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In the *Inter Partes* Review of:

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Title: ANTI-ERBB2 ANTIBODY ADJUVANT THERAPY Panel: To Be Assigned

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PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 8,591,897
UNDER 35 U.S.C. § 311 AND 37 C.F.R. § 42.100

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1006	<i>Sledge et al.</i> , Pilot Trial of Paclitaxel-Herceptin Adjuvant Therapy for Early Stage Breast Cancer (E2198), 4 General Sessions 209 (2001)
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1011	Piccart-Gebhart et al., Herceptin: The Future in Adjuvant Breast Cancer Therapy, 12 Anti-Cancer Drugs Suppl. 4, S27-S33 (2001)
1012	Romond et al., Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer, 353 N. ENGL. J. MED. 1673 (Oct. 20, 2005)
1013	J. Horton, Trastuzumab Use in Breast Cancer: Clinical Issues, 9 CANCER CONTROL 499-507 (2002)

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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(8) J. CLIN. ONCOL. 1431-1439 (Apr. 15, 2003)
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)
1016	Early-stage breast cancer, NCI Dictionary of Cancer Terms, (Feb. 15, 2017) https://www.cancer.gov/publications/dictionaries/cancer-terms?CdrID=446564
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)
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1020	Herceptin (Trastuzumab) Herceptin® Product Label (Revised Dec. 2001), Physician’s Desk Reference 1399-1402 (2003)
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)
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)

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1032	Piccart-Gebhart et al., Trastuzumab After Adjuvant Chemotherapy in HER2-Positive Breast Cancer, 353 N. ENGL. J. MED. 1659 (Oct. 20, 2005)
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1038	Library of Congress Copyright Record for Devita '01

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1043	Declaration of Amanda Hollis
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I. INTRODUCTION

Petitioner Pfizer, 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 is the “sequential” administration of a taxoid and trastuzumab, as opposed to their concurrent administration. But this was not new. Use of these agents to treat non-metastatic HER2 positive breast cancer—in the exact claimed sequence—was disclosed in the prior art, including Piccart-Gebhart (Ex. 1011) and Perez (Ex. 1015), by 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—disclosing the claimed treatment regimen.

The claimed methods are also obvious. In 1998, the 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. Given the efficacy of trastuzumab in treatment of metastatic cancer, a person of ordinary skill in the art (“POSITA”) 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, rendering obvious the sequential addition of trastuzumab to the established therapy. Indeed, the prior art descriptions of the N9831 trial disclose sequential treatment with trastuzumab. Based on the known effectiveness of trastuzumab in combination with other therapies for treating HER2-positive breast cancer, a POSITA 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))

Pfizer, Inc. (“Pfizer” or “Petitioner”) is the real party-in-interest for Petitioner.

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

Petitioner concurrently files two IPR petitions for claims of the '897 patent. The '897 patent is also the subject of IPR2017-00959. Petitioner is not a party to that proceeding.

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

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

Petitioner designates the following counsel:

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

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

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. PAYMENT OF FEES (37 C.F.R. § 42.103)

The undersigned authorizes the PTO to charge the fee set forth in 37 C.F.R. § 42.15(a) for this Petition to Deposit Account No. 506092. The undersigned further authorizes payment for any additional fees that may be due in connection with this Petition to be charged to the referenced Deposit Account.

VI. SUMMARY OF THE '897 PATENT AND PROSECUTION HISTORY

The '897 patent issued November 26, 2013 from Application No. 11/400,638 ("the '638 application"), filed April 6, 2006. The '638 application claims priority to a May 13, 2005 provisional application. For purposes of this IPR only, Petitioner will assume that the '897 patent claims are entitled to a May 13, 2005 priority date. Therefore, any publication dated prior to May 13, 2005

qualifies as § 102(a) prior art and any publication dated prior to May 13, 2004 qualifies as § 102(b) prior art.

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

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

Claims 9 and 10 (dependent on claim 8) respectively add that the subject had 4–9 or 10 or more involved lymph nodes.

Claim 11 (dependent on claim 5) adds that the cancer was estrogen receptor (ER)-negative. Claim 12 (dependent on claim 5) adds that the cancer was progesterone receptor (PR)-negative.

Claim 13 (dependent on claim 1) 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 adjuvant use of Herceptin[®] in human 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.” (*Id.* at 10:10–19.)

The sole example (Example 1) 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 NSABP B-31 trial and the NCCTG Intergroup N9831 trial. (*Id.* at 62:36–63:9.) 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.)

chemotherapy, followed by sequential administration of paclitaxel and trastuzumab:

Arm B: anthracycline...plus cyclophosphamide...every 3 weeks, for four cycles (q3 w_x4), followed by paclitaxel...for 12 weeks, followed by trastuzumab (4 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, i.e., AC→T→H, as shown above. (Ex. 1003, Lipton Decl., ¶39.) The N9831 trial and the treatment regimens used in that study were disclosed in the prior art.

Although Example 1 reports the interim results of the NCCTG-N9831 and NSABP-31 trials, no results were reported from patients in Arm B of the NCCTG-N9831 trial. (*See* Ex. 1001, 9:39–42 (“Efficacy data in Example 1...excludes the patients from Intergroup who did not start HERCEPTIN[®] simultaneously with TAXOL[®] (arm 2).”); *id.* 63:8–9; Fig. 4B; Ex. 1003, Lipton Decl., ¶41.)

C. Prosecution History

The application leading to the '897 patent contained 44 claims covering various methods for adjuvant breast cancer therapy. (Ex. 1002, File History, Vol. 1 at 104–108.)

In response to a restriction requirement, PO elected claims directed to methods for treating non-metastatic HER2-positive breast cancer. (*Id.* at 194–96.)

