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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-01122
Patent 7,892,549

PATENT OWNER'S PRELIMINARY RESPONSE

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I. INTRODUCTION

The patent at issue in this proceeding (U.S. Patent No. 7,892,549) claims a new method of treating HER2-positive breast cancer—which is a particularly aggressive form of the disease. The claimed method of treatment involves using an "anti-ErbB2" antibody, which targets a cellular receptor associated with HER2-positive cancer, in combination with a chemotherapy called a "taxoid," along with "further growth inhibitory agent" (claims 1, 16) or "a further therapeutic agent" (claim 5). Those combinations achieve a specific clinical result: they "extend the time to disease progression"—*i.e.*, the time before tumors grow or spread to other parts of the body. The '549 specification contains the ***first*** disclosure of clinical results showing that combination therapies that include an anti-ErbB2 antibody and a taxoid are effective at extending the time to disease progression in patients with HER2-positive breast cancer.

The '549 patent is a continuation of U.S. Patent No. 7,846,441, which Petitioner has separately challenged in IPR2017-01121. 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 in the absence of another chemotherapeutic agent called an "anthracycline derivative." The '441 invention achieves 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 a 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.

Because the '549 and '441 patent are related, this petition overlaps with Petitioner's challenge to the '441 patent in IPR2017-01121.[1] The challenge to the '441 patent fails for the reasons described in Patent Owner's preliminary response in IPR2017-01121. Here, Petitioner also fails to demonstrate a reasonable likelihood of success for any of its proposed grounds with respect to the '549 patent. Instead, as detailed below, the petition provides only a conclusory explanation that conflicts with what the asserted references disclose and ignores what the claims of the '549 patent require.

First, claims 1-4 and 16-17 require a combination containing an anti-ErbB2 antibody and a taxoid that is effective to "extend the time to disease progression." Petitioner's obviousness theory rests on the notion that anti-ErbB2 antibodies and

[1] Hospira has filed two petitions (IPR2017-00737 and IPR2017-00739) challenging the '549 patent. Hospira's petition in IPR2017-00737 relies upon some of the same references asserted here.

taxoids had been shown to be effective to treat HER2-positive breast cancer.[2] But Petitioner has pointed to no prior art clinical results suggesting that an anti-ErbB2 antibody and a taxoid—alone or in combination—are effective to extend the time to disease progression in HER2-positive patients, which is the specific clinical result required by claims 1-4 and 16-17 of the '549 patent. The prior art only describes a clinical endpoint known as a "response rate"—which Petitioner acknowledges is ***different*** from extending the time to disease progression. Petitioner has not explained how a skilled artisan could have reasonably expected to achieve the specific clinical result claimed in the '549 patent based upon prior art addressing an entirely different clinical endpoint.

Claims 5-11 and 14-15 require that the claimed combination be clinically "effective." But Petitioner relies on the same deficient proof concerning "extend[ing] the time to disease progression" for those claims as well. The Board should deny institution of all grounds because Petitioner has failed to show that a

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[2] Patent Owner focuses this preliminary response on Petitioner's arguments directed to the claim elements relating to an anti-ErbB2 antibody and a taxoid, which are a required part of every claim of the '549 patent. If using an anti-ErbB2 antibody and a taxoid together would not have been obvious, adding a third drug to that combination as claimed in the '549 patent would not have been obvious either.

person of ordinary skill would have had a reasonable expectation of success in achieving the clinical efficacy results that the challenged claims require.

Second, all challenged claims require that the claimed combination therapy include a taxoid to treat HER2-positive breast cancer. Petitioner asserts that taxoids had "proven efficacy" in HER2-positive breast cancer based upon Seidman 1996 (Ex. 1011). But Seidman 1996 merely presented a preliminary hypothesis that HER2 overexpression "seems to confer sensitivity rather than resistance to taxanes" and acknowledged that the issue required further investigation. A skilled artisan at the time would not have accepted Seidman 1996's hypothesis as "proven" when even the Seidman authors continued to study the issue. And other contemporaneous references (which Petitioner ignores) specifically warned that HER2-positive breast cancer "will not respond well to Taxol." Given the uncertainty surrounding the use of taxoids in HER2-positive patients, there were ***no*** clinical studies combining an anti-ErbB2 antibody and a taxoid until '549 inventor Dr. Susan Hellmann proposed amending an ongoing Phase III clinical trial to test her invention. Before then, even those with the best information pursued other therapeutic options instead of the claimed combination. Petitioner's assertion that a skilled artisan would have had a reasonable expectation of success treating HER2-positive patients with taxoids rests on hindsight.

Third, Petitioner has not shown that it would have been obvious to treat patients "in the absence of an anthracycline derivative," as required by claim 16 and 17. Anthracyclines were the leading treatment for breast cancer at the time; in fact, the ***only*** combination of drugs initially studied in Phase III trials of Herceptin® was with an anthracycline. Petitioner's hindsight-driven assertion that it would have been obvious to treat breast cancer without anthracyclines is contradicted even by the references underlying its obviousness theory.

Petitioner attempts to distract from the deficiencies in its proof by criticizing Dr. Mark Sliwkowski's declaration. That declaration was submitted during prosecution to demonstrate unexpected results and to explain the shortcomings of preclinical mouse models to predict clinical results in humans. Petitioner's criticisms of Dr. Sliwkowski's declaration lack merit and mischaracterize his opinions—for example, by repeatedly attributing opinions and assumptions to Dr. Sliwkowski that appear nowhere in his declaration. Petitioner's arguments about that declaration also do not cure the many deficiencies in its obviousness theory.

The Board should deny institution.

II. TECHNOLOGY BACKGROUND

A. Prior Art Cancer Treatments Included Surgery, Radiation, And Chemotherapy.

Cancer is a disease involving an abnormal growth of cells (*i.e.*, a tumor) that invades the surrounding tissue and may spread to other parts of the body. (Ex.

1005 at 26; *see also* Ex. 1002, Earhart Decl. ¶ 30.) Early cancer treatments included surgery to remove the tumor and radiation to kill the cancer cells. (Ex. 1005 at 37.) However, even after surgery and/or radiation, some cancer cells may remain, which can cause the cancer to recur. (*Id.*)

To address that issue, scientists began to investigate drugs that kill cancer cells (*i.e.*, chemotherapies) that could be used with surgery and radiation. (*Id.*; Ex. 1016 at 7.) Over several decades, that research resulted in a wide variety of chemotherapies. (Ex. 1002, Earhart Decl. ¶ 35; Ex. 1016 at 16-23 (8-page list of prior art chemotherapies).) Out of the dozens of prior art chemotherapies, Petitioner's arguments in this proceeding relate to three classes of chemotherapies: anthracyclines, taxoids, and platinum-based drugs.

1. 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, at the time, treatments containing anthracyclines were the "standard therapy for cancers of the breast." (*Id.*)

As Petitioner notes, cardiotoxicity had been observed in some instances when anthracyclines were administered over time, resulting in high cumulative doses. (Paper 2 at 51.) However, by 1996, that side effect had been studied, and there were known techniques for reducing the 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.").)

Petitioner cites Dr. Earhart's declaration (Ex. 1002, ¶ 138) and a general cancer textbook ("Abeloff") (Ex. 1016 at 813) as evidence that "a POSA would have limited use of anthracycline derivatives in treatment whenever possible" (Paper 2 at 51), but neither supports that assertion. Dr. Earhart acknowledges that "treating patients with anthracyclines is often unavoidable" and states that "many patients" at the time of the invention would have received anthracyclines as "a first-line therapy for breast cancer." (Ex. 1002, Earhart Decl. ¶ 138.) And far from teaching avoidance of anthracyclines "whenever possible," Abeloff cautions ***against*** limiting anthracycline usage, which "may deprive patients who are continuing to benefit from therapy who do not show signs of toxicity." (Ex. 1016 at 29.)

Petitioner's other cited references reinforce that scientists at the time of the invention were not limiting anthracycline usage "whenever possible." For example, Baselga Abstract 53 described a preclinical study involving the anthracycline doxorubicin, which did not result in any observed increase in toxicity when combined with an anti-ErbB2 antibody. (Ex. 1019 at 4.) And Seidman 1995 noted that combinations with anthracyclines had shown "impressive antitumor activity" and were the subject of an "important" ongoing trial. (Ex. 1010 at 4.) Petitioner has cited nothing contemporaneous with the '549 invention indicating that anthracyclines were avoided "whenever possible." (Paper 2 at 51.)

2. 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.) The prior art thus warned oncologists "to maintain a high degree of caution" with taxoids. (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.)

The drug paclitaxel (Taxol®) is an example of a taxoid chemotherapy. The FDA approved paclitaxel for ovarian cancer in 1992 and for breast cancer in 1994. And even then, paclitaxel was approved to treat breast cancer only ***after*** other treatments failed (*i.e.*, paclitaxel was approved for "second-line" use). (Ex. 1012 at 6.) In fact, the approved Taxol® label from the time of the '549 invention—reflected in the asserted 1995 Taxol® PDR entry—advised that patients generally should be treated with an anthracycline ***before*** trying paclitaxel. (*Id.*)

3. 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.) 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." (*Id.* at 357.) However, prior to the '549 invention, platinum-based drugs were not "used widely in breast cancer," as even Petitioner's cited references acknowledge. (Ex. 1014 at 1.)

