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

Paper 108
Entered: October 3, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC., and
SAMSUNG BIOEPIS CO., LTD.
Petitioners,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00737[1]
Patent 7,892,549 B2

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

POLLOCK, *Administrative Patent Judge*.

FINAL WRITTEN DECISION AND RELATED ORDERS

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

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

---

[1] IPR2017-01960 has been joined with this proceeding. Paper 44, 7.

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

Granting Patent Owner's Motions to Seal and Entry of Stipulated Protective Order
Denying Petitioners' Motions to Seal without Prejudice to Patent Owner
37 C.F.R. § 42.55

I. INTRODUCTION

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

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

A. Procedural History

Petitioner Hospira, Inc. ("Pfizer") filed a Petition requesting *inter partes* review of claims 1–17 of the '549 patent. Paper 1 ("Pet.").[2] Patent Owner, Genentech, Inc., filed a Preliminary Response to the Petition. Paper 9 ("Prelim. Resp."). Based on the record before us at the time, we instituted trial with respect to all challenged claims. Paper 19, 25–26 ("Dec.").

Petitioner Samsung Bioepis Co., Ltd. ("Bioepis") timely submitted a Petition presenting substantially the same challenges as set forth in Pfizer's Petition along with a request for joinder. IPR2017-01960. Papers 1, 2. We granted Bioepis's

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

Petition and associated request for joinder to IPR2017-00737. IPR2017-01960, Paper 11, 6–7.

After institution of trial and our grant of joinder, Patent Owner filed its Patent Owner Response (Paper 47, "PO Resp.") and Petitioners filed a Reply to the Patent Owner Response (Paper 68, "Pet. Reply").

Patent Owner also filed a Contingent Motion to Amend. Paper 49. Petitioners opposed. Paper 66. Patent Owner responded with a Reply in support of its motion (Paper 73); Petitioner further submitted an authorized Sur-Reply (Paper 80).

With respect to technical experts, Petitioner rely on the declarations of Allan Lipton, MD. (Exs. 1011, 1085, and 1099) and Robert Clarke, Ph.D., D.Sc. (Exs. 1086, 1100); Patent Owner relies on the declarations of Robert S. Kerbel, Ph.D. (Exs. 2016, 2143), Dr. Susan Tannenbaum (Exs. 2062, 2144).

Patent Owner filed motions for observations on the depositions of Dr. Lipton and Dr. Clark (Papers 85, 90), to which Petitioners provide responses (Papers 92, 95).

We heard oral argument on May 18, 2018. A transcript of that proceeding is entered as Paper 102 ("Tr.").

The parties filed the following motions to exclude evidence. Patent Owner filed one motion to exclude evidence. Paper 77. Petitioners opposed (Paper 88) and Patent Owner submitted a reply in support of its motion (Paper 91). Petitioners filed a first motion to exclude evidence. Paper 81. Patent Owner opposed (Paper 86) and Petitioners submitted a reply in support of its first motion (Paper 93). Petitioners filed a second motion to exclude evidence. Paper 98. Patent Owner opposed (Paper 100) and Petitioners submitted a reply in support of

their second motion (Paper 101). The parties have also filed five motions to seal, all unopposed. Papers 8, 48, 74 (by Patent Owner); Papers 65, 79 (by Petitioners).

B. Related Applications and Proceedings

The '549 patent issued from Application No. 10/356,824, filed February 3, 2003, which is a continuation of Application No. 09/208,649, filed Dec. 10, 1998 (the "649 Application"). U.S. Patent No. 7,846,441 B2 ("the '441 Patent) issued from the '649 Application on December 7, 2010. The '549 and '441 Patents claim benefit of priority to Provisional Application No. 60/069,346, filed Dec. 12, 1997 ("the '346 application"). *See e.g.*, Ex. 1001, (21), (63) (60), and 1:4–9.

In addition to this proceeding, we previously denied Petitioner Pfizer's challenge to claims 1–11 and 14–17 of the '549 patent and claims 1–14 of the '441 patent. *See* IPR2017-00739, Paper 16; *see also* IPR2018-00016, Paper 25. Petitioner Pfizer also challenges claims of the '441 Patent in IPR2017-00731. The '549 and '441 Patents are also subject to challenges by Celltrion Inc. in IPR2017-01122 and IPR2017-01121, respectively.

Petitioner has also filed IPR2017-00804 and IPR2017-00805 involving claims of U.S. Patent Nos. 6,627,196 and 7,371,379 respectively. These patents are not in the chain of priority of the '549 and '441 Patents but involve subject matter similar to that at issue here.

We issue concurrently our Decisions in IPR2017-00731, IPR2017-01139, IPR2017-01140, IPR2017-01121, IPR2017-01122, IPR2017-00804, and IPR2017-00805.

Patent Owner identifies the following District Court actions, "that relate or may relate to U.S. Patent Application No. 10/356,824, which issued as U.S. Patent No. 7,892,549:" *Celltrion, Inc. v. Genentech, Inc.,* No. 18-cv-00274 (N.D. Cal.) and *Celltrion, Inc. v. Genentech, Inc.,* No. 18-cv-00095 (D. Del.). Paper 57, 2.

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

C. The '549 patent and Relevant Background

According to the Specification, 25% to 30% of human breast cancers overexpress a 185-kD transmembrane glycoprotein receptor ($p185^{HER2}$), also known as HER2 (human epidermal growth factor receptor-2) or ErbB2. Ex. 1001, 1:21–32, 5:16–21. These HER2-positive cancers are associated with poor prognoses and resistance to many chemotherapeutic regimens including anthracyclines (e.g., doxorubicin or epirubicin). *Id*. at 3:43–52; 4:11–12, and 11:41–45. Conversely, patients with HER2-positive cancers are three times more likely to respond to treatment with taxanes than those with HER2 negative tumors. *Id*. at 3:52–56 (citing Baselga '97 (Ex. 1007)).

Although "ErbB2 overexpression is commonly regarded as a predictor of poor prognosis," "a humanized version of the murine anti-ErbB2 antibody 4D5, referred to as rhuMAb HER2 or HERCEPTIN® has been clinically active in patients with ErbB2-overexpressing metastatic breast cancers that had received extensive prior anti-cancer therapy."[3] Ex. 1001, 3:35–61 (citing Baselga '96 (Ex. 1005)). Anti-ErbB2 4D5 antibodies also "enhance the activity of paclitaxel (TAXOL®) and doxorubicin against breast cancer xenographs in nude mice injected with BT-474 human breast adenocarcinoma cells, which express high levels of HER2." *Id*. at 3:56–61 (citing Baselga '94 (Ex. 1006)).

[3] "HERCEPTIN® is the tradename for the commercial product of the humanized antibody, trastuzumab." Paper 49, 3 fn.2.

According to the Specification,

> The present invention concerns the treatment of disorders characterized by overexpression of ErbB2, and is based on the recognition that while treatment with anti-ErbB2 antibodies markedly enhances the clinical benefit of the use of chemotherapeutic agents in general, a syndrome of myocardial dysfunction that has been observed as a side-effect of anthracycline derivatives is increased by the administration of anti-ErbB2 antibodies.

Id. at 3:65–4:5.

The '549 patent thus relates to the treatment of breast cancers that overexpress HER2/ErbB2 "comprising administering a therapeutically effective amount 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."[4] Ex. 1001, 4:6–13. In some embodiments, the anti-ERbB2 antibody of the combination is Herceptin® and the chemotherapeutic agent "is a taxoid, such as TAXOL® (paclitaxel) or a TAXOL® derivative." *Id*. at 4:23–25. The combination may further include one or more additional anti-ErbB2 antibodies, "antibodies which bind to the EGFR . . . ErbB3, ErbB4, or vascular endothelial factor (VEGF)," "one or more cytokines," or "a growth inhibitory agent." *Id*. at 11:4–40 (defining "chemotherapeutic agent" and "growth inhibitory agent"), 23:60–24:5, and 25:20–34.

The '549 patent also provides an Example disclosing the conduct and results of a clinical trial involving 469 women with metastatic HER2-positive breast cancer. *Id*. at 26:34–30:25. All patients were treated with one of two

---

[4] The Specification defines a "therapeutically effective amount" of the combination as "an amount having [an] antiproliferative effect," which can "be measured by assessing the time to disease progression (TTP) or determining the response rates (RR)." Ex. 1001, 10:41–50.

chemotherapy regimens (CRx) designated either "AC" for anthracycline (doxorubicin or epirubicin) and cyclophosphamide, or "T" for Taxol (paclitaxel). *See id*. at 28:5–47; 29:13–30:12. Half of the patients were also treated with the anti-ERbB2 antibody Herceptin, designated "H." *Id*. The Specification discloses that "[a]t a median follow-up of 10.5 months, assessments of time to disease progression (TTP in months) and response rates (RR) showed a significant augmentation of the chemotherapeutic effect by HERCEPTIN®, without increase in overall severe adverse events (AE)." *Id*. at 29:13–18. In addition, "[a] syndrome of myocardial dysfunction similar to that observed with anthracyclines was reported more commonly with a combined treatment of AC-H (18% Grade ¾) than with AC alone (3%), T (0%), or T+H (2%)." *Id*. at 30:13–16. According to the inventors:

> These data indicate that the combination of anti-ErbB2 antibody treatment with chemotherapy markedly increases the clinical benefit, as assessed by response rates and the evaluation of disease progression. However, due to the increased cardiac side-effects of doxorubicin or epirubicin, the combined use of anthracyclines with anti-ErbB2 antibody therapy is contraindicated. The results, taking into account risk and benefit, favor the combined treatment with HERCEPTIN® and paclitaxel (TAXOL®).

Id. at 30:17–25.

D. Challenged Claims

In accordance with the Petition, we instituted trial with respect to claims 1–17. Pet. 4. Claims 1, 5, and 16 are independent. Claim 1, reproduced below, requires "administering a combination" of three agents—an anti-ErbB2 antibody, a taxoid, and "a further growth inhibitory agent"—"in an amount effective to extend the time to disease progression:"

> 1. A method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor, comprising administering a

> combination of an antibody that binds ErbB2, a taxoid, and a further growth inhibitory agent to the human patient in an amount effective to extend the time to disease progression in the human patient, wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence.

Independent claim 16 is similar to claim 1, but further includes a negative limitation requiring the administration of an anti-ErbB2 antibody, a taxoid, and a further growth inhibitory agent "in the absence of an anthracycline derivative."

Independent claim 5 recites "administering an effective amount of a combination" of three agents similar to those of claims 1 and 16, wherein the antibody binds to the 4D5 epitope of ErbB2, the taxoid is paclitaxel, and the third element is broadly described as a "therapeutic agent." Depending from claim 5, claims 12, 13, and 14, respectively, specify that the "therapeutic agent" is another anti-ErbB2 antibody, a vascular endothelial growth factor (VEGF), or "a growth inhibitory agent" (as recited in claim 1). Depending from claims 1 and 5, respectively, claims 2 and 7 require that the anti-ErB2 4D5 antibody is humanized.

E. Reviewed Grounds of Unpatentability

We instituted trial to review the patentability of the challenged claims on each of the six grounds asserted in the Petition:

Ground	**Claim(s)**	**References**	**Basis**
1	1–11 and 14–17	Baselga '97[5] and Gelmon[6]	§ 103

[5] Baselga et al., *HER2 Overexpression and Paclitaxel Sensitivity in Breast Cancer: Therapeutic Implications*, Update on the Taxanes in Breast Cancer, Oncology, Vol. 11, No. 3 (Suppl. 2), 43–48 (1997) ("Ex. 1007").

[6] Gelmon et al., *Phase I/II Trial of Biweekly Paclitaxel and Cisplatin in the Treatment of Metastatic Breast Cancer,* Journal of Clinical Oncology, Vol. 14, No. 4, 1185–91 (1996) (also referred to as "Gelmon '96" "Ex. 1025").

