UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Celltrion, Inc.
Petitioner,
v.

Genentech, Inc.
Patent Owner

Title: TREATMENT WITH ANTI-ErbB2 ANTIBODIES

Inter Partes Review No. IPR2017-01122

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 7,892,549

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I. INTRODUCTION

Celltrion, Inc. petitions for *inter partes* review ("IPR") of claims 1-11 and 14-17 of U.S. Patent 7,892,549 ("'549 patent," Ex. 1001).

Claims 1-11 and 14-17 of the '549 patent recite methods of treating HER2-positive cancer patients by administering a combination of three drugs, an anti-ErbB2 antibody (*e.g.*, trastuzumab), a taxoid (*e.g.*, paclitaxel), and a third anti-cancer drug, such as a DNA alkylating agent. Trastuzumab and paclitaxel, when used alone, were each already known in the prior art to be clinically effective against HER2-positive cancer. Indeed, the prior art disclosed that the combination of trastuzumab and paclitaxel was already undergoing clinical trials for HER2-positive cancer. It was also known that the combination of trastuzumab and cisplatin, a DNA alkylating agent, was clinically effective against HER2-positive cancer. Cisplatin and paclitaxel were also already being used in combination to treat metastatic breast 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, cisplatin, and paclitaxel to treat HER2-positive patients, and would have reasonably expected the combination to work.

The '549 patent should have never issued, as evidenced by the repeated obviousness rejections Patent Owner faced during prosecution. The rejections

were based on prior art that showed trastuzumab's efficacy in HER2-positive breast cancer patients, preclinical xenograft data that showed synergistic activity between trastuzumab and paclitaxel against HER2-positive tumors without increased toxicity, and the efficacy of a combination of carboplatin (a DNA alkylating agent) and paclitaxel in treating metastatic breast cancer.[1] Patent Owner responded by arguing no *prima facie* obviousness and submitting a declaration from the named inventor alleging purported unexpected synergy from 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 individually taught in the prior art." (*See*, *e.g.*, Ex. 1004 at 1507-09.) The Examiner also explained that based on the preclinical data, any synergy would not have been unexpected.

[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*.)

The Examiner allowed the claims only after Patent Owner submitted a new declaration following the fourth 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 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, cisplatin, 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 Examiner during prosecution. These references disclose that paclitaxel and the combination of trastuzumab and cisplatin are both effective in treating patients with metastatic HER2-positive breast cancer, and explain the principles behind choosing drugs for combination therapies for breast cancer. The prior art clearly provided a motivation to combine trastuzumab, cisplatin, and paclitaxel to treat metastatic HER2-positive breast cancer patients, with a reasonable expectation that

the combination would be safe and effective. Claims 1-11 and 14-17 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 parties-in-interest are Celltrion, Inc., Celltrion Healthcare Co., Ltd., and Teva Pharmaceuticals International GmbH.

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

In IPR2017-00737 and IPR2017-00739, Hospira Inc., a third party, has asserted that claims of the ’549 patent are obvious based on grounds that are different than those in this Petition.

Petitioner is concurrently filing a petition for IPR of Genentech’s U.S. Patent No. 7,846,441, the parent of the ’549 patent. Hospira filed IPR2017-00731 directed to this patent.

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

Lead counsel is Cynthia Lambert Hardman, Reg. No. 53,179. Backup counsel are Elaine Herrmann Blais and Robert V. Cerwinski (both to seek *pro hac vice* admission). Counsel are with Goodwin Procter LLP. Ms. Hardman and Mr. Cerwinski are at 620 Eighth Avenue, New York, NY 10018, tel. 212-813-8800, fax 212-355-3333. Ms. Blais is at 100 Northern Avenue, Boston, MA 02210, tel. 617-570-1000, fax 617-523-1231. Email contact for counsel is

chardman@goodwinlaw.com, rcerwinski@goodwinlaw.com, and eblais@goodwinlaw.com.

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

Please direct all correspondence to counsel at the contact information above. Petitioner consents to service by electronic mail at the email addresses above.

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 506989.

V. '549 PATENT AND ITS PROSECUTION HISTORY

The '549 patent issued on February 22, 2011 from Application Ser. No. 10/356,824, filed on February 3, 2003 as a continuation of Application Ser. No. 09/208,649. That parent application was filed on December 10, 1998 and 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 '549 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 ’549 Patent Claims

The ’549 patent has 17 claims. Independent claim 1 reads:

> 1. A method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor, comprising administering a combination of an antibody that binds ErbB2, a taxoid, and a further growth inhibitory agent to the human patient in an amount effective to extend the time to disease progression in the human patient, wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence.

Independent claim 5 is similar to claim 1, but specifies “effective amount” instead of “amount effective to extend the time to disease progression in the human patient” and specifies a “further therapeutic agent” instead of a “further growth inhibitory agent.” Independent claim 16 is similar to claim 1, but further specifies that the combination is to be administered “in the absence of an anthracycline derivative.”

Claims 2-4 depend from claim 1, claims 6-15 depend from claim 5, and claim 17 depends from claim 16. These dependent claims specify further details on the antibody (claims 2-4 and 7), the administration (claims 8), the taxoid (claim

9), the "further therapeutic agent" (claims 12-14), the cancer type (claim 17), and the efficacy measure (claim 10).

B. '549 Patent Specification

The '549 patent specification acknowledges that trastuzumab has been "active in patients with ErbB2-overexpressing metastatic breast cancers that had received extensive prior anti-cancer therapy," and has enhanced the activity of paclitaxel in HER2-positive mouse xenografts. (Ex. 1001, 3:36-42; 3:56-61.)

The specification asserts that the "present invention" is a method of treating HER2-positive patients with trastuzumab and a taxoid (preferably paclitaxel), in the absence of anthracycline. (*Id.*, 1:12-18, 3:65-4:13, 4:23-25.) 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.*, 3:65-4:13.)

