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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-00804
Patent 6,627,196 B1

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

YANG, Administrative Patent Judge.

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

INTRODUCTION

Hospira, Inc. ("Petitioner")[1] filed a Petition requesting an *inter partes* review of claims 1–3, 5, 7, 9–11, and 17–33 of U.S. Patent No. 6,627,196 B1 (Ex. 1001, "the '196 patent"). Paper 1 ("Pet."). Genentech, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 6 ("Prelim. Resp."). We review the Petition under 35 U.S.C. § 314.

For the reasons provided below, we determine Petitioner has satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). Because Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim, we institute an *inter partes* review of claims 1–3, 5, 7, 9–11, and 17–33 of the '196 patent.

Related Proceedings

The '196 patent issued from an application filed on August 25, 2000, and claims benefit of priority to two provisional applications filed on June 23, 2000 and August 27, 1999, respectively. Ex. 1001, (22), (60). Also claiming benefit of priority to the two provisional applications is European Patent EP 1 210 115 ("the EP '115 patent"). Ex. 1005, (30). Petitioner informs us that the EP '115 patent is a European counterpart to the '196 patent and has been invalidated by the EPO and in UK proceedings. Pet. 2 (citing Exs. 1006, 1007, 1009).

Petitioner has concurrently filed IPR2017-00805, challenging certain claims of U.S. Patent No. 7,371,379, a patent in the same family of the '196 patent. Pet. 2; Paper 4, 4.

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[1] Petitioner identifies Pfizer, Inc. as "the real party in interest for Petitioner." Paper 7.

The '196 Patent

The '196 patent relates to the treatment of disorders characterized by the overexpression of ErbB2. Ex. 1001, Abstract, 1:13–14.

According to the Specification, "human ErbB2 gene (erbB2, also known as her2, or c-erbB-2), which encodes a 185-kd transmembrane glycoprotein receptor ($p185^{HER2}$) related to the epidermal growth factor receptor (EGFR), is overexpressed in about 25% to 30% of human breast cancer." *Id.* at 1:42–47. Before the '196 patent, a recombinant humanized anti-ErbB2 monoclonal antibody (a humanized version of the murine anti-ErbB2 antibody 4D5, also referred to as rhuMAb HER2, trastuzumab, or HERCEPTIN®) had been approved to treat patients with ErbB2-overexpressing metastatic breast cancers. *Id.* at 3:54–60. The recommended initial "loading dose" for Herceptin® was 4 mg/kg administered as a 90-minute infusion, and the recommended weekly "maintenance dose" was 2 mg/kg, which could be administered as a 30-minute infusion if the initial loading dose was well-tolerated. *Id.* at 3:61–65.

The alleged invention described in the '196 patent "concerns the discovery that an early attainment of an efficacious target trough serum concentration by providing an initial dose or doses of anti-ErbB2 antibodies followed by subsequent doses of equal or smaller amounts of antibody (greater front loading) is more efficacious than conventional treatments." *Id.* at 4:21–26. According to the '196 patent, "the method of treatment involves administration of an initial dose of anti-ErbB2 antibody of more than approximately 4 mg/kg, preferably more than approximately 5 mg/kg," with the maximum dose not to exceed 50 mg/kg. *Id.* at 4:47–51. "[T]he initial dose or doses is/are followed by subsequent doses of equal or smaller

amounts of antibody at intervals sufficiently close to maintain the trough serum concentration of antibody at or above an efficacious target level." *Id.* at 4:61–65. Preferably, "the amount of drug administered is sufficient to maintain the target trough serum concentration such that the interval between administration cycles is at least one week," and "the trough serum concentration does not exceed 2500 μg/ml and does not fall below 0.01 μg/ml during treatment." *Id.* at 4:67–5:5.

