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Paper 88
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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*.

FINAL WRITTEN DECISION AND RELATED ORDERS

Claims 1–11 and 14–17 Shown to Be Unpatentable
35 U.S.C. § 318(a); 37 C.F.R. § 42.73

Denying Patent Owner's Motion to Amend
35 U.S.C. § 316(d); 37 C.F.R. § 42.121

Denying Patent Owner's Motion to Exclude Evidence
Denying Petitioner's First and Second Motions to Exclude Evidence
37 C.F.R. § 42.64

Granting-In-Part Parties' Motions to Seal
37 C.F.R. § 42.55

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–11 and 14–17 of U.S. Patent No. 7,892,549 B2 (Ex. 1001, "the '549 patent"). We have jurisdiction under 35 U.S.C. § 6.

Having reviewed the arguments of the parties and the supporting evidence, we find that Petitioner has demonstrated by a preponderance of the evidence that each of the challenged claims is unpatentable.

A. Procedural History

Petitioner Celltrion, Inc. ("Celltrion")[1] filed a Petition requesting *inter partes* review of claims 1–11 and 14–17 of the '549 patent. Paper 2 ("Pet."). Patent Owner, Genentech, Inc., filed a Preliminary Response to the Petition. Paper 6 ("Prelim. Resp."). Based on the record then before us, we instituted trial with respect to all challenged claims. Paper 9, 27–28 ("Dec.").

After institution of trial, Patent Owner filed a Patent Owner Response (Paper 28, "PO Resp.") and Petitioner filed a Reply to the Patent Owner Response (Paper 45, "Pet. Reply").

Patent Owner also filed a Contingent Motion to Amend. Paper 26. Petitioner opposed. Paper 42. Patent Owner responded with a Reply in support of its motion (Paper 53); Petitioner further submitted an authorized Sur-Reply (Paper 64).

With respect to technical experts, Petitioner relies on the declarations of Robert Earhart, MD., Ph.D. (Exs. 1002, 1054, 1105); Patent Owner relies on the

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

declarations of Robert S. Kerbel, Ph.D. (Exs. 2061, 2143), Dr. Susan Tannenbaum (Exs. 2062, 2144).

Patent Owner filed motions for observations on the depositions of Dr. Earhart (Papers 69, 72), to which Petitioner provides responses (Papers 76, 80).

We heard oral argument on May 18, 2018. A transcript of that proceeding is entered as Paper 85 ("Tr.").

The parties filed the following motions to exclude evidence. Patent Owner filed one motion to exclude evidence. Paper 59. Petitioner opposed (Paper 72) and Patent Owner submitted a reply in support of its motion (Paper 75). Petitioner filed a first motion to exclude evidence. Paper 61. Patent Owner opposed (Paper 71) and Petitioner submitted a reply in support of its first motion (Paper 80). Petitioner filed a second motion to exclude evidence. Paper 81. Patent Owner opposed (Paper 83) and Petitioner submitted a reply in support of its second motion (Paper 84). Also before us are five unopposed motions to seal pursuant to the Modified Default Standing Protective Order governing this case: Papers 27 and 52 (by Patent Owner) and Papers 44, 47, and 62 (by Petitioner); *see also* Paper 24 (entering Modified Default Standing Protective Order (Exhibit 2036) and granting Patent Owner's motion to seal Exhibits 2001–2005, 2007, and 2008).

B. 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 copending IPR2017-01121. Petitioner has also filed IPR2017-01139 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, IPR2017-00804, and IPR2017-00805, respectively, brought by Hospira, Inc. ("Hospira").[2] 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).

We issue concurrently our Decisions in IPR2017-00731, IPR2017-00737, IPR2017-01139, IPR2017-01140, IPR2017-01121, IPR2017-00804, and IPR2017-00805.

Patent Owner identifies the following District Court actions, "that relate or may relate to U.S. Patent Application No. 10/356,824, which issued as U.S. Patent No. 7,892,549:" *Celltrion, Inc. v. Genentech, Inc.*, No. 18-cv-00274 (N.D. Cal.) and *Celltrion, Inc. v. Genentech, Inc.*, No. 18-cv-00095 (D. Del.). Paper 33, 2.

C. 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,

[2] Hospira also challenged claims of the '549 and '441 Patents in IPR2017-00739 and IPR2018-00016, respectively, which we denied. *See* IPR2017-00739, Paper 16; IPR2018-00016, Paper 25.

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, and 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®[3] 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. 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

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[3] As Patent Owner notes, "HERCEPTIN® is the tradename for the commercial product of the humanized antibody, trastuzumab." Paper 26, 3 fn.2.

[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) (designated "Baslega '94" in IPR2017-00737). Ex. 1019.

> 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[6] 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 11:4–40 (defining "chemotherapeutic agent" and "growth inhibitory agent"), 23:60–24:5, and 25:20–34.

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

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[6] 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.

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.

D. Challenged Claims and Reviewed Ground of Unpatentability

We instituted trial on the sole Ground set forth in the Petition, that claims 1–11 and 14–17 are unpatentable under 35 U.S.C. § 103 based on the combination of Baselga 1996, Seidman 1996,[7] Pegram,[8] 1995 TAXOL PDR,[9] and the

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[7] 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.

[8] 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.

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

knowledge of one of ordinary skill in the art. Dec. 27–28; *see* Pet. 24.

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 recites "administering an effective amount of a combination" of three agents similar to those of claims 1 and 16, wherein the antibody binds to the 4D5 epitope of ErbB2, the taxoid is paclitaxel, and the third element is broadly described as a "therapeutic agent."

Patent Owner does not separately argue the patentability of claims 2–4, 6–11, 14, 15, or 17.

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.[10] *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. Moreover, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (citations omitted).

We analyze the instituted ground of unpatentability in accordance with these principles.

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[10] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), amended 35 U.S.C. §§ 102 and 103. Because the challenged claims of the '405 patent have an effective filing date before the effective date of the applicable AIA amendments, throughout this Final Written Decision we refer to the pre-AIA versions of 35 U.S.C. §§ 102 and 103.

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; PO Resp. 33. 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.*

For the reasons set forth in our institution Decision, we agree with Patent Owner. Dec. 8–9. Petitioner has not explained 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. 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. Accordingly, we adopt Patent Owner's definition of the level of ordinary skill in the art as "a clinical or medical oncologist specializing in breast cancer with several years of experience with breast cancer research or clinical trials." *See also* Hospira Decision, 8–9 (defining the skill level the same way); Ex. 2020 ¶ 78

(implicitly adopting same definition). In any event, as Petitioner does not explain why its alternative definition would have any bearing on the outcome of the present case, and as we discern no appreciable difference in the parties' definitions, we note our findings and conclusions would be the same regardless of which definition were adopted. *See* PO Resp. 33 (arguing that the challenged claims would not have been obvious under either parties proposed definition).

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 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." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016). 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).

1. "*administering a combination*"

In IPR2017-00737 (involving claims 1–17 of the same patent), we initially 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. Patent Owner subsequently recast its proposed definition "to mean that the drugs are administered as part of the same treatment regimen," which we adopted. IPR2017-00737, PO Resp. 37, IPR2017-00737 Final Decision, 11–12. Also in that proceeding, we noted that Patent Owner's two definitions were interchangeable, as they would be here. *See* IPR2017-00737 Final Decision, 12. In the interests of clarity and consistency, we again define "administering a combination" to mean that the drugs are administered as part of the same treatment regimen.

2. "*an amount effective to extend the time of disease progression" and "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 [TTP] in the human patient." Claim 5, the remaining independent claim before us, similarly recites administering the three-part combination to a human patient in "an effective amount." To the extent that these terms may differ in scope, neither party contends that any difference affects the patentability analysis and we consider them together.

In our Decision to Institute, we construed "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*. Dec. 11–13. We also construed 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" and, thus, similarly indicating a comparison to an untreated patient. *See id.*

Patent Owner disagrees with our construction, contending that the proper comparator in both claim terms is not an untreated patient, but to a patient treated with taxoid alone. PO Resp. 34–37. In particular, Patent Owner argues that comparison to an untreated patient "is not consistent with the specification as understood by a POSA," and "makes no sense in the context of a disease like breast cancer." *Id.* at 34–35. Yet this is precisely the comparison Applicants made to obtain allowance of the challenged claims.

"A patent's specification, together with its prosecution history, constitutes intrinsic evidence to which the [the Board] gives priority when it construes claims." *Knowles Elecs. LLC v. Cirrus Logic, Inc.*, 883 F.3d 1358, 1361 (Fed. Cir. 2018). "The purpose of consulting the prosecution history in construing a claim is to exclude any interpretation that was disclaimed during prosecution." *Chimie v. PPG Indus., Inc.*, 402 F.3d 1371, 1384 (Fed. Cir. 2005) (internal quotation marks omitted). Prosecution disclaimer

> requires that the alleged disavowing actions or statements made during prosecution be both clear and unmistakable. Thus, when the patentee unequivocally and unambiguously disavows a certain meaning to obtain a patent, the doctrine of prosecution history disclaimer narrows the meaning of the claim consistent with the scope of the claim surrendered. Such disclaimer can occur through amendment or argument. . . . [and] includes all express representations made by or on behalf of the applicant to the examiner to induce a patent grant . . . includ[ing] amendments to the claims and arguments made to convince the examiner.

Aylus Networks, Inc. v. Apple Inc., 856 F.3d 1353, 1359 (Fed. Cir. 2017) (internal citations and quotations omitted); *see Arendi S.A.R.L. v. Google LLC*, 882 F.3d 1132, 1135–36 (Fed. Cir. 2018). Those conditions are satisfied here.

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 none of the challenged claims expressly identifies the intended comparator. The Examiner addressed this facial ambiguity 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, 400-402 (OA dated 7/17/01).[11] In response, Applicants asserted 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 416 (Response dated 1/17/2001); *see also* Ex. 3001-1, 19, (15:12–17), 46–47 (42–43). The Examiner withdrew the rejection in the next office action, stating that "[a]ll claims are allowable." *Id.* at 624 (OA dated 3/27/2002) (suspending prosecution due to potential interference); *see also id*. at 634–39 (OA dated

[11] Excerpts of prosecution history of US Application No. 09/208,649. Citations refer to pages of the exhibit overall rather than to the native pagination.

8/12/2003) (new grounds of rejection not relating to the phrase "extend the time to disease progression").

Accordingly, Applicants overcame the § 112 rejection by providing an express definition of the term "extend the time to disease progression" as meaning "relative to an untreated patient." Our construction reflects Applicants' choice. *See In re Paulsen*, 30 F.3d at 1480 (holding an applicant may choose to be his own lexicographer).