The specification includes an example relating to the treatment of HER2-positive metastatic breast cancer patients. (*Id.*, 26:34-30:25.) Half of the patients received chemotherapy alone, which comprised either cyclophosphamide and an

anthracycline derivative ("AC"), or paclitaxel ("T"). (*Id*., 28:17-23.) The other half received one of these chemotherapy regimens, plus trastuzumab ("H"). (*Id*., 28:5-15.) 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*., 29:11-30:12.) 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.*, 30:13-16.) 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.*, 30:17-25.)

C. Prosecution History

The ’549 patent issued after a restriction requirement and five rounds of rejection. Each round of rejection was met with arguments and claim amendments, and resulted in three interviews, two declarations regarding the alleged non-obviousness of the claims, and a request for continued examination. (*See* Ex. 1004.[2])

With respect to the restriction requirement, the Examiner required election of a particular species of “further chemotherapeutic agent” for purposes of examination. (*Id*. at 3-4.) Patent Owner elected carboplatin as the “further chemotherapeutic agent.” (*Id*. at 1406 (03/16/2006 Response, at 5).) The Examiner then considered only carboplatin as the elected species for examination purposes. (*See, e.g., id*. at 1419, 1788, 1839.)

With respect to the obviousness rejections, the Examiner relied on prior art that taught, *inter alia*, (1) trastuzumab’s efficacy against HER2-positive breast cancer (*e.g.*, Baselga 1996 (Ex. 1020)); (2) the efficacy of the combination of paclitaxel and carboplatin against metastatic breast cancer (*e.g.*, Perez (Ex. 1029));

[2] Prosecution history of U.S. Patent Application No. 10/356,824 (now U.S. Patent No. 7,892,549).

and (3) synergy between trastuzumab and taxoids in mouse xenografts (*e.g.* Abstract 53 (Ex. 1019)).

Patent Owner responded to these obviousness rejections 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/anthracycline combination (an unclaimed combination) in view of the lack of such toxicity shown by the claimed trastuzumab/taxoid combination. (Ex. 1004 at 1824-25 (12/29/2008 Amendment at 6-7).) ("Hellmann Declaration," Ex. 1008.[3]) The Examiner, however, maintained the obviousness rejections for several more rounds. (Ex. 1004 at 1506-09, 1837, 1976.)

On October 15, 2009, after a fourth round of rejections, Patent Owner submitted a new declaration, from Mark X. Sliwkowski, Ph.D., a Staff Scientist at Genentech. ("Sliwkowski Declaration," Ex. 1009.[4]) 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

[3] The Hellmann Declaration is also found in Ex. 1004 starting at page 1550.

[4] The Sliwkowski Declaration is also found in Ex. 1004 starting at page 2351.

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 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.)

The Examiner then withdrew the obviousness rejections, citing "the declaration of Mark X. Sliwkowski, Ph.D., and the applicants' persuasive arguments," and ultimately allowed the application. (*See* Ex. 1004 at 1978-79, 2016-20.)

As will be discussed below, during the *ex parte* prosecution, the Examiner did not consider or was not presented with prior art that (a) showed that paclitaxel was clinically effective against metastatic HER2-positive breast cancer; (b) reflected the core principles for combining cancer therapies; and (c) showed that the combination of trastuzumab and cisplatin was clinically effective against

metastatic HER2-positive breast cancer. Nor was the Examiner 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/cisplatin/paclitaxel was 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. "Therapeutic Agent"

The term "therapeutic agent" means "an agent with efficacy in the treatment of cancer." (*See* Ex. 1001 at 11:4-19; *see also id*. at 10:41-50.) "Therapeutic agent" includes, for example, cisplatin, which is a DNA alkylating agent. (*Id*. at 11:4-19.) The specification expressly defines "chemotherapeutic agent" as "a chemical compound useful in the treatment of cancer." (*Id*. at 11:4-19.)

Furthermore, independent claim 5, on which claims 11 and 14 depend, claims a method for the treatment of human patient with breast cancer characterized by overexpression of ErbB2 receptor and requires administering "an effective amount of a combination of an anti-ErbB2 antibody..., a taxoid, and a further therapeutic agent." Accordingly, in the context of claims 5, 11 and 14, the "further therapeutic agent" must have efficacy in treating cancer, rather than just general efficacy in treating any condition. This conclusion is supported by the specification, which defines "therapeutically effective amount" as "an amount having antiproliferative effect." (*Id*., 10:41-50.)

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. 1001, 29:3-9; Ex. 1002, ¶ 111.)

C. "Extend the Time to Disease Progression in the Human Patient"

The term "extend the time to disease progression in the human patient" 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. 1002, ¶ 111.) The Example in the specification reports a clinical study in which patients in one arm received either TAXOL® alone or with HERCEPTIN®. (Ex. 1001, 28:5-8, 17-25.) The specification shows that TTP and adverse events were evaluated based on the combination of TAXOL® with HERCEPTIN® versus treatment with TAXOL® alone. (*Id*., 29:11-30:25; Ex. 1002, ¶ 111.)

During prosecution of the parent application, 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."

To the extent the Board construes "extend the time to disease progression in said human patient" consistent with Patent Owner's assertion during prosecution, Petitioner's unpatentability arguments herein still show unpatentability of the claims. (*See infra*, at note 16.).

D. "Response Rate"

"Response rate" means the percentage of patients whose disease responds to treatment. (*See, e.g.*, Ex. 1001, 28:48-29:2, 29:11-30:25; Ex. 1002, ¶ 111.)

E. Defined Terms

The '549 patent specification defines several claim terms. For purposes of this IPR only, Petitioner adopts the following constructions as the BRI of each term:

The '549 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. 1001, 5:59-61.) Thus, the terms "**overexpresses ErbB2 receptor**"; "**overexpression of ErbB2 receptor**"; and "**ErbB2 overexpressing**" are defined as "having significantly higher than normal ErbB2 levels compared to a noncancerous cell of the same tissue type." (Ex. 1002, ¶ 110.)

"**Humanized**" is defined as "contain[ing] minimal sequence derived from non-human immunoglobulin." (*Id*., 9:17-22; Ex. 1002, ¶ 110.)

