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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 IPR2017-01121
Patent 7,846,441 B1

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

YANG, Administrative Patent Judge.

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

INTRODUCTION

Celltrion, Inc. ("Petitioner")[1] filed a Petition requesting an *inter partes* review of claims 1–14 of U.S. Patent No. 7,846,441 B1 (Ex. 1001, "the '441 patent"). Paper 1 ("Pet."). Genentech, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 8 ("Prelim. Resp.").

For the reasons provided below, we determine Petitioner has satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). Because Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim, we institute an *inter partes* review of claims 1–14 of the '441 patent.

Related Proceedings

The '441 patent is the subject of a petition for an *inter partes* review filed by Hospira, Inc. IPR2017-00731, Paper 1. We denied institution in that case (*Hospira, Inc. v. Genentech, Inc.*, IPR2017-00731 (PTAB July 27, 2017) (Paper 19)), and Hospira filed a request for reconsideration (IPR2017-00731, Paper 21). The decision on the request is currently pending.

Petitioner has also filed IPR2017-01122, challenging certain claims of U.S. Patent No. 7,892,549 ("the '549 patent"), a patent in the same family of the '441 patent. Pet. 12; Paper 4, 3. Previously, Hospira filed IPR2017-00737 and IPR2017-00739, challenging claims of the '549 patent. IPR2017-00737, Paper 1; IPR2017-00739, Paper 1. We denied institution in one (*Hospira, Inc. v. Genentech, Inc.*, IPR2017-00739 (PTAB July 27, 2017) (Paper 16)), but instituted trial in another (*Hospira, Inc. v. Genentech, Inc.*,

[1] Petitioner identifies Celltrion Healthcare Co., Ltd. and Teva Pharmaceuticals International GmbH as additional real parties-in-interest. Pet. 12.

IPR2017-00737 (PTAB July 27, 2017) (Paper 19)).

The '441 Patent

The '441 patent relates to the treatment of disorders characterized by the overexpression of ErbB2. Ex. 1001, Abstract, 1:11–12.

According to the Specification, "human ErbB2 gene (erbB2, also known as her2, or c-erbB-2), which encodes a 185-kd transmembrane glycoprotein receptor ($p185^{HER2}$) related to the epidermal growth factor receptor (EGFR), is overexpressed in about 25% to 30% of human breast cancer." *Id.* at 1:23–27. Before the '441 patent, a recombinant humanized anti-ErbB2 monoclonal antibody (a humanized version of the murine anti-ErbB2 antibody 4D5, also referred to as rhuMAb HER2, trastuzumab, or HERCEPTIN®) had been approved to treat patients with ErbB2-overexpressing metastatic breast cancers. *Id.* at 3:34–39.

According to the '441 patent, ErbB2 overexpression was known to be linked to resistance to chemotherapeutic regimens, including anthracyclines. *Id.* at 3:41–49. On the other hand, "the odds of HER2-positive patients responding clinically to treatment with taxanes were greater than three times those of HER2-negative patients." *Id.* at 3:51–54.

The '441 patent states that

> [T]he invention concerns a method for the treatment of a human patient susceptible to or diagnosed with a disorder characterized by overexpression of ErbB2 receptor comprising administering a therapeutically effective 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 4:4–11.

Illustrative Claim

Among the challenged claims, claims 1, 11, 13, and 14 are independent. Claim 1 is representative and is reproduced below:

> 1. A method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by overexpression of ErbB2 receptor, comprising administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence and a taxoid, in the absence of an anthracycline derivative, to the human patient in an amount effective to extend the time to disease progression in said human patient, without increase in overall severe adverse events.

Asserted Ground of Unpatentability

Petitioner asserts that claims 1–14 of the '441 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Baselga 1996,[2] Seidman 1996,[3] and the 1995 TAXOL PDR entry,[4] in view of the knowledge of a person of ordinary skill in the art. Pet. 24.

In support of its patentability challenges, Petitioner relies on the Declaration of Dr. Robert Earhart. (Ex. 1002).

ANALYSIS

Claim Construction

In an *inter partes* review, the Board interprets a claim term in an

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[2] 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 J. CLIN. ONCOL. 737–44 (1996) (Ex. 1020).

