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
Patent No. 7,892,549

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 claims 1 and 16 of U.S. Patent No. 7,892,549 (the "'549 patent"). Claim 17 is unchanged, except to update its dependency. The proposed amended claims are numbers 18-20 (collectively, the "Substitute Claims") and would be substituted for the original claims 1-17 (collectively, the "Challenged Claims"), in the event independent claim 1 or 16 (*i.e.*, the claims subject to amendment) is found unpatentable.[1]

The proposed Substitute Claims satisfy the requirements for a motion to amend. The Substitute Claims: (1) present a "reasonable number of substitute claims"; (2) do not "enlarge the scope of the claims"; (3) do not "introduce new subject matter"; and (4) "respond to a ground 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 amendments confirm patentability over the prior art. Accordingly, should Challenged Claims 1 or 16 be found unpatentable,

[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.

Patent Owner respectfully requests on a contingent basis that the '549 patent be amended to include the corresponding Substitute Claims.

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 two substitute claims for two of the Challenged Claims, and one claim is unchanged, except to update dependency from a Substitute Claim. Patent Owner further proposes to cancel the remainder of the Challenged Claims. Thus, Patent Owner proposes a reasonable number of substitute claims.

III. THE SUBSTITUTE CLAIMS DO NOT EXPAND THE SCOPE OF THE CLAIMS OF THE '549 PATENT

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

First, the Substitute Claims narrow the claimed antibody. Original claim 1 recites a genus encompassing "an antibody that binds ErbB2," and original claim 16 recites a genus encompassing "an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence." The Substitute Claims narrow

these limitations to recite a specific antibody species, "rhuMAb HER2," a recombinant humanized 4D5 anti-ErbB2 antibody also known as HERCEPTIN®.[2] (Ex. 1001 at 3:36-42, 4:26-33, 5:26-37; *see also* Paper 19 at 3 (July 27, 2017).) "rhuMAb HER2" is an antibody encompassed by original claims 1 and 16. (Ex. 1001 at 3:36-42; *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 Claims narrow the claimed taxoid. Original claims 1 and 16 recite the administration of a genus encompassing "a taxoid." The Substitute Claims narrow this limitation to recite "paclitaxel," which is a specific species of a taxoid. (Ex. 1001 at 4:23-25.)

Finally, original claims 1 and 16 have been amended 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" is a relative term, and construed the limitation to mean comparing the efficacy of the claimed

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

combination treatment relative to no treatment. (Paper 19 at 11-12.) Neither Patent Owner's expert nor Petitioners' expert agrees with the Board's construction. (Ex. 1011, Lipton Decl. ¶ 48; Ex. 2062, Tannenbaum Decl. ¶¶ 133-144; 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 Claims makes this explicit and directly corresponds to the specific clinical results reported in the '549 patent's specification (Ex. 1001 at 29:11-30:27). 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 Claims do 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.").

Substitute Claim 20 remains unchanged relative to its original form (*i.e.*, as original claim 17), except to update that it now depends from Substitute Claim 19.

In sum, the Substitute Claims narrow the Challenged Claims to correspond to the specific clinical trial disclosed in the '549 specification, which treated breast cancer in human patients with a combination of rhuMAb HER2 and paclitaxel in

an amount that extended time to disease progression as compared to human patients treated with paclitaxel alone. (*See, e.g.*, 1001 at 26:34-30:27.) Accordingly, the Substitute Claims do not expand the scope of the '549 patent claims.

IV. THE SUBSTITUTE CLAIMS DO NOT ADD NEW SUBJECT MATTER

Each of the proposed Substitute Claims is supported by the original disclosure of U.S. App. Ser. No. 10/356,824 (the '824 application) (Ex. 1019-1 at 7-56), which issued the '549 patent, and related Provisional Patent Application 60/069,346 (the '346 application) (Ex. 1020), to which the '824 application claims priority. Those applications are virtually identical and expressly disclose each and every limitation of the proposed Substitute Claims, as set forth in the chart below.

