

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the *Inter Partes* Review of:

Trial Number: To Be Assigned

U.S. Patent No. 7,846,441

Filed: December 10, 1998

Issued: December 7, 2010

Inventor(s): Susan D. Hellmann

Assignee: Genentech, Inc.

Title: Treatment with Anti-ErbB2 Antibodies

Panel: To Be Assigned

---

Mail Stop *Inter Partes* Review

Commissions for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

**PETITION FOR *INTER PARTES* REVIEW OF  
U.S. PATENT NO. 7,846,441  
UNDER 35 U.S.C. §311 AND 37 C.F.R. §42.100**

## TABLE OF CONTENTS

	<u>Page</u>
I. PRELIMINARY STATEMENT .....	1
II. MANDATORY NOTICES – 37 C.F.R. §42.8(A)(1) AND (B) .....	3
A. 37 C.F.R. §42.8(b)(1): Real Party-In-Interest.....	3
B. 37 C.F.R. §42.8(b)(2): Related Matters .....	3
C. 37 C.F.R. §42.8(b)(3): Lead And Back-Up Counsel .....	4
D. 37 C.F.R. §42.8(b)(4): Service Information.....	5
III. PAYMENT OF FEES – 37 C.F.R. §42.103 .....	6
IV. GROUNDS FOR STANDING – 37 C.F.R. §42.104(a) .....	6
V. IDENTIFICATION OF CHALLENGE –37 C.F.R. §42.104(b).....	6
VI. THE CLAIMS OF THE '441 PATENT ARE UNPATENTABLE .....	8
A. Level Of Ordinary Skill.....	8
B. State Of The Art .....	8
(1) rhuMAb HER2 And Paclitaxel .....	8
(2) Chemotherapeutic Combinations And Anthracyclines .....	9
C. The Prosecution History.....	10
D. Legal Standards For Obviousness And Prior Art Disclosure .....	12
E. 37 C.F.R. §42.104(b)(3): Claim Construction .....	14
(1) “in the absence of an anthracycline derivative” .....	14
F. The Prior Art .....	16
(1) Lottery.....	16
(2) Hayes17	

(3)	Baselga '96.....	18
(4)	Gelmon.....	20
(5)	Baselga '94.....	21
G.	Detailed Explanation Of Grounds Of Unpatentability.....	22
	Ground 1: Claims 1–14 Are Invalid Based On Lottery, In View Of Hayes And/Or Baselga '96, And Gelmon.....	22
(1)	Claim 1 .....	24
	a. Preamble: “A method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by over-expression of ErbB2 receptor, comprising” .....	24
	b. Element [a]: “administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence” .....	25
	c. Element [b]: “a taxoid” .....	27
	d. Element [c]: “in the absence of an anthracycline derivative” .....	29
	e. Element [d]: “to the human patient” .....	31
	f. Element [e]: “in an amount effective to extend the time to disease progression in the human patient” .....	32
	g. Element [f]: “without increase in overall severe adverse events” .....	34
(2)	Claim 2.....	35
	a. “The method of claim 1 wherein said patient has a malignant tumor” .....	35
(3)	Claim 3.....	35
	a. “The method of claim 1 wherein said patient has cancer” .....	35

(4) Claim 4.....36

    a. “The method of claim 3 wherein said cancer is selected from the group consisting of breast cancer [and other cancers]”.....36

(5) Claim 5.....36

    a. “The method of claim 4 wherein said cancer is breast cancer”.....36

(6) Claim 6.....36

    a. “The method of claim 5 wherein said cancer is metastatic breast carcinoma”.....36

(7) Claim 7.....36

    a. “The method of claim 1 wherein said antibody is a humanized 4D5 anti-ErbB2 antibody”.....36

(8) Claim 8.....37

    a. “The method of claim 1 wherein said taxoid is paclitaxel”.....37

(9) Claim 9.....37

    a. “The method of claim 8 wherein the effective amount of said combination is lower than the sum of the effective amounts of said anti-ErbB2 antibody and said taxoid, when administered individually, as single agents”.....37

(10) Claim 10.....39

    a. “The method of claim 1 wherein efficacy is further measured by determining the response rate”.....39

(11) Claim 11.....40

    a. Preamble: “A method for the treatment of a human patient with ErbB2 overexpressing progressing metastatic breast cancer, comprising”.....40

b.	Element [a]: “administering a combination of a humanized 4D5 anti-ErbB2 antibody” .....	40
c.	Element [b]: “a taxoid” .....	40
d.	Element [c]: “in the absence of an anthracycline derivative” .....	40
e.	Element [d]: “to the human patient” .....	40
f.	Element [e]: “in an amount effective to extend the time to disease progression in said human patient” .....	40
g.	Element [f]: “without increase in overall severe adverse events” .....	40
(12)	Claim 12 .....	40
a.	“The method of claim 11, wherein said taxoid is paclitaxel” .....	40
(13)	Claim 13 .....	41
a.	Preamble: “A method for the treatment of a human patient with a progressing malignant tumor or cancer characterized by overexpression of ErbB2 receptor, comprising” .....	41
b.	Element [a]: “administering a combination of a humanized 4D5 anti-ErbB2 antibody which comprises a human Fc region that binds to epitope 4D5 within the ErbB2 extracellular domain sequence” .....	41
c.	Element [b]: “and a taxoid” .....	42
d.	Element [c]: “in the absence of an anthracycline derivative” .....	42
e.	Element [d]: “to the human patient” .....	42
f.	Element [e]: “in an amount effective to extend the time to disease progression in said human patient” .....	42

g. Element [f]: “without increase in overall severe adverse events.” .....42

(14) Claim 14 .....42

a. Preamble: “A method for the treatment of a human patient with ErbB2 expressing progressing metastatic breast cancer, comprising” .....42

b. Element [a]: “administering a combination of an antibody which binds to epitope 4D5 within the extracellular domain sequence” .....43

c. Element [b]: “and a taxoid,” .....43

d. Element [c]: “in the absence of an anthracycline derivative,” .....43

e. Element [d]: “to the human patient.” .....43

f. Element [e]: “in an amount effective to extend the time to disease progression in said human patient.” .....43

g. Element [f]: “without increase in overall severe adverse events.” .....43

Ground 2: Claims 1–14 Are Invalid Based On Baselga ’96 In View Of Baselga ’94 And Gelmon .....44

(1) Claim 1 .....44

a. Preamble: “A method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by over-expression of ErbB2 receptor, comprising” .....44

b. Element [a]: “administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence” .....45

c. Element [b]: “a taxoid,” .....45

d.	Element [c]: “in the absence of an anthracycline derivative,” .....	46
e.	Element [d]: “to the human patient,” .....	48
f.	Element [e]: “in an amount effective to extend the time to disease progression in the human patient,” .....	48
g.	Element [f]: “without increase in overall severe adverse events.” .....	50
(2)	Claim 2 .....	51
a.	“The method of claim 1 wherein said patient has a malignant tumor.” .....	51
(3)	Claim 3 .....	51
a.	“The method of claim 1 wherein said patient has cancer.” .....	51
(4)	Claim 4 .....	51
a.	“The method of claim 3 wherein said cancer is selected from the group consisting of breast cancer [and other cancers].” .....	51
(5)	Claim 5 .....	52
a.	“The method of claim 4 wherein said cancer is breast cancer.” .....	52
(6)	Claim 6 .....	52
a.	“The method of claim 5 wherein said cancer is metastatic breast carcinoma.” .....	52
(7)	Claim 7 .....	52
a.	“The method of claim 1 wherein said antibody is a humanized 4D5 anti-ErbB2 antibody.” .....	52
(8)	Claim 8 .....	52

a. “The method of claim 1 wherein said taxoid is paclitaxel.” .....52

(9) Claim 9 .....53

a. “The method of claim 8 wherein the effective amount of said combination is lower than the sum of the effective amounts of said anti-ErbB2 antibody and said taxoid, when administered individually, as single agents.” .....53

(10) Claim 10 .....54

a. “The method of claim 1 wherein efficacy is further measured by determining the response rate.” .....54

(11) Claim 11 .....54

a. Preamble: “A method for the treatment of a human patient with ErbB2 overexpressing progressing metastatic breast cancer, comprising” .....54

b. Element [a]: “administering a combination of a humanized 4D5 anti-ErbB2 antibody,” .....54

c. Element [b]: “a taxoid,” .....54

d. Element [c]: “in the absence of an anthracycline derivative,” .....54

e. Element [d]: “to the human patient.” .....54

f. Element [e]: “in an amount effective to extent the time to disease progression in said human patient.” .....55

g. Element [f]: “without increase in overall severe adverse events.” .....55

(12) Claim 12 .....55

a. “The method of claim 11, wherein said taxoid is paclitaxel.” .....55

(13) Claim 13 .....55



a.	Preamble: “A method for the treatment of a human patient with a progressing malignant tumor or cancer characterized by overexpression of ErbB2 receptor, comprising” .....	55
b.	Element [a]: “administering a combination of a humanized 4D5 anti-ErbB2 antibody which comprises a human Fc region that binds to epitope 4D5 within the ErbB2 extracellular domain sequence” .....	55
c.	Element [b]: “and a taxoid,” .....	56
d.	Element [c]: “in the absence of an anthracycline derivative,” .....	56
e.	Element [d]: “to the human patient.” .....	56
f.	Element [e]: “in an amount effective to extend the time to disease progression in said human patient.” .....	56
g.	Element [f]: “without increase in overall severe adverse events.” .....	56
(14)	Claim 14 .....	56
a.	Preamble: “A method for the treatment of a human patient with ErbB2 expressing progressing metastatic breast cancer, comprising” .....	56
b.	Element [a]: “administering a combination of an antibody which binds to epitope 4D5 within the extracellular domain sequence” .....	57
c.	Element [b]: “and a taxoid,” .....	57
d.	Element [c]: “in the absence of an anthracycline derivative,” .....	57
e.	Element [d]: “to the human patient.” .....	57
f.	Element [e]: “in an amount effective to extend the time to disease progression in said human patient.” .....	57

g. Element [f]: “without increase in overall severe adverse events.” .....57

H. There Are No Secondary Considerations of Nonobviousness.....57

I. The Board Should Not Deny Institution Under 35 U.S.C. §§314 or 325(d) .....60

VII. CONCLUSION.....70

## TABLE OF AUTHORITIES

	<b>Page(s)</b>
<b>Cases</b>	
<i>Abbvie Inc. v. Kennedy Trust for Rheumatology Research</i> , No. 13 Civ. 1358(PAC), 2014 WL 3360722 (S.D.N.Y. July 9, 2014), <i>aff'd</i> 599 Fed. App'x. 956 (Fed. Cir. 2015).....	27, 45
<i>Dawson v. Dawson</i> , 710 F.3d 1347 (Fed. Cir. 2013) .....	14
<i>Dome Patent L.P. v. Lee</i> , 799 F.3d 1372 (Fed. Cir. 2015) .....	13
<i>Ex parte Gillis</i> , No. 2010-09318, 2011 WL 5884125 (B.P.A.I. Nov. 21, 2011).....	13
<i>Ex parte Litwin</i> , No. 2009-011704, 2011 WL 3414500 (B.P.A.I. Aug. 2, 2011).....	13, 15
<i>Ex parte Tsao</i> , No. 1996-2766, 2000 WL 1593621 (B.P.A.I. Feb. 22, 2000).....	15
<i>Hospira UK, Ltd. v. Genentech, Inc.</i> , No. A3 2015 3238, [2016] EWCA Civ 1185 (Nov. 30, 2016).....	3, 64
<i>Hospira UK, Ltd. v. Genentech, Inc.</i> , No. HP-2014-000034, [2015] EWHC (HC) 1796 (Pat), (Jun. 24, 2015) .....	3, 64
<i>In re Kubin</i> , 561 F.3d 1351 (Fed. Cir. 2009) .....	passim
<i>Invitrogen Corp. v. Biocrest Mfg., L.P.</i> , 327 F.3d 1364 (Fed. Cir. 2003) .....	66
<i>KSR Int'l Co. v. Teleflex, Inc.</i> , 550 U.S. 398 (2007).....	12

*Ortho-McNeil Pharm. Inc. v. Kali Labs. Inc.*,  
482 F. Supp. 2d 478 (D.N.J. 2007),  
*vacated on other grounds*, 344 Fed. App'x 595 (Fed. Cir. 2009) .....13

*Par Pharms., Inc. v. TWI Pharms., Inc.*,  
Civil No. CCB-11-2466, 2014 WL 3956024 (D. Md. Aug. 12, 2014) .....67

*Santarus, Inc. v. Par Pharm., Inc.*,  
694 F.3d 1344 (Fed. Cir. 2012) ..... passim

*Superguide Corp. v. DirecTV Enterprises, Inc.*,  
358 F.3d 870 (Fed. Cir. 2004) .....14

