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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00737
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 IPR2017-00731. 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 the "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, some of the art and arguments that Petitioner presents in this petition overlap with Petitioner's challenge to the '441 patent in IPR2017-00731. The challenge to the '441 patent fails for the reasons described in the preliminary response that Patent Owner has submitted in IPR2017-00731.[1] 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.

[1] Petitioner has also filed a second petition challenging the '549 patent in IPR2017-00739, which Patent Owner will address in a separate preliminary response.

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." ***None*** of Petitioner's cited references disclose results for that clinical outcome.

Petitioner attempts to excuse the lack of any such teaching in the prior art by arguing that the '549 patent discloses no results for the claimed combinations either. But the '549 specification differs from the prior art in a critical way: it discloses clinical results showing that combinations of an anti-ErbB2 antibody and a taxoid are effective to extend the time to disease progression. Petitioner has not explained how a person of ordinary skill could have had a reasonable expectation of success in extending the time to disease progression without data in the prior art addressing that specific clinical result for any combination that includes at least an anti-ErbB2 antibody and a taxoid, which is a required part of the combination of every claim of the '549 patent. Simply put, if the two-drug combination of anti-ErbB2 antibody and a taxoid would not have been obvious, adding a third drug to that combination as claimed in the '549 patent would not have been obvious either.

Claims 5-15 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 person of ordinary skill

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

Second, Petitioner's obviousness theory rests on the notion that it would have been obvious to treat HER2-positive breast cancer patients (*i.e.*, the specific patient population recited in the claims) with drug combinations that include a taxoid. But the prior art teaches away from such combinations. Indeed, Petitioners admit that the Gelmon '96 reference (Ex. 1025) underlying all proposed grounds teaches that "HER2 positive breast cancer patients are ***resistant*** to … paclitaxel" (*i.e.*, a taxoid). (Paper 1 at 28, 46-47.) That concern is reinforced by other contemporaneous references that explicitly warn that HER2-positive breast cancer "will not respond well to Taxol" (*i.e.*, the brand name for the taxoid paclitaxel). (Ex. 2029 at 1362.)

Petitioner's only response is a conclusory assertion—without ***any*** citation or explanation—that Baselga '97 (Ex. 1007) and Baselga '96 (Ex. 1005) teach that treatment with an anti-ErbB2 antibody "serves to sensitize HER2 positive tumors to both therapies." (Paper 1 at 28, 47.) But that is not what those references teach, and Petitioner's conclusory assertions cannot overcome the fact that even the asserted references teach away. The Board should deny institution of all grounds for this reason as well.

Third, for Grounds 4-6, Petitioner relies 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." But Baselga '96 involved only the treatment of patients with an anti-ErbB2 antibody alone. And Baselga '94 involved only preclinical ***mouse*** models, and would not have motivated a skilled artisan to treat human patients with the claimed combination. This conclusion is confirmed by the development history for anti-ErbB2 antibodies. Despite the preclinical results reported in Baselga '94, none of the Phase II or initial Phase III studies involved a combination containing an anti-ErbB2 antibody and a taxoid. Petitioner's assertion that a person of ordinary skill nevertheless would have been motivated to treat human patients based on the results disclosed in Baselga '94 rests on impermissible hindsight.

Fourth, claims 16 and 17 (Ground 1 and 4) require treatment "in the absence of an anthracycline derivative." Petitioner argues that a person of ordinary skill would have been motivated to treat patients in the absence of an anthracycline derivative "due to the known cardiotoxic effects of anthracyclines." (Paper 1 at 40.) But that argument is flatly refuted by the very references underlying Petitioner's proposed grounds. Gelmon '96 describes "[p]romising results" from combinations with anthracyclines. And Baselga '94 (Ex. 1006) reported that combinations with anthracyclines improved antitumor activity and did not increase

toxicity in mice. The first disclosure of the problem of increased cardiotoxicity for combinations involving anti-ErbB2 antibodies and anthracyclines was in the '549 specification, and the scientific literature described that result as "unexpected." Only in hindsight can Petitioner say that anthracyclines would have been avoided.

Fifth, Petitioner asserts that it would have been obvious to try the claimed combinations. But Petitioner has not established that any of the prerequisites to support that conclusion are satisfied here. For example, Petitioner has not shown that combinations containing an anti-ErbB2 antibody and a taxoid were among a finite number of options that a person of ordinary skill would have been motivated to try. Nor has Petitioner explained how such combinations could predictably achieve the claimed result of extending the time to disease progression.

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. 1011, Lipton Decl. ¶ 26.) Early cancer treatments included surgery to remove the tumor and radiation to kill the cancer cells. (Ex. 1037 at 7.) 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.*) Over several decades, that research resulted in a wide variety of chemotherapies. (*E.g.*, Ex. 1011, Lipton Decl. ¶ 27; Ex. 1037 at 7-8; Ex. 2023 at 77 ("Over the past 35 years or so, about 30 drugs have been defined as active in one or more tumor types.").) 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. 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" at the time. (*Id.*)

As Petitioner notes, cardiotoxicity had been observed in some instances when anthracyclines were administered over time, resulting in high cumulative

doses. (Paper 1 at 7-8.) However, by 1996, that side effect 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.").) There is thus no basis for Petitioner's suggestion that researchers were motivated to avoid anthracyclines altogether before the '549 invention.

Petitioner cites references that it asserts show that researchers were using "combination regimens avoiding anthracyclines." (Paper 1 at 8 (citing Exs. 1006, 1007).) But Petitioner's cited references actually show the opposite. Baselga '94 and Baselga '97 involved combinations with anthracyclines. (Ex. 1006 at 4 ("***doxorubicin*** plus 4D5 resulted in 70% tumor inhibition"); Ex. 1007 at 10 ("Patients receive one of two chemotherapy regimens for a minimum of six cycles: cyclophosphamide and ***doxorubicin or epirubicin*** ….").)[2] And although Pegram '95 (Ex. 1013) does not mention anthracyclines (let alone suggest that they should be avoided), the abstract appearing immediately below it on the page describes a study involving the anthracycline doxorubicin. (Ex. 1013 at 5 (Abstract 125).) Petitioner has cited nothing contemporaneous with the '549 invention indicating that skilled artisans were avoiding anthracyclines.

