2019-1263

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 IPR2017-00731.

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*.

Appx225 33:46-54 (disputed limitations emphasized).

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Regulations

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. 19-1265 (Fed. Cir.); *Genentech, Inc. v. Iancu*, No. 19-1267 (Fed. Cir.); and *Genentech, Inc. v. Iancu*, No. 19-1270 (Fed. Cir.).

The table below summarizes the four companion appeals:

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

STATEMENT OF THE ISSUES

Genentech's '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 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, Baselga '94 and '96, teach 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.

Before issuing its final decision, the Board denied Genentech's request for a *second* motion to amend, both as of right and for good cause. The Board instituted review pre-*SAS* on Ground 2 (Baselga '94 and '96), after which Genentech filed a contingent motion to amend. Following *SAS*, the Board modified the IPR to include Ground 1 (Baselga '94 and '97), and Genentech then sought a second (though non-contingent) motion to amend. The Board decided that 35 U.S.C. § 316(d)(1) permits just one motion as of right during an IPR. And the Board decided that because Genentech could have proposed its second amended claim in its first motion to amend, Genentech had not

shown good cause to file a second motion under 35 U.S.C. § 316(d)(2) and 37 C.F.R. § 42.121(c). Alternatively, because Genentech argued that the addition of Ground 1 after *SAS* justified the second amendment, the Board found the issue moot after the Board decided to grant the petitioner's request for a partial adverse judgment to end its challenge to any claim on Ground 1. A threshold issue on appeal is whether the Board's entire decision should be vacated to give Genentech a redo with a second amended claim.

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 were obvious over Baselga '94[1] and '96[2] (Ground 2); denied Genentech's first, contingent motion to amend; and granted an adverse judgment against petitioner Hospira, Inc. as to Baselga '94 and '97[3] (Ground

[1] 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). Appx1082-1085.

[2] 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 1066-1081.

[3] Baselga et al., *HER2 Overexpression and Paclitaxel Sensitivity in Breast Cancer: Therapeutic Implications*, 11(3) (Suppl. 2) Oncology 43-48 (1997). Appx1087-1097.

1). The Board also denied Genentech's request to file a second motion to amend. Genentech appealed the Board's decision to this Court, after which the parties settled and Hospira 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. Appx209 1:20-29; Appx211 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. Appx210 3:41-50; Appx12586-12587. The chemotherapeutic paclitaxel (Taxol®), in contrast, not only showed significant antitumor activity against breast cancer in general, with a time to disease progression (or "TTP") of 3.0 or 4.2 months (Appx10054), but also was reported in the mid-1990s to be particularly effective against HER2-overexpressing breast cancer (Appx1093-1094 (describing Seidman '96, Appx5811-5815)). Specifically, HER2-positive patients responded clinically to paclitaxel treatment at three times the rate of HER2-negative patients. Appx210 3:50-54.

Another treatment for HER2-overexpressing breast cancer also appeared in the mid-1990s: Herceptin. Appx210 3:34-40. Herceptin is a recombinant humanized version of the mouse anti-ErbB2 antibody 4D5 (humanized MAb 4D5). Appx209 2:1-29; Appx210 3:34-40. It targets HER2-overexpressing cells and acts clinically to treat HER2-positive breast cancer. Appx210 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 both "remarkably well tolerated" and clinically effective. Appx1074; Appx1076. The study reports minimal toxicity and a remission rate of 11.6% (5 out of 43 assessable patients). Appx1077. 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." Appx1077; Appx1078.

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. Appx1080. Baselga '94 describes these preclinical xenograft studies. Appx1085. 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. Appx1085. Based on these results, Baselga '94 and Baselga '96 both report that clinical trials of the combination therapy were underway. Appx1080; Appx1085.

Baselga '97, which Genentech has repeatedly antedated (Appx12136-12137; Appx12311-12312; Appx12891-12892), is a review article of studies aimed at treating HER2-overexpressing breast cancer. Appx1092. These include the earlier Baselga '94 and '96 studies, which Baselga '97 credits with leading to a phase III clinical trial of Herceptin and paclitaxel to treat HER2-overexpressing breast cancer. Appx1095-1096. Beyond Baselga '94 and '96, Baselga '97 discloses that this ongoing phase III trial includes a paclitaxel control arm and a TTP endpoint. Appx1096.

