UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC. and PFIZER, INC.,
Petitioner,

v.

GENENTECH, INC,
Patent Owner.

Case IPR2017-01121[1]
Patent 7,846,441 B1

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

YANG, *Administrative Patent Judge*.

[1] Case IPR2017-02063 has been joined with this proceeding.

DECISION
FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

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

Dismissing Petitioner's Motions to Exclude
37 C.F.R. § 42.64(c)

Denying-in-Part and Dismissing-in-Part Patent Owner's Motion to Exclude
37 C.F.R. § 42.64(c)

Denying Petitioner's Motions to Seal without Prejudice to Patent Owner
37 C.F.R. § 42.55

Granting Patent Owner's Motions to Seal
37 C.F.R. § 42.55

Modifying Previous Order Granting Patent Owner's Motions to Seal
37 C.F.R. § 42.55

INTRODUCTION

Celltrion, Inc. ("Petitioner") filed a Petition for an *inter partes* review of claims 1–14 of U.S. Patent No. 7,846,441 B1 (Ex. 1001, "the '441 patent"). Paper 1 ("Pet."). Genentech, Inc. ("Patent Owner") filed a Preliminary Response. Paper 8. On October 4, 2017, the Board instituted trial to review patentability of the challenged claims. Paper 9 ("Dec."). Thereafter, we joined IPR2017-02063, filed by Pfizer, Inc., and challenging the same claims of the '441 patent, with the instant proceeding. Paper 39.

Patent Owner filed a Response to the Petition (Paper 26, "PO Resp."), and Petitioner filed a Reply (Paper 45, "Reply"). Patent Owner also filed a contingent Motion to Amend (Paper 28, "MTA"), to which Petitioner filed an Opposition (Paper 47, "MTA Opp."). After Patent Owner filed a Reply in support of the Motion to Amend (Paper 55, "MTA Reply"), and with our authorization, Petitioner filed a Sur-reply (Paper 66, "MTA Sur-reply").

The parties also briefed whether certain exhibits should be excluded from the record. Papers 61, 63, 72, 74, 77, 79, 83, 85, 86. In addition, Patent Owner filed observations on the cross-examination of Petitioner's declarant (Papers 71, 76), and Petitioner filed responses thereto (Papers 78, 82).

An oral hearing for this proceeding was held on May 18, 2018. *See* Paper 87 ("Tr.").

The Board has jurisdiction under 35 U.S.C. § 6 and issues this final written decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons provided below, we conclude Petitioner has established by a preponderance of the evidence that (1) claims 1–14 of the '441 patent are

unpatentable, and (2) claim 15 proposed by Patent Owner in the contingent Motion to Amend is unpatentable.

Related Proceedings

The '441 patent is also the subject of IPR2017-00731. Concurrently with this Decision, we issue a final written decision in that case.

We also issue, concurrently with this Decision, final written decisions in IPR2017-00737 and IPR2017-01122 to address the patentability of certain claims of U.S. Patent No. 7,892,549, a patent in the same family as the '441 patent at issue here.

The '441 Patent

The '441 patent claims priority to a provisional application filed December 12, 1997. Ex. 1001, (60).

The '441 patent relates to the treatment of disorders characterized by the overexpression of ErbB2. Ex. 1001, Abstract, 1:11–12. According to the Specification, "human ErbB2 gene (erbB2, also known as her2, or c-erbB-2), which encodes a 185-kd transmembrane glycoprotein receptor ($p185^{HER2}$) related to the epidermal growth factor receptor (EGFR), is overexpressed in about 25% to 30% of human breast cancer." *Id.* at 1:23–27. Before the '441 patent, "[a] recombinant humanized anti-ErbB2 monoclonal antibody (a humanized version of the murine anti-ErbB2 antibody 4D5, referred to as rhuMAb HER2 or HERCEPTIN®) had been clinically active in patients with ErbB2-overexpressing metastatic breast cancers that had received extensive prior anti-cancer therapy." *Id.* at 3:34–39. The parties do not dispute that this recombinant humanized anti-ErbB2 monoclonal antibody is also referred to as trastuzumab.

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

The '441 patent states that

> [T]he invention concerns a method for the treatment of a human patient susceptible to or diagnosed with a disorder characterized by overexpression of ErbB2 receptor comprising administering a therapeutically effective amount of a combination of an anti-ErbB2 antibody and a chemotherapeutic agent other than an anthracycline derivative, e.g. doxorubicin or epirubicin, in the absence of an anthracycline derivative, to the human patient.

Id. at 4:4–11.

Illustrative Claim

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

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

Reviewed Ground of Unpatentability

We instituted *inter partes* review to determine whether the challenged claims would have been obvious over the combination of Baselga 1996,[2]

[2] Baselga et al., *Phase II Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients with HER2/neu-*

Seidman 1996,[3] and the 1995 TAXOL PDR entry,[4] in view of the knowledge of a person of ordinary skill in the art. Dec. 19.

In support of their respective arguments, Petitioner relies on the Declarations of Dr. Robert Earhart (Exs. 1002, 1054, 1105), and Patent Owner relies on the Declarations of Dr. Robert S. Kerbel (Exs. 2061, 2143), Dr. Susan Tannenbaum (Ex. 2062, 2144), and Dr. Susan Desmond-Hellmann (Ex. 2125).

ANALYSIS

Principles of Law

To prevail in this *inter partes* review of the challenged claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter 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 said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art;

Overexpressing Metastatic Breast Cancer, 14 J. CLIN. ONCOL. 737–44 (1996) (Ex. 1020, "Baselga 1996").

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

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

(2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). The strength of each of the *Graham* factors must be weighed in every case and must be weighted en route to the final obviousness determination. *See, e.g.*, *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983) (instructing that evidence of secondary considerations, when present, must always be considered in determining obviousness).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention does." *Id.* Moreover, a person of ordinary skill in the art must have had a reasonable expectation of success of doing so. *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014).

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

Claim Construction

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent

disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Each challenged claim, either explicitly or through dependency, recites "extend the time to disease progression [TTP] in said human patient, without increase in overall severe adverse events." In the Decision to Institute, we stated that "[g]iven the applicant's unequivocal statement to overcome the indefiniteness rejection during prosecution, we determine that the proper analysis of the term . . . is to compare the claimed combination treatment to no treatment." Dec. 6.

Patent Owner disputes this construction. PO Resp. 36–39. According to Patent Owner, "[b]oth parties' experts agree that the specification supports a construction that compares the claimed combination treatment to treatment with a taxoid alone." *Id.* at 36 (citing Ex. 1002 ¶ 112(h); Ex. 2062 ¶¶ 129–138). Patent Owner's representation is less than complete. Dr. Earhart, for example, specifically noted that, during prosecution, the applicant asserted that the comparison is between the claimed combination treatment and no treatment. Ex. 1002 ¶ 112(h) (citing Ex. 1004, 416). According to Dr. Earhart, this alternate claim construction does not impact his unpatentability analysis. *Id.*

It is well settled that "an invention is construed not only in the light of the claims, but also with reference to the . . . prosecution history in the Patent Office." *Graham*, 383 U.S. at 33. "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). Under the broadest reasonable interpretation standard, statements made during prosecution can be "relevant as reinforcing the evident meaning of the claim language at issue, whether or not it would meet standards for disclaimer or disavowal." *D'Agostino v. MasterCard Int'l Inc.*, 844 F.3d 945, 949 (Fed. Cir. 2016); *see also Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015) (the Board "should also consult the patent's prosecution history in proceedings in which the patent has been brought back to the agency for a second review").

During prosecution, the examiner rejected then-pending claims that included the term at issue as indefinite under 35 U.S.C. § 112. Ex. 1004, 400–01 (Office Action dated July 17, 2001). The examiner stated:

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

Id. The applicant responded that

> [T]he expression[] "extend the time to disease progression". . . [is] clear from the specification . . . and would be readily understood by the skilled oncologist. Clearly, the combination of anti-ErbB2 antibody and taxoid is administered in an amount effective to extend the time to disease progression **relative to an untreated patient**.

Id. at 416 (Response dated January 17, 2002) (emphasis added). In the next office action, the examiner withdrew the rejection. *See* Ex. 1004, 624 (Office Action dated March 27, 2002) (stating "[a]ll claims were allowable" but suspending prosecution due to potential interference). In other words, the applicant overcame the indefiniteness rejection by providing a specific definition of the term "extend the time to disease progression;" and our construction merely reflects that choice. *See 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. 36–37. 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 ¶ 130. As a result, an ordinary artisan would have understood, even without any explicit disclosure in the '441 patent, that administering the combination of rhuMAb HER2 and paclitaxel would extend the TTP as compared to untreated patients.

Dr. Tannenbaum also testifies that, "in context," the applicant used the term "untreated patient" to refer to "a patient that had not received the combination therapy, but instead received paclitaxel alone." Ex. 2062 ¶ 135. The relevant context, however, includes what was stated during prosecution, wherein the examiner listed three choices: "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. 1004, 400–01 (emphasis added). The applicant could have chosen "taxoid alone" as the comparator. It did not do so. Instead, the applicant 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). In view of the unambiguous evidence, we find Dr. Tannenbaum's opinion on this issue unpersuasive.

Patent Owner also argues that comparing the TTP in the claimed combination therapy with that in an untreated patient is "inconsistent with [our] construction of 'adverse event,' which contemplates a comparison against a patient treated with ***some*** therapy." PO Resp. 37. We are not persuaded by Patent Owner's argument.

