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CELLTRION, INC.
Petitioner

v.

BIOGEN INC.
Patent Owner

_____

Case No. IPR2017-_____

Patent No. 9,296,821

Filing Date: June 15, 2012
Issue Date: March 29, 2016

Title: COMBINATION THERAPIES FOR B-CELL LYMPHOMAS COMPRISING ADMINISTRATION OF ANTI-CD20 ANTIBODIES

Inventor: Antonio Grillo-López

_____

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,296,821

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EXHIBIT LIST

Exhibit No.	Description
1001	U.S. Patent No. 9,296,821 ("the '821 patent")
1002	Expert Declaration of Dr. Izidore Lossos
1003	Declaration of Walter Longo, MD
1004	Piro, L. *et al.*, *RITUXAN™ (rituximab, IDEC-C2B8): Interim analysis of a phase II study of once weekly times 8 dosing in patients with relapsed low-grade or follicular non-Hodgkin's lymphoma*, Blood 90(10, Supp. 1):510a (Abstract 2272) (Nov. 15, 1997)
1005	Marcus, R. *et al.*, *CVP Chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma,* Blood, 105(4):1417-1423 (Feb. 15, 2005) ("Marcus 2005")
1006	IDEC Pharmaceuticals Corporation, Form 10-K/A for the Fiscal Year ended December 31, 1997, filed with the U.S. Securities and Exchange Commission
1007	U.S. Patent No. 5,736,137 ("the '137 Patent")
1008	Foon, K.A. & Fisher, R.I., *Chapter 111: Lymphomas*, in Williams Hematology, Fifth Edition, 1076-96 (Beutler, E. *et al.*, eds., 1995)
1009	Dana, B. *et al.*, *Long-Term Follow-Up of Patients With Low-Grade Malignant Lymphomas Treated With Doxorubicin-Based Chemotherapy or Chemoimmunotherapy*, J. Clin. Oncol., 11(4):644-651 (Apr. 1993)
1010	Link, B.K. *et al.*, *Phase II Pilot Study of the Safety and Efficacy of Rituximab in Combination with CHOP Chemotherapy in Patients with Previously Untreated Intermediate- or High-Grade NHL*, Program/Proceedings Am. Soc. Clin. Oncol., 17:3a (Abstract 7) (1998)
1011	Czuczman, M.S. *et al.*, *IDEC-C2B8 and CHOP Chemoimmunotherapy of Low-Grade Lymphoma*, Blood 86(10, Supp. 1):55a (Abstract 206) (Nov. 15, 1995) ("Czuczman Nov. 1995")
1012	U.S. Patent No. 6,399,061 ("the '061 Patent")
1013	Nadler, L.M. *et al.*, *Serotherapy of a patient with a monoclonal antibody directed against a human lymphoma associated antigen*, Cancer Res., 40(9):3147-3154 (Sept. 1980) ("Nadler 1980")

1014	Stashenko, P. *et al.*, *Characterization of a Human B Lymphocyte-Specific Antigen*, J. Immunol., 125(4):1678-1685 (Oct. 1980) ("Stashenko 1980")
1015	Anderson, K.C. *et al.*, *Expression of Human B Cell-Associated Antigens on Leukemias and Lymphomas: A model of Human B Cell Differentiation*, Blood, 63(6):1424-1433 (June 1984) ("Anderson 1984")
1016	Reff, M.E. *et al.*, *Depletion of B Cells In Vivo by a Chimeric Mouse Human Monoclonal Antibody to CD20*, Blood, 83(2):435-445 (Jan. 15, 1994) ("Reff 1994")
1017	Czuczman, M. *et al.*, *Phase II Clinical Trial of IDEC-C2B8/CHOP Combination Chemotherapy in Low Grade Lymphoma: Preliminary Results*, Program/Proceedings Am. Soc. Clin. Oncol., 14:401 (Abstract 1261) (Apr. 1995) ("Czuczman April 1995")
1018	Devita, V. T., Jr. *et al.*, *Chapter 44: Hodgkin's Disease and the Non-Hodgkin's Lymphomas*, in Cancer: Principles & Practice of Oncology, Second Edition (DeVita, Jr. *et al.*, eds., 1985)
1019	Rituxan (Rituximab) label (Nov. 1997)
1020	Czuczman, M.S. et al, *Treatment of patients with Low-grade B-Cell Lymphoma with the Combination of Chimeric Anti-20 Monoclonal Antibody and CHOP Chemotherapy*, J. Clin. Oncol. 17(1):268-276 (Jan. 1999) ("Czuczman 1999")
1021	Leget, G.A. *et al.*, *Use of rituximab, the new FDA-approved antibody,* Curr. Opin. Oncol. 10(6):548-551 (Nov. 1998)
1022	Maloney, D.G. and Press, O.W., *Newer Treatments for Non-Hodgkin's Lymphoma: Monoclonal Antibodies*, Oncology 12(10, Supp. 8):63-76 (Oct. 1998)
1023	Exhibit Number Not Used
1024	Coiffier B., *et al.*, *Rituximab (Anti-CD20 Monoclonal Antibody) for the Treatment of Patients With Relapsing or Refractory Aggressive Lymphoma: A Multicenter Phase II Study*, Blood, 92(6):1927-1932 (Sept. 15, 1998)
1025	Horning S., *Treatment Approaches to the Low-Grade Lymphomas,* Blood 83(4):881-884 (Feb. 15, 1994)
1026	Exhibit Number Not Used
1027	Maloney, D.G. *et al.*, *IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients With Relapsed Low-Grade Non-Hodgkin's Lymphoma*, Blood, 90(6): 2188-2195 (Sept. 15, 1997)

1028	Czuczman, M.S., *et al., Prolonged Clinical and Molecular Remission in Patients With Low-Grade or Follicular Non-Hodgkin's Lymphoma Treated With Rituximab Plus CHOP Chemotherapy: 9-Year Follow-Up*, J. Clin. Oncol., 22(23):4711-4716 (Dec. 1, 2004)
1029	Exhibit Number Not Used
1030	Sriskandan, S. *et al.*, *Aggressive management of doxorubicin-induced cardiomyopathy associated with 'low' doses of doxorubicin*, Postgrad. Med. J., 70(828):759-761 (Oct. 1994)
1031	Steward, W.P. *et al.*, *Maintenance Chlorambucil After CVP in the Management of Advanced Stage, Low-Grade Histologic Type Non-Hodgkin's Lymphoma: A Randomized Prospective Study With an Assessment of Prognostic Factors*, Cancer 61(3):441-447 (Feb. 1, 1988)
1032	Maloney, D.G. *et al.*, *IDEC-C2B8: Results of a Phase I Multiple-Dose Trial in Patients With Relapsed Non-Hodgkin's Lymphoma*, J. Clin. Oncol., 15(10):3266-3274 (Oct. 1997)
1033	Berinstein, N.L., *et al.*, *Association of serum Rituximab (IDEC-C2B8) concentration and anti-tumor response in the treatment of recurrent low-grade or follicular non-Hodgkin's lymphoma*, Ann. Oncol., 9:995-1001 (July 1998)
1034	File History of U.S. Patent Application No. 09/372,202 ("the '202 application")
1035	Exhibit Number Not Used
1036	Bishop, J.F. *et al.*, *A Randomized Trial of High Dose Cyclophosphamide, Vincristine, and Prednisone Plus or Minus Doxorubicin (CVP versus CAVP) with Long-Term Follow-Up in Advanced Non-Hodgkin's Lymphoma,* Leukemia, 1(6):508-513 (June 1987)
1037	Exhibit Number Not Used
1038	Rogers, J. *et al.*, *Analysis of bcl-2 t(14;18) translocation in relapsed B-cell lymphoma patients treated with the chimeric anti-CD20 antibody IDEC-C2B8*, P. Am. Assoc. Canc. Res., 37:213 (Abstract 1456) (Mar. 1996)
1039	Czuczman, M.S. *et al.*, *IDEC-C2B8/CHOP chemoimmunotherapy in patients with low-grade lymphoma: interim clinical and bcl-2 (PCR) results*, Ann. Oncol., 7(Supp. 1):56 (Abstract 191) (1996)
1040	Exhibit Number Not Used

1041	Czuczman, M.S. *et al.*, *Chemoimmunotherapy of Low-Grade Lymphoma with Anti-CD20 Antibody IDEC-C2B8 in Combination with CHOP Chemotherapy*, Cancer Invest., 14(Supp. 1):59-61 (Abstract 53) (1996)
1042	Exhibit Number Not Used
1043	Czuczman, M. *et al.*, *IDEC-C2B8/CHOP Chemoimmunotherapy in Patients with Low-Grade Lymphoma: Clinical and bcl-2 (PCR) Final Results*, Blood, 88(10, Supp. 1):453a (Abstract 1799) (Nov. 15, 1996)
1044	Hoppe, T.E. *et al.*, *The Treatment of Advanced Stage Favorable Histology Non-Hodgkin's Lymphoma: A Preliminary Report of a Randomized Trial Comparing Single Agent Chemotherapy, Combination Chemotherapy, and Whole Body Irradiation*, Blood, 58(3):592-598 (Sept. 1981)
1045	Canellos, G.P. *et al.*, *Chemotherapy of the Non-Hodgkin's Lymphomas*, Cancer, 42(2):932-940 (Aug. 1978)
1046	Rosenberg, S.A., *The Low-Grade Non-Hodgkin's Lymphomas: Challenges and Opportunities*, J. Clin. Oncol., 3(3):299-310 (Mar. 1985)
1047	Kimby, E. *et al.*, *Chlorambucil/prednisone vs. CHOP in symptomatic low-grade non-Hodgkin's lymphomas: A randomized trial from the Lymphoma Group of Central Sweden*, Ann. Oncol., 5(Supp. 2):67-71 (1994)
1048	Czuczman, M. *et al.*, *IDEC-C2B8 clears bcl2 (t14;18) in patients (pts) with relapsed low grade or follicular lymphoma (LG/F NHL)*, P. Am. Assoc. Canc. Res., 38:84 (Abstract 565) (Mar. 1997)
1049	Czuczman, M. *et al.*, *Rituxan™/CHOP Chemo Immunotherapy in Patients with Low-Grade or Follicular (LG/F) Non-Hodgkin's Lymphoma (NHL)*, J. Immunother., 20(5):401 (1997)
1050	Czuczman, M.S. *et al.*, *IDEC-C2B8 (Rituximab) Alone and in Combination with CHOP in the Treatment of Low-Grade B-Cell Lymphoma*, Cancer Invest., 16 (Suppl. 1):21-22 (Abstract 17) (1998)
1051	IDEC Pharmaceuticals Corporation Press Release, *IDEC Pharmaceuticals and Genentech Announce Positive Final Results for Pivotal Phase III Trial of IDEC-C2B8 as Single Agent* (Dec. 9, 1996)
1052	Exhibit Number Not Used
1053	Smith, M.R., *Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance*, Oncogene, 22(47):7359-7368 (Oct. 20, 2003)

1054	Maloney, D.G. *et al.*, *Phase I Clinical Trial Using Escalating Single-Dose Infusion of Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients With Recurrent B-Cell Lymphoma*, Blood, 84(8):2457-2466 (Oct. 15, 1994) ("Maloney 1994")
1055	EDGAR® FILER MANUAL: Guide for Electronic Filing with the U.S. Securities and Exchange Commission, EDGAR® Release 5.10 (Sept. 1996) [excerpts]
1056	Attachment 2: IDEC Pharmaceuticals Filing Details on the EDGAR system, available at https://www.sec.gov/Archives/edgar/data/875045/0000936392-98-000361-index.html
1057	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")
1058	FDA FOIA response letter dated August 26, 2016
1059	McNeil, C., *Non-Hodgkin's Lymphoma Trials In Elderly Look Beyond CHOP*, J. Nat'l Cancer Inst., 90(4):266-67 (Feb. 18, 1998) ("McNeil")
1060	Rituxan (Rituximab) label (Feb. 28, 2006)
1061	Cabanillas, F. *et al.*, *Anti-CD20 Antibody (MAB), IDEC-C2B8: Clearance of Bcl-2 t(14:18) Positive Cells from Peripheral Blood (PB) and Bone Marrow (BM) in Patients (PTS) with Relapsed Low-Grade or Follicular Lymphoma (LG/F NHL)*, Blood, 1996; 88(10, Supp. 1):91a (Abstract 351) (Nov. 15, 1996)
1062	Exhibit Number Not Used
1063	Exhibit Number Not Used
1064	Grossbard, M.L. and Multani, P.S., *The McLaughlin, et al. Article [Clinical Status and Optimal Use of Rituximab for B-Cell Lymphomas] Reviewed*, Oncology, 12(12):1769-1781 (Dec. 1, 1998)
1065	Eastern Cooperative Oncology Group ("ECOG') E1496 Protocol (1998)
1066	ECOG E1496 Patient Consent Form
1067	Exhibit Number Not Used
1068	O'Brien, S. *et al.*, *Lack of Effect of 2-Chlorodeoxyadenosine Therapy in Patients with Chronic Lymphocytic Leukemia Refractory to Fludarabine Therapy*, New Engl. J. Med. 330(5):319-322 (Feb. 3, 1994)
1069	File History of U.S. Patent Application No. 13/524,896 ("the '896 application")

1070	Ruuls, S.R. *et al.*, *Novel human antibody therapeutics: the age of the Umabs*, Biotechnol. J., 3:1157-1171 (2008)
1071	ECOG Protocols Active as of 05/19/98
1072	Exhibit Number Not Used
1073	Exhibit Number Not Used
1074	E1496 Forms Packet
1075	E1496 On Study Dates
1076	Exhibit Number Not Used
1077	Exhibit Number Not Used
1078	Demiden, A. *et al.*, *Chimeric Anti-CD20 Antibody (IDEC-C2B8) Is Apoptotic and Sensitizes Drug Resistant Human B Cell Lymphomas and Aids Related Lymphomas to the Cytotoxic Effect of CDDP, VP-16 and Toxins*, Experimental Biology 95™, Atlanta, GA, Apr. 9-13, 1995, Abstracts 1-3621, Part I, A206 (Abstract 1197) (1995)
1079	Demidem A. *et al.*, *Chimeric Anti-CD20 (IDEC-C2B8) Monoclonal Antibody Sensitizes a B Cell Lymphoma Cell Line to Cell Killing by Cytotoxic Drugs*, Cancer Biother. Radio., 12(3):177-186 (1997)
1080	Haq, M.M. *et al.*, *Doxorubicin-Induced Congestive Heart Failure in Adults*, Cancer, 56(6):1361-1365 (Sept. 15, 1985)
1081	Harris, N.L. *et al.*, *A Revised European-American Classification of Lymphoid Neoplasms: A Proposal From the International Lymphoma Study Group*, Blood, 84(5):1361-1392 (Sept. 1, 1994)

CLAIMS LIST

1. A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL) comprising administering to a patient a therapeutically effective amount of rituximab during a chemotherapeutic regimen, wherein the chemotherapeutic regimen consists of cyclophosphamide, vincristine, and prednisone (CVP therapy), wherein the method comprises administering 375 mg/m^2 of rituximab, and wherein the method provides a beneficial synergistic effect in the patient.