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. Appx222-223 27:13-30:25. The trial's endpoints included response rate and TTP. Appx223 29:11-15; *see also* Appx213 10:47-50. Consistent with the prior art, the TTP for paclitaxel alone (T) was 4.2 months. In contrast, combination paclitaxel-Herceptin therapy (T+H) achieved a TTP of 7.1 months. Appx223 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 tested combination Herceptin-anthracycline/cyclophosphamide therapy (AC+H) and the latter alone (AC). Appx223 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). Appx225-226. 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*.

Appx225 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]." Appx2048-2051; Appx2080 (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?" Appx2051. 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*." Appx2081-2082 (emphasis added). The examiner then allowed the claims, but suspended prosecution due to a potential interference. Appx2356-2357. 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* Appx4524-4525. The claims issued with both limitations. Appx225.

II. The Proceedings

A. The Board's decision instituting an IPR, modifying that IPR, and denying a second motion to amend

Hospira filed a petition for *inter partes* review of the '441 patent. The petition challenged the claims as obvious over either Baselga '94 and '97 (Ground 1), or Baselga '94 and '96 (Ground 2). Appx31. The Board instituted

the review pre-*SAS* on Ground 2, but not Ground 1. Appx32. In its institution decision, the Board construed the claimed efficacy and safety effects as compared to untreated patients based on Genentech's unequivocal statement during prosecution. Appx12381-12383.

After institution, Genentech filed a response and a contingent motion to amend. Appx32; Appx12532. In its amendment, Genentech narrowed claim 11 to Herceptin and paclitaxel specifically and, to nullify the Board's claim construction, added that the claimed efficacy and safety were "compared to paclitaxel alone." Appx12536-12540. The petitioner then filed a reply and an opposition to Genentech's motion to amend. Appx32. In its opposition, the petitioner argued that the amendments added new matter as the specification failed to disclose that the claimed drug combination did not increase severe adverse events compared to paclitaxel alone. Appx12758-12762. The opposition also argued unpatentability of the amended claim over the prior art, including Baselga '97. Appx12764-12776. In reply, Genentech again sought to antedate Baselga '97. Appx12891-12892.

Six months after institution, the Supreme Court decided *SAS Institute, Inc. v. Iancu*, 138 S. Ct. 1348 (2018), and the Board modified its institution decision to add Ground 1 (Baselga '94 and '97). Appx34. Following several conferences with the parties, the Board denied Genentech's request

to file a second motion to amend as of right under 35 U.S.C. § 316(d)(1), instead requiring Genentech to file a good-cause motion under 35 U.S.C. § 316(d)(2) and 37 C.F.R. § 42.121(c). Appx35-36.

Genentech filed a request for rehearing, which the Board denied. Appx1-11. As the Board explained, § 316(d)(1) permits a patent owner just one motion to amend during an IPR, and Genentech had already filed such a motion. Appx4-6. The Board concluded that adding Ground 1 into an already-instituted IPR did not give the patentee the right to a second motion to amend. Appx6. And, according to the Board, this was especially true here where originally instituted Ground 2 challenged the same claims and relied on substantially similar disclosures as did Ground 1, with Baselga '96 disclosing the same clinical trial detailed in Baselga '97. Appx6. The Board also found that Genentech had received adequate notice of Baselga '97's relevance to its first motion to amend: Baselga '97 was part of the record and Genentech addressed it as such in its first motion. Appx6-7.

Finally, the Board rejected Genentech's assertion that the law had changed. The Board disagreed that any change to the Board's amendment practice after the de-designation of *Idle Free, Sys., Inc. v. Bergstrom, Inc.*, IPR2012-00027, Paper 26 (P.T.A.B. June 11, 2013), as "informative" and its replacement by *Western Digital Corp. v. SPEX Techs., Inc.*, IPR2018-00082,

-00084, Paper 13 (P.T.A.B. Apr. 25, 2018), justified a second motion to amend to respond to Baselga '97. Appx8. The Board pointed out that even before *Western Digital*, the Board's practice permitted amendments that did not specifically respond to an instituted ground and that Genentech's first motion to amend included such amendments. Appx9. The Board further found that Genentech's second amendment did not specifically respond to Baselga '97. Appx8.

For the same reasons, the Board denied Genentech's good-cause motion for a second amendment, even if non-contingent. Appx15-20. Regarding its non-contingency, the Board found that Genentech's second proposed claim would affect not only claim scope, but also inventorship, and thus would require additional discovery and briefing with only three months left before the Board had to issue its final decision. Appx20. Because the Board found that Genentech could have presented its second amended claim in its first motion to amend, the Board decided that Genentech had not shown good cause for a second motion to amend. Appx20-21.

