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Paper 10
Entered: December 9, 2014

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PHIGENIX, INC,
Petitioner,

v.

GENENTECH, INC. and IMMUNOGEN, INC.,
Patent Owner.

Case IPR2014-00842
Patent 7,575,748 B1

Before FRANCISCO C. PRATS, JACQUELINE WRIGHT BONILLA, and ZHENYU YANG, *Administrative Patent Judges*.

BONILLA, *Administrative Patent Judge.*

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Phigenix Inc. ("Petitioner") filed a Petition requesting *inter partes* review of claims 1–20 and 25–27 of U.S. Patent No. 7,575,748 ("the '748 patent"). Paper 1 ("Pet."). Genentech, Inc. and ImmunoGen, Inc. ("Patent Owner") filed a Preliminary Response. Paper 9 ("Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 314(a), which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

Upon consideration of the Petition and the Preliminary Response, and for the reasons explained below, we determine that Petitioner has not established a reasonable likelihood of prevailing on any of the claims challenged in the Petition. Accordingly, we do not institute an *inter partes* review.

A. Related Proceeding

About a month before filing the current Petition, Petitioner filed a Corrected Petition requesting *inter partes* review of claims 1–8 of U.S. Patent No. 8,337,856 ("the '856 patent") in Case IPR2014-00676, and, thereafter, Patent Owner filed a Preliminary Response. IPR2014-00676, Papers 5, 10. We instituted *inter partes* review in that case on October 29, 2014. IPR2014-00676, Paper 11. The '748 patent, at issue here, is a continuation application of U.S. Patent No. 7,097,840 ("the '840 patent"). Ex. 1001. The '856 patent is a divisional application of a continuation application of the '840 patent. IPR2014-00676, Ex. 1001. Claims of the '856 patent are directed to immunoconjugate compounds. *Id*. at cols. 81–82. As discussed below, claims of the '748 patent are directed to methods for treating a tumor comprising administering an immunoconjugate.

B. The '748 Patent (Ex. 1001)

The '748 patent relates to methods of treating cancer using ErbB receptor-directed cancer therapies. Ex. 1001, 1:2–23; 4:10–14. The '748 patent describes immunoconjugates comprising an anti-ErbB antibody, such as the humanized anti-ErbB2 antibody known as HERCEPTIN® (huMAb4D5-8), linked to a maytansinoid toxin. *Id*. at 1:20–52; 35:54–36:42; *see also id*. at 3:6–16 (discussing HERCEPTIN®); 6:51–67 (defining "ErbB2"); 10:41–65 (defining "humanized"); 16:26–31 (defining "epitope 4D5").

The term "ErbB2" is synonymous with "HER2," "p185^{neu}," or "*neu*," and refers to a member of the ErbB family of receptor tyrosine kinases, which mediate cell growth, differentiation, and survival. *Id*. at 1:45–59; 6:51–59. Overexpression of ErbB2 on cell surfaces can lead to cancer in humans, such as certain breast and ovarian cancers. *Id*. at 1:53–67; 8:56–60.

The Specification teaches that maytansinoids, such as DM1, are highly cytotoxic, i.e., inhibit or prevent cell function and/or destroy cells, but induce "severe systemic side-effects primarily attributed to their poor selectivity for tumors" when administered alone. *Id*. at 1:38–44; 17:48–55; *see also id.* at 5:7–12 (referring to Figure 3, showing the structure of the maytansinoid designated "DM1"). The Specification describes making anti-ErbB antibody-maytansinoid conjugates using "a variety of bifunctional protein coupling agents," i.e., linkers, such as N-succinimidyl-3-(2-pyridyldithio)propionate ("SPDP"), N-succinimidyl-4-(2-pyridylthio)pentanoate ("SPP"), and succinimidyl-4-(N-maleimidomethyl)-cyclohexane-l-carboxylate ("SMCC"). *Id*. at 36:16–32.

The Specification states that the "present invention is based on the

unexpected experimental finding that HERCEPTIN®-maytansinoid conjugates are highly effective in the treatment of HER2 (ErbB2) overexpressing tumors that do not respond, or respond poorly to HERCEPTIN® therapy." *Id*. at 4:10–14. The Specification describes that the conjugates "are expected to have superior clinical activity compared to treatment with HERCEPTIN® alone, including a better objective response rate and/or longer duration of response and/or increased survival." *Id*. at 4:14–18.

