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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00731
Patent 7,846,441

PATENT OWNER'S PRELIMINARY RESPONSE

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I. INTRODUCTION

U.S. Patent No. 7,846,441 claims a groundbreaking treatment for HER2-positive breast cancer—a particularly virulent form of the disease. Prior to the '441 invention, a diagnosis of HER2-positive breast cancer was effectively a death sentence; even with prior art treatments, the disease frequently recurred and rapidly spread. In 1996, HER2-positive breast cancer patients had an average life expectancy of only 18 months.

That all changed with the '441 invention, which disclosed the use of a new kind of antibody-based therapy targeting HER2-positive cancers, called an "anti-ErbB2" antibody. When administered with a chemotherapy called a "taxoid," and in the absence of another chemotherapy called an "anthracycline," this combination significantly extended patient lives without increasing the side effects of chemotherapy. Based on those impressive results, the FDA in 1998 approved Genentech's drug Herceptin® to treat HER2-positive breast cancer patients as claimed in the '441 patent—making it the ***first*** approved antibody-based therapy for solid tumors.

Petitioner attempts to cast the '441 invention as a routine combination based upon three references reporting preclinical and early-stage clinical experiments: Baselga '94 (Ex. 1005), Baselga '96 (Ex. 1004), and Baselga '97 (Ex. 1006). Those references were all considered extensively during prosecution, and the

challenged claims were deemed patentable over them. Petitioner has not provided any legitimate basis to reach a different conclusion now.

First, the challenged claims recite the specific clinical efficacy result of "extend[ing] the time to disease progression." The Baselga references contain ***no*** data demonstrating an improvement with respect to that claimed efficacy result—or, for that matter, any other clinical results for the combination of drugs claimed. Petitioner has not explained how a skilled artisan would have had a reasonable expectation of success in achieving the clinical result of "extend[ing] the time to disease progression" in the absence of any data addressing that endpoint.

Second, the challenged claims also recite a specific clinical safety result: "without increase in overall severe adverse events." Petitioner has not explained how a skilled artisan could have had a reasonable expectation of success in achieving that safety result either. Indeed, Baselga '94—which incorrectly suggests that combinations of anti-ErbB2 antibodies with anthracyclines do not increase toxicity—highlights the unpredictability of clinical safety and demonstrates Petitioner's reliance on hindsight.

Third, at the time of the '441 invention, taxoids were a relatively new class of chemotherapy and were perceived as having significant problems. Taxol®—the prototypical taxoid chemotherapy—was approved only for second-line use after prior breast cancer treatments had failed. And the prior art specifically warned that

HER2-positive breast cancer "will not respond well to Taxol." Consistent with those concerns (and despite Petitioner's unsupported assertions to the contrary), there were ***no*** clinical studies combining an anti-ErbB2 antibody and a taxoid until '441 inventor Dr. Susan Hellmann proposed amending an ongoing Phase III clinical trial to test her invention. Prior to this amendment by Dr. Hellmann, even those with the best information pursued other options, instead of the claimed combination.

Fourth, despite decades of research and numerous failed attempts, there were no approved antibody-based therapies for solid tumors prior to the '441 invention. And there were significant doubts at the time whether it would even be possible to develop such an antibody-based therapy. A skilled artisan would have known of those past failures and interpreted Petitioner's cited references in that light. Yet Petitioner does not even acknowledge that history, let alone explain how it was supposedly "routine" to succeed where nobody had before.

Those holes in Petitioner's theory are fatal to both proposed grounds. Petitioner has not demonstrated a reasonable expectation of success in achieving the claimed clinical efficacy and safety results that the '441 patent was the first to describe. Nor has Petitioner established that the claimed combination was obvious to try when it was not even among a finite number of treatments initially pursued and when the asserted references underscore the unpredictability of the field.

Additional reasons specific to each ground further confirm that Petitioner has not demonstrated a reasonable likelihood of success.

Ground 1: Baselga '97—the primary reference in Ground 1—is not prior art. Petitioner attempts to portray the '441 invention as a product of the Baselga references, but it is actually the other way around. The '441 invention was developed first by Dr. Hellmann at Genentech, who proposed and implemented an amendment to an ongoing Phase III clinical trial to treat patients with a combination of an anti-ErbB2 antibody and a taxoid in the absence of anthracycline derivative. By the time that Baselga '97 was published, at least one patient under Dr. Hellmann's direction had already been treated with the claimed invention, and Dr. Hellmann was diligently overseeing the completion of the Phase III trial that provided the clinical results first disclosed and claimed in the '441 patent. Baselga '97—a publication from outside clinical investigators at one of the study sites—merely describes the design of the clinical study ***after*** implementing Dr. Hellmann's amendment, and is not prior art.

Ground 2: The combination of Baselga '96 and Baselga '94 does not teach "administering a combination" of an anti-ErbB2 antibody and a taxoid "to the human patient," as required by the challenged claims. Baselga '96 treated 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. Baselga '96 and Baselga '94 also would not have led a person of ordinary skill to treat patients "in the absence of an anthracycline derivative," as the '441 patent requires. On the contrary, Baselga '94 showed that combinations with anthracyclines improved antitumor activity and did not increase toxicity in mice. Only in hindsight can Petitioner say that anthracyclines would have been avoided.

Finally, several objective indicia of non-obviousness confirm the patentability of the challenged claims, including satisfaction of a long-felt but unmet need, praise, unexpected results, and commercial success. Indeed, the need for the '441 invention was so significant that the FDA fast-tracked Herceptin® for approval in just a matter of months. And contrary to Petitioner's narrative that the claimed invention would have been obvious over the Baselga references, Dr. Larry Norton of Memorial Sloan-Kettering—a major figure in the treatment of breast cancer and co-author of the three asserted Baselga references—went on national television to tout the '441 invention's impressive efficacy: "This is a very big, dramatic advance, one of the biggest changes in the ability of chemotherapy to kill cancer cells that I've ever seen in my career." Petitioner's criticisms of Dr. Mark Sliwkowski's declaration submitted during prosecution are also incorrect and confirm Petitioner's reliance on hindsight.

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. 1007, Lipton Decl. ¶ 26.) Early cancer treatments included surgery to remove the tumor and radiation to kill the cancer cells. (Ex. 1017 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. 1007, Lipton Decl. ¶ 27; Ex. 1017 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, two drug classes are mentioned in the challenged claims: anthracyclines and taxoids.

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 13.) 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 '441 invention.

Petitioner cites Pegram '95 (Ex. 1010) for the proposition that researchers "avoided using anthracyclines." (Paper 1 at 13.) But the reference itself refutes that assertion: the abstract appearing immediately below Pegram '95 describes a study involving the anthracycline doxorubicin. (Ex. 1010 at 5 (Abstract 125).) Moreover, the references underlying Petitioner's proposed grounds confirm that anthracyclines were not being avoided. Both Baselga '94 and Baselga '97 involved combinations with anthracyclines. (Ex. 1005 at 4; Ex. 1006 at 10.)

