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Paper 14
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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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BOEHRINGER INGELHEIM INTERNATIONAL GMBH and
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.,
Petitioners,
v.

BIOGEN INC.,
Patent Owner.

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Case IPR2015-00418
Patent 8,329,172 B2

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Before FRANCISCO C. PRATS, ERICA A. FRANKLIN, and SHERIDAN K. SNEDDEN, *Administrative Patent Judges.*

PRATS, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

## I. INTRODUCTION

### *A. Statement of the Case*

Boehringer Ingelheim International GmbH and Boehringer Ingelheim Pharmaceuticals, Inc. (collectively, "Petitioner") filed a Petition (Paper 3, "Pet.") requesting *inter partes* review of claim 1, the sole claim of U.S. Patent No. 8,329,172 B2 (Ex. 1001, "the '172 patent"). Biogen Inc. ("Patent

Owner") filed a Preliminary Response. Paper 11 ("Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 314.

An *inter partes* review may be instituted only if "the information presented in the [Petition and Preliminary Response] shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Upon consideration of the Petition and Preliminary Response, we conclude that Petitioner has not established a reasonable likelihood that it would prevail in its challenges to claim 1 of the '172 patent. Accordingly, we decline to institute an *inter partes* review.

*B. Related Proceedings*

The parties identify no related proceedings that would affect, or be affected by, the instant case. *See* Paper 13, 2; Pet. 5.

*C. Proposed Grounds of Unpatentability*

Petitioner contends that claim 1 of the '172 patent is unpatentable based on the following specific grounds (Pet. iii, 38–56):[1]

| Reference[s] | Basis |
|---|---|
| ECOG 1496[2] | § 102(b) |

[1] Petitioner supports its challenge with a Declaration, executed December 5, 2014, by Michael L. Grossbard, M.D. ("Grossbard Decl.") (Ex. 1002).

[2] Eastern Cooperative Oncology Group E1496, *Randomized Phase III Study in Low Grade Lymphoma Comparing Cyclophosphamide/Fludarabine to Standard Therapy Followed by Maintenance Anti-CD20 Antibody*, (Howard Hochster et al. study chairs, Activation Date March 1998) (Ex. 1003).

| | |
|---|---|
| ECOG 4494[3] | § 103 |
| ECOG 4494, Unterhalt[4] | § 103 |
| ECOG 4494, the FDA Transcript[5] | § 103 |
| McNeil[6] | § 103 |
| McNeil, the 1997 Rituxan® Label[7] | § 103 |
| McNeil, the 1997 Rituxan® Label, Unterhalt | § 103 |
| McNeil, the 1997 Rituxan® Label, the FDA Transcript | § 103 |
| McLaughlin[8] | § 103 |
| McLaughlin, McNeil | § 103 |

[3] Eastern Cooperative Oncology Group E4494/Cancer and Leukemia Group B CALGB 9793, *Phase III Trial of CHOP versus CHOP and Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C288) in Older Patients with Diffuse Mixed, Diffuse Large Cell and lmmunoblastic Large Cell Histology Non-Hodgkin's Lymphoma* (Thomas Habermann et al. study chairs, Activation Date December 1997) (Ex. 1004).

[4] M. Unterhalt et al., *Significant Prolongation of Disease Free Survival in Advanced Low Grade Non Hodgkin's Lymphomas (nhl) by Interferon Alpha Maintenance*, 7 ANNALS OF ONCOLOGY 229 (Supp. 3 1996) (Ex. 1006).

[5] Transcript of Proceedings, Nineteenth Meeting, Biological Response Modifiers Advisory Committee, Department of Health and Human Services, Food and Drug Administration (July 25, 1997) (Ex. 1007).

[6] Caroline McNeil, *Non-Hodgkin's Lymphoma Trials In Elderly Look Beyond CHOP*, 90 J. NAT. CANCER INST. 266–67 (1998) (Ex. 1005).

[7] Rituxan® Product Label (1997) (Ex. 1008).

[8] Peter McLaughlin et al., *Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose· Treatment Program*, 16 J. CLIN. ONCOL. 2825–2833 (1998) (Ex. 1009).

*D. The '172 Patent*

The '172 patent describes treating B-cell lymphomas with anti-CD20 antibodies combined other therapeutic regimens, such as chemotherapy. Ex. 1001, 2:7–38. The '172 patent explains that CD20 is a B-cell-restricted differentiation antigen that is usually expressed at very high levels on cancerous B-cells, and is "appealing for targeted therapy, because it does not shed, modulate, or internalize." *Id.* at 1:33–41. The '172 patent explains that a preferred anti-CD20 antibody "is C2B8 (IDEC Pharmaceuticals, Rituximab)." *Id.* at 2:59–60.

The '172 discloses that rituximab, also known as "RITUXAN®" has been approved for use in relapsed and previously treated low-grade non-Hodgkin's lymphoma (LG-NHL), but that such patients may nonetheless still be subject to disease relapse. *Id.* at 1:47–58. Therefore, the '172 patent advises, "it would be advantageous if anti-CD20 antibodies had a beneficial effect in combination with other lymphoma treatments, and if new combined therapeutic regimens could be developed to lessen the likelihood or frequency of relapse." *Id.* at 1:60–64.

Claim 1, the only claim in the '172 patent, 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 $mg/m^2$ every 6 months, and wherein the maintenance therapy is provided for 2 years.

Ex. 1001, 22:56–63.

## II. ANALYSIS

### *A. Claim Construction*

The Board interprets claims in an unexpired patent using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, No. 2014-1301, slip op. at 10–19 (Fed. Cir. 2015). Under that standard, claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Based on our review of the Petition and Preliminary Response, we conclude that, for the purposes of this decision, the following claim terms warrant construction:

#### *1. "chemotherapy consisting of CVP therapy"*

Although the Specification of the '172 patent refers to "standard CVP therapy" (Ex. 1001, 13:10), the patent does not explain precisely what CVP therapy is. Both parties agree, however, that CVP therapy is 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. *See* Pet. 17; Prelim. Resp. viii.

The "consisting of" language used in connection with the CVP therapy limits the chemotherapeutic portion of the claimed regimen to only the CVP treatment, to the exclusion of other agents. *See AFG Indus., Inc. v. Cardinal IG Co., Inc.*, 239 F.3d 1239, 1245 (Fed. Cir. 2001) ("'[C]losed' transition phrases such as 'consisting of' are understood to exclude any elements, steps, or ingredients not specified in the claim.").

