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

Paper 19
Entered: July 27, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00737
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

Hospira, Inc. ("Petitioner")[1] filed a Petition requesting an *inter partes* review of claims 1–17 of U.S. Patent No. 7,892,549 B2 (Ex. 1001, "the '549 patent"). Paper 1 ("Pet."). Genentech, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 9 ("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 1–17 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 1–11 and 14–17 of the '549 Patent in IPR2017-00739. The related '441 Patent is presently the subject of IPR2017-00731.

---

[1] Petitioner identifies Pfizer, Inc. as "the real party in interest for Petitioner." Paper 10, 2.

Petitioner has also filed IPR2017-00804 and IPR2017-00805 involving the 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.

Petitioner further directs us to invalidation and revocation proceedings involving European Patent EP 1,037,926, which, like the '549 Patent at issue here, claims benefit of priority to the '346 application. *See* Pet. 1–2 (citing Ex. 1004, 1026, and 1049).

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, 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 '97 (Ex. 1007)).

Although "ErbB2 overexpression is commonly regarded as a predictor of 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 '96 (Ex. 1005)). 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 '94 (Ex. 1006)).

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 amount[[2]] 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").

[2] The Specification defines a "therapeutically effective amount" of the combination as "an amount having an antiproliferative effect," which can be measured by assessing the time to disease progression (TTP) or determining the response rates (RR)." *Id*. at 10:41–50.

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, designated “H”. *Id*. 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 1–17. Pet. 4. 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, claims 12, 13, and 14, respectively, specify that this "further therapeutic agent" is another anti-ErbB2 antibody, a vascular endothelial growth factor (VEGF), or "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 Grounds of Unpatentability*

Petitioner asserts the following grounds of unpatentability (Pet. 7):

Ground	**Claim(s)**	**References**	**Basis**
1	1–11 and 14–17	Baselga '97[3] and Gelmon[4]	§ 103
2	12	Baselga '97, Gelmon, and Drebin[5]	§ 103
3	13	Baselga '97, Gelmon, and Presta[6]	§ 103

[3] Baselga et al., 11(3) (Suppl. 2) ONCOLOGY 43–48 (1997). Ex. 1007.
[4] Gelmon et al., 14(4) J. CLIN. ONCOL. 1185–91 (1996). Ex. 1025.
[5] Drebin et al., 2(3) ONCOGENE 273–77 (1988). Ex. 1010.
[6] Presta et al., 57(20) CANCER RES. 4593–99 (1997). Ex. 1012.

Ground	Claim(s)	References	Basis
4	1–11 and 14–17	Baselga '96,[7] Baselga '94,[8] and Gelmon	§ 103
5	12	Baselga '96, Baselga '94, Gelmon, and Drebin	§ 103
6	13	Baselga '96, Baselga '94, Gelmon, and Presta	§ 103

Petitioner also relies on Ex. 1011, the declaration of its technical expert, Allan Lipton, MD.

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 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

[7] Baselga et al., 14(3) J. CLIN. ONCOL. 737–44 (1996). Ex. 1005.
[8] Baselga et al., 13 Proc. AM. SOC. CLIN. ONCOL. 63 (Abstract 53) (1994). Ex. 1006.

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 employing "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*

Petitioner argues that a person of ordinary skill in the art as of the effective filing date of the '549 patent "would be a clinical or medical oncologist

specializing in breast cancer with several years of experience with breast cancer research or clinical trials." Pet. 6 (citing Ex. 1011 ¶¶ 15–17; Ex. 1004 ¶¶ 29–31). Patent Owner does not dispute Petitioner's proposed definition. Prelim. Resp. 36. Based on our review of the '549 Patent, the cited art, and the testimony of Dr. Lipton, we adopt Petitioner's definition for the purposes of this Decision. We further note that 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. "*administering a combination*"

Patent Owner proposes that we interpret "administering a combination" as requiring "a single treatment regimen in which the patient receives all drugs that are part of the claimed combination" and sets forth a reasoned explanation of why this definition is supported by the Specification and claim language. Prelim. Resp. 36–37. Patent Owner argues, for example, that "the absence of an anthracycline derivative" language in dependent claims 16 and 17, "would make no sense if 'administering a combination' included drugs received as part of a different treatment regimen [because] [i]n the '549 patent's working example, patients were administered the combination of the anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative only if they had 'received any anthracycline therapy in the adjuvant setting'" *Id.* at 37). For the purpose of this Decision, and based on the present record, we adopt Patent Owner's presently unopposed argument and proposed 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."

