No. 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 No. IPR2017-01121

REPLY BRIEF FOR APPELLANT GENENTECH, INC.

DARALYN J. DURIE
ADAM R. BRAUSA
DURIE TANGRI LLP
217 Leidesdorff Street
San Francisco, CA 94111
(415) 362-6666

ANDREW J. DANFORD
WILMER CUTLER PICKERING
HALE AND DORR LLP
60 State Street
Boston, MA 02109
(617) 526-6000

ROBERT J. GUNTHER, JR.
WILMER CUTLER PICKERING
HALE AND DORR LLP
7 World Trade Center
250 Greenwich Street
New York, NY 10007
(212) 230-8800

NORA Q.E. PASSAMANECK
WILMER CUTLER PICKERING
HALE AND DORR LLP
1225 Seventeenth Street
Suite 2600
Denver, CO 80202
(720) 274-3135

THOMAS G. SPRANKLING
WILMER CUTLER PICKERING
HALE AND DORR LLP
950 Page Mill Road
Palo Alto, CA 94304
(650) 858-6000

THOMAS G. SAUNDERS
WILMER CUTLER PICKERING
HALE AND DORR LLP
1875 Pennsylvania Avenue NW
Washington, DC 20006
(202) 663-6000

October 15, 2019

CERTIFICATE OF INTEREST

Counsel for Appellant Genentech, Inc. certifies the following:

1. The full name of every party or *amicus* represented by me is:

Genentech, Inc.

2. The names of the real party in interest represented by me is:

Not applicable.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Genentech, Inc. is a wholly-owned subsidiary of Roche Holdings Inc. Roche Holdings Inc.'s ultimate parent, Roche Holdings Ltd, is a publicly held Swiss corporation traded on the Swiss Stock Exchange. Upon information and belief, more than 10% of Roche Holdings Ltd's voting shares are held either directly or indirectly by Novartis AG, a publicly held Swiss corporation.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this Court (and who have not or will not enter an appearance in this case) are:

WILMER CUTLER PICKERING HALE AND DORR LLP: Owen K. Allen (former), Lauren V. Blakely, David L. Cavanaugh, Lisa J. Pirozzolo, Kevin S. Prussia, Rebecca A. Whitfield (former)

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this Court's decision in the pending appeal:

Genentech, Inc. et al. 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.)
Genentech, Inc. v. Iancu, No. 19-1270 (Fed. Cir.)

Dated: October 15, 2019

/s/ Robert J. Gunther, Jr.

ROBERT J. GUNTHER, JR.
WILMER CUTLER PICKERING
HALE AND DORR LLP
7 World Trade Center
250 Greenwich Street
New York, NY 10007
(212) 230-8800

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INTRODUCTION

It is undisputed that when Genentech created the claimed drug combination, using drugs never before combined to treat humans, its invention revolutionized breast cancer treatment and became the first antibody-based first-line therapy for treatment of solid tumors ever approved by the FDA. The Board's decision deprived Genentech of its claims to that novel combination. But the Board's decision was flawed from start to finish, and the government's efforts to backfill on appeal cannot save it.

The government's brief is most notable for what it does not say. The government does not identify any language in the claims or specification that would support the Board's claim construction. It also does not dispute that the Board's construction—which compares the claimed combination to a patient left entirely untreated—makes no practical sense. The government instead relies on a single statement from the prosecution history, while disregarding the citations embedded in that statement and the subsequent amendment of the claims, both of which inform how a person of skill in the art would view the claims. The resulting ambiguity means that the statement falls short of meeting the demanding standard for establishing a prosecution disclaimer.

Similarly, in defending the Board's ruling that the claims are obvious under the correct construction, the government does not dispute that the Board's holding

depends on a faulty measure of efficacy that "excludes patients with no response [to treatment] … potentially skewing the results upward." PTO Br. 27. The government's contention that Genentech somehow waived this argument ignores that the petitioner never raised the issue in its petition and Genentech identified the reference's shortcomings at its first opportunity after the argument was eventually made. The government also fails to plug the holes in the Board's reasoning on the safety element in the claims and does not dispute that the Board relied on the inventor's own path to support its finding of obviousness.

