No. 2019-1265

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

GENENTECH, INC.,

Appellant,

v.

ANDREI IANCU, Director, U.S. Patent and Trademark Office,

Intervenor.

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

REPLY BRIEF FOR APPELLANT GENENTECH, INC.

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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. 19-1267 (Fed. Cir.)
Genentech, Inc. v. Iancu, No. 19-1270 (Fed. Cir.)

Dated: October 15, 2019

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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 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. But the government improperly discounts the citations embedded in that statement, 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 even attempt to defend the

Board's flawed inherency ruling. As discussed in Genentech's opening brief, the Board began its discussion of obviousness with a ruling on inherency that came nowhere close to meeting the established legal standard for inherency. The government's response does not dispute Genentech's argument or otherwise defend the Board's inherency ruling. That silence speaks volumes. The Board's misplaced reliance on the doctrine of inherency was indefensible and should be reversed.

The government also does not dispute that, in holding that there would have been a reasonable expectation of success in extending the time to disease progression compared to a taxoid alone, the Board relied on a report that "excludes patients with no response [to treatment] … ***potentially skewing the results upward***." PTO Br. 27.[1] Specifically, the Board compared (1) the time to disease progression for rhuMAb HER2 alone reported in the Baselga '96 reference to (2) the time to disease progression for a taxoid alone reported in another reference—without accounting for the fact that the number reported in Baselga '96 excluded 22 of the 43 patients who did not respond to treatment, while the taxoid reference reported a number for all patients. The Board was thus erroneously comparing apples and oranges. And the government's contention that Genentech somehow waived this argument ignores that the petitioner never raised the issue in

[1] All emphasis added unless otherwise indicated.

its petition and Genentech identified the reference's shortcomings at its first opportunity after the argument was eventually made. Nor can the government's unsupported speculation on appeal cancel out the Board's error.

The government also does not dispute that in turning to other references, the Board impermissibly relied on the inventor's own path to support its finding of obviousness and adopted a standard suggesting that a reasonable expectation exists based on the mere existence of a clinical trial. These findings are also unsupported by fact and law.

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), a taxoid (e.g., paclitaxel), and a further growth inhibitory agent to a patient receiving no treatment whatsoever. To the contrary, the specification makes 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 proving that a single sentence from the prosecution history unmistakably overrides the disclosure in the

specification. Viewed in context, that single sentence does not meet the demanding standard for establishing a disclaimer.

The claimed method of treating breast cancer in U.S. Patent No. 7,892,549 states that the claimed three-drug combination must be administered "in an amount effective to extend the time to disease progression in the human patient." Appx88(33:42-43). 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. 23; Appx9085. 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. Appx9085.

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. Appx86(29:11-30:25) (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 19), an attempt to import limitations from the specification into the claims. By their plain terms, the claims require a comparator.

The specification simply "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.[2]

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." Appx11017. 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).

The government improperly discounts the citations embedded in the very same statement on which it relies. The alleged disclaimer said that the comparator

[2] 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," Appx86(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.

for extending TTP is "clear from the specification (see, in particular, page 15, lines 15-17; and pages 42-43)." Appx11017. The government (at 18) 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. Appx1526-1527. 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***. *See also* Appx8709 (petitioner's expert: "There's frequently a control which I guess you could say is untreated.").[3]

"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). That is exactly the case here. The statement on which the government relies may appear clear on its face, but the embedded citations render it ambiguous.

[3] 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.

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 (quoting *D'Agostino v. MasterCard Int'l Inc.*, 844 F.3d 945, 949 (Fed. Cir. 2016)). But the government is not seeking to "reinforc[e]" anything. It seeks to use the prosecution history to override the meaning evident from the specification. The demanding standard for disclaimer is thus 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 broader or narrower. The choice here is not between a broad or narrow construction, but between a comparator unsupported by anything other than an ambiguous, isolated statement in the prosecution history (the Board's construction) or a comparator supported by the specification (the correct construction).

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

The invention here arose from the extraordinary decision to add the combination of rhuMAb HER2 and paclitaxel to an ongoing Phase III study even though the combination had never before been studied in humans. As the Board's decision and the government's brief illustrate, it is tempting—with the benefit of knowing that the study succeeded—to view the extension of time to disease progression achieved in that study as obvious. Indeed, the Board relied on the very decision to test the combination without prior Phase I or Phase II studies—itself a product of the inventor's extraordinary knowledge and foresight—as evidence of obviousness. But looking at the references for what they actually were, and from the standpoint of an ordinary artisan as of 1997, it is clear that significant uncertainties existed. Baselga '97 described only the fact of, but no results from, a Phase III clinical trial testing rhuMAb HER2 in combination with paclitaxel; Baselga '96 described the results of a Phase II trial testing rhuMAb HER2 alone; and Baselga '94 described xenograft studies measuring a different clinical endpoint, which did not provide a sufficient basis for an ordinary artisan to reasonably expect—as opposed to merely hope for—a particular result in human patients. All of these references thus left too much uncertainty, and too big of a leap still to be made, to provide substantial evidence to support's the Board's decision.

