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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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CELLTRION, INC.
Petitioner

v.

BIOGEN INC.
Patent Owner

_____

Case No. IPR2017-_____

Patent No. 8,329,172

Filing Date: August 18, 2007
Issue Date: December 11, 2012

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

Inventor: Antonio Grillo-López

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PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,329,172

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EXHIBIT LIST

Exhibit No.	Description
1001	U.S. Patent No. 8,329,172 ("the '172 patent")
1002	Expert Declaration of Dr. Walter Longo
1003	Expert Declaration of Dr. Izidore Lossos
1004	Rituxan (Rituximab) label (Nov. 1997)
1005	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 1998")
1006	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)
1007	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)
1008	Eastern Cooperative Oncology Group ("ECOG") E1496 Patient Consent Form
1009	ECOG E1496 Protocol (1998)
1010	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)
1011	Hainsworth, J.D. *et al.*, *Rituximab Induction and Maintenance Therapy in Patients (pts) with Previously Untreated Low-Grade Non-Hodgkin's Lymphoma (NHL): Preliminary Results of a Minnie Pearl Cancer Research Network Phase II Trial*, Program/Proceedings Am. Soc. Clin. Oncol., 18:29a (Abstract 105) (May 1999)
1012	IDEC Pharmaceuticals Corporation, Form 10-K/A for the Fiscal Year ended December 31, 1997, filed with the U.S. Securities and Exchange Commission
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")

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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	Foon, K.A. & Fisher, R.I., *Chapter 111: Lymphomas*, in Williams Hematology, Fifth Edition, 1076-1096 (Beutler, E. *et al.*, eds., 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	U.S. Application No. 11/840,956 ("the '956 application")
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	Grillo-López, A.J. *et al.*, *Overview of the Clinical Development of Rituximab: First Monoclonal Antibody Approved for the Treatment of Lymphoma*, Semin. Oncol. 26(5, Supp. 14):66-73 (Oct. 1999)
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)

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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	Hochster H., *et al.*, *Maintenance Rituximab After Cyclophosphamide, Vincristine, and Prednisone Prolongs Progression-Free Survival in Advanced Indolent Lymphoma: Results of the Randomized Phase III ECOG1496 Study*, J. Clin. Oncol., 27(10):1607-1614 (Apr. 1, 2009)
1030	Exhibit Number Not Used
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)
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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	Hainsworth, J.D. *et al.*, *Rituximab as First-Line and Maintenance Therapy for Patients With Indolent Non-Hodgkin's Lymphoma*, J. Clin. Oncol., 20(20):4261-4267 (Oct. 15, 2002)
1035	White, C., *Rituximab Immunotherapy for Non-Hodgkin's Lymphoma*, Cancer Biother. Radio., 14(4):241-50 (Aug. 1999) ("White 1999")
1036	U.S. Application No. 09/372,202 ("the '202 application")
1037	Exhibit Number Not Used
1038	U.S. Provisional Application No. 60/096,180 ("the '180 provisional application")

Exhibit No.	Description
1039	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)
1040	Haq, M.M. *et al.*, *Doxorubicin-Induced Congestive Heart Failure in Adults*, Cancer, 56(6):1361-1365 (Sept. 15, 1985)
1041	Exhibit Number Not Used
1042	McLaughlin, P. *et al.*, *Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program*, J. Clin. Oncol., 16(8):2825-2833 (Aug. 1998) ("McLauglin 1998")
1043	Exhibit Number Not Used
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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)
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1048	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) (Mar. 1995)
1049	ECOG Protocols Active as of 05/19/98
1050	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")
1051	Smith, M.R., *Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance*, Oncogene, 22(47):7359-7368 (Oct. 20, 2003)

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1052	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)
1053	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)
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	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)
1056	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)
1057	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)
1058	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")
1059	Exhibit Number Not Used
1060	Ruuls, S.R. *et al.*, *Novel human antibody therapeutics: the age of the Umabs*, Biotechnol. J., 3:1157-1171 (2008)
1061	U.S. Application No. 13/524,896, Feb. 5, 2014 Amendment and Response to Office Action
1062	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)
1063	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)

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1064	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)
1065	Exhibit Number Not Used
1066	E1496 Forms Packet
1067	Exhibit Number Not Used
1068	E1496 On Study Dates
1069	Exhibit Number Not Used
1070	Exhibit Number Not Used
1071	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)

CLAIM LIST

1. A method of treating low grade B-cell non-Hodgkin's lymphoma in a human patient comprising administering to the patient chemotherapy consisting of CVP therapy to which the patient responds, followed by rituximab maintenance therapy, wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m^2 every 6 months, and wherein the maintenance therapy is provided for 2 years.

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 claim 1 of U.S. Patent No. 8,329,172 ("the '172 patent"). The '172 patent is assigned to Biogen, Inc. ("Biogen" or "Patent Owner" or "Applicant"). Challenged claim 1 is the sole claim of the '172 patent. Review should be instituted because there is a reasonable likelihood that Celltrion will prevail in demonstrating that the '172 patent is anticipated and/or obvious.

Claim 1 of the '172 patent recites a method for treating low-grade B-cell non-Hodgkin's lymphoma ("NHL") by administering a well-known chemotherapy regimen of cyclophosphamide, vincristine, and prednisone ("CVP"), followed by rituximab maintenance therapy administered in four weekly doses of 375 mg/m^2 every six months for two years. (Ex. 1001 at 22:56-65.)

Claim 1 is anticipated by documents associated with a clinical trial undertaken by the Eastern Cooperative Oncology Group ("ECOG") testing the very treatment protocol recited by the claim. The clinical trial protocol and patient consent form for ECOG 1496 ("E1496 Protocol" and "E1496 Patient Consent Form") each describe the claimed method of treatment for the claimed patient population. (Ex. 1009 at 007, 010-11; Ex. 1008 at 001.) For example, the E1496 Protocol describes the two phases of the E1496 clinical trial: a first randomization

to treatment with either CVP or cyclophosphamide/fludarabine and, for patients who respond to the initial treatment, a subsequent randomization to either rituximab maintenance therapy or observation. (Ex. 1009 at 011.) The E1496 Patient Consent Form likewise describes every limitation of claim 1. (Ex. 1008 at 001.)

As attested by Dr. Walter Longo, an oncologist at the University of Wisconsin, Madison who enrolled patients in the ECOG 1496 study, both the E1496 Protocol and the E1496 Patient Consent Form were freely available to the public without any obligations of confidentiality beginning March 1998. (Ex. 1002 ¶¶2, 3.) Accordingly, claim 1 is unpatentable under 35 U.S.C. §102 as anticipated. *See Schering Corp. v. Geneva Pharms. Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) ("A patent is invalid for anticipation [under 35 U.S.C. §102] if a single prior art reference discloses each and every limitation of the claimed invention.").

Separate from the E1496 Protocol and Patient Consent Form, the treatment of low-grade B-cell NHL with chemotherapy followed by maintenance therapy was not new as of the earliest filing date to which the '172 patent is entitled, August 11, 1999. As early as February 1998, publications described promising results from studies that used rituximab maintenance therapy following chemotherapy. (Ex. 1005 at 003; Ex. 1010 at 011.) Moreover, CVP and CHOP were known to be equally effective chemotherapies for low-grade NHL. (Ex. 1007

at 002; Ex. 1006 at 003; Ex. 1017 at 030; Ex. 1003 ¶36.) Rituximab had been approved to treat relapsed or refractory low-grade B-cell NHL for almost two years before August 11, 1999. (Ex. 1023 at 004.) The dosage amount is not new, as the 1997 Rituxan label teaches the administration of rituximab in four weekly doses of 375 mg/m^2. (Ex. 1004 at 001.)

The single claim of the '172 patent would thus have been obvious in light of the state of the art and the combinations of: (1) Grossbard and the Rituxan label; and (2) McNeil, Bishop, Dana, and the Rituxan Label. Moreover, numerous statements in the prior art by the Patent Owner and others demonstrate that the claim is obvious, as it represents merely "a routine optimization of the therapy outlined in [the prior art], which would have been achievable through the use of standard clinical trial procedures." *Biomarin Pharm. Inc. v. Genzyme Therapeutic Prods. Ltd. P'ship*, IPR2013-00534, Paper No. 81 at 12-14 (P.T.A.B. Feb. 23, 2015). Claim 1 is thus unpatentable under 35 U.S.C. §103.

Petitioner respectfully requests institution of *inter partes* review of claim 1, because there is a reasonable likelihood that claim 1 is 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. 9,296,821 and 8,557,244.

Biogen is the owner of the following U.S. applications and patents related to the '172: U.S. Patent Nos. 6,455,043 and 9,296,821 and pending U.S. Application Nos. 13/524,837, 14/070,256, and 15/225,594.

The '172 patent was the subject of *Boehringer Ingelheim International GmbH v. Biogen Idec, Inc.*, IPR2015-00418 (P.T.A.B.) (referred to hereinafter as IPR2015-00418). On July 13, 2015, the Board issued a decision denying institution.

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 claim 1 of the '172 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 '172 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 claim 1 of the '172 patent on the grounds set forth in the following table. The '172 patent is to be reviewed under pre-AIA §§102 and 103. This Petition and the accompanying declarations of Dr. Izidore Lossos and Dr. Walter Longo demonstrate that there is a reasonable likelihood that Petitioner will prevail with respect to challenged claim 1. (*See* Ex. 1003; Ex. 1002.)

Ground	Basis for Unpatentability
Ground 1	Anticipated under 35 U.S.C. §102(b) by E1496 Patient Consent Form
Ground 2	Anticipated under 35 U.S.C. §102(b) by E1496 Protocol
Ground 3	Obvious under 35 U.S.C. §103 over the combination of Grossbard and the Rituxan Label
Ground 4	Obvious under §103 over the combination of McNeil, Bishop, Dana, and the Rituxan Label

The E1496 Patient Consent Form, the E1496 Protocol, the Rituxan label, McNeil, Bishop, and Dana are all §102(b) prior art to the '172 patent because each reference was published or otherwise made publicly available by August 11, 1998, more than one year before the earliest effective filing date of the '172 patent. (*See* Sections IX.A, C-F, *infra*.) The Grossbard reference was published prior to the earliest effective filing date, August 11, 1999, and is §102(a) prior art. (*See* Sections IX.B, *infra*.)

