IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.,

Petitioner,

v.

GENENTECH, INC.,

Patent Owner.

Case IPR2017-00731
Patent No. 7,846,441

PATENT OWNER'S NOTICE OF APPEAL

Director of the United States Patent and Trademark Office
c/o Office of the General Counsel
P.O. Box 1450
Alexandria, VA 22314-5793

Pursuant to 35 U.S.C. §§ 141-44 and 319, and 37 C.F.R. § 90.2-90.3, notice is hereby given that Patent Owner Genentech, Inc. appeals to the United States Court of Appeals for the Federal Circuit from the Final Written Decision entered October 3, 2018 (Paper 120) in IPR2017-00731 (Exhibit A), and all prior and interlocutory rulings related thereto or subsumed therein.

In accordance with 37 C.F.R. § 90.2(a)(3)(ii), Patent Owner further indicates that the issues on appeal include, but are not limited to: whether the Patent Trial and Appeal Board ("the Board") erred in its claim construction of the term "extend the time to disease progression in said human patient, without increase in overall severe adverse events"; whether the Board erred in determining that Petitioner established by a preponderance of the evidence that claims 1–14 of U.S. Patent No. 7,846,441 are unpatentable under 35 U.S.C. § 103 as obvious; whether the Board erred in denying Patent Owner's motion to amend; whether the Board erred in refusing to allow Patent Owner to file a motion to amend following the institution of Ground 1; whether the Board's procedures in this proceeding violated the Administrative Procedures Act, including with respect to Patent Owner's motions to amend; whether the Board erred in allowing a partial adverse judgment that

disposed of Ground 1 at Petitioner's request and over Patent Owner's objection; whether *inter partes* review of pre-AIA patents is constitutional; and any finding or determination supporting or related to those issues, as well as all other issues decided adversely to Patent Owner in any orders, decisions, rulings, and opinions.

Pursuant to 37 C.F.R. § 90.3, this Notice of Appeal is timely, having been duly filed within 63 days after the date of the Final Written Decision.

Pursuant to 35 U.S.C. § 142 and 37 C.F.R. § 90.2(a), a copy of this Notice of Appeal is being filed simultaneously with the Patent Trial and Appeal Board, the Clerk's Office for the United States Court of Appeals for the Federal Circuit, and the Director of the Patent and Trademark Office.

Respectfully submitted,

Date: November 30, 2018

/David L. Cavanaugh/

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CERTIFICATE OF FILING & SERVICE

Pursuant to 37 C.F.R. §§ 90.2(a)(1) and 104.2(a), I hereby certify that, in addition to being filed electronically through the Patent Trial and Appeal Board's E2E system, a true and correct original version of the foregoing **PATENT OWNER'S NOTICE OF APPEAL** is being filed by Express Mail (Express Mail Label EL 061981721 US) on this 30th day of November, 2018, with the Director of the United States Patent and Trademark Office, at the following address:

Director of the United States Patent and Trademark Office
c/o Office of the General Counsel
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Pursuant to 37 C.F.R. § 90.2(a)(2) and Federal Circuit Rule 15(a)(1), and Rule 52(a), (e), I hereby certify that a true and correct copy of the foregoing **PATENT OWNER'S NOTICE OF APPEAL** is being filed in the United States Court of Appeals for the Federal Circuit on this day, November 30, 2018, and that the filing fee is being paid electronically using pay.gov.

The undersigned further certifies that the foregoing **PATENT OWNER'S NOTICE OF APPEAL** was served electronically via e-mail on November 30, 2018, in its entirety on the following counsel for Petitioner:

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Exhibit A

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.,
Petitioner,

v.

GENENTECH, INC,
Patent Owner.

Case IPR2017-00731
Patent 7,846,441 B1

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

YANG, *Administrative Patent Judge*.

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

Denying-in-Part and Dismissing-in-Part 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

Hospira, Inc. ("Petitioner")[1] filed a Petition (Paper 1, "Pet."), requesting an *inter partes* review of claims 1–14 of U.S. Patent No. 7,846,441 B1 (Ex. 1001, "the '441 patent"). During the trial, Petitioner filed papers and submitted evidence in support of its challenge, and Genentech, Inc. ("Patent Owner") filed papers and submitted evidence in response.

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.

Procedural History and Related Proceedings

This case has a rather convoluted history. Petitioner challenges claims 1–14 as obvious over the combination of (1) Baselga '97[2] and Baselga '94,[3] and (2) Baselga '96[4] and Baselga '94. Pet. 5. After Patent

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[1] Petitioner identifies Pfizer, Inc. as "the real party in interest for Petitioner." Paper 13.

[2] Baselga et al., *HER2 Overexpression and Paclitaxel Sensitivity in Breast Cancer: Therapeutic Implications*, 11(3) (Suppl. 2) ONCOLOGY 43–48 (1997) (Ex. 1006).

[3] 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. 1005).

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

Owner filed a Preliminary Response (Paper 9), we denied the Petition on both grounds. Paper 19. Specifically, we exercised our discretion and denied institution on Ground 1 (based on Baselga '97 and Baselga '94) under 35 U.S.C. § 325(d), because the applicant successfully antedated Baselga '97 during prosecution. *Id.* at 7–8. We denied institution on Ground 2 (based on Baselga '96 and Baselga '94) based on our substantive analysis. *Id.* at 8–11.

Thereafter, Petitioner filed a Request for Rehearing of our decision not to institute. Paper 21. On October 26, 2017, upon reconsideration of the record, we instituted an *inter partes* review on Ground 2. Paper 29 ("Dec."), 10–18. We, again, declined to institute review on Ground 1. *Id.* at 5. We set May 18, 2018 as the date for oral argument. Papers 30, 52.

On December 22, 2017, Patent Owner filed a Response to the Petition (Paper 50, "PO Resp."), and a contingent Motion to Amend (Paper 48, "MTA"). On March 30, 2018, Petitioner filed a Reply in support of its Petition (Paper 66, "Reply"), and an Opposition to Patent Owner's Motion to Amend (Paper 47, "MTA Opp."). After Patent Owner filed a Reply in support of the Motion to Amend (Paper 71, "MTA Reply"), and with our authorization, Petitioner filed a Sur-reply (Paper 77, "MTA Sur-reply").

On May 7, 2018, we granted the parties' requests for oral argument and confirmed May 18, 2018 as the date for oral argument. Paper 81.

Before explaining what happened in this case afterwards, we digress to the procedural history of the companion cases related to this proceeding.

Overexpressing Metastatic Breast Cancer, 14 J. CLIN. ONCOL. 737–44 (1996) (Ex. 1004).

