Trials@uspto.gov
Tel: 571-272-7822

Paper 9
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-01122
Patent 7,892,549 B2

Before ZHENYU YANG, CHRISTOPHER G. PAULRAJ, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

POLLOCK, *Administrative Patent Judge*.

DECISION
Instituting *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Celltrion, Inc. ("Petitioner" or "Celltrion")[1] filed a Petition requesting an *inter partes* review of claims 1–11 and 14–17 of U.S. Patent No. 7,892,549 B2 (Ex. 1001, "the '549 patent"). Paper 2 ("Pet."). Genentech, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 6 ("Prelim. Resp.").

Institution of an *inter partes* review is authorized by statute when "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314; *see* 37 C.F.R. §§ 42.4, 42.108. Upon considering the Petition and the Preliminary Response, we determine that Petitioner has shown a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim. For the reasons that follow, we institute an *inter partes* review of claims 1–11 and 14–17 of the '549 patent.

A. *Related Applications and Proceedings*

The '549 Patent issued from Application No. 10/356,824, filed February 3, 2003, which is a continuation of Application No. 09/208,649, filed Dec. 10, 1998 (the "'649 Application"). U.S. Patent No. 7,846,441 B2 ("the '441 Patent) issued from the '649 Application on December 7, 2010. The '549 and '441 Patents claim benefit of priority to Provisional Application No. 60/069,346, filed Dec. 12, 1997 ("the '346 application"). *See e.g.*, Ex. 1001, (21), (63) (60), 1:4–9.

In addition to this proceeding, Petitioner has challenged claims 1–14 of the related '441 Patent in IPR2017-01121. Petitioner has also filed IPR2017-01139

[1] Petitioner further identifies Celltrion Healthcare Co., Ltd. and Teva Pharmaceuticals International GmbH as real parties-in-interest. Paper 10, 2.

and IPR2017-01140 involving claims of U.S. Patent Nos. 6,627,196 and 7,371,379, respectively. These two patents are not in the chain of priority of the '549 and '441 Patents but involve subject matter similar to that at issue here.

The '549, '441, '196, and '379 Patents are also the subject of pending *inter partes* reviews, IPR2017-00737, IPR2017-00731,[2] IPR2017-00804, and IPR2017-00805, respectively, brought by Hospira, Inc. ("Hospira"). *Hospira, Inc. v. Genentech, Inc.*, IPR2017-00739 (PTAB July 27, 2017) (Paper 16). With respect to the '549 Patent, we refer herein to our Decision to institute trial in IPR2017-00737 as the "Hospira Decision." *See Hospira, Inc. v. Genentech, Inc.*, Case IPR2017-00737 (PTAB July 27, 2017) (Paper 19).[3]

B. *The '549 Patent and Relevant Background*

According to the Specification, 25% to 30% of human breast cancers overexpress a 185-kD transmembrane glycoprotein receptor ($p185^{HER2}$), also known as HER2 (human epidermal growth factor receptor-2) or ErbB2. Ex. 1001, 1:21–32, 5:16–21. These HER2-positive cancers are associated with poor prognoses and resistance to many chemotherapeutic regimens including anthracyclines (e.g., doxorubicin or epirubicin). *Id*. at 3:43–52; 4:11–12, 11:41–45. Conversely, the prior art teaches that patients with HER2-positive cancers are three times more likely to respond to treatment with taxanes than those with HER2 negative tumors. *Id*. at 3:52–56 (citing *Baselga et al*., 11(3, Supp. 2) ONCOLOGY 43–48 (1997)).

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[2] Although we denied institution in IPR2017-00731 (*Hospira, Inc. v. Genentech, Inc.*, IPR2017-00731 (PTAB July 27, 2017) (Paper 19)), Hospira filed a request for reconsideration (IPR2017-00731, Paper 21), which is currently pending.

[3] Hospira also challenged claims of the '549 Patent in IPR2017-00739, which we denied.

Although "ErbB2 overexpression is commonly regarded as a predictor of a poor prognosis," "a humanized version of the murine anti-ErbB2 antibody 4D5, referred to as rhuMAb HER2 or HERCEPTIN® [or trastuzumab] has been clinically active in patients with ErbB2-overexpressing metastatic breast cancers that had received extensive prior anti-cancer therapy." Ex. 1001, 3:35–61 (citing Baselga 1996 (Ex. 1020)).[4] Anti-ErbB2 4D5 antibodies also "enhance the activity of paclitaxel (TAXOL®) and doxorubicin against breast cancer xenographs in nude mice injected with BT-474 human breast adenocarcinoma cells, which express high levels of HER2." *Id*. at 3:56–61 (citing Baselga Abstract 53 (Ex. 1019)).[5]

According to the Specification:

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

Id. at 3:65–4:5.

The '549 Patent thus relates to the treatment of breast cancers that overexpress HER2/ErbB2 "comprising administering a therapeutically effective

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[4] Baselga et al., *Phase II Study of Weekly Intravenous Recombinant Humantized Anti-p195^{HER2} Monoclonal Antibody in Patients with HER2/neu-Overexpressing Metastatic Breast*, Cancer, 14(3) J. CLIN. ONCOL. 737–44 (1996). Ex. 1020.

