2019-1265

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

GENENTECH, INC.,
APPELLANT,
v.

ANDREI IANCU, DIRECTOR,
U.S. PATENT AND TRADEMARK OFFICE
INTERVENOR.

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in IPR2017-00737; IPR2017-01960

BRIEF FOR INTERVENOR

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REPRESENTATIVE CLAIM

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.

Appx88 33:38-45 (disputed limitation emphasized).

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STATEMENT OF RELATED CASES

The Director is not aware of any other appeal from the Patent Trial and Appeal Board ("the Board") of the United States Patent and Trademark Office ("the USPTO") in the same proceeding previously before this Court or any other court. The following cases will directly affect or be directly affected by the Court's decision in the pending appeal: *Genentech, Inc. v. Amgen Inc.*, No. 1:18-cv-00924 (D. Del.); *Genentech, Inc. v. Iancu*, No. 19-1263 (Fed. Cir.); *Genentech, Inc. v. Iancu*, No. 19-1267 (Fed. Cir.); and *Genentech, Inc. v. Iancu*, No. 19-1270 (Fed. Cir.).

The table below summarizes the four companion appeals:

Appeal	Patent	Claims	Prior art in Ground	IPR
19-1263	'441	1-14	Baselga '94 and '96	2017-00731
19-1265	'549	1-17	Gelmon and Baselga '97; Gelmon and Baselga '94 and '96	2017-00737; 2017-01960
19-1267	'441	1-14	Baselga '96, Seidman '96, and Taxol® PDR	2017-01121; 2017-02063
19-1270	'549	1-11, 14-17	Baselga '96, Seidman '96, Pegram, and Taxol® PDR	2017-01122

STATEMENT OF THE ISSUES

Genentech's '549 patent claims a method of treating HER2-overexpressing breast cancer by administering a combination of drugs already known to treat such cancers: paclitaxel, Herceptin, and a further growth inhibitory agent. The claims also recite an efficacy effect: the claimed drug combination is administered in an amount effective "to extend the time to disease progression [TTP]." Missing from the claims, however, is a comparator for this claimed efficacy; the drug combination extends TTP compared to what? Following an *inter partes* review, the Board found the claims obvious based on either of two comparators: untreated patients or patients treated with paclitaxel alone.

First, the Board construed the claims' comparator as untreated patients. The Board based its construction on Genentech's unambiguous statement during prosecution that the claimed drug combination extends TTP "relative to an untreated patient." The first issue on appeal is whether the Board correctly construed the claims based on Genentech's own proffered construction during prosecution. Genentech does not challenge the Board's obviousness decision under this construction.

Alternatively, the Board found the claims obvious even under Genentech's construction of the comparator as paclitaxel alone. The Board found

that the prior art teaches that Herceptin (1) is clinically effective in treating HER2-overexpressing breast cancer, with an unusually long TTP; (2) enhances the clinical efficacy of cisplatin (a growth inhibitor); (3) markedly potentiates paclitaxel's antitumor effect in preclinical studies; and (4) is being tested clinically with paclitaxel to assess TTP compared to paclitaxel alone. Based on these teachings, the Board found that a skilled artisan would have combined Herceptin with paclitaxel and cisplatin to treat HER2-overexpressing breast cancer with a reasonable expectation that the drug combination would extend TTP compared to paclitaxel alone. An alternate issue on appeal is thus whether substantial evidence supports the Board's reasonable-expectation finding under Genentech's construction.

STATEMENT OF THE CASE

This appeal arises from an *inter partes* review of Genentech's U.S. Patent No. 7,892,549 ("the '549 patent"). The Board decided that claims 1-17 of the '549 patent were obvious on several grounds. Appx8-9. Relevant here, the Board found independent claim 1 obvious over Gelmon[1] and Baselga

[1] Gelmon et al., *Phase I/II Trial of Biweekly Paclitaxel and Cisplatin in the Treatment of Metastatic Breast Cancer*, 14(4) J. Clin. Oncol. 1185-91 (1996). Appx4132-4146.

'97[2] (Ground 1) or Gelmon, Baselga '96[3], and Baselga '94[4] (Ground 4). Genentech appealed the Board's decision to this Court, after which the parties settled and the petitioners, Hospira Inc. and Samsung Bioepis Co., dropped out. The Director intervened in this appeal to defend the Board's decision. *See* 35 U.S.C. § 143.

I. Background

A. Paclitaxel, Herceptin, and cisplatin were all known to treat HER2-overexpressing breast cancer

The '549 patent relates to treating diseases that overexpress ErbB2 (also known as HER2), including breast cancer. Appx72 1: 22-30; Appx74 5:17-25. HER2-overexpressing breast cancers commonly have a poor prognosis and may be resistant to chemotherapeutics, including anthracyclines, which were standard therapies for breast cancer in the mid-1990s. Appx73 3:43-51; Appx13506-13507. The chemotherapeutic paclitaxel (Taxol®), in

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[2] Baselga et al., *HER2 Overexpression and Paclitaxel Sensitivity in Breast Cancer: Therapeutic Implications*, 11(3) (Suppl. 2) Oncology 43-48 (1997). Appx1094-1104.

