IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

U.S. Patent No. 7,892,549

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Inventor(s): Virginia E. Paton,

Steven Shak,

Susan D. Hellmann

Assignee: Genentech, Inc.

Title: Treatment with Anti-ErbB2 Antibodies Panel: To Be Assigned

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PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 7,892,549
UNDER 35 U.S.C. § 311 AND 37 C.F.R. § 42.100

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Pursuant to 35 U.S.C. § 311 and 37 C.F.R. § 42.100, Petitioner, Hospira, Inc. respectfully requests *inter partes* review ("IPR") of claims 1–11 and 14–17 ("Challenged Claims") of U.S. Patent No. 7,892,549 ("the '549 patent") (Ex. 1101).[1]

USPTO assignment records indicate that the '549 patent is assigned to Genentech, Inc. ("Genentech") (Ex. 1102).

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

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

Hospira, Inc. ("Hospira" or "Petitioner") is the real party-in-interest for Petitioner. Out of an abundance of caution, Petitioner also identifies Pfizer, Inc. as a real party-in-interest who, going forward, may have control or an interest in the outcome of this proceeding.

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

EP 1,037,926 B1 (the "EP '926 patent," Ex. 1103),[2] a European patent within the same family as the '549 patent, was recently invalidated and revoked in

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[1] All references to exhibits, *e.g.*, "Ex.," are to the table of exhibits attached hereto as Petitioner's Exhibit List.

[2] The EP '926 patent and the '549 patent both claim priority to U.S. Provisional Application No. 60/069,346.

two separate European proceedings as obvious. *Hospira UK, Ltd. v. Genentech, Inc.*, Case No. HP-2014-000034, [2015] EWHC (HC) 1796 (Pat), (Jun. 24, 2015), Approved Judgment (Ex. 1104); *Decision to Revoke European Patent EP 1,037,926 B1*, Application No. 98,963,840.8 (Jun. 13, 2016), ¶¶ 20–24 (Ex. 1126). The judgment of the UK Court was affirmed on appeal. *Hospira UK Ltd. v. Genentech Inc.*, Case No. A3 2015 3238, [2016] EWCA Civ 1185 (Nov. 30, 2016), Approved Judgment (Ex. 1149). Petitioner concurrently files an IPR petition for claims of U.S. Patent No. 7,846,441 and two IPR petitions for claims of U.S. Patent No. 7,892,549. Petitioner is not aware of any other judicial or administrative matters that would affect or be affected by a decision in the proceeding.

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

Petitioner designates:

Lead Counsel	**Back-up Counsel**
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D. 37 C.F.R. § 42.8(b)(4): Service Information

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

II. 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 and payment for any additional fees that may be due in connection with this Petition to be charged to the referenced Deposit Account.

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

Petitioner certifies that the ’549 patent is available for IPR and is not barred or estopped from requesting IPR on the grounds identified herein. 35 U.S.C. § 315.

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

The ’549 patent application was filed on February 3, 2003, and therefore, this Petition is governed by pre-AIA 35 U.S.C. § 102. *See* MPEP 2159.01.

Pursuant to 37 C.F.R. §§ 42.104(b)(1) and (2), Petitioner requests review of the Challenged Claims of the '549 patent on the following grounds:

Ground	Proposed Statutory Rejections for the '549 Patent
1	Nabholtz anticipates claims 1–8, 10–11, and 14–17 under 35 U.S.C. § 102(b).
2	Leyland-Jones anticipates claims 1–11 and 14–17 under 35 U.S.C. § 102(a).
3	Yardley anticipates claims 1–11 and 14–17 under 35 U.S.C. § 102(a).

The cited prior art is as follows:

- **Nabholtz.** Nabholtz *et al.*, 64(1) BREAST CANCER RES. AND TREATMENT 82 (Abstract 327) (2000) ("Nabholtz") (Ex. 1114). Nabholtz is a "printed publication," published in December 2000 that was accessible to the public more than one year before the filing date of the '549 patent.[3]
- **Yardley.** Yardley *et al.*, 76 (Suppl. 1) BREAST CANCER RESEARCH AND TREATMENT S113 (Abstract 439) (2002) ("Yardley") (Ex. 1153). Yardley is a "printed publication," published in December 2002 that was accessible to the public before the filing date of the '549 patent.
- **Leyland-Jones.** Leyland-Jones *et al*., 76 (Suppl. 1) BREAST CANCER RESEARCH

[3] Additional evidence authenticating various exhibits is provided in the Declaration of Amanda Hollis (Ex. 1110), Declaration of Christopher Lowden (Ex. 1112), and Declaration of Simon Cohen (Ex. 1117).

AND TREATMENT S37 (Abstract 35) (2002) ("Leyland-Jones") (Ex. 1150). Leyland-Jones is a "printed publication," published in December 2002 that was accessible to the public before the filing date of the '549 patent.

Below is a detailed explanation of the statutory grounds for the unpatentability of each claim that identifies examples of where each element is taught in the cited prior art and the relevance of that prior art. Additional evidence supporting each ground is provided in the accompanying Declaration of Allan Lipton, M.D. (Ex. 1111) and the other supporting exhibits. 37 C.F.R. § 1.68. The discussion below and supporting evidence establish that it is reasonably likely Petitioner will prevail with respect to at least one claim.

V. THE CLAIMS OF THE '549 PATENT ARE UNPATENTABLE

A. Level of Ordinary Skill

A person of ordinary skill in the art ("POSITA") is presumed to be aware of all pertinent art, think along the lines of conventional wisdom, and possess ordinary creativity in the pertinent field. A POSITA at the time of the alleged invention would be a clinical or medical oncologist specializing in breast cancer that has several years of experience with breast cancer research or clinical trials. Exs. 1111 ¶¶ 15–17; 1104 ¶¶ 29–31.

B. The State of the Art

As the '549 patent itself explains, before the alleged invention, an antibody known as humanized 4D5, rhuMAb HER2, or trastuzumab, was well-known as a

breast cancer treatment. *See, e.g.* Exs. 1101 at 1:23–32 (citing Exs. 1133; 1134); 1107 at 6; 1105 at 9; 1108 at 20:15–20. The antibody, commercially known as HERCEPTIN®, had already been well characterized and used in humans with cancer overexpressing the ErbB2 receptor. Ex. 1101 at 2:20–31, 3:36–42 (citing Baselga '96 as showing "HERCEPTIN®" to be "clinically active in patients with ErbB2-overexpressing metastatic breast cancers that had received extensive prior anti-cancer therapy," including prior treatment with paclitaxel); *see also* Exs. 1116 at 10; 1105 at 9–10. The mouse 4D5 antibody targets "the extracellular domain of" the ErbB2 receptor. Ex. 1115 at 8. rhuMAb HER2, trastuzumab, or Herceptin® "contain[s]…the antigen binding loops from [mouse 4D5] and human variable region framework residues plus IgG_1 constant domains" to form an intact humanized 4D5 antibody. Exs. 1116 at 10; 1111 ¶ 37; 1145 at 5–6. Thus, because rhuMAb HER2 has the antigen binding loops of the mouse 4D5 antibody, it binds to the same site on the ErbB2 receptor as the 4D5 antibody. Ex. 1111 ¶ 37.

C. Chemotherapeutic Drug Combinations With rhuMAb HER2 and the Known Toxicity of Anthracyclines

Since at least the 1960s, the field of clinical oncology has been working with combination chemotherapies, in which a patient would be treated either concurrently or sequentially with chemotherapeutic agents. Exs. 1137 at 12–14; 1111 ¶¶ 27–30. The assumption was that higher treatment intensity (more exposure to different drugs over a shorter period of time) resulted in greater tumor killing,

before the cancer could gain adaptive immunity to any one agent. *Id*. In breast cancer, beginning with "CMF"—or cyclophosphamide, methotrexate, 5-fluorouracil—treatment, combination therapies resulted in significant improvements in survival through the 1980s. Exs. 1137 at 14; 1111 ¶¶ 29–30. Thus, when rhuMAb HER2 was created, oncologists had over 20 years of experience and teachings that combination therapies were superior to single agent therapies. *See id.* ¶ 30. The result was, beginning concurrently with research into rhuMAb HER2 as a single therapy, that there was a significant amount of early research into established and new chemotherapeutic agents that could be combined with rhuMAb HER2. *E.g.*, Exs. 1106 at 4; 1113 at 5; 1115 at 8; 1140 at 5; 1141 at 6; 1123 at 3.

Two-drug combinations with rhuMAb HER2 were initially used. *See, e.g.*, Exs. 1105 at 15; 1106 at 4; 1107 at 8–10; 1109 at 14–15; 1113 at 5. Around the time that these two-drug combinations were found to be effective in treating breast cancers, researchers were already using rhuMAb HER2 in three-drug combinations. *See, e.g.*, Exs. 1114 at 29; 1148 at 29; 1150 at 31; 1151 at 5; 1152 at 5; 1153 at 31.

Indeed, it was common knowledge that beneficial treatments could be made from combinations of drugs that act upon different pathways while reducing the risk of increased toxicity or resistance from either drug individually. *See, e.g.*, Ex.