In IPR2017-01121, we instituted trial to review the same claims of the '441 patent, which are challenged by Celltrion, Inc., a different petitioner. *Celltrion, Inc. v. Genentech, Inc.*, IPR2017-01121, Paper 9 (PTAB Oct. 4, 2017). We also joined IPR2017-02063, filed by Pfizer, the real party in interest for Petitioner in the current proceeding, to IPR2017-01121.[5] *Pfizer, Inc. v. Genentech, Inc.*, IPR2017-02063, Paper 25 (PTAB Feb. 21, 2018). In IPR2017-01121, Patent Owner filed a motion to amend that is substantially identical to the one filed in this case. IPR2017-01121, Paper 28. By April 30, 2018, the parties in that case had completed briefing regarding Patent Owner's motion to amend. IPR2017-01121, Papers 47, 55, 66.

Further, we instituted trial in IPR2017-00737, filed by the same Petitioner in the current proceeding, to review claims of U.S. Patent No. 7,892,549, a patent in the same family as the '441 patent at issue here. *Hospira, Inc. v. Genentech, Inc.*, IPR2017-00737, Paper 19 (PTAB July 27, 2017). We later joined IPR2017-01960, filed by Samsung Bioepis Co., Ltd., to IPR2017-00737. *Samsung Bioepis Co., Ltd. v. Genentech, Inc.*, IPR2017-01960, Paper 11 (PTAB December 1, 2017). We also instituted trial in IPR2017-01122, filed by Celltrion, and challenging the same claims of the '549 patent. *Celltrion, Inc. v. Genentech, Inc.*, IPR2017-01122, Paper 9 (PTAB Oct. 4, 2018).

On May 7, 2018, the same day we granted the parties' requests for oral argument in this proceeding, we also granted the requests for oral

[5] We denied the third petition filed by Pfizer challenging the same claims of the '441 patent. *Pfizer, Inc. v. Genentech, Inc.*, IPR2018-00016, Paper 25 (PTAB February 21, 2018).

arguments in companion cases IPR2017-00737, -01121, -01122, -01960, and -02063. The hearing date for all these cases was set to May 18, 2018.

Returning to the procedural history of this case, on May 9, 2018, after the Supreme Court's decision in *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348 (2018), and in view of the Office Guidance on the Impact of *SAS* on AIA Trial Proceedings,[6] we modified our institution decision to include Ground 1. Paper 87.

On the same day, we held a conference with the parties to discuss the best approach going forward. Ex. 2149. During the conference, Patent Owner objected to keeping May 18, 2018 as the hearing date for all of the related cases scheduled for that day (IPR2017-00731, -00737, -01121, -01122, -01960, and -02063). *Id.* at 14:13–17. Instead, Patent Owner requested that we postpone the hearings in all of these cases, even though that schedule would extend the final written decision in this case to beyond the one-year deadline mandated by the statute. *Id.* at 12:9–13:16. We denied Patent Owner's request. *Id.* at 27:5–6. Instead, we maintained the May 18 date for oral hearings for all cases[7] and further ordered an August 2, 2018 supplemental hearing in the instant case directed to Ground 1. Paper 87, 3. We also instructed the parties to work out a supplemental briefing schedule. *Id*. at 4. We expressly limited the scope of both the supplemental hearing and related briefing to Ground 1, that is, the ground based on the combination of Baselga '97 and Baselga '94. *Id*. at 2–4.

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[6] Available at https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial.

[7] None of IPR2017-00737, -01121, -01122, -01960, and -2063 has any *SAS*-related issues.

On May 18, 2018, we held an oral hearing on Ground 2 and Patent Owner's Motion to Amend.[8] *See* Paper 104.

On June 7, 2018, at Patent Owner's request, we held a conference with the parties to discuss whether Patent Owner may file a second motion to amend in view of the newly instituted Ground 1. Ex. 2150. Based on 35 U.S.C. § 316(d)(1) and 37 C.F.R. § 121(a), we informed the parties that the panel would consider a single motion to amend. Paper 101, 3. In view of 35 U.S.C. § 316(d)(2) and 37 C.F.R. § 42.121(c), however, we authorized Patent Owner to file a second motion to amend with respect to Ground 1, but required that for any such motion to be considered, Patent Owner "must establish the 'good cause showing' as required in 37 C.F.R. 121(c)." *Id.*

On June 18, 2018, at Petitioner's request, we held another conference with the parties to discuss Petitioner's proposal to withdraw Ground 1 from further consideration in this proceeding. Ex. 2155. Patent Owner opposed Petitioner's proposal. *Id.* at 17:1–18:5. During the conference, Patent Owner also argued that it has, "as a matter of right," an opportunity to file the second motion to amend, contrary to our earlier instruction. *Id.* at 24:4–6.

In view of Patent Owner's argument that "the good cause standard should not be applicable in this particular situation" (*see id.* at 13:6–7), we modified our June 8 order (Paper 101) to require Patent Owner to first file a motion to show good cause for a second motion to amend. Paper 103, 3. We explained that if Patent Owner was able to establish the "good cause

[8] As indicated above, on May 18, we also heard arguments in IPR2017-00737, -01121, -01122, -01960, and -2063.

showing" required by 37 C.F.R. § 42.121(c), the panel would issue an order authorizing Patent Owner to file a second motion to amend. *Id.*

After the parties completed the briefing on this issue, Patent Owner filed a Request for Rehearing of our Order requiring Patent Owner to brief the issue of good cause before we authorized any additional motion to amend. Paper 113.

We denied Patent Owner's Request for Rehearing. Paper 114. We also denied its Motion Regarding Good Cause to file a second motion to amend. Paper 115.

Around the same timeframe, with our authorization, Petitioner filed a Request for Partial Adverse Judgment with Regard to Ground One under 37 C.F.R. § 42.73(b). Paper 109.

Because we declined to authorize Patent Owner to file a second motion to amend, and because Petitioner sought partial adverse judgment with regard to Ground 1, no issues remained in this proceeding to justify a supplemental hearing. Paper 116, 3. As a result, we denied Patent Owner's request for a supplemental oral hearing as moot. *Id.*

In this proceeding, the parties also briefed whether certain exhibits should be excluded from the record. Papers 74, 79, 83, 85, 89, 90, 98, 99, 100. In addition, Patent Owner filed observations on the cross-examination of Petitioner's declarant (Papers 82, 88), and Petitioner filed responses thereto (Papers 91, 93).

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 Grounds of Unpatentability

We instituted *inter partes* review on the following grounds:

Ground	Basis	References
1	§ 103	Baselga '97 and Baselga '94
2	§ 103	Baselga '96 and Baselga '94

In support of their respective arguments, Petitioner relies on the Declarations of Dr. Allan Lipton (Exs. 1007, 1085, 1099) and Dr. Robert Clarke (Exs. 1086, 1100), and Patent Owner relies on the Declarations of Dr. Susan Desmond-Hellmann (Ex. 2011), Dr. Robert S. Kerbel (Exs. 2061, 2143), Dr. Susan Tannenbaum (Ex. 2062, 2144).

