mean half-life of about 8.3 days. (*Id.*)

Third, Gelmon '96 discloses that biweekly administration of cisplatin with paclitaxel was an effective combination in patients with metastatic breast cancer.

(Ex. 1025 at 10, 14) The combination resulted in "an overall response rate of 85%" with a "median duration of overall response . . . [of] 7.9 months." (*Id.* at 13) Therefore, Gelmon '96 discloses a combined paclitaxel plus cisplatin treatment regimen that increases the time to disease progression. (*See* Ex. 1011 ¶ 85; Ex. 1070 ¶ 80)

Finally, Baselga '97 discloses that the combination of rhuMAb HER2 plus either cisplatin or paclitaxel results in synergistic increases in efficacy. (Ex. 1007 at 9–10) In the cisplatin trial, patients were administered 250 mg of rhuMAb HER2 followed by 100 mg weekly and 75 mg/m^2 of cisplatin every three weeks. (*Id.*) "[T]he observed response rate to the combined therapy was 25%, suggesting that the synergy observed in the laboratory was reproducible in the clinic" and "the combined therapy was no more toxic than cisplatin alone." (*Id.* at 10)

Baselga '97 also discloses that combined administration of paclitaxel and anti-ErbB2 antibodies showed "major antitumor activity" in preclinical models. (*Id.*) As a result, "a phase III multinational study of chemotherapy in combination with rhuMoAb HER2 in patients with HER2-overexpressing breast tumors" was designed. (*Id.*) "The main goal of [the] study [was] to determine whether the addition of [rhuMAb HER2] increases the time to disease progression compared with" the control group. (*Id.*; *see also* Ex. 1011 ¶¶ 86–89; Ex. 1070 ¶¶ 81-84)

g. Element [f]: "wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular sequence"

Baselga '97 in view of Gelmon '96 discloses "wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence." For the reasons stated above, a POSA would understand that because rhuMAb HER2 contains the antigen-binding portions of MAb 4D5, it binds to the same epitope as MAb 4D5 and therefore rhuMAb HER2, used in Baselga '97, binds to epitope 4D5 within the ErbB2 extracellular domain sequence. (Ex. 1007 at 9; Ex. 1011 ¶ 88; Ex. 1070 ¶ 83)

h. Conclusion

Given the established synergistic results of cisplatin plus paclitaxel, anti-ErbB2 antibody plus cisplatin, and anti-ErbB2 antibody plus paclitaxel, a POSA would have been motivated to combine rhuMAb HER2, paclitaxel, and cisplatin at the already effective doses disclosed by Gelmon '96 (for cisplatin and paclitaxel) and Baselga '97 (for rhuMAb HER2) and would have had a reasonable expectation of achieving—and improving upon—the already extended time to disease progression reported in Baselga '97 without an unreasonable risk of increasing toxicity. (*Id.* ¶¶ 89–90)

Every other combination of these therapies had been tried and yielded synergistic results with acceptable toxicity. (Ex. 1025 at 9–10; Ex. 1007 at 9–10; Ex. 1011 ¶¶ 89–90; Ex. 1070 ¶¶ 84-85) The three-drug combination was the only

combination left to try and required nothing more than common sense to try it for the same established purpose. (*Id.*) It would have been immediately apparent to a POSA to use an amount effective to extend the time to disease progression. Indeed, increasing time to disease progression is considered to be a surrogate measure of drug effectiveness by the FDA and is often the entire point of anti-ErbB2 antibodies, paclitaxel, and cisplatin, and metastatic breast cancer therapies in general. (*Id.*) The '549 patent itself discloses no amounts that should be used and no data showing time to disease progression is extended by its claimed three-drug combination therapy, thus Genentech cannot reasonably dispute that a POSA would have known to use and how to determine such amounts.

2. Claim 2: "The method of claim 1 wherein the antibody is a humanized 4D5 anti-ErbB2 antibody."

Baselga '97 in view of Gelmon '96 teaches the method of claim 1. (*See* Section IX.A.1) Baselga '97 teaches that "[t]he murine monoclonal antibody (MoAb) 4D5, directed against the extracellular domain of $p185^{HER2}$," was humanized. (Ex. 1007 at 7, 10; Ex. 1011 ¶¶ 91–92; Ex. 1070 ¶¶ 86-87; *see supra* Section IX.A.1.g)

3. Claim 3: "The method of claim 1 wherein the antibody crossblocks binding of 4D5 to the ErbB2 extracellular domain sequence."

Baselga '97 in view of Gelmon '96 teaches the method of claim 1. (*See supra* Section IX.A.1) Cross-blocking assays are routine laboratory experiments to

confirm two antibodies share overlapping binding specificity. (Ex. 1001 at 5:28–33; Ex. 1011 ¶¶ 93–94; Ex. 1070 ¶¶ 88-89) Baselga '97 teaches that rhuMAb HER2 possesses the same antigen-binding regions as 4D5, therefore it necessarily crossblocks binding of 4D5 to the ErbB2 extracellular domain sequence. (Ex. 1007 at 9; 1011 ¶¶ 93–94; Ex. 1070 ¶¶ 88-89; *see supra* Section IX.A.1.g)

4. Claim 4: "The method of claim 1 wherein the antibody binds to amino acid residues in the region from about residue 529 to about residue 625 of the ErbB2 extracellular domain sequence."

Baselga '97 in view of Gelmon '96 teaches the method of claim 1. (*See supra* Section IX.A.1) The '549 patent states that the 4D5 antibody binds to the region from about residue 529 to about residue 625 of the ErbB2 extracellular domain sequence. (Ex. 1001 at 5:32–37) Baselga '97 teaches that rhuMAb HER2 is a humanized form of the murine 4D5 antibody. (Ex. 1007 at 9; *see supra* Section IX.A.1.g) Because rhuMAb HER2 possesses the same antigen-binding regions as 4D5 it necessarily also binds to the claimed amino acid residues. (Ex. 1011 ¶¶ 95–96; Ex. 1070 ¶¶ 90-91)

5. Claim 5

a. Preamble: "A method for the treatment of a human patient with breast cancer characterized by overexpression of ErbB2 receptor, comprising"

Baselga '97 in view of Gelmon '96 discloses "[a] method for the treatment of a human patient with breast cancer characterized by overexpression of ErbB2

receptor." (*See supra* Section IX.A.1.a)

b. Element [a]: "administering an effective amount of a combination of an anti-ErbB2 antibody which binds epitope 4D5 within the ErbB2 extracellular domain sequence,"

Baselga '97 in view of Gelmon '96 discloses "administering an effective amount of a combination." Since "an amount effective to extend the time to disease progression," would be an "effective amount," Baselga '97 in view of Gelmon '96 discloses "an effective amount." (Ex. 1011 ¶¶ 98–99; Ex. 1070 ¶¶ 93-94; *see supra* Section IX.A.1.f)

