No. 2019-1267

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

GENENTECH, INC.,

Appellant,

v.

ANDREI IANCU, Director, U.S. Patent and Trademark Office,

Intervenor.

Appeal from the United States Patent and Trademark Office,
Patent Trial and Appeal Board in No. IPR2017-01121

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July 9, 2019

CERTIFICATE OF INTEREST

Counsel for Appellant Genentech, Inc. certifies the following:

1. The full name of every party or *amicus* represented by me is:

Genentech, Inc.

2. The names of the real party in interest represented by me is:

Not applicable.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Genentech, Inc. is a wholly-owned subsidiary of Roche Holdings Inc. Roche Holdings Inc.'s ultimate parent, Roche Holdings Ltd, is a publicly held Swiss corporation traded on the Swiss Stock Exchange. Upon information and belief, more than 10% of Roche Holdings Ltd's voting shares are held either directly or indirectly by Novartis AG, a publicly held Swiss corporation.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this Court (and who have not or will not enter an appearance in this case) are:

WILMER CUTLER PICKERING HALE AND DORR LLP: Owen K. Allen (former), Lauren V. Blakely, David L. Cavanaugh, Lisa J. Pirozzolo, Kevin S. Prussia, Rebecca A. Whitfield (former)

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this Court's decision in the pending appeal:

Genentech, Inc. et al. v. Amgen Inc., No. 1:18-cv-00924 (D. Del.)
In re Genentech, Inc., No. 19-1265 (Fed. Cir.)
Genentech, Inc. v. Iancu, No. 19-1263 (Fed. Cir.)
Genentech, Inc. v. Iancu, No. 19-1270 (Fed. Cir.)

Dated: July 9, 2019

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STATEMENT OF RELATED CASES

No appeal from the same proceeding was previously before this Court or any other appellate court. The following cases will directly affect or be directly affected by this Court's decision in the pending appeal: *Genentech, Inc. et al. v. Amgen Inc.*, No. 1:18-cv-00924 (D. Del.); *Genentech, Inc. v. Iancu*, No. 19-1263 (Fed. Cir.); *In re Genentech, Inc.*, No. 19-1265 (Fed. Cir.); and *Genentech, Inc. v. Iancu*, No. 19-1270 (Fed. Cir.).

JURISDICTIONAL STATEMENT

The Patent Trial and Appeal Board asserted jurisdiction under 35 U.S.C. §§ 311-319. This Court has jurisdiction over the appeal from the Board's final written decisions pursuant to 28 U.S.C. § 1295(a)(4)(A) and 35 U.S.C. §§ 141(c) & 319. Genentech filed a timely notice of appeal on November 30, 2018 in IPR2017-01121. Appx13107-13112.

INTRODUCTION

The invention in this case arises from Genentech's groundbreaking work in the treatment of breast cancer. As of the priority date, the FDA had never approved an antibody therapy for solid tumors, such as breast cancer. But Genentech made a critical discovery: an "anti-ErbB2" antibody could be used in combination with a relatively new type of chemotherapy drug called a "taxoid" to treat cancers that overexpress a protein called HER2. Specifically, Genentech's

priority application disclosed the first results ever reported from human trials of the combination of the anti-ErbB2 antibody "trastuzumab" (also called "rhuMAb HER2") and the taxoid "paclitaxel." Those results showed that rhuMAb HER2 and paclitaxel, in the absence of another common chemotherapy drug (an "anthracycline derivative"), could extend the time to disease progression (i.e., the time from diagnosis or treatment until the disease starts to worsen or spread), without increasing overall severe adverse events. Genentech claimed that invention in U.S. Patent No. 7,846,441 ("the '441 patent"), and when the FDA approved Genentech's drug Herceptin®, the combination became the only approved first-line antibody-based therapy for solid tumors.

Much of the dispute before the Board turned on the meaning of the claim term "extend the time to disease progression in said human patient, without increase in overall severe adverse events." Based on a single inartful statement in the prosecution history, the Board construed this term in a way that did not match what Genentech taught in its specification or the subject matter it wants to protect. Specifically, the Board misconstrued this term to require comparing the claimed combination with an untreated patient—i.e., a cancer patient receiving no treatment whatsoever. The Board did so even though (1) the specification disclosed comparisons to patients treated with paclitaxel alone, but no comparisons to untreated patients; (2) the claims speak in terms of not increasing "adverse events,"

plainly indicating a comparison to some treatment; (3) as a matter of basic medical ethics, a patient cannot be left untreated; and (4) when read in context, the statement from the prosecution history that the Board relied on was not a clear and unmistakable disclaimer. Under the correct construction, which requires comparing the combined treatment to treatment with paclitaxel alone, there was no sound basis to rule that Genentech's claims are unpatentable.

STATEMENT OF ISSUES ON APPEAL

I. Whether the Board incorrectly construed the term "extend the time to disease progression in said human patient, without increase in overall severe adverse events" to require a comparison to a patient who had received no treatment at all.

II. Whether, applying the proper construction of the term "extend the time to disease progression in said human patient, without increase in overall severe adverse events," the Board's decision should be reversed because it was not supported by substantial evidence and improperly relied on non-public statements reflecting the inventor's own insights as evidence of obviousness.

STATEMENT OF THE CASE

A. HER2-Positive Breast Cancer

"HER2-positive" cancers have a genetic mutation that causes them to overexpress human epidermal growth factor 2 ("HER2"), also known as human

ErbB2. Out of the hundreds of thousands of women each year who are diagnosed with breast cancer, roughly 25-30% are HER2-positive. Appx67(1:23-29); Appx8786. HER2-positive breast cancer is particularly aggressive: In the 1990s, it was "associated with poor prognosis," including a high rate of tumor recurrence and spreading to other areas of the body, shorter time to relapse, and shorter overall survival. Appx7985; Appx7918-7920; Appx7925. While HER2-normal breast cancer patients could expect to live for six to seven years post-diagnosis, the post-diagnosis life expectancy of HER2-positive breast cancer patients receiving standard chemotherapy treatment in 1996 was about 18 months. Appx7971; Appx7973; Appx8787-8788.

B. The Invention of the '441 Patent

The '441 patent claims a method for treating HER2-positive cancer patients with an anti-ErbB2 antibody such as "trastuzumab" (aka "rhuMAb HER2") in combination with a type of chemotherapy drug called a "taxoid," in an amount effective to extend time to disease progression without an increase in overall severe adverse events. Specifically, independent claim 1 recites:

> A method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by overexpression of ErbB2 receptor, comprising administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence and a taxoid, in the absence of an anthracycline derivative, to the human patient in an amount effective to extend the time to disease progression in said human patient, without increase in overall severe adverse events.

Appx83.

The invention of the ’441 patent was a novel and important development in the history of breast cancer treatment, both for its use of a specially engineered antibody and the combination of this antibody with a taxoid.

In the 1990s, engineered antibodies—proteins specially-designed to bind to molecular targets, called “antigens”—were a focus for therapeutic research. Appx70-71(8:44-9:3). However, the body’s immune system also tended to attack these antibodies, preventing them from having a therapeutic effect. Appx8082. Articles from the 1990s described antibody therapy for cancer as “a story of unending failures,” Appx8119, with “significant obstacles,” Appx8112, and “no hint of a consistent therapeutic efficacy,” Appx8007. When the provisional application for the ’441 patent was filed in December 1997, ***no antibody*** had been approved for the treatment of solid tumors such as breast cancer.

During this time, oncologists were also slow to adopt taxoids for treating breast cancer. The prior art came to conflicting conclusions about HER2 response to taxanes (a type of taxoids), with reports that “HER2 over-expression in [metastatic breast cancer] seems to confer sensitivity rather than resistance to taxanes,” Appx4041, and that “breast cancers that overexpress p185 [*i.e.*, HER2] ***will not respond well to Taxol***,” Appx8044 (emphasis added). As of December 1997, ***no clinical results*** had been reported for the claimed combination of

trastuzumab and a taxoid. The only results for the claimed combination were in preclinical mouse models. In these models, mice with suppressed immune systems are injected with human cancer cells and treated with therapies being considered for human testing. Preclinical mouse models were understood at the time to be a useful initial mechanism to screen for drugs that show some activity against particular cancer cells, and to understand their mechanism of function. Appx8616-8619; Appx8773-8775. However, as of 1997, it was also well-recognized that mouse studies failed to reliably predict what therapies would ultimately be successful in humans. *See* Appx8539 (noting "[t]he fundamental problem in drug discovery for cancer is that the model systems are not predictive" and "drugs tested in the xenografts appeared effective but worked poorly in humans"); Appx7989 ("very low" likelihood of mouse studies predicting responses in humans).

There are many reasons for this. Mouse studies are short-term and generally measure only "response rate"—i.e., the ability of therapy to shrink tumors—not effect on time to disease progression ("TTP"). Response rate and TTP are measuring different endpoints. A therapy may demonstrate a response rate by initially shrinking tumors, but fail to eradicate the most-aggressive cancer cells that cause the cancer to progress quickly. It was established that therapies may improve response rates but not affect TTP. Appx8783-8784; Appx8939. Mice are also often administered a proportionally larger dose than humans can tolerate, which

allows for positive outcomes not possible in humans. Appx7974. Therapies also frequently cause toxicity in humans, but not in mice, due to differences in cell and tissue types between mice and humans. Appx8625-8627; Appx8775-8776. Furthermore, mouse models are more likely to show positive outcomes because they use tumor cell lines from tissue culture. These divide more rapidly than human cells, which are heterogenous and therefore can display greater sensitivity to treatment. Appx8609-8610; Appx8775-8777.

In addition, prior to December 1997, no Phase III clinical results existed for the antibody trastuzumab, alone or in any combination. Clinical testing of a drug—that is, testing of a drug in humans—occurs in stages, beginning with initial small-scale studies (i.e., "Phase I" and "Phase II" studies), followed by large-scale "Phase III" controlled trials designed to evaluate specific clinical endpoints. Appx8779-8781. At each of these stages, a large number of therapies fail. In the 1990s, only 5% of cancer drugs that advanced to clinical trials resulted in an approved product. Appx7980-7981. Even for drugs that advanced to late-stage, Phase III clinical trials, nearly 60% ultimately failed to result in an approved drug. *Id.*

Without running a Phase I or Phase II study, Genentech decided to test the combination of trastuzumab and a taxoid—specifically paclitaxel—in a Phase III trial of HER2-positive metastatic breast cancer patients. Genentech tested this

combination not because of promising results in the prior art, but because Genentech's ongoing Phase III study involving a combination of trastuzumab and ***a different chemotherapeutic agent***—anthracyclines—was having difficulty enrolling patients. Appx9318. Moreover, the inventor who proposed the combination had just joined Genentech from the company that made Taxol (paclitaxel) and had unique familiarity with the drug well beyond the knowledge of an ordinary artisan. Appx9429; Appx9435.

Running a Phase III study without first testing the drug in Phases I and II is so unusual that, while the proposal to add a trastuzumab and paclitaxel arm to the Phase III study was adopted, it was met with skepticism both at Genentech and at the FDA. *See, e.g.*, Appx7090 ("[T]he expected clinical outcome for the administration of rhuMAb HER2 with taxol is less certain than co-administration with cisplatinum or doxorubicin"); Appx10022 (FDA noting that Genentech has "[redacted]").

Yet when the Phase III study reached its primary endpoint in late 1997, the results were surprising. Appx7639; Appx7658-7665; Appx7711-7716; Appx9415-9422. The study data showed that trastuzumab and paclitaxel in the absence of an anthracycline derivative extended TTP compared to paclitaxel alone, without an increase in overall severe adverse events. Appx7552. In fact, the combination of

trastuzumab and paclitaxel was dramatically more effective than paclitaxel alone. *See, e.g.*, Appx1432 ("[T]he combination is surprisingly synergistic with respect to extending TTP."); Appx8130 ("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 than I've ever seen in my career."). In addition, the combination of trastuzumab and paclitaxel unexpectedly avoided the surprising cardiotoxicity that resulted from the combination of trastuzumab and anthracyclines. Appx7551; Appx7012; Appx4226; Appx1431; Appx81. These data are reflected in the provisional patent application filed December 12, 1997, Appx7900-7905, and led to the FDA approval of Herceptin as a first-line treatment, Appx4511.

The therapy claimed in the '441 patent revolutionized the treatment of HER2-positive breast cancer. Appx7973 ("Genentech are now poised for another impressive therapeutic breakthrough for late-stage treatment of breast cancer," with clinical trials showing "particularly encouraging [results] in combination with chemotherapy using paclitaxel[.]"); Appx8856 ("Now, many of my patients with HER2-positive breast cancer live for several years even after metastasis begins.")

C. Prior Art

When the Board assessed the obviousness of claims 1-14 of the '441 patent, it focused on three references: Baselga '96,[1] the Taxol PDR '95,[2] and Seidman '96[3]. Appx13-14. None contained any clinical data showing the effect of trastuzumab plus a taxoid in humans. Indeed, no such clinical data was reported prior to December 12, 1997. Appx8794.

1. Baselga '96

Baselga '96 is an article published in March 1996. It describes the results of a Phase II clinical study in which 46 patients received rhuMAb HER2 ***alone***, not combined with a taxoid (or any other chemotherapy or agent). Appx4230.

The clinical endpoint evaluated in the trial was response rate, which was evaluated at 11 weeks. Appx4230; Appx4232-4233. Although Baselga '96 measured TTP for individual patients, every patient received rhuMAb HER2 and the study included no control. Baselga '96 thus provided no way to measure ***extension*** of TTP, which requires a comparator.

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[1] Baselga et al., *Phase II Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer*, 14 J. Clin. Oncol. 737-744 (1996). Appx4227-4236.

[2] *Taxol® (Paclitaxel) for Injection Concentrate*, Physicians' Desk Reference 682-685 (49th ed. 1995). Appx4042-4049.

[3] Seidman et al., *Over-Expression and Clinical Taxane Sensitivity: A Multivariate Analysis in Patients with Metastatic Breast Cancer (MBC)*, 15 Proc. Am. Soc'y Clin. Oncology 104 (1996) (Abstract 80). Appx4037-4041.

The vast majority of patients did not show a therapeutic response—only 5 out of the 43 assessable patients (11.6%) had complete or partial responses to treatment with rhuMAb HER2. Of the remaining patients, 2 had a minor response, 14 had stable disease, and 22 patients (over 50%) had disease progression at 11 weeks. Appx4233. While Baselga '96 measured a "median time to progression" of 5.1 months, it only measured this for the 16 patients with minor response or stable disease—it did not take into account the 22 patients whose disease progressed at 11 weeks or earlier. Appx4232.

Baselga '96 explained that the mechanism of action of rhuMAb HER2 was not understood, offering several possible explanations for the clinical results. Appx4234-4235. Baselga '96 also cited earlier preclinical mouse studies, which are described in the Baselga Abstract 53, Appx4226, and Baselga Abstract 2262, Appx4239 (collectively, the "Baselga abstracts"). Baselga '96 noted that in the Baselga abstracts, "rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity." Appx4235.

2. Taxol PDR '95

Taxol PDR '95 is the entry from the 1995 Physicians' Desk Reference corresponding with paclitaxel. It does not suggest combining paclitaxel with anti-ErbB2 antibodies, or even mention anti-ErbB2 antibodies. Appx8363. Moreover,

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

Taxol PDR ’95 further states that paclitaxel was approved only as a second-line therapy for metastatic breast cancer (i.e., after the failure of other treatments), and notes that, in general, paclitaxel should be used only after anthracycline therapy. Appx4047. Taxol PDR ’95 additionally 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. Appx4046-4047; *see also* Appx8361 (this warning is “the FDA’s way of flagging a drug, some things that you need to know about the drug.”); Appx8816-8817.

3. Seidman ’96

Seidman ’96 is an abstract published in March 1996, which 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).” Appx4041. Seidman ’96 does not mention antibody therapy at all. In addition, Seidman ’96 does not address whether taxoids extend TTP in HER2-positive patients, instead measuring the “response proportion”—a different clinical endpoint. *Id.* With respect to the single-agent chemotherapies studied, Seidman ’96 reports that the response proportion was 58.8% among HER2-positive patients

and 38.7% among HER2-negative patients. Appx4041. The Board did not rely on or discuss this reference in its analysis on reasonable expectation of success.

D. Prosecution of the '441 Patent

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. Appx59. As noted, the December 12, 1997 provisional application contained the first disclosure of results from testing the combination of rhuMAb HER2 and paclitaxel in humans, and the first data of any kind regarding the combination's extension of TTP compared to paclitaxel alone.

During prosecution, the Examiner made the following statement while rejecting the claims pending at the time as indefinite:

> The term "extend time to disease progression" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically, it is never set forth what the extension of time to disease progress is relative to, for example, is the extension of time to disease progress relative to untreated patients? Patients who received antibody or taxoid alone? Patients who received antibody and an anthracycline?

Appx1511-1512. In January 2002, the applicant responded that "the expression[] 'extend the time to disease progression' ... [is] clear from the specification (see, in particular, page 15, lines 15-17; and pages 42-43) and would be readily understood by the skilled oncologist." Appx1527. The portions of the specification cited by the applicant to indicate that the proper comparison was "clear from the

specification" stated that "efficacy can, for example, be measured by assessing the time for disease progression (TTP)," Appx1130, and then disclosed the Phase III data cited above that compared treatment with a combination of rhuMAb HER2 and paclitaxel to treatment ***with paclitaxel alone, not to a lack of treatment altogether***, Appx1158. The applicant's response to the Examiner followed these citations by saying: "Clearly, the combination of anti-ErbB2 antibody and taxoid is administered in an amount effective to extend the time to disease progression relative to an untreated patient." Appx1527.

In the next office action, the Examiner withdrew the indefiniteness rejection, but suspended prosecution in light of a potential interference. Appx1735. Prosecution later resumed, and the applicant eventually amended the claims. Of particular relevance, the applicant added the limitation "without increase in overall severe adverse events" on September 22, 2008. Appx3409-3412. This comparison of the adverse events produced by different treatments had not been in the claims when the Examiner and applicant originally discussed the proper baseline for measuring the improvements achieved by the claimed combination.

In October 2009, Genentech submitted a declaration from Dr. Mark Sliwkowski in response to obviousness rejections over, among other things, a combination of Baselga '96 and Baselga '94. Appx3462-3466; Appx3455. Dr. Sliwkowski explained that a skilled artisan would not have expected rhuMAb

HER2 combined with a taxoid to produce a synergistic response, since those drugs were known to exert their effects at different points in the cell cycle. Appx3463-3464. Dr. Sliwkowski also explained that preclinical results would not have provided a reasonable expectation of success as to the clinical results for the combination of rhuMAb HER2 and a taxoid; indeed, he expressed that xenograft models at that time were poor predictors of clinical results for breast cancer. Appx3465.

On December 19, 2009, the Examiner allowed the claims. Appx3572-3578. The Patent Office considered many of the references cited in the petition, including Baselga '96 (Appx4229-4236)—the primary reference underlying Petitioner's obviousness theory—and the Baselga abstracts, Appx4226; Appx4239, that describe the results of preclinical mouse studies involving trastuzumab.[4] Appx68.

E. The Board Proceedings

On March 21, 2017, Petitioner requested an *inter partes* review of claims 1-14 of the '441 patent in IPR2017-01121. Appx12001-12077. Petitioner

[4] Genentech has a related and pending application (14/141,232) in the '441 family. After considering the same prior art and the final written decision in this appeal and the related appeals, the Examiner issued a notice of allowance on April 17, 2019. Genentech then paid the issue fee, and, on June 5, 2019, the PTO transmitted an issue notification informing Genentech that its new patent was projected to issue on June 25, 2019 as U.S. Patent No. 10,328,047. The night before Genentech was set to dismiss these appeals, however, the Examiner withdrew the patent from issuance. On June 25, 2019, the Examiner issued a new, non-final office action rejecting the new claims.

challenged claims 1-14 as obvious over a combination of Baselga ’96, Seidman’96, and the Taxol PDR ’95. Genentech filed a preliminary response. Appx12100-12178. On September 6, 2017, Pfizer moved to join its proceeding, IPR2017-02063, with Celltrion’s (IPR2017-01121). Appx14081-14092. On October 4, 2017, the Board instituted trial in IPR2017-01121. On February 21, 2018, the Board instituted trial in IPR2017-02063, then joined that proceeding with IPR2017-01121, with Pfizer proceeding in a limited “understudy” role. Appx14238-14249.

The Board’s final written decision, issued on October 3, 2018, determined that Petitioner showed by a preponderance of the evidence that claims 1-14 of the ’441 patent would have been obvious over a combination of Baselga ’96, Seidman’96, the Taxol PDR ’95, and the knowledge of a person of ordinary skill in the art. Appx1-58. In so holding, the Board relied on a claim construction of “extend the time to disease progression [TTP] in said human patient, without increase in overall severe adverse events” that compared “the claimed combination treatment to no treatment.” Appx13. The Board also found that a skilled artisan would have been motivated to combine rhuMAb HER2 and paclitaxel to treat patients with ErbB2 overexpressing metastatic breast cancer, and that there would have been a reasonable expectation of success “even under Patent Owner’s proposed claim construction.” Appx36.

SUMMARY OF THE ARGUMENT

I. The Board adopted an incorrect claim construction of the term "extend the time to disease progression in said human patient, without increase in overall severe adverse events." The Board erroneously interpreted that term to require a comparison to an untreated patient. Instead, the appropriate comparison is to a patient treated with a taxoid alone, which is the only comparison described in the patent specification that is consistent with the language of the claims. The specification reports nothing about untreated patients, and the plain language of the claim requires a comparison of "adverse events," which occur during treatment.

The Board based its construction on a single statement in the file history about comparison to an "untreated patient." But that statement, which cites the example in the specification that compares patients treated with the claimed combination to patients treated with a taxoid (paclitaxel) alone, does not change how a skilled artisan would understand the term and does not meet the demanding standard to establish prosecution disclaimer.

II. The Board erred in finding that even under Genentech's construction, a skilled artisan would have had a reasonable expectation that the claimed combination treatment extends TTP and does not increase overall severe adverse events as compared to treatment with a taxoid alone.

A. The Board found that a skilled artisan would have a reasonable expectation that the combination would extend TTP as compared to treatment of a taxoid alone by improperly relying on Baselga '96's report that the TTP in patients administered rhuMAb HER2 alone was 5.1 months, as compared to the TTP of paclitaxel reported in the Taxol PDR '95 of 3.0 or 4.2 months. A skilled artisan would not make this comparison, much less draw the same conclusion as the Board. The 5.1 month TTP reported in Baselga '96 was only for those patients that reported a minor response or stable disease, and excluded over half of the patients— those whose cancer progressed.

B. The Board also erred in finding that the claimed safety of the combination was obvious where none of the prior art addressed the combination of rhuMAb HER2 in humans, the clinical results of rhuMAb HER2 and paclitaxel alone offered no information on how patients would react to the combination therapy, and preclinical studies are not reliable predictors of results in humans.

C. Finally, the Board erred in relying on the fact that Genentech had proposed a Phase III study administering the combination of rhuMAb HER2 and paclitaxel to human patients—without prior Phase I and II studies of the combination—as evidence of obviousness. It is legal error for the Board to rely on the inventor's own path to support its obviousness determination.

STANDARD OF REVIEW

The Board's claim construction is subject to *de novo* review where, as here, the Board relied on only intrinsic evidence to construe the claims. *Hamilton Beach Brands, Inc. v. f'real Foods, LLC*, 908 F.3d 1328, 1339 (Fed. Cir. 2018).

The Board's ultimate finding on obviousness is a legal conclusion, which this Court reviews de novo. *Personal Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 991 (Fed. Cir. 2017); *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1353 (Fed. Cir. 2013) ("[A]t bottom, this court confronts a question of law: whether, in light of the prior art references and objective indicia of nonobviousness, the claimed invention would have been obvious to a person of ordinary skill in the art at a time just before the time of invention.").

Underlying factual findings are reviewed for substantial evidence. Substantial evidence review asks "whether a reasonable fact finder could have arrived at the agency's decision, which requires examination of the record as a whole, taking into account evidence that both justifies and detracts from an agency's decision." *Personal Web Techs.*, 848 F.3d at 991 (quotation marks omitted).

ARGUMENT

The Court should reverse because the Board erroneously construed the claims and its alternative ruling under the correct construction was not supported

by substantial evidence and improperly relied on the inventor's own path to find obviousness.

I. THE BOARD INCORRECTLY CONSTRUED THE TERM "EXTEND THE TIME TO DISEASE PROGRESSION … WITHOUT INCREASE IN OVERALL SEVERE ADVERSE EVENTS" LIMITATION TO REQUIRE COMPARISON TO AN UNTREATED PATIENT

The claim language and specification make clear that the term "extend the time to disease progression…without increase in overall severe adverse events" requires comparing treatment with an anti-ErbB2 antibody (such as rhuMAb HER2) and taxoid (such as paclitaxel) to treatment with a taxoid alone. All of the data contained in the patent focuses on this comparison, and the reference to "adverse events"—a term of art encompassing solely events arising during treatment—makes clear that both comparators must involve some sort of intervention. The Board found otherwise based on an isolated, if inartful, statement in the prosecution history that does not satisfy the demanding standard for establishing a disclaimer. This Court should reverse.

