UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00731
Patent No. 7,846,441

PATENT OWNER'S CONTINGENT MOTION TO AMEND UNDER 37 C.F.R. § 42.121

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I. INTRODUCTION

Pursuant to 35 U.S.C. § 316(d) and 37 C.F.R. § 42.121, Patent Owner Genentech, Inc. submits this contingent motion to amend claim 11 of U.S. Patent No. 7,846,441 (the "'441 patent"). The proposed amended claim is number 15 (the "Substitute Claim") and would be substituted for original claims 1-14 (collectively, the "Challenged Claims"), in the event independent claim 11 (i.e., the claim subject to amendment) is found unpatentable. In the event claim 11 is amended pursuant to this Motion, Patent Owner agrees to cancel original claims 1-14.[1]

The proposed Substitute Claim satisfies the requirements for a motion to amend. The Motion presents a single Substitute Claim which satisfies the requirement of a "reasonable number of substitute claims." The Substitute Claim (1) does not "enlarge the scope of the claims"; (2) does not "introduce new subject matter"; and (3) "respond[s] to [the] ground[s] of unpatentability involved in the trial." 35 U.S.C. § 316(d); 37 C.F.R. § 42.121. Patent Owner has thus met its burden of production. Moreover, the amendment confirms patentability over the prior art. Accordingly, should Challenged Claim 11 be found unpatentable, Patent

[1] Pursuant to 37 C.F.R. § 42.121, Patent Owner conferred with the Board on December 8, 2017 and received authorization via email to file this Motion on December 11, 2017.

Owner respectfully requests on a contingent basis that the '441 patent be amended to include the corresponding Substitute Claim and the remaining claims be canceled.

II. PATENT OWNER PROPOSES A REASONABLE NUMBER OF SUBSTITUTE CLAIMS

35 U.S.C. § 316(d)(1)(B) and 37 C.F.R. § 42.121(a)(3) require the Patent Owner to "propose a reasonable number of substitute claims." "The presumption is that only one substitute claim would be needed to replace each challenged claim . . . ." *Id.* Here, Patent Owner proposes only one substitute claim and proposes to cancel the remaining Challenged Claims. Thus, Patent Owner proposes a reasonable number of substitute claims.

III. THE SUBSTITUTE CLAIM DOES NOT ENLARGE THE SCOPE OF THE CLAIMS OF THE '441 PATENT

The substitute claims must not enlarge the scope of the original claims. 35 U.S.C. § 316(d)(3) and 37 C.F.R. § 42.121(a)(2)(ii). Here, the proposed Substitute Claim narrows—rather than broadens—the original claims.

First, the Substitute Claim narrows the claimed antibody. Original claim 11 recites a genus encompassing "a humanized 4D5 anti-ErbB2 antibody." The Substitute Claim narrows this limitation to recite a specific antibody species, "rhuMAb HER2," a recombinant humanized 4D5 anti-ErbB2 antibody also known

as HERCEPTIN®.[2] (Ex. 1001 at 3:34-40; *see also* Paper 29 (Decision Granting Request for Rehearing) at 3.) "rhuMAb HER2" is an antibody encompassed by original claim 11. (Ex. 1001 at 3:34-40; *see also* Ex. 2110 at 4285 (describing the specific variant of humanized 4D5 anti-ErbB2 antibodies, *i.e.*, humAb4D5-8, that is HERCEPTIN®).)

Second, the Substitute Claim narrows the claimed taxoid. Original claim 11 recites the administration of a genus encompassing "a taxoid." The Substitute Claim narrows this limitation to recite "paclitaxel," which is a specific species of a taxoid. (Ex. 1001 at 4:21-23.)

Finally, Patent Owner proposes amending original claim 11 to include an additional limitation reciting a comparator by which to measure extension of time to disease progression ("TTP") of the claimed method of treatment, *i.e.*, "as compared to paclitaxel alone." The Board in its Institution Decision noted that "extend the time to disease progression in said human patient, without increase in overall severe adverse events" is a relative term, and construed the limitation to mean comparing the efficacy of the claimed combination treatment relative to no treatment whatsoever. (Paper 29 at 7-8.) Neither Patent Owner's expert nor

[2] HERCEPTIN® is the tradename for the commercial drug product of the humanized antibody, trastuzumab.