Baselga '97 in view of Gelmon '96 discloses "an anti-ErbB2 antibody which binds epitope 4D5 within the ErbB2 extracellular domain sequence." (*See supra* Section IX.A.1.g)

c. Element [b]: "a taxoid"

Baselga '97 in view of Gelmon '96 discloses a combination of rhuMAb HER2 and "a taxoid." (*See supra* Section IX.A.1.c)

d. Element [c]: "and a further therapeutic agent,"

Baselga '97 in view of Gelmon '96 discloses "a further therapeutic agent." (*See supra* Section IX.A.1.d) Claim 11 provides that a "therapeutic agent" may be a "growth inhibitory agent." (Ex. 1001 at claim 11) Therefore, a "therapeutic agent" includes a "growth inhibitory agent." (Ex. 1011 ¶ 101; Ex. 1070 ¶ 96)

e. Element [d]: "to the human patient."

Baselga '97 in view of Gelmon '96 discloses "to the human patient." (*See supra* Section IX.A.1.e)

f. Conclusion

For the same reasons discussed in Section IX.A.1.h, it would have been obvious to a POSA to try the combination of rhuMAb HER2, paclitaxel, and cisplatin as recited in claim 5 with a reasonable expectation of success.

6. Claim 6: "The method of claim 5 wherein the breast cancer is metastatic breast carcinoma."

Baselga '97 in view of Gelmon '96 teaches the method of claim 5. (*See supra* Section IX.A.5) Baselga '97 discloses that rhuMAb HER2 was used in "[p]atients with metastatic breast carcinomas overexpressing HER2." (Ex. 1007 at 9; Ex. 1011 ¶¶ 104–105; Ex. 1070 ¶¶ 99-100)

7. Claim 7: "The method of claim 5 wherein the antibody is a humanized 4D5 anti-ErbB2 antibody."

Baselga '97 in view of Gelmon '96 teaches the method of claim 5. (*See supra* Section IX.A.5) Baselga '97 teaches that rhuMAb HER2 is a humanized form of the murine 4D5 antibody. (*See supra* Section IX.A.1.g)

8. Claim 8: "The method of claim 7 wherein the antibody is administered as a 4 mg/kg dose and then weekly administration of 2 mg/kg."

Baselga '97 in view of Gelmon '96 teaches the method of claim 7. (*See*

supra Section IX.A.7) Baselga '97 treated patients with a "loading dose of 250 mg IV rhuMoAb HER2, then 10 weekly doses of 100 mg each." (Ex. 1007 at 9) This dose resulted in an amount effective to extend the time to disease progression by 5.1 months. (*Id.*) More than 90% of patients achieved adequate serum concentrations of the antibody. (*Id.*) A POSA would have understood that it is more reliable to administer drugs on a weight-based basis to more reliably achieve adequate serum concentrations of the drug. (Ex. 1011 ¶ 109; Ex. 1070 ¶ 104) Additionally, 55–85 kg is a reasonable range that a POSA would assume for patient weight. (*See* 1011 ¶ 39; Ex. 1070 ¶ 34; Ex. 1024 at 3; Ex. 1044 at 334 (Table 7-2)) Assuming a patient weight between 55–85 kg, the corresponding weight-based dose is a loading dose of approximately 2.9–4.5 mg/kg (*i.e.*, 250 mg divided by either 85 kg or 55 kg respectively) followed by a weekly maintenance dose of 1.2–1.8 mg/kg (*i.e.*, 100 mg divided by either 85 kg or 55 kg respectively). (Ex. 1011 ¶¶ 39 (citing Ex. 1044 at 334 (Table 7-2)), 108–110; Ex. 1070 ¶ 103-105) As taught by Baselga '97, this dose range will result in a plasma concentration above the target minimum in more than 90% of patients. (Ex. 1007 at 9) The '549 patent contains no data showing that this claimed dosing regimen had any unexpected properties or was otherwise distinguishable from the range of doses derived directly from Baselga '97. (Ex. 1011 ¶ 110; Ex. 1070 ¶ 105) *See In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) ("The law is replete with cases

in which the difference between the claimed invention and the prior art is some range or other variable within the claims…These cases have consistently held that in such a situation, the applicant must show that the particular range is *critical*, generally by showing that the claimed range achieves unexpected results relative to the prior art range.").

9. Claim 9: "The method of claim 5 wherein the taxoid is paclitaxel."

Baselga '97 in view of Gelmon '96 teaches the method of claim 5. (*See supra* Section IX.A.5) Baselga '97 discloses the taxoid paclitaxel. (*See supra* Section IX.A.1.c)

10. Claim 10: "The method of claim 5 wherein efficacy is measured by determining the time to disease progression or the response rate."

Baselga '97 in view of Gelmon '96 teaches the method of claim 5. (*See supra* Section IX.A.5) Baselga '97 in view of Gelmon '96 teaches measuring the results by the time to disease progression. (*See supra* Section IX.A.1.f) Baselga '97 also reports that, out of the patients treated with rhuMAb HER2, the overall response rate was 11.6%. (Ex. 1007 at 9) It would have been obvious to a POSA to measure the overall response rate of the combination therapy based on this disclosure from Baselga '97. (Ex. 1011 ¶¶ 113–114; Ex. 1070 ¶ 108-109)

11. Claim 11: "The method of claim 5 wherein the further therapeutic agent is selected from the group consisting of . . . growth inhibitory agent."

Baselga '97 in view of Gelmon '96 teaches the method of claim 5. (*See supra* Section IX.A.5) Baselga '97 in view of Gelmon '96 teaches a "growth inhibitory agent." (*See supra* Section IX.A.1.d)

12. Claim 14: "The method of claim 5 wherein the further therapeutic agent is a growth inhibitory agent."

Baselga '97 in view of Gelmon '96 teaches the method of claim 5. (*See supra* Section IX.A.5) Baselga '97 in view of Gelmon '96 teaches a "growth inhibitory agent." (*See supra* Section IX.A.1.d)

13. Claim 15: "The method of claim 14 wherein the growth inhibitory agent is a DNA alkylating agent."

Baselga '97 in view of Gelmon '96 teaches the method of claim 14. (*See supra* Section IX.A.12) Baselga '97 in view of Gelmon '96 teaches the combination of rhuMAb HER2 with paclitaxel and cisplatin. (*See supra* Section IX.A.1.d) Cisplatin is a DNA alkylating agent. (Ex. 1001 at 11:31–34; Ex. 1011 ¶¶ 119–120; Ex. 1070 ¶¶ 114-115)

