UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Pfizer, Inc.
Petitioner
v.

Genentech, Inc.
Patent Owner

Patent No. 7,846,441

Title: TREATMENT WITH ANTI-ErbB2 ANTIBODIES

Inter Partes Review No. To Be Assigned

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 7,846,441

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I. INTRODUCTION

Pfizer, Inc. petitions for *inter partes* review ("IPR") under 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42 *et seq.* of claims 1-14 of U.S. Patent No. 7,846,441 ("the '441 patent," Ex. 1101).

The '441 patent claims recite methods of treating patients who have cancer characterized by overexpression of the ErbB2 receptor (*i.e.*, the HER2 protein) by administering a combination of two drugs, an anti-ErbB2 antibody (*e.g.*, trastuzumab) and a taxoid (*e.g.*, paclitaxel), each of which was already known in the prior art to be individually effective against this type of cancer. Based on bedrock principles of cancer treatment and combination therapy, a person of ordinary skill in the art ("POSA") would have been motivated to use a combination of trastuzumab and paclitaxel to treat patients who had this type of cancer, and would have reasonably expected the combination to be safe and effective. Indeed, the prior art disclosed that clinical trials of this combination for this patient population were underway well before the filing of application that led to the '441 patent.

The '441 patent should have never issued, as evidenced by the nine rounds of obviousness rejections Patent Owner faced during prosecution. The rejections were based on prior art that showed the efficacy of trastuzumab in treating HER2-positive breast cancer patients, and preclinical xenograft data that showed the

claimed combination to be synergistic against human HER2-positive tumors without increased toxicity.[1] In response to these rejections, Patent Owner argued that the prior art teachings were insufficient to support *prima facie* obviousness, and also submitted a declaration from the named inventor that alleged clinical synergy as a purported unexpected result of the combination. The Examiner did not allow the claims in response to these arguments, explaining that "it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form the third composition that is to be used for the very same purpose: [the] idea of combining them flows logically from their having been taught individually in the prior art." (*See, e.g.*, Ex. 1104 at 272.) The Examiner also explained that based on the preclinical study data, any synergy would not have been unexpected.

The Examiner allowed the claims only after Patent Owner submitted a new declaration in response to the ninth round of obviousness rejections. This declaration purported to refute motivation to combine and reasonable expectation of success. The Examiner accepted the declaration as persuasive evidence, even

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[1] Xenografts are a preclinical model in which immunocompromised mice are injected with human cancer cells. (*See infra*, Section VII.A.4.) Because the mouse's immune system is disabled, the cancer cells form human tumors in the mouse. (*Id.*)

though the declarant (Mark Sliwkowski, Ph.D., a Genentech employee) relied on non-prior art to attack the Examiner's reliance on xenograft data, offered opinions that contradicted the prior art and well-established principles of cancer combination therapy, and contradicted his own publications. During prosecution, the Examiner did not have the benefit of expert testimony that explained that POSAs in fact relied on xenografts to inform their decisions on which drug combinations to pursue, and that POSAs would have been motivated to pursue the combination of trastuzumab and paclitaxel, because, among other reasons, it satisfied the principles of cancer combination therapy.

The prior art in this Petition includes references that were not before the Examiners during prosecution. These references disclose that paclitaxel is effective in treating patients with metastatic HER2-positive breast cancer (the specific type of cancer referenced in the claims), and explain the principles behind choosing drugs for combination therapies for breast cancer. The prior art clearly provided a motivation to combine trastuzumab and paclitaxel to treat metastatic HER2-positive breast cancer patients, with a reasonable expectation that the combination would be safe and effective. Indeed, the prior art taught that this combination was already undergoing clinical trials for this indication. The claims of the '441 patent are therefore unpatentable as obvious in view of the prior art.

II. MANDATORY NOTICES

A. Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1))

The real party-in-interest is Pfizer, Inc.

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

In IPR2017-00731, Petitioner[2] asserted all claims of the '441 patent are obvious based on grounds that are different than those in this Petition. The Board declined to institute IPR. IPR2017-00731, Paper 19. Petitioner filed a request for reconsideration on August 25, 2017. IPR2017-00731, Paper 22.

Third-party Celltrion Inc. has also filed an IPR challenging the '441 patent. IPR2017-01121. A motion for joinder with IPR2017-01121 accompanies this Petition.

Petitioner also filed two petitions for IPR of U.S. Patent No. 7,892,549 ("the '549 patent"), which is a continuation of the '441 patent. IPR2017-00737, IPR2017-00739. The Board instituted IPR in IPR2017-00737 on July 27, 2017. IPR2017-00737, Paper 19. Celltrion Inc. and third-party Samsung Bioepis have also filed IPRs challenging the '549 patent. IPR2017-01122; IPR2017-01960.

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

Petitioner designates the following counsel:

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[2] Updated mandatory notices were filed in IPR2017-00731 on June 2, 2017 identifying Petitioner as the real party-in-interest. IPR2017-00731, Paper 13.

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

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

III. CERTIFICATION OF GROUNDS FOR STANDING

Petitioner certifies pursuant to 37 C.F.R. § 42.104(a) that the patent for which review is sought is available for IPR and that Petitioner is not barred or estopped from requesting IPR challenging the patent claims on the ground identified in this petition.

IV. FEES

The Commissioner is authorized to charge all fees due in this IPR to Deposit Account 506092.

V. SUMMARY OF THE '441 PATENT AND ITS PROSECUTION HISTORY

The '441 patent issued on December 7, 2010 from Application Ser. No. 09/208,649 ("the '649 application"), filed on December 10, 1998. The '649 application claims priority to provisional application No. 60/069,346, filed on December 12, 1997.

For purposes of this IPR only, Petitioner will assume that December 12, 1997 is the earliest priority date to which the '441 patent claims are entitled. Therefore, for purposes of this IPR, any patent or printed publication prior to December 12, 1996 qualifies as prior art under 35 U.S.C. § 102(b), and any patent or printed publication prior to December 12, 1997 qualifies as prior art under 35 U.S.C. § 102(a).

A. The Claims of the ’441 Patent

The ’441 patent issued with 14 claims. Independent claim 1 reads:

> 1. A method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by overexpression of ErbB2 receptor, comprising 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, to the human patient in an amount effective to extend the time to disease progression in said human patient, without increase in overall severe adverse events.

Claims 2-10 depend from claim 1, and include further limitations regarding the condition of the patient or type of cancer (claims 2, 3, 4, 5 and 6), the antibody (claim 7), the taxoid (claim 8), drug amounts (claim 9), and means of determining efficacy (claim 10).

Independent claim 11 is similar to claim 1, but uses the terms “with ErbB2 overexpressing progressing metastatic breast cancer” instead of “with a malignant progressing tumor or cancer characterized by over-expression of ErbB2 receptor,” and “a humanized 4D5 anti-ErbB2 antibody” instead of “an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence.” Claim 12 depends from claim 11 and requires that the taxoid be paclitaxel.

Independent claim 13 is similar to claim 1, but uses the terms “progressing malignant tumor” instead of “malignant progressing tumor” and “a humanized 4D5 anti-ErbB2 antibody which comprises a human Fc region and that binds to epitope 4D5 within the ErbB2 extracellular domain sequence” instead of “an intact

antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence."

Independent claim 14 is similar to claim 1, but uses the term "an antibody which binds to epitope 4D5 within the extracellular domain sequence" instead of "an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence."

B. '441 Patent Specification

The '441 patent specification acknowledges that trastuzumab has been "active in patients with ErbB2-overexpressing metastatic breast cancers that had received extensive prior anti-cancer therapy." (Ex. 1101, 3:34-40.) It also acknowledges that trastuzumab enhanced the activity of paclitaxel in HER2-positive mouse xenografts. (*Id.*, 3:54-59.)

The specification asserts that the "present invention" is a method of treating a patient with a HER2-overexpressing tumor with trastuzumab and a taxoid (preferably paclitaxel), in the absence of anthracycline. (*Id.*, 1:10-16; 3:63-4:12; 4:21-23.) The specification explains that the "present invention" is "based on the recognition that...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" and concerns administering "a combination of an anti-ErbB2 antibody and a chemotherapeutic agent other than an anthracycline derivative, e.g.

doxorubicin or epirubicin, in the absence of an anthracycline derivative[.]" (*Id.*, 3:63-4:11.)

The specification includes an example relating to the treatment of HER2-positive metastatic breast cancer patients. (*Id.*, 26:32-30:25.) Half of the patients received chemotherapy alone, which comprised either cyclophosphamide and an anthracycline derivative ("AC"), or paclitaxel (T). (*Id.*, 28:15-21.) The other half received one of these chemotherapy regimens, plus trastuzumab (H). (*Id.*, 28:3-13.) The patent reports the following results, including time to progression (TTP), response rate (RR), and adverse event rates:

Treatment	**Number of patients**	**TTP (months)**	**RR (%)**	**AE(%)**
AC	145	6.5	42.1	71
AC + H	146	9.0	64.9	68
T	89	4.2	25.0	59
T + H	89	7.1	57.3	70

(*Id.*, 29:8-30:12.) The specification states that "[a] syndrome of myocardial dysfunction similar to that observed with anthracyclines was reported more commonly with a combined treatment of AC+H (18% Grade 3/4) than with AC alone (3%), T (0%), or T+H (2%)." (*Id.*, 30:13-25.) The specification states that the results favor the combination of trastuzumab and paclitaxel:

> These data indicate that the combination of anti-ErbB2 antibody treatment with chemotherapy markedly increases the clinical benefit, as assessed by response rates and the evaluation of disease progression. However, due to the increased cardiac side-effects of doxorubicin or epirubicin, the combined use of anthracyclines with anti-ErbB2 antibody therapy is contraindicated. The results, taking

> into account risk and benefit, favor the combined treatment with HERCEPTIN® and paclitaxel (TAXOL).

(*Id.*)

C. Prosecution History

The ’441 patent issued after nine rounds of rejections. Each round of rejection was met with arguments and claim amendments by Patent Owner, and resulted in five interviews, two declarations regarding the alleged non-obviousness of the claims, and a request for continued examination. (*See* Ex. 1104.)

With respect to the obviousness rejections, the Examiners relied on prior art that taught, *inter alia*, (1) trastuzumab’s efficacy against HER2-positive breast cancer in humans (*e.g.*, Ex. 1120 (Baselga 1996)); (2) the efficacy of taxoids against metastatic breast cancer in humans (*e.g.*, Ex. 1110 (Seidman 1995)); and (3) synergy between trastuzumab and taxoids in mouse xenografts (*e.g.*, Ex. 1119 (Baselga Abstract 53)).[3] The Examiners explained that a POSA “would have had a reasonable expectation of success in combining these two treatments, especially when considered in light of the preclinical data of Baselga 1994 demonstrating that the two treatments were synergistic.” (Ex. 1104 at 2322.)

[3] *See* Ex. 1104 at 271-73; 368-70; 404-09; 637-39; 2018-21; 2050-51; 2093-99; 2279-86; 2320-23.

