IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the *Inter Partes* Review of: Trial Number: To Be Assigned

U.S. Patent No. 8,591,897

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Inventor(s): John L. Bryant

Assignee: Genentech, Inc.

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

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Mail Stop *Inter Partes* Review
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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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Exhibit No.	**Description**
1101	U.S. Patent No. 8,591,897 (the "'897 patent")
1102	File History of U.S. Patent No. 8,591,897
1103	Declaration of Allan Lipton, M.D.
1103A	Dr. Allan Lipton, Curriculum Vitae and Materials Considered
1104	ClinicalTrials.gov, *Clinical Trial: Combination Chemotherapy With or Without Trastuzumab in Treating Women With Breast Cancer* (archived March 7, 2004), https://web.archive.org/web/20040307143738/http:/clinicaltrials.gov/show/NCT00005970
1105	Tan & Swain, *Ongoing Adjuvant Trials With Trastuzumab in Breast Cancer*, 30(5, Suppl. 16) SEMINARS IN ONCOL. 54–64 (2003) ("Tan")
1106	ClinicalTrials.gov, Background https://clinicaltrials.gov/ct2/about-site/background (Accessed June 10, 2017)
1107	Van Pelt *et al*., *Neoadjuvant Trastuzumab and Docetaxel in Patients with Breast Cancer: Preliminary Results*, 4(5) CLIN. BREAST CANCER 348–53 (2003) ("Van Pelt")
1108	Sledge *et al*., *Pilot Trial of Paclitaxel-Herceptin Adjuvant Therapy for Early Stage Breast Cancer (E2198)*, 69(3) BREAST CANCER RESEARCH AND TREATMENT (Abstracts - General Sessions 4) 209 (2001)
1109	Gradishar *et al*., *Progress in Systemic Adjuvant Therapy of Early-stage Breast Cancer*, 8(4) INT'L. J.CLIN. ONCOL. 239–47 (2003)
1110	Herceptin® (Trastuzumab) Product Label (Sept. 1998), PHYSICIAN'S DESK REFERENCE 1115–17 (2000)
1111	Slamon *et al*., *Use of Chemotherapy Plus a Monoclonal Antibody Against HER2 for Metastatic Breast Cancer that Overexpresses HER2*, 344(11) N. ENGL. J. MED. 783–92 (2001) ("Slamon")
1112	Piccart-Gebhart *et al*., *Herceptin: The Future in Adjuvant Breast Cancer Therapy*, 12(4) ANTI-CANCER DRUGS SUPPL. S27–S33 (2001)
1113	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(18) J. CLIN. ONCOL. 3700–04 (2004) ("Perez 2004")

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1114	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. 1431–39 (2003) ("Citron")
1115	Devita *et al*., PRINCIPLES AND PRACTICE OF ONCOLOGY, 289–304 (Principles of Cancer Management: Chemotherapy), 307–33 (Principles of Cancer Management: Biologic Therapy), 1633–1726 (Cancer of the Breast) (Lippincott, Williams & Wilkins 6th ed. 2001) ("Devita")
1116	Thomas *et al*., New Paradigms in Adjuvant Systemic Therapy of Breast Cancer, 10(1) ENDOCRINE-RELATED CANCER 75–89 (2003)
1117	ClinicalTrials.gov, History, Policies, and Laws https://clinicaltrials.gov/ct2/about-site/history (Accessed June 11, 2017)
1118	Pegram *et al*., *Phase II Study of Receptor-Enhanced Chemosensitivity Using Recombinant Humanized Anti-p185$^{HER2/neu}$ Monoclonal Antibody Plus Cisplatin in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer Refractory to Chemotherapy Treatment*, 16(8) J. CLIN. ONCOL. 2659–71 (1998)
1119	Pegram *et al*., *Phase II Study of Intravenous Recombinant Humanized Anti-p185 HER-2 Monoclonal Antibody (rhuMAb HER-2) Plus Cisplatin in Patients with HER-2/neu Overexpressing Metastatic Breast Cancer*, 14 PROGRAM/PROC. AM. SOC'Y CLIN. ONCOL., 106 (Abstract 124) (1995)
1120	Baselga *et al*., *Phase II Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer*, 14(3) J. CLIN. ONCOL. 737–44 (1996) ("Baselga")
1121	Herceptin® (Trastuzumab) Product Label (2017)
1122	Romond *et al*., *Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer*, 353 N. ENGL. J. MED. 1659-72 (2005) ("Romond")

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Exhibit No.	**Description**
1123	Perez *et al*., *Four-Year Follow-Up of Trastuzumab Plus Adjuvant Chemotherapy for Operable Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: Joint Analysis of Data from NCCTG N9831 and NSABP B-31*, 29(24) J. CLIN. ONCOL. 4491-97 (2011) ("Perez 2011")
1124	Harlow *et al*., Using Antibodies, A Laboratory Manual (Cold Spring Harbor Press), Ch. 1 and 11 (1999) ("Harlow")
1125	Fendly *et al*., *Characterization of Murine Monoclonal Antibodies Reactive to Either the Human Epiderman Growth Factor or HER2/neu Gene Product*, 50(5) CANCER RESEARCH, 1550–58 (1990) ("Fendly")
1126	Vogel *et al*., *Clinical Experience with Trastuzumab (Herceptin)*, 9(6) THE BREAST JOURNAL 452–62 (2003)
1127	Buzdar *et al*., *Significantly Higher Pathologic Complete Remission Rate After Neoadjuvant Therapy With Trastuzumab, Paclitaxel, and Epirubicin Chemotherapy: Results of a Randomized Trial in Human Epidermal Growth Factor Receptor 2–Positive Operable Breast Cancer*, 23(16) J. CLIN. ONCOL.3676-85 (2005)
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1130	Library of Congress Copyright Record for Slamon '01
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Exhibit No.	**Description**
1142	Library of Congress Copyright Record for Buzdar '05

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 (the "Challenged Claims") of U.S. Patent No. 8,591,897 ("'897 patent," Ex. 1101).

II. PRELIMINARY STATEMENT

Genentech argued that the invention claimed by its '897 patent is novel because it requires the "*sequential*" administration of a taxoid and trastuzumab following anthracycline/cyclophosphamide (AC) chemotherapy, as opposed to their concurrent administration. *See* File History of U.S. Patent No. 8,591,897 (Ex. 1102, Vol. 9) at 5785–86. But that same therapy in the exact same sequence was both widely known and overtly obvious before May 2005, the '897 patent's earliest possible priority date.