B. Developing New Cancer Drugs In The 1990s Was An Unpredictable Process.

Petitioner asserts that the discovery of new cancer treatments followed the simple application of "a set of reasoned principles" to identify predictable therapies that would be safe and effective. (Paper 2 at 39.) But the actual experience of cancer researchers at the time highlights the complexity and unpredictability of treating cancer, and refutes Petitioner's hindsight-driven narrative.

1. Preclinical studies

Preclinical studies in animal models (*e.g.*, mice) allow researchers to evaluate potential cancer therapies before testing them in humans. Those preclinical models are useful to screen out ineffective therapies. (Ex. 2023 at 79.) But it was well-known before the '549 invention that preclinical studies had a "very low" likelihood of predicting how humans would respond to a particular drug or combination of drugs for several reasons. (*Id.*)

First, mouse models at the time differed significantly from the physiology of treating cancer in humans. Prior art mouse xenograft studies involved injecting human cancer cells into mice that have their immune system suppressed, resulting in a "reduced capacity to reject 'foreign' tissue." (Ex. 1028 at 2.) The systems surrounding the tumor were not human, making the transplanted human tumors more susceptible to therapy than they would have been in humans. (*Id.* at 10, 16.)

Thus, it was known at the time that "the xenograft system markedly overestimates" drug activity. (*Id.* at 16.)

Second, prior art preclinical mouse models involved weight-based dosage amounts that are tolerable by a mouse, which are higher than human patients can receive. (Ex. 2019 at 1577.) At those higher doses, mouse models could show drug responses that human patients could not achieve. (*Id.*)

Third, the results of mouse xenograft studies at the time depended heavily on the cancer cell lines used. (*Id.* at 1581.) Demonstrating antitumor activity using a particular cell line might not translate into the same antitumor activity in other cell lines, let alone in humans. (*Id.*)

Petitioner cites a single reference from 1984 (Ex. 1026) as supposedly demonstrating the accuracy of mouse xenograft studies to predict responses in human patients. (Paper 2 at 40.) However, that assessment of the reliability of prior art mouse studies as predictive of human responses is refuted by later studies, including those cited by Petitioner. (*E.g.*, Ex. 1028 at 16 ("[T]he xenograft system markedly overestimates the activity of most of the standard drugs as single agents.").) Petitioner does not address the well-known limitations of prior art mouse studies to predict results in human patients or attempt to reconcile them with its obviousness theory.

2. Clinical trials

Therapies with favorable results in preclinical models might later advance to clinical studies in humans. Those clinical studies occur in stages with initial small-scale studies (*i.e.*, Phase I or Phase II) followed by large-scale controlled trials designed to evaluate specific clinical endpoints (*i.e.*, Phase III). For these studies, the drug developer typically works with outside physician investigators, who enroll their patients in the trial. For example, the authors of the asserted Baselga 1996 reference were outside investigators and Genentech scientists working together on a Genentech-sponsored study. (*See, e.g.*, Ex. 1020 at 3 ("Supported in part by … Genentech, Inc.").)

a. Clinical trials can evaluate different endpoints.

Clinical trials of cancer therapies can be designed to evaluate different endpoints, as Petitioner acknowledges. (*See* Paper 2 at 42-43.) For example, the Baselga 1996 reference reported a clinical endpoint known as "response rate," which is the percentage of patients who showed a specified reduction in tumor size. (Ex. 1020 at 4; *see also* Paper 2 at 42 ("Response Rate (RR) … measures changes in tumor size.").) A different clinical endpoint is "time to disease progression," which is the time following treatment before a patient's tumors grow or spread to other parts of the body. (Ex. 1001, 29:1-2; *see also* Paper 2 at 42.)

As Petitioner acknowledges (Paper 2 at 42), response rate and time to disease progression are different endpoints signifying different clinical outcomes. Response rate measures the initial effect on tumor size, whereas time to disease progression measures the long-term effect on disease progression. (*Id.*) As described below, Petitioner does not explain how a skilled artisan could have transformed the response rate data in the prior art to the very different time to disease progression results described and claimed in the '549 patent.

b. Clinical trials of cancer drugs in the 1990s often showed that new therapies lacked the desired efficacy or safety.

Petitioner's obviousness theory assumes that a skilled artisan would have had a reasonable expectation of success in obtaining the claimed clinical efficacy and safety results of the '549 invention simply because a clinical trial for a new cancer therapy was underway. (*See, e.g.*, Paper 2 at 53.) Petitioner's argument is directly contradicted by the experience of cancer researchers in the 1990s.

Only 5% of cancer drugs in the 1990s that advanced to clinical trials resulted in an approved product. (Ex. 2021 at 712-13.) And promising results in early-stage trials were not predictive of overall success. Nearly 60% of cancer drugs in Phase III clinical trials during the 1990s ultimately failed to result in an approved drug. (*Id.*) That a therapy had progressed through early-stage clinical trials was thus no indication that the therapy would have a clinical benefit when subjected to

more rigorous late-stage studies. These numerous failures during clinical development reinforce the limitations of preclinical studies at that time to predict clinical efficacy in humans. (*Id.* ("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.").)[3]

3. Combination therapies

Petitioner cites four supposed "principles" of combination chemotherapy, which it argues would have allowed a skilled artisan to identify drug combinations "achieving the greatest possible combined result." (Paper 2 at 39-40.) As an initial matter, those cited "principles" on their face only address combinations of different ***chemotherapies***. (Ex. 1016 at 10-11.) The '549 patent, however, claims treatment using combinations of an ***antibody*** with other agents, not combinations of different chemotherapies. At the time of the '549 invention, antibodies were an entirely new class of drug, and it was not clear how (if at all) they could be used to treat cancer. (*See* Ex. 2031 at 683-84; *infra* pp. 17-18.) Petitioner has not explained why a skilled artisan at the time would have believed that chemotherapy

[3] All emphases added unless otherwise indicated.

principles would be applicable to combinations with the new and unproven class of therapeutic antibodies.

But even if one of ordinary skill would have considered the cited chemotherapy principles relevant to antibodies, those general principles would not have diminished the unpredictability of treating cancer in the 1990s. Even Petitioner's cited references acknowledged the unpredictable challenges of combining cancer treatments. (*E.g.*, Ex. 1013 at 1 ("Combining two chemotherapy agents with distinctly different mechanisms of action and characteristics into a couplet remains a challenge."); Ex. 1006 at 33 (acknowledging the "[n]umerous pitfalls" to developing new cancer therapies).) Consistent with that high degree of unpredictability, patient survival for advanced (*i.e.*, "metastatic") breast cancer had "not consistently or substantially improved" in the decade before the '549 invention, "[d]espite innumerable trials" involving "various combinations" of drugs. (Ex. 1006 at 105.)

Moreover, there were particular concerns with using taxoids in combination with other drugs at the time of the invention. Petitioner's cited references disclose that "[t]here are few preclinical examples in which paclitaxel in combination with another drug was better than either drug alone" and warned that such combinations had produced worse (*i.e.*, "subadditive") results than single-agent therapy. (Ex. 1024 at 17.) Petitioner does not address the known "challenge of combining

paclitaxel with other drugs" (*id.*), or explain how general principles of combination chemotherapy could have provided a reasonable expectation of success in light of the specific challenges of combining taxoids with other drugs.

III. THE '549 PATENT

A. The Problem To Be Solved

1. HER2-positive breast cancer was a serious problem.

The '549 patent involves the treatment of "HER2-positive" breast cancers, which overexpress human epidermal growth factor receptor 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, 1:25-31.)

As Petitioner acknowledges, HER2-positive breast cancer is a serious and aggressive disease, which at the time of the invention was "particularly difficult to treat with traditional anti-cancer agents." (Paper 2 at 28.) In the 1990s, HER2-positive status was "associated with poor prognosis" with a high rate of tumor recurrence and spreading to other areas of the body. (Ex. 2022 at 1420; Ex. 2010 at 179-80.) Even after surgery, chemotherapy, and/or radiation, HER2-positive patients had "a shorter time to relapse as well as a shorter overall survival." (Ex. 2011 at 707; Ex. 2010 at 179-80.) Lacking effective treatments, 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.").)

2. No prior antibody-based cancer therapy had been approved for solid tumors, such as breast cancer.

The '549 patent claims a different approach to treating HER2-positive cancer, which involves combining an anti-ErbB2 antibody (*i.e.*, an antibody that targets HER2) and a taxoid, along with "a further growth inhibitory agent" (claims 1, 16) or "a further therapeutic agent" (claim 5).

