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BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner

v.

GENENTECH, INC.
Patent Owner

Case No.: IPR2017-01139

Patent No. 6,627,196

PETITION FOR *INTER PARTES* REVIEW U.S. PATENT NO. 6,627,196 PURSUANT TO 35 U.S.C. §§ 311–319 AND 37 C.F.R. § 42

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I. INTRODUCTION

Pursuant to 35 U.S.C. §§ 311–319 and 37 C.F.R. § 42, Celltrion, Inc. ("Petitioner" or "Celltrion") petitions for *Inter Partes* Review ("IPR") of claims 1-3, 5, 7, 9-11, 13-15, and 17-33 of U.S. Patent No. 6,627,196 ("the '196 patent," Ex. 1001). This Petition and supporting exhibits demonstrate that there is a reasonable likelihood that these claims are unpatentable because the subject matter of each claim would have been obvious to a person of ordinary skill in the art ("POSA").

All of the claims recite a method for treating cancer by administering trastuzumab. More than one year before the earliest claimed priority date, the use of trastuzumab was a known, safe, and effective cancer treatment. The only difference between the prior art and the challenged claims is the particular dosing regimen required by the claims. While the prior art regimen involved weekly administration, the claims require that doses be separated by at least two weeks. Notably, there is no indication anywhere in the specification that the inventors had actually attempted to administer a bi-weekly (or more) dosing regimen to patients at a less than weekly frequency prior to filing the application. The specification provides only a prophetic example of a proposed clinical trial for the treatment of metastatic breast cancer, involving administration of paclitaxel (a chemotherapeutic agent) and trastuzumab as an 8 mg/kg loading dose, followed by

6 mg/kg maintenance doses every three weeks. Ex. 1001 at 46:60-48:31. Nevertheless, the inventors assert that this regimen was expected to be effective.

As will be discussed below, more than one year before the '196 patent was filed, a person of ordinary skill in the art would have been motivated to administer trastuzumab at a reduced frequency in order to align its dosing schedule with that of other, less frequently-administered chemotherapeutic drugs, thereby improving patient convenience. Sufficient pharmacokinetic and pharmacodynamic data—including the drug's half-life and target efficacious trough serum concentration—had been reported in the prior art to allow a POSA to predict that such a trastuzumab dosing regimen would likely be efficacious. Ex. 1003 at ¶¶ 79, 88, 96, 97, 102,103, 104, 108; Ex. 1007; Ex. 1009.

The challenged claims are drawn exclusively to methods of using a *known* drug to treat a *known* medical condition, for which the drug was already *known* to be effective. Neither the discovery of the desirability of maintaining a particular efficacious serum trough concentration, the target efficacious serum trough concentration itself, nor a regimen that attains that target concentration early, can be attributed to the inventors.

Accordingly, the claimed dosing regimen was nothing more than an obvious variation of the prior art regimen, and the '196 patent claims should be cancelled as obvious.

II. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

A. Real Party-in-Interest

The real parties in interest are Celltrion, Inc., Celltrion Healthcare Co. Ltd., and Teva Pharmaceuticals International GmbH.

B. Related Matters

In IPR2017-00804, Hospira Inc., a third party, has asserted that claims 1-3, 5, 7, 9-11, and 17-33 of the ’196 patent are obvious based on grounds that are different than those in this Petition.

Petitioner is concurrently filing a petition for IPR of Genentech’s U.S. Patent No. 7,371,379 (“the ’379 patent”), which is a divisional of the ’196 patent. Hospira has also filed IPR2017-00805 directed to claims of the ’379 patent.

C. Lead and Back-up Counsel and Service Information:

Lead counsel is Cynthia Lambert Hardman, Reg. No. 53,179. Backup counsel are Elaine Herrmann Blais (to seek *pro hac vice* admission) and Robert V. Cerwinski (to seek *pro hac vice* admission). Counsel are with Goodwin Procter LLP. Ms. Hardman and Mr. Cerwinski are at 620 Eighth Avenue, New York, NY 10018, tel. 212-813-8800, fax 212-355-3333. Ms. Blais is at 100 Northern Avenue, Boston, MA 02210, tel. 617-570-1000, fax 617-523-1231. Email contact for counsel is chardman@goodwinlaw.com, eblais@goodwinlaw.com, and rcerwinski@goodwinlaw.com.

D. Service Information

Please direct all correspondence to counsel at the contact information above. Petitioner consents to service by electronic mail at chardman@goodwinlaw.com, eblais@goodwinlaw.com, and rcerwinski@goodwinlaw.com.

III. FEES

The Commissioner is hereby authorized to charge all fees due in connection with this matter to Attorney Deposit Account 506989.

IV. GROUNDS FOR STANDING UNDER 37 C.F.R. § 42.104(a)

Petitioner certifies that the patent for which review is sought is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this petition.

V. IDENTIFICATION OF CHALLENGE AND PRECISE RELIEF REQUESTED

Celltrion respectfully requests *inter partes* review and cancellation of claims 1-3, 5, 7, 9- 11, 13-15, and 17-33 ("the challenged claims") as obvious under 35 U.S.C. § 103 over Slamon (Ex. 1005) and Watanabe (Ex. 1006), in view of Baselga (Ex. 1007) and Pegram (Ex. 1009). This Petition is supported by the Declaration of Mark J. Ratain, M.D. (Ex. 1003).

The petition and supporting declaration show that there is at least a reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims. *See* 35 U.S.C. § 314(a).

VI. OVERVIEW OF THE '196 PATENT

The '196 patent issued on September 30, 2003, from U.S. Patent Application No. 09/648,067 ("the '067 application) filed on August 25, 2000. (Ex. 1001, '196 Patent.) The '067 application claims priority from Provisional Application No. 60/213,822 ("the '822 application) filed June 23, 2000 and Provisional Application No. 60/151,018 ("the '018 application) filed August 27, 1999.

For purposes of this IPR only, Petitioner will assume that the '196 patent claims are entitled to the earliest possible priority date, which is the August 27, 1999 filing date of the '018 application. Therefore, any printed publication dated prior to August 27, 1999 qualifies as prior art under 35 U.S.C. § 102(a), and any printed publication dated prior to August 27, 1998 qualifies as prior art under 35 U.S.C. § 102(b).

A. Claims of the '196 Patent

The '196 patent, entitled "Dosages for Treatment with Anti-ErbB2 Antibodies," issued on September 30, 2003, and is assigned to Genentech, Inc. ("Genentech" or "Patent Owner"). The challenged claims of the '196 patent read:

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.

2. The method of claim 1, wherein the initial dose is at least approximately 6 mg/kg.

3. The method of claim 2, wherein the initial dose is at least approximately 8 mg/kg.

5. The method of claim 1, wherein the subsequent doses are separated in time from each other by at least three weeks

7. The method of claim 1, wherein the initial dose is administered by intravenous injection, wherein at least two subsequent doses are administered, and wherein each subsequent dose is administered

by a method selected from the group consisting of intravenous injection and subcutaneous injection.

9. The method of claim 1, wherein the initial dose is selected from the group consisting of approximately 6 mg/kg, 8 mg/kg, or 12 mg/kg, wherein the plurality of subsequent doses are at least approximately 2 mg/kg.

10. The method of claim 9, wherein the plurality of subsequent doses are separated in time from each other by at least three weeks.

11. The method of claim 10, wherein the initial dose is approximately 8 mg/kg, and wherein at least one subsequent dose is approximately 6 mg/kg.

13. The method of claim 9, wherein the initial dose is approximately 8 mg/kg, and wherein at least one subsequent dose is approximately 8 mg/kg.

14. The method of claim 9, wherein the initial dose is approximately 8 mg/kg, wherein at least one subsequent dose is 8 mg/kg, and wherein administration of the initial dose and subsequent doses are separated in time by at least 2 weeks.

15. The method of claim 14, wherein the initial dose and subsequent doses are separated in time by at least 3 weeks

17. The method of claim 1, wherein said cancer is selected from the group consisting of breast cancer, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, colon cancer, colorectal cancer, endometrial carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer.

