

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD., Petitioner,

v.

GENENTECH, INC., Patent Owner.

United States Patent No. 7,846,441
Title: Treatment with Anti-ErbB2 Antibodies

Case No. IPR2018-00192

**PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 7,846,441**

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TABLE OF AUTHORITIES

Cases

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| <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)..... | 26, 45 |
| <i>Dawson v. Dawson</i> , 710 F.3d 1347 (Fed. Cir. 2013) | 21 |
| <i>Dome Patent L.P. v. Lee</i> , 799 F.3d 1372 (Fed. Cir. 2015) | 19 |
| <i>Ex parte Gillis</i> , No. 2010-09318 (B.P.A.I. Nov. 21, 2011) | 20 |
| <i>Ex parte Litwin</i> , No. No. 2009-011704, 2011 WL 3414500 (B.P.A.I. Aug. 2, 2011)..... | 20 |
| <i>In re Kubin</i> , 561 F.3d 1351 (Fed. Cir. 2009) | passim |
| <i>KSR Int'l Co. v. Teleflex, Inc.</i> , 550 U.S. 398 (2007)..... | 18, 19 |
| <i>Ortho-McNeil Pharm. Inc. v. Kali Labs. Inc.</i> , 482 F. Supp. 2d 478 (D.N.J. 2007), <i>vacated on other grounds</i> , 344 Fed. App'x 595 (Fed. Cir. 2009)..... | 19 |
| <i>Santarus, Inc. v. Par Pharm., Inc.</i> , 694 F.3d 1344 (Fed. Cir. 2012) | passim |

Statutes

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37 C.F.R. §42.1045

Other Authorities

3-8 Chisum on Patents §8.0620

T. Brody, *Negative Limitations in Patent Claims*,
41 Am. Intell. Prop. Q.J. 29 (2013).....20

| PETITIONER'S EXHIBIT LIST | |
|----------------------------------|--|
| Exhibit No. | Description |
| 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^{HER2} 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

| Exhibit No. | Description |
|--------------------|---|
| 1013 | Pegram <i>et al.</i> , <i>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 | Reserved |
| 1015 | Hudziak <i>et al.</i> , <i>p185^{HER2} 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 | Gelmon <i>et al.</i> , <i>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 | Phillips <i>et al.</i> , <i>Targeting HER2-Positive Breast Cancer with Trastuzumab-DM1, an Antibody–Cytotoxic Drug Conjugate</i> , 68(22) CANCER RES. 280–90 (2008) |
| 1018 | Phillips <i>et al.</i> , <i>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

| Exhibit No. | Description |
|--------------------|---|
| 1022 | Sorenson <i>et al.</i> , <i>Analysis of Events Associated with Cell Cycle Arrest at G₂ 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”) |
| 1033 | Johnson <i>et al.</i> , <i>Food and Drug Administration Requirements for Approval of New Anticancer Drugs</i> , 69(10) CANCER TREATMENT REPORTS 1155–57 (1985) |

| PETITIONER'S EXHIBIT LIST | |
|---------------------------|---|
| Exhibit No. | Description |
| 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, http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020262 (last visited Dec. 22, 2016) |
| 1041 | Gianni <i>et al.</i> , <i>Paclitaxel and Doxorubicin in Metastatic Breast Cancer</i> , 14(4) J. CLIN. ONCOL. 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) SEMINARS ONCOL. 46–56 (1996) (“Holmes '96”) |
| 1043 | Rodrigues <i>et al.</i> , <i>Development of a Humanized Disulfide-stabilized Anti-p185^{HER2} Fv-β-Lactamase Fusion Protein for Activation of a Cephalosporin Doxorubicin Prodrug</i> , 55(1) CANCER RES., 63–70 (1995) |
| 1044 | Park <i>et al.</i> , <i>Development of Anti-p185^{HER2} Immunoliposomes for Cancer Therapy</i> , 92(5) PROC. NATL. ACAD. SCI. USA, 1327–31 (1995) |
| 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 |

