Trials@uspto.gov
571-272-7822

Paper 10
Date: April 30, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

BIOGEN, INC. AND GENENTECH, INC.,
Patent Owner.

Case IPR2017-02126
Patent 7,682,612 B1

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

SNEDDEN, *Administrative Patent Judge*.

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

I. INTRODUCTION

Pfizer, Inc. ("Petitioner") filed a Petition to institute an *inter partes* review of claims 1–13, 15–35, and 37–60 (Paper 1; "Pet.") of U.S. Patent No. 7,682,612 B1 (Ex. 1001; "the '612 patent"). Biogen, Inc. and Genentech, Inc. (collectively, "Patent Owner") filed a Patent Owner Preliminary Response. Paper 8.

We have authority to determine whether to institute an *inter partes* review under 35 U.S.C. § 314 and 37 C.F.R. § 42.4(a). Upon considering the Petition and the Preliminary Response, we determine that Petitioner has not shown a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–13, 15–35, and 37–60. Accordingly, we deny the Petition and decline to institute an *inter partes* review.

A. Related Proceedings

Petitioner indicates that the '612 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 Owner 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 '612 patent was the subject of IPR2017-01227 and IPR2017-01230, filed by a different Petitioner, Celltrion Inc., on March 31, 2017. The Board denied institution of these petitions on October 12, 2017 (IPR2017-01230) and October 23, 2017 (IPR2017-01230).

Concurrently with this proceeding, Petitioner also filed a petition for *inter partes* review of U.S. Patent No. 8,206,711 (IPR2017-02127), which is

related to the ’612 patent. Celltrion also filed a petition for *inter partes* review of the ’711 patent, IPR2017-01229, on March 31, 2017. The Board denied institution of that petition on October 23, 2017.

B. The ’612 Patent (Ex. 1001)

The ’612 patent discloses therapeutic regimens involving the administration of anti-CD20 antibodies for the treatment of chronic lymphocytic leukemia (CLL). Ex. 1001, Abst., 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.

With regard to dosing, the ’612 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.” *Id.* at 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. “A particularly preferred dosage regimen will comprise administration of about 375 mg/m^2 weekly for a total of four infusions.” *Id.* at 3:64–66.

C. Illustrative Claims

Petitioner challenges claims 1–13, 15–35, and 37–60 of the ’612 patent. Independent claims 1, 6, 23, 28, and 58 are illustrative of the challenged claims and are reproduced below:

> 1. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the method does not include

treatment with a radiolabeled anti-CD20 antibody.

6. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 500 to about 1500 mg/m^2, wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.

23. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the anti-CD20 antibody therapy is combined with chemotherapy, wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.

28. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 500 to about 1500 mg/m^2, wherein the anti-CD20 antibody therapy is combined with chemotherapy, and wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.

58. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the patient is refractory to fludarabine previously administered for the chronic lymphocytic leukemia, and wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.

D. The Asserted Grounds

Petitioner challenges claims 1–13, 15–35, and 37–60 of the '612 patent on the following grounds. Pet. 30–62.

Ground	Reference[s]	Basis	Challenged Claims
1	Maloney 1994,[1] Maloney Sept. 1997[2] and Genentech Press Release[3]	§ 103	1–13, 15–22, 58, 60
2	Maloney 1994, Maloney Sept. 1997, Maloney Oct. 1997[4] and Genentech Press Release	§ 103	23–35, 37–45, 59
3	Maloney 1994, Maloney Sept. 1997, Maloney Oct. 1997, Genentech Press Release and Kipps[5]	§ 103	46–57

[1] Ex. 1003, David G. Maloney 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 (Oct. 15, 1994) ("Maloney 1994").

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

[3] Ex. 1005, David G. Maloney 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) ("Maloney Oct. 1997").

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

[5] Ex. 1008, Thomas J. Kipps, *Chapter 106: Chronic lymphocytic leukemia and related diseases*, in Williams Hematology Fifth Edition, 1017–1039 (Ernest Beutler et al., eds., 1995) ("Kipps").

Petitioner supports its challenge with the Declaration of Howard Ozer, M.D., Ph.D. (Ex. 1002).

II. ANALYSIS

A. Claim Interpretation

We interpret claims using 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, 2144–46 (2016). Under the broadest reasonable construction standard, claim terms are generally given their "ordinary and customary meaning," as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007) (quoting *Phillips v. AWH Corp*, 415 F.3d 1303, 1313 (Fed. Cir. 2005)).

We determine that no explicit construction of any claim term is necessary to determine whether to institute a trial in this case. *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))).

B. 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.[6] *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.*

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.

---

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

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 occurred 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.[7]

5. Kipps

Kipps is a textbook reference, which discloses the use of chlorambucil, cyclophosphamide, COP, CHOP, fludarabine, and cisplatin to treat CLL. Ex. 1008, 34–36.

[7] 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 Internet Archive attesting to the date the Genentech Press Release was captured by the Way Back Machine (Prelim. Resp. 17–18).

C. Challenges Based on the Combination of Maloney 1994, Maloney Sept. 1997, and Genentech Press Release

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.

1. 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." *Intelligent Bio-Sys.* 821 F.3d at 1367. A reasonable expectation of success "does not require a *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 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. 32–53. Namely, Petitioner contends that Maloney 1994, Maloney (Sept.) 1997, and the Genentech Press Release would have provided an ordinarily skilled artisan with a reasonable expectation of success for methods of using rituximab to treat CLL patients at the claimed doses. *Id.* at 33–34, 49.

