2019-1267

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 IPR2017-01121; IPR2017-02063.

BRIEF FOR INTERVENOR

THOMAS W. KRAUSE
Solicitor

SARAH E. CRAVEN
MAUREEN D. QUELER
Associate Solicitors

Office of the Solicitor
U.S. Patent & Trademark Office
Mail Stop 8, P.O. Box 1450
Alexandria, Virginia 22313
(571) 272-9035
Attorneys for the Director of the U.S. Patent & Trademark Office

September 3, 2019

REPRESENTATIVE CLAIM

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

Appx83 33:46-54 (disputed limitations emphasized).

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

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. 19-1270 (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 '441 patent claims a method of treating HER2-overexpressing breast cancer by administering a combination of two drugs already known to treat such cancers: paclitaxel and Herceptin. The claims also recite an efficacy and a safety effect: the claimed drug combination is administered in an amount effective to "[1] extend the time to disease progression [TTP] . . . [2] without [an] increase in overall severe adverse events." Missing from the claims, however, is a comparator for the claimed effects; the drug combination safely 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 safe and clinically effective in treating HER2-overexpressing breast cancer, with a longer TTP than standalone paclitaxel, and (2) in preclinical studies, markedly potentiates the antitumor effect of paclitaxel without increasing its toxicity. Based on these teachings, the Board found that a skilled artisan would have combined Herceptin and paclitaxel to treat HER2-overexpressing breast cancer with a reasonable expectation that the drug combination would extend TTP without increasing toxicity compared to paclitaxel alone. An alternate issue on appeal is thus whether substantial evidence supports the Board's reasonable-expectation findings under Genentech's construction.

STATEMENT OF THE CASE

This appeal arises from an *inter partes* review of Genentech's U.S. Patent No. 7,846,441 ("the '441 patent"). The Board decided that claims 1-14 of the '441 patent would have been 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 4227-4236.

[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). Appx4037-4041.

and the 1995 Taxol® PDR.[3] Genentech appealed the Board's decision to this Court, after which the parties settled and the petitioners, Celltrion, Inc. and Pfizer, 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 and Herceptin both were known to treat HER2-overexpressing breast cancer

The '441 patent relates to treating diseases that overexpress ErbB2 (also known as HER2), including breast cancer. Appx67 1:20-29; Appx69 5:15-19. 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. Appx68 3:41-50; Appx12400. The chemotherapeutic paclitaxel (Taxol®), in contrast, not only showed significant antitumor activity against breast cancer in general, with a time to disease progression ("TTP") of 3.0 or 4.2 months (Appx 4047), but also was reported in the mid-1990s to be particularly effective against HER2-overexpressing breast cancer (Appx4041). *See* Appx12026-12027. As Seidman '96 reports, 58.8% of HER2-positive patients responded

[3] TAXOL (paclitaxel) for Injection Concentrate, Physician's Desk Reference, 682-85 (49th ed. 1995). Appx4042-4049.

to paclitaxel treatment compared to just 38.7% of patients without HER2-overexpressing breast cancer. Appx4041.

Another treatment for HER2-overexpressing breast cancer also appeared in the mid-1990s: Herceptin. Appx68 3:34-40. Herceptin is a recombinant humanized version of the mouse anti-ErbB2 antibody 4D5 (humanized MAb 4D5). Appx67 2:1-29; Appx68 3:34-40. It targets HER2-overexpressing cells and acts clinically to treat HER2-positive breast cancer. Appx68 3:34-40. 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. Appx4229; Appx4231. The study reports minimal toxicity and a remission rate of 11.6% (5 out of 43 assessable patients). Appx4232. 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." Appx4232; Appx4233.

Baselga '96 also teaches the combination of Herceptin with other antitumor agents, including paclitaxel. Baselga '96 states that in preclinical studies, both *in vitro* and in xenografts, Herceptin "markedly potentiated" paclitaxel's antitumor effect without increasing its toxicity. Appx4235.

Baselga '94[4] describes these preclinical xenograft studies. Appx68 3:54-59; Appx4226. In this mouse model, treatment with Herceptin or paclitaxel alone produced a 35% inhibition of tumor growth, while combination treatment resulted in "major antitumor activity," with 93% growth inhibition. Appx4226. Based on these results, Baselga '96 states that clinical trials of the combination therapy were in progress. Appx4235.

