

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. IPR2017-01166

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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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., 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) (“Rituxan™ 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 State, Low-Grade Histologic Type Non-Hodgkin’s Lymphoma,” <i>Cancer</i> , 61:441-447 (1988) (“Steward”)

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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”)
1012	Unterhalt et al., “Significant Prolongation of Disease Free Survival in Advanced Low Grade Non Hodgkin’s Lymphomas (nhl) by Interfereon Alpha Maintenance,” <i>Int’l Conf. on Malignant Lymphoma</i> (1996) (“Unterhalt”)
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 Scott Bennett, 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)

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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”)
1026	Hoppe et al., “The Treatment of Advanced Stage Favorable Histology Non-Hodgkin’s Lymphoma: A Preliminary Report of a Randomized Trial Comparing Single Agent Chemotherapy, Combination Chemotherapy, and Whole Body Irradiation,” <i>Blood</i> , 58(3):592-598 (Sept. 1981) (“Hoppe”)
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
1034	Solal-Céligny et al., “Doxorubicin-Containing Regimen With or without Interferon Alfa-2b for Advanced follicular Lymphomas,” J. Clin. Oncol., 16:2332-2338 (July 1998) (“Solal-Céligny”)
1035	Wadler et al., “New Advances in Interferon Therapy of Cancer,” The Oncologist (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):3121-7 (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)”
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)

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”). This claim is directed to a method of treating low-grade non-Hodgkin’s lymphoma (“LG-NHL”)—a type of cancer—using (1) the combination of standard chemotherapy for LG-NHL, called “CVP,” followed by maintenance therapy with the antibody rituximab, which targets the “CD20” protein on cancerous B-cells, in which the maintenance therapy is (2) administered as a dose of 375 mg/m² 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 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.

First, the combination of CVP chemotherapy and maintenance therapy with an anti-CD20 agent was taught by a printed publication that is § 102(b) prior art to the ’172 patent—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 person of ordinary skill in the art (“POSA”) at the time would have understood that this

phrase referred to chemotherapy with CVP followed by maintenance therapy (*i.e.*, treatment that prolongs the remission induced by chemotherapy) with an agent that targets CD20. Ex. 1002 ¶¶ 40–48. When the '172 patent was filed, rituximab was the *only* anti-CD20 agent that had been approved by the FDA (under the brand name Rituxan™), and its approved commercial labeling—another § 102(b) printed publication—taught that “[r]ituximab binds specifically to the antigen CD20.” Ex. 1004, 1 (“the Rituxan™ label”).

Second, the claimed dosing regimen—four weekly doses of 375 mg/m²—was likewise the *only* approved dosing regimen for rituximab at the time, and was specifically “recommended” for treating LG-NHL in the Rituxan™ label. *Id.* at 2. Independently, the label disclosed that rituximab had been clinically tested at doses ranging from 10 to 500 mg/m², and both the “serum levels” and “half-life” of rituximab were, predictably, “proportional to dose.” *Id.* at 1. Even apart from the label’s specific disclosure of 375 mg/m², the fact that the prior art “discloses a range encompassing” the claimed dose “is sufficient to establish a *prima facie* case of obviousness.” *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003).

Third, the claimed six-month frequency and two-year duration for maintenance therapy was—once again—the *only* known schedule for administering rituximab maintenance, which was explicitly disclosed in a third § 102(b) printed publication. Ex. 1003, 1 (“McNeil”). The Rituxan™ label would have motivated a

POSA to select that maintenance schedule for rituximab, because it disclosed that “B-cell recovery began at approximately *six months* following completion of treatment.” Ex. 1004, 1 (emphasis added). Thus, it would have been obvious to administer rituximab maintenance therapy at six-month intervals, when cancerous B-cells returned. Ex. 1002 ¶¶ 101–104. 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.* ¶¶ 93–99.

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) versus 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—not the difference “in kind” that is required for unexpected results to be “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, the petitioner 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 ¶¶ 80–81. 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).

