No. 2019-1265

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

IN RE GENENTECH, INC.,

Appellant.

Appeal from the United States Patent and Trademark Office,
Patent Trial and Appeal Board in Nos. IPR2017-00737 and IPR2017-01960

NON-CONFIDENTIAL BRIEF FOR APPELLANT GENENTECH, INC.

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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.)
Genentech, Inc. v. Iancu, No. 19-1263 (Fed. Cir.)
Genentech, Inc. v. Iancu, No. 19-1267 (Fed. Cir.)
Genentech, Inc. v. Iancu, No. 19-1270 (Fed. Cir.)

Dated: July 9, 2019

/s/ Robert J. Gunther, Jr.

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TABLE OF CONTENTS

CONFIDENTIAL MATERIAL OMITTED

The material omitted from page 9 contains confidential communication from the FDA concerning Genentech's submission.

TABLE OF AUTHORITIES

CASES

Page(s)

STATUTES

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.); *Genentech, Inc. v. Iancu*, No. 19-1267 (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 IPR2017-00737. Appx14289-14294.

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. The patent in this appeal, U.S. Patent No. 7,892,549 ("the '549 patent"), is a continuation of the '441 patent and shares the same specification. While there are various differences between the '549 and '441 claims, the most notable is that all of the '549 claims recite the third agent (i.e., "further growth inhibitory agent" or "further therapeutic agent") in addition to the combination of an anti-ErbB2 antibody and a taxoid claimed in the '441 patent. The '549 patent has been terminally disclaimed over the '441 patent.

This appeal arises from a final written decision by the Patent Trial and Appeal Board declaring all claims of the '549 patent unpatentable. Much of the dispute before the Board turned on the meaning of the claim terms "in an amount

effective to extend the time to disease progression in the human patient" and "effective amount." Based on a single inartful statement in the prosecution history, the Board construed these terms 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 these terms 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) as a matter of basic medical ethics, a patient cannot be left untreated; and (3) 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 terms "in an amount effective to extend the time to disease progression in the human patient" and "effective amount" to require a comparison to a patient who had received no treatment at all.

II. Whether, applying the proper construction of the terms "in an amount effective to extend the time to disease progression in the human patient" and

"effective amount," the Board's decision should be reversed because it was not supported by substantial evidence.

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. Appx72(1:26-32); Appx8700; Appx9058. HER2-positive breast cancer is particularly aggressive: In the 1990s, it was "the worst prognosis in women with breast cancer." Appx8707. It was associated with a high rate of tumor recurrence and spreading to other areas of the body, shorter time to relapse, and shorter overall survival. Appx8481; Appx4307-4309; Appx4314. 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. Appx8467; Appx8469; Appx9058-9060.

B. The Invention of the '549 Patent

The '549 patent claims a method for treating HER2-positive breast cancer patients with an anti-ErbB2 antibody such as "trastuzumab" (aka "rhuMAb

HER2") in combination with a type of chemotherapy drug called a "taxoid," along with "a further growth inhibitory agent" (claims 1, 16) or "a further therapeutic agent" (claim 5). Specifically, the '549 claims reflect a novel method of treatment for cancer that overexpresses ErbB2 (e.g., HER2-positive breast cancer), which comprises (i) "administering a combination" of an anti-ErbB2 antibody (such as rhuMAb HER2), a taxoid (a type of chemotherapy drug), and "a further growth inhibitory agent" (claims 1, 16) or "a further therapeutic agent" (claim 5); (ii) "to the human patient"; (iii) "in an amount effective to extend the time to disease progression in the human patient" (claims 1, 16) or in "an effective amount" (claim 5). Claims 16 and 17 further require "the absence of an anthracycline derivative" from the claimed combination therapy.

In the 1990s, engineered antibodies—proteins specially-designed to bind to molecular targets, called "antigens"—were a focus for therapeutic research. Appx75-76(8:45-9:4). However, the body's immune system also tended to attack these antibodies, preventing them from having a therapeutic effect. Appx8591. Articles from the 1990s described antibody therapy for cancer as "a story of unending failures," Appx8628, with "significant obstacles," Appx8621, and "no hint of a consistent therapeutic efficacy," Appx8516. 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," Appx5892, and that "breast cancers that overexpress p185 [*i.e.*, HER2] ***will not respond well to Taxol***," Appx8553 (emphasis added). As of December 1997, ***no clinical results*** had been reported for the combination of trastuzumab and a taxoid. The only results for the 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. Appx8883-8886; Appx9045-9047. 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* Appx8802 (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"); Appx8485 ("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 a 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. Appx9055; Appx9208. Mice are also often administered a proportionally larger dose than humans can tolerate, which allows for positive outcomes not possible in humans. Appx8470. Therapies also frequently cause toxicity in humans, but not in mice, due to differences in cell and tissue types between mice and humans. Appx8892-8894; Appx9047-9049. 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. Appx8877-8878; Appx9047-9048.

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.

Appx9050-9053. 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. Appx8476-8477. Even for drugs that advanced to late-stage, Phase III clinical trials, nearly 60% ultimately failed to result in an approved drug. *Id.*; Appx8710-8711.

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. Appx9595. 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. Appx9069.

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.*, Appx8088 ("[T]he expected clinical outcome for the administration of rhuMAb HER2 with taxol is less certain than co-administration

with cisplatinum or doxorubicin."); Appx9990 (FDA noting that Genentech has "[redacted]").

Yet when the Phase III study reached its primary endpoint in late 1997, the results were surprising. Appx8233-8240; Appx8286-8291. 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. Appx8381. In fact, the combination of trastuzumab and paclitaxel was dramatically more effective than paclitaxel alone. *See, e.g.*, Appx3419 ("[T]he combination is surprisingly synergistic with respect to extending TTP."). In addition, the combination of trastuzumab and paclitaxel unexpectedly avoided the surprising cardiotoxicity that resulted from the combination of trastuzumab and anthracyclines. Appx8380; Appx8012; Appx1092; Appx3418; Appx86(30:13-16). These data are reflected in the provisional patent application filed December 12, 1997, Appx4027-4032, and led to the FDA approval of Herceptin as a first-line treatment.

Herceptin revolutionized the treatment of HER2-positive breast cancer. Appx8469 ("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[.]"). Petitioner's expert described the transformation as follows:

> Q. … And, sir, is that [HER2 overexpressing breast cancer] a particularly aggressive form of breast cancer?
>
> A. It used to have the worst prognosis in women with breast cancer.
>
> Q. Did something change that?
>
> A. Yes.
>
> Q. What changed that?
>
> A. Herceptin treatment.

Appx8707.

C. Prior Art

The Board's Final Written Decision addressed the validity of the '549 patent over the following prior art combinations. Appx1-64.

Ground	Claim(s)	References	Basis
1	1–11 and 14–17	Baselga '97[1] and Gelmon[2]	§ 103
2	12	Baselga '97, Gelmon, and Drebin[3]	§ 103

[1] Baselga et al., *HER2 Overexpression and Paclitaxel Sensitivity in Breast Cancer: Therapeutic Implications, Update on the Taxanes in Breast Cancer*, 11 Oncology 43-48 (1997). Appx1094-1104.

[2] Gelmon et al., *Phase I/II Trial of Biweekly Paclitaxel and Cisplatin in the Treatment of Metastatic Breast Cancer*, 14 J. Clin. Oncology 1185-1191 (1996). Appx4132-4146.

[3] Drebin et al., *Monoclonal antibodies reactive with distinct domains of the neu oncogene-encoded p185 molecule exert synergistic anti-tumor effects in vivo*, 2 Oncogene 273-277 (1988). Appx1145-1152.

3	13	Baselga '97, Gelmon, and Presta[4]	§ 103
4	1-11 and 14-17	Baselga '96, Baselga '94,[5] and Gelmon	§ 103
5	12	Baselga '96, Baselga '94, Gelmon, and Drebin	§ 103
6	13	Baselga '96, Baselga '94, Gelmon, and Presta	§ 103

None of these references contain any clinical data showing the effect of trastuzumab plus a taxoid in humans. Indeed, it is undisputed that no such clinical data was reported prior to December 12, 1997. Appx9066; Appx8717.

1. Baselga '94

Baselga '94 is a one-paragraph abstract published in March 1994. It describes the results of preclinical studies using a mouse model in which tumors were created subcutaneously (under the skin) to assess the antitumor activity of trastuzumab combined with either an anthracycline derivative (doxorubicin) or a taxoid (paclitaxel). Appx1092.

Baselga '94 only measured the response rate—i.e., the initial tumor-inhibition response—for both drug combinations after a period of five weeks. Because it measured only one point in time, Baselga '94 did not measure or assess

[4] Presta et al., *Humanization of an Anti-Vascular Endothelial Growth Factor Monoclonal Antibody for the Therapy of Solid Tumors and Other Disorders*, 57 Cancer Research 4593-4599 (1997). Appx1359-1372.

[5] 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. Oncology 63 (1994) (Abstract 53). Appx1089-1092.

the effect (if any) on TTP. Baselga '94 found that both drug combinations improved the antitumor response in mice as compared with trastuzumab or either chemotherapy alone. It also found that trastuzumab "did not increase the toxicity of paclitaxel or doxorubicin in animals as determined by animal survival and weight loss." Appx1092.

2. 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). Appx1082.

The clinical endpoint evaluated in the trial was response rate, which was evaluated at 11 weeks. Appx1082; Appx1084-1085. 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.

The vast majority of patients in Baselga '96 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. Appx1085. While Baselga '96 measured a "median time to progression" of 5.1 months, it measured this for only 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. Appx1084.

Baselga '96 explained that the mechanism of action of rhuMAb HER2 was not understood, offering several possible explanations for the clinical results. Appx1086-1087. Baselga '96 also cited earlier preclinical mouse studies, which are described in Baselga '94. Baselga '96 noted that in Baselga '94, "rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity." Appx1087.

3. Baselga '97

Baselga '97 is a review paper published in March 1997, describing a number of studies with rhuMAb HER2, including those described above in Baselga '94 and Baselga '96. Baselga '97 also described the design of the Phase III study for rhuMAb HER2 after Genentech amended the protocol to allow patients to be treated with the combination of rhuMAb HER2 and paclitaxel. Appx1103. Baselga '97 stated that the Phase III study was "ongoing" and provided no indication as to whether any of the drug combinations under evaluation would provide a clinical benefit (or even whether any patients had completed a course of therapy). In fact, the article acknowledged that it was uncertain whether those drug combinations would provide a clinical benefit. Appx1104 ("***If*** the results of these

studies are positive we ***might*** be faced with a novel paradox ….") (emphases added); *see also* Appx9092-9093.

4. Gelmon

Gelmon is an article published in April 1996 describing a Phase I/II study in which metastatic breast cancer patients were administered a combination of paclitaxel and cisplatin (another chemotherapy drug). Appx4140. Gelmon does not discuss treating HER2-positive patients, or treating patients with an anti-ErbB2 antibody or combinations involving an anti-ErbB2 antibody. Appx9093-9094.

The purpose of the study was to "determine the maximum-tolerated dose of escalating doses of paclitaxel … administered biweekly with a fixed dose of cisplatin, to assess the toxicity, and to evaluate the activity of this combination in a phase I/II trial in metastatic breast cancer." Appx4140. The clinical endpoint measured in the study was response rate. Appx4144.

Although it obtained encouraging results for the 29 patients in the study, Gelmon acknowledged that "[f]urther confirmatory trials of this combination and other novel schedules of paclitaxel are necessary to further our understanding of how to best use this novel agent." Appx4145. Indeed, Gelmon explained that its results differed from an NYU study on this same combination, which reported a much lower response rate and "significant neuropathy." *Id.*

5. Drebin

Drebin is an article published in March 1988 reporting on the antitumor effects of various anti-ErbB2 antibodies in mouse models. Appx1148-1152. Drebin does not describe any humanized antibodies, and it does not suggest administering antibodies to human patients (much less in combination with a taxoid or other chemotherapies). Appx9096-9097.

6. Presta

Presta is an article published in October 1997 reporting on the humanization of the anti-VEGF antibody. Appx1366. Presta does not discuss the possibility of combining this humanized anti-VEGF antibody with an anti-ErbB2 antibody. Presta also does not discuss combinations of an anti-ErbB2 antibody with a taxoid, or any other agent. Appx9097.

D. Prosecution of the ’549 Patent

The ’549 patent issued from Application No. 10/356,824 filed on February 3, 2003, which is a continuation of U.S. Patent Application No. 09/208,649, filed on December 10, 1998, which later issued as the ’441 patent. In turn, the ’649 application claims priority to Provisional Application No. 60/069,346, filed on December 12, 1997. Appx65. 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 of the '649 application, 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?

Appx11003-11004. 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." Appx11017. 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)," Appx1499, 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***, Appx1527-1527. 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." Appx11017.

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. Appx3820-3824. 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. Appx3822. 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. Appx3823-3824.

After Genentech provided a terminal disclaimer over the parent application (which issued as the '441 patent), Appx3943-3944, the Examiner allowed the claims on October 8, 2010, Appx3971-3972.

E. The Board Proceedings

On March 21, 2017, Petitioner requested an *inter partes* review of claims 1-17 of the '549 patent. Appx13001-13079. Petitioner challenged the patentability

of these claims on the six grounds noted above. The Board instituted *inter partes* review to all challenged claims on July 27, 2017.[6] Appx13302.

The Board's final written decision, issued on October 3, 2018, determined that Petitioner showed by a preponderance of the evidence that claims 1-17 of the '549 patent would have been obvious over the combinations of Baselga '97, Gelmon, Drebin, and Presta set forth in Grounds 1-3 and the combinations of Baselga '96, Baselga '94, Gelmon, Drebin, and Presta set forth in Grounds 4-6. Appx61. In so holding, the Board relied on a claim construction of "in an amount effective to extend the time to disease progression [TTP] in the human patient" and "an effective amount" that compared "the claimed combination treatment to no treatment." Appx17-18. The Board also found that an ordinary artisan would have been motivated to combine rhuMAb HER2 and paclitaxel to treat patients with ErbB2 overexpressing metastatic breast cancer, and that "the challenged claims are unpatentable" even applying "the construction advanced by Patent Owner." *Id.*

SUMMARY OF THE ARGUMENT

I. The Board adopted an incorrect claim construction of the terms "in an amount effective to extend the time to disease progression in the human patient"

[6] Petitioner Samsung Bioepis Co., Ltd. ("Bioepis") also petitioned for *inter partes* review in IPR2017-001960 with substantially the same challenges as Pfizer. Bioepis also requested a joinder. On December 1, 2017, the Board granted Bioepis's Petition and joined Bioepis to the IPR2017-00737 proceeding. Appx13466.

and "effective amount." The Board erroneously interpreted those terms 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.

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 combination of anti-ErbB2 antibody (rhuMAb HER2) and a taxoid (paclitaxel) 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 combination of anti-ErbB2 antibody and taxoid would extend TTP as compared to treatment with a taxoid alone.

First, the Board improperly held that the claimed extension of TTP is an inherent benefit of an otherwise obvious combination. This conclusion ignored the high standard for inherency, which requires that a missing limitation must be necessarily present or the natural result of the combination of elements explicitly

disclosed in the prior art. It is undisputed that administering the claimed combination does not extend TTP each and every time. Indeed, the record establishes that some patients who were administered rhuMAb HER2 and paclitaxel experienced no extension in TTP. Nor is extension of TTP the natural result expected for a claimed combination expressly taught in the prior art. There was no disclosure in the prior art of treating human patients with rhuMAb HER2, a taxoid, and a third agent. Moreover, there was no disclosure that the combination of rhuMAb HER2 and paclitaxel would extend TTP as compared to paclitaxel alone in human patients.

Second, substantial evidence did not support the Board's finding that the claimed efficacy was obvious based on the teachings of Baselga '97, Baselga '96, and Baselga '94. Baselga '97 described the Phase III clinical trial testing the combination of rhuMAb HER2 and paclitaxel, but disclosed no results from that clinical trial. The mere existence of a clinical trial is insufficient to create a reasonable expectation of a particular result. Even setting aside the well-known failure rate of oncology clinical trials, rhuMAb HER2 was not yet approved and the combination of rhuMAb HER2 plus paclitaxel had never previously been tested in human patients. Baselga '96 likewise does not provide any expectation of the claimed extension of TTP. It disclosed only TTP of rhuMAb HER2 alone, included no control as required to assess ***extension*** of TTP, and reported TTP only

for patients most likely to show a response (i.e., less than half of the patients administered rhuMAb HER2). Finally, the preclinical mouse xenograft study reported in Baselga '94 was incapable of reliably predicting that the combination would extend TTP in human patients and had been called into question by other preclinical studies.

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

This Court should reverse because the Board erroneously construed the claims and its alternative ruling under the correct construction was not supported by substantial evidence.

I. THE BOARD INCORRECTLY CONSTRUED THE TERMS "IN AN AMOUNT EFFECTIVE TO EXTEND THE TIME TO DISEASE PROGRESSION IN THE HUMAN PATIENT" AND "EFFECTIVE AMOUNT" TO REQUIRE COMPARISON TO AN UNTREATED PATIENT

The claim language and specification make clear that the terms "in an amount effective to extend the time to disease progression in the human patient" and "effective amount" require comparing the claimed combination treatment to treatment with a taxoid alone. All of the data contained in the patent focuses on this comparison. The Board nonetheless construed the claims to require a comparison to a patient who has received no treatment 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 '549 patent comparing the time to disease progression of patients treated with rhuMAb HER2 and paclitaxel against an untreated patient. *See* Appx8733

(agreeing that the patent does not include in its trial any patients that did not receive any treatment whatsoever). Rather, the '549 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***. Appx86(29:11-30:25) (comparing "T + H" (i.e., Taxol and Herceptin) to "T" (i.e., Taxol)).[7] 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. Appx9085 ("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.").

