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. 7,682,612

Filing Date: November 9, 1999
Issue Date: March 23, 2010

Inventors: Christine White, Antonio Grillo-López,
John Curd, and Susan Desmond-Hellmann

Title: TREATMENT OF HEMATOLOGIC MALIGNANCIES ASSOCIATED WITH CIRCULATING TUMOR CELLS USING CHIMERIC ANTI-CD20 ANTIBODY

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PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 7,682,612
(Single agent claims)

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APPENDIX A: EXHIBIT LIST

Exhibit No.	Description
1001	U.S. Patent No. 7,682,612
1002	U.S. Provisional Application No. 60/107,658
1003	Archived website for Leukemia Insights Newsletter, 3(2) (Last Updated July 2, 1998) ("MD Anderson Online Newsletter")
1004	File History for U.S. Patent No. 7,682,612 (Excerpts)
1005	Declaration of Michael Andreeff, M.D.
1006	Protocol for Phase I/II Study of IDEC-C2B8 (Rituximab) for Relapsed CLL (DM97-236) (dated December 10, 1997) ("O'Brien Protocol")
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. (Feb. 1998) 25(1):65-74
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. 14:59-61 (Abstract 53) (1996) ("Czuczman")
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.;*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. (Oct. 1997) 15(10):3266-3274 ("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)
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	Beigleiter, 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)
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	Exhibit Number Not Used
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")
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. 10:548-551 (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)
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	Exhibit Number Not Used
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)
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	Declaration of Christopher Butler, Internet Archive, dated December 20, 2016, authenticating Archived website for Leukemia Insights Newsletter, 3(2) (Last Updated July 2, 1998), Exhibit 1003
1063	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")

APPENDIX B: '612 PATENT CLAIMS

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

2. A method according to claim 1, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.001 to about 30 mg/kg.

3. A method according to claim 1, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.01 to about 25 mg/kg.

4. A method according to claim 1, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.1 to about 20 mg/kg.

5. A method according to claim 1, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 375 mg/m^2.

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

7. A method according to claim 6, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 500 mg/m^2.

8. A method according to claim 1 or 6, wherein the patient has relapsed following previous treatment for the chronic lymphocytic leukemia.

9. A method according to claim 1 or 6, wherein the patient is refractory to a treatment previously administered for the chronic lymphocytic leukemia.

10. A method according to claim 9, wherein the patient is refractory to fludarabine.

11. A method according to claim 1 or 6, wherein the anti-CD20 antibody is a chimeric antibody.

12. A method according to claim 11, wherein the anti-CD20 antibody is rituximab.

13. A method according to claim 1 or 6, wherein the anti-CD20 antibody is a humanized antibody.

15. A method according to claim 1 or 6, wherein the anti-CD20 antibody comprises a CD20-binding fragment of a chimeric, humanized, or human antibody.

16. A method according to claim 1 or 6, wherein the anti-CD20 antibody is administered to the patient repeatedly.

17. A method according to claim 16, wherein the anti-CD20 antibody is administered to the patient weekly.

18. A method according to claim 16, wherein the anti-CD20 antibody is administered to the patient weekly for about 2 to 10 weeks.

19. A method according to claim 16, wherein the anti-CD20 antibody is administered to the patient biweekly.

20. A method according to claim 16, wherein the anti-CD20 antibody is administered to the patient monthly.

21. A method according to claim 1 or 6, wherein the anti-CD20 antibody is administered to the patient parenterally.

22. A method according to claim 21, wherein the anti-CD20 antibody is administered to the patient by intravenous infusion.

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

59. A method according to claim 6, 28, or 58, wherein radiation is not used in conjunction with the anti-CD20 antibody.

60. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering a therapeutic non-radiolabeled anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein radiation is not used in conjunction with said anti-CD20 antibody.

(Ex. 1001 at 7:63-8:57, 10:35-51.)

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 1-13, 15-22, and 58-60 of U.S. Patent No. 7,682,612 ("the '612 patent"). Review should be instituted because there is a reasonable likelihood Celltrion will demonstrate that the challenged claims of the '612 patent are obvious and/or anticipated.

The '612 patent claims are directed to using an anti-CD20 antibody to treat patients with chronic lymphocytic leukemia ("CLL"), a disease caused by accumulation of B-cells in the blood. By November 9, 1997, one year before the filing date of the earliest ancestor application to the '612 patent, it was well-known that rituximab, an anti-CD20 antibody, was effective to 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 ¶43, 69.)

Independent claims 1, 6, 58, and 60 of the '612 patent challenged in this petition recite broad methods for treating CLL by administering an anti-CD20 antibody. 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.) Claim 6 recites the administration of the anti-CD20 antibody at "a dosage of about 500 to about 1500 mg/m^2." There was nothing non-obvious or novel about this dosage. By 1994, the prior art disclosed effective treatment of low-grade NHL patients by administering rituximab dosages of 10 mg/m^2 to 500 mg/m^2 dosage of rituximab, with no maximum tolerated dose. (Ex. 1005 ¶5; Ex. 1009 at 003 (Abstract).) A newsletter published in print and online by the MD Anderson Cancer Center ("MD Anderson") in July 1998 expressly disclosed treating CLL with once-weekly doses of rituximab at 500 mg/m^2. (Ex. 1005 ¶5; Ex. 1003 at 004; Ex. 1061 at 002; *see also* Ex. 1006 at 005.) The additional limitation in claim 58 that the method be used on a patient that is "refractory to fludarabine previously administered" is obvious because using rituximab to treat a patient that was otherwise no longer responding to fludarabine treatment would have been done as a matter of course. (Ex. 1005 ¶5.) Accordingly, all of the independent claims of the '612 patent are invalid for obviousness and/or anticipation under 35 U.S.C. §103. (*Id.*)

Nor do the challenged dependent claims add any limitations that make the recited methods non-obvious. Dependent claims 2-5 and 7 recite doses of the anti-CD20 antibody that include the 375 mg/m^2 or 500 mg/m^2 doses of rituximab disclosed in the prior art. Claims 8-10 recite the use of an anti-CD20 antibody to

treat patients who are not responding to other treatments. It was obvious to use rituximab to treat a patient if other treatments were not working. Claims 11-13 and 15 recite structural features of the claimed anti-CD20 antibody that are met by the structure of rituximab, which was known in the art. Claims 16-20 recite multi-dosing schedules of the anti-CD20 antibody that are weekly, biweekly, or monthly. 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). Finally, the prior art disclosed intravenous infusion as recited in claims 21-22, and the negative limitation of claim 59 was obvious. Dependent claims 2-5, 7-22, and 59 are therefore unpatentable under 35 U.S.C. §103. (Ex. 1005 ¶6.)

