

Filed on behalf of Patent Owner Genentech, Inc. by:

David L. Cavanaugh (Reg. No. 36,476)	Adam R. Brausa (Reg. No. 60,287)
Owen K. Allen (Reg. No. 71,118)	Daralyn J. Durie (<i>Pro Hac Vice to be filed</i>)
Robert J. Gunther, Jr. (<i>Pro Hac Vice to be filed</i>)	DURIE TANGRI LLP
Lisa J. Pirozzolo (<i>Pro Hac Vice to be filed</i>)	217 Leidesdorff Street
Kevin S. Prussia (<i>Pro Hac Vice to be filed</i>)	San Francisco, CA 94111
Andrew J. Danford (<i>Pro Hac Vice to be filed</i>)	
WILMER CUTLER PICKERING	
HALE AND DORR LLP	
1875 Pennsylvania Ave., NW	
Washington, DC 20006	

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-01121
Patent 7,846,441

PATENT OWNER'S PRELIMINARY RESPONSE

TABLE OF CONTENTS

	Page
I. INTRODUCTION	1
II. TECHNOLOGY BACKGROUND.....	5
A. Prior Art Cancer Treatments Included Surgery, Radiation, And Chemotherapy.....	5
1. Anthracyclines.....	6
2. Taxoids	8
B. Developing New Cancer Drugs In The 1990s Was An Unpredictable Process.	9
1. Preclinical studies.....	9
2. Clinical trials	11
a. Clinical trials can evaluate different endpoints.....	11
b. Clinical trials of cancer drugs in the 1990s often showed that new therapies lacked the desired efficacy or safety.....	12
3. Combination therapies.....	13
III. THE '441 PATENT	15
A. The Problem To Be Solved	15
1. HER2-positive breast cancer was a serious unsolved problem.	15
2. No prior therapeutic antibody had succeeded for solid tumors, such as breast cancer.	16
3. The prior art taught away from using taxoids with HER2- positive cancers.	17

4.	The increased cardiotoxicity of anthracyclines when combined with anti-ErbB2 antibodies was not known.	18
B.	The Invention.....	20
1.	Petitioner’s obviousness theory is inconsistent with the development history for trastuzumab.....	20
2.	Dr. Hellmann took the development of trastuzumab in a different direction.	21
3.	Dr. Hellmann’s invention produced unexpected results.	24
C.	Widespread Adoption And Praise	26
D.	Challenged Claims.....	27
E.	Prosecution History	27
IV.	PRIOR ART.....	29
A.	Asserted References	29
1.	Baselga 1996	30
2.	Seidman 1996	31
3.	1995 Taxol [®] PDR.....	33
B.	Other References	34
1.	Baselga Abstract 53.....	34
2.	Baselga Abstract 2262.....	35
3.	Pegram 1995.....	36
4.	Seidman 1995	36
V.	PERSON OF ORDINARY SKILL	36
VI.	CLAIM CONSTRUCTION	37

VII. ARGUMENT.....	38
A. Petitioner Has Not Demonstrated A Reasonable Likelihood Of Success With Respect To Any Challenged Claim.	38
1. Petitioner has not established a reasonable expectation of success in achieving the claimed clinical efficacy.....	39
a. The prior art does not teach that anti-ErbB2 antibodies or taxoids extend the time to disease progression in HER2-positive patients.....	39
b. The cited references do not support Petitioner’s conclusory assertions regarding the claimed clinical efficacy endpoint.	40
c. Prior art preclinical mouse studies would not have provided a reasonable expectation of success of achieving the claimed clinical efficacy in humans.....	45
d. Petitioner’s argument that ongoing clinical trials would have provided a reasonable expectation of success is factually incorrect and legally flawed.	47
2. Petitioner has not established a reasonable expectation of success in achieving the claimed clinical safety.	49
3. Petitioner has not shown that it would have been obvious to treat patients “in the absence of an anthracycline derivative.”	52
4. Petitioner’s assertion that taxoids had “proven efficacy” in HER2-positive patients is not supported and is directly refuted by prior art teaching away from the invention.	55
B. Petitioner’s Criticisms Of Dr. Sliwowski’s Declaration Lack Merit And Do Not Cure The Deficiencies In Petitioner’s Obviousness Theory.	57
C. Objective Indicia Of Non-Obviousness Confirm The Patentability Of The Challenged Claims.	59
1. Long-felt but unmet need	60

2.	Praise	61
3.	Unexpected results	62
4.	Commercial success	65
D.	<i>Inter Partes</i> Review Proceedings Violate The Constitution.	65
VIII.	CONCLUSION	67

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Amgen, Inc. v. Chugai Pharmaceutical Co.</i> , 927 F.2d 1200 (Fed. Cir. 1991)	46
<i>Brown & Williamson Tobacco Corp. v. Philip Morris, Inc.</i> , 229 F.3d 1120 (Fed. Cir. 2000)	65
<i>Coalition for Affordable Drugs V LLC v. Biogen MA Inc.</i> , IPR2015-01136, Paper 23 (Sept. 2, 2015)	48
<i>Crocs, Inc. v. International Trade Commission</i> , 598 F.3d 1294 (Fed. Cir. 2010)	59
<i>DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.</i> , 567 F.3d 1314 (Fed. Cir. 2009)	56
<i>Genetics Institute, LLC v. Novartis Vaccines & Diagnostics, Inc.</i> , 655 F.3d 1291 (Fed. Cir. 2011)	46, 54, 64
<i>InnoPharma Licensing, Inc. v. Senju Pharmaceutical Co.</i> , IPR2015-00902, Paper 90 (July 28, 2016)	60
<i>Institut Pasteur & Universite Pierre et Marie Curie v. Focarino</i> , 738 F.3d 1337 (Fed. Cir. 2013)	61
<i>Markman v. Westview Instruments, Inc.</i> , 517 U.S. 370 (1996)	66
<i>McCormick Harvesting Machine Co. v. C. Aultman & Co.</i> , 169 U.S. 606 (1898)	66
<i>Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.</i> , 566 F.3d 989 (Fed. Cir. 2009)	49, 62
<i>In re Soni</i> , 54 F.3d 746 (Fed. Cir. 1995)	63, 64

WBIP, LLC v. Kohler Co.,
829 F.3d 1317 (Fed. Cir. 2016)61

Constitutional Provisions

U.S. Constitution Amendment VII66

Regulations

37 C.F.R. § 42.104(b)(4).....29

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. Before 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 used a new 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 as claimed in the '441 patent—making it the *first* approved antibody-based therapy for solid tumors.

Now, decades later, Petitioner attempts to cast the '441 invention as a supposedly “straightforward” application of “principles” of combination chemotherapy. But Petitioner has not explained why a person of ordinary skill would have expected those supposed *chemotherapy* principles to apply to the entirely new class of therapeutic *antibodies*. Moreover, treating cancer is complex,

and Petitioner's arguments cannot be reconciled with the state of the art at the time, including the references cited in the petition. Petitioner also presents no more than a conclusory analysis for several claim limitations that ignores what the claims require. Although Petitioner's analysis has many flaws, there are at least four reasons why Petitioner has not demonstrated a reasonable likelihood of success with respect to any claim.¹

First, all challenged claims require a specific clinical efficacy result—*i.e.*, “to extend the time to disease progression.” Petitioner has pointed to no prior art suggesting that an anti-ErbB2 antibody and a taxoid—alone or in combination—are effective to extend the time to disease progression in HER2-positive patients. The prior art only describes a clinical endpoint known as a “response rate”—which Petitioner acknowledges is *different* from extending the time to disease progression. Petitioner has not explained how a skilled artisan could have reasonably expected to achieve the specific clinical result claimed in the '441 patent based upon prior art addressing an entirely different clinical endpoint.

Second, all challenged claims also require a specific clinical safety result—*i.e.*, “without increase in overall severe adverse events.” Petitioner has not shown

¹ Hospira has filed a petition (IPR2017-00731) challenging the '441 patent based upon some of the same references asserted here.

that a skilled artisan would have reasonably expected to achieve that specific safety result before the '441 invention. Petitioner relies on early-stage clinical results involving an anti-ErbB2 antibody as an individual agent, but those results do not address the safety of the claimed *combination*. Petitioner also cites preclinical mouse studies supposedly showing that the claimed combination did not increase toxicity. But those studies reported the same safety result for the combination of an anti-ErbB2 antibody and an anthracycline—a combination that produced significant cardiotoxicity when administered to humans. Petitioner's cited references thus highlight the well-known limitations of preclinical results to predict clinical safety and confirm the absence of any reasonable expectation of success in achieving the claimed clinical safety results in humans.