[7] The '549 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. Appx86(29:11-30:25). However, given that some of the claims expressly exclude anthracycline therapy (e.g. claim 16), the relevant comparison is the combination of rhuMAb HER2 and paclitaxel versus paclitaxel alone.

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." Appx11017.

The Board's use of this prosecution history to override the meaning evident from the 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, Appx11017. 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 combination of rhuMAb HER2 and paclitaxel because they were treated***

with paclitaxel alone. The applicant's statement thereby undermines, rather than supports, the Board's construction.

Indeed, when Petitioner's expert was asked whether he was "aware of any Phase III trials that have compared the drug to untreated patients," his immediate response was telling: "There's frequently a ***control which I guess you could say is untreated***." Appx8709 (emphasis added). Exactly so. In context, the statement in the prosecution history was referring to the control (paclitaxel alone) as being "untreated" compared to the experimental administration of rhuMAb HER2 and paclitaxel, which had never before been given in combination to human patients.

Consistent with the plain meaning of the claim and specification, this Court should construe the terms "in an amount effective to extend the time to disease progression in the human patient" and "effective amount" 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, claims 1-17 of the '549 patent are obvious because (1) the claimed extension of TTP is an inherent benefit of an otherwise obvious combination; and (2) an ordinary artisan would have expected the claimed extension of TTP based on the Baselga references describing results in preclinical models, the results of the Phase II study testing rhuMAb HER2 alone, and the mere existence of the ongoing Phase

III clinical trial. Appx40-46. The Board's conclusions cannot stand because they are based on a misunderstanding of the legal framework of inherency and 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 failure to recognize this unpredictability and willingness to stretch the references was error.

A. The Board Erred In Finding That The Claimed Efficacy Was An Inherent Result Of An Otherwise Obvious Combination

The Board's inherency ruling was legally flawed. Petitioner did not argue inherency in its petition or present any expert testimony on the subject, but the Board held the claimed extension of TTP "is an inherent benefit of an otherwise obvious combination, and … such an inherent result cannot establish patentability." Appx41. The Board reasoned that "when the combination of rhuMoAB HER2 and paclitaxel are administered in the absence of an anthracycline derivative for the treatment of HER2-positive breast cancer, the combined therapy significantly extends the time to disease progression as compared to taxoid therapy alone" and "Patent Owner does not argue that the addition of a further growth inhibitory agent such as cisplatin would abrogate this inherent benefit." Appx41. In making these findings, the Board did not honor the legal framework governing inherency and ignored the substantial shortcomings of the prior art.

A challenger must "meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis." *PAR Pharm., Inc. v. TWI Pharms., Inc*., 773 F.3d 1186, 1195-1196 (Fed. Cir. 2014); *see also id.* at 1195 ("inherency, a doctrine originally rooted in anticipation, must be carefully circumscribed in the context of obviousness"). "The limitation at issue ***necessarily*** must be present, or the ***natural result*** of the combination of elements ***explicitly disclosed*** by the prior art." *Id.* (emphasis

added); *see also Endo Pharms. Sols., Inc. v. Custopharm Inc*., 894 F.3d 1374, 1381-1382 (Fed. Cir. 2018) (outlining elements and describing them as a "rigorous" standard). The record evidence does not support a finding of inherency under either of these prongs.

First, extension of TTP does not "necessarily" result from the claimed combination. "The mere fact that a certain thing ***may result*** from a given set of circumstances is not sufficient to render the result inherent." *Millennium Pharms., Inc. v. Sandoz Inc*., 862 F.3d 1356, 1367 (Fed. Cir. 2017) (internal quotations omitted) (emphasis added). "Inherency … may not be established by probabilities or possibilities." *PAR Pharm.*, 773 F.3d at 1195. Rather, inherency requires that the claimed property result "***each and every time***" an ordinary artisan combines the other recited elements. *Endo Pharms. Sols., Inc*., 894 F.3d at 1382 (emphasis added); *see, e.g., In re Omeprazole Patent Litig*., 483 F.3d 1364, 1372-1373 (Fed. Cir. 2007).

Extension of time to disease progression does not result "each and every time" a patient is administered the claimed combination. Indeed, the record clearly shows that some patients who were administered rhuMAb HER2 and paclitaxel did not experience extension in time to disease progression. Appx8309 (showing that certain patients treated with rhuMAb HER2 and paclitaxel experienced a shorter TTP than certain patients treated with paclitaxel alone). Phase II studies for

rhuMAb HER2 alone, which were discussed in Baselga '96, likewise reported that the majority of patients did not even have a minor response to treatment. Appx40-46; Appx1084.[8]

Second, extension of TTP is not the "natural result" of elements "explicitly disclosed by the prior art." *PAR Pharm.*, 773 F.3d at 1196. There was no disclosure in the prior art of treating human patients with rhuMAb HER2, a taxoid, and a third agent.

Further, even focusing solely on the combination of rhuMAb HER2 and paclitaxel without a third agent, there was no disclosure inherently linking extension of TTP to that combination. Baselga '97 noted the existence of an ongoing Phase III clinical trial that included administration of rhuMAb HER2 and paclitaxel among other protocols, but it did not report any results from that study. The only other prior art addressing the combination of rhuMAb HER2 and paclitaxel was in preclinical xenograft models, and thus did not involve administration of the treatment to human patients. Accordingly, there was no basis for concluding that extending TTP is the "natural result" of such a combination.

[8] As discussed below, Baselga '96 had many shortcomings that would have prevented an ordinary artisan from drawing reliable conclusions regarding *extension* of TTP. *See infra* p. 34-35. But the lack of effectiveness in some patients is relevant to the issue of inherency, since failure in even a single patient would defeat a finding of inherency.

The Board's reliance on *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344 (Fed. Cir. 2012) in these circumstances was misplaced. The Board cited *Santarus* for the proposition that "an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the result[]." Appx41-42 (citing *Santarus*, 694 F.3d at 1354) (alterations in Board's decision). But *Santarus* involved a single prior art reference that disclosed all elements of the claimed formulation except the resulting serum concentrations listed in the claims. 694 F.3d at 1348. And, critically, "neither party disputed that the blood serum concentrations claimed in *Santarus* were expected in light of the dosages disclosed in the prior art." *PAR*, 773 F.3d at 1195. In contrast, the claimed extension of TTP does not necessarily or naturally result each time the combination of rhuMAb HER2 and paclitaxel is administered.

Finally, in the absence of any actual evidence of inherency presented by Petitioner, the Board relied on a purported concession from Genentech—namely, that Genentech "does not dispute" that the combination of rhuMAb HER2 and paclitaxel "extends the time to disease progression as compared to taxoid therapy alone." Appx41. But saying that the combination can achieve that result—as, indeed, Genentech proved in the data reported in its patents—does not mean that it necessarily will or that an ordinary artisan would expect such a result to naturally flow from the combination. An ordinary statement from a patent owner regarding

the enablement of its invention does not substitute for the evidence required to meet the demanding standard of proving inherency. That evidence was missing, and the Board's inherency decision cannot stand.

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

The Board found that an ordinary artisan would reasonably expect the claimed extension of TTP where: (1) Baselga '97 described the Phase III clinical trial testing the combination of rhuMAb HER2 and paclitaxel; (2) Baselga '96 reported on a Phase II trial in which human patients were administered rhuMAb HER2 alone and purportedly experienced a TTP of 5.1 months; and (3) Baselga '94 described preclinical xenograft studies which found a longer response rate for the combination of rhuMAb HER2 and paclitaxel as compared to paclitaxel alone. The Board reasoned that the fact of a Phase III trial (even without results) and the reported response rates in Baselga '96 and Baselga '94 (even without addressing extension of TTP) were sufficient to provide an ordinary artisan a reasonable expectation of the claimed extension of TTP. The record evidence fails to support the Board's finding.

First, the Board erred in finding that the mere existence of a Phase III clinical trial testing the combination of rhuMAb HER2 and paclitaxel as reported in Baselga '97 would provide an ordinarily skilled artisan a reasonable expectation that the claimed combination would extend TTP. Importantly, Baselga '97 does

not report any ***results*** from the clinical trial, and the mere existence of a clinical trial is insufficient to create a reasonable expectation of a particular result. The point of a clinical trial is to ***test*** whether a particular treatment is effective and safe, and the result is not preordained or predictable. Indeed, undisputed evidence establishes that 95% of oncology drugs failed in clinical trials, and even for drugs that advanced to late-stage, Phase III clinical trials, nearly 60% ultimately failed to result in an approved drug. Appx9056; Appx8476-8480; Appx9112-9113; Appx8711 (Dr. Lipton testifying he has "no reason … to doubt" this failure rate); Appx8710 (Dr. Lipton admitting "many" chemotherapeutic agents "fail in [clinical] development" for breast cancer).

The Board improperly dismissed this evidence, reasoning that the reported failure rate of clinical trials focused on "individual compounds (i.e., new chemical entities (NCEs) and biologics) rather than combinations of known or promising therapies." Appx43-44. The Board failed to recognize, however, that the combination of rhuMAb HER2 and paclitaxel created more, not less, uncertainty, than a single drug trial. The combination included a biologic, rhuMAb HER2, that was not yet approved by the FDA, and, in sharp contrast to most Phase III studies which follow Phase I and/or Phase II studies of the same treatment, there were no previous clinical trials testing rhuMAb HER2 and paclitaxel. Appx9112-9113.

Second, the Board erred in relying on Baselga '96 as supporting the expectation that the combination would extend TTP. Appx42. The Board reasoned that an ordinary artisan would expect the claimed combination to extend TTP because Baselga '96 indicated an extension of TTP with treatment of rhuMAb HER2 alone and further noted that the preclinical studies described in Baselga '94 treating mouse xenografts with rhuMAb HER2 and paclitaxel "markedly potentiated the antitumor effects" of paclitaxel alone. Appx42. Yet the record establishes that an ordinary artisan would not interpret either Baselga '96 or Baselga '94 in that manner.

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. 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. Appx9100-9101; Appx9109-9110. The Board also 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. Appx40-46; Appx1084. 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. Thus, an ordinary artisan could not draw any conclusion based on Baselga '96 as to whether the claimed combination would extend TTP. Appx10132-10138.

Third, the preclinical studies described in Baselga '94 do not fill in the holes of Baselga '96 and Baselga '97 sufficiently to support a reasonable expectation of success. It is undisputed that the only evidence of the combination of rhuMAb HER2 and paclitaxel reported in the prior art was in preclinical xenograft mouse models. Appx1089-1092; Appx9921-9922. There was no clinical data (i.e., in human patients) regarding the combination of rhuMAb HER2 and a taxoid, and there was no data in any model (human or otherwise) reporting the critical fact that rhuMAb HER2 plus a taxoid extended TTP as compared to paclitaxel alone. Rather, Baselga '94 analyzed response rate (i.e., tumor shrinkage) in mice, not TTP.

The Board found that response rate of the preclinical studies could be a "surrogate" for extension of TTP. Appx44. Not so. The record evidence established that an ordinary artisan would have understood that a therapy could

reduce tumor size without improving TTP because tumors can shrink and then grow back. Appx8896-8897; Appx9110-9111; Appx9549 ("The proportion of patients whose tumors shrink by at least 50% is the primary endpoint of most phase II trials although the durability of such responses is also of interest … such trials … do not determine the 'effectiveness' of the treatment."). Indeed, Petitioner's experts conceded that Baselga '94 did not measure TTP as an endpoint, and that it was difficult to extrapolate TTP in humans from the response rate seen in mice. Appx13991-13992; Appx13995; Appx14047-14048; Appx10498 ("It's hard to compare … animal results with human months."); Appx8721.

In any event, the record evidence further establishes that an ordinary artisan would not rely on Baselga '94 as providing a reasonable expectation of success of extending TTP in human patients. It is one thing to find (as the Board did) that Baselga '94's 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. Appx36-40. But it is an entirely different thing to find that this single preclinical study would suggest 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. Appx8883-8885; Appx10132-10136; Appx10098-10100.

Indeed, ordinary artisans would recognize that the significant limitations of Baselga '94's preclinical mouse xenografts undermine its predictive value in humans. Appx8883-8897; Appx9102-9103; Appx9114-9115. These limitations include that:

- Baselga '94 was a short-term study lasting only five weeks and measuring response rate, which would not inform an ordinary artisan as to a clinical endpoint (TTP) that takes several months to measure in humans. Appx86(29:20-30:12) (column titled "TTP(months)"); Appx8721; Appx8896-8897; Appx9087.
- Baselga '94 used a single cell line to make its mouse xenografts, which does not reflect a heterogenous human patient population. Appx8887-8892; Appx9102; Appx8810; Appx8889-8891; Appx9047-9049.

- The cell line Baselga ’94 chose, BT-474, was not representative of actual patients, but instead expressed the highest HER2 levels of any known breast-cancer cell line at the time. Appx8872-8873; Appx8879-8880; Appx8887-8892; Appx9162; Appx9178; Appx9153; Appx9048.
- The tumors in Baselga ’94 were implanted subcutaneously, and such tumors may react differently than those implanted in the tissues corresponding to cancer being studied. Appx8838; Appx8894-8896.
- The data reported in Baselga ’94 was limited and did not disclose the number of mice, did not provide a p-value (calculates statistical chance of result), and included only one data point (tumor size at five weeks). Appx13993-13994; Appx13994; Appx9719; Appx9731; Appx13994-13995; Appx9726.

Further compounding the shortcomings of Baselga ’94 is that other prior art preclinical studies came to the contrary conclusion of Baselga ’94. In in vitro studies, Yu found that “breast cancers that overexpress p185 ***will not respond well to Taxol***.” Appx8553 (emphasis added). In preclinical mouse studies, Hsu reported that “xenografts treated with rhuMAb HER-2 plus taxol ... were not significantly different from drug alone controls with the doses and dose schedules tested in this model.” Appx9922. Although the Board offered various reasons why an ordinary artisan may not view Hsu as discrediting Baselga ’94, Appx37-39,

the Board did not consider whether and how Hsu and/or Yu would affect the expectation of success analysis. Viewed as a whole, the prior art provides conflicting results from which an ordinary artisan would not draw any expectation of a particular result in humans. *See Honeywell International Inc. v. Mexichem Amanco Holding S.A. de C.V.*, 865 F.3d 1348, 1356 (Fed. Cir. 2017) ("Unpredictability of results equates more with nonobviousness rather than obviousness …"). Indeed, when Genentech was weighing whether to proceed with the Phase III clinical trial described in the '549 patent, individuals raised the concern that "[i]nconsistent results have been obtained with two different preclinical models." Appx8084.

In sum, the prior art establishes that significant uncertainties existed as to whether the combination of rhuMAb HER2, a taxoid, and a further agent would extend TTP as compared to a taxoid alone. Baselga '97's report on the existence of clinical trials does not provide a reasonable expectation of a particular result, Baselga '96 did not provide reliable information on the TTP of rhuMAb HER2 where it excluded more than half of the patients in its calculation, and the preclinical studies offered mixed results that offered no reasonable expectation of a particular result in humans. Therefore, the Board's finding that ordinary artisans would reasonably expect the claimed efficacy in the '549 patent claims is not supported by substantial evidence.

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.

Respectfully submitted,

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ADDENDUM

TABLE OF CONTENTS

Page(s)

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Paper 108
Entered: October 3, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC., and
SAMSUNG BIOEPIS CO., LTD.
Petitioners,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00737[1]
Patent 7,892,549 B2

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

POLLOCK, *Administrative Patent Judge*.

FINAL WRITTEN DECISION AND RELATED ORDERS

Claims 1–17 Shown to Be Unpatentable
35 U.S.C. § 318(a); 37 C.F.R. § 42.73

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

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[1] IPR2017-01960 has been joined with this proceeding. Paper 44, 7.

Denying Patent Owner's Motion to Exclude Evidence
Denying Petitioners' First and Second Motions to Exclude Evidence
37 C.F.R. § 42.64

Granting Patent Owner's Motions to Seal and Entry of Stipulated Protective Order
Denying Petitioners' Motions to Seal without Prejudice to Patent Owner
37 C.F.R. § 42.55

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–17 of U.S. Patent No. 7,892,549 B2 (Ex. 1001, "the '549 patent"). We have jurisdiction under 35 U.S.C. § 6.

Having reviewed the arguments of the parties and the supporting evidence, we find that Petitioners have demonstrated by a preponderance of the evidence that each of the challenged claims is unpatentable.

A. Procedural History

Petitioner Hospira, Inc. ("Pfizer") filed a Petition requesting *inter partes* review of claims 1–17 of the '549 patent. Paper 1 ("Pet.").[2] Patent Owner, Genentech, Inc., filed a Preliminary Response to the Petition. Paper 9 ("Prelim. Resp."). Based on the record before us at the time, we instituted trial with respect to all challenged claims. Paper 19, 25–26 ("Dec.").

Petitioner Samsung Bioepis Co., Ltd. ("Bioepis") timely submitted a Petition presenting substantially the same challenges as set forth in Pfizer's Petition along with a request for joinder. IPR2017-01960. Papers 1, 2. We granted Bioepis's

[2] Petitioner identifies Pfizer, Inc. as the real party in interest. Paper 10, 2.

Petition and associated request for joinder to IPR2017-00737. IPR2017-01960, Paper 11, 6–7.

