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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC., and
SAMSUNG BIOEPIS CO., LTD.[1],
Petitioners,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00737
Patent No. 7,892,549

PATENT OWNER'S RESPONSE

[1] Case IPR2017-01960 has been joined with this proceeding.

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Genentech, Inc. ("Patent Owner") submits this Response to the Petitions filed by Hospira, Inc. (IPR2017-00737) and Samsung Bioepis Co., Ltd. (originally IPR2017-01960) (collectively, "Petitioners").[2] 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. 7,892,549, 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

[2] The Board previously terminated IPR2017-01960 and joined it to the instant proceeding, IPR2017-00737. (IPR2017-01960, Paper-11 at 7-8.) In its motion for joinder, Petitioner Samsung Bioepis argued, and the Board agreed, that Samsung's petition was "essentially a copy of" and "substantially identical to" Hospira's petition; that Samsung's petition is "based on the same prior art analysis, the same expert testimony, and the same arguments that Hospira presented" and the petitions "do not differ[] in any substantive way"; and that Samsung is merely participating in an "understudy" capacity. (IPR2017-01960, Paper-1 at 1-4; *id.*, Paper-11 at 3-6.) Thus, while this response cites to Hospira's petition and evidence, Patent Owner's argument and evidence apply equally to Samsung's petition.

using an "anti-ErbB2" antibody, which targets a cellular receptor associated with HER2-positive cancer, in combination with a chemotherapy called a "taxoid," along with "further growth inhibitory agent" (claims 1, 16) or "a further therapeutic agent" (claim 5).

The '549 patent is a continuation of U.S. Patent No. 7,846,441, which Petitioner Hospira has separately challenged in IPR2017-00731, and Petitioner Samsung has separately challenged in IPR2018-00192. The two patents share the same specification, and the '441 claims relate to methods of treatment for HER2-positive cancer that combine an anti-ErbB2 antibody and a taxoid to achieve the clinical benefit of "extend[ing] the time to disease progression … without increase in overall severe adverse events." While there are various differences, a distinction between the '549 and '441 claims is that all of the '549 claims recite the third agent (i.e., "further growth inhibitory agent" or "further therapeutic agent") in addition to the combination of an anti-ErbB2 antibody and a taxoid claimed in the '441 patent. The '549 patent has been terminally disclaimed over the '441 patent.

Prior to these patents, 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 and '549 patents disclose 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, this claimed combination therapy significantly extends the time to disease progression ("TTP") as compared with patients receiving taxoid therapy alone.

Because the '549 and '441 patents are related, some of the art and arguments that Petitioners present in this petition overlap with Petitioner Hospira's challenge to the '441 patent in IPR2017-00731. The challenge to the '441 patent fails for the reasons described in the response that Patent Owner has submitted in IPR2017-00731.[3] As explained below, Petitioners' arguments fail with respect to the '549 patent for similar reasons.

First, the Board's institution decision rests on an incorrect claim construction of the terms "in an amount effective to extend the time to disease progression in said human patient," and "an effective amount." The Board

[3] Petitioner Hospira filed a second petition challenging the '549 patent in IPR2017-00739, which was denied.

interpreted these terms as measured relative to an untreated patient, but that is inconsistent with the '549 specification as understood by a person of ordinary skill in the art ("POSA"). Instead, the appropriate comparison is to a patient treated with a taxoid alone, which is the only comparison described in the patent specification that is consistent with the language of the claims. The specification reports nothing about untreated patients.

The Board based its construction on a single statement in the file history, but that statement, which cites to the example in the specification that compares patients treated with the claimed combination to patients treated ***with a taxoid (paclitaxel)*** alone, does not change how a POSA would understand the term. In fact, Petitioners' 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 agrees. 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. None of the references relied upon by Petitioners provides any results of this combination treatment in humans. The prior art preclinical mouse study discussed in the Baselga references 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 discussed in the Baselga references had significant limitations, thus minimizing the predictive value of the reported results.

Second, for Grounds 4-6, Petitioners rely on the Baselga '96 and Baselga '94 references for supposedly teaching "administering a combination" of an anti-ErbB2 antibody and a taxoid to a "human patient." The only disclosure of the combination of an anti-ErbB2 antibody and a taxoid in these references is the preclinical study reported by Baselga '94. However, there were well-known limitations with respect to xenograft mouse models of the type used in Baselga '94, which severely restricted their ability to predict safety and efficacy in human patients. In fact, before the '549 invention, even the persons of ***extra***ordinary skill involved in the development of Herceptin® (the trade name of Patent Owner's anti-ErbB2 antibody) did not view the Baselga '94 preclinical results as motivating a combination of an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative. To the contrary, the only Phase-II trials involved treatment with either the antibody alone or in combination with a different chemotherapeutic agent, cisplatin. And when Phase-III trials began, the only drug

combination under evaluation was an anti-ErbB2 antibody combined with an anthracycline.

That development history also reinforces what was known at the time about taxoids, which were a relatively-new class of chemotherapy that had a history of severe side effects and had only been approved as a second-line therapy for breast cancer. The first time that anyone ever treated a human patient with the claimed combination of an anti-ErbB2 antibody and a taxoid was when '549 inventor Dr. Susan Hellmann recommended the combination to address enrollment problems in an ongoing Phase-III study. Only in hindsight can Petitioners 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.

Third, all of the instituted grounds rely on Gelmon '96 for its disclosure of treating breast-cancer patients with a combination of cisplatin and paclitaxel. However, Gelmon '96 does not address HER2-positive breast-cancer patients, thus rendering its findings inapplicable to the challenged claims. Moreover, numerous other prior art references—along with Gelmon '96 itself—discredit the findings presented in Gelmon '96. Thus, the full record establishes that a POSA would not look to Gelmon '96 for any teachings for treating HER2-positive patients.

Finally, Petitioners assert that it would have been obvious to try the claimed combinations. But Petitioners have not explained how such combinations could

predictably achieve the claimed result of extending TTP, a necessary prerequisite to support such a conclusion.

The Board should reject Petitioners' 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 ¶¶34-40; 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. Many drugs that show activity in xenografts fail in humans, and retrospective studies have shown that some drugs that have been successfully used to treat

humans have not shown activity in xenografts. (Ex-2061 ¶¶54-60; Ex-2062 ¶¶67-71.)

By 1997, it was recognized that efficacy in mouse models was not reliably predictive of anti-cancer drug performance in humans.[4] (*See, e.g.*, Ex-2023 at 79 ("very low" likelihood of predicting response in humans); Ex-2051[5] 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

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

[5] During deposition, Petitioners' expert criticized the Gura article (Ex-2051) as "not something a person with experience in the art would rely on." (Ex-2050, 173:7-174:16.) However, as Dr. Tannenbaum explains, the Gura article appears in a well-regarded journal (Science), the particular issue had an entire section devoted to cancer research and treatment, the article was based on interviews with numerous oncologists, and clinical oncologists "would certainly read" such an article directed to their area of research and practice. (Ex-2062 ¶77.)

discovery for cancer is that the model systems are not predictive at all."); *id.* ("[D]rugs tested in the xenografts appeared effective but worked poorly in humans."); *cf.* Ex-2075 at 1633 ("[T]here is a commonly held belief amongst cancer researchers that transplantable tumors in rodents are sensitive to drug therapy, are easy to cure, and therefore are not predictive of responses in humans.").) (Ex-2061 ¶¶54-60; Ex-2062 ¶¶70-71.)

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; Ex-2062 ¶¶72-73.)

Third, mouse studies are short-term and generally measure only the clinical endpoint of response rate—i.e., the ability of therapy to shrink tumors—not effect on TTP. Response rate and TTP are different endpoints—e.g., a therapy may demonstrate a response rate by initially shrinking tumors, but fail to eradicate the most-aggressive cancer cells that cause the cancer to progress quickly. As Dr. Tannenbaum notes, for solid tumors such as breast cancer, it was well known that therapies may improve response rates but not affect TTP. (Ex-2062 ¶87; Ex-2067 at 353.) This fundamental difference is highlighted by the fact that Baselga '94's mouse studies occurred over a period of ***five weeks*** (Ex-1005), whereas the TTP for Herceptin® plus Taxol® in humans reported in the '549 patent was ***7.1 months*** (Ex-1001, 30:6). (Ex-2050 [Lipton], 103:10-13 ("This was just a five-week study. So time to disease progression was not assessed.").) (Ex-2061 ¶¶82-83; Ex-2062 ¶149.)

Fourth, mouse results are limited by the cell line used. Because of the complexities of most cancers, scientists knew by 1997 that, to obtain accurate results, they had to conduct preclinical studies using multiple cell lines. (Ex-2052 at 261 ("It is unlikely that any one tumor model will adequately represent the major biological characteristics of a particular malignancy. Thus, the use of a

series of tumors (where appropriate/available) may be required to determine the sensitivity of a particular neoplastic disease to either a single or a combination chemotherapy regimen."). (Ex-2061 ¶¶65-69; Ex-2062 ¶¶73-75.)

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-BR3 cell line had 31 copies on average per cell, and the MDA-453 cell line had 11 copies on average per cell. (Ex-2064 at 5402, Table 1.) BT-474—by far the most overexpressing of these cell lines—was the cell line used in the Baselga '94 mouse study. This variation in cell lines is similar to the heterogeneity of human chromosomes. (Ex-2064 at 5400; Ex-2065 at 262; Ex-2063 at 1457.) (Ex-2061 ¶¶26, 42, 44; Ex-2062 ¶74.)