Antibodies are proteins that bind to molecular targets, called "antigens." It is possible to create antibodies in a laboratory that target specific antigens. (Ex. 1001, 8:45-9:4.) However, the body's immune system may attack those specially-designed antibodies—called an "immunogenic" response—thereby preventing them from having a therapeutic effect. (Ex. 2031 at 655.) As of 1996, "much additional study" was required to determine whether that immunogenic response could be avoided. (*Id.* at 683.) Moreover, antibodies are large molecules that have difficulty penetrating tissue, which was a "significant obstacle[] to the effective use of mAbs for solid tumors," like breast cancer, because it was not certain whether the antibody could reach the cancer cells where it might be effective. (*Id.*)

By the early 1990s, numerous antibodies had been tested in patients with different cancers (including breast cancer); but consistent with the challenges just described, they 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 up to the invention of '549 patent. (Ex. 2031 at 683.)

3. The prior art taught away from using taxoids with HER2-positive cancers.

As discussed above (pp. 8-9), taxoids were approved only as a second-line therapy for breast cancer and had a history of problems that initially limited their clinical use, including hypersensitivity reactions and patient resistance.

Using taxoids to treat HER2-positive breast cancer presented even greater challenges. Petitioner argues that taxoids had "proven efficacy against metastatic HER2-positive breast cancer in humans" based upon Seidman 1996. (Paper 2 at 43.) As described in more detail below, however, that is not an accurate characterization of Seidman 1996, which merely speculated that "HER2 over-

expression in MBC [*i.e.*, metastatic breast cancer] seems to confer sensitivity rather than resistance to taxanes" and noted that "[c]ellular mechanisms for this effect are under investigation." (Ex. 1011 at 5.)

Indeed, far from "proven efficacy," some scientists at the time expressed doubt that taxoids could treat HER2-positive patients. For example, a 1996 paper (which Petitioner ignores) 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.)

4. The increased cardiotoxicity of anthracyclines when combined with anti-ErbB2 antibodies was not known.

In addition to those known challenges, there was another significant complication that was ***not*** known prior to the '549 invention. The combination of an anti-ErbB2 antibody and anthracyclines can produce severe cardiotoxicity. (Ex. 1001, 30:20-23.)

Petitioner asserts that a skilled artisan would have "limited use of anthracycline derivatives in treatment whenever possible" due to the risk of cumulative cardiotoxicity. (Paper 2 at 51-52.) But the prior art taught that the problem of cumulative cardiotoxicity was manageable. (Ex. 2030 at 423 ("Fortunately, much can now be done to lessen the risk of cardiac toxicity.").) Even Petitioner's cited references described techniques for reducing the risk of

anthracycline cardiotoxicity and warn against limiting or discontinuing the use of anthracyclines entirely, since that "may deprive patients who are continuing to benefit from therapy and who do not shown signs of toxicity." (Ex. 1016 at 29.)

Indeed, far from avoiding anthracyclines, Petitioner's cited references describe "important" ongoing studies involving anthracyclines. (Ex. 1010 at 4; *see* Ex. 1019 at 4.) And even contemporaneous references describing the preclinical studies for the anti-ErbB2 antibody trastuzumab focus on combinations with the anthracycline doxorubicin and do not even mention combinations with taxoids. (Ex. 1016 at 114.) Moreover, when the Phase III clinical trials for the anti-ErbB2 antibody trastuzumab began, the ***only*** combination therapy initially studied was with an anthracycline. (*See infra* pp. 21-23.) The known cumulative toxicity of anthracyclines thus did not discourage their use before the '549 invention.

Instead, as later discovered while conducting the clinical study described in the '549 patent, combining anti-ErbB2 antibodies and anthracyclines ***enhances*** the cardiotoxicity of anthracyclines, regardless of cumulative dose. (Ex. 2027 at 791 ("We found that concurrent treatment with an anthracycline, cyclophosphamide, and trastuzumab significantly increased the risk of cardiac dysfunction, as compared with treatment with only anthracycline and cyclophosphamide."); *id.* at 790 ("[t]he cumulative dose of anthracycline was not identified as a risk factor" for cardiotoxicity when combined with an anti-ErbB2 antibody).) That increased

cardiotoxicity was completely unexpected based on the prior art. (*Id.* at 791 ("a complication that had not been anticipated on the basis of the results of preclinical or early clinical studies"); Ex. 2016 at 79 ("Unexpectedly, cardiac dysfunction that had not been seen or predicted from the preclinical studies occurred in a number of patients.").) Treating HER2-positive patients was thus far more complicated than Petitioner's hindsight-driven obviousness theory suggests.

B. The Invention

1. Petitioner's obviousness theory is inconsistent with the development history for trastuzumab.

In the early 1990s, Genentech created an anti-ErbB2 antibody called "trastuzumab" or "rhuMAb HER2," which it studied as a potential new treatment for HER2-positive cancers. Petitioner repeatedly asserts that clinical trials combining an anti-ErbB2 antibody and a taxoid were already "underway" for years before the filing of the '549 patent, citing publications as early as 1994. (Paper 2 at 9, 34, 44, 53, 58.) But that is not what the prior art discloses, and not what actually happened.

Petitioner has not identified any clinical study as of 1994 involving the claimed combination—***because there was no such study***. The Phase II trials treated patients with trastuzumab alone (Ex. 1020) or combined with cisplatin (Ex. 1022), a different class of chemotherapy from taxoids. And when Genentech

began Phase III clinical trials for trastuzumab [redacted], the ***only*** combination therapy initially studied was with anthracyclines. (Ex. 2001 at 16, § 5.2.2.)

That development history reinforces what was known at time about treating HER2-positive breast cancer. Taxol®—a ***second-line*** therapy (Ex. 1012 at 6) that the prior art warned HER2-positive patients "will not respond well to" (Ex. 2029 at 1362)—was not used with trastuzumab 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 chemotherapies (*e.g.*, cisplatin) were the preferred candidates for clinical development.

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

As discussed above (p. 21), the early-stage clinical trials for trastuzumab did not involve any combinations with taxoids. And when Genentech began Phase III clinical trials [redacted], the ***only*** combination therapy initially being studied was trastuzumab combined with the anthracycline derivative doxorubicin. (Ex. 2001 at 16, § 5.2.2.)

However, after several months, that study was having difficulty enrolling patients. (Ex. 2002 at 2; Ex. 2003 at 2; Ex. 2004 at 3.) Given the prevalence of anthracyclines to treat breast cancer, many patients had previously been treated

with anthracyclines and thus were ineligible for the study. (Ex. 2001 at 14, § 4.2; Ex. 2003 at 2.)

Genentech considered several proposals to improve enrollment in the study. For example, some advocated modifying the study protocol to allow patients to be treated with trastuzumab combined with cisplatin, a platinum-based chemotherapy, which was a combination tested previously in Phase II trials. (Ex. 2004 at 4; Ex. 1022 at 3.) Others advocated allowing patients previously treated with anthracycline therapy to receive additional anthracyclines. (Ex. 2002 at 2-3.)

Dr. Susan Hellmann (a named inventor of the '549 patent), however, proposed a different option. She advocated that Genentech amend the Phase III protocol to treat patients with prior anthracycline therapy with a combination of an anti-ErbB2 antibody (trastuzumab) and a taxoid (paclitaxel). (Ex. 2002 at 3; Ex. 2003 at 2; Ex. 2004 at 5-6; Ex. 2005 at 13.) That proposal was risky for several reasons.

First, as described above (p. 12), therapies are typically tested in smaller, early-stage clinical trials before advancing to larger-stage studies. However, no human had ***ever*** been treated with the combination of an anti-ErbB2 antibody and a taxoid. Testing that combination in a Phase III 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.

Second, the preclinical data for the combination of trastuzumab with paclitaxel was "inconsistent." (Ex. 2004 at 3, 6-7.) Petitioner cites the preclinical results reported in the Baselga abstracts (Exs. 1019, 1021), but a different group of scientists at UCLA had conducted their own mouse studies of trastuzumab combined with paclitaxel and obtained "equivocal results." (Ex. 2004 at 6.) In contrast with Petitioner's hindsight-driven perspective today, Genentech at the time thus viewed the success of Dr. Hellmann's proposed combination as "less certain" than combinations with other chemotherapies (*e.g.*, anthracyclines or cisplatin). (*Id.* at 7.)

Third, taxoids at the time were approved only as a second-line therapy for metastatic breast cancer. (Ex. 1012 at 6.) The patient population for the Phase III trial, however, were first-line metastatic breast cancer patients—*i.e.*, patients who had received no prior therapy for metastatic breast cancer. (Ex. 2001 at 12.) Dr. HHellmann's proposal to use a taxoid as part of a first-line metastatic therapy was thus not supported by its approved use.

Despite those uncertainties, Dr. Hellmann advocated that Genentech adopt her proposed amendment to the Phase III protocol, and she presented her proposal at several meetings of Genentech's Product Development Committee ("PDC") in [redacted]. (Ex. 2002 at 3; Ex. 2003 at 1-2; Ex. 2004 at 2.) Dr. Hellmann had previously worked at Bristol-Myers Squibb, where she was the project team leader

for the development of paclitaxel, and she thus had an understanding of taxoids well-beyond the knowledge of a person of ordinary skill. (Ex. 1008 at 1 (Hellmann Decl. ¶ 1); *id.* at 6.) Based on that personal experience, she 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 risks associated with pursuing a combination of an anti-ErbB2 antibody and a taxoid. (Ex. 2002 at 3.)