During the preliminary stage of this proceeding, neither party proposed any construction for the term "adverse event." In the Decision to Institute, we "observed" a piece of extrinsic evidence related to this term, that is, the National Cancer Institute's Dictionary of Cancer Terms defines an adverse event as "[a]n unexpected medical problem that happens during treatment with a drug or other therapy."[5] Dec. 14 (quoting Ex. 3001). Nonetheless, we repeated that "the proper analysis of 'without increase in

[5] During the trial stage, neither party briefed whether the NCI dictionary definition is applicable to the present context. At oral argument, when inquired, counsel for Petitioner stated that the NCI dictionary definition "is inconsistent with the specification of the patent." Tr. 16:15–23 (arguing that myocardial dysfunction, which the '441 patent suggests is an adverse event, is not "an unexpected medical problem").

overall severe adverse events' is to compare the claimed combination treatment to no treatment." *Id.*

Our understanding is supported by the fact the limitation "without increase in overall severe adverse events" was added during an amendment filed on September 22, 2008 (*see* Ex. 1004, 2299–2301), after the applicant explicitly defined the limitation "extend the time to disease progression" as "relative to an untreated patient" (*id.* at 416). Patent Owner does not argue, and we do not find, that the comparator for the increase in overall severe adverse events differs from that for the TTP extension. Thus, the requirement of "without increase in overall severe adverse events" is also "relative to an untreated patient."

Moreover, it is the job of the patentee to write a patent carefully and consistently. Here, the applicant could have easily adopted the construction Patent Owner attempts to give it today. Yet, the applicant chose a different, special definition "with reasonable clarity, deliberateness, and precision," and obtained the '441 patent only after doing so. *See 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."[6] *Source Vagabond Sys. Ltd. v. Hydrapak, Inc.*, 753 F.3d 1291, 1301 (Fed. Cir. 2014).

[6] We acknowledge the tension between the applicant's statement during prosecution (i.e., the comparator for the TTP is untreated patients) and Patent Owner's argument now (i.e., an adverse event happens during treatment with a drug or therapy). Because an *inter partes* review is limited to challenges based "only on the basis of prior art consisting of patents or printed publications," we do not address whether this constitutes an admission that the challenged claims are indefinite under 35 U.S.C. § 112.

In sum, we maintain that the proper analysis of the term "extend the time to disease progression in said human patient, without increase in overall severe adverse events" is to compare the claimed combination treatment to no treatment. As explained below, however, the challenged claims are unpatentable even if we apply the construction advanced by Patent Owner.

Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). On this record and for purposes of this Decision, we see no need to expressly construe any other claim terms. *See* PO Resp. 39 n.13.

Disclosures of Prior Art

Baselga 1996

Baselga 1996 reports the results of a phase II clinical trial in patients with ErbB2-overexpressing metastatic breast cancer who had received extensive prior therapy. Ex. 1020, 3. Baselga '96 teaches that "rhuMAb HER2 is well tolerated and clinically active in patients with HER2-overexpressing metastatic breast cancers that had received extensive prior therapy." *Id.*

According to Baselga 1996, "patients were selected to have many sites of metastatic involvement, one of the most dire prognostic characteristics regarding response to therapy." *Id.* at 7. Each patient received a loading dose of 250 mg of intravenous rhuMAb HER2, followed by 10 weekly doses of 100 mg. *Id.* In Baselga 1996, "[a]dequate pharmacokinetic levels of rhuMAb HER2 were obtained in 90% of the patients. Toxicity was minimal and no antibodies against rhuMAb HER2 were detected in any patients." *Id.* Baselga 1996 reports an 11.6%

remission rate. *Id.* at 7. In addition, "37% of patients achieved minimal responses or stable disease." *Id.*

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

Seidman 1996

Seidman 1996 teaches that, among metastatic breast cancer patients treated with paclitaxel, 58.8% HER2-positive patients responded to the treatment, whereas only 38.7% patients with breast cancer that did not overexpress the HER2 protein responded. Ex. 1011. Seidman 1996 suggests that HER2-overexpression "seems to confer sensitivity" to treatment with taxanes, "in spite of a positive correlation of HER2 positivity with poor prognostic features." *Id.*

TAXOL PDR

According to TAXOL PDR, paclitaxel "is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy." Ex. 1012, 6. The recommended dosage of paclitaxel to treat breast cancer was 175 mg/m^2, administered intravenously over the course of three hours, every three weeks. *Id.*, 8.

Level of Ordinary Skill in the Art

In the Decision to Institute, we stated that "[w]e do not discern an appreciable difference in the parties' respective definitions of the level of

ordinary skill in the art, and any perceived distinction does not impact our Decision." Dec. 9; *see also id.* at 9–10 (noting "both parties contend that a person of ordinary skill in the art would have had experience with breast-cancer research and treatment"). During trial, the parties did not dispute this determination. Having considered the complete record developed at trial, we see no reason to change our assessment. *See* Pet. 43; Prelim. Resp. 36–37.

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

Obviousness Analysis

Petitioner contends that claims 1–14 would have been obvious over the combination of Baselga 1996, Seidman 1996, and the 1995 TAXOL PDR entry, in view of the knowledge of a person of ordinary skill in the art. Pet. 24–74. After reviewing the entire record, we determine that Petitioner has established by a preponderance of the evidence that the challenged claims are unpatentable. We focus our analysis on claim 1.

Petitioner refers to Baselga 1996 for teaching that the rhuMAb HER2 antibody "was clinically effective in patients with advanced metastatic HER2-positive breast carcinoma, was 'remarkably well tolerated,' and lacked 'significant toxicity,' even though the patients had 'dire prognostic characteristics' based on the extensive metastasis of their cancers and prior

failures with other treatments." Pet. 43 (citing Ex. 1020, 7). Petitioner argues that before the priority date of the challenged claims, an ordinary artisan would have had a reason "to treat HER2-positive breast cancer patients with a combination of trastuzumab and paclitaxel." *Id.* at 44. According to Petitioner, this is because Baselga 1996 suggests the combination therapy of rhuMAb HER2 and paclitaxel (*id.* at 43–44 (citing Ex. 1020, 9)), and because Seidman 1996 teaches that "HER2-overexpression 'seems to confer sensitivity' to treatment with taxanes, even though this condition was known to be difficult to treat with other drugs" (*id.* at 34 (citing Ex. 1011), 44 (citing Ex. 1011)). To bolster its position, Petitioner also points to "preclinical data reporting synergy between trastuzumab and paclitaxel in mouse xenografts." *Id.* at 45 (citing Exs. 1019, 1021).

Petitioner asserts that an ordinary artisan would have had a reason to develop the combination of trastuzumab and paclitaxel without an anthracycline derivative, as required in the challenged claims. Pet. 50–51. According to Petitioner,

> [B]ecause anthracycline derivatives were a first-choice therapy for metastatic breast cancer, many patient candidates for treatment with the trastuzumab and paclitaxel combination would have already been treated with anthracycline-based therapy. (Ex. 1002, ¶ 137; Ex. 1016 (Abeloff), 810.) This means that many patients with metastatic disease who were prescribed a paclitaxel-containing regimen would have already endured extensive anthracycline-based therapy and would risk significant cardiotoxic effects with continued anthracycline-based therapy. (Ex. 1002, ¶ 137.)

Id. at 51. As a result, Petitioner contends that an ordinary artisan "would have avoided administering further anthracycline derivatives to the many

patients who had already been treated with this class of drug or to the many patients who are resistant to treatment with anthracyclines." *Id.*

Each challenged claim recites "an amount effective to extend the time to disease progression in said human patient, without increase in overall severe adverse events." Petitioner argues that an ordinary artisan would have started with "the known amounts that were effective to extend the time to disease progression of each drug when used as monotherapy." *Id.* at 47 (citing Ex. 1002 ¶ 131); *see also id.* at 48 (citing Ex. 1020, 4–5 (effective doses of trastuzumab); Ex. 1012 (effective doses of paclitaxel)). "To the extent any modification to the amounts of the combination was necessary," Petitioner continues, an ordinary artisan "would have readily optimized the combination treatment to arrive at an amount that results in the claimed efficacy and safety parameters," and "[s]uch optimization was routine in the art." *Id.* (citing Ex. 1002 ¶¶ 132–34; Ex. 1016,[7] 11, 13–14).

Relying on the clinical efficacy and toxicity profile of trastuzumab and paclitaxel, and the preclinical data showing a synergistic effect of the two therapeutics, Petitioner contends that there would have been reasonable expectation of success of the combination therapy with trastuzumab and paclitaxel, and without anthracycline derivatives. *Id.* at 52 (citing Ex. 1002 ¶¶ 117–35; Exs. 1011, 1019, 1020).

Patent Owner counters that an ordinary artisan would not have been motivated to treat patients with the claimed combination based on the teachings of the asserted prior art. PO Resp. 39–49. Patent Owner also

[7] Excerpts from CLINICAL ONCOLOGY (Martin D. Abeloff et al., eds., New York: Churchill Livingstone, 1995).

contends that Petitioner has not established a reasonable expectation of success in achieving either the claimed clinical efficacy or the claimed clinical safety. *Id.* at 49–57. In addition, Patent Owner argues that "several objective indicia conclusively establish the non-obviousness of the challenged claims." *Id.* at 60. We address Patent Owner's arguments in turn.

Motivation to Combine

Patent Owner contends that the asserted prior art references do not provide a motivation to treat patients with the claimed combination. PO Resp. 39–49. We disagree.

Petitioner contends that "[c]ombining trastuzumab and paclitaxel for metastatic HER2-positive breast cancer particularly made sense because the combination satisfied the four principles of combination therapy." *Id.* at 45–47 (citing Ex. 1002 ¶¶ 125–130); *see also id.* at 38–39 (stating the principles include "non-cross resistant drugs with single-agent activity, differing mechanisms of action, and nonoverlapping toxicity") (quoting Ex. 1024, 130–31 (emphases added by Petitioner)). Patent Owner argues that these principles "only address combinations of different ***chemotherapies***," while the claimed treatment in the '441 patent combines an antibody and chemotherapy. PO Resp. 48. According to Patent Owner, "[a]t the time of the '441 invention, antibodies were an entirely-new class of drug, and it was not clear how (or if at all) they could be used to treat cancer." *Id.* We do not find Patent Owner's argument persuasive.