As explained in Pfizer's concurrently filed petition ("First Filed Petition"), a clinical trial called "N9831" had been widely reported years before Genentech's alleged priority date and included a treatment protocol ("Arm B") that had all of the elements of the '897 patent's claimed method, including the sequential administration of a taxoid and trastuzumab following AC chemotherapy. The elements of the '897 patent's independent claim and many of its dependent claims were all disclosed in their entirety by ***two*** anticipating journal articles, each

disclosing the details of "Arm B." *See* First Filed Petition at 23–46, Ex. 1112[1], Ex. 1113[2]. Worse, Genentech discussed and relied on the very same N9831 clinical trial, including the already-disclosed "Arm B" details, as 35 U.S.C. § 112 support for its claims when it added them to its application. *See* Ex. 1102, Vol. 9 at 5785–86 (new claims 64–67 "are supported, at least, in Example 1 and Figures 4A and 4B"), 5784 (claims 64–67 issued, with additional dependent claims, as claims 1–4 of the '897 patent).

Genentech never brought these critical facts to the PTO's attention during prosecution. In fact, it obfuscated them. Another reference disclosing details of N9831, "Gradisher et al.,"[3] was in front of the PTO during prosecution. Instead of directing the PTO to the portion of Gradisher that disclosed the same "Arm B" of

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[1] Piccart-Gebhart *et al*., *Herceptin: The Future in Adjuvant Breast Cancer Therapy*, 12(4) ANTI-CANCER DRUGS SUPPL. S27–S33 (2001) (Ex. 1112).

[2] 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(18) J. CLIN. ONCOL. 3700–04 (2004) (Ex. 1113).

[3] Gradishar *et al*., *Progress in Systemic Adjuvant Therapy of Early-stage Breast Cancer*, 8(4) INT'L. J.CLIN. ONCOL. 239–47 (2003) (Ex. 1109).

N9831 that corresponds to the current '897 patent claims, Genentech pointed the Examiner to portions of that reference that discussed other, less relevant clinical trials. *Id.* at 5786.

Pfizer now files this second Petition to bring to the Board's attention to *another*, and different, set of invalidating prior art that was not before the PTO when it issued the '897 patent. Apparently unbeknownst to the Examiner of the '897 patent during prosecution, a detailed description of the N9831 trial was available for all to see at least as early as 2004 on the widely popular and preeminent clinical trials ***internet website and database***, Clinicaltrials.gov[4]. ClinicalTrials.gov "was created as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA)" which "required the U.S. Department of Health and Human Services (HHS), through NIH, to establish a registry of clinical trials information for both federally and privately funded trials…to test the effectiveness of experimental drugs for serious or life-threatening diseases or

[4] Clinicaltrials.gov, *Clinical Trial: Combination Chemotherapy With or Without Trastuzumab in Treating Women With Breast Cancer* (archived March 7, 2004), https://web.archive.org/web/20040307143738/http:/clinicaltrials.gov/show/NCT00005970 ("Clinicaltrials.gov") (Ex. 1104).

conditions." Ex. 1106[5] at 2. "The information in the registry was intended for ***a wide audience,*** including individuals with serious or life-threatening diseases or conditions, members of the public, health care providers, and researchers." Ex. 1117[6] at 2. It is a one-stop, go-to reference for nearly all audiences seeking information about the clinical trials that have been or are being conducted using particular drugs, including Herceptin® and other cancer treatments.

Although the Clinicaltrials.gov reference anticipates many of the '897 patent claims, to further distinguish this Petition from its First Filed Petition, Pfizer argues here that it alone or in combination with Tan[7] renders the '897 claims at minimum unpatentable as obvious under 35 U.S.C. § 103. As shown below, despite the prior art, Genentech is attempting through the '897 patent to monopolize a previously-disclosed therapeutic method. There is no evidence of any unexpected property, and no results from Arm B were disclosed in the '897

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[5] ClinicalTrials.gov, Background https://clinicaltrials.gov/ct2/about-site/background (Accessed June 10, 2017).

[6] ClinicalTrials.gov, History, Policies, and Laws https://clinicaltrials.gov/ct2/about-site/history (Accessed June 11, 2017) (Ex. 1117).

[7] Tan & Swain, *Ongoing Adjuvant Trials With Trastuzumab in Breast Cancer*, 30(5, Suppl. 16) SEMINARS IN ONCOLOGY 54–64 (2003) ("Tan") (Ex. 1105).

patent specification. But even if there were, efficacy of the method is inherent in the method itself and would have been expected by a POSITA (*see* Ex. 1103[8] at ¶¶43–44), and clinical data from a known process directed to a known purpose is not patentable.

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))

As mentioned above, Petitioner concurrently files two IPR petitions for claims of the '897 patent. The '897 patent is also the subject of IPR2017-00959, filed by third-party Celltrion, Inc. Petitioner intends to seek joinder of IPR2017-00959 and the First Filed Petition.

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:

[8] Declaration of Allan Lipton, M.D. (Ex. 1103).

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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. FEES

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

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") which was filed on April 6, 2006. The '638 application claims priority to a May 13, 2005 provisional application. For purposes of this IPR only, Petitioner assumes the Challenged Claims are entitled to a May 13, 2005 priority date. Therefore, any publication dated prior to May 13, 2005 qualifies as 35 U.S.C. § 102(a) prior art and any publication dated prior to May 13, 2004 qualifies as 35 U.S.C. § 102(b) prior art.

A. '897 Patent Claims

The '897 patent has 13 claims, of which claim 1 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 7) 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 adds that the antibody recited in the alternative in claim 1 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. 1101 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.

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 62:36–63:8. According to the '897 patent, the N9831 study "enrolled its first patient in June 2000 and has enrolled 3,406 patients to date." *Id*. at 62:40–43. Further, "[t]hese trials evaluated the efficacy of trastuzumab (HERCEPTIN®) as adjuvant therapy for high risk operable breast cancer." *Id*. at 62:45–47. "To qualify for these trials, patients were[] required to have invasive breast cancer, resected by either lumpectomy, or total mastectomy, plus axillary dissection, with pathologically involved axillary nodes." *Id*. at 63:22–25.