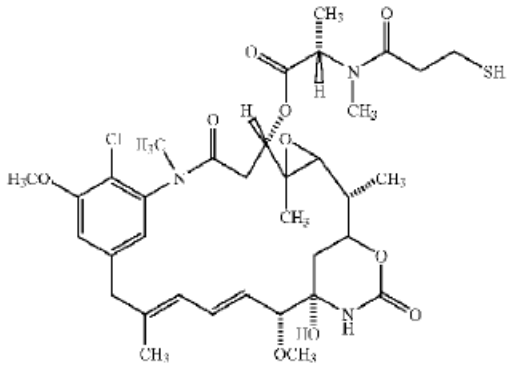
In this context, the Specification discusses "results obtained in a novel murine HER2-transgenic tumor model in which HERCEPTIN® or the murine antibody 4D5 from which HERCEPTIN® was derived, had little effect on tumor growth." *Id*. at 22:3–6. The Specification states that "it was surprisingly found that while the transplanted tumor obtained from such transgenic mice responded poorly to HERCEPTIN® treatment, the HERCEPTIN®-maytansinoid conjugates were highly efficacious." *Id*. at 22:7–12.

C. The Challenged Claims

Petitioner challenges claims 1–20 and 25–27 of the '748 patent. Of those, claims 1 and 2 are independent. Claim 1 is representative, and is reproduced below.

> 1. A method for the treatment of a tumor in a mammal, comprising the steps of
>
> (i) identifying said tumor as being characterized by overexpression of an ErbB2 receptor and as being a tumor that does not respond, or responds poorly, to treatment with an anti-ErbB antibody, and

(ii) intravenously administering to the mammal a therapeutically effective amount of a conjugate of a humanized antibody huMab 4D5-8 covalently linked via a thioether linking group with a maytansinoid DM1 having the structure



at a dose of between about 0.2 mg/kg and about 10 mg/kg (antibody-maytansinoid conjugate weight/body weight) and

at a frequency of dosing selected from the group of dosing frequencies consisting of bolus, less than about 1 time per week, one time per week, two times per week, more than two times per week, and continuous infusion,

whereby said tumor characterized by overexpression of an ErbB2 receptor and that does not respond, or responds poorly, to treatment with an anti-ErbB antibody, is treated.

Id. at 81:34–82:36 (spacing and indentation added). Independent claim 2 is identical to claim 1, but recites treating a human, rather than a mammal. *Id*. at 82:37–83:5. Dependent claims recite specific doses, tumors, linking groups, that the method further comprises administering a cytotoxic agent, or that the conjugate comprises 3 to 4 maytansinoid molecules per antibody. *Id*. at 83:6–84:60.

D. Asserted Grounds of Unpatentability

Petitioner contends that the challenged claims are unpatentable under 35 U.S.C. § 103(a) based on the following grounds. Pet. 9.

	References	Basis	Claims Challenged
1	Chari 1992 (Ex. 1012)[1] and HERCEPTIN® Label (Ex. 1008)[2]	§ 103	1–20 and 25–27
2	Chari 1992, HERCEPTIN® Label, and Baselga 1999 (Ex. 1032)[3]	§ 103	1–20 and 25–27
3	Chari 1992, HERCEPTIN® Label, and Morgan 1990 (Ex. 1021)[4]	§ 103	1–20 and 25–27
4	Chari 1992 and HERCEPTIN® Label, further in view of Morgan 1990, Hudziak 1998 (Ex. 1017)[5] and/or Rosenblum 1999 (Ex. 1018)[6]	§ 103	1–20 and 25–27

[1] Chari et al., *Immunoconjugates Containing Novel Maytansinoids: Promising Anticancer Drugs*, 52 CANCER RES. 127–131 (1992).

[2] HERCEPTIN® (Trastuzumab) Label, dated September 1998.

[3] Baselga et al., *Phase II Study of Weekly Intravenous Trastuzumab (Herceptin®) in Patients With HER2/neu-Overexpresing Metastatic Breast Cancer*, SEMIN. ONCOL. 26, Suppl 12:78–83 (1999).