Contrary to Patent Owner's assertion, at the time of the alleged invention, prior art already taught combining rhuMAb HER2 and chemotherapy agent cisplatin to treat patients with HER2 overexpressing

metastatic breast cancer in a phase II clinical trial. Ex. 1022,[8] 3. In addition, Patent Owner itself had relied on principles substantially the same as those advanced by Petitioner in designing a clinical trial. Ex. 1101,[9] 11. In that phase II trial, IDEC-C2B8 (later known as Rituxan), a monoclonal antibody, was combined with CHOP, a chemotherapeutic agent, to treat lymphoma. *Id.* "The rationale for combination of IDEC-C2B8 with CHOP includes: single agent efficacy, non cross-resistant mechanism of action, synergy with chemotherapeutic agents and non-overlapping toxicities." *Id.*; *see also* Ex. 1103, 2 (Patent Owner announcing the positive result in the phase II trial in a 1996 press release). This evidence directly contradicts Patent Owner's assertion that the four principles should not be applied to a combination of an antibody and a chemotherapeutic agent.

Patent Owner argues that this research is not comparable to the issue in this case because Rituxan is a chimeric monoclonal antibody, whereas Herceptin is a fully humanized monoclonal antibody. Tr. 30:16–25. According to Patent Owner, Rituxan and Herceptin have different mechanisms of action, biological behavior, and response rates, and were investigated for different therapeutic indications. *Id.* To the extent Patent Owner suggests that we should only consider prior art directed to a fully humanized monoclonal antibody with the same mechanisms of action,

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[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. CLIN. ONCOL.106, Abstract 124 (1995).

[9] Czuczman et al., *IDEC-C2B8 and Chop Chemoimmunotherapy of Lowgrade Lymphoma*, 86 BLOOD, 208 (1995).

biological behavior, response rates, and therapeutic indication as Herceptin, we reject this unreasonably stringent standard. After all, "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." *See KSR*, 550 U.S. at 421.

Even if we were to disregard Petitioner's reliance on the four principles of combination therapy, we still would find an ordinary artisan would have had a reason to combine trastuzumab and paclitaxel for metastatic HER2-positive breast cancer. Indeed, as detailed below, the prior art repeatedly and explicitly teaches this combination.

Baselga 1996 teaches that "rhuMAb HER2 is well tolerated and clinically active in patients with HER2-overexpressing metastatic breast cancers that had received extensive prior therapy." Ex. 1020, 3. Patent Owner does not dispute Petitioner's reliance on this "observed clinical efficacy of trastuzumab in patients with HER2-positive breast cancer." *See* Pet. 24; *see also* Ex. 1001, 3:34–40 (citing Baselga 1996 for the same proposition).

Patent Owner, however, challenges Petitioner's characterization of Seidman 1996 as showing "proven efficacy" of paclitaxel against metastatic HER2-positive breast cancer in humans. PO Resp. 41 (citing Pet. 43). According to Patent Owner, because Seidman 1996 is an abstract, it merely reflects a preliminary hypothesis, and an ordinary artisan "would await an expanded analysis in a peer-reviewed journal before drawing any conclusions." *Id.* We do not find this argument persuasive.

The '441 patent cites numerous abstracts on its face. *See* Ex. 1001, (56) References Cited. In fact, in a declaration submitted during prosecution, the inventor relied on an abstract to overcome prior-art

rejections. *See* Ex. 1004, 321. We also find persuasive the testimony of Dr. Earhart that

> Peer review is most important for analysis and discussion. It is not as important for short reports of data. The Seidman 1996 abstract simply reports the facts as its authors observed them: HER2+ patients were sensitive to taxanes. There is no editorial and no analysis that needs peer review. 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.

Ex. 1054 ¶ 16.

Indeed, the research reported in Seidman 1996 was supported in part by a grant from the National Cancer Institute. Ex. 1011. In addition, the authors of Seidman 1996 are from 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—"leading practitioner" in the field (PO Resp. 62). 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[10] showing the same). 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.

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[10] Baselga et al., *Anti-HER2 Humanized Monoclonal Antibody (MAb) Alone and in Combination with Chemotherapy Against Human Breast Carcinoma Xenografts*, 13 PROC. AM. SOC. CLIN. ONCOL. 63 (Abstract 53) (1994) (Ex. 1019, "Baselga Abstract 53").

Relying on Van Poznak,[11] a 2002 publication, Patent Owner also contends that "[t]he Seidman authors themselves continued to research the issue" and reached a conclusion inconsistent with the one in Seidman 1996. PO Resp. 41 (citing Ex. 2024, 2322). According to Patent Owner, "[t]hat the authors of the Seidman abstract did not view their initial finding as one of 'proven efficacy' and continued to study the issue further confirms that a POSA would not have attributed the same significance to Seidman that Petitioner suggested and the Board accepted." *Id.* at 41–42 (citing Ex. 2062 ¶ 183). We are not persuaded by this argument either.

As a preliminary matter, it is common for artisans to seek further in-depth understanding of the mechanism of action of a drug or improvement over an existing treatment. More importantly, a proper obviousness analysis requires us to step back in time and compare the subject matter sought to be patented and the prior art at the time of the invention. 35 U.S.C. § 103(a); *see also KSR*, 550 U.S. at 421 ("A factfinder should be aware . . . of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning."). Indeed, Patent Owner in this case has repeatedly emphasized this point. *See, e.g.*, PO Resp. 3, 21, 40, 46, 52, 60, 61.

Patent Owner argues that Van Poznak shows that the results reported in Seidman 1996 are unreliable. PO Resp. 41 (citing Ex. 2024, 2322, 2323). Van Poznak, however, was published in May 2002, four and half years after the time of the alleged invention in the '441 patent. It, therefore, could not have informed the opinion of an ordinary artisan at that relevant time. To

[11] Van Poznak, et al., *Assessment of Molecular Markers of Clinical Sensitivity to Single-Agent Taxane Therapy for Metastatic Breast Cancer*, 20 J. CLIN. ONCOL. 2319 (2002) (Ex. 2024, "Van Poznak").

import the disclosures of Van Poznak into the obviousness inquiry would be to engage in the very hindsight bias Patent Owner rightly urges must be avoided.

Substantively, we are not persuaded that the results of Van Poznak contradict those of Seidman 1996. Patent Owner emphasizes that Van Poznak "found no 'statistically significant association with clinical response to taxane therapy' for patients who are HER2-positive," and "described that finding as 'noteworthy' because it was 'partly in contrast to our earlier analysis.'"[12] PO Resp. 41 (citing Ex. 2024, 2322, 2323). This summary, however, is incomplete. The relevant part of Van Poznak reads:

> Our results are noteworthy for the lack of correlation between HER2 status as assessed by either HercepTest or CB-11 and response to single-agent taxane therapy. These findings are partly in contrast to our earlier analysis. In this earlier analysis of fewer cases, HER2 status as assessed by the monoclonal antibody 4D5 was predictive of positive response to taxane monotherapy, whereas HER2 assessment with the polyclonal antibody pAb-1, was not.

Ex. 2024, 2323. Apparently, even in the earlier study—which is not Seidman 1996—the correlation of HER2 status and the sensitivity to treatment with taxanes depends on the antibody used. Because the antibodies used Van Poznak are different from 4D5 used in the earlier study—HercepTest is another polyclonal antibody; whereas CB-11, though a monoclonal antibody, has specificity and sensitivity different from those of 4D5 (*id.* at 2321)—we are not persuaded that Van Poznak shows that the results reported in Seidman 1996 are unreliable.

[12] As Petitioner points out, Van Poznak does not cite Seidman 1996. Reply 6.

Patent Owner further argues that Yu[13] discourages the use of taxoids in HER2-positive patients. PO Resp. 42. According to Patent Owner, Yu explicitly warns that "breast cancers that overexpress p185 [*i.e.*, HER2] will not respond well to Taxol." *Id.* (citing Ex. 2029, 1362). Yu drew that conclusion, however, based on an *in vitro* study, using cell lines growing on culture plates. Ex. 2029, 1360–62. On this issue, we agree with Dr. Earhart and Petitioner that an ordinary artisan "would have regarded the *in vivo* preclinical and clinical results reported in Baselga-1996 and Seidman-1996, which were obtained from studies of actual tumor cells in live animals and human patients, as being far more predictive than Yu's results, which were obtained in artificially-engineered cells on culture plates." Reply 6 (citing Ex. 1054 ¶ 17); *see also* Ex. 1040, 222:11–224:9 (Dr. Kerbel, Patent Owner's expert witness, testifying that a living animal model, though imperfect, is "closer" to a human and "better than a petri dish").

Moreover, in an obviousness inquiry, we must analyze the prior art as a whole, not individually. *See In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004). Other evidence of record shows paclitaxel was known at the relevant time to be effective in treating HER2-positive cancers (*see, e.g.*, Ex. 1011), demonstrates "strong synergy" of paclitaxel and an anti-ErbB2 antibody in human breast cancer xenografts (*see, e.g.*, Ex. 1010,[14] 5; Ex. 1019, 4;

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[13] 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 1359–65 (1996) (Ex. 2029).