ANALYSIS

Ground 1

Petitioner contends that claims 1–14 would have been obvious over the teachings of Baselga '97 and Baselga '94. Pet. 25–41. After we instituted a review on this Ground, Petitioner filed a Request for Partial Adverse Judgment with Regard to Ground One under 37 C.F.R. § 42.73(b). Paper 109. Patent Owner opposes Petitioner's Request. According to Patent Owner, Petitioner cannot unilaterally withdraw an instituted ground.

Paper 105, 11. Instead, Patent Owner contends the only available mechanism for Petitioner to abandon Ground 1 requires Petitioner to seek adverse judgment as to all instituted grounds. *Id.* (citing 37 C.F.R. §§ 42.73(a), (b)); *see also* Ex. 2155, 17:14–18:6. We disagree with Patent Owner.

Section 42.73(b) provides that a party "may request judgment against itself at any time during a proceeding." Nothing in this subsection requires that a request for adverse judgment must be on all grounds. Section 42.73(a) requires that a "judgment" disposes of all issues that were, or reasonably could have been raised or decided. Patent Owner, however, has not sufficiently explained why this requirement applies to § 42.73(b), such that an adverse judgment must be sought as to all grounds. In addition, this Final Written Decision, addressing the patentability of the original claims under Ground 2 and the proposed claim in the first Motion to Amend, and granting Petitioner's Request for Partial Adverse Judgment as to Ground 1, disposes of all issues, and thus, is consistent with the requirement under § 42.73(a).

Our reading of the Rules is confirmed by the Supreme Court's decision in *SAS*, as well as the Board's practice. Indeed, the Court instructed us that "the petitioner's contentions . . . define the scope of the litigation all the way from institution through to conclusion." *SAS*, 138 S. Ct. at 1357; *see also id.* (noting that "only claims still challenged 'by the petitioner' at the litigations' end must be addressed in the Board's final written decision"). In view of this decision, the

Office issued Frequently Asked Questions about *SAS* Implications (June 5, 2018).[9] One of the Q&As is directly on point:

> **B12. Q: If the parties cannot agree to waive additional claims, is there anything a party can do on its own to limit the scope of the proceeding?**
>
> A: Yes.
>
> . . .
>
> b. The Petitioner can request adverse judgment on claims and/or grounds at any time.

In view of the above, and upon considering the parties' arguments and evidence, we grant Petitioner's Request for Partial Adverse Judgment.

Ground 2

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; (2) any differences between the claimed subject matter and the prior art;

[9] Available at https://www.uspto.gov/sites/default/files/documents/sas_qas_20180605.pdf.

(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).

In the Decision to Institute, we construed the term "administering a combination" as requiring "a single treatment regimen in which the patient receives all drugs that are part of the claimed combination." Dec. 6 (adopting the construction proposed by Patent Owner). During trial, the parties do not dispute this construction. *See* PO Resp. 33–35 (reiterating its position); Reply 2 (agreeing the term means administering drugs "as part of the same treatment regimen"). Having considered the complete record developed at trial, we see no reason to change our interpretation of this term.

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 "given 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. 8.

Patent Owner disputes this construction. PO Resp. 35–38. 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 35 (citing IPR2017-2063, Ex. 1102[10] ¶ 112(h); Ex. 2062 ¶¶ 132–141; Ex. 1007 ¶ 46, Ex. 2050, 56:11–14). Patent

[10] Patent Owner cites "Ex. 1002" from IPR2017-2063. PO Resp. 35. That case, however, does not include such an exhibit. We presume that Patent Owner intends to refer to Exhibit 1102 of IPR2017-2063.

Owner's representation is less than complete. Dr. Lipton, for example, specifically noted that, during prosecution, the applicant asserted that the comparison is between the claimed combination treatment and no treatment. IPR2017-2063, Ex. 1102 ¶ 112(h) (citing IPR2017-2063, Ex. 1004, 416). According to Dr. Lipton, 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. 1011, Vol. 2, 324–25 (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 356 (Response dated January 17, 2002) (emphasis added). In the next office action, the examiner withdrew the rejection. *See* Ex. 1011, Vol. 3, 230 (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 indefinite 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. That may well be the case; yet, it does not render our construction inconsistent with the Specification of the '441 patent. As Dr. Tannenbaum, an expert for Patent Owner, explains, "cancer

generally continues to progress without treatment." Ex. 2062 ¶ 133. As a result, an ordinary artisan would have understood, 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 ¶ 138. 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. 1011, Vol. 2, 325 (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 356 (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."[11] Dec. 16 (quoting Ex. 3001). Nonetheless, we repeated that "the proper analysis of 'without increase in 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. 1011, Vol. 8, 357–59), after the applicant explicitly defined the limitation "extend the time to disease progression" as "relative to an untreated patient" (Ex. 1011, Vol. 2, 356). 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

[11] During the trial stage, neither party briefed whether the NCI dictionary definition is applicable to the present context.

applicant set out, even if such construction would lead to a "nonsensical result."[12] *Source Vagabond Sys. Ltd. v. Hydrapak, Inc.*, 753 F.3d 1291, 1301 (Fed. Cir. 2014).

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 '96

Baselga '96 reports the results of a phase II clinical trial in patients with ErbB2-overexpressing metastatic breast cancer who had received extensive prior therapy. Ex. 1004, 9. 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.*

[12] 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 the this constitutes an admission that the challenged claims are indefinite under 35 U.S.C. § 112.

According to Baselga '96, "patients were selected to have many sites of metastatic involvement, one of the most dire prognostic characteristics regarding response to therapy." *Id.* at 13. Each patient received a loading dose of 250 mg of intravenous rhuMAb HER2, followed by 10 weekly doses of 100 mg. *Id.* at 10. In Baselga '96, "[a]dequate pharmacokinetic levels of rhuMAb HER2 were obtained in 90% of the patients. Toxicity was minimal and no antibodies against rhuMAb HER2 were detected in any patients." *Id.* at 9. Baselga '96 reports an 11.6% remission rate. *Id.* In addition, "37% of patients achieved minimal responses or stable disease." *Id.* at 13.

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

Baselga '94

Baselga '94 teaches that HER2 overexpressing tumors were grown in nude mice followed by treatment with the 4D5-antibody in combination with paclitaxel. Ex. 1005, 4. Although each of the antibody or paclitaxel alone produced 35% growth inhibition, the combination of the two resulted in 93% growth inhibition without increasing toxicity. *Id.* Baselga '94 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.*

Level of Ordinary Skill in the Art

Petitioner proposes that one of ordinary skill in the art "at the time of the alleged invention would be [a] clinical or medical oncologist specializing in breast cancer with several years of experience with breast cancer research or clinical trials." Pet. 7 (citing Ex. 1003 ¶¶ 29–31; Ex. 1007 ¶¶ 15–17). Patent Owner does not dispute (PO Resp. 33), and we adopt, this definition.

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 teachings of Baselga '96 and Baselga '94. Pet. 42–58. 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 '96 for teaching using rhuMAb HER2 to treat "adult women whose metastatic breast carcinomas overexpressed HER2." Pet. 42 (citing Ex. 1004, 9–10). According to Petitioner, rhuMAb HER2 is a therapeutic antibody that binds to epitope 4D5 of the ErbB2 receptor, as recited in claim 1.