[4] Morgan et al., *Immunotoxins of Pseudomonas exotoxin A (PE): effect of linkage on conjugate yield, potency, selectivity and toxicity*, 27(3) MOL. IMMUNOL. 273–282 (1990).

[5] Hudziak et al., U.S. Patent No. 5,770,195, issued June 23, 1998.

[6] Rosenblum et al., *Recombinant Immunotoxins Directed against the c-erbB-2/HER2/neu Oncogene Product: In Vitro Cytotoxicity, Pharmacokinetics, and In Vivo Efficacy Studies in Xenograft Models*, 5 CLIN. CANCER RES. 865–874 (1999).

	References	Basis	Claims Challenged
5	Chari 1992 and HERCEPTIN® Label, further in view of Morgan 1990, Hudziak 1998 and/or Rosenblum 1999, and further in view of Baselga 1998 (Ex. 1019)[7] and/or Pegram 1999 (Ex.1020)[8]	§ 103	1–20 and 25–27
6	Cohen 1999 (Ex. 1022)[9] in view of HERCEPTIN® Label, and Morgan 1990	§ 103	1–20 and 25–27

II. ANALYSIS

A. Claim Construction

The Board interprets claims in an unexpired patent using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R. § 42.100(b); *see also* Office Patent Trial Practice Guide ("Practice Guide"), 77 Fed. Reg. 48756, 48766 (Aug. 14, 2012). There is a "heavy presumption" that a claim term carries its ordinary and customary meaning. *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002).

Neither party offers construction of any claims terms. Generally, we construe claim terms of the '748 patent as carrying their ordinary meaning,

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[7] Baselga et al., *Recombinant Humanized Anti-HER2 Antibody (Herceptin^{TM}) Enhances the Antitumor Activity of Paclitaxel and Doxorubicin against HER2/neu Overexpressing Human Breast Cancer Xenografts*, 58 CANCER RES. 2825–2831 (1998).

[8] Pegram et al., *Inhibitory effects of combinations of HER-2/neu antibody and chemotherapeutic agents used for treatment of human breast cancers*, 18 ONCOGENE 2241–2251 (1999).

[9] Cohen, U.S. Pat. Appl. Publ. No. 2003/0170235 A1, published Sept. 11, 2003.

consistent with their use in the Specification. Most relevant to our analysis here, we note that the last phrase in each independent claim requires treatment of a tumor that "does not respond, or responds poorly, to treatment with an anti-ErbB antibody." We consider the phrase "method for the treatment of a tumor" in the preamble to be limiting, especially when read in combination with the "whereby" clause reciting that "said tumor" is "characterized by overexpression of an ErbB2 receptor" and "does not respond, or responds poorly, to treatment with an anti-ErbB antibody, is treated."[10] Those limitations define a critical component of the challenged claims.

As defined in the Specification, a "tumor which 'does not respond, or responds poorly, to treatment with a monoclonal anti-ErbB antibody' does not show statistically significant improvement in response to anti-ErbB antibody treatment when compared to no treatment or treatment with placebo in a recognized animal model or a human clinical trial, or which responds to initial treatment with anti-ErbB antibodies but grows as treatment is continued." Ex.

[10] "A claim's preamble may limit the claim when the claim drafter uses the preamble to define the subject matter of the claim." *August Tech. Corp. v. Camtek, Ltd.*, 655 F.3d 1278, 1284 (Fed. Cir. 2011). A preamble generally limits a claim if it "recites essential structure or steps, or if it is necessary to give life, meaning, and vitality to the claim." *NTP, Inc. v. Research In Motion, Ltd.*, 418 F.3d 1282, 1305 (Fed. Cir. 2005) (quoting *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002)). For example, when "limitations in the body of the claim rely upon and derive antecedent basis from the preamble, then the preamble may act as a necessary component of the claimed invention." *Id*. at 1306 (quoting *Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1339 (Fed. Cir. 2003)).

1001, 16:56–63.

B. Obviousness over Chari 1992 and HERCEPTIN® Label

Petitioner contends that claims 1–20 and 25–27 would have been obvious over Chari 1992 and the HERCEPTIN® Label, relying on a Declaration by Dr. Michael G. Rosenblum (Ex. 1016). Pet. 10–26.