[14] Seidman et al., *Memorial Sloan-Kettering Cancer Center Experience with Paclitaxel in the Treatment of Breast Cancer*, 22 SEMINARS in ONCOL. (Suppl.) 108–16 (1995) (Ex. 1010, "Seidman 1995")

Ex. 1021,[15] 3), and suggests clinical trials of the claimed combination therapy (*see, e.g.*, Ex. 1010, 5; Ex. 1020, 9). Weighing all evidence of record, we are not persuaded that Yu, a single reference based on an *in vitro* study, would have dissuaded an ordinary artisan from combining paclitaxel and an anti-ErbB2 antibody in treating HER2-positive cancers. *See also* MTA Sur-reply 6 (citing Ex. 1043,[16] 6–9 (noting a review paper regarding paclitaxel sensitivity in breast cancer does not 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").

This is especially so because Baselga 1996 further reports 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. Laboratory studies of the mechanism of this effect and **clinical trials of such combination therapy are currently in progress**." Ex. 1020, 9 (emphasis added).

Acknowledging this statement, Patent Owner nevertheless argues that Baselga 1996 "provides no motivation to choose paclitaxel from among the 'several chemotherapeutic agents' identified for treatment in human patients." PO Resp. 40. Patent Owner contends that there was no clinical

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[15] Baselga et al., *Antitumor Activity of Paclitaxel in Combination with Anti-growth Factor Receptor Monoclonal Antibodies in Breast Cancer Xenografts*, 35 PROC. AM. ASSOC. CLINICAL CANCER RES. 380 (Abstract 2262) (1994) (Ex. 1021, "Baselga Abstract 2262").

[16] Baselga et al., *HER2 Overexpression and Paclitaxel Sensitivity in Breast Cancer: Therapeutic Implications*, 11(3) (Suppl. 2) ONCOLOGY 43–48 (1997).

study involving the claimed combination at the time that Baselga 1996 was submitted or accepted. PO Resp. 32, 40. The evidence Patent Owner relies on for support, however, was and still remains confidential. *See, e.g.*, Ex. 2125 ¶¶ 18–46 (citing exhibits submitted under seal by Patent Owner). An ordinary artisan would not have been privy to Patent Owner's internal documents, and, thus, would have accepted the statement in Baselga '96 that clinical trials of trastuzumab with each of the named chemotherapeutics, including paclitaxel, were ongoing, at face value. Reply 16. And in any event, the relevant time for assessing obviousness is not the submission or acceptance date of Baselga '96, but the time of the alleged invention, which, in this case, is after the publication of Baselga '96. It is undisputed that at the that time, in fact, at the time Baselga 1996 was published, a clinical study involving the claimed combination was indeed in progress.

Patent Owner also contends that there were "significant safety concerns regarding treatment with taxoids." PO Resp. 47. As a result, Patent Owner continues, an ordinary artisan, when considering whether to combine the anti-ErbB2 antibody with an existing anti-cancer drug, would have been motivated to use an anthracycline, rather than a taxoid. *Id.* We are not persuaded.

Generally, there are always safety concerns associated with pharmaceutical agents. Indeed, it is undisputed that anthracyclines produce "cumulative cardiac injury" that "causes the greatest concern." *See, e.g.*, Ex. 1016, 810; Ex. 2030,[17] 409, 423 (anthracycline-induced cardiac toxicity

[17] Doroshow, Anthracyclines and Anthracenediones, in Cancer Chemotherapy & Biotherapy: Principles and Practice 409 (1996).

"is difficult to treat and is associated with a high mortality"). It was known that with each dose of an anthracycline, "there is progressive injury to the myocardium so that the grade increases steadily with total dose of drug administered." Ex. 2030, 423.

As Patent Owner acknowledges, paclitaxel was approved by the FDA for ovarian cancer in 1992 and for breast cancer in 1994, years before the priority date of the '441 patent. *See* PO Resp. 17. Thus, we are not persuaded that the safety concerns over paclitaxel alone would have dissuaded an ordinary artisan from combining it with an anti-ErbB2 antibody.[18]

More importantly, the fact that the prior art "discloses a multitude of effective combinations does not render any particular formulation less obvious. This is especially true because the claimed composition is used for the identical purpose taught by the prior art." *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). In *Merck*, one reference expressly taught the combination of the compounds claimed in the patent. *Merck*, 874 F.2d at 807. Similarly in this case, Baselga 1996 expressly teaches paclitaxel as one of three specifically identified chemotherapeutic agents to be combined with rhuMAb HER2. *See In re Corkill*, 771 F.2d

[18] Moreover, as Patent Owner emphasizes, anthracyclines had been the most widely used, standard, first-choice therapy for metastatic breast cancer to the point that it was difficult to find patients who had not previously been treated with anthracylines. PO Resp. 14, 23 n.6. As a result, many patients had become resistant to it. Taxanes "demonstrated activity and safety . . . against anthracycline-refractory breast cancer." Ex. 1010, 1; *see also* Ex. 1024, 14–15 (stating "paclitaxel has activity in heavily pretreated patients").

1496, 1500 (Fed. Cir. 1985) (affirming an obviousness rejection in light of prior art teaching that "hydrated zeolites will work" in detergent formulations, even though "the inventors selected the zeolites of the claims from among 'thousands' of compounds").

In addition, in an obviousness analysis, "the question is whether there is something in the prior art as a whole to suggest the *desirability*, and thus the obviousness, of making the combination," not whether there is something in the prior art as a whole to suggest that the combination is the *most desirable* combination available. *See Fulton*, 391 F.3d at 1200 (quotation marks and alteration omitted). Thus, even if an ordinary artisan would have preferred the combination of rhuMAb HER2 and an anthracycline —which, given the undisputed significant and cumulative cardiac toxicity of anthracyclines (*see, e.g.*, Ex. 1016, 26; Ex. 2030, 423), is not a foregone conclusion—we are persuaded that an ordinary artisan also would have had a reason to, as Baselga 1996 specifically teaches, combine rhuMAb HER2 with paclitaxel. *See* Ex. 1020, 9.

Baselga 1996 and Seidman 1996 are not the only prior art references suggesting the combination of rhuMAb HER2 and paclitaxel. Seidman 1995, Baselga Abstract 53, and Baselga Abstract 2262 all suggested the same. *See* Ex. 1010, 5; Ex. 1019, 4; Ex. 1021, 3. Indeed, Baselga Abstract 53, which reports work collaborated between Patent Owner and some of the authors of Seidman 1996, teaches growing HER2 overexpressing tumors in nude mice followed by treatment with anti-HER2 4D5 antibody and paclitaxel. Ex. 1019, 4. According to Baselga Abstract 53, the antibody or paclitaxel alone produced 35% growth inhibition, but the combination of the two resulted in 93% growth inhibition without increasing toxicity. *Id.*

Baselga Abstract 53 concludes that "anti HER2 MAbs can eradicate well established tumors and enhance the activity of paclitaxel . . . against human breast cancer xenografts. Clinical trials are underway." *Id.*

Baselga Abstract 2262, which is another collaboration between Patent Owner and some of the authors of Seidman 1996, reports the same data and concludes that the antitumor effects of paclitaxel can be "markedly enhanced" by anti-HER2 4D5 antibody. Ex. 1021, 3. Baselga Abstract 2262 also specifically called out that the antitumor activity of the paclitaxel and anti-HER2 4D5 antibody combination "was markedly better than doxorubicin [i.e., an anthracycline drug] plus 4D5." *Id.*

Patent Owner introduced Hsu[19] in response to Petitioner's reliance on the Baselga xenograft data. Patent Owner introduced Hsu as Exhibit 2135 at the April 17, 2018 deposition of Dr. Earhart (Ex. 2130, 165:12–177:9), and submitted arguments with respect to Hsu in connection with its motions on observation (Paper 71, ¶ 8; Paper 76 ¶ 3), to which Petitioner replied (Paper 78, ¶¶ 7, 8; Paper 82 ¶ 3).

According to Hsu, *in vitro* cytotoxicity assays on HER2-expressing SKBR-3 human breast cancer cells showed that rhuMAb HER-2 and taxol in combination showed additive cytotoxic effects. Ex. 2135. Hsu also teaches that "in an athymic mouse model with HER-2/*neu*-transfected MCF-7 human breast cancer xenografts," "[x]enografts treated with rhuMAb HER-2

[19] 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.

plus taxol . . . were not significantly different from drug alone controls with the doses and dose schedules tested in this model." *Id.* Patent Owner appears to rely on Hsu to show that an ordinary artisan would have discounted Baselga xenograft results in light of Hsu's teaching. *See* Ex. 2130, 172:18–177:5; Paper 71, ¶ 8; Paper 76 ¶ 3. We are not persuaded.

We observe, and Dr. Earhart confirmed, that Hsu "does not detail the drug doses and schedules used in the xenograft study." Ex. 1105 ¶ 13. In addition, as Dr. Earhart further explained, "unlike in Baselga Abstract 53, Hsu 1997 did not use xenografts that naturally overexpress HER2. Rather, it used xenografts that were transfected, or artificially engineered, to overexpress HER2." *Id.* (internal citations omitted). Dr. Earhart reasonably concludes that an ordinary artisan "would not have regarded Hsu 1997 as negating the teachings of Baselga Abstract 53." *Id.* Thus, we agree with Petitioner that an ordinary artisan would not have concluded that the results in the Hsu abstract were inconsistent with those in the Baselga abstracts.[20] *See* Paper 78, ¶ 8.

Patent Owner also contends that the preclinical results from Baselga Abstract 53 and Baselga Abstract 2262 would not have motivated an ordinary artisan to treat patients with the claimed combination because the mouse study therein "was not a reliable predictor of success in humans." PO Resp. 43–46. Patent Owner argues that (1) "[t]he preclinical study described in the Baselga abstracts was based on a single cell line;" (2) "the particular cell line used in the Baselga abstracts was not representative of

[20] We also address Hsu in *Hospira, Inc. v. Genentech, Inc.*, IPR2017-00731, Paper 120 (PTAB Oct. 3, 2018), 23–25.

actual patients;" and (3) "the tumors in the Baselga abstracts were implanted subcutaneously [i.e., ectopic tumor models], rather than in tissue similar to how the disease would present in human patients [i.e., orthotopic tumor models]." *Id.* at 43–45. Petitioner contends otherwise. Reply 8–11. We find Petitioner's arguments more persuasive.

