

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner

v.

BIOGEN, INC.,
Patent Owner

Inter Partes Review No. IPR2018-00285

Patent No. 8,329,172 B2

Issued: December 11, 2012

Filed: August 18, 2007

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

PETITION FOR *INTER PARTES* REVIEW

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TABLE OF CONTENTS

	Page
TABLE OF AUTHORITIES	v
LIST OF EXHIBITS	ix
I. INTRODUCTION	1
II. MANDATORY NOTICES	7
III. REQUIREMENTS FOR REVIEW	9
IV. PETITIONER’S PREVIOUS ’172 PETITION	10
V. THE ’172 PATENT	13
VI. LEVEL OF ORDINARY SKILL IN THE ART	17
VII. CLAIM CONSTRUCTION	17
A. “chemotherapy consisting of CVP therapy”	17
B. “CVP therapy to which the patient responds, followed by rituxi- mab maintenance therapy”	18
C. “A method . . . comprising . . . [method steps], 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”	18
VIII. THE STATE OF THE PRIOR ART	19
A. CVP chemotherapy was the preferred first-line treatment for low-grade lymphoma, but patients would frequently relapse.	19
B. Maintenance therapy following CVP induction was a known method of extending remission in LG-NHL patients.	22
C. Rituximab was a widely known and used anti-CD20 agent.	24
D. It was known that a phase III trial was underway to test the com- bination of CVP induction followed by anti-CD20 maintenance.	27

IX.	PRIOR ART STATUS OF CITED REFERENCES	29
A.	Hochster I (Ex. 1005)	30
B.	Maloney (Ex. 1008)	30
C.	Rituxan™ label (Ex. 1004 or Ex. 1039 or Ex. 1041)	31
1.	FDA label (Ex. 1004)	33
2.	Website label (Ex. 1041)	33
3.	PDR label (Ex. 1039)	36
D.	McNeil (Ex. 1003)	37
X.	ANALYSIS OF GROUND FOR TRIAL	38
A.	Claim 1 would have been obvious over Hochster I (Ex. 1005) in view of Maloney (Ex. 1008) and McNeil (Ex. 1003).	38
1.	CVP chemotherapy followed by rituximab maintenance	39
a.	Hochster I discloses treating LG-NHL with CVP in- duction followed by “anti-CD20 maintenance.”	39
b.	A POSA would have been motivated to use rituxi- mab for “anti-CD20 maintenance.”	41
c.	A POSA would have had a reasonable expectation of success in using rituximab in the Hochster I method.	42
2.	Four weekly administrations of 375 mg/m ²	44
a.	It would have been obvious to use—or at least try— the claimed dosing regimen for rituximab	44
b.	The claimed dose falls within a range disclosed in the prior art, and is thus obvious.	47
3.	Administration every six months for two years	49
a.	McNeil disclosed the only known frequency and du- ration for rituximab maintenance therapy.	49

b.	Data in the prior art provided a reason to administer rituximab maintenance every six months.	50
c.	A POSA would have used maintenance therapy as long as needed—including for two years.	51
B.	Claim 1 would have been obvious over Hochster I (Ex. 1005) in view of the Rituxan™ label (Exs. 1004, 1039, or 1041) and McNeil (Ex. 1003).....	52
C.	McNeil does not “teach away.”	54
D.	The alleged secondary considerations asserted during prosecution fail to demonstrate that claim 1 is nonobvious.	57
1.	The claimed method produces no “unexpected results.”	58
a.	Rituximab maintenance therapy was not compared to the closest prior art.	59
b.	The benefits of CVP induction followed by rituximab maintenance therapy were expected.	60
c.	The asserted results show, at most, a mere difference in degree, not a probative difference in kind.	61
2.	The claimed method does not meet any “long-felt need” or overcome any “failure of others.”	62
XI.	CONCLUSION.....	63

TABLE OF AUTHORITIES

	Page(s)
CASES	
<i>Agrizap, Inc. v. Woodstream Corp.</i> , 520 F.3d 1337 (Fed. Cir. 2008)	58
<i>Amneal Pharm., LLC v. Supernus Pharm., Inc.</i> , IPR2013-00368, Paper 8 (PTAB Dec. 17, 2013)	58
<i>Ariosa Diagnostics v. Verinata Health, Inc.</i> , 805 F.3d 1359 (Fed. Cir. 2015)	19
<i>Bayer Schering Pharma AG v. Barr Labs., Inc.</i> , 575 F.3d 1341 (Fed. Cir. 2009)	45
<i>Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.</i> , 752 F.3d 967 (Fed. Cir. 2014)	55, 62
<i>Celltrion, Inc. v. Biogen, Inc.</i> , IPR2016-01614, Paper 12 (PTAB Feb. 24, 2017).....	12
<i>Frontier Therapeutics, LLC v. Medac Gesellschaft für klinische Spezialpräparate mbH</i> , IPR2016-00649, Paper 10 (PTAB Sept. 1, 2016).....	37
<i>Galderma Labs., L.P. v. Tolmar, Inc.</i> , 737 F.3d 731 (Fed. Cir. 2013)	6, 47, 56, 61
<i>Genentech, Inc. v. Chiron Corp.</i> , 112 F.3d 495 (Fed. Cir. 1997)	18
<i>General Plastic Indus. Co., Ltd. v. Canon Kabushiki Kaisha</i> , IPR2016-01357, Paper 19 (PTAB Sept. 6, 2017).....	1, 2, 11, 12
<i>Graham v. John Deere Co.</i> , 383 U.S. 1 (1966).....	63
<i>Hoffmann-La Roche Inc. v. Apotex Inc.</i> , 748 F.3d 1326 (Fed. Cir. 2014)	42, 46, 48, 62

<i>IBM Corp. v. Intellectual Ventures II LLC</i> , No. IPR2015-00089, Paper 44 (PTAB Apr. 25, 2016)	34
<i>In re Cavanagh</i> , 436 F.2d 491 (C.C.P.A. 1971)	63
<i>In re Copaxone Consol. Cases</i> , 2017 WL 401943 (D. Del. Jan. 30, 2017)	46
<i>In re Fulton</i> , 391 F.3d 1195 (Fed. Cir. 2004)	48, 56
<i>In re Gardner</i> , 449 F. App'x 914 (Fed. Cir. 2011)	62
<i>In re Klopfenstein</i> , 380 F.3d 1345 (Fed. Cir. 2004)	29
<i>In re Merck & Co., Inc.</i> , 800 F.2d 1091 (Fed. Cir. 1986)	56
<i>In re Montgomery</i> , 677 F.3d 1375 (Fed. Cir. 2012)	43
<i>In re Peterson</i> , 315 F.3d 1325 (Fed. Cir. 2003)	47
<i>Kao Corp. v. Unilever U.S., Inc.</i> , 441 F.3d 963 (Fed. Cir. 2006)	6, 59
<i>KSR Int'l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007).....	45
<i>Liberty Mutual Ins. Co. v. Progressive Cas. Co.</i> , CBM2012-00003, Paper 7 (PTAB Oct. 25, 2012)	12
<i>Merck & Co. v. Teva Pharm. USA, Inc.</i> , 395 F.3d 1364 (Fed. Cir. 2005)	44
<i>Mylan Pharm. Inc. v. Allergan, Inc.</i> , IPR2016-01127, Paper 8 (PTAB Dec. 8, 2016)	58

<i>Newell Cos., Inc. v. Kenney Mfg. Co.</i> , 864 F.2d 757 (Fed. Cir. 1988)	63
<i>Panduit Corp. v. CCS Tech., Inc.</i> , IPR2017-01323, Paper 8 (Nov. 8, 2017)	1, 11, 12
<i>Petroleum Geo-Services Inc. v. WesternGeco LLC</i> , IPR2014-01478, Paper 18 (PTAB Mar. 17, 2015)	58
<i>Pfizer, Inc. v. Apotex, Inc.</i> , 480 F.3d 1348 (Fed. Cir. 2007)	53
<i>Pfizer, Inc. v. Biogen, Inc.</i> , IPR2017-01166, Paper 9 (PTAB Nov. 13, 2017)	7, 10, 11, 34
<i>Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.</i> , 315 F.3d 1335 (Fed. Cir. 2003)	61
<i>Sega of Am., Inc. v. Uniloc USA, Inc.</i> , IPR2014-01453, Paper 11 (PTAB Mar. 10, 2015)	58
<i>SightSound Techs., LLC v. Apple Inc.</i> , 809 F.3d 1307 (Fed. Cir. 2015)	48
<i>Therasense, Inc. v. Becton, Dickinson & Co.</i> , 649 F.3d 1276 (Fed. Cir. 2011)	12
<i>Trivascular, Inc. v. Samuels</i> , 812 F.3d 1056 (Fed. Cir. 2016)	17
<i>Voter Verified Inc. v. Premier Election Sols., Inc.</i> , 698 F.3d 1374 (Fed. Cir. 2013)	34, 36

STATUTES

35 U.S.C. § 102	10
35 U.S.C. § 102(a)	passim
35 U.S.C. § 102(b)	passim
35 U.S.C. § 103(a)	3, 10, 38
35 U.S.C. § 112	43

OTHER AUTHORITIES

21 C.F.R. § 201.59 (1997)	32
37 C.F.R. § 42.8(b)	7
37 C.F.R. § 42.22(a)(1)	10
37 C.F.R. § 42.71	8
37 C.F.R. § 42.100(b)	17
37 C.F.R. § 42.104	9
37 C.F.R. § 42.104(b)	10
<i>Manual of Patent Examining Procedure</i> § 2107.03 (8th ed., rev. 6, Sept. 2007)	43
<i>Office Patent Trial Practice Guide</i> , 77 Fed. Reg. 48756, 48759–60 (Aug. 14, 2012)	7

LIST OF EXHIBITS

Exhibit	Description
1001	Grillo-López, U.S. Patent No. 8,329,172 B2, “Combination Therapies for B-Cell Lymphomas Comprising Administration of Anti-CD20 Antibody” (issued Dec. 11, 2012) (“the ’172 patent”)
1002	Declaration of Howard Ozer, M.D., Ph.D., in Support of Petition for <i>Inter Partes</i> Review
1003	Caroline McNeil, “Non-Hodgkin’s Lymphoma Trials In Elderly Look Beyond CHOP,” <i>J. Nat’l Cancer Inst.</i> , 90(4):266-267 (Feb. 18, 1998) (“McNeil”)
1004	Rituxan™ (rituximab) labeling (Nov. 1997) (“FDA label”)
1005	Hochster et al., “Prolonged Time to Progression (TTP) In Patients With Low Grade Lymphoma (LGL) Treated With Cyclophosphamide (C) and Fludarabine (F) [ECOG1491],” <i>American Society of Clinical Oncology, Program/Proceedings, Thirty-Fourth Annual Meeting</i> (May 1998) (“Hochster I”)
1006	McLaughlin et al., “Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program,” <i>J. Clin. Oncol.</i> , 16:2825-2833 (Aug. 7, 1998) (“McLaughlin”)
1007	Sriskandan et al., “Aggressive management of doxorubicin-induced cardiomyopathy associated with ‘low’ doses of doxorubicin,” <i>Postgrad. Med. J.</i> , 70(828):759-761 (Oct. 1994) (“Sriskandan”)
1008	Maloney et al., “IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients With Relapsed Low-Grade Non-Hodgkin’s Lymphoma,” <i>Blood</i> , 90(6):2188-2195 (Sept. 15, 1997) (“Maloney”)
1009	Avilés et al., “Interferon Alpha 2b as Maintenance Therapy in Low Grade Malignant Lymphoma Improves Duration of Remission and Survival,” <i>Leukemia & Lymphoma</i> , 20:495-499 (1996) (“Avilés”)
1010	Steward et al., “Maintenance Chlorambucil After CVP in the Management of Advanced Stage, Low-Grade Histologic Type Non-Hodgkin’s Lymphoma,” <i>Cancer</i> , 61:441-447 (1988) (“Steward”)

Exhibit	Description
1011	Hiddemann et al., “Non-Hodgkin’s Lymphomas—Current Status of Therapy and Future Perspectives,” <i>Eur. J. Cancer</i> , 31A:2141-2145 (1995) (“Hiddemann II”)
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1013	Kenneth A. Foon & Richard I. Fisher, “Lymphomas,” <i>Hematology</i> , 5th Ed. (1995), 1076-1096 (“Foon”)
1014	Michael J. Campbell & John E. Niederhuber, “B-Lymphocyte Responses,” <i>Clinical Oncology</i> , Abeloff et al., Eds. (1995), 100-126 (“Campbell”)
1015	Arthur T. Skarin & David M. Dorfman, “Non-Hodgkin’s Lymphomas: Current Classification and Management,” <i>CA Cancer J. Clinicians</i> , 47(6):351-372 (1997) (“Skarin”)
1016	Declaration of Sylvia D. Hall-Ellis, Ph.D.
1017	Hiddemann et al., “New Aspects in the Treatment of Advanced Low-Grade Non-Hodgkin’s Lymphomas: Prednimustine/Mitoxantrone Versus Cyclophosphamide/Vincristine/Prednisone Followed by Interferon Alfa Versus Observation Only—A Preliminary Update of the German Low-Grade Lymphoma Study Group,” <i>Seminars in Hematology</i> , Vol 31, No 2, Suppl 3:32-35, (1994) (“Hiddemann I”)
1018	Bishop 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,” <i>Leukemia</i> , 1(6):508-513(June 1987) (“Bishop”)
1019	Specification, U.S. Patent Application No. 11/840,956 (Aug. 18, 2007)
1020	U.S. Provisional Patent Application No. 60/096,180 (Aug. 11, 1998)
1021	Preliminary Amendment, U.S. Patent Application No. 11/840,956 (Oct. 31, 2007)