The Board's numerous errors deprived Genentech of protection for its foundational discovery, disclosed for the first time in its patent application. The Board's decision should be reversed or, at a minimum, vacated and remanded for correction of these errors.

ARGUMENT

I. THE GOVERNMENT'S ATTEMPT TO DEFEND THE BOARD'S CLAIM CONSTRUCTION FAILS

The government identifies *no* language in the original claims or specification that supports comparing the claimed combination of an anti-ErbB2 antibody (e.g., rhuMAb HER2) and a taxoid (e.g., paclitaxel) to a patient receiving no treatment whatsoever. To the contrary, both the claims and specification make clear that the proper comparison is to a patient who—although "untreated" with the claimed combination—is administered a drug, specifically a taxoid. The government's

claim construction argument thus depends on a theory of disclaimer—i.e., that a single sentence from the prosecution history unmistakably overrides the plain meaning of the claims and specification. Viewed in context, that single sentence does not meet the demanding standard for establishing a disclaimer.

The plain language of the claims makes clear that the relevant comparison cannot be to a patient receiving no treatment at all. The claims state that the claimed combination must be administered "in an amount effective to extend the time to disease progression … without increase in overall severe ***adverse events***." Appx83(33:52-55). The government does not dispute that an adverse event is "[a]n unexpected medical problem that happens ***during treatment with a drug or other therapy***."[1] Appx10501; *see also* Appx12271-12272; Genentech Br. 21-22. The plain language of the claims thus requires a comparison of (1) any severe medical problems that occur "during treatment" with the claimed combination to (2) the severe medical problems that occur "during treatment" with another drug.[2] To be sure, a patient left untreated would experience medical problems as the breast cancer progresses, but those are not "adverse events" within the meaning of the claims. The point is to measure the side-effects of the treatment itself.

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[1] All emphasis added unless otherwise indicated.

[2] The government argues (at 21) the Genentech could have added a "different comparator for its new safety limitation." But arguing that the claims could be ***rewritten*** does nothing to defend the Board's construction of the claims ***as drafted***. The claims provide no indication that they refer to two different comparators.

The specification drives home that the proper comparator is treatment with a taxoid alone. The specification does not disclose a single instance of the extension of time to disease progression (TTP) being measured relative to a patient receiving no treatment. Indeed, the government does not dispute that a patient would never be provided no treatment because it would be unethical to do so. Genentech Br. 21; Appx8810-8811. Breast cancer is a life-threatening disease for which there were already therapies approved by the FDA. A skilled artisan thus would have readily appreciated the illogic of interpreting the claims, as the Board did, to require a comparison to no treatment at all. Appx8810-8811. The government responds (at 19) that the claims "are not limited to an FDA-approved clinical study requiring that all patients be treated." But that is no answer. The issue is not just whether the FDA would approve a study, but whether any physician would undertake such a comparison—and the government does not dispute that the answer is "no."

The specification instead makes clear that the proper comparison for measuring the extension of TTP is between the claimed combination and a control arm of paclitaxel alone. Appx81(29:9-30:25) (comparing "T+H" (i.e., Taxol and Herceptin) to "T" (i.e., Taxol)). Reading the claims in light of that disclosure is not, as the government alleges (at 20), an attempt to import limitations from the specification into the claims. By their plain terms, the claims require the

comparator to be a form of treatment. The specification further "informs the proper construction of the claims," *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (en banc), by confirming that the comparator is a taxoid—the standalone treatment to which the specification compares the claimed combination.[3]