In the ensuing years, the Examiner issued five rounds of rejections, including rejecting the original claims and 19 additional claims as obvious or anticipated over prior art disclosing 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 metastatic [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, Vol. 1 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 patients 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 (H).” (Ex. 1002, Vol. 1 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, Vol. 1 at 285.)

No original claim was directed to the “sequential administration of a taxoid and trastuzumab,” let alone sequential administration of a taxoid and trastuzumab

“following AC-based chemotherapy in an adjuvant setting.” (*Id.* at 104–08 (claims).) The PO added claims 64–67, stating that they were supported “at least, in Example 1 and Figures 4A and 4B.” (*Id.* at 5784 (Dec. 23, 2011 Amendment).) Example 1 and these figures refer to the N9831-clinical trial, and contain the same information 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 different from Van Pelt, Sledge, and Gradishar because they did not disclose “sequential” administration of a taxoid and trastuzumab. (*Id.* at 5785–5786.) Likewise, with respect to Gradishar, PO argued it did not disclose the claimed method because:

[a]lthough 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, 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/ <i>neu</i> -positive	AC × 4, P × 4 AC × 4, P × 4 + Hqw × 52
Intergroup (N9831)	3150	Node-positive, HER 2/ <i>neu</i> -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/ <i>neu</i> -positive	AC × 4, T × 4 AC × 4, T × 4 + H × 1 year ^a Plat × 6 + H × 1 year ^a

AC, doxorubicin 60mg/m²; cyclophosphamide 600mg/m² IV every 3 weeks
P, paclitaxel 225 mg/m²
Hqw, trastuzumab 4 mg/kg loading, then 2 mg/kg per week IV
Pqw, paclitaxel 80 mg/m² IV every week
T, docetaxel 100 mg/m² IV every 3 weeks
Plat, cisplatin 75 mg/m² or carboplatin AUC 6
H, Herceptin
^aTrastuzumab given weekly during chemotherapy, then every 3 weeks for 1 year at 6 mg/kg

(Ex. 1007, Gradishar, at 13; Ex. 1003, Lipton Decl., ¶49.) 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×4” (doxorubicin and cyclophosphamide), followed by “Pqw×12” (paclitaxel), followed by “Hqw×52” (trastuzumab). (Ex. 1007, Gradishar, at 13.)

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, Vol. 9 at 5784.) 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, Lipton Decl., ¶51.) 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 are more likely to outweigh the potential risks. (*Id.* at ¶55.)

Development of trastuzumab 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.” (*Id.* 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 2; Ex. 1005, Van Pelt at 5;² Ex. 1003, Lipton Decl., ¶52.) For example, Slamon *et al.*, *Use of Chemotherapy Plus a Monoclonal Antibody Against HER2 for Metastatic Breast Cancer That Overexpresses HER2*, 344 *NEJM* 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, Slamon, at 10.) Both trastuzumab/chemotherapy combinations showed significant improvements in response rates, time to disease progression, and overall survival compared with chemotherapy alone. (*Id.* at 4–5.) 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 9.) Slamon concluded that “trastuzumab, when

² The prior art discusses the use of “taxanes.” (*See, e.g.*, Ex. 1005, Van Pelt at 6; Ex. 1011, Piccart-Gebhart at 6.) “Taxane” and “taxoid” are synonyms. (Ex. 1003, Lipton Decl., at ¶ 200 n.8.)

added to conventional chemotherapy, can benefit patients with metastatic breast cancer that overexpresses HER2.” (*Id.* at 10.) 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 HER2-positive breast cancer patients, who were known to be at high risk of recurrence after surgery, led to the evaluation of trastuzumab as both a “neo-adjuvant” (pre-surgery) and adjuvant (post-surgery) therapy. (Ex. 1003, Lipton Decl., ¶53; Ex. 1005, Van Pelt at 5–6 (discussing rationale for trastuzumab in neo-adjuvant therapy); Ex. 1007, Gradishar, at 12 (“The 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 Piccart-Gebhart *et al.*, *Herceptin: the future in adjuvant breast cancer therapy*, 12 *Anti-Cancer Drugs* S27 (2001) (“Piccart-Gebhart,” Ex. 1011):

“[N]ew 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 5.)

The N9831-clinical study, which began recruiting in 2000, was a phase III trial for women with HER2-positive breast cancer. (*See, e.g., id.* at 9.) Arm B involved administration of AC-based chemotherapy, followed by a taxoid, then Herceptin[®]. (*Id.* at 6.)

Because of the strong performance of trastuzumab in the N9831 study and the parallel NSABP B-31 study, a combined analysis was conducted of the early data from Arms A and C of the N9831 study (placebo and concurrent administration arms) together with data from the NSABP B-31 study; this was disclosed in October 2005. (Romond *et al.*, *Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer*, 353 *NEJM* 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 13.)

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. (*E.g.*, 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 *Catalina Mktg. Int’l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (a preamble limits the invention if “necessary to give life, meaning, and vitality” to the claim). However, a preamble is not limiting “when the claim body describes a structurally complete invention.” *Id.* at 809.

³ Even if the preamble were limiting, the prior art still discloses this additional limitation. (*See, e.g.*, Ex. 1003, Lipton Decl., at ¶ 128–29, 154.)

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.⁴ (Ex. 1003, Lipton Decl., ¶62.) Accordingly, the BRI is that the preamble is not limiting.

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 POSITA, 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, Lipton Decl., ¶64.)

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

⁴ Patent Owner did not rely on the preamble during prosecution to distinguish the claimed invention. *See Catalina Mktg. Int’l, Inc.*, 289 F.3d at 808 (“[R]eliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim limitation.”).

