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 of Challenged Claims 1–17 of U.S. Patent No. 7,892,549 ("the '549 patent") (Ex. 1001).[1]

USPTO assignment records indicate that the '549 patent is assigned to Genentech, Inc. ("Genentech") (Ex. 1002).

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

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

EP 1,037,926 B1 (the "EP '926 patent", Ex. 1003),[2] a European patent within the same family as the '549 patent, was recently invalidated and revoked in two separate European proceedings as obvious in light of certain references

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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.

asserted here. *Hospira UK, Ltd. v. Genentech, Inc.*, Case No. HP-2014-000034, [2015] EWHC (HC) 1796 (Pat), (Jun. 24, 2015), Approved Judgment (Ex. 1004); *Decision to Revoke European Patent EP 1,037,926*, Application No. 98,963,840.8 (Jun. 13, 2016) ¶¶ 20–24 (Ex. 1026). 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. 1049). 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**
Amanda Hollis (Reg. No. 55,629) amanda.hollis@kirkland.com **Postal and Hand-Delivery Address:** KIRKLAND & ELLIS LLP 300 North LaSalle Chicago, IL 60654 Telephone: (312) 862-2011 Facsimile: (312) 862-2200	Stefan Miller, Ph.D. (Reg. No. 57,623) stefan.miller@kirkland.com **Postal and Hand-Delivery Address:** KIRKLAND & ELLIS LLP 601 Lexington Avenue New York, NY 10022 Telephone: (212) 446-6479 Facsimile: (212) 446-4900 Karen Younkins (Reg. No. 67,554) karen.younkins@kirkland.com **Postal and Hand-Delivery Address:**

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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. § 103. *See* MPEP 2159.01. Pursuant to 37 C.F.R. §§ 42.104(b)(1) and (2), Petitioner requests review of the Challenged Claims 1–17 on the following grounds:

Ground	Proposed Statutory Rejections for the '549 Patent
1	**Baselga '97 (Ex. 1007)** in view of **Gelmon '96 (Ex. 1025)** renders obvious claims 1–11 and 14–17 under 35 U.S.C. § 103.
2	**Baselga '97 (Ex. 1007)** in view of **Gelmon '96 (Ex. 1025)** and **Drebin '88 (Ex. 1010)** renders obvious claim 12 under 35 U.S.C. § 103.
3	**Baselga '97 (Ex. 1007)** in view of **Gelmon '96 (Ex. 1025)** and **Presta '97 Ex. (1012)** renders obvious claim 13 under 35 U.S.C. § 103.
4	**Baselga '96 (Ex. 1005)** in view of **Baselga '94 (Ex. 1006)**, and **Gelmon '96 (Ex. 1025)** renders obvious claims 1–11 and 14–17 under 35 U.S.C. § 103.
5	**Baselga '96 (Ex. 1005)** in view of **Baselga '94 (Ex. 1006), Gelmon '96 (Ex. 1025)** and **Drebin '88 (Ex. 1010)** renders obvious claim 12 under 35 U.S.C. § 103.
6	**Baselga '96 (Ex. 1005)** in view of **Baselga '94 (Ex. 1006), Gelmon '96 (Ex. 1025)** and **Presta '97 (Ex. 1012)** renders obvious claim 13 under 35 U.S.C. § 103.

The cited prior art is as follows:[3]

- **Baselga '97.** Baselga *et al*., 11(3) (Suppl. 2) ONCOLOGY 43–48 (1997) (Ex. 1007) is prior art under 35 U.S.C. § 102(a) and a "printed publication"

[3] Additional evidence authenticating various exhibits is provided in the Declarations of Amanda Hollis (Ex. 1027), Christopher Lowden (Ex. 1031), and Simon Cohen (Ex. 1046).

published March 1, 1997 bearing a Health Sciences Libraries stamp date of April 24, 1997.

- **Baselga '96.** Baselga *et al*., 14(3) J. CLIN. ONCOL. 737–44 (1996) (Ex. 1005) is prior art under 35 U.S.C. § 102(b) and is a "printed publication" published March 1996 bearing a Biomedical Library, UC San Diego, stamp date of March 13, 1996.
- **Baselga '94.** Baselga *et al*., 13 PROC. AM. SOC. CLIN. ONCOL. 63 (Abstract 53) (1994) (Ex. 1006) is prior art under 35 U.S.C. § 102(b) and is a "printed publication" published March, 1994 bearing a Health Sciences Library stamp date of September 20, 1994.
- **Gelmon '96.** Gelmon *et al*., 14(4) J. CLIN. ONCOL. 1185–91 (1996) (Ex. 1025) is prior art under 35 U.S.C. § 102(b) and a "printed publication" published on April 1, 1996 accessible to the public more than one year prior to the earliest effective filing date of the '549 patent.
- **Drebin '88.** Drebin *et al*., 2(3) ONCOGENE 273–77 (1988) (Ex. 1010) is prior art under 35 U.S.C. § 102(b) and a "printed publication" published March 1988 accessible to the public more than one year prior to the earliest effective filing date of the '549 patent.
- **Presta '97.** Presta *et al*., 57(20) CANCER RES. 4593–99 (1997) (Ex. 1012) is prior art under 35 U.S.C. § 102(a) and a "printed publication" published on

October 15, 1997 accessible to the public prior to the earliest effective filing date of the '549 patent.

Below is a detailed explanation of the statutory grounds for the unpatentability of each claim. Additional evidence supporting each ground is provided in the Declaration of Allan Lipton, M.D. (Ex. 1011) and other supporting exhibits. 37 C.F.R. § 1.68. As detailed below, Petitioner is reasonably likely to 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 with several years of experience with breast cancer research or clinical trials. Exs. 1011 ¶¶ 15–17; 1004 ¶¶ 29–31. The Challenged Claims would be obvious even if the level of ordinary skill in the art were lower.

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. 1001 at 1:23–32 (citing Exs. 1033; 1034); 1007 at 6; 1005 at 9; 1008 at 20:15–20. The antibody, commercially known as

HERCEPTIN®, had already been characterized and used in humans with breast cancer overexpressing the ErbB2 receptor. Ex. 1001 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" including prior paclitaxel treatment); *see also* Exs. 1016 at 10; 1005 at 9–10. Paclitaxel also was a well-known treatment for breast cancer. *See* Exs. 1066 at 10; 1067.

C. Chemotherapeutic Drug Combinations and Known Toxicity of Anthracyclines

Since the 1960s, the field of clinical oncology has worked with combination chemotherapies. Exs. 1037 at 12–14; 1011 ¶¶ 28–31. Higher treatment intensity (more exposure to different drugs over a shorter period of time) has resulted in greater tumor killing before the cancer had the opportunity to gain adaptive immunity. *Id*. In breast cancer, beginning with "CMF"—or cyclophosphamide, methotrexate, 5-fluorouracil—treatment, these combination therapies resulted in improvements in survival through the 1980s. Exs. 1037 at 14; 1011 ¶¶ 30–31. When rhuMAb HER2 was created, oncologists had over 20 years of experience showing combination therapies were superior to single-agent therapies. *See id*. ¶¶ 32, 43; Exs. 1015 at 8; 1040 at 5; 1041 at 6.

Anthracyclines are common first-line chemotherapeutic agents for breast cancer. Exs. 1007 at 10; 1042 at 4, 12; 1011 ¶ 33. These drugs are effective but cardiotoxic, and by the mid-1990s, it was understood that cardiotoxicity was

cumulative irrespective of the time between treatments. Ex. 1042 at 5. It is unsurprising, then, that researchers were using several rhuMAb HER2 combination regimens avoiding anthracyclines. *See* Exs. 1013 at 5 (rhuMAb HER2 plus cisplatin); 1006 at 4 (rhuMAb HER2 plus paclitaxel); 1007 at 10 (rhuMAb HER2 plus paclitaxel); 1011 ¶ 33.

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. 1001 at claims 1, 5, 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 as one of the two tested combinations with no third agent administered. *See id*. at 28:17–23.

That same Example repeats, in large part, the prior art Baselga references. 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 id*. at 26:64–27:13 *with* Ex. 1005 at 10. The '549 patent goes on—without attribution—to repeat the description of the Baselga '97 clinical trial and reports the results of that trial. *Compare* Ex. 1001 at 27:14–29:9 *with* Ex. 1007 at 10. Despite this overlap, the '549 specification does not credit any of the Baselga '96 or '97 authors for any of the work 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. 1003 at 23 (claim 1). The specification reported the same experimental data (without attribution) as the '549 patent. *See id*. at 20 [¶¶ 0148–51]. Citing Baselga '97 and '96, the Patents Court invalidated EP '926 patent as lacking an "inventive step" (as obvious). Ex.

1004 ¶¶ 118–34.[4] The opinion of the Patents Court was then affirmed on appeal. *See* Ex. 1049.

On May 2, 2016, in a separate proceeding, the European Patent Office in Munich also revoked EP '926 as obvious. Ex. 1026 ¶¶ 20–24.

F. Overview of the '549 Patent Prosecution History

The '549 patent prosecution can be boiled down to two significant events:

(1) Genentech argued their application was entitled to the earlier priority of its parent application to antedate the Nabholtz reference discussed below, and

(2) Genentech submitted a declaration by Mark Sliwkowski, Ph.D., arguing that the combination of rhuMAb HER2 plus a taxoid demonstrated unexpected results.