Petitioner has cited nothing contemporaneous with the '441 invention indicating that skilled artisans were avoiding anthracyclines.

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. 1025 at 10.) In fact, the approved Taxol® label from the time of the '441 invention explicitly advised that patients should have been treated with an anthracycline ***first*** before trying paclitaxel. (*Id.*)

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

Petitioner's obviousness theory rests on the notion that the '441 invention was the result of a predictable process with positive results in preclinical and early clinical trials leading to the next stage of development. (Paper 1 at 8-13.) But that is inconsistent with the experience of cancer researchers at the time, as well as the actual development history of the '441 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 '441 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 '441 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 '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. 1007, Lipton Decl. ¶ 46.) 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. 1004 at 9 ("Supported in part by … Genentech, Inc.").)

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. (*Id.* at 10.) 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.) Response rate and time to disease progression measure different outcomes. Response rate measures the initial response to therapy, whereas 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 '441 patent.

Petitioner's obviousness theory rests on the notion that a skilled artisan would have had a reasonable expectation of success in obtaining the claimed clinical efficacy and safety results of the '441 invention simply because a clinical trial for a new cancer therapy was underway. (*See, e.g.*, Paper 1 at 48 ("Clinical trials can be time consuming and expensive; therefore, they would not be

conducted *without* a reasonable expectation of success." (emphasis in original)).) Petitioner has not offered any support for that position, and it 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 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.").)[1]

[1] All emphases added unless otherwise indicated.

III. THE '441 PATENT

A. The Problem To Be Solved

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

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

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. 1028 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. 1029 at 4; Ex. 1028 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 succeeded for solid tumors, such as breast cancer.

The '441 patent claims a different approach to treating HER2-positive cancer, which involves combining an anti-ErbB2 antibody (*i.e.*, that targets HER2) and a taxoid in the absence of an anthracycline derivative. 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, 8:44-9:3.) 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 '441 invention:

"[A]ntibody therapy of cancer has become a story of unending failures." (Ex. 2032 at 732.) As confirmed by a 1996 textbook, those "significant obstacles" persisted even up to the invention of '441 patent. (Ex. 2031 at 683.)

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

As discussed above (p. 8), 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 the '441 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.)

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 '441 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 13.) But the prior art taught that the problem of cumulative cardiotoxicity was manageable prior to the '441 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. 1033 at 11-12.)

Indeed, the asserted references teach that researchers were using anthracyclines and obtaining "encouraging" results. (Ex. 1006 at 10; *see* Ex. 1005 at 4.) 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. 18.) The known cumulative toxicity of anthracyclines thus did not discourage researchers from using those drugs prior to the '441 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 not 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 had been ongoing clinical trials involving the claimed combination of an anti-ErbB2 antibody and a taxoid beginning in 1994

and continuing for years before the '441 invention—an assertion that Petitioner repeats no less than a dozen times. (Paper 1 at 9, 23, 24, 28, 30, 31, 34, 45, 47, 51, 61, 62.) But that is not what the prior art discloses, and not what actually happened. Petitioner has not identified any clinical study as of 1994 involving the claimed combination—***because there was no such study***. The Phase II trials treated patients with rhuMAb HER2 alone (Ex. 1004) or in combination with cisplatin (Ex. 1010), a different class of chemotherapy from taxoids. And when Genentech began Phase III clinical trials 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. 1025 at 10) that the prior art warned HER2-positive patients "will not respond well to" (Ex. 2029 at 1362)—was not used in combination with rhuMAb HER2 to treat patients. On the other hand, combinations with anthracyclines—which at the time showed no hint of increased toxicity with anti-ErbB2 antibodies—and other chemotherapies (*e.g.*, cisplatin) were the preferred candidates for clinical development. As described below (pp. 19-22), it was only when '441 inventor Dr. Hellmann insisted that Genentech change course in the middle of an ongoing Phase III clinical trial that the claimed combination was pursued.

Second, Petitioner asserts that the '441 patent "relie[s] heavily" on the work reported in the Baselga references asserted in this proceeding. (Paper 1 at 14.) 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. 1004 at 9; Ex. 1005 at 4.) And Baselga '97 explains that Genentech discovered and developed rhuMAb HER2. (Ex. 1006 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 '441 patent includes a similar description of the development history for rhuMAb HER2. Both describe Genentech's own original work.

2. Dr. Hellmann took the development of rhuMAb HER2 in a different direction.

The clinical development of rhuMAb HER2 followed a vastly different course with Dr. Hellmann's arrival at Genentech in 1995. Dr. Hellmann joined Genentech after working at Bristol-Myers Squibb, where she helped obtain the approval of the taxoid chemotherapy paclitaxel (Taxol®) for breast cancer in 1994. (Ex. 2011, 2017 Hellmann Decl. ¶ 2.) She became Genentech's head of clinical

oncology and was responsible for managing the clinical development of rhuMAb HER2. (*Id.* ¶ 3.)

At the time, a Phase III clinical trial was already underway to test the combination of rhuMAb HER2 with an anthracycline (doxorubicin) as a treatment for HER2-positive breast cancer. (*Id.* ¶ 15; Ex. 2001 at 16, § 5.2.2.) However, the study was having difficulty enrolling patients. 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. 2011, 2017 Hellman Decl. ¶ 26; Ex. 2001 at 14, § 4.2.)

Genentech considered several proposals to improve enrollment in the Phase III study. [redacted]

However, as a result of her personal experience working with paclitaxel, Dr. Hellmann brought a different perspective. She proposed amending the Phase III protocol to allow patients to receive the combination of an anti-ErbB2 antibody

(rhuMAb HER2) and a taxoid (paclitaxel) in the absence of an anthracycline derivative. (Ex. 2011, 2017 Hellmann Decl. ¶ 18; Ex. 2005 at 13; Ex. 2002 at 3; Ex. 2003 at 2; Ex. 2004 at 5-6.)

Dr. Hellmann's proposal involved significant risks. ***First***, no human patient had ever been treated with the combination of an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative. (Ex. 2011, 2017 Hellmann Decl. ¶ 19.) Typically, therapies are tested in smaller trials first before advancing to a larger patient population in Phase III trials. (*Id.*) Dr. Hellmann's proposal to test a therapy without first studying it in smaller trials risked exposing a large number of patients to potential adverse events that could not have been predicted from preclinical models. (*Id.*)

Second, the preclinical data for the combination of rhuMAb HER2 with paclitaxel was "inconsistent." (Ex. 2004 at 3, 6-7; Ex. 2011, 2017 Hellmann Decl. ¶ 20.) Petitioner relies exclusively on the preclinical results reported in Baselga '94, 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; Ex. 2011, 2017 Hellmann Decl. ¶ 20.) 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. Dr. Hellmann's proposal to use a taxoid as part of a first-line metastatic therapy was thus not supported by its approved use. (Ex. 2005 at 10; Ex. 1025 at 10; Ex. 2011, 2017 Hellmann Decl. ¶ 21.)