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 is currently being challenged by a different petitioner in *Celltrion, Inc. v. Biogen Inc.*, IPR2017-01093, which was filed on March 15, 2017. The grounds of unpatentability asserted in IPR2017-01093 are not the same as the ground asserted by Petitioner here. In particular, Petitioner's primary reference—Hochster I—is not cited in IPR2017-01093.

The '172 patent was previously challenged by another petitioner in *Boehringer Ingelheim International GmbH v. Biogen Inc.*, IPR2015-00418. That petition was denied. The grounds of unpatentability asserted in IPR2015-00418 are not the same as the ground asserted by Petitioner here. In particular, Petitioner's primary reference—Hochster I—was not cited in IPR2015-00418.

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
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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. § 104.42, 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 ground 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); Rituxan™ label (Ex. 1004); and McNeil (Ex. 1003)

IV. 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).¹

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 meth-

¹ 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.

od 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.

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

V. 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.

VI. 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 ¶ 27.

- 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.

VII. 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.**

B-cell lymphoma 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 ¶ 30. Non-Hodgkin’s lymphoma (“NHL”) is a

type of B-cell lymphoma. *Id.* ¶ 34. “Low grade” (or “indolent”) NHL progresses more slowly than “high grade” and “intermediate grade” NHL, which are also known as “aggressive” NHL. *Id.* Low-grade NHL (“LG-NHL”) often affects “follicular” B-cells in the lymph nodes. *Id.*

Chemotherapy is the preferred first-line treatment for NHL. *Id.* ¶ 35. Typically, oncologists use a combination of chemotherapeutic drugs with different mechanisms of action in order 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.* ¶ 36. “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.* ¶ 37. 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 (discussing the “relationship between doxorubicin and the incidence of symptomatic cardiac failure,” even at low doses).

As of August 1999 (and for that matter, today), CHOP was the preferred treatment for intermediate- and high-grade lymphoma. Ex. 1002 ¶ 38. “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, Hiddemann 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.

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 ¶ 41.

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 ¶ 45. 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[idal] 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 ¶ 48.

C. Rituximab was the only approved anti-CD20 agent, and its only approved dosing regimen was 375 mg/m² as four weekly doses.

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; Ex. 1002 ¶ 49. Rituximab, also known by its code name “IDEC-C2B8,” is an antibody that binds to “CD20,” a protein that is only expressed on the surface of B-cells. Ex. 1004, 1; Ex. 1006, McLaughlin at 3. By targeting this specific protein, rituximab can selectively activate the immune system to kill only B-cells, without harming other cells in the body. Ex. 1002 ¶ 49.

As of August 1999, rituximab was the only anti-CD20 agent approved by the FDA. Ex. 1002 ¶ 50. 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.

Rituximab was approved at a single “recommended” dosing regimen of 375 mg/m² in four weekly doses. Ex. 1004, 2. As of 1998, this was the dosing “schedule that ha[d] been most extensively tested.” Ex. 1038, DeNardo at 4. Today, the 375 mg/m² dose remains the only approved rituximab dose for treating any kind of NHL. Ex. 1032, 1, 4 (current Rituxan™ label).

At this dose, it was known that “[r]ituximab was detectable in the serum of patients three to six months after completion of treatment.” Ex. 1004, 1. It was also known that “B-cell recovery began at approximately six months following

completion of treatment.” *Id.*; *see* Ex. 1006, McLaughlin at 7; Ex. 1038, DeNardo at 4 (“After treatment, B-cells return to normal levels within 6 months.”).

The Rituxan™ label as of August 1999 (which was published in November 1997) stated that “[t]here has been no experience with overdosage in human clinical trials.” Ex. 1004, 2. 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 ¶ 51.

Although rituximab was not yet approved for maintenance therapy, Maloney et al. were already advocating in 1997 that “[a]dditional areas that should be investigated using this new agent include (1) extended and repeated dosing regimens, [and] (2) combination with or after standard chemotherapy.” Ex. 1008, 7.