The '549 patent issued from U.S. Patent Application No. 10/356,824 (the

[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.

"'824 application"). *See* Ex. 1019–1:2.[5] The '824 application claims priority to U.S. Patent Application No. 09/208,649 (the "'649 application") (Ex. 1021) which itself claims priority to U.S. Provisional Patent Application No. 60/069,346 (the "'346 application") (Ex. 1020), filed on December 12, 1997. Ex. 1019–1:7.

The '549 patent began as a continuation of the '649 application. The originally filed claims recited both two- and three-drug combinations involving anti-ErbB2 antibodies and chemotherapeutic agents including taxoids. *Id*. at 1:51–53. 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 *et al*. (64(1) BREAST CANCER RESEARCH AND TREATMENT 82 (Abstract 327) (2000) ("Nabholtz")) (Ex. 1014). *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 this rejection, Genentech pointed to the following places in its '649 application purportedly disclosing the claimed elements of the

[5] Citations to Ex. 1019 are in the format: volume:page.

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 5:179–81 (citing Ex. 1021 at 20 (16:11–24), at 39 (35:6–14), at 41 (37:9–18), at 9 (5:14–17)). Relying on these "disclosures," Genentech argued a POSITA "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.

The Examiner maintained the rejection over Nabholtz and additionally issued obviousness rejections over a series of references including Baselga '96 and '94 for the remaining claims. *Id*. at 5:265–69. In response, Genentech argued, based on a declaration by inventor Dr. Susan Hellmann, 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 other grounds. Genentech had a call with the Examiner on August 25, 2009 and followed this call by filing Dr. Sliwkowski's Declaration. *Id*. at 6:329–7:38. This Declaration did not differ in substance from the Declaration by Dr. Sliwkowski filed in the '649 application. Ex. 1032. His 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.

Ex. 1019–6:343–44. Genentech's arguments reiterated and cited to the statements in Dr. Sliwkowski's Declaration. *Id*. at 6:333–40. In light of the Declaration, the Examiner withdrew all obviousness rejections to the '824 application. *Id*. at 7:45.

After the filing of a terminal disclaimer with the patent that issued from the '649 application, the Examiner allowed the claims. *Id*. at 7:90–96.

G. 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.

H. Statement of the Law

Analysis under 35 U.S.C. § 103(a) requires several steps: "[T]he scope and content of the prior art are…determined; differences between the prior art and the claims at issue are…ascertained; and the level of ordinary skill in the pertinent art [is] resolved." *KSR Int'l Co*. *v*. *Teleflex, Inc*., 550 U.S. 398, 406 (2007). Then, "[a]gainst this background, the obviousness or nonobviousness of the subject matter is determined." *Id*. Additionally, "secondary considerations [such] as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Id*.

A patent claim is invalid under § 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 to a POSITA at the time the invention was made. *Id*. at 406. And "[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 [POSITA] has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *Id*. at 421.

I. Summary of Grounds of Unpatentability

Nothing inventive is claimed by the '549 patent. Every component of the claimed three-drug combination was known in the prior art. 4D5-binding, anti-ErbB2 antibodies were known to treat ErbB2-overexpressing breast cancer since 1996,[6] and paclitaxel and platinum drugs had been known to treat breast cancer since the early 1990s and the 1970s, respectively. Exs. 1036 at 5; 1037 at 14. The thought to combine these known treatments was nothing more than the exercise of routine skill.

Combinations of an anti-ErbB2 antibody with chemotherapeutic agents had

[6] Exs. 1001 at 1:23–32, 2:20–31, 3:36–42; 1033 at 4; 1034 at 4; 1007 at 6; 1005 at 9; *see also* Exs. 1016 at 10; 1005 at 9–10; 1035; 1043 at 6.

been known since the early 1990s.[7] Scientists had already demonstrated that combined treatment with an anti-ErbB2 antibody and paclitaxel resulted in a synergistic increase in tumor-killing power. *See* Exs. 1001 at 3:56–61; 1005 at 15; 1006 at 4; 1007 at 9–10. Published studies demonstrated that breast cancer patients treated with anti-ErbB2 antibodies plus cisplatin had improved outcomes over cisplatin alone. Exs. 1007 at 9–10; 1013 at 5. And the combination of paclitaxel with cisplatin was also known to be synergistic. *See e.g.*, Ex. 1025 at 9.

A POSITA reviewing the prior art before the earliest claimed filing date at minimum would know:

1) anti-ErbB2 antibody + paclitaxel (a taxoid)→synergistic;

2) anti-ErbB2 antibody + cisplatin (a growth inhibitory agent)→synergistic;

3) paclitaxel (a taxoid) + cisplatin (a growth inhibitory agent)→synergistic;

The next logical step was to combine all three. MPEP 2144.06 ("It is *prima facie* obvious to combine two compositions…taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose…[T]he idea of combining them flows logically from their having been individually taught in the prior art.").

[7] *E.g.*, Exs. 1006 at 4; 1013 at 5; 1009 at 14–15; 1017 at 7; 1011 ¶ 41; 1043 at 6.

There was motivation to try the claimed combination therapies and reason to expect they would be successful before the '549 patent. Breast cancer had not been eradicated. Anti-ErbB2 antibodies, paclitaxel, and cisplatin had all been used in human patients in the prior art, and two-drug combinations of each of them were shown to be synergistic. Drug combinations generally, including two- and three-agent combinations, were routinely used to fight cancer, including breast cancer. *See, e.g.*, Exs. 1037 at 11–15; 1025 at 9–10; 1011 ¶¶ 28–31. And it was well-known that combination chemotherapies were superior to single agent therapies. Ex. 1011 ¶ 31. Combinations, like anti-ErbB2 antibodies, paclitaxel, and cisplatin, acting on different and complementary pathways were known to have a greater probability of exhibiting synergy without resulting in drug resistance or enhanced toxicity. Exs. 1025 at 9–10; 1011 ¶¶ 30, 41–43.

The '549 patent specification itself contains no suggestion that it was inventive to combine a known growth inhibitory agent with the known combination of an anti-ErbB2 antibody and paclitaxel. Indeed, similar multi-drug combinations were suggested in 1989 when the original applications for the murine 4D5 antibody were filed. Ex. 1016 at 10; *see also* Ex. 1045 at 5–6.

And, as discussed above, the '549 patent does not include any data showing that the named inventors had tried a combination of an anti-ErbB2 antibody, a taxoid, and a further growth inhibitory agent in a patient before purporting

(through their claims) to know it would be an amount effective to extend the time to disease progression in a human.

Indeed, if the prior art does not teach the claimed inventions (it does), the '549 patent would fail to meet the requirements of 35 U.S.C. § 112 ¶ 1. As explained in *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323–25 (Fed. Cir. 2005), the standard for satisfying the enablement requirement of 35 U.S.C. § 112 is higher than that for what constitutes proper enablement of a prior-art reference. For example, to obtain an earlier priority date for claims directed to an "effective" cancer treatment, the Federal Circuit has held an inventor "need[s] to provide experimental proof that his invention could be effective in treating cancer," whereas "proof of efficacy is not required…for a reference to be enabled for purposes of anticipation." *Id*. at 1326. As the '549 patent includes no experimental data at all for the claimed combination therapies, much less experimental proof of the claimed therapies' efficacy, the prior art should not be required to meet a higher standard.

In fact, the prior art discloses ***more*** than what Genentech argued was sufficient to establish an earlier priority date. *Id*. A POSITA reading Baselga '94 (rhuMAb HER2 + paclitaxel), Baselga '96 (rhuMAb HER2 + chemotherapy), Baselga '97 (rhuMAb HER2 + paclitaxel), Pegram '95 (rhuMAb HER2 + cisplatin), or Gelmon '96 (cisplatin + paclitaxel) would not merely see a recitation

of an idea or "desir[e]" to use a treatment that "may [] contain more than one active compound…preferably those with complementary activities that do not adversely affect each other." Exs. 1001 at 23:60–63; 1019–5:179–81. A POSITA would know that such combinations (including rhuMAb HER2 plus paclitaxel or cisplatin) ***had actually been tried***, both in mice and in humans, ***and experimental data*** showed they worked better than rhuMAb HER2 alone. Exs. 1005 at 15; 1006 at 4; 1007 at 9–10; 1013 at 5.

During prosecution, Genentech's main criticism of the prior art was that "data from clinical trials of the combination are needed to demonstrate that they can be usefully combined." Ex. 1019–5:308–09. But the Examiner seemingly overlooked that Genentech's patent specification contains no such data from clinical trials—or any data—of the claimed three-drug combination. *See* Ex. 1011 ¶¶ 51–52.

And yet Genentech affirmatively argued that same specification sufficed to "clearly…describe[]" the claimed invention by its use of plural words ("agents") and generic disclosures about combining chemotherapeutic agents. Ex. 1019–5:179–81. 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 the prior art. *See* Ex. 1011 ¶ 53.