Preclinical mouse results using a single cell line, therefore, were akin to conducting a clinical trial with a single patient and were known not to be a reliable indicator of success in a population of human patients. (Ex-2061 ¶63; Ex-2062 ¶74.)

Fifth, mouse models based on subcutaneous implantation[6] of tumors were known to be even less reliable than models that implanted the cells in the same type of tissue as the target disease. (Ex-2053 at 79 ("While the [subcutaneous] site is convenient, it is likely that it is not the optimal site for all xenografts."). Studies published in the 1990s showed that transplanted tumors often responded to drugs, including chemotherapy agents, when grown "ectopically" as subcutaneous tumors, but did not respond (or responded in a diminished manner) when transplanted and grown "orthotopically" (i.e., in the organ from which the cancer under study was derived). Thus, it was known that to obtain more-reliable results for breast cancer, the tumor must be implanted in breast tissue. (Ex-2053 at 79 ("The most appropriate site for breast tumor xenografts is the mammary fat pad (orthotopic site), a site we use routinely.").) (Ex-2061 ¶¶77-82.)

b) Clinical trials

Therapies with favorable results in preclinical models might advance to clinical studies conducted in humans. Those clinical studies occur in stages, beginning with initial small-scale studies (i.e., Phase I or Phase II), followed by

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

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. (Ex-2050 [Lipton], 57:3-9 ("a significant number of potential drugs fail during the clinical trial process").) In the 1990s, only 5% of cancer drugs that advanced to clinical trials resulted in an approved product. (Ex-2021 at 711-12.) Even for drugs that advanced to late-stage, Phase-III clinical trials, nearly 60% ultimately failed to result in an approved drug. (*Id.*; Ex-2050, 63:5-19 (Dr. Lipton testifying he has "no reason … to doubt" this failure rate); *id.*, 57:17-58:2 (Dr. Lipton admitting "many" chemotherapeutic agents "fail in [clinical] development" for breast cancer).) Thus, the fact that a therapy had progressed from preclinical studies through early-stage clinical trials was no indication that it would have a clinical benefit when subjected to more rigorous late-stage studies. Indeed, the myriad failures during clinical development reinforce the limitations of preclinical studies at that time to predict clinical efficacy in humans. (Ex-2021 at 712-13 ("The lack of efficacy might be contributing more significantly to therapeutic areas in which animal models of efficacy are ***notoriously unpredictive***,

such as CNS and ***oncology***, both of which have relatively higher failure rates in Phase II and III trials.").)[7] (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.)

[7] All emphases in quotations herein are added unless otherwise noted.

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

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

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

a) Anthracyclines

In the 1990s, anthracyclines were "among the most widely used antineoplastic [*i.e.*, anticancer] agents in current clinical practice." (Ex-2030 at 409.) Doxorubicin is an example of an anthracycline, and it was known to be "especially active" against breast cancer. (*Id.*) Doxorubicin had "no known antagonistic interactions with any of the other commonly used anticancer agents," and it was "active over a wide range of doses and in a variety of administration schedules," which made it "very useful in the design of drug combinations" with other cancer therapies. (*Id.*) As a result, treatments containing anthracyclines were the "standard therapy for cancers of the breast" in the 1990s. (*Id.*; *see also* Ex-

2050 [Lipton], 50:1-12 (anthracycline "Adriamycin was commonly used in breast cancer").) (Ex-2062 ¶¶43-45,52.)

As Petitioners note, cardiotoxicity had been observed in some instances when anthracyclines were administered for extended periods resulting in high cumulative doses. (Paper-1 at 7-8.) 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-19 at 21 ("We find instructive that in one arm of the clinical trial

reported by Baselga '97, patients were treated with anthracyclines in combination with anti-ErbB2 antibodies. … We find this disclosure at odds with Petitioner's contention that researchers would have avoided combinations with anthracyclines due to potential cardiotoxicity.").)

b) Taxoids

Unlike anthracyclines, taxoids were a relatively-new type of chemotherapy in the 1990s, which oncologists were slow to adopt for treating breast cancer. Taxoids were associated with serious hypersensitivity reactions, "varying from flushing, dyspnea and bronchospasm, and rashes to severe hypotension and asystole, resulting in death." (Ex-2028 at 1265.) Taxoids were also associated with neuropathy (i.e., weakness, numbness, and pain in the hands and feet) and cardiotoxicity. (Ex-2062 ¶60; Ex-2105 at 7; Ex-2026 at 1704, 1709 (taxoids cause "[a] diverse spectrum of cardiac disturbances").) The prior art thus warned oncologists "to maintain a high degree of caution" with those drugs. (Ex-2026 at 1704 (development of taxoids "has proceeded slowly due to serious hypersensitivity reactions").) The prior art also reported that 30-40% of breast cancer patients did not respond to taxoids. (Ex-2029 at 1359; *see also id.* at 1362 ("breast cancers that overexpress p185 [*i.e.*, HER2] ***will not respond well to Taxol***.").) (Ex-2062 ¶¶53-60.)

The drug paclitaxel (Taxol®) is an example of a taxoid chemotherapy. The FDA approved paclitaxel for ovarian cancer in 1992 and for breast cancer in 1994. Even then, paclitaxel was approved to treat breast cancer only ***after*** other treatments failed, i.e., for "second-line" use. (Ex-2105 at 6.) As a second-line treatment, a POSA would have understood Taxol® as generally having less efficacy and/or more significant side effects than first-line therapies. In fact, the approved Taxol® label at the time of the '549 invention explicitly advised that patients should have been treated with an anthracycline ***first*** before trying paclitaxel. (*Id.*) (Ex-2062 ¶¶53-56.)

c) Platinum-based drugs

It was discovered in the 1960s that platinum-containing compounds can inhibit cellular division by binding to DNA. (Ex-2038 at 357.) Those compounds include drugs like cisplatin and carboplatin, which contain different ligands bound to a platinum core. (*Id.* at 359.) (Ex-2062 ¶62.)

By the 1990s, platinum-based drugs were used to cure testicular cancer and had also produced "high response rates in patients with small cell carcinoma of the lung, bladder cancer, and ovarian cancer." (Ex-2038 at 357.) However, prior to the '549 invention, platinum-based drugs were not "used widely in breast cancer." (Ex-1025 at 9.) (Ex-2062 ¶62.)

Petitioners assert that platinum-based drugs had been used to treat breast cancer since "the 1970s." (Paper-1 at 15 (citing Ex-1037).) But that is not what the cited reference states. Exhibit 1037 describes treating ***testicular*** cancer with cisplatin in the 1970s, not breast cancer. (Ex-1037 at 14.) (Ex-2062 ¶62.)

3. Before the '549 invention, no antibody had been approved for the treatment of solid tumors.

Antibodies are proteins that bind to molecular targets, called "antigens." Antibodies that target specific antigens can be created in a laboratory. (Ex-1001, 8:44-9:3.) However, the body's immune system may attack such specially-designed antibodies, preventing them from having a therapeutic effect. (Ex-2031 at 655.) As of 1996, "much additional study" was required to determine whether there were ways to avoid triggering that immunogenic response. (*Id.* at 683.) Moreover, antibodies are large molecules that have difficulty penetrating tissue—a "significant obstacle[] to the effective use of mAbs for solid tumors," such as breast cancer. (*Id.*) (Ex-2062 ¶¶95-99.)

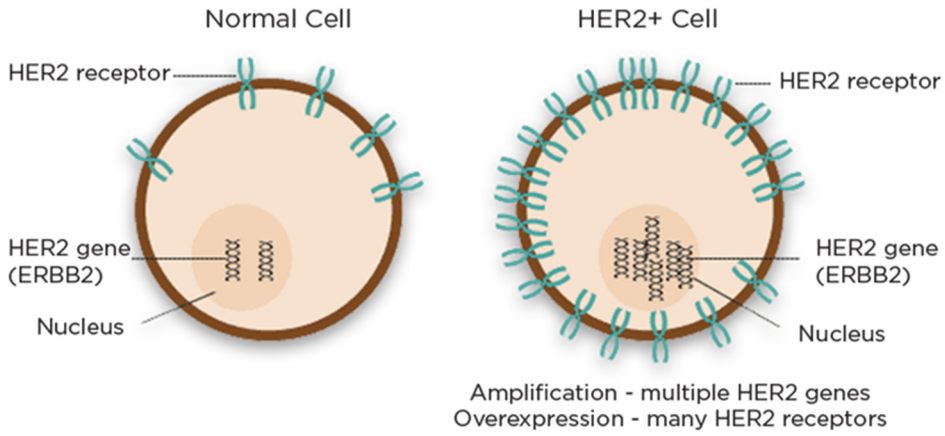
By the early 1990s, numerous antibodies had been tested in patients with different cancers (including breast cancer), but consistent with the challenges just described, these antibodies showed "no hint of a consistent therapeutic efficacy." (Ex-2025 at 649; *id.*, Table 2 (identifying failed antibody 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 '549 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 '549 patent. (Ex-2031 at 683.) (Ex-2062 ¶¶100-101.)