Patent Owner responded to the first obviousness rejection by submitting a declaration from inventor Dr. Hellmann, and arguing that the claimed invention purportedly resulted in two unexpected results: (1) unexpected synergy; and (2) unexpected toxicity shown by the trastuzumab/anthracyclines combination (an unclaimed combination), in view of the lack of such toxicity shown by the claimed trastuzumab/taxoid combination. (Ex. 1104 at 305, 319; "Hellmann Declaration," Ex. 1108.[4]) The Examiners, however, maintained their obviousness rejections for eight additional rounds. (Ex. 1104 at 368-70; 404-09; 637-39; 2018-21; 2050-51; 2093-99; 2279-86; 2320-23.)

On December 15, 2009, after a ninth round of obviousness rejections, Patent Owner submitted a new declaration, from Mark X. Sliwkowski, Ph.D., a Staff Scientist at Genentech. (Ex. 1109 (Sliwkowski Declaration))[5] Dr. Sliwkowski asserted that "a skilled scientist would have anticipated that paclitaxel would provide little or no additional benefit to treatment with trastuzumab alone since trastuzumab would arrest the cell cycle before paclitaxel would be able to act." (*Id.*, ¶ 7.) He also argued that a POSA would have reasonably expected an "antagonistic interaction between trastuzumab and paclitaxel" because "the addition of the anti-estrogen, tamoxifen, to standard chemotherapy regimens

[4] The Hellmann Declaration is also found in Ex. 1104 starting at page 319.

[5] The Sliwkowski Declaration is also found in Ex. 1104 starting at page 2351.

resulted in little or no benefit with either advanced breast cancer or in the adjuvant setting." (*Id*., ¶ 8.) He also questioned the utility of the xenograft model. Relying on an article published in 2001, about 4 years after the priority date, he argued that "significant controversy exists about the usefulness of these preclinical models in predicting response of human patients to therapy." (*Id*., ¶ 9.) He concluded that the xenograft data "would not have motivated" a POSA to combine trastuzumab with a taxoid to treat HER2-positive breast cancer, or provided a reasonable expectation of success. (*Id*., ¶ 10.)

On December 30, 2009, the Examiner allowed the application, stating only that the "declaration of Mark X. Sliwkowski, Ph.D., filed 10/15/2009 and the argument presented by applicant were persuasive to overcome the rejections of the claims under 35 § U.S.C. 103(a)." (Ex. 1104 at 2466.)

As will be discussed below, during the *ex parte* prosecution, the Examiners were not presented with prior art that (a) showed that paclitaxel was clinically effective against metastatic HER2-positive breast cancer; and (b) reflected the core principles for combining cancer therapies. Nor were the Examiners presented with counter-expert testimony that establishes that: (i) as of December 1996, POSAs relied on xenograft data in developing drugs for clinical trials; (ii) Dr. Sliwkowski's purported concern about potential antagonism between trastuzumab and paclitaxel was belied by the prior art, which showed that the combination was

synergistic in preclinical models and already in clinical trials; (iii) contrary to Dr. Sliwkowski's assertions, a POSA would have known that paclitaxel exhibited its anticancer effects during all phases of the cell cycle and not merely downstream of trastuzumab, and thus would have provided benefits over trastuzumab alone; and (iv) the combination of trastuzumab/paclitaxel was promising and attractive because it satisfied each of the four core principles of combination therapy.

VI. CLAIM CONSTRUCTION

The challenged claims should be given their broadest reasonable interpretation ("BRI") in light of the patent specification. 37 C.F.R. § 42.100(b); *see also Cuozzo Speed Techs. LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016). For purposes of this IPR only, Petitioner adopts the following constructions as the BRI of each term. Also for purposes of this IPR only, Petitioner will assume that the claims' preambles are limiting.

A. "Progressing"

"Progressing" means "worsening." (*See, e.g.*, Ex. 1101, 28:46-53; Ex. 1102, ¶ 112.)

B. "Time to Disease Progression"

"Time to disease progression" means "time period calculated from diagnosis or the start of therapy until the disease worsens." (*See* Ex. 1101, 29:1-2; Ex. 1104 at 2304; Ex. 1102, ¶ 112.)

C. "Extend the Time to Disease Progression in Said Human Patient, Without Increase in Overall Severe Adverse Events"

The term "extend the time to disease progression in said human patient, without increase in overall severe adverse events" is a relative term. Based on the specification, the appropriate comparison is to compare the claimed combination treatment to treatment with a taxoid alone. (Ex. 1102, ¶ 112.) The Example in the specification reports a clinical study in which patients in one arm received either TAXOL® alone or with HERCEPTIN®. (Ex. 1101, 28:3-6, 15-23.) The specification shows that TTP and adverse events were evaluated based on the combination of TAXOL® with HERCEPTIN® versus treatment with TAXOL® alone. (*Id.*, 29:9-30:25; Ex. 1102, ¶ 112.)

During prosecution, Patent Owner asserted that the appropriate comparison for the term "extend the time to disease progression" is to compare the claimed combination treatment to no treatment at all. For example, in response to an indefiniteness rejection, Patent Owner stated: "Clearly, the combination of anti-ErbB2 antibody and taxoid is administered in an amount effective to extend the time to disease progression relative to an untreated patient." (Ex. 1104 at 416.)

To the extent the Board construes the claim phrase "extend the time to disease progression in said human patient, without increase in overall severe adverse events" consistent with Patent Owner's assertion during prosecution,

Petitioner's unpatentability arguments herein still show unpatentability of the claims. (*See infra*, n.18.)

D. "Response Rate"

"Response rate" means the percentage of patients whose disease responds to treatment. (*See, e.g.*, Ex. 1101, 28:36-67, 29:11-30:20; Ex. 1102, ¶ 112.)

E. Defined Terms

The '441 patent specification defines several claim terms. For purposes of this IPR only, Petitioner adopts the following constructions as the BRI of each term:

1. "Overexpression of ErbB2 Receptor"/"ErbB2 Overexpressing"/"Overexpression of ErbB2 Receptor"

The '441 patent states: "A cell which 'overexpresses' ErbB2 has significantly higher than normal ErbB2 levels compared to a noncancerous cell of the same tissue type." (Ex. 1101, 5:57-59.) Thus, the claims terms "overexpression of ErbB2 receptor"; "ErbB2 overexpressing"; "overexpression of ErbB2 receptor" are defined as "having significantly higher than normal ErbB2 levels compared to a noncancerous cell of the same tissue type." (Ex. 1102, ¶ 111.)

2. "Humanized"

The term "humanized" is defined as "contain[ing] minimal sequence derived from non-human immunoglobulin." (*Id.*, 9:16-22; Ex. 1102, ¶ 111.)

3. "Epitope 4D5"

The term "epitope 4D5" is defined as "the region in the extracellular domain of ErbB2 to which the antibody 4D5 binds." (*Id.*, 5:24-26; Ex. 1102, ¶ 111.)

Petitioner's positions on claim construction should not be construed as an assertion regarding the appropriate claim scope in other adjudicative forums, where a different claim interpretation standard may apply.

VII. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED

Petitioner requests cancellation of claims 1-14 under 35 U.S.C. § 103 as obvious over **Baselga 1996** (Ex. 1120), **Seidman 1996** (Ex. 1111), and the **1995 TAXOL PDR** entry (Ex. 1112), in view of the knowledge of a POSA.

Petitioner's argument is based on the observed clinical efficacy of trastuzumab in patients with HER2-positive breast cancer (Baselga 1996) and the separately-observed clinical efficacy of paclitaxel in the same population of patients (Seidman 1996). Based on the four principles of combination therapy and the state of the art, which taught that agents with single agent anti-cancer efficacy should be evaluated as part of a combination therapy, a POSA would have been motivated to use a combination of paclitaxel and trastuzumab to treat patients with HER2-positive breast cancer. Determining the effective amounts of these agents for the combination would have been a straightforward matter of using the well-

known amounts of each agents as monotherapy (reported, for example, in Baselga 1996 and the 1995 TAXOL PDR) to maximize efficacy and tolerability.

This petition is supported by the Expert Declaration of Allan Lipton., M.D. (Ex. 1102.) Dr. Allan Lipton is a Professor of Medicine and Oncology at the Milton S. Hershey Medical Center of The Pennsylvania State University, with over 50 years of experience in the medical field and extensive experience in clinical oncology. (Ex. 1102, ¶¶ 11-23, Ex. 1103.)

The petition and supporting declaration establish that there is a reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims. *See* 35 U.S.C. § 314(a). Accordingly, IPR should be instituted, and the Board should cancel claims 1-14.

A. Scope and Content of the Prior Art

Cancer arises from abnormal and uncontrolled cell division. Cancers, including breast cancer, are caused by mutations in various genes that coordinate cellular processes, including cell division, cellular metabolism, and cell death. (Ex. 1102, ¶ 30.) Different cancer cells have different genetic mutations, sometimes even within a single tumor. This is called "intra-tumor heterogeneity." (*Id.*, ¶ 83; Ex. 1105 (Alberts)[6], 1271; Ex. 1120 (Baselga 1996)[7].) Benign tumors

[6] MOLECULAR BIOLOGY OF THE CELL 1255-1294 (Bruce Alberts et al., eds., 3rd. ed. 1994) (Ex. 1105, "Alberts").

remain in their original location, whereas malignant tumors can form secondary tumors elsewhere in the body, a process called metastasis. (Ex. 1102, ¶ 30; Ex. 1105 (Alberts), 1256.)

1. Chemotherapy

As of December 1996, breast cancer was most often treated with surgery, radiation, and pharmaceuticals such as chemotherapy. (Ex. 1102, ¶ 32; Ex. 1116 (Abeloff), 201-206; Ex. 1106 (DeVita),[8] 1280-1324.) Chemotherapeutic drugs are designed to interrupt the activity of a tumor cell by either killing the cell or stopping cellular processes. (Ex. 1102, ¶¶ 33-36, 49.) Different classes of drugs achieve these goals in different ways, and different cancers respond to drugs in different ways, depending on the cellular mutations at issue. (*Id.*)

With TAXOL® (paclitaxel) receiving FDA approval in December 1992 and TAXOTERE® (docetaxel) in May 1996, the taxoids (also known as taxanes) were among the most promising breast cancer chemotherapeutics in the mid-1990s. (Ex. 1102, ¶ 37.) It was known that taxoids successfully treated some cancers that did not respond to treatment with anthracyclines. (*Id.*; Ex. 1110 (Seidman 1995), 108.) It was also known that paclitaxel had anti-cancer activity in metastatic breast

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[7] J. CLINICAL ONCOLOGY, 737-744 (J. Baselga et al., MAR. 1996).

[8] CANCER: PRINCIPLES & PRACTICE OF ONCOLOGY (Vincent T. DeVita, Jr., et al. eds., 4th ed. 1993).

cancer patients, and that HER2-positive patients were particularly responsive to paclitaxel. (Ex. 1102, ¶ 37; Ex. 1110 (Seidman 1995) at 108-111.)

1995 TAXOL PDR: TAXOL (paclitaxel) for Injection Concentrate, *in* PHYSICIAN'S DESK REFERENCE, 682-685 (49th ed. 1995) (Ex. 1112, "**1995 TAXOL PDR**"), was published in 1995. (Ex. 1112 (1995 TAXOL PDR), 2.) It became publicly available as of its publication date. (Ex. 1102, ¶ 38.) 1995 TAXOL PDR is therefore a prior art printed publication under 35 U.S.C. § 102(b). The PDR listing was not before the Examiners during prosecution.