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. 2011, 2017 Hellmann Decl. ¶¶ 22-24; Ex. 2005 at 13; Ex. 2002 at 3; Ex. 2003 at 1-2; Ex. 2004 at 2.) 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. 2011, 2017 Hellmann Decl. ¶ 25; Ex. 2007 at 36-38; Ex. 2004 at 2.)

[redacted]

3. Dr. Hellmann's method of treatment produced unexpected clinical results.

After Genentech approved her proposed amendment, Dr. Hellmann diligently oversaw the completion of the Phase III study to test her new method of treatment. (Ex. 2011, 2017 Hellmann Decl. ¶¶ 29-48.)

[redacted], the Phase III study reached its primary endpoint. (Ex. 2008 at 51-69, 104-109.) The study data showed that the combination of an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative 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 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. 1027, 38:26-43:36.) And as described below (p. 25), the challenged claims are directed to Dr. Hellmann's new method of treatment.

Based upon those results, rhuMAb HER2 (brand name Herceptin®) was approved in September 1998 for treating HER2-positive metastatic breast cancer,

making it the first approved antibody-based therapy for solid tumors. At the time, the only approved first-line use of Herceptin® reflected Dr. Hellmann's novel method of treatment in combination with a taxoid. (Ex. 2012 at 1 ("HERCEPTIN in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumor overexpresses the HER2 protein and who have not received chemotherapy for their metastatic disease.").) The Herceptin® label specifically warned against administering Herceptin® in combination with anthracyclines due to the increased risk of cardiotoxicity. (*Id.*)

C. Widespread Adoption And Praise

The response to the '441 invention confirms that it was a non-obvious advance over the prior art. After the Phase III results were announced, the scientific community praised the invention as a "breakthrough" for the tens of thousands of women each year diagnosed with HER2-positive breast cancer who were "in dire need" of an effective therapy. (Ex. 2018 at 887 ("The results were particularly encouraging in combination with chemotherapy using paclitaxel, a form of taxol.").) Even leading oncologists recognized the '441 invention as a significant advance. For example, Dr. Larry Norton, co-author of the three Baselga references and a leading breast cancer clinician, went on national television to praise the unexpected efficacy of that new combination therapy: "It doubles or triples the efficacy of Taxol in killing these cancer cells. This is a very

big, dramatic advance, one of the biggest changes in the ability of chemotherapy to kill cancer cells that I've ever seen in my career." (Ex. 2034.)

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

D. Challenged Claims

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

E. Prosecution History

The '441 patent issued from Application No. 09/208,649 filed on December 10, 1998, and claims priority to Provisional Application No. 60/069,346 filed on December 12, 1997. (Ex. 1001, cover page.)[2]

The Patent Office considered each reference underlying Petitioner's proposed obviousness grounds during prosecution.[3] Petitioner asserts (Paper 1 at 15) that the '441 patent repeats the disclosure of the Baselga references without attribution. But the '441 patent does not conceal anything about the Baselga references. Indeed, it cites and discusses each of the Baselga references at length. (Ex. 1001, 3:34-59.) Moreover, Petitioner's suggestion (Paper 1 at 15) that the "experimental data" in the '441 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 in the absence of an

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[2] Petitioner has challenged U.S. Patent No. 7,892,549, which is a continuation of the '441 patent, in two pending petitions. (IPR2017-00737; IPR2017-00739.)

[3] Genentech has a pending application (14/141,232) in the '441 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.

anthracycline derivative. Clinical results for that combination are first described in the '441 patent itself. (Ex. 1001, 29:11-30:25.)

During prosecution, Genentech antedated Baselga '97 with a declaration from Dr. Hellmann explaining that she had conceived and reduced to practice the claimed invention before December 12, 1996. (Ex. 1011-2 at 237, 2001 Hellmann Decl. ¶ 2.) To demonstrate reduction to practice, Dr. Hellmann submitted case report forms from the Phase III trial showing that a patient had received "infusions of the combination of rhuMAb HER2 and paclitaxel for the total course of therapy" according to the claimed method of treatment prior to December 12, 1996. (Ex. 1011-2 at 239, 2001 Hellmann Decl. ¶ 7; *id.* at 310-12.)[4] The examiner accepted that evidence as sufficient to antedate Baselga '97. (Ex. 1011-2 at 324.)

In October 2009, Genentech submitted a declaration from Dr. Mark Sliwkowski in response to obviousness rejections over, among other things, Baselga '96 and Baselga '94. (Ex. 1011-9 at 9-13.) Dr. Sliwkowski explained that a 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

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[4] At the time of Dr. Hellmann's declaration, the pending claims did not recite the limitation "without overall increase in severe adverse events." That claim language was added later during prosecution. (Ex. 1011-8 at 357-59.)

effects at different points in the cell cycle. (Ex. 1011-9 at 10-11, 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 12, Sliwkowski Decl. ¶ 9.)

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

F. Foreign Counterparts

As Petitioner notes (Paper 1 at 15-16), the European counterpart to the '441 patent was found obvious over Baselga '97 in the United Kingdom and obvious over Baselga '97 or Baselga '96 before the European Patent Office. However, those foreign proceedings 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").

Contrary to Petitioner's suggestion (Paper 1 at 15-16 n.7), the issues here are different from those foreign proceedings. For example, one critical difference is

that Baselga '97 is not prior art in the United States because it has been antedated (*see infra* pp. 34-39), whereas it was considered prior art in Europe where antedation practices do not exist.

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. 1005 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 9). Indeed, Baselga '94 could not have been referring to

ongoing studies of the combination because, as discussed above (pp. 18-23), 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. 1004 at 10.)

The clinical endpoint evaluated in the trial was response rate. (*Id.* at 10, 12, 13.) Although Baselga '96 measured "[t]ime to tumor progression" for individual patients, all patients in the study received rhuMAb HER2. (*Id.* at 10.) The study thus had no control group against which to evaluate whether rhuMAb HER2 ***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. 20-23.)

C. Baselga '97

Baselga '97 is a review article published in March 1997. As explained below (pp. 34-39), Baselga '97 is not prior art because it was published after the invention of the '441 patent.

Baselga '97 described the design of the Phase III study for rhuMAb HER2 ***after*** implementing Dr. Hellmann's amendment. Patients received rhuMAb HER2 in combination with either (i) an anthracycline derivative (cyclophosphamide and doxorubicin or epirubicin); or (ii) a taxoid (paclitaxel). (Ex. 1006 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. 1006 at 11 ("***If*** the results of these studies are positive ….").)

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 7.)