Petitioner's expert agrees with the Board's construction. (Ex. 1007, Lipton Decl. ¶ 46; Ex. 2062, Tannenbaum Decl. ¶¶ 126-141; *see also* IPR2017-02063, Ex. 1102, Lipton Decl. ¶ 112(h).) A person of ordinary skill in the art ("POSA") would understand that the proper comparator by which to measure the claimed efficacy is to a patient treated with paclitaxel alone. (*Id.*) The additional limitation in the Substitute Claim makes this explicit and directly corresponds to the specific clinical results reported in the '441 patent's specification. (Ex. 1001 at 29:9-30:25.) In any event, 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 Claim does not enlarge the scope of the claims. *See* MPEP § 1412.03 (explaining in the context of reissue claims that a claim is broadened "if the patent owner would be able to sue any party for infringement who previously could not have been sued for infringement").

In sum, the Substitute Claim narrows the Challenged Claims to correspond to the specific clinical trial disclosed in the Example set forth in the '441 specification, in which ErbB2 (also known as HER2) overexpressing metastatic breast cancer patients were treated with a combination of rhuMAb HER2 and paclitaxel in the absence of an anthracycline derivative, in an amount that extended time to disease progression as compared to human patients treated with paclitaxel

alone, without increasing overall severe adverse events. (*See, e.g.*, Ex. 1001 at 26:33-30:27.) Accordingly, the Substitute Claim does not enlarge the scope of the '441 patent claims.

IV. THE SUBSTITUTE CLAIM DOES NOT ADD NEW SUBJECT MATTER

The proposed Substitute Claim is supported by the original disclosure of U.S. App. Ser. No. 09/208,649 (the '649 application) (Ex. 1004-1 at 5-56), which issued as the '441 patent, and related Provisional Patent Application 60/069,346 (the '346 application) (Ex. 2009), to which the '649 application claims priority. Those applications are virtually identical and expressly disclose each and every limitation of the proposed Substitute Claim, as set forth in the chart below.

Claim	Support in '649 Application	Support in '346 Application
Proposed Claim 15		
~~11.~~ 15. A method for the treatment of a human patient with ErbB2 overexpressing progressing metastatic breast cancer, comprising	Ex. 1011-1 at p. 104 (36:12-20); p. 108 (40:3-7).	Ex. 1027 at p. 37 (36:7-14); pp. 40-41 (39:26-40:1).
administering a combination of ~~a humanized 4D5 anti-ErbB2 antibody~~ rhuMAb HER2 and ~~a taxoid~~ paclitaxel,	Ex. 1011-1 at p. 109 (41:15-29); p. 110 (42:8-12).	Ex. 1027 at p. 42 (41:9-23); p. 43 (42:2-8).
in the absence of an anthracycline derivative,	Ex. 1011-1 at p. 104 (36:26-27); p. 109 (41:20-29); pp. 111-112 (43:23-44:2).	Ex. 1027 at p. 37, (36:20-21); p. 42 (41:14-23); p. 44 (43:4-26).
to the human patient	Ex. 1011-1 at p. 104 (36:21-25).	Ex. 1027 at pp. 42-43 (41:9-42:6).

in an amount effective to extend time to disease progression in said human patient, as compared to paclitaxel alone,	Ex. 1011-1 at p. 111-112 (43:1-44:3).	Ex. 1027 at pp. 43-44 (42:28-43:26).
without increase in overall severe adverse events.	Ex. 1011-1 at p. 111 (43:5-26).	Ex. 1027 at pp. 43-44 (42:28-43:26).

The excerpts cited above support the claim as narrowed by amendment—*i.e.*, a claim directed to treating "metastatic breast cancer" with a combination of "rhuMAb HER2" and "paclitaxel," in the absence of an anthracycline derivative, in an amount effective to extend TTP "as compared to paclitaxel alone," without increase in overall severe adverse events. The applications describe a clinical study in which overexpressing ErbB2 metastatic breast cancer patients were treated with a combination of a humanized version of the murine 4D5 antibody (HERCEPTIN®) (also known as rhuMAb HER2) and Taxol® (also known as paclitaxel) in the absence of an anthracycline derivative. (*See, e.g.*, Ex. 1011-1 at p. 104 (36:12-20), pp. 107-111 (39:3-43:4); Ex. 1027 at p. 37 (36:7-14), pp. 39-43 (38:25-42:27).) The results state that "assessments of time to disease progression (TTP in months) and response rates (RR) showed a significant augmentation of the chemotherapeutic effect by HERCEPTIN®, without increase in overall severe adverse events (AE)." (Ex. 1011-1 at p. 111 (43:5-8); Ex. 1027 at pp. 43-44 (42:28-43:2).) That the combination of the amended claims extends TTP as compared to treatment with paclitaxel alone can be seen in the following chart

included in both applications, which shows that patients treated with rhuMAb HER2 and paclitaxel ("H + T") had a TTP of 7.1 months, as compared to patients treated with paclitaxel alone ("T") who had a TTP of 4.2 months.