14. Claim 16

a. Preamble: "A method for the treatment of a human patient with ErbB2 overexpression breast cancer, comprising"

Baselga '97 in view of Gelmon '96 discloses "[a] method for the treatment

of a human patient with ErbB2 overexpressing breast cancer." (*See supra* Section IX.A.1.a)

b. Element [a]: "administering a combination of an antibody that binds epitope 4D5 within the ErbB2 extracellular domain sequence,"

Baselga '97 in view of Gelmon '96 discloses "administering a combination of an antibody that binds epitope 4D5 within the ErbB2 extracellular domain sequence." (*See supra* Section IX.A.1.g)

c. Element [b]: "a taxoid"

Baselga '97 in view of Gelmon '96 discloses a combination of rhuMAb HER2 and "a taxoid." (*See supra* Section IX.A.1.c)

d. Element [c]: "and a further growth inhibitory agent,"

Baselga '97 in view of Gelmon '96 discloses "a further growth inhibitory agent." (*See supra* Section IX.A.1.d)

e. Element [d]: "in the absence of an anthracycline derivative,"

Baselga '97 in view of Gelmon '96 discloses "in the absence of an anthracycline derivative." The cardiotoxicity of anthracycline derivatives were known in the prior art. (Ex. 1011 ¶¶ 125–128; Ex. 1070 ¶¶ 120-123) Baselga '97 in view of Gelmon '96 also teaches the absence of an anthracycline derivative because they teach the combination of rhuMAb HER2, paclitaxel and cisplatin. (*See, e.g.*, *supra* Sections IX.A.1.b-f) Accordingly, a POSA reading Baselga '97 in

view of Gelmon ’96 would have known there is a substantial likelihood that patients will have already received a course of anthracycline therapy, and thus it would be advantageous to pursue synergistic drug combinations—like paclitaxel with cisplatin—that include drugs other than anthracyclines. See Ex. 1007 at 10; Ex. 1025 at 9. A POSA therefore would *not* be motivated to combine rhuMAb HER2, a taxoid, and an anthracycline derivative due to the known cardiotoxic effects of anthracyclines. (Ex. 1011 ¶¶ 125–128; Ex. 1070 ¶¶ 120-123)

f. Element [e]: “to the human patient”

Baselga ’97 in view of Gelmon ’96 discloses administering the treatment “to the human patient.” (*See supra* Section IX.A.1.e)

g. Element [f]: “in an amount effective to extend the time to disease progression in the human patient.”

Baselga ’97 in view of Gelmon ’96 discloses “in an amount effective to extend the time to disease progression in the human patient.” (*See supra* Section IX.A.1.f)

h. Conclusion

For the same reasons discussed in Section IX.A.1.h, it would have been obvious to a POSA to try the combination of rhuMAb HER2, paclitaxel, and cisplatin as recited in claim 16 with a reasonable expectation of success.

15. Claim 17: "The method of claim 16 wherein the breast cancer is metastatic breast carcinoma."

Baselga '97 in view of Gelmon '96 discloses the method of claim 16. (*See supra* Section IX.A.14) Baselga '97 teaches "metastatic breast carcinoma." (*See supra* Section IX.A.6.a)

B. Ground 2: Claim 12 is unpatentable as obvious over Baselga '97 in view of Gelmon '96 and Drebin '88

Claim 12: "The method of claim 5 wherein the further therapeutic agent is another ErbB2 antibody."

Baselga '97 in view of Gelmon '96 discloses the method of claim 5. (*See supra* Section IX.A.5) Further, Drebin '88 teaches that antibodies against "two distinct regions on the p185 molecule" "resulted in synergistic anti-tumor effects." (Ex. 1010 at 4) A POSA would have been motivated to combine the teachings of Drebin '88, Baselga '97, and Gelmon '96 because they are all directed towards methods of treating HER2 positive breast cancer, and because anti-ErbB2 antibodies act to sensitize tumor cells to chemotherapeutic agents. (Ex. 1007 at 9)

Since the blockade of the 4D5 domain does not result in complete tumor suppression, (*id.*), a POSA would look to Drebin '88's teaching that blockade of multiple target domains could result in complete tumor suppression, and thus greater sensitization to those same chemotherapeutic agents. (Ex. 1011 ¶¶ 135–137; Ex. 1070 ¶¶ 130-132) As such, a POSA would have been motivated to try

another ErbB2 antibody, as taught by Drebin ’88. Notably, the ’549 patent discloses no experiments using “another ErbB2 antibody” providing confirmation that a POSA would have already known the claimed combination would work.

C. Ground 3: Claim 13 is unpatentable as obvious over Baselga ’97 in view of Gelmon ’96 and Presta ’97

Claim 13: “The method of claim 5 wherein the further therapeutic agent is a vascular endothelial growth factor (VEGF) antibody.”

Baselga ’97 in view of Gelmon ’96 discloses the method of claim 5. (*See supra* Section IX.A.5) Presta ’97 further teaches that antibodies against VEGF result in substantial tumor control. (Ex. 1012 at 8) And Presta ’97 provides a humanized antibody against VEGF ready for use in humans. (*Id.* at 11) All of Baselga ’97, Gelmon ’96 and Presta ’97 are directed to cancer therapies, and a POSA would have been motivated to combine the teachings of Baselga ’97 and Presta ’97 because it was well-understood that ErbB2 and VEGF act on unrelated pathways and thus are likely to have at least an additive, if not synergistic, effect with a low, or nonexistent, likelihood of overlapping toxicity. (*See* Ex. 1025 at 9–10)

For at least these reasons, it would have been obvious to combine the teachings of Presta ’97 with Baselga ’97 in view of Gelmon ’96 by trying a VEGF antibody. (Ex. 1011 ¶¶ 139–141; Ex. 1070 ¶¶ 134-136) Notably the ’549 patent discloses no experiment using a VEGF antibody providing confirmation that a

POSA would already have known the claimed combination would work.

