

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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PFIZER, INC.,  
Petitioner,

v.

BIOGEN, INC., and GENENTECH, INC.,  
Patent Owner.

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*Inter Partes* Review No. IPR2017-02127  
Patent 8,206,711 B2  
Issued: June 26, 2012  
Filed: December 2, 2009

Title: TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA  
USING ANTI-CD20 ANTIBODIES

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**PETITION FOR *INTER PARTES* REVIEW**

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1001	White et al., U.S. Patent No. 8,206,711 “Treatment of Chronic Lymphocytic Leukemia Using Anti-CD20 Antibodies” (issued June 26, 2012) (“the ’711 patent”)
1002	Declaration of Howard Ozer, M.D., Ph.D., in Support of Petition for <i>Inter Partes</i> Review
1003	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,” <i>Blood</i> , 84(8):2457–2466 (1994) (“Maloney 1994”)
1004	Maloney et al., “IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients with Relapsed Low-Grade Non-Hodgkin’s Lymphoma,” <i>Blood</i> , 90(6):2188–2195 (1997) (“Maloney Sept. 1997”)
1005	Maloney et al., “IDEC-C2B8: Results of a Phase I Multiple-Dose Trial in Patients with Relapsed Non-Hodgkin’s Lymphoma,” <i>J. Clinical Oncology</i> , 15(10):3266–3274 (1997) (“Maloney Oct. 1997”)
1006	Press Release, Genentech, Inc. “Genentech and IDEC Pharmaceuticals to Collaborate on Anti-CD20 Monoclonal Antibody for B-Cell Lymphomas,” (March 16, 1995), <a href="https://web.archive.org/web/19970613232048/http://www.gene.com:80/pressrelease/1995/IDEC_Release.html">https://web.archive.org/web/19970613232048/http://www.gene.com:80/pressrelease/1995/IDEC_Release.html</a> (last visited Sept. 26, 2017) (“Genentech Press Release”)
1007	O’Brien et al., “Fludarabine (FAMP) and Cyclophosphamide (CTX) Therapy in Chronic Lymphocytic Leukemia (CLL),” <i>Blood</i> , 88(10 Supp. 1):480a (1996) (“O’Brien”)
1008	Thomas J. Kipps, “Chronic Lymphocytic Leukemia and Related Diseases,” in <i>Williams Hematology</i> 5th Ed. (Beutler et al., eds.) 1017–1039 (1995) (“Kipps”)
1009	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),” <i>Ann.</i>

	Hematology, 77:89–91 (1998) (“Jensen”)
<b>1010</b>	Flinn et al., “Fludarabine and Cyclophosphamide as First Therapy for Indolent Lymphoproliferative Disorders: Response Rates and Toxicity,” Blood, 88(10):589a (1996) (“Flinn”)
<b>1011</b>	Czuczman et al., “IDEC-C2B8 and CHOP Chemoimmunotherapy of Low-Grade Lymphoma,” Blood, 86(10 Supp. 1):55a (1995) (“Czuczman”)
<b>1012</b>	McLaughlin et al., “Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program,” J. Clinical Oncology, 16(8):2825–2833 (1998) (“McLaughlin”)
<b>1013</b>	Rituxan™ (rituximab) labeling (Nov. 1997) (“Rituxan™ label”)
<b>1014</b>	Excerpts from Clinical Oncology, Abeloff et al., Eds. (1995) (“Abeloff”)
<b>1015</b>	Coiffier et al., “Rituximab (Anti-CD20 Monoclonal Antibody) for the Treatment of Patients with Relapsing or Refractory Aggressive Lymphoma: A multicenter Phase II Study,” Blood, 92(6):1927–1932 (1998) (“Coiffier”)
<b>1016</b>	Grossbard et al., “Monoclonal Antibody-Based Therapies of Leukemia and Lymphoma,” Blood, 80(4):863–878 (1992) (“Grossbard”)
<b>1017</b>	Caroline McNeil, “Non-Hodgkin’s Lymphoma Trials In Elderly Look Beyond CHOP,” J. Nat’l Cancer Inst., 90(4):266–267 (Feb. 18, 1998) (“McNeil”)
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<b>1019</b>	U.S. Application No. 09/436,347, Non-Final Office Action (dated Feb. 29, 2000)
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<b>1022</b>	U.S. Application No. 09/436,437, Final Office Action (dated Feb. 19, 2009)
<b>1023</b>	Second Declaration of David P. Schenkein, M.D. (May 5, 2009) (“Schenkein Decl.”)
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<b>1027</b>	U.S. Application No. 12/629,472, Amendment and Response to Rejection, (dated Apr. 24, 2012)
<b>1028</b>	<i>Celltrion, Inc. v. Biogen, Inc.</i> , Petition for <i>Inter Partes</i> Review, IPR2017-01229 (U.S. Patent No. 8,206,711), Paper 3 (Mar. 31, 2017)
<b>1029</b>	<i>Celltrion, Inc. v. Biogen, Inc.</i> , Patent Owner Preliminary Response, IPR2017-01229 (U.S. Patent No. 8,206,711), Paper 8 (July 24, 2017)
<b>1030</b>	<i>Pfizer, Inc. v. Biogen, Inc.</i> , Patent Owner Preliminary Response, IPR2017-01166 (U.S. Patent No. 8,329,172), Paper 7 (Aug. 15, 2017)
<b>1031</b>	Declaration of Scott Bennett, Ph.D.
<b>1032</b>	Demidem et al., “Chimeric Anti-CD20 (IDEC-C2B8) Monoclonal Antibody Sensitizes a B Cell Lymphoma Cell Line to Cell Killing by Cytotoxic Drugs,” <i>Cancer Biotherapy &amp; Radiopharmaceuticals</i> , 12(3):177–186 (1997)
<b>1033</b>	First Declaration of David P. Schenkein, M.D. (April 14, 2008) (“Schenkein Decl. I”)
<b>1034</b>	Genentech, Inc., “Rituximab: Full Prescribing Information,” <a href="https://web.archive.org/web/19980123110003/http://www.gene.com:80/Medicines/rituxan_insert.html">https://web.archive.org/web/19980123110003/http://www.gene.com:80/Medicines/rituxan_insert.html</a>

## I. INTRODUCTION

Petitioner, Pfizer, Inc. requests *inter partes* review and cancellation of claims 1-9 of U.S. Patent No. 8,206,711 (“the ’711 patent”). These claims are generally directed to methods of (1) treating chronic lymphocytic leukemia (“CLL”) with the monoclonal antibody rituximab (without a radiolabeled antibody<sup>1</sup>); (2) at a dosage of 500 mg/m<sup>2</sup> (“an amount effective to treat the CLL”); (3) administered monthly, biweekly or weekly; and, for some claims, (4) in combination with chemotherapy drugs, particularly cyclophosphamide and fludarabine. As shown below, the claimed invention would have been obvious to a person of ordinary skill in the art (“POSA”) as of the earliest filing date of November 9, 1998 in light of 35 U.S.C. § 102(b) prior art, including references never disclosed to the Patent Office during prosecution.

As for the first claim element, Patent Owners publicly reported three years before filing their patent application that they reasonably expected success in using rituximab to treat patients with CLL. Ex. 1006, 2. A 1995 press release from

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<sup>1</sup> Radiolabeled antibodies deliver irradiation directly to the targeted cells, in contrast to whole-body radiation therapy. *E.g.*, Ex. 1001, 2:40-43, 3:59; Ex. 1002 ¶ 52.

Genentech and IDEC<sup>2</sup> (“Genentech Press Release”) disclosed that they were “planning” clinical trials with rituximab to treat patients with “chronic lymphocytic leukemia” based on “encouraging results” using the drug for another cancer, low-grade non-Hodgkin’s lymphomas (“NHL”). *Id.* A POSA would not have been surprised by this public disclosure because both CLL and NHL are cancers marked by the uncontrollable growth of B-cells expressing the CD20 antigen, and clinical studies had already shown that rituximab can effectively treat NHL by targeting and destroying those cells by binding to that antigen. Ex. 1003, Maloney 1994 at 6-10; Ex. 1002 ¶¶ 79-80. By no later than November 1998, a POSA would have reasonably expected rituximab to effectively treat CLL patients by similarly inducing the death of cancerous B-cells in those patients.

As for the second claim element related to dosing, although the Genentech Press Release did not disclose the rituximab dose being used to treat CLL patients, it would have been obvious at the time of the alleged invention to use the claimed 500 mg/m<sup>2</sup> dose. This dose was within the range disclosed by the Maloney 1994 and two additional references from Maloney published in 1997, which together taught that doses as high as 500 mg/m<sup>2</sup> were safe and achieved a “rapid, and specific

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<sup>2</sup> IDEC has since merged with Biogen. Both Biogen and Genentech are assignees of the '711 Patent.

depletion of the B cells in all [NHL] patients.” Ex. 1003, Maloney 1994 at 6; Ex. 1004, Maloney (Sept.) 1997 at 2; Ex. 1005, Maloney (Oct.) 1997 at 3. The claimed 500 mg/m<sup>2</sup> dose thus is presumed to be *prima facie* obvious when used for this same purpose of depleting B cells. *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004) (“[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness.”).

Even putting aside this presumption, the claimed 500 mg/m<sup>2</sup> dose was obvious in light of the Maloney 1994 and the Maloney (Sept.) 1997 references, which together also taught that the amount of B-cell depletion was “dose-dependent” (meaning the greater the dose, the greater the depletion), and a 375 mg/m<sup>2</sup> weekly dose was preferred for NHL patients. Ex. 1003, Maloney 1994 at 6; Ex. 1004, Maloney (Sept.) 1997 at 2. By November 1998, a POSA would have known that a rituximab dose higher than the 375 mg/m<sup>2</sup> FDA-approved dose for treating low-grade NHL would likely be necessary to treat CLL patients because, among other reasons, CLL patients have many more (on average, a 100 times more) cancerous B-cells than NHL patients. Ex. 1002 ¶ 33. As Patent Owners’ own expert explained during prosecution, “patients with CLL have a much higher circulating tumor burden than patients with NHL.” Ex. 1023, ¶ 14; Ex. 1002 ¶ 33; *see also* Ex. 1008, Kipps at 28; Ex. 1012, McLaughlin at 7-8 & Fig 3. And as Patent Owners explain in a

related proceeding: “[A] POSA would have appreciated that the total amount of rituximab needed to bind to tumors is proportional to the total number of tumors that need to be destroyed.” Ex. 1030, 40. Maloney 1994 disclosed positive clinical results and low toxicity with only one rituximab dose above the 375 mg/m<sup>2</sup> dose for NHL: the claimed 500 mg/m<sup>2</sup> dose. Ex. 1003, 3. That dose was obvious to use to treat CLL patients. At a minimum, it was obvious as one of a “finite number of identified, predictable solutions” to a known problem—improving effective treatments for CLL. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

As for the third claim element addressing dose frequency, Maloney 1994 and Maloney (Sept.) 1997 further taught that rituximab can be taken safely and effectively as often as weekly, and should be taken at least once a month. Ex. 1003, Maloney 1994, at 9; Ex. 1004, Maloney (Sept.) 1997 at 2. It thus would have been obvious to a POSA to administer rituximab according to a dosing schedule within that dose-frequency range.