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[2] All emphases added unless otherwise indicated.

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 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.)

The drug paclitaxel (Taxol®) is an example of a taxoid chemotherapy. The FDA approved paclitaxel for ovarian cancer in 1992 and for breast cancer in 1994. And even then, paclitaxel was approved to treat breast cancer only ***after*** other treatments failed (*i.e.*, for "second-line" use). (Ex. 1066 at 10 ("TAXOL is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.").) In fact, the approved Taxol® label from the time of the '549 invention explicitly advised that patients should have been treated with an anthracycline ***first*** 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 "widely used in breast cancer." (Ex. 1025 at 9.)

Petitioner asserts 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.)

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

Petitioner's obviousness theory rests on the notion that the '549 invention was the "logical" and predictable result of preclinical and early clinical trials involving combinations of an anti-ErbB2 antibody, taxoids, and/or growth inhibitory agents. (Paper 1 at 16-17.) But that is inconsistent with the experience

of cancer researchers at the time, as well as the actual development history of the '549 invention.

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 at that time had a "very low" likelihood of predicting how humans would respond for several reasons. (*Id.*)

First, those mouse models differed significantly from the physiology of treating cancer in humans. Prior art mouse xenograft studies involved injecting human cancer cells into immunocompromised mice. (Ex. 2024 at 264.) 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 272, 278.) Thus, it was known at the time that "the xenograft system markedly overestimates" drug activity. (*Id.*)

Second, prior art preclinical mouse models involved weight-based dosage amounts that are tolerable by a mouse, which were higher than human patients could receive. (Ex. 2019 at 1577.) At those higher doses, mouse models could show drug responses that could never be achieved in human patients. (*Id.*)

Third, the results of mouse xenograft studies at the time of the '549 invention depended heavily on the cancer cell lines used. (*Id.* at 1581.) Demonstrating antitumor activity using a particular cell line might not have translated into the same antitumor activity in other cell lines, let alone in humans.

Petitioner's proposed grounds rest on the preclinical results reported in Baselga '97 and Baselga '94, and a skilled artisan would have interpreted that reference in light of the well-known limitations of mouse models at the time. Yet Petitioner does not address those limitations or attempt to reconcile them with its obviousness theory.

2. Clinical trials

Therapies with favorable results in preclinical models might advance to clinical studies conducted 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). (Ex. 1011, Lipton Decl. ¶¶ 46-48.) The drug developer typically works with outside physician investigators, who enroll their patients in the trial. For example, the authors of the cited Baselga references were outside investigators and Genentech scientists working together on Genentech-sponsored studies. (*See, e.g.*, Ex. 1005 at 9 ("Supported in part by … Genentech, Inc.").)

a) Clinical endpoints

Clinical trials of cancer therapies can be designed to evaluate different outcomes. For example, the Baselga '96 reference reported "response rate," which is the percentage of patients who showed a measurable reduction in tumor size. (Ex. 1005 at 10.) A different clinical endpoint is the "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, 29:3-4.) Response rate and time to disease progression measure different outcomes. Response rate measures the initial response to therapy, whereas the time to disease progression measures the long-term effect of the therapy on disease progression. As described below, Petitioner does not explain how a skilled artisan could have translated the response rate data in the prior art to the time to disease progression results described and claimed in the '549 patent.

b) Low success rate for cancer therapies

The mere fact that a clinical trial was ongoing is no indication that the therapy under evaluation would achieve its desired clinical result. 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 it would have a clinical benefit when subjected to more rigorous late-stage studies. The 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.").)

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 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, 1:25-31.)

HER2-positive breast cancer is an aggressive disease. 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. 1033 at 6-7.) Even after surgery, chemotherapy, and/or radiation, HER2-positive

patients had "a shorter time to relapse as well as a shorter overall survival." (Ex. 1034 at 4; Ex. 1033 at 6-7.) 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, 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.*)

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 even 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 (p. 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. Indeed, contemporaneous with '549 invention, some scientists expressed doubt that taxoids could be used to treat HER2-positive patients. 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.) That warning against using taxoids as a treatment for HER2-positive breast cancer is reflected even in the references underlying Petitioner's proposed grounds. Indeed, Petitioner admits the Gelmon '96 reference underlying all proposed grounds teaches that HER2-positive patients are ***resistant*** to paclitaxel. (Paper 1 at 28, 46-47 ("A POSITA reading Gelmon '96 would understand that HER2 positive breast cancer patients are resistant to both paclitaxel and cisplatin therapies[.]").)

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 ("[D]ue to increased cardiac side-effects of doxorubicin or epirubicin, the combined use of anthracyclines with anti-ErbB2 antibody therapy is contraindicated.").)

Petitioner asserts that a skilled artisan would have avoided combinations with anthracyclines due to the risk of cumulative cardiotoxicity. (Paper 1 at 7-8.) But the prior art taught that the problem of cumulative cardiotoxicity was

manageable prior to the '549 invention. (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 preventing anthracycline cardiotoxicity. (Ex. 1042 at 11-12.)

Indeed, the asserted references teach that researchers were using anthracyclines (*e.g.*, doxorubicin) and obtaining "encouraging" results. (Ex. 1007 at 10; *see* Ex. 1006 at 4 ("MAb 4D5 did not increase the toxicity of … doxorubicin in animals as determined by animal survival and weight loss.").) And far from avoiding anthracyclines, when the Phase III clinical trials for the anti-ErbB2 antibody rhuMAb HER2 began, the ***only*** combination therapy initially studied was with the anthracycline doxorubicin. (*See infra* p. 21.) The known cumulative toxicity of anthracyclines thus did not discourage researchers from using those drugs prior to the '549 invention.

Instead, as it turns out, combining anti-ErbB2 antibodies and anthracyclines ***enhances*** the cardiotoxicity of anthracyclines, regardless of cumulative dose, which is a problem no reported in any of the cited art. (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).)

