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UNITED STATES PATENT AND TRADEMARK OFFICE

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**BEFORE THE PATENT TRIAL AND APPEAL BOARD**

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CELLTRION, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

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Case IPR2017-01121
Patent No. 7,846,441

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# PATENT OWNER'S RESPONSE

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Genentech, Inc. ("Patent Owner") submits this Response to the Petition filed by Celltrion, 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 three references: (1) an article (Baselga-1996) describing the results of a Phase-II study treating patients with the antibody alone and briefly alluding to a preclinical mouse study involving combinations of the antibody and paclitaxel as well as the antibody plus an anthracycline; (2) an abstract (Seidman-1996) speculating that HER2-positive patients may respond to taxoid therapy; and (3) a Physician's Desk Reference entry for Taxol from 1995. In its institution decision, the Board concluded 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 unpatentable.

***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. Before the '441 invention, even persons of extraordinary 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 the combination with a different chemotherapeutic agent, called cisplatin. And when Phase-III trials began, the only drug combination under evaluation was the combination of antibody 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 patent 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. Patent Owner's expert came to the same conclusion. 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 mentioned in Baselga '96 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 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 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 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

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

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 nonobviousness, 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

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 ¶¶34-38; Ex-2062 ¶¶66-70.)

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. (Ex-2050 [Earhart], 170:12-13 (known as of 1997 that "a lot of drugs are screened and only a few make it to clinical use").) 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 ¶¶55-62; Ex-2062 ¶¶67-71.)

By 1997, it was recognized that efficacy in mouse models was not reliably predictive of anti-cancer drug performance in humans. (*See, e.g.*, Ex-2023 at 79 ("very low" likelihood of predicting response in humans); Ex-2051 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 ¶¶54-58; Ex-2062 ¶68.) 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 ¶72.)

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 ¶73.)

***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.)

***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. (Ex-2050 [Earhart], 202:7-12 (TTP is "not an endpoint that you report in xenograft studies").) 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 ¶87; Ex-2067 at 353.) This fundamental difference is highlighted by the fact that Baselga Abstract 53's mouse studies occurred over a period of ***five weeks*** (Ex-1019),[2] whereas the TTP for Herceptin plus Taxol in humans reported in the '441 patent was ***7.1 months*** (Ex-1001, 30:6). (Ex-2061 ¶¶82-83; Ex-2062 ¶¶140-147.)

[2] Along with Baselga Abstract 53 (Ex-1019), the Board cites another non-instituted reference—Baselga Abstract 2262 (Ex-1021)—when discussing whether the prior art demonstrates a motivation to treat with the claimed combination. (Paper-9 at 11, 18.) The disclosures of these two references are substantively similar—both are one-paragraph abstracts describing the results of the same mouse xenograft studies involving the 4D5 antibody, doxorubicin, and paclitaxel.

***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 ¶¶65-66; Ex-2062 ¶75.)

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-BR-3 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.)

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 ¶¶26, 42-44; Ex-2062 ¶72-77.)

***Fifth***, mouse models based on subcutaneous implantation[3] 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 is not the optimal site for all xenografts.").) 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 ¶¶78-82; Ex-2062 ¶¶161, 187-188.)

**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

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

large-scale controlled trials designed to evaluate specific clinical endpoints (i.e., Phase III). (Ex-2062 ¶¶78-83.)

That a drug proceeds to human clinical trials is hardly an indicator of eventual success. In the 1990s, only 5% of cancer drugs that advanced to clinical trials resulted in an approved product. (Ex-2021 at 711-12.) In particular, Petitioner's expert, Dr. Earhart, testified that during his entire 13-year career working on clinical trials at Upjohn, he did not work on a single drug that was ultimately approved by the FDA. (Ex-2050 [Earhart], 78:15-20.) And even for oncology drugs that advanced to late-stage, Phase-III clinical trials, nearly 60% ultimately failed to result in an approved drug. (Ex-2021 at 712.) 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. (*Id.* at 713 ("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 ¶¶88-91.)

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 ¶¶80-87.)

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 ¶87; Ex-2067 at 353.)

Indeed, even Petitioner recognizes that response rate is a different clinical endpoint than TTP. (*See* Paper-1 at 41-42 (defining "Response Rate" as "measur[ing] changes in tumor size" and "Time To Progression" as "the time from diagnosis or start of treatment until tumor progression"); Ex-1002, ¶92.)

### 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.) According to Petitioner's expert, the number of chemotherapeutic agents for breast cancer was in the "double figures." (Ex-2050 [Earhart], 117:11-12.) 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; Ex-2050 [Earhart], 120:7-13 (anthracycline derivatives a "major treatment for breast cancers" in mid to late 1990s and today).) Doxorubicin is an example of an anthracycline, and it was known to be "especially active" against breast cancer. (Ex-2030 at 409; Ex-2050 [Earhart],127:21-129:9.) 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. (Ex-2030 at 409.) As a result, treatments containing anthracyclines were the "standard therapy for cancers of the breast" in the 1990s. (*Id.*) (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 50.) 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 institution decision, the known cardiotoxicity of anthracyclines would not have motivated a POSA to exclude those drugs from therapy. (Paper-9 at 16 ("Thus, we determine that cardiotoxicity alone would not have motivated an ordinary artisan to avoid anthracyclines in treating breast cancer.").)

