UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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CELLTRION, INC.
Petitioner

v.

BIOGEN INC.
GENENTECH, INC.
Patent Owners

_____

Case No. IPR2017-_____

Patent No. 8,206,711

Filing Date: December 2, 2009
Issue Date: June 26, 2012

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

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PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,206,711

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APPENDIX A: EXHIBIT LIST

Exhibit No.	Description
1001	U.S. Patent No. 8,206,711
1002	U.S. Provisional Application No. 60/107,658
1003	File History for U.S. Patent No. 8,206,711 (Excerpts)
1004	File History for U.S. Patent No. 7,682,612 (Excerpts)
1005	Declaration of Michael Andreeff, M.D.
1006	Archived website for *Leukemia Insights Newsletter*, 3(2) (Last Updated July 2, 1998) ("MD Anderson Online Newsletter")
1007	Public Hearing Transcript, Biological Response Modifiers Advisory Committee, Center for Biological Evaluation and Research, Food and Drug Administration, nineteenth meeting (July 25, 1997) ("FDA Transcript")
1008	Batata, A. & Shen, B., *Relationship between Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: A Comparative Study of Membrane Phenotypes in 270 Cases*, Cancer, 70(3):625-632 (1992) ("Batata")
1009	Maloney, D.G. *et al.*, *Phase I Clinical Trial Using Escalating Single-Dose Infusion of Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients with Recurrent B-Cell Lymphoma*, Blood, 84(8):2457-2466 (Oct. 15, 1994) ("Maloney 1994")
1010	Byrd, J.C. *et al.*, *Old and New Therapies in Chronic Lymphocytic Leukemia: Now Is the Time for a Reassessment of Therapeutic Goals*, Semin. Oncol., 25(1):65-74 (Feb. 1998)
1011	Czuczman, M.S. *et al.*, *Chemoimmunotherapy of Low-Grade Lymphoma with the anti-CD20 Antibody IDEC-C2B8 in Combination with CHOP Chemotherapy*, Cancer Invest., 14(Supp. 1):59-61 (Abstract 53) (1996) ("Czuczman")

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1012	Harris, N.L. *et al.*, *World Health Organization Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Tissues: Report of the Clinical Advisory Committee Meeting-Airlie House, Virginia, November 1997*, J. Clin. Oncol., 17(12):3835-3849 (Dec. 1999)
1013	Anderson, D.R. *et al.*, *Targeted anti-cancer therapy using rituximab, a chimaeric anti-CD20 antibody (IDEC-C2B8) in the treatment of non-Hodgkin's B-cell lymphoma*, Biochemical Society Transactions, 25(2):705-708 (May 1997)
1014	Maloney, D.G. *et al.*, *IDEC-C2B8: Results of a Phase I Multiple-Dose Trial in Patients With Relapsed Non-Hodgkin's Lymphoma*, J. Clin. Oncol., 15(10):3266-3274 (Oct. 1997) ("Maloney Oct. 1997")
1015	Maloney, D.G. *et al.*, *IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients With Relapsed Low-Grade Non-Hodgkin's Lymphoma*, Blood, 90(6):2188-2195 (Sept. 15, 1997) ("Maloney Sept. 1997")
1016	McLaughlin, P. *et al.*, *Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program*, J. Clin. Oncol., 16(8):2825-2833 (Aug. 1998) ("McLaughlin")
1017	Link, B.K. *et al.*, *Phase II Pilot Study of the Safety and Efficacy of Rituximab in Combination with CHOP Chemotherapy in Patients with Previously Untreated Intermediate- or High-Grade NHL*, Program/Proceedings Am. Society Clinical Oncology, 17:3a (Abstract *7) (1998) ("Link")
1018	The Non-Hodgkin's Lymphoma Pathologic Classification Project, *National Cancer Institute Sponsored Study of Classifications of Non-Hodgkin 's Lymphomas: Summary and Description of a Working Formulation for Clinical Usage*, Cancer, 49(10):2112-2135 (May 15, 1982)

Exhibit No.	Description
1019	Harris, N.L. *et al.*, *A Revised European-American Classification of Lymphoid Neoplasms: A Proposal From the International Lymphoma Study Group*, Blood, 84(5):1361-1392 (Sept. 1, 1994)
1020	Hiddemann, W. *et al.*, *Lymphoma Classification – The Gap Between Biology and Clinical Management Is Closing*, Blood, 88(11):4085-4089 (Dec. 1. 1996)
1021	The Non-Hodgkin's Lymphoma Classification Project, *A Clinical Evaluation of the International Lymphoma Study Group Classification of Non-Hodgkin's Lymphoma*, Blood, 89(11):3909-3918 (June 1, 1997)
1022	Cheson, B.D. *et al.*, *National Cancer Institute-Sponsored Working Group Guidelines for Chronic Lymphocytic Leukemia: Revised Guidelines for Diagnosis and Treatment*, Blood, 87(12):4990-4997 (June 15, 1996)
1023	Ford, S.M. & Donegan, S.E., *Immunotherapeutic Approaches to Treatment of B-Cell Neoplasms: Focus on Unconjugated Antibodies*, Highlights in Oncology Practice, 16(2):40-50 (1998)
1024	Hall, A.G. & Tilby, M. J., *Mechanisms of Action of, and Modes of Resistance to, Alkylating Agents Used in the Treatment of Haematological Malignancies*, Blood Reviews, 163-173 (1992)
1025	Begleiter, A. *et al.*, *Chlorambucil in Chronic Lymphocytic Leukemia: Mechanism of Action*, Leuk. Lymphoma 23:187-201 (1996)
1026	Keating, M.J. *et al.*, *Long-Term Follow-Up of Patients With Chronic Lymphocytic Leukemia (CLL) Receiving Fludarabine Regimens as Initial Therapy*, Blood, 92(4):1165-1171 (Aug. 15, 1998)

Exhibit No.	Description
1027	Johnson, S. *et al.*, *Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukaemia*, Lancet, 347:1432-1438 (May 5, 1996)
1028	O'Brien, S.M. *et al.*, *Results of the Fludarabine and Cyclophosphamide Combination Regimen in Chronic Lymphocytic Leukemia*, J. Clin. Oncol., 19(5):1414-1420 (Mar. 1, 2001)
1029	*Protocol Activations and Closures*, The CALGAB, 7(1):2 (Spring 1998)
1030	Exhibit Number Not Used
1031	Koehl, U. *et al.*, *Fludarabine and cyclophosphamide: Synergistic cytotoxicity associated with inhibition of interstrand cross-link removal*, Proc. Am. Assn. Cancer Res., 38:2 (Abstract 10) (Mar. 1997)
1032	O'Brien, S. *et al.*, *Fludarabine (FAMP) and Cyclophosphamide (CTX) Therapy in Chronic Lymphocytic Leukemia (CLL)*, Blood, 88(10, Supp. 1):480 (Abstract 1910) (Nov. 15, 1996)
1033	Exhibit Number Not Used
1034	Genentech Press Release, Mar. 3, 1995
1035	Grillo-López, A.J., *Rituximab: An Insider's Historical Perspective*, Semin. Oncol., 27(6, Supp. 12):9-16 (Dec. 2000)
1036	Declaration of David P. Schenkein, M.D. Under 37 C.F.R. §1.132, in U.S. Patent Application No. 09/436,347, dated November 14, 2008 ("Schenkein Decl. I")
1037	Declaration of David P. Schenkein, M.D. Under 37 C.F.R. §1.132, in U.S. Patent Application No. 09/436,347, dated May 5, 2009 ("Schenkein Decl. II")

Exhibit No.	Description
1038	Jensen, M. *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)*, Ann. Hematol., 77:89-91 (1998)
1039	U.S. Patent Application No. 09/372,202
1040	Stashenko, P. *et al.*, *Characterization of a Human B Lymphocyte-Specific Antigen*, J. Immunol., 125(4):1678-1685 (Oct. 1980)
1041	Anderson, K.C. *et al.*, *Expression of Human B Cell-Associated Antigens on Leukemias and Lymphomas: A Model of Human B Cell Differentiation*, Blood, 63(6):1424-1433 (June 1984) ("Anderson 1984")
1042	Leget, G.A. *et al.*, *Use of rituximab, the new FDA-approved antibody*, Curr. Opin. Oncol., 10(6):548-551 (1998)
1043	Foon, K.A., *Laboratory and Clinical Applications of Monoclonal Antibodies for Leukemias and Non-Hodgkin's Lymphoma*, Curr. Probl. Cancer 63-128 (March/April 1989)
1044	Foon, K.A. & Fisher, R.I., *Chapter 111: Lymphomas*, in Williams Hematology, Fifth Edition, 1076-1096 (Beutler, E. *et al.*, eds., 1995)
1045	Almasri, N.M. *et al.*, *Reduced Expression of CD20 Antigen as a Characteristic Marker for Chronic Lymphocytic Leukemia*, Am. J. Hematol., 40(4):259-263 (1992)
1046	Demidem, A. *et al.*, *Chimeric Anti-CD20 (IDEC-C2B8) Monoclonal Antibody Sensitizes a B Cell Lymphoma Cell Line to Cell Killing by Cytotoxic Drugs*, Cancer Biother. Radiopharm., 12(3):177-186 (1997)

Exhibit No.	Description
1047	Piro, L. *et al.*, *RITUXAN™ (rituximab, IDEC-C2B8): Interim analysis of a Phase II study of once weekly times 8 dosing in patients with relapsed low-grade or follicular non-Hodgkin's lymphoma*, Blood, 90(10, Supp. 1):510a (Abstract 2272) (1997)
1048	Exhibit Number Not Used
1049	Second Declaration of David Schenkein, in opposition to European Patent No. EP-B1 1 616 572, dated June 5, 2013 ("Schenkein EP Decl., D71")
1050	Declaration of Dr. Michael Wenger, M.D., in opposition to European Patent No. EP-B1 1 616 572, dated January 31, 2014 ("Wenger EP Decl., D91")
1051	Declaration of Dr. Steven Edward Coutré, M.D., in opposition to European Patent No. EP-B1 1 616 572, dated February 3, 2014 ("Coutre EP Decl., D92")
1052	WO 94/11026
1053	U.S. Patent No. 6,455,043 ("the '043 patent")
1054	FDA FOIA Response Letter (August 26, 2016)
1055	Kipps, T.J., *Chapter 106: Chronic lymphocytic leukemia and related diseases*, in Williams Hematology, Fifth Edition, 1017-1039 (Beutler, E. *et al.*, eds., 1995)
1056	Declaration of Christopher Butler, Internet Archive, dated December 20, 2016, authenticating Archived website for *Leukemia Insights Newsletter*, 3(2) (Last Updated July 2, 1998), Ex. 1006
1057	Nguyen, D. *et al.*, *IDEC-C2B8 anti-CD20 phase II trial: results on bone marrow and peripheral blood tumor response in patients with low grade Non-Hodgkin's (NHL)lymphoma/lymphoproliferative disorders (LPD)*, Blood, 90(10, Supp. 1):511a (Abstract 2277) (Nov. 15, 1997)

Exhibit No.	Description
1058	Czuczman, M.S. *et al.*, *IDEC-C2B8 (Rituximab) Alone and in Combination with CHOP in the Treatment of Low-Grade B-Cell Lymphoma*, Cancer Invest., 16 (Suppl. 1):21-22 (Abstract 17) (1998) ("Czuczman Nov. 1997")
1059	Williams, W.J. *et al.*, *Chapter 2: Examination of the Blood*, in Williams Hematology, Fifth Edition, 8-15 (Beutler, E. *et al.*, eds., 1995)
1060	Seng, J.E. & Peterson, B.A., *Indolent B-cell Non-Hodgkin's Lymphomas*, Oncology, 1(12):1883-1897 (Dec. 1997)
1061	Leukemia Insights Newsletter, 3(2) (Summer 1998) ("MD Anderson Print Newsletter")
1062	Protocol for Phase I/II Study of IDEC-C2B8 (Rituximab) for Relapsed CLL (DM97-236) (Dec. 10, 1997) ("O'Brien Protocol")
1063	Exhibit Number Not Used
1064	M. Keating *et al.*, *Early Results of Chemoimmunotherapy Regimen of Fludarabine, Cyclophosphamide, and Rituximab As Initial Therapy for Chronic Lymphocytic Leukemia*, J. Clin. Oncol., 23(18):4079-4088 (June 20, 2005)

APPENDIX B: '711 PATENT CLAIMS

The challenged claims of the '711 patent recite:

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

(Ex. 1001 at 8:17-43.)