After institution of trial and our grant of joinder, Patent Owner filed its Patent Owner Response (Paper 47, "PO Resp.") and Petitioners filed a Reply to the Patent Owner Response (Paper 68, "Pet. Reply").

Patent Owner also filed a Contingent Motion to Amend. Paper 49. Petitioners opposed. Paper 66. Patent Owner responded with a Reply in support of its motion (Paper 73); Petitioner further submitted an authorized Sur-Reply (Paper 80).

With respect to technical experts, Petitioner rely on the declarations of Allan Lipton, MD. (Exs. 1011, 1085, and 1099) and Robert Clarke, Ph.D., D.Sc. (Exs. 1086, 1100); Patent Owner relies on the declarations of Robert S. Kerbel, Ph.D. (Exs. 2016, 2143), Dr. Susan Tannenbaum (Exs. 2062, 2144).

Patent Owner filed motions for observations on the depositions of Dr. Lipton and Dr. Clark (Papers 85, 90), to which Petitioners provide responses (Papers 92, 95).

We heard oral argument on May 18, 2018. A transcript of that proceeding is entered as Paper 102 ("Tr.").

The parties filed the following motions to exclude evidence. Patent Owner filed one motion to exclude evidence. Paper 77. Petitioners opposed (Paper 88) and Patent Owner submitted a reply in support of its motion (Paper 91). Petitioners filed a first motion to exclude evidence. Paper 81. Patent Owner opposed (Paper 86) and Petitioners submitted a reply in support of its first motion (Paper 93). Petitioners filed a second motion to exclude evidence. Paper 98. Patent Owner opposed (Paper 100) and Petitioners submitted a reply in support of

their second motion (Paper 101). The parties have also filed five motions to seal, all unopposed. Papers 8, 48, 74 (by Patent Owner); Papers 65, 79 (by Petitioners).

B. Related Applications and Proceedings

The '549 patent issued from Application No. 10/356,824, filed February 3, 2003, which is a continuation of Application No. 09/208,649, filed Dec. 10, 1998 (the "649 Application"). U.S. Patent No. 7,846,441 B2 ("the '441 Patent) issued from the '649 Application on December 7, 2010. The '549 and '441 Patents claim benefit of priority to Provisional Application No. 60/069,346, filed Dec. 12, 1997 ("the '346 application"). *See e.g.*, Ex. 1001, (21), (63) (60), and 1:4–9.

In addition to this proceeding, we previously denied Petitioner Pfizer's challenge to claims 1–11 and 14–17 of the '549 patent and claims 1–14 of the '441 patent. *See* IPR2017-00739, Paper 16; *see also* IPR2018-00016, Paper 25. Petitioner Pfizer also challenges claims of the '441 Patent in IPR2017-00731. The '549 and '441 Patents are also subject to challenges by Celltrion Inc. in IPR2017-01122 and IPR2017-01121, respectively.

Petitioner has also filed IPR2017-00804 and IPR2017-00805 involving claims of U.S. Patent Nos. 6,627,196 and 7,371,379 respectively. These patents are not in the chain of priority of the '549 and '441 Patents but involve subject matter similar to that at issue here.

We issue concurrently our Decisions in IPR2017-00731, IPR2017-01139, IPR2017-01140, IPR2017-01121, IPR2017-01122, IPR2017-00804, and IPR2017-00805.

Patent Owner identifies the following District Court actions, "that relate or may relate to U.S. Patent Application No. 10/356,824, which issued as U.S. Patent No. 7,892,549:" *Celltrion, Inc. v. Genentech, Inc.,* No. 18-cv-00274 (N.D. Cal.) and *Celltrion, Inc. v. Genentech, Inc.,* No. 18-cv-00095 (D. Del.). Paper 57, 2.

Petitioner further directs us to invalidation and revocation proceedings involving European Patent EP 1,037,926, which, like the '549 patent at issue here, claims benefit of priority to the '346 application. *See* Pet. 1–2 (citing Exs. 1004, 1026, and 1049).

C. The '549 patent and Relevant Background

According to the Specification, 25% to 30% of human breast cancers overexpress a 185-kD transmembrane glycoprotein receptor ($p185^{HER2}$), also known as HER2 (human epidermal growth factor receptor-2) or ErbB2. Ex. 1001, 1:21–32, 5:16–21. These HER2-positive cancers are associated with poor prognoses and resistance to many chemotherapeutic regimens including anthracyclines (e.g., doxorubicin or epirubicin). *Id*. at 3:43–52; 4:11–12, and 11:41–45. Conversely, patients with HER2-positive cancers are three times more likely to respond to treatment with taxanes than those with HER2 negative tumors. *Id*. at 3:52–56 (citing Baselga '97 (Ex. 1007)).

Although "ErbB2 overexpression is commonly regarded as a predictor of poor prognosis," "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."[3] Ex. 1001, 3:35–61 (citing Baselga '96 (Ex. 1005)). Anti-ErbB2 4D5 antibodies also "enhance the activity of paclitaxel (TAXOL®) and doxorubicin against breast cancer xenographs in nude mice injected with BT-474 human breast adenocarcinoma cells, which express high levels of HER2." *Id*. at 3:56–61 (citing Baselga '94 (Ex. 1006)).

[3] "HERCEPTIN® is the tradename for the commercial product of the humanized antibody, trastuzumab." Paper 49, 3 fn.2.

According to the Specification,

> 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.

Id. at 3:65–4:5.

The '549 patent thus relates to the treatment of breast cancers that overexpress HER2/ErbB2 "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."[4] Ex. 1001, 4:6–13. In some embodiments, the anti-ERbB2 antibody of the combination is Herceptin® and the chemotherapeutic agent "is a taxoid, such as TAXOL® (paclitaxel) or a TAXOL® derivative." *Id*. at 4:23–25. The combination may further include one or more additional anti-ErbB2 antibodies, "antibodies which bind to the EGFR . . . ErbB3, ErbB4, or vascular endothelial factor (VEGF)," "one or more cytokines," or "a growth inhibitory agent." *Id*. at 11:4–40 (defining "chemotherapeutic agent" and "growth inhibitory agent"), 23:60–24:5, and 25:20–34.

The '549 patent also provides an Example disclosing the conduct and results of a clinical trial involving 469 women with metastatic HER2-positive breast cancer. *Id*. at 26:34–30:25. All patients were treated with one of two

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[4] The Specification defines a "therapeutically effective amount" of the combination as "an amount having [an] antiproliferative effect," which can "be measured by assessing the time to disease progression (TTP) or determining the response rates (RR)." Ex. 1001, 10:41–50.

chemotherapy regimens (CRx) designated either "AC" for anthracycline (doxorubicin or epirubicin) and cyclophosphamide, or "T" for Taxol (paclitaxel). *See id*. at 28:5–47; 29:13–30:12. Half of the patients were also treated with the anti-ERbB2 antibody Herceptin, designated "H." *Id*. The Specification discloses that "[a]t 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)." *Id*. at 29:13–18. In addition, "[a] syndrome of myocardial dysfunction similar to that observed with anthracyclines was reported more commonly with a combined treatment of AC-H (18% Grade ¾) than with AC alone (3%), T (0%), or T+H (2%)." *Id*. at 30:13–16. According to the inventors:

> 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®).

Id. at 30:17–25.

D. Challenged Claims

In accordance with the Petition, we instituted trial with respect to claims 1–17. Pet. 4. Claims 1, 5, and 16 are independent. Claim 1, reproduced below, requires "administering a combination" of three agents—an anti-ErbB2 antibody, a taxoid, and "a further growth inhibitory agent"—"in an amount effective to extend the time to disease progression:"

> 1. A method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor, comprising administering a

> combination of an antibody that binds ErbB2, a taxoid, and a further growth inhibitory agent to the human patient in an amount effective to extend the time to disease progression in the human patient, wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence.

Independent claim 16 is similar to claim 1, but further includes a negative limitation requiring the administration of an anti-ErbB2 antibody, a taxoid, and a further growth inhibitory agent "in the absence of an anthracycline derivative."

Independent claim 5 recites "administering an effective amount of a combination" of three agents similar to those of claims 1 and 16, wherein the antibody binds to the 4D5 epitope of ErbB2, the taxoid is paclitaxel, and the third element is broadly described as a "therapeutic agent." Depending from claim 5, claims 12, 13, and 14, respectively, specify that the "therapeutic agent" is another anti-ErbB2 antibody, a vascular endothelial growth factor (VEGF), or "a growth inhibitory agent" (as recited in claim 1). Depending from claims 1 and 5, respectively, claims 2 and 7 require that the anti-ErB2 4D5 antibody is humanized.

E. Reviewed Grounds of Unpatentability

We instituted trial to review the patentability of the challenged claims on each of the six grounds asserted in the Petition:

Ground	**Claim(s)**	**References**	**Basis**
1	1–11 and 14–17	Baselga '97[5] and Gelmon[6]	§ 103

[5] Baselga et al., *HER2 Overexpression and Paclitaxel Sensitivity in Breast Cancer: Therapeutic Implications*, Update on the Taxanes in Breast Cancer, Oncology, Vol. 11, No. 3 (Suppl. 2), 43–48 (1997) ("Ex. 1007").

[6] Gelmon et al., *Phase I/II Trial of Biweekly Paclitaxel and Cisplatin in the Treatment of Metastatic Breast Cancer,* Journal of Clinical Oncology, Vol. 14, No. 4, 1185–91 (1996) (also referred to as "Gelmon '96" "Ex. 1025").

Ground	Claim(s)	References	Basis
2	12	Baselga '97, Gelmon, and Drebin[7]	§ 103
3	13	Baselga '97, Gelmon, and Presta[8]	§ 103
4	1–11 and 14–17	Baselga '96,[9] Baselga '94,[10] and Gelmon	§ 103
5	12	Baselga '96, Baselga '94, Gelmon, and Drebin	§ 103
6	13	Baselga '96, Baselga '94, Gelmon, and Presta	§ 103

II. ANALYSIS

A. Principles of Law

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented 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

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[7] Drebin et al., *Monoclonal antibodies reactive with distinct domains of the neu oncogene-encoded p185 molecule exert synergistic anti-tumor effects in vivo*, Oncogene, An International Journal, Vol. 2, No. 3, 273–77 (1988) ("Ex. 1010").
[8] Presta et al., *Humanization of an Anti-Vascular Endothelial Growth Factor Monoclonal Antibody for the Therapy of Solid Tumors and Other Disorders*, Cancer Research, Vol. 57, No. 20, 4593–99 (1997) ("Ex. 1012").
[9] Baselga et al., *Phase II Study of Weekly Intravenous Recombinant Humantized Anti-p195^{HER2} Monoclonal Antibody in Patients with HER2/neu-Overexpressing Metastatic Breast,* Cancer, Journal of Clinical Oncology, Vol. 14, No. 3, 737–44 (1996) ("Ex. 1005").
[10] Baselga et al., Program/Proceedings, 13th Annual Meeting, American Society of Clinical Oncology, Vol. 13, 63, Abstract 53 (1994). ("Ex. 1006").

person having ordinary skill in the art to which that subject matter pertains.[11] *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved based on underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness, if present. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"[T]he [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418. Moreover, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (citations omitted).

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

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[11] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), amended 35 U.S.C. §§ 102 and 103. Because the challenged claims of the '405 patent have an effective filing date before the effective date of the applicable AIA amendments, throughout this Final Written Decision we refer to the pre-AIA versions of 35 U.S.C. §§ 102 and 103.

B. Person of Ordinary Skill in the Art

Petitioner argues that a person of ordinary skill in the art as of the effective filing date of the '549 patent "would be a clinical or medical oncologist specializing in breast cancer with several years of experience with breast cancer research or clinical trials." Pet. 6 (citing Ex. 1011 ¶¶ 15–17; Ex. 1004 ¶¶ 29–31). Patent Owner does not dispute Petitioner's proposed definition. Prelim. Resp. 36; *see also* PO Resp. 37.

Based on our review of the '549 patent, the cited art, and the testimony of Dr. Lipton, we adopted Petitioner's definition for the purposes of instituting trial. Dec. 8–9. Upon consideration of the complete record, we do not find cause to modify that determination. We further note that 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)).

C. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S.Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016). 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).

1. "*administering a combination*"

In our Decision instituting *inter partes* review, we adopted Patent Owner's unopposed definition of "administering a combination" as requiring "a single treatment regimen in which the patient receives all drugs that are part of the claimed combination." Dec. 10 (citing Prelim. Resp. 36–37). In arriving at that decision, we found particularly persuasive Patent Owner's argument that

> "the absence of an anthracycline derivative" language in dependent claims 16 and 17, "would make no sense if 'administering a combination' included drugs received as part of a different treatment regimen [because] [i]n the '549 patent's working example, patients were administered the combination of the anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative only if they had 'received any anthracycline therapy in the adjuvant setting.'"

Id. Relying on essentially the same arguments, Patent Owner now recasts its proposed definition "to mean that the drugs are administered as part of the same treatment regimen." PO Resp. 37. Petitioners expressly agree with Patent Owner's proposal. *See* Pet. Reply 2 ("Petitioner agrees for this IPR that the BRI of 'administering a combination' is administering drugs 'as part of the same treatment regimen.' (*See also* Ex. 1085 ¶¶89–90.).").

For the purpose of this proceeding, we find Patent Owner's two definitions interchangeable. Nevertheless, in light of the agreement of parties, and as supported by the reasoning set forth on pages 37–39 of the Patent Owner Response, we interpret "administering a combination" to mean that the drugs are administered as part of the same treatment regimen.

2. "*an amount effective to extend the time of disease progression" and "an effective amount"*

Independent claims 1 and 16 require administering a combination of an anti-ErbB2 antibody, a taxoid, and a further agent, "in an amount effective to extend the time to disease progression [TTP] in the human patient." Claim 5, the remaining independent claim before us, more generically recites administering the three-part combination to a human patient in "an effective amount."[12]

In our Decision to Institute, we construed "an amount effective to extend the time to disease progression in the human patient" in independent claims 1 and 16 as an amount sufficient to extend the time to disease progression in a human patient having breast cancer that overexpresses ErbB2 receptor *as compared to one receiving no treatment*. Dec. 12–13. We also construed the language "an effective amount" of independent claim 5 as encompassing "an amount effective to extend the time to disease progression in the human patient" and, thus, similarly indicating a comparison to an untreated patient. *See id.*

Patent Owner disagrees with our construction, contending that the proper comparator in both claim terms is not an untreated patient, but a patient treated with taxoid alone. PO Resp. 39–42. In particular, Patent Owner argues that comparison to an untreated patient "is not consistent with the specification as understood by a POSA," and "makes no sense in the context of a disease like breast cancer." *Id.* at 39–40. Yet this is precisely the comparison Applicants made to obtain allowance of the challenged claims.

"A patent's specification, together with its prosecution history, constitutes intrinsic evidence to which the [the Board] gives priority when it construes

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[12] To the extent that these terms may differ in scope, neither party contends that any difference affects the patentability analysis and we consider them together.

claims." *Knowles Electronics LLC v. Cirrus Logic, Inc.*, 883 F.3d 1358, 1361–62 (Fed. Cir. 2018) (footnote omitted). "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). Prosecution disclaimer

> requires that the alleged disavowing actions or statements made during prosecution be both clear and unmistakable. Thus, when the patentee unequivocally and unambiguously disavows a certain meaning to obtain a patent, the doctrine of prosecution history disclaimer narrows the meaning of the claim consistent with the scope of the claim surrendered. Such disclaimer can occur through amendment or argument. . . . [and] includes all express representations made by or on behalf of the applicant to the examiner to induce a patent grant . . . includ[ing] amendments to the claims and arguments made to convince the examiner.

Aylus Networks, Inc. v. Apple Inc., 856 F.3d 1353, 1359 (Fed. Cir. 2017) (internal citations and quotations omitted); *see also Arendi S.A.R.L. v. Google LLC*, 882 F.3d 1132, 1135–36 (Fed. Cir. 2018). Those conditions are satisfied here.

The claim language "an amount effective to extend the time to disease progression" implies that time to disease progression is extended in relation to some metric, but none of the challenged claims expressly identifies the intended comparator. The Examiner addressed this facial ambiguity during the prosecution leading to the issuance of the '549 patent. In particular, during the prosecution of the '649 Application (the direct predecessor to the '842 Application, from which the '549 patent issued), the Examiner rejected then-pending claims under 35 U.S.C. § 112, second paragraph because:

> 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?

Ex. 3001, 3–4 (OA dated 7/17/01).[13] In response, Applicants asserted 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.

Id. at 17–18 (Response dated 1/17/2002); *see also* Ex. 1021, 19, (15:12–17), 46–47 (42–43).

The Examiner withdrew the rejection in the next office action, stating that "[a]ll claims are allowable." Ex. 3001, 24 (OA dated 3/27/2002) (suspending prosecution due to potential interference); *see also id*. at 27–317 (OA dated 8/12/2003) (new grounds of rejection not relating to the phrase "extend the time to disease progression"). Accordingly, Applicants overcame the § 112 rejection by providing an express definition of the term "extend the time to disease progression" as meaning relative to an untreated patient. Our construction reflects Applicants' choice. *See In re Paulsen*, 30 F.3d at 1480 (holding an applicant may choose to be his own lexicographer).

Patent Owner contends that we erred in our construction because "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)

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[13] Excerpts of prosecution history of US Application No. 09/208,649. Citations refer to pages of the exhibit overall rather than to the native pagination.