Exhibit	Description
1022	Amendment and Reply under 35 C.F.R. § 1.111, U.S. Patent Application No. 11/840,956 (Aug. 25, 2010)
1023	Office Action, U.S. Patent Application No. 11/840,956 (May 11, 2010)
1024	Notice of Allowance and Fee(s) Due, U.S. Patent Application No. 11/840,956 (June 26, 2012)
1025	Portlock and Rosenberg, “Combination Chemotherapy with Cyclophosphamide, Vincristine, and Prednisone in Advanced Non-Hodgkin’s Lymphomas,” <i>Cancer</i> 37:1275-1282 (1976) (“Portlock”)
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1027	Amendment Responsive to Examiner’s Request, U.S. Patent Application No. 11/840,956 (Oct. 28, 2011)
1028	Declaration Under 37 C.F.R. § 1.132 of Mark Benyunes, M.D.
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,” <i>J. Clin. Oncol.</i> , 27(10):1607-1614 (Apr. 1, 2009) (“Hochster II”)
1030	Patent Owner Preliminary Response, <i>Boehringer Ingelheim International GmbH v. Biogen Inc.</i> , IPR2015-00418, Paper 11 (PTAB)
1031	Decision Denying Institution of <i>Inter Partes</i> Review, <i>Boehringer Ingelheim International GmbH v. Biogen Inc.</i> , IPR2015-00418, Paper 14 (PTAB)
1032	Rituxan™ (rituximab) labeling (rev. 2014)
1033	Dana, B. et al., “Long-Term Follow-Up of Patients With Low-Grade Malignant Lymphomas Treated With Doxorubicin-Based Chemotherapy or Chemoimmunotherapy,” <i>J. Clin. Oncol.</i> , 11(4):644-651 (Apr. 1993) (“Dana”)

Exhibit	Description
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1035	Wadler et al., “New Advances in Interferon Therapy of Cancer,” The Oncologist, 2:254-267 (1997) (“Wadler”)
1036	Feugier, “A Review of Rituximab, the First Anti-CD20 Monoclonal Antibody Used in the Treatment of B Non-Hodgkin’s Lymphomas,” Future Oncology 11(9):1327-1342 (2015) (“Feugier”)
1037	Habermann et al., “Rituximab-CHOP Versus CHOP Alone or With Maintenance Rituximab in Older Patients With Diffuse Large B-Cell Lymphoma,” J. Clin. Oncol., 24(19):3121-3127 (July 1, 2006) (“Habermann”)
1038	De Nardo et al., “A Revolution in the Treatment of Non-Hodgkin’s Lymphoma,” Cancer Biotherapy & Radiopharmaceuticals, 13(4):213-223 (1998) (“De Nardo”)
1039	Physicians’ Desk Reference® (53rd ed. 1999) (excerpted), “Rituxan™ (Rituximab)” (“PDR label”)
1040	Anderson et al., U.S. Patent No. 5,736,137, “Therapeutic Application of Chimeric and Radiolabeled Antibodies to Human B Lymphocyte Restricted Differentiation Antigen for Treatment of B Cell Lymphoma” (issued Apr. 7, 1998)
1041	“Rituxan™ Full Prescribing Information,” Genentech Wayback Machine Website (dated January 23, 1998) (“Website label”)
1042	Gail A. Leget and Myron S. Czuczman “Use of Rituximab, the New FDA-Approved Antibody,” Current Opinion in Oncology, 10:548–551 (1998) (“Leget”)
1043	Charles Marwick, “Monoclonal Antibody to Treat Lymphoma,” J. Am. Med. Ass’n, 278(8):616, 618 (August 27, 1997) (“Marwick”)
1044	Sean Henahan, “Anti-CD20 Antibodies Combining Well in Lymphoma Patients,” Inpharma, 1136:9 (May 1998) (“Henahan”)

Exhibit	Description
1045	“Genentech, Inc., News,” Genentech Wayback Machine Website (dated January 23, 1998)
1046	“Genentech, Inc., Recent Press Releases,” Genentech Wayback Machine Website (dated January 23, 1998)
1047	“Genentech, Inc., The Access Excellence Collection of Science Updates,” Genentech Wayback Machine Website (dated January 23, 1998)
1048	“Genentech, Inc., Homepage,” Genentech Wayback Machine Website (dated January 23, 1998)
1049	“Genentech, Inc., Search the Genentech Web Site,” Genentech Wayback Machine Website (dated January 23, 1998)
1050	Genentech, Inc.’s Response to Petitioner’s Additional Discovery, IPR2016-01614 (U.S. Patent 7,820,161)
1051	Biogen, Inc.’s Response to Petitioner’s Additional Discovery, IPR2016-01614 (U.S. Patent 7,820,161)
1052	Press Release, Genentech, Inc. “New Drug for Non-Hodgkin’s Lymphomas Available Now,” (December 16, 1997) https://www.gene.com/media/press-releases/4835/1997-12-16/new-drug-for-non-hodgkins-lymphoma-avail (“Press Release”)
1053	Christine White and Antonio Grillo-López, PCT Application Number: PCT/US99/26308, “Treatment of Hematologic Malignancies Associated with Circulating Tumor Cells Using Chimeric Anti-CD20 Antibody,” (filed Nov. 9, 1998) (certified copy)
1054	Rituxan (rituximab), BLA Number 103705, Drugs@FDA: FDA Approved Drug Products, available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=103705

I. INTRODUCTION

Petitioner Pfizer, Inc. requests *inter partes* review and cancellation of the sole claim of U.S. Patent No. 8,329,172 B2 (“the ’172 patent”). Petitioner previously challenged the ’172 patent in IPR2017-01166, but institution was denied solely because a divided panel of the Board found insufficient evidence that one of the ground references—Ex. 1004, the FDA label for Rituxan[™]—was a prior-art printed publication under 35 U.S.C. § 102(b). In *Panduit Corp. v. CCS Tech., Inc.*, another panel similarly “denied institution . . . because one of the asserted references was not shown to have been a printed publication,” but nonetheless instituted a second petition by the same petitioner that cured the evidentiary defect because it did “not present a situation in which Petitioner is ‘using our decisions as a roadmap.’” IPR2017-01323, Paper 8 at 8–9 (PTAB Nov. 8, 2017) (quoting *Gen. Plastics Indus. Co., Ltd. v. Canon Kabushiki Kiasha*, IPR2016-01357, Paper 19 at 17 (PTAB Sept. 6, 2017) (precedential)). The same result is warranted here.

In particular, the present Petition cures the perceived procedural defects identified in the decision denying institution in IPR2017-01166 by substituting the disputed Rituxan[™] label with the September 1997 journal article by Maloney et al. (Ex. 1008)—a different prior art reference that contains the same relevant information as the Rituxan[™] label, but is undisputedly a printed publication that was publicly ac-

cessible as of the August 11, 1998, critical date. Although Petitioner’s previous petition cited Maloney, it did not expressly rely on Maloney in the ground presented for review (to avoid redundancy), and the panel declined to exercise its discretion to substitute the Rituxan™ label with Maloney. In contrast, the present Petition leaves no doubt that Petitioner is explicitly relying on Maloney in the first ground. In addition, the present Petition includes a second ground that relies on three separate (but substantively identical) versions of the Rituxan™ label, including an online version disseminated by Genentech—the original developer and manufacturer of Rituxan™—before the critical date, and a version disseminated in the well-known *Physician’s Desk Reference* publication (the “PDR”) before the priority date. Ex. 1004, FDA label; Ex. 1039, PDR label; Ex. 1041, Website label.

In the interest of avoiding any appearance of a “potential benefit from receiving and having the opportunity to study Patent Owner’s Preliminary Response . . . prior to its filing of [this] follow-on petition[],” Petitioner does not address the merits of Patent Owner’s arguments in IPR2017-01166; instead, Petitioner sets forth substantially the same arguments on the merits that Petitioner previously advanced. *See Gen. Plastic*, IPR2016-01357, Paper 19 at 17. In so doing, Petitioner does not concede any arguments raised by Patent Owner, but refrains from responding to them at this stage of the proceeding in an abundance of caution. Petitioner notes that at least one member of the panel in IPR2017-01166 would have instituted

review on the merits notwithstanding the arguments in the Patent Owner Preliminary Response. Petitioner thus respectfully requests that the Board institute *inter partes* review and cancel claim 1 of the '172 patent as unpatentable under 35 U.S.C. § 103(a), for the following reasons.

The sole claim of the '172 patent is directed to a method of treating low-grade non-Hodgkin's lymphoma ("LG-NHL")—a type of cancer—using (1) the standard combination chemotherapy for LG-NHL, called "CVP," followed by (2) maintenance therapy with 375 mg/m² of the anti-CD20 antibody rituximab administered once a week for four weeks (3) every six months for at least two years. As shown below, the claimed method would have been obvious to a person of ordinary skill in the art ("POSA") at the time the '172 patent was filed. Moreover, the allegedly "unexpected" results that were the sole basis for allowance failed to compare the closest prior art and, in any event, were entirely expected.

The combination of CVP chemotherapy and maintenance therapy with an anti-CD20 agent was taught by a printed publication that is prior art to the '172 patent under both § 102(a) and § 102(b)—the "Hochster I" reference (Ex. 1005), which was not considered during prosecution. That reference disclosed that a "phase III" clinical trial was underway for the treatment of LG-NHL with "CVP ± anti-CD20 maintenance." *Id.* at 5. As confirmed by Petitioner's expert oncologist, Dr. Howard

Ozer, a POSA at the time would have understood this reference as referring to treating LG-NHL with CVP chemotherapy followed by maintenance therapy with an agent that targets CD20. Ex. 1002 ¶¶ 42–49, 57.

When the '172 patent was filed, rituximab was the *only* available anti-CD20 agent. The Maloney reference, which is also prior art under both § 102(a) and (b), reported on a Phase II “multicenter study evaluating four weekly infusions of 375 mg/m² IDEC-C2B8 [rituximab] in patients with relapsed low-grade or follicular NHL.” Ex. 1008, 6. Maloney taught that “IDEC-C2B8 (Rituximab)” is “a chimeric anti-CD20 [monoclonal antibody]” that “binds [to] the CD20 antigen with high affinity” and “efficiently kills CD20⁺ cells.” *Id.* Maloney explained that rituximab monotherapy had also been previously administered at doses of 100, 125, 250, and 500 mg/m² in phase I trials, but that 375 mg/m² was selected for the phase II trials. *Id.* at 7. Maloney further taught that “[t]reatment with the chimeric anti-CD20 antibody rapidly and effectively depleted B cells from the peripheral blood circulation . . . until approximately 6 months posttreatment, followed by slow gradual recovery,” leading directly to “antitumor activity in patients with relapsed low-grade or follicular NHL.” *Id.* at 6, 9. Shortly after Maloney was published in September 1997, rituximab was approved by the FDA in November 1997 (and used shortly thereafter) for the treatment of relapsed or refractory LG-NHL at 375 mg/m² for four

weekly doses. Ex. 1004, 2 (“FDA label”); Ex. 1039, 12 (“PDR label”); Ex. 1041, 3 (“Website label”).

The claimed six-month frequency and two-year duration for maintenance therapy was also the *only* known schedule for administering rituximab maintenance, which was explicitly disclosed in a third printed publication that is also prior art under both § 102(a) and (b). Ex. 1003, McNeil at 5. As Dr. Ozer explains, Maloney and the Rituxan™ label also would have motivated a POSA to select that maintenance schedule for rituximab in the treatment of LG-NHL because they disclosed that B-cell recovery began approximately six months following completion of treatment. Ex. 1002 ¶¶ 102, 110; *see also* Ex. 1008, Maloney at 9; Ex. 1004, FDA label at 1; Ex. 1039, PDR label at 11; Ex. 1041, Website label at 1. Thus, it would have been obvious to administer rituximab maintenance therapy at six-month intervals, when cancerous B-cells returned. Ex. 1002 ¶¶ 100–106, 111. Likewise, it would have been obvious to administer rituximab maintenance therapy as long as possible to maintain remission, including for at least two years. *Id.* ¶¶ 103–104.

