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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

BIOGEN, INC., and GENENTECH, INC.,
Patent Owners.

Case IPR2017-02127
Patent 8,206,711 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

Pfizer, Inc. ("Petitioner"), filed a Petition requesting an *inter partes* review of claims 1–9 of U.S. Patent No. 8,206,711 B2 (Ex. 1001, "the '711 patent"). Paper 2 ("Pet."). Biogen, Inc., and Genentech, Inc. (collectively, "Patent Owners") filed a Preliminary Response. Paper 8 ("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*

Petitioner indicates that the '711 patent is at issue in *Genentech, Inc. v. Celltrion, Inc.*, Case No. 1:18-cv-00574 (D.N.J.), and *Celltrion, Inc. v. Genentech, Inc.*, Case No. 3:18-cv-00276 (N.D. Cal.). Paper 7. Patent Owners state that the '711 patent is at issue in *Genentech, Inc., Biogen Inc., and City of Hope v. Sandoz, Inc. and Sandoz International GMBH*, Case No. 2:17-cv-13507 (D.N.J.). Paper 6.

The '711 patent has previously been challenged by Celltrion, Inc. (IPR2017-01229); however, the Board declined to institute *inter partes* review in that proceeding. Pet. 6; Paper 4, 2; *Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01229 (PTAB Oct. 23, 2017) (Paper 10). The parties do not identify any additional proceedings involving the '711 patent.

Concurrent with this proceeding, Petitioner has also filed a petition for *inter partes* review of related U.S. Patent No. 7,682,612 B1 ("the '612 patent") (IPR2017-02126). Pet. 6; Paper 4, 2. The '612 patent has previously been challenged by Celltrion, Inc. (IPR2017-01227 and IPR2017-01230); however, the Board declined to institute *inter partes* review in those proceedings. Pet. 6; Paper 4, 2; *Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01227 (PTAB Oct. 23, 2017) (Paper 10); *Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01230 (PTAB Oct. 12, 2017) (Paper 12).

B. *The '711 Patent*

The '711 patent is titled "Treatment of Chronic Lymphocytic Leukemia Using Anti-CD20 Antibodies." Ex. 1001, [54]. The '711 patent discloses therapeutic regimens involving the administration of anti-CD20 antibodies for the treatment of chronic lymphocytic leukemia ("CLL"). *Id.* at Abstract, 2:16–21. "[A] particularly preferred chimeric anti-CD20 antibody is RITUXAN® (rituximab), which is a chimeric gamma 1 anti-human CD20 antibody." *Id.* at 3:18–20.

The '711 patent explains that the discovery that rituximab is effective in treating CLL is surprising, "notwithstanding the reported great success of RITUXAN® (rituximab) for the treatment of relapsed and previously treated low-grade non-Hodgkin's lymphoma [("LG-NHL")]" (Ex. 1001, 2:23–26), because of differences in the numbers of tumor cells and density of CD20 expression observed in these two patient populations. *Id.* at 2:16–35.

> In particular, this discovery is surprising given the very high numbers of tumor cells observed in such patients and also given

> the fact that such malignant cells, e.g., CLL cells, typically do not express the CD20 antigen at the high densities which are characteristic of some B-cell lymphomas, such as relapsed and previously-treated low-grade non-Hodgkin's lymphomas. Consequently, it could not have been reasonably predicted that the CD20 antigen would constitute an appropriate target for therapeutic antibody therapy of such malignancies.

Id. at 2:26–35.

With regard to dosing, the '711 patent discloses that "[t]ypically effective dosages will range from about 0.001 to about 30 mg/kg body weight, more preferably from about 0.01 to 25 mg/kg body weight, and most preferably from about 0.1 to about 20 mg/kg body weight." Ex. 1001, 3:50–54. "Such administration may be effected by various protocols, e.g., weekly, bi-weekly, or monthly, dependent on the dosage administered and patient response." *Id.* at 3:55–57. In Example 3, the '711 patent reports clinical trial results in which patients were treated with varying doses of rituximab, including a study of CLL patients treated with one dose of 375 mg/m^2, and three subsequent weekly doses of 500–1500 mg/m^2. *Id.* at 6:8–30.

C. *Illustrative Claims*

Independent claims 1 and 9, reproduced below, are illustrative of the challenged claims of the '711 patent.