"**Epitope 4D5**" is defined as "the region in the extracellular domain of ErbB2 to which the antibody 4D5 binds." (*Id.,* 5:26-28; Ex. 1002, ¶ 110.)

"**Growth inhibitory agent**" is defined as "a compound or composition which inhibits growth of a cell, especially an ErbB2-overexpressing cancer cell

either in vitro or in vivo." (*Id*. at 11:20-40.) "Growth inhibitory agent" includes, for example, cisplatin, which is a DNA alkylating agent. (*Id*.; Ex. 1002, ¶ 110.)

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 1-11 and 14-17 under 35 U.S.C. § 103 as obvious over **Baselga 1996** (Ex. 1020), **Seidman 1996** (Ex. 1011), **Pegram 1995** (Ex. 1022), and the **1995 TAXOL PDR** entry (Ex. 1012), in view of the knowledge of a POSA.

Petitioner's argument is based on the observed clinical efficacy of trastuzumab in HER2-positive breast cancer patients (Baselga 1996), the separately-observed clinical efficacy of the combination of trastuzumab/cisplatin in the same population of patients (Pegram 1995), 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 trastuzumab, cisplatin, and paclitaxel 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 (reported, for example, in Pegram 1995 and the 1995 TAXOL PDR) to maximize efficacy and tolerability.

This petition is supported by the Expert Declaration of Robert H. Earhart, Jr., M.D., Ph.D. (Ex. 1002.) Dr. Earhart has spent decades in the pharmaceutical industry researching and developing cancer drugs, consulting on cancer drug development, and teaching pharmacy and oncology. (Ex. 1002, ¶¶ 9-23; Ex. 1003.)

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 1-11 and 14-17.

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. 1002, ¶ 30.) Different cancer cells have different genetic mutations, sometimes even within a single tumor. This is called "intra-tumor heterogeneity."

(Ex. 1002, ¶ 83; Ex. 1005 (Alberts), 1288-90, 1263-64; Ex. 1020 (Baslega 1996)[5]), 206.) Benign tumors remain in their original location, whereas malignant tumors can form secondary tumors elsewhere in the body, a process called metastasis. (Ex. 1002, ¶ 30; Ex. 1005 (Alberts), 1256.)

1. Chemotherapy

As of December 1996, breast cancer was most often treated with surgery, radiation, and pharmaceuticals such as chemotherapy. (Ex. 1002, ¶ 32; Ex. 1016 (Abeloff), 201-06; Ex. 1006 (DeVita),[6] 1280-1324.) Chemotherapeutic drugs are designed to interrupt the activity of a tumor cell, by either killing the cell or stopping cellular processes. (Ex. 1002, ¶¶ 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. (*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. 1002, ¶ 37.) It was known that taxoids successfully treated some cancers that did

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

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

not respond to treatment with anthracyclines. (*Id*.; Ex. 1010 (Seidman 1995), 108.) It was also known that paclitaxel had anti-cancer activity in metastatic breast cancer patients, and that HER2-positive patients were particularly responsive to paclitaxel. (Ex. 1002, ¶ 37; Ex. 1011 (Seidman 1996).)

1995 TAXOL PDR: TAXOL (paclitaxel) for Injection Concentrate, *in* PHYSICIAN'S DESK REFERENCE, 682-685 (49th ed. 1995) (Ex. 1012, "**1995 TAXOL PDR**"), was published in 1995. (Ex. 1012 (1995 TAXOL PDR), 2.) It became publicly available as of its publication date. (Ex. 1002, ¶ 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. 1012 (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.

1002, ¶ 37; Ex. 1013 (Tolcher),[7] 37; Ex. 1014 (Gelmon 1996).) The PDR acknowledges that paclitaxel is sometimes used in combination with cisplatin, disclosing that in clinical trials, the combination of paclitaxel and cisplatin was less toxic when the paclitaxel was administered after the cisplatin than when the drugs were administered in the reverse sequence. (Ex. 1012 (1995 TAXOL PDR), 683.)

2. HER2-Positive Breast Cancer

In HER2-positive breast cancer, the HER2 protein is overexpressed by tumor cells. (Ex. 1002, ¶ 47.) HER2+ 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*., ¶ 48; Ex. 1020 (Baselga 1996), 737.) However, by December 1996, it was known that HER2-positive breast cancer responded to paclitaxel. (Ex. 1002, ¶¶ 51, 59-60; Ex. 1011 (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. 1002, ¶¶ 67-76; Ex. 1001, 3:34-40; Ex. 1019 (Baselga Abstract 53).) By 1996, phase II clinical

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

trials in humans had established that this antibody—variously known as "rhuMAb HER2 4D5," "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. 1020 (Baselga 1996), 739, 741.)

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

Baselga Abstract 53 (Ex. 1019): 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 30th Annual Meeting of the American Society of Clinical Oncology ("ASCO"), held May 14-17, 1994, in Texas. (Ex. 1002, ¶ 67.) Dr. Earhart 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*.) In fact, he submitted an abstract for the May 1994 ASCO meeting, which was published in the same Programs/Proceedings book in which Baselga Abstract 53 appears. (*Id*.) Dr. Earhart 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 '549 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
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. 1019 (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. 1021): 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. 1002, ¶ 72.) Dr. Earhart is very familiar with the annual AACR meetings, which thousands of oncology specialists and cancer researchers attend each year. (*Id*.) He often attends the AACR annual meetings, and knows that copies of the Proceedings are distributed to attendees during or before the meetings. (*Id*.) As indicated on page 2 of Exhibit 1021, 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 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/trastuzumab,[8] which were better than the results obtained with doxorubicin and trastuzumab:

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[8] Baselga Abstract 2262 references "anti-HER2 ARMA [anti-growth factor receptor monoclonal antibody] 4D5." As Dr. Earhart 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. 1002, ¶ 73, n.16.)

> 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.

(Ex. 1021(Baselga Abstract 2262) (emphases added); Ex. 1002, ¶¶ 73-76.)

Baselga 1996 (Ex. 1020): J. Baselga *et al.*, *Phase II Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer*, 14(3) J. 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. 1002, ¶ 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. 1020 (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. 1002, ¶ 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. 1002, ¶ 91.)