[redacted], Genentech's PDC approved Dr. Hellmann's proposal, and the Phase III study protocol was modified in [redacted] to permit patients to receive trastuzumab combined with a taxoid in the absence of an anthracycline derivative. (Ex. 2007 at 36-38; Ex. 2004 at 2.) However, the decision 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. (Ex. 2004 at 11 (Art DeVault: "a good gamble").)

2. The '549 specification is the first disclosure that combinations containing an anti-ErbB2 antibody and a taxoid extend the time to disease progression.

Following the amendment to the Phase III protocol, the study reached its primary endpoint in late 1997. (Ex. 2008 at 51-69, 104-109.) The study showed that the combination of an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative dramatically extended the time to disease progression

without overall increase in severe adverse events. (*Id.* at 199.) By contrast, the combination of an anti-ErbB2 antibody with an anthracycline resulted in cardiotoxicity in a significant number of patients. (*Id.* at 198.) The increased cardiotoxicity of trastuzumab combined with anthracyclines was completely unexpected—particularly because those patients had received ***no*** prior anthracycline-based therapy and thus could not have experienced the cumulative toxicity known in the art. (Ex. 2008 at 39; Ex. 2001 at 12.) These data are reflected in the provisional patent application filed December 12, 1997. (Ex. 2009, 38:26-43:26.) That was the first disclosure of any clinical results for patients receiving a combination containing an anti-ErbB2 antibody and a taxoid.

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-expressing cancer cell either in vitro or in vivo," and identifies representative examples of such growth inhibitory agents. (Ex. 1001, 11:20-40.)

C. Challenged Claims

Petitioner has challenged claims 1-11 and 14-17 of the '549 patent. Those claims recite a method of treatment for breast cancer that overexpresses ErbB2 (*i.e.*, 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.

D. Prosecution History

The '549 patent issued from U.S. Patent Application No. 10/356,824 filed on February 3, 2003. (Ex. 1001, cover page.) The '824 application is a continuation of U.S. Patent Application No. 09/208,649, filed on December 10, 1998, which later issued as U.S. Patent No. 7,846,441. (*Id.*) The '649 application claims priority to U.S. Provisional Application No. 60/069,346, filed December 12, 1997. (*Id.*)

During prosecution, the examiner considered many of the references cited in the petition, including Baselga 1996 (Ex. 1020)—the primary reference underlying

Petitioner's obviousness theory—and the Baselga abstracts (Exs. 1019, 1021) that describe the results of preclinical mouse studies involving trastuzumab.[4]

Petitioner asserts (Paper 2 at 19-20, 34) that the petition presents references not before the examiner during prosecution, such as Seidman 1996 (Ex. 1011) or the general "principles" of combination chemotherapy reflected, for example, in Abeloff (Ex. 1016). But Petitioner has not identified any critical information in those references that the examiner lacked.[5] For example, Seidman 1995 (Ex. 1010) was of record, and Petitioner has cited that reference for the same supposed teaching as Seidman 1996. (*E.g.*, IPR2017-01121, Paper 1 at 26 (citing Seidman

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[4] The claims in a related application (14/141,232) are under non-final obviousness rejection in view of Baselga 1996 combined with another reference not at issue here. Patent Owner has responded to that rejection and is awaiting further action by the examiner.

[5] Petitioner also asserts that the examiner was not presented with prior art showing "that the combination of trastuzumab and cisplatin was clinically effective against metastatic HER2-positive breast cancer." (Paper 2 at 19-20.) But the reference that Petitioner cites for that supposed teaching (Pegram 1995, Ex. 1022) was of record and is cited on the face of the '549 patent. (Ex. 1001 at 6 (right column, second reference from top).)

1995 (Ex. 1010) for the proposition "that HER2-positive patients were particularly responsive to paclitaxel").) And Petitioner does not even identify Abeloff (Ex. 1016)—or any other reference describing the purported "principles" of combination chemotherapy (Paper 2 at 19-20)—among the combination of references underlying its proposed obviousness ground. (*See* Paper 2 at 24.)

In October 2009, Genentech submitted a declaration from Dr. Mark Sliwkowski in response to obviousness rejections over, among other things, Baselga 1996 and Baselga Abstract 2262. (Ex. 1009.) Dr. Sliwkowski explained that a skilled artisan would not have expected trastuzumab combined with a taxoid to produce a synergistic response, since those drugs were known to exert their effects at different points in the cell cycle. (Ex. 1009, Sliwkowski Decl. ¶ 7.) 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 trastuzumab and a taxoid; indeed, xenograft models at that time were poor predictors of clinical results for breast cancer. (*Id.* ¶ 9.)

After Patent Owner provided a terminal disclaimer over the parent application (which issued as the '441 patent) (Ex. 1004 at 1995-96), the examiner allowed the claims on October 8, 2010 (*id.* at 2020).

IV. PRIOR ART

A. Asserted References

Petitioner's proposed obviousness ground rests on four references: Baselga 1996, Seidman 1996, Pegram 1995, and the 1995 Taxol® PDR entry. Those four references (addressed below) are the only references that the Board should consider when evaluating whether the claim limitations are taught in the prior art. *See* 37 C.F.R. § 42.104(b)(4) ("The petition must specify where each element of the claim is found in the prior art patents or printed publications relied upon.").

1. Baselga 1996

Baselga 1996 (Ex. 1020) is an article published in March 1996. It was considered during prosecution and is discussed in the '549 patent's specification. (Ex. 1001, 3:36-42.)

Baselga 1996 describes a Phase II clinical study in which patients received the anti-ErbB2 antibody trastuzumab ***alone***, not combined with a taxoid (or any other chemotherapy). (Ex. 1020 at 4.) The clinical endpoint evaluated in the trial was response rate. (*Id.* at 4, 6, 7.) Although Baselga 1996 measured "[t]ime to tumor progression" for individual patients, all patients in the study received trastuzumab. (*Id.* at 4.) The study thus had no control group against which to evaluate whether trastuzumab ***extended*** the time to disease progression.

According to Baselga 1996, the vast majority of patients receiving trastuzumab showed no therapeutic response. Only 5 out of the 43 assessable patients (11.6%) had complete or partial responses to trastuzumab. (*Id.* at 6.)

Baselga 1996 acknowledged that the mechanism of potential antitumor activity for trastuzumab was not understood and proposed several possible explanations for the observed clinical results. (*Id.* at 8-9.) Thus, it remained unclear at the time how other patient populations might respond (if at all) to trastuzumab, or to combinations of trastuzumab with chemotherapy. (*Id.* ("[C]ontinued research with this agent and other HER2-targeted treatment strategies appears warranted.").)

Baselga 1996 identified several chemotherapeutic agents (cisplatin, doxorubicin, and paclitaxel) that had been combined with trastuzumab in preclinical mouse studies and noted that "clinical trials of such combination therapy are currently in progress." (*Id.* at 9.) However, Baselga 1996 did not state that the combination of an anti-ErbB2 antibody and a taxoid in particular was being studied. Nor could it have been referring to that particular combination, since there was no clinical study involving that combination when Baselga 1996 was submitted (August 8, 1995) and accepted (October 10, 1995).

2. Seidman 1996

Seidman 1996 (Ex. 1011) is an abstract published in March 1996. Seidman 1996 was not itself of record during prosecution, but other references that Petitioner cites for the same supposed teaching as Seidman 1996 (*e.g.*, Seidman 1995) were of record during prosecution. (*See, e.g.*, IPR2017-01121, Paper 1 at 26 (citing Seidman 1995 (Ex. 1010) for the proposition "that HER2-positive patients were particularly responsive to paclitaxel").)

Seidman 1996 describes a retrospective analysis of tumor samples for metastatic breast cancer patients "who were treated on phase II protocols of single agent paclitaxel (n=106) or docetaxel (n=20)." (Ex. 1011 at 5.) Seidman 1996 reported that the "response proportion" was 58.8% among HER2-positive patient and 38.7% among HER2-negative patients. (*Id.*) However, the abstract noted a wide margin of error for the overall response rate ("95% C.I. 38.1-55.5%) and acknowledged several "confounding variables" making it difficult to interpret the data. (*Id.*)

Based upon those results, Seidman 1996 speculated that "HER2 over-expression in MBC seems to confer sensitivity rather than resistance to taxanes." (*Id.*) However, the authors had no explanation for why HER2-positive status might affect the response to taxoids and simply noted that "[c]ellular mechanisms for this effect are under investigation." (*Id.*) A person of ordinary skill at the time

therefore would have viewed Seidman 1996 as merely presenting a preliminary hypothesis that required further study.[6]

3. Pegram 1995

Pegram 1995 (Ex. 1022) is an abstract published in March 1995. It was considered during prosecution of the '549 patent.

Pegram 1995 describes the results of a Phase II study in which patients were administered a combination of trastuzumab and cisplatin. (Ex. 1022 at 3.) Pegram 1995 does not describe treating patients with a taxoid, or even mention taxoids.