Patent Owner contends that "the clinical trial results reported in the '441 specification measure efficacy of the combination of an anti-ErbB2 antibody (rhuMAb HER2) with a taxoid (paclitaxel) against a control arm of paclitaxel alone," whereas "[t]here is no data in the patent comparing the TTP of patients treated with an anti-ErbB2 antibody and a taxoid against an untreated patient." PO Resp. 34–35. That may well be the case; yet, it does not render our construction inconsistent with the Specification of the '441 patent. As Dr. Tannenbaum, an expert for Patent Owner, explains, "cancer generally continues to progress without treatment." Ex. 2062 ¶ 133. As a result, an ordinary artisan would have understood that, even without any explicit disclosure in the '549 Patent, administering the claimed combinations would extend the TTP as compared to untreated patients. *See e.g.*, Ex. 1002 ¶ 111 (Dr. Earhart indicating that the choice of claim construction does not impact the obviousness analysis); Ex. 1054 (Dr. Earhart testifying that "a person of ordinary skill would have had a reasonable expectation that a combination treatment with paclitaxel and trastuzumab would extend the time to disease progression relative to treatment with paclitaxel and relative to no treatment"); *id.* ¶ 24 (same analysis with respect to proposed amended claims).

With respect to the prosecution history, Dr. Tannenbaum testifies that, "in context," Applicants used the term "untreated patient" to refer to "a patient that had not received the combination therapy, but instead received paclitaxel alone." Ex. 2062 ¶ 138. We do not find Dr. Tannenbaum's argument persuasive.

The Examiner asked Applicants to choose from various potential meanings for the claim language: "is the extension of time to disease progress[ion] relative to untreated patients? Patients who received antibody or taxoid alone? Patients who received antibody and an anthracycline?" Ex. 3001, 401–402. Despite being presented with the option of selecting "taxoid alone" as the comparator, Applicant did not do choose that option. Applicant instead specifically excluded that possibility. *Id*. at 416 (stating "**[c]learly**, 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**") (emphases added). Indeed, Dr. Tannenbaum admitted that much at her deposition in the related Hospira case, agreeing that "there can be no confusion" that Applicants were "choosing the comparator untreated patients rather than taxoid alone." *See* IPR20117-00737 Ex. 1087, 225:15–226:13.

For the reasons set forth above, we maintain that the proper analysis of the claim language "in an amount effective to extend the time to disease progression [TTP] in the human patient" and administering the three-part combination to a human patient in "an effective amount" involves comparing the claimed combination treatments to no treatment. To the extent Patent Owner is correct that our construction "makes no sense in the context of a disease like breast cancer" (PO Resp, 35), Applicants chose this definition "with reasonable clarity, deliberateness, and precision," and obtained the '549 Patent only after doing so. *See In re Paulsen*, 30 F.3d at 1480. Under such circumstances, we must give the

term the construction the applicant set out, even if such construction would lead to a "nonsensical result." *Source Vagabond Sys. Ltd. v. Hydrapak, Inc.*, 753 F.3d 1291, 1301 (Fed. Cir. 2014).

D. Asserted Ground of Unpatentability

Petitioner challenges claims 1–11 and 14–17 as unpatentable under 35 U.S.C. § 103 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,[12] and Seidman 1995.[13] *See* Pet. 43–53; Pet Reply 4–22. Patent Owner opposes.[14] PO Resp. 37–54.

We begin with an overview of the above-recited references.

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 (citing Baselga Abstract 53). As a result, "[l]aboratory studies of the

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[12] 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.

[13] 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.

[14] Although Patent Owner objects to Petitioner's reliance of references other than Baselga 1996, Seidman 1996, Pegram, 1995 TAXOL PDR (PO Resp. 37, n.12.) to establish the knowledge of one of ordinary skill in the art, "it is permissible, and sometimes even necessary, to establish such background knowledge by pointing to other prior art." *Rovalma, S.A. v. Bohler-Edelstahl GmbH & Co. KG*, 856 F.3d 1019, 1027 n.1 (Fed. Cir. 2017) (citations omitted).

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.

Patients were administered 10 weekly doses of rhuMAb HER beginning with a 250 mg loading dose, and 100 mg doses thereafter. *Id.* at 4. "Adequate pharmacokinetic levels of rhuMAb HER2 were obtained in 90% of the patients." *Id.* at 3. "Treatment with rhuMAb HER2 was remarkably well tolerated." *Id.* at 5. "Toxicity was minimal and no antibodies against rhuMAb HER2 were detected in any patients." *Id.* at 3.

"37% of patients achieved minimal responses or stable disease." *Id*. at 7. "Objective responses were seen in five of 43 assessable patients, and included one complete remission and four partial remissions" for an overall response rate of 11.6%. *Id.* at Abstract*; see id.* at 3. Baselga 1996 predicts "that the percentage of patients who show objective tumor regression to rhuMAb HER2 will be higher when patients with less extensive breast cancer are treated, since laboratory studies have shown that the response to antireceptor antibodies is greater with lower tumor burden." *Id.* at 7.

"Time to tumor progression was calculated from the beginning of therapy to progression," and "[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 cytostatic 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]" and "[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 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.* Seidman concludes that "HER2 over-expression [sic] in MBC seems to confer sensitivity rather than resistance to taxanes," and although HER2 overexpression generally correlates with a poor prognosis, "stratified analysis controlling for confounding variables demonstrated the value of HER2 status in predicting good taxane response." *Id.*

3. *Overview of Pegram 1995 (Ex. 1022)*

Pegram 1995 reports on a phase II clinical trial of patients with HER2 positive metastatic breast cancer treated with a combination of cisplatin and rhuMAB HER2 (250 mg loading dose followed by 100 mg weekly doses for 8 weeks). Ex. 1022; *see* Ex. 1002 ¶¶ 62–65. Of the 36 patients evaluated, one had a complete response and 7 had partial responses. *Id.* According to the authors:

> 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.

Pegram 1995 also notes by way of background 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*." *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. The 1995 TAXOL PDR further discloses that when used in combination with cisplatin, "myelosuppression was more profound when TAXOL was given after cisplatin than with the alternate sequence." *Id.* at 6.

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

Baselga Abstract 53 (cited in Baselga 1996) describes xenograft studies in which BT-474 HER2 overexpressing human breast cancer 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 treatment resulted in "major antitumor activity with 93% inhibition of growth" without increasing toxicity. *Id*. In addition, whereas doxorubicin alone resulted in 27% growth inhibition in this model, the combination of doxorubicin and antibody resulted in 70% growth inhibition. *Id.*

According to Baselga Abstract 53, [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. *Id.* The authors conclude "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 provides additional details regarding the work reported in Baselga Abstract 53. *See* Ex. 1002 ¶ 53 & n.16. 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.

Ex. 1021.

7. *Overview of Seidman 1995 (Ex. 1010)*

Siedman 1995 is a review article regarding the clinical use and laboratory investigations of paclitaxel, "the most important new cytotoxic agent to be introduced for the management of breast cancer in many years." Ex. 1010, 1.

Siedman 1995 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 1995 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 Baselga Abstract 2262, among others, Seidman 1995 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. "[t]hese data provide a lead for translation into the clinic. Indeed, future clinical trials combining paclitaxel with anti-growth factor receptor MoAbs [e.g., rhuMAB HER2] are being planned." *Id.*

E. Analysis of Asserted Ground

Petitioner has provided a reasoned, claim-by-claim explanation for the basis of its contention that claims 1–11 and 14–17 would have been obvious over the combination of Baselga 1996, Seidman 1996, Pegram 1995, and 1995 TAXOL PDR, in view of the knowledge of a person of ordinary skill in the art. Pet. 24–75. 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). As articulated by Petitioner's expert, Dr. Earhart:

> Particularly for the population of metastatic HER2+ breast cancer patients, which typically had a worse prognosis than other cancer patients . . . a person of ordinary skill in the art would have been interested in testing combinations with any drug that had proven efficacy for metastatic HER2+ breast cancer. Baselga 1996, Pegram 1995, and Seidman 1996 respectively report the clinical efficacy of trastuzumab, trastuzumab/cisplatin, and paclitaxel in the metastatic HER2+ breast cancer population, and therefore provided a strong motivation to test those drugs in combination in human metastatic HER2+ breast cancer patients.

Ex. 1002 ¶ 119.

Petitioner, thus, points 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). As such, Petitioner notes that Baselga 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)); Pegram 1995 discloses that "the combination of trastuzumab/cisplatin was clinically effective in patients with metastatic HER2-positive breast cancer, with greater response rates and no apparent increase in toxicity relative to cisplatin

alone"; and "Seidman 1996 reports that paclitaxel is clinically effective against metastic HER2-positive breast cancer." *Id*. at 44–45.

Petitioner further argues that

> as of December 1996, paclitaxel was one of the "most promising" chemotherapeutic drugs with efficacy against metastatic breast cancer. (Ex. 1007 (Abrams), 1164.) As such, a POSA would have been motivated to treat HER2-positive breast cancer patients with paclitaxel and to incorporate paclitaxel into the known, effective trastuzumab/cisplatin combination. (Ex. 1002, ¶ 119.) A POSA would have been particularly encouraged to combine paclitaxel with trastuzumab/cisplatin because Seidman 1996 reports that paclitaxel is clinically effective against metastatic HER2-positive breast cancer. (*Id*., ¶ 119; Seidman 1996 (Ex. 1011).) The combination of trastuzumab and paclitaxel was already undergoing clinical trials for metastatic HER2+ breast cancer (Baselga 1996 (Ex. 1020), 743), and, indeed, paclitaxel and cisplatin were already being used in combination with one another to treat cancers, including metastatic breast cancer. (Ex. 1002, ¶ 119; Ex. 1012 (1995 TAXOL PDR), 683; *see also* Ex. 1013 (Tolcher), 37;[15] Ex. 1014 (Gelmon 1996), 1185.)[16]

Pet. 45.

In addition to clinical data, Petitioner also argues that "preclinical data reporting synergy between trastuzumab and paclitaxel in mouse xenografts would have provided even more motivation to a POSA to treat HER2-positive breast

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[15] Tolcher, *Paclitaxel Couplets with Cyclophosphamide or Cisplatin in Metastatic Breast Cancer*, 23(1) Supp. 1 SEMINARS ONCOLOGY 37–43 (1996) (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. 1013.

[16] 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) (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"). Ex. 1014.

cancer patients with this combination" as shown in Baselga 1996, Baselga Abstract 53 (cited in Baselga 1996), and Baselga Abstract 2262. Pet. at 46 (citing Exs. 1019, 1021); *see* sections II(D) (1),(5), and (6), *supra*.

Further with respect to motivation to combine, Petitioner contends that "[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. 1016, 204); Pet. Reply 15.

