

Petition for *Inter Partes* Review
U.S. Patent No. 7,682,612 (combination claims)

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

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

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APPENDIX A: EXHIBIT LIST

Exhibit No.	Description
1101	U.S. Patent No. 7,682,612
1102	U.S. Provisional Application No. 60/107,658
1103	Archived website for Leukemia Insights Newsletter, 3(2) (July 2, 1998) (“MD Anderson Online Newsletter”)
1104	File History for U.S. Patent No. 7,682,612 (Excerpts)
1105	Declaration of Michael Andreeff, M.D.
1106	Protocol for Phase I/II Study of IDEC-C2B8 (Rituximab) for Relapsed CLL (DM97-236) (dated December 10, 1997) (“O’Brien Protocol”)
1107	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”)
1108	Batata, A. & Shen, B., <i>Relationship between Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: A Comparative Study of Membrane Phenotypes in 270 Cases</i> , <i>Cancer</i> (1992) 70(3):625-632 (1992) (“Batata”)
1109	Maloney, D.G. <i>et al.</i> , <i>Phase I Clinical Trial Using Escalating Single-Dose Infusion of Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients with Recurrent B-Cell Lymphoma</i> , <i>Blood</i> 84(8):2457-2466 (Oct. 15, 1994) (“Maloney 1994”)
1110	Byrd, J.C. <i>et al.</i> , <i>Old and New Therapies in Chronic Lymphocytic Leukemia: Now Is the Time for a Reassessment of Therapeutic Goals</i> , <i>Semin. Oncol.</i> 25(1):65-74 (Feb. 1998)
1111	Czuczman, M.S. <i>et al.</i> , <i>Chemoimmunotherapy of Low-Grade Lymphoma with the anti-CD20 Antibody IDEC-C2B8 in Combination with CHOP Chemotherapy</i> , <i>Cancer Invest.</i> 14:59-61 (Abstract 53) (1996) (“Czuczman”)
1112	Harris, N.L. <i>et al.</i> , <i>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</i> , <i>J. Clin. Oncol.</i>

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1113	Anderson, D.R., <i>Targeted anti-cancer therapy using rituximab, a chimaeric anti-CD20 antibody (IDEC-C2B8) in the treatment of non-Hodgkin's B-cell lymphoma</i> , Biochemical Society Transactions 25(2):705-708 (May 1997)
1114	Maloney, D.G. <i>et al.</i> , <i>IDEC-C2B8: Results of a Phase I Multiple-Dose Trial in Patients With Relapsed Non-Hodgkin's Lymphoma</i> , J. Clin. Oncol. 15(10):3266-3274 (Oct. 1997) ("Maloney Oct. 1997")
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1116	McLaughlin. P. <i>et al.</i> , <i>Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program</i> , J. Clin. Oncol. 16(8):2825-2833 (Aug. 1998) ("McLaughlin")
1117	Link, B.K. <i>et al.</i> , <i>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</i> , Abstract 7, Program/Proceedings Am. Society Clinical Oncology, 17:3a (Abstract *7) (1998) ("Link")
1118	The Non-Hodgkin's Lymphoma Pathologic Classification Project, <i>National Cancer Institute Sponsored Study of Classifications of Non-Hodgkin's Lymphomas: Summary and Description of a Working Formulation for Clinical Usage</i> , Cancer 49(10):2112-2135 (May 15, 1982)
1119	Harris, N.L. <i>et al.</i> , <i>A Revised European-American Classification of Lymphoid Neoplasms: A Proposal From the International Lymphoma Study Group</i> , Blood 84(5):1361-1392 (Sept. 1, 1994)
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1122	Cheson, B.D. <i>et al.</i> , <i>National Cancer Institute-Sponsored Working Group Guidelines for Chronic Lymphocytic Leukemia: Revised Guidelines for Diagnosis and Treatment</i> , Blood 87(12):4990-4997 (June 15, 1996)
1123	Ford, S.M. & Donegan, S.E., <i>Immunotherapeutic Approaches to Treatment of B-Cell Neoplasms: Focus on Unconjugated Antibodies</i> , Highlights in Oncology Practice 16(2):40-50 (1998)
1124	Hall, A.G. & Tilby, M.J., <i>Mechanisms of Action of, and Modes of Resistance to, Alkylating Agents Used in the Treatment of Haematological Malignancies</i> , Blood Reviews 163-173 (1992)
1125	Begleiter, A. <i>et al.</i> , <i>Chlorambucil in Chronic Lymphocytic Leukemia: Mechanism of Action</i> , Leuk. Lymphoma 23:187-201 (1996)
1126	Keating, M.J. <i>et al.</i> , <i>Long-Term Follow-Up of Patients With Chronic Lymphocytic Leukemia (CLL) Receiving Fludarabine Regimens as Initial Therapy</i> , Blood 92(4):1165-1171 (Aug. 15, 1998)
1127	Johnson, S. <i>et al.</i> , <i>Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukaemia</i> , Lancet 347:1432-1438 (May 5, 1996)
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1136	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")
1137	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")
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1139	U.S. Patent Application No. 09/372,202
1140	Stashenko, P. <i>et al.</i> , <i>Characterization of a Human B Lymphocyte-Specific Antigen</i> , <i>J. Immunol.</i> 125(4):1678-1685 (Oct. 1980)
1141	Anderson, K.C. <i>et al.</i> , <i>Expression of Human B Cell-Associated Antigens on Leukemias and Lymphomas: A Model of Human B Cell Differentiation</i> , <i>Blood</i> 63(6):1424-1433 (June 1984) ("Anderson 1984")
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1144	Foon, K.A. & Fisher, <i>Chapter 111: Lymphomas</i> , in <i>Williams Hematology</i> , Fifth Edition, 1076-1096 (Beutler, E. <i>et al.</i> , eds., 1995)
1145	Almasri, N.M. <i>et al.</i> , <i>Reduced Expression of CD20 Antigen as a Characteristic Marker for Chronic Lymphocytic Leukemia</i> ,

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1150	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”)
1151	Declaration of Dr. Steven Edward Coutré, M.D., in opposition to European Patent No. EP-B1 1 616 572, dated February 3, 2014 (“Coutré EP Decl., D92”)
1152	WO 94/11026
1153	U.S. Patent No. 6,455,043 (“the ’043 patent”)
1154	FDA FOIA Response Letter (August 26, 2016)
1155	Kipps, T.J., <i>Chapter 106: Chronic lymphocytic leukemia and related diseases</i> , in <i>Williams Hematology</i> , Fifth Edition, 1017-1039 (Beutler, E. <i>et al.</i> , eds., 1995)
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1161	Exhibit Number Not Used
1162	Exhibit Number Not Used
1163	Leukemia Insights Newsletter, 3(2) (Summer 1998) (“MD Anderson Print Newsletter”)
1164	Declaration of Christopher Butler, Internet Archive, dated December 20, 2016, authenticating Archived website for Leukemia Insights Newsletter, 3(2) (July 2, 1998), Exhibit 1103
1165	IDEC Pharmaceuticals Corporation Press Release, <i>IDEC Pharmaceuticals and Genentech Announce Positive Final Results for Pivotal Phase III Trial of IDEC-C2B8 as Single Agent</i> (Dec. 9, 1996)
1166	Czuczman, M.S. <i>et al.</i> , <i>IDEC-C2B8 (Rituximab) Alone and in Combination with CHOP in the Treatment of Low-Grade B-Cell Lymphoma</i> , <i>Cancer Invest.</i> , 16 (Suppl. 1):21-22 (Abstract 17) (1998) (“Czuczman Nov. 1997”)

APPENDIX B: CLAIM LIST

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

24. A method according to claim 23, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.001 to about 30 mg/kg.

25. A method according to claim 23, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.01 to about 25 mg/kg.

26. A method according to claim 23, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.1 to about 20 mg/kg.

27. A method according to claim 23, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 375 mg/m².

28. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 500 to about 1500 mg/m², wherein the anti-CD20 antibody therapy is combined with chemotherapy,

and wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.

29. A method according to claim 28, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 500 mg/m².

30. A method according to claim 23 or 28, wherein the patient has relapsed following previous treatment for the chronic lymphocytic leukemia.

31. A method according to claim 23 or 28, wherein the patient is refractory to a treatment previously administered for the chronic lymphocytic leukemia.

32. A method according to claim 31, wherein the patient is refractory to fludarabine.

33. A method according to claim 23 or 28, wherein the anti-CD20 antibody is a chimeric antibody.

34. A method according to claim 33, wherein the anti-CD20 antibody is rituximab.

35. A method according to claim 23 or 28, wherein the anti-CD20 antibody is a humanized antibody.

37. A method according to claim 23 or 28, wherein the anti-CD20 antibody comprises a CD20-binding fragment of a chimeric, humanized, or human antibody.

