IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

U.S. Patent No. 7,846,441

Filed: December 10, 1998

Issued: December 7, 2010

Inventor(s): 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. 7,846,441
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 1–14 of U.S. Patent No. 7,846,441 ("the '441 patent") (Ex. 1001).[1]

USPTO assignment records state that the '441 patent is assigned to Genentech, Inc. ("Genentech") (Ex. 1016).

I. OVERVIEW

The '441 patent is directed to the well-known concept of combining two known treatments for cancers linked to the overexpression of the human ErbB2 protein. Claim 1 recites "administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence and a taxoid, in the absence of an anthracycline derivative." *See also* Ex. 1001 at Abstract.

The two recited cancer treatments, an anti-ErbB2 antibody that binds to epitope 4D5 and a taxoid chemotherapeutic agent, were known in the prior art. The '441 patent claims no credit for inventing these treatments, and rightly so. Genentech had already developed (and enjoyed many years of patent protection around) HERCEPTIN®, a humanized anti-ErbB2 antibody for treating breast cancer. *See* Exs. 1022; 1023; 1024. As discussed below, numerous prior art

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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.

publications discussed such an antibody as a known breast cancer treatment. Moreover, non-anthracycline chemotherapeutic agents, including the taxoid paclitaxel, recited in the '441 patent's dependent claims, were also known in the prior art.

Combining these two known therapies is not the result of any surprising discovery or ingenuity on the named inventor's part. That idea was also disclosed in multiple articles published as early as 1994, more than three years before the '441 patent's earliest claimed priority date. Indeed, the sole example in the '441 patent parrots the work and text of the prior art—even including that reference's typographical errors.

Like its invalidated European counterpart, the '441 patent simply combines known therapies for a known purpose. The purported invention is at best a product of routine experimentation and seeks to take back treatments that were already public. As the Supreme Court stated in *KSR*, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 416 (2007).

The Board should institute trial and find the '441 patent claims unpatentable.

II. 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 (the "EP '926 patent", Ex. 1002),[2] a European counterpart to the '441 patent, was recently invalidated and revoked in two separate European proceedings as obvious in light of certain references asserted here. *Hospira UK, Ltd. v. Genentech, Inc.*, Case No. HP-2014-000034, High Court of Justice, [2015] EWHC (HC) 1796 (Pat), (Jun. 24, 2015), Approved Judgment (Ex. 1003); Eur. Patent File History for EP 1,037,926 B1, *Decision to Revoke European Patent EP 1,037,926*, Application No. 98,963,840.8 (Jun. 13, 2016) ¶¶ 20–24 (Ex. 1020). 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. 1021). Petitioner concurrently files IPR petitions for claims of U.S.

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[2] The EP '926 patent and the '441 patent both claim priority to U.S. Provisional Application No. 60/069,346.

Patent Nos. 7,846,441 and 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:** KIRKLAND & ELLIS LLP 333 South Hope Street Los Angeles, CA 90071 Telephone: (213) 680-8140 Facsimile: (213) 680-8500

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 filed concurrently herewith. 37 C.F.R. § 42.10(b).

III. 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.

IV. GROUNDS FOR STANDING – 37 C.F.R. § 42.104(a)

Petitioner certifies that the '441 patent is available for IPR and is not barred or estopped from requesting IPR on the grounds identified herein. 35 U.S.C. § 315.

V. IDENTIFICATION OF CHALLENGE – 37 C.F.R. § 42.104(b)

The '441 patent application was filed on December 10, 1998, 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 1–14 on the following grounds:

Ground	Proposed Statutory Rejections for the '441 Patent
1	**Baselga '97 (Ex. 1006)** in view of **Baselga '94 (Ex. 1005)** renders obvious claims 1–14 under 35 U.S.C. § 103.
2	**Baselga '96 (Ex. 1004)** in view of **Baselga '94 (Ex. 1005)** renders obvious claims 1–14 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. 1006) is prior art under 35 U.S.C. § 102(a) and is a "printed publication" 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. 1004) is prior art under 35 U.S.C. § 102(b) and is a "printed publication" published March 1, 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. 1005) 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.

Below is a detailed explanation of the statutory grounds for the unpatentability of each claim. Additional evidence supporting each ground is provided in the accompanying Declaration of Allan Lipton, M.D. (Ex. 1007) and

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[3] Additional evidence authenticating various exhibits is provided in the Declarations of Amanda Hollis (Ex. 1046), Christopher Lowden (Ex. 1047), and Simon Cohen (Ex. 1048).

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.

VI. THE CLAIMS OF THE '441 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 clinical or medical oncologist specializing in breast cancer with several years of experience with breast cancer research or clinical trials. Exs. 1007 ¶¶ 15–17; 1003 ¶¶ 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 '441 patent 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 1:20–29 (citing Exs. 1028; 1029); 1006 at 6; 1004 at 9; 1030 at 20:15–20. The antibody, commercially known as HERCEPTIN®, was already well characterized and used in humans with ErbB2 overexpressing breast cancer. Ex. 1001 at 2:17–29, 3:34–40 (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. 1009 at 10; 1004 at 9–10. Paclitaxel also was a well-known treatment for

breast cancer. *See* Exs. 1025 at 10 (indicated for "the treatment of breast cancer"); 1026.

(1) RhuMAb HER2 Combined with Chemotherapeutic Agents was Well-Known

Since the 1960s, clinical oncologists have worked with combination chemotherapies. Exs. 1017 at 12–14; 1007 ¶ 28. The assumption was that higher treatment intensity (more exposure to different drugs over a shorter period of time) resulted in greater tumor killing prior to cancer gaining adaptive immunity to any one agent. *Id*.¶ 29. In breast cancer, beginning with "CMF"—or cyclophosphamide, methotrexate, 5-fluorouracil—treatment, combination therapies resulted in survival improvements through the 1980s. Exs. 1017 at 14; 1007 ¶ 30. Thus, when rhuMAb HER2 was created, oncologists had over 20 years of experience that combination therapies were superior to single-agent therapies. *Id*. ¶ 31.

rhuMAb HER2 has been used in combination with chemotherapeutic agents since the early 1990s. *E.g*., Exs. 1005 at 4; 1010 at 5; 1008 at 8; 1031 at 5; 1032 at 6; 1013 at 3. As was routine, this work began *in vitro* with cell assays, moved to *in vivo* preclinical models, then moved into humans. *E.g*., Exs. 1005 at 4; 1010 at 5; 1014 at 7; 1015 at 8; 1007 ¶ 39. One early combination was the platinum-based drug cisplatin and rhuMAb HER2. Ex. 1010 at 5. This stemmed from a phase I trial that showed "rhuMAb HER-2 has no substantial toxicity at any dose level and

localizes to malignant cells overexpressing the HER-2 receptor protein." *Id*. Preclinical studies demonstrated a synergistic effect between the two therapies. *Id*. As a result, this group, including Jose Baselga, administered the combination in patients and found a complete response, partial response, minor response, or stable disease in 50% of patients. *Id*.

(2) Baselga '94

Combinations of HER2 with taxoids also had been successfully used in the prior art. Baselga '94 reports the results of experiments in which HER2-overexpressing tumors were grown in nude mice then treated with the 4D5-antibody in combination with paclitaxel. *Id*. While the antibody or paclitaxel alone produced 35% tumor growth inhibition, the combination resulted in 93% inhibition without increasing the toxicity of paclitaxel. *Id*. Thus, combined treatment of rhuMAb HER2 with paclitaxel against "human breast adenocarcinoma cells, which express high levels of HER2," showed a synergistic increase in tumor-killing power. Exs. 1001 at 3:54–59; 1005 at 4. Baselga '94 teaches that clinical trials of this combination were already underway. *Id*.

(3) Baselga '96

Baselga '96 reports the results of a phase II clinical trial in patients with ErbB2-overexpressing metastatic breast cancer that received extensive prior therapy. Ex. 1004 at 9.

Baselga ’96 teaches “a direct role for HER2 in the pathogenesis and clinical aggressiveness of HER2-overexpressing tumors.” *Id*. First, tumor cells with induced HER2 overexpression become malignant and mice expressing HER2 “develop mammary tumors.” *Id*. Second, “HER2 overexpression is common in ductal carcinomas [(breast cancer)].” *Id*. Finally, “[a]ntibodies directed at $p185^{HER2}$ can inhibit the growth of tumors and of transformed cells that express high levels of this receptor” and “in xenograft models [] of human breast cancer cells that overexpress HER2.” *Id*.

After successful experiments in mouse models, Baselga ’96 taught that the 4D5 antibody (murine anti-ErbB2 antibody) was humanized (rhuMAb HER2). *Id*.; *see also* Exs. 1008 at 8; 1030 at claim 8; 1019 at 5–6. Baselga ’96 then reports the results of a phase II clinical trial using rhuMAb HER2. Ex. 1004 at 10. Baselga ’96 teaches a loading dose of 250 mg per patient delivered intravenously followed by ten weekly 100 mg doses. *Id*. The target minimum effective concentration in blood plasma was at least greater than 10 µg/mL. *Id*. “Serum levels of rhuMAb HER2 as a function of time were analyzed for each patient using a one-compartment model.” *Id*.