B. HER2-Positive Breast Cancer

The '549 patent involves the treatment of "HER2-positive" cancers, which have a genetic mutation that causes them to overexpress human epidermal growth factor 2 ("HER2"), also known as human ErbB2. Out of the hundreds of thousands of women each year who are diagnosed with breast cancer, roughly 25-30% are HER2-positive. (Ex-1001, 1:23-29; Ex-2050 [Lipton], 17:20-22.) (Ex-2062 ¶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. In the 1990s, HER2-positive status was "associated with poor prognosis," including a high rate of tumor recurrence and spreading to other areas of the body. (Ex-2022 at 1420; Ex-1028 at 6-8; Ex-2050, 45:4-7 (Dr. Lipton admitting that before Herceptin® HER2-positive status "used to have the worst prognosis in women with breast cancer").) HER2-positive patients had "a shorter time to relapse as well as a shorter overall survival." (Ex-1029 at 4; Ex-1028 at 7.) The life expectancy of HER2-positive patients in 1996 "was only 18 months post-diagnosis." (Ex-2017 at 138; *see also*

Ex-2018 at 887 ("[T]he reality is that breast cancer patients who overproduce HER2 can now expect to live some 10 to 12 months after metastasis begins, a horribly rapid progression compared to six or seven years for HER2-normal patients.").) (Ex-2062 ¶¶93-94.)

Before the '441 and '549 inventions, 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 '549 PATENT

A. The Invention

1. Petitioners' obviousness theory is inconsistent with the development history for rhuMAb HER2.

In the early 1990s, Genentech created an anti-ErbB2 antibody called "rhuMAb HER2," which it studied as a potential new treatment for HER2-positive cancers. Petitioners assert that there was an ongoing clinical trial involving the combination of an anti-ErbB2 antibody and a taxoid as of 1994 and that "the same clinical trial [was] underway two and three years later," as supposedly described in the Baselga references (Exs-1005-07). (Paper-1 at 64; *see also id.* at 25, 45, 63.) But that is not what the prior art discloses, and not what actually happened.

Petitioners have 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 rhuMAb HER2 alone (Ex-1005) or in combination with cisplatin (Ex-1013). And when Genentech began Phase-III clinical trials in 1995, the ***only*** combination therapy initially studied was with anthracyclines, not taxoids. (Ex-2001[8] at 16, §5.2.2; Ex-2050, 86:15-87:12 (Dr. Lipton admitting he was not aware of any Phase-I or Phase-II studies of Herceptin® plus paclitaxel, and that the first Phase-III protocol was Herceptin® plus an anthracycline).) (Ex-2062 ¶¶107-110.)

That development history reinforces what was known at the time about treating HER2-positive breast cancer. Taxol®—a ***second-line*** therapy (Ex-1066 at 10) that the prior art warned HER2-positive patients "will not respond well to" (Ex-2029 at 1362)—was not used in combination with rhuMAb HER2 to treat patients. On the other hand, combinations with anthracyclines—which at the time showed no hint of increased toxicity with anti-ErbB2 antibodies—and other

[8] 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.)

chemotherapies (e.g., cisplatin) were the preferred candidates for clinical development. (Ex-2062 ¶117.)

2. The first clinical study treating humans with a combination containing an anti-ErbB2 antibody and a taxoid occurred after Phase-III trials for rhuMAb HER2 began.

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.[9] (Ex-2002 at 2; Ex-2003 at 2; Ex-2004 at 3.) '549 inventor Dr. Susan Hellmann had recently joined Genentech after working at Bristol-Myers Squibb on the drug paclitaxel. (Ex-1019-5 at 338, 343.) 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

[9] 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; Ex-2111 at 73.)

antibody and a taxoid as a possible way to improve enrollment in the study. (Ex-2062 ¶¶115-117, 201.)

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-2062 ¶¶80-81, 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-2002 at 3; Ex-2003 at 1-2; Ex-2004 at 2.) Based on her unique expertise regarding paclitaxel, Dr. Hellmann believed that taxoids were "likely to be important for breast cancer therapy in the next decade," which is why she advocated that Genentech take the risk of pursuing a combination containing an anti-ErbB2 antibody and a taxoid. (Ex-2002 at 3.) (Ex-2062 ¶201.)

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").)

3. The '549 specification is the first disclosure that combinations containing an anti-ErbB2 antibody and a taxoid extend the time to disease progression as compared to patients treated with paclitaxel alone.

Following the amendment to the Phase-III protocol, the study reached its primary endpoint in late 1997. (Ex-2008 at 51-58, 104-109.) The study data showed that combinations containing 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.) (Ex-2062 ¶118.)

By contrast, the combination of an anti-ErbB2 antibody with an anthracycline resulted in cardiotoxicity in a significant number of patients. (Ex-2008 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-1020, 38:26-43:26.) That was the first disclosure of any clinical

results for patients receiving a combination containing an anti-ErbB2 antibody and a taxoid. (Ex-2062 ¶¶118-119.)

The '549 patent describes "the present invention" as "the combined administration of an anti-ErbB2 antibody and a chemotherapeutic agent other than an anthracycline derivative" (e.g., a taxoid). (Ex-1001, 25:1-3.) The '549 patent identifies other agents that may be "co-administered" as part of the invention, including "a preferred embodiment" that includes a further "growth inhibitory agent." (Ex-1001, 25:20-34.) The '549 patent defines a "growth inhibitory agent" as "a compound or composition which inhibits growth of a cell, especially an ErbB2-overexpressing cancer cell either in vitro or in vivo," and identifies representative examples of such growth inhibitory agents. (Ex-1001, 11:20-40.)

B. Challenged Claims

Petitioners have challenged every claim of the '549 patent. Those claims reflect a novel method of treatment for cancer that overexpresses ErbB2 (e.g., HER2-positive breast cancer), which comprises (i) "administering a combination" of an anti-ErbB2 antibody, a taxoid, and "a further growth inhibitory agent" (claims 1, 16) or "a further therapeutic agent" (claim 5); (ii) "to the human patient"; (iii) "in an amount effective to extend the time to disease progression in said human patient" (claims 1, 16) or in "an effective amount" (claim 5). Claims

16 and 17 further require "the absence of an anthracycline derivative" from the claimed combination therapy.

C. Prosecution History

The '549 patent issued from Application No. 10/356,824 filed on February 3, 2003, which is a continuation of U.S. Patent Application No. 09/208,649, filed on December 10, 1998, which later issued as the '441 patent. In turn, the '649 application claims priority to Provisional Application No. 60/069,346, filed on December 12, 1997. (Ex-1001, cover.)

The Patent Office considered the references underlying Petitioners' proposed obviousness grounds during prosecution.[10] Petitioners assert that the '549 patent repeats the disclosure of the Baselga references "without attribution." (Paper-1 at 8-9.) But the '549 patent does not conceal anything about the Baselga references. Indeed, it cites and discusses each of the Baselga references. (Ex-1001, 3:36-61.) Moreover, Petitioners' suggestion (Paper-1 at 9) that the

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

"experimental data" in the '549 patent was somehow lifted from the Baselga references is false. The Baselga references disclose ***no*** clinical results for the combination of an anti-ErbB2 antibody and a taxoid. Clinical results for that combination are first described in the '549 specification. (Ex-1001, 29:11-30:25.) (Ex-2062 ¶112.)

In October 2009, Genentech submitted a declaration from Dr. Mark Sliwkowski in response to obviousness rejections over, among other things, Baselga '96 and Baselga '94. (Ex-1019-6 at 341-45.) 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-1019-6 at 343.) Dr. Sliwkowski also explained that preclinical results would not have provided a reasonable expectation of success as to the clinical results for the combination of rhuMAb HER2 and a taxoid; indeed, xenograft models at that time were poor predictors of clinical results for breast cancer. (*Id.* at 344-45.)

After Patent Owner provided a terminal disclaimer over the parent application (which issued as the '441 patent) (Ex-1019-7 at 64-65), the examiner allowed the claims on October 8, 2010 (*id.* at 93).

D. Foreign Counterparts

As Petitioners note (Paper-1 at 9-10), the European counterpart to the '549 patent was found obvious over Baselga '97 in the United Kingdom and obvious over Baselga '97 or Baselga '96 before the European Patent Office. However, those foreign proceedings applying foreign law to different claims have little relevance here. *See Smith & Nephew v. ConvaTec Techs. Inc*., IPR2013-00097, Paper 76 at 3 (Feb. 24, 2014) (European Patent Office decision "does not involve the U.S. patents at issue in these proceedings, is not based on U.S. law, and is thus of limited relevance to the instant proceedings"); *see also Medtronic, Inc. v. Daig Corp.*, 789 F.2d 903, 907-08 (Fed. Cir. 1986) (rejecting challenger's position that the court should adopt a decision regarding the validity of a foreign counterpart patent as "specious").

IV. ASSERTED REFERENCES

A. Baselga '94

Baselga '94 is a one-paragraph abstract published in March 1994 describing the results of preclinical studies using mouse models to assess the antitumor activity of rhuMAb HER2 combined with either an anthracycline derivative (doxorubicin) or a taxoid (paclitaxel). (Ex-1006.) An abstract such as Baselga '94 is not peer-reviewed for content, and researchers and clinicians expect that the

authors will expand their work and provide a more detailed analysis in a peer-reviewed journal. (Ex-2062 ¶146.)