In sum, and 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. Pet. 52–53 (citing, Ex. 1002 ¶¶ 117–35); *see* Pet. Reply 1.

With respect to the limitation of claims 16 and 17, requiring administration of the claimed 3-part combination "in the absence of an anthracycline derivative," Petitioner asserts that an ordinary artisan would have had multiple reasons to administer the claimed combination without an anthracycline derivative. Pet. 51–53. Petitioner first 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. Moreover:

> [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.)[17] 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), we credit Dr. Earhart's testimony that "a person of ordinary skill in the art would have known that treatment with paclitaxel extends the time to disease progression relative to no treatment." Ex. 1002 ¶ 157, n.28. We also find persuasive Petitioner's argument 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. Pet. 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, 11, 13–14; Ex. 1001, 25:1–19, 43–54).

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

Patent Owner counters that Petitioner has not demonstrated that a person of ordinary skill in the art would have been motivated to combine rhuMAb HER2 with a taxoid; that the Board applied an incorrect claim construction, wherein under its preferred claim construction, Petitioner has not established a reasonable expectation of achieving the claimed clinical efficacy; and that the Sliwkowski Declaration, submitted during prosecution, confirms the patentability of the challenged claims. Patent Owner does not rely on evidence of secondary considerations. We address the relevant issues below.

a) Motivation to Combine rhuMAb HER2 with a Taxoid

On pages 37–41 of its Response, Patent Owner argues that the clinical and preclinical results discussed in Seidman 1996 and Baselga 1996 would not have motivated one of ordinary skill in the art to administer a combination of rhuMAb HER2 and a taxoid for the treatment of breast cancer.

(1) Seidman 1996

Relying on the testimony of Dr. Tannenbaum, Patent Owner contends that one of ordinary skill in the art would not have read the clinical data in Seidman 1996 as demonstrating that paclitaxel is clinically effective against metastatic HER2-positive breast cancer because "Seidman 1996 is an abstract, which a POSA would understand as reflecting a preliminary hypothesis, not proven efficacy; and a POSA would await an expanded analysis in a peer-reviewed journal before drawing any conclusions." PO Resp. 39 (citing Ex. 2062 ¶¶ 184–185).

For the following reasons, we do not find this argument persuasive. First, as Petitioner points out, Patent Owner's own experts rely on abstracts when favorable to its position. *See* Pet. Reply 5–6 (citing Ex. 1004, 321; Ex. 1056, ¶ 22); *see also* IPR2017-00737, Paper 102, Tr. 64:14–67:10 (Patent Owner admitting at oral argument that it relied on preclinical data from the Baselga Abstract 53 ("Baselga

'94") to justify to the FDA conducting phase III trials in the absence of phase II trials); *see also*, Ex. 2007, 63–64; Ex. 2001, 6–7, 39 (Patent Owner's reliance on abstracts in FDA submissions). Second, the inventors of the '549 patent do not appear to have considered abstracts unreliable as the patent cites numerous abstracts and posters on its face. *See* Ex. 1001, (56) References Cited. Indeed, in a declaration submitted during prosecution, Applicants expressly relied on an abstract to overcome prior-art rejections. *See* Ex. 1004-8, 1552; *see also* Ex. 1054 ¶ 16 ("Absent any allegation of misconduct on the part of the authors, a person of ordinary skill in the art would have had no reason to doubt their reported data.").

Under such circumstances, we are not persuaded that an ordinary artisan would have ignored or discounted the teachings of Seidman 1996 simply because it is an abstract.[18]

Patent Owner further appears to argue that a person of ordinary skill in the art would not have interpreted Seidman 1996 as showing the proven efficacy of taxoids in HER2-positive patients because "[t]he Seidman authors themselves continued to research the issue and ultimately found no 'statistically significant association with clinical response to taxane therapy' for patients who are HER2-positive." PO Resp. 39–40 (citing Ex. 2024, 2322). Patent Owner's argument,

[18] With respect to the reliability of the Seidman 1996 authors, we note that they hale from the highly-respected Memorial Sloan-Kettering Cancer Center, and include two recipients of awards from the American Society of Clinical Oncology (Ex. 1011) and at least one—in Patent Owner's own words— a "leading practitioner" in the field (PO Resp. 62; *see* Reply 5). These authors also appear to have been collaborating with scientists of Patent Owner in rhuMAb HER2 research and clinical trials. *See, e.g.*, Ex. 1020, 3 (showing some of the same authors in Baselga 1996 as in Seidman 1996 and attributing the work on rhuMAb HER2 to both Memorial Sloan-Kettering Cancer Center and Genentech); *see also* Ex. 1019, 4 (Baselga Abstract 53 showing the same).

however, relies on Exhibit 2024, a 2002 article by van Poznak. As with Patent Owner's unpublished internal documents evidencing the history of the invention and the development of its clinical trials, van Poznak was not available to one of ordinary skill in the art as of the date of the invention. *See* Ex. 1054 ¶ 14.

We are not persuaded that the van Poznak article, which reports on further research, fairly evidences what would have been understood by one of ordinary skill in the art at the time of the invention with respect to efficacy. *In re Kotzab,* 217 F3d. 1365, 1369 (Fed. Cir. 2000) ("A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field."); *see also Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017) ("obviousness is measured objectively in light of the prior art, as viewed by a person of ordinary skill in the field of the invention."). Nor are we persuaded that the substance of van Poznak supports Patent Owner's position. As Petitioner points out, van Poznak states, "[o]ur prior assessment of tumor HER2 expression through monoclonal antibody (45D5) and the polyclonal antibody (pAb-1) demonstrated that 4D5 positivity was predictive of positive response to taxane monotherapy." Pet. Reply 6 (quoting Ex. 2024, 2320); *see* Ex. 1054 ¶ 15 (explaining that a closer reading of van Poznak shows that it "did not negate the finding that HER2+ patients are sensitive to paclitaxel").[19]

[19] We further note that, as the basis for its "prior assessment," van Poznak references "Baselga J, Seidman AD, Rosen PP, et al: HER2 overexpression and paclitaxel sensitivity in Breast Cancer: Therapeutic Implications, Oncology, 2:43–48, 1997," which appears to be the Baselga '97 reference cited as prior art in IPR2017-00737 involving the same patent at issue here. *See* IPR2017-00737, Exhibit 1007. As noted in our Final Decision in that case, "Baselga '97 teaches

We also find unpersuasive Patent Owner's citation to Yu et al.'s statement that "breast cancers that overexpress p185 [*i.e.*, HER2] will not respond well to Taxol" as evidence that one of ordinary skill would have been discouraged from using taxoids to treat HER2-positive breast cancer patients. PO Resp. 40 (citing Ex. 2029, 1362).[20] Taken in context, the cited statement in Yu et al., refers to the use of standalone paclitaxel, whereas the claimed invention relates to a taxoid *in combination* with rhuMAb HER2. Moreover, we find persuasive Petitioner's explanation that because the work of Yu et al. was done in tissue culture on cells engineered to overexpress HER2, one of ordinary skill would have regarded those findings as less predictive than the in vivo preclinical and clinical teachings of Baselga 1996 (Ex. 1011) and Seidman 1996 (Ex. 1010). *See*, Pet. Reply 7 (citing e.g., Ex. 1054 ¶ 17; Ex. 1002 ¶¶ 60, 124); *see also* Ex. 1040, 55:10–56:20 (Dr. Kerbel admitting that one study does not give rise to a widespread assumption that HER2-positive cells are less responsive to paclitaxel); Paper 64 at 4–5 (noting Exhibit 1043[21] a review paper regarding paclitaxel sensitivity in breast cancer fails to cite Yu, but "cites Seidman '96, Baselga '96 and the Baselga xenograft studies as suggesting that HER2+ tumors are sensitive to paclitaxel, and that combining trastuzumab with paclitaxel increased its antitumor activity").

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that rhuMoAb HER2, alone, 'is clinically active in patients who have metastatic breast cancers that overexpress HER2 and have received extensive prior therapy.'" *Id.* Paper 106, 19.

[20] Yu *et al.*, *Overexpression of c-erbB-2/neu in breast cancer cells confers increased resistance to Taxol via mdr-1-independent mechanisms*, 13 ONCOGENE 1359–654 (1996).

[21] Baselga et al., *HER2 Overexpression and Paclitaxel Sensitivity in Breast Cancer: Therapeutic Implications*, Update on the Taxanes in Breast Cancer, Oncology, Vol. 11, No. 3 (Suppl. 2), 43–48 (1997) (cited as Baselga '97 in IPR2017-00737).

We therefore conclude that one of ordinary skill in the art would have understood that taxoids were 1) used in combination therapy for the treatment of metastatic breast cancer (Ex. 1012, 6; Ex, 1014; Ex. 1013), 2) were suggested to be particularly useful for HER 2 positive breast cancer (Ex. 1011), and 3) demonstrated synergy in combination with anti-HER-2 monoclonal antibodies in animal models of HER2 breast cancer (*see* Ex. 1020, 9 ("In preclinical studies . . . rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including . . . paclitaxel, without increasing their toxicity."); Ex. 1010, 5; Ex. 1021). We find no merit in Patent Owner's argument that safety concerns would have "dissuaded POSAs from using combination therapy involving taxoids." *See* PO Resp. 41 (citing Ex. 2062 ¶¶ 59–61, 194–198); *see also, e.g.,* Ex. 1010 (referencing paclitaxel as "the most important new cytotoxic agent to be introduced for the management of breast cancer in many years"); Ex. 1010, 5 (stating that "clinical trials combining paclitaxel with anti-growth factor receptor MoAbs [e.g., rhuMAB HER2] are being planned"); Ex. 1020, 9; Ex. 2111, 4 ("Paclitaxel was selected [to combine with rhuMAb HER2] because of its activity in metastatic breast cancer and preclinical studies that supported its use.").[22]

(2) Baselga 1996

With respect to Baselga 1996, Patent Owner argues that the reference merely discloses the administration of rhuMAb HER2 alone and "discusses preclinical combinations with 'several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel.'" PO Resp. 37–38. And although Patent Owner

[22] S. Shak, *Overview of the Trastuzumab (Herceptin) Anti-HER2 Monoclonal Antibody Clinical Program in HER2-Overexpressing Metastatic Breast Cancer*, Sem. Oncol. 26(4), Supp. 12 (1999).

admits that Baselga 1996 discloses that "clinical trials of such combination therapy are currently in progress," it argues that "it could not have been referring to rhuMAb HER2 plus paclitaxel because there was no clinical study involving that combination at the time Baselga-1996 was submitted." *Id.* at 38–39; *see also id.* at 20–23 (relying on non-prior art documents to establish the history of the invention and development of related clinical trials).