1125 at 9–10 (discussing the properties of paclitaxel and cisplatin); *see also* Exs. 1151 at 5; 1152 at 5; 1111 ¶¶ 27–30. And by early 2003, there were already many ongoing clinical trials of such three drug combinations, including combinations with taxoids. *See, e.g.*, Exs. 1114 at 29; 1148 at 29; 1150 at 31; 1151 at 5; 1152 at 5; 1153 at 31.

Anthracyclines were, and remain, common first-line chemotherapeutic agents for breast cancer. Exs. 1107 at 10; 1142 at 4, 12; 1111 ¶ 32. These drugs are effective but cardiotoxic, and by the mid-1990s, it was understood that the cardiotoxicity was cumulative. Ex. 1142 at 5. This meant that the more of the drug a patient had, the higher the patient's risk of cardiac injury irrespective of the time between treatments. *Id.* It is not surprising, then, that researchers were using several rhuMAb HER2 combination regimens that avoided using anthracyclines. *See* Exs. 1113 at 5 (rhuMAb HER2 + cisplatin); 1106 at 4 (rhuMAb HER2 + paclitaxel); 1107 at 10 (rhuMAb HER2 + paclitaxel); 1114 at 29 (rhuMAb HER2 + docetaxel and cisplatin or carboplatin); 1151 at 5 (rhuMAb HER2 + docetaxel and cisplatin); 1152 at 5 (rhuMAb HER2 + docetaxel and cisplatin); 1153 at 31 (rhuMAb HER2 + paclitaxel and carboplatin); 1150 at 31 (rhuMAb HER2 + paclitaxel with or without carboplatin); 1148 at 29 (rhuMAB HER2 + paclitaxel and carboplatin); 1111 ¶ 32.

D. The ’549 Patent Relies Upon the Work of Others

The ’549 patent states that it concerns “the treatment of disorders characterized by the overexpression of ErbB2,” including “cancer” with “a combination of an anti-ErbB2 antibody and a chemotherapeutic agent other than an anthracycline.” Other than claims 16–17, the claims do not exclude anthracycline derivatives. The claims require an anti-ErbB2 antibody, a taxoid, and either “a further growth inhibitory agent” or a “further therapeutic agent” administered “in an amount effective to extend the time to disease progression in [a] human patient.” Ex. 1101 at claims 1, 5 and 16.

There is no data in the ’549 patent showing the inventors attempted the claimed three-drug combination before filing their application and thus no data disclosing what “an amount effective” means. The sole Example uses an anti-ErbB2 antibody in combination with a taxoid and no third agent. *See* Ex. 1101 at 28:17–23 (“The patients received one of two chemotherapy regiments…a) cyclophosphamide and doxorubicin or epirubicin (AC)…or b) paclitaxel (T, TAXOL®).”).

That same Example repeats, in large part, the prior art Baselga references (Exs. 1105; 1106; 1107)—including the same typographical error. Baselga ’94 (Ex. 1106), Baselga ’96 (Ex. 1105), and Baselga ’97 (Ex. 1107) report synergy between rhuMAb HER2 and paclitaxel in pre-clinical models, successful phase I and II

trials of the combination, and an ongoing phase III clinical trial of the combination. *E.g.*, Exs. 1106 at 4; 1105 at 9; 1107 at 10.

When describing the preparation of the humanized antibody and its affinity for $p185^{HER2}$, the '549 patent's Example is virtually identical to Baselga '96, including the typographical error, "Dillohiation." *Compare* Ex. 1101 at 26:64–27:13 *with* Ex. 1105 at 10. The '549 patent goes on—without attribution—to repeat the description of the clinical trial published by Baselga '97, and reports the results of that trial. *Compare* Ex. 1101 at 27:14–29:9 *with* Ex. 1107 at 10. Despite this overlap, the '549 specification does not credit any of the Baselga '96 or Baselga '97 authors for any of the work or ideas in its Example.

E. The Related European Actions

The EP '926 patent claimed a method of using an anti-ErbB2 antibody to treat breast cancer patients overexpressing ErbB2 receptor in combination with a taxoid, in the absence of an anthracycline, where the combined administration has clinical efficacy as measured by time to disease progression. Ex. 1103 at 23 (claim 1). The specification reported the same experimental data (without attribution) as the '549 patent. *See* Ex. 1101 at 3:35–51. Citing Baselga '97 and Baselga '96, the Patents Court invalidated EP '926 patent as lacking an "inventive step," or in other

words, as obvious. Ex. 1104 ¶¶ 118–34.[4] The opinion of the Patents Court was then affirmed on appeal. *See* Ex. 1149.

On May 2, 2016, in a separate proceeding, the European Patent Office in Munich also revoked EP '926 as obvious. Ex. 1126 ¶¶ 20–24.

The Nabholtz, Leyland-Jones and Yardley references were not considered by the European Patent Office or by the Patents Court.

F. Overview of the '549 Patent Prosecution History

The '549 patent issued from U.S. Patent Application No. 10/356,824 (the "'824 application"). *See* Ex. 1119–1:2.[5] The '824 application claims priority to U.S. Patent Application No. 09/208,649 (the "'649 application") (Ex. 1121) which itself claims priority to U.S. Provisional Patent Application No. 60/069,346 (the "'346 application") (Ex. 1120), filed on December 12, 1997. Ex. 1119–1:7.

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[4] In the U.K., the standard for lack of inventive step is "obvious[ness] to a person skilled in the art." Patents Act, 37§ 3 (U.K.) ("An invention shall be taken to involve an inventive step if it is not obvious to a person skilled in the art….") A similar analysis to the *Graham* factors considered by U.S. Courts is performed. *See Pozzoli Spa v. BDMO SA & Anor.*, 2007 WL 1685192 [2007] EWCA Civ. 588 (Jun. 22, 2007) ¶ 23.

[5] Citations to Ex. 1119 are in the format: volume:page.

The originally filed claims were directed to both two- and three-drug combinations involving anti-ErbB2 antibodies and chemotherapeutic agents including taxoids. *Id.* at 1:51–52. Genentech dropped the claims to two-drug combinations in response to a restriction requirement. *Id.* at 5:19–23. Between that time and 2011, when the '549 patent issued, the claims of the '824 application were rejected six times.

The Examiner's initial Office Action provided five grounds for rejection, including one over Nabholtz. *Id.* at 5:36–43. The Examiner reasoned that Nabholtz was prior art because the remaining claims of the '824 application were not entitled to the earlier priority date of the '346 application. *Id.* at 5:41–42.

In an attempt to overcome the Nabholtz rejection, Genentech pointed to the following places in its '649 application specification that purportedly disclosed the claimed elements of the three drug combination:

- The reference to plural "chemotherapeutic regimen**s**" and "agent**s**";
- A statement that "[t]he formulation herein may also contain more than one active compound…preferably those with complementary activities that do not adversely affect each other";
- A statement that "[i]t may be desirable to also administer antibodies against other tumor associated antigens…one or more cytokines…[or, preferably,] a growth inhibitory agent";

- "The present invention…is based on the recognition that while treatment with anti-ErbB2 antibodies markedly enhances the clinical benefit of the use of chemotherapeutic agents in general, a syndrome of myocardial dysfunction that has been observed as a side-effect of anthracycline derivatives is increased by the administration of anti-ErbB2 antibodies."

See id. at 5:179–181 (citing Ex. 1121 at 9 (5:4), at 20 (16:11–24), at 39 (35:6–14), at 41 (37:9–18), at 9 (5:14–17) (emphasis in original). Relying on these "disclosures," Genentech argued "the skilled person reviewing the '649 disclosure at the relevant time would understand that the presently claimed combinations…were clearly contemplated and described therein." *Id.* at 5:181. Genentech further cited an article by Drs. Daniel and Roger Herzig for the notion that "combinations of two or more chemotherapeutic agents were well known in the art at the time the above application was filed in 1997." *Id.* at 5:180, 5:228–38.

In an Office Action dated December 5, 2006, the Examiner maintained the rejection over Nabholtz and additionally issued obviousness rejections over a series of references, including Baselga '96 and Baselga '94, for the remaining claims. *Id.* at 5:265–69. In response, Genentech argued, based on a Declaration by inventor Dr. Susan Hellmann that had been filed during the prosecution of the parent '649 application, that mouse models are not predictive of clinical results in

breast cancer, and the combination of paclitaxel and rhuMAb HER2 was "surprisingly synergistic" in humans. *Id.* at 5:308–13.

On June 26, 2008, the Examiner withdrew the rejection based on Nabholtz, finding that "the claims have priority to parent application 60/069,346 (filed 12/12/1997)." *Id.* at 6:245. The Examiner continued to reject the claims as obvious over a number of references, including Baselga '96, and on the ground of nonstatutory obviousness-type double patenting for another year. The Examiner issued the final substantive office action on March 20, 2009. *Id.* at 6:323. Genentech had a call with the Examiner on August 25, 2009 and submitted a Declaration by Mark Sliwkowski, Ph.D. on October 15, 2009. *Id.* at 6:329–7:38. Dr. Sliwkowski's Declaration argued that:

(1) a POSITA would not have had a reasonable expectation of success combining anti-ErbB2 antibodies with taxoids because the two treatments result in cell cycle arrest at different and incompatible points in the cell cycle, and

(2) data based on xenograft mouse models is not sufficiently predictable to provide a POSITA with a reasonable expectation of success.