[5] Baselga et al., *Anti Her2 Humanized Monoclonal Antibody (Mab) Alone And In Combination With Chemotherapy Against Human Breastcarcinoma Xenografts*, 15 PROC. AM. SOC'Y. CLIN. ONCOL. 63, Abstract 53 (1994). Ex. 1019. In the Hospira Decision, we refer to Baselga Abstract 53 as Baselga '94. *See*, *e.g.*, Hospira Decision, 7 & n.8.

amount of 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 to the human patient." *Id*. at 4:6–13. In some embodiments, the anti-ERbB2 antibody of the combination is Herceptin, and the chemotherapeutic agent "is a taxoid, such as TAXOL® (paclitaxel) or a TAXOL® derivative." *Id*. at 4:23–25. The combination may further include one or more additional anti-ErbB2 antibodies, "antibodies which bind to the EGFR . . . ErbB3, ErbB4, or vascular endothelial factor (VEGF)," "one or more cytokines," or "a growth inhibitory agent." *Id*. at 23:60–24:5, 25:20–34; *see also id.* at 11:4–40 (defining "chemotherapeutic agent" and "growth inhibitory agent").

The '549 Patent also provides an Example disclosing the conduct and results of a clinical trial involving 469 women with metastatic HER2-positive breast cancer *Id*. at 26:34–30:25. All patients were treated with one of two chemotherapy regimens (CRx) designated either "AC" for anthracycline (doxorubicin or epirubicin) and cyclophosphamide, or "T" for Taxol (paclitaxel). *See id*. at 28:5–47; 29:13–30:12. Half of the patients were also treated with the anti-ERbB2 antibody Herceptin ("H"). *Id*. For each treatment arm, the patent reports the number of patients enrolled, time to progression (TTP), response rate (RR), and adverse event rates (AE). *See id*. at 29:11–30:12.

The Specification discloses that "[a]t a median follow-up of 10.5 months, assessments of time to disease progression (TTP in months) and response rates (RR) showed a significant augmentation of the chemotherapeutic effect by HERCEPTIN®, without increase in overall severe adverse events (AE)." *Id*. at 29:13–18. In addition, "[a] syndrome of myocardial dysfunction similar to that observed with anthracyclines was reported more commonly with a combined

treatment of AC+H (18% Grade ¾) than with AC alone (3%), T (0%), or T+H (2%)." *Id*. at 30:13–16. According to the inventors:

> 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. at 30:17–25.

C. *Challenged Claims*

Petitioner challenges claims 1–11 and 14–17 of the '549 Patent. Pet. 9. Claims 1, 5, and 16 are independent. Claim 1, reproduced below, requires "administering a combination" of three agents—an anti-ErbB2 antibody, a taxoid, and "a further growth inhibitory agent"—"in an amount effective to extend the time to disease progression":

> 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 16 is similar to claim 1, but further includes a negative limitation requiring the administration of an anti-ErbB2 antibody, a taxoid, and a further growth inhibitory agent "in the absence of an anthracycline derivative."

Independent claim 5 is also similar to claim 1, but recites "administering an effective amount" of an anti-ErbB2 antibody, a taxoid, and "a further therapeutic agent," and further specifies that the taxoid is paclitaxel. Depending from claim 5,

claim 14 specifies that this "further therapeutic agent" is "a growth inhibitory agent." Depending from claims 1 and 5, respectively, claims 2 and 7 require that the 4D5 anti-ErB2 antibody is humanized.

D. *Asserted Prior Art and Ground of Unpatentability*

Petitioner asserts that claims 1–11 and 14–17 are unpatentable under 35 U.S.C. § 103 based on the combination of Baselga 1996, Seidman 1996,[6] Pegram,[7] 1995 TAXOL PDR,[8] and the knowledge of one of ordinary skill in the art. (Pet. 24).

Petitioner also relies on Exhibit 1002, the declaration of its technical expert, Robert H. Earhart Jr., M.D., Ph.D.

II. ANALYSIS

A. *Principles of Law*

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is

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[6] 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. CLIN. ONCOL. 104, Abstract 80 (1996). Ex. 1011.

[7] 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. CLIN. ONCOL 106, Abstract 124. Ex. 1022.

[8] TAXOL (paclitaxel) for Injection Concentrate, *in* PHYSICIAN'S DESK REFERENCE, 682–85 (49th ed. 1995). Ex. 1012.

resolved based on underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness, if present. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"[T]he [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418. "[I]nterrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all [can provide] . . . an apparent reason to combine the known elements in the fashion claimed . . . ." *Id.*

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review). Furthermore, Petitioner cannot satisfy its burden of proving obviousness by "employ[ing] mere conclusory statements." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016). Thus, to prevail in an *inter partes* review, Petitioner must explain how the proposed combinations of prior art would have rendered the challenged claims unpatentable. At this preliminary stage, we determine whether the information presented in the Petition and Preliminary Response shows there is a reasonable likelihood that

Petitioner would prevail in establishing that at least one challenged claim would have been obvious over the proposed combinations of prior art. 35 U.S.C. § 314(a).

