UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Celltrion, Inc.
Petitioner,
v.

Genentech, Inc.
Patent Owner

Patent No. 8,591,897
Issued: November 26, 2013

Inventor: John L. Bryant

Title: ANTI-ERBB2 ANTIBODY ADJUVANT THERAPY

Inter Partes Review No. IPR2017-00959

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 8,591,897

TABLE OF CONTENTS

Contents

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

EXHIBIT LIST

U.S. Patent 8,591,897

Exhibit	Description
Exh. 1001	U.S. Patent 8,591,897
Exh. 1002	File History of U.S. Patent 8,591,897
Exh. 1003	Declaration of Dr. Robert Leonard
Exh. 1004	Dr. Robert Leonard, curriculum vitae and Materials Considered
Exh. 1005	Van Pelt et al., Neoadjuvant Trastuzumab and Docetaxel in Patients with Breast Cancer: Preliminary Results, 4 CLIN. BREAST CANCER 348 (2003).
Exh. 1006	Sledge et al., Pilot Trial of Paclitaxel-herceptin Adjuvant Therapy for Early Stage Breast Cancer (E2198), 4 General Sessions 209 (2001).
Exh. 1007	Gradishar et al., Progress in Systemic Adjuvant Therapy of Early-stage Breast Cancer, 8 INT'L. J.CLIN. ONCOL. 239-247 (May 23, 2003).
Exh. 1008	Intentionally Omitted
Exh. 1009	Herceptin (Trastuzumab) Herceptin® Product Label (Sept. 1998), PHYSICIAN'S DESK REFERENCE 1115-117 (2000), at 3 (2000).
Exh. 1010	Slamon et al., Use of Chemotherapy Plus a Monoclonal Antibody Against HER2 for Metastatic Breast Cancer that Overexpresses HER2, 344 N. ENGL. J. MED. 11, 783-792 (Mar. 15, 2001).
Exh. 1011	Piccart-Gebhart et al., Herceptin: The Future in Adjuvant Breast Cancer Therapy, 12 Anti-Cancer Drugs Suppl. 4, S27-S33 (2001).
Exh. 1012	Romond et al., Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer, 353 N. ENGL. J. MED. 1673 (Oct. 20, 2005).
Exh. 1013	J. Horton, Trastuzumab Use in Breast Cancer: Clinical Issues, 9 CANCER CONTROL 499-507 (2002).
Exh. 1014	Citron et al., Randomized Trial of Dose-Dense Versus Conventionally Scheduled and Sequential Versus Concurrent Combination Chemotherapy as Postoperative Adjuvant Treatment of Node-Positive Primary Breast Cancer: First Report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741, 21 J. CLIN. ONCOL. 1431-1439 (Apr. 15, 2003).
Exh. 1015	Perez et al., Effect of Doxorubicin Plus Cyclophosphamide on Left Ventricular Ejection Fraction in Patients with Breast Cancer in the North Center Cancer Treatment Group N9831 Intergroup Adjuvant Trial, 22 J. CLIN. ONCOL. 3700 (Sept. 15, 2004).

Exh. 1016	Early-stage breast cancer, NCI Dictionary of Cancer Terms, (Feb. 15, 2017) https://www.cancer.gov/publications/dictionaries/cancer-terms?CdrID=446564.
Exh. 1017	Devita et al., PRINCIPLES AND PRACTICE OF ONCOLOGY, 289-304 (Principles of Cancer Management: Chemotherapy), 307-333 (Principles of Cancer Management: Biologic Therapy), 1633-1726 (Cancer of the Breast) (Lippincott, Williams & Wilkins 6th ed. 2001).
Exh. 1018	Thomas et al., New Paradigms in Adjuvant Systemic Therapy of Breast Cancer, 10 Endocrine-Related Cancer 75-89 (2003).
Exh. 1019	Perez et al., Sequential Versus Concurrent Trastuzumab in Adjuvant Chemotherapy for Breast Cancer, 29 J. CLIN. ONCOL. 4491 (2011).
Exh. 1020	Herceptin (Trastuzumab) Herceptin® Product Label (Revised Dec. 2001), Physician's Desk Reference 1399-1402 (2003).
Exh. 1021	J. Baselga, Herceptin Alone or in Combination with Chemotherapy in the Treatment of HER2-Positive Metastatic Breast Cancer: Pivotal Trials, 61 ONCOLOGY, 14-21 (2001).
Exh. 1022	Pegram et al., Inhibitory Effects of Combinations of HER-2/neu Antibody and Chemotherapeutic Agents used for Treatment of Human Breast Cancers, 18 ONCOGENE 2241-2251 (1999).
Exh. 1023	Buzzoni et al., Adjuvant Chemotherapy with Doxorubicin Plus Cyclophosphamide, Methotrexate, and Fluorouracil in the Treatment of Resectable Breast Cancer with More than Three Positive Axillary Nodes, 9 J. CLIN. ONCOL. 2134-2140 (1991).
Exh. 1024	Harries et al., The Development and Clinical Use of Trastuzumab (Herceptin), 9 Endocrine-Related Cancer 75-85 (2002).
Exh. 1025	Tan-Chiu et al., Moving Forward: Herceptin in the Adjuvant Setting,63 ONCOLOGY 57-63 (2002).
Exh. 1026	Affidavit of Christopher Butler.
Exh. 1027	S. Giordano, Update on Locally Advanced Breast Cancer, 8 ONCOLOGIST 521-530 (2003).
Exh. 1028	Herceptin (Trastuzumab) Product Label (2016).
Exh. 1029	Lasorsa et al., Probing the Interaction Between Cisplatin and the Therapeutic Monoclonal Antibody Trastuzumab, 6 RSC ADVANCE 29229-29232 (2016).
Exh. 1030	U.S. Provisional Application No. 60/681125
Exh. 1031	Clark, Do we really need prognostic factors for breast cancer, 30 BREAST CANCER RESEARCH AND TREATMENT 117 (1994)
Exh. 1032	Piccart-Gebhart et al., Trastuzumab After Adjuvant Chemotherapy in

	HER2-Positive Breast Cancer, 353 N. ENGL. J. MED. 1659 (Oct. 20, 2005).

I. INTRODUCTION

Celltrion, Inc. petitions for *inter partes* review ("IPR") under 35 U.S.C. §§ 311–319 and 37 C.F.R. § 42 et seq. of claims 1-13 of U.S. Patent No. 8,591,897 ("the '897 patent," Ex. 1001).

II. PRELIMINARY STATEMENT

The '897 patent is directed to methods for treating patients with non-metastatic HER2-positive breast cancer by administering anthracycline/ cyclophosphamide (AC) based chemotherapy, followed by sequential administration of a taxoid and trastuzumab. The purportedly novel aspect of the claims is the sequential administration of a taxoid and trastuzumab, as opposed to their concurrent administration. But sequential administration of these agents was not new. Use of these agents to treat non-metastatic HER2 positive breast cancer—in the exact claimed sequence—was disclosed in prior art printed publications, including Piccart-Gebhart (Ex. 1011) and Perez (Ex. 1015), at least as early as 2001, four years before Patent Owner ("PO") filed its patent application.

Each claim of the '897 patent is anticipated. During prosecution, PO incorrectly argued that the prior art did not teach sequential administration. The '897 patent issued because PO failed to direct the Examiner's attention to pertinent descriptions of a clinical trial, the N9831 trial, that disclose the exact claimed treatment regimen.

The claimed methods are also obvious in view of the prior art. In 1998, FDA approved Herceptin® (trastuzumab) for treatment of metastatic breast cancer. Trastuzumab was known to be highly effective in treating metastatic HER2-positive breast cancer, especially when used with AC-based chemotherapy. Development of anticancer drugs begins in the metastatic setting because the risks associated with unproven drugs are of less concern for patients with advanced disease and poor prognosis. Once a drug is shown to be safe and effective in treating metastatic disease, cancer researchers focus on use of the drug as adjuvant therapy, because earlier intervention in the disease can provide greater benefit to patients.

Given the efficacy of trastuzumab in treatment of metastatic cancer, a person of ordinary skill in the art ("POSA") would have been motivated to use trastuzumab for adjuvant therapy with known chemotherapy regimens. AC-based chemotherapy followed by taxoids was a widely used regimen before 2004, and it would have been obvious to add trastuzumab sequentially to that established therapy. Indeed, the prior art descriptions of the N9831 trial expressly disclose sequential treatment with trastuzumab. Based on the known effectiveness of trastuzumab in combination with other therapies for treating HER2-positive breast cancer, a POSA would have had a reasonable expectation of success in using the claimed methods of treatment.

III. MANDATORY NOTICES

A. Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1))

The real parties-in-interest are Celltrion, Inc., Celltrion Healthcare Co. Ltd., and Teva Pharmaceuticals International GmbH.

B. RELATED MATTERS (37 C.F.R. § 42.8(B)(2))

Petitioner is not aware of any other pending judicial or administrative matters concerning the '897 patent.

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

Lead counsel is Cynthia Lambert Hardman, Reg. No. 53,179. Backup counsel are Elaine Herrmann Blais and Robert V. Cerwinski (both to seek *pro hac vice* admission). Counsel are with Goodwin Procter LLP. Ms. Hardman and Mr. Cerwinski are at 620 Eighth Avenue, New York, NY 10018, tel. 212-813-8800, fax 212-355-3333. Ms. Blais is at 100 Northern Avenue, Boston, MA 02210, tel. 617-570-1000, fax 617-523-1231. Email contact is chardman@goodwinlaw.com, eblais@goodwinlaw.com, and rcerwinski@goodwinlaw.com.

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

Please direct all correspondence to counsel at the contact information above. Petitioner consents to service by electronic mail at the above email addresses.

IV. CERTIFICATION OF GROUNDS FOR STANDING

Pursuant to 37 C.F.R. § 42.104(a), Petitioner certifies that the '897 patent is available for IPR and that Petitioner is not barred or estopped from requesting an IPR challenging the patent claims on the grounds identified in this petition.

V. FEES

The Commissioner is hereby authorized to charge all fees due in connection with this matter to Attorney Deposit Account 506989.

VI. SUMMARY OF THE '897 PATENT AND PROSECUTION HISTORY

The '897 patent issued on November 26, 2013 from Application No. 11/400,638 ("the '638 application"), filed on April 6, 2006. The '638 application claims priority to a provisional application filed on May 13, 2005. For purposes of this IPR only, Petitioner will assume that the '897 patent claims are entitled to the earliest possible claimed priority date, *i.e.*, May 13, 2005. Therefore, any publication dated prior to May 13, 2005 qualifies as prior art under 35 U.S.C. § 102(a) and any publication dated prior to May 13, 2004 qualifies as prior art under § 102(b).

A. '897 Patent Claims

The '897 patent has 13 claims, of which claim 1 (below) is the only independent claim:

> A method of adjuvant therapy comprising administering to a human subject with nonmetastatic HER2 positive breast cancer, following

definitive surgery, anthracycline/cyclophosphamide (AC) based chemotherapy, followed by sequential administration of a taxoid and trastuzumab or an antibody that blocks binding of trastuzumab to HER2.

Claim 2 depends from claim 1, and adds that the taxoid is paclitaxel or docetaxel. Claim 3 depends from claim 2, and adds that trastuzumab is administered. Claim 4 depends from claim 3, and adds that trastuzumab is administered at an initial dose of 4 mg/kg, followed by subsequent weekly doses of 2 mg/kg.

Claim 5 depends from claim 1, and adds that the subject has a high risk of cancer recurrence. Claim 6 depends from claim 5, and adds that the subject is less than about 50 years old. Claim 7 depends from claim 5, and adds that the subject had a tumor greater than 2 centimeters in diameter. Claim 8 depends from claim 7, and adds that the cancer is lymph node-positive.

Claims 9 and 10 depend from claim 8, and respectively add that the subject had 4-9 or 10 or more involved lymph nodes.

Claim 11 depends from claim 5, and adds that the cancer was estrogen receptor (ER) negative. Claim 12 depends from claim 5, and adds that the cancer was progesterone receptor (PR) negative.

Claim 13 depends from claim 1, and adds that the antibody is an intact, naked antibody.

B. '897 Patent Specification

The specification states that the alleged invention concerns "adjuvant therapy of nonmetastatic breast cancer using Herceptin®" and "the results obtained in clinical studies of the subjects with nonmetastatic, high risk, breast cancer." (Ex. 1001 at 1:15-16, 6:66-7:1.) "Adjuvant therapy" is "therapy given after definitive surgery," whereas neoadjuvant therapy is treatment given "prior to definitive surgery." (Ex. 1001 at 10:10-19.)