We do not find Patent Owner's argument persuasive for the reasons set forth on pages 16–18 of Petitioner's Reply.[23] Baselga 1996 states 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" and, as a result, "clinical trials of such combination therapy are currently in progress." Ex. 1020, 9. Based on our reading of Baselga 1996 as a whole, we agree with Petitioner that one of ordinary skill in the art would have understood from this passage that clinical trials of rhuMAb HER2 in combination with each of cisplatin, doxorubicin, and paclitaxel were currently in progress for the treatment of breast cancer. *See* Pet. Reply 16 (citations omitted); *see also* Ex. 1010, 5 (stating that "clinical trials combining paclitaxel with anti-growth factor receptor MoAbs [e.g., rhuMAB HER2] are being planned").

That a clinical study involving rhuMAb HER2 in combination with paclitaxel may not have yet commenced when Baselga 1996 was published does not, as Petitioner points out, diminish its teachings because the record fails show

[23] We note that the relevant time for our obviousness analysis is not the submission date of the prior art, as Patent Owner appears to suggest, but the date of the alleged invention, which in this case, is later than the publication date of Baselga 1996. It is undisputed that at the time Baselga 1996 was published, a clinical study involving the claimed combination was indeed in progress.

that one of ordinary skill in the art would have been aware of this fact. In this respect, Patent Owner's citation to Shak[24] is unavailing as Shak merely indicates that a paclitaxel arm was added sometime after the trial began in June 1995. *See* Ex. 2111, 73. Patent Owner's reliance on non-public documents to establish when it added a paclitaxel arm is similarly insufficient because there is no evidence one of ordinary skill in the art would "have been privy to [Patent Owner's] internal, non-public development history." Pet. Reply 16.

Further, and though we do not find relevant Patent Owner's non-public documents evidencing the history of the invention and the development of clinical trials involving rhuMAb HER2 in combination with a taxoid, we agree with Petitioner that these documents do not evidence any uniform opposition or skepticism but "show[] that the suggestion to add the paclitaxel/trastuzumab arm was quickly accepted both internally and at FDA." Pet. Reply 17–18 & n.11; *see e.g.*, Ex. 1035 (reporting that FDA "thought our plan [regarding HER2 protocol changes] was reasonable" and that "[t]heir preliminary review of our plan seemed to be reasonable since we are having difficulties recruiting patients.") Ex. 2004, 4 (noting that "[i]nitial FDA feedback on the Taxol modification is positive.") 10, (quoting internal reviewers as stating: "I support the Taxol amendment"; "The parallel strategy is important and I support it"; suggested changes "are appropriate"; and "a good gamble"), (comments of non-supporting reviewer directed to statistical power rather than use of taxol, *per se*).

[24] Shak et al., *Overview of the Trastuzumab (Herceptin) Anti-HER2 Monoclonal Antibody Clinical Program in HER2-Overexpressing Metastatic Breast Cancer*, 26(4), Suppl. 12 SEMINARS ONCOLOGY 71-77 (1999). Ex. 2111.

(3) Reliability of Baselga Xenograft Data

Patent Owner also argues that the preclinical results referenced in Baselga 1996 (as further discussed in Baselga Abstract 53 (Ex. 1019) and Baselga Abstract 2262 (Ex. 1021)) fail to provide motivation to combine rhuMAb HER2 and a taxoid. PO Resp. 41–42. We do not find Patent Owner's argument persuasive for the reasons set forth on pages 7–12 of Petitioner's Reply. We find particularly compelling Petitioner's evidence that Patent Owner itself relied on the Baselga xenograft results to obtain FDA approval to test the rhuMAb HER2/paclitaxel combination in Phase III clinical trials. *See, e.g.*, Ex. 2007, 27, 64; Ex. 2001, 6–7, 39; Ex. 1052, 144:17–150:16; *see also* IPR2017-00737, Paper 102, Tr. 64:14–67:18 (Patent Owner's admission at oral argument that Baselga xenograft data was used, at least "[i]n part," to justify to the FDA conducting phase III trials in the absence of phase II trials). In this regard, the Federal Circuit has recognized that "FDA approval may be relevant to the obviousness inquiry." *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291 (Fed. Cir. 2013) (citing *Knoll Pharm. Co., Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004)).

Despite relying on the Baselga xenograft data in its FDA submissions, Patent Owner now argues that the design of the preclinical study renders that data unreliable. *See* PO Resp. 41–43. We do not, however, find persuasive Patent Owner's implication that one of ordinary skill in the art would have discounted Baselga's results because the authors used a single cell line (BT-474) with a high level of HER2 expression. *See* PO Resp. 42 (citing Ex. 2061 ¶ 62; Ex. 2062 ¶ 168).[25] We credit, instead, the testimony of Dr. Earhart that one of ordinary

[25] In Paper 26, Patent Owner further contends that model cell lines having 11 (MDA-435), 31 (SK-BR3), and 52 (BT-474) copies of ErbB2 per cell reflects "the heterogeneity of human chromosomes." Paper 26, 14–15 (citations omitted). To

skill in that art would consider this high level of HER2 gene expression "advantageous, rather than detrimental" because high levels of HER2 expression was known to be correlated with poor treatment outcomes. Ex. 1054 ¶ 10. Accordingly, "[a] person of ordinary skill in the art would consider positive results using the BT-474 cell line as a motivation to pursue the tested agent." *Id.*

With respect to the site of tumor implantation, we also credit Dr. Earhart's opinion that the subcutaneous implantation technique used by Baselga was reliable, routinely used, and still common today. *Id.*; *see also* Ex. 1105 ¶ 9 (explaining why Baselga's reporting of only a single time point was not evidence of unreliability). Accordingly, we find reasonable Dr. Earhart's opinion that "no person of ordinary skill in the art would question the validity of [Baselga's] subcutaneous xenograft studies in comparing proposed combination treatment regimens." *Id.* at ¶ 9.

Patent Owner also appears to argue that one of ordinary skill in the art would not have risked treating a patient with a combination of rhuMAb HER2 and a taxoid because the Baselga data lacked, "e.g., testing [of] multiple cell lines, creation of orthotopic xenograft models, and analysis of dosing amounts." PO Resp. 44. We do not find this argument persuasive in light of Patent Owner's reliance on the Baselga data in its FDA submissions, the known use of rhuMAb HER2 (Ex. 1020, Ex. 1022) and paclitaxel (Ex. 1010; Ex. 1011; Ex. 1012) in treating breast cancer, and Dr. Earhart's explanation that, "when each element of a combination therapy had previously been shown to be safe and effective on its own

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the extent Patent Owner intends to convey that the variation in ErbB2 copy number in the referenced cell lines reflects the heterogeneity of HER2 expression within or between HER2-positive tumors in human patients, this would appear to support Dr. Earhart's position that it was reasonable to rely on cell line BT-474 in preclinical trials, as it would be expected to have the highest, yet still physiologically relevant, expression level among the referenced cell lines.

in clinical studies [as is the case here], it would not be necessary to run preclinical studies on the combination" (Ex. 1054 ¶ 8).

Patent Owner also raises Hsu in response to Petitioner's reliance on the Baselga xenograft data. Patent Owner introduced Exhibit 2135 ("Hsu")[26] at Dr. Earhart's April 17, 2018 deposition (*see* Paper 83, 1), and submitted arguments with respect to Hsu in connection with its motions on observation (Paper 68, ¶ 8; Paper 76 ¶ 8), to which Petitioner replied (Paper 74, ¶¶ 3–4; Paper 80 ¶¶ 3–4). Hsu is also subject to Petitioner's motion to exclude, discussed below, in section III(C)(2).

Hsu is an abstract appearing in the Proceedings of a March 7–12, 1997 conference on Basic & Clinical Aspects of Breast Cancer. Ex. 2135. According to Hsu, in vitro cytotoxicity assays on HER2-expressing human breast cancer cells showed that rhuMAb HER2 in combination with taxol had additive cytotoxic effects, whereas in a mouse model involving these "HER-2/*neu*-transfected MCF-7 human breast cancer" cells, "[x]enografts treated with rhuMAb HER-2 plus taxol . . . were not significantly different from drug alone controls with the doses and dose schedules tested in this model." *Id.*

As we understand Patent Owner's position, one of ordinary skill in the art would have discounted Baselga's xenograft results in light of Hsu's (allegedly) contradictory teachings demonstrating a lack of synergy between rhuMAb HER2 and a taxoid. *See* Paper 68, ¶ 8; Paper 74, ¶¶ 3–4. We are not persuaded by the

[26] Hsu, et al., *Therapeutic Advantage of Chemotherapy Drugs in Combination with Recombinant, Humanized, Anti-HER-2/neu Monoclonal Antibody (rhuMAb HER-2) Against Human Breast Cancer Cells and Xenografts with HER-2/neu Overexpression*, Proc. Basic & Clin. Aspects of Breast Cancer, A-39 (March 7-12, 1997). Ex. 2135.

merits of Patent Owner's argument. Relying on the testimony of Dr. Earhart, Petitioner reasonably argues that Hsu fails to describe the doses and schedules tested such that one of ordinary skill in the art would not have known whether they were comparable to Baselga's. Paper 64, 8–9 (citing Ex. 1105 ¶ 13). Petitioner further distinguishes Hsu as using HER2-transfected cells, rather than naturally-HER2 overexpressing human tumor cells such as the BT-474 cell line used in Baselga. *Id.* Based on the evidence of record in this case, we agree with Petitioner that one of ordinary skill in the art would not conclude that Hsu's teachings were inconsistent with those of Baselga. *See also* IPR2017-00737, Paper 86 (Final Written Decision), section II(E)(1).

b) "In the Absence of an Anthracycline Derivative"

With respect to the limitation of independent claim 16, requiring the administration of an anti-ErbB2 antibody, a taxoid, and a further growth inhibitory agent "in the absence of an anthracycline derivative," Patent Owner argues that one of ordinary skill in the art would have been motivated to combine rhuMAb HER2 with an anthracycline rather than with a taxoid in light of safety and efficacy concerns associated with taxoids. PO Resp. 45–46 (citations omitted). For the reasons set forth at pages 12–15 of Petitioner's Reply Brief, we do not find Patent Owner's arguments persuasive.

As an initial matter, we credit Patent Owner's argument that one of ordinary skill in the art seeking to combine rhuMAb HER2 with an existing anti-cancer drug would have reasonably looked to anthracyclines because they were a common first-line chemotherapy agent with known, but manageable, side effects. PO Resp. 45–46. This, however, is insufficient to establish the non-obviousness of the rhuMAb HER2/taxoid combination. *See Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1329 (Fed. Cir. 2017) (quoting *In re Fulton,* 391 F.3d 1195, 1200

(Fed. Cir. 2004)) ("While a skilled artisan may have preferred a delayed-release formulation over the claimed immediate-release formulation, 'that the prior art as a whole suggests the desirability of a particular combination need not be supported by a finding that the prior art suggests that the combination claimed . . . is the preferred, or most desirable, combination.'").