Indeed, the increase in the cardiotoxicity of anthracyclines was completely unexpected based on the prior art. (Ex. 2027 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.").) The problem of treating HER2-positive patients was thus far more complicated than Petitioner's hindsight-driven obviousness theory acknowledges.

B. The Invention

1. Petitioner's 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. Petitioner's obvious theory rests on two mischaracterizations of the development of rhuMAb HER2, which Patent Owner wishes to dispel at the outset.

First, Petitioner asserts 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. Petitioner has not identified any clinical study as of 1994 involving the combination of an anti-ErbB2 antibody and a taxoid—***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 for rhuMAb HER2 [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. 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. As described below (pp. 21-24), it was only when Genentech faced enrollment problems in a study involving combinations with anthracyclines that the company changed course and studied the combination of an anti-ErbB2 antibody and a taxoid.

Second, Petitioner asserts that the '549 patent supposedly "relies upon the work of others"—namely, the Baselga references asserted in this proceeding. (Paper 1 at 8-9.) But Dr. José Baselga and his co-authors were investigators for ***Genentech's*** clinical studies to develop rhuMAb HER2. In fact, the Baselga references make that relationship clear. Genentech scientists (*e.g.*, Sharon

Baughman, Jackie Moore, Thomas Twaddell, and Refaat Shalaby) are co-authors of Baselga '94 and Baselga '96. (Ex. 1005 at 9; Ex. 1006 at 4.) And Baselga '97 explains that Genentech discovered and developed rhuMAb HER2. (Ex. 1007 at 8 ("In extensive studies conducted at Genentech, Inc. …."); *id.* at 9 (rhuMAb HER2 was "constructed by Genentech scientists").) It is therefore not surprising that the '549 patent includes a similar description of the development history for rhuMAb HER2. Both describe Genentech's own original work.

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.

As discussed above (p. 20), the early-stage clinical trials for rhuMAb HER2 did not involve any combinations with taxoids. And when Genentech began Phase III clinical trials [redacted], the ***only*** combination therapy initially being studied was rhuMAb HER2 combined with the anthracycline derivative doxorubicin. (Ex. 2001 at 16, § 5.2.2.)

However, after several months, that Phase III trial 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 Phase III study. [redacted]

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 and a taxoid. (Ex. 2002 at 3; Ex. 2003 at 2; Ex. 2004 at 5-6.) That proposal was risky for several reasons.

First, as Petitioner's own expert acknowledges, therapies are typically tested in smaller, early-stage clinical trials before advancing to larger-stage studies. (Ex. 1011, Lipton Decl. ¶ 48.) However, 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.

Second, the preclinical data for the combination of rhuMAb HER2 with paclitaxel was "inconsistent." (Ex. 2004 at 3, 6-7.) Petitioner relies exclusively on the preclinical results reported in the Baselga references, but a different group of scientists working at UCLA had conducted their own mouse studies of rhuMAb HER2 combined with paclitaxel and obtained "equivocal results." (Ex. 2004 at 6.) Genentech thus viewed the success of Dr. Hellmann's proposed combination as "less certain" than combinations with other chemotherapies (*e.g.*, anthracyclines, cisplatin). (*Id.* at 7.)

Third, taxoids at the time were approved only as a second-line therapy for metastatic breast cancer. (Ex. 1066 at 10.) The patient population for the Phase III clinical 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. Hellmann'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. 1019-5 at 338, 343.) 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 risk of pursuing a combination containing an anti-ErbB2 antibody and a taxoid. (Ex. 2002 at 3.)

On [redacted], Genentech's PDC approved Dr. Hellmann's proposal, and the Phase III study protocol was modified in [redacted] to permit patients to receive rhuMAb HER2 combined with a taxoid in the absence of an anthracycline derivative. (Ex. 2007 at 36-38; Ex. 2004 at 2.) [redacted]

3. 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 [redacted]. (Ex. 2008 at 51-69, 104-109.) The study data showed that combinations containing an anti-ErbB2 antibody and a taxoid extended the time to disease progression in HER2-positive breast cancer patients. (*Id.* at 199.) By contrast, the combination of an anti-ErbB2 antibody with an

anthracycline resulted in cardiotoxicity in a significant number of patients. (*Id.* at 198.) The increased cardiotoxicity of rhuMAb HER2 combined with anthracyclines was completely unexpected—particularly given 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.

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 every claim 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.*)

1. Priority determination

During prosecution, the examiner concluded that the challenged claims "have priority to parent application 60/069,346 (filed 12/12/1997)." (Ex. 1019-6 at 245.) Although Petitioner is not challenging that priority determination in this *inter partes* review, the petition mischaracterizes certain aspects of the prosecution

history relating to that priority determination.[3] To provide an accurate record, Patent Owner addresses the prosecution history relating to the priority issue below.

The examiner recognized in her initial office action that Patent Owner could claim priority back to the parent application for claims reciting a three-drug combination with an anti-ErbB2 antibody, a taxoid, and a "further growth inhibitory agent." (Ex. 1019-5 at 41.) The pending claims at the time, however, were directed to ***different*** three-drug combinations that the examiner believed did "not appear to have been contemplated" by the parent application. (*Id.* at 42; *see, e.g.*, *id.* at 21 (original claim 20: "a combination of an antibody that binds ErbB2, a taxoid and ***a further chemotherapeutic agent***").) Based on her initial priority determination, the examiner rejected the pending claims as anticipated by intervening art. (*Id.*)

Patent Owner then amended the pending claims to align with the three-drug combinations that the examiner acknowledged could properly claim priority to the parent application—*i.e.*, with a "further growth inhibitory agent." (Ex. 1019-5 at 179.) And as exemplary support for those amended claims, Patent Owner cited the parent application's discussion of combinations with growth inhibitory agents. (*Id.*

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[3] Petitioner has filed a separate petition in IPR2017-00739, which challenges the examiner's priority determination for the '549 patent.

("This is supported in the '649 specification on at least page 37, lines 9-18, page 35, lines 6-14, and page 16, lines 11-24.").)