Finally, none of the dependent claims adds anything inventive. Genentech

did not argue that any of the dependent claims of the ’549 patent added anything over and above what had already been disclosed by the prior art at any time during the prosecution history of the ’549 patent. *See generally*, Ex. 1019.

J. The Prior Art

(1) Baselga ’97

Baselga ’97 teaches that the ErbB2 receptor is overexpressed in 25–30% of malignant human breast cancer tumors. Ex. 1007 at 6. Based on this, a monoclonal mouse antibody, 4D5, was generated against the ErbB2 receptor. *Id*. at 7. The 4D5 anti-ErbB2 antibody demonstrated growth inhibition against tumor cells and in xenograft tumor models. *Id*.

The 4D5 antibody was humanized (rhuMAb HER2) and used in phase II clinical trials with a loading dose of 250 mg followed by ten weekly doses of 100 mg. *Id*. at 9. “Adequate serum levels of rhuMoAb HER2[8] were obtained in 90% of the patients” and a mean half-life of about 8.3 days was observed. *Id*. The overall response rate was 11.6%, and minor responses or stable disease occurred in an additional 37% of patients. *Id*. Baselga ’97 concludes that “rhuMoAb HER2 is clinically active in patients who have metastatic breast cancers that overexpress HER2 and have received extensive prior therapy.” *Id*.

[8] Baselga ’97 refers to rhuMAb HER2 as “rhuMoAb HER2.”

Baselga '97 further teaches that in human breast cancer cell culture and in tumor xenografts in nude mice, the 4D5 antibody combined with paclitaxel "resulted in major antitumor activity." *Id*. The synergistic effect (>90% growth inhibition) was substantial as each of the 4D5 antibody and paclitaxel produced only 35% growth inhibition alone. *Id*. The result with paclitaxel was also "markedly better than an equipotent dose of doxorubicin…and 4D5 (70% inhibition)." *Id*.

Baselga '97 teaches that the results from preclinical experiments and the phase II trials were encouraging and "led to the design of a phase III multinational study of chemotherapy in combination with rhuMoAb HER2 in patients with HER2-overexpressing breast tumors" that was underway. *Id*. at 10. In the trial, patients received either rhuMAb HER2 plus chemotherapy, or chemotherapy alone. *Id*. A clinical endpoint was "to determine whether the addition of this anti-HER2 antibody increases the time to disease progression compared with the group of patients treated with [chemotherapy] alone."[9] *Id*.; Ex. 1011 ¶ 57. Baselga '97 notes that "[b]ecause anthracyclines are widely used in the adjuvant setting, it is

[9] Figure 2, and the remainder of the article, show that the control group consisted of "cytotoxic chemotherapy alone"—the statement "antibody alone" is a typographical error. Exs. 1007 at 10, Fig. 2; 1011 ¶ 57, fn.5.

likely that a significant number of patients will be treated with paclitaxel." Ex. 1007 at 10.

(2) Gelmon '96

Gelmon '96 reports the results of a phase I/II clinical trial using biweekly combined treatment with paclitaxel and cisplatin in treating metastatic breast cancer. Ex. 1025 at 9. Phase II studies of paclitaxel as a single agent had demonstrated response rates between 17–62%. *Id*. Gelmon '96 states that its authors "were [] interested in combining [paclitaxel] with a non-cross-resistant drug with a different spectrum of toxicity[, and c]isplatin seemed to be an appropriate choice." *Id*. Gelmon '96 reports that 85% of the patients available for assessment showed a response. *Id*. at 13. The median time to disease progression was 7.9 months for the responding patients. *Id*.

(3) Drebin '88

Drebin '88 discusses experiments involving various antibodies against the ErbB2 receptor. Ex. 1010. The authors tested several antibodies in xenograft models including combinations of antibodies "reactive with two distinct regions on the p185 molecule." *Id* at 4. Such antibody combinations "resulted in synergistic anti-tumor effects and complete eradication of tumors." *Id*.

(4) Presta '97

Presta '97 discloses a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). Ex. 1012 at 8. VEGF is a cytokine promoting

angiogenesis (the growth of new blood vessels). *Id*. It is implicated in cancer and is upregulated in nearly every human tumor. *Id*. at 13. Presta '97 teaches that antibodies capable of interfering with the action of VEGF are pursued as a strategy for mitigating uncontrolled tumor angiogenesis. *Id*. at 8. Presta '97 reports a line of humanized murine antibodies that were tested in preclinical models—the *in vivo* preclinical testing revealed substantial tumor growth inhibition. *Id*. at 11.

(5) Baselga '96

Baselga '96 reports the results of a phase II clinical trial in patients with ErbB2-overexpressing metastatic breast cancer. Ex. 1005 at 9.

Baselga '96 teaches that after successful experiments in mouse models, the 4D5 anti-ErbB2 antibody was humanized (rhuMAb HER2) and used in a phase II clinical trial. *Id*. at 9–10. Baselga '96 teaches a loading dose of 250 mg per patient delivered intravenously followed by ten weekly 100 mg doses. *Id*. at 10. The target minimum effective concentration in blood plasma was greater than 10 μg/mL. *Id*. And "[s]erum levels of rhuMAb HER2 as a function of time were analyzed for each patient using a one-compartment model." *Id*.

Baselga '96 teaches that more than 90% of the study participants "had rhuMAb HER2 trough levels above the targeted 10 μg/mL level." *Id*. at 11. "Toxicity [from the antibody] was minimal," and no immune response against the antibody was detected. *Id*. at 9. Of the evaluated patients, one had a complete

remission and four had partial remissions. *Id*. at 13. In addition, 14 patients had stable disease at the conclusion of the study. *Id*. at 9. "The median time to progression for the patients with either minor or stable disease was 5.1 months." *Id*. at 12. Baselga '96 notes that "[t]he unusually long durations of minimal responses and stable disease seen in [the] clinical trial" may be indicative of the cytostatic effects of the antibody. *Id*. at 13. Accordingly, experimental measures such as time to disease progression—a metric used in the clinical setting since the 1980s—are especially appropriate in assessing treatment efficacy. *See* Exs. 1047 at 12; 1048 at 6.

Baselga '96 also teaches that "[i]n preclinical studies…rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity." Ex. 1005 at 15. As a result, "[l]aboratory studies of the mechanism of this effect and clinical trials of such combination therapy [we]re [] in progress." *Id*.

(6) Baselga '94

Baselga '94 reports the results of experiments using a mouse xenograft tumor model. Ex. 1006 at 4. HER2 overexpressing tumors were grown in mice followed by treatment with the 4D5-antibody in combination with paclitaxel. *Id*. While the antibody or paclitaxel alone produced 35% growth inhibition, the combination of the two resulted in 93% growth inhibition without increasing

toxicity. *Id*. Baselga '94 teaches that clinical trials of this drug combination were already underway. *Id*.

K. Explanation of Grounds of Unpatentability

Ground 1: Claims 1–11 and 14–17 are Invalid Based on Baselga '97 and Gelmon '96

(1) Claim 1

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

Baselga '97 in view of Gelmon '96 discloses "[a] method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor." Baselga '97 teaches that rhuMAb HER2 was used in "patients with metastatic breast carcinomas overexpressing HER2." Ex. 1007 at 9. Metastatic breast carcinoma is a malignant breast cancer that has spread to another area. Ex. 1011 ¶ 75. Baselga '97 further teaches that "[t]he HER2 gene (also known as *neu* and as *c-erb*B-2) encodes a…glycoprotein receptor ($p185^{HER2}$)." Ex. 1007 at 6. Thus the c-erbB-2 gene is also known as the HER2 gene—and a POSITA would know that the ErbB2 receptor protein is also known as the HER2 receptor protein. Ex. 1011 ¶ 76.

Baselga '97 teaches that positive results with single-therapy and mouse models "led to the design of a phase III multinational study of chemotherapy in combination with rhuMoAb HER2 in patients with HER2-overexpressing breast tumors." Ex. 1007 at 10.

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

Baselga '97 in view of Gelmon '96 discloses "administering a combination of an antibody that binds ErbB2." The phase III trial reported in Baselga '97 involved administering "rhuMoAb HER2 in combination with cytotoxic chemotherapy." *Id*.

Baselga '97 confirms that "[t]he murine monoclonal antibody (MoAb) 4D5 [is] directed against the extracellular domain of $p185^{HER2}$." *Id*. at 7; *see also* Ex. 1001 at 5:26–37. MAb 4D5 was then humanized by combining "the antigen-binding portions of murine MoAb 4D5…and a human immunoglobulin variable region framework" to produce "rhuMoAb HER2 IgG_1." Ex. 1007 at 9. The antigen-binding portions of an antibody are the portions of the antibody that determine what protein and where on that protein (the epitope) the antibody binds. Ex. 1011 ¶ 77. A POSITA would understand that, because rhuMAb HER2 contains the antigen-binding portions of MAb 4D5, it binds to the same epitope as MAb 4D5 and therefore rhuMAb HER2 binds to epitope 4D5 within the ErbB2 extracellular domain sequence of ErbB2. Exs. 1007 at 9; 1011 ¶ 77.

