UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Celltrion, Inc. and Pfizer, Inc.
Petitioners,

v.

Genentech, Inc.
Patent Owner.

Case IPR2017-01121[1]
Patent 7,846,441

PETITIONER CELLTRION'S REPLY TO PATENT OWNER'S RESPONSE

[1] Case IPR2017-02063 has been joined with this proceeding.

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Genentech cannot dispute that the prior art disclosed (1) dosages for single-agent trastuzumab and paclitaxel that were safe and effective in treating breast cancer; (2) the specific suggestion of combining trastuzumab and paclitaxel to treat HER2+ breast cancer; (3) pre-clinical test data suggesting that the combination would, like the single-agents, have efficacy without serious toxicity; (4) the fact that POSAs were focused on combining cancer therapies that lacked overlapping mechanisms of action, to increase efficacy and avoid resistance; (5) that trastuzumab and paclitaxel were good candidates for combination because they lacked overlapping mechanisms of action or toxicities; and (6) that POSAs were motivated to avoid anthracyclines, including in patients who neared the lifetime dose limit and those resistant to them. Crucially, the prior art contains no suggestion to avoid combining paclitaxel and trastuzumab. This prior art, when taken as a whole, compels the conclusion that POSAs would have been motivated to administer trastuzumab and paclitaxel in the prior-art dosage amounts to HER2+ breast cancer patients, and reasonably would have expected the combination to be both safe and efficacious.

Indeed, Genentech agrees that POSAs would have been motivated to combine trastuzumab with chemotherapy, but argues that they would have regarded anthracycline as a better choice than paclitaxel. (POR, 47.) Even if this were true, which it is not, Genentech ignores settled law: It does not matter whether POSAs

would have regarded anthracyclines as one obvious choice for combination. All that matters is the fact that—as the evidence as a whole overwhelmingly establishes—POSAs would have regarded paclitaxel as another viable choice. *See, e.g.*, *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1329 (Fed. Cir. 2017); *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) ("[T]he question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination, not whether there is something in the prior art as a whole to suggest that the combination is the most desirable combination available.") (internal quotations omitted).

Genentech's attempts to rebut the tide of evidence are ineffectual. While it argues that the prior art was unclear whether paclitaxel was effective in HER2+ patients, it relies only on (1) a paper that is not prior art, and in any event, does not teach what Genentech alleges it does, and (2) a paper concerning an *in vitro* study of the type its own experts characterized as unable to predict clinical outcomes. And while Genentech tries to minimize preclinical data it sponsored, which suggested that the trastuzumab/paclitaxel combination would produce increased efficacy in human patients without serious toxicity, [redacted]. Indeed, Genentech's own experts

conceded that POSAs and FDA routinely used such preclinical testing to guide which new drugs and combinations should be tested in humans.

Genentech's protests that POSAs would not have reasonably expected the combination to extend the time to disease progression (TTP) over no therapy, or over paclitaxel monotherapy, without an increase in severe adverse events, are equally unavailing. First, it cannot reasonably be disputed that treatment with the combination in the prior-art dosage amounts would produce the claimed benefits over no treatment. Second, it is undisputed that POSAs would have known that trastuzumab was both efficacious in HER2+ patients and worked in a different way than paclitaxel; it thus would have been more than reasonable for POSAs to believe that adding trastuzumab to paclitaxel would increase efficacy in HER2+ patients over paclitaxel alone. Since severe adverse events with paclitaxel and trastuzumab were known to be rare, and the toxicities of these agents were known to not overlap, POSAs would not have expected an increase in severe adverse events. Third, Genentech simply administered prior-art dosage amounts of trastuzumab and paclitaxel, then claimed the results. Its "discovery" of the results produced by administering the obvious combination of these conventional dosage amounts cannot confer patentability.

Finally, Genentech has failed to establish a nexus between its proffered secondary evidence of nonobviousness and the claims, and in any event, its arguments are insufficient to outweigh Petitioner's strong obviousness case.

Accordingly, as demonstrated in the Petition, the challenged claims should be cancelled for obviousness.[2]

I. The Prior Art Motivated the Trastuzumab/Paclitaxel Combination

POSAs[3] would have been motivated to combine trastuzumab and paclitaxel. (Petition, 43-52.) Genentech's arguments to the contrary lack merit.