As Genentech's opening brief explained, the Board did not appreciate this important context for viewing the prior art and made two errors in its obviousness analysis—first by finding that the claimed extension of TTP was an inherent benefit of an otherwise obvious combination, and second by finding that an ordinary artisan would have expected the claimed extension of TTP based on the Baselga references. In response, the government does not defend the Board's analysis on inherency, admits that the Board relied on skewed data, and repeats many of the Board's same errors.

A. The Government Does Not Even Attempt To Defend The Board's Inherency Ruling

The Board's very first reason for finding the claimed efficacy obvious was that it was an inherent result of an otherwise obvious combination. The Board's inherency determination was legally flawed, failing to honor the legal framework governing inherency that "[t]he limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195-1196 (Fed. Cir. 2014), and ignoring that the prior art did not inherently link extension of TTP to the claimed combination. Genentech Br. 29-32. Indeed, nothing in the record supported that extension of TTP would result "each and every time" as required by the inherency framework. *Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1382 (Fed. Cir. 2018). Nor could it in view of the record evidence showing

that some patients administered with rhuMAb HER2 and paclitaxel did not experience any extension of TTP. Genentech Br. 29 (citing Appx8309).

The government does not even attempt to defend the Board's flawed inherency ruling, either based on the law or the record evidence. The government's silence speaks for itself—the Board's inherency decision was indefensible and showed a fundamental misunderstanding of the record evidence. The Board's decision on this point should be reversed.

B. The Board Erred In Relying On The Fact Of A Phase III Clinical Trial As Reported In Baselga '97

The government argues that the Board properly relied on Baselga '97's report of a phase III trial testing the combination of rhuMAb HER2 and paclitaxel, because this clinical trial did not "materialize out of thin air" and clinical trial results are not required for purposes of providing a reasonable expectation of success. PTO Br. 23-25. The government misunderstands both Genentech's argument and the law.

Although Herceptin is now the standard of care, 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 this new therapy combined with not one, but two chemotherapy drugs.

The government never appreciates this important context for viewing the Baselga references, instead asserting that Genentech is setting too high a standard for a reasonable expectation of success. Not so. This Court recently confirmed that the fact of a clinical trial going forward does not automatically transform promising underlying data into data that provides a reasonable expectation of success. *OSI Pharms., LLC v. Apotex Inc.*, No. 2018-1925, __ F.3d __, 2019 WL 4892078, at *8 (Fed. Cir. Oct. 4, 2019). This is because clinical trials might proceed only upon the "hope"—which the Court explicitly distinguishes from "expectation"—of success. *Id.* Of course, Genentech had *hope* that its proposed trial would lead to a new, successful approach to the treatment of an aggressive form of cancer, but starting a Phase III trial without any prior clinical testing of the combination was very uncommon and further supports the uncertainty of the results. The Board's reasoning that the acceptance of a clinical trial on the basis of that data elevated that hope to an expectation is not supported by substantial evidence, and the government has not remedied that deficiency.

The government also incorrectly asserts that Genentech cited no evidence supporting the common-sense conclusion that combining rhuMAb HER2 with chemotherapies created more uncertainty than the single-drug trial reported in Baselga '96. Again, that is incorrect. As explained by Genentech's expert, the ***design*** of a Phase III study of a combination therapy does not teach or suggest the ***result*** of that study without any data regarding that combination, and this unpredictability is underscored by the high failure rate of clinical trials in oncology. Genentech Br. 33 (citing Appx9112-9113).

Baselga '97 therefore does not move the needle towards a finding of a reasonable expectation of success.

C. The Board's Analysis of Baselga '96 Is Based On Results That The Government Concedes Were "Skew[ed]"

Genentech's opening brief also showed that the Board's reliance on Baselga '96 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. Appx9514. 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. Appx33-34; Appx1084.

The government acknowledges the Board's critical mistake. It concedes (at 27) that Baselga '96 "excludes patients with no response … ***potentially skewing the results upward***." 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 26-27) 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 or any of its papers. *See* Appx13018-13023;

Appx13808-13833. 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* Appx13013-13077. Indeed, the petition itself acknowledged that Baselga's TTP figure included only those patients with "minor response[s]" and "stable disease[s]." Appx13036. 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*. Appx13312; Appx13318-13322; Appx13324. 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. On this basis alone, the Board's decision should be reversed or, at a minimum, vacated and remanded.