I. INTRODUCTION

Celltrion, Inc. ("Celltrion" or "Petitioner") petitions for *inter partes* review under 35 U.S.C. §§311–319 and 37 C.F.R. §42 of claims 1-9 of U.S. Patent No. 8,206,711 ("the '711 patent"). Review should be instituted because there is a reasonable likelihood Celltrion will demonstrate that the claims of the '711 patent are anticipated and/or obvious, as shown below.

The '711 patent claims are directed to using rituximab to treat patients with chronic lymphocytic leukemia ("CLL"), a disease caused by accumulation of B-cells in the blood. CLL is a subtype of low-grade non-Hodgkin's lymphoma ("NHL"). (*See* Ex. 1021 at 004, 006.) By November 9, 1997, one year before the filing date of the earliest filed application to the '711 patent, it was well-known that rituximab could eradicate the B-cells that cause CLL. (Ex. 1005 ¶43.) Specifically, it was known that rituximab could effectively treat small lymphocytic lymphoma ("SLL") and that SLL and CLL were "different tissue expressions of ***the same disease*** process." (Ex. 1008 at 002 (emphasis added); Ex. 1005 ¶27.)

Claim 1 recites a method for treating a patient with CLL by administering rituximab at a 500 mg/m^2 dosage. But the idea of treating CLL with rituximab was not new: a 1995 Genentech press release noted that rituximab was "being developed for certain lymphomas and leukemias characterized by excessive B-cell proliferation" and additional studies were planned in "other B-cell mediated

cancers such as . . . chronic lymphocytic leukemia." (Ex. 1034 at 002.)

Nor was the claimed dose new. By 1994, the prior art disclosed effective treatment of low-grade NHL patients by administering a 500 mg/m^2 rituximab dosage. (Ex. 1005 ¶5; Ex. 1009 at 003 (Abstract).) A newsletter published in print and online by the MD Anderson Cancer Center ("MD Anderson") expressly disclosed treating CLL with once-weekly doses of rituximab at 500 mg/m^2. (Ex. 1005 ¶5; Ex. 1006 at 004; Ex. 1061 at 002; *see also* Ex. 1062 at 005.) Accordingly, there was nothing novel or non-obvious about administering rituximab in a 500 mg/m^2 dosage to treat CLL. Claim 1 is unpatentable under 35 U.S.C. §102 and/or §103. (Ex. 1005 ¶5.)

Nor do dependent claims 5-8 add any limitations that make the recited methods novel or non-obvious. Claims 5-7 recite dosing intervals for rituximab treatment on weekly, bi-weekly, or monthly schedules. These dosing schedules were either expressly disclosed in the prior art or represent no more than "a routine optimization of the therapy outlined in [the prior art]." *Biomarin Pharm. Inc. v. Genzyme Therapeutic Prods. Ltd. P'ship*, IPR2013-00534, Paper No. 81 at 12-14 (P.T.A.B. Feb. 23, 2015). Claim 8, which excludes radiolabeled antibodies, is neither novel nor non-obvious because the prior art recognized rituximab's effectiveness to treat CLL without a radiolabel. (Ex. 1005 ¶6.) Thus, claims 5-8 are unpatentable under 35 U.S.C. §102 and/or §103.

Dependent claims 2-4 and independent claim 9 recite methods combining CLL treatment by a 500 mg/m^2 rituximab dosage with a chemotherapeutic regimen (claim 2), or particular chemotherapies including fludarabine (claim 3), cyclophosphamide (claim 4), or both fludarabine and cyclophosphamide (claim 9). Such combination therapies were anticipated and/or obvious. Using combination therapies was standard practice in treating B-cell cancers where, as here, rituximab had a "novel mechanism of action and a favorable toxicity profile" compared to traditional chemotherapy treatments, and "rituximab [could] be used with other agents with different mechanisms of action to give enhanced therapeutic benefits." (Ex. 1013 at 004-05; Ex. 1005 ¶100.) Furthermore, by February 1998, it was known that CLL could be treated with a combination of rituximab and fludarabine, and that there was a synergistic interaction between fludarabine and cyclophosphamide. (Ex. 1010 at 006.) Claims 2-4 and 9 are thus unpatentable under 35 U.S.C. §102 and/or 103.

Petitioner respectfully requests institution of *inter partes* review of claims 1-9 due to the reasonable likelihood the claims are anticipated and/or obvious.

II. MANDATORY NOTICES (37 C.F.R. §42.8(a)(1))

A. Real Party-In-Interest (37 C.F.R. §42.8(b)(1))

Celltrion; Celltrion Healthcare Co., Ltd.; and Teva Pharmaceuticals International GmbH are the real parties-in-interest.

B. Related Matters (37 C.F.R. §42.8(b)(2))

Simultaneously with the instant petition, Petitioner has filed petitions for *inter partes* review of U.S. Patent No. 7,682,612. Biogen, Inc. ("Biogen") and Genentech, Inc. ("Genentech") (collectively, "Patentees" or "Patent Owners") are the owners of the following U.S. applications and patents that the '711 patent claims priority from: Appl. No. 09/436,347, now U.S. Patent No. 7,682,612, and Provisional Appl. No. 60/107,658.

C. Lead and Back-Up Counsel (37 C.F.R. §42.8(b)(3))

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D. Service Information

Petitioner may be served at the address provided in Section II.C, above, and consents to electronic service at zCelltrion-PTAB-IPR@cooley.com.

E. Power of Attorney (37 C.F.R. §42.10(b))

Power of attorney is being filed concurrently with this petition.

III. PAYMENT OF FEES (37 C.F.R. §42.103)

This Petition requests review of claims 1-9 of the '711 patent and is accompanied by a payment of $23,000, which comprises a $9,000 request fee and $14,000 post-institution fee. 37 C.F.R. §42.15(a). This Petition meets the fee requirements of 35 U.S.C. §312(a)(1).

IV. REQUIREMENTS FOR *INTER PARTES* REVIEW (37 C.F.R. §§42.104, 42.108)

A. Grounds for Standing (37 C.F.R. §42.104(a))

Petitioner certifies that the '711 patent is eligible for *inter partes* review, and that the Petitioner is not barred or estopped from requesting *inter partes* review on the grounds identified in the present Petition.

B. Identification of Challenge (37 C.F.R. §42.104(b)) and Statement of Precise Relief Requested

Petitioner requests *inter partes* review of claims 1-9 of the '711 patent on the grounds set forth in the following table and requests that it be found unpatentable. The '711 patent is to be reviewed under pre-AIA §§102 and 103. This Petition, supported by the accompanying declaration of Dr. Michael Andreeff (Ex. 1005), demonstrates that there is a reasonable likelihood the challenged claims are invalid.

Ground	'711 Patent Claims	Basis for Unpatentability
Ground 1	1, 5, 8	Anticipated under §102 over MD Anderson Online Newsletter
Ground 2	7, 9	Anticipated under §102 over Keating
Ground 3	6	Obvious under §103 over Keating and MD Anderson

		Online Newsletter
Ground 4	2-4, 9	Obvious under §103 over the combination of MD Anderson Online Newsletter and Byrd
Ground 5	6, 7	Obvious under §103 over the combination of MD Anderson Online Newsletter, Byrd, and Kipps
Ground 6	1, 5-8	Obvious under §103 over the combination of FDA Transcript, Batata, and Maloney

The MD Anderson Online Newsletter, Byrd, Kipps, the FDA Transcript, Batata, and Maloney are prior art to the '711 patent because each reference was published or otherwise made publicly available more than one year before the earliest effective filing date or predates the invention of each challenged claim of the '711 patent.

V. TECHNICAL BACKGROUND

A. CLL and SLL Are Different Manifestations of the Same Disease Process

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are a subtype of B-cell NHL[1] caused by small lymphocytic B-cell tumors "involving peripheral blood, bone marrow, lymph nodes, spleen, and other organs." (Ex. 1045 at 002.)

Despite the labels "leukemia" and "lymphoma," SLL and CLL have been

[1] NHL is a form of lymphoma affecting B-cells or T-cells and is distinct from the cancer known as Hodgkin's Lymphoma. (Ex. 1044 at 023, 026-27.) B-cell NHLs comprise about 80% of adult NHLs. (*Id.* at 027.)

known as "different tissue expressions of ***the same disease*** process." (Ex. 1008 at 002 (emphasis added); Ex. 1005 ¶27.) In 1997, the World Health Organization concluded: "CLL and SLL are one disease at different stages, not two separate entities." (Ex. 1012 at 012.)

The SLL and CLL labels are merely based on the location of the patient's diseased B-cells. (Ex. 1005 ¶29.) When the malignant B-cells are primarily in the patient's lymph nodes, the disease is labeled small lymphocytic *lymphoma* (SLL). But, when those same B-cells are in the bloodstream in numbers above a certain concentration, the disease is called chronic lymphocytic *leukemia* (CLL). (*Id.*) Because the lymph nodes and blood are connected through the circulatory and immune systems, diseased cells move into and proliferate within different locations of the body such that "[s]ome patients with small lymphocytic lymphoma develop CLL." (Ex. 1044 at 026.) Clinical evidence suggests that in 40% of patients categorized under SLL, the disease "evolves into a leukemic phase indistinguishable from CLL." (Ex. 1005 ¶29; Ex. 1008 at 002; Ex. 1060 at 002.)

Clinical assessment of SLL versus CLL is often based on the patient's total lymphocyte count. (Ex. 1005 ¶30.) Lymphocytes are blood cells, including B-cells, T-cells, and NK cells. (*Id.*) There is no uniform dividing line between SLL and CLL: Different standards draw the line at 4,000 lymphocytes per microliter (/μl), 5,000 lymphocytes/μl, or 10,000 lymphocytes/μl. (*Id.*; Ex. 1008 at 003; Ex.

1022 at 003.) Hence, a patient with a given lymphocyte count may be deemed to have SLL under one standard and CLL under another, consistent with CLL and SLL being "different tissue expressions of the same disease." (Ex. 1005 ¶¶27, 30; Ex. 1008 at 008.)

Inventor Grillo-López recognized the equivalence between CLL and SLL in a patent application filed three months before the filing date of the application that became the '711 patent: "CLL is the liquid (leukemic) equivalent of small lymphocytic lymphoma (SLL)." (Ex. 1039 at 027.) Grillo-López captured this equivalence by grouping CLL and SLL together: "diffuse small lymphocytic lymphoma/chronic lymphocytic leukemia (CLL)." (*Id.* at 012.) Finally, the claims of the patent that issued from the co-pending application identify CLL as a type of "B-cell ***lymphoma***." (Ex. 1053 at 23:13-16 (claim 6) (emphasis added); Ex. 1005 ¶28.)

B. NHL Classifications Group CLL and SLL as the Same Disease

That CLL and SLL are the same disease process is reflected in their classification as a single low-grade NHL subtype: "CLL/SLL." (*E.g.*, Ex. 1019 at 010 ("Lymphoma Type: B-CLL/SLL"); Ex. 1045 at 002 (Abstract) (the "CLL/SLL cells").) The different NHLs have been classified into 3 grades of severity by the National Cancer Institute's Working Formulation ("IWF"), based on features displayed by the malignant B cells: low-grade (IWF types A-C), intermediate-

grade (IWF types D-G), and high-grade NHL (IWF types H-J). (Ex. 1018 at 012.) Because they are known to arise from the same B-cell disease process, SLL and CLL are identified together as IWF type A low-grade NHL. (*Id.*)

Additionally, in a seminal 1994 article, the Revised European and American Lymphoma ("REAL") Classification system for NHLs identifies CLL and SLL as one NHL type, "B-CLL/SLL." (*See* Ex. 1019 at 010 ("Lymphoma Type: B-CLL/SLL").) Other classifications also consistently group CLL and SLL together as the same NHL type. (Ex. 1005 ¶¶31-32.)

C. Standard Treatments for SLL and CLL Were Similar

By the late 1990s, it was well known that "[t]reatment of [SLL] is similar to that for CLL." (Ex. 1044 at 029.) Doctors with CLL patients regularly looked to SLL therapies, and vice versa, for treatment options. (*See* Ex. 1060 at 002; Ex. 1005 ¶33.)

Standard approaches to chemotherapy for CLL/SLL involved combining drugs with different mechanisms of action to kill tumor cells, including alkylating agents, purine nucleotide analogs, and combination therapies. (Ex. 1005 ¶34.) Alkylating agents, such as chlorambucil and cyclophosphamide, were considered valuable cytotoxic drugs for treating SLL and CLL. (*Id.*; Ex. 1024 at 003.) In addition to alkylating agents, fludarabine, a nucleotide analog, was used to treat CLL since the early 1990s. (Ex. 1005 ¶35.) By the late 1990s, fludarabine was

considered an acceptable first-line therapy for treating CLL, and combining fludarabine with cyclophosphamide was identified to have potential synergy. (*Id.* ¶¶36-37; Ex. 1010 at 006.) Combination chemotherapies were also known to be effective for treatment of CLL, including cyclophosphamide, vincristine, and prednisone ("CVP"), and cyclophosphamide, doxorubicin, vincristine, and prednisone ("CHOP") combinations. (Ex. 1055 at 035-36.)