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[2] Because Genentech does not argue the claims separately, they stand or fall together.

[3] Genentech's definition of POSA requires "specializing in breast cancer with several years of experience with breast cancer research or clinical trials." (POR, 35). Genentech criticizes Dr. Earhart for not specializing in breast cancer. (*Id.*) However, of the experts involved in this IPR, Dr. Earhart is the only one with significant experience designing and conducting clinical trials, including for breast cancer treatments. (Ex. 1052, 36:19-37:2; Ex. 1040, 16:17-17:2; Ex. 1054, ¶5.) Dr. Earhart is therefore eminently qualified to testify in this proceeding. His opinions remain unchanged under Genentech's definition of POSA. (Ex. 1054, ¶5.)

A. Trastuzumab and Paclitaxel Both Demonstrated Single-Agent Efficacy in HER2+ Patients

POSAs would have recognized that both trastuzumab and paclitaxel were effective in treating HER2+ breast cancer. (Petition, 24.) Genentech does not dispute trastuzumab's single-agent efficacy in such patients, but alleges that POSAs would have been skeptical about paclitaxel's efficacy in this population. Genentech's rationale is unpersuasive. First, it contends that POSAs would have ignored Seidman-1996 simply because it is an abstract, not a full paper. (POR, 41.) Genentech offers no objective evidence for this extreme position, which appears to be based on a desire to simply erase unfavorable prior art rather than an objective scientific justification. As Dr. Earhart explains, POSAs would not have had reason to doubt the reported data. (Ex-1054, ¶16.) Indeed, the authors were affiliated with Memorial Sloan-Kettering Cancer Center, and included Dr. Larry Norton, who Genentech itself cites as a "leading practitioner." (POR, 62.)

Genentech's own declarants rely on abstracts when favorable to Genentech's position. For example, in a declaration submitted to the Office to obtain the '441 patent, Dr. Hellmann relied on an abstract to argue that docetaxel + Herceptin® will behave like paclitaxel + Herceptin®. (Ex-1004, 321 (citing Raefsky *et al.*, *Proc. of ASCO*, 18:137a Abstract 523 (1999)).) Further, in a co-pending proceeding on another trastuzumab method-of-use patent, Genentech's expert characterized an abstract relating to "preliminary efficacy results" for trastuzumab as "finally" giving

oncologists "the level of proof they needed that a targeted treatment was effective in aggressive HER-positive cancers." (Ex-1056, ¶22).

Second, Genentech suggests that because the Seidman authors continued to study paclitaxel (as evidenced by a 2002 article, Ex-2024, which did not exist in 1997), they themselves did not consider paclitaxel to have "proven efficacy" in HER2+ patients as of the priority date. (POR, 41.) Genentech has not linked Seidman 1996 and 2002, as the 2002 article does not even cite the 1996 abstract. (*See* Ex-2024, 2325-26.) Further, even if the work is linked, Genentech fails to acknowledge that in the 2002 article, the authors reaffirmed that "[o]ur prior assessment of tumor HER2 expression through monoclonal antibody (4D5) and the polyclonal antibody (pAB-1) demonstrated that 4D5 positivity was predictive of positive response to taxane monotherapy." (Ex-2024, 2320; Ex-1054, ¶¶14-16.)

Genentech also asserts that a cell culture study reported in Yu (Ex-2029) would have convinced POSAs that paclitaxel was ineffective against HER2+ breast cancer. (POR, 42.) In Yu, cells in culture were engineered to artificially overexpress HER2. (Ex-2029, 1359.) As Dr. Earhart explains, POSAs would have regarded the *in vivo* preclinical and clinical results reported in Baselga-1996 and Seidman-1996, which were obtained from studies of actual tumor cells in live animals and human patients, as being far more predictive than Yu's results, which were obtained in artificially-engineered cells on culture plates. (Ex-1054, ¶17; Ex-1011, 104; Ex-

1002, ¶¶60, 124.) Indeed, Genentech's own expert Dr. Kerbel discounted Yu's work, noting that it was merely one paper and did *not* engender a "widespread assumption" that HER2+ cells were not responsive to paclitaxel. (Ex-1040, 53:22-54:2.)[4]