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

Petitioner contends that "'maintenance therapy' refers to administering rituximab after 'chemotherapy consisting of CVP' for the purpose of treating the patient's [minimal residual disease] MRD (for patients who responded with CR), prolonging remission, and/or to prevent relapse." Pet. 14. Patent Owner contends that Petitioner's proposed construction is "plainly incorrect insofar as it is read to encompass administering rituximab to treat relapsed disease. As [Petitioner] acknowledges, 'maintenance therapy' is therapy used for 'prolonging remission' and 'to prevent relapse.'" Prelim. Resp. 14.

We do not view the parties' proposed constructions being necessarily at odds. Nonetheless, for clarity, we construe claim 1 as requiring administration of CVP therapy, to which the patient responds according to the criteria set forth in the '172 patent. *See* Ex. 1001, 9:14–23 (the '172 patent providing specific criteria for a complete response (CR) and a partial response (PR) and distinguishing such patients from "non-responders"). The CVP must be followed at some time by the rituximab maintenance therapy, with no disease relapse occurring between the patient's response to the CVP therapy and the maintenance therapy.

*B. Effective Filing Date of Claimed Subject Matter*

Petitioner contends that the subject matter of claim 1 does not find support in the provisional application to which '172 patent claims priority.

Pet. 8–10. Accordingly, Petitioner argues, the effective filing date of the claimed subject matter at issue here is August 11, 1999. *Id.* at 9–10.[9]

Patent Owner, "[f]or simplicity in [its] Preliminary Response only, . . . will assume that the priority date is the non-provisional filing date of August 11, 1999, without waiving its right to argue otherwise later." Prelim. Resp. 8. Accordingly, for the purposes of this decision, we accord the subject matter of claim 1 of the '172 patent an effective filing date of August 11, 1999.

*C. Whether ECOG 1496 (Ex. 1003) and ECOG 4494 (Ex. 1004) Are Printed Publications*

Petitioner contends that ECOG 1496 and ECOG 4494 are published protocols of clinical trials for cancer treatments which are prior art under 35 U.S.C. § 102(b).[10] Pet. 28–31. Patent Owner contends that Petitioner has failed to show that either reference is a printed publication upon which unpatentability may be established in an *inter partes* review. Prelim. Resp. 1–3, 15–30.

Petitioner may challenge the patentability of a claim "only on the basis of prior art consisting of patents or printed publications." 35 U.S.C. § 311(b); *see also* 35 U.S.C. § 102(b) ("A person shall be entitled to a patent unless . . . the invention was patented or described in a *printed publication* in

[9] The '172 patent claims priority to a pair of continuation applications, the earliest of which was filed August 11, 1999. Ex. 1001, 1:9–12.

[10] Because the effective filing date of the claimed subject matter is August 11, 1999, § 102(b), in effect before the Leahy-Smith America Invents Act (AIA), applies to the claims of the '415 patent. *See* AIA, Public Law 112-29, § 3, 125 Stat. 288.

this or a foreign country . . . more than one year prior to the date of the application for patent . . . .") (emphasis added).

The Federal Circuit has held that "public accessibility" is "the touchstone" in determining whether a reference is a printed publication. *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986). "A given reference is 'publicly accessible' upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) (quoting *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006)).

We agree with Patent Owner that Petitioner has not shown that either ECOG 1496 or ECOG 4494 was publicly accessible to the extent required to establish its status as a printed publication under either § 311(b) or § 102(b).

ECOG 1496 is a document describing the protocol for a study by the Eastern Cooperative Oncology Group (ECOG) of a treatment for low-grade lymphoma. *See* Ex. 1003, generally. The cover letter to the study, dated March 19, 1998, indicates that the study was then active, and the cover page indicates a study activation date of March 1998. *Id.* at 1, 2.

ECOG 4494 is a document describing the protocol for a study, by the same cooperative group, of a treatment for older patients with diffuse mixed, diffuse large cell and immunoblastic large cell histology non-Hodgkin's lymphoma. *See* Ex. 1004, generally. The cover letter to the study, dated December 12, 1997, indicates that the study was then active, and the cover page indicates a study activation date of December 1997. *Id.* at 1, 2.

The ECOG is a cooperative group, funded primarily by the National Cancer Institute (NCI), composed of a large network of researchers, physicians, and health care professionals at public and private institutions across the country, and in other countries, which performs multicenter cancer clinical trials. Pet. 29 (citing Ex. 1051 (ECOG website list of member institutions));[11] Ex 2011, 2 (full ECOG website archived December 12, 1998).[12] Petitioner notes that on May 19, 1998, the ECOG website listed ECOG 1496 and ECOG 4494 as active trials. Pet. 28 (citing Ex. 1022 (ECOG website list of protocols active as of May 19, 1998))).[13]

Petitioner contends that, because those trial protocols were designated as active, the ECOG could provide them to member institutions, and physicians at ECOG institutions, in turn, could discuss the protocols freely, distribute them to other physicians and patients, obtain informed consent from patients, and enroll patients in the clinical trial. *Id.* at 28–29 (citing Ex. 1002 ¶ 98 (Grossbard Decl.)). Petitioner contends further that ECOG 1496 and ECOG 4494 "were distributed to all members of the cooperative shortly after activation and before May 19, 1998, with no confidentiality restrictions." *Id.* at 29 (citing Ex. 1002 ¶¶ 99–106).

Petitioner, however, presents no direct evidence from the ECOG, or from anyone directly associated with the ECOG, explaining specifically

[11] http://web.archive.org/web/19980519084032/http://ecog.dfci.harvard.edu/~ecogdba/general/insts_byname.html (archived May 19, 1998) (Ex. 1051).

[12] https://web.archive.org/web/19981212013740/http:/ecog.dfci.harvard.edu (Ex. 2011).

[13] https://web.archive.org/web/19980519084342/http://ecog.dfci.harvard.edu/~ecogdba/active_reports/Lymphoma.html (archived May 19, 1998) (Ex. 1022).

whether or how ECOG 1496 and ECOG 4494 were distributed, or whether the protocols were under confidentiality restrictions. Nor does Petitioner advance such firsthand evidence to support its contention that the ECOG protocols were actually disseminated to all members of the cooperative without confidentiality restrictions. Petitioner, moreover, does not explain how or where it obtained the ECOG protocols.

Instead, to support its contentions, Petitioner relies extensively on the explanation in paragraphs 98 through 106 of Dr. Grossbard's Declaration, and presents little of the discussion and evidence in those paragraphs of the Declaration in the Petition itself. *See id.* at 28–30.