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, Lipton Decl., ¶¶65–66.) The other 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, Lipton Decl., ¶¶66-67.) In contrast, “sequential administration” of a taxoid and trastuzumab refers to administration of a taxoid and trastuzumab in sequence and not concurrently. (*Id.* at ¶¶64, 66.)

This construction is consistent with use of the term “sequential administration” by a POSITA in 2005. (*Id.* at ¶¶67.) For example, Citron *et al.*, *Journal of Clinical Oncology* (2003) (“Citron,” Ex. 1014), details the treatment arms in the CALGB 9741 trial: “The study used a 2 × 2 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 14.) Citron further states that “[s]equential 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):

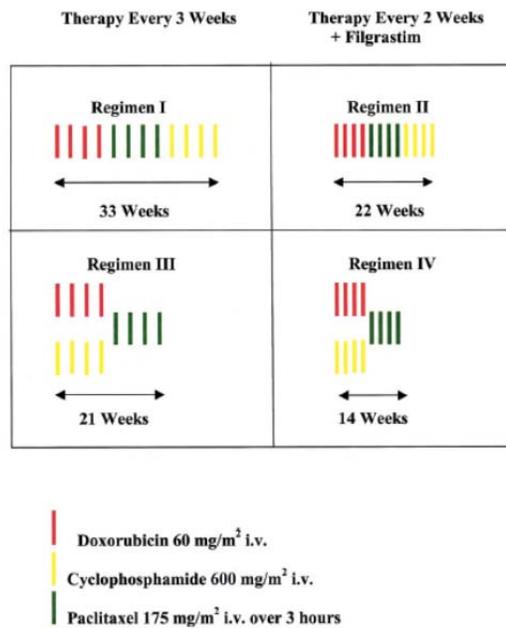


Fig 1. Treatment schema.

(*Id.*; Ex. 1003, Lipton Decl., ¶68.)

The prosecution history 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.”). During prosecution, PO made clear that the term “sequential” excludes “concurrent” administration. (Ex. 1003, Lipton Decl., ¶71; Ex. 1002, File History, Vol. 9 at 5786 (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.)

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, Lipton Decl., ¶¶ 73, 137; Ex. 1011, Piccart-Gebhart at 7; Ex. 1015, Perez, at 7.)

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

“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.” (Ex. 1003, Lipton Decl., ¶82.)

“[H]igh risk of cancer recurrence” is defined as “a greater chance of experiencing recurrence of cancer.” (Ex. 1001 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 POSITA 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, Lipton Decl., ¶¶83, 173.)

“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, Lipton Decl., ¶84.)

“Progesterone receptor (PR) positive cancer” is defined as “cancer which tests positive for expression of PR,” and “PR negative” is defined as “cancer [which] 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, Lipton Decl., ¶85.)

“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.” (*Id.* at 18:4–6.)

IX. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED

Below is a chart including the particular proposed statutory grounds:

Ground	Proposed Statutory Rejections of the '897 Patent
1	Claims 1–5 and 8–13 are invalid under § 102(b) as anticipated by the printed publication Piccart-Gebhart (published in 2001).
2	Claims 1–7 are invalid under § 102(a) as anticipated by the printed publication Perez (published Sept. 15, 2004).
3	Claims 1–13 are invalid under § 103(a) as obvious in view of printed publication Piccart-Gebhart and Thomas (published in 2003).

This petition is supported by the Declaration of Allan Lipton, M.D. (Ex. 1003.) Dr. Allan Lipton is a Professor of Medicine and Oncology at the Milton S. Hershey Medical Center of The Pennsylvania State University, with over 50 years of experience in the medical field and extensive experience in clinical oncology. *See* Ex. 1103 ¶¶4–10. Dr. Lipton has clinical experience prescribing trastuzumab in combination with chemotherapy in the treatment of breast cancer, and participated in the administration of clinical trials that led to FDA approval of the drug. *See id.* ¶¶7, 10.

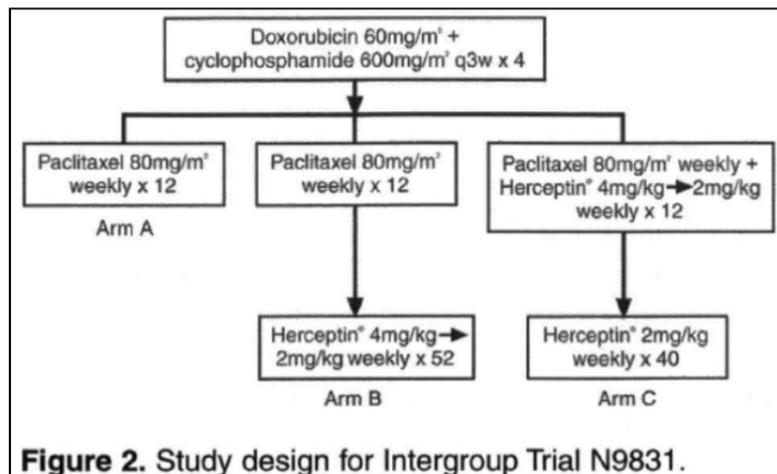
The petition establishes at least a reasonable likelihood that Petitioner will prevail with respect to at least one challenged claim. 35 U.S.C. § 314(a).

**A. Ground 1: Piccart-Gebhart (2001)
Anticipates Claims 1–5 and 8–13**

1. Claim 1

Piccart-Gebhart (2001) summarizes four clinical trials studying Herceptin[®] as adjuvant therapy for breast cancer. (Ex. 1011.) 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 comparing the disease-free survival of HER2-positive breast cancer when treated with doxorubicin/cyclophosphamide followed by paclitaxel with or without Herceptin:



(Ex. 1011, Piccart-Gebhart at 7.) As of May 2001, 242 patients had been enrolled in the trial.⁶ (*Id.*)

a. “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, Lipton Decl., ¶¶128-29.) 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 5–8 (noting that N9831 is a “major adjuvant trial[]”).) Piccart-Gebhart notes that the N9831

⁶ Final results were not reported until after the ’897 patent priority date; however, 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).

trial “will determine the role of weekly paclitaxel in adjuvant breast cancer treatment and the impact of Herceptin® on survival.” (*Id.* at 7. *See also* Section IX.A.1.c, below.)