The specification makes clear that the claims require comparing the claimed combination treatment to treatment with a taxoid alone. There is no data in the '441 patent comparing the time to disease progression of patients treated with rhuMAb HER2 and paclitaxel against an untreated patient. Rather, the '441 patent describes a Phase III clinical trial measuring the efficacy of the combination of an anti-ErbB2 antibody (rhuMAb HER2) with a taxoid (paclitaxel) ***against a control***

arm of paclitaxel alone. Appx81-82(29:9-30:25) (comparing "T + H" (i.e., Taxol and Herceptin) to "T" (i.e., Taxol)).[5] The specification thus refutes the Board's conclusion that the claims require comparing Genentech's combined treatment to no treatment at all.

Indeed, a comparison to an untreated patient makes no sense in the context of a disease like breast cancer where there were already therapies approved by the FDA. Undisputed expert testimony established that it would be unethical to conduct a study comparing the efficacy of a tested therapy against no therapy where there was already an approved therapy that would provide a clinical benefit to the target patient population for a life-threatening disease like breast cancer. Appx8810-8811 ("It would not be ethical to design a study to compare efficacy against no therapy alone where there was already an approved therapy that would provide a clinical benefit to the target patient population.").

The Board's construction is also inconsistent with the meaning of "adverse events," which contemplates a comparison against a patient treated with some therapy. An adverse event is "[a]n unexpected medical problem that happens

[5] The '441 patent also describes the efficacy of rhuMAb HER2 combined with chemotherapy (paclitaxel or anthracyclines) versus chemotherapy alone, or rhuMAb HER2 combined with anthracyclines versus anthracycline therapy alone. Appx223(29:9-30:25). However, given that the claims expressly exclude anthracycline therapy, the relevant comparison is the combination of rhuMAb HER2 and paclitaxel versus paclitaxel alone.

during treatment with a drug or other therapy." Appx10501 (emphasis added); *see also* Appx12271-12272. The requirement to "extend the time to disease progression … without increase in overall severe adverse events" thus can only be measured by comparing treatment with one therapy against another treatment with another therapy, not comparing treatment against a patient receiving no treatment at all. Appx8804-8811.

The Board did not dispute any of these points. Instead, it based its claim construction exclusively on the prosecution history. Specifically, the Board relied on the applicant's statement in January 2002 that "the expression[] 'extend the time to disease progression' … [is] clear from the specification (see, in particular, page 15, lines 15-17; and pages 42-43) and would be readily understood by the skilled oncologist. Clearly, the combination of anti-ErbB2 antibody and taxoid is administered in an amount effective to extend the time to disease progression relative to an untreated patient." Appx1527.

The Board's use of this prosecution history to override the meaning evident from the claim language and specification was error. The standard for establishing prosecution disclaimer is high: The statement must "show 'a clear and unmistakable surrender of subject matter.'" *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1251 (Fed. Cir. 2000). In other words, the statement must

"unequivocally disavow[] a certain meaning." *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1324 (Fed. Cir. 2003).

"There is no 'clear and unmistakable' disclaimer if a prosecution argument is subject to more than one reasonable interpretation, one of which is consistent with a proffered meaning of the disputed term." *SanDisk Corp. v. Memorex Prods., Inc.*, 415 F.3d 1278, 1287 (Fed. Cir. 2005); *see also 3M Innovative Props. Co. v. Tredegar Corp.*, 725 F.3d 1315, 1326 (Fed. Cir. 2013) ("Where an applicant's statements are amenable to multiple reasonable interpretations, they cannot be deemed clear and unmistakable."). Further, the clarity of a statement cannot be determined in isolation but must be considered in the context of the entire record. "Even if an isolated statement appears to disclaim subject matter, the prosecution history as a whole may demonstrate that the patentee committed no clear and unmistakable disclaimer." *Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335, 1342 (Fed. Cir. 2009).

The applicant's statement regarding an "untreated patient" was admittedly inartful when juxtaposed against the Examiner's questions. Read in context, however, it does not rise to the level of a "clear and unmistakable disclaimer." The Board failed to give any weight to the applicant's immediately preceding statement that the meaning of the limitation was "clear from the specification (see, in particular, page 15, lines 15-17; and pages 42-43)." The highlighted portions of

the specification introduced the concept of measuring TTP and disclosed the Phase III data cited above that compared treatment with a combination of rhuMAb HER2 and paclitaxel to treatment ***with paclitaxel alone***, not a lack of treatment altogether. Appx1158. From the outset, the applicant's reference to an "untreated patient" was thus made based on data showing a comparison to patients ***untreated with the claimed combination because they were treated with paclitaxel alone***. The applicant's statement thereby undermines, rather than supports, the Board's construction.

Moreover, even if the statement introduced ambiguity in 2002, it was dispelled in 2008 when the claims were amended to add the limitation "without increase in overall severe adverse events." "Adverse events" arise during treatment. Appx10501. Thus, it makes little sense to refer to adverse events in connection with an untreated patient. Accordingly, by the time the claims issued, the prosecution history did not dictate a comparison to a patient who has received no treatment whatsoever. Genentech "never repeated the allegedly disclaiming statement[]," and when the isolated statement relied on by the Board is "considered in the context of the prosecution history as a whole," it simply is "not clear and unmistakable enough to invoke the doctrine of prosecution history disclaimer." *Ecolab*, 569 F.3d at 1343.

Consistent with the plain meaning of the claim and specification, this Court should construe the term "extend the time to disease progression in said human patient, without increase in overall severe adverse events" as requiring a measurement against a patient treated with a taxoid alone.

II. UNDER A PROPER CONSTRUCTION, THE INVENTIONS OF THE CLAIMS ARE NONOBVIOUS

The Board held that even under Genentech's proposed claim construction, "an ordinary artisan would have had a reasonable expectation that the claimed combination treatment extends TTP and does not increase overall severe adverse events as compared to treatment with a taxoid alone." Appx36. But this conclusion cannot stand because it was not supported by substantial evidence.

It is undisputed that, as of December 1997, Genentech was at the leading edge of a fundamentally new approach to treating breast cancer. Instead of traditional chemotherapy, it was using rhuMAb HER2, a human-engineered antibody, to treat solid tumors—an approach that had never received approval from the FDA. Adding to the unpredictability, it was combining the use of a therapeutic antibody with a relatively new compound, paclitaxel, to achieve synergistic improvement to TTP without increasing adverse events compared to treatment with paclitaxel alone.

The prior art that the Board relied on to hold that Genentech's breakthrough would have been obvious left significant gaps that the Board never overcame. For

example, it is undisputed that no testing of the combination of rhuMAb HER2 and paclitaxel in humans had ever been reported before Genentech's patent application. Further, it is undisputed that no TTP results for the combination had ever been reported—even in a preclinical model. In an unpredictable art like breast cancer therapy, these holes in the prior art left the Board without a legally or scientifically sound basis for finding a reasonable expectation of success. The Board's attempts to overcome that deficiency by stretching the references and improperly relying on the inventor's own path to find obviousness only compounded its errors.

A. The Board Erred In Finding The Claimed Efficacy Was Obvious

The Board's conclusion that an ordinary artisan would reasonably expect that rhuMAb HER2 in combination with a taxoid would extend TTP in a human patient as compared to a taxoid alone was based on Baselga '96 and the Taxol PDR '95.[6] Baselga '96 reported results from a Phase II clinical trial of rhuMAb HER2 alone. But the Board compared the TTP of 5.1 months that Baselga '96 reported for certain patients administered rhuMAb HER2 alone to the TTP of 3.0 or 4.2 months reported for Taxol in the Physicians' Desk Reference. Appx36. The Board then reasoned that because the TTP of rhuMAb HER2 alone (5.1 months) was longer than the TTP of paclitaxel alone (3.0 to 4.2 months), an ordinary artisan

[6] Although the Board cited Seidman '96, it adds nothing to the analysis because it is a retrospective analysis measuring the "response proportion," not TTP, in tumor samples for metastatic breast cancer patients. Appx4041.

would have reasonably expected that the combination would extend TTP as compared to a taxoid alone. Appx36-37. This reliance on Baselga '96's reported TTP of rhuMAb HER2 was error because it ignored critical information and omissions.

Statements in the prior art must be "read in context." *Shire LLC v. Amneal Pharms., LLC*, 802 F.3d 1301, 1308 (Fed. Cir. 2015). The Board violated this principle when it read Baselga '96's reported TTP of 5.1 months in isolation. First, the Board failed to grapple with the fact that Baselga '96 measured only TTP, ***not extension of TTP*** as required by Genentech's claims. Baselga '96 included no control arm, and therefore provided no way to draw any conclusions regarding improvement in TTP compared to other patients in the same study. Appx8840-8842; Appx8284 (agreeing that Baselga '96 included no control).

Second, the Board overlooked the fact that Baselga '96 included in its calculation only a limited subset of patients: those patients with either a minor response or stable disease, which included ***only 16 of the 43 assessable patients***. Appx4232. Baselga '96 ***excluded*** from the calculation over half of the patients in the study, 22 of the 43 total, who showed progression of disease. In other words, Baselga '96 did not calculate TTP for the entire patient population. Rather, Baselga '96 calculated TTP for only the patients most likely to respond favorably to the treatment, skewing the result upward by excluding from its calculation the

patients who showed faster disease progression. Accounting for the patients Baselga '96 excluded, who all had TTP shorter than the median 5.1 months, the TTP would be necessarily shorter than the 5.1 months on which the Board relied. Thus, an ordinary artisan could not draw any comparison between the rhuMAb HER2 TTP reported in Baselga '96 and the paclitaxel TTP in the Taxol PDR. Appx10171-10172.

The Board's recitation of principles of combination therapy does not save its analysis. The Board cited a textbook that addresses combinations of two ***chemotherapies***, but does not address whether and how to combine therapies involving a novel biologic such as rhuMAb HER2. Appx5548 (discussing "studies of combination chemotherapy"). Rather, the prior art cautioned that "[t]he incorporation of biological agents ... into combination regimens with standard chemotherapeutic agents offers an important challenge to the medical oncologist since the assumptions for their use likely differ from those for chemotherapeutic agents." Appx9968. The properties of rhuMAb HER2 were not well-understood: No antibodies had been approved for treatment of solid tumors, no Phase III trial using rhuMAb HER2 had been conducted, there was no known and approved dose for rhuMAb HER2 as a single agent, and the mechanism of action of rhuMAb HER2 was uncertain. Appx10170-10171; Appx4234-4235. Even Petitioner's expert, Dr. Earhart, was unaware of any publication as of December 1996 applying

these principles to combine a chemotherapeutic agent and an antibody. Appx8274. As a result, a skilled artisan would not have simply applied a formula intended for two chemotherapies to rhuMAb HER2. Appx10176.

The only other evidence the Board relied upon was non-public correspondence between the FDA and Genentech regarding the Phase III clinical trial described in the '441 patent. Appx37. As discussed below, however, this reliance on the inventor's own path was legal error. *See infra* pp. 33-35. Thus, it not only fails to support the Board's decision as a matter of law, but tainted the Board's decision and independently requires vacatur.

B. The Board Erred In Finding The Claimed Safety Was Obvious

The Board's obviousness finding must also be vacated for a second, independent reason: Substantial evidence did not support the Board's finding that an ordinary artisan would reasonably expect that combining rhuMAb HER2 with a taxoid would not increase the number of severe adverse events. The Board found this "in view of the published safety information for each of [rhuMAb HER2] and paclitaxel, the fact that paclitaxel was previously FDA-approved, and the fact that [Genentech] proposed a Phase III trial with [rhuMAb HER2] /paclitaxel combination—which the FDA accepted—based on the same prior art disclosures." Appx40-41. The record evidence does not support the Board's decision.

As an initial matter, the known safety information for either rhuMAb HER2 or paclitaxel on its own does not address the possible toxicity of the ***combination*** of rhuMAb HER2 and a taxoid. And there was significant basis for concern here. Although Baselga '96 reported minimal toxicity of rhuMAb HER2 alone, taxoids were associated with both neuropathy (i.e., weakness, numbness, and pain in the hands and feet) and cardiotoxicity. Appx8771; Appx4048; Appx8014; Appx8019 (taxoids cause "[a] diverse spectrum of cardiac disturbances"]. Indeed, the Taxol PDR '95 reported that paclitaxel was approved only as a second-line therapy for metastatic breast cancer (i.e., after the failure of other treatments), and 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. Appx4046-4047; *see also* Appx8361 (this warning is "the FDA's way of flagging a drug, some things that you need to know about the drug"); Appx8816-8817.

Prior art references describing safety of individual drugs say nothing about potential safety issues of combination therapy. *Cf. United States v. Hiland*, 909 F.2d 1114, 1133 n.29 (8th Cir. 1990) ("[E]ven if the component parts of a drug are generally recognized as safe, the combination of those parts may not be safe."). An ordinary artisan simply could not predict how two drugs, one of which was a novel antibody therapeutic, would react together in a human patient without data from administration of the combination therapy. Appx8846-8847.

Further, the only data addressing the combination of rhuMAb HER2 and a taxoid was in preclinical studies (e.g., the Baselga abstracts), which did not involve humans. It is one thing to find (as the Board did) that the Baselga abstracts' description of mouse xenografts dosed with either chemotherapy alone or in combination with rhuMAb HER2 would motivate an ordinary artisan to combine rhuMAb HER2 and a taxoid to treat metastatic breast cancer patients. Appx32-35. But it is an entirely different thing to find that this single preclinical study would suggest that any particular result could be achieved with a reasonable expectation of success in human patients. *See Ericsson Inc. v. Intellectual Ventures I LLC*, 890 F.3d 1336, 1352-1353 (Fed. Cir. 2018) ("Reasonable expectation of success and motivation to combine are 'two different legal concepts' that should not be 'conflated.'" (quoting *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016))). While preclinical studies might assist in understanding the mechanism of action of therapeutics and identifying which therapies show activity against cancer cells, they do not reliably predict activity, effectiveness, or safety in humans. Appx8616-8618; Appx10165-10166; Appx10130-10131. As admitted by Petitioner's expert, when a scientist uses a "different model, you can get a different result." Appx9875.

The inability of the preclinical studies to predict safety in human patients applies with special force for combinations of rhuMAb HER2: Because rhuMAb

HER2 was engineered to bind to the human ErbB2 receptor, not the mouse ErbB2 receptor, Appx68(3:34-39), an ordinary artisan would have known that the antibody would affect only human cancer cells in the mouse, thus failing to provide insight as to the potentially-toxic effect of rhuMAb HER2, and its combination with other therapies, on other cells. Appx8624-8627.

The unpredictability of the art and the difficulty of forming a reasonable expectation of obtaining the claimed safety was confirmed by the fact that Baselga '94 tested the combination of rhuMAb HER2 and the anthracycline doxorubicin in preclinical xenografts and found no increased toxicity, Appx4226, but this combination produced a significant increase in cardiotoxicity when administered to human patients. Appx7629. The Board simply misinterpreted this evidence. It stated that the toxicity of rhuMAb HER2 combined with anthracyclines in human patients was "unexpected," and that this result therefore does not undermine the Baselga '94 xenograft models showing lack of toxicity of either paclitaxel or anthracycline in combination with rhuMAb HER2. Appx38. But the Board missed the point—as explained above, xenografts simply do not provide an expectation of safety in human patients. And because the claimed combination was tested in humans for the first time in Phase III trials, there was no Phase I or Phase II data from which an ordinary artisan could have formed a reasonable expectation of obtaining the claimed safety.

C. The Board Improperly Relied On The Inventor's Own Path To Find The Invention Obvious

Finally, the Board erred in relying on the fact that Genentech had proposed a Phase III study administering the combination of rhuMAb HER2 and paclitaxel to human patients—without prior Phase I and II studies of the combination—as evidence of obviousness. Appx38-39. This was improper reliance on the inventor's own path to prove obviousness. The statute is clear: "Patentability shall not be negatived by the manner in which the invention was made." 35 U.S.C. § 103(a) (pre-AIA).

Genentech submitted non-public documents regarding its FDA correspondence to show that, even from the perspective of the inventor, the combination of rhuMAb HER2 plus paclitaxel presented uncertainty. *See, e.g.*, Appx7090 ("[T]he expected clinical outcome for the administration of rhuMAb HER2 with Taxol is less certain than co-administration with cisplatinum or doxorubicin."); Appx10022 (FDA noting that Genentech has "[redacted]"). But the Board flipped the documents on their head and improperly relied on them as affirmative proof that the invention would have been obvious.

First, the Board noted that Genentech had cited Baselga '94 in its FDA submission and "anticipated" that rhuMAb HER2 in combination with certain chemotherapies would be more effective. Appx37. But this fact does not support

obviousness, which is determined from the perspective of a hypothetical person of ordinary skill in the art, not the inventor. "'The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art.'" *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017) (quoting *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012)); *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) ("[O]ne should not go about determining obviousness under § 103 by inquiring into what patentees (i.e., inventors) would have known or would likely have done."). This is because "[i]nventors, as a class, according to the concepts underlying the Constitution and the statutes that have created the patent system, possess something … which sets them apart from the workers of ordinary skill." *Id.*; *see also, e.g.*, *Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340, 1363 (Fed. Cir. 2009); *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325, 1326 (Fed. Cir. 2000). Accordingly, it was improper for the PTO to rely on the inventor's perspective on the prior art to support a finding of obviousness.

Second, the Board reasoned that "[i]n the absence of a reasonable likelihood that the proposed combination would not lead to an 'increase in overall severe adverse events,' it seems unlikely that the FDA would have approved

administering the claimed combination into a human patient." Appx39. But this hindsight reasoning does not show that a person of ordinary skill would have had a reasonable expectation of success. As an initial matter, the Board's assumption regarding the FDA's reasoning is pure speculation. "[T]he Board's own conjecture does not supply the requisite substantial evidence." *In re Huai-Hung Kao*, 639 F.3d 1057, 1067 (Fed. Cir. 2011). Moreover, the FDA's reasoning was not public before the priority date. Appx26. As the Board itself noted elsewhere in its decision, obviousness must be assessed based on evidence that "[a]n ordinary artisan would … have been privy to." Appx26. Finally, the FDA's views did not necessarily reflect the views of an ordinary artisan, as they could have been the product of extraordinary skill and certainly were informed by communication with the patent owner whose employee had brought her unique experience with Taxol to bear in making the inventive leap claimed in the '441 patent.

The Board's improper reliance on these non-public exchanges with the FDA is telling. The Board was making a huge leap, and it was only by resort to information not in the prior art that it could purport to do so. Stripped of such improper reasoning, the Board's decision is not supported by substantial evidence. And, at a minimum, the case must be remanded for the Board to reconsider its decision free from the taint of its reliance on the inventor's path and non-public communications that do not qualify as prior art.

CONCLUSION

For the foregoing reasons, the decision of the Board should be vacated and the case should be remanded for further proceedings on Genentech's non-contingent motion to amend. In the alternative, the Board's decision on the original claims should be reversed or, at a minimum, vacated.

Respectfully submitted,

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July 9, 2019

ADDENDUM

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U.S. Patent No. 7,846,441 (Exhibit 1001) Appx59-84

Trials@uspto.gov PARTIES AND BOARD ONLY Paper No. 90
Tel: 571-272-7822 Entered: October 3, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC. and PFIZER, INC.,
Petitioner,

v.

GENENTECH, INC,
Patent Owner.

Case IPR2017-01121[1]
Patent 7,846,441 B1

Before ZHENYU YANG, CHRISTOPHER G. PAULRAJ, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

YANG, *Administrative Patent Judge*.

[1] Case IPR2017-02063 has been joined with this proceeding.

DECISION
FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

ORDERS
Denying Patent Owner's Motion to Amend
35 U.S.C. § 316(d) and 37 C.F.R § 42.121

Dismissing Petitioner's Motions to Exclude
37 C.F.R. § 42.64(c)

Denying-in-Part and Dismissing-in-Part Patent Owner's Motion to Exclude
37 C.F.R. § 42.64(c)

Denying Petitioner's Motions to Seal without Prejudice to Patent Owner
37 C.F.R. § 42.55

Granting Patent Owner's Motions to Seal
37 C.F.R. § 42.55

Modifying Previous Order Granting Patent Owner's Motions to Seal
37 C.F.R. § 42.55

INTRODUCTION

Celltrion, Inc. ("Petitioner") filed a Petition for an *inter partes* review of claims 1–14 of U.S. Patent No. 7,846,441 B1 (Ex. 1001, "the '441 patent"). Paper 1 ("Pet."). Genentech, Inc. ("Patent Owner") filed a Preliminary Response. Paper 8. On October 4, 2017, the Board instituted trial to review patentability of the challenged claims. Paper 9 ("Dec."). Thereafter, we joined IPR2017-02063, filed by Pfizer, Inc., and challenging the same claims of the '441 patent, with the instant proceeding. Paper 39.

Patent Owner filed a Response to the Petition (Paper 26, "PO Resp."), and Petitioner filed a Reply (Paper 45, "Reply"). Patent Owner also filed a contingent Motion to Amend (Paper 28, "MTA"), to which Petitioner filed an Opposition (Paper 47, "MTA Opp."). After Patent Owner filed a Reply in support of the Motion to Amend (Paper 55, "MTA Reply"), and with our authorization, Petitioner filed a Sur-reply (Paper 66, "MTA Sur-reply").

The parties also briefed whether certain exhibits should be excluded from the record. Papers 61, 63, 72, 74, 77, 79, 83, 85, 86. In addition, Patent Owner filed observations on the cross-examination of Petitioner's declarant (Papers 71, 76), and Petitioner filed responses thereto (Papers 78, 82).

An oral hearing for this proceeding was held on May 18, 2018. *See* Paper 87 ("Tr.").

The Board has jurisdiction under 35 U.S.C. § 6 and issues this final written decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons provided below, we conclude Petitioner has established by a preponderance of the evidence that (1) claims 1–14 of the '441 patent are

unpatentable, and (2) claim 15 proposed by Patent Owner in the contingent Motion to Amend is unpatentable.

Related Proceedings

The '441 patent is also the subject of IPR2017-00731. Concurrently with this Decision, we issue a final written decision in that case.

We also issue, concurrently with this Decision, final written decisions in IPR2017-00737 and IPR2017-01122 to address the patentability of certain claims of U.S. Patent No. 7,892,549, a patent in the same family as the '441 patent at issue here.

The '441 Patent

The '441 patent claims priority to a provisional application filed December 12, 1997. Ex. 1001, (60).

The '441 patent relates to the treatment of disorders characterized by the overexpression of ErbB2. Ex. 1001, Abstract, 1:11–12. According to the Specification, "human ErbB2 gene (erbB2, also known as her2, or c-erbB-2), which encodes a 185-kd transmembrane glycoprotein receptor ($p185^{HER2}$) related to the epidermal growth factor receptor (EGFR), is overexpressed in about 25% to 30% of human breast cancer." *Id.* at 1:23–27. Before the '441 patent, "[a] recombinant humanized anti-ErbB2 monoclonal antibody (a humanized version of the murine anti-ErbB2 antibody 4D5, referred to as rhuMAb HER2 or HERCEPTIN®) had been clinically active in patients with ErbB2-overexpressing metastatic breast cancers that had received extensive prior anti-cancer therapy." *Id.* at 3:34–39. The parties do not dispute that this recombinant humanized anti-ErbB2 monoclonal antibody is also referred to as trastuzumab.

According to the '441 patent, ErbB2 overexpression was known to be linked to resistance to chemotherapeutic regimens, including anthracyclines. *Id.* at 3:41–49. On the other hand, "the odds of HER2-positive patients responding clinically to treatment with taxanes were greater than three times those of HER2-negative patients." *Id.* at 3:51–54.

The '441 patent states that

> [T]he invention concerns a method for the treatment of a human patient susceptible to or diagnosed with a disorder characterized by overexpression of ErbB2 receptor comprising administering a therapeutically effective amount of a combination of an anti-ErbB2 antibody and a chemotherapeutic agent other than an anthracycline derivative, e.g. doxorubicin or epirubicin, in the absence of an anthracycline derivative, to the human patient.

Id. at 4:4–11.

Illustrative Claim

Among the challenged claims, claims 1, 11, 13, and 14 are independent. Claim 1 is representative and is reproduced below:

1. A method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by overexpression of ErbB2 receptor, comprising administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence and a taxoid, in the absence of an anthracycline derivative, to the human patient in an amount effective to extend the time to disease progression in said human patient, without increase in overall severe adverse events.

Reviewed Ground of Unpatentability

We instituted *inter partes* review to determine whether the challenged claims would have been obvious over the combination of Baselga 1996,[2]

[2] Baselga et al., *Phase II Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients with HER2/neu-*

Seidman 1996,[3] and the 1995 TAXOL PDR entry,[4] in view of the knowledge of a person of ordinary skill in the art. Dec. 19.

In support of their respective arguments, Petitioner relies on the Declarations of Dr. Robert Earhart (Exs. 1002, 1054, 1105), and Patent Owner relies on the Declarations of Dr. Robert S. Kerbel (Exs. 2061, 2143), Dr. Susan Tannenbaum (Ex. 2062, 2144), and Dr. Susan Desmond-Hellmann (Ex. 2125).