Petitioner respectfully requests institution of *inter partes* review of claims 1-13, 15-22, and 58-60 due to the reasonable likelihood the claims are obvious and/or anticipated.

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 another petition for *inter partes* review of U.S. Patent No. 7,682,612 as well as a petition for *inter partes* review of U.S. Patent No. 8,206,711. Biogen, Inc. ("Biogen") and Genentech, Inc. ("Genentech") (collectively, "Patentees" or "Patent Owners") are the owners of the following U.S. applications and patents that are related to the '612 patent: Appl. No. 12/629,472, now U.S. Patent No. 8,206,711, 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 1-13, 15-22 and 58-60 of the '612 patent and is accompanied by a payment of $27,400, which comprises a $9,800 request fee and $17,600 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 '612 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 1-13, 15-22, and 58-60 of the '612 patent on the grounds set forth in the following table and requests that these claims be deemed unpatentable. The '612 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	'612 Patent Claims	Basis for Unpatentability
Ground 1	1-13, 15-22, 58-60	Obvious under §103 over the combination of FDA Transcript, Batata, and Maloney
Ground 2	19-20	Obvious under §103 over the combination of FDA Transcript, Batata, Maloney, Byrd, and Kipps
Ground 3	1-7, 11-13, 15-18, 21-22, 59-60	Anticipated under §102 over MD Anderson Online Newsletter
Ground 4	8-10, 19-20, 58	Obvious under §103 over MD Anderson Online Newsletter
Ground 5	19-20	Obvious under §103 over MD Anderson Online Newsletter, Byrd, and Kipps

The FDA Transcript, Batata, Maloney, and Kipps are §102(b) prior art to all claims of the '612 patent because each reference was published or otherwise made publicly available more than one year before the earliest effective filing date of the '612 patent. Byrd and the MD Anderson Online Newsletter are §102(b) prior art to claims 2-4, 8, 10, 18-20, and 58 because those claims are not entitled to claim priority to a filing date before November 9, 1999 and are §102(a) prior art to the remaining challenged claims.

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

[1] NHL is a form of lymphoma affecting B-cells or T-cells and is distinct from the

"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 known as "different tissue expressions of ***the same disease*** process." (Ex. 1008 at 002 (emphasis added); Ex. 1005 ¶26.) 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 ¶28.) 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

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cancer known as Hodgkin's Lymphoma. (Ex. 1044 at 023, 026-27.) B-cell NHLs comprise about 80% of all adult NHLs. (*Id.* at 027.)

indistinguishable from CLL." (Ex. 1008 at 002; Ex. 1005 ¶28; Ex. 1060 at 002.)

Clinical assessment of SLL versus CLL is often based on the patient's total lymphocyte count. (Ex. 1005 ¶29.) 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 ¶¶26, 29; Ex. 1008 at 008.)

Inventor Grillo-López recognized the equivalence between CLL and SLL in a patent application filed during prosecution of the '612 patent: "CLL is the liquid (leukemic) equivalent of small lymphocytic lymphoma (SLL)." (Ex. 1039 at 027.) Dr. 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 ¶27.)

B. NHL Classifications Group CLL and SLL Together

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 type of NHL. (Ex. 1005 ¶¶26-27, 29, 30-31.)

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 ¶32.)

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 ¶33.) 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 ¶34.) 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.* ¶¶34-35; 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 a Chimeric Anti-CD20 Antibody

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 ¶37; 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 ¶37.)

CD20 is a protein that appears on B-cells during certain phases of B-cell differentiation. (*Id.* ¶38; 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 ¶38; 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 ¶39; 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 ¶40; 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 ¶41; Ex. 1034 at 002.)

[2] By November 9, 1997, IDEC-C2B8 was also known as rituximab. (*See, e.g.*, Ex. 1013 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 ¶43; 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, 250, or ***500 mg/m^2*** 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," although some manageable infusion-related side effects were observed. (*Id.* at 009; Ex. 1005 ¶43.)

McLaughlin reported by August 7, 1998 that rituximab was an effective treatment for 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 indicated that patients with a lymphocyte count of over 5000 lymphocytes/μL were excluded from the study, referring 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 '612 patent[4], some CLL patients could have been included in the study. (Ex. 1005 ¶46.)

Further studies demonstrated that rituximab could be administered in

[3] 4,000 lymphocytes/μL is identical to 4 X 10^9 lymphocytes/L. (Ex. 1005 ¶46 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 ¶54 n.5.)

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 treatment. (*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 ¶¶48-49.)

VI. THE '612 PATENT AND ITS PROSECUTION HISTORY

A. The '612 Patent

The '612 patent contains 60 claims—25 claims recite methods for treating CLL "comprising administering an anti-CD20 antibody" and 35 claims recite methods for treating CLL "comprising administering an anti-CD20 antibody . . . wherein the anti-CD20 antibody therapy is combined with chemotherapy." (*See* Appendix B.)

This petition challenges the 25 claims of the '612 patent that require only that the claimed methods "comprise administering anti-CD20 antibody," and given the open-ended term "comprise," cover methods that include the administration of anti-CD20 antibody as a single agent as well as in combination with chemotherapy.