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 surrounding claim language further confirms that "administering a combination" refers only to the drugs administered in the same treatment regimen. For example, all claims require "the absence of an anthracycline derivative." That limitation would make no sense if "administering a combination" included drugs received as part of a different treatment regimen. In the '441 patent's working example, patients were administered the combination of the anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative only if they had "received any anthracycline therapy in the adjuvant setting" (*i.e.*, as part of a different treatment regimen). (Ex. 1001, 28:15-21.) 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. Ground 1: The Challenged Claims Would Not Have Been Obvious Based On Baselga '97 In View Of Baselga '94.

1. Baselga '97 is not prior art.

a) Conception

Dr. Hellmann conceived of the challenged claims well before the publication of Baselga '97 in March 1997. "[T]he test for conception is whether the inventor had an idea that was definite and permanent enough that one skilled in the art could understand the invention; the inventor must prove his conception by corroborating evidence, preferably by showing a contemporaneous disclosure." *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994).

Here, Dr. Hellmann proposed amending the Phase III protocol to treat patients with a combination of an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative at several meetings of Genentech's PDC [redacted]. (*See supra* pp. 20-22.) And the amended Phase III protocol dated [redacted] corroborates Dr. Hellmann's conception of the claims. As set forth in the table below for representative claim 1, the amended Phase III protocol reflects all limitations of the challenged claims:

Claim Limitation	Support in Amended Phase III Protocol
1. A method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by	The study involved metastatic breast cancer patients "with HER2 overexpression" (*i.e.*, overexpression of ErbB2 receptor). (Ex. 1011-2 at 251, § 4; Ex. 2007 at 33.)

Claim Limitation	Support in Amended Phase III Protocol
overexpression of ErbB2 receptor, comprising	
administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence and a taxoid	Patients received an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain (rhuMAb HER2) and a taxoid (paclitaxel). (Ex. 1011-2 at 254-55, § 5.3; Ex. 2007 at 36.)
in the absence of an anthracycline derivative	Patients received the combination of anti-ErbB2 antibody and a taxoid if they had "received any anthracycline therapy in the adjuvant setting" and therefore were ineligible to receive further anthracycline therapy due to the risk of cumulative toxicity. (Ex. 1011-2 at 255, § 5.3.2; Ex. 2007 at 36-37.)
in an amount effective to extend the time to disease progression in said human patient	Time to disease progression was a primary endpoint for the study. (Ex. 1011-2 at 249, § 2.1; Ex. 2007 at 30.) Patients were administered amounts of the drug sufficient to extend the time to disease progression. (Ex. 1011-2 at 254-555, § 5.3; Ex. 2007 at 36-37.)
without overall increase in severe adverse events.	The study was designed to "further characterize the safety profile of rhuMAb HER2." (Ex. 1011-2 at 249, § 2.1; Ex. 2007 at 30.) Patients were monitored to assess drug safety, and "any incidence of adverse events [was] recorded and classified according to body region and severity." (Ex. 1011-2 at 266, § 8.2.5; Ex. 2007 at 48.)

During prosecution, Patent Owner successfully antedated Baselga '97 and corroborated Dr. Hellmann's conception with the amended Phase III protocol. (Ex. 1011-2 at 238-239, 2001 Hellmann Decl. ¶¶ 4-6, 8; *id.* at 240-309, 2001 Hellmann Decl. Ex. A; *id.* at 324.)

Petitioner argues that evidence is insufficient to show conception. (Paper 1 at 21-22.) But Petitioner does not identify any limitation not supported by the amended Phase III protocol. Instead, Petitioner criticizes that evidence for supposedly showing only "a plan for a clinical trial." (*Id.* at 21.) But that is all that is required for conception: "a definite and permanent idea of the complete and operative invention." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376 (Fed. Cir. 1986). It is not necessary to have tested the invention to establish conception. *Burroughs*, 40 F.3d at 1228 ("[A]n inventor need not know that his invention will work for conception to be complete.").

Petitioner also argues that Patent Owner's position with respect to prior invention is "irreconcilable" with its position on novelty and obviousness. (Paper 1 at 21-22.) That argument mischaracterizes Patent Owner's antedation position. Patent Owner does not contend that a mere "plan" to conduct a clinical trial is sufficient to demonstrate ***reduction to practice***. As described below (pp. 37-39), the invention was reduced to practice by treating patients in the Phase III study. However, the detailed study design in the amended Phase III protocol—which reflects each claim limitation—is plainly sufficient to demonstrate ***conception***, which is the only purpose for which Patent Owner relies upon it.

b) Reduction to practice

During prosecution, Patent Owner submitted records showing that a patient had completed a "total course of therapy" according to the claimed invention prior to December 12, 1996. (Ex. 1011-2 at 239, 2001 Hellmann Decl. ¶ 7; *id.* at 310-12.) The examiner determined that evidence was sufficient to antedate Baselga '97. (*Id.* at 324.)

Petitioner argues that Patent Owner should have provided data from the Phase III trial to antedate Baselga '97. (Paper 1 at 18.) But Petitioner ignores that antedation only requires "priority with respect to so much of the claimed invention as the reference happens to show." *In re Clarke*, 356 F.2d 987, 991 (C.C.P.A. 1966). Baselga '97 does not contain data from the Phase III trial, and such data is therefore not necessary to antedate it. Dr. Hellmann's declaration submitted during prosecution—showing a patient's completion of a "total course of therapy" according to the claimed method—discloses even more than Baselga '97 and is sufficient to antedate that reference. (*See* Ex. 1011-2 at 239, 2001 Hellmann Decl. ¶ 7; *id.* at 310-12.)

But even under Petitioner's view that clinical results are necessary to antedate Baselga '97, that reference is not prior art. Dr. Hellmann has submitted an additional declaration with this preliminary response that further demonstrates

her diligent reduction to practice of the challenged claims. With this additional declaration, Petitioner has no basis to dispute that Baselga '97 has been antedated.

Specifically, Dr. Hellmann's additional declaration establishes that she and others at her direction were diligently working to complete the Phase III trial from at least February 28, 1997 (*i.e.*, before Baselga '97) though December 12, 1997 (*i.e.*, the filing of the priority application). During that period, at least [redacted] in the Phase III study were treated at Dr. Hellmann's direction with a combination of anti-ErbB2 antibody (rhuMAb HER2) and a taxoid (paclitaxel) in the absence of an anthracycline derivative. (Ex. 2011, 2017 Hellmann Decl. ¶ 42.) Patients records submitted with Dr. Hellmann's declaration confirm that those patients were treated and evaluated continuously throughout the period of at least February 28, 1997 through December 12, 1997. (Ex. 2011, 2017 Hellmann Decl. ¶¶ 43-44; Exs. 2009, 2010.) In addition, during that period, Dr. Hellmann and those working at her direction performed an intensive analysis of the data derived from the Phase III study. (Ex. 2011, 2017 Hellmann Decl. ¶ 46; Ex. 2008.)

