2019-1270

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 IPR2017-01122.

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. 19-1265 (Fed. Cir.); and *Genentech, Inc. v. Iancu*, No. 19-1267 (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 a longer TTP than standalone paclitaxel; (2) enhances the clinical efficacy of cisplatin (a further growth inhibitory agent); and (3) in preclinical studies, markedly potentiates the antitumor effect of paclitaxel without increasing toxicity. 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 1-11 and 14-17 of the '549 patent were obvious over Baselga '96[1], Seidman '96[2],

[1] 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 3665-3674.

[2] Seidman et al., *Her-2/*neu *Over-Expression and Clinical Taxane Sensitivity: A Multivariate Analysis in Patients with Metastatic Breast Cancer (MBC)*, 15 Proc. Am. Soc'y. Clin. Oncol. 104, Abstract 80 (1996). Appx3475-3479.

Pegram[3], and the 1995 Taxol® PDR[4], in view of the knowledge in the art, as evidenced by, *inter alia*, Baselga '94[5] (Baselga Abstract 53). Genentech appealed the Board's decision to this Court, after which the parties settled and the petitioner, Celltrion, Inc., 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; Appx14424. The chemotherapeutic paclitaxel (Taxol®), in contrast,

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[3] Pegram et al., *Phase II Study of Intravenous Recombinant Humanized Anti-p185 HER-2 Monoclonal Antibody (rhuMAB HER-2) Plus Cisplatin in Patients with HER-2/*NEU *Overexpressing Metastatic Breast Cancer*, 14 Proc. Am. Soc'y. Clin. Oncol. 106, Abstract 124 (1995). Appx3678-3680.

[4] TAXOL (paclitaxel) for Injection Concentrate, Physician's Desk Reference, 682-85 (49th ed. 1995). Appx3480-3487.

[5] 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). Appx3661-3664.

not only showed significant antitumor activity against breast cancer in general, with a median time to disease progression ("TTP") of 3.0 or 4.2 months (Appx3485), but also was reported in the mid-1990s to be particularly effective against HER2-overexpressing breast cancer (Appx3479). *See also* Appx14030-14032. As Seidman '96 reports, 58.8% of HER2-positive breast cancer patients responded to paclitaxel treatment compared to just 38.7% of patients without HER2-overexpression. Appx3479.

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. Appx3667; Appx3669. The study reports minimal toxicity and a remission rate of 11.6% (5 out of 43 assessable patients). Appx3670. 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." Appx3670; Appx3671.

Baselga '96 also teaches the combination of Herceptin with other antitumor agents, including paclitaxel and cisplatin. Appx3673; *see also* Appx14041-14044 (explaining the advantages of combination therapy). Baselga '96 states that in preclinical studies, both *in vitro* and in xenografts, Herceptin markedly potentiated the antitumor effect of paclitaxel and of cisplatin without increasing their toxicity. Appx3673. Baselga '94 describes the preclinical xenograft studies with paclitaxel. Appx3664. 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. Appx3664. Based on these results, Baselga '94 and Baselga '96 both report that clinical trials of the combination therapy were underway. Appx3664; Appx3673.

Pegram reports results from a phase II clinical study of Herceptin and cisplatin. The study treated patients with HER2-overexpressing metastatic breast cancer, and reported one complete and eight partial responses out of 36 evaluable patients. Appx3680. Pegram concludes that Herceptin and cisplatin in combination resulted in response rates above that expected from cisplatin alone and without any apparent increase in toxicity. *Id*.

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 10:47-50. Consistent with the prior art, the TTP for paclitaxel (T) was 4.2 months. In contrast, 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 combination 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,[6] the examiner rejected the claims as indefinite based on the lack of a comparator for the limitation "extend the [TTP]." Appx11398-11401; Appx11414 (then-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?" Appx11401. 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*."

[6] The '549 patent issued from a continuation application of the 09/208,649 application in which the rejection and the response described here occurred. Appx3; Appx14; Br. at 14.

Appx11415-11416 (emphasis added). In the next action, the examiner withdrew the rejection. *See* Appx11624. 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. Appx11-41. Alternatively, the Board found the claims obvious even under Genentech's construction. Appx41-47.

