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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

BIOGEN, INC.,
Patent Owner.

Case IPR2017-01093
Patent 8,329,172 B2

Before ERICA A. FRANKLIN, SHERIDAN K. SNEDDEN, and JACQUELINE T. HARLOW, *Administrative Patent Judges.*

HARLOW, *Administrative Patent Judge.*

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

I. INTRODUCTION

Celltrion, Inc. ("Petitioner"), filed a Petition requesting an *inter partes* review of claim 1 of U.S. Patent No. 8,329,172 B2 (Ex. 1001, "the '172 patent"). Paper 2 ("Pet."). Biogen, Inc. ("Patent Owner") filed a Preliminary Response. Paper 10 ("Prelim. Resp."). We have authority to determine whether to institute an *inter partes* review under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted unless the information presented in the petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." *See also* 37 C.F.R. § 42.4 (a).

For the reasons set forth below, we deny the Petition.

A. Related Matters

The parties state that they are not aware of any other pending proceedings involving the '172 patent. Pet. 4; Paper 6, 2. The '172 patent was previously challenged by Boehringer Ingelheim International GmbH in IPR2015-00418; however, the Board declined to institute *inter partes* review in that case. Pet. 4; Paper 6, 2; *Boehringer Ingelheim Int'l GmbH v. Biogen Idec, Inc.*, IPR2015-00418 (PTAB July 13, 2015) (Paper 14).

In addition, Petitioner has filed a petition for *inter partes* review involving related U.S. Patent Nos. 8,557,244 B1 (IPR2017-01094) and 9,296,821 B2 (IPR2017-01095). Pet. 4; Paper 6, 2.

B. The '172 Patent

The '172 patent is titled "Combination Therapies for B-Cell Lymphomas Comprising Administration of Anti-CD20 Antibody." Ex. 1001, [54]. The '172 patent issued from U.S. Patent Application No. 11/840,956, filed on August 18, 2007. *Id.* at [21], [22]. The '172 patent is a continuation of U.S. Patent Application No. 10/196,732, filed on July 17, 2002, now abandoned, which is a continuation of U.S. Patent Application No. 09/372,202, filed on August 11, 1999, now U.S. Patent No. 6,455,043. *Id*. at [63]. The '172 patent claims priority to U.S .Provisional Patent Application No. 60/096,180, filed on August 11, 1998. *Id*. at [60].

The '172 patent describes treating B-cell lymphomas with anti-CD20 antibodies combined other therapeutic regimens, such as chemotherapy. Ex. 1001, 2:7–38. The '172 patent explains that CD20 is a B-cell-restricted differentiation antigen that is usually expressed at very high levels on cancerous B-cells, and is "appealing for targeted therapy, because it does not shed, modulate, or internalize." *Id*. at 1:33–41. The '172 patent explains that a preferred anti-CD20 antibody "is C2B8 (IDEC Pharmaceuticals, Rituximab)." *Id*. at 2:59–60.

The '172 patent discloses that rituximab, also known as "RITUXAN®" has been approved for use in relapsed and previously treated low-grade non-Hodgkin's lymphoma ("LG-NHL"), but that such patients may nonetheless still be subject to disease relapse. *Id*. at 1:47–58. Therefore, the '172 patent advises, "it would be advantageous if anti-CD20

antibodies had a beneficial effect in combination with other lymphoma treatments, and if new combined therapeutic regimens could be developed to lessen the likelihood or frequency of relapse." *Id*. at 1:60–64.

Relevant to the instant Petition, the '172 patent describes a Phase III study conducted by the Eastern Cooperative Oncology Group ("ECOG") of patients with LG-NHL in which a subset of patients responsive to cyclophosphamide, vincristine, and prednisone ("CVP") chemotherapy "will undergo a second randomization to Rituximab maintenance therapy (375 mg/m2 weekly times 4 every 6 months for 2 years (Arm C)." Ex. 1001, 13:8–16.

C. Illustrative Claim

Claim 1, reproduced below, is the sole claim of the '172 patent.