B. Relevant Prosecution History of the '612 Patent

The '612 patent issued on March 23, 2010 from U.S. Application No. 09/436,347 ("the '347 application"), filed on November 9, 1999. The '347 application claims priority to U.S. Provisional Application No. 60/107,658 ("the '658 provisional application"), filed on November 9, 1998.

As described below, of the challenged claims, only claims 1, 5-7, 9, 11-13, 15-17, 21-22, and 59-60 of the '612 patent should have the November 9, 1998 priority date of the '658 provisional application. The priority date for claims 2-4, 8, 10, 18-20, and 58 is no earlier than the November 9, 1999 filing date of the '347 application.

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 non-Hodgkin's lymphoma. (*Id.* at 005.) The specification concedes that rituximab had "great success" in treating 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).)

With regard to dosing regimens for an anti-CD20 antibody, the specification of the '658 provisional application states generally:

> Effective dosages will depend on the specific antibody, condition of the patient, age, weight, or any other treatments, among other factors. Typically effective dosages will range from about 0.001 to about 30 mg/kg body weight, more preferably from about 0.01 to 25 mg/kg body weight, and most preferably from about 0.1 to about 20 mg/kg body weight.
>
> Such administration may be effected by various protocols, e.g., weekly, bi-weekly, or monthly, dependent on the dosage administered and patient response. . . .
>
> Typically, treatment will be effected weekly, for about 2 to 10 weeks, more typically about 4 weeks. A particularly preferred dosage regimen will comprise administration of about .375 mg/kg weekly for a total of four infusions. Also, stepped-up dosing schedules may be even more preferable.

(*Id.* at 014.) However, the disclosures in the specification related to treating CLL only describe dosing rituximab at 375 mg/m^2 for four weekly infusions, and four weekly doses of rituximab at "375 mg/m^3 [*sic*]" in week one followed by doses of "500-1500 mg/m^3 [sic]." (*Id.* at 019.) The '658 provisional application provides

no other dosage regimens for treating CLL. It provides no disclosure of administering an anti-CD20 antibody to CLL patients who relapsed following prior CLL treatment, and no disclosure of treating CLL patients who were refractory to fludarabine. (Ex. 1005 ¶60.) Indeed, the '658 provisional application does not mention fludarabine in any context. (*Id.*)

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.)

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 074-77; 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 only issued 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. (Ex. 1005 ¶¶26-29; Ex. 1008 at 008.)

The biological equivalence between CLL and SLL coupled with rituximab's ability to treat SLL refutes the Applicants' assertion that the "reduced level of CD20 expression on CLL tumor cells, relative to NHL tumor cells" justified the patentability of 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 cells, which, like CLL cells, exhibit low CD20 levels. (Ex. 1005 ¶¶26-29, 43, 46, 48-49.)

After receiving the Notice of Allowance in this application, the Applicants sought to change inventorship and asserted that "Susan Desmond-Hellman and John G. Curd made inventive contributions to the presently claimed subject matter." (Ex. 1004 at 784.) Applicants also provided documents allegedly supporting the contributions of the previously unnamed inventors. (*Id*. at 682-785.) Those documents included an August 15, 1995 email that suggested the use

of rituximab at dosing levels of 150, 375, and 500 mg/m^2 to treat CLL. (*Id*. at 735.) There is no evidence in the file history that any of the named inventors suggested treating CLL with a dosage of rituximab that was greater than 500 mg/m^2.

C. Claims 2-4, 8, 10, 18-20, and 58 Are Not Entitled to the Effective Filing Date of the '658 Provisional Application

To receive the priority date of the '658 provisional 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 application has 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.*, 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, claims 2-4, 8, 10, 18-20, and 58 lack written description or enablement support in the '658 provisional application. Claims 2, 3, and 4 require dosing the anti-CD20 antibody at "0.001 to about 30 mg/kg," "0.01 to about 25 mg/kg," and "0.1 to about 20 mg/kg," respectively. (Ex. 1001 at 8:1-9.) But there is not a single example, reference study, or any demonstrated results indicating to a person

of skill in the art that the inventors had possession of any therapeutic dose for treating CLL below 375 mg/m^2 (equivalent to approximately 10 mg/kg) to support the inclusion of such doses in the claims. (Ex. 1005 ¶60.) *See Bamberg v. Dalvey*, 815 F.3d 793, 797-98 (Fed. Cir. 2016) (holding specification describing a plastic layer that melts above 220ºC lacked written description for claims encompassing a plastic layer that melts above *and below* 220ºC).

Claim 8 requires administering the anti-CD20 antibody to a patient who "has relapsed following previous treatment for the chronic lymphocytic leukemia" (Ex. 1001 at 8:23-25), but the '658 provisional application makes no mention whatsoever of treating patients who relapsed following treatment for CLL. Likewise, claims 10 and 58 require administering the anti-CD20 antibody to a patient who "is refractory to fludarabine" (*id.*), but the '658 provisional application is silent regarding treatment of CLL patients who are refractory to fludarabine. (Ex. 1005 ¶60.) Fludarabine is not mentioned in the '658 provisional application at all. (*Id.*)

Claim 18 requires administering the anti-CD20 antibody "to the patient weekly for about 2 to 10 weeks." (Ex. 1001 at 8:46-48.) But the only dosing duration described in any of the examples or studies is 4 weeks. There is not a single example, reference study, or demonstrated results indicating that the inventors had possession of a dosage regimen for treating CLL that involved

weekly administration of an anti-CD20 antibody for any duration other than 4 weeks. (Ex. 1005 ¶60.)

Claims 19 and 20 require biweekly and monthly administration, respectively. (Ex. 1001 at 8:49-52.) The '658 provisional application is also devoid of a single example, reference study, or any demonstrated results to support the inventor's possession of bi-weekly or monthly administration for treating CLL. (Ex. 1005 ¶60.) Bi-weekly and monthly dosing are not discussed at all in the context of treating CLL. (*Id.*)

Thus, claims 2-4, 8, 10, 18-20, and 58 cannot rely on the '658 provisional application for priority.[5] The priority date for these claims 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. --,

[5] Petitioner reserves the right to respond to any assertion by Patent Owners that the '658 provisional application provides an adequate supporting disclosure for claims 2-4, 8, 10, 18-20, and 58.