PETITIONER’S EXHIBIT LIST

| Exhibit No. | Description |
|--------------------|--|
| 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 |
| 1060 | Pegram <i>et al.</i> , <i>Phase II Study of Receptor-Enhanced Chemosensitivity Using Recombinant Humanized Anti-p185HER2/neu Monoclonal Antibody Plus Cisplatin in Patients with HER2/neu- Overexpressing Metastatic Breast Cancer Refractory to Chemotherapy Treatment</i> , 16(8) J. CLIN. ONCOL. 2659–71 (1998) |
| 1061 | DeVita <i>et al.</i> , <i>A History of Cancer Chemotherapy</i> , 68(21) CANCER RES. 8643–53 (2008) |
| 1062 | U.S. Patent No. 5,677,171 |
| 1063 | Carter, <i>et al.</i> , <i>Humanization of an Anti-p185HER2 Antibody for Human Cancer Therapy</i> , 89(10) PROC. NATL. ACAD. SCI. USA 4285–89 (1992) (“Carter ’92”) |

PETITIONER'S EXHIBIT LIST

| Exhibit No. | Description |
|--------------------|--|
| 1064 | Library of Congress Copyright Record for Baselga '98 |
| 1065 | Library of Congress Copyright Record for Hayes '96 |
| 1098 | Declaration of Scott Weingaertner |
| 1099 | Declaration of Hilary Calvert, M.D. |

Pursuant to 35 U.S.C. § 311 and 37 C.F.R. § 42.100, Petitioner Samsung Bioepis Co., Ltd. (“Petitioner” or “Bioepis”) respectfully requests *inter partes* review (“IPR”) of claims 1–14 (the “Challenged Claims”) of U.S. Patent No. 7,846,441 (the “’441 patent”), assigned to Genentech, Inc. (“Genentech” or “Patent Owner” (“PO”)). The grounds raised in this petition are the same as those raised in the petition filed by Pfizer Inc. on October 3, 2017, regarding the ’441 patent (IPR2018-00016).

I. INTRODUCTION

The alleged invention of the ’441 patent was to combine two known treatments for HER2-overexpressing breast cancer: (i) the humanized 4D5, anti-ErbB2 antibody Herceptin[®] (rhuMAb HER2) and (ii) the taxoid Taxol[®] (paclitaxel). But the same combination was already under investigation in clinical trials and 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) prior 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. In particular, *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 that this treatment was “in the absence of an anthracycline derivative.” *Lottery* apparently was not identified by the Examiner’s prosecution searches and was not cited during prosecution of the ’441 patent.

The Challenged Claims are also obvious over Baselga ’96 in view of Baselga ’94 and Gelmon. The Board recently instituted IPR on the ’441 patent based on Baselga ’96 and Baselga ’94. IPR2017-00731, Paper No. 29. Furthermore, in instituting IPR2017-00737, the Board determined that the methods of U.S. Patent No. 7,892,549—*which are necessarily encompassed by the claims of the ’441 patent*—are likely invalid as obvious over this prior art combination. IPR2017-00737, Paper No. 19. Accordingly, consistent with the Board’s precedent, IPR should be instituted on Petitioner’s proposed grounds.

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

Bioepis is the real party-in-interest.

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

Petitioner identifies the following potentially related matters:

- EP 1,037,926 B1 (Ex. 1004)¹, the European counterpart to the ‘441 patent, 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: Hospira Inc. (“Hospira”) submitted an IPR petition on January 20, 2017, challenging the ’441 patent. Institution was initially denied on July 27, 2017, but subsequently granted on October 26, 2017, following a Request for Rehearing.
- IPR2017-01121: Celltrion, Inc. filed a petition challenging the ’441 patent on March 21, 2017. The Board instituted IPR on October 4, 2017.
- IPR2018-00016: Pfizer Inc. filed a petition challenging the ‘441 patent on October 3, 2017. An institution decision has not yet been entered.

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

- IPR2017-00737 and -00739: Hospira submitted IPR petitions on January 20, 2017 challenging claims of U.S. Patent No. 7,892,549, a continuation of the '441 patent. On July 27, 2017, the Board granted institution of IPR2017-00737 and denied institution of IPR2017-00739.
- IPR2017-01122: Celltrion Inc. filed an IPR petition challenging claims of the '549 patent on March 21, 2017. The Board instituted IPR on October 4, 2017.
- IPR2017-01960: Bioepis filed an IPR petition challenging claims of the '549 patent on August 25, 2017, and seeking joinder with IPR2017-00737. An institution decision has not yet been entered.

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

Petitioner designates:

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

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

Please address all correspondence to lead and backup counsel. Concurrently filed with the petition is a power of attorney pursuant to 37 C.F.R. § 42.10(b). Petitioner consents to service by electronic mail at ddrivas@whitecase.com and scott.weingaertner@whitecase.com.