The evidence of record shows that while anthracyclines were widely employed, one of ordinary skill in the art would also have been motivated to combine rhuMAb HER2 with a taxoid such as paclitaxel rather than with an anthracycline. Paclitaxel was approved for the treatment of metastatic breast cancer, recommended as a "highly active . . . initial chemotherapy for metastatic breast cancer," and shown to be clinically effective against HER2-positive breast cancers. Ex. 1012, 6; Ex. 1011; Ex. 1019; Ex. 1021; Ex. 1039, 1943; *see also* Ex. 1014 (disclosing that paclitaxel is active as a single agent in metastatic breast cancer, and exhibits advantageous, if not synergistic, effects in combination therapy); Ex. 1054 ¶13 (noting that paclitaxel side effects were controllable and generally not dose limiting). Moreover, in light of preclinical studies demonstrating that paclitaxel was synergistic with anti-HER2 antibodies, Baselga 1996 states that "clinical trials [including rhuMAb HER2/taxoid] combination therapy are currently in progress." *See* Ex. 1020, 9. Consistent with this considerable interest in taxoids for the treatment of breast cancer, a contemporary review of a wide variety of chemotherapeutic agents for breast cancer including anthracyclines, touts taxanes (i.e., taxoids, including paclitaxel and docetaxel), as "foremost among these new agents" and "one of the most exciting new classes of chemotherapeutic agents to be developed." Ex. 1007, 6.

The evidence of record also shows that one of ordinary skill in the art would have been motivated to administer the claimed combination "in the absence of an

anthracycline derivative," where prior treatment with anthracyclines was discontinued due to drug resistance or cumulative cardiotoxicity. *See* Pet. 51–52; Ex. 1002 ¶ 106, 138–139, 161; Ex. 1016, 26–30. The FDA-approved labeling for Taxol, for example, states that it "is indicated, after failure of first-line or subsequent chemotherapy" where "[p]rior therapy should have included an anthracycline." Ex. 2112, 6. The prior art of record confirms that many patients with metastatic breast cancer will have previously been treated with, and become resistant to, first-line anthracycline chemotherapeutics. Gelmon 1996, 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. 1014, 5. Thus, 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.

c) The Sliwkowski Declaration[27]

During the prosecution leading to the issuance of the '549 Patent, the Examiner withdrew an obviousness rejection involving Baselga 1996 "in view of the declaration of Mark X. Sliwkowski, PhD." Ex. 1019-7, 47–48. Although none of its experts address the Sliwkowski Declaration, Patent Owner states "if the Board considers Dr. Sliwkowski's declaration, it only confirms the patentability of

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

the challenged claims." PO Resp. 52; *see also id* at 27, 52–54 (discussing aspects of the Sliwkowski Declaration). Thus, although Patent Owner does not appear to rely on the Sliwkowski Declaration, in the interest of completeness, we accept Patent Owner's invitation to consider it.

The Sliwkowski Declaration asserted, inter alia, that "a skilled scientist would have anticipated that paclitaxel would provide little or no additional benefit to treatment with trastuzumab alone since trastuzumab would arrest the cell cycle before paclitaxel would be able to act," and that one of ordinary skill in the art would recognize that "anti-HER2 antibodies acting by inducing cell cycle arrest in the G1 phase, would antagonize the effect of taxoids, such as paclitaxel, since they arrest cell cycle before it reaches the G2/M phase, where taxoids exert their apoptotic antitumor activity." Ex. 1009, 341–345 ¶¶ 3, 4. Patent Owner's experts nowhere address this concept and we accept Dr. Earhart's well-reasoned conclusion that "Dr. Sliwkowski's theory and reasoning . . . are based on several false assumptions about how these agents work to treat cancer, and are contradicted by the data available in the prior art, which predicted a favorable interaction between trastuzumab and paclitaxel." Ex. 1002 ¶¶ 140–150.

According to Patent Owner, the Sliwkowski Declaration "also explained that preclinical results would not have provided a reasonable expectation of success as to the clinical results for the combination of rhuMAb HER2 and a taxoid; indeed, xenograft models at that time were poor predictors of clinical results for breast cancer." PO Resp. 27. With respect to these issues, the Sliwkowski Declaration adds nothing more to Patent Owner's position, and we agree with Petitioner that the Sliwkowski Declaration does not negate the motivation to combine or reasonable expectation of success demonstrated in the prior art. *See* Pet. 53–62.

d) Reasonable Expectation of Success

Patent Owner also contends that Petitioner has not established a reasonable expectation of success in achieving either the claimed clinical efficacy or the claimed clinical safety. PO Resp. 49–54. We do not find Patent Owner's argument persuasive.

As set forth in section II(C)(2), above, the proper interpretation of "extend the time to disease progression" requires a comparison of the claimed combination treatment to no treatment. Petitioner asserts that combining trastuzumab with paclitaxel 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." Pet. 50 n.16 (citing Ex. 1002 ¶¶ 137, 157 n.28; Ex. 1010); *see* Ex. 1020, 6–7 (describing time to tumor progression for the patients with either minor or stable disease as having "unusually long," with a median duration of 5.1 months). We find Petitioner's argument persuasive. Indeed, Patent Owner does not argue, and we do not find, that combining a taxoid with rhuMAb HER2 would abrogate the effect of either therapeutics. *See* Dec. 23–24. Thus, an ordinary artisan would have had a reasonable expectation of success in achieving the claimed clinical efficacy.

e) Patentability under Patent Owner's Claim Construction

We also address patentability under Patent Owner's proposed construction of "an amount effective to extend the time to disease progression in the human patient" and "an effective amount" as comparing the three-part treatment to treatment with taxoid alone. As an initial matter, Patent Owner argues that "no reference disclosed that the claimed combination extended TTP in human patients compared to patients treated with paclitaxel alone." *See* Paper 53, 11–12. Patent

Owner also admits, however, that when rhuMoAb is "administered with a chemotherapy in the 'taxoid' family, this claimed combination therapy significantly extends the time to disease progression ('TTP') as compared with patients receiving taxoid therapy alone." PO Resp. 2. The claimed extension of time to disease progression is, thus, an inherent benefit of an otherwise obvious combination, and such an inherent result cannot establish patentability. "[A]n obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the result[]." *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012). "To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." *Id.*

With respect to the parties' arguments, Patent Owner contends that under its preferred construction, Petitioner has not established that one of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed efficacy—i.e., administration of the claimed composition "in an amount effective to extend the time to disease progression" as compared to a patient treated with a taxoid alone. PO Resp. 47–52. In particular, Patent Owner argues that neither Seidman 1996 nor Pegram 1995 address TTP, and although the 1995 Taxol PDR and Baselga 1996, respectively, provide TTP data for patients treated with Taxol and rhuMoAb monotherapy, neither provides a basis to determine whether the claimed combination extends TTP compared to treatment with taxoid alone. *Id.* at 48–49. According to Patent Owner, these failings cannot be overcome by reference to patient response rates in Baselga 1996. *Id.* at 49–50.28

[28] Although we agree with Patent Owner that Petitioner has not shown that one of ordinary skill in the art would read the preclinical studies described in the Baselga

Upon careful consideration of all the evidence, we find that Petitioner has the better argument. *See* Pet. Reply 19–22. In particular, we credit the testimony of Dr. Earhart that because effective amounts of rhuMoAb and paclitaxel were known, one of ordinary skill in the art would have had a reasonable expectation that a combination of these agents would extend the time to disease progression relative to treatment with paclitaxel alone. *See, e.g.*, Ex. 1002 ¶¶ 119–120, 132, 132, 157; Ex. 1054 ¶¶ 20–23.

Although Patent Owner points out that the cited references do not expressly state that monotherapy with rhuMoAb or paclitaxel extends the time to disease progression, we credit Dr. Earhart's testimony that response rates and TTP are clinical surrogate endpoints used to estimate the likelihood of overall survival, and that a person of ordinary skill in the art would understand that a positive response rate would likely correlate with an increased TTP. Ex. 1054 ¶ 22; *see* Pet. Reply 20–22; Ex. 1002 ¶¶ 92–94, 136–137, 157, 166; Paper 64, 6. Consistent with this testimony, the '549 Specification also suggests time to disease progression and response rates as alternative measurements of efficacy. *See* Ex. 1057-1, 19 (15:12–17) ('649 priority application defining therapeutically effective amount; noting that "efficacy can . . . be measured by assessing the time for disease progression (TTP), or determining the response rates (RR)") 46–47 (42–43) (noting that clinical benefit is "assessed by response rates and the evaluation of disease progression").

Accordingly, we are persuaded that "a person of ordinary skill in the art would have understood that the response rate results reported in Baselga were

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references as supporting an increase in TTP (*see* PO Resp. 50), this does not affect our ultimate determination as to the obviousness of the challenged claims.

likely to correlate with an extension of time to disease progression and an increase in overall survival." Ex. 1054 ¶ 23; *see* Ex. 1020, 6, 7 & Table 4 (reporting "37% of patients achieved minimal responses or stable disease," and "an overall response rate of 11.6%"). As Dr. Earhart explains, "[a] person of ordinary skill in the art would have been motivated to combine trastuzumab with paclitaxel, with a reasonable expectation of success that the combination would perform better than no treatment and better than paclitaxel alone . . . . [and] achieve an extension of TTP over paclitaxel alone based on the superior TTP of trastuzumab." Ex. 1054 ¶¶ 19–20.

Patent Owner also emphasizes the high failure rate of clinical trials, in general, as evidence for the unpredictability of treating cancer. PO Resp. 11–12. Patent Owner relies on Exhibit 2021,[29] a review article on the pharmaceutical industry by Kola and Landis. PO Resp. 11–12. According to Patent Owner's expert, Kola and Landis "showed that approximately only five percent of oncology drugs were successful," and "that in oncology, the rate of failure in Phase III trials 'is as high as 59%,'" Ex. 2062 ¶¶ 91–92, 218.[30] Kola and Landis, however, focuses on clinical trials of individual compounds (i.e., new chemical entities (NCEs) and biologics) rather than combinations of known or promising therapies. *See e.g.,* Ex. 2021, 711 (discussing the "[d]epressing approval rates of NCEs and biologics"); *id.* at 712 (Table entitled, "NCEs required to achieve specific real growth targets as a function of 2002 revenues"); (addressing "the root causes of

[29] Kola and John Landis, *Can the Pharmaceutical Industry Reduce Attrition Rates?* 3 NATURE REV. 711-715 (2004) ("Ex. 2021").
[30] We further note that Dr. Tannenbaum appears to base "success" on FDA approval, which is a higher standard than required for patentabilty. *See* Ex. 2062 ¶ 214.

why ***compounds*** undergo attrition in the clinic," and stating that "more than 70% of oncology ***compounds*** fail [in Phase II trials]" and "approximately 45% of all ***compounds*** that enter [Phase III trials] undergo attrition and in some therapeutic areas, such as oncology, it is as high as 59%") (emphasis added).

