Trials@uspto.gov
Tel: 571-272-7822

Paper No. 68
Entered: October 3, 2018

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*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

ORDERS
Granting Petitioner's Motion to Exclude
37 C.F.R. § 42.64(c)

Denying-in-Part and Dismissing-in-Part Patent Owner's Motion to Exclude
37 C.F.R. § 42.64(c)

INTRODUCTION

Celltrion, Inc. ("Petitioner") filed a Petition (Paper 2 ("Pet.")), requesting an *inter partes* review of claims 1–3, 5, 7, 9–11, 13–15, and 17–33 of U.S. Patent No. 6,627,196 B1 (Ex. 1001, "the '196 patent"). We instituted trial to review patentability of the challenged claims.[1] Paper 30 ("Dec.").

Genentech, Inc. ("Patent Owner") filed a Response to the Petition (Paper 26, "PO Resp."), and Petitioner filed a Reply (Paper 39). The parties also briefed whether certain exhibits should be excluded from the record. Papers 51, 53, 55, 56, 58, 60. In addition, the parties briefed whether certain evidence and argument presented by Petitioner exceeded the proper scope of the Reply. Papers 52, 57, 61. Furthermore, Patent Owner filed a motion for observation on the cross-examination of Petitioner's declarant (Paper 54), and Petitioner filed an opposition thereto (Paper 59).

An oral hearing for this proceeding was held on May 8, 2018. *See* Paper 65.

The Board has jurisdiction under 35 U.S.C. § 6 and issues this final written decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons provided below, we conclude Petitioner has not established by a preponderance of the evidence that claims 1–3, 5, 7, 9–11, 13–15, and 17–33 of the '196 patent are unpatentable.

[1] We inadvertently omitted claims 13–15 in the original Decision to Institute dated October 4, 2017. On January 25, 2018, we reissued the Decision to correct that mistake.

Related Proceedings

The ’196 patent is also the subject of IPR2017-00804. Concurrently with this Decision, we issue a final written decision in that case.

We also issue, concurrently with this Decision, final written decisions in IPR2017-00805 and IPR2017-01140 to address the patentability of certain claims of U.S. Patent No. 7,371,379, a patent in the same family of the ’196 patent at issue here.

The ’196 Patent

The ’196 patent claims priority to a provisional application filed August 27, 1999. Ex. 1001, (60).

The ’196 patent relates to the treatment of disorders characterized by the overexpression of ErbB2. *Id.* at 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 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 two or three 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.

Of particular relevance, the ’196 patent includes a prophetic example describing the administration of trastuzumab intravenously every three weeks in combination with the chemotherapeutic agent paclitaxel. *Id.* at 46:5–48:4. According to this example, “[s]imulation of the proposed treatment regimen suggests that the trough serum concentrations will be 17 mcg/ml, in the range (10–20 mcg/ml) of the targeted trough serum concentrations from previous HERCEPTIN® IV clinical trials.” *Id.* at 46:12–16. The example sets forth inclusion and exclusion criteria for a study in which patients will be administered trastuzumab every three weeks. *Id.* at 46:20–65. The ’379 patent concludes that “[i]t is believed that the above treatment regimen will be effective in treating metastatic breast cancer, despite the infrequency with which HERCEPTIN® is administered to the patient.” *Id.* at 48:1–4.

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.

Reviewed Ground of Unpatentability

We instituted *inter partes* review to determine whether the challenged claims would have been obvious over the combination of Slamon,[2] Watanabe,[3] Baselga,[4] and Pegram.[5]

In support of their respective arguments, Petitioner relies on the Declarations of Dr. Mark J. Ratain (Exs. 1003, 1123), and Patent Owner relies on the Declarations of Dr. George M. Grass and Dr. Karen A. Gelmon (Exs. 2027, 2028).

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

---

[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).

[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).

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).

In the Decision to Institute, we stated that we see no need to expressly construe any claim terms. Dec. 7 (citing *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (stating claim terms need only be construed to the extent necessary to resolve the controversy)). During trial, the parties do not argue otherwise, and we see no reason to change our position. Thus, on this record and for purposes of this Decision, we do not 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, 5. The chemotherapy (doxorubicin-cyclophosphamide or paclitaxel) was administered once every three weeks. *Id.* The Herceptin was administered intravenously at a 4 mg/kg loading dose, followed by 2 mg/kg weekly doses. *Id.* 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, 5. 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 provides data regarding patients receiving the different dosages of anti-HER2:

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. The chart above reports the trough level, toxicity, and tumor response. 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, thereby leading to the conclusion that rhuMAb HER2 did not increase toxicity. *Id.* at 11.