38. A method according to claim 23 or 28, wherein the anti-CD20 antibody is administered to the patient repeatedly.

39. A method according to claim 38, wherein the anti-CD20 antibody is administered to the patient weekly.

40. A method according to claim 38, wherein the anti-CD20 antibody is administered to the patient weekly for about 2 to 10 weeks.

41. A method according to claim 38, wherein the anti-CD20 antibody is administered to the patient biweekly.

42. A method according to claim 38, wherein the anti-CD20 antibody is administered to the patient monthly.

43. A method according to claim 23 or 28, wherein the anti-CD20 antibody is administered to the patient parenterally.

44. A method according to claim 43, wherein the anti-CD20 antibody is administered to the patient by intravenous infusion.

45. A method according to claim 23 or 28, wherein the anti-CD20 antibody therapy and the chemotherapy are administered to the patient concurrently.

46. A method according to claim 23 or 28, wherein the chemotherapy comprises chlorambucil.

47. A method according to claim 23 or 28, wherein the chemotherapy comprises cyclophosphamide.

48. A method according to claim 47, wherein the chemotherapy comprises cyclophosphamide, vincristine, and prednisone (COP).

49. A method according to claim 47, wherein the chemotherapy comprises cyclophosphamide, vincristine, prednisone, and doxorubicin (CHOP).

50. A method according to claim 23 or 28, wherein the chemotherapy comprises vincristine.

51. A method according to claim 23 or 28, wherein the chemotherapy comprises prednisone.

52. A method according to claim 23 or 28, wherein the chemotherapy comprises doxorubicin.

53. A method according to claim 23 or 28, wherein the chemotherapy comprises fludarabine.

54. A method according to claim 23 or 28, wherein the chemotherapy comprises methotrexate.

55. A method according to claim 23 or 28, wherein the chemotherapy comprises cisplatin.

56. A method according to claim 23 or 28, wherein the chemotherapy comprises toremifene.

57. A method according to claim 23 or 28, chemotherapy comprises tamoxifen.

(Ex. 1101 at 8:58-10:35.)

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 23-35 and 37-57 of U.S. Patent No. 7,682,612 (“the ’612 patent”). The ’612 patent is assigned to Biogen, Inc. (“Biogen”) and Genentech, Inc. (“Genentech”) (collectively, “Patent Owners” or “Applicants”). Review should be instituted because there is a reasonable likelihood Celltrion will demonstrate that the challenged claims of the ’612 patent are obvious.

The challenged claims of the ’612 patent relate to the obvious use of an anti-CD20 antibody combined with chemotherapy to treat patients with chronic lymphocytic leukemia (“CLL”), a cancer 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, could eradicate the B-cells that cause CLL when administered in combination with chemotherapy. (Ex. 1105 ¶39.) Specifically, it was well-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. 1108 at 002 (emphasis added); Ex. 1105 ¶23.)

Independent claims 23 and 28 of the '612 patent challenged in this petition recite broad methods for treating CLL by administering anti-CD20 antibody therapy in combination with chemotherapy. Claim 23 has no dosing limitations for the anti-CD20 antibody or chemotherapy. Claim 28 recites the administration of anti-CD20 antibody at “a dosage of about 500 to about 1500 mg/m². As set forth in the Declaration of Dr. Michael Andreeff (Ex. 1105), a person of ordinary skill in the art (“POSA”) would have found obvious the administration of rituximab in a dosage of 375 mg/m² or higher, such as 500 mg/m², in combination with chemotherapy to treat CLL, since it was already known that such treatments were effective for treating SLL. Accordingly, independent claims 23 and 28 of the '612 patent are invalid under 35 U.S.C. §103.

The challenged dependent claims add nothing to negate a finding of obviousness. Claims 24-27 and 29 recite the combination of anti-CD20 antibody therapy and chemotherapy using doses of anti-CD20 antibody that cover the 375 and 500 mg/m² doses of rituximab disclosed in the prior art. Claims 30-32 recite using an anti-CD20 antibody in combination with chemotherapy to treat patients who are not responding to other treatments. It was obvious to use a combination of rituximab and chemotherapy to treat a patient if other treatments were not working. Claims 33-35 and 37 recite structural features of the claimed anti-CD20 antibody

that are all met by the structure of rituximab. Claims 38-42 recite multi-dosing schedules of the anti-CD20 antibody that are repeated, such as on a weekly, biweekly, or monthly basis. The prior art already disclosed multi-dosing rituximab regimens that included multiple doses on the same week, weekly dosing, and dosing intervals of three weeks and six weeks. The dosing schedules recited in claims 38-42 were therefore either expressly disclosed in the art or mere routine variations from within the range of dosing schedules already disclosed in the prior art. The prior art also used intravenous infusion as recited in claims 43-44. Claims 45-57 recite using specific chemotherapeutic agents in combination with rituximab that are either expressly disclosed in the prior art or obvious variations thereof. Dependent claims 24-27, 29-35, and 37-57 are therefore unpatentable under 35 U.S.C. §103.

Petitioner respectfully requests institution of *inter partes* review of 23-35, and 37-57 due to the reasonable likelihood the claims are obvious.

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

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

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

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

Simultaneously with the instant petition, Petitioner has filed another petition for *inter partes* review of U.S. Patent No. 7,682,612 (single agent claims) as well as a petition for *inter partes* review of U.S. Patent No. 8,206,711. Biogen, Inc. (“Biogen”) and Genentech, Inc. (“Genentech”) are the owners of the following U.S. applications and patent 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))

LEAD COUNSEL	BACK-UP COUNSEL
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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 23-35 and 37-57 of the '612 patent and is accompanied by a payment of \$33,400, which comprises an \$11,800 request fee and \$21,600 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 23-35 and 37-57 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 is supported by the accompanying declaration of Dr. Michael Andreeff.

Ground	'612 Patent Claims	Basis for Unpatentability
Ground 1	23-35, 37-57	Obvious under §103 over the combination of Czuczman, the FDA Transcript, Batata, and Maloney
Ground 2	23-35, 37-	Obvious under §103 over Byrd and the MD Anderson

	57	Online Newsletter
Ground 3	41-42	Obvious under §103 over Byrd, the MD Anderson Online Newsletter, and Kipps

Czuczman, the FDA Transcript, Batata, Maloney, and Kipps are §102(b) prior art to the '612 patent because each reference was published or made publicly available more than one year before the effective filing date of the earliest parent application for the '612 patent. Byrd and the MD Anderson Online Newsletter are also prior art under §102(b) to all claims challenged in this petition because the challenged claims are not entitled to a priority date before November 9, 1999.

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 NHL¹ caused by small lymphocytic B-cell tumors “involving peripheral blood, bone marrow, lymph nodes, spleen, and other organs.” (Ex. 1145 at 002.)

Despite the labels “leukemia” and “lymphoma,” SLL and CLL have been

¹ NHL is a form of lymphoma affecting B-cells or T-cells and is distinct from the cancer known as Hodgkin’s Lymphoma. (Ex. 1144 at 023, 026-27.) B-cell NHLs comprise about 80% of all adult NHLs and are more prevalent than T-cell NHLs. (*Id.* at 027.)

known as “different tissue expressions of *the same disease* process.” (Ex. 1108 at 002 (emphasis added); Ex. 1105 ¶23.) In 1997, the World Health Organization concluded: “CLL and SLL are one disease at different stages, not two separate entities.” (Ex. 1112 at 012.)

The SLL and CLL labels are merely based on the location of the diseased B-cells. (Ex. 1105 ¶25.) 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. 1144 at 026.) Clinical evidence suggests that in 40% of patients categorized under SLL, the disease “evolves into a leukemic phase indistinguishable from CLL.” (Ex. 1105 ¶25; Ex. 1108 at 002; Ex. 1160 at 002.)

Clinical assessment of SLL versus CLL is often based on the patient’s total lymphocyte count. (Ex. 1105 ¶26.) 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. 1108 at 003; Ex. 1122 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. 1105 ¶¶23, 26; Ex. 1108 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. 1139 at 027.) Grillo-López captured this equivalence by grouping CLL and SLL together: “diffuse small lymphocytic lymphoma/chronic lymphocytic leukemia (CLL).” (*Id.* at 012.) Finally, the claims of the patent that issued from the co-pending application identify CLL as a type of “B-cell *lymphoma*.” (Ex. 1153 at 23:13-16 (claim 6) (emphasis added).)