Kola and Landis does not discuss the likelihood of failure of combination therapies like those at issue here—wherein paclitaxel was already FDA approved for treatment of breast cancer, rhuMoAb HER2 showed promise in Phase II trials, and both paclitaxel and rhuMoAb HER2 had been used successfully in combination therapy with a third compound, cisplatin. Moreover, despite Dr. Tannenbaum's assertion that the increased cardiotoxicity of anthracyclines in combination with rhuMAb HER2 shows the lack of predictability of new combinations of existing therapies, such information was not in the prior art at the time of the invention. Ex. 2062 ¶ 207. Accordingly, we do not give substantial weight to Dr. Tannenbaum's opinions on this topic.

Also relying on Dr. Tannenbaum's testimony, Patent Owner argues that the four principles of combination therapy discussed by Dr. Earhart (*see* Ex. 1002 ¶¶ 125–130; Ex. 1024 ¶¶130–131)[31] only apply to small molecule chemotherapeutics and are inapplicable to combinations involving antibodies such as rhuMoAb HER2. *See* PO Resp 11–12, 46–47, 51 (citations omitted). We do not find Patent Owner's arguments persuasive.

At its core, Patent Owner's assertion is based on the fact that the "four principles" concept was established before the use of therapeutic antibodies such that there is no record evidence of researchers expressly applying these principles

[31] Although not necessary to our Decision, we find that Dr. Earhart's discussion of these principles underscores and further supports our patentability analysis.

to combinations involving antibodies. *See id.* But this merely reflects the historical use of small molecule chemotherapeutic combinations before the development of more complex therapeutic antibodies. *See* Ex. 2072, 365 (noting the introduction of chemotherapeutic combination therapy for advanced breast cancer in 1963).

Patent Owner further bases its assertion on evidence that combining chemotherapy with chemoendocrine (hormone) therapy "did not increase the response rate, TTP, or survival as compared to either treatment alone." PO Resp. 51–52. Patent Owner does not, however, suggest that such therapy involved therapeutic antibodies, nor persuade us that the failure of the chemotherapy/hormone therapy combination would dissuade one of ordinary skill in the art from combining chemotherapeutic treatments with other therapies. Moreover, Patent Owner's expert, Dr. Tannenbaum admitted that she was not aware of any prior art suggesting that that the four principles would not apply to chemotherapy/antibody combinations such as rhuMoAb HER2/paclitaxel. Ex. 1052, 71:25–72:6, 90:9–91:6; *see also id.* at 99:11–18, 102:17–106:20, 108:24–109:12 (admitting that the prior art suggested the use of antibodies with chemotherapies, including the rhuMoAb/paclitaxel combination).

Patent Owner also references Exhibit 2136[32] (Wadler) as indicating that incorporating various biological agents in combination regimens with chemotherapeutic "offers an important challenge to the medical oncologist." Paper 53, 7–8. While we do not completely discount the teachings of this reference, we note Petitioner's argument that Wadler is primarily focused on cytokines and

[32] Wadler & Schwartz, *Antineoplastic Activity of the Combination of Interferon and Cytotoxic Agents Against Experimental and Human Malignancies: A Review*, Cancer Res. 50:3473-3486 (1990) (Exhibit 2136).

growth factors, rather than antibodies, and does not take into account the body of knowledge in the art regarding the use of rhuMoAb HER2. *See* Paper 64; Ex. 1105 ¶ 15 (noting that Wadler "recommends further study of a combination of interferon alpha [sic] with 5-fluorouracil"). On balance, the record does not suggest that one of ordinary skill in the art would reject the four principles of combination therapy when considering rhuMoAb HER2 therapy. The record as a whole supports a finding that an ordinary artisan would have had a reason to combine trastuzumab and paclitaxel for the treatment of metastatic HER2-positive breast cancer.

a) Conclusion

Considering the evidence as a whole, we agree with Petitioner that one of ordinary skill in the art would have been motivated to combine the teachings of Baselga 1996, Seidman 1996, Pegram 1995, and 1995 TAXOL PDR with a reasonable expectation of success in achieving the invention of claims 1–11 and 14–17 of the '549 Patent. Accordingly, and applying either the construction set forth in section II(C)(2), above, or Patent Owner's preferred construction, we conclude that Petitioner has demonstrated by a preponderance of evidence that the challenged claims would have been obvious.

III. Motions

A. Patent Owner's Motion to Amend

Having concluded that claims 1–11 and 14–17 are unpatentable, we address Patent Owner's contingent Motion to Amend.

1. *Threshold Requirements*

In an *inter partes* review, amended claims are not added to a patent as of right, but rather must be proposed as a part of a motion to amend. 35 U.S.C. § 316(d). The Board must assess the patentability of the proposed substitute claims

"without placing the burden of persuasion on the patent owner." *Aqua Prods., Inc. v. Matal*, 872 F.3d 1290, 1328 (Fed. Cir. 2017). Patent Owner's proposed substitute claims, however, must still meet the statutory requirements of 35 U.S.C. § 316(d) and the procedural requirements of 37 C.F.R. § 42.121. *See* "Guidance on Motions to Amend in view of *Aqua Products*" (Nov. 21, 2017), available at https://www.uspto.gov/sites/default/files/documents/guidance_on_motions_to_amend_11_2017.pdf. Accordingly, Patent Owner must demonstrate (1) the amendment proposes a reasonable number of substitute claims; (2) the amendment does not seek to enlarge the scope of the claims of the patent or introduce new subject matter; (3) the amendment responds to a ground of unpatentability involved in the trial; and (4) the original disclosure sets forth written description support for each proposed claim. *See 35 U.S.C. § 316(d);* 37 C.F.R. § 42.121.

In its Motion to Amend, "Petitioner conditionally seeks to amend the claims to make explicit that the claimed comparison is against a patient treated with paclitaxel alone." PO Resp. 48, n.14; *see* Paper 26, 4. Accordingly, Patent Owner proposes to replace all existing claims (claims 1–17) with substitute claims 18–20, of which claims 18 and 19 are independent. Paper 26, 2 and Appendix A. Under the circumstances, we agree with Patent Owner that it proposes a reasonable number of substitute claims. *See Id.* at Abstract.

With respect to the substance of the proposed claims, Claim 18, submitted as a replacement for claim 1, recites:

> 18. A method of treatment of a human patient with breast cancer that overexpresses ErbB2 receptor, comprising administering a combination of rhuMAb HER2, paclitaxel, and a further growth inhibitory agent to a human patient in an amount effective to extend the time to disease progression in the human patient, as compared to paclitaxel alone, wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence.

Id. Claim 19, submitted as a replacement for claim 16 is similar, but further recites the administration of rhuMAb HER2, paclitaxel, and a further growth inhibitory agent "in the absence of an anthracycline derivative." *Id.* Depending from claim 19, claim 20 specifies that the ErbB2 overexpressing breast cancer is metastatic breast carcinoma and is identical to original claim 17 but for its dependency.

Patent Owner contends that the substitute claims do not enlarge but, instead, narrow the scope of the original claims. *Id.* at 2–5. According to Patent Owner, the proposed substitute claims narrow the scope of the claimed antibody by replacing the genus of "an antibody that binds ErbB2" of claim 1 or "an intact antibody which binds to epitope 4D5 with the ErbB2 extracellular domain sequence" of claim 16, with the "specific antibody species, 'rhuMAb HER2,' a recombinant humanized 4D5 anti-ErbB2 antibody also known as HERCEPTIN®." Paper 26, 2–3. Patent Owner similarly argues that the substitute claims narrow the genus encompassing "a taxoid" by reciting "'paclitaxel,' which is a specific species of taxoid." *Id.* at 3.

With respect to the claim language, "an amount effective to extend the time to disease progression in the human patient," Patent Owner contends that "the Challenged Claims do not expressly identify a comparator for the claimed 'time to disease progression'; therefore, by further limiting the claims with a specific comparator (patients treated with paclitaxel alone), the Substitute Claims do not enlarge the scope of the claims." *Id.* at 4. Alternatively, Patent Owner argues that the additional limitation merely makes explicit that, under Patent Owner's preferred construction of the original claims, "the proper comparator by which to measure the claimed efficacy is to a patient treated with paclitaxel alone." *Id.* With respect to the original claims, we apply our construction for the term "extend the time to disease progression" as indicating that the results of the claimed

combination therapy is compared to patients receiving no treatment. Because we do not discern, and Petitioner does not contend, that the comparator of patients receiving no treatment is broader that those receiving paclitaxel alone in the proposed amended claims , we agree with Patent Owner that the amendment does not seek to enlarge the scope of the claims as required under 35 U.S.C. § 316(d) and 37 C.F.R. § 42.121.

Petitioner argues that we should deny Patent Owner's Motion to Amend under 37 C.F.R. § 42.121(a)(2)(i) because the amendments narrowing the claims to specifically recite "rhuMAb HER2" and "paclitaxel" do not respond to the instituted grounds of unpatentability. Paper 43, 2–6; Paper 64, 1–2. According to Patent Owner, "[i]t is not required that ***every*** amended limitation be solely for the purpose of overcoming an instituted ground" such it is sufficient that the proposed claims have been amended to specify that the comparator for an amount effective to extend the time to disease progression is paclitaxel alone. *See* Paper 26, 9 & fn.3. (citing *Veeam Software Corp. v. Veritas Techs., LLC*, IPR2014-00090, Paper 48 at 28-29 (PTAB July 17, 2017)). We agree with Patent Owner. "[37 C.F.R. § 42.121(a)(2)(i)] does not require, however, that every word added to or removed from a claim in a motion to amend be solely for the purpose of overcoming an instituted ground. Additional modifications that address potential 35 U.S.C. § 101 or § 112 issues, ***for example***, are not precluded by rule or statute." *Western Digital Corp. v. SPEX Techs., Inc.*, Case IPR2018-00082 (PTAB Apr. 25, 2018) (Paper 13) (informative), slip op. at 6 (emphasis added). Although Patent Owner does not indicate whether the disputed limitations are intended to address 35 U.S.C. §§ 101 or 103 issues, this is not expressly required under our rules. Moreover, in indicating that addressing potential § 101 or § 112 issues are merely exemplary, *Western Digital* suggests that Patent Owner may have other reasons for entering

such amendments. As the disputed limitations are peripheral to our patentability analysis (*see* section III(A)(2), below) and do not otherwise unduly burden the just and speedy resolution of this matter, we do not reject Patent Owner's Motion to Amend under 37 C.F.R. § 42.121(a)(2)(i).

