UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-01121
Patent 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 cancelled.

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 broaden—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 9 at 3 (PTAB Oct. 4, 2017).) "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 9 at 6-7.) 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. 1002, Earhart Decl. ¶ 112(h); Ex. 2062, Tannenbaum Decl. ¶¶ 128-138.) 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. 1004-1at p. 40 (36:12-20); p. 44 (40:3-7).	Ex. 2009 at 36:7-14, 39:26-40:1.
administering a combination of ~~a humanized 4D5 anti-ErbB2 antibody~~ rhuMAb HER2 and ~~a taxoid~~ paclitaxel,	Ex. 1004-1at p. 45 (41:15-29); p. 46 (42:8-12).	Ex. 2009 at 41:9-23, 42:2-6.
in the absence of an anthracycline derivative,	Ex. 1004-1at p. 40 (36:26-27); p. 45 (41:20-29); pp. 47-48 (43:23-44:3).	Ex. 2009 at 36:20-21, 41:14-23, 43:18-26.
to the human patient	Ex. 1004-1at p. 40 (36:21-25).	Ex. 2009 at 41:9-42:6.
in an amount effective to extend time to disease progression in said human	Ex. 1004-1at p. 47-48 (43:5-44:3).	Ex. 2009 at 42:28-43:26.

patient, as compared to paclitaxel alone,		
without increase in overall severe adverse events.	Ex. 1004-1at p. 47 (43:5-26).	Ex. 2009 at 42:28-43:20.

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 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. 1004-1 at p. 40 (36:12-20), pp. 43-48 (39:3-43:4); Ex. 2009 at 36:7-14, 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. 1004-1 at p. 47 (43:5-8); Ex. 2009 at 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. 1004 at p. 47 (43:10-23); Ex. 2009 at 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. 1004 at pp. 47-48 (43:27-44:3); Ex. 2009 at 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. ¶¶ 122-125.)

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] In any event, it is not required that ***every*** amended limitation be solely for the purpose of overcoming an instituted ground. *Veeam Software Corp. v. Veritas*

A. A Person of Ordinary Skill Would Not Have Been Motivated to Treat Patients With a Combination of an Anti-ErbB2 Antibody and a Taxoid Based Upon Baselga 1996, Seidman 1996, and the 1995 Taxol PDR.

The Substitute Claim requires "administering a combination" of a rhuMAb HER2 and paclitaxel "to the human patient," but none of the references underlying the instituted ground discloses this limitation. Baselga 1996 involves treatment with rhuMAb HER2 alone. (Ex. 1020 at 3.) Seidman 1996 involves treatment with a taxoid alone. (Ex. 1011 at 5.) And the Taxol PDR involves treatment with a taxoid alone as a second-line therapy for breast cancer and does not even mention HER2-positive breast cancer. (Ex. 1012 at 6.)

1. Baselga 1996, Seidman 1996, and the 1995 Taxol PDR do not provide a motivation to treat patients with the claimed combination.

Baselga 1996 describes the first Phase II clinical trial with rhuMAb HER2 alone, and then mentions the fact of *in vitro* and preclinical mouse xenograft studies involving combinations with "several chemotherapeutic agents, including

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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.").

cisplatin, doxorubicin, and paclitaxel." (Ex. 1020 at 9.) Baselga 1996 provides no motivation to choose paclitaxel from among the "several chemotherapeutic agents" identified. Indeed, paclitaxel is described in the same exact way as anthracyclines (e.g., doxorubicin), which were the standard of care in the prior art (Ex. 2062, Tannenbaum Decl. ¶¶ 43-53), and which the Substitute Claim expressly avoids in the claimed combination therapy.