Petitioner cites Dr. Earhart's declaration (Ex-1002, ¶137) and a general cancer textbook ("Abeloff") (Ex-1016 at 813) as evidence that "a POSA would have limited use of anthracycline derivatives in treatment whenever possible" (Paper-1 at 51), but neither supports that assertion. Dr. Earhart acknowledges that "treating patients with anthracyclines is often unavoidable" and states that "many patients" at the time of the invention would have received anthracyclines as "a first-line therapy for breast cancer." (Ex-1002, ¶137.) And far from teaching avoidance of anthracyclines "whenever possible," Abeloff cautions ***against*** limiting anthracycline usage, which "may deprive patients who are continuing to benefit from therapy and who do not show signs of toxicity." (Ex-1016 at 29.) Moreover, Seidman-1995 noted that combinations with anthracyclines had shown "impressive antitumor activity" and were the subject of an "important" ongoing trial. (Ex-1010 at 4.) Petitioner has cited nothing contemporaneous with the '441 invention indicating that anthracyclines were avoided "whenever possible." (Paper-1 at 51.) (Ex-2062 ¶¶52-53.)

**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. (Ex-2050 [Earhart], 123:15-22 (paclitaxel still considered a "novel agent" in December 1996).) 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 ¶61; Ex-1012 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 ¶¶54-61.)

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. And even then, paclitaxel was approved to treat breast cancer only ***after*** other treatments failed, i.e., for "second-line" use. (Ex-1012 at 10.) 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 ¶¶54-57.)

### 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; *see also* Ex-2050 [Earhart], 242:8-243:2 (in the 1990s: "it wasn't like it looked like it was going to be smooth sailing for monoclonal antibody development").) 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 ¶¶95-99.)

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 ¶¶99-101.)

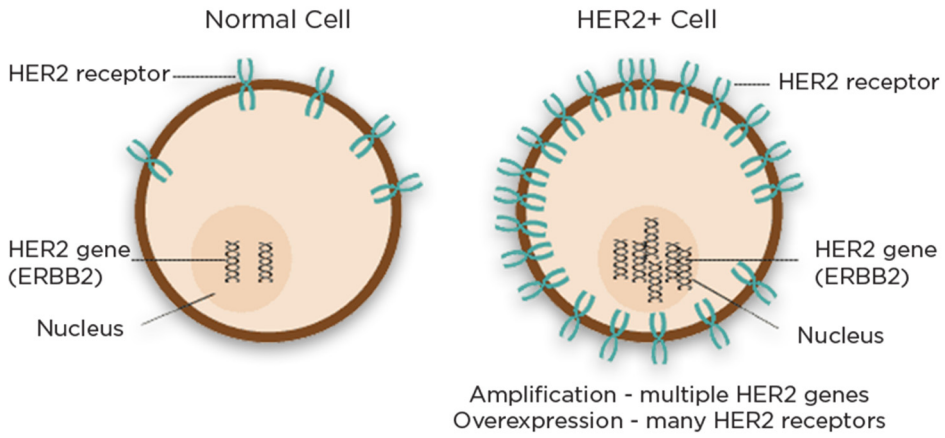
The Board's institution decision states that "[b]efore the '441 patent, a recombinant humanized anti-ErbB2 monoclonal antibody (a humanized version of the murine anti-ErbB2 antibody 4D5, also referred to as rhuMAb HER2, trastuzumab, or HERCEPTIN®) had been approved to treat patients with ErbB2-overexpressing metastatic breast cancers." (Paper-9 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 at 36:7-21, 38:26-43:26), 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-2062 ¶92.)

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, 92.)

HER2-positive breast cancer is an aggressive disease. (Ex-2050 [Earhart], 112:7-9 (HER2-positive status a factor that "determine[s] the aggressiveness of breast cancer"); *id.*, 109:20-110:1).) 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-2010 at 6-8; Ex-2050

[Earhart], 109:17-19).) HER2-positive patients had "a shorter time to relapse as well as a shorter overall survival." (Ex-2011 at 707; Ex-2010 at 180.) 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 ¶¶93-94.)

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 ¶94.)

## 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 on numerous occasions. (Paper-1 at 9, 11, 20, 30, 33, 43-44, 52, 58, 63.) 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***. The Phase-II trials treated patients with an anti-ErbB2 antibody alone (Ex-1020) or in combination with cisplatin (Ex-1022), 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-2125[4] ¶¶15-19; Ex-2001[5] at 16, § 5.2.2.) Accordingly, even Petitioner's own expert admits he was

[4] This declaration from named inventor Dr. Susan Hellmann was previously submitted in IPR2017-00731, in which the '441 patent is also at issue.

[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 ¶¶4-13.)

unaware as of the date of Baselga-1996 whether any clinical trials testing rhuMAb-HER2 and paclitaxel were ongoing. (Ex-2050, 327:10-328:22.)

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 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-2125 ¶¶2, 34; Ex-1008 at 1.) 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-2125 ¶18; Ex-2062 ¶¶115-117, 197.)

[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 ¶¶115, 197, 215; Ex-2111 at 73.)

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 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-2125 ¶¶19-21; Ex-2062 ¶¶80-91, 117.)

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-2125 ¶¶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 in 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-2125 ¶¶18, 22-28, 34.) (Ex-2062 ¶197.)

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-2125 ¶¶24, 28.)

By late 1997, the Phase-III study reached its primary endpoint. (Ex-2008 at 51-58, 104-109; Ex-2125 ¶¶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. (*Id.* 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. (Ex-2008 at 39; Ex-2001 at 12.) These data are reflected in the provisional patent application filed December 12, 1997. (Ex-2009, 38:26-43:26.) The challenged claims are directed to Dr. Hellmann's new method of treatment. (Ex-2062 ¶¶118-119, 124.)

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. 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 overexpresses 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 ¶120.)

**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 ¶238.)

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.) (Ex-2062 ¶120.)

### 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.)[7]

During prosecution, the examiner considered many of the references cited in the petition, including Baselga-1996 (Ex-1020)—the primary reference underlying Petitioner's obviousness theory—and the Baselga abstracts (Exs-1019,1021) that describe the results of preclinical mouse studies involving trastuzumab.[8]

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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 IPR2017-01122.