Finally, it would have been obvious to treat CLL with rituximab at the claimed dose in combination with conventional chemotherapy methods—particularly the combination of cyclophosphamide and fludarabine. By 1996, two years before Patent Owners filed their application, the O’Brien reference taught that the combination of these two chemotherapeutic drugs effectively treated CLL patients, resulting in at least partial clinical responses in most patients. Ex. 1007, 3. In a

reference from October 1997, Dr. Maloney taught that rituximab made cancerous B-cells more vulnerable to the effects of chemotherapy—specifically, that rituximab “increases sensitivity to the cytotoxic effect of chemotherapy/toxins in some resistant human lymphoma cell lines”—suggesting a rationale to combine all three drugs. Ex. 1005, Maloney (Oct.) 1997 at 4. Another Maloney reference published a month earlier, in September 1997, expressly suggested using rituximab in “combination with or after standard chemotherapy” (which, again, included fludarabine and cyclophosphamide). Ex. 1004, Maloney (Sept.) 1997 at 7. Thus, using rituximab with fludarabine and/or cyclophosphamide to treat diseases caused by cancerous B-cells such as CLL was an obvious concept well before the November 1998 priority date.

In sum, and as explained in the declaration of Petitioner’s expert, Dr. Howard Ozer, the “Maloney References”—i.e., Maloney 1994, Maloney (Sept.) 1997, and Maloney (Oct.) 1997—and the 1995 Genentech Press Release would have motivated a POSA before November 1998 to use rituximab to treat CLL patients at a dosage of 500 mg/m<sup>2</sup> administered monthly, biweekly, or weekly—with a reasonable expectation of success. Ex. 1002 ¶¶ 83-87. These references, especially in view of O’Brien, also would have motivated a POSA to combine this rituximab treatment regimen with the two standard chemotherapy drugs for CLL patients—fludarabine and cyclophosphamide—also with a reasonable expectation of success. Ex. 1002

¶¶ 104-106. These obvious treatments are what the Patent Owners claimed as the inventions of the '711 patent. Therefore, all claims of this patent should be cancelled as obvious.

## II. MANDATORY NOTICES

Pursuant to 37 C.F.R. § 42.8(b), Petitioner states as follows:

1. ***Real parties-in-interest.*** Petitioner Pfizer, Inc. is the real party-in-interest for this Petition. No other parties exercised or could have exercised control over this Petition; no other parties funded or directed this Petition. *See Office Patent Trial Practice Guide*, 77 Fed. Reg. 48,759-60.

2. ***Related matters.*** The '711 patent is currently being challenged by a different petition in *Celltrion, Inc. v. Biogen, Inc. and Genentech, Inc.*, IPR2017-01229, which was filed on March 31, 2017. The grounds of unpatentability asserted in this petition are different from the grounds asserted by petitioner Celltrion. This petition also includes prior art (e.g., Maloney (Sept.) 1997, Maloney (Oct.) 1997, and O'Brien) not relied upon by the petitioner Celltrion.

Petitioner has also concurrently filed a petition for *inter partes* review of U.S. Patent No. 7,682,612 ("the '612 patent") (IPR2017-02126), which is also being challenged by Celltrion in two different petitions in *Celltrion, Inc. v. Biogen, Inc. and Genentech, Inc.*, IPR2017-01230 (single agent claims) and IPR2017-01227 (combination claims), filed on March 31, 2017. The patent challenged in that

petition is also owned by Patent Owners here, is related to the '711 patent, and also claims methods of using rituximab to treat chronic lymphocytic leukemia.

**3. *Lead and back-up counsel.*** Petition identifies the following:

- *Lead counsel:* Jovial Wong (Reg. No. 60,115)
- *Back-up counsel:* Charles B. Klein\*
- *Back-up counsel:* Eimeric Reig-Plessis\*

\* Back-up counsel to seek *pro hac vice* admission.

**4. *Service information.*** Petitioner identifies the following:

- *Email address:* rituximabIPR@winston.com
- *Mailing address:* WINSTON & STRAWN LLP  
1700 K Street NW  
Washington, DC 20006
- *Telephone number:* (202) 282-5000
- *Fax number:* (202) 282-5100

Please address all correspondence to lead counsel at the address shown above.

Petitioner consents to electronic service at the above listed email address.

### **III. REQUIREMENTS FOR REVIEW**

Pursuant to 37 C.F.R. § 42.104, Petitioner states as follows:

**a. *Grounds for standing.*** Petitioner certifies that (i) the '711 patent is available for *inter partes* review; and (ii) Petitioner is not barred or estopped from requesting review of any claim of the '711 patent on the grounds identified in this

Petition. The required fee is paid through the Patent Review Processing System. The Office is authorized to charge fee deficiencies and credit overpayments to Deposit Acct. No. 50-1814.

**b. Identification of challenge.** Pursuant to 37 C.F.R. §§ 42.104(b) and 42.22(a)(1), Petitioner requests review and cancellation of claims 1-9 of the '711 patent pursuant to the following statement of the precise relief requested:

<b>Ground</b>	<b>Claims</b>	<b>Basis</b>	<b>Reference(s)</b>
<b>I</b>	1, 5-8	§ 103(a)	Maloney 1994 (Ex. 1003); Maloney (Sept.) 1997 (Ex. 1004); and Genentech Press Release (Ex. 1006)
<b>II</b>	2	§ 103(a)	Maloney 1994 (Ex. 1003), Maloney (Sept.) 1997 (Ex. 1004), and Maloney (Oct.) 1997 (Ex. 1005) (collectively, the "Maloney References"); and the Genentech Press Release (Ex. 1006)
<b>III</b>	3, 4, 9	§ 103(a)	The Maloney References (Exs. 1003, 1004, and 1005); the Genentech Press Release (Ex. 1006); and O'Brien (Ex 1007).

Pursuant to 37 C.F.R. § 42.22(a)(2), Petitioner sets forth a full statement of the reasons for the relief requested below in Section IX.

#### **IV. LEVEL OF ORDINARY SKILL IN THE ART**

The '711 patent claims priority to U.S. provisional application no. 60/107,658, which was filed on November 9, 1998. Without conceding that this priority claim

is valid, Petitioner and expert declarant, Dr. Howard Ozer, use November 9, 1998, as the relevant date for analysis of the level of skill and knowledge of a POSA. The analysis would not be different as of November 9, 1997—the critical date under 35 U.S.C. § 102(b)—because all prior art references relied on by Petitioner to support this petition were published before that date. Ex. 1002 ¶ 14.

In light of the specification, the prosecution history, and the state of the art as of November 9, 1998 (and also November 9, 1997), a POSA for purposes of the '711 patent 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. *Id.* ¶ 15.

## **V. THE PRIOR ART AND THE '711 PATENT**

In summarizing the state of the art as of November 1998, Petitioner cites additional references beyond “prior art presented as the basis for obviousness,” which “legitimately serve to document the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness.” *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015).

### **A. CLL is a disease of B-cells that express the CD20 antigen.**

CLL “is a neoplastic disease characterized by the accumulation of small mature-appearing lymphocytes in the blood, marrow, and lymphoid tissues,” which are “[g]enerally . . . of the B-cell lineage.” Ex. 1008, Kipps, at 23; Ex. 1002 ¶ 30. It

is “characterized by a relentless accumulation of monoclonal B cells.” Ex. 1008, Kipps at 25; Ex. 1002 ¶¶ 31-33. Thus, like NHL, another type of cancer, CLL patients experience the uncontrollable growth of the body’s B-cells. Ex. 1002 ¶ 34. As of 1998, “the disease [was] not considered curable,” thus motivating skilled artisans to find new and improved treatments. Ex. 1008, Kipps at 23; Ex. 1002 ¶¶ 34-37.

Although CLL could not be cured, a POSA would have known that it is caused by cancerous B-cells. The B-cells of CLL patients, like the B-cells of NHL patients, express certain surface “antigens” that are not found on the surface of the body’s other cells. Ex. 1002 ¶ 32.<sup>3</sup> “The leukemic cells of most patients with B-cell CLL express pan-B cell surface antigens, such as CD19 and CD20 . . . , indicating that they are derived from the B-lymphocyte lineage.” Ex. 1008, Kipps at 25; Ex. 1002 ¶ 32. However, “[t]he level at which the CD20 antigen is expressed . . . is substantially lower than that found on normal circulating B cells.” Ex. 1008, Kipps at 25-26; Ex. 1002 ¶ 32. That is, the CD20 antigen is expressed more weakly on the B-cells of CLL patients than NHL patients. Ex 1002 ¶ 32. Nevertheless, this antigen

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<sup>3</sup> Antigens are substances that normally trigger immunological responses in the human body, but fail to do so in cancer patients. Ex. 1002 ¶ 31.

is expressed on the B-cells of nearly all CLL patients. Ex. 1008, Kipps at 26, Fig. 106-1.

An important difference between CLL and NHL is that, generally speaking, CLL patients have a higher tumor burden. CLL has been associated with a lymphocyte count generally exceeding 10,000 lymphocytes per microliter ( $\mu\text{l}$ ) in the blood. *Id.* at 28; Ex. 1002 ¶ 33. In contrast, low-grade NHL has been associated with only 100 lymphocytes per microliter. *See, e.g.*, Ex. 1012, McLaughlin at 7-8 & Fig 3 (reporting on study of rituximab in low-grade NHL patients who had average of about 100 lymphocytes/ $\mu\text{l}$ ); Ex. 1002 ¶ 33. Thus, a POSA would have known by November 1998 that CLL patients had about 100 times more cancerous B-cells than NHL patients. This knowledge, as discussed below, suggested a higher dose of rituximab for CLL patients compared to NHL patients.

**B. Cyclophosphamide and fludarabine were first-line chemotherapy treatments for CLL with high response rates when used together.**

As with other cancers, chemotherapy was a standard therapy aimed at stopping the division (and thus growth) of cancerous cells. Chemotherapy affects cellular metabolism at the level of DNA, cell division, or RNA synthesis, or it interferes with epigenetics. In short, chemotherapy interferes with the process of cell division and growth in various ways, and thus affects all cells in the body but particularly cancer cells, which are prone to divide and grow at a rate faster than non-malignant cells. Ex. 1002 ¶ 34.

By the mid-1990s, two leading chemotherapeutic drugs for CLL patients were fludarabine and cyclophosphamide. “[P]urine analogs, such as fludarabine . . . , were found to be effective in the treatment of CLL”—inducing “hematologic complete and partial responses in 50 to 60 percent of previously treated and 70 to 90 percent of previously untreated patients.” Ex. 1008, Kipps at 23, 34; *see also* Ex. 1002 ¶ 35. Cyclophosphamide was another effective chemotherapeutic agents used to treat CLL. Ex. 1008, Kipps at 34; Ex. 1002 ¶¶ 34-36. The ’711 patent specification acknowledges that fludarabine and cyclophosphamide were “known to be useful for the treatment of CLL.” Ex. 1001, 7:10-11, 16-18, 22-24.