ANALYSIS

Principles of Law

To prevail in this *inter partes* review of the challenged claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art;

Overexpressing Metastatic Breast Cancer, 14 J. CLIN. ONCOL. 737–44 (1996) (Ex. 1020, "Baselga 1996").

[3] Seidman et al., *Over-Expression and Clinical Taxane Sensitivity: A Multivariate Analysis in Patients with Metastatic Breast Cancer (MBC)*, 15 PROC. AM. SOC. CLIN. ONCOL. 104, Abstract 80 (1996) (Ex. 1011, "Seidman 1996").

[4] Taxol® (Paclitaxel) for Injection Concentrate, PHYSICIANS' DESK REFERENCE, 682–85 (49th ed. 1995) (Ex. 1012).

(2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). The strength of each of the *Graham* factors must be weighed in every case and must be weighted en route to the final obviousness determination. *See, e.g.*, *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983) (instructing that evidence of secondary considerations, when present, must always be considered in determining obviousness).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention does." *Id.* Moreover, a person of ordinary skill in the art must have had a reasonable expectation of success of doing so. *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014).

We analyze the instituted ground of unpatentability in accordance with these principles.

Claim Construction

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent

disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Each challenged claim, either explicitly or through dependency, recites "extend the time to disease progression [TTP] in said human patient, without increase in overall severe adverse events." In the Decision to Institute, we stated that "[g]iven the applicant's unequivocal statement to overcome the indefiniteness rejection during prosecution, we determine that the proper analysis of the term . . . is to compare the claimed combination treatment to no treatment." Dec. 6.

Patent Owner disputes this construction. PO Resp. 36–39. According to Patent Owner, "[b]oth parties' experts agree that the specification supports a construction that compares the claimed combination treatment to treatment with a taxoid alone." *Id.* at 36 (citing Ex. 1002 ¶ 112(h); Ex. 2062 ¶¶ 129–138). Patent Owner's representation is less than complete. Dr. Earhart, for example, specifically noted that, during prosecution, the applicant asserted that the comparison is between the claimed combination treatment and no treatment. Ex. 1002 ¶ 112(h) (citing Ex. 1004, 416). According to Dr. Earhart, this alternate claim construction does not impact his unpatentability analysis. *Id.*

It is well settled that "an invention is construed not only in the light of the claims, but also with reference to the . . . prosecution history in the Patent Office." *Graham*, 383 U.S. at 33. "The purpose of consulting the prosecution history in construing a claim is to exclude any interpretation that was disclaimed during prosecution." *Chimie v. PPG Indus., Inc.*, 402 F.3d

1371, 1384 (Fed. Cir. 2005) (internal quotation marks omitted). Under the broadest reasonable interpretation standard, statements made during prosecution can be "relevant as reinforcing the evident meaning of the claim language at issue, whether or not it would meet standards for disclaimer or disavowal." *D'Agostino v. MasterCard Int'l Inc.*, 844 F.3d 945, 949 (Fed. Cir. 2016); *see also Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015) (the Board "should also consult the patent's prosecution history in proceedings in which the patent has been brought back to the agency for a second review").

During prosecution, the examiner rejected then-pending claims that included the term at issue as indefinite under 35 U.S.C. § 112. Ex. 1004, 400–01 (Office Action dated July 17, 2001). The examiner stated:

> The phrase "extend the time to disease progression" . . . is a relative term which renders the claim[s] indefinite. The term "extend time to disease progression" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically, it is never set forth what the extension of time to disease progress is relative to, for example, is the extension of time to disease progress relative to untreated patients? Patients who received antibody or taxoid alone? Patients who received antibody and an anthracycline?

Id. The applicant responded that

> [T]he expression[] "extend the time to disease progression". . . [is] clear from the specification . . . and would be readily understood by the skilled oncologist. Clearly, the combination of anti-ErbB2 antibody and taxoid is administered in an amount effective to extend the time to disease progression **relative to an untreated patient**.

Id. at 416 (Response dated January 17, 2002) (emphasis added). In the next office action, the examiner withdrew the rejection. *See* Ex. 1004, 624 (Office Action dated March 27, 2002) (stating "[a]ll claims were allowable" but suspending prosecution due to potential interference). In other words, the applicant overcame the indefiniteness rejection by providing a specific definition of the term "extend the time to disease progression;" and our construction merely reflects that choice. *See Paulsen*, 30 F.3d at 1480 (holding an applicant may choose to be his own lexicographer).

Patent Owner contends that "the clinical trial results reported in the '441 specification measure efficacy of the combination of an anti-ErbB2 antibody (rhuMAb HER2) with a taxoid (paclitaxel) against a control arm of paclitaxel alone," whereas "[t]here is no data in the patent comparing the TTP of patients treated with an anti-ErbB2 antibody and a taxoid against an untreated patient." PO Resp. 36–37. That may well be the case; yet, it does not render our construction inconsistent with the Specification of the '441 patent. As Dr. Tannenbaum, an expert for Patent Owner, explains, "cancer generally continues to progress without treatment." Ex. 2062 ¶ 130. As a result, an ordinary artisan would have understood, even without any explicit disclosure in the '441 patent, that administering the combination of rhuMAb HER2 and paclitaxel would extend the TTP as compared to untreated patients.

Dr. Tannenbaum also testifies that, "in context," the applicant used the term "untreated patient" to refer to "a patient that had not received the combination therapy, but instead received paclitaxel alone." Ex. 2062 ¶ 135. The relevant context, however, includes what was stated during prosecution, wherein the examiner listed three choices: "is the extension of time to

disease progress relative to untreated patients? Patients who received antibody or **taxoid alone**? Patients who received antibody and an anthracycline?" Ex. 1004, 400–01 (emphasis added). The applicant could have chosen "taxoid alone" as the comparator. It did not do so. Instead, the applicant specifically excluded that possibility. *Id*. at 416 (stating "**[c]learly**, the combination of anti-ErbB2 antibody and taxoid is administered in an amount effective to extend the time to disease progression **relative to an untreated patient**") (emphases added). In view of the unambiguous evidence, we find Dr. Tannenbaum's opinion on this issue unpersuasive.

Patent Owner also argues that comparing the TTP in the claimed combination therapy with that in an untreated patient is "inconsistent with [our] construction of 'adverse event,' which contemplates a comparison against a patient treated with ***some*** therapy." PO Resp. 37. We are not persuaded by Patent Owner's argument.

During the preliminary stage of this proceeding, neither party proposed any construction for the term "adverse event." In the Decision to Institute, we "observed" a piece of extrinsic evidence related to this term, that is, the National Cancer Institute's Dictionary of Cancer Terms defines an adverse event as "[a]n unexpected medical problem that happens during treatment with a drug or other therapy."[5] Dec. 14 (quoting Ex. 3001). Nonetheless, we repeated that "the proper analysis of 'without increase in

[5] During the trial stage, neither party briefed whether the NCI dictionary definition is applicable to the present context. At oral argument, when inquired, counsel for Petitioner stated that the NCI dictionary definition "is inconsistent with the specification of the patent." Tr. 16:15–23 (arguing that myocardial dysfunction, which the '441 patent suggests is an adverse event, is not "an unexpected medical problem").

overall severe adverse events' is to compare the claimed combination treatment to no treatment." *Id.*

Our understanding is supported by the fact the limitation "without increase in overall severe adverse events" was added during an amendment filed on September 22, 2008 (*see* Ex. 1004, 2299–2301), after the applicant explicitly defined the limitation "extend the time to disease progression" as "relative to an untreated patient" (*id.* at 416). Patent Owner does not argue, and we do not find, that the comparator for the increase in overall severe adverse events differs from that for the TTP extension. Thus, the requirement of "without increase in overall severe adverse events" is also "relative to an untreated patient."

Moreover, it is the job of the patentee to write a patent carefully and consistently. Here, the applicant could have easily adopted the construction Patent Owner attempts to give it today. Yet, the applicant chose a different, special definition "with reasonable clarity, deliberateness, and precision," and obtained the '441 patent only after doing so. *See Paulsen*, 30 F.3d at 1480. Under such circumstances, we must give the term the construction the applicant set out, even if such construction would lead to a "nonsensical result."[6] *Source Vagabond Sys. Ltd. v. Hydrapak, Inc.*, 753 F.3d 1291, 1301 (Fed. Cir. 2014).

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[6] We acknowledge the tension between the applicant's statement during prosecution (i.e., the comparator for the TTP is untreated patients) and Patent Owner's argument now (i.e., an adverse event happens during treatment with a drug or therapy). Because an *inter partes* review is limited to challenges based "only on the basis of prior art consisting of patents or printed publications," we do not address whether this constitutes an admission that the challenged claims are indefinite under 35 U.S.C. § 112.

In sum, we maintain that the proper analysis of the term "extend the time to disease progression in said human patient, without increase in overall severe adverse events" is to compare the claimed combination treatment to no treatment. As explained below, however, the challenged claims are unpatentable even if we apply the construction advanced by Patent Owner.

Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). On this record and for purposes of this Decision, we see no need to expressly construe any other claim terms. *See* PO Resp. 39 n.13.

Disclosures of Prior Art

Baselga 1996

Baselga 1996 reports the results of a phase II clinical trial in patients with ErbB2-overexpressing metastatic breast cancer who had received extensive prior therapy. Ex. 1020, 3. Baselga '96 teaches that "rhuMAb HER2 is well tolerated and clinically active in patients with HER2-overexpressing metastatic breast cancers that had received extensive prior therapy." *Id.*

According to Baselga 1996, "patients were selected to have many sites of metastatic involvement, one of the most dire prognostic characteristics regarding response to therapy." *Id.* at 7. Each patient received a loading dose of 250 mg of intravenous rhuMAb HER2, followed by 10 weekly doses of 100 mg. *Id.* In Baselga 1996, "[a]dequate pharmacokinetic levels of rhuMAb HER2 were obtained in 90% of the patients. Toxicity was minimal and no antibodies against rhuMAb HER2 were detected in any patients." *Id.* Baselga 1996 reports an 11.6%

remission rate. *Id.* at 7. In addition, "37% of patients achieved minimal responses or stable disease." *Id.*

Baselga 1996 further teaches that in preclinical studies, "rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity." *Id.* at 9. As a result, Baselga 1996 reports that "[l]aboratory studies of the mechanism of this effect and clinical trials of such combination therapy [were] . . . in progress." *Id.*

Seidman 1996

Seidman 1996 teaches that, among metastatic breast cancer patients treated with paclitaxel, 58.8% HER2-positive patients responded to the treatment, whereas only 38.7% patients with breast cancer that did not overexpress the HER2 protein responded. Ex. 1011. Seidman 1996 suggests that HER2-overexpression "seems to confer sensitivity" to treatment with taxanes, "in spite of a positive correlation of HER2 positivity with poor prognostic features." *Id.*

TAXOL PDR

According to TAXOL PDR, paclitaxel "is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy." Ex. 1012, 6. The recommended dosage of paclitaxel to treat breast cancer was 175 mg/m^2, administered intravenously over the course of three hours, every three weeks. *Id.*, 8.

Level of Ordinary Skill in the Art

In the Decision to Institute, we stated that "[w]e do not discern an appreciable difference in the parties' respective definitions of the level of

ordinary skill in the art, and any perceived distinction does not impact our Decision." Dec. 9; *see also id.* at 9–10 (noting "both parties contend that a person of ordinary skill in the art would have had experience with breast-cancer research and treatment"). During trial, the parties did not dispute this determination. Having considered the complete record developed at trial, we see no reason to change our assessment. *See* Pet. 43; Prelim. Resp. 36–37.

We further note that, in this case, the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

Obviousness Analysis

Petitioner contends that claims 1–14 would have been obvious over the combination of Baselga 1996, Seidman 1996, and the 1995 TAXOL PDR entry, in view of the knowledge of a person of ordinary skill in the art. Pet. 24–74. After reviewing the entire record, we determine that Petitioner has established by a preponderance of the evidence that the challenged claims are unpatentable. We focus our analysis on claim 1.

Petitioner refers to Baselga 1996 for teaching that the rhuMAb HER2 antibody "was clinically effective in patients with advanced metastatic HER2-positive breast carcinoma, was 'remarkably well tolerated,' and lacked 'significant toxicity,' even though the patients had 'dire prognostic characteristics' based on the extensive metastasis of their cancers and prior

failures with other treatments." Pet. 43 (citing Ex. 1020, 7). Petitioner argues that before the priority date of the challenged claims, an ordinary artisan would have had a reason "to treat HER2-positive breast cancer patients with a combination of trastuzumab and paclitaxel." *Id.* at 44. According to Petitioner, this is because Baselga 1996 suggests the combination therapy of rhuMAb HER2 and paclitaxel (*id.* at 43–44 (citing Ex. 1020, 9)), and because Seidman 1996 teaches that "HER2-overexpression 'seems to confer sensitivity' to treatment with taxanes, even though this condition was known to be difficult to treat with other drugs" (*id.* at 34 (citing Ex. 1011), 44 (citing Ex. 1011)). To bolster its position, Petitioner also points to "preclinical data reporting synergy between trastuzumab and paclitaxel in mouse xenografts." *Id.* at 45 (citing Exs. 1019, 1021).

Petitioner asserts that an ordinary artisan would have had a reason to develop the combination of trastuzumab and paclitaxel without an anthracycline derivative, as required in the challenged claims. Pet. 50–51. According to Petitioner,

> [B]ecause anthracycline derivatives were a first-choice therapy for metastatic breast cancer, many patient candidates for treatment with the trastuzumab and paclitaxel combination would have already been treated with anthracycline-based therapy. (Ex. 1002, ¶ 137; Ex. 1016 (Abeloff), 810.) This means that many patients with metastatic disease who were prescribed a paclitaxel-containing regimen would have already endured extensive anthracycline-based therapy and would risk significant cardiotoxic effects with continued anthracycline-based therapy. (Ex. 1002, ¶ 137.)

Id. at 51. As a result, Petitioner contends that an ordinary artisan "would have avoided administering further anthracycline derivatives to the many

patients who had already been treated with this class of drug or to the many patients who are resistant to treatment with anthracyclines." *Id.*

Each challenged claim recites "an amount effective to extend the time to disease progression in said human patient, without increase in overall severe adverse events." Petitioner argues that an ordinary artisan would have started with "the known amounts that were effective to extend the time to disease progression of each drug when used as monotherapy." *Id.* at 47 (citing Ex. 1002 ¶ 131); *see also id.* at 48 (citing Ex. 1020, 4–5 (effective doses of trastuzumab); Ex. 1012 (effective doses of paclitaxel)). "To the extent any modification to the amounts of the combination was necessary," Petitioner continues, an ordinary artisan "would have readily optimized the combination treatment to arrive at an amount that results in the claimed efficacy and safety parameters," and "[s]uch optimization was routine in the art." *Id.* (citing Ex. 1002 ¶¶ 132–34; Ex. 1016,[7] 11, 13–14).

Relying on the clinical efficacy and toxicity profile of trastuzumab and paclitaxel, and the preclinical data showing a synergistic effect of the two therapeutics, Petitioner contends that there would have been reasonable expectation of success of the combination therapy with trastuzumab and paclitaxel, and without anthracycline derivatives. *Id.* at 52 (citing Ex. 1002 ¶¶ 117–35; Exs. 1011, 1019, 1020).

Patent Owner counters that an ordinary artisan would not have been motivated to treat patients with the claimed combination based on the teachings of the asserted prior art. PO Resp. 39–49. Patent Owner also

[7] Excerpts from CLINICAL ONCOLOGY (Martin D. Abeloff et al., eds., New York: Churchill Livingstone, 1995).

contends that Petitioner has not established a reasonable expectation of success in achieving either the claimed clinical efficacy or the claimed clinical safety. *Id.* at 49–57. In addition, Patent Owner argues that "several objective indicia conclusively establish the non-obviousness of the challenged claims." *Id.* at 60. We address Patent Owner's arguments in turn.

Motivation to Combine

Patent Owner contends that the asserted prior art references do not provide a motivation to treat patients with the claimed combination. PO Resp. 39–49. We disagree.

Petitioner contends that "[c]ombining trastuzumab and paclitaxel for metastatic HER2-positive breast cancer particularly made sense because the combination satisfied the four principles of combination therapy." *Id.* at 45–47 (citing Ex. 1002 ¶¶ 125–130); *see also id.* at 38–39 (stating the principles include "non-cross resistant drugs with single-agent activity, differing mechanisms of action, and nonoverlapping toxicity") (quoting Ex. 1024, 130–31 (emphases added by Petitioner)). Patent Owner argues that these principles "only address combinations of different ***chemotherapies***," while the claimed treatment in the '441 patent combines an antibody and chemotherapy. PO Resp. 48. According to Patent Owner, "[a]t the time of the '441 invention, antibodies were an entirely-new class of drug, and it was not clear how (or if at all) they could be used to treat cancer." *Id.* We do not find Patent Owner's argument persuasive.

Contrary to Patent Owner's assertion, at the time of the alleged invention, prior art already taught combining rhuMAb HER2 and chemotherapy agent cisplatin to treat patients with HER2 overexpressing

metastatic breast cancer in a phase II clinical trial. Ex. 1022,[8] 3. In addition, Patent Owner itself had relied on principles substantially the same as those advanced by Petitioner in designing a clinical trial. Ex. 1101,[9] 11. In that phase II trial, IDEC-C2B8 (later known as Rituxan), a monoclonal antibody, was combined with CHOP, a chemotherapeutic agent, to treat lymphoma. *Id.* "The rationale for combination of IDEC-C2B8 with CHOP includes: single agent efficacy, non cross-resistant mechanism of action, synergy with chemotherapeutic agents and non-overlapping toxicities." *Id.*; *see also* Ex. 1103, 2 (Patent Owner announcing the positive result in the phase II trial in a 1996 press release). This evidence directly contradicts Patent Owner's assertion that the four principles should not be applied to a combination of an antibody and a chemotherapeutic agent.

Patent Owner argues that this research is not comparable to the issue in this case because Rituxan is a chimeric monoclonal antibody, whereas Herceptin is a fully humanized monoclonal antibody. Tr. 30:16–25. According to Patent Owner, Rituxan and Herceptin have different mechanisms of action, biological behavior, and response rates, and were investigated for different therapeutic indications. *Id.* To the extent Patent Owner suggests that we should only consider prior art directed to a fully humanized monoclonal antibody with the same mechanisms of action,

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[8] Pegram et al., *Phase II Study of Intravenous Recombinant Humanized Anti-p185 HER-2 Monoclonal Antibody (rhuMAB HER-2) Plus Cisplatin in Patients with HER-2/NEU Overexpressing Metastatic Breast Cancer*, 14 PROC. AM. SOC. CLIN. ONCOL.106, Abstract 124 (1995).

[9] Czuczman et al., *IDEC-C2B8 and Chop Chemoimmunotherapy of Lowgrade Lymphoma*, 86 BLOOD, 208 (1995).

biological behavior, response rates, and therapeutic indication as Herceptin, we reject this unreasonably stringent standard. After all, "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." *See KSR*, 550 U.S. at 421.

Even if we were to disregard Petitioner's reliance on the four principles of combination therapy, we still would find an ordinary artisan would have had a reason to combine trastuzumab and paclitaxel for metastatic HER2-positive breast cancer. Indeed, as detailed below, the prior art repeatedly and explicitly teaches this combination.

Baselga 1996 teaches that "rhuMAb HER2 is well tolerated and clinically active in patients with HER2-overexpressing metastatic breast cancers that had received extensive prior therapy." Ex. 1020, 3. Patent Owner does not dispute Petitioner's reliance on this "observed clinical efficacy of trastuzumab in patients with HER2-positive breast cancer." *See* Pet. 24; *see also* Ex. 1001, 3:34–40 (citing Baselga 1996 for the same proposition).

Patent Owner, however, challenges Petitioner's characterization of Seidman 1996 as showing "proven efficacy" of paclitaxel against metastatic HER2-positive breast cancer in humans. PO Resp. 41 (citing Pet. 43). According to Patent Owner, because Seidman 1996 is an abstract, it merely reflects a preliminary hypothesis, and an ordinary artisan "would await an expanded analysis in a peer-reviewed journal before drawing any conclusions." *Id.* We do not find this argument persuasive.

The '441 patent cites numerous abstracts on its face. *See* Ex. 1001, (56) References Cited. In fact, in a declaration submitted during prosecution, the inventor relied on an abstract to overcome prior-art

rejections. *See* Ex. 1004, 321. We also find persuasive the testimony of Dr. Earhart that

> Peer review is most important for analysis and discussion. It is not as important for short reports of data. The Seidman 1996 abstract simply reports the facts as its authors observed them: HER2+ patients were sensitive to taxanes. There is no editorial and no analysis that needs peer review. Absent any allegation of misconduct on the part of the authors, a person of ordinary skill in the art would have had no reason to doubt their reported data.

Ex. 1054 ¶ 16.

Indeed, the research reported in Seidman 1996 was supported in part by a grant from the National Cancer Institute. Ex. 1011. In addition, the authors of Seidman 1996 are from Memorial Sloan-Kettering Cancer Center, and include two recipients of awards from the American Society of Clinical Oncology (Ex. 1011) and at least one—in Patent Owner's own words—"leading practitioner" in the field (PO Resp. 62). These authors also appear to have been collaborating with scientists of Patent Owner in rhuMAb HER2 research and clinical trials. *See, e.g.*, Ex. 1020, 3 (showing some of the same authors in Baselga 1996 as in Seidman 1996 and attributing the work on rhuMAb HER2 to both Memorial Sloan-Kettering Cancer Center and Genentech); *see also* Ex. 1019, 4 (Baselga Abstract 53[10] showing the same). Under such circumstances, we are not persuaded that an ordinary artisan would have ignored or discounted the teachings of Seidman 1996 simply because it is an abstract.

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[10] Baselga et al., *Anti-HER2 Humanized Monoclonal Antibody (MAb) Alone and in Combination with Chemotherapy Against Human Breast Carcinoma Xenografts*, 13 PROC. AM. SOC. CLIN. ONCOL. 63 (Abstract 53) (1994) (Ex. 1019, "Baselga Abstract 53").

Relying on Van Poznak,[11] a 2002 publication, Patent Owner also contends that "[t]he Seidman authors themselves continued to research the issue" and reached a conclusion inconsistent with the one in Seidman 1996. PO Resp. 41 (citing Ex. 2024, 2322). According to Patent Owner, "[t]hat the authors of the Seidman abstract did not view their initial finding as one of 'proven efficacy' and continued to study the issue further confirms that a POSA would not have attributed the same significance to Seidman that Petitioner suggested and the Board accepted." *Id.* at 41–42 (citing Ex. 2062 ¶ 183). We are not persuaded by this argument either.

As a preliminary matter, it is common for artisans to seek further in-depth understanding of the mechanism of action of a drug or improvement over an existing treatment. More importantly, a proper obviousness analysis requires us to step back in time and compare the subject matter sought to be patented and the prior art at the time of the invention. 35 U.S.C. § 103(a); *see also KSR*, 550 U.S. at 421 ("A factfinder should be aware . . . of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning."). Indeed, Patent Owner in this case has repeatedly emphasized this point. *See, e.g.*, PO Resp. 3, 21, 40, 46, 52, 60, 61.

Patent Owner argues that Van Poznak shows that the results reported in Seidman 1996 are unreliable. PO Resp. 41 (citing Ex. 2024, 2322, 2323). Van Poznak, however, was published in May 2002, four and half years after the time of the alleged invention in the '441 patent. It, therefore, could not have informed the opinion of an ordinary artisan at that relevant time. To

[11] Van Poznak, et al., *Assessment of Molecular Markers of Clinical Sensitivity to Single-Agent Taxane Therapy for Metastatic Breast Cancer*, 20 J. CLIN. ONCOL. 2319 (2002) (Ex. 2024, "Van Poznak").

import the disclosures of Van Poznak into the obviousness inquiry would be to engage in the very hindsight bias Patent Owner rightly urges must be avoided.

Substantively, we are not persuaded that the results of Van Poznak contradict those of Seidman 1996. Patent Owner emphasizes that Van Poznak "found no 'statistically significant association with clinical response to taxane therapy' for patients who are HER2-positive," and "described that finding as 'noteworthy' because it was 'partly in contrast to our earlier analysis.'"[12] PO Resp. 41 (citing Ex. 2024, 2322, 2323). This summary, however, is incomplete. The relevant part of Van Poznak reads:

> Our results are noteworthy for the lack of correlation between HER2 status as assessed by either HercepTest or CB-11 and response to single-agent taxane therapy. These findings are partly in contrast to our earlier analysis. In this earlier analysis of fewer cases, HER2 status as assessed by the monoclonal antibody 4D5 was predictive of positive response to taxane monotherapy, whereas HER2 assessment with the polyclonal antibody pAb-1, was not.

Ex. 2024, 2323. Apparently, even in the earlier study—which is not Seidman 1996—the correlation of HER2 status and the sensitivity to treatment with taxanes depends on the antibody used. Because the antibodies used Van Poznak are different from 4D5 used in the earlier study—HercepTest is another polyclonal antibody; whereas CB-11, though a monoclonal antibody, has specificity and sensitivity different from those of 4D5 (*id.* at 2321)—we are not persuaded that Van Poznak shows that the results reported in Seidman 1996 are unreliable.