Level of Ordinary Skill in the Art

According to Petitioner,

> A POSA to whom the '196 patent is directed would have had either an M.D. with subspecialty training in oncology and/or a Ph.D. with substantial experience in oncology drug development. Such an individual would also have had familiarity with the treatment of breast cancer and substantial experience in the design and/or implementation of oncology clinical trials, as well as expertise in clinical pharmacology, including pharmacokinetics.

Pet. 14 (citations omitted). "Patent Owner does not dispute the areas of substantive expertise," but adds that "[a] skilled artisan would have had access to and worked on a team with a number of other individuals involved in drug development with expertise in clinical pharmacology, including pharmacokinetics." PO Resp. 23–24 (citation omitted).

We do not discern an appreciable difference in the parties' respective definitions of the level of ordinary skill in the art, and any perceived distinction does not impact our Decision. We further note that, in this case, the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown").

Obviousness Analysis

Petitioner contends that claims 1–3, 5, 7, 9–11, 13–15, and 17–33 of the '196 patent would have been obvious over the combination of Slamon, Watanabe, Baselga, and Pegram. Pet. 27–52. After reviewing the entire record, we determine that Petitioner has not established by a preponderance of the evidence that the challenged claims are unpatentable.

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."[6] *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" and would have administered an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses, 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,

[6] Even though some claims only require administering trastuzumab once every two weeks, our obviousness analysis assumes a treatment method in which trastuzumab is administered once every three weeks, as that dosing interval is encompassed by all the challenged claims and is the focus of the parties' arguments and evidence in this proceeding.

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 counters that an ordinary artisan would not have been motivated to administer trastuzumab in accordance with the claimed regimen. PO Resp. 26–42. Patent Owner also contends that Petitioner has not established "a reasonable expectation of success that extending the trastuzumab dosing regimen to three weeks with the claimed loading and maintenance doses would be safe and effective." *Id.* at 42–58.

Motivation to Modify

Dosing Frequency

Patent Owner asserts that an ordinary artisan would not have been motivated to administer trastuzumab on the every-three-week dosing schedule. PO Resp. 26–42. We are not persuaded.

Patent Owner asserts that an ordinary artisan "would not have been motivated to extend the dosing interval for the sake of convenience." *Id.* at 26. According to Patent Owner, in August 1999, the priority date of the '196 patent, an ordinary artisan would have been focused on improving efficacy of trastuzumab, and not convenience. *Id.* at 24, 26–28. We are not persuaded.

As a preliminary matter, we agree with Patent Owner that none of the asserted prior art references individually teaches the claimed dosing schedule explicitly. *See id.* at 17–23. Non-obviousness, however, cannot be established by attacking references individually where the patentability challenge is based upon the teachings of a combination of references. *See In re Keller*, 642 F.2d 413, 425 (CCPA 1981). Here, as explained below, the prior-art teachings as a whole, together with the knowledge of one of ordinary skill in the art, would have motivated an ordinary artisan to modify the dosing schedule of trastuzumab in order to improve patient convenience.

Patent Owner contends that Petitioner bases the obviousness challenge on a "generalized concern for 'convenience' untethered to the specific patient population of the claims." PO Resp. 29. According to Patent Owner, HER2-positive breast cancer is a serious, life-threatening disease, and "[p]atients thus need little additional convincing in the form of convenience to take trastuzumab." *Id.* at 36 (citing Ex. 2028 ¶¶ 42–47), *see also id.* (citing Ex. 2028 ¶¶ 50, 57) (arguing "compliance was not likely to be an issue for breast-cancer patients"). We are not persuaded.