B. The '441 patent claims treating HER2-overexpressing breast cancer with Herceptin and paclitaxel to improve efficacy without increasing toxicity

The '441 patent specification reports the results of a phase III clinical trial of Herceptin and chemotherapy, including paclitaxel, to treat HER2-overexpressing breast cancer. Appx80-81 27:13-30:25. The trial's endpoints included response rate and TTP. Appx81 29:11-15; *see also* Appx71 10:47-50. Consistent with the prior art, the TTP for paclitaxel alone (T) was 4.2 months. In contrast, paclitaxel-Herceptin therapy (T+H) achieved a TTP of 7.1 months. Appx81 30:1-12. Reports of adverse events (AE%), however, also increased, rising from 59% with paclitaxel alone to 70% with combination therapy. *Id.* In addition to Herceptin and paclitaxel, the phase III trial

[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). Appx4223-4226.

tested combination Herceptin-anthracycline/cyclophosphamide treatment (AC+H) and the latter alone (AC). Appx81 29:20-26.

The patent claims treating patients with HER2-overexpressing breast cancer by administering a combination of an anti-ErbB2 antibody (e.g., Herceptin) and a taxoid (e.g., paclitaxel). The claims also require that the administration be of an amount effective to extend the TTP (the claimed efficacy effect), but without an increase in overall severe adverse events (the claimed safety effect). Appx83-84. Claim 1, reproduced below, is representative on appeal.

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

Appx83 33:46-54 (disputed limitations emphasized).

During prosecution of the '441 patent, the examiner rejected the then-pending claims, which recited the claimed efficacy effect but not the safety effect, as indefinite based on the lack of a comparator for "extend the [TTP]."

Appx1509-1512; Appx1525 (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?" Appx1512. 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*." Appx1526-1527 (emphasis added). The examiner then allowed the claims, but suspended prosecution due to a potential interference. Appx1735-1736. Later, after prosecution reopened, the applicant added the limitation "without increase in overall severe adverse events," but failed to say anything about the comparator. *See* Appx3451-3452. The claims issued with both limitations. Appx83.

II. The Board's Obviousness Decision

In its final written decision following *inter partes* review of the '441 patent, the Board construed the challenged claims and concluded that they were obvious. Appx7-35. Alternatively, the Board found the claims obvious even under Genentech's construction. Appx36-41.

Starting with claim construction, the Board interpreted the limitation "extend the [TTP]" as being compared to a patient receiving no treatment.

Appx8. The Board relied on Genentech's unequivocal statement during prosecution that the claimed drug combination extends TTP "relative to an untreated patient." Appx9 (quoting Appx1527).

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. Appx10 (quoting Appx8805 ¶ 130). 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 untreated patients. Appx10-11.

Finally, the Board was unpersuaded that the claimed safety effect—"without [an] increase in overall severe adverse events"—required a comparison to *some* treatment. As the Board explained, the applicant added the safety limitation after explicitly defining the comparator as "an untreated

patient." Appx11. Then, citing the tension between Genentech's prosecution statement and its arguments now, the Board admonished Genentech for the inconsistency. In the Board's view, Genentech could have adopted during prosecution the construction of the comparator it wants now, but with reasonable clarity, deliberateness, and precision, it had not. Appx11-12; *see* Appx12 n.6.

Turning to obviousness, the Board found that Baselga '96, Seidman '96, and the Taxol® PDR, in view of the knowledge in the art, including Baselga '94, collectively teach administering a combination of Herceptin and paclitaxel to treat HER2-overexpressing breast cancer as claimed. Appx15-35. The Board also found that a skilled artisan would have had a reasonable expectation that administering an effective amount of the drug combination would achieve the claimed efficacy and safety effects compared to untreated patients. Appx35. Alternatively, the Board found a reasonable expectation of success even under Genentech's construction, i.e., compared to patients treated with paclitaxel alone. Appx36-41.