According to 1995 TAXOL PDR, paclitaxel was indicated for the "treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy." (Ex. 1112 (1995 TAXOL PDR), 683.) The recommended dosage of paclitaxel to treat breast cancer was 175 mg/m^2, administered intravenously over the course of three hours, every three weeks. (*Id.*, 685.) Paclitaxel was used as a monotherapy and as part of a combination of active agents for treating metastatic breast cancer patients. (Ex. 1102, ¶ 37; Ex. 1113 (Tolcher),[9] 37; Ex. 1107 (Abrams), 1164; Ex. 1114 (Gelmon 1996)[10].)

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[9] Anthony W. Tolcher, *Paclitaxel Couplets with Cyclophosphamide or Cisplatin in Metastatic Breast Cancer,* 23(1) Suppl. 1 SEMINARS ONCOLOGY 37-43 (Feb. 1996).

2. HER2-Positive Breast Cancer

In HER2-positive breast cancer, the HER2 protein is overexpressed by tumor cells. (Ex. 1102, ¶ 47.) HER2-positive breast cancer accounts for 25% to 30% of human breast cancers and, as of December 1996, was known to be aggressive, associated with a worse prognosis, and particularly difficult to treat with traditional anti-cancer agents. (*Id.*, ¶ 148; Ex. 1120 (Baselga 1996), 737.) However, by December 1996, it was known that HER2-positive breast cancer responded to paclitaxel. (Ex. 1102, ¶¶ 51, 59-60; Ex. 1111 (Seidman 1996).)

By 1994, preclinical studies had shown that a humanized antibody that targets HER2 was an effective anti-cancer agent in HER2-positive cells, both as monotherapy, and in combination with various chemotherapies. (Ex. 1102, ¶¶ 67-76; Ex. 1101, 3:34-40; Ex. 1119 (Baselga Abstract 53).) By 1996, phase II clinical trials in humans had established that this antibody—variously known as "humanized MAb 4D5," "rhuMAb HER2," "trastuzumab," and HERCEPTIN®—exhibited potent anti-tumor activity against metastatic HER2-positive breast cancers and was "remarkably well tolerated" and "absen[t] significant toxicity." (Ex. 1120 (Baselga 1996), 739, 741.)

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[10] Gelmon, *Phase I/II Trial of Biweekly Paclitaxel and Cisplatin in the Treatment of Metastatic Breast Cancer,* JOURNAL OF CLINICAL ONCOLOGY, 14(4) 1996.

The following references discuss known HER2-positive breast cancer treatments as of 1997:

Baselga Abstract 53 (Ex. 1119): J. Baselga *et al., Anti HER2 Humanized Monoclonal Antibody* (*MAb*) *Alone and in Combination with Chemotherapy Against Human Breast Xenografts*, 13 PROC. AM. SOC'Y CLINICAL ONCOLOGY 63, abs. 53 (Mar. 1994) ("Baselga Abstract 53") was published in May 1994 in conjunction with the 30 Annual Meeting of the American Society of Clinical Oncology ("ASCO"), held May 14-17, 1994, in Texas. (Ex. 1102, ¶ 67.) Dr. Lipton is very familiar with the annual ASCO meetings, which thousands of oncology specialists and cancer researchers attend each year. (*Id.*) He typically attends the ASCO annual meetings, and knows that copies of the Proceedings are distributed to attendees during or before the meetings. (*Id.*) Dr. Lipton attended the May 1994 meeting, where he and other cancer researchers received a copy of Programs/Proceedings book. (*Id.*) Accordingly, Baselga Abstract 53 published in May 1994, and is therefore a printed publication that is prior art to the '441 patent under 35 U.S.C. § 102(b).

Baselga Abstract 53 reports the effects of humanized "anti-HER2 4D5" antibody (*i.e.*, trastuzumab) and chemotherapeutic agents against HER2-positive breast carcinoma xenografts, alone and in various combinations:

Treatment	Result As Compared to Placebo
Trastuzumab	35% growth inhibition at 5 weeks

Treatment	Result As Compared to Placebo
Paclitaxel	35% growth inhibition at 5 weeks
Doxorubicin	27% growth inhibition at 5 weeks
Trastuzumab and paclitaxel	93% growth inhibition at 5 weeks
Trastuzumab and doxorubicin	70% growth inhibition at 5 weeks

(Ex. 1119 (Baselga Abstract 53).) The combination of trastuzumab and paclitaxel exhibited "major antitumor activity with 93% inhibition of growth." (*Id.*) Baselga Abstract 53 reports that the combination treatments "did not increase the toxicity" of either paclitaxel or doxorubicin alone. (*Id.*) The abstract concludes: "In summary, anti HER2 MAbs can eradicate well established tumors and enhance the activity of paclitaxel and doxorubicin against human breast cancer xenografts. Clinical trials are underway." (*Id.* (emphasis added).)

Baselga Abstract 2262 (Ex. 1121): J. Baselga *et al., Antitumor Activity of Paclitaxel in Combination with Anti-growth Factor Receptor Monoclonal Antibodies in Breast Cancer Xenografts*, 35 (380) PROC. AM. ASS'N FOR CANCER RES. 380, abs. 2262 (Mar. 1994) ("Baselga Abstract 2262"), published in March 1994, in the Proceedings for the 85th Annual Meeting of the American Association for Cancer Research ("AACR") that was held April 10-13, 1994 in California. (Ex. 1102, ¶ 72.) Dr. Lipton is familiar with the annual AACR meetings. (*Id.*) He has attended AACR annual meetings, and knows that copies of the Programs/Proceedings book are available once published by contacting the AACR (*Id.*) As indicated on page 2 of Exhibit 1121, the Proceedings in which Baselga

Abstract 2262 published was also available for sale as of April 1994. Accordingly, Baselga Abstract 2262 published in March 1994 was available for sale as of April 1994, and is therefore is a prior art printed publication under 35 U.S.C. § 102(b).

Baselga Abstract 2262 reports the same data as that in Baselga Abstract 53, and further highlights the favorable results obtained with the combination of paclitaxel and trastuzumab,[11] which were better than the results obtained with doxorubicin and trastuzumab:

> The combined treatment with paclitaxel plus 4D5 resulted in a major antitumor activity with 93% inhibition of growth. This result was markedly better than doxorubicin plus 4D5 (70% inhibition). Thus, equipotent doses of paclitaxel and doxorubicin differed in their combined effect with ARMAs, which suggests synergy between paclitaxel and 4D5. ARMAs did not increase the toxicity of paclitaxel in animals as determined by animal survival and weight loss. The antitumor effects of paclitaxel can be markedly enhanced by the addition of ARMAs.

[11] Baselga Abstract 2262 references "anti-HER2 ARMA [anti-growth factor receptor monoclonal antibody] 4D5." As Dr. Lipton explains, a POSA would have known that this was trastuzumab because the reported values in Baselga Abstract 2262 are identical to the reported values in Baselga Abstract 53, and Baselga Abstract 53 specifies that the antibody was humanized. (Ex. 1102, ¶ 73, n.16.).

(Ex. 1121 (Baselga Abstract 2262) (emphases added); Ex. 1102, ¶¶ 73-76.)

Baselga 1996 (Ex. 1120): J. Baselga *et al., Phase II Study of Weekly Intravenous Recombinant Humanized Anti-p 185^{HER2} Monoclonal Antibody in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer*, 14(3) J. CLINICAL ONCOLOGY 737-744 (Mar. 1996) ("Baselga 1996"), published in the Journal of Clinical Oncology in March 1996. As of March 1996, this was a reputable journal in the field and was widely available to and consulted by POSAs. (Ex. 1102, ¶ 53.) It published monthly, with issues becoming available during the month of their publication. (Id.) For example, the March 1996 issue became available to readers in March 1996. (Id.) Baselga 1996 therefore is a prior art printed publication under 35 U.S.C. § 102(b).

Baselga 1996 discloses the results of a phase II clinical study in which HER2-positive metastatic breast cancer patients were treated with rhuMAb HER2 (*i.e.*, trastuzumab). (*Id.*, ¶¶ 53-58.) The patients all had a dire prognosis due to extensive tumor metastasis. (Ex. 1120 (Baselga 1996), 741.) The patients each received the following regimen of trastuzumab: a loading dose of 250 mg on day 0, and beginning on day 7, 100 mg weekly for a total of 10 doses. (*Id.*, 738.) The article reports an overall response rate of 11.6%. (*Id.* at 741, Table 4.) Of the 43 patients, one had complete remission and four had partial remission. (*Id.*, 741.) Further, at day 77, "two patients had minor responses and 14 patients had stable

disease." (*Id.*, 740.) The median TTP for patients with minor responses or stable disease was 5.1 months. (*Id.*) The article suggests that the response rate would have been higher for patients with "less extensive breast cancer." (*Id.*, 741.) With respect to adverse events, the article reports an absence of "significant toxicity." (*Id.*)

Baselga 1996 states that "continued research with this agent and other HER2-targeted treatment strategies appears warranted." (*Id.*, 743.) Citing Abstract 53, Baselga 1996 further notes that "in preclinical studies, both *in vitro* and in xenografts, rhuMAb HER2 (*i.e.*, trastuzumab) markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity. Laboratory studies of the mechanism of this effect and clinical trials of such combination therapy are currently in progress." (*Id.*; *see also* Ex. 1102, ¶ 58.) In other words, researchers, encouraged by the preclinical results, were actively pursuing combination therapies of trastuzumab with the chemotherapeutic agents referenced in Baselga 1996, including paclitaxel. (Ex. 1102, ¶ 91)

Seidman 1996 (Ex. 1111): A. Seidman *et al., HER-2/neu Over-Expression and Clinical Taxane Sensitivity: A Multivariate Analysis in Patients with Metastatic Breast Cancer (MBC)*, 15 PROC. AM. SOC'Y CLINICAL ONCOLOGY 104, abs. 80 (Mar. 1996) ("Seidman 1996"), published in May 1996 in conjunction with

the 32nd ASCO Annual Meeting, held May 18-21, 1996, in Pennsylvania. (Ex. 1102, ¶ 59.) Dr. Lipton attended the May 1996 meeting, where he and other cancer researchers received a copy of the Proceedings during the meeting. (*Id*.) Seidman 1996 is therefore a prior art printed publication under 35 U.S.C. § 102(b). Seidman 1996 was not before the Examiners during prosecution.

Seidman 1996 reports on treatment of metastatic breast cancer patients with paclitaxel. (Ex. 1111 (Seidman 1996).) Of the patients, 40.5% were HER2-positive. (*Id.*) Thirty of the 51 (58.8%) HER2-positive patients responded to treatment, whereas only 29 of the 75 (38.7%) patients with breast cancer that did not overexpress the HER2 protein responded. (*Id.*) Seidman 1996 concluded that HER2-overexpression "seems to confer sensitivity" to treatment with taxanes, even though this condition was known to be difficult to treat with other drugs. (*Id.*; *see also* Ex. 1102, ¶ 60.)