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. 40. 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 ¶ 136. As a result, an ordinary artisan would have understood that, even without any explicit disclosure in the '549 patent, administering the claimed combinations would extend the TTP as compared to untreated patients. *See e.g.*, Ex. 1011 ¶ 67.

With respect to the prosecution history, Dr. Tannenbaum testifies that, "in context," Applicants used the term "untreated patient" to refer to "a patient that had not received the combination therapy, but instead received paclitaxel alone." Ex. 2062 ¶ 141. We do not find Dr. Tannenbaum's argument persuasive.

The Examiner asked Applicants to choose from various potential meanings for the claim language: "is the extension of time to disease progress[ion] relative to untreated patients? Patients who received antibody or taxoid alone? Patients who received antibody and an anthracycline?" Ex. 3001, 3–4. Despite being presented with the option of selecting "taxoid alone" as the comparator, Applicants did not choose that option. Applicant instead 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). Indeed, Dr. Tannenbaum admitted that much at her deposition, agreeing that "there can be no confusion" that Applicants were "choosing the comparator untreated patients rather than taxoid alone." *See* Ex. 1087, 225:15–226:13.

Patent Owner admits that Applicants were "asked very specifically by the patent examiner what's the comparator," but fails to persuade us that by citing to certain passages in the Specification, Applicants meant something quite different from the plain statement in the prosecution history. *See* Tr. 41:23–44:11. We, instead, find persuasive Dr. Lipton's testimony in a co-pending proceeding involving the '441 Patent that "during prosecution, Patent Owner asserted that the appropriate comparison for the term 'extend the time to disease progression'' is to compare the claimed combination treatment to no treatment at all."[14] IPR2017-02063, Ex. 1102 ¶ 112(h); *see* Pet. Reply, 3.

In view of the undisputed fact that "cancer generally continues to progress without treatment" (Ex. 2062 ¶ 136), we are not persuaded by Patent Owner's contention that our adopted construction "makes no sense in the context of a disease like breast cancer." PO Resp. 40. But even assuming that to be the case, Applicants chose this definition "with reasonable clarity, deliberateness, and precision," and obtained the '549 patent only after doing so. *See In re 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." *Source Vagabond Sys. Ltd. v. Hydrapak, Inc.*, 753 F.3d 1291, 1301 (Fed. Cir. 2014).

Accordingly, we maintain that the proper analysis of the claim language "in an amount effective to extend the time to disease progression [TTP] in the human patient" and administering the three-part combination to a human patient in "an effective amount" involves comparing the claimed combination treatments to no

[14] As is evident from section I(B), above, the '441 Patent and the '549 Patent are in the same chain of priority and have essentially the same Specification.

treatment. As explained below, however, the challenged claims are unpatentable even if we apply the construction advanced by Patent Owner.

D. Grounds 1–3

In Ground 1, Petitioner challenges claims 1–11 and 14–17 as obvious under 35 U.S.C. § 103 based on Baselga '97 and Gelmon. Pet. 25–41. In Grounds 2 and 3, respectively, Petitioner further asserts Drebin (claim 12) and Presta (claim 13). *Id.* at 41–43. Patent Owner opposes. PO Resp. 42–49.[15]

We begin with an overview of the asserted references.

1. *Overview of Baselga '97 (Ex. 1007)*

Baselga '97 reviews the relationship and clinical implications of HER2 overexpression and chemotherapeutics, most particularly taxanes, in the treatment of breast cancers. Baselga '97 states that HER2 positive tumors "have increased resistance to adjuvant CMF (cyclophosphamide, methotrexate, and fluorouracil)-based therapy and, conversely, increased dose-response effects to an anthracycline-containing regimen." Ex. 1007, 6. Moreover, the "[a]vailable data . . . suggest that HER2 overexpression may influence the response to paclitaxel in patients with metastatic breast cancer and that anti-HER2 monoclonal antibodies significantly increase the antitumor activity of paclitaxel in vitro and in vivo." *Id.*

Baselga '97 states that "[i]n preclinical models the combined therapy of breast cancer cells that overexpress HER2 with agents that interfere with HER2 function and paclitaxel results in a marked antitumor effect." *Id.* at 11. In particular, "[t]he murine monoclonal antibody (MoAb) 4D5, directed against the extracellular domain of $p185^{HER2}$ (ECD^{HER2}), is a potent inhibitor of in vitro growth

[15] Patent Owner does not separately argue that the limitations of claims 12 and 13. *See e.g.,* Pet. Reply 25.

and, in xenograft models, of human breast cancer cells overexpressing HER2." *Id*. at 7. In a mouse model using HER2-expressing BT-474 cell implants:

> Therapy with MoAb 4D5 alone produced a 35% growth inhibition, and paclitaxel alone resulted in a 35% growth inhibition when compared with animals treated with a control MoAb. The treatment with paclitaxel plus 4D5 resulted in major antitumor activity, with 93% inhibition of growth. This result was markedly better than an equipotent dose of doxorubicin (10 mg/kg IP) and 4D5 (70% inhibition). In addition, paclitaxel combined with 4D5 resulted in the disappearance of well-established xenografts.

Id. at 9.

According to Baselga '97, because the potential for immunogenic response limits the clinical application of murine antibodies, Genentech scientists developed a recombinant, humanized version of MoAb 4D5, designated rhuMoAb HER2, "to facilitate further clinical investigations." Ex. 1007, 44, 46. Referencing the Phase II clinical trials results of Baselga '96 (citation 39), Baselga '97 teaches that rhuMoAb HER2, alone, "is clinically active in patients who have metastatic breast cancers that overexpress HER2 and have received extensive prior therapy." *Id*. at 9–10. Baselga '97 further notes that another Phase II clinical trial involving HER2+ breast cancer patients demonstrated that the combination of rhuMoAb HER2 and cisplatin resulted in a 25% response rate "suggesting that the synergy observed in the laboratory was reproducible in the clinic" and did not increase toxicity as compared to cisplatin alone. *Id.* (referencing Pegram (Ex. 1013)).[16] With respect to the combination of rhuMoAb HER2 and paclitaxel, Baselga '97 states:

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[16] Pegram *et al*., *Phase II Study of Intra Venous 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).

> Results from the phase II studies and the activity of rhuMoAb HER2 against xenografts when given in combination with doxorubicin and paclitaxel have been encouraging. These positive results have led to the design of a phase III multinational study of chemotherapy in combination with rhuMoAb HER2 in patients with HER2-overexpressing breast tumors who have not received prior chemotherapy for metastatic disease.

Id. at 10. "The main goal of [the phase III] study is to determine whether the addition of this anti-HER2 antibody increases the time to disease progression compared with the group of patients treated with [sic], [chemotherapy alone]." *Id*.; *see, e.g, id*. at Figure 2 (showing randomization to either chemotherapy alone ("AC/Paclitaxel") or chemotherapy "+ rhuMab HER2"). "The study end point is time to disease progression." *Id*. at Figure 2.

Treatment consists of either cytotoxic chemotherapy or chemotherapy plus treatment with rhuMoAb HER2. *Id*. at 10. The chemotherapy regimen is selected based on whether the patients have been previously treated with anthracyclines (e.g., doxorubicin or epirubicin). *Id*. Patients that have not previously been treated with anthracyclines are administered a combination of cyclophosphamide and doxorubicin or epirubicin, whereas patients with a history of anthracycline therapy are treated with paclitaxel. *Id*. Besegla '97 notes that "[b]ecause anthracyclines are widely used in the adjuvant setting, it is likely that a significant number of patients will be treated with paclitaxel ± rhuMoAb HER2." *Id*. Baselga '97 describes the phase III trial as "ongoing" and presents no results from this study. *Id*.[17]

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[17] The Parties agree that results of the Phase III clinical trial discussed in Baselga '97 are disclosed in the '549 Patent. *See, e.g.,* Pet. 8–9; PO Resp. 20. Although Patent Owner discloses internal deliberations of Dr. Hellman and other Genentech employees regarding the design of that study (*see e.g.,* PO Resp. 24–26) we consider such discussion only by way of background and do not rely on the

2. *Overview of Gelmon (Ex. 1025)*

Gelmon states that, "Phase II studies have shown paclitaxel to be an active single agent in metastatic breast cancer, with reported response rates of 17% to 62%. . . . Promising results have also been reported with combinations of paclitaxel with other active agents such as doxorubicin, cyclophosphamide, and edatrexate." Ex. 1025 at 9. "We were also interested in combining [paclitaxel] with a non-cross-resistant drug with a different spectrum of toxicity. Cisplatin seemed to be an appropriate choice." *Id*. Gelmon further notes that paclitaxel and cisplatin have different resistance mechanisms and that "synergism between paclitaxel/cisplatin has been established in preclinical models and this has been translated as clear clinical benefits." *Id.* at 9–10 (noting that the combination has demonstrated "improved survival when administered as first-line therapy" for ovarian cancer). Accordingly, Gelmon presents the results of a Phase I/II clinical study designed

> (1) to determine the toxicity of paclitaxel and cisplatin in a biweekly schedule, (2) to establish the maximum-tolerated dose of paclitaxel in combination with a fixed dose of cisplatin (60 mg/m^2) for patients with metastatic breast cancer, (3) to determine the feasibility of repeated biweekly administrations, and (4) to evaluate the activity of this combination in this disease setting.

Id. at 10.

According to Gelmon, "[a]ll but two of the women in our trial had been treated with previous adjuvant chemotherapy, and 23 of 29 patients had previous exposure to anthracyclines." *Id*. at 13. Of the 27 patients assessed for efficacy,

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underlying documents insofar as they do not appear to have been publically available, and Patent Owner does not attempt qualify them as prior art. *See Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, No. 2017-2078, 2018 WL 4288982, at *7 (Fed. Cir. Sept. 10, 2018) (discounting patent owner's unpublished clinical trial data because it "could not have informed the legally relevant person of skill in the art").

three showed a complete response with a time to disease progression of 110 to 200 days, and 20 showed a partial response with a time to disease progression of 96 to 377+ days. *See, e.g.*, *id.* at Abstract. Overall, patients treated with the paclitaxel/cisplatin regimen showed an overall response rate of 85% and a median time to disease progression of 7.1 months. *Id*. Gelmon concludes that "[b]iweekly paclitaxel and cisplatin is an active combination in the treatment of metastatic breast cancer, including for patients with previous exposure to anthracyclines." *Id*.

3. *Overview of Drebin (Ex. 1010)*

Drebin discloses that administering combinations of anti-ErbB2 antibodies "reactive with two distinct regions on the p185 molecule" in a mouse model, "resulted in synergistic anti-tumor effects and complete eradication of tumors." Ex. 1010, Abstract, 5. Drebin concludes that antibodies specific for human p185 may "find application as adjuvant therapy for diseases like breast cancer." *Id*. at 7.

4. *Overview of Presta (Ex. 1012)*

Presta describes the preparation of recombinant, humanized anti-VEGF antibodies that inhibit VEGF-induced proliferation of endothelial cells in vitro and the growth of breast carcinoma cell tumors in a mouse model. *See, e.g.,* Ex. 1012, Abstract, 11. According to Presta, "[t]his humanized MAb is suitable for clinical trials to test the hypothesis that inhibition of VEGF action is an effective strategy for the treatment of cancer and other disorders in humans." *Id*. at 8.

5. *Analysis*

Petitioners have provided a reasoned, claim-by-claim explanation for the basis of its contention that claims 1–11 and 14–17 would have been obvious under 35 U.S.C. § 103 based on the combination of Baselga '97 and Gelmon, and that claims 12 and 13 would have been obvious in view of the further teachings of Drebin and Presta, respectively. Pet. 25–43.

As set forth in section II(D)(1),(2), above, Baselga '97: (1) teaches the clinical efficacy of rhuMoAb HER2 alone, or in combination with cisplatin in treating HER2-positive breast cancer; (2) notes that a non-humanized precursor of rhuMoAb HER2 is synergistic with paclitaxel in a mouse model of HER2-positive breast cancer; and (3) describes an on-going clinical trial of rhuMoAb HER2 in combination with paclitaxel. Gelmon teaches combining paclitaxel with cisplatin for the treatment of breast cancer based on synergism between the two compounds in preclinical models, non-cross reactivity, differing toxicity profiles, and observed efficacy of the combination in treating ovarian cancer. Gelmon further discloses the results of a Phase I/II clinical trial demonstrating that paclitaxel in combination with cisplatin is active in the treatment of metastic breast cancer.

According to Petitioners, "two- and three-agent combinations[] were routinely used to fight cancer, including breast cancer" such that "the claimed three-drug treatment is nothing more than the natural result of following the prior art's explicit teachings." Pet. Reply 1, 17 (citations omitted). In particular:

> Anti-ErbB2 antibodies, paclitaxel, and cisplatin had all been used in human patients in the prior art, and two-drug combinations of each of them were shown to be synergistic. Drug combinations generally, including two- and three- agent combinations, were routinely used to fight cancer, including breast cancer. And it was well known that combination chemotherapies were superior to single agent therapies. Combinations, like anti-ErbB2 antibodies, paclitaxel, and cisplatin, acting on different and complementary pathways were known to have a greater probability of exhibiting synergy without resulting in drug resistance or enhanced toxicity.

Pet. 17 (citations omitted). In sum, Petitioners argue, "[e]very component of the claimed three-drug combination was known in the prior art," and "[t]he thought to combine these known treatments was nothing more than the exercise of routine skill." Pet. 15.

According to Petitioners, Patent Owner "concede[s] that Baselga '97 teaches treating humans with the combination of trastuzumab and paclitaxel" and "does not dispute that Gelmon[] showed synergistic efficacy from the paclitaxel-cisplatin combination in treatment of metastatic breast cancer without undue toxicity, motivating POSAs to further investigate adding additional non-cross-resistant agents in three-drug combinations." Pet. Reply 1, 4, and 6. Petitioners further point out that Patent Owner does not contest that the claimed clinical efficacy benefit (extended TTP) would have been expected under the Board's construction, and that even under Patent Owner's construction, extended TTP would have been expected. *Id.* at 1–2, 4.

Pertinent to all Grounds, Patent Owner argues that the Board applies an incorrect claim construction; and that under its preferred construction "a POSA would not have had a reasonable expectation of success that the combination of an anti-ErbB2 antibody and a taxoid would extend TTP as compared to taxoid-only treatment." *See, e.g.,* PO Resp. 3–7. Also relevant to all Grounds, Patent Owner contends that one of ordinary skill in the art would not look to Gelmon with respect to treating HER2-positive patients. *Id.* at 6. We first address patentability under the Board's construction and certain issues raised with respect to Gelmon.

a) an amount effective to extend the time to disease progression

With respect to the limitation, "an amount effective to extend the time to disease progression," Dr. Lipton notes:

> Baselga '97 teaches that the single agent therapy with rhuMAb HER2 produced a measurable response in 11% of patients with a median increased time to disease progression of 5.1 months, and that a main clinical outcome for the phase III trial is measuring time to disease progression. Thus, since rhuMAb HER2 on its own extends the time to disease progression, other than trace administration of a

> taxoid and a further growth inhibitory agent, nothing more is required by claim 1 to meet this limitation.

Ex. 1011 ¶ 84. Under the Board's construction of "in an amount effective to extend the time to disease progression" of independent claims 1 and 16, or the more inclusive term, "an effective amount," of independent claim 5, Patent Owner does not dispute the conclusion reached by Dr. Lipton. *See* PO Resp. 42–52 (limiting arguments to comparison with taxoid alone in contravention of the Board's construction). Nor does Patent Owner, nor our own reading of the prior art, suggest that one of ordinary skill in the art would believe that the addition of paclitaxel and/or a further growth inhibitory agent would negate the increased time to disease progression mediated by rhuMAB HER2.

As noted above in section II(D)(1)(a), Baselga '97 further teaches the benefit of treating HER2+ breast cancer patients with rhuMAb HER2 alone, and that clinical trial with those antibodies in combination with chemotherapy agents (including paclitaxel) are underway. Baselga '97 further references Pegram's disclosure of a Phase II clinical trial of HER2+ breast cancer patients treated with a combination of rhuMoAb HER 2 and cisplatin. Ex. 1007, 9–10; *see also* Ex. 1013. According to Baselga '97, the combination therapy did not increase toxicity as compared to cisplatin alone but resulted in a 25% response rate "suggesting that the synergy observed in the laboratory was reproducible in the clinic." *Id.* at 10.

Gelmon similarly discloses that paclitaxel is active as a single agent in metastatic breast cancer, and exhibits advantageous, if not synergistic, results in combination with cisplatin. *See* Section II(D)(1)(b), *supra*; Ex. 1011 ¶¶ 58–60. We find particularly unpersuasive Patent Owner's argument that one of ordinary skill in the art would not have made the claimed combination "in the first place" because HER2-positive breast cancer "would not respond well" to standalone paclitaxel (*see* PO Resp. 8–9 (citing Yu (Ex. 2029)). Contrary to Patent Owner's

argument, the claimed combination does not relate to standalone paclitaxel, and the use of paclitaxel to treat HER2-positive breast cancer in combination therapies was well known. We note, for example, Gelmon's teaching to combine paclitaxel with cisplatin and Baselga '97's disclosure that paclitaxel was being combined with rhuMoAb HER2 in clinical trials based on promising preclinical data. *See also* Ex. 1085 ¶ 34 (citing Ex. 1078, 5 ("HER2 overexpression in MBC seems to confer *sensitivity* rather than resistance to taxanes").[18] We, thus, find persuasive Dr. Lipton's testimony that one of ordinary skill in the art would have been motivated to combine Baselga '97 and Gelmon with a reasonable expectation of success, particularly in light of Gelmon's teaching "that paclitaxel and cisplatin have different mechanisms of resistance, do not have overlapping toxicity, and have demonstrated synergism." *See* Ex. 1011 ¶ 85.