The studies in Baselga '94 measured the response rate—i.e., the initial tumor-inhibition response—in mice over a period of five weeks. They did not assess the effect (if any) on TTP, and thus they did not assess whether TTP was extended. (Ex-1006 at 4; Ex-2050 [Lipton], 103:10-13 ("This was just a five-week study. So time to disease progression was not assessed.").) Both drug combinations improved the antitumor response as compared with rhuMAb HER2 or chemotherapy alone, and rhuMAb HER2 "did not increase the toxicity of paclitaxel or doxorubicin in animals as determined by animal survival and weight loss." (*Id.*) However, the Phase-III trial showed that, in fact, the combination of rhuMAB HER2 and doxorubicin significantly increased the incidence of cardiotoxicity in human patients. (Ex-1001, 30:13-16.) (Ex-2062 ¶¶146-150.)

Baselga '94 notes that "[c]linical studies are underway." (Ex-1006 at 4.) But that is just a generic reference to clinical trials of rhuMAb HER2. It does not refer to studies involving the ***combination*** of rhuMAb HER2 and a taxoid, as Petitioners assert (Paper-1 at 24-25). Indeed, Baselga '94 could not have been referring to ongoing studies of the combination because there was no such study underway at the time. Indeed, Baselga '94 could not have been referring to ongoing studies of the combination because there was no such study underway at

the time. (Ex-2050, 153:6-11 (Dr. Lipton admitting he was not aware of "any trial that had human patients with Herceptin and Taxol prior to '97, prior to the patent").) (Ex-2062 ¶¶151-152.)

B. Baselga '96

Baselga '96 is an article published in March 1996. It describes the results of a Phase-II clinical study in which patients received rhuMAb HER2 ***alone***, not combined with a taxoid (or any other chemotherapy or agent). (Ex-1004 at 10 ("Chemotherapy … was not permitted.").)[11] (Ex-2062 ¶153.)

The clinical endpoint evaluated in the trial was response rate. (Ex-1004 at 10, 12, 13.) Although Baselga '96 measured "[t]ime to tumor progression" for individual patients, all patients in the study received rhuMAb HER2. (*Id.* at 10.) The study thus had no control group against which to evaluate whether rhuMAb HER2 (or any combination involving it) ***extended*** TTP. (Ex-2050 [Lipton], 156:4-21.) (Ex-2062 ¶¶154-155.)

[11] The study reported in Baselga '96 required patients to stop other treatments three weeks prior to entering the study, thus ensuring that any tumor response was due to the therapy being tested rather than the continuing effects of any prior treatment. (Ex. 1005 at 10.) (Ex-2062 ¶181.)

According to Baselga '96, the vast majority of patients receiving rhuMAb HER2 did not show a therapeutic response. In fact, only 5 out of the 43 assessable patients (11.6%) had complete or partial responses to treatment with rhuMAb HER2. (Ex. 1005 at 12.) (Ex-2062 ¶156.)

Baselga '96 acknowledged that the mechanism of potential antitumor activity for rhuMAb HER2 was not understood and proposed several possible explanations for the observed clinical results. (*Id.* at 14-15.) 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.* at 15 ("[C]ontinued research with this agent and other HER2-targeted treatment strategies appears warranted.").) (Ex-2062 ¶¶158-161.)

Baselga '96, citing Baselga '94, identified several chemotherapeutic agents (cisplatin, doxorubicin, and paclitaxel) that had been combined with rhuMAb HER2 in preclinical mouse studies and noted that "clinical trials of such combination therapy are currently in progress." (*Id.*) However, Baselga '96 did not state that the combination of an anti-ErbB2 antibody and a taxoid in particular was being studied in humans. Nor could it have been referring to that particular combination therapy, since there was no clinical study involving that combination at the time that Baselga '96 was submitted (August 8, 1995) or accepted (October 10, 1995). (Ex-2062 ¶161.)

C. Baselga '97

Baselga '97 is a review paper published in March 1997, describing a number of studies with rhuMAB HER2, including those described above in Baselga '94 and Baselga '96. (Ex-2062 ¶162.)

Baselga '97 also describes the design of the Phase-III study for rhuMAb HER2 after Genentech amended the protocol to allow patients to be treated with the combination of rhuMAb HER2 and paclitaxel. According to Baselga '97, the Phase-III study includes two arms—an active arm testing rhuMAb HER2 plus a cytotoxic chemotherapy, and a control arm testing cytotoxic chemotherapy alone. (Ex-1007 at 10.) Baselga '97 describes that the chemotherapy for these two arms is either paclitaxel if the patient has received prior anthracycline treatment, or cyclophosphamide with an anthracycline derivative (doxorubicin or epirubicin) if patient had not received prior anthracycline treatment. (*Id*.) (Ex-2062 ¶164.)

Baselga '97 stated that the Phase-III study was "ongoing" and provided no indication as to whether any of the drug combinations under evaluation would provide a clinical benefit (or even whether any patients had completed a course of therapy). In fact, the article acknowledged that it was uncertain whether those drug combinations would provide a clinical benefit. (Ex-1007 at 11 ("***If*** the results of these studies are positive ….").) (Ex-2062 ¶165.)

D. Gelmon '96

Gelmon '96 is an article published in April 1996 describing a Phase-I/II study in which metastatic breast cancer patients were administered a combination of paclitaxel and cisplatin. (Ex-1025 at 9.) Gelmon '96 does not discuss treating HER2-positive patients in particular, or treating patients with an anti-ErbB2 antibody or combinations involving an anti-ErbB2 antibody. (Ex-2062 ¶¶166-167.)

The purpose of the study was to "determine the maximum-tolerated dose of escalating doses of paclitaxel … administered biweekly with a fixed dose of cisplatin, to assess the toxicity, and to evaluate the activity of this combination in a phase I/II trial in metastatic breast cancer." (Ex-1025 at 9.) The clinical endpoint measured in the study was response rate. (*Id.* at 13.) Although the study also measured the TTP for individual patients, Gelmon '96 did not measure any ***extension*** in TTP because it contained no control arm against which to measure that endpoint. (*Id*.) (Ex-2062 ¶¶166-168.)

Although it obtained encouraging results for the 29 patients in the study, Gelmon '96 acknowledged that "further confirmatory trials of this combination and other novel schedules of paclitaxel are necessary to further our understanding of how to best use this novel agent." (Ex-1025 at 14.) Indeed, Gelmon '96 explained that its results differed from an NYU study on this same combination,

which reported a much lower response rate and "significant neuropathy." (*Id*.) This NYU study published its results in later 1996, finding that "the cumulative neurotoxicity was significant and dose-limiting in the majority of patients." (Ex-2068 at Abstract, 1997.) (Ex-2062 ¶¶169-171.)

Additional prior art confirms that the combination of paclitaxel and cisplatin resulted in significant toxicities. For example, a May 1997 publication reported the results of a multi-institutional Phase-II trial "to validate the high objective response rate observed with biweekly paclitaxel/cisplatin [in Gelmon '96]." (Ex-2120 at 1880.) The trial was terminated after "[s]evere and/or life-threatening toxicity occurred in 50% and 38% [of assessible patients], respectively, and consisted primarily of granulocytopenia, anemia, and neuropathy." (*Id.*) In addition, a March 1996 abstract reported a study that was likewise unable to replicate the results of the study reported in Gelmon '96. (Ex-2121.) Based on these studies, it was well known in the art that "serious toxicity concerns, particularly neurotoxicity, preclude [the] general use" of paclitaxel with cisplatin. (Ex-2124 at 380.) (Ex-2062 ¶172.)

E. Drebin '88

Drebin '88 is an article published in March 1988 reporting on the antitumor effects of various anti-ErbB2 antibodies in mouse models. (Ex-1010.) Drebin '88 does not describe any humanized antibodies, does not suggest administering these

or other antibodies to human patients (much less in combination with a taxoid or other chemotherapies). (Ex-2062 ¶¶173-174.)

F. Presta '97

Presta '97 is an article published in October 1997 reporting on the humanization of the anti-VEGF antibody. (Ex-1012 at 8.) Presta '97 does not discuss the possibility of combining this humanized anti-VEGF antibody with an anti-ErbB2 antibody. Presta '97 also does not discuss combinations of an anti-ErbB2 antibody with a taxoid, or any other agent. (Ex-2062 ¶¶175-176.)

V. PERSON OF ORDINARY SKILL

For purposes of this proceeding, Patent Owner does not dispute Petitioners' proposed definition of a POSA. (*See* Paper-1 at 6.)

VI. CLAIM CONSTRUCTION

A. "Administering A Combination"

For purposes of this proceeding, Patent Owner requests construction of "administering a combination" in all claims to mean that the drugs are administered as part of the same treatment regimen. In its institution decision, the Board found Patent Owner's position to be "reasoned" and adopted Patent Owner's proposed construction. (Paper-19 at 10.)

The Board gives a patent claim "its broadest reasonable construction in light of the specification of the patent in which it appears." *Cuozzo Speed Techs., LLC*

v. Lee, 136 S. Ct. 2131, 2142 (2016); 37 C.F.R. § 42.100(b). Here, the broadest reasonable interpretation of "administering a combination" requires a single treatment regimen in which the patient receives all drugs that are part of the claimed combination. By contrast, if a patient receives an anti-ErbB2 antibody and a taxoid as part of different treatment regimens, that is not a "***combination***." It is administering the drugs separately. (Ex-2062 ¶130.)