We decline to import the extensive discussion about the public accessibility of the ECOG protocols from Dr. Grossbard's Declaration into the Petition, based solely on the Petition's citation of certain paragraphs within the Declaration. As stated in 37 C.F.R. § 42.6(a)(3), "[a]rguments must not be incorporated by reference from one document into another document." We agree with our colleagues' reasoning in *Conopco, Inc. v. The Procter & Gamble Company*, in that "[w]e decline to consider information presented in a supporting declaration, but not discussed in a petition, because, among other reasons, doing so would encourage the use of declarations to circumvent the page limits that apply to petitions." IPR2013-00510, slip op. at 8 (PTAB February 12, 2014) (Paper 9).

Further, even considering the Petition as having presented Dr. Grossbard's discussion, we would not find Petitioner's contentions regarding public accessibility persuasive. Dr. Grossbard primarily bases his assertions on his experience, including as a principal investigator, in cooperative groups similar to, but distinct from, the ECOG. Ex. 1002 ¶¶ 99–100. Based

on that experience, Dr. Grossbard testifies that clinical trial protocols are "*typically* not provided to members of the cooperative under any confidentiality restrictions." *Id.* ¶ 99 (emphasis added).

Because he does not assert any firsthand knowledge of how, specifically, the ECOG protocols at issue here were distributed, Dr. Grossbard, at best, surmises that because clinical trial protocols were "typically" widely disseminated without confidentiality restrictions in his experiences with similar trials in similar groups (*id.* ¶¶ 99–100), the ECOG protocols at issue here necessarily were disseminated in the same way. We decline to recognize ECOG 1496 and ECOG 4494 as printed publications based merely on Dr. Grossbard's suppositions, even given his substantial credentials. *See* Ex. 1002 ¶¶ 3–16, Exhibit A (Dr. Grossbard's background and CV).

In the absence of specific firsthand knowledge about whether or how ECOG 1496 and ECOG 4494 were distributed, and the conditions of that distribution, that clinical trial protocols of that type "typically" may have been widely distributed without confidentiality restrictions does not persuade us that the specific documents at issue here were actually distributed in that manner. To that end, as Patent Owner contends, the NCI, which funds the ECOG trials, has established guidelines for maintaining confidentiality in trials using investigational agents that are proprietary to a pharmaceutical or biotech company. Prelim. Resp. 22 (citing Ex. 2013 (NCI - Cooperative Group - Industry Relationship Guidelines) ("All protocol documents, including Investigator's Brochures, for studies utilizing investigational agents under a collaborative agreement are also confidential

and must not be shared or distributed without the permission of the NCI.")).[14]

We acknowledge that the McNeil article, which was published February 18, 1998, discussed details of the ECOG 4494 study. *See* Ex. 1005, 266. That fact does not persuade us, however, that the actual document asserted by Petitioner as being the printed publication, ECOG 4494, was disseminated publicly or otherwise made available such that ordinarily skilled and interested persons exercising reasonable diligence would have been able to locate it, as of McNeil's publication date. In particular, Petitioner does not direct us to any specific mention in the McNeil article of either the ECOG, or of the ECOG 4494 protocol. For similar reasons, Petitioner does not persuade us that the White article[15] establishes that ECOG 1496 was publicly accessible, as Dr. Grossbard asserts. *See* Ex. 1002 ¶ 102. Moreover, Petitioner does not explain whether or how the White article constitutes prior art to the subject matter at issue here.

Petitioner also fails to direct us to clear or specific evidence supporting its assertion that the ECOG protocols submitted as Exhibits 1003 and 1004 would have been obtainable by simply searching the ECOG website or the PDQ database for clinical trials pertaining to rituximab before the critical date. *See* Pet. 29 (citing Ex. 1053 (PDQ database)).[16] Although

[14] http://ctep.cancer.gov/industryCollaborations2/guidelines.htm (Ex. 2013).

[15] Christine A. White, M.D., *Rituximab Immunotherapy for Non-Hodgkin's Lymphoma*, 14 CANCER BIOTHERAPY & RADIOPHARMACEUTICALS 241–250 (1999) (Ex. 1052).

[16] http://web.archive.org/web/19980116194104/http://cancernet.nci.nih.gov/pdq.htm (archived Jan. 16, 1998) (Ex. 1053).

we note that the archived ECOG website lists ECOG 1496 and ECOG 4494 among active trials (Ex. 1022), Petitioner does not direct us to where the website provided access to the actual protocols for those trials submitted as Exhibits 1003 and 1004. Rather, as Patent Owner contends (Prelim. Resp. 18–19, 22–23), the ECOG protocol listings are not in the form of hyperlinks (*see* Ex. 1022), the full archived website does not otherwise appear to contain the protocols at issue or links to them (*see* Ex. 2011, generally), the archived website lists the search function as "not yet available" (*id.* at 107), and the link to the ECOG members portion of the website indicates that a password is required for entry (*id.* at 2).

As to the PDQ database, we acknowledge the NCI website's description of the "PDQ" as "NCI's Comprehensive Cancer Database." Ex. 1053, 1. We acknowledge also the website's statement that the PDQ contains more than 1,600 summaries of trials that are open or approved for patient accrual, that "[y]ou can retrieve protocols by diagnosis, treatment modality, phase, locality or drug name, or a combination of these parameters," and that "[a]ll protocols supported by the NCI are listed in PDQ." *Id.* Petitioner, however, does not direct us to any specific entry in the PDQ database that would have provided unrestricted access to the actual documents Petitioner contends are printed publications, the ECOG protocols submitted as Exhibits 1003 and 1004. Nor has Petitioner directed us to clear or specific evidence suggesting that the PDQ database was accessible to ordinarily skilled and interested persons exercising reasonable diligence. Moreover, that the PDQ database may have included summaries of the protocols for ECOG 1496 and ECOG 4494 does not persuade us that the

actual documents Petitioner contends are printed publications were accessible without restriction.

In sum, for at least the reasons discussed, Petitioner does not persuade us that the actual documents asserted as being printed publications, the ECOG 1496 and ECOG 4494 protocols submitted as Exhibits 1003 and 1004, respectively, were disseminated publicly or otherwise made available such that ordinarily skilled and interested persons exercising reasonable diligence would have been able to locate and gain access to them, as of the critical date. Accordingly, we are not persuaded that Petitioner has shown that ECOG 1496 and ECOG 4494 were printed publications for the purposes of 35 U.S.C. §§ 102(b) and 311(b).