Moreover, we accept Dr. Lipton's testimony that because Baselga '97 teaches that rhuMAb HER2 extends time to disease progression and Gelmon teaches that cisplatin plus paclitaxel extends time to disease progression, "a POSITA would have had a reasonable expectation that the three-drug combination at the disclosed doses for each drug would be an amount effective to extend the time to disease progression." Ex. 1011 ¶ 86. As set forth below in section II(F), we reach the same conclusion under the claim construction advanced by Patent Owner.

b) Gelmon

As analyzed under the Board's claim construction, Patent Owner's arguments in favor of patentability collapse into the question of whether one of

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[18] Seidman et al., *HER-2/neu 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. 1078").

ordinary skill in the art would reasonably combine Baselga '97 with Gelmon. Patent Owner first contends that one of ordinary skill in the art would not look to Gelmon with respect to treating HER2-positive patients because only 25–30% of Gelmon's breast cancer patients were HER2-positive and "a POSA would have no way of knowing whether the results reported in Gelmon[] would be applicable to HER2-positive patients." PO Resp. 61 (citing Ex. 1001 1:23–29; Ex. 2027, 783; Ex. 2062 ¶ 219). We do not find this argument persuasive in light of the evidence set forth on page 17 of Petitioners' Reply Brief.

We note, for example, the testimony of Patent Owner's expert, Dr. Tannenbaum, agreeing that "persons skilled in the art would look generally to the experience with chemotherapeutic agent treatment in metastatic breast cancer generally" and "the fact that a particular study did not address the HER2-positive status . . . doesn't mean that it would have been discounted in determining which therapeutic agent to combine with Herceptin." Ex. 1087, 297:7–298:21. Patent Owner's argument is further rebutted by Baselga '97's disclosure that the combination of rhuMoAb HER2 and cisplatin was therapeutically synergistic in HER2+ breast cancer patients, thus indicating that one of ordinary skill in the art would have understood that the combination of rhuMoAb HER2 and cisplatin may be used to treat HER2+ breast cancer. *See* Ex. 1007, 9–10; Ex. 1013 (Pegram).

Patent Owner further characterizes Gelmon's results as an "anomaly" and argues that Gelmon's teachings are "undermined" by reports in Wasserheit (Ex. 2062), Sparano (Ex. 2120), and McCaskill-Sevens (Ex. 2121) that cisplatin in combination with paclitaxel did not appear to show any clinical benefit as compared to paclitaxel alone and/or was accompanied by unacceptable side effects. PO Resp. 47–48; 61–62. Distinguishing these references, Petitioners note that

> Wasserheit concluded that "higher doses of both agents per cycle" likely accounted for higher toxicity compared to Gelmon. (Exs. 2068

> at 1997; 1087_300:8-23.) Sparano stated lower response rates most likely were due to "the marked imbalance in number of disease sites." (Exs. 2120 at 1884; 1087_300:24-302:23.) And McCaskill-Stevens still showed a relatively high (***60%***) response rate for the paclitaxel/cisplatin combination. (Ex. 2121 at 2.)

Pet. Reply 18. Further with respect to the reliability of Gelmon's disclosure, we find persuasive the additional evidence in Petitioners' Reply Brief indicating that one of ordinary skill in the art would have been motivated to use cisplatin and paclitaxel in combination with other agents for the treatment of breast cancer. *See id.* at 18–19. Frasci, for example, reports that between June 1995 and January 1997, and based on Gelmon's "very promising response rate," forty-three women with metastatic breast cancer began treatment with paclitaxel and either cisplatin or doxorubicin. Ex. 1082, Abstract. Also relying on Wasserheit's and Gelmon's "promising early results" the investigators in Klaassen treated patients with a combination of paclitaxel, cisplatin, and 5-fluorouacil/leucovorin. Ex. 1083, Abstract, 5; *see also* Ex. 1085 ¶ 116; Ex. 1087, 313:23–314:24 (Dr. Tannenbaum agreeing that Klaassen indicated motivation to add additional drugs to the paclitaxel/cisplatin regimen.).[19]

c) *Anthracyclines*

For the reasons set forth at pages 13–15 of Petitioners' Reply Brief, we are also not persuaded that one of ordinary skill in the art would have been motivated to use anthracyclines instead of a taxoid as the chemotherapeutic in combination with rhuMAb HER2. *See* PO Resp. 59–60 (citing Ex. 2062 ¶¶196–199, 201, 216,

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[19] Klaassen *et al.*, *Phase II Study with Cisplatin and Paclitaxel in Combination with Weekly High-dose 24 h Infusional 5-fluorouracil/leucovorin for First-line Treatment of Metastatic Breast Cancer*, 9 ANTI-CANCER DRUGS 203-07 (1998).

226). As Petitioners point out, that persons of ordinary skill in the art may have been motivated to combine rhuMAb HER2 with an anthracycline for the treatment of breast cancer, does not establish non-obviousness of the rhuMAb HER2/taxoid combination. *See* Pet Reply 13 (citing *In re Fulton*, 391 F.3d 1195 (Fed. Cir. 2004)). To the contrary, evidence of record shows that although anthracyclines were widely employed, paclitaxel was approved as second-line therapy for breast cancer, and routinely used as a first-line therapy. *See* Ex. 1011 ¶¶ 15-16; Ex. 1066; Moreover, Nicolaou[20] described paclitaxel as "one of the most promising treatments for breast and ovarian cancer," and at least one treatment arm of the Phase II trial reported in Baselga '97 was conducted with paclitaxel rather than anthracycline. Ex. 1036, 5; *see also* section II(E)(1). Moreover, one of ordinary skill in the art would have been aware of Baselga '94, which is cited in Baselga '97, and expressly suggests the combination of rhuMAb HER2 with either anthracycline or a taxoid. *See* Ex. 1009, 14–15 (noting "a marked synergy of taxol in combination with anti-EGF receptor MAbs" in animal studies and stating that "[a] potentially more effective approach [to treating advanced breast cancer] involves combination therapy with anti-EGF receptor MAb plus a second agent, such as doxorubicin or taxol."). Accordingly, we are persuaded that as of the relevant date those of ordinary skill in the art were motivated to combine rhuMAb HER2 with paclitaxel rather than anthracyclines. *See also* Ex. 1086 ¶¶ 77–81 (concluding that "the preclinical results reported in Baselga '94, alone or in combination with the clinical results in Baselga '96, would have given those skilled in the art a reasonable expectation that adding rhuMAb HER2 to paclitaxel

[20] Nicolaou et al., Taxoids: New Weapons against Cancer, Scientific Am., Vol. 274, No. 6, 94–98 (1996) ("Ex. 1036").

would extend the time to disease progression in human HER2+ breast cancer patients without increasing overall severe adverse events."); Ex. 1085 ¶¶ 27–28.

Further, and particularly relevant to the treatment of a human patient "in the absence of an anthracycline derivative" as set forth in claim 16, we note that the FDA-approved labeling for Taxol states that it "is indicated, after failure of first-line or subsequent chemotherapy" where "[p]rior therapy should have included an anthracycline." Ex. 2105, 6. Accordingly, we rely on Dr. Lipton's testimony that there was "a need to use alternative treatments such as paclitaxel for patients susceptible to anthracycline cardiotoxicity and/or resistance." Ex. 1085 ¶¶ 27–28.

The prior art of record confirms that many patients with metastatic breast cancer will have previously been treated with, and become resistant to, first-line anthracycline chemotherapeutics. Gelmon, for example, discloses that "[a]ll but two of the women in our trial had been treated with previous adjuvant chemotherapy, and 23 of 29 patients had previous exposure to anthracyclines." Ex. 1025, 13. On the present record, we find persuasive Dr. Litton's testimony that one of ordinary skill in the art would have recognized that "'[b]ecause anthracyclines are widely used in the adjuvant setting,' there is a substantial likelihood that patients will have already received a course of anthracycline therapy, and thus it would be advantageous to pursue synergistic drug combinations—like paclitaxel with cisplatin—that include drugs other than anthracyclines." Ex. 1011 ¶ 128 (citing Ex. 1007, 10; Ex. 1025, 9).

We further note that only patients in Baselga '97 who had previously received anthracycline therapy were assigned to treatment with the combination of paclitaxel and rhuMoAb HER2, whereas those who had not been previously exposed to anthracyclines were assigned to anthracycline-based chemotherapy with or without the anti-ErbB2 antibody. *See* section II(D)(1), above; *see also*

Ex. 1007, 47 ("Because anthracyclines are widely used in the adjuvant setting, it is likely that a significant number of patients will be treated with paclitaxel ± rhuMoAb HER2."). Thus, patients in the paclitaxel/rhuMoAb HER2 antibody arms of the clinical trial were selected for treatment "in the absence of an anthracycline derivative" based on whether they had previously been treated with anthracyclines. The fact that patients administered the combination may have been previously treated with anthracyclines does not take such a treatment regimen out of the claim scope.

Accordingly, the evidence of record shows that in considering a patient's prior history of unsuccessful treatment with anthracycline therapy, one of ordinary skill in the art would have been motivated with a reasonable expectation of success to treat such patients with HER2-positive breast cancer by administering a combination of an rhuMoAb HER2, a taxoid such as paclitaxel, and a further growth inhibitory agent "in the absence of an anthracycline derivative."

d) Sliwkowski Declaration and Secondary Considerations

During the prosecution leading to the issuance and of the '549 patent, the Examiner withdrew an obviousness rejection involving Baselga '96 "in view of the declaration of Mark X. Sliwkowski, PhD." Ex. 1019-7, 47–48. The Sliwkowski Declaration asserted, inter alia, that "a skilled scientist would have anticipated that paclitaxel would provide little or no additional benefit to treatment with trastuzumab alone since trastuzumab would arrest the cell cycle before paclitaxel would be able to act," and that one of ordinary skill in the art would recognize that "anti-HER2 antibodies acting by inducing cell cycle arrest in the G1 phase, would antagonize the effect of taxoids, such as paclitaxel, since they arrest cell cycle before it reaches the G2/M phase, where taxoids exert their apoptotic antitumor

activity." Ex. 1019-6, 341–345 ¶¶ 7, 8. Patent Owner raises neither of these arguments here.

Although Patent Owner appears to suggest that the Sliwkowski Declaration indicates that the combination of rhuMAb HER2 and a taxoid demonstrated unexpected results (*see* Prelim. Resp. 30 (citing Ex. 1019-6, 341–45); PO Resp. 29 (same); *see* Pet. 10), we do not understand Patent Owner to rely on the Sliwkowski Declaration in this proceeding, nor to otherwise assert secondary considerations. *See* Pet. Reply. 26. Accordingly, Petitioners' arguments and evidence regarding the failings of the Sliwkowski Declaration and arguments that objective indicia do not establish non-obviousness in this case stand unrebutted. *See* Pet. 61–65; PO Resp. 26; Ex. 1011 ¶¶ 219–28.

e) Conclusion

Considering the evidence as a whole, we agree with Petitioners that one of ordinary skill in the art would have been motivated to combine the teachings of Baselga '97 with Gelmon with a reasonable expectation of success. In view of the entire record before us, and applying our construction set forth in section II(C)(2), above, we conclude that Petitioners have demonstrated by a preponderance of evidence that claims 1–17 would have been obvious under grounds 1–3.

E. Grounds 4–6

In Ground 4, Petitioners challenge claims 1–11 and 14–17 as obvious under 35 U.S.C. § 103 based on the combination of Baselga '96, Baselga '94, and Gelmon. Pet. 42–59. In Grounds 5 and 6, respectively, Petitioners further rely upon Drebin (claim 12) and Presta (claim 13). *Id.* at 59–61. Grounds 4–6 are, thus, similar to Grounds 1–3, except that the earlier-published Baselga '96 and Baselga '94 replace the Baselga '97. Accordingly, we begin with an overview of Baselga '96 and Baselga '94,

1. Overview of Baselga '96 (Ex. 1005)

Baselga '96 teaches 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." Ex. 1005, 15. As a result, "[l]aboratory studies of the mechanism of this effect and clinical trials of such combination therapy are currently in progress." *Id*.

Baselga '96 further teaches that after successful experiments in mouse models, a humanized version of the 4D5 anti-ErbB2 antibody, rhuMAb HER2, was used in a phase II clinical trial for patients with metastatic breast cancer that overexpressed HER2. *Id*. at 9–10. "[P]atients were selected to have many sites of metastatic involvement, one of the most dire prognostic characteristics regarding response to therapy." *Id.* at 13. Of the 46 patients enrolled, 82.6% had received at least one regimen for metastatic disease, and 63% had received two or more regimens. *Id*. at 11. "Adequate pharmacokinetic levels of rhuMAb HER2 were obtained in 90% of the patients." *Id.* at Abstract. "Treatment with rhuMAb HER2 was remarkably well tolerated." *Id.* at 11. "Toxicity was minimal and no antibodies against rhuMAb HER2 were detected in any patients." *Id.* at Abstract.

With respect to efficacy, "37% of patients achieved minimal responses or stable disease." *Id*. at 13. "Objective responses were seen in five of 43 assessable patients, and included one complete remission and four partial remissions" for an overall response rate of 11.6%. *Id. at* Abstract*; see id. at* 12. Baselga 1996 posits "that the percentage of patients who show objective tumor regression to rhuMAb HER2 will be higher when patients with less extensive breast cancer are treated, since laboratory studies have shown that the response to antireceptor antibodies is greater with lower tumor burden." *Id.*

"Time to tumor progression was calculated from the beginning of therapy to progression," and "[t]he median time to progression for the patients with either minor or stable disease was 5.1 months." *Id*. at 10, 12. Baselga 1996 notes that, in contrast to many anticancer drugs, rhuMAB HER2 elicits cytostatic growth arrest rather than cell death in laboratory studies. *See id*. at 13. Accordingly, the authors posit that "stable disease may be an authentic reflection of the biologic action of [rhuMAB HER2]" and "[t]he unusually long durations of minimal responses and stable disease seen in [the] trial" may be indicative of the cytostatic effects of the antibody. *Id.* at 12–13.

2. Overview of Baselga '94 (Ex. 1006)

Baselga '94 describes xenograft studies in which HER2 overexpressing human breast cancer cells were injected into nude mice followed by treatment with humanized 4D5-antibody alone, or in combination with various chemotherapeutic agents. Ex. 1006, 4. Whereas either the antibody or paclitaxel alone produced 35% tumor growth inhibition, the combination of the two resulted in "major antitumor activity with 93% inhibition of growth" without increasing toxicity. *Id*. In addition, whereas doxorubicin alone resulted in 27% growth inhibition, the combination of doxorubicin and antibody resulted in 70% growth inhibition. *Id.*

According to the authors, [t]hese observations suggest that dual insults to cell cycle transversal through checkpoints (Mab-mediated growth factor deprivation, and drug mediated damage to DNA or tubulin) may activate cell death in tumor cells which can survive either treatment given singly. *Id.* Baselga '94 concludes that "anti-HER2 MAbs can eradicate well established tumors and

enhance the activity of paclitaxel and doxorubicin against human breast cancer xenografts. *Id.*

1. Analysis

In light of our construction of the claim terms "in an amount effective to extend the time to disease progression" and the related term, "an effective amount," our analysis of claims 1–17 is substantially the same under Grounds 4–6 as it is under Grounds 1–3, above, and we incorporate that discussion herein. With respect to Petitioners' reliance on Baselga '94 and Baselga '96 as opposed to Baselga '97, we agree with and adopt the arguments set forth on pages 6–16 of Petitioners' Reply, the highlights of which we address herein.

On pages 53–60 of its Response, Patent Owner argues that Baselga '96 and Baselga '94 would not have motivated one of ordinary skill in the art to administer a combination of rhuMAb HER2 and a taxoid for the treatment of breast cancer. With respect to Baselga '96, Patent Owner argues that the reference merely discloses the administration of rhuMAb HER2 alone. Baselga '96, however, states 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" and, as a result, "clinical trials of such combination therapy are currently in progress." Ex. 1005, 15. Based on our reading of Baselga '96 as a whole and the testimony of the parties' experts, we agree with Petitioners that the only reasonable interpretation of the cited passage is that clinical trials of rhuMAb HER2 in combination with each of cisplatin, doxorubicin, and paclitaxel were currently in progress for the treatment of breast cancer. *See* Pet. Reply 7; Ex. 1085 ¶ 126; Ex. 1087, 252:20–253:22.

We are also unpersuaded by Patent Owner's argument that Baselga '94 would not have provided motivation to administer a combination of rhuMAb

HER2 and a taxoid for the treatment of breast cancer because the reference is a non-peer reviewed abstract disclosing the results of a single mouse model. PO Resp. 55–59. As an initial matter, we find that the teachings of Baselga '96, including its disclosure of on-going clinical trials of rhuMAb HER2 in combinations with paclitaxel and cisplatin provides sufficient motivation to combine rhuMAb HER2 with a taxoid and additionally cisplatin as a further growth inhibitory agent. *See In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) ("[A reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole."). Moreover, the inventors of the '549 patent do not appear to have considered abstracts unreliable as the patent cites numerous abstracts and posters on its face. *See* Ex. 1001, (56) References Cited. Indeed, in a declaration submitted during prosecution, Applicants relied on an abstract to overcome prior-art rejections. *See* Ex. 1019-5, 340; *see also* Ex. 1085 ¶ 96 (testifying that "POSITAs often apply the information in the abstract [before publication of a longer, peer reviewed article], particularly where the abstract describes results that might have significant, clinical benefit for patients").