> 1. A method of treating low grade B-cell non-Hodgkin's lymphoma in a human patient comprising administering to the patient chemotherapy consisting of CVP therapy to which the patient responds, followed by rituximab maintenance therapy, wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m^2 every 6 months, and wherein the maintenance therapy is provided for 2 years.

Ex. 1001, 22:56–63.

D. Evidence Relied Upon

Petitioner relies upon the following prior art references (Pet. 27–36):

Bishop, J.F. et al., *A Randomized Trial of High Dose Cyclophosphamide, Vincristine, and Prednisone Plus or Minus Doxorubicin (CVP versus CAVP) with Long-Term Follow-Up in Advanced Non-Hodgkin's Lymphoma*, 1(6) LEUKEMIA 508–513 (1987) (Ex. 1006) ("Bishop").

Dana, B. et al., *Long-Term Follow-Up of Patients With Low-Grade Malignant Lymphomas Treated With Doxorubicin-Based Chemotherapy or Chemoimmunotherapy*, 11(4) J. CLIN. ONCOL. 644–651 (1993) (Ex. 1007) ("Dana").

Grossbard, M.L. and Multani, P.S., *The McLaughlin, et al. Article Reviewed*, 12(12) ONCOLOGY 1769–1781 (1998) (Ex. 1010) ("Grossbard").

McNeil, *Non-Hodgkin's Lymphoma Trials In Elderly Look Beyond CHOP*, 90 J. NAT. CANCER INST. 266–67 (1998) (Ex. 1005).

Eastern Cooperative Oncology Group E1496, *Randomized Phase III Study in Low Grade Lymphoma Comparing Cyclophosphamide/Fludarabine to Standard Therapy Followed by Maintenance Anti-CD20 Antibody*, Appendix I: Suggested Patient Consent Form (undated) (Ex. 1008) ("ECOG Patient Consent Form").

Eastern Cooperative Oncology Group E1496, *Randomized Phase III Study in Low Grade Lymphoma Comparing Cyclophosphamide/Fludarabine to Standard Therapy Followed by Maintenance Anti-CD20 Antibody*, Protocol (Howard Hochster et al. study chairs, Activation Date March 1998) (Ex. 1009) ("ECOG Protocol").

IDEC Pharmaceuticals Corporation and Genentech, Inc., Product label for Rituxan® (1997) (Ex. 1004) ("Rituxan Label").

Petitioner also relies upon the Declarations of Walter Longo, M.D. (Ex. 1002) and Izidore Lossos, M.D. (Ex. 1003) to support its contentions.

E. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 6):

Claim	Basis	Reference(s)
1	§ 102(b)	E1496 Consent Form
1	§ 102(b)	E1496 Protocol
1	§ 103	Grossbard and Rituxan Label
1	§ 103	McNeil, Bishop, Dana, and Rituxan Label

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, and absent any special definitions, we give 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 disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner and Patent Owner propose constructions for certain claim terms. Pet. 25–26; Prelim. Resp. 12–14. In view of our analysis, we

determine that construction of claim terms is not necessary for purpose of this Decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (Only terms which are in controversy need to be construed, and only to the extent necessary to resolve the controversy).

B. Priority Date of the '172 Patent

Petitioner contends that the subject matter of claim 1 does not find support in the provisional application to which the '172 patent claims priority. Pet. 23–24. Accordingly, Petitioner argues, the effective filing date of the claimed subject matter at issue here is August 11, 1999. *Id*. at 24. Patent Owner does not dispute Petitioner's contention. *See, e.g.*, Prelim. Resp. 22. Accordingly, for the purposes of this decision, we accord the subject matter of claim 1 of the '172 patent an effective filing date of August 11, 1999.

C. Level of Ordinary Skill in the Art

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

According to Petitioner, a person of ordinary skill in the art at the time of the invention would have been "a practicing physician specializing in hematology or oncology, with at least three years of experience in treating patients with NHL." Pet. 27 (citing Ex. 1003 ¶ 22); *see also* Ex. 1002 ¶ 18.

Patent Owner does not address Petitioner's position on this matter and does not propose its own description for a person of ordinary skill in the art at the time of the invention.