18. The method of claim 17, wherein said cancer is breast cancer.

19. The method of claim 18, wherein said cancer is metastatic breast carcinoma.

20. The method of claim 1, wherein said antibody binds to the extracellular domain of the ErbB2 receptor.

21. The method of claim 20, wherein said antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence.

22. The method of claim 21, wherein said antibody is a humanized 4D5 anti-ErbB2 antibody.

23. The method of claim 1, wherein efficacy is measured by determining the time to disease progression or the response rate.

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.

25. The method of claim 24, wherein the first dose and a first subsequent dose are separated from each other in time by at least about three weeks.

26. The method of claim 24, wherein the first dose and subsequent doses are each from about 2 mg/kg to about 16 mg/kg.

27. The method of claim 26, wherein the first dose and subsequent doses are each from about 4 mg/kg to about 12 mg/kg.

28. The method of claim 27, wherein the first dose and subsequent doses are each from about 6 mg/kg to about 12 mg/kg.

29. The method of claim 24, wherein from about two to about ten subsequent doses of the antibody are administered to the patient.

30. The method of claim 24, wherein the subsequent doses are separated in time from each other by at least about three weeks.

31. The method of claim 24, wherein the two or more subsequent doses are each from about 2 mg/kg to about 16 mg/kg.

32. The method of claim 24, wherein the two or more subsequent doses are each from about 4 mg/kg to about 12 mg/kg.

33. The method of claim 24, wherein the two or more subsequent doses are each from about 6 mg/kg to about 12 mg/kg.

B. The '196 Patent Specification

The '196 patent is directed to methods of treating cancers characterized by the overexpression of ErbB2 by administering an anti-ErbB2 antibody. Ex. 1001 at Abstract.

The specification describes the alleged invention as a method of treating cancer patients who overexpress ErbB2 with an initial anti-ErbB2 antibody dose, followed by subsequent doses that are less than or equal to the initial dose, and explains that this "greater front loading[] is more efficacious than conventional treatments".[1] Ex. 1001 at Abstract, 4:21-34. The specific dosing amounts and

[1] It is unclear what "conventional treatments" the specification is referring to, since several prior art trastuzumab dosing regimens already included an initial loading dose followed by subsequent maintenance doses less than the initial dose. Ex. 1003 at ¶¶ 76, 81, 89; *see, e.g.*, Ex. 1005 at 5; Ex. 1007 at 3; Ex. 1009 at 2.

intervals are intended to maintain the trough serum concentration above an efficacious amount.[2] Ex. 1001 at 4:61-65; Ex. 1003 at ¶ 159.

The specification acknowledges that HERCEPTIN® is an anti-ErbB2 antibody, known in the prior art to be clinically active against ErbB2-overexpressing metastatic breast cancer.[3] Ex. 1001 at 3:54-60; Ex. 1003 at ¶ 24. The specification also acknowledges that the prior art trastuzumab dosing regimen consisted of a 4 mg/kg loading dose, followed by weekly 2 mg/kg maintenance doses. Ex. 1001 at 3:61-65; Ex. 1003 at ¶ 24. It further describes this regimen as attaining a mean serum trough concentration of 25.0 μg/ml immediately following the 4 mg/kg loading dose, and maintaining that level throughout treatment with the 2 mg/kg maintenance doses. Ex. 1001 at Table 2.

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[2] The trough serum concentration is the drug plasma concentration immediately before delivery of the next dose, when the concentration is at its lowest. *See* Ex. 1001 at 18:33-36. The prior art disclosed the importance of maintaining trough serum concentrations above an efficacious amount. Ex. 1003 at ¶¶ 84, 96; *see*, *e.g.*, Ex. 1006 at 5; Ex. 1007 at 4; Ex. 1009 at 3.

[3] HERCEPTIN® is the brand name of trastuzumab. Ex. 1008 at 1; HERCEPTIN® is also referred to as recombinant humanized anti-$p185^{HER2}$ monoclonal antibody, or rhuMAb HER2. Ex. 1016 at 4.

The specification further discloses that the anti-ErbB2 antibody can be administered in combination with a chemotherapeutic agent, which the inventors assert "markedly increases the clinical benefit." Ex. 1001 at 38:23-26.

The specification provides a prophetic example of a proposed clinical trial for the treatment of metastatic breast cancer, involving administration of paclitaxel (a chemotherapeutic agent) and trastuzumab as an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses every three weeks. Ex. 1001 at 46:5-48:14. The specification states that this regimen is expected to be effective because "[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." Ex. 1001 at 46:12-16, 48:1-4.[4]

[4] The same minimum efficacious trastuzumab serum concentration for trastuzumab was known in the prior art. *See*, *e.g.*, Ex. 1006 ("10 μg/ml was set as the target trough plasma concentration"); Ex. 1007 at 4 ("The pharmacokinetic goal was to achieve rhuMAb HER2 trough serum concentrations greater than 10 μg/mL"); Ex. 1009 at 3 ("These 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.").

C. Prosecution History of the ’196 Patent

During prosecution of the ’067 application, the Examiner rejected the pending claims, which each required at least two weeks between doses, as obvious over a number of prior art references that disclosed weekly administration of trastuzumab for the treatment of cancer. Ex. 1002 at 218 (citing Hudziak (Ex. 1012), Goldenberg (Ex. 1013), Watanabe (Ex. 1006), Baselga (Ex. 1007), and Vogel (Ex. 1015). The Examiner further explained that the prior art taught that doses higher than 4 mg/kg are tolerated and provide higher serum trough levels. Ex. 1002 at 223-224.

The applicants responded that the prior art taught away from the claimed invention because (1) a POSA would not have wanted to increase the interval between doses beyond trastuzumab’s known half-life (*i.e.*, either 5.8, 8.3, or 9.1 days) “for fear that insufficient levels of drug would remain in the patient to treat cancer;” and (2) Watanabe (Ex. 1006) recommended further studies with a 2 mg/kg or 4 mg/kg weekly dose, not a higher, less frequent dose. Ex. 1002 at 223-224.

The Examiner then allowed the claims with minimal explanation, stating only that “the prior art fails to teach or fairly suggest the recited minimum dosages or dosing schedules where the subsequent doses are separated from each other by at least two weeks.” Ex. 1002 at 246.

VII. LEVEL OF ORDINARY SKILL IN THE ART

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. Ex. 1003 at ¶ 44. 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. Ex. 1003 at ¶ 44.

VIII. CONSTRUCTION OF CLAIM TERMS

Because the '196 patent has not yet expired, and will not expire during the pendency of this proceeding, the challenged claims should be given their broadest reasonable construction in light of the patent specification. 37 C.F.R. § 42.100(b); *see also Cuozzo Speed Techs. LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016).

The '196 patent specification defines several terms that are recited in the claims. For purposes of this IPR only, Petitioner adopts the following constructions of each respective term:

"ErbB2" is defined "to refer to the human protein," and "the terms 'Her2', 'ErbB2', 'c-Erb-B2' are used interchangeably." Ex. 1001 at 9:45-49.

"Epitope 4D5" is defined as "the extracellular domain of ErbB2 to which the antibody 4D5 (ATCC CRL 10463) binds." Ex. 1001 at 9:54-57.

"Antibody" is defined "in the broadest sense and specifically covers intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g. bispecific antibodies) formed from at least two intact antibodies, and antibody fragments so long as they exhibit the desired biological activity." Ex. 1001 at 12:66-13:4.

"Treatment" is defined as "both therapeutic treatment and prophylactic or preventative measures." Ex. 1001 at 14:60-61.

"Cancer" is defined as "the physiological condition in mammals that is typically characterized by unregulated cell growth." Ex. 1001 at 15:24-26.

For purposes of the present petition only, claim terms not expressly defined in the specification are given their plain and ordinary meaning to the person of ordinary skill in the art. Also for purposes of the present petition only, Petitioner will assume that the claim preambles are limiting.

Petitioner's positions on claim construction should not be construed as an assertion regarding the appropriate claim scope in other adjudicative forums, where a different claim interpretation standard may apply.