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. (Ex. 1003 ¶33; Ex. 1017 at 026-27; Ex. 1018 at 026-27.) NHL can be divided into T-cell lymphoma and the more common B-cell lymphoma. (Ex. 1003 ¶33; Ex. 1017 at 023, 026; Ex. 1001 at 5:28-29.) B-cell NHL can be further divided into sub-types ranging from indolent, low-grade tumors to rapidly growing, highly aggressive intermediate- or high-

grade malignancies. (Ex. 1003 ¶34; Ex. 1017 at 024; Ex. 1025 at 003.) In the 1980s and 1990s, it was understood by persons of ordinary skill in the art that low-grade lymphoma is slow growing and typically responds well to initial treatment. (Ex. 1003 ¶34; Ex. 1017 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. 1003 ¶34; Ex. 1017 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. 1003 at ¶34; Ex. 1017 at 024; Ex. 1018 at 084; Ex. 1050 at 003.) Most patients eventually die from the disease or its complications. (Ex. 1003 at ¶34; Ex. 1031 at 007; Ex. 1044 at 005-06; Ex. 1046 at 004-05; Ex. 1050 at 003.)

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

For decades, clinicians studied various treatment protocols to improve time-to-progression and overall survival. (Ex. 1003 ¶35; *see*, *e.g.,* Ex. 1017; Ex. 1018; Ex. 1025; Ex. 1031; Ex. 1044; Ex. 1046.) 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 used to treat low-grade NHL were listed 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. 1017 at 029.)

Two of three listed combination therapies are CVP (cyclophosphamide, vincristine,[1] prednisone) and CHOP (cyclophosphamide, doxorubicin,[2] vincristine, and prednisone). (Ex. 1003 ¶36; Ex. 1017 at 029; Ex. 1031 at 007.) CVP and

[1] Vincristine is also known by the brand name Oncovin, and accordingly CVP is also known by the acronym COP (cyclophosphamide, Oncovin, prednisone). (Ex. 1003 ¶36 n.1.)

[2] Doxorubicin is also known by the brand name Adriamycin. (Ex. 1003 ¶36.)

CHOP each contain cyclophosphamide, vincristine, and prednisone. (Ex. 1003 ¶36; Ex. 1031 at 003, 007; Ex. 1050 at 003-04.) CHOP also contains doxorubicin, an anthracycline antibiotic. (Ex. 1003 ¶36; Ex. 1022 at 011; Ex. 1031 at 007; Ex. 1050 at 004.) Due to the toxicity associated with doxorubicin, CHOP is a more aggressive therapy than CVP. (Ex. 1003 ¶36; Ex. 1005 at 003; Ex. 1031 at 007.) Thus, for aggressive intermediate- and high-grade NHL, CHOP but not CVP is considered an appropriate treatment regimen. (Ex. 1003 ¶36.)

For low-grade NHL, however, 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. 1003 ¶37; Ex. 1007 at 002; Ex. 1050 at 003; Ex. 1044 at 006; Ex. 1045 at 004-06; Ex. 1031 at 007; Ex. 1047 at 003, Abstract.) 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. 1006 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 suggest that doxorubicin does not enhance the activity of the CVP regimen against lymphomas other than diffuse large cell." (*Id.* at 006.) Dana

[3] Diffuse large cell lymphoma is a type of aggressive (not low-grade) NHL. (Ex. 1003 ¶38 n. 2.)

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. 1007 at 002, 006.) Foon similarly concludes that there is no evidence that including doxorubicin in combination regimens prolongs survival for low-grade NHL. (Ex. 1017 at 030.) Therefore, as Dr. Lossos explains, in 1998, CHOP and CVP were equally effective standard chemotherapy treatments for low-grade NHL, even though CHOP was understood to be more toxic. (Ex. 1003 ¶36.)

Despite equivalent survival rates for low-grade NHL, CVP was, and is, considered less toxic than CHOP. (Ex. 1003 ¶¶36, 37; Ex. 1020 at 006-07; Ex. 1031 at 007; Ex. 1039 at 003-05; Ex. 1040 at 003-07; Ex. 1050 at 003; Ex. 1007 at 002; *see* Ex. 1005 at 003.) The doxorubicin in CHOP is associated with cardiomyopathy, which may occur acutely, even at low doses. (Ex. 1003 ¶36; Ex. 1031 at 007; Ex. 1039 at 003-05; Ex. 1040 at 003-07.) Doxorubicin is also associated with an increased risk of febrile neutropenia, which can result in serious infections. (Ex. 1003 ¶36; 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 patients because the addition of doxorubicin made CHOP more toxic without an increase in survival rate. (Ex. 1003 ¶41.)

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. 1003 ¶45; Ex. 1010 at 004; Ex. 1004 at 001.) CD20 is a hydrophobic transmembrane protein found on pre-B cells and mature B lymphocytes. (Ex. 1003 ¶42; Ex. 1021 at 003.) 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. 1003 ¶¶42, 43; Ex. 1014 at 002, Abstract; Ex. 1015 at 006; Ex. 1021 at 003.)

Rituximab binds selectively and with high affinity to cells expressing the CD20 antigen—including normal and malignant B cells. (Ex. 1003 ¶46; Ex. 1051 at 003, 006.) Rituximab is thought to induce direct apoptosis and mediate complement-dependent cell lysis. (Ex. 1003 ¶46; Ex. 1024 at 003.) This kills both normal and malignant B cells. (Ex. 1051 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. 1003 ¶46.)

D. Chemotherapy-Plus-Rituximab Combination Therapy And Rituximab Maintenance Therapy For NHL Treatment Were Known To A POSA As Of August 11, 1999.

As early as September 1997, prior art suggested using rituximab ***after*** chemotherapy for treatment of low-grade NHL. (Ex. 1027 at 009.) CHOP chemotherapy plus rituximab studies were started in 1994 and proved the principle

that administering rituximab with chemotherapy produced positive therapeutic outcomes. (Ex. 1003 ¶52; Ex. 1028 at 006.) By December 1998, multiple studies were publicized that used rituximab as maintenance therapy, including the E1496 Study, which involved using CVP induction therapy followed by rituximab maintenance therapy for low-grade lymphoma. (Ex. 1003 ¶47; Ex. 1010 at 010; 1002 ¶¶1, 53, 56.)

1. Rituximab Single-Agent Results Led To Suggestions To Use Rituximab After Chemotherapy For Low-Grade NHL

The first rituximab clinical trials started in March 1993, in patients who had relapsed or refractory low-grade B-cell NHL. (Ex. 1003 ¶48; *see, e.g.,* Ex. 1054 at 003, Abstract.) As described by Dr. Lossos, Phase I and II oncology clinical trials are typically conducted in patients who have no other treatment alternative. (Ex. 1003 ¶48.) As reported in two publications by Maloney, initial trials tested rituximab as a single agent and were designed to test different dosage strengths. (*Id.* ¶48; Ex. 1054 at 003, Abstract; Ex. 1032 at 003; *see also* Ex. 1021 at 003.) Patients who received 375 mg/m^2 had a higher response rate than patients who received lower doses (125 mg/m^2 or 250 mg/m^2). (Ex. 1003 ¶48; Ex. 1032 at 007-08.) Consequently, future studies selected 375 mg/m^2. (Ex. 1003 ¶48.) No dose-limiting toxicity was reported and no maximally tolerated dose was established. (*Id.* ¶48; Ex. 1032 at 008-09.) These early clinical trials demonstrated that rituximab was well tolerated. (Ex. 1003 ¶48.) Reported side effects were mild.

(*Id*. ¶48; Ex. 1021 at 003.) Most adverse events were infusion-related and included low-grade fever, chills, and nausea. (Ex. 1003 ¶48; Ex. 1021 at 003.)

Maloney then conducted one of the pivotal Phase II studies, testing rituximab as a single agent administered in four weekly doses of 375 mg/m^2 in patients with relapsed low-grade NHL. (Ex. 1003 ¶49; Ex. 1027 at 003, Abstract.) The results of this study were published in September 1997. (Ex. 1003 ¶49; Ex. 1027 at 003, Abstract.) Maloney reported that of the 34 patients who completed treatment, 50% had either a complete or partial response. (Ex. 1003 ¶49; Ex. 1027 at 007.) Maloney also reported that B cells were rapidly depleted from almost all patients' peripheral blood and remained depleted for nearly six months post-treatment. (Ex. 1003 ¶49; Ex. 1027 at 008.) In separate publications, Maloney reported that rituximab was detectable in the serum 3 to 6 months after four infusions. (Ex. 1003 ¶50; Ex. 1032 at 007 (serum detected after 3 months); Ex. 1033 at 004-05 (serum detected after 6 months).)

Maloney concluded:

> [Rituximab] presents the opportunity to obtain meaningful tumor reductions with minimal toxicity in patients with relapsed ***low-grade NHL***. . . . To date, experience using [rituximab] has been predominantly in patients with relapsed measurable disease. A clinical trial combining [rituximab] with 6 cycles of CHOP chemotherapy in newly diagnosed patients has recently been completed. Early evaluation of this experience suggests that this

> combination resulted in a PR or CR in all patients . . . . *Additional 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).)

These initial trials demonstrated that rituximab was relatively non-toxic, well-tolerated, and efficacious in patients with relapsed low-grade B-cell NHL. (Ex. 1003 ¶52.) Based on these trials, rituximab was approved by the FDA in November 1997 for use as a single agent to treat refractory or relapsed low-grade B-cell NHL. (Ex. 1004 at 001.)