Having found no good cause, the Board went on to conclude that the issue was also moot in light of the Board's decision to grant the petitioner's request for an adverse judgment as to Ground 1 under 37 C.F.R. § 42.73(b). Appx21-22. The Board disagreed with Genentech that an *adverse* judgment

must include all the instituted grounds to satisfy 37 C.F.R. § 42.73(a), which requires that a judgment dispose of all the issues. Appx21; Appx38-39. But regardless, the Board concluded that its final decision addressing the patentability of the original claims under Ground 2 and granting an adverse judgment on Ground 1 would satisfy § 42.73(a). Appx21; Appx39. The Board relied on *SAS* and the Board's practice as confirming its reading of the rules: they instruct that it is the petitioner's contentions that define the scope of the proceeding from institution to conclusion. Appx22; Appx39-40. Finally, the Board noted that, to the extent the rules did require an adverse judgment to dispose of all the issues in the case, the Board was exercising its authority to waive that requirement. Appx21-22 (citing 37 C.F.R. § 42.5(b)).

B. The Board's final decision holding that the claims would have been obvious over Baselga '94 and '96

The Board then issued its final written decision finding all of the challenged claims obvious. Appx40-74. Starting with claim construction, the Board maintained its construction of the limitation "extend the [TTP]" as being compared to no treatment. Appx42. The Board again relied on Genentech's unambiguous statement during prosecution that the claimed drug combination extends TTP "relative to an untreated patient." Appx44 (quoting Appx2082).

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. Appx44-45 (quoting Appx9626 ¶ 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 untreated patients. Appx45.

Finally, the Board was unpersuaded that the claimed safety effect—"without [an] increase in overall severe adverse events"—required a comparison to *some* treatment. Appx45. As the Board explained, the applicant added the safety limitation after explicitly defining the comparator as "an untreated patient." Appx46. 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. Appx46-47; Appx47 n.12.

Turning to obviousness, the Board found that Baselga '94 and '96 collectively teach administering a combination of Herceptin and paclitaxel to treat HER2-overexpressing breast cancer as claimed. Appx47-63. The Board also found that a skilled artisan would have had a reasonable expectation that administering an effective amount of the claimed drug combination would achieve the claimed efficacy and safety effects compared to untreated patients. Appx63-64. Alternatively, the Board found a reasonable expectation of success even under Genentech's claim construction, i.e., compared to patients treated with paclitaxel alone. Appx64-65.

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, described as "unusually long," to the Taxol® PDR's disclosure of a median TTP for paclitaxel of just 3.0 or 4.2 months. Appx65. Because Baselga '96 reports that Herceptin achieved a longer TTP than paclitaxel, at least for HER2-positive patients, the Board found a reasonable expectation that adding Herceptin to paclitaxel would extend the TTP relative to paclitaxel alone. Appx65-66. The Board then noted that its conclusion was

"further supported" by Genentech's FDA submissions, in which Genentech stated that, based on Baselga '94's preclinical studies, it is anticipated that Herceptin in combination with paclitaxel chemotherapy will "enhance efficacy" compared to either regimen used alone. Appx66.

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. Appx66. 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. Appx67; *see also* Appx57-58. Rejecting Genentech's argument that Baselga '94 had failed to predict the increased cardiotoxicity of combination Herceptin-doxorubicin therapy in human patients, 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. Appx66-68.

Finally, the Board denied Genentech's first, contingent motion to amend. Appx75. 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 claim, paclitaxel alone. Appx75-79.

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

As a threshold issue, Genentech seeks to vacate the Board's decision and secure a redo of its first, unsuccessful motion to amend. Neither the statute nor Genentech's good-cause motion supports granting Genentech a second motion to amend. Section 316(d)(1) provides for just one motion as of right during an IPR, and modifying the IPR post-*SAS* to add Ground 1 did not institute a new IPR with a new right to amend. Adding Ground 1 also did not introduce any new issue for a showing of good cause: Baselga '97's relevant disclosure not only is similar to Baselga '94 and '96's, but also was already of record and addressed during Genentech's first motion to amend. Nor did the law change. The Board's amendment guidance post-*Aqua Products* did not suddenly alter Genentech's ability to propose narrowing amendments. Accordingly, Genentech could have proposed its second amended claim, with all its narrowing amendments, in its first motion to amend and thus failed to show good cause for a second motion to amend.