Id. 6:343–44 (Sliwkowski Decl. ¶¶ 7–9). Genentech's arguments in support of allowance reiterated and cited to the statements in Dr. Sliwkowski's declaration. *Id.* at 6:333–40. In light of the Sliwkowski declaration, the Examiner withdrew all

of the obviousness rejections of the ’824 application claims. *Id.* at 7:45.

On January 10, 2011, after Applicant filed a terminal disclaimer with the patent that issued from the ’649 application, the Examiner allowed the claims of the ’549 patent. *Id.* at 7:90–96.

G. The ’549 Patent is Not Entitled to an Earlier Priority Date Based on the Disclosure of the ’649 Application

(1) The PTAB May Determine the Earliest Priority Date of Challenged Patent Claims

The PTAB has the authority to determine the earliest priority date of a patent, including, a claim of earlier priority from a parent application. *See, e.g.*, *Daiichi Sankyo Co., Ltd v. Alethia Biotherapeutics, Inc.*, IPR2015-00291, Paper 75 (P.T.A.B. Jun. 14, 2016) at 6 (holding patent was not entitled to the priority date of the parent application). To claim priority to an earlier filed parent application, “the invention claimed must have been disclosed in the parent application in the manner provided by 35 U.S.C. § 112, ¶ 1.” *Id.* (citing 35 U.S.C. § 120; *In re Lukach*, 442 F.2d 967, 968–69 (CCPA 1971); *Ariad Pharm., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1344–55 (Fed. Cir. 2010) (*en banc*)). Section 112, ¶ 1 contains both an enablement and a written description requirement. *Id.*

The written description requirement ensures “that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by the inventor.” *Arkema Inc. v. Honeywell Int’l, Inc.*,

PGR2016-00011, Paper No. 13 (P.T.A.B. Sept. 2, 2016) at 16 (citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561 (Fed. Cir. 1991); *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571–72 (Fed. Cir. 1997)). To satisfy the written description requirement, the inventor must demonstrate possession by "describing the invention, with all its claimed limitations, not simply that which makes it obvious." *Id.* Further, "[t]he enablement requirement of 35 U.S.C. § 112 ¶ 1 requires that the specification adequately discloses to [a POSITA] how to make, or in the case of a process, how to carry out, the claimed invention without undue experimentation." *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1323 (Fed. Cir. 2009).

(2) The Challenged Claims Are Not Adequately Supported By the '649 Application

All of the '549 patent claims require a method for treating breast cancer that comprises, among other things, administering a combination of an antibody that binds ErbB2, a taxoid, and a further "growth inhibitory" or "therapeutic" agent, to a human. The Board will look in vain for a disclosure of this alleged invention in either the '649 application or the provisional '346 application to which the '549 patent claims priority, however. It is not there. There is no disclosure of any method of treatment in which the claimed three-drug combination is administered.

None of the specification passages Genentech argued during prosecution disclosed what its claimed inventions actually do. The references to plural "chemotherapeutic regimen**s**" and "agent**s**" and the statement that the formulation

"may also contain more than one active compound" are generic and mention nothing of the three specific drugs that were ultimately claimed. The statement that "[i]t may be desirable to also administer antibodies against other tumor associated antigens…one or more cytokines…[or, preferably,] a growth inhibitory agent" likewise does not disclose administration of a combination of an anti-ErbB2 antibody, a taxoid, and a growth inhibitory agent. Ex. 1121 at 41 (37:9–18); *see also* Ex. 1111 ¶ 54.

The last passage Genentech relied upon is even further afield, explicitly referring to "chemotherapeutic agents *in general*," not a taxoid, *disparaging* treatments using combinations of anti-ErbB2 antibodies and *anthracycline derivatives*, and mentioning no third agent. Ex. 1121 at 9 (5:14–17) ("The present invention…is based on the recognition that while treatment with anti-ErbB2 antibodies markedly enhances the clinical benefit of the use of chemotherapeutic agents in general, a syndrome of myocardial dysfunction that has been observed as a side-effect of anthracycline derivatives is increased by the administration of anti-ErbB2 antibodies."); *see also* Ex. 1111 ¶ 54.

Genentech's position that the '649 and '346 applications adequately disclose its invention are also flatly contradicted by its arguments that the prior art disclosures do not. During prosecution, Genentech argued that the prior art Baselga references did not disclose its invention even though those references provide

detailed mouse data demonstrating synergistic effects of anti-ErbB2 antibodies with paclitaxel without increased toxicity and that there were ongoing clinical trials of rhuMAb HER2 combined with paclitaxel or carboplatin. Ex. 1119–5:308–13. Indeed, it argued that "**data from clinical trials of the combination** are needed to demonstrate that they can be usefully combined." *Id.* at 5:308–09 (emphasis in original). But there is no data from clinical trials of the claimed combination anywhere in the '649 or '346 applications. *See* Ex. 1111 ¶¶ 49–52, 55. There is not even data from any mouse or other animal trials, or even *in vitro* experiments. The applications do not indicate that the inventors ever used the three drug combination in any context at all. *See id*.

Genentech cannot, at once, argue that it is entitled to priority based on the '649 and '346 applications while arguing that the prior art, which disclosed significantly more, did not disclose its claimed inventions. The disclosure standard for invalidating prior art is not higher than the disclosure standard for the patent itself. In fact, it is the other way around. Plausibility is not the test for enablement under Section 112; if this were the case, "inventions" would consist "of little more than respectable guesses as to the likelihood of their success." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1325 (Fed. Cir. 2005). Therefore, in order to obtain earlier priority for claims directed to an "effective" use of a cancer drug treatment, the inventor must "provide experimental proof that his invention

could be effective in treating cancer." *Id.* at 1324. To declare Genentech's patent claims patentable would be to unfairly reward it with exclusionary rights for contributing ***less*** to the public about the claimed invention than what was already known in the prior art. *See* Ex. 1111 ¶ 55.

H. Summary of Grounds of Unpatentability

The '549 patent recites a method for treating a human with breast cancer overexpressing ErbB2 receptor by administering an ErbB2-antibody, a taxoid, and a further "growth inhibitory" or "therapeutic" agent in an effective amount. Claims 16–17 also specify that this is done in the absence of an anthracycline derivative. This purported invention is not entitled to an earlier priority date. *See* Section V.G. As such, the date of the claimed invention is no earlier than February 3, 2003 (the filing date of the '549 patent's claims), and the Nabholtz, Leyland-Jones, and Yardley references—detailed below in Section V.J—are prior art. Each of these references independently anticipates the claims.

In particular, these references are the result of work on clinical trials of ***three-drug combinations*** involving rhuMAb HER2, a taxoid (paclitaxel or docetaxel), and a further growth inhibitory agent (cisplatin or carboplatin), conducted by groups located around the world.[6] All three references report dose regimens that were effective without unreasonable toxicity. Exs. 1114 at 29; 1150

[6] Exs. 1114 at 29; 1148 at 29; 1150 at 31; 1151 at 5; 1152 at 5; 1153 at 31.

at 31; 1153 at 31. And none of these references combines the disclosed drug combination with an anthracycline. Exs. 1114 at 29; 1150 at 31; 1153 at 31.

4D5-binding, anti-ErbB2 antibodies were known to treat ErbB2-overexpressing breast cancer since at least 1996,[7] and taxoid and platinum drugs had been known to treat breast cancer since at least the early 1990s and the 1970s, respectively. Exs. 1136 at 5; 1137 at 14. The thought to combine these known treatments was nothing more than the exercise of routine skill, and this is precisely what each of Nabholtz, Leyland-Jones, Yardley, and others ***did*** prior to the filing date of the '824 application.[8] The claimed inventions of the '549 patent lack novelty and should be declared unpatentable.

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

A claim in an IPR is given its broadest reasonable interpretation ("BRI") in light of the specification. 37 C.F.R. § 42.100(b). For purposes of resolving this IPR, Hospira does not believe construction of claim terms is required.

J. Description of the Prior Art

(1) Nabholtz

Nabholtz teaches the claimed three-drug combination. Nabholtz reports the

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[7] Exs. 1101 at 1:23–32, 2:20–31; 1133 at 4; 1134 at 4; 1107 at 6; 1105 at 9; *see also* Exs. 1116 at 10; 1105 at 9–10; 1143 at 6.

[8] Exs. 1114 at 29; 1148 at 29; 1150 at 31; 1151 at 5; 1152 at 5; 1153 at 31.

results of two phase II trials in HER2-positive metastatic breast cancer patients of Herceptin® (rhuMAb HER2) antibodies with docetaxel and either cisplatin or carboplatin. Exs. 1114 at 29; 1111 ¶ 56. Nabholtz teaches that "pharmacologic synergy" had been demonstrated between "Herceptin® (trastuzumab) and either docetaxel or platinum analogs in terms of antitumor activity, as well as the cardiac toxicity associated with anthracycline-Herceptin®-based combination regimens." Ex. 1114 at 29. As a result, the group "proceeded with 2 pilot TCH phase II trials, one combining docetaxel/Herceptin® and carboplatin (TCH1) and one combining docetaxel/Herceptin® and cisplatin (TCH2)." *Id.* Nabholtz teaches that "[a]ll FISH-positive patients had objective responses including 2 [complete responses], 1 of which was confirmed pathologic [complete response]."[9] *Id.* Nabholtz concludes that "[t]hese pilot studies represent the clinical basis for the BCIRG TCH phase III program in first-line metastatic and adjuvant treatment of HER2/*neu*-positive breast cancer patients." *Id.*; *see also* Ex. 1111 ¶¶ 56–60.