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

* $p<0.001$ by log-rank test

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

CRx : chemotherapy

AC: anthracycline/cyclophosphamide treatment

H: HERCEPTIN®

T: TAXOL®

(Ex. 1011-1 at p. 48 (43:10-23); Ex. 1027 at 44 (43:4-17).)

In sum, the applications state:

> 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®).

(Ex. 1011-1 at pp. 111-112 (43:27-44:3); Ex. 1027 at p. 44 (43:21-26).) Thus, each and every limitation of the proposed Substitute Claim is expressly disclosed by the '649 and '346 applications.

Accordingly, a POSA would have understood that Patent Owner was in possession of the Substitute Claim as of the filing dates. 37 C.F.R. § 42.121(b)(1)-(2); *see also Nichia Corp. v. Emcore Corp.*, IPR2012-00005, Paper 27 at 3 (PTAB June 3, 2013). (Ex. 2062, Tannenbaum Decl. ¶¶ 120-124.)

V. THE SUBSTITUTE CLAIM RESPONDS TO AND OVERCOMES THE ASSERTED GROUNDS

The proposed Substitute Claim responds to the asserted grounds of unpatentability, as required by 37 C.F.R. § 42.121(a)(2)(i). For example, the Substitute Claim responds to the Board's construction of the original claim limitation "extend the time to disease progression in said human patient, without increase in overall severe adverse events," to make explicit that the term should properly be construed as extension of TTP relative to patients treated with paclitaxel alone. In fact, all aspects of Patent Owner's proposed amendment are designed to cause the Substitute Claim to read on the specific embodiment disclosed in the '441 patent specification at 26:32-30:27 (Ex. 1001), in which the claimed method of treatment, rhuMAb HER2 plus paclitaxel, is compared to paclitaxel alone with respect to TTP.[3]

[3] It is not required that ***every*** amended limitation be solely for the purpose of overcoming an instituted ground. *Veeam Software Corp. v. Veritas Techs., LLC*, IPR2014-00090, Paper 48 at 28-29 (PTAB July 17, 2017) ("We do not view the

A. A Person Of Ordinary Skill Would Not Have Been Motivated To "administer[] a combination" Of rhuMAb HER2 And Paclitaxel Based Upon Baselga '96 And Baselga 94.

The Substitute Claim requires "administering a combination" of rhuMAb HER2 and paclitaxel "to the human patient," but neither Baselga '96 nor Baselga '94 discloses or suggests this limitation.

1. Baselga '96 and Baselga '94 do not provide a motivation to treat patients with the claimed combination.

Baselga '96 describes the first Phase II clinical trial administering rhuMAb HER2 alone, and then mentions the fact of *in vitro* and preclinical mouse xenograft studies involving combinations with "several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel." (Ex. 1004 at 15.) The Phase II clinical trial would not motivate a POSA to administer the claimed combination where it administers rhuMAb HER2 alone, and describes patients who received treatment with an anti-ErbB2 antibody and ***separate***, prior treatment with a taxoid. (Ex. 1004 at 10 (requiring patients to discontinue any chemotherapy, including taxoids, at least three weeks prior to study).) The mention to other clinical trials does not provide a motivation either—Baselga '96 does not specify what "combination therapy" was being studied. In fact, there was ***no*** clinical studies testing the

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requirement to be that every word added to or removed from a claim in a motion to amend must be solely for the purpose of overcoming an instituted ground.").

combination of rhuMAb HER2 and paclitaxel at the time that Baselga '96 was submitted (Aug. 8, 1995) or accepted for publication (Oct. 19, 1995). (Ex. 2011, 2017 Hellmann Declaration ¶¶ 18, 19, 29, 42; Ex-2007 at 1 (amended protocol Nov. 13, 1995); Ex. 2062, Tannenbaum Decl. ¶ 115.)

Baselga '94 summarizes the preclinical study alluded to in Baselga '96. The Board concluded in its Institution Decision that Baselga '94 would have motivated a POSA to treat human patients with a combination of an anti-ErbB2 antibody and a taxoid. (Paper 29 at 12.) Respectfully, the full record now confirms that Baselga '94 would have provided no such motivation.