2. A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL) comprising administering to a patient 375 mg/m^2 of C2B8 during a chemotherapeutic regimen consisting of cyclophosphamide, vincristine, and prednisone (CVP therapy).

3. A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL) comprising administering to a patient 375 mg/m^2 of a chimeric anti-CD20 antibody during a chemotherapeutic regimen consisting of cyclophosphamide, vincristine, and prednisone (CVP therapy), wherein the chimeric anti-CD20 antibody is produced from nucleic acid encoding a light chain variable region comprising the amino acid sequence in SEQ ID NO: 1 and a heavy chain variable region comprising the amino acid sequence in SEQ ID NO: 2, and comprises human gamma 1 heavy-chain and kappa light-chain constant region sequences.

4. A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL) comprising administering to a patient a therapeutically effective amount of rituximab during a chemotherapeutic regimen, wherein the chemotherapeutic regimen consists of cyclophosphamide, vincristine, and prednisone (CVP therapy), wherein the method comprises administering 375

mg/m^2 of rituximab once every 3 weeks for 8 doses, and wherein the method provides a beneficial synergistic effect in the patient.

5. A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL) comprising administering to a patient 375 mg/m^2 of C2B8 once every 3 weeks for 8 doses during a chemotherapeutic regimen consisting of cyclophosphamide, vincristine, and prednisone (CVP therapy).

6. A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL) comprising administering to a patient 375 mg/m^2 of a chimeric anti-CD20 antibody once every 3 weeks for 8 doses during a chemotherapeutic regimen consisting of cyclophosphamide, vincristine, and prednisone (CVP therapy), wherein the chimeric anti-CD20 antibody is produced from nucleic acid encoding a light chain variable region comprising the amino acid sequence in SEQ ID NO: 1 and a heavy chain variable region comprising the amino acid sequence in SEQ ID NO: 2, and comprises human gamma 1 heavy-chain and kappa light-chain constant region sequences.

I. INTRODUCTION

Celltrion, Inc. ("Celltrion" or "Petitioner") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§311-319 and 37 C.F.R. §42 of claims 1-6 of U.S. Patent No. 9,296,821 ("the '821 patent"). The '821 patent is assigned to Biogen, Inc. ("Biogen," "Patent Owner," or "Applicant"). Review should be instituted because there is a reasonable likelihood Celltrion will prevail in demonstrating that all six claims of the '821 patent are anticipated or obvious.

None of the '821 patent claims are adequately described in the specification of the priority great-grandparent application, USSN 09/372,202 ("the '202 application"). All six claims recite methods for treating low-grade or follicular non-Hodgkin's lymphoma ("NHL") by administering rituximab during a chemotherapy regimen of cyclophosphamide, vincristine, and prednisone ("CVP"). Claims 4-6 limit the dosing regimen to rituximab administered once every three weeks for 8 doses. During prosecution, the Examiner repeatedly rejected proposed claims for failure to comply with the written description requirement. Applicant relied upon disclosures in the '202 application's specification that render the claimed invention obvious without disclosing the combined elements of the claims. Because "a disclosure in a parent application that merely renders the later-claimed invention obvious is not sufficient to meet the written description requirement," *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1158 (Fed. Cir. 1998), the '821 patent is not

entitled to the priority date of the '202 application and is not entitled to any date earlier than its June 15, 2012 filing date.

With a June 15, 2012 priority date, all claims of the '821 patent are anticipated by Marcus. (Ex. 1005.) Marcus discloses the recited treatment regimen and teaches that administering rituximab during CVP significantly improves the clinical outcome for previously-untreated NHL patients. (*Id.* at 003.) Claims 3 and 6 are also obvious over Marcus and U.S. Patent No. 5,736,137, which discloses the amino acid sequence of rituximab. (Ex. 1007 at SEQ ID Nos. 6, 9.)

If the '821 patent is given the '202 application's priority date of August 11, 1999, the claims are still obvious. Between 1995 and 1997, Czuczman and others repeatedly disclosed that rituximab administered during standard CHOP chemotherapy was safe and efficacious for low-grade NHL. (Ex. 1017; Ex. 1011; Ex. 1039; Ex. 1041; Ex. 1043.) Following these disclosures, IDEC (predecessor-in-interest to Patent Owner, Biogen) announced in its 10-K/A SEC filing that it would be testing rituximab with other "widely used chemotherapy regimens" for low-grade NHL. (Ex. 1006 at 012-13.) As of August 11, 1999, Foon, Bishop, and Dana had disclosed that CVP was a widely used chemotherapy regimen for low-grade NHL with equivalent survival rates as CHOP. (Ex. 1008 at 029-30; Ex. 1036 at 002; Ex. 1009 at 002.)

Petitioner respectfully requests institution of *inter partes* review of claims 1-6 of the '821 patent, because there is a reasonable likelihood all claims are anticipated and/or obvious.

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

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

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

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

Simultaneously with the filing of the instant petition, Petitioner has filed petitions for *inter partes* review of U.S. Patent Nos. 8,329,172, and 8,557,244.

Biogen is the owner of the following U.S. applications and patents related to the '821 patent. The '821 patent is a division of U.S. Application No. 11/840,956 ("the '956 application"), which issued as U.S. Patent No. 8,329,172 ("the '172 patent). The '956 application is a continuation of application No. 10/196,732, now abandoned, which is a continuation of U.S. Application 09/372,202 ("the '202 application"), which was filed August 11, 1999 and issued as U.S. Patent No. 6,455,043 ("the '043 patent").

The '172 patent was the subject of *Boehringer Ingelheim International GmbH v. Biogen Idec, Inc.*, No. IPR2015-00415 (P.T.A.B.). The Board denied institution on July 13, 2015. *Id.*, Paper No. 14.

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

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D. Service Information

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

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

Power of attorney is being filed concurrently with this petition.

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

This Petition requests review of claims 1-6 of the '821 patent and is accompanied by a payment of $23,000, which comprises a $9,000 request fee and $14,000 post-institution fee. 37 C.F.R. §42.15(a). This Petition meets the fee requirements of 35 U.S.C. §312(a)(1).

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

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

Petitioner certifies that the '821 patent is eligible for *inter partes* review, and that the Petitioner is not barred or estopped from requesting *inter partes* review on the grounds identified in the present Petition.

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

Petitioner requests *inter partes* review of claims 1-6 of the '821 patent on the grounds set forth in the following table and requests that it be found unpatentable. The '821 patent is to be reviewed under pre-AIA §§102 and 103. This Petition, supported by the accompanying declarations of Drs. Izidore Lossos and Walter Longo, demonstrates that there is a reasonable likelihood Petitioner will prevail with respect to challenged claims 1-6.

Ground	'821 Patent Claims	Basis for Unpatentability
Ground 1	1-6	Anticipated under 35 U.S.C. §102 over Marcus
Ground 2	3, 6	Obvious under 35 U.S.C. §103 over Marcus and '137 Patent
Ground 3	1-3	Obvious under 35 U.S.C. §103 over Czuczman November 1995, IDEC's 10-K/A, Foon, and Dana
Ground 4	4-6	Obvious under 35 U.S.C. §103 over Czuczman November 1995, IDEC's 10-K/A, Foon, Dana, Link, and Piro
Ground 5	3, 6	Obvious under 35 U.S.C. §103 over Czuczman November 1995, IDEC's 10-K/A, Foon, Dana, Link, Piro, and '137 Patent

As discussed in Section IX.B below, Marcus, the '137 patent, Czuczman November 1995, Link, IDEC's 10-K/A, Dana, and Piro are prior art to the '821 patent because each reference was published or otherwise made publicly available more than one year before the earliest priority date or predates the invention of each individually challenged claim of the '821 patent.

V. TECHNICAL BACKGROUND

A. Non-Hodgkin's Lymphoma Is Comprised Of A Diverse Group Of Lymphomas

NHL is a diverse group of malignant lymphomas that typically arise from the lymphoid cells of the immune system. NHL can be divided into T-cell lymphoma and the more common B-cell lymphoma. (Ex. 1002 ¶36; Ex. 1008 at 023, Ex. 1018 at 026-27.) B-cell NHL can be further divided into sub-types ranging from indolent, low-grade tumors to rapidly growing, aggressive intermediate- or high-grade malignancies. (Ex. 1002 ¶37; Ex. 1008 at 024; Ex. 1025 at 003.) In the 1980s and 1990s, persons of ordinary skill in the art understood that low-grade lymphoma is slow-growing and typically responds well to initial treatment. (Ex. 1002 ¶37; Ex. 1008 at 029; Ex. 1025 at 003; Ex. 1044 at 006; Ex. 1046 at 005.) Despite a high initial response rate to chemotherapy, this lymphoma demonstrates a relapse pattern. (Ex. 1002 ¶37; Ex. 1008 at 029; Ex. 1025 at 003; Ex. 1044 at 006; Ex. 1046 at 005.) Following treatment,

subsequent remissions occur at a lower rate with shorter response duration. (Ex. 1002 ¶37; Ex. 1008 at 024; Ex. 1018 at 084; Ex. 1005 at 003.) Most patients eventually die from the disease or its complications. (Ex. 1002 ¶37; Ex. 1031 at 007; Ex. 1044 at 005-06; Ex. 1046 at 004-05; Ex. 1005 at 003.)

B. CVP Was A Standard, Less Toxic Chemotherapy Alternative To CHOP For Low-Grade NHL Treatment

For decades, clinicians have studied various chemotherapy protocols to improve time-to-progression and overall survival. (Ex. 1002 ¶38; *see*, *e.g.,* Ex. 1008; Ex. 1018; Ex. 1025; Ex. 1031; Ex. 1044; Ex. 1046; Ex. 1038 (Abstract 1456).) As early as 1988, CVP was identified as the predominant combination chemotherapy used for treatment of advanced stage, low-grade NHL. (Ex. 1031 at 007.) In 1995, common single-agent and combination chemotherapies for low-grade NHL were named by Foon in the *Lymphomas* chapter of Williams Hematology, a renowned treatise for clinicians and biomedical researchers:

TABLE 111-7 Single and Combination Agents Used to Treat Low-Grade Lymphoma

Agent(s)	*Dose*	*Route*	*Day(s) of treatment*	*Repeat cycle, days*
SINGLE AGENTS				
Chlorambucil	0.08–0.12 mg/kg	PO	Daily	
	or 0.4–1.0 mg/kg	PO	1	28
Cyclophosphamide	50–100 mg/m^2	PO	Daily	
	or 300 mg/m^2/day	PO	1–5	28
Fludarabine	25 mg/m^2/day	IV	1–5	28
Pentostatin	4 mg/m^2	IV	1	14
Cladribine	0.1 mg/kg/day	IV (continuous)	1–7	28
	or 0.14 mg/kg/day	IV (2 h)	1–5	28
COMBINATION THERAPIES				
CVP				
Cylophosphamide	400 mg/m^2	PO	1–5	21
Vincristine	1.4 mg/m^2 (maximum 2mg)	IV	1	
Prednisone	100 mg/m^2	PO	1–5	
COPP				
Cylophosphamide	400–650 mg/m^2	IV	1 and 8	28
Vincristine	1.4 mg/m^2 (maximum 2mg)	IV	1 and 8	
Procarbazine	100 mg/m^2	PO	1–14	
Prednisone	40 mg/m^2	PO	1–14	
CHOP				
Cyclophosphamide	750 mg/m^2	IV	1	21
Doxorubicin	50 mg/m^2	IV	1	
Vincristine	1.4 mg/m^2 (maximum 2mg)	IV	1	
Prednisone	100 mg	PO	1–5	

(Ex. 1008 at 029; *see also* Ex. 1018 at 084.)