Seidman 1996 (Ex. 1011): 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. 1002, ¶ 59.) Dr. Earhart 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 Examiner during prosecution.

Seidman 1996 reports on treatment of metastatic breast cancer patients with paclitaxel. (Ex. 1011 (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. 1002, ¶ 60.)

Seidman 1995 (Ex. 1010): 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. 1002, ¶ 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. 1010 (Seidman 1995), 110-11.) The article also discusses the development of combination therapies that incorporate paclitaxel, including combinations with doxorubicin, cisplatin, and trastuzumab. (Ex. 1010, 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. 1022): 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. 1002, ¶ 61.) Dr. Earhart 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.) 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. 1020 (Baselga 1996), 738; *see also* Ex. 1002, ¶¶ 62-65.)

Pegram 1995 reports that of 36 patients, one had a complete response and 7 had a partial response. (Ex. 1022 (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. 1002, ¶ 82; Ex. 1006 (DeVita), 278-79; Ex. 1016 (Abeloff), 208.) POSAs understood that different cancers respond differently to different treatments. (Ex. 1002, ¶ 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. 1024 (Arbuck),[9] 130.) Cancer cells may develop "collateral sensitivity," wherein cells that are resistant to some drugs are hyper-sensitive to

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

others. (Ex. 1002, ¶¶ 84-85; Ex. 1025 (Hutchinson),[10] 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. 1002, ¶ 84; Ex. 1025 (Hutchinson), 246.)

This complicated web of mutations and resistance mechanisms arises in cells in a dynamic process that is interactive with treatment. (Ex. 1002, ¶ 87.) 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. 1016 (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

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

broader range of coverage of initially resistant clones of cells and preventing or slowing the development of resistant clones.

(Ex. 1016 (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. 1002, ¶¶ 89-91; Ex. 1024 (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. 1016 (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. 1002, ¶ 89; Ex. 1016 (Abeloff), 204-05.) This ensures that the combination has the best chance of producing a potent anti-cancer effect. (Ex. 1002, ¶ 89; Ex. 1016 (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. 1002, ¶ 89; Ex. 1016 (Abeloff), 204-05.) ***Third***, combinations of agents with different pharmacologic targets are preferred. (Ex. 1002, ¶ 89; Ex. 1016 (Abeloff), 204-05.) ***Fourth***, combinations of agents with different resistance mechanisms are preferred. (Ex. 1002, ¶ 89; Ex. 1016 (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. 1002, ¶ 89; Ex. 1016 (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. 1002, ¶ 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. 1026 (Fiebig).)[11] 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. 1002, ¶¶ 44-45.)

Xenograft results provide a "high[ly] correct prediction for resistance and sensitivity of a tumor" to a particular agent. (*Id.*, ¶ 45; Ex. 1026 (Fiebig), 349.) Because this predictive power is reproducible, the mouse xenograft system validates "human tumor xenografts as tumor models to test new drugs and

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

combinations." (Ex. 1026 (Fiebig), 343; *see also* Ex. 1006 (DeVita), 276 ("Development of new treatments is based on the effectiveness of the cancer drugs in rodent models."); Ex. 1028 ("Mattern"),[12] 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 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. 1002, ¶ 120; Ex. 1026 (Fiebig), 349; Ex. 1006 (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. 1002, ¶ 124.)

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

5. Measurements of Clinical Efficacy

In a clinical trial, the efficacy of a cancer treatment is determined by defining one or more endpoints. (Ex. 1002, ¶¶ 92-94; Ex. 1023 (ASCO Guidelines),[13] 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 progression; and (4) Response Rate (RR), which measures changes in tumor size. (Ex. 1002, ¶ 92; Ex. 1027 (ASCO Guidelines), 672-75; *see also, e.g.*, Ex. 1020 (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

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

remaining the same or changing by certain amounts. (Ex. 1002, ¶¶ 92-94; Ex. 1029, (Miller)[14] 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. 1002, ¶ 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*.)

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

Baselga 1996, Seidman 1996, and Pegram 1995 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 each independent claim. (Ex. 1002, ¶ 116.)

Baselga 1996 discloses that trastuzumab was clinically effective in patients with advanced metastatic HER2-positive breast carcinoma, was "remarkably well

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

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. (Baselga 1996 (Ex. 1020), 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. 1002, ¶¶ 58, 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. 1002, ¶¶ 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*.)

A POSA would have known that trastuzumab was clinically effective in combination with cisplatin, which was known to have broad anti-cancer efficacy. (Ex. 1002, ¶ 118.) Pegram 1995 discloses that the combination of trastuzumab/cisplatin was clinically effective in patients with metastatic HER2-positive breast cancer, with greater response rates and no apparent increase in toxicity relative to cisplatin alone. (Pegram 1995 (Ex. 1022).)

In addition, as of December 1996, paclitaxel was one of the "most promising" chemotherapeutic drugs with efficacy against metastatic breast cancer. (Ex. 1007 (Abrams), 1164.) As such, a POSA would have been motivated to treat HER2-positive breast cancer patients with paclitaxel and to incorporate paclitaxel into the known, effective trastuzumab/cisplatin combination. (Ex. 1002, ¶ 119.) A POSA would have been particularly encouraged to combine paclitaxel with trastuzumab/cisplatin because Seidman 1996 reports that paclitaxel is clinically effective against metastatic HER2-positive breast cancer. (*Id*., ¶ 119; Seidman 1996 (Ex. 1011).) The combination of trastuzumab and paclitaxel was already undergoing clinical trials for metastatic HER2+ breast cancer (Baselga 1996 (Ex. 1020), 743), and, indeed, paclitaxel and cisplatin were already being used in combination with one another to treat cancers, including metastatic breast cancer. (Ex. 1002, ¶ 119; Ex. 1012 (1995 TAXOL PDR), 683; *see also* Ex. 1013 (Tolcher), 37; Ex. 1014 (Gelmon 1996), 1185.)