(2) Leyland-Jones

Leyland-Jones teaches the claimed three-drug combination. Leyland-Jones

[9] "FISH" stands for fluorescence *in situ* hybridization. Ex. 1111 ¶ 58. FISH is a general technique that can be used to detect whether cells—in this case tumor cells collected from a biopsy—overexpress a particular gene—in this case ErbB2. *Id*.

reports the results of a phase III randomized trial in HER2-positive metastatic breast cancer patients comparing the combination of trastuzumab (rhuMAb HER2), paclitaxel and carboplatin with the combination of rhuMAb HER2 and paclitaxel. Exs. 1150 at 31; 1111 ¶¶ 61–63. Leyland-Jones reports that time to disease progression was 13 months for the three-drug combination compared to 7 months for the two-drug combination. Ex. 1150 at 31. As a result, Leyland-Jones concludes that "[t]rastuzumab+paclitaxel+carboplatin is superior to trastuzumab+paclitaxel in terms of both response and time to progression with acceptable toxicity." *Id.*; *see also* Ex. 1111 ¶¶ 61–63.

(3) Yardley

Yardley teaches the claimed three-drug combination. Yardley reports the results of "[a] phase II multicenter pilot study of weekly paclitaxel, carboplatin, and trastuzumab [that] was initiated in October 1999 as a first-line treatment in HER2 overexpressing metastatic breast cancer." Ex. 1153 at 31. The overall response rate was 66% and the median time to disease progression was 19 months. *Id.* Yardley concludes that the combination of "[w]eekly paclitaxel, carboplatin, and trastuzumab is well tolerated and highly active in HER2 overexpressing metastatic breast cancer." *Id.*; *see also* Ex. 1111 ¶¶ 64–66.

K. Statement of the Law

The anticipation analysis is a two-step process. *In re Crish*, 393 F.3d 1253, 1256 (Fed. Cir. 2004). The first step, to the extent necessary, is claim construction. *Id.* Second, "the Board must compare the construed claim to a prior art reference and make factual findings that each and every limitation is found either expressly or inherently in that single prior art reference." *Id.* (internal quotation omitted) (citation omitted). "[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005) (internal quotation and citation omitted).

"In order to anticipate, a prior art disclosure must also be enabling such that one of ordinary skill in the art could practice the invention without undue experimentation." *Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp*, 424 F.3d 1347, 1355 (Fed. Cir. 2005) (citing *SmithKline Beecham*, 403 F.3d at 1342). But "[t]he standard for enablement of a prior art reference for purposes of anticipation under section 102 differs from the enablement standard under 35 U.S.C. § 112." *Id.* (citing *SmithKline Beecham*, 403 F.3d at 1325). Thus, "anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only

requires that those suggestions be enabled to one of skill in the art." *Id.* (internal quotation and citations omitted).

L. Claim-By-Claim Explanation of Grounds of Unpatentability

Ground 1: Claims 1–8, 10–11, and 14–17 Are Invalid Based on Nabholtz

(1) Claim 1

a. Claim 1, preamble: "A method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor, comprising"

Nabholtz discloses "[a] method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor." Nabholtz discloses a phase II trial "to evaluate the efficacy and safety of TCH as therapy for patients (pts) with HER2-positive advanced breast cancer." Ex. 1114 at 29. HER2-positive breast cancer is breast cancer that overexpresses HER2, also known as ErbB2. Ex. 1111 ¶¶ 71–72. HER2 positive status was confirmed by immunohistochemistry, FISH, or both. Ex. 1114 at 29. Immunohistochemistry and FISH are laboratory techniques for confirming that a specific protein or gene, respectively, is overexpressed in a biopsy sample. Ex. 1111 ¶ 58.

b. Claim 1, element [a]: "administering a combination of an antibody that binds ErbB2,"

Nabholtz discloses "administering a combination of an antibody that binds ErbB2." Nabholtz teaches that rhuMAb HER2 (also known as Herceptin® and trastuzumab) was administered as a "combin[ation]" to patients. Ex. 1114 at 29.

The ’549 patent states that rhuMAb HER2 is the “humanized version of the murine 4D5 antibody.” Ex. 1101 at 26:58–59. The murine 4D5 antibody binds to ErbB2. *Id.* at 2:4–31; *see also* Ex. 1111 ¶ 73. A POSITA would have known rhuMAb HER2 contains the same complementarity determining region as murine 4D5 and, as such, rhuMAb HER2 binds to the same epitope as murine 4D5. Thus, rhuMAb HER2 binds to ErbB2. *Id.*

c. Claim 1, element [b]: “a taxoid,”

Nabholtz discloses “a taxoid.” Nabholtz teaches two phase II trials, “one combining docetaxel/Herceptin® and carboplatin (TCH1) and one combining docetaxel/Herceptin® and cisplatin (TCH2).” Ex. 1114 at 29. The ’549 patent states that docetaxel is a taxoid. Ex. 1101 at 11:5–16 (“taxoids, e.g. paclitaxel…and docetaxel”).

d. Claim 1, element [c]: “and a further growth inhibitory agent”

Nabholtz discloses “a further growth inhibitory agent.” Nabholtz teaches two phase II trials, “one combining docetaxel/Herceptin® and carboplatin (TCH1) and one combining docetaxel/Herceptin® and cisplatin (TCH2).” Ex. 1114 at 29. The ’549 patent states that DNA alkylating agents are growth inhibitory agents and include platinum-based compounds like cisplatin and carboplatin. Exs. 1101 at 11:31–34 (“DNA alkylating agents such as…cisplatin”); 1111 ¶ 75.

e. Claim 1, element [d]: "to the human patient"

Nabholtz teaches administration in human patients. Ex. 1114 at 29 ("The primary objectives of these pilot studies were to evaluate the efficacy and safety of TCH as therapy for patients (pts) with HER2-positive advanced breast cancer.").

f. Claim 1, element [e]: "in an amount effective to extend the time to disease progression in the human patient,"

Nabholtz discloses "an amount effective to extend the time to disease progression in the human patient." Nabholtz treated patients "with Herceptin® 4mg/kg on day 1…followed by 2 mg/kg weekly…plus docetaxel 75 mg/m^2…and either cisplatin 75 mg/m^2…or carboplatin (AUC of 6) on day 1 every 3 weeks (for 6-8 cycles)." "[O]bjectives" of the study included "duration of response, time to disease progression and survival." *Id*.

Nabholtz further teaches that "[a]ll FISH-positive patients had objective responses including 2 [complete responses], 1 of which was confirmed pathologic [complete response]." *Id.* A POSITA would understand that, since all FISH-positive patients had objective responses, including two complete responses, the patients had received an amount effective to extend the time to disease progression. Ex. 1111 ¶¶ 77–79.

Moreover, this dose schedule inherently discloses an amount effective to extend time to disease progression. The final results of these clinical trials were

published by Pegram and colleagues in 2004. *See* Pegram *et al.*, *Results of Two Open-Label, Multicenter Phase II Studies of Docetaxel, Platinum Salts, and Trastuzumab in HER2-Positive Advanced Breast Cancer*, 96(10) J. NATL. CANCER INST. 759–69 (2004) ("Pegram '04") (Ex. 1154) at 5. The results demonstrated that patients treated with the disclosed dose schedule resulted in a time to disease progression of 9.9 months for the combination with cisplatin and 12.7 months for the combination with carboplatin. *Id.*

g. Claim 1, element [f]: "wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence."

Nabholtz inherently discloses "wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence." Nabholtz discloses that rhuMAb HER2 was administered to patients. Ex. 1114 at 29. An inherent property of rhuMAb HER2 is that it binds to epitope 4D5 within the ErbB2 extracellular domain sequence. Ex. 1111 ¶ 80. The '549 patent explains that "[t]he 'epitope 4D5' is the region in the extracellular domain of ErbB2 to which the antibody 4D5…binds." Ex. 1101 at 5:26–28. The '549 patent states that rhuMAb HER2 is the "humanized version of the murine 4D5 antibody" and the 4D5 antibody is "specific for the extracellular domain of ErbB2." *Id.* at 26:38–47, 26:58–59.

(2) Claim 2

a. "The method of claim 1 wherein the antibody is a humanized 4D5 anti-ErbB2 antibody."

Nabholtz teaches the method of claim 1. *See* Section V.L.Ground 1:(1). Nabholtz teaches administration of rhuMAb HER2, which is a humanized 4D5 anti-ErbB2 antibody. Ex. 1114 at 29; *see* Section V.L.Ground 1:(1)g.

(3) Claim 3

a. "The method of claim 1 wherein the antibody crossblocks binding of 4D5 to the ErbB2 extracellular domain sequence."