"The design of the NSABP B-31 and NCCTG N9831 studies is depicted in FIG. 4A." *Id*. at 62:49–50. Figure 4A shows that patients enrolled in Arm B[9] of the

[9] Arm B is sometimes referred to as Arm II or Arm 2 but each name describes the same N9831-trial arm. *See, e.g.*, Ex. 1103 at ¶ 67; Ex. 1105 ("arm B"); Ex. 1104 ("arm II"); Ex. 1101 at Fig. 4a, 9:36–42 (using "arm 2" and "arm B"

N9831-trial were treated with doxorubicin/cyclophosphamide (AC), followed by paclitaxel (T), followed by trastuzumab (H):[10]

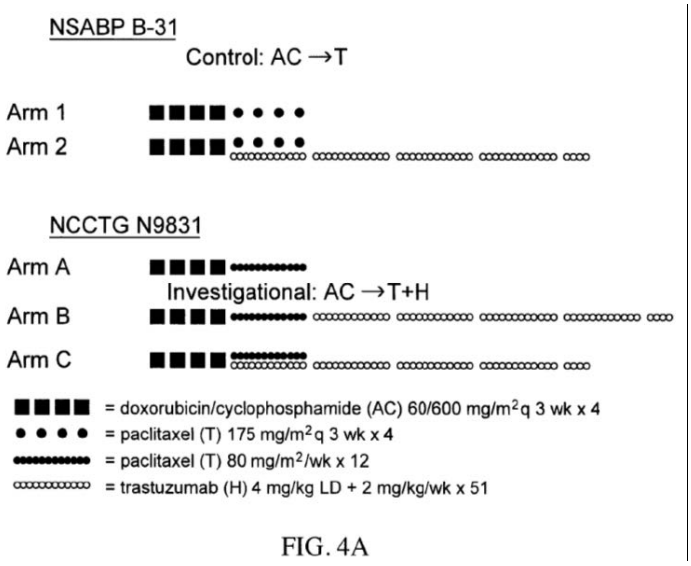

FIG. 4A

Id. at Fig. 4a.[11] In other words, patients in Arm B of N9831 were given

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interchangeably). Likewise, some references refer to Arm A as Arm I or Arm 1, and to Arm C as Arm III or Arm 3. *See id.*

[10] Doxorubicin is an anthracycline. Ex. 1103 at ¶¶ 13 (n.2), 39; Ex. 1101 at 9:1–3. An anthracycline (A) plus cyclophosphamide (C) is often abbreviated as "AC". Ex. 1103 at ¶ 13 (n.2); Ex. 1101 at 6:18–19. Paclitaxel is a taxoid (T). *See* Ex. 1103 at ¶ 13 (n.3); Ex. 1101 at 26:37–41.

[11] Although Fig. 4a says "Investigational: AC→T+H" above Arm B, this shorthand does not accurately describe what is shown in Fig. 4a for Arm B. Ex. 1103 at ¶59. POSITAs often denote concurrent use of drugs, for example concurrent use of drugs X and Y, as "XY" or "X+Y". *Id*. Sequential use of X

"anthracycline/cyclophosphamide (AC) based chemotherapy, followed by sequential administration of a taxoid and trastuzumab," *i.e.*, AC→T→H, as recited in independent claim 1.

The specification provides further details on each treatment arm in the N9831-trial. These details confirm patients in Arm B were given "anthracycline/cyclophosphamide (AC) based chemotherapy, followed by sequential administration of a taxoid and trastuzumab":

> Arm B: anthracycline…plus cyclophosphamide…every 3 weeks, for four cycles (q 3 wkx4), ***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.[12] That is, in Arm B, AC-based chemotherapy was administered

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and Y, on the other hand, can be expressed as "X→Y". *Id* at ¶60. Fig. 4a shows doxorubicin/cyclophosphamide were administered, followed by paclitaxel (alone), followed by trastuzumab (alone) in Arm B. A POSITA would have abbreviated this as AC→T→H. *Id*. Patients in Arm C were administered doxorubicin/cyclophosphamide, then paclitaxel and trastuzumab at the same time, and then trastuzumab (alone). A POSITA would have abbreviated this as AC→TH→H or A+C→T+H→H. *Id* at ¶61.

[12] All emphasis is added unless otherwise noted.

first, followed by paclitaxel, and then trastuzumab, *i.e*., AC→T→H. Ex. 1103 at ¶73. As discussed further in Section X below, the details of N9831 reported in the '897 patent specification were widely disclosed in the prior art years before Genentech filed their application. *See, e.g.*, Ex. 1104 at 4–7; Ex. 1105 at Table 1, 9–10; Ex. 1109 at Table 5; Ex. 1112 at 7; Ex. 1113 at 6–10.

Although Example 1 of the '897 patent reports interim results of Arms A and C of the N9831 trial and of the NSABP-31 trial, ***no results*** are reported in the '897 patent from patients ***in Arm B*** of the N9831-trial. *See* Ex. 1101 at 9:39–42 ("Efficacy data in Example 1…***excludes the patients from Intergroup [N9831] who did not start HERCEPTIN® simultaneously with TAXOL® (arm [B]***)."), 63:8–9, Fig. 4B.

C. Prosecution History

The application leading to the '897 patent contained 44 original claims covering methods for adjuvant breast-cancer therapy. Ex. 1102, Vol. 1 at 104–08. In response to a restriction requirement, Genentech elected claims directed to methods for treating nonmetastatic 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. 1107), which the Examiner stated "teaches a method of treating women with locally advanced breast cancer or primary breast cancer with our [*sic*] 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. 1102, Vol. 1 at 211);
>
> ***Sledge 2001*** (Ex. 1108), which the Examiner stated teaches 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." (Ex. 1102, Vol. 1 at 283); and
>
> ***Gradishar 2003*** (Ex. 1109), which the Examiner stated teaches that "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. 1102, Vol. 1 at 285).

No original claim was directed to the "sequential administration of a taxoid and trastuzumab." *Id.* at 104–08 (claims).

During prosecution, Genentech added new claims 64–67, stating that they were supported "at least, in Example 1 and Figures 4A and 4B." *Id.* at 5784, Vol. 8 (Dec. 23, 2011 Amendment). As mentioned above, Example 1 and these figures refer to the N9831-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.

Genentech 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. With respect to Gradishar, Genentech said 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 trastuzumab following AC-based chemotherapy in an adjuvant setting.***

Id. at 5786.

Notably, Genentech 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—including Arm B 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/*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. 1109 at 13; *see also* Ex. 1103 at ¶73. That is, the second treatment arm (Arm B) 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×12" (trastuzumab), *i.e.*, AC→T→H. *See id*; *see also* Ex. 1109 at 13 ("The Intergroup trial randomizes patients with node-positive breast cancer, to weekly paclitaxel, after AC alone or with trastuzumab, weekly for 52 weeks, starting either concomitantly or after paclitaxel.").

Although the N9831-trial referenced in Gradishar is ***the same trial that Genentech relied on as § 112 support for its claims to "sequential administration of a taxoid and trastuzumab***," Genentech still represented to the Examiner that "Gradishar has no teaching or disclosure of sequential administration of a taxoid and trastuzumab." Ex. 1102, Vol. 9 at 5784, 5786. In short, the '897 patent issued

because Genentech 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. 1103 at ¶36. 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 treatment options, so for these patients the potential benefits are more likely to outweigh the potential risks. *Id*. at ¶45.

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). *See* Ex. 1110[13] at 4, 6; Ex. 1113 at 9. 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. 1107 at 5. HER2 protein overexpression is observed in 25–

[13] Herceptin® (Trastuzumab) Product Label (Sept. 1998), PHYSICIAN'S DESK REFERENCE 1115-17 (2000) (Ex. 1110).