[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-1996 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.

Petitioner asserts that the petition presents references not before the examiner during prosecution, such as Seidman-1996 (Ex-1011) or the general "principles" of combination chemotherapy (Paper-1 at 20) reflected, for example, in Abeloff (Ex-1016). But Petitioner has not identified any critical information in those references that the examiner lacked. For example, Petitioner acknowledges that the examiner considered Seidman-1995 (Paper-1 at 17), which Petitioner cites for the same supposed teaching as Seidman-1996. (*E.g.*, Paper-1 at 26 (citing Seidman-1995 (Ex-1010) for the proposition "that HER2-positive patients were particularly responsive to paclitaxel").) And Petitioner does not even identify Abeloff (Ex-1016)—or any other reference describing the purported "principles" of combination chemotherapy (Paper-1 at 20)—among the combination of references underlying its proposed obviousness ground (Paper-1 at 24).

In October 2009, Genentech submitted a declaration from Dr. Mark Sliwkowski in response to obviousness rejections over, among other things, Baselga Abstract 2262. (Ex-1009 at 2.) 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. (Ex-1009 at 2-5.) 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. (Ex-1009 at 4.)

On December 30, 2009, the examiner allowed the claims. (Ex-1004 at 2465-67.)

## IV. PRIOR ART

### A. Baselga-1996

Baselga-1996 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-1020 at 4 ("Chemotherapy … was not permitted.").)[9] (Ex-2062 ¶¶140-149.)

The clinical endpoint evaluated in the trial was response rate. (*Id.* at 4, 6, 7.) Although Baselga-1996 measured "[t]ime to tumor progression" for individual

[9] The study reported in Baselga-1996 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-1020 at 4.)

patients,[10] all patients in the study received rhuMAb HER2. (*Id.* at 4.) The study thus had no control group against which to evaluate whether rhuMAb HER2 (or any combination involving it) ***extended*** TTP. (Ex-2050 [Earhart], 313:17-19.) (Ex-2062 ¶¶147-149.)

According to Baselga-1996, 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-1020 at 6.) (Ex-2062 ¶143.)

Baselga-1996 acknowledged that the mechanism of potential antitumor activity for rhuMAb HER2 was not understood and proposed several possible explanations for the observed clinical results. (*Id.* at 8-9.) Thus, it 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.* ("[C]ontinued research with this agent and other HER2-targeted treatment strategies appears warranted.").) (Ex-2062 ¶145.)

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[10] Dr. Earhart testified that he "did not find" a TTP measurement in Baselga-1996 and that such a measurement "wouldn't be … necessarily standard in a Phase 2 study." (Ex-2050, 316:11-22; *see also id.*, 318:21-320:6 ("[Baselga-1996] doesn't report the specific variable of time to progression at all ….").)

Baselga-1996, citing Baselga Abstract 53, 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." (*Id.* at 9.) However, Baselga-1996 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-1996 was submitted (August 8, 1995) or accepted (October 10, 1995). (Ex-2062 ¶149.)

**B. Seidman-1996**

Seidman-1996 (Ex-1011) is an abstract published in March 1996, which describes a retrospective analysis of tumor samples for metastatic breast cancer patients "who were treated on phase II protocols of single-agent paclitaxel (n=106) or docetaxel (n=20)." (Ex-1011 at 5; *see also* Ex-2050 [Earhart], 335:10-17 (agreeing that Seidman-1996 does not report any combination therapy).) Seidman-1996 does not mention antibody therapy at all. Rather, with respect to the single-agent chemotherapies studied, Seidman-1996 reported that the "response proportion" was 58.8% among HER2-positive patients and 38.7% among HER2-negative patients. (*Id.*) Seidman-1996 did not address whether taxoids extend

TTP in HER2-positive patients, instead measuring the "response proportion"—a different clinical endpoint. (*Id.*) (Ex-2062 ¶¶150-154.)

Given that Seidman-1996 was merely an abstract, a POSA would have understood that the results reported therein were preliminary and would have awaited more-detailed study to draw any conclusions. (Ex-2062 ¶154; *see also* Ex-2050 [Earhart], 338:2-7 (Seidman 1996 is "simply reporting an observation … that perhaps someone else will be able to shed greater light on").) Here, that more detailed study revealed that the hypothesis presented in Seidman-1996 was incorrect. In 2002, the Seidman authors published a paper reporting their continued work in this area and concluding that HER2 overexpression did ***not*** show "a statistically significant association with clinical response to taxane therapy." (Ex-2024 at 2322.) The Seidman authors recognized that those results were contrary to their preliminary hypothesis from Seidman-1996, which was based upon an "earlier analysis of fewer cases." (*Id.* at 2323.) (Ex-2062 ¶154.)

### C. 1995 Taxol® PDR

The 1995 Taxol® PDR (Ex-1012) is the entry from Physicians' Desk Reference from 1995 corresponding with paclitaxel. The Taxol® PDR was not itself considered during prosecution. But the only information that Petitioner cites from the reference is its disclosure of dosage amounts for paclitaxel (*see* Paper-1 at 48), which other references before the examiner (e.g., Seidman-1995) also

disclosed. (*Compare* Ex-1010 at 3 ("paclitaxel was administered via 3-hour infusion every 3 weeks, as a starting dose of 175 mg/m$^2$"), *with* Ex-1012 at 8 ("TAXOL at a dose of 175 mg/m$^2$ administered intravenously over 3 hours every three weeks has been shown to be effective").) (Ex-2062 ¶¶155-158.)