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

Baselga '97 in view of Gelmon '96 teaches a combination of an antibody and "a taxoid." Baselga '97 teaches that "[t]he treatment with paclitaxel plus 4D5 [in preclinical xenograft models] resulted in major antitumor activity." Ex. 1007 at

9. It also describes "a phase III multinational study of chemotherapy in combination with rhuMoAb HER2 in patients with HER2-overexpressing breast tumors" was underway. *Id*. at 10. The experimental group included patients receiving "paclitaxel, if patients have received anthracycline therapy in the adjuvant setting." *Id*.; Ex. 1001 at 4:23–25 (paclitaxel is a taxoid); *see also* Exs. 1007 at 7–8, 10 (discussing "encouraging" "[r]esults from the phase II studies and the activity of rhuMoAb HER2 against xenografts when given in combination with doxorubicin and paclitaxel"); 1011 ¶ 78.

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

Baselga '97 in view of Gelmon '96 discloses "a further growth inhibitory agent." Baselga '97 discusses the results of a phase II clinical trial of rhuMAb HER2 with cisplatin "in patients with breast carcinomas that overexpress $p185^{HER2}$." Ex. 1007 at 9. Baselga '97 reports an overall response rate of 25% "suggesting that the synergy observed in the laboratory was reproducible in the clinic. In addition, the combined therapy was no more toxic than cisplatin alone." *Id*. Thus, Baselga '97 teaches that the combination of rhuMAb HER2 with paclitaxel or cisplatin results in synergistic effects over single therapies without increasing toxicity. Ex. 1011 ¶ 79.

Gelmon '96 teaches a synergistic effect of paclitaxel combined with cisplatin in patients with metastatic breast cancer. Ex. 1025 at 9. Gelmon '96

explains the motivation to combine paclitaxel and cisplatin: "We were also interested in combining [paclitaxel] with a non-cross-resistant drug with a different spectrum of toxicity. Cisplatin seemed to be an appropriate choice." *Id*. In particular, "[t]he mechanisms of resistance for cisplatin and paclitaxel differ… [and], except for neurotoxicity, the toxicities associated with [the two drugs] do not overlap." *Id*. at 9–10; *see also* Ex. 1011 ¶ 80.

Both Baselga '97 and Gelmon '96 are directed toward finding appropriate therapies for breast cancer. A POSITA reading Gelmon '96 would understand that HER2 positive breast cancer patients are resistant to both paclitaxel and cisplatin therapies, but looking to Baselga '97 would know that rhuMAb HER2 serves to sensitize HER2 positive tumors to both therapies. For this reason, a POSITA looking to improve treatment of HER2 positive breast cancer patients would combine the teachings of Baselga '97 and Gelmon '96 with a reasonable expectation of success. *See id*. ¶ 84.

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

Baselga '97 in view of Gelmon '96 discloses administration in human patients. Ex. 1007 at 10.

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

Baselga '97 in view of Gelmon '96 discloses "in an amount effective to

extend the time to disease progression in the human patient." First, the claim itself purports to capture ***any*** "amount effective to extend the time to disease progression" even though the '549 patent describes no such effective amounts for the claimed three-drug combination. *See* Ex. 1011 ¶ 83. Thus, the patent itself relies on the fact that a POSITA would have known how to conduct the necessary experimentation to determine an appropriate dose of the combined treatment to extend the time to disease progression. *Id*.

Second, Baselga '97 discloses that a loading dose of 250 mg followed by weekly doses of 100 mg of rhuMAb HER2 as a single therapy results in an increase in time to disease progression. Ex. 1007 at 9. Specifically, the responses "lasted for a median of 5.1 months." *Id*.; *see also* Ex. 1011 ¶ 84. Baselga '97 additionally reports that "[a]dequate serum levels of rhuMoAb HER2 were obtained in 90% of the patients" with a mean half-life of about 8.3 days. *Id*.

Third, Gelmon '96 discloses that biweekly administration of cisplatin with paclitaxel was an effective combination in patients with metastatic breast cancer. Ex. 1025 at 10, 14. The combination resulted in "an overall response rate of 85%" with a "median duration of overall response…[of] 7.9 months." *Id*. at 13. Therefore, Gelmon '96 discloses a combined paclitaxel plus cisplatin treatment regimen that increases the time to disease progression. *See* Ex. 1011 ¶ 85.

Finally, Baselga '97 discloses that the combination of rhuMAb HER2 plus

either cisplatin or paclitaxel results in synergistic increases in treatment efficacy. Ex. 1007 at 9–10. In the cisplatin trial, patients were administered 250 mg of rhuMAb HER2 followed by 100 mg weekly and 75 mg/m^2 of cisplatin every three weeks. *Id*. "[T]he observed response rate to the combined therapy was 25%, suggesting that the synergy observed in the laboratory was reproducible in the clinic" and "the combined therapy was no more toxic than cisplatin alone." *Id*. at 10.

Baselga '97 also discloses that combined administration of paclitaxel and anti-ErbB2 antibodies showed "major antitumor activity" in preclinical models. *Id*. As a result, "a phase III multinational study of chemotherapy in combination with rhuMoAb HER2 in patients with HER2-overexpressing breast tumors" was designed. *Id*. "The main goal of [the] study [was] to determine whether the addition of [rhuMAb HER2] increases the time to disease progression compared with" the control group. *Id*.; *see also* Ex. 1011 ¶¶ 86–89.

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

Baselga '97 in view of Gelmon '96 discloses "wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence." For the reasons stated above, a POSITA would understand that because rhuMAb HER2 contains the antigen-binding portions of MAb 4D5, it binds to the same epitope as MAb

4D5 and therefore rhuMAb HER2, used in Baselga '97, binds to epitope 4D5 within the ErbB2 extracellular domain sequence. Exs. 1007 at 9; 1011 ¶ 88.

h. Conclusion

Given the established synergistic results of cisplatin plus paclitaxel, anti-ErbB2 antibody plus cisplatin, and anti-ErbB2 antibody plus paclitaxel, a POSITA would have been motivated to combine rhuMAb HER2, paclitaxel, and cisplatin at the already effective doses disclosed by Gelmon '96 (for cisplatin and paclitaxel) and Baselga '97 (for rhuMAb HER2) and would have had a reasonable expectation of achieving—and improving upon—the already extended time to disease progression reported in Baselga '97 without an unreasonable risk of increasing toxicity. *Id*.¶¶ 89–90.

Every other combination of these therapies had been tried and yielded synergistic results with acceptable toxicity. Exs. 1025 at 9–10; 1007 at 9–10; 1011 ¶¶ 89–90. The three-drug combination was the only combination left to try and required nothing more than common sense to try it for the same established purpose. *Id*. It would have been immediately apparent to a POSITA to use an amount effective to extend the time to disease progression. Indeed, increasing time to disease progression is considered to be a surrogate measure of drug effectiveness by the FDA and is often the entire point of anti-ErbB2 antibodies, paclitaxel, and cisplatin, and metastatic breast cancer therapies in general. *Id*. The

'549 patent itself discloses no amounts that should be used and no data showing time to disease progression is extended by its claimed three-drug combination therapy, thus Genentech cannot reasonably dispute that a POSITA would have known to use and how to determine such amounts.

(2) Claim 2

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

Baselga '97 in view of Gelmon '96 teaches the method of claim 1. *See* Section V.K.Ground 1:(1). Baselga '97 teaches that "[t]he murine monoclonal antibody (MoAb) 4D5, directed against the extracellular domain of $p185^{HER2}$," was humanized. Exs. 1007 at 7, 10; 1011 ¶¶ 91–92; *see* Section V.K.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."

Baselga '97 in view of Gelmon '96 teaches the method of claim 1. *See* Section V.K.Ground 1:(1). Cross-blocking assays are routine laboratory experiments to confirm two antibodies share overlapping binding specificity. Exs. 1001 at 5:28–33; 1011 ¶¶ 93–94. Baselga '97 teaches that rhuMAb HER2 possesses the same antigen-binding regions as 4D5, therefore it necessarily crossblocks binding of 4D5 to the ErbB2 extracellular domain sequence. Exs. 1007 at 9; 1011 ¶¶ 93–94; *see* Section V.K.Ground 1:(1)g.

(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."

Baselga '97 in view of Gelmon '96 teaches the method of claim 1. *See* Section V.K.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. 1001 at 5:32–37. Baselga '97 teaches that rhuMAb HER2 is a humanized form of the murine 4D5 antibody. Ex. 1007 at 9; *see* Section V.K.Ground 1:(1)g. Because rhuMAb HER2 possesses the same antigen-binding regions as 4D5 it necessarily also binds to the claimed amino acid residues. Ex. 1011 ¶¶ 95–96.

(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"

Baselga '97 in view of Gelmon '96 discloses "[a] method for the treatment of a human patient with breast cancer characterized by overexpression of ErbB2 receptor." *See* Section V.K.Ground 1:(1)a.

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,"

Baselga '97 in view of Gelmon '96 discloses "administering an effective

amount of a combination." Since "an amount effective to extend the time to disease progression," would be an "effective amount," Baselga '97 in view of Gelmon '96 discloses "an effective amount." Ex. 1011 ¶¶ 98–99; *see* Section V.K.Ground 1:(1)f.