Ground	Claim(s)	References	Basis
2	12	Baselga '97, Gelmon, and Drebin[7]	§ 103
3	13	Baselga '97, Gelmon, and Presta[8]	§ 103
4	1–11 and 14–17	Baselga '96,[9] Baselga '94,[10] and Gelmon	§ 103
5	12	Baselga '96, Baselga '94, Gelmon, and Drebin	§ 103
6	13	Baselga '96, Baselga '94, Gelmon, and Presta	§ 103

II. ANALYSIS

A. Principles of Law

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a

---

[7] Drebin et al., *Monoclonal antibodies reactive with distinct domains of the neu oncogene-encoded p185 molecule exert synergistic anti-tumor effects in vivo*, Oncogene, An International Journal, Vol. 2, No. 3, 273–77 (1988) ("Ex. 1010").
[8] Presta et al., *Humanization of an Anti-Vascular Endothelial Growth Factor Monoclonal Antibody for the Therapy of Solid Tumors and Other Disorders*, Cancer Research, Vol. 57, No. 20, 4593–99 (1997) ("Ex. 1012").
[9] Baselga et al., *Phase II Study of Weekly Intravenous Recombinant Humantized Anti-p195^{HER2} Monoclonal Antibody in Patients with HER2/neu-Overexpressing Metastatic Breast,* Cancer, Journal of Clinical Oncology, Vol. 14, No. 3, 737–44 (1996) ("Ex. 1005").
[10] Baselga et al., Program/Proceedings, 13th Annual Meeting, American Society of Clinical Oncology, Vol. 13, 63, Abstract 53 (1994). ("Ex. 1006").

person having ordinary skill in the art to which that subject matter pertains.[11] *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved based on underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness, if present. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"[T]he [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418. Moreover, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (citations omitted).

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

---

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

B. Person of Ordinary Skill in the Art

Petitioner argues that a person of ordinary skill in the art as of the effective filing date of the '549 patent "would be a clinical or medical oncologist specializing in breast cancer with several years of experience with breast cancer research or clinical trials." Pet. 6 (citing Ex. 1011 ¶¶ 15–17; Ex. 1004 ¶¶ 29–31). Patent Owner does not dispute Petitioner's proposed definition. Prelim. Resp. 36; *see also* PO Resp. 37.

Based on our review of the '549 patent, the cited art, and the testimony of Dr. Lipton, we adopted Petitioner's definition for the purposes of instituting trial. Dec. 8–9. Upon consideration of the complete record, we do not find cause to modify that determination. We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

C. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S.Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016). Any special definitions for claim

terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

1. "*administering a combination*"

In our Decision instituting *inter partes* review, we adopted Patent Owner's unopposed definition of "administering a combination" as requiring "a single treatment regimen in which the patient receives all drugs that are part of the claimed combination." Dec. 10 (citing Prelim. Resp. 36–37). In arriving at that decision, we found particularly persuasive Patent Owner's argument that

> "the absence of an anthracycline derivative" language in dependent claims 16 and 17, "would make no sense if 'administering a combination' included drugs received as part of a different treatment regimen [because] [i]n the '549 patent's working example, patients were administered the combination of the anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative only if they had 'received any anthracycline therapy in the adjuvant setting.'"

Id. Relying on essentially the same arguments, Patent Owner now recasts its proposed definition "to mean that the drugs are administered as part of the same treatment regimen." PO Resp. 37. Petitioners expressly agree with Patent Owner's proposal. *See* Pet. Reply 2 ("Petitioner agrees for this IPR that the BRI of 'administering a combination' is administering drugs 'as part of the same treatment regimen.' (*See also* Ex. 1085 ¶¶89–90.).").

For the purpose of this proceeding, we find Patent Owner's two definitions interchangeable. Nevertheless, in light of the agreement of parties, and as supported by the reasoning set forth on pages 37–39 of the Patent Owner Response, we interpret "administering a combination" to mean that the drugs are administered as part of the same treatment regimen.

2. "*an amount effective to extend the time of disease progression" and "an effective amount"*

Independent claims 1 and 16 require administering a combination of an anti-ErbB2 antibody, a taxoid, and a further agent, "in an amount effective to extend the time to disease progression [TTP] in the human patient." Claim 5, the remaining independent claim before us, more generically recites administering the three-part combination to a human patient in "an effective amount."[12]

In our Decision to Institute, we construed "an amount effective to extend the time to disease progression in the human patient" in independent claims 1 and 16 as an amount sufficient to extend the time to disease progression in a human patient having breast cancer that overexpresses ErbB2 receptor *as compared to one receiving no treatment*. Dec. 12–13. We also construed the language "an effective amount" of independent claim 5 as encompassing "an amount effective to extend the time to disease progression in the human patient" and, thus, similarly indicating a comparison to an untreated patient. *See id.*

Patent Owner disagrees with our construction, contending that the proper comparator in both claim terms is not an untreated patient, but a patient treated with taxoid alone. PO Resp. 39–42. In particular, Patent Owner argues that comparison to an untreated patient "is not consistent with the specification as understood by a POSA," and "makes no sense in the context of a disease like breast cancer." *Id.* at 39–40. Yet this is precisely the comparison Applicants made to obtain allowance of the challenged claims.

"A patent's specification, together with its prosecution history, constitutes intrinsic evidence to which the [the Board] gives priority when it construes

---

[12] To the extent that these terms may differ in scope, neither party contends that any difference affects the patentability analysis and we consider them together.

claims." *Knowles Electronics LLC v. Cirrus Logic, Inc.*, 883 F.3d 1358, 1361–62 (Fed. Cir. 2018) (footnote omitted). "The purpose of consulting the prosecution history in construing a claim is to 'exclude any interpretation that was disclaimed during prosecution.'" *Chimie v. PPG Indus., Inc.*, 402 F.3d 1371, 1384 (Fed. Cir. 2005) (internal quotation marks omitted). Prosecution disclaimer

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

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

The claim language "an amount effective to extend the time to disease progression" implies that time to disease progression is extended in relation to some metric, but none of the challenged claims expressly identifies the intended comparator. The Examiner addressed this facial ambiguity during the prosecution leading to the issuance of the '549 patent. In particular, during the prosecution of the '649 Application (the direct predecessor to the '842 Application, from which the '549 patent issued), the Examiner rejected then-pending claims under 35 U.S.C. § 112, second paragraph because:

> The phrase "extend the time to disease progression" . . . is a relative term which renders the claim[s] indefinite. The term "extend time to disease progression" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the

> scope of the invention. Specifically, it is never set forth what the extension of time to disease progress is relative to, for example, is the extension of time to disease progress relative to untreated patients? Patients who received antibody or taxoid alone? Patients who received antibody and an anthracycline?

Ex. 3001, 3–4 (OA dated 7/17/01).[13] In response, Applicants asserted that:

> the expression[] "extend the time to disease progression". . . [is] clear from the specification (see, in particular, page 15, lines 15-17; and pages 42-43) and would be readily understood by the skilled oncologist. Clearly, the combination of anti-ErbB2 antibody and taxoid is administered in an amount effective to extend the time to disease progression relative to an untreated patient.

Id. at 17–18 (Response dated 1/17/2002); *see also* Ex. 1021, 19, (15:12–17), 46–47 (42–43).

The Examiner withdrew the rejection in the next office action, stating that "[a]ll claims are allowable." Ex. 3001, 24 (OA dated 3/27/2002) (suspending prosecution due to potential interference); *see also id*. at 27–317 (OA dated 8/12/2003) (new grounds of rejection not relating to the phrase "extend the time to disease progression"). Accordingly, Applicants overcame the § 112 rejection by providing an express definition of the term "extend the time to disease progression" as meaning relative to an untreated patient. Our construction reflects Applicants' choice. *See In re Paulsen*, 30 F.3d at 1480 (holding an applicant may choose to be his own lexicographer).

Patent Owner contends that we erred in our construction because "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)

---

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

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. 40. 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 ¶ 136. As a result, an ordinary artisan would have understood that, even without any explicit disclosure in the '549 patent, administering the claimed combinations would extend the TTP as compared to untreated patients. *See e.g.*, Ex. 1011 ¶ 67.

With respect to the prosecution history, Dr. Tannenbaum testifies that, "in context," Applicants used the term "untreated patient" to refer to "a patient that had not received the combination therapy, but instead received paclitaxel alone." Ex. 2062 ¶ 141. We do not find Dr. Tannenbaum's argument persuasive.

The Examiner asked Applicants to choose from various potential meanings for the claim language: "is the extension of time to disease progress[ion] relative to untreated patients? Patients who received antibody or taxoid alone? Patients who received antibody and an anthracycline?" Ex. 3001, 3–4. Despite being presented with the option of selecting "taxoid alone" as the comparator, Applicants did not choose that option. Applicant instead specifically excluded that possibility. *Id*. at 416 (stating "**[c]learly**, the combination of anti-ErbB2 antibody and taxoid is administered in an amount effective to extend the time to disease progression **relative to an untreated patient**") (emphases added). Indeed, Dr. Tannenbaum admitted that much at her deposition, agreeing that "there can be no confusion" that Applicants were "choosing the comparator untreated patients rather than taxoid alone." *See* Ex. 1087, 225:15–226:13.

Patent Owner admits that Applicants were "asked very specifically by the patent examiner what's the comparator," but fails to persuade us that by citing to certain passages in the Specification, Applicants meant something quite different from the plain statement in the prosecution history. *See* Tr. 41:23–44:11. We, instead, find persuasive Dr. Lipton's testimony in a co-pending proceeding involving the '441 Patent that "during prosecution, Patent Owner asserted that the appropriate comparison for the term 'extend the time to disease progression'' is to compare the claimed combination treatment to no treatment at all."[14] IPR2017-02063, Ex. 1102 ¶ 112(h); *see* Pet. Reply, 3.

In view of the undisputed fact that "cancer generally continues to progress without treatment" (Ex. 2062 ¶ 136), we are not persuaded by Patent Owner's contention that our adopted construction "makes no sense in the context of a disease like breast cancer." PO Resp. 40. But even assuming that to be the case, Applicants chose this definition "with reasonable clarity, deliberateness, and precision," and obtained the '549 patent only after doing so. *See In re Paulsen*, 30 F.3d at 1480. Under such circumstances, we must give the term the construction the applicant set out, even if such construction would lead to a "nonsensical result." *Source Vagabond Sys. Ltd. v. Hydrapak, Inc.*, 753 F.3d 1291, 1301 (Fed. Cir. 2014).

Accordingly, we maintain that the proper analysis of the claim language "in an amount effective to extend the time to disease progression [TTP] in the human patient" and administering the three-part combination to a human patient in "an effective amount" involves comparing the claimed combination treatments to no

[14] As is evident from section I(B), above, the '441 Patent and the '549 Patent are in the same chain of priority and have essentially the same Specification.

treatment. As explained below, however, the challenged claims are unpatentable even if we apply the construction advanced by Patent Owner.

D. Grounds 1–3

In Ground 1, Petitioner challenges claims 1–11 and 14–17 as obvious under 35 U.S.C. § 103 based on Baselga '97 and Gelmon. Pet. 25–41. In Grounds 2 and 3, respectively, Petitioner further asserts Drebin (claim 12) and Presta (claim 13). *Id.* at 41–43. Patent Owner opposes. PO Resp. 42–49.[15]

We begin with an overview of the asserted references.

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

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

Baselga '97 states that "[i]n preclinical models the combined therapy of breast cancer cells that overexpress HER2 with agents that interfere with HER2 function and paclitaxel results in a marked antitumor effect." *Id.* at 11. In particular, "[t]he murine monoclonal antibody (MoAb) 4D5, directed against the extracellular domain of $p185^{HER2}$ (ECD^{HER2}), is a potent inhibitor of in vitro growth

[15] Patent Owner does not separately argue that the limitations of claims 12 and 13. *See e.g.,* Pet. Reply 25.

and, in xenograft models, of human breast cancer cells overexpressing HER2." *Id*. at 7. In a mouse model using HER2-expressing BT-474 cell implants:

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

Id. at 9.