Petitioner also argues that the substitute claims add new subject matter in contravention of Section 316(d) and Rule 42.121(a)(2)(ii). *See* Paper 43, 6–7; Paper 80, 3. Although Patent Owner asserts that each of the proposed substitute claims find support in the original disclosure (Paper 26, 5–9; Paper 53, 3–4), Petitioner argues that "a person of ordinary skill in the art would not have recognized from the specification [of the asserted priority documents] that the inventor had possession of a triple combination treatment that extends time to disease progression compared to paclitaxel alone," (Paper 43, 6–7), i.e., that the priority documents that Patent Owner relies on lack sufficient written descriptive support for the full scope of the proposed claims.

"In determining whether claims introduce new matter, we look to whether the original application provides adequate written description support for the claims." *Kapsch TrafficCom IVHS Inc. v. Neology, Inc.*, Case IPR2016-01763, slip op. at 47 (PTAB Mar. 20, 2018) (Paper 60). The written description requirement is met when the specification "conveys to those skilled in the art that the inventor had possession of" and "actually invented" the claimed subject matter. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*). "And while the description requirement does not demand any particular form of disclosure, or that the specification recite the claimed invention *in haec verba*, a description that merely renders the invention obvious does not satisfy the requirement." *Id.* at 1352 (citations omitted); *See also In re Wertheim*, 541 F.2d 257, 262 (CCPA 1976) ("It is not necessary that the application describe the claim

limitations exactly, . . . but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that appellants invented processes including those limitations.").

Patent Owner's proposed substitute claims require the administration of a three-drug combination —rhuMAb HER2, paclitaxel, and a further growth inhibitory agent— "in an amount effective to extend the time to disease progression in the human patient, as compared to paclitaxel alone." Patent Owner's support for the clinical effects of this three-drug combination, however, relates to the administration of a two-drug combination. *See* Paper 26, 5–8; Paper 53, 3. In particular, Patent Owner relies on "a clinical study in which patients with metastatic [HER2-positive] breast cancer or overexpression of the ErbB2 oncogene were treated with a combination of a humanized version of the murine 4D5 antibody (HERCEPTIN®) (also known as rhuMAb HER2) and Taxol® (also known as paclitaxel) in the absence of anthracycline derivative." Paper 26, 7. Patent Owner asserts that "[t]he results state that '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.* (citing Ex. 1004-1 49 (43:19–21) and Ex. 1009, 43–44 (42:29–43:2)).

The written description requirement demands that inventors "do more than merely disclose that which would render the claimed invention obvious." *ICU Medical, Inc. v. Alaris Medical Systems, Inc*. 558 F.3d 1368, 1377 (Fed. Cir. 2009). Considering the evidence of record, we agree with Petitioner that "a person of ordinary skill in the art would not have recognized from the specifications that the inventor had possession of a triple combination treatment that extends time to disease progression compared to paclitaxel alone." Paper 43, 7. "Showing

possession of a different, unclaimed combination is insufficient." *See Ariad*, 598 F.3d at 1352. Because Patent Owner has not shown, and we do not find adequate written description supporting the proposed substitute claims, they likewise fail to satisfy the no new matter requirement of 35 U.S.C. § 316(d) and 37 C.F.R. § 42.121(a)(2)(ii). Accordingly, we deny Patent Owner's Motion to Amend.

2. *Unpatentability of the Amended Claims*

In addition to its failure to meet the "no new matter" requirement for a motion to amend, we deny Patent Owner's Motion to Amend because Petitioner has shown by a preponderance of the evidence that claims 18–20 are obvious in view of the art of record. *See* Paper 43, 7–20. Paper 64, 3–10. In short, Patent Owner does not contend, nor do we discern, that narrowing the proposed claims to specifically recite "rhuMAb HER2" and "paclitaxel" bears on patentability, but relies on the addition of the words "as compared to paclitaxel alone" to make explicit the claim construction it argued with respect to the originally-challenged claims. PO Resp. 48, n.14; *see* Paper 26, 4. Patent Owner then recites substantially the same arguments it put forth with respect to claims 1–11 and 14–17 under its preferred construction. *Cf.* Paper, 26, 9–24; Paper 53, 4–12 with PO Resp. 37–54. Having found those arguments unavailing (*see* section II(E), above), we decline to revisit them here.

B. Patent Owner's Motion to Exclude Evidence

Patent Owner filed one motion to exclude evidence. Paper 59. Petitioners opposed (Paper 72) and Patent Owner submitted a reply in support of its motion (Paper 75).

1. *Evidence Relating to Secondary Considerations*

Patent Owner requests that we exclude Exhibits 1033, 1034, 1038, 1059, and 1060 as irrelevant. Paper 59, 1–2. According to Patent Owner, these exhibits

relate to secondary considerations, which it does not assert in this proceeding. *Id.*; Paper 75, 1. Petitioner concurs, noting that it has not cited these documents in this *inter partes* review. Paper 72, 1. Accordingly, we dismiss Patent Owner's request as moot.

2. *Evidence Concerning Surrogate Endpoints*

Patent Owner moves to exclude Exhibit 1055, as well as select paragraphs of Dr. Earhart's reply declaration (Ex. 1054 ¶¶ 22–23), which relate to Petitioner's argument that one of ordinary skill in the art would understand that response rates and time to disease progression are surrogates for time to disease progression, and that one of ordinary skill in the arm would expect some measure of correlation between these values. *See* Paper 59, 2–4; Paper 72, 1–2. Patent Owner argues that we should exclude this evidence as untimely because Petitioners raised it for the first time in their reply, "after which PO had no opportunity to respond." Paper 59, 2.

We do not find Patent Owner's arguments persuasive for the reasons set forth in Petitioners' opposition (Paper 72, 1–3), which we adopt. In particular, we agree with Petitioner that Exhibit 1055 and paragraphs 22–23 of Exhibit 1054 are proper rebuttal to Patent Owner's contention that "the 'response rates disclosed in the instituted references . . . do not suggest an extension of TTP when using the claimed combination.'" *Id.* at 3 (citing PO Resp. 49). *See Ericsson Inc. v. Intellectual Ventures I LLC*, No. 2017-1521, 2018 WL 4055815, at *6 (Fed. Cir. Aug. 27, 2018) (Board improperly refused to consider Reply testimony that "merely expands on a previously argued rationale"); *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1077–78 (Fed. Cir. 2015) (holding that a petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make

out a prima facie case of unpatentability, but may submit directly responsive rebuttal evidence in support of its reply).

Accordingly, we deny Patent Owner's motion to exclude Exhibit 1055 and paragraphs 22–23 of Exhibit 1054.

3. *Gelmon Declaration*

Patent Owner requests that we exclude Exhibit 1056, which is a declaration submitted by Dr. Karen Gelmon on behalf of Patent Owner in IPR2017-01139. Paper 59, 4–5; Paper 75, 2. As set forth in its opposition, Petitioner relies on Exhibit 1056 to rebut Patent Owner's argument that one of ordinary skill in the art would not rely on Seidman 1996 because it was "merely an abstract." *See* Paper 72, 3–4. Insofar as Dr. Gelmon relies on an abstract in arguments on behalf of Patent Owner, we find Petitioner's citation to Exhibit 1056 relevant. Although, as Patent Owner points out, Dr. Gelmon relies on additional information, this goes to the weight we accord Petitioner's evidence, not its admissibility. *See* Paper 59, 4–5. Patent Owner has not explained, nor do we discern, how this might "mislead or confuse" the Board. *See id.* at 5. Accordingly we deny Patent Owner's motion to exclude Exhibit 1056.

4. *Gottlieb Article*

Patent Owner requests that we "exclude Exhibit 1036, a 1980 article published in *Chest for Pulmonologists, Cardiologists, Cardiothoracic Surgeons and Related Specialists*, entitled, *Late, Late Doxorubicin Cardiotoxicity* ("Gottlieb"), and paragraph 38 of Dr. Earhart's reply declaration relying on Gottlieb (Exhibit 1054)" as untimely because Petitioner raised it for the first time in its reply. Paper 59, 5–6. According to Patent Owner, "to the extent Petitioner wished to present evidence that POSAs would have been motivated to avoid anthracyclines, it was obligated to do so in the Petition as part of its prima facie

case, rather than wait until its Reply, after which PO had no opportunity to respond." Paper 75, 3. We do not find Patent Owner's argument persuasive.

The Petition itself sets forth a reasoned explanation of why one of ordinary skill in the art would have been motivated to avoid anthracyclines, stating, for example, that one of ordinary skill in the art:

> would have been well-aware of the cardiotoxicity issues with anthracycline derivatives. (Ex. 1002, ¶ 138; Ex. 1016 (Abeloff), 813.) Anthracyclines were known to cause irreversible cardiotoxicity thereby limiting the total lifetime dose a patient can receive. (Ex. 1002, ¶ 138; Ex. 1016 (Abeloff), 813.) Accordingly, a POSA would have limited use of anthracycline derivatives in treatment whenever possible. (Ex. 1002, ¶ 139; Ex. 1016 (Abeloff), 813.) Further, because anthracycline derivatives were a first-choice therapy for metastatic breast cancer, many candidates for treatment with the trastuzumab and paclitaxel combination would have already been treated with anthracycline-based therapy. (Ex. 1002, ¶ 138; Ex. 1016 (Abeloff), 810.) This means that many patients with metastatic disease who were prescribed a paclitaxel-containing regimen would have already endured extensive anthracycline-based therapy and would risk significant cardiotoxic effects with continued anthracycline-based therapy. (Ex. 1002, ¶ 138.) POSAs would have avoided administering further anthracycline derivatives to the many patients who had already been treated with this class of drug or to the many patients who are resistant to treatment with anthracyclines, rendering the limitation "in the absence of an anthracycline derivative" obvious. (Ex. 1002, ¶ 138; *see also* Ex. 1020 (Baselga 1996), at 740 (reporting that a patient died during treatment with trastuzumab due to congestive heart failure associated with prior anthracycline use); Ex. 1024 (Arbuck), at 128-29 (reporting that many anthracycline-resistant patients responded to paclitaxel).)