First, Baselga '94 is a one-paragraph abstract that is not peer-reviewed. A POSA would have waited for a full, peer-reviewed paper describing the underlying experiments and bases before drawing any conclusions from it. (Ex. 2062, Tannenbaum Decl. ¶ 169.)

Second, a POSA would understand that mouse studies are not generally predictive of clinical efficacy or safety in humans. While a useful initial mechanism to screen for drugs that show some activity against particular cancer cells and to understand a mechanism of function, mouse models were known in the 1990s to be an inexact tool with several predictive shortcomings. (Ex. 2051 at 1041; Ex. 2062, Tannenbaum Decl. ¶¶ 66-75; Ex. 2061, Kerbel Decl. ¶¶ 51-83.) The cancer cells of mice in these models differ from those in humans several

respects, and these differences can meaningfully undermine the mouse model's predictive value. For example, mice have higher maximum tolerated dose of therapy, thus allowing them to be dosed with amounts of the drug not possible in humans. Moreover, humans often experience host-cell or tissue-dependent toxicity—*i.e.*, toxicity related to human cells or tissues that do not appear in xenograft mice—which can lead to inconsistent results between mice and humans. (Ex. 2019 at 1577; Ex. 2061, Kerbel Decl. ¶¶ 71-76.) In addition, mouse studies are more likely to show positive efficacy because they use tumor cell lines from tissue culture, which exhibit greater sensitivity to chemotherapy. (Ex. 2052 at 257-58; Ex. 2061, Kerbel Decl. ¶¶ 39-40, 65; Ex. 2062, Tannenbaum Decl. ¶¶ 69-74.)

The history of preclinical testing of paclitaxel provides a good example of the questionable predictive value of preclinical studies and that suggests a POSA would not have been motivated to use the drug in combination therapy. Early preclinical studies indicated that paclitaxel, administered as a single agent, was active in human breast, ovarian, and colorectal xenograft models. (Ex. 2070 at 184.) But by 1997, it had become clear that single-agent paclitaxel was ***in***active in human colorectal cancer patients (Ex. 2071 at 750), contrary to the preclinical evidence. (Kerbel Decl. ¶¶ 59-61.)

Third, a POSA would understand that the particular mouse study described in Baselga '94 was not a reliable predictor of success in humans. This study was

based on a single cell line, rather than multiple cell lines, and the particular cell line used (BT-474) expressed the highest HER2 levels of any known breast cancer cell line at the time—thus making it more susceptible to therapy than typical breast cancer cells with lower HER2 expression. (Ex. 2061, Kerbel Decl. ¶¶ 62-70; Ex. 2064 at 5400, 5402; Ex. 2065 at 262; Ex. 2062, Tannenbaum Decl. ¶¶ 73, 144.) In addition, the tumors in Baselga '94 were implanted subcutaneously, rather than in the tissue similar to how the disease would present in human patients (*e.g.*, mammary fat pad for breast cancer). These design flaws further undermine the predictive value of the study in humans. (Ex. 2053 at 79; Ex. 2061, Kerbel Decl. ¶¶ 77-81; Ex. 2062, Tannenbaum Decl. ¶¶ 144, 172.) Moreover, the mouse study described in Baselga '94 and Baselga '96 measured short-term response rate, which is a different clinical endpoint from—and not indicative of—extension of TTP (much less extension of TTP in humans). (Ex. 1004 at 9, 12; Ex. 1005 at 4; Ex. 2061, Kerbel Decl. ¶¶ 82-83.) Thus, these references would not have motivated a POSA to treat humans with the claimed combination. (Ex. 2061, Kerbel Decl. ¶¶ 51-53; Ex. 2062, Tannenbaum Decl. ¶¶ 74, 145-146, 172.)

Fourth, there were significant concerns with using paclitaxel to treat HER2-positive breast cancer before the '441 invention. At the time, patients experienced serious hypersensitivity reactions, neuropathy, and cardiotoxicity from paclitaxel, which was only approved for second-line use in breast cancer. (Ex. 1025 at 10, 12;

Ex. 2028 at 1265; Ex. 2026 at 1704 (warning oncologists "to maintain a high degree of caution" in treating patients with taxoids).) Moreover, the prior art taught away by explicitly warning that HER2-positive breast cancer "will not respond well to Taxol." (Ex. 2029 at 1362.) These safety and efficacy concerns would have further dissuaded POSAs from using combination therapy involving taxoids. (Ex. 2062, Tannenbaum Decl. ¶¶ 58-60, 176-179.)