First, except claims 18 and 19, the other challenged claims are not limited to breast cancer. *See* Ex. 1001, 58:3–12 (dependent claim 17 reciting the cancer is selected from at least 24 different types of cancer, including small-cell lung cancer and colorectal cancer), *see also id.* at 15:27–29 ("Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia."). Second, the record reflects that some patients, despite having metastatic breast cancer, and even in the context of a tightly controlled clinical study, in fact missed treatment due to reasons such as "social obligations" and other "commitments." Ex. 2016, 3355. Thus, prior art suggests convenience and compliance are important, even among patients with metastatic breast cancer.

Patent Owner argues that "[n]othing in the prior art suggests that skilled artisans treating patients with HER2-positive cancer were concerned with convenience in August 1999." PO Resp. 24. But the prior art relied upon by Petitioner need not expressly articulate or suggest patient convenience as a motivation to extend the dosing interval. Indeed,

> The motivation need not be found in the references sought to be combined, but may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the

> problem itself. As [the Federal Circuit] explained . . . "there is no requirement that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art."

DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1361 (Fed. Cir. 2006) (internal citations omitted).

Patent Owner is correct that one of ordinary skill in the art would have considered efficacy critical in treating cancer. PO Resp. 26. Efficacy, however, is not the sole consideration. *See, e.g.*, Ex. 1103, 1 (stating that a new regimen for treating small-cell lung cancer was designed with the objectives to "maintain efficacy, diminish toxicity, enhance compliance, and improve chemotherapy administration convenience at an acceptable cost").

Indeed, in 1998, the FDA issued the Guidance for Industry regarding "New Cancer Treatment Uses for Marketed Drug and Biological Products." Ex. 1118. According to the guideline, "[n]ew dosing regimens (including changes in the range of doses administered for approved indications and changes in the schedule of administration) can lead to improved effectiveness, tolerance, or convenience." *Id.* at 8.

Dr. Gelmon, an expert for Patent Owner, does not disagree. *See, e.g.*, Ex. 1104, 81:10–15 (testifying that when exploring an alternative dosing schedule, a clinician treating a cancer patient would look at efficacy, safety, and quality of life, "[a]nd one of the factors that comes in after those things is always [the] effect on the patient including convenience"). This approach had been borne out by data from clinical trials. For example, in an article Dr. Gelmon co-authored, the researchers studied bi-weekly paclitaxel as first-line treatment for metastatic breast cancer in a phase I-II trial. Ex. 1101, 1. Based on the results, they concluded that "[t]he good drug

tolerance, response rates, and convenience over weekly treatment suggest this may be a worthwhile regimen." *Id.*, *see also id.* at 3 ("The tolerance is similar to the weekly schedule but bi-weekly paclitaxel may be more convenient.").

Other prior art of record confirms that convenience was a motivating factor in exploiting new dosing regimens. Often, after a drug is introduced into clinical trials, an ordinary artisan would pursue different clinical strategies "in an attempt to identify the schedule with the optimal balance between clinical activity, safety, and convenience." Ex. 1017, 2 (discussing alternative dosing schedules for an anti-cancer drug in clinical trials for colorectal cancer, including a weekly schedule and an every-three-week schedule). When developing new dosing strategies for an anti-cancer drug, an ordinary artisan would take into account biology, pharmacology, and toxicity of the drug, as well as pragmatic factors, "including the regimen's cost, convenience, and ease of compliance. An additional pragmatic consideration is how well the schedule accommodates other drugs . . . that will be given with [the drug-at-issue]." *Id.* at 1–2.

Here, Slamon teaches the results of a combination therapy in which Herceptin "markedly increases anticancer activity" of chemotherapy in HER2 overexpressing metastatic breast cancer. Ex. 1005, 5. In that phase III clinical trial, chemotherapy was administered every three weeks, whereas Herceptin was administered weekly. *Id.* Herceptin Product Label teaches the same. Ex. 1008. In late 1998, the FDA approved Herceptin for treating patients with metastatic breast cancer whose tumors overexpress the HER2 protein. *Id.* at 1. As a first-line treatment, Herceptin is to be used in combination with paclitaxel. *Id.* Paclitaxel is administered once every three

weeks, and Herceptin is administered weekly. *Id.* Citing the Declaration of Dr. Ratain, Petitioner argues that an ordinary artisan would have recognized that weekly administration of trastuzumab would be inconvenient for patients, and would have sought to reduce the frequency of trastuzumab administration to that of paclitaxel in order to improve patient convenience. Pet. 27 (citing Ex. 1003 ¶¶ 89, 90; Ex. 1017, 1–4).