Baselga ’96 teaches that >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, four had partial remissions, and fourteen patients had stable disease at the conclusion of the study. *Id*. "The median time to progression…was 5.1 months." *Id*. Baselga '96 notes that "[t]he unusually long durations of minimal responses and stable disease" in the study may be due to cytostatic effects of the antibody. *Id*. at 13. Accordingly, experimental measures, such as time to disease progression—a clinical metric since the 1980's—were appropriate in assessing efficacy. *See* Exs. 1034 at 12; 1035 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. 1004 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*.

(4) Baselga '97

Baselga '97 teaches that ErbB2 receptor is overexpressed in 25–30% of malignant human breast cancers (Ex. 1006 at 6), and patients with ErbB2 overexpression are three-times more likely to respond to chemotherapy with taxanes (*id*. at 7–8).

Based on this evidence, Baselga '97 taught that a monoclonal mouse antibody (4D5) was generated against the ErbB2 receptor. *Id*. at 7. The antibody demonstrated growth inhibition in both *in vitro* and *in vivo* models. *Id*.

Baselga '97 taught that the 4D5 antibody was humanized (rhuMAb HER2) and used in phase I trials using a loading dose of 250 mg followed by ten weekly doses of 100 mg. *Id*. at 9. "Adequate serum levels of rhuMoAb HER2[4] were obtained in 90% of the patients" with a mean half-life of about 8.3 days. *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*.

When combined in mouse tumor models, the 4D5 antibody and paclitaxel "resulted in major antitumor activity, with 93% inhibition of growth." *Id*. The synergistic effect was substantial as each of the 4D5 antibody and paclitaxel produced only 35% growth inhibition alone. *Id*. The result with paclitaxel was "markedly better than an equipotent dose of doxorubicin…and 4D5." *Id*.

Baselga '97 taught these results were encouraging and that a "phase III multinational study of chemotherapy in combination with rhuMoAb HER2 in

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[4] Baselga '97 refers to rhuMAb HER2 as rhuMoAb HER2.

patients with HER2-overexpressing breast tumors who have not received prior chemotherapy for metastatic disease" was underway. *Id*. at 10. The trial compared the combination therapy against 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 [chemotherapy] alone."[5] *Id*. Baselga '97 notes that "[b]ecause anthracyclines are widely used in the adjuvant setting, it is likely that a significant number of patients will be treated with paclitaxel." *Id*.

(5) Anthracycline Toxicity was Known

Anthracyclines were and remain common first-line chemotherapies for breast cancer. Exs. 1006 at 10; 1033 at 4, 12. These drugs are effective but cardiotoxic, and by the mid-1990s it was understood that the cardiotoxicity was cumulative irrespective of the time between treatments. Ex. 1006 at 11. It is unsurprising that researchers were using several rhuMAb HER2 combination regimens that avoided using anthracyclines. *See* Exs. 1010 at 5; 1007 ¶ 33.

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[5] The statement "antibody alone" is a typographical error. Ex. 1006 at 10 ("the active arm, which consists of rhuMoAb HER2 in combination with cytotoxic chemotherapy; or the control arm, which consists of cytotoxic chemotherapy alone"), Figure 2; Ex. 1007 ¶ 65, n.5.

(6) The '441 Patent Relies Upon Baselga's Work

Although not highlighted for the Examiner during prosecution, the '441 patent relied heavily on Baselga's work. Indeed, the '441 patent specification relies on Baselga '97 to show that "the odds of HER2-positive patients responding clinically to treatment with taxanes[6] [are] greater than three times those of HER2 negative patients." Ex. 1001 at 3:50–54 (citing Baselga '97). And the '441 patent cites Baselga '94 to show that a humanized HER2 antibody "enhance[d] the activity of paclitaxel." *Id*. at 3:50–59. Indeed, the sole Example in the '441 patent is a disclosure of the Baselga prior art:

> "The resulting humanized anti-ErbB2 monoclonal antibody has high affinity for p185" (Dillohiation [*sic*] constant [K_d]=0.1 nmol/L), markedly inhibits, in vitro and in human xenografts, the growth of breast cancer cells that contain high levels of $p185^{HER2}$, induces antibody-dependent cellular cytotoxicity (ADCC), and has been found clinically active, as a single agent, in patients with ErbB2-overexpressing metastatic breast cancers that had received extensive prior therapy."

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[6] "Taxanes" is usually treated as synonymous with "taxoids," and refers to a class of chemotherapy agents. Ex. 1007 ¶ 53; *see also* Ex. 1018 at 5. Paclitaxel (TAXOL®) is a taxoid. Ex. 1007 ¶ 53, n.4.

Id. at 26:63–27:4. This includes verbatim—including the typographical error, "Dillohiation"—the teachings from Baselga '96 without attribution. *See id*.; Ex. 1004 at 10. The '441 patent goes on—without attribution—to repeat the description of the Baselga '97 clinical trial and reports its results. *Compare* Ex. 1001 at 27:15–29:6 *with* Ex. 1006 at 10.

C. Overview of the Related European Actions

The EP '926 patent claimed a method of using an anti-ErbB2 antibody to treat breast cancer 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. 1002 at 23 (claim 1). The specification reported the same experimental data (without attribution) as the '441 patent. *See id*. at 20 (¶¶ [0148–51]). Citing Baselga '97 and Baselga '96, the Patents Court invalidated the EP '926 patent as lacking an "inventive step," or in other words, as obvious.[7] Ex. 1003 ¶¶ 118–34. The opinion of the Patents Court was then affirmed on appeal. *See* Ex. 1021.

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[7] 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 applied. *See*

(continued…)

On May 2, 2016, in a separate proceeding, the European Patent Office in Munich also revoked EP '926 as obvious. Ex. 1020 ¶¶ 20–24.

D. Overview of the '441 Patent Prosecution History

The '441 patent prosecution spanned over ten years but can be boiled down to two significant events:

(1) Genentech submitted a declaration by inventor Susan Hellmann, M.D., to swear behind Baselga '97, and

(2) Genentech submitted a declaration by Mark Sliwkowski, Ph.D., arguing that the invention claimed in the '441 patent demonstrated unexpected results. Dr. Sliwkowski's declaration became the primary reason cited by the Examiner in the Notice of Allowance.

The '441 patent issued from U.S. Patent Application No. 09/208,649 ("'649 application"). *See* Ex. 1011–1:2.[8] The '649 application claims priority to U.S. Provisional Patent Application No. 60/069,346, filed on December 12, 1997 (Ex. 1027). *Id*. The claims were rejected ten times.

Pozzoli Spa v. *BDMO SA & Anor*., 2007 WL 1685192 [2007] EWCA Civ. 588 (Jun. 22, 2007) ¶ 23.

[8] Citations to Ex. 1011 are in the format: volume:page.

Originally filed independent claim 1 recited a method of treatment of a human patient with a disorder characterized by overexpression of ErbB2 receptor comprising administering an effective amount of a combination of an anti-ErbB2 antibody and a chemotherapeutic agent other than an anthracycline derivative, in the absence of an anthracycline derivative. The Examiner's initial Office Action provided ten grounds for rejection, Ex. 1011–1:375–86, including over Baselga '96 and Baselga '97. *Id*. at 1:379–85.

Genentech disagreed and argued that Baselga '97 did not anticipate because it "fails to answer the question as to whether or not the presently claimed combination is therapeutically effective in humans, but lacks significant undesirable side effects in human patients." *Id*. at 1:398. Genentech also submitted two declarations from Dr. Hellmann. In the first, Dr. Hellmann argued that the claimed methods provided unexpected results:

> "[S]uprisingly [*sic*], combining an anti-ErbB2 antibody…with paclitaxel, does not seriously exacerbate the toxic side effects of those drugs. However, this was not observed when the anti-ErbB2 antibody was combined with anthracycline/cyclophosphamide (AC) treatment."

Id. at 2:38. In the second declaration, Dr. Hellmann argued that Baselga '97 was not prior art because she had conceived of and reduced her invention to practice before Baselga '97 was published. *Id*. at 2:119–20.

The Examiner again rejected the claims over Baselga '97 and argued that Dr. Hellmann's declaration failed to antedate Baselga '97. *Id*. at 2:211–22. Genentech submitted another declaration. *Id*. at 2:237. In this declaration, as "[e]vidence of the reduction to practice," Dr. Hellmann pointed to a protocol for a "study of chemotherapy [(either anthracycline or paclitaxel)] alone or in combination with…[]rhuMAb HER2[] in women with HER2 overexpression." *Id*. at 2:238–39. To show the combination was "in the absence of an anthracycline derivative," Dr. Hellmann relied upon silence—the fact that rhuMAb HER2 was administered with *either* paclitaxel *or* an anthracycline, but not both. *Id*. Finally, Dr. Hellmann cited "[c]ase report forms (CRFs) detailing administration of rhuMAb HER2" to a single patient "followed by administration of paclitaxel to that patient the following day." *Id*. at 2:239.