- b. “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-positive⁷ breast cancer” and that “[p]atients with evidence of metastatic disease...are not eligible.” (*Id.* at 7; Ex. 1003, Lipton Decl., ¶130.) Breast cancer is either metastatic or non-metastatic. (Ex. 1003, Lipton Decl., ¶130) 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, Lipton Decl., ¶81.; Ex. 1001 at 10:30–31.)

⁷ Piccart-Gebhart teaches that only women with “HER-2 positive breast cancer” were enrolled in the N9831 trial. (Ex. 1011 at 7.) Accordingly, Piccart-Gebhart teaches treatment of “HER2 positive” breast cancer. (Ex. 1003, Lipton Decl., ¶130.)

c. “following definitive surgery”

Piccart-Gebhart also discloses that in the N9831 trial, chemotherapy would follow definitive surgery. (Ex. 1003, Lipton Decl., ¶¶131–35.) 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” (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 POSITA’s use of the term “adjuvant” to describe breast cancer treatment as of 2005. (Ex. 1003, Lipton Decl., ¶129; Ex. 1017, Devita *et al.*, *Principles And Practice Of Oncology* (6th Ed. 2001), Vol 1 at 51 (“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 7.) 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.*; *see also* Ex. 1001 at 63:22–25 (“To qualify for [the N9831 trial], patients were required to have invasive breast cancer, resected by either lumpectomy, or total mastectomy, plus axillary dissection, with pathologically involved axillary nodes.”))

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, Lipton Decl., ¶¶133–34.) 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.* ¶133.) Therefore, Piccart-Gebhart discloses a method that includes the claim limitation “following definitive surgery.”

d. “anthracycline/cyclophosphamide
(AC) based chemotherapy”

Piccart-Gebhart discloses that, after definitive surgery, patients would receive “initial treatment with doxorubicin...plus cyclophosphamide...i.v. every 3 weeks for 4 courses.” (Ex. 1011 at 7; Ex. 1003, Lipton Decl., ¶136.) Doxorubicin

is an anthracycline, and therefore doxorubicin plus cyclophosphamide is “anthracycline/cyclophosphamide (AC) based chemotherapy.” (Ex. 1003, Lipton Decl., ¶136.; *see also* Ex. 1001, 7:7–8.)

- e. “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, Lipton Decl., ¶137.) Following AC-based chemotherapy, patients in Arm B would receive “paclitaxel...followed immediately by Herceptin®.” (Ex. 1011 at 7.) This is shown in Figure 2:

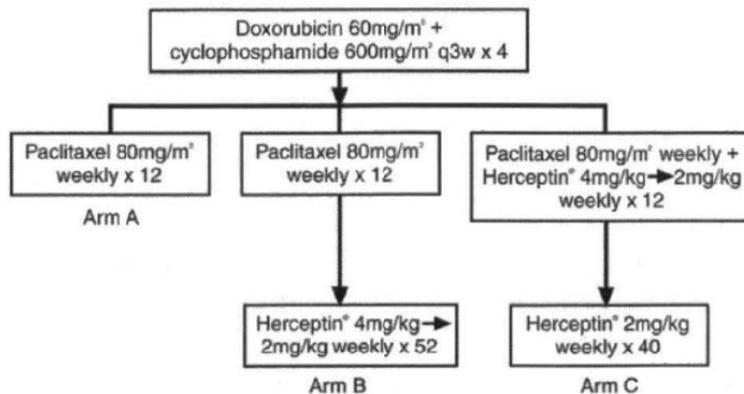


Figure 2. Study design for Intergroup Trial N9831.

(*Id.*) Paclitaxel is a taxoid, i.e., “chemotherapeutic agent that functions to inhibit microtubule depolymerization.” (Ex. 1001 at 26:37–41; Ex. 1003, Lipton Decl., ¶¶78, 38.) The active ingredient in Herceptin® is and was, as of 2001, trastuzumab. (Ex. 1009, Herceptin® Product Label (Sept. 1998); Ex. 1003, Lipton Decl., ¶138.) 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, Lipton Decl., ¶138.)

Furthermore, Piccart-Gebhart is enabling because it describes the claimed methods of treatment with sufficient detail such that a POSITA would be able to carry out the claimed methods. (*Id.* ¶151.) *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 [POSITA] to carry out the invention”). Based on Piccart-Gebhart’s description of the N9831-trial, a POSITA 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 POSITA would also have also known the appropriate dosage and duration of each drug regimen. (Ex. 1003, Lipton Decl., ¶151.)

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

a. 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.* ¶¶140–41.)

b. 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 “4 mg/kg initial dose i.v. followed by 2 mg/kg weekly” for a total of 52 weeks. (Ex. 1011 at 7 and Figure 2; Ex. 1003, Lipton Decl., ¶141.) Accordingly, Piccart-Gebhart anticipates claim 4. (Ex. 1003, Lipton Decl., ¶141.)

c. 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.” (Ex. 1001 at 12:1–2.) Piccart-Gebhart discloses that the N9831 trial was recruiting “node-positive, HER2-positive breast cancer” patients. (Ex. 1011 at 7.) As of 2005, a POSITA would have understood that such patients had a greater chance of experiencing cancer recurrence than patients without these disease characteristics. (Ex. 1003, Lipton Decl., ¶142.) 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 12:1–8; Ex. 1003, Lipton Decl., ¶¶83, 142.) 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 5, 6; Ex. 1003, Lipton Decl., ¶142.)