Nabholtz teaches the method of claim 1. *See* Section V.L.Ground 1:(1). Nabholtz also inherently discloses "wherein the antibody crossblocks binding of 4D5 to the ErbB2 extracellular domain sequence." Cross-blocking assays are routine laboratory experiments to confirm that two antibodies share overlapping binding specificity. Ex. 1101 at 5:28–33 (*citing Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988)). Nabholtz teaches administration of rhuMAb HER2, which is a humanized 4D5 anti-ErbB2 antibody. Ex. 1114 at 29; *see* Section V.L.Ground 1:(1)g. As discussed above in Section V.B, because rhuMAb HER2 possesses the same antigen binding loops as mouse 4D5, it will necessarily crossblock binding of 4D5 to the ErbB2 extracellular domain sequence. Ex. 1111 ¶¶ 83–84.

(4) Claim 4

a. "The method of claim 1 wherein the antibody binds to amino acid residues in the region from about residue 529 to about residue 625 of the ErbB2 extracellular domain sequence."

Nabholtz teaches the method of claim 1. *See* Section V.L.Ground 1:(1). The '549 patent states that the 4D5 antibody binds to the region from about residue 529 to about residue 625 of the ErbB2 extracellular domain sequence. Ex. 1101 at 5:33–37 ("Alternatively, epitope mapping can be performed (see FIG. 1) to assess whether the antibody binds to the 4D5 epitope of ErbB2 (i.e. any one or more residues in the region from about residue 529, e.g. about residue 561 to about residue 625, inclusive)").

As discussed above in Section V.L.Ground 1:(1)g, Nabholtz teaches administration of rhuMAb HER2, which is a humanized 4D5 anti-ErbB2 antibody. Ex. 1114 at 29. As discussed above in Section V.B, because rhuMAb HER2 possesses the same antigen binding loops as 4D5, it necessarily also "binds to the region from about residue 529 to about residue 625 of the ErbB2 extracellular domain sequence." Ex. 1111 ¶¶ 85–86.

(5) Claim 5

a. Claim 5, preamble: "A method for the treatment of a human patient with breast cancer characterized by overexpression of ErbB2 receptor, comprising"

For the reasons discussed above in Section V.L.Ground 1:(1)a, Nabholtz

discloses "[a] method for the treatment of a human patient with breast cancer characterized by overexpression of ErbB2 receptor."

b. Claim 5, element [a]: "administering an effective amount of a combination of an anti-ErbB2 antibody which binds epitope 4D5 within the ErbB2 extracellular domain sequence,"

Nabholtz discloses "administering an effective amount of a combination," since "an amount effective to extend the time to disease progression," would be an "effective amount," for the reasons discussed above in Section V.L.Ground 1:(1)f.

c. Claim 5, element [b]: "a taxoid,"

Nabholtz discloses "a taxoid" for the reasons discussed above in Section V.L.Ground 1:(1)c.

d. Claim 5, element [c]: "and a further therapeutic agent,"

Nabholtz discloses "a further therapeutic agent." As discussed above in Section V.L.Ground 1:(1)d, Nabholtz discloses "a further growth inhibitory agent," cisplatin or carboplatin. Exs. 1114 at 29; 1101 at 11:31–34; 1111 ¶ 91. Claim 11 provides that a "therapeutic agent" may be selected from the group consisting of "another ErbB2 antibody, EGFR antibody, ErbB3 antibody, ErbB4 antibody, vascular endothelial growth factor (VEGF) antibody, cytokine, and growth inhibitory agent." Ex. 1101 at claim 11. Therefore, a "therapeutic agent" includes a "growth inhibitory agent."

e. Claim 5, element [d]: "to the human patient."

Nabholtz discloses "to the human patient," for the reasons discussed above in Section V.L.Ground 1:(1)e.

(6) Claim 6

a. "The method of claim 5 wherein the breast cancer is metastatic breast carcinoma."

Nabholtz discloses the method of claim 5. *See* Section V.L.Ground 1:(5). Nabholtz discloses that patients with HER2 positive stage III/IV breast cancer were chosen for the reported studies. Ex. 1114 at 29. Patients with stage III/IV breast cancer have metastatic breast carcinoma. Ex. 1111 ¶¶ 93–94.

(7) Claim 7

a. "The method of claim 5 wherein the antibody is a humanized 4D5 anti-ErbB2 antibody."

Nabholtz discloses the method of claim 5. *See* Section V.L.Ground 1:(5). For the reasons discussed above in Section V.L.Ground 1:(1)g, Nabholtz discloses administration of rhuMAb HER2, which is a humanized 4D5 anti-ErbB2 antibody. Exs. 1114 at 29; 1101 at 3:36–42.

(8) Claim 8

a. "The method of claim 7 wherein the antibody is administered as a 4 mg/kg dose and then weekly administration of 2 mg/kg."

Nabholtz discloses the method of claim 7. *See* Section V.L.Ground 1:(7). Further, Nabholtz teaches that patients were "treated with Herceptin® 4 mg/kg on

day 1 (90-min IV infusion) followed by 2 mg/kg weekly (30-min IV infusion)." Ex. 1114 at 29.

(9) Claim 10

a. "The method of claim 5 wherein efficacy is measured by determining the time to disease progression or the response rate."

Nabholtz discloses the method of claim 5. *See* Section V.L.Ground 1:(5). As stated above in Section V.L.Ground 1:(1)f, Nabholtz discloses measuring the results by the time to disease progression as well as the response rate.

(10) Claim 11

a. "The method of claim 5, wherein the further therapeutic agent is selected from the group consisting of: another ErbB2 antibody, EGFR antibody, ErbB3 antibody, ErbB4 antibody, vascular endothelial growth factor (VEGF) antibody, cytokine, and growth inhibitory agent."

Nabholtz discloses the method of claim 5. *See* Section V.L.Ground 1:(5). As discussed in Section V.L.Ground 1:(1)d, Nabholtz discloses a "growth inhibitory agent" of cisplatin or carboplatin. Ex. 1114 at 29.

(11) Claim 14

a. "The method of claim 5 wherein the further therapeutic agent is a growth inhibitory agent."

Nabholtz discloses the method of claim 5. *See* Section V.L.Ground 1:(5). As discussed in Section V.L.Ground 1:(1)d, Nabholtz discloses a "growth inhibitory agent."

(12) Claim 15

a. "The method of claim 14 wherein the growth inhibitory agent is a DNA alkylating agent."

Nabholtz discloses the method of claim 14. *See* Section V.L.Ground 1:(11). As discussed above in Section V.L.Ground 1:(1)d, Nabholtz discloses a "growth inhibitory agent" that is either cisplatin or carboplatin, which are both DNA alkylating agents. Exs. 1101 at 11:31–34; 1111 ¶¶ 105–106.

(13) Claim 16

a. Claim 16, preamble: "A method for the treatment of a human patient with ErbB2 overexpressing breast cancer, comprising"

For the reasons discussed above in Section V.L.Ground 1:(1)a, Nabholtz discloses "[a] method for the treatment of a human patient with ErbB2 overexpressing breast cancer."

b. Claim 16, element [a]: "administering a combination of an antibody that binds epitope 4D5 within the ErbB2 extracellular domain sequence,"

Nabholtz discloses "administering a combination of an antibody that binds epitope 4D5 within the ErbB2 extracellular domain sequence" for the reasons discussed above in Section V.L.Ground 1:(1)g.

c. Claim 16, element [b]: "a taxoid"

Nabholtz discloses "a taxoid" for the reasons discussed above in Section V.L.Ground 1:(1)c.

d. Claim 16, element [c]: "and a further growth inhibitory agent,"

Nabholtz discloses "a further growth inhibitory agent" for the reasons discussed above in Section V.L.Ground 1:(1)d.

e. Claim 16, element [d]: "in the absence of an anthracycline derivative,"

Nabholtz discloses "in the absence of an anthracycline derivative." When discussing the specific combination therapy used during the two phase II trials, Nabholtz discusses that the specific compounds were chosen to avoid "the cardiac toxicity associated with anthracycline-Herceptin®-based combination regimes." Ex. 1114 at 29. In addition, Nabholtz discloses the combination of rhuMAb HER2, docetaxel, and either cisplatin or carboplatin; anthracyclines were not used. *Id*.

f. Claim 16, element [e]: "to the human patient"

Nabholtz discloses "to the human patient" for the reasons discussed above in Section V.L.Ground 1:(1)e.

g. Claim 16, element [f]: "in an amount effective to extend the time to disease progression in the human patient."

Nabholtz discloses "in an amount effective to extend the time to disease progression in the human patient" for the reasons discussed above in Section V.L.Ground 1:(1)f.

(14) Claim 17

a. "The method of claim 16 wherein the breast cancer is

metastatic breast carcinoma."

Nabholtz discloses the method of claim 16. *See* Section V.L.Ground 1:(13). Nabholtz teaches "metastatic breast carcinoma" for the reasons discussed above in Section V.L.Ground 1:(6)a.