1. Chari 1992 (Ex. 1012)

Chari 1992 describes immunoconjugates comprising an anti-ErbB2 mouse monoclonal antibody, TA.1, chemically coupled to the maytansinoid toxin, DM1, using SPDP or SMCC as a linker. Ex. 1012, ¶ spanning 128–129; *id*. at Fig. 2 (*see* maytansinoid 3 and figure legend). As stated in Chari 1992, the TA.1 antibody binds HER-2/*neu* oncogene protein (i.e., ErbB2), which is expressed at high levels on human breast tumor cells. *Id*. at 129, 1st col., ¶ 1. The reference discloses conjugates having a range of one to six maytansinoid molecules per antibody molecule, such as four maytansinoid molecules per antibody molecule. *Id*.; *see also id*. at 2d col., Table 2.

Chari 1992 teaches that the conjugates, called "TA.1(-SS-May)$_n$," were cytotoxic when tested *in vitro* on the human breast cancer cell line, SK-BR-2. *Id.* at 129, 1st col., ¶ 2, 2d col., Fig. 3. In addition, the reference teaches that conjugate TA.1(-SS-May)$_4$ was at least 1000-fold less cytotoxic toward *neu*-negative KB cells. *Id*. It teaches that cytotoxicity can be increased by linking more maytansinoid molecules per antibody molecule, "and it reached its maximum value at $n = 4$ (Table 2)." *Id*. at 1st col., ¶ 3. The reference also discloses that conjugate A7(-SS-May)$_6$, where A7 is an antibody directed against a human colon

cancer cells line antigen showed similar cytotoxicity results and was not toxic in mice. *Id*. at 1st col., ¶ 3–2d col., ¶ 2.

Chari 1992 states that the "high specific cytotoxicity of maytansinoid conjugates toward tumor cell lines in conjunction with their low systemic toxicity indicates that these potent conjugates may possess a therapeutic index sufficient for the effective treatment of human cancer." *Id*. at 130, 1st col., ¶ 2; *see also id.* at 127, Abstract (stating that the immunoconjugates "show high antigen-specific cytotoxicity for cultured human cancer cells [], low systemic toxicity in mice, and good pharmacokinetic behavior"). It also states that the "development of 'humanized' antibodies will offer an opportunity to produce drug conjugates that would be less immunogenic than similar conjugates of murine antibodies." *Id*. at ¶ 3.

2. HERCEPTIN® Label (Ex. 1008)

The HERCEPTIN® Label (or "the Label") describes HERCEPTIN®, also known as trastuzumab or huMAB4D5-8, as a humanized form of the mouse monoclonal antibody 4D5, which binds HER2. Ex. 1008, 1, 1st col. The Label describes intravenous injection administration of HERCEPTIN® after reconstitution with "Bacteriostatic Water for Injection (BWFI)," among other components. *Id*. at 1st col.

The Label describes HERCEPTIN® as being indicated for "the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease." *Id*. at 2d col. In addition, the Label describes HERCEPTIN® in combination with paclitaxel as being "indicated for treatment of patients with

metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for their metastatic disease." *Id*.

The Label describes a clinical trial with patients who "were randomized to receive chemotherapy alone or in combination with HERCEPTIN given intravenously as a 4 mg/kg loading dose followed by weekly doses of HERCEPTIN at 2mg/kg." *Id*. at 1st col. In that trial, all patients received "chemotherapy" of either: (1) paclitaxel; or (2) an anthracycline (i.e., doxorubicin or epirubicin) plus cyclophosphamide. *Id*. Table 1 in the Label presents data regarding "Phase III Clinical Efficacy in First-Line Treatment" in those patients. *Id*. at 1st col. The Label states that "[c]ompared with patients randomized to chemotherapy alone, the patients randomized to HERCEPTIN and chemotherapy experienced a significantly longer time to disease progression, a higher overall response rate (ORR), a longer median duration of response, and a higher one-year survival rate." *Id*. (citing Table 1).