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. 1119 at 010 (“Lymphoma Type: B-CLL/SLL”); Ex. 1145 at 002 (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. 1118 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. 1119 at 010 (“Lymphoma Type: B-CLL/SLL”).) Other classifications also consistently group CLL and SLL together as the same NHL type. (Ex. 1105 ¶¶27-28.)

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. 1144 at 029.) Doctors with CLL patients regularly looked to SLL therapies, and vice versa, for treatment options. (*See* Ex. 1160 at 002; Ex. 1105 ¶29.)

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. 1105 ¶30.) Alkylating agents, such as chlorambucil and cyclophosphamide, were considered valuable cytotoxic drugs for treating SLL and CLL. (*Id.*; Ex. 1124 at 003.) In

addition to alkylating agents, fludarabine, a nucleotide analog, was used to treat CLL since the early 1990s. (Ex. 1105 ¶31.) 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.* ¶¶31-32; Ex. 1110 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. 1155 at 035-036.)

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. 1105 ¶34; Ex. 1123 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. 1105 ¶34.)

CD20 is a protein that appears on B-cells during certain phases of B-cell differentiation. (*Id.* ¶35; Ex. 1140 at 002.) 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. 1105 ¶35; Ex. 1142 at 003; Ex. 1141 at 006.) That CLL and SLL cells express similar levels of CD20 was known in the early

1990s. (Ex. 1108 at 008.) Both CLL and SLL B-cells express CD20 at a lower level than other NHLs. (Ex. 1105 ¶36; Ex. 1145 at 003; Ex. 1107 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. 1105 ¶37; Ex. 1113 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. 1105 ¶38; Ex. 1134 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. 1105 ¶40; Ex. 1109 at 003.) In that study by Maloney, fifteen patients

² By November 9, 1997, IDEC-C2B8 was also known as rituximab. (*See, e.g.*, Ex. 1113 at 002.)

with relapsed low-grade B-cell NHL received one intravenous infusion of 10, 50, 100, 250, or **500 mg/m²** rituximab. (Ex. 1109 at 003 (Abstract).) One SLL (IWF group A) patient received a dose of 50 mg/m² 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/m² dose, and “no dose-limiting toxicities were identified,” though some manageable infusion-related side effects were observed. (Ex. 1105 ¶40; Ex. 1109 at 009.)

McLaughlin reported on August 7, 1998 that rituximab was an effective treatment for SLL. (Ex. 1116.) 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/m² 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 patent⁴, some CLL patients could have been included in the study. (Ex. 1105 ¶43.)

Further studies demonstrated that rituximab could be administered in combination with chemotherapy. For example, Czuczman reports on a Phase II study of patients with low-grade or follicular NHL; 23% were SLL patients. (Ex. 1166 at 003.) This study evaluated the safety and efficacy of rituximab combined with CHOP chemotherapy. (*Id.*) The rationale for combining rituximab with CHOP was their “single-agent efficacy; non-cross-resistant mechanisms of action; no apparent overlapping toxicities; and in-vitro data suggesting [rituximab’s] ability to sensitize drug-resistant human B-cell lymphoma cell lines to

³ 4,000 lymphocytes/ μL is identical to 4×10^9 lymphocytes/L. (Ex. 1105 ¶43 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. 1105 ¶51 n.5.)

chemotherapy.” (*Id.*) The response rate for the 35 patients completing all scheduled therapy was 100%. (*Id.*) The investigators concluded that “chemoimmunotherapy with RITUXAN/CHOP may be more efficacious than CHOP alone, with minimal additional toxicity.” (*Id.*)

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 35 claims of the '612 patent that require that the claimed methods “comprise administering anti-CD20 antibody,” and “wherein the anti-CD20 antibody therapy is combined with chemotherapy.” The claims cover administering rituximab in combination with chemotherapy generally and with a series of chemotherapeutic agents.

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, the priority date for all of the challenged claims 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. 1102 at 004-05.) Examples of such hematological malignancies include B-pro-lymphocytic leukemia (B-PLL), chronic lymphocytic leukemia (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).)

The disclosure states, “*it may be desirable* to combine” the administration of rituximab “with other treatments, e.g., radioactive therapy, both targeted and non-

targeted, chemotherapies, and lymphokine or cytokine administrations, e.g., interleukins, interferons, TNF's, colony stimulating factors, etc.” (*Id.* at 009 (emphasis added).) While the specification asserts that a “particularly preferred chemotherapeutic regimen that may be used with the subject antibody immunotherapy comprises CHOP” and identifies other chemotherapeutic agents such as “methotrexate, cisplatin, toremifene and tamoxifen” (*id.* at 010), it does not disclose fludarabine or chlorambucil. Nor does it disclose dosing regimens for any combination therapies or examples to support the efficacy of any such combination therapies. (*Id.*; Ex. 1105 ¶59.)

2. The '347 application

Like the '658 provisional application, the '347 application contends that the ability of rituximab to treat CLL was surprising. (Ex. 1104 at 010-11.)

The '347 application adds Example 5, labeled “Combination Antibody and Chemotherapy Protocol” (*Id.* at 021-23), which describes chemotherapy agents used to treat CLL. (Ex. 1105 ¶61.) This November 9, 1999 application is the first identification of fludarabine as a single agent to treat CLL. (*Id.*) Example 5 is a description of the CALGB trial of rituximab and fludarabine, which was disclosed in the prior art. (*Id.*; *See* Ex. 1110 at 006; Ex. 1129 at 007.) Furthermore, the example does not disclose any dosing regimens for a treatment combining both

chemotherapy and rituximab into a single treatment protocol. (Ex. 1105 ¶¶61.) The example merely states that a Phase II trial in which rituximab and fludarabine are administered concurrently is “currently being conducted.” (*Id.*; Ex. 1104 at 023.)

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. 1104 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. 1108 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. The 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. 1104 at 417.) Both of

these assertions are directly contradicted by the understanding in the prior art: CLL and SLL tumor cells are different tissue expressions of the same disease process. (Ex. 1105 ¶¶23, 142; Ex. 1108 at 002.)

The biological equivalence of 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. 1104 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. 1105 ¶¶23-24, 142.)

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. 1104 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 using rituximab at dosing levels of 150, 375, and 500 mg/m² 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/m².

C. The Challenged Claims of the '612 Patent 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. Techs.*, 627 F.3d at 870 (citations omitted). “A disclosure in a parent application that merely renders the later-claimed invention obvious is not sufficient to meet the written description requirement; the disclosure must describe the claimed invention with all its limitations.” *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1158 (Fed. Cir. 1998). Once Petitioner “has established a prima facie case of invalidity,” Patentees bear the burden “to come forward with evidence to prove entitlement to claim priority to an earlier filing date.” *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1305-06 (Fed. Cir. 2008).

Here, all challenged claims recite combination therapies with both rituximab and chemotherapeutic agents. The specification of the ’658 provisional application lacks legally sufficient written description or enablement support for these claims. There is not a single example, reference study or any demonstrated results indicating that the inventors had possession of and taught a POSA how to practice the full scope of these combination therapy claims in the ’658 provisional application. Moreover, there is no mention in the provisional application anywhere of using chemotherapeutic agents fludarabine or chlorambucil. Even if using such

agents was obvious, that is not sufficient to meet the requirement for adequate written description. *See Research Corp.*, 627 F.3d at 870. Accordingly, the claims of the '612 patent challenged in this petition cannot rely on the '658 provisional application to establish an earlier filing date than November 9, 1999.⁵

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

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

⁵ Petitioner reserves the right to respond to any assertion by Patent Owner that the '658 provisional application provides an adequate supporting disclosure of the challenged claims of the '612 patent to entitle them to an earlier priority date.

(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. 1105 ¶49; *see* Ex. 1155 at 023; Ex. 1108 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. 1139 at 027; Ex. 1108 at 002; Ex. 1105 ¶¶23, 49.)

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. 1101 at 1:58-67.) By 1998, there were various thresholds used to identify a patient under SLL or CLL. (*See* Ex. 1108 at 003 and Ex. 1155 at 030 (CLL determined based on “>4,000 lymphocytes/ μl ”); Ex. 1122 at 003 (identifying 5,000 cells/ μl and 10,000 cells/ μl as thresholds for CLL); Ex. 1105 ¶50.) In Example 3 of the patent, CLL patients are identified as having “[m]edian white blood cell count⁶ [of] $40 \times 10^9/\text{L}$ (range, 4-200).”⁷ (Ex. 1101 at 6:12-13.)