2. By 1997, A POSA Knew that Rituximab Was Effective In Combination With Standard Chemotherapy To Treat Low-Grade NHL

As early as 1994, clinicians began testing combinations of rituximab and standard chemotherapy in treatment-naïve patients. (Ex. 1003 ¶58; Ex. 1028 at 006). One such study, led by Czuczman, was designed to evaluate the safety and efficacy of rituximab in combination with CHOP chemotherapy. (Ex. 1003 ¶58; Ex. 1020 at 002, Abstract.) Beginning in 1994, this study enrolled patients with both newly-diagnosed and relapsed/refractory low-grade B-cell NHL. (Ex. 1003 ¶58; Ex. 1028 at 006.) Czuczman's treatment protocol included two doses of rituximab given after the last dose of chemotherapy. (Ex. 1003 ¶58; Ex. 1020 at

004.) Czuczman stated this approach was based on "*the generally well-accepted belief that monoclonal antibodies are extremely effective in a minimal residual disease setting*: *[these doses] could be viewed as being used as a 'mop up' of residual lymphoma after completion of systemic chemotherapy*." (*Id*. (emphasis added).) Czuczman published multiple interim reports, including in April 1995 (Ex. 1048), April 1996 (Ex. 1053), and November 1996 (Ex. 1055), reporting this trial's positive results. (Ex. 1003 ¶58.) Czuczman published final results in January 1999, reporting an overall response rate of 95%, with 55% of patients who received rituximab in combination with chemotherapy experiencing a complete remission. (*Id.*; Ex. 1020 at 006.) Given these encouraging results, Czuczman states that "many other clinical trials for the study of Rituxan [rituximab] in combination with *a variety of other cytotoxic agents* for the treatment of CD20-positive neoplasms are being planned for the future." (Ex. 1003 ¶58; Ex. 1020 at 009 (emphasis added).)

In July 1997, Dr. Antonio Grillo-López, inventor of the '172 patent, discussed the ongoing trials of rituximab and CHOP during a public FDA committee hearing. (Ex. 1003 ¶59; Ex. 1058.) Dr. Grillo-López discussed the Czuczman study combining rituximab and CHOP (Ex. 1058 at 026 (25:20-22)) and another study comparing rituximab and CHOP to CHOP alone (*id*. at 028 (27:1-7)). (Ex. 1003 ¶59.)

In December 1997, IDEC Pharmaceuticals Corporation (corporate predecessor to Patent Owner Biogen) publicly announced in a 10-K/A filing with the SEC that rituximab was being tested in combination with standard chemotherapy regimens.

> Rituxan is indicated for single agent use in relapsed or refractory, low grade or follicular, CD20 positive, B-cell non-Hodgkin's lymphoma . . . *Ongoing or completed Phase II studies suggest that Rituxan may also be useful in combination with chemotherapy in low grade or follicular lymphomas* . . . .
>
> . . .
>
> [IDEC Pharmaceuticals Corporation] and Genentech have committed to providing [rituximab] to a small group of trials to be undertaken by National Cancer Institute ("NCI") funded cooperative study groups. *At least two of these trials will be large Phase III studies designed to explore the utility of Rituxan in combination with standard chemotherapy regimens.*

(Ex. 1012 at 012-13.)[4]

[4] 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 statement, application, report, or other document filed with the Commission . . . shall be made available to the public . . . ." *See also Am. Stock Exch., LLC v. Mopex, Inc.*, 250 F. Supp. 2d 323, 326 (S.D.N.Y. 2003) ("Typically, applications

Thus, by December 1997, rituximab was known to be effective "in combination with chemotherapy" and there was a plan to conduct Phase III studies using rituximab in various combinations with standard chemotherapy regimens. (Ex. 1003 ¶61; Ex. 1012 at 012-13; Ex. 1056 at 003 (Abstract 565).) The combinations included administering rituximab "with or after standard chemotherapy." (Ex. 1003 ¶61; Ex. 1012 at 010; Ex. 1056 at 003 (Abstract 565); Ex. 1027 at 009.)

3. By 1998, A POSA Understood That Rituximab Maintenance Therapy Showed Promise

Well before rituximab was shown to be an effective treatment for low-grade lymphoma, clinicians studied the use of maintenance therapies in patients who had a complete or partial response to initial therapy in order to extend the duration of remission. (Ex. 1003 ¶66; Ex. 1025 at 003; Ex. 1026 at 003; Ex. 1031 at 004.) Patients who responded to first-line treatment received ongoing therapy with chemotherapy or interferon-α. (Ex. 1003 ¶66) Some trials showed that these maintenance therapies prolonged remission and improved overall survival. (*Id.*; Ex. 1025 at 003.) For example, Steward demonstrated that two years of maintenance therapy with chlorambucil after induction treatment with CVP and

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are entered into the SEC database and thereby made available to the public within one to three days after they are filed.")

radiotherapy prolonged time-to-progression. (Ex. 1003 ¶66; Ex. 1031 at 003, Abstract.) Steward noted the difficulties associated with a two-year course of maintenance chemotherapy, "but despite this, it prolonged the median [relapse-free survival] by 38 months and its use could be considered when future studies are being designed." (Ex. 1003 ¶66; Ex. 1031 at 003, Abstract.) Similarly, in 1996, Palmieri reported the results of an interferon maintenance therapy study in a small group of NHL patients who had achieved a complete remission after first-line chemotherapy. (Ex. 1003 ¶66; Ex. 1026 at 003, Abstract.) Patients who received a two-year course of interferon as maintenance therapy experienced lower rates of relapse and death as compared to patients who did not receive maintenance therapy. (Ex. 1003 ¶66; Ex. 1026 at 003, Abstract.) By 1998, persons of ordinary skill in the art understood that traditional first-line therapies could also be employed as maintenance therapies to improve progression-free survival for patients who could tolerate them. (Ex. 1003 ¶66.)

As rituximab was shown to be well-tolerated, safe, and efficacious, it was a prime candidate for use as maintenance therapy. (Ex. 1003 ¶67.) In particular, it was well-appreciated that the approved dosing schedule of rituximab of 375 mg/m^2 weekly for four weeks caused the depletion of normal and malignant B-cells for six to nine months. (Ex. 1003 ¶67; Ex. 1042 at 003, 006.) Pharmacokinetic data

demonstrated that after four weekly doses, rituximab was detectable in the serum for 3 to 6 months. (Ex. 1003 ¶67; Ex. 1033 at 004-05.)

In February 1998, McNeil published an article describing ongoing studies of various chemotherapy regimens and rituximab, including a trial for elderly patients with intermediate-grade NHL of CHOP chemotherapy followed by rituximab maintenance therapy administered "every six months for two years." (Ex. 1005 at 003; Ex. 1003 ¶68.)

In December 1998 Grossbard published a review article reporting that, "[s]everal large cooperative group trials are exploring the potential synergy between cytotoxic chemotherapy and rituximab *and its value as maintenance therapy*." (Ex. 1003 ¶69; Ex. 1010 at 011 (emphasis added).) Grossbard describes three trials testing rituximab as maintenance therapy:

- A study by the Cancer and Leukemia Group B ("CALGB") in which rituximab maintenance therapy was tested in elderly patients with aggressive NHL who responded to CHOP chemotherapy;
- A study by the Southwest Oncology Group ("SWOG"), in which rituximab was tested as maintenance therapy after patients were treated with CHOP chemotherapy;
- A study by the Eastern Cooperative Oncology Group ("ECOG"), in which rituximab maintenance therapy was tested in newly diagnosed

patients with low-grade NHL who responded to CVP chemotherapy. (Ex. 1003 ¶69; Ex. 1010 at 011)

In addition, a study by Hainsworth that began enrolling patients in 1998 tested rituximab as a single agent in treatment-naïve patients and also evaluated the feasibility, toxicity, and efficacy of maintenance rituximab administered at six-month intervals for two years. (Ex. 1003 ¶77; Ex. 1034 at 002, Abstract; Ex. 1011 at 004 (Abstract 105).)

Therefore, given the knowledge in the art of low-grade B-cell NHL chemotherapy and previous rituximab clinical trials—including the use of rituximab as maintenance therapy after induction chemotherapy, specifically after CVP chemotherapy—it would have been obvious to a person of skill in the art ("POSA") to develop the treatment regimen described in claim 1. (Ex. 1003 ¶79.)

4. By March 1998, The E1496 Trial Protocol And Patient Consent Form Described The Claimed Use Of Rituximab As A Maintenance Therapy Following CVP Chemotherapy

In March 1998, the ECOG activated a phase III clinical trial to evaluate administering CVP chemotherapy followed by rituximab maintenance therapy in treatment-naïve patients. (Ex. 1002 ¶34; Ex. 1029 at 002-03; *see* Section IX.A *infra*.) This trial was designated ECOG 1496 (or "E1496"). (Ex. 1029 at 002-03.)

The E1496 trial was activated in March 1998, and the University of Wisconsin Clinical Cancer Center ("UWCCC"), an ECOG institution, began

enrolling patients in E1496 as early as June 1998. (Ex. 1002 at ¶¶34, 40, 48; Ex. 1003 ¶82; Ex. 1009 at 001.) The E1496 Patient Consent Form describes the trial protocol:

> If you are assigned to the standard chemotherapy arm, CVP, you will receive cyclosphosphamide . . . and vincristine . . . and prednisone . . . These chemotherapy programs will be given for six to eight cycles depending on how quickly your tumor regresses. If your tumor remains the same or regresses with the chemotherapy you will then be assigned randomly to treatment with the monoclonal antibody [rituximab] or no maintenance therapy. The group receiving the antibody will receive 375 mg/m^2 of antibody weekly for 4 weeks every 6 months for two years. . . .

(Ex. 1008 at 001.) As discussed below, this trial protocol is the exact claim of the '172 patent. Moreover, both the E1496 Protocol and the E1496 Patient Consent Form were publicly available as of March 1998. (*See* Section IX.A *infra*; Ex. 1002 at ¶¶52, 63.)

VI. THE '172 PATENT AND ITS PROSECUTION HISTORY

A. The '172 Patent

The '172 patent (Ex. 1001) is entitled "Combination Therapies for B-Cell Lymphomas Comprising Administration of Anti-CD20 Antibody." It describes a therapeutic regimen to treat low-grade B-cell NHL with a combination of a specific course of chemotherapy followed by rituximab. (Ex. 1001 at Claim 1.)

The ’172 patent contains a single claim which is listed in the Claim List and in the claim charts below. (*See also* Ex. 1001 at 22:56-63.)