Combination therapy involving chemotherapy drugs was the standard practice in treating CLL. Ex. 1002 ¶ 35. Numerous combination therapies were found to be effective in the treatment of CLL, including chlorambucil and prednisone; cyclophosphamide, vincristine, and prednisone (“CVP”); cyclophosphamide, doxorubicin, vincristine, and prednisone (“CHOP”); vincristine, doxorubicin, and dexamethasone; cytosine, cisplatin, and etoposide; and chlorambucil and fludarabine. Ex. 1008, Kipps at 35-36.

By November 1998, the combination of fludarabine and cyclophosphamide promised to be one of the most effective treatments for CLL at the time. Numerous prior art references disclosed high response rates for the combination of these two drugs in treating CLL. For example, in 1996, O’Brien reported a study of

fludarabine and cyclophosphamide in CLL patients and concluded that the combination “is an extremely active regimen in CLL with a response rate of close to 100% in [patients] not previously refractory to [fludarabine].” Ex. 1007, 3; *see also*, *e.g.*, Ex. 1010, Flinn at 11 (reporting in 1996 a 100% partial response rate for patients taking the combination for two cycles, with five of six patients achieving a complete response after four cycles). This combination therapy, however, by no means cured CLL patients and, therefore, new and improved therapies were needed. *See* Ex. 1002 ¶ 37.

**C. Rituximab was a new immunotherapy for treating B-cell diseases that targeted the CD20 antigen.**

By 1993, investigations of numerous experimental immunotherapies were underway using monoclonal antibodies to target particular antigens expressed on the B-cells of CLL patients—namely the CD5, CD19, and CD25 antigens. Ex. 1008, Kipps at 36-37 & nn. 304-08. Antibodies target particular antigens and selectively activate the immune system to kill these cells, without harming other cells in the body. Ex. 1002 ¶ 39. As of 1993, these experimental antibodies “ha[d] not resulted in significant therapeutic benefit,” although an anti-CD5 monoclonal antibody showed “transient beneficial effects.” Ex. 1008, Kipps at 36.

By 1994, however, the monoclonal antibody rituximab, which targets the CD20 antigen, showed tremendous promise for treating B-cell cancers. Maloney 1994—a § 102(b) prior art study funded by Patent Owners—reported that the

monoclonal antibody treatments tried in the past for treating B-cell cancers were “not feasible for general application” because of the “difficulty and time required to produce patient-specific antibodies.” Ex. 1003, 3. “In contrast, the antigen CD20, . . . present on the surface of nearly all B cells[,] provides a more universal target for immunotherapy.” *Id.* Indeed, Maloney 1994 explained that “[m]ore than 90% of B-cell NHLs express this surface protein,” and “[i]t is also expressed” (although “at a lower density”) “on B-cell chronic lymphocytic leukemia”—making monoclonal antibodies targeting CD20 potentially ideal for both NHL and CLL because both diseases manifested in CD20-expressing B-cells. *Id.*; Ex. 1002 ¶¶ 40-44.

Maloney 1994 further taught that rituximab was successful in targeting CD20-expressing B-cells and reducing their presence in the body.<sup>4</sup> Maloney 1994 reported that “[p]reclinical studies” in animals showed that the anti-CD20 antibody rituximab “depleted around 80% of CD20<sup>+</sup> B cells in the peripheral blood, lymph nodes, spleen, and bone marrow, with gradual recovery over a period of seven months.” Ex. 1003, 4. Maloney 1994, the first Phase I clinical trial of rituximab “in patients with relapsed B-cell NHL,” tested five doses between 10 mg/m<sup>2</sup> to 500 mg/m<sup>2</sup> of

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<sup>4</sup> “IDEC-C2B8” referenced in Maloney 1994 is the code name for rituximab. *See* Ex. 1004, Maloney (Sept.) 1997 at 3.

rituximab (10, 50, 100, 250, and 500 mg/m<sup>2</sup>). *Id.* Maloney 1994 reported “dose-dependent, rapid, and specific depletion of the B cells in all [NHL] patients.” *Id.* at 6. “In all but 1 patient receiving the higher doses (>50 mg/m<sup>2</sup>), these depletions persisted for 1 to greater than 3 months”—teaching that rituximab should be administered at least once a month to achieve a continued reduction in circulating tumor cells. *Id.*; Ex. 1002 ¶ 50.

This reduction in circulating tumor cells led directly to anti-tumor clinical responses: “Despite the fact that this trial involved the administration of only a single infusion of antibody, tumor responses were observed. Partial tumor responses were documented in 2 patients and minor responses observed in 4 others.” Ex. 1003, Maloney 1994 at 8. Additionally, “no dose-limiting toxicities were identified,” meaning that all doses within the 10 mg/m<sup>2</sup> to 500 mg/m<sup>2</sup> range were tolerable. *Id.* at 9.

Maloney 1994 also suggested that rituximab was superior to radiolabeled antibodies,<sup>5</sup> stating: “The use of a chimeric *naked* antibody [i.e., without a

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<sup>5</sup> Radiolabeled antibodies deliver irradiation directly to the targeted cells, in contrast to whole-body radiation therapy. *E.g.*, Ex. 1001, 2:40-43, 3:59; Ex. 1002 ¶¶ 52-54. Claim 8 requires that rituximab be administered without a radiolabeled antibody. Ex. 1001, 8:34-35.

radiolabel] offers some advantages over similar trials using toxin-conjugated or radiolabeled antibodies against B-cell NHL.” *Id.* at 11 (emphasis added). Indeed, Maloney 1994 discouraged the use of radiolabeled antibodies, noting they “may not be stable after formation,” “may interfere with antigen binding,” “are unstable, and undergo autolysis,” are associated with “significant hematologic toxicity,” and are difficult to apply “in patients with impaired bone marrow function or significant involvement by lymphoma.” *Id.* “In contrast, this chimeric anti-CD20 antibody”—i.e., rituximab—“is stable and has been engineered to lyse [i.e., rupture and destroy] tumor cells through interaction with the patient’s own immune system.” *Id.*

Maloney 1994 did not limit its findings to NHL but, instead, concluded 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 (emphasis added)—a statement a POSA would understand to include CLL, mentioned earlier in the article. Ex. 1002 ¶ 54. Indeed, as reported in the prior art and explained by Dr. Ozer, CLL patients had on the order of 100 times more circulating tumors than low-grade NHL patients. Ex. 1002 ¶ 33; *compare* Ex. 1008, Kipps at 28 (CLL defined as more than 10,000 lymphocytes/ $\mu$ l), *with* Ex. 1012, McLaughlin at 7-8 & Fig 3 (low-grade NHL patients had average of about 100 lymphocytes/ $\mu$ l). Based on its encouraging findings, Maloney 1994 disclosed that a

“phase I/II trial using four weekly doses of antibody in patients with relapsed B-cell NHL has been initiated.” Ex. 1003, 11.

Building on the teachings of Maloney 1994, in 1995, the Genentech Press Release disclosed Patent Owners’ encouraging research involving the use of rituximab to treat CLL patients. Patent Owners reported that they would be studying rituximab in CLL patients because of rituximab’s ability to achieve a reduction in circulating tumor cells. Ex. 1002 ¶ 57. As the press release disclosed, “IDEC-C2B8 [rituximab] is being developed for certain lymphomas and *leukemias* characterized by excessive B-cell proliferation,” and “Phase II studies of [rituximab] in NHL reveal encouraging results indicating that it may provide an effective and well-tolerated treatment.” Ex. 1006, 1-2 (emphasis added). Patent Owners also announced that they “will conduct a Phase III trial . . . to attempt to confirm these results,” and “*Genentech and IDEC are planning additional studies with IDEC-C2B8 to support this primary indication . . . in other B-cell mediated cancers such as intermediate grade NHL and chronic lymphocytic leukemia.*” *Id.* (emphasis added). That is, Patent Owners told the public that they were conducting clinical trials to show that rituximab treated CLL. *See* Ex. 1002 ¶¶ 55-56.

In September 1997, Maloney reported on a clinical trial testing 375 mg/m<sup>2</sup> rituximab in four weekly doses in low-grade NHL patients, a study that demonstrated “clinical responses with no dose-limiting toxicity.” Ex. 1004, 1.

Maloney (Sept.) 1997 confirmed that rituximab “efficiently kills CD20<sup>+</sup> cells in vitro by augmented complement-mediated lysis and participates in antibody-dependent cell-mediated cytotoxicity (ADCC),” and in some cases “inhibits proliferation and directly induces apoptosis.” *Id.* at 1-2. This study confirmed to a POSA that weekly doses of rituximab were safe and effective in treating low-grade NHL. Ex. 1002 ¶ 59.

In November 1997, shortly after the § 102(b) critical date but before the earliest priority date for the '711 patent, the FDA approved rituximab under the brand name Rituxan<sup>™</sup> for the treatment of relapsed or refractory low-grade or follicular B-cell NHL. Ex. 1013, 1; Ex. 1034, 1.<sup>6</sup> The label disclosed 375 mg/m<sup>2</sup> weekly as the approved dose of rituximab for NHL, but also noted that “[s]ingle doses of up to 500 mg/m<sup>2</sup> were well-tolerated.” *Id.*

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<sup>6</sup> Ex. 1034 is a copy of the rituximab full prescribing information as it appeared on Genentech, Inc.’s website at least as of January 23, 1998 and is available at [https://web.archive.org/web/19980123110003/http://www.gene.com:80/Medicines/rituxan\\_insert.html](https://web.archive.org/web/19980123110003/http://www.gene.com:80/Medicines/rituxan_insert.html).

**D. The prior art also suggested using rituximab in combination with chemotherapeutic drugs to address diseases caused by cancerous B-cells.**

The prior art also showed the promise of rituximab in combination with chemotherapy to treat not only NHL, but other diseases caused by cancerous B-cells such as CLL. Maloney (Sept.) 1997 suggested that “[a]dditional areas that should be investigated using this new agent include (1) extended and repeated dosing regimens, (2) *combination with or after standard chemotherapy*, (3) . . . [and] (4) *evaluation in other B-cell histologies*”—e.g., CLL. Ex. 1004, 1-2, 7 (emphasis added); Ex. 1002 ¶ 60. One month later, in October 1997, Maloney further reported that rituximab “*increases sensitivity to the cytotoxic effect of chemotherapy/toxins in some resistant human lymphoma cell lines*”—that is, rituximab increased the ability of chemotherapy to combat cancerous B-cells. Ex. 1005, 4 (emphasis added); Ex. 1002 ¶¶ 61-62. Another prior art reference similarly noted that rituximab makes B-cells more sensitive to chemotherapy, concluding that the rituximab-induced apoptosis may be “*complemented and completed by the cytotoxic drugs.*” Ex. 1032, Demidem at 6-7. Indeed, combining rituximab and chemotherapy had already been used in low-grade NHL patients with great success. Ex. 1011, Czuczman at 3 (noting 100% partial or complete response rate and explaining that “[t]he rationale for combination of IDEC-C2B8 [rituximab] with CHOP includes: single agent efficacy,

non cross-resistant mechanism of action, synergy with chemotherapeutic agents and non-overlapping toxicities”).