The government also argues (at 21-22) that comparing the claimed combination to a taxoid alone would add new matter, and that Genentech somehow conceded that its construction of the original claims lacked written description support. But this Court has "certainly not endorsed a regime in which validity analysis is a regular component of claim construction." *Phillips*, 415 F.3d at 1327. In any event, Genentech has made no such concession; the original claims are different from the proposed amendment the Board analyzed. Appx46. Moreover, the percentages cited by the government compare "adverse events" (i.e., "AE") rather than "severe adverse events." PTO Br. 21; Appx81(29:9-30:12). And the specification supports the claims by showing no more than a negligible

[3] The government tries to muddy the waters by arguing (at 20) that anthracycline/cyclophosphamide might serve as a comparator even though "the claims exclude anthracycline therapy," based on "increased cardiac side-effects," Appx81(30:20-21). But in determining the comparator for the treatment that succeeded, an ordinary artisan would have naturally looked to the control in that same arm of the study (i.e., a taxoid alone), not the control in the arm that failed.

difference—i.e., no "overall" increase—in severe myocardial dysfunction. Appx81(30:13-16).

Unable to find support for its construction in the claims or specification, the government rests its argument on a statement in the prosecution history that "the expression[] 'extend the time to disease progression'" is "clear from the specification (see, in particular, page 15, lines 15-17; and pages 42-43)" and means "extend the time to disease progression relative to an untreated patient." Appx1527. But when that statement is read in the context of the prosecution history as a whole, and the patent specification to which it refers, it is not sufficiently "clear and unmistakable" to meet the demanding standard for establishing a disclaimer. *SanDisk Corp. v. Memorex Prods., Inc.*, 415 F.3d 1278, 1287 (Fed. Cir. 2005).

First, the government improperly discounts the citations embedded in the very same statement on which it relies. The alleged disclaimer said that the comparator for extending TTP is "clear from the specification (see, in particular, page 15, lines 15-17; and pages 42-43)." Appx1527. The government (at 19) dismisses these cross-references as "additional citations to descriptions of TTP." But the referenced "pages 42-43" explicitly disclose the results of Genentech's clinical trials in which the claimed combination ("T+H") was ***compared to a taxoid alone ("T")***, with no mention whatsoever of patients receiving no treatment.

Appx1157-1158. Thus, even at the moment of the alleged disclaimer, the prosecution history was pointing to the comparison with a taxoid as indicative of the meaning of the claims, signaling that "untreated patient" meant untreated ***with the claimed combination***. Moreover, the designated portion of the specification disclosing a taxoid as the comparator provided a "specific definition of the comparator," PTO Br. 18, sufficient to resolve any definiteness concerns.

Second, the government cannot get around the fact that the claims were amended ***after*** the alleged disclaimer to add the "serious adverse events" limitation, which, as explained above, is incompatible with comparing the claimed combination to a patient receiving no treatment. The government argues that "[r]ather than dispel ambiguity, the amendment created it" because it did not expressly "provide a different comparator" or "revisit its prior selection." PTO Br. 21. But the government's assessment that the amendment ***created ambiguity*** hardly helps the government. "Where the alleged disavowal is ambiguous, or even amenable to multiple reasonable interpretations," this Court has "declined to find prosecution disclaimer." *Massachusetts Inst. of Tech. v. Shire Pharms., Inc.*, 839 F.3d 1111, 1119 (Fed. Cir. 2016) (internal quotation marks omitted). And "[e]ven if an isolated statement appears to disclaim subject matter, the prosecution history as a whole may demonstrate that the patentee committed no clear and unmistakable

disclaimer." *Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335, 1342-1343 (Fed. Cir. 2009).[4] That is the case here.

Finally, the government implies that the prosecution history could be "'relevant as reinforcing the evident meaning of the claim language at issue, whether or not it would meet standards for disclaimer or disavowal.'" PTO Br. 17-18 (quoting *D'Agostino v. MasterCard Int'l Inc.*, 844 F.3d 945, 949 (Fed. Cir. 2016)). Given that the government seeks to use the prosecution history to override rather than "reinforc[e]" the language of the claims and specification, however, the demanding standard for disclaimer is the relevant standard here.