Moreover, rather than overcoming Baselga '97, Genentech's second amendment attempted to correct a new-matter issue with its first motion to amend. It changed the comparator for the safety effect (which it also amended) from paclitaxel alone (which the Board found the specification did not support) to a different drug combination (which the specification may support). In response, the petitioner requested an adverse judgment to end its challenge to all claims on Ground 1. Because the petitioner's contentions define the scope of any IPR, the Board did not err in granting a partial adverse judgment in its final decision and thus denying Genentech's good-cause motion for a second, independent reason: as moot. Genentech's request for a redo of its first, unsuccessful motion to amend should be denied.

On the merits, Genentech does not dispute much of the Board's obviousness decision. Genentech does not dispute that, based on the teachings of Baselga '96 and '94, 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 the Board relied on the Baselga references' collective disclosure that Herceptin is well tolerated in humans and, while increasing efficacy, does not increase the toxicity of FDA-approved paclitaxel in preclinical studies such that clinical trials of the combination therapy were underway. 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.

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 Board Properly Denied Genentech a Second Motion to Amend both as of Right and for Good Cause

The Board properly denied Genentech a second motion to amend, both as of right and for good cause. The statute, 35 U.S.C. § 316(d)(1), expressly limits patentees to one motion to amend as of right during an IPR. And, because Genentech could have presented its second amended claim in its first motion to amend, Genentech failed to show good cause for a second motion under 35 U.S.C. § 316(d)(2) and 37 C.F.R. § 42.121(c). The Board also properly denied Genentech's good-cause motion for a second, independent reason: the issue was mooted by the Board's decision to grant the petitioner's request for an adverse judgment against itself on Ground 1. In sum, Genentech exercised its right to amend its claims during the IPR. It fails to show entitlement to a redo now.

A. The statute limits patent owners to just one motion to amend as of right during an IPR proceeding

The statute is clear: "During an inter partes review instituted under this chapter, the patent owner may file 1 motion to amend the patent." 35 U.S.C. § 316(d)(1). While the statute permits additional motions to amend, it does so only in limited circumstances, including "as permitted by regula-

tions prescribed by the Director." *Id.* § 316(d)(2). And the relevant regulation, 37 C.F.R. § 42.121(c), requires a patentee to show good cause for a second amendment motion. The statutory and regulatory scheme thus contemplate only a single motion to amend as a matter of right during an IPR.

Here, Genentech exercised its right to a file a motion to amend under § 316(d)(1). After the Board instituted the IPR, Genentech filed a contingent motion to amend. That amendment responded, in part, to the Board's institution construction of "extend the [TTP]" as compared to untreated patients. Appx12381-12383. Genentech added a limitation to make the comparator "paclitaxel alone." Appx12537. Because Genentech exercised its statutory right to one motion to amend during the IPR, when Genentech requested a second motion, the Board properly required Genentech to show good cause.

Genentech argues that the Board erred because, after *SAS*, it added Ground 1 to the IPR. Appellant's Brief ("Br.") at 26-27. According to Genentech, "[w]hen Genentech filed its first motion to amend, no proceeding had been 'instituted' at all on Ground 1 nor was there an opportunity to amend 'during' the proceedings on Ground 1." Br. at 27. The statute, however, does not tie the amendment right to each ground of unpatentability, but to the IPR itself; it allows one motion to amend "[d]uring an inter partes review instituted under this chapter," regardless of how many grounds. 35 U.S.C.

§ 316(d)(1). Nor does the statute make each ground a separate IPR. Rather, a single petition identifies "each claim challenged" and on what "grounds" *id.* § 312(a)(3), after which the Director may authorize an IPR—a single review proceeding—if the petition meets the statutory threshold, *id.* § 314(a). By adding Ground 1, the Board simply modified an already-existing IPR. Appx13080-13082. It did not institute a new IPR, with a new one-year decision period, 35 U.S.C. § 316(a)(11); a new § 315(b) time-bar date; a new opportunity for § 315(c) joinder; or, as the Board decided here, a new right to amend.

Genentech's argument implies that the result is unfair: that because the Board had not initially instituted the IPR on Ground 1, it never had a chance to amend based on Ground 1. Br. at 27. Not so, as explained below. Yet, any alleged unfairness goes to whether Genentech showed good cause, not whether the statute permits a second motion as of right when the Board modifies an already-instituted IPR (an unlikely scenario after *SAS*). Because the statute is clear that a patentee is limited to one motion to amend as of right during an IPR, and Genentech filed such a motion during the IPR below, the Board did not violate Genentech's statutory right by requiring a good-cause motion for a second motion to amend.