The Label also describes a second "single agent" clinical trial, where patients "who had relapsed following one or two prior chemotherapy regimens for metastatic disease" received HERCEPTIN®. *Id*. In relation to that trial, "ORR (complete response + partial response) . . . was 14%, with a 2% complete response rate and a 12% partial response rate." *Id*. at ¶ spanning 1st and 2d cols. The Label states that the "degree of HER2 overexpression was a predictor of treatment effect." *Id*. at 2d col.

3. Analysis

Petitioner contends that Chari 1992 teaches the elements of the conjugate recited in the challenged claims of the '748 patent, except that Chari 1992 does not

disclose huMAB4D5-8 in particular. For example, Petitioner contends that Chari 1992 discloses an immunoconjugate comprising an anti-ErbB2 antibody conjugated to a maytansinoid, such as DMI having the structure recited in claims 1 and 2, where the immunoconjugate comprises four maytansinoid molecules per antibody molecule (as recited in claims 15, 16, 25 and 26), where the antibody and maytansinoid are conjugated by chemical linkers, such as SMCC (as recited in claims 14 and 27). Pet. 11–16 (citing Ex. 1012). Patent Owner does not contend otherwise. *See* Prelim. Resp. generally.

Petitioner further contends that the HERCEPTIN® Label describes the use of huMAB4D5-8 (i.e., HERCEPTIN®) for the treatment of human patients with metastatic breast cancer, and specifically tumors characterized by overexpression of an ErbB2 receptor. Pet. 10 (citing Ex. 1008, 1). Petitioner also contends that Chari 1992 teaches administering mice a dose of 8 mg/kg (by antibody) of the conjugate, and the HERCEPTIN® Label teaches administering humans doses of 4 mg/kg of the antibody as a 90-minute infusion. Pet. 12 (citing Ex. 1012, 129–130; Ex. 1008, 2, 2nd col.). Patent Owner does not contend otherwise.

The primary dispute between the parties relates to the limitations in the claims of identifying and treating a tumor that "does not respond, or responds poorly, to treatment with an anti-ErbB antibody." Petitioner contends that the HERCEPTIN® Label discloses the "identifying" such a tumor, and an ordinary artisan would have been motivated to treat such a tumor using a HERCEPTIN® conjugate. Pet. 10–12 (citing Ex. 1008, ¶ spanning 1st and 2d cols.).

Specifically, Petitioner points to the Label's teaching that in patients receiving HERCEPTIN, "ORR (complete response + partial response) . . . was

14%, with a 2% complete response rate and a 12% partial response rate." Ex. 1008, ¶ spanning 1st and 2d cols. Thus, according to Petitioner, "96% (48/50) of patients with 2+ HER2 overexpression and 83% (143/172) of patients with 3+ HER2 overexpression did not show complete or partial response to the HERCEPTIN® treatment." Pet. 18. Petitioner contends that this teaching indicates that the HERCEPTIN® Label discloses identifying a tumor that does not respond, or responds poorly, to treatment with an anti-ErbB antibody, i.e., HERCEPTIN®. We are persuaded that the HERCEPTIN® Label discloses or suggests this limitation, albeit indirectly.

We are not persuaded by Petitioner's contentions, however, in relation to treating a tumor that "does not respond, or responds poorly, to treatment with an anti-ErbB antibody," also required in the independent claims. In relation to this limitation, Petitioner points to the same "ORR" disclosure in the HERCEPTIN® Label that Petitioner cites regarding the "identifying" step. Pet. 10–11, 12 (citing Ex. 1008, ¶ spanning 1st and 2d cols.). We agree with Patent Owner that "[i]dentifying patients that do not respond (or respond poorly) to a particular type of therapy does not suggest *whether* or *how* to treat these patients." Prelim. Resp. 6.

Petitioner acknowledges that the Label does not describe conjugates containing the HERCEPTIN® antibody. Pet. 19. Petitioner relies on Chari 1992 in combination with the HERCEPTIN® Label for suggesting the recited conjugate. *Id*. at 19–20. As noted above, Petitioner points to Table 1 in the HERCEPTIN® Label as disclosing that, compared to patients receiving chemotherapy only, patients receiving chemotherapy plus HERCEPTIN® "experienced a significantly

longer time to disease progression, a higher overall response rate (ORR), a longer median duration of response, and a higher one-year survival rate." *Id*. at 20 (citing Ex. 1008, 1, 1st col., Table 1).