*D. Challenges Based on ECOG 1496 (Ex. 1003) and ECOG 4494 (Ex. 1004)*

Petitioner bases its first four challenges to claim 1 of the '172 patent solely, or in part, on ECOG 1496 and ECOG 4494. Pet. iii, 38–42. In view of our determination that Petitioner has not shown that those references are printed publications upon which we may institute an *inter partes* review, we determine further that Petitioner has not established a reasonable likelihood of prevailing as to those grounds.

*E. Obviousness—McNeil (Ex. 1005)*

Petitioner contends that McNeil reports on the ECOG 4494 clinical trial. Pet. 42. Therefore, Petitioner contends, for the same reasons advanced as to ECOG 4494, "it would have been obvious to those of ordinary skill to use the protocol described in McNeil to treat LG-NHL, and it further would have been obvious to do so using standard CVP induction therapy, instead of CHOP [cyclophosphamide, vincristine, doxorubicin, and prednisone], to treat LG-NHL." Pet. 43.

Petitioner does not persuade us that it has established a reasonable likelihood of prevailing as to this ground of unpatentability.

Section 103(a) of Title 35 states:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

When evaluating obviousness under § 103(a), under the controlling inquiry, "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *KSR Int' l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007) (quoting *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966)).

McNeil describes a clinical trial for elderly patients with intermediate-grade non-Hodgkin's lymphoma (IG-NHL) in which patients who responded to CHOP chemotherapy, "the standard chemotherapy for this form of NHL," were "assigned to receive [a] maintenance regimen – Rituxan every 6 months for 2 years - or observation." Ex. 1005, 266.

We agree with Patent Owner that McNeil differs from claim 1 of the '172 patent in at least three respects: (1) McNeil treats patients with intermediate grade NHL (IG-NHL), rather than the low grade NHL (LG-NHL) treated in claim 1, (2) McNeil does not teach rituximab maintenance therapy following CVP induction therapy as required by claim 1, but instead teaches CHOP induction therapy, and (3) McNeil is silent as to the dosing for maintenance therapy and, therefore, does not teach claim 1's rituximab

maintenance regimen of four weekly doses of 375 mg/m$^2$. *See* Prelim. Resp. 31.

Although Petitioner advances this ground of unpatentability as based on McNeil alone, Petitioner relies on a significant number of additional references to explain why claim 1 of the '172 patent would have been obvious over McNeil, despite the differences between the claimed subject matter and McNeil. Specifically, to show that an ordinary artisan would have been motivated to use rituximab maintenance therapy to treat patients with LG-NHL as required by claim 1, as opposed to the IG-NHL treated in McNeil, Petitioner cites two references authored by Maloney,[17,18] the McLaughlin reference, and refers to "others," as having "encouraged the use of rituximab maintenance therapy to treat the residual disease remaining after chemotherapy in LG-NHL patients." Pet. 39 (citing Ex. 1038, 3273; Ex. 1046, 2465; Ex. 1009, 2831; Ex. 1002 ¶ 124).

Moreover, to show that an ordinary artisan would have considered maintenance therapy an effective way to treat LG-NHL, Petitioner additionally cites Unterhalt for its disclosure of interferon maintenance therapy for LG-NHL. *Id.* (citing Ex. 1006). Petitioner further cites two articles by Avilés[19,20] to show that, because interferon maintenance therapy

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[17] David G. Maloney et al., *IDEC-C2B8: Results of a Phase I Multiple-Dose Trial in Patients With Relapsed Non-Hodgkin's Lymphoma*, 15 J. CLIN. ONCOL. 3266-3274 (1997) (Ex. 1038).

[18] D.G. Maloney et al., *Phase 1 Clinical Trial Using Escalating Single-Dose Infusion of Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients With Recurrent B-Cell Lymphoma*, 84 BLOOD 2457-2466 (1994) (Ex. 1046).

[19] Augustín Avilés et al., *Maintenance Therapy with Interferon Alfa 2b in Patients with Diffuse Large Cell Lymphoma*, 10 INVESTIGATIONAL NEW

had been tested in more aggressive NHL before LG-NHL trials were conducted, precedent existed "for adapting more aggressive NHL therapies for the treatment of LG-NHL." *Id.* Petitioner cites the Hiddemann reference,[21] to explain that an ordinary artisan would have been motivated to substitute CVP for CHOP because CVP had lower toxicity and was therefore a standard induction therapy for LG-NHL. *Id.* (citing Ex. 1011). Lastly, to address McNeil's failure to describe the dosage of rituximab administered to its IG-NHL patients, Petitioner cites the Rituxan® label as disclosing the dosage regimen required by claim 1 of the '172 patent. *Id.* at 43.

Petitioner, thus, represents this challenge as based on McNeil alone (*see* Pet. iii, 43, 44), yet relies on at least eight additional references to explain why claim 1 of the '172 patent would have been obvious over McNeil. Petitioner, therefore, fails to comply with 37 C.F.R § 42.104(b)(2), which requires Petitioner to identify "the patents or printed publications relied upon for each ground."

Moreover, although Petitioner directs us to specific portions of the Maloney references and McLaughlin (Pet. 39), Petitioner does not identify, in either reference, the specific teachings in those references Petitioner relies upon to support its assertion that the references encourage rituximab maintenance therapy in LG-NHL patients. Nor does Petitioner explain *why*

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DRUGS 351-355 (1992) (Ex. 1055).

[20] Augustín Avilés et al., *Interferon Alpha 2b as Maintenance Therapy in Low Grade Malignant Lymphoma Improves Duration of Remission and Survival*, 20 LEUKEMIA AND LYMPHOMA 495–99 (1996) (Ex. 1056).

[21] W. Hiddemann, *Review, Non-Hodgkin's Lymphomas—Current Status of Therapy and Future Perspectives*, 31A EUR. J. CANCER 2141-2145 (1995) (Ex. 1011).

the disclosures in those references would have suggested using rituximab maintenance therapy in the specific patient population required by claim 1 of the '172 patent. As the Supreme Court explained in *KSR*, "[unpatentability] on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning *with some rational underpinning* to support the legal conclusion of obviousness." *KSR*, 550 U.S. at 418 (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (emphasis added).