At this stage in the proceeding, we determine that Petitioner's description of the level of ordinary skill in the art is supported by the current record. Moreover, we have reviewed the credentials of Dr. Lossos (Ex. 1003, Exhibit A) and Dr. Longo (Ex. 1002, Exhibit A), and, at this stage in the proceeding, we consider each of them to be qualified to opine on the level of skill and the knowledge of a person of ordinary skill in the art at the time of the invention. We also note that the applied prior art reflects the appropriate level of skill at the time of the claimed invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

D. Anticipation by E1496 Patient Consent Form

Petitioner asserts that claim 1 is anticipated under § 102(b) by the E1496 Patient Consent Form. Pet. 29–33, 37–39. Patent Owner Disagrees. Prelim. Resp. 14–25, 27–33.

1. E1496 Patient Consent Form

The undated E1496 Patient Consent Form is a "model informed consent form" for the ECOG E1496 study. Ex. 1008, 1. The E1496 Patient Consent Form appears to be Appendix I of the E1496 Protocol. *Compare* Ex. 1008, 1–3 *with* Ex. 1009, 45–47.

The E1496 Patient Consent form invites LG-NHL patients to participate in a research study to assess "whether chemotherapy with a new

regimen (cyclophosphamide - fludarabine) causes more and longer remissions compared to standard chemotherapy (cyclophosphamide, vincristine, prednisone) and whether maintenance with a monoclonal antibody for two years adds to a longer remission duration." Ex. 1008, 1.

2. Discussion

Petitioner contends that the E1496 Patient Consent Form anticipates claim 1 of the '172 patent because it describes a study in which a subset of LG-NHL patients responsive to CVP chemotherapy are subsequently treated with four weekly doses of 375 mg/m^2 of rituximab every six months for two years. Pet. 37–38.

Patent Owner responds that the E1496 Patient Consent Form cannot qualify as a printed publication because Petitioner has not established a reasonable likelihood that the consent form was publicly accessible before the priority date of the '172 patent. Prelim. Resp. 14–25. Patent Owner contends, therefore, that the E1496 Patient Consent Form does not anticipate the challenged claim. *Id*. at 27–28

We agree with Patent Owner that Petitioner has not shown that the E1496 Patient Consent Form was publicly accessible to the extent required to establish it as a "printed publication" for purposes of this decision.

The Federal Circuit has held that "public accessibility" is "the touchstone" in determining whether a reference is a printed publication. *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986). "A given reference is 'publicly accessible' upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons

interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) (quoting *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006)).

Although Petitioner presents evidence to suggest that the E1496 Patient Consent Form was not treated as confidential, Petitioner fails to establish that it was disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, could have located it. For example, while Dr. Longo, a sub-investigator in the E1496 clinical trial, testifies that, with regard to the E1496 trial, "the physicians and the study coordinators would independently discuss the trial with the patient" (Ex. 1002 ¶ 45), and "E1496 sub-investigators were also encouraged and expected to discuss the trial protocols among ourselves to maximize the number of enrolled patients" (*id.*), he does not testify that the E1496 Consent Form was in fact disseminated to interested artisans.

Similarly, Dr. Longo's testimony that he "was free to distribute the E1496 patient consent form after March 1998 and did distribute the form to approximately 40 prospective patients, every prospective patient who inquired about the E1496 trial" (*id.* ¶ 49) is at best tangential to the issue here; namely, whether the E1496 Patient Consent Form was "publicly accessible" to ordinarily skilled artisans (rather than patients) before the priority date of the '172 patent. First, Dr. Longo identifies neither the date when he first received the E1496 Patient Consent Form, nor the dates on

which he distributed it to patients. *See id.*; *see also id.* ¶¶ 34, 37 (noting that Dr. Longo was a sub-investigator on the E1496 trial from March 1998 until May 2006, when the study closed). Second, although Dr. Longo articulates his expectation that "patients would take the consent form home and discuss the pros and cons of the clinical trial with their own physicians, other oncologists who might provide second opinions, family members, friends, co-workers, and anyone else before deciding whether to enroll" (*id*. at 49), neither he nor Petitioner provides evidence to support a finding that they in fact did so.