According to Baselga '97, because the potential for immunogenic response limits the clinical application of murine antibodies, Genentech scientists developed a recombinant, humanized version of MoAb 4D5, designated rhuMoAb HER2, "to facilitate further clinical investigations." Ex. 1007, 44, 46. Referencing the Phase II clinical trials results of Baselga '96 (citation 39), Baselga '97 teaches that rhuMoAb HER2, alone, "is clinically active in patients who have metastatic breast cancers that overexpress HER2 and have received extensive prior therapy." *Id*. at 9–10. Baselga '97 further notes that another Phase II clinical trial involving HER2+ breast cancer patients demonstrated that the combination of rhuMoAb HER2 and cisplatin resulted in a 25% response rate "suggesting that the synergy observed in the laboratory was reproducible in the clinic" and did not increase toxicity as compared to cisplatin alone. *Id.* (referencing Pegram (Ex. 1013)).[16] With respect to the combination of rhuMoAb HER2 and paclitaxel, Baselga '97 states:

---

[16] Pegram *et al*., *Phase II Study of Intra Venous Recombinant Humanized Anti-p185 HER-2 Monoclonal Antibody (rhuMAb HER-2) Plus Cisplatin in Patients with HER-2/neu Overexpressing Metastatic Breast Cancer*, 14 PROC. AM. SOC. CLIN. ONCOL. 106 (Abstract 124) (1995).

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

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

Treatment consists of either cytotoxic chemotherapy or chemotherapy plus treatment with rhuMoAb HER2. *Id*. at 10. The chemotherapy regimen is selected based on whether the patients have been previously treated with anthracyclines (e.g., doxorubicin or epirubicin). *Id*. Patients that have not previously been treated with anthracyclines are administered a combination of cyclophosphamide and doxorubicin or epirubicin, whereas patients with a history of anthracycline therapy are treated with paclitaxel. *Id*. Besegla '97 notes that "[b]ecause anthracyclines are widely used in the adjuvant setting, it is likely that a significant number of patients will be treated with paclitaxel ± rhuMoAb HER2." *Id*. Baselga '97 describes the phase III trial as "ongoing" and presents no results from this study. *Id*.[17]

---

[17] The Parties agree that results of the Phase III clinical trial discussed in Baselga '97 are disclosed in the '549 Patent. *See, e.g.,* Pet. 8–9; PO Resp. 20. Although Patent Owner discloses internal deliberations of Dr. Hellman and other Genentech employees regarding the design of that study (*see e.g.,* PO Resp. 24–26) we consider such discussion only by way of background and do not rely on the

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

Gelmon states that, "Phase II studies have shown paclitaxel to be an active single agent in metastatic breast cancer, with reported response rates of 17% to 62%. . . . Promising results have also been reported with combinations of paclitaxel with other active agents such as doxorubicin, cyclophosphamide, and edatrexate." Ex. 1025 at 9. "We were also interested in combining [paclitaxel] with a non-cross-resistant drug with a different spectrum of toxicity. Cisplatin seemed to be an appropriate choice." *Id*. Gelmon further notes that paclitaxel and cisplatin have different resistance mechanisms and that "synergism between paclitaxel/cisplatin has been established in preclinical models and this has been translated as clear clinical benefits." *Id.* at 9–10 (noting that the combination has demonstrated "improved survival when administered as first-line therapy" for ovarian cancer). Accordingly, Gelmon presents the results of a Phase I/II clinical study designed

> (1) to determine the toxicity of paclitaxel and cisplatin in a biweekly schedule, (2) to establish the maximum-tolerated dose of paclitaxel in combination with a fixed dose of cisplatin (60 mg/m^2) for patients with metastatic breast cancer, (3) to determine the feasibility of repeated biweekly administrations, and (4) to evaluate the activity of this combination in this disease setting.

Id. at 10.

According to Gelmon, "[a]ll but two of the women in our trial had been treated with previous adjuvant chemotherapy, and 23 of 29 patients had previous exposure to anthracyclines." *Id*. at 13. Of the 27 patients assessed for efficacy,

---

underlying documents insofar as they do not appear to have been publically available, and Patent Owner does not attempt qualify them as prior art. *See Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, No. 2017-2078, 2018 WL 4288982, at *7 (Fed. Cir. Sept. 10, 2018) (discounting patent owner's unpublished clinical trial data because it "could not have informed the legally relevant person of skill in the art").

three showed a complete response with a time to disease progression of 110 to 200 days, and 20 showed a partial response with a time to disease progression of 96 to 377+ days. *See, e.g.*, *id.* at Abstract. Overall, patients treated with the paclitaxel/cisplatin regimen showed an overall response rate of 85% and a median time to disease progression of 7.1 months. *Id*. Gelmon concludes that "[b]iweekly paclitaxel and cisplatin is an active combination in the treatment of metastatic breast cancer, including for patients with previous exposure to anthracyclines." *Id*.

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

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

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

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

5. *Analysis*

Petitioners have provided a reasoned, claim-by-claim explanation for the basis of its contention that claims 1–11 and 14–17 would have been obvious under 35 U.S.C. § 103 based on the combination of Baselga '97 and Gelmon, and that claims 12 and 13 would have been obvious in view of the further teachings of Drebin and Presta, respectively. Pet. 25–43.

As set forth in section II(D)(1),(2), above, Baselga '97: (1) teaches the clinical efficacy of rhuMoAb HER2 alone, or in combination with cisplatin in treating HER2-positive breast cancer; (2) notes that a non-humanized precursor of rhuMoAb HER2 is synergistic with paclitaxel in a mouse model of HER2-positive breast cancer; and (3) describes an on-going clinical trial of rhuMoAb HER2 in combination with paclitaxel. Gelmon teaches combining paclitaxel with cisplatin for the treatment of breast cancer based on synergism between the two compounds in preclinical models, non-cross reactivity, differing toxicity profiles, and observed efficacy of the combination in treating ovarian cancer. Gelmon further discloses the results of a Phase I/II clinical trial demonstrating that paclitaxel in combination with cisplatin is active in the treatment of metastic breast cancer.

According to Petitioners, "two- and three-agent combinations[] were routinely used to fight cancer, including breast cancer" such that "the claimed three-drug treatment is nothing more than the natural result of following the prior art's explicit teachings." Pet. Reply 1, 17 (citations omitted). In particular:

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

Pet. 17 (citations omitted). In sum, Petitioners argue, "[e]very component of the claimed three-drug combination was known in the prior art," and "[t]he thought to combine these known treatments was nothing more than the exercise of routine skill." Pet. 15.

According to Petitioners, Patent Owner "concede[s] that Baselga '97 teaches treating humans with the combination of trastuzumab and paclitaxel" and "does not dispute that Gelmon[] showed synergistic efficacy from the paclitaxel-cisplatin combination in treatment of metastatic breast cancer without undue toxicity, motivating POSAs to further investigate adding additional non-cross-resistant agents in three-drug combinations." Pet. Reply 1, 4, and 6. Petitioners further point out that Patent Owner does not contest that the claimed clinical efficacy benefit (extended TTP) would have been expected under the Board's construction, and that even under Patent Owner's construction, extended TTP would have been expected. *Id.* at 1–2, 4.

Pertinent to all Grounds, Patent Owner argues that the Board applies an incorrect claim construction; and that under its preferred construction "a POSA would not have had a reasonable expectation of success that the combination of an anti-ErbB2 antibody and a taxoid would extend TTP as compared to taxoid-only treatment." *See, e.g.,* PO Resp. 3–7. Also relevant to all Grounds, Patent Owner contends that one of ordinary skill in the art would not look to Gelmon with respect to treating HER2-positive patients. *Id.* at 6. We first address patentability under the Board's construction and certain issues raised with respect to Gelmon.

a) an amount effective to extend the time to disease progression

With respect to the limitation, "an amount effective to extend the time to disease progression," Dr. Lipton notes:

> Baselga '97 teaches that the single agent therapy with rhuMAb HER2 produced a measurable response in 11% of patients with a median increased time to disease progression of 5.1 months, and that a main clinical outcome for the phase III trial is measuring time to disease progression. Thus, since rhuMAb HER2 on its own extends the time to disease progression, other than trace administration of a

> taxoid and a further growth inhibitory agent, nothing more is required by claim 1 to meet this limitation.

Ex. 1011 ¶ 84. Under the Board's construction of "in an amount effective to extend the time to disease progression" of independent claims 1 and 16, or the more inclusive term, "an effective amount," of independent claim 5, Patent Owner does not dispute the conclusion reached by Dr. Lipton. *See* PO Resp. 42–52 (limiting arguments to comparison with taxoid alone in contravention of the Board's construction). Nor does Patent Owner, nor our own reading of the prior art, suggest that one of ordinary skill in the art would believe that the addition of paclitaxel and/or a further growth inhibitory agent would negate the increased time to disease progression mediated by rhuMAB HER2.

As noted above in section II(D)(1)(a), Baselga '97 further teaches the benefit of treating HER2+ breast cancer patients with rhuMAb HER2 alone, and that clinical trial with those antibodies in combination with chemotherapy agents (including paclitaxel) are underway. Baselga '97 further references Pegram's disclosure of a Phase II clinical trial of HER2+ breast cancer patients treated with a combination of rhuMoAb HER 2 and cisplatin. Ex. 1007, 9–10; *see also* Ex. 1013. According to Baselga '97, the combination therapy did not increase toxicity as compared to cisplatin alone but resulted in a 25% response rate "suggesting that the synergy observed in the laboratory was reproducible in the clinic." *Id.* at 10.

Gelmon similarly discloses that paclitaxel is active as a single agent in metastatic breast cancer, and exhibits advantageous, if not synergistic, results in combination with cisplatin. *See* Section II(D)(1)(b), *supra*; Ex. 1011 ¶¶ 58–60. We find particularly unpersuasive Patent Owner's argument that one of ordinary skill in the art would not have made the claimed combination "in the first place" because HER2-positive breast cancer "would not respond well" to standalone paclitaxel (*see* PO Resp. 8–9 (citing Yu (Ex. 2029)). Contrary to Patent Owner's

argument, the claimed combination does not relate to standalone paclitaxel, and the use of paclitaxel to treat HER2-positive breast cancer in combination therapies was well known. We note, for example, Gelmon's teaching to combine paclitaxel with cisplatin and Baselga '97's disclosure that paclitaxel was being combined with rhuMoAb HER2 in clinical trials based on promising preclinical data. *See also* Ex. 1085 ¶ 34 (citing Ex. 1078, 5 ("HER2 overexpression in MBC seems to confer *sensitivity* rather than resistance to taxanes").[18] We, thus, find persuasive Dr. Lipton's testimony that one of ordinary skill in the art would have been motivated to combine Baselga '97 and Gelmon with a reasonable expectation of success, particularly in light of Gelmon's teaching "that paclitaxel and cisplatin have different mechanisms of resistance, do not have overlapping toxicity, and have demonstrated synergism." *See* Ex. 1011 ¶ 85.

Moreover, we accept Dr. Lipton's testimony that because Baselga '97 teaches that rhuMAb HER2 extends time to disease progression and Gelmon teaches that cisplatin plus paclitaxel extends time to disease progression, "a POSITA would have had a reasonable expectation that the three-drug combination at the disclosed doses for each drug would be an amount effective to extend the time to disease progression." Ex. 1011 ¶ 86. As set forth below in section II(F), we reach the same conclusion under the claim construction advanced by Patent Owner.

b) Gelmon

As analyzed under the Board's claim construction, Patent Owner's arguments in favor of patentability collapse into the question of whether one of

---

[18] 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) ("Ex. 1078").

ordinary skill in the art would reasonably combine Baselga '97 with Gelmon. Patent Owner first contends that one of ordinary skill in the art would not look to Gelmon with respect to treating HER2-positive patients because only 25–30% of Gelmon's breast cancer patients were HER2-positive and "a POSA would have no way of knowing whether the results reported in Gelmon[] would be applicable to HER2-positive patients." PO Resp. 61 (citing Ex. 1001 1:23–29; Ex. 2027, 783; Ex. 2062 ¶ 219). We do not find this argument persuasive in light of the evidence set forth on page 17 of Petitioners' Reply Brief.