> 1. A method of treating chronic lymphocytic leukemia (CLL) in a human patient, comprising administering rituximab to the patient in an amount effective to treat the CLL, wherein the rituximab is administered to the patient at a dosage of 500 mg/m^2.

Ex. 1001, 8:17–21.

> 9. A method of treating chronic lymphocytic leukemia (CLL) in a human patient, comprising administering rituximab to the patient in an amount effective to treat the CLL, wherein the rituximab is administered to the patient at dosages of 500 mg/m^2, and further comprising administering a chemotherapeutic regimen to the patient, wherein the chemotherapeutic regimen comprises fludarabine and cyclophosphamide.

Id. at 8:36–43.

The challenged dependent claims variously add to claim 1 requirements concerning the administration of chemotherapeutic regimens, the frequency of rituximab administration, and the use of radiolabeled anti-CD20 antibody. *Id.* at 8:22–35.

D. *Evidence Relied Upon*

Petitioner relies upon the following prior art references (Pet. 8, 32–36):

Maloney, D.G., et al., *Phase I Clinical Trial Using Escalating Single-Dose Infusion of Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients with Recurrent B-Cell Lymphoma,* 84(8) BLOOD 2457–2466 (1994) ("Ex. 1003) ("Maloney 1994").

Maloney, D.G., et al., "*IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients with Relapsed Low-Grade Non-Hodgkin's Lymphoma*," 90(6) BLOOD 2188–2195 (1997) (Ex. 1004) ("Maloney Sept. 1997").

Maloney, D.G., et al., "*IDEC-C2B8: Results of a Phase I Multiple-Dose Trial in Patients with Relapsed Non-Hodgkin's Lymphoma*," 15(10) J. CLINICAL ONCOLOGY 3266–3274 (1997) (Ex. 1005) ("Maloney Oct. 1997").

Press Release, Genentech, Inc. "Genentech and IDEC Pharmaceuticals to Collaborate on Anti-CD20 Monoclonal Antibody for B-Cell Lymphomas," (March 16, 1995) (Ex. 1006) ("Genentech Press Release").

O'Brien, S., et al., "*Fludarabine (FAMP) and Cyclophosphamide (CTX) Therapy in Chronic Lymphocytic Leukemia (CLL)*," 88(10 Supp. 1) BLOOD 480a (1996) (Ex. 1007) ("O'Brien").

Petitioner also relies upon the Declaration of Howard Ozer, M.D. (Ex. 1002) to support its contentions.

E. *Asserted Grounds of Unpatentability*

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

Claim(s)	Basis	Reference(s)
1, 5, 8	§ 103(a)	Maloney 1994, Maloney Sept. 1997, and Genentech Press Release
2	§ 103(a)	Maloney 1994, Maloney Sept. 1997, Maloney Oct. 1997, and Genentech Press Release
3, 4, 9	§ 103(a)	Maloney 1994, Maloney Sept. 1997, Maloney Oct. 1997, Genentech Press Release, and O'Brien

II. ANALYSIS

A. *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 include a practicing oncologist with at least an M.D. degree and several years of experience treating patients with CLL and/or researching treatments for CLL, including with chemotherapeutic drugs." Pet. 9 (citing Ex. 1002 ¶ 15). Patent Owners do not address Petitioner's position on this matter and do not propose their 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. Ozer (Ex. 1002, Attachment A) and, at this stage in the proceeding, we consider him 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).

B. *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). 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 Owners propose constructions for the term "amount effective to treat the CLL." Pet. 28–31; Prelim. Resp. 8–18. In view of our analysis, we determine that construction of claim terms is not necessary for purpose of this Decision. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))). In this regard, we observe that our analysis below applies with equal force under either Petitioner or Patent Owners' proposed construction of "amount effective to treat the CLL." Nevertheless, for clarity, we apply Petitioner's proposed construction of "amount effective to treat the CLL," and treat that claim phrase as non-limiting for purposes of this decision. *See* Pet. 30–31 (noting that the recitation of a 500 mg/m^2 rituximab dose in the challenged claims "support a claim for a positive clinical benefit for treating CLL," but asserting that "amount effective to treat" does not further limit the claims).