As for showing that the E1496 Patient Consent Form was made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence could have located it, Petitioner and Dr. Longo explain that "any interested physician could have learned about the E1496 trial by viewing the list of active protocols on the ECOG website." Pet. 31 (citing Ex. 1002 ¶ 56; Ex. 1049, 4).[1] According to Petitioner and Dr. Longo, the website contains a list of protocols active by "at least May 19, 1998" (Ex. 1002 ¶ 56), indexed by subject matter under the heading "Lymphoma Committee" and provides the protocol number, such that an interested party could then access the protocol and patient consent form for that listed number. *Id*. at 31–32 (citing Ex. 1004 ¶¶ 56, 57). Petitioner and Dr. Longo, however, fail to support that assertion with

[1] ECOG Active Protocols List, https://web.archive.org/web/19980519084342/http:/ecog.dfci.harvard.edu/~ecogdba/active_reports/Lymphoma.html (archived May 19, 1998) (Ex. 1049, App'x A).

evidence that "any interested party" would know to visit the ECOG website to look for the E1496 Patient Consent Form, or that doing so would result in obtaining a copy of that document. The ECOG protocol listing on the website does not provide direct access to the E1496 Patient Consent Form, *e.g.*, in terms of a hyperlink, nor does the website provide information as to what E1946 documents are available or how a website visitor may access them. For at least those reasons, Petitioner has not established that the E1496 Patient Consent Form was "otherwise made available" in a manner required for that document to be recognized as a "printed publication."

Accordingly, because Petitioner has not adequately established, for purposes of this decision, that the E1496 Patient Consent Form is a prior art printed publication, we determine that Petitioner has not shown sufficiently that there is a reasonable likelihood that it would prevail in showing the unpatentability of claim 1 as anticipated by that reference.

E. Anticipation by E1496 Protocol

Petitioner asserts that claim 1 is anticipated under § 102(b) by the E1496 Protocol. Pet. 29–33, 39–41. Patent Owner Disagrees. Prelim. Resp. 14–25, 27–33.

1. E1496 Protocol

The E1496 Protocol is a document describing the protocol for a study by the ECOG of a treatment for low-grade lymphoma. *See* Ex. 1009, generally. The cover letter to the study, dated March 19, 1998, indicates that the study was then active, and the cover page indicates a study activation

date of March 1998. *Id*. at 1, 2. The E1496 Protocol identifies the objectives of the described research study as:

> 2.1 To compare the response rate, time to progression and survival for patients with low grade lymphoma treated with the cyclophosphamide - fludarabine regimen with a control arm consisting of standard treatment with CVP.
>
> 2.2 To determine the effect of maintenance with anti-CD20 (IDEC C2B8) on time to progression and survival and its effects on lymphocyte number, subsets, and quantitative immunoglobulin levels over time.

Id. at 7.

The E1496 Protocol appears to include, as "Appendix I," the E1496 Patient Consent Form discussed in Part II.C., above. *Compare id.* at 45–47 *with* Ex. 1008, 1–3.

2. Discussion

Petitioner contends that the E1496 Protocol anticipates claim 1 of the '172 patent because it describes a study in which a subset of low-grade lymphoma patients are treated with CVP chemotherapy, followed by four once-weekly doses of 375 mg/m^2 of rituximab every six months for two years. Pet. 39–41.

Patent Owner proffers arguments similar to those discussed above with regard to the E1496 Patient Consent Form in response to this asserted ground of unpatentability. In particular, Patent Owner asserts that Petitioner has not shown either that the E1496 Protocol qualifies as a printed publication, or that the E1496 Protocol discloses treating a LG-NHL patient

with "CVP therapy to which the patient responds, followed by rituximab maintenance therapy," as required by claim 1. Prelim. Resp. 14–25; 27–33.

We agree with Patent Owner that Petitioner has not shown that the E1496 Protocol was publicly accessible to the extent required to establish it as a "printed publication" for purposes of this decision.