B. The Preclinical Results Would Have Provided Further Motivation

Genentech argues that POSAs would have ignored the Baselga xenograft results, which demonstrated "major antitumor activity" for the trastuzumab/paclitaxel combination, because they would have regarded preclinical results as insufficiently "predictive" of clinical response.[5] (POR, 43-46, Ex-1019.) It is undisputed, however, that such studies were among the best tools available at the time to determine efficacy and safety of a new drug regimen prior to actual dosing in

[4] Genentech's reliance on *in vitro* results in an attempt to contradict Seidman-1996's clinical results is inconsistent with its position that even *in vivo* preclinical work cannot be used to "predict" clinical outcomes. (*See, e.g.*, POR, 7-8, 12, 24.)

[5] Genentech complains that the Baselga abstracts are not part of the instituted ground. (POR, 43.) They are referenced in Baselga-1996, which is in the instituted ground. (Ex. 1020, 743.) Moreover, other references "can legitimately serve to document the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness." *Genzyme Therapeutics Prods. Ltd. v. Biomarin Pharmaceutical Inc.*, 825 F.3d 1360, 1369 (Fed. Cir. 2016).

humans. (Ex-1002, ¶¶46, 149; Ex-1040, 18:10-17.) [redacted]

Genentech's experts do not appear to disagree with Petitioners. Drs. Kerbel and Tannenbaum both testified at deposition that xenografts help researchers decide which drug candidates or combinations to test in humans (Ex-1040, 21:9-12, 21:19-

[6] The Sample Informed Consent in Ex. 2007 appears in an amendment to the final H0648g phase III protocol Genentech submitted to FDA; the same text also appears in Ex. 1042, the H0648g protocol submitted during prosecution.

23), help predict the toxicity that a treatment will cause in humans (*id*., 24:9-25:5), help determine proper dosing (*id.*, 30:21-31:6), and are performed to investigate treatments for humans clinical use (Ex-1052, 109:13-16). Dr. Kerbel also confirmed that as of 1997, mouse models "have been very helpful in determining basic principles of cancer chemotherapy and . . . have been instrumental in identifying and evaluating" some clinically useful agents. (Ex-1040, 67:9-19; *see also* Petition, 40-41.)

Genentech's nitpicking critiques of the Baselga studies are not persuasive, especially given that [redacted] (Ex-2007, 5.) First, Genentech asserts that it was "well known" that multiple cell lines were needed "to obtain results that are reflective of a human patient population." (POR, 44.) While this may have been a consideration for a drug that previously had not been tested in any cancer model, here, both drugs were known to have single-agent efficacy in HER2+ patients. As Dr. Earhart explains, preclinical studies are usually not required to design a new combination when each agent in the combination has already shown clinical efficacy and met the other principles of combination therapy. (Ex-1054, ¶11; Ex-1004, 12 ("Development of new treatments is based on the effectiveness of the cancer drugs in rodent models. Combinations of drugs are fashioned based on the

effectiveness, the level of cross-resistance, and the limiting toxicity of the available drugs when used alone in similar patient populations.").)

Second, Genentech contends that the cell line used in the Baselga abstracts "was not representative of actual patients" because it had 20 times more HER2 genes than a "normal human cell." (POR, 44.) This criticism makes no sense—POSAs seeking to evaluate HER2+ cancer treatments would of course use a cell line that overexpresses HER2. Indeed, a cell line with a high level of overexpression would be advantageous because high levels of HER2 overexpression were correlated with poor outcomes. (Ex-1054, ¶10.) Further, Genentech has not cited any prior art suggesting that this cell line was an "outlier" or would skew results in favor of showing a response to trastuzumab (let alone to paclitaxel). (Ex-1040, 52:10-53:5, 58:5-10.) In any event, because Baselga tested all of the agents in the same cell line, the data can properly be used to compare the efficacy of those agents with each other. (Ex-1054, ¶10.)