2. "*in an amount effective to extend the time of disease progression in the human patient*"

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).

Although Petitioner proposes no express construction of any claim term (*see* Pet. 14), it reasonably asserts that the language of claims 1 and 16 "purports to capture ***any*** 'amount effective to extend the time to disease progression'" (*id*. at 29 (citing Ex. 1011 ¶ 83)) and that, "'an amount effective to extend the time to disease progression would be an 'effective amount'" as set forth in claim 5 (*id*. at 34 (citing Ex. 1011 ¶¶ 98–99); *id*. at 39). Patent Owner has not disputed these assertions but merely states that the language of claim 5 requires "clinically 'effective' results." *See* Prelim. Resp. 44.

The claim language "an amount effective to extend the time to disease progression" implies that time to disease progression is extended in relation to some metric, but we do not discern that the claims, standing alone, identify the intended comparator. The facial ambiguity of this phrase was expressly addressed by the Examiner during the prosecution leading to the issuance of the '549 Patent. In particular, during the prosecution of the '649 Application (the direct predecessor to the '842 Application, from which the '549 Patent issued), the Examiner rejected then-pending claims under 35 U.S.C. § 112, second paragraph because:

> 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?

Ex. 3001,[9] 3–4 (OA dated 7/17/01). Applicants responded that

> the expression[] "extend the time to disease progression". . . [is] clear from the specification (see, in particular, page 15, lines 15-17; and pages 42-43) 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 17–18 (Response dated 1/17/2001); *see* Ex. 1021, 19 (15:12–17), 46–47 (42–43). The Examiner stated that "[a]ll claims were allowable" in the next office action. Ex. 3001, 24 (OA dated 3/27/2002) (suspending prosecution due to potential interference); *see also id*. at 28 (OA dated 8/12/2003) (new grounds of rejection not relating to the phrase "extend the time to disease progression").

We further note that the language at issue references administration "to the human patient," where "the human patient" is identified in the preamble as one having "breast cancer that overexpresses ErbB2 receptor." "When limitations in the body of the claim rely upon and derive antecedent basis from the preamble, then the preamble may act as a necessary component of the claimed invention." *Eaton Corp. v. Rockwell Int'l Corp.,* 323 F.3d 1332, 1339 (Fed. Cir. 2003). In the present case, we read the preamble as defining and, thus, limiting "the human patient" recited in the body of the claim.

In view of the above, and for the purpose of this Decision, 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. We further construe the

[9] Excerpts of prosecution history of US Application No. 09/208,649.

language "an effective amount" of independent claim 5 as encompassing "an amount effective to extend the time to disease progression in the human patient."

D. *Grounds 1–3*

In Ground 1, Petitioner challenges claims 1–11 and 14–17 as obvious under 35 U.S.C. § 103 based on Baselga '97 and Gelmon. In Grounds 2 and 3, respectively, Petitioner further asserts Drebin (claim 12) and Presta (claim 13).

1. *Overview of Baselga '97 (Ex. 1007)*[10]

Baselga '97 reviews the relationship and clinical implications of HER2 overexpression and chemotherapeutics, most particularly taxanes, in the treatment of breast cancers. Baselga '97 states that HER2 positive tumors "have increased resistance to adjuvant CMF (cyclophosphamide, methotrexate, and fluorouracil)-based therapy and, conversely, increased dose-response effects to an anthracycline-containing regimen." Ex. 1007, 6. Moreover, the "[a]vailable data . . . suggest that HER2 overexpression may influence the response to paclitaxel in patients with metastatic breast cancer and that anti-HER2 monoclonal antibodies significantly increase the antitumor activity of paclitaxel in vitro and in vivo." *Id*.