D. The Board Erred In Relying On Baselga '94's Preclinical Xenograft Studies

The government argues that Baselga '94 fills in the gaps missing from the clinical trials described in the other Baselga references because it provides data—from ***preclinical*** xenografts—regarding the combination of rhuMAb HER2 and paclitaxel. PTO Br. 28-29. In making this argument, the government asks this Court to ignore the plain differences between preclinical studies and clinical studies, including the patients involved (human versus artificially-created tumors in mice), the end points (extension of TTP in humans over months versus the five-week study of response rate of tumor shrinkage reported in Baselga '94, which would again compare apples and oranges), as well as the significant limitations of the design of Baselga '94 study itself (outlined in Genentech's opening brief, at 37-38). Brushing these differences aside, the government baldly asserts that "the whole point of Baselga '94's study was to predict efficacy in humans, not to cure cancer in mice." PTO Br. 29.

The government's argument represents a fundamental misunderstanding of the purpose of preclinical studies, which are designed to identify possible therapies for further ***testing*** in human patients, with no likelihood—just a hope—that such testing in human patients would achieve the same results as any prior preclinical animal-model results. That is the case here. As explained in Genentech's opening brief, while a preclinical study may motivate an ordinary artisan to combine

rhuMAb HER2 and a taxoid for a trial in human patients, it would not suggest any particular result could be achieved with a reasonable expectation of success in human patients. Simply put, motivation to conduct a trial and an expectation of its success are two different things.[4] *See Ericsson Inc. v. Intellectual Ventures I LLC*, 890 F.3d 1336, 1352-1353 (Fed. Cir. 2018) ("Reasonable expectation of success and motivation to combine are 'two different legal concepts' that should not be 'conflated.'" (quoting *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016))).

The record evidence supports this conclusion. Indeed, the rate of eventual clinical success of positive preclinical mouse studies was known in the 1990s to be incredibly low because of (1) differences in responsiveness and activity between xenograft tumors in mice and tumors in humans (Appx8883-8885; Appx10132-10133); (2) differences in mouse and human physiology (Appx10133); and (3) different pharmacokinetic characteristics in mice and humans (*id.*). These limitations of preclinical trials generally are only amplified in Baselga '94, which did not take basic steps to more closely approximate what might occur in human

[4] The government's reliance on Genentech's communications with the FDA on its Phase III trial highlights this misstep. The government asserts that Appx5781 shows that "skilled artisans *did* consider Baselga '94 relevant to clinical efficacy," even though the portion of this communication the government cites asserted that Baselga '94's "data provide [a] ***motivation*** for clinical evaluation." PTO Br. 30 (emphasis in original).

patients by, for example, using multiple cell lines and/or a cell line that was representative of actual patients, implanting tumor cells in mammary glands of mice, or reporting key details and parameters of its study. *See* Genentech Br. 37-38.

Finally, the government attempts to bolster its argument by pointing to the fact that, as the Board noted, Genentech cited Baselga '94 in seeking to proceed with the Phase III trial ultimately described in Baselga '97. PTO Br. 30-31. The government's argument only magnifies the Board's improper reliance on the inventors' path to prove obviousness. The statute is clear: "Patentability shall not be negatived by the manner in which the invention was made." 35 U.S.C. § 103(a) (pre-AIA).

Genentech submitted non-public documents regarding its FDA correspondence to show that, even from the perspective of the inventor, the combination of rhuMAb HER2 plus paclitaxel presented uncertainty. *See, e.g.*, Appx8088 ("[T]he expected clinical outcome for the administration of rhuMAb HER2 with Taxol is less certain than co-administration with cisplatinum or doxorubicin."); Appx9990. But that does not suggest those documents are relevant to the reasonable expectation of an ordinary artisan. "'The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as

evidenced by the pertinent prior art.'" *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017) (quoting *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012)); *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) ("[O]ne should not go about determining obviousness under § 103 by inquiring into what patentees (i.e., inventors) would have known or would likely have done."). This is because "[i]nventors, as a class, according to the concepts underlying the Constitution and the statutes that have created the patent system, possess something … which sets them apart from the workers of ordinary skill." *Standard Oil Co.*, 774 F.2d at 454; *see also, e.g.*, *Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340, 1363 (Fed. Cir. 2009); *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325, 1326 (Fed. Cir. 2000).

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%). Appx9056; *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). Accordingly, it was improper for the PTO to rely on the inventor's perspective on the prior art to support a finding of obviousness.

CONCLUSION

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

Respectfully submitted,

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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.

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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 4,686 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.

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