Third, Genentech criticizes the Baselga results on the basis that the xenograft tumors were implanted subcutaneously, rather than orthotopically. (POR, 11, 46.) However, Dr. Kerbel confirmed that as of 1997, subcutaneous implantation was more common than orthotopic implantation—a fact that remains true today. (Ex-1040, 26:24-27:4; Ex-1054, ¶9.) After 1997, Dr. Kerbel himself filed a patent application with claims to a method of using a combination of anticancer drugs in

humans, which was supported using only subcutaneous xenograft results. (Ex-1100, 15:12-15; 21:23-29, 22:1-4; 23:10-19; 24:16-25:1; 26:5-27:7; 28:20; 32:6; Ex-1040, 42:14-17). In any event, POSAs would not consider the type of tumor to be a relevant consideration in evaluating xenograft results. (Ex-1054, ¶9.)

In sum, Genentech's attempts to minimize the Baselga xenograph results are not persuasive. Those results demonstrated that trastuzumab + paclitaxel showed greater efficacy than any of the other tested treatments (Exs. 1019, 1020), and would have provided further motivation to use the trastuzumab/paclitaxel combination in patients.[7] (Petition, 45.) But perhaps more importantly, the prior art indicated that on the basis of the xenograph results, clinical trials of the combination were already underway. (Ex-1019 ("In summary anti HER2 MAbs can eradicate well established

[7] Genentech argues that because paclitaxel had not shown efficacy in colorectal cancer patients after promising xenograft results, POSAs would have been dissuaded from relying on the Baselga xenograft results. (POR, 45 n.14.) This argument ignores that the efficacy of paclitaxel for the treatment of breast cancer in humans had been established prior to the Baselga studies, and that breast and colorectal cancer are different diseases. It was well-established that paclitaxel showed "excellent activity" both in xenografts and in breast cancer patients. (Ex. 1053, 112-14; Ex. 1007, 1164; Ex. 1011; Ex. 1054, ¶12.)

tumors and enhance the activity of paclitaxel and doxorubicin against human breast cancer xenographs. Clinical trials are underway."); Ex-1020, 743.)

C. POSAs Would Have Been Motivated to Develop the Combination Therapy Without Anthracyclines

The claim limitation "in the absence of an anthracycline derivative" is a negative limitation that does not require active "avoidance" of an anthracycline. As the Board previously recognized, this limitation is satisfied by a trastuzumab/paclitaxel combination that does not include an anthracycline. (IPR2017-00731, Paper 29, 17-18.) As demonstrated in the Petition, POSAs were motivated to pursue the trastuzumab/paclitaxel regimen, and this combination lacks anthracycline. (Petition, 50.)

Further still, POSAs would have been motivated to avoid anthracyclines, for example, in patients who were resistant to anthracyclines and patients who had reached the maximum lifetime dose of anthracyclines and needed further treatment. (Petition, 51; Paper 9, 16.) The cardiotoxicity of anthracyclines was the major factor limiting their use. (*See, e.g.*, Ex-2030, 409, 422; Ex-1036, 880; Ex-1050, 47.) Genentech asserts that anthracycline-induced cardiotoxicity was "manageable," *e.g.* with a cardioprotectant. (POR, 15, 47.) But the utility of the FDA-approved cardioprotectant was limited, as it appeared to reduce antitumor efficacy. (*See, e.g.*, Ex-1050, 54.) The only commonly-used way to control cardiotoxicity was to limit the total lifetime dosage, but even this approach did "not prevent toxicity in all

patients." (Ex-1002, ¶41; Ex-2030, 423; Ex-1016, 813.) Accordingly, once breast cancer patients reached the limit, they had to stop anthracycline treatment and switch to something else, which was often paclitaxel. (Ex-1007, 1166.)

Genentech argues that anthracyclines, not paclitaxel, were the obvious choice to combine with trastuzumab. (POR, 47-48; Ex-1052, 93:11-19.) This underscores that combining trastuzumab with existing chemotherapy treatments would have been obvious. Moreover, even if anthracycline was a "more obvious" choice, which it was not, that is irrelevant to the issue of whether the trastuzumab/paclitaxel combination was also obvious. *See, e.g.*, *Bayer Pharma AG*, 874 F.3d at 1329. Indeed, as the Board previously found, "whether an ordinary artisan would have had a reason to combine anti-HER2 MAb with a taxoid is separate and independent from whether an ordinary artisan would have had a reason to combine anti-HER2 MAb with anthracyclines." *Hospira, Inc. v. Genentech, Inc.*, IPR2017-00731, Paper 29, 13 (PTAB Oct. 26, 2017).