As an initial matter, we note that several of the arguments relied upon by Petitioner to support its contention that the E1496 Protocol was publicly accessible closely resemble those previously addressed by the Board in its Decision Denying Institution of *Inter Partes* Review in IPR2015-00418. *See Boehringer Ingelheim Int'l*, IPR2015-00418, slip op. at 7–14 (PTAB July 13, 2015) (Paper 14). Nevertheless, because Petitioner presents new evidence, in the form of Dr. Longo's testimony, concerning the dissemination of the E1496 Protocol, we evaluate Petitioner's arguments on the merits.

As with the E1496 Patient Consent Form, although Petitioner presents evidence to suggest that the E1496 Protocol was not treated as confidential, Petitioner fails to adequately establish that it was disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the art exercising reasonable diligence, could have located it. Notably, Dr. Longo does not testify that he received the E1496 Protocol before the priority date of the '172 patent (or that he received it at all). Furthermore, while Dr. Longo testifies that he "was at liberty to distribute the protocol and to discuss it with [inquiring] practicing physicians . . . under no obligation of confidentiality," (Ex. 1002 ¶ 53), Dr. Longo does not indicate that he did in

fact discussed the protocol with such physicians, or identify when any such discussions might have taken place (*id*.). Likewise, although Dr. Longo testifies that "the E1496 Protocol was freely disseminated to any referring doctor or prospective patient" (*id*. ¶ 55), he does not identify any particular instances or the timeframe of its dissemination.

Rather, Dr. Longo's testimony remains largely hypothetical, as it is directed to what he or other physicians "would" do. For example, Dr. Longo testifies that "ECOG would send out an updated list of all active clinical trials to all ECOG affiliate institutions. My institution would incorporate these ECOG trials into our 'menu' of open trials that was posted in clinician work spaces." Ex. 1002 ¶ 29. Dr. Longo further testifies that "[d]octors with patients seeking information regarding active clinical trials for low-grade B-cell NHL in the mid-1990s would have been able to contact ECOG or ECOG-affiliated institutions like mine to inquire about our ongoing clinical trials" (*id.* ¶ 55), and "ECOG affiliates would send letters listing all active ECOG trials to any community physician requesting such information." *Id.* ¶ 56. In addition, Dr. Longo testifies that "[a]fter learning about E1496, an interested physician would then contact ECOG or a local ECOG institute to learn more about how to enroll patients in E1496." *Id*. ¶ 57. Absent from Dr. Longo's testimony, however, is corroborating evidence to suggest that the events Dr. Longo speculates "would" have occurred in fact did occur. *See Finnigan Corp. v. United States ITC*, 180 F.3d 1354, 1366 (Fed. Cir. June 9, 1999) ("The law has long looked with

disfavor upon invalidating patents on the basis of mere testimonial evidence absent other evidence that corroborates that testimony.").

For the same reasons discussed in Part II.C.2., above, we are similarly unpersuaded by Petitioner's contention that a diligent artisan of ordinary skill could have located the E1496 Protocol via the list of then active protocols on the ECOG website. *See* Pet. 31–33.

Accordingly, because Petitioner has not adequately established, for purposes of this decision, that the E1496 Protocol is a prior art printed publication, we determine that Petitioner has not shown sufficiently that there is a reasonable likelihood that it would prevail in showing the unpatentability of claim 1 as anticipated by that reference.

F. Obviousness over Grossbard and Rituxan Label

Petitioner asserts that claim 1 is unpatentable under § 103 as obvious in view of the combination of Grossbard and the Rituxan Label. Pet. 34, 43–49. Patent Owner disagrees. Prelim. Resp. 26–27, 34–55.

1. Grossbard

Grossbard describes several ongoing clinical trials employing rituximab to treat cancer. Grossbard discloses one study in which "elderly patients with aggressive non-Hodgkin's lymphoma" responsive to cyclophosphamide, doxorubicin, vincristine, and prednisone ("CHOP") chemotherapy are subsequently treated with "four weekly doses of rituximab every 6 months for 2 years" as maintenance therapy. Ex. 1010, 1770.