Example 1—the only example in the specification—describes a joint interim analysis of results obtained in two clinical trials evaluating the use of Herceptin® in adjuvant therapy for high risk operable breast cancer: the National Surgical Adjuvant Breast and Bowel Project (NSABP B-31) trial and the North Central Cancer Treatment Group (NCCTG) Intergroup N9831 trial. (*Id.* at 62:36-63:8.) Study N9831 "enrolled its first patient in June 2000 and has enrolled 3,406 patients to date." (*Id.* at 62:40-43.) "These trials evaluated the efficacy of trastuzumab (Herceptin®) as adjuvant therapy for high risk operable breast cancer." (*Id.* at 62:45-47.)

The specification further states that "[t]he design of the NSABP B-31 and NCCTG N9831 studies is depicted in FIG. 4A." (*Id.* at 62:49-50.) Figure 4A (reproduced below) discloses that patients enrolled in Arm B of the N9831 trial

were treated with doxorubicin/cyclophosphamide (AC), followed by paclitaxel (T), followed by trastuzumab (H):[1]

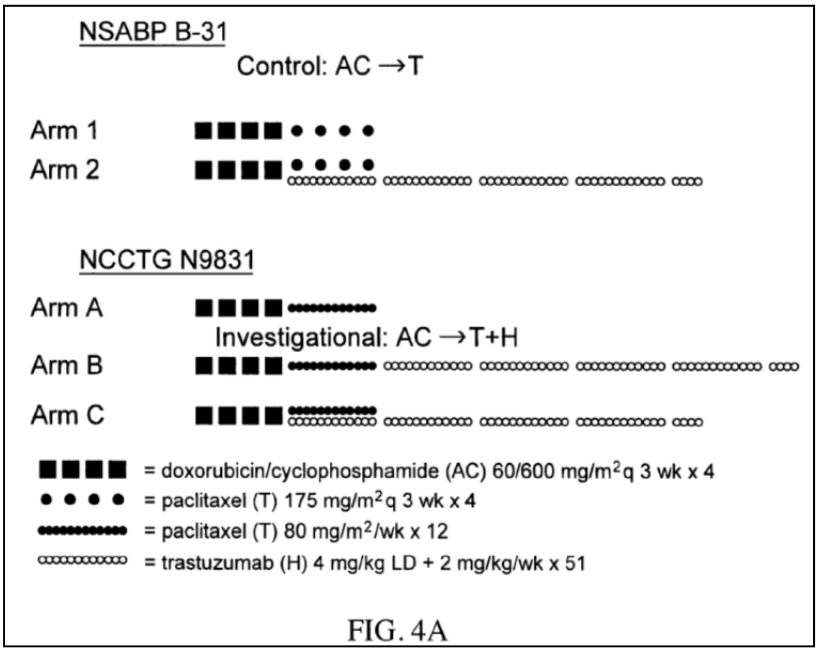

FIG. 4A

The specification provides further details on each treatment arm in the N9831 trial. Specifically, Arm B involved treating patients with AC-based chemotherapy, followed by sequential administration of paclitaxel and trastuzumab:

> Arm B: anthracycline (60 mg/m^2) plus cyclophosphamide (600 mg/m^2), every 3 weeks, for four cycles (q3 wk×4), followed by paclitaxel (80 mg/m^2/wk) for 12 weeks, followed by trastuzumab (4

[1] Doxorubicin is an anthracycline. *See, e.g.*, Ex. 1001 at 9:1-3. An anthracycline (A) plus cyclophosphamide (C) is abbreviated in the '897 patent as AC. *See, e.g.*, *id.* at 6:18-19. Paclitaxel is a taxoid (T). *See, e.g.*, *id.* at 26:37-41.

mg/kg/wk loading dose (LD) for 4 weeks and 2 mg/kg/wk maintenance dose for 51 weeks).

(*Id.* at 62:65-63:2.) That is, in Arm B, AC-based chemotherapy was administered first, followed by paclitaxel, and then trastuzumab, as shown in Figure 4A and described above. (Ex. 1003, Leonard Decl. at ¶ 40.) The N9831 trial, and the treatment regimens used in that study, was widely disclosed in the prior art.

Although Example 1 reports the joint interim results of the NCCT 9831 and NSABP-31 trials, no results were reported from patients in Arm B of the NCCT 9831 trial. (*See id*. col. 9, ll. 39-42 ("Efficacy data in Example 1 herein included all subjects from NSABP B-31 but excludes the patients from Intergroup who did not start HERCEPTIN® simultaneously with TAXOL® (arm 2)."); col. 63, ll. 8-9; Fig. 4B; Ex. 1003, Leonard Decl. at ¶ 42.)

C. Prosecution History

The original application that led to the '897 patent contained 44 claims covering various methods relating to adjuvant breast cancer therapy, including "promotional methods" and "business methods." (Ex. 1002, File History at 104-08.)

In response to a restriction requirement, PO elected claims directed to methods for treating non-metastatic HER2-positive breast cancer. (*Id.* at 194-196.) In the ensuing three years, the Examiner issued five rounds of rejections, including rejecting the original claims and 19 additional claims as obvious or anticipated

over references that disclosed the administration of trastuzumab to breast cancer patients, *e.g.*:

- Van Pelt 2003 (Ex. 1005), which the Examiner stated "teaches a method of treating women with locally advanced breast cancer or primary breast cancer with or without concomitant gross metstatic [sic] disease . . . with preoperative trastuzumab and docetaxel, followed by definitive surgery, then 4 cycles of doxorubicin/cyclophosphamide chemotherapy, after which weekly trastuzumab was resumed for 1 year." (Ex. 1002, at 211);

- Sledge 2001 (Ex. 1006), which the Examiner stated taught a "method of treating an adjuvant population (by definition post-surgery) of stage II breast cancer with… paclitaxel . . . in combination with trasutuxumab[sic] (H)… followed by either anthracycline for 4 weeks, or the same regimen followed by 52 weeks of trastuzumab." (Ex. 1002, at 283.); and

- Gradishar 2003 (Ex. 1007), which the Examiner stated teaches that the "in patients with early-stage breast cancer, the use of adjuvant therapies improves disease-free and overall survival" and "discusses ongoing trials where trastuzumab is combined with chemotherapy as an adjuvant treatment." (Ex. 1002 at 285.)

None of the original claims in the '635 application were directed to the "sequential administration of a taxoid and trastuzumab," let alone the sequential administration of a taxoid and trastuzumab "following AC-based chemotherapy in

an adjuvant setting." (Ex. 1002, File History at 104-06 (claims).) On December 23, 2011, PO added claims 64-67, stating that they were supported "at least in Example 1 and Figures 4A and 4B." (Ex. 1002 at 407 (Dec. 23, 2011 Amendment).) Example 1 and these figures all refer to the N9831 clinical trial, and contain the same information that was available in the prior art. These new claims, and additional dependent claims, issued as the thirteen claims of the '897 patent.

PO argued that its new claims to "sequential administration" were distinguished from the prior art because Van Pelt, Sledge, and Gradishar did not disclose sequential administration of a taxoid and trastuzumab. (*Id.* at 408 ("Van Pelt does not disclose adjuvant administration of a taxoid followed by the administration of trastuzumab."); *id.* at 409 ("Sledge et al. does not teach adjuvant sequential administration of a taxoid and trastuzumab after (following) AC-based chemotherapy either. Indeed, Sledge describes concurrent administration of paclitaxel plus trastuzumab prior to AC treatment.").)

Likewise, with respect to Gradishar, PO argued:

> Gradishar et al. does not disclose treatment of human subjects with nonmetastatic HER2 positive breast cancer following definitive surgery, with anthracycline/cyclophosphamide (AC) based chemotherapy, followed by sequential administration of a taxoid and trastuzumab . . . . Although Gradishar et al. refers to ongoing NSABP

B-31 and BCIRG clinical trials assessing the efficacy of trastuzumab in the adjuvant setting, in both of these trials trastuzumab and paclitaxel were administered concurrently, after completion of anthracycline-based chemotherapy. **Gradishar has no teaching or disclosure of sequential administration of a taxoid and trastuzuamab [sic] following AC-based chemotherapy in an adjuvant setting**.

(*Id.* (emphasis added).)

Notably, PO addressed the NSABP B-31 and BCIRG trials, but did not mention Gradishar's description of the more pertinent N9831 trial. Table 5 of Gradishar describes the N9831 trial for use of adjuvant trastuzumab in treating early-stage breast cancer, including one treatment arm where patients were administered AC-based chemotherapy (AC), followed by paclitaxel (Pqw), followed by trastuzumab (Hqw):

Table 5. Trials addressing the use of adjuvant trastuzumab in early-stage breast cancer

Trial source	Targeted accrual	Eligibility	Randomization
NSABP B-31	2700	Node positive, HER 2/*neu*-positive	AC × 4, P × 4 AC × 4, P × 4 + Hqw × 52
Intergroup (N9831)	3150	Node-positive, HER 2/*neu*-positive	AC × 4, Pqw × 12 AC × 4, Pqw × 12, Hqw × 52 AC × 4, Pqw × 12 + Hqw × 52
BCIRG 006	3150	Node-positive, high-risk node-negative, HER 2/*neu*-positive	AC × 4, T × 4 AC × 4, T × 4 + H × 1 year[a] Plat × 6 + H × 1 year[a]

AC, doxorubicin 60 mg/m^2; cyclophosphamide 600 mg/m^2 IV every 3 weeks
P, paclitaxel 225 mg/m^2
Hqw, trastuzumab 4 mg/kg loading, then 2 mg/kg per week IV
Pqw, paclitaxel 80 mg/m^2 IV every week
T, docetaxel 100 mg/m^2 IV every 3 weeks
Plat, cisplatin 75 mg/m^2 or carboplatin AUC 6
H, Herceptin
[a]Trastuzumab given weekly during chemotherapy, then every 3 weeks for 1 year at 6 mg/kg

(Ex. 1007 at 8; Ex. 1003, Leonard Decl., ¶ 50.) That is, the second treatment arm identified in Table 5 of Gradishar refers to sequential administration of a taxoid and trastuzumab after AC-based therapy: "AC x 4" (doxorubicin and cyclophosphamide), followed by "Pqw x 12" (paclitaxel), followed by "Hqw x 12" (trastuzumab).

The N9831 trial referenced in Gradishar is the same trial that PO relied on as § 112 support for its claims to "sequential administration of a taxoid and trastuzumab." (Ex. 1002 at 407.) In short, the '897 patent issued because PO failed to direct the Examiner to the pertinent prior art descriptions of the N9831 trial in Gradishar and elsewhere.

VII. BACKGROUND ON TRASTUZUMAB AND BREAST CANCER TREATMENT

A. Treatment of Metastatic Breast Cancer With Trastuzumab Plus Chemotherapy

In metastatic breast cancer, the disease has spread beyond the breast and lymph nodes. (Ex. 1003, Leonard Decl. at ¶ 52.) In contrast, in nonmetastatic breast cancer, the cancer has not spread beyond the lymph nodes. (*Id.* at ¶ 54.) Development of anticancer drugs typically begins in the metastatic setting to minimize the consequences of any unexpected toxicity. In the metastatic setting, patients with advanced disease whose prognosis is poor typically have limited

treatments, so for these patients the potential benefits of experimental therapies are more likely to outweigh the potential risks. (*Id.* at ¶ 56.)

Development of trastuzumab first began in the metastatic setting. In 1998, Herceptin® (trastuzumab) was approved as a first-line treatment for HER2-positive metastatic breast cancer in combination with paclitaxel (a taxoid). (Ex. 1009, Herceptin 1998 Label) Trastuzumab is "a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay… to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2." (Ex. 1009, Herceptin 1998 Label at 1.) HER2 protein overexpression is observed in 25%-30% of primary breast cancers. (*Id.*) By 1998, trastuzumab was known to have an antiproliferative effect, and patients with tumors that overexpress the HER2 protein were known to gain the most clinical benefit from treatment with trastuzumab. (*Id.*)

By 2005, Herceptin® had been used in combination with various chemotherapeutic agents, including taxoids and anthracyclines. (*See, e.g.*, Ex. 1010, Slamon at 1; Ex. 1005, Van Pelt at 1[2]; Ex. 1003, Leonard Decl. at ¶ 53.) For example, Slamon et al., *Use of Chemotherapy Plus a Monoclonal Antibody Against*

[2] Several prior art references discuss the use of "taxanes." (*See, e.g.*, Ex. 1005, Van Pelt at 2; Ex. 1011, Piccart-Gebhart at 2). "Taxane" and "taxoid" are synonyms. (Ex. 1003, Leonard Decl. at ¶ 199 n.7).