[3] Seidman et al., *Over-Expression and Clinical Taxane Sensitivity: A Multivariate Analysis in Patients with Metastatic Breast Cancer (MBC)*, 15 PROC. AM. SOC. CLIN. ONCOL. 104, Abstract 80 (Mar. 1996) (Ex. 1011).

[4] Taxol® (Paclitaxel) for Injection Concentrate, PHYSICIANS' DESK REFERENCE, 682–85 (49th ed. 1995) (Ex. 1012).

unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Each challenged claim, either explicitly or through dependency, recites "extend the time to disease progression in said human patient, without increase in overall severe adverse events." Petitioner argues this is "a relative term," and proposes that "the appropriate comparison is to compare the claimed combination treatment to treatment with a taxoid alone." Pet. 21 (citing Ex. 1002 ¶ 112). According to Petitioner, in the Example, 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, 29:9–30:25). Petitioner, however, acknowledges that during prosecution, the applicant asserted that the comparison is between the claimed combination treatment and no treatment. *Id.* at 22 (citing Ex. 1004, 416).

Indeed, during prosecution, the examiner rejected then-pending claims as indefinite under 35 U.S.C. § 112. Ex. 1004, 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. 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). In the next office action, the examiner withdrew the rejection. *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, we determine that the proper analysis of the term "extend the time to disease progression in said human patient, without increase in overall severe adverse events" is to compare the claimed combination treatment to no treatment.[5] *See also Hospira, Inc. v.*

[5] We recognize Petitioner has focused the unpatentability arguments based

Genentech, Inc., IPR2017-00737 (PTAB July 27, 2017), Paper 19, 12 (construing the term the same way).

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 any other claim terms. We, however, acknowledge the parties' facially different proposed constructions of the term "response rate." *See* Pet. 22 (stating the term "means the percentage of patients whose disease responds to treatment") (citing Ex. 1001, 28:36–67, 29:11–30:20); Prelim. Resp. 37 (arguing the term means "the percentage of patients whose tumor is reduced in size by a specified amount following treatment") (citing Ex. 1001, 28:46–65). We first note that during prosecution, the applicant stated that "response rate" is "an art-recognized term." Ex. 1004, 416. Also, the term only appears in claim 10, which depends from claim 1. 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 claim 1. *See* 35 U.S.C. § 314(a). Thus, it is unnecessary for us to construe the term "response rate." To the extent an explicit construction facilitates solidification of the parties' respective position, and to the extent the proposed constructions are in fact different, we provisionally adopt Patent

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on a different claim construction, one that Patent Owner does not dispute. Prelim. Resp. 38. To the extent necessary, Petitioner is reminded that our Rule provides an opportunity to, within one month of the date the trial is instituted, request for the authorization to file a motion to submit supplemental information that is "relevant to a claim for which the trial has been instituted." *See* 37 C.F.R. § 42.123(a).

Owner's proposed construction.

Disclosures of Prior Art

Baselga 1996

Baselga 1996 reports the results of a phase II clinical trial in patients with ErbB2-overexpressing metastatic breast cancer who had received extensive prior therapy. Ex. 1020, 3. According to Baselga 1996, "patients were selected to have many sites of metastatic involvement, one of the most dire prognostic characteristics regarding response to therapy." *Id.* at 7. Each patient received a loading dose of 250 mg of intravenous rhuMAb HER2, followed by 10 weekly doses of 100 mg. *Id.* According to Baselga '96, "[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.* Baselga 1996 reports an 11.6% remission rate. *Id.* at 7. In addition, "37% of patients achieved minimal responses or stable disease." *Id.*

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

Seidman 1996

Seidman 1996 teaches that, among metastatic breast cancer patients treated with paclitaxel, 58.8% HER2-positive patients responded to the treatment, whereas only 38.7% patients with breast cancer that did not overexpress the HER2 protein responded. Ex. 1011. Seidman 1996

suggests that HER2-overexpression "seems to confer sensitivity" to treatment with taxanes, "in spite of a positive correlation of HER2 positivity with poor prognostic features." *Id.*

1995 TAXOL PDR

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." Ex. 1012, 6. 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.*, 8.