The 1995 Taxol® PDR entry states that paclitaxel was approved only as a second-line therapy for metastatic breast cancer (i.e., after the failure of other treatments). (Ex-1012 at 6.) It also states that, in general, paclitaxel should be used only after anthracycline therapy. (*Id.*) The 1995 Taxol® PDR further includes a black box "WARNING" regarding the possibility of "[s]evere hypersensitivity reactions" and notes that at least one patient died from those side effects. (*Id.* at 5, 6; *see also* Ex-2050 [Earhart], 290:11-22 (this warning is "the FDA's way of flagging a drug, some things that you need to know about the drug").) (Ex-2062 ¶¶156-157.)

The 1995 Taxol® PDR does not suggest combining paclitaxel with anti-ErbB2 antibodies, or even mention anti-ErbB2 antibodies. (Ex-2050 [Earhart], 298:10-299:6.) Moreover, the reference does not mention HER2-positive breast cancer or suggest that taxoids would be effective to treat HER2-positive patients, which constitute only 25-30% of breast-cancer patients (Ex-1001, 1:23-29). Indeed, a paper published one year later found that HER2-positive breast cancer tends to be resistant to Taxol, and as a result predicted that "breast cancers that

overexpress p185 [i.e., HER2] will not respond well to Taxol." (Ex-2029 at 1362.) (Ex-2062 ¶195.)

## V. PERSON OF ORDINARY SKILL

The Board should apply the same definition of a POSA from IPR2017-00731, which also involves the '441 patent. In IPR2017-00731, the parties agreed that a POSA for purposes of the '441 patent would be a "clinical or medical oncologist specializing in breast cancer with several years of experience with breast cancer research or clinical trials." (IPR2017-00731, Paper-1 at 7; IPR2017-00731, Paper-9 at 32.) In its institution decision, the Board adopted that proposed definition of a POSA in this proceeding as well. (Paper-9 at 10.)

Petitioner describes the POSA in slightly different terms—for example, by including Ph.D. scientists and by requiring "substantial experience" with treating breast cancer and conducting breast-cancer clinical trials. (Paper-1 at 43.) Petitioner's refusal to require a focus on breast cancer is likely because, while Patent Owner's expert, Dr. Tannenbaum, has spent her last 20 years specializing in breast cancer treatment (Ex-2062 ¶5-12), Petitioner's expert, Dr. Earhart, admitted he has not focused his practice on treating breast cancer (Ex-2050, 22:4-13, 23:6-24:14). This lack of focus infects Dr. Earhart's, and thus Petitioner's, analysis.

In any event, for the reasons explained below, the challenged claims would not have been obvious under either Petitioner's proposed definition or the definition from IPR2017-00731. (Ex-2062 ¶172.)

## VI. CLAIM CONSTRUCTION

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

Both parties agreed that the term "extend the time to disease progression in said human patient, without increase in overall severe adverse events" is a "relative term" that "compare[s] the claimed combination treatment to treatment with a taxoid alone." (Paper-1 at 21; Paper-8 at 38 (not disputing Petitioner's construction).) In its institution decision, however, the Board construed this term as measured against a patient who had received no treatment. (Paper-9 at 6.)

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. (Ex-1002, ¶112(h); Ex-2062 ¶¶129-138.) 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.)[11] 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.

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 approved therapy that would provide a clinical benefit to the target patient population. (Ex-2062 ¶138.)

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-9 at 14-15.) The requirement to "extend the time to disease progression … without increase in

[11] 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.

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 ¶¶129-138.)

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-9 at 6.) 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-1004 at 416.) 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-2062 ¶135.) 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. (Ex-1002, ¶112(h).)[12] The understanding of a POSA is therefore not in dispute. (Ex-2062 ¶137.)

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.[13]

## VII. ARGUMENT

### A. A Person Of Ordinary Skill Would Not Have Been Motivated To Treat Patients With A Combination Of An Anti-ErbB2 Antibody And A Taxoid Based Upon Baselga-1996, Seidman-1996, And The Taxol® PDR.

None of the references underlying the instituted ground teaches treatment with a combination of an anti-ErbB2 antibody and a taxoid. Baselga-1996

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[12] Dr. Lipton, the expert for the Pfizer (IPR2017-02063) and Hospira (IPR2017-00731) IPRs against the '441 patent, also agrees that "[b]ased on the specification, the appropriate comparison is to compare the claimed combination treatment versus treatment with a taxoid alone." (IPR2017-02063, Ex-1102, ¶112(h).)

[13] Although in the POPR Patent Owner proposed a construction for "response rate," Patent Owner no longer believes a construction for this term is necessary, as none of the arguments in this proceeding turns on the meaning of this term.

involves treatment with rhuMAb HER2 alone. Seidman-1996 involves treatment with a taxoid alone. And the Taxol® PDR involves treatment with a taxoid alone as a second-line therapy for breast cancer and does not even mention HER2-positive breast cancer. (Ex-2062 ¶¶174, 180, 184.)

**1. Baselga-1996 and Seidman-1996 do not provide a motivation to treat patients with the claimed combination.**

Petitioner argues that a POSA would have been motivated "to treat patients with a combination of trastuzumab and paclitaxel" based upon Baselga-1996 and Seidman-1996. (Paper-1 at 43-44.) But that argument rests on hindsight.

Baselga-1996 discusses preclinical combinations with "several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel." (Ex-1020 at 9.) But Baselga-1996 provides no motivation to choose paclitaxel from among the "several chemotherapeutic agents" identified for treatment in human patients. (Ex-2062 ¶¶176-179.) Although Baselga-1996 states that "clinical trials of such combination therapy are currently in progress," it does not indicate which particular combination therapy it is referring to, and it could not have been referring to rhuMAb HER2 plus paclitaxel because there was no clinical study involving that combination at the time that Baselga-1996 was submitted (August 8, 1995) or accepted (October 10, 1995). (*Supra* p.32; Ex-2125 ¶¶18-19.) (Ex-2062 ¶149.)