Grossbard additionally discloses two studies of low-grade lymphoma patients, including "a phase II trial of CHOP followed by rituximab, with special attention to measurement of minimal residual disease" (*id*.), and the ECOG1496 study discussed above, which Grossbard describes as "a phase III trial of cyclophosphamide and fludarabine (Fludara) vs CVP (cyclophosphamide, vincristine, and prednisone), followed by rituximab or observation." *Id*.

With regard to dosing, Grossbard reports that "initial phase I studies with rituximab never reached a maximum tolerated dose" (*id*. at 1769), and notes that "[s]ome published studies have used larger doses than the currently approved 375 mg/m^2 weekly x 4 regimen. For example, Coiffier et al. used doses up to 500 mg/m^2 in a weekly x 8 regimen in patients with intermediate or high-grade lymphoma." *Id*. Grossbard further remarks that "the best dose and schedule of rituximab remain to be established." *Id*.

Grossbard observes that "rituximab represents a significant advance in the treatment of lymphoma" (*id*. at 1770); it cautions, however, that "[a]lthough the concept of MoAb therapy is simple, a host of unforeseen difficulties hindered the realization of clinical benefit from this therapeutic approach" (*id.* at 1769).

2. Rituxan Label

The Rituxan Label describes Rituxan (rituximab) as a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. Ex. 1008, 1. The product is formulated for intravenous

administration and is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, CD20 positive, B-cell NHL. *Id*. The reference reports results from various clinical trials in which 375 mg/m^2 of Rituxan was administered intravenously weekly for four doses to patients having relapsed or refractory NHL, including relapsed or refractory LG-NHL. *Id*.

3. Discussion

Petitioner contends that claim 1 of the '172 patent is rendered obvious by the combination of Grossbard and the Rituxan Label because Grossbard describes "three separate trials testing rituximab as maintenance therapy, including one in which CVP was given as the induction chemotherapy" (Pet. 45), and the rituximab dosage recited in claim 1 is disclosed in both Grossbard and the Rituxan Label (*id.*). Petitioner further asserts that an ordinarily skilled artisan would have reason to combine Grossbard and the Rituxan Label "to build on the treatment protocols for low-grade B-cell lymphoma discussed in Grossbard." *Id*. at 46. Petitioner contends that a relevant skilled artisan "wanting to implement the treatment protocol of CVP followed by rituximab maintenance therapy described in Grossbard would logically look to Grossbard's disclosed rituximab dosing" in adjacent portions of the reference directed to different studies. *Id*. at 47. Petitioner likewise asserts that a relevant skilled artisan would have had a reasonable expectation of success in making the proposed combination because rituximab had proven safe in previous trials, and was the first monoclonal antibody approved for cancer treatment. *Id*. 48–49.

Patent Owner responds first that the Rituxan Label does not qualify as prior art because Petitioner has not presented evidence that the label "is a copy of an actual document publicly disseminated before the priority date" of the '172 patent. Prelim. Resp. 26. Patent Owner additionally contends, among other things, that Grossbard does not disclose any dosing regimen for rituximab maintenance therapy in LG-NHL subsequent to CVP chemotherapy, and that Petitioner fails to establish a reasonable expectation of success in using the rituximab maintenance protocol recited in claim 1 of the '172 patent. *Id.* at 35–42, 47–55.

As an initial matter, we agree with Patent Owner that Petitioner has not shown that the Rituxan Label was publicly accessible to the extent required to establish it as a "printed publication." Prelim. Resp. 26–27. Petitioner asserts, without evidence or elaboration, that "[t]he Rituxan label was made publicly available in November 1997 when Rituxan was approved and is therefore § 102(b) prior art." Pet. 34. Petitioner does not explain, however, how regulatory approval of the pharmaceutical Rituxan evidences public accessibility of the Rituxan Label set forth in Exhibit 1008. Indeed, Petitioner does not explicitly assert on what specific date it alleges that the Rituxan Label was publicly accessible. Nor does Petitioner provide any documentary or testimonial evidence to support its contention that the Rituxan Label was included in the packaging of a disseminated drug product, or otherwise made available in a manner such that persons interested and ordinarily skilled in the art exercising reasonable diligence would have been able to locate it before the priority date of the '172 patent.