D. Ground 4: Claims 1-11 and 14-17 are unpatentable as obvious over Baselga '96 in view of Baselga '94 and Gelmon '96

1. Claim 1

a. Preamble: "A method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor, comprising"

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "[a] method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor." Baselga '96 teaches that rhuMAb HER2 was used in "[p]atients…whose metastatic breast carcinomas overexpressed HER2." (Ex. 1005 at 10) Metastatic breast carcinoma is a malignant breast cancer. (Ex. 1011 ¶ 143; Ex. 1070 ¶ 138)

Baselga '96 further teaches that "[t]he HER2 gene (also known as *neu* and as *c-erbB*-2) encodes a…glycoprotein receptor ($p185^{HER2}$)." (Ex. 1005 at 9) Thus the c-erbB-2 gene is also known as the HER2 gene—a POSA would have known that the ErbB2 receptor protein is also known as the HER2 receptor protein. (Ex. 1011 ¶¶ 144–145; Ex. 1070 ¶¶ 139-140)

Baselga '96 confirmed ErbB2 overexpression "by immunohistochemical analysis." (Ex. 1005 at 10; *see also id.* at 13, Table 5; Ex. 1011 ¶ 146; Ex. 1070 ¶ 141)

Table 5. Characteristics of Patients Who Achieved a Response to Treatment

Patient No.	HER2*	Site of Metastatic Disease	Prior Systemic Therapy	Best Response	Duration of Response (months)
1	3+	Chest wall	Doxorubicin	Complete response†	> 24
2	3+	Liver	Doxorubicin, mitoxantrone, paclitaxel	Partial response	6.7
3	2+	Mediastinum	CMFVP, doxorubicin, tamoxifen, paclitaxel	Partial response	7.7
4	3+	Liver + retroperitoneal lymph nodes + bone	CMF, docetaxel	Partial response	1
5	2+	Chest wall	Paclitaxel	Partial response	3.4

Abbreviations: CMFVP, cyclophosphamide, methotrexate, fluorouracil, vincristine, and prednisone; CMF, cyclophosphamide, methotrexate, and fluorouracil.

*By immunohistochemistry: 2+, 25% to 50% of tumor cells with cytoplasmic membrane staining; 3+, > 50% of tumor cells with cytoplasmic membrane staining.

†Patient's complete response was pathologically proven with several biopsies at tumor site. Patient bone scan, head, thoracic, abdominal, and pelvic computed tomographic scans are negative.

b. Element [a]: "administering a combination of an antibody that binds ErbB2,"

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "administering a combination of an antibody that binds ErbB2." The phase II trial reported in Baselga '96 involved administering "rhuMAb HER2…intravenously" weekly for ten weeks. (Ex. 1005 at 10)

RhuMAb HER2 was prepared by humanizing "[t]he murine monoclonal antibody (MAb) 4D5," which "[is] directed against the extracellular domain of $p185^{HER2}$." (*Id.* at 9; *see also* Ex. 1001 at 5:26–37) MAb 4D5 was humanized by "inserting the complementarity determining regions…into the framework of a consensus human immunoglobulin G1 (IgG1)." (Ex. 1005 at 10) The complementarity determining region of an antibody is the portion of the antibody determining what the antibody binds to, *i.e.*, the epitope. (Ex. 1011 ¶¶ 147–148; Ex. 1070 ¶¶ 142-143) Because rhuMAb HER2 contains the same complementarity

determining region as MAb 4D5, it binds to the same epitope as MAb 4D5 and therefore rhuMAb HER2, used in Baselga '96, binds to epitope 4D5 within the ErbB2 extracellular domain sequence. (Ex. 1005 at 10; Ex. 1011 ¶¶ 147–148; Ex. 1070 ¶¶ 142-143)

c. Element [b]: "a taxoid"

Baselga '96 in view of Baselga '94 and Gelmon '96 teaches a combination of an antibody and "a taxoid." In Table 5, Baselga '96 shows that all "five [patients who] experienced a complete or partial remission" had "[p]rior [s]ystemic [t]herapy" and 4 of 5 patients were given either paclitaxel or docetaxel (taxoids). (Ex. 1005 at 13, Table 5) Baselga '96 also teaches that "[i]n preclinical studies…rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including…paclitaxel without increasing their toxicity." (*Id.* at 15) As a result, "clinical trials of such combination therapy [we]re currently in progress." (*Id.*)

Baselga '96 cites to Baselga '94 in describing these results, and thus a POSA would look to Baselga '94 for additional details. Baselga '94 further teaches that individual treatment with either 4D5 or paclitaxel alone resulted in 35% growth inhibition. (Ex. 1006 at 4) Their *combination* "resulted in a major antitumor activity with 93% inhibition of growth" without increasing toxicity. (*Id.*) In light of this, Baselga '94 discloses that "[c]linical trials are underway." (*Id.*; *see also*

Ex. 1011 ¶¶ 149–152; Ex. 1070 ¶¶ 144-147)

d. Element [c]: "and a further growth inhibitory agent"

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "a further growth inhibitory agent." Baselga '96 teaches that "[i]n preclinical studies…rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity." (Ex. 1005 at 15) Thus, Baselga '96 individually teaches that the combination of rhuMAb HER2 plus paclitaxel or cisplatin both result in synergistic effects over single therapies without increasing toxicity. (Ex. 1011 ¶ 153; Ex. 1070 ¶ 148)

Gelmon '96 further teaches a synergistic effect of paclitaxel with cisplatin in patients with breast cancer. (Ex. 1025 at 9) It explains the motivation to combine paclitaxel and cisplatin: "We were also interested in combining [paclitaxel] with a non-cross-resistant drug with a different spectrum of toxicity. Cisplatin seemed to be an appropriate choice." (*Id.*) In particular, "[t]he mechanisms of resistance for cisplatin and paclitaxel differ…[and], except for neurotoxicity, the toxicities associated with cisplatin do not overlap with those of paclitaxel." (*Id.* at 9–10; Ex. 1011 ¶ 154; Ex. 1070 ¶ 149)

All of Baselga '96, Baselga '94, and Gelmon '96 are directed toward finding appropriate therapies for breast cancer. A POSA reading Gelmon '96 would

understand that HER2 positive breast cancer patients are resistant to both paclitaxel and cisplatin therapies, but looking to Baselga '96 would know that rhuMAb HER2 serves to sensitize HER2 positive tumors to both therapies. For this reason, a POSA would combine the teachings of Baselga '96, Baselga '94 and Gelmon '96 with a reasonable expectation of success. (*See* Ex. 1011 ¶ 155; Ex. 1070 ¶ 150)

e. Element [d]: "to the human patient"

Baselga '96, in view of Baselga '94 and Gelmon '96, discloses administration in human patients. (Ex. 1005 at 10)

f. Element [e]: "in an amount effective to extend the time to disease progression in the human patient"

Baselga '96, in view of Baselga '94 and Gelmon '96, discloses "an amount effective to extend the time to disease progression in the human patient." First, the claim itself purports to capture *any* "amount effective to extend the time to disease progression" even though the '549 patent describes no such effective amounts for the claimed three-drug combination. Thus, the patent itself must rest on the assumption that a POSA would have known how to conduct the necessary experimentation to determine an amount effective as per claim 1. (Ex. 1011 ¶ 157; Ex. 1070 ¶ 152)