We note, for example, the testimony of Patent Owner's expert, Dr. Tannenbaum, agreeing that "persons skilled in the art would look generally to the experience with chemotherapeutic agent treatment in metastatic breast cancer generally" and "the fact that a particular study did not address the HER2-positive status . . . doesn't mean that it would have been discounted in determining which therapeutic agent to combine with Herceptin." Ex. 1087, 297:7–298:21. Patent Owner's argument is further rebutted by Baselga '97's disclosure that the combination of rhuMoAb HER2 and cisplatin was therapeutically synergistic in HER2+ breast cancer patients, thus indicating that one of ordinary skill in the art would have understood that the combination of rhuMoAb HER2 and cisplatin may be used to treat HER2+ breast cancer. *See* Ex. 1007, 9–10; Ex. 1013 (Pegram).

Patent Owner further characterizes Gelmon's results as an "anomaly" and argues that Gelmon's teachings are "undermined" by reports in Wasserheit (Ex. 2062), Sparano (Ex. 2120), and McCaskill-Sevens (Ex. 2121) that cisplatin in combination with paclitaxel did not appear to show any clinical benefit as compared to paclitaxel alone and/or was accompanied by unacceptable side effects. PO Resp. 47–48; 61–62. Distinguishing these references, Petitioners note that

> Wasserheit concluded that "higher doses of both agents per cycle" likely accounted for higher toxicity compared to Gelmon. (Exs. 2068

> at 1997; 1087_300:8-23.) Sparano stated lower response rates most likely were due to "the marked imbalance in number of disease sites." (Exs. 2120 at 1884; 1087_300:24-302:23.) And McCaskill-Stevens still showed a relatively high (***60%***) response rate for the paclitaxel/cisplatin combination. (Ex. 2121 at 2.)

Pet. Reply 18. Further with respect to the reliability of Gelmon's disclosure, we find persuasive the additional evidence in Petitioners' Reply Brief indicating that one of ordinary skill in the art would have been motivated to use cisplatin and paclitaxel in combination with other agents for the treatment of breast cancer. *See id.* at 18–19. Frasci, for example, reports that between June 1995 and January 1997, and based on Gelmon's "very promising response rate," forty-three women with metastatic breast cancer began treatment with paclitaxel and either cisplatin or doxorubicin. Ex. 1082, Abstract. Also relying on Wasserheit's and Gelmon's "promising early results" the investigators in Klaassen treated patients with a combination of paclitaxel, cisplatin, and 5-fluorouacil/leucovorin. Ex. 1083, Abstract, 5; *see also* Ex. 1085 ¶ 116; Ex. 1087, 313:23–314:24 (Dr. Tannenbaum agreeing that Klaassen indicated motivation to add additional drugs to the paclitaxel/cisplatin regimen.).[19]

c) *Anthracyclines*

For the reasons set forth at pages 13–15 of Petitioners' Reply Brief, we are also not persuaded that one of ordinary skill in the art would have been motivated to use anthracyclines instead of a taxoid as the chemotherapeutic in combination with rhuMAb HER2. *See* PO Resp. 59–60 (citing Ex. 2062 ¶¶196–199, 201, 216,

[19] Klaassen *et al.*, *Phase II Study with Cisplatin and Paclitaxel in Combination with Weekly High-dose 24 h Infusional 5-fluorouracil/leucovorin for First-line Treatment of Metastatic Breast Cancer*, 9 ANTI-CANCER DRUGS 203-07 (1998).

226). As Petitioners point out, that persons of ordinary skill in the art may have been motivated to combine rhuMAb HER2 with an anthracycline for the treatment of breast cancer, does not establish non-obviousness of the rhuMAb HER2/taxoid combination. *See* Pet Reply 13 (citing *In re Fulton*, 391 F.3d 1195 (Fed. Cir. 2004)). To the contrary, evidence of record shows that although anthracyclines were widely employed, paclitaxel was approved as second-line therapy for breast cancer, and routinely used as a first-line therapy. *See* Ex. 1011 ¶¶ 15-16; Ex. 1066; Moreover, Nicolaou[20] described paclitaxel as "one of the most promising treatments for breast and ovarian cancer," and at least one treatment arm of the Phase II trial reported in Baselga '97 was conducted with paclitaxel rather than anthracycline. Ex. 1036, 5; *see also* section II(E)(1). Moreover, one of ordinary skill in the art would have been aware of Baselga '94, which is cited in Baselga '97, and expressly suggests the combination of rhuMAb HER2 with either anthracycline or a taxoid. *See* Ex. 1009, 14–15 (noting "a marked synergy of taxol in combination with anti-EGF receptor MAbs" in animal studies and stating that "[a] potentially more effective approach [to treating advanced breast cancer] involves combination therapy with anti-EGF receptor MAb plus a second agent, such as doxorubicin or taxol."). Accordingly, we are persuaded that as of the relevant date those of ordinary skill in the art were motivated to combine rhuMAb HER2 with paclitaxel rather than anthracyclines. *See also* Ex. 1086 ¶¶ 77–81 (concluding that "the preclinical results reported in Baselga '94, alone or in combination with the clinical results in Baselga '96, would have given those skilled in the art a reasonable expectation that adding rhuMAb HER2 to paclitaxel

[20] Nicolaou et al., Taxoids: New Weapons against Cancer, Scientific Am., Vol. 274, No. 6, 94–98 (1996) ("Ex. 1036").

would extend the time to disease progression in human HER2+ breast cancer patients without increasing overall severe adverse events."); Ex. 1085 ¶¶ 27–28.

Further, and particularly relevant to the treatment of a human patient "in the absence of an anthracycline derivative" as set forth in claim 16, we note that the FDA-approved labeling for Taxol states that it "is indicated, after failure of first-line or subsequent chemotherapy" where "[p]rior therapy should have included an anthracycline." Ex. 2105, 6. Accordingly, we rely on Dr. Lipton's testimony that there was "a need to use alternative treatments such as paclitaxel for patients susceptible to anthracycline cardiotoxicity and/or resistance." Ex. 1085 ¶¶ 27–28.

The prior art of record confirms that many patients with metastatic breast cancer will have previously been treated with, and become resistant to, first-line anthracycline chemotherapeutics. Gelmon, for example, discloses that "[a]ll but two of the women in our trial had been treated with previous adjuvant chemotherapy, and 23 of 29 patients had previous exposure to anthracyclines." Ex. 1025, 13. On the present record, we find persuasive Dr. Litton's testimony that one of ordinary skill in the art would have recognized that "'[b]ecause anthracyclines are widely used in the adjuvant setting,' there is a substantial likelihood that patients will have already received a course of anthracycline therapy, and thus it would be advantageous to pursue synergistic drug combinations—like paclitaxel with cisplatin—that include drugs other than anthracyclines." Ex. 1011 ¶ 128 (citing Ex. 1007, 10; Ex. 1025, 9).

We further note that only patients in Baselga '97 who had previously received anthracycline therapy were assigned to treatment with the combination of paclitaxel and rhuMoAb HER2, whereas those who had not been previously exposed to anthracyclines were assigned to anthracycline-based chemotherapy with or without the anti-ErbB2 antibody. *See* section II(D)(1), above; *see also*

Ex. 1007, 47 ("Because anthracyclines are widely used in the adjuvant setting, it is likely that a significant number of patients will be treated with paclitaxel ± rhuMoAb HER2."). Thus, patients in the paclitaxel/rhuMoAb HER2 antibody arms of the clinical trial were selected for treatment "in the absence of an anthracycline derivative" based on whether they had previously been treated with anthracyclines. The fact that patients administered the combination may have been previously treated with anthracyclines does not take such a treatment regimen out of the claim scope.

Accordingly, the evidence of record shows that in considering a patient's prior history of unsuccessful treatment with anthracycline therapy, one of ordinary skill in the art would have been motivated with a reasonable expectation of success to treat such patients with HER2-positive breast cancer by administering a combination of an rhuMoAb HER2, a taxoid such as paclitaxel, and a further growth inhibitory agent "in the absence of an anthracycline derivative."

d) Sliwkowski Declaration and Secondary Considerations

During the prosecution leading to the issuance and of the '549 patent, the Examiner withdrew an obviousness rejection involving Baselga '96 "in view of the declaration of Mark X. Sliwkowski, PhD." Ex. 1019-7, 47–48. The Sliwkowski Declaration asserted, inter alia, that "a skilled scientist would have anticipated that paclitaxel would provide little or no additional benefit to treatment with trastuzumab alone since trastuzumab would arrest the cell cycle before paclitaxel would be able to act," and that one of ordinary skill in the art would recognize that "anti-HER2 antibodies acting by inducing cell cycle arrest in the G1 phase, would antagonize the effect of taxoids, such as paclitaxel, since they arrest cell cycle before it reaches the G2/M phase, where taxoids exert their apoptotic antitumor

activity." Ex. 1019-6, 341–345 ¶¶ 7, 8. Patent Owner raises neither of these arguments here.

Although Patent Owner appears to suggest that the Sliwkowski Declaration indicates that the combination of rhuMAb HER2 and a taxoid demonstrated unexpected results (*see* Prelim. Resp. 30 (citing Ex. 1019-6, 341–45); PO Resp. 29 (same); *see* Pet. 10), we do not understand Patent Owner to rely on the Sliwkowski Declaration in this proceeding, nor to otherwise assert secondary considerations. *See* Pet. Reply. 26. Accordingly, Petitioners' arguments and evidence regarding the failings of the Sliwkowski Declaration and arguments that objective indicia do not establish non-obviousness in this case stand unrebutted. *See* Pet. 61–65; PO Resp. 26; Ex. 1011 ¶¶ 219–28.

e) Conclusion

Considering the evidence as a whole, we agree with Petitioners that one of ordinary skill in the art would have been motivated to combine the teachings of Baselga '97 with Gelmon with a reasonable expectation of success. In view of the entire record before us, and applying our construction set forth in section II(C)(2), above, we conclude that Petitioners have demonstrated by a preponderance of evidence that claims 1–17 would have been obvious under grounds 1–3.

E. Grounds 4–6

In Ground 4, Petitioners challenge claims 1–11 and 14–17 as obvious under 35 U.S.C. § 103 based on the combination of Baselga '96, Baselga '94, and Gelmon. Pet. 42–59. In Grounds 5 and 6, respectively, Petitioners further rely upon Drebin (claim 12) and Presta (claim 13). *Id.* at 59–61. Grounds 4–6 are, thus, similar to Grounds 1–3, except that the earlier-published Baselga '96 and Baselga '94 replace the Baselga '97. Accordingly, we begin with an overview of Baselga '96 and Baselga '94,

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

Baselga '96 teaches that "[i]n preclinical studies . . . rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity." Ex. 1005, 15. As a result, "[l]aboratory studies of the mechanism of this effect and clinical trials of such combination therapy are currently in progress." *Id*.

Baselga '96 further teaches that after successful experiments in mouse models, a humanized version of the 4D5 anti-ErbB2 antibody, rhuMAb HER2, was used in a phase II clinical trial for patients with metastatic breast cancer that overexpressed HER2. *Id*. at 9–10. "[P]atients were selected to have many sites of metastatic involvement, one of the most dire prognostic characteristics regarding response to therapy." *Id.* at 13. Of the 46 patients enrolled, 82.6% had received at least one regimen for metastatic disease, and 63% had received two or more regimens. *Id*. at 11. "Adequate pharmacokinetic levels of rhuMAb HER2 were obtained in 90% of the patients." *Id.* at Abstract. "Treatment with rhuMAb HER2 was remarkably well tolerated." *Id.* at 11. "Toxicity was minimal and no antibodies against rhuMAb HER2 were detected in any patients." *Id.* at Abstract.