## **VI. PATENT CLAIMS, SPECIFICATION, AND FILE HISTORY**

### **A. The '711 patent claims**

The '711 patent claims the following:

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<sup>2</sup>.
2. The method of claim 1 further comprising administering a chemotherapeutic regimen to the patient.
3. The method of claim 2 wherein the chemotherapeutic regimen comprises fludarabine.
4. The method of claim 2 wherein the chemotherapeutic regimen comprises cyclophosphamide.
5. The method of claim 1 wherein the rituximab is administered weekly.
6. The method of claim 1 wherein the rituximab is administered bi-weekly.
7. The method of claim 1 wherein the rituximab is administered monthly.
8. The method of claim 1 which does not include treatment with a radiolabeled anti-CD20 antibody.

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<sup>2</sup>, and further comprising administering a chemotherapeutic regimen to the patient, wherein the chemotherapeutic regimen comprises fludarabine and cyclophosphamide.

**B. The '711 patent specification**

The specification confirms in the “background of the invention” that “[t]he use of antibodies to CD20 as diagnostic and/or therapeutic agents for B-cell lymphoma has previously been reported,” and that “CD20 is a useful marker or target for B-cell lymphomas as this antigen is expressed at very high densities on the surface of malignant B-cells.” Ex. 1001, 1:23-27. The specification also confirms in the background section that anti-CD20 antibodies had been used “either alone or in conjunction with a second radiolabeled anti-CD20 antibody, or a chemotherapeutic agent.” *Id.* at 1:36-40. The specification confirms that both cyclophosphamide and fludarabine were chemotherapeutic agents “known to be useful for the treatment of CLL.” *Id.* at 7:10-11, 16-18, 22-24.

The claimed invention is described as “the discovery that hematologic malignancies and, in particular, those characterized by high numbers of tumor cells in the blood may be effectively treated by the administration of a therapeutic anti-CD20 antibody.” *Id.* at 2:17-20. Patent Owners asserted in the specification that

this result was “surprising notwithstanding the reported great success of” rituximab for the treatment of low-grade NHL, “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.” *Id.* at 2:23-32.

The specification included five examples, which “are intended to provide clinical evidence in support of the efficacy of the invention.” Ex. 1001, 4:24-26. Example 1 discusses two patients in whom were noticed “rapid reduction of blood tumor cells.” *Id.* at 4:30-31. The example goes on to describe initial adverse reactions, but that “[c]oncurrent with these symptoms, a rapid decrement in circulating tumor cell load . . . with mild electrolyte evidence of rapid tumor lysis was observed.” *Id.* at 4:45-49. The example then discusses two additional patients who were subsequently treated with rituximab “with demonstrated efficacy”—but does not define or explain what this efficacy was. *Id.* at 4:58-61.

Example 2 discusses low-grade NHL patients, not CLL patients. The example explains that low-grade NHL patients achieved “complete responses” and “partial responses.” *Id.* at 5:21-26. According to the prior art, “complete response” in the CLL context means that a patient is “free of clinical disease for at least two months.” Ex. 1008, Kipps at 34; Ex. 1002 ¶ 26 n.1. “Partial response” requires that the patient

experience “at least a 50 percent reduction in the number of blood lymphocytes.”

Ex. 1008, Kipps at 34; Ex. 1002 ¶ 26 n.1.<sup>7</sup>

Example 3, which reports the preliminary results of a Phase I/II study of CLL patients using rituximab, is the only example that discusses the claimed 500 mg/m<sup>2</sup> dose. Of the sixteen patients in the study, only eight had completed treatment. Of these eight, one had progressive disease, and one patient “achieved full remission” at a dose of “560 mg/m<sup>2</sup>.”<sup>8</sup> Ex. 1001, 6:25-27. The example does specify, however, that six of the eight patients, including up to four patients (the example does not specify) who were given the claimed dose, “had reduction in peripheral blood lymphocytosis.” *Id.* at 6:28-29. Example 3 does not otherwise report that the claimed rituximab dose resulted in a clinical benefit to the CLL patients.

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<sup>7</sup> Similar definitions apply to NHL. *See, e.g.*, Ex. 1005, Maloney (Oct.) 1997 at 4 (defining complete response as elimination of all detectable disease, and partial response as 50 percent reduction in measurable disease for at least 28 days).

<sup>8</sup> Although not material to this Petition, the reference in the specification to “560 mg/m<sup>2</sup>” is likely a typographical error, because the prior sentence does not reference this dose. This may refer to the “650 mg/m<sup>2</sup>” dose mentioned in the prior sentence in the specification. *Compare* Ex. 1001, 6:26, *with id.* at 6:27.

The remaining two examples, Examples 4 and 5, reported ongoing clinical trials for CLL. They did not report any results.

### **C. The '711 prosecution history**

The '711 patent issued on June 26, 2012, from application no. 12/629,472 (“the '472 application”). Ex. 1001, cover. The '472 application was filed on December 2, 2009, but claimed priority, through a series of continuation applications, to U.S. patent application no. 09/436,347 filed November 9, 1999, which issued as U.S. Patent No. 7,682,612 on March 23, 2010. This patent and application claimed priority to provisional application no. 60/107,658 (“the '658 application”), which was filed on November 9, 1998. 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. Therefore, any patent or printed publication prior to November 9, 1997, qualifies as prior art under 35 U.S.C. § 102(b).

As originally filed, the claims of the '347 application were directed toward a method of treating a hematologic malignancy by “administering a therapeutically effective amount” of an anti-CD20 antibody. Ex. 1018, 23, claim 1. In the application’s first rejection, the Examiner rejected this language under 35 U.S.C. § 112 because it was indefinite. Ex. 1019, 10-11. In response to the Examiner’s rejection, applicants amended the claims to specify that the method was directed

toward “a therapeutically effective amount of anti-CD20 antibody or antigen-binding fragment thereof, *said amount being effective to achieve a reduction in circulating tumor cells.*” Ex. 1020, 2 (emphasis in original). Applicants inserted this language to “give meaning to the phrase ‘therapeutically effective’ as suggested in the [2/29/2000 Office Action].” *Id.* at 6.

Although Applicants clarified how the method was therapeutically effective, the Examiner continued to reject the claims. When Applicants cancelled all of the remaining claims in the application and replaced them with 66 new claims on August 7, 2006, the claims were now directed toward “a method of treating [CLL]” using an anti-CD20 antibody “in an amount effective to treat the chronic lymphocytic leukemia.” Ex. 1021, 3. The Applicants explained that “[o]ne of skill in the art of clinical oncology would understand that effective treatments of CLL include, but are not necessarily limited to, those assessed with respect to a reduction in circulating tumor cells.” *Id.* at 15.

The Examiner continued to reject the claims, finding: “It would be obvious to one of skill in the art to implement a potential method for successful CLL treatment in light of [the fact that] rituximab has been administered to other B cell patients with relapsed and refractory B cell cancers, see declaration paragraphs 24-27. While the declarant suggests there would be decreased therapeutic efficacy that

suggestion is not equivalent to there would be *no* therapeutic effectiveness.” Ex. 1022, 6 (emphasis in original).

In a 2009 submission, Applicants told the Examiner that “effective treatment of CLL ‘must result in a positive clinical benefit to the CLL patients,’” and “the claims do require a specific, positive therapeutic outcome, and not simply induction of any type of response in the patient.” Ex. 1024, 16. But in the application—and throughout prosecution—the only evidence of a “specific, positive therapeutic outcome” submitted by the Applicant to the Examiner consisted of the examples in the specification showing a reduction in circulating tumor cells at the claimed dose.

Indeed, the only portion of the expert declaration cited by the Applicants to the Examiner for the proposition that the amount of rituximab must result in a positive clinical benefit is the following:

My opinion of what this expression in the claims would convey to an oncologist is consistent with the specification of the '347 application, which refers to treatment methods that result in, for example, demonstrated efficacy with minimal infusion-related toxicity (page 8, paragraph 0320), overall response rate (ORR), complete responses (CR), partial responses (PR), improved median time to progression or improved duration of response (page 9, paragraph 0340 as well as page 14, paragraph 0440), or remission upon treatment (page 11, paragraph 0370).

*Id.* But the only part of the specification that refers to ORR, CR, PR, and median time to progression is Example 2, which discusses NHL patients. In IPR2017-01229, however, Patent Owners *disclaimed* that teachings as to NHL necessarily apply to CLL. *See infra* Part IX.C. And as explained above, Example 3—the only example that reports on the use of rituximab to treat CLL with the claimed 500 mg/m<sup>2</sup>—does not report an ORR, CR, or PR for any patient taking that dose.

The Examiner allowed the claims that became the '612 patent after a phone interview with the Applicants in which they explained “the distinction between high prevalence of CD20 antigen expression on CLL and low antigen density on CLL cells, particularly in comparison to NHL cells” and the “high circulating tumor burden in CLL patients.” The Applicants further discussed in that phone interview the content of two submitted declarations as well as the “clinical observations” from a 1998 study of rituximab in CLL patients. Ex. 1025, 10; Ex. 1026, 4.

In April 2012, Patent Owners limited what ultimately became claim 1 of the '711 patent to a single dose (500 mg/m<sup>2</sup>) through the following amendment: “500-1500 mg/m<sup>2</sup>.” Ex. 1027, 2. In support, they referred to “paragraph 290 (page 9)” and “paragraph 370 (page 14).” *Id.* at 4. These paragraphs merely disclose that four patients who took the claimed dose had a “reduction in peripheral blood lymphocytosis.” Ex. 1001, 6:28-29. Again, Example 3 did not report any other

clinical results from this claimed dose. *See* Ex. 1002 ¶ 27. The claims of the '711 patent were then allowed on June 6, 2012.

## VII. CLAIM CONSTRUCTION

### A. “amount effective to treat the CLL”

The claim 1 term “effective to treat the CLL” is subject to dispute in IPR2017-01229. In its petition, Celltrion argues that this term means “a therapeutic response such as a reduction in the number of the small lymphocytic tumor cells.” Ex. 1028, 43. Patent Owners argue that this claim term should be construed more narrowly—namely, as “providing a positive clinical benefit to the chronic lymphocytic leukemia patient.” Ex. 1029, 31.<sup>9</sup> The ultimate construction of this claim term is not material to this petition for two independent reasons.

First, the claim term “amount effective to treat the CLL” is not a limiting part of any of the claims. As discussed above, after adding this claim language, the Patent Owners decided to limit all of the claims of the '711 patent to a specific amount of rituximab to effectively treat the CLL: 500 mg/m<sup>2</sup>. Ex. 1027, 2; *see also* Ex. 1001,

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<sup>9</sup> The district court in *Biogen IDEC, Inc. v. Glaxosmithkline LLC*, 2011 WL 4949042, at \*7 (S.D. Cal. Oct. 18, 2011), construed the claim term “effective to treat the chronic lymphocytic leukemia” in the related '612 patent as “providing a positive clinical benefit to the chronic lymphocytic leukemia patient.”

6:25-26 (discussing use of claimed rituximab dose to treat four CLL patients). The additional claim language saying that this express dosage amount must be “effective to treat the CLL” is duplicative and adds nothing to the claim limitations.