IX. SUMMARY OF THE PRIOR ART

A. State of the Art

Well before the priority date of the '196 patent, doctors and scientists recognized that the HER2 gene is overexpressed in 25–30% of human breast

cancers. Ex. 1016 at 4; Ex. 1007 at 3; Ex. 1003 at ¶ 75. It was also known that the HER2 gene encodes a 185 kd transmembrane glycoprotein receptor $p185^{HER2}$ that has a partial homology with the epidermal growth factor receptor, and that antibodies directed at $p185^{HER2}$ can inhibit the growth of tumors and transformed cells that express high levels of this receptor. Ex. 1016 at 4; Ex. 1007 at 3; Ex. 1003 at ¶ 75.

Preclinical studies had demonstrated that recombinant humanized monoclonal antibody (rhuMAb) HER2 ("trastuzumab" or "Herceptin") has a high affinity for $p185^{HER2}$ and inhibits growth of breast cancer cells that overexpress HER2. Ex. 1016 at 4; Ex. 1007 at 3; Ex. 1003 at ¶ 76. These preclinical studies indicated that trastuzumab would likely be a useful treatment for breast cancer, and established a target efficacious serum trough concentration for trastuzumab of 10 µg/ml, which was expected to provide efficacy in human patients. Ex. 1006 at 5; Ex. 1007 at 4. The same 10 µg/ml target efficacious serum trough concentration referred to by the inventors as "preferable" was widely recognized throughout the prior art as such, and had been identified as the goal in designing a multitude of prior art trastuzumab dosing regimens. *Compare* Ex. 1001 at 44:16-19 ("Preferably, a target trough serum concentration of HERCEPTIN anti-ErbB2 antibody of approximately 10-20 µg/ml is achieved (averaged for all patients in the treatment group)") *with* Ex. 1009 at 3 ("These 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."); Ex. 1007 at 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."); Ex. 1006 at 5 ("Based on the results of in vitro and in vivo preclinical studies, 10 µg/ml was set as the target trough plasma concentration.").

In view of the potential utility of trastuzumab for the treatment of ErbB2-overexpressing cancers, its safety and efficacy were studied in a number of clinical trials. *See*, *e.g.*, Ex. 1005 at 5; Ex. 1006 at 5; Ex. 1007 at 3; Ex. 1008 at 1; Ex. 1009 at 3. Several different dosing regimens were tested, targeting the 10 µg/ml minimum trough serum concentration. Ex. 1006 at 5; Ex. 1007 at 4; Ex. 1009 at 3. These studies measured and reported the pharmacokinetic properties of trastuzumab. It was revealed that the pharmacokinetic behavior of trastuzumab was predictable, and regimens capable of maintaining the target efficacious trough serum concentration were identified. Ex. 1009 at 3. Furthermore, those regimens that maintained the target trough serum concentration of at least 10 µg/ml elicited a positive clinical response. Ex. 1006 at 5; Ex. 1007 at 5-8; Ex. 1009 at 6-8.

These clinical studies also established that trastuzumab was very tolerable, with only minimal toxicity at doses as high as 8 mg/kg, administered weekly. Ex.

1023 at 3 ("Phase I studies conducted at UCLA show that rhuMAb HER-2 has no substantial toxicity at any dose level."); Ex. 1009 at 3 ("In addition, administration of this anti-HER2/neu antibody was safe; the only toxicity was low-grade fever that occurred with the first infusion and/or pain at the site of known tumor deposits in a minority of patients.")[5]; Ex. 1006 at 5 (reporting only one in six patients experienced severe generalized bone pain at the 8 mg/kg dose level, with the remaining five patients experiencing no adverse events).[6] Thus, the prior art established pharmacokinetic parameters predictive of trastuzumab's efficacy, as well as a range of dosage amounts that could be safely administered.

B. Scope and Content of the Prior Art

(i) Slamon (Ex. 1005)

Slamon is an abstract included in the Proceedings of the Thirty Fourth Annual Meeting of the American Society of Clinical Oncology ("ASCO"), May

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[5] The trastuzumab Phase I studies involved doses as high as 500 mg weekly, which is 8 mg/kg assuming an average 62.5 kg patient. Ex. 1003 at ¶¶ 70-72, 92; *see* Ex. 1008 at 1 ("Short duration intravenous infusions of 10 to 500 mg once weekly demonstrated dose-dependent pharmacokinetics."); Ex. 1003 at ¶ 94 (A typical patient with metastatic breast cancer weighs approximately 62.5 kg.)

[6] *Compare* Ex. 1006 *with* Ex. 1005 (reporting a 66% rate of severe adverse events for patients on chemotherapy for the treatment of metastatic breast cancer).

16-19, 1998. *See*, Ex. 1005, Slamon et al., *Annual Meeting of the American Society of Clinical Oncology*, 17 AM. SOC'Y CLIN. ONC. *377 at 98a (1998). These Proceedings were published in a fully searchable format, first to ASCO members on April 15, 1998, and then to the general public upon conclusion of the meeting, May 19, 1998. Ex. 1003 at ¶ 63; Ex. 1005 at 3. In 1998 and as is true today, the ASCO annual meeting is the premiere meeting in the field of oncology, and covers the latest in breakthrough treatments and cancer care information, and was and is well-attended by persons of ordinary skill in the art. Ex. 1003 at ¶ 63. Dr. Ratain attended the 1998 annual meeting, and confirms that the Proceedings of the Thirty Fourth Annual Meeting of the American Society of Clinical Oncology were disseminated to POSAs at the meeting. Ex. 1003 at ¶ 63. Accordingly, because Slamon was available to interested POSAs more than one year prior to the priority date of the '196 patent, it is a printed publication under 35 U.S.C. § 102(b). *See In re Klopfenstein*, 380 F.3d 1345, 1348 (Fed. Cir. 2004).

Slamon discloses the results of a phase III clinical trial of trastuzumab in combination with chemotherapy for the treatment of ErbB2-overexpressing metastatic breast cancer. Ex. 1005 at 5; Ex. 1003 at ¶ 64. The clinical trial studied the effects of administering trastuzumab with two different chemotherapy regimens: (1) doxorubicin-cyclophosphamide, and (2) paclitaxel, as compared to the chemotherapy alone. Ex. 1005 at 5; Ex. 1003 at ¶ 65. Each of the

chemotherapeutic agents was administered once every three weeks, while trastuzumab was administered as a 4 mg/kg loading dose, followed by weekly maintenance doses of 2 mg/kg. Ex. 1005 at 5; Ex. 1003 at ¶ 65.

Slamon reported that the "addition of Herceptin to CRx [chemotherapy] markedly increases clinical benefit" without increase in overall severe adverse events. *See*, Ex. 1005 at 5, Table; Ex. 1003 at ¶¶ 66-67.

(ii) **Watanabe (Ex. 1006)**

Watanabe is also included in the Proceedings of the Thirty Fourth Annual Meeting of the American Society of Clinical Oncology, May 16-19, 1998. *See*, Ex. 1006, Watanabe et al., *Annual Meeting of the American Society of Clinical Oncology*, 17 Am. Soc'y Clin. Onc. *702 at 182a (1998). As explained above, these Proceedings were published in a fully searchable format, first to members of the American Society of Clinical Oncology on April 15, 1998, and then to the general public upon conclusion of the meeting, May 19, 1998. Ex. 1003 at ¶ 68; Ex. 1006 at 3. Further, as explained above, Dr. Ratain attended the 1998 ASCO annual meeting, and received a copy of the Proceedings at that meeting. Ex. 1003 at ¶ 68. Accordingly, because Watanabe was available to interested POSAs more than one year prior to the priority date of the '196 patent, it is a printed publication under 35 U.S.C. § 102(b). *Klopfenstein*, 380 F.3d at 1348.

Watanabe discloses the results of a phase I dose escalation study of trastuzumab. Ex. 1006 at 5; Ex. 1003 at ¶ 69. Watanabe discloses a target efficacious trough plasma concentration of 10 µg/ml, and studied the effect and pharmacokinetics of four different dosage amounts administered to patients: 1 mg/kg, 2 mg/kg, 4 mg/kg, and 8 mg/kg. Ex. 1006 at 5; Ex. 1003 at ¶ 70. Each of these dosing regimens involved an initial dose, followed in three weeks by a series of 9 weekly doses of the initial dosage amount. Ex. 1006 at 5; Ex. 1003 at ¶ 70.