Patent Owner also continued to pursue claims relating to another three-drug combination (*i.e.*, original claim 32: "an antibody that binds ErbB2, a taxoid and carboplatin"). (*Id.*) The passages from the file history that Petitioner cites (Paper 1 at 11-13) relate to the written description support that Patent Owner provided for that specific three-drug combination, ***not*** the three-drug combination with a further growth inhibitory agent. The examiner, however, adhered to her initial priority determination for that claim and continued to reject it as anticipated by intervening art. (Ex. 1019-5 at 292-93.) Without acquiescing in the rejection, Patent Owner cancelled the claim to the other three-drug combination (*id.* at 307), and the priority issue with respect to that claim is thus irrelevant to the challenged claims.

The examiner ultimately concluded that the amended claims relating to the three-drug combination with a further growth inhibitory agent "have priority to

parent application 60/069,346 (filed 12/12/1997)" and withdrew the rejection over the intervening art. (Ex. 1019-6 at 245.)[4]

2. Consideration over the prior art

The Patent Office considered the Baselga references underlying Petitioner's proposed obviousness grounds during prosecution.[5] Petitioner asserts (Paper 1 at

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[4] Patent Owner added the claims reciting a "further therapeutic agent" in the same office action response in which it amended the claims reciting a "further growth inhibitory agent" to establish priority to the provisional application. (Ex. 1019-5 at 306.) Patent Owner cited the representative list of therapeutic agents in the application at page 37, lines 7-29 as support for those claims. (*Id.*) That list corresponds with the three-drug combinations that the examiner initially concluded could properly claim priority to the parent application. (*See id.* at 41.) The examiner determined that Patent Owner had established priority to the provisional application for the claims reciting a "further growth inhibitory agent" in the next office action (Ex. 1019-6 at 245), and she did not issue any further rejections based on intervening art during prosecution.

[5] Genentech has a pending application (14/141,232) in the '549 family in which the claims are under a non-final obvious rejection over Baselga '97 and Baselga '96. Genentech is preparing a response to that rejection.

8-9) that the '549 patent repeats the disclosure of the Baselga references without attribution. But the '549 patent does not conceal anything about the Baselga references. Indeed, it cites and discusses each of the Baselga references at length. (Ex. 1001, 3:36-61.) Moreover, Petitioner's suggestion (Paper 1 at 9) that the "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.)

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 skilled artisan 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, 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 rhuMAb HER2 and a taxoid; indeed, xenograft models at that time were poor predictors of clinical results for breast cancer. (*Id.* at 344-45, Sliwkowski Decl. ¶ 9.)

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).

E. Foreign Counterparts

As Petitioner notes (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 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. HOSPIRA'S ASSERTED REFERENCES

A. Baselga '94

Baselga '94 is an abstract published in March 1994. It describes the results of preclinical studies using mouse models to assess the antitumor activity of

rhuMAb HER2 combined with either an anthracycline derivative (doxorubicin) or a taxoid (paclitaxel).

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. 1006 at 4.) Both drug combinations improved the antitumor response as compared with rhuMAb HER2 or chemotherapy alone. (*Id.*) Moreover, rhuMAb HER2 "did not increase the toxicity of paclitaxel or doxorubicin in animals as determined by animal survival and weight loss." (*Id.*)

Baselga '94 notes that "[c]linical studies are underway." (*Id.*) But that is just a generic reference to clinical trials of rhuMAb HER2. It does not refer to studies involving the ***combination*** of rhuMAb HER2 and a taxoid, as Petitioner asserts (Paper 1 at 25). Indeed, Baselga '94 could not have been referring to ongoing studies of the combination because, as discussed above (pp. 19-20), there was no such study underway at the time.

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). (Ex. 1005 at 10.)

The clinical endpoint evaluated in the trial was response rate. (*Id.* at 10, 12.) 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 ***extended*** the time to disease progression.

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. (*Id.* at 12.)

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, or combinations of rhuMAb HER2 with chemotherapy. (*Id.* ("[C]ontinued research with this agent and other HER2-targeted treatment strategies appears warranted.").)

Baselga '96 identified several chemotherapeutic agents (cisplatin, doxorubicin, and paclitaxel) that had been combined with rhuMAb HER2 in preclinical mouse studies and noted that "clinical trials of such combination therapy are currently in progress." (*Id.* at 15.) However, Baselga '96 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

therapy, since there was no clinical study involving that combination at the time that Baselga '96 was submitted (August 8, 1995) and accepted (October 10, 1995). (*See supra* pp. 19-24.)

C. Baselga '97

Baselga '97 is a review article published in March 1997. It 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. Patients received rhuMAb HER2 in combination with either (i) an anthracycline derivative (cyclophosphamide and doxorubicin or epirubicin); or (ii) a taxoid (paclitaxel). (Ex. 1007 at 10.) Those patients were compared against a control arm in which patients received "cytotoxic chemotherapy alone." (*Id.*)

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 ….").)

D. Gelmon '96

Gelmon '96 is an article published in April 1996. Gelmon '96 describes a Phase I/II clinical study in which patients with metastatic breast cancer were

treated with a combination of two chemotherapeutic agents: paclitaxel and cisplatin. (Ex. 1025 at 9.) Gelmon '96 does not discuss treating patients with an anti-ErbB2 antibody, or combinations involving an anti-ErbB2 antibody.

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." (*Id.*) The clinical endpoint measured in the study was response rate. (*Id.* at 13.) Although the study measured the time to disease progression for individual patients, Gelmon '96 did not measure any ***extension*** in the time to disease progression because it contained no control arm against which to measure that endpoint. (*Id.*)

Gelmon '96 would have discouraged a person of ordinary skill from treating HER2-positive patients with a taxoid or cisplatin. Indeed, Petitioner admits that "[a] POSITA reading Gelmon '96 would understand that HER2 positive breast cancer patients are resistant to both paclitaxel and cisplatin therapies." (Paper 1 at 28, 46-47.)