Based on teachings in both references, according to Petitioner, an ordinary artisan would have been motivated to use a HERCEPTIN® conjugate (as suggested by Chari 1992 and the Label) to treat "tumors that overexpress HER2 and do not respond to HERCEPTIN® treatment" because it was known that: (1) humanized antibodies were preferred over murine counterparts; (2) the huMAB4D5-8 antibody (HERCEPTIN®) selectively bound HER2 with high affinity; (3) clinical studies, as described in the HERCEPTIN® Label, indicated that treatment with HERCEPTIN® alone was not effective in the majority of HER2 overexpressing tumors; and (4) conjugation of DM1 to huMAB4D5-8 allowed for selective delivery of DM1 toxin to cells, thereby reducing systemic toxicity. Pet. 22–23 (citing Exs. 1012, 1008).

In support, Petitioner contends that, "as described in the Declaration of Dr. Rosenblum, HERCEPTIN® Label 1998 provides a clear motivation for treating tumors that do not respond, or respond poorly, to treatment with an anti-ErbB antibody because of the low-responsive rate to HERCEPTIN® treatment alone." Pet. 18, 24 (citing Ex. 1016 ¶¶ 12–18). In addition, Petitioner contends that "the relatively low efficacy obtained with HERCEPTIN® alone (i.e., 14% ORR) mandates the need for a better treatment, including HERCEPTIN® in combination with a potent cytotoxic agent (maytansinoid DM1) with an established mechanism of action and good pharmacokinetic behavior as suggested by Chari 1992." Pet. 24–25.

Petitioner further contends that an ordinary artisan would have had a reasonable expectation of success in treating "HER2 overexpressing, HERCEPTIN®-resistant" tumors with a HERCEPTIN® conjugate because it was known that: (1) huMAB4D5-8 (HERCEPTIN®) was "more effective in treating breast cancer when used in combination with the microtubule targeting drug paclitaxel," as compared to chemotherapy alone, as described in the HERCEPTIN® Label; (2) conjugates of Chari 1992 would bind the same cells as huMAB4D5-8 to deliver the DM1 toxin; (3) an immunoconjugate containing a "humanized" antibody was less immunogenic than one with a mouse antibody; and (4) the effect of the conjugate in Chari 1992 was dose-dependent. *Id*. at 25–26 (citing Exs. 1008, 1012).

Even if we assume both sets of Petitioner's contentions (1)–(4), as discussed above, are accurate, we conclude that Petitioner does not establish a reasonable likelihood that it would prevail in showing that an ordinary artisan would have had reason to use the recited conjugate, i.e., one containing the HERCEPTIN® antibody, to treat ErbB2 receptor-overexpressing tumors in patients (or mammals) that failed to exhibit a complete or partial response rate when treated with the antibody in the non-conjugate form. We are not persuaded that Chari 1992 or the HERCEPTIN® Label alone, or when read together, provided a reason to do so.

We agree with Petitioner that the HERCEPTIN® Label teaches or suggests that certain patients failed to respond to HERCEPTIN®, and that HERCEPTIN® increased the effectiveness of chemotherapy, such as paclitaxel, in patients who responded to HERCEPTIN® and chemotherapy. We are not persuaded, however, that the Petition has advanced sufficient reasoning, based on a rational underpinning, to

support its contention that the Label (alone or in combination with Chari 1992) discloses or suggests that patients unresponsive to HERCEPTIN® would respond to the HERCEPTIN® antibody, if administered with chemotherapy.

We do not agree with Petitioner that the HERCEPTIN® Label teaches or suggests that "the efficacy of huMAB4D5-8 for treatment of breast cancer is improved in combination with paclitaxel." Pet. 23 (citing Ex. 1008, 1, 1st col.) Rather, the Label indicates that efficacy of paclitaxel is improved in combination with huMAB4D5-8 in patients who responded to huMAB4D5-8. Ex. 1008, 1, 1st col. In addition, while we can see from the discussion of the second "single agent" study that only 14% of patients responded to HERCEPTIN® when given alone, the Label does not disclose or suggest whether the other 86% patients (who did not respond to antibody alone) would have responded to HERCEPTIN® if also given chemotherapy, i.e., above and beyond a response to the chemotherapy alone.