B. Genentech failed to show good cause for a second motion to amend since it could have included its second amended claim in its first motion to amend

Section 316(d)(2) permits additional motions to amend, which by regulation require a showing of good cause. 37 C.F.R. § 42.121(c). The Board found that, since Genentech could have proposed its second amended claim in its first motion to amend, Genentech had not shown good cause. Genentech fails to show either a new issue raised by Ground 1 or a change in the Board's amendment practice that would support a finding of good cause.

Contrary to Genentech's argument, adding Ground 1 did not introduce a new issue into the IPR. Br. at 31-32. Ground 2 already challenged all of the claims based on Baselga '94 and '96's "similar" relevant disclosures to Baselga '97. Appx15-16; Appx18. As the Board found, Baselga '97 simply details the design—the paclitaxel comparator and the TTP endpoint—of an ongoing Herceptin-paclitaxel clinical trial already mentioned in the earlier Baselga references. Appx16; *compare* Appx1080; Appx1085, *with* Appx1095-1096. Contrary to Genentech's belief that "Baselga '96 lacked any disclosure of the combination of [Herceptin] and paclitaxel in human trials" (Br. at 31), both Baselga '96 and '94 state that clinical trials of that exact drug combination were underway. Appx48 (quoting Appx1080; Appx1085).

Yet, regardless of the similarity of the references' disclosures, Baselga '97 was cited in the petition and thus was part of the record that Genentech had to overcome for any amendment, including its first motion to amend. *See* Appx16-17 (citing *Aqua Products, Inc., v. Matal*, 872 F.3d 1290, 1325 (Fed. Cir. 2017) (en banc)). And Genentech appears to have understood this. In its first motion to amend, Genentech stated that its proposed substitute claim responded to the "asserted grounds"—plural—not simply instituted Ground 2. Appx12542 (emphasis added). And Genentech's reply in support of its first motion to amend addressed Baselga '97. Genentech argued—as it had during prosecution and in its preliminary response—that Baselga '97 was not prior art. Appx12891-12892.

Furthermore, Genentech's second amendment did not respond to Baselga '97's unique disclosure of a TTP endpoint and paclitaxel control arm. *See* Appx18-19. Rather, the amended claim again added a paclitaxel comparator to nullify the Board's construction of "extend the [TTP]" as compared to untreated patients, as Genentech admits. Br. at 2. And it further responded to petitioner's argument that adding a paclitaxel comparator for the safety effect introduced new matter, i.e., the specification failed to disclose "without [an] increase in overall severe adverse events" compared to

paclitaxel alone.[4] Appx12759-12760. Genentech's second amendment corrected the new-matter problem, changing "severe adverse events" to "Grade 3/4 myocardial dysfunction" and its comparator to "a combined treatment of doxorubicin or epirubicin [anthracyclines]; cyclophosphamide; and [Herceptin]," limitations that the specification appears to support. Appx18-19; Appx13333-13334; *see also* Appx223 30:13-16. Addressing a defect with its first motion, however, fails to show good cause for a second motion to amend.

Genentech also argues a change of law. Specifically, Genentech argues that the Board's guidance on narrowing amendments became less restrictive between Genentech's first motion, governed by *Idle Free*, and its second under *Western Digital*. Br. at 32-34. In other words, according to Genentech, the Board's practice restricted it from presenting amendments responsive to Baselga '97 in its first motion because Baselga '97 was not part of an instituted ground. But, as the Board found, Genentech's first motion already embraced the legal position that Genentech ascribes to *Western Digital*: that not all amendments need respond to a ground of unpatentability. Appx18-20 (citing Appx12542 n.3 ("It is not required that *every* amended limitation be solely for the purpose of overcoming an instituted ground.")). Indeed,

[4] The Board agreed and denied Genentech's first motion to amend for adding new matter. Appx74-79. Genentech did not appeal that decision.

Genentech's first amendment narrowed the claim specifically to Herceptin and paclitaxel, but those amendments did not respond to instituted Ground 2 as both Baselga '94 and '96 disclose Herceptin and paclitaxel specifically. Appx19; Appx12536-12537. Likewise, nothing prevented Genentech in its first motion from also narrowing "severe adverse events" to "Grade 3/4 myocardial dysfunction" and altering its comparator for any of the challenged claims. *See Idle Free*, IPR2012-00027, Paper 26 at 5 (quoting 35 U.S.C. § 316(d)(1)(B) as allowing a reasonable number of substitute claims for "each" challenged claim).