Through those efforts, Genentech obtained data [redacted] showing that the claimed combination of an anti-ErbB2 antibody (rhuMAb HER2) and a taxoid (paclitaxel) in the absence of an anthracycline derivative was effective to extend the time to disease progression without overall increase in severe adverse events. (Ex. 2011, 2017 Hellmann Decl. ¶ 47.) The provisional patent application

filed December 12, 1997 contains those results and confirms the reduction to practice of the challenged claims. (*See* Ex. 1027, 42:28-43:26.)

Accordingly, even if it were necessary to have clinical data, Dr. Hellmann's prior conception and diligence through reduction to practice is sufficient to antedate Baselga '97.

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The Board should deny Ground 1 because Baselga '97 has been antedated.

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

Each challenged claim requires a specific clinical efficacy result—*i.e.*, "to extend the time to disease progression." Even under Petitioner's theory that Baselga '97 is prior art, Petitioner has not shown that a person of ordinary skill would have had a reasonable expectation of success in achieving that specific efficacy result. 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).

a) The cited references do not address the clinical result of extending the time to disease progression.

The cited references do not disclose ***any*** data suggesting an ***extension*** in the time to disease progression for patients receiving a combination of an anti-ErbB2

antibody and a taxoid in the absence of an anthracycline derivative. The ***first*** disclosure of data addressing that clinical endpoint is in the '441 patent itself. (Ex. 1001, 29:11-30:25.)

The absence of any prior art data addressing that clinical endpoint is a critical omission given the state of the art prior to the '441 invention. As discussed above (pp. 14-15), no prior antibody-based therapy had been approved for the treatment of solid tumors, and it remained highly uncertain whether such therapies could ever be clinically effective. Moreover, as discussed above (p. 15), there were serious doubts that taxoids—a second-line therapy that the prior art specifically warned against using in HER2-positive patients—could be used to treat the specific patient population addressed in the '441 claims. Petitioner does not explain how a skilled artisan could have had a reasonable expectation of success in achieving the claimed result of extending the time to disease progression given those known challenges.

b) Petitioner's arguments ignore the claim requirements and rest on hindsight.

None of Petitioner's arguments demonstrate a reasonable expectation of success in extending the time to disease progression.

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 29-30 (citing Ex. 1006 at 9).) But those results are the "median" time to disease progression from 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* p. 30.) Petitioner's conclusory assertion that "a POSITA would have understood Baselga '97 teaches this claim element" (Paper 1 at 30) is insufficient to carry its burden because Petitioner has not addressed the claim requirement of ***extending*** the time to disease progression.

Second, Petitioner asserts that "a POSITA would be motivated to consider time to disease progression because this is one of the metrics reported in the phase II trial." (Paper 1 at 30.) But that argument again does not address what the claims require—which is an ***extension*** in the time to disease progression. Petitioner does not explain how merely conducting a study to evaluate time to disease progression would provide any expectation of success in ***extending*** the time to disease progression. Indeed, the high failure rate of Phase III trials in the 1990s belies Petitioner's assertion that merely conducting a study would provide an expectation of success in achieving the desired result. (*See supra* pp. 11-12.)

Third, Petitioner argues that the preclinical data in Baselga '97 and Baselga '94 demonstrated that the combination of rhuMAb HER2 with paclitaxel "'resulted in major antitumor activity.'" (Paper 1 at 30 (quoting Ex. 1006 at 9).) But the 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. (Ex. 1005 at 4; Ex. 1006 at 9.) Petitioner does not explain how those preclinical results could provide a reasonable expectation of success in achieving the ***different*** clinical endpoint of extending the time to disease progression.

Moreover, the preclinical results in mice reported in Baselga '97 and Baselga '94 were known at the time to be unreliable indicators of clinical outcomes in human patients. (*See supra* pp. 9-10.) Petitioner has not explained how a person of ordinary skill could have had a reasonable expectation of success based on preclinical results evaluating a different outcome in mice in light of the well-known limitations of mouse models at the time to predict responses in human patients.[5]

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[5] As discussed above (p. 21), the preclinical results for the claimed combination were "inconsistent." Petitioner's obviousness theory—which focuses exclusively on the preclinical results reported in Baselga '94—does not reflect the complexity of the problem actually solved by the '441 invention.

In fact, Baselga '94 confirms the unreliability of prior art mouse models to predict clinical results in humans. Petitioner argues that "Baselga '94 teaches that there was no increase in toxicity of paclitaxel when administered in combination with rhuMAb HER2 in preclinical models." (Paper 1 at 31.) But as discussed above (p. 29), Baselga '94 said the same thing about doxorubicin—a drug that produced a significant increase in cardiotoxicity when combined with rhuMAb HER2 in humans. Petitioner cannot rely on Baselga '94 to provide a reasonable expectation of success while ignoring the results in that same reference that proved wholly unsuccessful. That selective approach to the prior art is pure hindsight. *See Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) (holding that a party challenging the patent 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*").

Fourth, Petitioner argues that a person of ordinary skill would have had a reasonable expectation of success in achieving the clinical efficacy results required by the challenged claims because Baselga '94 supposedly indicates that "clinical trials of the combination were underway in humans" as early as 1994 and "these clinical trials were still underway in 1997." (Paper 1 at 31, 34; *see id.* at 30 ("The treatment was sufficiently effective that clinical trials were ongoing for at least

three years at the time that Baselga '97 was published.").) But that argument is not supported by the asserted references and is factually incorrect.

Baselga '94 states that "[c]linical trials are underway." (Ex. 1005 at 4.) But it does not say that the clinical trial involved the combination of an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative, as Petitioner contends. Nor could it have because there was no such trial underway at the time. (*See supra* p. 18-23.) The fact that Petitioner's obviousness theory rests on reading false assumptions into the prior art confirms Petitioner's reliance on hindsight.

Finally, Petitioner argues that the mere existence of an ongoing clinical study demonstrates a reasonable expectation of success because "[c]linical trials can be time consuming and expensive; therefore, they would not be conducted *without* a reasonable expectation of success." (Paper 1 at 48 (emphasis in original).) That argument, however, cannot be reconciled with the actual experience developing cancer drugs in the 1990s—nearly 60% of which failed in Phase III clinical trials. (Ex. 2021 at 712-13.) Moreover, although any cancer therapy in development during the 1990s had a high likelihood of failure, the '441 invention's success was even less certain because it involved an antibody-based therapy that had yet to prove successful for ***any*** solid tumor at the time.

Petitioner's theory is not only contrary to the actual experience of researchers in this field, but accepting its logic would also have sweeping

consequences. ***Every*** clinical invention is preceded by clinical trials. If the mere fact that those clinical trials are underway would provide a reasonable expectation of success, then no clinical invention 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).