A POSA would have been further motivated to combine trastuzumab, cisplatin, and paclitaxel based on the dire need for treatments of HER2-positive breast cancer. (Ex. 1002, ¶ 119.) 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*., ¶¶ 119-122; Ex. 1020 (Baselga 1996), 837; Ex. 1001, 3:41-50.) Accordingly, a POSA would have been

strongly encouraged by the clinical results reported in Baselga 1996, Pegram 1995, and Seidman 1996. (Ex. 1002, ¶ 123.)

Further, the preclinical data reporting synergy between trastuzumab and paclitaxel in mouse xenografts would have provided even more motivation to a POSA to treat HER2-positive breast cancer patients with this combination. (*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. (Baselga 1996 (Ex. 1020), 843.) In Baselga Abstract 53, the treatment with the highest observed anticancer activity was trastuzumab and paclitaxel. (Ex. 1019 (Abstract 53)); *see also* Ex. 1021 (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, cisplatin, and paclitaxel for metastatic HER2-positive breast cancer particularly made sense because the combination satisfied the four principles of combination therapy. (Ex. 1002, ¶¶ 125-130.) First, a POSA would have known from Baselga 1996, Pegram 1995, and Seidman 1996 that each of trastuzumab, trastuzumab/cisplatin, and paclitaxel had demonstrated anti-cancer activity in the target population of patients with metastatic HER2-positive breast cancer. (Ex. 1002, ¶ 126.) Further, because patients with HER2-positive breast

cancer typically also have other cancer-causing mutations (*see, e.g.*, Ex. 1005 (Alberts), 1288-90, 1263-64; Ex. 1016 (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, including in combination with cisplatin. (*See, e.g.*, Ex. 1007 (Abrams), 1164-65; Ex. 1002, ¶ 126.)

Second, trastuzumab, cisplatin, and paclitaxel were not known to have any significant overlapping toxicities. (Ex. 1002, ¶ 127.) Baselga 1996 had shown that trastuzumab, as a single agent, was well-tolerated and lacked significant toxicity. (*Id.*, ¶ 56; Ex. 1020 (Baselga 1996), 739, 741.) The combination of trastuzumab/cisplatin did not reveal any significant overlapping toxicities. (Ex. 1002, ¶ 127; Pegram 1995 (Ex. 1022).)

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) of paclitaxel was myelosuppression. (Ex. 1018 (Gelmon 1994)[15], 24.) This toxicity was not associated with trastuzumab. (Ex. 1002, ¶ 127; Ex. 1020 (Baselga 1996), 739, 741.) A POSA would have known that myelosuppression associated with the

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

paclitaxel/cisplatin combination could be minimized by adjusting the sequencing of administration, and that other adverse events were tolerable. (Ex. 1002, ¶ 128; 1995 TAXOL PDR (Ex. 1012) at 683; Ex. 1013 (Tolcher) at 38.) Further, the preclinical studies cited in Baselga 1996 did not reveal any unacceptable toxicities with the combination of paclitaxel and trastuzumab. (Ex. 1019 (Abstract 53); Ex. 1002, ¶¶ 127-129.)

Third, POSAs understood that trastuzumab, cisplatin, and paclitaxel had different mechanisms of action, with trastuzumab acting as a target-specific antibody and paclitaxel and cisplatin acting as non-specific chemotherapeutic agents. (Ex. 1002, ¶ 130.) Paclitaxel is plant alkaloid that acts on the cell's microtubules, and cisplatin is a DNA alkylating agent that modifies cellular DNA. (*Id*.) This satisfies the third principle of combination therapy. (*Id*.)

Fourth, because trastuzumab, cisplatin, and paclitaxel belong to different classes and have distinct mechanisms of action, a POSA reasonably would have expected that the drugs would not have overlapping resistance mechanisms. (*Id*., ¶ 131; *see also* Ex. 1013 (Tolcher) at 37 ("[C]isplatin … [has no] known mechanisms of cross-resistance with paclitaxel."); Ex. 1014 (Gelmon 1996) at 1185 ("We were also interested in combining the new agent [paclitaxel] with a non-cross-resistant drug with a different spectrum of toxicity. Cisplatin seemed to be an appropriate choice.").) 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 drugs, so the regimen would still remain effective. (*Id*., ¶ 131.) This satisfies the fourth principle of combination therapy. (*Id*.)

With respect to the limitations "***amount effective to extend the time to disease progression in the human***" (claims 1 and 16) and "***effective amount***" (claim 5), a POSA would have been motivated to start with the known amounts that were effective to extend the time to disease progression. (*Id*., ¶132.) 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 amounts of trastuzumab and cisplatin that had been shown to effectively treat metastatic HER2-positive breast cancer (*i.e*., for trastuzumab, a loading dose of 250 mg, followed by 100 mg per week, and for cisplatin, 75mg/m^2 on days 1, 29, and 57, *see* Ex. 1022 (Pegram 1995)), together with known effective amounts of paclitaxel, *i.e.*, the recommended amount in the PDR listing for TAXOL® (*i.e*., 135 mg/m^2 or 175 mg/m^2, *see* Ex. 1012 (1995 TAXOL PDR), 685; Ex. 1002, ¶ 132).

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. 1002, ¶¶ 133-34.) Such optimization was routine in the art. (*Id*.; Ex. 1016

(Abeloff), 205, 208-09, 216.) *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).