[3] Baselga et al., *Phase II Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients with HER2/* neu-*Overexpressing Metastatic Breast Cancer*, 14 J. Clin. Oncol. 737-744 (1996). Appx 1073-1088.

[4] Baselga et al., *Anti-HER2 Humanized Monoclonal Antibody (MAb) Alone and in Combination with Chemotherapy Against Human Breast Carcinoma Xenografts*, 13 Proc. Am. Soc. Clin. Oncol. 63 (Abstract53) (1994). Appx1089-1092.

contrast, not only showed significant antitumor activity against breast cancer in general, but also was reported in the mid-1990s to be particularly effective against HER2-overexpressing breast cancer. Appx1100-1101. Specifically, HER2-positive patients responded clinically to paclitaxel treatment at three times the rate of HER2-negative patients. Appx73 3:52-56.

Another treatment for HER2-positive breast cancer also appeared in the mid-1990s: Herceptin. Appx73 3:36-42. Herceptin is a recombinant humanized version of the mouse anti-ErbB2 antibody 4D5 (humanized MAb 4D5). Appx72 2:4-31; Appx73 3:36-42. It targets HER2-overexpressing cells and acts clinically to treat HER2-positive breast cancer. Appx73 3:36-42. Specifically, Baselga '96 reports the results of a phase II clinical trial to treat HER2-overexpressing metastatic breast cancer patients, finding Herceptin "remarkably well tolerated" and clinically effective. Appx1081; Appx1083. The study reports minimal toxicity and a remission rate of 11.6% (5 out of 43 assessable patients). Appx1084. And it reports that 37% of patients (16 patients) achieved minimal responses (4.6%) or stable disease (32.6%), with a median TTP of 5.1 months, which Baselga '96 characterizes as "unusually long." Appx1084; Appx1085.

Baselga '96 also teaches the combination of Herceptin with other antitumor agents, including paclitaxel and cisplatin. Appx1087. Baselga '96

states that in preclinical studies, both *in vitro* and in xenografts, Herceptin markedly potentiated the antitumor effects of paclitaxel and of cisplatin without increasing their toxicity. Appx1087. Baselga '94 describes the preclinical xenograft studies with paclitaxel. Appx1092. In this mouse model, treatment with either Herceptin or paclitaxel alone produced a 35% inhibition of tumor growth, while combination treatment resulted in "major antitumor activity," with 93% growth inhibition. Appx1092. Based on these results, Baselga '94 and Baselga '96 both report that clinical trials of the combination therapy were underway. Appx1087; Appx1092.

Baselga '97 is a review article of studies aimed at treating HER2-overexpressing breast cancer. Appx1099. These studies include the two earlier studies reported in Baselga '94 and '96. Appx1102. Baselga '97 credits the positive results from the earlier Baselga studies with leading to a phase III clinical trial of Herceptin and paclitaxel to treat HER2-overexpressing breast cancer. Appx1103. Baselga '97 discloses that this ongoing phase III trial includes a paclitaxel control arm and a TTP endpoint. Appx1103. The trial thus seeks to measure the TTP of combination Herceptin-paclitaxel therapy compared to paclitaxel alone. Appx1103, Figure 2.

By the time of the phase III trial reported in Baselga '97, both Herceptin and paclitaxel had been tested clinically with cisplatin. Specifically,

Baselga '97 describes a phase II study by Pegram of Herceptin and cisplatin to treat HER2-overexpressing breast cancer. Pegram reports that adding Herceptin to cisplatin increased response rates compared to cisplatin alone without any apparent increase in toxicity. Appx1102 (describing Appx1375-1379). According to Baselga '97, the 25% response rate with Herceptin-cisplatin therapy "suggest[s] that the synergy observed in the laboratory was reproducible in the clinic." Appx1103. Similarly, Gelmon conducted a phase I/II trial of paclitaxel and cisplatin in metastatic breast cancer patients, reporting that, while paclitaxel and cisplatin individually show response rates of 17-62%, the combination resulted in an 85% response rate. Appx4140.

B. The '549 patent claims treating HER2-overexpressing breast cancer with a combination of Herceptin, paclitaxel, and cisplatin to increase efficacy

The '549 patent specification reports the results of a phase III clinical trial of Herceptin and chemotherapy, including paclitaxel, to treat HER2-overexpressing breast cancer. Appx85-86 27:14-30:25. The trial's endpoints included response rate and TTP. Appx86 29:13-17; *see also* Appx76 10:47-49. While the TTP for paclitaxel alone (T) was 4.2 months, combination paclitaxel-Herceptin therapy (T+H) achieved a TTP of 7.1 months. Appx86 30:1-12. In addition to Herceptin and paclitaxel, the phase III trial tested Herceptin-anthracycline/cyclophosphamide therapy (AC+H) and the latter

alone (AC). Appx86 29:20-26. The specification also discloses cisplatin as a further growth inhibitory agent. *See* Appx77 11:34.