Watanabe found that when administered weekly, the 2 mg/kg, 4 mg/kg, and 8 mg/kg doses each achieved the target trough concentration and were associated with a positive tumor response, whereas the 1 mg/kg dose did not achieve the target trough concentration and displayed no tumor response. Ex. 1006 at 5; Ex. 1003 at ¶ 71. Watanabe also reported that some patients exhibited moderate or severe fevers and/or nausea and vomiting, and one patient receiving 8 mg/kg weekly suffered from severer generalized bone pain. Ex. 1006 at 5; Ex. 1003 at ¶ 72. Watanabe indicated that the weekly 2 mg/kg and 4 mg/kg doses warranted study in further clinical trials. Ex. 1006 at 5; Ex. 1003 at ¶ 71.

(iii) **Baselga (Ex. 1007)**

Baselga published in 1996, more than one year prior to the earliest claimed priority date of the ’196 patent. Baselga et al., Phase II Study of Weekly Intravenous Recombinant Humanized Anti-$p^{185HER2}$ Monoclonal Antibody in

Patients With HER2/*neu*-Overexpressing Metastatic Breast Cancer, 14 J. AM. ONC., 737 (1996). Ex. 1003 at ¶ 73. Baselga is therefore prior art to the '196 patent under 35 U.S.C. § 102(b).

Baselga reported the results of a phase II clinical trial of trastuzumab. Ex. 1007 at 4; Ex. 1003 at ¶ 74. Baselga explained that in preclinical studies, trastuzumab inhibited growth of human breast cancer cells that overexpress HER2. Ex. 1007 at 3; Ex. 1003 at ¶ 75. Baselga also explained that optimal inhibition occurred with serum target concentrations of greater than 10 µg/ml. Ex. 1007 at 4; Ex. 1003 at ¶ 76. Baselga therefore administered trastuzumab to patients with metastatic breast carcinomas that overexpressed HER2 using a loading dose of 250 mg, followed by weekly doses of 100 mg, with the goal of attaining trough concentrations of at least 10 µg/ml. Ex. 1007 at 3, 5; Ex. 1003 at ¶ 76.

Baselga reported that more than 90% of the patients had serum trough concentrations above the targeted level, and that the regimen provided adequate serum concentrations in the vast majority of patients. Ex. 1007 at 5; Ex. 1003 at ¶ 77. Baselga further reported that several of the patients had a positive response to the regimen, which was "remarkably well tolerated" (only eleven total adverse events, one of which was severe, were observed), and concluded that trastuzumab may be useful in the treatment of breast cancer. Ex. 1007 at 5, 9; Ex. 1003 at ¶ 78.

Baselga reported that trastuzumab had a mean serum half-life of 8.3 days. Ex. 1007 at 5; Ex. 1003 at ¶ 79. Representative pharmacokinetic profiles were reported for both typical and high circulating ECD^{HER2} patients. Ex. 1007 at 5-6; Ex. 1003 at ¶ 79.

(iv) **Pegram (Ex. 1009)**

Pegram published in August 1998 in the 16th Volume, Part 8, of the Journal of Clinical Oncology. Pegram et al., Phase II Study of Receptor-Enhanced Chemosensitivity Using Recombinant Humanized Anti-$p^{185HER2}$ Monoclonal Antibody Plus Cisplatin in Patients With HER2/*neu*-Overexpressing Metastatic Breast Cancer Refractory To Chemotherapy Treatment, 16 J. AM. ONC., 2659 (1998), Ex. 1009 at title (received, indexed, and catalogued as of August 10, 1998); Ex. 1003 at ¶ 80. Pegram is prior art to the '196 patent under 35 U.S.C. § 102(b).

Pegram reported the results of a Phase II clinical trial of trastuzumab in combination with the chemotherapeutic drug, cisplatin, for the treatment of patients with HER2-overexpressing metastatic breast cancer. Ex. 1009 at 2; Ex. 1003 at ¶ 81. Trastuzumab was administered as a 250 mg loading dose, followed by 100 mg weekly maintenance doses, for a total of eight doses, while cisplatin was administered three times at four week intervals. Ex. 1009 at 3; Ex. 1003 at ¶ 81.

Pegram reported that a synergistic effect had previously been demonstrated in preclinical trials between trastuzumab and cisplatin, suggesting potential clinical applications for the combination. Ex. 1009 at 3; Ex. 1003 at ¶ 82. Pegram reported that the response rate for the combination of trastuzumab with cisplatin was indeed higher than previous studies of either drug by itself. Ex.1009 at 10-11 (reporting a 24% response rate for the combination treatment, while treatment with trastuzumab and cisplatin individually had resulted in response rates of 12% and 7%, respectively); Ex. 1003 at ¶ 82. Pegram further suggested that a similar effect is expected for trastuzumab in combination with other chemotherapeutic agents, such as paclitaxel and doxorubicin-cyclophosphamide. Ex. 1009 at 12; Ex. 1003 at ¶ 82.

Pegram also reported that the toxicity of the combination of trastuzumab with cisplatin was similar to that observed with chemotherapy alone. Ex. 1009 at 11; Ex. 1003 at ¶ 83. Severe toxicities potentially attributable to trastuzumab were characterized as "infrequent," with only 6 of 39 patients reporting a grade III or IV toxicity possibly related to trastuzumab. Ex. 1009 at 6; Ex. 1003 at ¶ 83.

Pegram reiterated the desirability and practicability of maintaining trough serum concentrations above 10 μg/ml, stating that prior Phase I 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." Ex. 1009 at 3; Ex. 1003 at ¶ 84. Pegram then compared the pharmacokinetic data for its trastuzumab/cisplatin regimen with the pharmacokinetic data from the Baselga study, which, as described above, had involved administration of trastuzumab alone. Ex. 1009 at 8; Ex. 1003 at ¶ 84. Based on this comparison, Pegram concludes that co-administration with chemotherapy had no measureable effect on trastuzumab's pharmacokinetics. Ex. 1009 at 11; Ex. 1003 at ¶ 84.

X. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

Pursuant to 37 C.F.R. §42.104(b)(4)-(5), claims 1-3, 5, 7, 9-11, 13-15, and 17-33 are unpatentable for at least the reasons set forth in detail below.

A. The Law of Obviousness

A patent claim is invalid as obvious if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time of the alleged invention to a person having ordinary skill in the art. 35 U.S.C. § 103(a). Obviousness is a question of law premised on underlying issues of fact, including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective evidence such as commercial success, long-felt need, and the failure of others. *KSR Int'l Co. v. Teleflex Inc.*,

550 U.S. 398, 427 (2007); *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17-18 (1966).

In *KSR*, the Supreme Court found that "[w]hen a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *KSR*, 550 U.S. at 417. Specifically, "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill [in the art] has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *Id.* at 421. The Court also explained that obviousness may be shown "when a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement.'" *Id*. There need not be "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." *Id.* at 418.

B. Claims 1-3, 5, 7, 9- 11, 13-15, and 17-33 are Unpatentable under 35 U.S.C. § 103 as Obvious over Slamon and Watanabe, in View of Baselga and Pegram

More than one year prior to the earliest claimed priority date of the '196 patent, Slamon disclosed that administration of trastuzumab in combination with chemotherapy was effective for treating HER2-overexpressing metastatic breast cancer, and that it "markedly increases clinical benefit" as compared to administration of chemotherapy alone "without increase in overall severe side effects." Ex. 1005 at 5; Ex. 1003 at ¶¶ 63-67. Slamon further disclosed that while the chemotherapeutic agents are administered only once every three weeks, trastuzumab is administered weekly, with a loading dose of 4 mg/kg, followed by weekly maintenance doses of 2 mg/kg. Ex. 1005 at 5; Ex. 1003 at ¶¶ 65.

A POSA 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. Ex. 1003 at ¶ 89; *see, e.g.*, Ex. 1017 at 1-4 (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"). Therefore, a POSA 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. Ex. 1003 at ¶ 90. After designing a new dosing regimen, a POSA would evaluate the safety and efficacy of the new, less frequent, dosing regimen. Ex. 1003 at ¶¶ 89-112.