Indeed, the obviousness of arriving at an effective amount was conceded in the '549 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. 1001, 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 . . . ." (*Id.*, 25:43-54; *see* Ex. 1002, ¶ 134.)[16]

[16] To the extent "amount effective to extend the time to disease progression in the human" is construed to refer to an amount of the combination that extends time to

With respect to the claim limitation "***in the absence of an anthracycline derivative***" (claim 16), a POSA would have been motivated to develop the trastuzumab/cisplatin/paclitaxel combination without an anthracycline derivative because that triple combination was obvious, as explained above. Further, a POSA would have been well-aware of the cardiotoxicity issues with anthracycline derivatives. (Ex. 1002, ¶ 138; Ex. 1016 (Abeloff), 813.) Anthracyclines were known to cause irreversible cardiotoxicity thereby limiting the total lifetime dose a patient can receive. (Ex. 1002, ¶ 138; Ex. 1016 (Abeloff), 813.) Accordingly, a POSA would have limited use of anthracycline derivatives in treatment whenever possible. (Ex. 1002, ¶ 139; Ex. 1016 (Abeloff), 813.) Further, because anthracycline derivatives were a first-choice therapy for metastatic breast cancer,

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disease progression relative to no treatment, as Patent Owner contended during prosecution of the '549 patent's parent application, the claim would still be satisfied by the cited references because each of these three agents had been proven to extend TTP relative to no treatment, and a POSA would not have expected the combination to change this. (Ex. 1002, ¶¶ 137, 157 n.28.) Further, as a matter of logic, since paclitaxel alone extends TTP relative to no treatment (*see, e.g.*, Ex. 1010 (Seidman 1995)), a treatment that extends TTP relative to treatment with paclitaxel must also extend the TTP relative to no treatment. (Ex. 1002, ¶ 137.)

many candidates for treatment with the trastuzumab and paclitaxel combination would have already been treated with anthracycline-based therapy. (Ex. 1002, ¶ 138; Ex. 1016 (Abeloff), 810.) This means that many patients with metastatic disease who were prescribed a paclitaxel-containing regimen would have already endured extensive anthracycline-based therapy and would risk significant cardiotoxic effects with continued anthracycline-based therapy. (Ex. 1002, ¶ 138.) 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. 1002, ¶ 138; *see also* Ex. 1020 (Baselga 1996), at 740 (reporting that a patient died during treatment with trastuzumab due to congestive heart failure associated with prior anthracycline use); Ex. 1024 (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 metastatic HER2-positive breast cancer patients with the trastuzumab/cisplatin/paclitaxel combination. (*Id.*, ¶ 119.) Given the known clinical efficacy of trastuzumab alone, the trastuzumab/cisplatin combination, and paclitaxel alone against this type of cancer (Baselga 1996; Pegram 1995; Seidman 1996), the good tolerability and absence of significant toxicity observed in the trastuzumab clinical trial (Baselga

1996, 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 metastatic HER2-positive breast cancer than paclitaxel alone. (Ex. 1002, ¶¶ 117-35.) Indeed, positive clinical trial results for trastuzumab/cisplatin and paclitaxel/cisplatin had already been reported (Pegram 1995; 1995 TAXOL PDR at 683; *see also* Ex. 1014 (Gelmon 1996)), and a clinical trial with the trastuzumab/paclitaxel combination was already underway (Baselga 1996 at 743), which confirmed that POSAs reasonably expected each of the components of this three-drug combination to work safely with one another. (Ex. 1002, ¶ 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 trastuzumab/paclitaxel combination was greater than the effect of trastuzumab and any other tested chemotherapeutic drug, including trastuzumab/doxorubicin. (Baselga 1996 (Ex. 1020), 843, citing Ex. 1019 (Abstract 53).) This preclinical data would have reinforced the reasonable expectation of success. (Ex. 1002, ¶ 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. 1009), which argued that the prior art did not provide a motivation to combine

trastuzumab and paclitaxel, or a reasonable expectation of success with that combination. There are numerous flaws in Dr. Sliwkowski's analysis, which did not even address three-drug combinations as claimed by the '549 patent. (Ex. 1002, ¶¶ 140-55.)

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*., ¶ 140.) 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. 1009 (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. 1002, ¶ 143.) However, as of December 1996, a POSA would have known that paclitaxel exhibited its anticancer effects during all phases of the cell cycle, not only while the microtubules were active in the G2/M phase. (*Id*.; Ex. 1007 (Abrams), 1165; Ex. 1006 (DeVita), 415.) Indeed, one of the articles 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. 1002, ¶ 143; Ex. 1009 (Sliwkowski Dec.), 33-38 (Exhibit B, Woods article); *see also* Ex. 1006 (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. 1002, ¶ 143; Ex. 1009 (Sliwkowski Dec.), 33-38 (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 both work at the same cell cycle phase, albeit by different mechanisms of action and on different targets. (Ex. 1002, ¶ 143.)

Other flawed assumptions in Dr. Sliwkowski's hypothesis are that all tumor cells 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*., ¶ 144.) 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. (*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 that may be present in a HER2-positive tumor. (Ex. 1002, ¶ 145; *see* Ex. 1020 (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. 1009 (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. 1002, ¶¶ 146-48; *see also* Ex. 1009, 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. 1009, 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. 1002, ¶ 148; Exhibit G (Woods) at 1450-51.)

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. (*Id*., ¶ 149.) A POSA would have known from prior art that Dr. Sliwkowski did not discuss that his hypothesis was incorrect for combinations of trastuzumab and chemotherapies that cause G2/M cell cycle arrest. (*Id*., ¶ 149.) Like paclitaxel, cisplatin was known to arrest the cell cycle at the G2/M phase. (*Id.*, ¶ 149; Ex. 1027 (Sorenson).[17]) According to Dr. Sliwkowski's hypothesis, trastuzumab should have antagonized cisplatin or prevented it from working. But

[17] 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).

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. 1002, ¶ 149; Ex. 1022 (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 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. 1010 (Seidman 1995), 112; Ex. 1021 (Baselga Abstract 2262).) Whereas paclitaxel alone resulted in 35% inhibition of tumor growth, the trastuzumab/paclitaxel combination produced 93% inhibition. (Ex. 1021 (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. 1002, ¶ 150.) 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. 1019 (Baselga Abstract 53); Baselga 1996 (Ex.

1020); Seidman 1995 (Ex. 1011)) further demonstrates that POSAs had confidence that the benefits of the combination seen in the preclinical studies would also be seen in patients. (Ex. 1002, ¶ 150.) 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. 1009 (Sliwkowski Dec.), ¶ 9.) As support for this assertion, Dr. Sliwkowski relied on a single reference, Johnson, which he asserts shows that 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. 1002, ¶¶ 151-55.) 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. 1026 (Fiebig), 343; Ex. 1006 (DeVita), 276; Ex. 1028 (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. 1017 (Pegram 1999).[18]) 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. 1017 (Pegram 1999), 2241, 2249; Ex. 1002, ¶ 151.)