4. 1995 Taxol® PDR

The 1995 Taxol® PDR (Ex. 1012) is the entry from Physicians' Desk Reference from 1995 corresponding with paclitaxel. The 1995 Taxol® PDR was not itself considered during prosecution. But the only information that Petitioner

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[6] That is how the Seidman authors viewed it. They studied the issue further and reported in 2002 that HER2 overexpression did ***not*** show "a statistically significant association with clinical response to taxane therapy." (Ex. 2024 at 2322.) The Seidman authors recognized that those results were contrary to their preliminary hypothesis from Seidman 1996, which was based upon an "earlier analysis of fewer cases." (*Id.* at 2323.)

cites from the reference is its disclosure of dosage amounts for paclitaxel (*see* Paper 2 at 49), which other references before the examiner (*e.g.*, Seidman 1995) also disclosed. (*Compare* Ex. 1010 at 3 ("paclitaxel was administered via 3-hour infusion every 3 weeks, as a starting dose of 175 mg/m^2"), *with* Ex. 1012 at 8 ("TAXOL at a dose of 175 mg/m^2 administered intravenously over 3 hours every three weeks has been shown to be effective").)

The 1995 Taxol® PDR entry states that paclitaxel was approved only as a second-line therapy for metastatic breast cancer (*i.e.*, after the failure of other treatments). (Ex. 1012 at 6.) Moreover, the 1995 Taxol® PDR states that, in general, paclitaxel should be used only after first trying anthracycline therapy. (*Id.*)

The 1995 Taxol® PDR includes a black box warning regarding the possibility of "[s]evere hypersensitivity reactions" and notes that at least one patient died from those side effects. (*Id.* at 5, 6.)

The 1995 Taxol® PDR does not suggest combining paclitaxel with anti-ErbB2 antibodies, or even mention anti-ErbB2 antibodies. Moreover, the reference does not mention HER2-positive breast cancer or suggest that taxoids would be effective to treat HER2-positive patients.

B. Other References

Although not cited in its proposed ground, Petitioner also discusses various other references in its description of the state of the art. (*See* Paper 2 at 27-37.) Petitioner does not rely upon those references for the disclosure of any claim limitations. Nevertheless, for completeness, Patent Owner briefly addresses those other references below.

1. Baselga Abstract 53

Baselga Abstract 53 (Ex. 1019) is an abstract published in March 1994. It was cited during prosecution and is discussed in the '549 patent's specification. (Ex. 1001, 3:56-61.)

Baselga Abstract 53 describes the results of preclinical studies using mouse models to assess the antitumor activity of trastuzumab combined with either an anthracycline (doxorubicin) or a taxoid (paclitaxel). Those studies measured the initial tumor inhibition response in mice; they did not assess the effect, if any, on the time to disease progression. (Ex. 1019 at 4.) Both drug combinations improved the antitumor response as compared with trastuzumab or chemotherapy alone. (*Id.*) Moreover, trastuzumab "did not increase the toxicity of paclitaxel or doxorubicin in animals as determined by animal survival and weight loss." (*Id.*)

Baselga Abstract 53 notes that "[c]linical studies are underway." (*Id.*) But that is just a generic reference to clinical trials of trastuzumab. It does not refer to

studies involving the ***combination*** of trastuzumab and a taxoid, as Petitioner asserts (Paper 2 at 58). Indeed, Baselga Abstract 53 could not have been referring to ongoing studies of this combination because, as discussed above (pp. 21-23), there was no such study underway at the time.

2. Baselga Abstract 2262

Baselga Abstract 2262 (Ex. 1021) is an abstract published in March 1994. It was considered during prosecution and reports the same results from preclinical mouse models as Baselga Abstract 53.

As Petitioner notes (Paper 2 at 31-32), Baselga Abstract 2262 states that the rate of tumor inhibition was "markedly better" for combinations with paclitaxel (93%) versus doxorubicin (70%). (Ex. 1021 at 3.) But cancer researchers at the time did not view any preliminarily-observed difference in activity as favoring combinations with taxoids over anthracyclines. (*See, e.g.*, Ex. 1016 at 114 (citing Baselga's work and discussing only combinations with anthracyclines, not taxoids).) As discussed above (pp. 21-23), when the Herceptin® Phase III trials began, the ***only*** combination therapy studied was with an anthracycline, not a taxoid.

3. Seidman 1995

Seidman 1995 (Ex. 1010) is a review article published in October 1995. It was considered during prosecution of the '549 patent.

Seidman 1995 discusses the use of paclitaxel in the treatment of breast cancer. It describes studies combining paclitaxel with various other drugs, including anthracyclines. (Ex. 1010 at 4.) The article concludes by noting that there were many "important questions" concerning the use of paclitaxel to treat breast cancer that remained unanswered. (*Id.* at 7.)

V. PERSON OF ORDINARY SKILL

The Board should apply the same definition of a person of ordinary skill adopted from IPR2017-00737, which also involves the '549 patent. In IPR2017-00737, the parties agreed that a person of ordinary skill for purposes of the '549 patent would be a "clinical or medical oncologist specializing in breast cancer with several years of experience with breast cancer research or clinical trials." (IPR2017-00737, Paper 1 at 6; IPR2017-00737, Paper 7 at 36.)

Petitioner describes the person of ordinary skill in slightly different terms—for example, by including Ph.D. scientists and by requiring "substantial experience" with treating breast cancer and conducting breast cancer clinical trials. (Paper 2 at 43.) Those differences, however, do not have any bearing on the outcome here. For the reasons explained below, the challenged claims would not have been obvious under either Petitioner's proposed definition or the definition from IPR2017-00737.

VI. CLAIM CONSTRUCTION

For purposes of this proceeding, Patent Owner requests construction of "response rate" in claim 10 to mean "the percentage of patients whose tumor is reduced in size by a specified amount following treatment." That construction is supported by the specification, which defines a "response" as involving a reduction in tumor size by a specified amount (*e.g.*, 25%). (Ex. 1001, 28:48-67.)

Petitioner proposes construing "response rate" to mean "the percentage of patients whose disease responds to treatment." (Paper 2 at 23.) That is not consistent with the '549 patent's usage of the term or its ordinary meaning in the art—which is limited to the specific response of reducing tumor size. Indeed, even Petitioner contradicts its proposed construction by defining "response rate" in terms of a reduction in tumor size elsewhere in the petition and its supporting expert declaration. (*See* Paper 2 at 42 ("Response Rate (RR), which measures changes in tumor size"); Ex. 1002, Earhart Decl. ¶ 92 ("Response Rate ('RR'), which measures the percentage of patients whose tumor is reduced in size by a specified amount following treatment").)

Other than "response rate," Patent Owner does not dispute Petitioner's proposed claim constructions for purposes of this proceeding.

VII. ARGUMENT

A. Petitioner Has Not Demonstrated A Reasonable Likelihood Of Success With Respect To Any Challenged Claim.

Petitioner has asserted a single ground against the challenged claims of the '549 patent: obviousness over Baselga 1996, Seidman 1996, Pegram 1995, and the 1995 Taxol PDR entry, in view of the knowledge of a person of ordinary skill in the art. (Paper 2 at 24.)

None of those references discloses clinical efficacy results for the combination of an anti-ErbB2 antibody and a taxoid, and none even addresses whether those drugs as single agents are effective "to extend the time to disease progression" in the claimed HER2-positive patient population. Petitioner therefore has not shown a reasonable likelihood of success with respect to claim 1-4 and 16-17, which require the specific clinical efficacy result of extending the time to disease progression in HER2-positive patients using a combination that contains an anti-ErbB2 antibody and a taxoid. Claims 5-11 and 14-15 require that the claimed therapy be "effective," but Petitioner's argument for those claims rests on its same flawed theory with respect to extending time to disease progression and fails to demonstrate a reasonable likelihood of success for the same reasons.

In addition, Petitioner's assertion that taxoids had "proven efficacy" in HER2-positive patients (Paper 2 at 43) is not supported by Seidman 1996 and is directly refuted by other prior art references that Petitioner ignores. Petitioner has

not shown a reasonable likelihood of success with respect to any challenged claim for this reason as well.

Finally, none of these references teach the limitation "in the absence of an anthracycline derivative," as required by claims 16 and 17. Indeed, the development history of Herceptin®—where the only combination therapy initially studied in Phase III trials was with an anthracycline—confirms that it would not have been obvious at the time to treat patients "in the absence of an anthracycline derivative." Petitioner has not shown a reasonable likelihood of success with respect to claims 16 and 17 for this additional reason.

1. Petitioner has not established a reasonable expectation of success in achieving the claimed clinical efficacy.

a. The prior art does not teach that anti-ErbB2 antibodies or taxoids extend the time to disease progression in HER2-positive patients.

Claims 1-4 and 16-17 expressly require that the claimed combination achieve a specific clinical efficacy result—*i.e.*, "to extend the time to disease progression in the human patient." Petitioner has not shown that a skilled artisan would have reasonably expected to achieve that specific efficacy result. Indeed, the cited references contain no teaching that anti-ErbB2 antibodies and taxoids—alone or in combination—extend the time to disease progression in HER2-positive

patients.[7] The first disclosure of data addressing that clinical endpoint for anti-ErbB2 antibodies or taxoids in HER2-positive patients is in the '549 specification. (Ex. 1001, 29:13-30:25.)