D. Rituximab Is an Antibody Against CD20, a Protein Expressed on the Surface of B-Cells

B-cell cancers, including CLL/SLL, generally arise when a defect in the normal B-cell maturation process causes an over-production of cells arrested in an immature state. (Ex. 1005 ¶38; Ex. 1023 at 004.) The presence of certain biological markers on the surface of the cells characterizes the different stages of B-cell maturation from a "pre-B-cell" to a plasma cell. (Ex. 1005 ¶38.)

CD20 is a protein that appears on B-cells during certain phases of B-cell differentiation. (*Id.* ¶39; Ex. 1040 at 002 (discussing the B1 antigen, which is CD20).) CD20 is present on more than 90% of B-cell NHLs and over 95% of B-cell CLL, and can therefore be used as a targeted tumor marker for such diseases. (Ex. 1005 ¶39; Ex. 1042 at 003; Ex. 1041 at 006.) That CLL and SLL cells express similar levels of CD20 was known in the early 1990s. (Ex. 1008 at 008.)

Both CLL and SLL B-cells express CD20 at a lower level than other NHLs. (Ex. 1005 ¶40; Ex. 1045 at 003; Ex. 1007 at 069 (68:12-20).)

Rituximab is an anti-CD20 chimeric (human-mouse) monoclonal antibody that binds to and kills cells expressing the CD20 antigen.[2] (Ex. 1005 ¶41; Ex. 1013 at 002.) Binding of rituximab to CD20 leads to death of normal and malignant B-cells expressing CD20. (*Id*.) Because it kills B-cells selectively, rituximab was "developed for certain lymphomas and leukemias characterized by excessive B-cell proliferation." (Ex. 1005 ¶42; Ex. 1034 at 002.)

E. Rituximab Clinical Trial Results Demonstrated Safety and Efficacy of Rituximab and Rituximab-Chemotherapy Combination Therapy

By November 1998, published results from several rituximab clinical trials showed that rituximab was safe and effective, both as a single agent and combined with chemotherapy, for treating low-grade NHL patients, including patients with SLL.

Rituximab was first tested in human patients in a 1993 dose escalation study. (Ex. 1005 ¶44; Ex. 1009 at 003.) In that study by Maloney, fifteen patients with relapsed low-grade B-cell NHL received one intravenous infusion of 10, 50, 100,

[2] By November 9, 1997, IDEC-C2B8 was also known as rituximab. (*See, e.g.*, Ex. 1013 at 002.)

250, or ***500 mg/m²*** rituximab. (Ex. 1009 at 003 (Abstract).) One SLL (IWF group A) patient received a dose of 50 mg/m^2 rituximab. (*Id.* at 005-06.) The investigators observed that "CD20+ B cells were rapidly and specifically depleted in the peripheral blood at 24 to 72 hours and remained depleted for at least 2 to 3 months in most patients." (*Id.* at 003.) Ultimately, all tested doses were well tolerated, including the highest 500 mg/m^2 dose, and "no dose-limiting toxicities were identified," though some manageable infusion-related side effects were observed. (*Id.* at 009; Ex. 1005 ¶44.)

McLaughlin reported on August 7, 1998 that rituximab was effective to treat SLL. (Ex. 1016.) McLaughlin reported results from a Phase III trial involving 166 patients with relapsed low-grade or follicular B-cell NHL, including 33 SLL patients. (*Id*. at 004.) The patients participating in the Phase III trial received four weekly infusions of 375 mg/m^2 rituximab. (*Id.*) The investigators characterized the overall response rate of 48% from the trial as "high" and "encouraging." (*Id.* at 009.) The SLL patients also showed a beneficial response, although they had a lower overall response rate (13%) compared to other NHL patients. (*Id.* at 006.) The investigators reasoned that the lower response rate may be related to the high tumor burden in SLL patients' blood, which would more rapidly consume the rituximab antibody and serve as an "antigen sink." (*Id.* at 009.) The investigators concluded that "[c]onceivably, higher doses or more protracted dosing schedules"

could enhance effectiveness for SLL. (*Id.*) McLaughlin indicates that patients with a lymphocyte count of over 5,000 lymphocytes/μL were excluded from the study, and refers to those patients as CLL patients. (*Id.* at 004.) However, under CLL categories drawing the line at 4,000 lymphocytes/μL[3] or 4,000 white blood cells/μL as used by the '711 patent[4], some CLL patients could have been included in the study. (Ex. 1005 ¶47.)

Further studies demonstrated that rituximab could be administered in combination with chemotherapy. For example, Czuczman reports on a Phase II study of patients with low-grade or follicular NHL; 23% were SLL patients. (Ex. 1058 at 003.) This study evaluated safety and efficacy of rituximab combined with CHOP chemotherapy. (*Id.*) The rationale for combining rituximab with CHOP was their "single-agent efficacy; non-cross-resistant mechanisms of action; no apparent overlapping toxicities; and in-vitro data suggesting [rituximab's] ability to sensitize drug-resistant human B-cell lymphoma cell lines to chemotherapy." (*Id.*) The response rate for the 35 patients completing all scheduled therapy was 100%. (*Id.;* Ex. 1005 ¶50.)

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[3] 4,000 lymphocytes/μL is identical to 4 X 10^9 lymphocytes/L. (Ex. 1005 ¶47 n.3.)

[4] A threshold of 4,000 ***white blood cells***/μL corresponds to fewer than 4,000 ***lymphocytes***/μL as explained by Dr. Andreeff. (Ex. 1005 ¶55 n.5.)

VI. THE '711 PATENT AND ITS PROSECUTION HISTORY

A. The '711 Patent

The '711 patent (Ex. 1001), entitled "Treatment of Chronic Lymphocytic Leukemia Using Anti-CD20 Antibodies," relates to treatment of hematological malignancies associated with high numbers of circulating tumor cells by administering a therapeutically effective amount of a chimeric or humanized anti-CD20 antibody. (Ex. 1001 at Abstract.) A preferred embodiment is treatment of CLL by administering a therapeutically effective amount of rituximab. (Ex. 1001 at 2:9-12.)

The '711 patent contains nine claims including two independent claims. (*See* Appendix B.)

B. Prosecution History of the '711 Patent

The '711 patent issued on June 26, 2012 from U.S. Application No. 12/629,472 (the '472 application"), filed on December 2, 2009. The '711 patent is a continuation of U.S. Application No. 09/436,347 ("the '347 application"), which issued as U.S. Patent No. 7,682,612 ("the '612 patent"). The '347 application, filed November 9, 1999, in turn claims priority to U.S. Provisional Application No. 60/107,658 ("the '658 provisional application") filed on November 9, 1998.

As described below, only claims 1, 5, and 8 of the '711 patent should have the November 9, 1998 priority date of the '658 provisional application. The priority date for claims 2-4 (combining rituximab with chemotherapy, fludarabine, or cyclophasphamide) is no earlier than the November 9, 1999 filing date of the '347 application. The priority date for claims 9 (combination with cyclophosphamide-fludarabine), 6 and 7 (bi-weekly and monthly dosing) is no earlier than the December 2, 2009 filing date of the '711 patent.

1. The '658 provisional application

The '658 provisional application purports to disclose a novel treatment for hematological malignancies characterized by high numbers of tumor cells in the blood by administering a therapeutically effective amount of an anti-CD20 antibody. (Ex. 1002 at 004-05.) Examples of such hematological malignancies include B-pro-lymphocytic leukemia (B-PLL), CLL, and transformed NHL. (*Id.* at 005.) The specification concedes that rituximab had "great success" for the treatment of low-grade NHL. (*Id.* at 006.) However, it contends that the ability of rituximab to treat CLL was "surprising given the very high numbers of tumor cells observed in such patients and also given the fact that such malignant cells, e.g., CLL cells, typically do not express the CD20 antigen at the high densities which is characteristic of ***some*** B-cell lymphomas, such as relapsed and previously-treated low-grade non-Hodgkin's lymphomas." (*Id.* (emphasis added).)

The disclosure states, "***it may be desirable*** to combine" the administration of rituximab "with other treatments, e.g., radioactive therapy, both targeted and non-targeted, chemotherapies, and lymphokine or cytokine administrations, e.g., interleukins, interferons, TNF's, colony stimulating factors, etc." (*Id.* at 009 (emphasis added).) While the specification asserts that a "particularly preferred chemotherapeutic regimen that may be used in conjunction with the subject antibody immunotherapy comprises CHOP" and identifies other chemotherapeutic agents such as "methotrexate, cisplatin, toremifene and tamoxifen" (*id.* at 010), it does not disclose fludarabine. Nor does it disclose dosing regimens for any combination therapies or examples to support the efficacy of such combination therapies. (Ex. 1005 ¶¶60-61.)

Further, the '658 provisional application recites that rituximab administration "may be effected by various protocols, e.g., weekly, bi-weekly, or monthly, dependent on the dosage administered and patient response." (Ex. 1002 at 009.) But it does not disclose using these dosing regimens specifically for CLL and provides no examples to support the efficacy of either bi-weekly or monthly dosing regimens. Instead, it notes that "[t]ypically, treatment will be effected weekly," with no further discussion of bi-weekly or monthly treatment. (*Id.*; Ex. 1005 ¶62.)

2. The ’347 application

Like the ’658 provisional application, the ’347 application contends that the ability of rituximab to treat CLL was surprising. (Ex. 1004 at 010-11.) The ’347 application adds Example 5, labeled “Combination Antibody and Chemotherapy Protocol” (*Id.* at 021-23), which describes chemotherapy agents used to treat CLL. (Ex. 1005 ¶64.) This November 9, 1999 application is the first time fludarabine is identified as a single agent to treat CLL. (*Id.*) Example 5 is a description of the CALGB trial of rituximab and fludarabine, which was disclosed in the prior art. (*Id.*; *see* Ex. 1010 at 006; Ex. 1029 at 007.) Furthermore, the example does not disclose any dosing regimens for a treatment combining both chemotherapy and rituximab into a single treatment protocol. (Ex. 1005 ¶64.) Rather, the example merely states that a Phase II trial in which rituximab and fludarabine are administered concurrently is “currently being conducted.” (*Id.*; Ex. 1004 at 023.) Moreover, none of the new examples disclose the combination of fludarabine ***and*** cyclophosphamide with rituximab, nor do they disclose bi-weekly or monthly rituximab administration for CLL treatment. (Ex. 1005 ¶65.)

3. Prosecution of the ’612 patent

During the ***10-year*** prosecution of the ’347 application that ultimately issued as the ’612 patent, the examiner repeatedly rejected claims directed to the treatment of CLL using rituximab over the prior art’s disclosure that rituximab was

effective for treating B-cell NHL. (Ex. 1004 at 074-077; 138-42; 169-71; 197-200; 225-29; 326-29; 361-64; 397-404; 521-26.) Throughout these ten years, there was no acknowledgement by the examiner or the applicants of the fact that CLL and SLL were different tissue expressions of the same disease process. (Ex. 1008 at 002.)

The patent issued only in view of arguments that obscured the fact that CLL and SLL are the leukemic and lymphatic equivalents of the same malignancy. Applicants argued that "[a] person of ordinary skill in the art would not have found the description in the prior art of treatments for NHL highly relevant for understanding what kinds of treatments might be tried, let alone effective for CLL" and that "CLL tumor cells and NHL tumor cells exhibit characteristic phenotypic features that reflect their different cellular origins." (Ex. 1004 at 417.) Both of these assertions are directly contradicted by the understanding in the prior art: CLL and SLL tumor cells are different tissue expressions of the same disease process. (Ex. 1005 ¶27, 133; Ex. 1008 at 002.)

The biological equivalence of CLL and SLL coupled with rituximab's ability to treat SLL undermines the Applicants' assertion that the "reduced level of CD20 expression on CLL tumor cells, relative to NHL tumor cells" justified patenting the claims in the '612 patent. (Ex. 1004 at 417.) It was known in the art

that SLL and CLL tumor cells are the same and that rituximab could treat SLL, which, like CLL, exhibits low CD20 levels. (Ex. 1005 ¶¶27-28, 40, 43.)