Genentech submitted no data from the trial, let alone data obtained prior to Baselga '97's publication, even though Genentech repeatedly argued such data was required to render the claims obvious. *Id*. at 1:398, 2:233, 2:359, 7:182, 8:54, 8:135–38. The Examiner accepted Dr. Hellmann's second declaration as sufficient

to overcome Baselga '97 but proceeded to reject the '649 application for the next eight years over other prior art. *Id*. at 2:322.

On January 27, 2009, the Examiner issued its final office action in the '441 patent prosecution. *Id*. at 8:376. In response, Genentech filed a declaration by Dr. Sliwkowski, *id*. at 9:9, arguing that:

(1) a POSITA would not have 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. at 9:9–13 (Sliwkowski Decl. ¶¶ 7–9). Genentech's arguments in support of allowance reiterated and cited to Dr. Sliwkowski's declaration. *Id*. at 9:3–6.

The Examiner allowed the claims of the '441 patent, stating the reason for allowance was that the Sliwkowski Declaration "filed 10/15/2009 and the arguments presented by applicant were persuasive to overcome the rejections of the claims." *Id*. at 9:119, 9:124.

E. Taking Genentech at its Word, The '441 Patent is Not Entitled to an Earlier Priority Date Based on the Hellmann Declarations

The PTAB has the authority to determine the earliest priority date of a patent, including prior conception and reduction to practice. *See, e.g*., *NHK Seating*

of Am., Inc. v. Lear Corp., IPR2014–01200, Paper 29 (P.T.A.B. Feb. 2, 2016) at 15–17; *Daiichi Sankyo Co., Ltd v. Alethia Biotherapeutics, Inc.*, IPR2015-00291, Paper 75 (P.T.A.B. Jun. 14, 2016) at 6. It is settled law that "[t]he word 'invention' must refer to a concept that is complete, rather than merely one that is 'substantially complete.'" *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 66 (1998). Thus, the Federal Circuit has held that "[a] conception must encompass all limitations of the claimed invention…and is complete only when the idea is so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation." *Singh v. Brake*, 222 F.3d 1362, 1367 (Fed. Cir. 2000) (citation and internal quotation omitted). "[A]n inventor who failed to appreciate the claimed inventive features of a device at the time of alleged conception cannot use his later recognition of those features to retroactively cure his imperfect conception." *Hitzeman v. Rutter*, 243 F.3d 1345, 1358–59 (Fed. Cir. 2001); *see also Pfaff*, 525 U.S. at 66.

As discussed above, during prosecution, Genentech submitted declarations to swear behind Baselga '97. Ex. 1011–2:119, 2:209, 2:322, 2:237. The Examiner apparently did not realize the contradiction between the positions Genentech took to swear behind Baselga '97, on the one hand, and to distinguish other prior art like Baselga '96 on the other. Genentech contended that Dr. Hellmann had "conceived

of and reduced to practice" the alleged invention by December 1996 (*id*. at 2:237) based on:

(1) ***a study protocol that calls for*** combination therapy of rhuMAb HER2 plus either anthracyclines or paclitaxel, *id*. at 2:255 (Hellmann Decl. Ex. A ¶ 5.3.2), and

(2) documentation indicating that ***one patient was administered the antibody and paclitaxel combination therapy***, *id*. at 2:310 (Hellmann Decl. Ex. B).

However, Genentech told the Examiner that Baselga '96 (and other prior art) did ***not*** show the alleged invention and were so deficient that a POSITA reading them "could not" and "would not have known" of the alleged invention. *See id*. at 1:398, 2:233 ("Hence, Applicants submit that the cited art ***failed to teach the presently claimed method***"), 2:359, 7:183, 8:54, 8:135–38. Yet, just like the Hellmann Declaration, Baselga '96 discloses that ***clinical trials combining therapy of rhuMAb HER2 plus paclitaxel were underway—***patients were being administered the antibody plus paclitaxel. Ex. 1004 at 15.

Genentech's positions are irreconcilable. It cannot be true that a plan for a clinical trial *can* demonstrate the invention for conception and reduction to practice, but a clinical trial actually in progress *cannot* demonstrate the invention for novelty or obviousness. The Board should hold Genentech to the positions

Genentech took to obtain the '441 patent, and if it does, the Hellmann declarations do not show prior conception. Ex. 1007 ¶¶ 124–127.

F. 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.

G. 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*, 550 U.S. at 406. "Against 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 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*. 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.

H. Summary of Argument

Claims 1–14 of the '441 patent are invalid as obvious over Baselga '97 or '96 in view of Baselga '94. Baselga '94 discloses that the combination of paclitaxel and anti-ErbB2 antibodies demonstrated synergistic tumor growth suppression. And, as a result, clinical trials of the combination were underway.

Baselga '97 and Baselga '96 both teach that anti-ErbB2 antibody treatment extends time to disease progression in breast cancer patients overexpressing ErbB2. Both references teach a dosing protocol and repeat the encouraging preclinical results of the combination therapy. Moreover, both references teach that clinical trials of the combination were still ongoing. Baselga '97 further teaches details of those clinical trials, including the experimental and control groups.

At a minimum, it would have been obvious to a POSITA reading Baselga '97 or '96 in view of Baselga '94 at the time of the '441 patent's earliest possible priority date to try the combination of rhuMAb HER2 with paclitaxel in the absence of an anthracycline in human breast cancer patients with a reasonable expectation of success. That is precisely what was disclosed by and done in all three of Baselga '94, '96, and '97:

- Baselga '94 (Ex. 1005) at 4 ("Clinical trials are underway.");
- Baselga '96 (Ex. 1004) at 15 ("[C]linical trials of such combination therapy are currently in progress."); and
- Baselga '97 (Ex. 1006) at 10 ("These positive results have led to the design of a phase III multinational study of chemotherapy in combination with rhuMoAb HER2 in patients with HER2-overexpressing breast tumors who have not received prior chemotherapy for metastatic disease.").

Genentech's purported "discovery," that a combination of rhuMAb HER2 with anthracycline had side effects and was worse than a combination with paclitaxel was nothing new. The combination of paclitaxel with rhuMAb HER2 was disclosed in the prior art. Discovering another combination that is worse does not give Genentech the right to patent that which was already known.

Likewise Genentech's arguments that a POSITA would not try the combination of anti-ErbB2 antibodies with taxoids are meritless. *See* Exs. 1004 at 15; 1005 at 4; 1006 at 10. POSITAs already ***had*** tried the exact same combinations claimed, in amounts effective to extend the time to disease progression, before the earliest possible priority date of the '441 patent.

A POSITA would have known to combine the Baselga references given a number of factors. Both Baselga '97 and '96 reference Baselga '94. Exs. 1006 at 9; 1004 at 15. A POSITA would understand this cross-referencing to demonstrate that

Dr. Baselga was engaged in a progression of research from cell assays to human testing. Two of the four co-authors on Baselga '97 are authors on all three publications, and all four co-authors on Baselga '97 are authors on Baselga '96. Exs. 1005 at 4; 1004 at 9; 1006 at 6. These factors show a motivation to combine. *See Optivus Tech., Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 990–91 (Fed. Cir. 2006); *Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1328 (Fed. Cir. 2004).

Finally, none of the dependent claims adds anything inventive. Genentech did not argue that any of the dependent claims of the '441 patent added anything over and above what had already been disclosed by the prior art at any time during the prosecution history of the '441 patent. *See generally*, Ex. 1011.

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

Ground 1: Claims 1–14 Are Invalid Based on Baselga '97 in view of Baselga '94

(1) Claim 1

a. Claim 1, preamble: "A method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by overexpression of ErbB2 receptor, comprising"

Baselga '97 in view of Baselga '94 discloses "[a] method for the treatment of a human patient with a malignant progressing tumor or cancer." Baselga '97 teaches that rhuMAb HER2 was used in women with metastatic breast carcinoma. Ex. 1006 at 9. Metastatic breast carcinoma is a malignant cancer derived from epithelial cells that has spread to other areas. Ex. 1007 ¶ 36.

Baselga '97 in view of Baselga '94 further discloses a method of treating patients whose cancer is "characterized by overexpression of ErbB2 receptor." Baselga '97 teaches that "[t]he HER2 gene (also known as *neu* and as *c-erbB-2*) encodes a…glycoprotein receptor ($p185^{HER2}$)." Ex. 1006 at 6. Thus, Baselga '97 explains that the c-erbB-2 gene is also known as the HER2 gene—and by extension that the ErbB2 receptor protein is also known as the HER2 receptor protein. Ex. 1007 ¶ 34. Next, Baselga '97 teaches that positive results with single-therapy "have led to the design of a phase III multinational study of chemotherapy in combination with rhuMoAb HER2 in patients with HER2-overexpressing breast tumors[,]" *i.e.*, patients whose cancer overexpressed ErbB2. Ex. 1006 at 10; *see also* Ex. 1007 ¶¶ 129–130.

b. Claim 1, element [a]: "administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence"

Baselga '97 in view of Baselga '94 discloses "administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence." The phase III trial reported in Baselga '97 involved administering "rhuMoAb HER2 in combination with cytotoxic chemotherapy." Ex. 1006 at 10. The rhuMAb HER2 antibody—humanized mouse 4D5 antibody—is an intact antibody because it is comprised of "the antigen-binding portions of murine MoAb 4D5…and a human immunoglobulin variable region framework" to

produce "rhuMoAb HER2 IgG_1." *Id*. at 9. The antigen-binding portions are the portions of the antibody that determine what protein and where on that protein (the epitope) the antibody binds. Ex. 1007 ¶ 131. A POSITA would have understood that the combination of antigen-binding portions of murine MoAb 4D5 with a human immunoglobulin variable region framework to produce an IgG_1 antibody refers to an intact antibody. *Id*. ¶ 38.