This is especially so given that the shift from *Idle Free* to *Western Digital* did not work the dramatic shift in the law that Genentech contends. Br. at 32-33. *Idle Free* states that to respond to a ground of unpatentability, a proposed substitute claim must "either include or narrow each feature of the challenged claim being replaced." IPR2012-00027, Paper 26 at 5. Nowhere does *Idle Free* prohibit further narrowing amendments that do not respond to a ground of unpatentability. And *Idle Free*'s loss of "informative" status resulted not because of anything it said about narrowing amendments, but because it put the burden of proof on the patentee, a framework this Court later rejected in *Aqua Products*, 872 F.3d 1290. In response, the Board elevated *Western Digital*. IPR2018-00082, Paper 13 at 3-4. Notably,

Western Digital's statement on amendments cites the same case law that Genentech cited in its first motion to amend. *Compare id.* at 6 (citing *Veeam Software Corp. v. Veritas Techs., LLC*, IPR2014-00090, Paper 48 at 26-29 (P.T.A.B. July 17, 2017)), *with* Appx12542 n.3.

Finally, Genentech argues that its second, non-contingent motion to amend "would not have unduly delayed the proceedings." Br. at 34-35. The Board disagreed. The Board found that this second motion would require complicated briefing, including on inventorship of the newly claimed subject matter, with only three months remaining before the statutory deadline to issue a final decision. Appx20. Thus, given that Genentech could have presented its second amended claim in its first motion to amend, the Board did not abuse its discretion in denying Genentech an additional motion to amend. Appx20.

C. Alternatively, the Board properly denied Genentech's second motion to amend as moot after deciding to grant petitioner a partial adverse judgment

Having found no good cause, the Board also denied Genentech's motion as moot after the Board decided to grant an adverse judgment against the petitioner on Ground 1 under 37 C.F.R. § 42.73(b). Appx21-22; *see also* Appx38-40. The Board did not err in denying Genentech's good-cause motion for this second, independent reason.

Genentech argues that the rule does not permit *partial* adverse judgments, i.e., judgments that do not dispose of all of the grounds. Br. at 28-30. The Board disagreed but concluded that even if true, its final decision satisfied the rule by disposing of Ground 2 on the merits and Ground 1 as an adverse judgment. Appx21. In any event, to the extent the rule does not contemplate partial adverse judgments, the Board expressly exercised its discretion to waive the rule and allow a partial adverse judgment against the petitioner here. Appx22 (citing 37 C.F.R. § 42.5(b)). Genentech does not contest the latter decision, and thus the Board's decision should stand. Regardless, since the petitioner's contentions define the scope of any IPR, *SAS*, 138 S. Ct. at 1357, the petitioner could easily accomplish the same result by simply conceding an instituted ground. The patent owner thus faces no prejudice if the petitioner formally drops its challenge on any ground via an adverse judgment.

Genentech claims "gamesmanship" here, however, as it believes the petitioner sought an adverse judgment on Ground 1 for the sole purpose of scuttling its second amendment. Br. at 28-29. And Genentech suggests that other petitioners may play games by raising and then dropping a wide array of shifting arguments. Br. at 29. Genentech's position incorrectly presumes

no negative effects of such conduct on petitioners. To the contrary, incomplete arguments may doom institution of the petition, and the Board's adverse judgment as part of its final written decision triggers the estoppel provisions of 35 U.S.C. § 315(e)(1), preventing petitioners from raising any of same grounds in any later proceeding. Genentech asserts no prejudice here other than losing its chance at a second motion to amend, which it independently lost when it failed to show good cause. Moreover, because Genentech's second amendment attempted to correct a new-matter defect with its first motion, not to address Ground 1 or Baselga '97 as it contended, the petitioner likely viewed Genentech's second amendment as the opening salvo in IPR "gamesmanship," making the petitioner's request for a partial adverse judgment a proportional response. *See* Appx13228-13231 (order allowing Genentech to file a good-cause motion); Appx13333-13334 (good-cause motion with second amended claim); Appx13392-13396 (order authorizing filing of a partial adverse judgment). The Board did not abuse its discretion, or otherwise err, in denying Genentech a second motion to amend.