With respect to efficacy, "37% of patients achieved minimal responses or stable disease." *Id*. at 13. "Objective responses were seen in five of 43 assessable patients, and included one complete remission and four partial remissions" for an overall response rate of 11.6%. *Id. at* Abstract*; see id. at* 12. Baselga 1996 posits "that the percentage of patients who show objective tumor regression to rhuMAb HER2 will be higher when patients with less extensive breast cancer are treated, since laboratory studies have shown that the response to antireceptor antibodies is greater with lower tumor burden." *Id.*

"Time to tumor progression was calculated from the beginning of therapy to progression," and "[t]he median time to progression for the patients with either minor or stable disease was 5.1 months." *Id*. at 10, 12. Baselga 1996 notes that, in contrast to many anticancer drugs, rhuMAB HER2 elicits cytostatic growth arrest rather than cell death in laboratory studies. *See id*. at 13. Accordingly, the authors posit that "stable disease may be an authentic reflection of the biologic action of [rhuMAB HER2]" and "[t]he unusually long durations of minimal responses and stable disease seen in [the] trial" may be indicative of the cytostatic effects of the antibody. *Id.* at 12–13.

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

Baselga '94 describes xenograft studies in which HER2 overexpressing human breast cancer cells were injected into nude mice followed by treatment with humanized 4D5-antibody alone, or in combination with various chemotherapeutic agents. Ex. 1006, 4. Whereas either the antibody or paclitaxel alone produced 35% tumor growth inhibition, the combination of the two resulted in "major antitumor activity with 93% inhibition of growth" without increasing toxicity. *Id*. In addition, whereas doxorubicin alone resulted in 27% growth inhibition, the combination of doxorubicin and antibody resulted in 70% growth inhibition. *Id.*

According to the authors, [t]hese observations suggest that dual insults to cell cycle transversal through checkpoints (Mab-mediated growth factor deprivation, and drug mediated damage to DNA or tubulin) may activate cell death in tumor cells which can survive either treatment given singly. *Id.* Baselga '94 concludes that "anti-HER2 MAbs can eradicate well established tumors and

enhance the activity of paclitaxel and doxorubicin against human breast cancer xenografts. *Id.*

1. Analysis

In light of our construction of the claim terms "in an amount effective to extend the time to disease progression" and the related term, "an effective amount," our analysis of claims 1–17 is substantially the same under Grounds 4–6 as it is under Grounds 1–3, above, and we incorporate that discussion herein. With respect to Petitioners' reliance on Baselga '94 and Baselga '96 as opposed to Baselga '97, we agree with and adopt the arguments set forth on pages 6–16 of Petitioners' Reply, the highlights of which we address herein.

On pages 53–60 of its Response, Patent Owner argues that Baselga '96 and Baselga '94 would not have motivated one of ordinary skill in the art to administer a combination of rhuMAb HER2 and a taxoid for the treatment of breast cancer. With respect to Baselga '96, Patent Owner argues that the reference merely discloses the administration of rhuMAb HER2 alone. Baselga '96, however, states that "[i]n preclinical studies . . . rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity" and, as a result, "clinical trials of such combination therapy are currently in progress." Ex. 1005, 15. Based on our reading of Baselga '96 as a whole and the testimony of the parties' experts, we agree with Petitioners that the only reasonable interpretation of the cited passage is that clinical trials of rhuMAb HER2 in combination with each of cisplatin, doxorubicin, and paclitaxel were currently in progress for the treatment of breast cancer. *See* Pet. Reply 7; Ex. 1085 ¶ 126; Ex. 1087, 252:20–253:22.

We are also unpersuaded by Patent Owner's argument that Baselga '94 would not have provided motivation to administer a combination of rhuMAb

HER2 and a taxoid for the treatment of breast cancer because the reference is a non-peer reviewed abstract disclosing the results of a single mouse model. PO Resp. 55–59. As an initial matter, we find that the teachings of Baselga '96, including its disclosure of on-going clinical trials of rhuMAb HER2 in combinations with paclitaxel and cisplatin provides sufficient motivation to combine rhuMAb HER2 with a taxoid and additionally cisplatin as a further growth inhibitory agent. *See In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) ("[A reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole."). Moreover, the inventors of the '549 patent do not appear to have considered abstracts unreliable as the patent cites numerous abstracts and posters on its face. *See* Ex. 1001, (56) References Cited. Indeed, in a declaration submitted during prosecution, Applicants relied on an abstract to overcome prior-art rejections. *See* Ex. 1019-5, 340; *see also* Ex. 1085 ¶ 96 (testifying that "POSITAs often apply the information in the abstract [before publication of a longer, peer reviewed article], particularly where the abstract describes results that might have significant, clinical benefit for patients").

Further, we do not find persuasive Dr. Tannenbaum's opinion that one of ordinary skill in the art "would wait for the full paper describing these experiments and bases before drawing any conclusions from it," (Ex. 2062 ¶ 188) or Patent Owner's contention that one of ordinary skill in the art would not rely on preclinical studies in the relevant context (PO Resp. 7–9, 56–57 & n.17). To the contrary, evidence of record indicates that those of ordinary skill in the art did consider the Baselga '94 abstract relevant to clinical efficacy. *See* Pet. Reply 11 (noting that Baselga '94 was "published in the Proceedings of the American Society of *Clinical* Oncology") (emphasis in original); Ex. 1085 ¶ 97 ("Baselga '94 was subsequently cited in peer-reviewed publications, which viewed the study

results with approval"). Moreover, Baselga '94 was expressly cited in the prior art as providing "motivation for clinical evaluation" and "the basis for a planned clinical trial." Exs. 1072, 8;[21] 1073, 11;[22] *see also* Ex. 1085 ¶¶ 40, 140; Ex. 2111, 8 ("Paclitaxel was selected [to combine with rhuMAb HER2] because of its activity in metastatic breast cancer and preclinical studies that supported its use.");[23] Ex. 2130 at 53:1–56:1. Indeed, Patent Owner admitted at oral argument that the Baselga '94 data was used, at least "[i]n part," to justify to the FDA conducting phase III trials in the absence of phase II trials." Tr. 64:14–67:10.

We also do not find persuasive Patent Owner's argument that one of ordinary skill in the art would disregard Baselga 94's admittedly "good effect in combining the Herceptin plus paclitaxel" in light of the teachings of the Hsu abstract (Ex. 2135).[24] *See* Paper 73, 7; Tr. 62:7–64:13, 67:25–68:23; Ex. 2143 ¶ 25; Ex. 2144 ¶ 32; Paper 85 ¶ 14. According to Hsu, in vitro cytotoxicity assays on HER2-expressing SKBR-3 human breast cancer cells showed that rhuMAb HER-2 and taxol in combination showed additive cytotoxic effects, whereas, in a

---

[21] Siedman et al., *Memorial Sloan-Kettering Cancer Center Experience With Paclitaxel in the Treatment of Breast Cancer: From Advanced Disease to Adjuvant Therapy*, Sem. Oncol., Vol. 22, No. 4, Supp. 8:3–8 (1995) ("Ex. 1072").

[22] F .A. Holmes, *Paclitaxel Combination Therapy in the Treatment of Metastic Breast Cancer: A Review.* Sem. Oncol. Vol. 23, No. 5, Supp. 11 (1996) ("Ex. 1073").

[23] S. Shak, *Overview of the Trastuzumab (Herceptin) Anti-HER2 Monoclonal Antibody Clinical Program in HER2-Overexpressing Metastatic Breast Cancer*, Sem. Oncology, Vol. 26, No. 4, Supp. 12 (1999) ("Ex. 2011").

[24] 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) ("Ex. 2135").

mouse model involving transplanted "HER-2/*neu*-transfected MCF-7 human breast cancer" cells, "[x]enografts treated with rhuMAb HER-2 plus taxol . . . were not significantly different from drug alone controls with the doses and dose schedules tested in this model." Ex. 2135. In light of Hsu's xenograft results, 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; *see also* Ex. 2144 ¶¶ 32–34.

We are more persuaded, however, by Dr. Lipton's testimony 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. 1085 ¶ 43; *see also* Ex. 1099 ¶ 39–48.

We also credit Dr. Clarke's explanation that significant differences between the Baselga '94 and Hsu disclosures make clear that Hsu was not intended to "replicate" the results of Baselga '94, which may account for the differences in outcome. Ex. 1100 ¶¶ 40–43. Dr. Clarke notes that the two groups used different target cells for their xenograft studies; whereas Baselga '94 used cell line BT-474, which naturally overexpressed HER2, Hsu transfected a HER2-negative cell line with HER2/*neu* to achieve HER2-overexpression. Ex. 1099 ¶ 42. Dr. Clarke notes that Hsu provides no data showing the level of HER2-overexpression achieved by the transfection, nor any dosage information indicating that the dosage of either rhuMAb HER2 or the taxoid was reduced to ensure that the experiment had the ability to detect possible interactions between the two drugs. *Id.* ¶ 42.

We are also not persuaded by Patent Owner's arguments regarding the design of the preclinical study set forth in Baselga '94. *See* PO Resp. 55–57. We do not, for example, find persuasive Patent Owner's implication that one of ordinary skill in the art would have discounted Baselga '94's results because it used a single cell line with a high level of HER2 expression. *See* PO Resp. 56. To the contrary, we credit Dr. Clarke's testimony that: (1) Baselga's cell-line was "the most obvious first choice" because it expressed high levels of HER2 and responded well to anti-HER2 antibody, and (2) given the study's purpose and results, testing multiple cell lines would not have been considered necessary. Ex. 1086 ¶¶ 61–63, 69, and 99–116.[25]

Finally, we determine that the concerns Patent Owner raises regarding the credibility of Baselga' 94 are outweighed by the evidence, discussed above, that those of ordinary skill in the art ***did***, in fact, rely on the results set forth in Baselga '94 in designing human clinical trials.

2. Conclusion

Considering the evidence as a whole, we agree with Petitioners that one of ordinary skill in the art would have been motivated to combine the teachings of Baselga '96 and Baselga '94 with Gelmon and have a reasonable expectation of

---

[25] Patent Owner further contends that model cell lines having 11 (MDA-435), 31 (SK-BR3), and 52 (BT-474) copies of ErbB2 per cell reflects "the heterogeneity of human chromosomes." PO Resp. 11 (citing Ex. 2054, 5400, 5402; Ex. 2065, 262, Ex. 2063, 1457; Ex. 2061 ¶¶ 26, 42, 44; and Ex. 2062 ¶ 74). To the extent Patent Owner intends to convey that the variation in ErbB2 copy number in the referenced cell lines reflects the heterogeneity of HER2 expression within or between HER2-positive tumors in human patients, this would appear to support Dr. Clarke's position that it was reasonable to rely on cell line BT-474 in preclinical trials, as it would be expected to have the highest, yet still physiologically relevant, expression level among the referenced cell lines.

success. In view of the entire record before us, and applying our construction set forth in section II(C)(2), above, we conclude that Petitioners have demonstrated by a preponderance of evidence that claims 1–17 would have been obvious under grounds 4–6.

F. Patentability Under Patent Owner's Preferred Construction

We also address patentability under Patent Owner's proposed construction of "an amount effective to extend the time to disease progression in the human patient" and "an effective amount" as comparing the three-part treatment to treatment with taxoid alone. Applying its preferred construction, Patent Owner contends that the challenged claims are not unpatentable with respect to Grounds 1–3 because neither Baselga '97 nor Gelmon teach or suggest that the claimed combination would extend the time to disease progression as compared to treatment with a taxoid alone. PO Resp. 42–49. With respect to Grounds 4–6, Patent Owner makes similar and overlapping arguments regarding the combination of Baselga '96, Baselga '94, and Gelmon. *Id.* at 49–53.