The patent claims treating patients with HER2-overexpressing breast cancer by administering a combination of an anti-ErbB2 antibody (e.g., Herceptin), a taxoid (e.g., paclitaxel), and a further growth inhibitory agent (e.g., cisplatin). The claims also require that the administration be of an amount effective to extend the TTP (the claimed efficacy effect). Appx88. Claim 1, reproduced below, is representative on appeal.

> 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.

Appx88 33:38-45 (disputed limitation emphasized).

During prosecution of the '549 patent's parent application,[5] the examiner rejected the claims as indefinite based on the lack of a comparator for the limitation "extend the [TTP]." Appx11001-11004; Appx11015 (then-

[5] The '549 patent issued from a continuation application of the 09/208,649 application in which the rejection and the response described here occurred. Appx4; Appx14; Br. at 15-16.

pending claim 1). Specifically, the examiner asked applicant Genentech to pick a comparator: "[I]s 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?" Appx11004. In response, Genentech chose untreated patients: "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*." Appx11016-11017 (emphasis added). In the next action, the examiner withdrew the rejection. *See* Appx11024. The patent later issued.

II. The Board's Obviousness Decision

In its final written decision following *inter partes* review of the '549 patent, the Board construed the challenged claims and concluded that they were obvious. Appx11-40. Alternatively, the Board found the claims obvious even under Genentech's construction. Appx40-46.

Starting with claim construction, the Board interpreted the limitation "extend the [TTP]" as being compared to a patient receiving no treatment. Appx13. The Board relied on Genentech's unequivocal statement during prosecution that the claimed drug combination extends TTP "relative to an untreated patient." Appx15 (quoting Appx11017).

The Board rejected Genentech's counterarguments. The Board disagreed that its construction was inconsistent with the specification because the specification's phase III clinical trial discloses extending TTP relative to paclitaxel alone. Appx15-16. Pointing to testimony from Genentech's expert that "cancer generally continues to progress without treatment," the Board found that a skilled artisan would have understood that administering the claimed drug combination would extend TTP compared to an untreated patient. Appx16 (quoting Appx9079 ¶ 136). The Board also disagreed that, in the context of the specification, Genentech's selection of "untreated patient" during prosecution referred to a patient treated with paclitaxel alone. To the Board, the relevant context encompassed the examiner's explicit list of possible comparators—e.g., untreated patients *or* treatment with a taxoid alone—from which Genentech unambiguously chose an untreated patient. Appx16. Finally, the Board was unpersuaded that "untreated patients" makes no sense in the context of a disease like breast cancer, explaining that Genentech chose this definition to obtain the '549 patent with reasonable clarity, deliberateness, and precision, and the Board must give that choice effect even if it leads to a nonsensical result. Appx17.

Turning to obviousness, the Board found that Gelmon and Baselga '97 or Gelmon, Baselga '94, and Baselga '96 collectively teach administering a

combination of Herceptin, paclitaxel, and cisplatin to treat HER2-overexpressing breast cancer. Appx22-31; Appx32-40. The Board also found that an ordinary artisan would have reasonably expected that administering an effective amount of the drug combination would extend TTP compared to untreated patients. Appx24-25; Appx26.

Alternatively, the Board found a reasonable expectation of success even under Genentech's construction, i.e., compared to treatment with paclitaxel alone. Appx40-46. The Board relied on Baselga '96's disclosure of a median TTP for Herceptin of 5.1 months, which Baselga '96 characterized as "unusually long." Appx42. The Board also relied on Baselga '96's disclosure that based on Baselga '94's xenograft studies showing that Herceptin markedly potentiated paclitaxel's antitumor effect without increasing toxicity, clinical trials of combination Herceptin-paclitaxel therapy had begun. Appx42. And the Board relied on Baselga '97's description of such an ongoing clinical trial: a phase III trial to compare Herceptin-paclitaxel therapy to standalone paclitaxel, with TTP as a primary endpoint. Appx42. Based on these teachings, the Board concluded that a skilled artisan would have expected Herceptin to extend TTP compared to paclitaxel alone. Appx42.

The Board rejected Genentech's attacks on Baselga '94 as a preclinical study unable to predict efficacy in humans and Baselga '97 as lacking clinical results from the Herceptin-paclitaxel phase III trial. Appx39. As the Board explained, skilled artisans *did* rely on Baselga '94's preclinical results as a motivation to proceed with human trials, including Genentech (Appx37; Appx39), and conclusive clinical proof of efficacy is not necessary to show obviousness (Appx43). The Board also rejected Genentech's data on the high failure rate of oncology drugs in phase III clinical trials. According to the Board, the data based success on FDA approval of individual compounds—i.e., new chemical entities and biologics—which for an obviousness analysis of a specific pharmaceutical combination of already approved and promising therapies was "irrelevant." Appx43-44.

Finally, the Board relied on the positive response rates in Baselga '96 for Herceptin and in Baselga '94 for Herceptin and paclitaxel as further support for a finding of a reasonable expectation of success. Appx46. The Board noted that the '549 patent suggests response rate and TTP are alternative measurements of drug efficacy. Appx45. And the Board credited petitioners' expert testimony that tumor response rates in mice (i.e., 93% for Herceptin-paclitaxel therapy compared to 35% for each drug alone) provide a reasona-

ble expectation of a clinical benefit, e.g., an extension of TTP, in human patients. Appx44-45. Accordingly, the Board concluded that the claims of the '549 patent would have been obvious even under Genentech's construction of the comparator as paclitaxel alone.