E. Drebin '88

Drebin '88 (Ex. 1010) is an article published in March 1988. Drebin '88 studied the antitumor effects of various "anti-p185" (*i.e.*, anti-ErbB2) antibodies in

mouse models. (Ex. 1010 at 4.) Drebin '88 never discussed the possibility of combining an anti-ErbB2 antibody with a taxoid or other chemotherapies.

F. Presta '97

Presta '97 (Ex. 1012) is an article published in October 1997. Presta '97 describes the preparation of a humanized 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.

V. PERSON OF ORDINARY SKILL

For purposes of this proceeding, Patent Owner does not dispute Petitioner's proposed definition of a person of ordinary skill. (Paper 1 at 6.)

VI. CLAIM CONSTRUCTION

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.

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.

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.) The further "growth inhibitory agent" recited in the challenged claims is also "co-administered" as part of that combination. (*Id.*, 25:26-28.)

The surrounding claim language further confirms that "administering a combination" refers only to the drugs administered in the same treatment regimen. For example, claims 16 and 17 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 treatment regimen). (Ex. 1001, 28:17-23.) A person of

ordinary skill 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.

VII. ARGUMENT

A. Grounds 1-6: Petitioner Has Not Established A Reasonable Expectation Of Success In Achieving The Clinical Efficacy Results 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." 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 the time to disease progression is in the '549 specification. (Ex. 1001, 29:13-30:25.)[6] Absent a similar disclosure

[6] Petitioner's obviousness theory rests on the notion that the third drug (*i.e.*, "a further therapeutic agent" (claims 1, 16) or "a further therapeutic agent" (claim 5)) does not add anything inventive to the combination of an anti-ErbB2 antibody and a taxoid. (Paper 1 at 17; Ex. 1011, Lipton Decl. ¶ 81 ("it would have required nothing more than routine skill and common sense to try it for the same purpose as the two-drug combinations").) For purposes of this preliminary response, Patent

in the prior art, Petitioner cannot show that a person of ordinary skill would have had a reasonable expectation of success in achieving that clinical result with the combinations claimed in the '549 patent.

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.

For Ground 1-3, Petitioner relies on the combination of Baselga '97 and Gelmon '96 for its supposed disclosure of the claimed clinical efficacy limitations. But Petitioner's arguments are not supported by those references.

First, Petitioner points 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" time to disease progression for patients who received rhuMAb HER2. They do not describe an ***extension*** in the time to disease progression, which is a ***comparative*** result. The Phase II study described in Baselga '97 (originally reported in Baselga '96) contained no control arm against which to compare the time to disease progression and thus disclosed no ***extension*** in the time to disease progression. (*See supra* pp. 32-33.)

Owner focuses on the deficiencies in Petitioner's proof that the combination an anti-ErbB2 antibody and a taxoid would have been obvious.

Second, Petitioner relies on Baselga '97's description of preclinical mouse results obtained from combinations of 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 the time to disease progression, let alone demonstrating an extension in the time to disease progression. Petitioner argues that combinations of rhuMAb HER2 with paclitaxel or cisplatin produced "synergistic increases in treatment efficacy" (Paper 1 at 30), but Petitioner never explains how those supposed "synergistic" interactions would suggest a clinical result that was not evaluated.

Third, Petitioner points to Baselga '97's disclosure of an ongoing Phase III trial to evaluate whether combinations of rhuMAb HER2 with paclitaxel increased the time to disease progression compared with a control group. (Paper 1 at 30 (citing Ex. 1007 at 10).) But Baselga '97 reports ***no*** results from that study, which was still "ongoing." (Ex. 1007 at 10.) Petitioner never explains how the mere disclosure 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. (*See supra* pp. 13-14.)

Fourth, Petitioner argues 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" time to disease progression, but contains no comparative data showing any ***extension*** in the time to disease progression. (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 the time to disease progression. (*Id.*)

Fifth, Petitioner attempts to minimize the significance of the clinical efficacy limitation by arguing that "any" extension in the time to disease progression would suffice. (Paper 1 at 29.) But that does not relieve Petitioner of the obligation to show a reasonable expectation of success in achieving ***some*** extension in the time to disease progression. Petitioner has not explained how a person of ordinary skill would have had a reasonable expectation of success in obtaining even a minimal extension in the time to disease progression when that clinical outcome is not described in the prior art.

Finally, Petitioner attempts to excuse the complete absence of the claimed extension of the time to disease progression 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 Petitioner ignores that the '549 patent discloses clinical results showing an extension in the time to disease progression 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, Petitioner 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.[7]

2. Grounds 4-6: Baselga '96 in view of Gelmon '96 and Baselga '94 does not teach that the claimed combination would extend the time to disease progression.

For Ground 4-6, Petitioner relies on Baselga '96 in view of Gelmon '96 and Baselga '94 for the supposed disclosure of the claimed clinical efficacy limitations. Those arguments are similar to Petitioner's arguments for Grounds 1-3 and fail for the same reasons.

First, Petitioner argues that Baselga '96 discloses an extension in the time to disease progression 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. 39-40), that is not the ***extension*** in the time to disease progression required by the claims, which is a ***comparative*** result. Baselga '96 had no control

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

arm to measure that comparative result, and Petitioner has not explained how a person of ordinary skill could have had a reasonable expectation of success in achieving a result that Baselga '96 does not describe.

Second, Petitioner argues that Baselga '96 describes preclinical results supposedly showing "synergistic increases in treatment efficacy." (Paper 1 at 48 (citing Ex. 1005 at 15).) But Petitioner ignores that those preclinical results did ***not*** involve the time to disease progression, let alone an extension in the time to disease progression. (*See supra* p. 32.) Petitioner again does not explain how "synergistic results" in mice would provide an expectation of success in achieving a completely different result in humans.

Third, Petitioner repeats its 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. (*See supra* p. 35.)

Fourth, Petitioner asserts that the challenged claims are satisfied by "any" minimal extension in the time to disease progression. But as discussed above (p. 41), that does not excuse Petitioner from presenting evidence showing that the prior art would have led a person of ordinary skill in the art to have a reasonable

expectation of achieving such an extension in the time to disease progression (which Petitioner has not done).