According to Patent Owner, "[t]he Phase-II study described in Baselga '97 (originally reported in Baselga '96) contained no control arm against which to compare the TTP and thus disclosed no ***extension*** in TTP." *Id.* at 45 (citations omitted). Although it is undisputed that Baselga '97 and Baselga '96 report a median increase in TTP of 5.1 months, Patent Owner argues that this refers to patients who received rhuMAb HER2 alone and "do[es] not describe an extension in TTP, which is a comparative result, let alone an extension in TTP as compared to patients treated with taxoid alone." *Id.* at 44–45. Patent Owner similarly argues that "Gelmon[] discloses a 'median' TTP, but contains no comparative data showing any ***extension*** in TTP." *Id.* at 47. Accordingly, Gelmon "did not evaluate

any ***extension*** in the time to disease progression and could not have done so because it lacked a control arm." *Id.* at 51.

Patent Owner further argues that the alleged failings of the clinical data are not remedied by the preclinical mouse data reported in Baselga '97 and Baselga '96 because the preclinical studies "measured response rate, which is not predictive of TTP." PO Resp. 45–46, 50–51; *see, e.g.*, Ex. 1005, 15 ("In preclinical studies . . . rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity.")

Assuming *arguendo* Patent Owner's claim construction, we do not find these arguments persuasive for the reasons set forth at pages 20–25 of Petitioners' Reply Brief. As an initial matter, we credit and adopt Petitioners' argument that the claimed extension of time to disease progression is an inherent benefit of an otherwise obvious combination, and that such an inherent result cannot establish patentability. *See* Pet. Reply 20–22 (citations omitted). As discussed in sections II(D)(5) and II(E)(3), above, it was obvious to combine rhuMoAb HER2 with a taxoid (e.g. paclitaxel) and a further growth inhibitory factor such as cisplatin for the treatment of HER2-positive breast cancer. Patent Owner does not dispute that when the combination of rhuMoAb HER2 and paclitaxel are administered in the absence of an anthracycline derivative for the treatment of HER2-positive breast cancer, the combined therapy significantly extends the time to disease progression as compared to taxoid therapy alone. *See id.* at 20–21. And Patent Owner does not argue that the addition of a further growth inhibitory agent such as cisplatin would abrogate this inherent benefit. *Id.* at 21. The claimed combination is obvious, and "an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the result[]." *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d

1344, 1354 (Fed. Cir. 2012). "To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." *Id.*

We further agree with Petitioners' argument that one of ordinary skill in the art would reasonably have expected the claimed extension in time to disease progression. *See* Pet. Reply 22–24. We note in particular that Baselga '96 reported that treatment with rhuMoAb HER2 resulted in "unusually long durations of minimal responses and stable disease" with a "median time to progression for the patients with either minor or stable disease was 5.1 months," thus indicating an extension of time of disease progression with the antibody alone. Ex. 1005, 12–13. And though Patent Owner contends that HER2-positive patients were thought not to respond well to paclitaxel alone (*see* Ex. 1005, 9, 13; Ex. 1007, 9; PO Resp. 17, 22, 23, 58; Ex. 2062 ¶ 57), Baselga '96 discloses that clinical trials of rhuMoAb HER2 in combination with paclitaxel had begun in light of preclinical studies showing that the antibody "markedly potentiated the antitumor effects of . . . paclitaxel," without increasing toxicity. Ex. 1005, 15; *see also* Ex. 1006 (same). Also referencing Baselga '96 and relevant preclinical data, Baselga '97 described an on-going Phase III clinical trial of HER2-positive breast cancer patients involving paclitaxel in combination with rhuMoAb HER2, with extension of TTP being a primary endpoint. Ex. 1007, 10. Accordingly, in view of the available evidence, we credit Dr. Litton's testimony that "even without a 'control arm' in Baselga '96, skilled artisans reasonably would have expected rhuMAb HER2 to extend time to disease progression compared to standalone paclitaxel in HER2+ patients." Ex. 1085 ¶ 76.

Patent Owner also argues that "[t]he mere disclosure of [the Phase III study in Baselga '97] would not provide a reasonable expectation of the result of such

study, particularly in view of the high failure rate of cancer clinical trials in the 1990s." Paper 49, 12; *see also* PO Resp., 46, 52 (collectively citing Ex. 2021, 712–13; Ex. 2062 ¶¶ 89–91, 211–216). According to Patent Owner's expert, Kola and Landis[26] "showed that approximately only five percent of oncology drugs were successful," and "that in oncology, the rate of failure in Phase III trials 'is as high as 59%.'" *See e.g.*, Ex. 2026 ¶¶ 89–90.

In relying on Kola and Landis, Dr. Tannenbaum appears to base "success" on FDA approval. Although the finder of fact may take into account failure of others to obtain FDA approval of a particular pharmaceutical combination (*see Knoll Pharm. Co., Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed.Cir.2004)), we agree with Petitioners that in this context, "the general failure rate in the industry is irrelevant." *See* Paper 80, 8 (citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007)). *See also*, *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291 (Fed. Cir. 2013) (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."). Moreover, "[c]onclusive proof of efficacy is not necessary to show obviousness." *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014). "[O]nly a reasonable expectation of success, not a guarantee, is needed." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (citations omitted).

Kola and Landis, on which Dr. Tannenbaum relies, focuses on clinical trials of individual compounds (i.e., new chemical entities (NCEs) and biologics) rather

---

[26] Kola and John Landis, *Can the Pharmaceutical Industry Reduce Attrition Rates?* 3 NATURE REV. 711-715 (2004) ("Ex. 2021").

than combinations of known or promising therapies. *See e.g.,* Ex. 2021, 711 (discussing the "[d]epressing approval rates of NCEs and biologics), 712 (Table entitled, "NCEs required to achieve specific real growth targets as a function of 2002 revenues;" addressing "the root causes of why ***compounds*** undergo attrition in the clinic," and stating that "more than 70% of oncology ***compounds*** fail [in Phase II trials]" and "approximately 45% of all ***compounds*** that enter [Phase III trials] undergo attrition and in some therapeutic areas, such as oncology, it is as high as 59%") (emphases added).

Notably, Dr. Tannenbaum does not discuss the likelihood of failure of combination therapies such as that at issue here, wherein paclitaxel was already FDA approved for treatment of breast cancer, rhuMoAb HER2 showed promise in Phase II trials, and both paclitaxel and rhuMoAb HER2 had been used successfully in combination therapy with a third compound, cisplatin. Accordingly, we do not give substantial weight to Dr. Tannenbaum's opinion on this topic.

In light of the evidence of record, one of ordinary skill in the art learning of the on-going Phase III study reported in Baselga '97 would reasonably have expected that the combination of rhuMoAb HER2 and paclitaxel would increase in time to disease progression, such that the challenged claims are obvious. *See, e.g.*, Ex. 1085 ¶¶ 162–176.

Petitioners further contend that response rate is widely accepted as a surrogate endpoint for time to disease progression, and that one of ordinary skill in the art would reasonably have expected from the response rates indicated in the cited references that combination of rhuMoAb HER2, paclitaxel, and a further growth inhibitory agent would likely increase in time to disease progression. *See*

Pet. Reply 23; *see also* Ex. 1080, 3–4.[27] With respect to preclinical data, Dr. Clarke explains that,

> as of the mid-1990s, it was not standard practice to assess time to disease progression or survival in xenograft models. However, tumor response was, and still is, used as a surrogate endpoint for these measures in mice. Specifically, if a particular drug or drug combination produced a strong anticancer response in mice, particularly tumor shrinkage or eradication, this provided researchers with a reasonable expectation that clinical benefit would be obtained in human patients.

Ex. 1086 ¶¶ 78, 133; 1100 ¶¶ 25–31; and Ex. 1085 ¶¶ 77, 99, 163. Dr. Lipton further explains that with respect to clinical trials,

> the response rate endpoint from a Phase II study is often relied on by clinicians as a "surrogate endpoint" to predict a drug's impact on time to progression, and survival, in humans. That is based on the established belief that tumor reduction is "likely to predict for prolonged survival as compared with a patient whose tumors continued to grow." (Ex. 1080 at 3-4.) Although response rate does not always predict for extended time to disease progression (*id.*), it provides POSITAs with the motivation to move forward with the Phase III trial, and a reasonable expectation that the time to disease progression will be extended in at least some patients in that trial.

Ex. 1085 ¶ 53; Ex. 2130, 100:7–19.

Dr. Lipton's and Dr. Clarke's opinions on this matter are not inconsistent with the Specification, which suggests time to disease progression and response rates as alternative measurements of efficacy. *See* Ex. 1021, 19 (15:12–17) ('649 priority application defining therapeutically effective amount; noting that "efficacy can . . . be measured by assessing the time for disease progression (TTP), or

---

[27] S.S. Ellenberg, *Surrogate Endpoints in Clinical Trials: Cancer,* 8 Statistics in Medicine 405–13 (1989) ("Ex. 1080").

determining the response rates (RR)"), 46–47 (42–43) (noting that clinical benefit is "assessed by response rates and the evaluation of disease progression").

Although not necessary to our determination, we agree with Petitioners and their experts that one of ordinary skill in the art would have reasonably expected that the claimed three-part combination would result in increased time to disease progression in light of the response rates in the cited Phase II clinical trials and preclinical studies. Ex. 1085 ¶¶ 53–53 (response rate in Phase II trials including Baselga '96), 76–77, 99 (response rates in Baselga '94)), 163–164 (response rates in Baselga '94 and Gelmon preclinical studies); Ex. 1086 ¶¶ 132–36 (response rates generally, and with respect to Baselga '94 preclinical and Baselga '96 clinical results), and 162 (response rates in Baselga '94).

a) Conclusion

Considering the evidence as a whole, we conclude that, even under Patent Owner's preferred construction of "an amount effective to extend the time to disease progression in the human patient" and "an effective amount," as indicating a comparison to a patient treated with taxoid alone, Petitioners have demonstrated by a preponderance of evidence that claims 1–17 would have been obvious under grounds 1–6.

III. Motions

A. Patent Owner's Motion to Amend

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

1. *Threshold Requirements*

In an *inter partes* review, amended claims are not added to a patent as of right, but rather must be proposed as a part of a motion to amend. 35 U.S.C.

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

In its Motion to Amend, Patent Owner proposes to replace all challenged claims with substitute claims 18–20, of which claims 18 and 19 are independent. Paper 49, Appendix A. Under the circumstances, we agree with Patent Owner that it proposes a reasonable number of substitute claims. *See* Paper 49, 2.

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

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

Id. Claim 19, submitted as a replacement for claim 16 is similar, but further recites the administration of rhuMAb HER2, paclitaxel, and a further growth inhibitory

agent "in the absence of an anthracycline derivative." *Id.* Depending from claim 19, claim 20 specifies that the ErbB2 overexpressing breast cancer is metastatic breast carcinoma and is identical to original claim 17 but for its dependency.

Patent Owner contends that the substitute claims do not enlarge but, instead, narrow the scope of the original claims. *Id.* at 2–5. According to Patent Owner, the proposed substitute claims narrow the scope of the claimed antibody by replacing the genus of "an antibody that binds ErbB2" of claim 1 or "an intact antibody which binds to epitope 4D5 with the ErbB2 extracellular domain sequence" of claim 16, with the "specific antibody species, 'rhuMAb HER2,' a recombinant humanized 4D5 anti-ErbB2 antibody also known as HERCEPTIN®." Paper 49, 2–3. Patent Owner similarly argues that the substitute claims narrow the genus encompassing "a taxoid" by reciting "paclitaxel," which is a species of taxoid. *Id.* at 3.