The specification supports that interpretation. It describes "the present invention" as "the ***combined*** administration of an anti-ErbB2 antibody and a chemotherapeutic agent, other than an anthracycline derivative"—either through "coadministration" or "consecutive administration" in the same therapeutic regimen (i.e., "wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities"). (Ex-1001, 25:1-8.) (Ex-2062 ¶131.)

The surrounding claim language further confirms that "administering a combination" refers only to the drugs administered in the same treatment regimen. For example, all claims require "the absence of an anthracycline derivative." That limitation would make no sense if "administering a combination" included drugs received as part of a different treatment regimen. In the '549 patent's working example, patients were administered the combination of the anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative only if they had

"received any anthracycline therapy in the adjuvant setting" (i.e., as part of a different, earlier treatment regimen). (Ex-1001, 28:15-21.) A POSA would thus understand that "administering a combination" refers only to the drugs used in the same treatment regimen, and not as part of a different regimen. (Ex-2062 ¶132.)

B. "In An Amount Effective To Extend The Time To Disease Progression In The Human Patient," and "An Effective Amount"

Although neither party had requested construction of the terms "in an amount effective to extend the time of disease progression in the human patient" (claims 1,16) and "an effective amount" (claim 5), the Board construed these as relative terms measured against a patient who had received no treatment. (Paper 19 at 12-13.)

Respectfully, that claim construction is not consistent with the specification as understood by a POSA. Both parties' experts agree that the specification supports a construction that compares the claimed combination treatment to treatment with a taxoid alone. (IPR2017-02063, Ex-1002 ¶112(h); Ex-2062 ¶¶134-144; *see also* Ex-1011 ¶48 (Dr. Lipton opining that clinical efficacy evaluated for a new therapy is typically measured "against a standard therapy (as a control arm)"); Ex-2050 [Lipton], 56:11-14 (in a Phase-III trial the drug combination under study is tested against "[a] standard of therapy").)

In particular, the clinical trial results reported in the '549 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.)[12] There is no data in the patent comparing the TTP of patients treated with an anti-ErbB2 antibody and a taxoid against an untreated patient. (Ex-2050 [Lipton], 152:3-21.) (Ex-2062 ¶138.)

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 ¶144.)

[12] The '549 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 some claims expressly exclude anthracycline therapy, the relevant comparison is the combination of rhuMAb HER2 and paclitaxel versus paclitaxel alone.

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-19 at 11-12.) 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-3001 at 17-18.) 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 ¶141; *see also* Ex-2050 [Lipton], 152:3-21).)

Moreover, Petitioners' own expert admits that the example in the specification describes a comparison of rhuMAb HER2 and paclitaxel to paclitaxel alone, not to a patient who has received no therapy whatsoever, and that therefore the term should be construed as requiring a comparison to treatment with a taxoid alone. (*See* IPR2017-02063, Ex-1102 ¶112(h) (Dr. Lipton opining that "[b]ased on the specification, the appropriate comparison is to compare the claimed

combination treatment versus treatment with a taxoid alone").)[13] The understanding of a POSA is therefore not in dispute. (Ex-2062 ¶143.)

Accordingly, the Board should construe the term "extend the time to disease progression in the human patient" as measured against a patient treated with a taxoid alone, not a patient who has received no treatment whatsoever. Further, the term "an effective amount," which the Board defined as "an amount effective to extend the time to disease progression in the human patient" (Paper-19 at 12-13), should likewise require comparison to a patient treated with a taxoid alone.

VII. ARGUMENT

A. Grounds 1-6: Under The Correct Claim Construction, Petitioners Have Not Established A Reasonable Expectation Of Success In Achieving The Clinical Efficacy Required By The Challenged Claims.

Claims 1-4 and 16-17 expressly require that the claimed combination achieve a specific clinical result—i.e., "to extend the time to disease progression in the human patient." For claims 5-15, the Board construed "an effective amount" to impose the same requirement. (Paper-19 at 12-13.)

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[13] Dr. Earhart, the expert for the Celltrion IPR against the '549 patent (IPR2017-01122), also agrees that "[b]ased on the specification, the appropriate comparison is to compare the claimed combination treatment versus treatment with a taxoid alone." (IPR2017-01122, Ex-1002 ¶111(d).)

The Board's institution decision rested on a claim construction that measured the claimed extension in TTP against a patient who received no treatment whatsoever. (Paper-19 at 12, 18.) 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.

Under the correct claim construction, Petitioners have not shown that the prior art taught that the claimed combination therapy would extend TTP relative to a patient treated with a taxoid alone. That clinical result is not taught by any of the cited references. Indeed, the ***first*** disclosure of clinical results showing that combinations that include an anti-ErbB2 antibody and a taxoid extend TTP is in the '549 specification. (Ex-2062 ¶112.) (Ex-1001, 29:13-30:25.)[14] Absent a similar disclosure in the prior art, Petitioners cannot show that a POSA would have

[14] All challenged claims require a third drug (i.e., "a further growth inhibitory agent" (claims 1, 16) or "a further therapeutic agent" (claim 5)). However, for the reasons set forth herein, Petitioners' instituted references do not even establish obviousness as to the narrower two-drug combination of an anti-ErbB2 antibody and a taxoid.

had a reasonable expectation of success in achieving that clinical result with the combinations claimed in the '549 patent.[15]

1. Grounds 1-3: Baselga '97 in view of Gelmon '96 does not teach that the claimed combination would extend the time to disease progression as compared to treatment with a taxoid alone.

For Grounds 1-3, Petitioners rely on the combination of Baselga '97 and Gelmon '96 for its supposed disclosure of the claimed clinical efficacy. But Petitioners' arguments are not supported by those references.

First, Petitioners point to Baselga '97's description of the Phase-II clinical study results, which showed that responses "lasted for a median of 5.1 months" and reports serum concentrations of rhuMAb HER2 in patients. (Paper-1 at 29 (citing Ex-1007 at 9).) But those results are the "median" TTP for patients who received rhuMAb HER2 alone. They do not describe an ***extension*** in TTP, which is a ***comparative*** result, let alone an extension in TTP as compared to patients treated

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

with a taxoid alone. The Phase-II study described in Baselga '97 (originally reported in Baselga '96) contained no control arm against which to compare the TTP and thus disclosed no ***extension*** in TTP. (*Supra* pp.32, 34.) (Ex-2062 ¶¶203-205, 210.)

In its institution decision, the Board stated that the prior art does not suggest "the addition of paclitaxel and/or a further growth inhibitory or therapeutic agent to a rhuMAb HER2 treatment regimen would abrogate the chemotherapeutic effect of anti-ErbB2 antibodies." (Paper-19 at 19.) However, under the claims as properly construed, the relevant question is not whether the antibody and the other drugs in the claimed combination would have an antagonistic interaction; rather, the question is whether adding the antibody to a taxoid would improve the clinical response to the taxoid with respect to the specific clinical endpoint of extending TTP. The data for patients treated with rhuMAb HER2 alone disclosed in Baselga '97 does not address that question. (Ex-2062 ¶¶213-216.)

Second, Petitioners rely on Baselga '97's description of preclinical mouse results obtained from combinations with paclitaxel and cisplatin, as well as the paper's discussion of the Phase-II study testing the combination of rhuMAb HER2 and cisplatin. (Paper-1 at 29-30 (citing Ex-1007 at 9-10).) But Baselga '97 reports no results from those studies relating to TTP, let alone demonstrating an ***extension*** of TTP. Instead, the preclinical mouse study combining rhuMAb HER2 with

paclitaxel measured response rate, which is not predictive of TTP. (*Supra* pp.31, 34; *infra* pp.50-51.) Petitioners argue that combinations of rhuMAb HER2 with paclitaxel or cisplatin produced "synergistic increases in treatment efficacy" (Paper-1 at 30), but never explain how those supposed "synergistic" interactions would suggest a clinical result for a combination that was not evaluated in human patients. Moreover, as explained elsewhere herein, a POSA would have understood that the preclinical mouse studies mentioned in Baselga '97 (the same studies discussed in Baselga '94) are not reliable predictors of success in humans. (*Supra* p.31; *infra* pp.55-58.) (Ex-2061 ¶¶51-83; Ex-2062 ¶¶149, 206.)

Third, Petitioners point to Baselga '97's disclosure of an ongoing Phase-III trial to evaluate whether combinations of rhuMAb HER2 with paclitaxel increased TTP compared with a control group. (Paper-1 at 30 (citing Ex-1007 at 10).) But as the Board acknowledged in its institution decision (Paper-19 at 15), Baselga '97 reports ***no*** results from that study, which was still "ongoing." (Ex-1007 at 10.) Petitioners never explain how the mere fact of a study would provide a reasonable expectation of success that the study would meet its endpoint. Indeed, the high failure rate of cancer clinical trials in the 1990s belies that assertion. (*Supra* pp.12-13.) (Ex-2062 ¶¶211-212.)

Fourth, Petitioners argue that "Gelmon '96 discloses a combined paclitaxel plus cisplatin treatment regimen that increases the time to disease progression."