⁶ A white blood cell count of 4,000 *cells*/ μl corresponds to fewer than 4,000

lymphocytes/ μl (Ex. 1005 ¶51 n.5.)

⁷ $4-200 \times 10^9/\text{L}$ is the same as 4,000-200,000 per μl . (Ex. 1105 ¶51.)

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/ μ l. However, Petitioner's arguments apply with or without a white blood cell count limitation.

2. “effective to treat the chronic lymphocytic leukemia”

The broadest reasonable construction of “effective to treat the CLL” is “a therapeutic response such as a reduction in the number of the small lymphocytic tumor cells.” During prosecution, the Applicants 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. 1104 at 256 (emphasis added); Ex. 1105 ¶¶52-53.) Petitioner's construction is consistent with this broad prosecution statement.⁸

⁸ Applying a different claim construction standard than the “broadest reasonable 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

3. “concurrently”

The broadest reasonable construction of “concurrently” in the context of claim 45 is “an overlap in the administration of the anti-CD20 antibody therapy and chemotherapy.” Claim 45 recites “wherein the anti-CD20 antibody therapy and the chemotherapy are administered to the patient concurrently.” As recited, the claim is directed to concurrent administration of the singular anti-CD20 antibody *therapy* and singular chemotherapy. Since it was known in the art that both anti-CD20 antibody therapy and chemotherapy can be and, in fact, were commonly delivered over the course of multiple administrations spanning many weeks, the broadest reasonable construction of “concurrent” in the context of the ’612 patent is that there need only be some overlap of the therapies being administered. (Ex. 1105 ¶54.)

This construction is further consistent with the different antecedent bases for the “administering an anti-CD20 antibody to the patient” and “the anti-CD20 antibody *therapy*” limitations of the claims. For example, independent claim 23 recites, in part: “administering an anti-CD20 antibody to the patient in an amount

the broadest reasonable construction that a POSA would apply to the term.

Nevertheless, even under that construction, the ’612 patent is obvious as explained in each of the Grounds below.

effective to treat the chronic lymphocytic leukemia, wherein the anti-CD20 antibody therapy is combined with chemotherapy.” The antecedent basis for the singular “the anti-CD20 antibody therapy” is the dosing regimen associated with “administering an anti-CD20 antibody to the patient.” For the claims expressly reciting the administration of multiple doses of anti-CD20 antibody to the patient, such as “wherein the anti-CD20 antibody is administered to the patient weekly for about 2 to 10 weeks” recited in dependent claim 40, “the anti-CD20 antibody *therapy*” is the weekly administration of the anti-CD20 antibody for about 2 to 10 weeks. Hence, the claim language further confirms that the “anti-CD20 antibody therapy” and the “chemotherapy” cover the full course of the dosing protocols associated with the administration of the anti-CD20 antibody and chemotherapeutic agents. When there is an overlap in the administration of these therapies, the administration occurs “concurrently.” (Ex. 1105 ¶¶54-55.)

VIII. PERSON OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art 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. (Ex. 1105 ¶15.)

IX. THE SCOPE AND CONTENT OF THE PRIOR ART

Petitioner relies on the following publications:

A. Czuczman (Ex. 1111)

Czuczman is an abstract entitled “Chemoimmunotherapy of Low-Grade Lymphoma with the Anti-CD20 Antibody IDEC-C2B8 in Combination with CHOP Chemotherapy.” The disclosure in Czuczman describes results from a clinical trial using rituximab in combination with CHOP chemotherapy (cyclophosphamide), as set forth above in Section V.E. It was published in 1996 in the journal *Cancer Investigations*. Czuczman is §102(b) prior art to all claims of the ’612 patent.

B. July 1997 FDA Biological Response Modifiers Advisory Committee Hearing (“FDA Transcript”) (Ex. 1107)

On July 25, 1997, the FDA’s Biological Response Modifiers Advisory Committee held an open public hearing with representatives from IDEC Pharmaceuticals, including two of the named inventors of the ’612 patent, Dr. Antonio Grillo-López and Dr. Christine A. White. (Ex. 1107.) 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. 1154 (“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.

C. Batata (Ex. 1108)

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.

D. Maloney (Ex. 1109)

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 therefore §102(b) prior art to all claims of the ’612 patent.

E. Byrd (Ex. 1110)

Byrd is an article entitled “Old and New Therapies in Chronic Lymphocytic Leukemia: Now Is the Time for a Reassessment of Therapeutic Goals.” (Ex. 1110 at 003.) It was published in February 1998 in the journal *Seminars in Oncology*.

(*Id.*) Byrd is §102(b) prior art to all challenged claims, assuming that the claims are not entitled to the November 9, 1998 provisional filing date.

F. The MD Anderson Online Newsletter (Ex. 1103)

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. 1105 ¶¶77; Ex. 1106.) As detailed in his declaration, Dr. Andreeff collaborated in the study. (Ex. 1105 ¶¶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 patients⁹. (Ex. 1105 ¶¶79-80; Ex. 1163.) MD Anderson distributed printed copies of the MD Anderson Print Newsletter to several thousand referring Hematology-Oncology physicians in the U.S. (Ex. 1105 ¶¶81.)

Dr. Andreeff explains that Dr. Charles Koller was in charge of making the MD Anderson Print Newsletter available online. (Ex. 1105 ¶¶82.) The Summer

⁹ As explained by Dr. Andreeff, due to a printing error, the newsletter was originally printed with the date “Summer 1997,” and the editor manually corrected the printed edition to read “Summer 1998.” (Ex. 1105 ¶¶79-80.)

1998 edition of the MD Anderson Online Newsletter appears in the Internet Archive Wayback Machine beginning February 8, 1999. (Ex. 1103; accessed December 14, 2016.)¹⁰ As shown in the Internet Archive Wayback Machine, the online newsletter was last modified on July 2, 1998, and Dr. Andreeff explains that the content of the online newsletter would have been publicly available online as of this “last modified” date. (Ex. 1105 ¶¶82; Ex. 1103 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 both §102(b) prior

¹⁰ The Butler Declaration verifies that the Wayback Machine Archive assigns a URL in the format [http://web.archive.org/web/\[Year in yyyy\]\[Month in mm\]\[Day in dd\]\[Time code in hh:mm:ss\]/\[Archived URL\]](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. 1164 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-C2B8>, the record of the file was archived on February 8, 1999. (*Id.* at 004.)

art to all challenged claims, assuming that the claims are not entitled to the November 9, 1998 provisional filing date. Both newsletters include identical descriptions of the O'Brien study. (Ex. 1103 at 004; Ex. 1163 at 002; Ex. 1105 ¶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. 1105 ¶¶82-85.) 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 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. Kipps (Ex. 1155)

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.

H. Background Art

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

X. THERE IS A REASONABLE LIKELIHOOD THE CLAIMS OF THE '612 PATENT ARE INVALID

A. Legal Standard for Obviousness

The question of 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 (P.T.A.B. Feb. 23, 2015). The Board further noted that the experimentation to achieve the claimed regimen was “‘nothing more than the routine’ application of a well-known problem solving strategy . . . ‘the work of a skilled [artisan], not of an inventor.’” *Id.* at 14 (citing *Pfizer*, 480 F.3d at 1368).

B. Ground 1: All Challenged Claims Are Obvious Under §103 Over Czuczman, the FDA Transcript, Batata, and Maloney

This ground assumes a priority date for all challenged claims of November 9, 1998. All of the challenged claims are obvious under §103 over Czuczman (Ex. 1111), the FDA Transcript (Ex. 1107), Batata (Ex. 1108), and Maloney (Ex. 1109).

This ground first discusses why the independent claims (claims 23 and 28) are obvious before addressing the added limitations of the remaining challenged dependent claims.

1. Independent Claims 23 and 28

Claim 23 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) wherein the anti-CD20 antibody therapy is combined with chemotherapy; and (3) the method does not include treatment with a radiolabeled anti-CD20 antibody. Claim 28 adds a fourth limitation: administering the anti-CD20 antibody “at a dosage of about 500 to about 1500 mg/m².”

Czuczman is an abstract published in Cancer Investigation reporting on an ongoing phase II study of patients with low-grade or follicular NHL. (Ex. 1111 at 002-03.) This study evaluated the safety and efficacy of rituximab in combination with the chemotherapy treatment of cyclophosphamide, doxorubicin, vincristine,

and prednisone (“CHOP”). (*Id.*) Czuczman explains that rituximab has “synergistic antitumor activity with certain chemotherapeutic agents” and that, compared to CHOP, rituximab has “non-cross-resistant mechanisms of action, individual efficacy, [and] nonoverlapping toxicities.” (*Id.* at 003.) Rituximab was administered at 375 mg/m² on weeks 1 (2 doses), 7, 13, 20, and 21. (*Id.*) Czuczman reports results from 14 patients, of which twelve were previously untreated, and four were IWF type A (SLL/CLL) Overall the response rate for the 11 patients completing all scheduled therapy was 100%. (*Id.*) The investigators concluded that “[c]urrent efficacy and toxicity data appear encouraging and the finding of molecular remissions by PCR suggests that the antitumor activity of CHOP and [rituximab] is superior to CHOP therapy alone.” (*Id.*; Ex. 1105 ¶¶62-64.)