We analyze the challenges presented in the Petition in accordance with the above-stated principles.

B. *Person of Ordinary Skill in the Art*

Patent Owner argues that we should apply the same definition of a person of ordinary skill as set forth in the Hospira Petition, which also involves the '549 Patent. Prelim. Resp. 37. In that case, we adopted Petitioner Hospira's definition of one of ordinary skill as "a clinical or medical oncologist specializing in breast cancer with several years of experience with breast cancer research or clinical trials." Hospira Decision at 8–9 (quoting IPR2017-00737 Pet. 6). In the present Petition, however, Celltrion argues that a person of ordinary skill in the art as of the effective filing date of the '549 patent "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." Pet. 43 (citing Ex. 1002, ¶ 29). According to Petitioner, "[s]uch 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*.

We agree with Patent Owner. Petitioner does not explain why its proposed definition better defines the level of ordinary skill in the art, nor why its alternative definition would have any bearing on the outcome of the present case. To the contrary, we do not discern an appreciable difference in the parties' respective definitions of the level of ordinary skill in the art. Indeed, both parties contend that a person of ordinary skill in the art would have had experience with breast-cancer

research and treatment, and our findings and conclusions would be the same regardless of which definition were adopted. Accordingly, we adopt Patent Owner's definition of the level of ordinary skill in the art. *See also* Hospira Decision, 8–9 (defining the skill level the same way).

We further note that, in this case, the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp*., 755 F.2d 158, 163 (Fed. Cir. 1985)).

C. *Claim Construction*

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard). Under that standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007); *see also Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016) ("Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history."). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Limitations, however, are not to be read from the specification into the claims (*In re Van Geuns*, 988 F.2d 1181, 1184

(Fed. Cir. 1993)), nor may the Board "construe claims during [an *inter partes* review] so broadly that its constructions are unreasonable under general claim construction principles" (*Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015)).

1. *"in an amount effective to extend the time to disease progression in the human patient" and in "an effective amount"*

Independent claims 1 and 16 require administering a combination of an anti-ErbB2 antibody, a taxoid, and a further agent "in an amount effective to extend the time to disease progression in the human patient" (claims 1 and 16), or more generically, administering the three-part combination to a human patient in "an effective amount" (claim 5). Petitioner reasonably proposes that "time to disease progression" refers to a "time period calculated from diagnosis or the start of therapy until the disease worsens." Pet. 21 (citing Ex. 1001, 29:3–9; Ex. 1002 ¶ 111). Petitioner further argues that this is "a relative term" and that "the appropriate comparison is to compare the claimed combination treatment to treatment with a taxoid alone." Pet. 22 (citing Ex. 1002 ¶ 111). According to Petitioner, the Example disclosed in the '441 patent Specification compares time to disease progression and adverse events of combination therapy of TAXOL® with HERCEPTIN® against treatment with TAXOL® alone. *Id.* (citing Ex. 1001, 29:11–30:25). Petitioner, however, acknowledges that during prosecution, the applicant asserted that the comparison is between the claimed combination treatment and no treatment. *Id.*; *see* Ex. 1002 ¶ 111 (citing Ex. 1004, 416); Ex. 3001, 416.[9]

[9] Petitioner and Petitioner's expert refer to a portion of the prosecution history that we do not find in Exhibit 1004, but that is present in Exhibit 1004 of co-pending IPR2017-01121, which we reproduce here as Exhibit 3001.

Indeed, during prosecution of the '649 Application, the Examiner rejected then-pending claims as indefinite under 35 U.S.C. § 112. Ex. 3001, 401–02 (OA dated 7/17/2001). The Examiner stated:

> The phrase "extend the time to disease progression" . . . is a relative term which renders the claim[s] indefinite. The term "extend time to disease progression" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically, it is never set forth what the extension of time to disease progress is relative to, for example, is the extension of time to disease progress relative to untreated patients? Patients who received antibody or taxoid alone? Patients who received antibody and an anthracycline?

Id. at 400–401. The applicant responded that

> the expression[] "extend the time to disease progression". . . [is] clear from the specification . . . and would be readily understood by the skilled oncologist. 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.

Id. at 416 (Response dated 1/17/2002). The Examiner withdrew the rejection in the next office action. *See id.* at 624 (OA dated 3/27/2002) (stating "[a]ll claims were allowable" but suspending prosecution due to potential interference); *see also id*. at 634–39 (OA dated 8/12/2003) (new grounds of rejection not relating to the phrase "extend the time to disease progression").

Given the applicant's unequivocal statement to overcome the indefiniteness rejection during prosecution, under the proper analysis of the term, we interpret "an amount effective to extend the time to disease progression in the human patient" in independent claims 1 and 16 as an amount sufficient to extend the time to disease progression in a human patient having breast cancer that overexpresses

ErbB2 receptor as compared to one receiving no treatment. *See also* Hospira Decision, 12 (construing the term the same way).

We further construe the language "an effective amount" of independent claim 5 as encompassing "an amount effective to extend the time to disease progression in the human patient." *Id.* This definition is consistent with the Specification's definition of "therapeutically effective amount" as "an amount having an antiproliferative effect," wherein the efficacy of that effect can "be measured by assessing the time to disease progression (TTP), or determining the response rates (RR)." Ex. 1001, 10:41–50; *see also* claim 10 (depending from claim 5 and reciting "wherein efficacy is measured by determining the time to disease progression or the response rate.")