As explained by the Federal Circuit, where, as here, a method claim requires “express dosage amounts” of a drug, the specifically recited amounts “are material claim limitations” and, thus, “the statement of the intended result of administering those amounts does not change those amounts or otherwise limit the claim.” *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001). There, the Court found the claim language “an antineoplastically effective amount” to be a mere “expression of intended result” that “essentially duplicates the dosage amounts recited in the claims.” *Id.* That “expression of intended result,” the Court held, is “non-limiting.” *Id.* Here, too, the claim term “amount effective to treat the CLL” is non-limiting, especially given the express dosage amount (500 mg/m<sup>2</sup>) required by the claims of the ’711 patent.

Second, and consistent with Patent Owners’ representations during prosecution, achieving a reduction in circulating CLL tumor cells is sufficient to provide a POSA with a reasonable expectation of a clinical benefit. During prosecution, when the Examiner first asked for a clarification of what a “therapeutically effective” amount of rituximab meant, Patent Owners amended the claims to require “a reduction in circulating tumor cells.” *See supra* Part VI.C.

Applicants inserted this language to “give meaning to the phrase ‘therapeutically effective’ as suggested in the [2/29/2000 Office Action].” Ex. 1020, 2, 6.

To be sure, Applicants later amended the claims to require “an amount effective to treat the CLL.” But the *only* specification support for using the claimed 500 mg/m<sup>2</sup> rituximab dose to achieve an amount effective to treat the CLL is Example 3. And Example 3 merely discloses that the claimed dose caused a “reduction of peripheral blood lymphocytosis” in CLL patients, i.e., a reduction in circulating tumor cells. Ex. 1002 ¶ 27.

For purposes of this petition, Petitioner does not dispute Patent Owners’ argument during prosecution that this limited patent disclosure—teaching that 500 mg/m<sup>2</sup> rituximab has the effect of reducing circulating tumor cells—is sufficient under 35 U.S.C. § 112 to support a claim for a positive clinical benefit for treating the CLL. *See* Ex. 1024, 16 (describing expert’s opinion that specification’s examples show that effective treatment “must result in a positive clinical benefit to the CLL patient”). Indeed, when the Patent Owners amended the claims from a dose range of 500-1500 mg/m<sup>2</sup> to a dose of only 500 mg/m<sup>2</sup>, they cited to the four patients in Example 3 treated with 500 mg/m<sup>2</sup> who are reported as having achieved a “reduction in peripheral blood lymphocytosis.” Ex. 1027, 2, 4. As Patent Owners’ § 112 disclosure makes clear, a POSA would have reasonably expected a positive clinical benefit for treating the CLL upon learning, as the prior art taught, that

rituximab reduces circulating tumor cells. Ex. 1002 ¶ 27; *see also Biogen IDEC, Inc.*, 2011 WL 4949042, at \*4 (“Defendants are correct that depletion of tumor cells is a key event in treating CLL.”).

In sum, the claim term “amount effective to treat the CLL” does not limit the claims. Alternatively, Patent Owners’ construction of that term does not materially affect the obviousness analysis set forth below. A POSA would have reasonably expected a positive clinical effect in treating the CLL based on the knowledge and expectation that rituximab reduces circulating tumor cells.

### **VIII. STATUS OF PRIOR ART**

As shown below and in the Declaration of Petitioner’s expert librarian Dr. Scott Bennett (Ex. 1031), all of the references that Petitioner relies upon for the grounds of unpatentability asserted in this Petition are printed publications that were publicly accessible before November 9, 1997, and therefore qualify as prior art to the ’711 patent under 35 U.S.C. § 102(b). *See In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004) (“[P]ublic accessibility has been the criterion by which a prior art reference will be judged for the purposes of § 102(b).”).

All of the references described below were published in journals or books that have long been cataloged or indexed in a meaningful way. Ex. 1031 ¶¶ 39–93. Thus, these references were sufficiently accessible to the public, and ordinarily skilled artisans exercising reasonable diligence would have had no difficulty finding copies

of them. *Id.* at ¶ 97. Moreover, each date stamp on each of the references has the general appearance of date stamps that libraries have long affixed to periodicals, and there is no reason to believe it was affixed by anyone other than library personnel, or on any other date than the date stamped on the reference. *Id.* ¶¶ 39–93.

**A. Maloney 1994 (Ex. 1003)**

Maloney 1994 is an authentic copy of an article from *Blood*, a periodical first published in 1946 and held by 953 libraries worldwide. *Id.* ¶¶ 85, 89. A date stamp from the Cornell University Library indicates that the 1994 issue of *Blood* containing Maloney 1994 was processed on October 19, 1994. *Id.* ¶ 90. Therefore, Maloney 1994 was available to the public long before November 9, 1997 (*id.* ¶ 93) and is a prior-art publication under § 102(b).

**B. Maloney (Sept.) 1997 (Ex. 1004)**

Maloney (Sept.) 1997 is an authentic copy of another article from the September 1997 issue of *Blood*. *Id.* ¶ 55. *Blood* has long been cataloged or indexed in a meaningful way, including by subject. *Id.* ¶ 56. Thus, it is—and was—sufficiently accessible to the public interested in the art and an ordinarily skilled researcher or artisan, exercising reasonable diligence, would have had no difficulty finding copies of it. *Id.*

A date stamp from the Cornell University Library indicates that the September 1997 issue of *Blood* containing Maloney (Sept.) 1997 was date stamped, received

and processed by that library on September 15, 1997. *Id.* ¶ 60. This date stamp has the general appearance of date stamps that libraries have long affixed to periodicals in processing them, and there is no indication or reason to believe this date label was affixed by anyone other than library personnel or on any other date other than September 15, 1997. *Id.* Therefore, Maloney (Sept.) 1997 was available to the public before November 9, 1997 (*id.* ¶ 63) and is a prior-art publication under § 102(b).

**C. Maloney (Oct.) 1997 (Ex. 1005)**

Maloney (Oct.) 1997 is an authentic copy of an article from the October 1997 issue of *Journal of Clinical Oncology*, a publication first published in 1983 and held by 774 libraries worldwide. *Id.* ¶¶ 65, 69. The *Journal of Clinical Oncology* has long been cataloged or indexed in a meaningful way, including by subject. *Id.* ¶ 69. Thus, it is—and was—sufficiently accessible to the public interested in the art and an ordinarily skilled researcher or artisan, exercising reasonable diligence, would have had no difficulty finding copies of it. *Id.* ¶ 69.

A date stamp from the University of Wisconsin Library indicates that the issue of the *Journal of Clinical Oncology*, containing Maloney (Oct.) 1997 was date stamped, received, and processed by that library on October 14, 1997. *Id.* ¶ 70. This date stamp has the general appearance of date stamps that libraries have long affixed to periodicals in processing them, and there is no indication or reason to believe this

date label was affixed by anyone other than library personnel or on any other date other than October 14, 1997. *Id.* Therefore, Maloney (Oct.) 1997 was available to the public before November 9, 1997 (*id.* ¶ 73) and is a prior-art publication under § 102(b).

**D. Genentech Press Release (Ex. 1006)**

The Genentech Press Release was publicly available before the priority date. As Dr. Bennett explains, this press release, which has a 1995 date, was captured on the “Internet Archive” on 13 June 1997, suggesting it was available on the Internet no later than that date. *Id.* ¶ 42. The well-known Internet Archive is a non-profit digital library founded in 1996 that maintains an archive of webpages collected from the Internet by automated “crawlers.” *Id.* ¶¶ 27–32. The archived webpages are available for search and retrieval through an interface called the “Wayback Machine,” which renders accurate snapshots of webpages as they existed at the time they were collected. *Id.* Based on the press release’s appearance in the Internet Archive as of June 13, 1997, public Internet search engines at the time would have been able to find and index the press release, and a POSA exercising reasonable diligence and using typical Internet search tools would have readily found a copy of it. *Id.* ¶¶ 40–41; *see also, e.g., IBM Corp. v. Intellectual Ventures II LLC*, No. IPR2015-00089, Paper 44, at 57 (PTAB Apr. 25, 2016) (relying on “Wayback Machine evidence” to “determine that Petitioner has shown that [a reference] was

publicly available”); *Suffolk Techs., LLC v. AOL, Inc.*, 752 F.3d 1358, 1365 (Fed. Cir. 2014) (holding person interested in publication can “easily locate” the material if available on a website “organized in a hierarchical manner”).

Regardless of whether Genentech’s website was indexed through Internet search engines, Dr. Ozer explains that POSAs would have been independently aware of press releases issued by prominent companies undertaking clinical investigations of new cancer drugs, and would have specifically been aware of press releases from Patent Owners due to the collaboration between scientists and industry. Ex. 1002 ¶ 56. That is also sufficient to establish public accessibility. *Cf., e.g., Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1349 (Fed. Cir. 2016) (explaining that “whether or not” a website is itself “indexed” by “search engines or otherwise,” if there is evidence POSAs “would have been independently aware” of the website as a prominent public forum, the site is publicly accessible) (quoting *Voter Verified, Inc. v. Premier Election Sols., Inc.*, 698 F.3d 1374, 1381 (Fed. Cir. 2012)) (alteration omitted).

**E. O’Brien 1996 (Ex. 1007)**

O’Brien is an authentic copy of an abstract from *Blood*. Ex. 1031 ¶ 44. A date stamp from the University of California at Los Angeles Library indicates that the issue of *Blood* containing O’Brien was processed on December 3, 1996. *Id.* ¶ 50.

Therefore, O'Brien was available to the public before November 9, 1997 (*id.* ¶ 53) and is a prior-art publication under § 102(b).

## **IX. ANALYSIS OF GROUNDS FOR TRIAL**

As discussed in more depth below, the patent claims are generally directed to methods of (1) treating CLL with rituximab (without a radiolabeled antibody); (2) at a dose of 500 mg/m<sup>2</sup> (“an amount effective to treat the CLL”); (3) administered monthly, biweekly or weekly; and, for some claims, (4) in combination with chemotherapy drugs, particularly cyclophosphamide and fludarabine. The claims of the '711 patent would have been obvious to a POSA as of November 9, 1998, the date of the claimed invention, in view of the Maloney References, the Genentech Press Release, and O'Brien—all 35 U.S.C. § 102(b) references.

Maloney 1994 and the Genentech Press Release provided a POSA a reasonable expectation of success in using rituximab to treat CLL by reducing cancerous B-cells. The Maloney 1994 and Maloney (Sept.) 1997 references, taken together, made the claimed dose of 500 mg/m<sup>2</sup> and the claimed dosing frequencies (weekly, biweekly, or monthly) obvious as well. These references, combined with Maloney (Oct.) 1997 and O'Brien, also made it obvious to combine this rituximab treatment regimen with the known CLL chemotherapy treatment of cyclophosphamide and fludarabine.