Starting with claim construction, the Board interpreted the limitation "extend the [TTP]" as being compared to a patient receiving no treatment. Appx12. The Board relied on Genentech's unequivocal statement during prosecution that the claimed drug combination extends TTP "relative to an untreated patient." Appx14 (quoting Appx11416).

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. 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. Appx15 (quoting Appx9761 ¶ 133). 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. Appx16-17.

Turning to obviousness, the Board found that Baselga '96, Seidman '96, Pegram, and the Taxol® PDR, in view of the knowledge in the art, collectively teach administering a combination of Herceptin, paclitaxel, and cisplatin to treat HER2-overexpressing breast cancer. Appx17-37. 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. Appx26; Appx41.

Alternatively, the Board found a reasonable expectation of success even under Genentech's construction, i.e., compared to treatment with paclitaxel alone. Appx41-47. Addressing the parties' arguments, the Board

found that since effective amounts of Herceptin and paclitaxel were known (i.e., reported in Baselga '96 and the Taxol® PDR as achieving, for example, a median TTP of 5.1 months for Herceptin versus just 3.0 or 4.2 months for paclitaxel), a skilled artisan would have reasonably expected the combination to extend TTP relative to paclitaxel alone based on Herceptin's "superior TTP." Appx43 (citing Appx14646-14647); Appx44 (citing Appx4823 ¶ 20). The Board also relied on Baselga '96's reported response rate for Herceptin: a 37% rate for minimal responses and stable disease and an 11.6% response (or remission) rate. Appx44. The Board credited the petitioner's expert testimony, finding that because response rates likely correlate with an extension of TTP, Baselga 96's positive response rate would have added to the expectation that the drug combination would improve TTP versus paclitaxel alone. Appx43-44 (citing Appx14647-14649; Appx4824 ¶¶ 22-23).

The Board found support for its analysis in the principles of combination therapy. Appx45. The principles require that the drugs (1) each have proven clinical efficacy in the target patient population, (2) do not have any significant overlapping toxicities, (3) have different mechanisms of action, and (4) do not exhibit cross-resistance. *See* Appx1065-1068 ¶¶ 125-131. The Board disagreed that these principles were not applicable to antibody ther-

apies like Herceptin, explaining that the absence of record evidence of researchers expressly applying the principles to antibodies simply reflected the historical use of small-molecule chemotherapeutics before the development of therapeutic antibodies. Appx45-46. The Board also rejected Genentech's data on the general failure rate of oncology drugs in phase III clinical trials as evidence of unpredictability. The Board found that the data focused on individual compounds—i.e., new chemical entities and biologics—rather than combinations of FDA-approved and promising therapies, like the claimed drug combination here. Appx44-45. Accordingly, the Board concluded that claims 1-11 and 14-17 of the '549 patent would have been obvious even under Genentech's construction of the comparator as paclitaxel alone. Appx47.

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 '96s disclosure of a "superior" TTP for Herceptin (5.1 months) compared to the known TTP for paclitaxel (3.0 or

4.2 months). The Board then found further support both in Baselga '96's disclosure of Herceptin's positive response rate, which the Board found would likely correlate with an improvement in TTP, and in the principles of combination therapy. Substantial evidence thus supports the Board's reasonable-expectation finding.

Genentech's attacks on Baselga '96 individually fall flat. First, the Board found that since Baselga '96 discloses a superior TTP for Herceptin than the known TTP for paclitaxel, in the context of the prior art as a whole, it provides a reasonable expectation that adding Herceptin to paclitaxel would *extend* TTP, as claimed, compared to paclitaxel alone. Second, the Board also correctly relied on Baselga '96's reported positive response rate for Herceptin. As the Board found, response rates, like TTP, measure drug efficacy, and positive rates likely correlate with an improved TTP, further supporting a reasonable expectation of success. Finally, Genentech's challenge to the 5.1 months specifically comes for the first time on appeal; the argument is waived. It is also factually incomplete and thus cannot undermine the Board's decision.

Genentech's criticism that the Board wrongly rejected other counter-arguments and evidence fares no better. The Board did not err in reciting the principles of combination therapy as further support for its obviousness

analysis. None of Genentech's evidence shows that these principles are irrelevant to antibody biologics like Herceptin. Nor did the Board err in rejecting evidence of the general failure rate of individual oncology drugs in phase III trials when Genentech's claims recite a specific combination of three drugs already shown to be safe and clinically effective in treating HER2-overexpressing breast cancer.