Level of Ordinary Skill in the Art

Petitioner argues that, to analyze the obviousness of the '441 patent, a person of ordinary skill in the art "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*. (citing Ex. 1002, ¶ 29). Patent Owner contends that an ordinary artisan is "a clinical or medical oncologist specializing in breast cancer with several years of experience with breast cancer research or clinical trials." Prelim. Resp. 36–37.

We do not discern an appreciable difference in the parties' respective definitions of the level of ordinary skill in the art, and any perceived distinction does not impact our Decision. Indeed, both parties contend that a

person of ordinary skill in the art would have had experience with breast-cancer research and treatment. On this record, we adopt Patent Owner's definition of the level of ordinary skill in the art. *See also Hospira, Inc. v. Genentech, Inc.*, IPR2017-00737 (PTAB July 27, 2017), Paper 19, 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)).

Asserted Obviousness Ground

Petitioner contends that claims 1–14 would have been obvious over the combination of Baselga 1996, Seidman 1996, and the 1995 TAXOL PDR entry, in view of the knowledge of a person of ordinary skill in the art. Pet. 24–74. Based on the current record, we determine Petitioner has established a reasonable likelihood that it would prevail on this assertion at least in relation to claim 1.

Petitioner refers to Baselga 1996 for 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 (citing Ex. 1020, 7). Petitioner argues that before the priority date of the challenged claims, an ordinary

artisan would have had a reason "to treat HER2-positive breast cancer patients with a combination of trastuzumab and paclitaxel." *Id.* at 44. According to Petitioner, this is because Baselga 1996 suggests the combination therapy of rhuMAb HER2 and paclitaxel (*id.* at 43–44 (citing Ex. 1020, 9)), and because Seidman 1996 teaches 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.* at 34 (citing Ex. 1011), 44 (citing Ex. 1011)).

To bolster its position, Petitioner points to "preclinical data reporting synergy between trastuzumab and paclitaxel in mouse xenografts." *Id.* at 45 (citing Exs. 1019, 1021). Petitioner further contends that "[c]ombining trastuzumab and paclitaxel for metastatic HER2-positive breast cancer particularly made sense because the combination satisfied the four principles of combination therapy." *Id.* at 45–47 (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 (emphasis added by Petitioner)).

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 in the challenged claims. Pet. 50–51. 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.* 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, ¶ 137; 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, ¶ 137.)

Id. at 51. 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.*

Each challenged claim recites "an effective amount to extend the time to disease progression in said human patient, without increase in overall severe adverse events." Petitioner argues that an ordinary artisan would have started with "the known amounts that were effective to extend the time to disease progression of each drug when used as monotherapy." *Id.* at 47 (citing Ex. 1002 ¶ 131); *see also id.* at 48 (citing 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," and "[s]uch optimization was routine in the art." *Id.* (citing Ex. 1002 ¶¶ 132–34; Ex. 1016, 11, 13–14).

Relying on the clinical efficacy and toxicity profile of trastuzumab and paclitaxel, and the preclinical data showing a synergistic effect of the two therapeutics, Petitioner contends that there would have been reasonable expectation of success of the combination therapy with trastuzumab and

paclitaxel, and without anthracycline derivatives. *Id.* at 52 (citing Ex. 1002 ¶¶ 117–35; Exs. 1011, 1019, 1020). In addition, Petitioner argues that the Sliwkowski Declaration (Ex. 1009)[6] submitted during the prosecution does not negate the motivation to combine or a reasonable expectation of success. *Id.* at 53–61 (citing Ex. 1002 ¶¶ 138–53). Petitioner further asserts that secondary considerations do not support a conclusion of non-obviousness. *Id.* at 69–74 (citing Ex. 1002 ¶¶ 90, 175–77, 179).

Patent Owner counters that Petitioner has not established a reasonable expectation of success in achieving either the claimed clinical efficacy or the claimed clinical safety. Prelim. Resp. 2–3, 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 52–54. In addition, Patent Owner challenges Petitioner's assertions that taxoids had "proven efficacy against metastatic HER2-positive breast cancer in humans" (*id.* at 55–56), 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 59–65). Based on the current record, we find Petitioner's arguments more persuasive.