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

Petitioner authorizes the USPTO to charge the fees enumerated in 37 C.F.R. § 42.15(a), and any additional fees in connection with this Petition, to Deposit Account 50-3672.

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

Petitioner certifies that the '441 patent is available for IPR and that 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:

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

| Ground | Proposed Statutory Rejections |
|--------|--|
| 2 | Baselga '96 in view of Baselga '94 and Gelmon renders claims 1–14 obvious under 35 U.S.C. §103. |

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

- **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.

² Additional evidence authenticating various exhibits is provided in the Declarations of Scott Weingaertner (Ex. 1098), Karen Younkings (Ex. 1014), Christopher Lowden (Ex. 1024), and Simon Cohen (Ex. 1048). The Younkings, Lowden, and Cohen declarations are exact copies of the documents submitted in IPR2018-00016.

Additional evidence is provided in the Declaration of Allan Lipton, M.D. (Ex. 1011)³, the Declaration of Hilary Calvert, M.D. (Ex. 1099) and other supporting exhibits. 37 C.F.R. §1.68.

VI. THE LEVEL OF ORDINARY SKILL IN THE RELEVANT ART

A person of ordinary skill in the art (“POSITA”) would have been a clinical or medical oncologist with expertise in breast cancer and several years of experience with breast cancer research or clinical trials. Ex. 1011 ¶¶15–17; Ex. 1099 ¶¶11-13. In prior proceedings, Genentech did not dispute this definition. *See, e.g.*, IPR2017-00731, Paper 9 at 32; IPR2017-01121, Paper 8 at 36-37. The Board also adopted this definition in instituting IPR of the ’549 and ’441 patents. *See, e.g.*, IPR2017-00737, Paper 19 at 8–9; IPR2017-01121, Paper 9 at 9-10.

VII. THE SCOPE AND CONTENT OF THE PRIOR ART

A. The 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[®], was humanized by “inserting the complementarity determining regions [of murine 4D5 antibody]...into the

³ Ex. 1011 is an exact copy of the declaration submitted by Dr. Lipton in IPR2018-00016. The declaration is cited here to avoid unnecessary cost and to advance efficiency.

framework of a consensus human immunoglobulin G1 (IgG1).” 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 of experience showing their superiority over single-agent therapies. Exs. 1015 at 8; 1030 at 5; 1011 ¶¶29–33, 1099 ¶¶24–29. 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; 1099 ¶¶36-37.

Anthracyclines are, and were in the mid-1990s, often first-line treatment for breast cancer. Exs. 1031 at 4, 12; 1011 ¶35; 1099 ¶31. They are effective but cardiotoxic, and by the mid-1990s, it was understood that 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. *See, e.g.*, Ex. 1016 at 11. For these patients in particular, it was known further that anthracycline therapy should be avoided. Exs. 1011 ¶35; 1099 ¶31. This was clearly well-known before the alleged invention of the '441 patent—patients who previously had been treated with anthracyclines were excluded from the anthracycline arm of PO's clinical studies. Ex. 1019 at 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; 1099 ¶¶31, 39-40.

B. The Prior Art

1. Lottery

Lottery describes 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 antibody 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; 1099 ¶55.

2. Hayes

The Hayes editorial, entitled “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 discussed 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 had 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/m² 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; 1099 ¶70. Baselga '94 teaches that clinical trials of these combinations were underway. *Id.*

VIII. THE '441 PATENT AND ITS PROSECUTION HISTORY

The '441 patent issued from U.S. Ser. No. 09/208,649 (“'649 application”),

which claims priority to U.S. Provisional App. No. 60/069,346 (Ex. 1012), filed December 12, 1997. The patent issued with 14 claims. Independent claim 1 is as follows:

1. A method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by overexpression of ErbB2 receptor, comprising administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence and a taxoid, in the absence of an anthracycline derivative, to 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.

Claims 2-10 depend from claim 1 and include further limitations regarding the patient or type of cancer (claims 2-6), the antibody (claim 7), the taxoid (claim 8), the amount of drug (claim 9), and the means for determining efficacy (claim 10). Independent claims 11, 13, and 14 are similar to claim 1.