As Petitioner acknowledges, NHL and CLL are different cancers. Pet. 9 ("[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 '612 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. 10), with "about 100 times more cancerous B-cells than NHL patients" (*id.*; *see also* Ex. 1002 ¶ 33). 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 ¶ 48); *see also* 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. 39 (citing Ex. 1002 ¶ 77). 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.[8] For example, Jensen,[9] confirms that as of mid-1998, the "[e]fficacy and safety in the treatment of chronic lymphocytic leukemia (CLL) and other blood-born tumors [with rituximab] ha[d] not been investigated." Ex. 1009, 1.

Nevertheless, 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 32. 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 patients with CLL." *Id.* at 33.

---

[8] Petitioner states "The earliest priority date to which the claims of the '612 patent is entitled is the filing date of the '658 provisional patent application—i.e., November 9, 1998." Pet. 20–21.

[9] M. Jensen et al., *Rapid Tumor Lysis in a Patient with B-cell Chronic Lymphocytic Leukemia and Lymphocytosis Treated with an Anti-CD20 Monoclonal Antibody (IDEC-C2B8, Rituximab)*, 77 ANN. HEMATOLOGY 89–91 (1998) (Ex. 1009) ("Jensen").

Consistent with the discussion of the record evidence above, however, neither Maloney 1994 nor the Genentech Press Release reports any study 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. 1004, 6; Ex. 1005, 7; Ex. 1023 ¶ 14; Ex. 1002 ¶ 101; Ex. 1033 ¶¶ 22–24 (stating that that higher tumor burden "serves in part to distinguish CLL from small lymphocytic lymphoma," that "CLL and NHL also typically affect different patient populations," and that "[c]linicians approach CLL and NHL with different expectations for therapy and different treatment plans."). 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).[10] Nor does it discuss 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. 33). 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.*).

---

[10] As explained above with regard to Maloney Sept. 1997, SLL B-cells, like CLL B-cells, express CD20 at lower levels that NHL B-cells. *See, e.g.*, Ex. 2003, 4.

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 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.

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. 33–34 (quoting *Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 619 F.3d 1329, 1343 (Fed. Cir. 2010) (quoting MPEP § 2107.03 at IV(2008)))). 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. 34). 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 '612 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. 34), 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.

2. Dosage limitations

With regard to the recited dosages of rituximab, Petitioner contends that Maloney 1994 reference discloses doses ranging from 10 mg/m^2 to 500 mg/m^2 were safe and achieved a "dose-dependent, rapid, and specific depletion of the B cells in all patients." Pet. 37 (citing Ex. 1003, 6). Petitioner further contends as follows:

> Maloney 1994 taught that the amount of B-cell depletion was "dose-dependent," meaning the greater the dose, the greater the effect. Ex. 1003, 6. Maloney (Sept.) 1997 taught that 375 mg/m^2 was the dose of choice for treating NHL patients. Ex. 1004, 2. The teachings from these two references, when combined with the knowledge of a [person of ordinary skill in the art] that CLL patients had approximately 100 times more tumor cells than NHL patients, suggested that a higher rituximab dose likely would be needed to treat CLL. Ex. 1002 ¶ 75; *compare* Ex. 1008, Kipps at 28 (CLL defined as more than 10,000 lymphocytes/μl), *with* Ex. 1012, McLaughlin at 7–8 & Fig 3 (low-grade NHL patients had average of about 100 lymphocytes/μl).
>
> The only dose above 375 mg/m^2 disclosed as safe and effective in Maloney was 500 mg/m^2. That claimed dose, therefore, would have been obvious for use in CLL patients. Ex. 1002 ¶ 86.

Id. at 38.

In view of the 100-fold increase in tumor burden and significant decrease in CD20 expression observed in CLL relative to NHL, however, 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. 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.*) 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.[11]

[11] It is also factually incomplete, as Maloney 1994 does not identify any theoretical maximum dose for rituximab. To the contrary, Maloney 1994

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. 38 (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 any dose of rituximab would have been obvious to try. Pet. 37–42; Prelim. Resp. 37–38.

3. Chemotherapy limitations

We do not find persuasive Petitioner's arguments concerning the complementarity of rituximab and chemotherapeutic regimens, specifically, "that rituximab makes B-cells more sensitive to chemotherapy." *See* Pet. 49–52. 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 fewer "targets" for rituximab to bind. Petitioner does not address why an ordinarily skilled artisan would reasonably have expected under those

---

reports that "no dose-limiting toxicities were identified" at even the highest tested dose level. Ex. 1003, 9.

conditions that rituximab would sensitize CLL B-cells to chemotherapeutic agents.

III. CONCLUSION

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 showing the unpatentability of any challenged claim of the ’612 patent based on any ground that relies on the combination of Maloney 1994, Maloney Sept. 1997, and Genentech Press Release, namely, Grounds 1–3 as set forth in the Petition.

IV. ORDER

In consideration of the foregoing, it is

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

PETITIONER:
WINSTON & STRAWN, LLP
Jovial Wong
jwong@winston.com

PATENT OWNER:
IRELL & MANELLA
Michael R. Fleming
Gary N. Frischling
Keith A. Orso
Yite John Lu
Andrew E. Krause
mfleming@irell.com
gfrischling@irell.com
korso@irell.com
yjlu@irell.com
akrause@irell.com