C. *References Relied Upon*

1. Maloney 1994

Maloney 1994 describes a phase I clinical trial dose escalation study to ascertain the toxicity of rituximab in human patients. Ex. 1003, 3. Patients with relapsed low-grade B-cell non-Hodgkin's lymphoma, including one small lymphocytic lymphoma ("SLL") patient, received a single intravenous infusion of up to 500 mg/m^2 rituximab.[1] *Id.* at 5–6. All tested doses were well-tolerated, including the 500 mg/m^2 dose, and "no dose-limiting toxicities were identified," though some infusion-related side effects were observed. *Id.* at 9. Maloney 1994 reports that "[t]here was a does-dependent, rapid, and specific depletion of the B cells in all patients, especially those receiving doses of more than 100 mg." *Id.* at 6. Maloney 1994 goes on to suggest that "[e]xtension of these studies using multiple doses to achieve prolonged, tumor-saturating levels may lead to responses in patients with more extensive disease." *Id.* at 11.

In discussing treatment targets for NHL patients, Maloney 1994 states that, in contrast to other antigens, CD20 is "present on the surface of nearly all B cells" and, thus, "provides a more universal target for immunotherapy." Ex. 1003, 3. For example, Maloney 1994 observes that "[m]ore than 90% of B-cell NHLs express this surface protein." *Id.* With regard to CLL patients, however, Maloney 1994 notes that CD20 is "expressed at a lower density on B-cell chronic lymphocytic leukemia" than on B-cell NHLs. *Id.*

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[1] The SLL patient received a dose of 50 mg/m^2. Ex. 1003, Table 1.

2. Maloney Sept. 1997

Maloney Sept. 1997 describes a "phase II, multicenter study evaluating four weekly infusions of 375 mg/m^2 IDEC-C2B8 in patients with relapsed low-grade or follicular NHL." Ex. 1004, 1. In that study, 17 of the 37 patients enrolled exhibited clinical responses, i.e., partial or complete remission, to rituximab treatment. *Id.* at 5, Table 3.

Notably, however, "none of the 4 patients with small lymphocytic lymphoma (WF group A) responded." *Id.* at 6; *see also id.* at 5. Maloney Sept. 1997 reasons that the absence of response in SLL patients may result from the decreased expression of CD20 on the B-cells of SLL patients relative to the B-cells of NHL patients. *Id.* at 6.

> Although patients with chronic lymphocytic leukemia (CLL) were excluded from this trial (based on the presence of >5,000 lymphocytes/μL for this histologic subgroup), it is possible that the decreased response rate in this [SLL] subgroup was due to a lower expression of the CD20 surface antigen that has been observed in cases of CLL.

Id. at 6.

3. Maloney Oct. 1997

Maloney Oct. 1997 describes a phase I trial to evaluate the safety, pharmacokinetics, and biologic effect of four weekly infusions of rituximab, administered in doses of 125 mg/m^2 to 375 mg/m^2, to patients with relapsed NHL. Ex. 1005, 3. Maloney Oct. 1997 reports a 33% rituximab response rate (partial remission) for patients who completed the study protocol, at each dose tested. *Id.* at Table 6. Notably, treatment was discontinued for two patients, including an SLL patient who experienced "[g]rade 4-related

thrombocytopenia within 24 hours of the first infusion" of rituximab. *Id.* at 6.

In summarizing prior *in vitro* work, Maloney Oct. 1997 reports that rituximab "increases sensitivity to the cytotoxic effect of chemotherapy/toxins in some resistant human lymphoma cell lines." Ex. 1005, 3–4.

4. Genentech Press Release

The Genentech Press Release discloses that "IDEC-C2B8 is being developed for certain lymphomas and leukemias characterized by excessive B-cell proliferation, including low grade and follicular non-Hodgkin's B-cell lymphomas." Ex. 1006, 1. The Genentech Press Release goes on to explain:

> Phase II studies of IDEC-C2B8 in NHL reveal encouraging results indicating that it may provide an effective and well-tolerated treatment. IDEC, in cooperation with Genentech, will conduct a Phase III trial scheduled to begin by mid-1995 to attempt to confirm these results. Genentech and IDEC are planning additional studies with IDEC-C2B8 to support this primary indication in NHL and in other B-cell mediated cancers such as intermediate grade NHL and chronic lymphocytic leukemia."