HER2 for Metastatic Breast Cancer That Overexpresses HER2, 344 N. Engl. J. Med. 783 (2001) ("Slamon"), reports the results of a phase 3 study of trastuzumab in combination with paclitaxel or anthracycline and cyclophosphamide to treat HER2-positive metastatic breast cancer. (Ex. 1010 at 1.) Both trastuzumab/chemotherapy combinations showed significant improvements in response rates, time to disease progression, and overall survival compared with chemotherapy alone. (*Id.* at 3-4.) Slamon observed that "trastuzumab-based combination therapy… reduced the relative risk of death by 20 percent at a median follow-up of 30 months" and that "[f]ew studies of metastatic breast cancer have demonstrated a survival advantage of this magnitude in association with the addition of a single agent." (*Id.* at 8.) Slamon concluded that "trastuzumab, when added to conventional chemotherapy, can benefit patients with metastatic breast cancer that overexpresses HER2." (*Id.* at 9.) Slamon therefore teaches that trastuzumab improves outcomes when used in combination treatments, particularly with paclitaxel or AC. (*Id.*)

B. Treatment of Non-Metastatic Breast Cancer and the N9831 Clinical Study

The efficacy of trastuzumab for metastatic cancer, coupled with the need for more effective therapies to treat early-stage breast cancer in patients with HER2-positive breast cancer, who were known to be at high risk of recurrence after surgery, led to the natural evaluation of trastuzumab as both a "neo-adjuvant" (pre-

surgery) and adjuvant (post-surgery) therapy. (Ex.1003, Leonard Decl. at ¶ 54; Ex. 1005, Van Pelt at 1-2 (discussing rationale for trastuzumab in neo-adjuvant therapy); Ex. 1007, Gradishar at 7 ("[t]he rationale for the trials is based on preclinical synergy between chemotherapy and trastuzumab and the clinical findings from the pivotal combination trial in metastatic breast cancer").) As explained in Martine J. Piccart-Gebhart et al., *Herceptin: the future in adjuvant breast cancer therapy*, 12 Anti-Cancer Drugs S27 (2001) ("Piccart-Gebhart," Ex. 1011), "new drugs for the treatment of breast cancer are generally introduced into the clinical practice in the metastatic setting. However, it is well known that therapeutic response improves when drugs are used earlier in the disease. Therefore, once drugs have shown a major therapeutic impact in the metastatic setting, investigation in the adjuvant setting should be prioritized." (Ex. 1011 at 1.)

The N9831 clinical study, which began recruiting in 2000, was a prospective, randomized, three-arm, phase III trial for women with HER2-positive breast cancer. (*See, e.g.*, *id.* at 3.) Arm B involved administration of AC-based chemotherapy, followed by a taxoid, then Herceptin®. (*Id.*)

Because of the strong performance of trastuzumab in the N9831 study and the parallel NSABP B-31 study, the study coordinators conducted a combined analysis of the early data from Arms A and C of the N9831 study (the placebo and concurrent administration arms) together with the early data from the NSABP B-31

study, and released the interim results in October, 2005. (Romond et al., *Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer*, 353 N. Engl. J. Med. 1673 (2005), Ex. 1012.) In 2011, NCCTG released results comparing the sequential and concurrent administration of trastuzumab and paclitaxel following AC chemotherapy in adjuvant breast cancer therapy. (Perez et al., *Sequential Versus Concurrent Trastuzumab in Adjuvant Chemotherapy for Breast Cancer*, 29 J. Clin. Oncol. 4491 (2011), Ex. 1019.) The study found that concurrent administration resulted in longer average disease free survival than sequential administration, and accordingly recommended concurrent instead of sequential administration of paclitaxel and trastuzumab for adjuvant therapy. (*Id*. at 7.)

As described above, during prosecution PO pointed to the description of the N9831 adjuvant trial in the '897 patent specification as support for its newly added claims. But that same description was widely publicized in the prior art, such as in Piccart-Gebhart (Ex. 1011) and Perez (Ex. 1015).

VIII. CLAIM CONSTRUCTION

The challenged claims should be given their broadest reasonable interpretation ("BRI") in light of the patent specification. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs. LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016).

A. The Preamble Is Not Limiting

The preamble of each claim, "a method of adjuvant therapy," is not limiting because it merely states the purpose or intended use of the claimed steps.[3] A preamble may limit the invention if it is "necessary to give life, meaning, and vitality" to the claim. *Catalina Marketing Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002). However, "[a] preamble generally is not limiting when the claim body describes a structurally complete invention such that deletion of the preamble phrase does not affect the structure or steps of the claimed invention." *Id.* at 809.

Each claim recites administering "anthracycline/cyclophosphamide (AC) based chemotherapy, followed by sequential administration of a taxoid and trastuzumab or an antibody that blocks binding of trastuzumab to HER2." The body of each claim provides a complete description of a method, and the preamble phrase does not affect the steps. (Ex. 1003, Leonard Decl. at ¶ 63.)[4] Accordingly,

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[3] Even if the preamble were limiting, the prior art still discloses this additional limitation. (*See, e.g.*, Ex. 1003, Leonard Decl. at ¶ 129-30, 155.)

[4] The preamble is also not limiting because Patent Owner did not rely on it during prosecution to distinguish the claimed invention from the prior art. *See Catalina Marketing Int'l, Inc.*, 289 F.3d at 808 ("[C]lear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the

the BRI of the challenged claims is that the preamble is not limiting. *See, e.g.*, *Ex Parte Kristensson*, 2016 WL 4151097, at *3 (PTAB July 28, 2016) (holding that preamble reciting a "method of treating atopic eczema" was not limiting where the "causing and placing steps of claim 10 stand on their own").

B. "Sequential Administration" of a Taxoid and Trastuzumab Means Administration in Sequence and Not Overlapping in Time

The BRI of "sequential administration" of a taxoid and trastuzumab in light of its use in the specification, and the plain meaning of the term as understood by a POSA, is administration of a taxoid and trastuzumab in sequence, meaning one after the other, where the administrations of the two drugs do not overlap in time. (Ex. 1003, Leonard Decl. at ¶ 65.)

The only use of the term "sequential" in the specification is in describing the treatment regimens in the CALGB 9741 clinical trial: "CALGB 9741 was a dose dense trial comparing ACx4 to Tx4; **sequential** Ax4 to Tx4 to Cx4; dose dense **sequential** Ax4 to Tx4 to Cx4; and dose dense ACx4 to Tx4 (A=anthracycline; C=cyclophosphamide; T=paclitaxel)." (Ex. 1001 at 6:27-31 (emphasis added).) The two "sequential" regimens involved administration of A alone, followed by T alone, followed by C alone. (*Id.*; Ex. 1003, Leonard Decl. at ¶ 66-67.) The other

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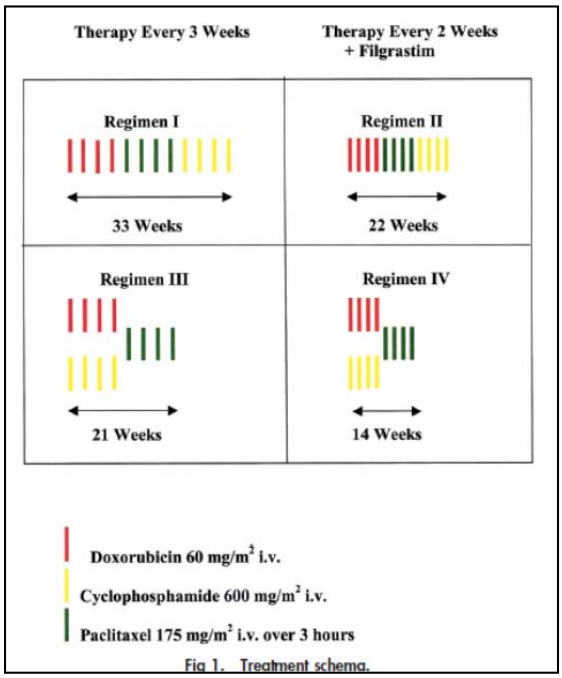
preamble into a claim limitation because such reliance indicates use of the preamble to define, in part, the claimed invention.").

two regimens involved administration of anthracycline (A) and cyclophosphamide (C) together (i.e., "AC"), and are not described as "sequential."

The specification defines "concurrently" as "administration of two or more therapeutic agents, where at least part of the administration overlaps in time." (Ex. 1001 at 11:23-25.) That is, in the CALGB 9741 trial, the concurrent regimens had treatment with AC, which is A (anthracycline) concurrent with C (cyclophosphamide). (Ex. 1003, Leonard Decl. at ¶ 67.) In contrast, "sequential administration" of a taxoid and trastuzumab refers to administration of a taxoid and trastuzumab in sequence and not concurrently. (*Id.* at ¶ 65, 67.)

This construction is consistent with use of the term "sequential administration" by a POSA in 2005. (Id. at ¶ 68.) For example, Citron et al., *Randomized Trial of Dose-Dense Versus Conventionally Scheduled and Sequential Versus Concurrent Combination Chemotherapy as Postoperative Adjuvant Treatment of Node-Positive Primary Breast Cancer: First Report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741*, Journal of Clinical Oncology (2003) ("Citron," Ex. 1014), details the treatment arms in the CALGB 9741 trial: "The study used a 2x2 factorial experimental design to assess the two factors of dose density (2 weeks v 3 weeks) and treatment sequence (concurrent v sequential) and the possible interaction between them." (Ex. 1014 at 2.) Citron further states that "sequential therapy refers to the ***application of treatments one at***

a time rather than concurrently." (*Id.*) (emphasis added). Like PO's description of the CALGB 9741 trial, Citron Figure 1 discloses that two of the treatment regimens used sequential administration (Regimens I and II) and two used concurrent administration (Regimens III and IV):



(*Id.*; Ex. 1003, Leonard Decl. at ¶ 69.)

The prosecution history further supports this construction. *Tempo Lighting, Inc. v. Tivoli, LLC*, 742 F.3d 973, 977 (Fed. Cir. 2014) (holding that the prosecution history "serves as intrinsic evidence for purposes of claim construction. This remains true in construing patent claims before the PTO."). During prosecution, PO made clear that the term "sequential" excludes "concurrent" administration. (Ex. 1003, Leonard Decl. at ¶ 72; Ex. 1002, File History at 409 (December 23, 2011 Amendment).)

Accordingly, the BRI of "sequential administration" is administration of a taxoid and trastuzumab in sequence and not at the same time.[5]

C. Defined Terms

The '897 patent specification defines several claim terms. For purposes of this IPR only, Petitioner adopts the following constructions as the BRI of each respective term:

"Adjuvant therapy" is defined as "therapy given after definitive surgery, where no evidence of residual disease can be detected, so as to reduce the risk of disease recurrence." (Ex. 1001 at 10:11-13.)

"Nonmetastatic breast cancer" is defined as "cancer which is confined to the breast and/or regional lymph nodes." (*Id.* at 10:30-31.)

"HER2 positive" breast cancer is defined as breast cancer "which expresses HER2 at a level which exceeds the level found on normal breast cells or tissue." (*Id.* at 13:64-66.)

"Definitive surgery" is defined as "complete removal of tumor and surrounding tissue as well as any involved lymph nodes." (*Id.* at 10:20-24.) The

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5 Even if the term does not exclude concurrent administration, the prior art discloses "sequential administration of a taxoid and trastuzumab." (*See, e.g.*, Ex. 1003, Leonard Decl. at ¶ 74, 138; Ex. 1011, Piccart-Gebhart at 3; Ex. 1015, Perez at 2.)

specification provides examples of "definitive surgery," including "lumpectomy, mastectomy, such as total mastectomy plus axillary dissection, double mastectomy etc." (*Id.*)

"Taxoid" is defined as "a chemotherapeutic agent that functions to inhibit microtubule depolymerization. Examples include paclitaxel… and docetaxel." (*Id.* at 26:37-40.)

An antibody that "blocks binding of trastuzumab… to HER2" is defined as an antibody that "can be demonstrated to block trastuzumab's binding to HER2, or compete with trastuzumab for binding to HER2." (*Id.* at 13:35-38.)

"Node-positive breast cancer" is defined as "breast cancer that has spread to the regional lymph nodes." (*Id.* at 11:57-63.) The BRI of "wherein the cancer is lymph-node positive" is "wherein the cancer has spread to the regional lymph nodes."

"High risk of cancer recurrence" is defined as "a greater chance of experiencing recurrence of cancer." (*Id.* at 12:1-2.) The specification provides examples of patients with a "high risk of cancer recurrence," including "relatively young subjects (e.g., less than about 50 years old), those with positive lymph nodes, particularly 4 or more involved lymph nodes (including 4-9 involved lymph nodes, and 10 or more involved lymph nodes), those with tumors greater than 2 cm in diameter, those with HER2-positive breast cancer, and those with hormone

receptor negative breast cancer (i.e., estrogen receptor (ER) negative and progesterone receptor (PR) negative)." (*Id.* at 12:2-10.) Based on the specification, a POSA would understand that the presence of one or more patient or disease characteristics, such as those listed above, was correlated with a higher risk of recurrence in patients. (Ex. 1003, Leonard Decl. at ¶¶ 84, 171.)