Seidman 1995 (Ex. 1110): A. Seidman *et al., Memorial Sloan-Kettering Cancer Center Experience with Paclitaxel in the Treatment of Breast Cancer*, 22 (5) Suppl. 5 SEMINARS ONCOLOGY 108-116 (Oct. 1995) ("Seidman 1995") published in October 1995. As of October 1995, Seminars in Oncology was a reputable journal in the field and was widely available to and consulted by POSAs. (Ex. 1102, ¶ 77.) It published monthly, with issues becoming available during the month of their publication. (*Id.*) For example, the October 1995 issue became

available to readers in October 1995. (*Id.*) Seidman 1995 therefore is a prior art printed publication under 35 U.S.C. § 102(b).

Seidman 1995 reports on the use of paclitaxel to treat metastatic breast cancer, and discusses development via routine trial and error of the optimal dosing schedule for paclitaxel monotherapy. (*Id.*, ¶¶ 78-80; Ex. 1110 (Seidman 1995), 110-11.) The article also discusses the development of combination therapies that incorporate paclitaxel, including combinations with doxorubicin, cisplatin, and trastuzumab. (Ex. 1110, at 111-12.) Seidman 1995, citing Baselga Abstract 2262, reports that the "striking antitumor" effects, "strong synergy," and "no increased toxicity" of paclitaxel and trastuzumab in xenograft models "provide a lead for translation into the clinic. Indeed, future clinical trials combining paclitaxel with anti-growth factor receptor MoAbs [*e.g.*, trastuzumab] are being planned." (*Id.*, 112.)

Pegram 1995 (Ex. 1122): M. Pegram *et al., Phase II Study of Intravenous Recombinant Humanized Anti-p185 HER-2 Monoclonal Antibody (rhuMAB HER-2) Plus Cisplatin in Patients with HER-2/NEU Overexpressing Metastatic Breast Cancer*, 14 PROC. AM. SOC'Y CLINICAL ONCOLOGY 106, abs. 124 (Mar. 1995) ("Pegram 1995") is an abstract published in May 1995 in conjunction with the 31st ASCO Annual Meeting, which took place in Los Angeles on May 20-23, 1995. (Ex. 1102, ¶ 61.) Dr. Lipton was a co-author on Pegram 95 and attended the May

1995 meeting, where he and other cancer researchers received a copy of the Proceedings. (*Id.*) Pegram 1995 is therefore a prior art printed publication under 35 U.S.C. § 102(b).

Pegram 1995 reports the results of a phase II clinical study using a combination of trastuzumab and cisplatin in metastatic HER2-positive breast cancer patients. (*Id.*, ¶¶ 62-65.) This study followed preclinical studies that showed that the combination of trastuzumab and cisplatin was synergistic in HER2-positive tumor cells. (*Id.*)

In addition to cisplatin, the patients in the Pegram 1995 study received a 250 mg loading dose of trastuzumab followed by weekly doses of 100 mg for 8 weeks. (*Id.*) This is the same trastuzumab regimen studied in Baselga 1996, except that the Baselga study continued for 10 weeks, while the Pegram study lasted 9 weeks. (Ex. 1120 (Baselga 1996), 738; *see also* Ex. 1102, ¶ 63.)

Pegram 1995 reports that of 36 patients, one had a complete response and 7 had a partial response. (Ex. 1122 (Pegram 1995).) Pegram 1995 concludes that the "use of [trastuzumab plus cisplatin] in patients with [HER2] overexpressing MBC [metastatic breast cancer] resulted in response rates above that expected from [cisplatin] alone, and the combination showed no apparent increase in toxicity." (*Id.*)

3. Combination Therapy for Cancer

Since the 1960s, it has been common to treat cancer with combinations of anti-cancer drugs. (Ex. 1102, ¶ 82; Ex. 1106 (DeVita), 278-279; Ex. 1116 (Abeloff), 208.) POSAs understood that different cancers respond differently to different treatments. (Ex. 1102, ¶ 83.) They also understood that, due to intra-tumor heterogeneity, different cells within a single tumor respond to different treatments. (*Id.*) POSAs also knew that cancer cells have resistance mechanisms wherein various mutations arise as a result of treatment with pharmacologic agents. (*Id.*, ¶¶ 84-85; Ex. 1124 (Arbuck),[12] 130.) Cancer cells may develop "collateral sensitivity," wherein cells that are resistant to some drugs are hyper-sensitive to others. (Ex. 1102, ¶¶ 84-85; Ex. 1125 (Hutchinson),[13] 246.) Treatment with a drug can also cause the cancer to develop resistance to other drugs within the same class, a phenomenon called "cross-resistance." (Ex. 1102, ¶ 84; Ex. 1125 (Hutchinson), 246.)

This complicated web of mutations and resistance mechanisms arises in cells in a dynamic process that is interactive with treatment. (Ex. 1102, ¶ 87.)

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[12] S. Arbuck *et al., Paclitaxel* (*Taxol*) *in Breast Cancer*, 8 HEMATOLOGY/ONCOLOGY CLINICS N. AM. 121-140 (Feb. 1994).

[13] Doris J. Hutchinson, *Cross Resistance and Collateral Sensitivity Studies in Cancer Chemotherapy*, 7 ADVANCES CANCER RES. 235-348 (1963).

Accordingly, POSAs knew that combination therapy, which attacks cells in different ways at the same time, gives patients their best chance of survival. (*Id.*, ¶¶ 87-88; *see also* Ex. 1116 (Abeloff), 204 ("[W]ith rare exceptions single agents do not cure cancer.") As stated in Abeloff:

> The superior results achieved by combination chemotherapy can be explained in several ways. Resistance to any given single agent is almost always present, even in clinically responsive tumors, at diagnosis. Tumors that are initially 'sensitive' rapidly acquire resistance to single agents either as a result of selection of a pre-existing clone of resistant tumor cells or due to an increased rate of mutation leading to drug resistance. Combination chemotherapy theoretically addresses both important phenomena by providing a broader range of coverage of initially resistant clones of cells and preventing or slowing the development of resistant clones.

(Ex. 1116 (Abeloff), 204.)

As of December 1996—and as is still the practice today—POSAs followed a set of reasoned principles when developing combination therapies. (Ex. 1102, ¶¶ 89-91; Ex. 1124 (Arbuck), 130-31 ("The best therapeutic results in cancer chemotherapy are usually achieved with combinations of two or more drugs. When possible, efforts are made to combine full doses of non-cross resistant drugs

with single-agent activity, differing mechanisms of action, and nonoverlapping toxicity.") (emphasis added); Ex. 1116 (Abeloff), 204, listing the Principles of Combination Chemotherapy.) ***First,*** each component of the combination should be active as a single agent in the intended population. (Ex. 1102, ¶ 89; Ex. 1116 (Abeloff), 204-05.) This ensures that the combination has the best chance of producing a potent anti-cancer effect. (Ex. 1102, ¶ 89; Ex. 1116 (Abeloff), 204-05.) ***Second***, combinations of agents with non-overlapping toxicities are preferred. (*Id.*) This allows for a full dose of each drug to be given in the combination, while minimizing the risk of increasing toxicity. (Ex. 1102, ¶ 89; Ex. 1116 (Abeloff), 204-05.) ***Third***, combinations of agents with different pharmacologic targets are preferred. (Ex. 1102, ¶ 89; Ex. 1116 (Abeloff), 204-05.) ***Fourth***, combinations of agents with different resistance mechanisms are preferred. (Ex. 1102, ¶ 89; Ex. 1116 (Abeloff), 204-05.) The third and fourth principles ensure that the combination is broad-spectrum in that it attacks cells in multiple ways, thereby achieving the greatest possible combined result. (Ex. 1102, ¶ 89; Ex. 1116 (Abeloff), 204-05.)

4. Use of Preclinical Studies

In preclinical studies designed to test cancer treatments, researchers seek to replicate human cancers outside the human body and observe how a given treatment affects these cancers. (Ex. 1102, ¶ 43.) Xenografts are an *in vivo*

preclinical model in which an immunocompromised mouse is injected with human cancer cells. (*Id*, ¶¶ 44-46.) Because the mouse's immune system is disabled, the cancer cells form "human" tumors in the mouse. (*Id.*, *see also* Ex. 1126 (Fiebig).[14]) By administering an agent or combination of agents to the mouse, researchers can evaluate the treatment on live human tumor cells that have the same genetic mutations that cause the cancer in humans. (Ex. 1102, ¶¶ 44-45.)

Xenograft results provide a "high[ly] correct prediction for resistance and sensitivity of a tumor" to a particular agent. (*Id.*, ¶ 45; Ex. 1126 (Fiebig), 349.) Because this predictive power is reproducible, the mouse xenograft system validates "human tumor xenografts as tumor models to test new drugs and combinations." (Ex. 1126 (Fiebig), 343; *see also* Ex. 1106 (DeVita), 276 ("Development of new treatments is based on the effectiveness of the cancer drugs in rodent models."); Ex. 1128 ("Mattern"),[15] 279-80 ("Xenografts of a particular tumor type are often able to identify agents of known clinical activity against that disease. This fact strongly supports the validity of using established lines of heterotransplants of human tumors as a predictive system for testing new

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[14] H. H. Fiebig *et al., Comparison of Tumor Response in Nude Mice and in the Patients*, 74 BEHRING INST. MITTEILUNGEN, 343-352 (1984).

[15] Mattern, *Human Tumor Xenografts as Model for Drug Testing*, CANCER AND METASTASIS REVIEW, Vol. 7 (1998).

anticancer agents, and also supports the use of xenografts as a model system for studying many human cancers *in vivo*.").)

For combination therapies, clinical evidence that each treatment works individually in humans in the target population is often sufficient to support their combined use in human patients. (Ex. 1102, ¶ 120; Ex. 1126 (Fiebig), 349; Ex. 1106 (DeVita), 276 ("Combinations of drugs are fashioned based on the effectiveness, the level of cross-resistance, and the limiting toxicity of the available drugs when used alone in similar patient populations.").) Nevertheless, xenograft data can provide further evidence of efficacy or toxicity that researchers may find informative in developing new treatments. (Ex. 1102, ¶ 124.)

5. Measurements of Clinical Efficacy

In a clinical trial, the efficacy of a cancer treatment is determined by defining one or more endpoints. (Ex. 1102, ¶¶ 92-94; Ex. 1123 (ASCO Guidelines),[16] 671.) As of December 1996, common clinical endpoints included: (1) Overall Survival, *i.e.*, the percentage of patients alive at a defined time after initiation of the treatment; (2) Progression Free Survival, *i.e.*, the proportion of patients who continue to live with a disease that is not getting worse; (3) Time To Progression (TTP), *i.e.*, the time from diagnosis or start of treatment until tumor

[16] *Outcomes of Cancer Treatment for Technology Assessment and Cancer Treatment Guidelines,* 14(2) J. CLINICAL ONCOLOGY 671-679 (Feb. 1996).

progression; and (4) Response Rate (RR), which measures changes in tumor size. (Ex. 1102, ¶ 92; Ex. 1127 (ASCO Guidelines), 672-75; *see also, e.g.*, Ex. 1120 (Baselga 1996), 738-41.) Response rates are categorized as (1) Complete Response, characterized by the disappearance of clinical evidence of disease; (2) Partial Response, characterized by a certain reduction in one dimension of the size of all measurable tumors; and (3) Stable Disease, characterized by tumor size remaining the same or changing by certain amounts. (Ex. 1102, ¶ 92-94; Ex. 1129, (Miller)[17] 211-212.)