**Statutes**

35 U.S.C. § 311 .....1

35 U.S.C. § 314 ..... 3, 60

35 U.S.C. § 315 .....6

35 U.S.C. § 325 .....3

35 U.S.C. §103 .....6

35 U.S.C. § 325(d) .....60

**Regulations**

37 C.F.R. §1.68 .....7

37 C.F.R. §42.10(b) .....5

37 C.F.R. §42.100 .....1

37 C.F.R. §42.100(b) .....14

37 C.F.R. §42.104(b)(1) .....6

37 C.F.R. §42.104(b)(2) .....6

37 C.F.R. §42.15(a) .....6

<b>PETITIONER’S EXHIBIT LIST</b>	
<b>Exhibit No.</b>	<b>Description</b>
1001	U.S. Patent No. 7,846,441
1002	Assignment to Genentech, Inc. filed in U.S. Patent No. 7,846,441
1003	<i>Hospira UK, Ltd. v. Genentech, Inc.</i> , Case No. HP-2014-000034, [2015] EWHC (CH) 1796 (Pat), (Jun. 24, 2015), Approved Judgment
1004	Eur. Patent Specification No. 1,037,926 B1
1005	Baselga <i>et al.</i> , <i>Phase II Study of Weekly Intravenous Recombinant Humanized Anti-p185<sup>HER2</sup> Monoclonal Antibody in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer</i> , 14(3) J. CLIN. ONCOL. 737–44 (1996) (“Baselga ’96”)
1006	Baselga <i>et al.</i> , <i>Anti-HER2 Humanized Monoclonal Antibody (Mab) Alone and in Combination with Chemotherapy Against Human Breast Carcinoma Xenografts</i> , 13 PROC. AM. SOC. CLIN. ONCOL. 63 (Abstract 53) (1994) (“Baselga ’94”)
1007	Baselga <i>et al.</i> , <i>HER2 Overexpression and Paclitaxel Sensitivity in Breast Cancer: Therapeutic Implications</i> , 11(3)(Suppl. 2) ONCOL. 43–48 (1997) (“Baselga ’97”)
1008	Monmaney, T., <i>A Lottery of Life, Death—and Hope</i> , L.A. Times, Aug. 3, 1996, A1, A16–17 (“Lottery”)
1009	Hayes, D.T., <i>Editorial: Should We Treat HER, Too?</i> 14(3) J. CLIN. ONCOL. 697–99 (1996)
1010	U.S. Patent No. 7,892,549
1011	Declaration of Allan Lipton, M.D.
1012	U.S. Provisional Patent Application No. 60/069,346, Dec. 12, 1997

**PETITIONER’S EXHIBIT LIST**

<b>Exhibit No.</b>	<b>Description</b>
1013	<i>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</i> , 14 PROC. AM. SOC. CLIN. ONCOL. 106 (Abstract 124) (1995) (“Pegram ’95”)
1014	Declaration of Karen Younkins
1015	<i>Hudziak et al., p185<sup>HER2</sup> Monoclonal Antibody has Antiproliferative Effects in Vitro and Sensitizes Human Breast Tumor Cells to Tumor Necrosis Factor</i> , 9(3) MOLECULAR AND CELLULAR BIOLOGY 1165–72, (1989) (“Hudziak ’89”)
1016	<i>Gelmon et al., Phase I/II Trial of Biweekly Paclitaxel and Cisplatin in the Treatment of Metastatic Breast Cancer</i> , 14(4) J. CLIN. ONCOL. 1185–91 (1996) (“Gelmon”)
1017	<i>Phillips et al., Targeting HER2-Positive Breast Cancer with Trastuzumab-DM1, an Antibody–Cytotoxic Drug Conjugate</i> , 68(22) CANCER RES. 280–90 (2008)
1018	<i>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</i> , 20(2) CLIN. CANCER RES. 456–68 (2014)
1019	Certified File History of U.S. Patent No. 7,846,441 (9 Volumes)
1020	Eur. Patent File History for EP 1,037,926 B1, <i>Decision to Revoke European Patent EP 1,037,926 B1 in Opposition Proceedings Before the European Patent Office in Munich on 02 May 2016</i> , Application No. 98,963,840.8 (Jun. 13, 2016)
1021	<i>Hospira UK Ltd. v. Genentech Inc.</i> , Case No. A3 2015 3238, [2016] EWCA Civ 1185, (Nov. 30, 2016), Approved Judgment

**PETITIONER’S EXHIBIT LIST**

<b>Exhibit No.</b>	<b>Description</b>
1022	Sorenson <i>et al.</i> , <i>Analysis of Events Associated with Cell Cycle Arrest at G<sub>2</sub> Phase and Cell Death Induced by Cisplatin</i> , 82(9) J. NAT’L. CANCER INST. 749–55 (1990)
1023	Pietras <i>et al.</i> , <i>Antibody to HER-2/neu Receptor Blocks DNA Repair After Cisplatin in Human Breast and Ovarian Cancer Cells</i> , 9(7) ONCOGENE 1829–38 (1994)
1024	Declaration of Christopher Lowden
1025	Declaration of Mark Sliwkowski, Ph.D, Oct. 15, 2009
1026	Slamon <i>et al.</i> , <i>Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/neu Oncogene</i> , 235(4785) SCIENCE 177–82 (1987) (“Slamon ’87”)
1027	Slamon <i>et al.</i> , <i>Studies of the HER-2/neu Proto-Oncogene in Human Breast and Ovarian Cancer</i> , 244(4905) SCIENCE 707–12 (1989) (“Slamon ’89”)
1028	Excerpt from Webster’s New World College Dictionary (3d ed. 1996)
1029	Excerpt from The Oxford Dictionary and Thesaurus (Am. ed. 1996)
1030	Pegram <i>et al.</i> , <i>Monoclonal Antibody to HER-2/neu Gene Product Potentiates Cytotoxicity of Carboplatin and Doxorubicin in Human Breast Tumor Cells</i> , 33 PROC. AM. ASS’N FOR CANCER RES., 442 (Abstract 2639) (1992) (“Pegram ’92”)
1031	Shan <i>et al.</i> , <i>Anthracycline-Induced Cardiotoxicity</i> , 125(1) ANN. INTERN. MED. 47–58, (1996) (“Shan ’96”)
1032	Miller <i>et al.</i> , <i>Reporting Results of Cancer Treatment</i> , 47(1) CANCER 207–14 (1981) (“Miller ’81”)

<b>PETITIONER'S EXHIBIT LIST</b>	
<b>Exhibit No.</b>	<b>Description</b>
1033	Johnson <i>et al.</i> , <i>Food and Drug Administration Requirements for Approval of New Anticancer Drugs</i> , 69(10) <i>CANCER TREATMENT REPORTS</i> 1155–57 (1985)
1034	Library of Congress Copyright Record for Baselga '96
1035	Library of Congress Copyright Record for Baselga '97
1036	Library of Congress Copyright Record for Hudziak '89
1037	Library of Congress Copyright Record for Carter '92
1038	Library of Congress Copyright Record for Gelmon
1039	1998 FDA Approved Label for Taxol®
1040	Drugs@FDA: FDA Approved Drug Products for TAXOL, <a href="http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&amp;AppNo=020262">http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&amp;AppNo=020262</a> (last visited Dec. 22, 2016)
1041	Gianni <i>et al.</i> , <i>Paclitaxel and Doxorubicin in Metastatic Breast Cancer</i> , 14(4) <i>J. CLIN. ONCOL.</i> 1403 (1996) (“Gianni '96”)
1042	Holmes, F.A., <i>Paclitaxel Combination Therapy in the Treatment of Metastatic Breast Cancer: A Review</i> , 23(5)(Suppl. 11) <i>SEMINARS ONCOL.</i> 46–56 (1996) (“Holmes '96”)
1043	Rodrigues <i>et al.</i> , <i>Development of a Humanized Disulfide-stabilized Anti-p185<sup>HER2</sup> Fv-β-Lactamase Fusion Protein for Activation of a Cephalosporin Doxorubicin Prodrug</i> , 55(1) <i>CANCER RES.</i> , 63–70 (1995)
1044	Park <i>et al.</i> , <i>Development of Anti-p185<sup>HER2</sup> Immunoliposomes for Cancer Therapy</i> , 92(5) <i>PROC. NATL. ACAD. SCI. USA</i> , 1327–31 (1995)



**PETITIONER’S EXHIBIT LIST**

<b>Exhibit No.</b>	<b>Description</b>
1045	Harries <i>et al.</i> , <i>The Development and Clinical Use of Trastuzumab (Herceptin)</i> , ENDOCRINE-RELATED CANCER 9, 75–85 (2002)
1046	<i>Antibody Showing Promise in Killing Cancer Cells</i> , Chicago TR., April 25, 1996
1047	Library of Congress Copyright Record for Slamon ’87
1048	Declaration of Simon Cohen
1049	Library of Congress Copyright Record for Slamon ’89
1050	Excerpts from Eur. Patent File History for EP 1,037,926 B1
1051	Library of Congress Copyright Record for Pegram ’92
1052	Library of Congress Copyright Record for Shan ’96
1053	Library of Congress Copyright Record for <i>Monmaney</i>
1054	Library of Congress Copyright Record for the Chicago Tribune
1055	Library of Congress Copyright Record for Miller ’81
1056	Library of Congress Copyright Record for Gianni ’96
1057	Library of Congress Copyright Record for Holmes ’96
1058	T. Brody, <i>Negative Limitations in Patent Claims</i> , 41 AM. INTELL. PROP. Q.J. 29, 58 (2013)
1059	3-8 Chisum on Patents §8.06

**PETITIONER’S EXHIBIT LIST**

<b>Exhibit No.</b>	<b>Description</b>
1060	<i>Pegram et al., Phase II Study of Receptor-Enhanced Chemosensitivity Using Recombinant Humanized Anti-p185<sup>HER2/neu</sup> 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)</i>
1061	<i>DeVita et al., A History of Cancer Chemotherapy, 68(21) CANCER RES. 8643–53 (2008)</i>
1062	U.S. Patent No. 5,677,171
1063	<i>Carter, et al., Humanization of an Anti-p185HER2 Antibody for Human Cancer Therapy, 89(10) PROC. NATL. ACAD. SCI. USA 4285–89 (1992) (“Carter ’92”)</i>
1064	Library of Congress Copyright Record for Baselga ’98
1065	Library of Congress Copyright Record for Hayes ’ 96

Pursuant to 35 U.S.C. §311 and 37 C.F.R. §42.100, Petitioner Pfizer Inc. respectfully requests *inter partes* review of claims 1–14 of U.S. Patent No. 7,846,441 (Ex. 1001) (“Challenged Claims”). According to USPTO records, the ’441 patent is assigned to Genentech, Inc. (Ex. 1002).

## **I. PRELIMINARY STATEMENT**

The ’441 patent’s “invention” was the idea to combine two known treatments for HER2-overexpressing breast cancer, the humanized 4D5, anti-ErbB2 antibody Herceptin<sup>®</sup> (rhuMAb HER2) and the taxoid Taxol<sup>®</sup> (paclitaxel). But the same combination was made public over a year before the ’441 patent was filed, *in the LA Times*.

*A Lottery of Life, Death—and Hope* (“*Lottery*”) was published August 3, 1996 in one of the largest metropolitan newspapers in circulation. It is §102(b) art, and cannot be antedated. *Lottery* disclosed to the world that HER2-overexpressing breast cancer patients were being treated with the same combination therapy Patent Owner (“PO”) later claimed.

This Petition’s first Ground, based on *Lottery*, is new and distinct from those presented previously. IPR2017-00731, Paper 1 at 5; IPR2017-02063, Paper 2 at 24. As described in Section VI.I, *Lottery* was only recently discovered by Petitioner’s counsel, and apparently was not identified by the Examiner’s prosecution searches. *Lottery* discloses a clinical trial in which, “[t]o test whether the HER2 antibody

really boosts the effectiveness of taxol, half the women in [the] study receive[d] taxol plus antibody, while the other half receive[d] just taxol.” Ex. 1008 at 3. A POSITA would have known this was the same antibody/taxoid combination of the ’441 patent. And there is no question this treatment was “in the absence of an anthracycline derivative.” There is no way to read *Lottery* as suggesting the three-drug antibody/taxoid/anthracycline derivative combination excluded by that limitation; anthracyclines were not in any “option” discussed in *Lottery*.

The claimed method also is obvious over Baselga ’96 in view of Baselga ’94 and Gelmon. In instituting IPR2017-00737, the Board already determined that the methods of U.S. Patent No. 7,892,549—***which are necessarily encompassed by the challenged ’441 patent claims***—are likely invalid as obvious over this prior art combination. IPR2017-00737, Paper 19. Although Petitioner knew of Gelmon when it filed its first ’441 petition, it reasonably believed Baselga ’96 and ’94 were sufficient to satisfy the “in the absence of an anthracycline derivative” limitation. The Examiner found those references disclosed it during prosecution. Ex. 1019\_1:382–84. PO never argued it was ***not*** disclosed, or even that anyone would be inclined to try the three-drug antibody/taxoid/anthracycline combination it excludes. *Id.* at 1:399–401. Rather, both PO and the Examiner repeatedly took the view that the antibody/taxoid combination would be enough to satisfy that limitation.

Accordingly, consistent with the Board's precedent, these grounds should not be discretionarily denied under 35 U.S.C. §§314 or 325 or otherwise.

## II. MANDATORY NOTICES – 37 C.F.R. §42.8(A)(1) AND (B)

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

Pfizer is the real party-in-interest.

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

Petitioner identifies the following potentially related matters:

- European patent EP 1,037,926 B1 (Ex. 1004)<sup>1</sup> was invalidated and revoked as obvious in two proceedings: (1) *Hospira UK, Ltd. v. Genentech, Inc.*, No. HP-2014-000034, [2015] EWHC (HC) 1796 (Pat), (Jun. 24, 2015) (Ex. 1003), *aff'd Hospira UK, Ltd. v. Genentech, Inc.*, No. A3 2015 3238, [2016] EWCA Civ 1185 (Nov. 30, 2016) (Ex. 1021); and (2) *Decision to Revoke European Patent EP 1,037,926*, Application No. 98,963,840.8 (Jun. 13, 2016) (Ex. 1020).
- IPR2017-00731: Pfizer's subsidiary Hospira Inc. submitted an IPR petition challenging the '441 patent. Institution was denied on July 27,

---

<sup>1</sup> The EP '926 patent and the '441 patent both claim priority to U.S. Provisional Application No. 60/069,346 (Ex. 1012).

2017. A decision on a Request for Rehearing filed by Pfizer (the current sole RPI) on August 25, 2017 has not yet been entered.

