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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-01139
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

Celltrion, 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 2 ("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

We previously instituted an *inter partes* review of the same challenged claims of the '196 patent, based on a petition filed by Hospira, Inc. *Hospira, Inc. v. Genentech, Inc.*, IPR2017-00804 (PTAB July 27, 2017) (Paper 13).

Petitioner has also filed IPR2017-01140, challenging certain claims of U.S. Patent No. 7,371,379 B2 ("the '379 patent"), a patent in the same family of the '196 patent. Pet. 3; Paper 4, 4. We previously instituted an *inter partes* review of the '379 patent, based on a petition filed by Hospira. *Hospira, Inc. v. Genentech, Inc.*, IPR2017-00805 (PTAB July 27, 2017) (Paper 13).

[1] Petitioner identifies Celltrion Healthcare Co., Ltd. and Teva Pharmaceuticals International GmbH as additional real parties-in-interest. Pet. 3.

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 Claim

Among the challenged claims, claims 1 and 24 are independent. Independent claim 1 is illustrative, and is 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.

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 Slamon,[2] Watanabe,[3] Baselga,[4] and

[2] D. Slamon et al., *Addition of Herceptin(™) (Humanized Anti-HER2 Antibody) to First Line Chemotherapy for HER2 Overexpressing Metastatic Breast Cancer (HER2 +/MBC) Markedly Increases Anticancer Activity: A Randomized Multinational Controlled Phase III Trial*, 17 J. CLIN. ONCOL. 98a, Abstract *377 (1998) (Ex. 1005).

[3] T. Watanabe et al., *Pharmacokinetically Guided Dose Escalation Study of Anti-HER2 Monoclonal Antibody in Patients with HER2/NEU-Overexpressing Metastatic Breast Cancer*, 17 JOURNAL OF CLINICAL ONCOLOGY 182a, Abstract *702 (1998) (Ex. 1006).

[4] 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. 1007).

Pegram.[5]

In support of its patentability challenges, Petitioner relies on the Declaration of Mark J. Ratain, M.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).

Petitioner adopts constructions for "ErbB2 receptor," "Epitope 4D5," "antibody," "treatment," "cancer," "chemotherapeutic agent," and "doxorubicin" based on definitions set forth in the Specification. Pet. 14–15. Patent Owner proposes a construction for "effective amount" based on the Specification. *See* Prelim. Resp. 24–25.

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[5] 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 Cancer Refractory to Chemotherapy Treatment*, 16 J. CLIN. ONCOL. 2659–71 (1998) (Ex. 1009).

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.

Prior Art Disclosures

Slamon

Slamon summarizes the results of a Phase III clinical trial in which patients received Herceptin (H) along with chemotherapy (CRx). Ex. 1005, Abstract *377. The chemotherapy (doxorubicin-cyclophosphamide or paclitaxel) was administered once every three weeks. *Id.* The Herceptin was administered intravenously at a 4 kg/mg loading dose, followed by 2 mg/kg weekly doses. Slamon indicates that "[a]t a median follow-up of 10.5 months, investigator assessments of time to disease progression (TTP) and response rates (RR) show a significant augmentation of CRx effect by H, without increase in overall severe adverse events (AE)." *Id.* As such, Slamon concludes that the data from the clinical trial "indicate that addition of Herceptin to CRx markedly increases clinical benefit, as assessed by RR and TTP." *Id.*

Watanabe

Watanabe summarizes a phase I dose escalation study of an anti-HER2 monoclonal antibody (MAb 4D5 (MKC-454)) in patients with chemotherapy-resistant metastatic breast cancer. Ex. 1006, Abstract *702. In the study, the first dose of antibody was followed in 3 weeks by 9 weekly doses. *Id.* Doses of 1, 2, 4, and 8 mg/kg were administered as 90-minute intravenous infusions. *Id.* Watanabe reports the following data:

MKC454 dose	# of Pts	trough level (μg/ml)	toxicity		tumor response
			grade 2	grade 3≤	
1 mg/kg	6	9		1 fever, 1 n/v	
2 mg/kg	3	19	1 fever, 1 pain		1 MR
4 mg/kg	3	102	1 fever		1 PR
8 mg/kg	6	248		1 pain	1 MR, 2 PR

Id. According to Watanabe, "[t]arget trough plasma concentration was achieved with 2 mg/kg weekly intravenous infusions." *Id.* Thus, Watanabe concludes that "[f]urther clinical trials examining the efficacy of MAb 4D5 (MKC-454) with 2–4 mg/kg weekly intravenous infusions is warranted." *Id.*

Baselga

Baselga reports the results of a phase II clinical trial in patients with ErbB2-overexpressing metastatic breast cancer who had received extensive prior therapy. Ex. 1007, 3. Each patient received a loading dose of 250 mg of intravenous rhuMAb HER2, followed by 10 weekly doses of 100 mg. *Id.* 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 4. 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, "[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 3. 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 5. Baselga 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 9.