Indeed, the development history of rhuMAb HER2 confirms that the Baselga references would not have motivated a skilled artisan to treat humans with rhuMAb HER2 and paclitaxel. Despite studying combinations with other chemotherapies (e.g., cisplatin (Ex. 1013), doxorubicin (Ex. 2001)), ***none*** of the Phase-II and initial Phase-III clinical trials tested the combination of an anti-ErbB2 antibody and a taxoid in the absence of an anthracycline derivative. And when the '441 patent's inventor Dr. Hellman finally modified the Phase-III trial to include a combination of rhuMAb HER2 and paclitaxel, she did so based on her unique knowledge of paclitaxel and in response to enrollment issues with the study, not because of the preclinical results involving the combination of rhuMAb HER2 and paclitaxel. (Ex. 2011, 2017 Hellmann Decl. ¶¶ 2, 18, 34; Ex. 2111 at 73.) Given the well-known problems with taxoids, a POSA would not have been motivated to pursue the claimed combination based on Baselga '94, and it would be inappropriate to attribute Dr. Hellmann's extraordinary knowledge to a POSA. *See*

Standard Oil Co. v. American Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985) (inventor possesses knowledge "which sets them apart from the workers of *ordinary* skill" (emphasis in original)). Only in hindsight can Petitioner contend that a skilled artisan would have been motivated to use a combination that even those with the best information about rhuMAb HER2 at the time did not pursue.

2. A person of ordinary skill would have been motivated to use an anthracycline rather than a taxoid.

In the late 1990s, antibodies were a new and uncertain therapy that faced "significant obstacles" in treating solid tumors, such as breast cancer, and required "much additional study." (Ex. 2031 at 683; Ex. 2025 at 649; Ex. 2062, Tannenbaum Decl. ¶¶ 93-97.) Meanwhile, the prior art reflected significant safety concerns regarding treatment with taxoids, and the efficacy of taxoids in treating HER2-positive breast cancer was questionable at best (*supra* pp. 12-13). Because of these risks and uncertainties, a POSA would not have been motivated to use paclitaxel in combination with rhuMAb HER2 as a treatment for HER2-positive breast cancer. (Ex. 2062, Tannenbaum Decl. ¶¶ 55-60.) That a POSA would not have risked using taxoids is especially the case when considering the other drug in the combination—an anti-ErbB2 antibody—was still a new therapy with its own uncertainties at the time. (Ex. 2062, Tannenbaum Decl. ¶¶ 95-99, 175.)

Instead, a POSA would have chosen to limit the number of variables by using a first-line chemotherapy such as anthracyclines, which were the standard of care and most common treatment for breast cancer at the time. The efficacy of anthracyclines in treating breast cancer was well established in the art, and the side effect of such treatment—cardiotoxicity in some individuals—had been thoroughly studied and was understood to be manageable. (Ex. 2030 at 409, 423, 425; Ex. 2055 at Abstract, 5; Ex. 2103 at 3118.) At this time, anthracyclines were the standard and most common treatment for breast cancer. (Ex. 2055 at 3; Ex. 2030 at 409.) In fact, when Genentech initially designed the protocol for the Phase-III trial, the method of treatment chosen was rhuMAb HER2 in combination with doxorubicin, an anthracycline derivative. (Ex. 2002 at 2; Ex. 2003 at 2; Ex. 2004 at 3.) Thus, contrary to the '441 patent's novel idea of treating HER2-positive breast cancer with a combination "in the absence of an anthracycline derivative," a POSA would have deemed anthracyclines the obvious chemotherapeutic agent for any drug combination. (Ex. 2062, Tannenbaum Decl. ¶¶ 45-52.)

B. Petitioner Has Not Established A Reasonable Expectation Of Success In Achieving The Claimed Clinical Efficacy Recited By The Substitute Claim.

The Substitute Claim requires, inter alia, that treatment with rhuMAb HER2 and paclitaxel extend TTP relative to treatment with paclitaxel alone, contrary to the Board's construction of the Challenged Claims as requiring, inter alia,

extension of TTP relative to an untreated patient. This amendment confirms the patentability of the Substitute Claim.