The specification of the '441 patent includes an example relating to the treatment of HER2-positive metastatic breast cancer patients. Half of the patients received chemotherapy alone, which comprised either cyclophosphamide and an anthracycline derivative ("AC"), or paclitaxel (T). The other half received one of these chemotherapy regimens, plus trastuzumab (H). The results are reported as follows:

| Treatment | Number of Patients | TTP (months) | RR (%) | AE(%) |
|-----------|--------------------|--------------|--------|-------|
| AC | 145 | 6.5 | 42.1 | 71 |
| AC + H | 146 | 9.0 | 64.9 | 68 |
| T | 89 | 4.2 | 25.0 | 59 |
| T + H | 89 | 7.1 | 57.3 | 70 |

The specification states that the results favor the combination of trastuzumab and paclitaxel:

These data indicate that the combination of anti-ErbB2 antibody treatment with chemotherapy markedly increases the clinical benefit, as assessed by response rates and the evaluation of disease progression. However, due to the increased cardiac side-effects of doxorubicin or epirubicin, the combined use of anthracyclines with anti-ErbB2 antibody therapy is contraindicated. The results, taking into account risk and benefit, favor the combined treatment with HERCEPTIN® and paclitaxel (TAXOL).

(‘441 patent, col. 30, ll. 17-25.)

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. 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.

IX. LEGAL STANDARDS FOR OBVIOUSNESS

Analysis under 35 U.S.C. §103(a) requires a determination of the scope and content of the prior art, the differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art. *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).

X. 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).

In prior proceedings, the Board construed the claim term “extend the time to disease progression, without increase in overall severe adverse events” to involve a comparison of the claimed combination to no treatment. *See, e.g.*, IPR2017-01121, Paper 9. The Board also recently held that the claim term “in the absence of an anthracycline derivative” is satisfied by anti-ErbB2 antibody–paclitaxel combinations that do not include an anthracycline derivative. IPR2017-00731, Paper 29 at 17-18. Petitioner agrees with these interpretations.

XI. DETAILED STATEMENT OF GROUNDS FOR UNPATENTABILITY

A. 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. 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 positive 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; 1099 ¶75. A POSITA would have known the HER2/*neu* receptor is the “ErbB2 receptor.” *Id.* *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; 1099 ¶¶55, 77. 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 G1 (IgG1),” 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; 1099 ¶¶ 36, 77. 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-TNFa antibody].”) (emphasis added).

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^{HER2}.” Exs. 1009 at 10; 1005 at 10; 1011 ¶82; 1099 ¶78.

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; 1099 ¶80.

During prosecution, Dr. Sliwowski asserted a skilled artisan would not have expected rhuMAb HER2 with taxoid to produce synergistic effects. Ex. 1019 at 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; 1099 ¶81.

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 (emphasis added); 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; 1099 ¶82. 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 (emphasis added). From this statement and its clinical trial context, a POSITA would understand that anthracyclines were not part of the regimen. Ex. 1011 ¶88; 1099 ¶84. 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; 1099 ¶84.

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. *See, e.g.*, Ex. 1016 at 11. For these patients in particular it was known that further anthracycline therapy should be avoided. Ex. 1011 ¶35; 1099 ¶31. This was clearly well-known at the time, as PO's own studies excluded patients previously treated with anthracyclines from the anthracycline treatment arm. Ex. 1019 at 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; 1099 ¶¶31, 39-40.

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. Furthermore, *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; 1099 ¶85. 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 at 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, expressly 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 that the claimed combination treatment was *reduced to practice* by inclusion in a protocol *before data was available*. Ex. 1019 at 2:37, 2:119–120, 2:230–31, 2:237–39.

This limitation at the very least would have been obvious in view of the disclosures in *Lottery* discussed above. In addition, 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 ¶97; 1099 ¶93.

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; 1099 ¶¶65-68, 93.

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 expressly 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 at 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 at 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

“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; 1099 ¶100.

(3) Claim 3

“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; 1099 ¶102.

(4) Claim 4

“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; 1099 ¶104.

(5) **Claim 5**

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

Lottery discloses this limitation as discussed above (*see* claim 3).

(6) **Claim 6**

“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. Exs. 1009 at 2; 1011 ¶¶112; 1099 ¶¶108.

(7) **Claim 7**

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

Lottery discloses this limitation, either expressly 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; 1099 ¶¶110. Thus, a POSITA would have understood “MAB HER2” in *Lottery* is a humanized 4D5 anti-ErbB2 antibody. Exs. 1011 ¶¶59, 114; 1099 ¶¶55, 110.

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

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

As discussed above for claim 1, element [b], *Lottery* discloses this limitation, *i.e.*, the taxoid paclitaxel (or “taxol”). Exs. 1008 at 3; 1011 ¶¶58, 84–85; 1099 ¶113.