With respect to the claim language, "an amount effective to extend the time to disease progression in the human patient," Patent Owner contends that "the Challenged Claims do not expressly identify a comparator for the claimed 'time to disease progression'; therefore, by further limiting the claims with a specific comparator (patients treated with paclitaxel alone), the Substitute Claims do not enlarge the scope of the claims." *Id.* at 4. Alternatively, Patent Owner argues that the additional limitation merely makes explicit that, under Patent Owner's preferred construction of the original claims, "the proper comparator by which to measure the claimed efficacy is to a patient treated with paclitaxel alone." *Id.* We, nevertheless, apply our construction for the term "extend the time to disease progression" as indicating that the results of the claimed combination therapy is compared to patients receiving no treatment. Because we do not discern, and Petitioners do not contend, that the comparator of patients receiving no treatment is

broader that those receiving paclitaxel alone, we agree with Patent Owner that the amendment does not seek to enlarge the scope of the claims as required under 35 U.S.C. § 316(d) and 37 C.F.R. § 42.121.

Petitioners argue that we should deny Patent Owner's Motion to Amend under 37 C.F.R. § 42.121(a)(2)(i) because the amendments narrowing the claims to specifically recite "rhuMAb HER2" and "paclitaxel" do not respond to the instituted grounds of unpatentability. Paper 66, 6–8; Paper 80, 1. According to Patent Owner, "[i]t is not require[d] that every amended limitation be solely for the purpose of overcoming an instituted ground" and it is sufficient that the proposed claims have been amended to specify that the comparator for an amount effective to extend the time to disease progression is paclitaxel alone. Paper 49, 9 & fn.3. (citing *Veeam Software Corp. v. Veritas Techs., LLC*, IPR2014-00090, Paper 48 at 28-29 (PTAB July 17, 2017)). We agree with Patent Owner. "[37 C.F.R. § 42.121(a)(2)(i)] does not require, however, that every word added to or removed from a claim in a motion to amend be solely for the purpose of overcoming an instituted ground. Additional modifications that address potential 35 U.S.C. § 101 or § 112 issues, ***for example***, are not precluded by rule or statute." *Western Digital Corp. v. SPEX Techs., Inc.*, Case IPR2018-00082 (PTAB Apr. 25, 2018) (Paper 13) (informative), slip op. at 6 (emphasis added). Although Patent Owner does not indicate whether the disputed limitations are intended to address 35 U.S.C. §§ 101 or 103 issues, this is not expressly required under our rules. Moreover, in indicating that addressing potential § 101 or § 112 issues are merely exemplary, *Western Digital* suggests that Patent Owner may have other reasons for entering such amendments. As the disputed limitations are peripheral to our patentability analysis (*see* section III(A)(2), below) and do not otherwise unduly burden the just

and speedy resolution of this matter, we do not reject Patent Owner's Motion to Amend under 37 C.F.R. § 42.121(a)(2)(i).

Petitioners also argue that the substitute claims add new subject matter in contravention of Section 316(d) and Rule 42.121(a)(2)(ii). *See* Paper 66, 8–11; Paper 80, 1–3. Although Patent Owner asserts that each of the proposed substitute claims find support in the original disclosure (Paper 49, 5–9; Paper 73, 3), Petitioners argue that the asserted priority documents fail to "show[] that the named inventor was in possession of the claimed combination of trastuzumab and paclitaxel plus a further growth inhibitory agent, much less in a way that extends TTP relative to paclitaxel alone" (Paper 66, 9), i.e., that the priority documents that Patent Owner relies on lack sufficient written descriptive support for the full scope of the proposed claims.

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

recognize from the disclosure that appellants invented processes including those limitations.").

Patent Owner's proposed substitute claims require the administration of a three-drug combination —rhuMAb HER2, paclitaxel, and a further growth inhibitory agent— "in an amount effective to extend the time to disease progression in the human patient, as compared to paclitaxel alone." Patent Owner, however, admits that the support for the clinical effects of this three-drug combination is found in "the administration of rhuMAb HER2 and paclitaxel described in the original disclosure, ***where the two-way combination administration extended TTP as compared to paclitaxel alone***." *See* Paper 73, 3 (emphasis added). In particular, Patent Owner relies on "a clinical study in which patients with metastatic HER2-positive breast cancer or overexpression of the ErbB2 oncogene were treated with a combination of a humanized version of the murine 4D5 antibody (HERCEPTIN®) (also known as rhuMAb HER2) and Taxol® (also known as paclitaxel) in the absence of anthracycline derivative." Paper 49, 7. PO asserts that "[t]he results state that 'assessments of time to disease progression (TTP) in months) and response rates (RR) showed a significant augmentation of the chemotherapeutic effect by HERCEPTIN®, without increase in overall severe adverse events (AE).'" *Id.* (citing Ex. 1019-1 49 (43:19–21) and Ex. 1020, 43–44 (42:29–43:2)).

The written description requirement demands that inventors "do more than merely disclose that which would render the claimed invention obvious." *ICU Medical, Inc. v. Alaris Medical Systems, Inc*. 558 F.3d 1368, 1377 (Fed. Cir. 2009). Considering the evidence of record, we agree with Petitioners that "[e]ach asserted claim recites a ***three-drug*** combination and so PO must show the inventors were in possession of a ***three-drug*** combination. Showing possession of a different,

unclaimed combination is insufficient." Paper 80, 2; *see also Ariad* 598 F.3d at 1352. Because Patent Owner has not shown, and we do not find adequate written description supporting the proposed substitute claims, they likewise fail to satisfy the no new matter requirement of 35 U.S.C. § 316(d) and 37 C.F.R. § 42.121(a)(2)(ii). Accordingly, we deny Patent Owner's Motion to Amend.

2. *Unpatentability of the Amended Claims*

In addition to its failure to meet the no new matter requirement for a motion to amend, we determine that Patent Owner's Motion to Amend should be denied because Petitioners have shown by a preponderance of the evidence that claims 18–20 are obvious in view of the art of record, most particularly Baselga '97, Baselga '96, Baselga '94, and Gelmon. *See* Paper 66, 10–21. Paper 80, 3–10. In short, Patent Owner does not contend, nor do we discern, that narrowing the proposed claims to specifically recite "rhuMAb HER2" and "paclitaxel" bears on patentability, but relies on the addition of the words "as compared to paclitaxel alone" to make explicit the claim construction it argued with respect to the originally-challenged claims. *See* Paper 49, 3–4. Patent Owner then recites essentially the same arguments it put forth with respect to claims 1–17 under its preferred construction. *Cf.* Paper 49, 9–23, Paper 73, 4–9 with PO Resp. 42–64. Having previously found those arguments unavailing (*see* section II(F), above), we decline to revisit them here.

B. Patent Owner's Motion to Exclude Evidence

Patent Owner filed one motion to exclude evidence. Paper 77. Petitioners opposed (Paper 88) and Patent Owner submitted a reply in support of its motion (Paper 91).

1. *Clark Declaration and Related Evidence*

Patent Owner moves to exclude the declaration of Petitioners' preclinical expert, Robert Clarke, PhD., D.SC. (Exhibit 1086), and the portions of the reply declaration of Petitioners' clinical expert, Dr. Lipton, that rely on Dr. Clarke's testimony (Exhibit 1085 ¶¶ 5, 8, 44, 47, 48, 98-100, 129, 135-139). Paper 77, 1–7; Paper 91, 1–3. In short, Patent Owner argues that Dr. Clarke's testimony should be excluded as irrelevant under FRE 402 because he is not "a clinical or medical oncologist" as required under our definition of a person of ordinary skill in the art. *See e.g.,* Paper 77, 1, 3–4 (further arguing that because he is not a person of ordinary skill in the art, Dr. Clarke's testimony should also be excluded under FRE 403, 602, 801, and 802).

On pages 4–6 of Paper 88, Petitioners persuasively set forth arguments in opposition of Patent Owner's motion, noting for example, that Dr. Clarke's testimony was submitted in direct response to Patent Owner's submission of the declaration of Dr. Kerbel, Ph.D.—also not qualified as a clinical or medical oncologist as set forth under our definition of one of ordinary skill in the art. *See* Paper 88, 2. Petitioners further points to Dr. Clarke's extensive experience in relevant preclinical research, history of collaboration with those of ordinary skill in the art, and that both Dr. Kerbel and Dr. Tannenbaum rely on Dr. Clarke's publications to support their own opinions. *See id.* at 2–4. Moreover, there is no requirement that the Board exclude the testimony of an expert that does not qualify as one of ordinary skill in the art. To the contrary, as recently noted in the August 13, 2018 update to our Trial Practice Guide:

> 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. There is, however, no requirement of a perfect match between the expert's experience and the relevant field. *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." *Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1363–64 (Fed. Cir. 2008).

See Notice of Update to Office Patent Trial Practice Guide, 83 Fed. Reg. 156, (Aug. 13, 2018) (text of update available at https://www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf).

In sum, we agree with Petitioners that Dr. Clarke is qualified to provide expert testimony on the relevant art, his testimony is highly relevant to issues raised in this proceeding, and Patent Owner's objections go to the weight, not admissibility of this testimony. *See* Paper 88, 6. Accordingly, we deny Patent Owner's motion to exclude Exhibit 1086 and Exhibit 1085 ¶¶ 5, 8, 44, 47, 48, 98–100, 129, and 135–139.

2. *Evidence Concerning Surrogate Endpoints*

Patent Owner moves to exclude Exhibit 1080, as well as select paragraphs of Dr. Lipton's reply declaration (Ex. 1085 ¶¶ 53, 77, 99, and 163) and Dr. Clarke's Declaration (Ex. 1086 ¶¶ 78, 132–136, and 162), all of which relate to Petitioner's argument that one of ordinary skill in the art would understand that response rates in clinical and preclinical studies were used as "surrogate endpoints" for time to disease progression. Paper 77, 4–7; *see also* Paper 91, 3. Patent Owner argues that we should exclude this evidence as untimely because Petitioners raised it for the first time in their reply, "after which PO had no opportunity to respond." *Id.*

We do not find Patent Owner's arguments persuasive for the reasons set forth in Petitioners' opposition (Paper 88, 8–11), which we adopt. In particular, we agree with Petitioners that in the Petition, it "relied on the 'response rate' disclosures of Baselga '94 and '96 as providing a POSA with a reasonable expectation of achieving an extension of TTP." Paper 88, 9 (citations omitted).

And, in response to Patent Owner's argument that "Petitioners have not explained how a POSA 'could have translated the response rate data in the prior art to the time of disease progression results," Petitioners reasonably responded with rebuttal evidence identifying response rate as a surrogate endpoint for time to disease progression. *See id.* at 9–10 (citations omitted). *See Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1077–78 (Fed. Cir. 2015) (holding that a petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability, but may submit directly responsive rebuttal evidence in support of its reply); *Ericsson Inc. v. Intellectual Ventures I LLC*, No. 2017-1521, 2018 WL 4055815, at *6 (Fed. Cir. Aug. 27, 2018) (Board improperly refused to consider Reply testimony that "merely expands on a previously argued rationale").

Accordingly, we deny Patent Owner's motion to exclude Exhibit 1080, Ex. 1085 ¶¶ 53, 77, 99, and 163, and Ex. 1086 ¶¶ 78, 132–136, 162.

3. *Foreign Patent Office Documents*

Patent Owner requests that we "exclude certain foreign patent office documents (Exhibits 1004, 1026, and 1049)" under FRE 402 and/or 403. Paper 77, 7–8; *see also* Paper 91, 3–4. Patent Owner contends that the records of "these foreign proceedings are irrelevant to the issues to be decided in this IPR, which involves a different patent with different claims adjudicated under different law." Paper 77, 7. According to Petitioners, the disputed Exhibits were merely cited "to satisfy Petitioners' obligation to identify 'related matters' in its mandatory notices." Paper 88, 11.

While we agree with Patent Owner that Petitioners' obligation to identify related matters under 37 C.F.R. § 42.8(b) contains "no requirement to formally submit other court judgements as evidence" (see Paper 91, 4), we do not rely on

Exhibits 1004, 1026, or 1049 and, therefore, deny this portion of Patent Owner's motion as moot.