Baselga '97 in view of Gelmon '96 discloses "an anti-ErbB2 antibody which binds epitope 4D5 within the ErbB2 extracellular domain sequence." *See* Section V.K.Ground 1:(1)g.

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

Baselga '97 in view of Gelmon '96 discloses a combination of rhuMAb HER2 and "a taxoid." *See* Section V.K.Ground 1:(1)c.

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

Baselga '97 in view of Gelmon '96 discloses "a further therapeutic agent." *See* Section V.K.Ground 1:(1)d. Claim 11 provides that a "therapeutic agent" may be a "growth inhibitory agent." Ex. 1001 at claim 11. Therefore, a "therapeutic agent" includes a "growth inhibitory agent." Ex. 1011 ¶ 101.

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

Baselga '97 in view of Gelmon '96 discloses "to the human patient." *See* Section V.K.Ground 1:(1)e.

f. Conclusion

For the same reasons discussed in Section V.K.Ground 1:(1)h, it would have been obvious to a POSITA to try the combination of rhuMAb HER2, paclitaxel, and cisplatin as recited in claim 5 with a reasonable expectation of success.

(6) Claim 6

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

Baselga '97 in view of Gelmon '96 teaches the method of claim 5. *See* Section V.K.Ground 1:(5). Baselga '97 discloses that rhuMAb HER2 was used in "[p]atients with metastatic breast carcinomas overexpressing HER2." Exs. 1007 at 9; 1011 ¶¶ 104–105.

(7) Claim 7

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

Baselga '97 in view of Gelmon '96 teaches the method of claim 5. *See* Section V.K.Ground 1:(5). Baselga '97 teaches that rhuMAb HER2 is a humanized form of the murine 4D5 antibody. *See* Section V.K.Ground 1:(1)g.

(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."

Baselga '97 in view of Gelmon '96 teaches the method of claim 7. *See* Section V.K.Ground 1:(7). Baselga '97 treated patients with a "loading dose of 250

mg IV rhuMoAb HER2, then 10 weekly doses of 100 mg each." Ex. 1007 at 9. This dose resulted in an amount effective to extend the time to disease progression by 5.1 months. *Id*. More than 90% of patients achieved adequate serum concentrations of the antibody. *Id*. A POSITA would have understood that it is more reliable to administer drugs on a weight-based basis to more reliably achieve adequate serum concentrations of the drug. Ex. 1011 ¶ 109. Additionally, 55–85 kg is a reasonable range that a POSITA would assume for patient weight. *See id*. ¶ 39; Exs. 1024 at 3; 1044 at 334 (Table 7-2). Assuming a patient weight between 55–85 kg, the corresponding weight-based dose is a loading dose of approximately 2.9–4.5 mg/kg (*i.e*., 250 mg divided by either 85 kg or 55 kg respectively) followed by a weekly maintenance dose of 1.2–1.8 mg/kg (*i.e*., 100 mg divided by either 85 kg or 55 kg respectively). *Id*. ¶¶ 39 (citing Ex. 1044 at 334 (Table 7-2)), 108–110. As taught by Baselga '97, this dose range will result in a plasma concentration above the target minimum in more than 90% of patients. Ex. 1007 at 9. The '549 patent contains no data showing that this claimed dosing regimen had any unexpected properties or was otherwise distinguishable from the range of doses derived directly from Baselga '97. Ex. 1011 ¶ 110; *see also In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) ("The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims…These cases have consistently held that in such a situation, the

applicant must show that the particular range is *critical*, generally by showing that the claimed range achieves unexpected results relative to the prior art range.").

(9) Claim 9

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

Baselga '97 in view of Gelmon '96 teaches the method of claim 5. *See* Section V.K.Ground 1:(5). Baselga '97 discloses the taxoid paclitaxel. *See* Section V.K.Ground 1:(1)c.

(10) Claim 10

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

Baselga '97 in view of Gelmon '96 teaches the method of claim 5. *See* Section V.K.Ground 1:(5). Baselga '97 in view of Gelmon '96 teaches measuring the results by the time to disease progression. *See* Section V.K.Ground 1:(1)f. Baselga '97 also reports that, out of the patients treated with rhuMAb HER2, the overall response rate was 11.6%. Ex. 1007 at 9. It would have been obvious to a POSITA to measure the overall response rate of the combination therapy based on this disclosure from Baselga '97. Ex. 1011 ¶¶ 113–114.

(11) Claim 11

a. "The method of claim 5 wherein the further therapeutic agent is selected from the group consisting of…growth inhibitory agent."

Baselga '97 in view of Gelmon '96 teaches the method of claim 5. *See* Section V.K.Ground 1:(5). Baselga '97 in view of Gelmon '96 teaches a "growth inhibitory agent." *See* Section V.K.Ground 1:(1)d.

(12) Claim 14

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

Baselga '97 in view of Gelmon '96 teaches the method of claim 5. *See* Section V.K.Ground 1:(5). Baselga '97 in view of Gelmon '96 teaches a "growth inhibitory agent." *See* Section V.K.Ground 1:(1)d.

(13) Claim 15

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

Baselga '97 in view of Gelmon '96 teaches the method of claim 14. *See* Section V.K.Ground 1:(12). Baselga '97 in view of Gelmon '96 teaches the combination of rhuMAb HER2 with paclitaxel and cisplatin. *See* Section V.K.Ground 1:(1)d. Cisplatin is a DNA alkylating agent. Exs. 1001 at 11:31–34; 1011 ¶¶ 119–120.

(14) Claim 16

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

Baselga '97 in view of Gelmon '96 discloses "[a] method for the treatment of a human patient with ErbB2 overexpressing breast cancer." *See* Section V.K.Ground 1:(1)a.

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

Baselga '97 in view of Gelmon '96 discloses "administering a combination of an antibody that binds epitope 4D5 within the ErbB2 extracellular domain sequence." *See* Section V.K.Ground 1:(1)g.

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

Baselga '97 in view of Gelmon '96 discloses a combination of rhuMAb HER2 and "a taxoid." *See* Section V.K.Ground 1:(1)c.

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

Baselga '97 in view of Gelmon '96 discloses "a further growth inhibitory agent." *See* Section V.K.Ground 1:(1)d.

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

Baselga '97 in view of Gelmon '96 discloses "in the absence of an anthracycline derivative." The cardiotoxicity of anthracycline derivatives were

known in the prior art. Ex. 1011 ¶¶ 125–128. Baselga '97 in view of Gelmon '96 also teaches the absence of an anthracycline derivative because they teach the combination of rhuMAb HER2, paclitaxel and cisplatin. *See, e.g.*, Sections V.K.Ground 1:(1)b–(1)f. Accordingly, a POSITA reading Baselga '97 in view of Gelmon '96 would not be motivated to combine rhuMAb HER2, a taxoid, and an anthracycline derivative and in fact, would be motivated not to do so due to the known cardiotoxic effects of anthracyclines. Ex. 1011 ¶¶ 125–128.

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

Baselga '97 in view of Gelmon '96 discloses administering the treatment "to the human patient." *See* Section V.K.Ground 1:(1)e.

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

Baselga '97 in view of Gelmon '96 discloses "in an amount effective to extend the time to disease progression in the human patient." *See* Section V.K.Ground 1:(1)f.

a. Conclusion

For the same reasons discussed in Section V.K.Ground 1:(1)h, it would have been obvious to a POSITA to try the combination of rhuMAb HER2, paclitaxel, and cisplatin as recited in claim 16 with a reasonable expectation of success.

(15) Claim 17

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

Baselga '97 in view of Gelmon '96 discloses the method of claim 16. *See* Section V.K.Ground 1:(14). Baselga '97 teaches "metastatic breast carcinoma." *See* Section V.K.Ground 1:(6)a.

Ground 2: Claim 12 is Invalid Based on Baselga '97 in view of Gelmon '96 and Drebin '88

(1) Claim 12

a. "The method of claim 5 wherein the further therapeutic agent is another ErbB2 antibody."

Baselga '97 in view of Gelmon '96 discloses the method of claim 5. *See* Section V.K.Ground 1:(5). Further, Drebin '88 teaches that antibodies against "two distinct regions on the p185 molecule" "resulted in synergistic anti-tumor effects." Ex. 1010 at 4. A POSITA would have been motivated to combine the teachings of Drebin '88 with those of Baselga '97 in view of Gelmon '96 because they are all directed toward methods of treatment for HER2 positive breast cancer, and because anti-ErbB2 antibodies act to sensitize tumor cells to chemotherapeutic agents. Ex. 1007 at 9.

Since the blockade of the 4D5 domain does not result in complete tumor suppression, *id*., a POSITA would look to Drebin '88's teaching that blockade of multiple target domains could result in complete tumor suppression, and thus

greater sensitization to those same chemotherapeutic agents. Ex. 1011 ¶¶ 135–137. As such, a POSITA would have been motivated to try another ErbB2 antibody, as taught by Drebin '88. Notably the '549 patent discloses no experiments using "another ErbB2 antibody" providing confirmation that a POSITA would have already known the claimed combination would work.

Ground 3: Claim 13 is Invalid Based on Baselga '97 in view of Gelmon '96 and Presta '97

(1) Claim 13

a. "The method of claim 5 wherein the further therapeutic agent is a vascular endothelial growth factor (VEGF) antibody."