B. Level of Ordinary Skill in the Art

A POSA at the time of the alleged invention would have been an M.D. with subspecialty training in oncology and substantial experience treating breast cancer patients and/or a Ph.D. with substantial experience in researching and developing oncologic therapies. (Ex. 1102, ¶ 29.) Such an individual would also have had substantial experience in the design and/or implementation of clinical trials for breast cancer treatments, and/or an active research role relating to breast cancer treatments. (*Id.*)

[17] Miller, A. B. et al., *Reporting Results of Cancer Treatment*, 47 CANCER, 207-214 (Jan. 1981). ("Miller")

C. Differences Between the Claims and the Prior Art and Conclusion of Obviousness

Baselga 1996 and Seidman 1996 each teach a treatment with proven efficacy against metastatic HER2-positive breast cancer in humans. Treating metastatic HER2-positive breast cancer is within the scope of all of the independent claims. (Ex. 1102, ¶¶ 155, 157, 158, 160.)

Baselga 1996 discloses that trastuzumab was clinically effective in patients with advanced metastatic HER2-positive breast carcinoma, was "remarkably well tolerated," and lacked "significant toxicity," even though the patients had "dire prognostic characteristics" based on the extensive metastasis of their cancers and prior failures with other treatments. (Ex. 1120 (Baselga 1996), 741.) Baselga 1996 teaches that clinical trials of trastuzumab in combination with each of paclitaxel, doxorubicin, and cisplatin were already in progress. (*Id.*, 743; Ex. 1102, ¶¶ 58, 118, 123.)

Based on its efficacy as a monotherapy and on the understanding that cancer is more effectively treated with combination agents than with a single agent, a POSA would have been motivated to pursue combination therapies that incorporate trastuzumab. (Ex. 1102, ¶¶ 119-121.) Because most breast cancers that contain HER2-positive cancer cells also contain cancer cells with other mutations, a POSA would have been motivated to treat this patient population with

trastuzumab in combination with drugs that had shown broad efficacy against all types of metastatic cancer. (*Id.*, ¶¶ 119-121.)

As of December 1996, paclitaxel was one of the "most promising" chemotherapeutic drugs with efficacy against metastatic breast cancer. (Ex. 1107 (Abrams), 1164.) As such, a POSA would have been motivated to treat HER2-positive breast cancer patients with a combination of trastuzumab and paclitaxel. (Ex. 1102, ¶ 122.) A POSA would have been particularly encouraged to combine paclitaxel with trastuzumab because Seidman 1996 reports that paclitaxel is clinically effective against metastatic HER2-positive breast cancer. (*Id.*; Ex. 1111 (Seidman 1996).)

A POSA would have been further motivated to combine trastuzumab and paclitaxel based on the dire need for treatments of HER2-positive breast cancer. (Ex. 1102, ¶ 120.) The HER2-positive breast cancer population was notoriously difficult to treat because HER2-positive breast cancer frequently did not respond to traditional anti-cancer treatments. (*Id.*; Ex. 1120 (Baselga 1996), 737; Ex. 1101, 3:41-50.) Accordingly, a POSA would have been strongly encouraged by the clinical results reported in Baselga 1996 and Seidman 1996. (Ex. 1102, ¶ 120.)

Further, the preclinical data reporting synergy between trastuzumab and paclitaxel in mouse xenografts would have provided even more motivation to a POSA to treat patients with HER2-positive breast cancer with a combination of

trastuzumab and paclitaxel. (*Id.*, ¶ 124.) Baselga 1996 cites Baselga Abstract 53, which reports data from HER2-positive breast cancer xenograft studies of trastuzumab plus each of paclitaxel and doxorubicin. (Ex. 1120 (Baselga 1996), 843.) In Baselga Abstract 53, the treatment with the highest observed anticancer activity was trastuzumab and paclitaxel. (Ex. 1119 (Baselga Abstract 53); *see also* Ex. 1121 (Abstract 2262) ("The combined treatment with paclitaxel plus 4D5 resulted in a major antitumor activity with 93% inhibition of growth. This result was markedly better than doxorubicin plus 4D5 (70% inhibition).").)

Combining trastuzumab and paclitaxel for metastatic HER2-positive breast cancer particularly made sense because the combination satisfied the four principles of combination therapy. (Ex. 1102, ¶¶ 125-130.) First, a POSA would have known from Baselga 1996 and Seidman 1996 that trastuzumab and paclitaxel had each demonstrated anti-cancer activity as monotherapies in metastatic HER2-positive breast cancer patients. (*Id.*, ¶ 126.) Further, because patients with HER2-positive breast cancer typically also have other cancer-causing mutations (*see, e.g.*, Ex. 1105 (Alberts), 1288-90, 1263-64; Ex. 1116 (Abeloff), 206), a POSA would have been motivated to treat these patients with a drug like paclitaxel, which had proven efficacy in patients in the larger metastatic breast cancer population. (*See, e.g.*, Ex. 1107 (Abrams), 1164-1165; Ex. 1102, ¶ 126.)

Second, trastuzumab and paclitaxel were not known to have any significant overlapping toxicities. (Ex. 1102, ¶ 127.) Baselga 1996 had shown that trastuzumab, as a single agent, was well-tolerated and did not have significant toxicity. (*Id.*, ¶ 56; Ex. 1120 (Baselga 1996), 739, 741.) It was also known that for paclitaxel, the dose-limiting toxicity (*i.e.*, the toxicity that determines the maximum dose of a drug that may be administered to a patient) was myelosuppression. (Ex. 1118 (Gelmon 1994),[18] 24.) This toxicity was not associated with trastuzumab. (Ex. 1102, ¶ 127; Ex. 1120 (Baselga 1996), 739, 741.) Further, the preclinical studies cited in Baselga 1996 did not reveal any unacceptable toxicities with the combination of paclitaxel and trastuzumab. (Ex. 1120 (Baselga, 1996); *see also* Ex. 1119 (Baselga Abstract 53); Ex. 1102, ¶ 127.)

Third, POSAs understood that trastuzumab and paclitaxel had different mechanisms of action, with trastuzumab acting as a target-specific antibody and paclitaxel acting as a non-specific chemotherapeutic agent. (Ex. 1102, ¶ 129.) This satisfies the third principle of combination therapy. (*Id.*)

Fourth, because trastuzumab and paclitaxel belong to different classes and have distinct mechanisms of action, a POSA reasonably would have expected that

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[18] Karen A. Gelmon, *Biweekly Paclitaxel* (*Taxol*) *and Cisplatin in Breast and Ovarian Breast Cancer,* 21(5) Suppl. 8 SEMINARS ONCOLOGY 24-28 (Oct. 1994).

the drugs would not have overlapping resistance mechanisms. (*Id.*, ¶ 130.) This means that even if the cancer started to develop resistance to one of the drugs, the cancer would not simultaneously develop resistance to the other drug, so the regimen would still remain effective. (*Id.*) This satisfies the fourth principle of combination therapy. (*Id.*)

With respect to the claim limitation "***amount effective to extend the time to disease progression in said human, without increase in overall severe adverse events***," a POSA would have been motivated to start with the known amounts that were effective to extend the time to disease progression of each drug when used as monotherapy. (*Id.*, ¶ 131.) As discussed above, the principles of combination therapy provided that each agent in a combination preferably should be given at its effective dose. A POSA would have been motivated to use the amount of trastuzumab that had been shown in Baselga 1996 to effectively treat metastatic HER2-positive breast cancer (*i.e.*, a loading dose of 250 mg, followed by 100 mg per week, *see* Ex. 1120 (Baselga 1996) at 738-39), together with known effective amounts of paclitaxel (*i.e.*, 135 mg/m^2 or 175 mg/m^2, *see* Ex. 1112 (1995 TAXOL PDR), 685; Ex. 1102, ¶ 131).

To the extent any modification to the amounts of the combination was necessary, a POSA would have readily optimized the combination treatment to arrive at an amount that results in the claimed efficacy and safety parameters. (Ex.

1102, ¶¶ 132-34.) Such optimization was routine in the art. (*Id.*; Ex. 1116 (Abeloff), 205, 208-09).) *See, e.g.*, *Genzyme Therapeutic Prods. Ltd. P'ship v. Biomarin Pharm. Inc.*, 825 F.3d 1360, 1373 (Fed. Cir. 2016) (affirming Board's finding that, when all of the limitations of the claim to a combination of therapies used to treat Pompe's disease were disclosed in the prior art other than the dosing schedule, that schedule would have been arrived at via routine optimization, and therefore, the claims were obvious over the prior art).

Indeed, the obviousness of arriving at an effective amount was conceded in the '441 patent specification. The specification admits that the amount of the chemotherapeutic agents to use in combination with trastuzumab can be determined by conventional techniques: "Preparation and dosing schedules for such chemotherapeutic agents may be used according to manufacturers' instructions or as determined empirically by the skilled practitioner. Preparation and dosing schedules for such chemotherapy are also described in [the prior art]." (Ex. 1101, 25:1-19.) With respect to the amount of trastuzumab, the specification provides an extremely broad range of possible doses, acknowledges that the dose can be optimized based on many well-known factors, and admits that "progress of this therapy is easily monitored by conventional techniques and assays." (*Id.*, 25:43-54; *see also* Ex. 1102, ¶ 134.)

A POSA would have reasonably expected the claimed effect, and without increase in overall severe adverse events, based on the promising clinical results reported for these drugs in Baselga 1996 and Seidman 1996, the lack of severe toxicity associated with trastuzumab, the lack of increased toxicity from adding trastuzumab to paclitaxel in preclinical studies, and lack of known significant overlapping toxicities between trastuzumab and paclitaxel.[19] (Ex. 1102, ¶¶ 131-35.)

[19] To the extent the "amount" claim term is construed to refer to an amount of the combination that extends time to disease progression relative to no treatment, as Patent Owner contended during prosecution, the claim would still be satisfied by the cited references because each of these two agents had been proven to extend TTP relative to no treatment, and a POSA would not have expected the combination to change this. (Ex. 1102, ¶¶ 136, 155 n.28.) Further, as a matter of logic, since paclitaxel alone extends TTP relative to no treatment (*see, e.g.*, Ex. 1110 (Seidman 1995)), a treatment that extends TTP relative to treatment with paclitaxel must also extend TTP relative to no treatment. (Ex. 1102, ¶ 136.) A POSA would have also expected that the trastuzumab/paclitaxel combination would not have resulted in an overall increase in severe adverse events compared to no treatment, because a patient with untreated HER2-positive cancer will experience more overall severe adverse events due to the underlying

See Genzyme, 825 F.3d at 1373 (When the prior art "provided a sound basis for a belief that a [particular] dosage interval ... would be effective, ... there was little left to do but to confirm that the strategy suggested by the various prior art references would work").