Baselga '96 and Baselga '94 do not disclose that the claimed combination extends TTP relative to a patient treated with paclitaxel alone. Baselga '96 discloses that patients who responded to antibody therapy had a median time to disease progression of 5.1 months. (Ex. 1004 at 12.) But all patients in Baselga '96 were treated with rhuMAb HER2; the study contained no control arm. Baselga '96 therefore discloses no ***extension*** in TTP, let alone an extension in TTP for patients treated with the claimed combination as compared to those treated with paclitaxel alone. (Ex. 2062, Tannenbaum Decl. ¶¶ 183-185.)

In its Institution Decision, the Board stated that the prior art does not suggest "that combining a taxoid with rhuMAb HER2 would abrogate the effect of the antibody." (Paper 29 at 16.) However, in assessing the Substitute Claims, the relevant question is not whether rhuMAb HER2 and paclitaxel would have an antagonistic interaction; rather, the question is whether adding rhuMAb HER2 to paclitaxel would improve the clinical response to paclitaxel alone with respect to the specific clinical endpoint of extending TTP. The data for patients treated with rhuMAb HER2 alone disclosed in Baselga '96 does not address that question.

Nor does Baselga '94 disclose that the combination of rhuMAb HER2 and paclitaxel would have extended TTP relative to treatment with paclitaxel alone. As

an initial matter, Baselga '94 is a one-paragraph abstract, nor peer-reviewed for content, which POSAs would have given little weight without first seeing the full, peer-reviewed paper. (Ex. 2062, Tannenbaum Decl. ¶ 169.)

Furthermore, although the combination of rhuMAb HER2 and paclitaxel was more effective at reducing tumor size than paclitaxel alone in the particular mouse model used, shrinking tumors is ***different*** from extending TTP. Indeed, a POSA would have understood that a therapy could reduce tumor size without improving TTP. (*See* IPR2017-02063; Ex. 1102 ¶ 112(f)-(g); Ex. 2062, Tannenbaum Decl. ¶¶ 84-85, 186.) Moreover, the mouse studies lasted only ***five weeks*** (Ex. 1005), which would not inform a POSA as to a clinical endpoint (TTP) that takes ***several months*** to measure (Ex. 1001, 29:20-30:12 (column titled "TTP(months)")). As discussed above, the particular mouse model used in Baselga '94 had significant design flaws that undermined the predictive value in assessing any clinical therapeutic effect in human patients. (*Supra* pp. 10-12.)

Indeed, the development history of rhuMAb HER2 confirms that the preclinical results in Baselga '94 would not have provided a POSA a reasonable expectation of success in achieving the specific clinical result claimed in the '441 patent. Despite the results reported in Baselga '94, no one pursued a clinical trial combining rhuMAb HER2 and paclitaxel until the '441 patent's inventor Dr.

Hellmann, using her unique knowledge of paclitaxel, suggested modifying an ongoing Phase-III trial to address enrollment issues. (*Supra* p. 13.)

C. Petitioner Has Not Established A Reasonable Expectation Of Success In Achieving The Claimed Clinical Safety.

Petitioner also has not shown a reasonable expectation of success that the claimed combination therapy would not result in "increase in overall severe adverse events."

The Board relies on Baselga '96's statement that rhuMAb HER2 produced "minimal" toxicity. (Paper 29 at 17.) But Baselga '96 did not address the toxicity of the ***combination*** of rhuMAb HER2 and paclitaxel. The minimal toxicity of rhuMAb HER2 alone says nothing about potential safety issues when combined with other drugs.[4]

Petitioner cites Baselga '94's teaching that the combination of rhuMAb HER2 and paclitaxel did not increase toxicity in mouse models. (Paper 1 at 31.) However, Baselga '94 made the same statement about combinations with the anthracycline doxorubicin (Ex. 1005 at 4)—which produced a significant increase in cardiotoxicity when administered to human patients. These results further

[4] The Board's reliance upon the Taxol label (Paper 29 at 17 (citing Ex. 1025, 10)) fails for the same reason. Moreover, the Taxol label is not part of a ground of unpatentability instituted in this proceeding and thus its disclosure is irrelevant.

confirm the limitations of mouse models for predicting results in human patients. (*Supra* pp. 10-12.) This is especially true for a combination involving the rhuMAb HER2; because it was engineered to bind to the human ErbB2 receptor (not the mouse ErbB2 receptor) and have similarities to antibodies produced in humans, testing the antibody in mice would not have produced toxicity results predictive of treatment in humans. In addition, because rhuMAb HER2 originally was produced in mice immunized with human ErbB2, a POSA would have known that the antibody would affect only human cancer cells in the mouse, thus failing to provide insight as to the potentially-toxic effect of rhuMAb HER2 on other cells. (Ex. 2061, Kerbel Decl. ¶¶ 71-76; Ex. 2062, Tannenbaum Decl. ¶¶ 73-75.)