For at least those reasons, we agree with Patent Owner that Petitioner has not met its burden of establishing that the Rituxan Label is a "printed publication." Prelim. Resp. 26.

We further agree with Patent Owner that Grossbard does not disclose or suggest the rituximab maintenance therapy dosing regimen required by claim 1 of the '172 patent. Although Grossbard observes that "[t]he value of rituximab maintenance therapy in low-grade lymphoma is the subject of two other cooperative group trials" (Ex. 1010, 1770), including the previously described ECOG1496 trial, the reference is silent as to the rituximab dosing regimen or amount employed (*id*.). In addition, Grossbard explicitly states that "the best dose and schedule of rituximab remain to be established." *Id.* at 1769.

Petitioner points to separate disclosures in Grossbard in an attempt to fill the gap regarding the treatment regimen and dosage amount recited in claim 1. In particular, Petitioner contends that a relevant skilled artisan would have employed the treatment frequency Grossbard discloses in its discussion of a study involving "elderly patients with aggressive non-Hodgkin's lymphoma" who received rituximab maintenance therapy subsequent to CHOP chemotherapy (*id*. at 1770), and dosage amount Grossbard identifies as the currently approved dosing for rituximab (*id.* at 1769) as rituximab maintenance therapy to treat LG-NHL patients responsive to CVP chemotherapy.

Neither Petitioner nor its experts adequately explains, however, why a relevant skilled artisan would have sought to treat LG-NHL patients with the

same rituximab dosing regimen employed in a study of a wholly different patient population—namely, *elderly patients* having *aggressive* non-Hodgkin's lymphoma that is responsive to *CHOP* chemotherapy—and for which no results are described. Nor has Petitioner or its experts sufficiently explained why an ordinarily skilled artisan would have used, or had a reasonable expectation of success in using, a rituximab dose of 375 mg/m^2 in such a treatment regimen, given Grossbard's express teachings that "doses up to 500 mg/m2 in a weekly x 8 regimen" had been used in patients with intermediate- or high-grade lymphoma, and that "the best dose and schedule of rituximab remain to be established." Ex. 1010, 1769.

In this regard, we observe that the spatial proximity of Grossbard's disclosures concerning separate ongoing studies involving distinct patient populations, as well as the approved dosage for rituximab, without more, is insufficient to establish a reason to, or reasonable expectation of success in, arriving at the claimed rituximab maintenance treatment regimen for LG-NHL patients. Contrary to Petitioner's suggestion (Pet. 47), the proposed combination of treatment steps from separate studies of distinct patient populations for a pharmaceutical for which "the best dose and schedule of rituximab remain to be established" (Ex. 1010, 1769) is not a simple case of combining embodiments disclosed adjacent to each other in a prior art patent to arrive at a predictable variation of the invention disclosed. Rather, because of the differences between patient populations at issue, and uncertainty surrounding the appropriate dosage regimen for rituximab highlighted by Grossbard, the rationale for making the cited combination

should have been made explicit. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417–18 (2007).

Accordingly, for the foregoing reasons, we conclude that Petitioner has not shown a reasonable likelihood of prevailing on its assertion that claim 1 is obvious in view of Grossbard and the Rituxan Label.

G. Obviousness over McNeil, Bishop, Dana, and Rituxan Label

Petitioner asserts that claim 1 is unpatentable under § 103 as obvious in view of the combination of McNeil, Bishop, Dana, and the Rituxan Label. Pet. 34, 49–58. Patent Owner disagrees. Prelim. Resp. 26–27, 55–68.