- IPR2017-01121: Celltrion, Inc. filed a petition challenging the '441 patent on March 21, 2017. On September 7, 2017, Pfizer moved to join this proceeding with a simultaneously filed petition challenging the same claims on identical grounds, IPR2017-02063. Institution decisions for these IPRs have not yet been entered.
- IPR2017-00737 and -00739: Hospira submitted IPR petitions challenging claims of U.S. Patent No. 7,892,549, a continuation of the '441 patent, on January 20, 2017. On July 27, 2017, institution of IPR2017-00737 was granted but institution of IPR2017-00739 was denied.
- IPR2017-01122: Celltrion filed an IPR petition challenging claims of the '549 patent on March 21, 2017. An institution decision has not yet been entered.
- IPR2017-01960: Samsung Bioepis Co. Ltd. filed an IPR petition challenging claims of the '549 patent on August 25, 2017. An institution decision has not yet been entered.

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

Petitioner designates:

<b>Lead Counsel</b>	<b>Back-up Counsel</b>
<p>Amanda Hollis (Reg. No. 55,629) amanda.hollis@kirkland.com</p> <p><b><u>Postal and Hand-Delivery Address:</u></b></p> <p>KIRKLAND &amp; ELLIS LLP 300 North LaSalle Chicago, IL 60654 Telephone: (312) 862-2011 Facsimile: (312) 862-2200</p>	<p>Karen Younkins (Reg. No. 67,554) karen.younkins@kirkland.com</p> <p><b><u>Postal and Hand-Delivery Address:</u></b></p> <p>KIRKLAND &amp; ELLIS LLP 333 South Hope Street Los Angeles, CA 90071 Telephone: (213) 680-8140 Facsimile: (213) 680-8500</p> <p>Benjamin A. Lasky (to seek <i>pro hac vice</i> admission) benjamin.lasky@kirkland.com Christopher Citro (to seek <i>pro hac vice</i> admission) christopher.citro@kirkland.com</p> <p><b><u>Postal and Hand-Delivery Address:</u></b></p> <p>KIRKLAND &amp; ELLIS LLP 601 Lexington Avenue New York, NY 10022 Telephone: (212) 446-4800 Facsimile: (212) 446-4900</p>

**D. 37 C.F.R. §42.8(b)(4): Service Information**

Please address all correspondence to lead counsel. Petitioner consents to service by electronic mail at Pfizer\_Genentech\_IPRs@kirkland.com. A Power of Attorney is being filed concurrently herewith. 37 C.F.R. §42.10(b).

**III. PAYMENT OF FEES – 37 C.F.R. §42.103**

The undersigned authorizes the USPTO to charge the fee in 37 C.F.R. §42.15(a), and any additional fees in connection with this Petition, to Deposit Account 506092.

**IV. GROUNDS FOR STANDING – 37 C.F.R. §42.104(A)**

The '441 patent is available for IPR and Petitioner is not barred or estopped from requesting IPR on the grounds identified herein. 35 U.S.C. §315.

**V. IDENTIFICATION OF CHALLENGE –37 C.F.R. §42.104(B)**

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 as follows:

<b>Ground</b>	<b>Proposed Statutory Rejections</b>
1	<b>Lottery</b> in view of <b>Hayes</b> and/or <b>Baselga '96</b> , and <b>Gelmon</b> renders claims 1–14 obvious under 35 U.S.C. §103.
2	<b>Baselga '96</b> in view of <b>Baselga '94</b> and <b>Gelmon</b> renders claims 1–14 obvious under 35 U.S.C. §103.



The cited prior art is as follows. All are §102(b) art, published more than one year prior to the earliest effective filing date of the '441 patent:<sup>2</sup>

- **Lottery.** *A Lottery of Life, Death—and Hope*, LA Times (Ex. 1008), published August 3, 1996.
- **Hayes.** Hayes, *Editorial: Should We Treat HER, Too?* 14(3) J. CLIN. ONCOL. 697–99 (1996) (Ex. 1009), published March 1996.
- **Baselga '96.** Baselga, *et al.*, 14(3) J. CLIN. ONCOL. 737–44 (1996) (Ex. 1005), published March 1996.
- **Gelmon.** Gelmon, *et al.*, 14(4) J. CLIN. ONCOL. 1185–91 (1996) (Ex. 1016), published April 1, 1996.
- **Baselga '94.** Baselga, *et al.*, 13 PROC. AM. SOC. CLIN. ONCOL. 63 (Abstract 53) (1994) (Ex. 1006), published March 1994.

The statutory grounds for unpatentability of each claim are below. Additional evidence is provided in the Declaration of Allan Lipton, M.D. (Ex. 1011) and other supporting exhibits. 37 C.F.R. §1.68.

---

<sup>2</sup> Additional authenticating evidence is in the Declarations of Karen Younkins (Ex. 1014), Christopher Lowden (Ex. 1024), and Simon Cohen (Ex. 1048).

## **VI. THE CLAIMS OF THE '441 PATENT ARE UNPATENTABLE**

### **A. Level Of Ordinary Skill**

A POSITA would have been a clinical or medical oncologist specializing in breast cancer with several years of experience with breast cancer research or clinical trials. Ex. 1011¶¶15–17. In prior proceedings, Genentech did not dispute this definition. IPR2017-00731, Paper 9 at 32. And the Board adopted it in instituting IPR of the '549 patent. IPR2017-00737, Paper 19 at 8–9.

### **B. State Of The Art**

#### **(1) rhuMAb HER2 And Paclitaxel**

As the '441 patent explains, before the alleged invention, humanized 4D5, [rhu]MAb HER2 was a well-known breast cancer treatment. Exs. 1001 at 1:20–32 (citing Exs. 1026; 1027); 1005 at 9; 1008 at 1–3; 1009 at 9–10; 1043 at 6, 11; 1044 at 9, 12–13. The antibody, sold as HERCEPTIN<sup>®</sup>, was humanized by “inserting the complementarity determining regions [of murine 4D5 antibody]...into the framework of a consensus human immunoglobulin G<sub>1</sub> (IgG<sub>1</sub>).” Ex. 1005 at 10. It therefore binds to the same region, or “epitope,” as murine 4D5, *i.e.*, 4D5 within the ErbB2 extracellular domain sequence. *Id.* rhuMAb HER2 was “clinically active in patients with ErbB2-overexpressing metastatic breast cancers.” Exs. 1001 at 3:36–40; 1005 at 9–10; 1008 at 1–3; 1009 at 10; 1043 at 6; 1044 at 9–10. Paclitaxel (a taxoid) also was a well-known treatment for breast cancer, which had

been used with rhuMAb HER2. Exs. 1006 at 4; 1008 at 3; 1016 at 9; 1039 at 10; 1040; 1042 at 6–12.

## (2) Chemotherapeutic Combinations And Anthracyclines

Oncologists have worked with combination chemotherapies since the 1960s so by the time rhuMAb HER2 was developed, oncologists had over 20 years experience showing their superiority over single-agent therapies. Exs. 1015 at 8; 1030 at 5; 1011¶¶29–33. Although initial results with the antibody alone showed “promise,” they were considered “modest,” and it was understood, based on data showing the antibody enhanced chemotherapy effectiveness without increasing toxicity, that combination therapy was “key.” Exs. 1046 at 7; 1005 at 15; 1006 at 4; 1008 at 3; 1009 at 10. Thus, combinations with rhuMAb HER2 had been used since the early-1990s. Exs. 1006 at 4; 1008 at 3; 1013 at 5; 1015 at 8; 1030 at 5; 1023 at 5. As was routine, this began *in vitro* with cell assays, moved to *in vivo* preclinical models, then humans. Exs. 1006 at 4; 1008; 1013 at 5; 1017 at 7; 1018 at 8; 1011¶¶40–41.

Anthracyclines are, and were in the mid-1990s, often first-line treatment for breast cancer. Exs. 1031 at 4, 12; 1011¶35. They are effective but cardiotoxic, and by the mid-1990s, it was understood their cardiotoxicity was *cumulative*. Ex. 1031 at 5, 12. If a patient had previously taken anthracyclines, the risk for that patient was more pronounced for any additional anthracycline therapy. *Id.* As of the mid-

1990s, most patients with HER2-overexpressing breast cancer, including those involved in trials of HER2 antibodies and/or paclitaxel, were known to have been previously treated with anthracyclines. *E.g.*, Ex. 1016 at 11. For these patients in particular, it was known further anthracycline therapy should be avoided. Ex. 1011¶35. This was clearly well-known before the alleged '441 patent invention—patients who previously had been treated with anthracyclines were excluded from the anthracycline arm of PO's clinical studies. Ex. 1019\_2:38, 2:119–120. Moreover, combinations of rhuMAb HER2 with paclitaxel had superior efficacy and favorable safety compared to anthracycline combinations. Exs. 1006 at 4; 1013 at 5; 1016 at 13–14. It was unsurprising, therefore, that researchers were using rhuMAb HER2 combinations in the absence of anthracyclines. Exs. 1006 at 4 (with paclitaxel); 1008 (same); 1013 at 5 (with cisplatin); 1011¶¶35, 43–44.

### **C. The Prosecution History**

The '441 patent issued from U.S. App. 09/208,649 (“'649 application”) (Ex. 1010), which claims priority to U.S. Provisional App. 60/069,346 (Ex. 1012), filed December 12, 1997. Ex. 1019–1:2.

During prosecution, PO and the named inventor, Dr. Susan Hellmann, took certain positions to successfully antedate cited prior art. *Id.* at 1:379–85, 2:211–22. For example, to antedate Baselga '97 (Ex. 1007), they argued that a *protocol* for a

“study of chemotherapy [(paclitaxel *or anthracycline*)] alone or in combination with... [rhuMAb HER2] in women with HER2 overexpression” sufficed to show *reduction to practice* of the invention. *Id.* at 2:119–20, 2:238–39. They further argued that “absence of an anthracycline derivative” was “clear[ly]” proven to be reduced to practice by the protocol’s presentation of “*Taxol + rhuMAb HER2*” as an alternative to “rhuMAb HER2 + anthracyclines.” *Id.* at 2:231. Notably, this showed PO and Dr. Hellmann *still intended to administer antibody/anthracycline combinations*, just in separate patients. The Examiner accepted these arguments. *Id.* at 2:324.

The Examiner continued to reject the claims for the next eight years over other references, including Baselga ’96 and ’94. Finally, PO filed a declaration from Dr. Mark Sliwkowski (Ex. 1025), arguing that:

- (1) a POSITA would not have had a reasonable expectation of success combining anti-ErbB2 antibodies with taxoids because they result in cell cycle arrest at different, incompatible cell cycle points, and
- (2) data from xenograft mouse models is not sufficiently predictable to provide a POSITA with a reasonable expectation of success.

*Id.* at 9:9–13. The Examiner allowed the claims. *Id.* at 9:119, 124.

#### **D. Legal Standards For Obviousness And Prior Art Disclosure**

Analysis under §103(a) requires several steps: “[T]he scope and content 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.* “[S]econdary 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.*

Obviousness is found 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 to a POSITA at the time the invention was made. *Id.* at 406. “When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a [POSITA] 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.” *Id.* at 421.

Obviousness requires only this expectation of success; there is no requirement that a particular option be the only one or even preferred to others. *See*

*Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1381 (Fed. Cir. 2015) (“[J]ust because ‘better alternatives’ may exist in the prior art ‘does not mean that an inferior combination is inapt for obviousness purposes.’”). And when an element exists in the prior art, “it is not necessary for [the challenger] to demonstrate a suggestion or motivation to use” it. *Ortho-McNeil Pharm. Inc. v. Kali Labs. Inc.*, 482 F. Supp. 2d 478, 520 (D.N.J. 2007), *vacated on other grounds*, 344 Fed. App’x 595 (Fed. Cir. 2009). Moreover, where an element is inherent in the prior art, the lack of explicit disclosure cannot defeat obviousness. *See Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012); *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009).

For a negative claim limitation (*e.g.* “in the absence of”) to distinguish prior art, it “must” be shown “that the cited prior art has those features.” *Ex parte Litwin*, No. 2009-011704, 2011 WL 3414500, at \*3 (B.P.A.I. Aug. 2, 2011). Thus, prior art “[f]requently” renders claims with negative limitations invalid by “silence.” T. Brody, *Negative Limitations in Patent Claims*, 41 Am. Intell. Prop. Q.J. 29, 58 (2013) (Ex. 1058); 3-8 Chisum on Patents §8.06 (Ex. 1059) (citing cases). Even where prior art includes an example containing what a negative limitation excludes, it still discloses that limitation when it includes another example compliant with the exclusion. *See Ex parte Gillis*, No. 2010-09318, at 12 (B.P.A.I. Nov. 21, 2011); Ex. 1058 at 14.

The legal standard for obviousness is not as high as that set for conception: “In the context of U.S. patent law, [the Federal Circuit] has distinguished conception from obviousness, explaining that the Patent and Trademark Office’s determination that a claimed method was obvious ‘is irrelevant to the question whether the...inventors had conceived of the invention [at a particular point in time]. For conception, we look not to whether one skilled in the art could have thought of the invention, but whether the alleged inventors actually had in their minds the required definite and permanent idea.’” *Dawson v. Dawson*, 710 F.3d 1347, 1356 (Fed. Cir. 2013).

**E. 37 C.F.R. §42.104(b)(3): Claim Construction**

A claim in an IPR is given its broadest reasonable interpretation (“BRI”) in light of the specification. 37 C.F.R. §42.100(b).

**(1) “in the absence of an anthracycline derivative”**

Pfizer submits the BRI of “in the absence of an anthracycline derivative” is “not together with an anthracycline derivative.” The only thing it excludes is the *three-drug* antibody/taxoid/anthracycline combination. This is the plain and ordinary meaning, supported by intrinsic evidence. In contrast, PO’s apparent construction—requiring something more, *i.e.*, “*avoidance*”—is unsupported; indeed, it would impermissibly import a non-existent positive limitation. *See Superguide Corp. v. DirecTV Enterprises, Inc.*, 358 F.3d 870, 875 (Fed. Cir. 2004)



(“It is important not to import into a claim limitations that are not part of the claim”).