(i) Less Frequent Dosing Regimen

When 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. Ex. 1003 at ¶ 91; *see, e.g.*, Ex. 1024 at 1-5 ("The importance of drug scheduling and dose intensity on efficacy and toxicity of treatment have been increasingly appreciated."); *see also* Ex. 1029 (concluding that equal dose intensity once-weekly and every three week regimens of doxorubicin were equivalently efficacious for the treatment of metastatic breast cancer, while the less frequent regimen provided additional psychological benefits). 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		

Ex. 1005 at 5; Ex. 1003 at ¶ 91. Thus, to account for an every-three-week schedule, a POSA would have administered an 8 mg/kg loading dose, followed by

6 mg/kg maintenance doses, each administered three weeks apart. Ex. 1003 at ¶ 91.

To the extent the Patent Owner argues that Watanabe teaches away from a less frequent dosing regimen because it suggests a weekly regimen, this argument is meritless. Watanabe was published in the same proceedings as Slamon, and there is no reason to believe that Watanabe was aware of Slamon's results prior to its publication. Ex. 1003 at ¶¶ 63, 68. Thus, because Watanabe's suggestion to pursue a weekly regimen was made without the benefit of Slamon's disclosure, it is not reflective of all of the prior art available to a POSA at the time of the alleged invention. As discussed above, a POSA would have known from Slamon that trastuzumab would be beneficial in combination with chemotherapy agents that were given every three weeks, and would have been motivated to reduce the frequency of trastuzumab administration accordingly. *See supra* pp. 26-27.

(ii) **Safety**

Although the total dosage amount administered would have been the same, a POSA would have recognized that the unit doses were higher than those administered by Slamon. Ex. 1003 at ¶ 91. As such, a POSA would have sought to evaluate the safety of this proposed 8 mg/kg loading dose and 6 mg/kg 3 weekly maintenance dose.

Watanabe disclosed that administration of weekly doses as high as 8 mg/kg were safe and relatively well-tolerated. Ex. 1006 at 5. Accordingly, a POSA would not have expected an increase in toxicity, or any other safety concerns, for the higher doses required by the every three week regimen. Ex. 1003 at ¶¶ 72, 92-93. While the Applicants pointed out during prosecution that Watanabe disclosed that one of six patients experienced severer (i.e. grade 3) generalized bone pain, this was the only grade 2+ adverse event reported for the 8 mg/kg group, and 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. Ex. 1006 at 5; Ex. 1003 at ¶ 93; Ex. 1011 at 224. Thus, a POSA would not have understood Watanabe to suggest that increasing dosage to 8 mg/kg was associated with an overall increase in adverse events. Ex. 1003 at ¶¶ 72, 92-93. Furthermore, given that standard Phase 1 methods defined the recommended Phase 2 dose as less than 33% of patients with grade 3 (i.e., severe) toxicity, the toxicities reported

in Watanabe would not dissuade a POSA from further evaluation of the 8 mg/kg dose. *See*, Ex. 1030 at 2; Ex. 1003 at ¶ 92.

Other prior art references also taught that trastuzumab was safe at doses as high as 8 mg/kg. Ex. 1003 at ¶ 94. For example, Vogel disclosed that trastuzumab "was generally very well tolerated" when administered as an 8 mg/kg loading dose, followed by 4 mg/kg weekly maintenance doses. Ex. 1014 at 4; *see also, e.g.*, Ex. 1012 at 11:54-56 ("[t]he amount of antibody administered will typically be in the range of about 0.1 to about 10 mg/kg of patient weight"); Ex. 1015 at 2:60-61 ("rhuMab HER2 is administered in a dosage of about 2 to 10 mg/kg"); Ex. 1018 at 48:19-52 ("one or more doses of about 0.5 mg/kg, 2.0 mg/kg, 4.0mg/kg or 10 mg/kg (or any combination thereof) may be administered to the patient. Such doses may be administered intermittently, e.g. every week or every three weeks (e.g. such that the patient receives from about two to about twenty, e/g. about six doses of the anti-ErbB2 antibody)"); Ex. 1013 at 4 ("[s]hort-duration IV infusions of 10-500 mg once weekly"); Ex. 1008 at 1 ("[s]hort duration intravenous infusions of 10-500 mg once weekly").

Finally, a POSA would not have viewed Watanabe's suggestion to pursue a 2 mg/kg or 4 mg/kg dose as teaching away from an 8 mg/kg loading dose, 6 mg/kg maintenance dose trastuzumab regimen, as suggested by the Applicants during prosecution. Ex. 1002 at 223-224; Ex. 1003 at ¶ 111. Watanabe's suggestion to

pursue those lower doses presupposes a weekly regimen, and was premised on the fact that these doses would attain the target trough serum concentration. Ex. 1003 at ¶¶ 71, 111. A POSA would have understood that a greater dose would be required to maintain the same serum trough concentrations if administered less frequently. Ex. 1006 at 5 ("Target trough plasma concentration was achieved with 2 mg/kg weekly intravenous infusions … Further clinical trials examining the efficacy of [trastuzumab] with 2-4 mg/kg weekly intravenous infusions is warranted."); Ex. 1003 at ¶ 111. Watanabe's suggestion to proceed with lower doses on a weekly basis therefore does not teach away from an 8 mg/kg dose on a less frequent schedule.

(iii) **Efficacy**

A POSA would also have been aware that a longer interval between doses would impact patients' serum concentration profiles, and therefore could potentially affect the drug's efficacy. Ex 1003 at ¶¶ 96-97. To determine whether any such differences would be clinically meaningful, a POSA would have turned to the pharmacokinetic data disclosed in the prior art. Ex. 1003 at ¶¶ 97-105. As discussed above, the prior art repeatedly disclosed a target efficacious serum concentration of 10 µg/ml. *See, e.g.*, Ex. 1007 at 4; Ex. 1009 at 3; Ex. 1006 at 5; Ex. 1003 at ¶ 96. A POSA therefore would reasonably expect that a regimen

resulting in a trough serum concentration above this threshold would remain effective. Ex. 1003 at ¶¶ 96-97.

To determine whether the every three week regimen discussed above would meet the target trough serum concentration, a POSA would have considered whether the serum concentration would remain above 10 µg/ml just before the next dose is administered, *i.e.*, three weeks after administration of a 6 mg/kg dose. Ex. 1003 at ¶ 97. While a POSA would have understood that, due to drug accumulation over multiple doses, the actual serum trough concentration could be higher than calculated by this method, this approach would have provided the most conservative estimate of whether the serum trough concentration would remain above the 10 µg/ml efficacious threshold over the duration of treatment. Ex. 1003 at ¶ 97.

Baselga and Pegram disclosed pharmacokinetic data that would have enabled a POSA to perform this calculation. Ex. 1003 at ¶¶ 76-79, 84, 98-104. First, Baselga and Pegram disclosed that trastuzumab has a mean half-life of at least one week. Ex. 1007 at 5 (reporting a trastuzumab half-life of 8.3 days); Ex. 1009 at 8 (reporting a trastuzumab half-life of 9.2 days); Ex. 1003 at ¶ 103. Baselga further discloses that trastuzumab has dose-dependent pharmacokinetics, and therefore a POSA would have understood that its half-life would actually be longer at higher doses. Ex. 1003 at ¶ 102; Ex. 1007 at 3. A POSA would therefore

have considered the half-lives disclosed by Baselga and Pegram to be conservative estimates of the half-life at a 6 mg/kg dose, and would have expected that no more than three half-lives would pass over the course of the three week dosing interval – i.e., the serum concentration would decrease by half no more than three times following administration of the 6 mg/kg dose. Ex. 1003 at ¶¶ 104-105.

Second, as Dr. Ratain explains, Baselga and Pegram disclosed that a 250 mg dose provides an initial serum concentration of 113 µg/ml. Ex. 1003 at ¶ 100. A 6 mg/kg dose would require 375 mg for an average 62.5 kg patient.[7] Ex. 1003 at ¶ 100. This amount of drug is 1.5 times greater than the 250 mg dose disclosed in Baselga and Pegram, and would therefore provide an initial serum concentration 1.5 times greater than that provided by a 250 mg dose, or 169 µg/ml. Ex. 1003 at ¶ 100. Thus, a POSA would have understood from Baselga and Pegram that the 6 mg/kg dose of the every three week regimen would provide an initial serum concentration of 169 µg/ml. Ex. 1003 at ¶ 100.