The '441 patent explains that "[t]he 'epitope 4D5' is the region in the extracellular domain of ErbB2 to which the antibody 4D5…binds." Ex. 1001 at 5:24–26. Baselga '97 confirms that "[t]he murine monoclonal antibody (MoAb) 4D5 [is] directed against the extracellular domain of $p185^{HER2}$." Ex. 1006 at 7. A POSITA would have understood that because rhuMAb HER2 contains the same antigen-binding portions as 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. 1006 at 9; 1007 ¶ 131.

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

Baselga '97 in view of Baselga '94 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. 1006 at 9. And as noted above, Baselga '97 further teaches that a phase III trial of the combination therapy was underway. *Id*. at 10. The experimental group included

patients receiving "paclitaxel, if patients have received anthracycline therapy in the adjuvant setting." *Id*.

A POSITA reading Baselga '97 would have understood that the authors conducted phase I and phase II trials of rhuMAb HER2 single therapy based on preclinical models. Exs. 1006 at 7–8; 1007 ¶¶ 44–46. A POSITA would have further understood that Baselga '97 teaches there were major antitumor effects from paclitaxel with 4D5 in mice and that, based on this data, a clinical trial of the combination was underway. Ex. 1006 at 10; Ex. 1007 ¶¶ 46, 132.

Baselga '94 also discloses that, in light of the major anti-tumor activity of the 4D5 plus paclitaxel combination in the mouse model, "[c]linical trials are underway." Ex. 1005 at 4. Thus, a POSITA at the time of the alleged invention of the '441 patent would have understood that Baselga and colleagues reported the combination was synergistic in preclinical models and clinical trials had been underway since 1994. Ex. 1007 ¶ 132. A POSITA reading Baselga '97 would have known to look to Baselga '94 because Baselga '97 cites to Baselga '94 and the two references have overlapping authors. Exs. 1006 at 11; 1005 at 4.

d. Claim 1, element [c]: "in the absence of an anthracycline derivative,"

Baselga '97 in view of Baselga '94 discloses "in the absence of an anthracycline derivative." The cardiotoxicity of anthracycline derivatives was well known in the prior art and part of a POSITA's general knowledge. Ex. 1007 ¶ 33.

Further, Baselga '97 teaches the absence of an anthracycline derivative; the ongoing drug trials in humans involved the combination of rhuMAb HER2 and ***either*** paclitaxel or anthracycline, not both. Exs. 1006 at 10; 1007 ¶ 133. Baselga '97 provides mouse data about the combination of the 4D5 antibody and either paclitaxel or doxorubicin. Ex. 1006 at 9.

The combination with paclitaxel was "markedly better than an equipotent dose of doxorubicin" *Id*. Based upon the superior results and the POSITA's general understanding about the cardiotoxicity of anthracycline compounds, a POSITA would not have been motivated to add doxorubicin to a combination therapy with rhuMAb HER2 and paclitaxel. Ex. 1007 ¶ 133.

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

Baselga '97 in view of Baselga '94 teaches administration in human patients. Ex. 1006 at 10.

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

Baselga '97 in view of Baselga '94 discloses "an amount effective to extend the time to disease progression in said human patient." Baselga '97 teaches a dose regimen consisting of "a loading dose of 250 mg of IV rhuMoAb HER2, then 10 weekly doses of 100 mg each." *Id*. at 9.

Baselga '97 reports that "[a]dequate serum levels of rhuMoAb HER2 were obtained" with a mean half-life of about 8.3 days. *Id*. "Objective responses were

seen in 5 of the 43 evaluable patients…(overall response rate, 11.6%...)." *Id*. And "[m]inor responses, seen in 2 patients, and stable disease, [which] occur[ed] in 14 patients, lasted for a median of 5.1 months." *Id*. Thus a POSITA would have understood Baselga '97 teaches this claim element.

Moreover, a POSITA would be motivated to consider time to disease progression because this is one of the metrics reported in the phase II trial thereby making direct comparison with those results possible. *Id*. Baselga '97 teaches that patients in the combined treatment phase III study "receive weekly administration of the antibody at a dose similar to the phase II studies." *Id*.at 10.

Baselga '97 in view of Baselga '94 also teaches that MoAb 4D5 and paclitaxel "resulted in major antitumor activity." *Id*. at 9. The combination improved the antitumor effect of rhuMAb HER2 or paclitaxel individually—each showing 35% tumor inhibition—to above 90%. *Id*. The treatment was sufficiently effective that clinical trials were ongoing for at least three years at the time that Baselga '97 was published. *Id*. at 10; Ex. 1005 at 4. A POSITA would have understood the disclosures in Baselga '97 and Baselga '94 to mean that the addition of paclitaxel to rhuMAb HER2 therapy would improve time to disease progression. Ex. 1007 ¶¶ 135–136.

g. Claim 1, element [f]: "without increase in overall severe adverse events."

Baselga '97 in view of Baselga '94 discloses "without increase in overall severe adverse events." Baselga '97 teaches that rhuMAb HER2 "[t]oxicity was minimal." Ex. 1006 at 9. Baselga '94 teaches that there was no increase in the toxicity of paclitaxel when administered in combination with rhuMAb HER2 in preclinical models. Ex. 1005 at 4. A POSITA at the time of the alleged invention in the '441 patent would have understood that Baselga reported as early as 1994 that the combination of paclitaxel and rhuMAb HER2 was synergistic in preclinical models, that clinical trials of the combination were underway in humans, and that these clinical trials were still underway in 1997. Ex. 1007 ¶¶ 132, 137.

h. Conclusion

Since a POSITA would have only had to follow the clinical trial as described by Baselga '97 in view of Baselga '94, it would have been obvious to try the combination of rhuMAb HER2 and a taxoid. Exs. 1006 at 10; 1007 ¶¶ 128–138. A POSITA would have understood Baselga '97 in view of Baselga '94 to teach an amount of rhuMAb HER2 that was effective to extend the time to disease progression and would have had a reasonable expectation that the combination of rhuMAb HER2 with paclitaxel would improve the time to disease progression without increasing the toxicity of paclitaxel. *Id*.¶¶ 132, 135–137. A POSITA would not have been motivated to add an anthracycline to the combination because of its

known cardiotoxicity and because Baselga '97 taught that the combination with paclitaxel was superior. *Id*. ¶ 133. Thus, a POSITA would have found it obvious to try combining rhuMAb HER2 with paclitaxel as recited in claim 1. *Id*. ¶ 138.

(2) Claim 2

a. "The method of claim 1 wherein said patient has a malignant tumor."

Baselga '97 in view of Baselga '94 teaches the method of claim 1. *See* Section VI.I.Ground 1:(1). Baselga '97 teaches that rhuMAb HER2 was used in patients with metastatic breast carcinoma—a malignant cancer forming tumors. Exs. 1006 at 9; 1007 ¶¶ 139–140.

(3) Claim 3

a. "The method of claim 1 wherein said patient has cancer."

Baselga '97 in view of Baselga '94 teaches the method of claim 1. *See* Section VI.I.Ground 1:(1). Baselga '97 teaches that rhuMAb HER2 was used in patients with metastatic breast carcinoma, a cancer. Exs. 1006 at 9; 1007 ¶¶ 141–142.

(4) Claim 4

a. "The method of claim 3 wherein said cancer is selected from the group consisting of breast cancer [and other cancers]."

Baselga '97 in view of Baselga '94 teaches the method of claim 3. *See* Section VI.I.Ground 1:(3). Baselga '97 teaches that rhuMAb HER2 was used in

patients with metastatic breast carcinoma, a breast cancer. Exs. 1006 at 9; 1007 ¶¶ 143–144.

(5) Claim 5

a. "The method of claim 4 wherein said cancer is breast cancer."

Baselga '97 in view of Baselga '94 teaches the method of claim 4. *See* Section VI.I.Ground 1:(4). Baselga '97 teaches that rhuMAb HER2 was used in patients with metastatic breast carcinoma, a breast cancer. Exs. 1006 at 9; 1007 ¶¶ 145–146.

(6) Claim 6

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

Baselga '97 in view of Baselga '94 teaches the method of claim 5. *See* Section VI.I.Ground 1:(5). Baselga '97 teaches that rhuMAb HER2 was used in patients with metastatic breast carcinoma. Exs. 1006 at 9; 1007 ¶¶ 147–148.