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[12] As Petitioner points out, Van Poznak does not cite Seidman 1996. Reply 6.

Patent Owner further argues that Yu[13] discourages the use of taxoids in HER2-positive patients. PO Resp. 42. According to Patent Owner, Yu explicitly warns that "breast cancers that overexpress p185 [*i.e.*, HER2] will not respond well to Taxol." *Id.* (citing Ex. 2029, 1362). Yu drew that conclusion, however, based on an *in vitro* study, using cell lines growing on culture plates. Ex. 2029, 1360–62. On this issue, we agree with Dr. Earhart and Petitioner that an ordinary artisan "would have regarded the *in vivo* preclinical and clinical results reported in Baselga-1996 and Seidman-1996, which were obtained from studies of actual tumor cells in live animals and human patients, as being far more predictive than Yu's results, which were obtained in artificially-engineered cells on culture plates." Reply 6 (citing Ex. 1054 ¶ 17); *see also* Ex. 1040, 222:11–224:9 (Dr. Kerbel, Patent Owner's expert witness, testifying that a living animal model, though imperfect, is "closer" to a human and "better than a petri dish").

Moreover, in an obviousness inquiry, we must analyze the prior art as a whole, not individually. *See In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004). Other evidence of record shows paclitaxel was known at the relevant time to be effective in treating HER2-positive cancers (*see, e.g.*, Ex. 1011), demonstrates "strong synergy" of paclitaxel and an anti-ErbB2 antibody in human breast cancer xenografts (*see, e.g.*, Ex. 1010,[14] 5; Ex. 1019, 4;

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[13] Yu et al., *Overexpression of c-erbB-2/neu in Breast Cancer Cells Confers Increased Resistance to Taxol Via mdr-1-independent Mechanisms*, 13 ONCOGENE 1359–65 (1996) (Ex. 2029).

[14] Seidman et al., *Memorial Sloan-Kettering Cancer Center Experience with Paclitaxel in the Treatment of Breast Cancer*, 22 SEMINARS in ONCOL. (Suppl.) 108–16 (1995) (Ex. 1010, "Seidman 1995")

Ex. 1021,[15] 3), and suggests clinical trials of the claimed combination therapy (*see, e.g.*, Ex. 1010, 5; Ex. 1020, 9). Weighing all evidence of record, we are not persuaded that Yu, a single reference based on an *in vitro* study, would have dissuaded an ordinary artisan from combining paclitaxel and an anti-ErbB2 antibody in treating HER2-positive cancers. *See also* MTA Sur-reply 6 (citing Ex. 1043,[16] 6–9 (noting a review paper regarding paclitaxel sensitivity in breast cancer does not cite Yu, but "cites Seidman '96, Baselga '96 and the Baselga xenograft studies as suggesting that HER2+ tumors are sensitive to paclitaxel, and that combining trastuzumab with paclitaxel increased its antitumor activity").

This is especially so because Baselga 1996 further reports that "[i]n preclinical studies . . . rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity. Laboratory studies of the mechanism of this effect and **clinical trials of such combination therapy are currently in progress**." Ex. 1020, 9 (emphasis added).

Acknowledging this statement, Patent Owner nevertheless argues that Baselga 1996 "provides no motivation to choose paclitaxel from among the 'several chemotherapeutic agents' identified for treatment in human patients." PO Resp. 40. Patent Owner contends that there was no clinical

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[15] Baselga et al., *Antitumor Activity of Paclitaxel in Combination with Anti-growth Factor Receptor Monoclonal Antibodies in Breast Cancer Xenografts*, 35 PROC. AM. ASSOC. CLINICAL CANCER RES. 380 (Abstract 2262) (1994) (Ex. 1021, "Baselga Abstract 2262").

[16] Baselga et al., *HER2 Overexpression and Paclitaxel Sensitivity in Breast Cancer: Therapeutic Implications*, 11(3) (Suppl. 2) ONCOLOGY 43–48 (1997).

study involving the claimed combination at the time that Baselga 1996 was submitted or accepted. PO Resp. 32, 40. The evidence Patent Owner relies on for support, however, was and still remains confidential. *See, e.g.*, Ex. 2125 ¶¶ 18–46 (citing exhibits submitted under seal by Patent Owner). An ordinary artisan would not have been privy to Patent Owner's internal documents, and, thus, would have accepted the statement in Baselga '96 that clinical trials of trastuzumab with each of the named chemotherapeutics, including paclitaxel, were ongoing, at face value. Reply 16. And in any event, the relevant time for assessing obviousness is not the submission or acceptance date of Baselga '96, but the time of the alleged invention, which, in this case, is after the publication of Baselga '96. It is undisputed that at the that time, in fact, at the time Baselga 1996 was published, a clinical study involving the claimed combination was indeed in progress.

Patent Owner also contends that there were "significant safety concerns regarding treatment with taxoids." PO Resp. 47. As a result, Patent Owner continues, an ordinary artisan, when considering whether to combine the anti-ErbB2 antibody with an existing anti-cancer drug, would have been motivated to use an anthracycline, rather than a taxoid. *Id.* We are not persuaded.

Generally, there are always safety concerns associated with pharmaceutical agents. Indeed, it is undisputed that anthracyclines produce "cumulative cardiac injury" that "causes the greatest concern." *See, e.g.*, Ex. 1016, 810; Ex. 2030,[17] 409, 423 (anthracycline-induced cardiac toxicity

[17] Doroshow, Anthracyclines and Anthracenediones, in Cancer Chemotherapy & Biotherapy: Principles and Practice 409 (1996).

"is difficult to treat and is associated with a high mortality"). It was known that with each dose of an anthracycline, "there is progressive injury to the myocardium so that the grade increases steadily with total dose of drug administered." Ex. 2030, 423.

As Patent Owner acknowledges, paclitaxel was approved by the FDA for ovarian cancer in 1992 and for breast cancer in 1994, years before the priority date of the '441 patent. *See* PO Resp. 17. Thus, we are not persuaded that the safety concerns over paclitaxel alone would have dissuaded an ordinary artisan from combining it with an anti-ErbB2 antibody.[18]

More importantly, the fact that the prior art "discloses a multitude of effective combinations does not render any particular formulation less obvious. This is especially true because the claimed composition is used for the identical purpose taught by the prior art." *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). In *Merck*, one reference expressly taught the combination of the compounds claimed in the patent. *Merck*, 874 F.2d at 807. Similarly in this case, Baselga 1996 expressly teaches paclitaxel as one of three specifically identified chemotherapeutic agents to be combined with rhuMAb HER2. *See In re Corkill*, 771 F.2d

[18] Moreover, as Patent Owner emphasizes, anthracyclines had been the most widely used, standard, first-choice therapy for metastatic breast cancer to the point that it was difficult to find patients who had not previously been treated with anthracylines. PO Resp. 14, 23 n.6. As a result, many patients had become resistant to it. Taxanes "demonstrated activity and safety . . . against anthracycline-refractory breast cancer." Ex. 1010, 1; *see also* Ex. 1024, 14–15 (stating "paclitaxel has activity in heavily pretreated patients").

1496, 1500 (Fed. Cir. 1985) (affirming an obviousness rejection in light of prior art teaching that "hydrated zeolites will work" in detergent formulations, even though "the inventors selected the zeolites of the claims from among 'thousands' of compounds").

In addition, in an obviousness analysis, "the question is whether there is something in the prior art as a whole to suggest the *desirability*, and thus the obviousness, of making the combination," not whether there is something in the prior art as a whole to suggest that the combination is the *most desirable* combination available. *See Fulton*, 391 F.3d at 1200 (quotation marks and alteration omitted). Thus, even if an ordinary artisan would have preferred the combination of rhuMAb HER2 and an anthracycline —which, given the undisputed significant and cumulative cardiac toxicity of anthracyclines (*see, e.g.*, Ex. 1016, 26; Ex. 2030, 423), is not a foregone conclusion—we are persuaded that an ordinary artisan also would have had a reason to, as Baselga 1996 specifically teaches, combine rhuMAb HER2 with paclitaxel. *See* Ex. 1020, 9.

Baselga 1996 and Seidman 1996 are not the only prior art references suggesting the combination of rhuMAb HER2 and paclitaxel. Seidman 1995, Baselga Abstract 53, and Baselga Abstract 2262 all suggested the same. *See* Ex. 1010, 5; Ex. 1019, 4; Ex. 1021, 3. Indeed, Baselga Abstract 53, which reports work collaborated between Patent Owner and some of the authors of Seidman 1996, teaches growing HER2 overexpressing tumors in nude mice followed by treatment with anti-HER2 4D5 antibody and paclitaxel. Ex. 1019, 4. According to Baselga Abstract 53, the antibody or paclitaxel alone produced 35% growth inhibition, but the combination of the two resulted in 93% growth inhibition without increasing toxicity. *Id.*

Baselga Abstract 53 concludes that "anti HER2 MAbs can eradicate well established tumors and enhance the activity of paclitaxel . . . against human breast cancer xenografts. Clinical trials are underway." *Id.*

Baselga Abstract 2262, which is another collaboration between Patent Owner and some of the authors of Seidman 1996, reports the same data and concludes that the antitumor effects of paclitaxel can be "markedly enhanced" by anti-HER2 4D5 antibody. Ex. 1021, 3. Baselga Abstract 2262 also specifically called out that the antitumor activity of the paclitaxel and anti-HER2 4D5 antibody combination "was markedly better than doxorubicin [i.e., an anthracycline drug] plus 4D5." *Id.*

Patent Owner introduced Hsu[19] in response to Petitioner's reliance on the Baselga xenograft data. Patent Owner introduced Hsu as Exhibit 2135 at the April 17, 2018 deposition of Dr. Earhart (Ex. 2130, 165:12–177:9), and submitted arguments with respect to Hsu in connection with its motions on observation (Paper 71, ¶ 8; Paper 76 ¶ 3), to which Petitioner replied (Paper 78, ¶¶ 7, 8; Paper 82 ¶ 3).

According to Hsu, *in vitro* cytotoxicity assays on HER2-expressing SKBR-3 human breast cancer cells showed that rhuMAb HER-2 and taxol in combination showed additive cytotoxic effects. Ex. 2135. Hsu also teaches that "in an athymic mouse model with HER-2/*neu*-transfected MCF-7 human breast cancer xenografts," "[x]enografts treated with rhuMAb HER-2

[19] Hsu, et al., *Therapeutic Advantage of Chemotherapy Drugs in Combination with Recombinant, Humanized, Anti-HER-2/neu Monoclonal Antibody (rhuMAb HER-2) Against Human Breast Cancer Cells and Xenografts with HER-2/neu Overexpression*, Proc. Basic & Clin. Aspects of Breast Cancer, A-39 (March 7-12, 1997). Ex. 2135.

plus taxol . . . were not significantly different from drug alone controls with the doses and dose schedules tested in this model." *Id.* Patent Owner appears to rely on Hsu to show that an ordinary artisan would have discounted Baselga xenograft results in light of Hsu's teaching. *See* Ex. 2130, 172:18–177:5; Paper 71, ¶ 8; Paper 76 ¶ 3. We are not persuaded.

We observe, and Dr. Earhart confirmed, that Hsu "does not detail the drug doses and schedules used in the xenograft study." Ex. 1105 ¶ 13. In addition, as Dr. Earhart further explained, "unlike in Baselga Abstract 53, Hsu 1997 did not use xenografts that naturally overexpress HER2. Rather, it used xenografts that were transfected, or artificially engineered, to overexpress HER2." *Id.* (internal citations omitted). Dr. Earhart reasonably concludes that an ordinary artisan "would not have regarded Hsu 1997 as negating the teachings of Baselga Abstract 53." *Id.* Thus, we agree with Petitioner that an ordinary artisan would not have concluded that the results in the Hsu abstract were inconsistent with those in the Baselga abstracts.[20] *See* Paper 78, ¶ 8.

Patent Owner also contends that the preclinical results from Baselga Abstract 53 and Baselga Abstract 2262 would not have motivated an ordinary artisan to treat patients with the claimed combination because the mouse study therein "was not a reliable predictor of success in humans." PO Resp. 43–46. Patent Owner argues that (1) "[t]he preclinical study described in the Baselga abstracts was based on a single cell line;" (2) "the particular cell line used in the Baselga abstracts was not representative of

[20] We also address Hsu in *Hospira, Inc. v. Genentech, Inc.*, IPR2017-00731, Paper 120 (PTAB Oct. 3, 2018), 23–25.

actual patients;" and (3) "the tumors in the Baselga abstracts were implanted subcutaneously [i.e., ectopic tumor models], rather than in tissue similar to how the disease would present in human patients [i.e., orthotopic tumor models]." *Id.* at 43–45. Petitioner contends otherwise. Reply 8–11. We find Petitioner's arguments more persuasive.

According to Dr. Earhart, "[a]lthough xenografts are not conclusive evidence of efficacy or toxicity in humans, they serve as a helpful tool that can provide further evidence of efficacy or safety that researchers may find informative in developing new treatments or designing clinical studies." Ex. 1002 ¶ 46. Prior art supports Dr. Earhart's opinion. For example, in an article reviewing xenografts as model for drug testing, after efforts "to correlate the published xenograft data with the clinical data," the authors concluded that "[d]rug testing with different types of xenotransplanted tumors has shown that the response of xenografts obtained in immune-deficient animals is comparable to that in clinical practice." Ex. 1028,[21] 1. In addition,

> Xenografts of a particular tumor type are often able to identify agents of known clinical activity against that disease. This fact strongly supports the validity of using established lines of heterotransplants of human tumors as a predictive system for testing new anticancer agents, and also supports the use of xenografts as a model system for studying many human cancers *in vivo.*

[21] Mattern et al., *Human Tumor Xenografts as Model for Drug Testing*, 7 CANCER AND METASTASIS REVIEWS, 263–84 (1988).

Id. at 17–18. *See also* Ex. 1026,[22] 1 (concluding that despite some limitations, "the highly correct prediction rates for tumor sensitivity and resistence [sic] validates human tumor xenografts as tumor models to test new drugs and combinations").

Patent Owner's expert does not disagree. For example, Dr. Kerbel testified that, in the relevant time frame, xenograft studies were common in the development of drugs for use in cancer treatment. Ex. 1040, 20:14–17. He also testified that such preclinical studies help an ordinary artisan to decide which drug candidate to test in human, and to decide, if two drugs are already used in human, whether to test the combination therapy in human. *Id.* at 23:9–12, 19–23.

In addition, Dr. Kerbel co-authored Francia,[23] a peer reviewed research paper published a decade after the priority date of the '441 patent. Francia tested the efficacy and toxicity of trastuzumab combined with chemotherapy, using a xenograft model only. Ex. 2080, 6359; Ex. 1040, 23:24–27:5. According to Francia, "the majority of preclinical therapies reported in the literature are routinely assessed using only primary tumor models, either ectopic or orthotopic." Ex. 2080, 6363. The xenograft model used in Baselga Abstract 53 and Baselga Abstract 2262 is an ectopic model. Dr. Kerbel testified that ectopic models not only were more commonly used

[22] Fiebig et al., *Comparison of Tumor Response in Nude Mice and in the Patients*, 74 BEHRING INST. MITTEILUNGEN, 343–52 (1984).

[23] Francia et al., *Comparative Impact of Trastuzumab and Cyclophosphamide on HER-2–Positive Human Breast Cancer Xenografts*, 15 CLIN. CANCER RES. 6358–66 (2009) (Ex. 2080, "Francia").

than orthotopic models in the relevant time period, but, in fact, remain in use even today. Ex. 1040, 28:19–29:6.

Similarly, Dr. Kerbel co-authored Ng,[24] another peer reviewed research paper published years after the priority date of the '441 patent. Ng tested a new formulation of paclitaxel in a xenograft model using a **single cell line**. Ex. 2082, 4331; Ex. 1040, 29:14–30:12. Based on the xenograft results, Dr. Kerbel and others concluded that the new formulation of paclitaxel "warrants investigation in the clinical setting."[25] Ex. 2082, 4337; Ex. 1040, 32:21–33:13.

In view of evidence of record, we find the xenograft study reported in the Baselga abstracts would have motivated an ordinarily skilled artisan to combine rhuMAb HER2 and paclitaxel. Seidman 1995 confirms our understanding. Seidman 1995 teaches that paclitaxel was, at the time, "the most important new cytotoxic agent to be introduced for the management of breast cancer in many years." Ex. 1010, 1. According to Seidman 1995, "[p]aclitaxel combination with various cytotoxic agent [we]re being actively explored." *Id.* Specifically, Seidman 1995 reports:

> Since 1992, we and others have developed strong experimental data suggesting that combining maximally tolerated doses of chemotherapeutic agents with MoAb [monoclonal antibody]-mediated blockade of either EGFR or HER-2/*neu* receptors can eradicate well-established human tumor xenografts that were

[24] Ng et al., *Influence of Formulation Vehicle on Metronomic Taxane Chemotherapy: Albumin-Bound versus Cremophor EL-Based Paclitaxel*, 12 CLIN. CANCER RES. 4331–38 (2006) (Ex. 2082, "Ng").

[25] Although Francia and Ng do not qualify as prior art themselves, we find that they undermine the credibility of Dr. Kerbel's contrary testimony. *See* PO Resp. 44–45 (citing Ex. 2061 ¶¶ 62–70, 77–83).

> resistant to either treatment given singly. Striking antitumor effects are observed when paclitaxel is given in human breast cancer xenografts in combination with either anti-EGFR or anti-HER-2 MoAbs. This strong synergy is achieved with no increased toxicity in the animal model. . . . While mechanisms for the apparent synergy are being explored, **these data provide a lead for translation into the clinic**. Indeed, future clinical trials combining paclitaxel with anti-growth factor receptor MoAbs are being planned.

Id. at 5 (emphasis added).

Patent Owner's protocol seeking FDA approval to test the combination of trastuzumab and paclitaxel undermines its arguments. In this regard, the Federal Circuit has recognized that "FDA approval may be relevant to the obviousness inquiry." *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291 (Fed. Cir. 2013) (citing *Knoll Pharm. Co., Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004)). According to Patent Owner, "[a]lthough neither the combination of rhuMAb HER2 and cyclophosphamide and doxorubicin nor the combination of rhuMAb HER2 and paclitaxel have been used together in humans, it is anticipated that rhuMAb HER2 in combination with these chemotherapies may be more effective than either regimen used alone." Ex. 2007, 88. In reaching this conclusion, Patent Owner relied on the very Baselga xenograft results it now challenges:

> In vivo nude mouse xenograft models utilizing HER2 transfected cell lines have demonstrated an additive effect in reducing tumor volume when rhuMAb HER2 is given in combination with doxorubicin, compared with rhuMAb HER2 or doxorubicin given alone. *Similar findings using a different in vivo model were reported with rhuMAb HER2 and pactlitaxel.* It is anticipated that, in a population of patients with HER2

> overexpressing metastatic breast cancer, the addition of rhuMAb HER2 to *cyctotoxic chemotherapy* will enhance efficacy.

Id. at 30 (citing Baselga Abstract 53 and Baselga Abstract 2262).

In sum, given the repeated and explicit suggestion in the prior art, which are consistent with Patent Owner's statement in seeking FDA approval of the rhuMAb HER2/pactlitaxel combination, we are persuaded that an ordinary artisan would have been motivated to combine rhuMAb HER2 and pactlitaxel to treat patients with ErbB2 overexpressing metastatic breast cancer.

Reasonable Expectation of Success

Patent Owner also contends that Petitioner has not established a reasonable expectation of success in achieving either the claimed clinical efficacy or the claimed clinical safety. PO Resp. 49–57. We, again, disagree.

On the claimed efficacy, we reiterate that the proper analysis of "extend the time to disease progression" is to compare the claimed combination treatment to no treatment. *Supra* at 11. Petitioner asserts that combining trastuzumab with paclitaxel satisfies the limitation of clinical efficacy because each of trastuzumab and paclitaxel extends time to disease progression relative to no treatment, and an ordinary artisan "would not have expected the combination to change this." Pet. 49 n.18 (citing Ex. 1002 ¶¶ 136, 155 n.28; Ex. 1010). We find Petitioner's argument persuasive. Indeed, Patent Owner does not argue, and we do not find, that combining a taxoid with rhuMAb HER2 would abrogate the effect of either therapeutics. Thus, an ordinary artisan would have had a reasonable expectation of success in achieving the claimed clinical efficacy.

Our conclusion remains the same even under Patent Owner's proposed claim construction. In other words, an ordinary artisan would have had a reasonable expectation that the claimed combination treatment extends TTP and does not increase overall severe adverse events as compared to treatment with a taxoid alone.

Petitioner argues that

> Given the known clinical efficacy of each agent alone against this type of cancer (Baselga 1996; Seidman 1996), the good tolerability and absence of significant toxicity observed in the trastuzumab clinical trial (Baselga 1996 at 739, 741), and the lack of increased toxicity when trastuzumab was added to paclitaxel in preclinical studies (*id.* at 743), a POSA would have reasonably expected the combined regimen to be more effective against HER2-positive breast cancer than paclitaxel alone, without increasing severe adverse events. (Ex. 1002, ¶¶ 117-135.)

Pet. 52.

Patent Owner contends that none of the asserted prior art includes data showing an extension of TTP. PO Resp. 50. But, as Patent Owner acknowledges, Baselga 1996 teaches the median TTP with trastuzumab was 5.1 months (Ex. 1020, 6), and TAXOL PDR teaches the median TTP with paclitaxel was 3.0 or 4.2 months in a Phase III breast carcinoma study (Ex. 1012, 6). PO Resp. 50. Because Baselga '96 reports that rhuMAb HER2 achieved a longer TTP at least for HER2+ breast cancer patients, we agree with Petitioner that "POSAs would have had a reasonable expectation that adding trastuzumab would achieve an extension of TTP over paclitaxel alone based on the superior TTP of trastuzumab." Reply 19 (citing Ex. 1054 ¶ 20).

This is especially so because when developing a combination therapy by adding a new agent to a standard treatment, if the new agent, "because of

differing dose-limiting toxicity, can be added without compromising dose, there is a reasonable expectation that [the combination] will be superior to [the standard treatment alone]." Ex. 1053,[26] 28. Here, trastuzumab and paclitaxel have non-overlapping mechanisms of action and toxicities. *See* Pet. 46–47 and evidence cited therein. Thus, each can be administered in its full effective dose. *Id.* at 39 (citing Ex. 1002 ¶ 89; Ex. 1016, 10–11). As a result, an ordinary artisan would have had a reasonable expectation that treatment with the combination of trastuzumab and paclitaxel would extend TTP as compared to treatment with a paclitaxel alone.

Our conclusion is further supported by the representations Patent Owner made in its submission to the FDA. *See* Ex. 2007, 30 (Patent Owner relying on Baselga Abstract 53 and Baselga Abstract 2262 to support the proposal of the claimed combination because "[i]t is anticipated that, in a population of patients with HER2 overexpressing metastatic breast cancer, the addition of rhuMAb HER2 to *cyctotoxic chemotherapy* will enhance efficacy"), 88 (Patent Owner stating that although the combination of rhuMAb HER2 and paclitaxel had not been used together in humans, "it is anticipated that rhuMAb HER2 in combination with these chemotherapies may be more effective than either regimen used alone").

On the claimed safety, Petitioner relies on "the lack of severe toxicity associated with trastuzumab, the lack of increased toxicity from adding trastuzumab to paclitaxel in preclinical studies, and lack of known significant overlapping toxicities between trastuzumab and paclitaxel."

[26] Excerpts from ANTICANCER DRUG DEVELOPMENT GUIDE (Beverly A. Teicher, ed., Humana Press 1997).

Pet. 49, 52. Patent Owner argues that Baselga 1996 and Baselga Abstract 53 also showed no increased toxicity for the trastuzumab/anthracycline doxorubicin; yet, that combination "produced a significant increase in cardiotoxicity when administered to human patients." PO Resp. 56 (citing Ex. 1019, 4; Ex. 1020, 9). According to Patent Owner, "[t]hese disconnects highlight the inability of the Baselga references' mouse models to predict clinical safety." *Id.* (citing Ex. 2061 ¶¶ 54–61; Ex. 2062 ¶¶ 219–221). But, in Patent Owner's own words, "[t]he increased cardiotoxicity of rhuMAb HER2 combined with anthracyclines was **completely unexpected**." *Id.* at 25 (emphasis added). Thus, we decline to discount the significance of Baselga xenograft models in predicting clinical safety because of the unexpected cardiotoxicity of rhuMAb HER2/anthracyclines combination.

Patent Owner also asserts that the Baselga xenograft models would not reliably predict the effects of the claimed combination in humans for other reasons. PO Resp. 56. We, again, are not persuaded. Putting aside the general recognition of xenografts as "tumor models to test new drugs and combinations" because of "the highly correct prediction rates" (*see* Ex. 1026, 1; Ex. 1028, 17–18), Patent Owner's own documents refute its assertion.