The absence of any prior art data addressing the claimed clinical endpoint is a critical omission given the state of the art before the '549 invention. As discussed above (pp. 17-18), no prior antibody-based therapy had been approved for the treatment of solid tumors, and it remained highly uncertain before the '549 invention whether such therapies could ever be clinically effective. Moreover, as discussed above (pp. 18-19), there were serious doubts that taxoids—a second-line therapy that the prior art warned against using in HER2-positive patients—could be used to treat the specific patient population addressed in the '549 claims. Indeed, Petitioner admits that HER2-positive patients were "notoriously difficult to treat." (Paper 2 at 45.) Petitioner does not explain how a skilled artisan could

[7] For purposes of this preliminary response, Patent Owner focuses on the claim elements relating to an anti-ErbB2 antibody and a taxoid that are recited in each challenged claim. If it would not have been obvious to treat patients with a combination of those two drugs, the addition of a third agent to that combination as claimed in the '549 patent would not have been obvious either.

have reasonably expected to extend the time to disease progression in HER2-positive patients given those known challenges.

b. The cited references do not support Petitioner's conclusory assertions regarding the claimed clinical efficacy endpoint.

Petitioner cites Baselga 1996 and Seidman 1996 to argue that anti-ErbB2 antibodies and taxoids had "proven efficacy against metastatic HER2-positive breast cancer in humans." (Paper 2 at 43.) The 11.6% response rate in Baselga 1996's early-stage clinical trial (Ex. 1020 at 6) and Seidman 1996's retrospective analysis of tissue samples (Ex. 1011 at 5) fall far short of "proven efficacy" for either anti-ErbB2 antibodies or taxoids. In fact, even the authors of Seidman 1996 did not view that reference as demonstrating the "proven efficacy" of taxoids in HER2-positive patients. Instead, they continued to study the issue and subsequently determined that HER2-positive patients do ***not*** have any sensitivity to taxoids. (Ex. 2024 at 2322-23.)

In any case, Petitioner's obviousness theory fails for the simple reason that none of Petitioner's asserted references addresses the claimed clinical endpoint—*i.e.*, "to extend the time to disease progression." The clinical endpoint evaluated in Baselga 1996 was "response rate," which reflects the percentage of patients showing a reduction in tumor ***size*** by a specified amount. (Ex. 1020 at 4.) As Petitioner admits, "response rate" is ***different*** from "time to disease progression,"

which measures the ***time*** before the disease worsens—not the effect of therapy on tumor ***size***. (Paper 2 at 42; Ex. 1002, Earhart Decl. ¶ 92.)

Petitioner notes that Baselga 1996 reported that the "median time to progression for patients with either minor or stable disease was 5.1 months." (Ex. 1020 at 6; *see* Paper 2 at 33.) But that data does not reflect any ***extension*** in the time to disease progression, as required by the challenged claims. As Petitioner admits, the claim limitation "'extend the time to disease progression' … is a ***relative*** term." (Paper 2 at 22.) The data reported in Baselga 1996, however, is not a relative measure. All patients in the study received trastuzumab, and there was no control arm against which to evaluate whether there was any ***extension*** in the time to disease progression. (Ex. 1020 at 4.) Given the lack of a control group in the study reported in Baselga 1996 against which to measure the clinical endpoint of extending the time to disease progression, this reference does not teach the claimed comparative result.

Similarly, Seidman 1996 does not teach that taxoids are effective to extend the time to disease progression in HER2-positive patients. The only clinical endpoint reported in Seidman 1996 was response rate (*i.e.*, effect on tumor size); indeed, Seidman 1996 does not mention time to disease progression at all. (Ex. 1011 at 5.) Petitioner fails to explain how a person of ordinary skill could have

reasonably expected to obtain the claimed clinical efficacy when it is not reported in the prior art.

Nor does Pegram 1995 teach any extension in the time to disease progression. That abstract described preliminary response rate data for patients treated with trastuzumab in combination with cisplatin. (Ex. 1022 at 3.) It does not mention time to disease progression at all, let alone suggest than any of the components of the claimed combination are effective to extend the time to disease progression.

Petitioner points to the 1995 Taxol® PDR entry for its supposed disclosure of "known effective amounts of paclitaxel." (Paper 2 at 49.) But Petitioner does not contend that the 1995 Taxol® PDR entry teaches that taxoids are effective to extend the time to disease progression in HER2-positive patients. (*See id.* at 27, 49.) Indeed, the 1995 Taxol® PDR entry does not mention HER2-positive breast cancer, let alone provide clinical results showing an extension of the time to disease progression in those patients. (*See* Ex. 1012.) Petitioner's conclusory assertion that the disclosed amounts were "effective" (Paper 2 at 49) does not address the specific disease or the specific efficacy limitation recited in the challenged claims.

Finally, Petitioner cites four "principles" of combination chemotherapy (Paper 2 at 46-49), but those supposed "principles" do not render the challenged

claims obvious. As discussed above (pp. 14-15), Petitioner's cited principles apply to ***chemotherapy*** combinations, not combinations with ***antibodies***. That is significant difference because antibodies at the time were a new and unproven class of drug, and it was not clear how (if at all) antibodies could be used to treat breast cancer. (*See supra* pp. 17-18.)

And even if Petitioner's cited chemotherapy "principles" had any application to antibodies, Petitioner has failed to demonstrate that the claimed combination satisfies those four principles. For example, with respect to the first principle (*i.e.*, "each component of the combination should be active as a single agent in the intended population" (Paper 2 at 39)), neither anti-ErbB2 antibodies nor taxoids had been demonstrated to be effective as single agents to extend the time to disease progression in HER2-positive patients. Indeed, far from demonstrated efficacy in the intended population, Seidman 1996 merely presented a preliminary hypothesis that even the Seidman authors recognized required further study and that other contemporaneous publications (*e.g.*, Ex. 2029 at 1362) directly refuted. (*See infra* pp. 51-52.)

Moreover, even with those general guiding principles, treating cancer was highly unpredictable in the 1990s, as even Petitioner's cited references acknowledge. (*See supra* p. 15.) Petitioner has not explained how general principles could have provided a reasonable expectation of success in achieving the

specific clinical efficacy result claimed in the '549 patent in light of those uncertainties.

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Petitioner's obviousness theory assumes that a person of ordinary skill would have arrived at the claimed method of treatment by treating patients with an anti-ErbB2 antibody and a taxoid in "the ***known*** amounts that were effective to ***extend*** the time to disease progression." (Paper 2 at 49.) But Petitioner ignores that, in the prior art, there was ***no*** amount of an anti-ErbB2 antibody or a taxoid known to be effective to extend the time to disease progression; the first disclosure of that data is in the '549 specification. (Ex. 1001, 29:13-30:25.) In sum, Petitioner has failed to demonstrate a reasonable likelihood of success with respect to the challenged claims because the specific teaching underlying its obviousness theory was absent from the prior art.

c. Prior art preclinical mouse studies would not have provided a reasonable expectation of success of achieving the claimed clinical efficacy in humans.

Lacking prior art data in humans, Petitioner argues that a skilled artisan would have had a reasonable expectation of success based upon the "synergistic anti-tumor interaction between trastuzumab and paclitaxel" observed in preclinical mouse studies. (Paper 2 at 53.) But those preclinical studies merely showed an initial effect on tumor size (*i.e.*, "growth inhibition"), not a longer-term extension

in the time to disease progression as the challenged claims require. (Ex. 1019 at 4; Ex. 1021 at 3.) Petitioner does not explain how those preclinical results could have provided a reasonable expectation of success in achieving the ***different*** clinical endpoint of extending the time to disease progression.

Moreover, preclinical mouse studies were known at the time to be unreliable indicators of clinical outcomes in humans. (*See supra* pp. 10-11.) Petitioner has not explained how a skilled artisan could have had a reasonable expectation of success based on preclinical results evaluating a different outcome in mice given the well-known limitations of mouse models at the time to predict responses in humans.[8] *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1208-09 (Fed. Cir. 1991) (finding no reasonable expectation of success where "[t]here were many pitfalls" to achieving the claimed invention).

Petitioner points to "the lack of increased toxicity when trastuzumab was added to paclitaxel in preclinical studies" as evidence that a person of ordinary

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[8] As discussed above (p. 24), the preclinical results for the claimed combination were "inconsistent." Petitioner's obviousness theory—which focuses exclusively on the preclinical results reported in the Baselga references (Exs. 1019-21)—does not reflect the complexity of the problem addressed by the '549 invention.

skill would have had a reasonable expectation of success. (Paper 2 at 53.) But the prior art disclosed the same result for combinations of trastuzumab with the anthracycline doxorubicin—a drug combination that was later shown to produce a significant increase in cardiotoxicity when administered to humans. (Ex. 1019 at 4 ("MAb 4D5 did not increase the toxicity of paclitaxel or doxorubicin in animals as determined by animal survival and weight loss.").)

Petitioner cannot rely on those preclinical results to provide a reasonable expectation of success while ignoring results in that same study that proved wholly unsuccessful. *See Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) (patent challenger may not dismiss the portions of the prior art demonstrating non-obviousness because a reference "must be considered in its entirety, *i.e.*, as a *whole*" (emphasis in original)).

d. Petitioner's argument that ongoing clinical trials would have provided a reasonable expectation of success is factually incorrect and legally flawed.