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The cited references do not disclose the clinical result of extending the time to disease progression for ***any*** therapy, and Petitioner's arguments relating to that limitation are flatly contradicted by what the references actually say. Petitioner therefore cannot establish that a person of ordinary skill would have had a reasonable expectation of success in achieving the clinical result 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 5-15 require clinically "effective" results. Petitioner relies on the same deficient proof relating to extending the time to disease progression for those claims (*see* Paper 1 at 33-34, 51-52), and its arguments fail for the same reasons just discussed. Accordingly, the Board should deny institution of all grounds.

B. Grounds 1-6: Petitioner Has Not Established A Reasonable Expectation Of Success Because The Prior Art Taught Away From Using Taxoids To Treat HER2-Positive Patients.

All claims of the '549 patent relate to the treatment of HER2-positive breast cancer (*i.e.*, "breast cancer that overexpresses ErbB2 receptor" (claim 1), "breast cancer characterized by overexpression of ErbB2 receptor" (claim 5), or "ErbB2 overexpressing breast cancer" (claim 16)) with drug combinations that include a taxoid. But it would not have been obvious to a person of ordinary skill prior to the '549 invention that combinations that include a taxoid would be effective in HER2-positive patients.

Indeed, the prior art expressly teaches away from the use of taxoids to treat HER2-positive breast cancer. For example, a paper published in 1996 warns that "breast cancers that overexpress p185 [*i.e.*, HER2] will not respond well to Taxol." (Ex. 2029 at 1362.) And even Petitioner admits that Gelmon '96—the reference underlying all proposed grounds—teaches that "HER2 positive breast cancer patients are resistant to both paclitaxel and cisplatin therapies." (Paper 1 at 28, 46-47.) It is no wonder then that the Phase II and initial Phase III clinical development of rhuMAb HER2 did not involve any combinations with taxoids. (*See supra* pp. 19-20.) Only in hindsight can Petitioner assert that it would have been obvious to treat HER2-positive patients with taxoids prior to the '549 invention.

In the face of that express teaching away, the only explanation that Petitioner offers is that Baselga '97 and Baselga '96 supposedly disclose "rhuMAb HER2 serves to sensitize HER2 positive tumors to" taxoid therapy. (Paper 1 at 28, 57.) Petitioner does not cite anything in support of that proposition—because that is not what the references disclose. On the contrary, Baselga '96 emphasized that the mechanism of activity for rhuMAb HER2 was unknown. (Ex. 1005 at 14-15.) And Baselga '97 explained that it was not clear how human patients might respond to the combination of rhuMAb HER2 and paclitaxel, which was "currently being evaluated" in a clinical trial. (Ex. 1007 at 11.)

To the extent that Petitioner is relying on the preclinical results disclosed in Baselga '96 and Baselga '97 to demonstrate that rhuMAb HER2 "sensitizes" HER2-positive breast cancers to taxoids, that is not what the references say. At most, those references state that "rhuMAb HER2 markedly potentiated the antitumor activity of several chemotherapeutic agents" without providing any explanation why. (Ex. 1005 at 15; Ex. 1007 at 9-10.) In fact, Baselga '96 says the same thing about the combination with the anthracycline doxorubicin (Ex. 1005 at 15), and Baselga '97 characterizes those preclinical results with doxorubicin as "encouraging" (Ex. 1006 at 10). Yet Petitioner nevertheless argues that a person of ordinary skill would have avoided combinations with anthracyclines. (Paper 1 at

7-8.) The inconsistency in Petitioner's argument confirms its reliance on hindsight.

And in any case, those prior art preclinical results for the combination of rhuMAb HER2 and paclitaxel were far from conclusive. As discussed above (pp. 22-23), other preclinical studies involving that combination produced only "equivocal" results. And Petitioner also ignores the well-known limitations of preclinical studies at that time to predict outcomes in human patients. (*See supra* pp. 13-14.) As such, Petitioner has not shown that a person of ordinary skill would have had a reasonable expectation of success given the express teachings in the prior art that HER2-positive patients would not respond to taxoids.

C. 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, Petitioner argues that the combination of Baselga '96 and Baselga '94 teaches that limitation. But those arguments are not supported by those references.

1. Baselga '96

Baselga '96 does not teach "administering a combination" of an anti-ErbB2 antibody and a taxoid. It discloses the treatment of patients with rhuMAb HER2

alone, not with a taxoid. (Ex. 1005 at 10 ("Chemotherapy … was not permitted.").)

Petitioner argues that Baselga '96 teaches a combination of an anti-ErbB2 antibody and a taxoid because four patients had "***prior*** systemic therapy" with a taxoid. (Paper 1 at 45.) But those patients were not "administered a ***combination***" of anti-ErbB2 antibody and a taxoid, as that term is properly construed. (*See supra* pp. 36-38.) 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.)

Petitioner also argues that Baselga '96 teaches a combination of an anti-ErbB2 antibody and a taxoid because it (i) describes 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.) But Baselga '96 does not state that the combination of rhuMAb HER2 and paclitaxel was being pursued; it does not specify what "combination therapy" was being studied.

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) and accepted for publication (October 19, 1995). (*See supra* pp. 19-24.) The fact

that Petitioner's obviousness theory requires reading incorrect assumptions into Baselga '96 confirms Petitioner's reliance on hindsight.

2. Baselga '94

Baselga '94 would not have motivated a person of ordinary skill 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. A skilled artisan would not have been motivated to treat human patients with an anti-ErbB2 antibody and a taxoid based upon Baselga '94 for several reasons.

First, Baselga '94 also discloses treating patients with rhuMAb HER2 and the anthracycline derivative doxorubicin. (Ex. 1006 at 4.) That combination provided an improved antitumor response and did not result in any apparent toxicity. (*Id.*) Yet Petitioner argues that a person of ordinary skill would not have pursued a therapy combining rhuMAb HER2 with anthracyclines. (Paper 1 at 7-8, 57-58.) Petitioner cannot have it both ways. If the disclosures in Baselga '94 would not have motivated a skilled artisan to treat patients with the combination of rhuMAb HER2 and anthracyclines, then they would not have caused a skilled artisan to pursue rhuMAb HER2 combined with a taxoid either. The inconsistency in Petitioner's obviousness theory demonstrates that Petitioner is using hindsight to

selectively focus on the portions of the prior art that support its position while disregarding the teachings that do not.