136 S. Ct. 2131 (2016). The constructions proposed in this Petition represent the broadest reasonable interpretation one of ordinary skill in the art would give 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 4,000 cells per μL." (Ex. 1005 ¶52; *see* 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 ¶¶26-29, 52.)

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 ¶¶26-29, 52.) 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 6:12-13.) 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." (Ex. 1005 ¶55.) 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.) 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 ¶54 n.5.)

[7] 4-200 x 10^9/L is the same as 4,000-200,000 per µl. (Ex. 1005 ¶ 54.)

[8] Applying a different claim construction standard than the "broadest reasonable

VIII. PERSON OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art ("POSA") at the time of the alleged invention of the '612 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.

IX. THE PRIOR ART

Petitioner relies on the following publications:

A. 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

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construction" standard applicable to this Petition, the Southern District of 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 '612 patent is anticipated and/or obvious as explained in each of the Grounds below.

Pharmaceuticals, including two of the inventors of the '612 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 '612 patent.

B. 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 all claims of the '612 patent.

C. Maloney (Ex. 1009)

Maloney 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 §102(b) prior art to all claims of the '612 patent.

D. 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, 8, 10, 18-20, and 58, and §102(a) art to the remaining challenged claims.

E. 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 '612 patent.

F. MD Anderson Online Newsletter (Ex. 1003)

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

¶77; Ex. 1006.) As detailed in his declaration, Dr. Andreeff collaborated in the study. (Ex. 1005 ¶77.)

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 ¶¶79-80; 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 ¶¶81, 83.)

Dr. Andreeff explains that Dr. Charles Koller was in charge of making the MD Anderson Print Newsletter available online. (*Id.* ¶82.) The Summer 1998 edition of the MD Anderson Online Newsletter appears in the Internet Archive Wayback Machine beginning February 8, 1999. (Ex. 1003; accessed December 14, 2016.)[9] As shown in the Internet Archive Wayback Machine, the online

[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. 1062 at 001.) Accordingly, as the URL assigned for MD Anderson Online Newsletter is https://web.archive.org/web/19990208234814/http://www.mdanderson.org/~leukemia/letter32.html#IDEC-

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 ¶82; Ex. 1062 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, 8, 10, 18-20, and 58, and §102(a) art to the remaining challenged claims. Both newsletters include identical descriptions of the O'Brien study. (Ex. 1003 at 004; Ex. 1061 at 002; Ex. 1005 ¶82.)

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 ¶¶78-85.) 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 available to the extent that persons interested and ordinarily skilled in the subject

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C2B8, the record of the file was archived on February 8, 1999. (*Id.* at 004.)

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.

G. 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 '612 PATENT ARE INVALID

A. Legal Standards for Obviousness

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). 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., Inc. v. Biocraft Labs, Inc*., 874 F.2d 804, 809 (Fed. Cir. 1989) (internal 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." Similarly, in *Biomarin Pharmaceuticals Inc. v. Genzyme Therapeutic Products Ltd. Partnership*, 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. 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 1-13, 15-22, and 58-60 Are Obvious Under §103 Over the FDA Transcript, Batata, and Maloney

This Ground assumes that the priority date for all challenged claims is November 9, 1998. All challenged claims are obvious under §103 over the FDA Transcript (Ex. 1007), Batata (Ex. 1008), and Maloney (Ex. 1009).

This ground first discusses why the independent claims (claims 1, 6, 58, and 60) are obvious, then addresses the challenged dependent claims.

1. Independent Claims 1 and 6

Claim 1 of the '612 patent recites two limitations: (1) administering an anti-

CD20 antibody to the patient in an amount effective to treat a patient with CLL and (2) the method does not include treatment with a radiolabeled anti-CD20 antibody. Claim 6 adds a third limitation: administering the anti-CD20 antibody "at a dosage of about 500 to about 1500 mg/m^2." (Ex. 1001 at 8:13-19.)

The July 1997 FDA Transcript includes statements from two of the named inventors of the '612 patent, Dr. Antonio Grillo-López and Dr. Christine A. White. (Ex. 1007 at 020 (19:15-23).) Dr. Grillo-López discusses 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 ¶¶30-31, 65; 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), 045 (44:18-19).)) Despite the lower response rate in IWF Type A

patients, 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 (43:20-21), 044-45 (43:23-44:8).) 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 ¶66, 90.)

Dr. Berman, a member of the review Committee, summarizes 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 ¶67, 92.)

Moreover, when asked to comment on the lower response rate of 11% among Class A patients (Ex. 1007 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 ¶68.)

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 expressions of the same disease." (*Id.* at 008.)

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 ¶43; 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. (*Id.* 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. (*Id.* at 009; Ex. 1005 ¶43.)

The examiner did not consider the FDA Transcript during prosecution of the '612 patent. The only difference between what is disclosed in the FDA Transcript and what is recited in claim 1 is that 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).) Batata makes clear that CLL and SLL are different tissue expressions of the same disease process with nearly identical phenotypes. The only difference between claim 1 and claim 6 is that claim 6 requires at least one dosage of 500 to 1500 mg/m^2. The FDA Transcript suggests using such a higher dosage for SLL/CLL patients, Maloney discloses dosing rituximab at 500 mg/m^2. None of these three references used a radiolabeled anti-CD20 antibody. Thus, claims 1 and 6 are obvious under §103 over the FDA Transcript, Batata, and Maloney as shown below (Ex. 1005 ¶¶88-100):