3. Petitioner has not established a reasonable expectation of success in achieving the claimed clinical safety.

The challenged claims also require a specific safety result—*i.e.*, "without increase in overall severe adverse events." Petitioner's cited references contain no clinical safety data for the claimed combination of an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative. Petitioner has not demonstrated a reasonable expectation of success in achieving that clinical result in the absence of such data.

First, Petitioner points to Baselga '97's statement that rhuMAb HER2 produced "minimal" toxicity. (Paper 1 at 31 (quoting Ex. 1006 at 9).) But that statement refers to the results of the Phase II trial involving rhuMAb HER2 ***alone***. (Ex. 1006 at 9.) It does not address the safety of rhuMAb HER2 when ***combined***

with a taxoid, as in the challenged claims. That is a significant difference given the safety concerns with using taxoids, discussed above (p. 8).

Second, Petitioner cites Baselga '94's teaching that the combination of rhuMAb HER2 and paclitaxel did not increase toxicity in mouse models. (Paper 1 at 31.) But as discussed above (pp. 29), Baselga '94 made the same statement about combinations with the anthracycline doxorubicin—which produced a significant increase in cardiotoxicity when administered to human patients. Thus, if anything, Baselga '94 highlights the unpredictability of mouse models to predict clinical safety and does not support Petitioner's obviousness theory.

Third, Petitioner argues that a person of ordinary skill would have had a reasonable expectation of success in achieving the claimed clinical safety results because the Baselga references supposedly "reported as early as 1994 … that clinical trials of the combination were underway in humans, and that these clinical trials were still underway in 1997." (Paper 1 at 31.) As discussed above (pp. 18-23, 29-31), that argument is not supported by the Baselga references and is inconsistent with the development timeline for rhuMAb HER2; Petitioner cannot demonstrate a reasonable expectation of success based on false assumptions about a non-existent study. That argument also cannot be reconciled with the experience of cancer researchers in the 1990s; the mere fact that a treatment was under

evaluation was no indication of success, given the high failure rate of therapies in clinical trials. (*See supra* pp. 11-12.)

4. Petitioner has not shown that the claimed combination would have been obvious to try.

Petitioner alternatively contends that the challenged claims would have been obvious to try. (Paper 1 at 31-32, 49, 61.) But that argument too rests on hindsight in several respects.

First, prior to the '441 invention, the combination of an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative was not even among a finite number of options that a person of ordinary skill would have pursued. There were dozens of chemotherapies known in the prior art (*see supra* p. 6), and there were numerous other possibilities that a skilled artisan would have pursued instead.

That is confirmed by the development history of rhuMAb HER2. As discussed above (pp. 18-23), Genentech pursued several alternative therapies (*e.g.*, anti-ErbB2 antibody alone (Ex. 1004), combined with cisplatin (Ex. 1010), or combined with doxorubicin (Ex. 2001)) and only pursued the claimed combination after '441 inventor Dr. Hellmann convinced the company to change course. The fact that the claimed combination was 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 it was not obvious to try. *See, e.g.*, *Leo Pharm.*

Prods., Ltd. v. Rea, 726 F.3d 1346, 1356-57 (Fed. Cir. 2013) (holding that the alternatives disclosed in the art and the fact that no one had pursued the claimed invention before the inventors confirmed that the invention was not obvious to try).

Second, Petitioner's obvious-to-try theory fails for the further reason that the claimed invention was not one of "a finite number of identified, ***predictable*** solutions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). The '441 invention is in a highly unpredictable field—as confirmed, for example, by the nearly 60% failure rate of cancer drugs in Phase III trials during the 1990s and the fact that Baselga '94 itself failed to predict the toxicity of the rhuMAb HER2 combined with anthracyclines. (*See supra* pp. 43-44.) Petitioner cannot demonstrate that the art was predictable when the asserted references show that it was not. Petitioner does not address that unpredictability, let alone explain how the invention could have been obvious to try given those uncertainties.

B. Ground 2: The Challenged Claims Would Not Have Been Obvious Based On Baselga '96 In View Of Baselga '94.

1. A person of ordinary skill would not have been motivated to "administer[] a combination" of an anti-ErbB2 antibody and a taxoid based upon Baselga '96 and Baselga '94.

a) Baselga '96

All challenged claims require "administering a combination" of an anti-ErbB2 antibody and a taxoid "to the human patient." Baselga '96 does not teach

that limitation; it discloses the treatment of patients with rhuMAb HER2 ***alone***, not with a taxoid. (Ex. 1004 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 44.) But those patients were not "administered a ***combination***" of anti-ErbB2 antibody and a taxoid, as that term is properly construed. (*See supra* pp. 32-33.) Baselga '96 describes patients who received treatment with an anti-ErbB2 antibody and ***separate*** treatment with a taxoid. In fact, patients in the study were required to discontinue any chemotherapy (including taxoids) for at least three weeks before enrolling. (Ex. 1004 at 10.)

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 44.) But Baselga '96 does not state that the combination of rhuMAb HER2 and paclitaxel in the absence of an anthracycline derivative 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. 18-23.) The fact

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

b) 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 combination to a "***human*** patient," as claimed in the '441 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 doxorubicin. (Ex. 1005 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 29, 31-32, 46.) 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 (an established breast cancer chemotherapy), 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 '441 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. 8.) Moreover, the prior art taught away by explicitly warning that HER2-positive breast cancer "will not respond well to Taxol." (Ex. 2029 at 1362.) 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 at that time 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. (*See supra* pp. 9-10.) 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 in the absence of an anthracycline derivative. 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.

The Board should deny institution of Ground 2 because Petitioner has not shown that Baselga '96 in view of 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."

2. Neither Baselga '96 nor Baselga '94 discloses or suggests treating patients "in the absence of an anthracycline derivative."

Combining Baselga '96 with Baselga '94 also would not have led to a treatment "in the absence of an anthracycline derivative," as required by all claims. 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.)

Even if a person of ordinary skill would have chosen to combine an anti-ErbB2 antibody and a taxoid, there is no reason an ordinarily skilled artisan would have avoided anthracyclines as part of that treatment. On the contrary, there was

"considerable interest" in combining taxoids and anthracyclines prior to the '441 invention. (Ex. 2014 at 774.) And clinical trials showed that the combination of paclitaxel and doxorubicin ***improved*** clinical results. (Ex. 2015 at 2698; Ex. 2013 at abstract, 14-17.) Petitioner's assertion that a person of ordinary skill would have avoided combinations with anthracyclines (Paper 1 at 13) is pure hindsight based upon the disclosure of the '441 patent itself. (*See supra* pp. 15-17.)

Petitioner's obviousness theory also cannot be reconciled with Baselga '94, which indicates that combinations with anthracyclines were safe. (*See supra* pp. 29.) Petitioner cannot say Baselga '94 would have motivated a person of ordinary skill to combine an anti-ErbB2 antibody with a taxoid, while arguing that a skilled artisan would not have been motivated to treat patients with combinations including anthracyclines too. That selective approach to interpreting the prior art confirms Petitioner's reliance on hindsight.