Second, Baselga '96 discloses that a loading dose of 250 mg followed by weekly doses of 100 mg of rhuMAb HER2 as a single therapy results in an increase in time to disease progression. (Ex. 1005 at 10) Specifically, the

responses "lasted for a median of 5.1 months." (*Id.* at 9; *see also id.* at 13, Table 5 (Duration of Response (months)); Ex. 1011 ¶ 158; Ex. 1070 ¶ 153)

Third, Gelmon '96 discloses that biweekly administration of cisplatin with paclitaxel was an effective combination in breast cancer patients. (Ex. 1025 at 10, 14) The combination resulted in "an overall response rate of 85%" with a "median duration of overall response . . . [of] 7.9 months." (*Id.* at 13) Therefore, Gelmon '96 discloses a combined paclitaxel plus cisplatin treatment regimen that increases the time to disease progression. (Ex. 1011 ¶¶ 159–161; Ex. 1070 ¶¶ 154-156)

Finally, Baselga '96 discloses that the combination of rhuMAb HER2 with cisplatin or paclitaxel in preclinical models results in synergistic increases in treatment efficacy over single therapies without increasing toxicity. (Ex. 1005 at 15; Ex. 1011 ¶¶ 161–162; Ex. 1070 ¶¶ 156-157)

g. Element [f]: "wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular sequence"

Baselga '96 discloses "wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence." For the reasons stated above, a POSA would understand that, because rhuMAb HER2 contains the complementarity determining region of MAb 4D5, it binds to the same epitope as MAb 4D5 and therefore rhuMAb HER2, used in Baselga '96, binds to epitope 4D5 within the ErbB2 extracellular domain sequence. (Ex. 1007 at 9; Ex. 1011 ¶ 163; Ex. 1070 ¶

158)

h. Conclusion

Given the established synergistic effects of cisplatin plus paclitaxel, anti-ErbB2 antibody plus cisplatin, and anti-ErbB2 antibody plus paclitaxel, a POSA would have combined rhuMAb HER2, paclitaxel, and cisplatin at the already effective doses disclosed by Gelmon ’96 (for cisplatin and paclitaxel) and Baselga ’96 (for rhuMAb HER2) with a reasonable expectation of achieving—and improving upon—the already extended time to disease progression reported in Baselga ’96 without an unreasonable risk of increasing toxicity. (Ex. 1011 ¶¶ 164–166; Ex. 1070 ¶¶ 159-161)

Every other possible combination of these therapies had been tried and yielded synergistic results with acceptable toxicity. (Ex. 1025 at 9–10; Ex. 1005 at 15; Ex. 1011 ¶¶ 164–166; Ex. 1070 ¶¶ 159-161) The three-drug combination was the only combination left to try and it required nothing more than common sense to try it for the same established purpose. (*Id.*) It would have been immediately apparent to a POSA to use an amount effective to extend the time to disease progression in the human patient. Indeed, increasing time to disease progression is considered to be a surrogate measure of drug effectiveness by the FDA, and is often the entire point of anti-ErbB2 antibodies, paclitaxel, and cisplatin, and metastatic breast cancer therapies in general. (*Id.*)

The ’549 patent itself discloses no amounts that should be used and no data showing time to disease progression is extended by its claimed combination therapy, thus Genentech cannot reasonably dispute that a POSA would have known to use and how to determine such amounts.

2. Claim 2: “The method of claim 1 wherein the antibody is a humanized 4D5 anti-ErbB2 antibody.”

Baselga ’96 in view of Baselga ’94 and Gelmon ’96 teaches the method of claim 1. (*See supra* Section IX.D.1) Baselga ’96 in view of Baselga ’94 and Gelmon ’96 teaches that rhuMAb HER2 is a humanized form of the murine 4D5 antibody, therefore “the antibody is a humanized 4D5 anti-ErbB2 antibody.” (Ex. 1005 at 9; Ex. 1011 ¶¶ 167–168; Ex. 1070 ¶¶ 162-163; *see supra* Section IX.D.1.g)

3. Claim 3: “The method of claim 1 wherein the antibody crossblocks binding of 4D5 to the ErbB2 extracellular domain sequence.”

Baselga ’96 in view of Baselga ’94 and Gelmon ’96 teaches the method of claim 1. (*See supra* Section IX.D.1) Cross-blocking assays are routine experiments to confirm that two antibodies share overlapping binding specificity. Ex. 1001 at 5:28–33; Ex. 1011 ¶ 170; Ex. 1070 ¶ 165) Baselga ’96 teaches that rhuMAb HER2 possesses the same complementarity determining regions as 4D5, therefore it will necessarily crossblock binding of 4D5 to the ErbB2 extracellular domain sequence. (Ex. 1005 at 9; Ex. 1011 ¶¶ 169–171; Ex. 1070 ¶¶ 164-166; *see supra* Section IX.D.1.g)

4. Claim 4: "The method of claim 1 wherein the antibody binds to amino acid residues in the region from about residue 529 to about residue 625 of the ErbB2 extracellular domain sequence."

Baselga '96 in view of Baselga '94 and Gelmon '96 teaches the method of claim 1. (*See supra* Section IX.D.1) The '549 patent concedes that the 4D5 antibody binds to the claimed amino acid residues. (Ex. 1001 at 5:32–37) Baselga '96 teaches that rhuMAb HER2 is a humanized form of the murine 4D5 antibody. (Ex. 1005 at 9; *see supra* Section IX.D.1.g) Because rhuMAb HER2 possesses the same complementarity determining regions as 4D5 it necessarily also binds to the claimed amino acid residues. (Ex. 1011 ¶¶ 172–174; Ex. 1070 ¶¶ 167-169)

5. Claim 5

a. Preamble: "A method for the treatment of a human patient with breast cancer characterized by overexpression of ErbB2 receptor, comprising"

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "[a] method for the treatment of a human patient with breast cancer characterized by overexpression of ErbB2 receptor." (*See supra* Section IX.D.1.a)

b. Element [a]: "administering an effective amount of a combination of an anti-ErbB2 antibody which binds epitope 4D5 within the ErbB2 extracellular domain sequence,"

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "administering an effective amount of a combination." Since "an amount effective to extend the

time to disease progression," would be an "effective amount," Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "an effective amount." (Ex. 1011 ¶¶ 176–177; Ex. 1070 ¶¶ 171-172; *see supra* Section IX.D.1.f)

Baselga '96 also discloses "an anti-ErbB2 antibody which binds epitope 4D5 within the ErbB2 extracellular domain sequence." (*See supra* Section IX.D.1.g; Ex. 1011 ¶¶ 176–177; Ex. 1070 ¶¶ 171-172)

c. Element [b]: "a taxoid"

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses a combination of rhuMAb HER2 and "a taxoid." (*See supra* Section IX.D.1.c)

d. Element [c]: "and a further therapeutic agent,"

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "a further therapeutic agent." Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "a further growth inhibitory agent." (*See supra* Section IX.D.1.d) Claim 11 provides that a "therapeutic agent" may be a "growth inhibitory agent." (Ex. 1001 at claim 11) Therefore, a "therapeutic agent" includes a "growth inhibitory agent." (Ex. 1011 ¶ 179; Ex. 1070 ¶ 174)

e. Element [d]: "to the human patient."