Claim	Support in '824 Application	Support in '346 Application
Proposed Claim 18		
~~1.~~ 18. A method of treatment of a human patient with breast cancer that overexpresses ErbB2 receptor, comprising	Ex. 1019-1 at pp. 42-43 (36:23-37:1); p. 46 (40:15-19).	Ex. 1020 at p. 37 (36:7-14); pp. 40-41 (39:26-40:1).
administering a combination of an ~~antibody that binds ErbB2~~ rhuMAb HER2, ~~a taxoid~~ paclitaxel, and a further growth inhibitory agent	Ex. 1019-1 at p. 22 (16:13-26); p. 43 (37:24-27); pp. 47-48 (41:28-42:15); p. 48 (42:21-25).	Ex. 1020 at p. 17 (16:8-20); p. 38 (37:7-10); p. 42 (41:9-23); p. 43 (42:2-6).
to a human patient	Ex. 1019-1 at 43 (37:2-6).	Ex. 1020 at p. 37 (36:15-19).

in an amount effective to extend the time to disease progression in the human patient, as compared to paclitaxel alone,	Ex. 1019-1 at pp. 49-50 (43:18-44:15).	Ex. 1020 at pp. 43-44 (42:28-43:26).
wherein the antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence.	Ex. 1019-1 at pp. 12-13 (6:17-7:3); p. 35 (29:3-6); p. 46 (40:1-9); p. 56.	Ex. 1020 at p. 7 (6:13-28); p. 29 (28:18-21); p. 40 (39:11-20); p. 52.
Proposed Claim 19		
~~16.~~ 19. A method for the treatment of a human patient with ErbB2 overexpressing breast cancer, comprising	Ex. 1019-1 at pp. 42-43 (36:23-37:1); p. 46 (40:15-19).	Ex. 1020 at p. 37 (36:7-14); pp. 40-41 (39:26-40:1).
administering a combination of ~~an antibody that binds epitope 4D5 within the ErbB2 extracellular domain sequence~~ rhuMAb HER2, ~~a taxoid~~ paclitaxel and a further growth inhibitory agent,	Ex. 1019-1 at p. 22 (16:13-26); p. 43 (37:24-27); pp. 47-48 (41:28-42:15); p. 48 (42:21-25).	Ex. 1020 at p. 17 (16:8-20); p. 38 (37:7-10); p. 42 (41:9-23); p. 43 (42:2-6).
in the absence of an anthracycline derivative,	Ex. 1019-1 at p. 43 (37:7-8); p. 48 (42:4-13); p. 50 (44:7-15).	Ex. 1020 at p. 37, (36:20-21); p. 42 (41:14-23); p. 44 (43:18-26).
to the human patient	Ex. 1019-1 at 43 (37:2-6).	Ex. 1020 at p. 37 (36:15-19).
in an amount effective to extend time to disease progression, as compared to paclitaxel alone, in the human patient.	Ex. 1019-1 at pp. 49-50 (43:18-44:15).	Ex. 1020 at pp. 43-44 (42:28-43:26).
Proposed Claim 20		
~~17.~~ 20. The method of claim ~~16~~ **19** wherein the breast cancer is metastatic breast carcinoma.	Ex. 1019-1 at pp. 46-47 (40:1-41:11).	Ex. 1020 at pp. 40-41 (39:11-40:11).

The excerpts cited above support the claims as narrowed by amendment—*i.e.*, claims directed to treating ErbB2 (*i.e.*, HER2) overexpressing breast cancer with a combination of "rhuMAb HER2," "paclitaxel," and a further growth

inhibitory agent in an amount effective to extend TTP "as compared to paclitaxel alone." The applications describe 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. (*See, e.g.*, Ex. 1019-1 at pp. 42-43 (36:18-37:1), pp. 45-50 (39:15-43:17); Ex. 1020 at pp. 37 (36:7-14), 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. 1019-1 at p. 49 (43:19-21); Ex. 1020 at pp. 43-44 (42:29-43:2).) 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. 1019-1 at pp. 49-50 (43:23-44:6); Ex. 1020 at p. 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. 1019-1 at p. 50 (44:10-15); Ex. 1020 at p. 44 (43:21-26).) Thus, each and every amended limitation of the proposed Substitute Claims is expressly disclosed by the '824 and '346 applications.