For the recited combination of an antibody and "a taxoid," Petitioner argues that because certain patients were previously treated with taxoids,

Baselga '96 teaches this limitation. *Id.* at 44 (citing Ex. 1004, 13, Table 5). Petitioner also relies on the preclinical studies combining anti-HER2 MAbs with paclitaxel, as taught in Baselga '96 and Baselga '94. Pet. 44–45 (citing Ex. 1004, 15; Ex. 1005, 4).

For the limitation of "an amount effective to extend the time to disease progression in said human patient," Petitioner refers to the dosing regimen of rhuMAb HER2 in Baselga '96. *Id.* at 46–47 (citing Ex. 1004, 9–11). Under that dosing regimen, more than 90% of the patients achieved adequate pharmacokinetic levels of rhuMAb HER2, that is, "rhuMAb HER2 trough serum concentrations greater than 10 μg/mL, a level associated with optimal inhibition of cell growth." *Id.* at 46–47 (citing Ex. 1004, 9–11). Petitioner points out that in Baselga '96, some patients experienced a partial or complete remission, while others achieved minor responses or stable disease state, which "lasted for a median of 5.1 months." *Id.* at 47 (citing Ex. 1004, 9, 13). According to Petitioner, because Baselga '96 and Baselga '94 teach that rhuMAb HER2 "markedly potentiated the antitumor effects" of paclitaxel in preclinical models, they suggest that the combination of rhuMAb HER2 of paclitaxel would improve time to disease progression, as claim 1 recites. *Id.* at 47–48.

Petitioner also argues the combination of Baselga '96 and Baselga '94 teaches the limitation "without increase in overall severe adverse events" because rhuMAb HER2 "was remarkably well tolerated" in clinical trials, and because there was no increase in the toxicity of paclitaxel when administered in combination with rhuMAb HER2 in preclinical models. *Id.* at 48 (citing Ex. 1004, 11, 13, 15; Ex. 1005, 4).

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, and it would not have been obvious to try the claimed combination. PO Resp. 39–45, 53–54. 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. *Id.* at 46–53. In addition, Patent Owner argues that "several objective indicia conclusively establish the non-obviousness of the challenged claims." *Id.* at 55. We address Patent Owner's arguments in turn.

Motivation to Combine

Patent Owner contends that Baselga '94 and Baselga '96 do not provide a motivation to treat patients with the claimed combination. PO Resp. 39–45. We disagree.

Patent Owner argues that neither Baselga '94 nor Baselga '96 individually teaches the claimed combination. *See id.* at 39–44. As a preliminary matter, non-obviousness cannot be established by attacking references individually where the patentability challenge is based upon the teachings of a combination of references. *See In re Keller*, 642 F.2d 413, 425 (CCPA 1981). Furthermore, as explained below, the teachings of Baselga '94 and Baselga '96, either individually or as a whole, together with the knowledge of one of ordinary skill in the art, suggest the claimed combination.

Petitioner refers to Baselga '94 for teaching that, in mouse xenografts, "individual treatment with either anti-HER2 4D5 or paclitaxel alone resulted in 35% growth inhibition whereas the combination 'resulted in a major

antitumor activity with 93% inhibition of growth' without increasing toxicity." Pet. 45 (citing Ex. 1005, 4). As Petitioner points out, Baselga '94 states that "[c]linical trials are underway." *Id.* (citing Ex. 1005, 4).

Patent Owner challenges Baselga '94 because it is an abstract. PO Resp. 41. According to Patent Owner, an ordinary artisan "would wait for the full, peer-reviewed paper describing the underlying experiments and bases before drawing any conclusions from it." *Id.* (citing Ex. 2062 ¶¶ 168–169). We do not find this argument persuasive.

First, the '441 patent cites numerous abstracts on its face. *See* Ex. 1001, (56) References Cited. In addition, in a declaration submitted during prosecution, the inventor relied on an abstract to overcome prior-art rejections. *See* Ex. 1011, Vol. 2, 54.

Second, Baselga '94 reports work collaborated between Patent Owner and Memorial Sloan-Kettering Cancer Center. In Patent Owner's own words, at least one author is a "leading practitioner" in the field. PO Resp. 57. These authors also appear to have been collaborating with scientists of Patent Owner in rhuMAb HER2 researches and clinical trials. *See, e.g.*, Ex. 1004, 9 (showing some of the same authors in Baselga '96 as in Baselga '94 and attributing the work on rhuMAb HER2 to both Memorial Sloan-Kettering Cancer Center and Genentech).

Third, we find persuasive the testimony of Dr. Lipton that abstracts such as Baselga '94 "are generally the first disclosure of important research. A subsequent peer reviewed, detailed description of the research might not be published for years thereafter, yet POSITAs often apply the information in the abstract beforehand, particularly where the abstract describes results that might have significant, clinical benefit for patients." Ex. 1085 ¶ 90.

Indeed, "Baselga '94 was subsequently cited in peer-reviewed publications, which viewed the study results with approval." *Id.* ¶ 91. For example, one article states that the data in Baselga '94, which show "apparent synergy" between rhuMAb HER2 and paclitaxel, "provide motivation for clinical evaluation" of the combination. Ex. 1072,[13] 8. Another one describes the study of the combination of rhuMAb HER2 and paclitaxel reported in Baselga '94 as "the basis for a planned clinical trial." Ex. 1073,[14] 11. Under such circumstances, we are not persuaded that an ordinary artisan would have ignored or discounted the teachings of Baselga '94 simply because it is an abstract.

Relying on Hsu,[15] Patent Owner asserts that "prior art information closer in time to the priority date than Baselga 94, and involving the same xenograft models that Petitioner proclaims here as predictive, clearly concluded that there was ***no*** 'synergistic efficacy' between trastuzumab and paclitaxel." MTA Reply 7–8 (citing Ex. 2135). 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

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[13] Seidman et al., *Memorial Sloan-Kettering Cancer Center Experience with Paclitaxel in the Treatment of Breast Cancer: From Advanced Disease to Adjuvant Therapy*, 22(4) (suppl. 8) SEMINARS in ONCOLOGY 3–8 (1995).

[14] F. A. Holmes, *Paclitaxel Combination Therapy in the Treatment of Metastatic Breast Cancer: A Review*, 23(5) (suppl. 11) SEMINARS in ONCOLOGY 46–56 (1996).

[15] 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 (1997).

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 plus taxol . . . were not significantly different from drug alone controls with the doses and dose schedules tested in this model." *Id.* In light of Hsu, Dr. Kerbel testifies that because "Baselga '94's results were not replicated in this study further indicates that any claim to synergy between rhuMAb HER2 and paclitaxel based on Baselga '94 would be unfounded." Ex. 2143 ¶ 25. We are not persuaded.