The '196 patent explains that "[t]he front loading drug treatment method of the invention has the advantage of increased efficacy by reaching a target serum drug concentration early in treatment." *Id.* at 5:5–8. As a result, "[t]he efficacious target trough serum concentration is reached in 4 weeks or less . . . and most preferably 1 week or less, including 1 day or less." *Id.* at 4:26–29. Additionally, it states that the method of therapy may involve "infrequent dosing" of the anti-ErbB2 antibody, wherein the first and subsequent doses are separated from each other by at least about two weeks, and optionally at least about three weeks. *Id.* at 6:20–31.

The '196 patent describes embodiments in which the initial dose of anti-ErbB2 is 6 mg/kg, 8 mg/kg, or 12 mg/kg, followed by subsequent maintenance doses of 6 mg/kg or 8 mg/kg administered once every 2 or 3 weeks, in a manner such that the trough serum concentration is maintained at approximately 10–20 μg/ml during the treatment period. *Id.* at 5:30–48, 44:30–67. The treatment regimen according to the invention may further comprise administration of a chemotherapeutic agent, such as a taxoid, along with the anti-ErbB2 antibody. *Id.* at 6:4–8, 7:22–28, 45:40–46:3.

Illustrative Claims

Among the challenged claims, claims 1 and 24 are independent and are reproduced below:

> 1. A method for the treatment of a human patient diagnosed with cancer characterized by overexpression of ErbB2 receptor, comprising administering an effective amount of an anti-ErbB2 antibody to the human patient, the method comprising:
>
> administering to the patient an initial dose of at least approximately 5 mg/kg of the anti-ErbB2 antibody; and
>
> administering to the patient a plurality of subsequent doses of the antibody in an amount that is approximately the same or less than the initial dose, wherein the subsequent doses are separated in time from each other by at least two weeks.
>
> 24. A method for the treatment of cancer in a human patient comprising administering to the patient a first dose of an anti-ErbB2 antibody followed by two or more subsequent doses of the antibody, wherein the subsequent doses are separated in time from each other by at least two weeks.

Asserted Ground of Unpatentability

Petitioner asserts a single ground of unpatentability, challenging claims 1–3, 5, 7, 9–11, and 17–33 of the '196 patent as obvious under 35 U.S.C. § 103(a) over the combination of the Herceptin Label,[2] Baselga '96,[3] Pegram '98,[4] and the Knowledge of a Person of Ordinary Skill in the Art.

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[2] 1998 FDA Approved Label for Herceptin® (Ex. 1008).

[3] Baselga et al., *Phase II Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer*, 14 J. CLIN. ONCOL. 737–44 (1996) (Ex. 1013).

[4] Pegram, et al., *Phase II Study of Receptor-Enhanced Chemosensitivity Using Recombinant Humanized Anti-p185$^{HER2/neu}$ Monoclonal Antibody Plus Cisplatin in Patients with HER2/neu-Overexpressing Metastatic Breast*

In support of its patentability challenges, Petitioner relies on the declarations of Allan Lipton, M.D. (Ex. 1002) and William Jusko, Ph.D. (Ex. 1003).

ANALYSIS

Claim Construction

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). On this record and for purposes of this Decision, we see no need to expressly construe any claim terms.

Cancer Refractory to Chemotherapy Treatment, 16 J. CLIN. ONCOL. 2659–71 (1998) (Ex. 1014).

Prior Art Disclosures

Herceptin Label

As recognized in the '196 patent, rhuMAb HER2 (trastuzumab) was already FDA-approved and commercially sold in the U.S. by 1998 under the tradename Herceptin. Ex. 1001, 3:54–60. The Herceptin Label teaches:

> The pharmacokinetics of Trastuzumab were studied in breast cancer patients with metastatic disease. Short duration intravenous infusions of 10 to 500 mg once weekly demonstrated dose-dependent pharmacokinetics. Mean half-life increased and clearance decreased with increasing dose level. The half-life averaged 1.7 and 12 days at the 10 and 500 mg dose levels, respectively. Trastuzumab's volume of distribution was approximately that of serum volume (44 mL/kg). At the highest weekly dose studied (500 mg), mean peak serum concentrations were 377 microgram/mL.