"Estrogen receptor (ER) positive cancer" is defined as "cancer which tests positive for expression of ER," and "ER negative" is defined as cancer that "tests negative for such expression." (Ex. 1001 at 12:16-18.) Accordingly, the BRI of "wherein the subject's cancer was estrogen receptor (ER) negative" is "wherein the subject's cancer tests negative for expression of estrogen receptor." (Ex. 1003, Leonard Decl. at ¶ 85.)

"Progesterone receptor (PR) positive cancer" is defined as "cancer which tests positive for expression of PR," and "PR negative" is defined as "cancer tests negative for such expression." (Ex. 1001 at 12:26-28.) The specification uses the abbreviations "PG" and "PR" interchangeably to refer to progesterone receptor. (*See id.* at 12:26-28; *id.* at 9:11-12; *id.* at 59:15.) Accordingly, the BRI of "wherein the subject's cancer was progesterone receptor (PG) negative" is "wherein the subject's cancer tests negative for expression of progesterone receptor." (Ex. 1003, Leonard Decl. at ¶ 86.)

"Naked antibody" is defined as "an antibody that is not conjugated to a cytotoxic moiety or radiolabel." (Ex. 1001 at 21:51-52.)

An "intact antibody" is defined as "one which comprises two antigen binding regions, and an Fc region" (Ex. 1001 at col. 18, ll. 4-6.)

Petitioner's positions on claim construction should not be construed as an assertion regarding the appropriate claim scope in other adjudicative forums, where a different claim interpretation standard may apply.

IX. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED

In Ground 1, Petitioner requests IPR and cancellation of claims 1-5 and 8-13 as anticipated by Piccart-Gebhart.

In Ground 2, Petitioner requests IPR and cancellation of claims 1 and 5-7 as anticipated by Perez.

In Ground 3, Petitioner requests IPR and cancellation of claims 1-13 as obvious in view of Piccart-Gebhart and Thomas. Ground 3 is not redundant because it relates to obviousness, not anticipation, and relies on an additional reference, Thomas, which contains information not found in Piccart-Gebhart or Perez. +

This petition is supported by the Declaration of Robert Leonard, M.D. (Ex. 1003.) Dr. Leonard has been a practicing clinician for over 40 years, with

expertise in the treatment of breast cancer and an academic appointment since 1981 in the field of clinical oncology.

The petition establishes at least a reasonable likelihood that Petitioner will prevail with respect to at least one challenged claim. 35 U.S.C. § 314(a).

A. Ground 1: Piccart-Gebhart Anticipates Claims 1-5 and 8-13

1. Claim 1

Piccart-Gebhart, a review article published in 2001, summarizes the designs and objectives of four clinical trials studying Herceptin® as adjuvant therapy for breast cancer. (Ex. 1011.) In particular, it discloses details of the then-ongoing N9831 trial, including the same details PO relied on during prosecution as support for the issued claims. (*See supra* at Section VI.B.) Piccart-Gebhart discloses each and every limitation of claim 1.

The N9831 trial had several objectives, including to compare the disease-free survival of HER2-positive breast cancer when treated with doxorubicin/ cyclophosphamide followed by paclitaxel with or without Herceptin® in the following regimens:

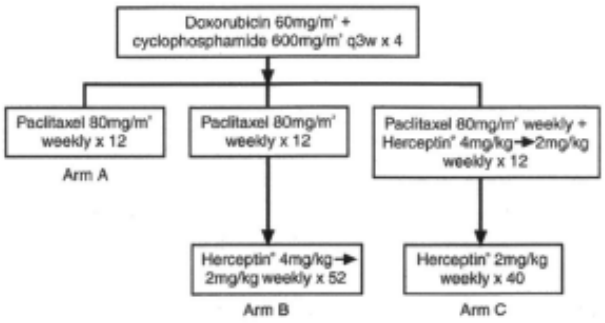


Figure 2. Study design for Intergroup Trial N9831.

(Ex. 1011, Piccart-Gebhart at 2.) Piccart-Gebhart notes that the study "will determine the role of weekly paclitaxel in adjuvant breast cancer treatment and the impact of Herceptin on survival." (*Id.*) As of May 2001, 242 patients had been enrolled in the trial.[6] (*Id.*)

[6] Although final results of the N9831 clinical trial were not reported until after the priority date of the '879 patent, Piccart-Gebhart's description of the trial protocol anticipates because the claims do not require any particular efficacy or result. *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005) ("proof of efficacy is not required in order for a reference to be enabled for purposes of anticipation"). In addition, "anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art." *Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001).

i. "A method of adjuvant therapy"

As discussed above, the preamble is not limiting. Accordingly, to anticipate claim 1, a prior art reference need not teach "a method of adjuvant therapy."

Nonetheless, Piccart-Gebhart discloses "a method of adjuvant therapy." (Ex. 1003, Leonard Decl. at ¶¶ 129-30.) Piccart-Gebhart is titled "*Herceptin: the future in adjuvant breast cancer therapy*," and discloses the designs of four "adjuvant clinical trials" of Herceptin®, including the N9831 trial. (Ex. 1011 at 2-5 (noting that N9831 is a "major adjuvant[] trial").) Piccart-Gebhart notes that the N9831 trial "will determine the role of weekly paclitaxel in adjuvant breast cancer treatment and the impact of Herceptin® on survival." (*Id.* at 3. *See also* Section IX.A.1.iii, below.)

ii. "administering to a human subject with non-metastatic HER2-positive breast cancer"

Piccart-Gebhart discloses "administering to a human subject with nonmetastatic HER-2 positive breast cancer." The article states that the N9831 trial was recruiting "women with node-positive, HER2-positive[7] breast cancer" and

[7] Piccart-Gebhart teaches that "[a]mplification of the human epidermal growth factor receptor-2 (HER2) gene and subsequent overexpression of the encoded protein are known to be early events in breast cancer pathogenesis," (Ex. 1011 at 1), and that only women with "HER-2 positive breast cancer" were enrolled in the

that "[p]atients with evidence of metastatic disease . . . are not eligible." (*Id.* at 3; Ex. 1003, Leonard Decl. at ¶ 131.) Breast cancer is either metastatic or non-metastatic, based on whether or not detectable cancer cells have spread beyond the primary tumor and nearby lymph nodes. (Ex. 1003, Leonard Decl. at ¶ 131; *see also* definition of "nonmetastatic breast cancer," Section VIII.C, above.) Because patients with metastatic disease were not eligible, the article discloses treatment of non-metastatic breast cancer patients (i.e., patients having cancer "which is confined to the breast and/or regional lymph nodes"). (Ex. 1003, Leonard Decl. at ¶ 131; Ex. 1001 at 10:30-31.)

iii. *"following definitive surgery"*

Piccart-Gebhart also discloses that in the N9831 trial, chemotherapy would follow definitive surgery. (Ex. 1003, Leonard Decl. at ¶¶ 132-36.) The '897 patent defines "definitive surgery" as "complete removal of tumor and surrounding tissue as well as any involved lymph nodes," and provides examples including "lumpectomy" (removal of the tumor and surrounding tissue), "mastectomy"

N9831 trial. (*Id.* at 3.) Accordingly, Piccart-Gebhart teaches treatment of "HER2 positive" breast cancer (i.e., breast cancer "which expresses HER2 at a level which exceeds the level found on normal breast cells or tissues." (Ex. 1003, Leonard Decl. at ¶ 131.)

(removal of all breast tissue from the breast), and "mastectomy plus axillary dissection" (the removal of lymph nodes under the arm). (Ex. 1001 at 10:20-24.)

Piccart-Gebhart discloses that the N9831 trial was an "adjuvant" trial, meaning that chemotherapy is administered following definitive surgery. "Adjuvant therapy" is defined in the specification as "therapy given after definitive surgery, where no evidence of residual disease can be detected, so as to reduce the risk of disease recurrence." (*Id.* at 10:11-13.) This is consistent with a POSA's use of the term "adjuvant" to describe breast cancer treatment as of 2005. (Ex. 1003, Leonard Decl. at ¶ 130; Ex. 1017, Devita et al., Principles And Practice Of Oncology (6th Ed. 2001) at 5 ("DeVita") ("Adjuvant chemotherapy denotes the use of systemic treatment after the primary tumor has been controlled by an alternative modality, such as surgery and radiation therapy.").)

Piccart-Gebhart further specifies that the N9831 trial involved patients with "breast cancer who are operable with either lumpectomy plus irradiation or mastectomy." (Ex. 1011 at 3.) Prior to randomization into treatment groups, the protocol called for stratifying patients based on the number of positive lymph nodes identified after "axillary dissection" (removal of some or all of the axillary lymph nodes) or sentinel node biopsy (removal of any positive sentinel nodes). (*Id.*)

Accordingly, Piccart-Gebhart discloses that patients in the N9831 trial would receive surgery to remove the primary tumor, such as a lumpectomy or mastectomy, along with removal of any positive lymph nodes through axillary dissection or sentinel node biopsy, followed by the claimed chemotherapy regimen (discussed below). (Ex. 1003, Leonard Decl. ¶¶ 133-35.) Indeed, any protocol that did not include surgery to remove operable tumors would have been both unethical and contrary to the purpose of adjuvant therapy. (*Id.* at ¶ 134.) Therefore, Piccart-Gebhart discloses a method that includes the claim limitation "following definitive surgery."

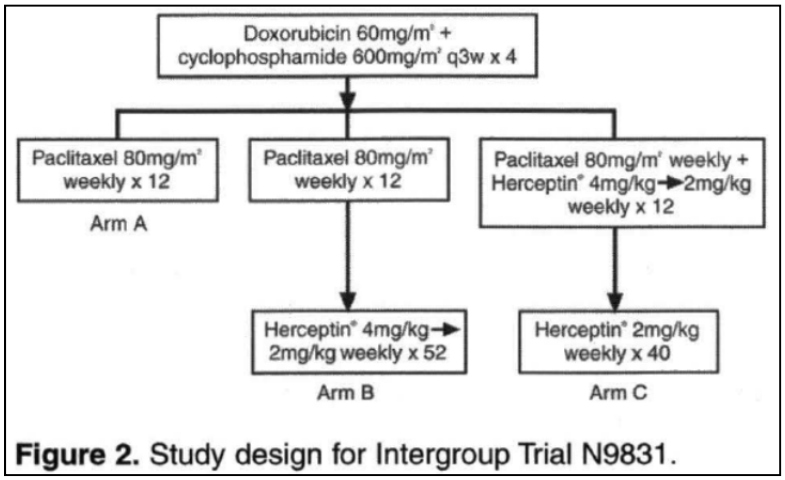
iv. *"anthracycline/cyclophosphamide(AC) based chemotherapy"*

Piccart-Gebhart discloses that, after definitive surgery, patients would receive "initial treatment with doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 i.v. every 3 weeks for 4 courses." (Ex. 1011 at 3; Ex. 1003, Leonard Decl. at 137.) Doxorubicin is an anthracycline, and therefore doxorubicin plus cyclophosphamide is "anthracyline/cyclophosphamide (AC) based chemotherapy." (*Id.*; *see also* Ex. 1001, 7:8.)

v. *"sequential administration of a taxoid and trastuzumab or an antibody that blocks binding of trastuzumab to HER2"*

Piccart-Gebhart also discloses the sequential administration of a taxoid and trastuzumab. (Ex. 1003, Leonard Decl. at ¶ 138.) Following AC-based

chemotherapy, patients in Arm B would receive "paclitaxel… followed immediately by Herceptin®." (Ex. 1011 at 3.) This is shown graphically in Figure 2:



(*Id.*) Paclitaxel is a taxoid, i.e., "chemotherapeutic agent that functions to inhibit microtubule depolymerization." (Ex. 1001 at 26:37-41; Ex. 1003, Leonard Decl. at ¶¶ 138-39.) The active ingredient in Herceptin® is and was, as of 2001, trastuzumab. (Ex. 1009, Herceptin® Product Label (Sept. 1998); Ex. 1003, Leonard Decl. at ¶ 139.) Accordingly, Piccart-Gebhart discloses "sequential administration of a taxoid and trastuzumab" to a human subject with nonmetastatic HER2-positive breast cancer following definitive surgery and AC-based chemotherapy, thereby anticipating claim 1. (Ex. 1003, Leonard Decl. at ¶ 139.)