According to Dr. Earhart, "[a]lthough xenografts are not conclusive evidence of efficacy or toxicity in humans, they serve as a helpful tool that can provide further evidence of efficacy or safety that researchers may find informative in developing new treatments or designing clinical studies." Ex. 1002 ¶ 46. Prior art supports Dr. Earhart's opinion. For example, in an article reviewing xenografts as model for drug testing, after efforts "to correlate the published xenograft data with the clinical data," the authors concluded that "[d]rug testing with different types of xenotransplanted tumors has shown that the response of xenografts obtained in immune-deficient animals is comparable to that in clinical practice." Ex. 1028,[21] 1. In addition,

> Xenografts of a particular tumor type are often able to identify agents of known clinical activity against that disease. This fact strongly supports the validity of using established lines of heterotransplants of human tumors as a predictive system for testing new anticancer agents, and also supports the use of xenografts as a model system for studying many human cancers *in vivo.*

[21] Mattern et al., *Human Tumor Xenografts as Model for Drug Testing*, 7 CANCER AND METASTASIS REVIEWS, 263–84 (1988).

Id. at 17–18. *See also* Ex. 1026,[22] 1 (concluding that despite some limitations, "the highly correct prediction rates for tumor sensitivity and resistence [sic] validates human tumor xenografts as tumor models to test new drugs and combinations").

Patent Owner's expert does not disagree. For example, Dr. Kerbel testified that, in the relevant time frame, xenograft studies were common in the development of drugs for use in cancer treatment. Ex. 1040, 20:14–17. He also testified that such preclinical studies help an ordinary artisan to decide which drug candidate to test in human, and to decide, if two drugs are already used in human, whether to test the combination therapy in human. *Id.* at 23:9–12, 19–23.

In addition, Dr. Kerbel co-authored Francia,[23] a peer reviewed research paper published a decade after the priority date of the '441 patent. Francia tested the efficacy and toxicity of trastuzumab combined with chemotherapy, using a xenograft model only. Ex. 2080, 6359; Ex. 1040, 23:24–27:5. According to Francia, "the majority of preclinical therapies reported in the literature are routinely assessed using only primary tumor models, either ectopic or orthotopic." Ex. 2080, 6363. The xenograft model used in Baselga Abstract 53 and Baselga Abstract 2262 is an ectopic model. Dr. Kerbel testified that ectopic models not only were more commonly used

[22] Fiebig et al., *Comparison of Tumor Response in Nude Mice and in the Patients*, 74 BEHRING INST. MITTEILUNGEN, 343–52 (1984).

[23] Francia et al., *Comparative Impact of Trastuzumab and Cyclophosphamide on HER-2–Positive Human Breast Cancer Xenografts*, 15 CLIN. CANCER RES. 6358–66 (2009) (Ex. 2080, "Francia").

than orthotopic models in the relevant time period, but, in fact, remain in use even today. Ex. 1040, 28:19–29:6.

Similarly, Dr. Kerbel co-authored Ng,[24] another peer reviewed research paper published years after the priority date of the '441 patent. Ng tested a new formulation of paclitaxel in a xenograft model using a **single cell line**. Ex. 2082, 4331; Ex. 1040, 29:14–30:12. Based on the xenograft results, Dr. Kerbel and others concluded that the new formulation of paclitaxel "warrants investigation in the clinical setting."[25] Ex. 2082, 4337; Ex. 1040, 32:21–33:13.

In view of evidence of record, we find the xenograft study reported in the Baselga abstracts would have motivated an ordinarily skilled artisan to combine rhuMAb HER2 and paclitaxel. Seidman 1995 confirms our understanding. Seidman 1995 teaches that paclitaxel was, at the time, "the most important new cytotoxic agent to be introduced for the management of breast cancer in many years." Ex. 1010, 1. According to Seidman 1995, "[p]aclitaxel combination with various cytotoxic agent [we]re being actively explored." *Id.* Specifically, Seidman 1995 reports:

> Since 1992, we and others have developed strong experimental data suggesting that combining maximally tolerated doses of chemotherapeutic agents with MoAb [monoclonal antibody]-mediated blockade of either EGFR or HER-2/*neu* receptors can eradicate well-established human tumor xenografts that were

[24] Ng et al., *Influence of Formulation Vehicle on Metronomic Taxane Chemotherapy: Albumin-Bound versus Cremophor EL-Based Paclitaxel*, 12 CLIN. CANCER RES. 4331–38 (2006) (Ex. 2082, "Ng").

[25] Although Francia and Ng do not qualify as prior art themselves, we find that they undermine the credibility of Dr. Kerbel's contrary testimony. *See* PO Resp. 44–45 (citing Ex. 2061 ¶¶ 62–70, 77–83).

> resistant to either treatment given singly. Striking antitumor effects are observed when paclitaxel is given in human breast cancer xenografts in combination with either anti-EGFR or anti-HER-2 MoAbs. This strong synergy is achieved with no increased toxicity in the animal model. . . . While mechanisms for the apparent synergy are being explored, **these data provide a lead for translation into the clinic**. Indeed, future clinical trials combining paclitaxel with anti-growth factor receptor MoAbs are being planned.

Id. at 5 (emphasis added).

Patent Owner's protocol seeking FDA approval to test the combination of trastuzumab and paclitaxel undermines its arguments. 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)). According to Patent Owner, "[a]lthough neither the combination of rhuMAb HER2 and cyclophosphamide and doxorubicin nor the combination of rhuMAb HER2 and paclitaxel have been used together in humans, it is anticipated that rhuMAb HER2 in combination with these chemotherapies may be more effective than either regimen used alone." Ex. 2007, 88. In reaching this conclusion, Patent Owner relied on the very Baselga xenograft results it now challenges:

> In vivo nude mouse xenograft models utilizing HER2 transfected cell lines have demonstrated an additive effect in reducing tumor volume when rhuMAb HER2 is given in combination with doxorubicin, compared with rhuMAb HER2 or doxorubicin given alone. *Similar findings using a different in vivo model were reported with rhuMAb HER2 and pactlitaxel.* It is anticipated that, in a population of patients with HER2

> overexpressing metastatic breast cancer, the addition of rhuMAb HER2 to *cyctotoxic chemotherapy* will enhance efficacy.

Id. at 30 (citing Baselga Abstract 53 and Baselga Abstract 2262).

In sum, given the repeated and explicit suggestion in the prior art, which are consistent with Patent Owner's statement in seeking FDA approval of the rhuMAb HER2/pactlitaxel combination, we are persuaded that an ordinary artisan would have been motivated to combine rhuMAb HER2 and pactlitaxel to treat patients with ErbB2 overexpressing metastatic breast cancer.

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. 49–57. We, again, disagree.

On the claimed efficacy, we reiterate that the proper analysis of "extend the time to disease progression" is to compare the claimed combination treatment to no treatment. *Supra* at 11. 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. 49 n.18 (citing Ex. 1002 ¶¶ 136, 155 n.28; Ex. 1010). 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. Thus, an ordinary artisan would have had a reasonable expectation of success in achieving the claimed clinical efficacy.

Our conclusion remains the same even under Patent Owner's proposed claim construction. In other words, an ordinary artisan would have had a reasonable expectation that the claimed combination treatment extends TTP and does not increase overall severe adverse events as compared to treatment with a taxoid alone.

Petitioner argues that

> Given the known clinical efficacy of each agent alone against this type of cancer (Baselga 1996; Seidman 1996), the good tolerability and absence of significant toxicity observed in the trastuzumab clinical trial (Baselga 1996 at 739, 741), and the lack of increased toxicity when trastuzumab was added to paclitaxel in preclinical studies (*id.* at 743), a POSA would have reasonably expected the combined regimen to be more effective against HER2-positive breast cancer than paclitaxel alone, without increasing severe adverse events. (Ex. 1002, ¶¶ 117-135.)

Pet. 52.

Patent Owner contends that none of the asserted prior art includes data showing an extension of TTP. PO Resp. 50. But, as Patent Owner acknowledges, Baselga 1996 teaches the median TTP with trastuzumab was 5.1 months (Ex. 1020, 6), and TAXOL PDR teaches the median TTP with paclitaxel was 3.0 or 4.2 months in a Phase III breast carcinoma study (Ex. 1012, 6). PO Resp. 50. Because Baselga '96 reports that rhuMAb HER2 achieved a longer TTP at least for HER2+ breast cancer patients, we agree with Petitioner that "POSAs would have had a reasonable expectation that adding trastuzumab would achieve an extension of TTP over paclitaxel alone based on the superior TTP of trastuzumab." Reply 19 (citing Ex. 1054 ¶ 20).

This is especially so because when developing a combination therapy by adding a new agent to a standard treatment, if the new agent, "because of

differing dose-limiting toxicity, can be added without compromising dose, there is a reasonable expectation that [the combination] will be superior to [the standard treatment alone]." Ex. 1053,[26] 28. Here, trastuzumab and paclitaxel have non-overlapping mechanisms of action and toxicities. *See* Pet. 46–47 and evidence cited therein. Thus, each can be administered in its full effective dose. *Id.* at 39 (citing Ex. 1002 ¶ 89; Ex. 1016, 10–11). As a result, an ordinary artisan would have had a reasonable expectation that treatment with the combination of trastuzumab and paclitaxel would extend TTP as compared to treatment with a paclitaxel alone.