Because even the references underlying Petitioner's obviousness theory contradict Petitioner's argument with respect to the "absence of an anthracycline derivative" limitation, the Board should deny Ground 2.

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

Petitioner's arguments with respect to the claimed clinical efficacy requirement of "extend[ing] the time to disease progression" are the same as for Ground 1 and fail for the same reasons addressed above.

Neither Baselga '96 nor Baselga '94 disclose data addressing the clinical endpoint of "extend[ing] the time to disease progression." Petitioner points to Baselga '96's disclosure of data showing the duration of response for patients treated with rhuMAb HER2. (Paper 1 at 47.) But as discussed above (p. 30), Baselga '96 does not demonstrate an ***extension*** in the time to disease progression and lacked a control arm necessary to evaluate that result.

Petitioner also relies on the preclinical results reported in Baselga '94. (Paper 1 at 47.) But as discussed above (p. 29), those results did not address the time to disease progression, let alone show an ***extension*** in the time to disease progression. Moreover, Petitioner has not addressed the well-known limitations of mouse models at the time to predict clinical results in humans.

Petitioner argues that a person of ordinary skill would have had a reasonable expectation of success because clinical trials were supposedly "ongoing for at least two years when Baselga '96 was published." But as discussed above (pp. 18-23, 29-31), that is not what the Baselga references disclose, or factually correct.

Petitioner's argument also cannot be reconciled with the high failure rate of cancer therapies in clinical trials, which demonstrates that a skilled artisan would not have had a reasonable expectation of success merely because a study was ongoing. (*See supra* pp. 11-12.)

4. Petitioner has not established a reasonable expectation of success in achieving the claimed clinical safety.

Petitioner's arguments with respect to the claimed clinical safety requirement (*i.e.*, "without increase in overall severe adverse events") are the same as for Ground 1 and fail for the same reasons addressed above. (*See* Paper 1 at 48.) As discussed above (pp. 45-46), the reported clinical safety for rhuMAb HER2 ***alone*** in Baselga '96 would not have provided a reasonable expectation of success with respect to the safety of the combination with a taxoid. Moreover, as discussed above (p. 46), Baselga '94 cannot provide a reasonable expectation of success achieving the claimed clinical safety result when the safety predictions in that reference proved incorrect.

5. Petitioner has not shown that the claimed combination would have been obvious to try.

The challenged claims also would not have been obvious to try based upon the combination of Baselga '96 and Baselga '94. Petitioner's obvious-to-try argument for Ground 2 is the same as for Ground 1, and it therefore fails for the same reasons. The claimed combination would not have been among a finite

number of options that a person of ordinary skill would have pursued. And the oncology field is highly unpredictable, as confirmed, for example, by the unexpected increase in toxicity observed in patients receiving rhuMAb HER2 combined with anthracyclines. (*See supra* pp. 47-48.)

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

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

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

First, the '441 invention satisfied a long-felt but unmet need for an effective treatment for HER2-positive breast cancer. Before the '441 invention, HER2-positive patients experienced "horribly rapid progression" and were "in dire need" of an effective therapy. (Ex. 2018 at 887.) Yet no one prior to the '441 invention had developed an adequate therapy for those patients; indeed, at the time, patients

with metastatic HER2-positive breast cancer had a life expectancy of just 10 to 12 months. (*Id.*)

The '441 invention satisfied the long-felt need for an effective therapy for HER2-positive patients. After the results of Phase III clinical trials showing that the claimed combination produced a "dramatic" increase in the time to disease progression, the '441 invention was immediately heralded as a "breakthrough" therapy—"the Holy Grail" for patients suffering from HER2-positive breast cancer. (*Id.*) And in recognition of the long-felt need satisfied by the '441 invention, the FDA fast tracked that therapy for approval. (*Id.*) Petitioner's hindsight-driven narrative that the challenged claims were merely the result of ordinary skill cannot be reconciled with the critical, long-standing need that the '441 invention satisfied. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1332 (Fed. Cir. 2016) ("Evidence of a long felt but unresolved need tends to show non-obviousness because it is reasonable to infer that the need would have not persisted had the solution been obvious.").

Second, after the results of the rhuMAb HER2 Phase III trial were announced, the '441 invention was widely praised as an "anti-cancer breakthrough" that produced "impressive results." (Ex. 2018 at 887; Ex. 2033 at 1.) Petitioner can hardly contend that those results would have been obvious from the Baselga references—when Dr. Larry Norton, a leading practitioner and co-

author of the three Baselga references, went on national television to praise the impressive results of the '441 invention: "It doubles or triples the efficacy of Taxol in killing these cancer cells. This is a very big, dramatic advance, one of the biggest changes in the ability of chemotherapy to kill cancer cells that I've ever seen in my career." (Ex. 2034.) The strong praise for the specific combination therapy claimed in the '441 patent confirms that there is nothing ordinary or routine about the '441 invention. *Institut Pasteur & Universite Pierre et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013) ("[I]ndustry praise … provides probative and cogent evidence that one of ordinary skill in the art would not have reasonably expected [the claimed invention].").

Third, the combination of an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative produced unexpectedly superior clinical efficacy results as compared with either the antibody or a taxoid alone. (Ex. 1011-2 at 54, 2000 Hellmann Decl. ¶ 6 ("[T]he combination is surprisingly synergistic with respect to extending TTP.").) Petitioner argues that those results would have been expected because preclinical mouse models testing that drug combination "demonstrated synergistic effects." (Paper 1 at 62.) But the preclinical results did not address the specific clinical endpoint of time to disease progression, let alone show an improvement in that outcome. (*See supra* p. 29.) And in any case, preclinical results at that time were known to be poor predictors of clinical

outcomes. (*See supra* pp. 11-12.) In fact, other preclinical studies involving the claimed combination produced "inconsistent results." (Ex. 2004 at 3, 6.) And the efficacy of the claimed combination is especially remarkable given that paclitaxel was merely a second-line therapy that the prior art warned would not work in HER2-positive patients. (*See supra* p. 15.) A person of ordinary skill therefore would have considered those vastly superior clinical efficacy results to be unexpected, which further confirms the nonobviousness of the claimed invention. *See Procter & Gamble*, 566 F.3d at 994 (explaining that evidence "that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected" is strong evidence of nonobviousness); *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) ("[T]hat which would have been surprising to a person of ordinary skill in a particular art would not have been obvious.").