Furthermore, Piccart-Gebhart is enabling because it describes the claimed methods of treatment with sufficient detail such that a POSA would be able to carry out the claimed methods. (*Id.* at ¶ 152.) *Impax Labs. Inc. v. Aventis Pharms.*

Inc., 468 F.3d 1366, 1383 (Fed. Cir. 2006) ("the proper issue is whether the . . . [prior art] is enabling in the sense that it describes the claimed invention sufficiently to enable a person of ordinary skill in the art to carry out the invention"). Based on Piccart-Gebhart's description of the N9831 trial, a POSA would have known how to administer, following definitive surgery, an adjuvant therapy regimen comprising AC-based chemotherapy, followed by a taxoid, followed by trastuzumab to non-metastatic, HER2-positive breast cancer patients. A POSA would also have also known the appropriate dosage and duration of each drug regimen. (Ex. 1003, Leonard Decl. at ¶ 152.)

2. Piccart-Gebhart Anticipates Dependent Claims 2-5 and 8-13

i. *Claims 2* and *3*

Claim 2 recites the "*method of claim 1, wherein the taxoid is paclitaxel or docetaxel.*" **Claim 3** recites the "*method of claim 2, wherein trastuzumab is administered*." As discussed above with respect to claim 1, Piccart-Gebhart discloses the administration of the taxoid "paclitaxel" before administration of "trastuzumab." Accordingly, Piccart-Gebhart anticipates claims 2 and 3. (*Id.* at ¶¶ 140-41.)

ii. *Claim 4*

Claim 4 recites the "*method of claim 3, wherein trastuzumab is administered at an initial dose or [sic] 4 mg/kg, followed by subsequent weekly*

doses of 2 mg/kg." Piccart-Gebhart discloses that patients in Arm B of the N9831 trial would receive trastuzumab at "4mg/kg initial dose i.v. followed by 2 mg/kg weekly" for a total of 52 weeks. (Ex. 1011 at 3 and Figure 2; Ex. 1003, Leonard Decl. at ¶ 142.) Accordingly, Piccart-Gebhart anticipates claim 4. (Ex. 1003, Leonard Decl. at ¶ 142.)

iii. Claims 5 and 8-10

Claim 5 recites the "method of claim 1, wherein the subject has a *high risk of cancer recurrence*." The '897 patent defines a subject at "high risk of cancer recurrence" as having "a greater chance of experiencing recurrence of cancer." (*Id.* at 12:1-2.) Piccart-Gebhart discloses that the N9831 trial was recruiting "node-positive, HER2-positive breast cancer" patients. (Ex. 1011 at 3.) As of 2005, a POSA would have understood that such patients had a greater chance of experiencing cancer recurrence than patients without these disease characteristics. (Ex. 1003, Leonard Decl. at ¶ 143.) Indeed, this is consistent with the patent specification, which provides examples of patients with a "high risk of cancer recurrence," including those with HER2-positive breast cancer and "those with positive lymph nodes ["node-positive"], particularly 4 or more involved lymph nodes (including 4-9 involved lymph nodes, and 10 or more involved lymph nodes)." (Ex. 1001 at 12:2-15; Ex. 1003, Leonard Decl. at ¶¶ 84, 143.) Moreover, Piccart-Gebhart discloses that "HER2-positive breast cancer patients form a high-

risk group with a poor overall prognosis," and that the adjuvant trials including N9831 were conducted to "*examine the role of Herceptin® in the* ***prevention of disease recurrence.***" (Ex. 1011 at 1, 2; Ex. 1003, Leonard Decl. at ¶ 143.)

Claims 8-10 each depend from claim 5, and are directed to treating a patient with a specific disease characteristic. **Claim 8** recites the "method of claim 5, wherein the cancer is *lymph node-positive*." Piccart-Gebhart discloses that the N9831 trial was recruiting "node-positive, HER2-positive breast cancer" patients, and a POSA would know that "node-positive" refers to a patient that is "lymph node-positive." (Ex. 1011 at 3; Ex. 1003, Leonard Decl. at ¶ 145.)

Claims 9 and 10 each depend from claim 8, and respectively recite that the subject had "*4-9 involved lymph nodes*" and "*10 or more involved lymph nodes*." Piccart-Gebhart discloses that, before being randomly assigned a treatment regimen, the protocol called for stratifying patients based in part on the number of involved lymph nodes detected: 1) those who had received axillary lymph node dissection identifying 1-3 involved lymph nodes; 2) those who had received axillary lymph node dissection identifying 4-9 involved lymph nodes; 3) those who had received axillary lymph node dissection identifying $\geq$ 10 lymph nodes; and 4) those who had a positive sentinel lymph node but did not undergo complete axillary dissection. (Ex. 1011 at 3.) Because patients would be stratified prior to randomization, and randomization is designed to ensure that study patients from

each of these strata would be fairly distributed among each of the study arms, some patients in each of the four lymph node groups were therefore assigned to each treatment regimen. (Ex. 1003, Leonard Decl. at ¶ 146.) Therefore, some patients in Arm B of the N9831 trial would have had 4-9 positive lymph nodes, and some patients had 10 or more positive lymph nodes, as required in claims 9 and 10, respectively. (*Id.*)[8]

[8] It is immaterial that Piccart-Gebhart does not disclose how many patients randomized to the Arm B treatment regimen had "4-9 involved lymph nodes" or "10 or more involved lymph nodes." Even if no patients with those characteristics were assigned to the Arm B treatment group, the dependent claims would still be anticipated. "[A]nticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art." *Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001). Piccart-Gebhart discloses that patients having the claimed number of lymph nodes were randomized into the Arm B treatment regimen, in which they would receive the claimed sequence of drugs. This disclosure is enabling to a POSA. (Ex. 1003, Leonard Decl. at ¶¶ 146, 152.)

iv. Claims 11-12

Claim 11 recites the "method of claim 5, wherein the subject's cancer was *estrogen receptor (ER) negative*," and **Claim 12** recites the "method of claim 5, wherein the subject's cancer was *progesterone receptor (PG) negative*."

Piccart-Gebhart discloses that before being randomly assigned a treatment regimen, patients would be "stratified by number of positive lymph nodes . . . and receptor status (ER- or PgR-positive versus other)." (Ex. 1011 at 3.) Patients were categorized into one of two groups: 1) those who had a positive ER status or positive PG or PR status; and 2) those who were negative for both receptors. (*Id.*; Ex. 1003, Leonard Decl. at ¶ 148.) Patients within each group would then be randomly assigned to each of the treatment groups. (Ex. 1011 at 3; Ex. 1003, Leonard Decl. at ¶ 148.) Therefore, some patients in Arm B of the N9831 trial, who would be treated with the sequence of drugs recited in claim 1, were ER negative and PG or PR negative.[9] (Ex. 1003, Leonard Decl. at ¶ 148.) Moreover, such patients had a "high risk of cancer recurrence" as recited in Claim 5 because of their ER and PG receptor negative status, and their HER2-positive status. (Ex.

[9] That is, Piccart-Gebhart discloses treatment of patients whose "cancer tests negative for expression of estrogen receptor" and also treatment of patients whose "cancer tests negative for expression of progesterone receptor." (Ex. 1003, Leonard Decl. at ¶ 148.)

1001 at 12:1-15.) Accordingly, Piccart-Gebhart discloses all elements of claims 11 and 12.[10]

v. *Claim 13*

Claim 13 recites the "method of claim 1, wherein *the antibody is a naked, intact antibody*." Reading in the antecedent basis from claim 1 for "the antibody," claim 13 requires a naked, intact antibody that blocks binding of trastuzumab to HER2. Trastuzumab is a naked, intact antibody that blocks binding of trastuzumab to HER2. (Ex. 1003, Leonard Decl.at ¶ 150.) Moreover, even if trastuzumab was not an antibody with these characteristics, the administration of trastuzumab according to claims 1 and 3 would anticipate claim 13 because claim 13, as dependent on claim 1, is satisfied through the administration of "trastuzumab ***or***" a "naked, intact antibody . . ." Accordingly, for the same reasons discussed above with respect to claims 1 and 3, Piccart-Gebhart anticipates claim 13. (*Id.* at ¶¶ 127-39, 151.)

[10] As explained above in footnote 8, Piccart-Gebhart is enabling, and therefore anticipates claims 11 and 12. (Ex. 1003, Leonard Decl. at ¶¶ 148, 152; *Bristol-Myers Squibb Co.*, 246 F.3d at 1379.)

vi. Claim Chart: Anticipation of Claims 1-5 and 8-13 by Piccart-Gebhart

As charted below, Piccart-Gebhart discloses each and every limitation of claims 1-5 and 8-13 of the '897 patent, and therefore anticipates these claims. (Ex. 1003, Leonard Decl. at ¶ 152.)

Claim	Limitation	Support in Piccart-Gebhart (Ex. __)
Claim 1	A method of adjuvant therapy comprising	1 ("adjuvant breast cancer therapy") 2 (N9831 is "major adjuvant[] trial") 3 (N9831 trial "will determine the role of weekly paclitaxel in adjuvant breast cancer treatment) *see also* "following definitive surgery" limitation below
	administering to a human subject with nonmetastatic HER2 positive breast cancer	3 ("patients with evidence of metastatic cancer . . . are not eligible") 3 ("HER2-positive breast cancer")
	following definitive surgery	2 (N9831 is "major adjuvant[] trial") 3 ("adjuvant breast cancer treatment;" "operable with either lumpectomy plus irradiation or mastectomy;" "axillary dissection;" "positive sentinel node")
	anthracycline/cyclophosphamide (AC) based chemotherapy followed by	3 ("All patients will receive initial treatment with doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 i.v. every 3 weeks for 4 courses."; Figure 2, Arm B)

Claim	Limitation	Support in Piccart-Gebhart (Ex. __)
	sequential administration of a taxoid and trastuzumab.	3 ("The second arm will receive the same paclitaxel dose which will be followed immediately by Herceptin (4mg/kg initial dose i.v. followed by 2 mg/kg weekly) for a total of 52 weeks."); Figure 2, Arm B.
Claim 2	wherein the taxoid is paclitaxel or docetaxel	3 ("paclitaxel")
Claim 3	wherein trastuzumab is administered	3 ("trastuzumab")
Claim 4	wherein trastuzumab is administered at an initial dose of 4mg/kg, followed by weekly doses of 2 mg/kg	3 ("4 mg/kg initial dose i.v. followed by 2 mg/kg weekly"); *see also* Figure 2, Arm B.
Claim 5	wherein the subject has a high risk of cancer recurrence	1 ("high-risk group"); 2 ("disease recurrence"); 3 ("node-positive, HER2-positive breast cancer")
Claim 8	wherein the cancer is lymph node-positive	3 ("node-positive")
Claim 9	wherein the subject had 4-9 lymph nodes	3 ("Before randomization, patients are stratified by number of positive lymph nodes (axillary dissection with 1-3 versus 4-9 versus $\geq$ 10...")
Claim 10	wherein the subject had 10 or more lymph nodes	3 ("Before randomization, patients are stratified by number of positive lymph nodes (axillary dissection with 1-3 versus 4-9 versus $\geq$ 10...")
Claim 11	wherein the subject's cancer was estrogen receptor (ER) negative	3 ("receptor status (ER- or PgR-positive versus other")

Claim	Limitation	Support in Piccart-Gebhart (Ex. __)
Claim 12	wherein the subject's cancer was progesterone receptor (PG) negative	3 ("receptor status (ER- or PgR-positive versus other")
Claim 13	wherein the antibody is an intact naked body	3 ("trastuzumab"); *see also* claims 1 and 3

B. Ground 2: Perez Anticipates Claims 1 and 5-7

Perez[11] discusses cardiovascular data from patients in the N9831 trial. The data was obtained after the patients received AC-based chemotherapy and before they were randomized to the treatment arms. Ex. 1015, Perez, at 1-2. Like Piccart-Gebhart, Perez details the treatment regimens administered to patients in each arm of the N9831 study. Perez discloses each and every limitation of claims 1 and 5-7. (*See also* claim chart in Section IX.B.5 below.)

1. Claim 1

i. *"A method of adjuvant therapy"*

As discussed above, pp. 17-18, the preamble "a method of adjuvant therapy" is not limiting. Nevertheless, Perez discloses the use of trastuzumab in the "N9831

[11] Perez et al., *Effect of Doxorubicin Plus Cyclophosphamide on Left Ventricular Ejection Fraction in Patients with Breast Cancer in the North Center Cancer Treatment Group N9831 Intergroup Adjuvant Trial*, 22 J. Clinical Oncology 3700 (2004) ("Perez," Ex. 1015).