(Paper-1 at 29.) But that is not what Gelmon '96 discloses. Gelmon '96 discloses a "median" TTP, but contains no comparative data showing any ***extension*** in TTP. (Ex-1025 at 13.) Like the Phase-II studies for rhuMAb HER2, Gelmon '96 had no control arm against which to measure an ***extension*** in TTP. (*Id.*) (Ex-2062 ¶207.)

In its institution decision, the Board stated that Gelmon '96 supposedly "discloses that paclitaxel is active as a single agent in metastatic breast cancer, but exhibits advantageous, if not synergistic, results in combination with cisplatin." (Paper-19 at 18.) But there are numerous other prior art references that undermine that supposed teaching. (*Supra* pp.35-36.) For example, Wasserheit '96 studied the combination of paclitaxel and cisplatin, and concluded that the combination did not provide any clinical benefit as compared with single-agent therapy. (Ex-2068 at 1998 ("While the combination with cisplatin in our trial had clear activity, it is not different from the data with single-agent paclitaxel.").) (Ex-2062 ¶¶171.)

Furthermore, other prior art references were unable to reproduce Gelmon '96's results. For example, Sparano '97 terminated the study early because it was unlikely to show a clinical benefit as compared with treatment with single-agent paclitaxel. (Ex-2120 at 1880 ("The trial was terminated after the first interim analysis as per its two-stage design, since it was unlikely that the response rate would exceed 70%.").) Petitioners' expert, Dr. Lipton, admitted that he had not

reviewed "whether the results reported in [Gelmon] '96 were reproducible by others." (Ex-2050, 165:18-22.) (Ex-2062 ¶172.)

Petitioners may not selectively rely on Gelmon '96 for the teaching that the addition of cisplatin to the combination would result in improved clinical results when other prior art references directly refute that supposed teaching. (Ex-2062 ¶¶171-172.)

Fifth, Petitioners attempt to minimize the significance of the clinical-efficacy limitation by arguing that "any" extension in TTP would suffice. (Paper-1 at 29.) But that does not relieve Petitioners of the obligation to show a reasonable expectation of success in achieving ***some*** extension in TTP. Petitioners have not explained how a POSA would have had a reasonable expectation of success in obtaining even a minimal extension in TTP when that clinical outcome is not described in the prior art. (Ex-2062 ¶¶213-216.)

To the contrary, as Dr. Tannenbaum explains, due to the uncertainties of antibody therapy and combining chemotherapeutic and non-chemotherapeutic agents at the time, a POSA would not assume that combining rhuMAb HER2 and paclitaxel would extend TTP simply because each therapy on its own provides some benefit to the patient. This uncertainty was exemplified by the failure to combine chemotherapy with hormone therapy, which did not increase response rate, TTP, or survival as compared to either treatment alone. (Ex- 2072 at

Abstract; Ex-2073 at Abstract.) In fact, in one study, combination therapy produced worse results than hormone therapy alone. (Ex-2074 at 8.) (Ex-2062 ¶¶215.)

Finally, Petitioners attempt to excuse the complete absence of the claimed extension of TTP in the prior art on the basis that the '549 patent itself supposedly contains no such data for the claimed three-drug combination. (Paper-1 at 19.) But Petitioners ignore that the '549 patent discloses clinical results showing an extension in TTP for the combination of an anti-ErbB2 antibody and a taxoid. (Ex-1001, 29:13-30:25.) Without a similar disclosure in the prior art, Petitioners cannot demonstrate that even the two-drug combination of an anti-ErbB2 antibody and a taxoid would have been obvious. Adding a third drug to that combination as claimed in the '549 patent would not have been obvious either.[16] (Ex-2062 ¶211.)

2. Grounds 4-6: Baselga '96 in view of Gelmon '96 and Baselga '94 does not teach that the claimed combination

[16] Petitioners are also incorrect to suggest that Patent Owner's arguments during prosecution are somehow inconsistent with the disclosure of the '549 patent. (Paper-1 at 19.) The '549 patent's disclosure of clinical results showing an extension in TTP for the combination of an anti-ErbB2 antibody and a taxoid is precisely what is absent from the prior art.

would extend the time to disease progression as compared to treatment with a taxoid alone.

For Grounds 4-6, Petitioners rely on Baselga '96 in view of Gelmon '96 and Baselga '94 for the supposed disclosure of the claimed clinical efficacy. Those arguments are similar to Petitioners' arguments for Grounds 1-3 and fail for the same reasons. (*See supra* §VII.A.1.)

First, Petitioners argue that Baselga '96 discloses an extension in TTP because it teaches that responses to rhuMAb HER2 lasted "for a median of 5.1 months." (Paper-1 at 47 (citing Ex-1005 at 10).) But as discussed above (pp.44-45), that is not the ***extension*** in TTP required by the claims, which is a ***comparative*** result. Baselga '96 had no control arm to measure that comparative result, and Petitioners have not explained how a POSA could have had a reasonable expectation of success in achieving a result that Baselga '96 does not describe. (Ex-2062 ¶¶203-205.)

Second, Petitioners argue that Baselga '96 describes preclinical results supposedly showing "synergistic increases in treatment efficacy." (Paper-1 at 48 (citing Ex-1005 at 15).) But Petitioners ignore that those preclinical results did ***not*** involve TTP, let alone an extension in TTP as compared to treatment with paclitaxel alone in a human patient. (*Supra* pp.45-46.) Petitioners again do not explain how "synergistic results" in mice would provide an expectation of success

in achieving a completely-different result in humans. And in fact, the full record now confirms that the particular preclinical mouse models described in Baselga '94 had significant design flaws that undermine their predictive value. (*Supra* p.31; *infra* pp.55-58.) (Ex-2061 ¶¶51-83; Ex-2062 ¶¶188-191, 206.)

Indeed, the development history of rhuMAb HER2 confirms that the preclinical results in Baselga '94 would not have provided a POSA a reasonable expectation of success in achieving the specific clinical result claimed in the '549 patent. Despite the results reported in Baselga '94, no one pursued a clinical trial combining an anti-ErbB2 antibody and a taxoid until '549 inventor Dr. Hellmann suggested modifying an ongoing Phase-III trial to address enrollment issues. Only in hindsight can Petitioners reinterpret the preclinical results reported in Baselga '94 to provide a reasonable expectation of success. (Ex-2062 ¶216.)

Third, Petitioners repeat their assertion that Gelmon '96 supposedly shows that combination of paclitaxel and cisplatin "increase[] the time to disease progression." (Paper-1 at 48.) But that argument is a gross mischaracterization of what that reference discloses. Gelmon '96 did not evaluate any ***extension*** in the time to disease progression and could not have done so because it lacked a control arm. (*Supra* pp.46-47.) Moreover, as discussed above, other prior art references (which Petitioners ignore) directly refute Gelmon '96's supposed teaching that the combination of paclitaxel and cisplatin provides improved clinical results as

compared with paclitaxel therapy alone. (*Supra* p.35-37, 47.) (Ex-2062 ¶¶171-172, 207.)

Fourth, Petitioners assert that the challenged claims are satisfied by "any" minimal extension in TTP. But as discussed above (pp.48-49), that does not excuse Petitioners from presenting evidence showing that the prior art would have led a POSA to have a reasonable expectation of achieving such an extension in TTP by using the claimed combination (which Petitioners have not done). (Ex-2062 ¶¶213-216.)

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The cited references do not disclose the clinical result of extending TTP as compared to treatment with paclitaxel alone, and Petitioners' arguments relating to that limitation are flatly contradicted by what the references actually say. Petitioners therefore cannot establish that a POSA would have had a reasonable expectation of success in achieving the clinical result of extending TTP as required by claims 1-4 and 16-17. That failure of proof is fatal to Petitioners' obviousness challenge. *See, e.g.*, *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 995-97 (Fed. Cir. 2009) (rejecting obviousness argument where challenger had not established a reasonable expectation of success).

Claims 5-15 require clinically "effective" results. Petitioners rely on the same deficient proof relating to extending TTP for claims 5-15 (*see* Paper-1 at 33-34, 51-52), and their arguments fail for the same reasons just discussed.

B. Grounds 4-6: Baselga '96 In View Of Gelmon '96 And Baselga '94 Does Not Teach "Administering A Combination" Of An Anti-ErbB2 Antibody And A Taxoid "To The Human Patient."

All challenged claims require "administering a combination" of an anti-ErbB2 antibody and a taxoid "to the human patient." For Grounds 4-6, Petitioners argue that the combination of Baselga '96 and Baselga '94 teaches that limitation. Petitioners' arguments are not supported by those references.

1. Baselga '96 does not suggest treating a human patient with an anti-ErbB2 antibody and a taxoid.

Baselga '96 does not teach "administering a combination" of an anti-ErbB2 antibody and a taxoid "to the human patient." Instead, it discloses the treatment of human patients with rhuMAb HER2 ***alone***, not with a taxoid (or any other combination therapy). (Ex-1005 at 10 ("Chemotherapy … was not permitted.").) (Ex-2062 ¶179.)