Two of three listed combination therapies are CVP and CHOP. (Ex. 1002 ¶39; Ex. 1008 at 029.) CVP and CHOP each contain cyclophosphamide, vincristine,[1] and prednisone. (Ex. 1002 ¶39; Ex. 1008 at 029; Ex. 1031 at 003,

[1] Vincristine is also known by the brand name Oncovin, and accordingly CVP is also known by the acronym COP (cyclophosphamide, Oncovin, prednisone). (Ex. 1002 ¶39 n.1.)

007; Ex. 1005 at 003-04.) CHOP also contains doxorubicin,[2] an anthracycline antibiotic. (Ex. 1002 ¶39; Ex. 1022 at 011; Ex. 1031 at 007; Ex. 1050 at 004.) Due to toxicity associated with doxorubicin, CHOP is a more aggressive therapy than CVP. (Ex. 1002 ¶39; Ex. 1022 at 011; Ex. 1059 at 003; Ex. 1031 at 007; Ex. 1005 at 003; Ex. 1009 at 002.) Thus, for aggressive intermediate- and high-grade NHL, CHOP but not CVP is considered an appropriate treatment regimen. (Ex. 1002 ¶39.)

For low-grade NHL, CVP and CHOP were equally effective treatments as of August 11, 1998. Survival rates following treatment with CVP or CHOP (which is CVP + doxorubicin) are indistinguishable. (Ex. 1002 ¶40; Ex. 1008 at 029-30; Ex.1009 at 002; Ex. 1005 at 003; Ex. 1031 at 007; Ex. 1044 at 006; Ex. 1045 at 004-06; Ex. 1047 at 003.) Bishop reported on a randomized control trial of CVP versus CAVP (cyclophosphamide, Adriamycin, vincristine, and prednisone—the same components as CHOP) in NHL patients. (Ex. 1036 at 002.) Bishop found that "[h]igh dose CVP was as effective as high dose CAVP in all histological subsets except IWF diffuse large cell lymphoma,"[3] and concluded "[t]hese data

[2] Doxorubicin is also known by the brand name Adriamycin. (Ex. 1002 ¶39.)

[3] Diffuse large cell lymphoma is a type of aggressive (not low-grade) NHL. (Ex. 1002 ¶41 n.2.)

suggest that doxorubicin does not enhance the activity of the CVP regimen against lymphomas other than diffuse large cell." (*Id.* at 006.) Dana likewise concluded from a retrospective study that "[d]oxorubicin-containing treatment did not prolong the overall median survival of low-grade lymphoma patients compared with results with less-aggressive programs." (Ex. 1009 at 002, Abstract, 006.) Foon similarly concludes that there is no evidence including doxorubicin in combination regimens prolongs survival for low-grade NHL. (Ex. 1008 at 030.) Therefore, as Dr. Lossos explains, in 1998, CHOP and CVP were equally effective standard chemotherapy treatments for low-grade NHL, although CHOP was understood to be more toxic. (Ex. 1002 ¶41.)

Despite equivalent survival rates for low-grade NHL, CVP was, and is, considered less toxic than CHOP. (Ex. 1002 ¶39; Ex. 1022 at 011; Ex. 1059 at 003; Ex. 1031 at 007; Ex. 1005 at 003; Ex. 1009 at 002.) The doxorubicin in CHOP is associated with cardiomyopathy, which may occur acutely, even at low doses. (Ex. 1002 ¶39; Ex. 1030 at 003-05; Ex. 1080 at 003-07.) Doxorubicin is also associated with an increased risk of neutropenia, which can result in serious infections. (Ex. 1002 ¶39; Ex. 1020 at 006.) As explained by Dr. Lossos, for physicians concerned about doxorubicin's toxicity, CVP was a better choice than CHOP for low-grade NHL because the addition of doxorubicin made CHOP more toxic without an increase in survival rate. (Ex. 1002 ¶44.)

C. Rituximab Is An Antibody Against CD20, A Protein Expressed On The Surface Of B-Cells

Rituximab is a chimeric (human-mouse) monoclonal antibody directed against the CD20 antigen. (Ex. 1002 ¶48; Ex. 1064 at 004; Ex. 1019 at 001.) CD20 is a hydrophobic transmembrane protein found on pre-B cells and mature B lymphocytes. (Ex. 1002 ¶45; Ex. 1021 at 003; Ex. 1015 at 004.) Previously described as "human B lymphocyte-specific antigen," CD20 is restricted to B cells and is present on more than 90% of B-cell lymphomas. (Ex. 1002 ¶45; Ex. 1014 at 002, Abstract.)

Rituximab binds selectively and with high affinity to cells expressing the CD20 antigen—including normal and malignant B cells. (Ex. 1002 ¶49; Ex. 1053 at 003, 006.) Rituximab is thought to induce direct apoptosis and mediate complement-dependent cell lysis. (Ex. 1002 ¶49; Ex. 1024 at 003.) This kills both normal and malignant B cells. (Ex. 1053 at 003.) Because of its ability to kill B cells selectively, rituximab was developed for cancers characterized by excessive B cell proliferation, such as B-cell NHL. (Ex. 1002 ¶49.)

D. Combining Rituximab With Various Chemotherapies For NHL Treatment Was Known To A POSA As Of August 11, 1998

Patent Owner announced in March 1998 that it wanted "to identify expanded applications for Rituxan" and had authorized over 35 Rituxan post-marketing trials, including "combination therapy with <u>*widely used chemotherapy regimens*</u>

for both low grade and intermediate/high grade disease." (Ex. 1006 at 013 (emphasis added).) By then, numerous publications indicated that rituximab plus CHOP chemotherapy was safe and effective. (Ex. 1028 at 003, 006.) But Patent Owner was not satisfied with only CHOP combination therapy and wanted to expand rituximab's applications to combinations with other chemotherapy regimens. (Ex. 1006 at 013.)

1. Rituximab Single-Agent Studies Led To Suggestions To Use Rituximab During Chemotherapy For Low-Grade NHL

The first rituximab clinical trials were initiated in March 1993, in patients with relapsed or refractory low-grade B-cell NHL. (Ex. 1002 ¶52; *see, e.g.,* Ex. 1054 at 003, Abstract.) The first studies tested rituximab as a single agent and evaluated the safety and efficacy of different dosage strengths. (Ex. 1002 ¶52; Ex. 1054 at 003, Abstract; Ex. 1032 at 003, Abstract; *see also* Ex. 1021 at 003.) From these studies, 375 mg/m^2 was selected as the dose for future studies. (Ex. 1002 ¶52; Ex. 1032 at 007-08.) No dose limiting toxicity was reported and no maximally tolerated dose was established. (Ex. 1002 ¶52; Ex. 1032 at 008-09.) Reported side effects were mild. (Ex. 1002 ¶52; Ex. 1032 at 006; Ex. 1021 at 003.) Most adverse events were infusion-related and included low-grade fever, chills, and nausea. (Ex. 1002 ¶52; Ex. 1032 at 006; Ex. 1021 at 003.)

In a subsequent Phase II study, rituximab was administered as a single agent in four weekly doses of 375 mg/m^2 to patients with relapsed or refractory low-grade NHL. (Ex. 1002 ¶53; Ex. 1027 at 003, Abstract.) Among patients who completed treatment, 50% had either a complete or partial response. (Ex. 1002 ¶53 Ex. 1027 at 007.) Consistent with earlier studies, rituximab was well tolerated and no dose limiting toxicity was reported. (Ex. 1002 ¶53; Ex. 1027 at 004.) The study concluded, "[a]dditional areas that should be investigated using this new agent include (1) extended and repeated dosing regimens, *(2) combinations with or after standard chemotherapy,* . . . [and] evaluation in other B-cell histologies." (Ex. 1027 at 009 (emphasis added).)

2. By August 1998, Numerous Publications Disclosed That Rituximab Was Effective In Combination With CHOP

As early as 1994, clinicians began testing combinations of rituximab and standard chemotherapy in treatment-naïve patients. (Ex. 1002 ¶56; Ex. 1028 at 006). In 1994, researchers including Dr. Myron Czuczman and the current inventor, Dr. Antonio Grillo-López, initiated a trial in which rituximab was administered to patients with low-grade B-cell NHL in combination with CHOP chemotherapy. (Ex. 1002 ¶56; Ex. 1020 at 002, Abstract.) Czuczman April 1996 describes the study administering rituximab before the first dose of CHOP; after the second and fourth cycles of six total cycles of CHOP; and after the last dose of

CHOP. (Ex. 1002 ¶56; Ex. 1039 at 003 (Abstract 191); *see also* Ex. 1011 at 003 (Abstract 206).) Czuczman 1996 explains that rituximab administered during CHOP chemotherapy was well tolerated, with no increased adverse events beyond what was expected with CHOP alone. (Ex. 1002 ¶56; Ex. 1039 at 003.) Cabanillas 1996 discloses combining rituximab "with standard dose CHOP chemotherapy" and notes rituximab's "known synergism with chemotherapeutic agents is being studied further in combination chemotherapy trials."[4] (Ex. 1002 ¶58; Ex. 1061 at 002; *see also* Ex. 1049, Ex. 1050.)[5]

[4] "IDEC-C2B8" is another designation for rituximab. (Ex. 1001 at 3:3-5.)

[5] Additionally, in July 1997, Dr. Grillo- López, inventor of the '821 patent, discussed the ongoing trials of rituximab and CHOP during an FDA hearing for approval of rituximab. The FDA Transcript was made publicly available on August 8, 1997, as confirmed by the Division of Dockets Management (DDM) at the FDA. (Ex. 1058.) The August 8, 1997 stamp on page 2 of the transcript indicates DDM received it on that date. (Ex. 1057 at 002; Ex. 1058 at 001.) In 1997, documents received by the DDM could be obtained by the public if one filled out a form requesting the document. (Ex. 1058 at 001.)

3. By August 1998, Publications Taught Combining Rituximab With Other Standard Chemotherapy Regimens, Including CVP

After the successful rituximab/CHOP clinical trial results were published, numerous publications discussed combining rituximab with standard chemotherapy to treat low-grade B-cell NHL. For example, in a December 1996 press release, IDEC (predecessor-in-interest to Patent Owner) first discussed the ongoing Phase II trial combining rituximab with CHOP, then described IDEC's plan to study "further uses for [rituximab] . . . *in combination with other anti-cancer treatments*." (Ex. 1051 at 002 (emphasis added).) In December 1997, after rituximab received FDA approval for use as a single agent to treat relapsed/refactory low-grade B-cell NHL (Ex. 1019 at 001), IDEC stated in its December 1997 10-K/A SEC Disclosure that "[o]ngoing or completed Phase II studies suggest that [rituximab] may also be useful in combination with chemotherapy in low grade or follicular lymphomas" and disclosed that rituximab will be tested in "combination therapy with *widely used chemotherapy regimens* for both low grade and intermediate/high grade disease." (Ex. 1006 at 012-13 (emphasis added).)[6] IDEC further disclosed that "[a]t least two of these trials will

[6] IDEC's 10-K/A was made public by at least March 3, 1998 pursuant to 15 U.S.C. §80a-44, which requires that "[t]he information contained in any registration

be large Phase III studies designed to explore the utility of Rituxan in combination with standard chemotherapy regimens." (*Id.* (emphasis added).)

In March 1997, Drs. Czuczman and Grillo-López reported that **"**[rituximab] has been effective in combination with chemotherapy. Further studies are planned." (Ex. 1002 ¶62; Ex. 1048 at 003 (Abstract 565); *see also* Ex. 1027 at 009 (urging rituximab "combinations with or after standard chemotherapy").)

Thus, long before August 1998, it was well known that rituximab was effective in combination with chemotherapy, and Phase III studies were planned to test rituximab in "combinations with standard chemotherapy." (Ex. 1006 at 012-13; Ex. 1048 at 003; Ex. 1002 ¶66.) It was further understood that CVP was a standard chemotherapy for low-grade NHL and that CVP was a less toxic, equally effective alternative to CHOP for low-grade lymphoma. (*See supra*, Section V.B.)

In March 1998, the Eastern Cooperative Oncology Group ("ECOG") activated a Phase III clinical trial to test the effectiveness of rituximab maintenance therapy following CVP chemotherapy. (Ex. 1065 at 007; Ex. 1066 at 001; Ex. 1003 ¶¶26, 40; Ex. 1002 ¶67.) The trial was entitled "Randomized Phase III

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statement, application, report, or other document filed with the Commission . . . shall be made available to the public . . . ." (*See also* Ex. 1055 at 019 ("Public portions of a live filing are immediately disseminated to the public.").)

Study in Low Grade Lymphoma Comparing Maintenance Anti-CD20 Antibody Versus Observation Following Induction Therapy" and received the designation "E1496." (Ex. 1065; Ex. 1066; Ex. 1002 ¶67.) As described in the declaration of Dr. Walter Longo, a medical oncologist at University of Wisconsin, Madison who was a sub-investigator in the E1496 clinical trial and enrolled patients in that trial, the E1496 Protocol and Patient Consent Form were freely available to potential patients and interested clinicians beginning March 1998 without any confidentiality restrictions. (Ex. 1003 ¶¶2, 3, 29, 32, 41, 51.)