Petitioner argues that Seidman-1996 demonstrates that taxoids have "proven efficacy against metastatic HER2-positive breast cancer in humans" (Paper-1 at 43), and the Board agreed with that characterization based upon the preliminary record at the institution stage (Paper-9 at 17-18). However, the full record now confirms that is not how a POSA would have interpreted Seidman-1996 at the time. As Dr. Tannenbaum explains, Seidman-1996 is an abstract, which a POSA would understand as reflecting a preliminary hypothesis, not "proven efficacy"; and a POSA would await an expanded analysis in a peer-reviewed journal before drawing any conclusions. (Ex-2062 ¶¶181-182.) In the words of Petitioner's expert, Dr. Earhart, Seidman-1996 is "simply reporting an observation … that perhaps someone else will be able to shed greater light on." (Ex-2050, 338:2-7.)

In fact, the Seidman authors' own actions confirm that a POSA would not have interpreted Seidman-1996 as showing the "proven efficacy" of taxoids in HER2-positive patients, but would instead have awaited further study. The Seidman authors themselves continued to research the issue and ultimately found no "statistically significant association with clinical response to taxane therapy" for patients who are HER2-positive. (Ex-2024 at 2322.) Indeed, the Seidman authors described that finding as "noteworthy" because it was "partly in contrast to our earlier analysis." (Ex-2024 at 2323.) That the authors of the Seidman abstract did not view their initial finding as one of "proven efficacy" and continued to study the

issue further confirms that a POSA would not have attributed the same significance to Seidman that Petitioner suggested and the Board accepted. (Ex-2062 ¶183.)

Moreover, other references contradict Petitioner's conclusion that a POSA would have understood taxoids to have "proven efficacy" based on Seidman-1996. For example, a paper published by Yu et al. in September 1996 explicitly taught that "breast cancers that overexpress p185 [*i.e.*, HER2] will not respond well to Taxol." (Ex-2029 at 1362.) Those statements contemporaneous with invention of the '441 patent discouraging the use of taxoids in HER2-positive patients are strong evidence of non-obviousness. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) ("An inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements."). (Ex-2062 ¶195.)

In its institution decision, the Board concluded that the Yu reference did not undermine Petitioner's obviousness theory because "we must analyze the prior art as a whole, and not individually." (Paper-9 at 17-18.) But that it is precisely the point. Petitioner's obviousness theory rests on a selective reconstruction of the state of the art that ignores what others were saying at the time about the use of taxoids in HER2-positive patients and instead rests on a supposed teaching in Seidman 1996 that ultimately turned out not to be true. At best, the state of the art

as to the efficacy of taxoids in HER2-positive patients was mixed and cannot support a motivation to combine. (Ex-2062 ¶195.)

Furthermore, there are other reasons why a POSA would not have been motivated to treat HER2-positive patients with a combination of an anti-ErbB2 antibody and a taxoid. For example, at the time, patients experienced serious hypersensitivity reactions, neuropathy, and cardiotoxicity from taxoids, which were only approved for second-line use in breast cancer. These safety concerns would have further dissuaded POSAs from using combination therapy involving taxoids. (Ex-2062 ¶¶59-61, 190-194.)

**2. The preclinical results alluded to in Baselga-1996 do not provide a motivation to treat patients with the claimed combination.**

In its institution decision, the Board also pointed to preclinical results supposedly "reporting synergy between trastuzumab and paclitaxel in mouse xenografts" as providing a motivation to combine. (Paper-9 at 11.) But the full record now confirms that those preclinical results (Exs-1019, 1021)—which are not even part of the instituted ground—would not have motivated a POSA to treat patients with a combination of an anti-ErbB2 antibody and a taxoid. (Ex-2062 ¶¶160-165, 176.)

A POSA would understand that the mouse study in Baselga Abstract 53 (Ex-1019) and Baselga Abstract 2262 (Ex-1021) (and briefly alluded to in Baselga-

1996) was not a reliable predictor of success in humans. The preclinical study described in the Baselga abstracts 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. (*Supra* pp.10-11.) A study based on a single cell line is akin to a clinical trial involving a single patient, which has minimal predictive value. (Ex-2061 ¶¶63-70; Ex-2062 ¶187.)

Moreover, a POSA also would have understood that the particular cell line used in the Baselga abstracts 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 the Baselga abstracts are not representative of how actual HER2-positive patients would respond. (Ex-2061 ¶62; Ex-2062 ¶161.)

In addition, the tumors in the Baselga abstracts 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* p.11.) (Ex-2061 ¶¶77-80; Ex-2062 ¶161.) Thus, these references would not have motivated a

POSA to treat humans with the claimed combination.[14] (Ex-2061 ¶¶82-83; Ex-2062 ¶¶162-163.)

Furthermore, the development history of rhuMAb HER2 confirms that the Baselga abstracts 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-1015), 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

[14] 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.)

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. 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 the Baselga abstracts, and it would be inappropriate to attribute Dr. Hellmann's extraordinary knowledge (Ex-2125 ¶¶2, 18, 34) 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 the 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 ¶¶179,197.)

These specific deficiencies with the preclinical models disclosed in the Baselga abstracts, coupled with the lack of predictive value for mouse xenograft studies generally (*supra* pp.6-11), confirm that the Baselga abstracts would not have motivated a POSA to treat patients with a combination of rhuMAb HER2 and paclitaxel. 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 ¶¶160-165, 176.)

### 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.18-19; 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 ¶¶191-195.) 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 ¶¶97-101.)