4. *Lottery Article*

Patent Owner requests that we exclude Exhibit 1090, an LA Times article from 1996 entitled, *A Lottery of Life, Death —And Hope* ("the Lottery article"), along with portions of Dr. Lipton's reply declaration relating to it (Ex.1085 ¶¶ 107, 132). Paper 77, 8–10; *see also* Paper 91, 4–5. According to Patent Owner, the Lottery article "is not relevant to the issues to be decided in this case," "its probative value is outweighed by the risk of confusing the issues (FRE 403)" and it comprises "hearsay from a declarant (Dr. Slamon) who [Patent Owner] was not given an opportunity to depose (FRE 801, 802)." *Id.*

We do not find Patent Owner's arguments persuasive for the reasons set forth on pages 12–13 of Petitioners' reply brief (Paper 88), which we adopt. Most particularly, we agree with Petitioners that the Dr. Lipton's discussion of the Lottery article is relevant because it responds to a position taken by Patent Owner's expert, Dr. Tannenbaum. *See* Paper 88, 12.

Patent Owner has also not adequately explained why this panel would find this discussion so confusing as to warrant exclusion under FRE 403. Nor has Patent Owner persuaded us that the quotation cited in the Lottery article should be excluded as hearsay, insofar as Petitioners and their expert reference it for the non-hearsay purpose of showing what a person of ordinary skill in the art would have known as of the date of the invention. Accordingly, we deny Patent Owner's motion with respect to Exhibit 1090 and Exhibit 1085, paragraphs 107 and 132.

5. *Sliwkowski and Kerbel Patents*

Patent Owner requests that we exclude Exhibit 1076 ("the Sliwkowski Patent" and Exhibit 1077 ("the Kerbel Patent") as irrelevant under FRE 402 or, in

the alternative, as "tend[ing] to mislead and confuse the issues" in contravention of FRE 403. Paper 77, 10–12; *see also* Paper 91, 5. Patent Owner has not explained, nor do we discern, how the Board might be misled or confused by the Sliwkowski and Kerbel Patents, and Patent Owner's relevance argument goes to the weight we might accord those references rather than their admissibility. Moreover, Petitioners have adequately explained the relevance of these exhibits to the present case. *See* Paper 88, 14–15. Accordingly, we deny Patent Owner's motion with respect to Exhibits 1076 and 1077.

C. Petitioners' Motions to Exclude Evidence Relating to Exhibit 2135 and Exhibit 2145

Petitioners filed a first motion to exclude evidence. Paper 81. Patent Owner opposed (Paper 86) and Petitioners submitted a reply in support of its first motion (Paper 93). Petitioners filed a second motion to exclude evidence. Paper 98. Patent Owner opposed (Paper 100) and Petitioners submitted a reply in support of their second motion (Paper 101).

In its first motion, Petitioners seek to exclude paragraphs 11–14, 16–17, and 31–32 of Dr. Tannenbaum's Supplemental Declaration (Ex. 2144) as "improperly seeking to recant" her prior testimony. Paper 81, 11–13. We agree with Patent Owner that any inconsistencies between Dr. Tannenbaum's deposition testimony and expert reports go to weight, not admissibly and, moreover, Petitioners were afforded the opportunity to address those issues in their sur-reply. *See* Paper 86, 14. Accordingly, we deny this portion of Petitioners' first motion on its merits.

The remainder of Petitioners' first motion seeks to exclude the Hsu Abstract (Ex. 2135), and Patent Owners' evidence attempting to authenticate and prove the publication date of that document, including the deposition testimony from IPR2017-01122 of Dr. Robert Earhart, M.D. Ph.D., who is not retained by any

party to this proceeding. Petitioners' second motion is similarly directed to Exhibit 2146, an abstract book containing a copy of the Hsu Abstract.

As set forth in section II(E)(3), we do not find persuasive Patent Owner's evidence regarding the substance of Hsu. Accordingly, and taking no position as to the merits of the parties' arguments relating to the admissibility of the Hsu references, we deny this portion of Petitioners' motion as moot. *See* Ex. 2135; Ex. 2145; Ex. 2143 ¶¶ 25; and Ex. 2144 ¶ 33.

D. Motions to Seal

The parties, collectively, filed five unopposed motions to seal. Papers 8, 48, 74 (by Patent Owner); Papers 65, 79 (by Petitioners).

The Board's standards for granting motions to seal are discussed in *Garmin International v. Cuozzo Speed Technologies, LLC*, IPR2012-00001 (PTAB Mar. 14, 2013) (Paper 34). In summary, there is a strong public policy for making all information filed in *inter partes* review proceedings open to the public, especially because the proceeding determines the patentability of claims in an issued patent and, therefore, affects the rights of the public. *Id*. at slip op. 1–2. Under 35 U.S.C. § 316(a)(1) and 37 C.F.R. § 42.14, the default rule is that all papers filed in an inter partes review are open and available for access by the public; a party, however, may file a concurrent motion to seal and the information at issue is sealed pending the outcome of the motion. It is only "confidential information" that is protected from disclosure. 35 U.S.C. § 316(a)(7); *see* Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,760 (Aug. 14, 2012). The standard for granting a motion to seal is "for good cause." 37 C.F.R. § 42.54(a). The party moving to seal bears the burden of proof in showing entitlement to the requested relief, and must explain why the information sought to be sealed constitutes confidential information. 37 C.F.R. § 42.20(c).

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

As an initial matter, Patent Owner avers that the parties have agreed to be bound by the "Modified Default Standing Protective Order set forth in Exhibit 2036." Paper 8, 1. Upon review of the motion we determine that the parties have identified sufficiently how the proposed Stipulated Protective Order departs from the Board's default protective order set forth in the Office Patent Trial Practice Guide, 77 Fed. Reg. 48756, 48769–71 (Aug. 14, 2012). Paper 8, 1–2; *see also* Ex. 2093 (comparing the proposed Stipulated Protective Order to the Board's default protective order). We find that the parties have shown sufficiently good cause for the proposed modifications from the Board's default protective order and that the proposed Stipulated Protective Order is warranted. The motion for entry of the Modified Default Standing Protective Order is granted.

In Paper 8, Patent Owner seeks to seal the confidential version of its Patent Owner Preliminary Response (Paper 7), Exhibits 2001, 2007, and 2008; and Exhibits 2002–2004. 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 our final Decision, Patent Owner's request is granted.

In Paper 48, Patent Owner seeks to seal the confidential version of the Declaration of Stephanie Mendelsohn (Exhibit 2069), which purports to authenticate Exhibits recited in Paper 8. Patent Owner has shown good cause

supporting the motion. Insofar as none of the material sought to be protected is relied on in our final Decision, Patent Owner's request is granted.

In Paper 74, 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 our final Decision, Patent Owner's request is granted.

In Papers 65 and 79, Petitioners seek to seal the confidential versions of their Opposition to Patent Owner's Motion to Amend (Paper 66); Reply to Patent Owner's Response (Paper 68), Surreply to Patent Owner's Reply in Support of its Motion to Amend (Paper 80), Reply Declaration of Allan Lipton, M.D. (Ex. 1085), Surreply Declaration of Allan Lipton, M.D. (Ex. 1099), and the Transcript of the Deposition of Susan Tannenbaum, M.D. (Ex. 1087). Petitioners seek to seal these documents because they "contain references to subject matter filed under seal by Patent Owner." Paper 65, 2; *see also* Paper 79, 1. Petitioners provide no other justification for why the redacted portions of the cited documents should be kept confidential and, thus, fail to satisfy the good cause requirement. Accordingly, Petitioners' motions are denied.

Patent Owner is invited to file, within 14 days of this Decision, a motion to seal any presently redacted portion of Paper 66, Paper 68, Paper 80, Exhibit 1085, Exhibit 1099, and/or Exhibit 1087. The motion must explain why the information sought to be protected is truly confidential and attest that such information is not directly or indirectly relied on in our final Decision. Petitioner may respond within one week of Patent Owner's motion, if desired. The Exhibits and Petitioner's Reply will remain designated Board and Parties Only for 21 days from this Decision or until consideration of any such motion and reply.

IV. CONCLUSION

After considering Petitioners' and Patent Owner's arguments and evidence, we conclude that Petitioners have shown, by a preponderance of the evidence, that claims 1–17 of the '549 patent would have been obvious over the combinations of Baselga '97, Gelmon, Drebin, and Presta set forth in Grounds 1–3 and the combinations of Baselga '96, Baselga '94, Gelmon, Drebin, and Presta set forth in Grounds 4–6.

Based on the evidence of record, we conclude that proposed amended claims 18–20 are not patentable over the art of record. The parties' motions to exclude evidence and to seal are addressed in the following Order.

V. ORDER

In consideration of the foregoing, it is:

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

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

FURTHER ORDERED that Patent Owner's motion to exclude Exhibit 1080; Exhibit 1085, paragraphs 5, 8, 44, 47, 48, 53, 77, 98-100, 129, 135–139, and 163; and the entirety of Exhibit 1086, including paragraphs 78, 132–136, and 162, is denied.

FURTHER ORDERED that Patent Owner's motion to exclude Exhibits 1004, 1026, and 1049 is denied as moot.

FURTHER ORDERED that Patent Owner's motion to exclude Exhibit 1090; Exhibit 1085, paragraphs 107 and 132; Exhibit 1076; and Exhibit 1077 is denied.

FURTHER ORDERED that Petitioners' motion to exclude Exhibit 2144, paragraphs 11–14, 16–17, and 31–32 is denied.

FURTHER ORDERED that Petitioners' motion to exclude Exhibit 2135; Exhibit 2145; Ex. 2143 paragraph 25; and Ex. 2144 paragraph 33 is denied as moot.

FURTHER ORDERED that the Modified Default Standing Protective Order set forth in Exhibit 2036 is entered and shall govern the conduct of this proceeding.

FURTHER ORDERED that Patent Owner's motions to seal confidential versions of Paper 7, and Exhibits 2001, 2007, 2008, 2069, 2144, 2141, and 2142 are granted.

FURTHER ORDERED that Petitioners' motions to seal confidential versions of Paper 66, Paper 68, Paper 80, and Exhibits 1085, 1099, and 1087 are denied. Within 14 days of this Decision, Patent Owner may file a motion to seal any presently redacted portions of these documents. Any such motion must explain why the information sought to be protected is truly confidential and attest that such information is not directly or indirectly relied on in this Decision. Petitioner may file a response within one week of Patent Owner's motion. The Exhibits and Papers will remain designated Board and Parties Only for 21 days from the date of this Decision or until consideration of any such motion and reply.

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

PETITIONERS:

For Hospira, Inc.:

Amanda Hollis
Stefan M. Miller
Benjamin A. Lasky
Sarah K. Tsou
Mark C. McLennan
Christopher J. Citro
Kirkland & Ellis LLP
amanda.hollis@kirkland.com
stefan.miller@kirkland.com
benjamin.lasky@kirkland.com
sarah.tsou@kirkland.com
mark.mclennan@kirkland.com
christopher.citro@kirkland.com

For Samsung Bioepis Co., Ltd.:

Dimitrios T. Drivas
Scott T. Weingaertner
Amit H. Thakore
Eric Majchrzak
White & Case LLP
ddrivas@whitecase.com
scott.weingaertner@whitecase.com
athakore@whitecase.com
eric.majchrzak@whitecase.com

PATENT OWNER:

David L. Cavanaugh
Lauren V. Blakely
Robert J. Gunther, Jr.
Lisa J. Pirozzolo
Kevin S. Prussia

Andrew J. Danford
Robert Galvin
Wilmer Cutler Pickering Hale and Dorr LLP
david.cavanaugh@wilmerhale.com
lauren.blakely@wilmerhale.com
robert.gunther@wilmerhale.com
lisa.pirozzolo@wilmerhale.com
kevin.prussia@wilmerhale.com
andrew.danford@wilmerhale.com
robert.galvin@wilmerhale.com

Adam R. Brausa
Daralyn J. Durie
Durie Tangri LLP
abrausa@durietangri.com
ddurie@durietangri.com