Even under Petitioner's obviousness theory, the '441 invention produced an unexpected improvement in safety as compared with other drug combinations—for example, the combination of rhuMAb HER2 with anthracyclines that Baselga '94 said did not increase toxicity. (Ex. 1005 at 4; *see also* Ex. 1011-2 at 53, 2000 Hellmann Decl. ¶¶ 4-5.) Petitioner may not argue that the preclinical results disclosed in Baselga '94 would have provided a reasonable expectation of success,

but dismiss the reference's other teachings that demonstrate unexpected results. *See Genetics Inst.*, 655 F.3d at 1305.

Petitioner argues that the safety difference is irrelevant because it supposedly involved "[d]iscovering another combination that is worse" than the claimed invention. (Paper 1 at 24.) But the combination of rhuMAb HER2 with an anthracycline derivative is not just "another combination"; each challenged claim expressly requires "the absence of an anthracycline derivative." The unexpected improvement in safety attributable to that claim element confirms the nonobviousness of the challenged claims. *In re Soni*, 54 F.3d at 750.[6]

Fourth, the '441 invention has been an enormous commercial success. Herceptin® is the commercial embodiment of the '441 invention, and it is one of the most successful drugs of all time. There is a direct nexus between Herceptin®'s commercial success and the '441 invention. Indeed, from 1998 until 2006, the

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

only approved first-line use of Herceptin® was in combination with a taxoid, as claimed in the '441 patent. (Ex. 2012 at 1.) Following its launch, Herceptin® was quickly adopted, resulting in hundreds of millions of dollars in sales in those years immediately following its approval. (Ex. 2035 at 17.) Where, as here, the commercial product embodies the claimed invention, a nexus is presumed. *Brown & Williamson Tobacco Corp. v. Philip Morris, Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000). Petitioner has not even addressed the nexus between the '441 invention and Herceptin® for purposes of commercial success, let alone rebut the presumption of a nexus. (Paper 1 at 62.)

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

Petitioner argues that Baselga '97 demonstrates "near-simultaneous invention of the Challenged Claims." (Paper 1 at 62.) But simultaneous invention is only relevant if it involves individuals working ***independently*** from the inventor. *Trustees of Columbia Univ. v. Illumina, Inc.*, 620 F. App'x 916, 930 (Fed. Cir. 2015). Baselga '97 involves no such independent work; it describes the amended Phase III study protocol that the inventor of the '441 patent proposed. (*See supra* pp. 20-23.) Indeed, Petitioner expressly relies on Dr. Hellmann's own work to demonstrate "simultaneous invention." (Paper 1 at 62-63 ("POSITAs like Drs.

Baselga, Pegram, and Hellmann turned to the most obvious targets: combinations of known therapies seeking synergistic effects.").)

Nor is it legally permissible for Petitioner to label Dr. Hellmann a person of ordinary skill. On the contrary, the law recognizes that inventors possess knowledge "which sets them apart from workers of ordinary skill." *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985). There is no factual or legal basis for Petitioner's attempt to impute Dr. Hellmann's unique perspective to persons of ordinary skill.

3. Dr. Sliwkowski's declaration confirms the non-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 '441 invention based upon what was known about the biological mechanism of rhuMAb HER2, taxoids, and other anti-cancer drugs at the time. (Ex. 1011-9 at 10-12, Sliwkowski Decl. ¶¶ 7-8.) Dr. Sliwkowski also described the well-known limitations of prior art preclinical mouse models to predict success in humans. (Ex. 1011-9 at 12, Sliwkowski Decl. ¶ 9.)

Petitioner criticizes various aspects of Dr. Sliwkowski's declaration. (Paper 1 at 59-62.) The Board need not reach Petitioner's arguments with respect to Dr.

Sliwkowski's declaration because Petitioner's proposed grounds fail for the numerous reasons described above. But if the Board considers Dr. Sliwkowski's declaration, it only confirms the patentability of the challenged claims.

First, Petitioner criticizes Dr. Sliwkowski's declaration for not citing papers involving the combination of rhuMAb HER2 and a taxoid. (Paper 1 at 59.) But Petitioner has not 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 '441 invention.

Second, Petitioner argues that the declaration is supposedly inconsistent with the "synergistic" results in preclinical mouse studies involving cisplatin and paclitaxel. (Paper 1 at 60-61.) Dr. Sliwkowski's declaration, however, explained why those prior art preclinical results are not a reliable predictor of clinical outcomes. (Ex. 1011-9 at 12, Sliwkowski Decl. ¶ 9.) Petitioner does not address—let alone dispute—the many well-known limitations of preclinical mouse models at that time.

Third, Petitioner contends that Dr. Sliwkowski's declaration is flawed because it cites an article published in 2001 (after the '441 invention date) as evidence of the unreliability of mouse models. (Paper 1 at 61.) But the article

published in 2001 is a retrospective analysis involving drugs developed before the '441 invention. (Ex. 1011-9 at 99.) 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 61-62) does not suggest otherwise. Petitioner cites no evidence suggesting that Genentech (or anyone else) relied on those models at the time of the '441 invention as anything other than a preliminary screening tool, consistent with their well-known limitations to predict clinical results at the time.

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 13,991 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 2001-2019, 2021-2037

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	Genentech, Inc. PDC Presentation PROTECTIVE ORDER MATERIAL
2006	Genentech, Inc. PDC Presentation PROTECTIVE ORDER MATERIAL
2007	Genentech, Inc. Amended H0648g Protocol PROTECTIVE ORDER MATERIAL
2008	Genentech, Inc. H0648g Final Report PROTECTIVE ORDER MATERIAL
2009	Genentech, Inc. Representative Case Report Form PROTECTIVE ORDER MATERIAL
2010	Genentech, Inc. Case Report Form Compilation PROTECTIVE ORDER MATERIAL
2011	2017 Declaration of Dr. Susan Desmond-Hellmann PROTECTIVE ORDER MATERIAL
2012	1998 Herceptin Label
2013	Per Dombernowsky, et al., *Paclitaxel and Doxorubicin, a Highly Active Combination in the Treatment of Metastatic Breast Cancer*, 23 SEMINARS IN ONCOLOGY 13 (1996).
2014	Jason S. Fisherman, et al., *Phase I/II Study of 72-Hour Infusional Paclitaxel and Doxorubicin with Granulocyte Colony-Stimulating Factor in Patients with Metastatic Breast Cancer*, 14 J. CLINICAL ONCOLOGY 774 (1996).

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

Patent Owner's Exhibit Number	Exhibit Name
2029	Dihua Yu, *Overexpression of c-erbB-2/neu in Breast Cancer Cells Confers Increased 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	Richard Saltus, *New Treatment for Breast Cancer Called Promising*, BOSTON GLOBE, May 18, 1998.
2034	*TODAY: FDA Expected to Approve Two New Breast Cancer Drugs* (NBC television broadcast Sept. 2, 1998).
2035	Genentech Annual Report 2000
2036	Modified Default Standing Protective Order and Patent Owner's Certification of Agreement to Terms
2037	Modified Default Standing Protective Order – Redline