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 benefit from trastuzumab treatment. *Id*.; *see also* Ex. 1105 at 6.

By 2005, Herceptin® had been used in combination with various chemotherapeutic agents, including taxoids and anthracyclines. *See, e.g., id.*; Ex. 1107[14] at 5; Ex. 1111[15] at 2; *see also* Ex. 1103 at ¶¶39–41. For example, Slamon reports the results of a phase 3 study of trastuzumab in combination with paclitaxel or anthracycline and cyclophosphamide (i.e., AC) to treat HER2-positive metastatic breast cancer. Ex. 1111 at 2-3. 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

[14] The prior art discuss the use of "taxanes." *See, e.g.*, Ex. 1107 at 6; Ex. 1112 at S28. "Taxane" and "taxoid" are synonyms. Ex. 1103 at ¶ 40, n. 11.

[15] Slamon *et al*., *Use of Chemotherapy Plus a Monoclonal Antibody Against HER2 for Metastatic Breast Cancer that Overexpresses HER2*, 344(11) N. ENGL. J. MED. 783–92 (2001) ("Slamon") (Ex. 1111).

of this magnitude in association with the addition of a single agent." *Id*. at 9. Slamon concluded that "trastuzumab, when 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 with chemotherapy 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 a high risk of recurrence after surgery, led to the evaluation of trastuzumab as both a "neo-adjuvant" (pre-surgery) and adjuvant (post-surgery) therapy. *See* Ex. 1103 at ¶42; Ex. 1105 at 5 ("Given its proven efficacy in the metastatic setting, the combination and sequential use of trastuzumab with adjuvant and neoadjuvant chemotherapy are the focus of several ongoing clinical studies."); Ex. 1107 at 5–6 (discussing rationale for trastuzumab in neo-adjuvant therapy); Ex. 1109 at 12 ("The rationale for the [adjuvant] trials is based on preclinical synergy between chemotherapy and trastuzumab and the clinical findings from the pivotal combination trial in metastatic breast cancer").

As mentioned above, POSITAs were encouraged that adjuvant use of trastuzumab would be successful. *See* Ex. 1103 at ¶¶43–44; Ex. 1112 at 5–6; Ex. 1116 at 15; Ex. 1109 at 12; Ex 1126 at 10; Ex. 1127 at 12. For example, according

to Tan, "[t]he testing of trastuzumab in the adjuvant setting is currently in progress, given the demonstration of survival benefit with trastuzumab and chemotherapy in advanced-stage disease, and the observation of poorer outcomes in patients with HER2-positive breast cancer." Ex. 1105 at 5. Further, "[f]or now, the use of trastuzumab as adjuvant therapy…has ***tremendous potential*** to improve treatment outcomes in patients with primary breast cancer." Ex. 1105 at 5.

The N9831 clinical trial started in May of 2000. *Id.* at 6, Table 1. N9831 was a "major adjuvant trastuzumab trial" and "[o]nly patients whose tumors overexpress the HER2 protein or have HER2 gene amplification" were eligible. *Id.* at 6–7. N9831 was a "three-arm trial with an accrual goal of 3,000 HER2-positive, node-positive patients." *Id.* at 9; *see also* Ex. 1104 at 5.

All patients in the N9831-trial received "four cycles of AC." Ex. 1105 at 9; *see also* Ex. 1104 at 5. Patients were then randomized into one of three treatment arms:

- **Arm A [AC→T]**: weekly paclitaxel (80 mg/m^2) for 12 weeks
- **Arm B [AC→T→H]**: weekly paclitaxel (80 mg/m^2) for 12 weeks ***followed by*** weekly trastuzumab (4 mg/kg loading dose, followed by 2 mg/kg/week) for 1 year

- **Arm C [AC→TH→H]**: weekly paclitaxel (80 mg/m^2) for 12 weeks and weekly trastuzumab (4 mg/kg loading dose, followed by 2 mg/kg/week) for 1 year initiated concurrently with paclitaxel

See Ex. 1105 at 9–10; Ex. 1104 at 5. Arm B, therefore, involved administration of AC-based chemotherapy, followed by a taxoid, and then trastuzumab.

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.[16] *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.

Each claim recites administering:

[16] Even if the preamble were limiting, the prior art still discloses this additional limitation. *See* Section X.B.1(a) (ground 1, claim 1, element (a)).

"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 therefore provides a complete description of a method, and the preamble phrase does not affect the method steps. *See* Ex. 1103 at ¶¶25–26. Accordingly, 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. 1103 at ¶27.

The '897 patent supports this construction. 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. 1101 at 6:27–31. The two "sequential" regimens in CALGB 9741 involved administration of anthracycline (A) alone, followed by paclitaxel (T) alone, followed by cyclophosphamide (C) alone. *Id*.; Ex. 1103 at ¶28. The other two regimens involved administration of anthracycline (A) and cyclophosphamide (C) together (i.e., "AC"), and are not described as "sequential."

The specification of the '897 patent defines "concurrently" as "administration of two or more therapeutic agents, where at least part of the administration overlaps in time." Ex. 1101 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). *See* Ex. 1103 at ¶¶28–29. In contrast, therefore, "sequential administration" of a taxoid and trastuzumab refers to administration of a taxoid and trastuzumab in sequence and not concurrently. *Id*. at ¶28.

Additionally, this construction is consistent with use of the term "sequential administration" by a POSITA in 2005. *Id*. at ¶29. For example, Citron[17] details the

[17] 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. 1431–39 (2003) (Ex. 1114) ("Citron").

treatment arms in the CALGB 9741 trial as follows:

> 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. 1114 at 14. Further, Citron states that "sequential therapy refers to the ***application of treatments one at a time rather than concurrently***." *Id*. Like Genentech's description of the CALGB 9741 trial, Citron Figure 1 shows that two of the treatment regimens used sequential administration (Regimens I and II) and two used concurrent administration (Regimens III and IV):