II. The Claims of the '441 Patent Would Have Been Obvious

Turning to the merits, the Board properly concluded that the claims of the '441 patent would have been obvious over Baselga '94 and '96. 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

[5] The petition in this IPR was filed on January 20, 2017, before the Board switched the IPR claim-construction standard from the broadest reasonable interpretation to the *Phillips* standard. The rule change applies only to IPR

be "relevant as reinforcing the evident meaning of the claim language at issue, whether or not it would meet standards for disclaimer or disavowal." *D'Agostino v. MasterCard Int'l Inc.*, 844 F.3d 945, 949 (Fed. Cir. 2016).

Here, during prosecution, Genentech unambiguously stated that the limitation "extend the time to disease progression" was "[c]learly . . . relative to an untreated patient." Appx44; Appx2082. Genentech argues that the statement does not rise to the level of a clear and unmistakable disclaimer, but was simply "inartful." Br. at 38-39. 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?" Appx2051. From this list, Genentech selected "an untreated patient." Appx2082. That Genentech never repeated this statement (Br. at 41) is unsurprising as its original statement sufficed to overcome the rejection. Appx2356. At bottom,

---

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).

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 39-40. 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." Appx2051. And, again, Genentech expressly chose untreated patients. Appx2082. 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. Appx2082 (citing Appx1345; Appx1372-1373); Br. at 39-40 (citing Appx1373).

This choice also did not create any conflict with the claims or specification, as Genentech implies. Br. at 36-37. 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 37. Second, though the specification's phase III trial com-

pared 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. Appx44-45. 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." Appx221 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. Appx223. And, contrary to Genentech's assertion (Br. at 37 n.6), 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 37-38, 40-41. 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* Appx46-47. Claim interpretation cannot give a term a different construction than did the applicant to avoid a "nonsensical result." Appx47 (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* Appx75-79. As the Board found, the percentage of adverse events for the paclitaxel-Herceptin combination at 70% is *higher* than the 59% for paclitaxel alone. Appx77 (citing Appx223 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 (*see supra* Argument I.B. n.4); 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 '94 and '96. Genentech limits its challenge of the

Board's decision to the Board's findings of a reasonable expectation of success. Br. at 41-42.

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 overall severe adverse events (the claimed safety effect) compared to paclitaxel alone. Appx51-70. Substantial evidence supports the Board's findings.

The Board first found that the Baselga references collectively teach administering a combination of Herceptin and paclitaxel to treat HER2-overexpressing breast cancer in human patients. Appx59; Appx63. As the Board found, Baselga '96 teaches that Herceptin, similar to already FDA-approved paclitaxel, is safe and clinically effective in treating HER2-overexpressing breast cancer. Appx47-48; Appx49-50; Appx59; Appx61-62. And Baselga '94 reports that Herceptin markedly potentiated paclitaxel's anti-tumor effect without increasing its toxicity in preclinical xenograft studies. Appx48; Appx50; Appx59. Based on these results, both Baselga references state that clinical trials of the combination therapy were underway. Appx48;

Appx59. 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. Appx64-70. For extending the TTP, the Board found that Baselga '96 discloses a median TTP for Herceptin of 5.1 months, described as "unusually long," while the Taxol® PDR reports a median TTP for paclitaxel of just 3.0 or 4.2 months. Appx65 (citing Appx1078; Appx10054). The Board thus 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. Appx65-66. The Board also properly found its conclusion further supported by Genentech's representations to the FDA, including Genentech's statement 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. Appx66.

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, while both Baselga references teach that adding Herceptin to FDA-approved paclitaxel, while increasing efficacy, did not increase paclitaxel's toxicity in preclinical studies. Appx66 (citing Appx1076; Appx1078; Appx1080; Appx1085). Responding to Genentech's challenge to Baselga '94's preclinical data as not a reliable predictor of success in humans, the Board properly found Genentech's assertion "refute[d]" by its own reliance on Baselga '94 when seeking FDA approval to test the drug combination in humans. Appx67. Substantial evidence thus backs the Board findings that a skilled artisan would have reasonably expected the claimed drug combination to extend TTP without increasing severe adverse effects compared to paclitaxel alone. Appx69-70.