Pegram

Pegram reports the results of a phase II clinical trial using a combination of rhuMAb HER2 plus cisplatin. Ex. 1009, 2. 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 3. 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 11.

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 Slamon, Watanabe, Baselga, and Pegram. Pet. 27–52. Based on the current record, we determine Petitioner has established a reasonable likelihood that it would prevail in this assertion.

For claim 1, Petitioner refers to Slamon for teaching an effective treatment regimen that combined Herceptin with chemotherapy, wherein Herceptin was administered at a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg. Pet. 27 (citing Ex. 1005, 5). Petitioner argues that an ordinary artisan "would have been motivated to administer trastuzumab as disclosed by Slamon, but would have recognized that weekly administration would be inconvenient for patients, who otherwise would need infusions only once every three weeks." *Id.* (citing Ex. 1003 ¶ 89; Ex. 1017, 1–4). Petitioner contends that an ordinary artisan

"would have sought to reduce the frequency of trastuzumab administration to align it with the less arduous chemotherapy regimen in order to improve patient convenience." *Id.* (citing Ex. 1003 ¶ 90). When modifying the dosing schedule, according to Petitioner, an ordinary artisan "would have recognized the importance of maintaining dose intensity, i.e., the amount of drug administered over a period of time." *Id.* at 28 (citing Ex. 1003 ¶ 91; Ex. 1024, 1–5; Ex. 1029). Thus, Petitioner concludes that to account for an every-three-week schedule, an ordinary artisan would have administered an 8 mg/kg loading dose (i.e., 4 mg/kg + 2 mg/kg + 2mg/kg), followed by 6 mg/kg maintenance doses (i.e., 2 mg/kg + 2 mg/kg + 2mg/kg), each administered three weeks apart. *Id.* at 28–29 (citing Ex. 1003 ¶ 91).

With regard to safety concerns, Petitioner contends that based on Watanabe's disclosure that weekly doses as high as 8 mg/kg were safe and well-tolerated, an ordinary artisan "would not have expected an increase in toxicity, or any other safety concerns, for the higher doses required by the every-three-week regimen." *Id.* at 30 (citing Ex. 1006, 5; Ex. 1003 ¶¶ 72, 92–93). Petitioner emphasizes that "the overall number of severe adverse events was in fact ***lower*** for the six patients treated at the 8 mg/kg dose than Watanabe disclosed for the 1 mg/kg dose." *Id.* Petitioner also cites other prior art references as teaching that trastuzumab was safe at doses as high as 8 mg/kg. *Id.* at 31 (citing Ex. 1008, 1; Ex. 1013, 4; Ex. 1014, 4; Ex. 1012, 11:54–56; Ex. 1015, 2:60–61; Ex. 1018, 48:19–52).

With regard to efficacy, Petitioner relies upon the prior art's disclosure of a target serum concentration (trough concentration) of 10 µg/ml. *Id.* at 32 (citing Ex. 1003 ¶ 96; Ex. 1006, 5; Ex. 1007, 4; Ex. 1009, 3). In determining whether the every-three-week regimen would

satisfy this trough concentration, Petitioner relies upon the disclosures in Baselga and Pegram that trastuzumab has a mean half-life of at least one week. *Id.* at 33 (citing Ex. 1003 ¶ 103; Ex. 1007, 5; Ex. 1009, 8). Petitioner argues that because "Baselga further discloses that trastuzumab has dose-dependent pharmacokinetics," an ordinary artisan "would have understood that its half-life would actually be longer at higher doses." *Id.* (citing Ex. 1003 ¶ 102; Ex. 1007, 3). Thus, Petitioner contends that "the serum concentration would decrease by half no more than three times" before the next 6 mg/kg maintenance dose is administered. *Id.* at 34 (citing Ex. 1003 ¶¶ 104–105). Based on an initial serum concentration of 169 µg/ml (calculated based on Pegram's disclosure), Petitioner estimates that approximately 21.1 µg/ml would remain after three weeks, which is above the 10 µg/ml trough concentration required for efficacy. *Id.* at 34–35 (citing Ex. 1003 ¶¶ 100, 104). Petitioner comes to a similar conclusion based on the pharmacokinetic data disclosed in the 1998 Herceptin label. *Id.* at 37–38.