Patent Owner contends that "Dr. Ratain did not cite any evidence to support these assertions." PO Resp. 28. That, however, is not fatal to Petitioner's position, because an obviousness analysis "not only permits, but *requires*, consideration of common knowledge and common sense." *DyStar*, 464 F.3d at 1367. Furthermore, as discussed above, Petitioners have supported Dr. Ratain's opinions with citations to the prior art. Relying on this prior art, Petitioner argues that "a once every three week regimen 'has the added advantage of greater patient convenience, as it entails less frequent dosing than is required on a weekly schedule.'" Pet. 27 (citing Ex. 1017, 1–4). Having established that this knowledge was in the art, Dr. Ratain and Petitioner "could then properly rely . . . on a conclusion of obviousness from common knowledge and common sense of the person of ordinary skill in the art without any specific hint or suggestion in a particular reference." *DyStar*, 464 F.3d at 1368 (internal quotation marks omitted).

Patent Owner argues that at the time of the '196 patent, "treatment with weekly trastuzumab could ***improve*** patient quality of life in comparison to treatment with chemotherapy regimens alone, despite the weekly regimen." PO Resp. 27. Patent Owner misses the point. It is undisputed that weekly trastuzumab was known to be efficacious and thus, could improve quality of life for patients in comparison to chemotherapy treatment

alone. The proper comparison here though, is not weekly trastuzumab versus chemotherapy regimens, but every-three-week versus weekly trastuzumab.

Patent Owner also asserts that "[s]killed artisans at the time of the invention were motivated by trastuzumab's Phase III results to explore the weekly co-administration of trastuzumab and paclitaxel—not extending trastuzumab to match paclitaxel." PO Resp. 32. Even if this were true, it would not have dissuaded an ordinary artisan from pursuing a regimen to administer trastuzumab every three weeks. That is because, in an obviousness analysis, "the question is whether there is something in the prior art as a whole to suggest the *desirability*, and thus the obviousness, of making the combination," not whether the prior art suggests the combination as the most desirable combination available. *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (quotation marks and alteration omitted).

Moreover, the only paclitaxel dosing regimen approved by the FDA for treating breast cancer was, and still is, one administered every three weeks. Ex. 1117, 6. Even in the references Patent Owner points to, the ordinary artisan recognized that paclitaxel is effective on either an every-three-week or weekly schedule. Ex. 2036, 385. In addition, "a dose of 175 mg/m^2 by 3-h infusion every three weeks appears to be very reasonable in the treatment of advanced breast cancer. In combination therapy, this dose is often easily combined with other agents, producing manageable toxicity and not usually requiring hematopoietic growth factor support." *Id.* In the challenged '196 patent, paclitaxel is indeed combined with another agent, trastuzumab. Thus, even if an ordinary artisan had tried, or would have preferred, to decrease the dosing interval of paclitaxel to

weekly to match that of trastuzumab, we are persuaded that the artisan would also have been motivated to extend the dosing interval of trastuzumab to every three weeks to match that of paclitaxel.

Dosage Amount

Each of claims 1–3, 5, 7, 9–11, 13–15, and 17–23 requires, either explicitly or through dependency, "an initial dose of at least approximately 5 mg/kg of the anti-ErbB2 antibody," and "a plurality of subsequent doses of the antibody in an amount that is approximately the same or less than the initial dose." Ex. 1001, 56:63–67. In addition, each of claims 27 and 32 requires at least two or more subsequent doses that "are each from about 4 mg/kg to about 12 mg/kg," and each of claims 28 and 33 requires at least two or more subsequent doses that "are each from about 6 mg/kg to about 12 mg/kg." Patent Owner argues the prior art does not suggest the claimed loading and maintenance doses. PO Resp. 37–42. After reviewing the entire record, we agree that Petitioner has not met its burden in this regard.

As an initial matter, we are not persuaded by Patent Owner's contention that "the prior art's statements that weekly dosing of trastuzumab was 'optimal' (Ex. 1007 at 4) and 'warranted' (Ex. 1006 at 5) would have pointed a skilled artisan away from three-week dosing." PO Resp. 37. Prior art may not teach away even if a particular solution is not the preferred solution or is inferior to another solution. *In re Fulton*, 391 F.3d at 1200. Instead, a reference teaches away if it criticizes, discredits, or otherwise discourages the solution claimed. *Id.* at 1201.