Ex. 1008, 1.

The Herceptin Label also teaches that "[i]n studies using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a mean half-life of 5.8 days . . . was observed," and "[b]etween week 16 and 32, Trastuzumab serum concentration reached a steady state with a mean trough and peak concentrations of approximately 79 [mg]/mL and 123 [mg]/mL, respectively." *Id.* The Herceptin Label further describes clinical studies in which metastatic breast cancer patients with certain levels of HER2 overexpression were administered either chemotherapy alone or in combination with Herceptin given intravenously as a 4 mg/kg loading dose followed by weekly doses at 2 mg/kg. *Id.* The chemotherapy in these clinical studies (e.g., paclitaxel) was administered every 3 weeks (21 days). *Id.*

Baselga ’96

Baselga ’96 reports the results of a phase II clinical trial in patients with ErbB2-overexpressing metastatic breast cancer who had received extensive prior therapy. Ex. 1013, 9. Each patient received a loading dose of 250 mg of intravenous rhuMAb HER2, followed by 10 weekly doses of 100 mg. *Id.* at 10. The pharmacokinetic goal of the trial “was to achieve rhuMAb HER2 trough serum concentrations greater than 10 μg/mL, a level associated with optimal inhibition of cell grown in the preclinical model.” *Id.* at 10. Further, the “[s]erum levels of rhuMAb HER2 as a function of time were analyzed for each patient using a one-compartment model.” *Id.*

According to Baselga ’96, “[a]dequate pharmacokinetic levels of rhuMAb HER2 were obtained in 90% of the patients. Toxicity was minimal and no antibodies against rhuMAb HER2 were detected in any patients.” *Id.* at 9. Out of the 768 times rhuMAb HER2 was administered, “only 11 events occurred that were considered to be related to the use of the antibody.” *Id.* at 11. Baselga ’96 also teaches that “[i]n preclinical studies, both in vitro and in xenografts, rhuMAb HER2 markedly potentiated the antitumor effects of several chemotherapeutic agents, including cisplatin, doxorubicin, and paclitaxel, without increasing their toxicity.” *Id.* at 15.

Pegram ’98

Pegram ’98 reports the results of a phase II clinical trial using a combination of rhuMAb HER2 plus cisplatin. Ex. 1014, 8. It states that “[t]hese studies showed that the pharmacokinetics of rhuMAb HER2 were predictable, and that the doses delivered achieved a target trough serum concentration of 10 to 20 μg/mL, which is associated with antitumor activity in preclinical models.” *Id.* at 9. It also reports a toxicity profile of the

combination that paralleled the toxicity of cisplatin alone, which led to the conclusion that rhuMAb HER2 did not increase toxicity. *Id.* at 17.

Asserted Obviousness Ground

Petitioner contends that claims 1–3, 5, 7, 9–11, and 17–33 of the '196 patent would have been obvious over the combination of Herceptin Label, Baselga '96, Pegram '98, and the knowledge of a person of ordinary skill in the art. Pet. 29–57. Based on the current record, we determine Petitioner has established a reasonable likelihood that it would prevail in this assertion.

For claim 1, Petitioner argues that the Herceptin Label teaches rhuMAb HER2 doses of up to 500 mg had been successfully administered to patients. Pet. 31 (citing Ex. 1008, 1). Based on a patient weight range of 55–85 kg, Petitioner calculates that the weight-based dose for the 500 mg absolute dose taught by the Herceptin Label ranges from 5.88–9.09 mg/kg. *Id.* at 31–32 (citing Ex. 1002 ¶¶ 54–57; Ex. 1003 ¶ 45; Ex. 1026, 3; Ex. 1027, 334 (Table 7-2)). Petitioner refers to the Herceptin Label for teaching that rhuMAb HER2 doses should be front-loaded. *Id.* at 33 (citing Ex. 1008, 1).