Our conclusion is further supported by the representations Patent Owner made in its submission to the FDA. *See* Ex. 2007, 30 (Patent Owner relying on Baselga Abstract 53 and Baselga Abstract 2262 to support the proposal of the claimed combination because "[i]t is anticipated that, in a population of patients with HER2 overexpressing metastatic breast cancer, the addition of rhuMAb HER2 to *cyctotoxic chemotherapy* will enhance efficacy"), 88 (Patent Owner stating that although the combination of rhuMAb HER2 and paclitaxel had not been used together in humans, "it is anticipated that rhuMAb HER2 in combination with these chemotherapies may be more effective than either regimen used alone").

On the claimed safety, Petitioner relies on "the lack of severe toxicity associated with trastuzumab, the lack of increased toxicity from adding trastuzumab to paclitaxel in preclinical studies, and lack of known significant overlapping toxicities between trastuzumab and paclitaxel."

[26] Excerpts from ANTICANCER DRUG DEVELOPMENT GUIDE (Beverly A. Teicher, ed., Humana Press 1997).

Pet. 49, 52. Patent Owner argues that Baselga 1996 and Baselga Abstract 53 also showed no increased toxicity for the trastuzumab/anthracycline doxorubicin; yet, that combination "produced a significant increase in cardiotoxicity when administered to human patients." PO Resp. 56 (citing Ex. 1019, 4; Ex. 1020, 9). According to Patent Owner, "[t]hese disconnects highlight the inability of the Baselga references' mouse models to predict clinical safety." *Id.* (citing Ex. 2061 ¶¶ 54–61; Ex. 2062 ¶¶ 219–221). But, in Patent Owner's own words, "[t]he increased cardiotoxicity of rhuMAb HER2 combined with anthracyclines was **completely unexpected**." *Id.* at 25 (emphasis added). Thus, we decline to discount the significance of Baselga xenograft models in predicting clinical safety because of the unexpected cardiotoxicity of rhuMAb HER2/anthracyclines combination.

Patent Owner also asserts that the Baselga xenograft models would not reliably predict the effects of the claimed combination in humans for other reasons. PO Resp. 56. We, again, are not persuaded. Putting aside the general recognition of xenografts as "tumor models to test new drugs and combinations" because of "the highly correct prediction rates" (*see* Ex. 1026, 1; Ex. 1028, 17–18), Patent Owner's own documents refute its assertion.

As explained above, in seeking FDA approval to test the combination of trastuzumab and paclitaxel, Patent Owner acknowledged that "neither the combination of rhuMAb HER2 and cyclophosphamide and doxorubicin nor the combination of rhuMAb HER2 and paclitaxel have been used together in humans." Ex. 2007, 88. Instead, to support its "Study Rationale," Patent Owner relied on the very same Baselga xenograft results it now challenges. *Id.* at 30 (citing Baselga Abstract 53 and Baselga Abstract 2262). And those

data apparently were sufficient for the FDA to regard the planned phase III trial with trastuzumab/paclitaxel combination—without corresponding phase I and/or II trials—as "reasonable" merely one week after receiving the protocol. *See* Ex. 1035.[27] In the absence of a reasonable likelihood that the proposed combination would not lead to an "increase in overall severe adverse events," it seems unlikely that the FDA would have approved administering the claimed combination into a human patient.

We have considered other arguments advanced by Patent Owner but find them equally unavailing. For example, Patent Owner contends that "the development history of rhuMAb HER2 confirms that the preclinical results in the Baselga abstracts would not have provided a POSA a reasonable expectation of success in achieving the specific clinical result claimed in the '441 patent." PO Resp. 52. But, patentability is assessed from the perspective of the hypothetical person of ordinary skill in the art. *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325–26 (Fed. Cir. 2000). Thus, how the inventor developed the claimed combination is not material to our objective analysis of obviousness.[28] Moreover, we analyze

[27] Petitioner points out that "The FDA did raise concerns about the revised trial, but not with respect to the use of paclitaxel per se. Rather, their concerns related to how the use of separate anthracycline and paclitaxel tracks would complicate the statistical analyses." Reply 17 (citing Ex. 1058.)

[28] Even if we consider the development history of rhuMAb HER2, we are not persuaded that it shows the inventor, as Patent Owner argues, encountered resistance from her colleagues to include rhuMAb HER2/paclitaxel in the clinical trial. *See* PO Resp. 25. Instead, the comments Patent Owner relies on, when read in context, do not appear to relate to either clinical efficacy or safety. *See* Ex. 2004, 10.

the reasonable expectation of success based on, not only the Baselga abstracts, but the prior art as a whole, including Baselga 1996, Seidman 1996, the 1995 TAXOL PDR entry, and the knowledge of a person of ordinary skill in the art.

Dr. Tannenbaum testifies that "in the 1990s[,] the mere fact that a treatment was under evaluation was no indication of success in light of the high failure rate of therapies in clinical trials." Ex. 2062 ¶ 222. We acknowledge the inherent unpredictability in the pharmaceutical industry. *See, e.g.*, PO Resp. 6–13, 53. We also recognize that the finder of fact may take into account failure of others to obtain FDA approval of a particular pharmaceutical combination. *Knoll Pharm. Co.*, 367 F.3d at 1385. But, "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007); *see also Allergan, Inc.*, 726 F.3d at 1291 (the Federal Circuit agreeing that the district court properly considered the basis for FDA approval decisions in assessing motivation to combine but "find[ing] clear error in the court's conclusion that one of ordinary skill would not be motivated to develop fixed combinations [of known drugs] with a reasonable expectation of success.").

Here, in view of the published safety information for each of trastuzumab and paclitaxel, the fact that paclitaxel was previously FDA approved, and the fact that Patent Owner proposed a phase III trial with trastuzumab/paclitaxel combination—which the FDA accepted—based on the same prior art disclosures, we are persuaded that, despite the uncertainties Patent Owner emphasizes, an ordinary artisan would have had

a reasonable expectation of success regarding the claimed safety. *See Pfizer*, 480 F.3d at 1365 (stating the expectation of success need only be reasonable, not absolute).

In sum, Petitioner has established, by a preponderance of the evidence, that an ordinary artisan would have been motivated to treat patients with ErbB2-overexpressing breast cancer by administering a combination of trastuzumab and paclitaxel, and in the absence of an anthracycline derivative. In addition, an ordinary artisan would have had a reasonable expectation that the combination therapy would have extended TTP, without increase in overall severe adverse events, even under Patent Owner's proposed claim construction.

Secondary Considerations

Patent Owner argues that the nonobviousness of the challenged claims are supported by secondary considerations, including the satisfaction of a long-felt-but-unmet need, praise, unexpected results, and commercial success. PO Resp. 60–66. We are not persuaded.

"For objective evidence of secondary considerations to be accorded substantial weight, its proponents must establish a nexus between the evidence and the merits of the claimed invention." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). Where objective indicia "result[ ] from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention." *Id*. We find that the nexus between the merits of the invention and the evidence of long-felt-but-unmet need, praise, and commercial success, if any, is weak.

Patent Owner asserts that Herceptin is the commercial embodiment of the '441 patent. PO Resp. 65. For commercial success, "if the marketed

product embodies the claimed features, and is coextensive with them, then a nexus is presumed." *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000). The patent challenger, however, may rebut the presumed nexus. *Id.* And here, Petitioner has sufficiently rebutted that presumption.

For example, each challenged claim in this proceeding requires the combination of an anti-HER2 antibody and a taxoid. Herceptin, however, was also approved for single-agent use. Reply 25 (citing Ex. 2012). Patent Owner has not shown what portion of the sales of Herceptin is attributable to the claimed combination, and not the single-agent use.[29] *Id.*

Furthermore, "evidence related solely to the number of units sold provides a very weak showing of commercial success." *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996). Patent Owner only present the product sales figure (Ex. 2035, 17) and has not shown what percentage of the market Herceptin commanded. Reply 26. As a result, we find the evidence of commercial success presented by Patent Owner is insufficient to support the nonobviousness of the challenged claims.

Regarding praise, Patent Owner relies on three pieces of evidence (PO Resp. 62 (citing Exs. 2018, 2033, 2034)), none of which shows that the praise is for the claimed combination. For example, Exhibit 2018 states that

[29] In addition, elsewhere, Patent Owner has asserted that the success of Herceptin "is attributable, in part," to the claims directed to the unique sequence provided in a different, earlier patent. Reply 24–25 (citing Ex. 1060, 66). Unlike the challenged claims here, those claims do not require the combination therapy. *Id.* Yet, Patent Owner does not explain what portion of the sales of Herceptin is attributable to the '441 patent, and not the other patent.

"[a]s early as 1995, Genentech was swamped by demand for the highly targeted, yet-to-be-approved new drug" Herceptin. Ex. 2018. The news article reported the clinical results of Herceptin alone and "[i]n combination with other chemotherapy," without specifying the chemotherapeutic agent. *Id.* Although it mentioned—in a single sentence, and without clinical results—about the combination with paclitaxel, the article describes it as "particularly encouraging" (*id.*), not the "breakthrough," or "Holy Grail," as Patent Owner alleges. PO Resp. 61, 62.

Similarly, Exhibit 2033 describes "Herceptin[] worked best when combined with standard chemotherapy." *Id.* at 1. The exhibit does not, however, mention combining Herceptin with a taxoid, but with the anthracycline derivative Adriamycin. *Id.* (noting that this combination "caused heart malfunction in some patients, though most continued on the combination").

Patent Owner quotes a statement by Dr. Larry Norton, alleging that it was directed to the "impressive results of the '441 invention." PO Resp. 62 (citing Ex. 2034). When read in context, however, it is unclear whether Dr. Norton was discussing Herceptin alone, a combination with a chemotherapy drug in general, or a combination with a taxol specifically. Ex. 2034. Thus, we determine Patent Owner has not presented sufficient evidence of praise to support a nonobviousness conclusion.