4. Rituximab Was Approved For Administration During CVP Chemotherapy Regimens In September 2006

In February 2005, Marcus reported that low-grade NHL patients treated with rituximab and CVP had a statistically significant improvement in progression-free survival compared to those receiving CVP alone. (Ex. 1002 ¶71; Ex. 1005 at 003, Abstract, 007-08.) These results were submitted to the FDA and on September 29, 2006, the FDA granted approval to rituximab for use in first-line treatment of patients with low-grade or follicular B-cell, CD20-positive NHL. (Ex. 1002 ¶74; Ex. 1060 at 002.) One approval was for use of rituximab during CVP chemotherapy; the second was for use of rituximab following CVP chemotherapy. (Ex. 1060 at 002.)

Thus, nearly six years before the June 15, 2012 priority date of the '821 patent, it was well-known in the art that rituximab was being administered during CVP chemotherapy. (Ex. 1002 ¶75.)

VI. THE '821 PATENT

The '821 patent (Ex. 1001) is entitled "Combination Therapies for B-Cell Lymphomas Comprising Administration of Anti-CD20 Antibodies." It describes a therapeutic regimen to treat low-grade B-cell NHL with a combination of a specific course of chemotherapy and rituximab. (Ex. 1001 at Abstract.) The '821 patent contains six independent claims, which are listed in the Claim List, and in the claim charts below. (*See also* Ex. 1001 at 23:60-26:16.)

VII. THE '821 PATENT IS NOT ENTITLED TO A PRIORITY DATE EARLIER THAN JUNE 15, 2012

The '821 patent issued on March 29, 2016 from U.S. Application No. 13/524,896 ("the '896 application"), filed on June 15, 2012. The '896 application is a divisional application of the '956 application, filed August 18, 2007, which issued as the '172 patent. The '956 application is a continuation of U.S. Application No. 10/196,732, which is a continuation of the '202 application. The '202 application was filed August 11, 1999 and issued as the '043 patent. The '202 application, in turn, claims priority to U.S. Provisional Application No. 60/096,180 filed on August 11, 1998.

The claims of the '821 patent are not entitled to a priority date earlier than June 15, 2012 because the challenged claims lack written description support in the '202 application.[7] To have the benefit of the '202 application's August 11, 1999 filing date, both the '202 application and the later-filed '896 application must satisfy the written description and enablement requirements of 35 U.S.C. §112. M.P.E.P. (2015) §211.05(I) (*citing Transco Prods., Inc. v. Performance Contracting, Inc.*, 38 F.3d 551 (Fed. Cir. 1994)).

To satisfy the written description requirement, the patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude the inventor had possession of the claimed invention as of the filing date. M.P.E.P. §2163(I). 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

[7] During prosecution, Applicant asserted that the '202 application contained an adequate disclosure to support the issued claims of the '821 patent, but never argued that the '180 Provisional Application, filed on August 11, 1998, contained an adequate written description. Accordingly, Celltrion challenges Applicant's assertion of priority based on the '202 application filing date of August 11, 1999.

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., Inc. v. Microsoft Corp.*, 627 F.3d. 859, 870 (Fed. Cir. 2010) (internal citations omitted.) "[T]he question [of adequate written description] is not whether a claimed invention is an obvious variant of that which is disclosed in the specification." *Eli Lilly & Co. v. L.A. Biomedical Research Inst. at Harbor-UCLA Med. Ctr.*, No. IPR2014-00752, Paper No. 44 at 10 (P.T.A.B. Oct. 22, 2015) (citing *Lockwood v. Am. Airlines, Inc*., 107 F.3d 1565, 1572 (Fed. Cir. 1997)); *see also Tronzo*, 156 F.3d at 1158 ("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.").

Because Petitioner has identified invalidating prior art, it is the Patent Owner's burden to establish that the '821 patent is entitled to a priority date set by the August 1999 filing of the '202 application. *Research Corp. Techs.,* 627 F.3d. at 870 (internal citation omitted).

A. The '202 Application Does Not Describe Administering Rituximab During CVP Chemotherapy To Treat Low-Grade B-Cell NHL With Synergistic Effect

The '202 application does not describe the combination of administering rituximab ***during CVP*** chemotherapy to treat low-grade or follicular lymphoma,

where the method provides a beneficial synergistic effect. The Examiner repeatedly rejected applicant's attempts to claim priority to the '202 application on this basis. (*See* Ex. 1069 at 081 (Dec. 31, 2012 Non-Final Rejection); *see also id*. at 126 (Nov. 5, 2013 Final Rejection); *id*. at 151 (Mar. 26, 2014 Non-Final Rejection); *id*. at 174 (Sept. 16, 2014 Final Rejection); *id*. at 190-91 (Mar. 18, 2015 Non-Final Rejection).) These rejections were maintained until the September 16, 2015 interview and the December 18, 2015 Notice of Allowance, but the Examiner did not provide any detail regarding Applicant's priority date argument. (*See id.* at 210-11 (Summary of Interview); *id.* at 212-19 (Notice of Allowance).)

In response to the repeated rejection of priority to the '202 application, Applicant tried to combine various lines from the '202 specification and argued these fragments provided adequate support. These arguments are exemplified by Applicant's March 28, 2013 Response to Office Action, in which Applicant cited the following passages in the '202 application for new claims reciting administering rituximab during CVP chemotherapy to treat low-grade or follicular lymphoma:

> Exemplary support in the great-grandparent application, the '202 application, includes claim 17 and page 6, lines 12-14 disclosing a method for treating B-cell lymphoma (e.g. low grade NHL; see claim 29, and page 7, line 19) comprising administering to a patient a therapeutically effective amount of anti-CD20 antibody (e.g.

> rituximab; see claim 20 and page 11, lines 6-8) before, during or subsequent to a chemotherapeutic regimen (e.g. CVP chemotherapy; see page 25, lines 16-19, and page 28, line 18, disclosing COP/CVP therapy). Support for beneficial synergistic effect (of the combination) was found on page 3, line 8.

(Ex. 1069 at 116.) While the cited portions of the specification mention the words in the recited elements, they do not describe combining these elements to achieve the claimed methods of treatment. Indeed, the references to the cited elements are dispersed throughout the specification of the '202 application, at pages 3, 6, 7, 20, 25, 28, and claims 17, 20, and 29. (*Id.*) Nothing in these passages suggests that as of August 1999, Applicant had possession of the combination of (1) a method of treating low grade NHL; (2) comprising administering anti-CD20 antibody ***during CVP*** chemotherapy; (3) to achieve a beneficial synergistic effect. (Ex. 1002 ¶80.)

1. Original Claim 17 And Page 6, Lines 12-14 Of The '202 Application Fail To Identify Treating Low-Grade NHL, Administering CVP, And Achieving A Beneficial Synergistic Effect

Original claim 17 recites: "A method for treating B-cell lymphoma comprising administering to a patient a therapeutically effective amount of anti-CD20 antibody before, during or subsequent to a chemotherapeutic regimen." (Ex. 1034 at 058.) Page 6, lines 12-14 of the '202 application states essentially the same language. (*Id.* at 009.) This disclosure does not identify CVP, does not

specify low-grade NHL, and does not indicate a beneficial synergistic effect. Indeed the sentence immediately following lines 12-14 on page 6 states the chemotherapeutic regimens "may be selected *from the group consisting of*, at the very least, CHOP, ICE, Mitozantrone, Cytarabine, DVP, ATRA, Idarubicin, hoelzer [sic] chemotherapy regime, La La chemotherapy regime, ABVD, CEOP, 2-CdA, FLAG & IDA with or without subsequent G-CSF treatment), VAD, M&P, C-Weekly, ABCM, MOPP and DHAP." (*Id.* (emphasis added).) CVP is not included in this list of suggested chemotherapeutic regimens. It is axiomatic that "the group consisting of" in patent lexicon exclusively means a closed term. *Vehicular Techs. Corp. v. Titan Wheel Int'l, Inc.*, 212 F.3d 1377, 1382-83 (Fed. Cir. 2000). The omission of CVP from this list means this disclosure does not support CVP. (Ex. 1002 ¶81.)

2. Original Claim 29 And Page 7, Line 19 Of The '202 Application Fails To Specify Administering Rituximab During CVP Or Achieving A Beneficial Synergistic Effect

Original claim 29 depends from claim 17 and recites the subtypes of B-cell lymphoma, including "low grade/follicular . . . NHL," that can be treated using the method of claim 17. (Ex. 1034 at 061.) Page 7, line 19 of the '202 application recites similar language. (*Id.* at 010.) Nothing in this portion of the specification specifies administering rituximab during CVP chemotherapy or indicates a beneficial synergistic effect of such a combination. The disclosure regarding

treatment of low-grade and follicular NHL with a combination of rituximab and chemotherapy merely reports what was known in the art from at least Czuczman April 1995 (Ex. 1017) and the E1496 Patient Consent Form (Ex. 1066). (Ex. 1002 ¶82.)

3. Original Claim 20 And Page 11, Lines 6-8 Of The '202 Application Fails To Specify Administering Rituximab During CVP Or Achieving A Beneficial Synergistic Effect

Original claim 20 depends from claim 19, which depends from claim 17. Claim 20 recites use of the chimeric antibody C2B8 (rituximab) in the method of claim 17. (Ex. 1034 at 059.) Page 11, lines 6-8 of the '202 application describes rituximab. (*Id.* at 014.) Nothing in this portion of the specification specifies administering rituximab during CVP chemotherapy or indicates a beneficial synergistic effect of such a combination. The disclosure of using rituximab with chemotherapy to treat low-grade and follicular NHL merely reports what was known in the art from at least Czuczman April 1995 (Ex. 1017) and the E1496 Patient Consent Form (Ex. 1066). *See also supra,* Section V.D.2-3.

4. Page 25, Lines 16-19 Of The '202 Application Fails To Discuss Treatment Of Low-Grade NHL, Administering Rituximab With CVP, Or Achieving A Beneficial Synergistic Effect

The cited disclosure at page 25, lines 16-19 of the '202 application states:

> Cyclophosphamide is an alternative to chlorambucil, the usual dose being 1-2 g/m^2 every 3-4 weeks together with vincristine and steroids

> (e.g., COP regimen).
>
> Various drug combinations have been used for CLL, including COP (cyclophosphamide, Oncovin, and prednisone), and CHOP (these three drugs plus doxorubicin).

(Ex. 1034 at 029.) The discussion of CVP ("COP") in this passage refers to treatment of CLL (chronic lymphocytic leukemia). (*Id.* at 021.) The inventors do not suggest using CVP for low-grade NHL. (*Id.*) The passage also makes no mention of combining anti-CD20 antibody with CVP, much less administering the antibody during CVP chemotherapy to achieve a beneficial synergistic effect in low-grade NHL. The discussion of using CVP to treat CLL merely discloses what was known in the art. (Ex. 1068; Ex. 1002 ¶85.) Even though CVP was a standard therapy for lymphoma, this disclosure does not indicate to a POSA that the inventors possessed the concept of using CVP and rituximab for the treatment of low-grade NHL. (Ex. 1002 ¶85.)

5. Page 28, Line 18 Of The '202 Application Fails To Describe Administering Rituximab During CVP Or Achieving A Beneficial Synergistic Effect

The cited disclosure at page 28, line 18 of the '202 application consists of fragments of a discussion of a clinical trial. The complete paragraph states:

> A Phase III study conducted by ECOG in patients with low-grade NHL is comparing the combination of cyclophosphamide and fludarabine (Arm A) with standard CVP therapy (Arm B). In the

> randomization to Arm A or Arm B, patients are stratified by age, tumor burden, histology, and B symptoms. Responders in both arms will undergo a second randomization to Rituximab® maintenance therapy (375 mg/m2 weekly times 4 every 6 months for 2 years (Arm C) or to observation (Arm D).

(Ex. 1034 at 032.) This paragraph refers to the E1496 study, which is described in detail in the E1496 Patient Consent Form. (Ex. 1066.) The disclosure does not suggest administering anti-CD20 antibody ***during CVP*** chemotherapy to achieve a beneficial synergistic effect. Instead, the described trial first administers standard CVP and ***follows*** with administration of rituximab ***maintenance therapy*** to Responders after a second randomization of the Responders. (Ex. 1002 ¶87.)

6. Page 3, Line 8 Of The '202 Application Fails To Disclose A Beneficial Synergistic Effect Of Administering Rituximab During CVP Therapy

The referenced disclosure at page 3, line 8 of the '202 application is a sentence fragment, which states in full: "In particular, it has been found that treatment with anti-CD20 antibody provides a beneficial synergistic effect when administered in combination with cytokines, radiotherapy, myeloablative therapy, or chemotherapy." (Ex. 1034 at 006.) Again, this disclosure makes no specific reference to a beneficial, synergistic effect of administering rituximab ***during CVP*** therapy. Thus, a POSA would not have understood that the inventors possessed the concept of administering rituximab during CVP therapy. (Ex. 1002 ¶88.) Nor

would a POSA have understood that the inventors possessed the concept that rituximab and CVP would have a beneficial, synergistic effect in light of the specification. (Ex. 1002 ¶88.)

The Patent Owner cannot establish adequate written description of the recited combination of steps in the claimed methods by pulling together unrelated passages of the '202 application that never describe the combination. The specification does not identify treating low-grade NHL by administering rituximab ***during CVP*** chemotherapy for a beneficial synergistic effect. (*Id.* ¶89.) Instead, the cited portions merely discuss known, published information from clinical trials which, as discussed below, render the '821 claims obvious. The specification's identification of information that would make the patent claims obvious is insufficient to establish that the inventor possessed the claimed method. *Lockwood*, 107 F.3d at 1572. These inadequate disclosures fail to satisfy the written description requirement. *See, e.g.*, *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1353 (Fed. Cir. 2011) (finding claims invalid for lack of written description because the specification did not demonstrate "constructive possession" of the claimed subject matter).