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. 1107 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) involving a total of 203 patients with relapsed or refractory low-grade or follicular B-cell NHL. (Ex. 1107 at 036 (35:13-17).) These patients were administered “375 mg/m² [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. 1105 ¶¶27-28, 67; Ex. 1119 at 010 (Table 4); Ex. 1120 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. 1107 at 043 (42:18-19), 044 (43:18-19).) 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 044-45 (43:18-44:8).) Further, Dr. Grillo-López stated that the “Class A” patients who did respond had “a time to progression and a duration of response which was not significantly different from the rest of the population, so they did have responses that were as durable as that of the other B, C, D patients.” (*Id.* at 069-70 (68:22-69:2).)

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).)

Moreover, when asked to comment on the lower response rate of 11% among Class A patients (*id.* at 068(67:10-15)), Dr. Grillo-López acknowledged that “the Class As tend to have a lower antigen density on the cell surface” and referred to observations of samples obtained from M.D. Anderson showing “the CLL’s have a lower and more heterogeneous CD20 expression.” (*Id.* at 069 (68:12-20).) Dr. Grillo-López explained that Class As “did not deplete their circulating cells as well as the B, C, D’s, and there is a correlation between response and B-cell depletion.” (*Id.* at 070 (69:6-8).) Thus, Dr. Grillo-López concluded: “there is the implication here that [Class As] may benefit from higher doses or more doses of the antibody [rituximab]” (*Id.* at 071 (70:13-16); Ex. 1105 ¶¶65-70.)

Batata is an August 1, 1992 Cancer article. (Ex. 1108.) 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; Ex. 1105 ¶¶71-72.)

Maloney is an October 1994 article published in *Blood*. (Ex. 1109.) Maloney describes a dose escalation study to ascertain rituximab’s toxicity in human patients. (Ex. 1105 ¶40; Ex. 1109 at 003.) Patients with relapsed low-grade B-cell NHL, including one SLL patient, received one intravenous infusion of up to 500 mg/m² rituximab. (Ex. 1109 at 005-06.) Ultimately, all tested doses were well tolerated, including the 500 mg/m² dose, and “no dose-limiting toxicities were identified,” though some manageable infusion-related side effects were observed. (Ex. 1105 ¶40; Ex. 1109 at 009.)

The examiner did not consider Czuczman or the FDA Transcript during prosecution of the ’612 patent. The only difference between what is disclosed in Czuczman and what is recited in claim 23 is that in claim 23, rituximab is used to treat CLL patients specifically, rather than Czuczman’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, and the FDA Transcript explicitly states that rituximab had shown “sufficient evidence of efficacy” for CLL patients. (Ex. 1107 at 117 (116:12-18).)

The only difference between claim 23 and claim 28 is that claim 28 requires at least one dosage of 500 to 1500 mg/m². The FDA Transcript suggests using such a higher dosage for SLL/CLL patients, and Maloney discloses dosing rituximab at 500 mg/m². None of these three references used a radiolabeled anti-CD20 antibody. Thus, claims 23 and 28 are obvious under §103 over Czuczman, the FDA Transcript, Batata, and Maloney as shown below (Ex. 1105 ¶¶90):

GROUND 1	
<u>Claim Language</u>	<i>Obvious Over Czuczman (Ex. 1111), the FDA Transcript (Ex. 1107), Batata (Ex. 1108), and Maloney (Ex. 1109)</i>
<p>23. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia,</p>	<p>“Overall response rate for the 11 patients completing all scheduled therapy is 100%.” (Ex. 1111 at 003.)</p> <p>The FDA Transcript describes study results of treatment with rituximab/IDEC-C2B8, which is “a chimeric anti-CD20 antibody.” (Ex. 1107 at 026 (25:4-5).)</p> <p>“Treatment consisted of the antibody at 375 mg/m² by intravenous infusion given once weekly times 4.” (<i>Id.</i> at 036 (35:23-24).)</p> <p>FDA Transcript discloses that 37 IWF type A patients were treated with rituximab, that the patients “do have important clinical benefit,” and that “of the 37 patients, 28 had some tumor shrinkage” (<i>Id.</i> at 044 (43:16-24).)</p> <p>“I think we already heard that this Group A population contained a number of patients . . . presumably <i>some with a lymphomatous phase of CLL.</i>” (<i>Id.</i> at 117</p>

GROUND 1	
<u>Claim Language</u>	<i>Obvious Over Czuczman (Ex. 1111), the FDA Transcript (Ex. 1107), Batata (Ex. 1108), and Maloney (Ex. 1109)</i>
	(116:12-18) (emphasis added). “[T]he similarity of membrane phenotypes between <i>CLL and SLL</i> provided evidence that the two are different tissue expressions of <i>the same disease process.</i> ” (Ex. 1108 at 002 (Abstract) (emphasis added).)
wherein the anti-CD20 antibody therapy is combined with chemotherapy,	Czuczman describes treating low-grade NHL patients, including 4 IWF type A patients, with a combination of 375 mg/m ² rituximab/IDEC-C2B8 and CHOP. Czuczman explains that rituximab is “a chimeric anti-CD20 antibody.” (Ex. 1111 at 003.) “Characteristics of these 14 patients include . . . IWF A = 4 . . . Overall response rate for the 11 patients completing all scheduled therapy is 100% (8 complete remission-CR and 3 partial remission-PR).” (<i>Id.</i>)
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.
28. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia,	<i>See claim 23.</i>
wherein the anti-CD20 antibody is administered to the patient at a dosage	“[Class A patients] did not deplete their circulating cells as well as the B, C, D’s, and there is a correlation between response and B-cell depletion” and “there is

GROUND 1	
<u>Claim Language</u>	<i>Obvious Over Czuczman (Ex. 1111), the FDA Transcript (Ex. 1107), Batata (Ex. 1108), and Maloney (Ex. 1109)</i>
of about 500 to about 1500 mg/m ² ,	the implication here that <i>these patients may benefit from higher doses</i> or more doses of the antibody” (Ex. 1107 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. No dose-limiting toxicities were identified. (Ex. 1109 at 009.)
wherein the anti-CD20 antibody therapy is combined with chemotherapy,	<i>See claim 23.</i>
and wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.	<i>See claim 23.</i>

a. Motivation To Combine

(1) A POSA would have been motivated to use rituximab, an anti-CD20 antibody, in combination with chemotherapy for CLL

Czuczman discloses that rituximab administered at 375 mg/m² in combination with CHOP chemotherapy yielded the beneficial therapeutic 100% response rate in all patients completing all therapy. (Ex. 1111 at 003; Ex. 1105 ¶91.) Czuczman’s study included 4 IWF Type A patients. (*Id.*) The FDA Transcript further discloses that rituximab administered at 375 mg/m² 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. 1107 at 044-45 (43:23-44:8).) A POSA would have known that IWF Type A patients were SLL/CLL patients. (Ex. 1118 at 012; 1105 ¶92.)

As disclosed by Batata, SLL and CLL are “different tissue expressions of the same disease process.” (Ex. 1108 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. 1105 ¶23.) Indeed, the World Health Organization expressly concluded, “CLL and SLL are one disease at different stages, not two separate entities.” (Ex. 1112 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. 1139 at 027; Ex. 1105 ¶24.)

Because it was known in the art that SLL and CLL are different tissue expressions of the same disease process, Czuczman’s disclosure of the 100% effective treatment of SLL/CLL through rituximab combined with CHOP chemotherapy would have motivated a POSA to use rituximab in combination with

chemotherapy to treat CLL patients specifically. (Ex. 1105 ¶¶91.) 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. 1144 at 029; Ex. 1105 ¶¶29.)

Furthermore, the FDA Transcript explicitly contemplates using rituximab to treat patients diagnosed with CLL. (Ex. 1107 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. 1105 ¶¶95.)