Accordingly, a POSA would have understood that Patent Owner was in possession of the Substitute Claims 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 (June 3, 2013). (Ex. 2062, Tannenbaum Decl. ¶¶ 122-126.)

V. THE SUBSTITUTE CLAIMS RESPOND TO AND OVERCOME THE ASSERTED GROUNDS

The proposed Substitute Claims respond to the asserted grounds of unpatentability, as required by 37 C.F.R. § 42.121(a)(2)(i). For example, the Substitute Claims respond to the Board's construction of the original claim limitation "extend the time to disease progression in said human patient," to make explicit that the term should properly be construed as extension of TTP relative to patients treated with paclitaxel alone, as described in the example in the '549 patent specification.[3]

A. Grounds 1-6: Petitioners Have Not Established A Reasonable Expectation Of Success In Achieving The Clinical Efficacy Recited By The Substitute Claims.

Petitioners have not shown that the prior art taught that the claimed combination therapy would extend the TTP relative to a patient treated with

[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 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.").

paclitaxel alone. Indeed, the ***first*** disclosure of clinical results showing that combinations that include rhuMAb HER2 and paclitaxel extend the TTP is in the '549 specification. (Ex. 1001, 29:13-30:25.)[4] Absent a similar disclosure, Petitioners cannot show that a POSA would have had a reasonable expectation of success in achieving that clinical result with the claimed combinations.

1. Grounds 1-3: Baselga '97 in view of Gelmon '96 does not teach that the claimed combination would extend the time to disease progression as compared to treatment with paclitaxel alone.

For Grounds 1-3, Petitioners rely on the combination of Baselga '97 and Gelmon '96 for its supposed disclosure of the claimed clinical-efficacy limitations. Baselga '97 is a review paper that describes a number of studies with rhuMAb HER2, including preclinical mouse xenograft studies assessing the antitumor activity of rhuMAb HER2 combined with either an anthracycline derivative or paclitaxel (Baselga '94, Ex. 1006); a Phase-II clinical study in which patients received rhuMAb HER2 monotherapy (Baselga '96, Ex. 1005 at 9); and the design

[4] All Substitute Claims require a third drug (*i.e.*, "a further growth inhibitory agent"). However, for the reasons set forth herein, Petitioners' instituted references do not even establish obviousness as to the narrower two-drug combination of rhuMAb HER2 and paclitaxel.

of a Phase-III study for combination therapy of rhuMAb HER2 and paclitaxel (Ex. 1007 at 10). Gelmon '96 describes a Phase-I/II study in which metastatic breast cancer patients were treated with a combination of paclitaxel and cisplatin. (Ex. 1025 at 9.) But Petitioners' arguments are not supported by those references.

First, Petitioners point to Baselga '97's description of the Phase II clinical study results involving rhuMAb HER2 alone, which showed that responses "lasted for a median of 5.1 months" and serum concentrations of rhuMAb HER2 in patients. (Paper 1 at 29.) But those results are the "median" TTP for patients who received rhuMAb HER2 only. They do not describe an ***extension*** in the TTP, which is a ***comparative*** result, let alone as compared to patients treated with a paclitaxel alone. (Ex. 2062, Tannenbaum Decl. ¶¶ 203-208.) The Phase II study described in Baselga '97 (originally reported in Baselga '96) contained no control arm to compare the TTP and disclosed no ***extension*** in the TTP. (Ex. 1005 at 10.)