According to Petitioner, the Herceptin Label teaches administering rhuMAb HER2 in combination with chemotherapeutic agents, and that these chemotherapeutic agents are administered once every three weeks to patients. *Id.* at 35–36 (citing Ex. 1008, 1). Petitioner also relies upon Baselga '96 and Pegram '98 insofar as they confirm that the weekly dosing regimen encompassed by the Herceptin Label was successfully administered to patients in phase II clinical trials, and that an ordinary artisan would have been aware of a target trough serum concentration of 10–20 µg/mL for rhuMAb HER2. *Id.* at 37.

Petitioner acknowledges that the Herceptin Label, along with Baselga '96 and Pegram '98, teach only a *weekly* dosing regimen, but asserts that an ordinary artisan would nonetheless have been motivated to decrease the frequency of rhuMAb HER2 injections to once every three weeks for several reasons. *Id.* at 34–42. First, Petitioner contends that an ordinary artisan "would decrease the frequency of injections to improve efficiency, to provide a more convenient dosing regimen—particularly for terminally ill patients—, and to improve patient compliance and quality of life." *Id.* at 34. Second, Petitioner argues that a tri-weekly regimen for the antibody would align with the dosing schedules of the chemotherapy so that a patient would have to only make one trip to the clinic to receive both therapies. *Id.* at 36.

Third, Petitioner asserts that an ordinary artisan would decrease the frequency of injections and use a tri-weekly dosing regimen in view of "rhuMAb HER2's known pharmacokinetic properties." *Id.* Specifically, relying on the testimony of Dr. Jusko, Petitioner asserts that it would have been "a matter of routine calculation" for an ordinary artisan to determine that "a tri-weekly rhuMAb HER2 dosing regimen would have resulted in a serum concentration well above the target minimum trough concentration of 10–20 μg/ml." *Id.* at 37–39 (citing Ex. 1003 ¶¶ 46–47, 49–51, 56–58, 62). Also relying on the testimony of Dr. Jusko, Petitioner contends that an initial loading dose of approximately 712 mg, with a maintenance dose of 500 mg and a dose interval of three weeks, would be such a dosing regimen. *Id.* at 39–41 (citing Ex. 1003 ¶¶ 59, 61–62).

Patent Owner first urges that we deny institution pursuant to 35 U.S.C. § 325(d), because the Examiner, during prosecution of the '196

patent, considered the teachings of "Goldenberg '99,"[5] a reference that includes the same information as set forth in the Herceptin Label. Prelim. Resp. 19–22, 27–30. We acknowledge Patent Owner's argument but decline to deny consideration of Petitioner's patentability challenge under § 325(d).

Under 35 U.S.C. § 325(d), in determining whether to institute an *inter partes* review, we "may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." Here, relying on the Lipton and Jusko Declarations, which were not before the Examiner during prosecution, Petitioner presents the prior art in a new light. For example, the Examiner did not consider the calculations set forth by Dr. Jusko showing that a tri-weekly dosing regimen would have resulted in an acceptable trough serum concentration above 10–20 μg/ml. *See* Ex. 1003 ¶¶ 61–62. As a result, we exercise our discretion not to deny the Petition under § 325(d).

On the merits, Patent Owner argues that (1) the prior-art references upon which Petitioner relies only describe weekly dosing of the antibody, (2) the reported half-life of trastuzumab would have discouraged an ordinary artisan from applying a tri-weekly dosing regimen, (3) the prior art does not articulate or suggest the alleged desire for convenience in the dosing regimen, which would have been secondary to efficacy, and (4) Petitioner's argument concerning "routine calculation and optimization" is based on hindsight, and contradicts historical reality and the prior art. Prelim. Resp.

[5] Marvin M. Goldenberg, *Trastuzumab, a Recombinant DNA Derived Humanized Monoclonal Antibody, a Novel Agent for the Treatment of Metastatic Breast Cancer*, 21 CLINICAL THERAPEUTICS 309 (1999) (Ex. 2001).