Petitioners argue that Baselga '96 teaches a combination of an anti-ErbB2 antibody and a taxoid because four patients had "***prior*** systemic therapy" with a taxoid. (Paper-1 at 45.) But as the Board correctly concluded in its institution decision, those patients were not "administered a ***combination***" of anti-ErbB2

antibody and a taxoid, as that term is properly construed. (Paper-29 at 10.) Baselga '96 describes patients who received treatment with an anti-ErbB2 antibody and ***separate*** treatment with a taxoid. In fact, patients in the study were required to discontinue any chemotherapy (including taxoids) for at least three weeks before enrolling. (Ex-1005 at 10.) (Ex-2062 ¶181.)

Petitioners also argue that Baselga '96 teaches a combination of an anti-ErbB2 antibody and a taxoid because it (i) mentions preclinical studies involving the combination of rhuMAb HER2 with cisplatin, doxorubicin, and paclitaxel, and (ii) notes that "clinical trials of such combination therapy are currently in progress." (Paper-1 at 45.) The preclinical studies alluded to in Baselga '96 are the same studies disclosed in Baselga '94, and thus fail to establish a motivation to combine an antibody and taxoid for the same reasons explained in Section VII.B.2 below. Moreover, Baselga '96 does not state that the combination of rhuMAb HER2 and paclitaxel was being pursued; indeed, it does not specify what "combination therapy" was being studied. (Ex-2062 ¶¶182-183.)

In fact, there was ***no*** clinical study testing the combination of rhuMAb HER2 and paclitaxel at the time that Baselga '96 was submitted (August 8, 1995) or accepted for publication (October 19, 1995). (Ex-2007 at 1 (amended protocol dated November 13, 1995).) That Petitioners' obviousness theory requires reading

incorrect assumptions into Baselga '96 confirms that it rests on hindsight. (Ex-2062 ¶¶184-186.)

2. Baselga '94 does not suggest treating a human patient with an anti-ErbB2 antibody and a taxoid.

Baselga '94 would not have motivated a POSA to "administer a combination" of an anti-ErbB2 antibody and a taxoid "to the human patient" either. It merely describes preclinical ***mouse*** xenograft models, and thus does not involve administering the claimed combination to a "***human*** patient," as claimed in the '549 patent. The full record now confirms that a POSA would not have been motivated to treat human patients with an anti-ErbB2 antibody and a taxoid based upon Baselga '94 for several reasons. (*See also supra* pp.7-12.) (Ex-2061 ¶¶51-83; Ex-2062 ¶188.)

First, Baselga '94 is a one-paragraph abstract that was not peer-reviewed for content. As Dr. Tannenbaum explains, to the extent a POSA would pay any attention to Baselga '94, she would wait for the full, peer-reviewed paper describing the underlying experiments and bases before drawing any conclusions from it. (Ex-2062 ¶188.)

Second, a POSA would understand that the mouse study in Baselga '94 was not a reliable predictor of success in humans. That preclinical study was based on a single cell line, but it was known prior to the '549 patent that it was necessary to

use multiple cell lines to obtain results that are reflective of a human patient population. A study like Baselga '94 based on a single cell line is akin to a clinical trial involving a single patient, which has minimal predictive value. (*Supra* p.11.) (Ex-2061 ¶¶63-70; Ex-2062 ¶¶189-191.)

Moreover, a POSA also would have understood that the particular cell line used in Baselga '94 was not representative of actual patients. The cell line (BT-474) expressed the highest HER2 levels of any known breast-cancer cell line at the time—i.e., more than ***20 times*** the number of HER2 genes per cell than in a normal human cell. With such a high level of HER2 expression, a POSA would have understood that the results disclosed in Baselga '94 are not representative of how actual HER2-positive patients would respond. (*Supra* p.10-11.) (Ex-2061 ¶¶62-70; Ex-2062 ¶¶189-191.)

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

These specific deficiencies with the preclinical models disclosed in Baselga '94, coupled with the lack of predictive value for mouse xenograft studies

generally (*supra* pp.7-9),[17] confirm that a POSA would not have been motivated to treat patients with a combination of rhuMAb HER2 and paclitaxel based upon the results reported in Baselga '94. Missing from this record are the types of robust preclinical studies on the claimed combination (e.g., testing multiple cell lines, creation of orthotopic xenograft models, and analysis of dosing amounts) that a POSA would want before risking such combination in humans. (Ex-2061 ¶¶52-53; Ex-2062 ¶194.)

Third, there were significant concerns with using taxoids to treat HER2-positive breast cancer before the '549 invention. (*Supra* pp.17-18.) At the time, patients experienced serious hypersensitivity reactions, neuropathy, and cardiotoxicity from taxoids, which were only approved for second-line use in

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[17] 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 177.) 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 ¶60.)

breast cancer. Moreover, the prior art taught away by explicitly warning that HER2-positive breast cancer "will not respond well to Taxol." (Ex-2029 at 1362.) Indeed, Petitioners admit that Gelmon '96 teaches that "HER2 positive breast cancer patients are resistant to … paclitaxel." (Paper-1 at 28, 46-47.) Petitioners do not address these significant concerns with taxoids or explain how Baselga '94 addressed them. (Ex-2062 ¶¶196-199.)

The development history of rhuMAb HER2 confirms that Baselga '94 would not have motivated a skilled artisan to treat humans with an anti-ErbB2 antibody and a taxoid. Despite studying combinations with other chemotherapies (e.g., cisplatin (Ex-1013), 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'549 inventor Dr. Hellmann finally modified the Phase-III trial over objection to include a combination of rhuMAb HER2 and paclitaxel, she did so based on her unique knowledge of paclitaxel and in response to enrollment issues with the study, not because of the preclinical results involving the combination of rhuMAb HER2 and paclitaxel. Given the well-known problems with taxoids (*supra* pp.17-18), a POSA would not have been motivated to pursue the claimed combination based on Baselga '94, and it would be inappropriate to attribute Dr. Hellmann's extraordinary knowledge to a POSA. *See Standard Oil Co. v. American Cyanamid*

Co., 774 F.2d 448, 454 (Fed. Cir. 1985) (inventor possesses knowledge "which sets them apart from workers of ordinary skill"). Only in hindsight can Petitioners 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 ¶¶200-201.)

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.19-20; Ex-2031 at 683.) Moreover, the prior art reflected significant safety concerns regarding treatment with taxoids (*supra* pp.17-18), and the efficacy of taxoids in treating HER2-positive breast cancer was questionable at best (*supra* p.22). 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 ¶¶196-199.) That a POSA would not have risked using taxoids is especially the case when considering that one of the other drugs in the combination—the anti-ErbB2 antibody—was still a new therapy with its own uncertainties at the time. (Ex-2062 ¶195.)

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 ¶195.) As explained above, the efficacy of anthracyclines in treating breast cancer was well established in the art, and the side effect of such treatment—cardiotoxicity in some individuals—had been thoroughly studied and was understood to be manageable. (*Supra* pp.15-16.) At this time, anthracyclines were the standard and most common treatment for breast cancer. (*Id.*) In fact, when Genentech initially designed the protocol for the Phase III-trial, the method of treatment chosen was rhuMAb HER2 in combination with doxorubicin, an anthracycline derivative. (Ex-2002 at 2; Ex-2003 at 2; Ex-2004 at 3.) Thus, contrary to the '549 patent's novel idea of treating HER2-positive breast cancer with a combination of an anti-ErbB2 antibody and a taxoid (and in claims 16 and 17, explicitly "in the absence of an anthracycline derivative"), a POSA would have deemed anthracyclines the obvious chemotherapeutic agent for any drug combination. (Ex-2062 ¶¶201, 216, 226.)

C. Grounds 1-6: A POSA Would Not Rely Upon Gelmon '96 To Treat a HER-Positive Patient With a Combination Including Cisplatin and Paclitaxel.

Grounds 1-6 rely on Gelmon '96 for its disclosure of treating breast cancer patients with a combination of cisplatin and paclitaxel. Petitioners assert that a POSA would combine that teaching with the various Baselga references showing that rhuMAB-HER2 "serves to sensitize HER2 positive tumors to both therapies."

(Paper-1 at 28, 46-47.) Contrary to Petitioners' argument, and as explained above (*supra* pp.35-36, 47-48), the full record establishes that a POSA would not look to Gelmon '96 for any teachings for treating HER2-positive patients.

As an initial matter, a POSA would not look to Gelmon '96 in proposing a new treatment for HER2-positive patients because ***Gelmon '96 did not even address whether any of the patients were HER2-positive***. (Ex-1025.) Given that Gelmon '96 administered the combination to only 29 patients (*id.* at 11), and only 25-30% of breast cancer patients are HER2-positive (Ex-1001, 1:23-29; Ex-2027 783), a POSA would have no way of knowing whether the results reported in Gelmon '96 would be applicable to HER2-positive patients (much less a statistically-significant sample of HER2-positive patients). For this reason alone, Grounds 1-6—all of which include Gelmon '96 as a necessary reference—should be rejected. (Ex-2062 ¶219.)

Furthermore, it was well known by 1997 that Gelmon '96's results for the paclitaxel/cisplatin combination were not reliable. As explained above, several subsequent prior art studies were unable to reproduce the efficacy results presented in Gelmon '96. (*Supra* pp.35-36, 47-48; Ex-2068 at 1998; Ex-2120 at 1880; Ex-2121 at Abstract; *see also* Ex-2050, 165:18-22 (Dr. Lipton admitting he had not reviewed "whether the results reported in Gelman '96 were reproducible by others").) Worse yet, these studies reported significant, dose-limiting toxicity, in

one case requiring study termination. (*Supra* pp.35-36, 47-48; Ex-2068 at 1998; Ex-2120 at 1880.) (Ex-2062 ¶¶220-223.)