1. McNeil

McNeil describes a randomized trial for elderly patients with intermediate-grade NHL involving a combination treatment of CHOP and Rituxan (IDEC-C2B8). Ex. 1005, 266. McNeil explains that the trial, organized by the ECOG, "will recruit 630 patients age 60 and over" to receive the combination therapy. *Id*. McNeil additionally discloses that the trial will test the efficacy of CHOP plus rituxan maintenance therapy. *Id*. McNeil states that "[a]fter initial therapy, patients who responded will be again randomly assigned to receive the maintenance regimen — Rituxan every 6 months for 2 years — or observation." *Id*. McNeil further observes that "[t]his is the first randomized trial to address maintenance therapy in any kind of NHL." *Id*.

2. Bishop

Bishop discloses a study comparing the efficacy of CVP chemotherapy and cyclophosphamide, doxorubicin, vincristine, and prednisone ("CAVP") chemotherapy. Ex. 1006, 1. Bishop teaches that adding doxorubicin to CVP chemotherapy does not provide a clinical benefit over CVP for LG-NHL patients. *Id.* at 509, 510.

3. Dana

Dana describes a review of survival data for low-grade lymphoma patients from multiple studies to examine the efficacy of CHOP chemotherapy for such patients. Ex. 1007, 644. Dana reports that "[d]oxorubicin-containing treatment did not prolong the overall median survival of low-grade lymphoma patients compared with results with less-aggressive programs." *Id.*; *see also id.* at 645.

4. Discussion

Petitioner asserts that the combination of McNeil, Bishop, Dana, and the Rituxan Label renders obvious claim 1. In particular, Petitioner relies on McNeil, which is the underlying study of CHOP chemotherapy followed by rituximab maintenance therapy in elderly patients having intermediate-grade NHL described by Grossbard, as disclosing the recited frequency of rituximab treatment for maintenance therapy subsequent to chemotherapy. Pet. 50. Petitioner acknowledges that McNeil is directed to a different patient population and chemotherapy regimen than recited in the challenged claim, but contends that a relevant skilled artisan "reading McNeil's disclosure of CHOP followed by rituximab maintenance therapy for

intermediate-grade NHL and the Rituxan Label's disclosure of the effectiveness of rituximab for low-grade NHL would be encouraged to use rituximab maintenance therapy after standard induction chemotherapy for low-grade NHL." *Id.* at 54. Petitioner further asserts that an ordinarily skilled artisan would have employed the dosage amount disclosed by the Rituximab Label in such a maintenance therapy regimen. *Id.* at 52–53, 55–56. Relying on McNeil, Bishop and Dana, Petitioner also contends that an ordinarily skilled artisan would have known that, for LG-NHL patient, "CVP was both less toxic and equally effective as CHOP" (Pet. 50), and, therefore, had reason to substitute CVP chemotherapy in place of CHOP (*id.* at 55).

Patent Owner responds that the Rituximab Label does not qualify as a printed publication, and is therefore unavailable as prior art to the '172 patent. Prelim. Resp. 26–27. Of particular relevance to this decision, Patent Owner additionally asserts that McNeil fails to disclose the claimed rituximab maintenance dosing of four weekly doses of 375 mg/m^2 every six months for two years. *Id*. at 67–68.

For the reasons set forth in Part II.E.3., above, we agree with Patent Owner that Petitioner has not shown that the Rituxan Label was publicly accessible to the extent required to establish it as a "printed publication." Prelim. Resp. 26–27. The unavailability of the Rituxan Label as prior art undermines Petitioner's obviousness argument, as Petitioner relies on the Rituximab Label as disclosing the recited rituximab dosage amount of 375 mg/m^2 per week. Pet. 49–58. Indeed, although McNeil describes the

timing of rituximab maintenance doses, *i.e.*, "Rituxan every 6 months for 2 years" (Ex. 1005, 266), nowhere does it disclose the claimed weekly dosage amount of 375 mg/m^2. Bishop and Dana, which do not address rituximab therapy at all, likewise do not cure this defect.

Accordingly, for the foregoing reasons, we conclude that Petitioner has not shown a reasonable likelihood of prevailing on its assertion that claim 1 is obvious in view of McNeil, Bishop, Dana, and the Rituxan Label.

III. ORDER

In consideration of the foregoing, it is

ORDERED that the Petition is DENIED and no trial is instituted.

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