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 ¶189.) 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.14-

15.) 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 "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, 117.)

**4. Petitioner's four "principles" of chemotherapy do not suggest the claimed combination.**

Petitioner also relies on four "principles" of combination chemotherapy (Paper-1 at 45-46), but those supposed "principles" do not supply a motivation to treat with the claimed combination.

The "principles" on their face only address combinations of different ***chemotherapies***. (Ex-1016 at 10-11.) The '441 patent, however, claims treatment using combinations of an ***antibody*** and chemotherapy, not combinations of different chemotherapies. At the time of the '441 invention, antibodies were an entirely-new class of drug, and it was not clear how (if at all) they could be used to treat cancer. (*See* Ex-2031 at 683; *supra* pp.18-19.) Petitioner has not explained why a skilled artisan at the time would have believed that chemotherapy principles

would be applicable to combinations with the new and unproven class of therapeutic antibodies. Indeed, Petitioner's expert was not "aware of any publication prior to December of 1996 that applied the four principles" to an anticancer agent that included both an antibody and chemotherapeutic drug. (Ex-2050, 274:1-10.) (Ex-2062 ¶¶198-206.)

* * *

For the reasons set forth above, the instituted prior art would not have motivated a POSA to treat with the claimed combination.

### 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-9 at 6, 13-14.) 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.36-39.) Under the correct claim construction, Petitioner has not

shown that the prior art taught that the claimed combination therapy would extend TTP relative to a patient treated with a taxoid alone.[15] (Ex-2062 ¶¶128-138, 207.)

Neither Baselga-1996, Seidman-1996, nor the Taxol® PDR includes data showing an ***extension*** in TTP. (Ex-2050 [Earhart], 341:15-17; Ex-2062 ¶¶208-211.) Baselga-1996 includes data for "time to progression" (Ex-1020 at 6), but this is for treatment with the antibody alone, and the study has no control arm against which to compare treatment with a taxoid alone; thus, Baselga-1996 provides no basis to determine that the claimed combination extends TTP compared to treatment with a taxoid alone. Seidman-1996 does not even address TTP; it describes only response rate. (Ex-1011.) The Taxol® PDR includes data for "time to progression" (Ex-1012 at 6), but this is for treatment with Taxol alone, and the study has no control arm; thus, similar to Baselga-1996, the Taxol® PDR provides no basis to determine that the claimed combination extends TTP compared to treatment with a taxoid alone. (Ex-2062 ¶215.)

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[15] Alternatively, to the extent the Board believes that the claims are not patentable as written, Petitioner 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. (Ex-1002, ¶112(h).)

In its institution decision, the Board noted that Baselga-1996 teaches that treatment with rhuMAb HER2 would extend TTP relative to an untreated patient, and Seidman-1996 teaches that treatment with Taxol would extend TTP relative to an untreated patient, and reasoned that nothing "suggests that combining a taxoid with rhuMAb HER2 would abrogate the effect of either therapeutic[]." (Paper-9 at 14.) 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 ¶¶208-212.)

Furthermore, the response rates disclosed in the instituted references, including the mouse models alluded to in Baselga-1996, do not suggest an extension in TTP when using the claimed combination. 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.9.) Indeed, Petitioner and its expert concede that response rate and TTP are different endpoints that are measured differently. (*See* Paper-1 at 41-42; Ex-1002, ¶¶92, 112(f)-(g).) (Ex-2062 ¶¶83-87, 213.)

As to the mouse studies in the Baselga abstracts 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)")). In any case, as discussed above, the particular mouse model used in the Baselga abstracts would have limited predictive value in assessing the clinical response in human patients. (*Supra* pp.43-46.) (Ex-2061 ¶¶62-70, 77-81; Ex-2062 ¶¶160-165.)

Indeed, the development history of rhuMAb HER2 confirms that the preclinical results in the Baselga abstracts would not have provided a POSA a reasonable expectation of success in achieving the specific clinical result claimed in the '441 patent. Despite these abstracts, 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-2125 ¶¶14-21.) Only in hindsight can Petitioner reinterpret the preclinical results reported in the Baselga abstracts to provide a reasonable expectation of success. (Ex-2062 ¶¶197, 205, 215.)

Finally, Petitioner's "principles" of combination chemotherapy do not suggest a reasonable expectation of success in achieving the claimed efficacy. As explained above (*supra* pp.48-49), these principles apply to chemotherapy combinations, not combinations with antibodies. (Ex-2062 ¶¶199, 214.)

But even if a POSA would have considered the cited chemotherapy principles relevant to antibodies, those general principles would not have diminished the unpredictability of treating cancer in the 1990s. Even Petitioner's cited references acknowledged the unpredictable challenges of combining cancer treatments. (*E.g.*, Ex-1013 at 1 ("Combining two chemotherapy agents with distinctly different mechanisms of action and characteristics into a couplet represents a challenge."); Ex-1006 at 33 (acknowledging the "[n]umerous pitfalls" to developing new cancer therapies).) Consistent with that high degree of unpredictability, patient survival for advanced (i.e., "metastatic") breast cancer had "not consistently or substantially improved" in the decade before the '441 invention, "[d]espite innumerable trials" involving "various combinations" of drugs. (Ex-1006 at 105.) (Ex-2062 ¶¶203, 214.)

This difficulty in combining chemotherapy with other cancer treatments can be seen in the failure to combine chemotherapy with hormone therapy, which did not increase the response rate, TTP, or survival as compared to either treatment alone. (Ex- 2072 at Abstract; Ex-2073 at Abstract.) Some studies even suggested that hormone therapy alone provided better results than combined treatment with chemotherapy. (Ex-2074 at 8.) (Ex-2062 ¶¶204, 214.)