During prosecution, Patent Owner overcame obviousness rejections over a different combination of references, which were only “withdrawn in view of [the] applicants[’] arguments regarding unexpected results.” Ex. 1024, 8. Yet, Patent Owner’s evidence merely compared the claimed “maintenance rituximab (MR) ver-

sus observation”—*i.e.*, to *nothing*. Ex. 1029, 2. Patent Owner never compared rituximab maintenance to *other* known maintenance therapies for LG-NHL, and thus failed to show any results that were “unexpected compared with the closest prior art.” *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006).

In any event, the benefits of rituximab maintenance would have been expected: Patent Owner’s own publication reporting the results of the study disclosed in Hochster I acknowledged that the “study *confirmed the hypothesis* that rituximab would be an effective and safe maintenance after CVP chemotherapy.” Ex. 1029, 5 (“Hochster II”) (emphasis added). At most, moreover, the study showed improvements “merely in degree from the results” obtained with chemotherapy alone and not a difference “in kind” that is “probative of nonobviousness.” *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013).

Although the Board previously denied *inter partes* review of the ’172 patent in IPR2015-00418 and IPR2017-01093, the petitioners there did not cite Hochster I, or any other prior art “teach[ing] rituximab maintenance therapy following CVP induction therapy.” Ex. 1031, 15. Here, by contrast, Hochster I expressly discloses the use of anti-CD20 maintenance therapy following CVP induction therapy, and it would have been obvious to use rituximab as the anti-CD20 agent with the exact claimed dosing regimen and maintenance schedule. Ex. 1002 ¶¶ 78–79.

II. MANDATORY NOTICES

Pursuant to 37 C.F.R. § 42.8(b), Petitioner states as follows:

1. ***Real parties-in-interest.*** Petitioner Pfizer, Inc. is the real party-in-interest for this Petition. No other parties exercised or could have exercised control over this Petition; no other parties funded or directed this Petition. *See Office Patent Trial Practice Guide*, 77 Fed. Reg. 48756, 48759–60 (Aug. 14, 2012).

2. ***Related matters.*** The '172 patent was previously challenged by other petitioners in *Boehringer Ingelheim International GmbH v. Biogen Inc.*, IPR2015-00418 and in *Celltrion, Inc. v. Biogen Inc.*, IPR2017-01093. Both petitions were denied. The grounds of unpatentability asserted in IPR2015-00418 and IPR2017-01093 are not the same as the ground asserted by Petitioner here. In particular, Petitioner's primary reference—Hochster I—was not cited in either IPR2015-00418 or IPR2017-01093.

As discussed above (and also discussed below in Section IV), Petitioner previously challenged the '172 patent in *Pfizer, Inc. v. Biogen, Inc.*, IPR2017-01166. A split panel of the Board denied institution on the basis that Petitioner failed to provide sufficient evidence that one of the references (Ex. 1004) used in the sole ground was not a prior-art printed publication under 35 U.S.C. § 102(b). IPR2017-01166, Paper 9 at 17 (PTAB Nov. 13, 2017). Using the same art previously identified in IPR2017-01166, Petitioner submits this Petition to expressly rely on both Maloney

and the three versions of the Rituxan™ label (*infra* part IX.C) in its grounds and to satisfy the threshold showing that the “Rituxan™ label” used in IPR2017-01166 is a prior-art printed publication under both 35 U.S.C. § 102(a) and (b).¹

Petitioner has also filed a request for rehearing in IPR2017-01166 pursuant to 37 C.F.R. § 42.71. Petitioner submits that if this Petition were instituted, the request for rehearing in case IPR2017-01166 (filed in an abundance of caution) would become moot.

U.S. Patent No. 9,296,821 B2 (“the ’821 patent”) issued from a divisional application of the application that issued as the ’172 patent. Celltrion, Inc. has previously filed a petition challenging the claims of the ’821 patent and the Board instituted proceedings on claims 1–3 and 5–6 of the ’821 patent. *See Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01095, Paper 12 at 34 (PTAB Oct. 6, 2017). Petitioner has also filed a petition for *inter partes* review challenging the ’821 patent, which is pending. *See Pfizer, Inc. v. Biogen, Inc.*, IPR2018-00186, Paper 2 (PTAB Dec. 1, 2017). The claims of the ’821 patent are generally directed to methods of treating low-grade NHL using rituximab and CVP as front-line therapy, whereas the ’172

¹ To the extent the Board finds these grounds redundant, it can exercise its discretion to institute solely on ground 1, which uses the Maloney reference in lieu of the Rituxan™ label.

patent is generally directed to methods of treating low-grade NHL using rituximab as maintenance therapy following CVP.

3. *Lead and back-up counsel.* Petitioner identifies the following:

- *Lead counsel:* Jovial Wong (Reg. No. 60,115)
- *Back-up counsel:* Charles B. Klein*
- *Back-up counsel:* Eimeric Reig-Plessis*

* Back-up counsel to seek *pro hac vice* admission.

4. *Service information.* Petitioner identifies the following:

- *Email address:* rituximabIPR@winston.com
- *Mailing address:* WINSTON & STRAWN LLP
1700 K Street, NW
Washington, DC 20006
- *Telephone number:* (202) 282-5000
- *Fax number:* (202) 282-5100

Please address all correspondence to lead counsel at the address shown above.

Petitioner consents to electronic service at the above listed email address.

III. REQUIREMENTS FOR REVIEW

Pursuant to 37 C.F.R. § 42.104, Petitioner states as follows:

a. *Grounds for standing.* Petitioner certifies that (1) the '172 patent is available for *inter partes* review; and (2) Petitioner is not barred or estopped from requesting review of the '172 patent on the grounds identified in this Petition. The

required fee is paid through the Patent Review Processing System. The Office is authorized to charge fee deficiencies and credit overpayments to Deposit Acct. No. 50-1814.

b. Identification of challenge. Pursuant to 37 C.F.R. §§ 42.104(b) and 42.22(a)(1), Petitioner requests review and cancellation of claim 1 of the '172 patent pursuant to the following statement of the precise relief requested:

Ground	Claim	Basis	References
I	1	§ 103(a)	Hochster I (Ex. 1005); Maloney (Ex. 1008); and McNeil (Ex. 1003)
II	1	§ 103(a)	Hochster I (Ex. 1005); Rituxan™ label (Ex. 1004 or Ex. 1039 or Ex. 1041); and McNeil (Ex. 1003)

IV. PETITIONER'S PREVIOUS '172 PETITION

Petitioner previously filed a petition for *inter partes* review of the '172 patent, which was denied by a panel of the Board in a 2-1 decision. *Pfizer, Inc. v. Biogen, Inc.*, IPR2017-01166, Paper 9 (PTAB Nov. 13, 2017). The majority held: "Petitioner has failed to establish sufficiently in the Petition that the Rituxan Label was publically accessible as of the critical date of August 11, 1998. Thus, on this record, the Rituxan label fails to qualify as prior art under 35 U.S.C. § 102 and Petitioner

has not established a reasonable likelihood of prevailing in demonstrating the obviousness of claim 1 without the Rituxan Label.” *Id.* at 17. Thus, although the dissent would have instituted the petition (Diss. 2, 8), the majority never reached the merits of the arguments presented by Petitioner.

Because the panel did not deny the previous petition on the merits, under the Board’s precedential opinion in *General Plastic Indus. Co., Ltd. v. Canon Kabushiki Kisha*, IPR2016-01357, Paper 19 at 16 (PTAB Sept. 6, 2017), the present Petition should not be rejected as an improper “follow-on” petition. *General Plastics* established a “non-exhaustive list of factors . . . in evaluating follow-on petitions” to “determin[e] whether to exercise . . . discretion” to deny institution. *Id.* at 15–16. Critically, the Board recognized that “there may be circumstances where multiple petitions by the same petitioner against the same claims of a patent should be permitted, and that such a determination is dependent on the facts at issue in the case.” *Id.* at 18.

Those factual circumstances are unquestionably present here, just as they were in the recent institution decision in *Panduit Corp. v. CCS Tech., Inc.*, IPR2017-01323 Paper 8 at 8–9 (Nov. 8, 2017). The panel in *Panduit* declined to deny institution of a “follow-on petition” because the panel had “previously denied institution . . . because one of the asserted references was not shown to have been a printed publication.” *Id.* at 9. Because the previous decision had not reached the *merits* of

the petitioner's challenge, the panel concluded that the petitioner's second challenge to the patent "do[es] not present a situation in which Petitioner is 'using our decisions as a roadmap.'" *Id.* (quoting *Gen. Plastics*, IPR2016-01357, Paper 19 at 17).

This Petition involves the same situation. Petitioner is filing a petition that is substantially the same solely to cure the perceived procedural deficiencies raised by the decision denying institution of the first petition. This second petition is appropriate not only for the reasons discussed in the *Panduit* proceeding, but also because, when the first petition was filed, Petitioner reasonably relied on the fact that, at the time, the Board already had instituted trial on a related patent in which the RituxanTM label (Ex. 1004) had been used in the grounds (and Patent Owner had not challenged the public accessibility of that exhibit). *Celltrion, Inc. v. Biogen, Inc.*, IPR2016-01614, Paper 12 at 4, 12 (PTAB Feb. 24, 2017). Thus, in its first petition, Petitioner submitted only one ground to avoid using duplicative and redundant grounds and prior art, thus respecting the Board's finite resources. *See Gen. Plastics*, IPR2016-01357, Paper 19 at 16; *Liberty Mutual Ins. Co. v. Progressive Cas. Co.*, CBM2012-00003, Paper 7 at 2, (PTAB Oct. 25, 2012) ("[M]ultiple grounds, which are presented in a redundant manner by a petitioner who makes no meaningful distinction between them, are contrary to the regulatory and statutory mandates, and therefore are not all entitled to consideration."); *cf. Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1289 (Fed. Cir. 2011) (en banc) (noting in the context of prior

art disclosures in examination that the “tidal wave of disclosure makes identifying the most relevant prior art more difficult”). In view of the procedural issues raised, however, Petitioner has now expressly included in the grounds of this Petition three prior-art printed publications that were cited in the text and declarations (but not the grounds) of the first petition that disclose the same teachings as the disputed Rituxan™ label (Ex. 1004)—i.e., Ex. 1008 (Maloney); Ex. 1039 (the PDR version of the Rituxan™ label); and Ex. 1041 (the full prescribing information disclosed on Genentech’s website). Therefore, Petitioner respectfully submits that the Board should decline any invitation by Patent Owner to use its discretionary authority to deny this Petition.

V. THE ’172 PATENT

The ’172 patent issued on December 11, 2012, from application no. 11/840,956. Ex. 1019 (“the ’956 application”). The ’956 application was filed on August 18, 2007, but claimed priority, through a series of continuation applications, to U.S. patent application no. 09/372,202 (“the ’202 application”), which in turn was filed on August 11, 1999. The ’202 application claimed priority to provisional application no. 60/096,180, which was filed on August 11, 1998. Ex. 1020 (“the ’180 provisional application”). As explained below, however, the ’180 provisional application does not adequately describe claim 1 of the ’172 patent as issued. Therefore,

August 11, 1999—the filing date of the '202 application—is the earliest effective filing date for the '172 patent.

Claim 1—the '172 patent's only claim—reads as follows:

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/m² every 6 months, and wherein the maintenance therapy is provided for 2 years.

This claim originates from claims 41–43 of the '956 application, which were added on October 31, 2007. Ex. 1021, 3. Those claims read as follows:

41. A method of treating low grade B-cell non-Hodgkin's lymphoma in a human patient comprising administering to the patient CVP therapy followed by rituximab maintenance therapy, wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m² every 6 months.

42. A method according to claim 42, wherein the patient exhibits a response to the CVP therapy.

43. A method according to claim 42, wherein the maintenance therapy is provided for 2 years.

Claim 41 was later amended to incorporate the elements of claims 42 and 43, and subsequently issued as claim 1 of the '172 patent. Ex. 1022, 2, 5.

When the applicants added claims 41–43 to the '956 application, they did not cite any supporting disclosure from the '180 provisional application. Instead, they cited only “page 28, lines 16–21” of the '956 application, which corresponds to column 13, lines 8–16 of the '172 patent, and provides as follows:

A Phase III study conducted by ECOG in patients with low-grade NHL is comparing the combination of cyclophosphamide and fludarabine (Arm A) with standard CVP therapy (Arm B). In the randomization to Arm A or Arm B, patients are stratified by age, tumor burden, histology, and B symptoms. Responders in both arms will undergo a second randomization to Rituximab maintenance therapy (375 mg/m² weekly times 4 every 6 months for 2 years (Arm C) or to observation (Arm D).

Ex. 1021, 5; *see* Ex. 1001, 13:8–16.