Petitioner also argues that a person of ordinary skill would have had a reasonable expectation of success because Baselga 1996 supposedly discloses that "a clinical trial with the trastuzumab/paclitaxel combination was already underway," which it contends "confirmed that POSAs reasonably expected" success with the claimed combination. (Paper 2 at 53.) But that argument is not supported by the asserted references and is factually incorrect.

Baselga 1996 does not state that a clinical study combining trastuzumab and paclitaxel was underway. It identifies "several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel" that had been combined with trastuzumab in preclinical studies and notes that "clinical trials of such combination therapy are currently in progress." (Ex. 1020 at 9.) But Baselga 1996 does not state that the combination of trastuzumab and paclitaxel in the absence of an anthracycline derivative was being pursued; it does not specify what "combination therapy" was being studied. Nor could Baselga 1996 have been referring to the claimed combination. There was ***no*** clinical study testing the claimed combination when Baselga '96 was submitted (August 8, 1995) and accepted for publication (October 19, 1995). (*See supra* pp. 21-25.) In short, Petitioner's obviousness theory requires reading incorrect assumptions into Baselga 1996.

Petitioner's argument that a skilled artisan would have had a reasonable expectation of success based upon the mere existence of an ongoing clinical study also cannot be reconciled with the actual experience of cancer researchers in the 1990s. As discussed above (pp. 13-14), even the cancer therapies that advanced to Phase III trials failed nearly 60% of the time. Moreover, although any cancer therapy in development during the 1990s had a high likelihood of failure, the '549 invention's success was even less certain because it involved an antibody-based therapy that had yet to result in any approved drug for ***any*** solid tumor at the time.

Petitioner's theory is also legally incorrect, and adopting Petitioner's reasoning would have sweeping consequences. Clinical trials precede ***every*** drug approval. If the mere fact that those clinical trials are underway would have provided a reasonable expectation of success, then no invention relating to the efficacy of a new therapy would be patentable. That is not the law. *See, e.g.*, *Coalition for Affordable Drugs V LLC v. Biogen MA Inc.*, IPR2015-01136, Paper 23, at 10, 14, 15 (Sept. 2, 2015) (denying institution of obviousness grounds based upon ongoing clinical studies because those studies merely reflected a "hope" that "may or may not come true," not a reasonable expectation of success).

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Petitioner has failed to demonstrate that a person of ordinary skill would have had a reasonable expectation of success of extending the time to disease progression as required by claims 1-4 and 16-17. That failure of proof is fatal to Petitioner's 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 5-11 and 14-15 require clinically "effective" results. Petitioner relies on the same deficient proof relating to extending the time to disease progression for those claims, and its arguments fail for the same reasons just discussed. (*See*

Paper 2 at 49 ("With respect to the limitations 'amount effective to extend the time to disease progression in the human' (claims 1 and 16) and 'effective amount' (claim 5), a POSA would have been motivated to start with known amounts that were effective to extend the time to disease progression." (emphasis omitted)); *see also id.* at 65.) Accordingly, the Board should deny institution with respect to all challenged claims.

2. Petitioner's assertion that taxoids had "proven efficacy" in HER2-positive patients is not supported and is directly refuted by prior art teaching away from the invention.

Petitioner asserts that taxoids had "proven efficacy against metastatic HER2-positive breast cancer in humans" based upon the supposed teachings of Seidman 1996. (Paper 2 at 43.) But Seidman 1996 did not purport to demonstrate that taxoids are effective against HER2-positive cancer; it merely speculated that "HER2 over-expression in MBC seems to confer sensitivity rather than resistance to taxanes" based upon a retrospective analysis with a wide margin of error ("95% C.I. 38.1-55.5%") and several "confounding variables." (Ex. 1011 at 5.)

Seidman 1996 acknowledged that its hypothesis required further study and noted that "[c]ellular mechanisms for this effect are under investigation." (*Id.*) Even the Seidman authors at the time did not view Seidman 1996 as demonstrating

the "proven efficacy" of taxoids in HER2-positive patients; instead, they continued to study the issue. (Ex. 2024 at 2322-23.)[9]

Indeed, contrary to Petitioner's unsupported assertion of "proven efficacy," a paper published in September 1996 explicitly taught that "breast cancers that overexpress p185 [*i.e.*, HER2] will not respond well to Taxol." (Ex. 2029 at 1362.) Those statements contemporaneous with invention of the '549 patent discouraging the use of taxoids in HER2-positive patients are strong evidence of non-obviousness. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) ("An inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements."). And the fact that Petitioner selectively ignores those teachings leading away from the challenged claims confirms its reliance on hindsight.

The Board should deny institution for this reason as well.

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[9] Although not prior art, the subsequent publication from the Seidman authors determining that HER2 overexpression lacked "a statistically significant association with clinical response to taxane therapy" reinforces the preliminary nature of the hypothesis presented in Seidman 1996. (Ex. 2024 at 2322.)

3. Petitioner has not shown that it would have been obvious to treat patients "in the absence of an anthracycline derivative," as required by claims 16 and 17.

Claims 16 and 17 of the '549 patent require treatment "in the absence of an anthracycline derivative." Before the '549 invention, it would not have been obvious that patients receiving an anti-ErbB2 antibody should avoid anthracyclines. On the contrary, as discussed above (pp. 6-8), anthracyclines were the leading breast cancer therapy at the time. And anthracyclines had no known antagonistic interactions with other drugs and had flexible dosing schedules, which made them "very useful" for breast cancer combination therapies in the 1990s. (Ex. 2030 at 409.)

Petitioner now seeks to rewrite that history, arguing that "a POSA would have limited use of anthracyclines in treatment whenever possible." (Paper 2 at 51.) As discussed above (p. 7), that argument is not supported by Dr. Earhart's declaration or the prior art. Indeed, far from instructing physicians to avoid anthracyclines, Petitioner's cited reference cautions against limiting anthracycline usage, which "may deprive patients who are continuing to benefit from therapy who do not show signs of toxicity." (Ex. 1016 at 29.) Petitioner's argument also cannot be reconciled how researchers were using Herceptin® at the time. Petitioner can hardly contend that a person of ordinary skill would have limited anthracycline usage "whenever possible" when the ***only*** combination initially studied in the

Herceptin® Phase III clinical trials was with an anthracycline. (*See supra* pp. 21-23.) And contrary to Petitioner's hindsight-driven perspective today, even Petitioner's cited references from the time of the invention that describe the Baselga publications focus solely on combination with anthracyclines and do not even mention combinations with taxoids. (Ex. 1016 at 114.)

Petitioner also argues that treating patients with a taxoid would have favored avoiding anthracyclines. (Paper 2 at 51-52.) But that argument is inconsistent with the prior art, which demonstrated "considerable interest" in combining taxoids and anthracyclines. (Ex. 2014 at 774.) The prior art disclosed that combinations of paclitaxel and doxorubicin ***improved*** clinical results. (Ex. 2015 at 2698; Ex. 2013 at 13-17.) And even Petitioner's cited references acknowledge the "impressive antitumor activity" when combining taxoids with anthracyclines and describe an "important" ongoing study involving that combination. (Ex. 1010 at 4.)

Petitioner notes that Baselga 1996 reported that a patient died due to "prior anthracycline use." (Paper 2 at 52.) But Baselga 1996 did not suggest that trastuzumab contributed to that outcome or discourage the use of anthracyclines. In fact, the ***only*** patient in Baselga 1996 who experienced a complete response to trastuzumab therapy was also previously treated with anthracyclines. (Ex. 1020 at 7.) And when scientists chose a combination therapy to study in Phase III trials,

their first choice was combining trastuzumab with anthracyclines. (*See supra* pp. 21-23.)

Moreover, by Petitioner's reasoning, a person of ordinary skill would have also avoided taxoids. The 1995 Taxol® PDR entry describes a patient who died from a hypersensitivity reaction to paclitaxel. (Ex. 1012 at 6.) Only in hindsight can Petitioner say that Baselga 1996 would have discouraged the use of anthracyclines, while ignoring the same issue with taxoids.

Finally, Petitioner's obviousness theory cannot be reconciled with the preclinical studies involving trastuzumab, which indicated that combinations with anthracyclines were safe. (*See supra* p. 48.) Petitioner cannot say that those preclinical studies would have motivated skilled artisans to combine an anti-ErbB2 antibody with a taxoid, while arguing that they would not have been motivated to treat patients with combinations including anthracyclines too. Petitioner's selective interpretation of the prior art rests on hindsight and is contrary to the law. *See Genetics Inst.*, 655 F.3d at 1305.

The Board should deny institution with respect to claims 16 and 17 for the additional reason that Petitioner has not demonstrated that it would have been obvious to treat patients "in the absence of an anthracycline derivative."

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

During prosecution, Genentech submitted a declaration from Dr. Mark Sliwkowski. His declaration explained that a skilled artisan would not have had a reasonable expectation of success in achieving the '549 invention based upon what was known at the time about the biological mechanism of trastuzumab, taxoids, and other anti-cancer drugs. (Ex. 1009, Sliwkowski Decl. ¶¶ 7-8.) He also described the well-known limitations of prior art preclinical mouse models to predict success in humans. (*Id.* ¶ 9.)