B. The U.S. Prosecution History Of The ’172 Patent

The ’172 patent issued on December 11, 2012 from U.S. Application No. 11/840,956 (“the ’956 application”), filed on August 18, 2007. (Ex. 1001 at 001.) The ’172 patent is a continuation of abandoned U.S. Application No. 10/196,732 (“the ’732 application”), which is a continuation of U.S. Application No. 09/372,202 (“the ’202 application”). (*Id.*) The ’202 application, filed August 11, 1999, in turn claims priority to U.S. Provisional Application No. 60/096,180 (“the ’180 provision application”) filed on August 11, 1998. (*Id.*)

The ’180 provisional application consists of six scientific publications specific to treating relapsed or refractory B-cell lymphoma with rituximab submitted with eight claims drawn to treating relapsed B-cell lymphoma with rituximab. (*See* Ex. 1038.) Relapsed or refractory patients to whom rituximab is administered do not fall within the claim of the ’172 patent because the ’172 patent requires administering rituximab to a patient who ***has*** responded to CVP therapy—not one who has relapsed or is refractory to the CVP therapy. The ’180 provisional application thus does not disclose administering to a patient chemotherapy consisting of CVP therapy to which the patient responds, followed by rituximab maintenance therapy. (*Id.*)

The Applicants next filed the ’202 application, and claimed priority to the ’180 provisional. (Ex. 1036 at 006.) The ’202 application was filed with claims drawn to treating relapsed B-cell lymphoma with rituximab; treating B-cell lymphoma by administering rituximab and at least one cytokine; treating B-cell lymphoma by administering rituximab before, during, or subsequent to a chemotherapeutic regimen; and treating B-cell lymphoma by administering rituximab before, during, or subsequent to a bone marrow or stem cell transplant. (Ex. 1036 at 060-66.) The ’202 application issued as U.S. Patent No. 6,455,043 with claims directed to the use of rituximab after myeloablative therapy. (Ex. 1036 at 001.)

The ’956 application, which issued as the ’172 patent, has the same specification as the ’202 application. (Ex. 1001; Ex. 1019 at 015-55; Ex. 1036 at 008-49.)

C. The ’172 Patent Claim Is Not Entitled To The Priority Date Of The ’180 Provisional Application

During prosecution of the ’956 application, the examiner noted in a February 29, 2012 office action that “[t]he claimed inventions are not disclosed in parent application 60/096180. Therefore, regarding the application of prior art, the instant application is not entitled to priority to said application.” (Ex. 1019 at 076.) In responding to the office action, applicants failed to respond to the priority date issue and acquiesced to the examiner’s conclusion that the ’956 application was

not entitled to the provisional '180 application's priority date. (Ex. 1019 at 087-94.) The '956 application issued shortly thereafter as the '172 patent. (Ex. 1001.) Thus, the '172 patent is not entitled to a priority date based on the '180 provisional application's filing date of August 11, 1998 but rather a priority date based on the '202 application's filing date of August 11, 1999.[5]

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

A claim subject to IPR 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 that a POSA would assign to the terms below. For the claim terms not addressed below, Petitioner has applied the plain and ordinary meaning of the term.

[5] In IPR2015-00418, Patent Owner conceded that the appropriate priority date for the '172 patent was August 11, 1999 (the filing date of the '202 application), not August 11, 1998 (the filing date of the provisional '180 application). *See* IPR2015-00418, Paper No. 11 at 8 (P.T.A.B. Apr. 15, 2015) (Patent Owner Preliminary Response).

A. Terms For Construction

1. "chemotherapy consisting of CVP therapy"

Petitioner agrees with the Board's previous construction of "CVP therapy" to mean:

> [A] combination of the drugs cyclophosphamide, vincristine, and prednisone, which is sometimes referred to as "COP" because the drug vincristine is also known as oncovin. The "consisting of" language used in connection with the CVP therapy limits the chemotherapeutic portion of the claimed regimen to only the CVP treatment, to the exclusion of other agents

See IPR2015-00418, Paper No. 14 at 5 (P.T.A.B. July 13, 2015) ("IPR2015-00418 Decision") (citation omitted).

2. "CVP therapy to which the patient responds, followed by rituximab maintenance therapy"

Petitioner agrees with the Board's previous construction of "CVP therapy to which the patient responds, followed by rituximab maintenance therapy" to require:

> [A]dministration of CVP therapy, to which the patient responds according to the criteria set forth in the '172 patent. *See* Ex. 1001, 9:14-23 (the '172 patent providing specific criteria for a complete response (CR) and a partial response (PR) and distinguishing such patients from "non-responders"). The CVP must be followed at some time by the rituximab maintenance therapy, with no disease relapse

occurring between the patient's response to the CVP therapy and the maintenance therapy.

IPR2015-00418 Decision at 6.

3. "A method of treating . . . comprising"

Claim 1 is directed to a method of treatment *comprising* certain elements. (Ex. 1001 at 22:56-65.) "Comprising" is a term of art used in claim drafting to indicate "that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997).

The broadest reasonable interpretation of "a method of treating low-grade B-cell non-Hodgkin's lymphoma in a human patient *comprising*" therefore allows additional unrecited method steps to be performed, including the co-administration of other therapies, such as induction rituximab or myoablative therapy, in addition to CVP, followed by rituximab maintenance therapy. *See, e.g.*, *Teva Neuroscience, Inc. v. Watson Labs., Inc.*, Nos. 2:10-cv-05078 and 2:11-cv-3076, 2013 U.S. Dist. LEXIS 54871, at *8, 24-25 (D.N.J. Apr. 12, 2013) (construing "a method of treating a subject for Parkinson's disease which comprises administering to the subject an amount of R(+)-N-propargyl-l-aminoindan or a pharmaceutically acceptable salt thereof effective to treat the subject" to allow additional unrecited method steps to be performed including the co-administration of other Parkinson's disease therapies).

VIII. PERSON OF ORDINARY SKILL IN THE ART

As of August 11, 1999, a POSA at the time of the alleged invention of the '172 patent was a practicing physician specializing in hematology or oncology, with at least three years of experience in treating patients with NHL. (Ex. 1003 ¶22.)

IX. THE PRIOR ART

The '172 patent is not entitled to a filing date before August 11, 1999. Accordingly, prior art published before August 11, 1998 is §102(b) prior art. Prior art published in the year from August 11, 1998 to August 11, 1999 is §102(a) prior art. Petitioner relies on the following patent applications and publications:

A. E1496 Patient Consent Form (Ex. 1008) And E1496 Protocol (Ex. 1009)

As described below, the E1496 Patient Consent Form and the E1496 Protocol each qualify as prior art under 35 U.S.C. §102(b) because each was published and publicly available as of March 19, 1998—more than one year before the earliest filing date to which the '172 patent claim is entitled (August 11, 1999).

1. E1496 Clinical Trial

As described above in Section V.D.4, E1496 is a specific clinical trial coordinated by ECOG. The clinical trial E1496 is entitled "Randomized Phase III Study in Low Grade Lymphoma Comparing Cyclophosphamide/Fludarabine to Standard Therapy Followed by Maintenance Anti-CD20 Antibody." E1496 was

activated by ECOG on March 19, 1998. (Ex. 1002 at ¶¶2, 3, 34, 48; Ex. 1009 at 001; Ex. 1049 at 004.)

The purpose of E1496 was to compare whether chemotherapy with the regimen of cyclophosphamide-fludarabine caused more and longer remissions compared to the standard CVP chemotherapy regimen, and whether maintenance therapy with rituximab for two years increased the duration of remission. (Ex. 1002 ¶34; Ex. 1008 at 001.) The E1496 Patient Consent Form states:

> It has been explained to you that you have a non-aggressive (low grade) lymphoma. You have been invited to participate in this research study. This study involves treatment with one or two chemotherapy programs for six to eight cycles followed by maintenance therapy with an immunologic modifier (monoclonal antibody) . . . .
>
> . . . .
>
> . . . If you are assigned to the standard chemotherapy arm, CVP, you will receive cyclosphosphamide . . . and vincristine . . . and prednisone . . . . These chemotherapy programs will be given for six to eight cycles depending on how quickly your tumor regresses. If your tumor remains the same or regresses with the chemotherapy you will then be assigned randomly to treatment with the monoclonal antibody, IDEC C2B8 (anti-CD20 antibody), or no maintenance therapy. The group receiving the antibody will receive 375 mg/m^2 of antibody weekly for 4 weeks every 6 months for two years. . . .

(Ex. 1008 at 001.)

2. The E1496 Patient Consent Form And The E1496 Protocol Are Each Printed Publications Under 35 U.S.C. §102(b)

Dr. Walter Longo, a medical oncologist at University of Wisconsin, Madison, who was a sub-investigator in the E1496 clinical trial, verifies in his declaration that the E1496 Patient Consent Form and Protocol were freely available to potential patients and interested clinicians without any confidentiality restrictions as of March 1998. (Ex. 1002 ¶¶49, 52, 53, 63.) Thus, the E1496 Patient Consent Form and the E1496 Protocol were sufficiently publicly accessible to be printed publications under 35 U.S.C. §102(b).