Baselga '97 teaches that "[t]he murine monoclonal antibody (MoAb) 4D5, directed against the extracellular domain of $p185^{HER2}$ (ECD^{HER2}), is a potent inhibitor of in vitro growth and, in xenograft models, of human breast cancer cells overexpressing HER2." *Id*. at 7. For example, in a mouse model using HER2-expressing BT-474 cell implants, Baselga '97 states:

---

[10] In IPR2017-00731 we declined to revisit the Examiner's determination that Baselga '97 was not prior art with respect to the two-drug combination treatment claimed in the '441 patent. *See* IPR2017-00731, Paper 19, 7–8, 10, n.5. With respect to the three-drug combination treatments of the '549 claims at issue here, however, Applicants did not antedate Baselga '97 during prosecution and Patent Owner does not contest Petitioner's assertion that Baselga '97 is prior art.

> Therapy with MoAb 4D5 alone produced a 35% growth inhibition, and paclitaxel alone resulted in a 35% growth inhibition when compared with animals treated with a control MoAb. The treatment with paclitaxel plus 4D5 resulted in major antitumor activity, with 93% inhibition of growth. This result was markedly better than an equipotent dose of doxorubicin (10 mg/kg IP) and 4D5 (70% inhibition). In addition, paclitaxel combined with 4D5 resulted in the disappearance of well-established xenografts.

Id. at 9.

According to Baselga '97, because the potential for immunogenic response limits the clinical application of murine antibodies such as 4D5, Genentech scientists developed a recombinant, humanized version of this antibody, rhuMoAb HER2, "to facilitate further clinical investigations." *Id*. at 44, 46. Phase II clinical trials have shown that rhuMoAb HER2, alone, "is clinically active in patients who have metastatic breast cancers that overexpress HER2 and have received extensive prior therapy" and further suggest that the antibody may be synergistic in combination with cisplatin therapy. *Id*. at 9–10. In addition:

> Results from the phase II studies and the activity of rhuMoAb HER2 against xenografts when given in combination with doxorubicin and paclitaxel have been encouraging. These positive results have led to the design of a phase III multinational study of chemotherapy in combination with rhuMoAb HER2 in patients with HER2-overexpressing breast tumors who have not received prior chemotherapy for metastatic disease.

Id. at 10. "The main goal of this study is to determine whether the addition of this anti-HER2 antibody increases the time to disease progression compared with the group of patients treated with antibody alone [sic., chemotherapy alone]." *Id*.; *see, e.g, id*. at Figure 2 (showing randomization to either chemotherapy alone ("AC/Paclitaxel") or chemotherapy "+ rhuMab HER2"); *see also id*. ("The study end point is time to disease progression.").

Treatment consists of either cytotoxic chemotherapy or chemotherapy plus treatment with rhuMoAb HER2. *Id*. at 10. The chemotherapy regimen is selected based on whether the patients have been previously treated with anthracyclines (e.g., doxorubicin or epirubicin). *Id*. Patients that have not previously been treated with anthracyclines are administered a combination of cyclophosphamide and doxorubicin or epirubicin, whereas patients that have received anthracycline therapy in the adjuvant setting are treated with paclitaxel. *Id*. Besegla '97 notes that "[b]ecause anthracyclines are widely used in the adjuvant setting, it is likely that a significant number of patients will be treated with paclitaxel ± rhuMoAb HER2." *Id*. Baselga '97 describes the phase III trial as "ongoing" and presents no results from this study. *Id*.[11]

2. *Overview of Gelmon (Ex. 1025)*

Gelmon states that, "Phase II studies have shown paclitaxel to be an active single agent in metastatic breast cancer, with reported response rates of 17% to 62% . . . . Promising results have also been reported with combinations of paclitaxel with other active agents such as doxorubicin, cyclophosphamide, and edatrexate." Ex. 1025 at 9. "We were also interested in combining [paclitaxel] with a non-cross-resistant drug with a different spectrum of toxicity. Cisplatin seemed to be an appropriate choice." *Id*. Accordingly, Gelmon presents the results of a Phase I/II clinical study designed

> (1) to determine the toxicity of paclitaxel and cisplatin in a biweekly schedule, (2) to establish the maximum-tolerated dose of paclitaxel in combination with a fixed dose of cisplatin (60 mg/m^2) for patients with metastatic breast cancer, (3) to determine the feasibility of repeated

[11] As pointed out by Petitioner, the results of the Phase III clinical trial discussed in Baselga '97 are disclosed in the '549 Patent. *See* Pet. 8–9.