Genentech appealed the Board's decision to this Court. The Court has jurisdiction under 35 U.S.C. § 319 and 28 U.S.C. § 1295(a)(4)(A).

SUMMARY OF THE ARGUMENT

Genentech does not dispute much of the Board's obviousness decision. Genentech does not dispute that, based on the prior art, a skilled artisan would have combined Herceptin, paclitaxel, and cisplatin to treat HER2-overexpressing breast cancer as claimed. Nor does Genentech dispute that a skilled artisan would have reasonably expected the claimed drug combination to extend TTP compared to untreated patients. Rather, Genentech challenges the Board's construction of the claims' comparator as untreated patients. And Genentech challenges the Board's alternate finding of a reasonable expectation of success under Genentech's construction of the claims' comparator: treatment with paclitaxel alone. Neither challenge has merit.

Genentech unambiguously defined the comparator during prosecution as untreated patients. Untreated patients does not mean patients *treated* with paclitaxel, as Genentech now asserts. During prosecution, as part of

an indefiniteness rejection, the examiner provided a list of possible comparators. That list included untreated patients *or* patients treated with a taxoid (e.g., paclitaxel) alone. Genentech selected "an untreated patient." Genentech was free to draft its claims to recite a paclitaxel comparator. But, with reasonable clarity, deliberateness, and precision, it did not. The Board's claim construction, and thus its obviousness decision under that construction, should be affirmed.

Alternatively, the Board found a reasonable expectation that the claimed drug combination would also extend TTP compared to paclitaxel alone. The Board relied on Baselga '96's disclosure of an unusually long 5.1-month extension of TTP for Herceptin and on Baselga '96's report of an ongoing clinical trial of Herceptin-paclitaxel therapy, which was greenlighted by Baselga '94's preclinical studies showing that Herceptin markedly potentiated paclitaxel's antitumor effect without increasing toxicity. The Board also relied on Baselga '97's report of an ongoing phase III clinical trial of Herceptin-paclitaxel therapy designed to assess TTP of the drug combination compared to paclitaxel alone. As further support, the Board relied on the positive response rates reported both in Baselga '96 for Herceptin and in Baselga '94 for Herceptin with paclitaxel. Substantial evidence thus supports the Board's reasonable-expectation finding.

Genentech's attacks on each Baselga reference individually fall flat. Genentech first argues that the Board erred in relying on the mere existence of Baselga '97's reported phase III trial without any results. Not so. Genentech not only ignores the prior-art context, with Baselga '94 and '96's results prompting the clinical trial, but also misjudges the legal standard as requiring clinical certainty. Next, for Baselga '96, the Board properly relied on it as showing, in the context of the prior art as a whole, a 5.1-month *extension* of TTP for Herceptin and thus a reasonable expectation that Herceptin-paclitaxel therapy would extend TTP compared to paclitaxel alone. Genentech's challenge to the 5.1 months specifically comes for the first time on appeal; the argument is waived. Finally, the Board properly relied on Baselga '94's preclinical studies. Baselga '94's whole purpose was to predict the efficacy of combination Herceptin-paclitaxel therapy in humans, and skilled artisans, including Genentech, relied on its studies to do just that.

At bottom, Genentech believes that because there were no clinical results *proving* that the claimed drug combination extends TTP compared to standalone paclitaxel in humans, its claims cannot be obvious. Absolute certainty, however, is not the standard for a reasonable expectation of success. The Board's obviousness decision should be affirmed.

STANDARD OF REVIEW

Genentech bears the burden of showing that the Board committed reversible error. *In re Watts*, 354 F.3d 1362, 1369 (Fed. Cir. 2004). Claim construction based on the intrinsic record is a question of law. *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 840-42 (2015). Obviousness under 35 U.S.C. § 103 is a legal conclusion based on underlying findings of fact. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 417 (2007); *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 978 (Fed. Cir. 2014). The Federal Circuit has held that a reasonable expectation of success is a question of fact. *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1328 (Fed. Cir. 2018).

This Court reviews the Board's legal conclusions *de novo* and the Board's factual findings for substantial evidence. 5 U.S.C. § 706(2)(E); *In re Gartside*, 203 F.3d 1305, 1315 (Fed. Cir. 2000). Substantial evidence is "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *Universal Camera Corp. v. NLRB*, 340 U.S. 474, 477 (1951) (quoting *Consol. Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938)). "Where two different conclusions may be warranted based on the evidence of record, the Board's decision to favor one conclusion over the other is the type of decision that must be sustained by this court as supported by substantial evidence."

In re Bayer Aktiengesellschaft, 488 F.3d 960, 970 (Fed. Cir. 2007) (citing *In re Jolley*, 308 F.3d 1317, 1329 (Fed. Cir. 2002)).