Petitioner argues that Seidman 1996 demonstrates that taxoids have "proven efficacy against metastatic HER2-positive breast cancer in humans" such that a POSA would be motivated to combine rhuMAb HER2 with paclitaxel. (Paper 1 at 43.) But Seidman 1996 is an abstract, which a POSA would understand as reflecting a preliminary hypothesis, not "proven efficacy"; a POSA would have awaited an expanded analysis in a peer-reviewed journal before drawing any conclusions. (Ex. 2062, Tannenbaum Decl. ¶ 154; *see also* Ex. 2050 at 338:2-7.) In fact, the Seidman authors continued their research and ultimately found no "statistically significant association with clinical response to taxane therapy" for HER2-positive patients, which they found to be "partly in contrast to [their] earlier analysis." (Ex. 2024 at 2322-23.) A POSA would not have interpreted Seidman 1996 as demonstrating the "proven efficacy" of taxoids in HER2-positive patients when even the authors of that abstract continued to study the issue and ultimately repudiated their prior hypothesis.

The 1995 Taxol PDR similarly does not suggest combining rhuMAb with paclitaxel. The 1995 Taxol PDR states that paclitaxel was approved only as a second-line therapy for metastatic breast cancer and warns of "[s]evere hypersensitivity reactions." (Ex. 1012 at 6; Ex. 2028 at 1265; Ex. 2026 at 1704 (warning oncologists "to maintain a high degree of caution" in treating patients with taxoids).) These safety concerns would have dissuaded POSAs from using combination therapy involving paclitaxel. (Ex. 2062, Tannenbaum Decl. ¶¶ 54-61.)

Moreover, the 1995 Taxol PDR makes no mention of treating HER2-positive breast cancer. Indeed, other references at the time reached the opposite conclusion of Seidman 1996, concluding that "breast cancers that overexpress p185 [*i.e.*, HER2] will not respond well to Taxol." (Ex. 2029 at 1362; Ex. 2062, Tannenbaum Decl. ¶¶ 58-61, 195.) Those statements contemporaneous with the invention of the '441 patent discouraging the use of taxoids in HER2-positive patients are strong evidence of non-obviousness. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009).

In its Institution Decision, the Board concluded that the Yu reference did not undermine Petitioner's obviousness theory because "we must analyze the prior art as a whole, and not individually." (Paper 9 at 17-18.) But that it is precisely the point. Petitioner's obviousness theory rests on a selective reconstruction of the

state of the art that ignores what others were saying at the time about the use of taxoids in HER2-positive patients and instead rests on a supposed teaching in Seidman 1996 that ultimately turned out not to be true. At best, the state of the art as to the efficacy of taxoids in HER2-positive patients was mixed and cannot support a motivation to combine. (Ex. 2062, Tannenbaum Decl. ¶¶ 54-61, 195.)

2. The preclinical results alluded to in Baselga 1996 do not provide a motivation to treat patients with the claimed combination.

In its Institution Decision, the Board also pointed to preclinical results described in references outside of the Grounds supposedly "demonstrat[ing] strong synergy of paclitaxel and an anti-ErbB2 antibody in human breast cancer xenografts." (Paper 9 at 18 (internal quotation marks omitted).) But those preclinical results (e.g., Exs. 1019, 1021) would not have motivated a POSA to treat patients with a combination of rhuMAb HER2 and paclitaxel.

As an initial matter, 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 ("[M]odel systems are not predictive at all."); Ex. 2061, Kerbel Decl. ¶¶ 55-62.) 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. ¶ 68-71; Ex. 2061, Kerbel Decl. ¶¶ 55-62.)

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. (Ex. 2019 at 1577.) Second, 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. 2061, Kerbel Decl. ¶¶ 72-77.) 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. 2052 at 257-58;Ex. 2061, Kerbel Decl. ¶¶ 39-40, 65; Ex. 2062, Tannenbaum Decl. ¶¶ 72-77.)