“[I]n the absence of an anthracycline derivative” is a negative claim limitation. *See Ex parte Tsao*, No. 1996-2766, 2000 WL 1593621, at \*2 (B.P.A.I. Feb. 22, 2000). “Although permissible, negative limitations merely recite what a claim lacks and are thus broad by their very nature.” *Ex parte Litwin*, No. 2009-011704, 2011 WL 3414500, at \*3 (B.P.A.I. Aug. 3, 2011). The Webster’s New World College Dictionary (1996) defines “absence” as “the fact of being without.” Ex. 1028. Similarly, the Oxford Dictionary (1996) defines “absence” as “the nonexistence or lack of.” Ex. 1029. “In the absence of an anthracycline derivative” thus simply means “without,” “lack[ing]” or “not together with” an anthracycline derivative.

The sole patent Example describes a study in which the antibody is combined with *either* a taxoid (paclitaxel) *or* an anthracycline (doxorubicin). Ex. 1001 at 26:32–30:25. Anthracycline derivatives were not “avoided”—*they were to be administered separately with rhuMab HER2*. *Id.* Similarly, as noted above, during prosecution, PO and Dr. Hellmann cited as proof of reduction to practice a protocol for the study of antibody combinations with *either* taxoids *or* anthracyclines. Ex. 1019\_2:238–39. PO refuted the Examiner’s suggestion that the

inclusion of an antibody/anthracycline arm took the antibody/taxoid treatment out of the claims. *Id.* at 2:214, 2:231, 2:237–39, 2:240–312.

Because Petitioner’s proposed BRI is consistent with the plain and ordinary meaning, and the intrinsic evidence, it should be adopted.

## **F. The Prior Art**

### **(1) *Lottery***

*Lottery* profiles a new treatment for HER2-overexpressing breast cancer—a *combination of PO’s HER2 antibody + taxol*—through the story of a patient having “especially aggressive” cancer. Ex. 1008 at 3. *Lottery* reports that after years of unsuccessful treatment for her disease “spurred by overproduction of the so-called HER2/*neu* receptor,” Ms. Valli Lopez-Lasker became aware of clinical trials conducted by Dr. Dennis Slamon at UCLA. *Id.* at 1. These trials combined rhuMab HER2 with previously known chemotherapy. *Id.* at 1–2. One study combined the antibody with cisplatin. Lopez-Lasker “had taken cisplatin before and wanted no more of it” but signed up because she could be in the arm that “would receive the antibody drug without cisplatin.” *Id.* at 2. Her treatment showed initial progress. *Id.* But after she had “received HER2 antibody therapy for six months,” CT scans revealed new “incipient tumors.” *Id.* at 3. Dr. Slamon discussed other “options”: “She could start taking the HER2 antibody along with cisplatin. Or, if she still didn’t want that, there [wa]s a separate study involving taxol,” a

drug already known to be “used against ovarian cancer and breast cancer.” *Id.* Not wanting to try cisplatin again, Lopez-Lasker “settled on taxol.” The taxol study was “[t]o test whether the HER2 antibody really boosts the effectiveness of taxol.” “[H]alf the women in Slamon’s study [would] receive taxol plus antibody, while the other half receive just taxol.” *Id.*

The HER2 antibody in *Lottery* is the same one with the same properties as in the ’441 patent. *Lottery* refers to it as “MAb HER2, ‘MAb’ being short for ‘monoclonal antibody,’” “a genetically engineered antibody that sticks to the HER2/*neu* receptor, interfering with the cancer cells’ life cycle.” *Id.* at 1. “Genentech” was its “producer” and a funder of the UCLA studies. *Id.* at 2. At that time, it was well known that Genentech’s HER2 antibody in clinical trials was produced through humanization of the murine 4D5 antibody. Exs. 1009 at 10; 1043 at 7; 1044 at 9; 1045 at 7–9; 1005 at 10, 15, 1011¶59.

## (2) Hayes

The Hayes editorial, titled “Should We Treat HER, Too?” provides a summary of antibody treatment of cancer, particularly the HER2/*neu* oncogene. Ex. 1009. *Lottery* cites Hayes as stating HER2 antibody therapy “held enough promise that studies like the one Lopez-Lasker is involved in may someday be regarded as a ‘landmark’ in cancer research.” Ex. 1008 at 2. Hayes refers to the antibody as “a monoclonal antibody directed toward HER2/*neu* (rhuMAB HER2),”

and reports the results of two studies. Ex. 1009 at 10.

In the first study (reported in Baselga '96), investigators “observed objective responses in 11.6% and disease stabilization in another 37% of...patients,” for the antibody as a single agent such that, overall, “almost 50% of patients for whom no other effective therapy appeared to be available may have benefited from perturbation of the HER2/*neu* axis with a monoclonal antibody.” *Id.* The cited reference—Baselga '96—confirms the antibody is the humanized 4D5, anti-ErbB2 antibody known as rhuMAb HER2. Ex. 1005 at 10, 15. In the second study in Hayes, “this same monoclonal antibody was delivered in association with cisplatin to a group of metastatic breast cancer patients who had failed one or more prior therapies, and more than 25% of patients achieved a response.” Ex. 1009 at 10.

### **(3) Baselga '96**

Baselga '96 reports the results of a phase II clinical trial for HER2-overexpressing metastatic breast cancer. Ex. 1005 at 9. It teaches that, after successful mouse model experiments, the 4D5 anti-ErbB2 antibody was humanized (rhuMAb HER2). *Id.* at 9–10. 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. One patient had complete remission, and four partial remission. *Id.* at 13. Fourteen 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 “[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 efficacy. Exs. 1032 at 12; 1033 at 6.

Baselga ’96 also refers to the combination study with chemotherapy in Baselga ’94 (discussed below), reporting 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.*

The ’441 patent relies heavily on Baselga’s work. The patent cites Baselga ’94 to show that a humanized HER2 antibody “enhance[d] the activity of paclitaxel.” Ex. 1001 at 3:50–59. And the patent’s sole Example copies Baselga ’96, including typographical errors, without attribution. *Id.* at 26:63–27:4.

#### (4) Gelmon

Gelmon states “Phase II studies have shown paclitaxel to be an active single agent in metastatic breast cancer, with reported response rates of 17% to 62%.” Ex. 1016 at 9. It reports the results of a phase I/II clinical trial of paclitaxel and cisplatin for metastatic breast cancer. *Id.* According to Gelmon, “[a]ll but two of the women in our trial had been treated with previous adjuvant chemotherapy, and 23 of 29 patients had previous exposure to anthracyclines.” *Id.* at 13. Patients were excluded if they had “previous anthracycline treatment to a cumulative dose greater than 450 mg/m<sup>2</sup> with an abnormal serial gated cardiography (MUGA) scan.” *Id.* at 10.

In instituting IPR of the '549 patent, the Board acknowledged that Gelmon would have motivated a POSITA to avoid anthracyclines in antibody/paclitaxel combination therapy:

[T]he prior art of record indicates that many patients with metastatic breast cancer will have previously been treated with, and become resistant to, first-line anthracycline chemotherapeutics. Gelman [*sic*], for example, discloses that ‘[a]ll but two of the women in our trial had been treated with previous adjuvant chemotherapy, and 23 of 29 patients had previous exposure to anthracyclines.’ ... On the present record, we find persuasive Dr. Litton’s [*sic*] testimony that one of ordinary skill in the art would have recognized that “[b]ecause anthracyclines are

widely used in the adjuvant setting,’ 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.”

IPR2017-00737, Paper 19 at 21–22.

Of the 27 patients assessed for efficacy, three showed a complete response with time to disease progression of 110 to 200 days, and 20 showed a partial response with time to disease progression of 96 to 377+ days. Ex. 1016 at 13, Abstract. Patients treated with the paclitaxel combination regimen showed an overall response rate of 85% and a median time to disease progression of 7.1 months. *Id.*

**(5) Baselga ’94**

Baselga ’94 describes a preclinical study using a mouse xenograft tumor model in which HER2-overexpressing tumors were grown in mice and treated with anti-ErbB2 antibody and *either* paclitaxel *or* an anthracycline derivative, but not both. Ex. 1006 at 4; IPR2017-00737, Paper 19 at 25; IPR2017-00731, Paper 19 at 10. While the antibody or paclitaxel alone produced 35% growth inhibition, their combination resulted in 93% growth inhibition without increasing toxicity. *Id.* This was more than the 70% inhibition achieved by the combination with doxorubicin (an anthracycline derivative). *Id.* Notably, the antibody “did not increase the

toxicity of paclitaxel.” Exs. 1006 at 4; 1011¶74. Baselga ’94 teaches that clinical trials of these combinations were underway. *Id.*

### **G. Detailed Explanation Of Grounds Of Unpatentability**

#### **Ground 1: Claims 1–14 Are Invalid Based On *Lottery*, In View Of Hayes And/Or Baselga ’96, And Gelmon**

The Challenged Claims are obvious based on *Lottery*, in view of Hayes and/or Baselga ’96, and Gelmon. All elements are present, expressly or inherently, in *Lottery*, which discloses that the claimed anti-ErbB2 antibody/taxoid combination in the absence of an anthracycline derivative was already in clinical trials prior to the ’441 patent’s priority date. A POSITA would have known the inherent properties of the “MAb HER2” antibody, including that it is a humanized 4D5, anti-ErbB2 antibody that binds to epitope 4D5 within the ErbB2 extracellular domain sequence.

Alternatively, even if not inherent or known by a POSITA, these properties are confirmed by Baselga ’96, which is cited and discussed in Hayes, which in turn is referenced in *Lottery*. A POSITA would have been motivated to try the combination of rhuMAb HER2 with paclitaxel (which was described in *Lottery* as already in clinical trials), as it had “promising” results so far, and was known to be safe and not increase paclitaxel toxicity. The recited results of the claimed treatment—extending time to disease progression without increasing severe adverse events—also are inherent properties, as PO and the named inventor



confirmed during prosecution. In any event, these properties would reasonably have been expected by a POSITA reading *Lottery* alone or in view of Hayes and/or Baselga '96, and Gelmon.

Finally, *Lottery* itself teaches treatment with the antibody/taxoid combination “in the absence of an anthracycline derivative”—anthracyclines are not described as present or even an option. However, to the extent additional motivation to “*avoid*” anthracyclines is required, the Board has found Gelmon provides it. A POSITA reading Gelmon would have understood that most HER2-overexpressing breast cancer patients already would have been treated with anthracyclines. This, combined with anthracyclines’ known cumulative cardiotoxicity and drug resistance concerns, would have motivated a POSITA to try options that avoided them. A POSITA would have had a reasonable expectation of success doing so given this same knowledge. *Lottery*, including *inter alia* its disclosure that UCLA, Dr. Slamon, and Genentech were supporting ongoing human trials administering the antibody/taxoid combination, would provide additional motivation and additional reason to expect success. So would a POSITA’s general knowledge that, *inter alia*, HER2+ patients needed more treatment options, and although chemotherapy combinations could provide enhanced effectiveness, it was generally better to administer fewer medications if one could achieve equally effective results.

The “invention” here is obvious over *Lottery* alone, but a POSITA also would have been motivated to combine it with Hayes and/or Baselga '96. *Lottery* explicitly points to Hayes, published in the well-regarded, peer-reviewed Journal of Clinical Oncology, for more information about the antibody. Hayes in turn describes the results from, and cites, Baselga '96, published in the same journal volume. A POSITA also would have been motivated to combine these references with Gelmon. It also was published in the Journal of Clinical Oncology, in the volume following a month after Hayes and Baselga '96. It relates to the same disease—HER2 positive breast cancer—and provides further information about treatment with paclitaxel, the same drug used in *Lottery*'s combination. A POSITA would look to Gelmon to understand more about combination treatments for HER2 positive cancer, in particular combinations involving paclitaxel as in *Lottery*.

**(1) Claim 1**

- a. Preamble: “A method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by over-expression of ErbB2 receptor, comprising”**

*Lottery* discloses this limitation. It teaches that “HER2 antibody,” “MAB HER2,” was used in “women with advanced breast or ovarian cancer of an especially aggressive type: The tumors are spurred by overproduction of the so-called HER2/*neu* receptor, a protein structure on the cancer cells that appears to regulate their growth.” Ex. 1008 at 1. This would be understood to refer to

malignant, progressing cancer. Ex. 1011¶79. A POSITA would have known the HER2/*neu* receptor is the “ErbB2 receptor.” *Id.* ¶¶36, 79. *Lottery* further teaches the antibody is “suitable only for the 30% of women with breast or ovarian tumors abetted by an excess of the HER2/*neu* receptor”; that the profiled patient had “*incipient tumors*”; that prior therapy had “failed to hold the cancer in check”; that the HER2 antibody was the subject of FDA review; and that the FDA may approve such cancer therapy if it “shows evidence of *tumor shrinkage* for patients who have no satisfactory alternative therapy.” Ex. 1008 at 3.

This limitation is at least obvious over *Lottery*, alone or in view of Hayes and/or Baselga ’96. Hayes describes a clinical study (from Baselga ’96) in which “rhuMab HER2 was administered to 45 patients *with HER2/neu-overexpressing metastatic breast cancer* whose disease had become resistant to multiple previous therapies,” and a “separate study” where “this same monoclonal antibody was delivered in association with cisplatin to a group of metastatic breast cancer patients who had failed one or more prior therapies.” Exs. 1009 at 10; 1005 at 9–13.

**b. Element [a]: “administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence”**

*Lottery* discloses this limitation. It reports that women would “receive” “taxol plus [HER2] antibody” as part of a clinical trial “[t]o test whether the HER2

antibody really boosts the effectiveness of taxol.” Ex. 1008 at 3. The “HER2 antibody” is “specific for” cancer overexpressing HER2 and is “a genetically engineered antibody that sticks to the HER2/*neu* receptor, interfering with the cancer cells’ life cycle.” *Id.* at 1. *Lottery* further describes the antibody as being administered to patients in clinical trials “funded largely by...Genentech, producer of the HER2 antibody.” *Id.* at 2.