Additionally, the success of rituximab at treating low-grade NHL patients generally, as described in the FDA Transcript, and the success of rituximab with chemotherapy to treat low-grade NHL patients, as described in Czuczman, would have led a POSA to use rituximab with chemotherapy to treat CLL. (Ex. 1105 ¶¶91, 97.) A 1995 Genentech press release expressly proposed using rituximab to treat CLL based on the results of rituximab studies in NHL patients. (*See* Ex. 1134; *see also* Ex. 1157 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).) Moreover a 1996 IDEC/Genentech press release touted the success of the Czuczman trial combining rituximab with CHOP, and announced Genentech's intent to explore rituximab "in combination with other anti-cancer treatments." (Ex. 1165 at 001; Ex. 1105 ¶91.)

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. 1105 ¶¶145-47.) 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.* ¶146.) A POSA would have anticipated the likelihood of TLS when treating 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 using drugs such as diphenhydramine and acetaminophen. (*Id.*; Ex. 1109 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. 1105 ¶146; Ex. 1109 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. 1105 ¶147.)

(2) A POSA would have been motivated to dose rituximab at 500 mg/m²

In the FDA Transcript, Dr. Grillo-López states that the IWF Type 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/m² for SLL and CLL patients. (Ex. 1107 at 069 (68:11-12); Ex. 1105 ¶98.) Maloney teaches that the 500 mg/m² dose is safe and effective. (*Id.* ¶102.) 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. 1107 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. 1105 ¶99.) 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/m² in this group 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.*) 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.* ¶¶93, 146.) Therefore, it would have been obvious to use a 500 mg/m² dose of rituximab in SLL/CLL patients to produce a higher response rate. (*Id.* ¶¶100-02.)

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/m² during the first infusion may be prudent. (*Id.* ¶102.) But because adverse events were substantially lower on subsequent infusions, a POSA would have been motivated to dose rituximab at a higher rate after the first infusion for CLL patients. (*Id.*) A logical higher dose for one or more of the weekly infusions taught by the FDA Transcript would have been 500 mg/m² 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/m² of rituximab for treatment of CLL as of at least July 1998, confirming that such a

selection would have been obvious over the prior art at the time. (*Id.*; Ex. 1103 at 006.).

b. Reasonable Expectation of Success

A POSA would have understood Czuczman to demonstrate a significant therapeutic response—specifically, a 100% response rate—to administration of rituximab at 375 mg/m² with chemotherapy to low-grade NHL patients, including SLL/CLL patients. Likewise, a POSA would have understood the FDA Transcript to demonstrate a detectable therapeutic response after four administrations of rituximab at 375 mg/m² in SLL/CLL patients. A POSA would further have understood Maloney to teach the safety and efficacy of administering rituximab at doses ranging from 50 mg/m² to 500 mg/m², thus supporting the POSA’s reasonable expectation of success at implementing the rituximab regimen of a higher dose than 375 mg/m², as described in Czuczman and the FDA Transcript. Thus, claims 23 and 28 are obvious over Czuczman, the FDA Transcript, Batata, and Maloney. (Ex. 1105 ¶¶103-04.)

2. The Dependent Claims

a. Dependent Claims 24-27 and 29

Dependent claims 24-27 disclose specific dosages of an anti-CD20 antibody for use in the method of claim 23 that are expressly met by the 375 mg/m² dosage

used in Czuczman and the trials disclosed in the FDA Transcript.¹¹ (*Id.* ¶105.) 375 mg/m² is equivalent to approximately 10 mg/kg. 500 mg/m² is equivalent to approximately 13.5 mg/kg. (*Id.*) Dependent claim 29 discloses a 500 mg/m² dosage, as taught by Maloney. These claims add nothing to overcome the obviousness of independent claims 23 and 28 and are also obvious over Czuczman, the FDA Transcript, Batata, and Maloney. (*Id.*)

b. Dependent Claims 30-32

Dependent claims 30-32 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 require a patient that has "relapsed following previous treatment" (claim 30), "is refractory to a treatment previously administered" (claim 31), or "is refractory to fludarabine" (claim 32, dependent on claim 31). Administering rituximab in combination with chemotherapy to these previously treated patients would have been obvious.

The efficacy study results described in the FDA Transcript were from a study conducted in patients who were all relapsed or refractory. (Ex. 1107 at 037 (36:20-24).) These study results included 37 IWF type A patients, *i.e.*, SLL or CLL patients, who were relapsed or refractory to previous treatment. The FDA

¹¹ The conversion between mg/kg and mg/m² is a factor of 37. (Ex. 1105 ¶105.)

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 would read 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. 1105 ¶106.)

Furthermore, Czuczman disclosed that combining rituximab with chemotherapy was beneficial because, *inter alia*, anti-CD20 antibodies such as rituximab were known to have a different mechanism of action than chemotherapeutic agents and rituximab specifically was known to have “synergistic antitumor activity with certain chemotherapeutic agents.” (Ex. 1111 at 003.) Based on rituximab’s benefits with and in addition to chemotherapy, it would have been obvious to one of skill in the art to employ the effective rituximab-chemotherapy combination treatment regimen of Czuczman to patients who were no longer responsive to a standard first-line CLL chemotherapeutic agent such as fludarabine. Claims 30-32 are therefore obvious. (Ex. 1105 ¶¶106-07.)

c. Dependent Claims 33-35, 37

Dependent claims 33-35 and 37 recite specific structural features of the claimed anti-CD20 antibody. These features include that the anti-CD20 antibody:

“is a chimeric antibody” (claim 33); “is rituximab” (claim 34, dependent on claim 33); “is a humanized antibody” (claim 35); or “comprises a CD20-binding fragment of a chimeric, humanized, or human antibody” (claim 37). Claims 33-34 and 37 are each met by rituximab, which is a chimeric antibody with a CD20-binding fragment. (*Id.* ¶108.) To the extent that the Patent Owners contend that the claimed anti-CD20 antibodies of claim 35 to “humanized” antibody can be read to cover the structural features of rituximab, those claims are likewise disclosed by Czuczman and the FDA Transcript and the methods recited in claims 33-35 and 37 are obvious. (*Id.*)

d. Dependent Claims 38-42

Dependent claims 38-42 recite broad aspects of dosing schedules for administration of the anti-CD20 antibody according to claims 23 and 28. Claim 38 recites that “the anti-CD20 antibody is administered to the patient repeatedly,” and claims 39 and 40, which are themselves dependent on claim 38 recite weekly administration (claim 39) for about 2 to 10 weeks (claim 40). Czuczman teaches the administration of rituximab on weeks 1 (2 infusions), 7, 13, 20, and 21. (Ex. 1111 at 003.) These expressly disclose both repeated and weekly rituximab administration for about 2 weeks (weeks 20 and 21), as recited in claims 38-40. (Ex. 1105 ¶109.) The four once-weekly doses of rituximab used in the FDA

Transcript likewise expressly satisfy claims 38-40. (*Id.*)

Claims 41 and 42, also dependent on claim 38, recite bi-weekly or monthly limitations on the anti-CD20 antibody dosing regimen. It would have been routine to a POSA to adjust rituximab's dosing schedule to biweekly or monthly administration of claims 41 and 42 within the context of the different administration frequencies disclosed by Czuczman, which discloses inter-administration gaps from 1 week to 7 weeks. (*Id.* ¶110.) Given this range of dosing frequencies, selecting a gap of 2 weeks (biweekly administration) or 4 weeks (monthly administration) would be “‘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)). Additionally, 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. (Ex. 1105 ¶110.)

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/m² dosages,” particularly when used

in combination therapy. (Ex. 1149 at 003, ¶15; *see also* Ex. 1150 at 002-03; Ex. 1151 at 002-03.) Thus, a bi-weekly or monthly dosing schedule would have been obvious to a POSA contemplating using rituximab at 500 mg/m² (as described by Maloney) in combination with chemotherapy. (Ex. 1105 ¶110.)

e. Dependent Claims 43-45

Dependent claim 43 requires the anti-CD20 of claims 23 or 28 be administered parenterally (non-orally) and claim 44 further recites administration by intravenous infusion. Czuczman and the FDA Transcript disclosed that rituximab was administered by intravenous infusions and such administration was obvious. (*Id.* ¶111.)

Claim 45 recites that the anti-CD20 antibody therapy and the chemotherapy be “administered to the patient concurrently.” Czuczman discloses concurrent administration of rituximab and CHOP chemotherapy, with rituximab administered on weeks 1 (2 infusions), 7, 13, 20, and 21 during CHOP chemotherapy. (Ex. 1111 at 003.) Thus claims 43-45 are obvious. (Ex. 1105 ¶111.)

f. Dependent Claims 46-57

Dependent claims 46-57 recite limitations related to specific chemotherapeutic agents used as part of the chemotherapy recited in independent claim 23. The limitations of claims 47-52 recite various combinations of cyclophosphamide, vincristine, prednisone, and doxorubicin, which are the

components of CHOP. Accordingly, claims 47-52 are each expressly met by use of CHOP chemotherapy, as disclosed in Czuczman, and therefore do not add anything to overcome their obviousness. (Ex. 1105 ¶112.)