First, on 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. *Supra* at 6. 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

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

minimal responses or stable disease. Ex. 1020, 7. In Baselga 1996, "[t]ime to tumor progression was calculated from the beginning of therapy to progression," the same as the '441 patent defines the term "time to disease progression." *Compare id.* at 4 *with* Ex.1001, 29:1–2. According to Baselga 1996, the median time to progression for the patients with either minor or stable disease was "unusually long durations" 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. 49 n.18 (citing Ex. 1002 ¶¶ 136, 155 n.28; Ex. 1010). Petitioner asserts that the combination therapy satisfies the limitation of clinical efficacy, because each of trastuzumab and 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 ¶¶ 136, 155 n.28). We find Petitioner's argument persuasive. Indeed, neither Patent Owner, nor our present reading of the prior art, suggests that combining a taxoid with rhuMAb HER2 would abrogate the effect of either therapeutics.

Second, on the claimed safety, we, again, repeat that the proper analysis of "without increase in overall severe adverse events" is to compare the claimed combination treatment to no treatment. *Supra* at 6. We observe that an adverse event is "[a]n unexpected medical problem that happens during treatment with a drug or other therapy. Adverse events do not have to be caused by the drug or therapy, and they may be mild, moderate, or

severe." Ex. 3001.[7]

Dr. Earhart testifies that "[a] person of ordinary skill in the art would have also expected that the trastuzumab/paclitaxel combination would not have resulted in an overall increase in severe adverse events compared to no treatment, because a patient with untreated HER2-positive cancer will experience more overall severe adverse events due to the underlying disease itself, compared to severe adverse events experienced due to treatment." Ex. 1002 ¶ 155 n.28; *see also* Pet. 49 n.18 (the same). Patent Owner's argument appears to support Dr. Earhart's testimony. As Patent Owner points out, before the priority date of the challenged claims, "a diagnosis of HER2-positive breast cancer was effectively a death sentence; even with prior art treatments, the disease frequently recurred and rapidly spread. In 1996, HER2-positive breast cancer patients had an average life expectancy of only 18 months." Prelim. Resp. 1; *see also* Ex. 1020, 6 (teaching HER2-positive cancers are associated with poor prognoses). Based on the current record, we find Dr. Earhart's testimony and Petitioner's argument on the clinical safety of the combined therapy persuasive.

Third, on avoiding anthracyclines in the combination therapy, Petitioner is correct that irreversible cardiotoxicity of anthracyclines was well known at the priority date of the challenged claims. *See* Pet. 50 (citing Ex. 1002 ¶ 137; Ex. 1016, 813). Cardiotoxicity caused by anthracyclines is "a phenomenon associated with the total lifetime dose a patient receives." Ex. 1002 ¶ 137 (citing Ex. 1016, 29). Thus, we find reasonable

[7] NCI [National Cancer Institute] Dictionary of Cancer Terms, entry for "adverse event."

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. 52–54.

But an ordinary artisan does not have to 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 (citing Ex. 1002 ¶ 137). In particular, the prior art of record 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, 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 ¶ 137.

In sum, 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."

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. 55 (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.

Seidman 1996 reports that for patients with metastatic breast cancer, when treated with paclitaxel, 58.8% of HER-2(+) patients and 38.7% in HER-2(–) patients responded. 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.

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. 56 (citing Ex. 2029,[8] 1362). We are not persuaded. In an obviousness inquiry, we

[8] Yu et al., *Overexpression of c-erbB-2/neu in Breast Cancer Cells Confers Increased Resistance to Taxol Via mdr-1-independent Mechanisms*, 13

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

We acknowledge the evidence of secondary considerations and Patent Owner's argument that such evidence establishes the non-obviousness of the challenged claims. Prelim. Resp. 59–65. Indeed, evidence of secondary considerations, when present, must always be considered in determining obviousness. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983). Here, most of the secondary-considerations evidence Patent Owner relies on is first presented together with the Preliminary Response (*see* Prelim. Resp. 59–65 (citing Exs. 2004, 2012, 2018, 2033, 2034, 2035), and Petitioner has not yet had an opportunity to respond to those evidence and arguments. Thus, in this case, a better course of action is to permit the parties to fully develop the record during trial before further weighing the alleged evidence of secondary considerations.

ONCOGENE 1359–65 (1996).

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 claim 1 of the '441 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.

ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted to determine whether claims 1–14 of the '441 patent would have been obvious over the combination of Baselga 1996, Seidman 1996, 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.

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