Baselga '97 in view of Gelmon '96 discloses the method of claim 5. *See* Section V.K.Ground 1:(5). Presta '97 further teaches that antibodies against VEGF result in substantial tumor control. Ex. 1012 at 8. And Presta '97 provides a humanized antibody against VEGF ready for use in humans. *Id*. at 11. All of Baselga '97, Gelmon '96 and Presta '97 are directed to cancer therapies, and a POSITA would have been motivated to combine the teachings of Baselga '97 and Presta '97 because it was well-understood that ErbB2 and VEGF act on unrelated pathways and thus are likely to have at least an additive, if not a synergistic effect with a low, or nonexistent, likelihood of overlapping toxicity. *See* Ex. 1025 at 9–10.

For at least these reasons, it would have been obvious to combine the teachings of Presta '97 with Baselga '97 in view of Gelmon '96 by trying a VEGF antibody. Ex. 1011 ¶¶ 139–141. Notably the '549 patent discloses no experiment using a VEGF antibody providing confirmation that a POSITA would already have known the claimed combination would work.

Ground 4: Claims 1–11 and 14–17 are Invalid Based on Baselga '96 in view of Baselga '94 and Gelmon '96

(1) Claim 1

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

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "[a] method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor." Baselga '96 teaches that rhuMAb HER2 was used in "[p]atients…whose metastatic breast carcinomas overexpressed HER2." Ex. 1005 at 10. Metastatic breast carcinoma is a malignant breast cancer. Ex. 1011 ¶ 143.

Baselga '96 further teaches that "[t]he HER2 gene (also known as *neu* and as *c-erbB*-2) encodes a…glycoprotein receptor ($p185^{HER2}$)." Ex. 1005 at 9. Thus the c-erbB-2 gene is also known as the HER2 gene—a POSITA would have known that the ErbB2 receptor protein is also known as the HER2 receptor protein. Ex. 1011 ¶¶ 144–145.

Baselga '96 confirmed ErbB2 overexpression "by immunohistochemical

analysis." Ex. 1005 at 10; *see also id*. at 13, Table 5; Ex. 1011 ¶ 146.

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

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

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

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

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

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

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "administering a combination of an antibody that binds ErbB2." The phase II trial reported in Baselga '96 involved administering "rhuMAb HER2…intravenously" weekly for ten weeks. Ex. 1005 at 10.

RhuMAb HER2 was prepared by humanizing "[t]he murine monoclonal antibody (MAb) 4D5," which "[is] directed against the extracellular domain of $p185^{HER2}$." *Id*. at 9; *see also* Ex. 1001 at 5:26–37. MAb 4D5 was humanized by "inserting the complementarity determining regions…into the framework of a consensus human immunoglobulin G_1 (IgG_1)." Ex. 1005 at 10. The complementarity determining region of an antibody is the portion of the antibody determining what the antibody binds to, *i.e*., the epitope. Ex. 1011 ¶¶ 147–148. Because rhuMAb HER2 contains the same complementarity determining region as

MAb 4D5, it binds to the same epitope as MAb 4D5 and therefore rhuMAb HER2, used in Baselga '96, binds to epitope 4D5 within the ErbB2 extracellular domain sequence. Exs. 1005 at 10; 1011 ¶¶ 147–148.

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

Baselga '96 in view of Baselga '94 and Gelmon '96 teaches a combination of an antibody and "a taxoid." In Table 5, Baselga '96 shows that all "five [patients who] experienced a complete or partial remission" had "[p]rior [s]ystemic [t]herapy" and 4 of 5 patients were given either paclitaxel or docetaxel (taxoids). Ex. 1005 at 13, Table 5. Baselga '96 also teaches that "[i]n preclinical studies…rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including…paclitaxel without increasing their toxicity." *Id*. at 15. As a result, "clinical trials of such combination therapy [we]re currently in progress." *Id*.

Baselga '96 cites to Baselga '94 in describing these results, and thus a POSITA would look to Baselga '94 for additional details. Baselga '94 further teaches that individual treatment with either 4D5 or paclitaxel alone resulted in 35% growth inhibition. Ex. 1006 at 4. Their *combination* "resulted in a major antitumor activity with 93% inhibition of growth" without increasing toxicity. *Id*. In light of this, Baselga '94 discloses that "[c]linical trials are underway." *Id*.; *see also* Ex. 1011 ¶¶ 149–152.

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

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "a further growth inhibitory agent." Baselga '96 teaches that "[i]n preclinical studies…rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity." Ex. 1005 at 15. Thus, Baselga '96 individually teaches that the combination of rhuMAb HER2 plus paclitaxel or cisplatin both result in synergistic effects over single therapies without increasing toxicity. Ex. 1011 ¶ 153.

Gelmon '96 further teaches a synergistic effect of paclitaxel with cisplatin in patients with breast cancer. Ex. 1025 at 9. It explains the motivation to combine paclitaxel and cisplatin: "We were also interested in combining [paclitaxel] with a non-cross-resistant drug with a different spectrum of toxicity. Cisplatin seemed to be an appropriate choice." *Id*. In particular, "[t]he mechanisms of resistance for cisplatin and paclitaxel differ…[and], except for neurotoxicity, the toxicities associated with cisplatin do not overlap with those of paclitaxel." *Id*. at 9–10; Ex. 1011 ¶ 154.

All of Baselga '96, Baselga '94, and Gelmon '96 are directed toward finding appropriate therapies for breast cancer. A POSITA reading Gelmon '96 would understand that HER2 positive breast cancer patients are resistant to both paclitaxel

and cisplatin therapies, but looking to Baselga '96 would know that rhuMAb HER2 serves to sensitize HER2 positive tumors to both therapies. For this reason, a POSITA would combine the teachings of Baselga '96, Baselga '94 and Gelmon '96 with a reasonable expectation of success. *See* Ex. 1011 ¶ 155.

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

Baselga '96, in view of Baselga '94 and Gelmon '96, discloses administration in human patients. Ex. 1005 at 10.

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

Baselga '96, in view of Baselga '94 and Gelmon '96, discloses "an amount effective to extend the time to disease progression in the human patient." First, the claim itself purports to capture ***any*** "amount effective to extend the time to disease progression" even though the '549 patent describes no such effective amounts for the claimed three-drug combination. Thus, the patent itself must rest on the assumption that a POSITA would have known how to conduct the necessary experimentation to determine an amount effective as per claim 1. Ex. 1011 ¶ 157.

Second, Baselga '96 discloses that a loading dose of 250 mg followed by weekly doses of 100 mg of rhuMAb HER2 as a single therapy results in an increase in time to disease progression. Ex. 1005 at 10. Specifically, the responses "lasted for a median of 5.1 months." *Id*. at 9; *see also id*. at 13, Table 5 (Duration

of Response (months)); Ex. 1011 ¶ 158.

Third, Gelmon '96 discloses that biweekly administration of cisplatin with paclitaxel was an effective combination in breast cancer patients. Ex. 1025 at 10, 14. The combination resulted in "an overall response rate of 85%" with a "median duration of overall response…[of] 7.9 months." *Id*. at 13. Therefore, Gelmon '96 discloses a combined paclitaxel plus cisplatin treatment regimen that increases the time to disease progression. Ex. 1011 ¶¶ 159–161.

Finally, Baselga '96 discloses that the combination of rhuMAb HER2 with cisplatin or paclitaxel in preclinical models results in synergistic increases in treatment efficacy over single therapies without increasing toxicity. Exs. 1005 at 15; 1011 ¶¶ 161–162.

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

Baselga '96 discloses "wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence." For the reasons stated above, a POSITA would understand that, because rhuMAb HER2 contains the complementarity determining region of MAb 4D5, it binds to the same epitope as MAb 4D5 and therefore rhuMAb HER2, used in Baselga '96, binds to epitope 4D5 within the ErbB2 extracellular domain sequence. Exs. 1007 at 9; 1011 ¶ 163.

h. Conclusion

Given the established synergistic effects of cisplatin plus paclitaxel, anti-ErbB2 antibody plus cisplatin, and anti-ErbB2 antibody plus paclitaxel, a POSITA would have combined rhuMAb HER2, paclitaxel, and cisplatin at the already effective doses disclosed by Gelmon '96 (for cisplatin and paclitaxel) and Baselga '96 (for rhuMAb HER2) with a reasonable expectation of achieving—and improving upon—the already extended time to disease progression reported in Baselga '96 without an unreasonable risk of increasing toxicity. *Id*.¶¶ 164–166.

Every other possible combination of these therapies had been tried and yielded synergistic results with acceptable toxicity. Exs. 1025 at 9–10; 1005 at 15; 1011 ¶¶ 164–166. The three-drug combination was the only combination left to try and it required nothing more than common sense to try it for the same established purpose. *Id*. It would have been immediately apparent to a POSITA to use an amount effective to extend the time to disease progression in the human patient. Indeed, increasing time to disease progression is considered to be a surrogate measure of drug effectiveness by the FDA, and is often the entire point of anti-ErbB2 antibodies, paclitaxel, and cisplatin, and metastatic breast cancer therapies in general. *Id*.