The ’441 patent itself acknowledges that “rhuMAb HER2” refers to “[a] recombinant humanized anti-ErbB2 monoclonal antibody (a humanized version of the murine anti-ErbB2 anti-body, 4D5)” or “HERCEPTIN®.” Ex. 1001 at 3:34–40. At the time *Lottery* was published, it was well-known that Genentech’s antibody in clinical trials was produced through humanization of the murine 4D5 antibody. Exs. 1009 at 10; 1043 at 7; 1044 at 11; 1045 at 7–9; *see also* Exs. 1005 at 10, 15; 1011¶¶59, 81. A POSITA would have known that rhuMAb HER2 was humanized by “inserting the complementarity determining regions [of the murine 4D5 antibody]...into the framework of a consensus human immunoglobulin G<sub>1</sub> (IgG<sub>1</sub>),” that the complementarity determining region is the portion of the antibody determining what it binds to, *i.e.*, the epitope, and because rhuMAb HER2 contains the same complementarity determining region as the murine 4D5 antibody, it binds to the same epitope, *i.e.*, 4D5 within the ErbB2 extracellular domain sequence. Ex. 1011¶¶40, 81. In any event, the binding properties of “MAb HER2” in *Lottery*

are inherent and cannot defeat obviousness. *See Santarus*, 694 F.3d at 1354; *In re Kubin*, 561 F.3d at 1357; *see also Abbvie Inc. v. Kennedy Trust for Rheumatology Research*, No. 13 Civ. 1358(PAC), 2014 WL 3360722, \*6–7 (S.D.N.Y. July 9, 2014), *aff’d* 599 Fed. App’x. 956 (Fed. Cir. 2015) (“[T]here is also no dispute that *the [binding] mechanism is an inherent feature* of the [claimed anti-TNF $\alpha$  antibody].”).

This limitation is at least obvious over *Lottery*, alone or in view of Hayes and/or Baselga ’96. *Lottery* points to Hayes as providing further information about the antibody. Ex. 1008 at 2. Hayes identifies it as “rhuMAB HER2,” and cites to Baselga ’96, which confirms that it was prepared by humanizing “[t]he murine monoclonal antibody (MAb) 4D5,” which “[is] directed against the extracellular domain of p185<sup>HER2</sup>.” Exs. 1009 at 10; 1005 at 10; 1011¶82.

**c. Element [b]: “a taxoid”**

*Lottery* discloses this limitation. It states “[t]o test whether the HER2 antibody really boosts the effectiveness of taxol,” “half the women...receive *taxol plus antibody*, while the other half receive *just taxol*.” Ex. 1008 at 3. Taxol is another name for paclitaxel, a well-known taxoid. Exs. 1001 at 4:21–23; 1011¶84.

During prosecution, Dr. Sliwkowski asserted a skilled artisan would not have expected rhuMAb HER2 with taxoid to produce synergistic effects. Ex. 1019\_9:11–12). But that is precisely what a POSITA would have expected upon reading

*Lottery's* disclosure that ongoing clinical trials would test whether the antibody "boosts" taxol's "effectiveness." Ex. 1008 at 3. Indeed, even PO's expert in proceedings relating to the '441 patent's European counterpart stated that "phase III trials are very expensive to conduct—the costs are significantly greater than for any of the earlier stages of preclinical or clinical development," that "even if an agent had demonstrated activity in phase II, the company developing it would have considered very carefully indeed whether to move ahead into phase III," and that:

A great deal of thought would go into the design of phase III trials as, having already invested large amounts of money into development of a new agent and being about to invest a great deal more, the company developing it would wish to ensure that the data generated would be meaningful and reliable such that the study had the best possible chance of supporting a successful application for regulatory approval.

Ex. 1050 at 51 (Barrett-Lee Decl., ¶¶37–38, 41). A POSITA would consider that the phase III trial would not have been commenced without reasonable expectation of success. Ex. 1011¶85.

This limitation is at least obvious over *Lottery*, alone or in view of Hayes and/or Baselga '96, and Gelmon. From the results of studies testing the antibody (including Baselga '96's study), Hayes concludes that "perturbation of HER2/*neu*

[by the antibody], in and of itself, may result in tumor regression and, perhaps as importantly, *may also modulate resistance to conventional chemotherapy.*” Exs. 1009 at 10; 1005 at 15 (noting that, “[i]n preclinical studies...rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including...paclitaxel, without increasing their toxicity,” and that clinical trials were in progress). Gelmon further teaches a synergistic effect of paclitaxel in combination therapy for breast cancer. Exs. 1016 at 9; 1011¶86. Based on these teachings, a POSITA would consider the antibody/paclitaxel combination from *Lottery* to have at least a reasonable chance of success.

**d. Element [c]: “in the absence of an anthracycline derivative”**

*Lottery* discloses this limitation. In the study, “half the women...receive *taxol plus antibody*, while the other half receive *just taxol.*” Ex. 1008 at 3. From this statement and its clinical trial context, a POSITA would understand that anthracyclines were not part of the regimen. Ex. 1011¶88. This is made even clearer by *Lottery*’s statement that the study was performed “[t]o test whether the HER2 antibody really boosts the effectiveness of taxol.” Ex. 1008 at 3. A POSITA would know that an anthracycline derivative, if present, could interfere with this test. Ex. 1011¶88.

To the extent motivation to “*avoid*” anthracyclines was somehow needed, it existed in the prior art. Anthracyclines were known to be effective but cardiotoxic,

with the cardiotoxicity being *cumulative*. Ex. 1031 at 5, 12. If a patient had previously taken anthracyclines, the cardiotoxicity risk was more pronounced for any additional anthracycline therapy. *Id.* Furthermore, as of the mid-1990s, most patients with HER2-overexpressing breast cancer, including those involved in clinical trials of rhuMAb HER2 and/or paclitaxel, were known to have been previously treated with anthracyclines. *E.g.*, Ex. 1016 at 11. For these patients in particular it was known that further anthracycline therapy should be avoided. Ex. 1011¶35. This was clearly well-known at the time, as PO's own studies excluded patients previously treated with anthracyclines from the anthracycline treatment arm. *See* Ex. 1019\_2:37, 2:119–120.

In addition, rhuMAb HER2/paclitaxel combinations had been shown to have superior efficacy and favorable safety compared to anthracycline combinations. Exs. 1006 at 4; 1013 at 5; 1016 at 13–14. Therefore, it was unsurprising that researchers were using rhuMAb HER2 combinations in the absence of anthracyclines. Exs. 1006 at 4 (with paclitaxel); 1008 (same); 1013 at 5 (with cisplatin); 1011¶¶35, 43–44.

Indeed, as the Board acknowledged in instituting IPR of the '549 patent, the prior art, including Gelmon, evidenced “other reasons to avoid anthracyclines in a treatment regimen, such as concerns with drug resistance.” *See* IPR2017-00737, Paper 19 at 21–22. In that regard, Hayes describes rhuMAb HER2 as being



administered to patients “whose disease had become resistant to multiple previous therapies,” or “who had failed one or more prior therapies.” Ex. 1009 at 10. And, *Lottery* describes the profiled patient as having received “a barrage of treatments, including radiation therapies, chemotherapies and a...bone marrow transplant” before being included in the rhuMAb HER2 studies. Ex. 1008 at 1. *Lottery* also teaches that cancer patients can experience side effects with chemotherapy; patients may find some side effects too difficult to tolerate and want to try other chemotherapies to see if side effects will be lessened. *Id.* at 2. Under such circumstances, a POSITA would understand that the best option would be to combine the antibody with paclitaxel without anthracycline derivatives, providing an option to patients who could not tolerate anthracyclines. Ex. 1011¶89. In this way, *Lottery* provides additional motivation to avoid anthracycline derivatives.

Notably, during prosecution and in other IPRs, PO has not identified any instance in which anyone (including itself) tried the three-drug antibody/taxoid/anthracycline derivative combination excluded by this limitation.

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

*Lottery* discloses this limitation. It describes providing the combination treatment to human patients. Ex. 1008 at 3 (“[H]alf the women in Slamon’s study [would] receive taxol plus antibody, while the other half receive just taxol.”). During prosecution, Dr. Sliwowski asserted that POSITAs would not be able to

predict the effects of the combination treatment in humans based on animal data, such as in Baselga '94. Ex. 1019\_9:9–13. Here, *Lottery* explicitly describes treatment in humans and, as described below, a POSITA would have had a reasonable expectation that it would be successful.

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

*Lottery* discloses this limitation, explicitly and inherently. It explicitly teaches that the antibody is effective to extend the time to disease progression, stating that “early findings are very promising with some outstanding results,” that “[o]f the six women that UCLA had tested by then, one had her tumors disappear completely, three...had tumors shrink,” and that “[i]n preliminary studies the drug has reduced tumors in 12% of those eligible patients who received it.” Ex. 1008 at 1–3. It also teaches that combining taxol could *boost* effectiveness. *Id.* at 3.

Moreover, this limitation merely recites an inherent result of the combination treatment, which cannot support non-obviousness. *See Santarus*, 694 F.3d at 1354. “To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property.” *Id.*; *see also In re Kubin*, 561 F.3d at 1357. Indeed, PO and the named inventor asserted the claimed combination treatment was *reduced to practice* by inclusion in a protocol *before data was available*. Ex. 1019\_2:37, 2:119–120, 2:230–31, 2:237–39.

This limitation at the very least would have been obvious. In addition to *Lottery*'s disclosures discussed above, a POSITA would have considered it unlikely that the *Lottery* trial would have been undertaken without an expectation of success. Exs. 1050 at 51; 1011¶98.

Hayes further reports the results of two studies of rhuMAb HER2 as stand-alone or combination therapies. Ex. 1009 at 10. In the first trial (described in Baselga '96), the investigators "observed objective responses in 11.6% and disease stabilization in another 37% of...patients," such that, overall, "almost 50% of patients for whom no other effective therapy appeared to be available may have benefited from perturbation of the HER2/*neu* axis with a monoclonal antibody." *Id.*; Ex. 1005 at 9–15 (describing the results of Phase II rhuMAb HER2 clinical trials, as well as preclinical results of the antibody combined with paclitaxel). In the second study, "this same monoclonal antibody was delivered in association with cisplatin to a group of metastatic breast cancer patients who had failed one or more prior therapies, and more than 25% of patients achieved a response." Ex. 1009 at 10.

Gelmon further discloses that biweekly administration of cisplatin with paclitaxel was effective in breast cancer patients. Ex. 1016 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 discloses a

paclitaxel combination regimen that increases time to disease progression. Ex. 1011¶¶69–72, 97.

Based on these teachings, a POSITA would have had a reasonable expectation that the combination treatment in *Lottery* would be successful to extend time to disease progression in human patients.

**g. Element [f]: “without increase in overall severe adverse events”**

*Lottery* discloses this limitation, either explicitly or inherently. Again, this limitation recites an inherent property, which cannot support non-obviousness. *See Santarus*, 694 F.3d at 1354; *In re Kubin*, 561 F.3d at 1357. This is consistent with PO and the named inventor’s position during prosecution that the invention was reduced to practice by preparation of the study protocol before adverse event data existed. Ex. 1019\_2:37, 2:119–120, 2:230–31, 2:237–39. Indeed, PO said that “reduced cardiac side effects naturally flow” from the antibody/taxol combination. Ex. 1019\_2:233–34.

At the very least this limitation would have been obvious. Based on *Lottery*, a POSITA would have had a reasonable expectation that the antibody/paclitaxel combination treatment would not increase overall severe adverse events when compared with paclitaxel alone. *Lottery* describes “serious side effects” associated with certain chemotherapies, including cisplatin. Ex. 1008 at 2. For rhuMAb HER2, in contrast, *Lottery* reports that, when taken by the profiled patient, “the

drug had no side effects except a mild fever the first time she received it.” *Id.* Although she experienced side-effects during later treatment, it was from paclitaxel treatment alone. *Id.*

Furthermore, based on clinical studies (including the Baselga ’96 study), Hayes reports rhuMAb HER2 has a “relative lack of toxicity.” Ex. 1009 at 10.

**(2) Claim 2**

**a. “The method of claim 1 wherein said patient has a malignant tumor”**

*Lottery* discloses this limitation. It teaches rhuMAb HER2 was used in “women with advanced breast or ovarian cancer of an especially aggressive type,” and is “suitable only for the 30% of women with breast or ovarian tumors abetted by an excess of the HER2/neu receptor.” Ex. 1008 at 1. A POSITA would understand “aggressive type” of cancer to refer to malignant cancer that forms a tumor in places where it grows in the body. Ex. 1011¶104.

**(3) Claim 3**

**a. “The method of claim 1 wherein said patient has cancer”**

*Lottery* discloses this limitation. It teaches rhuMAb HER2 was used in “women with advanced breast or ovarian cancer....” Exs. 1008 at 1, 1011¶106.

**(4) Claim 4**

- a. “The method of claim 3 wherein said cancer is selected from the group consisting of breast cancer [and other cancers]”**

*Lottery* discloses this limitation. It teaches that rhuMAb HER2 was used in “women with advanced breast or ovarian cancer....” Exs. 1008 at 1, 1011¶108.

**(5) Claim 5**

- a. “The method of claim 4 wherein said cancer is breast cancer”**

*See* §(4).

**(6) Claim 6**

- a. “The method of claim 5 wherein said cancer is metastatic breast carcinoma”**

*Lottery* discloses this limitation. It teaches rhuMAb HER2 was used in “women with advanced breast or ovarian cancer of an especially aggressive type.” Ex. 1008 at 1. *Lottery* also refers to Hayes, which reports studies in which rhuMAb HER2 was administered to patients with “metastatic breast cancer,” *i.e.*, carcinoma. Ex. 1009 at 2; Ex. 1011¶112.