Genentech also asserts that because paclitaxel was approved as a second-line therapy, POSAs would have regarded it as inferior to anthracyclines, which were first-line treatment. (POR, 17.) Paclitaxel's second-line approval merely reflects how it was tested in clinical trials, not any belief about its relative efficacy. (Ex-1054, ¶12.) Moreover, POSAs knew that paclitaxel could be successfully used as a first-line therapy [redacted]. (*See, e.g.*, Ex-

1039, 1943 ("Taxol is highly active as initial chemotherapy for metastatic breast cancer."); [redacted]

Genentech also argues that purported safety concerns would have dissuaded POSAs from using paclitaxel. (POR, 16-17, 43.) However, paclitaxel was regarded as one of the most important chemotherapeutic agents developed in the previous decade. (Ex-1007, 1164; Ex-1006, 50.) The principal side effects of neutropenia and hypersensitivity were controllable, and the other side effects were generally not dose-limiting. (Ex-1006, 50-51; Ex-1054, ¶13; Ex-1012, 684.) [redacted] In contrast, anthracycline cardiotoxicity limited their use, as explained above.

D. Genentech Identifies No Incompatibilities Between Trastuzumab and Paclitaxel

Genentech does not dispute that combination therapies were common and their development was guided by the underlying principles Dr. Earhart explained. (Petition, 38-39; Ex-1016, 204.) Genentech instead contends that these principles applied only to chemotherapy combinations, not chemotherapy/antibody combinations. (POR, 48-49.) However, the prior art already taught chemotherapy/antibody combinations, and that those combinations were expected to have greater efficacy than the monotherapies. (*See, e.g.*, Ex-1022; Petition, 37-39.)

Dr. Tannenbaum admitted that the prior art suggested use of antibodies with chemotherapies, including the trastuzumab/paclitaxel combination. (Ex-1052, 99:11-18, 104:3-8, 106:13-20, 108:24-109:12.) She also admitted that the prior art provided no reason why the four principles would not apply to chemotherapy/antibody combinations (s*ee* Ex-1052, 71:26-72:6), and that trastuzumab+paclitaxel satisfies those principles. (*Id*., 90:8-91:6.) Tellingly, Genentech did not propose substitute principles for such combinations, or point to any properties of trastuzumab or paclitaxel that would make them incompatible in combination.[8]

E. Genentech's Non-Public Development History is Irrelevant

POSAs would have understood Baselga-1996's statement that "clinical trials . . . are currently in progress" as referring to studies of trastuzumab with each of the named chemotherapeutics, including paclitaxel. (Ex-1002, ¶¶118, 151.) Genentech does not dispute this reading, but rather argues, based on information that indisputably was not available to POSAs, that there was "no clinical study involving

[8] Genentech instead resorts to purported generalized difficulties with cancer combination therapies (including chemotherapy/hormone regimens) (POR, 53), but these generalized arguments are insufficient to undercut the specific arguments presented in the Petition regarding the obviousness of the trastuzumab/paclitaxel combination.

that combination at the time that Baselga1996 was submitted." (POR, 40.) This does not diminish Baselga teaching's, however, [redacted] Moreover, Genentech's reliance on its non-public development (*e.g.*, POR, 23-26, 40, 52) should be rejected. An inventor's development path is irrelevant to patentability. *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000).

Even if the development history were relevant, Genentech mischaracterized it. It asserts that Dr. Hellmann's[9] idea to use paclitaxel was met with opposition, *e.g.* a Genentech employee stated that he "can't recommend any changes" to the study protocol to add the trastuzumab/paclitaxel arm. (POR, 25.) Genentech's truncated quote is a mischaracterization. The full statement clearly concerned the statistical power of the trial, not the safety or efficacy of adding paclitaxel: "We may or may not be powered enough, I can't predict, so I can't recommend any changes to the trial." (Ex-2004, 10.) [redacted]

[9] Genentech argues that Dr. Hellmann arrived at the idea to use paclitaxel with trastuzumab only because of her purportedly extraordinary knowledge of paclitaxel. (POR, 46.) Genentech has not cited or described any specific facts or data that allegedly guided Dr. Hellmann that were not also disclosed in the prior art. Thus, Genentech has not established that Dr. Hellmann had knowledge unavailable to the POSA that guided her alleged invention.