A printed "publication" is a publication that is "'sufficiently accessible to the public interested in the art.'" *In re Lister*, 583 F.3d 1307, 1311 (Fed. Cir. 2009) (citation omitted). A reference is deemed a "printed publication," therefore, "'upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it.'" *In re Wyer,* 655 F.2d 221, 226 (C.C.P.A. 1981) (citation omitted); *see also Voter Verified, Inc. v. Premier Election Solutions, Inc.*, 698 F.3d 1374, 1379-80 (Fed. Cir. Nov. 5, 2012) (finding public accessibility where the reference was well known to the community interested in the art); *see also Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1379 (Fed. Cir. 2006) (finding public accessibility when an indexed "research aid" would have directed interested researchers to the

potentially invalidating reference). Once accessibility is shown, it is unnecessary to show that anyone actually inspected the reference. *Lister*, 583 F.3d at 1314.

a. The E1496 Protocol And Patient Consent Form Were Each Publicly Accessible Beginning March 19, 1998

Dr. Longo was a sub-investigator on the E1496 trial and participated in the trial through his clinical institution, the University of Wisconsin Clinical Cancer Center (now re-named the Carbone Clinical Cancer Center) (hereinafter "UWCCC"). (Ex. 1002 ¶¶25, 37.) Dr. Longo states that he first received copies of the E1496 Protocol and Patient Consent Form from the UWCCC data coordinators, who did not instruct him to keep any portion of the documents confidential. (*Id.* ¶39.) To the contrary, Dr. Longo states that the data coordinators encouraged and expected him to share the E1496 Protocol freely with others to drum up interest in the trial. (*Id.*) He did not sign a confidentiality agreement or any other agreement in connection with his role as a sub-investigator and he felt at liberty to share the protocol with others, including patients, other oncologists, other professors, students, family, friends, and any member of the public. (*Id.*)

Dr. Longo also states that the E1496 Patient Consent Form (Ex. 1008) was distributed to potential patients with no expectation of confidentiality. (Ex. 1002 ¶49.) He personally distributed the consent form to approximately 40 prospective patients, every prospective patient who inquired about the E1496 trial. (*Id.*) It was expected that such patients would take the consent form home and discuss the pros

and cons of the clinical study with their own physicians, other oncologists who might provide second opinions, family, friends, or anyone else before deciding whether to participate. (*Id.*)

Dr. Longo further states that the UWCCC published a list of open trials, including E1496, and posted the list in clinician work spaces. (*Id.* ¶29.). ECOG affiliates would also distribute letters listing all active ECOG trials to any physician requesting such information. (*Id.* ¶56.) Starting in March 1998, the E1496 Protocol would have been included in this distribution. (*Id.*) There was no expectation that the clinical trial protocol was confidential or could not be shared with other interested clinicians. (*Id.* ¶59.) Indeed, the UWCCC would routinely disclose the E1496 Protocol to any inquiring physician, so that the physician could be fully informed about the potential risks and benefits of the E1496 trial before referring patients to the institution. (*Id.* ¶57.)

Dr. Longo additionally testifies that any interested physician could have learned about the E1496 trial by viewing the list of active protocols on the ECOG website. (Ex. 1002 ¶56; Ex. 1049 at 004.) Like the "research aid" in *Bruckelmyer*, this list of active protocols was indexed by subject matter under the heading "Lymphoma Committee." *See, e.g.,* 445 F.3d at 1379. (Ex. 1002 ¶56; Ex. 1049 at 004.) The indexed list provides sufficient detail—namely, the protocol number—to lead an interested party directly to both the E1496 Protocol and Patient Consent

Form by contacting an ECOG institution and inquiring about the trial. (Ex. 1002 ¶¶56, 57.)

Dr. Longo concludes that the E1496 Patient Consent Form and E1496 Protocol were each known to the community interested in the subject matter of the references—namely, physicians and patients interested in treatments for low-grade B-cell NHL—as of at least March 19, 1998. *Voter Verified*, 698 F.3d at 1379-80. (Ex. 1002 ¶¶52, 63.)

b. The Board's Previous Findings

In IPR2015-00418, the petitioner attempted to rely on the E1496 Protocol as an anticipatory reference. *See, e.g.*, IPR2015-00418, Paper No. 1 at 31-32 (P.T.A.B. Dec. 15, 2014). In denying institution, the Board found that the petitioner had failed to show that the E1496 Protocol "was publicly accessible to the extent required to establish its status as a printed publication under either §311(b) or §102(b)." IPR2015-00418 Decision at 8.

The Board noted that the petitioner presented "no direct evidence from the ECOG, or from anyone directly associated with the ECOG, explaining specifically whether or how ECOG 1496 and ECOG 4494 [another ECOG study on which the petitioner relied] were distributed, or whether the protocols were under confidentiality restrictions." *Id.* at 9-10. The Board noted that petitioner's declarant did not have "specific firsthand knowledge about whether or how ECOG

1496 and ECOG 4494 were distributed." *Id.* at 11. The Board was not persuaded that the specific documents "were disseminated publicly or otherwise made available such that ordinarily skilled and interested persons exercising reasonable diligence would have been able to locate and gain access to them, as of the critical date." *Id.* at 14. Accordingly, the Board declined to find that the ECOG 1496 and ECOG 4494 protocols are printed publications for the purposes of 35 U.S.C. §§102(b) and 311(b). *Id.*

In contrast to the petitioner's declarant in IPR2015-00418, Dr. Longo has specific, first-hand knowledge of the E1496 Protocol and Patient Consent Form and attests to the public accessibility of these documents beginning March 19, 1998. (Ex. 1002 ¶¶2, 3, 37-40.) Therefore, the E1496 Patient Consent Form and the E1496 Protocol were publicly accessible and qualify as §102(b) anticipatory prior art

B. Grossbard (Ex. 1010)

Grossbard is a December 1, 1998 article published in the journal Oncology entitled, "The McLaughlin et al Article Reviewed." (Ex. 1010 at 010-11.) Grossbard qualifies as prior art under 35 U.S.C. §102(a) because it was published prior to August 11, 1999, the earliest filing date to which the '172 patent claim is entitled.

Grossbard describes ongoing rituximab maintenance trials in low-grade lymphoma, including the E1496 trial: "Eastern Cooperative Oncology Group (ECOG) is conducting a phase III trial of cyclophosphamide and fludarabine (Fludara) vs. CVP (cyclophosphamide, vincristine, and prednisone) followed by rituximab or observation." (Ex. 1010 at 011.)

C. 1997 Rituxan Label (Ex. 1004)

The Rituxan label was made publicly available in November 1997 when Rituxan was approved and is therefore §102(b) prior art.

The Rituxan label states that "[t]he recommended dosage of RITUXAN is 375 mg/m^2 given as an IV infusion once weekly for four doses." (Ex. 1004 at 002.) The label further describes that "[a]dministration of RITUXAN resulted in a rapid and sustained depletion of circulating and tissue-based B cells. . . . Among the 166 patients in the pivotal study, circulating B-cells (measured as CD19+ cells) were depleted within the first three doses with sustained depletion for up to 6 to 9 months post-treatment in 83% of patients." (*Id.* at 001.)

D. McNeil (Ex. 1005)

McNeil is an article published in February 1998 in the Journal of the National Cancer Institute, entitled "Non-Hodgkin's Lymphoma Trials in Elderly Look Beyond CHOP." McNeil is §102(b) prior art as it was publicly available more than a year before the '172 patent's earliest priority date.

McNeil describes ongoing studies of various chemotherapy regimens and rituximab, including a trial for elderly patients with intermediate-grade NHL of CHOP chemotherapy followed by rituximab maintenance therapy administered "every six months for two years." (Ex. 1005 at 003.)

E. Bishop (Ex. 1006)

Bishop is a 1987 publication entitled "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" in the journal Leukemia. CAVP has the same components as CHOP. Bishop is §102(b) prior art as it was publicly available more than a year before the '172 patent's earliest possible priority date.

Bishop teaches that adding doxorubicin to CVP chemotherapy does not provide a clinical benefit over CVP for low-grade NHL patients. (Ex. 1006 at 003, 006.)

F. Dana (Ex. 1007)

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 §102(b) prior art as it was publicly available more than a year before the '172 patent's earliest possible priority date.

Dana teaches that CHOP chemotherapy does not provide any survival advantage over CVP in advanced low-grade lymphoma. (Ex. 1007 at 002.)

G. Background Art

In addition to the specific references discussed above, Dr. Lossos has considered additional references, as described in his declaration, reflecting the state of the art in August 1999. *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 THAT CLAIM 1 OF THE '172 PATENT IS ANTICIPATED

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) (citing *Celeritas Techs., Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1360 (Fed. Cir. 1998)). 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).

Further, "[a]s long as the reference discloses all of the claim limitations and enables the 'subject matter that falls within the scope of the claims at issue,' the reference anticipates—no 'actual creation or reduction to practice' is required." *Id.* at 1334 (citations omitted). The standard for enablement of a prior art reference is less exacting than it is for patentability under 35 U.S.C. §112 and the anticipatory reference need not demonstrate utility. *Impax Labs., Inc. v. Aventis Pharms., Inc.*, 468 F. 3d 1366, 1381-82 (Fed. Cir. 2006). Proof of efficacy is not required in order for a reference to be enabled for purposes of anticipation. *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005).

A. Ground 1: Claim 1 Is Anticipated Under §102 By E1496 Patient Consent Form

As discussed in the declaration of Dr. Longo and summarized in the claim chart below, the treatment regimen disclosed in the E1496 Patient Consent Form contains all of the elements of claim 1 of the '172 Patent. (Ex. 1002 ¶¶64-67.)[6]

Specifically, the E1496 Patient Consent Form describes a "study involv[ing] treatment with one or two chemotherapy programs for six to eight cycles followed by maintenance therapy with an immunologic modifier (monoclonal antibody)" for

[6] Dr. Lossos concurs: assuming the E1496 Patient Consent Form and the E1496 Protocol were publicly available, the Patient Consent Form and Protocol each anticipate the '172 patent. (Ex. 1003 ¶85.)

patients with "a non-aggressive (low grade) lymphoma." (Ex. 1008 at 001.) The E1496 Patient Consent Form further specifies CVP as one of the chemotherapy arms used in the study and states that patients whose "tumor remains the same or regresses with the chemotherapy . . . will then be assigned randomly to treatment with the monoclonal antibody, IDEC C2B8 (anti-CD20 antibody), or no maintenance therapy." (*Id.*) Patients receiving the anti-CD20 antibody (rituximab) would "receive 375 mg/m^2 of antibody weekly for 4 weeks every 6 months for two years. . . ." (*Id.*; Ex. 1002 ¶65.)

Thus, the E1496 Patient Consent Form teaches treating low-grade NHL by first administering CVP chemotherapy, then, if the patient responds, administering rituximab maintenance therapy in weekly doses of 375 mg/m^2 for four weeks every six months for two years. (Ex. 1002 ¶¶64-67; Ex. 1008 at 001.) This covers each of the elements of Claim 1, so Claim 1 is anticipated.