The '180 provisional application does not contain this passage, and nothing in the application describes the claimed method of using rituximab as maintenance therapy after CVP chemotherapy. Instead, the '180 provisional application describes only the treatment of relapsed or refractory NHL—not the use of rituximab for maintenance therapy. Accordingly, the '180 provisional application does not adequately describe claims 41–43 of the '956 application and, for the same reason, does not adequately describe claim 1 of the '172 patent.

During prosecution, the Examiner reached the same conclusion: “The claimed inventions [including claims 41–43 of the ’956 application] 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. 1023, 6. The applicants never traversed that finding. It follows that the earliest priority date to which claim 1 of the ’172 patent is entitled is the filing date of the ’202 application—*i.e.*, August 11, 1999. Therefore, any patent or printed publication prior to August 11, 1998, qualifies as prior art under 35 U.S.C. § 102(b).²

The claims that ultimately issued as claim 1 of the ’172 patent were rejected multiple times for obviousness (over references that are different than the ones Petitioner relies on here). In response, Patent Owner asserted that the claimed method produces “unexpected results,” and also alleged “both failure of others and long-felt need.” Ex. 1022, 12. In the Notice of Allowance, the Examiner indicated that the previous rejections for obviousness were “withdrawn in view of [the] applicants[’] arguments regarding unexpected results.” Ex. 1024, 8.

² In IPR2015-00418, Patent Owner did not dispute that the earliest priority date for the ’172 patent is August 11, 1999 (the filing date of the ’202 application), not August 11, 1998 (the filing date of the provisional ’180 application). Ex. 1030, 16.

As shown below in Part X.D., Patent Owner’s evidence of “unexpected” results was legally and factually flawed, and, in any event, insufficient in view of the strong evidence of obviousness discussed in Part X.A–B.

VI. LEVEL OF ORDINARY SKILL IN THE ART

In light of the specification, the prosecution history, and the state of the art as of August 11, 1999, a person of ordinary skill in the art for purposes of the ’172 patent would include a practicing oncologist with at least an M.D. degree and several years of experience treating patients with NHL and/or researching treatments for NHL, including with chemotherapeutic drugs. Ex. 1002 ¶ 15.

VII. CLAIM CONSTRUCTION

“A claim in an unexpired patent that will not expire before a final written decision is issued shall be given its broadest reasonable construction in light of the specification of the patent.” 37 C.F.R. § 42.100(b). “Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history.” *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016).

A. “chemotherapy consisting of CVP therapy”

Petitioner does not contest the Board’s construction of this term in IPR2015-00418 as “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.” Ex. 1031, 5. Petitioner also does not contest the Board’s conclusion that “[t]he ‘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.” *Id.*

B. “CVP therapy to which the patient responds, followed by rituximab maintenance therapy”

Petitioner does not contest the Board’s construction of this term in IPR2015-00418 as “requiring administration of CVP therapy, to which the patient responds according to the criteria set forth in the ’172 patent.” Ex. 1031, 6 (citing Ex. 1001, 9:14–23). Nor does Petitioner contest that “[t]he 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.” *Id.*

As Dr. Ozer confirms, the plain and ordinary meaning of “maintenance therapy” to a POSA necessarily implies that the patient has responded to a previously administered “induction” therapy (in this case, CVP). Ex. 1002 ¶ 28.

C. “A method . . . comprising . . . [method steps], 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 term “[c]omprising” 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). Thus, because claim 1 provides that the “maintenance therapy *comprises*” certain steps, it covers methods with additional steps beyond those expressly recited. For example, the scope of the claim includes maintenance therapy that continues after an initial two-year period.

VIII. THE STATE OF THE PRIOR ART

In summarizing the state of the art as of August 1999, Petitioner cites additional references beyond “the three pieces of prior art presented as the basis for obviousness,” which “legitimately serve to document the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness,” and “as evidence of the background understanding of skilled artisans.” *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015).

A. CVP chemotherapy was the preferred first-line treatment for low-grade lymphoma, but patients would frequently relapse.

Non-Hodgkin’s B-cell lymphoma (“NHL”) is a class of malignant diseases characterized by the uncontrolled growth of “B-cells,” which are white blood cells that are part of the body’s immune system. Ex. 1002 ¶ 31. “Low grade” (or “indolent”) NHL progresses more slowly than “high grade” and “intermediate grade” NHL, which are also known as “aggressive” NHL. *Id.* LG-NHL often affects “follicular” B-cells in the lymph nodes. *Id.* ¶ 35.

Chemotherapy is the preferred first-line treatment for NHL. *Id.* ¶ 36. Typically, oncologists use a combination of chemotherapeutic drugs with different mechanisms of action to attack multiple targets in malignant B-cells and reduce the chance of developing drug-resistant B-cells. *Id.*

The two main combinations of chemotherapeutic drugs for treating NHL as of August 1999 are commonly abbreviated as “CVP” and “CHOP.” *Id.* ¶ 37. “CVP” consists of cyclophosphamide, vincristine, and prednisone. *Id.* Because vincristine is also known as Oncovin[®], CVP is also sometimes referred to as “COP.” *Id.* CHOP contains the same three drugs as CVP, but additionally combines a fourth drug called hydroxydaunorubicin (the “H” in CHOP), which is also called doxorubicin. *Id.* ¶ 38. CHOP is generally considered a more potent therapy than CVP. *Id.* Due to the addition of doxorubicin, it has better efficacy against more aggressive forms of NHL, but is also significantly more toxic. *Id.*; *e.g.*, Ex. 1007, Sriskandan at 3.

As of August 1999 (and, for that matter, today), CHOP was the preferred treatment for intermediate- and high-grade lymphoma. Ex. 1002 ¶ 39. “In low-grade lymphomas,” however, the main “therapeutic intervention” at the time (and again, today) “consist[ed] preferentially of chemotherapy of moderate intensity such as cyclophosphamide, vincristine and prednisone (COP)”—*i.e.*, CVP. Ex. 1011, Hid-

demann II at 1. Indeed, as far back as 1988, “combination chemotherapy (predominantly CVP)” was known to have the “greatest and complete response rates” for LG-NHL. Ex. 1010, Steward at 7.

“Despite these high response rates” to initial chemotherapy, LG-NHL was understood as being characterized by “a pattern of continuing relapse with RFS [*i.e.*, relapse-free survival] of only 2 to 3 years” following chemotherapy. *Id.* At first, oncologists attempted to address the problem of relapses with “more aggressive regimens of combination chemotherapy including . . . CHOP,” but “[u]nfortunately these studies have not produced obvious improvements of the percentage or duration of responses or survival, and often have resulted in more toxicity.” *Id.*

Researchers similarly found in 1987 that “CVP was as effective” as CHOP for LG-NHL, and “doxorubicin does not enhance the activity of the CVP regimen against lymphomas other than diffuse large cell [lymphoma],” a type of intermediate-grade NHL. Ex. 1018, Bishop at 6. Other researchers confirmed again in 1993 that “[d]oxorubicin-containing treatment [*i.e.*, CHOP] did not prolong the overall median survival of low-grade lymphoma patients compared with results with less-aggressive programs,” *i.e.*, CVP. Ex. 1033, Dana at 2. Thus, CVP remained the preferred first-line treatment for LG-NHL, despite the problem of relapses following the initial response to chemotherapy. Ex. 1002 ¶ 41.

B. Maintenance therapy following CVP induction was a known method of extending remission in LG-NHL patients.

As of August 1999, a known method of delaying relapses (and thus prolonging remission) was “maintenance” therapy, which oncologists administered after chemotherapy successfully “induced” remission. Ex. 1002 ¶ 42.

The first maintenance therapy that oncologists attempted was simply more chemotherapy. *Id.* In 1976, for example, Portlock and Rosenberg conducted a study in which “complete responders” to induction CVP “receive[d] 2 years of planned maintenance CVP (at the same drug dosages [as induction]).” Ex. 1025, 2. Likewise, in 1981, Hoppe et al. administered CVP “until complete remission was achieved,” “followed by maintenance CVP.” Ex. 1026, 4.

In 1987, following these preliminary attempts, Steward et al. conducted a larger study in which “[o]ne hundred sixty-two patients with Stages III and IV non-Hodgkin’s lymphoma of low-grade histologic type were treated with combination chemotherapy using cyclophosphamide, vincristine, and prednisolone (CVP),” and then “randomized to receive either follow-up alone or ‘maintenance’ chemotherapy with 2 years of intermittent chlorambucil,” another chemotherapeutic drug. Ex. 1010, 3. Steward found that “maintenance therapy with chlorambucil for a full 2 years was” limited by factors including adverse events, “but despite this it prolonged the median RFS by 38 months.” *Id.* In other words, maintenance therapy “significantly delayed the time of relapse.” *Id.* at 8.

“An alternative” to chlorambucil maintenance, Steward predicted, “is the use of alpha interferon,” a biologic agent that modulates the immune system. *Id.* Steward concluded that “long-term intermittent interferon or chlorambucil . . . may [] help to improve the survival rate” for LG-NHL patients. *Id.* at 8–9.

Following Steward’s prediction, a number of researchers studied the effects of interferon maintenance therapy, with promising results. Ex. 1002 ¶ 46. In 1995, Avilés et al. published the results of a study that “assessed the efficacy and toxicity of interferon alpha 2b (IFN) as maintenance therapy in patients with low grade malignant lymphoma” who were “in complete remission after conventional chemotherapy” with CVP. Ex. 1009, 1–2. Avilés “conclude[d] that IFN as maintenance therapy in low-grade malignant lymphoma is an excellent therapeutic option because it improves the duration of remission and survival without producing severe side effects or reducing the quality of life.” *Id.* at 1.

In 1994, Hiddemann et al. observed that previous studies with interferon maintenance “strongly suggest a prolongation of the disease-free interval by IFN- α maintenance,” but noted that the success of maintenance therapy “may depend on the duration of IFN therapy.” Ex. 1017, Hiddemann I at 5. Hiddemann thus advocated maintenance therapy “without a time limitation, which means that it will be continued until relapse or intolerable toxicity.” *Id.*

Adopting this recommendation, in 1996, Unterhalt et al. published preliminary findings of a study in which “IFN- α was given without a fixed time limitation” as maintenance after induction CVP. Ex. 1012, 3. Unterhalt concluded that the “data clearly demonstrate a prolonged effect of IFN- α maintenance in low grade lymphoma which provides a significant prolongation of DFS [*i.e.*, disease-free survival] and the interval without the requirement of further cyto[oidal] therapy [*i.e.*, cell-killing drugs like chemotherapy] in patients with advanced low grade NHL.” *Id.* In 1998, Solal-Céligny et al. confirmed that interferon maintenance “not only increased PFS [*i.e.*, progression-free survival], as in most other similar trials, but also prolonged OS [*i.e.*, overall survival].” Ex. 1034, 1.

As summarized in a 1997 review article, however, while interferon maintenance was shown in multiple clinical trials to produce “a significant improvement in progression-free survival,” this benefit came at the expense of “the toxicities of IFN[,] [which] were formidable in most trials.” Ex. 1035, Wadler at 8. Thus, there remained a need for a maintenance therapy that would “improve the constitutional symptoms associated with IFN.” *Id.*; Ex. 1002 ¶ 49.

C. Rituximab was a widely known and used anti-CD20 agent.

In September 1997, Maloney reported on a Phase II “multicenter study evaluating four weekly infusions of 375 mg/m² IDEC-C2B8 [rituximab] in patients with relapsed low-grade or follicular NHL.” Ex. 1008, 6. Maloney taught that “IDEC-

C2B8 (Rituximab)” is “a chimeric anti-CD20 [monoclonal antibody]” that “binds [to] the CD20 antigen with high affinity” and “efficiently kills CD20⁺ cells.” *Id.* Maloney explained that rituximab monotherapy had also been previously administered at doses of 100, 125, 250, and 500 mg/m² in phase I trials “with no dose limiting toxicity” (*id.*), but that 375 mg/m² was selected for the phase II trials. *Id.* at 7. Maloney further taught that “[t]reatment with the chimeric anti-CD20 antibody rapidly and effectively depleted B cells from the peripheral blood circulation . . . until approximately 6 months posttreatment, followed by slow gradual recovery.” *Id.* at 9. Maloney disclosed that 375 mg/m² of rituximab in four weekly doses had a favorable “safety profile” and led to “antitumor activity in patients with relapsed low-grade or follicular NHL.” *Id.* at 6. Maloney recommended studying rituximab in “combination with *or after* standard chemotherapy.” *Id.* at 12 (emphasis added); *see also* Ex 1002 ¶ 61.

In November 1997, the FDA approved rituximab under the brand name Rituxan[™] for the treatment of relapsed or refractory low-grade or follicular B-cell NHL. Ex. 1004, 1; Ex. 1039, 10; Ex. 1041, 1; Ex. 1002 ¶ 50. As of August 1999, rituximab was the only anti-CD20 agent approved by the FDA. Ex. 1002 ¶ 51. It is widely recognized as “the first anti-CD20 monoclonal antibody used in the treatment of B non-Hodgkin’s lymphomas,” and “the first targeted therapy used in B-cell malignancies.” Ex. 1036, Feugier at 1.