Pet. 51–52. In addition, we agree with Petitioner that its introduction of Gottlieb was a reasonable rebuttal to Patent Owner's argument that one of ordinary skill in the art "would have not have been motivated to avoid anthracycline due to the cardiotoxicity caused by anthracyclines because the cardiotoxicity caused by anthracyclines was 'manageable.'" Paper 72, 5; *see* Pet. Reply 13 (citing Gottlieb

(among others) as teaching that "[t]he cardiotoxicity of anthracyclines was the major factor limiting their use"). Accordingly, we deny Patent Owner's motion to exclude Exhibit 1036 and Exhibit 1054 ¶38.

5. *Dr. Kerbel's Patent Application*

Patent Owner requests that we exclude Exhibit 1100, an international patent application naming Dr. Kerbel as an inventor as irrelevant under FRE 402 and as "tend[ing] to mislead and confuse the issues" in contravention of FRE 403. Paper 59, 7–8; Paper 75, 3. Patent Owner has not explained, nor do we discern, how the Board might be misled or confused by Exhibit 1100. Moreover, Petitioners have adequately explained the relevance of these exhibits to the present case. *See* Paper 72, 5–7. Accordingly, we deny Patent Owner's motion to exclude Exhibit 1100.

C. Petitioners' First and Second Motions to Exclude Evidence

In its first motion (Paper 61), Petitioner moves to exclude Exhibits 2052, 2055, 2070, 2075, 2106, 2133, 2135 and 2139, and portions of expert declarations submitted on behalf of Patent Owner that rely on them (Ex. 2061 ¶ 56; Ex. 2143 ¶¶ 11, 15; Ex. 2144 ¶¶ 27–28). Patent Owner opposed (Paper 70) and Petitioner submitted a reply in support of its first motion (Paper 77). In its second motion, Petitioner moves to exclude Exhibit 2146. Paper 81. Patent Owner opposed (Paper 83) and Petitioner submitted a reply in support of its first motion (Paper 84).

1. Exhibits 2052, 2055, 2070, 2075, 2106, 2133, and 2139

Petitioner contends that Exhibits 2075, 2133, and 2139 are dated after December 12, 1997, the priority date of the '441 patent, and that Patent Owner has not established that Exhibits 2052, 2055, 2070, and 2106, were published before this date, such that each of these exhibits are "irrelevant for the purpose of establishing the teachings of the prior art, and Patent Owner is relying on them for improper purposes." Paper 61, 1, 3. We do not, however, expressly rely on

Exhibits 2052, 2055, 2070, 2075, 2106, 2133, or 2139 in our Decision. Moreover, having considered the merits of Patent Owner's arguments in light of these teachings, our decision as to the patentability of the challenged claims would not change if they were excluded from evidence. Accordingly, we need not decide the merits of Petitioner's motion with respect to these documents and dismiss Petitioner's request as moot.

2. Exhibits 2135 and 2146 (Hsu)

In its first and second motions, Petitioner also requests that we exclude the Hsu Abstract (Exhibit 2135), a related document encompassing Hsu (Exhibit 2146), and certain expert testimony relying on those exhibits. Among other things, Petitioner contends Patent Owner has not established the authenticity or prior art status of Exhibits 2135 and 2146, and that they are hearsay under FRE 802. *See* Paper 61, 7–9; Paper 81, 4–7. As set forth in section II(E)(a)(3), above, we do not find persuasive Patent Owner's evidence regarding the substance of Hsu. Accordingly, and taking no position as to the merits of the parties' arguments relating to the admissibility of the Hsu references, we deny this remaining portion of Petitioner's request as moot.

D. Motions to Seal

We also address the five unopposed motions to seal pursuant to the Modified Default Standing Protective Order set forth in Exhibit 2036 (*see* Paper 24, 3): Papers 27 and 52 (by Patent Owner) and Papers 44, 47, and 62 (by Petitioner).

The Board's standards for granting motions to seal are discussed in *Garmin International v. Cuozzo Speed Technologies, LLC*, IPR2012-00001 (PTAB Mar. 14, 2013) (Paper 34). In summary, there is a strong public policy for making all information filed in *inter partes* review proceedings open to the public, especially because the proceeding determines the patentability of claims in an issued patent

and, therefore, affects the rights of the public. *Id*. at slip op. 1–2. Under 35 U.S.C. § 316(a)(1) and 37 C.F.R. § 42.14, the default rule is that all papers filed in an inter partes review are open and available for access by the public; a party, however, may file a concurrent motion to seal and the information at issue is sealed pending the outcome of the motion. It is only "confidential information" that is protected from disclosure. 35 U.S.C. § 316(a)(7); *see* Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,760 (Aug. 14, 2012). The standard for granting a motion to seal is "for good cause." 37 C.F.R. § 42.54(a). The party moving to seal bears the burden of proof in showing entitlement to the requested relief, and must explain why the information sought to be sealed constitutes confidential information. 37 C.F.R. § 42.20(c).

We remind the parties of the expectation that confidential information relied upon or identified in a final written decision will be made public. *See* Office Trial Practice Guide, 77 Fed. Reg. 48756, 48761 (Aug. 14, 2012). Confidential information that is subject to a protective order ordinarily becomes public 45 days after final judgment in a trial. A party seeking to maintain the confidentiality of the information may file a motion to expunge the information from the record prior to the information becoming public. 37 C.F.R. § 42.56.

1. Patent Owner's Motions to Seal

In Paper 27, Patent Owner seeks to seal the unredacted version of Exhibit 2050 (the Deposition Transcript of Robert Howard Earhart, Jr., M.D., Ph.D.), and the unredacted version of Exhibit 2069 (the Declaration of Stephanie Mendelsohn, which purports to authenticate previously sealed Exhibits 2001–2005, 2007, and 2008). Patent Owner has shown good cause supporting the motion. Insofar as, none of the material in Exhibits 2050 or 2069 is relied on in our final Decision, Patent Owner's request is granted. Because we rely herein on Exhibits 2001, 2004,

and 2008, we rescind our grant of Patent Owner's motion to seal with respect to those documents. *See* Paper 24, 2. Within 14 days of this Decision, Patent Owner may submit redacted versions of Exhibits 2001, 2004, and/or 2008 that fairly disclose the material relied on in this Decision along with a renewed motion to seal, filed jointly.

In Paper 52, Patent Owner seeks to seal Exhibit 2142 (Genentech, Inc. Document GENENTECH_0000034-GENENTECH-0000139) and the unredacted version of Exhibit 2144 (Supplemental Expert Declaration of Dr. Susan Tannenbaum). Patent Owner has shown good cause supporting the motion. Insofar as, we do not rely on material in Exhibits 2142 or Exhibit 2144 in our final Decision, Patent Owner's request is granted with respect to those documents.

Also in Paper 52, Patent Owner seeks to seal the unredacted version of Paper 53 (Patent Owner's Reply in Support of Contingent Motion to Amend Under 37 C.F.R. § 42.121). Patent Owner's request is denied without prejudice, subject to the conditions set forth in the Order, below.

2. Petitioner's Motions to Seal

Petitioner seeks to seal the confidential versions of its Reply (Paper 45), and its Opposition and Sur-Reply to Patent Owner's Motion to Amend (Papers 42, 64, and respectively), because they "refer to materials that Patent Owner Genentech has designated as Confidential pursuant to the Modified Default Standing Protective Order." Paper 44, 1; Paper 62, 1. Petitioner seeks to seal Exhibits 1035, 1046, 1049, and 1058 for the same reason. Paper 47, 1.

Petitioners provide no other justification for why the redacted portions of the cited documents should be kept confidential and, thus, fail to satisfy the good cause requirement. Accordingly, Petitioners' motions are denied. Petitioner's request is further denied with respect to Exhibit 1035, which we rely on in our Decision.

Patent Owner is invited to file, within 14 days of this Decision, a motion to seal any presently redacted portion(s) of Papers 42, 45, 53, and 64 or Exhibits 1046, 1049, and 1058. The motion must explain why the information sought to be protected is truly confidential and attest that such information is not directly or indirectly relied on in our Final Written Decision. Petitioner may respond within one week of Patent Owner's motion, if desired. These Papers and Exhibits will remain designated Board and Parties Only for 21 days from this Decision or until consideration of any such motion and reply.

IV. CONCLUSION

After considering Petitioners' and Patent Owner's arguments and evidence, we conclude that Petitioners have shown, by a preponderance of the evidence, that claims 1–11 and 14–17 of the '549 patent would have been obvious over the combination Baselga 1996, Seidman 1996, Pegram, and the 1995 TAXOL PDR as set forth in the Petition.

Based on the evidence of record, we conclude that proposed amended claims 18–20 introduce new matter in contravention of Section 316(d) and Rule 42.121(a)(2)(ii) and, moreover, would not be patentable over the art of record. The parties' motions to exclude evidence and to seal are addressed in the following Order.

V. ORDER

In consideration of the foregoing, it is:

ORDERED that claims 1–11 and 14–17 of the '549 patent are unpatentable;

FURTHER ORDERED that Patent Owners' motion to amend is denied;

FURTHER ORDERED that Patent Owner's motion to exclude Exhibits 1033, 1034, 1038, 1059, and 1060 is denied as moot;

FURTHER ORDERED that Patent Owner's motion to exclude Exhibits 1100, 1036, 1055, 1056, and paragraphs 22–23, and 38 of Exhibit 1054 is denied.

FURTHER ORDERED that Petitioners' motion to exclude Exhibits 2052, 2055, 2070, 2075, 2106, 2133, 2135, 2139, and 2146 is denied as moot.

FURTHER ORDERED that Patent Owner's motions to seal Exhibits 2069 and 2142, and the confidential versions of Exhibits 2050 and 2144 is granted.

FURTHER ORDERED that, notwithstanding our prior Order in Paper 24, we rescind our Order to seal Exhibits 2001, 2004, and 2008. Within 14 days of this Decision, Patent Owner may submit redacted versions of Exhibits 2001, 2004, and/or 2008 that fairly disclose the material relied on in this Decision along with a renewed motion to seal, filed jointly.

FURTHER ORDERED that Petitioner's motion to seal Exhibit 1035 is denied.

FURTHER ORDERED that Petitioner's motion to seal Exhibits 1046, 1049, and 1058, and the confidential versions of Papers 42, 45, and 64 is denied without prejudice to Patent Owner.

FURTHER ORDERED that Patent Owner may file, within 14 days of this Decision, a motion to seal any of Exhibits 1046, 1049, and 1058 or the presently redacted portion(s) of Papers 42, 45, 52, and 64. The motion must explain why the information sought to be protected is truly confidential and attest that such information is not directly or indirectly relied on in our final Decision. Petitioner may respond within one week of Patent Owner's motion, if desired. These Papers and Exhibits will remain designated Board and Parties Only for 21 days from this Decision or until consideration of any such motion and reply.

FURTHER ORDERED that, because this is a final written decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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