Indeed, Baselga '94 stated that the 4D5 antibody "did not increase the toxicity of paclitaxel or doxorubicin in animals"—which turned out to be an unreliable prediction for humans as to doxorubicin when the combination was later tested in humans and produced a significant increase in cardiotoxicity. This disconnect highlights the inability of Baselga '94's mouse models to predict clinical safety. (*Supra* pp. 10-12.)

Petitioner also argues that a POSA would have had a reasonable expectation of success in achieving the claimed clinical safety results because the Baselga references supposedly "reported as early as 1994 … that clinical trials of the combination were underway in humans, and that these clinical trials were still

underway in 1997." (Paper 1 at 31.) As discussed above, that argument is not supported by the Baselga references and is inconsistent with the development timeline for rhuMAb HER2. (*Supra* p. 13.) Petitioner cannot demonstrate a reasonable expectation of success based on false assumptions about a non-existent study. That argument also cannot be reconciled with the experience of cancer researchers in the 1990s; the mere fact that a treatment was under evaluation was no indication of success, given the high failure rate of therapies in clinical trials. (Ex. 2021 at 2-3.)

D. The Claimed Combination Would Not Have Been Obvious To Try.

Contrary to Petitioner's argument as to the Challenged Claims (Paper 1 at 31-32, 49, 61), the Substitute Claims would not have been obvious to try. Petitioner's argument rests on hindsight.

First, prior to the '441 invention, the combination of a rhuMAb HER2 and paclitaxel in the absence of an anthracycline derivative was not even among a finite number of options that a POSA would have pursued. There were dozens of chemotherapies known in the prior art, and numerous other possibilities that a skilled artisan would have pursued instead. (Ex. 2062, Tannenbaum Decl. ¶ 42.)

That is confirmed by the development history of rhuMAb HER2. As discussed above (*supra* p. 13), Genentech pursued several alternative therapies

(*e.g.*, anti-ErbB2 antibody alone (Ex. 1004), combined with cisplatin (Ex. 1013), or combined with doxorubicin (Ex. 2001)) and only pursued the claimed combination after '441 inventor Dr. Hellmann, based on her unique knowledge of paclitaxel, proposed the idea over objection. That the claimed combination was not among treatment regimens pursued in any clinical trials confirms that it was not obvious to try. *See, e.g.*, *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1356-57 (Fed. Cir. 2013) (holding that the alternatives disclosed in the art and the fact that no one had pursued the claimed invention before the inventors confirmed that the invention was not obvious to try). And it would be improper to impute Dr. Hellman's ***extra***ordinary knowledge to a person of ***ordinary*** skill in the art. *See Standard Oil Co.*, 774 F.2d at 454 (inventors possess knowledge "which sets them apart from the workers of *ordinary* skill" (emphasis in original)). (Ex. 2062, Tannenbaum Decl. ¶ 115.)

Second, Petitioner's obvious-to-try theory fails for the further reason that the claimed invention was not one of "a finite number of identified, ***predictable*** solutions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). The '441 invention is in a highly-unpredictable field—as confirmed, for example, by the nearly 60% failure rate of cancer drugs in Phase-III trials during the 1990s and the fact that Baselga '94 itself failed to predict the toxicity of rhuMAb HER2 combined with anthracyclines. (Ex. 2016 at 79; Ex. 2115 at S77; Ex. 2062,

Tannenbaum Decl. ¶¶ 117, 195.) Petitioner cannot demonstrate that the art was predictable when the asserted references show that it was not. Petitioner does not address that unpredictability, let alone explain how the invention could have been obvious to try given those uncertainties. (Ex. 2062, Tannenbaum Decl. ¶¶ 115-116.)

E. Objective Indicia Of Non-Obviousness Confirm The Patentability Of The Substitute Claim.

Evidence concerning the real-world impact of a patented invention is a critical safeguard against hindsight reasoning. *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010). Indeed, the Board has recognized that such evidence alone may rebut other evidence of obviousness. *InnoPharma Licensing, Inc. v. Senju Pharm. Co.*, IPR2015-00902, Paper-90 at 14-22, 25-27 (July 28, 2016). Here, several objective indicia conclusively establish the non-obviousness of the challenged claims. (Ex. 2062, Tannenbaum Decl. ¶¶ 202-218.)