Here, Dr. Gelmon, an expert for Patent Owner, testified that even after a drug is approved, an ordinary artisan would keep on optimizing the dosing regimen by "changing schedule or changing dosing." Ex. 1104, 64:16–65:4.

As explained above, an ordinary artisan would have been motivated to modify the dosing frequency in order to improve patient convenience. And an ordinary artisan would have adjusted the dosage amount accordingly. Thus, just because Watanabe and Baselga described the dosage amount of trastuzumab for a **weekly** dosing regimen as "optimal" or "warranted" would not have dissuaded an ordinary artisan from adjusting the dosage amount for an every-three-week dosing regimen.

We, however, find Petitioner has not met its burden in addressing the motivation for an ordinary artisan to modify the loading and the maintenance dosage as the challenged claims require. Petitioner asserts that "[w]hen modifying the dosing schedule, a POSA would have recognized the importance of maintaining dose intensity, *i.e.*, the amount of drug administered over a period of time." Pet. 28 (citing Ex. 1003 ¶ 91; Ex. 1024, 1–5; Ex. 1029). According to Petitioner,

> As shown in the table below, when accounting for dose intensity, Slamon's trastuzumab regimen calls for administration of a total of 8 mg/kg over the first three week period, followed by 6 mg/kg every three weeks thereafter:

week	1	2	3	4	5	6	7	8	9	10	11	12
weekly dose (mg/kg)	4	2	2	2	2	2	2	2	2	2	2	2
q 3 week dose (mg/kg)	8			6			6			6		

Id. (citing Ex. 1005, 5; Ex. 1003 ¶ 91).

Patent Owner argues that this approach is flawed because "Petitioner has failed to articulate ***why*** a skilled artisan would apply a chemotherapy

dosing strategy to trastuzumab, a targeted antibody treatment." PO Resp. 40 (citing Ex. 2028 ¶ 58). We find Patent Owner's argument persuasive.

When resorting to the principle of "dose intensity," Petitioner and Dr. Ratain initially relied on Exhibits 1024 and 1029. Pet. 28 (citing Exs. 1024, 1029); Ex. 1003 ¶ 91 (citing Ex. 1024, 1; Ex. 1029, 9–10). Both of those two references, however, describe the dosing of doxorubicin, a chemotherapy agent. *See* Exs. 1024, 1029. In response to Patent Owner's challenge that dose intensity is a chemotherapy dosing strategy, Petitioner contends that "POSAs understood that the concept of dose intensity was applicable to a variety of oncology drugs, including targeted antibodies." Reply 15 (citing Ex. 1123 ¶ 36; Ex. 1126, 4); Ex. 1123 ¶ 36 (citing Exs. 1111, 1121, 1124, 1125, 1126, 1130).

Among the references submitted with the Reply to support the applicability of the concept of dose intensity in this case, only Cheson[7] is directed to an antibody. Cheson teaches Mabthera, an anti-CD20 antibody, "demonstrated activity in intermediate-grade NHL, mantle cell lymphoma, lymphoplasmacytic NHL, and post-transplant lymphoproliferative disorder." Ex. 1126, 4. According to Cheson, "[l]ower response rates in small lymphocytic NHL and CLL, reflecting the low density of CD20 on the malignant cells, may be overcome by **increasing the dose intensity** of Mabthera." *Id.* (emphasis added). Read in this context, the phrase "dose intensity," as used in Cheson, appears to refer to the amount of a single dose, rather than "the amount of drug administered **over a period of time**," as that

[7] B. Cheson, *Future Perspective: Mabthera® in the Next Millennium*, Abstracts of Satellite Symposia, Mabthera Future Applications In CD20+ Malignancies (June 1, 1999) (Ex. 1126).

phrase is defined by Petitioner. *See* Pet. 28 (emphasis added). Thus, we agree with Patent Owner that Petitioner has not "cite[d] any evidence that skilled artisans would have applied the concept of 'dose intensity' to antibody treatment." *See* PO Resp. 40.