The Rituxan™ label disclosed that rituximab was approved at a single “recommended” dosing regimen of 375 mg/m² in four weekly doses—the same dosing schedule tested and disclosed in Maloney. Ex. 1004, 2; Ex. 1039, 12; Ex. 1041, 3. This was the dosing “schedule that ha[d] been most extensively tested.” Ex. 1038, DeNardo at 4. The label confirmed that at this dose, “[r]ituximab was detectable in the serum of patients three to six months after completion of treatment.” Ex. 1004, 1; Ex. 1039, 11; Ex. 1041, 1; *see also* Ex. 1006, McLaughlin at 7 (“B-cell recovery began at approximately six months following completion of treatment.”); Ex. 1038, DeNardo at 4 (“After treatment, B-cells return to normal levels within 6 months.”). Ex. 1002 ¶ 69.

The label also confirmed that “[t]here has been no experience with overdosage in human clinical trials.” Ex. 1004, 2; Ex. 1039, 12; Ex. 1041, 3. In contrast to interferon, moreover, clinical studies by 1998 had shown that rituximab’s “[t]oxicity was mild.” Ex. 1006, McLaughlin at 3. “After the first infusion, most patients [] had no toxicity for the remainder of treatment,” and “[a]dverse events were typically brief.” *Id.* at 6; *see id.* at 8 (“The toxicity of the current program was notably mild.”). “By virtue of the modest toxicities of this agent, which do not overlap with the toxicities of standard chemotherapy,” researchers concluded that rituximab—which has

a mechanism of action that is different than and complementary to that of chemotherapies like CVP—“lends itself to integration with chemotherapy programs.” *Id.* at 9; Ex. 1002 ¶ 52.

Soon after, in 1998, McNeil reported the initiation of the first clinical trial for rituximab maintenance therapy after induction chemotherapy. Ex. 1003, 5. This trial studied patients with intermediate-grade NHL, but McNeil made clear that rituximab’s only regulatory “approval [at the time] was for low-grade NHL.” *Id.* “After initial therapy” in the reported study, “patients who responded [were] . . . randomly assigned to receive the maintenance regimen—Rituxan every 6 months for 2 years—or observation.” *Id.* As of August 1999 (to Petitioner’s and Dr. Ozer’s knowledge), this was the only frequency and duration reported for rituximab maintenance therapy of any kind. Ex. 1002 ¶ 73.

D. It was known that a phase III trial was underway to test the combination of CVP induction followed by anti-CD20 maintenance.

On May 16–19, 1998, the American Society of Clinical Oncology (“ASCO”) held its 34th annual meeting in Los Angeles. Ex. 1005, 1. ASCO’s annual meeting “brings together more than 30,000 oncology professionals from around the world to discuss state-of-the-art treatment modalities, new therapies, and ongoing controversies in the field.”³ Ex. 1002 ¶ 55. Abstracts of presentations at the 34th annual

³ ASCO About Page, *available at* <http://am.asco.org/about>.

meeting—including Hochster I—were compiled, published, and distributed by ASCO, and, as discussed below, this publication was indexed, shelved, and publicly available before August 11, 1998. Ex. 1005, 9; Ex. 1016 ¶¶ 46–48.

Hochster I describes a Phase I/II clinical trial “in patients with low grade lymphoma (LGL) treated with cyclophosphamide (C) and fludarabine (F),” a combination of chemotherapeutic drugs. Ex. 1005, 9 (capitalization omitted). The patients in the study had “stage III, IV” LG-NHL. *Id.* The abstract concludes: “Based on these promising results we are conducting [a] phase III study of CF vs. *CVP ± anti-CD20 maintenance* with PCP & H-Z prophylaxis (E1496).” *Id.* (emphasis added). In other words, the abstract disclosed a phase III clinical trial in LG-NHL patients comparing CF chemotherapy with CVP induction chemotherapy followed by maintenance therapy using an anti-CD20 agent. Ex. 1002 ¶ 57. “PCP & H-Z prophylaxis” refers to standard treatments to prevent infections associated with chemotherapy and drugs that affect the immune system. *Id.*

Hochster I was not before the Examiner during prosecution of the ’172 patent, and was not before the Board in IPR2015-00418 or IPR2017-01093.

IX. PRIOR ART STATUS OF CITED REFERENCES

As shown below and in the Declaration of Petitioner’s expert librarian, Dr. Sylvia Hall-Ellis (Ex. 1016),⁴ each of the six references that Petitioner relies upon for the grounds of unpatentability asserted in this Petition—*i.e.*, Hochster I (Ex. 1005), Maloney (Ex. 1008), the FDA label (Ex. 1004), the PDR label (Ex. 1039), the Website label (Ex. 1041), and McNeil (Ex. 1003)—is a printed publication that was publicly accessible before August 11, 1999, and therefore qualifies as a prior-art printed publication to the ’172 patent under 35 U.S.C. § 102(a). With the exception of the PDR label (Ex. 1039), each of the references also qualifies as a prior-art printed publication under 35 U.S.C. § 102(b) as each was publicly accessible before August 11, 1998. *See In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004) (“[P]ublic accessibility has been the criterion by which a prior art reference will be judged for the purposes of § 102(b).”).

All of the references described below have long been cataloged or indexed in a meaningful way. Ex. 1016 ¶¶ 37–42. Thus, these references were sufficiently accessible to the public, and a POSA exercising reasonable diligence would have had no difficulty finding copies of them. *Id.*

⁴ Petitioner’s previous librarian declaration, Dr. Scott Bennett, has retired.

A. Hochster I (Ex. 1005)

Hochster I is an authentic copy of an excerpt from the *Program Proceedings of the 34th Annual Meeting of the American Society of Clinical Oncology*, May 16–19, 1998, Los Angeles, California, Volume 17 (1998) (“Program Proceedings”) (which was received by UC Berkeley on April 28, 1998, Ex. 1005, 1) and is available in 457 libraries world-wide. Ex. 1016 ¶ 38. The teachings of Hochster I entered the realm of public discourse at least as of May 1998, when it was presented at ASCO’s 34th annual meeting. *Id.* The attendees of the meeting included numerous oncologists with experience treating NHL patients. Ex. 1002 ¶ 55. Indeed, ASCO’s annual meeting was well known to persons of ordinary skill as of August 1998, many of whom would have attended in person. *Id.*

A MARC record generated by the National Serials Data Program at the Library of Congress indicates that the Program Proceedings containing Hochster I was catalogued, indexed, and publicly accessible in at least one library by May 31, 1998. Ex. 1016 ¶ 38. Accordingly, Hochster I is prior art to the ’172 patent as a publicly accessible printed publication under 35 U.S.C. § 102(a) and § 102(b).

B. Maloney (Ex. 1008)

Maloney is an authentic copy of an article from the September 1997 issue of *Blood*. *Id.* ¶ 39. A MARC record generated by the University of Minnesota Library indicates that the 1997 issue of *Blood* containing Maloney was catalogued, indexed,

and publicly accessible in at least one library by September 15, 1997. *Id.* Therefore, Maloney was available to the public before August 11, 1999 and August 11, 1998 and is a prior-art publication under § 102(b) and § 102(a).

C. Rituxan™ label (Ex. 1004 or Ex. 1039 or Ex. 1041)

As of August 1999, the Rituxan™ label was printed and disseminated in at least three different versions as evidenced by exhibits 1004 (“FDA label”), 1039 (“PDR label”),⁵ and 1041 (“Website label”). In the grounds below, Petitioner cites to and relies on each of these three exhibits in parallel and refers to them collectively as the “Rituxan™ label.” As shown below, each of these three exhibits are prior-art printed publications under § 102(a) and/or § 102(b). Also, should the Board deter-

⁵ The Board has not had the occasion to determine whether the “PDR label” (Ex. 1039) which contains the same substantive disclosures as the FDA label (Ex. 1004) and the Website label (Ex. 1041) is a prior art printed-publication under 35 U.S.C. § 102(a).

mine that one of the versions of the Rituxan™ label is not a prior-art printed publication, either one of the remaining versions can serve as suitable replacement because all three exhibits contain the identical teachings relied upon in this Petition.⁶

Irrespective of the specific document that was used, the teachings of the FDA-approved Rituxan™ label entered the public domain and were *in use* as of August 11, 1998. It is undisputed that when Rituxan™ vials were sold, they were accompanied with a product label as required by FDA regulations. *See* 21 C.F.R. § 201.59 (1997); *see also* Ex. 1053, 5, 7 (“[T]he [FDA] has approved the therapeutic use of one such therapeutic anti-CD20 antibody, RITUXAN®, for the use in treatment of relapsed and previously treated low-grade [NHL].”). Indeed Genentech, Rituxan’s manufacturer, admitted in a related proceeding (IPR2016-01614) that the “vials of rituximab that were sold under the brand name Rituxan® in the U.S. prior to May 7, 1999, were shipped by Genentech with labels,” and denied that any were shipped “without labels.” Ex. 1050, 8–10; Ex. 1051, 18–20. Genentech further admitted that the labels “included with vials of rituximab that were then sold under the brand name Rituxan® in the U.S. Prior to May 7, 1999 included a section called ‘WARNINGS,’ a section

⁶ Petitioner has also sufficiently identified that Ground II of this Petition relies on any one of the three versions of the Rituxan™ label exhibits in the grounds. *Supra* III.b.

called ‘ADVERSE REACTIONS,’ and a section called ‘DOSAGE AND ADMINISTRATION.’” Ex. 1050, 11–12. Exhibits 1004, 1039, and 1041 all contain those same sections, and teach the same FDA-approved dosing regimen for Rituxan™: “the recommend dosage of RITUXAN is 375mg/m² given as an IV infusion once weekly for four doses (days 1, 8, 15, and 22).” Ex. 1004, 2; Ex. 1039, 12; Ex. 1041, 3. Moreover, multiple prior art references confirm that Rituxan™ was on sale before August 1998. *See, e.g.*, Ex. 1042, Leget at 1; Ex. 1044, Henahan at 3; Ex. 1050, 11.

Thus, in view of Genentech’s representations and the prior-art disclosures, the teachings of the Rituxan™ label relevant to the grounds in this Petition were in the prior art as of the August 1998 critical date.

1. FDA label (Ex. 1004)

The FDA label (Ex. 1004) is a true and accurate copy of the original 1997 drug label for Rituxan™ that was approved by the FDA in November 1997. Ex. 1016 ¶ 42. As Dr. Hall-Ellis confirms, the FDA label is available today from the FDA’s website, which represents that it is the original approved label for Rituxan™ as of November 26, 1997. *Id.*

2. Website label (Ex. 1041)

The well-known “Internet Archive” service shows that the Website label (Ex. 1041) was available on the website of Genentech, which markets Rituxan™, as of January 23, 1998. *Id.* ¶ 41. The Internet Archive maintains an archive of webpages

collected from the internet by automated “crawlers.” *Id.* ¶ 21. The archived webpages are available for search and retrieval through an interface called the “Wayback Machine,” which renders accurate snapshots of webpages open to any Internet user as they existed at the time they were captured based on the date stamp on the top of the webpage. *Id.*

Based on the Website label’s appearance in the Internet Archive as of January 23, 1998, it is clear that a POSA exercising reasonable diligence and using typical internet search tools would have readily found a copy of it. *See, e.g., IBM Corp. v. Intellectual Ventures II LLC*, No. IPR2015-00089, Paper 44 at 57 (PTAB Apr. 25, 2016) (relying on “Wayback Machine evidence” to “determine that Petitioner has shown that [a reference] was publicly available”).

“[E]vidence of indexing is not an absolute prerequisite to establishing online references like the [webpage] as printed publications within the prior art.” *Voter Verified Inc. v. Premier Election Sols., Inc.*, 698 F.3d 1374, 1380 (Fed. Cir. 2013). As the Board previously explained, “various additional factors, including testimony indicating that the particular online publication in question was well-known to the community interested in the subject matter of the reference, and the existence of numerous related articles located within the same publication can support a determination of public accessibility.” *Pfizer, Inc. v. Biogen, Inc.*, IPR2017-01166, Paper 9 at 14–15 (PTAB Nov. 13, 2017) (citing *Voter Verified*, 696 F.3d at 1380–81).

Dr. Ozer has explained that it was an increasingly common practice for physicians in the late 1990s to locate information about a drug manufacturer's product on the drug manufacturer's website. Ex. 1002 ¶ 63. Further, rituximab's launch was a watershed moment in the field of oncology and a POSA not only would have closely followed the various clinical trials, but would have known (as the prior art disclosed) that Genentech was involved with the manufacturing of rituximab. *Id.*; *see also, e.g.*, Ex. 1042, Leget at 1; Ex. 1044, Henahan at 3; *cf.* Ex. 1052, Press Release at 1 (“Genentech, Inc. . . . and IDEC Pharmaceuticals Corporation . . . announced that RITUXAN™ (Rituximab) is being shipped today to the oncology medical community. Rituxan was cleared for marketing by the [FDA] on November 26, 1997.”).