With respect to the claim limitation "***in the absence of an anthracycline derivative***," a POSA would have been motivated to develop the combination of trastuzumab and paclitaxel without an anthracycline derivative because that double combination was obvious, as explained above. Further, a POSA would have been well-aware of the cardiotoxicity issues with anthracycline derivatives. (Ex. 1102, ¶ 137; Ex. 1116 (Abeloff), 813.) Anthracyclines were known to cause irreversible cardiotoxicity thereby limiting the total lifetime dose a patient can receive. (Ex. 1102, ¶ 137; Ex. 1116 (Abeloff), 813.) Accordingly, a POSA would have limited use of anthracycline derivatives in treatment whenever possible. (Ex. 1102, ¶ 137; Ex. 1116 (Abeloff), 813.) Further, because anthracycline derivatives were a first-choice therapy for metastatic breast cancer, many patient candidates for treatment with the trastuzumab and paclitaxel combination would have already been treated with anthracycline-based therapy. (Ex. 1102, ¶ 137; Ex. 1116 (Abeloff), 810.) This means that many patients with metastatic disease who were prescribed a paclitaxel-

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disease itself, compared to severe adverse events experienced due to treatment. (*Id.*)

containing regimen would have already endured extensive anthracycline-based therapy and would risk significant cardiotoxic effects with continued anthracycline-based therapy. (Ex. 1102, ¶ 137.) POSAs would have avoided administering further anthracycline derivatives to the many patients who had already been treated with this class of drug or to the many patients who are resistant to treatment with anthracyclines, rendering the limitation "in the absence of an anthracycline derivative" obvious. (Ex. 1102, ¶ 137; *see also* Ex. 1120 (Baselga 1996), at 740 (reporting that a patient died during treatment with trastuzumab due to congestive heart failure associated with prior anthracycline use); Ex. 1124 (Arbuck), at 128-29 (reporting that many anthracycline-resistant patients responded to paclitaxel).)

Based on the above, a POSA would have been motivated to treat patients who had metastatic HER2-positive breast cancer with the combination of trastuzumab and paclitaxel. (*Id.*, ¶ 119.) Given the known clinical efficacy of each agent alone against this type of cancer (Baselga 1996; Seidman 1996), the good tolerability and absence of significant toxicity observed in the trastuzumab clinical trial (Baselga 1996 at 739, 741), and the lack of increased toxicity when trastuzumab was added to paclitaxel in preclinical studies (*id.* at 743), a POSA would have reasonably expected the combined regimen to be more effective against HER2-positive breast cancer than paclitaxel alone, without increasing

severe adverse events. (Ex. 1102, ¶¶ 117-135.) Indeed, a clinical trial with the combination was already underway (Ex. 1120 (Baselga 1996), 743), which confirmed that POSAs reasonably expected the combination to be safe and effective. (Ex. 1102, ¶ 123.) Further, the preclinical data cited in Baselga 1996 showed a synergistic anti-tumor interaction between trastuzumab and paclitaxel, and showed that the effect of the combination of trastuzumab and paclitaxel was greater than the effect of trastuzumab and any other tested chemotherapeutic drug, including trastuzumab/doxorubicin. (Baselga 1996 (Ex. 1120), 743, citing Ex. 1119 (Baselga Abstract 53).) This preclinical data would have reinforced the reasonable expectation of success. (Ex. 1102, ¶ 124.)

1. The Sliwkowski Declaration Does Not Negate the Motivation to Combine or Reasonable Expectation of Success

During prosecution, Patent Owner submitted the Sliwkowski Declaration (Ex. 1109), which argued that the prior art did not provide a motivation to combine trastuzumab and paclitaxel, or reasonable expectation of success with that combination. There are numerous flaws in Dr. Sliwkowski's analysis. (Ex. 1102, ¶¶ 138-53.)

The Sliwkowski Declaration first argued that "a skilled scientist would have anticipated that paclitaxel would provide little or no additional benefit to treatment with trastuzumab alone" because, according to Dr. Sliwkowski, trastuzumab

arrests the cell cycle at the G1 phase, which precedes the G2/M phase at which paclitaxel purportedly arrests the cell cycle. (*Id.*, ¶ 138.) Dr. Sliwkowski therefore asserted that combining trastuzumab with paclitaxel "would provide little or no additional benefit," because trastuzumab would "arrest [the] cell cycle before it reaches the G2/M phase, where taxoids exert their apoptotic antitumor activity." (Ex. 1109 (Sliwkowski Dec.), ¶ 8.)

Dr. Sliwkowski's hypothesis was premised on the flawed assertion that paclitaxel, which causes cell death by attacking microtubules, only works when a cell is in the G2/M phase, in which microtubules are active. (Ex. 1102, ¶ 140.) However, as of December 1996, a POSA would have known that paclitaxel exhibited its anticancer effects during all phases of the cell cycle, and not only while the microtubules were active in the G2/M phase. (*Id.*; Ex. 1107 (Abrams), 1165; Ex. 1106 (DeVita), 415.) Indeed, one of the articles that Dr. Sliwkowski relied on acknowledges that paclitaxel causes cell death at two different phases of the cell cycle: (1) during the G2/M phase, as mentioned by Dr. Sliwkowski, and (2) during the G1 phase, which Dr. Sliwkowski failed to mention. (Ex. 1102, ¶ 141; Ex. 1109 (Sliwkowski Dec.), 21 (Exhibit B, Woods article); *see also* Ex. 1106 (DeVita), 60-66.)

This omission by Dr. Sliwkowski is important because, according to Dr. Sliwkowski, the G1 phase is the same phase in the cell cycle at which trastuzumab

exerts its anti-tumor effects. (Ex. 1102, ¶ 141; Ex. 1109 (Sliwkowski Dec.), ¶ 8 (Exhibit B).) This means that, even if Dr. Sliwkowski were correct (which he is not) that administering a drug that arrests the cell cycle in an early phase will prevent a drug that arrests the cell cycle at a later phase from exerting its antitumor effects, a POSA would have known that this would not be an issue for the combination of trastuzumab and paclitaxel, which also work at the same cell cycle phase, albeit by different mechanisms of action and on different targets. (Ex. 1102, ¶ 141.)

Other flawed assumptions in Dr. Sliwkowski's hypothesis are that all cells in a tumor have the same cancerous mutations, behave in the same way, and exist at precisely the same phase in the cell cycle as one another. (*Id.*, ¶ 142.) In reality, none of these assumptions are true. Rather, a tumor typically consists of cancer cells that have a variety of mutations that are growing at different stages from one another. (*Id.*) Therefore, even if Dr. Sliwkowski were correct that trastuzumab and paclitaxel induce cell cycle arrest only at different phases of the cell cycle (which he is not), the cells within a given tumor exist at different phases of the cell cycle and would thus be simultaneously susceptible to attack from both trastuzumab and paclitaxel, depending on where each cell is in its cycle. (*Id.*)

Dr. Sliwkowski also wrongly assumed that 100% of the cancerous cells are arrested by trastuzumab at the G1 phase. In reality, trastuzumab targets HER2-

positive cells, while paclitaxel could affect cells with the many types of mutations which may be present in a HER2-positive tumor. (Ex. 1102, ¶ 143; *see* Ex. 1120 (Baselga 1996), 738 ("Tumors were considered to overexpress HER2 if at least 25% of tumor cells exhibited characteristic membrane staining for $p185^{HER2}$.").)

Dr. Sliwkowski further asserted that "an antagonistic interaction between trastuzumab and paclitaxel would have been viewed as a reasonable possibility." (Ex. 1109 (Sliwkowski Dec.), ¶ 8.) He based this hypothesis on the observation that tamoxifen, a hormone that causes antitumor effects at the G0-G1 phase of the cell cycle, exhibited an antagonistic interaction when combined with anthracyclines, which act later in the cell cycle. (*Id.*, ¶ 8.) But, according to the very articles cited by Dr. Sliwkowski to support his theory of antagonism, the antagonism seen with tamoxifen and doxorubicin cannot be extrapolated to combinations of tamoxifen with other chemotherapeutic drugs, let alone to combinations that do not include tamoxifen. (Ex. 1102, ¶¶ 144-46; *see also* Ex. 1109, Exhibit F to Sliwkowski Declaration (Osborne) at 715) ("The antagonism is drug specific and even alkylating agent specific.").) These same articles also state that the antagonism between tamoxifen and doxorubicin is not always seen (Ex. 1109, Exhibit F (Osborne) at 715 and Exhibit G (Woods) at 1449), and that any antagonism that is observed may be due to many factors. (Ex. 1102, ¶ 146; Ex. 1109, Exhibit G (Woods) at 1450-51.)

Moreover, even if, *arguendo*, POSAs were concerned with potential antagonism when combining drugs that induce cell death at different phases of the cell cycle, a POSA would not have had such a concern with the trastuzumab/paclitaxel combination. (*See* Ex. 1102, ¶¶ 146-148.) A POSA would have known from prior art that Dr. Sliwkowski did not discuss in his declaration that his hypothesis was incorrect for combinations of trastuzumab and chemotherapies that cause G2/M cell cycle arrest. (*Id.*, 1147.) Like paclitaxel, cisplatin was known to arrest the cell cycle at the G2/M phase. (*Id.*, 1147; Ex. 1127 (Sorenson).[20]) According to Dr. Sliwkowski's hypothesis, trastuzumab should have antagonized cisplatin or prevented it from working. But that is not what the prior art shows. Rather, a POSA would have known from Pegram 1995 that the trastuzumab/cisplatin combination exhibited synergistic effects against HER2-positive cancer cells *in vitro* and was clinically effective in humans with metastatic HER2-positive breast cancer, with response rates above that expected from cisplatin alone. (Ex. 1102, ¶ 147; Ex. 1122 (Pegram 1995).)

The prior art data on the trastuzumab/paclitaxel combination also refutes the application of Dr. Sliwkowski's hypothesis to this combination. The prior art

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[20] C.M. Sorenson *et al., Analysis of Events Associated With Cell Cycle Arrest at G2 Phase and Cell Death Induced by Cisplatin*, 82(9) J. NAT'L CANCER INST. 749-755 (May 1990).

taught that combining trastuzumab with paclitaxel led to "[s]triking antitumor effects" and "strong synergy" in preclinical studies in HER2-positive breast cancer xenografts (*i.e.*, in human cancer cells in live animals). (Ex. 1110 (Seidman 1995), 112; Ex. 1121 (Baselga Abstract 2262).) Whereas paclitaxel alone resulted in 35% inhibition of tumor growth, the trastuzumab/paclitaxel combination produced 93% inhibition. (Ex. 1121 (Baselga Abstract 2262).) These prior art teachings would have extinguished any concerns that a POSA might have had about potential antagonism of the combination because, clearly, trastuzumab was not preventing paclitaxel from exerting its antitumor effects against human HER2- positive carcinomas *in vivo*. (Ex. 1102, ¶¶ 143, 148.) Dr. Sliwkowski's hypothesis is thus belied by the prior art. (*Id.*)

The prior art's indication that clinical trials of the trastuzumab/paclitaxel combination were underway (Ex. 1119 (Baselga Abstract 53); Baselga 1996 (Ex. 1120); Seidman 1995 (Ex. 1111)) further demonstrates that POSAs had confidence that the benefits of the combination seen in the preclinical studies would also be seen in patients. (Ex. 1102, ¶ 148.) Indeed, Dr. Sliwkowski's suggestion that a POSA would not have attempted the combination of trastuzumab and paclitaxel should not be credited because it is directly contrary to the teaching in the prior art that POSAs were actively pursuing the claimed combination. *See, e.g.*, *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1361 (Fed. Cir.