Soon after, in 1998, McNeil et al. reported the initiation of the first clinical trial for rituximab maintenance therapy after induction chemotherapy. Ex. 1003, 1. 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 w[ere] . . . 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 ¶¶ 65–66.

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, 2. 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.”² Ex. 1002 ¶ 54. Abstracts of presentations at the 34th annual 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, 2; 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, 5 (capitalization omitted). The pa-

² ASCO About Page, *available at* <http://am.asco.org/about>.

tients 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 ¶ 56. “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.

VIII. PRIOR ART STATUS OF CITED REFERENCES

As shown below and in the Declaration of Petitioner’s expert librarian, Dr. Scott Bennett (Ex. 1016), each of the three references that Petitioner relies upon for the ground of unpatentability asserted in this Petition—*i.e.*, Hochster I (Ex. 1005), the Rituxan™ label (Ex. 1004), and McNeil (Ex. 1003)—is a printed publication that was publicly accessible before August 11, 1998, and therefore qualifies as prior art to the ’172 patent under 35 U.S.C. § 102(b). *See In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004) (“public accessibility has been the criterion by which a prior art reference will be judged for the purposes of § 102(b)”).

A. Hochster I (Ex. 1005)

First, as Dr. Bennett shows, 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). Ex. 1016 ¶¶ 37–41. 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.* ¶ 43. The attendees of the meeting included numerous oncologists with experience treating NHL patients. Ex. 1002 ¶ 54. Indeed, ASCO’s annual meeting was well known to persons of ordinary skill as of August 1998, many of whom would have attended it in person. *Id.*

Public records indicate that the program proceedings of ASCO’s meetings, including the Hochster I excerpt, are held by 154 libraries worldwide, where they were cataloged and indexed by subject matter such that members of the public—including ordinarily skilled artisans exercising reasonable diligence—would have had no difficulty finding copies of the program proceedings. Ex. 1016 ¶ 45; *see In re Wyer*, 655 F.2d 221, 226 (C.C.P.A. 1981) (reference is publicly accessible as prior art where it is “disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it”) (quotation omitted).

In particular, Hochster I includes a date stamp printed with the words: “BIOMEDICAL LIBRARY”, “JUL 22 1998”, and “UNIVERSITY OF CALIFORNIA LOS ANGELES”. Ex. 1005, 2; Ex. 1016 ¶ 46. Based on 50 years of experience as a professional librarian, Dr. Bennett affirms that this date stamp has the general appearance of date stamps that libraries have long affixed to periodicals and series publications, and there is no indication or reason to believe that the date stamp was affixed by anyone other than UCLA’s library personnel, or on any date other than the stamped date of July 22, 1998. Ex. 1016 ¶ 46.

Therefore, allowing for as much as two or three weeks between this date stamp and its appearance on library shelves, where it would have been publicly accessible, Hochster I was available to the public before August 11, 1998. *Id.* ¶¶ 47–48; *see also In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986) (finding that, where only a reference’s receipt date was available, affidavit regarding “general library procedure as to indexing, cataloging, and shelving . . . in estimating the time it would have taken to make the [reference] available to the interested public” was “competent . . . [and] persuasive evidence that the [reference] was accessible prior to the critical date” as a § 102(b) printed publication).

Accordingly, Hochster I is prior art to the ’172 patent as a publicly accessible printed publication under 35 U.S.C. § 102(b).