Moreover, a POSA would have been independently aware of Genentech's website because it contained numerous articles relating to new developments in biotechnology. Ex. 1045, 1 (“Here you will find news about Genentech, as well as news about the biotechnology industry. You will also find links to newsgroups on the Internet that address biotechnology.”). As an example, Genentech's website included two pages replete with articles related to new developments in oncology, rituximab, and biotechnology. Ex. 1046; Ex. 1047 (also displaying an archive of past articles).

Lastly, the Website label is a prior-art printed publication because the search tool on Genentech’s website would have been able to retrieve any document that mentioned rituximab using its basic search features. *See* Ex. 1048 (listing search tool on Genentech’s website homepage). The search tool as of January 1998 indicated that users can “search for a whole or a part of a word. For example, enter ‘lab’ to find documents that contain the word ‘laboratory.’ . . . You may also search for multiple words at once, divided by a space.” Ex. 1049. Based on the instructions for Genentech’s search tool, a POSA would have been able to retrieve the “Rituxan Full Prescribing Information” using reasonable diligence and ordinary search tools. *See also Voter Verified*, 698 F.3d at 1381 (finding that webpage was prior art because it “included a search tool that would have retrieved the [article] in response to search terms”).

Thus, the Website label is a prior-art printed publication under 35 U.S.C. § 102(a) and § 102(b).

3. PDR label (Ex. 1039)

The PDR is a well-known reference that reproduces drug labels in their entirety. Ex. 1039. The 1999 edition of the PDR (which was received by the National Library of Medicine on December 30, 1998, *see id.* at 3) contains the labeling information for Rituxan[™] and is available in 218 libraries worldwide. Ex. 1039, 10–15; Ex. 1016 ¶ 40. A previous panel of the Board held that excerpts from “the PDR” are

“portions of a reference book that were published on the dates indicated on the documents” and “sufficiently establish that they constitute printed publication prior art, absent additional evidence indicating otherwise.” *Frontier Therapeutics, LLC v. Medac Gesellschaft für klinische Spezialpräparate mbH*, IPR2016-00649, Paper 10 at 21–22 & 6 n.4 (PTAB Sept. 1, 2016).

A MARC record generated by the Elon University Library indicates that the 53rd Edition of the PDR containing the full prescribing information for Rituxan was cataloged, indexed and publicly accessible in at least one library by January 31, 1999. Ex. 1016 ¶ 40. Accordingly, the PDR label is prior art to the ’172 patent as a publicly accessible printed publication under 35 U.S.C. § 102(a).

D. McNeil (Ex. 1003)

McNeil is an authentic copy of a news report by Caroline McNeil published in the February 18, 1998, issue of the *Journal of the National Cancer Institute* and is available in 1,283 libraries. *Id.* ¶ 37. A MARC record generated by the National Library of Medicine indicates that the issue of the journal containing McNeil was catalogued, indexed, and publicly accessible in at least one library by March 31, 1998. *Id.* Accordingly, McNeil is prior art to the ’172 patent as a publicly accessible printed publication under 35 U.S.C. § 102(a) and § 102(b).

X. ANALYSIS OF GROUND FOR TRIAL

As shown below, claim 1 of the '172 patent is unpatentable under 35 U.S.C. § 103(a). First, claim 1 would have been obvious to a POSA as of August 1999 over Hochster I (Ex. 1005), Maloney (Ex. 1008) and McNeil (Ex. 1003). Additionally, it would have been obvious over Hochster I, the Rituxan™ label (Ex. 1004, Ex. 1039, or Ex. 1041) and McNeil. Second, the alleged secondary considerations asserted by Patent Owner during prosecution fail to show nonobviousness. Claim 1 is thus unpatentable as obvious and should be cancelled.

A. Claim 1 would have been obvious over Hochster I (Ex. 1005) in view of Maloney (Ex. 1008) and McNeil (Ex. 1003).

Claim 1 of the '172 patent is directed to the following method of treatment (brackets added): “A method of treating low grade B-cell non-Hodgkin’s lymphoma in a human patient comprising administering to the patient [1] chemotherapy consisting of CVP therapy to which the patient responds, followed by rituximab maintenance therapy, [2] wherein the maintenance therapy comprises four weekly administrations of rituximab at a dose of 375 mg/m² [3] every 6 months, and wherein the maintenance therapy is provided for 2 years.”

As shown below, each of these limitations was disclosed by the combination of Hochster I, Maloney, and McNeil, and these references further provided a motivation for a POSA as of August 1999 to combine the limitations in the manner claimed with a reasonable expectation of success. Ex. 1002 ¶¶ 75–108.

1. CVP chemotherapy followed by rituximab maintenance

First, a method of treating LG-NHL with induction CVP chemotherapy followed by maintenance therapy using an anti-CD20 agent was disclosed in Hochster I—a prior art reference that was not before the Examiner or the Board in any other IPR—and a POSA as of August 1999 would have been motivated, with a reasonable expectation of success, to use rituximab as the anti-CD20 agent for the maintenance therapy disclosed in the method of Hochster I.

a. Hochster I discloses treating LG-NHL with CVP induction followed by “anti-CD20 maintenance.”

Hochster I describes the results of a Phase I/II study “in patients with low grade lymphoma,” *i.e.*, LG-NHL. Ex. 1005, 9 (capitalization omitted); Ex. 1002 ¶ 56. “Based on the[] promising results” of that Phase I/II study, Hochster I discloses that the investigators were “conducting [a] *phase III study* of CF vs. CVP ± *anti-CD20 maintenance*” Ex. 1005, 9 (emphasis added).

As Dr. Ozer confirms, a POSA as of August 1999 would have understood that Hochster I’s disclosure of “CVP ± anti-CD20 maintenance” referred to induction chemotherapy consisting of CVP followed by maintenance therapy—*i.e.*, therapy used to maintain and prolong the remission obtained after a patient responded to CVP induction—using an anti-CD20 agent. Ex. 1002 ¶ 79. Specifically, a POSA would have understood that the “±” symbol, which is used in clinical trial abstracts to mean “with or without” as a comparison of two treatment arms, denoted that one

patient group in the clinical trial would receive only CVP induction chemotherapy, whereas another group would receive CVP induction chemotherapy followed by anti-CD20 maintenance therapy. *Id.* ¶ 80.

By definition, the “maintenance” disclosed in Hochster I necessarily requires that patients responded to the CVP induction therapy. As Patent Owner argued in IPR2015-00418, “[t]he ordinary understanding of maintenance therapy is therapy that prolongs *remission* and prevents *relapse*.” Ex. 1030, 21 (emphasis added). Patent Owner quoted a prior art article summarizing a known oncological approach that “has been to *induce remission* and *then* to administer maintenance therapy of one type or another, to try to prevent recurrence.” *Id.* (citation omitted; emphasis added). In other words, “maintenance therapy,” by definition, is therapy that comes after an initial therapy to which the patient responds, and which has therefore already “induce[d] remission” in the patient. *Id.* Likewise, Patent Owner argued that “maintenance therapy” following CVP connotes a therapy that is administered “*after the patient has responded* to the chemotherapy consisting of CVP therapy.” *Id.* at 23 (emphasis added). Dr. Ozer agrees. Ex. 1002 ¶ 81.

Accordingly, a POSA in August 1999 would have understood that Hochster I’s disclosure of “CVP ± anti-CD20 maintenance” referred to a method of treating low grade B-cell NHL in a human patient comprising administering to the patient

chemotherapy consisting of CVP therapy, to which the patient responds, followed by anti-CD20 maintenance therapy. *Id.* ¶ 82.

b. A POSA would have been motivated to use rituximab for “anti-CD20 maintenance.”

A POSA would have had compelling reasons to select rituximab as the “anti-CD20” agent disclosed for maintenance therapy in Hochster I. Maloney taught that rituximab “binds [to] the CD20 antigen with high affinity,” “efficiently kills CD20⁺ cells,” and has “antitumor activity.” Ex. 1008, 6. A POSA would have been motivated to select rituximab for anti-CD20 maintenance for this reason alone. Ex. 1002 ¶¶ 83, 85. Indeed, Maloney suggested that rituximab should be studied in “combination with *or after* standard chemotherapy.” Ex. 1008, 12 (emphasis added). A POSA would have understood standard chemotherapy to include CVP for LG-NHL, and would have understood “after” standard chemotherapy to include maintenance therapy. Ex. 1002 ¶ 85.

McNeil likewise confirmed that “Rituxan . . . targets the B-cell protein CD20.” Ex. 1003, 5. Moreover, this understanding is consistent with contemporaneous disclosures describing the “*anti-CD20* monoclonal antibody, *Rituximab*.” Ex. 1006, McLaughlin at 3 (emphasis added); Ex. 1038, DeNardo at 4 (same); Ex. 1002 ¶ 84. A POSA would have understood these disclosures to mean that rituximab is an anti-CD20 agent. Ex. 1002 ¶ 85. Therefore, the prior art would have led a POSA straight to rituximab. *Id.* ¶ 86.

Thus, although Hochster I did not disclose a particular anti-CD20 agent, a POSA reading this reference in August 1999 would have either assumed the reference was referring to rituximab, or otherwise understood that rituximab would be a top choice for an anti-CD20 agent from a finite number of available anti-CD20 agents. *Id.* ¶ 85. Accordingly, a POSA would have been motivated to use rituximab for the “anti-CD20 maintenance” following CVP induction disclosed in Hochster I. Ex. 1002 ¶¶ 85–86.

c. A POSA would have had a reasonable expectation of success in using rituximab in the Hochster I method.

A POSA would have reasonably expected the combination of CVP induction therapy followed by rituximab maintenance therapy to provide effective treatment of LG-NHL. *Id.* ¶ 87. Although Hochster I did not report the results of the study, “[c]onclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success.” *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014).

Here, Hochster I disclosed that CVP induction followed by anti-CD20 maintenance therapy was being evaluated in a “phase III” clinical trial. Ex. 1005, 9. Such a clinical trial “protocol . . . is far from an abstract theory—it is an advanced stage of testing designed to secure regulatory approval”—and thus the “initiat[ion] of human clinical trials . . . is reasonably predictive” even before any results are ob-

tained. *In re Montgomery*, 677 F.3d 1375, 1382–83 (Fed. Cir. 2012) (quoting *Manual of Patent Examining Procedure* § 2107.03 (8th ed., rev. 6, Sept. 2007) (“[I]f 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.”)).

Patent Owner here cannot contend otherwise. During prosecution, the applicants overcame a rejection under 35 U.S.C. § 112 after “[t]he Examiner questioned whether the specification [of the ’172 patent] supported the claims by describing prospective clinical protocols without patient data.” Ex. 1027, 5. The applicants argued that “the specification clearly shows that the inventors were in the possession of the methods claimed.” *Id.* at 7 (quotation omitted). In support, the applicants submitted a declaration by an expert who opined that the specification “clearly conveys the [claimed] method of treatment” based on “the particular protocol” disclosed in the specification—*i.e.*, the protocol for the same clinical trial referenced in Hochster I, which was ongoing when the application for the ’172 patent was filed in August 1999. Ex. 1028 ¶ 11; Ex. 1001, 13:7–16.

Therefore, with respect to the combination of CVP induction followed by rituximab maintenance therapy, Hochster I’s disclosure “is identical to the [’172] patent itself, which does not disclose actual results” of the clinical trial. *Montgom-*

ery, 677 F.3d at 1383. Because the '172 patent “sets forth no human clinical . . . data,” it “adds nothing beyond the teachings of” Hochster I. *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1374 (Fed. Cir. 2005).

Accordingly, at least in view of Hochster I and Maloney, a POSA as of August 1999 would have been motivated, with a reasonable expectation of success, to treat LG-NHL with chemotherapy consisting of CVP therapy to which the patient responds, followed by rituximab maintenance therapy, as required by claim 1 of the '172 patent. Ex. 1002 ¶¶ 87–90.

2. Four weekly administrations of 375 mg/m²

One of the primary considerations for a POSA carrying out Hochster I's method of treating LG-NHL by administering CVP chemotherapy followed by anti-CD20 maintenance with rituximab would have been the dosing regimen of rituximab. Ex. 1002 ¶ 91. As shown below, it would have been obvious to administer rituximab maintenance as four weekly doses of 375 mg/m².

a. It would have been obvious to use—or at least try—the claimed dosing regimen for rituximab.