GROUND 1	
<u>Claim Language</u>	***Obvious Over the FDA Transcript (Ex. 1007), Batata (Ex. 1008), and Maloney 1994 (Ex. 1009)***
1. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-	The FDA Transcript describes study results of treatment with rituximab, also known as IDEC-C2B8, which is "a chimeric anti-CD20 antibody." (Ex. 1007 at 026 (25:4-5).) "Treatment consisted of the antibody at 375 mg/m^2 by

GROUND 1	
<u>Claim Language</u>	***Obvious Over the FDA Transcript (Ex. 1007), Batata (Ex. 1008), and Maloney 1994 (Ex. 1009)***
CD20 anti body to the patient in an amount effective to treat the chronic lymphocytic leukemia,	intravenous infusion given once weekly times 4." (*Id.* 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).) Batata teaches that "the 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 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. (Exs. 1007, 1008, 1009.)
6. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia,	*See claim 1.*
wherein the anti-CD20 antibody is	"[Class A patients] did not deplete their circulating cells as well as the B, C, D's, and there is a correlation between

GROUND 1	
Claim Language	***Obvious Over the FDA Transcript (Ex. 1007), Batata (Ex. 1008), and Maloney 1994 (Ex. 1009)***
administered to the patient at a dosage of about 500 to about 1500 mg/m^2,	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 discloses that a 500 mg/m^2 dose was effective and well tolerated in patients with relapsed low-grade NHL. (Ex. 1009 at 009.)
wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.	*See claim 1.*

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 IWF Type A patients (75%). (Ex. 1007 at 044-45 (43:23-44:8).) A POSA would have known that IWF Type A patients were SLL/CLL patients. (Ex. 1008 at 002; Ex. 1005 ¶65.)

As disclosed by Batata, SLL and CLL are "different tissue expressions of the same disease process." (Ex. 1008 at 002 (Abstract).) 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 ¶¶69-70.) 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 '612 patent, recognized this equivalence in a patent application filed during prosecution of the '612 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 ¶¶89-94.) 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 ¶32.)

Furthermore, the FDA Transcript explicitly contemplates the use of 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 ¶67, 92.)

Additionally, rituximab's success at treating low-grade NHL patients, as described in the FDA Transcript, would have led a POSA to use 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 ¶94.)

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 ¶¶125-27.) 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.* at ¶126.) 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 ¶126; 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 ¶¶126-27.)

(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.* at ¶95; Ex. 1007 at 069 (68:11-12).) Maloney teaches that the 500 mg/m^2 dose is safe and may be effective. (Ex. 1005 ¶¶43, 99.) 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 ¶96.) 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 (*Id.*) and would have understood

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.* ¶97.) A POSA would further have understood that Dr. Grillo-López was not concerned about the effects of tumor lysis, and that any risk of tumor lysis could be managed prophylactically. (*Id.* ¶¶90, 126.) Therefore, it would have been obvious to use a 500 mg/m^2 dose of rituximab in SLL/CLL patients to produce a higher response rate. (*Id.* ¶¶95-100.)

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 prudent. (*Id.* ¶99.) 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 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. (*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. 1003 at 006.)

b. Reasonable 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. A POSA would further have understood Maloney to teach the safety and efficacy of administering rituximab at doses ranging from 50 mg/m^2 to 500 mg/m^2, thus supporting the POSA's reasonable expectation of success at implementing the rituximab regimen of a higher dose than 375 mg/m^2, as described in the FDA Transcript. (Ex. 1005 ¶¶93, 100.) Thus, claims 1 and 6 are obvious over the FDA Transcript, Batata, and Maloney. (*Id.*)

2. Independent Claim 58

Claim 58 of the '612 patent recites three limitations: (1) administering an anti-CD20 antibody to the patient in an amount effective to treat a patient with CLL, (2) the patient is refractory to fludarabine previously administered for the CLL, and (3) the method does not include treatment with a radiolabeled anti-CD20 antibody. As described for claim 1, *supra*, the first and third limitations are obvious over the FDA Transcript, Batata, and Maloney.

As to the requirement that the patient be refractory to fludarabine, the

efficacy study results described in the FDA Transcript were from a study conducted in patients who were all relapsed or refractory. (Ex. 1007 at 037 (36:20-24).) These study results included 37 IWF type A patients—that is, 37 patients with SLL or CLL who were relapsed or refractory to previous treatment. The FDA Transcript additionally notes that fludarabine and cladribine "are the more frequently reported single agents evaluated in this patient population." (*Id.* at 025 (24:8-11).) Thus, a POSA reading the FDA Transcript's disclosure of rituximab's efficacy to apply to patients who were refractory to previous treatment, likely including patients refractory to fludarabine. (Ex. 1005 ¶101.)

Furthermore, because anti-CD20 antibodies such as rituximab were known to have a different mechanism of action than chemotherapeutic agents, it would have been obvious to one of skill in the art to employ the effective rituximab treatment regimen of the FDA Transcript at 375 mg/m^2 over four weeks to patients who were no longer responsive to a standard first-line CLL chemotherapeutic agent such as fludarabine. (*Id.* ¶102.) Claim 58 is therefore obvious. (*Id.*)

3. Independent Claim 60

Claim 60 recites the same limitations as claim 1 and adds the negative limitation "wherein radiation is not used in conjunction with said anti-CD20 antibody." The use of rituximab to treat IWF type A patients disclosed in the FDA Transcript was performed without using radiation. (*Id.* ¶103.) Therefore, claim 60

is obvious for the same reasons as claim 1. (*Id*.)