Petitioner contends that "[t]here was nothing in the prior art about trastuzumab that would have dissuaded a POSA from using the approach of keeping the same dosage amount over time," and "Patent Owner has failed to identify any alternative approach to dose selection that would have been appropriate." Reply 16–17. But it is not Patent Owner's burden to identify an "alternative approach." Rather, Petitioner must prove unpatentability by a preponderance of the evidence (*see* 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d)), and that burden never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

Patent Owner asserts that because the goal of antibody dosing is different from that of chemotherapy dosing, an approach that would be desired for chemotherapy may not be necessarily a desired one when administering an antibody. PO Resp. 5–7, 40–41; *see also* Ex. 2028 ¶ 58 ("In 1999, oncologists did not know enough about trastuzumab's mechanism of action to feel comfortable automatically applying principles from chemotherapy dosing to trastuzumab dosing.").

According to Patent Owner, at the time of the '196 patent invention, "the goal of most chemotherapy dosing was to kill the greatest number of tumor cells without causing life-threatening toxicity." *Id.* at 5 (citing Ex. 2028 ¶¶ 30–31). This was achieved, Patent Owner continues, by administering "the highest tolerable dose (typically resulting in a high peak

concentration) followed by sufficient time for recovery (and very low troughs)." *Id.* at 40 (citing Ex. 2028 ¶ 31). Dr. Ratain does not appear to disagree. Ex. 2026, 54:12–59:6.

In contrast, Patent Owner argues, "at the time of the invention, skilled artisans believed that trastuzumab should be dosed to maintain a minimum trough concentration over the entire dose interval." *Id.* at 40–41 (citing Ex. 2028 ¶ 36); *see also* Ex. 2027 ¶¶ 45–47 (Dr. Grass testifying that an ordinary artisan would "want to ensure that any alternative dosing regimen maintained therapeutic trough concentrations throughout the course of treatment"). The prior art confirms this. *See, e.g.*, Ex. 1006, 5 (setting 10 μg/ml as the target trough plasma concentration); Ex. 1007, 4 ("The pharmacokinetic goal was to achieve rhuMAb HER2 trough serum concentrations greater than 10 μg/mL, a level associated with optimal inhibition of cell growth in the preclinical model.").

As Petitioner's expert, Dr. Ratain, explains, for a drug at a given total cumulative dose, "as the intervals between doses increase, the fluctuation increases, with higher peaks and lower trough concentrations." Ex. 1003 ¶ 57. In view of the prior-art teaching that trastuzumab should be dosed to maintain a minimum trough concentration over the entire dose interval, this testimony by Dr. Ratain casts doubt as to whether an ordinary artisan would have applied the concept of dose intensity to an antibody treatment, such as trastuzumab.

Further compounding the complexity of the issue is the presence of shed antigen. At the relevant time, it was known that

> Detectable concentrations of the circulating extracellular domain ["ECD"] of the HER2 receptor (shed antigen) are found in the serum of some patients with HER2 overexpressing tumors.

> Determination of shed antigen in baseline serum samples revealed that 64% (286/447) of patients had detectable shed antigen, which ranged as high as 1880 ng/mL (median = 11 ng/mL). Patients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations.

Ex. 1008, 1. *See also* Ex. 1009, 8 ("[P]atients with any measurable shed HER2/*neu* ECD serum level, compared with patients without measurable circulating ECD, had lower mean trough rhuMAb HER2 concentrations . . . across all time points.").

Accordingly, considering (1) the lack of sufficient evidence from Petitioner to show that an ordinary artisan would have applied the concept of dose intensity to an antibody treatment; (2) the presence of shed antigen, which shows an inverse relationship to serum trough concentration; (3) the acknowledgment by Dr. Ratain that "there were not enough publications about trastuzumab . . . for those [dose-intensity] analyses to be presented" (Ex. 2026, 64:8–10); and (4) the testimony of Dr. Ratain that "the rationale that would lead [an ordinary artisan] to dose chemotherapy every three weeks would not apply to dosing trastuzumab every three weeks" (*id.* at 59:13–18), we conclude that Petitioner has not met its burden to demonstrate that an ordinary artisan would have had a reason to modify the loading and maintenance doses as claimed.