As explained below and in the declaration of Dr. Ozer, this combination of prior art references thus taught a POSA to use rituximab at the claimed dose and frequencies, alone or in combination with cyclophosphamide/fludarabine chemotherapy, with a reasonable expectation of achieving a positive clinical outcome in CLL patients. Ex. 1002 ¶¶ 77-106; *see also In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988) (“Obviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success.”). At a minimum, these prior art references provided a POSA a “finite number of identified, predictable solutions” to a known problem—improving effective treatments for CLL. *KSR* 550 U.S. at 421. Patent Owners cannot argue that the prior art taught away, or that any secondary considerations of non-obviousness should save their patent.

**A. Ground I: Claims 1 and 5-8 would have been obvious over Maloney 1994, Maloney (Sept.) 1997, and the Genentech Press Release.**

Claims 1 and 5-8 of the '711 patent would have been obvious as of November 9, 1998, in view of Maloney 1994, Maloney (Sept.) 1997, and the Genentech Press Release.

**1. Claim 1 would have been obvious.**

Claim 1 describes “[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<sup>2</sup>.” Because these claims use the term “comprising,” they also encompass the use of rituximab in combination with chemotherapy regimens. *CIAS, Inc. v. All. Gaming Corp.*, 504 F.3d 1356, 1360 (Fed. Cir. 2007) (“In the patent claim context the term ‘comprising’ is well understood to mean ‘including but not limited to.’”); MPEP (2015) § 2111.03 (the term “comprising” is “open-ended and does not exclude additional, unrecited elements or method steps”). This claim would have been obvious to a POSA in view of Maloney 1994, Maloney (Sept.) 1997 and the Genentech Press Release. Ex. 1002 ¶ 78.

**a. Maloney 1994 suggested that rituximab could be used to treat CLL.**

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. Ex. 1002 ¶ 79. Maloney 1994 taught that CD20 was “present on the surface of nearly all B cells[,] provid[ing] a more universal target for immunotherapy” than other antigens, in NHL patients as well as patients with “B-cell chronic lymphocytic leukemia.” Ex. 1003, 3. According to Maloney 1994, in low-grade NHL patients, rituximab in doses between 10 mg/m<sup>2</sup> to 500 mg/m<sup>2</sup> led to “dose-dependent, rapid, and *specific depletion of the B cells* in all patients.” *Id.* at 6 (emphasis added). These dosages in even a single administration led to partial or minor tumor responses in six patients. *Id.* at 8.

Maloney 1994 suggested that, given the “modest tumor responses observed in this trial . . . after the administration of a single infusion[,] . . . [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. As explained by Dr. Ozer, a POSA would understand this teaching related to “more extensive disease” to include CLL, which was discussed earlier in the article and which was known to entail a more extensive tumor burden than low-grade NHL (on the order of 100-fold). Ex. 1002 ¶ 79; *compare* Ex. 1008, Kipps at 28 (CLL defined as more than 10,000 lymphocytes/ $\mu$ l), *with* Ex. 1012, McLaughlin at 7-8 & Fig 3 (low-grade NHL patients had average of about 100 lymphocytes/ $\mu$ l).

**b. The Genentech Press Release provided a POSA with a reasonable expectation of success in using rituximab to treat CLL.**

In 1995, the Genentech Press Release applied the teachings from Maloney 1994 by reporting on Patent Owners’ further development of rituximab to treat patients with CLL. As that press release reported: “Genentech and IDEC are planning additional studies with IDEC-C2B8 [rituximab] to support” treatment of “B-cell mediated cancers such as . . . *chronic lymphocytic leukemia.*” Ex. 1006, 2 (emphasis added).

This disclosure that Patent Owners were conducting rituximab clinical trials with CLL patients, alone, would have provided a POSA with a reasonable

expectation of success in using rituximab to effectively treat CLL. Ex. 1002 ¶¶ 80-84. Even where “there [is] no reliable way to predict” a particular result, the “case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Indeed, “the expectation of success need only be reasonable, not absolute.” *Id.*

Of particular relevance here, the Federal Circuit has held: “Before a drug can enter human clinical trials, the sponsor . . . must provide a convincing rationale to those especially skilled in the art (e.g., the [FDA]) that the investigation may be successful. Such a rationale would provide a basis for the sponsor’s expectation that the investigation may be successful.” *Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 619 F.3d 1329, 1343 (Fed. Cir. 2010) (quoting MPEP (2008) § 2107.03 at IV). “Thus, as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.” *Id.* (quoting MPEP (2008) § 2107.03 at IV).

MPEP (2015) § 2107.03 specifically addresses “therapeutic utility”—precisely what is at issue here, i.e., clinical effectiveness. The Federal Circuit recently confirmed that “studies are frequently conducted to confirm what is suspected to be true. An incentive to conduct a confirmatory study frequently exists

even when one has every reason to expect success.” *Soft Gel Techs., Inc., v. Jarrow Formulas, Inc.* 864 F.3d 1334, 1342 (Fed. Cir. 2017). And another panel of this Board recently held that a POSA “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 Pharm. Inc., v. Genzyme Therapeutic Prods. Ltd. P’ship*, IPR2013-00534, Paper 81, at 17 (PTAB Feb. 23, 2015).

**c. The claimed 500 mg/m<sup>2</sup> rituximab dose would have been obvious in view of Maloney 1994 and Maloney (Sept.) 1997.**

Although the Genentech Press Release did not disclose the claimed 500 mg/m<sup>2</sup> dose, that dose is presumed to be *prima facie* obvious. Ex. 1002 ¶ 84. That dose was within the range disclosed by the Maloney 1994 reference, which taught that doses ranging from 10 mg/m<sup>2</sup> to 500 mg/m<sup>2</sup> were safe and achieved a “dose-dependent, rapid, and specific depletion of the B cells in all patients.” Ex. 1003, 6. Any dose within that range is presumed *prima facie* obvious when used to achieve that same effect of depleting B cells. *Iron Grip Barbell Co.*, 392 F.3d at 1322 (“[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness.”).

Even putting aside that legal presumption, it would have been obvious to use the claimed 500 mg/m<sup>2</sup> dose when treating CLL patients. 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<sup>2</sup> 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 POSA 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 ¶ 85; *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<sup>2</sup> disclosed as safe and effective in Maloney 1994 was 500 mg/m<sup>2</sup>. That claimed dose, therefore, would have been obvious for use in CLL patients. Ex. 1002 ¶ 84.

Indeed, the lower density of CD20 on CLL B-cells would have further encouraged a POSA to use the higher 500 mg/m<sup>2</sup> dose. As Dr. Ozer explains, a POSA would have understood that the weaker density of CD20 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. Ex. 1002 ¶ 85. Thus, a POSA would have been encouraged to use more rituximab to increase the likelihood of the drug successfully “hitting” the target and binding to the CD20. *Id.*

This lower density of CD20 on CLL B-cells also would have encouraged a POSA to combine a rituximab dose of 500 mg/m<sup>2</sup> with chemotherapy, with a reasonable expectation of success in treating CLL patients.<sup>10</sup> Ex. 1002 ¶ 87. In particular, a POSA would have been aware that rituximab therapy might not be as successful when used alone to completely treat the CLL, but this POSA also would have been aware that rituximab and chemotherapy act with different and complementary mechanism of action—thus increasing the chances of positive clinical results when combined in treating CLL patients.<sup>11</sup> *Id.* As Maloney (Oct.) 1997 explained, rituximab increased the ability of chemotherapy to combat cancerous B-cells. Ex. 1005, 4; *see also* Ex. 1032, Demidem at 6-7 (rituximab makes B-cells more sensitive to chemotherapy and rituximab-induced apoptosis may be “complemented and completed by the cytotoxic drugs”).

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<sup>10</sup> As discussed above, even though claim 1 does not require use with chemotherapy, it is a “comprising” claim and thus covers use of rituximab with chemotherapy.

<sup>11</sup> As explained above, chemotherapy affects cellular metabolism at the level of DNA, cell division, or RNA synthesis, or it interferes with epigenetics. *Supra* V.B. Rituximab, by contrast, binds to a specific antigen and induces cell death through complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC). *Supra* V.C.

At a minimum, the claimed dosage for rituximab represented one of a “finite number of identified, predictable solutions” to a known problem in the art—optimizing the rituximab dose to treat CLL. *KSR*, 550 U.S. at 421. Because it was known that rituximab would deplete CD20-expressing B-cells, which causes CLL, and it was also known that Patent Owners were clinically testing rituximab in CLL patients, a POSA would have reasonably expected success in optimizing a dose that was effective to treat the CLL. *O’Farrell*, 853 F.2d at 903-04. Indeed, Patent Owners acknowledged in a related proceeding that “a POSA would have appreciated that the total amount of rituximab needed to bind to tumors is proportional to the total number of tumors that need to be destroyed.” Ex. 1030, 40. Patent Owners’ statement confirms what the prior art already showed: that the dose and frequency of rituximab administration are result-effective variables within the grasp of a POSA to optimize. *See In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980) (“[D]iscovery of an optimum value of a result effective variable . . . is ordinarily within the skill of the art.”); *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (quoting same). As Dr. Ozer explains, the claimed dose falls within a finite number of identified, predictable solutions for treating CLL with rituximab. Ex. 1002 ¶¶ 86-88; *see also KSR*, 550 U.S. at 421.

For all of these reasons, claim 1 should be cancelled as obvious in view of Maloney 1994, Maloney (Sept.) 1997, and the Genentech Press Release.

**2. Claims 5-7 would have been obvious.**

Claim 5 describes “[t]he method of claim 1 wherein the rituximab is administered weekly.” Claim 6 describes “[t]he method of claim 1 wherein the rituximab is administered bi-weekly.” Claim 7 describes “[t]he method of claim 1 wherein the rituximab is administered monthly.” These claims would have been obvious to a POSA over Maloney 1994, Maloney (Sept.) 1997, and the Genentech Press Release.

As previously explained, it would have been obvious to use the 500 mg/m<sup>2</sup> dose of rituximab in claim 1 and reasonably expect success in effectively treating the CLL by achieving a reduction in circulating, CD20-positive tumor cells. Ex. 1002 ¶ 91. Maloney 1994 further taught that single doses between 50 mg/m<sup>2</sup> to 500 mg/m<sup>2</sup> depleted CD20-positive B-cells for between one and three months in NHL patients. Ex. 1003, 6 (“In all but 1 patient receiving the higher doses (>50 mg/m<sup>2</sup>), these depletions persisted for 1 to greater than 3 months.”). This reference thus taught a POSA that rituximab, when administered in a dose within this range, should be administered at least once a month. Ex. 1002 ¶ 92. The Maloney (Sept.) 1997 reference later disclosed using 375 mg/m<sup>2</sup> of rituximab in each of four weekly doses as the preferred regimen for NHL patients. Ex. 1004, 2.

Taken together, Maloney 1994 and Maloney (Sept.) 1997 taught a dose range from 50 mg/m<sup>2</sup> to 500 mg/m<sup>2</sup>, and a range of dose frequency from once a week to

once a month. Both studies noted that no dose-limiting toxicities were observed, meaning that dosing within the disclosed range—and as often as once a week—was safe. Ex. 1003, Maloney 1994 at 9 (“no dose-limiting toxicities were identified”); Ex. 1004, Maloney (Sept.) 1997 at 1 (“Phase I trials of single doses up to 500 mg/m<sup>2</sup> and 4 weekly doses of 375 mg/m<sup>2</sup> showed clinical responses with no dose-limiting toxicity.”). The prior art thus created a known range of dosing frequencies within which claims 5-7 fall. Ex. 1002 ¶¶ 93-94.