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,[6] a reference that cites the Slamon abstract and discusses the same Phase III clinical trials in more detail. Prelim. Resp. 19–20, 26–31. We recognize that Goldenberg '99 contains substantially the same teachings as Slamon with regard to the

[6] 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. 1013).

dosing regimen, but we 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 Declaration of Dr. Ratain, which were not before the Examiner during prosecution, Petitioner presents the prior art in a new light. For example, there is no basis to suggest that the Examiner considered the calculations set forth by Dr. Ratain showing that a tri-weekly dosing regimen would have resulted in an acceptable trough serum concentration above 10 μg/ml. *See* Ex. 1003 ¶¶ 100–06. Based upon these differences in the current record, we exercise our discretion not to deny the Petition under § 325(d).

We are also unpersuaded by Patent Owner's preliminary arguments on the merits, which focus primarily on whether it would have been obvious to employ the extended dosing interval required by the claimed methods. *See* Prelim. Resp. 33–43. In particular, Patent Owner argues that the prior art does not support Petitioner's claim that convenience would have motivated skilled artisans to administer trastuzumab at three-week dosing intervals. *Id.* at 36–42. We recognize that the prior art only explicitly described weekly dosing intervals for administration of the antibody. However, Petitioner has presented a sufficient evidentiary basis on this record, supported by expert testimony, to support its argument that the skilled artisan would have been motivated to use a three week dosing interval in order to align both the antibody and chemotherapy infusion treatments on the same schedule.

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.").

Patent Owner also argues the prior art does not suggest the claimed loading and maintenance doses. Prelim. Resp. 44–44. With regard to Petitioner's assertion that the skilled artisan would apply the concept of "dose intensity" to match the total dose amount provided according to Slamon's regimen in an equivalent three week period, Patent Owner argues that this approach is flawed because (1) the skilled artisan would not have used the chemotherapy dosing strategy of maintaining dose intensity to adjust the antibody dose; and (2) increasing the dose amount and extending the dosing interval was known to cause higher peak and lower trough concentrations as compared to smaller dose amounts administered more frequently. *Id.* We are unpersuaded by this argument at this stage of this proceeding.

As discussed above, Petitioner has presented expert testimony indicating that the skilled artisan would have chosen to apply a strategy of maintaining dose intensity, and that applying such a strategy to a triweekly regimen would have resulted in acceptable serum concentration levels for

the antibody during the treatment period. *See* Ex. 1003 ¶¶ 91, 100–06. Patent Owner has not presented any expert testimony of its own at this stage of the proceeding to support its argument that the skilled artisan would not have chosen to take such an approach. We, therefore, decline to give Petitioner's arguments, which are based on expert testimony, less weight in comparison to Patent Owner's attorney arguments.

Patent Owner further argues that Petitioner has failed to establish a reasonable expectation of success with respect to efficacy due to the non-linear kinetics of trastuzumab. Prelim. Resp. 45–48. Patent Owner contends that "[d]espite recognizing that the prior art taught that trastuzumab had documented non-linear kinetics, the foundation of Petitioner's analysis is the application of simple equations that apply only to drugs that exhibit linear kinetics." *Id.* at 45 (citing Ex. 1003 ¶¶51–55). According to Patent Owner, "[t]his is erroneous." *Id.*

We 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. In this regard, we have taken into account Petitioner's contention that an ordinary artisan "would have expected the trough serum concentration to be even higher if its non-linear pharmacokinetics were taken into account." Pet. 35 n. 8 (citing Ex. 1003 ¶ 102). Again, at this stage of the proceeding, and without the benefit of expert testimony from Patent Owner, we decline to give Petitioner's arguments, which are based on expert testimony, less weight in comparison to Patent Owner's attorney arguments. As a result, we determine that, under the reasonable-likelihood standard for instituting trial,

Petitioner has shown a reasonable expectation of success based on the calculations set forth in the Declaration of Dr. Ratain.

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 Slamon, Watanabe, Baselga, and Pegram, in combination with the knowledge of an ordinary artisan as set forth in the Declaration of Dr. Ratain. We have considered Petitioner's arguments and evidence with respect to the remaining claims (Pet. 43–52), 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 Slamon, Watanabe, Baselga, and Pegram;

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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