Even if that were not the case, the prosecution history does not control. Prosecution history is often "less useful for claim construction purposes" than the specification "because the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation." *Phillips*, 415 F.3d at 1317. Nor does the government's invocation of the broadest reasonable interpretation standard help it. The government never explains how choosing one comparator over another would make the claims

[4] The government's citation (at 21) of *Amgen Inc. v. Coherus BioSciences Inc.*, 931 F.3d 1154 (Fed. Cir. 2019) is not to the contrary. *Amgen* rejected a bright-line rule limiting prosecution disclaimer to "arguments made in the most recent submission before allowance." *Id*. at 1161. Mere failure to repeat a disclaimer is easily distinguished from amending claims in a manner inconsistent with the alleged disclaimer.

broader or narrower. The choice here is not between a broad or narrow construction, but between a comparator unsupported by anything other than an isolated statement early in the prosecution history (the Board's construction) or a comparator supported by the claims and specification (the correct construction).

II. UNDER A PROPER CONSTRUCTION, THE BOARD'S OBVIOUSNESS RULING CANNOT STAND

The claimed combination is now the standard of care but, in 1997, rhuMAb HER2 offered a completely new approach to treating breast cancer using a human-engineered antibody. Such treatment of solid tumors had never before been approved by the FDA, there were no other clinical trials testing the combination of rhuMAb HER2 and paclitaxel, and measurement of TTP for the combination had never been reported in *any* model, not even a preclinical model. With this minimal data on a fundamentally new therapy, and well aware of the high failure rate of oncology drugs in clinical trials, an ordinary artisan simply did not have enough information to form a reasonable expectation of success about the efficacy and safety of combining rhuMAb HER2 and a taxoid in human patients.

As Genentech's opening brief explained, there are three critical defects in the Board's determination that Genentech's groundbreaking claims would have been obvious even under the correct claim construction. *First,* the Board erred in finding that an ordinary artisan would have reasonably expected the claimed ***efficacy***—extension of time to disease progression in human patients, compared to

a taxoid alone—achieved by the combination of rhuMAb HER2 and a taxoid. *Second*, the Board erred in finding that an ordinary artisan would have reasonably expected the claimed ***safety***—without increase in overall serve adverse events—that was also achieved. *Third*, the Board improperly relied on the ***inventor's own path*** in finding the claims obvious.

The government's response fails to meaningfully rebut any of these errors. Indeed, on the issue of efficacy, the government reinforces the lack of substantial evidence by conceding that the Board's primary basis for finding a reasonable expectation of extending TTP rested on a comparison between two studies, one of which ***excluded more than half of the patients*** administered rhuMAb HER2 in a manner that the government admits would have "potentially ***skew[ed] the results upward***." PTO Br. 27. On the issue of safety, the government simply ignores that the toxicity of a new combination cannot be predicted by looking at its individual components in isolation, and that ***mouse studies*** do not provide the information needed to predict the effect of a combination ***in humans***. Finally, the government's attempt to explain away the Board's reliance on Genentech's own path as "additional evidence" of obviousness only underscores the need to enforce the rule that the inventors' path is not a proper consideration in the obviousness analysis.

A. The Board's Decision On Efficacy Was Based On Results That The Government Concedes Were "Skew[ed]"

Genentech's opening brief showed that the Board's key determination—that an ordinary artisan would have reasonably expected the combination of rhuMAb HER2 with a taxoid to extend TTP in a human patient, as compared to a taxoid alone—rested on a simple, fundamental error: The Board compared apples to oranges. The Board read Baselga '96 to disclose that the TTP for patients treated with rhuMAb HER2 alone was 5.1 months. It compared that to the Physician's Desk Reference's statement that the TTP for a taxoid (paclitaxel) was 3 or 4.2 months. It then concluded that, because the TTP for rhuMAb HER2 appeared to be greater than the TTP for paclitaxel, combining rhuMAb HER2 with paclitaxel would necessarily result in a longer TTP than paclitaxel alone.

