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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00731
Patent No. 7,846,441

PATENT OWNER'S RESPONSE

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Genentech, Inc. ("Patent Owner") submits this Response to the Petition filed by Hospira, Inc. ("Petitioner"). Patent Owner's Response is supported by the Expert Declarations of Drs. Susan H. Tannenbaum (Ex-2062) and Robert S. Kerbel (Ex-2061).

I. INTRODUCTION

The patent at issue, U.S. Patent No. 7,846,441, claims a new method of treating cancers that overexpress a protein called "HER2," which is associated with an aggressive form of breast cancer. The claimed method of treatment involves using an "anti-ErbB2" antibody, which targets a cellular receptor associated with HER2-positive cancer, in combination with a chemotherapy called a "taxoid."

Prior to the '441 patent, it was not clear what role, if any, antibodies would play in the treatment of cancer. Despite decades of research, there were no FDA-approved antibody therapies for solid tumors, like breast cancer. And even if antibodies might someday prove effective, it was not clear how those drugs would fit into a patient's overall therapy—for example, as a drug administered alone or as part of a combination with traditional chemotherapy.

The '441 patent discloses the results of the first controlled clinical trial demonstrating the ability of an antibody to treat solid tumors. That antibody, the "anti-ErbB2" antibody, specifically targets cancers that overexpress the "HER2" protein. When administered with a chemotherapy in the "taxoid" family, and in

the absence of another family of chemotherapeutic agents known as "anthracyclines," this claimed combination therapy significantly extends the time to disease progression ("TTP") as compared with patients receiving taxoid therapy alone, without increasing the side effects of chemotherapy.

Petitioner argues that the claimed combination would have been obvious over the results of a Phase-II study treating patients with the antibody alone (Baselga '96) and a preclinical mouse study involving the combination of the antibody and paclitaxel as well as the antibody and an anthracycline (Baselga '94). After initially denying institution, the Board granted Petitioner's rehearing request and found that Petitioner had demonstrated a reasonable likelihood that it would prevail in proving the invalidity of the challenged claims. However, the full record now confirms that Petitioner has not carried its burden of proving that the challenged claims are patentable.

First, Petitioner has not demonstrated a motivation to combine an anti-ErbB2 antibody with a taxoid in the absence of an anthracycline derivative as claimed in the '441 patent. The only disclosure of the combination of an anti-ErbB2 antibody and a taxoid in the prior art is the preclinical study reported by Baselga '94. However, there were well-known limitations with respect to xenograft mouse models of the type used in Baselga '94, which severely restricted their ability to predict safety and efficacy in human patients. In fact, before the

'441 invention, even the persons of ***extra***ordinary skill involved in the development of Herceptin® (the trade name of Patent Owner's anti-ErbB2 antibody) did not view this limited evidence as motivating a combination of an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative. Indeed, the only Phase-II trials involved treatment with either the antibody alone or in combination with a different chemotherapeutic agent, called cisplatin. And when Phase-III trials began, the only drug combination under evaluation was an anti-ErbB2 antibody combined with an anthracycline.

That development history also reinforces what was known at the time about taxoids, which were a relatively-new class of chemotherapy that had a history of severe side effects and had only been approved as a second-line therapy for breast cancer. The first time that anyone ever treated a human patient with the claimed combination of an anti-ErbB2 antibody and a taxoid was when '441 inventor Dr. Susan Hellmann recommended the combination to address enrollment problems in an ongoing Phase-III study. The results of that first-in-man clinical trial are reported in the '441 patent. Only in hindsight can Petitioner say that it would have been obvious to pursue a combination that even those with the best information about the drug chose not to pursue.

Second, the Board's institution decision rested on an incorrect claim construction of the term "extend the time to disease progression in said human

patient, without increase in overall severe adverse events." The Board interpreted that term as measured relative to an untreated patient, but that is inconsistent with the '441 specification as understood by a person of ordinary skill in the art ("POSA"). Instead, the appropriate comparison is to a patient treated with a taxoid alone, which is the only comparison described in the patent specification that is consistent with the language of the claims. The specification reports nothing about untreated patients.

The Board based its construction on a single statement in the file history, but that statement, which cites to the example in the specification that compares patients treated with the claimed combination to patients treated ***with a taxoid (paclitaxel)*** alone, does not change how a POSA would understand the term. In fact, Petitioner's own expert discussed the applicant's prosecution statement and nevertheless opined that a POSA would understand that the appropriate comparison is to a patient treated with a taxoid alone. Thus, the understanding of a POSA is not in dispute.

Under this correct claim construction, a POSA would not have had a reasonable expectation of success that the combination of an anti-ErbB2 antibody and a taxoid would extend TTP as compared with taxoid-only treatment. The prior art preclinical mouse study in Baselga '94 measured the response rate of tumors grown in mice—i.e., the ability of the drug combination to shrink tumor size. It

did not measure the TTP (much less ***extension*** of TTP), which is a different endpoint that may not be predicted by an effect on response rate. In any case, the full record now demonstrates that a POSA would have understood that the preclinical mouse model disclosed in Baselga '94 had significant limitations, thus minimizing the predictive value of the reported results.

Moreover, the Board's construction of "extend the time to disease progression in said human patient, without increase in overall severe adverse events," as requiring comparison to untreated patients, conflicts with the Board's construction of the embedded term "adverse events," which only applies to patients who have been treated. This inconsistency is yet another reason supporting a comparison to treatment with paclitaxel alone, rather than no treatment at all.

Third, even under the Board's claim construction, Petitioner has not demonstrated that a POSA would have had a reasonable expectation of success that the combination therapy would not lead to an overall increase in severe adverse events. The only justification that the Board offered for why this limitation would be satisfied under its claim construction is that the effects of the disease in an untreated patient are supposedly an adverse event. But that argument (which even Petitioner did not advance) is directly refuted by the definition of adverse event relied on by the Board, which makes clear that an adverse event is "[a]n ***unexpected*** medical problem that happened ***during treatment*** with a drug or other

therapy."[1] The effects of the disease in an untreated patient are neither unexpected nor something that occurs "during treatment." Because a POSA would have expected treatment with the claimed combination to produce at least ***some*** adverse events, the POSA would also have expected it to cause an "increase in overall severe adverse events" relative to untreated patients who, by the Board's definition, experience no adverse events at all.

Finally, although not addressed in the institution decision, there are several strong objective indicia of non-obviousness, including satisfaction of a long-felt-but-unmet need, praise, unexpected results, and commercial success. Simply put, the claimed method of treatment was a breakthrough that fundamentally improved the previously very-poor prognosis of patients with HER2-positive breast cancer.

The Board should reject Petitioner's challenge to the patentability of the challenged claims.

II. TECHNOLOGY BACKGROUND

A. Oncology Drug Discovery

1. Developing new cancer therapies is an unpredictable process.

a) Preclinical animal models

[1] All quoted emphases herein are added unless otherwise noted.

Before a new cancer therapy is ever tested in humans, it is evaluated in preclinical *in vitro* and/or animal models. For example, mouse xenograft studies involve implanting human tumor cells in an immunocompromised mouse. (Ex-2051 at 1041 ("NCI researchers came up with the xenograft models, in which investigators implant human tumors underneath the skin of mice with faulty immune systems.").) (Ex-2061 ¶¶34-40; Ex-2062 ¶¶64-68.)

As Drs. Tannenbaum and Kerbel explain, preclinical mouse studies are a useful initial mechanism to screen for drugs that show some activity against particular cancer cells, and to understand their mechanism of function. However, it was known in the 1990s that mouse models were (and are still today) an inexact tool. Many drugs that show activity in xenografts fail in humans, and retrospective studies have shown that some drugs that have been successfully used to treat humans have not shown activity in xenografts. (Ex-2061 ¶¶54-60; Ex-2062 ¶¶65-69.)

By 1997, it was recognized that efficacy in mouse models was not reliably predictive of anti-cancer drug performance in humans.[2] (*See, e.g.*, Ex-2023 at 79

[2] Petitioner's expert, Dr. Lipton, testified that assessing whether xenografts handle drugs differently than human patients is "beyond my area of expertise." (Ex-2050, 78:21-79:6.)

("very low" likelihood of predicting response in humans); Ex-2051[3] at 1041 ("Screening potential anticancer drugs sounds easy. Just take a candidate drug, add it to a tumor type of choice, and then monitor whether the agent kills the cells or inhibits cancer growth. Too bad it hasn't been that simple."); *id.* (Executive Director for Cancer Research at Merck: "The fundamental problem in drug discovery for cancer is that the model systems are not predictive at all."); *id.* ("[D]rugs tested in the xenografts appeared effective but worked poorly in humans."); *cf.* Ex-2075 at 1633 ("[T]here is a commonly held belief amongst cancer researchers that transplantable tumors in rodents are sensitive to drug therapy, are easy to cure, and therefore are not predictive of responses in humans.").) (Ex-2061 ¶¶54-60; Ex-2062 ¶¶68-69.)

[3] During deposition, Petitioner's expert criticized the Gura article (Ex-2051) as "not something a person with experience in the art would rely on." (Ex-2050, 173:7-174:16.) However, as Dr. Tannenbaum explains, the Gura article appears in a well-regarded journal (Science), the particular issue had an entire section devoted to cancer research and treatment, the article was based on interviews with numerous oncologists, and clinical oncologists "would certainly read" such an article directed to their area of research and practice. (Ex-2062 ¶75.)

Mouse studies failed to reliably predict results in humans for several reasons.

First, the mice being tested are different from humans in important ways. For example, mice have a higher maximum tolerated dose of therapy, which often allows for outcomes that are not possible in humans. (Ex-2019 at 1577.) (Ex-2061 ¶67; Ex-2062 ¶70.)

In addition, drugs often have adverse effects in humans, but not in mice, due to differences in cell and tissue types between mice and humans. That is, because xenograft mice have different cells and tissue than humans (other than the implanted human tumor), humans often experience host-cell or tissue-dependent toxicity that does not show up in mice tested with the same drugs. (Ex-2061 ¶¶72-77; Ex-2062 ¶71.)

Second, mouse studies are more likely to show positive efficacy because they use tumor cell lines from tissue culture. Cells held in culture divide more rapidly than human cells, and rapidly-dividing cells exhibit greater sensitivity to chemotherapy. (Ex-2061 ¶39; Ex-2062 ¶¶70-71.)

Third, mouse studies are short-term and generally measure only the clinical endpoint of response rate—i.e., the ability of therapy to shrink tumors—not effect on TTP. Response rate and TTP are different endpoints—e.g., a therapy may demonstrate a response rate by initially shrinking tumors, but fail to eradicate the

most-aggressive cancer cells that cause the cancer to progress quickly. As Dr. Tannenbaum notes, for solid tumors such as breast cancer, it was well known that therapies may improve response rates but not affect TTP. (Ex-2062 ¶85; Ex-2067 at 353.) This fundamental difference is highlighted by the fact that Baselga '94's mouse studies occurred over a period of ***five weeks*** (Ex-1005), whereas the TTP for Herceptin® plus Taxol® in humans reported in the '441 patent was ***7.1 months*** (Ex-1001, 30:6). (Ex-2050 [Lipton], 103:10-13 ("This was just a five-week study. So time to disease progression was not assessed.").) (Ex-2061 ¶¶82-83; Ex-2062 ¶146.)