As explained above, in seeking FDA approval to test the combination of trastuzumab and paclitaxel, Patent Owner acknowledged that "neither the combination of rhuMAb HER2 and cyclophosphamide and doxorubicin nor the combination of rhuMAb HER2 and paclitaxel have been used together in humans." Ex. 2007, 88. Instead, to support its "Study Rationale," Patent Owner relied on the very same Baselga xenograft results it now challenges. *Id.* at 30 (citing Baselga Abstract 53 and Baselga Abstract 2262). And those

data apparently were sufficient for the FDA to regard the planned phase III trial with trastuzumab/paclitaxel combination—without corresponding phase I and/or II trials—as "reasonable" merely one week after receiving the protocol. *See* Ex. 1035.[27] In the absence of a reasonable likelihood that the proposed combination would not lead to an "increase in overall severe adverse events," it seems unlikely that the FDA would have approved administering the claimed combination into a human patient.

We have considered other arguments advanced by Patent Owner but find them equally unavailing. For example, Patent Owner contends that "the development history of rhuMAb HER2 confirms that the preclinical results in the Baselga abstracts would not have provided a POSA a reasonable expectation of success in achieving the specific clinical result claimed in the '441 patent." PO Resp. 52. But, patentability is assessed from the perspective of the hypothetical person of ordinary skill in the art. *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325–26 (Fed. Cir. 2000). Thus, how the inventor developed the claimed combination is not material to our objective analysis of obviousness.[28] Moreover, we analyze

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[27] Petitioner points out that "The FDA did raise concerns about the revised trial, but not with respect to the use of paclitaxel per se. Rather, their concerns related to how the use of separate anthracycline and paclitaxel tracks would complicate the statistical analyses." Reply 17 (citing Ex. 1058.)

[28] Even if we consider the development history of rhuMAb HER2, we are not persuaded that it shows the inventor, as Patent Owner argues, encountered resistance from her colleagues to include rhuMAb HER2/paclitaxel in the clinical trial. *See* PO Resp. 25. Instead, the comments Patent Owner relies on, when read in context, do not appear to relate to either clinical efficacy or safety. *See* Ex. 2004, 10.

the reasonable expectation of success based on, not only the Baselga abstracts, but the prior art as a whole, including Baselga 1996, Seidman 1996, the 1995 TAXOL PDR entry, and the knowledge of a person of ordinary skill in the art.

Dr. Tannenbaum testifies that "in the 1990s[,] the mere fact that a treatment was under evaluation was no indication of success in light of the high failure rate of therapies in clinical trials." Ex. 2062 ¶ 222. We acknowledge the inherent unpredictability in the pharmaceutical industry. *See, e.g.*, PO Resp. 6–13, 53. We also recognize that the finder of fact may take into account failure of others to obtain FDA approval of a particular pharmaceutical combination. *Knoll Pharm. Co.*, 367 F.3d at 1385. But, "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007); *see also Allergan, Inc.*, 726 F.3d at 1291 (the Federal Circuit agreeing that the district court properly considered the basis for FDA approval decisions in assessing motivation to combine but "find[ing] clear error in the court's conclusion that one of ordinary skill would not be motivated to develop fixed combinations [of known drugs] with a reasonable expectation of success.").

Here, in view of the published safety information for each of trastuzumab and paclitaxel, the fact that paclitaxel was previously FDA approved, and the fact that Patent Owner proposed a phase III trial with trastuzumab/paclitaxel combination—which the FDA accepted—based on the same prior art disclosures, we are persuaded that, despite the uncertainties Patent Owner emphasizes, an ordinary artisan would have had

a reasonable expectation of success regarding the claimed safety. *See Pfizer*, 480 F.3d at 1365 (stating the expectation of success need only be reasonable, not absolute).

In sum, Petitioner has established, by a preponderance of the evidence, that an ordinary artisan would have been motivated to treat patients with ErbB2-overexpressing breast cancer by administering a combination of trastuzumab and paclitaxel, and in the absence of an anthracycline derivative. In addition, an ordinary artisan would have had a reasonable expectation that the combination therapy would have extended TTP, without increase in overall severe adverse events, even under Patent Owner's proposed claim construction.

Secondary Considerations

Patent Owner argues that the nonobviousness of the challenged claims are supported by secondary considerations, including the satisfaction of a long-felt-but-unmet need, praise, unexpected results, and commercial success. PO Resp. 60–66. We are not persuaded.

"For objective evidence of secondary considerations to be accorded substantial weight, its proponents must establish a nexus between the evidence and the merits of the claimed invention." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). Where objective indicia "result[ ] from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention." *Id*. We find that the nexus between the merits of the invention and the evidence of long-felt-but-unmet need, praise, and commercial success, if any, is weak.

Patent Owner asserts that Herceptin is the commercial embodiment of the '441 patent. PO Resp. 65. For commercial success, "if the marketed

product embodies the claimed features, and is coextensive with them, then a nexus is presumed." *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000). The patent challenger, however, may rebut the presumed nexus. *Id.* And here, Petitioner has sufficiently rebutted that presumption.

For example, each challenged claim in this proceeding requires the combination of an anti-HER2 antibody and a taxoid. Herceptin, however, was also approved for single-agent use. Reply 25 (citing Ex. 2012). Patent Owner has not shown what portion of the sales of Herceptin is attributable to the claimed combination, and not the single-agent use.[29] *Id.*

Furthermore, "evidence related solely to the number of units sold provides a very weak showing of commercial success." *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996). Patent Owner only present the product sales figure (Ex. 2035, 17) and has not shown what percentage of the market Herceptin commanded. Reply 26. As a result, we find the evidence of commercial success presented by Patent Owner is insufficient to support the nonobviousness of the challenged claims.

Regarding praise, Patent Owner relies on three pieces of evidence (PO Resp. 62 (citing Exs. 2018, 2033, 2034)), none of which shows that the praise is for the claimed combination. For example, Exhibit 2018 states that

[29] In addition, elsewhere, Patent Owner has asserted that the success of Herceptin "is attributable, in part," to the claims directed to the unique sequence provided in a different, earlier patent. Reply 24–25 (citing Ex. 1060, 66). Unlike the challenged claims here, those claims do not require the combination therapy. *Id.* Yet, Patent Owner does not explain what portion of the sales of Herceptin is attributable to the '441 patent, and not the other patent.

"[a]s early as 1995, Genentech was swamped by demand for the highly targeted, yet-to-be-approved new drug" Herceptin. Ex. 2018. The news article reported the clinical results of Herceptin alone and "[i]n combination with other chemotherapy," without specifying the chemotherapeutic agent. *Id.* Although it mentioned—in a single sentence, and without clinical results—about the combination with paclitaxel, the article describes it as "particularly encouraging" (*id.*), not the "breakthrough," or "Holy Grail," as Patent Owner alleges. PO Resp. 61, 62.

Similarly, Exhibit 2033 describes "Herceptin[] worked best when combined with standard chemotherapy." *Id.* at 1. The exhibit does not, however, mention combining Herceptin with a taxoid, but with the anthracycline derivative Adriamycin. *Id.* (noting that this combination "caused heart malfunction in some patients, though most continued on the combination").

Patent Owner quotes a statement by Dr. Larry Norton, alleging that it was directed to the "impressive results of the '441 invention." PO Resp. 62 (citing Ex. 2034). When read in context, however, it is unclear whether Dr. Norton was discussing Herceptin alone, a combination with a chemotherapy drug in general, or a combination with a taxol specifically. Ex. 2034. Thus, we determine Patent Owner has not presented sufficient evidence of praise to support a nonobviousness conclusion.

Patent Owner also relies on Exhibit 2018 as evidence of long-felt need. PO Resp. 60–61 (citing Ex. 2018); Ex. 2062 ¶¶ 224–225 (citing Ex. 2018). As discussed above, because Exhibit 2018 appears to discuss treatment with Herceptin alone and Herceptin in combination with chemotherapy generally, but not with a taxoid specifically, we are not

persuaded that Patent Owner has shown sufficient evidence of long-felt, but unmet, need.

Patent Owner further asserts that the claimed combination "produced unexpectedly-superior clinical efficacy as compared with either the antibody or a taxoid alone." PO Resp. 62–63. In support, Patent Owner relies on a single sentence from a declaration submitted by the inventor during prosecution. *Id.* at 63 (citing Ex. 1008 ¶ 6). As Petitioner points out, Patent Owner "fails to address any of Petitioner's criticisms of this statement presented in the Petition, or to cite any scientific proof demonstrating synergy in any clinical trial." Reply 23 (citing Pet. 70–72). In addition, as Seidman 1995 summarizes, in human breast cancer xenografts, paclitaxel and anti-HER2 antibody exhibited "strong synergy" and those data "provide a lead for translation into the clinic." Ex. 1010, 5. Because we are not persuaded by Patent Owner's criticism of the xenograft model (PO Resp. 63), we find the alleged "superior clinical efficacy" does not amount to unexpected results. *See supra* 29–33.

Patent Owner further contends that the claimed combination "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, but in fact did increase toxicity in the Phase-III study disclosed in the '441 patent." PO Resp. 64 (citing Ex-1019, 4) (emphasis added). As a preliminary matter, "when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected **compared with the closest prior art**." *Kao Corp. v. Unilever U. S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006) (emphasis added). Comparison of trastuzumab/paclitaxel with

trastuzumab/anthracycline does not satisfy this requirement. Moreover, as Patent Owner conceded, "[t]he increased cardiotoxicity of rhuMAb HER2 combined with anthracyclines was completely unexpected." PO Resp. 25. Thus, the safety profile of trastuzumab/paclitaxel is not unexpected merely because is better than that of trastuzumab/anthracycline.

In sum, after weighing the secondary consideration evidence against the other evidence of obviousness, we conclude that evidence of secondary consideration is not sufficient to outweigh the showing of obviousness arising from an analysis of the prior art. *See Cubist Pharmaceuticals, Inc. v. Hospira, Inc.*, 805 F.3d 1112, 1126 (Fed. Cir. 2015); *see also Bristol–Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (stating that objective indicia, even when present, "do not necessarily control the obviousness determination").

After reviewing the entire record, we determine that the combination of Baselga 1996, Seidman 1996, and the 1995 TAXOL PDR entry teaches or suggests each limitation of claim 1, that a person of ordinary skill in the art would have had a reason to combine the references and would have had a reasonable expectation to achieve the claimed clinical efficacy and safety. We further determine that evidence of the objective indicia is not sufficient to outweigh the primary findings. As a result, we conclude that Petitioner has established by a preponderance of the evidence that claim 1 is unpatentable over the combination of Baselga 1996, Seidman 1996, and the 1995 TAXOL PDR entry.

Patent Owner does not argue claims 2–14 separately. After reviewing the entire record (*see, e.g.*, Pet. 64–69), we conclude that Petitioner has established by a preponderance of the evidence that claims 2–14 are

unpatentable over the combination of Baselga 1996, Seidman 1996, and the 1995 TAXOL PDR entry.

Patent Owner's Contingent Motion to Amend

In an *inter partes* review, an amended claim is not added to the challenged patent as of right, but rather must be proposed as a part of a motion to amend. 35 U.S.C. § 316(d). We assess the patentability of the proposed substitute claims "without placing the burden of persuasion on the patent owner." *Aqua Prods., Inc. v. Matal*, 872 F.3d 1290, 1296 (Fed. Cir. 2017).

Patent Owner proposes a single amended claim 15 to substitute original claim 11. MTA 1. Claim 15 is reproduced below (showing deletions and additions to claim 11):

> ~~11.~~ 15. A method for the treatment of a human patient with ErbB2 overexpressing progressing metastatic breast cancer, comprising administering a combination of ~~a humanized 4D5 anti-ErbB2 antibody~~ rhuMAb HER2 and ~~a taxoid~~ paclitaxel, in the absence of an anthracycline derivative, to the human patient in an amount effective to extend time to disease progression in said human patient, as compared to paclitaxel alone, without increase in overall severe adverse events.

Id., Appendix A.

A Motion to Amend must meet the following statutory and regulatory requirements: (1) the amendment responds to a ground of unpatentability involved in the review; (2) the amendment does not seek to enlarge the scope of the claims of the patent or introduce new subject matter; and (3) the amendment proposes a reasonable number of substitute claims. *See* 35 U.S.C. § 316(d); 37 C.F.R. § 42.221. Petitioner does not dispute, and we agree, that one is a reasonable number of substitute claims. Petitioner,

however, disputes whether the Motion to Amend complies with the first two requirements. MTA Opp. 1–7. We agree with Petitioner that Patent Owner's proposed amendment fails, at least, because it seeks to introduce new matter.

To determine whether an amended claim introduces new matter, we look to whether the original application provides adequate written description support. In other words, we must determine whether the disclosure of the application reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). Because possession of the claimed invention is required, "a description that merely renders the invention obvious does not satisfy the requirement." *Id.* at 1352.

Proposed claim 15 specifies that a combination of rhuMAb HER2 and paclitaxel would not result in an increase in overall severe adverse events, as compared to paclitaxel alone. MTA 4. Patent Owner contends that the proposed substitute claim is supported by the original application and the provisional application. *Id.* at 5–6 (citing Ex. 1004; Ex. 2009). According to Patent Owner,

> The applications describe a clinical study in which overexpressing ErbB2 metastatic breast cancer were treated with a combination of a humanized version of the murine 4D5 antibody (HERCEPTIN®) (also known as rhuMAb HER2) and Taxol® (also known as paclitaxel) in the absence of an anthracycline derivative. The results state that "assessments of time to disease progression (TTP in months) and response rates (RR) showed a significant augmentation of the chemotherapeutic effect by HERCEPTIN®, without increase in overall severe adverse events (AE)."

Id. at 6 (internal citations omitted). Specifically, Patent Owner relies on the following chart:

	Enrolled	TTP(months)	RR(%)	AE(%)
CRx	234	5.5	36.2	66
CRx +H	235	8.6*	62.00**	69
AC	145	6.5	42.1	71
AC+H	146	9.0	64.9	68
T	89	4.2	25.0	59
T+H	89	7.1	57.3	70

* $p<0.001$ by log-rank test

** $p<0.01$ by X^2 test

CRx : chemotherapy

AC: anthracycline/cyclophosphamide treatment

H: HERCEPTIN®

T: TAXOL®

Id. at 7 (citing Ex. 1004, 47; Ex. 2009, 43).

As shown in the chart above, AE (%) for paclitaxel/Herceptin® ("T+H") is 70%, higher than AE (%) for paclitaxel ("T") alone, which is 59%. Patent Owner argues that "a POSA would conclude that the 'AE%' column of this table represents adverse events, not severe adverse events." MTA Reply 3 (citing Ex. 2130, 150:20–151:5; Ex. 2144 ¶ 12). Instead, Patent Owner would have us construe "overall severe adverse events" to mean Grade 3/4 myocardial dysfunction. *Id.* at 2–3. Petitioner disagrees. MTA Sur-reply 3. We do not need to resolve this dispute because, even if we agree with Patent Owner on this point, we still do not find sufficient written description support for the proposed amended claim.

Both the original application and the provisional application disclose that "[a] syndrome of myocardial dysfunction similar to that observed with

anthracyclines was reported more commonly with a combined treatment of AC+H (18% Grade 3/4) than with AC alone (3%), T (0%), or T +H (2%)." Ex. 1004, 47; Ex. 2009, 43; *see also* Ex. 1001, 30:1–16. Here, again, the reported Grade 3/4 myocardial dysfunction incidence for paclitaxel/Herceptin® (T+H (2%)) is higher than that for paclitaxel alone (T (0%)). According to Patent Owner,

> However, a POSA would recognize that this difference is negligible—only one to two patients—and would constitute effectively no increase in overall severe adverse events. A POSA would contrast this data with the substantial increase in myocardial dysfunction observed in the anthracycline arm of the study, and understand that to be the type of 'increase in overall severe adverse events' that the claim is describing."

MTA Reply 3 (internal citations omitted). We are not persuaded by Patent Owner's argument for three reasons.

First, the proposed amendment specifies that the comparator is "paclitaxel alone," not the "anthracycline arm of the study." Second, the proposed amended claim recites, in absolute terms, "without increase in overall severe adverse events," and does not qualify the increase with modifiers such as "substantial," "effective," or "non-negligible." Third, even if we were to rewrite the claim to recite "without substantial increase in overall severe adverse events"—which we cannot—neither the original application nor the provisional application provides any information to determine what constitutes "substantial increase." *See* MTA Sur-reply 4.

In sum, Patent Owner has not pointed to, and we do not find, adequate description support in the original disclosure for proposed substitute claim 15. Because proposed substitute claim 15 introduces new matter,

which is prohibited under 35 U.S.C. § 316(d)(3) and 37 C.F.R. § 42.121(a)(2)(ii), we deny Patent Owner's Contingent Motion to Amend.[30]

Motions to Exclude Evidence

Petitioner's Motions to Exclude

Petitioner filed two Motions to Exclude, seeking to exclude Exhibits 2052, 2055, 2070, 2075, 2106, 2133, 2135, 2139, and 2146, as well as paragraph 56 of Exhibit 2061, paragraphs 11 and 15 of Exhibit 2143, and paragraphs 31 and 32 of Exhibit 2144. Papers 63, 83.

Petitioner contends that Patent Owner has not established that Exhibits 2052, 2055, 2070, 2106, and 2139 were available as prior art, and Exhibits 2075 and 2133 are dated after the priority date of the '441 patent. Paper 63, 3–5. As a result, Petitioner argues that these exhibits are "irrelevant for the purpose of establishing the teachings of the prior art, and Patent Owner is relying on them for improper purposes." *Id.* at 3. Petitioner also seeks to exclude paragraph 56 of Exhibit 2061 and paragraph 11 of Exhibit 2143, because Dr. Kerbel relied on Exhibits 2075 and 2133, respectively, in his Declarations. *Id.* at 4–5.

Our determination of the patentability of the challenged claims remain unchanged regardless of whether Exhibits 2052, 2055, 2070, 2075, 2106,

[30] For the reasons explained above in our analysis of the original claims under patent owner's proposed claim construction, we also conclude that proposed substitute claim 15 (which makes that construction explicit by reciting "as compared to paclitaxel alone") is unpatentable over the prior art of the record. *See supra* at 13–44. In short, Patent Owner does not contend, nor do we discern, that further narrowing the proposed claim to specifically recite "rhuMAb HER2" and "paclitaxel" renders the claim patentable over the prior art.

2133, and 2139, as well as paragraph 56 of Exhibit 2061 and paragraph 11 of Exhibit 2143 are excluded. Further, we do not rely on these references and the reliance by Dr. Kerbel and Patent Owner thereof in our Decision. Thus, we dismiss as moot Petitioner's Motion to Exclude with respect to these exhibits.

Petitioner seeks to exclude Exhibit 2135 "because it is not authenticated under FRE 901, Patent Owner has not demonstrated that it is prior art, and it is hearsay under FRE 802, not within a hearsay exception." Paper 63, 7. Exhibit 2135 is the Hsu abstract discussed above. Petitioner also seeks to exclude Exhibit 2146 "as not authenticated, not prior art, and inadmissible hearsay." Paper 83, 1. Exhibit 2146 is a full copy of the conference proceedings, which contains a copy of the Hsu abstract. Patent Owner relies on Exhibit 2146 to authenticate and to prove the publication date of Hsu. Petitioner further seeks to exclude paragraph 15 of Exhibit 2143, and paragraphs 31 and 32 of Exhibit 2144 because Dr. Kerbel and Dr. Tannenbaum, respectively, relied on Exhibit 2135 in their Declarations. Paper 63, 7.

As explained above, we do not find persuasive Patent Owner's arguments based on the substance of Hsu. *See supra* at 27–28. Accordingly, and taking no position as to the merits of the parties' arguments relating to the admissibility of the Hsu abstract, we dismiss as moot Petitioner's Motion to Exclude as to Exhibits 2135, 2146, as well as paragraph 15 of Exhibit 2143, and paragraphs 31 and 32 of Exhibit 2144.

Patent Owner's Motion to Exclude

Patent Owner filed a Motion to Exclude Exhibits 1033, 1034, 1036, 1055, 1056, 1059, 1060, and 1100, and paragraphs 22, 23, and 38 of Exhibit 1054. Paper 61.

Because we do not rely on Exhibits 1033, 1034, 1036, 1055, 1056, 1059, and 1100, and paragraphs 22, 23, and 38 of Exhibit 1054 in rendering our Decision, we dismiss these aspects of Patent Owner's Motion to Exclude as moot.

Exhibit 1060 is Patent Owner's response submitted in another *inter partes* review IPR2017-01139. As an initial matter, Patent Owner submitted Exhibit 1060 as a public document. We, thus, may take judicial notice of it even if Petitioner has not submitted it in this proceeding. Moreover, as explained above, we presume there is a nexus between Herceptin's success and the challenged claims of the '441 patent. This nexus, however, is weak. This is because Patent Owner has also asserted that the success of Herceptin "is attributable, in part," to the claims of an earlier patent that do not require the combination claimed here. Ex. 1060, 66. And Patent Owner has not apportioned the sales of Herceptin to these two different patents. *Supra* at 40. Because Petitioner's reliance on Exhibit 1060 directly responds to Patent Owner's assertion of commercial success, we deny Patent Owner's Motion to Exclude Exhibit 1060.

Motions to Seal

There is a strong public policy for making all information filed in an *inter partes* review open to the public, especially because the proceeding determines the patentability of claims in an issued patent and, therefore, affects the rights of the public. Generally, all papers filed in an *inter partes*

review shall be made available to the public. *See* 35 U.S.C. § 316(a)(1); 37 C.F.R. § 42.14. Our rules, however, "aim to strike a balance between the public's interest in maintaining a complete and understandable file history and the parties' interest in protecting truly sensitive information." Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,760 (Aug. 14, 2012). Thus, a party may move to seal certain information (37 C.F.R. § 42.14); but only "confidential information" is protected from disclosure (35 U.S.C. § 326(a)(7)). Confidential information means trade secret or other confidential research, development, or commercial information. 37 C.F.R. § 42.2.

The standard for granting a motion to seal is "for good cause." 37 C.F.R. § 42.54(a). The party moving to seal bears the burden of proof and must explain why the information sought to be sealed constitutes confidential information. 37 C.F.R. § 42.20(c).

Confidential information that is subject to a protective order ordinarily becomes public 45 days after final judgment in a trial. Trial Practice Guide, 77 Fed. Reg. at 48761. There is an expectation that confidential information relied upon or identified in a final written decision will be made public. *Id.* A party seeking to maintain the confidentiality of the information may file a motion to expunge the information from the record prior to the information becoming public. 37 C.F.R. § 42.56.

Petitioner's Motions to Seal

In Papers 43 and 64, Petitioner seeks to seal the confidential version of the Reply to Patent Owner's Response (Paper 44), Opposition to Patent Owner's Motion to Amend (Paper 46), and Surreply in Opposition to Patent Owner's Motion to Amend (Paper 67). Petitioner seeks to seal these

documents because they "refer to materials that Patent Owner Genentech has designated as Confidential pursuant to the Modified Default Standing Protective Order." *See, e.g.*, Paper 43, 1. Petitioner seeks to seal Exhibits 1035, 1046, 1049, and 1058 for the same reason. Paper 49, 1.

Petitioner does not provide any other justification for why the redacted portions of these documents should be kept confidential and thus, fails to satisfy the good cause requirement. Accordingly, we deny Petitioner's Motions to Seal.

Patent Owner is invited to file, within 14 days of this Decision, a motion to seal any presently redacted portion of Papers 44, 46, and 67, and Exhibits 1035, 1046, 1049, and 1058. The motion shall (1) attest that the material sought to be protected is not directly or indirectly relied on in this Decision; or (2) to the extent we rely on any of the material sought to be protected in this Decision, provide sufficient justification that outweighs the heightened public interest in understanding the basis for our decision on patentability. Together with the motion to seal, Patent Owner shall file narrowly redacted public version of the documents sought to be sealed.

In the absence of any action on the part of Patent Owner, at the expiration of 14 days from the date of this Decision, the documents-at-issue will be made available to the public.

Patent Owner's Motions to Seal

In Paper 27, Patent Owner seeks to seal the confidential version of the transcript of the deposition of Dr. Earhart (Ex. 2050), the Declaration of Stephanie Mendelsohn (Ex. 2069), and the Declaration of Dr. Hellmann (Ex. 2125). Patent Owner seeks to seal Exhibits 2006, 2126, and 2127. Patent Owner has shown good cause supporting the motion. Insofar as we

do not rely on any of the material sought to be protected in this Decision, Patent Owner's Motion to Seal is granted.

In Paper 54, Patent Owner seeks to seal the confidential version of Patent Owner's Reply in Support of Contingent Motion to Amend (Paper 56), the Supplemental Expert Declaration of Dr. Tannenbaum (Exhibit 2144), as well as Exhibit 2142. Patent Owner has shown good cause supporting the motion. Insofar as we do not expressly rely on any of the material sought to be protected in this Decision, Patent Owner's Motion to Seal is granted.

Modification of Previous Order on Patent Owner's Motion to Seal

We previously granted Patent Owner's Motion to Seal (Paper 7) Exhibit 2001 and the redacted portions of Patent Owner's Preliminary Response, and Exhibits 2002–2005, 2007, and 2008. Paper 24, 2–3.

As explained before, the exhibits sought to be sealed appear to contain confidential business information. *Id.* Insofar as we do not expressly rely on any of the material sought to be protected in this Decision, our decision granting Patent Owner's Motion to Seal remains unchanged.