We are persuaded by Patent Owner's position that that neither the Petition nor Dr. Rosenblum's Declaration adequately explains how, or provides sufficient evidence indicating that, the teaching in HERCEPTIN® Label that certain patients failed to respond to HERCEPTIN® would have motivated an ordinary artisan to treat such patients using a HERCEPTIN® (huMab 4D5-8) conjugate. Prelim. Resp. 9; *see, e.g.*, 1016 ¶ 12 (stating, without support, that "this provides motivation to treat this patient population with a modified HERCEPTIN® product, such as HERCEPTIN®-DMI conjugate"), ¶ 15 (stating, without support, that it would have been "common practice" to subject patients "first to the available HERCEPTIN® treatment, and starting the HERCEPTIN®-DMI conjugate treatment in those patients who are resistant to the HERCEPTIN® treatment"),

¶¶ 16–18 (stating, without support, that it would have been obvious to treat such patients with a HERCEPTIN®-DMI conjugate—explaining only why a HERCEPTIN®-DMI conjugate would have been obvious over the corresponding mouse antibody conjugate disclosed in Chari 1992 in view of the HERCEPTIN® Label, but not why one would have thought such a conjugate might be useful to treat mammals/patients resistant to the antibody); *see also* Pet. 18–26 (citing same).

We also are persuaded by evidence offered by Patent Owner indicating that ordinary artisans would have thought it likely that HERCEPTIN® resistance occurred in patients because obstacles prevented the antibody from binding its ErbB2 receptor target, or due to other events that prevented HERCEPTIN® from working as expected. Prelim. Resp. 11 (citing Ex. 2001, Abstract). The Petition and Dr. Rosenblum do not explain why an ordinary person skilled in the art would have thought HERCEPTIN® would be a good choice, rather than "a particularly poor choice for an immunoconjugate to treat such patients." *Id*. at 12.

Based on the record before us, we are not persuaded that Petitioner has established a reasonable likelihood that an ordinary artisan, reading Chari 1992 and the HERCEPTIN® Label, would have been motivated to treat a tumor "characterized by overexpression of an ErbB2 receptor and that does not respond, or responds poorly, [e.g., does not "show statistically significant improvement in response to"] to treatment with an anti-ErbB antibody" using the recited huMab 4D5-8 conjugate, or would have had a reasonable expectation of success in doing so. Ex. 1001, 16:56–63 (defining "does not respond, or responds poorly"). Thus, we are not persuaded that there is a reasonable likelihood that Petitioner would

prevail in relation to the ground that claims 1–20 and 25–27 would have been obvious over Chari 1992 and the HERCEPTIN® Label.

C. Obviousness over Chari 1992, HERCEPTIN® Label, and Baselga 1999

Petitioner contends that Baselga 1999 (Ex. 1032) provides further motivation for a method comprising "identifying" a tumor "characterized by overexpression of an ErbB2 receptor and as being a tumor that does not respond, or responds poorly, to treatment with an anti-ErbB antibody." Pet. 27. In support, Petitioner notes that Baselga 1999 states that "while not achieving a complete or partial response, 37% of patients in this trial achieved minimal responses or stable disease." *Id.* (quoting Ex. 1032, 82, 1st col.). Petitioner also contends that Baselga 1999 teaches that its results "support the concept that trastuzumab, given alone or in combination with chemotherapy, will be a useful tool for the treatment of patients with HER2-over-expressing breast cancer." *Id.* at 28 (quoting Ex. 1032, 82, 2d col.).

Petitioner relies on Dr. Rosenblum's Declaration to support its assertion that because Baselga 1999 "identifies" relevant tumors (by teaching that trastuzumab did not work on some patients), an ordinary artisan would have been motivated "to treat such patient population with trastuzumab in combination with chemotherapy." *Id*. at 28 (citing Ex. 1016, ¶¶ 13–14).