Fourth, mouse results are limited by the cell line used. Because of the complexities of most cancers, scientists knew by 1997 that, to obtain accurate results, they had to conduct preclinical studies using multiple cell lines. (Ex-2052 at 261 ("It is unlikely that any one tumor model will adequately represent the major biological characteristics of a particular malignancy. Thus, the use of a series of tumors (where appropriate/available) may be required to determine the sensitivity of a particular neoplastic disease to either a single or a combination chemotherapy regimen."). (Ex-2061 ¶¶65-69; Ex-2062 ¶¶71-73.)

The differences in cell lines, and thus the need to conduct studies on multiple cell lines, was especially important for breast cancer. (Ex-2052 at 261 ("For breast cancer, there [we]re several potential models available for screening"

by 1997.) For example, one study in 1995 (Szöllösi) estimated that the BT-474 breast-cancer cell line had 52 copies of the ErbB2 gene on average per cell, the SK-BR3 cell line had 31 copies on average per cell, and the MDA-453 cell line had 11 copies on average per cell. (Ex-2064 at 5402, Table 1.) BT-474—by far the most overexpressing of these cell lines—was the cell line used in the Baselga '94 mouse study. This variation in cell lines is similar to the heterogeneity of human chromosomes. (Ex-2064 at 5400; Ex-2065 at 262; Ex-2063 at 1457.) (Ex-2061 ¶¶26, 42-44; Ex-2062 ¶72.)

Preclinical mouse results using a single cell line, therefore, were akin to conducting a clinical trial with a single patient and were known not to be a reliable indicator of success in a population of human patients. (Ex-2061 ¶63; Ex-2062 ¶¶72.)

Fifth, mouse models based on subcutaneous implantation[4] of tumors were known to be even less reliable than models that implanted the cells in the same type of tissue as the target disease. (Ex-2053 at 79 ("While the [subcutaneous] site is convenient, it is likely that it is not the optimal site for all xenografts."). Studies

[4] As Dr. Kerbel explains, "subcutaneous" implantation of tumors in mouse models typically referred to implantation beneath this skin in the hind leg or flank of the mouse. (Ex-2061 ¶30.)

published in the 1990s showed that transplanted tumors often responded to drugs, including chemotherapy agents, when grown "ectopically" as subcutaneous tumors, but did not respond (or responded in a diminished manner) when transplanted and grown "orthotopically" (i.e., in the organ from which the cancer under study was derived). Thus, it was known that to obtain more-reliable results for breast cancer, the tumor must be implanted in breast tissue. (Ex-2053 at 79 ("The most appropriate site for breast tumor xenografts is the mammary fat pad (orthotopic site), a site we use routinely.").) (Ex-2061 ¶¶77-82.)

b) Clinical trials

Therapies with favorable results in preclinical models might advance to clinical studies conducted in humans. Those clinical studies occur in stages, beginning with initial small-scale studies (i.e., Phase I or Phase II), followed by large-scale controlled trials designed to evaluate specific clinical endpoints (i.e., Phase III). (Ex-2062 ¶¶76-81.)

That a drug proceeds to human clinical trials is hardly an indicator of eventual success. (Ex-2050 [Lipton], 57:3-9 ("a significant number of potential drugs fail during the clinical trial process").) In the 1990s, only 5% of cancer drugs that advanced to clinical trials resulted in an approved product. (Ex-2021 at 711-12.) Even for drugs that advanced to late-stage, Phase-III clinical trials, nearly 60% ultimately failed to result in an approved drug. (*Id.*; Ex-2050, 63:5-19 (Dr.

Lipton testifying he has "no reason … to doubt" this failure rate); *id.*, 57:17-58:2 (Dr. Lipton admitting "many" chemotherapeutic agents "fail in [clinical] development" for breast cancer).) Thus, the fact that a therapy had progressed from preclinical studies through early-stage clinical trials was no indication that it would have a clinical benefit when subjected to more rigorous late-stage studies. Indeed, the myriad failures during clinical development reinforce the limitations of preclinical studies at that time to predict clinical efficacy in humans. (Ex-2021 at 712-13 ("The lack of efficacy might be contributing more significantly to therapeutic areas in which animal models of efficacy are ***notoriously unpredictive***, such as CNS and ***oncology***, both of which have relatively higher failure rates in Phase II and III trials.").) (Ex-2062 ¶¶86-89.)

Clinical trials also can be designed to measure different endpoints. As noted above, one such endpoint is "response rate," which measures tumor shrinkage. A different clinical endpoint, "time to disease progression," is the time following treatment before a patient's tumors begin to grow or to spread to other parts of the body. (Ex-1001, 29:1-2.) Thus, response rate and TTP measure different outcomes over vastly-different time horizons. Response rate measures tumor shrinkage as an initial response to therapy, whereas TTP measures the longer-term effect of the therapy on disease progression. (Ex-2062 ¶¶78-85.)

Because they measure different outcomes, a positive response rate is not indicative of whether a therapy will affect TTP. For example, a therapy may demonstrate a response rate by shrinking tumors, but fail to eradicate the most aggressive cancer cells that cause the cancer to progress quickly. As Dr. Tannenbaum notes, for solid tumors such as breast cancer, it was well known that therapies may improve response rates but not affect TTP. (Ex-2062 ¶85; Ex-2067 at 353.)

Indeed, Petitioner's own expert recognizes that response rate is a different clinical endpoint than TTP. (*See* IPR2017-02063, Ex-1002 ¶112(f)-(g) (Dr. Lipton defining "response rate" as "the percentage of patients whose disease responds to treatment" and "time to disease progression" as "the time period calculated from the beginning of therapy until the disease worsens").)

2. The prior art favored anthracyclines over taxoids as a treatment for breast cancer.

In the 1990s, there were a wide variety of chemotherapeutic agents either available for treatment or in development. (Ex-2062 ¶42.) Two chemotherapeutic drug classes are mentioned in the challenged claims: anthracyclines and taxoids.

a) Anthracyclines

In the 1990s, anthracyclines were "among the most widely used antineoplastic [*i.e.*, anticancer] agents in current clinical practice." (Ex-2030 at

409.) Doxorubicin is an example of an anthracycline, and it was known to be "especially active" against breast cancer. (*Id.*) Doxorubicin had "no known antagonistic interactions with any of the other commonly used anticancer agents," and it was "active over a wide range of doses and in a variety of administration schedules," which made it "very useful in the design of drug combinations" with other cancer therapies. (*Id.*) As a result, treatments containing anthracyclines were the "standard therapy for cancers of the breast" in the 1990s. (*Id.*; *see also* Ex-2050 [Lipton], 50:1-12 (anthracycline "Adriamycin was commonly used in breast cancer").) (Ex-2062 ¶¶43-45, 52.)

As Petitioner notes, cardiotoxicity had been observed in some instances when anthracyclines were administered for extended periods resulting in high cumulative doses. (Paper-1 at 13.) However, by 1996, that side effect was well-known and had been studied, and there were available techniques for reducing the risk of cardiotoxicity from anthracyclines, while at the same time maintaining their proven efficacy. (Ex-2030 at 423 ("Fortunately, much can now be done to lessen the risk of cardiac toxicity.").) For example, clinicians knew that cardiotoxicity could be reduced by adopting an administration schedule that minimized the peak concentrations of anthracycline in the blood. (Ex-2055 at Abstract; Ex-2030 at 425.) Dexrazoxane could also be administered along with anthracyclines to provide cardioprotection. (Ex-2055 at Abstract; Ex-2103 at Abstract.) It was also

known that reducing the total lifetime anthracycline dose significantly reduced the chances of a patient experiencing cardiotoxicity. (Ex-2055 at 5; Ex-2103 at 3118.) Moreover, it was known that few patients ever reached the cardiotoxic threshold for anthracyclines. (Ex-2055 at 5.) (Ex-2062 ¶¶47-51.)

As the Board concluded in its initial decision denying institution, the known cardiotoxicity of anthracyclines would not have motivated a POSA to exclude those drugs from therapy. (Paper-19 at 9 ("Thus, cardiotoxicity does not appear to have motivated an ordinary artisan to avoid anthracyclines in treating breast cancer.").)

b) Taxoids

Unlike anthracyclines, taxoids were a relatively-new type of chemotherapy in the 1990s, which oncologists were slow to adopt for treating breast cancer. Taxoids were associated with serious hypersensitivity reactions, "varying from flushing, dyspnea and bronchospasm, and rashes to severe hypotension and asystole, resulting in death." (Ex-2028 at 1265.) Taxoids were also associated with neuropathy (i.e., weakness, numbness, and pain in the hands and feet) and cardiotoxicity. (Ex-2062 ¶60; Ex-2105 at 7; Ex-2026 at 1704, 1709 (taxoids cause "[a] diverse spectrum of cardiac disturbances").) The prior art thus warned oncologists "to maintain a high degree of caution" with those drugs. (Ex-2026 at 1704 (development of taxoids "has proceeded slowly due to serious

hypersensitivity reactions").) The prior art also reported that 30-40% of breast cancer patients did not respond to taxoids. (Ex-2029 at 1359; *see also id.* at 1362 ("breast cancers that overexpress p185 [*i.e.*, HER2] ***will not respond well to Taxol***.").) (Ex-2062 ¶¶53-60.)

The drug paclitaxel (Taxol®) is an example of a taxoid chemotherapy. The FDA approved paclitaxel for ovarian cancer in 1992 and for breast cancer in 1994. Even then, paclitaxel was approved to treat breast cancer only ***after*** other treatments failed, i.e., for "second-line" use. (Ex-2105 at 6.) As a second-line treatment, a POSA would have understood Taxol® as generally having less efficacy and/or more significant side effects than first-line therapies. In fact, the approved Taxol® label at the time of the '441 invention explicitly advised that patients should have been treated with an anthracycline ***first*** before trying paclitaxel. (*Id.*) (Ex-2062 ¶¶53-56.)

3. Before the '441 invention, no antibody had been approved for the treatment of solid tumors.

Antibodies are proteins that bind to molecular targets, called "antigens." Antibodies that target specific antigens can be created in a laboratory. (Ex-1001, 8:44-9:3.) However, the body's immune system may attack such specially-designed antibodies, preventing them from having a therapeutic effect. (Ex-2031 at 655.) As of 1996, "much additional study" was required to determine whether

there were ways to avoid triggering that immunogenic response. (*Id.* at 683.) Moreover, antibodies are large molecules that have difficulty penetrating tissue—a "significant obstacle[] to the effective use of mAbs for solid tumors," such as breast cancer. (*Id.*) (Ex-2062 ¶¶93-97.)

By the early 1990s, numerous antibodies had been tested in patients with different cancers (including breast cancer), but consistent with the challenges just described, these antibodies showed "no hint of a consistent therapeutic efficacy." (Ex-2025 at 649; *id.*, Table 2 (identifying failed antibody clinical trials for gastrointestinal tumors; breast, colon, ovarian, and lung cancer; pancreatic adenocarcinoma; neuroblastoma; and melanoma).) Given that poor track record, a 1993 review article aptly summarized the state of the art prior to the '441 invention: "[A]ntibody therapy of cancer has become a story of unending failures." (Ex-2032 at 732.) As confirmed by a 1996 textbook, those "significant obstacles" persisted even up to the invention of the '441 patent. (Ex-2031 at 683.) (Ex-2062 ¶¶98-99.)