Patent Owner also relies on Exhibit 2018 as evidence of long-felt need. PO Resp. 60–61 (citing Ex. 2018); Ex. 2062 ¶¶ 224–225 (citing Ex. 2018). As discussed above, because Exhibit 2018 appears to discuss treatment with Herceptin alone and Herceptin in combination with chemotherapy generally, but not with a taxoid specifically, we are not

persuaded that Patent Owner has shown sufficient evidence of long-felt, but unmet, need.

Patent Owner further asserts that the claimed combination "produced unexpectedly-superior clinical efficacy as compared with either the antibody or a taxoid alone." PO Resp. 62–63. In support, Patent Owner relies on a single sentence from a declaration submitted by the inventor during prosecution. *Id.* at 63 (citing Ex. 1008 ¶ 6). As Petitioner points out, Patent Owner "fails to address any of Petitioner's criticisms of this statement presented in the Petition, or to cite any scientific proof demonstrating synergy in any clinical trial." Reply 23 (citing Pet. 70–72). In addition, as Seidman 1995 summarizes, in human breast cancer xenografts, paclitaxel and anti-HER2 antibody exhibited "strong synergy" and those data "provide a lead for translation into the clinic." Ex. 1010, 5. Because we are not persuaded by Patent Owner's criticism of the xenograft model (PO Resp. 63), we find the alleged "superior clinical efficacy" does not amount to unexpected results. *See supra* 29–33.

Patent Owner further contends that the claimed combination "produced an unexpected safety improvement as **compared with other combinations**—for example, the combination of trastuzumab with anthracyclines that Baselga Abstract 53 said did not increase toxicity, but in fact did increase toxicity in the Phase-III study disclosed in the '441 patent." PO Resp. 64 (citing Ex-1019, 4) (emphasis added). As a preliminary matter, "when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected **compared with the closest prior art**." *Kao Corp. v. Unilever U. S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006) (emphasis added). Comparison of trastuzumab/paclitaxel with

trastuzumab/anthracycline does not satisfy this requirement. Moreover, as Patent Owner conceded, "[t]he increased cardiotoxicity of rhuMAb HER2 combined with anthracyclines was completely unexpected." PO Resp. 25. Thus, the safety profile of trastuzumab/paclitaxel is not unexpected merely because is better than that of trastuzumab/anthracycline.

In sum, after weighing the secondary consideration evidence against the other evidence of obviousness, we conclude that evidence of secondary consideration is not sufficient to outweigh the showing of obviousness arising from an analysis of the prior art. *See Cubist Pharmaceuticals, Inc. v. Hospira, Inc.*, 805 F.3d 1112, 1126 (Fed. Cir. 2015); *see also Bristol–Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (stating that objective indicia, even when present, "do not necessarily control the obviousness determination").

After reviewing the entire record, we determine that the combination of Baselga 1996, Seidman 1996, and the 1995 TAXOL PDR entry teaches or suggests each limitation of claim 1, that a person of ordinary skill in the art would have had a reason to combine the references and would have had a reasonable expectation to achieve the claimed clinical efficacy and safety. We further determine that evidence of the objective indicia is not sufficient to outweigh the primary findings. As a result, we conclude that Petitioner has established by a preponderance of the evidence that claim 1 is unpatentable over the combination of Baselga 1996, Seidman 1996, and the 1995 TAXOL PDR entry.

Patent Owner does not argue claims 2–14 separately. After reviewing the entire record (*see, e.g.*, Pet. 64–69), we conclude that Petitioner has established by a preponderance of the evidence that claims 2–14 are

unpatentable over the combination of Baselga 1996, Seidman 1996, and the 1995 TAXOL PDR entry.

Patent Owner's Contingent Motion to Amend

In an *inter partes* review, an amended claim is not added to the challenged patent as of right, but rather must be proposed as a part of a motion to amend. 35 U.S.C. § 316(d). We 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, 1296 (Fed. Cir. 2017).

Patent Owner proposes a single amended claim 15 to substitute original claim 11. MTA 1. Claim 15 is reproduced below (showing deletions and additions to claim 11):

> ~~11.~~ 15. A method for the treatment of a human patient with ErbB2 overexpressing progressing metastatic breast cancer, comprising administering a combination of ~~a humanized 4D5 anti-ErbB2 antibody~~ rhuMAb HER2 and ~~a taxoid~~ paclitaxel, in the absence of an anthracycline derivative, to the human patient in an amount effective to extend time to disease progression in said human patient, as compared to paclitaxel alone, without increase in overall severe adverse events.

Id., Appendix A.

A Motion to Amend must meet the following statutory and regulatory requirements: (1) the amendment responds to a ground of unpatentability involved in the review; (2) the amendment does not seek to enlarge the scope of the claims of the patent or introduce new subject matter; and (3) the amendment proposes a reasonable number of substitute claims. *See* 35 U.S.C. § 316(d); 37 C.F.R. § 42.221. Petitioner does not dispute, and we agree, that one is a reasonable number of substitute claims. Petitioner,

however, disputes whether the Motion to Amend complies with the first two requirements. MTA Opp. 1–7. We agree with Petitioner that Patent Owner's proposed amendment fails, at least, because it seeks to introduce new matter.

To determine whether an amended claim introduces new matter, we look to whether the original application provides adequate written description support. In other words, we must determine whether the disclosure of the application reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). Because possession of the claimed invention is required, "a description that merely renders the invention obvious does not satisfy the requirement." *Id.* at 1352.

Proposed claim 15 specifies that a combination of rhuMAb HER2 and paclitaxel would not result in an increase in overall severe adverse events, as compared to paclitaxel alone. MTA 4. Patent Owner contends that the proposed substitute claim is supported by the original application and the provisional application. *Id.* at 5–6 (citing Ex. 1004; Ex. 2009). According to Patent Owner,

> The applications describe a clinical study in which overexpressing ErbB2 metastatic breast cancer 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 an anthracycline derivative. The 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. at 6 (internal citations omitted). Specifically, Patent Owner relies on the following chart:

	Enrolled	TTP(months)	RR(%)	AE(%)
CRx	234	5.5	36.2	66
CRx +H	235	8.6*	62.00**	69
AC	145	6.5	42.1	71
AC+H	146	9.0	64.9	68
T	89	4.2	25.0	59
T+H	89	7.1	57.3	70

* $p<0.001$ by log-rank test

** $p<0.01$ by X^2 test

CRx : chemotherapy

AC: anthracycline/cyclophosphamide treatment

H: HERCEPTIN®

T: TAXOL®

Id. at 7 (citing Ex. 1004, 47; Ex. 2009, 43).

As shown in the chart above, AE (%) for paclitaxel/Herceptin® ("T+H") is 70%, higher than AE (%) for paclitaxel ("T") alone, which is 59%. Patent Owner argues that "a POSA would conclude that the 'AE%' column of this table represents adverse events, not severe adverse events." MTA Reply 3 (citing Ex. 2130, 150:20–151:5; Ex. 2144 ¶ 12). Instead, Patent Owner would have us construe "overall severe adverse events" to mean Grade 3/4 myocardial dysfunction. *Id.* at 2–3. Petitioner disagrees. MTA Sur-reply 3. We do not need to resolve this dispute because, even if we agree with Patent Owner on this point, we still do not find sufficient written description support for the proposed amended claim.

Both the original application and the provisional application disclose that "[a] syndrome of myocardial dysfunction similar to that observed with

anthracyclines was reported more commonly with a combined treatment of AC+H (18% Grade 3/4) than with AC alone (3%), T (0%), or T +H (2%)." Ex. 1004, 47; Ex. 2009, 43; *see also* Ex. 1001, 30:1–16. Here, again, the reported Grade 3/4 myocardial dysfunction incidence for paclitaxel/Herceptin® (T+H (2%)) is higher than that for paclitaxel alone (T (0%)). According to Patent Owner,

> However, a POSA would recognize that this difference is negligible—only one to two patients—and would constitute effectively no increase in overall severe adverse events. A POSA would contrast this data with the substantial increase in myocardial dysfunction observed in the anthracycline arm of the study, and understand that to be the type of 'increase in overall severe adverse events' that the claim is describing."

MTA Reply 3 (internal citations omitted). We are not persuaded by Patent Owner's argument for three reasons.

First, the proposed amendment specifies that the comparator is "paclitaxel alone," not the "anthracycline arm of the study." Second, the proposed amended claim recites, in absolute terms, "without increase in overall severe adverse events," and does not qualify the increase with modifiers such as "substantial," "effective," or "non-negligible." Third, even if we were to rewrite the claim to recite "without substantial increase in overall severe adverse events"—which we cannot—neither the original application nor the provisional application provides any information to determine what constitutes "substantial increase." *See* MTA Sur-reply 4.

In sum, Patent Owner has not pointed to, and we do not find, adequate description support in the original disclosure for proposed substitute claim 15. Because proposed substitute claim 15 introduces new matter,

which is prohibited under 35 U.S.C. § 316(d)(3) and 37 C.F.R. § 42.121(a)(2)(ii), we deny Patent Owner's Contingent Motion to Amend.[30]

Motions to Exclude Evidence

Petitioner's Motions to Exclude

Petitioner filed two Motions to Exclude, seeking to exclude Exhibits 2052, 2055, 2070, 2075, 2106, 2133, 2135, 2139, and 2146, as well as paragraph 56 of Exhibit 2061, paragraphs 11 and 15 of Exhibit 2143, and paragraphs 31 and 32 of Exhibit 2144. Papers 63, 83.