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

Fourth, Petitioner asserts that taxoids had “proven efficacy” in HER2-positive cancer based upon Seidman 1996 (Ex. 1011). But Seidman 1996 merely

presented a preliminary hypothesis that HER2 overexpression “seems to confer sensitivity rather than resistance to taxanes” and acknowledged that the issue required further investigation. A skilled artisan at the time would not have accepted Seidman 1996’s hypothesis as “proven” when even the Seidman authors continued to study the issue. And other contemporaneous references (which Petitioner ignores) specifically warned that HER2-positive breast cancer “will not respond well to Taxol.” Given the uncertainty surrounding the use of taxoids in HER2-positive patients, there were *no* clinical studies combining an anti-ErbB2 antibody and a taxoid until ’441 inventor Dr. Susan Hellmann proposed amending an ongoing Phase III clinical trial to test her invention. Before then, even those with the best information pursued other therapeutic options instead of the claimed combination. Petitioner’s assertion that a skilled artisan would have had a reasonable expectation of success treating HER2-positive patients with taxoids rests on hindsight.

Petitioner attempts to distract from the deficiencies in its proof by criticizing Dr. Mark Sliwowski’s declaration. That declaration was submitted during prosecution to demonstrate unexpected results and to explain the shortcomings of preclinical mouse models to predict clinical results in humans. Petitioner’s criticisms of Dr. Sliwowski’s declaration lack merit and mischaracterize his opinions—for example, by repeatedly attributing opinions and assumptions to Dr.

Sliwkowski that appear nowhere in his declaration. Petitioner's arguments about that declaration also do not cure the many deficiencies in its obviousness theory.

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. And contrary to Petitioner's narrative that the claimed invention would have been obvious, Dr. Larry Norton of Memorial Sloan-Kettering—a major figure in the treatment of breast cancer and co-author of the primary reference asserted here—went on national television to tout the '441 invention's impressive efficacy, stating: “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 arguments with respect to objective indicia do not address this key evidence or diminish its applicability to the challenged claims.

The Board should deny institution.

II. TECHNOLOGY BACKGROUND

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

Cancer is a disease involving an abnormal growth of cells (*i.e.*, a tumor) that invades the surrounding tissue and may spread to other parts of the body. (Ex. 1005 at 26; *see also* Ex. 1002, Earhart Decl. ¶ 30.) Early cancer treatments

included surgery to remove the tumor and radiation to kill the cancer cells. (Ex. 1005 at 37.) However, even after surgery and/or radiation, some cancer cells may remain, which can cause the cancer to recur. (*Id.*)

To address that issue, scientists began to investigate drugs that kill cancer cells (*i.e.*, chemotherapies) that could be used with surgery and radiation. (*Id.*; Ex. 1016 at 7.) Over several decades, that research resulted in a wide variety of chemotherapies. (Ex. 1002, Earhart Decl. ¶ 35; Ex. 1016 at 16-23 (8-page list of prior art chemotherapies).) Out of the dozens of prior art chemotherapies, 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. (*Id.*) Doxorubicin had “no known antagonistic interactions with any of the other commonly used anticancer agents,” and it was “active over a wide range of doses and in a variety of administration schedules,” which made it “very useful in the design of drug combinations” with other cancer therapies. (*Id.*) As a result, at the time, treatments containing anthracyclines were the “standard therapy for cancers of the breast.” (*Id.*)

As Petitioner notes, cardiotoxicity had been observed in some instances when anthracyclines were administered over time, resulting in high cumulative doses. (Paper 1 at 50.) However, by 1996, that side effect had been studied, and there were known techniques for reducing the cardiotoxicity from anthracyclines, while at the same time maintaining their proven efficacy. (Ex. 2030 at 423 (“Fortunately, much can now be done to lessen the risk of cardiac toxicity.”).)

Petitioner cites Dr. Earhart's declaration (Ex. 1002, ¶ 137) and a general cancer textbook (“Abeloff”) (Ex. 1016 at 813) as evidence that “a POSA would have limited use of anthracycline derivatives in treatment whenever possible” (Paper 1 at 51), but neither supports that assertion. Dr. Earhart acknowledges that “treating patients with anthracyclines is often unavoidable” and states that “many patients” at the time of the invention would have received anthracyclines as “a first-line therapy for breast cancer.” (Ex. 1002, Earhart Decl. ¶ 137.) And far from teaching avoidance of anthracyclines “whenever possible,” Abeloff cautions *against* limiting anthracycline usage, which “may deprive patients who are continuing to benefit from therapy who do not show signs of toxicity.” (Ex. 1016 at 29.)

Petitioner's other cited references reinforce that scientists at the time of the invention were not limiting anthracycline usage “whenever possible.” For example, Baselga Abstract 53 described a preclinical study involving the

anthracycline doxorubicin, which did not result in any observed increase in toxicity when combined with an anti-ErbB2 antibody. (Ex. 1019 at 4.) And Seidman 1995 noted that combinations with anthracyclines had shown “impressive antitumor activity” and were the subject of an “important” ongoing trial. (Ex. 1010 at 4.) Petitioner has cited nothing contemporaneous with the '441 invention indicating that anthracyclines were avoided “whenever possible.” (Paper 1 at 51.)

2. Taxoids

Unlike anthracyclines, taxoids were a relatively new type of chemotherapy in the 1990s, which oncologists were slow to adopt for treating breast cancer. Taxoids were associated with serious hypersensitivity reactions, “varying from flushing, dyspnea and bronchospasm, and rashes to severe hypotension and asystole, resulting in death.” (Ex. 2028 at 1265.) The prior art thus warned oncologists “to maintain a high degree of caution” with taxoids. (Ex. 2026 at 1704 (development of taxoids “has proceeded slowly due to serious hypersensitivity reactions”).) The prior art also reported that 30-40% of breast cancer patients did not respond to taxoids. (Ex. 2029 at 1359.)

The drug paclitaxel (Taxol[®]) is an example of a taxoid chemotherapy. The FDA approved paclitaxel for ovarian cancer in 1992 and for breast cancer in 1994. And even then, paclitaxel was approved to treat breast cancer only *after* other treatments failed (*i.e.*, paclitaxel was approved for “second-line” use). (Ex. 1012 at

6.) In fact, the approved Taxol[®] label from the time of the '441 invention—reflected in the asserted 1995 Taxol[®] PDR entry—advised that patients generally should be treated with an anthracycline *before* trying paclitaxel. (*Id.*)

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

Petitioner asserts that the discovery of new cancer treatments followed the simple application of “a set of reasoned principles” to identify predictable therapies that would be safe and effective. (Paper 1 at 38-39.) But the actual experience of cancer researchers at the time highlights the complexity and unpredictability of treating cancer, and refutes Petitioner's hindsight-driven narrative.

1. Preclinical studies

Preclinical studies in animal models (*e.g.*, mice) allow researchers to evaluate potential cancer therapies before testing them in humans. Those preclinical models are useful to screen out ineffective therapies. (Ex. 2023 at 79.) But it was well-known before the '441 invention that preclinical studies had a “very low” likelihood of predicting how humans would respond to a particular drug or combination of drugs for several reasons. (*Id.*)

First, mouse models at the time differed significantly from the physiology of treating cancer in humans. Prior art mouse xenograft studies involved injecting human cancer cells into mice that have their immune system suppressed, resulting

in a “reduced capacity to reject ‘foreign’ tissue.” (Ex. 1028 at 2.) The systems surrounding the tumor were not human, making the transplanted human tumors more susceptible to therapy than they would have been in humans. (*Id.* at 10, 16.) Thus, it was known at the time that “the xenograft system markedly overestimates” drug activity. (*Id.* at 16.)

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

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

Petitioner cites a single reference from 1984 (Ex. 1026) as supposedly demonstrating the accuracy of mouse xenograft studies to predict responses in human patients. (Paper 1 at 40.) However, that assessment of the reliability of prior art mouse studies as predictive of human responses is refuted by later studies, including those cited by Petitioner. (*E.g.*, Ex. 1028 at 16 (“[T]he xenograft system markedly overestimates the activity of most of the standard drugs as single agents.”).) Petitioner does not address the well-known limitations of prior art

mouse studies to predict results in human patients or attempt to reconcile them with its obviousness theory.

2. Clinical trials

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

a. Clinical trials can evaluate different endpoints.

Clinical trials of cancer therapies can be designed to evaluate different endpoints, as Petitioner acknowledges. (*See* Paper 1 at 41-42.) For example, the Baselga 1996 reference reported a clinical endpoint known as “response rate,” which is the percentage of patients who showed a specified reduction in tumor size. (Ex. 1020 at 4; *see also* Paper 1 at 42 (“Response Rate (RR) ... measures changes in tumor size.”).) A different clinical endpoint is “time to disease

progression,” which is the time following treatment before a patient's tumors grow or spread to other parts of the body. (Ex. 1001, 29:1-2; *see also* Paper 1 at 42.)

As Petitioner acknowledges (Paper 1 at 42), response rate and time to disease progression are different endpoints signifying different clinical outcomes. Response rate measures the initial effect on tumor size, whereas time to disease progression measures the long-term effect on disease progression. (*Id.*) As described below, Petitioner does not explain how a skilled artisan could have transformed the response rate data in the prior art to the very different time to disease progression results described and claimed in the '441 patent.