2. *"Response rate"*

We also acknowledge the parties' facially different proposed constructions of the term "response rate." Although we note that during prosecution, Applicants stated that "response rate" is "an art-recognized term" (Ex. 3001, 416), Petitioner contends that it "means the percentage of patients whose disease responds to treatment" (Pet. 23 (citing Ex. 1001, 28:48–29:2, 29:11–30:25)); whereas, Patent Owner argues that it refers to "the percentage of patients whose tumor is reduced in size by a specified amount following treatment" (Prelim. Resp. 38 (citing Ex. 1001, 28:48–67)).

Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). On this record and for purposes of this Decision, we see no need to expressly construe "response rate" at this time, as the term only appears in claim 10, which depends from claim 5. As explained below, we institute trial to review all challenged claims because Petitioner has established a reasonable likelihood

that it would prevail in showing the unpatentability of at least independent claims 1, 5, and 16. *See* 35 U.S.C. § 314(a). It is, thus, unnecessary for us to construe this term for purposes of institution.

To the extent an explicit construction facilitates solidification of the parties' respective positions—and to the extent any differences in the parties' proposed definitions bear on the patentability of claim 10—we provisionally adopt Patent Owner's proposed construction of "response rate."

3. *"administering a combination"*

Further, in IPR2017-00737, we adopted Patent Owner's unopposed definition of "administering a combination" as requiring "a single treatment regimen in which the patient receives all drugs that are part of the claimed combination." Hospira Decision, 10. Although neither party expressly addresses that term in the instant case, in the interests of clarity and consistency, we provisionally adopt that same definition here.

D. *Overview of Asserted Prior Art*

Petitioner challenges the patentability of the asserted claims based on the combination of Baselga 1996, Seidman 1996, Pegram, 1995 TAXOL PDR, and the knowledge of one of ordinary skill in the art, evidenced, in part, by Baselga Abstract 53, Baselga Abstract 2262,[10] and Seidman '95.[11] *See* Pet. 29–32, 25–26. We address the content of these references below.

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[10] Baselga *et al.*, *Antitumor Activity of Paclitaxel in Combination with Anti-growth Factor Receptor Monoclonal Antibodies in Breast Cancer Xenografts*, 35 PROC. AM. ASS'N FOR CANCER RES. 380, Abstract 2262. Ex. 1021.
[11] Seidman *et al.*, *Memorial Sloan-Kettering Cancer Center Experience with Paclitaxel in the Treatment of Breast Cancer*, 22(5) Suppl. 12 SEMINARS ONCOLOGY 108–16. Ex. 1010.

1. *Overview of Baselga 1996 (Ex. 1020)*

Baselga 1996 teaches that "[i]n preclinical studies . . . rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity." Ex. 1020 at 9. As a result, "[l]aboratory studies of the mechanism of this effect and clinical trials of such combination therapy are currently in progress." *Id*.

Baselga 1996 further teaches that after successful experiments in mouse models, a humanized version of the 4D5 anti-ErbB2 antibody, rhuMAb HER2, was used in a phase II clinical trial for patients with metastatic breast cancer that overexpressed HER2. *Id*. at 3–4. "[P]atients were selected to have many sites of metastatic involvement, one of the most dire prognostic characteristics regarding response to therapy." *Id.* at 7. Of the 46 patients enrolled, 82.6% had received at least one regimen for metastatic disease, and 63% had received two or more regimens. *Id*. at 5.

According to Baselga 1996, "[a]dequate pharmacokinetic levels of rhuMAb HER2 were obtained in 90% of the patients. Toxicity was minimal and no antibodies against rhuMAb HER2 were detected in any patients." *Id.* at 3; *see also id*. at 5 (stating that "[t]reatment with rhuMAb HER2 was remarkably well tolerated"). Of 43 patients assessed after treatment, "five experienced a complete or partial remission, for an overall response rate of 11.6%." *Id*. at 7; *see id.* at 3 ("Objective responses were seen" with an 11.6% remission rate.). "37% of patients achieved minimal responses or stable disease." *Id*. at 7.

Baselga 1996 reports that "[t]ime to tumor progression was calculated from the beginning of therapy to progression"; whereas, "[t]he median time to progression for the patients with either minor or stable disease was 5.1 months." *Id*. at 4, 6. Baselga 1996 notes that, in contrast to many anticancer drugs, rhuMAB

HER2 elicits growth arrest rather than cell death in laboratory studies. *See id*. at 7. Accordingly, the authors posit that "stable disease may be an authentic reflection of the biologic action of [rhuMAB HER2]" such that "[t]he unusually long durations of minimal responses and stable disease seen in [the] trial" may be indicative of the cytostatic effects of the antibody. *Id.*