The problem is that Baselga '96 and the Desk Reference reported TTP figures calculated in very different ways. The Desk Reference reported the median TTP for paclitaxel based on ***every*** patient treated in a 471-patient study, including the 338 patients who did not respond to treatment. Appx4047. Baselga '96, by contrast, reported median TTP for rhuMAb HER2 based on ***only 16 of the 43*** assessable patients in the study, excluding 22 patients who did not respond to treatment and showed disease progression. Appx36-39; Appx4232.

The government acknowledges the Board's critical mistake. It concedes (at 42) that Baselga '96 "excludes patients with no response … ***potentially skewing***

the results upward." PTO Br. 27. This admission should end this Court's analysis. There is simply no way of telling from these partial, admittedly "skew[ed]" results what rhuMAb HER2's actual effect on extension of disease progression was likely to be compared to treatment with a taxoid alone.

The government's attempts to argue around this clear flaw in the Board's decision fail. The government's first contention (at 26-28) is that Genentech waived any argument that Baselga '96's TTP could not be used as a comparator for paclitaxel's reported TTP because Genentech failed to make this argument in its Patent Owner Response and "accepted 5.1 months as Herceptin's TTP." PTO Br. 26-28. But there was no waiver because the petitioner never suggested comparing those TTPs in its petition. *See* Appx12001-12077. To be sure, the petition described Baselga '96 and mentioned that it reported a 5.1-month TTP. But it nowhere suggested that this TTP could or should be compared to the TTP for paclitaxel disclosed in the Desk Reference to establish a reasonable expectation of success. *See generally id*. Indeed, the petition itself acknowledged that Baselga's TTP figure included only those patients with "[m]inor responses" and "stable disease[s]." Appx12033. Nor did the Board suggest this reasoning in its Institution Decision, which was based on its erroneous claim construction requiring comparison to patients who received *no treatment*. Appx12270-12271. Genentech could not rebut an argument in its Patent Owner Response that was not made in the

first place. *See Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1080 (Fed. Cir. 2015) ("A patent owner … is undoubtedly entitled to notice of and a fair opportunity to meet the grounds of rejection."); *see, e.g.*, *EmeraChem Holdings, LLC v. Volkswagen Grp. of Am., Inc*., 859 F.3d 1341, 1348-1349 (Fed. Cir. 2017) (vacating and remanding because certain grounds for reversal were not raised with sufficient specificity in the Board's institution decision or in the briefing); *In re NuVasive, Inc*., 841 F.3d 966, 971-973 (Fed. Cir. 2016) (vacating and remanding in part where grounds for Board's rejection was raised for the first time in petitioner's reply, even though there had been notice of the grounds in parallel IPR proceedings).

The government also misses the mark when it argues that Genentech failed to show that Baselga '96's exclusion of patients without any tumor response in the calculation of TTP would matter because Baselga '96 also excluded patients in remission, possibly skewing the results in the opposite direction. PTO Br. 27-28. This argument fails for at least three reasons.

First, the record contains no evidence that would permit anyone to draw a reliable conclusion based on the government's unsupported speculation that multiple omissions in Baselga '96 might have cancelled each other out. *See In re Kao*, 639 F.3d 1057, 1067 (Fed. Cir. 2011) ("conjecture does not supply the requisite substantial evidence"). This absence of proof is a shortcoming in

petitioners' case, not Genentech's, and means that the Board's decision is not based on substantial evidence.

Second, the government cannot shift the burden to Genentech to establish the actual TTP for rhuMAb HER2. *See In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1377-1379 (Fed. Cir. 2016) (reversing final written decision because the Board shifted the burden of proof on obviousness from the petitioner to the patent owner); *see also Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. de C.V.*, 865 F.3d 1348, 1355-1356 (Fed. Cir. 2017) ("In an *inter partes* reexamination involving obviousness, the standard is not whether the patent owner can persuasively show that one of ordinary skill would have expected failure. Rather, the burden is on the Examiner to show that one of ordinary skill would have had a motivation to combine the references with a reasonable expectation of success."). Genentech has demonstrated that the Board's obviousness finding depended on a comparison from which no reliable conclusion can be drawn, thereby showing that the decision was unsupported by substantial evidence. Genentech does not have an *additional* burden to produce evidence showing what the result of a study with a comparable calculation would have been.