4. Prosecution of the '711 patent

The '711 patent is a continuation of the '612 patent. After a single rejection for obviousness-type double patenting, the initially filed claims were allowed by the examiner. In a post-issuance amendment, Patentees cancelled three claims and amended what became claim 9 of the '711 patent—prosecuted as claim 22—to recite a combination therapy of rituximab, fludarabine, ***and*** cyclophosphamide that was not present in the allowed claims. (Ex. 1003 at 102.) The previously allowed claims recited only using rituximab with "fludarabine ***or*** cyclophosphamide." (*Id.* at 053, 071, 086 (emphasis added).) The portions of the specification cited by Patentees as allegedly providing support for the amendment do not disclose any treatment regimen for using rituximab in combination with both fludarabine ***and*** cyclophosphamide. (Ex. 1005 ¶66.) After an applicant-initiated interview, the claims of the '711 patent issued. (Ex. 1003 at 107.)

C. The Combination Therapy Claims (Claims 2-4 and 9) and Bi-Weekly and Monthly Dosing Claims (Claims 6-7) of the '711 Patent Are Not Entitled to the Effective Filing Date of the '658 Provisional Application

To receive the priority date of the '658 provisional application or the '347 application, Patent Owners have the burden of demonstrating that "a person of

ordinary skill in the art would recognize that the applicant possessed what is claimed in the later filed application as of the filing date of the earlier filed application." *Noelle v. Lederman*, 355 F.3d 1343, 1348 (Fed. Cir. 2004). This is true even if the alleged priority applications have the same written description as the issued patent. *See In re NTP, Inc.*, 654 F.3d 1268, 1277-79 (Fed. Cir. 2011) (in analogous reexamination proceedings, rejecting argument that the same written description in issued patent as in priority application entitled patent to priority application's date in absence of evidence the patent examiner considered written description); *Research Corp. Techs., Inc. v. Microsoft*, 627 F.3d 859, 870 (Fed. Cir. 2010) (holding patent not entitled to priority date of parent application because parent application lacked written description to support claims of patent where parent application and patent had the same specification).

To satisfy written description, the patent specification "must clearly allow persons of ordinary skill in the art to recognize that an inventor invented what is claimed." *Ariad Pharms., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (internal brackets and quotation marks omitted). "Entitlement to a filing date extends only to subject matter that is disclosed; not to that which is obvious. . . . Therefore the parent application must actually or inherently disclose the elements of the later-filed claims." *Research Corp. Techs.*, 627 F.3d at 870 (citations omitted). "A disclosure in a parent application that merely renders the

later-claimed invention obvious is not sufficient to meet the written description requirement; the disclosure must describe the claimed invention with all its limitations." *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1158 (Fed. Cir. 1998). Once Petitioner "has established a prima facie case of invalidity," Patentees bear the burden "to come forward with evidence to prove entitlement to claim priority to an earlier filing date." *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1305-06 (Fed. Cir. 2008).

Here, the claims reciting combination therapies with both rituximab and chemotherapeutic agents—claims 2-4 and 9—lack written description or enablement support in the '658 provisional application. There is not a single example, reference study, or any demonstrated results indicating that the inventors had possession of and taught a POSA how to practice the full scope of these combination therapy claims in the provisional application. (Ex. 1005 ¶61.) Moreover, there is no mention in that application of using fludarabine. (*Id.*) Accordingly, claims 2-4, and 9 of the '711 patent cannot rely on the provisional application for priority.

Likewise, the claims reciting bi-weekly and monthly rituximab administration—claims 6 and 7—lack written description or enablement support in either the '658 provisional application or the '347 application. There is not a single example, reference study or any demonstrated results indicating that the

inventors had possession of and taught a POSA how to practice bi-weekly or monthly administration of rituximab. (*Id.* ¶62.) Bi-weekly and monthly dosing are not discussed anywhere in the context of treating CLL. (*Id.*) Thus, claims 6 and 7 of the '711 patent also cannot rely on the provisional application for priority.[5]

D. The Cyclophosphamide-Fludarabine Claim (Claim 9) and the Bi-Weekly and Monthly Dosing Claims (Claims 6 and 7) of the '711 Patent Are Not Entitled to the Effective Filing Date of the '347 Application

The only difference between the specification of the '658 provisional application and the '347 application is the addition of several new examples regarding rituximab use. Although one of these examples—Example 5—discusses a trial of a fludarabine-rituximab combination, none of the additions to the '347 application provide any examples, dosing information, or studies of any combination of fludarabine plus cyclophosphamide with rituximab. Added Example 5 is a description of the CALGB trial of rituximab and fludarabine, which was disclosed in the prior art and does not disclose the combined use of cyclophosphamide, fludarabine, and rituximab. (*See* Ex. 1010 at 006; Ex. 1029 at

[5] Petitioner reserves the right to respond to any assertion by Patent Owners that the '658 provisional application provides an adequate supporting disclosure of claims 2-4, 6-7, and 9, or that the '347 application provides an adequate supporting disclosure of claims 6, 7 and 9.

007.) Because claim 9 of the '711 patent is directed to combining cyclophosphamide, fludarabine, and rituximab, the '347 application lacks written description support for claim 9 of the '711 patent. (*See* Ex. 1005 ¶¶64-65.) Similarly, as none of the added information in the '347 application discusses bi-weekly or monthly rituximab administration for treating CLL, the '347 application also lacks written description support for claims 6 and 7. (*See id.*)

Accordingly, the priority date for claims 6, 7, and 9 of the '711 patent is no earlier than the December 2, 2009 filing date of the '711 patent. The priority date for claims 2-4 is no earlier than the November 9, 1999 filing date of the '347 application.

VII. CLAIM CONSTRUCTION UNDER 37 C.F.R. §42.104(b)(3)

A claim subject to inter partes review must be given its "broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. §42.100(b); *see also In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1275-76 (Fed. Cir. 2015), *aff'd sub nom. Cuozzo Speed Techs, LLC v. Lee*, 579 U.S. --, 136 S. Ct. 2131 (2016). The constructions proposed in this Petition represent the broadest reasonable interpretation a POSA would have given the terms below. For the remaining terms, Petitioner applies their plain and ordinary meaning.

A. Terms for Construction

1. "chronic lymphocytic leukemia (CLL)"

The broadest reasonable construction of "chronic lymphocytic leukemia (CLL)" is a B-cell cancer "characterized by an excessive number of small lymphocytes in the blood and bone marrow, where the white blood cell count is at least 4000 cells per μL." (Ex. 1005 ¶53; s*ee* Ex. 1055 at 023; Ex. 1008 at 002.) This construction is consistent with the intrinsic record and the understanding of a POSA in 1998 that "CLL is the liquid (leukemic) equivalent of small lymphocytic lymphoma (SLL)" and that CLL and SLL are the same disease process characterized by different tissue manifestations. (Ex. 1039 at 027; Ex. 1008 at 002; Ex. 1005 ¶¶27, 53.)

The specification states that the disclosed hematological malignancies are associated with diseases characterized by "a high number of tumor cells in the blood." (*E.g.*, Ex. 1001 at 1:58-67.) By 1998, there were various thresholds used to identify a patient under SLL or CLL. (*See* Ex. 1008 at 003 and Ex. 1055 at 030 (CLL determined based on ">4,000 lymphocytes/μl"); Ex.1022 at 003 (identifying 5,000 cells/μl and 10,000 cells/μl as thresholds for CLL); Ex. 1005 ¶¶30, 54.) In Example 3 of the patent, CLL patients are identified as having "[m]edian white

blood cell count[6] [of] $40x10^9$/L (range, 4-200[7]).” (Ex. 1001 at 6:16-17.) Accordingly, the broadest definition for CLL identified in the prior art and the patent requires a white blood cell count greater than 4,000 cells/μl. However, Petitioner's arguments apply with or without a white blood cell count limitation.

2. “effective to treat the CLL”

The broadest reasonable construction of “effective to treat the CLL” is “a therapeutic response such as a reduction in the number of the small lymphocytic tumor cells.” During prosecution, Patentees asserted a broad scope for what constitutes an effective treatment: “One 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***.” (Ex. 1004 at 256 (emphasis added); Ex. 1005 ¶¶56-57.) Petitioner's construction is consistent with this broad prosecution statement.[8]

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[6] A white blood cell count of 4,000 ***cells***/μl corresponds to fewer than 4,000 ***lymphocytes***/μl. (Ex. 1005 ¶55 n.5.)

[7] 4-200 x 10^9 lymphocytes/L is the same as 4,000-200,000 lymphocytes per μl. (Ex. 1005 ¶55.)

[8] Applying a different claim construction standard than the “broadest reasonable construction” standard applicable to this Petition, the Southern District of

VIII. PERSON OF ORDINARY SKILL IN THE ART

A POSA at the time of the alleged invention of the '711 patent would have been a practicing physician specializing in hematology or oncology, with at least three years of experience in treating patients with hematological malignancies. (Ex. 1005 ¶18.)

IX. THE PRIOR ART

Petitioner relies on the following publications:

A. MD Anderson Online Newsletter (Ex. 1006)

In 1998, researchers at the University of Texas M.D. Anderson Cancer Center ("MD Anderson"), led by principal investigator Dr. Susan O'Brien, activated a Phase I/II trial of rituximab in patients with relapsed CLL. (Ex. 1005

California construed "effective to treat the chronic lymphocytic leukemia" in the '612 patent as "providing a positive clinical benefit to the chronic lymphocytic leukemia patient." *Biogen Idec, Inc. v. Glaxosmithkline LLC*, No. 10-CV-00608-BEN (BGS), 2011 WL 4949042, at *2-3 (S.D. Cal. Oct. 18, 2011.) Petitioner contends that the district court's construction is inapplicable here because it is not the broadest reasonable construction that a POSA would apply to the term. Nevertheless, even under that construction, the '711 patent is anticipated and/or obvious as explained in each of the Grounds below.

¶67; Ex. 1062.) As detailed in his declaration, Dr. Andreeff collaborated in the study. (Ex. 1005 ¶67.)

In July 1998, MD Anderson published in print the Summer 1998 edition of its Leukemia Insights Newsletter ("MD Anderson Print Newsletter"), including an article describing the O'Brien study of rituximab in CLL patients. (Ex. 1005 ¶¶69-70; Ex. 1061.) MD Anderson distributed printed copies of the MD Anderson Print Newsletter to several thousand referring Hematology-Oncology physicians in the U.S. (Ex. 1005 ¶71.)

Dr. Andreeff explains that Dr. Charles Koller was in charge of making the MD Anderson Print Newsletter available online. (Ex. 1005 ¶72.) The Summer 1998 edition of the MD Anderson Online Newsletter appears in the Internet Archive Wayback Machine beginning February 8, 1999. (Ex. 1006; accessed December 14, 2016.)[9] As shown in the Internet Archive Wayback Machine, the

[9] The Butler Declaration verifies that the Wayback Machine Archive assigns a URL in the format http://web.archive.org/web/[Year in yyyy][Month in mm][Day in dd][Time code in hh:mm:ss]/[Archived URL], wherein the date corresponds to the date of archiving the record of the file. (Ex. 1056 at 001.) Accordingly, as the URL assigned for MD Anderson Online Newsletter is https://web.archive.org/web/19990208234814/http://www.mdanderson.org/~leuke

online newsletter was last modified on July 2, 1998, and Dr. Andreeff explains that the content of the online newsletter would have been publicly available online as of this "last modified" date. (Ex. 1005 ¶72; Ex. 1006 at 006.) *See Stamps.com Inc. v. Endicia Inc.*, 437 F. App'x 897, 903 (Fed. Cir. 2011) (unpublished) (using "last modified" date on a website as evidence of public availability as of that date); *BLD Servs., LLC v. LMK Techs., LLC*, IPR2014-00770, Paper 40, 2015 Pat. App. LEXIS 12927, at *20-21 (P.T.A.B. Nov. 18, 2015) (same). The MD Anderson Online Newsletter and the MD Anderson Print Newsletter are §102(b) prior art to claims 2-4, 6-7, and 9, and §102(a) prior art to the remaining claims. Both newsletters include identical descriptions of the O'Brien study. (Ex. 1006 at 004; Ex. 1061 at 002; Ex. 1005 ¶72.)

Dr. Andreeff explains that both the online and printed copies of the MD Anderson Newsletter were published on or about July 2, 1998. (Ex. 1005 ¶¶72-75.) A printed "publication" is a publication "sufficiently accessible to the public interested in the art." *In re Lister*, 583 F.3d 1307, 1311 (Fed. Cir. 2009) (citation omitted). A reference is proven to be a "printed publication," therefore, "upon a satisfactory showing that such document has been disseminated or otherwise made

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mia/letter32.html#IDEC-C2B8, the record of the file was archived on February 8, 1999. (*Id.* at 004.)

available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it." *In re Wyer*, 655 F.2d 221, 226 (C.C.P.A. 1981) (citation omitted). Once accessibility is shown, it is unnecessary to show anyone actually inspected the reference. *Lister*, 583 F.3d at 1314.