(7) Claim 7

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

Baselga '97 in view of Baselga '94 teaches the method of claim 1. *See* Section VI.I.Ground 1:(1). Baselga '97 teaches that "[t]he murine monoclonal antibody (MoAb) 4D5, directed against the extracellular domain of $p185^{HER2}$," was humanized for use in humans. Exs. 1006 at 7, 9; 1007 ¶¶ 149–150.

(8) Claim 8

a. "The method of claim 1 wherein said taxoid is paclitaxel."

Baselga '97 in view of Baselga '94 teaches the method of claim 1. *See* Section VI.I.Ground 1:(1). A POSITA reading Baselga '97 in view of Baselga '94 would have been motivated to try the combination of paclitaxel and rhuMAb HER2 with a reasonable expectation of success because Baselga reported as early as 1994 that the combination was synergistic, that clinical trials of the combination were underway in humans, and that these clinical trials were still underway in 1997. *Id*.¶¶ 151–152.

(9) Claim 9

a. "The method of claim 8 wherein the effective amount of said combination is lower than the sum of the effective amounts of said anti-ErbB2 antibody and said taxoid, when administered individually, as single agents."

Baselga '97 in view of Baselga '94 teaches the method of claim 8. *See* Section VI.I.Ground 1:(8). Baselga '97 and Baselga '94 each teach that the combination of rhuMAb HER2 and paclitaxel resulted in a synergistic improvement in the antitumor effect of each treatment individually. Exs. 1006 at 9; 1005 at 4. A POSITA reading Baselga '97 in light of Baselga '94 would have had a reasonable expectation that the combination of rhuMAb HER2 and paclitaxel treatments would be synergistic in humans and thus that an effective amount of the

combination would be lower than the sum of effective amounts of each treatment individually. Ex. 1007 ¶¶ 153–154.

A synergistic increase in tumor killing power means that if one drug at a given dose is combined with a second drug given at a second dose, the magnitude of the combined effect is greater than the magnitude of the sum of the individual effects ("synergistic effect"). Absent synergy, a higher dose of one or both of the drugs to achieve the same effect as the synergistic effect is required. Thus, the "effective amount" of the synergistic combination—*i.e.*, the sum of the doses of the drugs that produces a given synergistic effect—is less than the "effective amount"—*i.e.*, the sum of the doses of drugs to produce that same effect—if there was no synergy. Therefore, because Baselga '97 and '94 teach that the combination of rhuMAb HER2 and paclitaxel is synergistic, a POSITA would have had a reasonable expectation that the effective amount of the combination would be lower than the sum of the effective amounts of rhuMAb HER2 and paclitaxel administered individually.

(10) Claim 10

a. "The method of claim 1 wherein efficacy is further measured by determining the response rate."

Baselga '97 in view of Baselga '94 teaches the method of claim 1. *See* Section VI.I.Ground 1:(1). Baselga '97 reports that out of the patients treated with rhuMAb HER2, "[o]bjective responses were seen in 5 of the 43 evaluable

patients…(overall response rate, 11.6%…).” Ex. 1006 at 9. Based on this and the general knowledge of a POSITA, it would have been obvious to have measured the response rate of the combination therapy in patients. Ex. 1007 ¶¶ 155–156.

(11) Claim 11

a. Claim 11, preamble: “A method for the treatment of a human patient with ErbB2 overexpressing progressing metastatic breast cancer, comprising”

The preamble of claim 11 is worded differently from claim 1 with regard to “a human patient with ErbB2 overexpressing progressing metastatic breast cancer.” Baselga ’97 in view of Baselga ’94 teaches that rhuMAb HER2 was used to treat women with metastatic breast carcinoma, a malignant cancer derived from epithelial cells. Exs. 1006 at 9; 1007 ¶ 157; *see also* Section VI.I.Ground 1:(1)a, (5)–(6). The remainder of the preamble of claim 11 is identical to claim 1, thus the same reasoning applies. *See* Section VI.I.Ground 1:(1)a.

b. Claim 11, element [a]: “administering a combination of a humanized 4D5 anti-ErbB2 antibody”

Baselga ’97 in view of Baselga ’94 teaches administering a combination including rhuMAb HER2, which is a humanized 4D5 anti-ErbB2 antibody. *See* Section VI.I.Ground 1:(1)b, (7).

c. Claim 11, element [b]: “and a taxoid,”

Baselga ’97 in view of Baselga ’94 discloses a combination of rhuMAb HER2 and a taxoid. *See* Section VI.I.Ground 1:(1)c.

d. Claim 11, element [c]: "in the absence of an anthracycline derivative,"

Baselga '97 in view of Baselga '94 discloses a combination of rhuMAb HER2 and a taxoid, in the absence of an anthracycline derivative. *See* Section VI.I.Ground 1:(1)d.

e. Claim 11, element [d]: "to the human patient"

Baselga '97 in view of Baselga '94 discloses treating human patients. *See* Section VI.I.Ground 1:(1)e.

f. Claim 11, element [e]: "in an amount effective to extend the time to disease progression in said human patient,"

Baselga '97 in view of Baselga '94 discloses an amount effective to extend the time to disease progression in said human patient. *See* Section VI.I.Ground 1:(1)f.

g. Claim 11, element [f]: "without increase in overall severe adverse events."

Baselga '97 in view of Baselga '94 discloses without an increase in overall severe adverse events. *See* Section VI.I.Ground 1:(1)g.

h. Conclusion

For the same reasons discussed in Section VI.I.Ground 1:(1)h, it would have been obvious to a POSITA to try the combination of rhuMAb HER2 and paclitaxel as recited by claim 11.

(12) Claim 12

a. "The method of claim 11, wherein said taxoid is paclitaxel."

Baselga '97 in view of Baselga '94 teaches the method of claim 11. *See* Section VI.I.Ground 1:(11). Baselga '97 in view of Baselga '94 discloses the taxoid is paclitaxel. *See* Section VI.I.Ground 1:(8).

(13) Claim 13

a. Claim 13, preamble: "A method for the treatment of a human patient with a progressing malignant tumor or cancer characterized by overexpression of ErbB2 receptor, comprising"

Baselga '97 in view of Baselga '94 discloses a method for the treatment of a human patient with a progressing malignant tumor or cancer characterized by overexpression of ErbB2 receptor. *See* Section VI.I.Ground 1:(1)a.

b. Claim 13, element [a]: "administering a combination of a humanized 4D5 anti-ErbB2 antibody which comprises a human F_c region that binds to epitope 4D5 within the ErbB2 extracellular domain sequence"

Baselga '97 in view of Baselga '94 teaches administering rhuMAb HER2, which is a humanized 4D5 anti-ErbB2 antibody. In addition, Baselga '97 in view of Baselga '94 discloses a humanized 4D5 anti-ErbB2 antibody which comprises a human F_c region that binds to epitope 4D5 because rhuMAb HER2 is comprised of "the antigen-binding portions of murine MoAb 4D5" and "a human immunoglobulin variable region framework." Ex. 1006 at 9. A POSITA would have understood that the resulting "rhuMoAb HER2 IgG_1" contains a human F_c

region as claimed. *Id*.; Ex. 1007 ¶¶ 38, 168; *see also* Section VI.I.Ground 1:(1)b, (7).

c. Claim 13, element [b]: "and a taxoid,"

Baselga '97 in view of Baselga '94 discloses a combination of rhuMAb HER2 and a taxoid. *See* Section VI.I.Ground 1:(1)c.

d. Claim 13, element [c]: "in the absence of an anthracycline derivative,"

Baselga '97 in view of Baselga '94 discloses a combination of rhuMAb HER2 and a taxoid, in the absence of an anthracycline derivative. *See* Section VI.I.Ground 1:(1)d.

e. Claim 13, element [d]: "to the human patient"

Baselga '97 in view of Baselga '94 discloses treating human patients. *See* Section VI.I.Ground 1:(1)e.

f. Claim 13, element [e]: "in an amount effective to extend the time to disease progression in said human patient,"

Baselga '97 in view of Baselga '94 discloses an amount effective to extend the time to disease progression in said human patient. *See* Section VI.I.Ground 1:(1)f.

g. Claim 13, element [f]: "without increase in overall severe adverse events."

Baselga '97 in view of Baselga '94 discloses without an increase in overall severe adverse events. *See* Section VI.I.Ground 1:(1)g.

h. Conclusion

For the same reasons discussed in Section VI.I.Ground 1:(1)h, it would have been obvious to a POSITA to try the combination of rhuMAb HER2 and paclitaxel as recited by claim 13.