3–4, 31–48. With regard to the last point, Patent Owner contends that trastuzumab was known to have "dose-dependent" (i.e., non-linear) kinetics, which would have made any prediction concerning drug concentration in the body difficult because the elimination rate changes over time. *Id.* at 10–14. Because Dr. Jusko assumes linear kinetics in making his calculations (Ex. 1003 ¶¶ 60, 71), Patent Owner contends that Petitioner has failed to establish a reasonable expectation of success. Prelim. Resp. 44–48.

On this record, we are unpersuaded by Patent Owner's preliminary arguments on the merits, which mostly focus on whether it would have been obvious to utilize the extended dosing interval required by the claimed methods. We recognize that the prior art only explicitly described weekly dosing intervals for administration of the rhuMAb HER2 antibody, but we do not find that the current record supports a conclusion that an ordinary artisan would have been discouraged from extending the dosing interval to once every three weeks. We do not find any basis in the current record to conclude that an ordinary artisan would have limited the dosing interval in view of the disclosed half-life of the antibody; rather, the record suggests that half-life may be one factor to consider among others in determining the dosing frequency. *See, e.g.*, Ex. 2007, 152 (teaching that "dosage interval can *generally* be extended in relation to half-life," but further identifying "therapeutic index," "body clearance," and "side effects" as other factors to consider) (emphasis added).

Furthermore, contrary to Patent Owner's arguments, the prior art need not have expressly articulated or suggested patient convenience as a motivation to extend the dosing interval. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("[T]he [obviousness] analysis need not seek out

precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ."); *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1329 (Fed. Cir. 2014) ("A relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance.").

We nonetheless recognize that the desire for patient convenience must be balanced with the desire for efficacy in determining the appropriate dosing interval, but note that "[c]onclusive proof of efficacy is not necessary to show obviousness." *Hoffmann-La Roche Inc.*, 748 F.3d at 1331. Patent Owner contends that Petitioner failed to establish a reasonable expectation of success because the calculations by Dr. Jusko are erroneously based on linear (dose-independent) kinetics rather than the non-linear (dose-dependent) kinetics taught in the prior art for trastuzumab. Prelim. Resp. 44–48. At this stage of the proceeding, and without the benefit of expert testimony from Patent Owner, we decline to give Petitioner's arguments based on expert testimony less weight in comparison to Patent Owner's attorney arguments. Thus, we determine that Petitioner has shown a reasonable expectation of success based, among others, on the calculations set forth in the Jusko Declaration.

In sum, based on the current record, we conclude that Petitioner has established a reasonable likelihood of prevailing on its assertion that claim 1 would have been obvious over the combined teachings of the Herceptin Label, Baselga '96, and Pegram '98, in combination with the knowledge of an ordinary artisan as set forth in the declarations of Dr. Lipton and Dr. Jusko. We have considered Petitioner's arguments and evidence with

respect to the remaining claims (Pet. 42–57), which Patent Owner does not argue separately, and we determine that Petitioner has made a sufficient showing as to those claims, as well.

CONCLUSION

For the foregoing reasons, we find that Petitioner has offered sufficient evidence to institute an *inter partes* review. The information presented in the Petition and accompanying evidence establishes a reasonable likelihood that Petitioner would prevail in showing the unpatentability of claims 1–3, 5, 7, 9–11, and 17–33 of the '196 patent.

At this stage of the proceeding, the Board has not made a final determination as to the construction of any claim term or the patentability of any challenged claim. Thus, our view with regard to any conclusion reached in the foregoing could change upon consideration of Patent Owner's merits response and upon completion of the current record.

ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted to determine whether claims 1–3, 5, 7, 9–11, and 17–33 of the '196 patent would have been obvious over the combination of the Herceptin Label in view of Baselga '96, Pegram '98, and the knowledge of a person of ordinary skill in the art;

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '196 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

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