2007) (giving no weight to expert testimony that "cannot be reconciled with ...the prior art references themselves").

Dr. Sliwkowski's second main assertion was that a POSA purportedly would not have had a reasonable expectation of success in using the claimed combination to treat HER2-positive breast cancer because "many agents which show high activity in xenograft models prove to be inactive, or show disappointingly low or different activity, in the clinical setting." (Ex. 1109 (Sliwkowski Dec.), ¶ 9.) As support for this assertion, Dr. Sliwkowski relied on a single reference, Johnson, which he asserts shows that xenograft are "useful for predicting clinical response against *any* disease, ... but *not with clinical cancer!*" (*Id.*) But, fatal to Dr. Sliwkowski's argument, Johnson published in 2001 and thus is not prior art and is thus not relevant to the obviousness analysis. (*Id.*) *See, e.g., Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1377 (Fed. Cir. 2011). Dr. Sliwkowski offered no evidence that a POSA, as of December 1996, would have had this belief about xenografts. (Ex. 1102, ¶¶ 149-53.) To the contrary, the prior art established that POSAs commonly relied on xenograft data as a basis or support for clinically evaluating a drug or combination. (*Id.*; Ex. 1126 (Fiebig), 343; Ex. 1106 (DeVita), 276; Ex. 1128 (Mattern), 279-80.)

Further, Dr. Sliwkowski's opinion that xenografts are not predictive of clinical results is contrary to his own publications. In an article he co-authored in

1999—which is not prior art, but is earlier than the non-prior art upon which Dr. Sliwkowski relied—he stated that xenografts are helpful in cancer research, and particularly in determining whether two agents act synergistically. (Ex. 1117 (Pegram 1999).[21]) Dr. Sliwkowski concluded that positive results in HER2-positive breast xenografts treated with trastuzumab/chemotherapy combinations "demonstrate that these are rational combinations to test in human clinical trials" and "suggest[] that such combinations could be successfully exploited in future human clinical trials." (Ex. 1117 (Pegram 1999), 2241, 2249; Ex. 1102, ¶ 152.)

In any event, Dr. Sliwkowski's arguments about xenografts do not refute the motivation to combine and reasonable expectation, both of which come from the observed clinical efficacy of paclitaxel and trastuzumab individually in the target population, and from the four principles of combination therapy. Xenograft data only serves to bolster the motivation to combine and reasonable expectation of success.

Although Dr. Sliwkowski referenced a "reasonable expectation of success" in his declaration, in actuality he improperly applied an absolute predictability standard. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1365 (Fed. Cir. 2007)

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[21] M. Pegram *et al, Inhibitory Effects of Combinations of HER-2/neu Antibody and Chemotherapeutic Agents Used for Treatment of Human Breast Cancers*, 18 ONCOGENE 2241-2251 (1999).

("[A]bsolute predictability of success is not required" in the obviousness analysis.). The "case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Id.* at 1364. Indeed, the uncertainties inherent in biomedical research do not negate a reasonable expectation of success. For example, in *Cubist Pharmaceuticals, Inc. v. Hospira, Inc.*, the Federal Circuit considered the obviousness of claims to methods of treatment using the drug daptomycin, wherein the drug was given every day or every two days, "a dosage interval that minimizes skeletal muscle toxicity." 805 F.3d 1112, 1122 (Fed. Cir. 2015). The Federal Circuit affirmed the district court's conclusion that the claims were obvious over prior art (Woodworth) that suggested once daily dosing of daptomycin. *Id.* at 1125. The court acknowledged that Woodworth was based on suggestive "laboratory studies, not clinical trials," but held that Woodworth's "predictions of the efficacy of a dosage regimen [in the claimed range] at daily intervals give rise to a reasonable expectation that dosages in that amount would be effective in patients." *Id.* at 1124.

In this case, the inherent degree of uncertainty involved in designing and testing new cancer therapies would not have deprived a POSA of having a reasonable expectation of success. (*See* Ex. 1102, ¶¶ 117-137.) In the development of cancer treatments, meeting all four principles of combination therapy, plus

confirmatory evidence of synergy from xenografts, was more than sufficient to establish and confirm a reasonable expectation of success. (*Id.*)

For these reasons, Dr. Sliwkowski's Declaration should have carried little, if any, weight. The '441 patent should never have issued over the Examiners' obviousness rejections. In any event, Seidman 1996 (Ex. 1111), which teaches that paclitaxel is clinically effective against metastatic HER2-positive breast cancer, was not of record during prosecution, nor were Dr. Lipton's views on the prior art and Dr. Sliwkowski's assertions. Thus, the combination of references in this Petition—Baselga 1996, Seidman 1996, and the 1995 TAXOL PDR—was never addressed nor rebutted during prosecution.

2. Claim-by-Claim Analysis

As explained above, based on the cited references, a POSA would have been motivated to treat metastatic HER2-positive breast cancer patients with trastuzumab and paclitaxel, in the absence of an anthracycline derivative, and would have had a reasonable expectation of success that the combination would effectively treat the cancer without an increase overall severe adverse events. Claims 1-14 are therefore unpatentable as obvious, as explained in more detail below.

a. Independent Claims 1, 11, 13, and 14 are Obvious

Independent claim 1 is directed to a method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by overexpression of ErbB2 receptor. This method covers the treatment of metastatic HER2-positive breast cancer in a human patient. (*See* Ex. 1102, ¶¶ 154-55.) The claimed method requires administering to the patient 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, in an amount effective to extend the time to disease progression in said human patient, without increase in overall severe adverse events. Trastuzumab is such an antibody and paclitaxel is a taxoid. (*Id.*)

As set forth above, a POSA would have been motivated by Baselga 1996 and Seidman 1996 to administer a combination of trastuzumab (an anti-HER2 antibody) and paclitaxel (a taxoid) for the treatment of a human patient with metastatic HER2-positive breast cancer in amounts that would reasonably be expected to extend the time to disease progression, without increasing overall severe adverse events. (*See supra*, Section VII.C; Ex. 1102, ¶ 154.) There was a particularly strong motivation to combine trastuzumab and paclitaxel because the combination satisfied the four principles of combination therapy, due to (1) each agent's individual effectiveness in the target population, (2) their lack of known

significant overlapping toxicities, (3) their different mechanisms of action, and (4) their lack of cross-resistance. (*See supra*, Section VII.C; Ex. 1102, ¶¶ 126-130.) That the combination was already undergoing clinical trials and was synergistic without increased toxicity in preclinical studies would have further reinforced the POSA's motivation and reasonable expectation of success. (Ex. 1102, ¶123.) A POSA would have used the known amounts of trastuzumab and paclitaxel disclosed in Baselga 1996 and the 1995 TAXOL PDR for treatment of metastatic breast cancer, and, if needed, would have used routine and conventional methods to optimize the known amounts to achieve a safe and effective treatment. (*See supra*, at p. 46; Ex. 1102, ¶ 155.) The cited prior art therefore renders independent claim 1 unpatentable as obvious. (Ex. 1102, ¶¶ 117-137, 154-155.)

Independent claims 11, 13, and 14 are identical to claim 1 except that: (1) as to the type of cancer, they recite a method for the treatment of a human patient "with a ErbB2 overexpressing metastatic breast cancer" (claim 11), "with a progressing malignant tumor or cancer characterized by overexpression of ErbB2 receptor" (claim 13), or "with ErbB2 expressing progressing metastatic breast cancer" (claim 14); and (2) as the antibody, they recite "a humanized 4D5 anti-ErbB2 antibody" (claim 11), "a humanized 4D5 anti-ErbB2 antibody which comprises a human Fc region and that bind to the epitope 4D5 within the ErbB2 extracellular domain sequence" (claim 13), or "an antibody which binds to epitope

4D5 within the extracellular domain sequence" (claim 14). As with claim 1, the methods of claims 11, 13, and 14 cover the treatment of a human patient with metastatic HER2-positive breast cancer, and the antibody recited in these claims covers trastuzumab. (*See* Ex. 1102, ¶¶ 156-160.) All other elements in claims 11, 13 and 14 are the same as in claim 1. Accordingly, for the same reasons as for claim 1, Baselga 1996, Seidman 1996, and the 1995 TAXOL PDR render independent claims 11, 13, and 14 unpatentable as obvious. (*Id.*)

b. Dependent Claims 2-10 and 12 are Obvious

Claim 2 depends from claim 1 and further requires that the patient have a malignant tumor. **Claim 3** depends from claim 1 and further requires that the patient have cancer. **Claim 4** depends from claim 3 and limits the type of cancer to a list that includes breast cancer. **Claim 5** depends from claim 4 and limits the type of cancer to breast cancer. **Claim 6** depends from claim 5 and limits the 21 cancer to metastatic breast carcinoma.[22]

The patients successfully treated with trastuzumab in Baselga 1996 (Ex. 1120) and with paclitaxel in Seidman 1996 (Ex. 1111) had metastatic HER2-positive breast carcinoma, and thus met the limitations of each of these claims. In addition, the 1995 TAXOL PDR provides a recommended dosing regimen of

[22] "Carcinoma" is a cancer derived from epithelial cells; most breast cancers are carcinomas. (Ex. 1102, ¶ 31.)

paclitaxel for patients with metastatic carcinoma of the breast. (Ex. 1112 (1995 TAXOL PDR), 685; Ex. 1102, ¶ 39.) Accordingly, claims 2-6 would have been obvious over Baselga 1996, Seidman 1996, and the 1995 TAXOL PDR for the same reasons that the independent claims would have been obvious. (Ex. 1102, ¶ 161.)

Claim 7 depends from claim 1 and further requires that the antibody be a humanized 4D5 anti-ErbB2 antibody. Trastuzumab is such an antibody. (*Id.*, ¶¶ 157, 162.) As discussed above, a POSA would have been motivated to combine trastuzumab with paclitaxel. Accordingly, for the same reasons discussed above for claim 1, Baselga 1996, Seidman 1996, and the 1995 TAXOL PDR render claim 7 unpatentable as obvious. (*Id.*, ¶ 162.)

Claims 8 and **12** depend from claims 1 and 11, respectively, and further require that the taxoid be paclitaxel. As discussed above, a POSA would have been motivated to combine trastuzumab with paclitaxel. Accordingly, for the same reasons discussed above for claim 1, Baselga 1996, Seidman 1996, and the 1995 TAXOL PDR render claims 8 and 12 unpatentable as obvious. (*Id.*, ¶ 162.)