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

Petitioner's obviousness theory assumes that a skilled artisan would have had a reasonable expectation of success in obtaining the claimed clinical efficacy and safety results of the '441 invention simply because a clinical trial for a new cancer therapy was underway. (*See, e.g.*, Paper 1 at 52.) Petitioner's argument is directly contradicted by the experience of cancer researchers in the 1990s.

Only 5% of cancer drugs in the 1990s that advanced to clinical trials resulted in an approved product. (Ex. 2021 at 712-13.) And promising results in early-stage trials were not predictive of overall success. Nearly 60% of cancer drugs in Phase III clinical trials during the 1990s ultimately failed to result in an approved

drug. (*Id.*) That a therapy had progressed through early-stage clinical trials was thus no indication that the therapy would have a clinical benefit when subjected to more rigorous late-stage studies. These numerous failures during clinical development reinforce the limitations of preclinical studies at that time to predict clinical efficacy in humans. (*Id.* (“The lack of efficacy might be contributing more significantly to therapeutic areas in which animal models of efficacy are *notoriously unpredictable*, such as CNS and *oncology*, both of which have relatively higher failure rates in Phase II and III trials.”).)²

3. Combination therapies

Petitioner cites four supposed “principles” of combination chemotherapy, which it argues would have allowed a skilled artisan to identify drug combinations “achieving the greatest possible combined result.” (Paper 1 at 38-39.) As an initial matter, those cited “principles” on their face only address combinations of different *chemotherapies*. (Ex. 1016 at 10-11.) The ’441 patent, however, claims treatment using combinations of an *antibody* and chemotherapy, not combinations of different chemotherapies. At the time of the ’441 invention, antibodies were an entirely new class of drug, and it was not clear how (if at all) they could be used to treat cancer. (See Ex. 2031 at 683-84; *infra* pp. 16-17.) Petitioner has not

² All emphases added unless otherwise indicated.

explained why a skilled artisan at the time would have believed that chemotherapy principles would be applicable to combinations with the new and unproven class of therapeutic antibodies.

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

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

1024 at 17.) Petitioner does not address the known “challenge of combining paclitaxel with other drugs” (*id.*), or explain how general principles of combination chemotherapy could have provided a reasonable expectation of success in light of the specific challenges of combining taxoids with other drugs.

III. THE '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 overexpress human epidermal growth factor receptor 2 (“HER2”), also known as human ErbB2. Out of the hundreds of thousands of women each year who are diagnosed with breast cancer, roughly 25-30% are HER2-positive. (Ex. 1001, 1:23-29.)

As Petitioner acknowledges, HER2-positive breast cancer is a serious and aggressive disease, which at the time of the invention was “particularly difficult to treat with traditional anti-cancer agents.” (Paper 1 at 28.) In the 1990s, HER2-positive status was “associated with poor prognosis” with a high rate of tumor recurrence and spreading to other areas of the body. (Ex. 2022 at 1420; Ex. 2010 at 179-80.) Even after surgery, chemotherapy, and/or radiation, HER2-positive patients had “a shorter time to relapse as well as a shorter overall survival.” (Ex. 2011 at 707; Ex. 2010 at 179-80.) Lacking effective treatments, the life

expectancy of HER2-positive patients in 1996 “was only 18 months post-diagnosis.” (Ex. 2017 at 138; *see also* Ex. 2018 at 887 (“[T]he reality is that breast cancer patients who overproduce HER2 can now expect to live some 10 to 12 months after metastasis begins, a horribly rapid progression compared to six or seven years for HER2-normal patients.”).)

2. No prior therapeutic antibody 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—called an “immunogenic” response—thereby preventing them from having a therapeutic effect. (Ex. 2031 at 655.) As of 1996, “much additional study” was required to determine whether that immunogenic response could be avoided. (*Id.* at 683.) Moreover, antibodies are large molecules that have difficulty penetrating tissue, which was a “significant obstacle[] to the effective use of mAbs for solid tumors,” like breast cancer, because it was not certain whether the antibody could reach the cancer cells where it might be effective. (*Id.*)

By the early 1990s, numerous antibodies had been tested in patients with different cancers (including breast cancer); but consistent with the challenges just described, they showed “no hint of a consistent therapeutic efficacy.” (Ex. 2025 at 649; *id.*, Table 2 (identifying failed antibody clinical trials for gastrointestinal tumors; breast, colon, ovarian, and lung cancer; pancreatic adenocarcinoma; neuroblastoma; and melanoma).) Given that poor track record, a 1993 review article aptly summarized the state of the art prior to the '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 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 (pp. 8-9), taxoids were approved only as a second-line therapy for breast cancer and had a history of problems that initially limited their clinical use, including hypersensitivity reactions and patient resistance.

Using taxoids to treat HER2-positive breast cancer presented even greater challenges. Petitioner argues that taxoids had “proven efficacy against metastatic HER2-positive breast cancer in humans” based upon Seidman 1996. (Paper 1 at 43.) As described in more detail below, however, that is not an accurate characterization of Seidman 1996, which merely speculated that “HER2 over-

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

Indeed, far from “proven efficacy,” some scientists at the time expressed doubt that taxoids could treat HER2-positive patients. For example, a 1996 paper (which Petitioner ignores) taught that HER2-positive cancers are *resistant* to taxoids and explicitly warned that “breast cancers that overexpress p185 [*i.e.*, HER2] *will not respond well to Taxol.*” (Ex. 2029 at 1362.)

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

In addition to those known challenges, there was another significant complication that was *not* known prior to the '441 invention. The combination of an anti-ErbB2 antibody and anthracyclines can produce severe cardiotoxicity. (Ex. 1001, 30:20-23.)

Petitioner asserts that a skilled artisan would have “limited use of anthracycline derivatives in treatment whenever possible” due to the risk of cumulative cardiotoxicity. (Paper 1 at 50-51.) But the prior art taught that the problem of cumulative cardiotoxicity was manageable. (Ex. 2030 at 423 (“Fortunately, much can now be done to lessen the risk of cardiac toxicity.”).) Even Petitioner’s cited references described techniques for reducing the risk of

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

Indeed, far from avoiding anthracyclines, Petitioner's cited references describe “important” ongoing studies involving anthracyclines. (Ex. 1010 at 4; *see* Ex. 1019 at 4.) And even contemporaneous references describing the preclinical studies for the anti-ErbB2 antibody trastuzumab focus on combinations with the anthracycline doxorubicin and do not even mention combinations with taxoids. (Ex. 1016 at 114.) Moreover, when the Phase III clinical trials for the anti-ErbB2 antibody trastuzumab began, the *only* combination therapy initially studied was with an anthracycline. (*See infra* pp. 20-22.) The known cumulative toxicity of anthracyclines thus did not discourage their use before the '441 invention.

Instead, as later discovered while conducting the clinical study that led to the '441 patent, combining anti-ErbB2 antibodies and anthracyclines *enhances* the cardiotoxicity of anthracyclines, regardless of cumulative dose. (Ex. 2027 at 791 (“We found that concurrent treatment with an anthracycline, cyclophosphamide, and trastuzumab significantly increased the risk of cardiac dysfunction, as compared with treatment with only anthracycline and cyclophosphamide.”); *id.* at 790 (“[t]he cumulative dose of anthracycline was not identified as a risk factor” for cardiotoxicity when combined with an anti-ErbB2 antibody).) That increased

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

B. The Invention

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

In the early 1990s, Genentech created an anti-ErbB2 antibody called “trastuzumab” or “rhuMAb HER2,” which it studied as a potential new treatment for HER2-positive cancers. Petitioner repeatedly asserts that clinical trials combining an anti-ErbB2 antibody and a taxoid “were underway well before the filing of [the] application that led to the ’441 patent,” citing publications as early as 1994. (Paper 1 at 9, 11, 33, 52, 58.) But that is not what the prior art discloses, and not what actually happened.

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

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

That development history reinforces what was known at time about treating HER2-positive breast cancer. Taxol[®]—a *second-line* therapy (Ex. 1012 at 6) that the prior art warned HER2-positive patients “will not respond well to” (Ex. 2029 at 1362)—was not used with trastuzumab to treat patients. On the other hand, combinations with anthracyclines—which at the time showed no hint of increased toxicity with anti-ErbB2 antibodies—and other chemotherapies (*e.g.*, cisplatin) were the preferred candidates for clinical development.

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

The clinical development of trastuzumab followed a vastly different course with Dr. Susan 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. 1008 at 1 (Hellmann Decl. ¶ 1); *id.* at 6.) She became Genentech's head of clinical oncology and was responsible for managing the clinical development of trastuzumab. (*Id.* at 1 (Hellmann Decl. ¶ 1); *id.* at 5.)