B. Rituxan™ label (Ex. 1004)

Second, the Rituxan™ label 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 ¶¶ 49–53. As Dr. Bennett confirms, the Rituxan™ 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.* ¶ 50.³

Furthermore, the well-known “Internet Archive” service shows that the Rituxan™ label was available on the website of Genentech, which markets Rituxan™, as of January 23, 1998. *Id.* ¶ 51. The Internet Archive is a non-profit digital library founded in 1996 that maintains an archive of webpages collected from the internet by automated “crawlers.” *Id.* ¶¶ 23–24. The archived webpages are available for search and retrieval through an interface called the “Wayback Machine,” which renders accurate snapshots of webpages as they existed at the time they were collected. *Id.* ¶¶ 24–27. Based on the Rituxan™ label’s appearance in the Internet Archive as of January 23, 1998, it is clear that public internet search engines at the time would have been able to find and index the Rituxan™ label, and that a POSA

³ The Rituxan™ label as of November 1997 can be located by searching the *Drugs@FDA: FDA Approved Drug Products* database at <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>.

exercising reasonable diligence and using typical internet search tools would have readily found a copy of it. *Id.* ¶ 51; *see also, 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”).

Moreover, a paper by third-party researchers published in November 1998 lists the Rituxan[™] label as a reference. Ex. 1016 ¶ 52. Given the time that is generally required to research and write a paper, to submit it and have it reviewed, and to have it published, the paper was reasonably in preparation prior to August 1998, which further confirms that the Rituxan[™] label was accessible in the public domain and in use before that time. *Id.* ¶¶ 52–53.

In addition, the Rituxan[™] label’s authenticity is evident from the 1999 edition of the *Physician’s Desk Reference*[®] (“PDR”), 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 2) contains the same labeling information as the Rituxan[™] label. *Compare* Ex. 1004 *with* Ex. 1039, 6–11. In any event, the relevant information cited below from the Rituxan[™] label (*e.g.*, the dosage regimen of “4 weekly doses of 375 mg/m²”) was also publicly available in the Maloney paper, which was published in September 1997. Ex. 1008, 1.

Accordingly, the Rituxan™ label is prior art to the '172 patent as a publicly accessible printed publication under 35 U.S.C. § 102(b).

C. McNeil (Ex. 1003)

Third, 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*. Ex. 1016 ¶¶ 54–58. Public records confirm that the *Journal* is a periodical that was first published in 1940 and is held by 1,302 libraries worldwide. *Id.* ¶ 59. The *Journal* has long been cataloged or indexed in a meaningful way, including by subject matter. *Id.* Thus, it is—and was—sufficiently accessible to the public interested in the art, and an ordinarily skilled researcher or artisan, exercising reasonable diligence, would have had no difficulty finding copies of it. *Id.*

A date stamp from the University of Illinois at Urbana-Champaign Library indicates that the February 18, 1998, issue of the *Journal of the National Cancer Institute*, which contains McNeil, was processed by that library on March 13, 1998. *Id.* ¶ 60. This date stamp has the general appearance of date stamps that libraries have long affixed to periodicals in processing them, and there is no indication or reason to believe this date label was affixed by anyone other than library personnel, or on any date other than March 13, 1998. *Id.* Therefore, allowing for as much as two or three weeks between this date stamp and its appearance on library

shelves, where it would have been publicly accessible, McNeil was available to the public before August 11, 1998. *Id.* ¶¶ 61–62.

Accordingly, McNeil is prior art to the '172 patent as a publicly accessible printed publication under 35 U.S.C. § 102(b).

IX. 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 *prima facie* obvious to a POSA as of August 1999 over Hochster I (Ex. 1005) in view of the Rituxan™ label (Ex. 1004) and McNeil (Ex. 1003). 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 canceled.

A. Claim 1 is *prima facie* obvious over Hochster I (Ex. 1005) in view of the Rituxan™ label (Ex. 1004) and McNeil (Ex. 1003).

Claim 1 of the '172 patent is directed to the following method of treatment, with bracketed numbers added to delineate the three limitations in the body of the claim: “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, the Rituxan™ label, and McNeil, and these references further provided a reason for a POSA as of August 1999 to combine the limitations in the manner claimed with a reasonable expectation of success, particularly considering the knowledge available to such a person as outlined above.

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, 5 (capitalization omitted); Ex. 1002 ¶ 55. “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, 5 (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 induc-

tion 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 ¶ 71. 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.* ¶ 72.