As of August 1999, Maloney taught that 375 mg/m² of rituximab in four weekly doses had been selected for Phase II clinical trials, and proved effective in depleting CD20+ B-cells. Ex. 1008, 6–7. Maloney studied “four weekly infusions of 375 mg/m² IDEC-C2B8 in patients with relapsed low-grade or follicular NHL”

and concluded that this regimen had a favorable “safety profile” and led to “anti-tumor activity in patients with relapsed low-grade or follicular NHL.” *Id.* at 6. Maloney further taught that “[t]reatment with the chimeric anti-CD20 antibody rapidly and effectively depleted B cells from the peripheral blood circulation . . . until approximately 6 months posttreatment, followed by slow gradual recovery.” *Id.* at 6, 9.

Thus, to a POSA designing a dosing regimen for the anti-CD20 maintenance therapy taught by Hochster I, it would have been obvious to select a clinically proven dosing regimen and one that “has been most extensively tested” in clinical trials. Ex. 1002 ¶ 92; Ex. 1038, DeNardo at 4.

At a minimum, the claimed four weekly doses of 375 mg/m² would have been obvious to try. Ex. 1002 ¶ 94. “When . . . there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). Under this standard, a set of solutions is “obvious to try” where the prior art provides direction about “which parameters were critical” or “which of many possible choices is likely to be successful,” and “finite” where the prior art thereby reduces the options to a set that is “small or easily traversed.” *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009) (internal quotation marks omitted). That is the case here. The claimed regimen was at least

“obvious to try because it was . . . studied extensively,” and had been shown to be “safe, effective, and tolerable” in patients with LG-NHL. *In re Copaxone Consol. Cases*, 2017 WL 401943, at *19 (D. Del. Jan. 30, 2017). “It was therefore obvious . . . to experiment with and have a reasonable probability of success with that dose.” *Id.*

Indeed, Patent Owner acknowledged during prosecution that it would have been obvious to continue using the regimen of four weekly doses. In arguing that it would not have been obvious to use *eight* doses (for another claim that was withdrawn before allowance), Patent Owner acknowledged that the prior art “showed that the dosing [of rituximab] had been optimized as 4 doses.” Ex. 1022, 16. The regimen of four weekly doses had been “found to be effective,” and “[t]here was no incentive to optimize further” because “[s]uch optimization had already been done at the time of filing.” *Id.* at 15.

Accordingly, it would have been obvious to use, or at least to try, four weekly doses of 375 mg/m² for LG-NHL in the method of using “anti-CD20 maintenance” therapy disclosed in Hochster I. Ex. 1002 ¶¶ 93–94. *See also Hoffmann-La Roche*, 748 F.3d at 1332 (finding the claimed dose obvious because “[a] person skilled in the art looking to scale to a monthly dose of oral ibandronate from a known-effective daily dose was [] faced with a very limited set of possibilities”).

b. The claimed dose falls within a range disclosed in the prior art, and is thus obvious.

Independently, Maloney also disclosed a range that includes the claimed dose. Ex. 1002 ¶ 95. Specifically, Maloney disclosed that rituximab had been tested in at least doses of 100, 125, 250, and 500 mg/m², “with no dose-limiting toxicity.” Ex. 1008, 6–7. This disclosure, too, would have provided a POSA with a reason to use the claimed dose. Ex. 1002 ¶ 96.

“The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum” specific value, and thus “the existence of overlapping or encompassing ranges shifts the burden [of production] to the [patentee] to show [evidence] that his invention would not have been obvious.” *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). In particular, “[w]here there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations.” *Galderma*, 737 F.3d at 738. Patent Owner cannot meet that burden here.

Nothing in the prior art teaches away from four weekly administrations of 375 mg/m². Ex. 1002 ¶ 97. On the contrary, Maloney expressly selected that regimen for its successful Phase II study and that dose continued to be most “extensively

tested” as of August 1999. Ex. 1008, 6–7; Ex. 1038, DeNardo at 4. And while Patent Owner in IPR2015-00418 argued that pharmacokinetic data suggested a lower dose would also work for maintenance therapy (Ex. 1030, 49–50), this does not amount to teaching away, which requires a reference to “criticize, discredit, or otherwise discourage the solution claimed.” *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004); *see also SightSound Techs., LLC v. Apple Inc.*, 809 F.3d 1307, 1320 (Fed. Cir. 2015) (“‘[M]ere disclosure of more than one alternative’ does not amount to teaching away from one of the alternatives where the [prior art] does not ‘criticize, discredit, or otherwise discourage the solution claimed.’”) (citation omitted).

In fact, because there was “no dose-limiting toxicity” even at doses of 500 mg/m² (Ex. 1008, 6), Patent Owner has “not point[ed] to any references suggesting that there were safety concerns associated with the [claimed] dose.” *Hoffmann-La Roche*, 748 F.3d at 1333. Moreover, prior maintenance therapies (*e.g.*, CVP) had likewise been given “at the same drug dosages” that were used for first-line induction therapy. Ex. 1025, Portlock at 2; Ex. 1002 ¶ 98.

Nor is there any evidence of unexpected results or other pertinent secondary considerations related to the claimed dosing regimen. Ex. 1002 ¶ 97. The only secondary considerations that Patent Owner asserted concern the combination of CVP induction and anti-CD20 maintenance, which was taught by Hochster I, and are not probative of nonobviousness for the reasons discussed below in Part X.D.

Thus, in view of Maloney, a POSA as of August 1999 implementing Hochster I's method of treating LG-NHL would have been motivated to select (or at a minimum, try) the known dosing regimen of four weekly doses of 375 mg/m², with a reasonable expectation of success. Ex. 1002 ¶ 99.

3. Administration every six months for two years

Another important consideration for a POSA implementing Hochster I's method would have been the frequency and duration of the rituximab maintenance therapy. *Id.* ¶ 100. As shown below, it would have been obvious to administer rituximab every six months for at least two years.

a. McNeil disclosed the *only* known frequency and duration for rituximab maintenance therapy.

In determining the frequency and duration of maintenance therapy with rituximab, a POSA would have begun by searching the prior art for an existing maintenance schedule for rituximab. *Id.*

To Petitioner's and Dr. Ozer's knowledge, only a *single* schedule of frequency and duration for rituximab maintenance was known as of August 1999: McNeil disclosed that a phase III clinical trial was evaluating "the maintenance regimen [of] Rituxan *every 6 months for 2 years.*" Ex. 1003, 5 (emphasis added).

Thus, it would have been obvious for a POSA to use, or at least try, a six-month frequency and two-year duration in designing a rituximab maintenance therapy with a reasonable expectation of success. Ex. 1002 ¶¶ 100–106. Indeed, for at

least the following reasons, a POSA would have been motivated to use these parameters in the specific context of the method disclosed in Hochster I.

b. Data in the prior art provided a reason to administer rituximab maintenance every six months.

Although the study discussed in McNeil concerned intermediate-grade NHL, a POSA would have been motivated to select McNeil's six-month frequency for maintenance therapy against LG-NHL—particularly for a 375 mg/m² dose of rituximab—because Maloney taught “[p]eripheral blood B-cell depletion occurred rapidly, with recovery beginning 6 months posttreatment.” Ex. 1008, 6. That is, the cancerous B-cells began to reappear after six months, suggesting the need for renewed treatment. Thus, a POSA would have been motivated to re-administer rituximab maintenance therapy every six months, because that was how long it took for the target of rituximab therapy—*i.e.*, cancerous B-cells—to recover in patients with LG-NHL. Ex. 1002 ¶¶ 102.⁷

⁷ Indeed, Patent Owner selected a six-month frequency of rituximab maintenance for this very reason. Ex. 1029, 6 (“The maintenance schedule devised for E1496 was based on the observed time to B-cell recovery with rituximab monotherapy.”).

c. A POSA would have used maintenance therapy as long as needed—including for two years.

The duration of “2 years” for maintenance therapy was also expressly disclosed in McNeil. Ex. 1003, 5. And logically, it would have been obvious to prolong remission (and therefore survival of the patient) for as long as possible. Ex. 1002 ¶ 103. If this could be accomplished for at least two years, that would have been highly desirable. *Id.* Indeed, if feasible, it would have been obvious to continue maintenance therapy indefinitely. For example, in Hiddemann I, researchers expressly found it desirable to administer maintenance therapy (with interferon after CVP) “without a time limitation.” Ex. 1017, 5.

In selecting a specific two-year period, McNeil followed previous studies on maintenance therapy following CVP to treat LG-NHL, including the regimen in Portlock, where patients “receive[d] 2 years of planned maintenance CVP” (Ex. 1025, 2), and the regimen in Steward, where patients received “‘maintenance’ chemotherapy with 2 years of intermittent chlorambucil” (Ex. 1010, 3).

Likewise, here, Patent Owner selected a two-year duration because that was how long the E1496 clinical trial lasted (*i.e.*, the phase III trial disclosed in Hochster I), which is the only support for claim 1 in the ’172 patent’s specification. Ex. 1001, 13:8–16. Of course, the fact that clinical trials, by necessity, have a limited duration, does not alter the fact that a POSA would have wanted to prolong remission in a patient for as long as possible. Ex. 1002 ¶¶ 103–105.

Accordingly, it would have been obvious to continue rituximab maintenance therapy in the method of Hochster I for at least two years (if not longer), as required by claim 1 of the '172 patent. *Id.* ¶ 106.

B. Claim 1 would have been obvious over Hochster I (Ex. 1005) in view of the Rituxan™ label (Exs. 1004, 1039, or 1041) and McNeil (Ex. 1003).

For substantially similar reasons, claim 1 would have been obvious over Hochster I in view of the Rituxan™ label and McNeil. This was the ground Petitioner presented in its prior petition. As explained, Petitioner has remedied any defect in public accessibility, and now expressly uses the 1999 *Physicians' Desk Reference* ("PDR label"), which is a prior-art printed publication under 35 U.S.C. § 102(a), and the "Rituxan™ Full Prescribing Information on Genentech's website" ("Website label") and the "FDA label", which is a prior-art printed publication under 35 U.S.C. § 102(a) and § 102(b). The Rituxan™ label, as shown in the PDR label, for example, made the same relevant disclosures as Maloney and thus, in combination with Hochster I and McNeil, would have rendered claim 1 of the '172 patent obvious to a POSA.

Indeed, the first line of the Rituxan™ label confirms that "[r]ituximab . . . is a genetically engineered chimeric murine/human monoclonal antibody *directed against the CD20 antigen* found on the surface of normal and malignant B lymphocytes." Ex. 1004, 1 (emphasis added); Ex. 1039, 10; Ex. 1041, 1. The Rituxan™

label further explains that “[r]ituximab binds specifically to the antigen CD20,” which is “expressed on >90% of B-cell non-Hodgkin’s lymphomas (NHL).” Ex. 1004, 1 (emphasis added); Ex. 1039, 10; Ex. 1041, 1. The label further confirmed that 375 mg/m² was the only dosing regimen approved by the FDA for rituximab: “[t]he recommended dosage of RITUXAN is 375 mg/m² given as an IV infusion once weekly for four doses.” Ex. 1004, 2 (emphases added); Ex. 1039, 12; Ex. 1041, 3. The label also taught rituximab was detectable in the blood for up to six months that B-cells regenerated after six months: “[r]ituximab was detectable in the serum of [LG-NHL] patients [who took that dose] three to six months after completion of treatment,” and “B-cell recovery began at approximately six months following completion of treatment.” Ex. 1004, 1; Ex. 1039, 11; Ex. 1041, 1.

The fact that other hypothetical dosing regimens were also conceivable, or that this dosing regimen was not yet specifically approved for maintenance, is beside the point. Here, similar to other cases, “one skilled in the art” would first look to regimens “previously approved by the FDA and used successfully.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1365–66 (Fed. Cir. 2007). A new regimen “can always be made or attempted,” but “a skilled [artisan] at the time would simply [use] known” regimens first before attempting others. *Id.* at 1362.

In sum, a POSA would have been motivated by Hochster I’s teaching—to use anti-CD20 maintenance therapy following CVP—to use rituximab specifically,

which was the only FDA approved anti-CD20 agent. Ex. 1002 ¶ 111. Further, a POSA would have been motivated to use, or at least to try, the only FDA approved dosing—375 mg/m² weekly for four weeks—as disclosed in the Rituxan™ label. *Id.* A POSA would have been motivated to use this regimen every six months in light of the label’s teaching that B-cells began to recover after six months and that rituximab takes approximately 6 months to leave the human body. *Id.* Finally, a POSA would have been motivated to use this regimen for at least two years, as disclosed in McNeil. *Id.* Thus, a POSA would have found claim 1 obvious over Hochster I, the Rituxan™ label (in any of its three versions), and McNeil. *Id.*

C. McNeil does not “teach away.”

In IPR2015-00418, Patent Owner argued that the claimed method would not have been obvious over McNeil, in part because the maintenance regimen it disclosed turned out to be unsuccessful in the context of intermediate-grade NHL. Ex. 1030, 41. For several reasons, this argument is misplaced.