> biweekly administrations, and (4) to evaluate the activity of this combination in this disease setting.

Id. at 10.

According to Gelmon, "[a]ll but two of the women in our trial had been treated with previous adjuvant chemotherapy, and 23 of 29 patients had previous exposure to anthracyclines." *Id*. at 13. Of the 27 patients assessed for efficacy, three showed a complete response with a time to disease progression of 110 to 200 days, and 20 showed a partial response with a time to disease progression of 96 to 377+ days. *See, e.g*., *id.* at Abstract. Overall, patients treated with the paclitaxel/cisplatin regimen showed an overall response rate of 85% and a median time to disease progression of 7.1 months. *Id*. Gelmon concludes that "Biweekly paclitaxel and cisplatin is an active combination in the treatment of metastatic breast cancer, including for patients with previous exposure to anthracyclines." *Id*.

3. *Overview of Drebin (Ex. 1010)*

Drebin discloses that administering combinations of anti-ErbB2 antibodies "reactive with two distinct regions on the p185 molecule" in a mouse model, "resulted in synergistic anti-tumor effects and complete eradication of tumors." Ex. 1010, Abstract, 5. Drebin concludes that antibodies specific for human p185 may "find application as adjuvant therapy for diseases like breast cancer." *Id*. at 7.

4. *Overview of Presta (Ex. 1012)*

Presta describes the preparation of recombinant, humanized anti-VEGF antibodies that inhibit VEGF-induced proliferation of endothelial cells in vitro and the growth of breast carcinoma cell tumors in a mouse model. *See, e.g.,* Ex. 1012, abstract, 11. According to Presta, "[t]his humanized MAb is suitable for clinical trials to test the hypothesis that inhibition of VEGF action is an effective strategy for the treatment of cancer and other disorders in humans." *Id*. at 8.

5. *Analysis*

Petitioner has provided a claim-by-claim explanation for the basis of its contention that claims 1–11 and 14–17 are obvious under 35 U.S.C. § 103 based on Baselga '97 and Gelmon and that claims 12 and 13 are obvious further in view of Drebin and Presta, respectively. Pet. 25–43. In short, Petitioner argues that "[e]very component of the claimed three-drug combination was known in the prior art." Pet. 15.

According to Petitioner:

> Anti-ErbB2 antibodies, paclitaxel, and cisplatin had all been used in human patients in the prior art, and two-drug combinations of each of them were shown to be synergistic. Drug combinations generally, including two- and three- agent combinations, were routinely used to fight cancer, including breast cancer. And it was well known that combination chemotherapies were superior to single agent therapies. Combinations, like anti-ErbB2 antibodies, paclitaxel, and cisplatin, acting on different and complementary pathways were known to have a greater probability of exhibiting synergy without resulting in drug resistance or enhanced toxicity.

Id. at 17 (internal citations omitted). We find Petitioner's argument persuasive.

Further, as set forth in section II(D)(1),(2), the combination of Baselga '97 and Gelmon teaches the clinical efficacy of anti-ErbB2 antibodies in treating HER2-positive breast cancer; that paclitaxel in combination with another chemotherapeutic compound is clinically active in treating metastatic breast cancer; that anti-ErbB2 antibodies are synergistic with paclitaxel in inhibiting tumor growth in a mouse model of HER2-positive breast cancer; and that an on-going clinical trial involves the treatment of HER2-positive breast cancer with a combination of anti-ErbB2 antibodies and paclitaxel. On the present record, we agree with Petitioner that "[t]he thought to combine these known treatments was nothing more than the exercise of routine skill." *Id*. at 15.

Focusing on the two-drug combination of anti-ErbB2 antibodies and a taxoid, Patent Owner argues that "[t]he '549 Specification contains the ***first*** disclosure of clinical results showing that combination therapies that include an anti-ErbB2 antibody and a taxoid are effective at extending the time to disease progression in patients with HER2-positive breast cancer," whereas, "***[n]one*** of Petitioner's cited references disclose results for that clinical outcome." Prelim. Resp. 1–2. Thus, according to Patent Owner, "Petitioner has failed to show that a person of ordinary skill would have had a reasonable expectation of success in achieving the clinical efficacy results that the challenged claims require." *Id*. at 3–4.