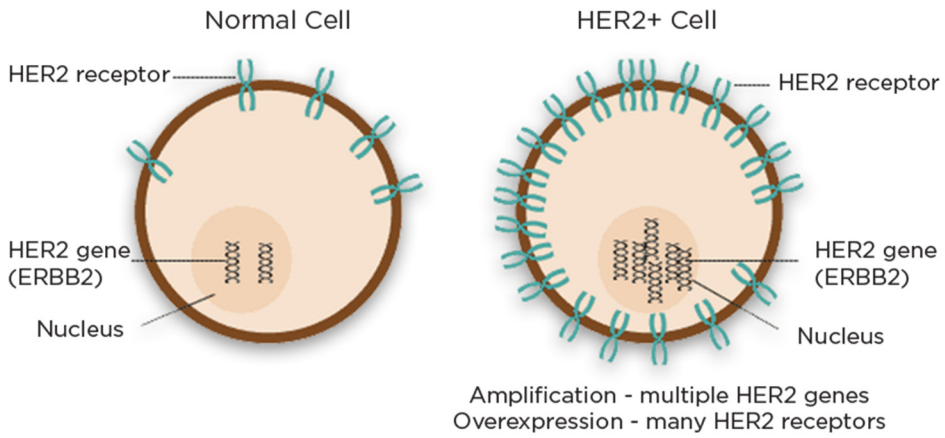
The Board's decision on rehearing states that "[b]efore the '441 patent, a recombinant humanized anti-ErbB2 monoclonal antibody (a humanized version of the murine anti-ErbB2 antibody 4D5, also referred to as rhuMAb HER2, trastuzumab, or HERCEPTIN®) had been approved to treat patients with ErbB2-overexpressing metastatic breast cancers." (Paper-29 at 3.) While the filing date

of the utility application for the '441 patent (December 1998) was after the approval date of Herceptin® (September 1998), the appropriate comparison is to the filing date of the ***provisional application*** (December 1997) (*see* Ex-2009, 36:7-21, 38:26-43:36), which was nearly a year before Herceptin® was approved. The passage from the '441 patent cited by the Board (Ex-1001, 3:34-39) refers to the results of a Phase-II study, not the rigorous demonstration of long-term clinical benefit required for FDA approval.

B. HER2-Positive Breast Cancer

The '441 patent involves the treatment of "HER2-positive" cancers, which have a genetic mutation that causes them to overexpress human epidermal growth factor 2 ("HER2"), also known as human ErbB2. Out of the hundreds of thousands of women each year who are diagnosed with breast cancer, roughly 25-30% are HER2-positive. (Ex-1001, 1:23-29; Ex-2050 [Lipton], 17:20-22.) (Ex-2062 ¶90.)

The following graphic depicts a normal cell versus a HER2-positive cell:



While a normal cell has two HER2 genes, which form a small number of HER2 receptors at the cell surface (as shown above, on the left), a HER2-positive cell has several additional copies of the HER2 gene, resulting in many more HER2 receptors at the cell surface. These additional HER2 receptors enhance cell growth. (Ex-2062 ¶¶30, 90.)

HER2-positive breast cancer is an aggressive disease. In the 1990s, HER2-positive status was "associated with poor prognosis," including a high rate of tumor recurrence and spreading to other areas of the body. (Ex-2022 at 1420; Ex-1028 at 6-8; Ex-2050, 45:4-7 (Dr. Lipton admitting that before Herceptin® HER2-positive status "used to have the worst prognosis in women with breast cancer").) HER2-positive patients had "a shorter time to relapse as well as a shorter overall survival." (Ex-1029 at 4; Ex-1028 at 7.) The life expectancy of HER2-positive patients in 1996 "was only 18 months post-diagnosis." (Ex-2017 at 138; *see also*

Ex-2018 at 887 ("[T]he reality is that breast cancer patients who overproduce HER2 can now expect to live some 10 to 12 months after metastasis begins, a horribly rapid progression compared to six or seven years for HER2-normal patients.").) (Ex-2062 ¶¶91-92.)

Before the '441 claimed invention, HER2-positive breast cancer was particularly difficult to treat with existing chemotherapies. For example, a paper published in 1996 taught that HER2-positive cancers are ***resistant*** to taxoids and explicitly warned that "breast cancers that overexpress p185 [*i.e.*, HER2] ***will not respond well to Taxol***." (Ex-2029 at 1362.) (Ex-2062 ¶92.)

III. THE '441 PATENT

A. The Invention

Petitioner asserts that the '441 invention resulted from the logical progression of therapy from preclinical studies to clinical studies that ultimately confirmed the efficacy and safety of an anti-ErbB2 antibody in combination with chemotherapy. (*See generally* Paper-1.) But this is a hindsight-driven narrative that is not consistent with the perspective of a POSA at the time, or with what actually happened.

Petitioner asserts that there had been ongoing clinical trials involving the claimed combination of an anti-ErbB2 antibody and a taxoid beginning in 1994 and continuing for years before the '441 invention—an assertion that Petitioner

repeats no fewer than a dozen times. (Paper-1 at 9, 23, 24, 28, 30, 31, 34, 45, 47, 51, 61, 62.) But that is not what the prior art discloses, and not what actually happened. Petitioner has not identified any clinical study as of 1994 involving the claimed combination—***because there was no such study***. (Ex-2050, 153:6-11 (Dr. Lipton admitting he was not aware of "any trial that had human patients with Herceptin and Taxol prior to '97, prior to the patent").) The Phase-II trials treated patients with an anti-ErbB2 antibody alone (Ex-1004) or in combination with cisplatin (Ex-1010), a different class of chemotherapy from taxoids. And when Genentech began Phase-III clinical trials in 1995, the ***only*** combination therapy initially studied was with anthracyclines, not taxoids. (Ex-2011 ¶¶15-19; Ex-2001[5] at 16, §5.2.2; Ex-2050, 86:15-87:12 (Dr. Lipton admitting he was not aware of any Phase-I or Phase-II studies of Herceptin® plus paclitaxel, and that the first Phase-III protocol was Herceptin® plus an anthracycline).) (Ex-2062 ¶¶105-108.)

In fact, Genentech ultimately pursued a combination of an anti-ErbB2 antibody and a taxoid not because of any promising preclinical, Phase-I, or Phase-II data for that combination, but rather because its ongoing Phase-III study

[5] Patent Owner submits the declaration of Stephanie Mendelsohn, who attests to the authenticity and admissibility of certain Genentech documents as business records, including Exhibits 2001-2005, 2007, 2008, 2012, and 2035. (Ex-2069 ¶.)

involving a combination of an anti-ErbB2 antibody and an anthracycline was having difficulty enrolling patients.[6] (Ex-2002 at 2; Ex-2003 at 2; Ex-2004 at 3.) '441 inventor Dr. Susan Hellmann had recently joined Genentech after working at Bristol-Myers Squibb on the drug paclitaxel. (Ex-2011 ¶¶2, 34; Ex-1011-2 at 52, 57.) As someone uniquely familiar with the use of taxoids to treat breast cancer, Dr. Hellmann advocated amending the ongoing Phase-III trial to include the combination of an anti-ErbB2 antibody and a taxoid as a possible way to improve enrollment in the study. (Ex-2011 ¶¶18, 34; Ex-2062 ¶¶113-115, 181.)

That proposal was risky because of the known safety and efficacy concerns regarding taxoids, and because therapies are typically tested in smaller, early-stage clinical trials (i.e., Phase I or II) before advancing to larger, Phase-III studies. No human patient had ever been treated with the combination of an anti-ErbB2 antibody and a taxoid. Testing that combination in a Phase-III clinical trial without first studying it in a smaller-scale trial risked exposing a large number of patients

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[6] A requirement for entry into the study was no previous anthracycline treatment. Due to the broad use of standard anthracycline therapy, those conducting the study were having difficulty finding a sufficient number of patients who had not previously been treated with anthracyclines. (Ex-2062 ¶¶113-114, 181, 190; Ex-2111 at 73.)

to potential adverse events that could not have been predicted from preclinical models. It also presented a higher risk of failure to achieve the desired outcome, since there was ***no*** data from any patients treated with the combination whatsoever. (Ex-2011 ¶¶19-21; Ex-2062 ¶¶78-89, 115.)

Over the course of several meetings with Genentech's Product Development Committee, Dr. Hellmann convinced Genentech to amend the Phase-III study to treat certain patients with the combination of an anti-ErbB2 antibody and a taxoid. (Ex-2011 ¶¶22-28; Ex-2002 at 3; Ex-2003 at 1-2; Ex-2004 at 2.) Based on her unique expertise regarding paclitaxel, Dr. Hellmann believed that taxoids were "likely to be important for breast cancer therapy in the next decade," which is why she advocated that Genentech take the risk of pursuing a combination containing an anti-ErbB2 antibody and a taxoid. (Ex-2002 at 3; Ex-2011 ¶¶18, 22-28, 34.) (Ex-2062 ¶181.)

However, the decision to modify the Phase-III study was not unanimous. (Ex-2004 at 10 (Todd Rich: "I can't recommend any changes to the trial.").) Even those who supported Dr. Hellmann's proposal recognized that it presented risks and uncertainties. (*Id.* at 11 (Art DeVault: "a good gamble").) (Ex-2011 ¶¶24, 28.)

By late 1997, the Phase-III study reached its primary endpoint. (Ex-2008 at 51-58, 104-109; Ex-2011 ¶¶37-47.) The study data showed that the combination

of an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative extended TTP without overall increase in severe adverse events. (Ex-2008 at 199.) By contrast, the combination of an anti-ErbB2 antibody with an anthracycline resulted in cardiotoxicity in a significant number of patients. (*Id.* at 198.) The increased cardiotoxicity of rhuMAb HER2 combined with anthracyclines was completely unexpected—particularly given that those patients had received ***no*** prior anthracycline-based therapy and thus could not have experienced the cumulative toxicity known in the art. (*Id*. at 39; Ex-2001 at 12.) These data are reflected in the provisional patent application filed December 12, 1997. (Ex-1027, 38:26-43:26.) The challenged claims are directed to Dr. Hellmann's new method of treatment. (Ex-2062 ¶¶116-117.)

Based upon those results, rhuMAb HER2 (brand name Herceptin®) was approved in September 1998 for treating HER2-positive metastatic breast cancer, making it the first approved antibody-based therapy for solid tumors. (Ex-2050 [Lipton], 19:7-10 (agreeing that "Herceptin was the first approved monoclonal antibody for treatment of solid tumors").) At the time, the only approved first-line use of Herceptin® reflected Dr. Hellmann's novel method of treatment in combination with a taxoid. (Ex-2012 at 1 ("HERCEPTIN in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for

their metastatic disease.").) The Herceptin® label specifically warned against administering Herceptin® in combination with anthracyclines due to the increased risk of cardiotoxicity. (*Id.*) (Ex-2062 ¶118.)