Id.[2]

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[2] Because we determine that Petitioner has not established a reasonable likelihood of prevailing on its assertion that an ordinarily skilled artisan would have had a reasonable expectation of success in combining the cited references to arrive at the claimed invention, we need not address whether Petitioner has sufficiently established that the Genentech Press Release qualifies as a printed publication. Nevertheless, we highlight, as Patent Owners point out, that Petitioner failed to submit a declaration from the

5. O'Brien

O'Brien describes a study of fludarabine and cyclophosphamide combination therapy in CLL patients. Ex. 1007, 3. In particular, O'Brien discloses that fludarabine and cyclophosphamide combination therapy "is an extremely active regimen in CLL with a response rate of close to 100% in [patients] not previously refractory to [fludarabine]." *Id.*

D. *Reasonable Expectation of Success*

"An obviousness determination requires finding both 'that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.'" *CRFD Research, Inc. v. Matal*, 876 F.3d 1330, 1340 (Fed. Cir. 2017) (quoting *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–1368 (Fed. Cir. 2016)).

"The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Id.* at 1367. A reasonable expectation of success "does not require *certainty* of success." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006).

> However, to have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly

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Internet Archive attesting to the date the Genentech Press Release was captured by the Way Back Machine (Prelim. Resp. 19).

> arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. Similarly, prior art fails to provide the requisite reasonable expectation of success where it teaches merely to pursue a general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Id. (internal quotations omitted).

Each of the three grounds of unpatentability presented by Petitioner relies on the same arguments concerning the existence of a reasonable expectation of success in treating CLL with rituximab. Pet. 36, 37–53. Namely, Petitioner contends that Maloney 1994 and the Genentech Press Release would have provided an ordinarily skilled artisan with a reasonable expectation of success in arriving at the claimed invention. *Id.* On the record before us, and for purposes of this decision, we agree with Patent Owners that Petitioner has not met its burden to establish a reasonable likelihood of success that it would prevail in showing that an ordinarily skilled artisan would have had a reasonable expectation of success in using any dosage of rituximab to treat CLL. Rather, as explained below, although the evidence of record suggests a rationale for exploring the possibility of treating CLL with rituximab, such suggestion amounts to no more than an invitation to experiment, and is, therefore, inadequate to establish a reasonable expectation of success in CLL treatment for purposes of this decision.

As Petitioner acknowledges, NHL and CLL are different cancers. Pet. 10 ("[L]ike NHL, another type of cancer, CLL patients experience the uncontrollable growth of the body's B-cells."). Indeed, Petitioner highlights two important differences between CLL and NHL that would have been known to an ordinarily skilled artisan at the time of invention of the '711 patent, and would have influenced such an artisan's expectation of success in applying an NHL therapy to treat CLL. First, "generally speaking, CLL patients have a higher tumor burden" (Pet. 11), with "about 100 times more cancerous B-cells than NHL patients" (*id.*; *see also* Ex. 1002 ¶ 33; Ex. 1008, 28). Second, CD20, the antigen to which rituximab binds, is expressed at a lower density on CLL B-cells than on NHL B-cells or normal B-cells. Pet. 42 (citing Ex. 1002 ¶ 85); *see also* Ex. 1008, 25–26; Ex. 2003, 1, 5. "[T]he weaker density of CD20 [in CLL] is akin to having a smaller 'target' for rituximab to hit, making it less likely that any given unit of rituximab successfully binds to the CD20 antigen." Pet. 42 (citing Ex. 1002 ¶ 85). Taken together, these characteristics of CLL mean that a CLL patient has 100-fold more cancerous B-cells than an NHL patient, and rituximab is significantly less likely to bind to any one of those cancerous CLL B-cells than it would be to bind an NHL B-cell.

Despite the acknowledged differences in tumor burden and rituximab antigen expression between CLL B-cells and NHL B-cells, none of the references on which Petitioner relies describes studies of, or treatment parameters for, the use of rituximab to treat CLL. Nor do those studies discuss the specifics of how rituximab treatment might be modified to

address the characteristics of CLL. Rather, the cited rituximab references simply disclose studies employing rituximab to treat NHL. Indeed, the rituximab trial described in Maloney Sept. 1997 *expressly excludes* CLL patients, based on their high tumor burden relative to NHL patients. Ex. 1004, 6 ("patients with chronic lymphocytic leukemia (CLL) were excluded from this trial (based on the presence of >5,000 lymphocytes/μL for this histologic subgroup)"). Furthermore, when the four SLL patients who took part in the Maloney Sept. 1997 study failed to respond to rituximab treatment, the investigators reasoned that "it is possible that the decreased response rate in this [SLL] subgroup was due to a lower expression of the CD20 surface antigen that has been observed in cases of CLL." Ex. 1004, 6. Similarly, in the Maloney Oct. 1997 study, rituximab treatment was discontinued for an SLL patient who experienced grade 4 thrombocytopenia subsequent to rituximab infusion. Ex. 1005, 6.