At the time, a Phase III clinical trial was already underway to test the combination of trastuzumab with an anthracycline (doxorubicin) as a treatment for

HER2-positive breast cancer. (Ex. 2001 at 16, § 5.2.2.) However, after several months, that study was having difficulty enrolling patients. (Ex. 2002 at 2; Ex. 2003 at 2; Ex. 2004 at 3.) Given the prevalence of anthracyclines to treat breast cancer, many patients had previously been treated with anthracyclines and thus were ineligible for the study. (Ex. 2001 at 14, § 4.2; Ex. 2003 at 2.)

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

However, based on 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 (trastuzumab) and a taxoid (paclitaxel) in the absence of an anthracycline derivative. (Ex. 2005 at 13; Ex. 2002 at 3; Ex. 2003 at 2; Ex. 2004 at 5-6.) That proposal was risky for several reasons.

First, as described above (p. 11), therapies are typically tested in smaller, early-stage clinical trials before advancing to larger-stage studies. However, no human had *ever* been treated with the combination of an anti-ErbB2 antibody and a

taxoid. Testing that combination in a Phase III trial without first studying it in a smaller scale trial risked exposing a large number of patients to potential adverse events that could not have been predicted from preclinical models.

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

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

Despite those uncertainties, Dr. Hellmann advocated that Genentech adopt her proposed amendment to the Phase III protocol, and she presented her proposal

at several meetings of Genentech's Product Development Committee ("PDC") in [REDACTED]. (Ex. 2002 at 3; Ex. 2003 at 1-2; Ex. 2004 at 2.) Dr. Hellmann's prior work at Bristol-Myers Squibb, where she was the project team leader for the development of paclitaxel, provided her with an understanding of taxoids well-beyond the knowledge of a person of ordinary skill. (Ex. 1008 at 1 (Hellmann Decl. ¶ 1); *id.* at 6.) Based on that personal experience, she believed that taxoids were "likely to be important for breast cancer therapy in the next decade," which is why she advocated that Genentech take the risks associated with pursuing a combination of an anti-ErbB2 antibody and a taxoid. (Ex. 2002 at 3.)

[REDACTED], Genentech's PDC approved Dr. Hellmann's proposal, and the Phase III study protocol was modified in [REDACTED] to permit patients to receive trastuzumab combined with a taxoid in the absence of an anthracycline derivative. (Ex. 2007 at 36-38; Ex. 2004 at 2.) However, the decision was not unanimous. (Ex. 2004 at 10 (Todd Rich: "I can't recommend any changes to the trial.")) Even those who supported Dr. Hellmann's proposal recognized that it presented risks and uncertainties. (Ex. 2004 at 11 (Art DeVault: "a good gamble").)

3. Dr. Hellmann's invention produced unexpected results.

Following the amendment to the Phase III protocol, the study reached its primary endpoint in late 1997. (Ex. 2008 at 51-69, 104-109.) The study showed

that the combination of an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative dramatically extended the time to disease progression without overall increase in severe adverse events. (*Id.* at 199.) By contrast, the combination of an anti-ErbB2 antibody with an anthracycline resulted in cardiotoxicity in a significant number of patients. (*Id.* at 198.) The increased cardiotoxicity of trastuzumab combined with anthracyclines was completely unexpected—particularly because those patients had received *no* prior anthracycline-based therapy and thus could not have experienced the cumulative toxicity known in the art. (Ex. 2008 at 39; Ex. 2001 at 12.) These data are reflected in the provisional patent application filed December 12, 1997. (Ex. 2009, 38:26-43:26.) And as described below (p. 27), the challenged claims are directed to Dr. Hellmann's new method of treatment.

Based upon those results, trastuzumab (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.) 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 asserted 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.)³

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

³ Petitioner has challenged U.S. Patent No. 7,892,549, which is a continuation of the '441 patent, in a separate petition (IPR2017-01122).

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

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

⁴ The claims in a related application (14/141,232) are under non-final obviousness rejection in view of Baselga 1996 combined with another reference (which was antedated during the '441 prosecution). Patent Owner has responded to that rejection and is awaiting further action by the examiner.

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

On December 30, 2009, the examiner allowed the claims. (Ex. 1004 at 2466.)

IV. PRIOR ART

A. Asserted References

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

1. Baselga 1996

Baselga 1996 (Ex. 1020) is an article published in March 1996. It was considered during prosecution and is discussed in the '441 patent's specification. (Ex. 1001, 3:34-40.)

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

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

Baselga 1996 acknowledged that the mechanism of potential antitumor activity for trastuzumab was not understood and proposed several possible explanations for the observed clinical results. (*Id.* at 8-9.) Thus, it remained unclear at the time how other patient populations might respond (if at all) to trastuzumab, or to combinations of trastuzumab with chemotherapy. (*Id.*

("[C]ontinued research with this agent and other HER2-targeted treatment strategies appears warranted.")

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

2. Seidman 1996

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

Seidman 1996 describes a retrospective analysis of tumor samples for metastatic breast cancer patients "who were treated on phase II protocols of single agent paclitaxel (n=106) or docetaxel (n=20)." (Ex. 1011 at 5.) Seidman 1996

reported that the “response proportion” was 58.8% among HER2-positive patient and 38.7% among HER2-negative patients. (*Id.*) However, the abstract noted a wide margin of error for the overall response rate (“95% C.I. 38.1-55.5%) and acknowledged several “confounding variables” making it difficult to interpret the data. (*Id.*)

Based upon those results, Seidman 1996 speculated that “HER2 over-expression in MBC seems to confer sensitivity rather than resistance to taxanes.” (*Id.*) However, the authors had no explanation for why HER2-positive status might affect the response to taxoids and simply noted that “[c]ellular mechanisms for this effect are under investigation.” (*Id.*) A person of ordinary skill at the time therefore would have viewed Seidman 1996 as merely presenting a preliminary hypothesis that required further study.⁵

⁵ That is how the Seidman authors viewed it. They studied the issue further and reported in 2002 that HER2 overexpression did *not* show “a statistically significant association with clinical response to taxane therapy.” (Ex. 2024 at 2322.) The Seidman authors recognized that those results were contrary to their preliminary hypothesis from Seidman 1996, which was based upon an “earlier analysis of fewer cases.” (*Id.* at 2323.)

3. 1995 Taxol[®] PDR

The 1995 Taxol[®] PDR (Ex. 1012) is the entry from Physicians' Desk Reference from 1995 corresponding with paclitaxel. The 1995 Taxol[®] PDR was not itself considered during prosecution. But the only information that Petitioner cites from the reference is its disclosure of dosage amounts for paclitaxel (*see* Paper 1 at 48), which other references before the examiner (*e.g.*, Seidman 1995) also disclosed. (*Compare* Ex. 1010 at 3 (“paclitaxel was administered via 3-hour infusion every 3 weeks, as a starting dose of 175 mg/m²”), *with* Ex. 1012 at 8 (“TAXOL at a dose of 175 mg/m² administered intravenously over 3 hours every three weeks has been shown to be effective”).)

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

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

The 1995 Taxol[®] PDR does not suggest combining paclitaxel with anti-ErbB2 antibodies, or even mention anti-ErbB2 antibodies. Moreover, the reference

does not mention HER2-positive breast cancer or suggest that taxoids would be effective to treat HER2-positive patients.

B. Other References

Although not cited in its proposed ground, Petitioner also discusses various other references in its description of the state of the art. (*See* Paper 1 at 27-37.) Petitioner does not rely upon those references for the disclosure of any claim limitations. Nevertheless, for completeness, Patent Owner briefly addresses those other references below.

1. Baselga Abstract 53

Baselga Abstract 53 (Ex. 1019) is an abstract published in March 1994. It was cited during prosecution and is discussed in the '441 patent's specification. (Ex. 1001, 3:54-59.)

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

Baselga Abstract 53 notes that “[c]linical studies are underway.” (*Id.*) But that is just a generic reference to clinical trials of trastuzumab. It does not refer to studies involving the **combination** of trastuzumab and a taxoid, as Petitioner asserts (Paper 1 at 58). Indeed, Baselga Abstract 53 could not have been referring to ongoing studies of this combination because, as discussed above (pp. 20-22), there was no such study underway at the time.

2. Baselga Abstract 2262

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

As Petitioner notes (Paper 1 at 31), Baselga Abstract 2262 states that the rate of tumor inhibition was “markedly better” for combinations with paclitaxel (93%) versus doxorubicin (70%). (Ex. 1021 at 3.) But cancer researchers at the time did not view any preliminarily-observed difference in activity as favoring combinations with taxoids over anthracyclines. (*See, e.g.*, Ex. 1016 at 114 (citing Baselga’s work and discussing only combinations with anthracyclines, not taxoids).) As discussed above (pp. 20-22), when the Herceptin[®] Phase III trials began, the **only** combination therapy studied was with an anthracycline, not a taxoid.

3. Pegram 1995

Pegram 1995 (Ex. 1022) is an abstract published in March 1995. It was considered during prosecution of the '441 patent.

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

4. Seidman 1995

Seidman 1995 (Ex. 1010) is a review article published in October 1995. It was considered during prosecution of the '441 patent.