GROUND 1	
'172 Claim 1	**E1496 Patient Consent Form (Ex. 1008)**
A method of treating low grade B-cell non-Hodgkin's lymphoma in a human patient	"It has been explained to you that you have a non-aggressive (low grade) lymphoma. You have been invited to participate in this study. This study involves treatment with one or two chemotherapy programs for six to eight cycles followed by maintenance therapy with an immunologic modifier (monoclonal antibody) in half of the patients.)" (Ex. 1008 at 001; Ex. 1002

	¶65.)
comprising administering to the patient chemotherapy consisting of CVP therapy to which the patient responds,	"If you are assigned to the standard chemotherapy arm, CVP, you will receive cyclosphosphamide . . . and vincristine . . . and prednisone . . . These chemotherapy programs will be given for six to eight cycles depending on how quickly your tumor regresses. If your tumor remains the same or regresses with the chemotherapy you will then be assigned randomly to treatment with the monoclonal antibody, IDEC C2B8 (anti-CD20 antibody) or no maintenance therapy." (Ex. 1008 at 001; Ex. 1002 ¶65.)
followed by rituximab maintenance therapy,	"If your tumor remains the same or regresses with the chemotherapy you will then be assigned randomly to treatment with the monoclonal antibody, IDEC C2B8 (anti-CD20 antibody), or no maintenance therapy." (Ex. 1008 at 001; Ex. 1002 ¶65.)
wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m2 every 6 months, and wherein the maintenance therapy is provided for 2 years	"The group receiving the antibody will receive 375 mg/m^2 of antibody weekly for 4 weeks every 6 months for two years. . . ." (Ex. 1008 at 001; Ex. 1002 ¶65.)

B. Ground 2: Claim 1 Is Anticipated Under §102 By The E1496 Protocol

As described in the declaration of Dr. Longo and summarized in the claim chart below, the treatment regimen disclosed in the E1496 Protocol contains all of the elements of claim 1 of the '172 Patent. (Ex. 1002 ¶¶64-67.) Like the E1496

Patient Consent Form, the E1496 Protocol describes an arm of the study in which "Low Grade Lymphoma" is treated by CVP chemotherapy followed by rituximab maintenance therapy in weekly doses of 375 mg/m^2 for four weeks every six months for two years. (Ex. 1002 ¶65; Ex. 1009 at 002, 010, 011.) Claim 1 is therefore anticipated.

GROUND 2	
'172 Claim 1	**E1496 Protocol (Ex. 1009)**
A method of treating low grade B-cell non-Hodgkin's lymphoma in a human patient	"Eastern Cooperative Oncology Group[:] Randomized Phase III Study in Low Grade Lymphoma Comparing Cyclophosphamide/Fludarabine to Standard Therapy Followed by Maintenance Anti-CD20 Antibody" (Ex. 1009 at 002 (Title); Ex. 1002 at ¶34.) "Selection of Patients . . . [n]o prior chemotherapy, radiotherapy, or immunotherapy." (Ex. 1009 at 007-08.)
comprising administering to the patient chemotherapy consisting of CVP therapy to which the patient responds,	"Patients randomized [in first randomization to treatment regimen B] (standard therapy) will receive cyclophosphamide 1000 mg/m2 . . ., vincristine 1.4 mg/m2 . . . and prednisone 100 mg/m2 . . . . Cycles will be repeated q 21 days. . . . All patients who have not progressed on induction chemotherapy will be randomized to either maintenance therapy with chimeric anti-CD20 antibody or observation." (Ex. 1009 at 011, 010; Ex. 1002 ¶66.)

followed by rituximab maintenance therapy,	"Patients randomized [in second randomization to treatment regimen C] will receive Anti-CD20 . . . ." (Ex. 1009 at 011; Ex. 1002 ¶66.)
wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m2 every 6 months, and wherein the maintenance therapy is provided for 2 years	"at a dose of 375 mg/m^2 weekly x 4 every 6 months for a total of 2 years beginning 4 weeks after the last chemotherapy" (Ex. 1009 at 011; Ex. 1002 ¶66.)

XI. THERE IS A REASONABLE LIKELIHOOD THAT THE CLAIM OF THE '172 PATENT IS OBVIOUS

The obviousness inquiry 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." *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007).

In *Coherus Biosciences Inc. v. AbbVie Biotechnology Ltd.*, IPR2016-00172, Paper No. 9 at 16 (P.T.A.B. May 17, 2016), the Board noted, "all that is required to show obviousness is a reasonable expectation of success, not conclusive proof of superior efficacy." *Id.* (citing *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1363-64 (Fed. Cir. 2007); *Pfizer*, 480 F.3d at 1364). In *Coherus*, the Board found that a claimed method of treatment was likely obvious and instituted the *inter partes* review because a POSA "would have been led to optimize the dosing regimens disclosed in [the prior art] in order to treat the patient with as little drug as possible to reduce potential side effects, while at the same time attaining a therapeutic response and improving patient compliance." *Id*. at 20.

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). The Board further noted that the experimentation to achieve the claimed regimen was "'nothing more than the routine' application of a well-known problem solving strategy . . . 'the work of a skilled [artisan], not of an inventor.'" *Id.* at 14 (citing *Pfizer*, 480 F.3d at 1368). Finally, the "motivation to optimize the therapy disclosed in [the prior art] flows from the 'normal desire of scientists or artisans to improve upon what is already generally known.'" *Id.* (citation omitted).

Here, the single claim of the '172 patent combines a well-known chemotherapy regimen (CVP) with a well-known rituximab dosing regimen (375 mg/m^2 weekly for four weeks, repeated every six months for two years) and uses rituximab as "maintenance therapy" in the manner described and directed in the prior art. Rituximab was already known to be safe and efficacious, and a Phase III clinical trial was testing the claimed regimen. The '172 patent simply represents "routine optimization" of the therapy outlined in the prior art.

A. Ground 3: Claim 1 Is Obvious Over Grossbard And The Rituxan Label

The claim of the '172 patent would have been obvious over Grossbard (Ex. 1010) and the Rituxan label (Ex. 1004).

Grossbard is a December 1, 1998 publication in the journal Oncology. Grossbard describes three ongoing trials testing rituximab as maintenance therapy following chemotherapy. (Ex. 1010 at 011.) The first study reported by Grossbard

is the CALGB study of rituximab maintenance therapy for elderly patients with aggressive NHL who responded to CHOP chemotherapy. (*Id.*) Grossbard explains that "[g]iven the stability of CD20 expression, this trial also is exploring *the value of rituximab maintenance by randomizing all patients with responsive disease to observation or four weekly doses of rituximab every 6 months for 2 years*." (*Id.* (emphasis added).)

The second study reported by Grossbard is the E1496 trial, discussed above. Grossbard states that ECOG "is conducting a phase III trial of *cyclophosphamide and fludarabine (Fludara) vs CVP (cyclophosphamide, vincristine, and prednisone), followed by rituximab* or observation." (*Id.* (emphasis added).) Thus Grossbard discloses treatment with CVP followed by rituximab maintenance therapy. (*Id.*)

The third study reported by Grossbard is the SWOG study of rituximab maintenance therapy following CHOP chemotherapy in patients with low-grade lymphoma. Grossbard explains that SWOG "is performing a phase II trial of CHOP followed by rituximab, with special attention to measurement of minimal residual disease." (*Id.*; Ex. 1003 ¶¶69-76.)

A POSA would understand that maintenance therapy is given only after successful induction chemotherapy, after a patient has experienced a complete or partial response and is in remission. (Ex. 1003 ¶73; *see also* Ex. 1005 at 003

(maintenance therapy given only to responders); Ex. 1011 at 004 (same).) Grossbard teaches that rituximab maintenance therapy should be dosed at "four weekly doses of rituximab every 6 months for 2 years" (Ex. 1010 at 011). Both Grossbard and the Rituxan label teach that the doses should be 375 mg/m^2 per week for four weeks. (Ex. 1010 at 010; Ex. 1004 at 001.)

Based on the description of three separate trials testing rituximab as maintenance therapy, including one in which CVP was given as the induction chemotherapy, and the specific dosage as described in both Grossbard and the Rituxan label, each element of claim 1 is disclosed, as shown in the table below. (*See also* Ex. 1003 ¶¶86-89.)

GROUND 3	
'172 Claim 1	**Grossbard (Ex. 1010) and Rituxan Label (Ex. 1004)**
A method of treating low grade B-cell non-Hodgkin's lymphoma in a human patient	"The value of rituximab maintenance therapy in low-grade lymphoma is the subject of two other cooperative group trials. . . . The Eastern Cooperative Oncology Group (ECOG) is conducting a phase III trial [in low-grade lymphoma]." (Ex. 1010 at 011; Ex. 1003 ¶89.)
comprising administering to the patient chemotherapy consisting of CVP therapy to which the patient responds,	"[ECOG] is conducting a phase III trial of cyclophosphamide and fludarabine (Fludara) vs CVP" (Ex. 1010 at 011; Ex. 1003 ¶89.)
followed by rituximab maintenance therapy,	"[ECOG] is conducting a phase III trial of cyclophosphamide and fludarabine (Fludara) vs CVP . . . followed by rituximab or observation." (Ex. 1010 at

	011; Ex. 1003 ¶89.) "[T]his [CALGB] trial also is exploring the value of rituximab maintenance by randomizing all patients with responsive disease to observation or four weekly doses of rituximab every 6 months for 2 years." (Ex. 1010 at 011; Ex. 1003 ¶89.)
wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m2 every 6 months, and wherein the maintenance therapy is provided for 2 years	"[T]his [CALGB] trial also is exploring the value of rituximab maintenance by randomizing all patients with responsive disease to observation or four weekly doses of rituximab every 6 months for 2 years." (Ex. 1010 at 011.) "[T]he currently approved 375 mg/m^2 weekly x 4 regimen." (*Id.* at 010.) "The recommended dosage of RITUXAN is 375 mg/m^2 given as an IV infusion once weekly for four doses (days 1, 8, 15, and 22)." (Ex. 1004 at 002; Ex. 1003 ¶89.)

1. Motivation To Combine

A POSA would have been motivated to combine the teachings of Grossbard and the Rituxan label to build on the treatment protocols for low-grade B-cell lymphoma discussed in Grossbard. (Ex. 1003 ¶90.) The desire of scientists and researchers to optimize therapy by improving what is already known as disclosed in the combined references "flows from the 'normal desire of scientists or artisans to improve upon what is already known.'" *Pfizer*, 480 F.3d at 1368 (quoting *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003)).