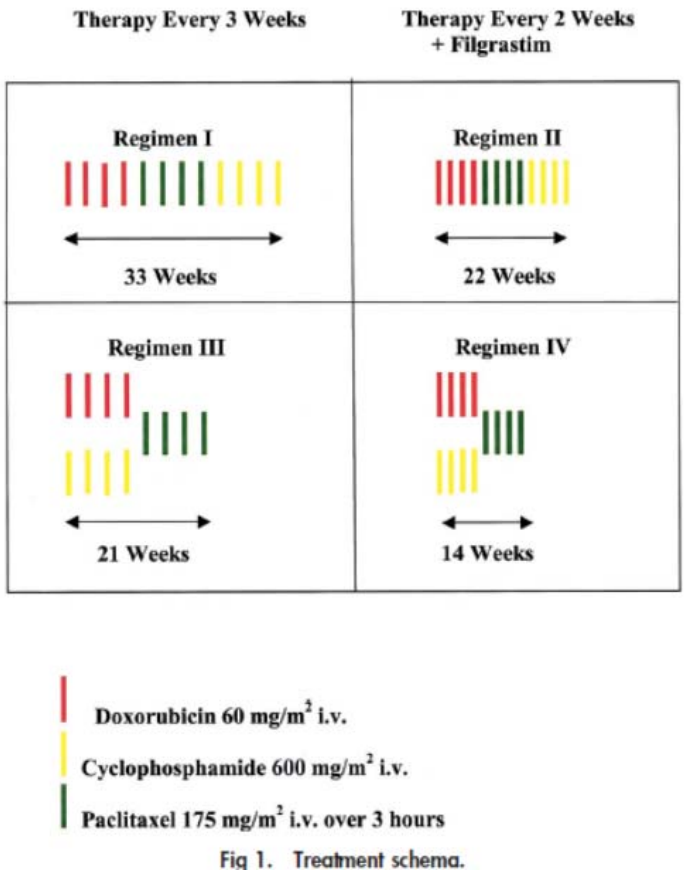

Fig 1. Treatment schema.

Id.; *see also* Ex. 1103 at ¶29.

The prosecution history also supports this construction as Genentech made clear that the term "sequential" excludes "concurrent" administration. *See* Ex. 1102, 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."[18]

IX. LEVEL OF ORDINARY SKILL

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. *See* Ex. 1103 at ¶¶12–15.

[18] Even if the term does not exclude concurrent administration, the prior art discloses "sequential administration of a taxoid and trastuzumab" because Arm C of N9831 teaches concurrent administration of a taxoid and trastuzumab. *See* Ex. 1103 at ¶61; Ex. 1104 at 5; Ex. 1105 at Fig. 3.

X. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED

The '638 application was filed on April 6, 2006. Because the application was filed before March 16, 2013, this Petition is governed by pre-AIA 35 U.S.C. §§ 102 and 103.[19] *See* MPEP 2159.01. Pursuant to 37 C.F.R. §§ 42.104(b)(1) and (2), Petitioner requests review of the Challenged Claims on the following grounds:

Ground	Proposed Statutory Rejection of the '897 Patent
1	Claims 1–3 and 5–13 are invalid under 35 U.S.C. § 103(a) as obvious in view of: **Clinicaltrials.gov** (archived March 7, 2004).
2	Claim 4 is invalid under 35 U.S.C. § 103(a) as obvious in view of: **Clinicaltrials.gov** (archived March 7, 2004) and **Tan** (published October 2003).

The cited prior art is as follows:

- **Clinicaltrials.gov:** An archived page describing the N9831 study from the National Institutes of Health's Clinicaltrials.gov website is attached as Exhibit 1104. Clinicaltrials.gov is a printed publication that was accessible to the relevant public more than one year prior to the claimed priority date. Clinicaltrials.gov was published in the Clinicaltrials.gov database of the

[19] References to 35 U.S.C. §§ 102 and 103 throughout this Petition are to the pre-AIA versions of those provisions.

National Library of Medicine and National Institutes of Health, and archived by The Internet Archive on March 7, 2004 (as authenticated by the affidavit of Christopher Butler, Ex. 1104 at 1–2). An electronic publication such as an on-line database or Internet publication is considered to be a "printed publication" within the meaning of 35 U.S.C. 102(a) and (b) so long as the "publication was accessible to persons concerned with the art to which the document relates." MPEP 2128. Further, "[p]rior art disclosures on the Internet or on an on-line database are considered to be publicly available as of the date the item was publicly posted." *Id.* Thus, Clinicaltrials.gov is prior art to the '897 patent claims under 35 U.S.C. § 102(b). *See also Mylan Laboratories v. Aventis Pharma S.A.*, IPR2016-00712, Paper 9 (September 22, 2016) (instituting IPR based, in part, on an archived clinicaltrials.gov page supported by an affidavit from The Internet Archive).

- **Tan:** Tan is a printed publication that was accessible to the public more than one year prior to the claimed priority date (i.e., Tan is § 102(b) prior art because it was published in October 2003).

As noted previously, Petitioner concurrently files two IPR petitions for claims of the '897 patent. These petitions are not duplicative and raise distinct proposed statutory grounds for the reasons provided in Section II.B.

Below is a detailed explanation of the statutory grounds for the

unpatentability of each of the Challenged Claims that identifies examples of where each element can be found in the cited prior art and the relevance of that prior art.

Additional evidence is provided in the accompanying Declaration of Allan Lipton, M.D. (Ex. 1103). 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. Dr. Lipton was a POSITA at the time of the alleged invention. *Id.* at ¶15.

A. Statement of the Law

A patent claim is invalid under 35 U.S.C. § 103(a) if the differences between the patented subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the pertinent art. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007). In addition, "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or

her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *See id*. at 421.

B. Ground 1: Claims 1–3 and 5–13 Are Invalid Under 35 U.S.C. § 103 as Obvious in View of Clinicaltrials.gov

Clinicaltrials.gov (archived on March 7, 2004) describes the N9831 adjuvant trial design. It teaches that the N9831-trial involved randomizing patients into one of three treatment arms. Patients were stratified among the three arms according to nodal status and receptor status. Ex. 1104 at 5. In one arm (Arm B), patients were administered anthracycline/cyclophosphamide (AC) chemotherapy followed by sequential paclitaxel and trastuzumab (i.e., AC→T→H). *Id*.

Clinicaltrials.gov also describes some requirements for patients to enroll in the N9831-trial. For example, patients had to be 18 years of age or older and have HER-2 positive breast cancer. *Id*. at 5-6. In addition, the N9831-trial was recruiting patients with "[n]ode-positive disease" as well as those with "[h]igh-risk node-negative disease." *Id*. at 4.

1. Claim 1

As discussed below, claim 1 is invalid under § 103 as obvious in view of Clinicaltrials.gov.

(a) "A method of adjuvant therapy"

The preamble is not limiting. *See* Section VIII.A. Accordingly, Clinicaltrials.gov does not need to teach "a method of adjuvant therapy."

Nonetheless, Clinicaltrials.gov discloses that the clinical trial is "adjuvant therapy." *See* Ex. 1104 at 4. Therefore, Clinicaltrials.gov teaches a method of adjuvant therapy.

(b) "administering to a human subject with nonmetastatic HER2-positive breast cancer"

Clinicaltrials.gov also discloses "administering to a human subject with nonmetastatic HER-2 positive breast cancer." Clinicaltrials.gov states that "HER-2 positive" is a required "disease characteristic[]" for human patients enrolling in the N9831-trial. *See* Ex. 1104 at 4–5. Further, one of the objectives of the N9831-trial was to "[c]ompare the disease-free survival of women with ***HER-2-overexpressing*** node-positive or high-risk node-negative breast cancer treated with doxorubicin plus cyclophosphamide followed by paclitaxel with or without trastuzumab (Herceptin)." *Id.* at 4. A POSITA would have known that "HER-2 overexpressing" is synonymous with "HER-2 positive." Ex. 1103 at ¶38, fn. 8.