Moreover, a POSA would understand that the particular mouse study described in Baselga Abstract 53 (Ex. 1019) and Baselga Abstract 2262 (Ex. 1021) (and briefly alluded to in Baselga 1996) was not a reliable predictor of success in humans. This study was based on a single cell line. (Ex. 2061, Kerbel Decl. ¶¶ 63-71.) But it was known prior to the '441 patent that it was necessary to use multiple cell lines to obtain results that are reflective of a human patient population, especially for breast cancer patients. (Ex. 2061, Kerbel Decl. ¶¶ 65-66; Ex. 2052 at 261.) For example, one study in 1995 (Szöllösi) estimated that the BT-

474 breast-cancer cell line had 52 copies of the ErbB2 gene on average per cell, the SK-BT3 cell line had 31 copies on average per cell, and the MSA-453 cell line had 11 copies on average per cell. (Ex. 2064 at 5402.) This variation in cell lines is similar to the heterogeneity of human chromosomes. (Ex. 2064 at 5400; Ex. 2065 at 262; Ex. 2063 at 1457; Ex. 2061, Kerbel Decl. ¶¶ 26, 42-44.). A study based on a single cell line is akin to a clinical trial involving a single patient, which has minimal predictive value. (Ex. 2062, Tannenbaum Decl. ¶¶ 72-77.)

Moreover, a POSA also would have understood that the particular cell line used in the Baselga abstracts was not representative of actual patients. The cell line (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. 2064 at 5402; Ex. 2061, Kerbel Decl. ¶¶ 63-71.) With such a high level of HER2 expression, a POSA would have understood that the mouse models in the Baselga abstracts would not be representative of actual HER2-positive patients. (Ex. 2062, Tannenbaum Decl. ¶¶ 160-165.)

In addition, mouse models based on subcutaneous implantation of tumors, such as those in the Baselga abstracts, were known to be even less reliable than models that implanted the cells in the same type of tissue as the target disease. (Ex. 2053 at 79 ("While the [subcutaneous] site is convenient, it is likely that it is not the optimal site for all xenografts.").) Studies published in the 1990s showed

that transplanted tumors often responded to drugs, including chemotherapy agents, when grown "ectopically" as subcutaneous tumors, but did not respond (or responded in a diminished manner) when transplanted and grown "orthotopically" (*i.e.*, in the organ from which the cancer under study was derived). Thus, it was known that to obtain more reliable results for breast cancer, the tumor must be implanted in breast tissue. (Ex. 2053 at 79; Ex. 2061, Kerbel Decl. ¶¶ 78-82; Ex. 2062, Tannenbaum Decl. ¶¶ 161, 187-188.) However, the tumors in the Baselga abstracts were implanted subcutaneously, rather than in breast tissue, thereby undermining the predictive value of this study for human use. (Ex. 2061, Kerbel Decl. ¶¶ 78-82; Ex. 2062, Tannenbaum Decl. ¶¶ 160-165.)

Moreover, the mouse study described in the Baselga abstracts measured short-term response rate, which is a different clinical endpoint from—and is not indicative of—extension of TTP. (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. ¶¶ 83-84; Ex. 2062, Tannenbaum Decl. ¶¶ 162-165, 208.)

Further, the development history of rhuMAb HER2 confirms that the Baselga abstracts would not have motivated a skilled artisan to treat humans with rhuMAb HER2 and paclitaxel. Despite preclinical studies of combinations of rhuMAb HER2 with other chemotherapies (e.g., cisplatin (Ex. 1015), doxorubicin

(Ex. 2001 at 7)), 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 over objection 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. 2111 at 73.) Given the well-known problems with taxoids (*supra* p. 11), a POSA would not have been motivated to pursue the claimed combination based on the Baselga abstracts, 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).

These specific deficiencies with the preclinical models disclosed in the Baselga abstracts, coupled with the lack of predictive value for mouse xenograft studies generally, confirm that the preclinical studies would not have motivated a POSA to treat patients with a combination of rhuMAb HER2 and paclitaxel.

3. 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" and required "much additional study." (Ex. 2031 at

683.) Moreover, 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* p. 11). Because of these risks and uncertainties, a POSA would not have been motivated to use a taxoid in combination with an anti-ErbB2 antibody as a treatment for HER2-positive breast cancer. (Ex. 2062, Tannenbaum Decl. ¶¶ 54-61.)

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. 2050 at 120:7-13; Ex. 2055 at Abstract, 5; Ex. 2103 at 3118.) At this time, anthracyclines were the standard and most common treatment for breast cancer. (*Id.*) 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. ¶¶ 43-53.)