For the claimed efficacy under Genentech's claim construction, the Board compared Baselga '96's disclosure of a median TTP for Herceptin of 5.1 months to the Taxol® PDR's disclosure of a median TTP for paclitaxel of just 3.0 or 4.2 months. Appx36. Because Baselga '96 reports that Herceptin

achieved a longer TTP than paclitaxel, the Board found a reasonable expectation that adding Herceptin to paclitaxel would extend the TTP relative to paclitaxel alone. Appx36. This finding, according to the Board, was "especially so" here based on the principles of combination therapy, which require that the drugs have (1) single-agent efficacy in the target population, (2) non-overlapping toxicities, (3) different mechanisms of action, and (4) different mechanisms of resistance. Appx36-37 (citing Appx12038-12039). The Board found that Herceptin and paclitaxel have non-overlapping toxicities and mechanisms of action such that each can be administered in its full effective dose. Appx37 (citing Appx12045-12048). The Board disagreed with Genentech that these principles do not apply to antibodies like Herceptin, observing that the prior art already taught combining Herceptin with the chemotherapeutic cisplatin, and that Genentech itself had relied on these principles to combine a different antibody (Rituxan) with chemotherapy. Appx18-19. Finally, the Board also noted that its conclusion was "further supported" by Genentech's FDA submissions, in which Genentech relied on Baselga '94 to predict that Herceptin in combination with paclitaxel "will enhance efficacy" compared to either regimen used alone. Appx37.

For the claimed safety under Genentech's construction, the Board relied on Baselga '96's disclosure that Herceptin had no significant toxicity in

humans; paclitaxel's prior FDA approval; and Baselga '94's disclosure that, in preclinical studies, Herceptin did not increase paclitaxel's toxicity when combined. Appx37-38; Appx40. The Board then found that Baselga '94's studies would reliably predict the effects of the claimed combination in humans, again noting that Genentech's argument to the contrary was "refuse[d]" by its own reliance on Baselga '94 to gain FDA approval to test the drug combination in humans. Appx38-39; *see also* Appx34-35. Rejecting Genentech's argument that Baselga '94 had failed to predict the increased cardiotoxicity of combination Herceptin-doxorubicin therapy in humans, the Board explained that Genentech had admitted that the increased toxicity was "completely unexpected," and thus it did not detract from the reasonable expectation that Herceptin-paclitaxel therapy would be safe. Appx38.

Finally, the Board denied Genentech's contingent motion to amend. Appx49-50. The Board concluded that the amendment introduced new matter, finding that the specification failed to teach that the claimed drug combination does not increase severe adverse events compared to, as Genentech had amended the claims, paclitaxel alone. Appx46-50.

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 and paclitaxel 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 without increasing severe adverse effects 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." And that selection was in no way altered or disavowed by Genentech's later addition of the adverse-events limitation to the claims. Genentech was free to draft

its claims to recite a paclitaxel comparator. Instead, with reasonable clarity, deliberateness, and precision, Genentech defined the comparator as an untreated patient. 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 drug combination would achieve the claimed efficacy and safety effects compared to paclitaxel alone. The Board relied on Baselga '96's disclosure of a longer median TTP for Herceptin (5.1 months) than the known TTP for paclitaxel (3.0 or 4.2 months), and on Baselga '96's disclosure that Herceptin is well tolerated in humans and, while increasing efficacy, does not increase the toxicity of FDA-approved paclitaxel in preclinical studies. Substantial evidence thus supports the Board's reasonable-expectation findings.

Genentech's arguments fail to show otherwise. For the claimed efficacy, Genentech's attacks on Baselga '96 fall flat. First, the Board properly found that since Baselga '96 discloses a longer 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, Genentech's challenge to Baselga '96's disclosure of a TTP of 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. The Board also did not err in reciting the principles of combination therapy as further support. None of Genentech's evidence shows that these principles are irrelevant to antibody biologics like Herceptin, and Genentech itself relied on these principles in combining another therapeutic antibody (Rituxan) with chemotherapy.