B. The '202 Application Does Not Disclose A Rituximab Dosing Regimen Of 375 Mg/M^2 Once Every 3 Weeks For 8 Doses

The rituximab dosing regimen in claims 4-6, 375 mg/m^2 "once every 3 weeks for 8 doses," (Ex. 1001 at 25:14-15, 26:6-7) appears nowhere in the '202 application. Applicants again tried the jigsaw puzzle approach, citing to disclosures of infusions once every 3 weeks in some portions of the specification, and reference to 8 doses in other parts of the specification. While those prior art studies render the '821 claims obvious, they do not establish written description of these combined elements. (Ex. 1002 ¶94.)

Applicants cited page 25, lines 16-17, page 28, line 2, and page 36, lines 2 and 14 of the '202 application as providing support for the "once every 3 weeks" element. (Ex. 1069 at 186-87.) But the disclosure at page 25, lines 16-17 of the '202 application refers to the dosage of "Cyclophosphamide [as] an alternative to chlorambucil, the usual dose being 1-2 g/m^2 every 3-4 weeks together with vincristine and steroids (e.g., COP regimen)." (Ex. 1034 at 029.) The disclosure makes no mention of rituximab. Page 28, line 2 refers to a rituximab combination with CHOP (*id*. at 032), not the claimed CVP, and states, "CHOP was administered at standard doses every three weeks *for six cycles with six infusions* of Rituximab" (*id.* (emphasis added)), not the claimed 8 doses.[8]

[8] Czuczman 1995 published this dosing regimen. (Ex. 1017; Ex. 1011.)

Page 36, line 2 refers to treatment of intermediate- or high-grade NHL (not the claimed low-grade or follicular NHL), combination with CHOP (not the claimed CVP) and treatment for six cycles (not the claimed 8 doses).[9] (Ex. 1034 at 040.) Page 36, line 14 refers to treatment of mantle-cell lymphoma (not the claimed low-grade or follicular NHL), combination with CHOP (not the claimed CVP) and treatment for six cycles (not the claimed 8 doses). (*Id*.)

Likewise, the claimed element of "for 8 doses" is never disclosed in the '202 application in the context in which it is claimed. Applicant stated that page 22, line 4; page 28, line 14; and page 35, line 15 of the '202 application provide support for the "for 8 doses" element. (Ex. 1069 at 186-87.) Page 22, line 4 refers to eight weekly doses of rituximab given as a single agent, not the claimed every 3 weeks dose given during CVP therapy.[10] (Ex. 1034 at 026.) Page 28, line 14 refers to combination with cyclophosphamide (not the claimed CVP) and rituximab given weekly (not the claimed every 3 weeks dose). (*Id.* at 032.) Page 35, line 15 refers to treatment of intermediate- or high-grade NHL (not the claimed low-grade or follicular NHL), rituximab administration as a single-agent (not the claimed

[9] Link 1998 published this dosing regimen. (Ex. 1064.)

[10] Piro 1997 (Ex. 1004) and a 1997 FDA Transcript (Ex. 1057 at 027) published this dosing regimen.

administration during CVP therapy) and rituximab given weekly (not the claimed every 3 weeks dose). (*Id.* at 039.)

The '202 specification disclosures demonstrate that the inventor did not possess the dosing regimen recited in claims 4-6. Because the '202 specification does not describe that dosing regimen, the priority date of all claims of the '821 patent is June 15, 2012, the filing date of the '896 application.

VIII. 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, 2136 (2016). Accordingly, the constructions proposed in this Petition represent the broadest reasonable interpretation one of ordinary skill in the art would assign to the terms below. For the claim terms not addressed below, Petitioner has applied the plain and ordinary meaning of the term.

A. Terms For Construction

1. "beneficial synergistic effect"

Claims 1 and 4 recite that the "method provides a beneficial synergistic effect in the patient." Although the specification does not expressly define "beneficial synergistic effect," it does state that it would be "beneficial if more

effective treatment regimens could be developed." (Ex. 1001 at 2:3-4.) Further, the specification states, "it has been found that treatment with anti-CD20 antibody provides a beneficial synergistic effect when administered in combination with cytokines, radiotherapy, myeloablative therapy, or chemotherapy." (*Id*. at 2:24-28.)

During prosecution, Applicant argued that data referenced in the 2006 label (Ex. 1060) and the Marcus publication (Ex. 1005) showed that patients who received rituximab during CVP chemotherapy "experienced median progression free survival (PFS) of 2.4 years compared with 1.4 years in patients treated with CVP only, demonstrating a beneficial synergistic effect in the patient." (Ex. 1069 at 120.) Under Applicant's argument, an improvement in clinical outcome demonstrates a beneficial synergistic effect.

Under the broadest reasonable interpretation standard, "beneficial synergistic effect" should be construed to mean "an improvement in clinical outcome."

IX. THE CLAIMS OF THE '821 PATENT ARE UNPATENTABLE

A. PERSON OF ORDINARY SKILL IN THE ART

As of August 11, 1998, August 11, 1999 and June 15, 2012, a person of ordinary skill in the art ("POSA") at the time of the alleged invention of the '821 patent would be a practicing physician specializing in hematology or oncology,

with at least three years of experience in treating patients with NHL. (Ex. 1002 ¶24.)

B. The Prior Art

Petitioner relies on the following patent applications and publications:

1. Marcus (Ex. 1005)

Marcus is an article published in the journal *Blood* in February 2005 and entitled, "CVP Chemotherapy plus Rituximab Compared with CVP as First-Line Treatment For Advanced Follicular Lymphoma." Marcus qualifies as prior art under 35 U.S.C. §102(b) because it was published and publicly available in February 2005—more than one year before the earliest priority date to which the '821 patent claim is entitled (June 15, 2012).

2. U.S. Patent No. 5,736,137 (Ex. 1007)

The '137 patent by Anderson et al. is entitled "Therapeutic application of chimeric and radiolabeled antibodies to human B lymphocyte restricted differentiation antigen for treatment of B-cell lymphoma" and was filed on November 3, 1993 and issued on April 7, 1998. The '137 patent therefore qualifies as prior art under 35 U.S.C. §102(b) because it was published and publicly available more than one year before both the earliest priority date to which the '821 patent claim is entitled (June 15, 2012) and the priority date of the '202 application (August 11, 1999).

3. Czuczman November 1995 (Ex. 1011)

Czuczman November 1995 is an abstract published in the journal *Blood* in November 1995 and entitled, "IDEC-C2B8 and CHOP Chemoimmunotherapy of Low-Grade Lymphoma." Czuczman November 1995 qualifies as prior art under 35 U.S.C. §102(b) because it was published and publicly available more than one year before either possible priority date for the '821 patent.

4. IDEC 10-K/A SEC Disclosure (Ex. 1006)

The IDEC 10-K/A SEC Disclosure is an amendment to a report required by the Securities and Exchange Commission ("SEC"). It describes IDEC's financial performance for the fiscal year ending Dec. 31, 1997. Pursuant to federal securities laws, it was made publicly available in the SEC's Electronic Data Gathering, Analysis, and Retrieval ("EDGAR") system by at least March 3, 1998. (15 U.S.C. §80a-44; Ex. 1056.)[11] The IDEC 10-K/A SEC disclosure qualifies as prior art under 35 U.S.C. §102(b) because it was published and publicly available

[11] The EDGAR Filing Details indicate that the IDEC 10-K/A was accepted and filed on March 3, 1998. (Ex. 1056.) The EDGAR Filer Manual from September 1996 explains that the public portions of live filings, such as the IDEC 10-K/A, are "immediately disseminated to the public." (Ex. 1055 at 020 (distinguishing live filings from test filings).)

more than one year before either possible priority date for the '821 patent. This is consistent with *Coalition for Affordable Drugs (ADROCA) LLC v. Acorda Therapeutics, Inc.*, in which the Board found an SEC submission a "printed publication" under 35 U.S.C. §102(b). IPR2015-01850, Paper No. 14 at 14 (P.T.A.B. Mar. 11, 2016).[12]

5. Foon (Ex. 1008)

Williams Hematology, 5th Edition, was published in 1995. Chapter 111, entitled "Lymphomas," is authored by Foon and Fisher (hereinafter "Foon"). Foon qualifies as prior art under 35 U.S.C. §102(b) because it was published and publicly available more than one year before either possible priority date for the '821 patent.

6. Dana (Ex. 1009)

Dana is a 1993 publication in the Journal of Clinical Oncology and is entitled "Long-term follow-up of patients with low-grade malignant lymphomas treated with doxorubicin-based chemotherapy or chemoimmunotherapy." Dana is

[12] District courts recognize that documents filed with the SEC are "printed publications" under 35 U.S.C. §102. *See, e.g., Am. Stock Exch., LLC v. Mopex, Inc.*, 250 F. Supp. 2d 323, 328-29 (S.D.N.Y. Feb. 4, 2003); *see, e.g., Wynn v. Chanos*, 75 F. Supp. 3d 1228, 1235 (N.D. Cal. 2014).

§102(b) prior art because it was published and publicly available more than one year before either possible priority date for the '821 patent.

7. Link (Ex. 1010)

Link is an April 1998 publication in the Program/Proceedings of the American Society of Clinical Oncology and is entitled "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." Link is §102(b) prior art as it was publicly available more than a year before either possible priority date for the '821 patent.

8. Piro (Ex. 1004)

Piro is an abstract published in the journal *Blood* in November 1997 and entitled, "Rituxan™ (rituximab, IDEC-C2B8): Interim analysis of a phase II study of once weekly times 8 dosing in patients with relapsed low-grade or follicular non-Hodgkin's lymphoma." Piro therefore qualifies as prior art under 35 U.S.C. §102(b) because it was published and publicly available more than one year before either possible priority date for the '821 patent.

C. Background Art

In addition to the specific references discussed above, Dr. Lossos considered additional references, as described in his declaration, reflecting the state of the art in August 1999 and June 2012. *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 '821 PATENT ARE ANTICIPATED OR OBVIOUS

A. Applicable Legal Standards

1. Anticipation

Under 35 U.S.C. §102(b), a patent is invalid if the purported invention "was patented or described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for a patent in the United States." A patent claim is anticipated when every limitation is found either expressly or inherently in a single prior art reference. *King Pharms., Inc. v. Eon Labs, Inc.* 616 F.3d 1267, 1274 (Fed. Cir. 2010) (internal citation omitted). Although "the elements must be arranged or combined in the same way as in the claim, . . . the reference need not satisfy an *ipsissimis verbis* [*i.e*. verbatim] test[.]" *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (internal quotation marks and citations omitted).

2. Obviousness

Obviousness requires analyzing (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v.*

John Deere Co., 383 U.S. 1, 17-18 (1966). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 416 (2007).

Claims reciting a process, such as a method of treatment, are not patentable if "the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *Merck & Co., 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." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007).

In *Coherus Biosciences Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2016-00172, Paper No. 9 at 16 (P.T.A.B. May 17, 2016), the Board noted, "all that is required to show obviousness is a reasonable expectation of success, not conclusive proof of superior efficacy." *Id.* (instituting IPR because dosing regimens would have been obvious) (citing *PharmaStem Therapeutics, Inc. v. ViaCell, Inc*., 491 F.3d 1342, 1363-64 (Fed. Cir. 2007); *Pfizer*, 480 F.3d at 1364.).

Similarly, in *Biomarin Pharm. Inc. v. Genzyme Therapeutic Prods. Ltd. P'ship*, the Board found claims directed to specific dosing regimen were obvious.

The Board acknowledged that although "a person of ordinary skill in the art could not have predicted with absolute certainty . . . a safe and effective dosing regimen," "the selection of the dose and dosing schedule would have been a routine optimization of the therapy outlined in [the prior art], which would have been achievable through the use of standard clinical trial procedures." IPR2013-00534, Paper No. 81 at 12-14 (P.T.A.B. Feb. 23, 2015).

B. Ground 1: Claims 1-6 Are Anticipated By Marcus

Marcus is a publication from February 2005 describing the results of a clinical trial comparing CVP with CVP plus rituximab in previously untreated patients with advanced follicular lymphoma. Patients assigned to the rituximab-CVP arm received 375 mg/m^2 of rituximab every three weeks for eight total doses. (Ex. 1002 ¶95; Ex. 1005 at 003, Abstract, 004.) Marcus discloses that patients who received CVP plus rituximab demonstrated "major improvement in all clinical endpoints." (Ex. 1002 ¶95; Ex. 1005 at 007.) More specifically, Marcus states:

> At a median follow-up of 30 months, the addition of rituximab to a standard CVP regimen significantly lengthened time to treatment failure and more than doubled time to progression, with significantly improved response rates, duration of response, disease-free survival, and time to next antilymphoma treatment.

(Ex. 1005 at 007.) Based on this reported improvement in clinical outcomes, Marcus accordingly reports a beneficial synergistic effect of the combination. (Ex. 1002 ¶95.)