Petitioner criticizes various aspects of that declaration. (Paper 2 at 53-62.) The Board need not reach those arguments because Petitioner's proposed ground fails for the reasons described above. But if the Board considers Dr. Sliwkowski's declaration, it only confirms the patentability of the challenged claims.

First, Petitioner notes that the declaration addressed only the combination of an anti-ErbB2 antibody and a taxoid, not the '549 patent's claimed three-drug combination. (Paper 2 at 54.) But the combination of an anti-ErbB2 antibody and a taxoid is a required part of each challenged claim. The non-obviousness of that two-drug combination demonstrates that non-obviousness of the challenged claims, which add a further agent to that combination.

Second, Petitioner repeatedly misrepresents what Dr. Sliwkowski's declaration says to challenge opinions that he did not provide and assumptions that he did not make. For example, Petitioner criticizes Dr. Sliwkowski for supposedly assuming that paclitaxel "only works when a cell is in the G2/M phase" (Paper 2 at 54), that "all tumor cells have the same cancerous mutations" (*id.* at 55), and that "100% of the cancerous cells are arrested by trastuzumab at the G1 phase" (*id.* at 56). Yet Petitioner cites nothing from Dr. Sliwkowski's declaration that supports Petitioner's assertions.

Petitioner also criticizes Dr. Sliwkowski (again without citation to his declaration) for supposedly applying "an absolute predictability standard." (Paper 2 at 61.) But Dr. Sliwkowski explicitly applied a reasonable expectation of success standard. (Ex. 1009, Sliwkowski Decl. ¶ 9 ("one of ordinary skill at the priority date of this application would not have had a reasonable expectation of success"); *id.* ¶ 10 ("one of ordinary skill at that time would not have had a reasonable expectation that a combination of an anti-ErbB2 antibody binding to the 4D5 epitope and a taxoid, such as paclitaxel, could be successfully used to treat human cancer patients").) The Board should disregard Petitioner's arguments that mischaracterize the actual language of the declaration.

Third, Petitioner argues that Dr. Sliwkowski's declaration is supposedly inconsistent with preclinical mouse studies involving cisplatin and paclitaxel.

(Paper 2 at 57-58.) Dr. Sliwkowski, however, explained why those prior art preclinical results are not a reliable predictor of clinical outcomes. (Ex. 1009, Sliwkowski Decl. ¶ 9.) Petitioner does not address—let alone dispute—the many well-known limitations of preclinical mouse models at that time.

Fourth, Petitioner contends that Dr. Sliwkowski's declaration is flawed because it cites an article published in 2001 (after the '549 invention date) as evidence of the unreliability of mouse models. (Paper 2 at 59-60.) But that 2001 article is a retrospective analysis involving drugs developed before the '549 invention. (Ex. 1009 at 91.) And as discussed above (pp. 10-11), numerous pre-1997 publications echo the conclusion of the 2001 article that mouse models are a poor indicator of clinical success.

Fourth, contrary to Petitioner's assertions (Paper 2 at 59-60), the Pegram 1999 reference (Ex. 1017), on which Dr. Sliwkowski is a co-author, reinforces the opinions in Dr. Sliwkowski's declaration. Consistent with Dr. Sliwkowski's description of preclinical mouse models as a "screening" tool to identify therapies to test in clinical studies (Ex. 1009, Sliwkowski Decl. ¶ 9), Pegram 1999 simply describes the use of preclinical studies to identify "rational combinations to test in human clinical studies" (Ex. 1017 at 1).

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

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

The Board should deny institution because this proceeding would violate Patent Owner's constitutional rights. Adversarial challenges to an issued patent—like *inter partes* reviews—are "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, because patents are private property rights, disputes concerning their 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). The Supreme Court has granted certiorari in *Oil States Energy Services, LLC v. Greene's Energy Group, LLC*, No. 16-712, to consider the constitutionality of *inter partes* reviews. Patent Owner presents this constitutional challenge now to preserve the issue pending the Supreme Court's decision.

VIII. CONCLUSION

The Board should deny institution.

Respectfully submitted,

Date: July 11, 2017

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CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Preliminary Response, contains 12,517 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: July 11, 2017

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CERTIFICATE OF SERVICE

I hereby certify that, on July 11, 2017, I caused a true and correct copy of the following materials:

- Patent Owner's Preliminary Response
- Certificate of Compliance
- Patent Owner's Motion to Seal
- Patent Owner's Exhibit List
- Exhibits 2001-2005, 2007-2011, 2013-2019, 2021-2032, 2036-2038

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

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IPR2017-01122
Patent Owner's Exhibit List

Patent Owner's Exhibit Number	Exhibit Name
2001	Genentech, Inc. Original H0648g Protocol PROTECTIVE ORDER MATERIAL
2002	Genentech, Inc. PDC Minutes PROTECTIVE ORDER MATERIAL
2003	Genentech, Inc. PDC Minutes PROTECTIVE ORDER MATERIAL
2004	Genentech, Inc. PDC Minutes PROTECTIVE ORDER MATERIAL
2005	Genentech, Inc. PDC Presentation PROTECTIVE ORDER MATERIAL
2006	Reserved
2007	Genentech, Inc. Amended H0648g Protocol PROTECTIVE ORDER MATERIAL
2008	Genentech, Inc. H0648g Final Report PROTECTIVE ORDER MATERIAL
2009	U.S. Provisional Application No. 60/069346
2010	Dennis J. Slamon, et al., *Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/neu Oncogene*, 235 SCIENCE 177 (1987)
2011	Dennis J. Slamon, et al., *Studies of the HER-2/neu Proto-oncogene in Human Breast and Ovarian Cancer*, 244 SCIENCE 707 (1989)
2012	Reserved
2013	Per Dombernowsky, et al., *Paclitaxel and Doxorubicin, a Highly Active Combination in the Treatment of Metastatic Breast Cancer*, 23 SEMINARS IN ONCOLOGY 13 (1996)
2014	Jason S. Fisherman, et al., *Phase I/II Study of 72-Hour Infusional Paclitaxel and Doxorubicin with Granulocyte Colony-Stimulating Factor in Patients with Metastatic Breast Cancer*, 14 J. CLINICAL ONCOLOGY 774 (1996)

Patent Owner's Exhibit Number	**Exhibit Name**
2015	Luca Gianni, et al., *Paclitaxel by 3-Hour Infusion in Combination with Bolus Doxorubicin in Women with Untreated Metastatic Breast Cancer: High Antitumor Efficacy and Cardiac Effects in a Dose-Finding and Sequence-Finding Study*, 13 J. CLINICAL ONCOLOGY 2688 (1995)
2016	M. Harries & I. Smith, *The Development and Clinical Use of Trastuzumab (Herceptin)*, 9 ENDOCRINE-RELATED CANCER 75 (2002)
2017	David Holzman, *Gene Therapy for HER-2-related Cancer*, MOLECULAR MEDICINE TODAY 138 (1996)
2018	Russ Hoyle, *Genentech Is Poised for an Anti-cancer Breakthrough*, 16 NATURE BIOTECHNOLOGY 887 (1998)
2019	Makoto Inaba, et al., *Evaluation of Antitumor Activity in a Human Breast Tumor/Nude Mouse Model with a Special Emphasis on Treatment Dose*, 64 CANCER 1577 (1989)
2020	Reserved
2021	Ismail Kola & John Landis, *Can the Pharmaceutical Industry Reduce Attrition Rates?*, 3 NATURE REV. 711 (2004)
2022	Steven Lehrer, et al., *Tumour HER2 Protein in Breast Cancer and Family History*, 341 LANCET 1420 (1993)
2023	Silvia Marsoni & Robert Wittes, *Clinical Development of Anticancer Agents—A National Cancer Institute Perspective*, 68 CANCER TREATMENT REPORTS 77 (1984)
2024	Catherine Van Poznak, et al., *Assessment of Molecular Markers of Clinical Sensitivity to Single-Agent Taxane Therapy for Metastatic Breast Cancer*, 20 J. CLINICAL ONCOLOGY 2319 (2002)
2025	Gert Riethmüller & Judith P. Johnson, *Monoclonal Antibodies in the Detection and Therapy of Micrometastatic Epithelial Cancers*, 4 CURRENT OPINION IN IMMUNOLOGY 647 (1992)
2026	Eric K. Rowinsky, et al., *Cardiac Disturbances During the Administration of Taxol*, 9 J. CLINICAL ONCOLOGY 1704 (1991)
2027	Dennis J. Slamon, et al., *Use of Chemotherapy Plus a Monoclonal Antibody Against HER2 for Metastatic Breast Cancer that Overexpresses HER2*, 344 N. ENGL. J. MED. 783 (2001)

Patent Owner's Exhibit Number	Exhibit Name
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
2038	Eddie Reed, et al., *Platinum Analogues*, *in* CANCER CHEMOTHERAPY & BIOTHERAPY: PRINCIPLES AND PRACTICE 357 (1996)