Ground 2: Claims 1–11 and 14–17 Are Invalid Based on Leyland-Jones

(1) Claim 1

a. Claim 1, preamble: "A method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor, comprising"

Leyland-Jones discloses "[a] method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor." Leyland-Jones discloses "a randomized Phase III trial, comparing the combination of trastuzumab, paclitaxel, and carboplatin (TPC) with trastuzumab and paclitaxel (TP) in HER-2/*neu* positive patients with advanced breast cancer." Ex. 1150 at 31. HER-2/*neu* positive breast cancer is breast cancer that overexpresses HER2, also known as ErbB2. Ex. 1111 ¶ 118.

b. Claim 1, element [a]: "administering a combination of an antibody that binds ErbB2,"

Leyland-Jones discloses "administering a combination of an antibody that binds ErbB2." Leyland-Jones teaches that rhuMAb HER2 was administered as a "combination" to patients. Ex. 1150 at 31. rhuMAb HER2, is the "humanized version of the murine 4D5 antibody." Exs. 1101 at 26:58–59; 1111 ¶ 119. The

murine 4D5 antibody binds to ErbB2. Exs. 1101 at 2:4–31; 1111 ¶ 119. A POSITA would have known rhuMAb HER2 contains the same complementarity determining region as murine 4D5 and, as such, rhuMAb HER2 binds to the same epitope as murine 4D5. Thus, rhuMAb HER2 binds to ErbB2.

c. Claim 1, element [b]: "a taxoid,"

Leyland-Jones discloses "a taxoid." Leyland-Jones teaches "a randomized Phase III trial, comparing the combination of trastuzumab, paclitaxel, and carboplatin (TPC) with trastuzumab and paclitaxel (TP) in HER-2/*neu* positive patients with advanced breast cancer." Ex. 1150 at 31. The '549 patent states that paclitaxel is a taxoid. Ex. 1101 at 11:5–16.

d. Claim 1, element [c]: "and a further growth inhibitory agent"

Leyland-Jones discloses "a further growth inhibitory agent." Leyland-Jones teaches "a randomized Phase III trial, comparing the combination of trastuzumab, paclitaxel, and carboplatin (TPC) with trastuzumab and paclitaxel (TP) in HER-2/*neu* positive patients with advanced breast cancer." Ex. 1150 at 31. The '549 patent states that DNA alkylating agents, like cisplatin and carboplatin, are growth inhibitory agents. Exs. 1101 at 11:31–34; 1111 ¶ 121.

e. Claim 1, element [d]: "to the human patient"

Leyland-Jones teaches administration in human patients. Ex. 1150 at 31 ("we conducted a randomized Phase III trial…in HER-2/*neu* positive patients with

advanced breast cancer").

f. Claim 1, element [e]: "in an amount effective to extend the time to disease progression in the human patient,"

Leyland-Jones discloses "an amount effective to extend the time to disease progression in the human patient." Leyland-Jones treated patients "[t]rastuzumab dosing was a standard loading dose of 4 mg/kg followed by weekly 2 mg/kg, paclitaxel was administered at 175 mg/m^2 over 3 hours every 3 weeks, and carboplatin was administered at an AUC of 6 every 3 weeks." *Id.* The results demonstrated that time to disease progression was 13 months for patients on the three-drug combination compared to 7 months for patients on the two-drug combination. *Id.* If patients with the highest ErbB2 receptor expression were selected, the time to disease progression increased to 17 months for the three-drug combination and 9 months for the two-drug combination. *Id.*

g. Claim 1, element [f]: "wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence."

Leyland-Jones discloses "wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence." Leyland-Jones teaches that rhuMAb HER2 was administered to patients. *Id*. An inherent property of rhuMAb HER2 is that it binds to epitope 4D5 within the ErbB2 extracellular domain sequence. Ex. 1111 ¶ 127. The '549 patent explains that "[t]he 'epitope 4D5' is the region in the

extracellular domain of ErbB2 to which the antibody 4D5…binds." Ex. 1101 at 5:26–28. rhuMAb HER2 is the "humanized version of the murine 4D5 antibody." Exs. 1101 at 26:58–59; 1111 ¶ 127. The '549 patent states that rhuMAb HER2 is the "humanized version of the murine 4D5 antibody" and the 4D5 antibody is "specific for the extracellular domain of ErbB2." Ex. 1101 at 26:38–47, 26:58–59.

(2) Claim 2

a. "The method of claim 1 wherein the antibody is a humanized 4D5 anti-ErbB2 antibody."

Leyland-Jones discloses the method of claim 1. *See* Section V.L.Ground 2:(1). Leyland-Jones teaches administration of rhuMAb HER2, which is a humanized 4D5 anti-ErbB2 antibody. Ex. 1150 at 31; *see* Section V.L.Ground 2:(1)g.

(3) Claim 3

a. "The method of claim 1 wherein the antibody crossblocks binding of 4D5 to the ErbB2 extracellular domain sequence."

Leyland-Jones discloses the method of claim 1. *See* Section V.L.Ground 2:(1). Leyland-Jones also inherently discloses "wherein the antibody crossblocks binding of 4D5 to the ErbB2 extracellular domain sequence." Cross-blocking assays are routine laboratory experiments to confirm that two antibodies share overlapping binding specificity. Ex. 1101 at 5:28–33 (*citing Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory, Ed Harlow and David Lane

(1988)). Leyland-Jones discloses administration of rhuMAb HER2, which is a humanized 4D5 anti-ErbB2 antibody. Ex. 1150 at 31; *see* Section V.L.Ground 2:(1)g. As discussed above in Section V.B, because rhuMAb HER2 possesses the same antigen binding loops as mouse 4D5, it will necessarily crossblock binding of 4D5 to the ErbB2 extracellular domain sequence. Ex. 1111 ¶¶ 130–131.

(4) Claim 4

a. "The method of claim 1 wherein the antibody binds to amino acid residues in the region from about residue 529 to about residue 625 of the ErbB2 extracellular domain sequence."

Leyland-Jones discloses the method of claim 1. *See* Section V.L.Ground 2:(1). Leyland-Jones also discloses "wherein the antibody binds to amino acid residues in the region from about residue 529 to about residue 625 of the ErbB2 extracellular domain sequence." The '549 patent states that the 4D5 antibody binds to the region from about residue 529 to about residue 625 of the ErbB2 extracellular domain sequence. Ex. 1101 at 5:26–37 ("Alternatively, epitope mapping can be performed (see FIG. 1) to assess whether the antibody binds to the 4D5 epitope of ErbB2 (i.e. any one or more residues in the region from about residue 529, e.g. about residue 561 to about residue 625, inclusive)"). As discussed above in Section V.L.Ground 2:(1)g, Leyland-Jones teaches administration of rhuMAb HER2, which is a humanized 4D5 anti-ErbB2 antibody. Ex. 1150 at 31. As discussed above in Section V.B, because rhuMAb HER2 possesses the same

antigen binding loops as 4D5, it necessarily also "binds to the region from about residue 529 to about residue 625 of the ErbB2 extracellular domain sequence." Ex. 1111 ¶¶ 132–133.

(5) Claim 5

a. Claim 5, preamble: "A method for the treatment of a human patient with breast cancer characterized by overexpression of ErbB2 receptor, comprising"

For the reasons discussed above in Section V.L.Ground 2:(1)a, Leyland-Jones discloses "[a] method for the treatment of a human patient with breast cancer characterized by overexpression of ErbB2 receptor."

b. Claim 5, element [a]: "administering an effective amount of a combination of an anti-ErbB2 antibody which binds epitope 4D5 within the ErbB2 extracellular domain sequence,"

Leyland-Jones discloses "administering an effective amount of a combination." "[A]n amount effective to extend the time to disease progression" would be an "effective amount." Therefore, for the reasons discussed above in Section V.L.Ground 2:(1)f, Leyland-Jones discloses "an effective amount."

c. Claim 5, element [b]: "a taxoid,"

Leyland-Jones discloses "a taxoid" for the reasons discussed above in Section V.L.Ground 2:(1)c.

d. Claim 5, element [c]: "and a further therapeutic agent,"

Leyland-Jones discloses "a further therapeutic agent." As discussed above in

Section V.L.Ground 2:(1)d, Leyland-Jones discloses "a further growth inhibitory agent." Claim 11 provides that a "therapeutic agent" may be selected from the group consisting of "another ErbB2 antibody, EGFR antibody, ErbB3 antibody, ErbB4 antibody, vascular endothelial growth factor (VEGF) antibody, cytokine, and growth inhibitory agent." Ex. 1101 at claim 11. Therefore, a "therapeutic agent" includes a "growth inhibitory agent."

e. Claim 5, element [d]: "to the human patient."

Leyland-Jones discloses "to the human patient," for the reasons discussed above in Section V.L.Ground 2:(1)e.

(6) Claim 6

a. "The method of claim 5 wherein the breast cancer is metastatic breast carcinoma."

Leyland-Jones teaches the method of claim 5. *See* Section V.L.Ground 2:(5). Leyland-Jones discloses that patients with HER-2/*neu* positive advanced breast cancer were chosen for the reported studies. Ex. 1150 at 31. "Advanced breast cancer" means the patient has metastatic breast carcinoma. Ex. 1111 ¶¶ 140–141.

(7) Claim 7

a. "The method of claim 5 wherein the antibody is a humanized 4D5 anti-ErbB2 antibody."