We do not find Patent Owner's arguments persuasive in light of our construction of the claim terms "in an amount effective to extend the time to disease progression" of independent claims 1 and 16, or the more inclusive term, "an effective amount," of independent claim 5. *See* section II(C)(1), above. In particular, Baselga '97 discloses that anti-ErbB2 antibodies (rhuMAb HER2) alone are clinically active in patients with HER2-positive breast cancer, and that clinical trials with those antibodies in combination with chemotherapy agents (including paclitaxel) were underway. *See* section II(D)(1), *supra*. Gelmon similarly discloses that paclitaxel is active as a single agent in metastatic breast cancer, but exhibits advantageous, if not synergistic, results in combination with cisplatin. *See* section II(C)(2), *supra*; Ex. 1011 ¶¶ 58–60.

On the present record, Patent Owner does not dispute that anti-ErbB2 antibodies alone extend the time to disease progression in patients with breast cancer. According to Petitioner's expert, Dr. Lipton, "since rhuMAb HER2 on its own extends the time to disease progression, other than trace administration of a taxoid and a further growth inhibitory agent, nothing more is required by claim 1 to

meet this limitation." Ex. 1011 ¶ 84. Neither Patent Owner, nor our present reading of the prior art, suggest that the addition of paclitaxel and/or a further growth inhibitory or therapeutic agent to a rhuMAb HER2 treatment regimen would abrogate the chemotherapeutic effect of anti-ErbB2 antibodies.

Patent Owner further argues that the prior art teaches away from the combination of anti-ErbB2 antibodies and a taxoid because "some scientists expressed doubt that taxoids could be used to treat HER2-positive patients," and "Petitioner admits that [Gelmon] . . . teaches that 'HER2 positive breast cancer patients are ***resistant*** to . . . paclitaxel.'" Prelim. Resp. 4, 16, 17 (quoting Pet. 28, 46–47). In context, the passage from the Petition quoted by Patent Owner reads: "A POSITA reading Gelmon '96 would understand that HER2 positive breast cancer patients are resistant to both paclitaxel and cisplatin therapies, *but looking to Baselga '97 would know that rhuMAb HER2 serves to sensitize HER2 positive tumors to both therapies*." Pet. 28, 46–47.[12] Taken in context, we do not read this passage as evidence of teaching away.

[12] Although Patent Owner disputes that either Baselga '97 or Baselga '96 "teach that treatment with an anti-ErbB2 antibody 'serves to sensitize HER2 positive tumors to both therapies,'" we note that Baselga '96 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. 1005 at 15), and that Baselga '97 teaches "that HER2 overexpression may influence the response to paclitaxel in patients with metastatic breast cancer and [] anti-HER2 monoclonal antibodies significantly increase the antitumor activity of paclitaxel in vitro and in vivo" (Ex. 1007, 43). We further note that the inventors of the '549 Patent admit that Baselga '94 demonstrates that anti-ErbB2 antibodies "enhance the activity of paclitaxel (TAXOL®)" in a mouse model of HER2-postitive breast cancer. *See* Ex. 1001, 3:56–61.

Moreover, while some scientists may have expressed doubts regarding the treatment of HER2-positive cancers with paclitaxel alone, that must be weighed against the evidence of treatment of HER2-positive cancers in vitro and in vivo using paclitaxel *in combination* with other therapeutic agents. Basegla '97's description of an ongoing clinical trial involving the combination of anti-ErbB2 antibodies and paclitaxel in HER2 positive breast cancer patients, for example, is inconsistent with any suggestion that the art taught away from such combinations.

Independent claim 16 and its dependent claim 17 differ from claims 1–15 in requiring the administration of an anti-ErbB2 antibody, a taxoid, and a further growth inhibitory agent "in the absence of an anthracycline derivative." To account for this limitation, Petitioner argues that researchers would have avoided combinations with anthracyclines due to the well-known risk of cumulative cardiotoxicity. Pet. 7–8; *see* Ex. 1011 ¶ 33. Noting that Baselga '97 and Gelmon teach some combinations that do not include anthracyclines, Petitioner concludes that "a POSITA reading Baselga '97 in view of Gelmon '96 would not be motivated to combine rhuMAb HER2, a taxoid, and an anthracycline derivative and in fact, would be motivated not to do so due to the known cardiotoxic effects of anthracyclines." Pet. 39–40 (citing Ex. 1011 ¶¶ 125–28). Patent Owner counters that Petitioner has not shown that an ordinary artisan would have avoided anthracyclines when pursuing anti-ErbB2 antibody combination therapies. Prelim. Resp. 17–19, 51–54.