We observe, and Dr. Lipton confirms that

> the [Hsu] authors are careful to make clear that their results are specific to the "doses and dose schedules tested in this model," and a POSITA would not read them as saying that the same result could be generalized across all doses and dose schedules. In that regard, in contrast to the Baselga '94 reference, this abstract provides no information whatsoever regarding which doses and dose schedules were provided, and so a POSITA would not conclude that these results were inconsistent with those of Baselga '94, particularly given the *in vitro* results showing additive effects.

Ex. 1099 ¶ 48; *see also* Ex. 1100 ¶ 41 (the same).

In addition, for the *in vitro* cytotoxicity assay, Hsu used cells similar to those employed in Baselga '94, that is, human breast cancer cells with natural HER2 overexpression. *Compare* Ex. 1005, 4 (studying mouse injected with "BT-474 human breast adenocarcinoma cells which express high levels of HER2"), *with* Ex. 2135 ("SKBR-3 cells, human breast cancer cells with HER2/*neu* amplification/overexpression, served as the target cell line in these [*in vitro*] experiments."). And, similar to the synergistic effect

reported in Baselga '94, Hsu reported additive cytotoxic effects of rhuMAb HER-2 and taxol. Ex. 2135.

In contrast, Hsu conducted the *in vivo* xenograft study in a mouse model with HER2-negative MCF-7 cell line transfected with HER-2/*neu* to achieve artificial HER2-overexpression. *Id.* We observe, and Dr. Clarke confirms, that "there is no data in the [Hsu] abstract showing the level of HER2-overexpression achieved by this transfection, if any." Ex. 1100 ¶ 42.

> Furthermore, we find persuasive the testimony of Dr. Clarke that
>
> > Nor is there any dose information [in Hsu] (such as in the Baselga '94 abstract) which confirms that the dosage of either drug was reduced to ensure that the experiment had the ability to detect the possible interactions between the two drugs. For example, the rhuMAb HER2 could have been dosed at a level that would completely overshadow the contribution of paclitaxel treatment to the combination regimen.

Id. As a result, we are not persuaded by Patent Owner's argument that Hsu shows "any claim to synergy between rhuMAb HER2 and paclitaxel based on Baselga '94 would be unfounded." *See* Ex. 2143 ¶ 25.

Patent Owner also contends that the mouse study in Baselga '94 would not have motivated an ordinary artisan to treat patients with the claimed combination because it "was not a reliable predictor of success in humans." PO Resp. 41–43. Patent Owner argues that (1) "[t]he preclinical study was based on a single cell line;" (2) "the particular cell line used in Baselga '94 was not representative of actual patients;" and (3) "the tumors in Baselga '94 were implanted subcutaneously, rather than in tissue similar to how the disease would present in human patients (i.e., mammary fat pad)." *Id.* at 41–42. We find Patent Owner's arguments unpersuasive.

First, as explained above, Baselga '94 was cited with approval in numerous peer-reviewed publications. For example, citing Baselga '94, Baselga '96 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." Ex. 1004, 15. As a result, Baselga '96 reports that "[l]aboratory studies of the mechanism of this effect and clinical trials of such combination therapy [were] . . . in progress." *Id.*; *see also* Ex. 1072, 8 (stating the data in Baselga '94 "provide motivation for clinical evaluation"); Ex. 1073, 11 (stating Baselga '94 is "the basis for a planned clinical trial"). In other words, contrary to Patent Owner's assertion, ordinary artisans did consider the mouse study in Baselga '94 a reliable predictor of success in humans.

Second, evidence of record does not support Patent Owner's specific criticisms of Baselga '94. For example, Dr. Kerbel, Patent Owner's expert co-authored Francia,[16] 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. According to Francia, "the majority of preclinical therapies reported in the literature are routinely assessed using only primary tumor models, either ectopic or orthotopic." *Id.* at 6363.

The xenograft model used in Baselga '94 is an ectopic model. Dr. Kerbel testified that, when Baselga '94 was published, ectopic models

[16] 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").

not only were "widely used," but were "more widely used than orthotopic" models. Ex. 1088, 223:6–18. Dr. Kerbel also testified that, around the priority date of the '441 patent, an ordinary artisan would not have considered the use of subcutaneous ectopic implantation to be a design flaw in the Baselga '94 study. *Id.* at 224:21–225:2.

In addition, Dr. Kerbel co-authored Ng,[17] 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. Based on the xenograft results, Dr. Kerbel and others concluded that the new formulation of paclitaxel "warrants investigation in the clinical setting."[18] *Id.* at 4337.

Third, 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

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[17] 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").

[18] 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. 41–42 (citing Ex. 2061 ¶¶ 62–70, 77–81).

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 '94). In view of the evidence of record, we are not persuaded by Patent Owner's argument that the mouse study in Baselga '94 "was not a reliable predictor of success in humans." *See* PO Resp. 41.

Patent Owner further argues that Yu[19] teaches away from the use of taxoids in HER2-positive patients. PO Resp. 43. According to Patent Owner, Yu explicitly warns that breast cancers that overexpress 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. Lipton and Petitioner that Dr. Tannenbaum and Patent Owner do not explain why, nor do we find, "it would be reasonable for a POSITA to rely on *in vitro* preclinical results in Yu as being indicative of the effect of paclitaxel treatment in humans, while simultaneously dismissing the *in vivo* Baselga '94 study." Ex. 1085 ¶ 127); *see also* Ex. 1087, 93:22–94:16

[19] 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).

(Dr. Tannenbaum testifying that Yu would not have dissuaded physicians from using paclitaxel in HER2-positive patients).

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. For example, it had been reported from a study of human patients that "HER2 over-expression in MBC [i.e., metastatic breast cancer] seems to confer sensitivity rather than resistance to taxanes, in spite of a positive correlation of HER2 positivity with poor prognostic features." Ex. 1078[20], 5. Prior art also demonstrates synergy of paclitaxel and an anti-ErbB2 antibody in human breast cancer xenografts, and suggests clinical trials of the claimed combination therapy. *See*, *e.g.*, Ex. 1004, 15; Ex. 1005, 4; Ex. 1072, 8; Ex. 1073, 11. Weighing all evidence of record, we are not persuaded that Yu, a single reference based on an *in vitro* study, teaches away from combining paclitaxel and an anti-ErbB2 antibody in treating HER2-positive cancers.

This is especially so because Baselga '96 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. 1004, 15 (emphasis added).

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[20] Seidman et al., *HER-2/*neu *Over-Expression and Clinical Taxane Sensitivity: A Multivariate Analysis in Patients with Metastatic Breast Cancer (MBC)*, 15 PROC. AM. SOC. CLIN. ONCOL. 104, Abstract 80 (1996).