Starting with an initial serum concentration of 169 µg/ml, and applying the conservative one week half-life discussed above, a POSA would have calculated that the serum concentration would still remain well above the 10 µg/ml target efficacious serum concentration three weeks after the 6 mg/kg dose is administered

[7] Were a POSA to instead assume a 70 kg patient, the calculated initial serum concentration for a 6 mg/kg dose would be even higher. Ex. 1003 at ¶ 101.

(i.e., 50% would remain after one week, 25 % after two weeks, and 12.5%, or approximately 21.1 µg/ml would remain after three weeks). Ex. 1003 at ¶¶ 100, 104. A POSA therefore would have reasonably expected that a once every three week trastuzumab regimen consisting of an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses, would be effective to treat metastatic breast cancer. [8] Ex. 1003 at ¶¶ 96-106.

The '196 patent is consistent with this expectation. The specification asserts that "[i]t is believed" that a trastuzumab regimen consisting of an 8 mg/kg loading

[8] Though a POSA would have understood from Baselga (Ex. 1007) and the Herceptin Label (Ex. 1008) that the pharmacokinetics of trastuzumab are, in fact, non-linear, a POSA would also have understood from Watanabe (Ex. 1006) and the Herceptin Label (Ex. 1008) that this means that the half-life of trastuzumab would actually be ***longer*** at higher doses than at lower doses. Ex. 1003 at ¶ 102. Therefore, a POSA would have expected the trough serum concentration to be even higher if its non-linear pharmacokinetics were taken into account. Ex. 1003 at ¶ 102. As such, Dr. Ratain has used a conservative estimate; to the extent a POSA were inclined to apply a non-linear pharmacokinetic model, he or she would likewise find that a once every three week trastuzumab regimen consisting of an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses, would be effective to treat metastatic breast cancer. Ex. 1003 at ¶ 102.

dose, followed by 6 mg/kg maintenance doses every three weeks "will be effective," notwithstanding that no actual testing was disclosed in the specification of ***any*** dosing less frequent than a weekly dosing regimen. Ex. 1001 at 48:1-4. The only basis provided in support of this "belief" is that "[s]imulation of the proposed treatment regimen suggests that the trough serum concentration will be 17 mcg/ml, in the range (10-20 mcg/ml) of the targeted trough serum concentrations from previous HERCEPTIN® IV clinical trials." Ex. 1001 at 46:12-16; *see also* Ex. 1003 ¶ 96.

To the extent Patent Owners argue, as they did during prosecution, that a POSA would not have wanted to increase the dosing interval beyond the half-life "for fear that insufficient levels of drug would remain in the patient to treat cancer," a POSA would not have drawn this conclusion based on half-life alone. Ex. 1003 at ¶ 110; Ex. 1011 at 223-224. Half-life is only one piece of the relevant information. Ex 1003 at ¶ 110. Rather, when determining whether a less frequent regimen was likely to be effective, a POSA would have considered half-life together with initial serum concentration and target trough serum concentration. Ex. 1003 at ¶¶ 96-98, 110. Furthermore, the Applicants' assertion that a POSA would not have considered a dosing interval longer than trastuzumab's half-life is belied by the fact that the regimen approved for trastuzumab involved weekly

administration, notwithstanding that the half-life for this regimen was reported in the Herceptin label to be only 5.8 days. Ex. 1008 at 1.

Patent Owner may argue that the proper pharmacokinetic data for a POSA to use would have been that disclosed in the 1998 Herceptin label. However, if a POSA had analyzed these data, he or she likewise would have concluded that the every three week regimen discussed above would provide sufficient drug to maintain efficacy. Ex. 1003 at ¶¶ 107-109.

The 1998 Herceptin label published in September 1998, 11 months before the priority date of the '196 patent, and is therefore prior art to the '196 patent under at least 35 U.S.C. § 102(a). Ex. 1003 at ¶ 85. The label reported that a 4 mg/kg loading dose followed by weekly 2 mg/kg maintenance doses resulted in mean peak and trough serum concentrations of 123 µg/ml and 79 µg/ml, respectively. Ex. 1008 at 1. The initial serum concentration associated with the 2 mg/kg dose is 44 µg/ml, which is calculated by determining the difference between the peak and trough serum concentrations (123 µg/ml – 79 µg/ml = 44 µg/ml). Ex. 1003 at ¶ 107. The initial serum concentration for a 6 mg/kg dose would therefore be 132 µg/ml, or three times that of the 2 mg/kg dose. Ex. 1003 at ¶ 107. The 1998 Herceptin label also disclosed a half-life of 5.8 days, which means that 3.6 half-lives would pass during a three week dosing interval. Ex. 1003 at ¶¶ 88, 108.

Given these data, a POSA would have easily confirmed that a dosing regimen of an 8 mg/kg loading dose, followed by maintenance doses of 6 mg/kg every three weeks, would provide sufficient drug to remain above the target trough serum concentration of 10 µg/ml. Specifically, the trastuzumab serum concentration would drop to 8% of its original concentration over 3.6 half-lives. Ex. 1003 at ¶ 109. Starting with a serum concentration of 132 µg/ml, a POSA would have determined that after administration of a 6 mg/kg dose, greater than 10 µg/ml would still remain three weeks later. Ex. 1003 at ¶ 109. As such, though not necessary for any conclusion of unpatentability of the '196 patent claims, analysis of the Herceptin label serves as a useful check on efficacy of an 8 mg/kg loading dose and 6 mg/kg 3-weekly maintenance dosing regimen.

In view of the above, a POSA would have been motivated to administer trastuzumab in an every three week regimen as an 8 mg/kg loading dose, followed by maintenance doses of 6 mg/kg to treat metastatic breast cancer, and would have had a reasonable expectation that the treatment would be both safe and effective. Ex. 1003 at ¶¶ 89-112.

To the extent Patent Owner argues that this petition should be denied under 35 U.S.C. § 325(d) because the prior art and arguments at issue in this petition were before the Office during prosecution, this argument should be rejected. One of the primary references relied upon here, Slamon (Ex. 1005), was not before the

Examiner during prosecution of the '196 patent. As discussed above, Slamon disclosed beneficial effects from a combination of trastuzumab and chemotherapy, which would have motivated a POSA to align the dosing schedules of the two types of drugs. *See supra* pp. 26-27. Further, the Examiner was presented only with the Applicants' conclusory assertion that a POSA would have had a "fear" that a less frequent dose would be ineffective, and that Watanabe's suggestion to pursue lower doses on a weekly basis implies that higher doses should be avoided in all cases, even with a less frequent regimen. Ex. 1011 at 223-225. The Examiner did not have the benefit of Dr. Ratain's opinion that a POSA could have easily predicted from the pharmacokinetic data disclosed in the prior art, *e.g.*, Pegram (Ex. 1009) and Baselga (Ex. 1005), that sufficient levels of drug would remain if trastuzumab were administered less frequently, and that Watanabe (Ex. 1006) did in fact support the use of higher doses with a less frequent regimen, as discussed above.

Given that Slamon (Ex. 1005) and Dr. Ratain's declaration were not before the Examiner during prosecution of the '196 patent, Petitioner asserts that the arguments presented in the instant petition are not the same or substantially the same as arguments previously presented to the office. The petition establishes that the challenged claims are unpatentable, and IPR should be instituted and the claims cancelled.

(iv) Independent Claims 1 and 24 of the '196 Patent are Obvious

Claim 1 of the '196 patent recites:

> 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.

Accordingly, the claim is directed to 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, comprising administering an initial dose of at least approximately 5 mg/kg of the anti-ErbB2 antibody, and administering a plurality of subsequent doses of the antibody in an amount the same as or less than the initial dose, wherein the subsequent doses are separated in time from each other by at least two weeks. Ex. 1003, ¶ 114.

