UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Celltrion, Inc.
Petitioner,

v.

Genentech, Inc.
Patent Owner.

Case IPR2017-01122
Patent 7,892,549

PETITIONER CELLTRION'S REPLY TO PATENT OWNER'S RESPONSE

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Genentech cannot dispute that the prior art disclosed (1) dosages for (a) single-agent trastuzumab, (b) trastuzumab+cisplatin, and (c) single-agent paclitaxel that were safe and effective in treating breast cancer patients; (2) the specific suggestion of combining trastuzumab and paclitaxel to treat HER2+breast cancer; (3) pre-clinical test data suggesting that the combination of trastuzumab and paclitaxel, like the single-agents and like the combination of trastuzumab and cisplatin, 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, along with another chemotherapeutic agent, such as cisplatin. The prior art, when taken as a whole, compels the conclusion that POSAs would have been motivated to administer trastuzumab and paclitaxel, along with another chemotherapeutic agent like cisplatin, 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]

[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, is 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 and other chemotherapy agents; it thus would have been more than reasonable for POSAs to believe that adding trastuzumab to paclitaxel therapy, along with another chemotherapeutic agent, would increase efficacy in HER2+ patients over paclitaxel alone. Third, Genentech simply administered prior-art dosage amounts of trastuzumab and paclitaxel, then claimed the results.[1] Its "discovery" of the results produced by administering the obvious combination of these conventional dosage amounts cannot confer patentability.

[1] The specification does not reflect any results from administration of a combination of trastuzumab, paclitaxel, and a further growth inhibitory agent or further therapeutic agent to a patient.

Finally, Genentech has failed to respond to Petitioner's contentions that there is no secondary evidence of nonobviousness supporting the claims. (Petition, 70-75.)

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

I. The Prior Art Motivated the Trastuzumab+Cisplatin and Paclitaxel Combination

As demonstrated in the Petition, POSAs[3] would have been motivated to combine trastuzumab+cisplatin and paclitaxel. 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, 33.) 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 POSAs. (Ex-1054, ¶5.)

A. Trastuzumab+Cisplatin and Paclitaxel Both Demonstrated Efficacy in HER2+ Patients

POSAs would have recognized that each of trastuzumab, trastuzumab+cisplatin, and paclitaxel were effective in treating HER2+ breast cancer.[4] (Petition, 24.) Genentech does not dispute the efficacy of trastuzumab or trastuzumab+cisplatin in such patients, but alleges that POSAs would have been skeptical about paclitaxel's efficacy in this population. Genentech's rationale is unpersuasive. First, Genentech contends that POSAs would have ignored Seidman 1996 simply because it is an abstract, not a full paper. (POR, 30.) 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

[4] Genentech argues that cisplatin was not widely used to treat breast cancer. (POR, 17.) Genentech is incorrect. Cisplatin was indicated to treat breast cancer, and the combination of cisplatin+trastuzumab had been shown to be effective. (Ex-1016, 211; Ex 1022.)

patent, Dr. Hellmann relied on an abstract to argue that docetaxel and Herceptin® will behave like paclitaxel and 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 even exist as of the priority date), they themselves did not consider paclitaxel to have "proven efficacy" in HER2+ patients as of the priority date. (POR, 41.) Genentech has not linked the Seidman 1996 and 2002 work, 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, 40.) 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.)[5]

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.[6] (POR, 42-44.) It is undisputed, however, that

[5] 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, 5-7, 12, 22.)

[6] Genentech complains that certain references are not part of the instituted ground. (POR, 26.) However, references that are not part of the ground "can legitimately

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

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).

[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, 21:19-23), 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 human 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 [redacted] 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, 42.) While

[redacted]

this may have been a consideration for a drug that previously had not been tested in any cancer model, here, the drugs proposed for the combination were known to have efficacy in HER2+ patients. As Dr. Earhart explains, preclinical studies are not 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, 42.) 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, 10, 42-43.) 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). 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 xenograft 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.[8] (Petition, 45.) But perhaps more importantly, the prior art indicated that,

[8] 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, 43 n.13.) This argument

on the basis of the xenograft results, clinical trials of the combination were already underway. (Ex-1019 ("In summary anti HER2 MAbs can eradicate well established tumors and enhance the activity of paclitaxel and doxorubicin against human breast cancer xenografts. 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 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/cisplatin regimen, and this combination lacks anthracycline. (Petition, 51.)