(14) Claim 14

a. Claim 14, preamble: "A method for the treatment of a human patient with ErbB2 expressing progressing metastatic breast cancer, comprising"

Baselga '97 in view of Baselga '94 discloses a method for the treatment of a human patient with ErbB2 expressing progressing metastatic breast cancer. *See* Section VI.I.Ground 1:(1)a, (6).

b. Claim 14, element [a]: "administering a combination of an antibody which binds to epitope 4D5 within the extracellular domain sequence"

Baselga '97 in view of Baselga '94 teaches administering an antibody binding to epitope 4D5 within the extracellular domain sequence. An "antibody" is broader than an "intact antibody" and thus the disclosure of Section VI.I.Ground 1:(1)b also meets claim 14, element [a]. Ex. 1007 ¶ 176; *see also* Section VI.I.Ground 1:(1)b, (7).

c. Claim 14, element [b]: "and a taxoid,"

Baselga '97 in view of Baselga '94 discloses a combination of rhuMAb HER2 and a taxoid. *See* Section VI.I.Ground 1:(1)c.

d. Claim 14, element [c]: "in the absence of an anthracycline derivative,"

Baselga '97 in view of Baselga '94 discloses a combination of rhuMAb HER2 and a taxoid, in the absence of an anthracycline derivative. *See* Section VI.I.Ground 1:(1)d.

e. Claim 14, element [d]: "to the human patient"

Baselga '97 in view of Baselga '94 discloses treating human patients. *See* Section VI.I.Ground 1:(1)e.

f. Claim 14, element [e]: "in an amount effective to extend the time to disease progression in said human patient,"

Baselga '97 in view of Baselga '94 discloses an amount effective to extend the time to disease progression in said human patient. *See* Section VI.I.Ground 1:(1)f.

g. Claim 14, element [f]: "without increase in overall severe adverse events."

Baselga '97 in view of Baselga '94 discloses without an increase in overall severe adverse events. *See* Section VI.I.Ground 1:(1)g.

h. Conclusion

For the same reasons discussed in Section VI.I.Ground 1:(1)h, it would have been obvious to a POSITA to try the combination of rhuMAb HER2 and paclitaxel as recited by claim 14.

Ground 2: Claims 1–14 Are Invalid Based on Baselga '96 in View of Baselga '94

(1) Claim 1

a. Claim 1, preamble: "A method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by overexpression of ErbB2 receptor, comprising"

Baselga '96 in view of Baselga '94 discloses "[a] method for the treatment of a human patient with a malignant progressing tumor or cancer." Baselga '96 teaches that rhuMAb HER2 was used in patients with metastatic breast carcinoma, a malignant cancer that has spread to another area. Exs. 1004 at 10; 1007 ¶¶ 70–71.

Baselga '96 in view of Baselga '94 further discloses a method of treating patients whose cancer is "characterized by overexpression of ErbB2 receptor." Baselga '96 teaches that "[t]he HER2 gene (also known as *neu* and as *c-erbB-2*) encodes a…glycoprotein receptor ($p185^{HER2}$)." Ex. 1004 at 9. Thus Baselga '96 explains that the c-erbB-2 gene is also known as the HER2 gene—accordingly, the ErbB2 receptor protein is also known as the HER2 receptor protein. Ex. 1007 ¶ 71. Baselga '96 selected "adult women whose metastatic breast carcinomas overexpressed HER2," *i.e.*, women whose cancer overexpressed ErbB2. Ex. 1004 at 10. Baselga '96 reports the ErbB2 overexpression status of the study participants who achieved a response to treatment in Table 5. *Id*. at 13.

b. Claim 1, element [a]: "administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence"

Baselga '96 in view of Baselga '94 discloses "administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence." Genentech did not dispute that Baselga '96 disclosed this limitation during prosecution. *See* Ex. 1011–1:392, 2:31, 2:34, 2:229, 2:353, 4:73, 7:175, 7:222, 7:344, 8:50, 8:131, 8:356, 8:397. Baselga '96 discloses a method for "[p]reparation and humanization of rhuMAb HER2 antibody" that is administered to patients. Ex. 1004 at 10. The phase II trial reported in Baselga '96 involved administering "rhuMAb HER2…intravenously" weekly for ten weeks. *Id*.

A POSITA would have understood that the rhuMAb HER2 antibody is an intact antibody because it is comprised of "the complementarity determining regions of MAb 4D5" and "the framework of a consensus human immunoglobulin G_1 (IgG_1)." *Id*. (citation omitted). The combination of complementarity determining regions and the framework of a consensus human immunoglobulin G_1 describes an intact antibody. Ex. 1007 ¶ 72.

The '441 patent explains that "[t]he 'epitope 4D5' is the region in the extracellular domain of ErbB2 to which the antibody 4D5…binds." Ex. 1001 at 5:24–27. Baselga '96 confirms that "[t]he murine monoclonal antibody (MAb) 4D5 [is] directed against the extracellular domain of $p185^{HER2}$." Ex. 1004 at 9. The

complementarity determining region of an antibody determines what the antibody binds to, *i.e.*, the epitope. *See* Ex. 1007 ¶ 72. A POSITA would have understood that 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 in Baselga '96 binds to epitope 4D5 within the ErbB2 extracellular domain sequence. Exs. 1004 at 10; 1007 ¶ 72.

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

Baselga '96 teaches a combination of an antibody and "a taxoid." First, in Table 5, Baselga '96 shows that all "five [patients] experienced a complete or partial remission" had "[p]rior [s]ystemic [t]herapy" and four out of those five patients were given either paclitaxel or docetaxel (taxoids). Ex. 1004 at 13, Table 5. Baselga '96 also teaches that "[i]n preclinical studies, both in vitro and in xenografts, rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including…paclitaxel without increasing their toxicity." *Id*. at 15 (citations omitted). Baselga '96 further teaches that "clinical trials of such combination therapy are currently in progress." *Id*.

Baselga '96 teaches that the authors conducted phase I and phase II trials of rhuMAb HER2 based on preclinical models. *Id*.at 9; Ex. 1007 ¶ 73. Baselga '96 also teaches that the antitumor effects of paclitaxel were "markedly potentiated" by

combination with rhuMAb HER2 and that based on this preclinical data, a clinical trial of the combination was underway. Exs. 1004 at 15; 1007 ¶¶ 59, 73.

Baselga '96 cites to Baselga '94 in the discussion of preclinical testing. Ex. 1004 at 15. Baselga '94 teaches that individual treatment with either anti-HER2 4D5 or paclitaxel alone resulted in 35% growth inhibition whereas the combination "resulted in a major antitumor activity with 93% inhibition of growth" without increasing toxicity. Ex. 1005 at 4. In light of this, Baselga '94 discloses that "[c]linical trials are underway." *Id*. Baselga thus reported the combination was synergistic in preclinical models and clinical trials had been underway since 1994. Ex. 1007 ¶ 73. A POSITA reading Baselga '96 would have known to look to Baselga '94 because Baselga '96 cites to Baselga '94 and the two references have overlapping authors. Exs. 1004 at 15–16; 1005 at 4.

d. Claim 1, element [c]: "in the absence of an anthracycline derivative,"

Baselga '96 in view of Baselga '94 discloses "in the absence of an anthracycline derivative." The cardiotoxicity of anthracycline derivatives was well known in the prior art and a POSITA's general knowledge. Ex. 1007 ¶ 74. Consistent with this, Baselga '96 reports a patient died "of congestive heart failure associated with prior doxorubicin treatment" prior to follow-up. Ex. 1004 at 12.

Further, the experimental design of both preclinical as well as clinical studies of combination therapies administered rhuMAb HER2 (or the 4D5

antibody) with paclitaxel ***or*** anthracycline, ***not*** together. Baselga '96 teaches ongoing drug trials in humans involving the combination of rhuMAb HER2 and a single other therapeutic compound per patient (*i.e.*, either paclitaxel or doxorubicin). *Id*. at 15. Ex. 1007 ¶ 74. Baselga '94 provides data about this combination demonstrating that the combination with paclitaxel was superior to the combination with doxorubicin. Ex. 1005 at 4.

Based upon these superior results and the knowledge of anthracycline cardiotoxicity, a POSITA would not have been motivated to add doxorubicin to the combination therapy with rhuMAb HER2 and paclitaxel already taught by Baselga '96. Ex. 1007 ¶ 74.

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

Baselga '96 teaches administration in human patients. Ex. 1004 at 10 ("Patients eligible for this study were adult women.").

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

Baselga '96 in view of Baselga '94 discloses "an amount effective to extend the time to disease progression in said human patient." Baselga '96 teaches that "[t]he pharmacokinetic goal was to achieve rhuMAb HER2 trough serum concentrations greater than 10 μg/mL, a level associated with optimal inhibition of cell growth." *Id*. Baselga '96 teaches a dose regimen in breast cancer patients consisting of "a loading dose of 250 mg of rhuMAb HER2 on day 0, and beginning

on day 7, 100 mg weekly for a total of 10 doses." *Id*. "Serum levels of rhuMAb HER2…were analyzed for each patient using a one-compartment model." *Id*.

Baselga '96 reports that "[m]ore than 90%...had rhuMAb HER2 trough levels above the targeted 10 μg/mL level," and the "mean serum [half-life] of rhuMAb HER2 was 8.3 ± 5.0 days." *Id*. at 11. Moreover, "[o]f 43 patients with $p185^{HER2}$-positive tumors assessable for response…five experienced a complete or partial remission." *Id*. at 13; *see also id*. at Table 5 (Duration of Response (months). "Minor responses, seen in two patients, and stable disease, which occurred in 14 patients, lasted for a median of 5.1 months." *Id*. at 9.

Moreover, a POSITA would have been motivated to consider time to disease progression specifically because this is one of the metrics reported in the phase II trial thereby making direct comparison with those results possible. *Id*. Thus a POSITA would have understood Baselga '96 to teach this claim element. *Id*.