Furthermore, Marcus inherently discloses rituximab's amino acid sequence, as depicted in SEQ ID NO: 1 and SEQ ID NO: 2 of the '821 patent. (Ex. 1002 ¶96; *see* Ex. 1012, SEQ ID Nos: 7, 10 (amino acid sequences for rituximab, also known as C2B8).) Under the doctrine of inherent disclosure, a reference that describes an invention with "certain undisclosed yet inherent properties" is deemed to inherently disclose the invention's inherent properties. *Yeda Research & Dev. Co. v. Abbott GMBH & Co. KG*, 837 F.3d 1341, 1345 (Fed. Cir. 2016); *see also In re Crish*, 393 F.3d 1253, 1258 (Fed. Cir. 2004) ("A long line of cases confirms that one cannot establish novelty by claiming a known material by its properties."). Thus, in *In re Crish*, the Federal Circuit held that prior art references disclosing a specific plasmid, though not its DNA sequence, anticipated a claim for the DNA sequence of that plasmid. *In re Crish*, 393 F.3d at 1258-59. The Federal Circuit stated, "just as the discovery of properties of a known material does not make it novel, the identification and characterization of a prior art material also does not make it novel." *Id.* at 1258. Similarly, in *Yeda*, the Federal Circuit held that a patent application describing a partial N-terminus sequence inherently disclosed the full amino acid sequence of the only protein described by the disclosed partial

N-terminus sequence. *Yeda*, 837 F.3d at 1345. Likewise, the amino acid sequences disclosed in SEQ ID NO: 1 and SEQ ID NO: 2 in the '821 merely identify and characterize rituximab. Therefore, Marcus's disclosure of rituximab inherently discloses rituximab's amino acid sequences as depicted in SEQ ID NO: 1 and SEQ ID NO: 2 of the '821 patent.

Thus, Marcus discloses the treatment of follicular NHL by administering CVP concurrent with 375 mg/m^2 of rituximab every three weeks for up to eight doses and the benefit to patients of combining CVP and rituximab. (Ex. 1002 ¶96; Ex. 1005 at 004-06.) Each claim of the '821 patent is directed towards treatment of low-grade or follicular NHL through concurrent use of CVP and 375 mg/m^2 of either a chimeric anti-CD20 antibody or rituximab—a specific chimeric anti-CD20 antibody also known as C2B8. (Ex. 1001 at 23:59-26:16.) Claims 3 and 6 describe rituximab by its amino acid sequence, depicted in SEQ ID NO: 1 and SEQ ID NO: 2. (*Compare id.* at SEQ ID Nos. 1, 2 *with* Ex. 1012 at SEQ ID Nos. 7, 10 (U.S. Patent No. 6,399,061 providing the amino acid sequences for C2B8).) Claims 4-6 add the limitation that the anti-CD20 antibody be administered every three weeks for eight doses. (Ex. 1001 at 25:8-26:16) Therefore, as depicted in the claim chart below, Marcus's disclosure encompasses each of the elements of the claims of the '821 patent, so Marcus anticipates all claims of the '821 patent. (Ex. 1002 ¶¶96-97.)

GROUND 1		
	'821 Claim	**Marcus (Ex. 1005)**
1.	A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL)	"Eligible patients were 18 years or older with untreated CD20+ follicular lymphoma." (Ex. 1005 at 004.)
	comprising administering to a patient a therapeutically effective amount of **rituximab** during a chemotherapeutic regimen, wherein the chemotherapeutic regimen consists of cyclophosphamide, vincristine, and prednisone (CVP therapy),	"Patients . . . [treated] with CVP plus rituximab (R-CVP) or CVP alone." (*Id*.)
	wherein the method comprises administering 375 mg/m^2 of rituximab,	"Patients treated with R-CVP also received 375 mg/m^2 of rituximab intravenously on day 1 of each therapy cycle." (Ex. 1005 at 004; Ex. 1002 ¶97.)
	and wherein the method provides a beneficial synergistic effect in the patient.	"Treatment with R-CVP significantly lengthened [time to treatment failure]. . . the addition of rituximab to CVP reduced the risk of experiencing disease progression across all patient subgroups . . . compared with CVP." (Ex. 1005 at 005-06; Ex. 1002 ¶97.)
2.	A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL)	*See above*.
	comprising administering to a patient 375 mg/m^2 of C2B8	*See above*. The '821 patent states that C2B8 is rituximab. (Ex. 1001 at 3:3-5.)
	during a chemotherapeutic regimen consisting of cyclophosphamide, vincristine, and prednisone (CVP therapy)	*See above*.

3.	A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL)	*See above*.
	comprising administering to a patient 375 mg/m^2 of a chimeric anti-CD20 antibody	*See above*. "Rituximab, a chimeric monoclonal antibody against CD20" (Ex. 1005 at 003, Abstract; Ex. 1002 ¶97.)
	during a chemotherapeutic regimen consisting of cyclophosphamide, vincristine, and prednisone (CVP therapy)	*See above*.
	wherein the chimeric anti-CD20 antibody is produced from nucleic acid encoding a light chain variable region comprising the amino acid sequence in SEQ ID NO: 1 and a heavy chain variable region comprising the amino acid sequence in SEQ ID NO: 2, and comprises human gamma 1 heavy -chain and kappa light chain constant region sequences.	This is a description of the C2B8 chimeric antibody, which the '821 patent states is the preferred chimeric antibody. (Ex. 1001 at 3:3-5.) Accordingly, SEQ ID NO: 1 and SEQ ID NO: 2 are inherently disclosed by Marcus. *See Yeda*, 837 F.3d at 1345; *In re Crish*, 393 F.3d at 1258.
4.	A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL) comprising administering to a patient a therapeutically effective amount of rituximab during a chemotherapeutic regimen, wherein the chemotherapeutic regimen consists of cyclophosphamide, vincristine, and prednisone (CVP therapy),	*See* Claim 1*, above*.
	wherein the method comprises administering 375 mg/m^2 of rituximab once every 3 weeks for 8 doses, and	"Patients treated with R-CVP also received 375 mg/m^2 of rituximab intravenously on day 1 of each therapy cycle. . . . Patients . . . were treated every 21 days for a maximum

		of 8 cycles." (Ex. 1005 at 004; Ex. 1002 ¶97.)
	wherein the method provides a beneficial synergistic effect in the patient.	*See* Claim 1*, above*.
5.	A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL)	*See* Claim 2, *above*.
	comprising administering to a patient 375 mg/m^2 of C2B8 once every 3 weeks for 8 doses during a chemotherapeutic regimen	"Patients treated with R-CVP also received 375 mg/m^2 of rituximab intravenously on day 1 of each therapy cycle. . . . Patients . . . were treated every 21 days for a maximum of 8 cycles." (Ex. 1005 at 004; Ex. 1002 ¶97.)
	consisting of cyclophosphamide, vincristine, and prednisone (CVP therapy).	*See* Claim 2*, above*.
6.	A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL)	*See* Claim 3, *above*.
	comprising administering to a patient 375 mg/m^2 of a chimeric anti-CD20 antibody once every 3 weeks for 8 doses	"Patients treated with R-CVP also received 375 mg/m^2 of rituximab intravenously on day 1 of each therapy cycle. . . . Patients . . . were treated every 21 days for a maximum of 8 cycles." (Ex. 1005 at 004; Ex. 1002 ¶97.)
	during a chemotherapeutic regimen consisting of cyclophosphamide, vincristine, and prednisone (CVP therapy)	*See* Claim 3*, above.*
	wherein the chimeric anti-CD20 antibody is produced from nucleic acid encoding a light chain variable region comprising the amino acid	*See* Claim 3*, above.*

	sequence in SEQ ID NO: 1 and a heavy chain variable region comprising the amino acid sequence in SEQ ID NO: 2, and comprises human gamma 1 heavy -chain and kappa light chain constant region sequences.	

C. Ground 2: Claims 3 And 6 Are Obvious Under §103 Over Marcus And The '137 Patent

Claims 3 and 6 of the '821 patent would have been obvious over Marcus (Ex. 1005) in view of the '137 patent (Ex. 1007.) Marcus is a February 2005 publication describing the results of a clinical trial comparing CVP with CVP plus rituximab in previously untreated patients with advanced follicular lymphoma. As described above, Marcus discloses both the treatment of follicular NHL by administering CVP concurrent with 375 mg/m^2 of rituximab every three weeks for up to eight doses and the benefit to patients attributable to this combination of CVP and rituximab. (Ex. 1002 ¶95; Ex. 1005 at 004-06.) The '137 patent, which issued in April 1998, discloses the amino acid sequence of rituximab. (Ex. 1007 at SEQ ID Nos. 6, 9.) *See Biogen Idec Inc. v. GlaxoSmithKline LLC*, 713 F.3d 1090, 1093 (Fed. Cir. 2013) ("U.S. Patent No. 5,736,137 . . . teaches the isolation, screening, and characterization of Rituxan®.").

Thus, to the extent the Board finds that Marcus does not inherently disclose and therefore anticipate the SEQ ID NO: 1 and SEQ ID NO: 2 claim elements in

claims 3 and 6, the combination of Marcus and the '137 patent renders those claim elements obvious. (Ex. 1002 ¶¶98-99.) A POSA would be motivated to combine Marcus and the '137 patent in order to successfully administer Marcus's CVP + rituximab treatment plan using rituximab, as described by the '137 patent. (*Id.* ¶100.) Because the '137 patent discloses rituximab's amino acid sequence, a POSA would have a reasonable expectation of success administering rituximab as identified by the '137 patent using Marcus's successful treatment plan. (*Id.* ¶101.)

D. Ground 3: Claims 1-3 Are Obvious Under § 103 Over Czuczman, IDEC's 10-K/A, Foon, And Dana

Claims 1-3 of the '821 patent would have been obvious over Czuczman (Ex. 1011) in view of IDEC's 10-K/A (Ex. 1006), Foon (Ex. 1008), and Dana (Ex. 1009). (Ex. 1002 ¶¶102-12.)

Czuczman is a scientific abstract published in November 1995 in the journal *Blood*. (Ex. 1011 at 003 (Abstract 206).) Czuczman explains that rituximab "has been shown to induce apoptosis and to sensitize drug resistant human lymphoma cell lines to the cytotoxic effects of ricin and chemotherapeutic agents." (*Id.*) According to Czuczman, combining rituximab with chemotherapy is desirable due to "single agent efficacy, non-cross-resistant mechanism of action, synergy with chemotherapeutic agents and non-overlapping toxicities." (*Id*.) Czuczman suggests that "the anti-tumor activity of CHOP and [rituximab] is superior to

CHOP chemotherapy alone." (Ex. 1011 at 003; Ex. 1002 ¶¶103, 104.) All patients who completed therapy had either complete or partial responses. (Ex. 1011 at 003.) Moreover, Czuczman reports data for patients who at the start of the study tested positive for the oncogene bcl-2, a molecular marker of NHL. All patients who began the study bcl-2 positive converted to bcl-2 negativity at the conclusion of treatment. (*Id*.) Czuczman notes that standard chemotherapy regimens alone have been unable to clear bcl-2 positive cells from the bone marrow. (*Id*.) Czuczman teaches that both relapsed patients and patients who had previously not received any chemotherapy could successfully be treated with six 375 mg/m^2 doses of rituximab administered during a CHOP regimen. (*Id*.) Czuczman thus teaches that rituximab can be safely and efficaciously administered during a chemotherapeutic regimen with a beneficial synergistic effect. (Ex. 1002 ¶¶103, 104.)

IDEC's 10-K/A for the Fiscal Year ending December 31, 1997 and published in March 1998 explicitly suggests combining rituximab with widely used chemotherapy regimens (plural) for both low-grade and intermediate/high-grade disease:

> [Idec Corporation] in conjunction with Genentech has authorized over 35 Rituxan post-marketing trials to date. Several of these trials will explore the use of Rituxan in a

> variety of investigational B-cell non-Hodgkin's lymphoma clinical settings including: *(i) combination therapy with widely used chemotherapy regimens for both low grade and intermediate/high grade disease . . . .*

(Ex. 1006 at 013 (emphasis added).) It further reports that "[o]ngoing or completed Phase II studies suggest that [rituximab] may also be useful in combination with chemotherapy in low grade or follicular lymphomas." (*Id.* at 012.) (Ex. 1002, ¶105.)

Foon is the *Lymphomas* chapter from the treatise, Williams Hematology, 5th Edition, published in 1995. Foon teaches that CVP, along with CHOP and COPP, were standard combination chemotherapies for the treatment of low-grade B-cell NHL. (Ex. 1002 ¶106; Ex. 1008 at 029 (Table 111-7).) Foon further discloses that there is no evidence adding doxorubicin to CVP (as in CHOP) prolongs survival. (Ex. 1008 at 030.)

Dana is a 1993 publication in the Journal of Clinical Oncology. Dana reviews survival data from multiple studies on low-grade lymphoma to analyze CHOP's effectiveness for these patients. (Ex. 1009 at 002, Abstract.) Dana teaches that CHOP does not provide any survival advantage over CVP in advanced low-grade lymphoma. (*Id.* at 002, Abstract, 006; Ex. 1002 ¶106.)

Thus, Czuczman describes treating low-grade NHL with rituximab and CHOP, and the synergistic benefits of administering rituximab with standard

chemotherapy, which resulted in Czuczman's reported improvement in clinical outcomes. Czuczman additionally teaches the safety and efficacy of administering rituximab to NHL patients at doses of 375 mg/m^2 during CHOP. IDEC's 10-K/A suggests combining rituximab with other standard chemotherapy regimens for low-grade lymphoma, Foon teaches that CVP is a standard chemotherapy regimen for low-grade lymphoma, and Foon and Dana teach that for low-grade NHL, adding doxorubicin—the compound in CHOP that differentiates CHOP from CVP—does not improve survival or response rates.