In its Institution Decision, the Board stated that the prior art does not suggest "the addition of paclitaxel and/or a further growth inhibitory or therapeutic agent to a rhuMAb HER2 treatment regimen would abrogate the chemotherapeutic effect of anti-ErbB2 antibodies." (Paper 19 at 19.) However, the relevant question is not whether rhuMAb HER2 and the other drugs in the claimed combination would have an antagonistic interaction, but rather whether adding rhuMAb HER2 to paclitaxel would improve the TTP as compared to paclitaxel alone. The data for

patients treated with rhuMAb HER2 alone disclosed in Baselga '97 do not address that question. (Ex. 2062, Tannenbaum Decl. ¶¶ 213-216.)

Second, Petitioners rely on Baselga '97's description of preclinical mouse results of response rate in testing combinations of rhuMAb HER2 and paclitaxel or cisplatin. (Paper 1 at 29-30.) But Baselga '97 reports no results from those studies relating to an ***extension*** in the TTP. Petitioners argue that combinations of rhuMAb HER2 with paclitaxel or cisplatin produced "synergistic increases in treatment efficacy" (Paper 1 at 30), but never explains how those supposed "synergistic" interactions would suggest a clinical result that was not evaluated, particularly when response rate is a different clinical endpoint than—and not indicative of—extension of TTP. (Ex. 1005 at 9, 12; Ex. 1006 at 4; Ex. 2061, Kerbel Decl. ¶¶ 82-83; Ex. 2062, Tannenbaum Decl. ¶¶ 86-88.)

Third, Petitioners point to Baselga '97's disclosure of an ongoing Phase III trial to evaluate whether combinations of rhuMAb HER2 with paclitaxel or anthracycline increased the TTP compared with a control group. (Paper 1 at 30.) But Baselga '97 reports ***no*** results from this "ongoing" study." (Ex. 1007 at 10.) The mere disclosure of a study 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. (Ex. 2021 at 712-13.) (Ex. 2062, Tannenbaum Decl. ¶¶ 89-91.)

Fourth, Petitioners argue that "Gelmon '96 discloses a combined paclitaxel plus cisplatin treatment regimen that increases the time to disease progression." (Paper 1 at 29.) Beyond failing to address any combination involving rhuMAb HER2, Gelmon '96 only discloses a "median" TTP and contains no comparative data showing any ***extension*** in the TTP because it had no control arm. (Ex. 1025 at 13.) (Ex. 2062, Tannenbaum Decl. ¶ 167.)

Fifth, Petitioners attempt to minimize the significance of the clinical-efficacy limitation by arguing that "any" extension in TTP would suffice. (Paper 1 at 29.) But that does not relieve Petitioners of the obligation to show a reasonable expectation of success in achieving ***some*** extension in the TTP. Petitioners have not explained how a POSA would have had a reasonable expectation of success in obtaining even a minimal extension in the TTP when that clinical outcome is not described in the prior art.

Finally, Petitioners attempt to excuse the complete absence of the claimed extension of TTP in the prior art on the basis that the '549 patent supposedly contains no such data for the claimed three-drug combination. (Paper 1 at 19.) But Petitioners ignore that the '549 patent discloses clinical results showing an extension in the TTP for the combination of rhuMAb HER2 and paclitaxel. (Ex. 1001, 29:13-30:25.) Without a similar disclosure in the prior art, Petitioners cannot demonstrate that even the two-drug combination of rhuMAb HER2 and

paclitaxel would have been obvious, let alone a third drug added to that combination. (Ex. 2062, Tannenbaum Decl. ¶¶ 181-184.)

2. Grounds 4-6: Baselga '96 in view of Gelmon '96 and Baselga '94 does not teach that the claimed combination would extend the time to disease progression as compared to treatment with paclitaxel alone.

For Grounds 4-6, Petitioners rely on Baselga '96 in view of Gelmon '96 and Baselga '94 for the supposed disclosure of the claimed efficacy limitations. Those arguments fail for the same reasons as do Grounds 1-3.

Petitioners argue that Baselga '96 discloses an extension in the TTP because it teaches that responses to rhuMAb HER2 lasted "for a median of 5.1 months." (Paper 1 at 47.) Petitioners also argue that the preclinical results supposedly showed "synergistic increases in treatment efficacy." (Paper 1 at 48.) But this argument fails for the reasons discussed above (pp. 11-12).