For the claimed safety, Genentech attacks the Board's reliance on the safety profiles of Herceptin and paclitaxel alone and on the combination in preclinical studies. But Herceptin is undisputedly well tolerated in humans. And nothing in the record suggests that adding paclitaxel, the baseline comparator under Genentech's construction, would abrogate Herceptin's own lack of toxicity. Indeed, Baselga '94 shows that Herceptin does not increase paclitaxel's toxicity, and skilled artisans relied on such preclinical results to predict safety in humans. At bottom, Genentech believes that because there were no clinical results *proving* that the claimed drug combination extends TTP without increasing toxicity compared to standalone paclitaxel in humans, its claims cannot be obvious. Absolute certainty, however, is not the legal standard for a reasonable expectation of success.

Finally, Genentech faults the Board for noting its past inconsistent statements to the FDA. The Board remarked that, for all its criticism of Baselga '94 as an unreliable predictor of success in humans, Genentech itself relied on it to get FDA approval to test Herceptin-paclitaxel therapy in humans. Such remarks did not constitute a finding of obviousness based on Genentech's own developmental pathway. Rather, Genentech's past statements were fair game for the Board to question the veracity of Genentech's litigation-inspired attacks on Baselga '94 now. 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 '441 Patent Would Have Been Obvious

The Board properly concluded that the claims of the '441 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 backs the Board's decision that, even under Genentech's construction, a

skilled artisan would have reasonably expected the claimed drug combination to extend TTP without an increase in severe adverse events 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,[5] statements made during prosecution can be "relevant as reinforcing the evident meaning of the claim language at

[5] 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." Appx9; Appx1527. Genentech argues that the statement does not rise to the level of a clear and unmistakable disclaimer, but was simply "inartful." Appellant 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?" Appx1512. From this list, Genentech selected "an untreated patient." Appx1527. That Genentech never repeated this statement (Br. at 24) is unsurprising as its original statement sufficed to overcome the examiner's rejection. Appx1735. 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 23-24. 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." Appx1512. And, again, Genentech expressly chose untreated patients. Appx1527. 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. Appx1527 (citing Appx1130; Appx1157-1158); Br. at 24 (citing Appx1158).

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 with 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. Appx10. 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." Appx79 26:30-31. 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 '441 patent also describes the efficacy of anthracycline/cyclophosphamide treatment alone. Appx81 29:26–30:16. And, contrary to Genentech's assertion (Br. at 21 n.5), while the 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. Again, Genentech does not argue otherwise.

Rather, Genentech argues that its later amendment to add "without [an] increase in overall severe adverse events" dispelled any ambiguity because adverse events arise only during treatment. Br. at 21-22, 24. Rather than dispel ambiguity, the amendment created it when Genentech failed either to provide a different comparator for its new safety limitation or to revisit its prior selection. *See Amgen Inc. v. Coherus BioSciences Inc.*, 931 F.3d 1154, 1161 (Fed. Cir. 2019) (holding that subsequent prosecution statements did not erase an earlier clear and unmistakable surrender of claim scope). Thus, even if the applicant's earlier-chosen comparator—untreated patients—makes no sense, as Genentech argues now, the fault lies squarely with Genentech. *See* Appx12. Claim interpretation cannot give a term a different construction than did the applicant to avoid a "nonsensical result." Appx12 (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).

Moreover, the comparator allegedly dictated by adding the safety effect—paclitaxel alone—adds new matter. *See* Appx46-50. As the Board

found, the percentage of adverse events for the paclitaxel-Herceptin combination at 70% is *higher* than the 59% for paclitaxel alone. Appx48 (citing Appx81 30:1-12). In other words, the specification fails to disclose that the drug combination results in no increase in overall severe adverse events compared to paclitaxel alone. Genentech does not challenge the Board's new-matter finding on appeal; the argument is waived. Because Genentech's proposed construction of the claims' comparator is not consistent with either the specification or the prosecution history, the Board's 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 Baselga '96, Seidman '96, and the 1995 Taxol® PDR. Genentech limits its challenge of the Board's decision to the Board's findings of a reasonable expectation of success. Br. at 25-26.

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 and paclitaxel to treat HER2-overexpressing breast cancer and, under Genentech's claim construction, found a reasonable expectation that the combination would extend the TTP (the claimed efficacy effect) without an increase in severe adverse events (the claimed safety effect) compared to paclitaxel alone. Appx18-41. Substantial evidence supports the Board's findings.