[redacted]

II. The Prior Art Provides a Reasonable Expectation of Success, Whether Compared to No Treatment or Paclitaxel Alone

Based on an explicit disclaimer made by Genentech during prosecution to overcome an indefiniteness rejection, the Board determined that the claim term "extend the time to disease progression in said human patient, without increase in overall severe adverse events" should be compared to no treatment. (Paper 9, 6.) Having made the statement to get the patent, Genentech now attempts to do an about-face and assert that the correct comparator is paclitaxel. (POR, 36-39.) Whatever the comparator, Genentech's attempt to hinge patentability on expected clinical results fails as a matter of law. Genentech did no more than administer an obvious combination of agents in conventional dosage regimens. (*Compare* prior art

[10] [redacted]

doses noted in Petition, 47-48 *with* Ex-1001, 28:9-13, 28:38-39.) One cannot render an otherwise obvious treatment regimen patentable by claiming the result produced by that regimen, especially where, as here, that result was reasonably expected. *Santarus, Inc. v. Par Pharms., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) ("An obvious formulation cannot become nonobvious simply by administering it to a patient and claiming [the result]."); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

A. There Was a Reasonable Expectation of Achieving the Claimed Clinical Efficacy

The prior art disclosed effective dosage amounts of trastuzumab and paclitaxel in breast cancer patients, together with TTP data. (Ex-1020, 740 (median TTP with trastuzumab was 5.1 months); Ex-1012, 683 (median TTP with paclitaxel was 3.0 or 4.2 months).)[11] Genentech argues that because the prior art studies lacked control arms, they provided no basis to determine that the claimed combination would

[11] To the extent the conventional doses, when used in combination, did not extend TTP compared to paclitaxel alone, Genentech does not dispute that POSAs would have used routine optimization to fine-tune the combination to achieve the claimed clinical results. (Petition, 48.)

extend TTP compared to treatment with a taxoid alone.[12] (POR, 50-51.) This is not the case. The prior art showed that trastuzumab achieved a longer TTP than paclitaxel. POSAs would have had a reasonable expectation that adding trastuzumab would achieve an extension of TTP over paclitaxel alone based on the superior TTP of trastuzumab. (Ex-1054, ¶20.)

Moreover, because trastuzumab and paclitaxel have non-overlapping mechanisms of action and toxicities, each can be administered in its full effective dose. (Petition, 39.) Under such circumstances, the prior art taught that "If … the new agent X, because of different dose-limiting toxicity, can be added [to the first agent] without compromising dose, there is a *reasonable expectation* that A + B + X will be superior to A + B." (Ex-1053, 291; *see also* Petition, 60-61.) Accordingly, POSAs would have had a reasonable expectation of success that administering the known effective singe-agent doses in combination would perform better than taxoid alone. (Petition, 18; Ex-1002, ¶119; Ex-1054, ¶20.)

Genentech also argues that the response rates ("RR") disclosed in Baselga-1996 do not suggest an extension in TTP when using the claimed combination, because shrinking tumors is different than extending TTP. (POR, 51.) However, as Dr. Earhart explains, the RR would have given POSAs a reasonable expectation of

[12] Genentech does not dispute that the claimed combination extends TTP compared to no treatment. (Petition, 49.)

success with respect to extending TTP. (Ex-1054, ¶22.) The most important measure of efficacy of a cancer treatment is overall survival ("OS"). (Ex-1002, ¶94; Ex-1023, 672-73.) However, when a therapy is successful, data for the OS endpoint may not be available for many years. (Ex-1002, ¶94.) Accordingly, clinical trials often use changes in biological markers like RR and TTP to measure the efficacy of a treatment. (*Id.*) FDA accepts these markers because data and experience have shown that they correlate well with OS. (Ex-1054, ¶22.) Thus, POSAs would have expected RR, like TTP, to correlate with an improvement in OS.

Positive statements in publications describing the efficacy of cancer treatments, such as Baselga-1996's statement that "rhuMAb HER2 is well tolerated and clinically active in patients with HER2 overexpressing metastatic breast cancers that had received extensive prior therapy" (Ex-1020, 737), coupled with stated plans to further test the treatment (*id.*), would have added to POSAs' expectation that the trastuzumab/paclitaxel combination would improve overall survival and TTP versus either of those treatments alone, and certainly versus no treatment. (Ex-1002, ¶136.)