As discussed above, Slamon discloses a method of treating a human patient diagnosed with ErbB2-overexpressing metastatic breast cancer comprising administering an effective amount of trastuzumab, an anti-ErbB2 antibody,[9] and an effective amount of a chemotherapeutic agent. *See also* Ex. 1005 at 5 ("Addition of Herceptin (Humanized Anti-HER2 Antibody) to First Line Chemotherapy for HER2 Overexpressing Metastatic Breast Cancer"); Ex. 1003 at ¶¶ 64-67, 117. The method disclosed by Slamon requires administration of an initial dose, followed by a plurality of subsequent doses in an amount the same as or less than the initial dose. Ex. 1005 at 5 ("4 mg/kg loading, then 2 mg/kg intravenously q week"); Ex. 1003 at ¶¶ 65, 117.

Thus, Slamon and claim 1 differ in that the latter requires the initial dose to be at least approximately 5 mg/kg and the subsequent doses to be separated by at least two weeks, compared to an initial dose of 4 mg/kg and subsequent doses separated by one week, in Slamon. Watanabe is directed to treatment of the same disease as Slamon—ErbB2-overexpressing metastatic breast cancer—and discloses administration of an initial dose within the claimed range (*i.e.*, 8 mg/kg), and a trastuzumab dose separation of at least two weeks (*i.e.*, three weeks between the initial and subsequent doses). Ex. 1006 at 5; Ex. 1003 at ¶¶ 69-70. A POSA

[9] *See* Ex. 1007 at 3 ("The HER2 gene (also known as neu or c-erbB-2)"); Ex. 1001 at 9:45-46 ("The terms "HER2", "ErbB2" "c-Erb-B2" are used interchangeably").

would have been motivated to combine the higher initial dose and three week dosing interval disclosed by Watanabe with Slamon's regimen to arrive at the claimed invention, for the reasons discussed above Sections X.B(i)-(iii). *See also* Ex. 1003 at ¶¶ 117-118.

More specifically, a POSA would have been motivated to administer trastuzumab in combination with a chemotherapeutic agent to treat ErbB2-overexpressing metastatic breast cancer, as disclosed by Slamon. Ex. 1003 at ¶¶ 89, 118. However, a POSA would have wanted to reduce the frequency of trastuzumab administration from once weekly to once every three weeks in order to align it with the chemotherapy regimen to improve patient convenience. Ex. 1003 at ¶¶ 89-90, 118. As discussed above, the resulting regimen would have involved administering trastuzumab as an 8 mg/kg loading dose, followed by a plurality of 6 mg/kg maintenance doses, given every three weeks. Ex. 1003 at ¶ 91. A POSA would have reasonably expected this regimen to be safe because Watanabe had disclosed an acceptable toxicity profile for an 8 mg/kg dose. Ex. 1003 at ¶¶ 92-95, 118. A POSA would also have reasonably expected this regimen to be effective, in view of the pharmacokinetic data disclosed by Baselga and Pegram. Ex. 1003 at ¶¶ 96-105, 118. Because this regimen would have satisfied each and every element of claim 1 of the '196 patent, claim 1 is obvious. Ex. 1003 at ¶¶ 113-118.

Claim 24 of the ’196 patent recites:

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.

Accordingly, the claim is directed to a method for treating cancer in a human patient, comprising administering a first dose of an anti-ErbB2 antibody followed by two or more subsequent doses, wherein the subsequent doses are separated from each other in time by at least two weeks. Ex. 1003, ¶¶ 114, 116.

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.

(v) **Claims 2, 3, 9, 26-28, and 31-33 are Obvious**

Claim 2 depends from

claim 1, and further requires that the initial dose is at least approximately 6 mg/kg. **Claim 3** depends from claim 2, and further requires that the initial dose is

at least approximately 8 mg/kg. As discussed with respect to claim 1, a POSA would have found it obvious to administer trastuzumab as an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses every three weeks. *See also* Ex. 1003 at ¶¶ 89-112. This regimen would have included an initial dose of at least approximately 6 mg/kg (claim 2) and at least approximately 8 mg/kg (claim 3). Ex. 1003 at ¶ 119. Therefore, claims 2 and 3 of the '196 patent are obvious for substantially the same reasons as set forth with respect to claim 1. Ex. 1003 at ¶ 119.

Claim 9 depends from claim 1, and further requires that the initial dose is either approximately 6 mg/kg, 8 mg/kg, or 12 mg/kg, and the subsequent doses are at least approximately 2 mg/kg. As discussed with respect to claim 1, a POSA would have found it obvious to administer trastuzumab as an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses every three weeks. *See also* Ex. 1003 at ¶¶ 89-112. This regimen would have included an initial dose of approximately 8 mg/kg and subsequent doses of at least approximately 2 mg/kg. Ex. 1003 at ¶ 120. Therefore, claim 9 of the '196 patent is obvious for substantially the same reasons as set forth with respect to claim 1. Ex. 1003 at ¶ 120.

Claim 26 depends from claim 24, and further requires that the first dose and subsequent doses are each from about 2 mg/kg to about 16 mg/kg. **Claim 27**

depends from claim 26, and further requires that the first dose and subsequent doses are each from about 4 mg/kg to about 12 mg/kg. **Claim 28** depends from claim 37, and further requires that the first dose and subsequent doses are each from about 6 mg/kg to about 12 mg/kg.

As discussed with respect to claim 24, a POSA would have found it obvious to administer trastuzumab as an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses every three weeks. *See also* Ex. 1003 at ¶¶ 89-118. The first dose and subsequent doses of this regimen would have been from about 2 mg/kg to about 16 mg/kg (claim 26), from about 4 mg/kg to about 12 mg/kg (claim 27), and from about 6 mg/kg to about 12 mg/kg (claim 28). Ex. 1003 at ¶ 121. Therefore, claims 26-28 of the '196 patent are obvious for substantially the same reasons as set forth with respect to claim 24. Ex. 1003 at ¶ 121.

Claim 31, **32**, and **33** each depend from claim 24, and further require that the subsequent doses are each from about 2 mg/kg to about 16 mg/kg, from about 4 mg/kg to about 12 mg/kg, and from about 6 mg/kg to about 12 mg/kg, respectively.

As discussed with respect to claim 24, a POSA would have found it obvious to administer trastuzumab as an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses every three weeks. *See also* Ex. 1003 at ¶¶ 89-118. The subsequent doses of this regimen would have each been from about 2 mg/kg to about 16 mg/kg (claim 31), from about 4 mg/kg to about 12 mg/kg (claim 32), and

from about 6 mg/kg to about 12 mg/kg (claim 33). Ex. 1003 at ¶ 122. Therefore, claims 31-33 of the '196 patent are obvious for substantially the same reasons as set forth with respect to claim 30, above. Ex. 1003 at ¶ 122.

(vi) Claims 5, 25, and 30 are Obvious

Claims 5 and **30** depend from claims 1 and 24, respectively, and each further requires that the subsequent doses are separated from each other by at least three weeks. **Claim 25** depends from claim 24, and further requires that the first dose and first subsequent dose are separated from each other by at least three weeks.

As discussed with respect to claims 1 and 24, a POSA would have found it obvious to administer trastuzumab as an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses every three weeks. *See also* Ex. 1003 at ¶¶ 89-118. The subsequent doses in this regimen would have been separated by at least three weeks (claims 5 and 30) and the initial dose and first subsequent dose would also have been separated by at least three weeks (claim 25). Ex. 1003 at ¶ 123. Therefore, claims 5, 25, and 30 of the '196 patent are obvious for substantially the same reasons as set forth with respect to claims 1 and 24. Ex. 1003 at ¶ 123.

(vii) Claims 10 and 11 are Obvious

Claim 10 depends from claim 9, and further requires that the subsequent doses are separated from each other by at least three weeks. **Claim 11** depends

from claim 10, and further requires that the initial dose is approximately 8 mg/kg and at least one subsequent dose is approximately 6 mg/kg.