Furthermore, Czuczman inherently discloses rituximab's amino acid sequence, as depicted in SEQ ID No: 1 and SEQ ID NO:2 of the '821 patent. (Ex. 1002 ¶107; *see* Ex. 1012, SEQ ID Nos: 7, 10 (amino acid sequences for rituximab, also known as C2B8).) *See Yeda*, 837 F.3d at 1345 (under the doctrine of inherent disclosure, a reference that describes an invention with "certain undisclosed yet inherent properties" is deemed to inherently disclose the invention's inherent properties); *In re Crish*, 393 F.3d at 1258 ("[O]ne cannot establish novelty by claiming a known material by its properties.").

Therefore, as depicted in the claim chart below, a POSA viewing this art as of August 1998 or August 1999 would find the claimed inventions obvious. (Ex. 1002 ¶107.)

GROUND 3		
	'821 Claim	**Czuczman (Ex. 1011), IDEC's 10-K/A (Ex. 1006), Foon (Ex. 1008), and Dana (Ex. 1009)**
1.	A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL)	Czuczman describes clinical trial results in low-grade NHL patients. "The chimeric monoclonal anti-CD20 antibody IDEC-C2B8 has shown clinical activity in pts with low grade or follicular lymphoma." (Ex. 1011 at 003.)
	comprising administering to a patient a therapeutically effective amount of **rituximab** during a chemotherapeutic regimen, wherein the chemotherapeutic regimen consists of cyclophosphamide, vincristine, and prednisone (CVP therapy),	Czuczman describes effectively treating patients with rituximab and standard chemotherapy. IDEC's 10-K/A suggests combining rituximab with standard chemotherapy regimens for low-grade NHL. (Ex. 1006 at 013.) The '821 patent states that C2B8 is rituximab. (Ex. 1001 at 3:3-5.) "In this study, IDEC-C2B8 is given at a dose of 375 mg/m^2 . . . [for] 6 doses]. CHOP . . . is given . . . [for] 6 cycles." (Ex. 1011 at 003.) --- Foon teaches that CVP is a standard chemotherapy regimen for low-grade NHL. (Ex. 1008 at 029.) Foon and Dana teach that CVP is as effective as CHOP for low-grade NHL. (Ex. 1008 at 030; Ex. 1009 at 002, Abstract.)
	wherein the method comprises	"In this study, IDEC-C2B8 is given at

	administering 375 mg/m^2 of rituximab,	a dose of 375 mg/m^2 . . . [for] 6 doses]. CHOP . . . is given . . . [for] 6 cycles." (Ex. 1011 at 003.)
	and wherein the method provides a beneficial synergistic effect in the patient.	Czuczman describes the improvement in clinical outcome for the patients who received rituximab during standard chemotherapy. "Overall response rate for the 14 pts completing all scheduled therapy to date is 100% (11 CR and 3 PR) . . . The finding of molecular remissions by PCR suggests that the anti-tumor activity of CHOP and IDEC-C2B8 is superior to CHOP therapy alone." (Ex. 1011 at 003.) Czuczman further explains that rituximab exhibits "synergy with chemotherapeutic agents . . . ." (*Id*.)
2.	A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL)	*See above*.
	comprising administering to a patient 375 mg/m^2 of C2B8	*See above*.
	during a chemotherapeutic regimen consisting of cyclophosphamide, vincristine, and prednisone (CVP therapy)	*See above*.
3.	A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL)	*See above*.
	comprising administering to a patient 375 mg/m^2 of a chimeric anti-CD20 antibody	*See above*.
	during a chemotherapeutic regimen consisting of cyclophosphamide, vincristine, and prednisone (CVP therapy)	*See above*.

	wherein the chimeric anti-CD20 antibody is produced from nucleic acid encoding a light chain variable region comprising the amino acid sequence in SEQ ID NO: 1 and a heavy chain variable region comprising the amino acid sequence in SEQ ID NO: 2, and comprises human gamma 1 heavy -chain and kappa light chain constant region sequences.	This is a description of the C2B8 chimeric antibody, which the '821 patent states is the preferred chimeric antibody. (Ex. 1001 at 3:3-5.) Accordingly, SEQ ID NO: 1 and SEQ ID NO: 2 are inherently disclosed by Czuczman. *See Yeda*, 837 F.3d at 1345; *In re Crish*, 393 F.3d at 1258.

1. Motivation To Combine

A POSA would have known about Czuczman's results demonstrating the safety and efficacy of administering rituximab during CHOP chemotherapy, and in view of IDEC's 10-K/A would have been motivated to combine rituximab *with other standard chemotherapy regimens* to treat low-grade NHL patients. (Ex. 1002 ¶108.) A POSA would have understood from Foon and Dana that CVP was a standard chemotherapy regimen that was less toxic but equally effective as CHOP for low-grade NHL. (*Id.*; Ex. 1022 at 011; Ex. 1059 at 003; Ex. 1005 at 003; Ex. 1009 at 002; Ex. 1031 at 007.) Thus, a POSA would have considered CVP an obvious choice of standard chemotherapy to combine with rituximab, as suggested by IDEC's 10-K/A. (Ex. 1002 ¶108.) Additionally, in light of the toxicity of doxorubicin, as well as the recognition that doxorubicin provides no added benefit to low-grade NHL patients, a POSA would have been encouraged by Dana to use CVP instead of Czuczman's CHOP in combination with rituximab.

(*Id.* ¶109; Ex. 1022 at 011; Ex. 1059 at 003; Ex. 1005 at 003; Ex. 1009 at 002; Ex. 1031 at 007.) A POSA would further have appreciated that Bishop reinforces Dana's conclusion that doxorubicin does not enhance the activity of the CVP regimen against low-grade lymphomas. (Ex. 1036 at 006; Ex. 1002 ¶109.)

Applicant's argument during examination of the '896 application that matured into the '821 patent supports the conclusion that it would have been obvious to a POSA to combine CVP—a standard chemotherapy regimen—with rituximab in light of the prior art. Applicant specifically argued that a POSA would consider CVP a standard chemotherapy regimen for combination therapy. In order to overcome the Examiner's argument that the '202 priority application did not disclose CVP, Applicant stated:

> This "combination therapy" disclosure was not confined to particular chemotherapy regimens, but was a general teaching that the skilled person would have known to apply to the CVP chemotherapy.

(Ex. 1069 at 162.) Applicant also argued that CVP was one of three exemplified chemotherapy regimens for low-grade NHL, with the other two being CHOP and cyclophosphamide. (*Id.*) Applicant's argument thus supports the obviousness of using the rituximab–CVP combination to treat low-grade NHL, in view of the disclosures in the prior art.

2. Reasonable Expectation Of Success

A POSA evaluating the combination of Czuczman, IDEC's 10-K/A, Foon, and Dana would have had a reasonable expectation that the claimed treatment regimen would be safe and efficacious. "All that is required to show obviousness is a reasonable expectation of success, not conclusive proof of efficacy." *Coherus Biosciences Inc.*, IPR2016-00172, Paper No. 9 at 16.

Czuczman teaches the safety and efficacy of rituximab administered during CHOP. (Ex. 1011 at 003; Ex. 1002 ¶111.) Czuczman further describes rituximab's "synergy with chemotherapeutic agents," and suggests that CHOP and rituximab together may exhibit superior anti-tumor activity than CHOP alone. (Ex. 1011 at 003.) IDEC's 10-K/A expressly suggests combining rituximab with "widely used chemotherapy regimens" for low-grade lymphoma. (Ex. 1006 at 013.) Given that CVP was a widely used, standard chemotherapy regimen for low-grade lymphoma with survival and response rates indistinguishable from CHOP, a POSA would have expected the combination of CVP and rituximab to be similarly successful to CHOP in extending remissions. (Ex. 1002 ¶111; Ex. 1022 at 011; Ex. 1059 at 003; Ex. 1005 at 003; Ex. 1009 at 002; Ex. 1031 at 007.)

Czuczman also provides a rationale for combining rituximab with CHOP that a POSA would have understood to apply equally to CVP: "single agent efficacy, non cross-resistant mechanism of action, synergy with chemotherapeutic

agents and non-overlapping toxicities." (Ex. 1011 at 003; Ex. 1002 ¶112.) Thus, a POSA would have expected rituximab administered during a CVP regimen also to be efficacious, with the added benefit of being less toxic than CHOP. (Ex. 1002 ¶112.)

E. Ground 4: Claims 4-6 Are Obvious Under §103 Over Czuczman, IDEC's 10-K/A, Foon, Dana, Link, And Piro

Claims 4-6 of the '821 patent would have been obvious over Czuczman (Ex. 1011) in view of IDEC's 10-K/A (Ex. 1006), Foon (Ex. 1008), Dana (Ex. 1009), Link (Ex. 1010), and Piro (Ex. 1004).

The core relevant teachings of Czuczman, IDEC's 10-K/A, Foon, and Dana are discussed in Ground 3 above. Czuczman further teaches that both relapsed patients and patients who had previously not received any chemotherapy could successfully be treated with six cycles of rituximab administered at a dose of 375 mg/m^2 during a chemotherapy regimen. (Ex. 1011 at 003 (Abstract 206); Ex. 1002 ¶¶113, 114.).)

Link is an April 1998 publication that reports early results from a Phase II study testing the safety and efficacy of rituximab with CHOP in previously untreated intermediate- or high-grade NHL patients. (Ex. 1010 at 002 (Abstract 7).) Patients received rituximab at 375 mg/m^2 on the first day of every three-week cycle followed 48 hours later by CHOP for six cycles. (Ex. 1010 at 002.) Link

concluded, "[t]his regimen represents a tolerable therapy with serious adverse events occurring with a frequency similar to that seen with conventional CHOP therapy alone and may offer higher response rates." (*Id*.) Accordingly, Link teaches that rituximab can be safely and efficaciously administered in combination with CHOP to patients suffering from intermediate- or high-grade B-cell NHL every three weeks for six cycles. (*Id.*; Ex. 1002 ¶115.)

Piro teaches that rituximab can be safely and efficaciously administered in eight weekly doses. (Ex. 1002 ¶115; Ex. 1004 at 003.)

Thus, Czuczman describes treating low-grade NHL with rituximab and CHOP, and the synergistic benefits of administering rituximab with standard chemotherapy. Czuczman additionally teaches the safety and efficacy of administering rituximab to NHL patients *at doses of 375 mg/m^2* during CHOP. IDEC's 10-K/A suggests combining rituximab with other standard chemotherapy regimens for low-grade lymphoma, Foon teaches that CVP is a standard chemotherapy regimen for low-grade lymphoma, and Foon and Dana teach that for low-grade NHL, adding doxorubicin—the compound in CHOP that differentiates CHOP from CVP—does not improve survival or response rates. Link also teaches the safety and efficacy of administering rituximab to NHL patients at *doses of 375 mg/m^2* during a CHOP regimen, and Link specifically teaches administering a dose

of rituximab *once every three weeks* during CHOP. Finally, Piro teaches administering rituximab in *eight weekly cycles.*

Furthermore, Czuczman, Link, and Piro inherently disclose rituximab's amino acid sequence, as depicted in SEQ ID NO: 1 and SEQ ID NO: 2 of the '821 patent. (Ex. 1002 ¶116; *see* Ex. 1012, SEQ ID Nos: 7, 10 (amino acid sequences for rituximab, also known as C2B8).) *See Yeda*, 837 F.3d at 1345 (under the doctrine of inherent disclosure, a reference that describes an invention with "certain undisclosed yet inherent properties" is deemed to inherently disclose the invention's inherent properties); *In re Crish*, 393 F.3d at 1258 ("[O]ne cannot establish novelty by claiming a known material by its properties.").

Therefore, as depicted in the claim chart below, a POSA viewing this art as of August 1998 or August 1999 would have found the claimed inventions obvious.