Petitioner has shown that cardiotoxicity of anthracyclines was well known as of the filing date of the '549 Patent (*see, e.g.*, Ex. 1042[13]), yet concedes that

[13] Shan et al., *Anthracycline-Induced Cardiotoxicity*, 125(1) ANN. INTERN. MED. 47–58 (1996).

anthracyclines were common first-line chemotherapies for the treatment of breast cancer (Pet. 7; *see* Ex. 1011 ¶ 33). Moreover, as Patent Owner points out, skilled artisans had developed methods to minimize the risks associated with anthracycline in clinical practice (*see* Prelim. Resp. 17–18 (citing Ex. 2030, 423; Ex. 1042, 11–13). As also documented by Patent Owner, despite its cardiotoxic side effects, researchers were seeking to develop combination therapies involving anthracyclines, and at least in some cases reporting "encouraging" and "promising" results. *See* Prelim. Resp. 18, 52–53 (citing Ex. 1005, 15; Ex. 1006, 4; Ex. 1007, 10; Ex. 1025, 9); *but see* Ex. 1011 ¶ 127 (testifying that Baselga '97 teaches that the combination of [anti-ErbB2 antibodies] and paclitaxel was significantly more powerful than the combination of [anti-ErbB2 antibodies and [an anthracycline]"). We find instructive that in one arm of the clinical trial reported by Baselga '97, patients were treated with anthracyclines in combination with anti-ErbB2 antibodies. *See* section II(D)(1), above. We find this disclosure at odds with Petitioner's contention that researchers would have avoided combinations with anthracyclines due to potential cardiotoxicity.

But claims 16 and 17 do not require administration of the three-drug combination in the absence of anthracyclines solely to avoid cardiotoxic side effects. Petitioner has shown there may be other reasons to avoid anthacylines in a treatment regimen, such as concerns with drug resistance. Pet. 17, 21-22. In particular, the prior art of record indicates that many patients with metastatic breast cancer will have previously been treated with, and become resistant to, first-line anthracycline chemotherapeutics. Gelman, for example, discloses that "[a]ll but two of the women in our trial had been treated with previous adjuvant chemotherapy, and 23 of 29 patients had previous exposure to anthracyclines." Ex. 1025, 13. On the present record, we find persuasive Dr. Litton's testimony that

one of ordinary skill in the art would have recognized that "'[b]ecause anthracyclines are widely used in the adjuvant setting,' there is a substantial likelihood that patients will have already received a course of anthracycline therapy, and thus it would be advantageous to pursue synergistic drug combinations—like paclitaxel with cisplatin—that include drugs other than anthracyclines." Ex. 1011 ¶ 128 (citing Ex. 1007, 10; Ex. 1025, 9).

We further note that only patients in Baselga '97 who had previously received anthracycline therapy were assigned to treatment with paclitaxel and anti-ErbB2 antibodies, whereas those who had not been previously exposed to anthracyclines were assigned to anthracycline-based chemotherapy with or without the anti-ErbB2 antibody. *See* section II(D)(1), above; *see also* Ex. 1007, 47 ("Because anthracyclines are widely used in the adjuvant setting, it is likely that a significant number of patients will be treated with paclitaxel ± rhuMoAb HER2."). Thus, patients in the paclitaxel/anti-ErbB2 antibody arms of the clinical trial were selected for treatment "in the absence of an anthracycline derivative" based on whether they had previously been treated with anthracyclines. *See also* Prelim. Resp. 37 ("In the '549 patent's working example, patients were administered the combination of the anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative only if they had 'received any anthracycline therapy in the adjuvant setting.'").