Second, there were significant concerns with using taxoids to treat HER2-positive breast cancer before the '549 invention. At the time, patients had experienced serious hypersensitivity reactions, and taxoids were only approved for second-line use in breast cancer. (*See supra* p. 9.) 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, Petitioner admits that Gelmon '96 teaches that "HER2 positive breast cancer patients are resistant to … paclitaxel." (Paper 1 at 28, 46-47.) Petitioner does not address these significant concerns with taxoids, or explain how Baselga '94 addressed them.

Third, a person of ordinary skill would have known that preclinical results were not a reliable predictor of clinical efficacy and safety, and interpreted the results reported in Baselga '94 in light of those well-known limitations of preclinical models at the time. (*See supra* pp. 13-14.) Petitioner has not provided any explanation why a skilled artisan would have believed that the results reported in Baselga '94 were any different than the numerous other therapies that initially showed promise in mouse models, but ultimately failed in humans.

Indeed, the development history of rhuMAb HER2 confirms that Baselga '94 would not have motivated a skilled artisan to treat humans with an anti-ErbB2

antibody and a taxoid. Despite studying combinations with other chemotherapies (*e.g.*, cisplatin (Ex. 1010), doxorubicin (Ex. 2001)), ***none*** of the Phase II and initial Phase III clinical trials tested the combination of an anti-ErbB2 antibody and a taxoid. Only in hindsight can Petitioner contend that a skilled artisan would have been motivated to use a combination that even those with the best information about rhuMAb HER2 at the time did not pursue.

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Because Petitioner has not shown that the combination of Baselga '96 with Baselga '94 would have motivated a person of ordinary skill to "administer[] a combination" of an anti-ErbB2 antibody and a taxoid "to the human patient," Grounds 4-6 fail.

D. Grounds 1 And 4: The Asserted References Do Not Teach Treatment "In The Absence Of An Anthracycline Derivative" As Required By Claims 16 And 17.

Claims 16 and 17 expressly require treatment "in the absence of an anthracycline derivative." Petitioner has not demonstrated that the asserted references teach that limitation.

For both Grounds 1 and 4, Petitioner argues that a person of ordinary skill would have been motivated to treat patients in the absence of an anthracycline derivative because "[t]he cardiotoxicity of anthracycline derivatives were known in the prior art." (Paper 1 at 39-40, 57-58.) But Petitioner ignores that the problem

with combining anthracyclines with an anti-ErbB2 antibody is not the cumulative cardiotoxicity that was known in the art, but rather the increase in cardiotoxicity that results from the combination with anti-ErbB2 therapy. (*See supra* pp. 17-19.) That increase in cardiotoxicity was completely unexpected. (Ex. 2027 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.").)

Indeed, contrary to Petitioner's assertion that anthracyclines were being avoided, the references underlying Grounds 1 and 4 disclose treatments with anthracycline combinations and repeatedly suggest that combinations with anthracyclines were "promising" and safe. (*E.g.*, Ex. 1005 at 15 ("In preclinical studies, both in vitro and in xenografts, rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, ***doxorubicin***, and paclitaxel, ***without increasing their toxicity***."); Ex. 1006 at 4 ("MAb 4D5 ***did not increase the toxicity of*** paclitaxel or ***doxorubicin*** in animals as determined by animal survival and weight loss."); Ex. 1007 at 10 ("Patients receive one of two chemotherapy regimens for a minimum of six cycles: cyclophosphamide and ***doxorubicin or epirubicin*** …."); Ex. 1025 at 9 ("***Promising results*** have also been reported with combinations of paclitaxel and

other active agents such as ***doxorubicin***, cyclophosphamide, and edatrexate.").) Petitioner's obviousness theory therefore cannot be reconciled with what the asserted references actually say.[8]

Petitioner alternatively argues that its asserted references teach the absence of an anthracycline derivative because they teach "the combination of rhuMAb HER2, paclitaxel and cisplatin." (Paper 1 at 40, 58.) But that argument depends on a selective interpretation of the references that ignores their teachings as a whole. As just discussed, each of the references underlying Grounds 1 and 4 discloses combinations with an anthracycline derivative. Petitioner may not demonstrate the absence of an anthracycline derivative by selectively ignoring those teachings. *See Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc*.,

[8] For Ground 4, Petitioner also argues that Baselga '96 would have led a person of ordinary skill to treat patients in the absence of an anthracycline derivative because one patient in the study "died of heart failure associated with prior doxorubicin treatment." (Paper 1 at 58.) But that argument cannot be reconciled with the actual development history for rhuMAb HER2, which proceeded with a Phase III study that initially included ***only*** the combination of rhuMAb HER2 with an anthracycline. (*See supra* pp. 19-24.)

655 F.3d 1291, 1305 (Fed. Cir. 2011) (a reference "must be considered in its entirety, *i.e.*, as a *whole*").

Accordingly, the Board should deny institution with respect to claims 16 and 17 for this additional reason.

E. Grounds 1-6: Petitioner Has Not Demonstrated That The Claimed Combinations Would Have Been Obvious To Try.

The proposed grounds ultimately rest on the theory that claimed combinations would have been obvious to try. But Petitioner has not established that the claimed combinations were among "a ***finite*** number of identified, ***predictable*** solutions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

First, Petitioner argues the claimed combination was "the only combination left to try." (Paper 1 at 31, 49.) But that assertion cannot be reconciled with Petitioner's 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 ….").)