Further, the Maloney references and McLaughlin are directed to relapsed patients (Ex. 1038, 3266; Ex. 1046, 2457; Ex. 1009, 2825), which as discussed above, are beyond the scope of claim 1. In addition to being directed to a different patient population, those references, at best, suggest potential rituximab treatments that require further study. *See* Ex. 1038, 3273 ("*Potentially*, the agent could be used singly, in combination with standard chemotherapy, or following standard chemotherapy in an attempt to decrease minimal residual lymphoma and extend the duration of remission.") (emphasis added); Ex. 1046, 2465 ("Ultimately, extension of these studies to patients with minimal residual disease, using antibody alone or in combination with conventional therapies, may provide the greatest benefit."); Ex. 1009, 2831 ("Many additional issues about this agent remain to be explored. . . . With its established efficacy in the setting of measurable disease, the use of this agent in a minimal or subclinical disease setting is a consideration . . . ."). Accordingly, Petitioner does not persuade us that it has explained adequately why an ordinary artisan would have been encouraged to use rituximab maintenance therapy in a patient population distinct from that described in McNeil.

Petitioner also does not persuade us that it has explained adequately why the cited references 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. Although Petitioner urges Hiddemann as disclosing that CVP was the "standard" chemotherapy regimen for LG-NHL (Pet. 39), that reference discloses only that CVP was one of two preferred treatments for LG-NHL. Ex. 1011, 2141. Moreover, rather than suggesting adoption of the CVP therapy required by claim 1 for reducing CHOP toxicity, McNeil instead teaches a "mini-CHOP" regimen using the same drugs as CHOP, but at reduced doses. Ex. 1005, 267.

Further, Patent Owner advances evidence that the doxorubicin component in CHOP therapy was known to act synergistically with rituximab. Prelim. Resp. 38–39 (citing Exs. 2021, 2023).[22,23] Given McNeil's express teaching that mini-CHOP can be used to reduce toxicity, alongside evidence in the art of synergy between rituximab and doxorubicin, Petitioner does not persuade us that an ordinary artisan would have omitted the doxorubicin component of CHOP, and instead use CVP therapy followed by rituximab as required by claim 1 of the '172 patent, even assuming that CVP therapy was known to be less toxic than CHOP.

Petitioner also does not persuade us that it has explained adequately why Unterhalt's use of interferon alpha maintenance therapy in CVP-treated patients (Ex. 1006, 229) would have suggested the use of rituximab

[22] Robert Carlson, *Rituximab Plus CHOP: A New Approach For Non-Hodgkin's Lymphoma?*, INPHARMA No. 1116 (1997).

[23] Gail A. Leget, M.D. and Myron S. Czuczman, M.D., *Use of Rituximab, The New FDA-Approved Antibody*, 10 ONCOLOGY 548–551 (1998).

maintenance therapy in those patients, even assuming that the Avilés articles establish precedent in the prior art for adapting more aggressive NHL therapies to the treatment of LG-NHL. As Patent Owner argues (Prelim. Resp. 44), interferons were thought to *boost* the patient's immune system, including stimulating B-cells:

> [I]nterferons can improve a cancer patient's immune response against cancer cells. In addition, interferons may act directly on cancer cells by inhibiting their growth or promoting their development into cells with more normal behavior. Researchers believe that some interferons also may stimulate B cells and T cells, strengthening the immune system's anticancer function.

Ex. 1027, 2. In contrast, rituximab *inhibits* the immune system by killing B-cells. *See* Ex. 1008, 1 (Rituximab administration "resulted in a rapid and sustained depletion of circulating and tissue-based B-cells."). Given the significant differences in their biological activities, Petitioner does not persuade us, on this record, that interferon and rituximab would have been considered functionally equivalent biologics, such that an ordinary artisan would have been prompted to substitute one for the other.

As to the dosage required by claim 1 of the '172 patent, Petitioner contends that an ordinary artisan "reading McNeil would understand that each course of the rituximab maintenance therapy to which the article is referring is the standard rituximab dosing regimen of four weekly doses of 375mg/$m^2$." Pet. 43 (citing Ex. 1002 ¶ 129). Indeed, Petitioner contends, "that is the precise regimen described in the 1997 FDA Label (Ex. 1008)." *Id.*

We acknowledge that the Rituxan® label discloses that, "for the treatment of relapsed or refractory low-grade or follicular, CD20 positive, B-

cell non-Hodgkin's lymphoma, the "recommended dosage of RITUXAN is 375mg/$m^2$ given as an IV infusion once weekly for four doses (days 1, 8, 15, and 22)." Ex. 1008, 1, 2. However, that the FDA-approved/recommended weekly rituximab dosage for relapsed or refractory LG-NHL might be the same as the dosage recited in claim 1 does not demonstrate that a skilled artisan would have understood that those dosages were necessarily given in McNeil's study of intermediate grade NHL, a different patient population. Because Petitioner directs us to no clear or specific evidence showing that the dosage used in McNeil's study was the same as that recited in claim 1 of the '172 patent, we are not persuaded that McNeil inherently describes administering the weekly dosage required by claim 1.

In sum, for at least the reasons discussed, Petitioner does not persuade us that an ordinary artisan would have been prompted to modify McNeil's treatment of patients with intermediate grade NHL to instead treat the LG-NHL required by claim 1 of the '172 patent. For at least the reasons discussed, Petitioner also fails to persuade us that an ordinary artisan would have been prompted to modify McNeil's CHOP treatment to instead use the CVP treatment required by claim 1. Petitioner also fails to persuade us, for at least the reasons discussed, that an ordinary artisan would have been prompted to substitute, as a maintenance therapy following CVP induction, the rituximab required by claim 1 for the interferon described in the prior art. Lastly, Petitioner fails to persuade us that McNeil inherently describes the daily dosage regimen required by claim 1 of the '172 patent. In light of these determinations, we determine further that Petitioner has not established a reasonable likelihood of prevailing in its challenge to claim 1 over McNeil alone.

*F. Obviousness—McNeil (Ex. 1005) and the Rituxan® Label (Ex. 1008)*

Petitioner contends that, although McNeil would have rendered claim 1 of the '172 patent obvious, claim 1 is "further rendered obvious by the 1997 Rituxan® Label, which makes explicit what oncologists would understand from McNeil—namely, that each course of rituximab therapy is the standard rituximab dosing regimen of 4 weekly doses of 375mg/$m^2$." Pet 43 (citing Ex. 1002 ¶ 130). Petitioner contends further that an ordinary artisan would have been motivated to modify McNeil "with what was discussed in the 1997 Rituxan® Label and would have reasonably expected to succeed in obtaining claim 1 of the '172 patent in view of, for example, the fact that the 1997 Rituxan® Label disclosed the FDA-approved standard dosing regimen of rituximab for the treatment of LG-NHL." *Id.*

Even if an ordinary artisan would have been prompted to use the Rituxan® Label's rituximab dosage regimen in McNeil's IG-NHL treatment, Petitioner directs us to no specific teachings in the Rituxan® Label that remedy the other deficiencies, discussed above, in Petitioner's explanation as to why the process recited in claim 1 would have been obvious to an ordinary artisan, despite the differences between claim 1 and McNeil. Accordingly, for reasons similar to those discussed above, we determine that Petitioner has not established a reasonable likelihood of prevailing in its challenge to claim 1 over McNeil and the Rituxan® Label.