Claims 46 and 53 recite using chemotherapy comprising chlorambucil and fludarabine, respectively. Like cyclophosphamide (the “C” in CHOP), chlorambucil is as an alkylating agent, and it has been the main alkylating agent used for CLL since the early 1950s. (Ex. 1155 at 034.) Fludarabine—a purine nucleotide analog—was another popular treatment for CLL and had relatively high response rates compared to other single agents. (Ex. 1105 ¶113; Ex. 1124 at 003.) A POSA’s motivation to combine chlorambucil or fludarabine with rituximab is the same motivation as set forth in Czuczman: non-cross-resistant mechanisms of action, individual efficacy, non-overlapping toxicities, and potential beneficial synergies. (Ex. 1105 ¶113.) A POSA’s reasonable expectation of being able to effectively treat CLL by combining rituximab with either chlorambucil or fludarabine was premised on the fact that combination therapies tend to be more effective than single agent therapies due to multiple mechanisms of action as well as the demonstrated enhanced effectiveness of the rituximab + CHOP combination in Czuczman. (*Id.*) Hence, claims 46 and 53 are obvious. (*Id.*)

Methotrexate, cisplatin, toremifene, and tamoxifen are additional well-

known chemotherapeutic agents. (*Id.*) Combining rituximab with the chemotherapeutic agents of methotrexate, cisplatin, toremifene, and tamoxifen recited in claims 54-57, respectively, render the claims obvious for the same reasons as claims 46 and 53. (*Id.*)

C. Ground 2: All Challenged Claims Are Obvious Under §103 Over Byrd and the MD Anderson Online Newsletter

This ground assumes the priority date for all challenged claims is either November 9, 1998 or November 9, 1999. All the challenged claims are obvious under §103 over Byrd (Ex. 1110) and the MD Anderson Online Newsletter (Ex. 1103). Alternatively, because the MD Anderson Online Newsletter and the MD Anderson Print Newsletter have identical disclosures, all challenged claims are equally obvious of Byrd and the MD Anderson Print Newsletter. (Ex. 1105 ¶114.)

This ground first discusses why each of the independent claims (claims 23 and 28) is obvious before addressing the remaining challenged dependent claims.

1. Independent Claims 23 and 28

Byrd is an article published in February 1998 in *Seminars in Oncology*. (Ex. 1110.) It summarizes various established and emerging CLL therapies. In particular, Byrd outlines clinical studies with combination therapy of fludarabine and cyclophosphamide, as well as fludarabine and rituximab, to treat CLL. (*Id.* at 006.) Byrd discusses the synergistic effect of fludarabine and cyclophosphamide

shown by both preclinical and clinical data:

[P]reclinical data from several groups suggest synergistic interaction between alkylator agents and fludarabine combination. . . . Based on the 88% complete response rate observed phase I/II study of untreated low-grade NHL patients receiving fludarabine and modified doses of cyclophosphamide, the Baltimore/Washington, DC CLL Consortium group initiated a study of these agents with filgrastim in patients with untreated CLL and related low-grade lymphomas and ***noted a similar promisingly high response rates***. A second group combined all categories of CLL patients and ***noted impressive activity*** in both previously untreated and fludarabine-refractory individuals.

(Ex. 1110 at 006 (emphasis added).)

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

“Cancer and Leukemia Group B is planning a Phase II/III study of fludarabine + IDEC-C2B8 in untreated CLL patients.” (*Id.*)

The MD Anderson Online Newsletter describes a trial of rituximab in patients with CLL. (Ex. 1103 at 004). The MD Anderson Online Newsletter explains that “CLL should be an excellent target disease” for using rituximab based on 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/m² of the previous clinical trials. (*Id.*; Ex. 1105 ¶86.)

As described in the MD Anderson Online Newsletter, the investigators administered 375 mg/m² rituximab at the first infusion, then escalated doses for the subsequent infusions to 500 mg/m². (Ex. 1105 ¶87; Ex. 1103 at 004.) Because it was clear from the Phase I trial that the 500 mg/m² dose was well tolerated and did not reach the Maximum Tolerated Dose (MTD), the treatment plan started the dose at 500 mg/m² with further escalation by 33% increments. (Ex. 1105 ¶87; Ex. 1103 at 004.)

GROUND 2	
<u>Claim Language</u>	<i>Obvious Over Byrd (Ex. 1110) and the MD Anderson Online Newsletter (Ex. 1103)</i>
<p>23. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia,</p>	<p>“Cancer and Leukemia Group B is planning a Phase II/III study of fludarabine + IDEC-C2B8 in untreated CLL patients.” (Ex. 1110 at 006.)</p> <p>“IDEC [rituximab], a new monoclonal antibody approved for the treatment of lymphoma, is under investigation in patients with CLL.” (Ex. 1103 at 004.)</p> <p>“CLL should be an excellent target disease for the use of the IDEC antibody.” (<i>Id.</i>)</p>
<p>wherein the anti-CD20 antibody therapy is combined with chemotherapy,</p>	<p>“Cancer and Leukemia Group B is planning a Phase II/III study of fludarabine + IDEC-C2B8 in untreated CLL patients.” (Ex. 1110 at 006.)</p> <p>“Because of <i>in vitro</i> 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%.” (<i>Id.</i>)</p>
<p>wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.</p>	<p>There is no use of radiolabeled anti-CD20 in any of the references relied on in this petition.</p>
<p>28. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic</p>	<p><i>See claim 23.</i></p>

GROUND 2	
<u>Claim Language</u>	<i>Obvious Over Byrd (Ex. 1110) and the MD Anderson Online Newsletter (Ex. 1103)</i>
leukemia,	
wherein the anti-CD20 antibody is administered to the patient at a dosage of about 500 to about 1500 mg/m ² ,	“[T]he first dose would be 375 mg/m ² (about 6 hour infusion) but <i>all subsequent doses would be higher, starting with 500 mg/m²</i> and escalating by 33% with subsequent patients.” (Ex. 1103 at 004 (emphasis added).)
wherein the anti-CD20 antibody therapy is combined with chemotherapy,	<i>See claim 23.</i>
and wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.	<i>See claim 23.</i>

a. Motivation To Combine

By the late 1990s, it was common to combine various cytotoxic agents that demonstrated single-agent activity, different mechanisms of action, and non-overlapping toxicities to achieve higher response rates and longer remission in lymphoma and leukemia patients. (Ex. 1105 ¶116; Ex. 1166 at 003; Ex. 1113 at 005.) Such combination therapies were used extensively for patients that were not susceptible to treatment by single agents. (Ex. 1105 ¶116.) Byrd discloses multiple standard chemotherapeutic agents that meet all properties that would have motivated a POSA to combine them with rituximab to treat CLL effectively. (*Id.* ¶¶119-21.)

In particular, Byrd describes combining rituximab with fludarabine and with CHOP (cyclophosphamide, vincristine, prednisone, and doxorubicin). With regard to the combination of fludarabine with rituximab, Byrd describes a plan for a “Phase II/III study of fludarabine + [rituximab] in untreated CLL patients.” (Ex. 1110 at 006.) This study was initiated on March 15, 1998. (Ex. 1129 at 007.) Such a planned study demonstrates that there existed an express motivation within the art to combine rituximab and fludarabine to treat CLL patients and an expectation that the combination would be effective. (Ex. 1105 ¶120.) Byrd similarly describes a recently completed study “of interdigitated IDEC-C2B8 with CHOP chemotherapy in relapsed low-grade NHL.” (*Id.* ¶119.)

Based on the MD Anderson Online Newsletter, the specific 500 mg/m² dosage would have been a logical dose of rituximab to increase the effectiveness of the rituximab. A POSA seeking to implement Byrd’s combination therapy for CLL patients would have turned to rituximab’s dosing regimen described in the MD Anderson Online Newsletter as a matter of course in order to achieve enhanced therapeutic benefits from the “higher doses and/or more frequent exposure” sought by the O’Brien study described in the newsletter. (Ex. 1105 ¶122; Ex. 1103 at 004.)