Moreover, by 1997, it was known that efficacy in mouse models was not reliably predictive of anti-cancer drug performance in humans. (*See, e.g.*, Ex. 2023 at 79; Ex. 2051 at 1041; Ex. 2061, Kerbel Decl. ¶ 55.) 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. ¶¶ 66-77; Ex. 2061, Kerbel Decl. ¶¶ 54-61.)

Mouse studies generally failed to reliably predict results in humans for several reasons. First, mice have a higher maximum tolerated dose of therapy, thus allowing them to be dosed with amounts of the drug not possible in humans. Second, humans often experience host-cell or tissue-dependent toxicity—*i.e.*, toxicity in 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.) Third, 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. 2019 at 1577; Ex. 2061, Kerbel Decl. ¶¶ 39-40; Ex. 2062, Tannenbaum Decl. ¶¶ 72-75.)

Moreover, a POSA would understand that the mouse study described in Baselga '96 (Ex. 1005) and Baselga '94 (Ex. 1006) 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—*i.e.*, more than 20 times the number of HER2 genes per cell than in a normal human cell. (Ex. 2061, Kerbel Decl. ¶¶ 62-70; Ex. 2064 at 5400, 5402; Ex. 2065 at 262; Ex. 2062, Tannenbaum Decl. ¶ 147.) In addition, the tumors in Baselga '94 were implanted subcutaneously, rather than in breast tissue, how the disease would present in human patients. 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. ¶¶ 147, 149, 191.)

The development history of rhuMAb HER2 confirms that the preclinical results in the Baselga references would not have provided a POSA a reasonable expectation of success in achieving the specific clinical result claimed in the '549 patent. Despite the preclinical results in the Baselga references, no one pursued a clinical trial combining rhuMAb HER2 and paclitaxel until the one of the '549 patent's inventors Dr. Hellmann suggested modifying an ongoing Phase III trial to address enrollment issues. (Ex. 2111 at 73.) (Ex. 2062, Tannenbaum Decl. ¶ 226.)

Petitioners repeat arguments from above (*e.g.*, Gelmon '96 supposedly shows that the combination of paclitaxel and cisplatin increased TTP; the Challenged Claims are satisfied by "any" minimal extension in the TTP), which fail for the same reasons. (*See supra* p. 15.)

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The cited references do not disclose the clinical result of extending the TTP as compared to treatment with paclitaxel alone, and Petitioners' arguments relating to that limitation are flatly contradicted by what the references actually say. Petitioners therefore cannot establish that a POSA would have had a reasonable expectation of success in achieving the clinical result of extending the TTP as

required by the Substitute Claims. *See, e.g.*, *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 995-97 (Fed. Cir. 2009).

B. Grounds 4-6: Baselga '96 In View Of Gelmon '96 And Baselga '94 Does Not Teach "Administering A Combination" Of rhuMAb HER2 And Paclitaxel "To The Human Patient."

All Substitute Claims require "administering a combination" of rhuMAb HER2 and paclitaxel "to the human patient." For Grounds 4-6, Petitioners argue that the combination of Baselga '96 and Baselga '94 teaches that limitation. Petitioners' arguments are not supported by those references.

1. Baselga '96 would not have motivated POSA to administer the combination of rhuMAb HER2 and paclitaxel.

Petitioners argue that Baselga '96 teaches a combination of an anti-ErbB2 antibody and a taxoid because four patients had "***prior*** systemic therapy" with a taxoid. (Paper 1 at 45.) But those patients were not "administered a ***combination***" of rhuMAb HER2 and paclitaxel. (Paper 29 at 10.) Baselga '96 describes patients who received treatment with an anti-ErbB2 antibody and ***separate*** prior treatment with a taxoid. (Ex. 1005 at 10, 13.)