B. <u>There Was A Reasonable Expectation of Achieving the Claimed Safety Parameter</u>

Under the Board's construction, the comparator for the claimed safety limitation is no treatment at all. The adverse events associated with aggressive breast cancer are more severe than any adverse events caused by treatment; without

treatment, patients with HER2+ metastatic breast cancer have a very short life expectancy.[13] (Petition, 49-50; Paper 9, 13-15; Ex-1054, ¶13.)

If the correct comparator is to treatment with paclitaxel,[14] because trastuzumab was reported to have very low toxicity and trastuzumab and paclitaxel have no overlapping toxicities, any toxicities seen with paclitaxel alone would not have been expected to increase with the combination. (Petition, 46-47.) Genentech does not dispute this or identify any potential incompatibilities for these two agents. Rather, it resorts to relying on the purported uncertainty of antibody therapy and safety issues surrounding paclitaxel. (POR, 55.) This challenge fails in view of the published safety information for the single agents, the fact that paclitaxel was FDA-approved,

[13] Genentech argues that the Board's claim construction is incorrect because the effect of the disease on an untreated patient is not an "adverse event." (POR, 54-55.) This ignores the portion of Ex. 3001 that is directly on point, which states that "Adverse events do not have to be caused by the drug or therapy . . . ."

[14] The prosecution statement cited by the Board was specifically directed to the "time to disease progression." (Ex. 1002, 416.) But whether the safety and efficacy comparators are to no treatment, to paclitaxel alone, or to a combination of the two, the prior art provided a reasonable expectation of success of achieving the claimed results. (Petition, 47-50, n.18.)

and the prior art's teachings that the trastuzumab/paclitaxel combination was already in clinical trials. (Ex-1020, 743; Ex-1019; Ex-1012.)

III. Secondary Considerations Do Not Establish Non-Obviousness

Long-Felt Need: Genentech argues that "before the '441 invention, [no one] had developed an adequate therapy" for HER2+ patients. (POR, 60.) This ignores that the value of trastuzumab was recognized. As early as 1995, "Genentech was swamped by demand" for trastuzumab, which was known to treat HER2+ metastatic breast cancer as monotherapy. (Ex-2018, 887; *see also* Ex-1059, 2 (discussing impressive clinical results in HER2+ patients using trastuzumab alone); Ex-2018 (discussing "significant tumor reduction" for trastuzumab alone).) Further, Genentech alone "had access to [trastuzumab] for clinical trials." (Ex-1044, 135:1-17.)

Further, there were known prior art combinations, such as trastuzumab/cisplatin. (Ex-1022.) Genentech itself alleges that the combination of trastuzumab with anthracyclines would have been obvious to POSAs. (POR, 47-48.)

Genentech has failed to prove the magnitude of the alleged need that was unmet by these known or admittedly obvious treatments. Moreover, the alleged unmet need for the claimed combination was not "long felt." Researchers such as Baselga proposed combining trastuzumab with paclitaxel soon after the efficacy of trastuzumab was published. That this happened so quickly after the benefits of

trastuzumab became known is further support that the claimed combination was obvious. Genentech's proffered secondary evidence is thus entitled to little or no weight.

Praise: Genentech cites three instances of alleged praise for the claimed invention, consisting of journalist characterizations and statements by Larry Norton, a coauthor of the Genentech-sponsored research reported in Baselga-1996. Relevant industry praise comes from competitors, *In re Cree, Inc.*, 818 F.3d 694, 702 (Fed. Cir. 2016), and Genentech has not cited any such praise.

Unexpected Results: Genentech argues that the combination was "surprisingly synergistic" compared with either the antibody or taxoid alone (POR, 63), based solely on a single, unsupported sentence in Dr. Hellmann's prosecution declaration. Genentech fails to address any of Petitioner's criticisms of this statement presented in the Petition, or to cite any scientific proof demonstrating synergy in any clinical trial. (Petition, 70-72.) In any event, the prior art xenograft studies demonstrated synergy in animal models, thus would not have been unexpected. (Petition, 70; Ex-1019; Ex-1004, 408.)