4. The Dependent Claims Are Obvious

a. Dependent Claims 2-5 and 7

Dependent claims 2-5 disclose specific dosages of an anti-CD20 for use in the method of claim 1 that are expressly met by the dosage of 375 mg/m^2 used in the trials disclosed in FDA Transcript.[10] (*Id.* ¶104.) 375 mg/m^2 is equivalent to approximately 10 mg/kg. 500 mg/m^2 is equivalent to approximately 13.5 mg/kg. (*Id.*) Dependent claim 7 discloses a dosage of 500 mg/m^2, as taught by Maloney. These claims therefore add nothing to overcome the obviousness of independent claims 1 and 6 and are also obvious over the FDA Transcript, Batata, and Maloney. (*Id*.)

b. Dependent Claims 8-10

Dependent claims 8-10 recite limitations related to using the method of treating CLL using an anti-CD20 antibody based on the patient's previous treatment(s) for CLL. These limitations include a patient that has "relapsed following previous treatment" (claim 8), "is refractory to a treatment previously administered" (claim 9), or "is refractory to fludarabine" (claim 10, dependent on claim 9). As described in claim 58, *supra*, the FDA Transcript discloses efficacy results for rituximab administered to patients, including IWF type A patients, who

[10] The conversion between mg/kg and mg/m^2 is a factor of 37. (Ex. 1005 ¶104.)

were either relapsed or refractory. (Ex. 1007 at 037 (36:20-24).) Additionally, because anti-CD20 antibodies such as rituximab were known to have a different mechanism of action than chemotherapeutic agents, it would have been obvious to a POSA to employ the effective rituximab treatment regimen of FDA Transcript at 375mg/m^2 over four weeks to patients that were no longer responsive to such chemotherapeutic agents. (Ex. 1005 ¶¶101-02.) Thus, for the same reasons as claim 58, claims 8-10 are obvious.

c. Dependent Claims 11-13 and 15

Dependent claims 11-13 and 15 recite specific structural features of the claimed anti-CD20 antibody. These features include that the anti-CD20 antibody: "is a chimeric antibody" (claim 11); "is rituximab" (claim 12, dependent on claim 11); "is a humanized antibody" (claim 13); or that "comprises a CD20-binding fragment of a chimeric, humanized, or human antibody" (claim 15). Claims 11, 12, and 15 are each met by rituximab, which is a chimeric antibody with a CD20-binding fragment. (Ex. 1005 ¶105.) To the extent that the Patent Owners contend that the claimed anti-CD20 antibodies of claims 13 to "humanized" antibody can be read to cover the structural features of rituximab, those claims are likewise disclosed by the FDA Transcript and the methods recited in claims 11-13 and 15 are obvious. (*Id*.)

d. Dependent Claims 16-20

Dependent claims 16-20 recite broad aspects of dosing schedules for administration of the anti-CD20 antibody according to claims 1 and 6. Claim 16 recites that "the anti-CD20 antibody is administered to the patient repeatedly," and claims 17 and 18, which are themselves dependent on claim 16 recite weekly administration (claim 17) for about 2 to 10 weeks (claim 18). The four once-weekly doses of rituximab used in the FDA Transcript expressly satisfy claims 16-18. (*Id.* ¶106.)

Claims 19 and 20, also dependent on claim 16, recite bi-weekly or monthly limitations on the anti-CD20 antibody dosing regimen. Modifying the weekly dosing regimen of the FDA Transcript to a biweekly or a monthly dosing schedule would have been part of routine efforts to improve the regimen, once a POSA began using higher doses of rituximab to treat CLL. (*Id.* ¶107.) Altering dosing strategies constitutes "'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 ¶107.)

Tellingly, Patent Owners' own experts asserted 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 bi-weekly or monthly dosing schedule would have been obvious to a POSA contemplating using rituximab at 500 mg/m^2 (as described by Maloney) in combination with chemotherapy. (Ex. 1005 ¶107.)

e. Dependent Claims 21-22

Dependent claim 21 recites the anti-CD20 of claims 1 or 6 be administered parenterally (non-orally) and claim 22 further recites the administration by intravenous infusion. FDA Transcript disclosed that rituximab was administered by intravenous infusions and such administration was obvious. (*Id.* ¶108.)

f. Dependent Claim 59

Claim 59 is dependent on either claim 6, 28, or 58 and adds the negative limitation "wherein radiation is not used in conjunction with the anti-CD20 antibody." None of the references for Ground I uses radiation. Accordingly claim 59 is obvious. (*Id.* ¶103.)

C. Ground 2: Claims 19-20 Are Obvious Under §103 Over the FDA Transcript, Batata, Maloney, Byrd, and Kipps

This Ground assumes that the priority date for claims 19 and 20 is either November 9, 1998 or November 9, 1999. Claims 19 and 20 recite methods for treating CLL using an anti-CD20 antibody according to independent claims 1 or 6 administered to the patient bi-weekly and monthly, respectively.

Claims 19 and 20 are obvious over the FDA Transcript, Batata, Maloney, Byrd, and Kipps. The FDA Transcript, Batata, and Maloney satisfy all limitations of claims 1 and 6, as set forth above. (Ex. 1005 ¶¶88-100.)

Thus, the only limitations of claims 19 and 20 not disclosed in the FDA Transcript, Batata, and Maloney are the requirements that rituximab be administered bi-weekly (claim 19) or monthly (claim 20). These dosing regimens would have been obvious to a POSA in light of Byrd and Kipps.

Byrd was published in February 1998 in Seminars in Oncology. (Ex. 1010.) It summarizes established and emerging therapies for CLL. 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 also discusses combination therapy of rituximab and purine analogs, such as fludarabine. The authors first note the efficacy of rituximab, both as a single agent and in combination CHOP chemotherapy, demonstrated in the 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, it discloses that "Cancer and Leukemia Group B is planning a Phase II/III study of fludarabine + IDEC-C2B8 in untreated CLL patients." (*Id.*)

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.*)

Thus, the FDA Transcript, Batata, and Maloney teach the use of unlabeled rituximab, including doses of 375 mg/m^2 and 500 mg/m^2, to treat CLL. Byrd teaches that rituximab can be combined effectively with chemotherapy for CLL, and that rituximab can chemosensitize chemotherapy-resistant NHL cell lines. It would have been obvious to a POSA seeking to take advantage of rituximab's ability to chemosensitize chemotherapy-resistant NHL cell lines, as described by Byrd, to administer rituximab bi-weekly or monthly to align with chemotherapy administration. (Ex. 1005 ¶¶109-12.)