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

V. PERSON OF ORDINARY SKILL

The Board should apply the same definition of a person of ordinary skill from IPR2017-00731, which also involves the '441 patent. In IPR2017-00731, the parties agreed that a person of ordinary skill for purposes of the '441 patent would be a “clinical or medical oncologist specializing in breast cancer with several years

of experience with breast cancer research or clinical trials.” (IPR2017-00731, Paper 1 at 7; IPR2017-00731, Paper 9 at 32.)

Petitioner describes the person of ordinary skill in slightly different terms—for example, by including Ph.D. scientists and by requiring “substantial experience” with treating breast cancer and conducting breast cancer clinical trials. (Paper 1 at 43.) Those differences, however, do not have any bearing on the outcome here. For the reasons explained below, the challenged claims would not have been obvious under either Petitioner's proposed definition or the definition from IPR2017-00731.

VI. CLAIM CONSTRUCTION

For purposes of this proceeding, Patent Owner requests construction of “response rate” in claim 10 to mean “the percentage of patients whose tumor is reduced in size by a specified amount following treatment.” That construction is supported by the specification, which defines a “response” as involving a reduction in tumor size by a specified amount (*e.g.*, 25%). (Ex. 1001, 28:46-65.)

Petitioner proposes construing “response rate” to mean “the percentage of patients whose disease responds to treatment.” (Paper 1 at 22.) That is not consistent with the '441 patent's usage of the term or its ordinary meaning in the art—which is limited to the specific response of reducing tumor size. Indeed, even Petitioner contradicts its proposed construction by defining “response rate” in

terms of a reduction in tumor size elsewhere in the petition and its supporting expert declaration. (*See* Paper 1 at 42 (“Response Rate (RR), which measures changes in tumor size”); Ex. 1002, Earhart Decl. ¶ 92 (“Response Rate (‘RR’), which measures the percentage of patients whose tumor is reduced in size by a specified amount following treatment”).)

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

VII. ARGUMENT

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

Petitioner has asserted a single ground against all challenged claims: obviousness over Baselga 1996, Seidman 1996, and the 1995 Taxol PDR entry, in view of the knowledge of a person of ordinary skill in the art. (Paper 1 at 24.)

None of those references discloses clinical efficacy and safety results for the claimed combination of an anti-ErbB2 antibody and a taxoid, and none even addresses whether those drugs as single agents are effective “to extend the time to disease progression” in the claimed HER2-positive patient population.

In addition, none of these references teach the claim limitation “in the absence of an anthracycline derivative.” Indeed, the development history of Herceptin[®]—where the only combination therapy initially studied in Phase III

trials was with an anthracycline—confirms that it would not have been obvious at the time to treat patients “in the absence of an anthracycline derivative.”

Finally, Petitioner's assertion that taxoids had “proven efficacy” in HER2-positive patients (Paper 1 at 43) is not supported by Seidman 1996 and is directly refuted by other prior art references that Petitioner ignores.

Accordingly, as explained below, Petitioner has not demonstrated a reasonable likelihood of success with respect to any challenged claim.

- 1. Petitioner has not established a reasonable expectation of success in achieving the claimed clinical efficacy.**
 - a. The prior art does not teach that anti-ErbB2 antibodies or taxoids extend the time to disease progression in HER2-positive patients.**

Each challenged claim requires a specific clinical efficacy result—*i.e.*, “to extend the time to disease progression.” Petitioner has not shown that a skilled artisan would have reasonably expected to achieve that specific efficacy result. Indeed, the cited references contain no teaching that anti-ErbB2 antibodies and taxoids—alone or in combination—extend the time to disease progression in HER2-positive patients. The first disclosure of data addressing that clinical endpoint for anti-ErbB2 antibodies or taxoids in HER2-positive patients is in the '441 patent itself. (Ex. 1001, 29:11-30:25.)

The absence of any prior art data addressing the claimed clinical endpoint is a critical omission given the state of the art before the '441 invention. As discussed above (pp. 16-17), no prior antibody-based therapy had been approved for the treatment of solid tumors, and it was highly uncertain whether such therapies could ever be clinically effective. Moreover, as discussed above (pp. 17-18), there were serious doubts that taxoids—a second-line therapy that the prior art warned against using in HER2-positive patients—could be used to treat the specific patient population addressed in the '441 claims. Indeed, Petitioner admits that HER2-positive patients were “notoriously difficult to treat.” (Paper 1 at 45.) Petitioner does not explain how a skilled artisan could have reasonably expected to extend the time to disease progression in HER2-positive patients given those known challenges.

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

Petitioner cites Baselga 1996 and Seidman 1996 to argue that anti-ErbB2 antibodies and taxoids had “proven efficacy against metastatic HER2-positive breast cancer in humans.” (Paper 1 at 43.) The 11.6% response rate in Baselga 1996's early-stage clinical trial (Ex. 1020 at 6) and Seidman 1996's retrospective analysis of tissue samples (Ex. 1011 at 5) fall far short of “proven efficacy” for either anti-ErbB2 antibodies or taxoids. In fact, even the authors of Seidman 1996

did not view that reference as demonstrating the “proven efficacy” of taxoids in HER2-positive patients. Instead, they continued to study the issue and subsequently determined that HER2-positive patients do *not* have any sensitivity to taxoids. (Ex. 2024 at 2322-23.)

In any case, Petitioner's obviousness theory fails for the simple reason that neither Baselga 1996 nor Seidman 1996 addresses the claimed clinical endpoint—*i.e.*, “to extend the time to disease progression.” The clinical endpoint evaluated in Baselga 1996 was “response rate,” which reflects the percentage of patients showing a reduction in tumor *size* by a specified amount. (Ex. 1020 at 4.) As Petitioner admits, “response rate” is *different* from “time to disease progression,” which measures the *time* before the disease worsens—not the effect of therapy on tumor *size*. (Paper 1 at 42; Ex. 1002, Earhart Decl. ¶ 92.)

Petitioner notes that Baselga 1996 reported that the “median time to progression for patients with either minor or stable disease was 5.1 months.” (Ex. 1020 at 6; *see* Paper 1 at 33.) But that data does not reflect any *extension* in the time to disease progression, as required by the challenged claims. As Petitioner admits, the claim limitation “‘extend the time to disease progression’ ... is a *relative* term.” (Paper 1 at 21.) The data reported in Baselga 1996, however, is not a relative measure. All patients in the study received trastuzumab, and there was no control arm against which to evaluate whether there was any *extension* in the

time to disease progression. (Ex. 1020 at 4.) Given the lack of a control group in the study reported in Baselga 1996 against which to measure the clinical endpoint of extending the time to disease progression, this reference does not teach the claimed comparative result.

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

Petitioner points to the 1995 Taxol[®] PDR entry for its supposed disclosure of “known effective amounts of paclitaxel.” (Paper 1 at 48.) But Petitioner does not contend that the 1995 Taxol[®] PDR entry teaches that taxoids are effective to extend the time to disease progression in HER2-positive patients. (*See id.* at 27, 48.) Indeed, the 1995 Taxol[®] PDR entry does not mention HER2-positive breast cancer, let alone provide clinical results showing an extension of the time to disease progression in those patients. (*See* Ex. 1012.) Petitioner's conclusory assertion that the disclosed amounts were “effective” (Paper 1 at 48) does not

address the specific disease or the specific efficacy limitation recited in the challenged claims.

Finally, Petitioner cites four “principles” of combination chemotherapy (Paper 1 at 45-46), but those supposed “principles” do not render the challenged claims obvious. As discussed above (pp. 13-14), Petitioner’s cited principles apply to *chemotherapy* combinations, not combinations with *antibodies*. That is significant difference because antibodies at the time were a new and unproven class of drug, and it was not clear how (if at all) antibodies could be used to treat breast cancer. (*See supra* pp. 16-17.)

And even if Petitioner’s cited chemotherapy “principles” had any application to antibodies, Petitioner has failed to demonstrate that the claimed combination satisfies those four principles. For example, with respect to the first principle (*i.e.*, “each component of the combination should be active as a single agent in the intended population” (Paper 1 at 39)), neither anti-ErbB2 antibodies nor taxoids had been demonstrated to be effective as single agents to extend the time to disease progression in HER2-positive patients. Indeed, far from demonstrated efficacy in the intended population, Seidman 1996 merely presented a preliminary hypothesis that even the Seidman authors recognized required further study and that other contemporaneous publications (*e.g.*, Ex. 2029 at 1362) directly refuted. (*See infra* pp. 55-56.)

Moreover, even with those general guiding principles, treating cancer was highly unpredictable in the 1990s, as even Petitioner's cited references acknowledge. (*See supra* pp. 14-15.) Petitioner has not explained how general principles could have provided a reasonable expectation of success in achieving the specific clinical efficacy result claimed in the '441 patent in light of those uncertainties.