Leyland-Jones teaches the method of claim 5. *See* Section V.L.Ground 2:(5). For the reasons discussed above in Section V.L.Ground 2:(1)g, Leyland-Jones teaches administration of rhuMAb HER2 which is a humanized 4D5 anti-ErbB2

antibody. Exs. 1150 at 31; 1101 at 1:23–32.

(8) Claim 8

a. "The method of claim 7 wherein the antibody is administered as a 4 mg/kg dose and then weekly administration of 2 mg/kg."

Leyland-Jones teaches the method of claim 7. *See* Section V.L.Ground 2:(7). Leyland-Jones teaches that "[t]rastuzumab dosing was a standard loading dose of 4 mg/kg followed by weekly 2 mg/kg." Ex. 1150 at 31.

(9) Claim 9

a. "The method of claim 5 wherein the taxoid is paclitaxel."

Leyland-Jones teaches the method of claim 5. *See* Section V.L.Ground 2:(5). Leyland-Jones teaches that patients were administered "paclitaxel…at 175 mg/m^2 over 3 hours every 3 weeks." Ex. 1150 at 31.

(10) Claim 10

a. "The method of claim 5 wherein efficacy is measured by determining the time to disease progression or the response rate."

Leyland-Jones discloses the method of claim 5. *See* Section V.L.Ground 2:(5). As discussed above in Section V.L.Ground 2:(1)f, Leyland-Jones discloses measuring the results by the time to disease progression.

(11) Claim 11

a. "The method of claim 5, wherein the further therapeutic agent is selected from the group consisting of: another ErbB2 antibody, EGFR antibody, ErbB3 antibody, ErbB4 antibody, vascular endothelial growth factor (VEGF) antibody, cytokine, and growth inhibitory agent."

Leyland-Jones discloses the method of claim 5. *See* Section V.L.Ground 2:(5). As discussed in Section V.L.Ground 2:(1)d, Leyland-Jones discloses a "growth inhibitory agent."

(12) Claim 14

a. "The method of claim 5 wherein the further therapeutic agent is a growth inhibitory agent."

Leyland-Jones teaches the method of claim 5. *See* Section V.L.Ground 2:(5). As discussed in Section V.L.Ground 2:(1)d, Leyland-Jones teaches a "growth inhibitory agent."

(13) Claim 15

a. "The method of claim 14 wherein the growth inhibitory agent is a DNA alkylating agent."

Leyland-Jones discloses the method of claim 14. *See* Section V.L.Ground 2:(12). As discussed above in Section V.L.Ground 2:(1)d, Leyland-Jones discloses a "growth inhibitory agent" that is carboplatin, which is a DNA alkylating agent. Exs. 1101 at 11:31–34; 1111 ¶¶ 154–55.

(14) Claim 16

a. Claim 16, preamble: "A method for the treatment of a human patient with ErbB2 overexpressing breast cancer, comprising"

For the reasons discussed above in Section V.L.Ground 2:(1)a, Leyland-Jones discloses "[a] method for the treatment of a human patient with ErbB2 overexpressing breast cancer."

b. Claim 16, element [a]: "administering a combination of an antibody that binds epitope 4D5 within the ErbB2 extracellular domain sequence,"

Leyland-Jones discloses "administering a combination of an antibody that binds epitope 4D5 within the ErbB2 extracellular domain sequence" for the reasons discussed above in Section V.L.Ground 2:(1)g.

c. Claim 16, element [b]: "a taxoid"

Leyland-Jones discloses "a taxoid" for the reasons discussed above in Section V.L.Ground 2:(1)c.

d. Claim 16, element [c]: "and a further growth inhibitory agent,"

Leyland-Jones discloses "a further growth inhibitory agent" for the reasons discussed above in Section V.L.Ground 2:(1)d.

e. Claim 16, element [d]: "in the absence of an anthracycline derivative,"

Leyland-Jones discloses "in the absence of an anthracycline derivative." Leyland-Jones discloses the combination of rhuMAb HER2, paclitaxel, and

carboplatin; anthracyclines were not used. Ex. 1150 at 31.

f. Claim 16, element [e]: "to the human patient"

Leyland-Jones discloses "to the human patient" for the reasons discussed above in Section V.L.Ground 2:(1)e.

g. Claim 16, element [f]: "in an amount effective to extend the time to disease progression in the human patient."

Leyland-Jones discloses "in an amount effective to extend the time to disease progression in the human patient" for the reasons discussed above in Section V.L.Ground 2:(1)f.

(15) Claim 17

a. "The method of claim 16 wherein the breast cancer is metastatic breast carcinoma."

Leyland-Jones discloses the method of claim 16. *See* Section V.L.Ground 2:(14). Leyland-Jones discloses "metastatic breast carcinoma" for the reasons discussed above in Section V.L.Ground 2:(6)a.

Ground 3: Claims 1–11 and 14–17 Are Invalid Based on Yardley

(1) Claim 1

a. Claim 1, preamble: "A method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor, comprising"

Yardley discloses "[a] method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor." Yardley discloses "[a] phase II multicenter pilot study of weekly paclitaxel, carboplatin, and trastuzumab []

initiated in October 1999 as first-line treatment in HER2 overexpressing metastatic breast cancer." Ex. 1153 at 31. HER2 is also known as ErbB2. Ex. 1111 ¶ 168.

b. Claim 1, element [a]: "administering a combination of an antibody that binds ErbB2,"

Yardley discloses "administering a combination of an antibody that binds ErbB2." Yardley discloses that rhuMAb HER2 was administered to patients in combination with other therapeutic agents. Ex. 1153 at 31. rhuMAb HER2 is the "humanized version of the murine 4D5 antibody." Exs. 1101 at 26:58–59; 1111 ¶ 169. The murine 4D5 antibody binds to ErbB2. Exs. 1101 at 2:4–31; 1111 ¶ 169. A POSITA would have known rhuMAb HER2 contains the same complementarity determining region as murine 4D5 and, as such, rhuMAb HER2 binds to the same epitope as murine 4D5. Thus, rhuMAb HER2 binds to ErbB2.

c. Claim 1, element [b]: "a taxoid,"

Yardley discloses "a taxoid." Yardley teaches "[a] phase II multicenter pilot study of weekly paclitaxel, carboplatin, and trastuzumab [] initiated in October 1999 as first-line treatment in HER2 overexpressing metastatic breast cancer." Ex. 1153 at 31. The '549 patent states that paclitaxel is a taxoid. Ex. 1101 at 11:5–16.

d. Claim 1, element [c]: "and a further growth inhibitory agent"

Yardley discloses "a further growth inhibitory agent." Yardley discloses "[a] phase II multicenter pilot study of weekly paclitaxel, carboplatin, and trastuzumab [] initiated in October 1999 as first-line treatment in HER2 overexpressing

metastatic breast cancer." Ex. 1153 at 31. The '549 patent states that DNA alkylating agents are growth inhibitory agents and include platinum-based compounds like cisplatin and carboplatin. Exs. 1101 at 11:31–34 ("DNA alkylating agents such as…cisplatin"); 1111 ¶ 171.

e. Claim 1, element [d]: "to the human patient"

Yardley teaches administration in human patients. Ex. 1153 at 31 ("61 patients (pts) with 2+ or 3+ HER2 expression by immunohistochemistry (IHC) were enrolled.").

f. Claim 1, element [e]: "in an amount effective to extend the time to disease progression in the human patient,"

Yardley discloses "an amount effective to extend the time to disease progression in the human patient." Yardley treated patients with "weekly paclitaxel 70 mg/m^2, carboplatin AUC 2, and trastuzumab 2 mg/kg." *Id.* The results demonstrated an overall response rate of 66% and a median time to disease progression of 12 months. *Id.* In FISH-positive patients, the overall response rate was 89% and median time to disease progression was 19 months. *Id.* Yardley concludes that "[w]eekly paclitaxel, carboplatin, and trastuzumab is well tolerated and highly active in HER2 overexpressing metastatic breast cancer." *Id.*

g. Claim 1, element [f]: "wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence."

Yardley inherently discloses "wherein the antibody binds to epitope 4D5

within the ErbB2 extracellular domain sequence." Yardley discloses that rhuMAb HER2 was administered to patients. *Id*. An inherent property of rhuMAb HER2 is that it binds to epitope 4D5 within the ErbB2 extracellular domain sequence. Ex. 1111 ¶ 176. The '549 patent explains that "[t]he 'epitope 4D5' is the region in the extracellular domain of ErbB2 to which the antibody 4D5 (ATCC CRL 10463) binds." Ex. 1101 at 5:26–28. The '549 patent states that rhuMAb HER2 is the "humanized version of the murine 4D5 antibody" and the 4D5 antibody is "specific for the extracellular domain of ErbB2." *Id.* at 26:38–47, 26:58–59.

(2) Claim 2

a. "The method of claim 1 wherein the antibody is a humanized 4D5 anti-ErbB2 antibody."

Yardley discloses the method of claim 1. *See* Section V.L.Ground 3:(1). Yardley discloses administration of rhuMAb HER2, which is a humanized 4D5 anti-ErbB2 antibody. Ex. 1153 at 31; *see* Section V.L.Ground 3:(1)g.