Clinicaltrials.gov also teaches patients enrolled in N9831 had nonmetastatic disease. Breast cancer is either metastatic or nonmetastatic, based on whether or not detectable cancer cells have spread beyond the primary tumor and nearby lymph nodes. *Id.* at ¶36. Clinical trials of new cancer drugs usually begin in metastatic setting and move to the nonmetastatic/adjuvant setting once proven efficacious in the metastatic setting. Indeed, this is what happened with trastuzumab. *See Id.* at ¶45.

As discussed in Section X.B.1(a) (ground 1, claim 1, element (a)) above, N9831 is an adjuvant trial. Adjuvant therapy is ***only*** given to patients with no evidence of metastatic disease (i.e., patients with nonmetastatic disease). *See Id.* at ¶63. Therefore, the patients in N9831 had nonmetastatic HER2-positive breast cancer. *Id.* Clinicaltrials.gov thus teaches "administering to a human subject with nonmetastatic HER-2 positive breast cancer."

(c) "following definitive surgery"

Clinicaltrials.gov teaches that the N9831-trial is adjuvant therapy. *See* Section X.B.1(a) (ground 1, claim 1, element (a)); Ex. 1104 at 4. Although Clinicaltrials.gov does not specifically use the words "definitive surgery," this limitation would have at least been obvious based on the well-understood definition of adjuvant therapy, which is expressly taught by the prior art and the '897 patent, as meaning following surgery. *See* Ex. 1103 at ¶¶63–64, 65; Ex. 1101 at 10:11–13 (defining "Adjuvant therapy" 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. 1115[20], Vol. 1 at 51 ("Adjuvant chemotherapy

[20] Devita *et al*., PRINCIPLES AND PRACTICE OF ONCOLOGY, 289–304 (Principles of Cancer Management: Chemotherapy), 307–33 (Principles of Cancer Management: Biologic Therapy), 1633–1726 (Cancer of the Breast) (Lippincott, Williams & Wilkins 6th ed. 2001) (Ex. 1115) ("DeVita").

denotes the use of systemic treatment after the primary tumor has been controlled by an alternative modality, such as surgery and radiation therapy."). Since N9831 was adjuvant therapy, patient enrollment in N9831 would have necessarily followed definitive surgery. *See* Ex. 1103 at ¶¶63–64.

Further, ClinicalTrials.gov teaches patients must have "[n]o more than 84 days since prior mastectomy or axillary or sentinel node dissection," and that "[p]atients are stratified according to nodal status." Ex. 1104 at 5–6. Mastectomy (removal of the whole breast), axillary dissection (removal of axillary lymph nodes), and sentinel node dissection (removal of any positive sentinel nodes) are examples of definitive surgery. *See* Ex. 1103 at ¶52; Ex. 1101 at 10:20–24 ("'Definitive surgery' refers to complete removal of tumor and surrounding tissue as well as any involved lymph nodes. Such surgery includes lumpectomy, mastectomy, such as total mastectomy plus axillary dissection, double mastectomy, etc.") For these reasons, Clinicaltrials.gov teaches "following definitive surgery." *See also* Ex. 1101 at t 63:22–25 (admitting that to qualify for N9831, "patients were[] required to have invasive breast cancer, resected by either lumpectomy, or total mastectomy, plus axillary dissection, with pathologically involved axillary nodes.")

This limitation would also have been obvious to a POSITA and/or arrived at through routine experimentation because the patients in N9831 had ***operable***

cancer. Ex. 1104 at 5 ("Histologically confirmed ***operable*** adenocarcinoma of the breast."). Indeed, any regimen that did not perform definitive surgery on an operable breast cancer patient prior to adjuvant therapy would have been unethical and contrary to the goals of the clinical trial. Ex. 1103 at ¶64.

(d) "anthracycline/cyclophosphamide (AC) based chemotherapy"

Clinicaltrials.gov teaches N9831 involved randomizing patients into three treatment arms. Ex. 1104 at 4. In Arm A [AC→T]:

> Patients receive doxorubicin IV and cyclophosphamide IV over 20–30 minutes on day 1. Treatment repeats every 3 weeks for 4 courses. Patients then receive paclitaxel IV over 1 hour beginning on day 1 of week 13 and continuing weekly for 12 courses in the absence of disease progression or unacceptable toxicity.

Id. In Arm B [AC→T→H]:

> Patients receive ***doxorubicin, cyclophosphamide, and paclitaxel as in arm I***. Patients ***then receive trastuzumab (Herceptin®)*** IV over 30–90 minutes beginning on day 1 of week 25 and continuing weekly for 52 courses in the absence of disease progression or unacceptable toxicity.

Id. In Arm C [AC→TH→H]:

> Patients receive doxorubicin and cyclophosphamide as in arm I. Patients then receive paclitaxel IV over 1 hour and trastuzumab IV

> over 30–90 minutes beginning on day 1 of week 13 and continuing weekly for 12 courses. Patients then receive trastuzumab IV over 30 minutes beginning on day 1 of week 25 and continuing weekly for 40 courses in the absence of disease progression or unacceptable toxicity.

Id.

Doxorubicin is an anthracycline, and therefore doxorubicin plus cyclophosphamide is "anthracycline/cyclophosphamide (AC) based chemotherapy." Ex. 1103 at ¶39; *see also* Ex. 1101 at 7:7–9 ("following anthracycline (doxorubicin)/cyclophosphamide (AC) chemotherapy.") As patients in all three arms of N9831 received doxorubicin and cyclophosphamide together, all trial participants received "anthracycline/cyclophosphamide (AC) based chemotherapy," and Clinicaltrials.gov teaches the same.

(e) "sequential administration of a taxoid and trastuzumab or an antibody that blocks binding of trastuzumab to HER2"

Clinicaltrials.gov teaches that patients in Arm B of N9831 received sequential administration of a taxoid (paclitaxel) and trastuzumab [AC→T→H]. As discussed above in Section X.B.1(d) (ground 1, claim 1, element (d)), patients in arm B received "doxorubicin, cyclophosphamide, and paclitaxel as in arm [A]. Patients ***then receive[d]*** trastuzumab (Herceptin) IV over 30–90 minutes beginning on day 1 of week 25 and continuing weekly for 52 courses." Ex. 1104 at 5.