Third, the government cannot defend the Board's decision based on a factual rationale the Board itself did not adopt. Nowhere did the Board address the defects with Baselga '96's TTP calculation or endorse the speculative reasoning the

government now advances. This kind of backfilling is legally impermissible under basic principles of administrative law. "The Board's judgment must be reviewed on the grounds upon which the Board actually relied." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1294 (Fed. Cir. 2012) (citing *SEC v. Chenery Corp.*, 332 U.S. 194, 196 (1947), and *In re Lee*, 277 F.3d 1338, 1345-1346 (Fed. Cir. 2002)).

Where the only reference relied on by the Board as establishing the claimed efficacy in fact provided an incomplete calculation of TTP, an ordinary artisan could not conclude that rhuMAb HER2 in combination with a taxoid would extend TTP as compared to a taxoid alone.

Finally, the government falls into the same hindsight bias as the Board in defending application of the principles of combination therapy to support a reasonable expectation of efficacy. In particular, the government asserts that Genentech's expert admitted that she was unaware of any prior art suggesting that the principles would not apply to a chemotherapy-antibody combination (PTO Br. 29), but this argument ignores that antibodies were relatively new therapies, with rhuMAb HER2 the first humanized antibody to treat solid tumors. Appx10170-10171; Appx4234-4235. Indeed, as Genentech's opening brief explains (at 28-29), the prior art cautioned regarding the uncertainty of, and acknowledged the potential challenges facing, incorporating biological agents such as antibodies with combination regimens. The prior art explicitly acknowledged the failure to

combine chemotherapy with hormone therapy, which did not increase the response rate, TTP, or survival as compared to either treatment alone. Appx8976; Appx8983. Some studies even suggested that hormone therapy alone provided better results than combined treatment with chemotherapy. Appx8990; Appx8838 (¶204); Appx8843-8844 (¶214). Under these facts, Genentech's experts did not need to prove a negative; rather, the record evidence established that an ordinary artisan would not apply these principles to this novel antibody therapy.

B. The Board Erred In Finding The Claimed Safety Obvious

The government also fails to rehabilitate the Board's holding that the claimed level of safety was obvious. The Board concluded that an ordinary artisan would reasonably expect that combining rhuMAb HER2 and paclitaxel would not increase the number of severe adverse events compared to a taxoid alone. Genentech's opening brief outlined the lack of substantial evidence supporting this conclusion: None of the prior art described any testing of the combination of rhuMAb HER2 and paclitaxel in human patients, and safety results of each therapy alone and data regarding the combination of rhuMAb HER2 and paclitaxel from xenograft preclinical models was insufficient to establish a reasonable expectation that the combination would not increase severe adverse events in humans. Genentech Br. 30-32. Instead of addressing Genentech's argument, the government largely repeats the Board's hind-sight driven analysis.

The prior art must be read from the perspective of an ordinary artisan in 1997, not with the benefit of knowing the extraordinary success that Herceptin became. This prior art disclosed minimal data on this fundamentally new therapy, leaving an ordinary artisan without enough information to form a reasonable expectation of success about combining this new therapy with a chemotherapy drug.

Supporting this conclusion is the fact that a new combination's toxicity cannot be predicted simply by adding together the adverse events of each drug alone. Genentech Br. 30. Rather, "[e]ven if the component parts of a drug are generally recognized as safe, the combination of those parts may not be safe." *United States v. Hiland*, 909 F.2d 1114, 1133 n.29 (8th Cir. 1990); *see also Honeywell*, 865 F.3d at 1355-1356 (Fed. Cir. 2017) (patent owner need not prove expectation of failure).