The paucity of record evidence concerning clinical trials of rituximab in CLL patients, or other results from, or treatment parameters for, studies of rituximab in CLL is consistent with the evidence before us suggesting that no such studies had been performed in the relevant time frame.[3] For example, Jensen,[4] confirms that as of mid-1998, the "[e]fficacy and safety in

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[3] Petitioner states "The earliest priority date to which the claims of the '711 patent is entitled is the filing date of the '658 provisional patent application—i.e., November 9, 1998." Pet. 24; *see also id.* at 8–9 (applying November 9, 1998 priority date).

[4] Jensen, M., et al., "*Rapid Tumor Lysis in a Patient with B-cell Chronic*

the treatment of chronic lymphocytic leukemia (CLL) and other blood-born tumors [with rituximab] ha[d] not been investigated." Ex. 1009, 1.

Nevertheless, Petitioner contends that Maloney 1994 and the Genentech Press Release would have afforded an ordinarily skilled artisan "a reasonable expectation of success in using rituximab to treat CLL by reducing cancerous B-cells." Pet. 36. In particular, Petitioner asserts that "Maloney 1994 suggested that anti-CD20 antibodies (e.g., rituximab) could be useful therapies for both NHL and CLL cancers, because both diseases manifested in CD20-positive B-cells." *Id.* at 38. Petitioner also contends that an ordinarily skilled artisan would have had a reasonable expectation of success in using rituximab to treat CLL based on the Genentech Press Release's "reporting on Patent Owners' further development of rituximab to treat CLL."[5] *Id.* at 39.

Consistent with the discussion of the record evidence above, however, neither Maloney 1994 nor the Genentech Press Release reports any study

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Lymphocytic Leukemia and Lymphocytosis Treated with an Anti-CD20 Monoclonal Antibody (IDEC-C2B8, Rituximab)," 77 ANN. HEMATOLOGY 89–91 (1998) (Ex. 1009) ("Jensen").

[5] Petitioner variously argues that: Maloney 1994 and the Genentech Press Release would have provided a reasonable expectation of success in arriving at the claimed invention (Pet. 36); Maloney 1994 suggested that rituximab could have been used to treat CLL (*id.* at 38–39); and the Genentech Press Release provided a reasonable expectation of success is using rituximab to treat CLL (*id.* at 39–41). Our analysis applies with equal force regardless of whether Maloney 1994 and the Genentech Press Release are considered together, individually, or in combination with additional cited references.

results, clinical endpoints, treatment parameters, or other information relating to how one would treat CLL with rituximab, or why one would reasonably expect such treatment to be successful in view of the higher tumor burden and lower expression of CD20 observed in CLL relative to NHL. Ex. 1006, 1–2. Maloney 1994, at best, indicates that CD20 is a "more universal target for immunotherapy" than patient-specific anti-idiotype monoclonal antibodies (Ex. 1003, 3), and that rituximab treatment warrants further study in "patients with more extensive disease" (*id.* at 11). Maloney 1994 does not, however, disclose any study of rituximab in CLL patients, or teach any treatment parameters for using rituximab in CLL patients. In fact, the only explicit discussion of CLL in Maloney 1994 is the disclosure that CD20, the target for rituximab, is "expressed at a lower density on B-cell chronic lymphocytic leukemia." *Id.* at 3. Thus, to the extent Maloney 1994 suggests anything at all regarding CLL treatment, it is that there is a lower probability that rituximab would be useful to treat CLL than NHL, because CLL cancer cells are a smaller target that is more difficult for rituximab to hit.

Moreover, although Maloney 1994 states that LG-NHL patients treated with rituximab in doses of 10 mg/m^2 up to 500 mg/m^2 exhibited a "dose-dependent, rapid, and specific depletion of the B cells" (Ex. 1003, 6), that reference does not report a positive "maximal response" result for the sole SLL patient enrolled in the study (*id.* at Table 1).[6] Nor does it discuss

[6] As explained above with regard to Maloney Sept. 1997, SLL B-cells, like

any particulars as to how the trial results, or rituximab treatment more broadly, might be applied in the context of CLL. Accordingly, at most, Maloney 1994 might be said to encourage investigation of using rituximab to treat CLL; it does not provide, however, any reasonable expectation of success in such treatment.