B. Keating (Ex. 1064)

Keating is an article entitled "Early Results of a Chemoimmunotherapy Regimen of Fludarabine, Cyclophosphamide, and Rituximab As Initial Therapy for Chronic Lymphocytic Leukemia." It was published in June 2005 in the Journal of Clinical Oncology. Keating is §102(b) prior art to claims 6, 7, and 9.

C. Byrd (Ex. 1010)

Byrd is an article entitled "Old and New Therapies in Chronic Lymphocytic Leukemia: Now Is the Time for a Reassessment of Therapeutic Goals." (Ex. 1010 at 003.) It was published in February 1998 in the journal Seminars in Oncology. (*Id.*) Byrd is §102(b) prior art to claims 2-4, 6-7, and 9 and §102(a) art to the remaining claims.

D. Kipps (Ex. 1055)

Williams Hematology, 5th Edition, was published in 1995. Chapter 106, entitled "Chronic lymphocytic leukemia and related diseases," is authored by Kipps. Kipps qualifies as prior art under 35 U.S.C. §102(b) for all claims of the

'711 patent.

E. July 1997 FDA Biological Response Modifiers Advisory Committee Hearing ("FDA Transcript") (Ex. 1007)

On July 25, 1997, the FDA's Biological Response Modifiers Advisory Committee held an open public hearing with representatives from IDEC Pharmaceuticals, including two of the inventors of the '711 patent, Dr. Antonio Grillo-López and Dr. Christine A. White. (Ex. 1007.) During this hearing, Dr. Grillo-López and Dr. White presented results from rituximab clinical trials and responded to questions. The hearing was transcribed and made available to the public on August 8, 1997 as confirmed by a letter from Dynna Bigby from the Division of Dockets Management (DDM) at the FDA. (*See* Ex. 1054 ("DDM letter").)

As the DDM letter details, the August 8, 1997 stamp on page 2 of the FDA Transcript indicates "the Division of Dockets Management (DDM) would have received the transcript on that date." (*Id.* at 001.) The DDM letter further states, "[i]n 1997, once the DDM received a document, it made that document publicly available via the DDM Public Reading Room. Following August 8, 1997, any member of the public could have requested and received a copy of the transcript in question by filling out a reading room request form." (*Id.*) Thus, this transcript qualifies as prior art under 35 U.S.C. §102(b) for all claims of the '711 patent.

F. Batata (Ex. 1008)

Batata is an article entitled "Relationship between Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma." It was published on August 1, 1992 in the journal Cancer and is §102(b) prior art to the '711 patent.

G. Maloney 1994 (Ex. 1009)

Maloney 1994 is entitled "Phase I Clinical Trial Using Escalating Single-Dose Infusion of Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients with Recurrent B-Cell Lymphoma." It was published on October 15, 1994 in the journal Blood and is therefore §102(b) prior art to the '711 patent.

H. Background Art

In addition to the specific references discussed above, Dr. Andreeff has considered additional references, as described in his declaration, reflecting the state of the art in November 1998. *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015) ("Art can legitimately serve to document the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness.").

X. THERE IS A REASONABLE LIKELIHOOD THE CLAIMS OF THE '711 PATENT ARE INVALID

A. Legal Standards

1. Obviousness

Assessing obviousness requires analyzing (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co*., 383 U.S. 1, 17-18 (1966). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 416 (2007). Claims reciting a process, such as a method of treatment, are not patentable if "the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *Merck & Co. v. Biocraft Labs., Inc*., 874 F.2d 804, 809 (Fed. Cir. 1989) (citation omitted). The standard does not require absolute predictability, and "[a determination of] 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." *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007).

In *Coherus Biosciences Inc. v. AbbVie Biotechnology Ltd.*, IPR2016-00172, Paper No. 9 at 16 (P.T.A.B. May 17, 2016), the Board noted in the context of

optimizing drug dosing regimens that "all that is required to show obviousness is a reasonable expectation of success, not conclusive proof of superior efficacy." (citing *PharmaStem Therapeutics, Inc. v. ViaCell, Inc*., 491 F.3d 1342, 1363–64 (Fed. Cir. 2007); *Pfizer, Inc.*, 480 F.3d at 1364). Similarly, in *Biomarin Pharmaceuticals Inc. v. Genzyme Therapeutic Products Ltd. Partnership*, the Board found claims directed to specific dosing regimen were obvious. The Board acknowledged that although "a person of ordinary skill in the art could not have predicted with absolute certainty . . . a safe and effective dosing regimen," "the selection of the dose and dosing schedule would have been a routine optimization of the therapy outlined in [the prior art], which would have been achievable through the use of standard clinical trial procedures." IPR2013-00534, Paper No. 81 at 12-14 (P.T.A.B. Feb. 23, 2015). The Board further noted that the experimentation to achieve the claimed regimen was "'nothing more than the routine' application of a well-known problem solving strategy . . . 'the work of a skilled [artisan], not of an inventor.'" *Id*. at 14 (citing *Pfizer*, 480 F.3d at 1368). Finally, the "motivation to optimize the therapy disclosed in [the prior art] flows from the normal desire of scientists or artisans to improve upon what is already generally known." *Id*.

2. Anticipation

A patent claim is anticipated when every limitation is found either expressly

or inherently in a single prior art reference. *King Pharms., Inc. v. Elan Pharms., Inc.* 616 F.3d 1267, 1274 (Fed. Cir. 2010) (citing *Celeritas Techs., Ltd. v. Rockwell Int'l Corp*., 150 F.3d 1354, 1360 (Fed. Cir. 1998)); *see also In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) ("no 'actual creation or reduction to practice' is required.") (citations omitted). "[P]roof of efficacy is not required in order for a reference to be enabled for purposes of anticipation." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005).

B. Ground 1: Claims 1, 5, and 8 Are Anticipated Under §102 by the MD Anderson Online Newsletter (Ex. 1006)

The priority date for claims 1, 5, and 8 is no earlier than November 9, 1998.

The MD Anderson Online Newsletter describes a trial of rituximab in relapsed CLL patients. (Ex. 1006 at 004). The MD Anderson Online Newsletter explains that "CLL should be an excellent target disease" for rituximab based on studies of rituximab in NHL patients and expression of CD20 in 97% of CLL cases. (*Id*.) While the MD Anderson Online Newsletter acknowledges that SLL patients had a lower response rate to rituximab treatment compared to other lymphomas, the researchers expected that the response rates of CLL patients could be enhanced by using dosages higher than the 375 mg/m^2 of the previous clinical trials. (*Id.*; Ex. 1005 ¶76.) The rationale for the study was explained in the MD Anderson Newsletter:

> Studies in lymphoma have shown a lower response rate in WDL[L][10], the tissue equivalent of CLL. Serum levels of the IDEC antibody [rituximab] are also lower in patients with bulky disease. CLL patients have a significant amount of disease in the blood which may bind with most of the administered IDEC. Therefore it is possible that higher doses and/or more frequent exposure may be useful in CLL.

(Ex. 1006 at 004.)

The MD Anderson Online Newsletter explains that the investigators administered 375 mg/m^2 rituximab at the first infusion, then escalated doses for subsequent infusions to 500 mg/m^2. (*Id.*; Ex. 1005 ¶77.) Because it was clear from the Phase I trial that the 500 mg/m^2 dose was well tolerated and did not reach the Maximum Tolerated Dose (MTD), the treatment plan started the dose at 500 mg/m^2 with further escalation by 33% increments. (Ex. 1005 ¶77; Ex. 1006 at 004.)

A POSA would have had a reasonable expectation that the 500 mg/m^2 dose was an "an amount effective to treat CLL" in view of the ongoing MD Anderson trial. *See Eli Lilly and Co. v. Teva* ("*Lilly II"*), 619 F.3d 1329, 1343 (Fed. Cir. 2010) (court presumed the treatment method was enabled and had therapeutic utility because human clinical trials had been initiated); *Manual of Patent Examining Procedure* §2107.03(IV) (2015) ("[I]f an applicant has initiated human

[10] WDL[L] is equivalent to SLL. (Ex. 1005 ¶76 n.6.)

clinical trials for a therapeutic product or process, [Patent & Trademark] 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.") (Ex. 1005 ¶93.)

Thus, the MD Anderson Online Newsletter expressly discloses a rituximab regimen for CLL patients, including an initial dose of 375 mg/m^2 followed by three subsequent doses of 500 mg/m^2 given weekly for 3 weeks. (Ex. 1005 ¶¶76-77, 93.) The initiation of the clinical trial indicates this dose was reasonably expected to be an effective dose for treating CLL. The method of treating CLL disclosed in the MD Anderson Online Newsletter meets all of the elements of claims 1, 5, and 8, as shown below. (*Id.*) Alternatively, because the MD Anderson Online Newsletter and the MD Anderson Print Newsletter have identical disclosures, claims 1, 5, and 8 are equally anticipated by the MD Anderson Print Newsletter. (*Id.*)

GROUND 1	
Claim Language	***The MD Anderson Online Newsletter***
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,	"IDEC [rituximab], a new monoclonal antibody approved for the treatment of lymphoma, is under investigation in patients with CLL." (Ex. 1006 at 004.) "CLL should be an excellent target disease for the use of the IDEC antibody." (*Id.*)
wherein the rituximab is administered to the patient at	"[T]he first dose would be 375 mg/m2 (about 6 hour infusion) but ***all subsequent doses would be***

GROUND 1	
Claim Language	***The MD Anderson Online Newsletter***
a dosage of 500 mg/m^2.	***higher, starting with 500 mg/m2*** and escalating by 33% with subsequent patients." (*Id.* (emphasis added))
5. The method of claim 1 wherein the rituximab is administered weekly.	"A minimum of 1 course (***4 weekly infusions***) will be required for a patient to be considered as having received an adequate trial to evaluate efficacy." (*Id.* (emphasis added))
8. The method of claim 1 which does not include treatment with a radiolabeled anti-CD20 antibody.	The rituximab administered in this trial was not radiolabeled. (*Id.*)

C. Ground 2: Claims 7 and 9 Are Anticipated Under §102 by Keating (Ex. 1064)

This Ground assumes that the priority date for claims 7 and 9 is no earlier than December 2, 2009.[11]

Keating is a 2005 article in the Journal of Clinical Oncology reporting results from a study of a fludarabine-cyclophosphamide-rituximab ("FCR") combination therapy in 224 CLL patients. (Ex. 1064 at 006.) Patients received 375 mg/m^2 rituximab on day 1 of the first cycle of treatment, and 500 mg/m^2 rituximab on day 1 of subsequent cycles given every 4 weeks for six total treatment cycles. (*Id.* at 007.) Keating reports a 70% complete response rate, which "is the highest rate reported for initial therapy for CLL" and "supports the concept of additive or synergistic interactions of these three agents." (*Id.* at 013.)

[11] The applicable priority dates are discussed in Sections VI.C and D *supra*.

"Preclinical data suggested that rituximab sensitized cells to both fludarabine and cyclophosphamide." (*Id.*) Only 3 of 224 patients experienced an adverse reaction to the 500 mg/m^2 doses of rituximab in cycles 2-6. (*Id.* at 010; Ex. 1005 ¶78.)

Thus, Keating expressly discloses a rituximab regimen for CLL patients, including an initial dose of 375 mg/m^2 followed by five subsequent 500 mg/m^2 doses given monthly (every 4 weeks). (Ex. 1005 ¶94.) Rituximab was given in combination with fludarabine and cyclophosphamide. Keating's results indicate this treatment regimen was effective for treating CLL. The method of treating CLL disclosed in Keating meets all of the elements of claims 7 and 9, as shown below. (*Id*.)

GROUND 2	
Claim Language	***Keating***
1 and 9 (part). A method of treating chronic lymphocytic leukemia (CLL) in a human patient, comprising administering rituximab to the patient in an amount effective to treat the CLL, wherein the rituximab is administered to the patient at a dosage of 500 mg/m^2.	"We conducted a single-arm study of FCR [fludarabine-cyclophosphamide-rituximab] as initial therapy in 224 patients with progressive or advanced CLL." (Ex. 1064 at 006.) "In cycles 2 to 6, the rituximab dose was increased to 500 mg/m^2 on day 1." (*Id.* at 007.) "The CR rate of 70% with FCR . . . is the highest rate reported for initial therapy for CLL . . . ." (*Id.* at 013.)
7. The method of claim 1 wherein the rituximab is administered monthly.	"Courses were repeated every 4 weeks . . . ." (*Id.* at 007.)
9 (cont'd) and further comprising administering a chemotherapeutic	"We conducted a single-arm study of FCR as initial therapy in 224 patients with progressive or advanced CLL." (*Id.* at 006.)