Petitioners also argue that Baselga '96 teaches a combination of an anti-ErbB2 antibody and a taxoid because it (i) describes preclinical studies involving the combination of rhuMAb HER2 with cisplatin, doxorubicin, and paclitaxel, and (ii) notes that "clinical trials of such combination therapy [are] currently in

progress." (Paper 1 at 45.) The preclinical studies mentioned in Baselga '96, and further described in Baselga '94, would be insufficient to suggest the combination given its design flaws and minimal predictive value. (*Supra* pp. 14-16.) And Baselga '96 does not specify what "combination therapy" was studied. In fact, there was ***no*** clinical study testing the combination of rhuMAb HER2 and paclitaxel at the time that Baselga '96 was submitted (August 8, 1995) or accepted for publication (October 19, 1995). (Ex. 2062, Tannenbaum Decl. ¶¶ 183-186.)

2. Baselga '94 would not have motivated POSA to administer the combination of rhuMAb HER2 and paclitaxel.

Baselga '94 would not have motivated a POSA to "administer a combination" of rhuMAb HER2 and paclitaxel "to the human patient" either. It merely describes preclinical ***mouse*** xenograft models, and thus does not involve administering the claimed combination to a "***human*** patient." A POSA would not have been motivated to treat human patients with rhuMAb HER2 and paclitaxel based upon Baselga '94 for several reasons.

First, Baselga '94 is a one-paragraph abstract that was not peer-reviewed for content. To the extent a POSA would pay any attention to Baselga '94, she would wait for the full, peer-reviewed paper describing the underlying experiments and bases before drawing any conclusions from it. (Tannenbaum Decl. ¶ 188.)

Second, a POSA would understand that the particular mouse study in Baselga '94 was not a reliable predictor of success in humans given its many shortcomings. (*Supra* pp. 15-16.)

Third, there were significant concerns with using taxoids to treat HER2-positive breast cancer before the '549 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. 1066 at 10, 12; Ex. 2028 at 1265; Ex. 2026 at 1704.) Moreover, the prior art warned that HER2-positive breast cancer "will not respond well to Taxol." (Ex. 2029 at 1362.) Indeed, Petitioners admit that Gelmon '96 teaches that "HER2 positive breast cancer patients are resistant to … paclitaxel." (Paper 1 at 28, 46-47.) (Ex. 2062, Tannenbaum Decl. ¶¶ 57, 94.)

The development history of rhuMAb HER2 confirms that Baselga '94 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. 1023), doxorubicin (Ex. 2001)), ***no*** clinical trials tested the combination of rhuMAb HER2 and paclitaxel in the absence of an anthracycline derivative. Dr. Hellmann, one of the '549 patent's inventors, only modified the Phase III trial to include a combination of rhuMAb HER2 and paclitaxel 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. 2111 at 73; Ex. 1019-5 at 338 ¶ 1; Ex. 2062, Tannenbaum Decl. ¶¶ 115, 201.) 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).

C. Grounds 1-6: A POSA Would Not Rely Upon Gelmon '96 To Treat A HER2-Positive Patient With A Combination Including Cisplatin and Paclitaxel.

Grounds 1-6 rely on Gelmon '96 for its disclosure of treating breast cancer patients with a combination of cisplatin and paclitaxel. Petitioners assert that a POSA would combine that teaching with the various Baselga references showing that rhuMAB-HER2 "serves to sensitize HER2 positive tumors to both therapies." (Paper 1 at 28, 46-47.) Contrary to Petitioners' arguments, a POSA would not look to Gelmon '96 for any teachings for treating HER2-positive patients, particularly when Gelmon '96 did not even address whether any of the patients were HER2-positive in its already small patient population. (Ex. 1025 at 1186).

In its Institution Decision, the Board stated that Gelmon '96 supposedly "discloses that paclitaxel is active as a single agent in metastatic breast cancer, but exhibits advantageous, if not synergistic, results in combination with cisplatin."