(3) Claim 3

a. "The method of claim 1 wherein the antibody crossblocks binding of 4D5 to the ErbB2 extracellular domain sequence."

Yardley discloses the method of claim 1. *See* Section V.L.Ground 3:(1). Yardley further inherently discloses "wherein the antibody crossblocks binding of 4D5 to the ErbB2 extracellular domain sequence." Cross-blocking assays are routine laboratory experiments to confirm that two antibodies share overlapping

binding specificity. Ex. 1101 at 5:28–33 (*citing Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988)). Yardley teaches administration of rhuMAb HER2, which is a humanized 4D5 anti-ErbB2 antibody. Ex. 1153 at 31; *see* Section V.L.Ground 3:(1)g. As discussed above in Section V.B, because rhuMAb HER2 possesses the same antigen binding loops as mouse 4D5, it will necessarily crossblock binding of 4D5 to the ErbB2 extracellular domain sequence. Ex. 1111 ¶¶ 179–80.

(4) Claim 4

a. "The method of claim 1 wherein the antibody binds to amino acid residues in the region from about residue 529 to about residue 625 of the ErbB2 extracellular domain sequence."

Yardley discloses the method of claim 1. *See* Section V.L.Ground 3:(1). Yardley further inherently discloses "wherein the antibody binds to amino acid residues in the region from about residue 529 to about residue 625 of the ErbB2 extracellular domain sequence." The '549 patent concedes that the 4D5 antibody binds to the region from about residue 529 to about residue 625 of the ErbB2 extracellular domain sequence. Ex. 1101 at 5:26–37 ("Alternatively, epitope mapping can be performed (see FIG. 1) to assess whether the antibody binds to the 4D5 epitope of ErbB2 (i.e. any one or more residues in the region from about residue 529, e.g. about residue 561 to about residue 625, inclusive)").

As discussed above in Section V.L.Ground 3:(1)g, Yardley teaches

administration of rhuMAb HER2, which is a humanized 4D5 anti-ErbB2 antibody. Ex. 1153 at 31. As discussed above in Section V.B, because rhuMAb HER2 possesses the same antigen binding loops as 4D5, it necessarily also "binds to the region from about residue 529 to about residue 625 of the ErbB2 extracellular domain sequence." Ex. 1111 ¶¶ 181–82.

(5) Claim 5

a. Claim 5, preamble: "A method for the treatment of a human patient with breast cancer characterized by overexpression of ErbB2 receptor, comprising"

For the reasons discussed above in Section V.L.Ground 3:(1)a, Yardley discloses "[a] method for the treatment of a human patient with breast cancer characterized by overexpression of ErbB2 receptor."

b. Claim 5, element [a]: "administering an effective amount of a combination of an anti-ErbB2 antibody which binds epitope 4D5 within the ErbB2 extracellular domain sequence,"

Yardley discloses "administering an effective amount of a combination." Since "an amount effective to extend the time to disease progression," would be an "effective amount," for the reasons discussed above in Section V.L.Ground 3:(1)f, Yardley discloses "an effective amount."

c. Claim 5, element [b]: "a taxoid,"

Yardley discloses "a taxoid" for the reasons discussed above in Section V.L.Ground 3:(1)c.

d. Claim 5, element [c]: "and a further therapeutic agent,"

Yardley discloses "a further therapeutic agent." As discussed above in Section V.L.Ground 3:(1)d, Yardley discloses "a further growth inhibitory agent." Claim 11 provides that a "therapeutic agent" may be selected from the group consisting of "another ErbB2 antibody, EGFR antibody, ErbB3 antibody, ErbB4 antibody, vascular endothelial growth factor (VEGF) antibody, cytokine, and growth inhibitory agent." Ex. 1101 at claim 11. Therefore, a "therapeutic agent" includes a "growth inhibitory agent."

e. Claim 5, element [d]: "to the human patient."

Yardley discloses "to the human patient," for the reasons discussed above in Section V.L.Ground 3:(1)e.

(6) Claim 6

a. "The method of claim 5 wherein the breast cancer is metastatic breast carcinoma."

Yardley discloses the method of claim 5. *See* Section V.L.Ground 3:(5). Yardley discloses treatment of patients with "HER2 overexpressing metastatic breast cancer." Ex. 1153 at 31. A POSITA would have understood metastatic breast cancer and metastatic breast carcinoma to mean the same thing. Ex. 1111 ¶¶ 189–90.

(7) Claim 7

a. "The method of claim 5 wherein the antibody is a

humanized 4D5 anti-ErbB2 antibody."

Yardley discloses the method of claim 5. *See* Section V.L.Ground 3:(5). For the reasons discussed above in Section V.L.Ground 3:(1)g, Yardley discloses administration of rhuMAb HER2 which is a humanized 4D5 anti-ErbB2 antibody. Exs. 1153 at 31; 1101 at 1:23–32.

(8) Claim 9

a. "The method of claim 5 wherein the taxoid is paclitaxel."

Yardley teaches the method of claim 5. *See* Section V.L.Ground 3:(5). Yardley teaches that patients were administered "paclitaxel 70 mg/m^2." Ex. 1153 at 31.

(9) Claim 10

a. "The method of claim 5 wherein efficacy is measured by determining the time to disease progression or the response rate."

Yardley discloses the method of claim 5. *See* Section V.L.Ground 3:(5). As stated above in Section V.L.Ground 3:(1)f, Yardley discloses measuring the results by the time to disease progression.

(10) Claim 11

a. "The method of claim 5, wherein the further therapeutic agent is selected from the group consisting of: another ErbB2 antibody, EGFR antibody, ErbB3 antibody, ErbB4 antibody, vascular endothelial growth factor (VEGF) antibody, cytokine, and growth inhibitory agent."

Yardley discloses the method of claim 5. *See* Section V.L.Ground 3:(5). As discussed in Section V.L.Ground 3:(1)d, Yardley discloses a "growth inhibitory agent."

(11) Claim 14

a. "The method of claim 5 wherein the further therapeutic agent is a growth inhibitory agent."

Yardley discloses the method of claim 5. *See* Section V.L.Ground 3:(5). As discussed in Section V.L.Ground 3:(1)d, Yardley discloses a "growth inhibitory agent."

(12) Claim 15

a. "The method of claim 14 wherein the growth inhibitory agent is a DNA alkylating agent."

Yardley teaches the method of claim 14. *See* Section V.L.Ground 3:(11). As discussed above in Section V.L.Ground 3:(1)d, Yardley teaches a "growth inhibitory agent" that is carboplatin, which is a DNA alkylating agent. Exs. 1101 at 11:31–34; 1111 ¶¶ 201–02.

(13) Claim 16

a. Claim 16, preamble: "A method for the treatment of a

human patient with ErbB2 overexpressing breast cancer, comprising"

For the reasons discussed above in Section V.L.Ground 3:(1)a, Yardley discloses "[a] method for the treatment of a human patient with ErbB2 overexpressing breast cancer."

b. Claim 16, element [a]: "administering a combination of an antibody that binds epitope 4D5 within the ErbB2 extracellular domain sequence,"

Yardley discloses "administering a combination of an antibody that binds epitope 4D5 within the ErbB2 extracellular domain sequence" for the reasons discussed above in Section V.L.Ground 3:(1)g.

c. Claim 16, element [b]: "a taxoid"

Yardley discloses "a taxoid" for the reasons discussed above in Section V.L.Ground 3:(1)c.

d. Claim 16, element [c]: "and a further growth inhibitory agent,"

Yardley discloses "a further growth inhibitory agent" for the reasons discussed above in Section V.L.Ground 3:(1)d.

e. Claim 16, element [d]: "in the absence of an anthracycline derivative,"

Yardley discloses "in the absence of an anthracycline derivative." Yardley discloses the combination of rhuMAb HER2, paclitaxel, and carboplatin; anthracyclines were not used. Ex. 1153 at 31.

f. Claim 16, element [e]: "to the human patient"

Yardley discloses "to the human patient" for the reasons discussed above in Section V.L.Ground 3:(1)e.

g. Claim 16, element [f]: "in an amount effective to extend the time to disease progression in the human patient."

Yardley discloses "in an amount effective to extend the time to disease progression in the human patient" for the reasons discussed above in Section V.L.Ground 3:(1)f.

(14) Claim 17

a. "The method of claim 16 wherein the breast cancer is metastatic breast carcinoma."

Yardley discloses the method of claim 16. *See* Section V.L.Ground 3:(13). Yardley discloses "metastatic breast carcinoma" for the reasons discussed above in Section V.L.Ground 3:(6)a.

VI. CONCLUSION

Hospira respectfully requests IPR of the Challenged Claims.

Date: January 20, 2017

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 11,232 words. Counsel has relied upon the word count feature provided by Microsoft Word.

/Amanda Hollis/
Amanda Hollis

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 7,892,549, along with all exhibits and other supporting documents, was served on January 20, 2017, via FedEx Overnight delivery directed to the assignee for the patent at the following address:

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The undersigned further certifies that a copy of the foregoing Petition, along with all exhibits and other supporting documents, was served on January 20, 2017, via FedEx Overnight delivery directed to the attorney of record for the patent at the following address:

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/Amanda Hollis/
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