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 admin-

istered “*after the patient has responded to the chemotherapy consisting of CVP therapy.*” *Id.* at 23 (emphasis added). Dr. Ozer agrees. Ex. 1002 ¶ 73.

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.* ¶ 74.

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, at least because rituximab was the *only* anti-CD20 agent that had been approved by the FDA as of August 1999. Ex. 1002 ¶ 75. Indeed, the very 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). 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).” *Id.* at 1 (emphasis added).

McNeil likewise confirms that “Rituxan . . . targets the B-cell protein CD20.” Ex. 1003, 1. Moreover, this understanding is consistent with contempora-

neous disclosures describing the “*anti-CD20* monoclonal antibody, *Rituximab*.” Ex. 1006, McLaughlin at 3 (emphasis added); Ex. 1008, Maloney at 1 (same); Ex. 1002 ¶ 77. A POSA would have understood these disclosures to mean that rituximab is an anti-CD20 agent. Ex. 1002 ¶ 77. Therefore, the prior art would have led a POSA straight to rituximab. *Id.* ¶ 78.

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.* ¶ 79. Accordingly, a POSA would have been motivated to use rituximab, which was well known to target CD20 and was the only approved agent for doing so, for the “anti-CD20 maintenance” following CVP induction disclosed in Hochster I. Ex. 1002 ¶¶ 78–79.

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.* ¶ 80. 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, 5. 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 “in-
itiat[ion] of human clinical trials . . . is reasonably predictive” even before any results are obtained. *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 refer-

enced 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. *Montgomery*, 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 the Rituxan™ label, 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 ¶¶ 81–83.

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 ¶ 83. 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 *only* approved dosing regimen for rituximab.

As of August 1999, only *one* dosing regimen had been approved by the FDA for rituximab. *Id.* This was the regimen expressly disclosed in the Rituxan™ label, which taught that “[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). The Rituxan™ label further cited multiple clinical trials establishing the safety and efficacy of this exact dosing regimen. *Id.* at 1–2; Ex. 1002 ¶ 85; *see also* Ex. 1008.

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 the already-approved and clinically proven dosing regimen that was explicitly “recommended” by the Rituxan™ label for LG-NHL. Ex. 1002 ¶ 87.

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.

At a minimum, the claimed four weekly doses of 375 mg/m²—the only approved dosing regimen for rituximab as of August 1999—would have been at least

obvious to try. Ex. 1002 ¶ 87. “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 and 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 approved 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, the only known approved dosing regimen for rituximab—*i.e.*, 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 ¶¶ 87–92. *See also Hoffman-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 *prima facie* obvious.

Independently, even apart from the Rituxan™ label’s specific disclosure and “recommend[ation]” of 375 mg/m² for LG-NHL, the label also disclosed a range that includes this dose. Ex. 1002 ¶ 88. Specifically, the label disclosed that rituximab “doses [of] 10, 50, 100, 250 [and] 500 mg/m²” had also been tested in human patients, and, predictably, “serum levels and the half-life of Rituximab were proportional to [the] dose.” Ex. 1004, 1; *see* Ex. 1008, 2. This disclosure, too, would have provided a POSA with a reason to use the claimed dose. Ex. 1002 ¶ 88.

“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 over-

lapping 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 at 1330. 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 ¶ 90. On the contrary, the FDA-approved Rituxan™ label expressly “recommended” that regimen. Ex. 1004, 2. 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, the Rituxan[™] label teaches that “[t]here has been no experience with overdosage in human clinical trials,” even at a higher “500 mg/m²” dose. Ex. 1004, 2; Ex. 1002 ¶ 91; *see also* Ex. 1008, Maloney at 1 (“doses up to 500 mg/m² . . . showed clinical responses with no dose-limiting toxicity”). Certainly 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 ¶ 91.

Nor is there any evidence of unexpected results or other pertinent secondary considerations related to the claimed dosing regimen. Ex. 1002 ¶ 90. 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 IX.B.

Thus, in view of the Rituxan[™] label, 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 ¶ 92.