It would have been presumptively *prima facie* obvious to a POSA to use rituximab to treat CLL on a weekly, biweekly, or monthly basis as claimed in claims 5-7. “[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness.” *Iron Grip Barbell Co.*, 392 F.3d at 1322. That is the situation here.

Even putting aside this presumption, the claimed dosing frequencies would have been obvious. As previously explained, it would have been obvious to use a rituximab dose of 500 mg/m<sup>2</sup>—the *only* dose above 375 mg/m<sup>2</sup> disclosed by the prior art as both safe and effective—because CLL patients have more extensive disease, the depletion of B-cells was dose dependent, and CD20 was more weakly expressed on the B-cells. It also would have been obvious to administer this rituximab dose monthly, weekly, or bi-weekly to treat CLL patients.

First, it would have been obvious to use this 500 mg/m<sup>2</sup> rituximab dose on at least a monthly basis because Maloney 1994 taught that the depletions in CD20-positive B-cells at that dose lasts only one to three months. Ex. 1003, 6 (“In all but 1 patient receiving the higher doses (>50 mg/m<sup>2</sup>), these depletions persisted for 1 to greater than 3 months.”); Ex. 1002 ¶ 92. Claim 7, which adds a limitation for monthly rituximab administration, would have been obvious. *Id.* ¶ 94.

Second, it also would have been obvious to use 500 mg/m<sup>2</sup> weekly because, as explained, the preferred NHL dosing was administered on a weekly basis. Ex. 1004, Maloney (Sept.) 1997 at 2. As Dr. Ozer explains, weekly dosing therefore would also have made sense for treating CLL patients, who have more extensive disease. Ex. 1002 ¶ 94. Claim 5, which adds a limitation for weekly rituximab administration, would have been obvious. *Id.*

Third, because it would have been obvious to use 500 mg/m<sup>2</sup> either weekly or monthly and reasonably expect to effectively treat the CLL, it would have been equally obvious to optimize a dosing frequency within that range, such as bi-weekly, and reasonably expect positive clinical results. *Boesch*, 617 F.2d at 276; *Applied Materials, Inc.*, 692 F.3d at 1295; Ex. 1002 ¶¶ 92-93. Claim 6, which adds a limitation for bi-weekly rituximab administration, thus also would have also been obvious. Ex. 1002 ¶ 94.

In sum, the doses and frequencies reported by the Maloney 1994 and September 1997 references created a presumption of *prima facie* obviousness. Alternatively, they also disclosed a “finite number of identified, predictable solutions”—that is, a finite number of identified, predictable doses and frequencies—that would achieve a reduction in circulating tumor cells. *KSR*, 550 U.S. at 421. As such, a POSA would have reasonably anticipated success using the methods of claims 5-7 to achieve a positive clinical benefit. Ex. 1002 ¶ 91; *O’Farrell*, 853 F.2d at 903-04. For all of these reasons, these claims should be cancelled as obvious.

### **3. Claim 8 would have been obvious.**

Claim 8 describes a negative limitation: “The method of claim 1 which does not include treatment with a radiolabeled anti-CD20 antibody.” As previously explained, claim 1 would have been obvious over Maloney 1994, Maloney (Sept.) 1997, and the Genentech Press Release. Ex. 1002 ¶ 96. A POSA would have further found the negative limitation of claim 8 obvious over Maloney 1994, which specifically states: “The use of a chimeric *naked* antibody [i.e., without a radiolabel] offers some advantages over similar trials using toxin-conjugated or *radiolabeled antibodies* against B-cell NHL.” Ex. 1003, 11 (emphasis added).

Indeed, Maloney 1994 disparaged the use of radiolabeled antibodies, teaching that they “may not be stable after formation,” “may interfere with antigen binding,”

“are unstable, and undergo autolysis,” are associated with “significant hematologic toxicity,” and are difficult to apply “in patients with impaired bone marrow function or significant involvement by lymphoma.” *Id.* “In contrast,” according to Maloney 1994, “this chimeric anti-CD20 antibody”—i.e., rituximab—“is stable and has been engineered to lyse tumor cells through interaction with the patient’s own immune system.” *Id.*

In short, a POSA would not have practiced any of the methods of the ’711 patent claims with a radiolabeled antibody. For all of these reasons, claim 8 should be cancelled as obvious. Ex. 1002 ¶¶ 96-97.

**B. Ground II: Claim 2 would have been obvious over the Maloney References and the Genentech Press Release.**

Claim 2 describes “[t]he method of claim 1 further comprising administering a chemotherapeutic regimen to the patient.” Claim 2 would have been obvious over the Maloney References and the Genentech Press Release.

As explained with respect to claim 1, Maloney 1994, Maloney (Sept.) 1997, and the Genentech Press Release would have rendered obvious the use of rituximab in CLL patients at a dose of 500 mg/m<sup>2</sup>. And as Dr. Ozer explains, it would have been obvious to add chemotherapy treatment because of the higher tumor burdens and lower CD20 expression, which made it potentially harder for rituximab to completely treat CLL on its own. Ex. 1002 ¶ 100.

The two Maloney References from 1997 also made it obvious to use rituximab with chemotherapy to treat CLL patients. Maloney (Oct.) 1997 taught that rituximab “*increases sensitivity to the cytotoxic effect of chemotherapy/toxins in some resistant human lymphoma cell lines,*” i.e., rituximab makes tumor cells more vulnerable to chemotherapy. Ex. 1005, 4 (emphasis added); Ex. 1002 ¶ 100. *See also, e.g.,* Ex. 1032, Demidem at 6-7 (noting that rituximab makes B-cells more sensitive to chemotherapy, and concluding that the rituximab-induced apoptosis may be “*complemented and completed by the cytotoxic drugs*”). This suggested a rationale for combining rituximab and chemotherapy. Ex. 1002 ¶ 101. And Maloney (Sept.) 1997 explicitly suggested combining rituximab with chemotherapy for NHL and further encouraged studying rituximab in other B-cell histologies—e.g., CLL. Ex. 1004, 7 (“Additional areas that should be investigated using this new agent include (1) extended and repeated dosing regimens, (2) *combination with or after standard chemotherapy*, (3) . . . [and] (4) *evaluation in other B-cell histologies . . .*”) (emphasis added).

In light of these teachings, a POSA would have found it obvious to combine rituximab with chemotherapeutic agents in CLL patients and would have reasonably expected this combination to treat the CLL effectively. Ex. 1002 ¶ 101; *O’Farrell*, 853 F.2d at 903-04. Where “[i]t was apparently well-known in the art that two drugs having different mechanisms for attacking [the disease] may be more effective than

one”—as here, where chemotherapy has various mechanisms of action to induce cell death or chemically prevent cell division, and where rituximab independently attaches to CD20 antigens and induces lysis—it is at minimum “obvious to try combination therapy.” *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1351 (Fed. Cir. 2013); *see also Accord Healthcare Inc., USA v. Daiichi Sankyo Co.*, IPR2015-00864, Paper 104, at 19-20 (PTAB Sept. 12, 2016) (quoting *Novo Nordisk*). In fact, the combination of chemotherapy and rituximab was one of a “finite number of identified, predictable solutions” for treating CLL and, thus, was at least “obvious to try.” *KSR*, 550 U.S. at 421; *see also* Ex. 1002 ¶¶ 101-102.

For all of these reasons, claim 2 should be cancelled as obvious.

**C. Ground III: Claims 3, 4, and 9 would have been obvious over the Maloney References, the Genentech Press Release, and O’Brien.**

For similar reasons, claims 3, 4, and 9 also would have been obvious. Claim 3 describes “[t]he method of claim 2 wherein the chemotherapeutic regimen comprises fludarabine.” Claim 4 describes “[t]he method of claim 2 wherein the chemotherapeutic regimen comprises cyclophosphamide.” Because these claims use the term “comprises,” they cover the use of a combined fludarabine/cyclophosphamide regimen. *CIAS, Inc.*, 504 F.3d at 1360. Claim 9 claims “[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<sup>2</sup>, and further comprising administering a chemotherapeutic regimen to the patient, wherein the chemotherapeutic regimen comprises fludarabine and cyclophosphamide.” A POSA would have found these claims obvious over the Maloney References and the Genentech Press Release in view of O’Brien—again, all § 102(b) art to the claims. Ex. 1002 ¶¶ 103-104.

The specification acknowledges that fludarabine and cyclophosphamide were both “*known* to be useful for the treatment of CLL.” Ex. 1001, 7:10-11, 16-18, 22-24 (emphasis added). “A statement in a patent that something is in the prior art is binding on the applicant and patentee for determinations of anticipation and obviousness.” *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1570 (Fed. Cir. 1988).

Even putting aside this admission by the Patent Owners, numerous references by November 1998 had already disclosed that the combination of the chemotherapy drugs cyclophosphamide and fludarabine was used to treat CLL. For example, in 1996, O’Brien reported a study of fludarabine and cyclophosphamide in CLL patients and concluded that the combination “is an extremely active regimen in CLL with a response rate of close to 100% in [patients] not previously refractory to [fludarabine].” Ex. 1007, 3; *see also, e.g.*, Ex. 1010, Flinn at 11 (reporting in 1996 a 100% partial response rate for patients taking the combination for two cycles, with five of six patients achieving a complete response after four cycles).

As discussed above, the Maloney references from 1997 would have motivated a POSA to combine the obvious rituximab therapy described above with chemotherapy with a reasonable expectation of effectively treating the CLL. A POSA would have found claims 3, 4, and 9 obvious in light of these references in combination with O'Brien, which identified the combination of fludarabine and cyclophosphamide as an effective chemotherapy regimen for treating the CLL. Ex. 1002 ¶ 105. As explained by Dr. Ozer, combination therapy was a common way to treat CLL, and this was an obvious combination therapy option given what was known at the time—particularly given that there was nothing in the art to discourage the combined use of these three drugs for CLL patients. Ex. 1002 ¶¶105-106; *O'Farrell*, 853 F.2d at 903-04. To the extent claim 9 requires multiples dosages of rituximab, it would have been equally obvious to combine chemotherapy with any of the obvious frequencies of rituximab administration—weekly, biweekly, or monthly. Ex. 1002 ¶ 105.

For all of these reasons, claims 3, 4, and 9 should be cancelled as obvious.

**D. Patent Owners' potential rebuttal arguments and secondary considerations**

**1. There was no teaching away.**

Based on its response to Celltrion's petition in IPR2017-01229, Patent Owners may argue that the prior art—in particular, Jensen, published in July 1998—taught away from the claimed invention. Such an argument would fail as a matter

of both fact and law. Indeed, Jensen confirms that it was obvious as of November 1998 to use rituximab to treat CLL patients.