2. *Overview of Seidman 1996 (Ex. 1011)*

Seidman 1996 analyzes tissue samples from 126 patients with metastatic breast cancer (MBC) who had received single-agent taxane treatment (paclitaxel or docetaxel). Ex. 1011. Of the 51 of these patients determined to be HER2 positive, 58.8% responded to taxane treatment, as compared to only 38.7% of the 75 patients that did not overexpress HER2. *Id.* According to Seidman, "stratified analysis controlling for confounding variables demonstrated the value of HER2 status in predicting good taxane response." *Id.* Seidman concludes that, although HER2 overexpression is correlated with a poor prognosis, "HER2 over-expression [sic] in MBC seems to confer sensitivity rather than resistance to taxanes." *Id.*

3. *Overview of Pegram (Ex. 1022)*

By way of background, Pegram notes that, in Phase I studies, "rhuMAB HER-2 has no substantial toxicity at any dose level and localizes to malignant cells overexpressing the HER-2 receptor protein. In preclinical studies, therapy with this antibody plus cisplatin (CDDP) elicits a synergistic and cytocidal effect on tumor cells which express p185HER-2/*neu*." Ex. 1022.

Pegram reports on a phase II clinical trial of patients with HER2 positive metastatic breast cancer treated with rhuMAB HER-2 plus cisplatin. *Id*. According to Pegram:

> The toxicity profile was that expected from [cisplatin], and there were no acute serious adverse events recorded following treatment with rhuMAB HER-2. The use of rhuMAb HER-2 plus [cisplatin] in

> patients with HER2/*neu* overexpressing MBC resulted in response rates above that expected from [cisplatin] alone, and the combination showed no apparent increase in toxicity.

Id.

4. *Overview of 1995 Taxol PDR (Ex. 1012)*

According to 1995 TAXOL PDR, paclitaxel "is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated." Ex. 1012, 6. "For patients with carcinoma of the breast, TAXOL at a dose of 175 mg/m^2 administered intravenously over 3 hours every three weeks has been shown to be effective after failure of chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy." *Id.* at 8.

5. *Overview of Baselga Abstract 53 (Ex. 1019)*

Baselga Abstract 53 describes xenograft studies in which HER2 overexpressing human breast tumor cells were injected into nude mice followed by treatment with humanized 4D5-antibody alone, or in combination with various chemotherapeutic agents. Ex. 1019, 4. Whereas either the antibody or paclitaxel alone produced 35% tumor growth inhibition, the combination of the two resulted in "major antitumor activity with 93% inhibition of growth" without increasing toxicity. *Id.* In addition, whereas doxorubicin alone resulted in 27% growth inhibition, the combination of doxorubicin and antibody resulted in 70% growth inhibition. *Id.*

According to the authors,

> [t]hese observations suggest that dual insults to cell cycle transversal through checkpoints (Mab-mediated growth factor deprivation, and drug mediated damage to DNA or tubulin) may activate cell death in tumor cells which can survive either treatment given singly. In

> summary anti-HER2 MAbs can eradicate well established tumors and enhance the activity of paclitaxel and doxorubicin against human breast cancer xenografts.

Id.

6. *Overview of Baselga Abstract 2262 (Ex. 1021)*

Baselga Abstract 2262 describes the effect of paclitaxel alone, and in combination with anti-growth factor receptor monoclonal antibodies (ARMAs) (including anti-ErbB2 antibody 4D5) in a mouse xenograft model. Ex. 1021. According to Baselga 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). 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.

Id.

7. *Overview of Seidman '95 (Ex. 1010)*

Siedman '95 reports that in a phase II trial for metatastic breast cancer, paclitaxel monotherapy showed "significant antitumor activity in patients with minimal prior treatment." Ex. 1010, 2. Subsequent investigation of paclitaxel in patients who had previously been treated with anthracyclines also showed anti-tumor activity and a "lack of significant cross-resistance between paclitaxel and doxorubicin." *Id.* at 2–3, Fig. 1. Seidman '95 further discusses the development of optimal dosing schedules for paclitaxel therapy (*id.* at 3–4), and the development of combination therapies of paclitaxel, with doxorubicin, cisplatin, and trastuzumab (*id.* at 4–5). Referencing, among others, Baselga Abstract 2262, Seidman '95 states that "[s]triking antitumor effects are observed when paclitaxel

is given in human breast cancer xenografts in combination with . . . anti-HER-2 MoAbs. This strong synergy is achieved with no increased toxicity in the animal model." *Id*. at 5 (footnotes omitted).

E. *Asserted Obviousness Ground*

Petitioner contends that claims 1–11 and 14–17 would have been obvious over the combination of Baselga 1996, Seidman 1996, Pegram, and the 1995 TAXOL PDR entry, in view of the knowledge of a person of ordinary skill in the art. Pet. 24–75. The Petition includes a claim by claim analysis of each challenged claim. *Id.* at 63–70. Based on the current record, we determine Petitioner has established a reasonable likelihood that it would prevail on this assertion with respect to at least claims 1, 5, and 16.