The Board first found that the prior art teaches administering a combination of Herceptin and paclitaxel to treat HER2-overexpressing breast cancer in human patients. Appx20; Appx35. 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. Appx13-15; Appx20; Appx24-25. Baselga '96 further discloses that, in Baselga '94's preclinical trials, Herceptin markedly potentiated paclitaxel's antitumor effect—from 35% with each drug alone to 93% combined—without increasing its toxicity. Appx11; Appx25; Appx28-29. Based on these results, both Baselga references state that clinical trials of the combination therapy were in progress. Appx25; Appx29. 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 achieve the claimed efficacy and safety when compared to treatment with paclitaxel alone. Appx36-41. For extending the TTP, the Board found that Baselga '96 discloses a median TTP for Herceptin of 5.1 months, while the Taxol® PDR reports a median TTP for paclitaxel of just 3.0 or 4.2 months. Appx36 (citing Appx4232; Appx4047). Accordingly, the Board properly concluded that, because Baselga '96 reports a longer TTP for Herceptin than known for paclitaxel, a skilled artisan would have reasonably expected that adding Herceptin to paclitaxel would extend the TTP over paclitaxel alone. Appx37. The Board found its conclusion "especially so" in light of Herceptin and paclitaxel's non-overlapping toxicities and mechanisms of action, and "further supported" by Genentech's representations to the FDA 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 drug used alone. Appx37.

Turning to the safety limitation, the Board found that Baselga '96 discloses that Herceptin was "remarkably well tolerated" in human patients

with no significant toxicity, and discloses that adding Herceptin to paclitaxel, which was already FDA approved, did not increase paclitaxel's toxicity in Baselga '94's preclinical studies. Appx37-38 (citing Appx12040; Appx12052); Appx40. Responding to Genentech's challenge to Baselga '94's preclinical data as not a reliable predictor of success in humans, the Board found Genentech's assertion "refute[d]" by its own reliance on Baselga '94 when seeking FDA approval to test the combination in humans. Appx38-39. The Board thus properly concluded that a skilled artisan would have reasonably expected that the claimed drug combination would extend TTP without increasing severe adverse effects compared to paclitaxel alone. Appx40-41.

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

Genentech argues that the Board erred in finding a reasonable expectation of success for both the claimed efficacy and the claimed safety. Br. at 26-32. Genentech also alleges error in the Board's use of its past FDA statements, statements that contradict its assertions about the prior art now. Br. at 33-35. None of Genentech's arguments shows error in the Board's findings.

i. No error in finding a reasonable expectation of achieving the claimed efficacy

For the claimed efficacy, Genentech argues that the Board erred in relying on Baselga '96's report of a 5.1-month TTP for Herceptin and on the principles of combination therapy. The Board properly relied on both.

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 27. Not so. As Baselga '96 reports, Herceptin's TTP was "unusually long"; it improves TTP compared to expectations. *See* Appx4233. The Board then directly compared Baselga '96's disclosure of Herceptin's TTP to paclitaxel's known TTP—5.1 months compared to 3.0 or 4.2 months. Appx36. Thus, in the context of prior art as a whole, Baselga '96 provides a reasonable expectation that adding Herceptin to paclitaxel would extend TTP compared to paclitaxel alone. Appx36; *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 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 27-28. Genentech, however, never made this argument

before the Board. While the petition relied on Baselga '96's 5.1-month TTP (Appx12032-12033), 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 (Appx12436 (citing Appx4232; Appx4047) (dated December 21, 2017)). Now, before this Court, Genentech cites testimony filed with its reply in support of its motion to amend. Br. at 28 (citing Ex. 2144 (Appx10171-10172) (dated April 20, 2018)); Appx12750 (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 patient population. *See* Appx10172-10173. 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. Appx4232. It thus excludes patients with no response, as Genentech notes, potentially skewing the results upward (Br. at 27-28), but it also excludes patients with a tumor response (or remission), and this latter omission would skew the

results in the other direction: downward.[6] *See* Appx4233, Table 5. Genentech 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 '441 patent provides no guidance, though it too reports a significant number of non-responders. *See* Appx81. It is thus far from clear that the median TTP for Baselga '96's entire patient population would, as Genentech argues, necessarily be shorter than 5.1 months (Br. at 28), 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* Appx12436 (citing Appx4232). Genentech's new and factually incomplete attack on Baselga '96 should be rejected.