**a. Jensen merely warned doctors that rituximab could be associated with a particular side effect—tumor lysis syndrome.**

Jensen was a “rapid communication” intended to inform doctors of a potential side effect of administering rituximab; it was not designed to report on rituximab’s efficacy. This warning addressed experiences with a single patient who had low-grade NHL, not CLL. The patient had been “heavily pretreated” with “intensive chemotherapy and high dose chemotherapy with peripheral stem cell support.” Ex. 1009, 1. Because the “CD20 surface marker was expressed on 100% of [B] cells” that “phenotypically resemble[e] B-cell chronic lymphocytic leukemia,” “treatment with the anti-CD20 antibody rituximab was initiated.” *Id.*

After being administered 375 mg/m<sup>2</sup> of rituximab, the patient suffered a side effect known as tumor lysis syndrome (sometimes referred to as “TLS”). *Id.* This adverse effect occurs when chemotherapy or other treatments rupture a high number of cancerous cells too quickly, and the cells then release large amounts of harmful substances such as anions and cations into the blood, which results in metabolic disorders. Ex. 1002 ¶¶ 110-111; Ex. 1014, Abeloff at 35. After the patient in Jensen gradually improved, “[t]hree further infusions of rituximab were administered in full

dose on days 8, 15, and 22 without clinical problems.” Ex. 1009, 2. The patient then “showed signs of progressive disease, requiring salvage chemotherapy.” *Id.*

After describing certain effects from using a different monoclonal antibody, Jensen speculated: “The recommended standard dose of 375 mg/m<sup>2</sup> for rituximab was established in patients with follicular lymphoma and lymphocyte counts of less than 5.0x10<sup>9</sup>/L. Thus, this dose might be too high for the treatment of patients with substantial peripheral tumor load. Alternatively, high peripheral tumor cell counts must be reduced using cytostatic drugs prior to administration of rituximab.” *Id.*

Jensen also vaguely mentions a separate study involving six “B-CLL patients,” noting that the “clinical side effects were minor in three [of those] patients.” *Id.* But there were “[s]igns of acute tumor lysis” in patients with lymphocytes of certain amounts. *Id.* Jensen does not cite any reference that reports on this study. Nor does Jensen disclose the dose used in the study. Instead, the point of the article was simply to warn doctors that “[w]hen”—not if—they use rituximab to treat patients with CLL, they should be aware of the risk of acute tumor lysis side effects: “*When* treating patients with CLL and marked lymphocytosis with the monoclonal antibody rituximab, physicians need to be aware of the risk of hitherto unreported acute tumor lysis and intravascular coagulation.” *Id.* (emphasis added).

**b. Jensen did not teach away from the claimed invention and, in fact, assumed that doctors would continue to use rituximab to treat CLL patients.**

Jensen did *not* teach away from the claimed invention for two independent reasons. First, it does not come close to meeting the strict legal standard: “A reference does not teach away if it does not criticize, discredit, or otherwise discourage investigation into the invention claimed.” *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (ellipses and quotation marks omitted). Instead of teaching away, Jensen *assumed* doctors would continue treating CLL patients with rituximab and simply warned physicians to be aware of the acute tumor lysis side effect. The Federal Circuit has held that a reference does not teach away where, as here, it merely “cautions” skilled artisans about potential “side effects.” *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1199 (Fed. Cir. 2014) (reference “did not teach away” where it “merely cautioned a person skilled in the art”) (alteration omitted); *Galderma*, 737 F.3d at 738-39 (“articles show[ing] increased side effects associated with” higher drug concentrations did not teach away).

Moreover, this side effect was nothing new. A textbook chapter from 1995 explained that the “incidence [of tumor lysis syndrome] in high-grade non-Hodgkin’s lymphoma is approximately 40 percent.” Ex. 1014, Abeloff at 35. It is “most commonly associated with acute lymphocytic leukemia and high-grade”

NHL, “but it occurs in a variety of hematologic and solid malignancies” as well. *Id.* Acute tumor lysis has been “observed with the administration of chemotherapy, corticosteroids, hormonal agents, radiation therapy, and biologic response modifiers”—*all common treatments for a variety of B-cell malignancies. Id.*; Ex. 1002 ¶¶ 112-116.

Thus, Jensen is not reporting on a new side effect associated with CLL. Instead, it is simply noting that this appears to be the first time this side effect manifested in a patient taking rituximab. This disclosure in Jensen would not have taught away from treating CLL patients with rituximab, as confirmed by the language of Jensen itself (noting that “[w]hen treating patients with CLL . . . with the monoclonal antibody rituximab . . .”). Ex. 1009, 2. That is because a POSA would have known how to monitor patients for and address acute tumor lysis.

As taught by the prior art, a POSA would have known to begin patients at lower rituximab doses and then escalate the dose because “[t]he incidence of TLS declines after the first 48 to 72 hours of treatment.” Ex. 1014, Abeloff at 38. Indeed, Jensen’s low-grade NHL patient received “further infusions of rituximab” after recovering from the acute tumor lysis. Ex. 1009, 2. This was how a POSA would have handled other infusion-related toxicity as well. Ex 1003, Maloney 1994 at 6 (noting that “the antibody infusion was temporarily discontinued when significant side effects were observed,” but that the “[a]ntibody infusions were usually restarted

within 30 to 45 minutes at 50 to 100 mg/h and then escalated as tolerated to 200 mg/h,” and noting that “[n]o significant further toxicity except fever was observed” afterward).

Critically, no claim of the '711 patent requires the CLL patient to *start* treatment at the claimed 500 mg/m<sup>2</sup> dose. Thus, Jensen’s remark that “[t]he recommended standard dose of 375 mg/m<sup>2</sup> for rituximab . . . might be too high for the treatment of patients with substantial peripheral tumor load,” Ex. 1009, 2, does not teach away from using rituximab to treat CLL, or the claimed dose of 500 mg/m<sup>2</sup>. Instead, as confirmed by Dr. Ozer, a POSA would construe this teaching as urging caution before starting a CLL patient with a relatively high rituximab dose until tolerability is confirmed. At that point, the dose could be increased—e.g., to 500 mg/m<sup>2</sup>—to achieve the desired efficacy. Ex. 1009, Jensen at 1; Ex. 1003, Maloney 1994 at 6; Ex. 1002 ¶¶ 115-116. Again, the point of Jensen was not to assess the effective rituximab dose for treating CLL patients. Thus, Jensen—which, again, contemplates that physicians will use rituximab to treat CLL patients—is entirely consistent with, and supports, the obviousness theories discussed above.<sup>12</sup>

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<sup>12</sup> The fact that the patient at issue in Jensen needed “salvage chemotherapy” would also not have discouraged the use of rituximab in CLL patients. Ex. 1009, 2. Such patients are very sick, often close to death, and a POSA would not necessarily have

Second, and independently, Jensen does not teach away because it reported on a single patient with “low-grade B-cell lymphoma”—a form of NHL, *not* CLL. Ex. 1009, 1. To be sure, Jensen characterized the patient’s NHL as “phenotypically *resembling* B-cell chronic lymphocytic leukemia.” *Id.* (emphasis added). But Patent Owners have disputed in IPR2017-01229 that teachings about low-grade NHL, the disease the patient in Jensen had, translate to CLL. Patent Owners stressed that prior art references do “not equate CLL and SLL [small lymphocytic lymphoma, a type of low-grade NHL],” but rather “simply describe SLL as ‘consistent with’—not identical to—CLL, and they describe SLL as a *lymphoma* type ‘B-CLL/SLL.’” Ex. 1029, 15 (emphasis in petition); *see also id.* at 14 (“Although their acronyms may appear similar, CLL and SLL are distinct diseases. Unlike CLL, which is a leukemia, SLL, which stands for ‘Small Lymphocytic Lymphoma,’ belongs to a group of cancers called lymphomas . . . . A *key* differentiator between CLL and SLL is the level of circulating lymphocytes in afflicted patients, as reflected by lymphocyte count.”) (emphasis in original); *id.* at 65 (“skilled artisans maintained

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expected rituximab to have a positive clinical result in all patients. Ex. 1002 ¶ 111 n.8. Again, the authors themselves did not discourage the use of rituximab in treating CLL but, instead, assumed that this practice would continue.

the distinction between SLL and CLL”); *id.* at 67 (“But CLL and SLL are *not* the same disease”) (emphasis in original).

Patent Owners made similar claims during prosecution. For example, they submitted an expert declaration explaining 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.” Ex. 1033 ¶¶ 22-24.

Patent Owners cannot tell the Examiner that teachings as to NHL do not necessarily translate to CLL to support their patent, only to retract that position when trying to assert teaching away in connection with an obviousness challenge. *Data Gen. Corp. v. Johnson*, 78 F.3d 1556, 1565 (Fed. Cir. 1996) (“The doctrine of judicial estoppel is that where a party successfully urges a particular position in a legal proceeding, it is estopped from taking a contrary position in a subsequent proceeding where its interests have changed,” and noting that “[a]lthough the Board is not a court, we assume it has authority by analogy to apply the doctrine in an appropriate case”). This point, alone, would defeat any argument by Patent Owners that Jensen’s report on an NHL patient teaches away from the claimed invention.

**2. There is no evidence of secondary considerations.**

Patent Owners did not rely on any evidence of secondary considerations to support their application, and Petitioner is aware of none. Even if there were secondary considerations, however, that would not render this patent nonobvious because even “substantial evidence” of secondary considerations is insufficient to “overcome the clear and convincing evidence that the subject matter sought to be patented is obvious.” *Richardson-Vicks, Inc. v. Upjohn Co.*, 122 F.3d 1476, 1484 (Fed. Cir. 1997).

Furthermore, Petitioner has no burden to identify and rebut secondary considerations. It is the patentee who must first present a prima facie case for such considerations which Petitioners may then rebut. *Sega of Am., Inc. v. Uniloc USA, Inc.*, IPR2014-01453, Paper 11, at 20 (PTAB Mar. 10, 2015). Thus, panels routinely reject arguments against institution based on secondary considerations. *See, e.g., Mylan Pharm. Inc. v. Allergan, Inc.*, IPR2016-01127, Paper 8, at 18 n.4 (PTAB Dec. 8, 2016); *Petroleum Geo-Services, Inc. v. WesternGeco LLC*, IPR2014-01478 Paper 18, at 36 (PTAB Mar. 17, 2015).

Petitioner reserves the right to respond to any new evidence of secondary considerations raised by the patentee.

**X. CONCLUSION**

For the foregoing reasons, the Board should institute *inter partes* review and cancel claims 1-9 of the '711 patent as unpatentable.

Dated: October 6, 2017

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**CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION**

Pursuant to 37 C.F.R. § 42.24, I certify that the foregoing PETITION FOR *INTER PARTES* REVIEW contains 13,754 words (as calculated by the word processing system used to prepare the Petition), excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

Dated: October 6, 2017

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**CERTIFICATE OF SERVICE ON PATENT OWNER**

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), I certify that, on October 6, 2017, true and correct copies of the foregoing PETITION FOR *INTER PARTES* REVIEW, and all Exhibits thereto, were served by overnight courier service on Patent Owner at the correspondence address of record for U.S. Patent No. 8,206,711 B2, and at another address known as likely to affect service, as follows:

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