Petitioner's assertion is also inconsistent with the development history of rhuMAb HER2. As discussed above (pp. 19-24), Genentech pursued several alternative therapies (*e.g.*, anti-ErbB2 antibody alone (Ex. 1004), combined with

cisplatin (Ex. 1010), or combined with doxorubicin (Ex. 2001) and only pursued the combinations containing an anti-ErbB2 antibody and a taxoid after '549 inventor Dr. Hellmann convinced the company to change course. The fact that such combinations were not even among the treatment regimens pursued in any Phase I, 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 person of ordinary skill would have pursued—and actually did pursue—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).

Second, Petitioner's obvious-to-try theory fails for the further reason that the claimed invention was not one of "a finite number of identified, ***predictable*** solutions." *KSR*, 550 U.S. at 421. 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 the rhuMAb HER2 combined with anthracyclines. (*See supra* pp. 13-14, 32.) Petitioner cannot demonstrate that the art was predictable when the very references underlying its obviousness theory show that it was not. Petitioner

does not address the unpredictability of the field, let alone explain how the invention could have been obvious to try given those uncertainties.

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

F. Petitioner's Criticisms Of Dr. Sliwkowski's Declaration Do Not Demonstrate The Obviousness Of The Challenged Claims.

During prosecution, Genentech submitted the declaration of Dr. Mark Sliwkowski. His declaration explained that a person of ordinary skill would not have had a reasonable expectation of success in achieving the '549 invention based upon what was known about the biological mechanism of rhuMAb HER2, taxoids, and other anti-cancer drugs at the time. (Ex. 1019-6 at 343-44, Sliwkowski Decl. ¶¶ 7-8.) Dr. Sliwkowski also described the well-known limitations of prior art preclinical mouse models to predict success in human patients. (Ex. 1019-6 at 344-45, Sliwkowski Decl. ¶ 9.)

Petitioner criticizes various aspects of Dr. Sliwkowski's declaration. (Paper 1 at 61-65.) The Board need not reach Petitioner's arguments with respect to Dr. Sliwkowski's declaration because Petitioner's proposed grounds fail for the numerous reasons described above. But if the Board considers 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

combinations. (Paper 1 at 61.) 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 the non-obviousness of the challenged claims, which add a further agent to that combination.

Second, Petitioner criticizes Dr. Sliwkowski's declaration for not citing papers involving the combination of rhuMAb HER2 and a taxoid. (Paper 1 at 62.) But Petitioner has not explained why those papers would have been necessary to the point addressed in the declaration, or identified any such prior art paper that could have been cited. If anything, the absence of such papers confirms the ***non-obviousness*** of that combination as a therapeutic regimen, since it suggests that combination was not an area of interest prior to the '549 invention.

Third, Petitioner argues that the declaration is supposedly inconsistent with the "synergistic" results in preclinical mouse studies involving cisplatin and paclitaxel. (Paper 1 at 62-63.) Dr. Sliwkowski's declaration, however, explained why those prior art preclinical results are not a reliable predictor of clinical outcomes. (Ex. 1019-6 at 344-45, Sliwkowski Decl. ¶ 9.) Petitioner does not address—let alone dispute—those many well-known limitations of preclinical mouse models at that time.

Finally, 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 1 at 63.) But the article published in 2001 is a retrospective analysis involving drugs developed before the '549 invention. (Ex. 1019-7 at 32.) And as discussed above (pp. 11-12), numerous pre-1997 publications echo the conclusion of the 2001 article that mouse models are a poor indicator of clinical success. Genentech's use of preclinical models (*see* Paper 1 at 63-64) does not suggest otherwise. Petitioner cites no evidence suggesting that Genentech (or anyone else) relied on those models at the time of the '549 invention as anything other than a preliminary screening tool, consistent with their well-known limitations to predict clinical results at the time.

VIII. CONCLUSION

The Board should deny institution.

Respectfully submitted,

Date: May 2, 2017

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CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Preliminary Response, contains 12,450 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: May 2, 2017

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CERTIFICATE OF SERVICE

I hereby certify that, on May 2, 2017, I caused a true and correct copy of the following materials:

- Patent Owner's Preliminary Response
- Patent Owner's Motion to Seal
- Patent Owner's Exhibit List
- Exhibits 2001-2004, 2007-2008, 2016-2019, 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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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
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

Patent Owner's Exhibit Number	**Exhibit Name**
2021	Ismail Kola & John Landis, *Can the Pharmaceutical Industry Reduce Attrition Rates?*, 3 NATURE REV. 711 (2004).
2022	Steven Lehrer, et al., *Tumour HER2 Protein in Breast Cancer and Family History*, 341 LANCET 1420 (1993).
2023	Silvia Marsoni & Robert Wittes, *Clinical Development of Anticancer Agents—A National Cancer Institute Perspective*, 68 CANCER TREATMENT REPORTS 77 (1984).
2024	Jürgen Mattern, et al., *Human Tumor Xenografts as Model for Drug Testing*, 7 CANCER & METASTASIS REV. 263 (1988).
2025	Gert Riethmüller & Judith P. Johnson, *Monoclonal Antibodies in the Detection and Therapy of Micrometastatic Epithelial Cancers*, 4 CURRENT OPINION IN IMMUNOLOGY 647 (1992).
2026	Eric K. Rowinsky, et al., *Cardiac Disturbances During the Administration of Taxol*, 9 J. CLINICAL ONCOLOGY 1704 (1991).
2027	Dennis J. Slamon, et al., *Use of Chemotherapy Plus a Monoclonal Antibody Against HER2 for Metastatic Breast Cancer that Overexpresses HER2*, 344 N. ENGL. J. MED. 783 (2001)
2028	Raymond B. Weiss, et al., *Hypersensitivity Reactions from Taxol*, 8 J. CLINICAL ONCOLOGY 1263 (1990).
2029	Dihua Yu, *Overexpression of c-erbB-2/neu in Breast Cancer Cells Confers Increased Resisitance 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

Patent Owner's Exhibit Number	**Exhibit Name**
2037	Modified Default Standing Protective Order – Redline
2038	Eddie Reed, et al., *Platinum Analogues*, *in* CANCER CHEMOTHERAPY & BIOTHERAPY: PRINCIPLES AND PRACTICE 357 (1996)