In addition, Baselga '96 in view of Baselga '94 teaches that rhuMAb HER2 "markedly potentiated the antitumor effects" of paclitaxel in preclinical models. *Id*. at 15. The combination had more potent antitumor effect than either rhuMAb HER2 or paclitaxel individually; where each showed 35% inhibition individually, the combination was above 90%. Ex. 1005 at 4. The treatment was sufficiently effective that clinical trials were ongoing for at least two years when Baselga '96 was published. Exs. 1004 at 15; 1005 at 4. Baselga '96 and Baselga '94 therefore

teach that the addition of paclitaxel to rhuMAb HER2 therapy would improve time to disease progression. Ex. 1007 ¶¶ 76–77.

g. Claim 1, element [f]: "without increase in overall severe adverse events."

Baselga '96 in view of Baselga '94 discloses "without increase in overall severe adverse events," as recited in claim 1. Baselga '96 teaches that rhuMAb HER2 "was remarkably well tolerated." Ex. 1004 at 11. Overall, there was an "absence of significant toxicity." *Id*. at 13. Baselga '96 and Baselga '94 both teach that there was no increase in the toxicity of paclitaxel when administered in combination with rhuMAb HER2 in preclinical models. *Id*. at 15; Exs. 1005 at 4; 1007 ¶ 78.

h. Conclusion

It would have been obvious to a POSITA reading Baselga '96 in view of Baselga '94 to try the combination of rhuMAb HER2 and paclitaxel in humans as Baselga '96 makes clear that the combination *was already being used in humans* in clinical trials. A POSITA would have had a reasonable expectation of success in accomplishing and improving upon the already extended time to disease progression reported in Baselga '96 without increasing overall severe adverse events. *Id*. ¶¶ 76–78.

Clinical trials can be time consuming and expensive; therefore, they would not be conducted *without* a reasonable expectation of success. *Id*. A POSITA

would not have been motivated to add an anthracycline to the combination because of its known cardiotoxicity and because Baselga '94 taught that the combination with paclitaxel was superior. *Id*. ¶ 74. Therefore, a POSITA would have found it obvious to try the combination of rhuMAb HER2 with paclitaxel as recited by claim 1. *Id*. ¶ 79.

(2) Claim 2

a. "The method of claim 1 wherein said patient has a malignant tumor."

Baselga '96 in view of Baselga '94 teaches the method of claim 1. *See* Section VI.I.Ground 2:(1). Baselga '96 teaches that rhuMAb HER2 was used in women with metastatic breast carcinoma—a malignant cancer that forms a tumor in places where it grows in the body. Exs. 1004 at 10; 1007 ¶¶ 80–81.

(3) Claim 3

a. "The method of claim 1 wherein said patient has cancer."

Baselga '96 in view of Baselga '94 teaches the method of claim 1. *See* Section VI.I.Ground 2:(1). Baselga '96 teaches that rhuMAb HER2 was used in women with metastatic breast carcinoma, a cancer. Exs. 1004 at 10; 1007 ¶¶ 82–83.

(4) Claim 4

a. "The method of claim 3 wherein said cancer is selected from the group consisting of breast cancer [and other cancers]."

Baselga '96 in view of Baselga '94 teaches the method of claim 3. *See* Section VI.I.Ground 2:(3). Baselga '96 teaches that rhuMAb HER2 was used in women with metastatic breast carcinoma, a breast cancer. Exs. 1004 at 10; 1007 ¶¶ 84–85.

(5) Claim 5

a. "The method of claim 4 wherein said cancer is breast cancer."

Baselga '96 in view of Baselga '94 teaches the method of claim 4. *See* Section VI.I.Ground 2:(4). Baselga '96 teaches that rhuMAb HER2 was used in women with metastatic breast carcinoma, a breast cancer. Exs. 1004 at 10; 1007 ¶¶ 86–87.

(6) Claim 6

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

Baselga '96 in view of Baselga '94 teaches the method of claim 5. *See* Section VI.I.Ground 2:(5). Baselga '96 teaches that rhuMAb HER2 was used in women with metastatic breast carcinoma. Exs. 1004 at 10; 1007 ¶¶ 88–89.

(7) Claim 7

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

Baselga '96 in view of Baselga '94 teaches the method of claim 1. *See* Section VI.I.Ground 2:(1). Baselga '96 teaches that "[t]he murine monoclonal antibody (MAb) 4D5, directed against the extracellular domain of $p185^{HER2}$…was humanized" to "facilitate…clinical investigations." Ex. 1004 at 9; Ex. 1007 ¶ 90–91.

(8) Claim 8

a. "The method of claim 1 wherein said taxoid is paclitaxel."

Baselga '96 in view of Baselga '94 teaches the method of claim 1. *See* Section VI.I.Ground 2:(1). A POSITA reading Baselga '96 in view of Baselga '94 would have been motivated to try the combination of paclitaxel and rhuMAb HER2 in a human with a reasonable expectation of success because Baselga and colleagues reported as early as 1994 that the combination was synergistic in preclinical models, that clinical trials of the combination were underway in humans, and that these clinical trials were still underway in 1996. *Id*.¶¶ 92–93.

(9) Claim 9

a. "The method of claim 8 wherein the effective amount of said combination is lower than the sum of the effective amounts of said anti-ErbB2 antibody and said taxoid, when administered individually, as single agents."

Baselga '96 in view of Baselga '94 teaches the method of claim 8. *See* Section VI.I.Ground 2:(8). Baselga '96 and Baselga '94 each teach that the combination of rhuMAb HER2 and paclitaxel resulted in a synergistic improvement in the antitumor effect of each treatment individually. Exs. 1004 at 15; 1005 at 4. A POSITA reading Baselga '96 in light of Baselga '94 would have had a reasonable expectation that the combination of rhuMAb HER2 and paclitaxel treatments would be synergistic in humans and thus that an effective amount of the combination would be lower than the sum of effective amounts of each treatment individually. Ex. 1007 ¶¶ 94–95.

(10) Claim 10

a. "The method of claim 1 wherein efficacy is further measured by determining the response rate."

Baselga '96 in view of Baselga '94 teaches the method of claim 1. *See* Section VI.I.Ground 2:(1). Baselga '96 reports that, out of the patients treated with rhuMAb HER2, "five experienced a complete or partial remission, for an overall response rate of 11.6%." Ex. 1004 at 13. It would have been obvious for a POSITA to measure the response rate of the combination therapy in patients based on the

Baselga '96 teaching to use the response rate to measure the effect of the single agent. Ex. 1007 ¶¶ 96–97.

(11) Claim 11

a. Claim 11, preamble: "A method for the treatment of a human patient with ErbB2 overexpressing progressing metastatic breast cancer, comprising"

The preamble of claim 11 is worded differently from claim 1 with regard to "a human patient with ErbB2 overexpressing progressing metastatic breast cancer." Baselga '96 teaches that rhuMAb HER2 was used to treat women with metastatic breast carcinoma, a malignant cancer derived from epithelial cells. Exs. 1004 at 10; 1007 ¶ 98; *see also* Section VI.I.Ground 2:(1)a, (5)–(6). The remainder of the preamble of claim 11 is identical to claim 1, thus the same reasoning applies. *See* Section VI.I.Ground 2:(1)a.

b. Claim 11, element [a]: "administering a combination of a humanized 4D5 anti-ErbB2 antibody"

Baselga '96 in view of Baselga '94 teaches administering a combination with rhuMAb HER2, which is a humanized 4D5 anti-ErbB2 antibody. *See* Section VI.I.Ground 2:(1)b, (7).

c. Claim 11, element [b]: "and a taxoid,"

Baselga '96 in view of Baselga '94 discloses a combination of rhuMAb HER2 and a taxoid. *See* Section VI.I.Ground 2:(1)c.

d. Claim 11, element [c]: "in the absence of an anthracycline derivative,"

Baselga '96 in view of Baselga '94 discloses a combination of rhuMAb HER2 and a taxoid, in the absence of an anthracycline derivative. *See* Section VI.I.Ground 2:(1)d.

e. Claim 11, element [d]: "to the human patient"

Baselga '96 in view of Baselga '94 discloses treating human patients. *See* Section VI.I.Ground 2:(1)e.

f. Claim 11, element [e]: "in an amount effective to extend the time to disease progression in said human patient,"

Baselga '96 in view of Baselga '94 discloses an amount effective to extend the time to disease progression in said human patient. *See* Section VI.I.Ground 2:(1)f.

g. Claim 11, element [f]: "without increase in overall severe adverse events."

Baselga '96 in view of Baselga '94 discloses without an increase in overall severe adverse events. *See* Section VI.I.Ground 2:(1)g.

h. Conclusion

For the reasons discussed in Section VI.I.Ground 2:(1)h, it would have been obvious to a POSITA to try the combination of rhuMAb HER2 and paclitaxel as recited by claim 11.

(12) Claim 12

a. "The method of claim 11, wherein said taxoid is paclitaxel."