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 POSITA would know that “node-positive” refers to a patient that is “lymph node-positive.” (Ex. 1011 at 7; Ex. 1003, Lipton Decl., ¶144.)

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 ≥ 10 lymph nodes; and 4) those who had a positive sentinel lymph node but did not undergo complete axillary dissection. (Ex. 1011 at 7.) 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, Lipton Decl., ¶145.) 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.*)

d. 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 7.) Patients were categorized into one of two groups: 1) those who had a positive ER status or positive PR status; and 2) those who were negative for both receptors. (*Id.*; Ex.

1003, Lipton Decl., ¶147.) Patients within each group would then be randomly assigned to each of the treatment groups. (Ex. 1011 at 7; Ex. 1003, Lipton Decl., ¶147.) 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 PR negative.⁸ (Ex. 1003, Lipton Decl., ¶147.) Moreover, such patients had a “high risk of cancer recurrence” as recited in Claim 5 because of their ER and PR receptor negative status and their HER2-positive status. (Ex. 1001 at 12:1–15.) Accordingly, Piccart-Gebhart discloses all elements of claims 11 and 12.

e. Claim 13

Claim 13 recites the “method of claim 1, wherein *the antibody is an intact, naked antibody.*” Reading in the antecedent basis from claim 1 for “the antibody,” claim 13 requires an intact, naked antibody that blocks binding of trastuzumab to HER2. Trastuzumab is an intact, naked antibody that blocks binding of trastuzumab to HER2. (Ex. 1003, Lipton Decl., ¶149.) Moreover, even if trastuzumab was not an antibody with these characteristics, the administration of

⁸ 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, Lipton Decl., ¶ 147.)

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*” an “intact, naked antibody.” Accordingly, for the same reasons discussed above with respect to claims 1 and 3, Piccart-Gebhart anticipates claim 13. (Ex. 1003, Lipton Decl., ¶¶126–38, 148.)

3. 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. (*Id.* at ¶152.)

Claim	Limitation	Support in Piccart-Gebhart (Ex. 1011)
Claim 1	A method of adjuvant therapy comprising	5 (“adjuvant breast cancer therapy”) 6 (N9831 is “major adjuvant trial[.]”) 7 (N9831 trial “will determine the role of weekly paclitaxel in adjuvant breast cancer treatment) <i>see also</i> “following definitive surgery” limitation below
	administering to a human subject with nonmetastatic HER2 positive breast cancer	7 (“patients with evidence of metastatic cancer...are not eligible”) 7 (“HER2-positive breast cancer”)
	following definitive surgery	6 (N9831 is “major adjuvant trial[.]”) 7 (“adjuvant breast cancer treatment;” “operable with either lumpectomy plus irradiation or

Claim	Limitation	Support in Piccart-Gebhart (Ex. 1011)
	<p>anthracycline/cyclophosphamide (AC) based chemotherapy, followed by</p> <p>sequential administration of a taxoid and trastuzumab.</p>	<p>mastectomy;” “axillary dissection;” “positive sentinel node”)</p> <p>7 (“All patients will receive initial treatment with doxorubicin 60 mg/m² plus cyclophosphamide 600 mg/m² i.v. every 3 weeks for 4 courses.”; Figure 2, Arm B)</p> <p>7 (“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.</p>
Claim 2	wherein the taxoid is paclitaxel or docetaxel	7 (“paclitaxel”)
Claim 3	wherein trastuzumab is administered	7 (“trastuzumab”)
Claim 4	wherein trastuzumab is administered at an initial dose of 4mg/kg, followed by weekly doses of 2 mg/kg	7 (“4 mg/kg initial dose i.v. followed by 2 mg/kg weekly”); <i>see also</i> Figure 2, Arm B.
Claim 5	wherein the subject has a high risk of cancer recurrence	5 (“high-risk group”); 6 (“disease recurrence”); 6 (“node-positive, HER2-positive breast cancer”)
Claim 8	wherein the cancer is lymph node-positive	7 (“node-positive”)
Claim 9	wherein the subject had 4–9 lymph nodes	7 (“Before randomization, patients are stratified by number of positive lymph nodes (axillary dissection with 1–3 versus 4–9 versus ≥ 10...”)

Claim	Limitation	Support in Piccart-Gebhart (Ex. 1011)
Claim 10	wherein the subject had 10 or more lymph nodes	7 (“Before randomization, patients are stratified by number of positive lymph nodes (axillary dissection with 1–3 versus 4–9 versus ≥ 10 ...”)
Claim 11	wherein the subject’s cancer was estrogen receptor (ER) negative	7 (“receptor status (ER- or PgR-positive versus other”)
Claim 12	wherein the subject’s cancer was progesterone receptor (PG) negative	7 (“receptor status (ER- or PgR-positive versus other”)
Claim 13	wherein the antibody is an intact, naked body	7 (“trastuzumab”); <i>see also</i> claims 1 and 3

B. Ground 2: Perez (2004) Anticipates Claims 1–7

Perez (2004)⁹ 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 6–7.) Like Piccart-Gebhart, Perez details the treatment regimens administered to patients in

⁹ Perez et al., *Effect of Doxorubicin Plus Cyclophosphamide on Left Ventricular Ejection Fraction in Patients with Breast Cancer in the North Central Cancer Treatment Group N9831 Intergroup Adjuvant Trial*, 22 *J. Clinical Oncology* 3700 (2004) (“Perez” Ex. 1015).

each arm of the N9831 study. Perez discloses each and every limitation of claims 1–7. (*See also* claim chart in Section IX.B.7 below.)