B. Widespread Adoption And Praise

The overwhelming response to the '441 invention confirms that it was a non-obvious advance over the prior art. After the Phase-III results were announced, the scientific community praised the invention as a "breakthrough" for the tens of thousands of women each year diagnosed with HER2-positive breast cancer who were "in dire need" of an effective therapy. (Ex-2018 at 887 ("The results were particularly encouraging in combination with chemotherapy using paclitaxel, a form of taxol.").) Leading oncologists likewise recognized the '441 invention as a significant advance. For example, Dr. Larry Norton, co-author of the asserted Baselga references and a leading breast-cancer clinician, went on national television to praise the unexpected efficacy of the claimed combination therapy, specifically comparing it to treatment with Taxol® alone: "It doubles or triples the efficacy of Taxol in killing these cancer cells. This is a very big, dramatic advance, one of the biggest changes in the ability of chemotherapy to kill cancer cells that I've ever seen in my career." (Ex-2034.) Furthermore, Dr. Tannenbaum states that the "combination of Herceptin and paclitaxel" has "revolutionized" how she treats breast cancer patients, taking them from a

previously "grim" prognosis of "only a year or less of life expectancy" to a situation in which "many … patients with HER2-positive breast cancer live for several years even after metastasis begins." (Ex-2062 ¶¶216-218.)

The '441 invention also has been an enormous commercial success. Herceptin®—the commercial embodiment of the '441 invention—is one of the most successful drugs of all time, resulting in hundreds of millions of dollars in revenue in the years immediately following its approval. (Ex-2035 at 17.) That success is directly attributable to the '441 invention. Indeed, the method of treatment claimed in the '441 patent was the ***only*** FDA-approved first-line use of Herceptin® when the drug was initially approved. (Ex-2012 at 1.)

C. Challenged Claims

Petitioner has challenged every claim of the '441 patent. Those claims reflect Dr. Hellmann's novel method of treatment for cancer that overexpresses ErbB2, which comprises (i) "administering a combination" of an anti-ErbB2 antibody and a taxoid; (ii) "in the absence of an anthracycline derivative"; (iii) "to the human patient in an amount effective to extend the time to disease progression in said human patient"; and (iv) "without increase in overall severe adverse events." (Ex-1001, claims 1-14.)

D. Prosecution History

The '441 patent issued from Application No. 09/208,649 filed on December 10, 1998, and claims priority to Provisional Application No. 60/069,346 filed on December 12, 1997. (Ex-1001, cover page.)[7]

The Patent Office considered the references underlying Petitioner's proposed obviousness grounds during prosecution.[8] Petitioner asserts that the '441 patent repeats the disclosure of the Baselga references without attribution. (Paper-1 at 15.) But the '441 patent does not conceal anything about the Baselga references. Indeed, it cites and discusses the Baselga references at length. (Ex-1001, 3:34-59.) Moreover, Petitioner's suggestion that the "experimental data" in the '441 patent was somehow lifted from the Baselga references (Paper-1 at 15) is false. The Baselga references disclose ***no clinical results*** for the combination of

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[7] Petitioner has also challenged U.S. Patent No. 7,892,549, which is a continuation of the '441 patent, in IPR2017-00737.

[8] Genentech has a pending application (14/141,232) in the '441 family in which the claims are under non-final obviousness rejection in view of Baselga '96 combined with another reference that was antedated during the '441 prosecution. Patent Owner has responded to that rejection and is awaiting further action by the PTO.

an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative. Clinical results for that combination are first described in the '441 patent itself. (Ex-1001, 29:11-30:25.) (Ex-2062 ¶110.)

In October 2009, Genentech submitted a declaration from Dr. Mark Sliwkowski in response to obviousness rejections over, among other things, Baselga '96 and Baselga '94. (Ex-1011-9 at 9-13.) Dr. Sliwkowski explained that a POSA would not have expected rhuMAb HER2 combined with a taxoid to produce a synergistic response, since those drugs were known to exert their effects at different points in the cell cycle. (*Id.* at 10-11.) Dr. Sliwkowski also explained that preclinical results would not have provided a reasonable expectation of success as to the clinical results for the combination of rhuMAb HER2 and a taxoid; indeed, xenograft models at that time were poor predictors of clinical results for breast cancer. (*Id.* at 12.)

On December 30, 2009, the examiner allowed the claims. (*Id.* at 124.)

E. Foreign Counterparts

As Petitioner notes (Paper-1 at 15-16), the European counterpart to the '441 patent was found obvious in the United Kingdom and before the European Patent Office. However, those foreign proceedings have little relevance here. *See Smith & Nephew v. ConvaTec Techs. Inc.*, IPR2013-00097, Paper-76 at 3 (Feb. 24, 2014) (European Patent Office decision "does not involve the U.S. patents at issue in

these proceedings, is not based on U.S. law, and is thus of limited relevance to the instant proceedings"); *see also Medtronic, Inc. v. Daig Corp.*, 789 F.2d 903, 907-08 (Fed. Cir. 1986) (rejecting challenger's position that the court should adopt a decision regarding the validity of a foreign counterpart patent as "specious"). For example, the Baselga '97 reference at issue in those proceedings has been antedated here.

IV. ASSERTED REFERENCES

A. Baselga '94

Baselga '94 is a one-paragraph abstract, published in March 1994, that was not peer reviewed for content. It describes the results of preclinical studies using mouse models to assess the antitumor activity of rhuMAb HER2 combined with either an anthracycline derivative (doxorubicin) or a taxoid (paclitaxel). (Ex-2062 ¶143.)

Those studies measured the response rate—i.e., the initial tumor-inhibition response—in mice over a period of five weeks. They did not assess the effect (if any) on TTP, and thus there was no way to assess whether TTP was extended. (Ex-1005 at 4.) Both drug combinations improved the antitumor response as compared with rhuMAb HER2 or chemotherapy alone, and rhuMAb HER2 "did not increase the toxicity of paclitaxel or doxorubicin in animals as determined by animal survival and weight loss." (*Id.*) However, the Phase-III trial showed that,

in fact, the combination of rhuMAB HER2 and doxorubicin significantly increased the incidence of cardiotoxicity in human patients. (Ex-1001, 30:13-16.) (Ex-2062 ¶¶144-147.)

Baselga '94 notes that "[c]linical studies are underway." (*Id.*) But that is just a generic reference to clinical trials of rhuMAb HER2. It does not refer to studies involving the ***combination*** of rhuMAb HER2 and a taxoid, as Petitioner asserts (Paper-1 at 9). Indeed, Baselga '94 could not have been referring to ongoing studies of the combination because there was no such study underway at the time. (Ex-2011 ¶¶18-19; Ex-2050, 153:6-11 (Dr. Lipton admitting he was not aware of "any trial that had human patients with Herceptin and Taxol prior to '97, prior to the patent").) (Ex-2062 ¶¶148-149.)

B. Baselga '96

Baselga '96 is an article published in March 1996. It describes the results of a Phase-II clinical study in which patients received rhuMAb HER2 ***alone***, not

combined with a taxoid (or any other chemotherapy or agent). (Ex-1004 at 10 ("Chemotherapy … was not permitted.").)[9] (Ex-2062 ¶¶150-158.)

The clinical endpoint evaluated in the trial was response rate. (Ex-1004 at 10, 12, 13.) Although Baselga '96 measured "[t]ime to tumor progression" for individual patients, all patients in the study received rhuMAb HER2. (*Id.* at 10.) The study thus had no control group against which to evaluate whether rhuMAb HER2 (or any combination involving it) ***extended*** TTP. (Ex-2050 [Lipton], 156:4-21.) (Ex-2062 ¶¶151-153.)

According to Baselga '96, the vast majority of patients receiving rhuMAb HER2 did not show a therapeutic response. In fact, only 5 out of the 43 assessable patients (11.6%) had complete or partial responses to treatment with rhuMAb HER2. (Ex-1004 at 12.) (Ex-2062 ¶153.)

Baselga '96 acknowledged that the mechanism of potential antitumor activity for rhuMAb HER2 was not understood and proposed several possible explanations for the observed clinical results. (Ex-1004 at 14-15.) Thus, it

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[9] The study reported in Baselga '96 required patients to stop other treatments three weeks prior to entering the study, thus ensuring that any tumor response was due to the therapy being tested rather than the continuing effects of any prior treatment. (Ex-1004 at 10.) (Ex-2062 ¶163.)

remained unclear at the time how other patient populations might respond (if at all) to rhuMAb HER2, much less to combinations of rhuMAb HER2 with chemotherapy. (*Id.* at 15 ("[C]ontinued research with this agent and other HER2-targeted treatment strategies appears warranted.").) (Ex-2062 ¶¶155-158.)

Baselga '96, citing Baselga '94, identified several chemotherapeutic agents (cisplatin, doxorubicin, and paclitaxel) that had been combined with rhuMAb HER2 in preclinical mouse studies and noted that "clinical trials of such combination therapy are currently in progress." (Ex-1004 at 15.) However, Baselga '96 did not state that the combination of an anti-ErbB2 antibody and a taxoid in particular was being studied in humans. Nor could it have been referring to that particular combination therapy, since there was no clinical study involving that combination at the time that Baselga '96 was submitted (August 8, 1995) or accepted (October 10, 1995). (Ex-2062 ¶158.)

V. PERSON OF ORDINARY SKILL

For purposes of this proceeding, Patent Owner does not dispute Petitioner's proposed definition of a POSA. (*See* Paper-1 at 7.)

VI. CLAIM CONSTRUCTION

A. "Administering A Combination"

For purposes of this proceeding, Patent Owner requests construction of "administering a combination" in all claims to mean that the drugs are

administered as part of the same treatment regimen. In its institution decision, the Board found Patent Owner's position to be "reasonable" and adopted Patent Owner's proposed construction. (Paper-29 at 6.)

The Board gives a patent claim "its broadest reasonable construction in light of the specification of the patent in which it appears." *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016); 37 C.F.R. § 42.100(b). Here, the broadest reasonable interpretation of "administering a combination" requires a single treatment regimen in which the patient receives all drugs that are part of the claimed combination. By contrast, if a patient receives an anti-ErbB2 antibody and a taxoid as part of different treatment regimens, that is not a "***combination***." It is administering the drugs separately. (Ex-2062 ¶128.)

The specification supports that interpretation. It describes "the present invention" as "the ***combined*** administration of an anti-ErbB2 antibody and a chemotherapeutic agent, other than an anthracycline derivative"—either through "coadministration" or "consecutive administration" in the same therapeutic regimen (i.e., "wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities"). (Ex-1001, 25:1-8.) (Ex-2062 ¶129.)

The surrounding claim language further confirms that "administering a combination" refers only to the drugs administered in the same treatment regimen.

For example, all claims require "the absence of an anthracycline derivative." That limitation would make no sense if "administering a combination" included drugs received as part of a different treatment regimen. In the '441 patent's working example, patients were administered the combination of the anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative only if they had "received any anthracycline therapy in the adjuvant setting" (i.e., as part of a different, earlier treatment regimen). (Ex-1001, 28:15-21.) A POSA would thus understand that "administering a combination" refers only to the drugs used in the same treatment regimen, and not as part of a different regimen. (Ex-2062 ¶130.)

B. "Extend The Time To Disease Progression In Said Human Patient, Without Increase In Overall Severe Adverse Events"

Although neither party had requested construction of the term, the Board construed the term "extend the time to disease progression in said human patient, without increase in overall severe adverse events" as a relative term measured against a patient who had received no treatment. (Paper-29 at 8.)