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "to the human patient." (*See supra* Section IX.D.1.e)

f. Conclusion

For the same reasons discussed in Section IX.D.1.h, it would have been obvious to a POSA to try the combination of rhuMAb HER2, paclitaxel, and cisplatin as recited in claim 5 with a reasonable expectation of success.

6. Claim 6: "The method of claim 5 wherein the breast cancer is metastatic breast carcinoma."

Baselga '96, in view of Baselga '94 and Gelmon '96, teaches the method of claim 5. (*See supra* Section IX.D.5) Baselga '96 discloses that "[p]atients eligible for this study were adult women whose metastatic breast carcinomas overexpressed HER2." (Ex. 1005 at 10; Ex. 1011 ¶¶ 182–183; Ex. 1070 ¶¶ 177-178)

7. Claim 7: "The method of claim 5 wherein the antibody is a humanized 4D5 anti-ErbB2 antibody."

Baselga '96 in view of Baselga '94 and Gelmon '96 teaches the method of claim 5. (*See supra* Section IX.D.5) Baselga '96 teaches that rhuMAb HER2 is a humanized form of the murine 4D5 antibody. (*See supra* Section IX.D.1.g)

8. Claim 8: "The method of claim 7 wherein the antibody is administered as a 4 mg/kg dose and then weekly administration of 2 mg/kg."

Baselga '96 in view of Baselga '94 and Gelmon '96 teaches the method of claim 7. (*See supra* Section IX.D.7) Baselga '96 treated patients with "a loading dose of 250 mg of intravenous rhuMAb HER2, then 10 weekly doses of 100 mg

each." (Ex. 1005 at 9) This dose resulted in an amount effective to extend the time to disease progression by 5.1 months. (*Id.*) In addition, more than 90% of patients achieved adequate serum concentrations of the antibody. (*Id.*)

A POSA in clinical oncology would know that it is more reliable to administer drugs on a weight-based basis to more reliably achieve adequate serum concentrations of the drug. (Ex. 1011 ¶¶ 187–188; Ex. 1070 ¶¶ 182-183) In this case, assuming a patient weight between 55–85 kg, the corresponding weight-based dose is a loading dose of approximately 2.9–4.5 mg/kg (*i.e.*, 250 mg divided by either 85 kg or 55 kg respectively) followed by a weekly maintenance dose of 1.2–1.8 mg/kg (*i.e.*, 100 mg divided by either 85 kg or 55 kg respectively). (Ex. 1011 ¶¶ 39 (citing Ex. 1044 at 334 (Table 7-2)), 187–188; Ex. 1070 ¶¶ 34, 182-183)

As taught by Baselga '96, this dose range will result in a plasma concentration above the target minimum in more than 90% of patients. (Ex. 1005 at 9) The '549 patent contains no data showing that this claimed dosing regimen had any unexpected properties or was otherwise distinguishable from the range of doses derived directly from Baselga '96. (Ex. 1011 ¶ 189; Ex. 1070 ¶ 184) *See Woodruff*, 919 F.2d at 1578 ("The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims . . . These cases have consistently held that in such a situation,

the applicant must show that the particular range is *critical*, generally by showing that the claimed range achieves unexpected results relative to the prior art range.").

9. Claim 9: "The method of claim 5 wherein the taxoid is paclitaxel."

Baselga '96 in view of Baselga '94 and Gelmon '96 teaches the method of claim 5. (*See supra* Section IX.D.5) As discussed above in Section IX.D.1.c, Baselga '96 discloses the taxoid paclitaxel. (Ex. 1005 at 13; Ex. 1011 ¶¶ 190–191; Ex. 1070 ¶¶ 185-186)

10. Claim 10: "The method of claim 5 wherein efficacy is measured by determining the time to disease progression or the response rate."

Baselga '96 in view of Baselga '94 and Gelmon '96 teaches the method of claim 5. (*See supra* Section IX.D.5) Baselga '96 in view of Baselga '94 and Gelmon '96 teaches measuring the results by the time to disease progression. (*See supra* Section IX.D.1.f) Baselga '96 also reports that, out of the patients treated with rhuMAb HER2, the overall response rate was 11.6%. (Ex. 1005 at 13) It would have been obvious to a POSA to measure the overall response rate of the combination therapy based on this disclosure. (Ex. 1011 ¶¶ 192–193; Ex. 1070 ¶¶ 187-188)

11. Claim 11: "The method of claim 5 wherein the further therapeutic agent is selected from the group consisting of . . . growth inhibitory agent."

Baselga '96 in view of Baselga '94 and Gelmon '96 teaches the method of

claim 5. (*See supra* Section IX.D.5) Baselga '96 in view of Baselga '94 and Gelmon '96 teaches a "growth inhibitory agent." (*See supra* Section IX.D.1.d)

12. Claim 14: "The method of claim 5 wherein the further therapeutic agent is a growth inhibitory agent."

Baselga '96, in view of Baselga '94 and Gelmon '96, teaches the method of claim 5. (*See supra* Section IX.D.5) Baselga '96, in view of Baselga '94 and Gelmon '96, teaches a "growth inhibitory agent." (*See supra* Section IX.D.1.d)

13. Claim 15: "The method of claim 14 wherein the growth inhibitory agent is a DNA alkylating agent."

Baselga '96 in view of Baselga '94 and Gelmon '96 teaches the method of claim 14. (*See supra* Section IX.D.12) Baselga '96 in view of Baselga '94 and Gelmon '96 teaches the combination of rhuMAb HER2 with paclitaxel and cisplatin. (*See supra* Section IX.D.1.d) Cisplatin is a DNA alkylating agent. (Ex. 1001 at 11:31–34; Ex. 1011 ¶¶ 198–199; Ex. 1070 ¶¶ 193-194)

14. Claim 16

a. Preamble: "A method for the treatment of a human patient with ErbB2 overexpression breast cancer, comprising"

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "[a] method for the treatment of a human patient with ErbB2 overexpressing breast cancer." (*See supra* Section IX.D.1.a)

b. Element [a]: "administering a combination of an antibody that binds epitope 4D5 within the ErbB2 extracellular domain sequence,"

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "[a] method for the treatment of a human patient with ErbB2 overexpressing breast cancer." (*See supra* Section IX.D.1.a)

c. Element [b]: "a taxoid"