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.* ¶ 93. 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, 1 (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 ¶¶ 95–99. 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 the Rituxan[™] label taught that “[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; *see also* Ex. 1008, 6.

In other words, the Rituxan[™] label disclosed that rituximab, after administration at four weekly doses of 375 mg/m², remained detectable in the blood for up to six months, and that B-cells likewise began building up again after six months. Ex. 1002 ¶ 95. Thus, a POSA would have been motivated to re-administer rituximab maintenance therapy every six months, because that was how long it took for rituximab to leave the human body and for the target of rituximab therapy—*i.e.*, cancerous B-cells—to recover in patients with LG-NHL. *Id.* ¶¶ 99, 103.⁴

⁴ 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, 1. And logically, it would have been obvious to prolong remission (and therefore survival of the patient) for as long as possible. Ex. 1002 ¶ 96. 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 ¶¶ 96–98.

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.* ¶ 100.

d. 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 VII.C, IX.A.3.a; Ex. 1002 ¶ 103.

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.* ¶ 104.

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, 2). Again, McNeil was referring to treatment for *intermediate*-grade NHL, which differs from LG-NHL, where less potent chemotherapy—CVP—is preferred. Ex. 1002 ¶ 107; *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 LH-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 1195, 1201 (Fed. Cir. 2004).

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 IX.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 ¶¶ 108–109. *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 the 1997 Rituxan™ label disclosed that rituximab was a suitable anti-CD20 agent—indeed, it was the *only* anti-CD20 agent that had been approved by the FDA as of August 1999. The Rituxan™ label also disclosed the *only* “recommended” dosing regimen for rituximab therapy of 375 mg/m² in four weekly doses. And McNeil 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 *prima facie* obvious.

B. 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 *prima facie* obviousness discussed above. Ex. 1002 ¶ 110. 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 Pharms. Inc. v. Allergan, Inc.*, IPR2016-01127, Paper 8 at 18 n.4 (PTAB Dec. 8, 2016); *Amneal Pharms., LLC v. Supernus Pharms., 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 ¶ 113.

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 ¶¶ 113–114.

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.* ¶ 114. 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 ¶¶ 114–115. 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 ¶¶ 116–117. *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 ¶ 116. 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. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014).

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 (Fed. Cir. 2014). “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 ¶ 116.

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 four 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 ¶¶ 118–122.

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)).

Third, the claimed combination of CVP induction and anti-CD20 maintenance therapy was *known*—it was disclosed in Hochster I. While the final results of the disclosed study were not yet available, the method itself was. Indeed, the only support in the ’172 patent for the claimed method is the same disclosure of the same clinical trial in Hochster I, without any clinical data or final results. That is fatal to any allegation of long-felt need: “Where the differences between the prior art and the claimed invention are as minimal as they are here [], it cannot be said

that any long-felt need was unsolved.” *Geo. M. Martin Co. v. Alliance Mach. Sys. Int’l LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010).

Fourth, the patent claiming the genetic sequence for rituximab—U.S. Patent No. 5,736,137 (“the ’137 patent”)—issued on April 7, 1998, and did not expire until 2015. Ex. 1040. This patent, which was assigned to Patent Owner, legally precluded others from developing the method claimed in the ’172 patent as of August 1999. *See* 35 U.S.C. § 271(a). It follows that any “evidence relating to the ‘failure of others,’ a[nd] ‘long-felt but unsolved need,’ . . . is undermined by the fact that those phenomena—to the extent they exist in this case—could have been derived from [Patent Owner’s] ownership of [the ’137 patent] patent as much as from the nonobviousness of [the claimed invention].” *Sanofi-Synthelabo v. Apotex Inc.*, 492 F. Supp. 2d 353, 392 (S.D.N.Y. 2007), *aff’d*, 550 F.3d 1075 (Fed. Cir. 2008).

X. CONCLUSION

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

Dated: April 21, 2017

Respectfully submitted,

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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 11,859 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).

Dated: April 21, 2017

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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 April 21, 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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