ARGUMENT

I. The Claims of the '549 Patent Would Have Been Obvious

The Board properly concluded that the claims of the '549 patent would have been obvious. First, the Board correctly construed the claim term "extend the [TTP]" as compared to untreated patients, the comparator Genentech expressly chose during prosecution. Genentech does not contest obviousness under the Board's construction. Alternatively, substantial evidence supports the Board's decision that, even under Genentech's construction, a skilled artisan would have reasonably expected the claimed drug combination to extend TTP compared to paclitaxel treatment alone. The Board's obviousness decision should be affirmed.

A. The Board correctly construed "extend the TTP" as compared to untreated patients based on Genentech's unambiguous statement during prosecution

Claim construction is incomplete without reference to a patent's prosecution history. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 33 (1966); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005) (en banc). "The purpose of consulting the prosecution history in construing a

claim is to exclude any interpretation that was disclaimed during prosecution." *Chimie v. PPG Indus., Inc.*, 402 F.3d 1371, 1384 (Fed. Cir. 2005) (internal quotation marks omitted). Under the broadest reasonable interpretation, which applies in this case,[6] statements made during prosecution can be "relevant as reinforcing the evident meaning of the claim language at issue, whether or not it would meet standards for disclaimer or disavowal." *D'Agostino v. MasterCard Int'l Inc.*, 844 F.3d 945, 949 (Fed. Cir. 2016).

Here, during prosecution, Genentech unambiguously stated that the limitation "extend the time to disease progression" was "[c]learly . . . relative to an untreated patient." Appx15; Appx11017. Genentech argues that the statement does not rise to the level of a clear and unmistakable disclaimer, but was simply "inartful." Appellant's Brief ("Br.") at 22, 25. Yet, the statement could not be more explicit. It directly responded to the examiner's indefiniteness rejection of the phrase "extend the TTP" as a relative

[6] The petition in this IPR was filed on January 20, 2017, before the Board switched the IPR claim-construction standard from the broadest reasonable interpretation to the *Phillips* standard. The rule change applies only to IPR petitions filed on or after the effective date of the final rule, November 13, 2018. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51340 (Oct. 11, 2018).

term undefined by the claims or specification. And it complied with the examiner's request that the applicant pick a comparator: "[I]s 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?" Appx11004. From this list, Genentech selected "an untreated patient." Appx11017. At bottom, Genentech overcame an indefiniteness rejection by picking a specific definition of the comparator for "extend the [TTP]." And the Board properly construed the claims to reflect that choice.

Regretting its selection now, Genentech argues that there is a different reasonable interpretation of untreated patients: patients *treated* with paclitaxel alone. Br. at 24-25. But, in making the rejection, the examiner gave Genentech an explicit choice between possible comparators, one of which was "untreated patients," another of which was "[p]atients who received . . . taxoid alone." Appx11004. And, again, Genentech expressly chose untreated patients. Appx11017. Genentech's additional citations to descriptions of TTP (e.g., "[t]ime to tumor progression (TTP) was calculated from the beginning of therapy to progression") did not render ambiguous its clear statement of what the claimed comparator is. Appx11017 (citing Appx4061; Appx4088-4089); Br. at 25 (citing Appx11017).

This choice also did not create any conflict with the claims or specification, as Genentech implies. Br. at 22-23. First, the claims recite no comparator (hence the indefiniteness problem in the first place), and they are not limited to an FDA-approved clinical study requiring that all patients be treated. *See* Br. at 23. Second, though the specification's phase III trial compared Herceptin and paclitaxel therapy to paclitaxel alone, "cancer generally continues to progress without treatment," as Genentech's own expert opined, and thus the Board found that an ordinary artisan would have understood that the drug combination would also extend TTP compared to untreated patients. Appx16. Genentech does not argue otherwise.

Genentech's reliance on one example in the specification is additionally unpersuasive because the specification discloses that it is a "non-limiting Example." Appx84 26:31-32. While the specification is a helpful guide in construing the claims, "this court will not at any time import limitations from the specification into the claims." *CollegeNet, Inc. v. ApplyYourself, Inc.*, 418 F.3d 1225, 1231 (Fed. Cir. 2005). This is true even if all of the embodiments described in the specification feature the same (unclaimed) limitation. *In re Trans Texas Holdings Corp.*, 498 F.3d 1290, 1298-99 (Fed. Cir. 2007) (explaining that even when every example in the specification used an immediate inflation adjustment, it was improper to incorporate this

limitation into the claims). Moreover, the specification is not as laser focused on a paclitaxel comparator as Genentech asserts. The '549 patent also describes the efficacy of anthracycline/cyclophosphamide treatment alone. Appx86. And, contrary to Genentech's assertion (Br. at 23 n.7), while certain claims exclude anthracycline therapy as the drug *administered*, neither the claims nor the specification exclude it as a *comparator*. Nor does the specification exclude a comparison to untreated patients.