Paclitaxel is a taxoid, i.e., a "chemotherapeutic agent that functions to inhibit

microtubule depolymerization." Ex. 1101 at 26:37–41; *see also id.* at claim 2 ("wherein the taxoid is paclitaxel"); Ex. 1103 at ¶40. Accordingly, Clinicaltrials.gov also discloses "sequential administration of a taxoid and trastuzumab."

For these reasons, Clinicaltrials.gov renders obvious claim 1. Further, a POSITA would have had a reasonable expectation of success in performing the method of claim 1 because trastuzumab had been successfully used in combination with taxoids as well as anthracycline/cyclophosphamide (AC) based chemotherapy and a POSITA would have known that the claimed regimen had been given to patients in N9831 since 2000. *See* Ex. 1103 at ¶66.

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 in Section X.B.1 (ground 1, claim 1), Clinicaltrials.gov renders obvious claim 1. Further, Clinicaltrials.gov discloses the administration of the taxoid "paclitaxel" before administration of "trastuzumab" in Arm B of N9831. Ex. 1104 at 5; *see also* Section X.B.1(e) (ground 1, claim 1, element (e)). Accordingly, claims 2 and 3 are also obvious in view of Clinicaltrials.gov.

3. Claims 5–10

Claim 5 recites the "method of claim 1, wherein the subject has a high risk of cancer recurrence." As discussed above in Section X.B.1 (ground 1, claim 1), Clinicaltrials.gov renders obvious claim 1. Further, Clinicaltrials.gov teaches that patients must have HER2 positive and either (1) "node-positive" or (2) "high-risk node negative" breast cancer. Ex. 1104 at 4.

As of 2005, a POSITA would have known patients with HER2 positive cancer have a high risk of cancer recurrence. Ex. 1103 at ¶42; *see also* Ex. 1101 at 12:1–8 (providing HER2-positive as an example of patients with a "high risk of cancer recurrence."). A POSITA would have also known that a patient with a node-positive tumor had a high risk of cancer recurrence. Ex. 1103 at ¶¶55–56; *see also* Ex. 1101 at 12:1–4 (providing "those with positive lymph nodes ['node-positive']" as an example of patients with a "high risk of cancer recurrence."). Additionally, a POSITA would have known that a patient with a "high-risk node negative breast cancer" had a high risk of cancer recurrence. Ex. 1103 at ¶¶55–56, 70; Ex. 1101 at 12:1–15. Therefore, Clinicaltrials.gov teaches that patients in the N9831 clinical trial had a high risk of cancer recurrence, and thus teaches "wherein the subject has a high risk of cancer recurrence."

Claims 6–10 each depend from claim 5, and are directed to treating a patient with a specific disease characteristic.

Claim 6 recites the "method of claim 5 wherein the subject is less than about 50 years old." Clinicaltrials.gov teaches that the N9831-trial was recruiting patients "18 and over." Ex. 1104 at 5. Further, a POSITA would have known that clinical trials recruit patients across an entire age spectrum so that they can compare results based on age. Ex. 1103 at ¶72. Since N9831 was recruiting patients over 18, at least some patients in the trial would have been younger than 50. At a minimum, it would have been obvious to have tried the claimed method on a patient less than 50 years old because the N9831-trial was recruiting patients 18 and over. *Id*.

Claim 7 recites the "method of claim 5 wherein the subject had a tumor greater than 2 centimeters in diameter." Clinicaltrials.gov teaches that a patient's "[t]umor must be greater than 2.0 cm if estrogen-receptor (ER)- and progesterone-receptor (PR)-positive disease is present." Ex. 1104 at 5. A POSITA would have known that "2 cm" meant 2 cm in diameter as tumor diameter was used as a metric for classifying patients in breast cancer clinical trials. Ex. 1103 at ¶71.

Therefore, at least some patients in N9831 had tumors greater than 2 centimeters in diameter. At a minimum, it would have been obvious to a POSITA to have tried the claimed method on a patient with a tumor greater than 2 centimeters in diameter as Clinicaltrials.gov clearly contemplates these patients being included in the N9831-trial. *Id.*

Claim 8 recites the "method of claim 5, wherein the cancer is lymph node-

positive." Clinicaltrials.gov also teaches the N9831-trial was recruiting "node-positive" patients. Ex. 1104 at 4. Indeed, the "Official Title" of N9831 was "Phase III randomized study of doxorubicin plus cyclophosphamide followed by paclitaxel with or without trastuzumab (Herceptin) in women with her-2-overexpressing ***node-positive*** or high-risk node-negative breast cancer." *Id.* A POSITA would have known that "node-positive" refers to a patient that is "lymph node-positive." Ex. 1103 at ¶65; fn. 19.

And later publications confirm that patients in N9831 in fact had cancer that was lymph node-positive. *See, e.g.*, Ex. 1122[21] at 6-7 (Table 1); Ex. 1123[22] at 10 (Table 1). At a minimum, it would have been obvious to a POSITA to have tried the claimed method on a patient with lymph node-positive cancer as Clinicaltrials.gov clearly contemplates these patients being included in the N9831-trial. *See* Ex. 1103 at ¶69.

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[21] Romond *et al*., *Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer*, 353 N. ENGL. J. MED. 1673 (Oct. 20, 2005) (Ex. 1122).

[22] Perez *et al*., *Four-Year Follow-Up of Trastuzumab Plus Adjuvant Chemotherapy for Operable Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: Joint Analysis of Data from NCCTG N9831 and NSABP B-31*, 29 J. CLIN. ONCOLOGY 3366 (Sept. 1, 2011) (Ex. 1123).

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." Clinicaltrials.gov discloses that "[p]atients are stratified according to nodal status (0 vs 1–3 positive nodes by axillary nodal dissection vs 4–9 positive nodes by axillary nodal dissection vs at least 10 positive nodes.)" Ex. 1104 at 5. 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. 1103 at ¶69.

Indeed, later publications confirm that patients in N9831 in fact had "4–9 involved lymph nodes" and "10 or more involved lymph nodes." *See*, *e.g.*, Ex. 1122 at 6-7 (Table 1)??; Ex. 1123 at 10 (Table 1). At a minimum, it would have been obvious to a POSITA to have included some patients in Arm B of the trial with 4–9 positive lymph nodes and some patients with 10 or more positive lymph nodes to study whether the experimental method was effective in these patients. Clinicaltrials.gov clearly contemplates including patients with 4–9 and 10 or more positive lymph nodes in N9831. Ex. 1103 at ¶¶65, 69.

4. 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 (PR) negative." As discussed above, Clinicaltrials.gov renders obvious claim 5. *See* Section X.B.3 (claims 5–10).

Further, Clinicaltrials.gov discloses that patients would also be stratified according to "receptor status (estrogen receptor [ER] or progesterone receptor [PR] positive vs other)." Ex. 1104 at 5. This means that patients were organized 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. *See id*.; Ex. 1103 at ¶70. Patients within each group would then be randomly assigned to each of the treatment arms A, B, and C. Ex. 1103 at ¶70.