Respectfully, that claim construction is not consistent with the specification as understood by a POSA. Both parties' experts agree that the specification supports a construction that compares the claimed combination treatment to treatment with a taxoid alone. (IPR2017-02063, Ex-1002 ¶112(h); Ex-2062 ¶¶132-141; *see also* Ex-1007 ¶46 (Dr. Lipton opining that clinical efficacy evaluated for a

new therapy is typically measured "against a standard therapy (as a control arm)"); Ex-2050 [Lipton], 56:11-14 (in a Phase-III trial the drug combination under study is tested against "[a] standard of therapy").)

In particular, the clinical trial results reported in the '441 specification measure efficacy of the combination of an anti-ErbB2 antibody (rhuMAb HER2) with a taxoid (paclitaxel) against a control arm of paclitaxel alone. (Ex-1001, 29:9-30:25.)[10] There is no data in the patent comparing the TTP of patients treated with an anti-ErbB2 antibody and a taxoid against an untreated patient. (Ex-2050 [Lipton], 152:3-21.)

Indeed, such a comparison makes no sense in the context of a disease like breast cancer where there were already therapies approved by the FDA. As Dr. Tannenbaum confirms, it would be unethical to conduct a study comparing the efficacy of a tested therapy against no therapy where there was already an

[10] The '441 patent also describes the efficacy of rhuMAb HER2 combined with chemotherapy (paclitaxel or anthracyclines) versus chemotherapy alone, or rhuMAb HER2 combined with anthracyclines versus anthracycline therapy alone. (Ex-1001, 29:9-30:25.) However, given that the claims expressly exclude anthracycline therapy, the relevant comparison is the combination of rhuMAb HER2 and paclitaxel versus paclitaxel alone.

approved therapy that would provide a clinical benefit to the target patient population. (Ex-2062 ¶141.)

Moreover, the Board's construction is inconsistent with its construction of "adverse event," which contemplates a comparison against a patient treated with ***some*** therapy. Under the definition applied by the Board, an adverse event "happens during treatment with a drug or other therapy." (Paper-29 at 16.) The requirement to "extend the time to disease progression … without increase in overall severe adverse events" thus can only be measured by comparing treatment with one therapy against another, not treatment with one therapy against an untreated patient. (Ex-2062 ¶¶132-141.)

The Board relied upon a statement that the applicants made during prosecution in response to an indefiniteness rejection in which the applicants stated that the appropriate comparison for this claim limitation was against an untreated patient. (Paper-29 at 7-8.) However, in making this statement, the applicant cited the specification's example comparing treatment with the combination of rhuMAb HER2 and paclitaxel to treatment ***with paclitaxel alone***. (Ex-1011-2 at 356.) As Dr. Tannenbaum explains, in this context, a POSA would have understood the applicant's statement to be referring to a comparison against a patient treated with a taxoid alone, not a comparison against an untreated patient (which appears nowhere in the specification (Ex-2050 [Lipton], 152:3-21)). (Ex-2062 ¶138.)

Moreover, Petitioner's own expert admits that the example in the specification describes a comparison of rhuMAb HER2 and paclitaxel to paclitaxel alone, not to a patient who has received no therapy whatsoever, and that therefore the term should be construed as requiring a comparison to treatment with a taxoid alone. (*See* IPR2017-02063, Ex-1002 ¶112(h) (Dr. Lipton opining that "[b]ased on the specification, the appropriate comparison is to compare the claimed combination treatment versus treatment with a taxoid alone").)[11] The understanding of a POSA is therefore not in dispute. (Ex-2062 ¶140.)

Accordingly, the Board should construe the term "extend the time to disease progression in said human patient, without increase in overall severe adverse events" as measured against a patient treated with a taxoid alone, not a patient who has received no treatment whatsoever.

[11] Dr. Earhart, the expert for the Celltrion IPR against the '441 patent (IPR2017-01121), also agrees that "[b]ased on the specification, the appropriate comparison is to compare the claimed combination treatment versus treatment with a taxoid alone." (IPR2017-01121, Ex-1002 ¶112(h).)

VII. ARGUMENT

A. A Person Of Ordinary Skill Would Not Have Been Motivated To "Administer[] A Combination" Of An Anti-ErbB2 Antibody And A Taxoid Based Upon Baselga '96 and Baselga '94.

1. Baselga '96 does not suggest treating human patients with the claimed combination.

All challenged claims require "administering a combination" of an anti-ErbB2 antibody and a taxoid "to the human patient." Baselga '96 does not teach that limitation; it discloses the treatment of human patients with rhuMAb HER2 ***alone***, not with a taxoid (or any other combination therapy). (Ex-1004 at 10 ("Chemotherapy … was not permitted.").) (Ex-2062 ¶¶150-158, 162.)

Petitioner argues that Baselga '96 teaches a combination of an anti-ErbB2 antibody and a taxoid because four patients had "***prior*** systemic therapy" with a taxoid. (Paper-1 at 44.) But as the Board correctly concluded in its institution decision, those patients were not "administered a ***combination***" of anti-ErbB2 antibody and a taxoid, as that term is properly construed. (Paper-29 at 12.) Baselga '96 describes patients who received treatment with an anti-ErbB2 antibody and ***separate*** treatment with a taxoid. In fact, patients in the study were required to discontinue any chemotherapy (including taxoids) for at least three weeks before enrolling. (Ex-1004 at 10.) (Ex-2062 ¶163.)

Petitioner also argues that Baselga '96 teaches a combination of an anti-ErbB2 antibody and a taxoid because it (i) mentions preclinical studies involving

the combination of rhuMAb HER2 with cisplatin, doxorubicin, and paclitaxel, and (ii) notes that "clinical trials of such combination therapy are currently in progress." (Paper-1 at 44.) The preclinical studies alluded to in Baselga '96 are the same studies disclosed in Baselga '94, and thus fail to establish a motivation to combine an antibody and taxoid for the same reasons explained in SectionVII.A.2 below. Moreover, Baselga '96 does not state that the combination of rhuMAb HER2 and paclitaxel in the absence of an anthracycline derivative was being pursued; indeed, it does not specify what "combination therapy" was being studied. (Ex-2062 ¶¶164-167.)

In fact, there was ***no*** clinical study testing the combination of rhuMAb HER2 and paclitaxel at the time that Baselga '96 was submitted (August 8, 1995) or accepted for publication (October 19, 1995). (Ex-2011 ¶¶18, 19, 29, 42; Ex-2007 at 1 (amended protocol dated November 13, 1995).) That Petitioner's obviousness theory requires reading incorrect assumptions into Baselga '96 confirms that it rests on hindsight. (Ex-2062 ¶158.)

2. Baselga '94 does not suggest treating human patients with the claimed combination.

The Board concluded in its institution decision that Baselga '94 would have motivated a POSA to treat human patients with a combination of an anti-ErbB2

antibody and a taxoid. Respectfully, the full record now confirms that Baselga '94 would have provided no such motivation.

First, Baselga '94 is a one-paragraph abstract that was not peer-reviewed for content. As Dr. Tannenbaum explains, to the extent a POSA would pay any attention to Baselga '94, she would wait for the full, peer-reviewed paper describing the underlying experiments and bases before drawing any conclusions from it. (Ex-2062 ¶¶168-169.)

Second, a POSA would understand that the mouse study in Baselga '94 was not a reliable predictor of success in humans. That preclinical study was based on a single cell line, but it was known prior to the '441 patent that it was necessary to use multiple cell lines to obtain results that are reflective of a human patient population. A study like Baselga '94 based on a single cell line is akin to a clinical trial involving a single patient, which has minimal predictive value. (*Supra* pp.10-11.) (Ex-2061 ¶¶63-70; Ex-2062 ¶¶170-171.)

Moreover, a POSA also would have understood that the particular cell line used in Baselga '94 was not representative of actual patients. The cell line (BT-474) expressed the highest HER2 levels of any known breast-cancer cell line at the time—i.e., more than ***20 times*** the number of HER2 genes per cell than in a normal human cell. With such a high level of HER2 expression, a POSA would have understood that the results disclosed in Baselga '94 are not representative of how

actual HER2-positive patients would respond. (*Supra* pp.10-11.) (Ex-2061 ¶¶62-70.)

In addition, the tumors in Baselga '94 were implanted subcutaneously, rather than in tissue similar to how the disease would present in human patients (i.e., mammary fat pad). As explained above, this makes the results not predictive of drug performance in humans. (*Supra* pp.11-12.) (Ex-2061 ¶¶77-81.)

These specific deficiencies with the preclinical models disclosed in Baselga '94, coupled with the lack of predictive value for mouse xenograft studies generally (*supra* pp.7-8),[12] confirm that a POSA would not have been motivated to treat patients with a combination of rhuMAb HER2 and paclitaxel based upon the

[12] The history of preclinical testing of paclitaxel also suggests that preclinical evidence would not have motivated a POSA to use that drug in a combination to treat breast-cancer patients. Early preclinical studies indicated that paclitaxel, administered as a single agent, was active in human breast, ovarian, and colorectal xenograft models. (Ex-2070 at 184.) But by 1997, it had become clear that single-agent paclitaxel was ***in***active in human colorectal cancer patients (Ex-2071 at 750), contrary to the preclinical evidence. POSAs therefore would have realized that preclinical evidence showing paclitaxel efficacy was unreliable. (Ex-2061 ¶¶59-61.)

results reported in Baselga '94. Missing from this record are the types of robust preclinical studies on the claimed combination (e.g., testing multiple cell lines, creation of orthotopic xenograft models, and analysis of dosing amounts) that a POSA would want before risking such combination in humans. (Ex-2062 ¶174.)

Third, there were significant concerns with using taxoids to treat HER2-positive breast cancer before the '441 invention. (*Supra* pp.16-17.) At the time, patients experienced serious hypersensitivity reactions, neuropathy, and cardiotoxicity from taxoids, which were only approved for second-line use in breast cancer. Moreover, the prior art taught away by explicitly warning that HER2-positive breast cancer "will not respond well to Taxol." (Ex-2029 at 1362.) These safety and efficacy concerns would have further dissuaded POSAs from using combination therapy involving taxoids. (Ex-2062 ¶¶58-60, 176-178.)

Indeed, the development history of rhuMAb HER2 confirms that Baselga '94 would not have motivated a skilled artisan to treat humans with an anti-ErbB2 antibody and a taxoid. Despite studying combinations with other chemotherapies (e.g., cisplatin (Ex-1010), doxorubicin (Ex-2001)), ***none*** of the Phase-II and initial Phase-III clinical trials tested the combination of an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative. And when '441 inventor Dr. Hellmann finally modified the Phase-III trial over objection to include a combination of rhuMAb HER2 and paclitaxel, she did so based on her unique

knowledge of paclitaxel and in response to enrollment issues with the study, not because of the preclinical results involving the combination of rhuMAb HER2 and paclitaxel. (Ex-2011 ¶¶2, 18, 34.) Given the well-known problems with taxoids (*supra* pp.16-17), a POSA would not have been motivated to pursue the claimed combination based on Baselga '94, and it would be inappropriate to attribute Dr. Hellmann's extraordinary knowledge to a POSA. *See Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) (inventor possesses knowledge "which sets them apart from workers of ordinary skill"). Only in hindsight can Petitioner contend that a POSA would have been motivated to use a combination that even those with the best information about rhuMAb HER2 at the time did not pursue. (Ex-2062 ¶¶180-181.)