(9) Claim 9

“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 claimed invention reduced to practice by preparation of the study protocol before data was received demonstrating synergy of the combination confirms that they considered this limitation inherent. Ex. 1019 at 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. Exs. 1011 ¶¶118–20; 1099 ¶¶ 114-116.

(10) Claim 10

“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. Exs. 1011 ¶122; 1099 ¶118.

(11) Claim 11

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

This limitation is at least obvious for the same reasons described above for claim 1.

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

This limitation is at least obvious for the same reasons described above for claim 1, element [a].

c. Element [b]: “a taxoid”

This limitation is at least obvious for the same reasons described above for claim 1, element [b].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [c].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [d].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [e].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [f].

(12) Claim 12

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

As discussed above for claim 1, element [b], *Lottery* discloses this limitation, *i.e.*, the taxoid paclitaxel (or “taxol”).

(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”**

This limitation is at least obvious for the same reasons described above for claim 1.

- 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”**

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 Fc 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 G1 (IgG1).” Exs. 1011 ¶134; 1099 ¶130; 1005 at 10. A consensus human immunoglobulin G1 contains a human Fc region. Exs. 1011 ¶134; 1099 ¶130. 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. Exs. 1011 ¶135; 1099 ¶130.

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 Fc 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 G1 (IgG1).” Ex. 1005 at 10.

c. Element [b]: “and a taxoid”

This limitation is at least obvious for the same reasons described above for claim 1, element [b].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [c].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [d].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [e].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [f].

(14) Claim 14

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

This limitation is at least obvious for the same reasons described above for claim 1.

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

“[A]ntibody” is broader than “intact antibody”; the reasoning in claim 1, element [a], thus applies. Exs. 1011 ¶143; 1099 ¶139.

- c. Element [b]: “and a taxoid,”**

This limitation is at least obvious for the same reasons described above for claim 1, element [b].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [c].

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

This limitation is at least obvious for the same reasons described above for

claim 1, element [d].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [e].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [f].

B. 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”:

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

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

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

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

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

Exs. 1005 at 10, 13, Table 5; 1011 ¶152; 1099 ¶147. Metastatic breast carcinoma is a malignant cancer derived from epithelial cells that has spread to other areas, *i.e.*, progressed. Exs. 1011 ¶¶38, 151–52; 1099 ¶¶34, 147-148. Baselga '96 further teaches that “[t]he HER2 gene (also known as *neu* and as *c-erbB-2*) encodes a...glycoprotein receptor (p185^{HER2}).” Ex. 1005 at 9. A POSITA would have known that the ErbB2 receptor protein is also known as the HER2 receptor protein. Exs. 1011 ¶¶36, 151–52; 1099 ¶¶32, 147-148.

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, expressly 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 α antibody].”) (emphasis added). 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^{HER2}.” *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 G1 (IgG1).” Ex. 1005 at 10. The complementarity determining region determines what the antibody binds to, *i.e.*, the epitope. Exs. 1011 ¶¶40, 153; 1099 ¶36, 149. 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; 1099 ¶¶ 36, 149.

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* Exs. 1011 ¶¶154–55; 1099 ¶¶150-151. 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; 1099 ¶152.

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.”

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. Ex. 1016 at 11. For these patients in particular it was known that further anthracyclines should be avoided. Exs. 1011 ¶¶35; 1099 ¶¶31. As noted above, this was clearly well-known as PO’s own studies excluded patients previously treated with anthracyclines from the anthracycline treatment arm. Ex. 1019 at 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; 1099 ¶¶31, 39, 156-157.

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. Moreover, the inventor, Dr. Hellmann, did not teach avoiding anthracyclines—as her prosecution declaration makes clear, the anthracycline arm

of the clinical study already excluded patients with prior anthracycline treatment. Ex. 1019 at 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; Ex. 1099 ¶¶158-159.

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

Baselga ’96 discloses this limitation. It discloses clinical trials administering antibody plus 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 that the claimed combination treatment was *reduced to practice* by inclusion in a protocol *before any data was available*. Ex. 1019 at 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; Ex. 1099 ¶162. 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; 1099 ¶¶162-163. 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. Exs. 1011 ¶168; 1099 ¶164. 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 or no treatment.

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 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 at 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 at 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; 1099 ¶167. Thus, a POSITA would have had a reasonable expectation that the HER2 antibody/paclitaxel combination would not increase overall severe adverse events.

(2) Claim 2

“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. Exs. 1011 ¶176; 1099 ¶172.