Yet, even if the applicant's earlier-chosen comparator—untreated patients—makes no sense, as Genentech argues now, the fault lies squarely with Genentech. *See* Appx17. Claim interpretation cannot give a term a different construction than did the applicant to avoid a "nonsensical result." Appx17 (quoting *Source Vagabond Sys. Ltd. v. Hydrapak, Inc.*, 753 F.3d 1291, 1301 (Fed. Cir. 2014)). And the "interested public has the right to rely on the inventor's statements made during prosecution." *Fenner Investments, Ltd. v. Cellco P'ship*, 778 F.3d 1320, 1325 (Fed. Cir. 2015). The Board's claim construction should be affirmed.

Genentech does not separately challenge the Board's obviousness decision under the Board's construction of the comparator as untreated patients. Thus, if the Court affirms the Board's construction, the Board's obviousness decision also must be affirmed.

B. Alternatively, the Board correctly decided that the claims would have been obvious even under Genentech's construction of a paclitaxel comparator

Alternatively, the Board decided that even under Genentech's construction of the comparator as paclitaxel alone, the claims would have been obvious over the cited prior art. Genentech limits its challenge of the Board's decision to the Board's finding of a reasonable expectation of success. Br. at 26-27.

1. Substantial evidence backs the Board's findings underlying its conclusion of obviousness

In its final written decision, the Board found a motivation to combine Herceptin, paclitaxel, and cisplatin to treat HER2-overexpressing breast cancer and found, under Genentech's claim construction, a reasonable expectation that the combination would extend TTP (the claimed efficacy) compared to paclitaxel alone. Substantial evidence supports the Board's findings.

The Board first found that the prior art teaches administering a combination of Herceptin, paclitaxel, and cisplatin to treat HER2-overexpressing breast cancer in human patients. *See* Appx25-28; Appx35-39. As the Board found, Baselga '96 teaches that administering Herceptin is safe and clinically effective in treating HER2-overexpressing breast cancer. Appx33-34. Baselga '96 also reports that, in light of Baselga '94's preclinical studies

in which Herceptin markedly potentiated paclitaxel's antitumor effect without increasing toxicity, clinical trials of the combination therapy were underway. Appx35. Baselga '97 elaborates on this, reporting the design of an ongoing phase III clinical trial of Herceptin and paclitaxel to treat HER2-postitive breast cancer. Appx18-20; Appx25. For cisplatin, the Board found that Baselga '97 (via Pegram) and Gelmon disclose clinical trials of cisplatin with Herceptin and paclitaxel, respectively, and both report that the combination increased response rates compared to cisplatin or paclitaxel alone. Appx21; Appx23-26. References that teach combining different drugs that treat the same disease, as here, provide a "clear motivation to combine." *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292-93 (Fed. Cir. 2013). Genentech does not dispute the Board's finding of a motivation to combine.

The Board then found a reasonable expectation that the claimed drug combination would extend TTP when compared to treatment with paclitaxel alone. The Board relied on Baselga '96's disclosure that Herceptin has an "unusually long" 5.1-month TTP, and thus properly concluded that Baselga '96 indicates an extension of TTP with antibody alone. Appx42. The Board also relied on (1) Baselga '96's disclosure that Herceptin markedly potentiated paclitaxel's antitumor response rate in Baselga '94's preclinical work, leading to clinical trials; and (2) Baselga '97's disclosure that the ongoing

phase III trial of Herceptin and paclitaxel would assess the drug combination's TTP compared to paclitaxel alone. Appx42. Based on these teachings and petitioners' expert testimony, including that response rates in mice provide a reasonable expectation of a clinical benefit in human patients, substantial evidence supports the Board's finding that a skilled artisan would have expected the three-drug combination to increase TTP compared to paclitaxel alone. Appx42; Appx44-46.

2. Genentech fails to show error in the Board's reasonable-expectation-of-success finding

Genentech attacks each of the Baselga references as failing to support a finding of a reasonable expectation of success. Br. at 32-39. None of Genentech's arguments shows error in the Board's finding based on the combined teachings of these references. *See In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) ("Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references.").

i. No error in relying on Baselga '97's phase III Herceptin-paclitaxel clinical trial

Genentech first argues that the Board erred in relying on the "mere existence" of a phase III Herceptin-paclitaxel clinical trial, as reported in Baselga '97. Br. at 32. This clinical trial, however, did not materialize out of

thin air. As the Board found, Baselga '96 and '94 collectively teach that Herceptin itself has an unusually long 5.1-month TTP and that Herceptin markedly potentiates paclitaxel's antitumor effect. Appx42. It was these results, as Baselga '97 admits, that led to the phase III trial designed to measure an extension of TTP for Herceptin-paclitaxel therapy compared to a paclitaxel control. Appx42; Appx1103. Taken together, these teachings provide substantial evidence for a reasonable expectation that the drug combination would extend the TTP compared to paclitaxel alone. *See* Appx42 (citing Appx5981-5982 ¶ 76).