To the extent we rely on any of the material sought to be protected in this Decision, we modify our previous Order (Paper 24). For example, Patent Owner affirmatively relies upon certain exhibits, including Exhibits 2004 and 2007. We have addressed these exhibits in this Decision.

Patent Owner may, within 14 days of this Decision, renew its motion to seal any portion of the presently protected exhibits that are discussed in this Decision. Because the public has a heightened interest in understanding the basis for our decision on patentability, any renewed motion shall provide sufficient justification that outweighs the public interest. Together with the

renewed motion to seal, Patent Owner shall file narrowly redacted public version of the exhibits sought to be sealed.

In the absence of any action on the part of Patent Owner, at the expiration of 14 days from the date of this Decision, the exhibits-at-issue will be made available to the public.

Redaction of the Final Written Decision

The parties may, within 14 days of this Decision, jointly propose redactions for this Final Written Decision. In the absence of such proposal, at the expiration of 14 days from the date of this Decision, the entirety of the Final Written Decision will be made available to the public.

CONCLUSION

After reviewing the entire record and weighing evidence offered by both parties, we determine that Petitioner has shown, by a preponderance of the evidence, that claims 1–14 of the '441 patent would have been obvious over the combination of Baselga 1996, Seidman 1996, and the 1995 TAXOL PDR entry, and the knowledge of a person of ordinary skill in the art.

We further deny Patent Owner's Motion to Amend because the proposed amended claim improperly introduces new matter.

ORDER

Accordingly, it is

ORDERED that claims 1–14 of the '441 patent are held unpatentable;

FURTHER ORDERED that Patent Owner's Contingent Motion to Amend is denied;

FURTHER ORDERED that Petitioner's Motion to Exclude is dismissed as moot;

FURTHER ORDERED that Patent Owner's Motion to Exclude is denied-in-part and dismissed-in-part; and

FURTHER ORDERED that, because this is a final written decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2017-01121
Patent 7,846,441 B1

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(12) **United States Patent**
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(10) **Patent No.: US 7,846,441 B1**
(45) **Date of Patent: Dec. 7, 2010**

(54) **TREATMENT WITH ANTI-ERBB2 ANTIBODIES**

(75) Inventor: **Susan D. Hellmann**, San Carlos, CA (US)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/208,649**

(22) Filed: **Dec. 10, 1998**

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A61K 39/395 (2006.01)

(52) **U.S. Cl.** **424/143.1**; 424/130.1; 424/133.1; 424/135.1; 424/136.1; 424/141.1; 424/142.1; 424/152.1; 424/155.1; 424/156.1; 424/172.1; 424/174.1

(58) **Field of Classification Search** 424/137.1, 424/138.1, 141.1, 227.1, 152.1, 130.1, 133.1, 424/135.1, 136.1, 142.1, 143.1, 155.1, 156.1, 424/172.1, 174.1
See application file for complete search history.

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(57) **ABSTRACT**

The present invention concerns the treatment of disorders characterized by the overexpression of ErbB2. More specifically, the invention concerns the treatment of human patients susceptible to or diagnosed with cancer overexpressing ErbB2 with a combination of an anti-ErbB2 antibody and a chemotherapeutic agent other than an anthracycline, e.g. doxorubicin or epirubicin.

14 Claims, 2 Drawing Sheets

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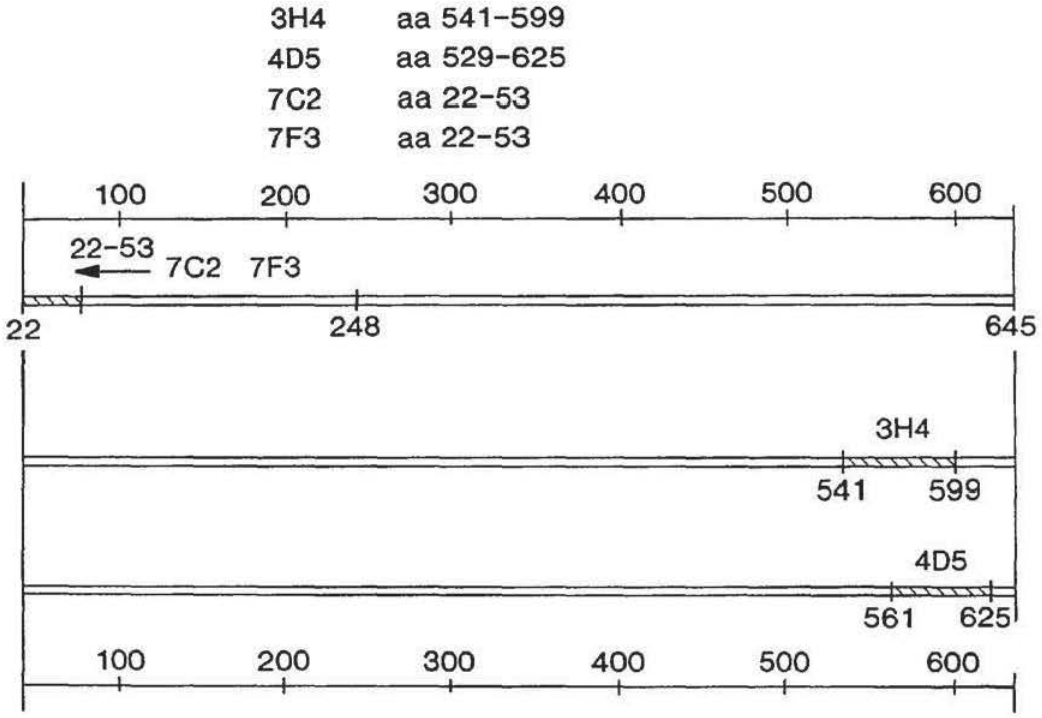
FIG. 1



3H4 epitope (SEQ ID NO:8) 58 residues

VEECRVLQGLPREYVNARHCLPCHPECQPQNGSVTCFGPEADQCVACAHYKDPPFCVAR

541 599

4D5 epitope (SEQ ID NO:9) (64 residues)

LPCHPECQPQNGSVTCFGPEADQCVACAHYKDPPFCVARCPSGVKPDLSYMPIWKFPDEEGACQP

561 625

```
1   MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPA
38  SPETHLDMLRHLYQGCQVVQGNLELTYLPTNASLSFL
75  QDIQEVQGYVLIAHNQVRQVPLQRLRIVRGTQLFEDN
112 YALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTEI
149 LKGGVLIQRNPQLCYQDTILWKDIFHKNNQLALTLID
186 TNRSRA
```

FIG. 2

TREATMENT WITH ANTI-ERBB2 ANTIBODIES

This is a non-provisional application claiming priority to provisional application No. 60/069,346, filed Dec. 12, 1997, the entire disclosure of which is hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention concerns the treatment of disorders characterized by the overexpression of ErbB2. More specifically, the invention concerns the treatment of human patients susceptible to or diagnosed with cancer overexpressing ErbB2 with a combination of an anti-ErbB2 antibody and a chemotherapeutic agent other than an anthracycline, e.g. doxorubicin or epirubicin.

BACKGROUND OF THE INVENTION

Proto-oncogenes that encode growth factors and growth factor receptors have been identified to play important roles in the pathogenesis of various human malignancies, including breast cancer. It has been found that the human ErbB2 gene (erbB2, also known as her2, or c-erbB-2), which encodes a 185-kd transmembrane glycoprotein receptor ($p185^{HER2}$) related to the epidermal growth factor receptor (EGFR), is overexpressed in about 25% to 30% of human breast cancer (Slamon et al., *Science* 235:177-182 [1987]; Slamon et al., *Science* 244:707-712 [1989]).

Several lines of evidence support a direct role for ErbB2 in the pathogenesis and clinical aggressiveness of ErbB2-overexpressing tumors. The introduction of ErbB2 into non-neoplastic cells has been shown to cause their malignant transformation (Hudziak et al., *Proc. Natl. Acad. Sci. USA* 84:7159-7163 [1987]; DiFiore et al., *Science* 237: 178-182 [1987]). Transgenic mice that express HER2 were found to develop mammary tumors (Guy et al., *Proc. Natl. Acad. Sci. USA* 89:10578-10582 [1992]).

Antibodies directed against human erbB2 protein products and proteins encoded by the rat equivalent of the erbB2 gene (neu) have been described. Drebin et al., *Cell* 41:695-706 (1985) refer to an IgG2a monoclonal antibody which is directed against the rat neu gene product. This antibody called 7.16.4 causes down-modulation of cell surface p185 expression on B104-1-1 cells (NIH-3T3 cells transfected with the neu proto-oncogene) and inhibits colony formation of these cells. In Drebin et al. *PNAS* (*USA*) 83:9129-9133 (1986), the 7.16.4 antibody was shown to inhibit the tumorigenic growth of neu-transformed NIH-3T3 cells as well as rat neuroblastoma cells (from which the neu oncogene was initially isolated) implanted into nude mice. Drebin et al. in *Oncogene* 2:387-394 (1988) discuss the production of a panel of antibodies against the rat neu gene product. All of the antibodies were found to exert a cytostatic effect on the growth of neu-transformed cells suspended in soft agar. Antibodies of the IgM, IgG2a and IgG2b isotypes were able to mediate significant in vitro lysis of neu-transformed cells in the presence of complement, whereas none of the antibodies were able to mediate high levels of antibody-dependent cellular cytotoxicity (ADCC) of the neu-transformed cells. Drebin et al. *Oncogene* 2:273-277 (1988) report that mixtures of antibodies reactive with two distinct regions on the p185 molecule result in synergistic anti-tumor effects on neu-transformed NIH-3T3 cells implanted into nude mice. Biological effects of anti-neu antibodies are reviewed in Myers et al., *Meth. Enzym.* 198:277-290 (1991). See also WO94/22478 published Oct. 13, 1994.

Hudziak et al., *Mol. Cell. Biol.* 9(3):1165-1172 (1989) describe the generation of a panel of anti-ErbB2 antibodies which were characterized using the human breast tumor cell line SKBR3. Relative cell proliferation of the SKBR3 cells following exposure to the antibodies was determined by crystal violet staining of the monolayers after 72 hours. Using this assay, maximum inhibition was obtained with the antibody called 4D5 which inhibited cellular proliferation by 56%. Other antibodies in the panel, including 7C2 and 7F3, reduced cellular proliferation to a lesser extent in this assay. Hudziak et al. conclude that the effect of the 4D5 antibody on SKBR3 cells was cytostatic rather than cytotoxic, since SKBR3 cells resumed growth at a nearly normal rate following removal of the antibody from the medium. The antibody 4D5 was further found to sensitize $p185^{erbB2}$-overexpressing breast tumor cell lines to the cytotoxic effects of TNF-α. See also WO89/06692 published Jul. 27, 1989. The anti-ErbB2 antibodies discussed in Hudziak et al. are further characterized in Fendly et al. *Cancer Research* 50:1550-1558 (1990); Kotts et al. *In Vitro* 26(3):59A (1990); Sarup et al. *Growth Regulation* 1:72-82 (1991); Shepard et al. *J. Clin. Immunol.* 11(3):117-127 (1991); Kumar et al. *Mol. Cell. Biol.* 11(2): 979-986 (1991); Lewis et al. *Cancer Immunol. Immunother.* 37:255-263 (1993); Pietras et al. *Oncogene* 9:1829-1838 (1994); Vitetta et al. *Cancer Research* 54:5301-5309 (1994); Sliwkowski et al. *J. Biol. Chem.* 269(20):14661-14665 (1994); Scott et al. *J. Biol. Chem.* 266:14300-5 (1991); and D'souza et al. *Proc. Natl. Acad. Sci.* 91:7202-7206 (1994).

Tagliabue et al. *Int. J. Cancer* 47:933-937 (1991) describe two antibodies which were selected for their reactivity on the lung adenocarcinoma cell line (Calu-3) which overexpresses ErbB2. One of the antibodies, called MGR3, was found to internalize, induce phosphorylation of ErbB2, and inhibit tumor cell growth in vitro.

McKenzie et al. *Oncogene* 4:543-548 (1989) generated a panel of anti-ErbB2 antibodies with varying epitope specificities, including the antibody designated TA1. This TA1 antibody was found to induce accelerated endocytosis of ErbB2 (see Maier et al. *Cancer Res.* 51:5361-5369 [1991]). Bacus et al. *Molecular Carcinogenesis* 3:350-362 (1990) reported that the TA1 antibody induced maturation of the breast cancer cell lines AU-565 (which overexpresses the erbB2 gene) and MCF-7 (which does not). Inhibition of growth and acquisition of a mature phenotype in these cells was found to be associated with reduced levels of ErbB2 receptor at the cell surface and transient increased levels in the cytoplasm.

Stancovski et al. *PNAS* (*USA*) 88:8691-8695 (1991) generated a panel of anti-ErbB2 antibodies, injected them i.p. into nude mice and evaluated their effect on tumor growth of murine fibroblasts transformed by overexpression of the erbB2 gene. Various levels of tumor inhibition were detected for four of the antibodies, but one of the antibodies (N28) consistently stimulated tumor growth. Monoclonal antibody N28 induced significant phosphorylation of the ErbB2 receptor, whereas the other four antibodies generally displayed low or no phosphorylation-inducing activity. The effect of the anti-ErbB2 antibodies on proliferation of SKBR3 cells was also assessed. In this SKBR3 cell proliferation assay, two of the antibodies (N12 and N29) caused a reduction in cell proliferation relative to control. The ability of the various antibodies to induce cell lysis in vitro via complement-dependent cytotoxicity (CDC) and antibody-mediated cell-dependent cytotoxicity (ADCC) was assessed, with the authors of this paper concluding that the inhibitory function of the antibodies was not attributed significantly to CDC or ADCC.

Bacus et al. *Cancer Research* 52:2580-2589 (1992) further characterized the antibodies described in Bacus et al. (1990) and Stancovski et al. of the preceding paragraphs. Extending the i.p. studies of Stancovski et al., the effect of the antibodies after i.v. injection into nude mice harboring mouse fibroblasts overexpressing human ErbB2 was assessed. As observed in their earlier work, N28 accelerated tumor growth whereas N12 and N29 significantly inhibited growth of the ErbB2-expressing cells. Partial tumor inhibition was also observed with the N24 antibody. Bacus et al. also tested the ability of the antibodies to promote a mature phenotype in the human breast cancer cell lines AU-565 and MDA-MB453 (which overexpress ErbB2) as well as MCF-7 (containing low levels of the receptor). Bacus et al. saw a correlation between tumor inhibition in vivo and cellular differentiation; the tumor-stimulatory antibody N28 had no effect on differentiation, and the tumor inhibitory action of the N12, N29 and N24 antibodies correlated with the extent of differentiation they induced.

Xu et al. *Int. J. Cancer* 53:401-408 (1993) evaluated a panel of anti-ErbB2 antibodies for their epitope binding specificities, as well as their ability to inhibit anchorage-independent and anchorage-dependent growth of SKBR3 cells (by individual antibodies and in combinations), modulate cell-surface ErbB2, and inhibit ligand stimulated anchorage-independent growth. See also WO94/00136 published Jan. 6, 1994 and Kasprzyk et al. *Cancer Research* 52:2771-2776 (1992) concerning anti-ErbB2 antibody combinations. Other anti-ErbB2 antibodies are discussed in Hancock et al. *Cancer Res.* 51:4575-4580 (1991); Shawver et al. *Cancer Res.* 54:1367-1373 (1994); Arteaga et al. *Cancer Res.* 54:3758-3765 (1994); and Harwerth et al. *J. Biol. Chem.* 267:15160-15167 (1992).

A recombinant humanized anti-ErbB2 monoclonal antibody (a humanized version of the murine anti-ErbB2 antibody 4D5, referred to as rhuMAb HER2 or HERCEPTIN®) has been clinically active in patients with ErbB2-overexpressing metastatic breast cancers that had received extensive prior anti-cancer therapy (Baselga et al., *J. Clin. Oncol.* 14:737-744 [1996]).

ErbB2 overexpression is commonly regarded as a predictor of a poor prognosis, especially in patients with primary disease that involves axillary lymph nodes (Slamon et al., [1987] and [1989], supra; Ravdin and Chamness, *Gene* 159:19-27 [1995]; and Hynes and Stern, *Biochim Biophys Acta* 1198: 165-184 [1994]), and has been linked to sensitivity and/or resistance to hormone therapy and chemotherapeutic regimens, including CMF (cyclophosphamide, methotrexate, and fluoruracil) and anthracyclines (Baselga et al., *Oncology* 11(3 Suppl 2):43-48 [1997]). However, despite the association of ErbB2 overexpression with poor prognosis, the odds of HER2-positive patients responding clinically to treatment with taxanes were greater than three times those of HER2-negative patients (Ibid). rhuMab HER2 was shown to enhance the activity of paclitaxel (TAXOL®) and doxorubicin against breast cancer xenografts in nude mice injected with BT-474 human breast adenocarcinoma cells, which express high levels of HER2 (Baselga et al., *Breast Cancer, Proceedings of ASCO*, Vol. 13, Abstract 53 [1994]).

SUMMARY OF THE INVENTION

The present invention concerns the treatment of disorders characterized by overexpression of ErbB2, and is based on the recognition that while treatment with anti-ErbB2 antibodies markedly enhances the clinical benefit of the use of chemotherapeutic agents in general, a syndrome of myocardial dysfunction that has been observed as a side-effect of anthracycline derivatives is increased by the administration of anti-ErbB2 antibodies.

Accordingly, the invention concerns a method for the treatment of a human patient susceptible to or diagnosed with a disorder characterized by overexpression of ErbB2 receptor comprising administering a therapeutically effective amount of a combination of an anti-ErbB2 antibody and a chemotherapeutic agent other than an anthracycline derivative, e.g. doxorubicin or epirubicin, in the absence of an anthracycline derivative, to the human patient.

The disorder preferably is a benign or malignant tumor characterized by the overexpression of the ErbB2 receptor, e.g. a cancer, such as, breast cancer, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, colon cancer, colorectal cancer, endometrial carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer. The chemotherapeutic agent preferably is a taxoid, such as TAXOL® (paclitaxel) or a TAXOL® derivative.

Although an antiproliferative effect is sufficient, in a preferred embodiment, the anti-ErbB2 antibody is capable of inducing cell death or is capable of inducing apoptosis. Preferred anti-ErbB2 antibodies bind the extracellular domain of the ErbB2 receptor, and preferably bind to the epitope 4D5 or 3H4 within the ErbB2 extracellular domain sequence. More preferably, the antibody is the antibody 4D5, most preferably in a humanized form.

The method of the present invention is particularly suitable for the treatment of breast or ovarian cancer, characterized by the overexpression of the ErbB2 receptor.

In another aspect, the invention concerns an article of manufacture, comprising a container, a composition within the container comprising an anti-ErbB2 antibody, optionally a label on or associated with the container that indicates that the composition can be used for treating a condition characterized by overexpression of ErbB2 receptor, and a package insert containing instructions to avoid the use of anthracycline-type chemotherapeutics in combination with the composition.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows epitope-mapping of the extracellular domain of ErbB2 as determined by truncation mutant analysis and site-directed mutagenesis (Nakamura et al. *J. of Virology* 67(10):6179-6191 [October 1993]; Renz et al. *J. Cell Biol.* 125(6):1395-1406 [June 1994]). The anti-proliferative MAbs 4D5 and 3H4 bind adjacent to the transmembrane domain. The various ErbB2-ECD truncations or point mutations were prepared from cDNA using polymerase chain reaction technology. The ErbB2 mutants were expressed as gD fusion proteins in a mammalian expression plasmid. This expression plasmid uses the cytomegalovirus promoter/enhancer with SV40 termination and polyadenylation signals located downstream of the inserted cDNA. Plasmid DNA was transfected into 293S cells. One day following transfection, the cells were metabolically labeled overnight in methionine and cysteine-free, low glucose DMEM containing 1% dialyzed fetal bovine serum and 25 μCi each of ^{35}S methionine and ^{35}S cysteine. Supernatants were harvested either the ErbB2 MAbs or control antibodies were added to the supernatant and incubated 2-4 hours at 4° C. The complexes were precipitated, applied to a 10-20% Tricine SDS gradient gel and

electrophoresed at 100 V. The gel was electroblotted onto a membrane and analyzed by autoradiography. SEQ ID NOs:8 and 9 depict the 3H4 and 4D5 epitopes, respectively.

FIG. **2** depicts with underlining the amino acid sequence of Domain 1 of ErbB2 (SEQ ID NO:1). Bold amino acids indicate the location of the epitope recognized by MAbs 7C2 and 7F3 as determined by deletion mapping, i.e. the "7C2/7F3 epitope" (SEQ ID NO:2).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. Definitions

The terms "HER2", "ErbB2" "c-Erb-B2" are used interchangeably. Unless indicated otherwise, the terms "ErbB2" "c-Erb-B2" and "HER2" when used herein refer to the human protein and "her2", "erbB2" and "c-erb-B2" refer to human gene. The human erbB2 gene and ErbB2 protein are, for example, described in Semba et al, *PNAS* (*USA*) 82:6497-6501 (1985) and Yamamoto et al. *Nature* 319:230-234 (1986) (Genebank accession number X03363). ErbB2 comprises four domains (Domains 1-**4**).

The "epitope 4D5" is the region in the extracellular domain of ErbB2 to which the antibody 4D5 (ATCC CRL 10463) binds. This epitope is close to the transmembrane region of ErbB2. To screen for antibodies which bind to the 4D5 epitope, a routine cross-blocking assay such as that described in *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988), can be performed. Alternatively, epitope mapping can be performed (see FIG. **1**) to assess whether the antibody binds to the 4D5 epitope of ErbB2 (i.e. any one or more residues in the region from about residue 529, e.g. about residue 561 to about residue 625, inclusive).

The "epitope 3H4" is the region in the extracellular domain of ErbB2 to which the antibody 3H4 binds. This epitope is shown in FIG. **1**, and includes residues from about 541 to about 599, inclusive, in the amino acid sequence of ErbB2 extracellular domain.

The "epitope 7C2/7F3" is the region at the N terminus of the extracellular domain of ErbB2 to which the 7C2 and/or 7F3 antibodies (each deposited with the ATCC, see below) bind. To screen for antibodies which bind to the 7C2/7F3 epitope, a routine cross-blocking assay such as that described in *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988), can be performed. Alternatively, epitope mapping can be performed to establish whether the antibody binds to the 7C2/7F3 epitope on ErbB2 (i.e. any one or more of residues in the region from about residue 22 to about residue 53 of ErbB2; SEQ ID NO:2).

The term "induces cell death" or "capable of inducing cell death" refers to the ability of the antibody to make a viable cell become nonviable. The "cell" here is one which expresses the ErbB2 receptor, especially where the cell overexpresses the ErbB2 receptor. A cell which "overexpresses" ErbB2 has significantly higher than normal ErbB2 levels compared to a noncancerous cell of the same tissue type. Preferably, the cell is a cancer cell, e.g. a breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon, thyroid, pancreatic or bladder cell. In vitro, the cell may be a SKBR3, BT474, Calu 3, MDA-MB-453, MDA-MB-361 or SKOV3 cell. Cell death in vitro may be determined in the absence of complement and immune effector cells to distinguish cell death induced by antibody dependent cellular cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC). Thus, the assay for cell death may be performed using heat inactivated serum (i.e. in the absence of complement) and in the absence of immune effector cells. To determine whether the antibody is able to induce cell death, loss of membrane integrity as evaluated by uptake of propidium iodide (PI), trypan blue (see Moore et al. *Cytotechnology* 17:1-11 [1995]) or 7AAD can be assessed relative to untreated cells. Preferred cell death-inducing antibodies are those which induce PI uptake in the "PI uptake assay in BT474 cells".

The phrase "induces apoptosis" or "capable of inducing apoptosis" refers to the ability of the antibody to induce programmed cell death as determined by binding of annexin V, fragmentation of DNA, cell shrinkage, dilation of endoplasmic reticulum, cell fragmentation, and/or formation of membrane vesicles (called apoptotic bodies). The cell is one which overexpresses the ErbB2 receptor. Preferably the "cell" is a tumor cell, e.g. a breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon, thyroid, pancreatic or bladder cell. In vitro, the cell may be a SKBR3, BT474, Calu 3 cell, MDA-MB-453, MDA-MB-361 or SKOV3 cell. Various methods are available for evaluating the cellular events associated with apoptosis. For example, phosphatidyl serine (PS) translocation can be measured by annexin binding; DNA fragmentation can be evaluated through DNA laddering as disclosed in the example herein; and nuclear/chromatin condensation along with DNA fragmentation can be evaluated by any increase in hypodiploid cells. Preferably, the antibody which induces apoptosis is one which results in about 2 to 50 fold, preferably about 5 to 50 fold, and most preferably about 10 to 50 fold, induction of annexin binding relative to untreated cell in an "annexin binding assay using BT474 cells" (see below).

Sometimes the pro-apoptotic antibody will be one which blocks HRG binding/activation of the ErbB2/ErbB3 complex (e.g. 7F3 antibody). In other situations, the antibody is one which does not significantly block activation of the ErbB2/ErbB3 receptor complex by HRG (e.g. 7C2). Further, the antibody may be one like 7C2 which, while inducing apoptosis, does not induce a large reduction in the percent of cells in S phase (e.g. one which only induces about 0-10% reduction in the percent of these cells relative to control).