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 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,[7] statements made during prosecution can be "relevant as reinforcing the evident meaning of the claim language at

[7] The petition in this IPR was filed on March 21, 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).

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." Appx14; Appx11416. 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 20, 23. 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 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?" Appx11401. From this list, Genentech selected "an untreated patient." Appx11416. 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 22-24. 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." Appx11401. And, again, Genentech expressly chose untreated patients. Appx11416. 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. Br. at 23 (citing Appx11019; Appx11046-11047).

This choice also did not create any conflict with the claims or specification, as Genentech implies. Br. at 20-21. 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 21. 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 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. Appx15. 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 21 n.8), 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* Appx16-17. 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 24-25.

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. Appx23-25; Appx31. As the Board found, Seidman '96 and Baselga '96 teach that paclitaxel and Herceptin, respectively, are safe and clinically effective against HER2-overexpressing breast cancer, and Pegram teaches the same for a combination of Herceptin and cisplatin, with Herceptin enhancing cisplatin's efficacy but not its toxicity. Appx23-24. Baselga '96 further reports that, in Baselga '94's preclinical studies, Herceptin markedly potentiated paclitaxel's antitumor effect without increasing its toxicity and that based on these results, clinical trials of the combination were underway. Appx23-25. 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. Appx41-43. The Board properly relied on Baselga '96 and the Taxol® PDR's disclosure of effective amounts of Herceptin and paclitaxel, respectively, resulting in a median TTP for Herceptin of 5.1 months compared to 3.0 or 4.2 months for paclitaxel alone. Appx43 (citing Appx14646; Appx4823 ¶ 20); Appx44. The Board also properly found support in Baselga '96's disclosure of a positive response rate for Herceptin, finding that it would likely correlate with an increase in TTP. Appx43-44 (citing Appx4824 ¶ 22). Because Herceptin's 5.1-month TTP is "superior" to paclitaxel's TTP (Appx44), and because administering the drug combination would not be expected to abrogate the effect of either therapeutic (Appx41; Appx14647), indeed, the combination enhanced efficacy in preclinical studies (Appx20-21), substantial evidence supports the Board's finding of a reasonable expectation of success.

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

In challenging the Board's reasonable-expectation-of-success finding, Genentech attacks Baselga '96 individually and criticizes the Board's rejection of its evidence related to the principles of combination therapy and the general failure rate of individual cancer drugs. Br. at 29-33. None shows

error in the Board's finding.

i. No error in relying on Baselga '96's reported 5.1-month TTP and positive response rate

According to Genentech, the Board repeatedly erred in its reliance on Baselga '96's clinical results. Br. at 30-31. 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 30. Not so. As Baselga '96 reports, Herceptin's TTP was "unusually long"; it improves TTP compared to expectations. *See* Appx41 (citing Appx3671). And the Board directly compared Baselga '96's disclosure of Herceptin's "superior" TTP to paclitaxel's—5.1 months versus 3.0 or 4.2 months. Appx43 (citing Appx4823 ¶ 20). Thus, in the context of the prior art as a whole, Baselga '96 provides a reasonable expectation that adding Herceptin (and cisplatin) to paclitaxel would extend TTP compared to paclitaxel alone. Appx43; *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.").

Second, Genentech contends that the Board improperly relied on Baselga '96's reported response rate for Herceptin as supporting a reasonable expectation of an improved TTP. Br. at 30. Response rate, like TTP, is a

measurement of drug efficacy; both are surrogate endpoints for the likelihood of improved overall survival. Appx43 (citing Appx4824 ¶ 22); Appx76 10:46-49. Thus, as the Board found, a skilled artisan would have understood that a positive response rate likely correlates with a longer TTP, thereby adding to the reasonable expectation that the claimed drug combination would improve TTP compared to paclitaxel alone. Appx43 (citing Appx1041-1044 ¶¶ 92-94; Appx4824 ¶¶ 22-23; Appx14647-14649). Genentech's evidence does not undermine that finding. Br. at 30. The evidence relates to response rate in xenografts (Appx9582), Baselga '96's lack of a control arm (Appx9796), or the inability of response rates to determine effectiveness, meaning survival (Appx10211), not to any lack of correlation between response rate and TTP. Indeed, response rate and TTP correlate in Genentech's own data. Taxol (T) has a lowest response rate at 25.0% and the shortest TTP at 4.2 months. From there, response rate and TTP increase in parallel. Topping the chart: Herceptin-anthracycline/cyclophosphamide therapy (AC + H), which has the highest response rate at 64.9% and the longest TTP at 9.0 months. Appx86.