4. Petitioner's four "principles" of chemotherapy do not suggest the claimed combination.

Petitioner relies on four "principles" of combination chemotherapy (Paper 1 at 45-46), but those "principles" do not render the Substitute Claims obvious.

As an initial matter, those cited "principles" on their face only address combinations of different chemotherapies. (Ex. 1016 at 10-11.) The '441 patent, however, claims treatment using combinations of an antibody and chemotherapy, not combinations of different chemotherapies. At the time of the '441 patent invention, antibodies were an entirely new class of drug, and it was not clear how (if at all) they could be used to treat cancer. (*See* Ex. 2031 at 683-84; Ex. 2050 at 242:17-22.) Petitioner has not explained why a POSA would have believed that chemotherapy principles would be applicable to combinations with the new and unproven class of therapeutic antibodies. Indeed, Petitioner's expert was not "aware of any publication prior to December of 1996 that applied the four principles" to a combination that included both an antibody and chemotherapeutic drug. (Ex. 2050 at 274:1-10) (Ex. 2062, Tannenbaum Decl. ¶¶ 198-206.)

But even if a POSA would have considered the cited chemotherapy principles relevant to antibodies, those general principles would not have diminished the unpredictability of treating cancer in the 1990s. These "principles" are just generalized considerations, and even Petitioner's cited references

acknowledged the unpredictable challenges of combining cancer treatments. (*E.g.*, Ex. 1013 at 1; Ex. 1006 at 33.) Consistent with that high degree of unpredictability, patient survival for advanced (i.e., "metastatic") breast cancer had "not consistently or substantially improved" in the decade before the '549 invention, "[d]espite innumerable trials" involving "various combinations" of drugs. (Ex. 1006 at 105). (*See also* Ex. 2072 at Abstract (describing failure to combine chemotherapy with hormone therapy); Ex. 2073 at 2747-48; Ex. 2073 at 8 (suggesting hormone therapy alone provided better results than combined treatment with chemotherapy).) (Ex. 2062, Tannenbaum Decl. ¶ 204.)

* * *

For the reasons set forth above, the instituted prior art would not have motivated a POSA to treat with the combination of the Substitute Claim.

B. The Prior Art Does Not Show a Reasonable Expectation of Success in Achieving the Clinical Efficacy of 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.

Neither Baselga 1996, Seidman 1996, nor the Taxol PDR includes data showing an ***extension*** in TTP. In fact, as Petitioner's expert admitted during deposition, none of the prior art cited in his declarations even measured TTP (much less extension in TTP). (Ex. 2050 at 341:15-17.)

Contrary to Petitioner's expert, Baselga 1996 includes data for what it calls "time to progression" (Ex. 1020 at 6),[4] but this is for treatment with the antibody alone, and the study has no control arm against which to compare treatment with a taxoid alone. Conversely, the Taxol PDR includes data for "time to progression" (Ex. 1012 at 6), but this is for treatment with Taxol (*i.e.*, paclitaxel) alone, and the study has no control arm. Thus, neither Baselga 1996 nor the Taxol PDR provides any basis to determine that the claimed ***combination*** extends TTP compared to treatment with a taxoid alone. And Seidman 1996 does not even address TTP; it describes only response rate. (Ex. 1011.)

[4] Dr. Earhart testified that he "did not find" a TTP measurement in Baselga 1996 and that such a measurement "wouldn't be … necessarily standard in a Phase 2 study." (Ex. 2050 at 316:11-22; *see also id.*, 318:21-320:5 ("[Baselga 1996] doesn't report the specific variable of time to progression at all, much less relative to previously untreated patients.").)