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.

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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-1039, 112-14; Ex-1007, 1164; Ex-1011; Ex-1054, ¶12.)

(Petition, 51; Paper 9, 24.) 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, 14, 45.) 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/cisplatin 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." IPR2017-00731, Paper 29, 13 (citing *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989)).

Genentech also asserts that because paclitaxel was approved as a second-line therapy, POSAs would have regarded it as inferior to anthracyclines, which were approved for first-line treatment. (POR, 16.) This misrepresents the science. 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, the prior art [redacted] make clear that POSAs knew 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, 41; 45.) However, as of 1997, 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 reactions were controllable with co-medication and premedication regimens, and the other side effects were generally not dose-limiting. (Ex-1006, 50-51; Ex-1054, ¶13; Ex-1012, 684.) [redacted]

[redacted] In contrast, the cardiotoxicity seen with anthracycline did limit the use of anthracyclines, as explained above.

D. Genentech Identifies No Incompatibilities Between Trastuzumab+Cisplatin and Paclitaxel

Genentech does not dispute that cancer combination therapies were common and that their development was guided by the four underlying principles explained by Dr. Earhart. (Petition, 38-39; Ex-1016, 204.) Genentech instead contends that these principles applied only to combinations of chemotherapy agents, not to chemotherapy/antibody combinations. (POR, 46-47.) However, the prior art already taught combinations of antibodies with chemotherapies, and that those combinations were expected to have greater efficacy than the monotherapies. (*See*, *e.g.*, Ex-1022 (trastuzumab/cisplatin better than cisplatin alone); Petition, 39-40.) Dr. Tannenbaum admitted that the prior art suggested the 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 would satisfy those principles. (*Id.*, 90:8-91:6.) Tellingly, Genentech did not propose substitute

principles that should be applied for such combinations, or point to any properties of trastuzumab or paclitaxel that would make them incompatible in combination.[9]

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

POSAs would have understood the statement in Baselga 1996 that "clinical trials . . . are currently in progress" as referring to studies of the combinations of trastuzumab with each of the named chemotherapeutics, including paclitaxel. (Ex-1002, ¶¶58, 118, 151.) Genentech does not dispute this reading, but rather argues, based on information that indisputably would not have been available to POSAs as of the priority date, that in fact there was "no clinical study involving that combination at the time that Baselga1996 was submitted." (POR, 38.) This does not diminish the teaching in Baselga, however, [redacted]. Moreover, Genentech's attempts to rely on its non-public development history to rebut obviousness (*see, e.g.*, POR, 22-24, 46) should be rejected, because an inventor's development path is irrelevant to patentability. *Life Techs., Inc. v. Clontech Labs.*,

[9] Genentech instead resorts to purported generalized difficulties with cancer combination therapies (including chemotherapy/hormone regimens) (POR, 51), but these generalized arguments are insufficient to undercut the specific arguments presented in the Petition regarding the obviousness of the trastuzumab/paclitaxel/cisplatin combination.

Inc., 224 F.3d 1320, 1325 (Fed. Cir. 2000) ("Furthermore, the path that leads an inventor to the invention is expressly made irrelevant to patentability by statute.").

Even if the development history were relevant, Genentech has blatantly mischaracterized it. It asserts that Dr. Hellmann's[10] 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. When read in its entirety, the statement clearly concerned only 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]

[10] Genentech argues that Dr. Hellmann arrived at the idea to use paclitaxel with trastuzumab only because of her purportedly extraordinary knowledge of paclitaxel. (POR, 44.) 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 POSAs that guided her alleged invention.

[redacted] Ex-2004, 10 (quoting a reviewer as stating: "I support the Taxol amendment.").)