Grossbard describes three different clinical trials of rituximab maintenance therapy after induction chemotherapy, including CVP chemotherapy. (Ex. 1010 at 011.) A POSA wanting to implement the treatment protocol of CVP followed by rituximab maintenance therapy described in Grossbard would logically look to Grossbard's disclosed rituximab dosing. (Ex. 1003 ¶90.) Indeed, the Federal Circuit has held that combining elements "disclosed adjacent to each other in a prior art patent does not require a leap of inventiveness." *Boston Scientific Scimed, Inc. v. Cordis Corp.*, 554 F.3d 982, 991 (Fed. Cir. 2009). Likewise, no "leap of inventiveness" is required to combine the treatment of CVP plus rituximab maintenance therapy described in Grossbard with the rituximab dosing regimen also described in Grossbard. It would have been obvious to a POSA to combine these disclosures on rituximab maintenance therapy, which are adjacent within the same two-page reference. (Ex. 1003 ¶90.)

Grossbard teaches administering rituximab in four weekly doses every six weeks for two years when used as maintenance therapy, and further discloses that the currently approved dosage of rituximab is 375 mg/m^2 weekly for four weeks. (Ex. 1010 at 010-11.) The dosage of 375 mg/m^2 weekly for four weeks disclosed in Grossbard is confirmed by the Rituxan label's teaching of the same dosage. (Ex. 1004 at 001.) A POSA seeking a dosage for rituximab maintenance therapy would be guided by the Rituxan label's dosage. (Ex. 1003 ¶¶91, 94.) It would

have been obvious to a POSA seeking to implement Grossbard's disclosed regimen of CVP followed by rituximab maintenance therapy to dose rituximab at 375 mg/m^2 weekly for four weeks every six months for two years. (*Id.* ¶91.) This combined information is the exact regimen of claim 1.

2. Reasonable Expectation Of Success

A POSA evaluating the combination of Grossbard and the Rituxan label would have had a reasonable expectation that the claimed treatment regimen would be safe and efficacious. (*Id.* ¶92.) "All that is required to show obviousness is a reasonable expectation of success, not conclusive proof of efficacy." *Boehringer Ingelheim Int'l GmbH v. Genentech, Inc.,* IPR2015-00417, Paper No. 11 at 22 (P.T.A.B. July 14, 2015).

A POSA would have expected rituximab maintenance therapy to be safe and efficacious based on the previous trials of rituximab. Indeed, rituximab had been demonstrated safe in all previous trials. (Ex. 1003 ¶92.) As Grossbard teaches, "[r]ituximab (Rituxan), the first [monoclonal antibody] approved for the treatment of cancer, describes one of the success stories in this field." (Ex. 1010 at 010; Ex. 1003 ¶92.) Thus, based on Grossbard and previous trials, a POSA would reasonably expect rituximab maintenance therapy to be safe and efficacious. (Ex. 1003 ¶92.)

Further, a POSA would have expected that the dosing schedule for rituximab maintenance therapy could be administered safely. Grossbard teaches:

> Unlike studies with conventional cytotoxic agents, initial phase I studies with rituximab never reached a maximum tolerated dose. Some published studies have used larger doses than the currently approved 375 mg/m^2 weekly x 4 regimen. For example, Coiffier et al used doses up to 500 mg/m^2 in a weekly x 8 regimen in patients with intermediate- or high-grade lymphoma. . . .
>
> . . . .
>
> To date, no major toxicity has been seen with rituximab, despite prolonged B-cell depletion following therapy. This minimal side effects profile therefore makes rituximab an attractive agent for combination therapies . . . .

(Ex. 1010 at 010; Ex. 1003 ¶93.)

Given these teachings, a POSA would have a reasonable expectation that rituximab could successfully be used as maintenance therapy after a course of routine CVP chemotherapy. Therefore, the combination of Grossbard and Rituxan label render the claim 1 of the '172 patent obvious. (Ex. 1003 at ¶95.)

B. Ground 4: Claim 1 Is Obvious Under §103 In View Of McNeil, Bishop, Dana, And The Rituxan Label

The sole claim of the '172 patent would also have been obvious over the combination of McNeil (Ex. 1005), Bishop (Ex. 1006), Dana (Ex. 1007), and the Rituxan Label (Ex. 1004).

McNeil is a Journal of the National Cancer Institute article published in February 1998. It describes an upcoming trial for elderly patients with intermediate-grade NHL of CHOP chemotherapy followed by rituximab maintenance therapy every six months for two years. (Ex. 1005 at 003.) McNeil therefore discloses a dosing strategy and duration for rituximab maintenance therapy following induction chemotherapy. Significantly, McNeil explains that "CHOP alternatives could also turn out [to] be less toxic chemotherapy regimens," particularly among elderly patients. (*Id.* at 003-04.) Under the heading "Less Toxic Options," McNeil describes the search for "other drug combinations that may be as effective but less toxic than CHOP" and refers to a trial "comparing CHOP to CIEP, in which the less toxic idararubicin and VP16(P) are substituted for CHOP's doxorubicin and vincristine." (*Id.*) Thus, McNeil teaches the use of rituximab maintenance therapy following chemotherapy and suggests the use of a less toxic but equally effective alternative to CHOP for chemotherapy. For McNeil's intermediate-grade NHL patients, CVP was not a valuable chemotherapy option; however, a POSA would have known that for low-grade NHL, CVP was both less toxic and equally effective as CHOP. (Ex. 1003 ¶97.)

Bishop is an article in Leukemia published in 1987. It describes the results of a randomized control trial comparing CVP to CAVP in NHL patients. (Ex. 1006 at 002.) CAVP, like CHOP, is CVP plus doxorubicin. (Ex. 1003 ¶98.)

Bishop found that "overall CR rates were identical" for CVP and CAVP, and "no differences in CR duration were detected between the two study arms." (Ex. 1006 at 003.) Bishop further found that, for all NHL subtypes except diffuse large cell lymphoma (which is not a form of low-grade NHL), "[h]igh dose CVP was as effective as high dose CAVP." (*Id.* at 006.) Bishop concludes that "[t]hese data suggest that doxorubicin does not enhance the activity of the CVP regimen against lymphomas other than diffuse large cell." (*Id.*) Thus, Bishop teaches that, for low-grade NHL, CVP with doxorubicin is not more effective than CVP without doxorubicin. (Ex. 1003 ¶98.) A POSA reading Bishop would have understood that adding doxorubicin to CVP does not increase effectiveness for low-grade NHL. (*Id.*)

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. 1007 at 002, Abstract.) Dana teaches that CHOP chemotherapy does not provide any survival advantage over CVP in advanced low-grade lymphoma. (*Id.* at 002, Abstract, 006.) That is, CVP is equally effective as CHOP. (Ex. 1003 ¶99.)

The Rituxan label teaches that rituximab is safe and efficacious for patients with low-grade or follicular B-cell NHL, and the rituximab dosage should be 375 mg/m^2 per week for four weeks. (Ex. 1004 at 001-02.) The Rituxan Label further

describes that this rituximab regimen depletes B cells for 6 to 9 months, which bolsters McNeil's teaching that maintenance therapy should be dosed every 6 months. (*Id.* at 001; Ex. 1003 ¶100.)

Thus, the Rituxan Label teaches the efficacy of rituximab to treat low-grade B-cell NHL, McNeil teaches the use of rituximab maintenance therapy following CHOP chemotherapy and also describes looking for less toxic alternatives to CHOP, and Bishop and Dana teach that CVP is as effective as CHOP for low-grade NHL. The Rituxan Label teaches the use of a 375 mg/m^2 weekly dose of rituximab for four weeks, and McNeil teaches that rituximab should be administered every six months when given as maintenance therapy. Therefore, McNeil, Bishop, Dana, and the Rituxan Label together disclose each element of claim 1. (Ex. 1003 ¶¶96-101.)

GROUND 4	
'172 Claim 1	**McNeil (Ex. 1005), Bishop (Ex. 1006), Dana (Ex. 1007), and the Rituxan Label (Ex. 1004)**
A method of treating low grade B-cell non-Hodgkin's lymphoma in a human patient	"A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or refractory low-grade or follicular B-cell NHL . . ." (Ex. 1004 at 001; Ex. 1003 ¶101.)
comprising administering to the patient chemotherapy consisting of CVP therapy to which the patient responds,	The subjects of McNeil's planned study were to receive "either CHOP alone or CHOP with rituximab. . . . After initial therapy, patients who responded will be . . . randomly assigned to receive [rituximab] maintenance therapy."

	(Ex. 1005 at 003; Ex. 1003 ¶101.) McNeil teaches "the search for other drug combinations that may be as effective but less toxic than CHOP continues. At Aviano [doctors] have launched a trial comparing CHOP to CIEP, in which the less toxic idarubicin and VP16(P) are substituted for CHOP's doxorubicin and vincristine." (Ex. 1005 at 003; Ex. 1003 ¶101.) Bishop and Dana teach that CVP is as effective as CHOP for low-grade NHL. (Ex. 1007 at 002, Abstract; Ex. 1006 at 006; Ex. 1003 ¶101.)
followed by rituximab maintenance therapy,	"After initial therapy, patients who responded will be again randomly assigned to receive the maintenance regimen" (Ex. 1005 at 003; Ex. 1003 ¶101.)
wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m2 every 6 months, and wherein the maintenance therapy is provided for 2 years	"the maintenance regimen – Rituxan every six months for two years" (Ex. 1005 at 003; Ex. 1003 ¶101.) "The recommended dosage of RITUXAN is 375 mg/m^2 given as an IV infusion once weekly for four doses (days 1, 8, 15, and 22)." (Ex. 1004 at 002; Ex. 1003 ¶101.)

1. Motivation To Combine

A POSA would have been motivated to combine the teachings of McNeil, Bishop, Dana, and the Rituxan Label to optimize existing treatment protocols for low-grade B-cell lymphoma. (Ex. 1003 ¶102.) Scientists have a motivation to optimize therapy by improving upon what is already disclosed in the combined

references and this motivation "flows from the 'normal desire of scientists or artisans to improve upon what is already known.'" *Pfizer*, 480 F.3d at 1368 (quoting *In re Peterson*, 315 F.3d at 1330).

A POSA reading McNeil's disclosure of CHOP followed by rituximab maintenance therapy for intermediate-grade NHL and the Rituxan Label's disclosure of the effectiveness of rituximab for low-grade NHL would be encouraged to use rituximab maintenance therapy after standard induction chemotherapy for low-grade NHL. (Ex. 1003 ¶102.)