Later publications confirm that patients in N9831 in fact had "estrogen receptor (ER) negative" and "progesterone receptor (PR) negative" cancer. *See*, *e.g.*, Ex. 1122 at -7 (Table 1); Ex. 1123 at 10 (Table 1). At a minimum, it would have been obvious to a POSITA to have included some patients in Arm B of the trial with ER and PR negative tumors in order to study whether the clinical trial method was effective in these patients. Clinicaltrials.gov clearly contemplates including patients with ER negative and PR negative tumors in N9831. Ex. 1103 at ¶70.

Moreover, such patients had a "high risk of cancer recurrence" as recited in Claim 5 because of their ER and PR receptor negative status, as well as because of

their HER2-positive status. A POSITA would have known patients with negative ER and PR receptor status have a high risk of cancer recurrence because they do not respond to certain types of hormone therapy. *See Id.* at ¶70; *see also* Ex. 1101 at 12:1–15 (explaining that patients with ER negative and PR negative status have a high risk of cancer recurrence). Accordingly, Clinicaltrials.gov discloses or renders obvious all elements of claims 11 and 12.

5. **Claim 13**

Claim 13 recites the "method of claim 1, wherein the antibody is an intact, naked antibody." Trastuzumab is a naked, intact antibody that blocks binding of trastuzumab to HER2. First, the '897 patent defines a naked antibody as "an antibody that is not conjugated to a cytotoxic moiety or radiolabel." Ex. 1101 at 21:51–52. A POSITA would have known that trastuzumab is not conjugated to a cytotoxic moiety or a radiolabel and, thus, that it is a naked antibody. *See* Ex. 1103 at ¶47; *see also* Ex. 1110 (description of trastuzumab antibody and drug components in product label does not include cytotoxic moiety or radiolabel).

Second, the '897 patent defines an intact antibody as "one which comprises two antigen binding regions, and an Fc region." Ex. 1101 at 18:4–5. A POSITA would have known trastuzumab comprises two antigen binding regions and an Fc region. *See* Ex. 1103 at ¶48. Indeed, the '897 patent admits IgG antibodies like trastuzumab are intact. Ex. 1101 at 20:28–31 ("There are five major classes of

intact antibodies: IgA, IgD, IgE, ***IgG***, and IgM, and several of these may be further divided into Asubclasses@ [sic] (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2."). *See also* Ex. 1124 at 21 (explaining that the structure of an IgG antibody has two antigen binding regions and an Fc domain).

Third, trastuzumab is an example of an antibody that blocks binding of trastuzumab to HER2. An antibody that blocks binding of trastuzumab to HER2 would be an antibody that is expected to bind to the same epitope of HER2 of trastuzumab. *See* Ex. 1103 at ¶49; Ex. 1124 at 399 (explaining competition assays). Since trastuzumab binds to the same location as trastuzumab, trastuzumab blocks binding of trastuzumab to HER2. Ex. 1103 at ¶49; *see also* Ex. 1101 at 8:53–56 (admitting trastuzumab blocks binding of trastuzumab to HER2).

Moreover, claim 1 requires "administering…trastuzumab ***or*** an antibody that blocks binding of trastuzumab to HER2." Therefore, claims 1 and 13 are satisfied by the administration of trastuzumab ***or*** "an antibody that blocks binding of trastuzumab to HER2" (claim 1) wherein that antibody is a "intact, naked antibody" (claim 13). In other words, nothing in the claims actually requires administration of an "intact, naked antibody" so long as trastuzumab is administered. *See* IPR2014-01412, Final Written Decision, Paper 36 at 19 ("the Federal Circuit consistently has interpreted the meaning of the word '***or***' to mean the items in the sequence are alternatives to each other."). Accordingly, for the

same reasons discussed above with respect to claims 1 and 3, Clinicaltrials.gov renders obvious claim 13. *See* Sections X.B.1 (ground 1, claim 1) and X.B.2 (ground 1, claims 2 and 3) (Clinicaltrials.gov teaches administering trastuzumab).

C. Ground 2: Claim 4 Is Invalid Under 35 U.S.C. § 103 as Obvious in View of Clinicaltrials.gov and Tan

Claim 4 depends from claim 3 and recites "wherein trastuzumab is administered at an initial dose or [*sic*] 4 mg/kg, followed by subsequent weekly doses of 2 mg/kg." As discussed above in Section X.B.2 (ground 1, claims 2 and 3), Clinicaltrials.gov renders obvious claim 3. Although Clinicaltrials.gov doesn't specify the trastuzumab dosing regimen used in arm B of the N9831-trial, Tan (published October 2003) does. Tan teaches that trastuzumab was administered as a "4 mg/kg loading dose, followed by 2 mg/kg/week[] for 1 year" in arm B of the N9831-trial. Ex. 1105 at 9.

A POSITA considering Clinicaltrials.gov would have looked to other references describing the design of N9831, including Tan, for further information about the trial. A POSITA would have been motivated to use the trastuzumab dosing regimen described in Tan in the method taught by Clinicaltrials.gov because Tan specifies the trastuzumab dosing regimen for the method of Clinicaltrials.gov. Additionally, a POSITA would have known trastuzumab was approved by the FDA for the regimen recited in claim 4. *See* Ex. 1103 at ¶74–75; Ex. 1110 at 4, 6.

In view of Tan, it would have been obvious to a POSITA to have administered trastuzumab at an initial dose of 4 mg/kg followed by subsequent weekly doses of 2 mg/kg in the method of Arm B since Tan provides further information about the same method of administering trastuzumab that is described in Clinicaltrials.gov (namely, the N9831-trial). A POSITA would have had a reasonable expectation that the claimed dosing regimen would work both because it was being administered in the N9831-trial and because the claimed trastuzumab regimen was approved by the FDA. *See* Ex. 1103 at ¶¶74–75; Ex. 1110 at 4, 6.

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 Genentech argues that any purported commercial success of Herceptin® is pertinent to patentability, Genentech will be unable to establish that such purported commercial success is attributable to the claimed regimen. The FDA approved Herceptin® in 1998, and it was widely used prior to filing of the application that led to the ’897 patent. *See* Ex. 1103 at ¶77; Ex. 1110 at 4, 6; Ex. 1113 at 9. 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. 1103 at ¶77.

To the extent Genentech argues long-felt but unmet need, it will be unable to show that any such need was long-felt. The 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 nonmetastatic cancer. *See* Ex. 1103 at ¶78; Ex. 1110 at 4, 6. 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." Ex. 1103 at ¶78.

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

XI. 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.

* * *

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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 8,926 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 will all exhibits and other supporting documents, were served on June 30, 2017, via FedEx Overnight delivery directed to the assignee for the patent and the correspondence address as follows:

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