Further, the only testing of the combination in the record was the preclinical xenograft studies in the Baselga abstracts, which were insufficient to support a reasonable expectation of success in humans. Preclinical models are important because they can help identify promising avenues for experimentation in humans, but such models do not necessarily provide a reliable prediction of a particular result in human patients, especially on issues of safety. Genentech Br. 31. Indeed, the statements in the Baselga abstracts were hardly enlightening as to a result in

humans, with one abstract reciting that trastuzumab "did not increase toxicity of paclitaxel or doxorubicin in animals as determined by animal survival and weight loss." Appx4226. This statement says nothing about what adverse effects may occur in humans, and the evidence suggests that the study itself described in the abstracts were not designed to offer such prediction. *See* Genentech Br. 31 (citing Appx10165-10166, Appx10130-10131). The government's argument conflates what an ordinary artisan might ***hope*** with what an ordinary artisan would ***reasonably expect***. *OSI Pharms., Inc. v. Apotex, Inc.*, No. 2018-1925, __ F.3d __, 2019 WL 4892078, at *8 (Fed. Cir. Oct. 4, 2019) ("hope that a potentially promising drug will treat a particular cancer is not enough to create a reasonable expectation of success in a highly unpredictable art").

Beyond blanket assertions regarding the predictive value of preclinical studies, the government argues that Genentech itself relied on the Baselga abstracts' mouse studies in applying for approval of its proposed Phase III studies, and that one of the named inventors explained that the purpose of these preclinical studies was "to look at trying to predict what can be helpful in patients." PTO Br. 31. As an initial matter, "trying to predict what can be helpful in patients" is very different from forming a reasonable expectation of achieving a particular result. Further, to accept the government's argument would lead to the untenable conclusion that any time an inventor relies on a certain reference to propose a trial

before the FDA, and the trial is ultimately successful, such reference has necessarily provided a reasonable expectation of success. Unless the inventions underlying every successful clinical trial are obvious in view of the references submitted to justify the clinical trial, this clearly cannot be correct. *See Novartis Pharms. Corp. v. West-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051, 1060-1062 (Fed. Cir. 2019) (phase I data did not provide a reasonable expectation of success).

Finally, the government argues that the Board properly disregarded the Baselga abstracts' failure to predict that rhuMAb HER2 and doxorubicin increased toxicity because Genentech characterized these results as "unexpected." PTO Br. 32. However characterized, these results show that an ordinary artisan could not reliably predict the toxicity of any combination of rhuMAb HER2 and another drug from the study without more data. For these reasons, this Court should reverse on this basis as well.

C. The Board Failed To Offer A Proper Basis For Its Reliance On The Inventors' Path In Its Obviousness Determination

The government does not dispute that the Board relied on the inventors' path to support its obviousness determination. On the claimed efficacy limitation, the Board cited the inventors' FDA communications in support of its conclusion that "an ordinary artisan would have had a reasonable expectation that treatment with the combination of trastuzumab and paclitaxel would extend TTP as compared to treatment with a paclitaxel alone." Appx37. The very next sentence reads, "[o]ur

conclusion is further supported by the representations Patent Owner made in its submission to the FDA." *Id.* On the claimed safety limitation, the Board strung together a series of inferences—that Genentech cited Baselga '94 to support its proposed phase III trial, that the FDA must have found Genentech's planned phase III trial "reasonable," and therefore that an ordinary artisan would have had a reasonable expectation that the proposed combination would not lead to an increase in severe adverse events. Appx36-37. This reliance on the inventors' path infected the Board's decision with impermissible hindsight.