1. Claim 1

a. “A method of adjuvant therapy”

As discussed above, the preamble is not limiting. Nevertheless, Perez discloses the use of trastuzumab in the “N9831 Intergroup Adjuvant Trial.” (Ex. 1015, Perez at 6; Ex. 1003, Lipton Decl., ¶¶61–62. *See also* Section IX.B.1.e, below.)

b. “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 7.) 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, Lipton Decl., ¶157.) This means that Perez teaches treatment of patients with HER2-positive breast cancer.

Perez also discloses that only non-metastatic patients were recruited for the N9831 trial. (Ex. 1003, Lipton Decl., ¶¶155–56.) 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 breast cancer.” (Ex. 1015 at 7.) “Early-stage” breast cancer has not spread beyond the breast and axillary lymph nodes, i.e., is non-metastatic. (Ex. 1003, Lipton Decl., ¶156; *see also* Ex. 1016, NCI Dictionary of Cancer, at 1.) Accordingly, Perez discloses treatment of patients with non-metastatic HER2-positive breast cancer.

c. “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 6–7.) A POSITA 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, Lipton Decl., ¶161.) 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 7.) A POSITA 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, Lipton Decl., ¶162.)

Therefore, Perez discloses a method that includes the claim limitation “following definitive surgery.” (Ex. 1003, Lipton Decl., ¶163.)

d. “anthracycline/cyclophosphamide (AC) based chemotherapy”

Perez discloses that patients in each arm of the N9831 study were treated with “AC (...doxorubicin plus...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 7.) Doxorubicin is an anthracycline, and therefore doxorubicin plus cyclophosphamide is “anthracycline/cyclophosphamide (AC) based chemotherapy.” (Ex. 1003, Lipton Decl., ¶164.)

e. “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, Lipton Decl., ¶¶165–66.) Following AC-based chemotherapy, patients would be randomized into one of three treatment arms. (Ex. 1015 at 7 and 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, Lipton Decl., ¶165.) 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, Lipton Decl., ¶166.) Furthermore, Perez is enabling because it describes the claimed method with sufficient detail such that a POSITA would be able to perform it. (Ex. 1003, Lipton Decl., ¶175; *Impax Labs. Inc.*, 468 F.3d at 1383.) Therefore, Perez anticipates claim 1.

2. 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, Perez discloses the administration of the taxoid “paclitaxel” before administration of “trastuzumab.” Accordingly, Perez anticipates claims 2 and 3. (Ex. 1003, Lipton Decl., ¶168).

3. Claim 4

Claim 4 recites “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.” Perez discloses that patients in Arm B of the N9831-trial would receive trastuzumab at “4 mg/kg loading dose followed by 2 mg/kg/wk for 1 year.” (Ex.

1015, Perez, at 7; Ex. 1003, Lipton Decl., ¶169.) Accordingly, Perez anticipates claim 4. (*Id.*)

4. 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 12:1–2.) 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 7.) Perez also teaches that over half of the N9831 patients were under 50 years old. (*Id.* at 8.) As of 2005, a POSITA would have understood that such patients had a greater chance of experiencing cancer recurrence than patients without these disease characteristics. (Ex. 1003, Lipton Decl., ¶172.) 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 12:2–15; Ex. 1003, Lipton Decl., ¶172.) 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, Lipton Decl., ¶172.) Accordingly, Perez discloses all of the elements of claim 5. (*Id.*) Because Perez also enables a POSITA to perform the steps of claim 5, Perez anticipates this claim. (*Id.* at ¶175.)

5. Claim 6

Claim 6 depends from claim 5, and further adds that “the subject is less than about 50 years old.” Perez discloses that patients over the age of 18 were eligible for the N9831 study. (Ex. 1015 at 7.) 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 8.) As shown in the table, over half of the patients enrolled in the study were less than 50 years old.¹⁰ (Ex. 1003, Lipton Decl., ¶173.)

¹⁰ 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

(continued...)

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” because “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 F.3d at 1379. As noted above, Perez is enabling, including with respect to such subjects. (Ex. 1003, Lipton Decl., ¶173) Accordingly, Perez anticipates claim 6.

6. 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 tumors had to have tumors that were “more than 2.0 cm.” (Ex. 1015 at 7.) 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, Lipton Decl., ¶174.) Moreover, the disclosures in Perez enables claim 7 because it teaches a POSITA to administer the drug regimen

old who had a high risk of cancer reoccurrence. (Ex. 1019, Perez 2011, at 10 Table 1; Ex. 1003, Lipton Decl., ¶ 173 n. 5.)

of claim 1 to patients with tumors greater than 2 centimeters as required in claim 7.

(*Id.* ¶175.) Accordingly, Perez anticipates claim 7 of the '897 patent.

7. Claim Chart: Anticipation of Claims 1–7 by Perez

As charted below, Perez discloses each and every limitation of claims 1–7 of the '897 patent, and therefore anticipates these claims. (Ex. 1003, Lipton Decl., ¶175.)

Claim	Limitation	Perez (Ex. 1015)
Claim 1	A method of adjuvant therapy comprising administering to a human subject with	6 (“adjuvant”)
	Nonmetastatic	7 (“early stage,” “operable”)
	HER2 positive breast cancer	7 (“Patients had to have human epidermal growth factor receptor 2 (HER2) - positive tumors”)
	following definitive surgery	7 (“adjuvant;” “operable;” “axillary node dissection;” “sentinel node biopsy”)
	anthracycline/cyclophosphamide (AC) based chemotherapy followed by	6 (“standard doxorubicin ... plus cyclophosphamide ... followed by”)
	sequential administration of a taxoid and trastuzumab	6 (“weekly paclitaxel for 12 weeks, then weekly trastuzumab for 52 weeks”)
Claim 2	wherein the taxoid is paclitaxel or docetaxel	6 (“paclitaxel”)
Claim 3	wherein trastuzumab is administered	6 (“trastuzumab”)
Claim 4	wherein trastuzumab is administered at an initial dose of 4mg/kg, followed by weekly doses of 2 mg/kg	7 (“4 mg/kg loading dose followed by 2 mg/kg/wk for 1 year.”)