GROUND 2	
Claim Language	***Keating***
regimen to the patient, wherein the chemotherapeutic regimen comprises fludarabine and cyclophosphamide.	

D. Ground 3: Claim 6 Is Obvious Under §103 Over Keating (Ex. 1064) and the MD Anderson Online Newsletter (Ex. 1006)

This Ground assumes that the priority date for Claim 6 is no earlier than December 2, 2009. Claim 6 adds to claim 1 the limitation that rituximab be administered bi-weekly. As described above, Keating teaches successful treatment of CLL through monthly administration of rituximab at 500 mg/m^2 (Ex. 1064 at 007) and the MD Anderson Online Newsletter teaches weekly administration of rituximab at 500 mg/m^2 (Ex. 1006 at 004). Given a POSA's knowledge that 500 mg/m^2 rituximab administered weekly *or* monthly could be used to treat CLL, it would have been obvious to a POSA to try the intermediary schedule of bi-weekly rituximab administration. (Ex. 1005 ¶95.) Such modifications were known in the art and are "'nothing more than the routine' application of a well-known problem-solving strategy, . . . 'the work of a skilled [artisan], not of an inventor.'" *Pfizer*, 480 F.3d at 1368 (quoting *Merck & Co.*, 874 F.2d at 809; *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1371 (Fed. Cir.

2006)). (Ex. 1005 ¶95.) Alternatively, claim 6 is equally obvious over Keating and the MD Anderson Print Newsletter. (*Id*.)

E. Ground 4: Claims 2-4, 9 Are Obvious Under §103 Over the MD Anderson Online Newsletter (Ex. 1006) and Byrd (Ex. 1010)

This Ground assumes that the priority date for claims 2-4 and 9 is either November 9, 1998 or November 9, 1999.

Claims 2-4 and 9 recite combination therapies of a 500 mg/m^2 dose of rituximab with known chemotherapeutic agents to treat CLL. As discussed in Ground 1, treating CLL with a 500 mg/m^2 dose of rituximab was anticipated by the MD Anderson Online Newsletter.

Byrd is an article published in February 1998 in Seminars in Oncology. (Ex. 1010.) It summarizes various established and emerging CLL therapies. In particular, Byrd outlines clinical studies with combination therapy of fludarabine and cyclophosphamide, as well as fludarabine and rituximab, to treat CLL. (*Id.* at 006.) Byrd discusses the synergistic effect of fludarabine and cyclophosphamide shown by both preclinical and clinical data:

> [P]reclinical data from several groups suggest synergistic interaction between alkylator agents and fludarabine combination. . . . Based on the 88% complete response rate observed phase I/II study of untreated low-grade NHL patients receiving fludarabine and modified doses of cyclophosphamide, the Baltimore/Washington, DC CLL Consortium group initiated a study of these agents with filgrastrim in patients with

> untreated CLL and related low-grade lymphomas and ***noted a similar promisingly high response rates***. A second group combined all categories of CLL patients and ***noted impressive activity*** in both previously untreated and fludarabine-refractory individuals.

(*Id.* (emphasis added).)

Byrd also discusses combination therapy of rituximab and purine analogs, such as fludarabine. The authors first note rituximab's efficacy, both as a single agent and in combination CHOP, demonstrated in Phase II clinical trials in low-grade NHL patients. (*Id.*) Citing Czuczman's report of the rituximab Phase II trial, Byrd notes that "[b]ecause of *in vitro* data suggesting that IDEC-C2B8 can chemosensitize chemotherapy-resistant NHL cell lines and the absence of competing toxicities, a study of interdigitated IDEC-C2B8 with CHOP chemotherapy in relapsed low grade NHL was initiated and recently completed noting [an] overall response rate of 100%." (*Id.*) In addition, Byrd discloses that "Cancer and Leukemia Group B is planning a Phase II/III study of fludarabine + IDEC-C2B8 in untreated CLL patients." (*Id.*)

Thus, the MD Anderson Online Newsletter discloses using rituximab at the claimed dosage for patients with CLL, and Byrd discloses combining rituximab with chemotherapeutic agents, including fludarabine and cyclophosphamide. The motivation and reasonable expectation of success in using rituximab in

combination with the chemotherapeutic agents fludarabine and/or cyclophosphamide was obvious to a POSA over the disclosures in Byrd. Together, Byrd and the MD Anderson Online Newsletter disclose all elements of claims 2-4, and 9. Alternatively, claims 2-4 and 9 are equally obvious over Byrd and the MD Anderson Print Newsletter. (Ex. 1005 ¶¶96-97.)

GROUND 4	
Claim Language	***Byrd and MD Anderson Online Newsletter***
1 and 9 (part). A method of treating chronic lymphocytic leukemia (CLL) in a human patient, comprising administering rituximab to the patient in an amount effective to treat the CLL, wherein the rituximab is administered to the patient at a dosage of 500 mg/m^2.	*See Ground 1, above.*
2. The method of claim 1 further comprising administering a chemotherapeutic regimen to the patient.	Byrd teaches combination of fludarabine and rituximab to treat CLL patients. (Ex. 1010 at 006.) Fludarabine is a chemotherapeutic regimen.
3. The method of claim 2 wherein the chemotherapeutic regimen comprises fludarabine.	"Cancer and Leukemia Group B is planning a Phase II/III study of fludarabine + IDEC-C2B8 in untreated CLL patients." (*Id.*)
4. The method of claim 2 wherein the chemotherapeutic regimen comprises cyclophosphamide.	Byrd teaches therapy combining fludarabine and cyclophosphamide: "Based on the 88% complete response rate observed phase I/II study of untreated low-grade NHL patients receiving ***fludarabine and modified doses of cyclophosphamide***, the Baltimore/Washington, DC CLL Consortium group initiated a study of these agents with filgrastrim in

GROUND 4	
Claim Language	***Byrd and MD Anderson Online Newsletter***
	patients with untreated ***CLL*** and related low-grade lymphomas and noted a ***similar promisingly high response rates***. A second group combined all categories of CLL patients and noted ***impressive activity*** in both previously untreated and fludarabine-refractory individuals." (*Id.* (emphasis added))
9 (cont'd) and further comprising administering a chemotherapeutic regimen to the patient, wherein the chemotherapeutic regimen comprises fludarabine and cyclophosphamide.	"Cancer and Leukemia Group B is planning a Phase II/III study of fludarabine + [rituximab] in untreated ***CLL patients***." (*Id.*) In addition to the combination of rituximab and fludarabine, Byrd further teaches the synergistic effect of the combination of fludarabine and cyclophosphamide: "preclinical data from several groups suggest ***synergistic interaction between alkylator agents and fludarabine*** combination. . . . Based on the 88% complete response rate observed phase I/II study of untreated low-grade NHL patients receiving ***fludarabine and modified doses of cyclophosphamide***, the Baltimore/Washington, DC CLL Consortium group initiated a study of these agents with filgrastrim in patients with untreated ***CLL*** and related low-grade lymphomas and noted a ***similar promisingly high response rates***. A second group combined all categories of CLL patients and noted ***impressive activity*** in both previously untreated and fludarabine-refractory individuals." (*Id.* (emphasis added))

1. Motivation To Combine

By the late 1990s, it was common to combine various cytotoxic agents that demonstrated single-agent activity, different mechanisms of action, and non-overlapping toxicities to achieve higher response rates and longer remission in

lymphoma and leukemia patients. (Ex. 1005 ¶¶98-102; Ex. 1058 at 003; Ex. 1013 at 005.) Such combination therapies were used extensively for patients that were not susceptible to treatment by single agents. (Ex. 1005 ¶98.) Here, rituximab, fludarabine, and cyclophosphamide meet all of the properties that would have motivated a POSA to combine them together to treat CLL effectively. (*Id.*)

Regarding the combination of fludarabine with rituximab, Byrd describes a plan for a "Phase II/III study of fludarabine + [rituximab] in untreated CLL patients." (Ex. 1010 at 006.) This study was initiated on March 15, 1998. (Ex. 1029 at 007.) Such a planned study demonstrates that there existed an express motivation within the art to combine rituximab and fludarabine to treat CLL patients and an expectation that the combination will be effective. (Ex. 1005 ¶102.) This combination is built on Byrd's teaching that "[f]ludarabine has been the most frequently studied purine analog in CLL and probably the most efficacious." (Ex. 1010 at 004.) Based on the MD Anderson Online Newsletter, the specific dosage of 500 mg/m^2 would have been a logical dose of rituximab to increase the effectiveness of the rituximab. (Ex. 1005 ¶102.)

As to combining cyclophosphamide, fludarabine, and rituximab, Byrd first suggests a "synergistic interaction between alkylator agents and fludarabine." (Ex. 1010 at 006.) Byrd goes on to discuss the fludarabine and cyclophosphamide combination, both as sequential and concurrent therapy. (*Id.* at 006.) In the next

column, Byrd discusses the 100% effective combination therapy of rituximab [IDEC-C2B8] and CHOP—which includes cyclophosphamide—for treating low-grade NHL. (*See id.*; Ex. 1005 ¶103.) Byrd explains that rituximab acts by a distinct mechanism, binding the CD20 antigen and inducing "both complement and effector cell tumor lysis." (Ex. 1010 at 006; Ex. 1005 ¶103.) Byrd thus discloses that (1) fludarabine is probably the most efficacious purine analog in treating CLL; (2) fludarabine has a synergistic interaction with cyclophosphamide; (3) cyclophosphamide (within CHOP) may be combined with rituximab to treat low-grade NHL; and (4) rituximab acts via a distinct mechanism from fludarabine and cyclophosphamide. (Ex. 1010 at 005-06.) A POSA would have been motivated by these disclosures in Byrd to use the fludarabine-cyclophosphamide-rituximab combination to treat CLL effectively. (Ex. 1005 ¶¶98-103.) The Federal Circuit has held that combining elements "disclosed adjacent to each other in a prior art patent does not require a leap of inventiveness." *Boston Sci. Scimed, Inc. v. Cordis Corp.*, 554 F.3d 982, 991 (Fed. Cir. 2009).

A POSA seeking to implement this combination therapy for CLL patients would have turned to the rituximab dosing regimen described in the MD Anderson Online Newsletter as a matter of course in order to achieve enhanced therapeutic benefits from the "higher doses and/or more frequent exposure" sought by the O'Brien study described in the newsletter. (Ex. 1005 ¶104; Ex. 1006 at 004.)

A POSA would therefore have been motivated to add the beneficial synergy of cyclophosphamide to a rituximab (500 mg/m^2) + fludarabine regimen, which meets all elements of claims 2-4 and 9, to achieve better results. (Ex. 1005 ¶104.) Accordingly the combination of rituximab (500 mg/m^2) + fludarabine + cyclophosphamide to treat CLL was obvious. (*Id*.)

2. Reasonable Expectation of Success

The expectation of success in combining fludarabine and rituximab to treat CLL patients is evident by the fact that Byrd expressly disclosed that the "Cancer and Leukemia Group B" was using the combination in a Phase II/III study. (Ex. 1010 at 006.) Such studies are rarely undertaken where there is not a justifiable expectation that the trial would prove successful. *Lilly II*, 619 F.3d at 1343. (Ex. 1005 ¶105.) Furthermore, a POSA would have had a reasonable expectation that rituximab's dose of 500 mg/m^2 would be effective based on the MD Anderson Online Newsletter's choice of that dosage. (Ex. 1005 ¶106; Ex. 1006 at 004.)

The beneficial synergy of adding cyclophosphamide to a treatment regimen of rituximab (500 mg/m^2) + fludarabine would have enhanced the expectation of success, as it had already been demonstrated that cyclophosphamide + fludarabine was more effective at treating CLL than fludarabine alone. (Ex. 1005 ¶106; Ex. 1010 at 006) A POSA would have expected the combination to provide a

therapeutic response, as required by the claims. Thus claims 2-4 and 9 are obvious over the MD Anderson Online Newsletter and Byrd. (Ex. 1005 ¶¶96-106.)

F. Ground 5: Claims 6 and 7 Are Obvious Under §103 Over the MD Anderson Online Newsletter (Ex. 1006) in Light of Byrd (Ex. 1010) and Kipps (Ex. 1055)

This Ground assumes that the priority date for claims 6 and 7 is either November 9, 1998 or November 9, 1999. Claims 6 and 7 recite methods for treating CLL using the rituximab dosing regimen of Claim 1 (500 mg/m^2) administered bi-weekly and monthly, respectively.

Claims 6 and 7 are obvious in light of the MD Anderson Online Newsletter, Byrd, and Kipps. The MD Anderson Online Newsletter satisfies all limitations of claim 1, as discussed in Ground 1. (Ex. 1006 at 004; Ex. 1005 ¶¶93, 107.)