3. A person of ordinary skill would have been motivated to use an anthracycline rather than a taxoid.

As explained above, in the late 1990s, antibodies were a new and uncertain therapy that faced "significant obstacles" and required "much additional study." (*Supra* pp.17-19; Ex-2031 at 683.) Moreover, the prior art reflected significant safety concerns regarding treatment with taxoids (*supra* pp.16-17), and the efficacy of taxoids in treating HER2-positive breast cancer was questionable at best (*supra* p.21). Because of these risks and uncertainties, a POSA would not have been motivated to use a taxoid in combination with an anti-ErbB2 antibody as a

treatment for HER2-positive breast cancer. (Ex-2062 ¶¶176-179.) That a POSA would not have risked using taxoids is especially the case when considering that the other drug in the combination—the anti-ErbB2 antibody—was still a new therapy with its own uncertainties at the time. (Ex-2062 ¶¶95-99, 175.)

Instead, in the event that a POSA were to have considered whether to combine the new anti-ErbB2 antibody with an existing anti-cancer drug, he or she would have chosen to limit the number of variables by using a first-line chemotherapy such as anthracyclines. (Ex-2062 ¶175.) As explained above, the efficacy of anthracyclines in treating breast cancer was well established in the art, and the side effect of such treatment—cardiotoxicity in some individuals—had been thoroughly studied and was understood to be manageable. (*Supra* pp.15-16.) At this time, anthracyclines were the standard and most common treatment for breast cancer. (*Id.*) In fact, when Genentech initially designed the protocol for the Phase III-trial, the method of treatment chosen was rhuMAb HER2 in combination with doxorubicin, an anthracycline derivative. (Ex-2002 at 2; Ex-2003 at 2; Ex-2004 at 3.) Thus, contrary to the '441 patent's novel idea of treating HER2-positive breast cancer with a combination of an anti-ErbB2 antibody and a taxoid "in the absence of an anthracycline derivative," a POSA would have deemed anthracyclines the obvious chemotherapeutic agent for any drug combination. (Ex-2062 ¶¶45-46, 52, 115.)

B. Under The Proper Claim Construction, Petitioner Has Not Established A Reasonable Expectation Of Success In Achieving The Claimed Clinical Efficacy.

The Board's institution decision rested on a claim construction that measured the claimed efficacy against a patient who received no treatment whatsoever. (Paper-29 at 15-16.) As explained above, that claim construction is not consistent with the understanding of a POSA, given that the specification only discloses measuring an extension in TTP against a patient treated with a taxoid alone. (*Supra* pp.35-38.) Under the correct claim construction, Petitioner has not shown that a POSA would have had a reasonable expectation of success that the claimed combination therapy would extend TTP relative to a patient treated with a taxoid alone.[13] (Ex-2062 ¶¶131-141, 182.)

Baselga '96 and Baselga '94 do not disclose that the claimed combination extends TTP relative to a patient treated with paclitaxel alone. Baselga '96 discloses that patients who responded to antibody therapy had a median TTP of 5.1

[13] Alternatively, to the extent the Board believes that the claims are not patentable as written, Patent Owner conditionally seeks to amend the claims to make explicit that the claimed comparison is against a patient treated with paclitaxel alone. As Petitioner's own expert acknowledges, the specification clearly supports such a comparison. (IPR2017-02063, Ex-1102 ¶112(h).)

months. (Ex-1004 at 12.) But all patients in Baselga '96 were treated with rhuMAb HER2; the study contained no control arm. Baselga '96 therefore discloses no ***extension*** in TTP, let alone an extension in TTP for patients treated with the claimed combination as compared to those treated with a taxoid alone. (Ex-2062 ¶¶183-185.)

In its institution decision, the Board stated that the prior art does not suggest "that combining a taxoid with rhuMAb HER2 would abrogate the effect of the antibody." (Paper-29 at 16.) However, under the claims as properly construed, the relevant question is not whether the antibody and a taxoid would have an antagonistic interaction; rather, the question is whether combining the antibody and a taxoid would improve the clinical response to the taxoid alone with respect to the specific clinical endpoint of extending TTP. Data for patients treated with rhuMAb HER2 alone or Taxol® alone does not address that question. (Ex-2062 ¶187.)

Nor does Baselga '94 disclose or suggest that the combination of an anti-ErbB2 antibody and a taxoid would extend TTP relative to treatment with a taxoid alone. The response rates in Baselga '94's mouse models do not suggest an extension in TTP when using the claimed combination because, as explained above, shrinking tumors is ***different*** from extending TTP, and a POSA would have understood that a therapy could reduce tumor size without improving TTP. (*Supra*

p.14.) Indeed, Petitioner's expert concedes that response rate and TTP are different endpoints that are measured differently. (*See* IPR2017-02063, Ex-1002 ¶112(f)-(g) (Dr. Lipton defining "response rate" as "the percentage of patients whose disease responds to treatment" and "time to disease progression" as "the time period calculated from the beginning of therapy until the disease worsens").) (Ex-2061 ¶¶82-83; Ex-2062 ¶186.)

As to the mouse studies in Baselga '94 in particular, those studies lasted only ***five weeks*** (Ex-1005), which would not inform a POSA as to a clinical endpoint (TTP) that takes ***several months*** to measure (Ex-1001, 29:20-30:12 (column titled "TTP(months)")). (Ex-2050 [Lipton], 103:10-13 ("This was just a five-week study. So time to disease progression was not assessed.").) (Ex-2061 ¶¶82-83; Ex-2062 ¶146.) In any case, as discussed above, the particular mouse model used in Baselga '94 would have limited predictive value in assessing the clinical response in human patients. (*Supra* pp.41-44.)

In its institution decision, the Board dismissed the limitations of preclinical mouse models because "[o]bviousness does not require absolute predictability of success." (Paper 29 at 15.) But as the full record now confirms, the primary deficiency of Baselga '94 is not that mouse models are generally imperfect at predicting responses in human patients, although that is certainly an issue. Rather, the fundamental problem with Baselga '94 is that the particular preclinical mouse

models described in the reference had significant design flaws that undermine their predictive value. (Ex-2061 ¶¶54-83; Ex-2062 ¶¶172, 188.)

Indeed, the development history of rhuMAb HER2 confirms that the preclinical results in Baselga '94 would not have provided a POSA a reasonable expectation of success in achieving the specific clinical result claimed in the '441 patent. Despite this abstract, no one pursued a clinical trial combining an anti-ErbB2 antibody and a taxoid until the '441 inventor Dr. Hellmann suggested modifying an ongoing Phase-III trial to address enrollment issues. (Ex-2011 ¶¶14-21.) Only in hindsight can Petitioner reinterpret the preclinical results reported in Baselga '94 to provide a reasonable expectation of success. (Ex-2062 ¶¶189-90.)

C. Petitioner Has Not Established A Reasonable Expectation Of Success In Achieving The Claimed Clinical Safety.

Even under the Board's claim construction, Petitioner has not shown a reasonable expectation of success that the claimed combination therapy would not result in "increase in overall severe adverse events."[14]

[14] For the same reasons discussed herein, Petitioner has not shown that this limitation is taught by Baselga '96 in view of Baselga '94 under the proper claim construction comparing treatment with the claimed combination to treatment with a taxoid alone. (Ex-2062 ¶182.)

In its institution decision, the Board concluded that this limitation is taught by Baselga '96 in view of Baselga '94 because patients treated with the claimed combination would fare no worse than untreated patients whose disease would worsen. (Paper-29 at 16.) Respectfully, however, a POSA would not understand the effect of the disease on an untreated patient to be an "adverse event." Indeed, even Petitioner did not advocate that theory, and the definition of an "adverse event" that the Board apparently identified through its own investigation refutes that analysis. (Ex-2062 ¶191.)

Under the Board's definition, an adverse event is "[a]n ***unexpected*** medical problem." (Paper-29 at 16.) The effects of untreated HER2-positive breast cancer, however, are entirely expected. The Board's definition further requires that an adverse event "happens ***during treatment*** with a drug or other therapy." Again, the effects of the disease in an ***untreated*** patient do not meet that definition. Thus, under the Board's definition, an untreated patient does not experience any "adverse events." Neither the Petition nor the institution decision demonstrates a reasonable expectation of success that the claimed combination does not increase "overall severe adverse effects" relative to patients who, by the Board's definition, experience no "adverse events" at all. (Ex-2062 ¶191.)

The Board also relied on Baselga '96's statement that rhuMAb HER2 produced "minimal" toxicity. (Paper-29 at 17.) But Baselga '96 did not address

the toxicity of the ***combination*** of an anti-ErbB2 antibody and a taxoid. The minimal toxicity of rhuMAb HER2 alone says nothing about potential safety issues when combined with other drugs.[15] As of 1997, a clinician could not predict how two drugs, one of which was a novel antibody therapeutic, would react together in a human patient until such combination therapy was administered. (Ex-2062 ¶¶192-193.)

Petitioner cites the lack of increased toxicity from combining trastuzumab and paclitaxel in preclinical mouse studies. (Paper-1 at 31.) However, Baselga '94 made the same statement about combinations with the anthracycline doxorubicin (Ex-1005), which produced a significant increase in cardiotoxicity when administered to human patients. (*Supra* pp.30-31.) This disconnect highlights the

[15] The Board's reliance upon the Taxol® label (Paper-29 at 17 (citing Ex-1025, 10)) fails for the same reason—i.e., FDA approval of Taxol® alone says nothing about the toxicity of the combination of rhuMAb HER2 and a taxoid. Moreover, the Taxol® label is not part of a ground of unpatentability instituted in this proceeding and thus its disclosure is irrelevant. *See* 37 C.F.R. § 42.104(b)(4) ("The petition must specify where each element of the claim is found in the prior art patents or printed publications relied upon.").

inability of Baselga '94's mouse models to predict clinical safety. (Ex-2061 ¶¶54-61, 75; Ex-2062 ¶¶194-195.)

Moreover, as explained above, a POSA would understand that the mouse model described in the Baselga references would not reliably predict results in humans. (*Supra* pp.41-44.) This was especially the case for a combination involving the 4D5 antibody: because it was engineered to bind to the human ErbB2 receptor (not the mouse ErbB2 receptor) and have similarities to antibodies produced in humans (Ex-1001, 3:34-39), testing the antibody in mice would not have produced toxicity results predictive of treatment in humans. In addition, because 4D5 originally was produced in mice immunized with human ErbB2, a POSA would have known that the antibody would affect only human cancer cells in the mouse, thus failing to provide insight as to the potentially-toxic effect of 4D5 on other cells. (Ex-2061 ¶¶71-76.)

Petitioner also argues that a POSA would have had a reasonable expectation of success in achieving the claimed clinical safety results because the Baselga references supposedly "reported as early as 1994 … that clinical trials of the combination were underway in humans, and that these clinical trials were still underway in 1997." (Paper-1 at 31.) As discussed above, that argument is not supported by the Baselga references and is inconsistent with the development timeline for rhuMAb HER2. (*Supra* pp.31,33.) Petitioner cannot demonstrate a

reasonable expectation of success based on false assumptions about a non-existent study. That argument also cannot be reconciled with the experience of cancer researchers in the 1990s: the mere fact that a treatment was under evaluation was no indication of success, given the high failure rate of therapies in clinical trials. (*Supra* pp.12-14.) (Ex-2062 ¶194.)