*G. Obviousness— McNeil (Ex. 1005), the Rituxan® Label (Ex. 1008), and Unterhalt (Ex. 1006)*

Petitioner contends that, although "both McNeil alone and McNeil in combination with the 1997 Rituxan® Label render obvious claim 1," claim 1 "is further rendered obvious by Unterhalt, which discusses successfully

treating LG-NHL with CVP induction therapy followed by IFN maintenance therapy." Pet 44 (citing Ex. 1002 ¶ 131). Petitioner contends that Unterhalt "emphasizes what would have been apparent to one of ordinary skill from McNeil—specifically, that the method described in McNeil could be used for the treatment of LG-NHL and that CVP induction therapy could be used instead of CHOP induction therapy." *Id.*

Petitioner contends further:

> One of ordinary skill would have been motivated to modify McNeil with what was discussed in Unterhalt and would have reasonably expected to succeed in arriving at claim 1 of the '172 patent in view of, for example, the fact that both address NHL, other maintenance therapies for the treatment of LG-NHL had first been done in higher grades of NHL, CHOP had previously been used as induction therapy in LG-NHL, others had encouraged the use of rituximab maintenance therapy following chemotherapeutic induction therapy to treat LG-NHL, and Unterhalt had treated LG-NHL using CVP induction therapy followed by BRM [biological response modifier] maintenance therapy and demonstrated a "significant prolongation of DFS [disease-free survival]."

*Id.* (citing Ex. 1002 ¶ 131) (brackets in internal quote in original).

We acknowledge that Unterhalt describes treating patients who responded to CVP therapy with interferon alpha maintenance therapy. *See* Ex. 1006. Although Petitioner presents a chart explaining which disclosures in the prior art are alleged to correspond to which claim features (Pet. 49–56), Petitioner, nonetheless, does not explain specifically how it proposes that an ordinary artisan would have modified McNeil's process, with the teachings of Unterhalt, to arrive at the process recited in claim 1 of the '172 patent.

Moreover, as discussed above, given the prior art evidence of synergy between the doxorubicin component of CHOP and rituximab, viewed alongside McNeil's express teaching of reducing CHOP toxicity by performing mini-CHOP, Petitioner does not persuade us that an ordinary artisan would have omitted the doxorubicin component of McNeil's CHOP, and instead used CVP therapy followed by rituximab as required by claim 1 of the '172 patent. As discussed above also, because interferon was thought to boost the immune system, including stimulating B-cells, whereas rituximab was known to kill B-cells, Petitioner does not persuade us that Unterhalt's interferon and rituximab would have been considered functionally equivalent biologics, such that an ordinary artisan would have been prompted to substitute one for the other in maintenance therapy. As discussed above also, because the Maloney and McLaughlin references at best suggest that rituximab maintenance therapy might warrant further study, Petitioner does not persuade us that those references would have been viewed as encouraging rituximab maintenance therapy in LG-NHL patients.

Accordingly, Petitioner has not adequately explained why an ordinary artisan would have been prompted to modify McNeil's process according to the teachings of the Rituxan® Label and Unterhalt to arrive at the process recited in claim 1 of the '172 patent. We, therefore, determine that Petitioner has not established a reasonable likelihood of prevailing in its challenge to claim 1 over McNeil, the Rituxan® Label, and Unterhalt.

*H. Obviousness—McNeil (Ex. 1005), the Rituxan® Label (Ex. 1008), and the FDA Transcript (Ex. 1007)*

Petitioner contends that, while "both McNeil alone and McNeil in combination with the 1997 Rituxan® Label render obvious claim 1[, c]laim 1 is further rendered obvious by the 1997 FDA Transcript, which discusses

the use of CVP to treat a form of LG-NHL, followed by multiple courses of rituximab therapy." Pet 45 (citing Ex. 1002 ¶ 132).

Petitioner contends further:

> One of ordinary skill would have been motivated to modify McNeil with what was discussed in the 1997 FDA Transcript and would have reasonably expected to succeed in obtaining claim 1 of the '172 patent in view of, for example, the fact that both address NHL, other maintenance therapies for the treatment of LG-NHL had first been done in higher grades of NHL, CHOP had previously been used as induction therapy in LG-NHL, others had encouraged the use of rituximab maintenance therapy following chemotherapeutic induction therapy to treat LG-NHL, and the 1997 FDA Transcript encouraged the use of multiple courses of rituximab following CVP therapy to treat LG-NHL and discussed the benefits of using rituximab when tumor burden was reduced (e.g., following CVP induction therapy). Ex. 1002 ¶ 132.

*Id.*

We acknowledge the discussions in the FDA Transcript of LG-NHL patients having relapsed after chemotherapy, including CVP therapy, and having achieved significant improvement after rituximab treatment. *See* Ex. 1007, 35 (study was for relapsed or refractory LG-HNL); *id.* at 9–15 (patient Dr. Wendy Harpham received three rituximab infusions in 1993 and 1997 with positive results after multiple post-chemo relapses); *id.* at 125–127 (30 year-old male patient treated with multiple rounds of chemotherapy, including CVP, as well as radiotherapy, received two infusions of rituximab after relapses, with positive results); *id.* at 111–112 (total of 22 patients treated twice, 2 patients threated three times, all responded to rituximab treatment).

Although Petitioner presents a chart explaining which disclosures in the prior art are alleged to correspond to which claim features (Pet. 49–56), Petitioner, nonetheless, does not explain specifically how it proposes that an ordinary artisan would have modified McNeil's process, with the teachings in the FDA Transcript, to arrive at the process recited in claim 1 of the '172 patent. As noted above, McNeil differs from claim 1 of the '172 patent at least in that (1) McNeil treats patients with IG-NHL rather than LG-NHL, (2) McNeil teaches CHOP induction therapy, rather than CVP, and (3) McNeil is silent as to the dosing for maintenance therapy.