As a result, we conclude that Petitioner has not established by a preponderance of the evidence that claims 1–3, 5, 7, 9–11, 13–15, 17–23, 27, 28, 32, and 33 of the '196 patent are unpatentable. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("[T]here must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.").

Reasonable Expectation of Success

Claims 24, 25, 29, and 30 do not recite either the first or any subsequent dosage amount of trastuzumab. In addition, claims 26 and 31 recite the first dose and subsequent doses "are each from about 2 mg/kg to about 16 mg/kg." As explained above, we find an ordinary artisan would have been motivated to modify the dosing frequency of trastuzumab as claimed. In addition, both Slamon and Herceptin Product Label teach the loading dose of 4 mg/kg and the maintenance doses of 2 mg/kg. Ex. 1005, 5; Ex. 1008, 2. Even so, we find Petitioner has not established by a preponderance of the evidence that claims 24–26 and 29–31 of the '196 patent are unpatentable. This is because Petitioner's analysis of these claims hinges on the same argument of 8 mg/kg loading dose and 6 mg/kg maintenance doses Petitioner asserts in the other claims. For example, the substantive analysis of claim 24, in its entirety, appears in a single paragraph:

> As discussed above with respect to claim 1, it would have been obvious to administer trastuzumab on an every-three-week regimen as an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses. *See also* Ex. 1003 at ¶¶ 89–112. This regimen would have satisfied each and every element of claim 24 of the '196 patent, and therefore claim 24 is obvious for the same reasons as set forth with respect to claim 1. Ex. 1003 at ¶¶ 89–112, 115–118.

Pet. 43.

For claim 1, Petitioner analyzes the reasonable expectation of success with respect to efficacy based on an 8 mg/kg loading dose and 6 mg/kg maintenance doses. Pet. 32–38, 42. Because Petitioner has not met its burden to show that an ordinary artisan would have been motivated to modify the dosage amount in the first instance, its reasonable-expectation-

of-success arguments, premised upon efficacy associated with administering those modified dosage amounts over the every-three-week dosing frequency, also fail.

As a result, we conclude that Petitioner has not established by a preponderance of the evidence that claims 24–26 and 29–31 of the '196 patent are unpatentable.

Motions to Exclude

Petitioner's Motion to Exclude

Petitioner filed a Motion to Exclude Exhibits 2004, 2039, 2041, 2061, 2062, and 2067. Paper 51. Patent Owner does not oppose. Paper 55.

Petitioner's Motion to Exclude is granted.

Patent Owner's Motion to Exclude

Patent Owner filed a Motion to Exclude Exhibits 1100, 1102, 1105, 1107, 1111, 1121, 1124, 1125, 1126, 1128, and 1130, as well as paragraphs 22, 29, 35–37, 44, 53–58, and 60–73 of Exhibit 1123, i.e., the Reply Declaration of Dr. Ratain. Paper 53. Patent Owner filed an Identification of Improper New Reply Materials, challenging the same exhibits. Paper 52.

As a preliminary matter, a motion to exclude is not a proper vehicle for addressing "arguments or evidence that a party believes exceeds the proper scope of reply." Trial Practice Guide Update (August 13, 2018),[8] 16. Instead, "[i]f a party believes that a brief filed by the opposing party raises new issues, is accompanied by belatedly presented evidence, or otherwise exceeds the proper scope of reply . . . it may request authorization to file a

[8] Available at https://www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf.

motion to strike." *Id.* at 17. "In most cases, the Board is capable of identifying new issues or belatedly presented evidence when weighing the evidence at the close of trial, and disregarding any new issues or belatedly presented evidence that exceeds the proper scope of reply or sur-reply." *Id.*

Nevertheless, to the extent necessary, we treat Patent Owner's Motion to Exclude and Identification of Improper New Reply Materials as a motion to strike. Patent Owner argues that in paragraphs 35–37 of Ratain Reply Declaration (Ex. 1123), Dr. Ratain relies on Exhibits 1111, 1121, 1124, 1125, 1126, and 1130, and introduces new arguments related to the alleged use of the concept of dose intensity in the development of new dosing regimens. Paper 53, 1, 8–11. According to Patent Owner, these six new exhibits, as well as paragraphs 35–37 of Exhibit 1123 "should be excluded as improper reply evidence used to fill a gap in Petitioner's *prima facie* case." *Id.* at 1. We disagree.