Claim	Limitation	Perez (Ex. 1015)
Claim 5	high risk of cancer recurrence	7 ((HER2)-positive tumors;” “high-risk;” “node positive”)
Claim 6	subject is less than 50 years old	7 (“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	7 (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 9.) This discussion included the following points:

- “[W]omen younger than 40 years derive the greatest reduction in risk of recurrence from systemic poly chemotherapy.” (*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 15.)
- “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 (FAC). (*Id.* at

10–11.) Thomas concludes that there is a consistent benefit from the use of such combinations compared to other chemotherapy options for adjuvant therapy. (*Id.* at 11.) 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 12), 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 13.)

2. Level of Ordinary Skill in the Art

A POSITA 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, Lipton Decl., ¶¶34–35.)

3. Differences Between the Claims and the Prior Art

As set forth above in Section IX.A, Piccart-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 7–8; Ex. 1003, Lipton Decl., ¶¶173–75.)

Thomas teaches these limitations. (Ex. 1003, Lipton Decl., ¶¶180–82.) Thomas teaches that “women younger than 40 years derive the greatest reduction in risk of recurrence from systemic polychemotherapy.” (Ex. 1018 at 9.) 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 15.) 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, Lipton Decl., ¶182.)

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 2004 to derive the most benefit from adjuvant therapy. (Ex. 1003, Lipton Decl., ¶¶108–110; Ex. 1018, Thomas, at 9, 15.) The teachings of Thomas, which reflect general knowledge and common practices in the field at the time, combined with Piccart-Gebhart, render the '897 patent claims obvious. (Ex. 1003, Lipton Decl., ¶¶108, 176)

The claimed methods also would have been obvious to try in view of Piccart-Gebhart and Thomas. (*Id.* ¶183.) A POSITA 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)).

a. Claim 1

A POSITA would have known that trastuzumab was effective for treating HER2-positive metastatic breast cancer in combination with AC- or taxoid-based chemotherapy. (Ex. 1003, Lipton Decl., ¶184; Ex. 1011, Piccart-Gebhart at 5; Ex. 1018, Thomas, at 12.) A POSITA 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 5; Ex. 1003, Lipton Decl., ¶¶185–87.) A POSITA 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, Lipton Decl., ¶¶183, 188–89.)

Because using trastuzumab in the adjuvant setting was the logical next step in the development of trastuzumab, a POSITA 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.*, ¶189.) Thomas teaches that combination chemotherapy regimens were widely used as adjuvant therapy. (*Id.*, ¶190; Ex. 1018, Thomas, at 9–15; *see also* Ex. 1014, Citron, at 13 (“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 POSITA to add trastuzumab to established regimens for adjuvant therapy. (Ex. 1003, Lipton Decl., ¶¶188–92.)

A POSITA would also have known that concurrent anthracycline/cyclophosphamide followed by taxoid treatment (“AC→T”) was in widespread use for adjuvant therapy. (Ex. 1003, Lipton Decl., ¶191; *see also* Ex. 1011, Piccart-Gebhart at 6 (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.*, 56:40–57:40 (identifying patient populations).) A POSITA 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, Lipton Decl., ¶192.)

A POSITA 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 POSITA to try. (*Id.* ¶¶193–94.) Indeed, Piccart-Gebhart discloses that the N9831 clinical trial was underway to test both options. (Ex. 1011, Piccart-Gebhart at 7–9, Fig. 2.)

A POSITA 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, Lipton Decl., ¶194 n.7; Ex. 1009, Herceptin 1998 Label.) A POSITA 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 to eliminate any remaining cancer cells before they multiply is lost.¹¹ (Ex. 1003, Lipton Decl., ¶194 n.7.)

¹¹ In any case, AC→H→T also falls within the claimed regimen of “sequential administration of a taxoid and trastuzumab.”

A POSITA 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.*, ¶193; Ex. 1013, Horton at 7–8.) 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 7.) Therefore, POSITAs 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, Lipton Decl., ¶195.)

A POSITA 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.* ¶196–7.) Trastuzumab was 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.* ¶¶188, 197; *see also, e.g.*, Ex. 1005, Van Pelt at 5; Ex. 1010, Slamon 2001; Ex. 1017, de Vita, Vol. 2 at 166) Based on this knowledge, a

POSITA 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.¹² (Ex. 1003, Lipton Decl., ¶¶197–98.) Indeed, Piccart-Gebhart teaches that considering the prior success of trastuzumab and the typical sequence

¹² Although Thomas notes safety concerns when administering trastuzumab and anthracyclines due to potential cardiotoxicity, a POSITA would have known that the cardiotoxicity arose primarily with the use of trastuzumab and an anthracycline concurrently or in close proximity. (Ex. 1003, Lipton Decl., ¶ 197; *see* Ex. 1013, Horton, at 8, 12.) For example, a POSITA 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 8, 12.) Horton also indicates that “[a]djuvant trials of trastuzumab plus chemotherapy are well underway, with rather reassuring early reports that suggest a low incidence of significant cardiac events.” (*Id.*; Ex. 1003, Lipton Decl., ¶ 197.)