Acknowledging this statement, Patent Owner nevertheless argues that Baselga '96 does not suggest treating patients with the claimed combination. PO Resp. 39–40. Patent Owner contends that there was no clinical study involving the claimed combination at the time that Baselga '96 was submitted or accepted. *Id.* at 33, 40. The evidence Patent Owner relies on for support, however, was and still remains confidential. *See, e.g.*, Ex. 2011 ¶¶ 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. 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 time Baselga '96 was published, a clinical study involving the claimed combination was indeed in progress.

Patent Owner also contends that an ordinary artisan would not have treated patients with the claimed combination because there were safety concerns regarding treatment with taxoids.[21] PO Resp. 16–17, 43. As a result, Patent Owner continues, an ordinary artisan, when considering whether to combine the anti-ErbB2 antibody with an existing anti-cancer

[21] Patent Owner asserts that taxoids "were only approved for second-line use in breast cancer." PO Resp. 43. Patent Owner's own document, however, shows that before the '441 patent, the then-"current standards of therapy" are for high risk patients "to receive Adriamycin in the adjuvant setting and **Taxol first-line**." Ex. 2004, 3 (emphasis added).

drug, would have been motivated to use an anthracycline, rather than a taxoid. *Id.* at 44–45. 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. 2030,[22] 409, 423 (anthracycline-induced cardiac toxicity "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." *Id.* at 423.

As Dr. Tannenbaum acknowledges, "[t]he most commonly used method to prevent anthracycline cardiotoxicity is to stop the administration of these drugs when a predetermined empiric cumulative dose has been reached." Ex. 2062 ¶ 50 (quoting Ex. 2103, 3118). As a result, Dr. Tannenbaum agreed that even though an ordinary artisan would not have abandoned anthracyclines, "it would have made sense to go ahead with Herceptin plus a different chemotherapy, at least in patients who had been found to be either resistant to anthracyclines, or who had reached the cardiotoxic cumulative dose of anthracyclines," with paclitaxel "being one of them," i.e., a different chemotherapy. Ex. 1087, 275:9–23.

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

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

dissuaded an ordinary artisan from combining it with an anti-ErbB2 antibody.[23]

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 '96 expressly teaches paclitaxel as one of three specifically identified chemotherapeutic agents to be combined with rhuMAb HER2. *See In re Corkill*, 771 F.2d 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

[23] 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. 15, 23 n.6. As a result, many patients had become resistant to it. There is a "lack of significant clinical cross-resistance" between paclitaxel and anthracycline. Ex. 1072, 5; *see also id.* at 4 (noting FDA's approval of using paclitaxel "against chemotherapy-refractory metastatic breast cancer").

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. 2030, 423), is not a foregone conclusion—we are persuaded that an ordinary artisan also would have had a reason to, as Baselga '96 specifically teaches, combine rhuMAb HER2 with paclitaxel. *See* Ex. 1004, 15.

In sum, given the repeated and explicit suggestions 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 HER2-overexpressing metastatic breast cancer.[24]

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. 46–55. 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 17. Petitioner refers to

[24] The parties also dispute whether it would have been obvious to try the claimed combination. *See, e.g.*, Pet. 49, 61; PO Resp. 53–54, Reply 22–23. We do not need to resolve this issue because we conclude that prior art explicitly suggests the claimed combination.

Baselga '96 for teaching that when treated with rhuMAb HER2, 11.6% of patients with metastatic breast cancer experienced a complete or partial remission, and 37% achieved minor responses or stable disease. Pet. 47 (citing Ex. 1004, 9, 13). Petitioner also notes that minor responses and stable disease "lasted for a median of 5.1 months." *Id.* (citing Ex. 1004, 9). Thus, rhuMAb HER2 extends time to disease progression relative to no treatment. *See* Ex. 1004, 10 (showing the same definition of "time to disease progression" in Baselga '96 as in the '441 patent).

Patent Owner does not argue, and we do not find, that combining a taxoid with rhuMAb HER2 would abrogate the effect of the antibody. *See* Ex. 1087, 274:22–275:4 (Dr. Tannenbaum testifying that her opinion does not address the comparison with untreated patients). Thus, an ordinary artisan would have had a reasonable expectation of success in achieving the claimed clinical efficacy under our claim construction.

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.

In addition to pointing out the TTP of 5.1 months reported in Baselga '96, Petitioner argues

> Baselga '96 in view of Baselga '94 teaches that rhuMAb HER2 "markedly potentiated the antitumor effects" of paclitaxel in preclinical models. [Ex. 1004] at 15. The combination had more potent antitumor effect than either rhuMAb HER2 or paclitaxel individually; where each showed 35% inhibition individually, the combination was above 90%. Ex. 1005 at 4. The treatment was sufficiently effective that clinical trials were ongoing for at

> least two years when Baselga '96 was published. Exs. 1004 at 15; 1005 at 4. Baselga '96 and Baselga '94 therefore teach that the addition of paclitaxel to rhuMAb HER2 therapy would improve time to disease progression. Ex. 1007 ¶¶ 76–77.

Pet. 47–48.

Patent Owner contends that neither Baselga '96 nor Baselga '94 teaches "the claimed combination extends TTP relative to a patient treated with paclitaxel alone." PO Resp. 46. Patent Owner points out that Baselga '94 measured response rate, an endpoint different from TTP. *Id.* at 13–14, 47. Petitioner counters that response rate was widely used as a surrogate endpoint for TTP in preclinical and early-phase trials. Reply 21. We do not need to resolve this dispute because Baselga '96 teaches this limitation regardless.

According to Petitioner, "Baselga '96 described TTP from trastuzumab treatment as '***unusually long***,' while PO and its expert contend HER2+ patients were believed to '***not respond well***' to standalone paclitaxel." Reply 20 (citing Ex. 1004, 9, 13; PO Resp. 17, 21, 43; Ex. 2062 ¶ 57). As a result, Petitioner argues that an ordinary artisan "would have expected the claimed combination to extend TTP compared to ***paclitaxel alone***." *Id.*

We find Petitioner's argument more persuasive. Indeed, Baselga '96 teaches the median TTP with rhuMAb HER2 was 5.1 months (Ex. 1004, 13), and 1995 TAXOL PDR teaches the median TTP with paclitaxel was 3.0 or 4.2 months in a Phase III breast carcinoma study (Ex. 2105, 6). Because Baselga '96 reports that rhuMAb HER2 achieved a longer TTP at least for HER2+ breast cancer patients, we find that an ordinary artisan would have had a reasonable expectation that adding rhuMAb HER2 would achieve an

extension of TTP over paclitaxel alone based on the superior TTP of rhuMAb HER2.

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 '94 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 Baselga '96 for teaching there was an "absence of significant toxicity" associated with rhuMAb HER2, which "was remarkably well tolerated." Pet. 48 (citing Ex. 1004, 11, 13). Petitioner also refers to both Baselga '94 and Baselga '96 for teaching that "there was no increase in the toxicity of paclitaxel when administered in combination with rhuMAb HER2 in preclinical models." *Id.* (citing Ex. 1004, 15; Ex. 1005, 4).