Petitioner's obviousness theory assumes that a person of ordinary skill would have arrived at the claimed method of treatment by treating patients with an anti-ErbB2 antibody and a taxoid in "the *known* amounts that were effective to *extend* the time to disease progression of each drug when used as monotherapy." (Paper 1 at 47.) But Petitioner ignores that, in the prior art, there was *no* amount of an anti-ErbB2 antibody or a taxoid known to be effective to extend the time to disease progression; the first disclosure of that data is in the '441 patent itself. (Ex. 1001, 29:11-30:25.) In sum, Petitioner has failed to demonstrate a reasonable likelihood of success with respect to the challenged claims because the specific teaching underlying its obviousness theory was absent from the prior art.

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

Lacking prior art data in humans, Petitioner argues that a skilled artisan would have had a reasonable expectation of success based upon the “synergistic anti-tumor interaction between trastuzumab and paclitaxel” observed in preclinical mouse studies. (Paper 1 at 52.) But those preclinical studies merely showed an initial effect on tumor size (*i.e.*, “growth inhibition”), not a longer-term extension in the time to disease progression as the challenged claims require. (Ex. 1019 at 4; Ex. 1021 at 3.) Petitioner does not explain how those preclinical results could have provided a reasonable expectation of success in achieving the *different* clinical endpoint of extending the time to disease progression.

Moreover, preclinical mouse studies were known at the time to be unreliable indicators of clinical outcomes in humans. (*See supra* pp. 9-11.) Petitioner has not explained how a skilled artisan could have had a reasonable expectation of success based on preclinical results evaluating a different outcome in mice given the well-

known limitations of mouse models at the time to predict responses in humans.⁶

See Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1208-09 (Fed. Cir. 1991)

(finding no reasonable expectation of success where “[t]here were many pitfalls” to achieving the claimed invention).

Petitioner points to “the lack of increased toxicity when trastuzumab was added to paclitaxel in preclinical studies” as evidence that a person of ordinary skill would have had a reasonable expectation of success. (Paper 1 at 52.) But the prior art disclosed the same result for combinations of trastuzumab with the anthracycline doxorubicin—a drug combination that was later shown to produce a significant increase in cardiotoxicity when administered to humans. (Ex. 1019 at 4 (“MAb 4D5 did not increase the toxicity of paclitaxel or doxorubicin in animals as determined by animal survival and weight loss.”).)

Petitioner cannot rely on those preclinical results to provide a reasonable expectation of success while ignoring results in that same study that proved wholly unsuccessful. *See Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*,

⁶ As discussed above (p. 23), the preclinical results for the claimed combination were “inconsistent.” Petitioner’s obviousness theory—which focuses exclusively on the preclinical results reported in the Baselga references (Exs. 1019-21)—does not reflect the complexity of the problem solved by the ’441 invention.

655 F.3d 1291, 1305 (Fed. Cir. 2011) (patent challenger may not dismiss the portions of the prior art demonstrating non-obviousness because a reference “must be considered in its entirety, *i.e.*, as a *whole*” (emphasis in original)).

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

Petitioner also argues that a person of ordinary skill would have had a reasonable expectation of success because Baselga 1996 supposedly discloses that “a clinical trial with the combination was already underway,” which it contends “confirmed that POSAs reasonably expected the combination to be safe and effective.” (Paper 1 at 52.) But that argument is not supported by the asserted references and is factually incorrect.

Baselga 1996 does not state that a clinical study combining trastuzumab and paclitaxel was underway. It identifies “several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel” that had been combined with trastuzumab in preclinical studies and notes that “clinical trials of such combination therapy are currently in progress.” (Ex. 1020 at 9.) But Baselga 1996 does not state that the combination of trastuzumab and paclitaxel in the absence of an anthracycline derivative was being pursued; it does not specify what “combination therapy” was being studied. Nor could Baselga 1996 have been referring to the claimed combination. There was *no* clinical study testing the claimed combination when

Baselga '96 was submitted (August 8, 1995) and accepted for publication (October 19, 1995). (*See supra* pp. 20-24.) In short, Petitioner's obviousness theory requires reading incorrect assumptions into Baselga 1996.

Petitioner's argument that a skilled artisan would have had a reasonable expectation of success based upon the mere existence of an ongoing clinical study also cannot be reconciled with the actual experience of cancer researchers in the 1990s. As discussed above (pp. 12-13), even the cancer therapies that advanced to Phase III trials failed nearly 60% of the time. Moreover, although any cancer therapy in development during the 1990s had a high likelihood of failure, the '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 also legally incorrect, and adopting Petitioner's reasoning would have sweeping consequences. Clinical trials precede *every* drug approval. If the mere fact that those clinical trials are underway would have provided a reasonable expectation of success, then no invention relating to the efficacy of a new therapy would be patentable. That is not the law. *See, e.g., Coalition for Affordable Drugs V LLC v. Biogen MA Inc.*, IPR2015-01136, Paper 23, at 10, 14, 15 (Sept. 2, 2015) (denying institution of obviousness grounds based upon ongoing clinical studies because those studies merely reflected a "hope" that "may or may not come true," not a reasonable expectation of success).

Petitioner has failed to demonstrate that a person of ordinary skill would have had a reasonable expectation of success in achieving the specific clinical efficacy limitation required by all challenged claims. 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). Accordingly, the Board should deny institution.

2. 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. In the absence of such data, Petitioner has not demonstrated a reasonable expectation of success in achieving that claimed clinical result.

First, Petitioner points to Baselga 1996's description of trastuzumab as “well tolerated” and lacking “significant toxicity” (Ex. 1020 at 5, 7) as evidence that a skilled artisan supposedly would have had a reasonable expectation of success that the claimed combination with a taxoid could be administered to

patients safely. (Paper 1 at 46, 49.) But Baselga 1996 addressed the safety of trastuzumab alone—not when *combined* with a taxoid, as in the challenged claims. That is a significant difference given the then-existing safety concerns that taxoids would produce severe side effects, which could be exacerbated in combination with other drugs. (*See supra* pp. 8-9.)

Nor was that risk a mere hypothetical possibility. As discussed above (pp. 18-20), treating patients with an anti-ErbB2 antibody combined with an anthracycline unexpectedly produced severe cardiotoxicity, even in patients who had no prior anthracycline exposure. Given the unpredictability of clinical safety—as confirmed by the development history of Herceptin[®] itself—a skilled artisan would not have had a reasonable expectation of success concerning the safety of the claimed combination based upon results obtained from administering an anti-ErbB2 antibody alone.

Second, Petitioner argues that “the lack of increased toxicity from adding trastuzumab to paclitaxel in preclinical studies” would have provided a reasonable expectation of success with respect to the claimed clinical safety limitation. (Paper 1 at 49.) But those preclinical studies made the same observation about combinations with the anthracycline doxorubicin—which produced a significant increase in cardiotoxicity when administered to humans. (*See Ex. 1019 at 4; supra* pp. 18-20.) Thus, if anything, those preclinical studies merely confirm the

limitations of prior art mouse models to predict clinical safety and do not support Petitioner's obviousness theory.

Third, pointing to general "principles" of combination chemotherapy, Petitioner asserts that a skilled artisan would have had a reasonable expectation of success because of the "lack of known significant overlapping toxicities between trastuzumab and paclitaxel." (Paper 1 at 49.) But by that reasoning, a skilled artisan would have had a reasonable expectation of success with respect to combinations with anthracyclines too, given the lack of known overlapping toxicities for those drugs. (*See* Ex. 1020 at 5.) Yet Petitioner nevertheless argues that anthracyclines would have been avoided. (Paper 1 at 50-51.) Petitioner's selective application of its supposed "principles" of combination chemotherapy rests on impermissible hindsight.

Finally, Petitioner asserts that a skilled artisan would have reasonably expected to achieve the claimed clinical safety based upon Baselga 1996's supposed disclosure that "a clinical trial with the combination was already underway." (Paper 1 at 52.) However, as discussed above (p. 31), that argument is not supported by Baselga 1996; in fact, there was no ongoing study at the time that the reference was submitted or accepted for publication. And even under Petitioner's counterfactual theory, the mere existence of an ongoing study would not have provided a reasonable expectation of success. On the contrary, cancer

research in the 1990s had a high rate of failure, even for drugs in Phase III studies.

(*See supra* pp. 12-13.)

The Board should deny institution because Petitioner has not demonstrated a reasonable expectation of success with respect to the claimed clinical safety limitation.

3. Petitioner has not shown that it would have been obvious to treat patients “in the absence of an anthracycline derivative.”

All claims of the '441 patent require treatment “in the absence of an anthracycline derivative.” Before the '441 invention, it would not have been obvious that patients receiving an anti-ErbB2 antibody should avoid anthracyclines. On the contrary, as discussed above (pp. 6-8), anthracyclines were the leading breast cancer therapy at the time. And anthracyclines had no known antagonistic interactions with other drugs and had flexible dosing schedules, which made them “very useful” for breast cancer combination therapies in the 1990s.

(Ex. 2030 at 409.)