**(7) Claim 7**

- a. “The method of claim 1 wherein said antibody is a humanized 4D5 anti-ErbB2 antibody”**

*Lottery* discloses this limitation, either explicitly or inherently. When *Lottery* was published, it was well-known that Genentech’s HER2 antibody in clinical trials was produced through humanization of the murine 4D5 antibody. Exs. 1009

at 10; 1043 at 7; 1044 at 11; 1045 at 7–9; 1005 at 10, 15; 1011¶¶114. Thus, a POSITA would have understood “MAb HER2” in *Lottery* is a humanized 4D5 anti-ErbB2 antibody. Ex. 1011¶¶59, 114.

This limitation is at least obvious over *Lottery* in view of Hayes and/or Baselga '96. *Lottery* refers readers to Hayes, which describes the antibody as “a monoclonal antibody directed toward HER2/*neu* (rhuMAB HER2).” Ex. 1009 at 2. Hayes in turn cites Baselga '96, which teaches that rhuMAB HER2 is a humanized form of the murine 4D5 antibody; therefore it is a humanized 4D5 anti-ErbB2 antibody. Ex. 1005 at 9.

**(8) Claim 8**

- a. “The method of claim 1 wherein said taxoid is paclitaxel”**

As discussed above in §(1)c, *Lottery* discloses this limitation, *i.e.*, the taxoid paclitaxel (or “taxol”). Exs. 1008 at 3; 1011¶¶58, 84–85.

**(9) Claim 9**

- a. “The method of claim 8 wherein the effective amount of said combination is lower than the sum of the effective amounts of said anti-ErbB2 antibody and said taxoid, when administered individually, as single agents”**

This limitation recites an inherent property of the claimed treatment, which cannot render it non-obvious. *See Santarus*, 694 F.3d at 1354; *In re Kubin*, 561 F.3d at 1357. Again, that PO and the named inventor considered the invention

reduced to practice by preparation of the study protocol before data was received demonstrating synergy of the combination confirms they considered this limitation inherent. Ex. 1019\_2:37, 2:119–120, 2:230–31, 2:237–39.

At the very least, this limitation would have been obvious over *Lottery* in view of Hayes and/or Baselga '96, and Gelmon. *Lottery* teaches a clinical study in which “half the women...receive *taxol plus antibody*, while the other half receive *just taxol*.” Ex. 1008 at 3. A POSITA would have been aware of the “promising” results of clinical studies with rhuMAB HER2. *Id.* at 2–3; Ex. 1009 at 10. The POSITA also would have been aware of other prior art studies, including Gelmon’s, where paclitaxel was shown to have a synergistic effect in combination for breast cancer. Exs. 1016 at 9; 1005 at 15 (Baselga '96 teaching the rhuMAB HER2/paclitaxel combination in preclinical studies resulted in synergistic improvement in antitumor effect of each treatment individually). Thus, a POSITA would have had a reasonable expectation that the rhuMAB HER2/paclitaxel combination also would be synergistic in humans and an effective amount of the drugs in combination would be lower than the effective amounts individually. Ex. 1011¶¶118–20.



**(10) Claim 10**

**a. “The method of claim 1 wherein efficacy is further measured by determining the response rate”**

*Lottery* discloses this limitation. It reports that “[i]n preliminary studies the drug [rhuMAB HER2] has reduced tumors in 12% of those eligible patients who received it.” Ex. 1008 at 2. Hayes further teaches that in a clinical study of rhuMAB HER2 (reported in Baselga ’96), investigators “observed objective responses in 11.6% and disease stabilization in another 37% of...patients,” such that, overall, “almost 50% of patients for whom no other effective therapy appeared to be available may have benefited from perturbation of the HER2/*neu* axis with a monoclonal antibody.” Exs. 1009 at 10; 1005 at 13 (Baselga ’96 reporting that, out of the patients treated with rhuMAB HER2, “five experienced a complete or partial remission, for an overall response rate of 11.6%”). In a different study in Hayes, “this same monoclonal antibody was delivered in association with cisplatin to a group of metastatic breast cancer patients who had failed one or more prior therapies, and more than 25% of patients achieved a response.” Ex. 1009 at 10.

It would have been obvious for a POSITA to measure the response rate of the combination therapy based on prior art teachings using response rate to measure effects of single agents. Ex. 1011¶122.

**(11) Claim 11**

- a. Preamble: “A method for the treatment of a human patient with ErbB2 overexpressing progressing metastatic breast cancer, comprising”**

*See* §§(1)a, (6).

- b. Element [a]: “administering a combination of a humanized 4D5 anti-ErbB2 antibody”**

*See* §§(1)b, (7).

- c. Element [b]: “a taxoid”**

*See* §(1)c.

- d. Element [c]: “in the absence of an anthracycline derivative”**

*See* §(1)d.

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

*See* §(1)e.

- f. Element [e]: “in an amount effective to extent the time to disease progression in said human patient”**

*See* §(1)f.

- g. Element [f]: “without increase in overall severe adverse events”**

*See* §(1)g.

**(12) Claim 12**

- a. “The method of claim 11, wherein said taxoid is paclitaxel”**

*See* §§(11) and (8).

**(13) Claim 13**

- a. Preamble: “A method for the treatment of a human patient with a progressing malignant tumor or cancer characterized by overexpression of ErbB2 receptor, comprising”**

*See* §(1)a.

- b. Element [a]: “administering a combination of a humanized 4D5 anti-ErbB2 antibody which comprises a human F<sub>c</sub> region that binds to epitope 4D5 within the ErbB2 extracellular domain sequence”**

*Lottery* inherently discloses this limitation. *See Santarus*, 694 F.3d at 1354; *In re Kubin*, 561 F.3d at 1357. “MAb HER2” is a humanized 4D5 anti-ErbB2 antibody which comprises a human F<sub>c</sub> region that binds to epitope 4D5 because rhuMAb HER2 is comprised of “the complementarity determining regions of MAb 4D5” and “the framework of a consensus human immunoglobulin G<sub>1</sub> (IgG<sub>1</sub>).” Ex. 1011¶134; Ex. 1005 at 10. A consensus human immunoglobulin G<sub>1</sub> contains a human F<sub>c</sub> region. Ex. 1011¶134. 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 in *Lottery* binds to epitope 4D5 within the ErbB2 extracellular domain sequence. Ex. 1011¶135.

At the very least, this limitation would have been obvious over *Lottery* in view of Hayes and/or Baselga '96. *Lottery* refers readers to Hayes, which describes the antibody as “a monoclonal antibody directed toward HER2/*neu* (rhuMAB HER2).” Ex. 1009 at 2. Hayes in turn cites to Baselga '96, which teaches that

rhuMAb HER2 is a humanized 4D5 anti-ErbB2 antibody which comprises a human F<sub>c</sub> region that binds to epitope 4D5 because rhuMAb HER2 is comprised of “the complementarity determining regions of MAb 4D5” and “the framework of a consensus human immunoglobulin G<sub>1</sub> (IgG<sub>1</sub>).” Ex. 1005 at 10.

**c. Element [b]: “and a taxoid”**

*See* §(1)c.

**d. Element [c]: “in the absence of an anthracycline derivative”**

*See* §(1)d.

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

*See* §(1)e.

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

*See* §(1)f.

**g. Element [f]: “without increase in overall severe adverse events.”**

*See* §(1)g.

**(14) Claim 14**

**a. Preamble: “A method for the treatment of a human patient with ErbB2 expressing progressing metastatic breast cancer, comprising”**

*See* §§(1)a, (6).

- b. Element [a]: “administering a combination of an antibody which binds to epitope 4D5 within the extracellular domain sequence”**

*See* §§(1)b, (7). “[A]ntibody” is broader than “intact antibody”; the reasoning in §(1)b thus applies. Ex. 1011¶143.

- c. Element [b]: “and a taxoid,”**

*See* §(1)c.

- d. Element [c]: “in the absence of an anthracycline derivative,”**

*See* §(1)d.

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

*See* §(1)e.

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

*See* §(1)f.

- g. Element [f]: “without increase in overall severe adverse events.”**

*See* §(1)g.

**Ground 2: Claims 1–14 Are Invalid Based On Baselga '96 In View Of Baselga '94 And Gelmon**

**(1) Claim 1**

- a. Preamble: “A method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by over-expression of ErbB2 receptor, comprising”**

Baselga '96 discloses this limitation. It teaches rhuMAb HER2 was used in “[p]atients...whose metastatic breast carcinomas overexpressed HER2,” as confirmed by “by immunohistochemical analysis”:

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.

Exs. 1005 at 10, 13, Table 5; 1011¶152. Metastatic breast carcinoma is a malignant cancer derived from epithelial cells that has spread to other areas, *i.e.*, progressed. Ex. 1011¶¶38, 151–52. Baselga '96 further teaches that “[t]he HER2 gene (also known as *neu* and as *c-erbB-2*) encodes a...glycoprotein receptor (p185<sup>HER2</sup>).” Ex. 1005 at 9. A POSITA would have known that the ErbB2 receptor protein is also known as the HER2 receptor protein. Ex. 1011¶¶36, 151–52.

**b. Element [a]: “administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence”**

Baselga '96 discloses this limitation, explicitly or inherently. *See Santarus*, 694 F.3d at 1354; *In re Kubin*, 561 F.3d at 1357; *see also Abbvie*, 2014 WL 3360722, at \*6–7 (“[T]here is also no dispute that *the [binding] mechanism is an inherent feature* of the [claimed anti-TNF $\alpha$  antibody].”). The phase II trial 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<sup>HER2</sup>.” *Id.* at 9; Ex. 1001 at 5:26–37. This was done by “inserting the complementarity determining regions [of the murine 4D5 antibody]...into the framework of a consensus human immunoglobulin G<sub>1</sub> (IgG<sub>1</sub>).” Ex. 1005 at 10. The complementarity determining region determines what the antibody binds to, *i.e.*, the epitope. Ex. 1011¶¶40, 153. Because rhuMAb HER2 contains the same complementarity determining region as murine 4D5, it binds to the same epitope, *i.e.*, 4D5 within the ErbB2 extracellular domain sequence. Exs. 1005 at 10; 1011¶¶40, 153.

**c. Element [b]: “a taxoid,”**

Baselga '96 discloses this limitation. It 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, and thus a POSITA would look to Baselga ’94 for additional details. Baselga ’94 teaches that individual treatment with either antibody 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.* Baselga ’94 also discloses that “[c]linical trials are underway.” *Id.*; *see also* Ex. 1011¶¶154–55. At the very least, this limitation would have been obvious.

Gelmon further teaches a synergistic effect of paclitaxel in combination therapy for breast cancer. Exs. 1016 at 9, 1011¶156.

**d. Element [c]: “in the absence of an anthracycline derivative,”**

Baselga ’96 discloses this limitation. Baselga ’96 teaches that “[i]n preclinical studies...rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including...paclitaxel without increasing their toxicity.” Ex. 1005 at 15. As a result, “clinical trials of such combination therapy [we]re currently in progress.” *Id.* Baselga ’94 teaches individual treatment with either antibody 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.* As a result, “clinical trials of such



combination therapy [we]re currently in progress.” *Id.* Notably, Baselga combined antibody with *either* paclitaxel (a taxoid) *or* doxorubicin (an anthracycline), *but not both*. *Id.*; IPR2017-00731, Paper 19 at 10. Thus, Baselga’s combination was “in the absence of an anthracycline derivative,” as properly construed.

To the extent further motivation to “*avoid*” anthracyclines was somehow needed, it existed in the prior art. As of the ’441 patent priority date, anthracyclines were known to be effective but cumulatively cardiotoxic. Ex. 1031 at 5, 12. If a patient had previously taken anthracyclines, the risk for that patient was more pronounced for any additional anthracycline therapy. *Id.* Furthermore, as of the mid-1990s, most patients with HER2-overexpressing breast cancer, including those involved in clinical trials of antibodies and/or paclitaxel, had been previously treated with anthracyclines. *E.g.*, Ex. 1016 at 11. For these patients in particular it was known that further anthracyclines should be avoided. Ex. 1011¶35. As noted above, this was clearly well-known as PO’s own studies excluded patients previously treated with anthracyclines from the anthracycline treatment arm. *See* Ex. 1019\_2:37, 2:119–120. Combinations of rhuMAb HER2 with paclitaxel also had been shown to have superior efficacy and favorable safety compared to anthracycline combinations. Exs. 1006 at 4; 1013 at 5; 1016 at 13–14. Therefore, it was unsurprising that researchers were using rhuMAb HER2 combinations in the

absence of anthracyclines. Exs. 1006 at 4 (with paclitaxel); 1008 (same); 1013 at 5 (with cisplatin); 1011 ¶¶35, 43.

Indeed, as the Board acknowledged in instituting IPR of the '549 patent, the prior art, including Gelmon, evidenced “other reasons to avoid anthracyclines in a treatment regimen, such as concerns with drug resistance.” *See* IPR2017-00737, Paper 19 at 21–22. Any assertion this limitation somehow creates non-obviousness is further rebutted by the fact that the inventor, Dr. Hellmann, did not teach to avoid anthracyclines—as her prosecution declaration makes clear, the anthracycline arm of the clinical study already excluded patients with prior anthracycline treatment. Ex. 1019\_2:124, 2:132–47. The evidence that PO and Dr. Hellmann relied upon as *reduction to practice* did not “avoid” anthracyclines, instead including them as a separate study arm. *Id.*, 2:231, 2:237–39, 2:240–312.

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

Baselga '96 discloses this limitation. It discloses clinical trials administering antibody + paclitaxel to 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 discloses this limitation. As noted above, the limitation merely recites an inherent result of the treatment, which cannot support non-obviousness. *See Santarus*, 694 F.3d at 1354; *In re Kubin*, 561 F.3d at 1357. Indeed, PO and the named inventor asserted the claimed combination treatment was *reduced to*

*practice* by inclusion in a protocol *before any data was available*. Ex. 1019\_2:37, 2:119–120, 2:230–31, 2:237–39. This suggests they considered the results, including extension of time to disease progression, to be inherent in the combination treatment.