In other words, it was well known that Gelmon '96's results were an anomaly that could not be relied upon in suggesting treatment for breast-cancer patients, much less HER2-positive breast-cancer patients whose cancer is more aggressive and who were not specifically addressed in Gelmon '96. A POSA therefore would not be motivated by Gelmon '96 to treat HER2-positive patients with a combination including paclitaxel and cisplatin, as required by Petitioners' obviousness theory.

Petitioners' instituted grounds, all of which rely on the discredited results in Gelmon '96, should be denied.

D. Grounds 1-6: Petitioners Have Not Shown That The Claimed Combination Would Have Been Obvious To Try.

Although not addressed in the Board's institution decision, Petitioners briefly contend that the challenged claims would have been obvious to try. (Paper-1 at 17, 31, 35, 40, 42, 49, 53, 59, 60, 61, 63.) But that argument too rests on hindsight in several respects.

First, Petitioners argue the claimed combination was "the only combination left to try." (Paper-1 at 31, 49.) But that assertion cannot be reconciled with Petitioners' own asserted references. For example, even the patients in Gelmon

'96 had been treated with a host of other breast cancer therapies. (*E.g.*, Ex-1025 at 11 (cyclophosphamide, doxorubicin, methotrexate, 5FU, etoposide, and prednisone); *id.* at 9 ("There are a number of drugs with activity in metastatic breast cancer ….").)

Petitioners' assertion is also inconsistent with the development history of rhuMAb HER2. As discussed above (pp.22-23), Genentech pursued several alternative therapies (e.g., anti-ErbB2 antibody alone (Ex-1005), combined with cisplatin (Ex-1013), or combined with doxorubicin (Ex-2001)) and only pursued the combinations containing an anti-ErbB2 antibody and a taxoid after '549 inventor Dr. Hellmann convinced the company to change course. That such combinations were not even among the treatment regimens pursued in any Phase-I, Phase-II, or initial Phase-III clinical trials—led by extremely skilled scientists—confirms that they were not obvious to try. There were numerous alternative treatment regimens that a POSA would have pursued—and that actually were pursued—instead. *See, e.g.*, *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1356-57 (Fed. Cir. 2013) (holding that the alternatives disclosed in the art and the fact that no one had pursued the claimed invention before the inventors confirmed that the invention was not obvious to try). And it would be improper to impute Dr. Hellmann's ***extra***ordinary knowledge to a person of ***ordinary*** skill in the art. *See*

Standard Oil Co., 774 F.2d at 454 (inventor possesses knowledge "which sets them apart from workers of ordinary skill"). (Ex-2062 ¶226.)

Second, Petitioners' obvious-to-try theory fails for the further reason that the claimed invention was not one of "a finite number of identified, ***predictable*** solutions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). The '549 invention is in a highly-unpredictable field—as confirmed, for example, by the nearly 60% failure rate of cancer drugs in Phase-III trials during the 1990s and the fact that Baselga '94 itself failed to predict the toxicity of rhuMAb HER2 combined with anthracyclines. (*Supra* pp.13-14, 31.) Petitioners cannot demonstrate that the art was predictable when the very references underlying their obviousness theory show that it was not. Petitioners do not address the unpredictability of the field, let alone explain how the invention could have been obvious to try given those uncertainties. (Ex-2062 ¶¶227-228.)

Accordingly, the Board should reject Petitioners' obvious-to-try theory.

E. *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 '549 patent—that issued before passage of the America Invents Act.

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

VIII. CONCLUSION

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

Respectfully submitted,

Date: December 22, 2017

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CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Preliminary Response, contains 13,508 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. § 42.24(d).

Respectfully submitted,

Dated: December 22, 2017

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

CERTIFICATE OF SERVICE

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

- Patent Owner's Response
- Patent Owner's Exhibit List
- Patent Owner's Motion to Amend
- Patent Owner's Motion to Seal
- Exhibits 2050-2055, 2061-2075, 2077-2083, 2085-2095, 2097-2099, 2101-2113, 2115-2117, 2120-2124, 2128

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

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Patent Owner's Exhibit List

Patent Owner's Exhibit Number	Exhibit Name
2001	Genentech, Inc. Original H0648g Protocol PROTECTIVE ORDER MATERIAL
2002	Genentech, Inc. PDC Minutes PROTECTIVE ORDER MATERIAL
2003	Genentech, Inc. PDC Minutes PROTECTIVE ORDER MATERIAL
2004	Genentech, Inc. PDC Minutes PROTECTIVE ORDER MATERIAL
2005	RESERVED
2006	RESERVED
2007	Genentech, Inc. Amended H0648g Protocol PROTECTIVE ORDER MATERIAL
2008	Genentech, Inc. H0648g Final Report PROTECTIVE ORDER MATERIAL
2009	RESERVED
2010	RESERVED
2011	RESERVED
2012	RESERVED
2013	RESERVED
2014	RESERVED
2015	RESERVED

Patent Owner's Exhibit Number	**Exhibit Name**
2016	M. Harries & I. Smith, *The Development and Clinical Use of Trastuzumab (Herceptin)*, 9 Endocrine Related Cancer 75 (2002)
2017	David Holzman, *Gene Therapy for HER-2-related Cancer*, Molecular Medicine Today 138 (1996)
2018	Russ Hoyle, *Genentech Is Poised for an Anti-cancer Breakthrough*, 16 Nature Biotechnology 887 (1998)
2019	Makoto Inaba, et al., *Evaluation of Antitumor Activity in a Human Breast Tumor/Nude Mouse Model with a Special Emphasis on Treatment Dose*, 64 Cancer 1577 (1989)
2020	RESERVED
2021	Ismail Kola & John Landis, *Can the Pharmaceutical Industry Reduce Attrition Rates?*, 3 Nature Rev. 711 (2004)
2022	Steven Lehrer, et al., *Tumour HER2 Protein in Breast Cancer and Family History*, 341 Lancet 1420 (1993)
2023	Silvia Marsoni & Robert Wittes, *Clinical Development of Anticancer Agents—A National Cancer Institute Perspective*, 68 Cancer Treatment Reports 77 (1984)
2024	Jürgen Mattern, et al., *Human Tumor Xenografts as Model for Drug Testing*, 7 Cancer & Metastasis Rev. 263 (1988)
2025	Gert Riethmüller & Judith P. Johnson, *Monoclonal Antibodies in the Detection and Therapy of Micrometastatic Epithelial Cancers*, 4 Current Opinion in Immunology 647 (1992)
2026	Eric K. Rowinsky, et al., *Cardiac Disturbances During the Administration of Taxol*, 9 J. Clinical Oncology 1704 (1991).

Patent Owner's Exhibit Number	**Exhibit Name**
2027	Dennis J. Slamon, et al., *Use of Chemotherapy Plus a Monoclonal Antibody Against HER2 for Metastatic Breast Cancer that Overexpresses HER2*, 344 N. Engl. J. Med. 783 (2001)
2028	Raymond B. Weiss, et al., *Hypersensitivity Reactions from Taxol*, 8 J. Clinical Oncology 1263 (1990)
2029	Dihua Yu, *Overexpression of c-erbB-2/neu in Breast Cancer Cells Confers Increased Resistance to Taxol Via mdr-1-independent Mechanisms*, 13 Oncogene 1359 (1996).
2030	James H. Doroshow, *Anthracyclines and Anthracenediones*, in Cancer Chemotherapy & Biotherapy: Principles and Practice 409 (1996)
2031	Richard P. Junghans, et al., *Antibody-Based Immunotherapies for Cancer*, in Cancer Chemotherapy & Biotherapy: Principles and Practice 655 (1996)
2032	Gert Riethmüller, et al., *Monoclonal Antibodies in Cancer Therapy*, 5 Current Opinion in Immunology 732 (1993)
2033	RESERVED
2034	RESERVED
2035	RESERVED
2036	Modified Default Standing Protective Order and Patent Owner's Certification of Agreement to Terms
2037	Modified Default Standing Protective Order – Redline

Patent Owner's Exhibit Number	**Exhibit Name**
2038	Eddie Reed, et al., *Platinum Analogues*, in Cancer Chemotherapy & Biotherapy: Principles and Practice 357 (1996)
2039	Declaration of Robert J. Gunther, Jr. in Support of Motion for Admission Pro Hac Vice
2040	Declaration of Daralyn J. Durie in Support of Motion for Admission Pro Hac Vice
2041	Declaration of Lisa J. Pirozzolo in Support of Motion for Admission Pro Hac Vice
2042	Declaration of Kevin S. Prussia in Support of Motion for Admission Pro Hac Vice
2043	Declaration of Andrew J. Danford in Support of Motion for Admission Pro Hac Vice
2044	RESERVED
2045	RESERVED
2046	RESERVED
2047	RESERVED
2048	RESERVED
2049	RESERVED
2050	Deposition Transcript of Allan Lipton, December 14, 2017, Hospira, Inc. v Genentech, Inc.
2051	Gura, T., *Systems for identifying new drugs are often faulty*, Science, 278(5340):1041-1042 (1997)

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