[18] 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).

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) ("[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 a reasonable expectation of success. (Ex. 1002, ¶¶ 118-119.) 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 '549 patent should never have issued over the Examiner's obviousness rejections. In any event, Seidman 1996 (Ex. 1011), which teaches that paclitaxel is clinically effective against metastatic HER2-positive breast cancer, was not of record during prosecution, nor were Dr. Earhart's views on the prior art and Dr. Sliwkowski's assertions. Thus, the combination of references in this Petition—Baselga 1996, Pegram 1995, 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, paclitaxel and cisplatin, in the absence of an anthracycline derivative, and would have had a reasonable expectation of success that the combination would effectively treat the cancer. Claims 1-11 and 14-17 are therefore unpatentable as obvious, as explained in more detail below.

a. Independent Claims 1, 5, and 16

Independent claim 1 is directed to a method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor. This method covers the treatment of metastatic HER2-positive breast cancer in a human patient. (*See* Ex. 1002, ¶¶ 156-57.) The claimed method requires administering to the patient a combination of an antibody that binds to epitope 4D5 within the ErbB2 extracellular domain sequence, a taxoid, and a further growth inhibitory agent, in an amount effective to extend the time to disease progression in the human patient. Trastuzumab is such an antibody, paclitaxel is a taxoid, and cisplatin is a growth inhibitory agent. (*Id*., ¶ 157.)

As set forth above, a POSA would have been motivated by Baselga 1996, Pegram 1995, and Seidman 1996 to administer a combination of trastuzumab, paclitaxel, and cisplatin 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 relative to paclitaxel alone. (*See supra*, Section VII.C; Ex. 1002, ¶ 157.) There was a particularly strong motivation to combine trastuzumab, paclitaxel, and cisplatin 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. 1002, ¶¶ 125-31.) The facts that the trastuzumab/paclitaxel 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. 1002, ¶¶ 123-24.) A POSA would have used the known amounts of trastuzumab, cisplatin and paclitaxel disclosed in Pegram 1995 and the 1995 TAXOL PDR entry 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 49-50; Ex. 1002, ¶¶ 133-34.) The cited prior art therefore renders independent claim 1 unpatentable as obvious. (Ex. 1002, ¶¶ 117-39, 156-57.)

Independent claim 5 is identical to claim 1 except that it recites: (1) a method for the treatment of a human patient "with breast cancer characterized by

overexpression of ErbB2 receptor"; (2) "an anti-ErbB2 antibody which binds epitope 4D5 within the ErbB2 extracellular domain sequence"; and (3) an "effective amount" of the combination, rather than an amount effective to extend the time to disease progression. As with claim 1, claim 5 covers the treatment of a human patient with metastatic HER2-positive breast cancer, and the antibody recited in claim 5 covers trastuzumab. (*Id.*, ¶ 159.) All the other claim elements in claim 5 are the same as in claim 1. Accordingly, like claim 1, claim 5 would have been obvious over Baselga 1996, Pegram 1995, Seidman 1996, and the 1995 TAXOL PDR. (*See also id.*, ¶¶ 158-59.)

Independent claim 16 is identical to claim 1 except that it recites: (1) a method for the treatment of a human patient "with ErbB2 overexpressing breast cancer"; (2) "an antibody that binds epitope 4D5 within the ErbB2 extracellular domain sequence" as the antibody; and (3) "in the absence of an anthracycline derivative." As with claim 1, the method of claim 16 covers the treatment of a human patient with metastatic HER2-positive breast cancer, and the antibody recited in claim 16 covers trastuzumab. (*Id.*, ¶ 160.)

A POSA would have been motivated to use the trastuzumab/cisplatin/paclitaxel combination because that combination, which does not include an anthracycline derivative, was rendered obvious, as explained above. Further, a POSA would have been well-aware of the cardiotoxicity issues with

anthracycline derivatives. (*Id.*, ¶¶ 138, 161; Ex. 1016 (Abeloff), 1693.) Anthracyclines were known to cause irreversible cardiotoxicity thereby limiting the total lifetime dose a patient can receive. (Ex. 1002, ¶¶ 138, 161; Ex. 1016 (Abeloff), 1693.) Accordingly, a POSA would have limited use of anthracycline derivatives in treatment whenever possible. (Ex. 1002, ¶¶ 138, 161; Ex. 1016 (Abeloff), 1693.) 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. 1002, ¶¶ 138, 161; Ex. 1016 (Abeloff), 810.) This means that many patients with metastatic disease who were prescribed a paclitaxel-containing regimen would have already endured extensive anthracycline-based therapy and would risk significant cardiotoxic effects with continued anthracycline-based therapy. (Ex. 1002, ¶ 161.) POSAs would have avoided administering further anthracycline derivatives to the many patients who had already been treated with this class of drug, rendering the limitation "in the absence of an anthracycline derivative" obvious. (*Id.*, ¶¶ 138-39, 161; *see also* Ex. 1020 (Baselga 1996), at 740 (reporting that a patient died during treatment with trastuzumab due to congestive heart failure associated with prior anthracycline use).)

All the other claim elements in claim 16 are the same as in claim 1. Accordingly, claim 16 would have been obvious over Baselga 1996, Pegram 1995, Seidman 1996, and the 1995 TAXOL PDR for the same reasons discussed above for claim 1, and for the additional reasons discussed here. (Ex. 1002, ¶¶ 161-62.)

b. Dependent Claims 2-4, 6-11, 14, 15 and 17

Claims 2-4 and 7 recite further properties of the antibody described in the independent claims 1 or 5. **Claim 2** depends from claim 1 and **claim 7** depends from claim 5. These claims and require that the antibody is a humanized 4D5 anti-ErbB2 antibody. **Claim 3** depends from claim 1 and further requires that the antibody cross-blocks binding of 4D5 to the ErbB2 extracellular domain sequence. **Claim 4** depends from claim 1 and further requires that that antibody binds to the amino acid residues in the region from about residue 529 to about residue 625 or the ErbB2 extracellular domain sequence. All of these claim limitations are satisfied by trastuzumab. (Ex. 1002, ¶ 162.) Accordingly, like claim 1, claims 2-4 and 7 would have been obvious over Baselga 1996, Pegram 1995, Seidman 1996, and the 1995 TAXOL PDR. (*Id*.)