As discussed above regarding the HERCEPTIN® Label, "identifying" patients that do not respond, or respond poorly, to an anti-ErbB antibody does not teach or suggest how to treat such patients, much less teach or suggest treating such patients with an anti-ErbB antibody conjugate. Patent Owner does not point us to where Baselga 1999 suggests treating patients who do not respond well to

trastuzumab with a conjugate comprising an anti-ErbB antibody. Pet. 27–29. Dr. Rosenblum's conclusory statements to the contrary do not persuade us otherwise. Ex. 1016 ¶¶ 13–14.

Thus, we are not persuaded that there is a reasonable likelihood that Petitioner would prevail in relation to ground that claims 1–20 and 25–27 would have been obvious over Chari 1992, the HERCEPTIN® Label, and Baselga 1999.

D. Obviousness over Chari 1992, HERCEPTIN® Label, and Other Cited References

Petitioner contends that Morgan 1990 (Ex. 1021) provided reason to use SMCC to link huMAB4D5-8 antibody to maytansinoid DM1. Pet. 29–30. Petitioner also contends that Hudziak 1998 (Ex. 1017) and Rosenblum 1999 (Ex. 1018) provided reasons to modify "the TA.l-maytansinoid conjugate with huMAB4D5-8" to form the recited conjugate "for [the] treatment of breast cancer." *Id*. at 32–34. In addition, Petitioner contends that Baselga 1998 (Ex. 1019) and Pegram 1999 (Ex. 1020) provided reasons "for modifying Chari 1992's TA.l-maytansinoid conjugate into a HERCEPTIN®-maytansinoid conjugate." *Id*. at 35–38.

Petitioner cites the above-mentioned references to show that an ordinary artisan would have been motivated to make the recited conjugate and use it in a method for treating tumors that overexpress an ErbB2 receptor generally. Petitioner does not indicate, however, where or how those references cure the deficiencies of Chari 1992, HERCEPTIN® Label and/or Baselga 1999, i.e., none teach or suggest treating patients who do not respond well to trastuzumab with a conjugate comprising an anti-ErbB antibody, as discussed above.

Thus, we are not persuaded that there is a reasonable likelihood that Petitioner would prevail in relation to ground that claims 1–20 and 25–27 would have been obvious over Chari 1992, the HERCEPTIN® Label, and Morgan 1990 alone, or Morgan 1990, Hudziak 1998 and/or Rosenblum 1999, alone or further in view of Baselga 1998 and/or Pegram 1999.

E. Obviousness over Cohen 1999, HERCEPTIN® Label, and Morgan 1990

Petitioner argues that Cohen 1999 teaches or suggests the recited conjugate containing huMab4D5-8 linked to maytansinoid through the linker SMCC. *Id*. at 47–48, 51–53. Petitioner relies on Morgan 1990 (Ex. 1021) as providing an additional reason to use SMCC to link huMAB4D5-8 antibody to maytansinoid DM1. *Id*. at 49–50.

Again, Petitioner relies on the same "ORR" disclosure in the HERCEPTIN® Label, discussed above, to support its contention that the Label discloses the "identifying" step in the challenged independent claims, and "provides a motivation for treating tumors that do not respond, or respond poorly, to treatment with an anti-ErbB antibody." Pet. 43, 48–49, 51 (citing Ex. 1008, ¶ spanning 1st and 2d cols.; Ex. 1016 ¶ 12). As with other grounds, the Petition and Dr. Rosenblum do not explain adequately how, nor provide sufficient evidence indicating that, the teaching in HERCEPTIN® Label that certain patients failed to respond to HERCEPTIN® would have motivated an ordinary artisan to treat such patients using a HERCEPTIN® (huMab 4D5-8) conjugate.

Thus, we are not persuaded that there is a reasonable likelihood that Petitioner would prevail in relation to ground that claims 1–20 and 25–27 would have been obvious over Cohen 1999, the HERCEPTIN® Label, and Morgan 1990.

III. CONCLUSION

For the foregoing reasons, we are not persuaded that there is a reasonable likelihood that Petitioner would prevail with respect to at least one of claims 1–20 and 25–27 of the ’748 patent based on the grounds of unpatentability advanced in the Petition.

IV. ORDER

It is

ORDERED that the Petition is *denied* as to all challenged claims and no trial is instituted.

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