(Paper 19 at 18.) But numerous prior art references undermine that supposed teaching. For example, Wasserheit 1996 studied the combination paclitaxel and cisplatin, and concluded that the combination did not provide any clinical benefit as compared with single-agent therapy. (Ex. 2068 at 1998.) Further, other prior art references were unable to reproduce Gelmon '96's results. (Ex. 2120 at 1880; Ex. 2121 at 2 (abstract 144).) (Ex. 2062, Tannenbaum Decl. ¶¶ 169-172.) Petitioners may not selectively rely on Gelmon '96 for the teaching that the addition of cisplatin to the combination would result in improved clinical results when other prior art references directly refute that supposed teaching.

Given its inconsistent results, a POSA would not have relied on Gelmon '96 for its disclosure. As Gelmon '96 is a basis for all of the grounds raised in the Petition, the Petition should be denied on this basis alone.

D. Grounds 1-6: Petitioners Have Not Shown That The Claimed Combination Would Have Been Obvious To Try.

Petitioners' obviousness arguments ultimately rest on the theory that the claimed combinations would have been obvious to try. (Paper 1 at 17, 31, 35, 40, 42, 43, 49, 53, 59, 60, 61, 63.) But Petitioners have not established that the claimed combinations were among "a ***finite*** number of identified, ***predictable*** solutions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) (emphasis added).

First, Petitioners argue the claimed combination was "the only combination left to try." (Paper 1 at 31, 49.) But that assertion cannot be reconciled with Petitioners' own asserted references. (*E.g.*, Ex. 1025 at 11 (cyclophosphamide, doxorubicin, methotrexate, 5FU, etoposide, and prednisone); *id.* at 9 ("There are a number of drugs with activity in metastatic breast cancer ….").)

Petitioners' assertion is also inconsistent with the development history of rhuMAb HER2. As discussed above (pp. 16, 19-20), the combination of rhuMAb HER2 and paclitaxel only arose after the '549 patent's inventor Dr. Hellmann convinced the company to change course. That such combinations were not even among the treatment regimens pursued in any clinical trials confirms that they were not obvious to try. (Ex. 2062, Tannenbaum Decl. ¶ 226.)

Second, Petitioners' 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*, 550 U.S. at 421. The '549 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 (*supra* p. 12) and 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. ¶ 150, 227.) Petitioners do not address the unpredictability of the field, let alone explain how the invention could

have been obvious to try given those uncertainties. (Ex. 2062, Tannenbaum Decl. ¶¶ 63-65, 195, 227.)

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Accordingly, the Substitute Claims are responsive to the asserted grounds.

VI. CONCLUSION

Accordingly, should any of Challenged Claims be determined to be unpatentable, Patent Owner respectfully requests that the Board grant this contingent Motion such that the '549 patent be amended to include the corresponding Substitute Claim(s) 18-20, respectively.

Respectfully submitted,

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APPENDIX A

CLAIM LISTING

Substitute Claims Showing Amendments to Original Claims

~~1.~~ 18. A method of treatment of a human patient with breast cancer that overexpresses ErbB2 receptor, comprising administering a combination of ~~an antibody that binds ErbB2~~ rhuMAb HER2, ~~a taxoid~~ 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.

2-15. (Canceled)

~~16.~~ 19. 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~~ rhuMAb HER2, ~~a taxoid~~ paclitaxel and a further growth inhibitory agent, in the absence of an anthracycline derivative, to the human patient in an amount effective to extend time to disease progression, as compared to paclitaxel alone, in the human patient.

~~17.~~ 20. (Unchanged original claim 17 to depend from proposed Substitute Claim 19)

Clean Version of Claims

18. (Proposed substitute for original claim 1) 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.

19. (Proposed substitute for original claim 16) A method for the treatment of a human patient with ErbB2 overexpressing breast cancer, comprising administering a combination of rhuMAb HER2, paclitaxel and a further growth inhibitory agent, in the absence of an anthracycline derivative, to the human patient in an amount effective to extend time to disease progression, as compared to paclitaxel alone, in the human patient.

20. (Proposed substitute for original claim 17) The method of claim **19** wherein the breast cancer is metastatic breast carcinoma.