Further, the response rates disclosed in the Baselga 1996 and Seidman 1996, including the mouse models alluded to in Baselga 1996, do not suggest an extension in TTP when using the claimed combination. Shrinking tumors is different from extending TTP, and a POSA would have understood that a therapy could reduce tumor size without improving TTP. As Dr. Tannenbaum notes, for solid tumors such as breast cancer, it was well known that therapies may improve response rates but not affect TTP. (Ex. 2062, Tannenbaum Decl. ¶ 87; Ex. 2066 at 57-78; Ex. 2067 at 353.) Indeed, Petitioner and its expert concede that response rate and TTP are different endpoints that are measured differently. (*See* Paper 1 at 41-42; Ex. 1002, Earhart Decl. ¶¶ 92, 112(f)-(g); *see also* Ex. 2050 at 202:7-12.)

In addition, the mouse studies in the Baselga abstracts 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)")). In any case, as discussed above, the particular mouse model used in the Baselga abstracts would have limited predictive value in assessing the clinical response in human patients. (*Supra* pp. 12-16.)

Indeed, the development history of rhuMAb HER2 confirms that the preclinical results in the Baselga abstracts would not have provided a POSA a reasonable expectation of success in achieving the clinical result of the Substitute Claim. Despite these abstracts, no one pursued a clinical trial combining rhuMAb

HER2 and paclitaxel until the '441 inventor Dr. Hellmann suggested modifying an ongoing Phase-III trial to address enrollment issues. (*Supra* p. 15.)

Finally, Petitioner's "principles" of combination chemotherapy do not suggest a reasonable expectation of success in achieving the efficacy of the Substitute Claim. (*Supra* pp. 17-19.)

C. Petitioner Has Not Established a Reasonable Expectation of Success in Achieving the Claimed Clinical Safety.

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

Petitioner cites the "promising clinical results in Baselga 1996 and Seidman 1996" and "lack of severe toxicity associated with trastuzumab." (Paper 1 at 49.) But neither suggests that a patient treated with the claimed combination would not experience an increase in "overall severe adverse effects." (Ex. 2062, Tannenbaum Decl. ¶¶ 217-218.)

Petitioner cites the lack of increased toxicity from combining trastuzumab and paclitaxel in preclinical mouse studies. (Paper 1 at 49.) However, Baselga 1996 and Baselga Abstract 53 made the same statement about combinations with the anthracycline doxorubicin (Ex. 1020 at 9; Ex. 1019 at 4), which produced a significant increase in cardiotoxicity when administered to human patients. (*See*

also Ex. 2050 at 206:10-207:3.) And Petitioner's own expert admits that, in assessing toxicity, mouse xenografts are "pretty crude" and "more crude … than we have available in the clinic." (Ex. 2050 at 205:15-206:15.) These disconnects highlight the inability of the Baselga references' mouse models to predict clinical safety. (Ex. 2062, Tannenbaum Decl., ¶¶ 219-222.)

Moreover, as explained above, a POSA would understand that the mouse model described in the Baselga references would not reliably predict results in humans. (*Supra* pp. 12-16.) This was especially the case for a combination involving the antibody 4D5: 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. Because 4D5 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 4D5 on other cells. (Kerbel Decl. ¶¶ 72-77.)

As Petitioner's own expert admits, none of the references cited in his declaration even discusses the key point at issue for this limitation—i.e., whether the combination of trastuzumab and paclitaxel would increase severe adverse events in a patient. (Ex. 2050 at 342:6-19.)

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

Several objective indicia conclusively establish the non-obviousness of the Substitute Claim. (Ex. 2062, Tannenbaum Decl. ¶¶ 223-238.)

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), yet no one before the '441 invention had developed an adequate therapy for those patients. 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. (*Id.*)

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.)

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. 1008, Hellmann Decl. ¶ 6.) In fact, other preclinical studies involving the claimed combination produced "inconsistent results." (Ex. 2004 at 3, 6.) A POSA therefore would have

considered those superior 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).

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.) There is a direct nexus between HERCEPTIN®'s commercial success and the '441 invention. *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 ground 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,

Date: December 21, 2017 /David L. Cavanaugh/

David L. Cavanaugh
Registration No. 36,476

Robert J. Gunther, Jr.
Pro Hac Vice

Counsel for Patent Owner Genentech, Inc.

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

APPENDIX A

CLAIM LISTING

Substitute Claim Showing Amendments to Original Claim

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 Claim

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.