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

Based on an explicit disclaimer made by Genentech during prosecution of the parent '441 patent to overcome an indefiniteness rejection, the Board determined that the claim term "an amount effective to extend the time to disease progression in the human patient" should be compared to no treatment. (Paper 9, 12.) Having made the statement to get the patent, Genentech now attempts to do an about-face and assert that the correct comparator is treatment with paclitaxel. (POR, 34-37.) 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 doses noted in Petition at 47-48 *with* Ex-1001, 28:9-13, 28:38-39.) One cannot render an otherwise obvious treatment regimen patentable by claiming the result

[11] [redacted]

produced by that regimen, especially where, as here, that result was reasonably expected. *Santarus, Inc. v. Par Pharms., Inc.*, 694 F.3d 1344, 1366 (Fed. Cir. 2012) ("An obvious formulation cannot become nonobvious simply by administering it to a patient and claiming [the result]."); *see also KSR International 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, cisplatin, and paclitaxel in breast cancer patients. (Ex-1020, 737; Ex-1012, 682; Ex-1022).[12] The prior art also provided TTP data for trastuzumab and paclitaxel. (Ex-1020,740 (trastuzumab median TTP was 5.1 months); Ex-1012, 683 (paclitaxel median TTP was 3.0 or 4.2 months, depending on dose).) Genentech argues that because the prior art studies lacked control arms, they provided no basis to determine that the claimed combination would *extend* TTP compared to treatment with a taxoid alone. (POR, 47-49.) This is not the case. The prior art showed that trastuzumab achieved a

[12] To the extent the conventional effective 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, 49.)

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 the agents have different mechanisms of action and non-overlapping 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 two agents] without compromising dose, there is a *reasonable expectation* that A + B + X will be superior to A + B." (Ex-1053, 291; *see also* Petition, 61-62.) Accordingly, POSAs would have had a reasonable expectation of success that administering the known effective doses in combination would perform better than paclitaxel alone. (Petition, 62; Ex-1002., ¶119; Ex-1054, ¶20.)

Genentech does not dispute that the claimed combination extends TTP compared to no treatment, as required under the Board's claim construction. (Petition, 50-51.)

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, 49-50.) However, as Dr. Earhart explains, the RR results would have given POSAs a reasonable expectation of success with respect to extending TTP. (Ex-1054 ¶22.) The most

important measure of the efficacy of a cancer treatment is overall survival. (Ex-1002, ¶94; Ex-1023, 672-73.) However, when a therapy is successful, overall survival data 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 overall survival. (Ex-1054, ¶22.) Thus, POSAs would have expected RR, like TTP, to correlate with an improvement in overall survival.

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), Pegram's statement that "the use of rhuMAb-HER-2 plus [cisplatin] in patients with HER-2/neu overexpressing [metastatic breast cancer] resulted in response rates above that expected from [cisplatin] alone" (Ex-1022), along with stated plans to further test the treatment of paclitaxel with trastuzumab, such as Baselga 1996's statement that "studies are currently in progress" (*id.*), would have added to POSAs' expectation that the combination of trastuzumab, paclitaxel, and cisplatin would improve overall survival and TTP versus either of those treatments alone, and certainly versus no treatment. (Ex-1002, ¶136.) Because of the known correlation between overall

survival and TTP, this prior art also teaches the expected efficacy with respect to extension of TTP, whether measured as compared to no treatment or to paclitaxel alone. (*Id*.)

III. Genentech Did Not Proffer Any Secondary Considerations of Non-Obviousness

In its Reply, Genentech did not raise any alleged secondary considerations of non-obviousness. Nor did it attempt to rebut the arguments Petitioner made in the Petition regarding lack of any secondary considerations. (Petition, 70-75.)

IV. Conclusion

For the reasons raised here and in the Petition, Petitioner respectfully requests that the Board cancel the challenged claims as obvious in view of the prior art.

Respectfully submitted,

Dated: March 30, 2018

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WORD COUNT CERTIFICATION

The undersigned certifies that the attached Petitioner Celltrion's Reply to Patent Owner's Response contains 4,783 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 1033-60 and 1100 to be served via email on the following counsel for Patent Owners:

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