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 6.)

b. Claim 2

Claim 2 recites the “method of claim 1, wherein the taxoid is paclitaxel or docetaxel.” In 2004, paclitaxel and docetaxel were the most commonly used taxoid drugs. (Ex. 1003, Lipton Decl., ¶200.) Indeed, the only two drugs disclosed in the section of Thomas titled “Taxanes” are paclitaxel and docetaxel. (Ex. 1018, Thomas, at 11.) 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 6–8.) Therefore, a POSITA 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 obvious to use paclitaxel or docetaxel as the taxoid in the method of claim 1. (Ex. 1003, Lipton Decl., ¶200.)

c. Claim 3

Claim 3 recites the “method of claim 2, wherein trastuzumab is administered.” As of May 2005, trastuzumab was the only FDA-approved antibody

directed to HER2. (*Id.*, ¶201.) Thomas describes trastuzumab as “a monoclonal antibody directed against the HER-2/neu receptor.” (Ex. 1018, Thomas, at 12.) Likewise, Piccart-Gebhart discloses administration of Herceptin (trastuzumab). No other antibody that interacts with HER2 is mentioned in Piccart-Gebhart or Thomas. (Ex. 1003, Lipton Decl., ¶201.) Therefore, it would have been obvious to use trastuzumab in the method of claim 2. (*Id.*)

d. Claim 4

Claim 4 recites the “method of claim 3, wherein trastuzumab is administered at an initial dose o[f] 4 mg/kg, followed by subsequent weekly doses of 2 mg/kg.” A POSITA would have known that this was the standard dosing protocol for trastuzumab in 2005. (*Id.* ¶202; *see also* Ex. 1009.) Furthermore, three of the four clinical studies described in Piccart-Gebhart, including N9831, used this dosing schedule. (Ex. 1011, Piccart-Gebhart at 6–9.) It would have been obvious for a POSITA 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, Lipton Decl., ¶202.)

e. Claim 5

Claim 5 recites the “method of claim 1, wherein the subject has a high risk of cancer recurrence.” A POSITA would have known that women at high risk of cancer recurrence receive the most benefit from adjuvant therapy. (*Id.*, ¶203; Ex.

1018, Thomas, at 5, 9.) Furthermore, a POSITA 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, Lipton Decl., ¶203–04; *see also* Ex. 1011, Piccart-Gebhart at 5; Ex. 1018, Thomas, at 12.) 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 9.)

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 POSITA in 2005, would have motivated a POSITA to use adjuvant therapy in patients with high risk of cancer recurrence. (Ex. 1003, Lipton Decl., ¶205.) Moreover, as discussed above, a POSITA 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.*)

f. Claim 6

Claim 6 recites the “method of claim 5 wherein the subject is less than about 50 years old.” A POSITA would have known that younger women tend to derive more benefit from adjuvant therapy. (Ex. 1003, Lipton Decl., ¶206.) For example,

Thomas teaches that “women younger than 40 years derive the greatest reduction in risk of recurrence from systemic polychemotherapy.” (Ex. 1018, Thomas, at 9.)

Thomas further teaches that the risk reduction from adjuvant chemotherapy is much lower in women over 50 years old than in patients younger than 50 years old. (*Id.*) From these teachings, a POSITA 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, Lipton Decl., ¶208.) 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.*)

g. Claim 7

Claim 7 recites the “method of claim 5 wherein the subject had a tumor greater than 2 centimeters in diameter.” A POSITA 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.* ¶209.) For example, Thomas teaches that the benefit of adjuvant chemotherapy must be weighed against the potential adverse effects of treatment. (Ex. 1018, Thomas, at 15.) 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 POSITA 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, Lipton Decl., ¶209. *See also, e.g.*, Ex. 1031, Clark at 7 (identifying tumors greater than 2 cm as a “bad prognostic factor”); Ex. 1015, Perez at 7 (requiring ER-positive tumors to be more than 2 cm for inclusion in the study). From teachings such as these, a POSITA 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, Lipton Decl., ¶209.) Therefore, it would have been obvious to use the AC→T→H regimen to treat such patients. (*Id.*)

h. Claim 8

Claim 8 recites the “method of claim 5 wherein the cancer is lymph node-positive.” A POSITA would have known that lymph node-positive patients are at higher risk of recurrence and thus derive more benefit from adjuvant therapy. (*Id.*, ¶210; *see also* Ex. 1018, Thomas, at 15 (“[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 6–7.) Based on these teachings, a POSITA 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, Lipton Decl., ¶210.) It would therefore have been obvious to use the AC→T→H regimen to treat lymph-node positive patients. (*Id.*)

i. 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 POSITA 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.* ¶211.) A POSITA 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.* ¶212.)

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

7.) From this, a POSITA 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, Lipton Decl., ¶213.) Accordingly a POSITA 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.*)

j. 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 15.) 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 9.) Piccart-Gebhart discloses that patients with ER-negative tumors were included in the N9831 study. (Ex. 1011, Piccart-Gebhart at 7.) From these teachings a POSITA 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, Lipton Decl., ¶214.) It therefore would have been obvious to use the claimed method of adjuvant therapy to treat patients with ER negative cancer. (*Id.*)

k. 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 7.) A POSITA also would have known that patients with progesterone receptor-negative tumors are at higher risk of relapse. (Ex. 1003, Lipton Decl., ¶215.) From these teachings a POSITA 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.*)

l. 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 an intact, naked 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 2004, 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.*, ¶216.) Accordingly, claim 13 is 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, Lipton Decl., ¶218.)

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

Petitioner respectfully requests IPR of the Challenged Claims.

* * *

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Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

This Petition complies with the type-volume limitations as mandated in 37 C.F.R. § 42.24, totaling 12,960 words. Counsel has relied upon the word count feature provided by Microsoft Word.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 8,591,897, along with all exhibits and other supporting documents, were served on June 30, 2017, via FedEx Overnight delivery directed to the assignee for the patent and correspondence address as follows:

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