This limitation at least would have been obvious over Baselga '96 in view of Baselga '94 and Gelmon. Baselga '96 discloses a loading dose of 250 mg followed by weekly doses of 100 mg of rhuMAb HER2 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, 13, Table 5; Ex. 1011¶166. Baselga '96 further discloses that the combination of rhuMAb HER2 with paclitaxel in preclinical models resulted in synergistic increases in efficacy over single therapies without increasing toxicity. Exs. 1005 at 15; 1011¶¶166–67. These preclinical models are further described in Baselga '94. Ex. 1006.

Gelmon further discloses that biweekly administration of cisplatin with paclitaxel resulted in “an overall response rate of 85%” with a “median duration of overall response...[of] 7.9 months.” Ex. 1016 at 13. Therefore, it discloses a paclitaxel combination treatment that increases time to disease progression. Ex. 1011¶168. Thus, a POSITA would have had a reasonable expectation that the HER2 antibody/paclitaxel combination would extend time to disease progression in a patient, compared to paclitaxel alone.

**g. Element [f]: “without increase in overall severe adverse events.”**

Baselga '96 discloses this limitation. As noted above, this is an inherent result of the treatment, which cannot support non-obviousness. *See Santarus*, 694 F.3d at 1354; *In re Kubin*, 561 F.3d at 1357. Again, PO and the named inventor asserted that the claimed combination treatment was *reduced to practice* by its inclusion in a protocol *before any data was available*. Ex. 1019\_2:37, 2:119–120, 2:230–31, 2:237–39. And PO represented during prosecution that “reduced cardiac side effects naturally flow” from the antibody/taxol combination. *Id.*, 1019\_2:233–34.

Moreover, this limitation at least would have been obvious over Baselga '96 in view of Baselga '94 and Gelmon. Baselga '96 teaches rhuMAb HER2 “was remarkably well tolerated.” Ex. 1005 at 11. Overall, there was an “absence of significant toxicity.” *Id.* at 13. Baselga '96 and '94 both teach there was no increase in the toxicity of paclitaxel when administered in combination with rhuMAb HER2 in preclinical models. *Id.* at 15; Exs. 1006 at 4; 1011¶171. Thus, a POSITA would have a reasonable expectation that the HER2 antibody/paclitaxel combination would not increase overall severe adverse events.

**(2) Claim 2**

- a. “The method of claim 1 wherein said patient has a malignant tumor.”**

Baselga '96 discloses this limitation. It states “[p]atients eligible for this study were adult women whose metastatic breast carcinomas overexpressed HER2.” Ex. 1005 at 10. Metastatic breast carcinoma is a malignant cancer that forms a tumor in places where it grows in the body. Ex. 1011¶176.

**(3) Claim 3**

- a. “The method of claim 1 wherein said patient has cancer.”**

Baselga '96 discloses this limitation. It discloses that “[p]atients eligible for this study were adult women whose metastatic breast carcinomas overexpressed HER2.” Ex. 1005 at 10. Metastatic breast carcinoma is a cancer. Ex. 1011¶178.

**(4) Claim 4**

- a. “The method of claim 3 wherein said cancer is selected from the group consisting of breast cancer [and other cancers].”**

Baselga '96 discloses this limitation. It discloses “[p]atients eligible for this study were adult women whose metastatic breast carcinomas overexpressed HER2.” Ex. 1005 at 10. Metastatic breast carcinoma is breast cancer. Ex. 1011¶180.

**(5) Claim 5**

- a. “The method of claim 4 wherein said cancer is breast cancer.”**

*See* §(4).

**(6) Claim 6**

- a. “The method of claim 5 wherein said cancer is metastatic breast carcinoma.”**

Baselga '96 discloses this limitation. It discloses “[p]atients eligible for this study were adult women whose metastatic breast carcinomas overexpressed HER2.” Ex. 1005 at 10.

**(7) Claim 7**

- a. “The method of claim 1 wherein said antibody is a humanized 4D5 anti-ErbB2 antibody.”**

Baselga '96 discloses this limitation. It teaches that rhuMAb HER2 is a humanized form of the murine 4D5 antibody, *i.e.*, a humanized 4D5 anti-ErbB2 antibody. Exs. 1005 at 9; 1011¶¶40, 186.

**(8) Claim 8**

- a. “The method of claim 1 wherein said taxoid is paclitaxel.”**

As discussed above in §(1)c, Baselga '96 in view of Baselga '94 and Gelmon discloses this limitation, *i.e.*, the taxoid paclitaxel. Exs. 1005 at 13; 1006 at 4; 1016, *generally*; 1011¶¶64-67, 188.

**(9) Claim 9**

- a. “The method of claim 8 wherein the effective amount of said combination is lower than the sum of the effective amounts of said anti-ErbB2 antibody and said taxoid, when administered individually, as single agents.”**

Baselga '96 discloses this limitation, either explicitly or inherently. This limitation recites an inherent property of the claimed treatment method, which cannot support non-obviousness. *See Santarus*, 694 F.3d at 1354; *In re Kubin*, 561 F.3d at 1357. Again, that PO and the named inventor considered the invention reduced to practice by preparation of the study protocol before data was received demonstrating synergy confirms they considered this limitation to be inherent. Ex. 1019\_2:37, 2:119–120, 2:230–31, 2:237–39.

Moreover, this limitation would at least have been obvious. Baselga '96 and '94 teach that the combination of rhuMAb HER2 and paclitaxel resulted in a synergistic improvement in the antitumor effect of each treatment individually. Exs. 1005 at 15; 1006 at 4. The POSITA also would have been aware of other prior art studies, including Gelmon's, where paclitaxel was shown to have a synergistic effect in combination for breast cancer. Ex. 1016 at 9. A POSITA would have had a reasonable expectation that the combination would also be synergistic in humans and thus that an effective amount of the combination would be lower than the sum of effective amounts of each treatment individually. Ex. 1011¶¶190–91.

**(10) Claim 10**

- a. “The method of claim 1 wherein efficacy is further measured by determining the response rate.”**

Baselga '96 discloses this limitation. It reports that, of the patients treated with rhuMAB HER2, “five experienced a complete or partial remission, for an overall response rate of 11.6%.” Ex. 1005 at 13. It would have been obvious for a POSITA to measure the response rate of the therapy in patients because Baselga '96 used response rate to measure the effect of the single agent. Ex. 1011¶193.

**(11) Claim 11**

- a. Preamble: “A method for the treatment of a human patient with ErbB2 overexpressing progressing metastatic breast cancer, comprising”**

*See* §§(1)a, (6).

- b. Element [a]: “administering a combination of a humanized 4D5 anti-ErbB2 antibody,”**

*See* §§(1)b, (7).

- c. Element [b]: “a taxoid,”**

*See* §(1)c.

- d. Element [c]: “in the absence of an anthracycline derivative,”**

*See* §(1)d.

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

*See* §(1)e.



- f. **Element [e]: “in an amount effective to extent the time to disease progression in said human patient.”**

*See* §(1)f.

- g. **Element [f]: “without increase in overall severe adverse events.”**

*See* §(1)g.

**(12) Claim 12**

- a. **“The method of claim 11, wherein said taxoid is paclitaxel.”**

*See* §§(11), (8).

**(13) Claim 13**

- a. **Preamble: “A method for the treatment of a human patient with a progressing malignant tumor or cancer characterized by overexpression of ErbB2 receptor, comprising”**

*See* §(1)a.

- b. **Element [a]: “administering a combination of a humanized 4D5 anti-ErbB2 antibody which comprises a human F<sub>c</sub> region that binds to epitope 4D5 within the ErbB2 extracellular domain sequence”**

Baselga '96 discloses this limitation, either explicitly or inherently. *See Santarus*, 694 F.3d at 1354; *In re Kubin*, 561 F.3d at 1357. It discloses a humanized 4D5 anti-ErbB2 antibody which comprises a human F<sub>c</sub> region that binds to epitope 4D5 because rhuMAb HER2 is comprised of “the complementarity determining regions of MAb 4D5” and “the framework of a consensus human immunoglobulin G<sub>1</sub> (IgG<sub>1</sub>).” Ex. 1005 at 10. A consensus human

immunoglobulin G<sub>1</sub> contains a human F<sub>c</sub> region. Ex. 1011¶205. 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 in Baselga '96 binds to epitope 4D5 within the ErbB2 extracellular domain sequence. Exs. 1005 at 10; 1011¶206.

**c. Element [b]: “and a taxoid,”**

*See* §(1)c.

**d. Element [c]: “in the absence of an anthracycline derivative,”**

*See* §(1)d.

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

*See* §(1)e.

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

*See* §(1)f.

**g. Element [f]: “without increase in overall severe adverse events.”**

*See* §(1)g.

**(14) Claim 14**

**a. Preamble: “A method for the treatment of a human patient with ErbB2 expressing progressing metastatic breast cancer, comprising”**

*See* §§(11)a, (6).

- b. Element [a]: “administering a combination of an antibody which binds to epitope 4D5 within the extracellular domain sequence”**

*See* §§(1)b, (7). “[A]ntibody” is broader than “intact antibody” and thus the reasoning in §(1)b applies. Ex. 1011¶143

- c. Element [b]: “and a taxoid,”**

*See* §(1)c.

- d. Element [c]: “in the absence of an anthracycline derivative,”**

*See* §(1)d.

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

*See* §(1)e.

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

*See* §(1)f.

- g. Element [f]: “without increase in overall severe adverse events.”**

*See* §(1)g.

## **H. There Are No Secondary Considerations of Nonobviousness**

Dr. Sliwowski’s secondary considerations arguments during prosecution are unavailing. He first argued that, because paclitaxel and rhuMAb HER2 cause cell cycle arrest at different times, a POSITA would have thought that rhuMAb HER2 would prevent paclitaxel from working. This fails for three reasons.

*First*, none of the papers Dr. Sliwowski relied upon examined rhuMAB HER2 and paclitaxel. Ex. 1019\_9:51 (Ex. C), 9:60 (Ex. D); Ex. 1011¶223. *Second*, by 1994, other research had demonstrated rhuMAB HER2 was compatible with chemotherapies, such as cisplatin, that showed the same cell cycle arrest point as paclitaxel. Ex. 1011¶224.<sup>3</sup> Indeed, as disclosed in Baselga '96 and '94, as well as *Lottery*, clinical trials of the combination were already underway and disclosed to the public. Ex. 1008 at 3. *Third*, a POSITA would have understood the data Dr. Sliwowski cited related to tamoxifen and anthracycline, not rhuMAB HER2 and paclitaxel. Baselga '94 reports *in vivo* data demonstrating synergistic effect between the antibody and paclitaxel. Exs. 1019\_9:85 (Ex. F), 9:94 (Ex. G); 1006 at 4. If Dr. Sliwowski's hypothesis were correct, the preclinical data should have shown less than additive effect when the drugs were both administered. Exs. 1019\_9:94 (Ex. G); 1011¶225. Since Baselga '94 reports the opposite and that

---

<sup>3</sup> Sorenson et al., 82(9) J. NATL. CANCER INST. 749–55, (1990) (Ex. 1022) at 7 (cisplatin causes G2 cell cycle arrest); Pietras et al., 9(7) ONCOGENE 1829–38 (1994) (Ex. 1023) at 3 (combination of 4D5 anti-ErbB2 antibody and cisplatin caused synergistic decrease in cell growth); and Pegram '95 (Ex. 1013) at 5 (rhuMAB HER2/cisplatin combination in breast cancer patients resulted in 50% of patients with stable disease or better without increasing cisplatin toxicity).

clinical trials are ongoing, a POSITA would have found it obvious to try the combination in humans with reasonable expectation of success.

Dr. Sliwkowski's second argument was that a POSITA would not have relied on preclinical models. Ex. 1019\_9:12. But, PO relied on information disclosed by Baselga when it determined it would proceed with clinical trials. Indeed, it cites it as written description of its invention. Moreover, Dr. Sliwkowski cites a 2001 article, dated well after the '441 patent's priority date. *Id.* And the purported controversy regarding preclinical models does not appear to affect their use to determine treatments for humans. Indeed, Dr. Sliwkowski is co-author on many papers sponsored by PO using preclinical data to screen and select treatments using anti-ErbB2 antibodies. Exs. 1017; 1018. A POSITA would have seen Baselga '94 demonstrated synergistic effects of the combination in a mouse model and reported a clinical trial underway, then Baselga '96 reports the same clinical trial as underway two years later. Ex. 1005 at 12. *Lottery* confirms clinical studies of the combination were underway. Ex. 1008 at 3. A POSITA would have understood this to mean the trial had not been halted for lack of efficacy or safety. Ex. 1011¶¶226–27.

PO's purported unexpected results also lack a nexus to the claimed inventions. Dr. Sliwkowski's assertions are directed to a paclitaxel/rhuMAb HER2 combination, but that therapy already appeared in the prior art. PO identified no

secondary indicia associated with claim elements not already in the prior art. PO's purported unexpected results further are not commensurate with the Challenged Claims, many of which are generally directed to treatment involving any "taxoid." Ex. 1011¶228.

**I. The Board Should Not Deny Institution Under 35 U.S.C. §§314 or 325(d)**

Petitioner respectfully submits that the Board should not discretionarily deny this petition under 35 U.S.C. §§314 or 325(d), or otherwise. *No party* has previously raised the combinations relied upon here. Ground 1 raises prior art and arguments not presented in any prior petition, including art Petitioner reasonably was not aware of at the time of its first petition. In such cases the Board generally has not denied institution. *See Microsoft Corp. v. Bradium Techs. LLC*, IPR2016-00448, Paper 9 at 7–11; *Baker Hughes Inc. v. Packers Plus Energy Servs., Inc.*, IPR2016-01505, Paper 19 at 8–9. The Board also has not denied institution where, as in Ground 2, the prior art overlaps with a prior petition but an additional reference materially impacts the analysis. *Valeo N. Am. v. Magna Elecs., Inc.*, IPR2014-01206, Paper 13 at 11 (“We are not persuaded that the art and arguments presented in this Petition are the same or substantially the same prior art or arguments....For example, *the Petition relies upon a combination of Hitachi and Ohtsuka..., while in contrast the petitions in the 227 IPR relied upon Hitachi alone.*”).