(3) Claim 3

“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; 1099 ¶174.

(4) Claim 4

“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; 1099 ¶176.

(5) Claim 5

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

Baselga '96 discloses this limitation as discussed above (*see* claim 3).

(6) Claim 6

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

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

(7) Claim 7

“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; 1099 ¶¶36, 182.

(8) Claim 8

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

As discussed above for claim 1, element [b], 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; 1099 ¶¶60-63, 184.

(9) Claim 9

“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 expressly 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 at 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. A 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. Exs. 1011 ¶¶190–91; 1099 ¶¶186-187.

(10) Claim 10

“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. Exs. 1011 ¶¶193; 1099 ¶¶189.

(11) Claim 11

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

This limitation is at least obvious for the same reasons described above for claim 1.

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

This limitation is at least obvious for the same reasons described above for claim 1, element [a].

- c. Element [b]: “a taxoid,”**

This limitation is at least obvious for the same reasons described above for claim 1, element [b].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [c].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [d].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [e].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [f].

(12) **Claim 12**

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

As discussed above for claim 1, element [b], Baselga '96 discloses this limitation, *i.e.*, the taxoid paclitaxel (or “taxol”).

(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”

This limitation is at least obvious for the same reasons described above for claim 1.

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”

Baselga '96 discloses this limitation, either expressly 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 Fc 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 G1 (IgG1).” Ex. 1005 at 10. A consensus human immunoglobulin G1 contains a human Fc region. Exs. 1011 ¶205; 1099 ¶201. 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; 1099 ¶202.

c. Element [b]: “and a taxoid,”

This limitation is at least obvious for the same reasons described above for claim 1, element [b].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [c].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [d].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [e].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [f].

(14) **Claim 14**

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

This limitation is at least obvious for the same reasons described above for claim 1.

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

“[A]ntibody” is broader than “intact antibody” and thus the reasoning above for claim 1 applies. Exs. 1011 ¶143; 1099 ¶210.

- c. **Element [b]: “and a taxoid,”**

This limitation is at least obvious for the same reasons described above for claim 1, element [b].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [c].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [d].

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

This limitation is at least obvious for the same reasons described above for

claim 1, element [e].

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

This limitation is at least obvious for the same reasons described above for claim 1, element [f].

XII. 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. Exs. 1019 at 9:51 (Ex. C), 9:60 (Ex. D); 1011 ¶223; 1099 ¶219. *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. Exs. 1011 ¶224; 1099 ¶220.⁴ Indeed, as disclosed in Baselga ’96 and ’94, as well as *Lottery*, clinical trials of the combination were

⁴ 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).

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 at 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 at 9:94 (Ex. G); 1011 ¶225; 1099 ¶221. Since Baselga '94 reports the opposite and that clinical trials were ongoing, a POSITA would have found it obvious to try the combination in humans with reasonable expectation of success.

Dr. Sliwowski's second argument was that a POSITA would not have relied on preclinical models. Ex. 1019 at 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. Sliwowski 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. Sliwowski 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 that Baselga '94 demonstrated synergistic effects of the combination in a

mouse model and reported a clinical trial underway, and then Baselga '96 reported 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. Exs. 1011 ¶¶226–27; 1099 ¶¶222-223.

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." Exs. 1011 ¶228; 1099 ¶224.

XIII. CONCLUSION

For the foregoing reasons, Petitioner respectfully requests cancellation of claims 1-14 of the '441 patent.

Date: November 30, 2017

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §§ 42.24(a)(1)(i) and 42.24(d), I hereby certify that the number of words in this Petition is 12,459, excluding the Table of Contents, the Table of Authorities, the Mandatory Notices under § 42.8, Certificate of Service, Certificate of Word Count, signature block, and appendix listing of exhibits. In determining the number of words, Counsel relied upon Microsoft Word's word count feature.

Date: November 30, 2017

Signed,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6 and 42.105, I hereby certify that on this 30th day of November, 2017, the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 7,846,441 and accompanying exhibits referenced therein were served via PRIORITY MAIL EXPRESS for single-day overnight delivery on the Patent Owner at the following correspondence address of record in PAIR:

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The foregoing Petition and accompanying exhibits referenced therein were also served on this 30th day of November, 2017 via PRIORITY MAIL EXPRESS for single-day overnight delivery on the Patent Owner at an address known to the Petitioner as likely to affect service.

David L. Cavanaugh
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Date: November 30, 2017

Signed,

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