Baselga '96 in view of Baselga '94 teaches the method of claim 11. *See* Section VI.I.Ground 2:(11). Baselga '96 in view of Baselga '94 discloses the taxoid is paclitaxel. *See* Section VI.I.Ground 2:(8).

(13) Claim 13

a. Claim 13, preamble: "A method for the treatment of a human patient with a progressing malignant tumor or cancer characterized by overexpression of ErbB2 receptor, comprising"

Baselga '96 in view of Baselga '94 discloses a method for the treatment of a human patient with a progressing malignant tumor or cancer characterized by overexpression of ErbB2 receptor. *See* Section VI.I.Ground 2:(1)a; Ex. 1007 ¶ 108.

b. Claim 13, element [a]: "administering a combination of a humanized 4D5 anti-ErbB2 antibody which comprises a human F_c region that binds to epitope 4D5 within the ErbB2 extracellular domain sequence"

Baselga '96 in view of Baselga '94 teaches administering a humanized 4D5 anti-ErbB2 antibody. *See* Section VI.I.Ground 2:(1)b, (7). Baselga '96 in view of Baselga '94 also discloses a humanized 4D5 anti-ErbB2 antibody which comprises a human F_c region that binds to epitope 4D5 because rhuMAb HER2 is comprised of "the complementarity determining regions of MAb 4D5" and "the framework of a consensus human immunoglobulin G_1 (IgG_1)." Ex. 1004 at 10. A consensus human immunoglobulin G_1 contains a human F_c region. Ex. 1007 ¶ 109. 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 in Baselga '96 binds to epitope 4D5 within the ErbB2 extracellular domain sequence. Exs. 1004 at 10; 1007 ¶ 109.

c. Claim 13, element [b]: "and a taxoid,"

Baselga '96 in view of Baselga '94 discloses a combination of rhuMAb HER2 and a taxoid. *See* Section VI.I.Ground 2:(1)c.

d. Claim 13, element [c]: "in the absence of an anthracycline derivative,"

Baselga '96 in view of Baselga '94 discloses a combination of rhuMAb HER2 and a taxoid, in the absence of an anthracycline derivative. *See* Section VI.I.Ground 2:(1)d.

e. Claim 13, element [d]: "to the human patient"

Baselga '96 in view of Baselga '94 discloses treating human patients. *See* Section VI.I.Ground 2:(1)e.

f. Claim 13, element [e]: "in an amount effective to extend the time to disease progression in said human patient,"

Baselga '96 in view of Baselga '94 discloses an amount effective to extend the time to disease progression in said human patient. *See* Section VI.I.Ground 2:(1)f.

g. Claim 13, element [f]: "without increase in overall severe adverse events."

Baselga '96 in view of Baselga '94 discloses without an increase in overall severe adverse events. *See* Section VI.I.Ground 2:(1)g.

h. Conclusion

For the reasons discussed in Section VI.I.Ground 2:(1)h, it would have been obvious to a POSITA to try the combination of rhuMAb HER2 and paclitaxel as recited by claim 13.

(14) Claim 14

a. Claim 14, preamble: "A method for the treatment of a human patient with ErbB2 expressing progressing metastatic breast cancer, comprising"

Baselga '96 in view of Baselga '94 discloses a method for the treatment of a human patient with ErbB2 expressing progressing metastatic breast cancer. *See* Section VI.I.Ground 2:(11)a, (6); Ex. 1007 ¶ 116.

b. Claim 14, element [a]: "administering a combination of an antibody which binds to epitope 4D5 within the extracellular domain sequence"

Baselga '96 in view of Baselga '94 teaches administering an antibody which binds to epitope 4D5 within the extracellular domain sequence. *See* Section VI.I.Ground 2:(1)b, (7). An "antibody" is broader than an "intact antibody" and thus the reasoning in Section VI.I.Ground 2:(1)b also meets claim 14, element [a].

c. Claim 14, element [b]: "and a taxoid,"

Baselga '96 in view of Baselga '94 discloses a combination of rhuMAb HER2 and a taxoid. *See* Section VI.I.Ground 2:(1)c.

d. Claim 14, element [c]: "in the absence of an anthracycline derivative,"

Baselga '96 in view of Baselga '94 discloses a combination of rhuMAb HER2 and a taxoid, in the absence of an anthracycline derivative. *See* Section VI.I.Ground 2:(1)d.

e. Claim 14, element [d]: "to the human patient"

Baselga '96 in view of Baselga '94 discloses treating human patients. *See* Section VI.I.Ground 2:(1)e.

f. Claim 14, element [e]: "in an amount effective to extend the time to disease progression in said human patient,"

Baselga '96 in view of Baselga '94 discloses an amount effective to extend the time to disease progression in said human patient. *See* Section VI.I.Ground 2:(1)f.

g. Claim 14, element [f]: "without increase in overall severe adverse events."

Baselga '96 in view of Baselga '94 discloses without an increase in overall severe adverse events. *See* Section VI.I.Ground 2:(1)g.

h. Conclusion

For the reasons discussed in Section VI.I.Ground 2:(1)h, it would have been obvious to a POSITA to try the combination of rhuMAb HER2 and paclitaxel as recited by claim 14.

J. There are no Secondary Considerations of Nonobviousness

During prosecution, Genentech submitted the declaration of Mark Sliwkowski, Ph.D. Ex. 1011–9:9. It argued that the '649 application claims were patentable because a POSITA would not have had a reasonable expectation of success treating humans with the combination therapy. *Id*. 9:9–13 (Sliwkowski Decl. ¶¶ 7–9). 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 9:10–11 (Sliwkowski Decl. ¶ 7). Since the two treatments cause cell cycle arrest at different times, Dr. Sliwkowski argued that 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*. (Sliwkowski Decl. ¶¶ 7–8).

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*. 1011–9:51 (Ex. C), 9:60 (Ex. D); Ex. 1007 ¶ 184.

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:

- Sorenson *et al*., 82(9) J. NATL. CANCER INST. 749–55, (1990) (Ex. 1012) at 7 (noting that cisplatin causes G_2 cell cyle arrest);
- Pietras *et al*., 9(7) ONCOGENE 1829–38 (1994) (Ex. 1013) at 3 (combination of 4D5 anti-ErbB2 antibody and cisplatin caused a synergistic decrease in cell growth *in vitro*); and
- Pegram '95 (Ex. 1010) 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. 1007 ¶¶ 184–185.

Third, a POSITA in 1997 would have understood the data Dr. Sliwkowski cited was related to tamoxifen and anthracycline combinations, not rhuMAb HER2 and paclitaxel combinations. While both articles he cites report *in vitro* data showing tamoxifen reduced cell killing effects of anthracyclines, Baselga '94 reports *in vivo* data that demonstrates a synergistic effect between the 4D5 antibody and paclitaxel. Exs. 1011–9:85 (Ex. F), 9:94 (Ex. G); 1005 at 4.

If his hypothesis were correct, the preclinical data should have shown a ***less than additive*** effect when the drugs are both administered. *See* Exs. 1011–9:94

(Ex. G); 1007 ¶ 186. 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 in humans with a reasonable expectation of success.

Dr. Sliwkowski's second argument was that a POSITA would not have had a reasonable expectation of success in humans based on preclinical models because purportedly "significant controversy exists about the usefulness of these preclinical models in predicting the response of human patients to therapy." Ex. 1011–9:12 (Sliwkowski Decl. ¶ 9). 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 preclinical data) when it determined it would proceed with a phase III trial of the 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 2001 article, dated well after the '441 patent's priority date. *Id*.

And the purported controversy regarding preclinical models does not appear to affect their use in research, nor does it appear to affect whether a POSITA would use such models to determine which treatments should be pursued in humans. Indeed, Dr. Sliwkowski is a co-author on many research papers sponsored by Genentech that use preclinical data to screen and select for novel treatments using anti-ErbB2 antibodies. *See*, *e.g.*, Exs. 1014; 1015.

Thus, POSITAs regularly use such models to screen treatments and select promising drugs for trial. And 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. 1005 at 4; 1004 at 15. A POSITA would have understood this to mean that the trial had not been halted for lack of efficacy or safety. Ex. 1007 ¶¶ 73, 132.

Genentech's purported unexpected results also lack a nexus to the claimed inventions. The assertions in Dr. Slikowski'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, Baselga '96, and Baselga '94. Genentech identified no secondary indicia of non-obviousness associated with any elements of the claimed invention that were 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." Ex. 1007 ¶¶ 183–189.

Moreover, Baselga '97 demonstrates, at a minimum, near-simultaneous invention of the Challenged Claims. *See I/P Engine, Inc. v. AOL, Inc.*, 576 Fed. Appx. 982, 990 (Fed. Cir. 2014). POSITAs like Drs. Baselga, Pegram, and Hellmann turned to the most obvious targets: combinations of known therapies

seeking synergistic effects. *See* Ex. 1007 ¶ 187. Accordingly, there are no secondary considerations supporting nonobviousness of the '441 patent.

VII. CONCLUSION

Hospira respectfully requests IPR of the Challenged Claims.

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Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

This Petition complies with the type-volume limitations as mandated in 37 C.F.R § 42.24, totaling 13,068 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. 7,846,441, 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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