Further, we do not find persuasive Dr. Tannenbaum's opinion that one of ordinary skill in the art "would wait for the full paper describing these experiments and bases before drawing any conclusions from it," (Ex. 2062 ¶ 188) or Patent Owner's contention that one of ordinary skill in the art would not rely on preclinical studies in the relevant context (PO Resp. 7–9, 56–57 & n.17). To the contrary, evidence of record indicates that those of ordinary skill in the art did consider the Baselga '94 abstract relevant to clinical efficacy. *See* Pet. Reply 11 (noting that Baselga '94 was "published in the Proceedings of the American Society of *Clinical* Oncology") (emphasis in original); Ex. 1085 ¶ 97 ("Baselga '94 was subsequently cited in peer-reviewed publications, which viewed the study

results with approval"). Moreover, Baselga '94 was expressly cited in the prior art as providing "motivation for clinical evaluation" and "the basis for a planned clinical trial." Exs. 1072, 8;[21] 1073, 11;[22] *see also* Ex. 1085 ¶¶ 40, 140; Ex. 2111, 8 ("Paclitaxel was selected [to combine with rhuMAb HER2] because of its activity in metastatic breast cancer and preclinical studies that supported its use.");[23] Ex. 2130 at 53:1–56:1. Indeed, Patent Owner admitted at oral argument that the Baselga '94 data was used, at least "[i]n part," to justify to the FDA conducting phase III trials in the absence of phase II trials." Tr. 64:14–67:10.

We also do not find persuasive Patent Owner's argument that one of ordinary skill in the art would disregard Baselga 94's admittedly "good effect in combining the Herceptin plus paclitaxel" in light of the teachings of the Hsu abstract (Ex. 2135).[24] *See* Paper 73, 7; Tr. 62:7–64:13, 67:25–68:23; Ex. 2143 ¶ 25; Ex. 2144 ¶ 32; Paper 85 ¶ 14. 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, whereas, in a

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[21] Siedman et al., *Memorial Sloan-Kettering Cancer Center Experience With Paclitaxel in the Treatment of Breast Cancer: From Advanced Disease to Adjuvant Therapy*, Sem. Oncol., Vol. 22, No. 4, Supp. 8:3–8 (1995) ("Ex. 1072").

[22] F .A. Holmes, *Paclitaxel Combination Therapy in the Treatment of Metastic Breast Cancer: A Review.* Sem. Oncol. Vol. 23, No. 5, Supp. 11 (1996) ("Ex. 1073").

[23] S. Shak, *Overview of the Trastuzumab (Herceptin) Anti-HER2 Monoclonal Antibody Clinical Program in HER2-Overexpressing Metastatic Breast Cancer*, Sem. Oncology, Vol. 26, No. 4, Supp. 12 (1999) ("Ex. 2011").

[24] 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 (1997) ("Ex. 2135").

mouse model involving transplanted "HER-2/*neu*-transfected MCF-7 human breast cancer" cells, "[x]enografts treated with rhuMAb HER-2 plus taxol . . . were not significantly different from drug alone controls with the doses and dose schedules tested in this model." Ex. 2135. In light of Hsu's xenograft results, Dr. Kerbel testifies that because "Baselga '94's results were not replicated in this study further indicates that any claim to synergy between rhuMAb HER2 and paclitaxel based on Baselga '94 would be unfounded." Ex. 2143 ¶ 25; *see also* Ex. 2144 ¶¶ 32–34.

We are more persuaded, however, by Dr. Lipton's testimony that:

> the [Hsu] authors are careful to make clear that their results are specific to the "doses and dose schedules tested in this model," and a POSITA would not read them as saying that the same result could be generalized across all doses and dose schedules. In that regard, in contrast to the Baselga '94 reference, this abstract provides no information whatsoever regarding which doses and dose schedules were provided, and so a POSITA would not conclude that these results were inconsistent with those of Baselga '94, particularly given the *in vitro* results showing additive effects.

Ex. 1085 ¶ 43; *see also* Ex. 1099 ¶ 39–48.

We also credit Dr. Clarke's explanation that significant differences between the Baselga '94 and Hsu disclosures make clear that Hsu was not intended to "replicate" the results of Baselga '94, which may account for the differences in outcome. Ex. 1100 ¶¶ 40–43. Dr. Clarke notes that the two groups used different target cells for their xenograft studies; whereas Baselga '94 used cell line BT-474, which naturally overexpressed HER2, Hsu transfected a HER2-negative cell line with HER2/*neu* to achieve HER2-overexpression. Ex. 1099 ¶ 42. Dr. Clarke notes that Hsu provides no data showing the level of HER2-overexpression achieved by the transfection, nor any dosage information indicating that the dosage of either rhuMAb HER2 or the taxoid was reduced to ensure that the experiment had the ability to detect possible interactions between the two drugs. *Id.* ¶ 42.

We are also not persuaded by Patent Owner's arguments regarding the design of the preclinical study set forth in Baselga '94. *See* PO Resp. 55–57. We do not, for example, find persuasive Patent Owner's implication that one of ordinary skill in the art would have discounted Baselga '94's results because it used a single cell line with a high level of HER2 expression. *See* PO Resp. 56. To the contrary, we credit Dr. Clarke's testimony that: (1) Baselga's cell-line was "the most obvious first choice" because it expressed high levels of HER2 and responded well to anti-HER2 antibody, and (2) given the study's purpose and results, testing multiple cell lines would not have been considered necessary. Ex. 1086 ¶¶ 61–63, 69, and 99–116.[25]

Finally, we determine that the concerns Patent Owner raises regarding the credibility of Baselga' 94 are outweighed by the evidence, discussed above, that those of ordinary skill in the art ***did***, in fact, rely on the results set forth in Baselga '94 in designing human clinical trials.

2. Conclusion

Considering the evidence as a whole, we agree with Petitioners that one of ordinary skill in the art would have been motivated to combine the teachings of Baselga '96 and Baselga '94 with Gelmon and have a reasonable expectation of

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[25] Patent Owner further contends that model cell lines having 11 (MDA-435), 31 (SK-BR3), and 52 (BT-474) copies of ErbB2 per cell reflects "the heterogeneity of human chromosomes." PO Resp. 11 (citing Ex. 2054, 5400, 5402; Ex. 2065, 262, Ex. 2063, 1457; Ex. 2061 ¶¶ 26, 42, 44; and Ex. 2062 ¶ 74). To the extent Patent Owner intends to convey that the variation in ErbB2 copy number in the referenced cell lines reflects the heterogeneity of HER2 expression within or between HER2-positive tumors in human patients, this would appear to support Dr. Clarke's position that it was reasonable to rely on cell line BT-474 in preclinical trials, as it would be expected to have the highest, yet still physiologically relevant, expression level among the referenced cell lines.

success. In view of the entire record before us, and applying our construction set forth in section II(C)(2), above, we conclude that Petitioners have demonstrated by a preponderance of evidence that claims 1–17 would have been obvious under grounds 4–6.

F. Patentability Under Patent Owner's Preferred Construction

We also address patentability under Patent Owner's proposed construction of "an amount effective to extend the time to disease progression in the human patient" and "an effective amount" as comparing the three-part treatment to treatment with taxoid alone. Applying its preferred construction, Patent Owner contends that the challenged claims are not unpatentable with respect to Grounds 1–3 because neither Baselga '97 nor Gelmon teach or suggest that the claimed combination would extend the time to disease progression as compared to treatment with a taxoid alone. PO Resp. 42–49. With respect to Grounds 4–6, Patent Owner makes similar and overlapping arguments regarding the combination of Baselga '96, Baselga '94, and Gelmon. *Id.* at 49–53.

According to Patent Owner, "[t]he Phase-II study described in Baselga '97 (originally reported in Baselga '96) contained no control arm against which to compare the TTP and thus disclosed no ***extension*** in TTP." *Id.* at 45 (citations omitted). Although it is undisputed that Baselga '97 and Baselga '96 report a median increase in TTP of 5.1 months, Patent Owner argues that this refers to patients who received rhuMAb HER2 alone and "do[es] not describe an extension in TTP, which is a comparative result, let alone an extension in TTP as compared to patients treated with taxoid alone." *Id.* at 44–45. Patent Owner similarly argues that "Gelmon[] discloses a 'median' TTP, but contains no comparative data showing any ***extension*** in TTP." *Id.* at 47. Accordingly, Gelmon "did not evaluate

any ***extension*** in the time to disease progression and could not have done so because it lacked a control arm." *Id.* at 51.

Patent Owner further argues that the alleged failings of the clinical data are not remedied by the preclinical mouse data reported in Baselga '97 and Baselga '96 because the preclinical studies "measured response rate, which is not predictive of TTP." PO Resp. 45–46, 50–51; *see, e.g.*, Ex. 1005, 15 ("In preclinical studies . . . rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity.")

Assuming *arguendo* Patent Owner's claim construction, we do not find these arguments persuasive for the reasons set forth at pages 20–25 of Petitioners' Reply Brief. As an initial matter, we credit and adopt Petitioners' argument that the claimed extension of time to disease progression is an inherent benefit of an otherwise obvious combination, and that such an inherent result cannot establish patentability. *See* Pet. Reply 20–22 (citations omitted). As discussed in sections II(D)(5) and II(E)(3), above, it was obvious to combine rhuMoAb HER2 with a taxoid (e.g. paclitaxel) and a further growth inhibitory factor such as cisplatin for the treatment of HER2-positive breast cancer. Patent Owner does not dispute that when the combination of rhuMoAb HER2 and paclitaxel are administered in the absence of an anthracycline derivative for the treatment of HER2-positive breast cancer, the combined therapy significantly extends the time to disease progression as compared to taxoid therapy alone. *See id.* at 20–21. And Patent Owner does not argue that the addition of a further growth inhibitory agent such as cisplatin would abrogate this inherent benefit. *Id.* at 21. The claimed combination is obvious, and "an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the result[]." *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d

1344, 1354 (Fed. Cir. 2012). "To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." *Id.*

We further agree with Petitioners' argument that one of ordinary skill in the art would reasonably have expected the claimed extension in time to disease progression. *See* Pet. Reply 22–24. We note in particular that Baselga '96 reported that treatment with rhuMoAb HER2 resulted in "unusually long durations of minimal responses and stable disease" with a "median time to progression for the patients with either minor or stable disease was 5.1 months," thus indicating an extension of time of disease progression with the antibody alone. Ex. 1005, 12–13. And though Patent Owner contends that HER2-positive patients were thought not to respond well to paclitaxel alone (*see* Ex. 1005, 9, 13; Ex. 1007, 9; PO Resp. 17, 22, 23, 58; Ex. 2062 ¶ 57), Baselga '96 discloses that clinical trials of rhuMoAb HER2 in combination with paclitaxel had begun in light of preclinical studies showing that the antibody "markedly potentiated the antitumor effects of . . . paclitaxel," without increasing toxicity. Ex. 1005, 15; *see also* Ex. 1006 (same). Also referencing Baselga '96 and relevant preclinical data, Baselga '97 described an on-going Phase III clinical trial of HER2-positive breast cancer patients involving paclitaxel in combination with rhuMoAb HER2, with extension of TTP being a primary endpoint. Ex. 1007, 10. Accordingly, in view of the available evidence, we credit Dr. Litton's testimony that "even without a 'control arm' in Baselga '96, skilled artisans reasonably would have expected rhuMAb HER2 to extend time to disease progression compared to standalone paclitaxel in HER2+ patients." Ex. 1085 ¶ 76.

Patent Owner also argues that "[t]he mere disclosure of [the Phase III study in Baselga '97] would not provide a reasonable expectation of the result of such

study, particularly in view of the high failure rate of cancer clinical trials in the 1990s." Paper 49, 12; *see also* PO Resp., 46, 52 (collectively citing Ex. 2021, 712–13; Ex. 2062 ¶¶ 89–91, 211–216). According to Patent Owner's expert, Kola and Landis[26] "showed that approximately only five percent of oncology drugs were successful," and "that in oncology, the rate of failure in Phase III trials 'is as high as 59%.'" *See e.g.*, Ex. 2026 ¶¶ 89–90.

In relying on Kola and Landis, Dr. Tannenbaum appears to base "success" on FDA approval. Although the finder of fact may take into account failure of others to obtain FDA approval of a particular pharmaceutical combination (*see Knoll Pharm. Co., Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed.Cir.2004)), we agree with Petitioners that in this context, "the general failure rate in the industry is irrelevant." *See* Paper 80, 8 (citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007)). *See also*, *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291 (Fed. Cir. 2013) (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."). Moreover, "[c]onclusive proof of efficacy is not necessary to show obviousness." *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014). "[O]nly a reasonable expectation of success, not a guarantee, is needed." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (citations omitted).

Kola and Landis, on which Dr. Tannenbaum relies, focuses on clinical trials of individual compounds (i.e., new chemical entities (NCEs) and biologics) rather

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[26] Kola and John Landis, *Can the Pharmaceutical Industry Reduce Attrition Rates?* 3 NATURE REV. 711-715 (2004) ("Ex. 2021").

than combinations of known or promising therapies. *See e.g.,* Ex. 2021, 711 (discussing the "[d]epressing approval rates of NCEs and biologics), 712 (Table entitled, "NCEs required to achieve specific real growth targets as a function of 2002 revenues;" addressing "the root causes of why ***compounds*** undergo attrition in the clinic," and stating that "more than 70% of oncology ***compounds*** fail [in Phase II trials]" and "approximately 45% of all ***compounds*** that enter [Phase III trials] undergo attrition and in some therapeutic areas, such as oncology, it is as high as 59%") (emphases added).

Notably, Dr. Tannenbaum does not discuss the likelihood of failure of combination therapies such as that at issue here, wherein paclitaxel was already FDA approved for treatment of breast cancer, rhuMoAb HER2 showed promise in Phase II trials, and both paclitaxel and rhuMoAb HER2 had been used successfully in combination therapy with a third compound, cisplatin. Accordingly, we do not give substantial weight to Dr. Tannenbaum's opinion on this topic.

In light of the evidence of record, one of ordinary skill in the art learning of the on-going Phase III study reported in Baselga '97 would reasonably have expected that the combination of rhuMoAb HER2 and paclitaxel would increase in time to disease progression, such that the challenged claims are obvious. *See, e.g.*, Ex. 1085 ¶¶ 162–176.

Petitioners further contend that response rate is widely accepted as a surrogate endpoint for time to disease progression, and that one of ordinary skill in the art would reasonably have expected from the response rates indicated in the cited references that combination of rhuMoAb HER2, paclitaxel, and a further growth inhibitory agent would likely increase in time to disease progression. *See*

Pet. Reply 23; *see also* Ex. 1080, 3–4.[27] With respect to preclinical data, Dr. Clarke explains that,

> as of the mid-1990s, it was not standard practice to assess time to disease progression or survival in xenograft models. However, tumor response was, and still is, used as a surrogate endpoint for these measures in mice. Specifically, if a particular drug or drug combination produced a strong anticancer response in mice, particularly tumor shrinkage or eradication, this provided researchers with a reasonable expectation that clinical benefit would be obtained in human patients.

Ex. 1086 ¶¶ 78, 133; 1100 ¶¶ 25–31; and Ex. 1085 ¶¶ 77, 99, 163. Dr. Lipton further explains that with respect to clinical trials,

> the response rate endpoint from a Phase II study is often relied on by clinicians as a "surrogate endpoint" to predict a drug's impact on time to progression, and survival, in humans. That is based on the established belief that tumor reduction is "likely to predict for prolonged survival as compared with a patient whose tumors continued to grow." (Ex. 1080 at 3-4.) Although response rate does not always predict for extended time to disease progression (*id.*), it provides POSITAs with the motivation to move forward with the Phase III trial, and a reasonable expectation that the time to disease progression will be extended in at least some patients in that trial.

Ex. 1085 ¶ 53; Ex. 2130, 100:7–19.

Dr. Lipton's and Dr. Clarke's opinions on this matter are not inconsistent with the Specification, which suggests time to disease progression and response rates as alternative measurements of efficacy. *See* Ex. 1021, 19 (15:12–17) ('649 priority application defining therapeutically effective amount; noting that "efficacy can . . . be measured by assessing the time for disease progression (TTP), or

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[27] S.S. Ellenberg, *Surrogate Endpoints in Clinical Trials: Cancer,* 8 Statistics in Medicine 405–13 (1989) ("Ex. 1080").

determining the response rates (RR)"), 46–47 (42–43) (noting that clinical benefit is "assessed by response rates and the evaluation of disease progression").

Although not necessary to our determination, we agree with Petitioners and their experts that one of ordinary skill in the art would have reasonably expected that the claimed three-part combination would result in increased time to disease progression in light of the response rates in the cited Phase II clinical trials and preclinical studies. Ex. 1085 ¶¶ 53–53 (response rate in Phase II trials including Baselga '96), 76–77, 99 (response rates in Baselga '94)), 163–164 (response rates in Baselga '94 and Gelmon preclinical studies); Ex. 1086 ¶¶ 132–36 (response rates generally, and with respect to Baselga '94 preclinical and Baselga '96 clinical results), and 162 (response rates in Baselga '94).

a) Conclusion

Considering the evidence as a whole, we conclude that, even under Patent Owner's preferred construction of "an amount effective to extend the time to disease progression in the human patient" and "an effective amount," as indicating a comparison to a patient treated with taxoid alone, Petitioners have demonstrated by a preponderance of evidence that claims 1–17 would have been obvious under grounds 1–6.