Intergroup Adjuvant Trial." (Ex. 1015, Perez at 1; Ex. 1003, Leonard Decl., ¶¶62-63. *See also* Section IX.B.4, below.)

ii. "administering to a human subject with non-metastatic HER2-positive breast cancer"

Perez discloses administering therapy to a human subject with HER2-positive breast cancer. Perez teaches that patients in the N9831 trial "had to have human epidermal growth factor receptor 2 (HER2)-positive tumors, defined as HER2 3+, as determined by immunohistochemistry." Ex. 1015 at 2. Thus, Perez discloses treatment of cancer "which expresses HER2 at a level which exceeds the level found on normal breast cells or tissue." (Ex. 1003, Leonard Decl., ¶158.)

Perez also discloses that only non-metastatic patients were recruited for the N9831 trial. (Ex. 1003, Leonard Decl., ¶¶156-57.) Adjuvant therapy is only administered to patients without detectable traces of cancer. *Id.* Metastatic cancer patients would have detectable cancer in their body following surgery, and thus could not receive "adjuvant" therapy. *Id.* Moreover, Perez discloses that the N9831 study was designed to augment the existing published data on the potential cardiotoxicity of doxorubicin in "early-stage cancer." (Ex. 1015 at 1.) "Early-stage" breast cancer has not spread beyond the breast and axillary lymph nodes, *i.e.*, is non-metastatic. (Ex. 1003, Leonard Decl., ¶157; *see also* Ex. 1016, NCI Dictionary of Cancer, at 1.) Accordingly, Perez discloses treatment of patients with non-metastatic HER2-positive breast cancer.

iii. "following definitive surgery"

As described in Perez, N9831 was an "adjuvant" trial, and only patients with "operable" invasive breast cancer were eligible. (Ex. 1015, at 1-2.) A POSA would have understood that as part of the protocol, patients who enrolled in the N9831 study would receive surgery to remove the tumor and affected tissue. (Ex. 1003, Leonard Decl. ¶162.) Indeed, any protocol that did not include surgery to remove operable tumors would have been both unethical and contrary to the purpose of adjuvant therapy. (*Id*.)

Furthermore, patients in the N9831 study also "had to have node-positive or high-risk, node-negative tumors as determined by sentinel node biopsy or axillary node dissection followed by hematoxylin and eosin staining." (Ex. 1015 at 2.) A POSA would have recognized that sentinel node biopsy and axillary node dissection involve the removal of "any involved lymph nodes." Accordingly, because the patients in the N9831 study would have had any involved lymph nodes in addition to their operable tumors removed prior to receiving treatment in the N9831 study, these patients would have received "definitive surgery" within the definition of the '897 patent. (Ex. 1003, Leonard Decl. ¶ 163.)

Therefore, Perez discloses a method that includes the claim limitation "following definitive surgery." (Ex. 1003, Leonard Decl. ¶ 164.)

iv. *"anthracycline/cyclophosphamide (AC) based chemotherapy"*

Perez discloses that patients in each arm of the N9831 study were treated with "AC (60 mg/m^2 doxorubicin plus 600 mg/m^2 cyclophosphamide on day 1 of weeks 1, 4, 7, and 10) for four cycles and then continued treatment per randomization to one of three arms." (Ex. 1015 at 2.) Doxorubicin is an anthracycline, and therefore doxorubicin plus cyclophosphamide is "anthracycline/cyclophosphamide (AC) based chemotherapy." (Ex. 1003, Leonard Decl. ¶ 165.)

v. *"followed by sequential administration of a taxoid and trastuzumab or an antibody that blocks binding of trastuzumab to HER2"*

Perez also discloses the sequential administration of a taxoid and trastuzumab after AC-based chemotherapy. (Ex. 1003, Leonard Decl. ¶¶ 166-67.) Following AC-based chemotherapy, patients would be randomized into one of three treatment arms. Ex. 1015 at 2 & Figure 1. In one of the arms, patients would receive paclitaxel (a taxoid) for 12 weeks, followed by trastuzumab for 52 weeks. (*Id.*; Ex. 1003, Leonard Decl. ¶166.) Accordingly, Perez discloses "sequential administration of a taxoid and trastuzumab" to a human subject with nonmetastatic HER2-positive breast cancer following definitive surgery and AC-based chemotherapy, thereby disclosing every element of claim 1. (Ex. 1003, Leonard Decl. ¶ 167.) Furthermore, Perez is enabling because it describes the claimed

method with sufficient detail such that a POSA would be able to perform it. (Ex. 1003, Leonard Decl., 174; *Impax Labs. Inc.*, 468 F.3d at 1383.Therefore, Perez anticipates claim 1.)

2. Claim 5

Claim 5 recites the "method of claim 1, wherein the subject has a high risk of cancer recurrence." As discussed above, Perez discloses every element of claim 1. It also discloses the additional limitation of claim 5.

The '897 patent defines having a "high risk of cancer recurrence" as having "a greater chance of experiencing recurrence of cancer." (Ex. 1001 at col. 12, ll. 1-2.) Perez discloses that the N9831 trial only recruited patients with "node positive or high risk, node-negative tumors," including tumors with diameters greater than 2 centimeters. (Ex. 1015, Perez, at 2.) Perez also teaches that over half of the N9831 patients were under 50 years old. *Id.* at 3. As of 2005, a POSA would have understood that such patients had a greater chance of experiencing cancer recurrence than patients without these disease characteristics. (Ex. 1003, Leonard Decl. ¶171.) Indeed, this is consistent with the specification, which provides examples of patients with a "high risk of cancer recurrence," including those with HER2-positive breast cancer; "those with positive lymph nodes ["node-positive"];" those who are "relatively young subjects (e.g., less than about 50 years old);" and "those with tumors greater than 2 cm in diameter." (Ex. 1001 at col. 12, ll. 2-15;

Ex. 1003, Leonard Decl. ¶ 171.) A subset of these "high risk" patients were randomized to the Arm B regimen to receive the treatment set forth in claim 1. (Ex. 1003, Leonard Decl., ¶171.) Accordingly, Perez discloses all of the elements of claim 5. (*Id.*) Because Perez also enables a POSA to perform the steps of claim 5, Perez anticipates this claim. (*Id*. at 174.)

3. Claim 6

Claim 6 depends from claim 5, and further adds that "the patient is less than 50 years old." Perez discloses that patients over the age of 18 were eligible for the N9831 study. (Ex. 1015 at 2.) Table 2 of Perez also discloses the ages of patients enrolled in the N9831 study, including patients in age groups younger than 50 years old:

Table 2. Baseline Patient Characteristics

Characteristic	% of Patients (N = 1,572)				
	MUGA/MUGA (n = 1,153)	ECHO/ECHO (n = 305)	MUGA/ECHO (n = 27)	ECHO/MUGA (n = 53)	Post-AC LVEF not Obtained (n = 34)
Race					
White	84.8	89.2	88.9	79.3	85.3
Black	6.0	3.9	3.7	7.6	5.9
Other	9.2	6.9	7.4	13.1	8.8
Age, years					
18-29	1.9	2.3	0	1.9	0
30-39	16.6	16.1	14.8	20.8	14.7
40-49	33.9	33.4	44.4	26.4	32.4
50-59	33.0	30.2	22.2	26.4	14.6
60-69	12.4	14.4	11.1	18.9	29.4
70+	2.2	3.6	7.4	5.7	8.8

(*Id.* at 3.) As shown in the table, over half of the patients enrolled in the study were less than 50 years old. The patients in the study across all age groups were randomized to each of the three treatment arms of the N9831 study, including Arm B, in which patients received the treatment regimen recited in claim 1. (*Id*. at 2.)

Because randomization is designed to ensure that the study patients would be fairly assigned to each of the study treatment groups, some of the patients who received the drug dosing regimen recited in claim 1 were less than 50 years old.[12] (Ex. 1003, Leonard Decl., ¶ 172)

Nevertheless, to anticipate, Perez need not disclose actual performance of the claimed method of treatment on a subject less than about 50 years old who had a "high risk of cancer recurrence." As noted above, "anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art." *Bristol-Myers Squibb Co.*, 246 at 1379. As noted above, Perez is enabling, including with respect to such subjects. (Ex. 1003, Leonard Decl., ¶ 174) Accordingly, Perez anticipates claim 6.

4. Claim 7

Claim 7 depends from claim 5, and further adds that "the subject had a tumor greater than 2 centimeters in diameter." Perez discloses that one eligibility criterion for the N9831 trial was that patients with estrogen receptor-positive

[12] Further, as reported in a 2011 paper that reports the results of the N9831 trial, Arm B of the N9831 trial indeed included patients less than 50 years old who had a high risk of cancer reoccurrence. (Ex. 1019, Perez 2011, at 4 tbl. 1; Ex. 1003, Leonard Decl. at ¶ 174 n. 4.)

tumors had to have tumors that were "more than 2.0 cm." (Ex. 1015 at 2.) Because patients were randomized to each of the study treatment groups, some of the patients with tumors greater than 2 cm in diameter received the treatment regimen recited in claim 1. (Ex. 1003, Leonard Decl., ¶ 173.) Moreover, the disclosures in Perez is enables claim 7 because it teaches a POSA to administer the drug regimen of claim 1 to patients with tumors greater than 2 centimeters as required in claim 7. *Id*. Accordingly, Perez anticipates claim 7 of the '897 patent.

5. Claim Chart: Anticipation of Claims 1 and 5-7 by Perez

As charted below, Perez discloses each and every limitation of claims 1 and 5-7 of the '897 patent, and therefore anticipates these claims. (Ex. 1003, Leonard Decl., ¶ 174.)

Claim	Limitation	Perez (Ex. 1015)
Claim 1	A method of adjuvant therapy comprising administering to a human subject with	p. 1 ("adjuvant")
	Nonmetastatic	p. 2 ("early stage," "operable")
	HER2 positive breast cancer	p. 2 ("Patients had to have human epidermal growth factor receptor 2 (HER2) – positive tumors")
	following definitive surgery	p. 2 ("adjuvant;" "operable;" "axillary node dissection;" "sentinel node biopsy")

Claim	Limitation	Perez (Ex. 1015)
	anthracycline/cyclophosphamide (AC) based chemotherapy followed by	p. 1 ("standard doxorubicin . . . plus cyclophosphamide . . . followed by")
	sequential administration of a taxoid and trastuzumab	p. 1 ("weekly paclitaxel for 12 weeks, then weekly trastuzumab for 52 weeks")
Claim 5	high risk of cancer recurrence	p. 2 ((HER2)-positive tumors;" "high-risk;" "node positive")
Claim 6	subject is less than 50 years old	p. 2 ("Women aged > 18 years"); Table 2 (referring to baseline patient characteristics, including patients less than 50 years old)
Claim 7	tumor greater than 2 centimeters in diameter	p. 2 (estrogen receptor-positive tumors had to be "more than 2.0 cm")

C. Ground 3: Claims 1-13 are Obvious Over Piccart-Gebhart in View of Thomas

Each claim of the '897 patent is obvious over Piccart-Gebhart (Ex. 1011) in view of Thomas (Ex. 1018).

1. Scope and Content of the Prior Art

The scope and content of the prior art is described above in Section VII. In addition, Piccart-Gebhart and Perez, discussed above, are part of the prior art. The prior art also included Thomas et al., *New paradigms in adjuvant systemic therapy of breast cancer*, 10 Endocrine-Related Cancer 75-89 (2003) ("Thomas") (Ex.

1018). Thomas is a review of then-current adjuvant therapies for breast cancer, including discussion of standards of care in adjuvant therapy and common practices for different patient populations.

Thomas discloses that "the vast majority of patients with invasive breast cancer will derive benefit from systemic adjuvant therapy" with chemotherapeutic drugs such as anthracycline and cyclophosphamide, and discusses several factors that can affect the magnitude of the benefit. (Ex. 1018, Thomas at 5.) This discussion included the following points:

- "Women younger than 40 years derive the greatest reduction in risk of recurrence from systemic polychemotherapy." (*Id.*)
- Although adjuvant chemotherapy is beneficial regardless of ER status, the relative benefit can depend on age. In women younger than 50, the risk reduction from adjuvant chemotherapy was not significantly different between those with ER-negative tumors and those with ER-positive tumors, but in women older than 50, the risk reduction was nearly double for those with ER-negative tumors compared with those with ER-positive tumors. (*Id.*)
- The benefit of adjuvant chemotherapy is higher for patients who are lymph-node positive. (*Id.* at 11.)