The antibody of interest may be one like 7C2 which binds specifically to human ErbB2 and does not significantly cross-react with other proteins such as those encoded by the erbB1, erbB3 and/or erbB4 genes. Sometimes, the antibody may not significantly cross-react with the rat neu protein, e.g., as described in Schecter et al. *Nature* 312:513 (1984) and Drebin et al., *Nature* 312:545-548 (1984). In such embodiments, the extent of binding of the antibody to these proteins (e.g., cell surface binding to endogenous receptor) will be less than about 10% as determined by fluorescence activated cell sorting (FACS) analysis or radioimmunoprecipitation (RIA).

"Heregulin" (HRG) when used herein refers to a polypeptide which activates the ErbB2-ErbB3 and ErbB2-ErbB4 protein complexes (i.e. induces phosphorylation of tyrosine residues in the complex upon binding thereto). Various heregulin polypeptides encompassed by this term are disclosed in Holmes et al., *Science,* 256:1205-1210 (1992); WO 92/20798; Wen et al., *Mol. Cell. Biol.,* 14(3):1909-1919 (1994); and Marchionni et al., *Nature,* 362:312-318 (1993), for example. The term includes biologically active fragments and/or variants of a naturally occurring HRG polypeptide, such as an EGF-like domain fragment thereof (e.g. $HRG\beta1_{177-244}$).

The "ErbB2-ErbB3 protein complex" and "ErbB2-ErbB4 protein complex" are noncovalently associated oligomers of

the ErbB2 receptor and the ErbB3 receptor or ErbB4 receptor, respectively. The complexes form when a cell expressing both of these receptors is exposed to HRG and can be isolated by immunoprecipitation and analyzed by SDS-PAGE as described in Sliwkowski et al., *J. Biol. Chem.*, 269(20): 14661-14665 (1994).

"Antibodies" (Abs) and "immunoglobulins" (Igs) are glycoproteins having the same structural characteristics. While antibodies exhibit binding specificity to a specific antigen, immunoglobulins include both antibodies and other antibody-like molecules which lack antigen specificity. Polypeptides of the latter kind are, for example, produced at low levels by the lymph system and at increased levels by myelomas.

"Native antibodies" and "native immunoglobulins" are usually heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain at one end (V_L) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light-chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light- and heavy-chain variable domains.

The term "variable" refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. However, the variability is not evenly distributed throughout the variable domains of antibodies. It is concentrated in three segments called complementarity-determining regions (CDRs) or hypervariable regions both in the light-chain and the heavy-chain variable domains. The more highly conserved portions of variable domains are called the framework region (FR). The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a n-sheet configuration, connected by three CDRs, which form loops connecting, and in some cases forming part of, the n-sheet structure. The CDRs in each chain are held together in close proximity by the FRs and, with the CDRs from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat et al., *NIH Publ. No.* 91-3242, Vol. I, pages 647-669 [1991]). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an $F(ab')_2$ fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2. The heavy-chain constant domains that correspond to the different classes of immunoglobulins are called α, δ, ε, γ, and μ, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

The term "antibody" is used in the broadest sense and specifically covers intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g. bispecific antibodies) formed from at least two intact antibodies, and antibody fragments so long as they exhibit the desired biological activity.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies (Zapata et al. *Protein Eng.* 8(10):1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler et al., *Nature*, 256:495 (1975), or may be made by recombinant DNA methods (see, e.g., U.S. Pat. No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the

techniques described in Clackson et al., *Nature,* 352:624-628 (1991) and Marks et al., *J. Mol. Biol.,* 222:581-597 (1991), for example.

The monoclonal antibodies herein specifically include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Pat. No. 4,816,567; Morrison et al, *Proc. Natl. Acad. Sci. USA,* 81; 6851-6855 [1984]).

"Humanized" forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementarity determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications are made to further refine and maximize antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDRs correspond to those of a non-human immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones et al., *Nature,* 321:522-525 (1986); Reichmann et al, *Nature,* 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.,* 2:593-596 (1992). The humanized antibody includes a PRIMATIZEDT™ antibody wherein the antigen-binding region of the antibody is derived from an antibody produced by immunizing macaque monkeys with the antigen of interest.

"Single-chain Fv" or "sFv" antibody fragments comprise the V_H and V_L domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv see Plückthun in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenburg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) in the same polypeptide chain (V_H-V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., *Proc. Natl. Acad. Sci. USA,* 90:6444-6448 (1993).

An "isolated" antibody is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

As used herein, the term "salvage receptor binding epitope" refers to an epitope of the Fc region of an IgG molecule (e.g., IgG_1, IgG_2, IgG_3, or IgG_4) that is responsible for increasing the in vivo serum half-life of the IgG molecule.

"Treatment" refers to both therapeutic treatment and prophylactic or preventative measures. Those in need of treatment include those already with the disorder as well as those in which the disorder is to be prevented.

"Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, etc. Preferably, the mammal is human.

A "disorder" is any condition that would benefit from treatment with the anti-ErbB2 antibody. This includes chronic and acute disorders or diseases including those pathological conditions which predispose the mammal to the disorder in question. Non-limiting examples of disorders to be treated herein include benign and malignant tumors; leukemias and lymphoid malignancies; neuronal, glial, astrocytal, hypothalamic and other glandular, macrophagal, epithelial, stromal and blastocoelic disorders; and inflammatory, angiogenic and immunologic disorders.

The term "therapeutically effective amount" is used to refer to an amount having antiproliferative effect. Preferably, the therapeutically effective amount has apoptotic activity, or is capable of inducing cell death, and preferably death of benign or malignant tumor cells, in particular cancer cells. Efficacy can be measured in conventional ways, depending on the condition to be treated. For cancer therapy, efficacy can, for example, be measured by assessing the time to disease progression (TTP), or determining the response rates (RR) (see the Example below).

The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia. More particular examples of such cancers include squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer.

The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (e.g., I^{131}, I^{125}, Y^{90} and Re^{186}), chemo-

therapeutic agents, and toxins such as enzymatically active toxins of bacterial, fungal, plant or animal origin, or fragments thereof.

A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include adriamycin, doxorubicin, epirubicin, 5-fluorouracil, cytosine arabinoside ("Ara-C"), cyclophosphamide, thiotepa, busulfan, cytoxin, taxoids, e.g. paclitaxel (TAXOL®, Bristol-Myers Squibb Oncology, Princeton, N.J.) and docetaxel (Taxotere®, Rhône-Poulenc Rorer, Antony, France), methotrexate, cisplatin, melphalan, vinblastine, bleomycin, etoposide, ifosfamide, mitomycin C, mitoxantrone, vincristine, vinorelbine, carboplatin, teniposide, daunomycin, caminomycin, aminopterin, dactinomycin, mitomycins, esperamicins (see U.S. Pat. No. 4,675,187), melphalan and other related nitrogen mustards. Also included in this definition are hormonal agents that act to regulate or inhibit hormone action on tumors such as tamoxifen and onapristone.

A "growth inhibitory agent" when used herein refers to a compound or composition which inhibits growth of a cell, especially an ErbB2-overexpressing cancer cell either in vitro or in vivo. Thus, the growth inhibitory agent is one which significantly reduces the percentage of ErbB2 overexpressing cells in S phase. Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), TAXOL®, and topo II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in *The Molecular Basis of Cancer*, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogenes, and antineoplastic drugs" by Murakami et al. (WB Saunders: Philadelphia, 1995), especially p. 13. The 4D5 antibody (and functional equivalents thereof) can also be employed for this purpose.

"Doxorubicin" is an athracycline antibiotic. The full chemical name of doxorubicin is (8S-cis)-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione.

The term "cytokine" is a generic term for proteins released by one cell population which act on another cell as intercellular mediators. Examples of such cytokines are lymphokines, monokines, and traditional polypeptide hormones. Included among the cytokines are growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor-α and -β; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF-β; platelet-growth factor; transforming growth factors (TGFs) such as TGF-α and TGF-β; insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as interferon-α, -β, and -γ; colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1α, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12; a tumor necrosis factor such as TNF-α or TNF-β; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native sequence cytokines.

The term "prodrug" as used in this application refers to a precursor or derivative form of a pharmaceutically active substance that is less cytotoxic to tumor cells compared to the parent drug and is capable of being enzymatically activated or converted into the more active parent form. See, e.g., Wilman, "Prodrugs in Cancer Chemotherapy" *Biochemical Society Transactions*, 14, pp. 375-382, 615th Meeting Belfast (1986) and Stella et al., "Prodrugs: A Chemical Approach to Targeted Drug Delivery," *Directed Drug Delivery*, Borchardt et al., (ed.), pp. 247-267, Humana Press (1985). The prodrugs of this invention include, but are not limited to, phosphate-containing prodrugs, thiophosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs, D-amino acid-modified prodrugs, glycosylated prodrugs, β-lactam-containing prodrugs, optionally substituted phenoxyacetamide-containing prodrugs or optionally substituted phenylacetamide-containing prodrugs, 5-fluorocytosine and other 5-fluorouridine prodrugs which can be converted into the more active cytotoxic free drug. Examples of cytotoxic drugs that can be derivatized into a prodrug form for use in this invention include, but are not limited to, those chemotherapeutic agents described above.

By "solid phase" is meant a non-aqueous matrix to which the antibodies used in accordance with the present invention can adhere. Examples of solid phases encompassed herein include those formed partially or entirely of glass (e.g., controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (e.g., an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U.S. Pat. No. 4,275,149.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as the anti-ErbB2 antibodies disclosed herein and, optionally, a chemotherapeutic agent) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

II. Production of Anti-ErbB2 Antibodies

A description follows as to exemplary techniques for the production of the antibodies used in accordance with the present invention. The ErbB2 antigen to be used for production of antibodies may be, e.g., a soluble form of the extracellular domain of ErbB2 or a portion thereof, containing the desired epitope. Alternatively, cells expressing ErbB2 at their cell surface (e.g. NIH-3T3 cells transformed to overexpress ErbB2; or a carcinoma cell line such as SKBR3 cells, see Stancovski et al. *PNAS* (*USA*) 88:8691-8695 [1991]) can be used to generate antibodies. Other forms of ErbB2 useful for generating antibodies will be apparent to those skilled in the art.

(i) Polyclonal Antibodies

Polyclonal antibodies are preferably raised in animals by multiple subcutaneous (sc) or intraperitoneal (ip) injections of the relevant antigen and an adjuvant. It may be useful to conjugate the relevant antigen to a protein that is immunogenic in the species to be immunized, e.g., keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor using a bifunctional or derivatizing agent, for example, maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-hydroxysuccinimide (through lysine residues), glutaraldehyde, succinic anhydride, $SOCl_2$, or $R^1N{=}C{=}NR$, where R and R^1 are different alkyl groups.

Animals are immunized against the antigen, immunogenic conjugates, or derivatives by combining, e.g., 100 μg or 5 μg of the protein or conjugate (for rabbits or mice, respectively) with 3 volumes of Freund's complete adjuvant and injecting the solution intradermally at multiple sites. One month later the animals are boosted with ⅕ to 1/10 the original amount of peptide or conjugate in Freund's complete adjuvant by subcutaneous injection at multiple sites. Seven to 14 days later the animals are bled and the serum is assayed for antibody titer. Animals are boosted until the titer plateaus. Preferably, the animal is boosted with the conjugate of the same antigen, but conjugated to a different protein and/or through a different cross-linking reagent. Conjugates also can be made in recombinant cell culture as protein fusions. Also, aggregating agents such as alum are suitably used to enhance the immune response.

(ii) Monoclonal Antibodies

Monoclonal antibodies are obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Thus, the modifier "monoclonal" indicates the character of the antibody as not being a mixture of discrete antibodies.

For example, the monoclonal antibodies may be made using the hybridoma method first described by Kohler et al., *Nature,* 256:495 (1975), or may be made by recombinant DNA methods (U.S. Pat. No. 4,816,567).

In the hybridoma method, a mouse or other appropriate host animal, such as a hamster, is immunized as hereinabove described to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized in vitro. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, *Monoclonal Antibodies: Principles and Practice*, pp. 59-103 [Academic Press, 1986]).

The hybridoma cells thus prepared are seeded and grown in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

Preferred myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. Among these, preferred myeloma cell lines are murine myeloma lines, such as those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, Calif. USA, and SP-2 or X63-Ag8-653 cells available from the American Type Culture Collection, Rockville, Md. USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, *J. Immunol.,* 133:3001 (1984); Brodeur et al., *Monoclonal Antibody Production Techniques and Applications*, pp. 51-63 [Marcel Dekker, Inc., New York, 1987]).

Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA).

The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson et al., *Anal. Biochem.,* 107:220 (1980).

After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding, *Monoclonal Antibodies: Principles and Practice*, pp. 59-103 [Academic Press, 1986]). Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown in vivo as ascites tumors in an animal.

The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Review articles on recombinant expression in bacteria of DNA encoding the antibody include Skerra et al., *Curr. Opinion in Immunol.,* 5:256-262 (1993) and Plückthun, *Immunol. Revs.,* 130:151-188 (1992).

In a further embodiment, antibodies or antibody fragments can be isolated from antibody phage libraries generated using the techniques described in McCafferty et al., *Nature,* 348:552-554 (1990). Clackson et al., *Nature,* 352:624-628 (1991) and Marks et al., *J. Mol. Biol.,* 222:581-597 (1991) describe the isolation of murine and human antibodies, respectively, using phage libraries. Subsequent publications describe the production of high affinity (nM range) human antibodies by chain shuffling (Marks et al., *Bio/Technology,* 10:779-783 [1992]), as well as combinatorial infection and in vivo recombination as a strategy for constructing very large phage libraries (Waterhouse et al., *Nuc. Acids. Res.,* 21:2265-2266 [1993]). Thus, these techniques are viable alternatives to traditional monoclonal antibody hybridoma techniques for isolation of monoclonal antibodies.

The DNA also may be modified, for example, by substituting the coding sequence for human heavy- and light-chain constant domains in place of the homologous murine sequences (U.S. Pat. No. 4,816,567; Morrison, et al., *Proc.*

Natl. Acad. Sci. USA, 81:6851 [1984]), or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide.

Typically such non-immunoglobulin polypeptides are substituted for the constant domains of an antibody, or they are substituted for the variable domains of one antigen-combining site of an antibody to create a chimeric bivalent antibody comprising one antigen-combining site having specificity for an antigen and another antigen-combining site having specificity for a different antigen.

(iii) Humanized and Human Antibodies

Methods for humanizing non-human antibodies are well known in the art. Preferably, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers (Jones et al., *Nature,* 321:522-525 (1986); Riechmann et al., *Nature,* 332:323-327 (1988); Verhoeyen et al., *Science,* 239:1534-1536 [1988]), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Pat. No. 4,816,567) wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies is very important to reduce antigenicity. According to the so-called "best-fit" method, the sequence of the variable domain of a rodent antibody is screened against the entire library of known human variable-domain sequences. The human sequence which is closest to that of the rodent is then accepted as the human framework region (FR) for the humanized antibody (Sims et al., *J. Immunol.,* 151:2296 (1993); Chothia et al., *J. Mol. Biol.,* 196:901 [1987]). Another method uses a particular framework region derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies (Carter et al., *Proc. Natl. Acad. Sci. USA,* 89:4285 (1992); Presta et al., *J. Immunol.,* 151:2623 [1993]).

It is further important that antibodies be humanized with retention of high affinity for the antigen and other favorable biological properties. To achieve this goal, according to a preferred method, humanized antibodies are prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the CDR residues are directly and most substantially involved in influencing antigen binding.

Alternatively, it is now possible to produce transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, it has been described that the homozygous deletion of the antibody heavy-chain joining region (J_H) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array in such germ-line mutant mice will result in the production of human antibodies upon antigen challenge. See, e.g., Jakobovits et al., *Proc. Natl. Acad. Sci. USA,* 90:2551 (1993); Jakobovits et al., *Nature,* 362:255-258 (1993); Bruggermann et al., *Year in Immuno.,* 7:33 (1993). Human antibodies can also be derived from phage-display libraries (Hoogenboom et al., *J. Mol. Biol.,* 227:381 (1991); Marks et al., *J. Mol. Biol.,* 222:581-597 [1991]).

(iv) Antibody Fragments

Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (see, e.g., Morimoto et al., *Journal of Biochemical and Biophysical Methods* 24:107-117 (1992) and Brennan et al., *Science,* 229:81 [1985]). However, these fragments can now be produced directly by recombinant host cells. For example, the antibody fragments can be isolated from the antibody phage libraries discussed above. Alternatively, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form $F(ab')_2$ fragments (Carter et al., Bio/Technology 10:163-167 [1992]). According to another approach, $F(ab')_2$ fragments can be isolated directly from recombinant host cell culture. Other techniques for the production of antibody fragments will be apparent to the skilled practitioner. In other embodiments, the antibody of choice is a single chain Fv fragment (scFv). See WO 93/16185.

(v) Bispecific Antibodies

Bispecific antibodies are antibodies that have binding specificities for at least two different epitopes. Exemplary bispecific antibodies may bind to two different epitopes of the ErbB2 protein. For example, one arm may bind an epitope in Domain 1 of ErbB2 such as the 7C2/7F3 epitope, the other may bind a different ErbB2 epitope, e.g. the 4D5 epitope. Other such antibodies may combine an ErbB2 binding site with binding site(s) for EGFR, ErbB3 and/or ErbB4. Alternatively, an anti-ErbB2 arm may be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD2 or CD3), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) so as to focus cellular defense mechanisms to the ErbB2-expressing cell. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express ErbB2. These antibodies possess an ErbB2-binding arm and an arm which binds the cytotoxic agent (e.g. saporin, anti-interferon-α, vinca alkaloid, ricin A chain, methotrexate or radioactive isotope hapten). Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. $F(ab')_2$ bispecific antibodies).

Methods for making bispecific antibodies are known in the art. Traditional production of full length bispecific antibodies is based on the coexpression of two immunoglobulin heavy chain-light chain pairs, where the two chains have different specificities (Millstein et al., *Nature,* 305:537-539 [1983]). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. Purification of the correct molecule, which is usually done by affinity

chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed in WO 93/08829, and in Traunecker et al., *EMBO J.*, 10:3655-3659 (1991).

According to a different approach, antibody variable domains with the desired binding specificities (antibody-antigen combining sites) are fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light chain binding, present in at least one of the fusions. DNAs encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. This provides for great flexibility in adjusting the mutual proportions of the three polypeptide fragments in embodiments when unequal ratios of the three polypeptide chains used in the construction provide the optimum yields. It is, however, possible to insert the coding sequences for two or all three polypeptide chains in one expression vector when the expression of at least two polypeptide chains in equal ratios results in high yields or when the ratios are of no particular significance.

In a preferred embodiment of this approach, the bispecific antibodies are composed of a hybrid immunoglobulin heavy chain with a first binding specificity in one arm, and a hybrid immunoglobulin heavy chain-light chain pair (providing a second binding specificity) in the other arm. It was found that this asymmetric structure facilitates the separation of the desired bispecific compound from unwanted immunoglobulin chain combinations, as the presence of an immunoglobulin light chain in only one half of the bispecific molecule provides for a facile way of separation. This approach is disclosed in WO 94/04690. For further details of generating bispecific antibodies see, for example, Suresh et al., *Methods in Enzymology,* 121:210 (1986).

According to another approach described in WO96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the C_H3 domain of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies include cross-linked or "heteroconjugate" antibodies. For example, one of the antibodies in the heteroconjugate can be coupled to avidin, the other to biotin. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Pat. No. 4,676,980), and for treatment of HIV infection (WO 91/00360, WO 92/200373, and EP 03089). Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in U.S. Pat. No. 4,676,980, along with a number of cross-linking techniques.

Techniques for generating bispecific antibodies from antibody fragments have also been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., *Science,* 229: 81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate $F(ab')_2$ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Recent progress has facilitated the direct recovery of Fab'-SH fragments from *E. coli*, which can be chemically coupled to form bispecific antibodies. Shalaby et al., *J. Exp. Med,* 175: 217-225 (1992) describe the production of a fully humanized bispecific antibody $F(ab')_2$ molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling in vitro to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., *J. Immunol.,* 148(5): 1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al., *Proc. Natl. Acad. Sci. USA,* 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See Gruber et al., *J. Immunol.,* 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt et al. *J. Immunol.* 147: 60 (1991).

(vi) Screening for Antibodies with the Desired Properties

Techniques for generating antibodies have been described above. Those antibodies having the characteristics described herein are selected.

To select for antibodies which induce cell death, loss of membrane integrity as indicated by, e.g., PI, trypan blue or 7AAD uptake is assessed relative to control. The preferred assay is the "PI uptake assay using BT474 cells". According to this assay, BT474 cells (which can be obtained from the American Type Culture Collection [Rockville, Md.]) are cultured in Dulbecco's Modified Eagle Medium (D-MEM): Ham's F-12 (50:50) supplemented with 10% heat-inactivated FBS (Hyclone) and 2 mM L-glutamine. (Thus, the assay is performed in the absence of complement and immune effector cells). The BT474 cells are seeded at a density of 3×10^6 per dish in 100×20 mm dishes and allowed to attach overnight. The medium is then removed and replaced with fresh medium alone or medium containing 10 μg/ml of the appropriate

MAb. The cells are incubated for a 3 day time period. Following each treatment, monolayers are washed with PBS and detached by trypsinization. Cells are then centrifuged at 1200 rpm for 5 minutes at 4° C., the pellet resuspended in 3 ml ice cold Ca^{2+} binding buffer (10 mM Hepes, pH 7.4, 140 mM NaCl, 2.5 mM $CaCl_2$) and aliquoted into 35 mm strainer-capped 12×75 tubes (1 ml per tube, 3 tubes per treatment group) for removal of cell clumps. Tubes then receive PI (10 μg/ml). Samples may be analyzed using a FACSCAN™ flow cytometer and FACSCONVERT™ CellQuest software (Becton Dickinson). Those antibodies which induce statistically significant levels of cell death as determined by PI uptake are selected.

In order to select for antibodies which induce apoptosis, an "annexin binding assay using BT474 cells" is available. The BT474 cells are cultured and seeded in dishes as discussed in the preceding paragraph. The medium is then removed and replaced with fresh medium alone or medium containing 10 μg/ml of the MAb. Following a three day incubation period, monolayers are washed with PBS and detached by trypsinization. Cells are then centrifuged, resuspended in Ca^{2+} binding buffer and aliquoted into tubes as discussed above for the cell death assay. Tubes then receive labeled annexin (e.g. annexin V-FTIC) (1 μg/ml). Samples may be analyzed using a FACSCAN™ flow cytometer and FACSCONVERT™ CellQuest software (Becton Dickinson). Those antibodies which induce statistically significant levels of annexin binding relative to control are selected as apoptosis-inducing antibodies.

In addition to the annexin binding assay, a "DNA staining assay using BT474 cells" is available. In order to perform this assay, BT474 cells which have been treated with the antibody of interest as described in the preceding two paragraphs are incubated with 9 μg/ml HOECHST 33342™ for 2 hr at 37° C., then analyzed on an EPICS ELITE™ flow cytometer (Coulter Corporation) using MODFIT LT™ software (Verity Software House). Antibodies which induce a change in the percentage of apoptotic cells which is 2 fold or greater (and preferably 3 fold or greater) than untreated cells (up to 100% apoptotic cells) may be selected as pro-apoptotic antibodies using this assay.

To screen for antibodies which bind to an epitope on ErbB2 bound by an antibody of interest, a routine cross-blocking assay such as that described in *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988), can be performed. Alternatively, epitope mapping can be performed by methods known in the art.

To identify anti-ErbB2 antibodies which inhibit growth of SKBR3 cells in cell culture by 50-100%, the SKBR3 assay described in WO89/06692 can be performed. According to this assay, SKBR3 cells are grown in a 1:1 mixture of F12 and DMEM medium supplemented with 10% fetal bovine serum, glutamine and penicillinstreptomycin. The SKBR3 cells are plated at 20,000 cells in a 35 mm cell culture dish (2 mls/35 mm dish). 2.5 μg/ml of the anti-ErbB2 antibody is added per dish. After six days, the number of cells, compared to untreated cells are counted using an electronic COULTER™ cell counter. Those antibodies which inhibit growth of the SKBR3 cells by 50-100% are selected for combination with the apoptotic antibodies as desired.

(vii) Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, so as to enhance the effectiveness of the antibody in treating cancer, for example. For example cysteine residue(s) may be introduced in the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron et al., *J. Exp Med.* 176:1191-1195 (1992) and Shopes, B. *J. Immunol.* 148:2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff et al. *Cancer Research* 53:2560-2565 (1993). Alternatively, an antibody can be engineered which has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson et al. *Anti-Cancer Drug Design* 3:219-230 (1989).

(viii) Immunoconjugates

The invention also pertains to immunoconjugates comprising the antibody described herein conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (e.g. an enzymatically active toxin of bacterial, fungal, plant or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof which can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), *momordica charantia* inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated anti-ErbB2 antibodies. Examples include ^{212}Bi, ^{131}I, ^{131}In, ^{90}Y and ^{186}Re.