III. Motions

A. Patent Owner's Motion to Amend

Having concluded that claims 1–17 are unpatentable, we address Patent Owner's Contingent Motion to Amend.

1. *Threshold Requirements*

In an *inter partes* review, amended claims are not added to a patent as of right, but rather must be proposed as a part of a motion to amend. 35 U.S.C.

§ 316(d). The Board must 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, 1328 (Fed. Cir. 2017). Patent Owner's proposed substitute claims, however, must still meet the statutory requirements of 35 U.S.C. § 316(d) and the procedural requirements of 37 C.F.R. § 42.121. *See* "Guidance on Motions to Amend in view of *Aqua Products*" (2017), available at https://www.uspto.gov/sites/default/files/documents/guidance_on_motions_to_amend_11_2017.pdf. Accordingly, Patent Owner must demonstrate: (1) the amendment proposes a reasonable number of substitute claims; (2) the amendment does not seek to enlarge the scope of the claims of the patent or introduce new subject matter; (3) the amendment responds to a ground of unpatentability involved in the trial; and (4) the original disclosure sets forth written description support for each proposed claim. *See* 35 U.S.C. § 316(d)*;* 37 C.F.R. § 42.121.

In its Motion to Amend, Patent Owner proposes to replace all challenged claims with substitute claims 18–20, of which claims 18 and 19 are independent. Paper 49, Appendix A. Under the circumstances, we agree with Patent Owner that it proposes a reasonable number of substitute claims. *See* Paper 49, 2.

With respect to the substance of the proposed claims, claim 18, submitted as a replacement for claim 1, recites:

> 18. A method of treatment of a human patient with breast cancer that overexpresses ErbB2 receptor, comprising administering a combination of rhuMAb HER2, paclitaxel, and a further growth inhibitory agent to a human patient in an amount effective to extend the time to disease progression in the human patient, as compared to paclitaxel alone, wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence.

Id. Claim 19, submitted as a replacement for claim 16 is similar, but further recites the administration of rhuMAb HER2, paclitaxel, and a further growth inhibitory

agent "in the absence of an anthracycline derivative." *Id.* Depending from claim 19, claim 20 specifies that the ErbB2 overexpressing breast cancer is metastatic breast carcinoma and is identical to original claim 17 but for its dependency.

Patent Owner contends that the substitute claims do not enlarge but, instead, narrow the scope of the original claims. *Id.* at 2–5. According to Patent Owner, the proposed substitute claims narrow the scope of the claimed antibody by replacing the genus of "an antibody that binds ErbB2" of claim 1 or "an intact antibody which binds to epitope 4D5 with the ErbB2 extracellular domain sequence" of claim 16, with the "specific antibody species, 'rhuMAb HER2,' a recombinant humanized 4D5 anti-ErbB2 antibody also known as HERCEPTIN®." Paper 49, 2–3. Patent Owner similarly argues that the substitute claims narrow the genus encompassing "a taxoid" by reciting "paclitaxel," which is a species of taxoid. *Id.* at 3.

With respect to the claim language, "an amount effective to extend the time to disease progression in the human patient," Patent Owner contends that "the Challenged Claims do not expressly identify a comparator for the claimed 'time to disease progression'; therefore, by further limiting the claims with a specific comparator (patients treated with paclitaxel alone), the Substitute Claims do not enlarge the scope of the claims." *Id.* at 4. Alternatively, Patent Owner argues that the additional limitation merely makes explicit that, under Patent Owner's preferred construction of the original claims, "the proper comparator by which to measure the claimed efficacy is to a patient treated with paclitaxel alone." *Id.* We, nevertheless, apply our construction for the term "extend the time to disease progression" as indicating that the results of the claimed combination therapy is compared to patients receiving no treatment. Because we do not discern, and Petitioners do not contend, that the comparator of patients receiving no treatment is

broader that those receiving paclitaxel alone, we agree with Patent Owner that the amendment does not seek to enlarge the scope of the claims as required under 35 U.S.C. § 316(d) and 37 C.F.R. § 42.121.

Petitioners argue that we should deny Patent Owner's Motion to Amend under 37 C.F.R. § 42.121(a)(2)(i) because the amendments narrowing the claims to specifically recite "rhuMAb HER2" and "paclitaxel" do not respond to the instituted grounds of unpatentability. Paper 66, 6–8; Paper 80, 1. According to Patent Owner, "[i]t is not require[d] that every amended limitation be solely for the purpose of overcoming an instituted ground" and it is sufficient that the proposed claims have been amended to specify that the comparator for an amount effective to extend the time to disease progression is paclitaxel alone. Paper 49, 9 & fn.3. (citing *Veeam Software Corp. v. Veritas Techs., LLC*, IPR2014-00090, Paper 48 at 28-29 (PTAB July 17, 2017)). We agree with Patent Owner. "[37 C.F.R. § 42.121(a)(2)(i)] does not require, however, that every word added to or removed from a claim in a motion to amend be solely for the purpose of overcoming an instituted ground. Additional modifications that address potential 35 U.S.C. § 101 or § 112 issues, ***for example***, are not precluded by rule or statute." *Western Digital Corp. v. SPEX Techs., Inc.*, Case IPR2018-00082 (PTAB Apr. 25, 2018) (Paper 13) (informative), slip op. at 6 (emphasis added). Although Patent Owner does not indicate whether the disputed limitations are intended to address 35 U.S.C. §§ 101 or 103 issues, this is not expressly required under our rules. Moreover, in indicating that addressing potential § 101 or § 112 issues are merely exemplary, *Western Digital* suggests that Patent Owner may have other reasons for entering such amendments. As the disputed limitations are peripheral to our patentability analysis (*see* section III(A)(2), below) and do not otherwise unduly burden the just

and speedy resolution of this matter, we do not reject Patent Owner's Motion to Amend under 37 C.F.R. § 42.121(a)(2)(i).

Petitioners also argue that the substitute claims add new subject matter in contravention of Section 316(d) and Rule 42.121(a)(2)(ii). *See* Paper 66, 8–11; Paper 80, 1–3. Although Patent Owner asserts that each of the proposed substitute claims find support in the original disclosure (Paper 49, 5–9; Paper 73, 3), Petitioners argue that the asserted priority documents fail to "show[] that the named inventor was in possession of the claimed combination of trastuzumab and paclitaxel plus a further growth inhibitory agent, much less in a way that extends TTP relative to paclitaxel alone" (Paper 66, 9), i.e., that the priority documents that Patent Owner relies on lack sufficient written descriptive support for the full scope of the proposed claims.

"In determining whether claims introduce new matter, we look to whether the original application provides adequate written description support for the claims." *Kapsch TrafficCom IVHS Inc. v. Neology, Inc.*, Case IPR2016-01763, slip op. at 47 (PTAB Mar. 20, 2018) (Paper 60). The written description requirement is met when the specification "conveys to those skilled in the art that the inventor had possession of" and "actually invented" the claimed subject matter. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*). "And while the description requirement does not demand any particular form of disclosure, or that the specification recite the claimed invention *in haec verba,* a description that merely renders the invention obvious does not satisfy the requirement." *Id.* at 1352 (citations omitted); *See also In re Wertheim*, 541 F.2d 257, 262 (CCPA 1976) ("It is not necessary that the application describe the claim limitations exactly, but only so clearly that persons of ordinary skill in the art will

recognize from the disclosure that appellants invented processes including those limitations.").

Patent Owner's proposed substitute claims require the administration of a three-drug combination —rhuMAb HER2, paclitaxel, and a further growth inhibitory agent— "in an amount effective to extend the time to disease progression in the human patient, as compared to paclitaxel alone." Patent Owner, however, admits that the support for the clinical effects of this three-drug combination is found in "the administration of rhuMAb HER2 and paclitaxel described in the original disclosure, ***where the two-way combination administration extended TTP as compared to paclitaxel alone***." *See* Paper 73, 3 (emphasis added). In particular, Patent Owner relies on "a clinical study in which patients with metastatic HER2-positive breast cancer or overexpression of the ErbB2 oncogene 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 anthracycline derivative." Paper 49, 7. PO asserts that "[t]he 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.* (citing Ex. 1019-1 49 (43:19–21) and Ex. 1020, 43–44 (42:29–43:2)).

The written description requirement demands that inventors "do more than merely disclose that which would render the claimed invention obvious." *ICU Medical, Inc. v. Alaris Medical Systems, Inc*. 558 F.3d 1368, 1377 (Fed. Cir. 2009). Considering the evidence of record, we agree with Petitioners that "[e]ach asserted claim recites a ***three-drug*** combination and so PO must show the inventors were in possession of a ***three-drug*** combination. Showing possession of a different,

unclaimed combination is insufficient." Paper 80, 2; *see also Ariad* 598 F.3d at 1352. Because Patent Owner has not shown, and we do not find adequate written description supporting the proposed substitute claims, they likewise fail to satisfy the no new matter requirement of 35 U.S.C. § 316(d) and 37 C.F.R. § 42.121(a)(2)(ii). Accordingly, we deny Patent Owner's Motion to Amend.

2. *Unpatentability of the Amended Claims*

In addition to its failure to meet the no new matter requirement for a motion to amend, we determine that Patent Owner's Motion to Amend should be denied because Petitioners have shown by a preponderance of the evidence that claims 18–20 are obvious in view of the art of record, most particularly Baselga '97, Baselga '96, Baselga '94, and Gelmon. *See* Paper 66, 10–21. Paper 80, 3–10. In short, Patent Owner does not contend, nor do we discern, that narrowing the proposed claims to specifically recite "rhuMAb HER2" and "paclitaxel" bears on patentability, but relies on the addition of the words "as compared to paclitaxel alone" to make explicit the claim construction it argued with respect to the originally-challenged claims. *See* Paper 49, 3–4. Patent Owner then recites essentially the same arguments it put forth with respect to claims 1–17 under its preferred construction. *Cf.* Paper 49, 9–23, Paper 73, 4–9 with PO Resp. 42–64. Having previously found those arguments unavailing (*see* section II(F), above), we decline to revisit them here.

B. Patent Owner's Motion to Exclude Evidence

Patent Owner filed one motion to exclude evidence. Paper 77. Petitioners opposed (Paper 88) and Patent Owner submitted a reply in support of its motion (Paper 91).

1. *Clark Declaration and Related Evidence*

Patent Owner moves to exclude the declaration of Petitioners' preclinical expert, Robert Clarke, PhD., D.SC. (Exhibit 1086), and the portions of the reply declaration of Petitioners' clinical expert, Dr. Lipton, that rely on Dr. Clarke's testimony (Exhibit 1085 ¶¶ 5, 8, 44, 47, 48, 98-100, 129, 135-139). Paper 77, 1–7; Paper 91, 1–3. In short, Patent Owner argues that Dr. Clarke's testimony should be excluded as irrelevant under FRE 402 because he is not "a clinical or medical oncologist" as required under our definition of a person of ordinary skill in the art. *See e.g.,* Paper 77, 1, 3–4 (further arguing that because he is not a person of ordinary skill in the art, Dr. Clarke's testimony should also be excluded under FRE 403, 602, 801, and 802).

On pages 4–6 of Paper 88, Petitioners persuasively set forth arguments in opposition of Patent Owner's motion, noting for example, that Dr. Clarke's testimony was submitted in direct response to Patent Owner's submission of the declaration of Dr. Kerbel, Ph.D.—also not qualified as a clinical or medical oncologist as set forth under our definition of one of ordinary skill in the art. *See* Paper 88, 2. Petitioners further points to Dr. Clarke's extensive experience in relevant preclinical research, history of collaboration with those of ordinary skill in the art, and that both Dr. Kerbel and Dr. Tannenbaum rely on Dr. Clarke's publications to support their own opinions. *See id.* at 2–4. Moreover, there is no requirement that the Board exclude the testimony of an expert that does not qualify as one of ordinary skill in the art. To the contrary, as recently noted in the August 13, 2018 update to our Trial Practice Guide:

> An expert witness must be qualified as an expert by knowledge, skill, experience, training, or education to testify in the form of an opinion. Fed. R. Evid. 702. There is, however, no requirement of a perfect match between the expert's experience and the relevant field. *SEB S.A. v. Montgomery Ward & Co.*, 594 F.3d 1360, 1373 (Fed. Cir.

> 2010). A person may not need to be a person of ordinary skill in the art in order to testify as an expert under Rule 702, but rather must be "qualified in the pertinent art." *Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1363–64 (Fed. Cir. 2008).

See Notice of Update to Office Patent Trial Practice Guide, 83 Fed. Reg. 156, (Aug. 13, 2018) (text of update available at https://www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf).

In sum, we agree with Petitioners that Dr. Clarke is qualified to provide expert testimony on the relevant art, his testimony is highly relevant to issues raised in this proceeding, and Patent Owner's objections go to the weight, not admissibility of this testimony. *See* Paper 88, 6. Accordingly, we deny Patent Owner's motion to exclude Exhibit 1086 and Exhibit 1085 ¶¶ 5, 8, 44, 47, 48, 98–100, 129, and 135–139.

2. *Evidence Concerning Surrogate Endpoints*

Patent Owner moves to exclude Exhibit 1080, as well as select paragraphs of Dr. Lipton's reply declaration (Ex. 1085 ¶¶ 53, 77, 99, and 163) and Dr. Clarke's Declaration (Ex. 1086 ¶¶ 78, 132–136, and 162), all of which relate to Petitioner's argument that one of ordinary skill in the art would understand that response rates in clinical and preclinical studies were used as "surrogate endpoints" for time to disease progression. Paper 77, 4–7; *see also* Paper 91, 3. Patent Owner argues that we should exclude this evidence as untimely because Petitioners raised it for the first time in their reply, "after which PO had no opportunity to respond." *Id.*

We do not find Patent Owner's arguments persuasive for the reasons set forth in Petitioners' opposition (Paper 88, 8–11), which we adopt. In particular, we agree with Petitioners that in the Petition, it "relied on the 'response rate' disclosures of Baselga '94 and '96 as providing a POSA with a reasonable expectation of achieving an extension of TTP." Paper 88, 9 (citations omitted).

And, in response to Patent Owner's argument that "Petitioners have not explained how a POSA 'could have translated the response rate data in the prior art to the time of disease progression results," Petitioners reasonably responded with rebuttal evidence identifying response rate as a surrogate endpoint for time to disease progression. *See id.* at 9–10 (citations omitted). *See Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1077–78 (Fed. Cir. 2015) (holding that a petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability, but may submit directly responsive rebuttal evidence in support of its reply); *Ericsson Inc. v. Intellectual Ventures I LLC*, No. 2017-1521, 2018 WL 4055815, at *6 (Fed. Cir. Aug. 27, 2018) (Board improperly refused to consider Reply testimony that "merely expands on a previously argued rationale").

Accordingly, we deny Patent Owner's motion to exclude Exhibit 1080, Ex. 1085 ¶¶ 53, 77, 99, and 163, and Ex. 1086 ¶¶ 78, 132–136, 162.

3. *Foreign Patent Office Documents*

Patent Owner requests that we "exclude certain foreign patent office documents (Exhibits 1004, 1026, and 1049)" under FRE 402 and/or 403. Paper 77, 7–8; *see also* Paper 91, 3–4. Patent Owner contends that the records of "these foreign proceedings are irrelevant to the issues to be decided in this IPR, which involves a different patent with different claims adjudicated under different law." Paper 77, 7. According to Petitioners, the disputed Exhibits were merely cited "to satisfy Petitioners' obligation to identify 'related matters' in its mandatory notices." Paper 88, 11.

While we agree with Patent Owner that Petitioners' obligation to identify related matters under 37 C.F.R. § 42.8(b) contains "no requirement to formally submit other court judgements as evidence" (see Paper 91, 4), we do not rely on

Exhibits 1004, 1026, or 1049 and, therefore, deny this portion of Patent Owner's motion as moot.

4. *Lottery Article*

Patent Owner requests that we exclude Exhibit 1090, an LA Times article from 1996 entitled, *A Lottery of Life, Death —And Hope* ("the Lottery article"), along with portions of Dr. Lipton's reply declaration relating to it (Ex.1085 ¶¶ 107, 132). Paper 77, 8–10; *see also* Paper 91, 4–5. According to Patent Owner, the Lottery article "is not relevant to the issues to be decided in this case," "its probative value is outweighed by the risk of confusing the issues (FRE 403)" and it comprises "hearsay from a declarant (Dr. Slamon) who [Patent Owner] was not given an opportunity to depose (FRE 801, 802)." *Id.*

We do not find Patent Owner's arguments persuasive for the reasons set forth on pages 12–13 of Petitioners' reply brief (Paper 88), which we adopt. Most particularly, we agree with Petitioners that the Dr. Lipton's discussion of the Lottery article is relevant because it responds to a position taken by Patent Owner's expert, Dr. Tannenbaum. *See* Paper 88, 12.

Patent Owner has also not adequately explained why this panel would find this discussion so confusing as to warrant exclusion under FRE 403. Nor has Patent Owner persuaded us that the quotation cited in the Lottery article should be excluded as hearsay, insofar as Petitioners and their expert reference it for the non-hearsay purpose of showing what a person of ordinary skill in the art would have known as of the date of the invention. Accordingly, we deny Patent Owner's motion with respect to Exhibit 1090 and Exhibit 1085, paragraphs 107 and 132.