Finally, Genentech argues that the "Board's recitation of [the] principles of combination therapy does not save its analysis." Br. at 28. The Board's analysis does not need saving; the Board recited the principles of

[6] 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. Appx4233; *see also* Appx4235 ("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.

combination therapy only as further support, not as necessary to its obviousness decision. Appx36 (stating that its finding was "especially so" based on the principles).

Genentech nevertheless asserts that the principles do not apply to antibody biologics like Herceptin. Br. at 28-29. But 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 an antibody therapy, even if certain assumptions about their use may differ from those for chemotherapeutics. *See* Br. at 28; Appx1064-1067. As Genentech's expert admitted, 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. Appx5196-5197 71:23-72:6; Appx5215-5216 90:8-91:2. Indeed, as the Board found, Genentech itself relied on the principles to combine a different antibody therapeutic (Rituxan) with chemotherapy. Appx19. And Genentech does not challenge the Board's specific findings that Herceptin and paclitaxel have different toxicities and mechanisms of action (Appx37), seeking instead to impose new requirements—phase III clinical data, FDA approval, and a certain

mechanism of action (Br. at 28)—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.

ii. No error in finding a reasonable expectation of achieving the claimed safety

For the claimed safety, Genentech argues that the Board erred in relying on the known safety of both (1) Herceptin and paclitaxel alone and (2) the drug combination in preclinical studies only. Such information, says Genentech, fails to address the "possible toxicity" of the combination in humans. Br. at 30. Genentech's arguments again fail to undermine the Board's finding of a reasonable expectation of success.

Genentech first argues that while Baselga '96 reported minimal toxicity for Herceptin, taxoids were associated with both neuropathy and cardiotoxicity. Br. at 30. The Taxol® PDR, however, reports few *severe* neuropathic and cardiovascular events in 812 patients receiving paclitaxel. Appx4048 (reporting three patients with severe peripheral neuropathy and one with a significant cardiovascular event). Regardless, under Genentech's claim construction, the comparator *is* paclitaxel; paclitaxel's toxicity sets the baseline. As such, Baselga '96's disclosure that Herceptin is well tolerated in humans—who express the *human* ErbB2 receptor (*see* Br. at 31-32)—provides a reasonable expectation that the addition of Herceptin will not

increase severe adverse compared to any toxicity associated with paclitaxel alone. Indeed, as Baselga '96 reports, Baselga '94 administered the combination in xenografts and reported that Herceptin did not increase toxicity compared to paclitaxel alone. Appx37; Appx4235 (citing Appx4226).

Genentech next attacks Baselga '94, arguing that its preclinical studies do not reliably predict effectiveness or safety in humans. Br. at 31. The Board rejected all of Genentech's alleged limitations with Baselga '94's study. Appx28-35. Genentech does not repeat these arguments on appeal. Furthermore, as the inventor of '441 patent testified, the whole point of Baselga '94's study was "to look at trying to predict what can be helpful in patients," not to cure cancer in mice. Appx4826-4827 48:19–49:1. Genentech's experts agreed, testifying that xenograft studies aid researchers in deciding which drug combinations to test clinically and in predicting toxicity in humans. Appx12627-12628 (citing Appx4578-4583; Appx5233-5234).

Moreover, Baselga '94's studies *did* provide skilled artisans, including Genentech, a motivation for clinical evaluation. As the Board remarked, contrary to Genentech's current litigation-inspired attacks on Baselga '94's studies, Genentech relied on these studies to convince the FDA to approve its phase III trial of Herceptin-paclitaxel therapy against paclitaxel alone. Appx37. At bottom, though Baselga '94 showed that Herceptin markedly

potentiates paclitaxel's antitumor effect with increasing toxicity in mice, skilled artisans relied on it as reasonably predicting success in humans. The Board did not err in doing the same.