Even assuming that an ordinary artisan would have considered it obvious to adopt the rituximab dosage taught in the Rituxan® Label, Petitioner has not adequately explained, with sufficient specificity, why the FDA Transcript's disclosure of positive results using rituximab in relapsed LG-NHL patients would have prompted an ordinary artisan to use McNeil's maintenance therapy regimen in non-relapsed LG-NHL patients, and additionally change McNeil's induction chemotherapy from CHOP to CVP. As discussed above, given the prior art evidence of synergy between the doxorubicin component of CHOP and rituximab, viewed alongside McNeil's express teaching of reducing CHOP toxicity by performing mini-CHOP, Petitioner does not persuade us that an ordinary artisan would have omitted the doxorubicin component of McNeil's CHOP, and instead used CVP therapy followed by rituximab as required by claim 1 of the '172 patent.

As discussed above also, because interferon was thought to boost the immune system, including stimulating B-cells, whereas rituximab was known to kill B-cells, Petitioner does not persuade us that interferon and rituximab would have been considered functionally equivalent biologics,

such that an ordinary artisan would have been prompted to substitute one for the other in maintenance therapy. As also discussed above, because the Maloney and McLaughlin references at best suggest that rituximab maintenance therapy might warrant further study, Petitioner does not persuade us that those references would have been viewed as encouraging rituximab maintenance therapy in LG-NHL patients.

Accordingly, for at least these reasons, Petitioner does not persuade us that an ordinary artisan would have been prompted to modify McNeil's process according to the teachings of the Rituxan® Label and the FDA Transcript to arrive at the process recited in claim 1 of the '172 patent. We, therefore, determine that Petitioner has not established a reasonable likelihood of prevailing in its challenge to claim 1 over McNeil, the Rituxan® Label, and the FDA transcript.

*I. Obviousness—McLaughlin (Ex. 1009)*

Petitioner cites McLaughlin as describing a clinical trial "in which LG-NHL patients were first treated with chemotherapy, including necessarily CVP, and subsequently treated with 375mg/$m^2$ rituximab, administered once weekly for a total of four infusions." Pet. 45–46. Petitioner summarizes its position as follows:

> Given it was known that CVP induction therapy followed by maintenance therapy using interferon had successfully treated LG-NHL, and that rituximab had a mild toxicity profile, one of ordinary skill would have reasonably expected to successfully use rituximab maintenance therapy following CVP induction therapy to treat LG-NHL as encouraged by McLaughlin 1998.

*Id.* at 48 (citing Ex. 1002 ¶¶ 133–135).

Petitioner does not persuade us that it has established a reasonable likelihood of prevailing as to this ground of unpatentability.

McLaughlin describes a multi-institutional trial of rituximab in patients with relapsed low grade or follicular lymphoma. Ex. 1009, 2825. The patients received 375 mg/m$^2$ rituximab weekly for four doses. *Id.* McLaughlin discloses that the response rate of 48% was comparable to results with single-agent chemotherapy, and notes that "[t]oxicity was mild." *Id.* Based on its results, McLaughlin discloses that "[f]urther investigation of this agent is warranted, including its use in conjunction with standard chemotherapy." *Id.*

We agree with Patent Owner that McLaughlin differs from claim 1 of the '172 patent at least in that (1) McLaughlin describes treating patients with relapsed LG-NHL and, therefore, does not describe the use of rituximab maintenance therapy, (2) McLaughlin does not describe expressly rituximab maintenance therapy following CVP induction therapy, and (3) McLaughlin does not describe a rituximab maintenance regimen of four weekly doses of 375 mg/m$^2$ every six months for two years. Prelim. Resp. 50–51.

Petitioner does not direct us to any express teaching in McLaughlin regarding the rituximab maintenance therapy required by claim 1 of the '172 patent. Instead, to show that McLaughlin would have suggested using rituximab in maintenance therapy following chemotherapy, Petitioner contends that, although McLaughlin's patients had relapsed after chemotherapy, McLaughlin taught that rituximab produced a better response in patients who had experienced a complete response (CR) or partial response (PR) from chemotherapy and had lower tumor burdens. *Id.* at 46. Therefore, Petitioner contends, "[t]hese results caused McLaughlin to

strongly encourage using rituximab in a maintenance therapy setting." *Id.* (citing Ex. 1009, 2831).

We are not persuaded. As to Petitioner's assertion that patients experiencing a complete or partial response achieved better results with rituximab, McLaughlin discloses that "[p]atients who had achieved a CR or PR with their last prior chemotherapy course *had a nonsignificant* but somewhat better response to the antibody than those who were resistant to chemotherapy . . . ." Ex. 1009, 2827 (emphasis added). As to Petitioner's assertion that McLaughlin strongly encouraged using rituximab in a maintenance therapy setting, McLaughlin discloses that, "[w]ith its established efficacy in the setting of measurable disease, the use of this agent in a minimal or subclinical disease setting is a consideration." *Id.* at 2831.

We are not persuaded that an improvement characterized as "nonsigificant" would have suggested to an ordinary artisan that rituximab should be employed as maintenance therapy in patients who responded to chemotherapy. Nor are we persuaded that ordinary artisans would have been strongly encouraged to perform rituximab maintenance therapy after chemotherapy, based on McLaughlin's statement that rituximab was merely "a consideration" in a minimal or subclinical disease setting. In that regard, moreover, Patent Owner advances evidence (Prelim. Resp. 51) that ordinary artisans, as well as Dr. Grossbard, recognized a difference between treating minimal disease and using an agent in maintenance therapy:

> The best role for unconjugated MoAbs [monoclonal antibodies] remains to be determined. Although they show activity as single agents, they may eventually have a greater role in conjunction with conventional cytotoxic chemotherapy *or in the minimal disease setting*, in which the problems of tumor bulk and circulating disease can be avoided. *Maintenance therapy*

> *may be another possible use for these agents*, although antigen mutation or modulation may limit repetitive administration.

Ex. 2008, 3704 (emphasis added).[24]

As to the CVP therapy required by claim 1 of the '172 patent, Petitioner does not direct us to any express teaching in McLaughlin regarding CVP therapy. Rather, Petitioner contends that McLaughlin's patients necessarily had been treated with CVP to achieve a CR or PR because CVP was the preferred combination chemotherapy to treat LG-NHL. Pet. 47 (citing Ex. 1011 (Hiddemann)). We are not persuaded.