5. *Sliwkowski and Kerbel Patents*

Patent Owner requests that we exclude Exhibit 1076 ("the Sliwkowski Patent" and Exhibit 1077 ("the Kerbel Patent") as irrelevant under FRE 402 or, in

the alternative, as "tend[ing] to mislead and confuse the issues" in contravention of FRE 403. Paper 77, 10–12; *see also* Paper 91, 5. Patent Owner has not explained, nor do we discern, how the Board might be misled or confused by the Sliwkowski and Kerbel Patents, and Patent Owner's relevance argument goes to the weight we might accord those references rather than their admissibility. Moreover, Petitioners have adequately explained the relevance of these exhibits to the present case. *See* Paper 88, 14–15. Accordingly, we deny Patent Owner's motion with respect to Exhibits 1076 and 1077.

C. Petitioners' Motions to Exclude Evidence Relating to Exhibit 2135 and Exhibit 2145

Petitioners filed a first motion to exclude evidence. Paper 81. Patent Owner opposed (Paper 86) and Petitioners submitted a reply in support of its first motion (Paper 93). Petitioners filed a second motion to exclude evidence. Paper 98. Patent Owner opposed (Paper 100) and Petitioners submitted a reply in support of their second motion (Paper 101).

In its first motion, Petitioners seek to exclude paragraphs 11–14, 16–17, and 31–32 of Dr. Tannenbaum's Supplemental Declaration (Ex. 2144) as "improperly seeking to recant" her prior testimony. Paper 81, 11–13. We agree with Patent Owner that any inconsistencies between Dr. Tannenbaum's deposition testimony and expert reports go to weight, not admissibly and, moreover, Petitioners were afforded the opportunity to address those issues in their sur-reply. *See* Paper 86, 14. Accordingly, we deny this portion of Petitioners' first motion on its merits.

The remainder of Petitioners' first motion seeks to exclude the Hsu Abstract (Ex. 2135), and Patent Owners' evidence attempting to authenticate and prove the publication date of that document, including the deposition testimony from IPR2017-01122 of Dr. Robert Earhart, M.D. Ph.D., who is not retained by any

party to this proceeding. Petitioners' second motion is similarly directed to Exhibit 2146, an abstract book containing a copy of the Hsu Abstract.

As set forth in section II(E)(3), we do not find persuasive Patent Owner's evidence regarding the substance of Hsu. Accordingly, and taking no position as to the merits of the parties' arguments relating to the admissibility of the Hsu references, we deny this portion of Petitioners' motion as moot. *See* Ex. 2135; Ex. 2145; Ex. 2143 ¶¶ 25; and Ex. 2144 ¶ 33.

D. Motions to Seal

The parties, collectively, filed five unopposed motions to seal. Papers 8, 48, 74 (by Patent Owner); Papers 65, 79 (by Petitioners).

The Board's standards for granting motions to seal are discussed in *Garmin International v. Cuozzo Speed Technologies, LLC*, IPR2012-00001 (PTAB Mar. 14, 2013) (Paper 34). In summary, there is a strong public policy for making all information filed in *inter partes* review proceedings 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. *Id*. at slip op. 1–2. Under 35 U.S.C. § 316(a)(1) and 37 C.F.R. § 42.14, the default rule is that all papers filed in an inter partes review are open and available for access by the public; a party, however, may file a concurrent motion to seal and the information at issue is sealed pending the outcome of the motion. It is only "confidential information" that is protected from disclosure. 35 U.S.C. § 316(a)(7); *see* Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,760 (Aug. 14, 2012). 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 in showing entitlement to the requested relief, and must explain why the information sought to be sealed constitutes confidential information. 37 C.F.R. § 42.20(c).

We remind the parties of the expectation that confidential information relied upon or identified in a final written decision will be made public. *See* Office Trial Practice Guide, 77 Fed. Reg. 48756, 48761 (Aug. 14, 2012). Confidential information that is subject to a protective order ordinarily becomes public 45 days after final judgment in a trial. 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.

As an initial matter, Patent Owner avers that the parties have agreed to be bound by the "Modified Default Standing Protective Order set forth in Exhibit 2036." Paper 8, 1. Upon review of the motion we determine that the parties have identified sufficiently how the proposed Stipulated Protective Order departs from the Board's default protective order set forth in the Office Patent Trial Practice Guide, 77 Fed. Reg. 48756, 48769–71 (Aug. 14, 2012). Paper 8, 1–2; *see also* Ex. 2093 (comparing the proposed Stipulated Protective Order to the Board's default protective order). We find that the parties have shown sufficiently good cause for the proposed modifications from the Board's default protective order and that the proposed Stipulated Protective Order is warranted. The motion for entry of the Modified Default Standing Protective Order is granted.

In Paper 8, Patent Owner seeks to seal the confidential version of its Patent Owner Preliminary Response (Paper 7), Exhibits 2001, 2007, and 2008; and Exhibits 2002–2004. 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 our final Decision, Patent Owner's request is granted.

In Paper 48, Patent Owner seeks to seal the confidential version of the Declaration of Stephanie Mendelsohn (Exhibit 2069), which purports to authenticate Exhibits recited in Paper 8. Patent Owner has shown good cause

supporting the motion. Insofar as none of the material sought to be protected is relied on in our final Decision, Patent Owner's request is granted.

In Paper 74, Patent Owner seeks to seal the confidential version of the Supplemental Expert Declaration of Dr. Susan Tannenbaum (Exhibit 2144) as well as Exhibits 2141 and 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 our final Decision, Patent Owner's request is granted.

In Papers 65 and 79, Petitioners seek to seal the confidential versions of their Opposition to Patent Owner's Motion to Amend (Paper 66); Reply to Patent Owner's Response (Paper 68), Surreply to Patent Owner's Reply in Support of its Motion to Amend (Paper 80), Reply Declaration of Allan Lipton, M.D. (Ex. 1085), Surreply Declaration of Allan Lipton, M.D. (Ex. 1099), and the Transcript of the Deposition of Susan Tannenbaum, M.D. (Ex. 1087). Petitioners seek to seal these documents because they "contain references to subject matter filed under seal by Patent Owner." Paper 65, 2; *see also* Paper 79, 1. Petitioners provide no other justification for why the redacted portions of the cited documents should be kept confidential and, thus, fail to satisfy the good cause requirement. Accordingly, Petitioners' motions are denied.

Patent Owner is invited to file, within 14 days of this Decision, a motion to seal any presently redacted portion of Paper 66, Paper 68, Paper 80, Exhibit 1085, Exhibit 1099, and/or Exhibit 1087. The motion must explain why the information sought to be protected is truly confidential and attest that such information is not directly or indirectly relied on in our final Decision. Petitioner may respond within one week of Patent Owner's motion, if desired. The Exhibits and Petitioner's Reply will remain designated Board and Parties Only for 21 days from this Decision or until consideration of any such motion and reply.

IV. CONCLUSION

After considering Petitioners' and Patent Owner's arguments and evidence, we conclude that Petitioners have shown, by a preponderance of the evidence, that claims 1–17 of the '549 patent would have been obvious over the combinations of Baselga '97, Gelmon, Drebin, and Presta set forth in Grounds 1–3 and the combinations of Baselga '96, Baselga '94, Gelmon, Drebin, and Presta set forth in Grounds 4–6.

Based on the evidence of record, we conclude that proposed amended claims 18–20 are not patentable over the art of record. The parties' motions to exclude evidence and to seal are addressed in the following Order.

V. ORDER

In consideration of the foregoing, it is:

ORDERED that claims 1–17 of the '549 patent are unpatentable;

FURTHER ORDERED that Patent Owners' motion to amend is denied;

FURTHER ORDERED that Patent Owner's motion to exclude Exhibit 1080; Exhibit 1085, paragraphs 5, 8, 44, 47, 48, 53, 77, 98-100, 129, 135–139, and 163; and the entirety of Exhibit 1086, including paragraphs 78, 132–136, and 162, is denied.

FURTHER ORDERED that Patent Owner's motion to exclude Exhibits 1004, 1026, and 1049 is denied as moot.

FURTHER ORDERED that Patent Owner's motion to exclude Exhibit 1090; Exhibit 1085, paragraphs 107 and 132; Exhibit 1076; and Exhibit 1077 is denied.

FURTHER ORDERED that Petitioners' motion to exclude Exhibit 2144, paragraphs 11–14, 16–17, and 31–32 is denied.

FURTHER ORDERED that Petitioners' motion to exclude Exhibit 2135; Exhibit 2145; Ex. 2143 paragraph 25; and Ex. 2144 paragraph 33 is denied as moot.

FURTHER ORDERED that the Modified Default Standing Protective Order set forth in Exhibit 2036 is entered and shall govern the conduct of this proceeding.

FURTHER ORDERED that Patent Owner's motions to seal confidential versions of Paper 7, and Exhibits 2001, 2007, 2008, 2069, 2144, 2141, and 2142 are granted.

FURTHER ORDERED that Petitioners' motions to seal confidential versions of Paper 66, Paper 68, Paper 80, and Exhibits 1085, 1099, and 1087 are denied. Within 14 days of this Decision, Patent Owner may file a motion to seal any presently redacted portions of these documents. Any such motion must explain why the information sought to be protected is truly confidential and attest that such information is not directly or indirectly relied on in this Decision. Petitioner may file a response within one week of Patent Owner's motion. The Exhibits and Papers will remain designated Board and Parties Only for 21 days from the date of this Decision or until consideration of any such motion and reply.

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

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(12) **United States Patent**
Paton et al.

(10) **Patent No.: US 7,892,549 B2**
(45) **Date of Patent: *Feb. 22, 2011**

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

(75) Inventors: **Virginia E. Paton**, Oakland, CA (US); **Steven Shak**, Burlingame, CA (US); **Susan D. Hellmann**, San Carlos, CA (US)

(73) Assignee: **Genentech, Inc.**, South San Francisco, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1827 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/356,824**

(22) Filed: **Feb. 3, 2003**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 09/208,649, filed on Dec. 10, 1998.

(60) Provisional application No. 60/069,346, filed on Dec. 12, 1997.

(51) **Int. Cl.**
A61K 39/395 (2006.01)
C07K 16/28 (2006.01)
C07K 16/30 (2006.01)

(52) **U.S. Cl.** **424/143.1**; 424/130.1; 424/133.1; 424/134.1; 424/135.1; 424/136.1; 424/138.1; 424/141.1; 424/152.1; 424/155.1; 424/156.1; 424/172.1; 424/174.1

(58) **Field of Classification Search** 424/130.1, 424/133.1, 138.1, 141.1, 143.1, 155.1, 174.1, 424/134.1, 135.1, 136.1, 152.1, 156.1, 172.1
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.

17 Claims, 1 Drawing Sheet

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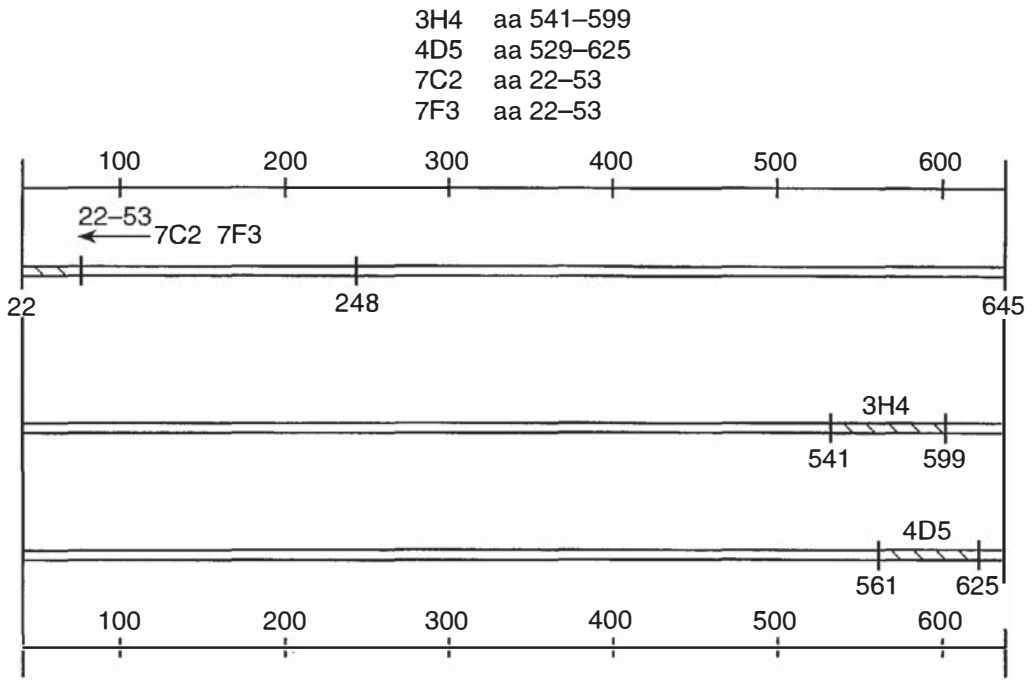

3H4 epitope (SEQ ID NO:8)

VEECRVLQGLPREYVNARHCLPCHPECQPQNGSVTCFGPEADQCVACAHYKDPPFCVAR
541 **599**

4D5 epitope (SEQ ID NO:9)

LPCHPECQPQNGSVTCFGPEADQCVACAHYKDPPFCVARCPSGVKPDLSYMPIWKFPDEEGACQP
561 **625**

FIG._1

```
1    MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPA
38   SPETHLDMLRHLYQGCQVVQGNLELTYLPTNASLSFL
75   QDIQEVQGYVLIAHNQVRQVPLQRLRIVRGTQLFEDN
112  YALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTEI
149  LKGGVLIQRNPQLCYQDTILWKDIFHKNNQLALTLID
186  TNRSRA
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FIG._2

TREATMENT WITH ANTI-ERBB2 ANTIBODIES

This is a continuation of non-provisional application Ser. No. 09/208,649, filed Dec. 10, 1998, which claims priority under 35 USC §119 to provisional application No. 60/069,346, filed Dec. 12, 1997, the entire disclosures of which are 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 B 104-1-1 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. Nail 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 P1 uptake in the "P1 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 β-sheet configuration, connected by three CDRs, which form loops connecting, and in some cases forming part of, the β-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. 1, 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 PRIMATIZED™ 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, carminomycin, 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 GI 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 GI 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-1a, IL-2, IL-3, IL-4, IL-5, L-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-lactamcontaining 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 Pluckthun, *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 "bestfit" 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. Immnol.,* 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 (MXDTPA) 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. *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. Immnol. 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, nanoparticles 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, 12301 Parklawn Drive, Rockville, Md., USA (ATCC):

Antibody Designation	ATCC No.	Deposit Date
7C2	ATCC HB-12215	Oct. 17, 1996
7F3	ATCC HB-12216	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_1K murine monoclonal antibody 4D5, specific for the extracellular domain of ErbB2, was produced as described in Fendly et al., *Cancer Research* 5o:1550-1558 (1990) and WO89/06692. Briefly, NIH 3T3HER2-3$_{400}$ 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 mycloma 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 $p185^{HER2}$ (Dillohiation constant [K_d]=0.1 nmol/L), markedly inhibits, in vitro and in human xenografts, the growth of breast cancer cells that con-

tain 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.

Eligihility 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 H2 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*	62.0**	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 < 0.001 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 ¾) 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.

SEQUENCE LISTING

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The invention claimed is:

1. A method for the treatment of a human patient with breast cancer that overexpresses ErbB2 receptor, comprising administering a combination of an antibody that binds ErbB2, a taxoid, and a further growth inhibitory agent to the human patient in an amount effective to extend the time to disease progression in the human patient, wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence.

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

3. The method of claim **1** wherein the antibody cross-blocks binding of 4D5 to the ErbB2 extracellular domain sequence.

4. The method of claim **1** wherein the antibody binds to amino acid residues in the region from about residue 529 to about residue 625 of the ErbB2 extracellular domain sequence.

5. A method for the treatment of a human patient with breast cancer characterized by overexpression of ErbB2 receptor, comprising administering an effective amount of a combination of an anti-ErbB2 antibody which binds epitope 4D5 within the ErbB2 extracellular domain sequence, a taxoid, and a further therapeutic agent, to the human patient.

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

7. The method of claim **5** wherein the antibody is a humanized 4D5 anti-ErbB2 antibody.

8. The method of claim **7** wherein the antibody is administered as a 4 mg/kg dose and then weekly administration of 2 mg/kg.

9. The method of claim **5** wherein the taxoid is paclitaxel.

10. The method of claim **5** wherein efficacy is measured by determining the time to disease progression or the response rate.

11. The method of claim **5**, wherein the further therapeutic agent is selected from the group consisting of: another ErbB2 antibody, EGFR antibody, ErbB3 antibody, ErbB4 antibody, vascular endothelial growth factor (VEGF) antibody, cytokine, and growth inhibitory agent.

12. The method of claim **5** wherein the further therapeutic agent is another ErbB2 antibody.

13. The method of claim **5** wherein the further therapeutic agent is a vascular endothelial growth factor (VEGF) antibody.

14. The method of claim **5** wherein the further therapeutic agent is a growth inhibitory agent.

15. The method of claim **14** wherein the growth inhibitory agent is a DNA alkylating agent.

16. A method for the treatment of a human patient with ErbB2 overexpressing breast cancer, comprising administering a combination of an antibody that binds epitope 4D5 within the ErbB2 extracellular domain sequence, a taxoid and a further growth inhibitory agent, in the absence of an anthracycline derivative, to the human patient in an amount effective to extend the time to disease progression in the human patient.

17. The method of claim **16** wherein the breast cancer is metastatic breast carcinoma.

* * * * *

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 8,607 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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July 9, 2019