Claims 6 and 17 depend from claims 5 and 16, respectively, and further require that the breast cancer is metastatic breast carcinoma. (*Id*., ¶ 163.) The patients treated in Baselga 1996, Pegram 1995, and Seidman 1996 had metastatic HER2-positive breast carcinoma, and thus met the limitations of each of these

claims. Accordingly, like claims 5 and 16, claims 6 and 17 would have been obvious over Baselga 1996, Pegram 1995, Seidman 1996, and the 1995 TAXOL PDR. (*Id*.)

Claim 8 depends from claim 7 and further requires that the antibody is administered as a 4 mg/kg dose and then weekly administration of 2 mg/kg. The dose of trastuzumab that was shown to be clinically effective when used alone in Baselga 1996 (Ex. 1020) and when used in combination with cisplatin in Pegram 1995 (Ex. 1022) was a 250 mg loading dose followed by weekly 100 mg doses. (Ex. 1002, ¶ 164.) For an average patient of about 62.5 kg, this regimen is the same as a 4 mg/kg loading dose, followed by 1.6 mg/kg weekly doses. (*Id*.) This regimen would have been the starting point for a POSA designing a combination therapy with trastuzumab, cisplatin, and paclitaxel, and a POSA would have been motivated to optimize this regimen using routine and conventional techniques, arriving at the claimed dosage amounts. (*Id*.) Accordingly, claim 8 would have been obvious over Baselga 1996, Pegram 1995, Seidman 1996, and the 1995 TAXOL PDR entry for the same reasons discussed above for claim 5, and these additional reasons. (*Id*.)

Claim 9 depends from claim 5 and further requires that the taxoid is paclitaxel. As explained, the trastuzumab/cisplatin/paclitaxel combination is

obvious. Accordingly, like claim 5, claim 9 would have been obvious over Baselga 1996, Pegram 1995, Seidman 1996, and the 1995 TAXOL PDR. (*Id*.)

Claim 10 depends from claim 5 and further requires that efficacy is measured by determining time to disease progression or 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* Section VII.A.5; Ex. 1002, ¶ 166.) The '549 patent admits this. (Ex. 1001, 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, like claim 5, claim 10 would have been obvious over Baselga 1996, Pegram 1995, Seidman 1996, and the 1995 TAXOL PDR. (Ex. 1002, ¶ 166.)

Claim 11 depends from claim 5 and further requires that the "further therapeutic agent" is selected from a group consisting of, among other things, a "growth inhibitory agent." **Claim 14** depends from claim 5 and further requires that the "further therapeutic agent" is a "growth inhibitory agent." **Claim 15** depends from claim 14 and further requires that the "growth inhibitory agent" is a "DNA alkylating agent." According to the specification, cisplatin is a "growth inhibitory agent" and a "DNA alkylating agent." (Ex. 1001 at 11:20-40; *see also*

Ex. 1002, ¶ 167; Ex. 1016 at 210.) Accordingly, like claim 5, claims 11, 14, and 15 would have been obvious over Baselga 1996, Pegram 1995, Seidman 1996, and the 1995 TAXOL PDR. (Ex. 1002, ¶ 167.)

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

In an obviousness analysis, if present, secondary considerations of non-obviousness 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. 1004 at 305.) Neither of these arguments succeeded in persuading the Examiners that the claims were non-obvious, and neither should succeed here.

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. 1019 (Abstract 53).) Indeed, during prosecution the Examiner rejected Patent Owner's evidence of clinical synergy 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. 1004 at 408.) 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. 1002, ¶ 171.)

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. 1008 (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. 1008 (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. 1002, ¶ 175.)

Further, Dr. Hellmann cited only the median TTP, but ignored the 95% confidence interval data reported for TTP. (*Id.*, ¶ 176.) 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. 1008 (Hellmann Dec.) at 13 (Exhibit B); Ex. 1002, ¶ 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. 1008 (Hellmann Dec.) at 14 (Exhibit C); Ex. 1002, ¶ 176.) 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. 1008 (Hellmann Dec.) at 14 (Exhibit C); (Ex. 1002, ¶ 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.*, ¶ 176.) 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. Unexpected 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 combination is not implicated by a

finding that some other, unclaimed combination turned out to be a less preferable choice. (*See also* Ex. 1002, ¶ 180.)

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. 1021 (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 patentability. 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.*,752 F.3d 967, 978 (Fed. Cir. 2014) (explaining that unexpected results must be shown to be unexpected compared with the closest prior art).

To the extent Patent Owner alleges other secondary considerations, Petitioner submits that any nexus is not to the claimed invention, but rather to the known trastuzumab/paclitaxel combination and its known use 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 unexpected results "unavailing"

because “the offered secondary consideration actually results from something other than what is both claimed and *novel* in the claim” (emphasis in original)).

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

VIII. CONCLUSION

Petitioner respectfully requests that this Petition be granted and claims 1-11 and 14-17 be cancelled.

Respectfully submitted,

Dated: March 21, 2017

/Cynthia Lambert Hardman/
Cynthia Lambert Hardman (Reg. No. 53,179)

Counsel for Petitioner

CERTIFICATE OF WORD COUNT

The undersigned certifies that the attached Petition for *Inter Partes* Review of U.S. Patent No. 6,892,549 contains 13,998 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: March 21, 2017 By: /Cynthia Lambert Hardman/
Cynthia Lambert Hardman (Reg. No. 53,179)

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that on this 21st day of March, 2017, I served a copy of this PETITION FOR INTER PARTES REVIEW and copies of all supporting exhibits by Federal Express Next Business Day Delivery on the following addresses for patent owner(s) and their representatives:

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