- "The only subsets of patients for whom the risks of chemotherapy often outweigh the benefits include those with tumors smaller than 1 cm and negative lymph nodes, and those with small tumors (<3 cm) with favorable histological types." (*Id.*)

Thomas discusses the use of anthracycline-based combination therapies, including AC and fluorouracil, doxorubicin and cyclophosphamide. (*Id.* at 6-7.) Thomas concludes that there is a consistent benefit from the use of such combinations compared to other chemotherapy options for adjuvant therapy. (*Id.* at 7.) Thomas also discusses the use of taxoids with anthracycline-based regimens. (*Id.*) Thomas discloses that clinical studies showed that AC therapy followed by paclitaxel improved disease free survival, but long term benefits were only seen in ER-negative patients. (*Id.*)

Thomas also discloses that trastuzumab increases survival in combination with AC or paclitaxel (*id.* at 8), but that cardiotoxicity is "associated with trastuzumab, particularly when it is combined with anthracyclines." (*Id.*) Thomas also discloses that the four trials disclosed in Piccart-Gebhart were ongoing to "evaluat[e] the potential benefit of trastuzumab in combination with adjuvant chemotherapy regimens." (*Id.*) Thomas discloses the dosing regimens being tested in each trial, including N9831. (*Id.* at 9)

2. Level of Ordinary Skill in the Art

A POSA at the time of the alleged invention would have been a physician (M.D. or equivalent) with subspecialty training in oncology and substantial experience treating breast cancer patients and/or a Ph.D. with substantial experience in researching and developing oncologic therapies. Such an individual would also have had substantial experience in the design and/or implementation of clinical trials for breast cancer treatments, and/or an active research role relating to breast cancer treatments. (Ex. 1003, Leonard Decl., ¶ 35-36.)

3. Differences Between the Claims and the Prior Art

As set forth above in Section IX.A, Piccard-Gebhart discloses every element of claims 1-5 and 8-13. It does not expressly teach the patient characteristics in claim 6 (less than about 50 years old) or claim 7 (tumor greater than 2 centimeters in diameter). Although those particular details were not disclosed in Piccart-Gebhart, they were, in fact, practiced in the N9831 study. (*See, e.g.*, Ex. 1015, Perez at 2-3; Ex. 1003, Leonard Decl. at ¶ 172-174.)

Thomas teaches these limitations. (Ex. 1003, Leonard Decl. at ¶ 179-181.) Thomas teaches that "women younger than 40 derive the greatest reduction in risk of recurrence from systemic polychemotherapy." (Ex. 1018 at 5.) Thomas also teaches that in patients with ER-positive tumors, the risk reduction from adjuvant

chemotherapy relative to patients with ER-negative tumors is much lower in women over 50 years old than in women younger than 50 years old. (*Id.*)

With respect to tumor size, Thomas teaches that the benefits of adjuvant chemotherapy must be weighed against the potential adverse effects. (*Id.* at 11.) For some patients, the risks outweigh the benefits, particularly "those with tumors smaller than 1 cm and negative lymph nodes," and "those with small tumors (< 3 cm) with favorable histological types." (*Id.*) Thus, Thomas teaches that, for patients with positive lymph nodes and tumors greater than 1 cm, the benefits of adjuvant therapy outweigh the risks. (Ex. 1003, Leonard Decl. at ¶ 181.)

4. Conclusion of Obviousness

The '897 claims are obvious over Piccart-Gebhart in view of Thomas. As discussed above, Piccart-Gebhart discloses each limitation of claims 1-5 and 8-13. Claims 6 and 7 add limitations regarding disease and patient characteristics. These limitations merely reflect the patient populations who were known as of 2004to derive the most benefit from adjuvant therapy. (Ex. 1003, Leonard Decl. at ¶¶ 109-111; Ex. 1018, Thomas at 5, 11.) The teachings of Thomas, which reflect general knowledge and common practices in the field at the time, combined Piccart-Gebhart, render the '897 patent claims obvious. (Ex. 1003, Leonard Decl. at ¶¶ 109, 175)

The claimed methods also would have been obvious to try in view of Piccart-Gebhart and Thomas. (*Id.* at ¶ 182.) A POSA would have seen a need for adjuvant therapy with trastuzumab, and there were only a finite number of ways to incorporate trastuzumab into an established chemotherapy regimen. *See, e.g.*, *Ex Parte Davis*, 2016 WL 3406576, at *4 (PTAB, June 17, 2016) ("Where there is a need or market pressure (as there would be here), picking one of a finite number of known solutions to a known problem is obvious.") (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)).

i. *Claim 1*

A POSA would have known that trastuzumab was effective for treating HER2-positive metastatic breast cancer in combination with AC- or taxoid-based chemotherapy. (Ex. 1003, Leonard Decl. at ¶ 183; Ex. 1011__, Piccart-Gebhart at 1; Ex. 1018, Thomas at 8.) A POSA would have also known that anticancer drugs are typically developed for treatment of patients with advanced metastatic disease, and that once a drug proves to be safe and effective in that setting, testing for adjuvant use is appropriate. (Ex. 1011, Piccart-Gebhart at 1; Ex. 1003, Leonard Decl. at ¶¶ 184-86.) A POSA would have seen a need for effective adjuvant therapies, and would have known that the logical next step for trastuzumab would be to develop it as an adjuvant therapy in HER2-positive non-metastatic patients. (Ex. 1003, Leonard Decl. at ¶¶ 182, 187-88.)

Because using trastuzumab in the adjuvant setting was the logical next step in the development of trastuzumab, a POSA would have been motivated to combine the teachings of Piccart-Gebhart about trastuzumab and development of adjuvant therapies using trastuzumab with existing knowledge in the field about adjuvant therapies, as found in, *e.g.*, Thomas. (*Id.* at ¶ 188.) Thomas teaches that combination chemotherapy regimens were widely used as adjuvant therapy. (*Id.* at ¶ 189; Ex. 1018, Thomas at 5-11; *see also* Ex. 1014, Citron at 1 ("Advances in the adjuvant chemotherapy of primary, operable breast cancer have come both from the introduction of effective agents and from the application of the principles of combination chemotherapy.").) These teachings would have motivated a POSA to add trastuzumab to established regimens for adjuvant therapy. (Ex. 1003, Leonard Decl. at ¶¶ 187-91.)

A POSA would also have known that concurrent anthracycline/ cyclophosphamide followed by taxoid treatment ("AC→T") was in widespread use for adjuvant therapy. (Ex. 1003, Leonard Decl. at ¶ 190; *see also* Ex. 1011, Piccart-Gebhart at 2 (calling AC→T the "American standard treatment regimen").) Indeed, the '897 patent specification acknowledges that AC→T was the "standard of care adjuvant chemotherapy," and was "routinely used" for some HER2-positive patients. (Ex. 1001 at 28:7-17; *see also id.* at 56:40-57:40 (identifying patient populations).) A POSA would also have known that although AC→T could

reduce the probability of cancer recurrence, recurrence was still common, and improved adjuvant therapies were needed. (Ex. 1003, Leonard Decl. at ¶ 191.)

A POSA therefore would have been motivated to combine these teachings by adding trastuzumab in adjuvant therapy in conjunction with AC→T because (1) the next logical step in developing trastuzumab was to introduce it as an adjuvant therapy; (2) trastuzumab was highly successful in combination with chemotherapy as a treatment for metastatic cancer; and (3) AC→T was one of the most widely used chemotherapy regimens for adjuvant therapy. (*Id.*)

In 2004, there were two plausible ways to add trastuzumab to the AC→T regimen. After AC, trastuzumab could be administered (1) concurrently with taxoid (AC→TH); or (2) sequentially after taxoid ("AC→T→H"). Both would have been obvious for a POSA to try. (*Id.* at ¶ 192-93.) Indeed, Piccart-Gebhart discloses that the N9831 clinical trial was underway to test both options. (Ex. 1011, Piccart-Gebhart at 3-5; Fig. 2.)

A POSA would not have administered a taxoid after completing trastuzumab treatment. Trastuzumab is typically administered for a year, whereas taxoids are typically administered for 12-18 weeks. (Ex. 1003, Leonard Decl. at ¶ 193 n.5; Ex. 1009, Herceptin 1998 Label.) A POSA would not have wanted to wait for one year after surgery to start the taxoid, because the purpose of adjuvant chemotherapy is to kill residual cancer cells before they have an opportunity to

reestablish tumors. By a year after surgery the opportunity eliminate any remaining cancer cells before they multiply is lost.[13] (Ex. 1003, Leonard Decl. at ¶ 193 n.6.)

A POSA also would not have tried a regimen in which trastuzumab was administered concurrently with anthracycline, because it was known that such concurrent administration was associated with cardiotoxicity. (*Id.* at ¶ 192; Ex. 1013, Horton at 5-6.) In fact, one of the objectives of the N9831 trial was to "determine whether a 3-month delay between doxorubicin exposure and Herceptin® therapy [in arm B of the study, which administered Herceptin after administration of paclitaxel] decreases the incidence of potential cardiotoxicity" that had been observed with combined administration of doxorubicin and Herceptin®. (Ex. 1011, Piccart-Gebhart, at 3.) This indicates that POSAs were motivated to try administering a course of taxoids before trastuzumab (*i.e.*, AC → T → H) to extend the time between administration of doxorubicin (part of the AC therapy) and the start of trastuzumab because of the increase in cardiotoxicity associated with administering doxorubicin and trastuzumab together. (Ex. 1003, Leonard Decl. at ¶ 194.)

[13] In any case, AC→H→T also falls within the claimed regimen of "sequential administration of a taxoid and trastuzumab."

A POSA would have reasonably expected the AC→T→H regimen to be successful as adjuvant therapy following definitive surgery in women with HER2-positive breast cancer. (*Id.* at ¶ 196.) Trastuzumab was well-known as a safe, well-tolerated, and highly effective therapy for treating HER2-positive breast cancer in the metastatic and neo-adjuvant settings, particularly in combination with chemotherapy. (Id. at ¶ 187, 196; *see also, e.g.*, Ex. 1005, Van Pelt at 1; Ex. 1010, Slamon 2001; Ex. 1017, de Vita at 126.) Based on this knowledge, a POSA would have expected trastuzumab to be similarly safe and effective for adjuvant treatment of non-metastatic breast cancer following surgery in conjunction with the standard AC→T regimen in either of the two combinations discussed above.[14] (Ex. 1003,

[14] Although Thomas notes safety concerns when administering trastuzumab and anthracyclines due to potential cardiotoxicity, a POSA would have known that the cardiotoxicity arose primarily with the use of trastuzumab and an anthracycline concurrently or in close proximity. (Ex. 1003, Leonard Decl. at ¶ 196; *see* Ex. 1013, Horton, at 6, 10.) For example, a POSA would have known that only "arm 3" of the N9831 trial, where patients were administered trastuzumab and paclitaxel concurrently following AC therapy, was briefly halted due to cardiotoxicity. Moreover, the arm subsequently reopened, "suggesting that the incidence and severity of trastuzumab-related cardiac events in these adjuvant studies is small." (Ex. 1013, Horton at 6,10.) Horton also indicates that "[a]djuvant trials

Leonard Decl. at ¶ 196-97.) Indeed, Piccart-Gebhart teaches that considering the prior success of trastuzumab and the typical sequence of development of anticancer drugs, "it is reasonable to expect that therapy targeting HER2 will have clinical benefit when used as adjuvant therapy." (Ex. 1011, Piccart-Gebhart at 2.)

ii. Claim 2

Claim 2 recites the "method of claim 1, wherein the taxoid is paclitaxel or docetaxel." In 2005, paclitaxel and docetaxel were the most commonly used taxoid drugs. (Ex. 1003, Leonard Decl. at ¶ 199.) Indeed, the only two drugs disclosed in the section of Thomas entitled "Taxanes" are paclitaxel and docetaxel. (Ex. 1018, Thomas at 7.) Paclitaxel or docetaxel were used in all four of the clinical trials described in Piccart-Gebhart, including the two that were studying "how to use Herceptin® with the American standard treatment regimen of anthracycline/ cyclophosphamide followed by a taxane." (Ex. 1011, Piccart-Gebhart at 2-4.) Therefore, a POSA would have been motivated to use paclitaxel or docetaxel as the taxoid in the method of claim 1, and would have had a reasonable expectation of success in doing so. It would therefore have been

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of trastuzumab plus chemotherapy are well underway, with rather reassuring early reports that suggest a low incidence of significant cardiac events." (*Id*., Ex. 1003, Leonard Decl. ¶ 196).

obvious to use paclitaxel or docetaxel as the taxoid in the method of claim 1. (Ex. 1003, Leonard Decl. at ¶ 199.)