Akin to Maloney 1994, the Genentech Press Release is devoid of any study results or parameters for the treatment of CLL. Furthermore, the Genentech Press Release does not, as Petitioner suggests, disclose "that Patent Owners were conducting rituximab clinical trials with CLL patients" (Pet. 39). Ex. 1006, 1–2. Rather, the rituximab clinical trials discussed in the press release relate exclusively to the treatment of NHL patients. *Id.* at 1. With regard to CLL, the Genentech Press Release indicates only that rituximab "is being developed for certain lymphomas and leukemias characterized by excessive B-cell proliferation" (Ex. 1006, 1), and that "Genentech and IDEC are planning additional studies with IDEC-C2B8 to support this primary indication in NHL and in other B-cell mediated cancers such as intermediate grade NHL and chronic lymphocytic leukemia" (*id.*). Thus, although we agree with Petitioner that the Genentech Press Release invites investigation of what "seem[s] to be a promising field of experimentation," we nevertheless find that the press release provides "only general guidance as to the particular form of the claimed invention or how to

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CLL B-cells, express CD20 at lower levels that NHL B-cells. *See, e.g.*, Ex. 2003, 4.

achieve it." *Medichem*, 437 F.3d at 1165. The Genentech Press Release is, therefore, insufficient to establish a reasonable expectation of success in treating CLL with rituximab for purposes of this decision.

Furthermore, because Maloney 1994 and the Genentech Press Release suffer from the same shortcomings, namely, an absence of any meaningful disclosure concerning studies of, or parameters for, treating CLL with rituximab, those references together also would have failed to supply an ordinarily skilled artisan with a reasonable expectation of success in arriving at the claimed invention.

Likewise, in view of the 100-fold increase in tumor burden and significant decrease in CD20 expression observed in CLL relative to NHL, we are unpersuaded by Petitioner's contention that an ordinarily skilled artisan would have had a reasonable expectation of success in administering rituximab in a dose of 500 mg/m^2 to treat CLL. Pet. 41–44. Even accepting Petitioner's contention that Maloney 1994 and Maloney Sept. 1997 taught the administration of rituximab in a dose of 500 mg/m^2 to treat NHL (*id.*), Petitioner does not adequately explain why, given the 100-fold increase in tumor burden and significant decrease in CD20 expression observed in CLL relative to NHL, an ordinarily skilled artisan would have expected a rituximab dose of 500 mg/m^2 to treat CLL. Rather, Petitioner assumes that an ordinarily skilled artisan would have considered the dose-dependent depletion of B-cells in NHL patients to be predictive of B-cell depletion in CLL patients, but does not endeavor to justify that assumption, or explain why an ordinarily skilled artisan would reasonably expect that increasing the

rituximab dose effective to treat NHL by about a third (from 375 mg/m^2 to 500 mg/m^2) would treat a disease with 100-fold more cancerous B-cells to which rituximab is less likely to bind. For example, Petitioner's statement that these differences between CLL and NHL would have "suggested that a higher rituximab dose likely would be needed to treat CLL" (*id.* at 42) is insufficient to support the contention that an ordinarily skilled artisan would have had a reasonable expectation of success in treating CLL with 500 mg/m^2 of rituximab. Petitioner's assertion that it would have been obvious to use 500 mg/m^2 of rituximab to treat CLL because that is the "only dose above 375 mg/m^2 disclosed as safe and effective in Maloney 1994" (*id.*) similarly misses the mark.[7]

Neither do we find persuasive Petitioner's arguments concerning the complementarity of rituximab and chemotherapeutic regimens (Pet. 43). First, Maloney Oct. 1997 only discloses that rituximab increases the sensitivity of "some resistant human lymphoma cell lines" to chemotherapy *in vitro* (Ex. 1005, 3–4)—it does not disclose any sensitization of leukemia cells. Second, the teaching that rituximab sensitizes lymphoma cells to chemotherapy does not cure the defects in Petitioner's reasonable expectation of success arguments, because the fact remains that CLL patients exhibit a 100-fold greater tumor burden, and CLL B-cells have

[7] It is also factually incomplete, as Maloney 1994 does not identify any theoretical maximum dose for rituximab. To the contrary, Maloney 1994 reports that "no dose-limiting toxicities were identified" at even the highest tested dose level. Ex. 1003, 9.

fewer "targets" for rituximab to bind. Petitioner does not adequately address why an ordinarily skilled artisan would reasonably have expected under those conditions that rituximab would sensitize CLL B-cells to chemotherapeutic agents.