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses a combination of rhuMAb HER2 and "a taxoid." (*See supra* Section IX.D.1.c)

d. Element [c]: "and a further growth inhibitory agent,"

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "a further growth inhibitory agent." (*See supra* Section IX.D.1.d)

e. Element [d]: "in the absence of an anthracycline derivative,"

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "in the absence of an anthracycline derivative." The cardiotoxicity of anthracycline derivatives were known in the prior art. (Ex. 1011 ¶ 204; Ex. 1070 ¶ 199) Consistent with this, Baselga '96 reports a patient that could not be examined at follow-up because she died of heart failure associated with prior doxorubicin treatment. (Ex. 1005 at 12)

Baselga '96, in view of Baselga '94 and Gelmon '96, teaches the absence of an anthracycline derivative because Baselga '96, in view of Baselga '94 and

Gelmon ’96, teaches the combination of rhuMAb HER2, paclitaxel and cisplatin. (*See, e.g.*, *supra* Section IX.D.1.b-f) Accordingly, a POSA reading Baselga ’96 in view of Baselga ’94 and Gelmon ’96 would have known there is a substantial likelihood that patients will have already received a course of anthracycline therapy, and thus it would be advantageous to pursue synergistic drug combinations—like paclitaxel with cisplatin—that include drugs other than anthracyclines. See Ex. 1025 at 9. A POSA therefore would not be motivated to combine rhuMAb HER2, a taxoid, and an anthracycline derivative and in fact, would be motivated not to do so due to the known cardiotoxic effects of anthracyclines. (Ex. 1011 ¶¶ 204–205; Ex. 1070 ¶ 199-200)

f. Element [e]: “to the human patient”

Baselga ’96 in view of Baselga ’94 and Gelmon ’96 discloses “to the human patient.” (*See supra* Section IX.D.1.e)

g. Element [f]: “in an amount effective to extend the time to disease progression in the human patient.”

Baselga ’96 in view of Baselga ’94 and Gelmon ’96 discloses “in an amount effective to extend the time to disease progression in the human patient.” (*See supra* Section IX.D.1.f)

h. Conclusion

For the same reasons discussed in Section IX.D.1.h, it would have been obvious to a POSA to try the combination of rhuMAb HER2, paclitaxel, and

cisplatin in the absence of an anthracycline as recited by claim 16 with a reasonable expectation of success.

15. Claim 17: "The method of claim 16 wherein the breast cancer is metastatic breast carcinoma."

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses the method of claim 16. (*See supra* Section IX.D.14) Baselga '96 teaches "metastatic breast carcinoma." (*See supra* Section IX.D.6.a)

E. Ground 5: Claim 12 is unpatentable as obvious over Baselga '96 in view of Baselga '94, Gelmon '96 and Drebin '88

Claim 12: "The method of claim 5 wherein the further therapeutic agent is another ErbB2 antibody."

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses the method of claim 5. (*See supra* Section IX.D.5) Further, Drebin '88 teaches that antibodies against "two distinct regions on the p185 molecule" "resulted in synergistic anti-tumor effects." (Ex. 1010 at 4) A POSA would have been motivated to combine the teachings of Drebin '88 with those of Baselga '96 because anti-ErbB2 antibodies act to sensitize tumor cells to the effects of chemotherapeutic agents. (Ex. 1005 at 15)

Since the blockade of the 4D5 domain does not result in complete tumor suppression, (Ex. 1006 at 4), a POSA would look to Drebin '88's teaching that blockade of multiple target domains could result in complete tumor suppression,

and thus greater sensitization to those same chemotherapeutic agents. (Ex. 1011 ¶¶ 212–214; Ex. 1070 ¶¶ 208-210) As such, a POSA would have been motivated to try another ErbB2 antibody, as taught by Drebin '88. Notably the '549 patent discloses no experiments using "another ErbB2 antibody" providing confirmation that a POSA would know the claimed combination would work.

F. Ground 6: Claim 13 is unpatentable as obvious over Baselga '96 in view of Baselga '94, Gelmon '96, and Presta '97

Claim 13: "The method of claim 5 wherein the further therapeutic agent is a vascular endothelial growth factor (VEGF) antibody."

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses the method of claim 5. (*See supra* Section IX.D.5) Presta '97 further teaches that antibodies against the cytokine VEGF can result in substantial tumor control. (Ex. 1012 at 8) And Presta '97 provides a humanized antibody against VEGF ready for use in humans. (*Id.* at 11) Baselga '96, Baselga '94, Gelmon '96 and Presta '97 are directed to cancer therapies, and a POSA would have been motivated to combine the teachings of Baselga '96 and Presta '97 because it was well-understood that ErbB2 and VEGF act on unrelated pathways, and so have at least an additive, if not a synergistic effect, with a low or nonexistent likelihood of overlapping toxicity. (*See* Ex. 1025 at 9–10; Ex. 1011 ¶¶ 216–218; Ex. 1070 ¶¶ 212-214) As such, a POSA would have been motivated to try a VEGF antibody, as taught by Presta '97.

Notably the ’549 patent discloses no experiment using a VEGF antibody providing confirmation that a POSA would have known the claimed combination would work.

G. Secondary India do not support a finding of nonobviousness

On October 15, 2009, Genentech submitted the Declaration of Mark Sliwkowski, Ph.D. (Ex. 1019–6:341) This Declaration argued the claims of the ’824 application were patentable over the prior art because a POSA would not have had a reasonable expectation of success treating humans with a two-drug combination of rhuMAb HER2 and paclitaxel. (*Id.* at 6:343–45) Dr. Sliwkowski’s Declaration did *not* address three-drug combinations as claimed by the ’549 patent. As to the two-drug combination, Dr. Sliwkowski’s argument was two-fold.