### 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."[16]

In its institution decision, the Board concluded that this limitation is taught by the instituted references because patients treated with the claimed combination would fare no worse than untreated patients whose disease would worsen. (Paper-9 at 14-15; *see also* Paper-1 at 49 n.18 & Ex-1002 ¶155 n.28 (advancing same argument).) Respectfully, however, a POSA would not understand the effect of the disease on an untreated patient to be an "adverse event." Indeed, the definition of an "adverse event" that the Board apparently identified through its own investigation refutes that analysis. (Ex-2062 ¶216.)

Under the Board's definition, an adverse event is "[a]n ***unexpected*** medical problem." (Paper-9 at 14-15.) The effects of untreated HER2-positive breast

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[16] For the same reasons discussed herein, Petitioner has not shown that this limitation is taught by the instituted references under the proper claim construction comparing treatment with the claimed combination to treatment with a taxoid alone. (Ex-2062 ¶207.)

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 ¶216.)

Petitioner cites the "promising clinical results" in Baselga-1996 and Seidman 1996 and "lack of severe toxicity associated with trastuzumab." (Paper-1 at 49.) But none of this suggests that a patient treated with the claimed combination would not experience an increase in "overall severe adverse effects" relative to untreated patients who, by the Board's definition, suffer no adverse events. Nor would these references suggest success as to the "without increase in overall severe adverse events" limitation under Patent Owner's construction requiring comparison to patients' treated with a taxoid alone, especially given the uncertainty of antibody therapy and known safety issues surrounding taxoid therapy. (*Supra* pp.16-19.) (Ex-2062 ¶¶97-101, 191-195, 219.)

Petitioner cites the lack of increased toxicity from combining trastuzumab and paclitaxel in preclinical mouse studies. (Paper-1 at 49.) However, Baselga-

1996 and Baselga Abstract 53 made the same statement about combinations with the anthracycline doxorubicin (Ex-1020 at 9; Ex-1019 at 4)—which produced a significant increase in cardiotoxicity when administered to human patients. (*Supra* pp.25, 45-46; *see also* Ex-2050 [Earhart], 206:10-207:3 (Baselga references did not measure cardiotoxicity because the mice "just aren't treated with that much drug or for that length of time").) And Petitioner's own expert admits that, in assessing toxicity, mouse xenografts are "pretty crude" and "more crude … than we have available in the clinic." (Ex-2050, 205:15-206:15.) These disconnects highlight the inability of the Baselga references' mouse models to predict clinical safety. (Ex-2061 ¶¶54-61; Ex-2062 ¶¶219-221.)

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.43-46.) This was especially the case for a combination involving the antibody 4D5: because it was engineered to bind to the human ErbB2 receptor (not the mouse ErbB2 receptor) and have similarities to antibodies produced in humans, 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; Ex-2062 ¶¶72-76, 220.)

As Petitioner's own expert admits, none of the references cited in his declaration even discusses the key point at issue for this limitation—i.e., whether the combination of trastuzumab and paclitaxel would increase severe adverse events in a patient. (Ex-2050, 342:6-19.)

### D. Petitioner's Criticisms Of Dr. Sliwkowski's Declaration Lack Merit And Do Not Cure The Deficiencies In Petitioner's Obviousness Theory.

During prosecution, Patent Owner submitted a declaration from 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-1009 at 2-4.) He also described the well-known limitations of prior art preclinical mouse models to predict success in humans. (*Id.* ¶9.)

Petitioner criticizes various aspects of that declaration. (Paper-1 at 53-62.) The Board did not address the merits of those arguments in its institution decision. And the Board need not reach those arguments because Petitioner's proposed ground fails for the reasons described above. But if the Board considers Dr.

Sliwkowski's declaration, it only confirms the patentability of the challenged claims.

***First***, Petitioner repeatedly misrepresents what Dr. Sliwkowski's declaration says to challenge opinions that he did not provide and assumptions that he did not make. For example, Petitioner criticizes Dr. Sliwkowski for supposedly assuming that paclitaxel "only works when a cell is in the G2/M phase" (Paper-1 at 53), that "all cells in a tumor have the same cancerous mutations" (*id.* at 54), and that "100% of the cancerous cells are arrested by trastuzumab at the G1 phase" (*id.* at 55). Yet Petitioner cites nothing from Dr. Sliwkowski's declaration that supports Petitioner's assertions.

Petitioner also criticizes Dr. Sliwkowski (again without citation to his declaration) for supposedly applying "an absolute predictability standard." (Paper-1 at 60.) But Dr. Sliwkowski explicitly applied a reasonable expectation of success standard. (Ex-1009 at 4 ("one of ordinary skill at the priority date of this application would not have had a reasonable expectation of success"); *id.* ¶10 ("one of ordinary skill at that time would not have had a reasonable expectation that a combination of an anti-ErbB2 antibody binding to the 4D5 epitope and a taxoid, such as paclitaxel could be successfully used to treat human cancer patients").) The Board should disregard Petitioner's arguments that mischaracterize the actual language of the declaration.

***Second***, Petitioner argues that Dr. Sliwkowski's declaration is supposedly inconsistent with preclinical mouse studies involving trastuzumab and paclitaxel. (Paper-1 at 57-58.) Dr. Sliwkowski, however, explained why those prior art preclinical results are not a reliable predictor of clinical outcomes. (Ex-1009 at 4.) Dr. Kerbel and Dr. Tannebaum agree. (Ex-2061 ¶¶54-60; Ex-2062 ¶¶68-77.) Petitioner does not address—let alone dispute—the many well-known limitations of preclinical mouse models at that time.

***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 59.) But that 2001 article is a retrospective analysis involving drugs developed before the '441 invention. (Ex-1009 at 91.) 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. (Ex-2061 ¶¶62-70; Ex-2062 ¶¶68-77.)