As noted above, Hiddemann discloses that CVP was one of two preferred chemotherapy treatments for LG-NHL. Ex. 1011, 2141. This, at best, establishes that there was a fair likelihood that some of McLaughlin's patients received CVP therapy. It is well settled, however, that inherency may not be based on probabilities or possibilities. *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981)

Petitioner contends, alternatively, that CVP chemotherapy "would have been a logical choice" as an induction therapy to use with rituximab maintenance therapy for LG-NHL, "particularly given that CVP induction therapy had previously been used to treat LG-NHL." Pet. 47. Despite relying on a prior art treatment of LG-NHL with CVP induction as motivation to use CVP in combination with rituximab maintenance therapy as required by claim 1, Petitioner does not explain clearly which reference it relies upon to support CVP induction therapy in the prior art. As to

[24] Pratik S. Multani and Michael L. Grossbard, *Monoclonal Antibody-Based Therapies for Hematologic Malignancies*, 16 J. CLIN. ONCOL. 3691–3710 (1998).

reasonable expectation, Petitioner contends similarly that it "was known that CVP induction therapy followed by maintenance therapy using interferon had successfully treated LG-NHL," yet fails to explain clearly which reference it relies upon to support that assertion. Pet. 48.

By not clearly identifying the references it relies upon to establish that the prior art teaches or suggests all elements of claim 1, Petitioner fails to comply with 37 C.F.R § 42.104(b)(2), which requires Petitioner to identify "the patents or printed publications relied upon for each ground." In addition to Hiddemann, we note that Unterhalt, which Petitioner does not cite in support of this ground, but which is identified in the claim chart (*see* Pet. 50–54), describes treating LG-NHL with CVP induction therapy followed by interferon maintenance therapy. Ex. 1006. As discussed above, however, because interferon was thought to boost the immune system, including B-cells, whereas rituximab killed B-cells, we are not persuaded that Petitioner has explained adequately why the prior art's use of interferon maintenance therapy in conjunction with CVP induction would have prompted an ordinary artisan to use rituximab maintenance therapy with CVP.

Lastly, Petitioner does not persuade us that, based the Rituxan® website (Ex. 1048)[25] statement that the B-cell depletion observed in McLaughlin formed the basis of the ECOG 1496 trial, Patent Owner has effectively conceded that claim 1 would have been obvious over McLaughlin. *See* Pet. 46. To the contrary, § 103(a) states expressly that "[p]atentability shall not be negatived by the manner in which the invention was made." Moreover, Petitioner does not allege that the asserted statement

[25] http://www.rituxan.com/hem/hcp/non-hodgkin/post-induction/ecog

on the Rituxan® website constitutes prior art. To the contrary, Petitioner's contention in this regard appears to be based on improper hindsight. *See Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008) (Even post-*KSR*, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention.").

In sum, for at least the reasons discussed, Petitioner does not persuade us that it has established a reasonable likelihood of prevailing in its obviousness challenge to claim 1 of the '172 patent based on McLaughlin alone.

*J. Obviousness—McLaughlin (Ex. 1009) and McNeil (Ex.1005)*

Petitioner contends that while "McLaughlin renders obvious claim 1 of the '172 patent[, c]laim 1 is further rendered obvious by McNeil, which discusses the treatment of intermediate-grade NHL by using CHOP induction therapy, followed by rituximab maintenance therapy every 6 months to provide maintenance therapy for two years." Pet. 48. Petitioner explains:

> Given, for example, the strong encouragement in McLaughlin to use rituximab maintenance therapy in a LG-NHL setting, one of ordinary skill would have viewed the rituximab maintenance therapy regimen discussed in McNeil as a logical choice. This particularly would have been the case given that the CHOP induction therapy used in McNeil had previously been used to treat LG-NHL (Ex. 1023 at 62), the maintenance therapy discussed in McNeil was consistent with the observation in McLaughlin that use of rituximab to treat LG-NHL resulted in B cell depletion that lasted at least 6 months (Ex. 1009 at 2829 and Figure 3), and maintenance therapies for the treatment of LG-NHL had previously been considered first in the context of

> treating higher grades of NHL, such as intermediate-grade NHL (Exs. 1055–6).

*Id.* at 48–49.

Petitioner presents a chart explaining which disclosures in the prior art are alleged to correspond to which claim features (Pet. 49–56). Petitioner, nonetheless, does not explain specifically how it proposes that an ordinary artisan would have modified McLaughlin's process with McNeil's teachings to arrive at the process recited in claim 1 of the '172 patent.

As noted above, McLaughlin differs from claim 1 of the '172 patent at least in that (1) McLaughlin describes treating patients with relapsed LG-NHL and, therefore, does not describe the use of rituximab maintenance therapy, (2) McLaughlin does not describe expressly rituximab maintenance therapy following CVP induction therapy, and (3) McLaughlin does not describe a rituximab maintenance regimen of four weekly doses of 375 $mg/m^2$ every six months for two years. As noted above also, McNeil differs from claim 1 at least in that (1) McNeil treats patients with IG-NHL rather than LG-NHL, (2) McNeil teaches CHOP induction therapy rather than CVP, and (3) McNeil is silent as to the dosing for maintenance therapy.

As discussed above, Petitioner does not persuade us that McLaughlin strongly encouraged using rituximab maintenance therapy in LG-NHL, as Petitioner contends. Petitioner also fails to explain convincingly why an ordinary artisan would have used the CVP induction therapy required in claim 1 of the '172 patent, instead of the CHOP therapy described in McNeil. We acknowledge Hiddemann's disclosure that CVP was one of two preferred chemotherapy treatments for LG-NHL. Ex. 1011, 2141. Petitioner, however, expressly acknowledges that CHOP had been used to

treat LG-NHL. Pet. 49. Moreover, as discussed above, there was evidence in the prior art of synergy between the doxorubicin component of CHOP and rituximab (*see* Ex. 2021, 7; Ex. 2023, 550), and McNeil expressly taught reducing CHOP toxicity by performing mini-CHOP, rather than removing the doxorubicin component of that regimen (*see* Ex. 1005, 267).

Given these teachings, and the admitted suitability of CHOP for treating LG-NHL, Petitioner does not persuade us that an ordinary artisan would have omitted the doxorubicin component of McNeil's CHOP, and instead used CVP therapy in LG-NHL patients. Thus, even assuming that McNeil would have suggested the two-year rituximab maintenance dosage regimen required by claim 1, Petitioner does not persuade us that the combination of McLaughlin and McNeil would have suggested the specific combination treatment regimen, CVP followed by rituximab, required by claim 1 of the '172 patent.

In sum, for at least the reasons discussed, Petitioner does not persuade us that it has established a reasonable likelihood of prevailing in its obviousness challenge to claim 1 based on McLaughlin and McNeil.

## III. CONCLUSION

For the reasons given, we determine based on the Petition and the Preliminary Response that Petitioner has not established a reasonable likelihood that it would prevail in its challenges to claim 1 of the '172 patent.

## IV. ORDER

It is

ORDERED that the petition is denied as to the challenged claim, and no trial is instituted.

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