In addition, Petitioner's reliance on the dictate that "where there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness" (Pet. 41 (quoting *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004)) is misplaced. The challenged claims relate to the treatment of an entirely different disease (CLL) than the cited rituximab references (NHL), and, as explained above, Petitioner has not adequately established a link between the treatment of those distinct diseases. For the same reasons, we find unpersuasive Petitioner's arguments that treating CLL with a 500 mg/m^2 dose of rituximab would have been obvious to try, or the result of routine optimization (Pet. 44).

We also find unavailing Petitioner's reliance on law pertaining to the utility requirement set forth in 35 U.S.C. § 101, to support the proposition that the purported initiation of clinical trials by Genentech warrants a presumption "that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility" (Pet. 40 (quoting *Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 619 F.3d 1329, 1343 (Fed. Cir. 2010) (quoting MPEP (2008) § 2107.03 at IV))). As explained above, Petitioner has not adequately established, for purposes of this decision, that Patent Owners had initiated clinical trials of rituximab in human CLL patients. By Petitioner's

own logic, it would at best be entitled to a presumption that rituximab is useful to treat NHL, but not CLL. Moreover, Petitioner does not identify any authority or provide a persuasive rationale for employing a § 101 utility analysis to satisfy the § 103 requirement for a reasonable expectation of success.

Neither are we persuaded by Petitioner's reference to *Soft Gel Technologies., Inc., v. Jarrow Formulas, Inc.*, 864 F.3d 1334 (Fed. Cir. 2017), in which our reviewing court rejected the argument that the performance of confirmatory or follow-up studies evinces the absence of any reasonable expectation of success in arriving at the invention claimed (Pet. 40–41). The court's determination in *Soft Gel* that "[a]n incentive to conduct a confirmatory study frequently exists even when one has every reason to expect success," 864 F.3d at 1342, is inapposite here, as Petitioner has not adequately established, for purposes of this decision, that any study of rituximab treatment in CLL patients had been performed prior to the invention of the '711 patent, much less a confirmatory study.

Similarly, Petitioner's resort to the Board's finding in *Biomarin Pharmaceutical. Inc., v. Genzyme Therapeutic Products Ltd. Partnership*, Case IPR2013-00534, Paper 81, at 17 (PTAB Feb. 23, 2015)) (Pet. 41), serves to underscore what is lacking from the instant Petition. In *Biomarin*, the Board explained that an ordinarily skilled artisan would have had a reasonable expectation of success when "[w]hat remained was the execution of human clinical trials, arguably 'routine' to a person of ordinary skill in the art, to verify the expectation that a specific dosage (within a previously

suggested dosage range) and corresponding dosage regimen would have been safe and effective." *Biomarin*, IPR2013-00534, Paper 81, at 17. Here, the prior art fails to provide guidance concerning clinical endpoints, treatment parameters, or other information relating to how one would treat CLL with rituximab, or why one would reasonably expect such treatment to be successful, but instead invites experimentation to determine whether rituximab may in fact treat CLL.

For the foregoing reasons, therefore, we determine that the information presented in the Petition fails to establish a reasonable likelihood that Petitioner would prevail in challenging: claims 1 and 5–8 of the '711 patent as obvious in view of Maloney 1994, Maloney Sept. 1997, and the Genentech Press Release; claim 2 of the '711 patent as obvious in view of Maloney 1994, Maloney Sept. 1997, Maloney Oct. 1997, and the Genentech Press Release; and claims 3, 4, and 9 of the '711 patent as obvious in view of Maloney 1994, Maloney Sept. 1997, Maloney Oct. 1997, the Genentech Press Release, and O'Brien.

III. CONCLUSION

For the foregoing reasons, we conclude that the information presented in the Petition does not establish a reasonable likelihood that Petitioner would prevail in showing that claims 1–9 of the '711 patent are unpatentable.

IV. ORDER

In consideration of the foregoing, it is

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

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