Petitioner now seeks to rewrite that history, arguing that “a POSA would have limited use of anthracyclines in treatment whenever possible.” (Paper 1 at 51.) As discussed above (p. 7), that argument is not supported by Dr. Earhart's declaration or the prior art. Indeed, far from instructing physicians to avoid anthracyclines, Petitioner's cited reference cautions against limiting anthracycline

usage, which “may deprive patients who are continuing to benefit from therapy who do not show signs of toxicity.” (Ex. 1016 at 29.) Petitioner’s argument also cannot be reconciled how researchers were using Herceptin® at the time. Petitioner can hardly contend that a person of ordinary skill would have limited anthracycline usage “whenever possible” when the *only* combination initially studied in the Herceptin® Phase III clinical trials was with an anthracycline. (*See supra* pp. 20-22.) And contrary to Petitioner’s hindsight-driven perspective today, even Petitioner’s cited references from the time of the invention that describe the Baselga publications focus solely on combination with anthracyclines and do not even mention combinations with taxoids. (Ex. 1016 at 114.)

Petitioner also argues that treating patients with a taxoid would have favored avoiding anthracyclines. (Paper 1 at 51.) But that argument is inconsistent with the prior art, which demonstrated “considerable interest” in combining taxoids and anthracyclines. (Ex. 2014 at 774.) The prior art disclosed that combinations of paclitaxel and doxorubicin *improved* clinical results. (Ex. 2015 at 2698; Ex. 2013 at 13-17.) And even Petitioner’s cited references acknowledge the “impressive antitumor activity” when combining taxoids with anthracyclines and describe an “important” ongoing study involving that combination. (Ex. 1010 at 4.)

Petitioner notes that Baselga 1996 reported that a patient died due to “prior anthracycline use.” (Paper 1 at 51.) But Baselga 1996 did not suggest that

trastuzumab contributed to that outcome or discourage the use of anthracyclines.

In fact, the *only* patient in Baselga 1996 who experienced a complete response to trastuzumab therapy was also previously treated with anthracyclines. (Ex. 1020 at 7.) And when scientists chose a combination therapy to study in Phase III trials, their first choice was combining trastuzumab with anthracyclines. (*See supra* pp. 20-22.)

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

Finally, Petitioner's obviousness theory cannot be reconciled with the preclinical studies involving trastuzumab, which indicated that combinations with anthracyclines were safe. (*See supra* p. 46.) Petitioner cannot say that those preclinical studies would have motivated skilled artisans to combine an anti-ErbB2 antibody with a taxoid, while arguing that they would not have been motivated to treat patients with combinations including anthracyclines too. Petitioner's selective interpretation of the prior art rests on hindsight and is contrary to the law. *See Genetics Inst.*, 655 F.3d at 1305.

The Board should deny institution because Petitioner has not demonstrated that it would have been obvious to treat patients “in the absence of an anthracycline derivative.”

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

Petitioner asserts that taxoids had “proven efficacy against metastatic HER2-positive breast cancer in humans” based upon the supposed teachings of Seidman 1996. (Paper 1 at 43.) But Seidman 1996 did not purport to demonstrate that taxoids are effective against HER2-positive cancer; it merely speculated that “HER2 over-expression in MBC seems to confer sensitivity rather than resistance to taxanes” based upon a retrospective analysis with a wide margin of error (“95% C.I. 38.1-55.5%”) and several “confounding variables.” (Ex. 1011 at 5.)

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

the “proven efficacy” of taxoids in HER2-positive patients; instead, they continued to study the issue. (Ex. 2024 at 2322-23.)⁷

Indeed, contrary to Petitioner's unsupported assertion of “proven efficacy,” a paper published in September 1996 explicitly taught that “breast cancers that overexpress p185 [*i.e.*, HER2] will not respond well to Taxol.” (Ex. 2029 at 1362.) Those statements contemporaneous with invention of the '441 patent discouraging the use of taxoids in HER2-positive patients are strong evidence of non-obviousness. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“An inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements.”). And the fact that Petitioner selectively ignores those teachings leading away from the challenged claims confirms its reliance on hindsight.

The Board should deny institution for this reason as well.

⁷ Although not prior art, the subsequent publication from the Seidman authors determining that HER2 overexpression lacked “a statistically significant association with clinical response to taxane therapy” reinforces the preliminary nature of the hypothesis presented in Seidman 1996. (Ex. 2024 at 2322.)

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

During prosecution, Genentech submitted a declaration from Dr. Mark Sliwowski. His declaration explained that a skilled artisan would not have had a reasonable expectation of success in achieving the '441 invention based upon what was known at the time about the biological mechanism of trastuzumab, taxoids, and other anti-cancer drugs. (Ex. 1009, Sliwowski Decl. ¶¶ 7-8.) He also described the well-known limitations of prior art preclinical mouse models to predict success in humans. (*Id.* ¶ 9.)

Petitioner criticizes various aspects of that declaration. (Paper 1 at 53-62.) The Board need not reach those arguments because Petitioner's proposed ground fails for the reasons described above. But if the Board considers Dr. Sliwowski's declaration, it only confirms the patentability of the challenged claims.

First, Petitioner repeatedly misrepresents what Dr. Sliwowski's declaration says to challenge opinions that he did not provide and assumptions that he did not make. For example, Petitioner criticizes Dr. Sliwowski for supposedly assuming that paclitaxel "only works when a cell is in the G2/M phase" (Paper 1 at 53), that "all cells in a tumor have the same cancerous mutations" (*id.* at 54), and that "100% of the cancerous cells are arrested by trastuzumab at the G1 phase" (*id.* at

55). Yet Petitioner cites nothing from Dr. Sliwkowski's declaration that supports Petitioner's assertions.

Petitioner also criticizes Dr. Sliwkowski (again without citation to his declaration) for supposedly applying "an absolute predictability standard." (Paper 1 at 60.) But Dr. Sliwkowski explicitly applied a reasonable expectation of success standard. (Ex. 1009, Sliwkowski Decl. ¶ 9 ("one of ordinary skill at the priority date of this application would not have had a reasonable expectation of success"); *id.* ¶ 10 ("one of ordinary skill at that time would not have had a reasonable expectation that a combination of an anti-ErbB2 antibody binding to the 4D5 epitope and a taxoid, such as paclitaxel, could be successfully used to treat human cancer patients").) The Board should disregard Petitioner's arguments that mischaracterize the actual language of the declaration.

Second, Petitioner argues that Dr. Sliwkowski's declaration is supposedly inconsistent with preclinical mouse studies involving cisplatin and paclitaxel. (Paper 1 at 57-58.) Dr. Sliwkowski, however, explained why those prior art preclinical results are not a reliable predictor of clinical outcomes. (Ex. 1009, 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 59.) But that 2001 article is a retrospective analysis involving drugs developed before the '441 invention. (Ex. 1009 at 91.) And as discussed above (pp. 9-11), numerous pre-1997 publications echo the conclusion of the 2001 article that mouse models are a poor indicator of clinical success.

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

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

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

Evidence concerning the real-world impact of a patented invention is a critical safeguard against hindsight reasoning. *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010). Indeed, the Board has recognized that such

evidence alone may rebut other evidence of obviousness. *InnoPharma Licensing, Inc. v. Senju Pharm. Co.*, IPR2015-00902, Paper 90 at 14-22, 25-27 (July 28, 2016). Here, several objective indicia conclusively establish the non-obviousness of the challenged claims.

1. Long-felt but unmet need

The '441 invention satisfied a long-felt but unmet need for an effective treatment for HER2-positive breast cancer. Before the '441 invention, HER2-positive patients experienced “horribly rapid progression” and were “in dire need” of an effective therapy. (Ex. 2018 at 887.) Yet no one before the '441 invention had developed an adequate therapy for those patients; indeed, at the time, patients with metastatic HER2-positive breast cancer had a life expectancy of just 10 to 12 months. (*Id.*)

The '441 invention satisfied the long-felt need for an effective therapy for HER2-positive patients. After the results of the Phase III trial showing that the claimed combination produced a “dramatic” increase in 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.”).

2. Praise

After the results of the Herceptin[®] Phase III trial were announced, the '441 invention was widely praised as an “anti-cancer breakthrough” that produced “impressive results.” (Ex. 2018 at 887; Ex. 2033 at 1.) Indeed, Petitioner can hardly contend that those results would have been obvious over Baselga 1996—when Dr. Larry Norton, a leading practitioner and co-author of Baselga 1996, went on national television to praise the impressive results of the '441 invention: “It doubles or triples the efficacy of Taxol in killing these cancer cells. This is a very big, dramatic advance, one of the biggest changes in the ability of chemotherapy to kill cancer cells that I've ever seen in my career.” (Ex. 2034.)

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].”).