Finally, 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 31. Genentech, however, never made this argument

before the Board. In its patent owner response, Genentech did not argue that the Board should disregard Baselga '96's reported TTP for Herceptin because it relied on a subset of patients (Appx14458-14461 (dated December 21, 2017)). Now, before this Court, Genentech cites testimony filed with its reply in support of its motion to amend. Br. at 31 (citing Ex. 2144 (Appx10661-10665) (dated April 20, 2018)); Appx14711 (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. Appx10664-10665. 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. Appx3670. It thus excludes patients with no response, as Genentech notes, potentially skewing the results upward (Br. at 31), but it also excludes patients with a tumor response (or remission), and this latter omission would skew the results in the other direction: downward.[8] *See* Appx3671, Table 5. Genentech

[8] The study also selected patients who had many sites of metastatic involvement and who had received prior chemotherapy, both factors believed to

does not proffer a TTP for Baselga 96's entire patient population. Nor 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 the median TTP for Baselga '96's entire patient population would, as Genentech argues (Br. at 31), necessarily be shorter than 5.1 months, or that it was unreasonable to rely on the TTP reported in Baselga '96. Genentech's new and factually incomplete attack on Baselga '96 should be rejected.

ii. No error in rejecting Genentech's other counterarguments and evidence

Genentech also criticizes the Board for rejecting its arguments and evidence (1) challenging the applicability of the principles of combination therapy and (2) showing a high failure rate for oncology drugs in phase III clinical trials. Genentech's arguments again fall short.

First, Genentech argues that the "Board's recitation of [the] principles of combination therapy does not save its analysis." Br. at 31. The Board's

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limit response rates and further skew the results downward. Appx3671; *see also* Appx3673 ("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.

analysis does not need saving; the Board recited the principles only as further support, not as necessary to its obviousness decision. Appx45 n.31.

Genentech nevertheless asserts that the principles do not apply to antibody biologics like Herceptin. Br. at 31-32. The Board disagreed. According to the Board, the record evidence's focus on small-molecule chemotherapeutics merely reflected their historical use before the development of therapeutic antibodies. Appx45-46; *see also* Appx4814-4815. Indeed, nothing about the principles themselves—(1) proven single-agent clinical efficacy; (2) no significant overlapping toxicity, (3) different mechanisms of action; and (4) no cross-resistance—appears irrelevant to antibody therapies, even if certain assumptions about their use may differ from those for chemotherapeutics. *See* Br. at 31-32; Appx1065-1068. Even Genentech's expert admitted that she was unaware of any prior art suggesting that the principles would not apply to chemotherapy-antibody combinations, and she believed that combining Herceptin with paclitaxel would satisfy these principles. Appx46 (citing Appx4451-4452 71:23-72:6; Appx4470-4471 90:8-91:6). Nor do the principles demand the requirements Genentech seeks to impose on them—phase III clinical data, FDA approval, or a certain mechanism of action (Br. at 32)—none of which is a requirement for a reasonable expectation

of success. Accordingly, the Board did not err in reciting the principles as further support for its obviousness analysis.

Second, Genentech argues that the Board improperly dismissed its evidence of the high failure rate of oncology drugs in phase III clinical trials. Br. at 32-33. Genentech's evidence, as the Board found, focused on clinical trials testing individual compounds, not a combination of FDA-approved or promising therapies with known safety and efficacy in humans, including as two-drug combinations. Appx44-45. Genentech does not argue otherwise. Instead, Genentech asserts that combining Herceptin and paclitaxel created more uncertainty than a single-drug trial. Br. at 32. 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 finding a reasonable expectation of success in the absence of clinical testing or FDA approval of the claimed drug combination. Br. at 32-33; *see also id.* at 6, 7, 25. Absolute certainty, however, is not what the law demands.

"[O]bviousness cannot be avoided simply by a showing of some degree of unpredictability"; "the expectation of success need only be reasonable, not absolute." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). 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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Respectfully submitted,

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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 5,792 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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