iii. *Claim 3*

Claim 3 recites the "method of claim 2, wherein trastuzumab is administered." In 2004, trastuzumab was the only FDA-approved antibody directed to HER2. (*Id.* at ¶ 200.) Thomas describes trastuzumab as "a monoclonal antibody directed against the HER-2/neu receptor." (Ex. 1018, Thomas at 8.) Likewise, Piccart-Gebhart discloses administration of Herceptin® (trastuzumab). No other antibody that interacts with HER2 is mentioned in Piccart-Gebhart or Thomas. (Ex. 1003, Leonard Decl. at ¶ 200.) Therefore, it would have been obvious to use trastuzumab in the method of claim 2. (*Id.*)

iv. *Claim 4*

Claim 4 recites the "method of claim 3, wherein trastuzumab is administered at an initial dose or [sic] 4 mg/kg, followed by subsequent weekly doses of 2 mg/kg." A POSA would have known that this was the standard dosing protocol for trastuzumab in 2004. (*Id.* at ¶ 201; *see also* Ex. 1009, Herceptin 1998 Label at 2 ("The recommended initial loading dose is 4 mg/kg Trastuzumab" and "[t]he recommended weekly maintenance dose is 2 mg/kg Trastuzumab").) Furthermore, three of the four clinical studies described in Piccart-Gebhart, including N9831, used this dosing schedule. (Ex. 1011, Piccart-Gebhart at 2-3.) It would have been

obvious for a POSA to administer the standard dosing regimen of trastuzumab, *i.e.*, an initial dose of 4 mg/kg, followed by weekly doses of 2 mg/kg. (Ex. 1003, Leonard Decl. at ¶ 201.)

v. *Claim 5*

Claim 5 recites the "method of claim 1, wherein the subject has a high risk of cancer recurrence." A POSA would have known that women at high risk of cancer recurrence receive the most benefit from adjuvant therapy. (*Id.* at ¶ 202; Ex. 1018, Thomas at 1, 5.) Furthermore, a POSA would have known that trastuzumab, an antibody that binds to HER2, is primarily indicated for treating HER2-positive breast cancer, and that HER-2 overexpression is associated with poor prognosis. (Ex. 1003, Leonard Decl. at ¶ 202-03; *see also* Ex. 1011, Piccart-Gebhart at 1; Ex. 1018, Thomas at 8.) Piccart-Gebhart also teaches that new adjuvant therapies are needed "particularly for high-risk patient groups," and identifies "HER2-positive patients" as such a group. (Ex. 1011, Piccart-Gebhart at 5.)

The AC→T→H regimen is a method of adjuvant therapy, and these disclosures in Piccart-Gebhart and Thomas, as well as related general knowledge of a POSA in 2005, would have motivated a POSA to use adjuvant therapy in patients with high risk of cancer recurrence. (Ex. 1003, Leonard Decl. at ¶ 204.) Moreover, as discussed above, a POSA would have had a reasonable expectation

of success in doing so. (*Id.*) It would therefore have been obvious to use the method of adjuvant therapy described in claim 1 to treat patients with high risk of recurrence. (*Id.*)

vi. *Claim 6*

Claim 6 recites the "method of claim 5, wherein the subject is less than about 50 years old." A POSA would have known that younger women tend to derive more benefit from adjuvant therapy. (Ex. 1003, Leonard Decl. at ¶ 205.) For example, Thomas teaches that "women younger than 40 derive the greatest reduction in risk of recurrence from systemic polychemotherapy." (Ex. 1018, Thomas at 5.) Thomas further teaches that in patients with ER-positive tumors, the risk reduction from adjuvant chemotherapy relative to patients with ER-negative tumors is much lower in women over 50 years old than in patients younger than 50 years old. (*Id.*) From these teachings, a POSA would have been motivated to use the AC→T→H regimen to treat women less than about 50 years old who have a high risk of cancer recurrence, and would have had a reasonable expectation of success in doing so. (Ex. 1003, Leonard Decl. at ¶ 207.) It therefore would have been obvious to use the AC→T→H regimen for adjuvant therapy in such patients, who could potentially derive greater benefit from the treatment. (*Id.*)

vii. Claim 7

Claim 7 recites the "method of claim 5, wherein the cancer has a tumor greater than 2 centimeters in diameter." A POSA would have known that patients with large tumors are at higher risk of relapse and thus derive more benefit from adjuvant therapy relative to the risks associated with treatment. (*Id.* at ¶ 208.) For example, Thomas teaches that the benefit of adjuvant chemotherapy must be weighed against the potential adverse effects of treatment. (Ex. 1018, Thomas at 11.) For some patients, the risks outweigh the benefits, particularly "those with tumors smaller than 1 cm and negative lymph nodes," and "those with small tumors (< 3 cm) with favorable histological types." (*Id.*) A POSA would also have known that physicians commonly used 2 cm as a cutoff for classifying tumors as indicative of high risk, thereby identifying patients as good candidates for adjuvant therapy. (Ex. 1003, Leonard Decl. at ¶ 208. *See also, e.g.*, Ex. 1031, Clark at 5 (identifying tumors greater than 2 cm as a "bad prognostic factor"); Ex. 1015, Perez at 2 (requiring ER-positive tumors to be more than 2 cm for inclusion in the study). From teachings such as these, a POSA would have known that the benefits of adjuvant chemotherapy would outweigh the risks in patients with tumors larger than 2 centimeters in diameter, and would have been motivated to use the AC→T→H regimen to treat patients with such large tumors and would have had a reasonable expectation of success in doing so. (Ex. 1003, Leonard

Decl. at ¶ 208.) Therefore, it would have been obvious to use the AC→T→H regimen to treat such patients. (*Id.*)

viii. Claim 8

Claim 8 recites the "method of claim 5, wherein the cancer is lymph node-positive." A POSA would have known that lymph node-positive patients are at higher risk of recurrence and thus derive more benefit from adjuvant therapy. (*Id.* at ¶209; *see also* Ex. 1018, Thomas at 11 ("[T]he absolute benefit [of adjuvant chemotherapy] is clearly higher for those with involved axillary lymph nodes.").) Moreover, in three of the four studies described in Piccart-Gebhart, including the N9831 trial, lymph-node positive status was expressly included in the inclusion criteria for the study. (Ex. 1011, Piccart-Gebhart at 2-3.) Based on these teachings, a POSA would have been motivated to use the AC→T→H regimen to treat patients with positive lymph nodes who have a high risk of cancer recurrence, and would have had a reasonable expectation of success in doing so. (Ex.1003, Leonard Decl. at ¶ 209.) It would therefore have been obvious to use the AC→T→H regimen to treat lymph-node positive patients. (*Id.*)

ix. Claims 9 and 10

Claim 9 recites the "method of claim 8, wherein the subject had 4-9 involved lymph nodes." Claim 10 recites the "method of claim 8, wherein the subject had 10 or more involved lymph nodes." As discussed above for claim 8, it would have

been obvious to use the claimed method of adjuvant therapy to treat lymph-node positive patients. A POSA also would have known that a patient's number of positive lymph nodes correlates with greater risk of relapse, and, as discussed above, higher risk patients derive more benefit from adjuvant therapy. (*Id.* at ¶ 210.) A POSA would have also known that patients with 4-9 involved lymph nodes and patients with more than 10 involved lymph nodes have a high risk of cancer recurrence. (*Id.* at ¶ 211.)

Moreover, Piccart-Gebhart discloses that patients in the N9831 study were categorized by number of positive lymph nodes in groups with 1-3 positive nodes, 4-9 positive nodes, and 10 or more positive nodes. (Ex. 1011, Piccart-Gebhart at 3.) From this, a POSA would have known that patients at relatively high risk of cancer recurrence, as reflected in their number of positive nodes, were included in the study. (Ex. 1003, Leonard Decl. at ¶ 212.) Accordingly a POSA would have been motivated to use the use the AC→T→H regimen to treat patients with a high risk of recurrence, such as having 4-9 positive nodes, or 10 or more positive nodes, and would have had a reasonable expectation of success in doing so. (*Id.*) It therefore would have been obvious to use the AC→T→H regimen to treat patients with 4-9 or 10 or more involved lymph nodes. (*Id.*)

x. *Claim 11*

Claim 11 recites the "method of claim 5, wherein the subject's cancer was estrogen receptor (ER) negative." Thomas teaches that adjuvant chemotherapy provides "substantial, durable benefits" irrespective of ER status, thus including patients with ER-negative cancer. (Ex. 1018, Thomas at 11.) Thomas further teaches that in women over 50 years old, patients with ER-negative cancer derive more benefit from adjuvant therapy because the reduction in risk derived was "nearly double for those with ER-negative tumors compared with those with ER-positive tumors." (*Id.* at 5.) Piccart-Gebhart discloses that patients with ER-negative tumors were included in the N9831 study. (Ex. 1011, Piccart-Gebhart at 3.) From these teachings a POSA would have been motivated to use the method of claim 1 in patients with ER-negative cancer, who have a high risk of cancer recurrence, and would have had a reasonable expectation of success in doing so. (Ex. 1003, Leonard Decl. at ¶ 213.) It therefore would have been obvious to use the claimed method of adjuvant therapy to treat patients with ER negative cancer. (*Id.*)

xi. *Claim 12*

Claim 12 recites the "method of claim 5, wherein the subject's cancer was progesterone receptor (PG) negative." Piccart-Gebhart discloses that patients with PR-negative tumors were included in the N9831 study. (Ex. 1011, Piccart-Gebhart

at 3.) A POSA also would have known that patients with progesterone receptor negative tumors are at higher risk of relapse. (Ex. 1003, Leonard Decl. at ¶ 214.) From these teachings a POSA would have been motivated to use the method of claim 1 in patients with progesterone receptor negative cancer, and would have had a reasonable expectation of success in doing so. (*Id.*) It therefore would have been obvious to use the claimed method of adjuvant therapy to treat patients with progesterone receptor negative cancer. (*Id.*)

xii. *Claim 13*

Claim 13 depends from claim 1. Claim 1 recites the step of administering "trastuzumab or an antibody that blocks binding of trastuzumab to HER2." Claim 13 recites further limitations on the "antibody" specified in claim 1, namely that "the antibody is a naked, intact antibody." This claim, however, still encompasses the "trastuzumab" recited in claim 1, and is thus obvious for the same reasons discussed above for claim 3. Moreover, Piccart-Gebhart and Thomas both disclose methods of administering trastuzumab. In 2005, Herceptin® was the only FDA-approved antibody that targeted HER2, and was thus the only available antibody that could have been used in the ways discussed in Thomas and Piccart-Gebhart. (*Id.* at ¶ 215.) Accordingly, claim 13 is unpatentable as obvious.

D. Lack of Secondary Considerations

Petitioner is not aware of any secondary considerations that would support a finding of non-obviousness. Further, even if such secondary considerations exist, they cannot overcome the strong *prima facie* case of obviousness discussed above. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010).

To the extent PO argues that any purported commercial success of Herceptin® is pertinent to patentability, PO will be unable to establish that such purported commercial success is attributable to the claimed regimen. FDA approved Herceptin® in 1998, and it was widely used prior to filing of the application that led to the '897 patent. Furthermore, Herceptin® has numerous uses that are not within the scope of the '897 patent claims, including treatment of metastatic breast cancer, adjuvant use concurrently with a taxoid, adjuvant use in conjunction with other chemotherapy regimens, and treatment of metastatic gastric cancer. (Ex. 1009, Herceptin 1998 label; Ex. 1003, Leonard Decl. at ¶ 217.)

To the extent PO argues long-felt, unmet need, it will be unable to show that any such need was long-felt. FDA approved Herceptin® in 1998 for treatment of metastatic cancer, and as early as 2000, clinical trials were underway for the use of Herceptin® as adjuvant therapy for the treatment of non-metastatic cancer. Therefore, the use of Herceptin® in adjuvant therapy, including in the dosing

regimen claimed in '897 patent, began essentially as soon as it could have and there was insufficient time for any unmet need to become "long-felt."

Petitioner reserves the right to respond to any assertions of secondary considerations that PO alleges during this proceeding.

X. CONCLUSION

For the reasons set forth above, Petitioner respectfully submits that it has established a reasonable likelihood of success with respect to the challenged claims and requests that trial be instituted and the challenged claims cancelled.

Respectfully submitted,

Dated: February 21, 2017

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the attached Petition for *Inter Partes* Review of U.S. Patent No. 8,591,897 contains 13,769 words (as calculated by the word processing system used to prepare this Petition), excluding the parts of the Petition exempted by 37 C.F.R. §42.24(a)(1).

Dated: February 21, 2017

By: /Cynthia Lambert Hardman/
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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that on this 21 day of February, 2017, I served a copy of this PETITION FOR INTER PARTES REVIEW and copies of all supporting materials and exhibits by Federal Express Next Business Day Delivery on the following addresses for patent owner(s) and their representatives:

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