Thus, the only limitations of claims 6 and 7 not disclosed in the MD Anderson Online Newsletter, which teaches weekly dosing of rituximab (Ex. 1006 at 004.), are that rituximab be administered bi-weekly (claim 6) or monthly (claim 7). These dosing regimens would have been obvious to a POSA in light of Byrd and Kipps. As described above, it would have been obvious to a POSA in light of the MD Anderson Online Newsletter and Byrd to administer rituximab at 500 mg/m^2 in combination with various standard chemotherapy regimens. (Ex. 1005 ¶107.)

Kipps further describes standard chemotherapy regimens for CLL, including

chlorambucil administered every 2-4 weeks, cyclophosphamide administered daily or every 3-4 weeks, chlorambucil and prednisone administered every 2-4 weeks, and fludarabine administered every 3-4 weeks. (Ex. 1055 at 034-35.) Kipps thus teaches both bi-weekly and monthly (every 4 weeks) administration of standard chemotherapy for CLL. (*Id.*) It would have been obvious to a POSA seeking to take advantage of rituximab's ability to chemosensitize chemotherapy-resistant NHL cell lines by interdigitating rituximab with chemotherapy, as described by Byrd, to administer rituximab bi-weekly or monthly to align with chemotherapy administration. (Ex. 1005 ¶¶108-09.) Alternatively, claims 6 and 7 are equally obvious over the MD Anderson Print Newsletter, Byrd, and Kipps. (*Id.*)

GROUND 5	
Claim Language	***MD Anderson Online Newsletter, Byrd, and Kipps***
6. The method of claim 1 wherein the rituximab is administered bi-weekly.	*See Ground 1, claim 1 above*. Byrd discloses rituximab's ability to chemosensitize NHL cells and describes interdigitated administration of rituximab with chemotherapy. (Ex. 1010 at 006.) Kipps teaches bi-weekly administration of multiple standard chemotherapies for CLL, including chlorambucil and chlorambucil plus prednisone. (Ex. 1055 at 034-35.)
7. The method of claim 1 wherein the rituximab is administered monthly.	*See Ground 1, claim 1 above*. Byrd discloses rituximab's ability to chemosensitize NHL cells and describes interdigitated administration of rituximab with chemotherapy. (Ex. 1010 at 006.) Kipps teaches monthly administration of multiple standard chemotherapies for CLL, including

GROUND 5	
Claim Language	***MD Anderson Online Newsletter, Byrd, and Kipps***
	fludarabine and cyclophosphamide. (Ex. 1055 at 034-35.)

1. Motivation To Combine

Scientists' desire to optimize therapy "flows from the 'normal desire of scientists or artisans to improve upon what is already known.'" *Pfizer*, 480 F.3d at 1368. For claims 6 and 7, a POSA would have been motivated to modify the weekly rituximab administration described in the MD Anderson Online Newsletter to optimize the combination of rituximab with standard chemotherapy. As described by Byrd, rituximab chemosensitized NHL cells and thus could be beneficially interdigitated with chemotherapy. (Ex. 1010 at 006.) A POSA seeking to combine rituximab with standard chemotherapy for CLL would have understood that administration of rituximab could be modified to better align with chemotherapy administration. (Ex. 1005 ¶110.) Because, as described by Kipps, standard chemotherapies for CLL including fludarabine were administered both bi-weekly and monthly (Ex. 1055 at 034-35), it would have been obvious to a POSA to also administer rituximab bi-weekly or monthly. (Ex. 1005 ¶110.)

The obviousness of modifying the weekly dosing described in the MD Anderson Online Newsletter to bi-weekly or monthly dosing is underscored by the fact that this modification was a simple shift in when rituximab was administered,

"'nothing more than the routine' application of a well-known problem-solving strategy, . . . 'the work of a skilled [artisan], not of an inventor.'" *Pfizer*, 480 F.3d at 1368 (quoting *Merck & Co.*, 874 F.2d at 809; *DyStar Textilfarben*, 464 F.3d at 1371); *see also In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."); *In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980).

Moreover, Patent Owners' own experts argued in proceedings before the European Patent Office that "[s]uch less frequent schedules would have been readily adopted for the increased 500-1500mg/m^2 dosages," particularly when used in combination therapy. (Ex. 1049 at 003, ¶15; *see also* Ex. 1050 at 002-03; Ex. 1051 at 002-03.) Thus, a POSA contemplating using rituximab at 500 mg/m^2 (as described by the MD Anderson Online Newsletter) in combination with chemotherapy (as described by Byrd) would have been motivated to use bi-weekly or monthly rituximab administration. (Ex. 1005 ¶¶110-11.)

2. Reasonable Expectation of Success

A POSA evaluating the combination of the MD Anderson Online Newsletter, Byrd, and Kipps would have had a reasonable expectation that the claimed treatment regimen would be safe and efficacious. (Ex. 1005 ¶112.) "All that is required to show obviousness is a reasonable expectation of success, not

conclusive proof of efficacy." *Boehringer Ingelheim Int'l GmbH v. Genentech, Inc.,* IPR2015-00417, Paper No. 11 at 22 (P.T.A.B. July 14, 2015).

As described in Section X.E.2., a POSA would have expected rituximab administered alone and with standard chemotherapy including fludarabine and cyclophosphamide to be safe and efficacious. (Ex. 1005 ¶112.) Additionally, modification of the dosing schedule of the MD Anderson Online Newsletter from a weekly to a bi-weekly or monthly schedule would not diminish the expectation that the course of treatment would result in a clinical benefit, including reducing the number of the patients' circulating tumor cells, as it was known that the initial dosage would have provided this therapeutic effect. (*Id.*)

Furthermore, a POSA would have known that rituximab could be administered using dosing schedules less frequent than weekly dosing because of published studies using less frequent dosing. For example, Czuczman 1996 described a study of rituximab administered in combination with CHOP in which rituximab was administered in weeks 1, 7, 13, 20, and 21. (Ex. 1011 at 003.) Link also taught administration of rituximab once every three weeks when administered in combination with CHOP. (Ex. 1017 at 002 (Abstract *7); Ex. 1005 ¶113.)

Indeed, Patent Owners' own experts explained that, in light of the various dosing schedules for CLL chemotherapy, prior art studies describing "less frequent dosing schedules for rituximab when it was combined with chemotherapy," and

because "combination therapy would improve 'patient response,'" a POSA would have used "less frequent bi-weekly or monthly dosages of 500-1500mg/m^2 of rituximab." (Ex. 1049 at 003; *see also* Ex. 1050 at 002-03; Ex. 1051 at 002-03.) Claims 6 and 7 are obvious in light of the MD Anderson Online Newsletter, Byrd, and Kipps. (Ex. 1005 ¶¶107-14.)

G. Ground 6: Claims 1, 5-8 Are Obvious Under §103 Over the FDA Transcript (Ex. 1007), Batata (Ex. 1008), and Maloney 1994 (Ex. 1009)

This Ground assumes the priority date for claims 1 and 5-8 is November 9, 1998.

Claims 1 and 5-8 are obvious under §103 over the FDA Transcript (Ex. 1007), Batata (Ex. 1008), and Maloney 1994 (Ex. 1009).

This ground first discusses why claim 1 is obvious in light of the FDA Transcript, Batata, and Maloney 1994 before addressing the dependent claims 5-8.

1. Claim 1

Claim 1 of the '711 patent recites only two limitations: (1) administering rituximab to the patient in an amount effective to treat CLL and (2) administering rituximab at a 500 mg/m^2 dosage.

The July 1997 FDA Transcript includes statements from two of the named inventors of the '711 patent, Dr. Antonio Grillo-López and Dr. Christine A. White. (Ex. 1007 at 020 (19:15-23).) Dr. Grillo-López discussed the results from a Phase

II trial (reported in Maloney Sept. 1997) and a Phase III trial (reported in McLaughlin) in a total of 203 patients with relapsed or refractory low-grade or follicular B-cell NHL. (Ex. 1007 at 036 (35:13-17).) These patients were administered "375 mg/m^2 [rituximab] for four doses . . . over a 22-day period." (*Id.* at 019 (18:16-18).) The trials included patients in IWF group A (*id.* at 044 (43:16-22)), and a POSA at the time would have understood that all IWF group A patients fall under the "SLL/CLL" category under the REAL Classification and the classification proposed by Hiddemann. (Ex. 1005 ¶¶31-32, 86; Ex. 1019 at 010 (Table 4); Ex. 1020 at 006.)

Dr. Grillo-López describes an overall response rate of 48% in the 203 patients, IWF Types B, C, and D patients having overall response rate of 58%, and "Type A patients have a lower overall response rate at 11 percent." (Ex. 1007 at 043 (42:18-19), 044 (43:18-19).)) Nevertheless, Dr. Grillo-López asserts that "these [Type A] patients, however, do have important clinical benefit," including "some tumor shrinkage" in 28 of the 37 Type A patients. (*Id.* at 044-45 (43:18-44:8).) Further, Dr. Grillo-López stated that the "Class A" patients who did respond had "a time to progression and a duration of response which was not significantly different from the rest of the population, so they did have responses that were as durable as that of the other B, C, D patients." (*Id.* at 069-70 (68:22-69:2); Ex. 1005 ¶87.)

Dr. Berman, a member of the review Committee, summarized the finding for the "Group A population:"

> I think we already heard that this Group A population contained a number of patients with different types of disease . . . ***presumably some with a lymphomatous phase of CLL***. So I think this is a very small population, and 11 percent is not to be disregarded. So I would say that it does provide sufficient evidence of efficacy.

(*Id.* at 117 (116:12-18) (emphasis added); Ex. 1005 ¶88.)

Moreover when asked to comment on the lower response rate of 11% among Class A patients (*id*. at 068 (67:10-15)), Dr. Grillo-López acknowledged that "the Class As tend to have a lower antigen density on the cell surface" and referred to observations of samples obtained from M.D. Anderson showing "the CLL's have a lower and more heterogeneous CD20 expression." (*Id.* at 069 (68:12-20).) Dr. Grillo-López explained that Class As "did not deplete their circulating cells as well as the B, C, D's, and there is a correlation between response and B-cell depletion." (*Id.* at 070 (69:6-8).) Thus, Dr. Grillo-López concluded: "there is the implication here that [Class As] may benefit from higher doses or more doses of the antibody [rituximab] . . . ." (*Id.* at 071 (70:13-16); Ex. 1005 ¶89.)

Batata is an August 1, 1992 Cancer article. (Ex. 1008.) Batata systematically compares cellular markers from the blood of 184 CLL patients, bone marrow cells from 23 CLL patients, and lymph nodes cells of 86 SLL

patients. (*Id.*) Batata concludes based on the study results that "a systematic comparison of surface markers between CLL and SLL demonstrated an almost identical phenotype, thus providing the evidence that they are different tissue expression of the same disease." (*Id.* at 008; Ex. 1005 ¶90.)

Maloney 1994 is an October 1994 article published in Blood. (Ex. 1009.) Maloney describes a dose escalation study to ascertain rituximab's toxicity in human patients. (Ex. 1005 ¶44; Ex. 1009 at 003.) Patients with relapsed low-grade B-cell NHL, including one SLL patient, received a single intravenous infusion of up to 500 mg/m^2 rituximab. (Ex. 1009 at 005-06.) Ultimately, all tested doses were well tolerated, including the 500 mg/m^2 dose, and "no dose-limiting toxicities were identified," though some manageable infusion-related side effects were observed. (Ex. 1005 ¶44; Ex. 1009 at 009.)

The examiner did not consider the FDA Transcript during prosecution of the '711 patent. The only differences between what is disclosed in the FDA transcript and what is recited in claim 1 are: (1) in claim 1, rituximab is used to treat CLL patients specifically, rather than the FDA Transcript's broader category of IWF group A, which presumably contains patients "with a lymphomatous phase of CLL" (Ex. 1007 at 117 (116:12-15)); and (2) in claim 1, at least one 500 mg/m^2 dosage is administered instead of the four 375 mg/m^2 dosages described in the FDA Transcript. Batata makes clear that CLL and SLL are different tissue

expressions of the same disease process with nearly identical phenotypes, and Maloney discloses dosing rituximab at 500 mg/m^2. Thus, claim 1 is obvious under §103 over the FDA Transcript, Batata, and Maloney, as shown below: (Ex. 1005 ¶115.)