First, the '441 invention satisfied a long-felt-but-unmet need for an effective treatment for HER2-positive breast cancer. Before the '441 invention, HER2-positive patients experienced "horribly rapid progression" and were "in dire need" of an effective therapy. (Ex. 2018 at 887.) After the results of Phase-III clinical trials showing that the claimed combination produced a "dramatic" increase in the time to disease progression, the '441 invention was heralded as a "breakthrough"

therapy, receiving FDA fast-tracked approval. (Ex. 2018 at 887.) Moreover, Dr. Tannenbaum recalls an urgent need for a new treatment for HER2-positive breast cancer that would extend patient lives by even a few months, which was met by the combination of Herceptin® and paclitaxel, and which allowed many of her patients to live for years after metastasis began. (Ex. 2062, Tannenbaum Decl. ¶¶ 203-207, 218.)

Second, following the results of the rhuMAb HER2 Phase-III trial, rhuMAb HER2 was widely praised as an "anti-cancer breakthrough" that produced "impressive" results. (Ex. 2018 at 887; Ex. 2033 at 1; Ex. 2034.) (Ex. 2062, Tannenbaum Decl. ¶¶ 216-218.) Petitioner can hardly contend that those results would have been obvious from the Baselga references—when Dr. Larry Norton, a leading practitioner and co-author of the Baselga references, went on national television to praise the impressive results of the '441 invention: "It doubles or triples the efficacy of Taxol in killing these cancer cells. This is a very big, dramatic advance, one of the biggest changes in the ability of chemotherapy to kill cancer cells that I've ever seen in my career." (Ex. 2034.) (Ex. 2062, Tannenbaum Decl. ¶¶ 216-218.)

Third, the combination of rhuMAb HER2 and paclitaxel in the absence of an anthracycline derivative produced unexpectedly-superior clinical-efficacy results as compared with either the antibody or paclitaxel alone. (Ex. 1011-2 at 53-54,

2000 Hellmann Decl. ¶ 6.) Petitioner argues that those results would have been expected because preclinical mouse models testing that drug combination "demonstrated synergistic effects." (Paper 1 at 62.) But the preclinical results did not address the specific clinical endpoint of TTP, let alone show an improvement in that outcome. (*Supra* p. 12.) In any case, preclinical results at that time were known to be poor predictors of clinical outcomes. (*Supra* pp. 10-12.) In fact, other preclinical studies involving the claimed combination produced "inconsistent results." (Ex. 2004 at 3, 6.) A POSA therefore would have considered those vastly-superior clinical-efficacy results to be unexpected, which further confirms the nonobviousness of the claimed invention. *See Procter & Gamble Co. v. Teva Pharms. USA, Inc*, 566 F.3d 989, 994 (Fed. Cir. 2009). (Ex. 2062, Tannenbaum Decl. ¶¶ 212-215.)

Fourth, the '441 invention has been an enormous commercial success. HERCEPTIN® is the commercial embodiment of the '441 invention and one of the most successful drugs of all time. (Ex. 2012 at 1; Ex. 2035 at 17.) From 1998 until 2006, the ***only*** approved first-line use of Herceptin® was in combination with a taxoid, as claimed in the '441 patent. (Ex. 2012 at 1.) Following its launch, Herceptin® was quickly adopted, resulting in hundreds of millions of dollars in sales in those years immediately following its approval. (Ex. 2035 at 17.) Where, as here, the commercial product embodies the claimed invention, a nexus is

presumed. *Brown & Williamson Tobacco Corp. v. Philip Morris, Inc*., 229 F.3d 1120, 1130 (Fed. Cir. 2000).

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Accordingly, the Substitute Claim is responsive to the asserted grounds and are patentable over the prior art.

VI. CONCLUSION

Accordingly, if independent claim 11 is determined to be unpatentable, Patent Owner respectfully requests that the Board grant this contingent Motion such that the '441 patent be amended to include the corresponding Substitute Claim 15.

Respectfully submitted,

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APPENDIX A

CLAIM LISTING

Substitute Claims Showing Amendments to Original Claims

1-10. (Canceled)

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

12-14. (Canceled)

Clean Version of Claims

15. (Proposed substitute for original claim 11) A method for the treatment of a human patient with ErbB2 overexpressing progressing metastatic breast cancer, comprising administering a combination of rhuMAb HER2 and paclitaxel, in the absence of an anthracycline derivative, to the human patient in an amount effective to extend time to disease progression in said human patient, as compared to paclitaxel alone, without increase in overall severe adverse events.