Genentech rejects such a conclusion based on the high failure rate of oncology drugs in phase III clinical trials. Br. at 33. Yet, as the Board explained, Genentech's evidence based success on FDA approval, too high a standard for a reasonable expectation of success, and on the industry's general failure rate, which in the context of a *particular* pharmaceutical combination was "irrelevant." Appx43. The Board also found that Genentech's evidence focused on individual compounds, not a combination of FDA-approved or promising therapies with known safety and efficacy in humans, including as two-drug combinations. Appx43-44. Genentech does not argue otherwise. Instead, Genentech asserts that combining Herceptin and paclitaxel created more uncertainty than a single-drug trial. Br. at 33.

Genentech cites nothing for this assertion. Nor does Genentech explain how combining two FDA-approved drugs (paclitaxel and cisplatin) with Herceptin, which had already proven safe and clinically effective, both in humans (including with cisplatin) and in preclinical studies with paclitaxel, could be more uncertain than testing individual oncology drugs in general.

Rather than the Board erring in its reasonable-expectation finding, Genentech misreads the legal standard. Genentech criticizes the Board for relying on Baselga '97's reported phase III trial because it does not report any clinical *results*. Br. at 32-33. But, as the Board explained, [c]onclusive proof of efficacy is not necessary to show obviousness." Appx43 (quoting *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014)). "[T]he expectation of success need only be reasonable, not absolute." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). By demanding absolute certainty for a reasonable expectation of success, Genentech demands too much.

ii. No error in relying on Baselga '96's reported 5.1-month extension of TTP for Herceptin

Genentech next argues that the Board erred in relying on Baselga '96's report of a 5.1-month TTP for Herceptin. Br. at 34-35. First, Genentech argues that Baselga '96 teaches its TTP in isolation, i.e., without a control arm, and thus does not allow any conclusion to be drawn about an *extension*

of TTP as required by Genentech's claims. Br. at 34. Not so. As Baselga '96 reports, Herceptin's TTP of 5.1 months was "unusually long"; it improves TTP compared to expectations. *See* Appx42 (quoting Appx1085). And Baselga '94's preclinical results show that the combination of Herceptin and paclitaxel markedly potentiated tumor responses compared to paclitaxel alone, prompting a phase III trial to assess TTP of Herceptin-paclitaxel therapy compared to paclitaxel alone. Appx42. Thus, in the context of the prior art as a whole, Baselga '96 provides a reasonable expectation that adding Herceptin to paclitaxel (and cisplatin, which clinically enhances paclitaxel's efficacy) would extend the TTP compared to paclitaxel alone. Appx42.

Second, Genentech attacks the Board's reliance on a TTP for Herceptin of 5.1 months specifically, arguing its calculation included just a subset of patients. Br. at 34-35. Genentech, however, never made this argument before the Board. While the petition relied on Baselga '96's 5.1 months to teach extending TTP (Appx13040-13041; Appx13059-13060), Genentech did not argue in its patent owner response that the Board should disregard Baselga '96's reported TTP for Herceptin because it relied on a subset of patients (Appx13535-13536 (dated December 22, 2017)). Now, before this Court, Genentech cites testimony filed with its reply in support of its motion

to amend. Br. at 35 (citing Ex. 2144 (Appx10132-10138) (dated April 20, 2018)); Appx13859 (citing Ex. 2144). This testimony, however, came too late: four months after Genentech's patent owner response. It is also not on point: it states that Baselga '96 relied on a *small* and thus allegedly unreliable patient population, not a *selective* and thus incorrect population. *See* Appx10127-10129. Genentech fails to explain why the Court should take up this fact-bound issue for the first time on appeal. The argument is waived.

Regardless, Genentech's argument lacks merit. Baselga '96 reports the TTP for patients with minor responses and stable baselines. Appx1084. It thus excludes patients with no response, as Genentech notes, potentially skewing the results upward (Br. at 34-35), but it also excludes patients with a tumor response (or remission), and this latter omission would skew the results in the other direction: downward.[7] *See* Appx1085, Table 5. Genentech does not proffer a TTP for Baselga 96's entire patient population. Nor

[7] The study also selected patients who had many sites of metastatic involvement and who had received prior chemotherapy, both factors believed to limit response rates and further skew the results downward. Appx1085; *see also* Appx1087 ("The response to [Herceptin] in a less heavily pretreated population and in those with less extensive metastatic disease would be of interest since both parameters have historically correlated with a higher response to drugs."). Thus, in a less-compromised patient population, the TTP would be expected to be longer.

does the record more broadly explain how (or even if) skilled artisans measure TTP for non-responders. The '549 patent provides no guidance, though it too reports a significant number of non-responders. *See* Appx86. It is thus far from clear that measuring TTP for Baselga '96's entire patient population would fail to extend TTP, as Genentech argues (Br. at 35), or that it was unreasonable to rely on the TTP reported in Baselga '96. And, again, Genentech accepted 5.1 months as Herceptin's TTP in its patent owner response. *See* Appx13535-13536. Genentech's new and factually incomplete attack on Baselga '96 should be rejected.

iii. No error in relying on Baselga '94's preclinical study of Herceptin and paclitaxel