Dr. Sliwkowski first argued that treatment with paclitaxel results in G2/M cell cycle arrest whereas rhuMAb HER2 results in G1 cell cycle arrest. (*Id.* at 6:343) Since the two treatments cause cell cycle arrest at different times, Dr. Sliwkowski argued a POSA in 1997 would have thought that rhuMAb HER2 would prevent paclitaxel from working since cells would arrest prior to the G_2/M phase. (*Id.* at 6:343–44) Dr. Sliwkowski further supported his argument by analogizing to combination treatments with tamoxifen and anthracyclines that similarly cause cell cycle arrest at different times, and exhibit an antagonistic effect. (*Id.*)

Dr. Sliwkowski's first argument fails for three reasons. *First*, none of the papers he relies upon examines the combination of rhuMAb HER2 and paclitaxel. (*Id.* at 6:383 (Ex. C), 6:392 (Ex. D); Ex. 1011 ¶¶ 221–222; Ex. 1070 ¶¶ 217-218)

Second, by 1994, other research had already demonstrated that rhuMAb HER2 was compatible with chemotherapies, such as cisplatin, that also show G2/M cell cycle arrest. (*See, e.g.*, Ex. 1022 at 7 (cisplatin causes G2 cell cycle arrest); Ex. 1023 (the combination of 4D5 anti-ErbB2 antibody and cisplatin caused a synergistic decrease in cell growth *in vitro*); and Ex. 1013 at 5 (combined treatment of rhuMAb HER2 and cisplatin in breast cancer patients resulted in 50% of patients with stable disease or better without increasing cisplatin toxicity); *see also* Ex. 1011 ¶¶ 223–224; Ex. 1070 ¶¶ 219-220)

Third, a POSA in 1997 would have understood the data that Dr. Sliwkowski cited related to tamoxifen and anthracyclines actually shows that his hypothesis regarding rhuMAb HER2 and paclitaxel is incorrect. Both articles he cites report *in vitro* data showing tamoxifen reduced cell killing effects of anthracyclines. (Ex. 1019–7:17 (Ex. F), 7:26 (Ex. G)) By contrast, Baselga '94 reports *in vivo* data demonstrating a synergistic effect between the 4D5 antibody and paclitaxel. (Ex. 1006 at 4) If Dr. Sliwkowski's hypothesis were correct, the preclinical data should have shown a *less than additive* effect when the drugs are both administered. (*See* Ex. 1019–7:26 (Ex. G); Ex. 1011 ¶ 225; Ex. 1070 ¶ 221) Since Baselga '94 reports

the opposite and further reports that clinical trials are ongoing, a POSA would have found it obvious to try the combination with a reasonable expectation of success.

Dr. Sliwkowski's second argument is that a POSA would not have a reasonable expectation of success in humans based on preclinical models because "significant controversy exists about the usefulness of these preclinical models in predicting the response of human patients to therapy." (Ex. 1019–6:344–45) But, Genentech relied on the information disclosed in the Baselga prior art, including at least Baselga '97 (*i.e.*, the phase II trial of the antibody single therapy, and the *in vitro* and *in vivo* preclinical data) when it determined it would proceed with a phase III trial of the drug combination. Indeed, it cites this prior art as the written description of its invention. Moreover, Dr. Sliwkowski's support for his argument comes from a non-prior art 2001 article. (*Id.*)

The purported controversy regarding preclinical models does not affect their use in research, nor does it affect whether a POSA will use such models to determine which treatments should be pursued in humans. Indeed, Dr. Sliwkowski is a co-author on many Genentech research papers using preclinical data in order to screen and select for novel treatments using anti-ErbB2 antibodies. (*See, e.g.*, Ex. 1017 at 7 ("Because trastuzumab linked to DM1 . . . offers improved efficacy and pharmacokinetics and reduced toxicity over the reducible disulfide linkers

evaluated, trastuzumab-MCC-DM1 was selected for clinical development."); Ex. 1018)

POSAs regularly use such models to screen treatments and select promising drugs for trial. Here, a POSA would have seen that Baselga '94 demonstrated synergistic effects of the drug combination in a mouse model and reported a clinical trial underway, then Baselga '96 and Baselga '97 report the same clinical trial as underway two and three years later, respectively. (Ex. 1006 at 4; Ex. 1005 at 15; Ex. 1007 at 10) A POSA would have understood this to mean that the trial had not been halted for lack of efficacy or safety. (Ex. 1011 ¶ 227; Ex. 1070 ¶ 223) POSAs like Drs. Baselga, Pegram, and Hellmann turned to the most obvious targets: combinations of known therapies seeking synergistic effects. Accordingly, there are no secondary considerations supporting nonobviousness of the '549 patent. (*Id.*)

Genentech's purported unexpected results also lack a nexus to the claimed inventions. The assertions in Dr. Sliwkowski's Declaration are directed to a paclitaxel and rhuMAb HER2 combination therapy, but that therapy already was disclosed in the prior art, including Baselga '97, '96, and '94. Genentech identified no secondary indicia of non-obviousness associated with any elements of the claimed invention not already in the prior art. Genentech's purported unexpected results further are not commensurate in scope with the Challenged

Claims, many of which are generally directed to methods of treatment involving any "taxoid." (*See* Ex. 1011 ¶ 228; Ex. 1070 ¶ 224)

X. CONCLUSION

For the foregoing reasons, Bioepis respectfully requests cancellation of claims 1-17 of the '549 patent.

* * *

Date: August 25, 2017

Respectfully submitted,

/s/ Dimitrios T. Drivas

Dimitrios T. Drivas
USPTO Reg. No. 32,218
Scott T. Weingaertner
USPTO Reg. No. 37,756
White & Case LLP
1221 Avenue of the Americas
New York, New York 10020
T: (212) 819-8200
ddrivas@whitecase.com
scott.weingaertner@whitecase.com

Counsel for
Samsung Bioepis Co., Ltd.

CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. 42.24(d)

Pursuant to 37 C.F.R. §§ 42.24(a)(1)(i) and 42.24(d), I hereby certify that the number of words in this Petition is 13,897, excluding the Table of Contents, the Table of Authorities, the Mandatory Notices under § 42.8, Certificate of Service, Certificate of Word Count, signature block, and appendix listing of exhibits. In determining the number of words, Counsel relied upon Microsoft Word's word count feature.

Date: August 25, 2017

Signed,

/s/ Dimitrios T. Drivas
Dimitrios T. Drivas
USPTO Reg. No. 32,218
Scott T. Weingaertner
USPTO Reg. No. 37,756

Counsel for
Samsung Bioepis Co., Ltd.

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6 and 42.105, I hereby certify that on this 25th day of August, 2017, the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 7,892,549 and accompanying exhibits referenced therein were served via PRIORITY MAIL EXPRESS for single-day overnight delivery on the Patent Owner at the following correspondence address of record in PAIR:

Genentech, Inc.
Wendy M. Lee
1 DNA Way
South San Francisco, CA 94080-4990

The foregoing Petition and accompanying exhibits referenced therein were also served on this 25th day of August, 2017 via PRIORITY MAIL EXPRESS for single-day overnight delivery on the Patent Owner at an address known to the Petitioner as likely to affect service.

David L. Cavanaugh
Wilmer Cutler Pickering Hale and Dorr LLP
1875 Pennsylvania Ave., NW
Washington DC 20006

Date: August 25, 2017

Signed,

/s/ Dimitrios T. Drivas
Dimitrios T. Drivas
USPTO Reg. No. 32,218
Scott T. Weingaertner
USPTO Reg. No. 37,756

Counsel for
Samsung Bioepis Co., Ltd.