***Fourth***, contrary to Petitioner's assertions (Paper-1 at 59-60), the Pegram 1999 reference (Ex-1017), on which Dr. Sliwkowski is a co-author, reinforces the opinions in Dr. Sliwkowski's declaration. Consistent with Dr. Sliwkowski's description of preclinical mouse models as a "screening" tool to identify therapies to test in clinical studies (Ex-1009 at 4), Pegram 1999 simply describes the use of

preclinical studies to identify "rational combinations to test in human clinical trials" (Ex-1017 at 1).

In sum, Petitioner's arguments with respect to Dr. Sliwkowski's declaration do not support institution because they lack merit and, in any event, do not cure the deficiencies in Petitioner's obviousness theory.

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

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 14-23, 25-27 (July 28, 2016). Here, several objective indicia conclusively establish the non-obviousness of the challenged claims.

#### 1. Long-felt but unmet need

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.) 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. (*Id.*) (Ex-2062 ¶¶93, 224-225.)

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. (*Id.*) 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 ¶¶ 226-227, 238.)

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. *See 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.").

**2. Praise**

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 over Baselga-1996—when Dr. Larry Norton, a leading practitioner and co-author of Baselga-1996, 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 ¶¶236-238.)

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. *See 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].").

**3. Unexpected results**

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-1008 ¶6 ("[T]he combination is surprisingly synergistic with respect to extending TTP.").) Petitioner argues that those results would have been expected because "the combination of trastuzumab and a taxoid was synergistic in human cancer cells in xenograft models." (Paper-1 at 70.) But the preclinical results did not address the specific clinical endpoint of TTP, let alone show an improvement in that outcome. (*Supra* pp.51-52.) In any case, preclinical results at that time were known to be poor predictors of clinical outcomes. (*Supra* pp.6-8.) 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* p.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, 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 ¶¶232-235.)

Moreover, when it comes to the evidence cited in support of Petitioner's obviousness theory, Petitioner is decidedly less discriminating—touting the supposedly "proven efficacy" of taxoids in HER2-positive patients based upon Seidman-1996, which reports a wide margin of error ("95% C.I. 38.1-55.5%"). (Ex-1011 at 5.) Petitioner cannot demand statistical rigor only when it suits its purposes. Its inconsistency undermines the affirmative evidence cited in the Petition and confirms the non-obviousness of the challenged claims.

In any event, 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 Abstract 53 said did not increase toxicity, but in fact did increase toxicity in the Phase-III study disclosed in the '441 patent. (Ex-1019 at 4; *see also* Ex-1008 ¶¶4-5; 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., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011). (Ex-2062 ¶¶232-235.)

Petitioner argues that the safety difference between combinations with taxoids versus anthracyclines is "irrelevant" because that toxicity difference supposedly relates to "some other, unclaimed combination." (Paper-1 at 73.) But

the combination of an anti-ErbB2 antibody with an anthracycline derivative is not just "some other, unclaimed 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. Petitioner's related argument (Paper-1 at 73-74) that a comparison to combinations with anthracyclines is inappropriate because they are not "the closest prior art" is nonsensical. Combinations with anthracyclines are an appropriate benchmark for claims that expressly require "the absence of an anthracycline derivative." (Ex-2062 ¶234.)

**4. Commercial success**

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's conclusory assertion that there is no nexus (Paper-1 at 74) is insufficient to rebut that presumption given the hundreds of millions of dollars in sales during the period when the claimed method of treatment was the only approved first-line use of the drug.

### 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 confirm the patentability of the challenged claims.

Respectfully submitted,

Date: December 21, 2017

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## CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Response, contains 13,842 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 21, 2017

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David L. Cavanaugh
Registration No. 36,476

## CERTIFICATE OF SERVICE

I hereby certify that, on December 21, 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 2006, 2050-2053, 2055, 2061-2067, 2069-2075, 2077-2083, 2085-2095, 2097-2099, 2101-2104, 2106-2113, 2115-2119, 2122-2123, 2125-2127

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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**IPR2017-01121**
**Patent Owner's Exhibit List**

| Patent Owner's Exhibit Number | Exhibit Name |
|---|---|
| 2001 | Genentech, Inc. Original H0648g Protocol<br>PROTECTIVE ORDER MATERIAL |
| 2002 | Genentech, Inc. PDC Minutes<br>PROTECTIVE ORDER MATERIAL |
| 2003 | Genentech, Inc. PDC Minutes<br>PROTECTIVE ORDER MATERIAL |
| 2004 | Genentech, Inc. PDC Minutes<br>PROTECTIVE ORDER MATERIAL |
| 2005 | Genentech, Inc. PDC Presentation<br>PROTECTIVE ORDER MATERIAL |
| 2006 | Genentech, Inc. PDC Presentation<br>PROTECTIVE ORDER MATERIAL |
| 2007 | Genentech, Inc. Amended H0648g Protocol<br>PROTECTIVE ORDER MATERIAL |
| 2008 | Genentech, Inc. H0648g Final Report<br>PROTECTIVE ORDER MATERIAL |
| 2009 | U.S. Provisional Application 60/069346 |
| 2010 | Dennis J. Slamon, et al., *Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/neu Oncogene*, 235 Science 177 (1987) |
| 2011 | Dennis Slamon et al., *Studies of the HER/2-neu proto-oncogene in human breast and ovarian cancer*, 224 Science 707-714, 707 (1989) |
| 2012 | 1998 Herceptin Label |

| **Patent Owner's Exhibit Number** | **Exhibit Name** |
|---|---|
| 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) |
| 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) |

| **Patent Owner's Exhibit Number** | **Exhibit Name** |
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