The '549 patent itself discloses no amounts that should be used and no data showing time to disease progression is extended by its claimed combination

therapy, thus Genentech cannot reasonably dispute that a POSITA would have known to use and how to determine such amounts.

(2) Claim 2

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

Baselga '96 in view of Baselga '94 and Gelmon '96 teaches the method of claim 1. *See* Section V.K.Ground 4:(1). Baselga '96 in view of Baselga '94 and Gelmon '96 teaches that rhuMAb HER2 is a humanized form of the murine 4D5 antibody, therefore "the antibody is a humanized 4D5 anti-ErbB2 antibody." Exs. 1005 at 9; 1011 ¶¶ 167–168; *see* Section V.K.Ground 4:(1)g.

(3) Claim 3

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

Baselga '96 in view of Baselga '94 and Gelmon '96 teaches the method of claim 1. *See* Section V.K.Ground 4:(1). Cross-blocking assays are routine experiments to confirm that two antibodies share overlapping binding specificity. Exs. 1001 at 5:28–33; 1011 ¶ 170. Baselga '96 teaches that rhuMAb HER2 possesses the same complementarity determining regions as 4D5, therefore it will necessarily crossblock binding of 4D5 to the ErbB2 extracellular domain sequence. Exs. 1005 at 9; 1011 ¶¶ 169–171; *see* Section V.K.Ground 4:(1)g.

(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."

Baselga '96 in view of Baselga '94 and Gelmon '96 teaches the method of claim 1. *See* Section V.K.Ground 4:(1). The '549 patent concedes that the 4D5 antibody binds to the claimed amino acid residues. Ex. 1001 at 5:32–37. Baselga '96 teaches that rhuMAb HER2 is a humanized form of the murine 4D5 antibody. Ex. 1005 at 9; *see* Section V.K.Ground 4:(1)g. Because rhuMAb HER2 possesses the same complementarity determining regions as 4D5 it necessarily also binds to the claimed amino acid residues. Ex. 1011 ¶¶ 172–174.

(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"

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "[a] method for the treatment of a human patient with breast cancer characterized by overexpression of ErbB2 receptor." *See* Section V.K.Ground 4:(1)a.

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,"

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "administering an effective amount of a combination." Since "an amount effective to extend the

time to disease progression," would be an "effective amount," Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "an effective amount." Ex. 1011 ¶¶ 176–177; *see* Section V.K.Ground 4:(1)f.

Baselga '96 discloses "an anti-ErbB2 antibody which binds epitope 4D5 within the ErbB2 extracellular domain sequence." *See* Section V.K.Ground 4:(1)g; Ex. 1011 ¶¶ 176–177.

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

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses a combination of rhuMAb HER2 and "a taxoid." *See* Section V.K.Ground 4:(1)c.

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

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "a further therapeutic agent." Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "a further growth inhibitory agent." *See* Section V.K.Ground 4:(1)d. Claim 11 provides that a "therapeutic agent" may be a "growth inhibitory agent." Ex. 1001 at claim 11. Therefore, a "therapeutic agent" includes a "growth inhibitory agent." Ex. 1011 ¶ 179.

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

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "to the human patient." *See* Section V.K.Ground 4:(1)e.

f. Conclusion

For the same reasons discussed in Section V.K.Ground 4:(1)h, it would have been obvious to a POSITA to try the combination of rhuMAb HER2, paclitaxel, and cisplatin as recited in claim 5 with a reasonable expectation of success.

(6) Claim 6

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

Baselga '96, in view of Baselga '94 and Gelmon '96, teaches the method of claim 5. *See* Section V.K.Ground 4:(5). Baselga '96 discloses that "[p]atients eligible for this study were adult women whose metastatic breast carcinomas overexpressed HER2." Exs. 1005 at 10; 1011 ¶¶ 182–183.

(7) Claim 7

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

Baselga '96 in view of Baselga '94 and Gelmon '96 teaches the method of claim 5. *See* Section V.K.Ground 4:(5). Baselga '96 teaches that rhuMAb HER2 is a humanized form of the murine 4D5 antibody. *See* Section V.K.Ground 4:(1)g.

(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."

Baselga '96 in view of Baselga '94 and Gelmon '96 teaches the method of claim 7. *See* Section V.K.Ground 4:(7). Baselga '96 treated patients with "a

loading dose of 250 mg of intravenous rhuMAb HER2, then 10 weekly doses of 100 mg each." Ex. 1005 at 9. This dose resulted in an amount effective to extend the time to disease progression by 5.1 months. *Id*. In addition, more than 90% of patients achieved adequate serum concentrations of the antibody. *Id*.

A POSITA in clinical oncology would know that it is more reliable to administer drugs on a weight-based basis to more reliably achieve adequate serum concentrations of the drug. Ex. 1011 ¶¶ 187–188. In this case, assuming a patient weight between 55–85 kg, the corresponding weight-based dose is a loading dose of approximately 2.9–4.5 mg/kg (*i.e*., 250 mg divided by either 85 kg or 55 kg respectively) followed by a weekly maintenance dose of 1.2–1.8 mg/kg (*i.e*., 100 mg divided by either 85 kg or 55 kg respectively). *Id*. ¶¶ 39 (citing Ex. 1044 at 334 (Table 7-2)), 187–188.

As taught by Baselga '96, this dose range will result in a plasma concentration above the target minimum in more than 90% of patients. Ex. 1005 at 9. The '549 patent contains no data showing that this claimed dosing regimen had any unexpected properties or was otherwise distinguishable from the range of doses derived directly from Baselga '96. Ex. 1011 ¶ 189; *see also Woodruff*, 919 F.2d at 1578 ("The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims… These cases have consistently held that in such a situation, the applicant

must show that the particular range is *critical*, generally by showing that the claimed range achieves unexpected results relative to the prior art range.").

(9) Claim 9

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

Baselga '96 in view of Baselga '94 and Gelmon '96 teaches the method of claim 5. *See* Section V.K.Ground 4:(5). As discussed above in Section V.K.Ground 4:(1)c, Baselga '96 discloses the taxoid paclitaxel. Exs. 1005 at 13; 1011 ¶¶ 190–191.

(10) Claim 10

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

Baselga '96 in view of Baselga '94 and Gelmon '96 teaches the method of claim 5. *See* Section V.K.Ground 4:(5). Baselga '96 in view of Baselga '94 and Gelmon '96 teaches measuring the results by the time to disease progression. *See* Section V.K.Ground 4:(1)f. Baselga '96 also reports that, out of the patients treated with rhuMAb HER2, the overall response rate was 11.6%. Ex. 1005 at 13. It would have been obvious to a POSITA to measure the overall response rate of the combination therapy based on this disclosure. Ex. 1011 ¶¶ 192–193.

(11) Claim 11

a. "The method of claim 5 wherein the further therapeutic agent is selected from the group consisting of…growth inhibitory agent."

Baselga '96 in view of Baselga '94 and Gelmon '96 teaches the method of claim 5. *See* Section V.K.Ground 4:(5). Baselga '96 in view of Baselga '94 and Gelmon '96 teaches a "growth inhibitory agent." *See* Section V.K.Ground 4:(1)d.

(12) Claim 14

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

Baselga '96, in view of Baselga '94 and Gelmon '96, teaches the method of claim 5. *See* Section V.K.Ground 4:(5). Baselga '96, in view of Baselga '94 and Gelmon '96, teaches a "growth inhibitory agent." *See* Section V.K.Ground 4:(1)d.

(13) Claim 15

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

Baselga '96 in view of Baselga '94 and Gelmon '96 teaches the method of claim 14. *See* Section V.K.Ground 4:(12). Baselga '96 in view of Baselga '94 and Gelmon '96 teaches the combination of rhuMAb HER2 with paclitaxel and cisplatin. *See* Section V.K.Ground 4:(1)d. Cisplatin is considered a DNA alkylating agent. Exs. 1001 at 11:31–34; 1011 ¶¶ 198–199.

(14) Claim 16

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

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "[a] method for the treatment of a human patient with ErbB2 overexpressing breast cancer." *See* Section V.K.Ground 4:(1)a.

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

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "administering a combination of an antibody that binds epitope 4D5 within the ErbB2 extracellular domain sequence." *See* Section V.K.Ground 4:(1)g.

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

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses a combination of rhuMAb HER2 and "a taxoid." *See* Section V.K.Ground 4:(1)c.

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

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "a further growth inhibitory agent." *See* Section V.K.Ground 4:(1)d.

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

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "in the absence of an anthracycline derivative." The cardiotoxicity of anthracycline

derivatives were known in the prior art. Ex. 1011 ¶ 204. Consistent with this, Baselga '96 reports a patient that could not be examined at follow-up because she died of heart failure associated with prior doxorubicin treatment. Ex. 1005 at 12.

Baselga '96, in view of Baselga '94 and Gelmon '96, teaches the absence of an anthracycline derivative because Baselga '96, in view of Baselga '94 and Gelmon '96, teaches the combination of rhuMAb HER2, paclitaxel and cisplatin. *See, e.g.*, Sections V.K.Ground 4:(1)b–(1)f. Accordingly, a POSITA reading Baselga '96 in view of Baselga '94 and Gelmon '96 would not be motivated to combine rhuMAb HER2, a taxoid, and an anthracycline derivative and in fact, would be motivated not to do so due to the known cardiotoxic effects of anthracyclines. Ex. 1011 ¶¶ 204–205.