Petitioner asserts that one of ordinary skill would have been "motivated to combine trastuzumab, cisplatin, and paclitaxel based on the dire need for treatments of HER2-positive breast cancer," which was "notoriously difficult to treat because HER2-positive breast cancer frequently did not respond to traditional anti-cancer treatments." *Id*. at 45 (citing Ex. 1002 ¶¶ 119–122, Ex. 1020, 837; Ex. 1001, 3:41–50). Petitioner refers to Baselga 1996 as teaching that the rhuMAb HER2 antibody "was clinically effective in patients with advanced metastatic HER2-positive breast carcinoma, was 'remarkably well tolerated,' and lacked 'significant toxicity,' even though the patients had 'dire prognostic characteristics' based on the extensive metastasis of their cancers and prior failures with other treatments." Pet. 43–44 (citing Ex. 1020, 7). Petitioner argues that before the priority date of the challenged claims, an ordinary artisan "would have been motivated to pursue combination therapies that incorporate trastuzumab . . . . in combination with drugs that had shown broad efficacy against all types of metastatic cancer." *Id*. at 44 (citing Ex. 1002 ¶¶ 119–121). Petitioner notes that

Beselga 1996 discloses ongoing clinical trials of trastuzumab in combination with each of paclitaxel, doxorubicin, and cisplatin (*id.* (citing Ex. 1020, 9, Ex. 1002 ¶¶ 58, 123)), and points to Pegram's disclosure 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." *Id*.; *see* section II(D)(3), *supra*.

Petitioner asserts that one of ordinary skill would have been motivated to further combine paclitaxel with trastuzumab/cisplatin treatment in light of Seidman 1996's report that paclitaxel is clinically effective against metastatic HER2-positive breast cancer, and was being used in combination with cisplatin to treat cancers, including metastatic breast cancer. *Id*. at 45 (citing, in part, Ex. 1002 ¶ 119); *see also* Ex. 1013,[12] 1, 3 (discussing "potential advantages" of paclitaxel/cisplatin therapy and concluding that "[t]he paclitaxel/cisplatin combination has demonstrated an encouraging level of antitumor activity in women with metastatic breast cancer and has an acceptable level of toxicity"); Ex. 1014,[13] 1185 (concluding that "[b]iweekly paclitaxel and cisplatin is an active combination for the treatment of metastatic breast cancer, including for patients with previous exposure to anthracyclines").

To bolster its position, Petitioner points to "preclinical data reporting synergy between trastuzumab and paclitaxel in mouse xenografts," as shown in Baselga Abstract 53 and Baslega Abstract 2262. Pet. at 46 (citing Exs. 1019, 1021); *see* sections II(D)(5), (6), *supra*. Petitioner further contends that

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[12] Tolcher, *Paclitaxel Couplets with Cyclophosphamide or Cisplatin in Metastatic Breast Cancer*, 23(1) Supp. 1 SEMINARS ONCOLOGY 37–43 (1996). Ex. 1013.
[13] Gelmon et al., *Phase I/II Trial of Biweekly Paclitaxel and Cisplatin in the Treatment of Metastatic Breast Cancer*, 14(4) J. CLINICAL ONCOLOGY 1185-91 (1996). Ex. 1014.

"[c]ombining trastuzumab, cisplatin, and paclitaxel for metastatic HER2-positive breast cancer particularly made sense because the combination satisfied the four principles of combination therapy." *Id.* at 45–49 (citing Ex. 1002 ¶¶ 125–130); *see also id.* at 38–39 (stating the principles include "non-cross resistant drugs with single-agent activity, differing mechanisms of action, and nonoverlapping toxicity") (quoting Ex. 1024, 130–31).

Petitioner asserts that an ordinary artisan would have had a reason to develop the combination of trastuzumab and paclitaxel without an anthracycline derivative, as required by challenged claim 16. Pet. 51–53. Petitioner argues that an ordinary artisan "would have limited use of anthracycline derivatives in treatment whenever possible" due to the cardiotoxicity issues with anthracycline derivatives. *Id.* at 51. In addition, according to Petitioner:

> [B]ecause 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; 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.)

Id. at 51–52. As a result, Petitioner contends that an ordinary artisan "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." *Id.*

With respect to the claim language "an amount effective to extend the time to disease progression in the human" (claims 1 and 16) and "effective amount" (claim 5), Petitioner argues that an ordinary artisan would have started with "the known amounts that were effective to extend the time to disease progression" in

amounts previously shown to effectively treat metastatic breast cancer. *Id.* at 49 (citing Ex. 1002 ¶ 132; Ex. 1020, 4–5 (effective doses of trastuzumab); Ex. 1012 (effective doses of paclitaxel)). "To the extent any modification to the amounts of the combination was necessary," Petitioner continues, an ordinary artisan "would have readily optimized the combination treatment to arrive at an amount that results in the claimed efficacy and safety parameters." *Id.* (citing Ex. 1002 ¶¶ 133–34; *see id.* at 50, n.16. Petitioner contends that "[s]uch optimization was routine in the art." *Id.* at 49–50 (citing Ex. 1002 ¶ 134; Ex. 1016,[14] 11, 13–14; Ex. 1001, 25:1–19, 43–54.).