Petitioner contends that Patent Owner has not established that Exhibits 2052, 2055, 2070, 2106, and 2139 were available as prior art, and Exhibits 2075 and 2133 are dated after the priority date of the '441 patent. Paper 63, 3–5. As a result, Petitioner argues that 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." *Id.* at 3. Petitioner also seeks to exclude paragraph 56 of Exhibit 2061 and paragraph 11 of Exhibit 2143, because Dr. Kerbel relied on Exhibits 2075 and 2133, respectively, in his Declarations. *Id.* at 4–5.

Our determination of the patentability of the challenged claims remain unchanged regardless of whether Exhibits 2052, 2055, 2070, 2075, 2106,

[30] For the reasons explained above in our analysis of the original claims under patent owner's proposed claim construction, we also conclude that proposed substitute claim 15 (which makes that construction explicit by reciting "as compared to paclitaxel alone") is unpatentable over the prior art of the record. *See supra* at 13–44. In short, Patent Owner does not contend, nor do we discern, that further narrowing the proposed claim to specifically recite "rhuMAb HER2" and "paclitaxel" renders the claim patentable over the prior art.

2133, and 2139, as well as paragraph 56 of Exhibit 2061 and paragraph 11 of Exhibit 2143 are excluded. Further, we do not rely on these references and the reliance by Dr. Kerbel and Patent Owner thereof in our Decision. Thus, we dismiss as moot Petitioner's Motion to Exclude with respect to these exhibits.

Petitioner seeks to exclude Exhibit 2135 "because it is not authenticated under FRE 901, Patent Owner has not demonstrated that it is prior art, and it is hearsay under FRE 802, not within a hearsay exception." Paper 63, 7. Exhibit 2135 is the Hsu abstract discussed above. Petitioner also seeks to exclude Exhibit 2146 "as not authenticated, not prior art, and inadmissible hearsay." Paper 83, 1. Exhibit 2146 is a full copy of the conference proceedings, which contains a copy of the Hsu abstract. Patent Owner relies on Exhibit 2146 to authenticate and to prove the publication date of Hsu. Petitioner further seeks to exclude paragraph 15 of Exhibit 2143, and paragraphs 31 and 32 of Exhibit 2144 because Dr. Kerbel and Dr. Tannenbaum, respectively, relied on Exhibit 2135 in their Declarations. Paper 63, 7.

As explained above, we do not find persuasive Patent Owner's arguments based on the substance of Hsu. *See supra* at 27–28. Accordingly, and taking no position as to the merits of the parties' arguments relating to the admissibility of the Hsu abstract, we dismiss as moot Petitioner's Motion to Exclude as to Exhibits 2135, 2146, as well as paragraph 15 of Exhibit 2143, and paragraphs 31 and 32 of Exhibit 2144.

Patent Owner's Motion to Exclude

Patent Owner filed a Motion to Exclude Exhibits 1033, 1034, 1036, 1055, 1056, 1059, 1060, and 1100, and paragraphs 22, 23, and 38 of Exhibit 1054. Paper 61.

Because we do not rely on Exhibits 1033, 1034, 1036, 1055, 1056, 1059, and 1100, and paragraphs 22, 23, and 38 of Exhibit 1054 in rendering our Decision, we dismiss these aspects of Patent Owner's Motion to Exclude as moot.

Exhibit 1060 is Patent Owner's response submitted in another *inter partes* review IPR2017-01139. As an initial matter, Patent Owner submitted Exhibit 1060 as a public document. We, thus, may take judicial notice of it even if Petitioner has not submitted it in this proceeding. Moreover, as explained above, we presume there is a nexus between Herceptin's success and the challenged claims of the '441 patent. This nexus, however, is weak. This is because Patent Owner has also asserted that the success of Herceptin "is attributable, in part," to the claims of an earlier patent that do not require the combination claimed here. Ex. 1060, 66. And Patent Owner has not apportioned the sales of Herceptin to these two different patents. *Supra* at 40. Because Petitioner's reliance on Exhibit 1060 directly responds to Patent Owner's assertion of commercial success, we deny Patent Owner's Motion to Exclude Exhibit 1060.

Motions to Seal

There is a strong public policy for making all information filed in an *inter partes* review 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. Generally, all papers filed in an *inter partes*

review shall be made available to the public. *See* 35 U.S.C. § 316(a)(1); 37 C.F.R. § 42.14. Our rules, however, "aim to strike a balance between the public's interest in maintaining a complete and understandable file history and the parties' interest in protecting truly sensitive information." Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,760 (Aug. 14, 2012). Thus, a party may move to seal certain information (37 C.F.R. § 42.14); but only "confidential information" is protected from disclosure (35 U.S.C. § 326(a)(7)). Confidential information means trade secret or other confidential research, development, or commercial information. 37 C.F.R. § 42.2.

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 and must explain why the information sought to be sealed constitutes confidential information. 37 C.F.R. § 42.20(c).

Confidential information that is subject to a protective order ordinarily becomes public 45 days after final judgment in a trial. Trial Practice Guide, 77 Fed. Reg. at 48761. There is an expectation that confidential information relied upon or identified in a final written decision will be made public. *Id.* 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.

Petitioner's Motions to Seal

In Papers 43 and 64, Petitioner seeks to seal the confidential version of the Reply to Patent Owner's Response (Paper 44), Opposition to Patent Owner's Motion to Amend (Paper 46), and Surreply in Opposition to Patent Owner's Motion to Amend (Paper 67). Petitioner seeks to seal these

documents because they "refer to materials that Patent Owner Genentech has designated as Confidential pursuant to the Modified Default Standing Protective Order." *See, e.g.*, Paper 43, 1. Petitioner seeks to seal Exhibits 1035, 1046, 1049, and 1058 for the same reason. Paper 49, 1.

Petitioner does not provide any other justification for why the redacted portions of these documents should be kept confidential and thus, fails to satisfy the good cause requirement. Accordingly, we deny Petitioner's Motions to Seal.

Patent Owner is invited to file, within 14 days of this Decision, a motion to seal any presently redacted portion of Papers 44, 46, and 67, and Exhibits 1035, 1046, 1049, and 1058. The motion shall (1) attest that the material sought to be protected is not directly or indirectly relied on in this Decision; or (2) to the extent we rely on any of the material sought to be protected in this Decision, provide sufficient justification that outweighs the heightened public interest in understanding the basis for our decision on patentability. Together with the motion to seal, Patent Owner shall file narrowly redacted public version of the documents sought to be sealed.

In the absence of any action on the part of Patent Owner, at the expiration of 14 days from the date of this Decision, the documents-at-issue will be made available to the public.

Patent Owner's Motions to Seal

In Paper 27, Patent Owner seeks to seal the confidential version of the transcript of the deposition of Dr. Earhart (Ex. 2050), the Declaration of Stephanie Mendelsohn (Ex. 2069), and the Declaration of Dr. Hellmann (Ex. 2125). Patent Owner seeks to seal Exhibits 2006, 2126, and 2127. Patent Owner has shown good cause supporting the motion. Insofar as we

do not rely on any of the material sought to be protected in this Decision, Patent Owner's Motion to Seal is granted.

In Paper 54, Patent Owner seeks to seal the confidential version of Patent Owner's Reply in Support of Contingent Motion to Amend (Paper 56), the Supplemental Expert Declaration of Dr. Tannenbaum (Exhibit 2144), as well as Exhibit 2142. Patent Owner has shown good cause supporting the motion. Insofar as we do not expressly rely on any of the material sought to be protected in this Decision, Patent Owner's Motion to Seal is granted.

Modification of Previous Order on Patent Owner's Motion to Seal

We previously granted Patent Owner's Motion to Seal (Paper 7) Exhibit 2001 and the redacted portions of Patent Owner's Preliminary Response, and Exhibits 2002–2005, 2007, and 2008. Paper 24, 2–3.

As explained before, the exhibits sought to be sealed appear to contain confidential business information. *Id.* Insofar as we do not expressly rely on any of the material sought to be protected in this Decision, our decision granting Patent Owner's Motion to Seal remains unchanged.

To the extent we rely on any of the material sought to be protected in this Decision, we modify our previous Order (Paper 24). For example, Patent Owner affirmatively relies upon certain exhibits, including Exhibits 2004 and 2007. We have addressed these exhibits in this Decision.

Patent Owner may, within 14 days of this Decision, renew its motion to seal any portion of the presently protected exhibits that are discussed in this Decision. Because the public has a heightened interest in understanding the basis for our decision on patentability, any renewed motion shall provide sufficient justification that outweighs the public interest. Together with the

renewed motion to seal, Patent Owner shall file narrowly redacted public version of the exhibits sought to be sealed.

In the absence of any action on the part of Patent Owner, at the expiration of 14 days from the date of this Decision, the exhibits-at-issue will be made available to the public.

Redaction of the Final Written Decision

The parties may, within 14 days of this Decision, jointly propose redactions for this Final Written Decision. In the absence of such proposal, at the expiration of 14 days from the date of this Decision, the entirety of the Final Written Decision will be made available to the public.

CONCLUSION

After reviewing the entire record and weighing evidence offered by both parties, we determine that Petitioner has shown, by a preponderance of the evidence, that claims 1–14 of the '441 patent would have been obvious over the combination of Baselga 1996, Seidman 1996, and the 1995 TAXOL PDR entry, and the knowledge of a person of ordinary skill in the art.

We further deny Patent Owner's Motion to Amend because the proposed amended claim improperly introduces new matter.

ORDER

Accordingly, it is

ORDERED that claims 1–14 of the '441 patent are held unpatentable;

FURTHER ORDERED that Patent Owner's Contingent Motion to Amend is denied;

FURTHER ORDERED that Petitioner's Motion to Exclude is dismissed as moot;

FURTHER ORDERED that Patent Owner's Motion to Exclude is denied-in-part and dismissed-in-part; and

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

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