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

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "to the human patient." *See* Section V.K.Ground 4:(1)e.

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

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses "in an amount effective to extend the time to disease progression in the human patient." *See* Section V.K.Ground 4:(1)f.

h. Conclusion

For the same reasons discussed in Section V.K.Ground 4:(1)h, it would have

been obvious to a POSITA to try the combination of rhuMAb HER2, paclitaxel, and cisplatin in the absence of an anthracycline as recited by claim 16 with a reasonable expectation of success.

(15) Claim 17

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

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses the method of claim 16. *See* Section V.K.Ground 4:(14). Baselga '96 teaches "metastatic breast carcinoma." *See* Section V.K.Ground 4:(6)a.

Ground 5: Claim 12 is Invalid Based on Baselga '96 in view of Baselga '94, Gelmon '96 and Drebin '88

(1) Claim 12

a. "The method of claim 5 wherein the further therapeutic agent is another ErbB2 antibody."

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses the method of claim 5. *See* Section V.K.Ground 4:(5). Further, Drebin '88 teaches that antibodies against "two distinct regions on the p185 molecule" "resulted in synergistic anti-tumor effects." Ex. 1010 at 4. A POSITA would have been motivated to combine the teachings of Drebin '88 with those of Baselga '96 because anti-ErbB2 antibodies act to sensitize tumor cells to the effects of chemotherapeutic agents. Ex. 1005 at 15.

Since the blockade of the 4D5 domain does not result in complete tumor suppression, Ex. 1006 at 4, a POSITA would look to Drebin '88's teaching that blockade of multiple target domains could result in complete tumor suppression, and thus greater sensitization to those same chemotherapeutic agents. Ex. 1011 ¶¶ 212–214. As such, a POSITA would have been motivated to try another ErbB2 antibody, as taught by Drebin '88. Notably the '549 patent discloses no experiments using "another ErbB2 antibody" providing confirmation that a POSITA would know the claimed combination would work.

Ground 6: Claim 13 is Invalid Based on Baselga '96 in view of Baselga '94, Gelmon '96 and Presta '97

(1) Claim 13

a. "The method of claim 5 wherein the further therapeutic agent is a vascular endothelial growth factor (VEGF) antibody."

Baselga '96 in view of Baselga '94 and Gelmon '96 discloses the method of claim 5. *See* Section V.K.Ground 4:(5). Presta '97 further teaches that antibodies against the cytokine VEGF can result in substantial tumor control. Ex. 1012 at 8. And Presta '97 provides a humanized antibody against VEGF ready for use in humans. *Id*. at 11. All of Baselga '96, Baselga '94, Gelmon '96 and Presta '97 are directed to cancer therapies, and a POSITA would have been motivated to combine the teachings of Baselga '96 and Presta '97 because it was well-understood that ErbB2 and VEGF act on unrelated pathways and thus are likely to have at least an

additive, if not a synergistic effect, with a low or nonexistent likelihood of overlapping toxicity. *See* Ex. 1025 at 9–10; Ex. 1011 ¶¶ 216–218. As such, a POSITA would have been motivated to try a VEGF antibody, as taught by Presta '97. Notably the '549 patent discloses no experiment using a VEGF antibody providing confirmation that a POSITA would have known the claimed combination would work.

L. Secondary Considerations of Nonobviousness Do Not Support a Finding of Nonobviousness

On October 15, 2009, Genentech submitted the Declaration of Mark Sliwkowski, Ph.D. Ex. 1019–6:341. This Declaration argued the claims of the '824 application were patentable over the prior art because a POSITA would not have had a reasonable expectation of success treating humans with a two-drug combination of rhuMAb HER2 and paclitaxel. *Id*. at 6:343–45. Dr. Sliwkowski's Declaration **did <u>not</u> address three-drug combinations** as claimed by the '549 patent. As to the two-drug combination, Dr. Sliwkowski's argument was two-fold.

Dr. Sliwkowski first argued that treatment with paclitaxel results in G_2/M cell cycle arrest whereas rhuMAb HER2 results in G_1 cell cycle arrest. *Id*. at 6:343. Since the two treatments cause cell cycle arrest at different times, Dr. Sliwkowski argued a POSITA in 1997 would have thought that rhuMAb HER2 would prevent paclitaxel from working since cells would arrest prior to the G_2/M phase. *Id*. at 6:343–44. Dr. Sliwkowski further supported his argument by analogizing to

combination treatments with tamoxifen and anthracyclines that similarly cause cell cycle arrest at different times, and exhibit an antagonistic effect. *Id*.

Dr. Sliwkowski's first argument fails for three reasons. ***First***, none of the papers he relies upon examines the combination of rhuMAb HER2 and paclitaxel. *Id*. at 6:383 (Ex. C), 6:392 (Ex. D); Ex. 1011 ¶¶ 221–222.

Second, by 1994, other research had already demonstrated that rhuMAb HER2 was compatible with chemotherapies, such as cisplatin, that also show G_2/M cell cycle arrest. *See, e.g.*, Sorenson '90 (Ex. 1022) at 7 (cisplatin causes G_2 cell cycle arrest); Peitras '94 (Ex. 1023) (the combination of 4D5 anti-ErbB2 antibody and cisplatin caused a synergistic decrease in cell growth *in vitro*); and Pegram '95 (Ex. 1013) at 5 (combined treatment of rhuMAb HER2 and cisplatin in breast cancer patients resulted in 50% of patients with stable disease or better without increasing cisplatin toxicity); *see also* Ex. 1011 ¶¶ 223–224.

Third, a POSITA in 1997 would have understood the data that Dr. Sliwkowski cited related to tamoxifen and anthracyclines actually shows that his hypothesis regarding rhuMAb HER2 and paclitaxel is incorrect. Both articles he cites report *in vitro* data showing tamoxifen reduced cell killing effects of anthracyclines. Ex. 1019–7:17 (Ex. F), 7:26 (Ex. G). By contrast, Baselga '94 reports *in vivo* data demonstrating a synergistic effect between the 4D5 antibody and paclitaxel. Ex. 1006 at 4. If Dr. Sliwkowski's hypothesis were correct, the

preclinical data should have shown a ***less than additive*** effect when the drugs are both administered. *See* Exs. 1019–7:26 (Ex. G); 1011 ¶ 225. Since Baselga '94 reports the opposite and further reports that clinical trials are ongoing, a POSITA would have found it obvious to try the combination with a reasonable expectation of success.

Dr. Sliwkowski's second argument is that a POSITA would not have a reasonable expectation of success in humans based on preclinical models because "significant controversy exists about the usefulness of these preclinical models in predicting the response of human patients to therapy." Ex. 1019–6:344–45. But, Genentech relied on the information disclosed in the Baselga prior art, including at least Baselga '97 (*i.e.*, the phase II trial of the antibody single therapy, and the *in vitro* and *in vivo* preclinical data) when it determined it would proceed with a phase III trial of the drug combination. Indeed, it cites this prior art as the written description of its invention. Moreover, Dr. Sliwkowski's support for his argument comes from a non-prior art 2001 article. *Id*.

And the purported controversy regarding preclinical models does not affect their use in research, nor does it affect whether a POSITA will use such models to determine which treatments should be pursued in humans. Indeed, Dr. Sliwkowski is a co-author on many Genentech research papers using preclinical data in order to screen and select for novel treatments using anti-ErbB2 antibodies. *See*, *e.g.*, Exs.

1017 at 7 ("Because trastuzumab linked to DM1…offers improved efficacy and pharmacokinetics and reduced toxicity over the reducible disulfide linkers evaluated, trastuzumab-MCC-DM1 was selected for clinical development."); 1018.

POSITAs regularly use such models to screen treatments and select promising drugs for trial. Here, a POSITA would have seen that Baselga '94 demonstrated synergistic effects of the drug combination in a mouse model and reported a clinical trial underway, then Baselga '96 and Baselga '97 report the same clinical trial as underway two and three years later, respectively. Exs. 1006 at 4; 1005 at 15; 1007 at 10. A POSITA would have understood this to mean that the trial had not been halted for lack of efficacy or safety. Ex. 1011 ¶ 227. POSITAs like Drs. Baselga, Pegram, and Hellmann turned to the most obvious targets: combinations of known therapies seeking synergistic effects. Accordingly, there are no secondary considerations supporting nonobviousness of the '549 patent. *Id*.

Genentech's purported unexpected results also lack a nexus to the claimed inventions. The assertions in Dr. Sliwkowski's Declaration are directed to a paclitaxel and rhuMAb HER2 combination therapy, but that therapy already was disclosed in the prior art, including Baselga '97, '96, '94. Genentech identified no secondary indicia of non-obviousness associated with any elements of the claimed invention not already in the prior art. Genentech's purported unexpected results further are not commensurate in scope with the Challenged Claims, many of which

are generally directed to methods of treatment involving any "taxoid." *See* Ex. 1011 ¶ 228.

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 13,838 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. 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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