3. Unexpected results

The combination of an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline produced unexpectedly superior clinical efficacy as compared with either the antibody or a taxoid alone. (Ex. 1008, Hellmann Decl. ¶ 6 (“[T]he combination is surprisingly synergistic with respect to extending TTP.”).) Petitioner argues that those results would have been expected because “the combination of trastuzumab and a taxoid was synergistic in human cancer cells in xenograft models.” (Paper 1 at 70.) But the preclinical results did not address the specific clinical endpoint of time to disease progression, let alone show an improvement in that outcome. (*See supra* p. 45.) And in any case, preclinical results at that time were known to be poor predictors of clinical outcomes. (*See supra* pp. 9-11.) 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. 8-9.) A skilled artisan therefore would have considered those vastly superior clinical efficacy results to be unexpected, which further confirms the non-obviousness of the claimed invention. *See Procter &*

Gamble, 566 F.3d at 994 (evidence “that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected” strongly supports non-obviousness); *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (“[T]hat which would have been surprising to a person of ordinary skill in a particular art would not have been obvious.”).

Petitioner alternatively argues that there is not sufficient evidence to conclude that the claimed combination produces a synergistic extension in the time to disease progression when factoring in the “confidence interval data for TTP.” (Paper 1 at 70-72.) But that does not help Petitioner’s case. Even if Petitioner were correct that the claimed combination produces no synergy (which it is not), that would only highlight the failure of the preclinical models underlying its obviousness theory to predict that result.

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

affirmative evidence cited in the petition and confirms the non-obviousness of the challenged claims.

In any case, even under Petitioner's obviousness theory, the '441 invention produced an unexpected safety improvement as compared with other combinations—for example, the combination of trastuzumab with anthracyclines that Baselga Abstract 53 said did not increase toxicity. (Ex. 1019 at 4; *see also* Ex. 1008, Hellmann Decl. ¶¶ 4-5.) Petitioner may not argue that prior art preclinical results would have provided a reasonable expectation of success, but dismiss other teachings from the same references that demonstrate unexpected results. *See Genetics Inst.*, 655 F.3d at 1305.

Petitioner argues that the safety difference between combinations with taxoids versus anthracyclines is “irrelevant” because that toxicity difference supposedly relates to “some other, unclaimed combination.” (Paper 1 at 73.) But the combination of an anti-ErbB2 antibody with an anthracycline derivative is not just “some other, unclaimed combination”; each challenged claim expressly requires “the absence of an anthracycline derivative.” The unexpected improvement in safety attributable to that claim element confirms the non-obviousness of the challenged claims. *In re Soni*, 54 F.3d at 750. Petitioner's related argument (Paper 1 at 73-74) that a comparison to combinations with anthracyclines is inappropriate because they are not “the closest prior art” is

nonsensical. Combinations with anthracyclines are an appropriate benchmark for claims that expressly require “the absence of an anthracycline derivative.”

4. Commercial success

The '441 invention has been an enormous commercial success. Herceptin[®] is the commercial embodiment of the '441 invention, and one of the most successful drugs of all time. There is a direct nexus between Herceptin[®]'s commercial success and the '441 invention. From 1998 until 2006, the *only* approved first-line use of Herceptin[®] was in combination with a taxoid, as claimed in the '441 patent. (Ex. 2012 at 1.) Following its launch, Herceptin[®] was quickly adopted, resulting in hundreds of millions of dollars in sales in those years immediately following its approval. (Ex. 2035 at 17.) Where, as here, the commercial product embodies the claimed invention, a nexus is presumed. *Brown & Williamson Tobacco Corp. v. Philip Morris, Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000). Petitioner's conclusory assertion that there is no nexus (Paper 1 at 74) is insufficient to rebut that presumption given the hundreds of millions of dollars in sales during the period when the claimed method of treatment was only approved first-line use of the drug.

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

The Board should deny institution because this proceeding would violate Patent Owner's constitutional rights. Adversarial challenges to an issued patent—

like *inter partes* reviews—are “Suits at common law” for which the Seventh Amendment guarantees a jury trial. U.S. Const. amend. VII; *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 377 (1996). Moreover, because patents are private property rights, disputes concerning their validity must be litigated in an Article III court, not before an executive branch agency. *McCormick Harvesting Mach. Co. v. C. Aultman & Co.*, 169 U.S. 606, 609 (1898). The Supreme Court has granted certiorari in *Oil States Energy Services, LLC v. Greene’s Energy Group, LLC*, No. 16-712, to consider the constitutionality of *inter partes* reviews. Patent Owner presents this constitutional challenge now to preserve the issue pending the Supreme Court’s decision.

VIII. CONCLUSION

The Board should deny institution.

Respectfully submitted,

Date: July 11, 2017

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

Robert J. Gunther, Jr.
Pro Hac Vice Motion To Be Filed

Counsel for Patent Owner

WILMER CUTLER PICKERING HALE AND DORR LLP
1875 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20006
TEL: 202-663-6000
FAX: 202-663-6363
EMAIL: david.cavanaugh@wilmerhale.com

CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Preliminary Response, contains 13,969 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. § 42.24(d).

Respectfully submitted,

Dated: July 11, 2017

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

CERTIFICATE OF SERVICE

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

- Patent Owner's Preliminary Response
- Certificate of Compliance
- Patent Owner's Motion to Seal
- Patent Owner's Exhibit List
- Exhibits 2001-2005, 2007-2019, 2021-2037

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

Cynthia Lambert Hardman
GOODWIN PROCTER LLP
chardman@goodwinlaw.com
620 Eighth Avenue New York, NY 10018

Robert V. Cerwinski
GOODWIN PROCTER LLP
rcerwinski@goodwinlaw.com
620 Eighth Avenue New York, NY 10018

Elaine Herrmann Blais
GOODWIN PROCTER LLP
eblais@goodwinlaw.com
100 Northern Avenue Boston, MA 02210

/Rebecca Whitfield/
Rebecca A. Whitfield
Reg. No. 73,756
Wilmer Cutler Pickering Hale and Dorr LLP
60 State Street, Boston, MA 02109

IPR2017-01121
Patent Owner's Exhibit List

<u>Patent Owner's Exhibit Number</u>	<u>Exhibit Name</u>
2001	Genentech, Inc. Original H0648g Protocol PROTECTIVE ORDER MATERIAL
2002	Genentech, Inc. PDC Minutes PROTECTIVE ORDER MATERIAL
2003	Genentech, Inc. PDC Minutes PROTECTIVE ORDER MATERIAL
2004	Genentech, Inc. PDC Minutes PROTECTIVE ORDER MATERIAL
2005	Genentech, Inc. PDC Presentation PROTECTIVE ORDER MATERIAL
2006	Reserved
2007	Genentech, Inc. Amended H0648g Protocol PROTECTIVE ORDER MATERIAL
2008	Genentech, Inc. H0648g Final Report PROTECTIVE ORDER MATERIAL
2009	U.S. Provisional Application No. 60/069346
2010	Dennis J. Slamon, et al., <i>Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/neu Oncogene</i> , 235 SCIENCE 177 (1987)
2011	Dennis J. Slamon, et al., <i>Studies of the HER-2/neu Proto-oncogene in Human Breast and Ovarian Cancer</i> , 244 SCIENCE 707 (1989)
2012	1998 Herceptin Label
2013	Per Dombornowsky, et al., <i>Paclitaxel and Doxorubicin, a Highly Active Combination in the Treatment of Metastatic Breast Cancer</i> , 23 SEMINARS IN ONCOLOGY 13 (1996)
2014	Jason S. Fisherman, et al., <i>Phase I/II Study of 72-Hour Infusional Paclitaxel and Doxorubicin with Granulocyte Colony-Stimulating Factor in Patients with Metastatic Breast Cancer</i> , 14 J. CLINICAL ONCOLOGY 774 (1996)

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

<u>Patent Owner's Exhibit Number</u>	<u>Exhibit Name</u>
2028	Raymond B. Weiss, et al., <i>Hypersensitivity Reactions from Taxol</i> , 8 J. CLINICAL ONCOLOGY 1263 (1990)
2029	Dihua Yu, <i>Overexpression of c-erbB-2/neu in Breast Cancer Cells Confers Increased Resistance to Taxol Via mdr-1-independent Mechanisms</i> , 13 ONCOGENE 1359 (1996)
2030	James H. Doroshow, <i>Anthracyclines and Anthracenediones</i> , in CANCER CHEMOTHERAPY & BIOTHERAPY: PRINCIPLES AND PRACTICE 409 (1996)
2031	Richard P. Junghans, et al., <i>Antibody-Based Immunotherapies for Cancer</i> , in CANCER CHEMOTHERAPY & BIOTHERAPY: PRINCIPLES AND PRACTICE 655 (1996)
2032	Gert Riethmüller, et al., <i>Monoclonal Antibodies in Cancer Therapy</i> , 5 CURRENT OPINION IN IMMUNOLOGY 732 (1993)
2033	Richard Saltus, <i>New Treatment for Breast Cancer Called Promising</i> , BOSTON GLOBE, May 18, 1998
2034	<i>TODAY: FDA Expected to Approve Two New Breast Cancer Drugs</i> (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