Genentech's argument regarding the supposed "unexpected safety improvements" as compared to combinations with anthracyclines is also unavailing. (Petition, 72-74.) While the cardiotoxicity of the anthracycline/trastuzumab combination may have been somewhat worse than anthracycline alone, this does not

transform the expected safety of the paclitaxel/trastuzumab combination into an "improvement" over the prior art. Further, the additional toxicity of the anthracycline/trastuzumab combination is entitled to little if any weight. To be considered truly "unexpected," the results must be "different in kind and not merely in degree from the results of the prior art." *See Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004) (citations omitted). As discussed above, anthracyclines were already known to cause cardiotoxicity. To the extent there was any additional cardiotoxicity when combined with trastuzumab, it was only a difference of degree. Finally, any argument that the long term cardiotoxicity of the trastuzumab/anthracycline combination was unexpected in light of the xenograft data is equally flawed. POSAs would not have formed an expectation regarding long-term cardiotoxicity from a xenograft study, given that such studies are usually relatively short and measure acute toxicities. (Ex-1054, ¶8.)

Commercial Success: "Evidence of commercial success . . . is only significant if there is a nexus between the claimed invention and the commercial success." *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311–12 (Fed. Cir. 2006). First, Genentech has failed to address its blocking patents on the trastuzumab molecule itself. For example, in a different IPR, Genentech claimed a nexus between the commercial success of Herceptin® and the earlier U.S. Patent 6,407,213 (filed on June 14, 1991). (Ex-1060, 10, 66) (asserting that success of Herceptin® "is

attributable, in part, to [its] unique sequence[] provided using the '213 patent's consensus approach"). "Where market entry by others was precluded due to blocking patents, the inference of non-obviousness of the asserted claims, from evidence of commercial success, is weak." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013).

Further, Genentech has failed to quantify the percentage of Herceptin®'s sales that are attributable to the claimed invention rather than to the invention of trastuzumab itself or to other combinations. Indeed, as set forth above, Genentech has taken the position in another IPR that the commercial success of Herceptin® can be attributed, at least in part, to the '213 patent. As the Federal Circuit has held, "[i]f the feature that creates the commercial success was known in the prior art, the success is not pertinent." *Galderma*, 737 F.3d at 740.

Genentech asserts that from 1998-2006, the only approved first-line use of Herceptin® was in combination with a taxoid. (POR, 65.) But Genentech ignores that during this same period, Herceptin® was approved for single-agent use as a second-line therapy, and is also approved as part of other combinations and for other cancers. (Ex-2012; Ex-1038.) Moreover, trastuzumab is commonly used off-label. (Ex-1034 (16% of uses were off-label); Ex-1033, 28 (trastuzumab identified as commonly used off label).) Genentech has failed to demonstrate what portion, if any, of Herceptin®'s sales are attributable to the claimed combination.

Finally, Genentech presents sales figures, without putting them in context of the market as a whole. (POR, 65-66.) This is insufficient to establish commercial success. *See, e.g., St. Jude Med., Cardiology Division, Inc. v. Board of Regents of the Univ. of Mich.*, IPR2013-00041, Paper 69, 24-28 (PTAB May 1, 2014).

IV. **Conclusion**

Petitioner respectfully requests that the Board cancel the challenged claims as obvious.

Respectfully submitted,

Dated: March 30, 2018

/Cynthia Lambert Hardman/
Cynthia Lambert Hardman (Reg. No. 53,179)
Robert V. Cerwinski (*pro hac vice*)

WORD COUNT CERTIFICATION

The undersigned certifies that the attached Petitioner Celltrion's Reply to Patent Owner's Response contains 5,599 words (as calculated by the word processing system used to prepare this Petition), excluding the parts of the Petition exempted by 37 C.F.R. §42.24(a)(1).

Dated: March 30, 2018 By: /Cynthia Lambert Hardman/

Cynthia Lambert Hardman (Reg. No. 53,179)

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), the undersigned certifies that on March 30, 2018, I caused copies of the foregoing PETITIONER CELLTRION'S REPLY TO PATENT OWNER'S RESPONSE and Exhibits 1033-56, 1058-60, and 1100 to be served via email on the following counsel for Patent Owner and for Petition Pfizer:

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