First, as Patent Owner acknowledged (and the Board held), the success or failure of a regimen in the context of *intermediate*-grade NHL says nothing about its success or failure in the context of *LG*-NHL, which is a different disease. *Id.* at 20, 22, 48–49; Ex. 1031, 15, 21. Moreover, as discussed, a POSA would have been motivated to select McNeil’s six-month frequency because of the B-cell recovery

observed with rituximab in the specific context of treating *LG-NHL*. *Supra* at VIII.C, X.A.3.a; Ex. 1002 ¶ 102, 110.

Second, there is no evidence that McNeil’s regimen turned out to be unsuccessful *because of* the six-month duration and two-year frequency. *Id.* ¶ 114.

Third, and in any event, whether a therapy that appeared promising as of August 1999 turned out to be unsuccessful *after* the priority date is immaterial. “Obviousness, and expectation of success, are evaluated from the perspective of a person having ordinary skill in the art *at the time of invention.*” *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 974 (Fed. Cir. 2014). Here, McNeil’s regimen “was *not yet known* to have” any efficacy issues. *Id.* To rely on such later-discovered failures would be impermissible hindsight.

Nor does McNeil “teach away” from using CVP chemotherapy, as Patent Owner argued in IPR2015-00418, merely because it cites data that ““provides more support for the use of the stronger, anthracyclin[e]-based regimens,”” such as CHOP. Ex. 1030, 46 (quoting Ex. 1003, 6). Again, McNeil was referring to treatment for *intermediate*-grade NHL, which differs from *LG-NHL*, where less potent chemotherapy—CVP—is preferred. Ex. 1002 ¶ 117; *see also* Ex. 1011, Hiddemann II at 1 (“In low grade lymphomas,” first-line therapy “consists preferentially of” CVP); Ex. 1010, Steward at 7 (CVP has the “greatest and complete response rates” for *LG-NHL*, and CHOP has “not produced obvious improvements” over CVP); Ex. 1018,

Bishop at 6 (CHOP “does not enhance the activity of the CVP regimen” in LG-NHL); Ex. 1033, Dana at 2 (CHOP “did not prolong the overall median survival of low-grade lymphoma patients compared with results with” CVP).

Even if McNeil’s teaching of CHOP could be applied to LG-NHL, a reference does not teach away if it “does not criticize, discredit, or otherwise discourage the solution claimed.” *In re Fulton*, 391 F.3d at 1201. McNeil does none of these things. At most, it expresses a *preference* for CHOP. “A reference does not teach away, however, if it merely expresses a general preference for an alternative invention.” *Galderma*, 737 F.3d at 738.

Moreover, the issue in IPR2015-00418 was whether the prior art references cited by the petitioner there “would have prompted an ordinary artisan to switch from McNeil’s CHOP induction chemotherapy to the CVP regimen required by claim 1 of the ’172 patent.” Ex. 1031, 19. By contrast, here, Hochster I (which the petitioner in IPR2015-00418 did not cite) already disclosed the combination of CVP chemotherapy followed by anti-CD20 maintenance with rituximab. *Supra* Part X.A.1. Thus, there is no need to “switch” anything in McNeil, which simply discloses the obvious frequency of six months and the obvious duration of at least two years, which a POSA would have been independently motivated to use for Hochster I’s method of treating LG-NGL. Ex. 1002 ¶¶ 118–119. *See also In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (“Non-obviousness cannot be established

by attacking references individually where the rejection is based upon the teachings of a combination of references. Thus, [a reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole.”) (citation omitted).

In summary, Hochster I disclosed the treatment of LG-NHL with the combination of CVP induction followed by “anti-CD20 maintenance.” Both Hochster I and Maloney disclosed that rituximab was a suitable anti-CD20 agent, and Maloney taught that a dose of 375 mg/m² weekly for four weeks was safe and effective. Maloney even recommended studying rituximab “after standard chemotherapy,” which a POSA would have understood as including maintenance therapy after CVP. McNeil further disclosed the *only* frequency and duration at the time for rituximab maintenance—*i.e.*, every six months for two years.

As discussed above, a POSA as of August 1999 would have been motivated to combine each of these known treatment methodologies with a reasonable expectation of success, thus satisfying each and every limitation of claim 1 of the ’172 patent. That claim is thus obvious.

D. The alleged secondary considerations asserted during prosecution fail to demonstrate that claim 1 is nonobvious.

Petitioner is not aware of any probative evidence of secondary considerations that would undermine the evidence of obviousness discussed above. Ex. 1002 ¶ 120. In any event, “objective evidence of nonobviousness simply cannot overcome such

a strong *prima facie* case of obviousness.” *Agrizap, Inc. v. Woodstream Corp.*, 520 F.3d 1337, 1344 (Fed. Cir. 2008).

At this stage, moreover, Petitioner has no burden to identify and rebut secondary considerations. Patent Owner must first present a *prima facie* case for such considerations, which Petitioner may then rebut. *Sega of Am., Inc. v. Uniloc USA, Inc.*, IPR2014-01453, Paper 11 at 20 (PTAB Mar. 10, 2015). Thus, panels routinely reject arguments against institution based on secondary considerations. *Petroleum Geo-Services Inc. v. WesternGeco LLC*, IPR2014-01478, Paper 18 at 36 (PTAB Mar. 17, 2015); *Mylan Pharm. Inc. v. Allergan, Inc.*, IPR2016-01127, Paper 8 at 18 n.4 (PTAB Dec. 8, 2016); *Amneal Pharm., LLC v. Supernus Pharm., Inc.*, IPR2013-00368, Paper 8 at 12–13 (PTAB Dec. 17, 2013).

Nevertheless, out of an abundance of caution, Petitioner preliminarily addresses (1) the alleged “unexpected results” asserted during prosecution (which were the sole basis for allowance); and (2) the alleged “failure of others and long-felt need” that were also asserted (but which the Examiner did not credit). Ex. 1023, 12. Petitioner reserves the right to address any evidence of secondary considerations that Patent Owner may present in this proceeding.

1. The claimed method produces no “unexpected results.”

As discussed, the ’172 patent issued only because the Examiner’s obviousness rejections were “withdrawn in view of applicant[’]s arguments regarding unexpected

results.” Ex. 1024, 8. Those arguments were based on the Hochster II article, which reports the results of the “E1496” trial disclosed in the prior art Hochster I reference. Ex. 1022, 12; Ex. 1029. However, as shown below, Hochster II fails to provide evidence of nonobviousness because (1) it did not compare the claimed therapy to the closest prior art; (2) the results would have been expected to a POSA as of August 1999; and (3), at most, the results show a mere difference in degree rather than a probative difference in kind.

a. Rituximab maintenance therapy was not compared to the closest prior art.

“[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.” *Kao*, 441 F.3d at 970. Here, however, Hochster II only compared the benefits of “maintenance rituximab (MR) *versus observation*”—*i.e.*, to nothing. Ex. 1029, 2 (emphasis added). Doing *nothing* was not the closest prior art to rituximab maintenance therapy. Ex. 1002 ¶ 123.

As Hochster II itself acknowledges, and as discussed above, maintenance “chemotherapy had been used to maintain the response after induction chemotherapy,” and “randomized studies supported the role of maintenance interferon (IFN)” as well. Ex. 1029, 1 & nn.1–4, 6 (citing studies published in 1987, 1988, and 1998, *e.g.*, Ex. 1010, Steward (1988) and Ex. 1034, Solal-Céligny (1998)). Yet Hochster II failed to compare rituximab maintenance therapy to these previously known

maintenance therapies for LG-NHL. Hochster II fails to show any probative “unexpected results” for this reason alone. Ex. 1002 ¶¶ 123–124.

b. The benefits of CVP induction followed by rituximab maintenance therapy were expected.

The results of the trial reported in Hochster II also would have been expected to a POSA as of August 1999. *Id.* ¶ 124. Hochster II reports that maintenance rituximab after CVP induction improved “progression-free survival (PFS), defined as progression or death at 2 years,” compared to mere observation—a favorable result. Ex. 1029, 2, 6. But nothing in Hochster II suggests that this result was surprising or unexpected. Ex. 1002 ¶¶ 124–125. On the contrary, Hochster II reports that the “study *confirmed the hypothesis* that rituximab would be an effective and safe maintenance after CVP chemotherapy.” Ex. 1029, 5 (emphasis added). In other words, the investigators *began* with an expectation of success—for a study that was disclosed as ongoing in the prior art Hochster I reference.

That expectation, moreover, was based on the same knowledge that would have been available to a POSA as of August 1999. As Hochster II explains, pre-1998 experiences with interferon “maintenance therapy suggested . . . that an active biologic agent with a favorable safety profile and high patient acceptability would improve clinical outcome in” LG-NHL. *Id.* at 1–2 & n.4. Rituximab was known to meet those criteria, having been “approved for use in [LG-NHL] in 1997” with a

favorable “objective response rate” and only “rare serious adverse effects.” *Id.* at 2 & n.8 (citing Ex. 1006, McLaughlin (1998)).

Thus, while confirmation of the investigators’ expectation of success was not published until after the priority date, that expectation was expressly based on information available in the prior art by 1998. That is, a POSA as of August 1999 would have had the same expectation that maintenance rituximab following CVP induction would be superior to observation alone. Ex. 1002 ¶¶ 126–127. *See also Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003) (“This court has approved use of later publications as evidence of the state of art existing on the filing date of an application.”) (quotation omitted).

c. The asserted results show, at most, a mere difference in degree, not a probative difference in kind.

“Unexpected results that are probative of nonobviousness are those that are different in kind and not merely in degree from the results of the prior art.” *Galderma*, 737 F.3d at 739. Here, at most, Hochster II shows only a difference in the *degree* of progression-free survival for two years—not a new difference in the *kind* of effects produced by the prior art. Ex. 1002 ¶ 126. In fact, Hochster II acknowledges that the data for overall three-year survival merely “show a positive trend” in favor of maintenance rituximab, but “do not achieve statistical significance.” Ex. 1029, 5. Thus, with respect to survival of patients, Hochster II does not even establish a “significant difference in degree of the same property amounting to a marked

superiority for purposes of evaluating unexpected results.” *Bristol-Myers Squibb Co.*, 752 F.3d at 977.

In the end, “[w]hile the evidence would support a finding of superior efficacy” for maintenance rituximab compared to observation (which would have been expected), “that improved efficacy does not rebut the strong showing that the prior art disclosed” the claimed method. *Hoffmann-La Roche*, 748 F.3d at 1334. “The evidence of superior efficacy does nothing to undercut the showing that there was a reasonable expectation of success . . . , even if the level of success may have turned out to be somewhat greater than would have been expected.” *Id.*; *see also* Ex. 1002 ¶ 126.

2. The claimed method does not meet any “long-felt need” or overcome any “failure of others.”

During prosecution, Patent Owner also alleged “both failure of others and long-felt need” based on statements in Hochster II that, despite previous efforts to improve patient outcomes, LG-NHL “followed a ‘continuous relapse pattern’ and ‘during a 30-year period of study, no single chemotherapy regimen has been considered to provide a definitive progression-free (PFS) or overall survival (OS) advantage.’” Ex. 1022, 12 (quoting Ex. 1029, 1). For at least two reasons, this argument does not support nonobviousness.

First, even assuming that “a long-felt need is established, evidence must show that the claimed invention satisfied that need.” *In re Gardner*, 449 F. App’x 914,

918 (Fed. Cir. 2011) (citing *In re Cavanagh*, 436 F.2d 491, 496 (C.C.P.A. 1971)). Here, Patent Owner pointed to an alleged need for an “overall survival (OS) advantage” (Ex. 1022, 12), yet Hochster II expressly acknowledges that any advantage of rituximab maintenance in that respect “d[id] not achieve statistical significance.” Ex. 1029, 5. Thus, there is no reliable evidence that the claimed invention actually satisfied the alleged long-felt need. Ex. 1002 ¶¶ 128–131.

Second, the claimed invention merely combines standard chemotherapy with rituximab, which had just become available for the first time in November 1997 with the FDA’s approval of Rituxan[™]. Given the fact that rituximab was not available before that time, any “failure of others” or “long-felt need” does not suggest that combining CVP and rituximab was nonobvious. “[O]nce another supplied the key element [of the combination], there was no long-felt need,” and ““unsuccessful attempts to reach a solution . . . before that time became wholly irrelevant.”” *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966)).

XI. CONCLUSION

For the foregoing reasons, the Board should institute *inter partes* review and cancel claim 1 of the ’172 patent as unpatentable.

Dated: December 14, 2017

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

Pursuant to 37 C.F.R. § 42.24, I certify that the foregoing PETITION FOR *INTER PARTES* REVIEW contains 13,985 words (as calculated by the word processing system used to prepare the Petition), excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

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CERTIFICATE OF SERVICE ON PATENT OWNER

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), I certify that, on December 14, 2017, true and correct copies of the foregoing PETITION FOR *INTER PARTES* REVIEW, and all Exhibits thereto, were served by overnight courier service on Patent Owner at the correspondence address of record for U.S. Patent No. 8,329,172 B2, and at another address known as likely to effect service, as follows:

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