GROUND 2	
Claim Language	***Obvious Over FDA Transcript (Ex. 1007), Batata (Ex. 1008), Byrd (Ex. 1010), and Kipps (Ex. 1055)***
19. A method according to claim 16,	*See Ground 1, claim 1, above.*

GROUND 2	
Claim Language	***Obvious Over FDA Transcript (Ex. 1007), Batata (Ex. 1008), Byrd (Ex. 1010), and Kipps (Ex. 1055)***
wherein the anti-CD20 antibody is administered to the patient biweekly.	"Treatment consisted of the antibody at 375 mg/m^2 by intravenous infusion given once weekly times 4." (Ex. 1007 at 036 (35:23-24).) Byrd discloses rituximab's ability to chemosensitize NHL cells and describes interdigitated administration of rituximab with chemotherapy. (Ex. 1010 at 006.) Kipps teaches biweekly and monthly administration of multiple standard chemotherapies for CLL. (Ex. 1055 at 034-35.)
20. A method according to claim 16, wherein the anti-CD20 antibody is administered to the patient monthly.	*See claim 19.*

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 18 and 20, a POSA would have been motivated to modify the weekly rituximab administration described in the FDA Transcript to optimize the combination of rituximab with standard chemotherapy for CLL. 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 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. v. Biocraft Labs., Inc*., 874 F.2d 804, 809 (Fed. Cir. 1989); *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).

Again, 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 Maloney) in combination with chemotherapy (as described by

Byrd) would have been motivated to use bi-weekly or monthly rituximab administration. (Ex. 1005 ¶110.)

2. Reasonable Expectation of Success

A POSA evaluating the combination of the FDA Transcript, Batata, Maloney, Byrd, and Kipps would have had a reasonable expectation that the claimed treatment regimen would be safe and efficacious. (*Id.* ¶111.) "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).

Modification of the dosing schedule 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. (Ex. 1005 ¶111.)

Furthermore, a POSA would have known that rituximab could be administered using dosing schedules less frequent than weekly dosing because of published study results using less frequent dosing. For example, Czuczman in 1996 described a study of rituximab administered in combination with CHOP in which the rituximab administration occurred on 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 ¶111.)

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, ¶18; *see also* Ex. 1050 at 002-03; Ex. 1051 at 002-03.) Claims 19 and 20 are obvious over the FDA Transcript, Batata, Maloney, Byrd, and Kipps. (Ex. 1005 ¶112.)

D. Ground 3: Claims 1-7, 11-13, 15-18, 21-22, and 59-60 Are Anticipated Under §102 by the MD Anderson Online Newsletter

This Ground assumes the priority date for claims 1, 5-7, 11-13, 15-17, 21-22, and 59-60 is November 9, 1998. This Ground assumes the priority date for claims 2-4, and 18 is either November 9, 1998 or November 9, 1999.

The MD Anderson Online Newsletter describes a trial of rituximab in patients with CLL. (Ex. 1003 at 004). The MD Anderson Online Newsletter explains that "CLL should be an excellent target disease" for use of rituximab based on the results of studies of rituximab in NHL patients and the 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 ¶86.)

As described in the MD Anderson Online Newsletter, the investigators administered 375 mg/m^2 rituximab at the first infusion, then escalated doses for the subsequent infusions to 500 mg/m^2. (Ex. 1005 ¶¶87, 113; Ex. 1003 at 004.) 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 ¶87; Ex. 1003 at 004.)

A POSA would have had a reasonable expectation that the 500 mg/m^2 dose was "an amount effective to treat CLL" in view of the MD Anderson ongoing 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 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

¶113.)

Thus, the MD Anderson Online Newsletter expressly discloses a rituximab treatment plan for CLL patients, which includes 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 ¶¶86-87, 113.) 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 1-7, 11-13, 15-18, 21-22, and 59-60, as shown below. (*Id.* ¶113.) In the alternative, because the MD Anderson Online Newsletter and the MD Anderson Print Newsletter have identical disclosures, these claims are equally anticipated by the MD Anderson Print Newsletter. (*Id.*)

GROUND 3	
Claim Language	***Anticipated By the MD Anderson Online Newsletter (Ex. 1003)***
1. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 anti body to the patient in an amount effective to treat the chronic lymphocytic leukemia,	The MD Anderson Online Newsletter describes a study of rituximab, also known as IDEC-C2B8, which is a "chimeric anti-CD20 antibody." (Ex. 1003 at 004.) "IDEC [rituximab], a new monoclonal antibody approved for the treatment of lymphoma, is under investigation in patients with CLL." (*Id.*) "CLL should be an excellent target disease for the use of the IDEC antibody." (*Id.*) "[T]he first dose would be 375 mg/m2 (about 6 hour infusion) but all subsequent doses would be higher, starting with 500 mg/m2 and escalating by 33% with

GROUND 3	
Claim Language	***Anticipated By the MD Anderson Online Newsletter (Ex. 1003)***
	subsequent patients." (*Id.*)
wherein 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.
2. A method according to claim 1, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.001 to about 30 mg/kg.	*See claim 1.* 375 mg/m^2 is equivalent to approximately 10 mg/kg and 500 mg/m^2 is equivalent to approximately 13.5 mg/kg. (Ex. 1005 ¶104.)
3. A method according to claim 1, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.01 to about 25 mg/kg.	*See claim 2.*
4. A method according to claim 1, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.1 to about 20 mg/kg.	*See claim 2.*
5. A method according to claim 1, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 375 mg/m^2.	*See claim 1.*
6. A method of treating chronic lymphocytic leukemia	*See claim 1.*