Nor did the Board err in disregarding Baselga '94's failure to predict Herceptin and doxorubicin's *unexpected* increase in cardiotoxicity in humans. *See* Br. at 32. As the Board explained, Genentech characterized the Herceptin-doxorubicin combination's increased human toxicity as "completely unexpected," and thus the Board declined to discount Baselga '94's significance in predicting the safety of combination Herceptin-paclitaxel therapy in humans. Appx38 (quoting Appx12411).

Rather than the Board "misinterpret[ing] this evidence" or "miss[ing] the point," Genentech misreads the standard for a reasonable expectation of success. Br. at 32. Genentech criticizes preclinical animal studies because they are less predictive than clinical trials in humans. Br. at 32. 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); *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).

iii. No error in relying on Genentech's own contradictory statements about the prior art

Finally, Genentech argues that the Board erred in relying on the inventor's own path—a phase III clinical trial of the claimed drug combination without prior phase I and II studies—as evidence of obviousness. Br. at 33-35. The Board, however, did not rely on Genentech's statements to the FDA about its phase III trial as evidence of obvious, but as contradicting Genentech's current litigation-motivated arguments regarding the same prior art—Baselga '94.

Regarding efficacy, Genentech's FDA papers relied on Baselga '94 to deduce that the addition of Herceptin to paclitaxel would enhance efficacy. Br. at 33-34 (citing Appx37). The Board first cited such statements, however, only after relying on the prior art and expert testimony to reject Genentech's numerous (now largely abandoned) attacks on Baselga '94's preclinical work as an unreliable predictor of success in humans. Appx29-34. Also undermining Genentech's attacks: Genentech's own reliance on Baselga '94 to convince the FDA to permit phase III clinical trials in humans. Appx34-35. For expectation of success, the Board relied on the longer

median TTP for Herceptin versus paclitaxel, but noted that its conclusion was "further supported" by Genentech's FDA statements of anticipated enhanced efficacy based on Baselga '94. Appx37. Hence, the Board did not "rely on the inventor's perspective on the prior art to support a finding of obviousness" (Br. at 34), but as additional evidence to rebut Genentech's attacks on Baselga '94's predictive power based on Genentech's *inconsistent* perspective on that prior art.

Same for statements regarding safety. Br. at 34-35 (citing Appx39). The Board relied, in part, on Baselga '94's disclosure that Herceptin did not increase paclitaxel's toxicity. Appx37. The Board then noted that Genentech's "own documents *refute* its assertion" that Baselga '94's xenograft model would not reliably predict the effects of the claimed drug combination in humans. Appx38 (emphasis added). The Board reasonably concluded that the FDA would not have allowed Genentech's phase III study if there were not a reasonable likelihood that the proposed drug combination would be safe in humans. Appx39. Could it have been otherwise? Regardless, countering Genentech's attacks on Baselga '94 with Genentech's own inconsistent statements about Baselga '94—and reasonable inferences from them—did not undermine the Board's reliance on the prior art or otherwise

introduce reversible error. 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 findings under Genentech's claim construction, the Board's obviousness decision should be affirmed.

Dated: September 3, 2019

Respectfully submitted,

/s/ Sarah E. Craven

THOMAS W. KRAUSE
Solicitor

SARAH E. CRAVEN
MAUREEN D. QUELER
Associate Solicitors

Office of the Solicitor
U.S. Patent & Trademark Office
Mail Stop 8, P.O. Box 1450
Alexandria, Virginia 22313
(571) 272-9035

Attorneys for the Director of the U.S. Patent & Trademark Office

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 6,912 words as calculated using the Word® software program.

/s/ Sarah E. Craven
Sarah E. Craven
Associate Solicitor
Office of the Solicitor
U.S. Patent and Trademark Office
Mail Stop 8, P.O. Box 1450
Alexandria, Virginia 22313
(571) 272-9035

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).

/s/ Sarah E. Craven
Sarah E. Craven
Associate Solicitor
Office of the Solicitor
U.S. Patent & Trademark Office
Mail Stop 8, P.O. Box 1450
Alexandria, Virginia 22313
(571) 272-9035