D. Petitioner Has Not Shown That The Claimed Combination Would Have Been Obvious To Try.

Although not addressed in the Board's institution decision, Petitioner briefly contends that the challenged claims would have been obvious to try. (Paper-1 at 31-32, 49, 61.) But that argument too rests on hindsight in several respects.

First, prior to the '441 invention, the combination of an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative was not even among a finite number of options that a POSA would have pursued. There were numerous other chemotherapies known in the prior art, and there were numerous other possibilities that a skilled artisan would have pursued instead. (Ex-2062 ¶198.)

That is confirmed by the development history of rhuMAb HER2. As discussed above (pp.22-26), Genentech pursued several alternative therapies (e.g., anti-ErbB2 antibody alone (Ex-1004), combined with cisplatin (Ex-1010), or combined with doxorubicin (Ex-2001)) and only pursued the claimed combination after '441 inventor Dr. Hellmann, based on her unique knowledge of paclitaxel,

convinced the company over objection to change course. That the claimed combination was not even among the treatment regimens pursued in any Phase-I, Phase-II, or initial Phase-III clinical trials—led by extremely-skilled scientists—confirms that it was not obvious to try. *See, e.g.*, *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1356-57 (Fed. Cir. 2013) (holding that the alternatives disclosed in the art and the fact that no one had pursued the claimed invention before the inventors confirmed that the invention was not obvious to try). And it would be improper to impute Dr. Hellmann's ***extra***ordinary knowledge to a person of ***ordinary*** skill in the art. *See Standard Oil*, 774 F.2d at 454 (inventor possesses knowledge "which sets them apart from workers of ordinary skill"). (Ex-2062 ¶199.)

Second, Petitioner's obvious-to-try theory fails for the further reason that the claimed invention was not one of "a finite number of identified, ***predictable*** solutions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). The '441 invention is in a highly-unpredictable field—as confirmed, for example, by the nearly 60% failure rate of cancer drugs in Phase-III trials during the 1990s and the fact that Baselga '94 itself failed to predict the increased toxicity of anthracyclines when combined with rhuMAb HER2. (*Supra* pp.12-13, 30-31.) Petitioner cannot demonstrate that the art was predictable when the asserted references show that it was not. Petitioner does not address that unpredictability, let alone explain how

the invention could have been obvious to try given those uncertainties. (Ex-2062 ¶200.)

E. Objective Indicia Of Non-Obviousness Confirm The Patentability Of The Challenged Claims.

1. There are several strong objective indicia of non-obviousness.

Evidence concerning the real-world impact of a patented invention is a critical safeguard against hindsight reasoning. *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010). Indeed, the Board has recognized that such evidence alone may rebut other evidence of obviousness. *InnoPharma Licensing, Inc. v. Senju Pharm. Co.*, IPR2015-00902, Paper-90 at 14-22, 25-27 (July 28, 2016). Here, several objective indicia conclusively establish the non-obviousness of the challenged claims.

First, the '441 invention satisfied a long-felt-but-unmet need for an effective treatment for HER2-positive breast cancer. Before the '441 invention, HER2-positive patients experienced "horribly rapid progression" and were "in dire need" of an effective therapy. (Ex-2018 at 887; Ex-2050, 45:4-7 (Dr. Lipton admitting that before Herceptin® HER2-positive status "used to have the worst prognosis in women with breast cancer").) Yet no one before the '441 invention had developed an adequate therapy for those patients; indeed, at the time, patients with metastatic

HER2-positive breast cancer had a life expectancy of just 10 to 12 months. (Ex-2018 at 887.) (Ex-2062 ¶¶91, 203-205.)

The '441 invention satisfied the long-felt need for an effective therapy for HER2-positive patients. After the results of the Phase-III trial showing that the claimed combination produced a "dramatic" increase in TTP, the '441 invention was immediately heralded as a "breakthrough" therapy—"the Holy Grail" for patients suffering from HER2-positive breast cancer. (Ex-2018 at 887.) And in recognition of the long-felt need satisfied by the '441 invention, the FDA fast-tracked that therapy for approval. (*Id.*) Moreover, Dr. Tannenbaum recalls an urgent need for a new treatment for HER2-positive breast cancer that would extend patient lives by even a few months, which was met by the combination of Herceptin® and paclitaxel, which allowed many of her patients to live for years after metastasis began. (Ex-2062 ¶¶206-207, 218.)

Petitioner's hindsight-driven narrative that the challenged claims were merely the result of ordinary skill cannot be reconciled with the critical, long-standing need that the '441 invention satisfied. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1332 (Fed. Cir. 2016) ("Evidence of a long felt but unresolved need tends to show non-obviousness because it is reasonable to infer that the need would have not persisted had the solution been obvious.").

Second, after the results of the Herceptin® Phase-III trial were announced, the '441 invention was widely praised as an "anti-cancer breakthrough" that produced "impressive results." (Ex-2018 at 887; Ex-2033 at 1.) Petitioner can hardly contend that those results would have been obvious from the Baselga references—when Dr. Larry Norton, a leading practitioner and co-author of the three Baselga references, went on national television to praise the impressive results of the '441 invention: "It doubles or triples the efficacy of Taxol in killing these cancer cells. This is a very big, dramatic advance, one of the biggest changes in the ability of chemotherapy to kill cancer cells that I've ever seen in my career." (Ex-2034.) (Ex-2062 ¶¶216-218.)

The strong praise for the specific combination therapy claimed in the '441 patent confirms that there is nothing ordinary or routine about the '441 invention. *Institut Pasteur & Universite Pierre et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013) ("[I]ndustry praise … provides probative and cogent evidence that one of ordinary skill in the art would not have reasonably expected [the claimed invention].").

Third, the combination of an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline produced unexpectedly-superior clinical efficacy as compared with either the antibody or a taxoid alone. (Ex-1011-2 at 54 ("[T]he combination is surprisingly synergistic with respect to extending TTP.").)

Petitioner argues that those results would have been expected because preclinical mouse models testing that drug combination "demonstrated synergistic effects." (Paper-1 at 62.) But the preclinical results did not address the specific clinical endpoint of TTP, let alone show an improvement in that outcome. (*Supra* pp.30-31.) In any case, preclinical results at that time were known to be poor predictors of clinical outcomes. (*Supra* pp.7-8.) In fact, other preclinical studies involving the claimed combination produced "inconsistent results." (Ex-2004 at 3, 6.) And the efficacy of the claimed combination is especially remarkable given that paclitaxel was merely a second-line therapy that the prior art warned would not work in HER2-positive patients. (*Supra* pp.16-17.) A POSA therefore would have considered those clinical-efficacy results to be unexpected, which further confirms the non-obviousness of the claimed invention. *See Procter & Gamble-Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, at 994 (Fed. Cir. 2009) (evidence "that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected" strongly supports non-obviousness); *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) ("[T]hat which would have been surprising to a person of ordinary skill in a particular art would not have been obvious."). (Ex-2062 ¶¶212-215.)

Even under Petitioner's obviousness theory, the '441 invention produced an unexpected safety improvement as compared with other combinations—for

example, the combination of trastuzumab with anthracyclines that Baselga '94 said did not increase toxicity, but in fact did increase toxicity in the Phase-III study disclosed in the '441 patent. (Ex-1005 at 4; *see also* Ex-1011-2 at 53; Ex-1001, 30:13-16.) Petitioner cannot reasonably argue that prior art preclinical results would have provided a reasonable expectation of success, but dismiss other teachings from the same references that demonstrate unexpected results. *See Genetics Inst.*, 655 F.3d at 1305. (Ex-2062 ¶¶212-215.)

Petitioner argues that the safety difference between combinations with taxoids versus anthracyclines is irrelevant because that toxicity difference supposedly involved "[d]iscovering another combination that is worse" than the claimed invention. (Paper-1 at 24.) But the combination of an anti-ErbB2 antibody with an anthracycline derivative is not just "another combination"; each challenged claim expressly requires "the absence of an anthracycline derivative." The unexpected improvement in safety attributable to that claim element confirms

the non-obviousness of the challenged claims. *In re Soni*, 54 F.3d at 750.[16] (Ex-2062 ¶214.)

Fourth, the '441 invention has been an enormous commercial success. Herceptin® is the commercial embodiment of the '441 invention and one of the most successful drugs of all time. There is a direct nexus between Herceptin®'s commercial success and the '441 invention. From 1998 until 2006, the ***only*** approved first-line use of Herceptin® was in combination with a taxoid, as claimed in the '441 patent. (Ex-2012 at 1.) Following its launch, Herceptin® was quickly adopted, resulting in hundreds of millions of dollars in sales in those years immediately following its approval. (Ex-2035 at 17.) Where, as here, the commercial product embodies the claimed invention, a nexus is presumed. *Brown & Williamson Tobacco Corp. v. Philip Morris, Inc*., 229 F.3d 1120, 1130 (Fed. Cir. 2000). Petitioner has not even addressed the nexus between the '441 invention

[16] Petitioner also argues that the unexpected results for the combination of rhuMAb HER2 with paclitaxel lack a nexus to the challenged claims, which encompass combinations with "any 'taxoid.'" (Paper-1 at 62.) But Petitioner has not offered any evidence that paclitaxel is not representative of taxoids generally. Moreover, Petitioner's nexus argument does not apply to at least claim 8, which is limited to combinations with paclitaxel.

and Herceptin® for purposes of commercial success, let alone rebutted the presumption of a nexus. (Paper-1 at 62.)

2. Petitioner's "simultaneous invention" argument is legally flawed because it rests on the inventor's own work.

Petitioner argues that Baselga '97 demonstrates "near-simultaneous invention of the Challenged Claims." (Paper-1 at 62.) But simultaneous invention is only relevant if it involves individuals working ***independently*** from the inventor. *Trustees of Columbia Univ. v. Illumina, Inc.*, 620 F. App'x 916, 930 (Fed. Cir. 2015). Baselga '97 involves no such independent work; it describes the amended Phase-III-study protocol that the inventor of the '441 patent proposed. (*Compare* Ex-1006 at 10, *with* Ex-2011 ¶¶29-36 & Ex-2007.) Indeed, Petitioner expressly relies on Dr. Hellmann's own work to demonstrate "simultaneous invention." (Paper-1 at 62-63 ("POSITAs like Drs. Baselga, Pegram, and Hellmann turned to the most obvious targets: combinations of known therapies seeking synergistic effects.").)

3. Petitioner's criticisms of Dr. Sliwkowski's declaration lack merit and do not cure the deficiencies in Petitioner's obviousness theory.

During prosecution, Genentech submitted the declaration of Dr. Mark Sliwkowski. His declaration explained that a POSA would not have had a reasonable expectation of success in achieving the '441 invention based upon what

was known at the time about the biological mechanism of trastuzumab, taxoids, and other anti-cancer drugs. (Ex-1011-9 at 10-12.) He also described the well-known limitations of prior art preclinical mouse models to predict success in humans. (*Id.* at 12.)

Petitioner criticizes various aspects of that declaration. (Paper-1 at 59-62.) The Board need not reach Petitioner's arguments with respect to Dr. Sliwkowski's declaration because Petitioner's proposed grounds fail for the numerous reasons described above. But if the Board considers the declaration, it only confirms the patentability of the challenged claims.