GROUND 3	
Claim Language	***Anticipated By the MD Anderson Online Newsletter (Ex. 1003)***
in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia,	
wherein the anti-CD20 antibody is administered to the patient at a dosage of about 500 to about 1500 mg/m^2,	*See claim 1.*
wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.	*See claim 1.*
7. A method according to claim 6, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 500 mg/m^2.	*See claim 6.*
11. A method according to claim 1 or 6, wherein the anti-CD20 antibody is a chimeric antibody.	*See claim 1.*
12. A method according to claim 11, wherein the anti-CD20 antibody is rituximab.	*See claims 1 and 11.*
13. A method according to claim 1	*See claim 1.*

GROUND 3	
Claim Language	***Anticipated By the MD Anderson Online Newsletter (Ex. 1003)***
or 6, wherein the anti-CD20 antibody is a humanized antibody.	To the extent Patent Owner contends "humanized antibody" can be read to cover rituximab, this claim is obvious for the same reasons as claim 1.
15. A method according to claim 1 or 6, wherein the anti-CD20 antibody comprises a CD20-binding fragment of a chimeric, humanized, or human antibody.	*See claim 1.*
16. A method according to claim 1 or 6, wherein the anti-CD20 antibody is administered to the patient repeatedly.	*See claim 1.* "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." (Ex. 1003 at 004.)
17. A method according to claim 16, wherein the anti-CD20 antibody is administered to the patient weekly.	*See claim 16.*
18. A method according to claim 16, wherein the anti-CD20 antibody is administered to the patient weekly for about 2 to 10 weeks.	*See claim 16.*
21. A method according to claim 1 or 6, wherein the anti-CD20 antibody is administered to the patient parenterally.	*See claim 1.*

GROUND 3	
Claim Language	***Anticipated By the MD Anderson Online Newsletter (Ex. 1003)***
22. A method according to claim 21, wherein the anti-CD20 antibody is administered to the patient by intravenous infusion.	*See claim 21.*
59. A method according to claim 6, 28, or 58, wherein radiation is not used in conjunction with the anti-CD20 antibody.	*See claim 58.* Radiation was not used in conjunction with the rituximab administered in the study described by the MD Anderson Online Newsletter.
60. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering a therapeutic non-radiolabeled anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia,	*See claim 1.*
wherein radiation is not used in conjunction with said anti-CD20 antibody.	*See claim 59.*

E. Ground 4: Claims 8-10, 19-20, and 58 Are Obvious Under §103 Over the MD Anderson Online Newsletter

This Ground assumes the priority date for claim 9 is November 9, 1998.

This Ground assumes the priority date for claims 8, 10, 19-20, and 58 is either November 9, 1998 or November 9, 1999.

Claims 8-10 and 58 recite limitations related to using the method of treating CLL using an anti-CD20 antibody based on the patient's previous treatment(s) for CLL. These limitations include a patient that has "relapsed following previous treatment' (claim 8), "is refractory to a treatment previously administered" (claim 9), or "is refractory to fludarabine" (claim 10 and claim 58). Because anti-CD20 antibodies such as rituximab were known to have a different mechanism of action than chemotherapeutic agents, it would have been obvious to one of skill in the art to employ the MD Anderson Online Newsletter's treatment regimen to patients that were no longer responsive to such chemotherapeutic agents. (Ex. 1005 ¶115.) Thus, claims 8-10 and 58 are obvious.

Claims 19 and 20 recite bi-weekly and monthly administration respectively of the anti-CD20 antibody. Modifying the weekly dosing regimen of the MD Anderson Newsletter to a biweekly or a monthly dosing schedule would have been part of routine efforts to improve the regimen, once a POSA began using higher doses of rituximab to treat CLL. (*Id.* ¶116.) Altering dosing strategies constitute "'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). (Ex. 1005 ¶116.) Claims 19 and 20 are therefore obvious. (*Id.*) In the alternative, these claims are equally obvious over the MD Anderson Print Newsletter. (*Id.*)

F. Ground 5: Claims 19-20 Are Obvious Under §103 Over the MD Anderson Online Newsletter, Byrd, and Kipps

This Ground assumes the priority date for claims 19-20 is either November 9, 1998 or November 9, 1999.

The sole difference between claim 1, which is anticipated by the MD Anderson Online Newsletter, *supra*, and claims 19-20 is that claims 19 and 20 require biweekly and monthly administration of rituximab, respectively. The MD Anderson Online Newsletter discloses weekly rituximab administration. (Ex. 1003 at 004.) As described in Ground 2, *supra*, Byrd teaches that rituximab can be combined effectively with chemotherapy for CLL, and that rituximab can chemosensitize chemotherapy-resistant NHL cell lines. Kipps teaches both bi-weekly and monthly (every 4 weeks) administration of standard chemotherapy for CLL. It would be 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 standard chemotherapy administration. In the alternative, these claims are equally obvious over the MD Anderson Print

Newsletter, Byrd, and Kipps. (Ex. 1005 ¶¶82, 117-19.)

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 '612 patent anticipated and/or obvious.

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 ¶¶120-27.) 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.* ¶122.) Additionally, the relatively higher number of circulating tumor load in CLL patients compared to SLL patients and the resulting potential of TLS did not result in an unexpected result. (*Id.* ¶¶123-27.) TLS was a known and manageable possibility that would not have prevented a POSA from pursuing rituximab as a treatment for CLL. (*Id.* ¶126.) 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.* ¶125.)

Petitioner is not aware of any compelling evidence of any secondary indicia

of non-obviousness having a nexus to the alleged claimed invention that challenge that conclusion that the '612 patent is obvious. Petitioner reserves the right to respond to any assertion of secondary indicia advanced by the Patent Owner.

XII. CONCLUSION

Petitioner respectfully requests institution of *inter partes* review of claims 1-13, 15-22 and 58-60 of the '612 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 13,623 words, as determined using the standard word counting feature of the Microsoft Word program.

Dated: March 31, 2017

By: */s / Michelle S. Rhyu*
Michelle S. Rhyu
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Counsel for Petitioner

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. 7,682,612,** including all exhibits (**Nos. 1001-1063)** 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
Dallas, TX 75201

Date: March 31, 2017

/s/ Maria Weiand
Maria Weiand