"Evidence admitted in rebuttal to respond to the patent owner's criticisms will commonly confirm the prima facie case. That does not make it necessary to the prima facie case." *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1078 (Fed. Cir. 2015). Such is the case here.

In the Petition, citing the Declaration of Dr. Ratain, Petitioner argues that "[w]hen modifying the dosing schedule, a POSA would have recognized the importance of maintaining dose intensity, *i.e.*, the amount of drug administered over a period of time." Pet. 28 (citing Ex. 1003 ¶ 91; Ex. 1024, 1–5; Ex. 1029). In its Response, citing the Declaration of Dr. Gelmon, Patent Owner counters that an ordinary artisan would not have relied on the concept of dose intensity because it is a chemotherapy concept,

whereas trastuzumab, an antibody, works differently from a chemotherapy agent. PO Resp. 40–41 (citing Ex. 2028 ¶¶ 31, 36, 58).

In his Reply Declaration, Dr. Ratain relies on the challenged exhibits to support his opinion that the concept of dose intensity "is applicable to other therapeutic areas and contexts," including antibodies. Ex. 1123 ¶¶ 35–37 (citing Ex. 1111, 1121, 1124, 1125, 1126, 1130). Thus, paragraphs 35–37 in the Ratain Reply Declaration, as well as the exhibits relied on therein, respond directly to Patent Owner's criticism of the dose-intensity principle. With such evidence, Petitioner intends to confirm, not to modify, its prima facie case. Although we find the new exhibits unpersuasive, that does not render them improper reply evidence. We, therefore, deny Patent Owner's Motion to Exclude regarding paragraphs 35–37 of Exhibit 1123, and Exhibits 1111, 1121, 1124, 1125, 1126, and 1130.

Patent Owner also seeks to exclude Exhibits 1100, 1102, 1105, 1107, and 1128, as well as paragraphs 22, 29, 44, 53–58, and 60–73 of Ratain Reply Declaration (Ex. 1123). Paper 53, 1–2, 5–8, 11–14. We do not rely on any of these exhibits in rendering this Decision. Thus, we dismiss this aspect of Patent Owner's Motion to Exclude as moot.

CONCLUSION

After reviewing the entire record and weighing evidence offered by both parties, we determine that although Petitioner has shown that an ordinary artisan would have modified the dosing frequency of trastuzumab from weekly to every-three-week, Petitioner has not met its burden to show that an ordinary artisan would have modified the dosage amounts as proposed. In addition, Petitioner has not met its burden to show a reasonable expectation of success because those arguments are solely based on its

proposed loading and maintenance dosage amounts. As a result, Petitioner has not shown, by a preponderance of the evidence, that claims 1–3, 5, 7, 9–11, 13–15, and 17–33 of the '196 patent would have been obvious over the combination of Slamon, Watanabe, Baselga, and Pegram.

ORDER

Accordingly, it is

ORDERED that claims 1–3, 5, 7, 9–11, 13–15, and 17–33 of the '196 patent have not been shown to be unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude is granted;

FURTHER ORDERED that Patent Owner's Motion to Exclude is denied-in-part and dismissed-in-part; and

FURTHER ORDERED that, because this is a final written decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

PETITIONER:

Cynthia Hardman
Elizabeth J. Holland
Robert Cerwinski
Daniel P. Margolis
GOODWIN PROCTER LLP
chardman@goodwinlaw.com
eholland@goodwinlaw.com
rcerwinski@goodwinlaw.com
dmargolis@goodwinlaw.com

PATENT OWNER:

David L. Cavanaugh
Lauren V. Blakely
Vera Shmidt
Robert J. Gunther, Jr.
Lisa J. Pirozzolo
Kevin S. Prussia
Andrew J. Danford
WILMER CUTLER PICKERING HALE AND DORR LLP
david.cavanaugh@wilmerhale.com
lauren.blakely@wilmerhale.com
vera.shmidt@wilmerhale.com
robert.gunther@wilmerhale.com
lisa.pirozzolo@wilmerhale.com
kevin.prussia@wilmerhale.com
andrew.danford@wilmerhale.com

Adam R. Brausa
Daralyn J. Durie
DURIE TANGRI LLP
abrausa@durietangri.com
ddurie@durietangri.com