First, Petitioner criticizes Dr. Sliwkowski's declaration for not citing papers involving the combination of rhuMAb HER2 and a taxoid. (Paper-1 at 59.) But Petitioner has not identified any such prior art paper that could have been cited, much less explained why any such citation would have been necessary to the points addressed in the declaration. If anything, the absence of such papers confirms the non-obviousness of the claimed combination as a therapeutic regimen, since it suggests that combination was not an area of interest prior to the '441 invention.

Second, Petitioner argues that the declaration is supposedly inconsistent with the "synergistic" results in preclinical mouse studies involving cisplatin and paclitaxel. (Paper-1 at 60-61.) Dr. Sliwkowski's declaration, however, explained

why those prior art preclinical results are not a reliable predictor of clinical outcomes. (Ex-1011-9 at 12.) Dr. Kerbel and Dr. Tannenbaum agree. (Ex-2061 ¶¶54-61; Ex-2062 ¶¶66-74.) Petitioner does not address—let alone dispute—the many well-known limitations of preclinical mouse models at that time. (*Supra* pp.9-12.)

Third, Petitioner contends that Dr. Sliwkowski's declaration is flawed because it cites an article published in 2001 (after the '441 invention date) as evidence of the unreliability of mouse models. (Paper-1 at 61.) But that 2001 article is a retrospective analysis involving drugs developed before the '441 invention. (Ex-1011-9 at 99.) And as discussed above (pp.7-8), numerous pre-1997 publications echo the conclusion of the 2001 article that mouse models are a poor indicator of clinical success. Genentech's use of preclinical models (*see* Paper-1 at 61-62) does not suggest otherwise. Petitioner cites no evidence suggesting that Genentech (or anyone else) relied on those models at the time of the '441 invention as anything other than a preliminary screening tool, consistent with their well-known limitations to predict clinical results at the time.

F. *Inter Partes* Review Proceedings Violate The Constitution.

Finally, the Board should terminate this proceeding because it violates Patent Owner's constitutional rights. Because patents are private property rights and disputes concerning their validity were traditionally decided by courts, patent

validity must be litigated in an Article-III court, not before an executive branch agency. *McCormick Harvesting Mach. Co. v. C. Aultman & Co.*, 169 U.S. 606, 609 (1898). Adversarial challenges to an issued patent—like *inter partes* reviews—are also "suits at common law" for which the Seventh Amendment guarantees a jury trial. U.S. Const. amend. VII; *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 377 (1996). Moreover, even if *inter partes* review is constitutional in other circumstances, it is unconstitutional for patents—like the '441 patent—that issued before passage of the America Invents Act.

The Supreme Court is currently considering the constitutionality of *inter partes* reviews in *Oil States Energy Services, LLC v. Greene's Energy Group, LLC*, No. 16-712. Patent Owner presents this constitutional challenge now to preserve the issue pending the Supreme Court's decision.

VIII. CONCLUSION

The Board should reject Petitioner's challenge to the patentability of the challenged claims.

Respectfully submitted,

Date: December 22, 2017

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CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Response, contains 13,413 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. § 42.24(d).

Respectfully submitted,

Dated: December 22, 2017

/David L. Cavanaugh/
David L. Cavanaugh
Registration No. 36,476

CERTIFICATE OF SERVICE

I hereby certify that, on December 22, 2017, I caused a true and correct copy of the following materials:

- Patent Owner's Response
- Patent Owner's Exhibit List
- Patent Owner's Motion to Seal
- Patent Owner's Motion to Amend
- Exhibits 2050-2055, 2061-2067, 2069-2075, 2077-2083, 2085-2095, 2097-2099, 2101-2113, 2115-2119, 2122-2123, 2128

to be served electronically via File Transfer Protocol (FTP), as previously agreed by the parties, on the following attorneys of record:

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IPR2017-00731
Patent Owner's Exhibit List

Patent Owner's Exhibit Number	Exhibit Name
2001	Genentech, Inc. Original H0648g Protocol PROTECTIVE ORDER MATERIAL
2002	Genentech, Inc. PDC Minutes PROTECTIVE ORDER MATERIAL
2003	Genentech, Inc. PDC Minutes PROTECTIVE ORDER MATERIAL
2004	Genentech, Inc. PDC Minutes PROTECTIVE ORDER MATERIAL
2005	Genentech, Inc. PDC Presentation PROTECTIVE ORDER MATERIAL
2006	Genentech, Inc. PDC Presentation PROTECTIVE ORDER MATERIAL
2007	Genentech, Inc. Amended H0648g Protocol PROTECTIVE ORDER MATERIAL
2008	Genentech, Inc. H0648g Final Report PROTECTIVE ORDER MATERIAL
2009	Genentech, Inc. Representative Case Report Form PROTECTIVE ORDER MATERIAL
2010	Genentech, Inc. Case Report Form Compilation PROTECTIVE ORDER MATERIAL
2011	2017 Declaration of Dr. Susan Desmond-Hellmann PROTECTIVE ORDER MATERIAL
2012	1998 Herceptin Label
2013	Per Dombernowsky, et al., *Paclitaxel and Doxorubicin, a Highly Active Combination in the Treatment of Metastatic Breast Cancer*, 23 Seminars in Oncology 13 (1996)
2014	Jason S. Fisherman, et al., *Phase I/II Study of 72-Hour Infusional Paclitaxel and Doxorubicin with Granulocyte Colony-Stimulating Factor in Patients with Metastatic Breast Cancer*, 14 J. Clinical Oncology 774 (1996)

Patent Owner's Exhibit Number	**Exhibit Name**
2015	Luca Gianni, et al., *Paclitaxel by 3-Hour Infusion in Combination with Bolus Doxorubicin in Women with Untreated Metastatic Breast Cancer: High Antitumor Efficacy and Cardiac Effects in a Dose-Finding and Sequence-Finding Study*, 13 J. Clinical Oncology 2688 (1995)
2016	M. Harries & I. Smith, *The Development and Clinical Use of Trastuzumab (Herceptin)*, 9 Endocrine-Related Cancer 75 (2002)
2017	David Holzman, *Gene Therapy for HER-2-related Cancer*, Molecular Medicine Today 138 (1996)
2018	Russ Hoyle, *Genentech Is Poised for an Anti-cancer Breakthrough*, 16 Nature Biotechnology 887 (1998)
2019	Makoto Inaba, et al., *Evaluation of Antitumor Activity in a Human Breast Tumor/Nude Mouse Model with a Special Emphasis on Treatment Dose*, 64 Cancer 1577 (1989)
2020	RESERVED
2021	Ismail Kola & John Landis, *Can the Pharmaceutical Industry Reduce Attrition Rates?*, 3 Nature Rev. 711 (2004)
2022	Steven Lehrer, et al., *Tumour HER2 Protein in Breast Cancer and Family History*, 341 Lancet 1420 (1993)
2023	Silvia Marsoni & Robert Wittes, *Clinical Development of Anticancer Agents—A National Cancer Institute Perspective*, 68 Cancer Treatment Reports 77 (1984)
2024	Jürgen Mattern, et al., *Human Tumor Xenografts as Model for Drug Testing*, 7 Cancer & Metastasis Rev. 263 (1988)
2025	Gert Riethmüller & Judith P. Johnson, *Monoclonal Antibodies in the Detection and Therapy of Micrometastatic Epithelial Cancers*, 4 Current Opinion in Immunology 647 (1992)
2026	Eric K. Rowinsky, et al., *Cardiac Disturbances During the Administration of Taxol*, 9 J. Clinical Oncology 1704 (1991)
2027	Dennis J. Slamon, et al., *Use of Chemotherapy Plus a Monoclonal Antibody Against HER2 for Metastatic Breast Cancer that Overexpresses HER2*, 344 N. Engl. J. Med. 783 (2001)
2028	Raymond B. Weiss, et al., *Hypersensitivity Reactions from Taxol*, 8 J. Clinical Oncology 1263 (1990)

Patent Owner's Exhibit Number	**Exhibit Name**
2029	Dihua Yu, *Overexpression of c-erbB-2/neu in Breast Cancer Cells Confers Increased Resistance to Taxol Via mdr-1-independent Mechanisms*, 13 Oncogene 1359 (1996)
2030	James H. Doroshow, *Anthracyclines and Anthracenediones*, *in* Cancer Chemotherapy & Biotherapy: Principles and Practice 409 (1996)
2031	Richard P. Junghans, et al., *Antibody-Based Immunotherapies for Cancer*, *in* Cancer Chemotherapy & Biotherapy: Principles and Practice 655 (1996)
2032	Gert Riethmüller, et al., *Monoclonal Antibodies in Cancer Therapy*, 5 Current Opinion in Immunology 732 (1993)
2033	Richard Saltus, *New Treatment for Breast Cancer Called Promising*, Boston Globe, May 18, 1998
2034	*TODAY: FDA Expected to Approve Two New Breast Cancer Drugs* (NBC television broadcast Sept. 2, 1998)
2035	Genentech Annual Report 2000
2036	Modified Default Standing Protective Order and Patent Owner's Certification of Agreement to Terms
2037	Modified Default Standing Protective Order – Redline
2038	Declaration of Robert J. Gunther, Jr. in Support of Motion for Admission Pro Hac Vice
2039	Declaration of Daralyn J. Durie in Support of Motion for Admission Pro Hac Vice
2040	Declaration of Lisa J. Pirozzolo in Support of Motion for Admission Pro Hac Vice
2041	Declaration of Kevin S. Prussia in Support of Motion for Admission Pro Hac Vice
2042	Declaration of Andrew J. Danford in Support of Motion for Admission Pro Hac Vice
2043	RESERVED
2044	RESERVED
2045	RESERVED

Patent Owner's Exhibit Number	**Exhibit Name**
2046	RESERVED
2047	RESERVED
2048	RESERVED
2049	RESERVED
2050	Deposition Transcript of Allan Lipton, December 14, 2017, Hospira, Inc. v Genentech, Inc.
2051	Gura, T., *Systems for identifying new drugs are often faulty*, Science, 278(5340), 1041-1042 (1997)
2052	Clarke, R., *Issues in experimental design and endpoint analysis in the study of experimental cytotoxic agents in vivo in breast cancer and other models*, Breast Cancer Research and Treatment 46:255-278 (1997)
2053	Clarke, R., *Human Breast Cancer Cell Lines Xenografts as Models of Breast Cancer - The Immunobiologies of Recipient Mice and the Characteristics of Several Tumorigenic Cell Lines*, Breast Cancer Research and Treatment, 39:69-86 (1996)
2054	Witters, et al., *Decreased Response to Paclitaxe. Versus Docetaxel in HER-2/neu Transfected Human Breast Cancer Cells*, Am. J. Clin. Oncol., 26(1):50-54 (2003)
2055	Hortobagyi, *Anthracyclines in the Treatment of Cancer*, Drugs, Vol. 54, Supp. 4:1-7 (1997)
2056	RESERVED
2057	RESERVED
2058	RESERVED
2059	RESERVED
2060	RESERVED
2061	Expert Declaration of Robert S. Kerbel, Ph.D.
2062	Expert Declaration of Dr. Susan Tannenbaum

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