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutareldehyde), bis-azido compounds (such as bis(p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al. *Science* 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

In another embodiment, the antibody may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (e.g. avidin) which is conjugated to a cytotoxic agent (e.g. a radionucleotide).

(ix) Immunoliposomes

The anti-ErbB2 antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein et al., *Proc. Natl. Acad. Sci. USA*, 82:3688 (1985); Hwang et al., *Proc. Natl. Acad. Sci. USA*, 77:4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Pat. No. 5,013,556.

Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-de-

rivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin et al. *J. Biol. Chem.* 257: 286-288 (1982) via a disulfide interchange reaction. A chemotherapeutic agent is optionally contained within the liposome. See Gabizon et al. *J. National Cancer Inst.* 81(19)1484 (1989).

(x) Antibody Dependent Enzyme Mediated Prodrug Therapy (ADEPT)

The antibodies of the present invention may also be used in ADEPT by conjugating the antibody to a prodrug-activating enzyme which converts a prodrug (e.g. a peptidyl chemotherapeutic agent, see WO81/01145) to an active anti-cancer drug. See, for example, WO 88/07378 and U.S. Pat. No. 4,975,278.

The enzyme component of the immunoconjugate useful for ADEPT includes any enzyme capable of acting on a prodrug in such a way so as to covert it into its more active, cytotoxic form.

Enzymes that are useful in the method of this invention include, but are not limited to, alkaline phosphatase useful for converting phosphate-containing prodrugs into free drugs; arylsulfatase useful for converting sulfate-containing prodrugs into free drugs; cytosine deaminase useful for converting non-toxic 5-fluorocytosine into the anti-cancer drug, 5-fluorouracil; proteases, such as serratia protease, thermolysin, subtilisin, carboxypeptidases and cathepsins (such as cathepsins B and L), that are useful for converting peptide-containing prodrugs into free drugs; D-alanylcarboxypeptidases, useful for converting prodrugs that contain D-amino acid substituents; carbohydrate-cleaving enzymes such as β-galactosidase and neuraminidase useful for converting glycosylated prodrugs into free drugs; β-lactamase useful for converting drugs derivatized with β-lactams into free drugs; and penicillin amidases, such as penicillin V amidase or penicillin G amidase, useful for converting drugs derivatized at their amine nitrogens with phenoxyacetyl or phenylacetyl groups, respectively, into free drugs. Alternatively, antibodies with enzymatic activity, also known in the art as "abzymes", can be used to convert the prodrugs of the invention into free active drugs (see, e.g., Massey, *Nature* 328: 457-458 [1987]). Antibody-abzyme conjugates can be prepared as described herein for delivery of the abzyme to a tumor cell population.

The enzymes of this invention can be covalently bound to the anti-ErbB2 antibodies by techniques well known in the art such as the use of the heterobifunctional crosslinking reagents discussed above. Alternatively, fusion proteins comprising at least the antigen binding region of an antibody of the invention linked to at least a functionally active portion of an enzyme of the invention can be constructed using recombinant DNA techniques well known in the art (see, e.g., Neuberger et al., *Nature,* 312: 604-608 [1984]).

(xi) Antibody-Salvage Receptor Binding Epitope Fusions

In certain embodiments of the invention, it may be desirable to use an antibody fragment, rather than an intact antibody, to increase tumor penetration, for example. In this case, it may be desirable to modify the antibody fragment in order to increase its serum half life. This may be achieved, for example, by incorporation of a salvage receptor binding epitope into the antibody fragment (e.g. by mutation of the appropriate region in the antibody fragment or by incorporating the epitope into a peptide tag that is then fused to the antibody fragment at either end or in the middle, e.g., by DNA or peptide synthesis).

A systematic method for preparing such an antibody variant having an increased in vivo half-life comprises several steps. The first involves identifying the sequence and conformation of a salvage receptor binding epitope of an Fc region of an IgG molecule. Once this epitope is identified, the sequence of the antibody of interest is modified to include the sequence and conformation of the identified binding epitope. After the sequence is mutated, the antibody variant is tested to see if it has a longer in vivo half-life than that of the original antibody. If the antibody variant does not have a longer in vivo half-life upon testing, its sequence is further altered to include the sequence and conformation of the identified binding epitope. The altered antibody is tested for longer in vivo half-life, and this process is continued until a molecule is obtained that exhibits a longer in vivo half-life.

The salvage receptor binding epitope being thus incorporated into the antibody of interest is any suitable such epitope as defined above, and its nature will depend, e.g., on the type of antibody being modified. The transfer is made such that the antibody of interest still possesses the biological activities described herein.

The epitope preferably constitutes a region wherein any one or more amino acid residues from one or two loops of a Fc domain are transferred to an analogous position of the antibody fragment. Even more preferably, three or more residues from one or two loops of the Fc domain are transferred. Still more preferred, the epitope is taken from the CH2 domain of the Fc region (e.g., of an IgG) and transferred to the CH1, CH3, or V_H region, or more than one such region, of the antibody. Alternatively, the epitope is taken from the CH2 domain of the Fc region and transferred to the C_L region or V_L region, or both, of the antibody fragment.

In one most preferred embodiment, the salvage receptor binding epitope comprises the sequence (5' to 3'): PKNSSMISNTP (SEQ ID NO:3), and optionally further comprises a sequence selected from the group consisting of HQSLGTQ (SEQ ID NO:4), HQNLSDGK (SEQ ID NO:5), HQNISDGK (SEQ ID NO:6), or VISSHLGQ (SEQ ID NO:7), particularly where the antibody fragment is a Fab or $F(ab')_2$. In another most preferred embodiment, the salvage receptor binding epitope is a polypeptide containing the sequence(s) (5' to 3'): HQNLSDGK (SEQ ID NO:5), HQNISDGK (SEQ ID NO:6), or VISSHLGQ (SEQ ID NO:7) and the sequence: PKNSSMISNTP (SEQ ID NO:3).

(xii) Purification of Anti-ErbB2 Antibody

When using recombinant techniques, the antibody can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the antibody is produced intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, is removed, for example, by centrifugation or ultrafiltration. Carter et al., *Bio/Technology* 10:163-167 (1992) describe a procedure for isolating antibodies which are secreted to the periplasmic space of *E. coli*. Briefly, cell paste is thawed in the presence of sodium acetate (pH 3.5), EDTA, and phenylmethylsulfonylfluoride (PMSF) over about 30 min. Cell debris can be removed by centrifugation. Where the antibody is secreted into the medium, supernatants from such expression systems are preferably first concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon ultrafiltration unit. A protease inhibitor such as PMSF may be included in any of the foregoing steps to inhibit proteolysis and antibiotics may be included to prevent the growth of adventitious contaminants.

The antibody composition prepared from the cells can be purified using, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatogra-

phy, with affinity chromatography being the preferred purification technique. The suitability of protein A as an affinity ligand depends on the species and isotype of any immunoglobulin Fc domain that is present in the antibody. Protein A can be used to purify antibodies that are based on human γ1, γ2, or γ4 heavy chains (Lindmark et al., *J. Immunol. Meth.* 62:1-13 [1983]). Protein G is recommended for all mouse isotypes and for human γ3 (Guss et al., *EMBO J.* 5:15671575 [1986]). The matrix to which the affinity ligand is attached is most often agarose, but other matrices are available. Mechanically stable matrices such as controlled pore glass or poly(styrenedivinyl)benzene allow for faster flow rates and shorter processing times than can be achieved with agarose. Where the antibody comprises a C_H3 domain, the Bakerbond ABX™ resin (J. T. Baker, Phillipsburg, N.J.) is useful for purification. Other techniques for protein purification such as fractionation on an ion-exchange column, ethanol precipitation, Reverse Phase HPLC, chromatography on silica, chromatography on heparin SEPHAROSE™ chromatography on an anion or cation exchange resin (such as a polyaspartic acid column), chromatofocusing, SDS-PAGE, and ammonium sulfate precipitation are also available depending on the antibody to be recovered.

Following any preliminary purification step(s), the mixture comprising the antibody of interest and contaminants may be subjected to low pH hydrophobic interaction chromatography using an elution buffer at a pH between about 2.5-4.5, preferably performed at low salt concentrations (e.g. from about 0-0.25M salt).

III. Pharmaceutical Formulations

Therapeutic formulations of the antibodies used in accordance with the present invention are prepared for storage by mixing an antibody having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. [1980]), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g. Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. For example, it may be desirable to further provide antibodies which bind to EGFR, ErbB2 (e.g. an antibody which binds a different epitope on ErbB2), ErbB3, ErbB4, or vascular endothelial factor (VEGF) in the one formulation. Alternatively, or in addition, the composition may comprise a cytotoxic agent, cytokine or growth inhibitory agent, provided that the cytotoxic agent is other than an anthracycline derivative, e.g. doxorubicin, or epirubicin. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980).

The formulations to be used for in vivo administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g. films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(−)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37° C., resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S—S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

IV. Treatment with the Anti-ErbB2 Antibodies

It is contemplated that, according to the present invention, the anti-ErbB2 antibodies may be used to treat various conditions characterized by overexpression and/or activation of the ErbB2 receptor. Exemplary conditions or disorders include benign or malignant tumors (e.g. renal, liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, lung, vulval, thyroid, hepatic carcinomas; sarcomas; glioblastomas; and various head and neck tumors); leukemias and lymphoid malignancies; other disorders such as neuronal, glial, astrocytal, hypothalamic and other glandular, macrophagal, epithelial, stromal and blastocoelic disorders; and inflammatory, angiogenic and immunologic disorders.

The antibodies of the invention are administered to a human patient, in accord with known methods, such as intravenous administration as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerobrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes. Intravenous administration of the antibody is preferred.

The treatment of the present invention involved the combined administration of an anti-ErbB2 antibody and a chemotherapeutic agent, other than an anthracycline derivative. The combined administration includes coadministration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities. Preparation and dosing schedules for such chemotherapeutic agents may be used according to manufacturers' instructions or as determined empirically by the skilled practitioner. Preparation and dosing schedules for such chemotherapy are also described in Chemotherapy Service Ed., M. C. Perry, Williams & Wilkins, Baltimore, Md. (1992). The chemotherapeutic agent may precede, or follow administration of the antibody or may be given simultaneously therewith. The antibody may be combined with an anti-estrogen compound such as tamoxifen or an anti-progesterone such as onapristone (see, EP 616 812) in dosages known for such molecules.

It may be desirable to also administer antibodies against other tumor associated antigens, such as antibodies which bind to the EGFR, ErbB3, ErbB4, or vascular endothelial factor (VEGF). Alternatively, or in addition, two or more anti-ErbB2 antibodies may be co-administered to the patient. Sometimes, it may be beneficial to also administer one or more cytokines to the patient. In a preferred embodiment, the ErbB2 antibody is co-administered with a growth inhibitory agent. For example, the growth inhibitory agent may be administered first, followed by the ErbB2 antibody. However, simultaneous administration or administration of the ErbB2 antibody first is also contemplated. Suitable dosages for the growth inhibitory agent are those presently used and may be lowered due to the combined action (synergy) of the growth inhibitory agent and anti-ErbB2 antibody.

For the prevention or treatment of disease, the appropriate dosage of antibody will depend on the type of disease to be treated, as defined above, the severity and course of the disease, whether the antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, and the discretion of the attending physician. The antibody is suitably administered to the patient at one time or over a series of treatments.

Depending on the type and severity of the disease, about 1 μg/kg to 15 mg/kg (e.g. 0.1-20 mg/kg) of antibody is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. A typical daily dosage might range from about 1 μg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

Further information about suitable dosages is provided in the Example below.

V. Articles of Manufacture

In another embodiment of the invention, an article of manufacture containing materials useful for the treatment of the disorders described above is provided. The article of manufacture comprises a container, a label and a package insert. Suitable containers include, for example, bottles, vials, syringes, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an anti-ErbB2 antibody. The label on, or associated with, the container indicates that the composition is used for treating the condition of choice. The article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes. In addition, the article of manufacture comprises a package inserts with instructions for use, including a warning that the composition is not to be used in combination with anthacycline-type chemotherapeutic agent, e.g. doxorubicin, or epirubicin.

Deposit of Materials

The following hybridoma cell lines have been deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, Va. 20110-2209 (ATCC):

Antibody Designation	ATCC No.	Deposit Date
7C2	ATCC HB-12215	Oct. 17, 1996
7F3	ATCC HB-12226	Oct. 17, 1996
4D5	ATCC CRL 10463	May 24, 1990

Further details of the invention are illustrated by the following non-limiting Example.

Example

Materials and Methods

Anti-ErbB2 monoclonal antibody The anti-ErbB2 $IgG_1\kappa$ murine monoclonal antibody 4D5, specific for the extracellular domain of ErbB2, was produced as described in Fendly et al., *Cancer Research* 50:1550-1558 (1990) and WO89/06692. Briefly, NIH 3T3/HER2-3_{400} cells (expressing approximately 1×10^5 ErbB2 molecules/cell) produced as described in Hudziak et al. *Proc. Natl. Acad. Sci.* (*USA*) 84:7159 (1987) were harvested with phosphate buffered saline (PBS) containing 25 mM EDTA and used to immunize BALB/c mice. The mice were given injections i.p. of 10^7 cells in 0.5 ml PBS on weeks, 0, 2, 5 and 7. The mice with antisera that immunoprecipitated ^{32}P-labeled ErbB2 were given i.p. injections of a wheat germ agglutinin-Sepharose (WGA) purified ErbB2 membrane extract on weeks 9 and 13. This was followed by an i.v. injection of 0.1 ml of the ErbB2 preparation and the splenocytes were fused with mouse myeloma line X63-Ag8.653. Hybridoma supernatants were screened for ErbB2-binding by ELISA and radioimmunoprecipitation. MOPC-21 (IgG1), (Cappell, Durham, N.C.), was used as an isotype-matched control.

The treatment was performed with a humanized version of the murine 4D5 antibody (HERCEPTIN®). The humanized antibody was engineered by inserting the complementarity determining regions of the murine 4D5 antibody into the framework of a consensus human immunoglobulin IgG_1 (IgG_1) (Carter et al., *Proc. Natl. Acad. Sci. USA* 89:4285-4289 [1992]). The resulting humanized anti-ErbB2 monoclonal antibody has high affinity for p185" (Dillohiation constant [K_d]=0.1 nmol/L), markedly inhibits, in vitro and in human xenografts, the growth of breast cancer cells that contain high levels of $p185^{HER2}$, induces antibody-dependent

cellular cytotoxicity (ADCC), and has been found clinically active, as a single agent, in patients with ErbB2-overexpressing metastatic breast cancers that had received extensive prior therapy. HERCEPTIN® is produced by a genetically engineered Chinese Hamster Ovary (CHO) cell line, grown in large scale, that secretes the antibody into the culture medium. The antibody is purified from the CHO culture media using standard chromatographic and filtration methods. Each lot of antibody used in this study was assayed to verify identity, purity, and potency, as well as to meet Food and Drug Administration requirements for sterility and safety.

Eligibility Criteria Patients had to fulfill all of the following criteria to be eligible for study admission:

- Metastatic breast cancer
- Overexpression of the ErbB2 (HER2) oncogene (2+ to 3+ as determined by immunohistochemistry or fluorescence in situ hybridization (FISH). [Tumor expression of ErbB2 can be determined by immunohistochemical analysis, as previously described (Slamon et al., [1987] and [1989], supra), of a set of thin sections prepared from the patient's paraffin-archived tumor blocks. The primary detecting antibody used is murine 4D5 MAb, which has the same CDRs as the humanized antibody used for the treatment. Tumors are considered to overexpress ErbB2 if at least 25% of tumor cells exhibit characteristic membrane staining for $p185^{HER2}$].
- Bidimensionally measurable disease (including lytic bone lesions) by radiographic means, physical examination, or photographs.

Measurable disease was defined as any mass reproducibly measurable in two perpendicular diameters by physical examination, X-ray (plain films), computerized tomography (CT), magnetic resonance imaging (MRI), ultrasound, or photographs.

Osteoblastic metastases, pleural effusions, or ascites were not considered to be measurable. Measurable lesions must be at least 1 cm in greatest dimension. Enumeration of evaluable sites of metastatic disease and number of lesions in an evaluable site (e.g. lung) had to be recorded on the appropriate Case Report Form (CRF). If a large number of pulmonary or hepatic lesions were present, the six largest lesions per site were followed.

- The ability to understand and willingness to sign a written informed consent form
- Women≧18 years
- Suitable candidates for receiving concomitant cytotoxic chemotherapy as evidenced by screening laboratory assessments of hematologic, renal, hepatic, and metabolic functions.

Exclusion Criteria Patients with any of the following were excluded from study entry:

- Prior cytotoxic chemotherapy for metastatic breast cancer
- Patients may have received prior hormonal therapy (e.g. tamoxifen) for metastatic disease or cytotoxic therapy in the adjuvant setting.
- Concomitant malignancy that has not been curatively treated
- A performance status of <60% on the Karnofsky scale
- Pregnant or nursing women; women of childbearing potential, unless using effective contraception as determined by the investigator
- Bilateral breast cancer (either both primary tumors must have 2+ to 3+ HER2 overexpression, or the metastatic site must have 2+ to 3+ HER2 overexpression)
- Use of investigational or unlicensed agents within 30 days prior to study entry
- Clinically unstable or untreated metastases to the brain (e.g. requiring radiation therapy)

Based upon the foregoing criteria, 469 patients were chosen, and enrolled in the study. Half the patients (stratified by chemotherapy) were randomized to additionally receive the HERCEPTIN® antibody (see below).

Administration and Dosage

Anti-ErbB2 Antibody

On day 0, a 4 mg/kg dose of humanized anti-ErbB2 antibody (HERCEPTIN®, H) was administered intravenously, over a 90-minute period. Beginning on day 7, patients received weekly administration of 2 mg/kg antibody (i.v.) over a 90-minute period.

Chemotherapy

The patients received one of two chemotherapy regiments for a minimum of six cycles, provided their disease was not progressing: a) cyclophosphamide and doxorubicin or epirubicin (AC), if patients have not received anthracycline therapy in the adjuvant setting, or b) paclitaxel (T, TAXOL®), if patients have received any anthracycline therapy in the adjuvant setting. The initial dose of the HERCEPTIN® antibody preceded the first cycle of either chemotherapy regimen by 24 hours. Subsequent doses of the antibody were given immediately before chemotherapy administration, if the initial dose of the antibody was well tolerated. If the first dose of the antibody was not well tolerated, subsequent infusions continued to precede chemotherapy administration by 24 hours. Patients were permitted to continue receiving chemotherapy beyond six cycles if, in the opinion of the treating physician, they were continuing to receive treatment benefit.

Cyclophosphamide (600 mg/m^2) was given either by iv push over a minimum period of 3 minutes or by infusion over a maximum period of 2 hours.

Doxorubicin (60 mg/m^2) or epirubicin (75 mg/m^2) were given either by slow iv push over a minimum period of 3-5 minutes or by infusion over a maximum period of 2 hours, according to institutional protocol.

Paciltaxel (TAXOL®) was given at a dose of 175 mg/m^2 over 3 hours by intravenous administration. All patients receiving paclitaxel were premedicated with dexamethasone (or its equivalent) 20 mg×2, administered orally 12 and 6 hours prior to paclitaxel; diphenhydramine (or its equivalent) 50 mg, iv, administered 30 minutes prior to paclitaxel, and dimetidine (or another H_2 blocker) 300 mg, iv, administered 30 minutes prior to paclitaxel.

Response Criteria

Progressive Disease Objective evidence of an increase of 25% or more in any measurable lesion. Progressive disease also includes those instances when new lesions have appeared. For bone lesions, progression is defined as a 25% increase in objective measurement by plain film, CT, MRI; symptomatic new lesions not due to fracture; or requirement for palliative radiotherapy.

Complete Response Disappearance of all radiographically and/or visually apparent tumor for a minimum of 4 weeks. Skin and chest wall complete responses had to be confirmed by biopsy.

Partial Response A reduction of at least 50% in the sum of the products of the perpendicular diameters of all measurable lesions for a minimum period of 4 weeks. No new lesions may have appeared, nor may any lesions have progressed in size.

Minor Response A reduction of 25% to 49% in the sum of the products of the perpendicular diameters of all measurable lesions. No new lesions may have appeared, nor may any lesions have progressed in size.

Stable Disease No change of greater than 25% in the size of measurable lesions. No lesions may have appeared.

Time to disease progression (TTP) was calculated from the beginning of therapy to progression. Confidence limits for response rates were calculated using the exact method for a single proportion. (Fleiss, J L, *Statistical Methods for Rates and Proportions* (ed. 2), New York, N.Y., Wiley, 1981, pp 13-17).

Results

At a median follow-up of 10.5 months, assessments of time to disease progression (TTP in months) and response rates (RR) showed a significant augmentation of the chemotherapeutic effect by HERCEPTIN®, without increase in overall severe adverse events (AE):

	Enrolled	TTP(months)	RR(%)	AE(%)
CRx	234	5.5	36.2	66
CRx + H	235	8.6*	62.00**	69
AC	145	6.5	42.1	71
AC + H	146	9.0	64.9	68
T	89	4.2	25.0	59
T + H	89	7.1	57.3	70

*p <0.001 by log-rank test
**p <0.01 by X^2 test
CRx: chemotherapy
AC: anthracycline/cyclophosphamide treatment
H: HERCEPTIN ®
T: TAXOL ®

A syndrome of myocardial dysfunction similar to that observed with anthracyclines was reported more commonly with a combined treatment of AC+H (18% Grade 3/4) than with AC alone (3%), T (0%), or T+H (2%).

These data indicate that the combination of anti-ErbB2 antibody treatment with chemotherapy markedly increases the clinical benefit, as assessed by response rates and the evaluation of disease progression. However, due to the increased cardiac side-effects of doxorubicin or epirubicin, the combined use of anthracyclines with anti-ErbB2 antibody therapy is contraindicated. The results, taking into account risk and benefit, favor the combined treatment with HERCEPTIN® and paclitaxel (TAXOL).

The disclosures of all citations in the specification are expressly incorporated herein by reference.

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The invention claimed is:

1. A method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by overexpression of ErbB2 receptor, comprising administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence and a taxoid, in the absence of an anthracycline derivative, to the human patient in an amount effective to extend the time to disease progression in said human patient, without increase in overall severe adverse events.

2. The method of claim **1** wherein said patient has a malignant tumor.

3. The method of claim **1** wherein said patient has cancer.

4. The method of claim **3** wherein said cancer is selected from the group consisting of breast cancer, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, colon cancer, colorectal cancer, endometrial carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer.

5. The method of claim **4** wherein said cancer is breast cancer.

6. The method of claim **5** wherein said cancer is metastatic breast carcinoma.

7. The method of claim **1** wherein said antibody is a humanized 4D5 anti-ErbB2 antibody.

8. The method of claim **1** wherein said taxoid is paclitaxel.

9. The method of claim **8** wherein the effective amount of said combination is lower than the sum of the effective amounts of said anti-ErbB2 antibody and said taxoid, when administered individually, as single agents.

10. The method of claim **1** wherein efficacy is further measured by determining the response rate.

11. A method for the treatment of a human patient with ErbB2 overexpressing progressing metastatic breast cancer, comprising administering a combination of a humanized 4D5 anti-ErbB2 antibody and a taxoid, in the absence of an anthracycline derivative, to the human patient in an amount effective to extend the time to disease progression in said human patient, without increase in overall severe adverse events.

12. The method of claim **11** wherein said taxoid is paclitaxel.

13. A method for the treatment of a human patient with a progressing malignant tumor or cancer characterized by over-expression of ErbB2 receptor, comprising administering a combination of a humanized 4D5 anti-ErbB2 antibody which comprises a human Fc region and that binds to epitope 4D5 within the ErbB2 extracellular domain sequence and a taxoid, in the absence of an anthracycline derivative, to the human patient in an amount effective to extend the time to disease progression in said human patient, without increase in overall severe adverse events.

14. A method for the treatment of a human patient with ErbB2 expressing progressing metastatic breast cancer, comprising administering a combination of an antibody which binds to epitope 4D5 within the extracellular domain sequence and a taxoid, in the absence of an anthracycline derivative, to the human patient in an amount effective to extend the time to disease progression in said human patient, without increase in overall severe adverse events.

* * * * *

CERTIFICATE OF SERVICE

I hereby certify that, on this 9th day of July, 2019 I filed the foregoing Non-Confidential Brief for Appellant Genentech, Inc. with the Clerk of the United States Court of Appeals for the Federal Circuit via the CM/ECF system, which will send notice of such filing to all registered CM/ECF users.

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CERTIFICATE OF COMPLIANCE

Pursuant to Fed. R. App. P. 32(g), the undersigned hereby certifies that this brief complies with the type-volume limitation of Federal Circuit Rule 32(a).

1. Exclusive of the exempted portions of the brief, as provided in Fed. R. App. P. 32(f) and Fed. Cir. R. 32(b), the brief contains 7,896 words.

2. The brief has been prepared in proportionally spaced typeface using Microsoft Word 2016 in 14-point Times New Roman font. As permitted by Fed. R. App. P. 32(g), the undersigned has relied upon the word count feature of this word processing system in preparing this certificate.

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