As discussed with respect to claim 1, a POSA would have found it obvious to administer trastuzumab as an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses every three weeks. *See also* Ex. 1003 at ¶¶ 89-118. This regimen would have included an initial dose of approximately 8 mg/kg (claim 11), at least one subsequent dose of approximately 6 mg/kg (claim 11), and the subsequent doses would have been separated from each other by at least three weeks (claim 10). Ex. 1003 at ¶ 124. Therefore, claims 10 and 11 of the '196 patent are obvious for substantially the same reasons as set forth with respect to claims 1 and 9, above. Ex. 1003 at ¶ 124.

(viii) **Claim 7 is Obvious**

Claim 7 depends from claim 1, and further requires that the initial dose is administered by intravenous injection, at least two subsequent doses are administered, and each subsequent dose is administered either by intravenous injection or subcutaneous injection.

As discussed with respect to claim 1, a POSA would have found it obvious to administer trastuzumab as an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses every three weeks. *See also* Ex. 1003 at ¶¶ 89-118. This regimen would have involved administration of at least two subsequent doses. Ex.

1003 at ¶ 125. Furthermore, a POSA would have been motivated to administer the doses by intravenous injection, at least because both Slamon and Watanabe disclose that trastuzumab is administered intravenously. Ex. 1003 at ¶ 125; Ex. 1005 at 5; Ex. 1006 at 5. Thus, claim 7 of the '196 patent is obvious for these reasons, as well as those set forth with respect to claim 1. Ex. 1003 at ¶ 125.

(ix) Claims 17-19 are Obvious

Claim 17 depends from claim 1, and further requires that the cancer is one of a number of types, including breast cancer. **Claim 18** depends from claim 17, and further requires that the cancer is breast cancer. **Claim 19** depends from claim 18, and further requires that the cancer is metastatic breast carcinoma.

As discussed with respect to claim 1, a POSA would have found it obvious to administer trastuzumab as an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses every three weeks. *See also* Ex. 1003 at ¶¶ 89-118. A POSA would have been motivated to use this regimen to treat patients diagnosed with breast cancer, specifically metastatic breast carcinoma, at least because both Slamon and Baselga disclose that trastuzumab is useful for the treatment of metastatic breast cancer. Ex. 1003 at ¶ 126; Ex. 1005 at 5; Ex. 1007 at 3-9. Therefore these claims are obvious for these reasons, as well as those set forth with respect to claim 1. Ex. 1003 at ¶ 126.

(x) Claims 20-22 are Obvious

Claim 20 depends from claim 1, and further requires that the antibody binds to the extracellular domain of the ErbB2 receptor. **Claim 21** depends from claim 20 and further requires that the antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence. **Claim 22** depends from claim 21 and further requires that the antibody is a humanized 4D5 anti-ErbB2 antibody.

As discussed with respect to claim 1, a POSA would have found it obvious to administer trastuzumab as an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses every three weeks. *See also* Ex. 1003 at ¶¶ 89-118. Baselga discloses that trastuzumab is a humanized 4D5 anti-ErbB2 antibody that binds to epitope 4D5 within the ErbB2 extracellular domain sequence. Ex. 1003 at ¶ 127; Ex. 1007 at 3. Thus, these claims are obvious for the same reasons as set forth with respect to claim 1. Ex. 1003 at ¶ 127.

(xi) Claim 23 is Obvious

Claim 23 depends from claim 1, and further requires that efficacy is measured by determining the time to disease progression or response rate.

As discussed with respect to claim 1, a POSA would have found it obvious to administer trastuzumab as an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses every three weeks. *See also* Ex. 1003 at ¶¶ 89-118. A POSA would have been motivated to measure the efficacy of this regimen by these well-

known methods. Ex. 1003 at ¶ 128. Indeed, Slamon and Baselga both disclose that time to disease progression and response rate are measures of trastuzumab's efficacy. Ex. 1003 at ¶ 128; Ex. 1005 at 5; Ex. 1007 at 4. Thus, claim 23 is obvious for the same reasons as set forth with respect to claim 1. Ex. 1003 at ¶ 128.

(xii) **Claim 29 is Obvious**

Claim 29 depends from claim 24, and further requires administration of about 2 to about 10 subsequent doses of the antibody.

As discussed with respect to claim 24, a POSA would have found it obvious to administer trastuzumab as an 8 mg/kg loading dose, followed by 6 mg/kg maintenance doses every three weeks. *See also* Ex. 1003 at ¶¶ 89-118. A POSA would have known to administer the trastuzumab regimen until disease progression occurred. Ex. 1003 at ¶ 129; *see also*, *e.g.*, Ex. 1009 at 3-4; Ex. 1007 at 4. Slamon disclosed a median time to disease progression for the paclitaxel plus trastuzumab regimen of 7.1 months, or approximately thirty weeks. Ex. 1003 at ¶ 129; Ex. 1005 at 5. An every three week regimen would involve ten subsequent doses over a thirty week period, so it would have been obvious to administer between 2 and 10 subsequent doses of the above-mentioned regimen. Ex. 1003 at ¶ 129. Furthermore, Watanabe discloses administration of nine subsequent doses. Ex.

1003 at ¶ 129; Ex. 1006 at 5. Thus, claim 29 is obvious for these reasons, as well as those set forth with respect to claim 24. Ex. 1003 at ¶ 129.

(xiii) Claims 13-15 are Obvious

Claims 13-15 of the '196 patent require that at least one of the subsequent doses is 8 mg/kg.

As discussed above, a POSA would have been motivated to administer trastuzumab every three weeks, as an 8 mg/kg loading dose and subsequent 6 mg/kg maintenance doses, and would have expected this regimen to be both safe and effective. *See also* Ex. 1003 at ¶¶ 89-112, 136. However, a POSA would have understood that some patients would have a relatively low trough serum concentration, and thus would have been motivated to measure the drug concentration and increase the dose as necessary for such patients so as to ensure that the serum trough concentration would be above 10 µg/mL, which would necessarily result in some patients receiving some subsequent doses of 8 mg/kg or more. Ex. 1003 at ¶ 157. As discussed above, a POSA would have also expected that unit doses as high as 8 mg/kg would be safe. Ex. 1003 at ¶ 157. Thus, a POSA would have been motivated to increase the maintenance dose to 8 mg/kg, and would have reasonably expected the regimen to be both safe and effective. Ex. 1003 at ¶ 157. Therefore, claims 13-15 of the '196 patent are obvious for

substantially the same reasons as set forth with respect to claim 1. Ex. 1003 at ¶ 157.

Accordingly, all of the challenged claims are obvious over Slamon and Watanabe, in view of Baselga and Pegram.

(xiv) Secondary Considerations Do Not Render the Claims Non-Obvious

Petitioner is unaware of any secondary considerations of non-obviousness that render the challenged claims patentable. "[W]here the inventions represented no more than the predictable use of prior art elements according to their established functions, the secondary considerations are inadequate to establish nonobviousness as a matter of law." *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)(internal quotation and citation omitted). While Applicants asserted in the specification that a dosing regimen involving greater front loading is "more efficacious than conventional treatments," this feature does not distinguish the claims from the prior art, which had already disclosed the use of a loading dose with trastuzumab regimens. Ex. 1003 at ¶ 159. Moreover, there is no evidence from which one can conclude that the claimed method is any more efficacious than the prior art methods. Ex. 1003 at ¶ 159.

Petitioner reserves the right to respond to any assertions of secondary considerations that Patent Owner alleges during this proceeding.

XI. CONCLUSION

For the reasons set forth above, Petitioner respectfully submits that it has established a reasonable likelihood of success with respect to the challenged claims and requests that this petition be granted, and the challenged claims be cancelled.

Respectfully submitted,

Dated: March 24, 2017

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. §42.24(d), Petitioner hereby certifies, in accordance with and reliance on the word count provided by the word-processing system used to prepare this petition, that the number of words in this paper is 10,873. Pursuant to 37 C.F.R. §42.24(d), this word count excludes the table of contents, table of authorities, mandatory notices under 37 C.F.R. §42.8, certificate of service, certificate of word count, appendix of exhibits, and any claim listing.

Dated: March 24, 2017

/Cynthia Lambert Hardman/
Cynthia Lambert Hardman

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that on this 24th day of March 2017, I served a copy of this PETITION FOR INTER PARTES REVIEW and copies of all supporting exhibits by Federal Express Next Business Day Delivery on the following addresses for patent owner:

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