A POSA therefore would be motivated to administer rituximab in combination with chemotherapy to CLL patients, and to select a 500 mg/m² dosage. (Ex. 1105 ¶122.)

b. Reasonable Expectation of Success

A POSA would have had a reasonable expectation that combining rituximab with chemotherapy would be safe and efficacious to treat CLL given the multiple trials of rituximab with chemotherapy described in Byrd. *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.”) For the same reason, a POSA would have had a reasonable expectation that the 500 mg/m² dose was “an amount effective to treat CLL” in view of the ongoing MD Anderson trial. *See id.* (Ex. 1105 ¶122.)

2. The Dependent Claims Are Obvious

a. Dependent Claims 24-27 and 29

Dependent claims 24-27 disclose specific dosages of an anti-CD20 for use in the method of claim 23 that are expressly met by the 500 mg/m² dosage described in the MD Anderson Online Newsletter.¹² (Ex. 1105 ¶123.) 500 mg/m² is equivalent to approximately 13.5 mg/kg. (*Id.* ¶105.) Dependent claim 29 discloses a 500 mg/m² dosage, as taught in the MD Anderson Online Newsletter. These claims therefore add nothing to overcome the obviousness of independent claims 23 and 28 and are also obvious over Byrd and the MD Anderson Online Newsletter. (*Id.* ¶123.)

b. Dependent Claims 30-32

Dependent claims 30-32 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 require a patient that has "relapsed following previous treatment" (claim 30), "is refractory to a treatment previously administered" (claim 31), or "is refractory to fludarabine" (claim 32, dependent on claim 31). Administering rituximab in combination with chemotherapy to these

¹² The conversion between mg/kg and mg/m² is a factor of 37. (*See* Ex. 1105 ¶105.)

previously treated patients would have been obvious. These types of combination therapies are standard in treating lymphomas and leukemias because they are typically more successful than single agent therapy. (*Id.* ¶124.) This combination would have been particularly obvious given Byrd’s teaching that rituximab “can chemosensitize chemotherapy-resistant NHL cell lines.” (Ex. 1110 at 004.) Claims 30-32 are therefore obvious. (Ex. 1105 ¶124.)

c. Dependent Claims 33-35, 37

Dependent claims 33-35 and 37 recite specific structural features of the claimed anti-CD20 antibody. These features include that the anti-CD20 antibody: “is a chimeric antibody” (claim 33); “is rituximab” (claim 34, dependent on claim 33); “is a humanized antibody” (claim 35); or “comprises a CD20-binding fragment of a chimeric, humanized, or human antibody” (claim 37). Claims 33-34 and 37 are each met by rituximab, which is a chimeric antibody with a CD20-binding fragment. (*Id.* ¶108.) To the extent that the Patent Owners contend that the claimed anti-CD20 antibodies of claims 35 to “humanized” antibody can be read to cover the structural features of rituximab, those claims are likewise disclosed by Byrd and the MD Anderson Online Newsletter and the methods recited in claims 33-35 and 37 are obvious. (*Id.* ¶125.)

d. Dependent Claims 38-42

Dependent claims 38-42 recite broad aspects of dosing schedules for

administration of the anti-CD20 antibody according to claims 23 and 28. Claim 38 recites that “the anti-CD20 antibody is administered to the patient repeatedly,” and claims 39 and 40, which are themselves dependent on claim 38 recite weekly administration (claim 39) for about 2 to 10 weeks (claim 40). The MD Anderson Online Newsletter teaches weekly administration of rituximab for four weeks. (Ex. 1103 at 004.) This expressly discloses the requirements of claims 38-40. (Ex. 1105 ¶126.)

Claims 41 and 42 recite biweekly and monthly dosing, respectively. Modifying the weekly dosing regimen of the MD Anderson Online 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. (Ex. 1105 ¶126.) 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*, 464 F.3d at 1371). (Ex. 1105 ¶126.) Further, as described above, Patent Owners’ own experts asserted in proceedings before the European Patent Office that “such less frequent schedules would have been readily adopted for the increased 500-1500mg/m² dosages,” particularly when used in combination therapy. (Ex. 1149 at 003 ¶15; *see also* Ex. 1150 at 002-03;

Ex. 1151 at 002-03.) Claims 41 and 42 are therefore obvious. (Ex. 1105 ¶126.)

e. Dependent Claims 43-45

Dependent claim 43 requires the anti-CD20 of claims 23 or 28 be administered parenterally (non-orally) and claim 44 further recites the administration by intravenous infusion. The MD Anderson Online Newsletter disclosed that rituximab was administered by intravenous infusions and such administration was obvious. (*Id.* ¶127.)

Claim 45 recites that the anti-CD20 antibody therapy and the chemotherapy be “administered to the patient concurrently.” Byrd describes “a study of interdigitated IDEC-C2B8 with CHOP chemotherapy,” which is concurrent administration of rituximab and CHOP. (Ex. 1103 at 004.) Thus claims 43-45 are obvious. (Ex. 1105 ¶128.)

f. Dependent Claims 46-57

Dependent claims 46-57 recite limitations related to specific chemotherapeutic agents used as part of the chemotherapy recited in independent claim 23. The limitations of claims 47-52 recite various combinations of cyclophosphamide, vincristine, prednisone, and doxorubicin, which are the components of CHOP. Accordingly, claims 47-52 are each expressly met by use of CHOP chemotherapy, as disclosed in Byrd, and therefore do not add anything to overcome their obviousness. (Ex. 1105 ¶129.) Claim 53 recites using

chemotherapy comprising fludarabine, which is also disclosed in Byrd. Claim 53 therefore is also obvious. (*Id.*)

As explained in Ground 1, a POSA would have been motivated to combine rituximab therapy with the well-known chemotherapeutic agents of chlorambucil, methotrexate, cisplatin, toremifene, and tamoxifen recited in claims 46 and 54-57, respectively. Thus, based on the combined teachings of Byrd and the MD Anderson Online Newsletter, these claims are obvious. (*Id.* ¶130.)

D. Ground 3: Claims 41 and 42 Are Obvious Under §103 Over Byrd, the MD Anderson Online Newsletter, and Kipps

This Ground assumes the priority date for claims 41-42 is either November 9, 1998 or November 9, 1999.

The sole difference between claim 23, which is obvious over Byrd and the MD Anderson Online Newsletter, *supra*, and claims 41-42 is that claims 41 and 42 require biweekly and monthly dosing, respectively. The MD Anderson Online Newsletter discloses weekly rituximab administration. (Ex. 1103 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 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. 1155 at 034-35.) Kipps thus teaches both bi-weekly and monthly (every 4 weeks) administration of standard chemotherapy for CLL. (*Id.*)

It would have been obvious to a POSA seeking to take advantage of rituximab's ability to chemosensitize chemotherapy-resistant NHL cell lines, as described by Byrd, to administer rituximab bi-weekly or monthly to align with chemotherapy administration. (Ex. 1105 ¶133.) 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. (*Id.* ¶134.) Because, as described by Kipps, standard chemotherapies for CLL including fludarabine were administered both bi-weekly and monthly (Ex. 1155 at 034-35), it would have been obvious to a POSA to also administer rituximab bi-weekly or monthly. (*Id.* ¶134.)

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. (*Id.* ¶136.)

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. 1111 at 003.) Link also taught administration of rituximab once every three weeks when administered in combination with CHOP. (Ex. 1117 at 002 (Abstract *7); Ex. 1105 ¶137.)

Additionally, as described above, such a modification would have been “‘nothing more than the routine’ application of a well-known problem-solving strategy,” *Pfizer*, 480 F.3d at 1368, and Patent Owner’s own experts conceded that such a modification would have been obvious. (Ex. 1149 at 003 ¶15; *see also* Ex. 1150 at 002-03; Ex. 1151 at 002-03.)

Thus, using biweekly or monthly rituximab dosing schedules in combination with chemotherapy would have been obvious to a POSA. (Ex. 1105 ¶¶131-39.) Alternatively, claims 41 and 42 are equally obvious over Byrd, the MD Anderson Print Newsletter, and Kipps. (*See id.* ¶126.)

XI. NO SECONDARY INDICIA OF NON-OBVIOUSNESS EXIST

As explained above, the prior art and a POSA’s knowledge render the challenged claims of the ’612 patent 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. 1105 ¶¶140-47.) 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.* ¶142.) 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.* ¶144.) TLS was a known and manageable possibility that would not prevent a POSA from pursuing rituximab as a treatment for CLL. (*Id.* ¶146.) 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.* ¶145.)

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 23-35 and 37-57 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,

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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 13,972 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
Reg. No. 41,268
Counsel for Petitioner

CERTIFICATION OF SERVICE

I, Maria Weiland, 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. 1101-1166**) 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 Weiland
Maria Weiland