Patent Owner argues that "Baselga '96 did not address the toxicity of the ***combination*** of an anti-ErbB2 antibody and a taxoid." PO Resp. 50–51. Patent Owner points out that Baselga '94 and Baselga '96 also showed no increased toxicity for the trastuzumab/anthracycline doxorubicin; yet, that combination "produced a significant increase in cardiotoxicity when administered to human patients." *Id.* at 51. According to Patent Owner, "[t]his disconnect highlights the inability of Baselga '94's mouse models to

predict clinical safety." *Id.* at 51–52 (citing Ex. 2061 ¶¶ 54–61, 75; Ex. 2062 ¶¶ 194–195). 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 '94 xenograft models in predicting clinical safety because of the unexpected cardiotoxicity of rhuMAb HER2/anthracyclines combination.

Patent Owner also asserts that Baselga '94 xenograft models would not reliably predict the effects of the claimed combination in humans for other reasons. PO Resp. 52. Again, 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 '94). 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. After all, 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 (1) "Baselga '94 would not have motivated a skilled artisan to treat humans with an anti-ErbB2 antibody and a taxoid," and (2) "the preclinical results in Baselga '94 would not have provided a POSA a reasonable expectation of success in achieving the specific clinical result claimed in the '441 patent." PO Resp. 43–44, 49.

As an initial matter, we note that we analyze the reasonable expectation of success not solely based on Baselga '94, but the prior art as a whole, including Baselga '96, the 1995 TAXOL PDR entry, and the knowledge of a person of ordinary skill in the art. More importantly, 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.[25]

Patent Owner argues that "in the 1990s[,] the mere fact that a treatment was under evaluation was no indication of success, given the high failure rate of therapies in clinical trials." PO Resp. 53 (citing Ex. 2062 ¶¶ 86–89, 194); *see also id.* at 12–14 (citing Ex. 2021, 711–13). We acknowledge the inherent unpredictability in the pharmaceutical industry. *See, e.g.*, PO Resp. 6–13, 48–52. We also recognize that the finder of fact

[25] 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. 24. 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.

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 known 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, even though there was no corresponding phase I or II trial—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 with regard to 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. 55–61. 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. 60. 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, 1).

Patent Owner has not shown what portion of the sales of Herceptin is attributable to the claimed combination, and not the single-agent use. *Id.*

In addition, "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. 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. 57 (citing Exs. 2018, 2033, 2034)), none of which shows that the praise is for the claimed combination. For example, Exhibit 2018 states that "[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. 56.

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. 55–56 (citing Ex. 2018); Ex. 2062 ¶¶ 204–205 (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. 57–58. In support, Patent Owner relies on a single sentence from a declaration submitted by the inventor during prosecution. *Id.* at 57 (citing Ex. 1011, Vol. 2, 54) ("[T]he combination is surprisingly synergistic with respect to extending TTP."). Petitioner contends that, in view of the teachings of Baselga '94 and Baselga '96, the extension of TTP by the claimed combination relative to paclitaxel alone was not unexpected. Reply 25. We find Petitioner's argument more persuasive.

Indeed, it was repeatedly observed in prior art that "apparent synergy" between rhuMAb HER2 and paclitaxel, as shown in preclinical models of

Baselga '94, "provide motivation for clinical evaluation" of the combination. Ex. 1072, 8; *see also* Ex. 1004, 15 (observing that, in preclinical studies, "rhuMAb HER2 markedly potentiated the antitumor effects of" paclitaxel, and stating that, as a result, "clinical trials of such combination therapy [were] . . . in progress"); Ex. 1073, 11 (stating Baselga '94 is "the basis for a planned clinical trial"). Patent Owner represented to the FDA that it was anticipated, solely based on the results of Baselga '94, that the combination of rhuMAb HER2 and paclitaxel would be more effective than either regimen used alone. Ex. 2007, 30, 88. As a result, we find the alleged "superior clinical efficacy" does not amount to unexpected results.

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 '94 said did not increase toxicity, but in fact did increase toxicity in the Phase-III study disclosed in the '441 patent." PO Resp. 58–59 (citing Ex. 1005, 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 it 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 '96 and Baselga '94 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 '96 and Baselga '94.

Patent Owner does not argue claims 2–14 separately. After reviewing the entire record (*see, e.g.*, Pet. 49–59), we conclude that Petitioner has established by a preponderance of the evidence that claims 2–14 are unpatentable over the combination of Baselga '96 and Baselga '94.

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 find, 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. 1–2, 7–11. 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 4–5. Patent Owner contends that the proposed substitute claim is supported by the original application and the provisional application. *Id.* at 5–6 (citing Exs. 1011, 1027). 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. 1011, Vol. 1, 48; Ex. 1027, 44).

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] skilled artisan would understand that the reference to 'AEs' in the table is directed to adverse events, not ***severe*** adverse events." MTA Reply 4 (citing Ex. 2144 ¶¶ 11–13). Instead, Patent Owner would have us construe "overall severe adverse events" to mean Grade 3/4 myocardial dysfunction. *Id.* at 3. Petitioner disagrees. MTA Sur-reply 2–3. 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. 1011, Vol. 1, 48; Ex. 1027, 44; *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%)).

Patent Owner argues that

> A POSA would recognize that the difference between the severe myocardial dysfunction in patients treated with rhuMAb HER2 and paclitaxel (2%) compared to paclitaxel alone (0%) was negligible—effectively no difference at all—and does not constitute an increase in such severe adverse events. This is especially so when considered in context with the increase in myocardial dysfunction reported in the anthracycline arm of the study (3% increased to 18%), and the observation in the specification that the combination use of Herceptin and anthracyclines was "contraindicated," while noting that "[t]he results . . . ***favor*** the combined treatment with HERCEPTIN and paclitaxel (TAXOL)."

MTA Reply 3–4 (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."

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.[26]

Motions to Exclude Evidence

Petitioner's Motions to Exclude

Petitioner filed two Motions to Exclude, seeking to exclude Exhibits 2135, and 2145–2147, as well as paragraph 25 of Exhibit 2143, and paragraphs 12, 13, 16–19, 21, 22, 35–37, 50, and 51 of Exhibit 2144. Papers 79, 98.

Because we do not rely on Exhibit 2147 in rendering our Decision, we dismiss this aspect of Petitioner's Motion to Exclude as moot.

Exhibit 2135 is the Hsu abstract discussed above. Exhibit 2145 is the deposition transcript of Dr. Robert Earhart, an expert from another *inter partes* review (IPR2017-01121). Dr. Earhart was not retained by either party in this proceeding. Exhibit 2146 is a full copy of the conference proceedings, which contains a copy of the Hsu abstract. Patent Owner relies on Exhibits 2145 and 2146 to authenticate and to prove the publication date of Hsu. In paragraph 25 of Exhibit 2143 and paragraphs 36 and 37 of Exhibit 2144, Dr. Kerbel and Dr. Tannenbaum cite the Hsu abstract (Ex. 2135) and/or the Earhart deposition testimony (Ex. 2145).