Finally, Genentech challenges the Board reliance on Baselga '94's preclinical studies. Genentech first argues that response rates in mouse xenografts cannot predict an extension of TTP in humans. Br. at 35-36. Yet, as the '549 patent states, response rate and TTP are both measures of drug efficacy. Appx76 10:47-49; *see* App45. The Board then credited testimony from petitioners' expert that a strong antitumor response in mice provides a reasonable expectation of a clinical benefit in human patients. Appx45 (quoting Appx6412-6413 ¶ 133); *see* Appx6383-6384 ¶ 78. In other words, even if not perfectly correlated, "a significant inhibition of tumor growth

would *reasonably* be expected to lead to an extension of time to disease progression." Appx6413 ¶ 134 (emphasis added); *see also* Appx7247-7251 ¶¶ 25-31. Indeed, both Herceptin and paclitaxel alone had a 35% response rate in mice (Appx1092), and an improved TTP in human patients: 5.1 months for Herceptin (Appx1081) and 3.0 or 4.2 months for paclitaxel (*Hospira, Inc. v. Genentech, Inc.*, IPR2017-00731, Paper 120 at 35 (P.T.A.B. Oct. 3, 2018)). A 93% response rate for Herceptin with paclitaxel in mice thus provides a reasonable expectation that the combination would extend TTP compared to paclitaxel alone in humans. While it may be hard to compare mouse tumor response rates to human *months*, as Genentech states (Br. at 36), the claims do not recite a specific TTP in months, just an extension of TTP. The prior art provides a reasonable expectation of an extension.

Genentech disagrees, arguing that preclinical results just do not provide a reasonable expectation of a particular efficacy in humans. Br. at 36-37. Genentech points to a number of limitations with Baselga '94's study. Br. at 37-38. The Board rejected them all. Appx37-39. More importantly, the whole point of Baselga '94's study was to predict efficacy in humans, not to cure cancer in mice. *See* Appx13817-13818 (citing Appx7074 48:11-49:1). As Genentech's expert testified, animal models are "critical for the evaluation

of new agents and therapeutic approaches for the treatment of breast cancer." Appx13817 (quoting Appx5796; Appx6846 195:22-197:2).

Moreover, as the Board found, skilled artisans *did* consider Baselga '94 relevant to clinical efficacy. Appx36-37 (citing Appx5781 (explaining that Baselga '94's "data provide [a] motivation for clinical evaluation"); Appx5793 (describing Baselga '94's data as "the basis for a planned clinical trial in patients")); Appx39. These skilled artisans included Genentech. As Genentech admitted, it relied on Baselga '94's study to help justify its phase III Herceptin-paclitaxel clinical trial to the FDA. Appx37. Specifically, Genentech represented that based on Baselga '94, "[i]t is anticipated that . . . the addition of [Herceptin] to cytotoxic chemotherapy [e.g., paclitaxel] will *enhance efficacy*" compared to either regimen used alone. *Hospira*, IPR2017-00731, Paper 120 at 36 (emphasis added). As the inventor of the '549 patent confirmed, she would not have conducted the clinical trial unless she thought that the combination would extend TTP. Appx7086 95:8-18.

Genentech may object to any reliance on its statements to the FDA, but Genentech's past inconsistent statements about the predictive power of Baselga '94 are fair game to question the veracity of Genentech's litigation-inspired attacks on Baselga '94 now. Regardless, Genentech's attacks on Baselga '94 fail to account for either the known clinical efficacy of Herceptin

and paclitaxel alone (including that both enhance the clinical efficacy of cisplatin), or the clinical trial that Baselga '94's studies inspired—a phase III trial testing Herceptin and paclitaxel for an extension of TTP compared to paclitaxel alone. And Genentech's attacks on the prior art as failing to provide clinical results proving that the claimed drug combination extends TTP compared to standalone paclitaxel (Br. at 35), misreads the legal standard. Conclusive proof of efficacy is not required for a reasonable expectation of success. *See supra* Argument I.B.2.i; *see also NantKwest, Inc. v. Lee*, 686 F. App'x 864, 870 (Fed. Cir. 2017) (explaining that there "is no general rule that a skilled artisan cannot reasonably extrapolate *in vivo* success" from preclinical results). The Board's obviousness decision should be affirmed.

CONCLUSION

Because the Board correctly construed the claims based on Genentech's unambiguous prosecution statement or, in the alternative, because substantial evidence supports the Board's reasonable-expectation-of-success finding under Genentech's claim construction, the Board's obviousness decision should be affirmed.

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RULE 32(a)(7)(C) CERTIFICATE OF COMPLIANCE

I certify pursuant to Fed. R. App. Proc. 32(a)(7) that the foregoing BRIEF FOR INTERVENOR complies with the type-volume limitation required by the Court's rule. The total number of words in the foregoing brief, excluding the table of contents and the table of authorities, is 6,345 words as calculated using the Word® software program.

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CERTIFICATE OF SERVICE

I hereby certify that on September 3, 2019, I electronically filed the foregoing BRIEF FOR INTERVENOR—DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE with the Court's CM/ECF filing system, which constitutes service, pursuant to Fed. R. App. P. 25(c)(2), Fed. Cir. R. 25(a), and the Court's Administrative Order Regarding Electronic Case Filing 6(A) (May 17, 2012).

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