GROUND 4		
'821 Claim		**Czuczman (Ex. 1011), IDEC's 10-K/A (Ex. 1006), Foon (Ex. 1008), Dana (Ex. 1009), Link (Ex. 1010), and Piro (Ex. 1004)**
4.	A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL)	*See* Ground 3.
	comprising administering to a patient a therapeutically effective amount of rituximab during a chemotherapeutic regimen, wherein the chemotherapeutic regimen consists of cyclophosphamide, vincristine, and	*See* Ground 3.

	prednisone (CVP therapy),	
	wherein the method comprises administering 375 mg/m^2 of rituximab once every 3 weeks for 8 doses, and	"In this study, IDEC-C2B8 is given at a dose of 375 mg/m^2 . . . [for] 6 doses]. CHOP . . . is given . . . [for] 6 cycles." (Ex. 1011 at 003.) "[Intermediate- or high-grade B-cell NHL] patients received rituximab 375 mg/m^2 on day 1 of each 21 day cycle followed 48 hrs later by CHOP. . . All patients received six cycles of therapy." (Ex. 1010 at 002.) Piro describes administering eight weekly doses of 375 mg/m^2 rituximab for low-grade or follicular NHL patients (Ex. 1002 ¶116; Ex. 1004 at 003.)
	wherein the method provides a beneficial synergistic effect in the patient.	Czuczman and Link each describe the improvement in clinical outcome for the patients who received rituximab during standard chemotherapy. "Overall response rate for the 14 pts completing all scheduled therapy to date is 100% (11 CR and 3 PR) . . . The finding of molecular remissions by PCR suggests that the anti-tumor activity of CHOP and IDEC-C2B8 is superior to CHOP therapy alone." (Ex. 1002 ¶116; Ex. 1011 at 003.) "Clinical trials with rituximab in patients with relapsed low-grade B-NHL demonstrated a 50% response rate with a toxicity profile non-overlapping that of combination chemotherapy. In vitro studies suggest synergistic cytotoxicity between rituximab and

		chemotherapy." (Ex. 1010 at 002.)
5.	A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL)	*See* Claim 4*, above.*
	comprising administering to a patient 375 mg/m^2 of C2B8 once every 3 weeks for 8 doses	*See* Claim 4*, above.*
	during a chemotherapeutic regimen consisting of cyclophosphamide, vincristine, and prednisone (CVP therapy).	*See* Claim 4, *above*.
6.	A method for treating low grade or follicular non-Hodgkin's lymphoma (NHL)	*See* Claim 4, *above.*
	comprising administering to a patient 375 mg/m^2 of a chimeric anti-CD20 antibody once every 3 weeks for 8 doses	*See* Claim 4, *above.*
	during a chemotherapeutic regimen consisting of cyclophosphamide, vincristine, and prednisone (CVP therapy)	*See* Claim 4, *above.*
	wherein the chimeric anti-CD20 antibody is produced from nucleic acid encoding a light chain variable region comprising the amino acid sequence in SEQ ID NO: 1 and a heavy chain variable region comprising the amino acid sequence in SEQ ID NO: 2, and comprises human gamma 1 heavy -chain and kappa light chain constant region sequences.	This is a description of the C2B8 chimeric antibody, which the '821 patent states is the preferred chimeric antibody. (Ex. 1001 at 3:3-5.) Accordingly, SEQ ID NO: 1 and SEQ ID NO: 2 are inherently disclosed by Czuczman, Link, and Piro. *See Yeda*, 837 F.3d at 1345; *In re Crish*, 393 F.3d at 1258.

1. Motivation To Combine

a. A POSA would have been motivated to optimize Czuczman's protocol by substituting CVP for CHOP

For all of the reasons as discussed above in Section X.D.1, a POSA would have been motivated to optimize Czuczman's protocol of administering rituximab during CHOP chemotherapy by instead administering rituximab during CVP chemotherapy. (Ex. 1002 ¶117.)

b. A POSA would have been motivated to administer 8 doses of Rituximab every 3 weeks

Furthermore, a POSA would have been motivated to optimize the dosing regimens taught in Czuczman, Link, and Piro by extending the rituximab dosing regimen of once every 3 weeks for **6** doses to once every 3 weeks for **8** doses. (Ex. 1002 ¶118.) This is "'nothing more than the routine' application of a well-known problem-solving strategy, . . . 'the work of a skilled [artisan], not of an inventor.'" *Pfizer*, 480 F.3d at 1368 (quoting *Merck & Co. v. Biocraft Labs., Inc*., 874 F.2d 804, 809 (Fed. Cir. 1989); *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co*., 464 F.3d 1356, 1371 (Fed. Cir. 2006)); *see also In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."); *In re Boesch*, 617 F.2d 272, 276

(C.C.P.A. 1980) ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art.").

In Czuczman, CHOP was administered every three weeks for six cycles. (Ex. 1002 ¶118; Ex. 1011 at 003.) Rituximab was administered on weeks 1 (2 doses), 7, 13, 20, and 21. (Ex. 1011 at 003.) In Link, rituximab was administered once every 21 days (*i.e.*, three weeks) for six cycles during CHOP therapy. (Ex. 1002 ¶118; Ex. 1010 at 002.) Piro administered rituximab as a single agent weekly for 8 doses. (Ex. 1002 ¶118; Ex. 1004 at 003.) Thus, it would have been merely the result of routine optimization to select an 8-cycle dosing regimen for CVP plus rituximab. (Ex. 1002 ¶118.)

Additionally, as discussed in Section VII, during prosecution of the '821 patent, Applicant argued that disclosures of the following distinct, published dosing regimens provided sufficient written description support for the "every 3 weeks for 8 doses" element of the '821 claims 4, 5, and 6:

(1) COP/CVP dosed every 3-4 weeks (Ex. 1011);

(2) Rituximab administered on weeks 1 (2 doses), 7, 13, 20, and 21 and CHOP administered every 21 days for six cycles (Ex. 1011);

(3) Rituximab administered on day 1 of each of six 21-day cycles of CHOP, for treatment of intermediate- or high-grade NHL (Ex. 1010);

(4) Rituximab administered "for 8 doses" (Ex. 1004).

(Ex. 1069 at 186.) Applicant thus conceded that a POSA would understand the disclosures of Czuczman, Link, and Piro to teach administering rituximab every 3 weeks for 8 doses.

Given the state of the art and Applicant's own statements during prosecution, a POSA would be motivated to modify the dosing regimen of Czuczman and Link to one dose of rituximab every three weeks for 8 cycles instead of 6. (Ex. 1002 ¶¶119.)

2. Reasonable Expectation Of Success

A POSA evaluating the combination of Czuczman, IDEC's 10-K/A, Foon, Dana, Link, and Piro would have had a reasonable expectation that the claimed treatment regimen would be safe and efficacious. Czuczman and Link teach the safety and efficacy of rituximab administered during CHOP. (Ex. 1002 ¶120; Ex. 1011 at 003; Ex. 1010 at 002.) Czuczman further describes rituximab's "synergy with chemotherapeutic agents," and suggests that CHOP and rituximab together may exhibit superior anti-tumor activity than CHOP alone. (Ex. 1011 at 003.) Given that Foon and Dana had taught that CHOP and CVP had similar efficacy, a POSA would expect the combination of CVP and rituximab to be similarly successful in extending remissions. (Ex. 1002 ¶120.)

F. Ground 5: Claims 3 And 6 Are Obvious Under §103 Over Czuczman, IDEC's 10-K/A, Foon, Dana, Link, Piro, And The '137 Patent

Claims 3 and 6 of the '821 patent would have been obvious over Czuczman (Ex. 1011) in view of IDEC's 10-K/A (Ex. 1006), Foon (Ex. 1008), Dana (Ex. 1009), Link (Ex. 1010), Piro (Ex. 1004), and the '137 patent (Ex. 1007).

The relevant teachings of Czuczman, IDEC's 10-K/A, Foon, Dana, Link, and Piro are discussed in Grounds 3 and 4. Czuczman describes the safety and efficacy of administering rituximab to low-grade NHL patients at doses of 375 mg/m^2 during CHOP. IDEC's 10-K/A suggests combining rituximab with other standard chemotherapy regimens for low-grade lymphoma, Foon teaches that CVP is a standard chemotherapy regimen for low-grade lymphoma, and Foon and Dana teach that for low-grade NHL, adding doxorubicin—the compound in CHOP that differentiates CHOP from CVP—does not improve survival or response rates. Czuczman, Link, and Piro discloses the claimed rituximab dosing schedules.

The '137 patent discloses the sequence of rituximab. *See Biogen Idec Inc.*, 713 F.3d at 1093 ("U.S. Patent No. 5,736,137 . . . teaches the isolation, screening, and characterization of Rituxan®."). Thus, to the extent the Board finds that Czuczman, Link, and Piro do not inherently disclose and therefore anticipate the SEQ ID NO: 1 and SEQ ID NO: 2 claim elements found in claims 3 and 6, the

combination of Czuczman, IDEC's 10-K/A, Foon, Dana, Link, Piro, and the '137 patent renders those claim elements obvious. (Ex. 1002 ¶¶121, 122.)

XI. NO SECONDARY INDICIA OF NON-OBVIOUSNESS EXIST

If this Board finds that the '821 patent can claim priority to the August 11, 1999 filing date, the challenged claims of the '821 patent are obvious for the reasons discussed in Grounds 3-5. During prosecution, Applicant advanced two arguments related to secondary indicia of non-obviousness, but neither is sufficient to overcome the strong prima facie case of obviousness as set forth above.

First, Applicant argued that the art at the time of filing taught away from CVP chemotherapy, which omits doxorubicin fromthe chemotherapy regimen. (Ex. 1069 at 139-40.) But Applicant also argued the opposite, that the disclosure of the generic term "chemotherapy" in the earlier '202 application was sufficient to provide adequate written description of CVP. (*Id.* at 162.) Patent Owner cannot have it both ways.

The art resoundingly supports synergy between rituximab and chemotherapy generally, not a unique synergy with doxorubicin. For example, several prior art publications describe rituximab's general "synergy with chemotherapeutic agents" that was not specific to doxorubicin. (*See, e.g.*, Ex. 1011 at 003 ("The rationale for combination of IDEC-C2B8 with CHOP includes: single agent efficacy, non cross-resistant mechanisms of action, *synergy with chemotherapeutic agents* and non-

overlapping toxicities") (emphasis added); *see also* Ex. 1049 at 003.) A POSA would not interpret those statements to mean doxorubicin alone was the synergistic component. (Ex. 1002 ¶70.)

Notably, the publications identifying a possible synergy between doxorubicin and rituximab cite back to a study by Demidem, published in 1995 and 1997. (Ex. 1078; Ex. 1079.) Demidem evaluated a B-cell lymphoma cell line, DHL-4, known to be resistant to ricin, tumor necrosis factor-alpha, cisplatinum diamine dichloride, and etoposide. (Ex. 1079 at 002, 006.) This cell line was relatively resistant to diphtheria toxin and Adriamycin (doxorubicin). (*Id*. at 006.) Demidem pretreated the cells with rituximab and then exposed the cells to these various cytotoxic agents. (*Id*. at 003-04.) Demidem reports that when the cells were pretreated with rituximab, "they were found to be more sensitive to *all cytotoxic agents tested*" except for etoposide. (*Id*. at 006 (emphasis added).) Demidem concludes, "[rituximab] sensitizes DHL-4 B lymphoma cells *to various cytotoxic drugs/toxins*." (*Id*. at 007 (emphasis added).) Demidem thus teaches a POSA that *various* chemotherapeutic agents would likely have a synergistic effect when combined with rituximab, not just doxorubicin. (Ex. 1002 ¶¶ 68, 69.)

Demidem therefore does not teach away from the use of chemotherapy regimens without doxorubicin, as Demidem contains no clear discouragement from using other chemotherapeutic agents in combination with rituximab. *See In re*

Fulton, 391 F.3d 1195, 1201 (Fed. Cir. 2004) (to teach away, a reference must "criticize, discredit, or otherwise discourage the solution claimed" in the patent-at-issue). (Ex. 1002 ¶¶68-70.)

Moreover, combining rituximab with CVP meets several of the published rationales for combining rituximab with chemotherapy. Those rationales include single-agent efficacy, non-cross-resistant mechanisms of action, and the absence of overlapping toxicities. (Ex. 1021 at 004.) Because CVP and rituximab satisfy these criteria, a POSA would have been motivated to combine the two treatments and would have expected beneficial synergistic results. (Ex. 1002 ¶70.) A POSA would also have understood that there was an ongoing clinical trial—the E1496 trial—studying the use of CVP with rituximab as maintenance therapy. That this study was underway leads to a presumption that the combination of rituximab and CVP was reasonably likely to be safe and efficacious. *See* MPEP §2107.03(IV).

Applicant's second asserted argument for indicia of non-obviousness was that the beneficial synergistic effect obtained from combining CVP and rituximab, as described in Marcus, was an unexpected result because the art taught away from using CVP. (Ex. 1069 at 141.) The Demidem articles discussed above refute this assertion. More tellingly, IDEC's 10-K/A, which proposes 35 additional clinical trials combining rituximab with "widely used chemotherapy regimens for both low grade and intermediate/high grade disease" soundly repudiate Applicant's claim

that rituximab was expected to synergize with only doxorubicin. (Ex. 1006 at 013.) Ultimately, if Applicant prevails in its assertion that the '202 specification's generic disclosure of a "chemotherapeutic regimen" provided written description for CVP, the inescapable conclusion is that the prior art's disclosure of combining standard chemotherapy with rituximab renders the claims obvious. (*See* Ex. 1002 ¶¶69-70.)

Petitioner is not aware of any compelling evidence of secondary indicia of non-obviousness having a nexus to the alleged claimed invention that challenge the conclusion that the '821 patent is obvious. Petitioner reserves the right to respond to any assertion of secondary indicia advanced by the Patent Owner.

XII. CONCLUSION

Petitioner respectfully requests institution of *inter partes* review of claims 1-6 of the '821 patent, and a finding that the claims are unpatentable, based on the grounds presented in this Petition.

Dated: March 15, 2017

Respectfully submitted,

By: */s / Michelle S. Rhyu*

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37 C.F.R. § 42.24(d) CERTIFICATION

The undersigned hereby certifies that this submission, excluding the parts of this petition that are exempted by 37 C.F.R. § 42.24(a) (including the tables of contents and authority, mandatory notices, claim listings, certificate of word count, exhibit list, and certificate of service), contains 13,983 words, as determined using the standard word counting feature of the Microsoft Word program.

Dated: March 15, 2017

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

I, Michelle S. Rhyu, 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. 9,296,821,** including all exhibits (**Nos. 1001-1081)** and related documents, are being served on the 15th 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:

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