That the inventors sought, and the FDA approved, a Phase III clinical trial ***testing*** the later-claimed combination does not mean that an ordinary artisan (or the inventors for that matter) would have reasonably expected success in obtaining the specific result recited in the claims. Indeed, the lack of data on the combination in humans is significant in light of the highly unpredictable nature of cancer treatments, as shown by the high failure rate of drugs entering Phase III trials (almost 60%). Appx8784-8785; *see also OSI Pharms.*, 2019 WL 4892078, at *7 (reversing obviousness determination that relied on fact of Phase II trials, and noting the high failure rate of drugs in clinical trials).

The government argues that this information is relevant as "additional evidence" to show that Genentech has allegedly taken inconsistent positions regarding the Baselga abstracts. PTO Br. 34. But that confuses what the inventor,

who possessed extraordinary skill and extensive information about taxoids, believed appropriate to propose to the FDA, with whether an ordinary artisan would reasonably expect the claimed results. Genentech Br. 35; Appx9402; Appx9408. The inventors' path is simply not a proper basis for an obviousness finding. *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1363 (Fed. Cir. 2009) (inventor's personal expectations do not demonstrate expectation of success of a POSA); *see also Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000) ("[T]he inventors' reliance on the [prior art] and the motivations that they derived from it have no bearing on the issue of patentability. … [T]his inquiry, as a matter of law, is independent of the motivations that led the inventors to the claimed invention.").

CONCLUSION

The Board's decision should be reversed or, at a minimum, vacated and remanded.

Respectfully submitted,

/s/ Robert J. Gunther, Jr.

ROBERT J. GUNTHER, JR.
WILMER CUTLER PICKERING
HALE AND DORR LLP
7 World Trade Center
250 Greenwich Street
New York, NY 10007
(212) 230-8800

DARALYN J. DURIE
ADAM R. BRAUSA
DURIE TANGRI LLP
217 Leidesdorff Street
San Francisco, CA 94111
(415) 362-6666

THOMAS G. SAUNDERS
WILMER CUTLER PICKERING
HALE AND DORR LLP
1875 Pennsylvania Avenue NW
Washington, DC 20006
(202) 663-6000

THOMAS G. SPRANKLING
WILMER CUTLER PICKERING
HALE AND DORR LLP
950 Page Mill Road
Palo Alto, CA 94304
(650) 858-6000

ANDREW J. DANFORD
WILMER CUTLER PICKERING
HALE AND DORR LLP
60 State Street
Boston, MA 02109
(617) 526-6000

NORA Q.E. PASSAMANECK
WILMER CUTLER PICKERING
HALE AND DORR LLP
1225 Seventeenth Street
Suite 2600
Denver, CO 80202
(720) 274-3135

October 15, 2019

CERTIFICATE OF SERVICE

I hereby certify that, on this 15th day of October, 2019, I filed the foregoing Reply Brief for Appellant Genentech, Inc. with the Clerk of the United States Court of Appeals for the Federal Circuit via the CM/ECF system, which will send notice of such filing to all registered CM/ECF users.

/s/ Robert J. Gunther, Jr.
ROBERT J. GUNTHER, JR.
WILMER CUTLER PICKERING
HALE AND DORR LLP
7 World Trade Center
250 Greenwich Street
New York, NY 10007
(212) 230-8800

CERTIFICATE OF COMPLIANCE

Pursuant to Fed. R. App. P. 32(g), the undersigned hereby certifies that this brief complies with the type-volume limitation of Federal Circuit Rule 32(a).

1. Exclusive of the exempted portions of the brief, as provided in Fed. R. App. P. 32(f) and Fed. Cir. R. 32(b), the brief contains 4,817 words.

2. The brief has been prepared in proportionally spaced typeface using Microsoft Word 2016 in 14-point Times New Roman font. As permitted by Fed. R. App. P. 32(g), the undersigned has relied upon the word count feature of this word processing system in preparing this certificate.

/s/ Robert J. Gunther, Jr.
ROBERT J. GUNTHER, JR.
WILMER CUTLER PICKERING
HALE AND DORR LLP
7 World Trade Center
250 Greenwich Street
New York, NY 10007
(212) 230-8800

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