Relying on the clinical efficacy and toxicity profiles of trastuzumab, trastuzumab with paclitaxel, paclitaxel with cisplatin, as well as the preclinical data showing a synergistic effect of trastuzumab with paclitaxel, Petitioner contends that there would have been reasonable expectation of success that the three-drug combination would have been safe and effective. *Id.* at 52–53 (citing, Ex. 1002 ¶¶ 117–35; Exs. 1011, 1012, 1014, 1019, 1020, 1033). Petitioner also argues that the Sliwkowski Declaration (Ex. 1009)[15] submitted during the prosecution does not negate the motivation to combine or a reasonable expectation of success. *Id.* at 53–62 (citing Ex. 1002 ¶¶ 140–55). Petitioner further asserts that secondary considerations do not support a conclusion of non-obviousness. *Id.* at 70–75 (citing Ex. 1002 ¶¶ 171, 175, 176, and 180).

Patent Owner counters that Petitioner has not established a reasonable expectation of success in achieving the claimed clinical results. Prelim. Resp. 2–3,

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[14] Excerpts from CLINICAL ONCOLOGY (Martin D. Abeloff et al., eds., Churchill Livingstone 1995). ("Abeloff"). Ex. 1016.

[15] Declaration of Mark X. Sliwkowski, Ph.D., executed October 15, 2009. Ex. 1009.

39–51. Patent Owner also contends that Petitioner has not shown an ordinary artisan would have avoided anthracyclines when pursuing the combination therapy of anti-ErbB2 antibody with a taxoid. *Id.* at 53–55. In addition, Patent Owner challenges Petitioner's assertions that taxoids had "proven efficacy against metastatic HER2-positive breast cancer in humans" (*id.* at 43; *see also* 51–52), defends the Sliwkowski Declaration (*id.* at 57–59), and argues that evidence of secondary considerations establish the non-obviousness of the challenged claims (*id.* at 56–58). Based on the current record, we find Petitioner's arguments more persuasive.

With respect to the claimed efficacy, we reiterate that the proper analysis of "extend the time to disease progression" is to compare the claimed combination treatment to no treatment. Section II(C), s*upra*. Baselga 1996 reports that, when treated with rhuMAb HER2, 11.6% of patients with metastatic breast cancer experienced a complete or partial remission, and 37% achieved minimal responses or stable disease. Ex. 1020, 9, 13. In Baselga 1996, "[t]ime to tumor progression was calculated from the beginning of therapy to progression," the same as how the '549 patent defines the term "time to disease progression." *Id.* at 4; *compare id.* at 7 *with* Ex. 1001, 29:4–5. According to Baselga 1996, the time to tumor progression for the patients with either minor or stable disease was of "unusually long durations" with a median of 5.1 months. Ex. 1020, 6, 7. On the present record, we determine that, compared with no treatment, anti-ErbB2 antibodies alone would extend the time to disease progression in patients with breast cancer.

Petitioner takes a different focus, arguing Seidman 1996 teaches that paclitaxel alone extends time to disease progression relative to no treatment. Pet. 50 n.16 (citing Ex. 1002 ¶¶ 137, 157 n.28; Ex. 1010). Petitioner asserts that the combination therapy satisfies the limitation of clinical efficacy, because treatment

with either trastuzumab or paclitaxel extends time to disease progression relative to no treatment, and an ordinary artisan "would not have expected the combination to change this." *Id.* (citing Ex. 1002 ¶¶ 137, 157 n.28). We find Petitioner's argument persuasive. Indeed, neither Patent Owner, nor our present reading of the prior art, suggest that combining a taxoid with rhuMAb HER2 would abrogate the effect of either therapeutic.

With respect to avoiding anthracyclines in the combination therapy as required by independent claim 16, we agree with Petitioner that irreversible cardiotoxicity of anthracyclines was well known at the priority date of the challenged claims. *See* Pet. 51 (citing Ex. 1002 ¶ 138; Ex. 1016, 29). Cardiotoxicity caused by anthracyclines is "a phenomenon associated with the total lifetime dose a patient receives." Ex. 1002 ¶ 138 (citing Ex. 1016, 29). Thus, we find reasonable Dr. Earhart's testimony that "[w]hile treating patients with anthracyclines is often unavoidable in the course of a patient's cancer treatment, limiting the total dose of an anthracycline is a goal." *Id.* (citing Ex. 1016, 26, 29). Yet, Petitioner concedes that "anthracycline derivatives were a first-choice therapy for metastatic breast cancer." *Id.* at 51. Thus, we determine that cardiotoxicity alone would not have motivated an ordinary artisan to avoid anthracyclines in treating breast cancer. *See* Prelim. Resp. 53–55.

But the record before us suggests that an ordinary artisan would not exclude anthracyclines from the combination therapy solely to avoid cardiotoxic side effects. Petitioner has shown there are other reasons to exclude anthracyclines in a treatment regimen, such as concerns with drug resistance. Pet. 51–52 (citing Ex. 1002 ¶ 138); *see* Ex. 1002 ¶¶ 84–88 (citations omitted). In particular, the prior art before us indicates that many patients with metastatic breast cancer would have previously been treated with, and become resistant to, first-line anthracycline

chemotherapeutics. *See, e.g.*, Ex. 1016, 1693; Ex. 1024,[16] 14–15; *see also* Ex. 1010, 1 (stating taxane has "demonstrated activity and safety . . . against anthracycline-refractory breast cancer"). On the present record, we find persuasive Dr. Earhart's testimony that:

> A person of ordinary skill in the art would have expected that many patients had previous anthracycline treatment, given that anthracyclines were a first-line therapy for breast cancer. (Ex. 1016 at 1693.) Therefore, particularly for patients who had already been treated with an anthracycline, it would have been obvious not to include the drug in the combination of trastuzumab and paclitaxel.