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 42-47. 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 48-51. 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. 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 43. Not so. As Baselga '96 reports, Herceptin's TTP was "unusually long"; it improves TTP compared to expectations. *See* Appx65 (quoting Appx1078). The Board then directly compared Baselga '96's disclosure of Herceptin's TTP to paclitaxel's known TTP—5.1 months versus 3.0 or 4.2 months. Appx65. Thus, in the context of the prior art as a whole, Baselga '96 provides a reasonable expectation that adding Herceptin to paclitaxel would extend TTP compared to paclitaxel alone. Appx65; *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 43-44. Genentech, however, never made this argument before the Board. While the petition relied on Baselga '96's 5.1-month TTP

to teach extending TTP (Appx12021-12022; Appx12057-12059), 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 (Appx12618-12619 (dated December 22, 2017)). Now, before this Court, Genentech cites testimony filed with its reply in support of its motion to amend. Br. at 44 (citing Ex. 2144 (Appx10659-10663) (dated April 20, 2018)); Appx12886-12889 (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. Appx10660-10661. 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. Appx1077. It thus excludes patients with no response, as Genentech notes, potentially skewing the results upward (Br. at 44), 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* Appx1078, Table 5. Genentech

[6] 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 '441 patent provides no guidance, though it too reports a significant number of non-responders. *See* Appx223. It is thus far from clear that the median TTP for Baselga '96's entire patient population would, as Genentech argues (Br. at 44), necessarily be shorter than 5.1 months, 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* Appx12618-12619. Genentech's new and factually incomplete attack on Baselga '96 should be rejected.

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 (1) Herceptin and paclitaxel alone and (2) the combination in preclinical studies only. Such information, says Genentech, fails to address the "possible toxicity" of the combination in humans. Br. at

---

limit response rates and further skew the results downward. Appx1078; *see also* Appx1080 ("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.

45. 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 45. The Taxol® PDR, however, reports few *severe* neuropathic and cardiovascular events in 812 patients receiving paclitaxel. Appx10055 (reporting three patients with severe peripheral neuropathy and one with a significant cardiovascular event); *see also* Appx12802-12803. Regardless, under Genentech's construction, the comparator *is* paclitaxel; paclitaxel's toxicity sets the baseline. As such, Baselga '96's disclosure that Herceptin is well tolerated in human—who express the *human* ErbB2 receptor (*see* Br. at 46-47)—provides a reasonable expectation that the addition of Herceptin will not increase severe adverse events compared to any toxicity associated with paclitaxel alone. Indeed, Baselga '94 administered the combination in xenografts and reported that Herceptin did not increase toxicity compared to paclitaxel alone. Appx66; Appx1085.

Genentech next attacks Baselga '94, arguing that its preclinical studies do not reliably predict effectiveness or safety in humans. Br. at 46. The Board rejected all of Genentech's alleged limitations with Baselga '94's study. Appx52-59. Genentech does not repeat these arguments on appeal.

Furthermore, as the inventor of the '441 patent testified, the whole point of Baselga '94 was "to look at trying to predict what can be helpful in patients," not to cure cancer in mice. Appx12790 (quoting Appx6804 48:19–49:1); Appx12793-12795. And skilled artisans *did* look to Baselga '94 as a "motivation for clinical evaluation." Appx5704; *see also* Appx5716 (describing Baselga '94's data as "the basis for a planned clinical trial in patients"). This included Genentech. As the Board remarked, contrary to Genentech's current litigation-inspired attacks on Baselga '94's preclinical studies here, Genentech relied on these studies to convince the FDA to approve its phase III clinical trial of Herceptin-paclitaxel therapy against paclitaxel alone. Appx67; *see also* Appx12806-12807. At bottom, though Baselga '94 showed that Herceptin markedly potentiates paclitaxel's antitumor effect without 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 47. As the Board explained, Genentech characterized the Herceptin-doxorubicin combination's increased 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. Appx67 (quoting Appx12597).

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 47. Genentech criticizes preclinical animal studies—studies "critical for the evaluation of new agents and therapeutic approaches for the treatment of breast cancer" (Appx12799 (quoting Appx5719; Appx6729 195:22-197:1))—because they are less predictive than clinical trials in humans. Br. at 47. 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 48-51. 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 48 (citing Appx66). 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. Appx55-58. Also undermining Genentech's attacks: Genentech's own reliance on Baselga '94 to convince the FDA to allow phase III trials in humans. Appx57-58. 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. Appx66. Hence, the Board did not "rely on the inventor's perspective on the prior art to support a finding of obviousness" (Br. at 49), 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 49-50 (citing Appx67). The Board relied, in part, on Baselga '94's disclosure that Herceptin did not

increase paclitaxel's toxicity. Appx66; Appx68. 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. Appx67 (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. Appx67. 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 did not err in denying Genentech's second motion to amend when neither the statute nor good cause merited it, the Court should affirm and rule on the Board's obviousness decision. And because the Board did not err in its claim construction based on Genentech's unambiguous prosecution statement or, alternatively, in finding a reasonable expectation of success 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 10,097 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