Ground 6	
Claim Language	***FDA Transcript, Batata, and Maloney 1994***
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,	"Treatment consisted of the antibody at 375 mg/m^2 by intravenous infusion given once weekly times 4." (*See* Ex. 1007 at 036 (35:23-24).) FDA Transcript discloses that 37 patients identified as having IWF type A were treated with rituximab, that the patients "do have important clinical benefit," and that "of the 37 patients, 28 had some tumor shrinkage . . . ." (*Id.* at 044 (43:16-24).) "I think we already heard that this Group A population contained a number of patients . . . presumably ***some with a lymphomatous phase of CLL***." (*Id.* at 117 (116:12-18) (emphasis added).) "[T]he similarity of membrane phenotypes between ***CLL and SLL*** provided evidence that the two are different tissue expressions of ***the same disease***." (Ex. 1008 at 002 (Abstract) (emphasis added).)
wherein the rituximab is administered to the patient at a dosage of 500 mg/m^2.	"[Class A patients] did not deplete their circulating cells as well as the B, C, D's, and there is a correlation between response and B-cell depletion" and "there is the implication here that ***these patients may benefit from higher doses or more doses of the antibody*** . . . ." (Ex. 1007 at 070 (69:6-8), 071 (70:13-16) (emphasis added).) *Maloney 1994* discloses that a 500 mg/m^2 dose was effective and well tolerated in patients with relapsed low-grade NHL. No dose-limiting toxicities were identified. (Ex. 1009 at

Ground 6	
Claim Language	***FDA Transcript, Batata, and Maloney 1994***
	009.)

a. Motivation To Combine

(1) A POSA would have been motivated to use rituximab for CLL

The FDA Transcript discloses that rituximab administered at 375 mg/m^2 in four weekly infusions yielded the beneficial therapeutic response of tumor shrinkage in at least 28 of the 37 SLL/CLL patients (75%). (Ex. 1007 at 044-45 (43:23-44:8).)

As disclosed by Batata, SLL and CLL are "different tissue expressions of the same disease process." (Ex. 1008 at 002 (Abstract).) Indeed, Batata found that SLL and CLL have "an almost identical phenotype." (*Id.* at 008.) Batata's findings confirm that, by the late 1990s, it was well-known that SLL and CLL were different tissue expressions of the same disease process. (Ex. 1005 ¶¶27, 90.) Indeed, the World Health Organization expressly concluded, "CLL and SLL are one disease at different stages, not two separate entities." (Ex. 1012 at 012.) Dr. Grillo-López, inventor of the '711 patent, recognized this equivalence in a patent application filed three months before the filing date of the application that became the '711 patent: "CLL is the liquid (leukemic) equivalent of small lymphocytic lymphoma (SLL)." (Ex. 1039 at 027.)

Because it was known in the art that SLL and CLL are different tissue expressions of the same disease process, a POSA would have been motivated by the FDA Transcript's disclosure of the effective treatment of SLL/CLL to use rituximab to treat CLL patients specifically. (Ex. 1005 ¶¶116-17, 119.) A POSA would have understood that the similarity between SLL and CLL meant "[t]reatment of small lymphocytic lymphoma is similar to that for CLL." (Ex. 1044 at 029; Ex. 1005 ¶¶33, 120.)

Furthermore, the FDA Transcript explicitly contemplates using rituximab to treat patients diagnosed with CLL. (Ex. 1007 at 069 (68:16-20) ("We also looked at a small group of CLL patients, samples that we obtained courtesy of Dr. Susan O'Brien from M.D. Anderson Hospital"); *id.* at 117 (116:12-18) ("I think we already heard that this Group A population contained a number of patients . . . presumably ***some with a lymphomatous phase of CLL***.") (emphasis added); Ex. 1005 ¶119.)

Additionally, the rituximab's success at treating low-grade NHL patients, as described in the FDA Transcript, would have led a POSA to try rituximab to treat CLL. A 1995 Genentech press release actually proposed using rituximab to treat CLL based on the results of rituximab studies in NHL patients. (*See* Ex. 1034; *see also* Ex. 1057 at 003 (Abstract 2277) (describing clinical trial results of rituximab in low-grade NHL patients, including 11 CLL/SLL patients, of which 1 CLL/SLL

patient obtained complete remission); Ex. 1005 ¶121.)

Contrary to patentee's arguments during prosecution of the '612 patent, the potential of tumor lysis syndrome ("TLS") does not undermine the strong motivation to use rituximab to treat CLL. (Ex. 1005 ¶¶136-38.) When over-proliferating cancer cells are lysed (*i.e.,* broken open) the contents of the cells are released into the bloodstream, leading to TLS. (*Id.* ¶137.) A POSA would have anticipated the likelihood of TLS when attacking CLL and would have employed known techniques to minimize TLS. (*Id.*)

For example, a POSA would have known of prophylactic therapy options to manage and mitigate the potential occurrence of TLS, including use of drugs such as diphenhydramine and acetaminophen. (*Id.*; Ex. 1009 at 006.) A POSA would also have known that using an initial lower dose or temporarily pausing an infusion would mitigate the likelihood of TLS. (Ex. 1005 ¶137; Ex. 1009 at 006.) Although TLS may require active monitoring and prophylactic treatment, the possibility of TLS would not have stopped a POSA from recognizing that rituximab was highly effective at killing B-cells and represented a promising treatment for CLL patients. (Ex. 1005 ¶138.)

(2) A POSA would have been motivated to dose rituximab at 500 mg/m^2

In the FDA Transcript, Dr. Grillo-López states that the IWF A patients "may benefit from higher doses and/or more doses of the antibody [rituximab]," providing an express motivation to try a dosage higher than 375 mg/m^2 for SLL and CLL patients. (*Id.* ¶122; Ex. 1007 at 069 (68:11-12).) Consequently, the FDA Transcript expressly suggests that a higher rituximab dose, such as the 500 mg/m^2 dose taught in Maloney 1994, would enhance effectiveness. (Ex. 1005 ¶122.) Dr. Grillo-López also stated, "there is a correlation between those measures of tumor volume or circulating B-cell mass and serum levels of the antibody, and the patients that have the larger tumor volume have lower levels of circulating antibody." (Ex. 1007 at 072-73 (71:20-72:4).) Because it was commonly known in 1998 that SLL/CLL patients have a larger number of circulating B-cells than patients in IWF groups B-D, a POSA would have understood from Dr. Grillo-López's statement that SLL/CLL patients had "lower levels of circulating antibody." (Ex. 1005 ¶123). Based on Dr. Grillo-López's disclosure, a POSA would have understood that SLL/CLL patients' lower serum levels of circulating antibody correlates with the lower response rate to 375 mg/m^2 in this group and that a higher dose of rituximab in SLL/CLL patients would increase the serum concentration of the antibody, and in turn increase the response rate. (*Id.*) A

POSA would further have understood that Dr. Grillo Lopez was not concerned about the effects of tumor lysis. (Ex. 1005 ¶¶136-38.) Therefore, it would have been obvious to use a dose higher than 375 mg/m^2 of rituximab in SLL/CLL patients to produce a higher response rate. (*Id.* ¶¶124-25.)

Furthermore, nothing in the prior art would have extinguished the strong motivation to use rituximab to treat CLL with modestly higher dosages, as suggested in the FDA Transcript. Having learned the adverse events reported in the prior clinical trials were mostly limited to the first infusion and were substantially diminished on subsequent infusions, a POSA would have understood that close monitoring of the infusion rate and a lower dose of 375 mg/m^2 during the first infusion may be necessary. (*Id.* ¶126.) But because adverse events were substantially lower on subsequent infusions, a POSA would have been motivated to dose rituximab at a higher rate after the first infusion for CLL patients. (*Id.*) A logical higher dose for one or more of the weekly infusions taught by the FDA Transcript would have been 500 mg/m^2 since that dose was shown to be safe and effective in the Phase I trial reported in Maloney 1994. (*Id.*) In fact, the MD Anderson Online Newsletter discloses that researchers actually selected 500 mg/m^2 of rituximab for treatment of CLL as of at least July 1998, confirming that such a selection would have been obvious in light of the prior art at the time. (Ex. 1006 at 006; Ex. 1005 ¶93.)

b. Expectation of success

A POSA would have understood the FDA Transcript to demonstrate a detectable therapeutic response after four administrations of rituximab at 375 mg/m^2 in patients with SLL/CLL. The expectation of success in obtaining a therapeutic response would increase with the increased 500 mg/m^2 dose of rituximab. (Ex. 1005 ¶127.) It was expressly recognized in the FDA Transcript that CLL/SLL patients had an "important clinical benefit" from the 375 mg/m^2 dose of rituximab, and that the CLL/SLL B-cells had lower relative expression of CD20 compared to other NHLs. A POSA would have expected a higher dose to provide at least the same if not a greater therapeutic response than that observed at dosages of 375 mg/m^2. (*Id.*) A POSA would have had a reasonable expectation that a 500 mg/m^2 rituximab dosage would have yielded a therapeutic response as taught by the FDA Transcript, including a reduction in the patient's tumor load. Thus, claim 1 is obvious over FDA Transcript, Batata, and Maloney. (*Id.* ¶¶115-27.)

2. Claims 5-8.

Claims 5, 6, and 7 are dependent on claim 1 and recite the further limitations that rituximab be administered weekly, bi-weekly, or monthly, respectively. These limitations do not render the claims non-obvious. The FDA Transcript discloses a weekly dosing regimen at 375 mg/m^2 over four weeks. (Ex. 1005 ¶¶116, 128.)

Expanding this regimen to include at least one dosage at 500 mg/m^2 would have been obvious in view of the statements in the FDA Transcript about the benefit of increasing dosage to increase the therapeutic response of SLL patients to rituximab. (*Id.* ¶128). Moreover, as described in Sections X.D. and X.F., using a bi-weekly or monthly dosing schedule would have been an obvious modification. (*Id*.)

Claim 8 recites the negative limitation that the method does not include treatment with a radiolabeled anti-CD20 antibody. There is no use of radiolabeled anti-CD20 in any of the references relied on in this petition. Claim 8 is therefore obvious for the same reason as claim 1. (Ex. 1005 ¶129.)

XI. NO SECONDARY INDICIA OF NON-OBVIOUSNESS EXIST

As explained above, the prior art and knowledge of a POSA renders the challenged claims of the ’711 patent anticipated and/or obvious. Petitioner is unaware of evidence of any secondary indicia to overcome the strong prima facie case of obviousness demonstrated by the foregoing grounds.

During prosecution of the ’612 patent, the Applicants asserted that the ability of rituximab to treat CLL was unexpected and that the prior art taught away from doing so. As noted in section VI.B.3 above, the arguments made by Applicants were both factually incorrect and misleading. (*See* Ex. 1005 ¶¶131-38.) Since the prior-art FDA Transcript taught that rituximab would successfully treat

SLL/CLL patients, the lower levels of CD20 on CLL/SLL cells relative to other NHLs would have been irrelevant to the expectation of success. (*Id.* ¶133.) Additionally, the relatively higher number of circulating tumor load in CLL patients compared to SLL patients and the potential of TLS did not result in an unexpected result. (*Id.* ¶135.) TLS was a known and manageable possibility that would not have prevented a POSA from pursuing rituximab as a treatment for CLL. (*Id.* ¶137.) To the contrary, the existence of a heightened risk of TLS would confirm the high activity of rituximab in killing the diseased B-cells and give a POSA a heightened expectation of success in reducing the tumor burden in a patient. (*Id.* ¶136.)

Petitioner reserves the right to respond to any assertion of secondary indicia advanced by Patent Owners.

XII. CONCLUSION

Petitioner respectfully requests institution of *inter partes* review of claims 1-9 of the ’711 patent, and a finding that the claims are unpatentable, based on the grounds presented in this Petition.

Dated: March 31, 2017

Respectfully submitted,

By: /s/*Michelle S. Rhyu*

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37 C.F.R. § 42.24(d) CERTIFICATION

The undersigned hereby certifies that this submission, excluding the parts of this petition that are exempted by 37 C.F.R. § 42.24(a) (including the tables of contents and authority, mandatory notices, claim listings, certificate of word count, exhibit list, and certificate of service), contains 13,990 words, as determined using the standard word counting feature of the Microsoft Word program.

Dated: March 31, 2017

By: */s / Michelle S. Rhyu*
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CERTIFICATION OF SERVICE

I, Maria Weiand, hereby certify that pursuant to 37 C.F.R. Sections 42.6 and 42.105, a complete copy of the attached **PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 8,206,711,** including all exhibits (**Nos. 1001-1064)** and related documents, are being served on the 31st day of March, 2017, the same day as the filing of the above-identified document in the United States Patent and Trademark Office/Patent Trial and Appeal Board, via Federal Express upon the Patent Owner at the following correspondence address of record with the USPTO:

Sidley Austin LLP
2021 McKinney Avenue, Suite 2000
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Date: March 31, 2017

/s/ Maria Weiand
Maria Weiand