A POSA would be further encouraged by Bishop and Dana to use CVP instead of McNeil's CHOP chemotherapy to implement the claimed treatment regimen. (Ex. 1003 ¶103.) A POSA would have understood that, whereas CHOP is a better choice than CVP for patients with aggressive NHL (such as the intermediate-grade NHL described in McNeil), CVP and CHOP are equally effective for low-grade NHL. (*Id.*; Ex. 1007 at 002; Ex. 1006 at 006; *see also* Ex. 1017 at 029-30; Ex. 1031 at 007.)

Furthermore, a POSA would have appreciated that CHOP was more toxic than CVP and that the doxorubicin component of CHOP has cardiotoxicity and increased risk of neutropenia issues. (Ex. 1003 ¶104.)[7] McNeil specifically

[7] Bishop's finding that high-dose CVP and CAVP were equitoxic was disproved by subsequent publications finding increased toxicity due specifically to

describes concerns about the toxicities associated with CHOP and suggests potential less-toxic alternatives, including "mini-CHOP" and substituting CHOP's doxorubicin and vincristine for less toxic compounds. (Ex. 1005 at 003-04.) A POSA would have understood Bishop and Dana to teach that CVP and CHOP are equally effective for low-grade NHL. (Ex. 1003 ¶104; Ex. 1007 at 002; Ex. 1006 at 006.) Moreover, a POSA concerned about doxorubicin's toxicity would have understood that CVP would be a better choice than CHOP for low-grade NHL because CVP and CHOP have the same efficacy for low-grade NHL but CVP omits the doxorubicin and is thus less toxic. (Ex. 1003 ¶104.)

It would have been obvious to a POSA reading McNeil that CVP could not be used for McNeil's intermediate-grade NHL patients, but that for low-grade NHL patients, CVP could be used instead of CHOP to preserve efficacy while addressing McNeil's concerns about toxicity. (Ex. 1003 ¶105; Ex. 1005 at 003.) Thus, it would have been obvious to a POSA to try CVP as the standard chemotherapy regimen in low-grade NHL patients.

McNeil further instructs a POSA to employ maintenance therapy every six months for two years. (Ex. 1005 at 003.) The Rituxan Label teaches administering

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doxorubicin. (Ex. 1003 ¶104 n. 3; Ex. 1020 at 006; Ex. 1031 at 007; Ex. 1039 at 003-05; Ex. 1040 at 003-07; Ex. 1050 at 003; Ex. 1007 at 002; *see* Ex. 1005 at 003.)

375 mg/m^2 for four weekly doses. The Rituxan Label discloses that this dosing regimen depletes B cells for 6 to 9 months, thus supporting the application of the Rituxan Label's dosing regimen to McNeil's schedule of administering rituximab maintenance therapy every six months. (Ex. 1004 at 001-02; Ex. 1003 ¶106.)

2. Reasonable Expectation Of Success

A POSA evaluating the combination of McNeil, Bishop, Dana, and the Rituxan Label would have had a reasonable expectation that the claimed treatment regimen would be safe and efficacious. (Ex. 1003 ¶107.) "All that is required to show obviousness is a reasonable expectation of success, not conclusive proof of efficacy." *Boehringer Ingelheim Int'l GmbH*, IPR2015-00417, Paper No. 11 at 22.

As described above, a POSA would have expected rituximab to be safe and efficacious. (Ex. 1003 ¶92.) Further, a POSA would have known that rituximab and CVP chemotherapy had non-overlapping toxicities. (*Id.* ¶107.)

Moreover, a POSA reading McNeil would have reasonably expected that rituximab maintenance therapy following standard chemotherapy would be safe and efficacious. (*Id.* ¶108; Ex. 1005 at 003.) McNeil discussed an imminent clinical trial of rituximab maintenance therapy following standard chemotherapy. (Ex. 1003 ¶108; Ex. 1005 at 003.) As Patent Owner stated during prosecution of the related '821 patent, "as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume

that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility." (Ex. 1061 at 016-17 (citing MPEP (2008) §2107.03 at IV) (emphasis omitted).) Thus, a POSA reading McNeil would have understood that rituximab maintenance therapy was reasonably likely to be effective.

Additionally, based on Bishop and Dana, a POSA would have expected treatment with CHOP and treatment with CVP to have a similar outcome in low-grade NHL patients. (Ex. 1003 ¶108; Ex. 1007 at 002, 006; Ex. 1006 at 006.) In IPR2015-00418, Patent Owner argued that if a POSA were to choose a less toxic chemotherapy regimen for the treatment of low-grade B-cell NHL, the POSA would be motivated to choose "mini-CHOP" or another anthracycline-based regimen, not CVP. IPR2015-00418, Paper No. 11 at 38 ("Patent Owner's Preliminary Response"). As explained by Dr. Lossos, this is incorrect. (Ex. 1003 ¶108.) "Mini-CHOP" was developed for use in elderly patients suffering from diffuse large cell lymphoma (a more aggressive NHL), for which CHOP was a standard chemotherapy and CVP was not a valuable choice. (Ex. 1003 ¶108.) As taught by Bishop and Dana, there was no evidence that doxorubicin-based regimens produced any better outcomes in *low-grade* NHL patients. (Ex. 1007 at 002; Ex. 1006 at 006; Ex. 1003 ¶108; *see also* Ex. 1017 at 030.) Indeed, Dr. Lossos explains that, because of doxorubicin's toxicity, CVP would have been a

better choice than CHOP for low-grade NHL patients. (Ex. 1003 ¶108.) Because CVP was understood to be equally effective as CHOP as a combination chemotherapy in low-grade NHL, a POSA would have had a reasonable expectation that CVP followed by rituximab maintenance therapy would be successful in treating low-grade NHL patients. (*Id.* ¶108.)

Furthermore, a POSA would understand the prior art to teach that rituximab would likely have a synergistic effect when combined with various chemotherapeutic agents, not just doxorubicin. (*Id.* ¶¶63, 64; Ex. 1062 at 003; Ex. 1063 at 003; Ex. 1064 at 007 ("[rituximab] sensitizes DHL-4 B lymphoma cells *to various cytotoxic drugs/toxins*." (emphasis added)).) Based on the prior art teachings regarding rituximab's synergistic effect with various chemotherapeutic agents, a POSA would have a reasonable expectation of success at treating low-grade NHL patients by combining rituximab with CVP—a standard chemotherapy regimen that omits the toxic doxorubicin from CHOP. (Ex. 1003 ¶¶63, 64.)

Given these teachings, a POSA would have had a reasonable expectation that rituximab would be safe and efficacious as maintenance therapy following CVP chemotherapy. (*Id.* ¶109.) Thus, the combination of McNeil, Bishop, Dana, and the Rituxan Label renders claim 1 of the '172 patent obvious. (*Id.*)

C. No Secondary Indicia Of Non-Obviousness Exist

The prior art and knowledge of a POSA renders the challenged claims of the '172 patent anticipated and/or obvious. There is no evidence of any secondary indicia of non-obviousness having a nexus to the alleged claimed invention to rebut this conclusion.

During prosecution, Applicants argued that the results of the E1496 trial, as published in 2009 in Hochster (Ex. 1029), were unexpected. (Ex. 1019 at 087.) The results, however, were not surprising. As described above, CVP was a standard chemotherapy for NHL. (Ex. 1017 at 029.) Similarly, rituximab was known to be efficacious in treating NHL as both a single agent and when combined with standard chemotherapy. (*See* Ex. 1011; Ex. 1032; Ex. 1048; Ex. 1053; Ex. 1055; Ex. 1056.) By December 1998, three large clinical trials were testing rituximab's value as maintenance therapy. (Ex. 1010 at 011.) As such, a POSA would not be surprised that rituximab maintenance therapy had a demonstrated positive effect on length of remission and overall survival. (Ex. 1003 ¶79.)

In IPR2015-00418, Patent Owner argued that the art, including McNeil, taught away from omitting the doxorubicin component from CHOP. *See* IPR2015-00418, Paper No. 11 at 37-39. Patent Owner's argument is based on references in a few publications to a "known synergy between rituximab and doxorubicin." *Id*. at 39. A reference only teaches away when it suggests that it is unlikely to produce

the objective of the invention. "A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005). Patent Owner's citation to a few publications remarking on the "known synergy between rituximab and doxorubicin" does not qualify as references teaching away from omitting doxorubicin.

First, and most importantly, a number of prior art publications not cited in IPR2015-00418 describe rituximab's general "synergy with chemotherapeutic agents" that was not specific to doxorubicin. (*See, e.g.*, Ex. 1062 at 003 (Abstract 206) ("The rationale for combination of IDEC-C2B8 with CHOP includes: single agent efficacy, non cross-resistant mechanism of action, *synergy with chemotherapeutic agents* and non-overlapping toxicities" (emphasis added)); *see also* Ex. 1063 at 003.) A POSA would not interpret those statements to mean that doxorubicin alone was the synergistic component. (Ex. 1003 ¶65.)

Further, the publications discussing a possible synergy between doxorubicin and rituximab cite back to the Demidem study. (Ex. 1064; Ex. 1071.) Demidem studied a B-cell lymphoma cell line, DHL-4, that was known to be resistant to ricin, tumor necrosis factor-alpha, cisplatinum diamine dichloride, and etoposide. (Ex. 1064 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 003-004.) 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 that "[rituximab] sensitizes DHL-4 B lymphoma cells *to various cytotoxic drugs/toxins*." (*Id*. at 007 (emphasis added).) As explained by Dr. Lossos, a POSA would understand Demidem to teach that *various* chemotherapeutic agents would likely have a synergistic effect when combined with rituximab, not just doxorubicin. (Ex. 1003 ¶64.)

Demidem therefore does not teach away from the use of chemotherapy regimens that omit 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).

Petitioner is therefore not aware of any compelling evidence of secondary indicia of non-obviousness having a nexus to the alleged claimed invention that challenge that conclusion. 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 claim 1 of the '172 patent, and a finding that the claim is 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 13,419 words, as determined using the standard word counting feature of the Microsoft Word program.

Dated: March 15, 2017

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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. 8,329,172,** including all exhibits (**Nos. 1001-1071)** 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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