Weighing the factors typically applied by the Board favors institution here.

With respect to **Ground 1**, Petitioner's counsel were not aware of *Lottery* at the time of the IPR2017-00731 petition. *Lottery* is a newspaper article. Earlier prior art searching was reasonably focused on scientific literature, which was the nature of the art disclosed on the face of the '441 patent and successful in invalidating its European counterpart. *Lottery* is not the type of reference typically identified by a routine prior art search. As such, it had not been identified by Petitioner. It was first identified by Petitioner's counsel on August 23, 2017, through a search for press, beyond the scientific community, regarding PO's clinical trials. This was spurred by PO's unexpected denial that the clinical trials referenced in Baselga '96 were ongoing as of the date of that reference. IPR2017-00731, Paper 9 at 31. The secondary reference in Ground 2, Hayes, was identified based on its referencing in *Lottery*.

With respect to **Ground 2**, although Petitioner was aware of Gelmon when the IPR2017-00371 petition was filed, Petitioner reasonably believed based on positions PO previously had taken that Baselga '96 and '94 were sufficient to satisfy the "in the absence of an anthracycline derivative" limitation. For example, in response to the Examiner rejecting the claims as anticipated by Baselga '97, PO submitted a declaration from Dr. Hellmann. According to Dr. Hellman, a Genentech-sponsored clinical trial was experiencing poor recruitment numbers due

to ineligibility of patients previously treated with anthracyclines, based on known cumulative cardiotoxicity and drug resistance concerns. Ex. 1019\_2:124, 2:132–47. The solution was to amend the protocol to add a non-anthracycline, paclitaxel arm. *Id.* The Examiner initially was not persuaded, stating that “[t]he evidence submitted fails to address the claimed limitation of ‘in the absence of an anthracycline derivative’, and *in fact includes trials which administer anthracycline derivatives.*” *Id.* at 2:214. In response, PO submitted another Hellmann declaration, stating:

[T]he protocol explains that patients further received *one of two chemotherapy regimens* for a minimum of six cycles: a) cyclophosphamide and *doxorubicin or epirubicin*, if patients had not received anthracycline therapy in the adjuvant setting, *or* b) *paclitaxel*, if patients had received any anthracycline therapy in the adjuvant setting....*It is clear from these sections of the protocol, that patients were being treated with a combination of an anti-ErbB2 antibody (rhuMab HER2) and a taxoid (paclitaxel), in the absence of an anthracycline derivative*, in an amount effective to extend TIP in the patients.

*Id.* at 2:237–312 (protocol). Based on Dr. Hellmann’s Declaration, PO told the Examiner that:



[i]t is clear from the attached §131 declaration...that the method of treatment was performed in the absence of an anthracycline derivative... Applicants further submit that the earlier §131 declaration by Dr. Hellmann also made it clear that *therapy with the ‘Taxol + rhuMab HER2’ combination was to be in the absence of an anthracycline derivative, since this was presented as an alternative to rhuMab HER2 + anthracycline treatment.*

*Id.* at 2:231 (emphasis added). Throughout prosecution, PO never waived from this position that HER2 antibody/taxoid treatment meets the “in the absence of an anthracycline derivative” limitation, never arguing the limitation required *avoidance* of anthracyclines. Indeed, when the Examiner rejected the claims over Baselga ’96 in view of Baselga ’94 or other references, PO never contended these references did not disclose treatment with the claimed combination in the absence of an anthracycline derivative. Rather, at most they argued the combination had unexpected advantages over the antibody/anthracycline combination, *i.e.*, lowered cardiac events. Ex. 1019\_1:400–01, 2:232–35, 2:359–60, 8:114–21, 8:136–37, 9:9.

Likewise, in proceedings involving the European counterpart to the ’441 patent—EP 1 037 926 B1—which included an equivalent requirement for antibody/taxoid combination treatment “not in combination with an anthracycline derivative,” PO similarly conceded that treatment with HER2 antibody + taxoid

met the requirement. In the U.K., the patent was revoked as obvious over Baselga '97. *See Hospira UK, Ltd. v. Genentech, Inc.*, No. HP-2014-000034, [2015] EWHC (HC) 1796 (Pat), (Jun. 24, 2015) (Ex. 1003), *aff'd Hospira UK, Ltd. v. Genentech, Inc.*, No. A3 2015 3238, [2016] EWCA Civ 1185 (Nov. 30, 2016) (Ex. 1021). PO never argued Baselga '97 did not meet the “not in combination with an anthracycline derivative” requirement, notwithstanding its disclosure of alternative treatment with antibody in combination with paclitaxel *or* anthracycline. *Id.*

In the European Patent Office, the EP '926 patent was opposed on the grounds, *inter alia*, that it was obvious over Baselga '97 and Baselga '96, each alone or in combination. Yet, again, in those proceedings, PO never argued the “not in combination with an anthracycline derivative” limitation was not met by the Baselga references' disclosure of treatment with antibody + paclitaxel *or* anthracycline derivative. Ex. 1050 at 26–35, 75–78, 135–38, 211–40, 246–51. Indeed, PO referred to administration of the three-drug combination of antibody + taxoid + anthracycline as merely a “theoretical possibility.” *Id.* at 13–14.

Thus, Petitioner could not have anticipated that Genentech would seek, and the Board would apply, a construction of “in the absence of an anthracycline derivative” that would require “*avoidance*” of anthracyclines, rather than simply their “*absence*” in a treatment regimen. It was only in its Preliminary Response in

IPR2017-00731 (to which Petitioner had no right of reply) that PO first raised the “avoidance” argument. *See* IPR2017-00731, Paper 9 at 7 (“Moreover, the references underlying Petitioner’s proposed grounds confirm that anthracyclines were not being avoided. ***Both Baselga ’94 and Baselga ’97 involved combinations with anthracyclines.***”). It was this unanticipated shift that led the Board to find the limitation not met by Baselga ’96 and ’94. *See* IPR2017-00731, Paper 19 at 9. Petitioner has moved for rehearing of that decision. *See id.*, Paper 22.

Notably, while the Board correctly cited Gelmon in its institution decision in IPR2017-00737 as demonstrating a further motivation to “avoid” anthracyclines, *i.e.*, “concerns with drug resistance,” the reference had primarily been cited in the petition as disclosing “a further growth inhibitory agent,” a requirement absent from the ’441 patent. *See* IPR2017-00737, Paper 1 at 46-47. At base, therefore, this is a circumstance of Genentech’s making.

Significantly, since Hospira submitted its petition in IPR2017-00731, the Board issued its institution decision in IPR2017-00737 holding, *inter alia*, that Petitioner is likely to prevail in demonstrating the ’549 patent claims are obvious. IPR2017-00737, Paper 19 at 23–24. As demonstrated in the following chart, the ’549 patent methods the Board has found are likely obvious are ***necessarily encompassed by*** the ’441 patent methods challenged here:

'549 Patent (Ex. 1010), claim 16	'441 Patent (Ex. 1001), claim 1
16. A method for the treatment of a human patient with ErbB2 overexpressing breast cancer, comprising	1. A method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by over-expression of ErbB2 receptor, comprising
administering a combination of an antibody that binds epitope 4D5 within the ErbB2 extracellular domain sequence	administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence
a taxoid,	and a taxoid,
and a further growth inhibitory agent,	
in the absence of an anthracycline derivative,	in the absence of an anthracycline derivative,
to the human patient	to the human patient
in an amount effective to extend the time to disease progression in the human patient.	in an amount effective to extend the time to disease progression in said human patient, without increase in overall severe adverse events

Although the '549 patent additionally requires “a further growth inhibitory agent,” the '441 patent does not preclude such a further agent. *See Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003) (“The transition ‘comprising’ in a method claim indicates that the claim is open-ended and allows for additional steps.”). And as described above, the additional limitation “without increase in overall severe adverse events” in the '441 patent is *inherent* in the

claimed treatment, and in any event was entirely expected based on the prior art. *See* IPR2017-00731, Paper 9 at 23; Ex. 1019\_2:37, 2:119–120, 2:230–31, 2:233–34, 2:237–39; Ground 1:(1)g, and Ground 2:(1)g.

Thus, the Board’s determination that Petitioner is likely to prevail for the ’549 patent also applies to the ’441 patent claims. If the Board were to exercise its discretion to deny institution here, that would lead to the untenable consequence that claims to methods the Board already has determined are likely unpatentable remain unchallenged. This would be contrary to the public interest in invalidation of patents claiming unpatentable methods and products, which is particularly strong here as PO may try to use the ’441 patent to delay low-cost alternative versions of life-saving cancer treatments. *See Par Pharms., Inc. v. TWI Pharms., Inc.*, Civil No. CCB-11-2466, 2014 WL 3956024, at \*5 (D. Md. Aug. 12, 2014) (“The court recognizes that the public is served by the availability of low-cost generic medications, especially where an invalid patent has previously barred their entry into the market.”).

Petitioner is not merely taking a “second bite of the apple.” Nor is it merely using the Board’s prior decision as a “roadmap” to remedy the deficiency in IPR2017-00731. Rather, Petitioner is appropriately responding to PO’s newly-minted claim construction on the one hand, and unexpected denial regarding the public broadcasting of clinical trials of its claimed combination on the other, while

also recognizing the Board's institution decision in IPR2017-00737 is necessarily applicable to the '441 patent. Instituting IPR in these very unique circumstances will not open the floodgates to repeated administrative attacks on the same claims, or the holding back of prior art for successive petitions.

Petitioner also has not unduly delayed. After the institution decisions in IPR2017-00731 and -00737, and Petitioner's subsequent identification of *Lottery*, Petitioner worked diligently to prepare and submit this petition within weeks. Because no IPR on the '441 patent has yet been instituted, this petition should not prejudice the Board's ability to issue a final determination within a year after the Board notices institution of review. Moreover, PO will not be unduly prejudiced. PO must defend against IPR of the '549 patent claims on substantively identical grounds to Ground 2, and it can be expected that PO's evidence and argument would also be substantively identical. And with respect to Ground 1, patent owners are routinely required to defend against IPR on multiple, non-redundant grounds. In any event, as noted above, any such additional expense or burden is of PO's own making.

Finally, Grounds 1 and 2 are not redundant of each other, nor are they redundant of the ground in pending IPR2017-02063—they establish obviousness in different ways. In Ground 2, the primary reference Baselga '96 describes stand-alone therapy with the anti-ErbB2 antibody, while reporting positive results of pre-

clinical studies of the combination with paclitaxel and indicating clinical studies are underway. The secondary reference, Baselga '94 provides further detail regarding these preclinical studies, reporting superior results of the antibody/paclitaxel combination in the pre-clinical setting. As noted above, although Petitioner submits the teaching that studies of the combination in humans are underway is clear, PO has sought to refute that. IPR2017-00731, Paper 9 at 31.

The references in Ground 1 confirm beyond doubt that clinical trials of the combination were ongoing prior to the '441 patent priority date. *Lottery* reports that clinical trial of the antibody with “taxol” was ongoing, describing recruitment of patients for the study. The secondary reference, Hayes, is referenced in *Lottery*, and, either alone or through its citation to Baselga '96, confirms that the antibody in question is the same anti-ErbB2 antibody claimed in the '441 patent. In sum, both Grounds establish obviousness, but do so in different, non-redundant ways.

Neither is redundant over the ground in IPR2017-02063. Although that ground also relies on Baselga '96, it further relies on Seidman 1996 and the 1995 TAXOL PDR. IPR2017-02063, Paper 1. Seidman 1996 teaches that HER2 overexpression confers sensitivity to taxoid treatment. *Id.* at 33–34. The 1995 TAXOL PDR explains that taxoids are used after a patient has failed treatment with adjuvant chemotherapy. *Id.* at 27. These references provide strong—but

different—motivation to combine antibody with taxoids in the absence of an anthracycline derivative.

For these reasons, Petitioner respectfully requests that the Board exercise its discretion *not* to reject this Petition under §§314 or 325(d), or otherwise.

## **VII. CONCLUSION**

Petitioner respectfully requests IPR of the Challenged Claims.



Date: October 3, 2017

Respectfully submitted,

*/Amanda Hollis/*

---

Amanda Hollis (Reg. No. 55,629)  
KIRKLAND & ELLIS LLP  
300 North LaSalle Street  
Chicago, Illinois 60654  
P: 312.862.2000; F: 312.862.2200  
amanda.hollis@kirkland.com

Karen Younkens (Reg. No. 67,554)  
karen.younkens@kirkland.com  
*Attorneys For Petitioner*

## CERTIFICATE OF COMPLIANCE

This Petition complies with the type-volume limitations as mandated in 37 C.F.R. §42.24, totaling 13,849 words. Counsel has relied upon the word count feature provided by Microsoft Word.

*/Amanda Hollis/*

---

Amanda Hollis

## CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 7,846,441, along with all exhibits and other supporting documents, was served on October 3, 2017, via FedEx Overnight delivery directed to the assignee for the patent at the following address:

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

The undersigned further certifies that a copy of the foregoing Petition, along with all exhibits and other supporting documents, was served on October 3, 2017, via FedEx Overnight delivery directed to the attorney of record for the patent at the following address:

Arnold & Porter Kaye Scholer LLP  
Three Embarcadero Center, 10th Floor  
San Francisco CA 94111

/Amanda Hollis/  
Amanda Hollis