Accordingly, the evidence of record shows that in considering a patient's prior history of receiving anthracycline therapy, one of ordinary skill in the art 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, a taxoid and a further growth inhibitory agent "in the absence of an anthracycline derivative." The fact that patients administered the

combination may have been previously treated with anthracyclines does not take such a treatment regimen out of the claim scope. As noted above, this is consistent with Patent Owner's own proposed construction of "administering a combination," which we adopt for purposes of this Decision, as requiring "a single treatment regimen in which the patient receives all drugs that are part of the claimed combination."

In view of the above, we determine that Petitioner has shown a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–17.

E. *Grounds 4–6*

In Ground 4, Petitioner challenges claims 1–11 and 14–17 as obvious under 35 U.S.C. § 103 based on Baselga '96 and Baselga '94 and Gelmon. In Grounds 5 and 6, respectively, Petitioner further asserts Drebin (claim 12) and Presta (claim 13).

1. *Overview of Baselga '96 (Ex. 1005)*

Baselga '96 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. 1005 at 15. As a result, "[l]aboratory studies of the mechanism of this effect and clinical trials of such combination therapy [were] . . . in progress." *Id*.

Baselga '96 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. *Id*. at 9–10. 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 11. "The objectives of this trial were to determine the antitumor activity of rhuMAb HER2

in this patient population, as well as to define further the toxicity profile and pharmacokinetics of rhuMAb HER2." *Id.* at 10.

Baselga '96 reports that the treatment "was remarkably well tolerated" and "[t]oxicity [from rhuMAb HER2] was minimal." *Id.* at 9, 11. Of 43 patients treated, "five experienced a complete or partial remission, for an overall response rate of 11.6%." *Id*. at 13; *see id.* at 9 ("Objective responses were seen . . . with an 11.6% remission rate."). In addition, "37% of patients achieved minimal responses or stable disease." *Id*.

According to Baselga '96, "[t]ime to tumor progression was calculated from the beginning of therapy to progression." *Id*. at 10. "The median time to progression for the patients with either minor or stable disease was 5.1 months." *Id*. at 12. "The unusually long durations of minimal responses and stable disease seen in [the] trial" may be indicative of the cytostatic effects of the antibody. *Id*. at 13.

2. *Overview of Baselga '94* (Ex. 1006)

Besegla '94 describes experiments in which HER2 overexpressing human breast tumor cells were injected into nude mice followed by treatment with the 4D5-antibody in combination with paclitaxel. Ex. 1006, 4. Whereas either the antibody or paclitaxel alone produced 35% growth inhibition, the combination of the two resulted in 93% growth inhibition without increasing toxicity. *Id*.

3. *Analysis*

In light of our construction of the claim terms "in an amount effective to extend the time to disease progression" and "an effective amount," our analysis of claims 1–17 is substantially the same under Grounds 4–6 as it is under Grounds 1–3, above. Accordingly, Petitioner has demonstrated a reasonable likelihood of prevailing with respect to this challenge.

III. CONCLUSION

We conclude that Petitioner has established a reasonable likelihood of prevailing on its assertion that claims 1–17 of the '549 patent are unpatentable as obvious.

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

IV. ORDER

In consideration of the foregoing, it is:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted as to claims 1–17 of U.S. Patent No. 7,892,549 B2 based on the following grounds of unpatentability:

1) Claims 1–11 and 14–17 under 35 U.S.C. § 103 as obvious over the combination of Baselga '97 and Gelmon;

2) Claim 12 under 35 U.S.C. § 103 as obvious over the combination of Baselga '97, Gelmon and Drebin;

3) Claim 13 under 35 U.S.C. § 103 as obvious over the combination of Baselga '97, Gelmon and Presta;

4) Claims 1–11 and 14–17 under 35 U.S.C. § 103 as obvious over the combination of Baselga '96, Baselga '94, and Gelmon;

5) Claim 12 under 35 U.S.C. § 103 as obvious over the combination of Baselga '96, Baselga '94, Gelmon, and Drebin;

6) Claim 13 under 35 U.S.C. § 103 as obvious over the combination of Baselga '96, Baselga '94, Gelmon, and Presta.

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '549 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:

Amanda Hollis
Stefan Miller
Karen Younkins
KIRKLAND & ELLIS LLP
Amanda.hollis@kirkland.com
dichromik@gmail.com
Karen.younkins@kirkland.com

PATENT OWNER:

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

Adam Brausa
DURIE TANGRI LLP
abrausa@durietangri.com