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[26] 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 19–44. 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.

As explained above, we do not find persuasive Patent Owner's arguments based on the substance of Hsu. *See supra* at 23–25. 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 Exhibits 2135, 2145, and 2146, as well as paragraph 25 of Exhibit 2143, and paragraphs 36 and 37 of Exhibit 2144.

Petitioner also seeks to exclude paragraphs 12, 13, 16–19, 21, 22, 35, 36, 50, and 51 of Exhibit 2144 "because Dr. Tannenbaum improperly seeks to recant from her sworn deposition testimony when the time for redirect is past." Paper 79, 3 (internal quotation marks and alteration omitted), 12–15. Patent Owner argues that, to the extent there is any inconsistency between Exhibit 2144, the supplemental declaration of Dr. Tannenbaum, and her previous testimony, Petitioners were afforded the opportunity to cross-examine Dr. Tannenbaum and address those issues in the sur-reply. Paper 83, 14. Patent Owner also contends that inconsistencies, if any, would go to the weight, not the admissibility of the supplemental declaration. We find Patent Owner's arguments persuasive. Accordingly, we deny Petitioner's Motion to Exclude paragraphs 12, 13, 16–19, 21, 22, 35, 36, 50, and 51 of Exhibit 2144.

Patent Owner's Motion to Exclude

Patent Owner filed a Motion to Exclude Exhibits 1003, 1020, 1021, 1076, 1077, 1080, 1086, 1090, as well as paragraphs 5, 7, 40, 43, 44, 49, 73, 92–94, 101, 107, 110, 113–117, and 138 of Exhibit 1085. Paper 74.

Because we do not rely on Exhibits 1003, 1020, 1021, 1076, 1077, 1080, and 1090, and related paragraphs of the Lipton reply Declaration

(Ex. 1085 ¶¶ 49, 73, 93, 101, 110, 138) in rendering our Decision, we dismiss these aspects of Patent Owner's Motion to Exclude as moot.

Patent Owner moves to exclude the Declaration of Dr. Clarke, Petitioner's preclinical expert (Exhibit 1086), and portions of the Lipton reply Declaration that rely on Dr. Clarke's testimony (Ex. 1085 ¶¶ 5, 7, 40, 43, 44, 92–94, 107, 113–117). Paper 74, 1–4. According to Patent Owner, "Dr. Clarke's declaration is irrelevant because it does not represent the views of a person of ordinary skill in the art," who is a "clinical or medical oncologist." *Id.* at 1. As a result, Patent Owner asks us to exclude Exhibit 1086 under FRE 402. *Id.* at 3; *see also id.* at 3–4 (further arguing that because Dr. Clarke is not a person of ordinary skill in the art, his testimony should also be excluded under FRE 403, 602, 801, and 802). We are not persuaded.

An expert witness must be qualified as an expert by knowledge, skill, experience, training, or education to testify in the form of an opinion. Fed. R. Evid. 702. Contrary to Patent Owner's assertion, "[t]here is, however, no requirement of a perfect match between the expert's experience and the relevant field." Trial Practice Guide Update (August 13, 2018),[27] 3 (citing *SEB S.A. v. Montgomery Ward & Co.*, 594 F.3d 1360, 1373 (Fed. Cir. 2010)). "A person may not need to be a person of ordinary skill in the art in order to testify as an expert under Rule 702, but rather must be 'qualified in the pertinent art.'" *Id.* (citing *Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1363–64 (Fed. Cir. 2008)).

[27] Available at https://www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf.

Here, Petitioner has presented sufficient evidence to show Dr. Clarke is qualified to provide expert testimony on the relevant art, and his testimony is highly relevant to issues raised in this proceeding. Paper 85, 5–6 (citing Ex. 1086 ¶¶ 16, 28). Indeed, Dr. Clarke has extensive experience in relevant preclinical research, and has regularly collaborated with those of ordinary skill in the art. Ex. 1086 ¶¶ 16, 28. It is especially telling that both Dr. Kerbel[28] and Dr. Tannenbaum rely on Dr. Clarke's publications to support their own opinions. *See, e.g.*, Ex. 2061 ¶¶ 62, 79, 83 (citing Ex. 2052, 2053); Ex. 2062 ¶ 73 (citing Ex. 2052); *see also* Ex. 1088, 180:9–181:17; Ex. 1087, 137:23–138:1 (Dr. Kerbel and Dr. Tannenbaum testifying during deposition that Dr. Clarke is "reputable" and "well-known breast cancer researcher," and a "knowledge leader" with respect to preclinical breast cancer research).

For these reasons, and because Dr. Clarke's declaration directly responds to Patent Owner's submission of the declaration of Dr. Kerbel (Paper 85, 2–3 (citing Ex. 2061 ¶¶ 3–9)), we deny Patent Owner's Motion to Exclude Exhibit 1086 and Exhibit 1085 ¶¶ 5, 7, 40, 43, 44, 92–94, 107, 113–117.

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*

[28] Petitioner notes that Dr. Kerbel admitted that he also "wouldn't consider [him]self to be a clinical or medical oncologist." Paper 85, 2–3 (citing Ex. 1088, 39:25–40:3, 49:4–56:22; Ex. 2061 ¶¶ 16, 17).

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 62 and 76, Petitioner seeks to seal the confidential version of the Opposition to Patent Owner's Motion to Amend (Paper 63), Reply to Patent Owner's Response (Paper 65), Surreply to Patent Owner's Reply in Support of its Motion to Amend (Paper 78), Reply and Surreply

Declarations of Dr. Lipton (Exs. 1085, 1099), and the transcript of the deposition of Dr. Tannenbaum (Ex. 1087).

Petitioner seeks to seal these documents because they "contain references to subject matter filed under seal by Patent Owner." *See, e.g.*, Paper 62, 2. 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 63, 65, and 78, and Exhibits 1085, 1087, and 1099. 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 49, Patent Owner seeks to seal the confidential version of the Declaration of Stephanie Mendelsohn (Exhibit 2069), which purports to authenticate several exhibits. 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 70, Patent Owner seeks to seal the confidential version of the Supplemental Expert Declaration of Dr. Susan Tannenbaum (Exhibit 2144) as well as Exhibits 2141 and 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 10) Exhibits 2001, 2003, 2006–2010 and the redacted portions of Patent Owner's Preliminary Response, and Exhibits 2002, 2004, 2005, and 2011. Paper 24, 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, 2007, and 2011. 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 '96 and Baselga '94, 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 Motions to Exclude is denied-in-part and dismissed-in-part;

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

FURTHER ORDERED that Petitioner's Motions to Seal (Papers 62, 76) are denied without prejudice to Patent Owner;

FURTHER ORDERED that Patent Owner's Motions to Seal (Papers 49, 70) are granted;

FURTHER ORDERED that Patent Owner may file/renew its request to seal any confidential information as instructed in this Decision; 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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