Ex. 1002 ¶ 138.

Accordingly, Petitioner has presented sufficient evidence, for purposes of instituting trial, to show that in considering prior therapy received, an ordinary artisan would have been motivated to treat patients having a prior history of anthracycline therapy with ErbB2-overexpressing breast cancer by administering a combination of an anti-ErbB2 antibody and a taxoid, and "in the absence of an anthracycline derivative" as set forth in claim 16.

We have considered, but do not find persuasive, other arguments presented by Patent Owner. For example, Patent Owner challenges Petitioner's characterization of Seidman 1996 as showing "proven efficacy [of paclitaxel] against metastatic HER2-positive breast cancer in humans." Prelim. Resp. 51 (citing Pet. 43). According to Patent Owner, Seidman 1996 "merely speculated" that HER-2 overexpression may confer sensitivity rather than resistance to taxanes, and that speculation was based on several "confounding variables." *Id.* We disagree with Patent Owner.

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[16] Arbuck et al., *Paclitaxel (Taxol) in Breast Cancer*, 8(1) HEMATOLOGY ONCOLOGY CLINICS NORTH AM. 121–40 (1994). Ex. 1024.

Seidman 1996 reports that for patients with metastatic breast cancer treated with paclitaxel response rates were 58.8% for HER-2 positive patients but only 38.7% for patients who did not overexpress HER-2. Ex. 1011. In fact, Seidman 1996 states that "stratified analysis controlling for confounding variables demonstrated the value of HER2 status in predicting good taxane response." *Id.* As a result, we find Petitioner's reliance on and characterization of Seidman 1996 reasonable. *See also* Ex. 1001, 3:52–56 (citing prior art reference as teaching that "the odds of HER2-positive patients responding clinically to treatment with taxanes were greater than three times those of HER2- negative patients").

Patent Owner appears to argue that Exhibit 2029, which states that "breast cancers that overexpress p185 [i.e., HER2] will not respond well to Taxol," teaches away from combining a taxoid with an anti-ErbB2 antibody to treat a patient with HER-2 overexpression. Prelim. Resp. 51–52 (citing Ex. 2029,[17] 1362). We are not persuaded. In an obviousness inquiry, we must analyze the prior art as a whole, and not individually. *See In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (explaining that the question is "whether there is something in the prior art as a whole to suggest the *desirability*, and thus the obviousness, of making the combination"). Other evidence of the record shows paclitaxel is effective in treating HER2-positive cancers (*see, e.g.*, Ex. 1011), demonstrates "strong synergy" of paclitaxel and an anti-ErbB2 antibody in human breast cancer xenografts (*see, e.g.*, Ex. 1010, 5; Ex. 1019; Ex. 1021), and suggests clinical trials of the combination therapy (*see, e.g.*, Ex. 1010, 5; Ex. 1020, 9). Weighing all

[17] Yu et al., *Overexpression of c-erbB-2/neu in Breast Cancer Cells Confers Increased Resistance to Taxol Via mdr-1-independent Mechanisms*, 13(6) ONCOGENE 1359–65 (1996). Ex. 2029.

evidence of the record,[18] we are not persuaded that the prior art as a whole teaches away from combining paclitaxel and an anti-ErbB2 antibody in treating HER2-positive cancers.

III. CONCLUSION

For the foregoing reasons, we find that Petitioner has offered sufficient evidence to institute an *inter partes* review. The information presented in the Petition and accompanying evidence establishes a reasonable likelihood that Petitioner would prevail in showing the unpatentability of independent claims 1, 5, and 16 of the '549 patent.

At this stage of the proceeding, the Board has not made a final determination as to the construction of any claim term or the patentability of any challenged claim. Thus, our view with regard to any conclusion reached in the foregoing could change upon consideration of Patent Owner's merits response and upon completion of the current record.

IV. ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted to determine whether claims 1–11 and 14–17 of the '549 Patent would have been obvious over the combination of Baselga 1996, Seidman 1996,

[18] Although evidence of secondary considerations, when present, must always be considered in determining obviousness (*see Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983), Patent Owner does not presently challenge Petitioner's assertion that secondary considerations do not support a conclusion of non-obviousness. *See* Pet. 70–75.

Pegram, and the 1995 TAXOL PDR entry, and the knowledge of a person of ordinary skill in the art;

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '196 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

PETITIONER:

Cynthia Lambert Hardman
GOODWIN PROCTER LLP
chardman@goodwinlaw.com

PATENT OWNER:

David L. Cavanaugh
Owen Allen
WILMER CUTLER PICKERING HALE AND DORR LLP
David.Cavanaugh@wilmerhale.com
Owen.Allen@wilmerhale.com

Adam Brausa
DURIE TANGRI LLP
brausa@durietangri.com