Claim 9 depends from claim 8 and further requires that "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." Conceivably, this limitation could be satisfied by any combination of

effective amounts of trastuzumab and paclitaxel since there will often be a higher possible combination of effective amounts, within safe administration limitations, of these same drugs than that being administered. (*Id.*, ¶¶ 164-67.) The limitation could also be read to require that the amounts of the antibody and paclitaxel administered as a combination is lower than the lowest effective amounts of those two drugs when administered individually. In either case, this claim is obvious. (*Id.*)

An amount that is effective generally and is recommended for administration to patients, may not be the appropriate amount for administration to a particular individual patient. (*Id.*, ¶ 164.) A POSA would have been motivated to titrate to an appropriate amount of the combination for each individual patient. (*Id.*) For some patients, this titration would necessarily result in an amount of the combination that is lower than the sum of ***any*** effective amounts of the anti-ErbB2 antibody and paclitaxel when administered individually. (*Id.*) Therefore, to the extent claim 9 requires that the combination of the anti-ErbB2 antibody and paclitaxel is lower than the sum of ***any*** effective amounts of the anti-ErbB2 antibody and chemotherapeutic agent when administered individually, it is obvious over Baselga 1996, Seidman 1996, and the 1995 TAXOL PDR for the same reasons discussed above with respect to claim 1. (*Id.*)

To the extent claim 9 requires that the combination of anti-ErbB2 antibody and paclitaxel be lower than the sum of the lowest effective amounts of the anti-ErbB2 antibody and paclitaxel when administered individually, it is also obvious. (*Id.*, ¶ 165.) A POSA would have been aware of prior art preclinical studies identifying a synergistic effect between trastuzumab and paclitaxel. (*Id.*, ¶ 166; Ex. 1119 (Baselga Abstract 53).) A POSA would also have known that the antitumor activity for the combination of trastuzumab with paclitaxel (93%) was higher than the sum of the observed antitumor activity for trastuzumab alone (35%) and paclitaxel alone (35%). (Ex. 1102, ¶ 166; Ex. 1119 (Baselga Abstract 53).)

In view of these data, a POSA would have reasonably expected the effect of trastuzumab plus paclitaxel to be greater than the effect of the sum of the two drugs individually. (Ex. 1102, ¶ 167.) Therefore, a POSA would have been motivated to use a lesser amount of each drug while retaining efficacy. (*Id.*) In an effort to minimize toxicity, a POSA could have carried out routine experimentation to arrive at doses of trastuzumab and/or paclitaxel that would still be effective, but where the doses in combination would be less than the sum of the doses if administered as single agents. (*Id.*) Thus, to the extent claim 9 requires that the combination of anti-ErbB2 antibody and paclitaxel is lower than the sum of the

lowest effective amounts of the anti-ErbB2 antibody and chemotherapeutic agent when administered individually, it is also obvious. (*Id.*)

Claim 10 depends from claim 1 and further requires that "efficacy is further measured by determining the response rate." As explained above, a POSA would have been well-aware of response rate as one of several clinical endpoints for efficacy and would have routinely determined response rate as part of a clinical trial. (*See supra*, at Section VII.A.5; Ex. 1101, ¶ 92.) The '441 patent admits this. (Ex. 1101, 10:46-49 ("Efficacy can be measured in conventional ways, depending on the condition to be treated. For cancer therapy, efficacy can, for example, be measured by assessing the time to disease progression (TTP), or determining the response rates (RR).").) Accordingly, claim 10 would have been obvious over Baselga 1996, Seidman 1996, and the 1995 TAXOL PDR for the same reasons discussed above with respect to claim 1. (Ex. 1102, ¶168.)

D. Secondary Considerations Do Not Overcome the Strong *Prima Facie* Case of Obviousness

In an obviousness analysis, secondary considerations of non-obviousness, such as commercial success, long-felt but unsolved needs, failure of others, and unexpected results, if present, must be considered. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-39 (Fed. Cir. 1983). However, for secondary considerations to be probative of non-obviousness, "its proponent must establish a

nexus between the evidence and the merits of the claimed invention." *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010) (quotation omitted).

During prosecution, Patent Owner argued that (1) the claimed combination resulted in unexpected synergy in the clinic; and (2) it was unexpected that the combination of trastuzumab and doxorubicin—an unclaimed combination—exacerbated the toxic effects of doxorubicin. (Ex. 1104 at 305.) Neither of these arguments succeeded in persuading the Examiners that the claims were non-obvious, and neither should succeed in this proceeding.

With respect to alleged unexpected synergy, to the extent Patent Owner showed data indicating synergy (which it did not), any synergy would not be unexpected. As discussed above, the prior art showed that the combination of trastuzumab and a taxoid was synergistic in human cancer cells in xenograft models. (Ex. 1119 (Baselga Abstract 53).) Indeed, the Examiner rejected Patent Owner's evidence of clinical synergy during prosecution because "the synergistic effect of the combination of an anti-ErbB2 antibody and a taxoid was well established in the art and thus could not be considered unexpected." (Ex. 1104 at 408 (Office Action dated Jun. 17, 2001, at 10).) Further, as explained above, it was expected that a combination of two anti-cancer agents would result in a greater effect than either agent alone, due to the different mutations and resistance mechanisms that exist in a cancer/treatment system. (Ex. 1102, ¶ 90.)

Second, Dr. Hellmann asserted that the combination of trastuzumab and paclitaxel "achieves a therapeutic effect in terms of TTP which is greater than that expected by the simple addition of the effects of the component drugs." (Ex. 1108 (Hellmann Dec.) at ¶ 6.) She asserted that Exhibit B attached to her declaration provides the results of the H0648 trial in which patients were treated with HERCEPTIN® and paclitaxel. (*Id.*) She further asserted that Exhibit C attached to her declaration provides the results of the H0650 study, in which patients were treated with HERCEPTIN® as a single agent at the same dose as in the H0648 trial. (*Id.*) According to Dr. Hellmann, these data show that paclitaxel alone extended TTP by 2.8 months and HERCEPTIN® alone extended TTP by 3.5 months (for a combined TTP of 2.8 + 3.5, or 6.3 months), whereas the combination of HERCEPTIN® and paclitaxel extended TTP by 6.9 months. (*Id.*) Dr. Hellmann concludes that "the combination is surprisingly synergistic with respect to extending TTP." (*Id.*)

The data presented in the Hellmann Declaration are insufficient to draw a conclusion of synergy. For example, the trastuzumab only and trastuzumab/paclitaxel combination studies were different. (*See* Ex. 1108 (Hellmann Dec. at 13-14 (Exhibits A-B).) Dr. Hellmann did not provide any information to conclude that a comparison of values across these separate studies,

which presumably used different protocols and included different patient populations, would be proper. (Ex. 1102, ¶ 175.)

Further, Dr. Hellmann cited only the median TTP, but ignored the 95% confidence interval data reported for TTP. (*Id.*, 1176) When factoring in the 95% confidence intervals—as is proper—the TTP values for monotherapy groups overlap with the values for the trastuzumab-plus-paclitaxel group. Specifically, in the H0650 study, the patients who received only Herceptin® had a median TTP of 3.5 months, with a 95% confidence interval of 2.8-5.5 months. (Ex. 1108 (Hellmann Dec.) at 13 (Exhibit B); Ex. 1102, ¶ 176.) In the H0648 study, the patients who received only paclitaxel had a median TTP of 2.8 months, with a 95% confidence interval of 1.6-5.4 months. (Ex. 1108 (Hellmann Dec.) at 14 (Exhibit C); Ex. 1102, ¶ 177.) In that same study, the patients who received Herceptin® plus paclitaxel had a median TTP of 6.9 months, with a 95% confidence interval of 5.3-9.9 months. (Ex. 1108 (Hellmann Dec.) at 14 (Exhibit C); (Ex. 1102, ¶ 176.)

Even assuming that TTP is properly additive (*i.e.*, assuming that it is meaningful to add the Herceptin®-only and paclitaxel-only TTPs together), and properly compared across studies, given the overlap in the confidence intervals, no conclusion can be drawn about relative TTPs. (*Id.*, ¶ 177.) The data show that the TTP for the Herceptin®-only group was somewhere in the range of 2.8-5.5 months; the TTP for the paclitaxel-only group was 1.6-5.4 months, and the TTP for

the Herceptin/paclitaxel group was 5.3-9.9 months. (*Id.*) Given these data, the TTP for each group could be the same, *e.g.*, 5.3, or 5.4, or even 5.5 months. (*Id.*) This means that based on the data presented by Dr. Hellmann, one is unable to discern whether there is actually any meaningful difference between TTP for trastuzumab alone versus the trastuzumab/paclitaxel combination. (*Id.*)

With respect to the alleged unexpected result that the combination of trastuzumab and doxorubicin exacerbated the toxic effects of doxorubicin administered alone, these toxic effects are not related to the claimed combinations of trastuzumab and paclitaxel and are therefore irrelevant. For unexpected results to support the non-obviousness of claims, the results must bear a nexus to the claimed invention. *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). The obviousness of the claimed trastuzumab/paclitaxel combination is not implicated by a finding that some other, unclaimed combination turned out to be a less preferable choice. (*See also* Ex. 1102, ¶ 179.)

Further, the prior art had already provided a motivation to pursue trastuzumab/paclitaxel over trastuzumab/doxorubicin: in preclinical studies, trastuzumab/paclitaxel was more effective than trastuzumab/doxorubicin. (*See, e.g.*, Ex. 1121 (Abstract 2262) ("The combined treatment with paclitaxel plus 4D5 resulted in a major antitumor activity with 93% inhibition of growth. This result was markedly better than doxorubicin plus 4D5 (70% inhibition).") (emphasis

added).) Patent Owner's purported finding that the trastuzumab/doxorubicin combination is associated with increased cardiac side effects versus doxorubicin alone, therefore, is insufficient as a matter of law to support the patentability of the claims. Moreover, Patent Owner did not establish that the trastuzumab/doxorubicin combination is the closest prior art. *See, e.g.*, *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 152 F.3d 967, 978 (Fed. Cir. 2014) (explaining that when unexpected results are used as evidence of a patent's nonobviousness, results must be shown to be unexpected compared with the closest prior art).

To the extent Patent Owner alleges that other secondary considerations support the non-obviousness of the claims, Petitioner submits that any nexus to the secondary considerations is not to the claimed invention, but rather to the known trastuzumab/paclitaxel combination and its known use as a therapy to treat metastatic HER2-positive breast cancer. *See, e.g.*, *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1385 (Fed. Cir. 2016) (finding Patent Owner's claim of unexpected results "unavailing" because the claimed combination was taught in the prior art and "the offered secondary consideration actually results from something other than what is both claimed and *novel* in the claim, so there is no nexus to the merits of the claimed invention." (emphasis in original)).

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

VIII. CONCLUSION

For the reasons set forth above, Petitioner respectfully submits that it has established a reasonable likelihood of success with respect to the challenged claims and requests that this petition be granted and claims 1–14 be cancelled.

Date: September 6, 2017

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the attached Petition contains 13,875 words (as calculated by the word processing system used to prepare this Petition), excluding the parts of the Petition exempted by 37 C.F.R. §42.24(a)(1).

Dated: September 6, 2017

/Amanda Hollis/
Amanda Hollis

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Petition, along with all exhibits and other supporting documents, was served on September 6, 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 September 6, 2017, via FedEx Overnight delivery directed to the attorney of record for the patent at the following address:

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